THE APPLICATION OF ARYNE CHEMISTRY AND USE OF α-DIAZO CARBONYL DERIVATIVES IN INDAZOLE SYNTHESIS WITH BIOLOGICAL EVALUATION

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Coláiste na hOllscoile Corcaigh, Éire
University College Cork, Ireland

Patricia M. Hanlon, B.Sc.

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University College Cork

Supervisor: Dr. Stuart G. Collins

Head of Department: Prof. Justin D. Holmes

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DECLARATION BY CANDIDATE

I hereby confirm that the body of work described within this thesis for the degree of Doctor of Philosophy, is my own research work, and has not been submitted for any other degree, either in University College Cork or elsewhere. All external references and sources are clearly acknowledged and identified within the contents. I have read and understood the regulations of University College Cork concerning plagiarism.

_____ _____

Patricia M. Hanlon Date: 6th January 2016

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Abstract

This thesis outlines the synthetic chemistry involved in the preparation of a range of novel indazole compounds and details the subsequent investigation into their potential as biologically active agents. The synthetic route utilised in this research to form the indazole structure was the [3+2] dipolar cycloaddition of diazo carbonyl compounds with reactive aryne intermediates generated *in situ.*

The preparation of further novel indazole derivatives containing different functional groups and substituents was performed by synthesising alternative 1,3-dipole and dipolarophile analogues and provided additionally diverse compounds. Further derivatisation of the indazole product was made possible by deacylation and alkylation methods. Transformation reactions were performed on alkene-containing ester side chains to provide novel epoxide, aldehyde and tertiary amine derivatives.

The first chapter is a review of the literature beginning with a short overview on the structure, reactivity and common synthetic routes to diazo carbonyl derivatives. More attention is given to the use of diazo compounds as 1,3-dipoles in cycloaddition reactions or where the diazo group is incorporated into the final product. A review of the interesting background, structure and reactivity of aryne intermediates is also presented. In addition, some common syntheses of indazole compounds are presented as well as a brief discussion on the importance of indazole compounds as therapeutic agents.

The second chapter discusses the synthetic routes employed towards the synthesis of the range of indazoles. Initially, the syntheses of the diazo carbonyl and aryne precursors are described. Next, the synthetic methods to prepare the indazole compounds are provided followed by discussion on derivatisation of the indazole compounds including *N*-deacylation, *N*-benzylation and ester side-chain transformation of some alkene-containing indazoles. A series of novel indazole derivatives were submitted for anti-cancer screening at the U.S National Cancer Institute (NCI). A number of these derivatives were identified as hit compounds, with excellent growth inhibition. The results obtained from biological evaluation from the NCI are provided with further results pending from the Community for Open Antimicrobial Drug Discovery.

The third chapter details the full experimental procedures, including spectroscopic and analytical data for all the compounds prepared during this research.

Table of Abbreviations

Å	angstrom
Ac	acetyl
AIDS	acquired immune deficiency syndrome
aq.	aqueous
Bn	benzyl
Boc	tert-butyloxycarbonyl
br s	broad singlet
Bu	butyl
BuLi	*n*-butyllithium
c	centi (10^{-2})
ºC	Celsius degrees
CCNSC	Cancer chemotherapy national service center
$CDCl_3$	deuterated chloroform
^{13}C NMR	carbon nuclear magnetic resonance
ca.	circa, about
CO-ADD	Community for Open Antimicrobial Drug Discovery
COX	cyclooxygenase
δ	NMR chemical shift
d	doublet
DCE	dichloroethane
DCM	dichloromethane
dd	doublet of doublets
ddd	doublet of doublets of doublets
DEPT	distortionless enhancement by polarization transfer
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
dq	doublet of quartets
dt	doublet of triplets
DTP	Developmental Therapeutics Programme
e.g.	for example
equiv.	equivalent(s)

ESI	electrospray ionization
Et	ethyl
Et_2O	diethyl ether
ESKAPE	*Enterococcus faecium* *Staphylococcus aureus* *Klebsiella pneumoniae* *Acinetobacter baumannii* *Pseudomonas aeruginosa* *Enterobacter* Species
Et_3N	triethylamine
EtOAc	ethyl acetate
EtOH	ethanol
et al.	and others
EDG	electron donating group
EWG	electron withdrawing group
FDA	food and drug administration
FT-IR	Fourier-transform infrared spectroscopy
g	gram(s)
GI_{50}	concentration of drug that inhibits growth by 50%
h	hour(s)
HCl	hydrochloric acid
HDDA	hexadehydro-Diels-Alder
^1H NMR	proton nuclear magnetic resonance
HIV	human immunodeficiency virus
HMBC	Heteronuclear Multiple Bond Correlation
HOMO	highest occupied molecular orbital
HRMS	High resolution mass spectrometry
Hz	Hertz
i	iso
IBX	2-iodobenzoic acid
IC_{50}	50% inhibition concentration

IR	infrared
J	coupling constant
k	rate constant
L	litre
LC_{50}	concentration which is lethal to 50% of cells
LDA	lithium diisopropylamide
Lit.	literature
LRMS	low resolution mass spectrometry
LSD	Lysergic acid diethylamide
LUMO	lowest unoccupied molecular orbital
μ	micro (10^{-6})
m	metre
	mili (10^{-3})
	multiplet
M	Molar
MDMA	3,4-methylenedioxy-methamphetamine
m/z	mass-to-charge ratio
max	maximum
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MeCN	acetonitrile
mg	milligram
MHz	megahertz
min	minute
mL	millilitre
mol	mole
mmol	millimole
μmol	micromole
mol%	mole percent
m.p.	melting point
MS	mass spectrometry
MW	microwave
ν_{max}	frequency of maximum absorption

n	nano (10^{-9})
n	normal
NBS	*N*-bromosuccinimide
NCI	National cancer institute
NMR	nuclear magnetic resonance
Nonaflate, ONf	nonafluoromethanesulfonate
NSAID	nonsteroidal anti-inflammatory drug
o	*ortho*
OAc	acetate
o/n	overnight
π	type of orbital, electron
p	para
$Pb(OAc)_4$	lead tetraacetate
PG	protecting group
Ph	phenyl
ppm	parts per million
Pr	propyl
q	quartet
RT	room temperature
s	second
	singlet
t	triplet
t, tert	tertiary
TBAF	tetrabutylammonium fluoride
TBAC	tetrabutylammonium chloride
td	triplet of doublets
TGI	total growth inhibition
TfO, triflate	trifluoromethanesulfonate
Tf_2O	trifluoromethanesulfonic anhydride
TFA	trifluoroacetic acid
THF	Tetrahydrofuran
TLC	thin-layer chromatography
TMS	tetramethylsilane

	trimethylsilyl
Ts	4-toluenesulfonyl, tosyl
UV	ultraviolet
vol	Volume
Δ	reflux

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To Mum

“The more you know, the more you know you don’t know.”

Aristotle

“If we knew what it was we were doing, it would not be called research, would it?”

Albert Einstein

"Son, if you really want something in this life, you have to work for it. Now quiet! They're about to announce the lottery numbers."

Homer Simpson

Chapter One

Introduction

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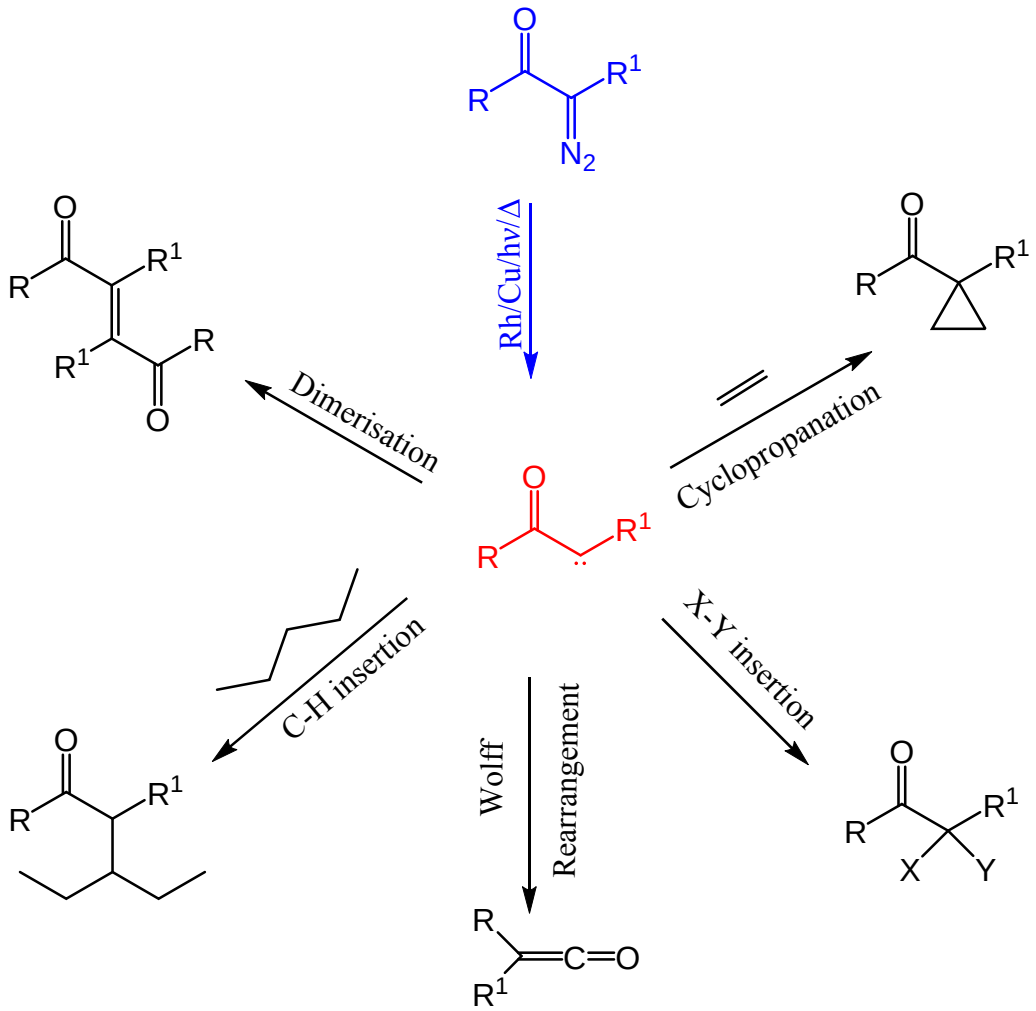
1.1 α-Diazocarbonyl compounds

1.1.1 Structure and reactivity

α-Diazocarbonyl compounds and their derivatives play an important role in organic synthesis. They are easily prepared in high yield and can undergo a range of chemical transformations due to their high reactivity, depending on the conditions employed.[1] Most of these transformations are initiated by loss of nitrogen from α-diazo carbonyl compounds, achieved under thermal, photochemical or catalytic conditions, generating reactive carbene intermediates which are known to undergo a significant number of reactions such as those outlined in **Scheme 1.1**.[2-6]



Scheme 1.1

The resonance structures of the α-diazocarbonyl group are shown in **Figure 1.1**. The carbon attached to the diazo group has a partial negative charge and exhibits nucleophilic character while the terminal nitrogen of the diazo group is electrophilic.

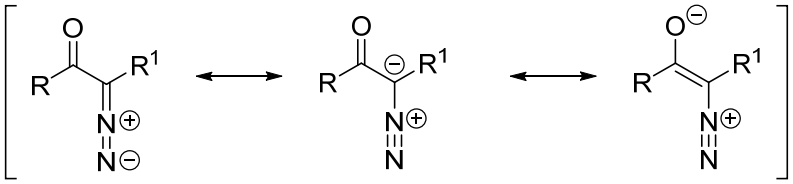


Figure 1.1 *Ambiphilic nature of diazo carbonyl derivatives*

Compounds containing diazo groups are some of the more synthetically useful 1,3-dipoles, however their participation in cycloaddition reactions has not been extensively examined in comparison to other 1,3-dipoles such as nitrile oxides, azomethine ylides, carbonyl ylides and nitrones.[7] This is possibly due to diazo compounds originally described in the literature not being readily available, being thermally unstable and not being suitable for prolonged storage.[8] The diazo group is analogous to propargyl/allenyl anion-type 1,3-dipoles which are linear in structure and contain a positive charge on the central nitrogen and the delocalisation of the anion over the carbon and the terminal nitrogen providing two contributing resonance forms (**Figure 1.2**).

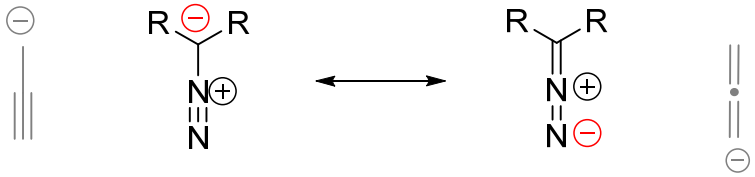
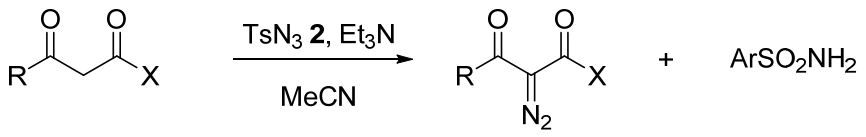


Figure 1.2 *Propargyl and allenyl anion-type diazo 1,3-dipoles*

1.1.2 Synthesis of α-diazocarbonyl compounds

The most common route to α-diazocarbonyl compounds involves the introduction of the diazo group using methodology developed by Regitz.[4] The complete diazo group is transferred from a donor, usually a sulfonyl azide, to an acceptor such as a ketone, ester or carboxylic acid by a reaction known as diazo transfer. The Regitz methodology requires a base of sufficient strength to deprotonate the α-protons and works well when the methylene group is activated

by two carbonyl groups. Compounds such β-diketones, β-ketoesters and β-ketoamides **1** are very reactive towards diazo transfer and form α-diazo-β-dicarbonyl products **3** (and *para*-toluenesulfonylamide by-product **4**) in a facile manner by reaction with a diazo transfer reagent such as *para*-toluenesulfonyl azide **2** in organic solvents like acetonitrile and dichlormethane using a base such as triethylamine, potassium carbonate, sodium hydride, etc. (**Scheme 1.2**).[5,9]



1 **3** **4**

R = H, alkyl, aryl
X = R, OR, NR^1R^2

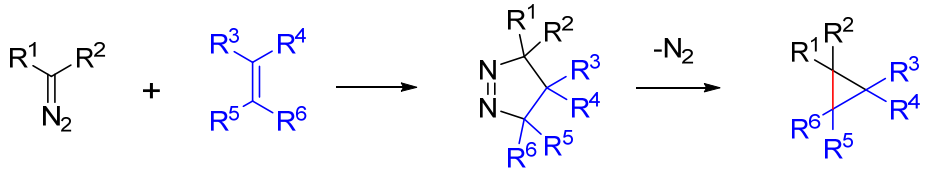
Scheme 1.2

There are a wide range of diazo transfer reagents available[10-15] with reviews in the literature on their utility[4,5,16] and on their individual properties such as stability, safety and associated hazards.[11,17] The least hazardous reagent described in the literature is *p*-dodecylbenzenesulfonyl azide **5** (**Figure 1.3**), which has a low impact sensitivity (exhibits no shock sensitivity at the highest test level of 150 kg.cm) and has been used in large scale reactions in industry for over a decade without incident.[8] Tosyl azide **2** (**Figure 1.3**), in comparison, is reported to be one of the most dangerous diazo transfer reagents due to its high impact sensitivity (50 kg.cm) and large heat of decomposition.[8,17] Tosyl azide **2** is still viewed as one of the more stable azides however, as the initiation temperature of the decomposition is >120 ºC. It is nevertheless regarded as a potential explosive and care should be taken during handling and storage.[8]

5 **2**

Figure 1.3 *p-Dodecylbenzenesulfonyl azide **5** and tosyl azide **2***

Cycloaddition reactions involving diazo compounds were first reported in the 1880s.[18,19] In the following 100 years, synthetic applications of these dipoles was limited to the preparation of pyrazole-type structures, after aromatisation of the initial [3+2] adduct and preparation of cyclopropane derivatives, following subsequent nitrogen extrusion from the initial cycloadduct (**Scheme 1.3**).

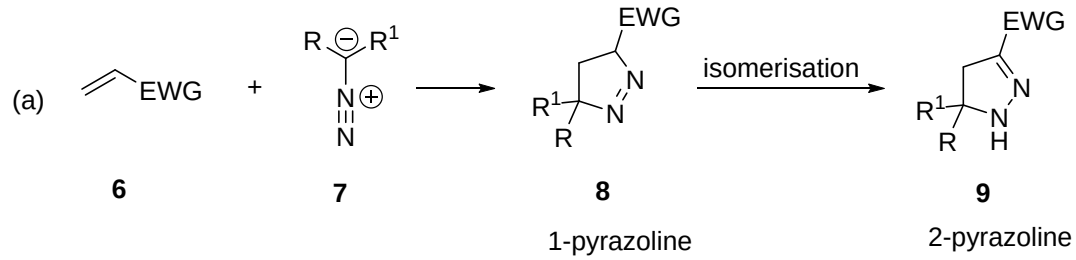


Scheme 1.3

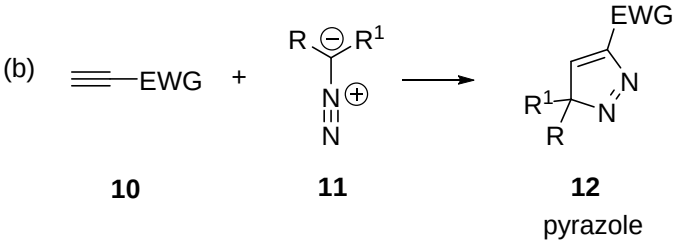
Since the 1980s, major developments in their use as substrates in cycloaddition reactions have occurred, including their reaction with a range of novel dipolarophiles leading to new and established heterocycles,[7] some of which will be discussed herein.

1.1.3 Cycloadditions with carbon-carbon double and triple bonds

The most common diazoalkane 1,3-dipolar cycloaddition reactions are addition to alkenes and alkynes. Diazo dipoles can participate in a range of cycloaddition reactions with both carbon-carbon double and triple bonds and the process can be promoted by electron-withdrawing substituents on the dipolarophiles. These general 1,3-dipolar cycloadditions are depicted in **Scheme 1.4**. The initial 1-pyrazoline adduct **8** of the diazo compound **7** and alkene dipolarophile **6** can isomerise to a 2-pyrazoline **9** [**Scheme 1.4** (a)],[20,21] and the product of the reaction with an alkyne dipolarophile **10** produces a pyrazole **12** [**Scheme 1.4** (b)].



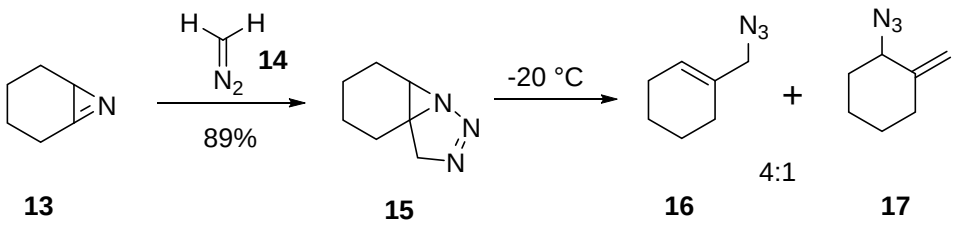
R = H, aryl, alkyl, vinyl, $RCOOR^1$
EWG = halogen, CN, NO_2, $RCOOR^1$



Scheme 1.4

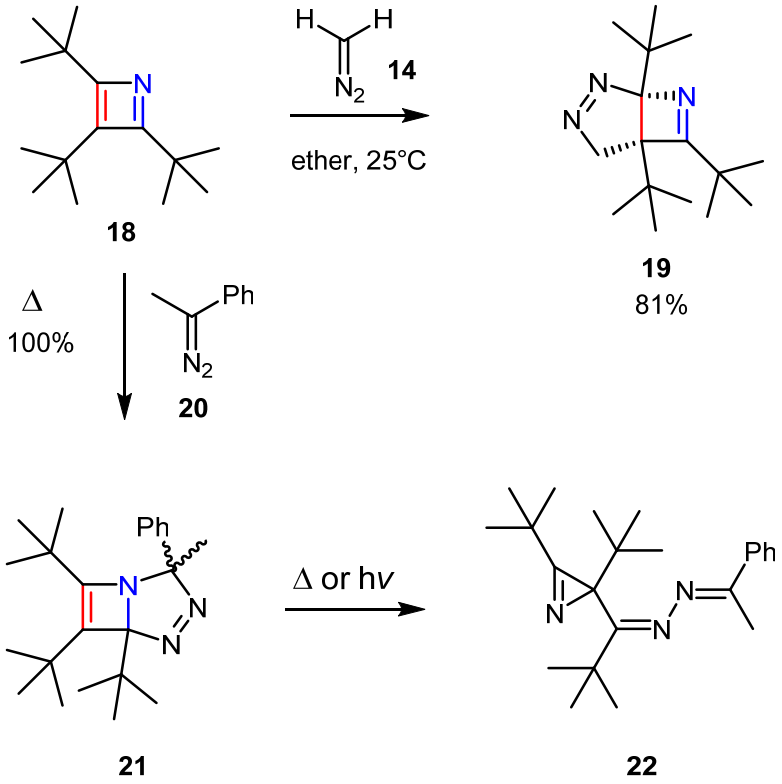
1.1.4 Cycloadditions with carbon-nitrogen double and triple bonds

The first reactions of strained cyclic imines, such as 2*H*-azirines **13** with diazomethane **14** to give allyl azides **16** and **17** *via* 1,2,3-triazabicyclo[3.1.0]hex-2-ene **15** was reported more than 50 years ago.[22] The 1,3-dipolar cycloaddition was found to proceed relatively slowly in comparison to the fragmentation of the postulated intermediate to yield the final products. Due to this, the structure of the short-lived 1,2,3-triazabicyclo[3.1.0]hex-2-ene **15** could not be proven by ^{1}H and ^{13}C NMR spectroscopy until 2006 (**Scheme 1.5**).[23]



Scheme 1.5

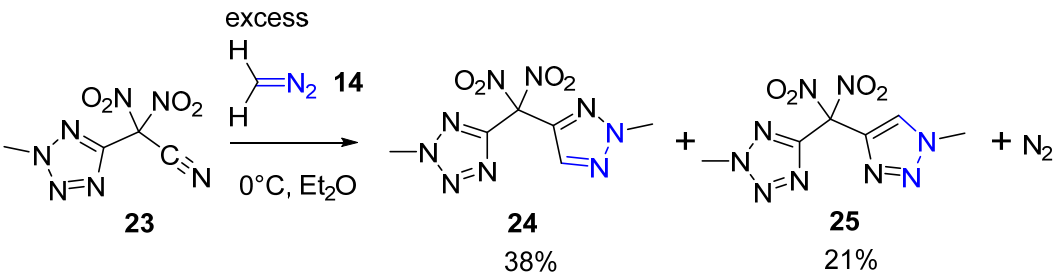
Further investigations into the reactions of strained cyclic imines were carried out by the Regitz group in 1988.[24] In their studies, the kinetically stabilised azete (azacyclobutadiene) **18** reacts with diazomethane **14** across the C=C bond to form the bicyclic 2,3,7-triazoline derivative **19**. More sterically hindered diazo compounds like 1-diazo-1-phenylethane **20** added across the C=N of the azete, to furnish two products in a quantitative overall yield. The bicyclic 1,3,4-triazoline derivative **21** is initially produced and attributed for 57% of the final product yield. Rearrangement occurs under thermal or photolytic conditions for *ca.* half of this product to form the ring-contracted isomeric 2*H*-azirinylketazine **22** in 43% yield (**Scheme 1.6**).



Scheme 1.6

Diazo compounds have been known to react with activated nitriles, such as those with an electron-withdrawing group attached, leading to 1,2,3-triazole derivatives.[25] In a recent publication by Tyrkov and co-workers, the cycloaddition of **23** with excess diazomethane **14** occurs under mild conditions to form two separable isomeric products **24** and **25**. The nitrile dipolarophile **23** is activated by the dinitrotetrazolylmethyl group. The initial N*H*-triazole cycloadduct is not

isolated due to rapid deprotonation and *N*-methylation with the excess diazomethane (**Scheme 1.7**).[26]

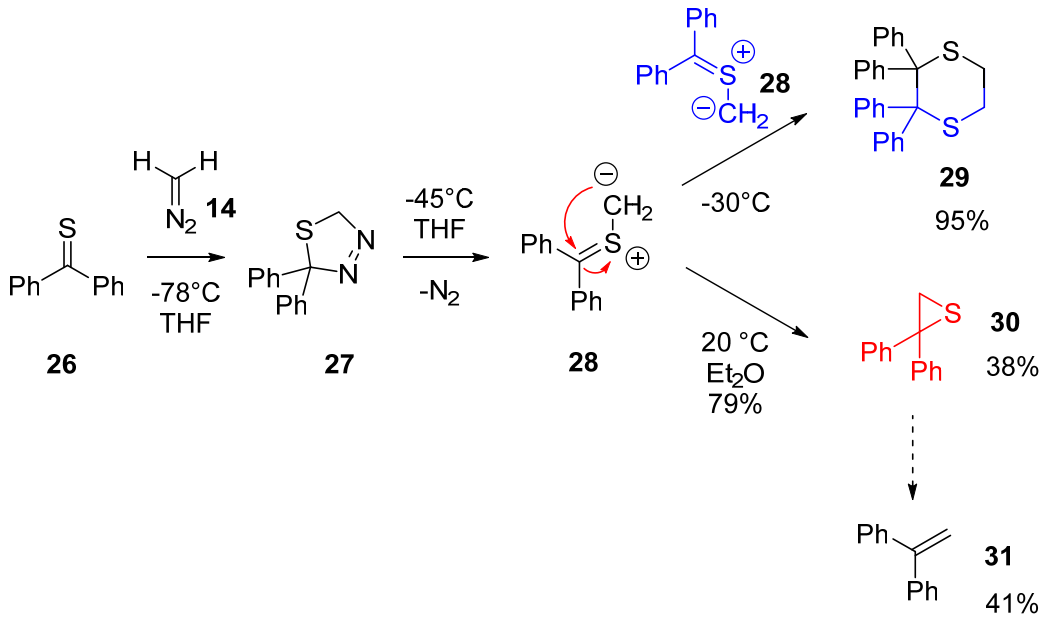


Scheme 1.7

1.1.5 Cycloaddition with thioketone C=S and subsequent nitrogen exclusion

Diazo compounds were shown to react with thioketones in a Schönberg cycloaddition reaction to yield 1,3-dithiolanes and/or thiiranes as far back as 1920,[27] with the mechanism being confirmed by Huisgen and co-workers in 1981.[28,29] The thioketone C=S bonds have high reactivity towards diazo dipoles in comparison to other common dipolarophiles. This can be explained by molecular orbital theory where the HOMO-LUMO energy separation of thiocarbonyl compounds are much smaller than their related C=O ketone compounds.[30]

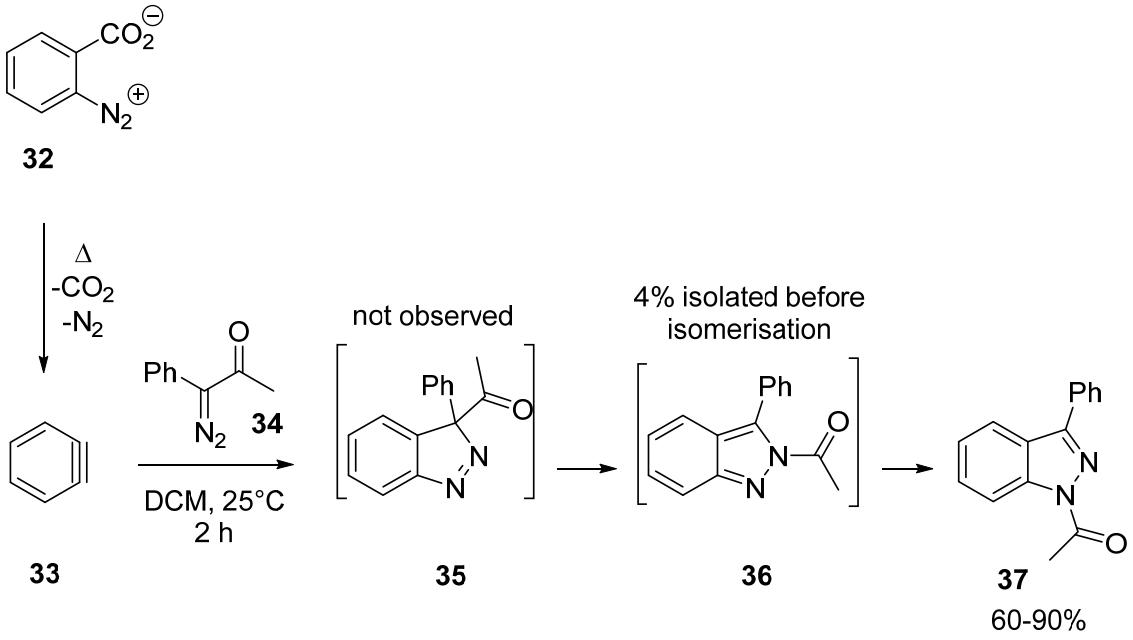
Thiobenzophenone **26** and diazomethane **14** react to form the thiadiazole cycloadduct intermediate **27**, which rapidly eliminates nitrogen to form the thiocarbonyl ylide **28**. This can then dimerise to form the dithiane **29** at -30 ºC; cyclise to form the thiirane **30** which can form product **31** by sulfur extrusion, or be trapped by a range of other dipolarophiles in another cycloaddition reaction (**Scheme 1.8**).[25,26]



Scheme 1.8

1.1.6 Cycloadditions with aryne intermediates

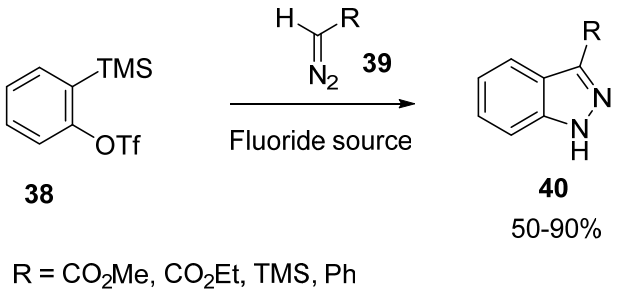
The first 1,3-dipolar cycloaddition reaction between diazo compounds and aryne intermediates was briefly mentioned by Huisgen in 1961[31] and again in publications by Shechter and co-workers in subsequent years[32,33] where the authors published their research on the synthesis of 1-acylindazole. The authors demonstrated that benzyne **33**, generated from the zwitterion of diazotised anthranilic acid **32** and 1-diazo-1-phenylpropan-2-one **34** undergo a cycloaddition reaction to give the 1,3-dipolar adduct intermediate **35**, which rapidly rearranges to the 2-acyl indazole **36** exclusively, before thermal isomerisation to the 1-acyl indazole **37** (**Scheme 1.9**).[33]



Scheme 1.9

However, due to limited methods to generate the aryne intermediate, research in this area did not advance greatly until 2007 when Yamamoto and co-workers[34] and Larock and co-workers[35] almost simultaneously reported 1,3-dipolar cycloaddition between diazo compounds and arynes to form 1*H*-indazole heterocycles. The development of commercially available aryne precursors and mild generation methods have paved the way for the aryne dipolarophile intermediate to be used in these cycloaddition reactions.

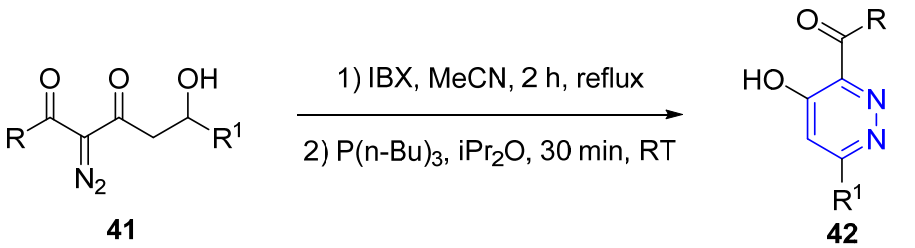
Yamamoto and co-workers were able to take advantage of the newly commercially available aryne precursors **38** in their reported synthesis of indazole derivatives **40**, using an efficient and general procedure employing the [3+2] cycloaddition of arynes and various diazo derivatives **39**.[34] Larock and co-workers reported similar findings in their publication a few months later, with slightly differing experimental procedures but the same outcome (**Scheme 1.10**).[35]



Scheme 1.10

1.1.7 Diaza-Wittig reactions

Although not a 1,3-dipole cycloaddition, the Diaza-Wittig reaction[36] is of interest as incorporation of the diazo group into heterocycles allows the preparation of "privileged" structures such as pyridazine **(Scheme 1.11)**[37,38] and phthalazine (**Scheme 1.12**). Privileged structures are defined as molecular frameworks which are capable of providing useful ligands for more than one type of receptor or enzyme target by judicious structural modifications.[39] Herdewijn and co-workers have reported novel syntheses of these derivatives that allow the introduction of various substitution patterns and do not require purification. Mild oxidation of the diazo **41** with IBX (2-iodobenzoic acid) followed by treatment with tributylphosphine in diisopropyl ether for 30 min in a Diazo-Wittig reaction led to the desired pyridazine derivatives **42** in good yields (**Scheme 1.11**).[37]



41

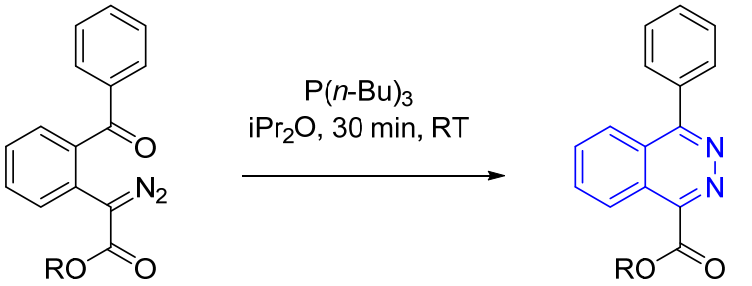
R = aryl
R^1 = alkyl, aryl

42

pyridazine
45-60%

Scheme 1.11

[1,6]-Ring closure of diazo **43** was achieved by an intramolecular Diaza-Wittig reaction in the same way as above to yield the phthalazine **44** (**Scheme 1.12**).[37]



43

R = alkyl, alkoxy

44

phthalazine
54-87%

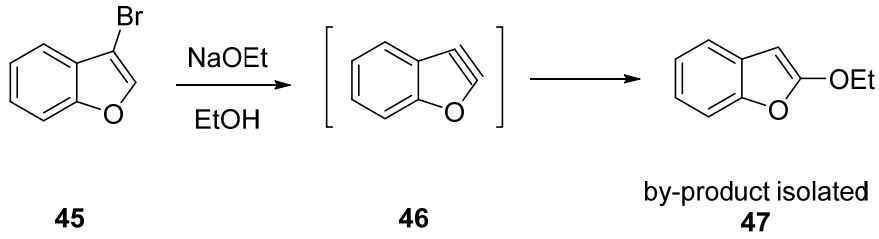
Scheme 1.12

Diazo compounds are important 1,3-dipoles in modern organic synthesis. They readily undergo a range of cycloaddition reactions, leading to a variety of interesting cycloadducts, dependant on the dipolarophile. These cycloadducts can contain the original diazo group or expel nitrogen from the product after the initial cycloaddition.[21]

1.2 Arynes

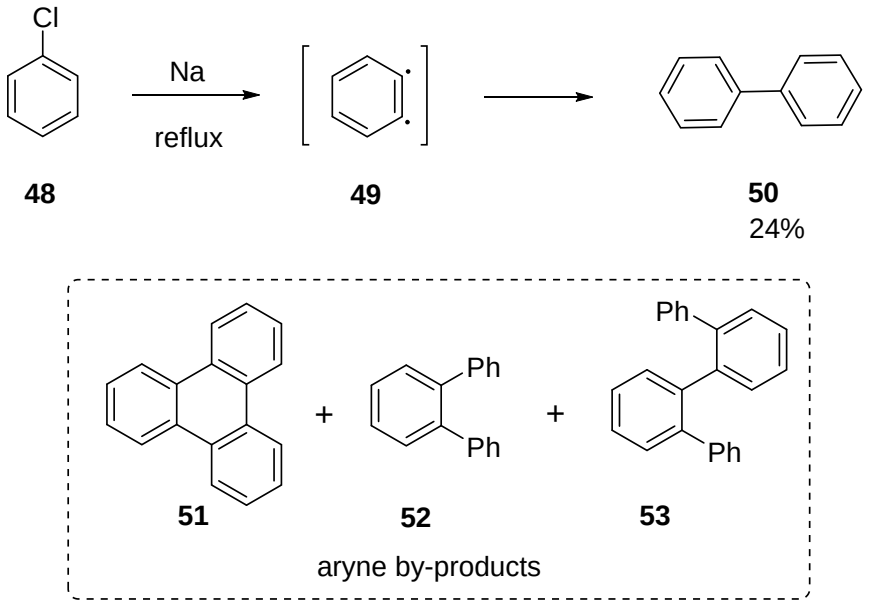
1.2.1 History and background

In 1902, Stoermer and co-workers were the first to postulate the existence of an aryne when they proposed the formation of 2,3-didehydrobenzofuran **46** as an intermediate on treatment of 3-bromobenzofuran **45** with sodium ethoxide in ethanol to form 2-ethoxybenzofuran **47** among other products (**Scheme 1.13**).[40] Although doubt has been cast over the conclusions drawn from these experiments by Reineke,[41] they influenced an interest in the field of aryne chemistry.



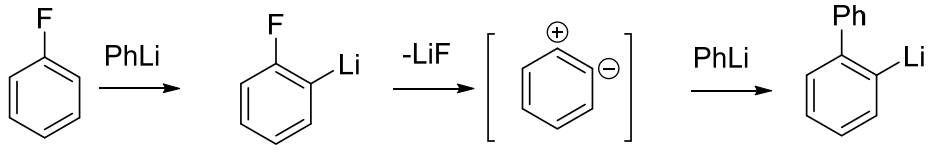
Scheme 1.13

Bachmann and co-workers then proposed 'free phenylene' **49** as a reactive intermediate in 1927 when the Wurtz-Fittig reactions with chlorobenzene **48** and sodium to produce biphenyl **50**, also produced compounds **51-53** that could not be explained by ionic mechanisms (**Scheme 1.14**).[42]



Scheme 1.14

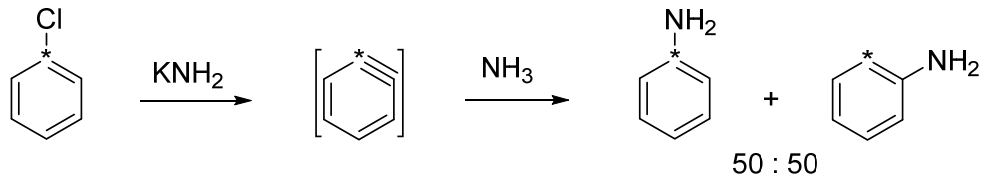
Several decades later, Wittig reported unusual rearrangements of benzene derivatives and initially suggested a zwitterionic intermediate structure **55** formed from loss of LiF from **55** in his work with fluorobenzene **54** and phenyllithium bases. It was thought that **56** underwent rapid reaction with phenyllithium to yield 2-lithiobiphenyl **57** (**Scheme 1.15**).[43]



54 **55** **56** **57**

Scheme 1.15

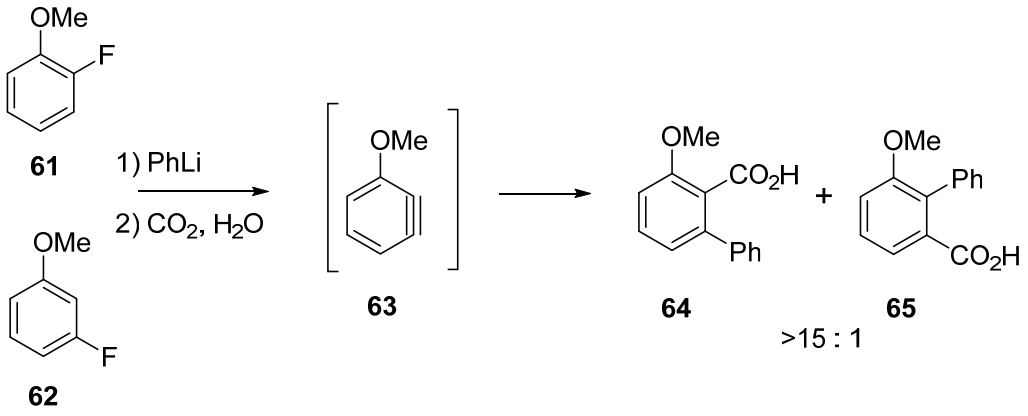
Roberts obtained definitive evidence for the existence of these reactive intermediates with his experiments on the reaction of ^{14}C-labelled chlorobenzene **58** with potassium amide to give equimolar mixture of products **59** and **60** (**Scheme 1.16**). This was rationalised by proposing the presence of benzyne intermediate **33**.[44]



58 **33** **59** **60**

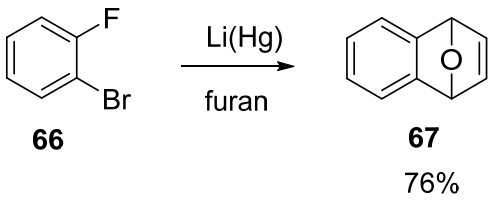
Scheme 1.16 * = ^{14}C label

Shortly after, Huisgen provided further evidence for the benzyne structure by demonstrating that identical major **64** and minor **65** carboxylic acid products were obtained on treatment of both 2- and 3-fluoroanisole **61** and **62** with phenyllithium followed by carboxylation (**Scheme 1.17**), and concluding that a common intermediate **63** must be involved.[45,46]



Scheme 1.17

Finally, the Diels-Alder trapping with furan by Wittig added more support to the existence of benzyne. Treatment of dihalobenzene **66** with lithium amalgam in furan led to the isolation of cycloadduct **67**, displaying the dienophilic character of the intermediate (**Scheme 1.18**).[47] These studies were the first concrete evidence of aryne intermediates and inspired the development of much of the aryne chemistry reported since.[48]



Scheme 1.18

1.2.2 Structure and reactivity

Arynes are neutral intermediates that can be derived from aromatic rings following di-elimination of substituents, leaving two atomic orbitals (perpendicular to the aromatic π system) occupied by two electrons. These intermediates possess a degree of triple bond character and their reactivity can be compared to that of alkynes **68**. Due to the nature of the triple bond, the intermediate is very reactive as the p orbitals are distorted to accommodate the triple bond within the ring system, impeding effective overlap and reducing stability.[49,50]

Radziszewski and co-workers investigated and analysed the IR spectra obtained of the benzyne triple bond from direct matrix isolation at low temperatures and assigned the frequency of the stretching vibration of the benzyne C-C triple bond to be ν_{max} 1846 cm^{-1} in 1992.[51] Radziszewski was also involved in a publication in 1996 that reported the bond length of the C-C triple bond, found experimentally to be 1.241 Å (**Figure 1.4**).[52]

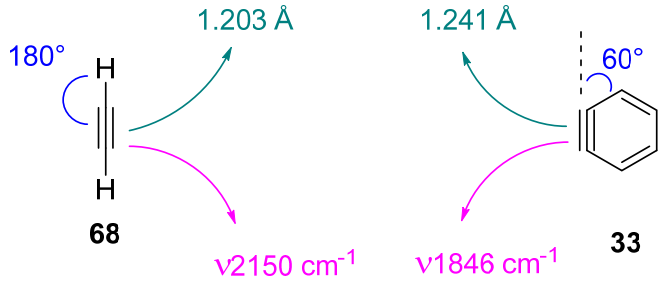


Figure 1.4 *Comparison of ethyne **68** and benzyne **33** triple bond*

Aryne systems are extensively studied and are no longer a chemical curiosity, even if some of their reactivity is still not fully understood. They have proven to be useful synthetic intermediates as milder methods for their generation have been reported, undergoing a range of chemical transformations, allowing for many synthetic applications.[37,50,53-61] Even at low temperatures arynes are very labile and are known to form dimers.[62] Their reactivity can be attributed to their kinetic instability and their highly strained structure.[48,50,58]

Despite this broad range of practical applications, their structural characterisation has been the subject of debate and remains a challenge. *ortho*-Benzyne **33**, which has the molecular formula C_6H_4, is the most well-known aryne. The original structure proposed for this reactive intermediate was a zwitterion of benzene **56**. After more research, this idea was then replaced by the strained alkyne structure **33**. This is now the widely accepted representation of *ortho*-benzyne **33** as its alkyne-like character is demonstrated by its reactivity patterns and will be employed herein. The biradical **49** and cumulene/cyclohexatetraene **69** representations are also significant resonance contributors. The two p orbitals in representation **70** are distorted to accommodate the triple bond, reducing their effective overlap, resulting in a highly reactive intermediate (**Figure 1.5**).

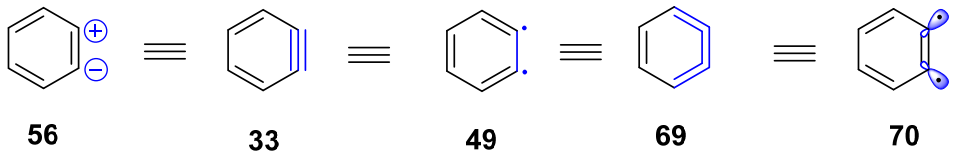


Figure 1.5 *Representations of o-benzyne structure*

Microwave and IR spectroscopic studies on benzyne **33** in the gas phase or isolated in cryogenic matrices have supported the electronic structure best portrayed by a resonant form with a triple bond between two adjacent carbon atoms.[63] Theoretical calculations also suggest a structure containing more triple bond character than cumulene character.[63,64] Solution ^{1}H and ^{13}C NMR spectra of benzyne **33**, generated inside a hemicarcerand molecular container, indicate a cumulene structure.[64]

Pavlicek and co-workers have recently been able to obtain direct imaging of the chemical structure of *ortho*-arynes for the first time using atomic force microscopy. Their experiments provided insight into the transient species that had been vague up until this point. Analysis of bond-order-related contrast indicated that the cumulene representation **71** was the dominant form for the aryne generated under these conditions, along with the triple bond **72** and biradical **73** resonance forms (**Figure 1.6**).[63]

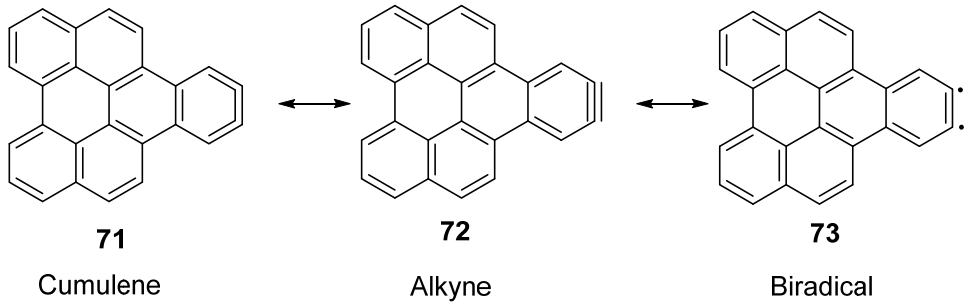
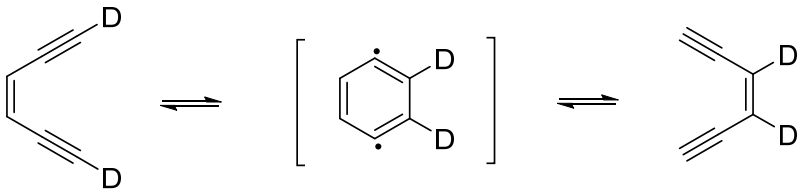


Figure 1.6 *Representations of dominant aryne structural forms*

Pyrolysis of *cis*-3-hexen-1,5-diyne **74** generated the first known *para*-benzyne **75** *via* the spontaneous Bergmann cycloaromatisation reaction which was

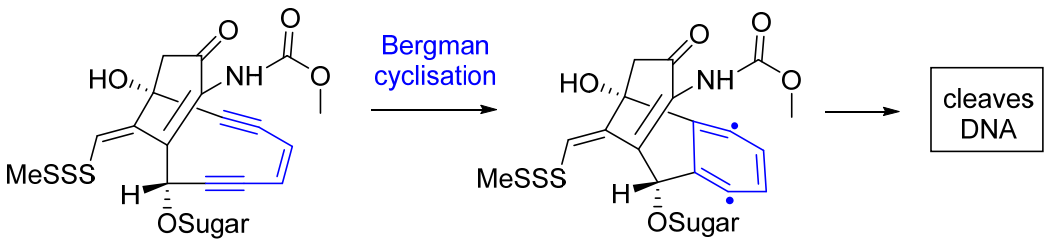
confirmed using product trapping experiments and isotope-labelling studies to form **76** (**Scheme 1.19**) in 1972 by Jones and Bergman.[65]



Scheme 1.19

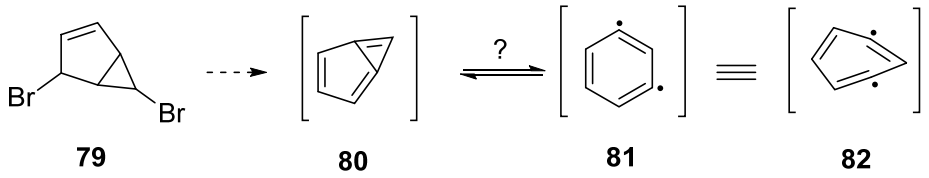
para-Benzyne has generated a lot of interest lately due to the discovery of the naturally occurring enediyne cytostatics (e.g. calicheamicin **77**), a class of antitumour-antibiotics.[66,67] The *para*-benzyne intermediate formed from these structures can undergo radical reactions, unlike its *ortho*-benzyne **33** counterpart; they can abstract a hydrogen atom from the deoxyribose sugar in both strands of double-stranded DNA, causing irreversible DNA cleavage *in vivo*, destroying the cancer cells.[66,68]

Calicheamicin **77**, isolated from a soil sample in 1987,[69,70] was found to be an incredibly potent cytotoxic agent by inciting DNA cleavage (**Scheme 1.20**).[46] It undergoes a Bergmann cyclisation, generating a biradical species **78** and causes double strand scission. The first total synthesis of calicheamicin **77** in its naturally occurring enantiomeric form was reported in 1992 by Nicolaou and co-workers.[71] Unfortunately, the delayed high cytotoxicity of the natural antibiotics hinders their clinical use but it is hoped that newer synthetic derivatives may provide effective treatment in the future.[66]



Scheme 1.20

Of the three benzynes possible (*ortho-*, *meta-* and *para*-benzyne), *meta*-benzyne has received the least attention. *meta*-Benzyne **81** was first generated by Washburn in 1975 by dehydrohalogenation of *exo,exo*-2,6-dibromobicyclo[3.1.0]-hex-2-ene **79**.[72] These early trapping experiments suggested that both bicyclic **80** and biradical **81** structures were possible for this intermediate. Since then, however, several methods have been developed for its generation and rather than the highly strained, anti-Bredt (bridged bicyclic systems containing ring strain due to the presence of a bridgehead alkene), tri-alkenyl bicyclic structure **80**, it was determined explicitly to have a biradical structure with major distortion of the benzene hexagon shape **82**. This distortion is due to the occurrence of coupling of the formally unpaired electrons by through-space and through-bond interactions of the radical lobes (**Scheme 1.21**).[73-78]



Scheme 1.21

The radical reactivity of the *meta*-benzyne structures is reduced due to strong coupling between the proximate radical sites which may pave the way for a more beneficial target for antitumor agents than the *para*-benzyne analogues.[73,74,77] An improved understanding of the reactivity of *meta*-benzyne could, therefore, be useful for the design of new synthetic DNA cleaving agents; however, this is still a challenge due to their high reactivities and the difficulty in generating them efficiently.

1.2.3 Heterocyclic arynes

Although the majority of aryne research has focused on carbocyclic aryne intermediates, there are many examples of well-known heterocyclic arynes and postulated hetaryne intermediates **83-91** (**Figure 1.7**).

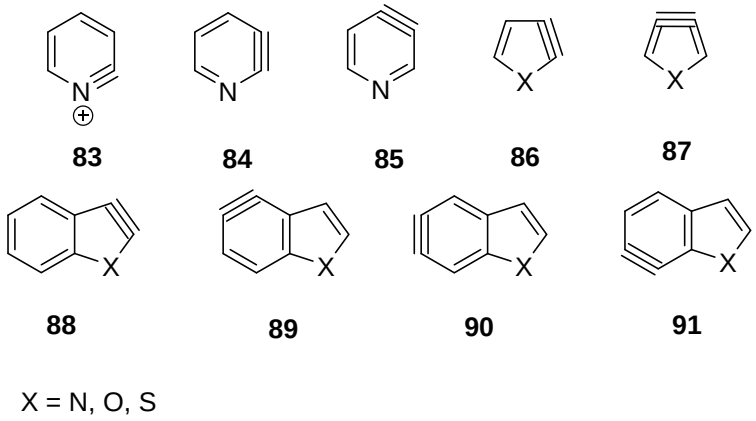


Figure 1.7 *Well-known and postulated hetaryne intermediates*

A major challenge in the early study of hetarynes had been that they could not be readily observed in reactions, with the evidence of their existence coming from the products formed in the reactions.[41] This could have led to incorrect conclusions due to multiple possible pathways that potentially led to proposed hetaryne products without forming the hetaryne intermediate. It is feasible also that aryne and non-aryne pathways are proceeding competitively in a given reaction.[41] Therefore, according to Reinecke, many of the heterocyclic arynes proposed in reported reactions may not actually be involved as an intermediate.[41]

Reported hetaryne reactions frequently give low yields of desired products, in part due to their high reactivity, with major side reactions causing the formation of unmanageable tars.[79] As a consequence of this, they have not been seen as synthetically useful and have not been studied to the same extent as carbocyclic arynes. The most well studied hetaryne intermediates are pyridynes **84** and **85**, and indolynes **88-91** (where X = O) derivatives, which have been employed as useful intermediates in organic synthesis and have been reviewed recently by Goetz and Garg.[48,80] Herein, some uses of pyridyne intermediates are described.

The 3,4-pyridyne isomer **85** is the most stable of the isomers (due to the formal C-C triple bond length being close in the length to the benzyne **33** C-C triple bond) followed by the 2,3-isomer **84** which contains a more elongated C-C triple bond (**Figure 1.8**). The 1,2-pyridyne **83** can also be represented as the 2-pyridyl cation but attempts to study this intermediate in solution were unsuccessful with only gas phase studies showing some evidence for its formation.[81] Much synthetic effort has gone into the study of these intermediates in the preparation of substituted pyridines. There is also evidence of *meta*- and *para*-type pyridyne intermediates.[82]

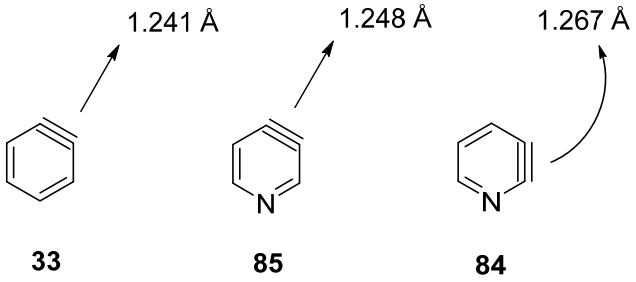
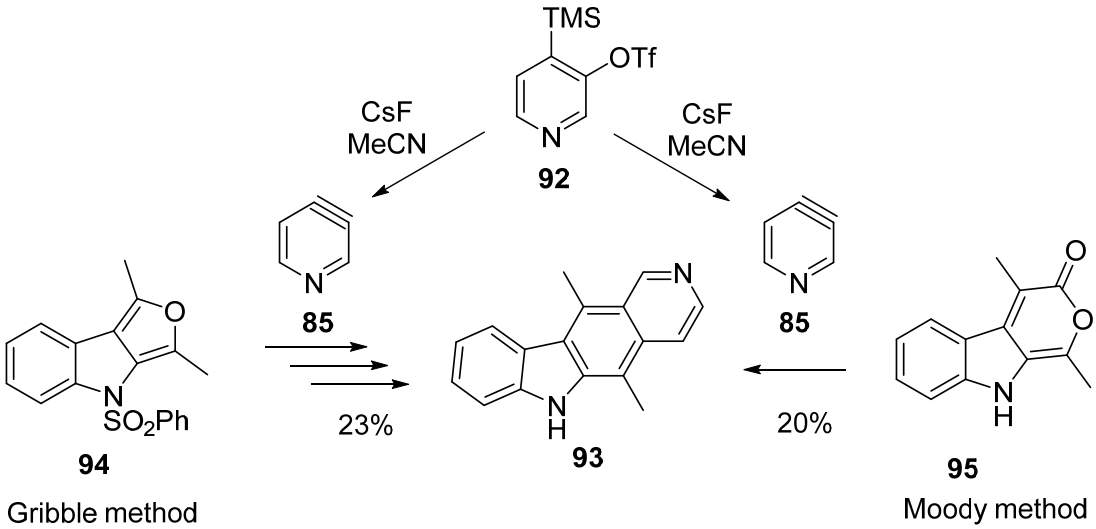


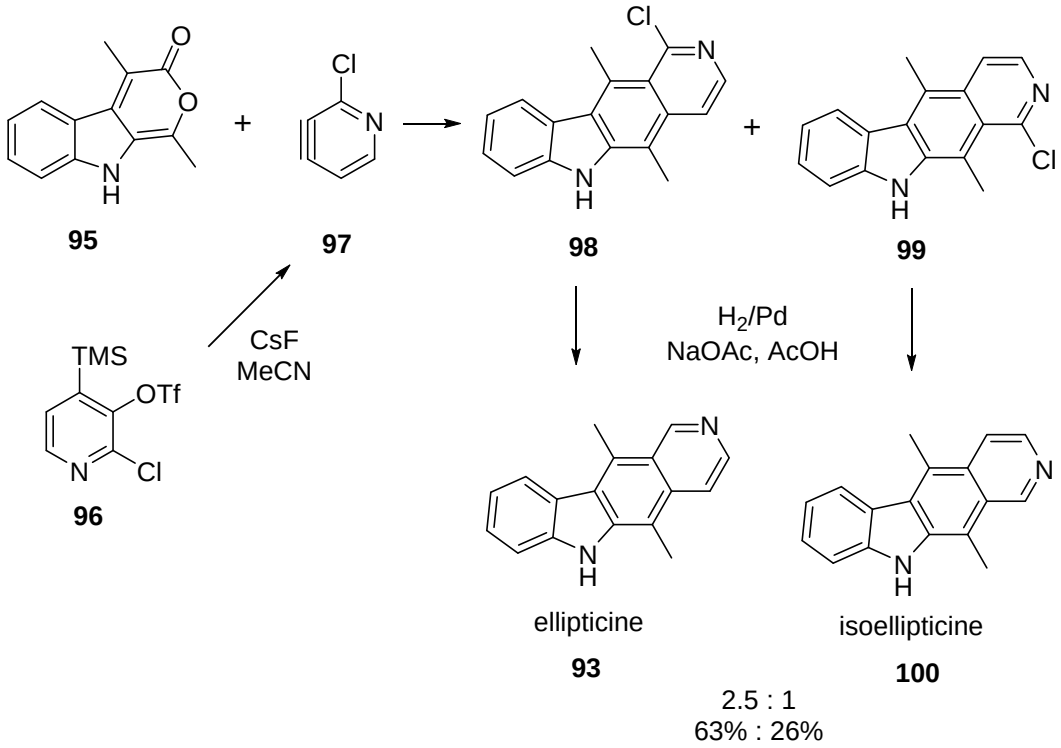
Figure 1.8 *Comparison of aryne triple bond lengths*

In the synthesis of ellipticine-type compounds **93**, procedures by both Gribble[83] and Moody[84] involve the use of 3,4-pyridyne **85** (generated from **92**) with furoindole **94** and indolopyrone **95** respectively. Both of these routes, although short and convergent, are of limited synthetic use due to low yielding reactions and lack of regioselectivity in the cycloadditions **(Scheme 1.22)**.[57]



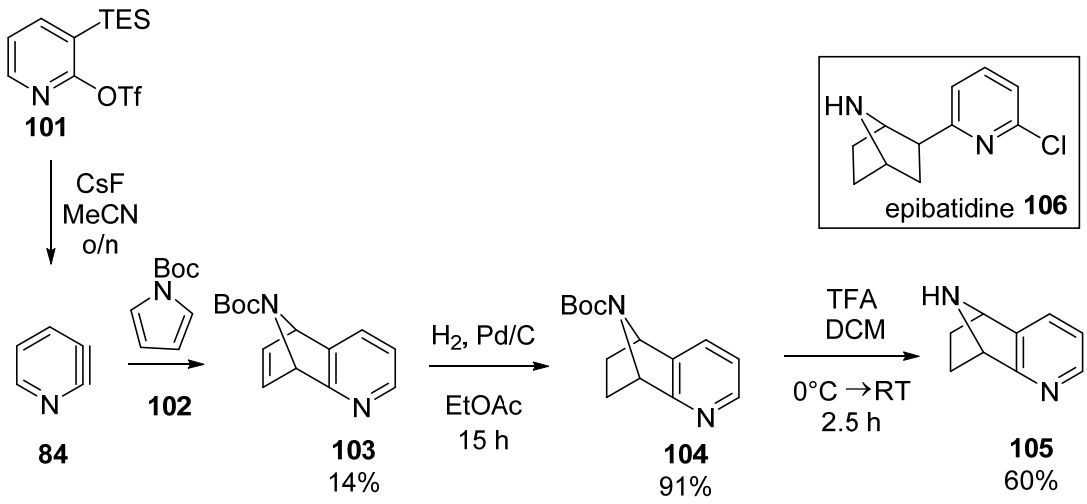
Scheme 1.22

Díaz and co-workers used a variation of these methodologies and were able to control the regiochemistry by introducing a chlorine substituent near the triple bond in **97** that could influence the inductive and/or steric effects of the reactions.[57] These halide directing group substituents, which were relatively easy to introduce by using pyridine precursor **96**, would cause the desired effect, and are easy to remove after the cycloaddition, forming the same compounds ellipticine **93** and isoellipticine **100** as described by Gribble and Moody (**Scheme 1.23**). Though the factors affecting the regioselectivity of the cycloadditions are not well understood, using Moody's indolopyrone **95**, protecting the nitrogen and having the 2-chloro substituent in the 3,4-pyridyne **97** improved the regioselectively and the overall yield of the reaction.



Scheme 1.23

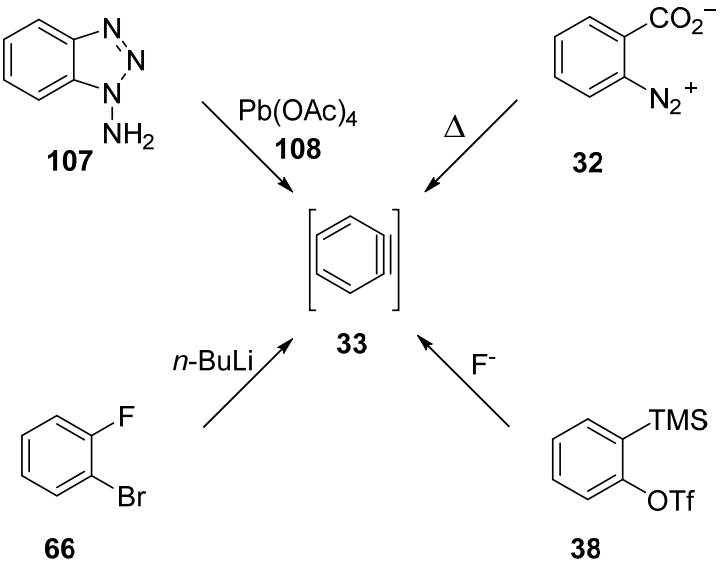
Carroll and co-workers used the trapping of 2,3-pyridyne **84** generated from **101** with *N*-protected pyrrole **102** as a key step in the synthesis of a range of epibatidine analogues. The initial cycloadduct **103** is reduced and deprotected to form **104** and **105** (**Scheme 1.24**).[85] Epibatidine **106** is a toxic alkaloid secreted by poisonous frogs found in Ecuador. Initially, it was thought that it could be useful as an analgesic drug but as of yet there have been no successful attempts in the synthesis of an analogue with reduced toxicity but effective analgesic effects.



Scheme 1.24

1.2.4 Generation of ortho-arynes

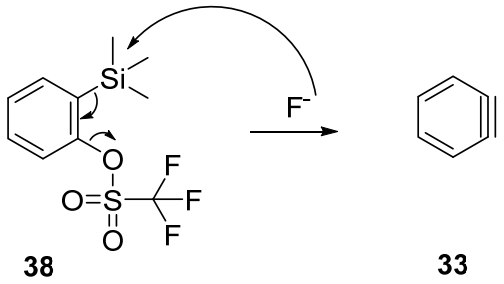
Even at low temperatures, arynes such as benzyne **33** are highly unstable reactive intermediates and must be generated *in situ*. Traditionally arynes were generated using harsh reaction conditions such as: fragmentation of aminotriazoles **107** using lead tetraacetate **108**, loss of carbon dioxide and nitrogen from the zwitterion of diazotised anthranilic acid **32** and 1,2-elimination from **66** using strong bases.[49] However, mild methods of generation, such as fluoride induced desilylation of **38** have been reported in recent years and is currently one of the most common generation methods reported in the literature (**Scheme 1.25**).[49,50,86-90]



Scheme 1.25

Mild generation methodologies have renewed the attractiveness of arynes as reagents in organic synthesis and a number of aryne precursors are also now commercially available. It is important to note that some routes have been shown to sometimes affect the reactivity of the intermediate, where a reaction does not proceed using one approach over another.[33,35]

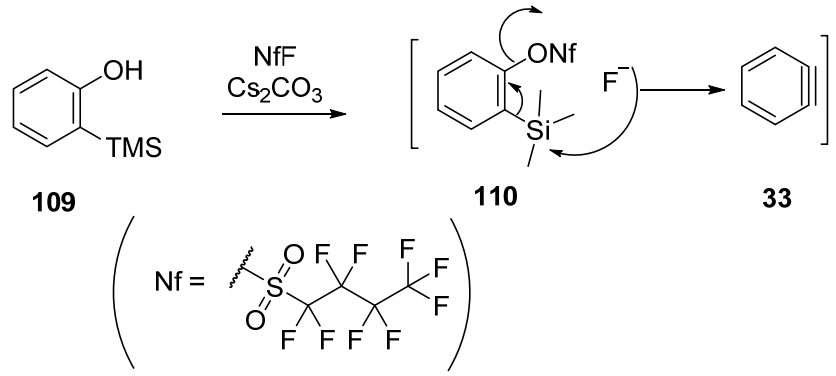
The attractiveness of arynes as reagents in organic synthesis was revolutionised in 1983, when a route for fluoride-ion induced aryne formation was designed.[91] Treatment of 2-trialkylsilylaryl triflates with a fluoride ion source is the most frequently reported method used for aryne generation in the literature today. In **Scheme 1.26**, a fluoride ion displaces a trimethylsilyl group from **38**, forming the benzyne **33** as the triflate leaving group is lost. Common fluoride ion sources are tetra-*n*-butyl-ammonium fluoride (TBAF) in THF or caesium fluoride in acetonitrile. Advantages of this method of aryne formation include the ease of handling of the reagents, commercial availability of precursors, it is very mild in comparison to some of the methods previously outlined above in which harsh conditions are employed and the rate of aryne production using a fluoride source in organic solvents can be controlled by modifying their solubility.



Scheme 1.26

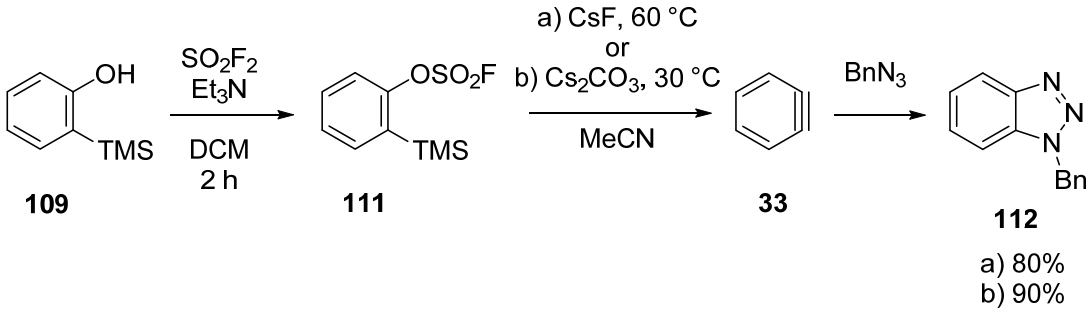
Recent research into altering the triflate group was undertaken to create a range of aryne precursors with excellent results. In 2011, Akai and co-workers described a novel preparation of benzyne **33** from 2-trimethylsilylphenol **109** by a process that uses the nonafluorobutanesulfonyl fluoride (the nonaflyl group is a C4 triflyl homologue) to prepare a 2-trimethylsilylphenylnonaflate derivative **110**.[92] This method is more beneficial than using the triflating reagents (which are more unstable and expensive); and it is also attractive from the viewpoint of atom economy because of its dual reactivity used to nonaflate the hydroxyl group and

subsequently as a fluoride ion carrier for the desilylation and aryne formation. This method does not require the isolation of the unstable 2-trimethylsilylarylnonaflate intermediate **110** (**Scheme 1.27**).[92,93]



Scheme 1.27

Chen and co-workers developed a similar class of aryne precursors where a sulfonyl fluoride group is used as a triflate alternative.[93] Sulfuryl fluoride is a cheap starting material and in the presence of triethylamine, can convert 2-trimethylsilylphenols **109** into aryne precursors **111** that have been successfully applied to a range of aryne-trapping reactions. The authors demonstrated that the arynes could be generated with or without an external fluoride source (**Scheme 1.28**).

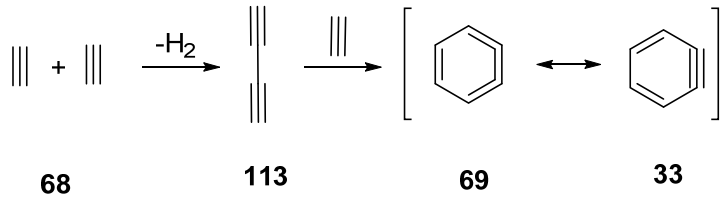


Scheme 1.28

Yoshida and co-workers concurrently reported the preparation of arynes from 2-trimethylsilylaryltriflates by caesium carbonate activation in the presence of a crown ether, negating the requirement for a fluoride source.[88]

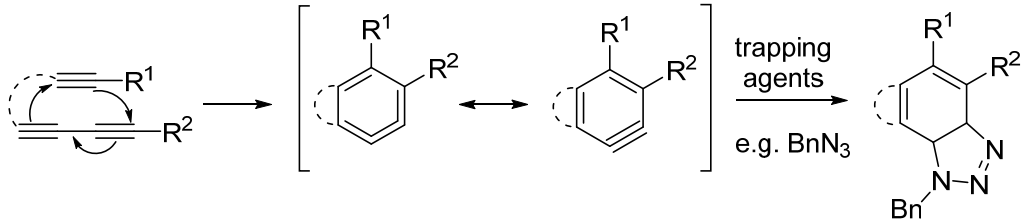
More recently, benzynes have been generated by cycloisomerization of triyne precursors, opening up even more opportunities in aryne chemistry.[94] Benzyne **33** was first suggested as an intermediate in a cycloaddition reaction

when benzene was isolated after the pyrolysis of ethyne **68** in 1967.[95] This was suggested to proceed *via* a cycloaddition reaction of ethyne **68** and butadiyne **113** to form the cumulene representation of benzyne **69** (**Scheme 1.29**).



Scheme 1.29

This route was reported as a viable route to arynes independently by both Miyawaki[96] and Bradley[97] in 1997 but it was not seen as a useful method of aryne generation and remained unexploited until Yun[98] and Hoye[99] demonstrated the broad scope of the reaction in recent years. This transformation was termed a hexadehydro-Diels-Alder (HDDA) by Hoye and involves inter- or intramolecular cycloaddition of triynes (which are easily accessed), mild and versatile reaction conditions and it is an efficient and novel approach to *ortho*-arynes. The most likely mechanism of the simple cycloaddition of 1,3,8-nonatriyne is a [4+2] cycloaddition to form the cumulene aryne, followed by a reduction under pyrolytic conditions, supported by deuterium labelling studies that ruled out a possible Bergman cyclisation pathway.[94,95] The HDDA reaction is a unique approach to *ortho*-arynes and diverse functional groups present in the starting material are preserved in the product, allowing strategic design and synthesis of complex aromatic compounds, further modifiable by the choice of trapping agents (**Scheme 1.30**).[100]



Scheme 1.30

1.2.5 Reactions of arynes

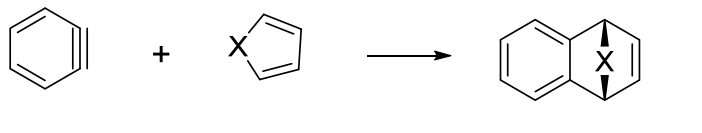
Arynes participate in a wide range of reactions with the three main categories being: 1) Pericyclic reactions of arynes; 2) nucleophilic additions to arynes and 3) transition metal-catalysed reactions of arynes. Examples from each category are discussed below.

1.2.5.1 Pericyclic reactions of arynes

Arynes readily partake in pericyclic reactions due to their electrophilic character, as long as they are generated in the absence of competing nucleophilic reactants. Some reactions of this type are described herein.

Diels-Alder cycloaddition reaction

Since Wittig reported trapping benzyne **33** with furan in 1955,[45] the Diels Alder reaction has become one of the most important reactions of arynes and is used both as an aryne detection method and in synthetic applications.[50] Because of the highly electrophilic character of arynes, they readily undergo reactions with a wide range of diene partners such as cyclic dienes and heterodienes (**Scheme 1.31**). Reactions with functionalised acyclic dienes are less common due to competing [2+2] cycloaddition and ene reaction pathways. Aromatic five-membered heterocycles **114** react efficiently with arynes **33** to furnish the [4+2] cycloadducts **115**. The cycloadducts of furan and its derivatives are useful intermediates in the synthesis of naphthalenes as the endoxide bridge readily undergoes acid cleavage.[50]



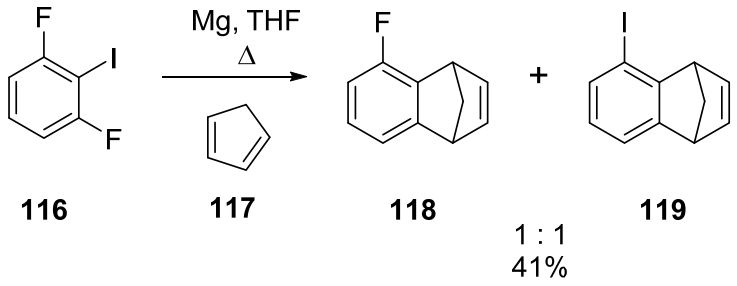
33 **114**

67 X = O
115 X = CH_2, NR_2

Scheme 1.31

The Diels-Alder reaction of arynes and cyclopentadiene **117**, remains the only direct approach to 5-haloderivatives of 1,4-dihydro-1,4-methano-naphthalenes. The original approach used to access these important pharmaceutical intermediates involved the zwitterion of diazotised anthranilic

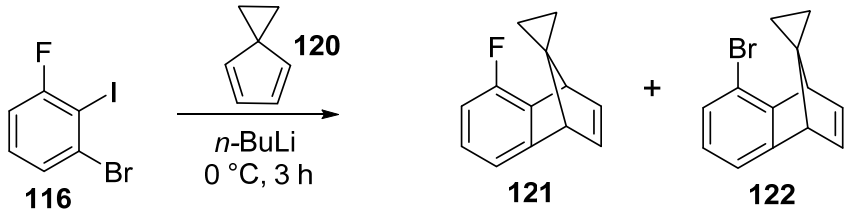
acid derived benzyne generation route over three steps in poor yield.[101] In search of a more controlled, scalable and direct synthesis towards these compounds, Coe and co-workers used trihalobenzenes **116** under halogen-magnesium conditions as aryne precursors with cyclopentadiene **117** derivatives and observed mixed fluoride **118** and iodide **119** products (**Scheme 1.32**).[102] The formation of the iodide product **119** was postulated to occur by exchange of iodide from the fluorobenzyne intermediate.



Scheme 1.32

Coe also revealed that when *n*-BuLi is used instead of magnesium and by altering the reaction solvent, they were able to control product formation (**Table 1.1**). The authors concluded that solvent association with intermediates and the departing lithium halide affected the reaction course. This cycloaddition reaction methodology allowed for a straightforward preparation of 1,4-methano-1,4-dihydronaphthalenes **121** and **122** from trihalobenzene **116** and cyclopentadiene derivative **120**.

Table 1.1

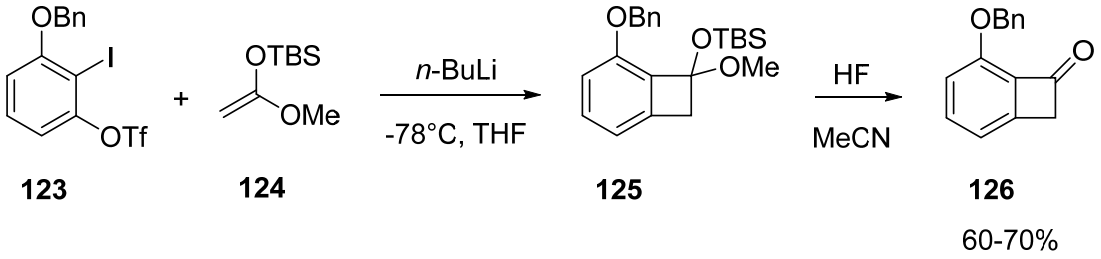


solvent	**121:122**	yield (%)
THF	> 97 : 3	75
Pentane	> 5 : 95	75

[2+2] Cycloaddition reactions

The [2+2] cycloadditions of arynes with alkenes are seen as an efficient route to benzocyclobutenes, a unique class of reactive molecules.[103] The thermodynamic stability of the aromatic system and the kinetic reactivity of the strained cyclobutene ring give rise to these polycyclic compounds having unique reactivity, such as isomerisation to *ortho*-xylylenes, which can be used as building blocks in the synthesis of natural products, new polymers and advanced materials.[104]

In a synthesis described by Tsujiyama and co-workers, treatment of *ortho*-iodoaryl triflate **123** with *n*-BuLi at -78 ºC rapidly generates an aryne which undergoes a [2+2]-cycloaddition with ketene silyl acetal **124** yielding the corresponding cycloadduct **125**.[86] Desilylation with hydrofluoric acid affords benzocyclobutenone **126** in high yields (**Scheme 1.33**). The methodology has allowed the development of an impressive approach towards polycyclic compound preparation.



123 **124** **125** **126**

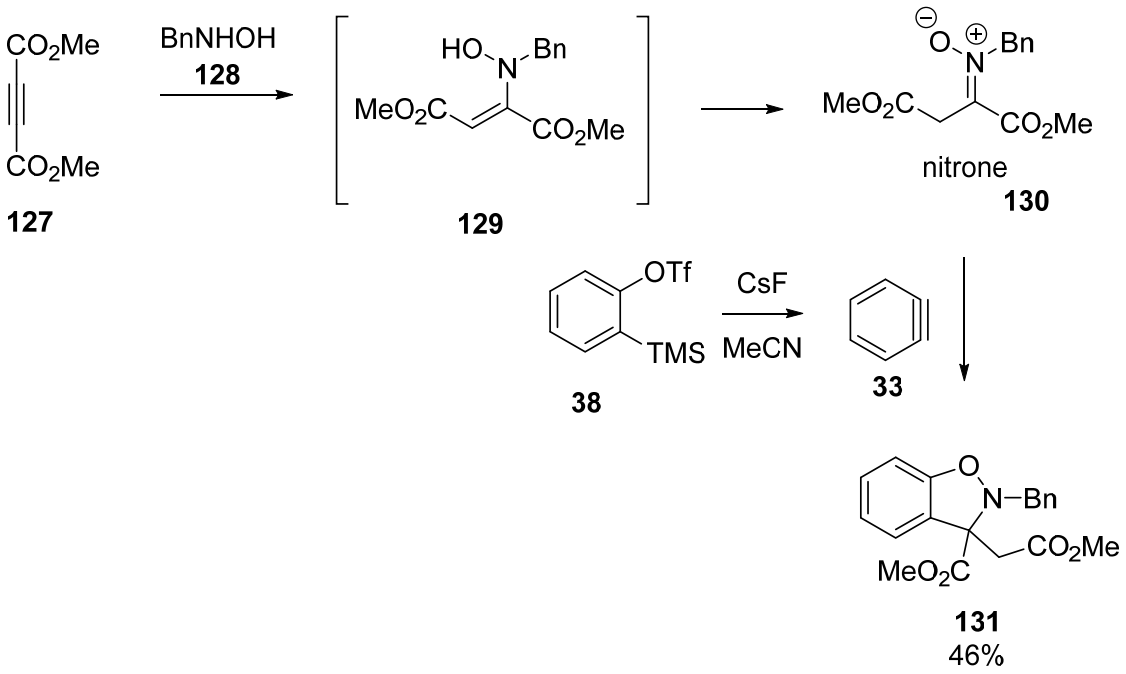
60-70%

Scheme 1.33

[3+2] Cycloaddition reactions

A range of 1,3-dipole compounds undergo cycloadditions with arynes. Diazo, azide, nitrone, sydnone and azomethine imine are among the most intensely investigated substrates.[34,35,59,87] The azide dipole in particular is used in trapping reactions of arynes, as well as a route towards benzotriazole synthesis.[34,35,59,87,105-108]

Li and co-workers developed a one-pot procedure for the synthesis of functionalized dihydrobenzisoxazoles **131** from arynes and nitrones without the need to isolate the nitrone dipole.[106] Using substituted hydroxylamines **128** and alkynyldicarboxylates **127**, a nitrone **130** is generated and undergoes a [3+2]-cycloaddition with the benzyne **33** *via* generation of both reactive intermediates *in situ* from **129** and **38** respectively (**Scheme 1.34**).

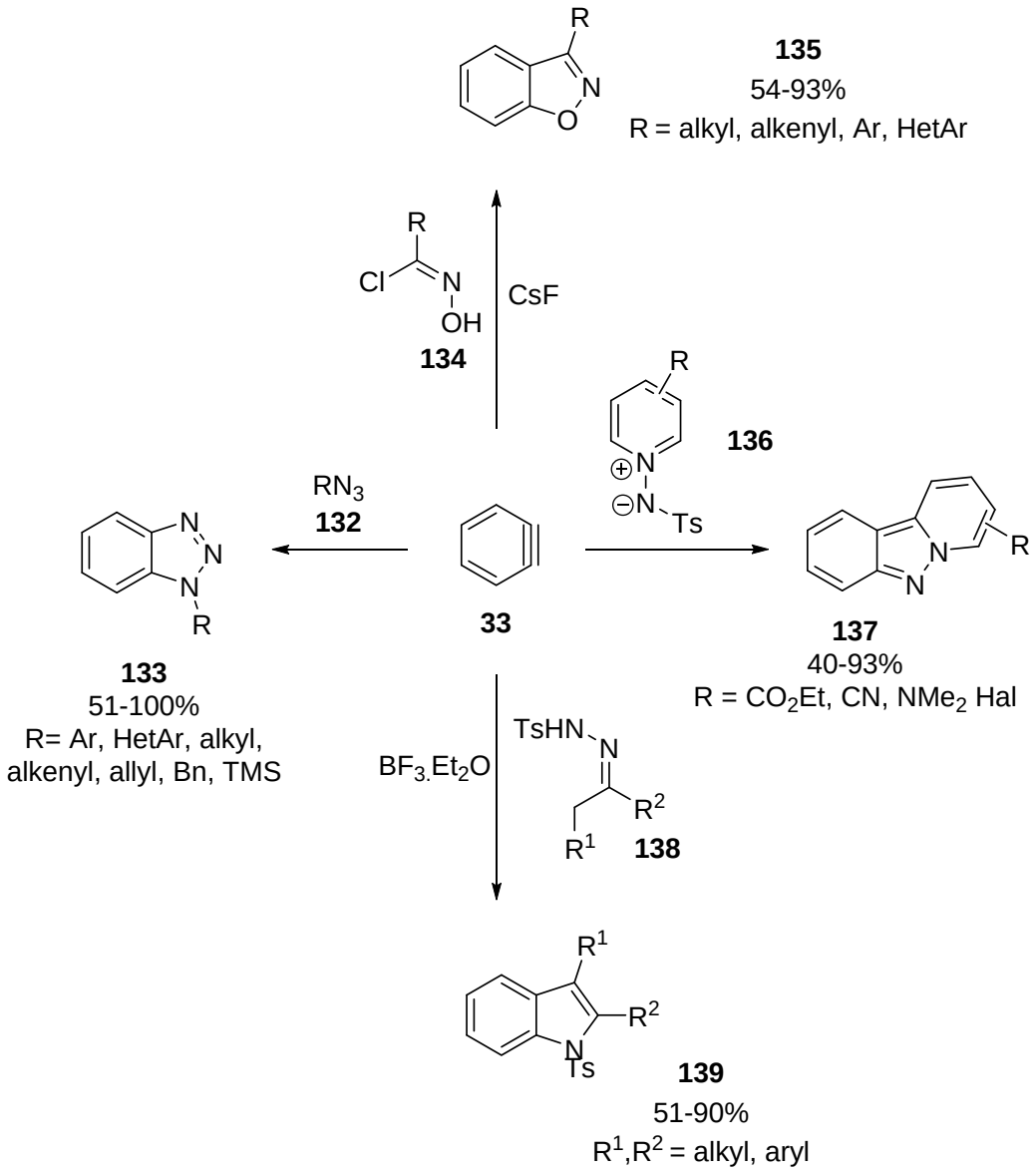


Scheme 1.34

Larock and co-workers have reported frequently on dipolar cycloaddition reactions involving arynes. In 2012, the group published a review on the use of arynes in heterocycle synthesis that included considerable work carried out in their laboratories over the last decade.[58] Some examples are outlined in **Scheme 1.35**.

The reaction of benzyne **33** and azides **132** give rise to benzotriazoles **133** in good to excellent yields.[109] Benzisoxalzoles **135** are prepared from reaction with nitrile oxides, generated from dehydrohalogenation of chlorooximes **134** by caesium fluoride.[110] The reaction with tosylate-stabilised pyridinium imides **136** proceeds to form pyrido[1,2-b]indazoles **137** in good yields and tolerates a variety of functional groups.[111] Indoles **139** are prepared in a two-step process whereby

N-tosylhydrazones **138** are arylated by an aryne, followed by acid-catalysed Fischer indole synthesis.[60]



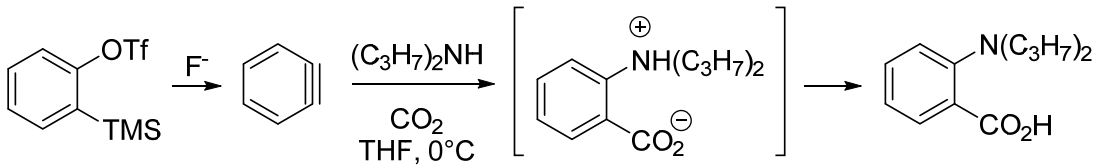
Scheme 1.35

1.2.5.2 Nucleophilic additions to arynes

Arynes are strong electrophiles due to their low-lying unoccupied molecular orbitals (LUMO) and even neutral nucleophiles readily react with arynes whereas no reaction would occur with alkynes. Nucleophilic addition leads to formation of an aryl carbocation or zwitterion which can then be trapped with an electrophile or proton. Herein, an example of each, neutral and anionic nucleophilic additions to arynes, will be discussed.

Neutral nucleophiles

The reaction of arynes with amines provides a convenient route to alkylated anilines and intramolecular nucleophilic addition of amines to arynes can be used to access alkaloid derivatives. Rather than the formation of an aniline derivative, Yoshida and co-workers reported the preparation of anthranilic acid derivatives **141** of great synthetic value *via* incorporation of a dialkylamine and carbon dioxide into an aryne to form intermediate **140** in a three-component coupling reaction.[89] These reactions occurred with nucleophilic attack of dipropylamine on benzyne **33** generated from **38** with a fluoride source in THF under a carbon dioxide atmosphere at 0 ºC (**Scheme 1.36**).



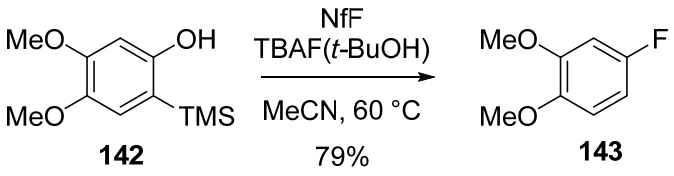
38 **33** **140** **141**

74%

Scheme 1.36

Anionic nucleophiles

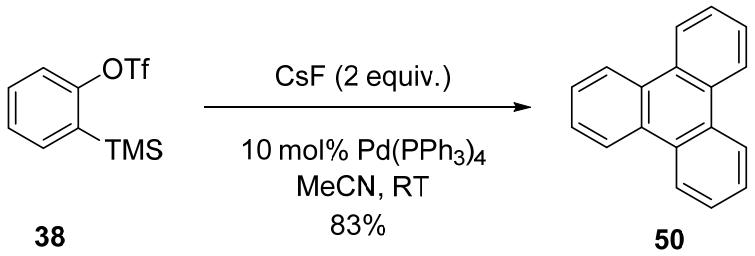
The nucleophilic addition of fluoride ions to substituted benzynes under mild conditions is an important approach to the synthesis of biologically active fluorinated aromatic scaffolds. In a recent publication by Ikawa and co-workers, the authors report that the nucleophilic fluorination of benzynes occurs in one-pot by the successive nonaflation of 2-trialkylsilylphenol **142**, benzyne generation and subsequent nucleophilic fluorination to form **143** (**Scheme 1.37**).[112]



Scheme 1.37

1.2.5.3 Transition metal-catalysed reactions of arynes

In 1998, Guitián and co-workers reported that palladium(0) complexes can catalyse the cyclotrimerization of benzyne, generated from **38**, to provide triphenylene **50** (**Scheme 1.38**).[113]



Scheme 1.38

Since then, the scope of the reaction has expanded to polycyclic aryne compounds in the formation of large polycyclic aromatic hydrocarbons in an effort to prepare and study applications of graphene-like materials like starphenes **144** and cloverphenes **145** (**Figure 1.9**).[114]

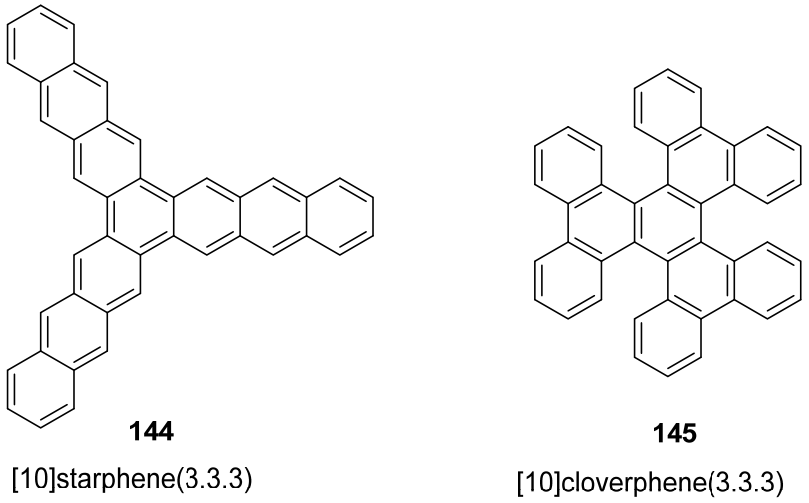
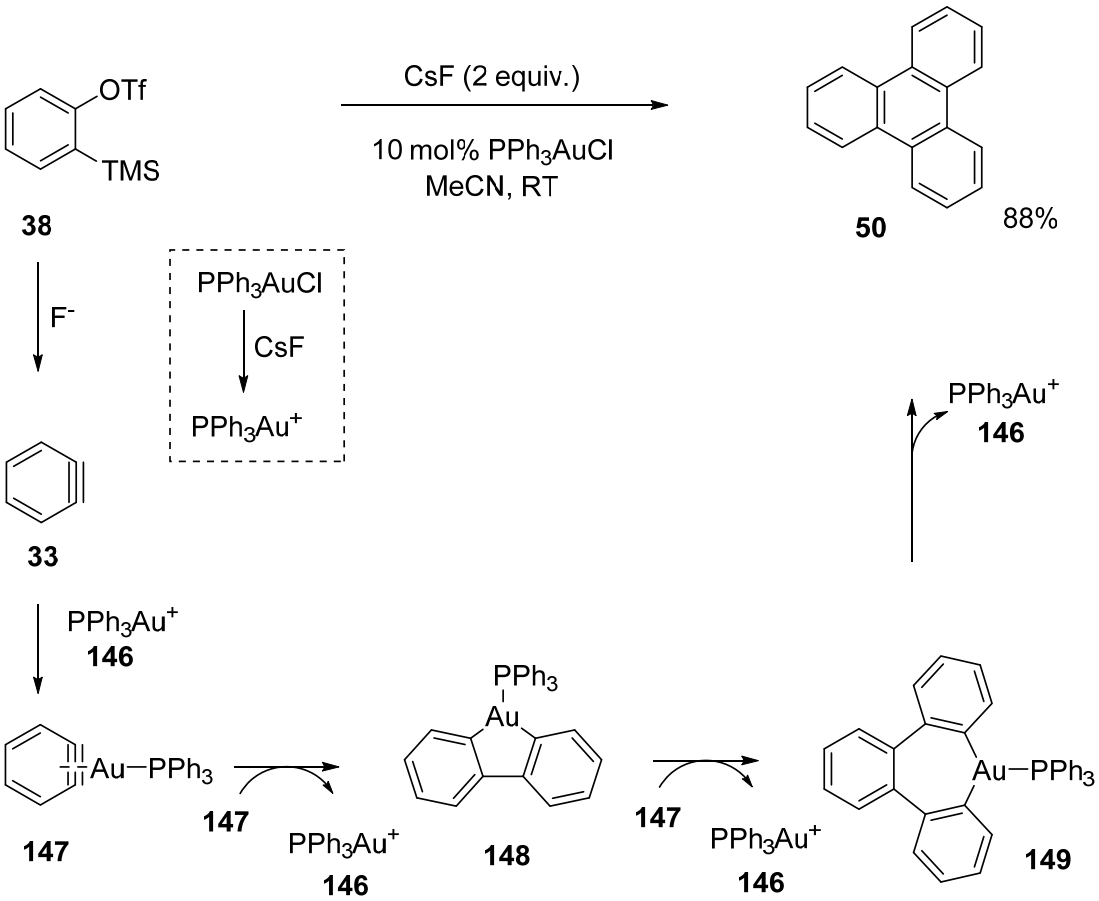


Figure 1.9 *Benzyne-derived polycyclic aromatic hydrocarbons*

Chen and co-workers reported a mild and general approach to triphenylene derivatives **50** recently under mild conditions that were not air or moisture sensitive.[115] The desired products can be prepared in good yields using PPh_3AuCl as an efficient catalyst for the cyclotrimerization of arynes. The authors proposed a plausible mechanism which is similar to Pd(0)-catalysed cyclotrimerisation. Benzyne **33** formed from **38** interacts with PPh_3Au^+ **146**, which is postulated to be formed in the presence of caesium fluoride, to form complex **147**. Cyclometallation with another molecule of **147** provides intermediate **148** followed by another benzyne insertion to produce **149** which eliminates PPh_3Au^+ **146** to provide the triphenylene product **50** (**Scheme 1.39**).[115]

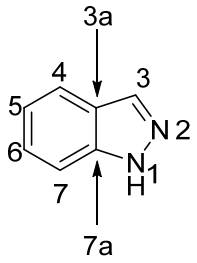


Scheme 1.39

1.3 Indazoles

1.3.1 Characterisation and background

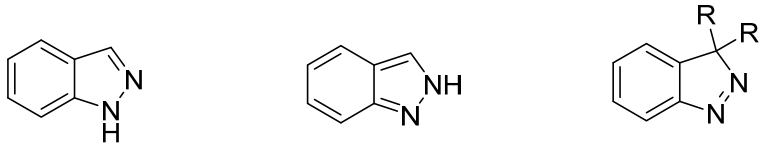
Indazole is a bicyclic ten π-electron heteroaromatic compound containing two adjacent nitrogen atoms. As a member of the azole family, it can be thought of as a pyrazole and benzene ring fused together. Alternative names such as benzo[*c*]pyrazole, 1,2-benzodiazole and isoindazone are rarely used. The "1H" indicates the nitrogen with the hydrogen and the structure is numbered around the rings excluding the bridging carbons (**Figure 1.10**).



150

Figure 1.10 *1H-Indazole numbering convention*

The 1*H*-indazole **150** has two other potential tautomers, however, these only exist in substituted derivatives; the prototropic annular quinonoid 2*H*-indazole **151** and the benzenoid 3*H*-indazole **152** (**Figure 1.11**). The 1*H*-indazole **150** is 2.3 kcal.mol^{-1} more stable than the 2*H*-indazole **151** and is the predominant form in both solid and gaseous states. 3*H*-Indazoles **152** lack heteroaromatic character and few examples are known.[116-120]

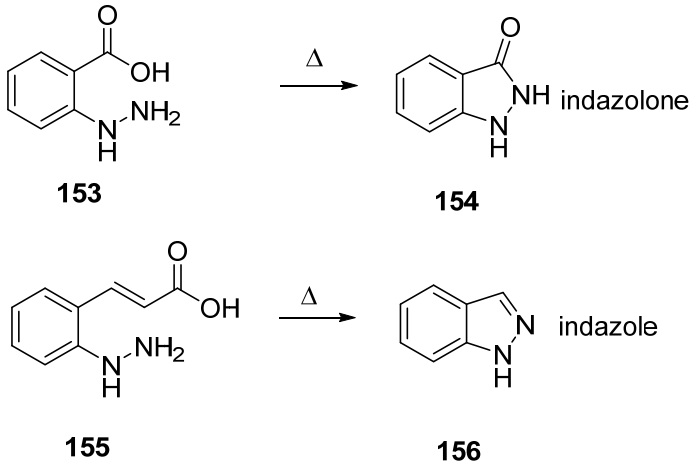


1*H*-indazole **150** | 2*H*-indazole **151** | 3*H*-indazole **152**

Figure 1.11 *Indazole tautomer forms*

The first reported indazole preparations were in the 1880s by Fischer and Kuzel.[121] On replicating the conditions to obtain indazolone **154** from 2-hydrazine benzoic acid **153**, heating 2-hydrazinocinnamic acid **155** provided low yields of

indazole **156** among other products (**Scheme 1.40**). Von Auwers carried out investigations on the indazole nucleus in the 1920s which provided the initial structural and reactivity data for these compounds.[122,123]



Scheme 1.40

Considerable interest has been directed towards indazole derivatives in the last few decades, due to the broad variety of biological activities associated with them, which has led to the development of a number of new syntheses.[124,125] In comparison to indole and benzimidazole derivatives, however, indazole heterocycles remain poorly studied.

1.3.2 Naturally occuring indazole compounds

Natural products containing the indazole moiety are rare with only eight examples currently known, four of which were isolated in the past two years (**Figure 1.12**): nigellicine **157**,[126] nigellidine **158**[127,128] and derivatives **159** and **160** from *Nigella sativa* (found in black cumin); nigeglanine **161**,[126,128] nigeglaquine **162**, nigeglipine **163** and methyl-derivative **164** from *Nigella glandulifera*.[126,128] The zwitterionic heterocyclic system represents an interesting class of pseudo-cross-conjugated mesomeric betaine molecules.

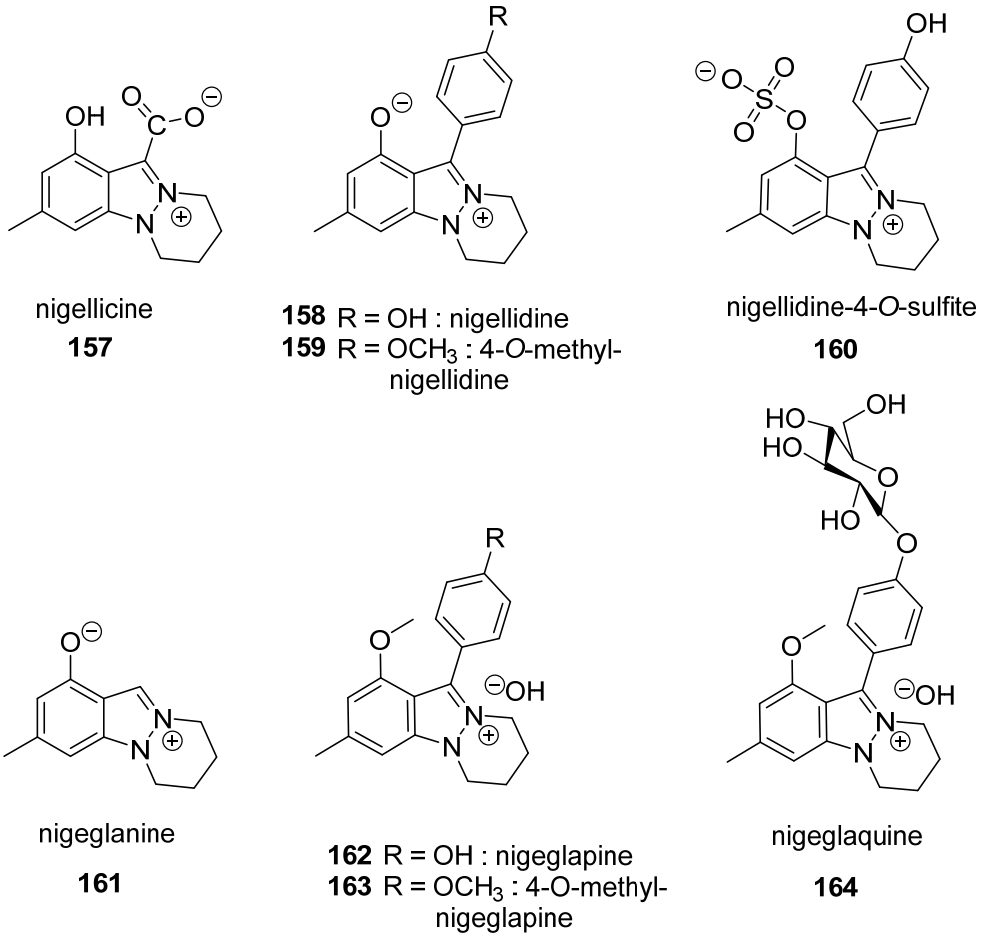


Figure 1.12 *Indazole natural products*

Nigellidine derivatives **158** and **159**, and nigeglanine **161** can also be represented by neutral canonical structures, setting them apart from classical mesomeric betaines (**Figure 1.13**).[120] Glycosylated and sulfated alkaloids are very uncommon in natural products. The plants from which the indazoles are isolated have been used in Middle-Eastern traditional medicine for centuries and some of the isolated derivatives are now undergoing biological testing.[129]

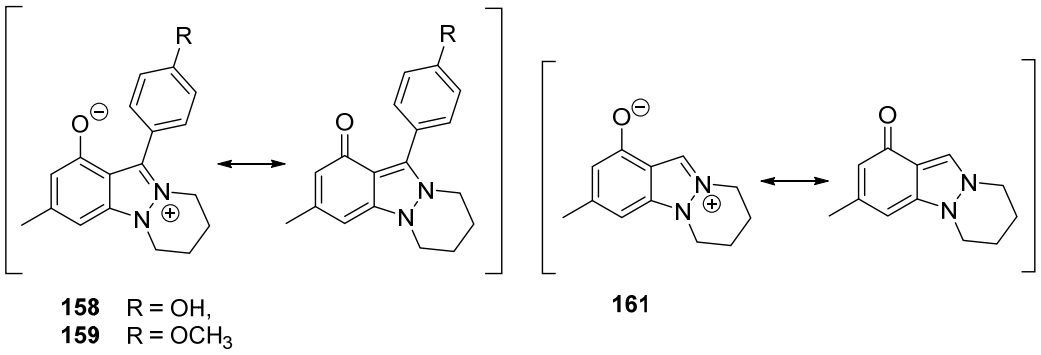


Figure 1.13 *Resonance forms with neutral structure*

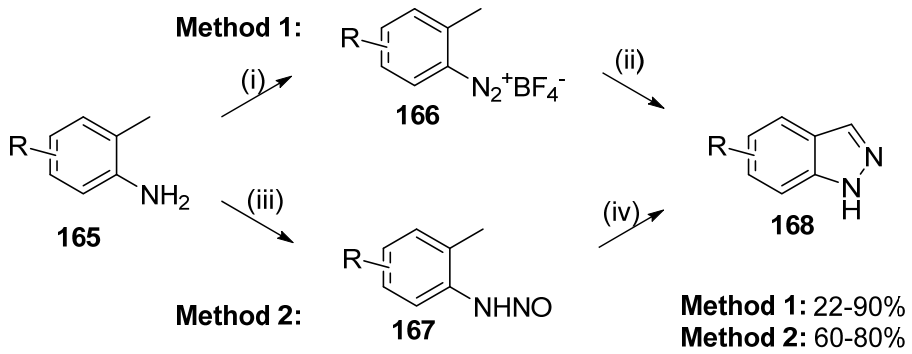
1.3.3 Synthesis of 1H-indazoles

Synthetic routes towards the synthesis of the indazole nucleus are desirable as they have been shown to be an effective pharmacophore in medicinal chemistry. There are two principal synthetically useful routes whereby indazoles are accessed. The first route involves ring-closure reactions of a range of possible indazole fragments.[125] Some of the more common routes are discussed below. The second route is by ring transformation, forming indazoles by rearrangement, insertion or extrusion reactions.[125] Indazoles with substituents that are difficult to obtain or could not be obtained by ring-closure routes can be accessed *via* this route. Usually, harsh reaction conditions are involved in these syntheses with the use of strong acids or high temperatures.[125]

1.3.3.1 Ring closure reactions

One of the the most common approaches used today for the synthesis of indazoles involves the diazotisation of 2-aminotoluenes followed by spontaneous cyclisation of an *N*-nitroso intermediate.[125] These reactions are often limited to indazoles bearing an electron-withdrawing substitutent. The Jacobson modification introduces an acetylation step that provides 1-acetyl indazoles which can be deacetylated to form 1*H*-indazoles **168** avoiding the necessity of an electron-withdrawing group.[130]

Schumann and co-workers reported using the Jacobson ring closure reaction with a range of substituted 2-aminotoluenes **165**.[131] The authors found that using a phase transfer catalyst to form a 2-methylbenzendiazonium tetrafluoroborate salt **166** (Method 1) operated best for most substituents but cyclisation of *N*-nitroso derivatives **167** (Method 2) was found to be more preferable for 5- and 7-methoxy substituted indazoles (**Scheme 1.41**).



Method 1: R = 5-Br, 5-F, 6-Cl, 6-Me, 6-OMe

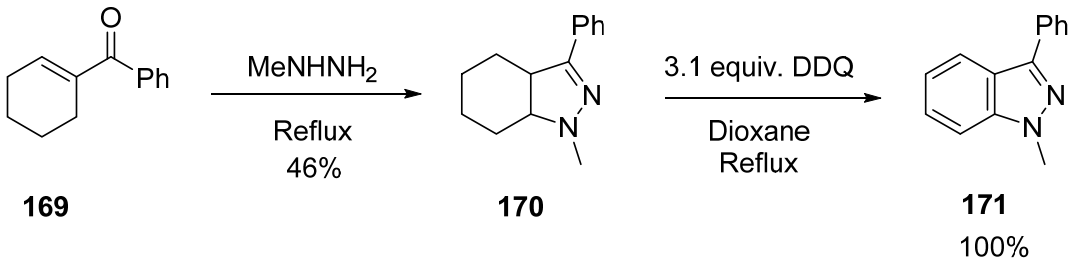
Method 2: R = 5-OMe, 7-OMe

Reagents:
(i)(1) HBF_4 (2) $NaNO_2$, 0°C; (ii) AcOK, 18-c-6, RT; (iii) AcOH, conc. HCl, $NaNO_2$; (iv) C_6H_6, Δ

Scheme 1.41

Another attractive route to indazoles is from the reaction of hydrazines with 1,2-disubstituted arenes.[125] One substituent is often a carbonyl group and the other is usually a good leaving group. The intermediate benzoyl hydrazine or arylhydrazine cyclises to form the indazole.

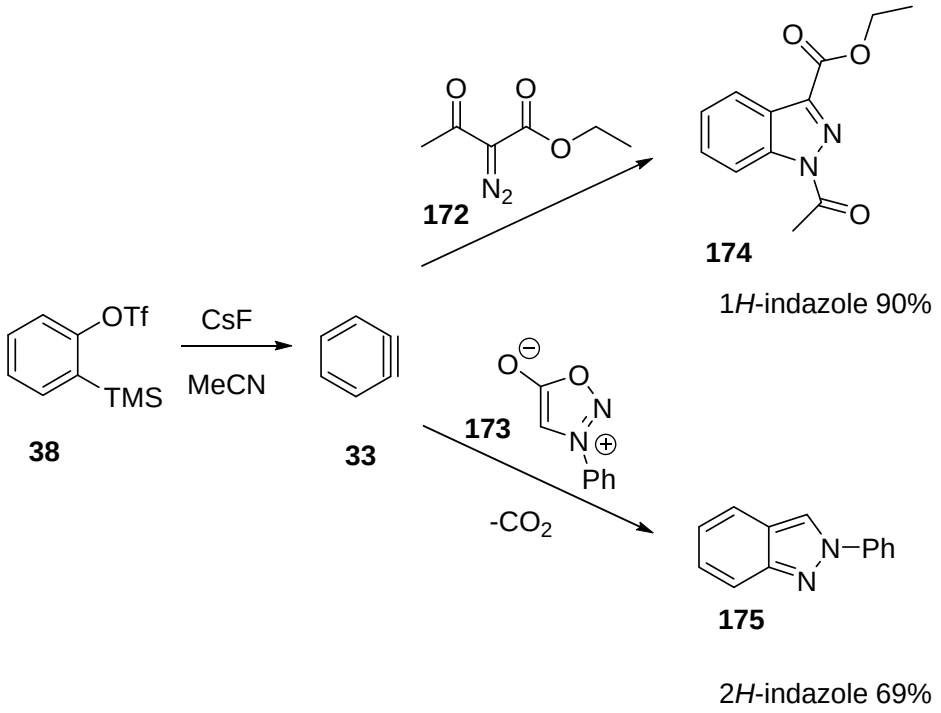
A modification involving cyclohexanones and hydrazines to form tetrahydroindazoles is also available.[124] Nakhai and Bergman have recently reported a route towards tetrahydroindazoles **170** from α-β-unsaturated ketone **169** and methylhydrazine which could be aromatised using DDQ in excellent yields to form 1*H*-indazoles **171** (**Scheme 1.42**).[132]



Scheme 1.42

An interesting approach to 1*H*-indazoles is the [3+2]-cycloaddition reaction of arynes and diazo 1,3-dipole derivatives. Notably, the Larock research group have developed efficient methods for the synthesis of both 1*H*- and 2*H*-indazole compounds using diazo and sydnone 1,3-dipoles, respectively (**Scheme 1.43**). The initial 3,3-disubstituted cycloadduct from the reaction with arynes **33**

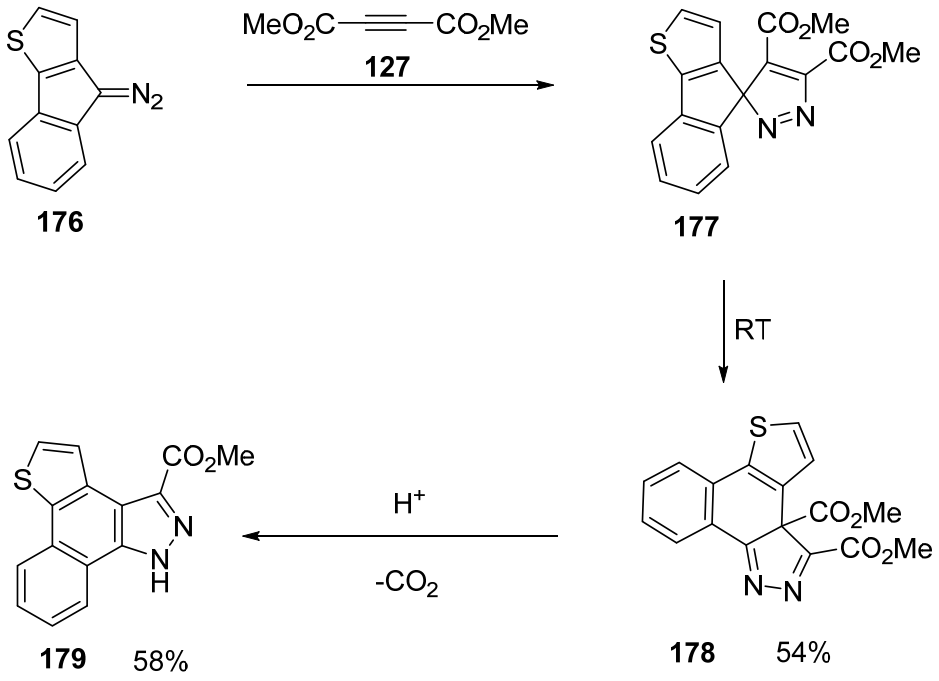
generated from 2-trimethylsilylaryltriflates **38** and the diazo compound **172** undergoes acyl migration to form 1*H*-indazole product **174**.[35] The initial cycloadduct from reaction with *N*-phenyl-sydnone **173** readily undergoes spontaneous extrusion of a molecule of carbon dioxide in a retro-[4 + 2] fashion to afford 2*H*-indazole **175**.[59]



Scheme 1.43

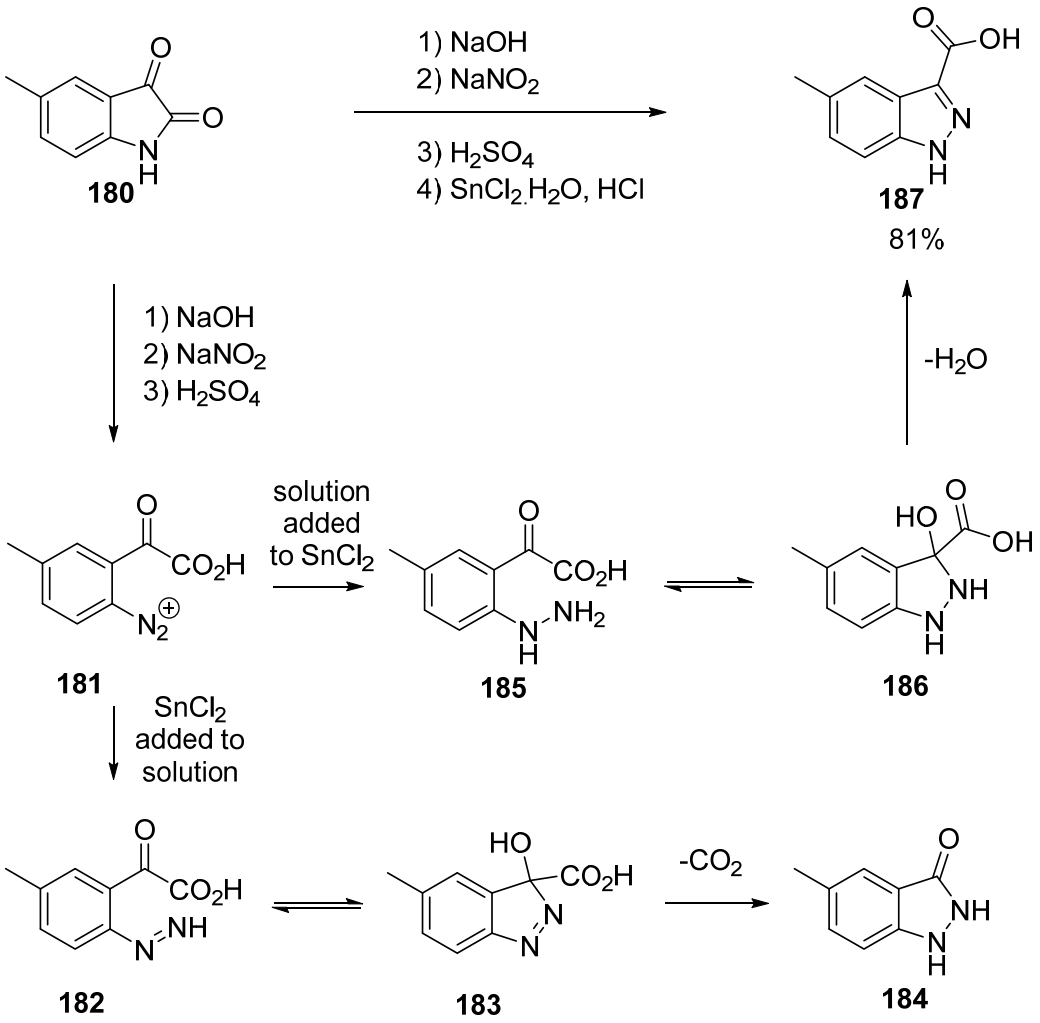
1.3.3.2 Ring-transformation

The van Alphen-Hüttel rearrangement is the expansion of diazocyclopentadienes on addition of alkynes with electron-withdrawing groups.[133] Mataka *et al*. investigated the reaction of diazoindenothiophenes **176** and dimethyl acetylenedicaboxylate **127**. The initial unstable spiro compound **177** formed readily rearranges to the isomer **178** at room temperature and acid hydrolysis affords the 1*H*-indazole product **179** in 58% yield (**Scheme 1.44**).[134]



Scheme 1.44

1*H*-Indazoles can be prepared from isatins (1*H*-indole-2,3-diones) **180** by the Schad 3-carboxyindazole synthesis, a commonly used synthetic route to indazoles in industrial preparations.[135] Johnson and Rodgers reported an approach to principal intermediates in HIV protease inhibitor synthesis using this methodology with a slight modification (**Scheme 1.45**).[136] Alkaline ring-opening of **180** followed by diazotisation forms **181**. Reduction by addition of the solution to tin(II) chloride provides **185** which is cyclised to **186** and subsequent dehydration provides the desired product **187** in reproducible and high yields. It was necessary to invert the key reduction step by adding the diazonium solution slowly to the tin chloride mixture to suppress the formation of the by-product **184** formed by cyclisation of the diazine **182** to form **183** with subsequent decarboxylation.


1) NaOH
2) NaNO2
3) H2SO4
4) SnCl2.H2O, HCl
180
187
81%
1) NaOH
2) NaNO2
3) H2SO4
-H2O
solution added to SnCl2
181
185
186
SnCl2 added to solution
182
183
184
-CO2

Scheme 1.45

1.3.4 Biological importance of indazole compounds

Interest in indazole compounds has greatly increased in recent years due to a number of derivatives linked to a broad variety of activities. As well as pharmaceutical applications, the heterocyclic moiety is present in herbicides,[137] dyes[138] and sweeteners.[139] In a 2012 review, Thangadurai *et al.*[140] documented the range of pharmacological activities of indazoles which include anti-inflammatory, anti-microbial, anti-HIV and anti-cancer effects.

Examples of anti-inflammatory drug compounds containing the indazole-scaffold currently on the market include bendazac **188** and benzydamine **189** (**Figure 1.14**).

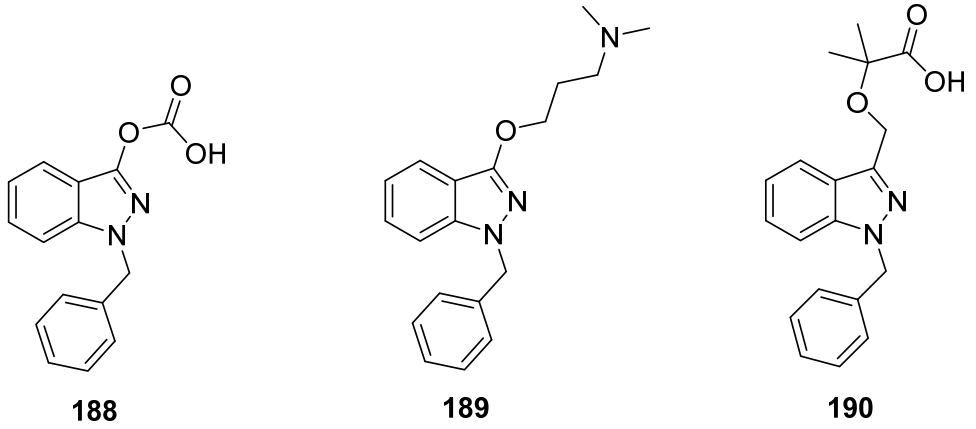


Figure 1.14 *Indazoles with anti-inflammatory properties*

Bendazac **188** is an oxyacetic acid and is marketed as its lysine salt for improved oral absorption.[141] It is an NSAID used topically in the treatment of joint and muscular pain and has also shown a beneficial effect in managing cataracts. In Ireland, benzydamine **189** is marketed as Difflam™ in its hydrochloride salt form. It is also an NSAID, acting *via* inhibition of the COX enzymes.[142] It possesses local anaesthetic and analgesic properties and is mostly used in treatment of mouth and throat inflammation.[143] Bindarit **190** has been investigated in multiple animal models of human disease and in human clinical trials to examine its potential as a therapeutic agent for a variety of inflammatory conditions such as arthritis, pancreatitis and diabetic nephropathy.[144-146] Encouraging results in all cases strongly support the development of Bindarit **190** as a potential therapeutically available agent.

Some indazole derivatives currently used therapeutically in cancer chemotherapy are shown in **Figure 1.15**. Indazolium *trans*-[tetrachlorobis-(1*H*-indazole)] ruthenate (III) **191** has a selective effect on solid metastasising tumours of the lung and is only the second ruthenium-based anti-cancer drug to reach clinical trial stages. The ruthenium species is thought to bind with transferrin and enter the cell using the transferrin receptor, targeting tumour cells which overexpress the transferrin receptor. It is reduced in the cell to the activated ruthenium (II) species, where it binds to DNA and induces apoptosis at a non-toxic level. Phase 1 clinical trials resulted in no serious side-effects experienced with disease stabilisation in five out of six cases and phase 2 clinical trials are in progress.[147]

Lonidamine **192** is an anti-cancer drug in its own right that impressively also increases the effectiveness of several experimental multiple chemotherapy protocols without increasing toxicity. It has an interesting mechanism of action whereby it interferes with energy metabolism of tumour cells.[148-150]

Pazopanib **193** is a tyrosine kinase inhibitor that blocks tumour growth and inhibits angiogenesis. It is approved for renal cancer treatment and has also demonstrated efficacy in patients with ovarian and non-small cell lung cancer.[151,152] Granisetron **194** is an anti-emetic drug used to treat vomiting and nausea following chemotherapy.[153]

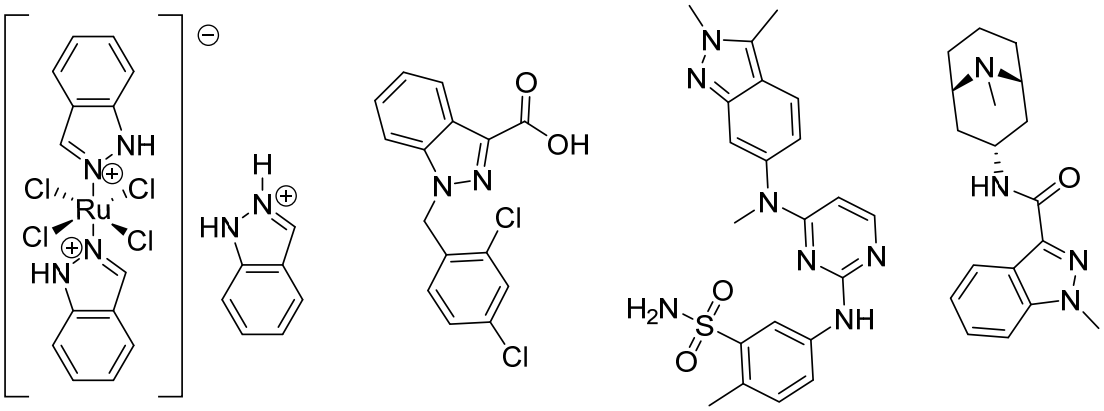


Figure 1.15 *Indazole-containing drugs used in cancer chemotherapy*

Gamendazole **195** and Adjudin **197** (**Figure 1.16**) are analogues of Lonidamine **192** that have shown potential to be developed as a non-hormonal male oral contraceptives due to potent anti-spermatogenic activity, with little associated toxicity and fertility recovery following withdrawal of the drug.[154-157] H2-Gamendazole **196** (**Figure 1.16**) is a derivative identified as being closest to human clinical trials, displaying 100% oral bioavailability, 100% infertility followed by 100% recovery of fertility in rats and similar results in non-human primate studies.[158-160]

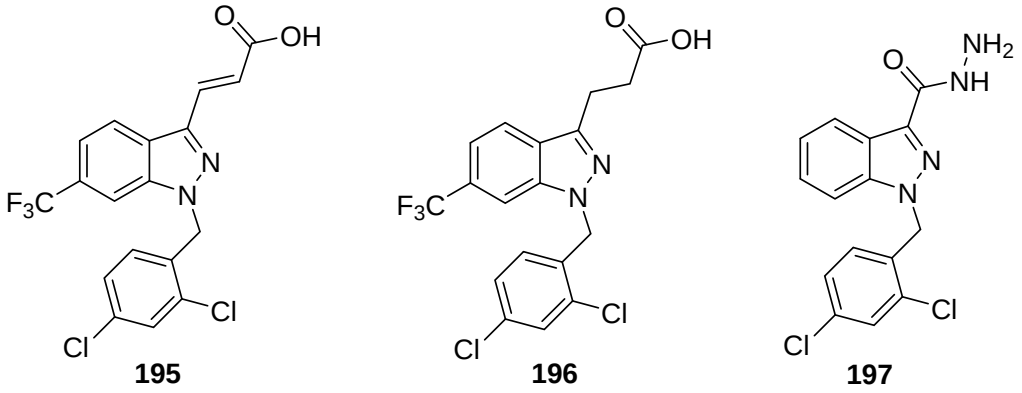
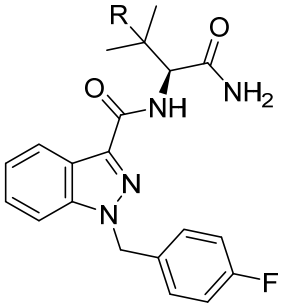


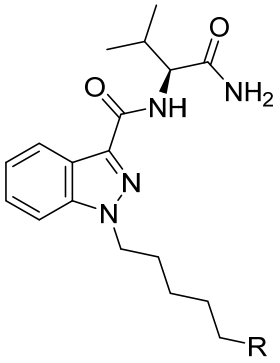
Figure 1.16 *Gamendazole, H2-Gamendazole and Adjudin*

A number of synthetic cannabinoid (SC) receptor agonists (a rapidly growing class of recreational psychoactive designer drugs) contain the indazole scaffold. These illicit drugs are being detected and identified increasingly by both forensic researchers and law enforcement.[161,162] Most of these novel indazoles had no precedent in scientific literature before their identification as designer drugs, although AB- and ADB-FUBINACA **198** and **199**, and 5F-AB- and AB-PINACA **200** and **201** were originally developed by Pfizer as analgesic agents, acting as potent agonists for the CB_1 and CB_2 receptors.[163] 5F-CUMYL-PINACA **202** is a derivative of 5F-AB-PINACA where the 1-amino-3-methyl-1-oxobutanyl group is replaced with a cumyl group. No official studies have been conducted on the physiological or toxicological effects of SCs in humans but reports have been published describing the effects seen in patients seeking medical care after taking SCs where the adverse reactions are often more severe in comparison to cannabis (**Figure 1.17**).[164]



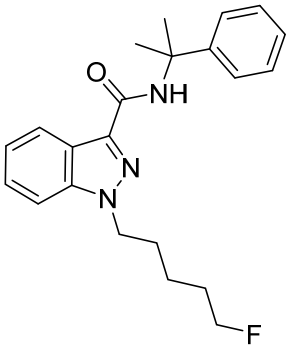
R = H AB-FUBINACA **198**

R = CH_3 ADB-FUBINACA **199**



R = F 5F-AB-PINACA **200**

R = H AB-PINACA **201**



5F-CUMYL-PINACA **202**

Figure 1.17 *Indazole-containing synthethic cannabinoids*

1.4 Summary

Some of the interesting reactivity of diazo and aryne derivatives has been described herein. Well-established synthetic routes to diazo compounds allows the facile preparation of a versatile range of diazo compounds which can be employed as 1,3-dipoles in cycloaddition reactions. Methods for the mild generation of aryne intermediates, as well as the commercial availability of inexpensive precursors, has placed arynes into an important role in organic synthesis.

An appealing synthetic application that utilises both reactive intermediates is in the formation of novel indazole compounds. Methods that construct the indazole nucleus in a mild manner compared to current common procedures are extremely desirable. Although indazole natural products are rare they have a disproportionate number of biologically active compounds exhibiting ability across many pharmaceutical applications without the expected associated toxicity. Of particular note is the large number of biologically active indazole compounds observed that contain benzyl groups and/or fluorine substituents.

The utilisation and modification of established procedures for [3+2]-cycloaddition reactions of aryne intermediates, generated from easily accessible precursors, and a range of diazocarbonyl 1,3-dipole analogues proved very appealing in the synthesis of novel indazole derivatives. Evaluation of novel indazole compounds for biological activity with well-known research agencies is an attractive route to pursue considering the potential of the indazole scaffold as a therapeutic agent.

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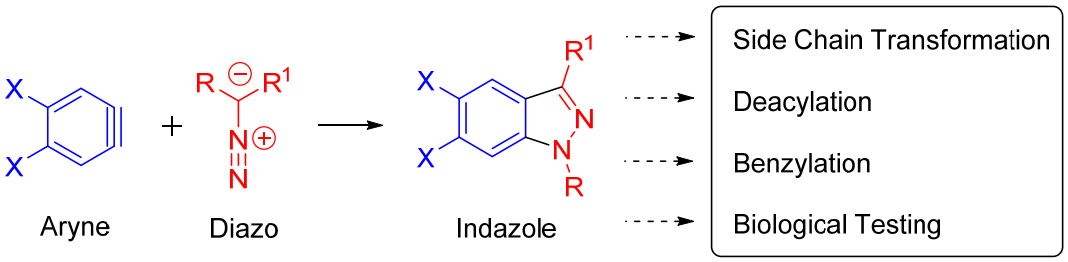
2.1 Introduction

2.1.1 Aims and Objectives

A number of projects within the research group are based around chemical transformations of diazo dicarbonyl derivatives, usually initiated by loss of nitrogen through transition metal catalysis, photolysis or heat, to generate a highly reactive carbene-type intermediate that allows them to participate in a variety of reaction pathways. This project is designed and aimed towards incorporating the diazo functionality into indazole products by using the diazo group as a 1,3-dipole and aryne dipolarophiles as reactive intermediates, *via* their subsequent cycloaddition reactions (**Scheme 2.1**).



Scheme 2.1

A search of the literature revealed that reactions between diazo compounds and arynes had been reported in 1961, but that process employed an explosive benzyne precursor, benzenediazonium 2-carboxylate,[1] and the only example reported did not quote a yield.[2] Research into this area has developed due to the commercial availability of aryne precursors, and in recent years more examples of 1,3-dipolar cycloaddition reactions of diazo compounds and arynes have been reported.[2-5] The initial aim of this work was to utilise the established method published by Jin and Yamamoto[4] and Larock,[5] using 2-trimethylsilylphenyltriflate derivatives and caesium fluoride to generate arynes *in situ*, which would undergo cycloaddition reactions as dipolarophiles with diazo dicarbonyl derivatives (as the 1,3-dipole) to form indazole intermediates. Using this methodology, it was envisioned that a range of novel indazoles could be synthesised and easily diversified by altering the diazo or aryne starting materials.

Another aim of the project was to establish a general, mild method for *N*-deacylation of *N*-acyl indazoles. This could allow the synthesis of a number of novel indazoles with the potential for derivatisation at the *N*-1 position. One of the main derivatisation reactions of interest was benzylation of the 1*H*-indazoles which would give rise to the formation of both *N*-1- and *N*-2-benzylated isomers.

Initial investigations into side chain transformations such as epoxidation, oxidative cleavage and reductive amination were to be conducted on the functionalisable, alkene-containing ester group of some indazole derivatives.

Due to the presence of the indazole core structure in many pharmaceutical compounds, novel indazole compounds would be sent to the National Cancer Institute (NCI) and the Community for Open Antimicrobial Drug Discovery (CO-ADD) for biological evaluation.

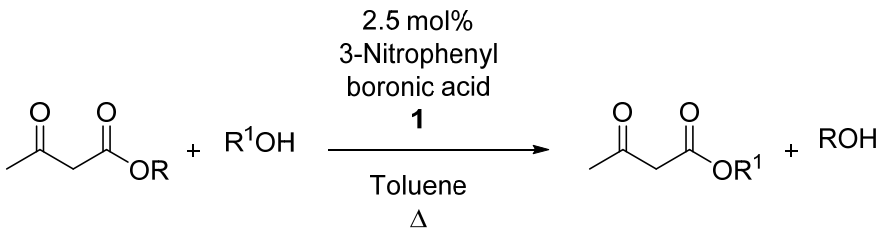
2.2 Synthesis of α-diazocarbonyl compounds

As a prerequisite for the indazole-forming cycloaddition reactions, a number of diazo compounds were required. Initially, commercially available β-ketoesters would be used to provide the α-diazo-β-ketoester derivatives. A method to prepare a wider range of β-ketoester derivatives, that were either not available commercially or prohibitively expensive, was required. Subsequent diazo transfer would give a broader variety of novel α-diazo-β-ketoesters starting materials for use in this project. The synthesis of α-diazo-β-diketone and α-diazo-β-ketoamide derivatives from commercially available starting materials would also provide a broad range of substrates to be used as 1,3-dipole compounds in the cycloaddition reactions.

2.2.1 Preparation of ester derivatives by transesterification

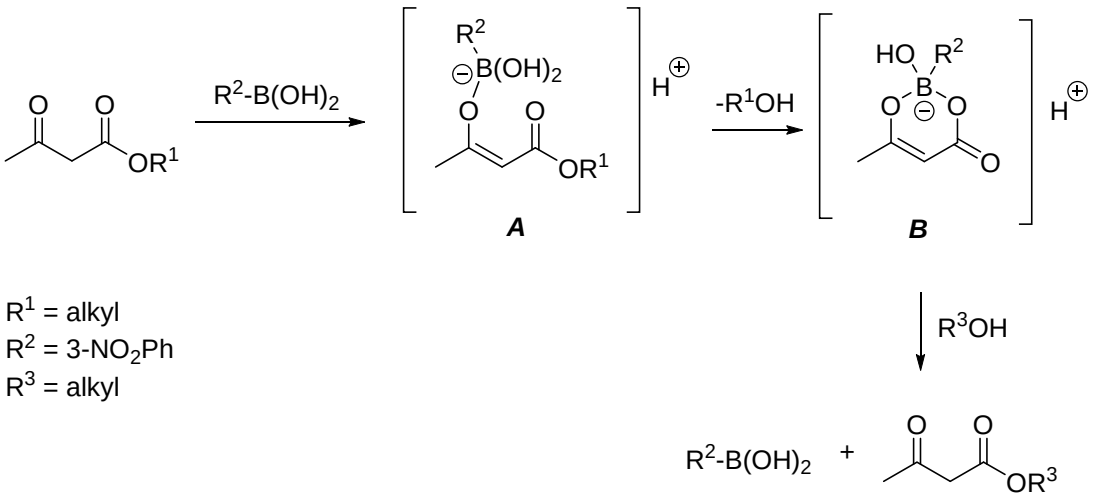
The method chosen for the formation of the β-ketoester derivatives was a transesterification reaction optimised within the group following a publication by Tale and co-workers that reported successful transesterification of a wide range of esters with various alcohols.[6] The reaction is catalysed by 3-nitrophenylboronic acid **1**, which is both an efficient and environmentally friendly catalyst. It is easy to handle, exhibits low toxicity and is highly stable, ultimately oxidising slowly to boric acid.

The standard procedure for the reaction involves heating the ester and desired alcohol in the presence of 2.5 mol% 3-nitrophenylboronic acid **1** in toluene under reflux. The toluene-alcohol azeotrope is continuously removed from the reaction mixture using a Dean-Stark condenser ensuring reaction completion. The general reaction is summarised in **Scheme 2.2**



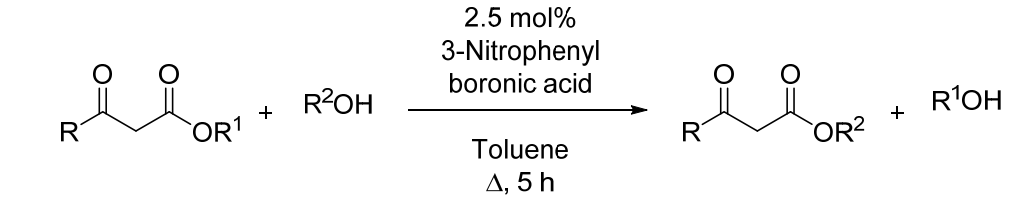
Scheme 2.2

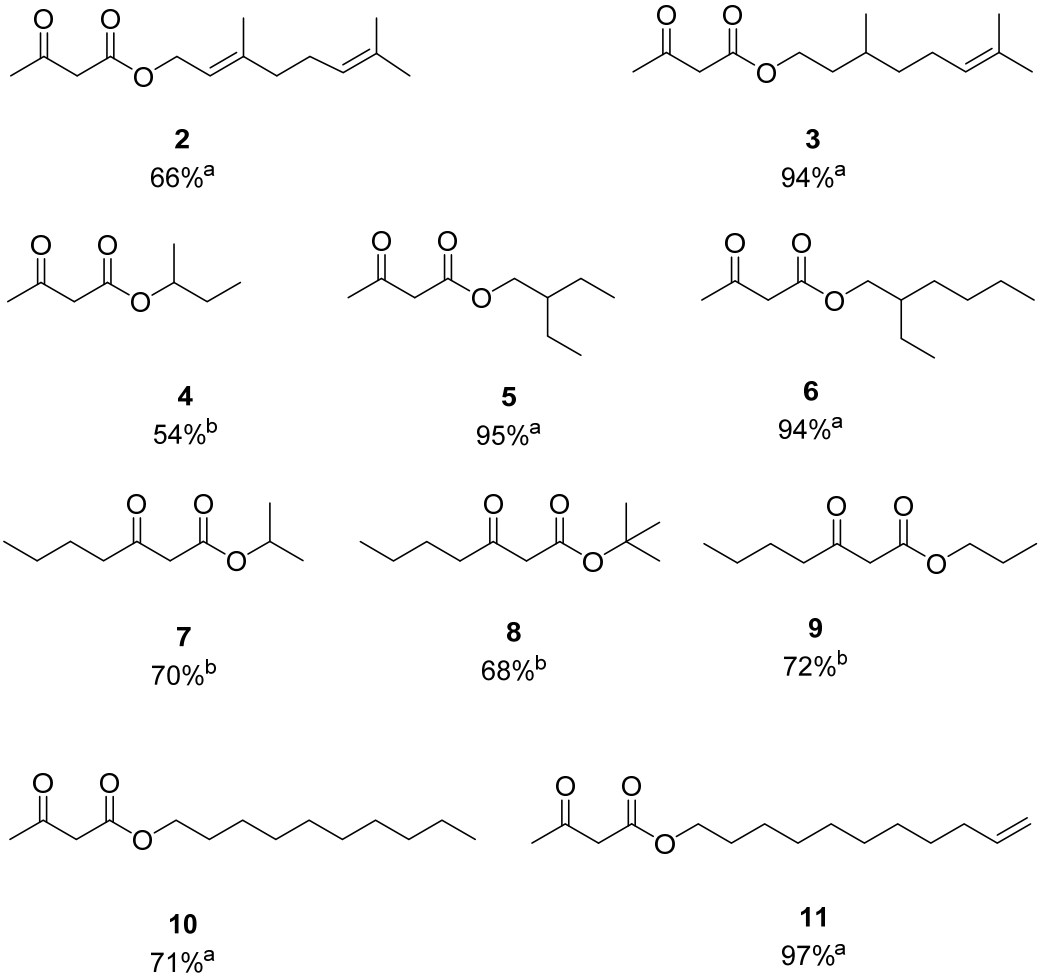
A mechanism for the reaction was proposed by Kondaiah as illustrated in **Scheme 2.3**. [7] It is believed that the boronic acid catalyses the enolisation of the β-ketoester to form intermediate **A**, which through the loss of R^1OH is converted to cyclic intermediate **B**. Subsequent nucleophilic ring-opening by the alcohol would give the desired ester product along with regeneration of the catalyst.



Scheme 2.3

This methodology was utilised as an efficient route for the synthesis of a variety of β-ketoester precursors required for this research. The reaction progress was monitored by TLC analysis and it was found that in general a reaction time of 5 h gave complete conversion to the desired β-ketoester products. A range of structurally diverse β-ketoesters were synthesised as shown in **Figure 2.1**, which allowed access to a series of non-commercially available esters to use as diazocarbonyl precursors. These esters were chosen for their side chain functionality and length variation of both the ester and ketone side chains.





[a]Yield refers to crude product obtained which was pure by ^{1}H NMR spectroscopy.
[b]Yield refers to product after purification by column chromatography on silica gel.

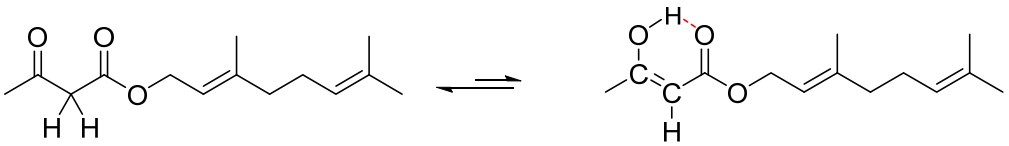
Figure 2.1 *Summary of β-ketoesters synthesised by transesterification*

The ^{1}H NMR spectra of the crude β-ketoesters **2, 3, 5, 6, 10** and **11** obtained after transesterification showed the compounds in high purity, with no further purification required. However, β-ketoesters **4** and **7-9** required purification by column chromatography on silica gel. All β-ketoesters were obtained as oils, which were stable in storage over a period of many months at room temperature without noticeable deterioration.

All ester derivatives were obtained in moderate to good yields, especially where the crude product was pure by ^{1}H NMR analysis, with slight reductions in yield for those requiring further purification by column chromatography on silica gel.

The most characteristic signal in the ^{1}H NMR spectra of the β-ketoesters is the 2H singlet in the region of δ_H 3.34-3.49 ppm, assigned to the methylene protons between the ester and the ketone. Characteristic absorption bands in the IR spectra for these β-ketoesters were seen at ν_{max} 1734-1750 cm^{-1} (carbonyl stretch of esters) and ν_{max} 1716-1720 cm^{-1} (carbonyl stretch of ketones).

Interestingly, most of the β-ketoester derivatives exhibited keto-enol tautomerisation which was visible in the ^{13}C NMR spectra but not the ^{1}H NMR spectra. Longer ester side chain derivatives had very visible enol tautomer peaks, while they were a lot less visible for the shorter chain ester derivatives. The more substituted enol is present in all cases as it is stabilised by the ester carbonyl through hydrogen bonding (**Scheme 2.4**).



2 **12**

Scheme 2.4

The enol-form **12** was characterised by the enolic *C*H and *C*OH signals in the regions of δ_C 89.3-90.1 and 175.2-175.4 ppm respectively and also the ester carbonyl signal from 172.4-172.8 ppm in the ^{13}C NMR spectrum.

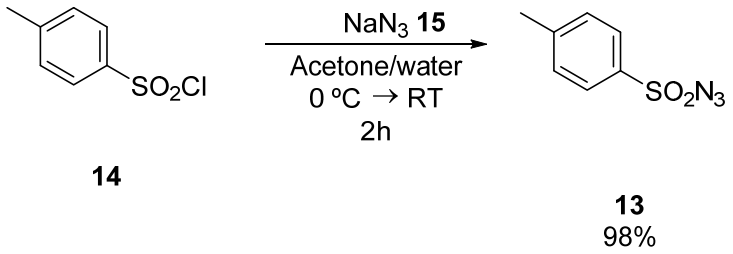
This transesterification methodology proved to be a very efficient and high yielding route to diverse β-ketoester derivatives and also provided novel derivative **9**. 3-Nitrophenylboronic acid is an inexpensive, mild and environmentally friendly and catalyst which is desirable in the move towards greener organic synthesis. The ease of preparation of the β-ketoester products would subsequently lead to a

number of diverse α-diazo-β-ketoester derivatives to be used as 1,3-dipoles in indazole synthesis.

2.2.2 Synthesis of *p*-toluenesulfonyl azide 14

Diazo transfer to compounds containing reactive methylene groups such as β-ketoesters, β-diketones, β-ketophosphonates and β-ketosulfones is readily achieved using the Regitz[8,9] methodology for diazo transfer. This involves initial deprotonation of the α-hydrogen using a base of sufficient strength (e.g. triethylamine) followed by addition of the diazo transfer reagent. Diazo transfer reagents have been reviewed,[10,11] most notably a review of their utility, safety and stability carried out by Bollinger and co-workers.[12,13]

p-Toluenesulfonyl azide (tosyl azide) **13** is the most commonly used diazo transfer reagent and was chosen as a key reagent for this research. Previous work within the group have also found this to be the most consistent and high yielding diazo transfer reagent available. It was prepared following a literature procedure using sodium azide **15** and *p*-toluenesulfonyl chloride **14** as illustrated in **Scheme 2.5**.[14]



14 **13**
98%

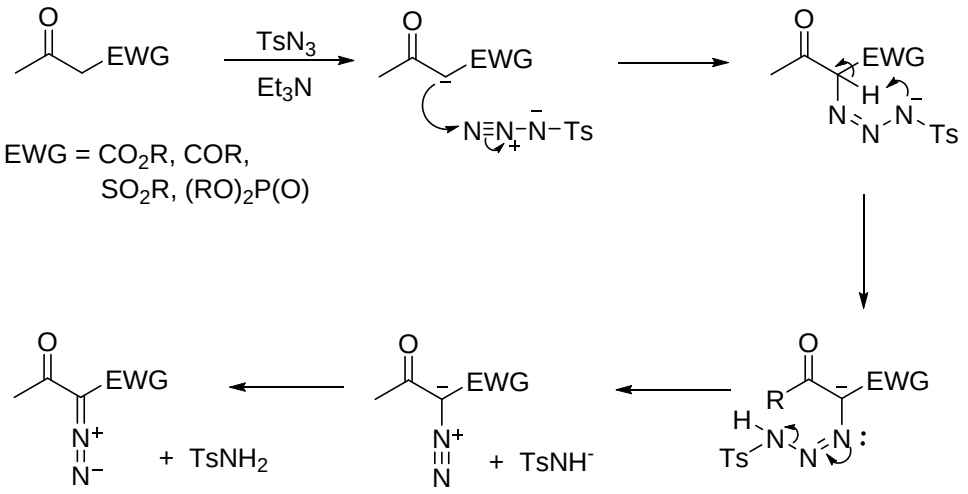
Scheme 2.5

Tosyl azide **13** is an extremely dangerous transfer reagent. Care must be taken when handling it and it should never be scraped out of its container because of its high impact sensitivity (50 kg.cm). The tosyl azide prepared during the course of this research was stored in a glass jar in the freezer in an isolated container. It crystallises to a white solid on freezing and for safety reasons only one batch of the azide was prepared and used at any one time in the laboratory. When needed, the tosyl azide **13** was carefully melted by placing in a beaker

containing luke warm water and the resulting clear oil was carefully removed from its container using a clean Pasteur pipette with no sharp edges.

2.2.3 Diazo transfer reactions to β-ketoesters using Regitz methodology

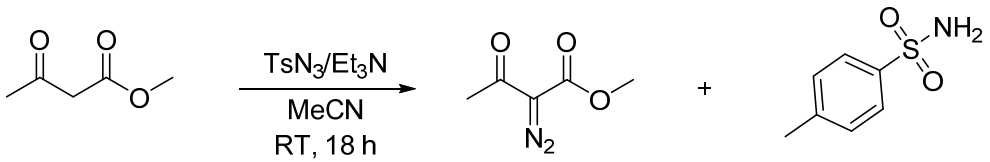
The α-diazo-β-ketoesters synthesised in this research were prepared using Regitz methodology[8,9,11,15] for diazo transfer. This involves the initial addition of triethylamine to the β-ketoester in acetonitrile followed by careful addition of tosyl azide. The side-product of the diazo transfer reaction is *p*-toluenesulfonamide **16**. The standard reaction mechanism for Regitz diazo transfer is shown in **Scheme 2.6**. This is the optimal method of diazo transfer established within the group for the preparation of α-diazo-β-ketoesters.



Scheme 2.6

The reaction included room temperature addition of the tosyl azide **13** which allows for a slight exothermic reaction, possibly facilitating faster diazo transfer from the azide to the β-ketoester **17**. This diazo transfer could be seen visually by a rapid appearance of a yellow coloured solution, which is characteristic of diazo transfer **(Scheme 2.7)**. This method involved a work-up that

included a 9% aq. potassium hydroxide wash, to remove the *p*-toluenesulfonamide **16**.[16]



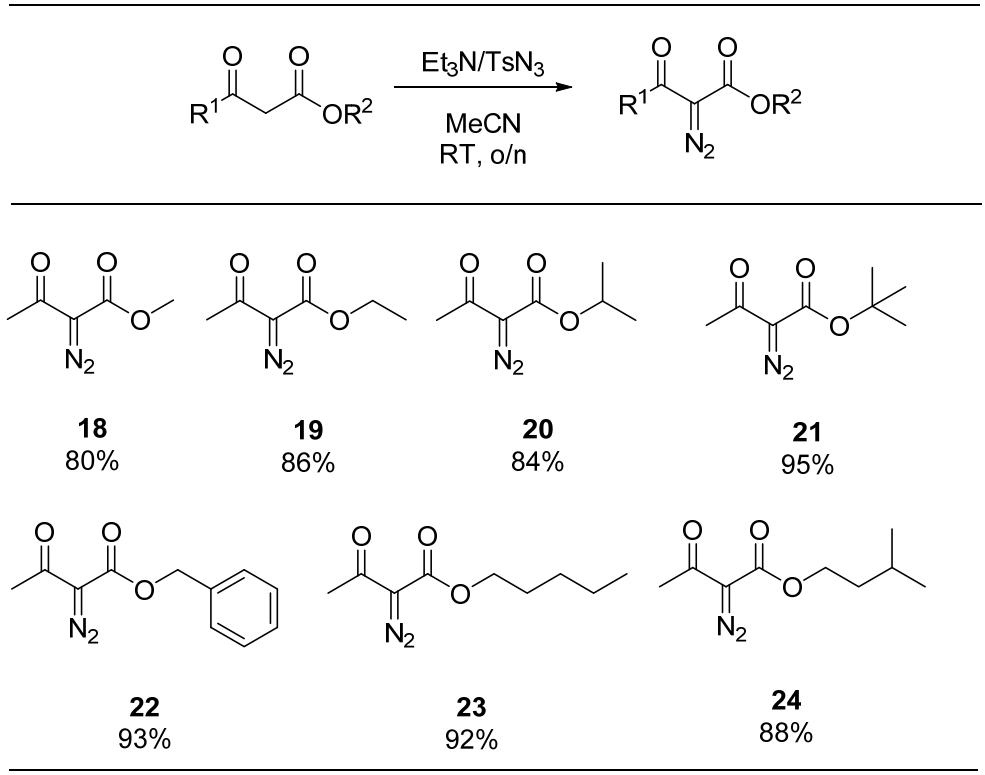
17 **18** 80% **16**

Scheme 2.7

After 18 h at room temperature the acetonitrile was removed under reduced pressure. The resulting cream residue was dissolved in diethyl ether and washed twice with 9% aq. potassium hydroxide and once with water and the desired diazocarbonyl product **18** was obtained as a bright yellow oil in 80% yield. The ^{1}H NMR spectrum showed the crude product with no *p*-toluenesulfonamide remaining. A range of α-diazo-β-ketoesters (22) required for this research were subsequently synthesised using this methodology.

Outline of α-diazocarbonyl compounds synthesised

The following is a brief summary of the wide range of α-diazo-β-ketoester compounds synthesised. The first series of α-diazocarbonyl compounds were synthesised from commercially available β-ketoesters and also provided **23** as a novel α-diazo-β-ketoester derivative. These were characterised by short ester side-chains while maintaining the methyl ketone moiety as displayed in **Figure 2.2**. All the α-diazocarbonyl compounds were synthesised as bright yellow oils in excellent yields which were stable over prolonged periods of storage at room temperature. The yields shown in **Figure 2.2** reflect the crude reaction material which was > 95% pure by ^{1}H NMR spectroscopy.



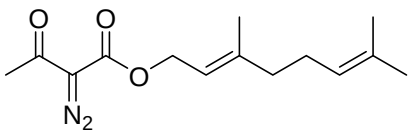
All yields herein refer to crude product obtained which was pure by ^{1}H NMR spectroscopy

Figure 2.2 *Summary of initial α-diazo-β-ketoester compounds*

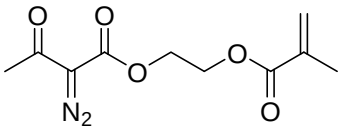
The two most characteristic features in the ^{1}H NMR spectra of the α-diazo-β-ketoesters in **Figure 2.2** are the disappearance of the 2H singlet in the region of δ_H 3.34-3.49 ppm assigned to the methylene protons between the ester and the ketone and the shift of the 3H singlet of the methyl ketone protons from δ_H 2.24-2.27 ppm to δ_H 2.48-2.51 ppm. The α-diazo-β-ketoesters are also characterised by absorptions in the IR spectra at ν_{max} 2136-2146 cm^{-1} ($C{=}N_2$ stretch) due to extended conjugation involving the diazo group and carbonyl bonds. In the ^{13}C NMR spectra the ketone group was seen to shift from the region of δ_C 200 ppm to δ_H 188.4-190.4 ppm. In all cases the quaternary carbon belonging to the $C{=}N_2$ group could not be observed in the ^{13}C NMR spectra.

Following on from these compounds diazo transfer was next achieved for a range of β-ketoesters prepared *via* transesterification as described in **Section 2.2.1**, with the exception of **26** which was prepared from commercially available starting material. This series contained products with both increased ester side-chain lengths **28-30** and **32** and functionalities (alkene groups, additional ester

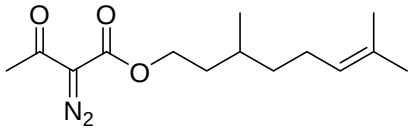
groups) **25-27** and **31** as illustrated in **Figure 2.3**, and included 5 novel derivatives **26-28**, **30** and **31**.



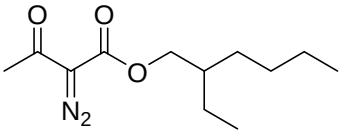
25
86%[a]



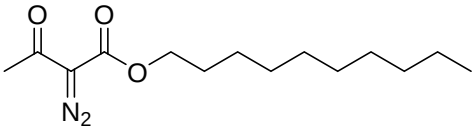
26
79%[a]



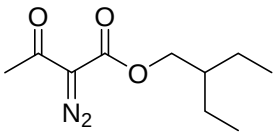
27
68%[a]



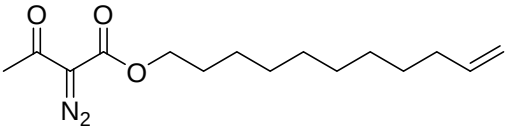
28
78%[a]



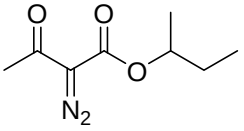
29
80%



30
78%



31
78%[a]



32
78%

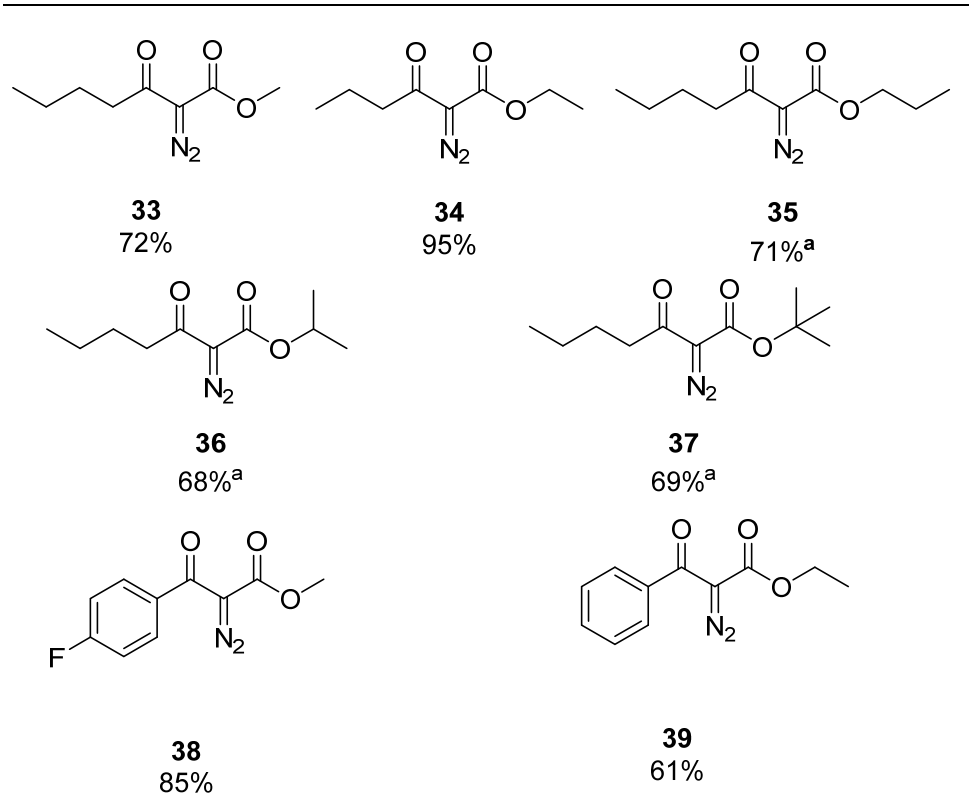
[a]Yield refers to product after purification by column chromatography on silica gel.

Figure 2.3 *Summary of series of alternative ester side-chain derivatives*

The yields of **29**, **30** and **32** in **Figure 2.3** reflect the crude reaction material which was pure by ^{1}H NMR spectroscopy and the diazocarbonyl compounds could be used without further purification. In the cases of **25-28** and **31**, further purification by column chromatography on silica gel was required. As with the compounds synthesised in **Figure 2.2**, the disappearance of the 2H singlet appearing at δ_H 3.34-3.49 ppm in the ^{1}H NMR spectra as well as the shift in the singlet belonging to the methyl ketone protons from the region δ_H 2.24-2.27 to δ_H

2.47-2.48 ppm were significant. The quaternary diazo carbon (*C*=N_2) was not visible in any of the ^{13}C NMR spectra.

The final series of α-diazocarbonyl compounds synthesised **(Figure 2.4)** had a variety of ketone side-chains with longer aliphatic chains and aryl ketones. **35-37** were prepared from β-ketoesters **7-9** *via* transesterification, while **33, 34, 38** and **39** were prepared using commercially available starting materials. These compounds had similar stability to the previous diazocarbonyl derivatives synthesised and no noticeable deterioration was observed following prolonged periods of storage at room temperature. The yields reflect the crude products obtained with the exception of **35**, **36** and **37** which required purification by column chromatography on silica gel due to the presence of unreacted starting material. This series contains 4 novel derivatives, **35-38**.



[a]Required further purification by column chromatography on silica gel.

Figure 2.4 *Summary of lengthened ketone side-chain α-diazo-β-ketoester derivatives*

Evidence for diazo transfer was again characterised by the disappearance of the 2H singlet belonging to the methylene protons between the ester and the ketone in the range of δ_H 3.34-3.49 ppm. The methylene CH_2 protons alpha to the ketone, in **33-37**, appear as a triplet and shift up to the region of δ_H 2.81-2.85 ppm. The quaternary diazo carbon ($C=N_2$) could be detected for three α-diazo-β-ketoesters in this series (**33**, **35** and **39**) in the ^{13}C NMR spectra in the range δ_C 60.9-75.8 ppm.

Overall, the range of α-diazo-β-ketoesters required for this research were successfully prepared using Regitz methodology for diazo transfer. The optimum conditions were found to be room temperature addition of the triethylamine followed by the tosyl azide **13**. The *p*-toluenesulfonamide by-product, which can be problematic to remove from some diazocarbonyl products, was completely removed using a potassium hydroxide wash negating the need for purification by chromatography on silica gel in most cases. The only observed effect of increasing the alkyl side-chain length on the ketone moiety was the yield of these compounds were slightly lower.

2.2.4 Diazo transfer reactions to β-diketones

Following on from the successful synthesis of fifteen α-diazo-β-ketoesters, the substrate scope was broadened to include two α-diazo-β-diketones that would provide alternative 1,3-dipoles in the indazole-forming reactions. The α-diazo-β-diketones synthesised in this research were prepared using Regitz methodology for diazo transfer.[17,18] The only difference in reaction procedure in comparison to the α-diazo-β-ketoester derivatives is the use of dichloromethane as solvent in the preparation of **42**. This allowed the reaction mixture to be worked up immediately using 9% potassium hydroxide (as the water miscible acetonitrile did not need to be removed first before the work-up is carried out using diethyl ether as in the α-diazo-β-ketoester work-up procedure). The use of dichlormethane is a slight modification of literature procedures where good yields and fast reaction times are seen for this substrate in dichloromethane and where there is difficulty extracting the desired product with diethyl ether.

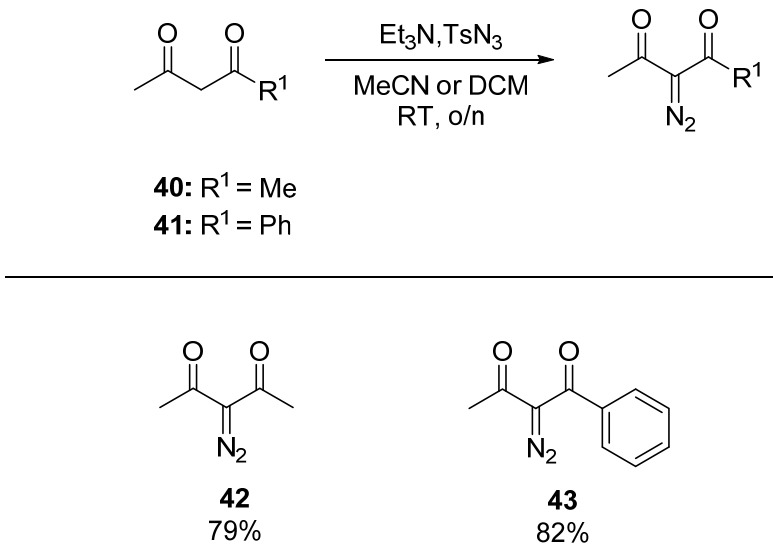


Figure 2.5 *Summary of α-diazo-β-diketone derivatives*

Acetylacetone **40** exists predominantly in the enol form and similarly, 1-phenylbutane-1,3-dione **41** exists almost entirely in the enol form so the differences in the NMR spectra in comparison to the diazo product are evident. The most characteristic features in the ^{1}H NMR spectra of the diazo-β-diketones in **Figure 2.5** are that in the case of **42**, the symmetrical product now shows only one signal in the ^{1}H NMR spectrum for the methyl groups at δ_H 2.44 ppm while the methyl group is at δ_H 2.57 ppm for **43**. In both cases the quaternary carbon belonging to the C=N_2 group was observed in the ^{13}C NMR spectra at δ_C 84.6 and 83.7 ppm, respectively. Both derivatives show absorptions in the IR spectra at ν_{max} 2120 and 2130 cm^{-1} for the C=N_2 stretch. Derivative **43** is the first solid diazo compound prepared so far and the melting point of 77-80 ºC obtained closely matches the literature value of 78-81 ºC,[19] indicating high purity after work-up. Only two α-diazo-β-diketone substrates were used in this project so there is scope in the future of this project to expand their use in cycloaddition reactions.

2.2.5 Diazo transfer reactions to β-ketoamides

The preparation of α-diazo-β-ketoamides would provide additional, diverse 1,3-dipoles for the indazole-forming reactions. The α-diazo-β-ketoamides **44-46** were prepared using the same method and workup used for the α-diazo-β-ketoesters.[20-22] More than one equivalent of base was employed for derivatives **47** and **48**, as there is more than one site of deprotonation, and the work-up involved the use of water and brine washes only with dichloromethane extraction. All α-diazo-β-ketoamides required further purification by column chromatography on silica gel as the *p*-toluenesulfonamide **16** by-product was more difficult to separate from the desired products.

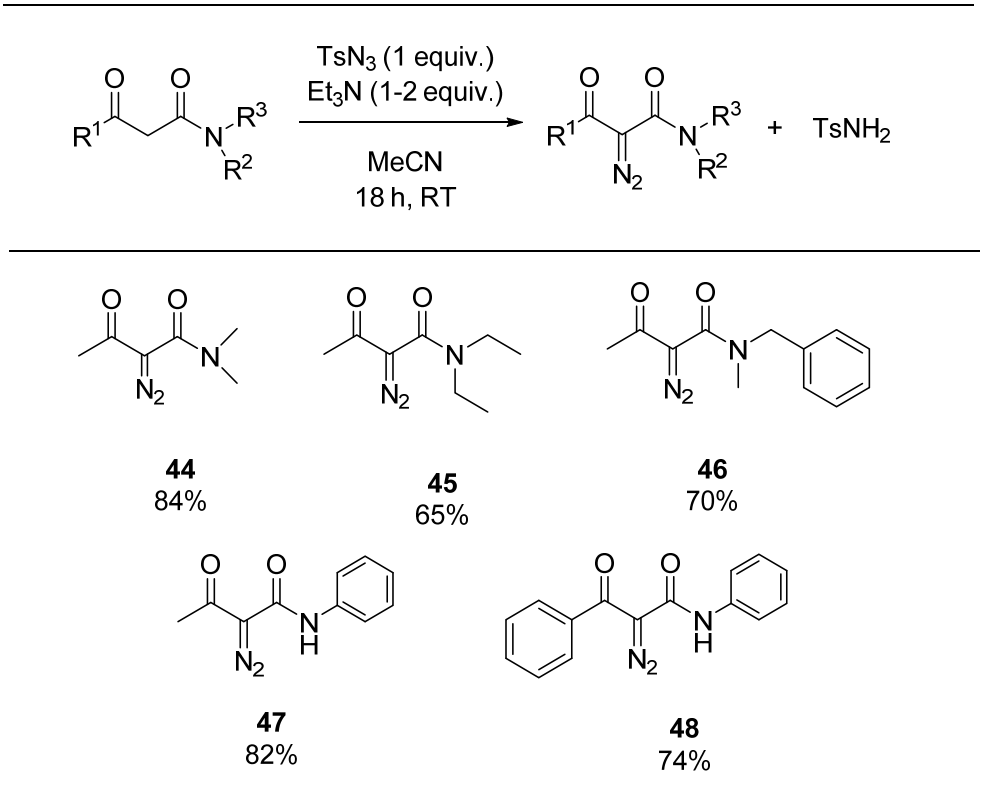


Figure 2.6 *Summary of α-diazo-β-ketoamide compounds synthesised*

Evidence for diazo transfer was again characterised by the disappearance of the 2H singlet belonging to the methylene protons and the enol peaks in the case of **44** and **48**. The quaternary diazo carbon ($C=N_2$) could be detected for two α-diazo-β-ketoamides in this series (**45** and **46**) in the ^{13}C NMR spectra at δ_C 72.4 and 73.5 ppm respectively. The derivatives show absorptions in the IR spectra in

the range ν_{max} 2106 to 2130 cm^{-1} for the $C=N_2$ stretch and spectra in the range ν_{max} 1607 to 1676 cm^{-1} for the carbonyl of the amide.

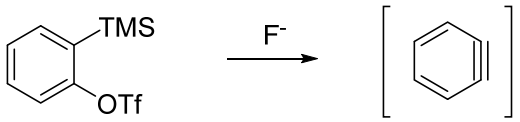
Overall, the α-diazo-β-ketoamide derivatives in **Figure 2.6** were the most difficult to prepare and purify, however, five amide-containing substrates were successfully synthesised in sufficient yields, including one novel derivative **46**.

To summarise, the synthesis of 22 diazo dicarbonyl compounds in this section provides a diverse range of 1,3-dipoles for the cycloaddition reactions that consists of 15 α-diazo-β-ketoesters, 5 α-diazo-β-ketoamides and 2 α-diazo-β-diketones.

2.3 Synthesis of 2-trimethylsilyl aryl triflates/nonaflates as aryne precursors

2.3.1 Synthesis of aryne precursors *via* triflation method

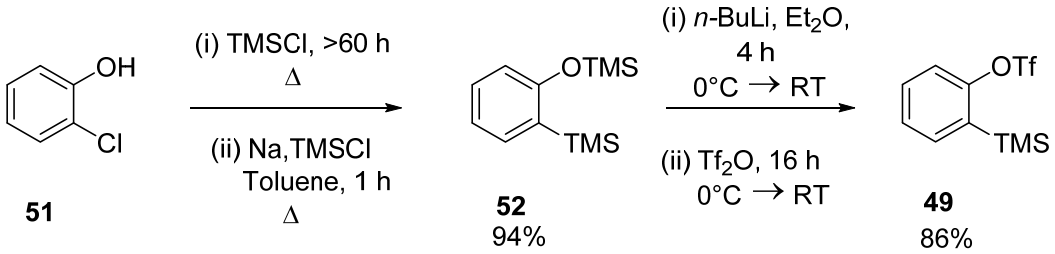
To produce a range of structurally varied indazoles, the indazole core structure could be altered by synthesising substituted aryne precursors which would lead to different substitution patterns on the benzene ring fragment of the indazole ring. Treatment of commercially available *o*-silylaryl triflates **49** with a fluoride ion source (**Scheme 2.8**) is a commonly reported route to aryne generation in current literature reports.[4,23-28]



49 **50**

Scheme 2.8

The use of arynes as reagents in organic synthesis was revolutionised when this route for fluoride-ion-induced aryne formation was designed by Himeshima and co-workers in 1983. This method involved silylation of 2-chlorophenol **51** using molten sodium and trimethylsilylchloride in refluxing toluene to form **52** initially before treatment with *n*-butyllithium and triflic anhydride to form **49** in good yields (**Scheme 2.9**).[29] The ease of preparation from phenol derivatives and the mild reaction conditions make this an attractive route for these derivatives to be used as aryne precursors in organic synthesis.



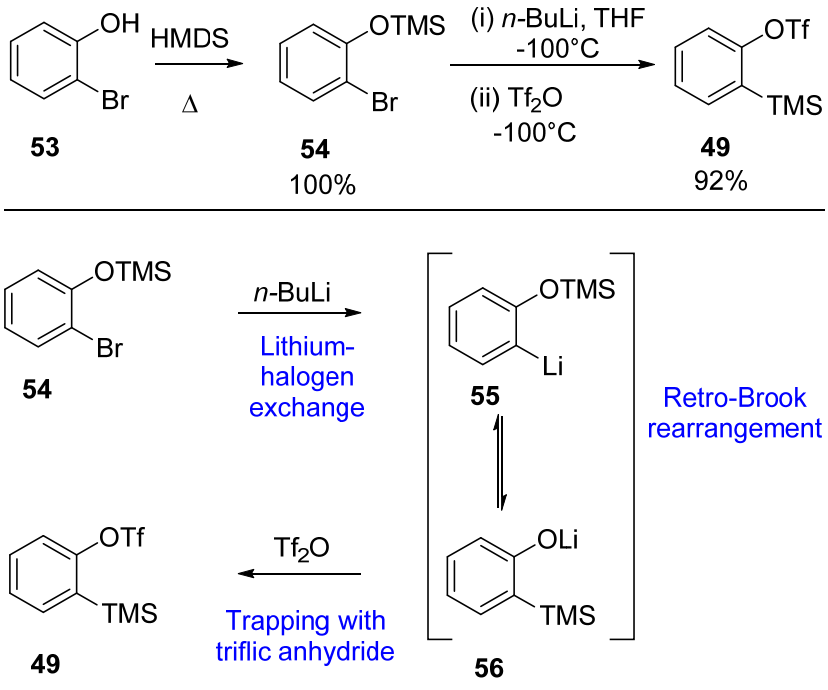
51 **52** 94% **49** 86%

Scheme 2.9

Some difficulties encountered with these aryl triflates, however, is their low hydrolytic stability during chemical transformations and the triflating reagents used in their synthesis can be unstable and expensive.[30]

An efficient, one-pot procedure for synthesising functionalised *o*-(trialkylsilyl)aryl triflates for easy access to functionalised aryne precursors was published by Peña and co-workers in 2002.[31] This was a modified version of Himeshima's original version.

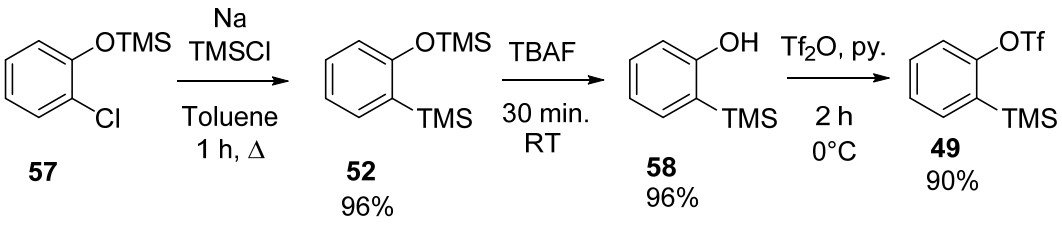
Peña's method involved silylation of 2-bromophenol **53** with hexamethyldisilazane (HMDS) in solvent-free conditions at 80 °C. The product of this step underwent lithium-halogen exchange in the presence of *n*-butyllithium at -100 °C, followed by silyl migration from oxygen to carbon in a Retro-Brook rearrangement and entrapment of the phenoxide group with triflic anhydride. (**Scheme 2.10**).



Scheme 2.10

Temperature must be strictly controlled during these reactions as higher temperatures can favour nucleophilic attack by the base on the silicon atom of the (2-bromophenoxy)trimethylsilane compound **54** and also may promote polymerisation of tetrahydrofuran where triflic acid is present in trace amounts.

Another modification procedure put forward by Brimble and co-workers in 2010 uses 2-chlorophenols and eliminates the use organolithium reagents which could be useful for scaling-up the reaction (**Scheme 2.11**).[32]

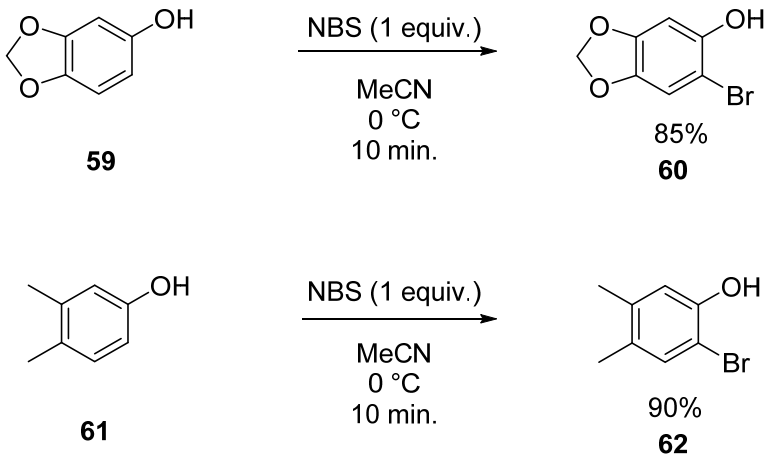


Scheme 2.11

The aryne precursor **49** is commercially available from a number of vendors at a reasonable cost but may alternatively be synthesised in a facile manner if required.[33]

2.3.2 Bromination of phenol derivatives

For the synthesis of a range of substituted aryne precursors, the project required the preparation of the 2-bromophenol starting materials **60** and **62** as they were not commercially available. These were prepared using a well-established method where phenols are selectively *ortho*-halogenated using *N*-halosuccinimides in polar solvents.[34] Using NBS in acetonitrile at 0 ºC, multi-gram quantities of **60** and **62** could be prepared successfully from **59** and **61** respectively **(Scheme 2.12)**.



Scheme 2.12

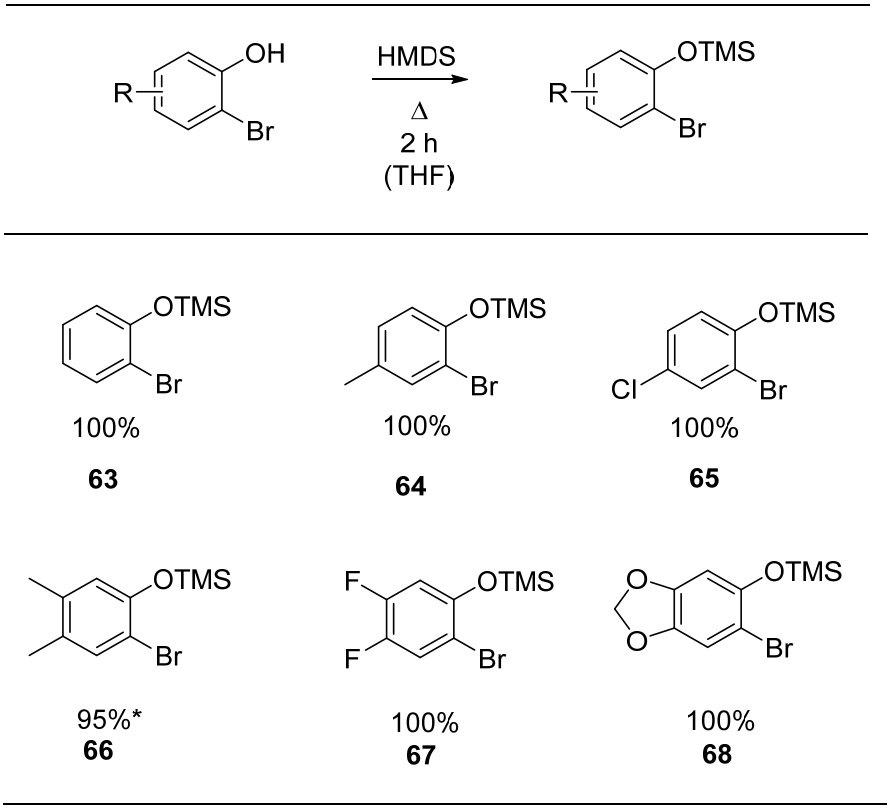
The ^{1}H NMR spectra for compounds **60** and **62** are very straightforward with two aromatic CH singlet signals in the range between δ_H 6.59-7.18 ppm and broad OH signals at δ_H 5.23 ppm (**62**) and δ_H 5.28 ppm (**60**).

A difficulty encountered in the preparation of **62** was that the reaction would not reach 100% conversion, even after attempting the reaction with up to 2 equivalents of NBS and increasing reaction times. The ^{1}H NMR spectrum showed the presence of up to 5% starting material after repeated column chromatography on silica gel.

Other methods in the literature report using bromine[35] or tetra-*N*-butylammonium tribromide[36] to give the desired product cleanly but it was decided to bring the 95% pure compound through to the next stages of the synthesis where the starting material could be removed.

2.3.3 Silylation of *ortho*-bromophenol derivatives

With these two bromophenol compounds **60** and **62** and four commercially available bromophenol derivatives in hand, the silylation step using HMDS could be explored. Using Peña's modified procedure,[31] the first step in aryne precursor generation was silylation of the 2-bromophenol derivatives using HMDS at 80 ºC to give the desired products in quantitative yield (**Figure 2.7**). (The only exception to this was the dimethyl derivative **66** which contained 5% starting material carried forward from the previous step). No solvent is required if the starting bromophenol is an oil, but for solid starting materials THF is used as solvent.



*Contains 5% starting material

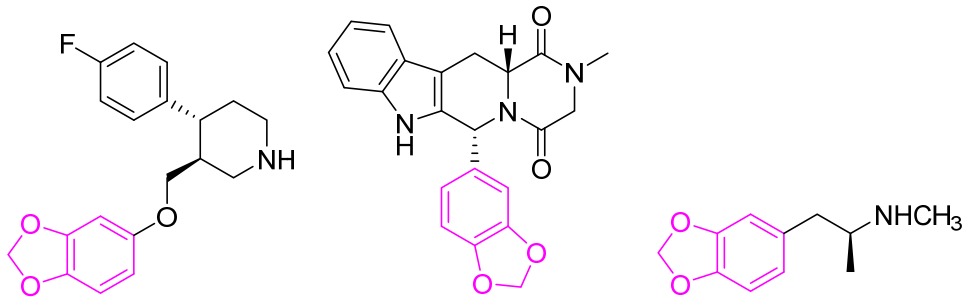
Figure 2.7 *2-Bromophenoxytrimethylsilane derivatives*

Derivative **63** can be used to synthesise the unsubstituted aryne precursor *in lieu* of purchasing expensive 2-trimethylsilylphenyltriflate **49** for the preparation of unsubstituted indazole derivatives.

The two aryne precursor starting materials **64** and **65** were chosen as they would generate unsymmetrical arynes which could possibly lead to mixtures of regioisomeric indazoles. The substituent effects could also have an effect on the regiochemistry of the product. Comparison of the electron donating methyl group attached to **64** and electron withdrawing chlorine atom on **65** could show that these opposing substituent effects could influence the regiochemistry of the cycloaddition.

Phenoxytrimethylsilane derivatives **63** and **66-68** were then chosen as symmetrical aryne intermediates would be formed. Many drug compounds on the market (e.g. Paroxetine **69** and Tadalafil **70**, **Figure 2.8**) and other drugs exerting biological effects (e.g. MDMA **71**, **Figure 2.8**) contain the methylenedioxy benzene moiety in **68**. It was, therefore, of key importance to prepare indazole

compounds with this structural feature to potentially provide favourable biological testing results, which will be discussed in **Section 2.10**.



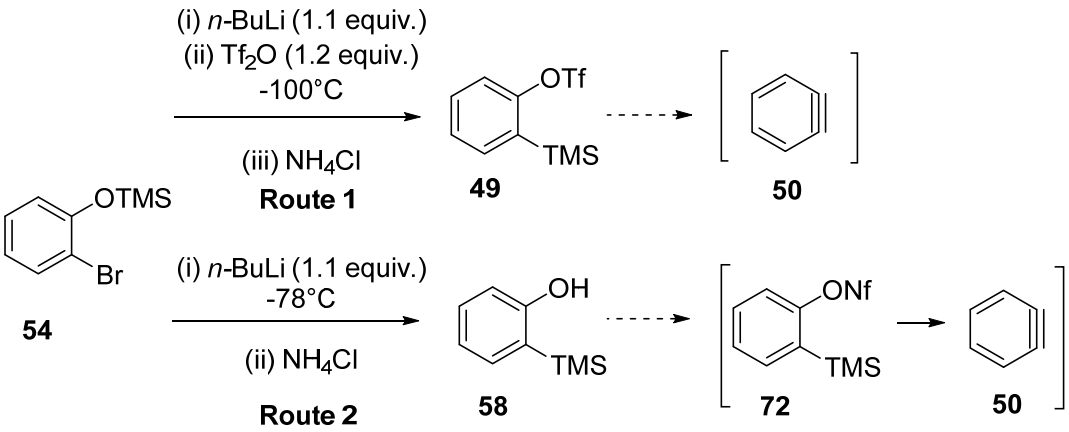
Paroxetine **69** Tadalafil **70** MDMA **71**

Figure 2.8 *Drug compounds containing methylenedioxybenzene*

The most characteristic features for these compounds in the ^{1}H NMR spectra is the disappearance of the OH signals and appearance of the trimethylsilyl signals between δ_H 0.23-0.37 ppm. In the ^{13}C NMR spectrum, the signal for the trimethylsilyl group appears between δ_C 0.3-0.4 ppm.

The 2-bromophenoxytrimethylsilane derivatives were unstable and converted back to the 2-bromophenol starting materials within a few days, therefore, were used almost immediately after ^{1}H NMR analysis confirmed their formation.

The project branched into two directions from here: the first followed the initial route to prepare aryltriflate derivatives in a one-pot, two-step reaction (**Route 1**); the second route involved preparation of trimethylsilylphenols which could be used to generate arylnonaflate derivatives (**Route 2**)[37] (**Scheme 2.13**).



Scheme 2.13 *Routes 1 and 2 used to access arynes in this project*

2.3.4 Synthesis of aryne precursors *via* triflation method (Route 1)

At the outset of this project, 2-trimethylsilylaryltriflate derivatives were synthesised as the reagents of choice for aryne generation. Before Route 2 was explored, three aryltriflate aryne precursors **73-75** were prepared using Peña's methodology. The 2-bromotrimethylphenoxysilane derivatives **64**, **65** and **68** are treated with *n*-butyllithium at -100 °C, followed by triflic anhydride. Quenching at low temperatures gives the crude triflate product which could then be isolated after column chromatography on silica gel (**Figure 2.9**).

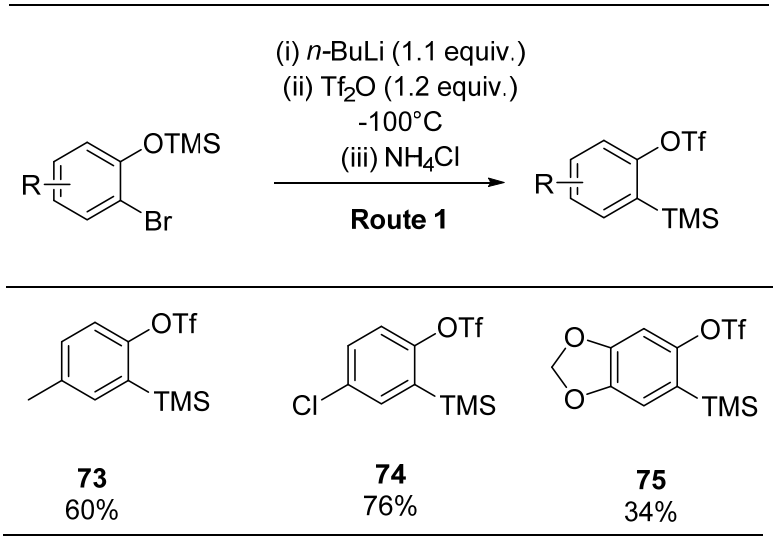


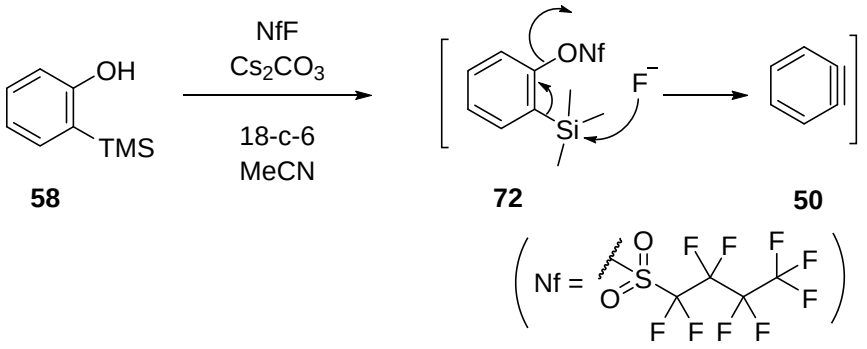
Figure 2.9 *2-Trimethylsilylaryltriflate derivatives*

The most characteristic features for these compounds in the ^{1}H NMR spectra is the slight downfield shift of the trimethylsilyl signals from between δ_H

0.23-0.30 ppm when the TMS group is on oxygen to δ_H 0.33-0.37 ppm when it is on carbon. In the ^{13}C NMR spectra, the signals for the trimethylsilyl group appears between δ_C -0.35-0.4 ppm and the CF_3 signal of the triflate group appears between δ_C 116.3 and 117.6 ppm.

2.3.5 Synthesis of aryne precursors *via* nonaflation methods (Route 2)

Route 2 involves the use of a relatively new method which was published by Ikawa and co-workers in 2011 and replaces the trifyl group ($–SO_2CF_3$) with the C4 homologue nonafyl group ($–SO_2C_4F_9$). This route does not require the isolation of the unstable 2-trimethylsilylarylnonaflate derivatives. The isolation of the 2-trimethylsilylphenol derivative **58**, after the Retro-Brook rearrangement, using *n*-butyllithium is required instead. Formation of 2-trimethylsilylarylnonaflate derivative **72**, in a one-pot, domino reaction subsequently generates benzyne **50** *in situ* that can undergo a variety of reactions (**Scheme 2.14**).[37]



Scheme 2.14

This method replaces the use of triflating reagents with nonafyl fluoride (perfluoro-1-butanesulfonyl fluoride or nonafluorobutanesulfonyl fluoride or NfF) as they are more expensive, less stable and have a lower atom economy than nonafyl fluoride. Nonafyl fluoride has a dual function as it is used to nonaflate the hydroxyl group and then as a fluoride ion carrier for desilylation and aryne formation. It is also one of the most stable and least expensive nonaflating reagents.

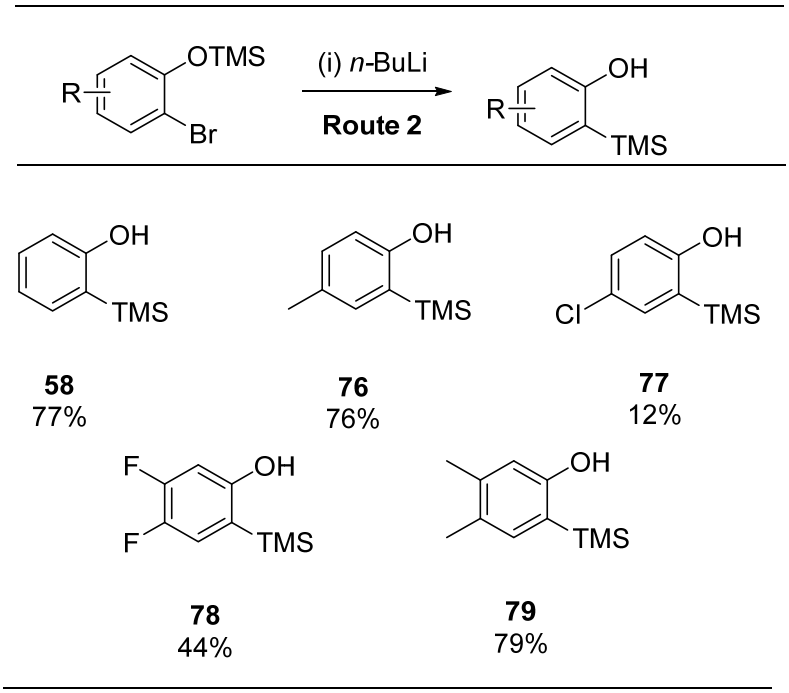


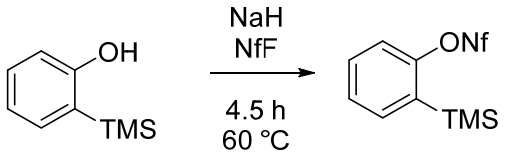
Figure 2.10 *2-Trimethylsilylphenol derivatives*

Five 2-trimethylsilylphenol derivatives were prepared as illustrated in **Figure 2.10**. The most characteristic features for these compounds in the ^{1}H NMR spectra is the trimethylsilyl signals between δ_H 0.30-0.36 ppm and the broad OH signals in the range δ_H 4.63-5.56 ppm. In the ^{13}C NMR spectra, the signals for the trimethylsilyl group appears in the range δ_C -1.2-0.35 ppm. The derivatives show a broad absorption in the IR spectra in the range ν_{max} 3521-3603 cm^{-1} for the OH stretch. As well as lithium-halogen exchange occurring in these reactions they can also undergo 1,2-elimination reactions of halides/hydrogens.

The yields for **58**, **76** and **79** are good, however, there is a considerable difference with the halide-containing derivatives. Most notable is the chloro-derivative **77** with a poor yield of 12%, most likely due to the choice of 1,2-elimination pathways it can undergo; however, the yield obtained is an almost fivefold improvement of the literature yield of 2.6%.[37] It is possibly the lower temperature of -100 ºC rather than the standard -78 ºC used for these type of alkyllithium reactions and preferential elimination of bromine rather than fluorine or chlorine which promotes the formation of the required product.

2.3.5.1 Synthesis of nonafyl aryne prescursor

To gain familiarity with the use of nonafyl fluoride, one nonafyl aryne precursor **72**[37] was isolated and fully characterised from those shown in **Figure 2.10**. Sodium hydride was used to deprotonate the phenol **58** and nonaflation occurs with nonaflyl fluoride (**Scheme 2.15**).



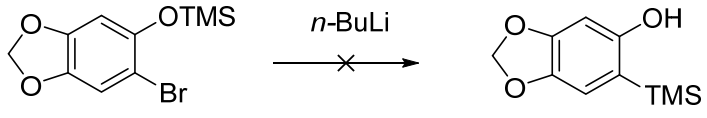
58 **72** 89%

Scheme 2.15

The most characteristic feature for this compound in the ^{1}H NMR spectrum is the trimethylsilyl signal which shifts from δ_H 0.31 ppm to δ_H 0.37 ppm and the disappearance of the OH signal. In the ^{13}C NMR spectrum, the signal for the trimethylsilyl group shifts upfield from δ_C 0.35 ppm to δ_C -0.9 ppm and the multiplet signals for the nonafluorobutane portion are too close to the baseline to report.

2.3.6 Attempted synthesis of 6-(trimethylsilyl)benzo[d][1,3]dioxol-5-ol

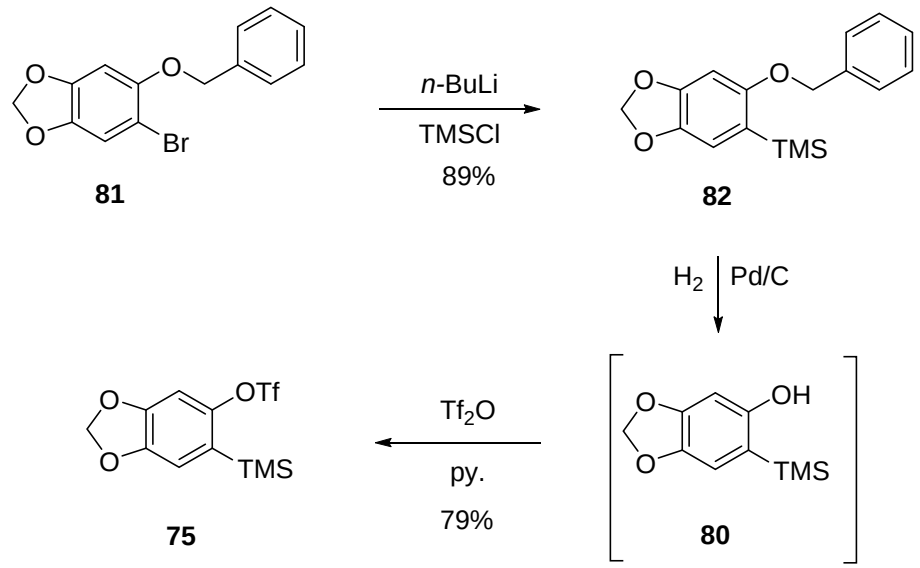
Formation of 2-trimethylsilylphenol derivative **80** from 2-bromotrimethylsilylphenoxy derivative **68** was attempted using the same procedure (**Route 2**),[37] however, this was unsuccessful with a complex mixture of unidentifiable material observed in the ^{1}H NMR spectrum and no material resembling the desired compound was recovered from the reaction (**Scheme 2.16**). No reason could be identified for the lack of product formation.



68 **80**

Scheme 2.16

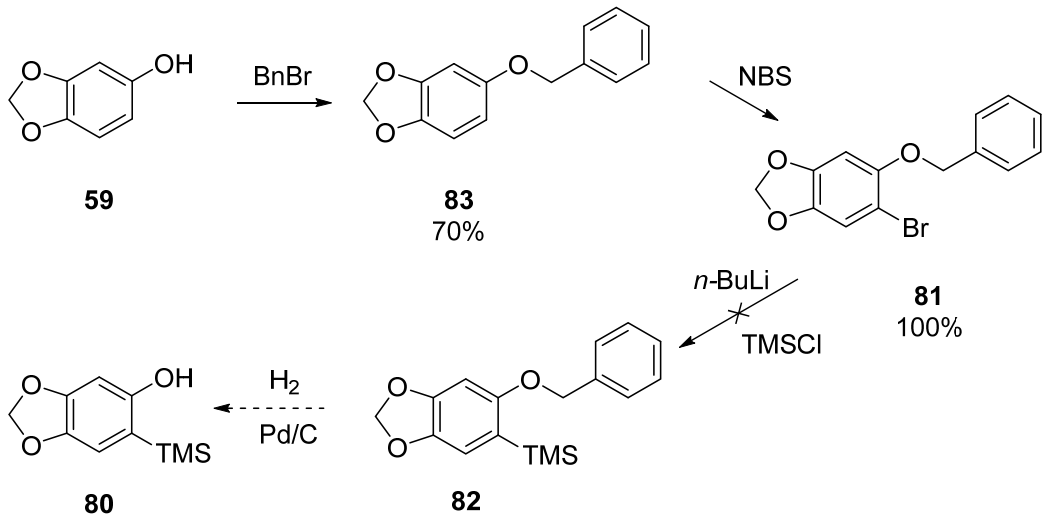
In 2005, Tambar and Stoltz reported a route towards aryne precursor **75** that involves **80** as an intermediate as shown in **Scheme 2.17**. Benzyl-protected bromosesamol **81** undergoes lithium-bromine exchange with *n*-butyllithium followed by silylation with trimethylsilylchloride to form **82**. On deprotecting the benzyl ether using palladium-catalysed hydrogenation,[38] **80** was prepared but is not isolated and is instead immediately trapped with triflic anhydride to form **75**.



Scheme 2.17

In a recent report by Chen *et al.* **80** is used as a starting material to prepare a 2-trimethylsilylarylfluorosulfate, presumably by isolating it initially.[39] No experimental or spectroscopic details are described in either paper.

The Tambar and Stoltz route was explored beginning from sesamol **59**. Protection using benzyl bromide provides **83** and selective *ortho*-bromination with NBS forms **81**. Unfortunately, in our hands, attempts to prepare **82** using *n*-butyllithium and trimethylsilylchloride were unsuccessful (**Scheme 2.18**).



Scheme 2.18

These reactions were attempted in the absence of organolithium reagents using Brimble's[32] procedure (**Scheme 2.11, Section 2.3.1**) but again with no success. In future work of this project, use of freshly distilled trimethylsilyl chloride could facilitate an improvement in this reaction. Nevertheless, sufficient amounts of the triflate **75** was prepared to bring forward and use in the cycloaddition reactions.

2.3.7 Synthesis of pyridyne precursors

In search of an even more diverse range of arynes for the cycloaddition reactions it was decided to include pyridyne precursors as additional aryne precursors to be prepared in this project. 3,4-Pyridynes **84** have been shown to be useful synthetic intermediates in the synthesis of natural products such as ellipticine **85** and (S)-macrostomine **86** (**Figure 2.11**).[40] Recent research work in Larock's group has also shown the utility of of the 2,3-pyridyne intermediate **87** in the synthesis of benzonaphthyridinones **88** in reasonable yields with high nucleophilic regioselectivity observed (**Figure 2.11**).[41]

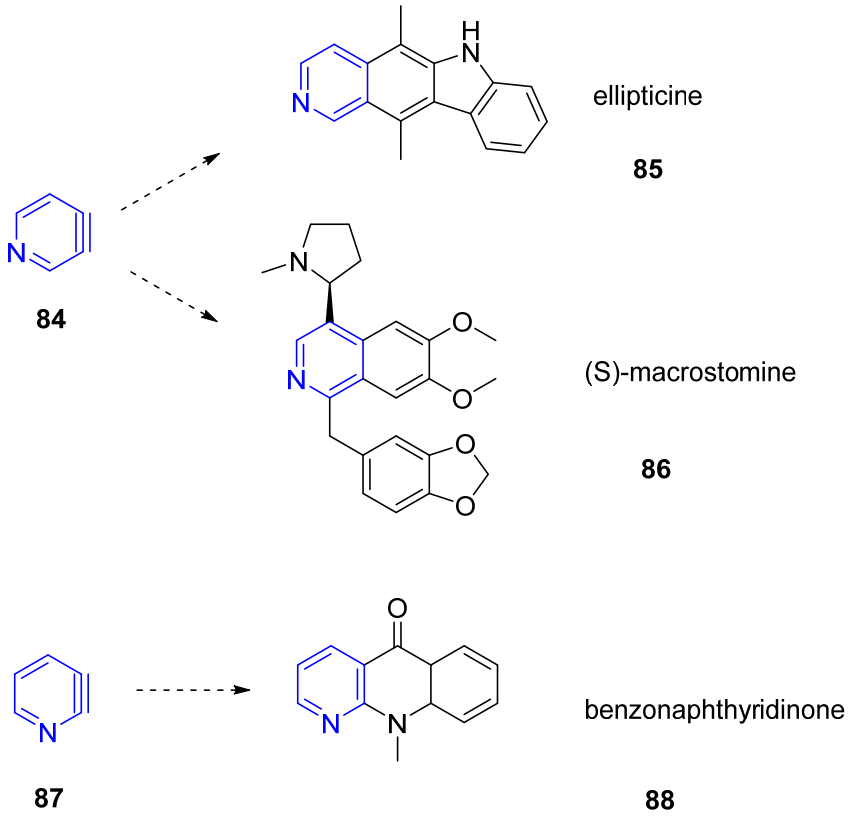
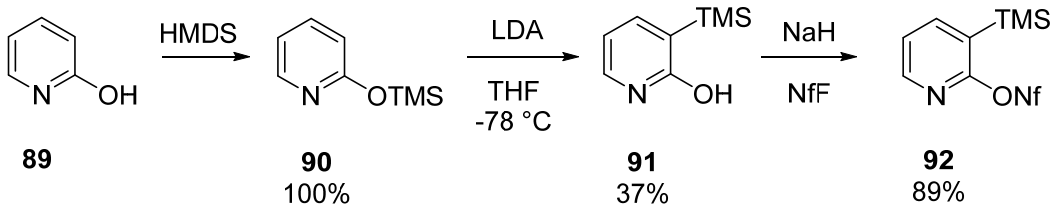


Figure 2.11 *Use of pyridyne intermediate in organic synthesis*

A literature procedure by Díaz and co-workers[42] reports that for transferral of the trimethylsilyl group from oxygen to carbon (Retro-Brook rearrangement) in the preparation of the precursors does not require a bromine group for the elimination step. The pyridine oxygen interacts with the lithium cation allowing directed *ortho*-deprotonation and lithiation to occur. The first derivative that was

investigated was 2-hydroxypyridine (2-pyridone) **89**, using the silylation procedure as used previously[31] to provide **90** in quantitative yield (**Scheme 2.19**). The most characteristic feature for this compound in the ^{1}H NMR spectrum is the trimethylsilyl signal at δ_H 0.29 ppm and loss of the NH broad singlet (2-pyridone tautomer) at δ_H 13.7 ppm.



Scheme 2.19

Efforts to replicate the reaction conditions applied in the synthesis of the benzyne precursors were attempted using with *n*-butyllithium but did not result in formation of any desired product in going from **90** to **91**. This is presumably due to the fact that organolithium bases can alkylate the nitrogen in the pyridine ring. Instead, freshly prepared LDA was used successfully to form **91**, following a publication from Diaz *et al.*[42] The most characteristic feature for this compound in the ^{1}H NMR spectrum are the trimethylsilyl signal, which changes very little from the precursor, at δ_H 0.28 ppm and the appearance of a broad OH singlet at δ_H 13.0 ppm. The IR spectrum shows an absorption at ν_{max} 3074 cm^{-1} for the OH stretch.

Using sodium hydride and nonafyl fluoride, we are delighted to report 3-(trimethylsilyl)pyridin-2-yl-nonaflate **92** was isolated in 89% yield as a novel 2,3-pyridyne precursor. Characteristic features for this compound in the ^{1}H NMR spectrum is the trimethylsilyl signal at δ_H 0.38 ppm and the disappearance of the broad OH singlet at δ_H 13.0 ppm (**Figure 2.12**).

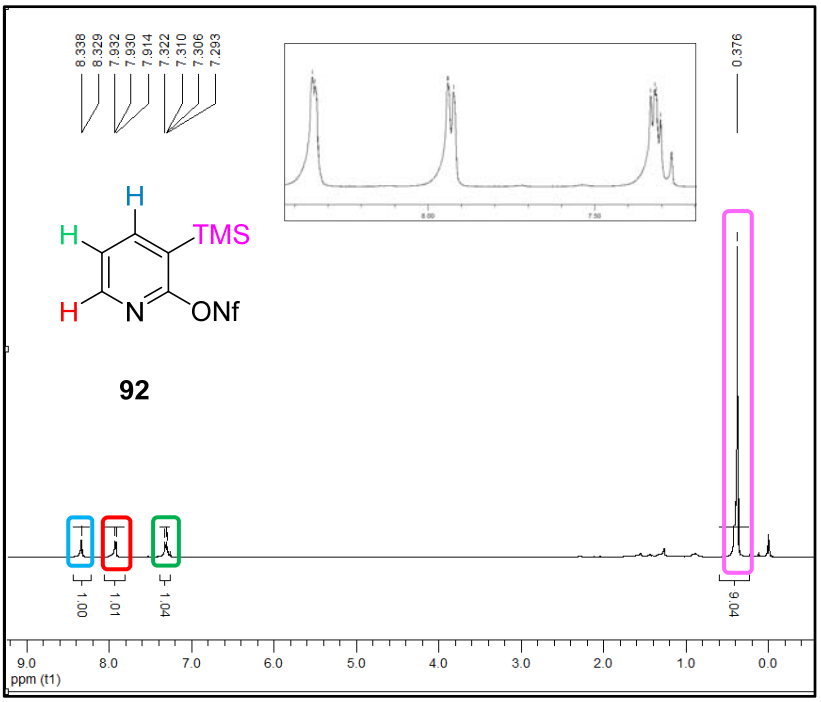


Figure 2.12 *^{1}H NMR spectrum of* ***92***

In the ^{13}C NMR spectrum, the signal for the trimethylsilyl group shifts upfield to δ_C -1.2 ppm and a 4C multiplet between δ_C 110.7 and 119.0 ppm is observed. In the ^{19}F NMR spectrum four signals are observed, confirming the presence of the nonafluorobutane group (**Figure 2.13**).

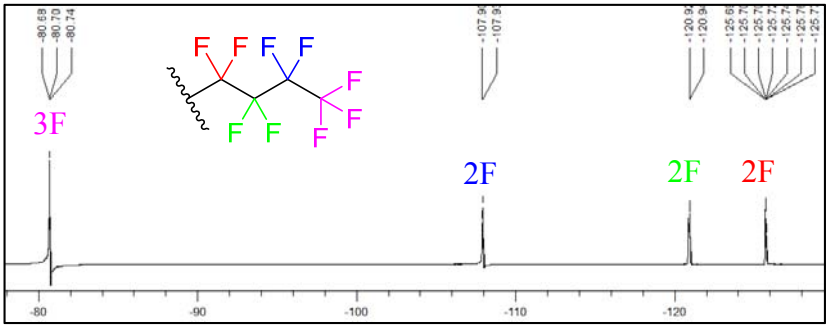
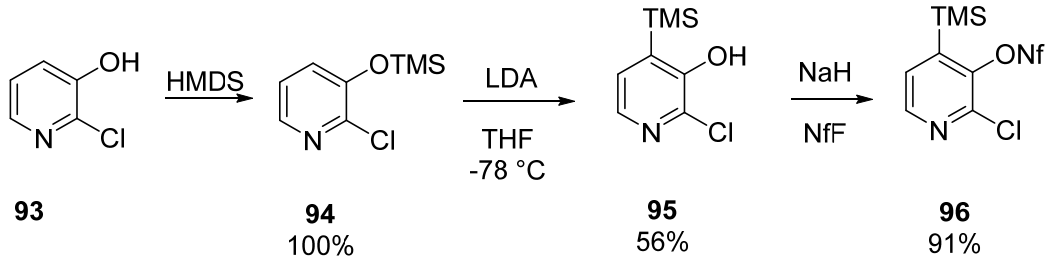


Figure 2.13 *^{19}F NMR* spectrum *of* ***92***

Pleasingly, another novel 3,4-pyridyne precursor, 2-chloro-4-(trimethylsilyl)pyridin-3-yl nonaflate, **96** was prepared similarly in three steps from 2-chloro-3-hydroxypyridine **93**. The first step was silylation using HMDS which provided **94** in quantitative yield. The most characteristic feature for this

compound in the ^{1}H NMR spectrum is the trimethylsilyl signal at δ_H 0.28 ppm and loss of the OH broad singlet at δ_H 10.75 ppm.



93 **94** 100% **95** 56% **96** 91%

Scheme 2.20

Using freshly prepared LDA, **95** was formed in moderate yield. The ^{1}H NMR spectra shows the trimethylsilyl signal at δ_H 0.33 ppm and the appearance of a broad OH singlet at δ_H 5.79 ppm. The IR spectrum shows an absorption at ν_{max} 3060 cm^{-1} for the OH stretch.

Using sodium hydride and nonafyl fluoride, **96** was isolated in an excellent yield of 91% as another novel pyridyne precursor (**Scheme 2.20**). The ^{1}H NMR spectrum of this compound displays just three signals, one at δ_H 0.43 ppm for the trimethylsilyl signal and two aromatic doublets. The disappearance of the broad OH singlet is also distinctive (**Figure 2.14**).

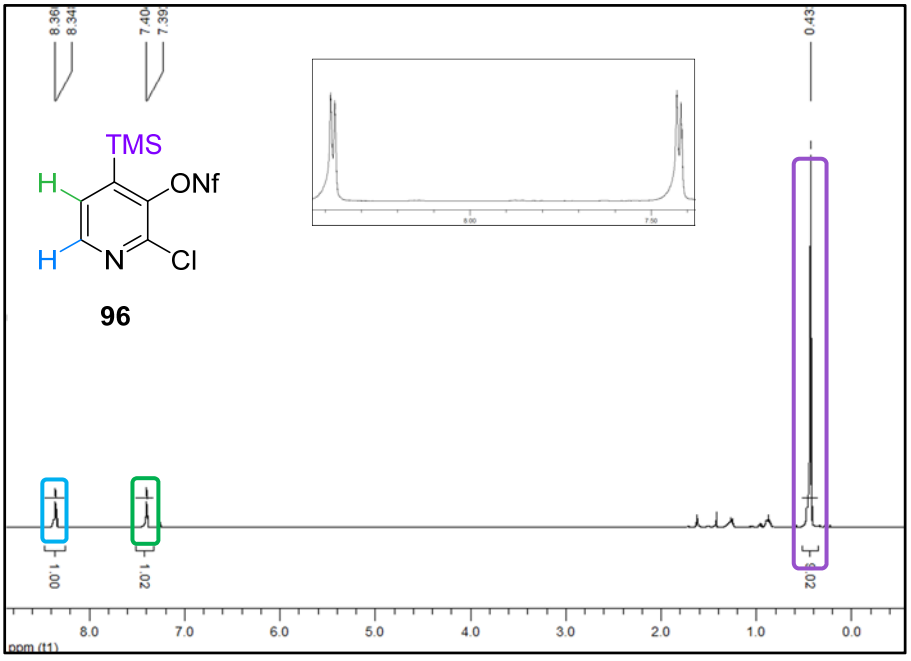


Figure 2.14 *^{1}H NMR* spectrum *of* ***96***

In the ^{13}C NMR spectrum, the signal for the trimethylsilyl group shifts upfield to δ_C -0.29 ppm and a 4C multiplet is seen between δ_C 109.6 and 118.7 ppm. In the ^{19}F NMR spectrum, four signals are present confirming the presence of a nonafluorobutane group again.

To summarise, in this section three aryne precursors were prepared in the form of 2-trimethylsilylaryltriflates using Peña's methodology.[31] Five aryne precursors were prepared using Ikawa's methodology[37] in the form of 2-trimethylsilylphenol derivatives, which could be used to generate arynes *in situ* *via* 2-trimethylsilylarylnonaflates and two novel pyridyne precursors were synthesised, using Ikawa's methodology again, while also isolating the pyridine-nonaflates.

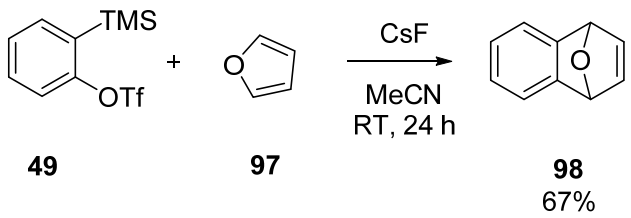
In total this provided 10 dipolarophiles for the cycloaddition reactions with our 22 previously described diazo 1,3-dipoles, and will be discussed in the following sections.

2.4 Synthesis of 1-acyl-1*H*-indazole compounds using Method 1

This section describes the initial [3+2] cycloaddition reactions performed to prepare indazole derivatives using diazo dicarbonyl derivatives and aryne derivatives. A procedure reported by Larock and co-workers was initially used to generate arynes *in situ* and react them with diazo derivatives to form indazole compounds.[5]

2.4.1 Generation of aryne and trapping with furan

To gain familiarity with the methodology put forward by Larock for aryne generation, a Diels-Alder trapping reaction with furan **97** was performed[5] with the aryne precursor 2-trimethylsilylphenyltriflate **49** and caesium fluoride in acetonitrile to provide **98** (**Scheme 2.21**).



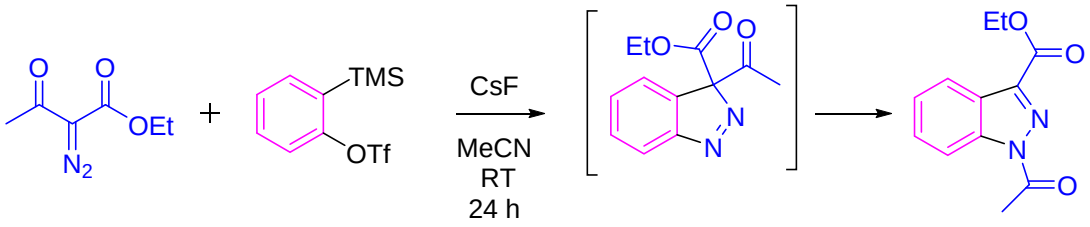
49 **97** **98** 67%

Scheme 2.21

Following column chromatography on silica gel, the symmetrical cycloadduct product **98** was isolated. This derivative showed four characteristic signals in the ^{1}H NMR spectrum including the alkenyl proton singlet at δ_H 5.71 ppm. All analysis is consistent with literature data,[43] verifying initial formation of an aryne under these conditions and isolation of a cycloaddition product in a moderate yield of 67%. Confident in using this methodology, initial indazole forming reactions under the same conditions and using the same stoichiometry were performed.

2.4.2 Synthesis of 1-acyl-1*H*-indazole compounds

Larock had investigated [3+2] cycloaddition reactions of arynes with just one α-diazo β-ketoester **19** and they reported the formation of product **99**, exclusively and in good yield after the initial cycloadduct **100** had undergone acyl migration (**Scheme 2.22**).[5]



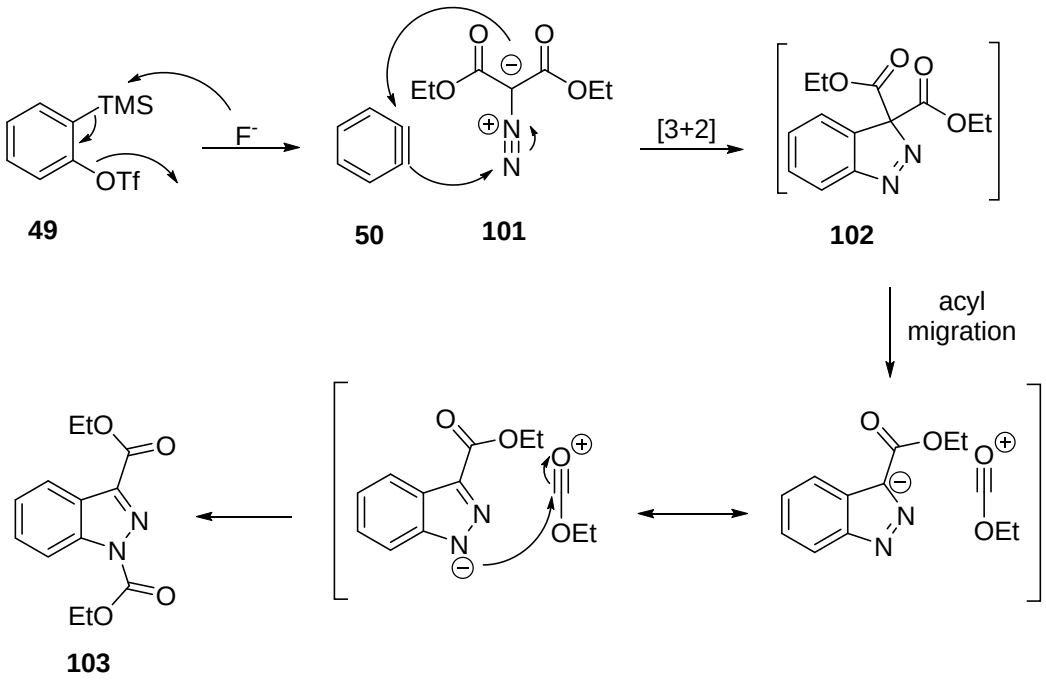
19 **49** **100** **99** 90%

Scheme 2.22

2.4.2.1 1-Acyl-1*H*-indazole-3-carboxylate derivatives

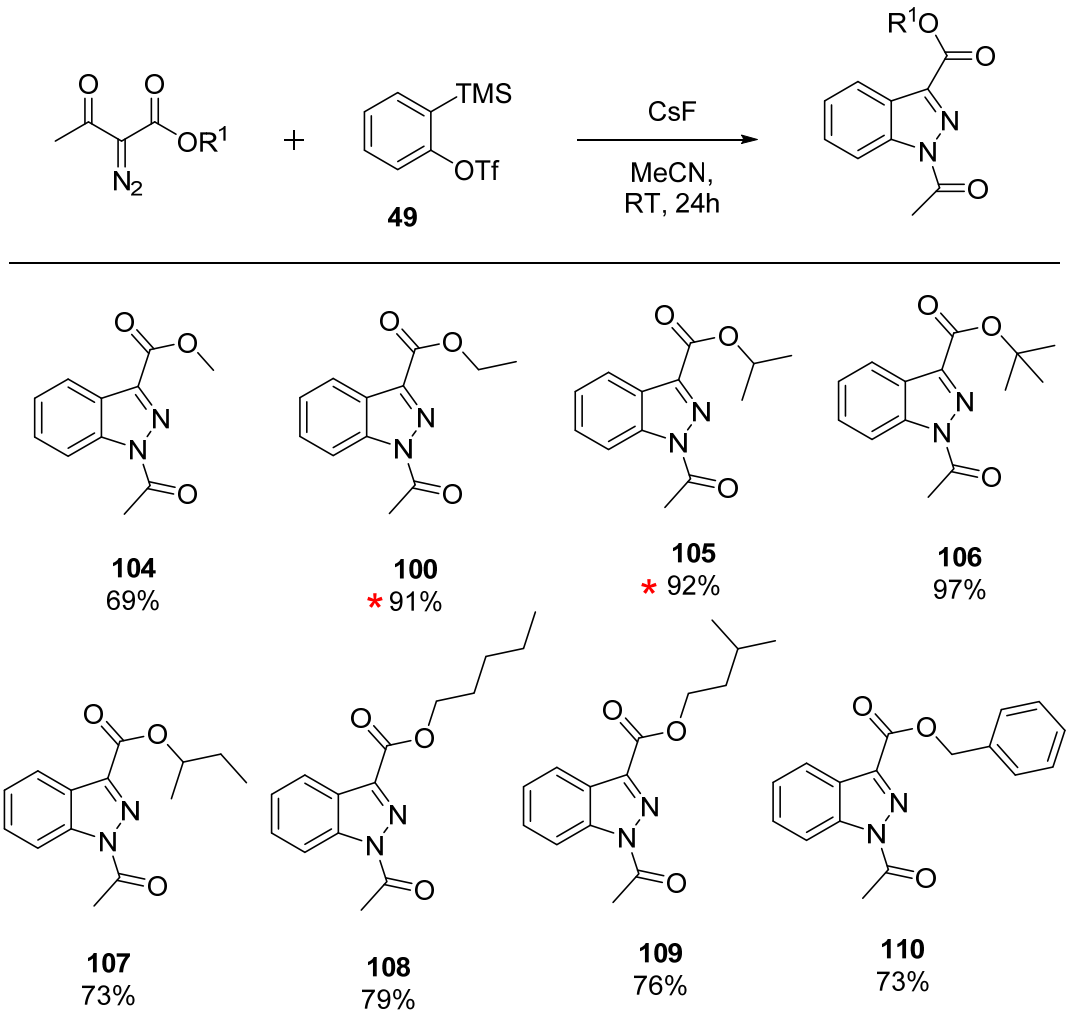
In the mechanism postulated by Larock (**Scheme 2.23**), the fluoride ion displaces the trimethylsilyl group on **49**, forming the aryne **50** as the triflate leaving group is lost. The aryne **50** and diazo 1,3-dipole **101** then undergo cycloaddition in a concerted fashion to form the initial 3,3 disubstituted intermediate **102**.[5]

The acyl migration step has been suggested to proceed by a "dissociation-ion pair intermediate-recombination" process where **102** dissociates to an ion pair, which can recombine to form the desired product **103**. The driving force for formation of the acyl-migration product is probably re-aromatisation of the indazole from the partially-aromatic 3,3-disubstituted cycloadduct.[5,44]



Scheme 2.23

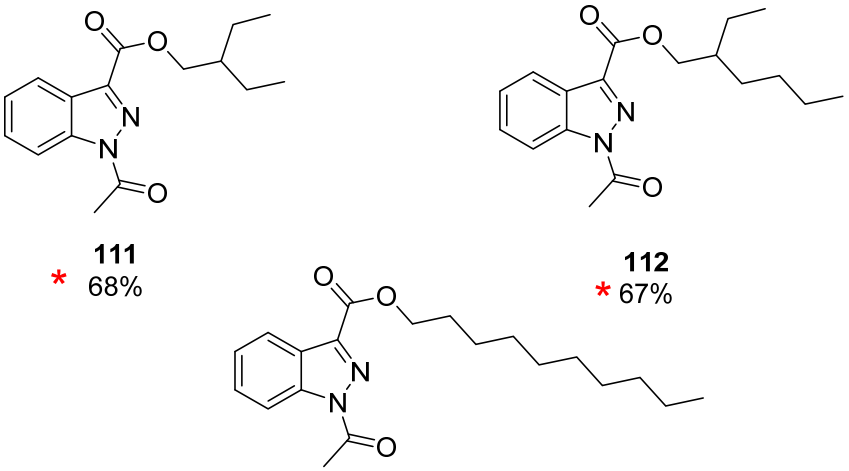
Following on from Larock's initial work,[5] a series of novel indazole products were prepared in this project from the wide-range of α-diazo-β-ketoesters, α-diazo-β-ketoamides and β-diketones previously synthesised within the laboratory.



*Presence of by-product detected

Figure 2.15 *Initial series of indazole compounds prepared*

The initial indazole derivatives prepared (**Figure 2.15**) have an *N*-acetyl group in the 1-position and the variable component was the ester functionality. The spectral details of **104** and **100** were consistent with those reported in the literature.[5,45] **105-110** are novel derivatives, some of which show interesting biological activity (will be discussed in **Section 2.10**). **Figure 2.16** shows the following series where the ester side chain was extended in length to provide novel indazole derivatives **111-113**.



*Presence of by-product detected

Figure 2.16 *Extending the length of the ester side chains*

The reaction conditions were mild and proceeded at room temperature stirring for 24 h. Although the literature procedure reported a hexane-ethyl acetate solvent system for column chromatography on silica gel purification, it was found that by changing the eluent to 95:5 dichloromethane-ethyl acetate, the solvent volume was reduced from *ca.* 1.5 L to less than 200 mL and the time required for purification decreased greatly.

The indazole compounds were visible under UV light on TLC silica gel plates as bright purple spots while the starting material diazo compounds showed up as dark red spots which eluted after the desired products were isolated. For the *t*-butyl derivative **106**, the desired product was obtained in high purity after the workup.

^{1}H NMR analysis showed a downfield shift of signals of *ca.* 0.2 ppm for substituents in close proximity to the indazole heterocyclic core but for bulkier substituents, this effect decreased the further away the group is from the indazole core. The aryl region contained four distinctive signals from δ_H 7.45-8.47 ppm in all compounds and was similar to the peaks observed by Larock for ethyl 1-acetyl-1*H*-indazole-3-carboxylate **100**.[5] All *N*-acetyl derivatives contained a distinct 3H singlet in the ^{1}H NMR spectra at δ_H 2.87 or 2.88 ppm for the acetyl group.

Characteristic absorption bands in the IR spectra were observed between ν_{max} 1716 -1736 cm^{-1} and ν_{max} 1618-1670 cm^{-1} for the ester carbonyl and amide carbonyl functional groups respectively. **Figure 2.17** shows the ^{1}H NMR spectra of the *t*-butyl 2-diazo-3-oxobutanoate **21** in comparison to *t*-butyl 1-acetyl-1*H*-indazole-3-carboxylate **106**. There is a notable downfield shift of the *t*-butyl substituent of the diazo compound in comparison to the *t*-butyl substituent of the indazole and of the the acyl group which is now in the *N*-1 position of the indazole. The four aromatic signals are also distinctive.

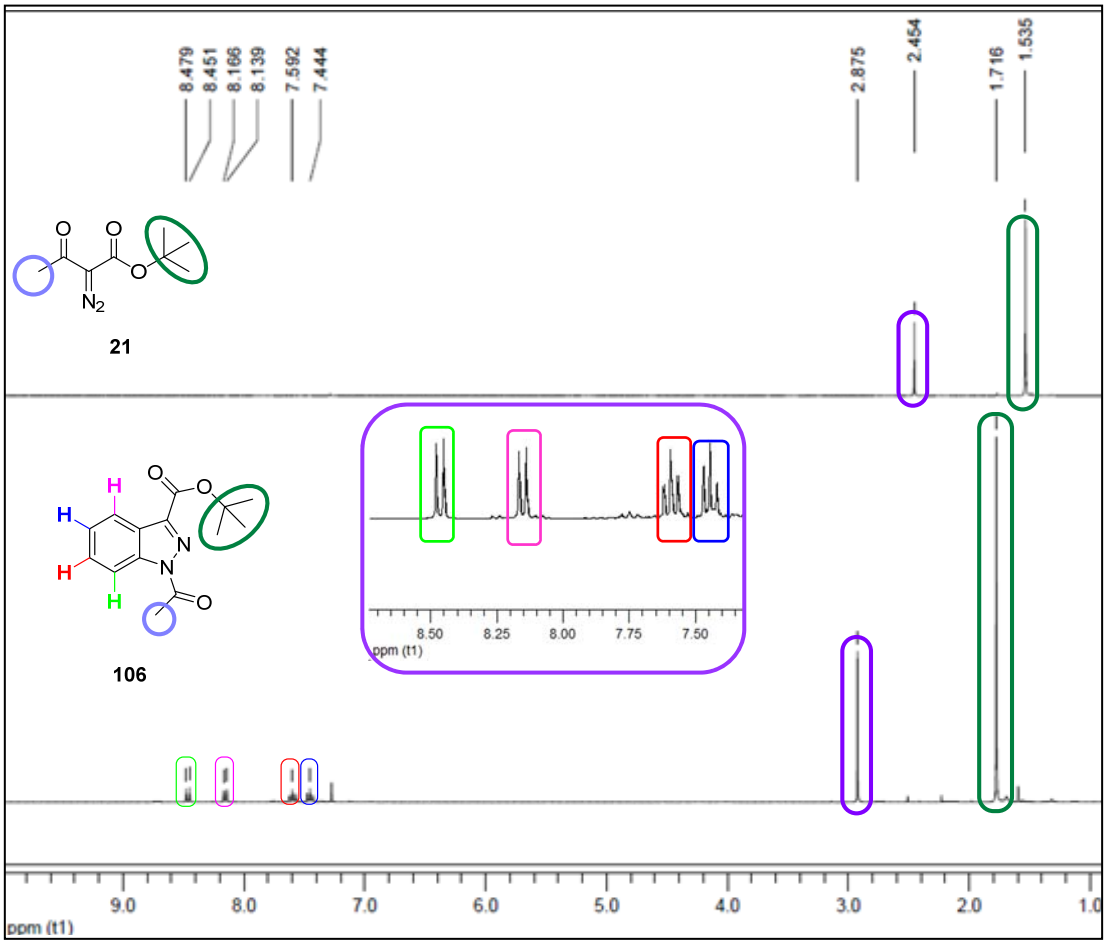


Figure. 2.17 *^{1}H NMR spectra of diazo **21** and indazole **106***

As indicated in **Figure 2.15** and **Figure 2.16**, the presence of an *N*-aryl by-product was detected for some reactions that had distinctive signals in the aromatic region of the ^{1}H NMR spectra. Following the procedure reported by Larock,[5] eleven 1,3-disubstituted indazole deriatives were isolated in high purity and good

yields. However, for six derivatives, **99**, **105**, **111**, **112**, **125** and **126** (**125** and **126** seen later), the aromatic region of the ^{1}H NMR spectra contained peaks belonging to an *N*-aryl by-product which is present in amounts from 4-10%. An example of the ^{1}H NMR of **111** contaminated with by-product **114** is shown in **Figure 2.18**. Unfortunately, the by-product could not be separated from the *N*-acyl products but they were isolated and characterised at a later stage (**Section 2.7**).

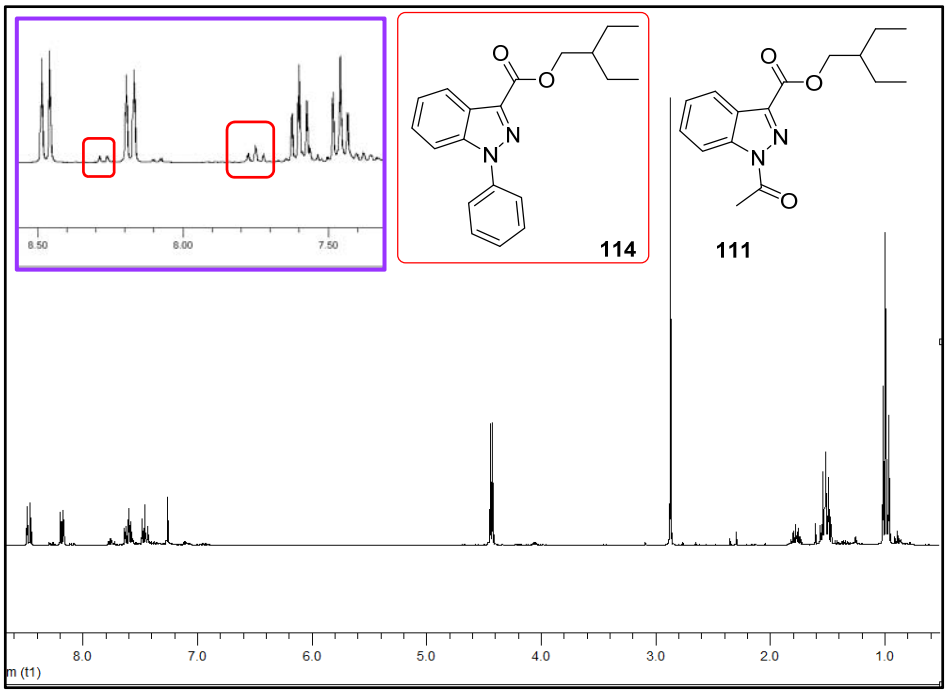
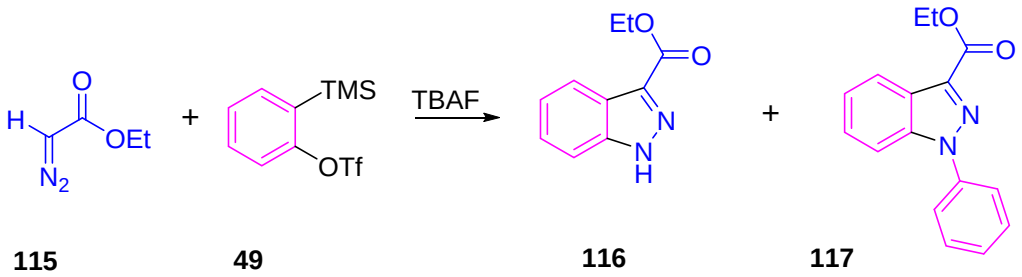


Figure 2.18 *Evidence of N-aryl by product being present (in red)*

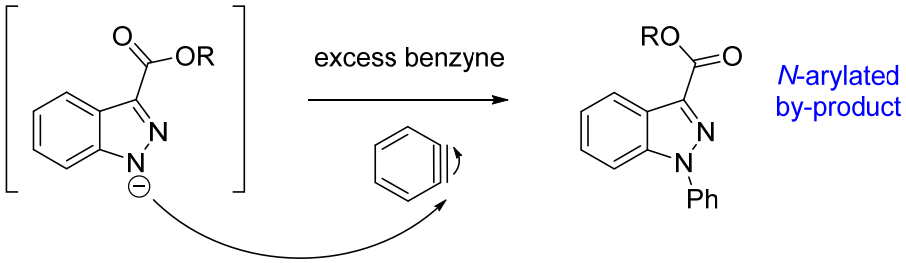
These *N*-aryl compounds were reported by Larock on use of mono-substituted diazo carbonyl derivatives (**Scheme 2.24**).[5] Changing the equivalents of the aryne precursor could influence the formation of the products formed.



Scheme 2.24

Evidence for this *N*-aryl product **117** could be seen in small amounts in the ^{1}H NMR spectra of the supplementary material with the original Larock

publication for their diazo dicarbonyl cycloadditions.[5] In comparison to some spectra obtained in this work, however, the by-product is present in amounts varying from 4 to 10% and 20% for one example, was seen in ^{1}H NMR analysis, even though the procedure was carried out using the exact same stoichiometry. The formation of the by-product is most likely due to the reaction of the ion pair with excess free benzyne (**Scheme 2.25**), generated during the acyl migration step in the proposed mechanism as described previously in **Scheme 2.23**.



Scheme 2.25

Separation of the *N*-aryl compounds from the *N*-acyl derivatives proved unsuccessful for these 6 derivatives by column chromatography on silica gel at this stage in the synthesis. Modifying the stoichiometric amounts using excess diazo dicarbonyl starting material resulted in a limit to the formation of the *N*-aryl by-product. This excess diazo material could be recovered after the reaction had gone to completion.

The mechanism proposed does not account for how the *N*-2 position does not lead to arylation in this pathway. If one of the intermediate anions formed has the negative charge on the *N*-1 position, the electrons could delocalise onto the *N*-2 position leading to arylation of the 2-position (**Figure 2.19**).[46-48] The lack of evidence of any *N*-2 reactivity could possibly be accounted for by the higher stability of the benzenoid *N*-1 tautomer over the quinonoid *N*-2 tautomer and fast arylation of the intermediate.

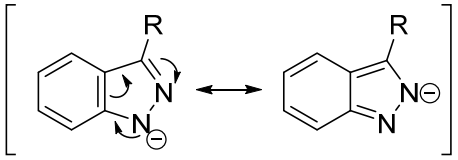
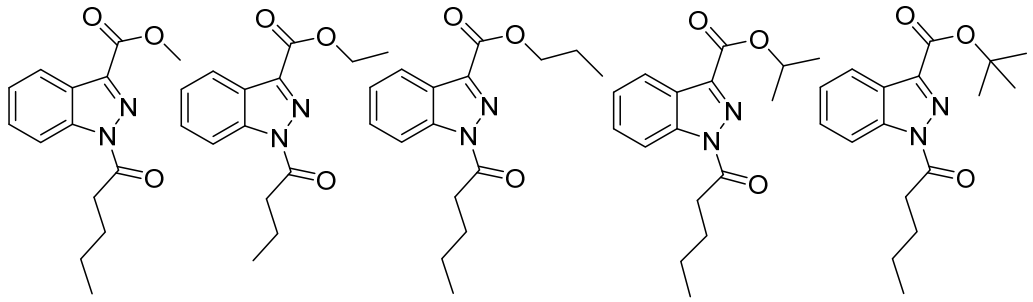


Figure 2.19 *Indazole tautomeric forms*

From work in this project it is thought that the use of excess fluoride ion as the desilylating aryne generator may possibly be involved in the by-product formation by deacylating the *N-1* position. Due to the low solubility of caesium fluoride in acetonitrile it was preferred to keep it in excess along with the diazo dicarbonyl derivative and to have the aryne precursor as the limiting reagent.

The next series of indazoles were prepared using α-diazo β-ketoester derivatives containing extended ketone side-chains. This was an important part of the project as it was not known in advance if the initial cycloadduct would undergo acyl migration as efficiently (or at all) as with the acetyl group to provide *N*-acyl indazoles with longer *N*-acyl side chains. Pleasingly, the cycloaddition reactions successfully provided five novel *N*-acyl indazoles **118-122** in moderate to good yields (**Figure 2.20**).



118 83% **119** 92% **120** 67% **121** 64% **122** 72%

Figure 2.20 *Extending the length of the N-1 amide side chains*

The ^{1}H NMR spectra for this series showed the derivatives in high purity with no observable by-product signals. This may be due to the decision taken to alter the stoichiometry of the reagents keeping the aryne precursor as the limiting reagent or perhaps the lengthened *N*-acylium ions are stronger electrophiles than *N*-acetylium ions. A common structural feature evident in the ^{1}H NMR spectra for these derivatives includes a distinct 2H triplet in the narrow range between δ_H 3.30-3.32 ppm for the CH_2 adjacent to the amide carbonyl. The aromatic region for **122** is completely clear of any signs of the *N*-arylated by-product (**Figure 2.21**).

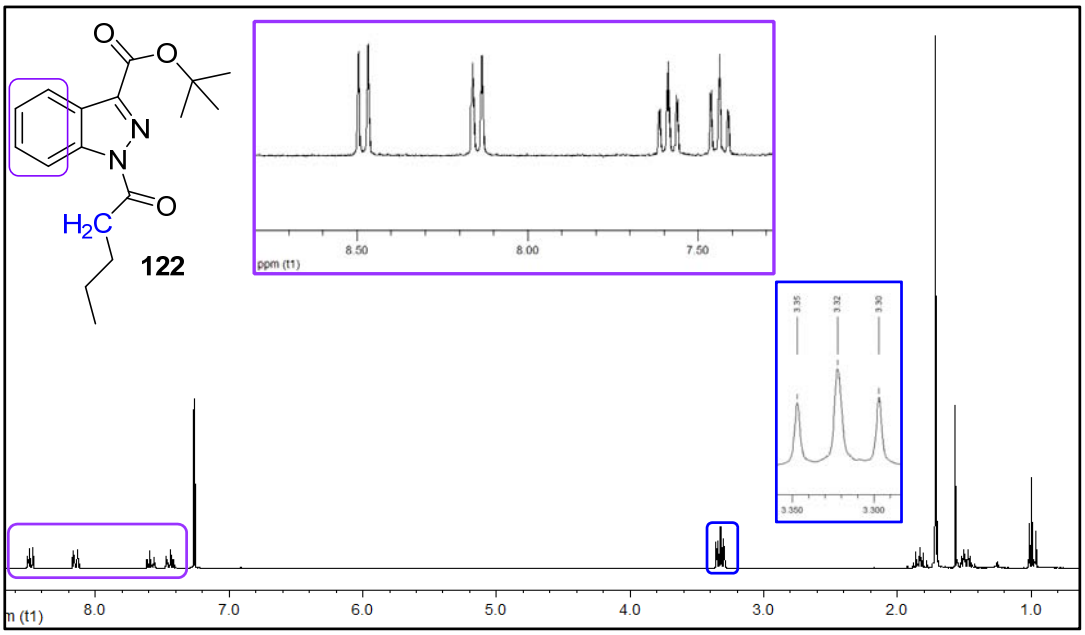


Figure 2.21 *^{1}H NMR* spectrum *of **122***

Similarly, the cycloaddition reactions with aryl ketone diazo derivatives successfully prepared two benzamide indazole derivatives, novel **123** and **124** (**Figure 2.22**). Though there are more aromatic protons to describe, the aromatic region is free from any evidence of the *N*-aryl by-product (**Figure 2.23**). Spectral details for **124** were not included in the literature reference.[49]

123
68%

124
71%

Figure 2.22 *Benzamide side chain derivatives*

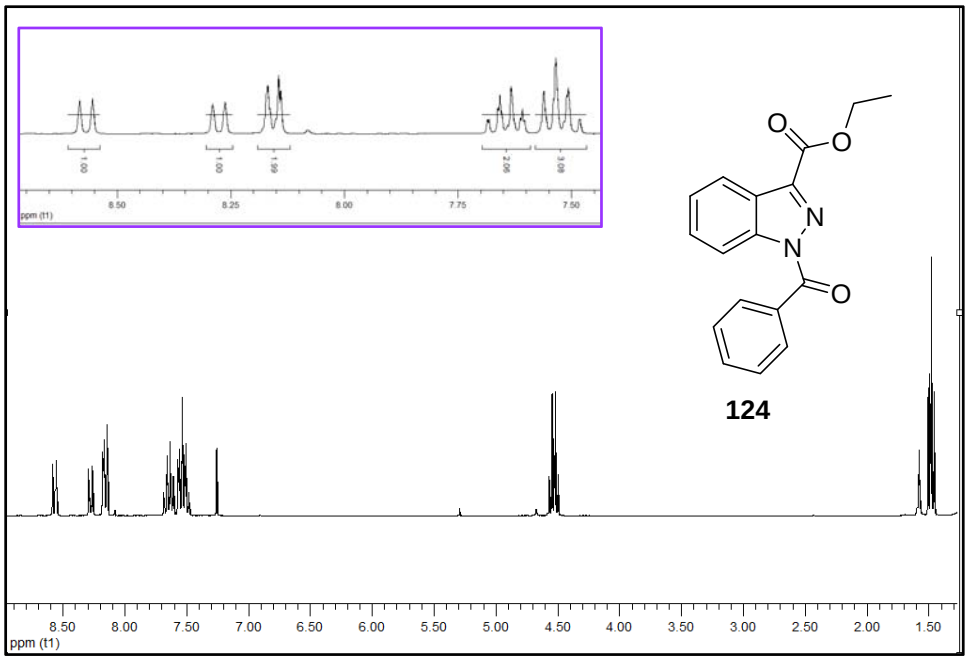
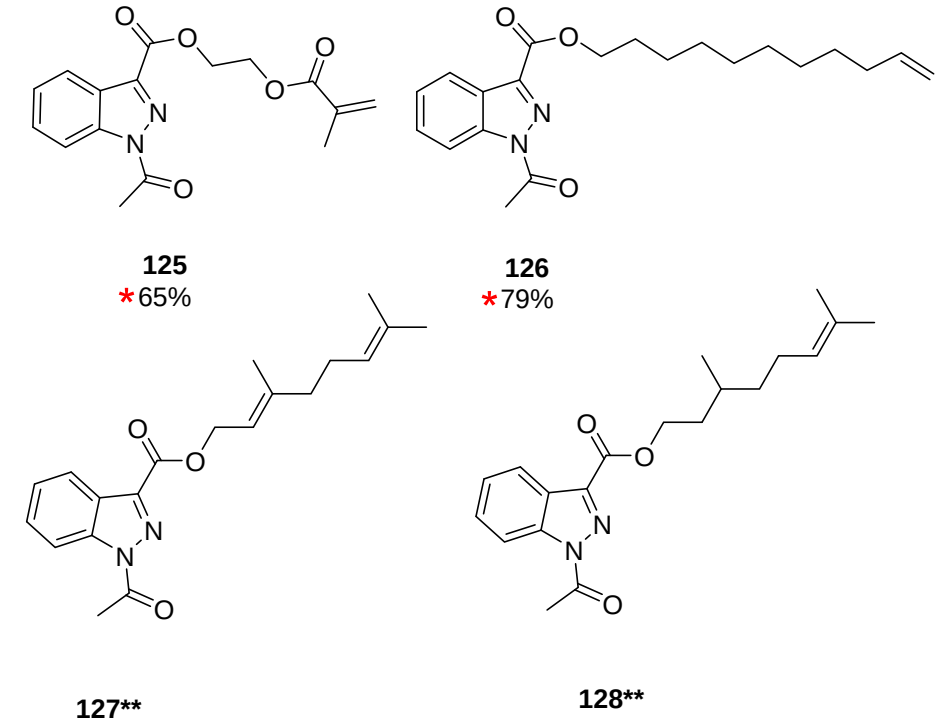


Figure 2.23 *^{1}H NMR* spectrum *of* ***124***

The next series prepared incorporated functionalised ester side chains (**Figure 2.24**). It was thought that problems with these derivatives may be encountered as the alkene functionality could also potentially participate in ene reactions or a [2+2] cycloaddition reaction with the aryne species. The first two derivatives **125** and **126** did not present any problems except for the *N*-aryl by-product formation in both cases.

The ^{1}H NMR spectrum of the crude material of the next two derivatives **127** and **128**, however, showed the presence of a complex mixture of unidentifiable material along with some desired product characteristic to the *N*-acetyl indazole derivatives. Purification by column chromatography on silica gel and preparative thin-layer chromatography on silica gel was unsuccessful in isolating the desired compounds.



*by-product detected **unable to isolate in a pure state

Figure 2.24 *Further indazole derivatives prepared*

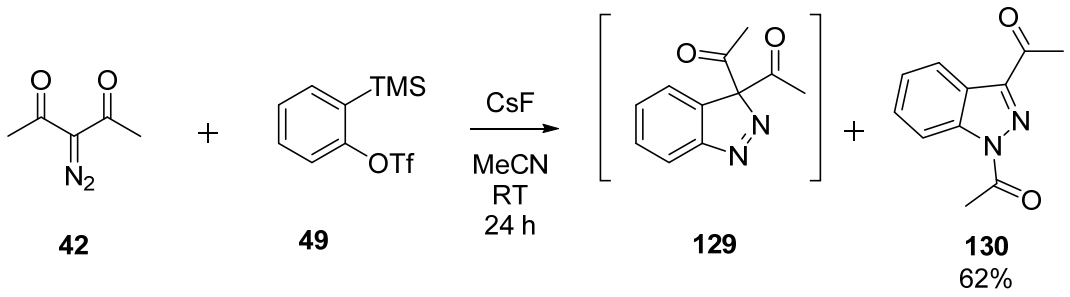
A total of 17 novel indazoles were isolated in high purity and good yields from this series of cycloadditions. The last two derivatives **127** and **128** will be discussed again in **Section 2.5.2** using "Method 2" of aryne generation.

Future work here could involve increasing the equivalents of aryne precursor to selectively form the *N*-aryl compound as the major product. *N*-Aryl heterocycles are found in many bioactive compounds and natural products but conventional methods for their preparation such as nucleophilic substitution of aryl halides have limitations for their general application.[50,51] Some *N*-aryl indazole derivatives were isolated and characterised at a later stage (**Section 2.7**).

2.4.2.2 1-Acyl-1*H*-indazole-3-one derivatives

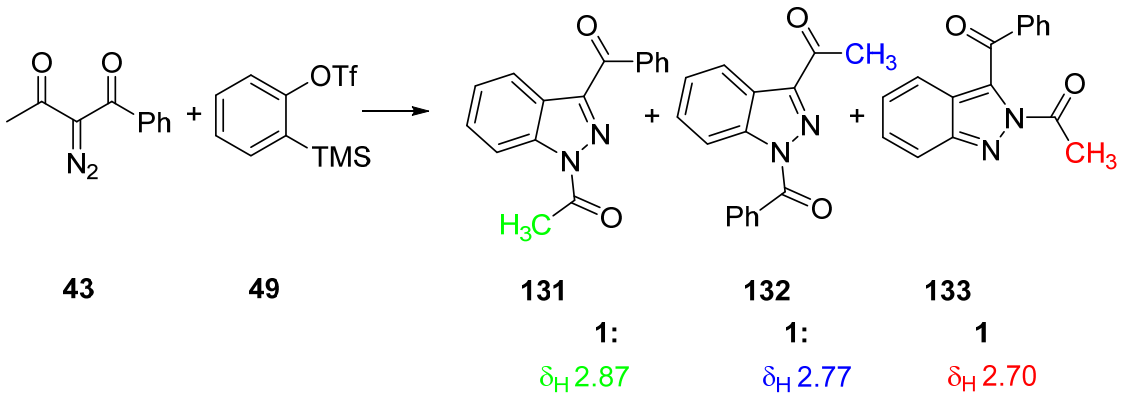
Two cycloaddition reactions using α-diazo-β-diketones and aryne precursor were also performed during this project and are now described. The investigation into using α-diazo-β-diketones substrates in cycloaddition reactions is interesting as with the α-diazo-β-ketoesters, the sole ketone group of the initial cycloadduct migrates in preference to the ester group.

The first reaction explored uses α-diazo-β-diketone **42** and is also reported in the literature.[5] The 3,3-disubstituted cycloadduct **129** was the expected product before the acyl migration step was shown to be a common pathway. On analysis of **130** it was quickly seen to be a 1,3-disubstituted adduct as the ^{1}H NMR spectrum contains two inequivalent CH_3 signals at δ_H 2.77 and 2.87 ppm and the ^{13}C NMR spectra has two distinct carbonyl signals at δ_C 171.3 and 195.1 ppm for an amide and ketone functional group. The compound also showed two characteristic absorptions in the IR spectra at ν_{max} 1727 and 1686 cm^{-1} for both ketone and amide carbonyl groups. This reaction proceeded smoothly to give **130** in 62% yield (**Scheme 2.26**).



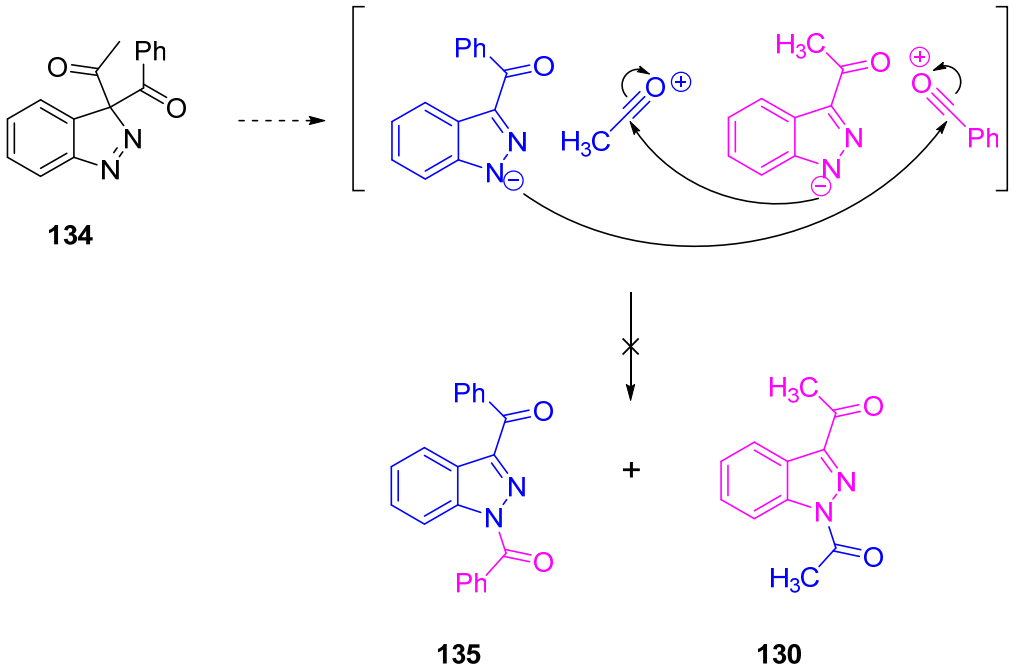
Scheme 2.26

The use of diazo compound **43** in the cycloaddition reaction however, resulted in a mixture of inseparable isomers (**Scheme 2.27**). As already stated, ketone groups have been shown to migrate preferentially in comparison to ester groups, but when two inequivalent ketone groups are present, either can migrate.[5] For this reaction, the mixture could not be separated and the acyl group chemical shift value was used to try to assign which compounds are present. Two possible products would be expected from this reaction: **131** and **132**, but three distinct CH_3 signals are present in the ^{1}H NMR spectrum. The acyl peak at δ_H 2.87 is attributed to **131** and the one at δ_H 2.77 is assigned to **132** from comparing the values to **130** which had those exact numbers for similar signals. The third acyl signal at δ_H 2.70 ppm is assigned to an *N-2*-acyl indazole **133** on comparison to amide derivatives that will be described in a later section (**Section 2.4.2.3**). 2-Acyl 2*H*-indazole derivatives have been mentioned in the literature previously using the zwitterion of anthranilic acid to generate an aryne, and a diazo group bearing an acyl group to give both 1-acyl and 2-acyl migration products depending on the substrate.[44]



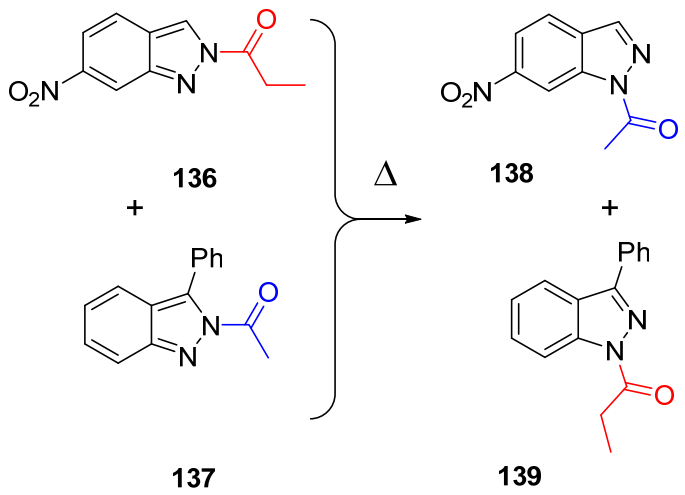
Scheme 2.27

The fact that there is no evidence of a dibenzoyl indazole **135** or diacetyl indazole **130** being formed (**Scheme 2.28**) suggests that perhaps there is more to the postulated mechanism of acyl migration described earlier where ion pairs dissociate and recombine.



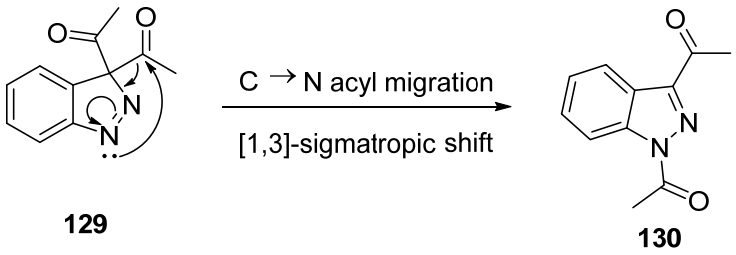
Scheme 2.28

Evidence for the ion-pair pathway includes where cross-over products were reported in the literature when a mixture of 2-acyl indazoles **136** and **137** are heated to form 1-acyl indazole derivatives **138** and **139** (**Scheme 2.29**), however, this only shows nitrogen to nitrogen migration.[44]

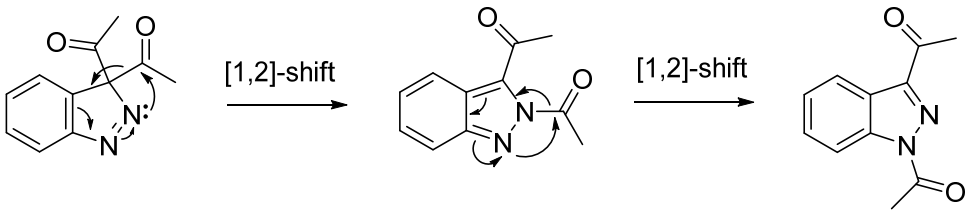


Scheme 2.29 *Cross-over products formed on heating*

Possibly, for the substrates in this project, the mechanism could involve an intramolecular [1,3]-acyl carbon to nitrogen shift (**Scheme 2.30**) or possibly two [1,2] carbon to nitrogen and then nitrogen to nitrogen shifts (**Scheme 2.31**).[44,52-54]



Scheme 2.30 *Postulated [1,3]-sigmatropic rearrangement*

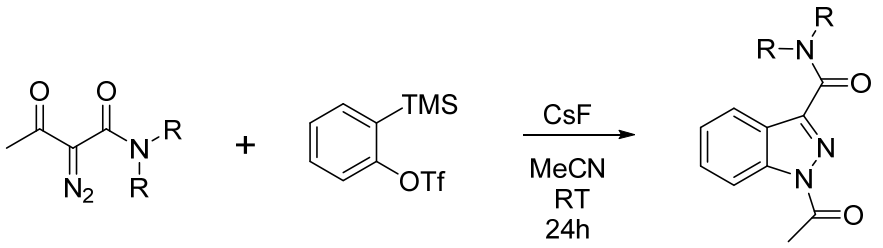


Scheme 2.31 *Postulated two successive [1,2]-sigmatropic rearrangements*

2.4.2.3 1-Acyl-*N*,*N*-disubstituted-1*H*-indazole-carboxamide derivatives

This section describes the use of α-diazo-β-ketoamides in the cycloaddition reactions with the arynes. Amides are abundant in nature and are also present in a number of well-known drug compounds such as penicillin, LSD and atorvastatin. It was thought that the replacement of the ester group with an amide moiety in the indazole would increase the anti-cancer activity of the indazole derivatives (will be discussed further in **Section 2.10**). It was also of interest to investigate the migratory aptitude of the amide group in comparison to the ester group as there is one example in the literature where the amide group was reported to migrate in a similar fashion to ester groups.[5]

The initial reactions of the aryne precursor **49** with the α-diazo-β-ketoamides **44** and **45** under the optimised conditions yielded 1,3-disubstituted indazole products **140** and **141** as expected (**Scheme 2.32**).



44 R = Me

45 R = Et

49

140 R = Me 84%

141 R = Et 95%

Scheme 2.32

The ^{1}H NMR spectra contains the characteristic aromatic hydrogen signals from δ_H 7.41-8.44 ppm as well as the *N*-acyl group CH_3 at δ_H 2.78 and 2.79 ppm for the dimethyl and diethyl derivatives respectively (**Figure 2.25**).

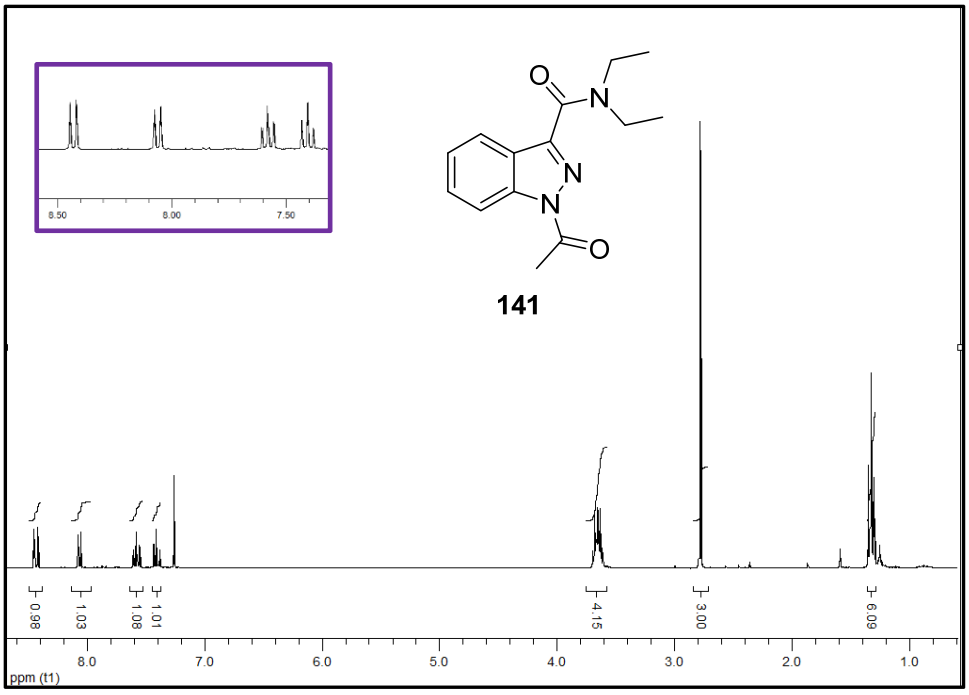


Figure 2.25 *^{1}H NMR* spectrum *of **141***

The absence of a ketone carbonyl signal in the ^{13}C NMR spectra and the observation of similar derivatives in the literature,[5,45] prepared by alternative synthetic routes, to give 1-acyl-3-carboxamide indazole derivatives with similar *N*-acetyl chemical shifts (at δ_H 2.78 ppm) confirmed the formation of 1-acyl-3-carboxamide derivatives **140** and **141** (**Figure 2.26**). Another characteristic set of signals in the ^{1}H NMR spectrum of **140** are at δ_H 3.23 and 3.36 ppm for the inequivalent sets of CH_3 groups on the nitrogen.

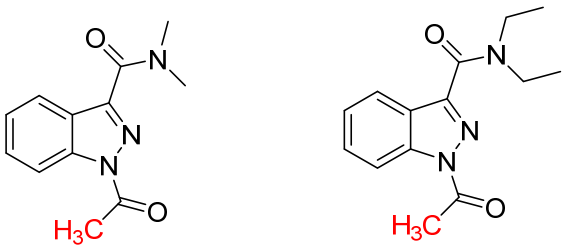


Figure 2.26 *Carboxamide indazole derivatives prepared*

Interestingly, these *N*-acyl CH_3 chemical shift values are quite similar to the value of the ketone CH_3 group in the 1-acyl-1*H*-indazole-3-one example **141**. This information, coupled with the observation of sharp absorptions in the infrared spectra at ν_{max} 1724-1726 and 1631-1634 cm^{-1}, initially suggested that for these

derivatives migration was not occurring to form the cycloadduct **142** or perhaps the amide group was migrating in preference to the ketone to form **143** (**Figure 2.27**), however, we now know this is not the case. The *N*-acyl amide carbonyl can be described as an 'unexpressed amide' where the nitrogen is part of a heterocyclic ring and therefore the lone pair is not involved in energy resonance to the carbonyl.[55]

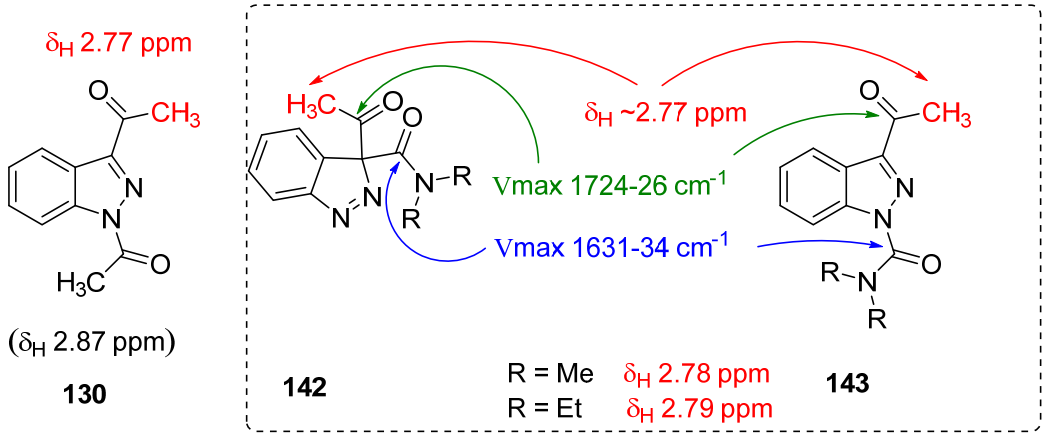
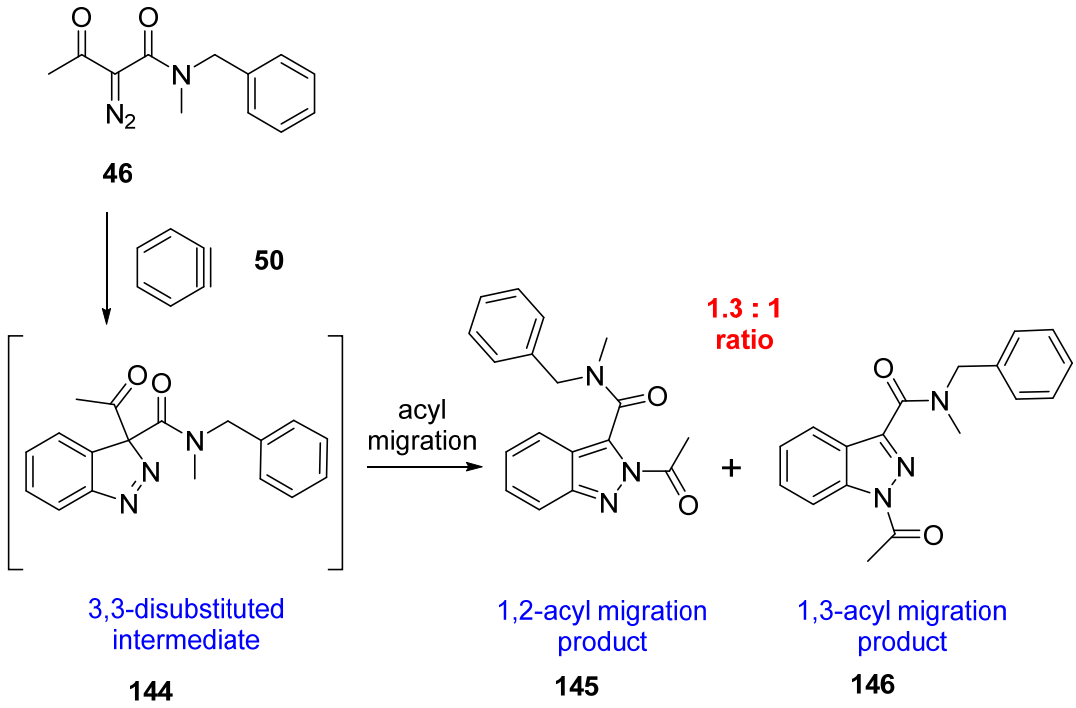


Figure 2.27 *Comparison of **130** to potential products **142** and **143***

The next derivative to undergo the cycloaddition reaction was *N*-benzyl-2-diazo-*N*-methyl-3-oxobutanamide **46**, where some interesting results were observed, as shown in **Scheme 2.33**. Firstly, there was a doubling up of signals in the aliphatic region of the ^{1}H NMR spectra for the *N*-acyl CH_3 and NCH_3 groups and the aromatic CH signals integrated for two protons rather than one. In the ^{13}C NMR spectra this duplication was repeated.



Scheme 2.33

Initially it was thought that the compound had only partially undergone acyl migration but the absence of a ketone carbonyl signal in the ^{13}C NMR spectrum suggests that the derivative may have undergone a 1,2-acyl migration in addition to a 1,3-acyl migration rearrangement. The major isomer is tentatively assigned as the 1,2-product **145**, as deduced from the integration of the ^{1}H NMR spectra signals (the mixture was inseparable) as well as the acyl CH_3 chemical shift appearing at δ_H 2.78 ppm for the minor isomer, attributed to the 1-acyl derivative by analogy to **140** and **141** (**Figure 2.28**).

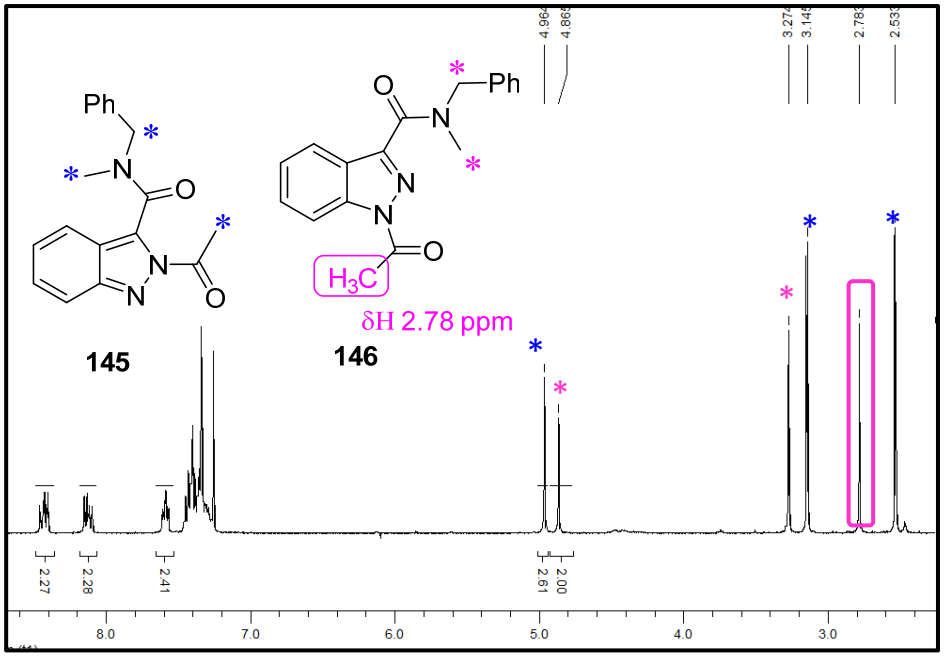
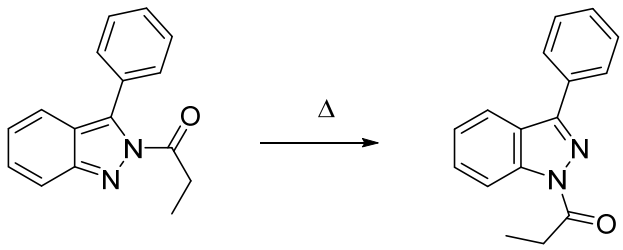


Figure 2.28 *^{1}H NMR spectrum of inseparable mixture of* ***145/146***

It was reasoned that it might be possible to induce the formation of the 1,3-acyl migration product **146** by heating the mixture, after reviewing a paper published by Baum which revealed that heating 2-acyl-indazole **147** led to formation of the 3-acyl product **148** (**Scheme 2.34**).[44]

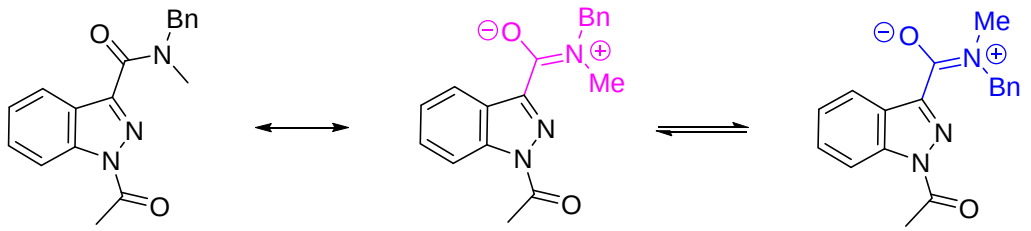


147 **148** 100%

Scheme 2.34

Efforts to force the migration of the acyl group by heating the mixture of **145** and **146**, however, were unsuccessful and even over a period of many months the ratio of products stayed consistent. As a result of this, more research into this compound was undertaken and it is now believed that the duplication of signals may actually be due to the presence of rotamers. The amide bond has sufficient double bond character between the carbonyl and nitrogen that restricts rotation about the C=N axis (**Structure 2.1**). The energy barrier of the rotation may be

relatively high and rotation will be slow enough for two distinct sets of signals to be observed. The more upfield signals in the ^{1}H NMR spectra usually corresponds to the *cis*-rotamer and the relative proportion of each rotamer is determined by both electronic factors and the relative sizes of the attached groups.[56]



Structure 2.1 *Partial double bond character of 3° amide leads to exhibition of two rotameric forms*

A fraction isolated during column chromatography on silica gel was a 1:1 mixture of the *N*-aryl by-products **149** and **150** (4%) of these derivatives (**Figure 2.29**) or indeed, the *N*-aryl by-product of both rotameric forms of **149**. This was interesting as the *N*-aryl by-products of the indazole carboxylate derivatives were unable to be isolated from the *N*-acyl-3-carboxylate derivatives (**Section 2.4**) at that stage.

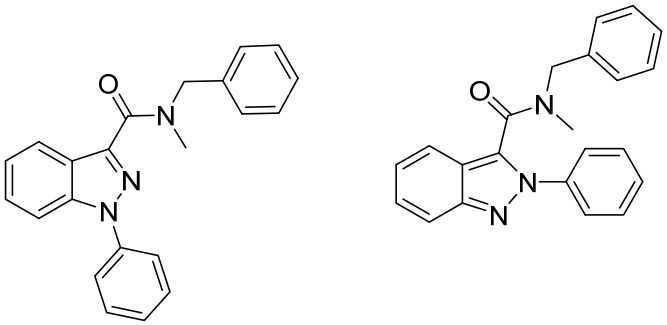


Figure 2.29 *N-aryl by-products **149** and **150***

The next substrate investigated was α-diazo-β-ketoamide **47** that gave another interesting result. The acetyl group shifts downfield by the standard distance of ~0.2 ppm from δ_H 2.42 in **47** to 2.65 ppm in **151**, seen previously for 1-acyl indazole derivatives, although it is a lower value than expected. Most noticeably, however, is the upfield shift of the aromatic signals in comparison to the range of 1-acyl indazoles seen previously (**Figure 2.30**).

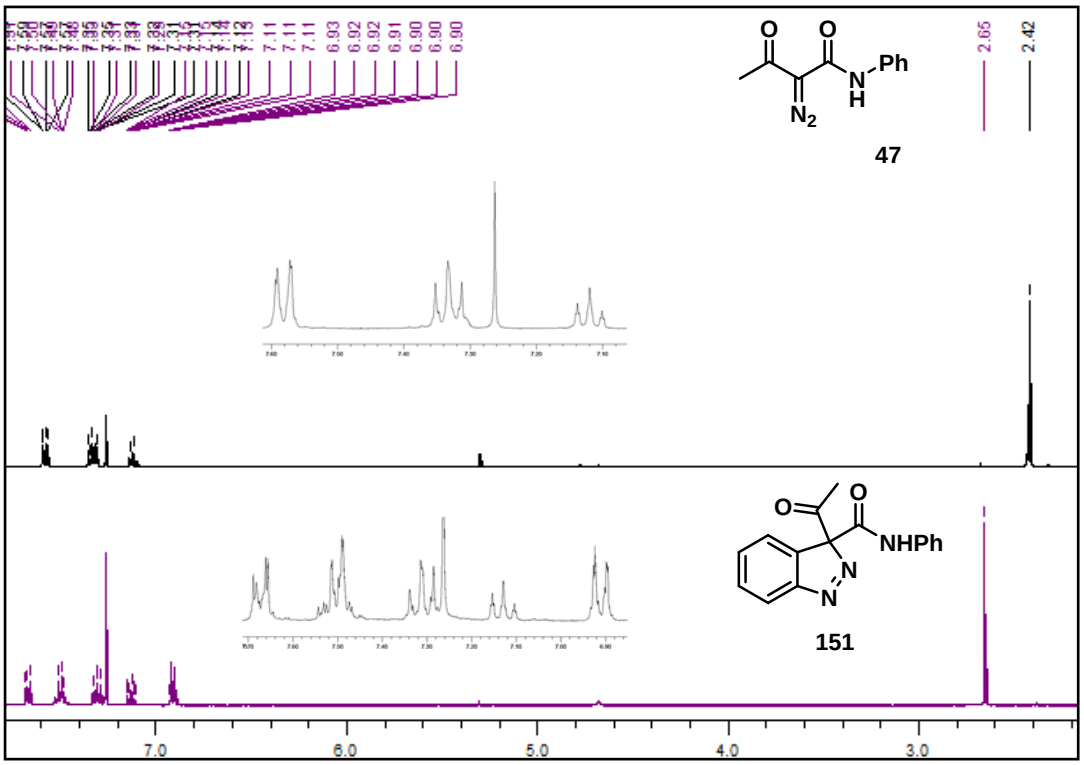
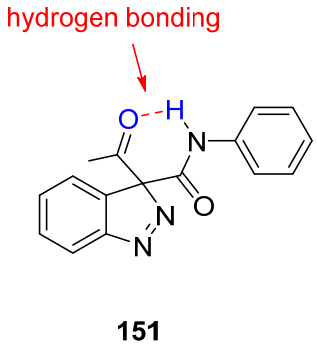


Figure 2.30 *^{1}H NMR spectra comparison of **47** and **151***

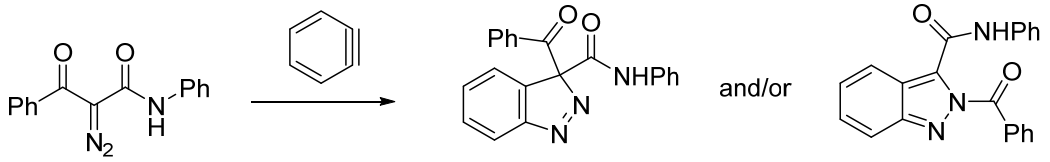
Signals for a quaternary carbon at δ_C 96.9 ppm and a ketone signal at δ_C 191.1 ppm were observed in the ^{13}C NMR spectrum, confirming that acyl migration had not taken place for this derivative and instead cycloadduct **151** was, in fact, the product of this reaction. Further support for structure **151** comes from the lack of evidence of the *N*-aryl by-product or 2-acyl indazole product observed when α-diazo-β-ketoamide **46** is utilised. These products are accounted for when the initial cycloadduct dissociates into ion pairs and recombine to form more stable, fully aromatic 1*H*- or 2*H*-indazoles. Hydrogen bonding between oxygen of the ketone and hydrogen of the 2º amide may be playing a part in the stability of this 3*H*-indazole **151** (**Figure 2.31**).



151

Figure 2.31 *Stability of **151** due to possible hydrogen bonding*

For the final α-diazo-β-ketoamide **48** used in the cycloaddition reactions, initially it was thought that the 3,3-disubstituted derivative **152** was isolated (**Scheme 2.35**).



48 **152** **153**

Scheme 2.35

The aromatic signals in the ^{1}H NMR spectra (**Figure 2.32)** are upfield in comparison to the 1-acyl indazole, similar to 3*H*-indazole **151** seen in the previous reaction and integration of the proton signals agrees with the correct number of protons.

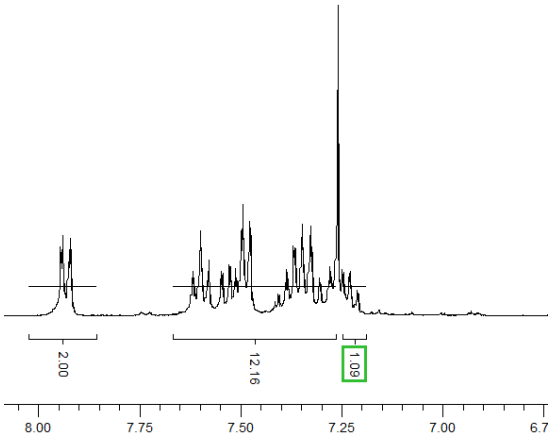


Figure 2.32 *^{1}H NMR spectrum of **152** and/or **153***

Also, the ^{13}C NMR spectrum contains a signal at δC 70.3 ppm that could potentially belong to the quaternary C-3 of **152**. However, the structure is tentatively assigned as the carbonyl carbons both show up in the range for amides at δC 145.4 and 149.3 ppm which argues that **153** is the product. The formation of **153** can be rationalised by noting that hydrogen bonding may be occurring between the oxygen of the benzoyl group and hydrogen of the 2º amide but the steric hindrance involved in **152** can be relieved by migration of the benzoyl group to the *N*-2 position to form **153** (**Figure 2.33**).

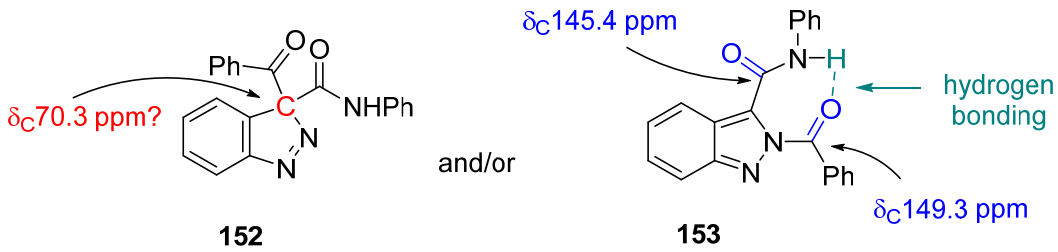


Figure 2.33 *Possible products **152** and/or **153***

This section has provided us with interesting results and 8 novel indazole carboxamide derivatives with the most useful results in terms of compounds that were sent for biological testing being the formation of the *N,N*-dimethyl- and *N,N*-diethyl-carboxamide derivatives (will be discussed further in **Section 2.10**). Future work here could involve confirmation of structure for the final two derivatives and observing their reaction with arynes generated by different methods to see if similar results are obtained.

2.4.2.4 1-Acyl-1*H*-[1,3]dioxolo[4,5-f]indazole-3-carboxylate derivatives

This section outlines the use of substituted aryne precursors to form indazole compounds. The first derivatives to be formed have a methylenedioxy bridge on the indazole core structure. It was envisioned that the anti-cancer activity of these derivatives might be increased in comparison to the unsubstituted aryl ring derivatives considering this methylenedioxyphenyl moiety is a precursor to quite a number of pharmaceuticals, as mentioned previously.[57]

These indazole compounds were prepared following the modified procedure disclosed in **Section 2.4.2.1** using the 2-trimethylsilyl-methylenedioxyphenyltriflate aryne precursor **75** and maintaining the diazo compound in excess for all derivatives. All reactions and purification went smoothly to produce the desired products **154-159** cleanly and in good yields with no evidence of the *N*-aryl by-product observed (**Figure 2.34**).

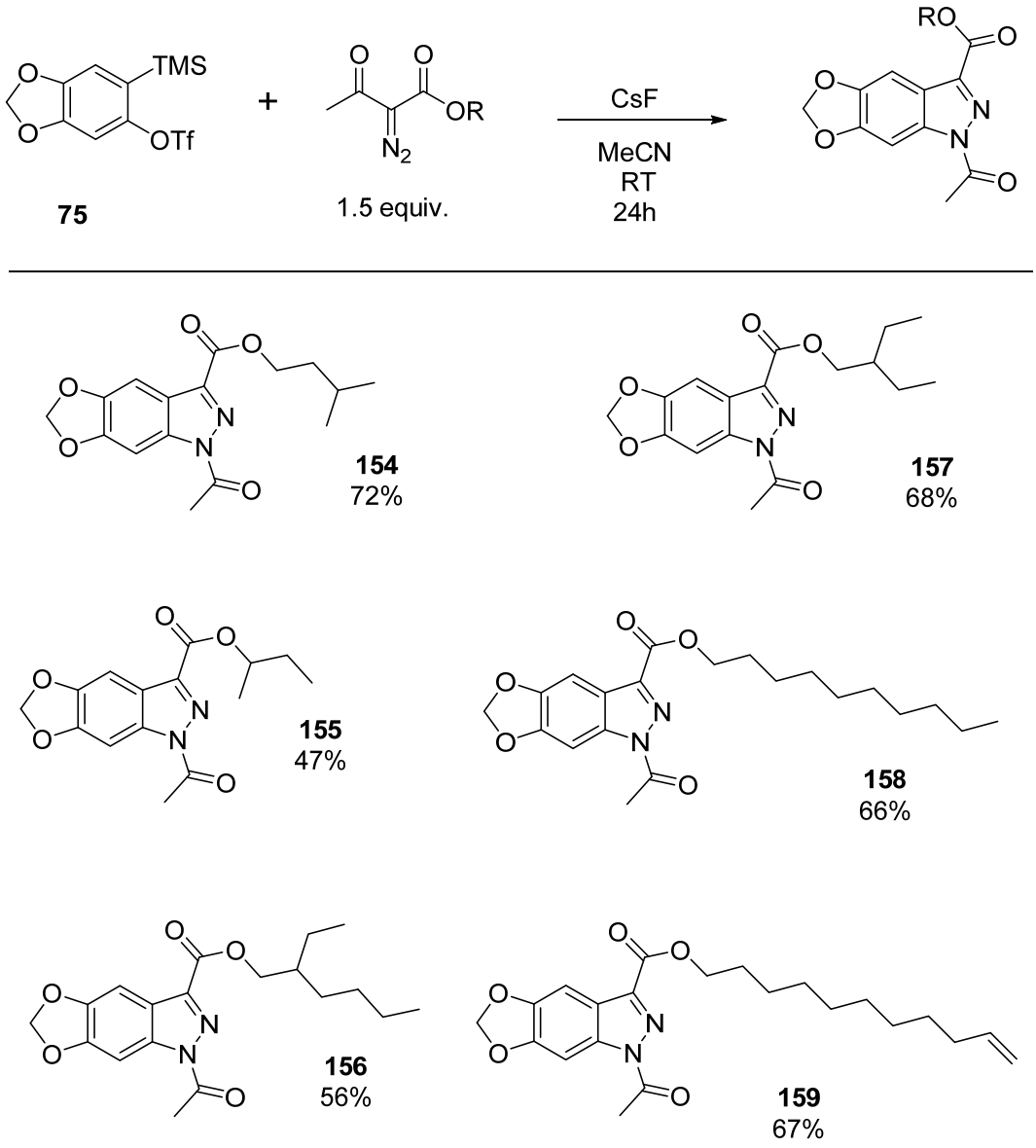


Figure 2.34 *Range of 1-acyl-1H-[1,3]dioxolo[4,5-f]indazole-3-carboxylate derivatives prepared*

^{1}H NMR spectra analysis showed that all the derivatives had very similar chemical shift values except for signals due to the ester side chain. The aryl region contained two distinctive singlet signals between the narrow ranges of δ_H 7.44-7.47 ppm and 7.88-7.89 ppm, the methylene protons of the methylenedioxy moiety was at δ_H 6.11 ppm in all spectra and the *N*-acetyl 3H singlet appears at δ_H 2.84 or 2.87 ppm. In the ^{13}C NMR spectra the acetyl group CH_3 is at δ_C 22.9 or 23.0 ppm, the methylene group appeared at δ_C 102.3 ppm and the aromatic CH signals moved upfield to δ_C 95.7 and 99.3-99.4 ppm in all cases.

Assignment of the quaternary carbon signals for these derivatives was aided by HMBC (Heteronuclear Multiple Bond Correlation) 2D (two-dimensional) NMR experiments as the chemical shift values of the quaternary carbons attached to the nitrogens were too similar to differentiate.

Characteristic absorption bands in the IR spectra were seen between ν_{max} 1720-1731 cm^{-1} and ν_{max} 1644-1651 cm^{-1} for the ester and amide carbonyl groups respectively. **Figure 2.35** shows an NMR spectrum of **157** after column chromatography on silica gel.

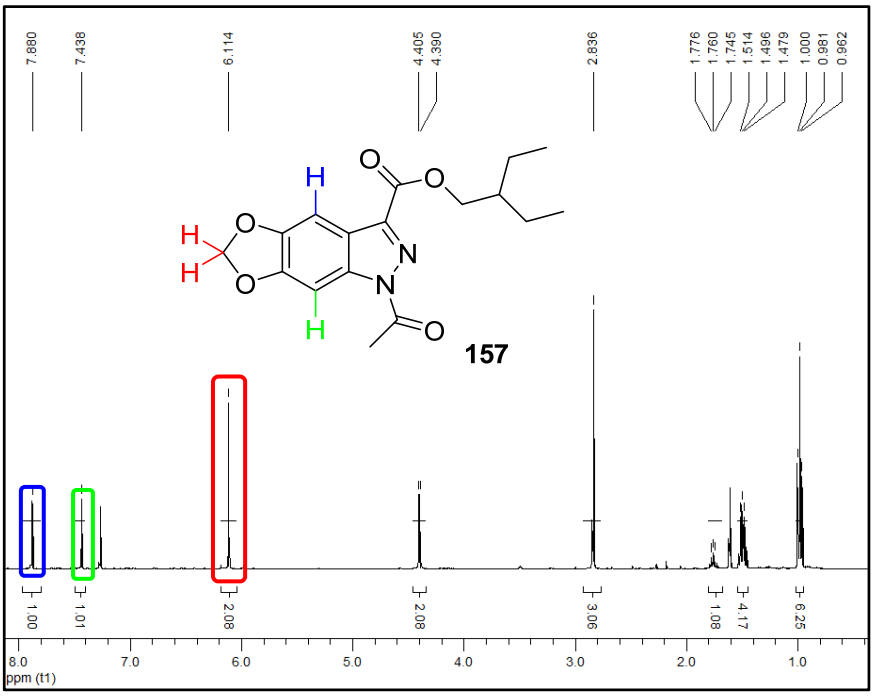
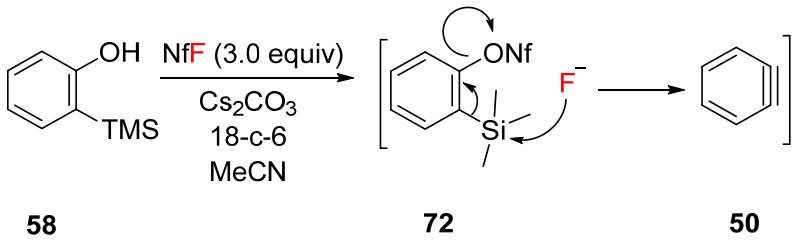


Figure 2.35 *^{1}H NMR spectrum of **157***

These six compounds were isolated in good yields and purities and were sent forward for biological testing (will be discussed in **Section 2.10**). The protocol designed in this project requiring excess diazo compound was successful in eliminating the formation of the by-product and the excess diazo could be recovered after the reaction reaches completion by column chromatography on silica gel. In future work, by increasing the equivalents of aryne precursor the *N*-aryl derivatives could be selectively formed.

2.5 Synthesis of 1-acyl-1*H*-indazole compounds using Method 2

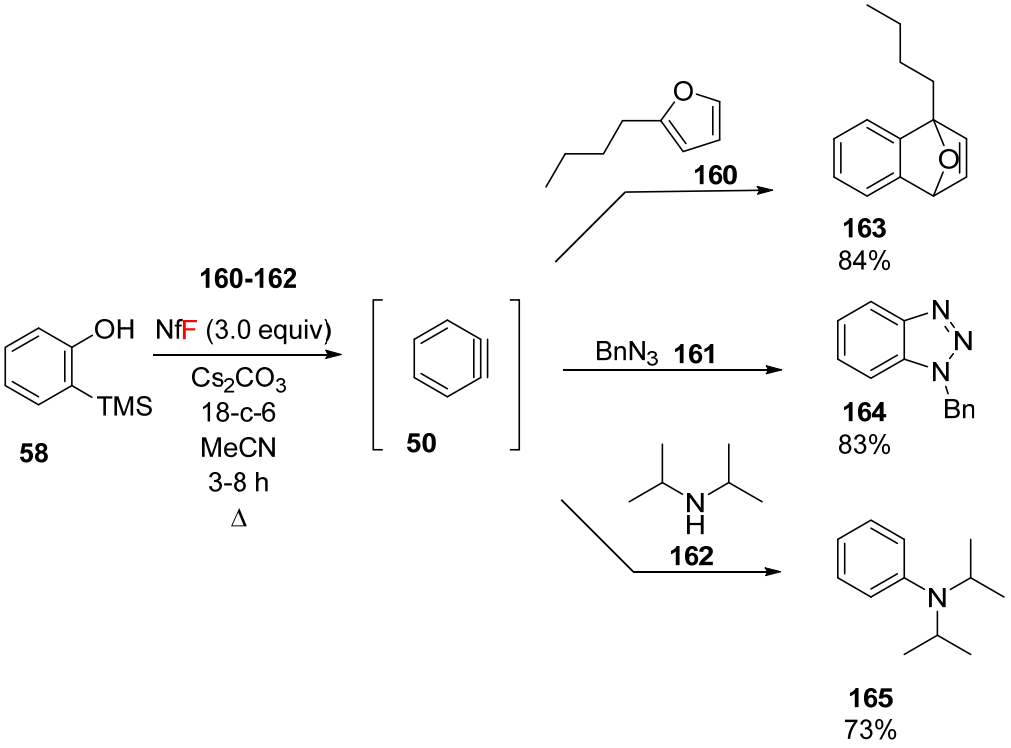
This section describes the use of the nonaflation of 2-trimethylsilylphenol derivatives to generate arynes which then undergo cycloaddition reactions to form indazole heterocycles. This method of aryne generation was published by Ikawa and co-workers in 2011 but has not yet received a lot of attention (**Scheme 2.36**).[37] This method has the appeal that the nonaflating reagent is much cheaper and more bench stable than the triflating reagent. It does not require the low temperatures required for triflation or the isolation of the immediate aryne precursor which was generated *in situ* before undergoing cycloaddition.



58 **72** **50**

Scheme 2.36

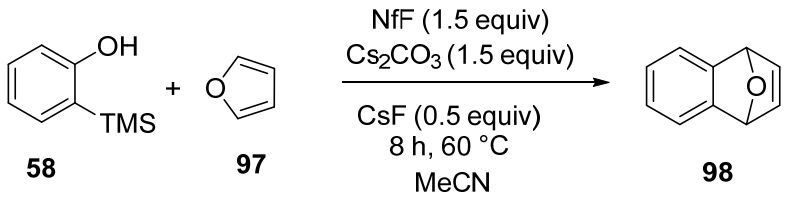
The authors demonstrated the applicability of their aryne generation method using standard Diels Alder trapping experiments with furan derivatives **160** to form epoxynaphthalene derivatives such as **163**, a [3+2]-cycloaddition reaction with benzylazide **161** to form benzotriazole **164** and a nucleophilic addition reaction with isopropylamine **162** to form aniline derivative **165** (**Scheme 2.37**).



Scheme 2.37

2.5.1 Generation of aryne and trapping with furan

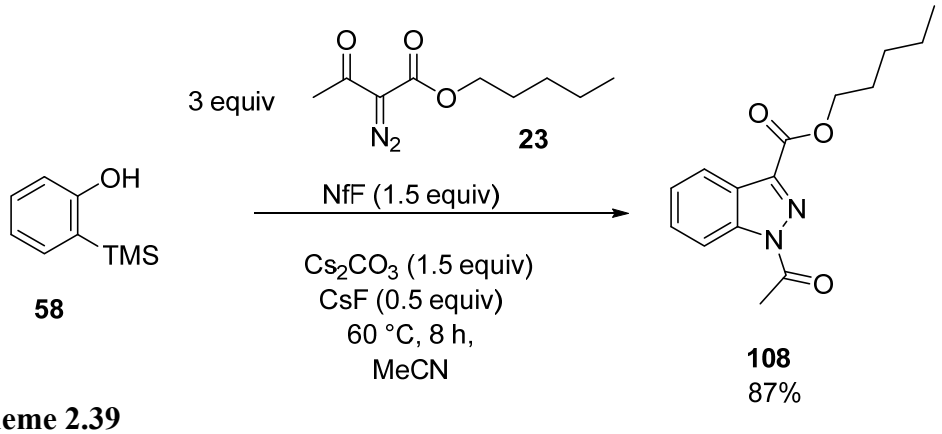
Process familiarisation was carried out again using a furan trapping test reaction and the characteristic peaks of the cycloadduct **98** could be identified in the ^{1}H NMR spectrum of the crude material. This technique was modified slightly by reducing the amount of nonafyl fluoride added to 1.5 equivalents and by excluding 18-crown-6 as an additive (to ensure the activation of the fluoride anion from NfF), and the introduction instead of 0.5 equivalents of caesium fluoride. This combined 2.0 equivalents amount of fluoride ion ensured complete generation of aryne from the precursors without requiring the expensive crown ether additive (**Scheme 2.38**).



Scheme 2.38

2.5.2 1-Acyl-1*H*-indazole-3-carboxylate derivatives

The first cycloaddition reaction performed using this nonaflation methodology prepared **108** in excellent yield (**Scheme 2.39**). It was initially thought that some diazo decomposition products might be observed in the ^{1}H NMR spectra of the crude reaction mixtures as the reactions were heated to 60 °C, however, those concerns were unfounded as the only compounds observed in the ^{1}H NMR spectra were the desired indazole and unreacted excess diazo compound **23**. An increase in yield (79 to 87%) was observed using this nonaflation methodology (Method 2) in comparison to the triflate methodology (Method 1, **Section 2.4.2.1**) due to the facile isolation of the pure derivative and recovery of the excess diazo compound which could be recycled. Method 2 was found to be much more preferable to the Method 1 using the triflate aryne precursor.



Scheme 2.39

After successful preparation of **108**, this method was used in the synthesis of **128** and **127** which could not be isolated in high purity using the previous procedure (Method 1, **Section 2.4.2.1**). These reactions proved more successful, with isolation of pure (>98%) material for **128** (**Figure 2.36**) and semi-pure (>94%) material for **127** (contaminated with 6% unknown impurities after repeated column chromatography on silica gel) (**Figure 2.37**). A pure sample of **125** was also obtained as the Method 1 procedure provided a product contaminated by 10% *N*-aryl by-product (**Figure 2.37**).

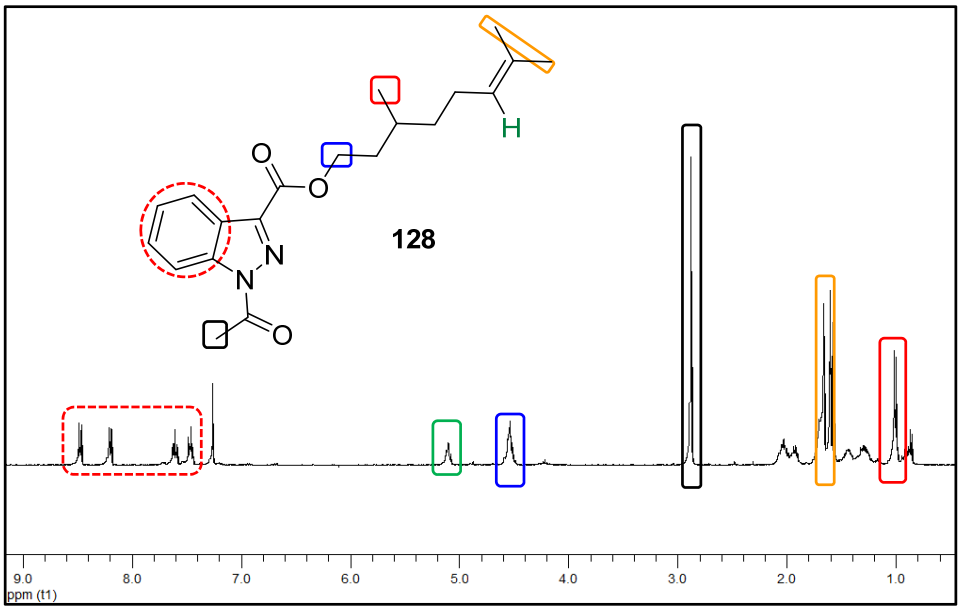
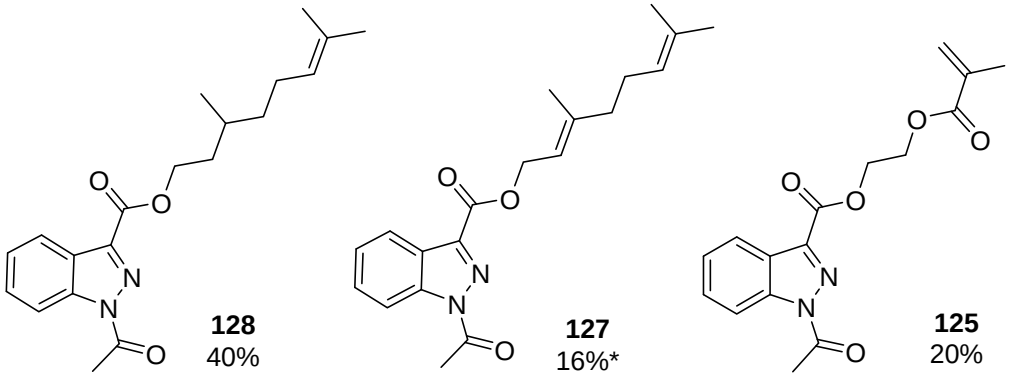


Figure 2.36 *^{1}H NMR spectrum of **128***

These results suggest that the conditions used to generate the aryne may affect the subsequent cycloaddition reactions. The yields for these particular reactions are quite low which may be related to the extra alkene functionality present which may be participating in a [2+2]-cycloaddition reaction itself with the aryne. These substrates did not work well regardless and further research is required that may optimise these reaction conditions to suit these functionalised substrates.



*contaminated with 6% unknown impurities

Figure 2.37 *1-Acyl-1H-indazole-3-carboxylate derivatives prepared using nonaflate methodology*

2.5.3 1-Acyl-substituted-1*H*-indazole-3-carboxylate compounds

This section describes efforts to further diversify the range of indazole derivatives being synthesised in this project by introducing a range of substituted aryne precursors with. Symmetrical disubstituted arynes were chosen so that one regioisomeric indazole derivative would be formed (**Figure 2.38**). As the aryne species can be classified as electrophilic, aryne precursors were chosen to investigate the efficiency of the cycloaddition reactions, e.g. dimethyl aryne **166** may reduce the electrophilic nature of the aryne by donating electron-density into the ring and difluoro aryne **167** may increase the electrophilic behaviour of the aryne. The biological effect of having two electron donating groups in comparison to two electron withdrawing groups on the indazole will be described in **Section 2.10**.

166 **167**

Figure 2.38 *Symmetrical aryne precursors with EDG and EWG*

2.5.3.1 1-Acyl 5,6-dimethyl-1*H*-indazole-3-carboxylate compounds

First the dimethyl aryne precursor **79** was used and reacted with three diazo 1,3-dipoles to give the three indazole products (**Figure 2.39**). The first cycloaddition reaction was high yielding and isolated derivative **168** in high purity. The other derivatives, **169** and **170**, however, were prepared using an impure sample of aryne precursor **79** (contained 15% starting material) and were difficult to purify. A reduction in yield was observed for **169** because of the need for repeated purification using preparative thin-layer-chromatography on silica gel.

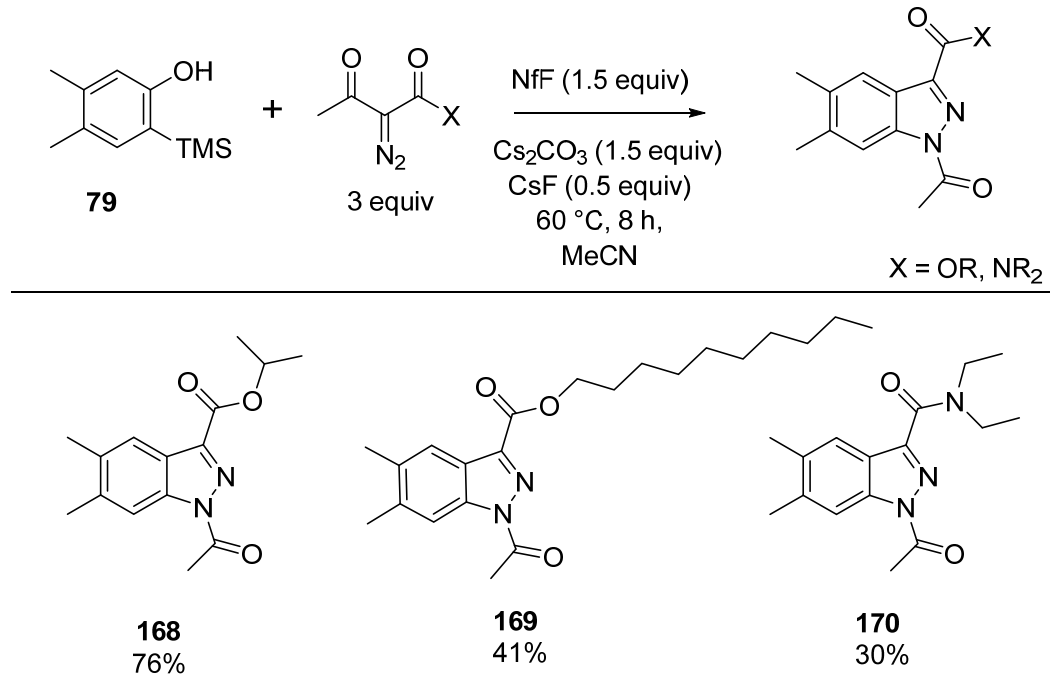


Figure 2.39 *1-Acyl 5,6-dimethyl-1H-indazole-3-carboxylate compounds*

^{1}H NMR analysis showed that the ester derivatives **168** and **169** had very similar chemical shift values, except of course for signals due to the ester side chain. The aryl region contained two distinctive singlet signals between the narrow ranges of δ_H 7.90-7.92 ppm and 8.23-8.25 ppm, the aryl-CH_3 groups were singlets between δ_H 2.40-2.44 ppm and the *N*-acetyl 3H singlet was at δ_H 2.85 ppm for both derivatives. In the ^{13}C NMR spectra the aryl-CH_3 groups appeared at δ_C 20.3 and 20.9 ppm and the aromatic CH signals are at δ_C 115.5 and 121.6 ppm in both cases.

Assignment of the quaternary carbon signals for these derivatives was aided by HMBC 2D NMR experiments as the chemical shift values of the quaternary carbons attached to the nitrogens were too similar to differentiate.

Characteristic absorption bands in the IR spectra for the ester and amide carbonyl functionalities were seen at the exact same wavelength for these derivatives at ν_{max} 1716 cm^{-1} and ν_{max} 1644 cm^{-1} respectively. **Figure 2.40** shows the ^{1}H NMR spectrum of **168** after column chromatography on silica gel.

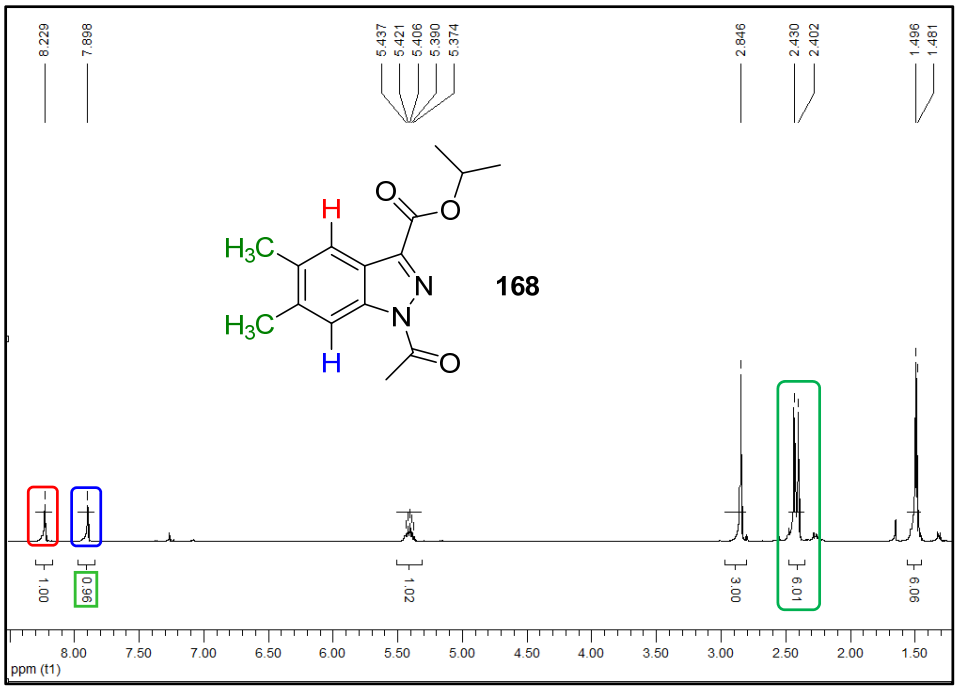


Figure 2.40 *^{1}H NMR* spectrum *of* ***168***

^{1}H NMR analysis of the carboxamide indazole derivative **170** shows the aryl region contains two singlets at δ_H 7.79 ppm and 8.21 ppm, the aryl-CH_3 groups at δ_H 2.37 and 2.43 ppm and the *N*-acetyl group at δ_H 2.75 ppm. In the ^{13}C NMR spectra the aryl-CH_3 groups appeared at δ_C 20.1 and 20.9 ppm with the aromatic CH signals are at δ_C 115.2 and 121.7 ppm. A characteristic absorption band for the amide carbonyl group was seen at ν_{max} 1635 cm^{-1} in the IR spectra.

2.5.3.2 1-Acyl 5,6-difluoro-1*H*-indazole-3-carboxylate compounds

The role of fluorine in drug design and development is growing quickly as more unique properties of the element are discovered. The addition of fluorine into a molecule can positively influence a range of effects including intrinsic potency, membrane permeability and pharmacokinetic properties.[58]

Some fluorine-containing drug compounds are shown in **Figure 2.41** that demonstrate the broad therapeutic effects caused by, but not limited to, the addition of fluorine to a drug molecule. Voriconazole **171** is a medication used to treat serious fungal infections. Fluorouracil **172** is a pyrimidine analogue used in the treatment of cancer. Atorvastatin (Lipitor®) **173** is a cholesterol-lowering drug. Fluoxetine (Prozac®) **174** is one of the most prescribed anti-depressants and maraviroc **175** is an anti-retroviral drug used in the treatment of HIV.

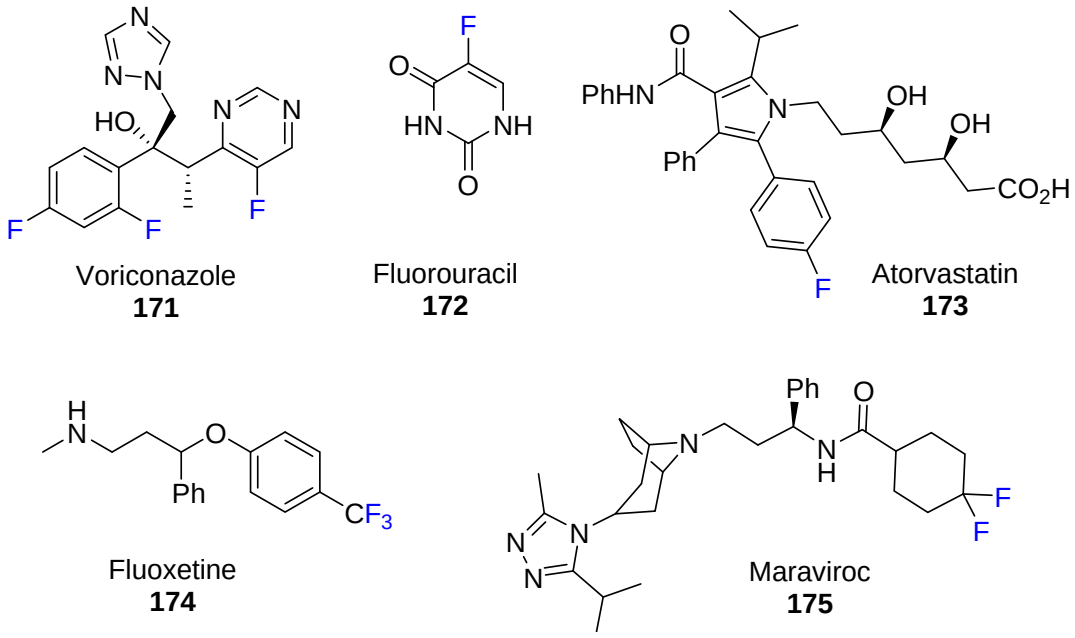
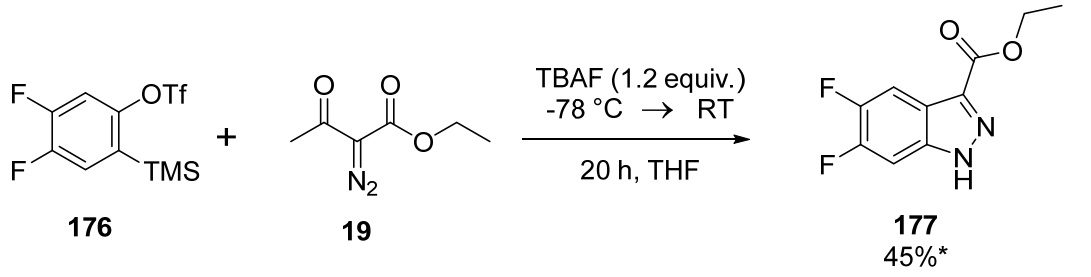


Figure 2.41 *Fluorine-containing pharmaceuticals*

Currently, pharmaceutical compounds containing at least one fluorine account for >18% of the market share and >30% of the agrochemicals market; of these, >47% are fluorinated aromatic derivatives.[59-62]

Larock reported unsuccessful reactions of the triflate aryne precursor **176** with diazo compounds due to the electron poor nature of the aryne (**Scheme 2.40**). For reactions with ethyl 2-diazo-3-oxobutanoate **19**, they reported a complex reaction mixture with poor yields of contaminated material **177**.[5]



Scheme 2.40 *Larock's only example of a difluoro indazole*

However, in this project, possibly due to the use of the nonaflate aryne precursor **78**, we are pleased to report successful cycloaddition reactions of the difluoro aryne **167** with a range of diazo derivatives were successful (**Figure 2.42**). These 11 novel difluoro-indazole derivatives were isolated in high purity, albeit in moderate yields. There is scope to optimise the conditions further to increase yields as both starting materials (aryne precursor and diazo dipole) were recovered even after extending the reaction times to 24 h. Seven derivatives contain an ester side chain and **185** incorporates an amide group in the side chain. All contain an *N*-acetyl group except for **186** which includes an *N*-benzoyl group. The fluorinated indazole derivatives synthesised in this project were strong candidates for biological testing, and subsequently turned out to be some of our most active compounds in the anti-cancer testing with the NCI, which will be discussed in **Section 2.10**.

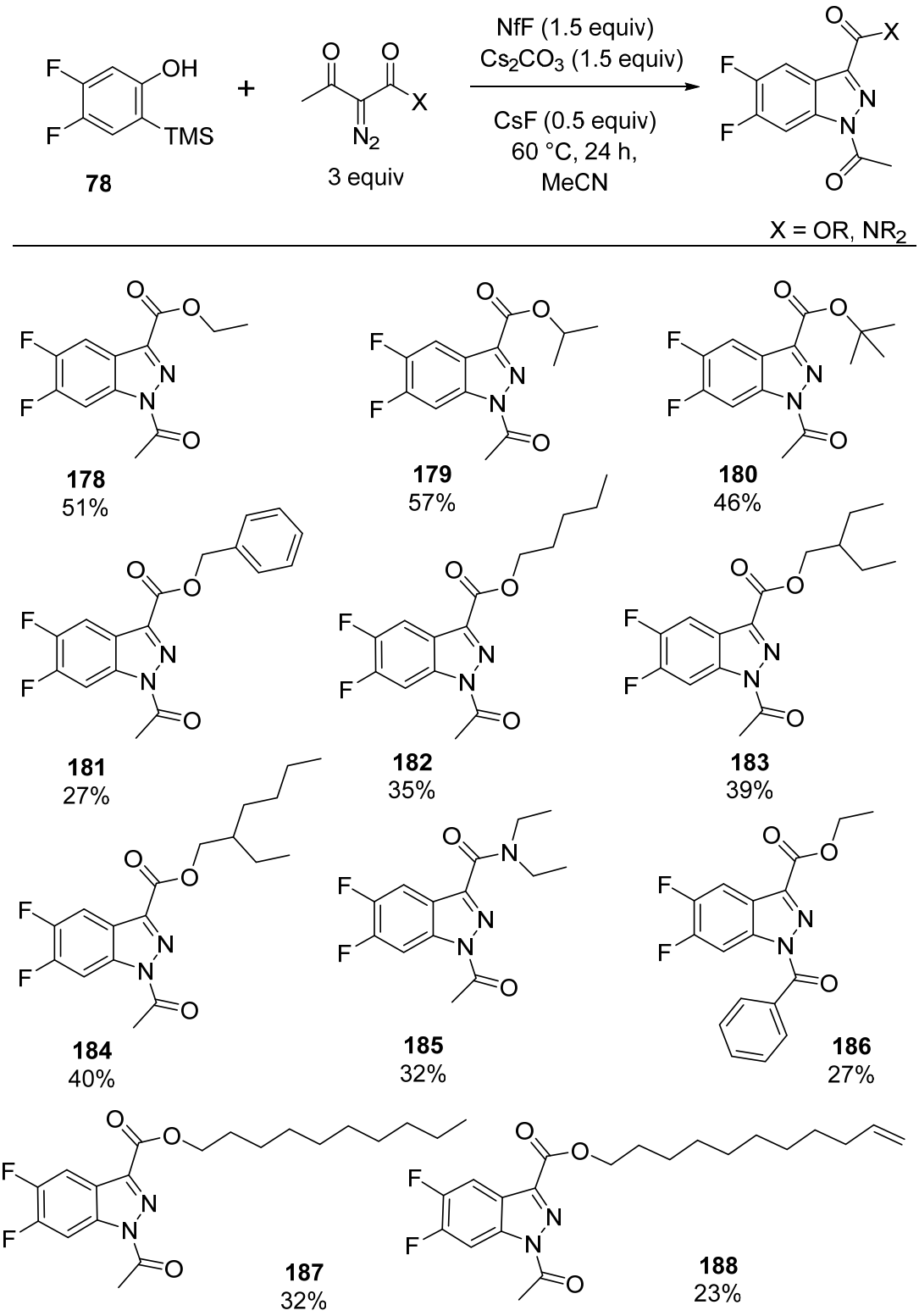


Figure 2.42 *Range of difluorosubstituted indazole deriatives*

The aromatic regions of the ^{1}H NMR spectra of the *N*-acetyl ester derivatives **178-184**, **187** and **188** are very similar with almost identical chemical

shift values. This region contained two distinctive doublet of doublet signals between the narrow ranges of δ_H 7.90-7.98 ppm and 8.30-8.31 ppm due to fluorine coupling, the *N*-acetyl 3H singlet was between δ_H 2.85-2.87 ppm for all derivatives. **Figure 2.43** shows a representative ^{1}H NMR spectrum of **179** where the high purity after column chromatography on silica gel and characteristic aromatic signalling of the derivative is observed.

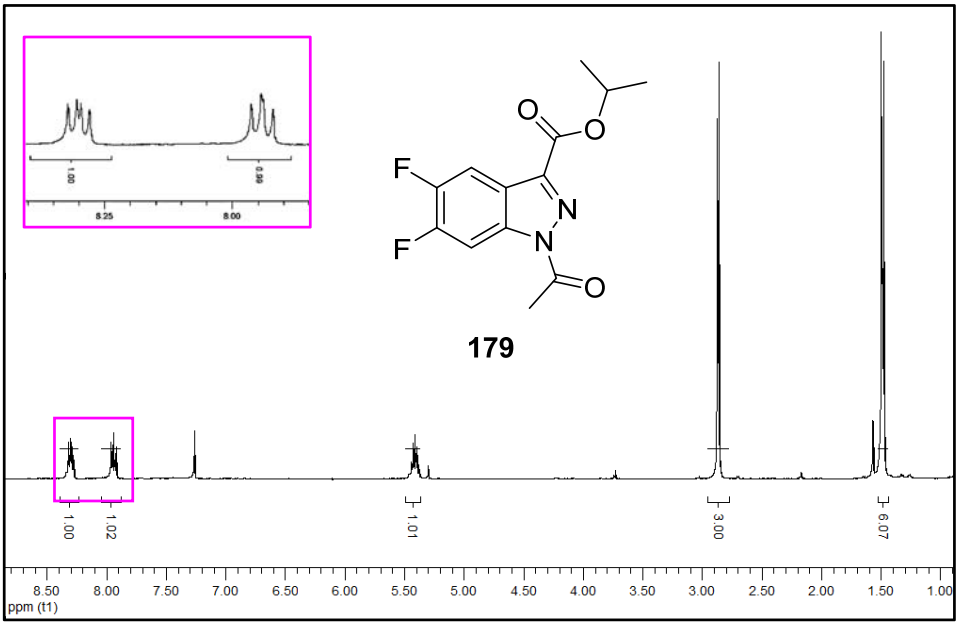


Figure 2.43 *^{1}H NMR spectrum of **179***

There is extensive coupling in the ^{13}C NMR spectra due to the two aromatic fluorines-the aromatic CH signals are doublets (unresolved coupling) or doublets of doublets at δ_C 104.0-104.1 and 108.9-109.1 ppm. In some cases the signals are too close to the baseline to analyse the C-F coupling constants and were consequently reported as a multiplet range.

Figure 2.44 shows a representative ^{13}C NMR spectrum of the same derivative **179** where the multiplet signals from ^{19}F coupling can be seen for the indazolic carbons between δ_C 103 and 154 ppm.

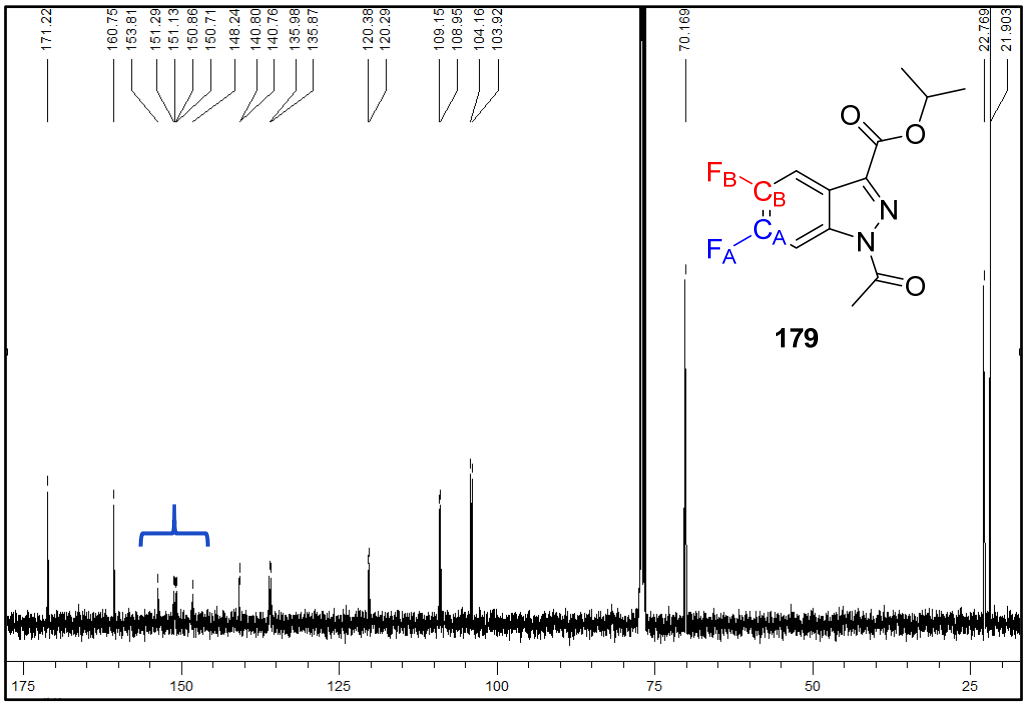


Figure 2.44 *^{13}C NMR spectrum of **179***

Figure 2.45 contains an expansion of the C-F coupling region and its associated splitting tree diagram.

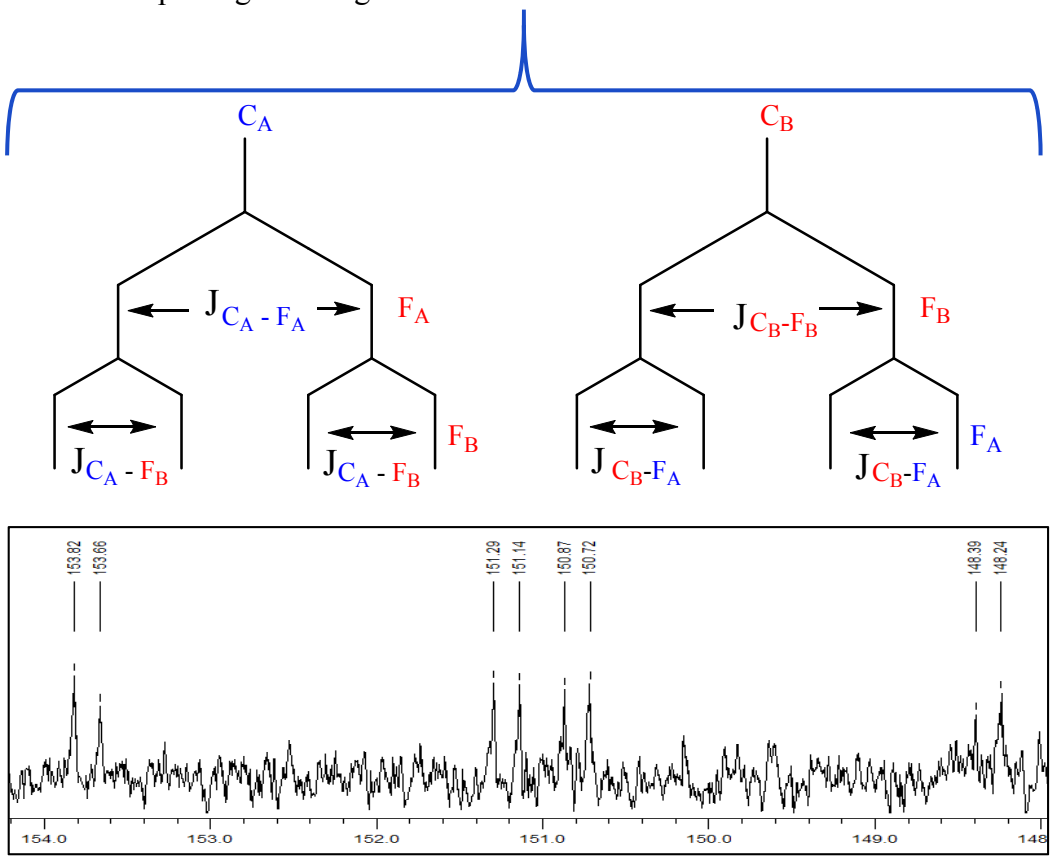


Figure 2.45 *^{13}C NMR* spectrum *splitting diagram for C-F signals in **179***

Absorption bands in the IR spectra are seen between ν_{max} 1643-1737 cm^{-1} for the carbonyl groups.

The aryl region in the ^{1}H NMR spectrum of benzoyl derivative **186** was more complex than those derivatives described above. The CH signals shift upfield in comparison to the *N*-acetyl compounds, one is a multiplet between δ_H 7.55-7.61 ppm and the other is a doublet of doublets at δ_H 8.07 ppm. In the ^{13}C NMR spectra the aromatic CH signals are doublets (unresolved coupling) or doublets of doublets at δ_C 98.4 (upfield shift) and 109.2 ppm. Absorption bands in the IR spectra are seen at ν_{max} 1726 cm^{-1} for the ester carbonyl and at ν_{max} 1645 cm^{-1} for the amide carbonyl.

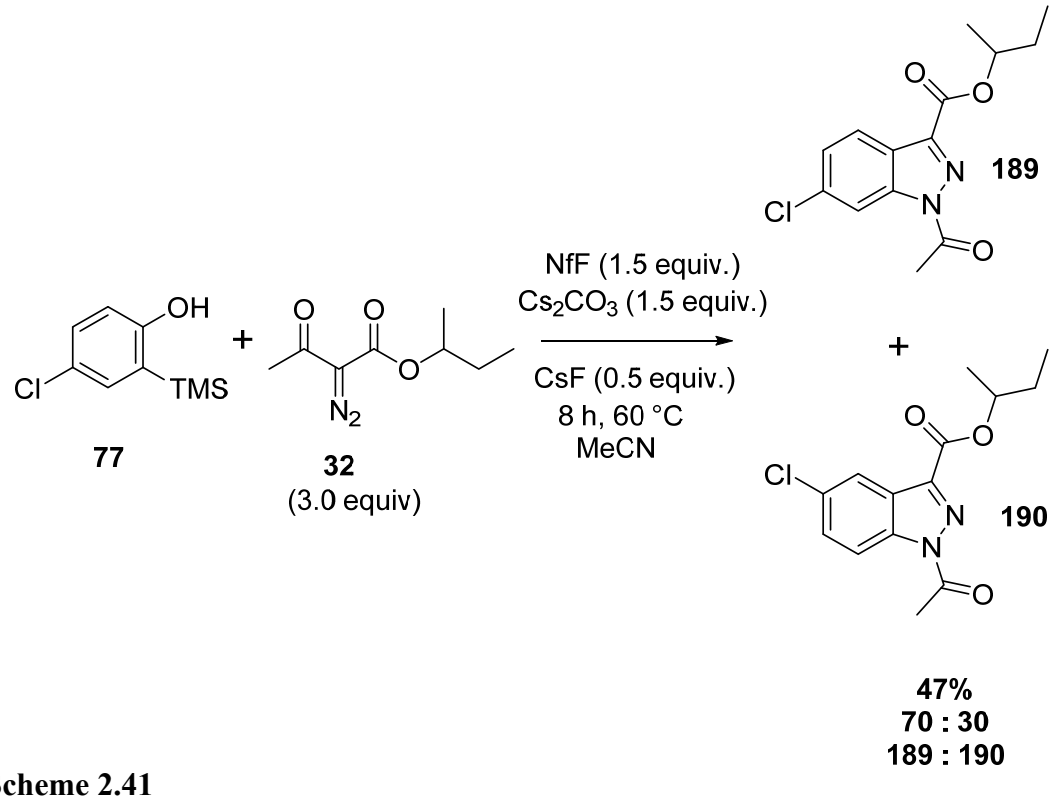
In amide derivative **185** the CH signals are doublets of doublets at δ_H 7.94 ppm and δ_H 8.25 ppm. In the ^{13}C NMR spectra the aromatic CH signals are doublets of doublets at δ_C 103.6 and 109.6 ppm. Absorption bands in the IR spectra are seen at ν_{max} 1734 for the *N*-acyl carbonyl and at 1629 cm^{-1} for the amide carbonyl.

11 novel difluoro substituted indazoles were prepared using this methodology which was of particular note as previous research groups reported trouble with synthesising derivatives of this nature.[5] This was a significant advancement in methodology for synthesising a series of these difluoro indazole derivatives which are very difficult to access. These compounds are compared to the dimethyl analogues in biological testing which will be discussed in **Section 2.10**.

2.5.3.3 1-Acyl 5/6-substituted 1*H*-indazole compounds

The use of unsymmetrical aryne precursors in the indazole cycloaddition reaction is described in this section. The arynes were generated using the methodology optimised in this research as described in **Section 2.5.3** that employed a nonaflate aryne precursor.[37] The intention was to investigate the effect of the substituent on the formation of regioisomers, to see if the isomers were separable and subsequently send the novel derivatives for biological testing.

The initial unsymmetrical aryne precursor used was 4-chloro-2-(trimethylsilyl)phenol **77** which underwent a cycloaddition reaction with *sec*-butyl 2-diazo-3-oxobutanoate **32** (**Scheme 2.41**) to give a mixture of inseparable regioisomers **189** and **190** in a 70:30 ratio. The major isomer was determined by ^{1}H NMR spectra proton integrations.



Scheme 2.41

^{1}H NMR analysis of the mixture showed some overlapping of signals for the two isomers in the aliphatic region but the aryl region contained three distinctive signals for each of the two isomers which could be used to differentiate between the two. Each isomer is characterised by a doublet of doublets signal and

two doublet signals. The *N*-acetyl 3H singlets were almost identical at δ_H 2.86 (major) and 2.87 (minor) ppm (**Figure 2.46**).

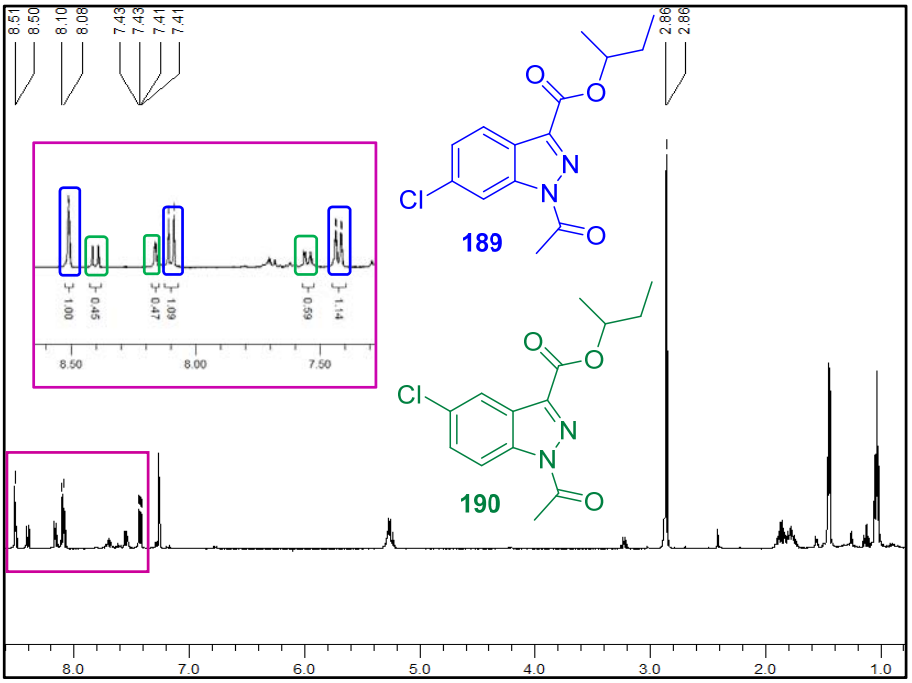


Figure 2.46 *^{1}H NMR* spectrum *of **189/190***

Assignment of the major isomer as the 6-substituted **189** was carried out by examination of the aromatic J values of both isomers and analogy to 5- and 6-substituted-1*H*-indazole derivatives including 5-chloro-substituted indazole **191** (**Figure 2.47**).[63-65]

Analysis of the ^{1}H NMR spectrum of **190**, reveals that at δ_H 8.16 ppm the 1H doublet (*J* 2, due to meta coupling to H6) can be compared to the singlet at δ_H 8.28 ppm in **191**. The doublet of doublets signal at δ_H 7.55 ppm (*J* 8.9, 2) couples to *ortho* H7 and *meta* H4 and the doublet signal at δ_H 8.40 (*J* 8.9) couples to *ortho* H6. In the same way, the aromatic signals in the ^{1}H NMR spectrum of the minor isomer can be assigned as **189**.

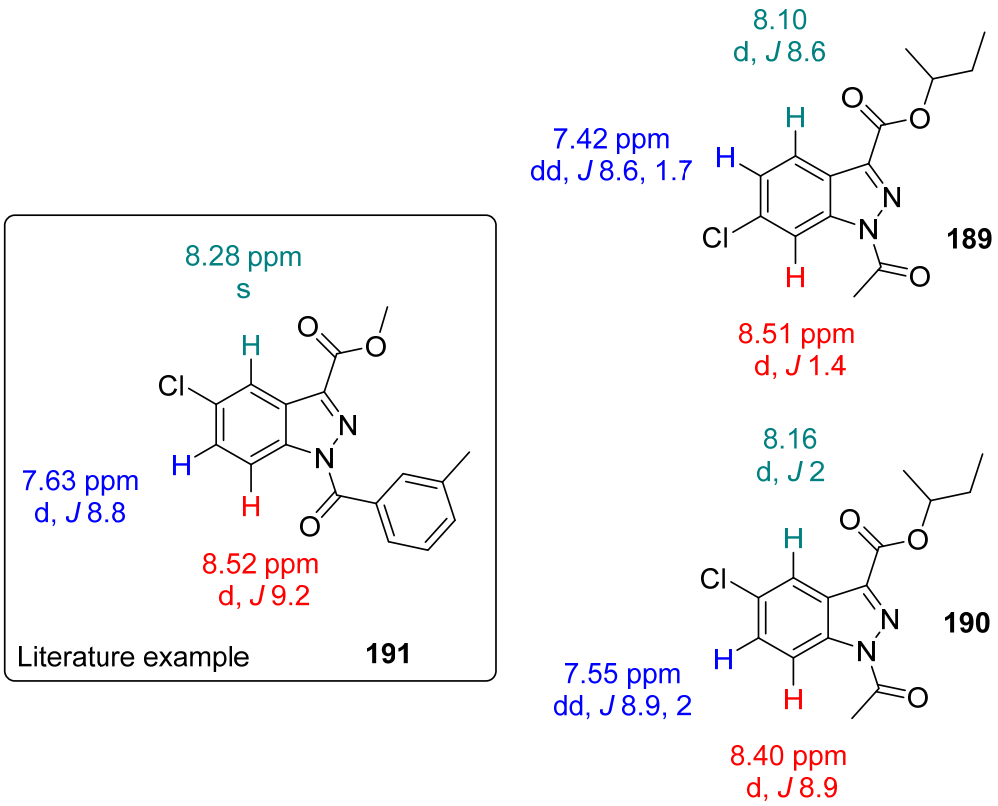
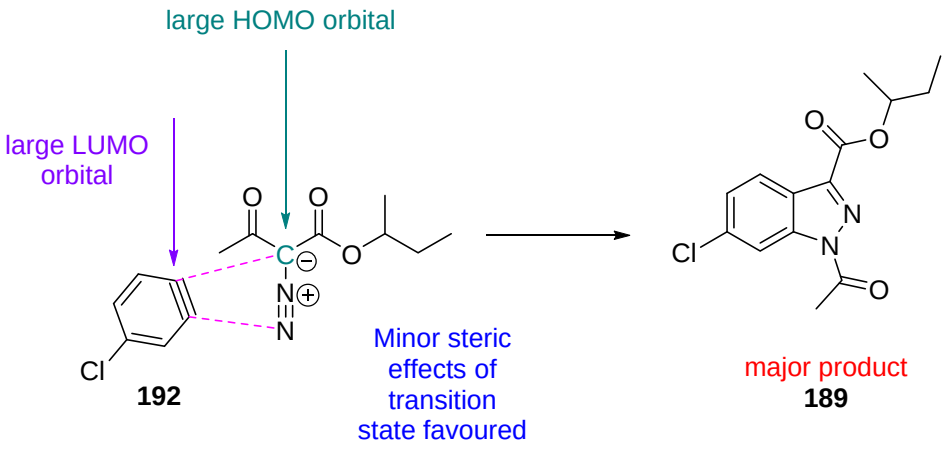


Figure 2.47 *Chemical shifts of aromatic protons in ^{1}H NMR spectra*

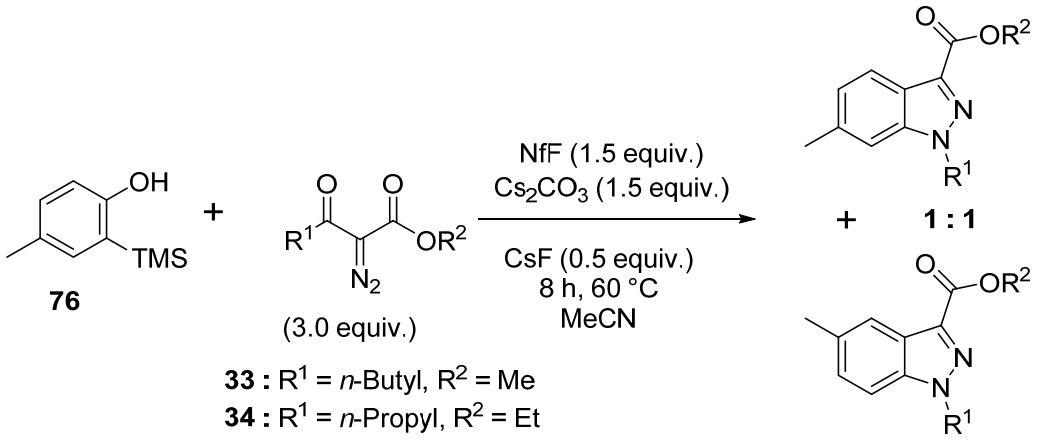
The ^{13}C NMR spectra was tentatively assigned for each isomer. Although the integration of carbon signal intensities may not be an accurate correlation between major/minor isomer and signal strength, the larger peak signals were tentatively assigned to the major isomer.

The formation of the major isomer could be rationalised by observing the contributing electronic and steric factors. The dominant electronic interaction governing regioselectivity is between the atoms bearing the largest HOMO and LUMO coefficients (**Scheme 2.42**). The carbon of the diazo carbonyl bears the largest HOMO and the carbon *para* to the chlorine substituent in the aryne **192** is the most electrophilic, therefore, the cycloaddition yields **189** as the major regioisomer. Steric effects are probably contributing very little to the regioselectivity of the cycloaddition reaction as the chlorine substituent is possibly too far from the reactive site to have much influence.



Scheme 2.42

For the methyl aryne precursor **76** it was thought that extending the length of the ketone side chain of the diazo compound **33/34** could influence the reaction outcome but no effect was observed on the formation of a particular isomer, with a 1:1 mixture of inseparable regioisomers **193/194** and **195/196** being formed under these conditions (**Scheme 2.43**).



33 : R^1 = *n*-Butyl, R^2 = Me
34 : R^1 = *n*-Propyl, R^2 = Et

193/194 : R^1 = *n*-Butyl, R^2 = Me, 65%
195/196 : R^1 = *n*-Propyl, R^2 = Et, 66%

Scheme 2.43

By analogy to similar compounds in the literature (**Figure 2.48**) [63-66] and using coupling constants, the ^{1}H NMR spectra for the aromatic protons was tentatively assigned (**Figure 2.49**). The chemical shift values in the ^{1}H NMR spectra of **197** and **193** are in similar ranges with comparable splitting patterns and the J values are almost identical.

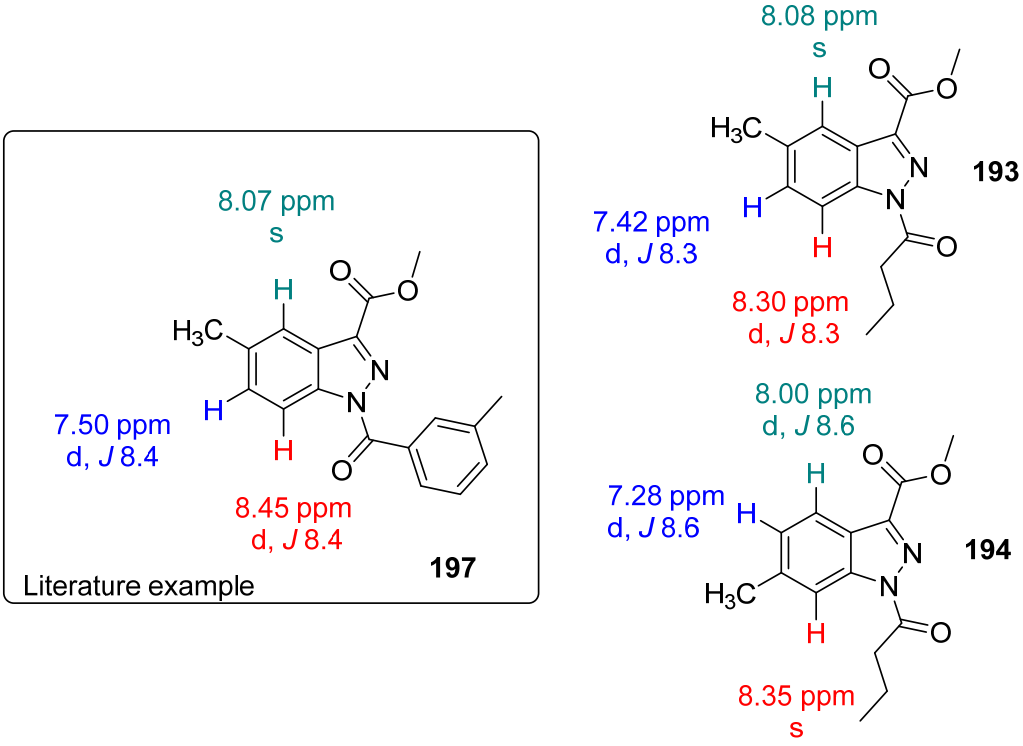


Figure 2.48 *Aromatic chemical shift values assigned by analogy to* ***197***

However, for the most part the isomers could not be described separately. The aryl-CH_3 singlets are almost identical at δ_H 2.52 and 2.54 ppm.

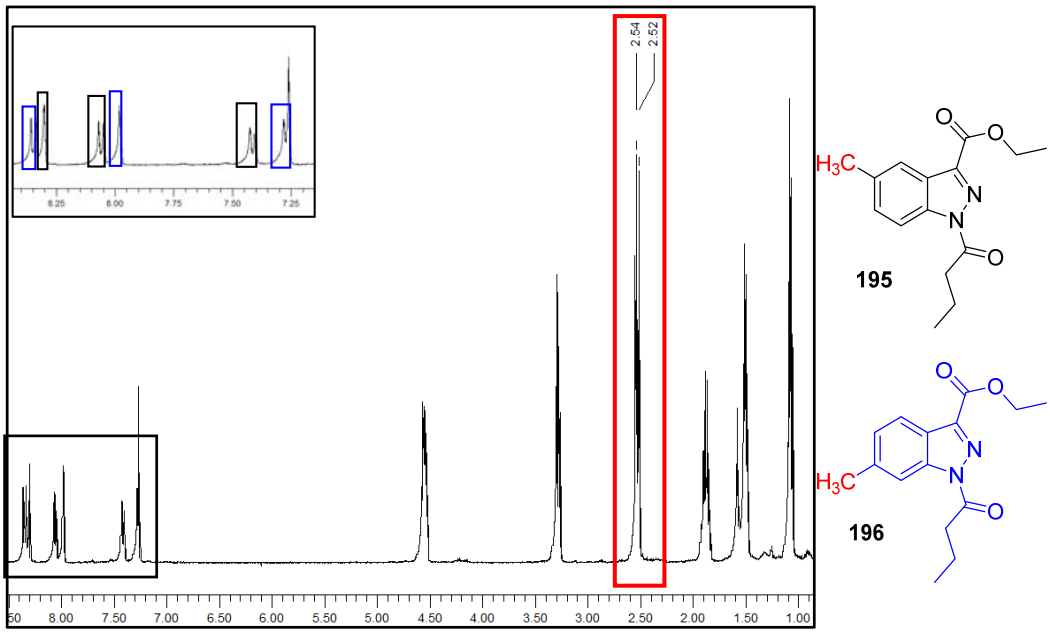
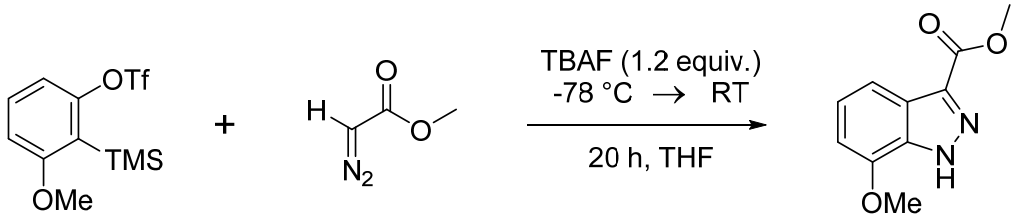


Figure 2.49 *^{1}H NMR spectra of* ***195/196***

The method for the synthesis of 5/6-substituted indazole derivatives shows some selectivity with a chlorine substituent on the aryne precursor but no

selectivity for a methyl group. Using unsymmetrical arynes, therefore, in the synthesis of 5/6-substituted indazole derivatives is not synthetically useful at this stage as the products are inseparable and, therefore, other routes, such as the Jacobsen Modification (described in **Section 1.3.3.1**) to 5- and 6-substituted indazoles are recommended.

Literature precedence has shown that when a methoxy group is present in the 3-position of the aryne, complete regioselectivity is observed. Larock demonstrated the cycloaddition of aryne precursor **198** with diazo **199** exclusively formed 7-methoxy indazole **200** (**Scheme 2.44**).[5] Indazole formation using arynes in such cases are useful, so future work could involve using a 3-methoxy aryne precursor for the synthesis and isolation of mono-substituted indazole derivatives.



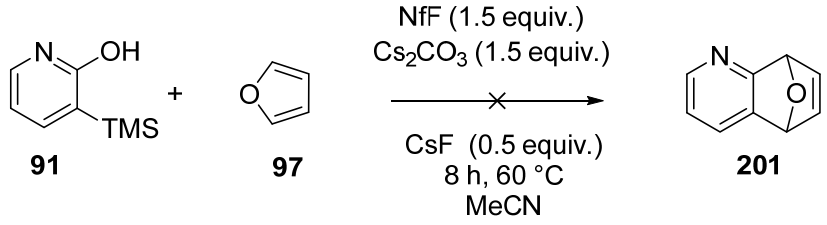
198 **199** **200**
65%

Scheme 2.44

2.6 Attempted Syntheses of Aza-Indazole Derivatives

Attempts to use the novel pyridyne precursors in the domino reaction[37] to form novel aza-indazole derivatives are discussed below.

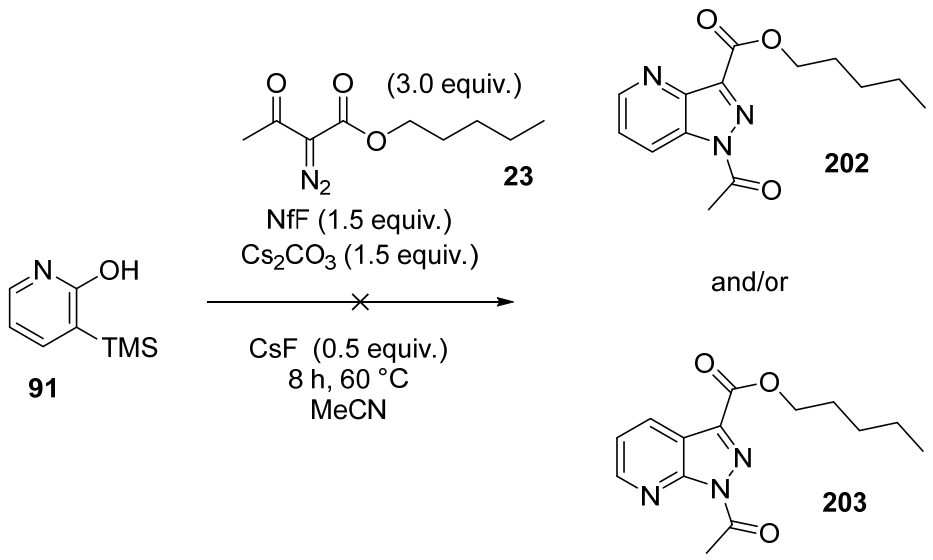
Although pyridyne intermediates have previously been generated from triflate precursors, they have not yet been used in aza-indazole synthesis or have not been generated using the nonaflate method so this would be an exciting new aspect to the project and would potentially provide excellent candidates for biological testing. Pyridyne intermediates are known to be very reactive and as a result they dimerise, decompose and form more impurities than their benzyne equivalent.[41,42,67,68] Consequently, they also tend towards low yielding reactions. The initial attempted pyridyne reaction (**Scheme 2.45**) was unsuccessful, with no evidence of the cycloadduct **201** being formed and only starting material was recovered after 8 hours.



Scheme 2.45

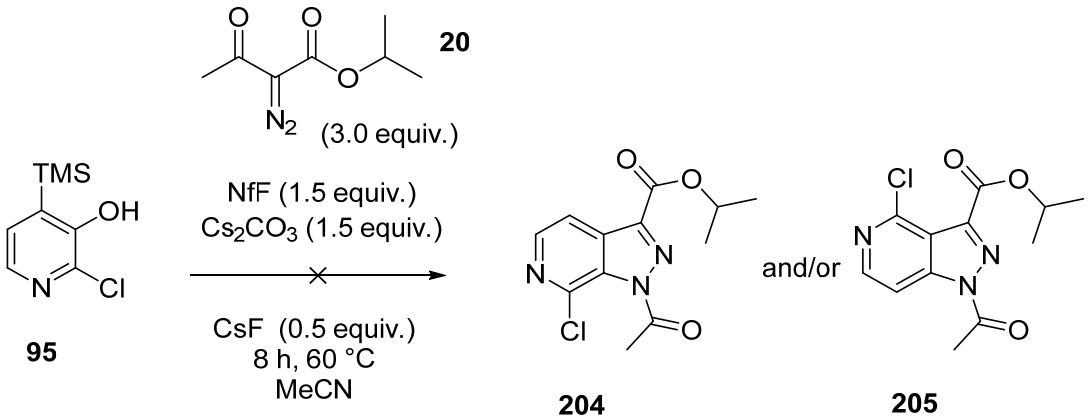
In spite of this, it was decided to pursue the aza-indazole forming reaction with the diazo dipoles. Unfortunately, these reactions were also unsuccessful, and only starting material was recovered in both cases **Scheme 2.46** and **Scheme 2.47**.

It was hoped that incorporating a chloro-substituent into the pyridine precursor could influence formation of one regioisomer over another as seen in comparable pyridyne derivatives generated from trimethylsilylpyridyltriflates. If two products are formed, separation by column chromatography on silica gel may be easier than separation of indazole regioisomers as similar aza-indole regioisomers can be isolated from each other during the synthesis of ellipticine.[42]



Scheme 2.46

The lack of success with this methodology so far proved disappointing. However, as these were initial reactions there is much scope for improvement of this work to achieve pyridyne generation using nonaflation. The inclusion of 18-crown-6 as an additive to ensure fluoride activation may be a potential aid in a successful reaction outcome by ensuring fluoride reactivity and aryne generation. The use of a stronger base instead of caesium carbonate is also an aspect to be considered as the pKa of the pyridinol hydrogen is higher than that of phenolic hydrogens.



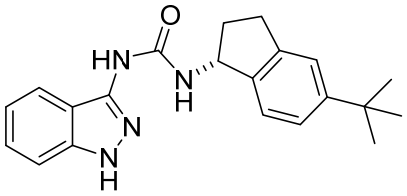
Scheme 2.47

The cycloaddition reactions of the range of diazo dicarbonyl compounds with the range of aryne precursors provided a pool of over 50 novel *N*-acyl-

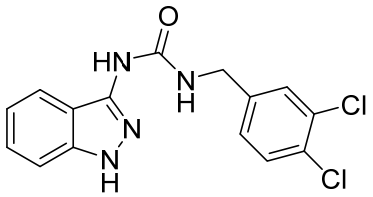
indazole derivatives, with much scope for the synthesis of analogues in future work, and over 40 derivatives which were prepared for biological testing (21 novel indazoles evaluated to date) and which were further derivatised as described in the next deacylation section.

2.7 *N*-Deacylation of 1-acyl indazoles

1*H*-Indazoles are biologically interesting compounds in their own right with many compounds showing biological activity such as **206** and **207** (**Figure 2.50**) which are undergoing investigation as pain management drugs due to their ability to block the vanilloid receptor which causes burning pain upon activation.[69]



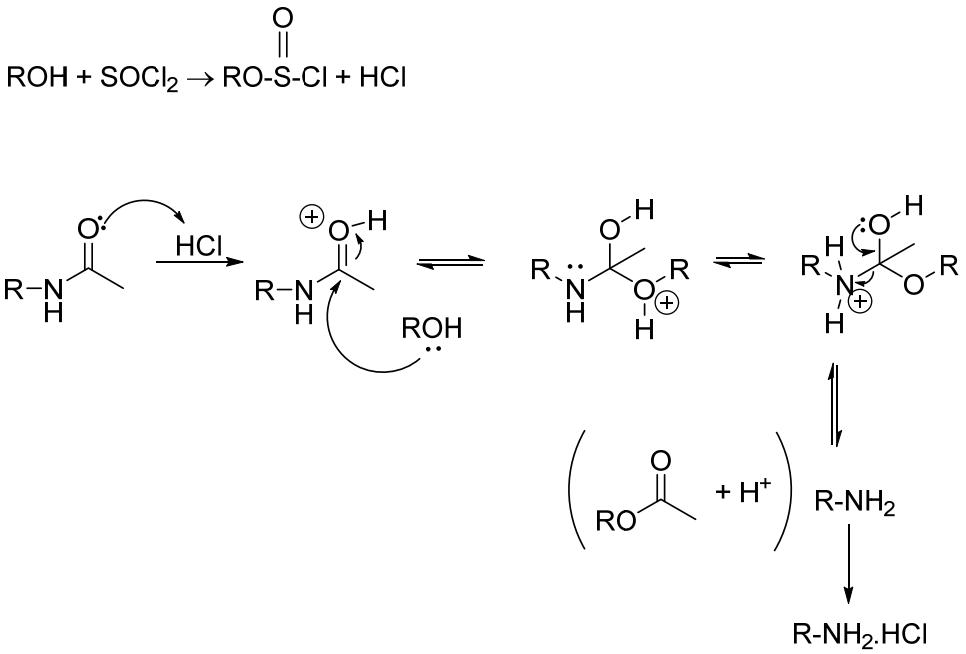
206



207

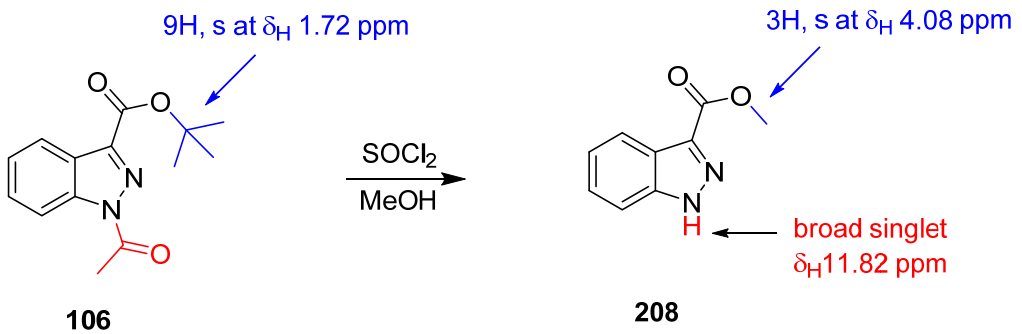
Figure 2.50 *Biologically active 1H-indazole derivatives*

N-Deacylation was beneficial to the project as the novel 1*H*-indazoles prepared constituted another library of candidates to be submitted for biological testing and the free nitrogen could be further derivatised to provide additional novel compounds. The next aim, therefore, was to adopt an approach to deacylate the *N*-1 position of the *N*-acyl indazoles prepared in **Section 2.6**. A general method to deacylate all derivatives that would not affect the ester side chain is desirable. Initially, a method using thionyl chloride in methanol was employed after Wang *et al.* reported a mild deacylation method of arylacetamides that tolerated ester, aminosulfonyl or benzyloxyamide functionalities.[70] In Wang's research a methyl ester group was present, which was not affected by the acidic conditions in methanol. The proposed mechanism proceeds by generating HCl from the alcohol and thionyl chloride (**Scheme 2.48**).



Scheme 2.48

This process employed cheap reagents, reported good yields and a short reaction time. However, when applied to indazole compound **106**, although deacetylation does occur, transesterification of the *t*-butyl ester side chain to a methyl ester **208** also occurs (**Scheme 2.49**). Rather than using Wang's conditions that required matching the ester side chains to the alcohol solvent, an alternative deacylation method was investigated.

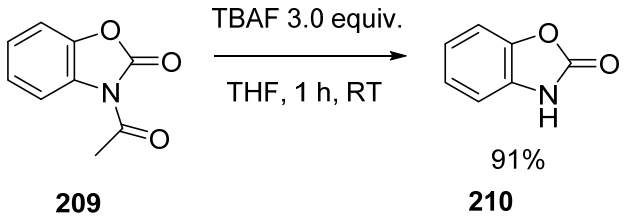


Scheme 2.49

2.7.1 *N*-Deacylation of aryl unsubstituted 1-acyl indazoles

Use of tetra-*n*-butylammonium fluoride (TBAF) in THF was investigated after Carato *et al.* researched protection and deprotection methods for compounds bearing a reactive free nitrogen. For example, the authors reported the facile

deacylation of benzooxazolone **209** after treatment with TBAF in THF at room temperature for one hour to form **210** in excellent yield (**Scheme 2.50**).[71]



Scheme 2.50

In this project, the procedure was slightly altered by using 4 equivalents of TBAF as some starting material *N*-acyl indazole derivatives were observed after 1 hour with 3 equivalents of TBAF.

This method efficiently deacylated all the *N*-acyl indazole compounds in short reaction times at room temperature, followed by an aqueous work up to isolate pure compounds in high yields. This is a general method that is suitable for all derivatives and tolerates all ester functional groups. It was initially applied to twelve 1-acyl indazole carboxylate derivatives (**Figure 2.51**) and provided eight novel 1*H*-indazoles **214-216** and **218-222**.

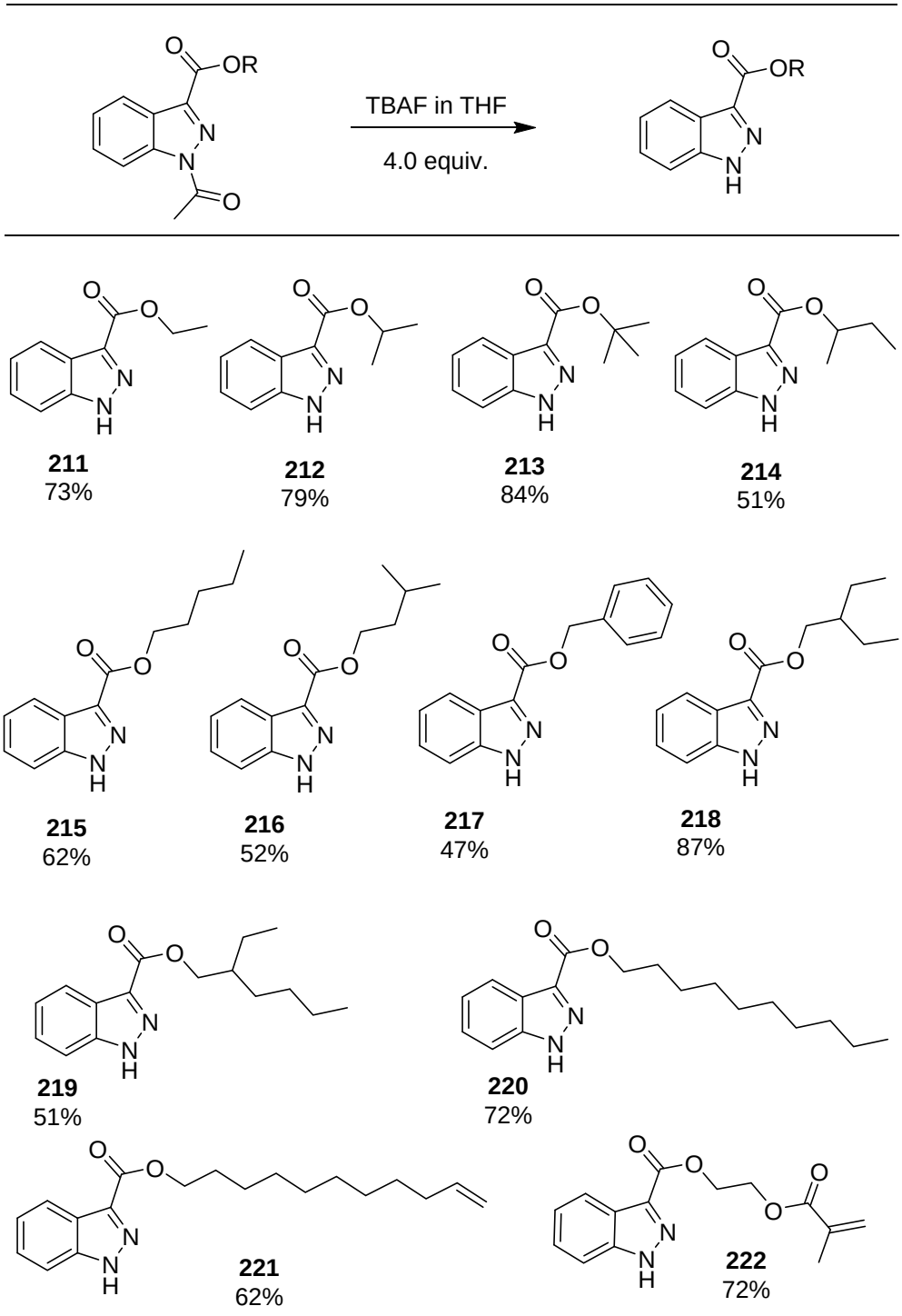


Figure 2.51 *First series of N-deacetylated compounds*

An example of ^{1}H NMR analysis for this work is shown in **Figure 2.52**. Characteristic peaks in the ^{1}H NMR spectra is the appearance of the broad NH singlet between δ_H 10.61-12.51 ppm, the upfield shift of an aromatic proton signal and the disappearance of the acetyl CH_3 peak in the region of δ_H 2.87 or 2.88 ppm for all relevant compounds.

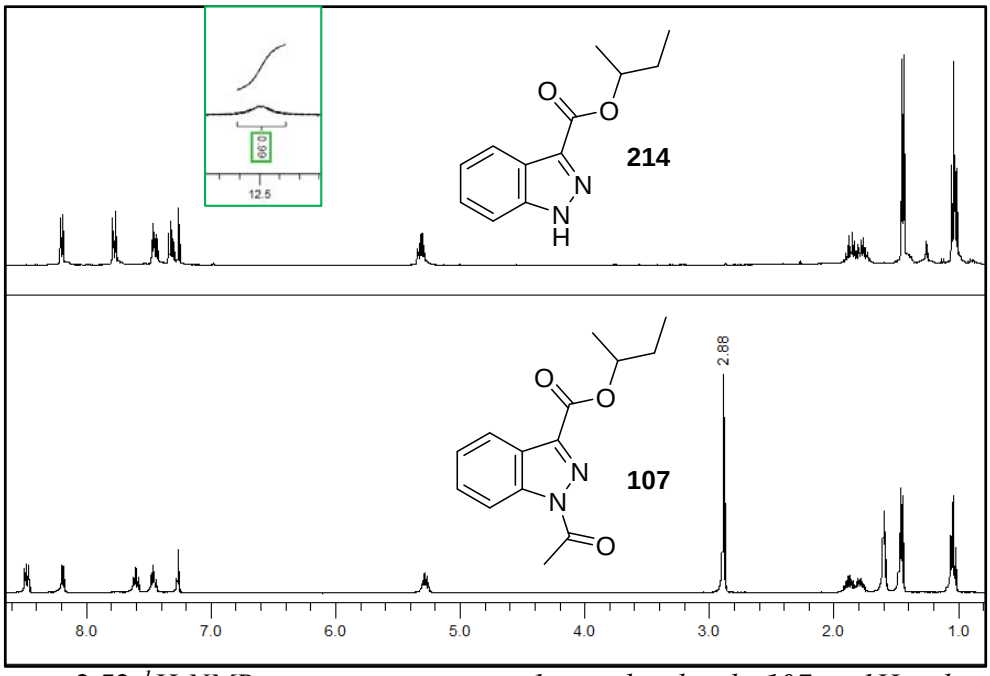
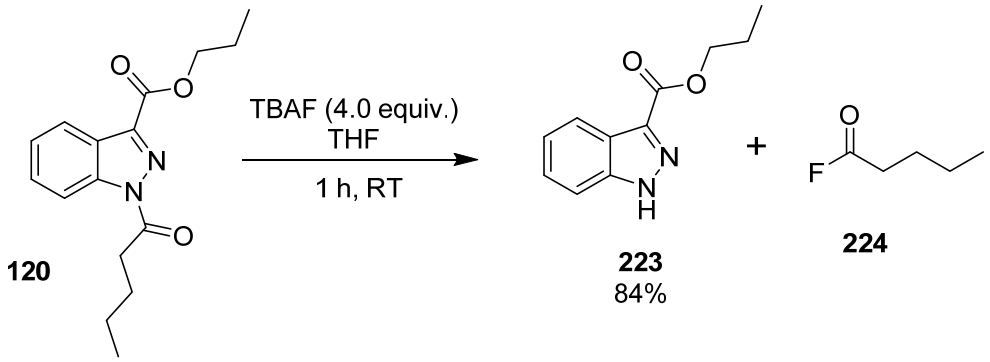


Figure 2.52 *^{1}H NMR* spectra *comparison 1-acetyl-indazole **107** vs 1H-indazole **214***

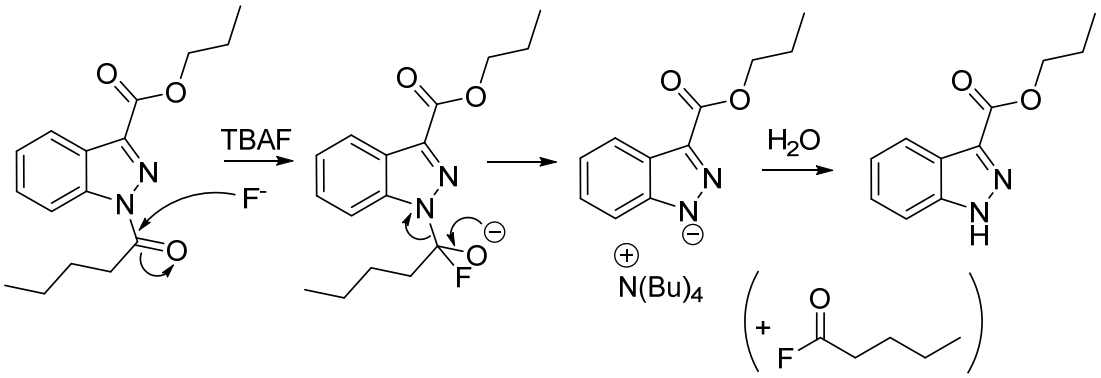
In the ^{13}C NMR spectra, the most noticeable difference is the loss of the amide carbonyl between δ_C 171.3 and 171.6 ppm. The IR spectra for the compounds contain broad bands in the region of ν_{max} 3000-3430 cm^{-1} for the amine NH and those 1-acyl-1*H*-indazole compounds that had two carbonyl stretches as *N*-acyl derivatives now have one sharp band at ν_{max} 1715 and 1730 cm^{-1}.

The next derivatives deacylated included a 1-pentanoyl derivative **120** which showed that this approach works well for acyl groups in general and not just acetyl groups (**Scheme 2.51**). This product **223** required a slightly extended period of time under vacuum to fully remove the side product **224**. In the ^{1}H NMR spectrum, the broad NH singlet is at δ_H 12.50 ppm and the disappearance of all signals from the pentanoyl group is observed. In the ^{13}C NMR spectrum, the most characteristic differences is the loss of four aliphatic carbon signals as well as the amide carbonyl at δ_C 174.4 ppm. The IR spectrum contains a broad amine band at ν_{max} 3278 cm^{-1}.



Scheme 2.51

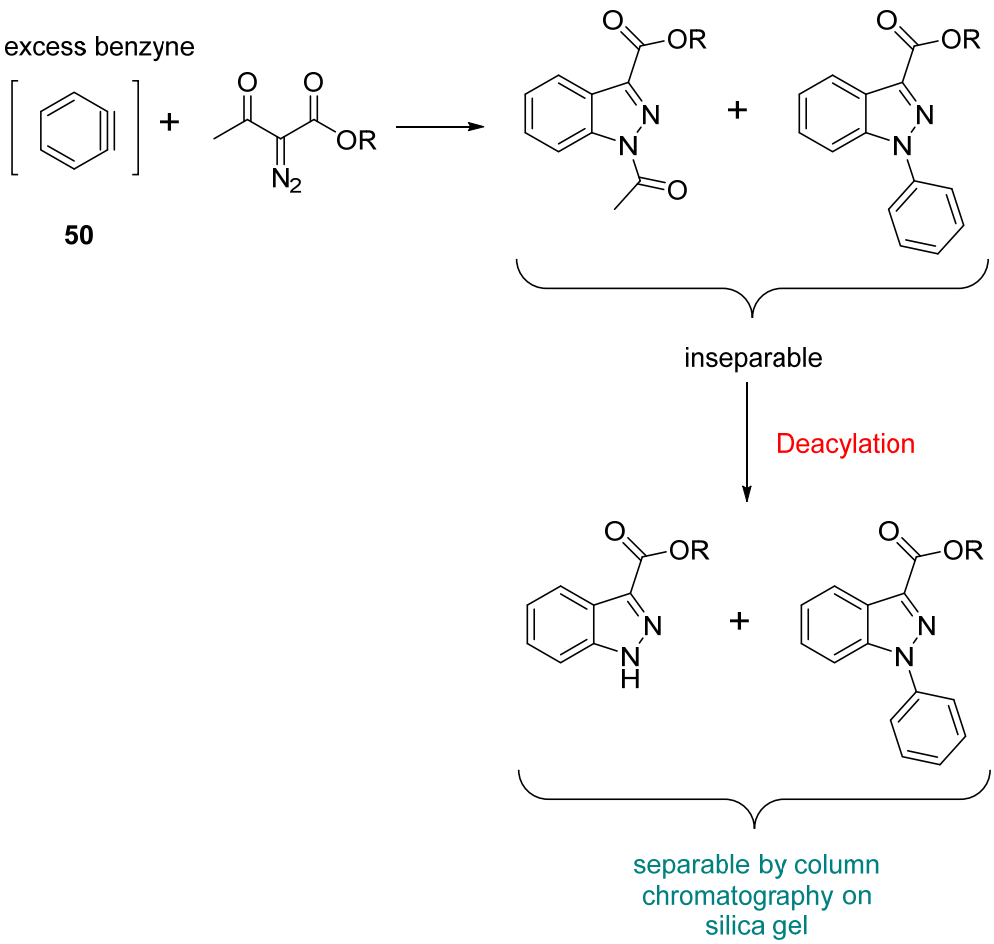
The proposed mechanism suggests the initial nucleophilic attack of fluoride ion on the amide carbonyl. The stable indazolic anion formed can delocalise the negative charge extensively until the reaction is quenched to give the 1*H*-indazole derivative (**Scheme 2.52**).[71,72]



Scheme 2.52

2.7.2 Isolation of *N*-aryl by-product

As alluded to in **Section 2.4**, the *N*-aryl by-products, which could not be separated from the 1-acyl derivatives at that stage, were isolated from these reactions. Their production is due to excess benzyne in the reaction (**Scheme 2.53**).



Scheme 2.53

Three derivatives **225-227** were isolated (**Figure 2.53**) but as the amount of material was minimal, full characterisation was only obtained for **225** which has previously been reported in the literature.[5] The separation of the 1*H*- and 1-acyl-indazole compounds from each other was relatively easy using column chromatography on silica gel.

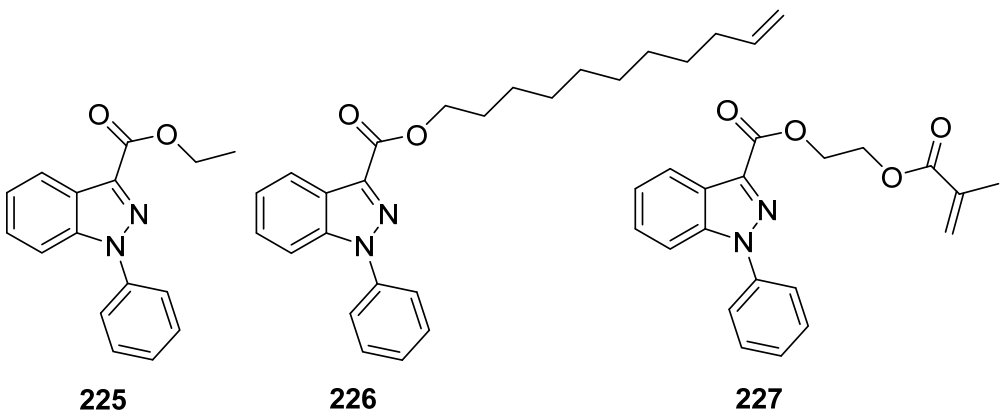


Figure 2.53 *N-aryl by-products isolated*

Figure 2.54 show the differences in the aromatic region of the 1*H*- and 1-phenyl-derivatives; the aliphatic regions for both compounds are almost identical. The aryl region of the *N*-phenyl derivatives show characteristic signals: a 1H doublet between δ_H 8.28-8.35 ppm and a 3H multiplet between δ_H 7.69-7.81 ppm.

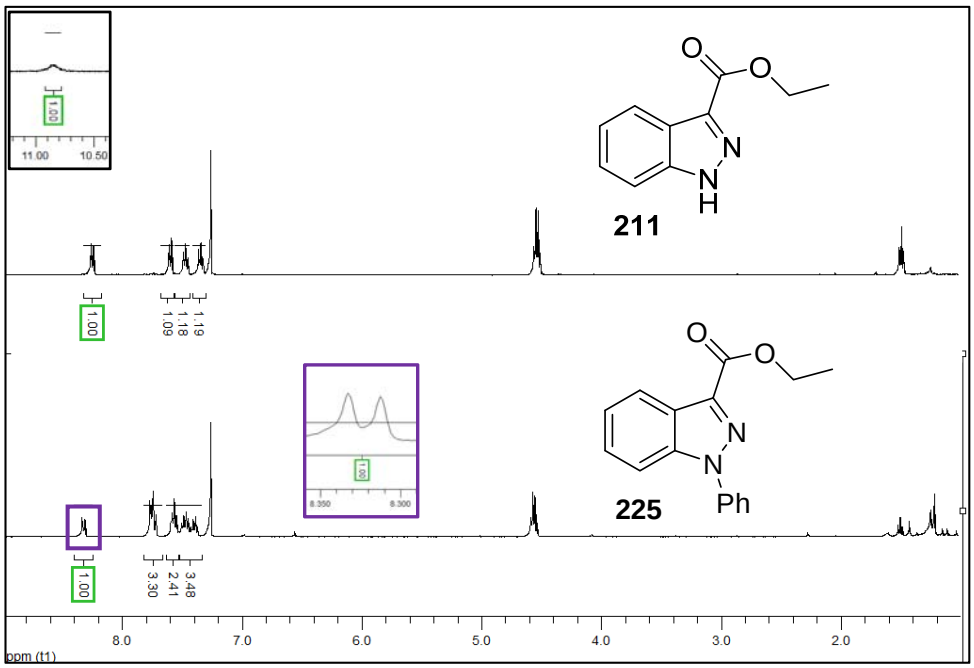


Figure 2.54 *^1H NMR* spectra *of aryl region of **225** vs **211***

Insufficient sample meant that ^{13}C analysis on these derivatives could not detect the quaternary carbon signals.

An apparent triplet of triplets is observed between δ_H 8.28-8.35 ppm for derivative **226** instead of the expected doublet (**Figure 2.55**). However, the intensities of the signals are not consistent with a true triplet of triplet. The signal is assigned here as a multiplet as there may possibly be unresolved ^5J coupling to the *ortho* protons in the *N*-phenyl ring.

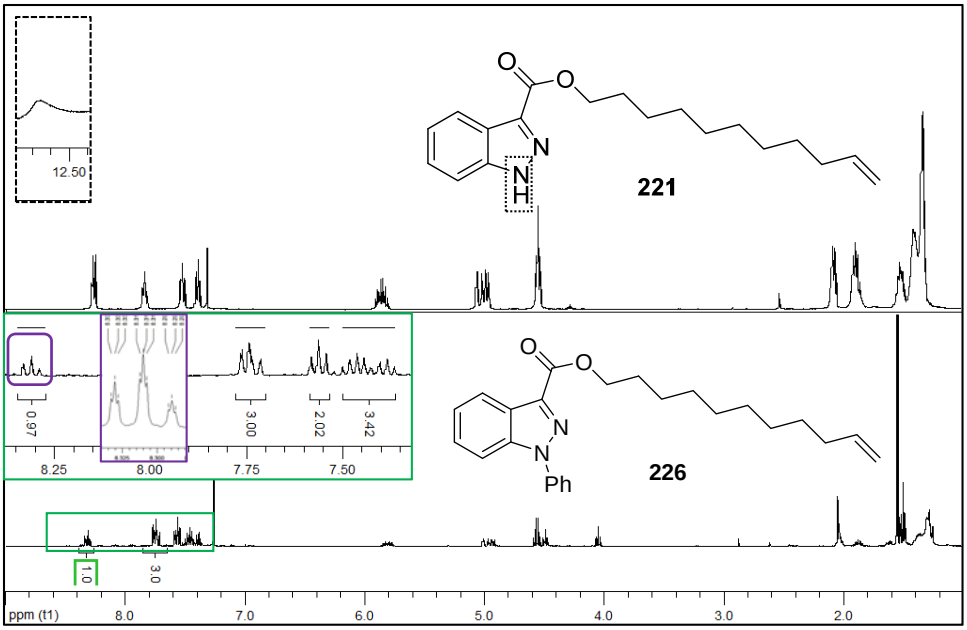
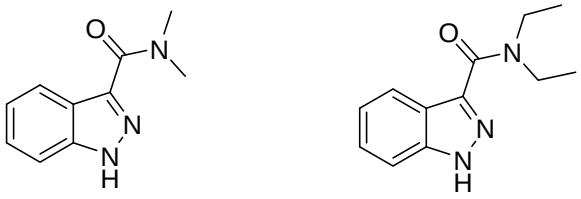


Figure 2.55 *NMR* spectra *comparison of **221** vs **226***

2.7.3 *N*-Deacylation of 1*H*-indazole carboxamide derivatives

The deacylation method described above also worked efficiently to furnish the two known 1*H*-indazole carboxamide derivatives **228** and **229** (**Figure 2.56**) as confirmed by their comparison to literature data.[73,74] The only difference in characteristic signals from the 1*H*-indazole carboxylate derivatives is the IR spectra for these compounds shows the amide carbonyl stretch is between ν_{max} 1629 and 1684 cm^{-1}.



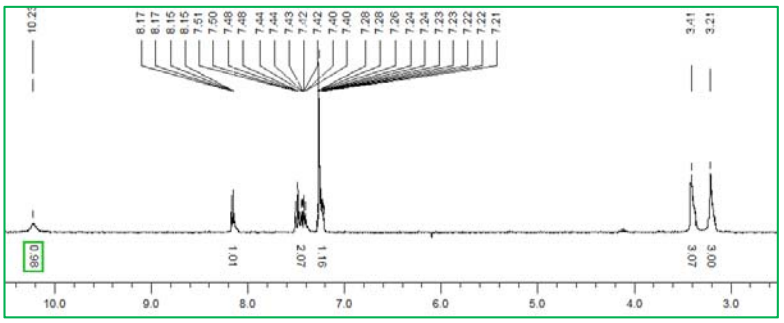
228
49%

229
55%

Figure 2.56 *1H-indazole carboxamide derivatives*

The ^{1}H NMR spectra of **228** is shown in **Figure 2.57** and characteristic peaks include: appearance of the broad NH singlet at δ_H 10.23 ppm, the upfield shift of the aromatic proton signals from δ_H 8.44-7.41 ppm to δ_H 8.16-7.26 ppm and the disappearance of the acetyl CH_3 peak from δ_H 2.78 ppm. Another set of distinct

signals in the ^{1}H NMR spectrum are at δ_H 3.21 and 3.41 ppm for the inequivalent sets of CH_3 groups on the nitrogen.



228

Figure 2.57 *^{1}H NMR spectrum of* ***228***

2.7.4 *N*-Deacylation of substituted 1-acyl indazoles

The next series of reactions involve the use of substituted 1-acyl indazole derivatives. These compounds had been prepared using the optimised procedure that utilised excess diazo starting material, to limit the formation of the *N*-aryl by-product. The optimised deacylation procedure that used increased equivalents (4 equiv. instead of 3 equiv.) of TBAF was also in place for these derivatives. For these reasons, the pure products could be isolated after the water work-up without further purification and with no evidence of starting material or by-products being present.

The first series of deacylation derivatives prepared have the methylenedioxy bridge on the indazole ring, an *N*-acetyl group and all contain ester side chains in the 3-position (**Figure 2.58**).

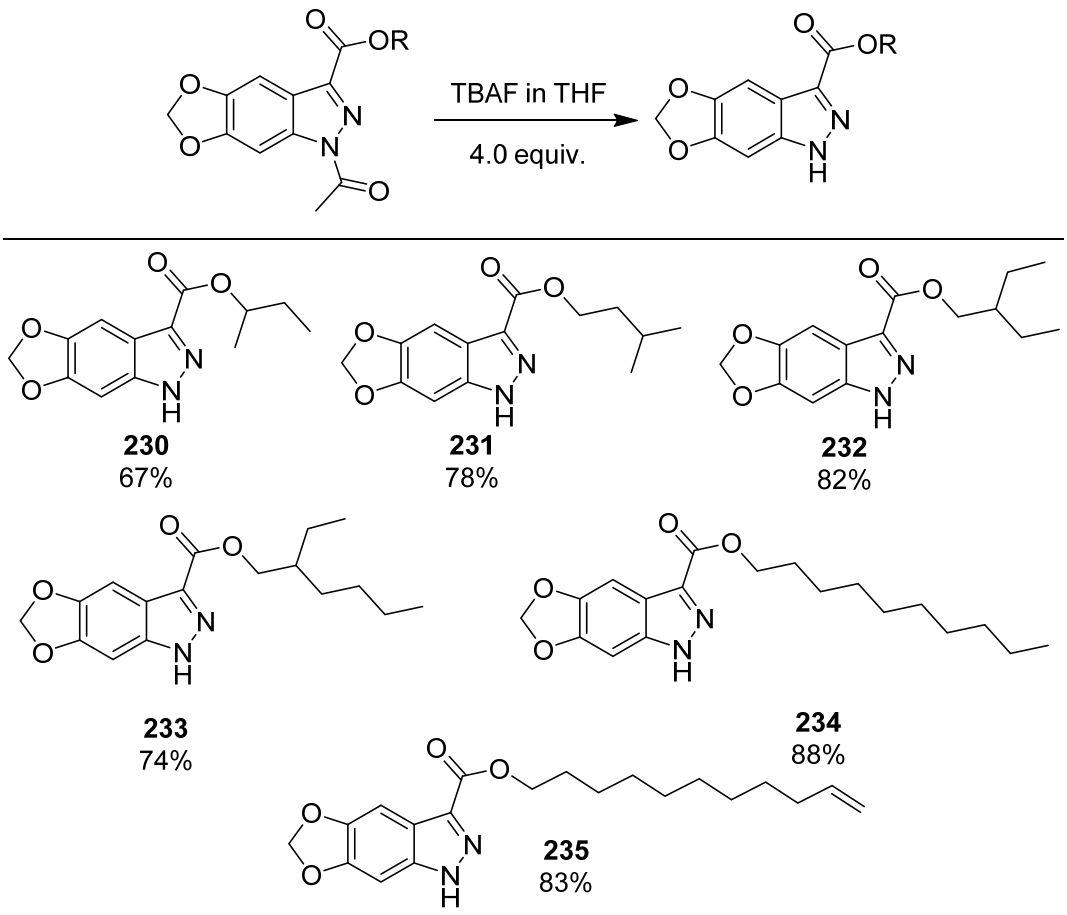


Figure 2.58 *First series of substituted N-deacetylated compounds*

All reactions proceeded smoothly to provide 6 novel methylenedioxy-containing indazole compounds in good yields and high purity. In the ^{1}H NMR spectrum, characteristic signals include the appearance of the broad NH singlet between δ_H 11.41-12.11 ppm (except in the cases of **232** and **235** where the NH signal was not visible), the upfield shift of the aromatic proton signals of about 0.4 ppm in both cases from δ_H 7.44-7.47 ppm and 7.88-7.89 ppm to δ_H 6.99-7.12 ppm and 7.42-7.46 ppm respectively and the disappearance of the acetyl CH_3 peak in the region of δ_H 2.84-2.87 ppm. The methylene protons of the methylenedioxy moiety are observed at δ_H 6.05-6.06 ppm in all spectra (**Figure 2.59**).

In the ^{13}C NMR spectrum, the most characteristic difference is the loss of the amide carbonyl at δ_C 171.6 ppm and the acetyl group CH_3 at δ_C 22.9 or 23.0 ppm, methylene group appeared at δ_C 101.7 or 101.8 ppm and the aromatic CH

signals shift upfield from the *N*-acyl compounds from δ_C 95.7 and 99.3 or 99.4 ppm to 90.5-90.8 and 98.3-98.5 ppm in all cases.

The IR spectra for the compounds contain broad bands in the region of ν_{max} 3193-3455 cm^{-1} for the amine NH and the two carbonyl stretches for the ester and amide now appear as one sharp band between ν_{max} 1727 and 1736 cm^{-1}. Six of these derivatives were prepared (**Figure 2.58**).

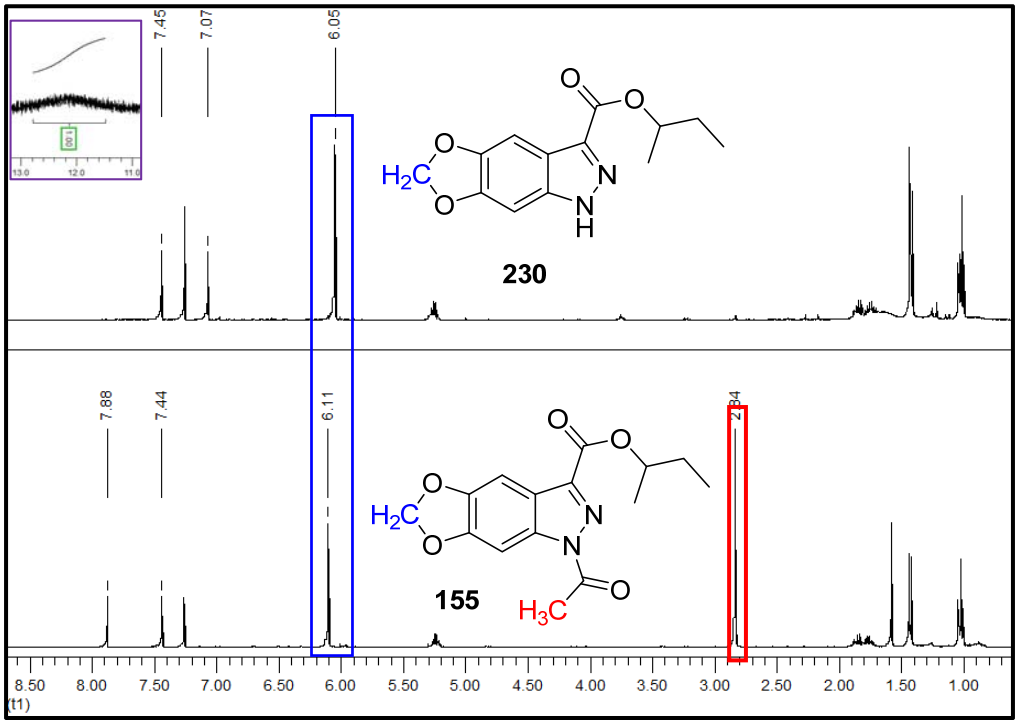


Figure 2.59 *^{1}H NMR* spectra *comparison N-acyl **155** vs deacylated **230***

The next series described are the derivatives prepared from deacylation of our difluoro- and dimethyl-indazole compounds described earlier. As encouraging biological testing results on the *N*-acyl versions of these compounds were obtained (which will be discussed further is **Section 2.10**), using the core structure for derivatisation was seen to be advantageous. Four disubstituted deacylated derivatives were prepared in good yields as white solids (**Figure 2.60**). In addition to being candidates for biological testing in their own right, further derivatisation of these compounds would provide excellent substrates also to be tested which will be discussed in **Section 2.8**.

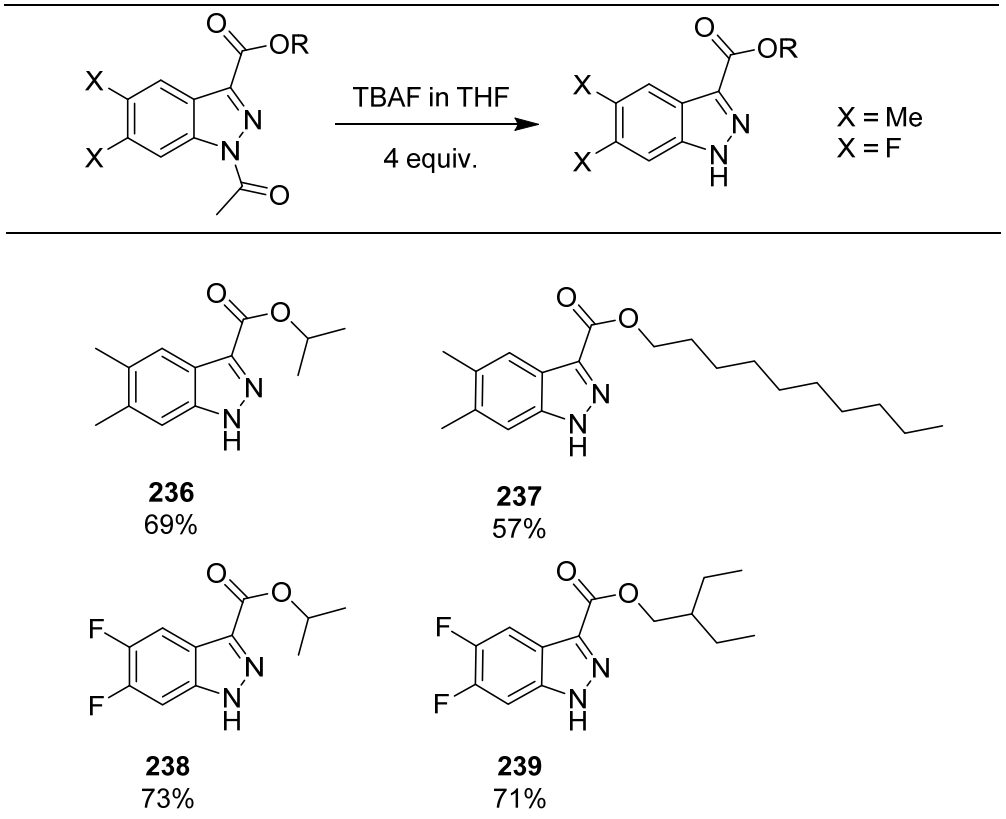


Figure 2.60 *Disubstituted deacylated indazole derivatives*

The ^{1}H NMR spectra of the dimethyl derivatives **236** and **237** show characteristic signal differences from the *N*-acyl derivatives include that the methyl groups attached to the aryl ring now appear as a 6H singlet at δ_H 2.40 ppm rather than two separate signals and the acetyl CH_3 signal has disappeared from δ_H 2.85 ppm (**Figure 2.61**). The amide carbonyl signal at δ_C 171.5 ppm and the acetyl CH_3 at δ_C 23.0 ppm from the starting material are not present in the ^{13}C NMR spectra. The IR spectra for the compounds contain broad bands in the region of ν_{max} 3267-3382 cm^{-1} for the amine NH and the amide carbonyl stretches are no longer present. The ester carbonyl stretches are observed from ν_{max} 1718 to 1732 cm^{-1}.

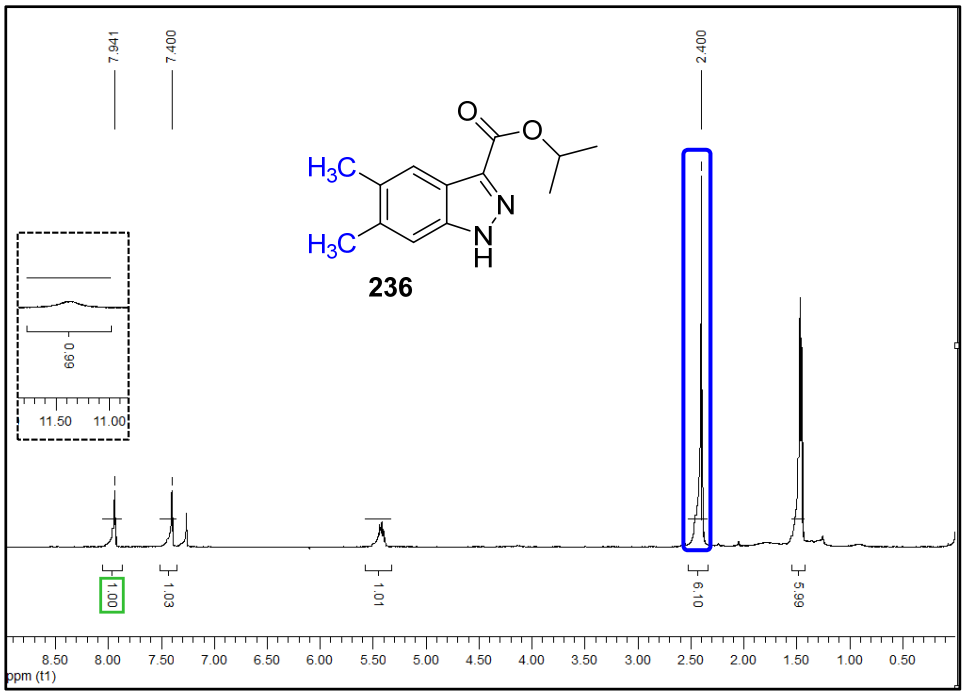


Figure 2.61 *^{1}H NMR spectrum of **236***

Similarly, for the difluoro-derivatives, characteristic features in the ^{1}H NMR spectra (**Figure 2.62**) include the disappearance of the acetyl CH_3 signal from δ_H 2.86 ppm and two doublet of doublets for the aromatic protons in the aryl region. In the ^{13}C NMR spectra, the amide carbonyl signal at δ_C 171.2 ppm and the acetyl CH_3 at δ_C 22.7 or 22.8 ppm are not present. Again in the IR spectra, a stretch from ν_{max} 3212-3647cm^{-1} for the amine NH is observed, the amide carbonyl stretches are no longer present and only ester carbonyl stretches at ν_{max} 1726 and 1733 cm^{-1} can be observed.

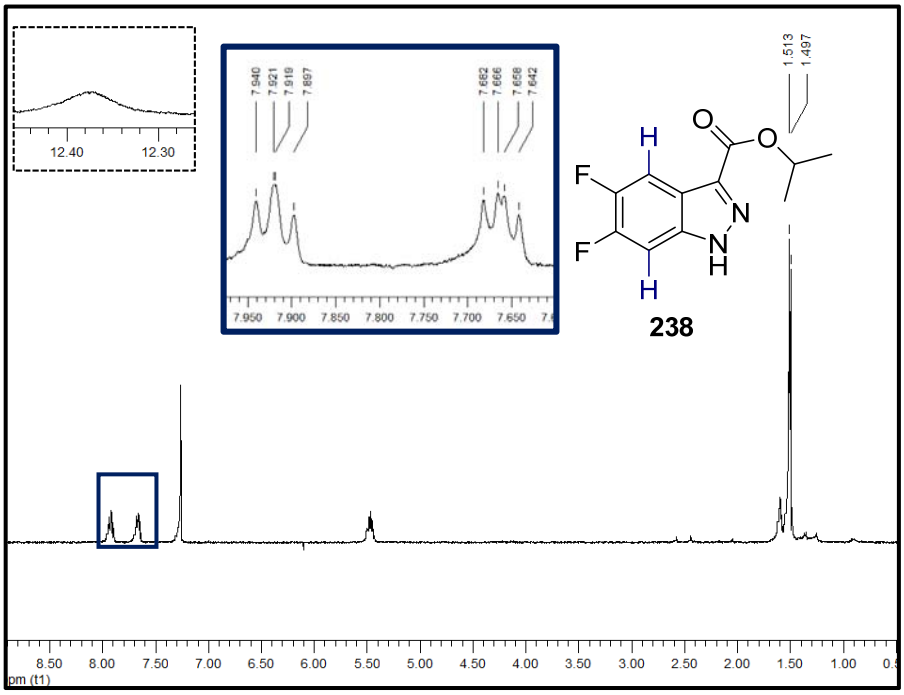


Figure 2.62 *^{1}H NMR spectrum of **238***

For **239** rather than 2 separate aryl doublet of doublets signals, usually observed as shown in **Figure 2.62**, an apparent triplet of doublets signal is observed (due to unresolved coupling) and is assigned as a multiplet (**Figure 2.63**).

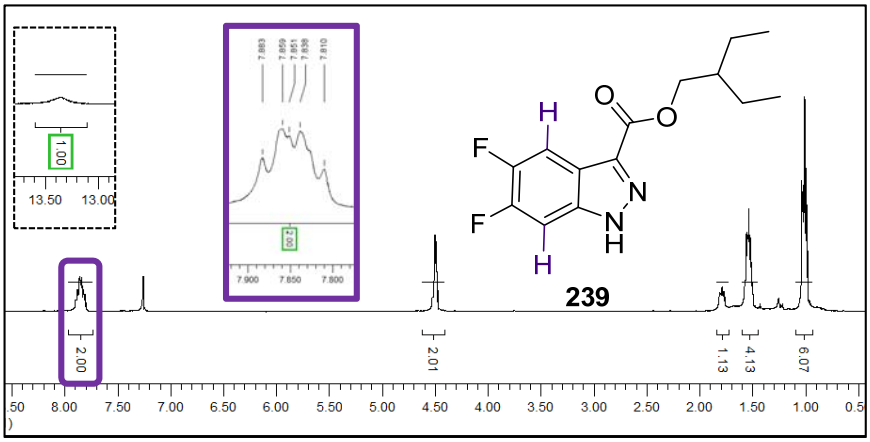
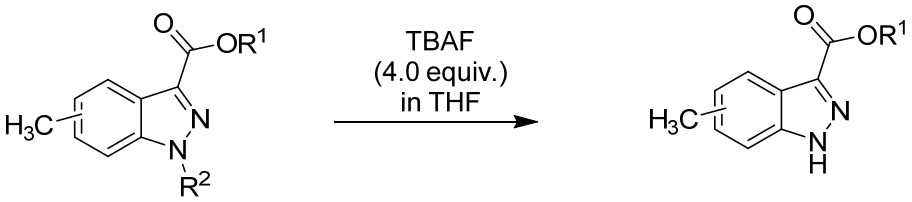


Figure 2.63 *^{1}H NMR spectrum of **239***

The last two reactions described in this deacylation section involve the 1:1 mixture of 5/6-methyl *N*-butyryl- and *N*-pentanoyl indazole derivatives **193/194** and **195/196**. Successful deacylation of these compounds was also achieved to provide a mixture of regioisomers (**Scheme 2.54**). This was confirmed again by ^{1}H NMR and ^{13}C NMR spectra where the characteristic disappearance of signals

for the *N*-acyl groups as well as the appearance of amide carbonyl signal at δ_C 174.1/174.2 ppm are observed. Again in the IR, a stretch from ν_{max} 3269-3281cm^{-1} for the amine NH is observed and the amide carbonyl stretches are no longer present leaving just ester carbonyl stretches at ν_{max} 1713 and 1722 cm^{-1}.



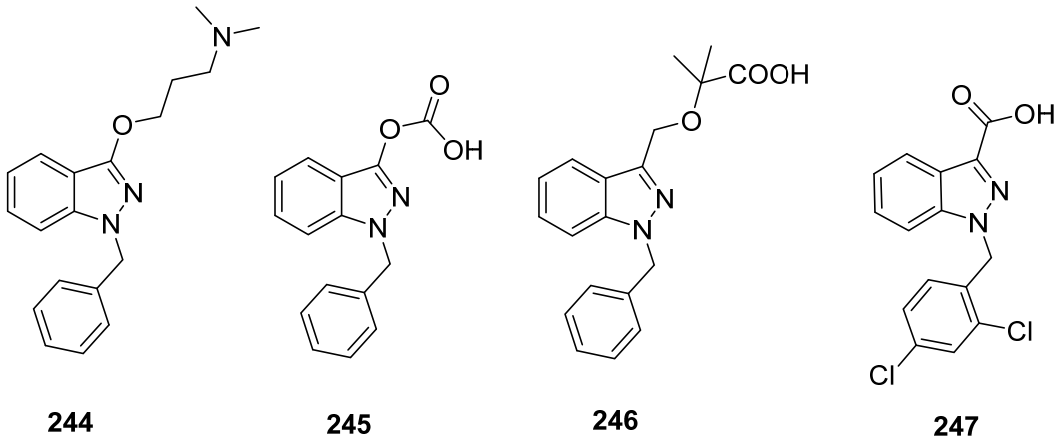
193/194 : R^1 = Me, R^2 = *n*-pentanoyl, 62% **240/241 :** R^1 = Me, R^2 = *n*-pentanoyl, 62%
195/196 : R^1 = Et, R^2 = *n*-butyryl, 80% **242/243 :** R^1 = Et, R^2 = *n*-butyryl, 80%

Scheme 2.54

This deacylation section described the chemistry that provided access to 22 novel and useful 1*H*-indazole derivatives which were prepared for biological testing. Alkylation of these derivatives will be described in the next section (**2.8**). It is a mild method that can be used with a range of substrates with varying functionality and does not usually require further purification after the aqueous workup.

2.8 Benzylation of 1*H*-indazole derivatives

A major aim in this project was to synthesis *N*-benzyl indazole derivatives as many indazole drugs on the market or in late stage clinical trials for therapeutic activities contain a benzyl group in the structure including those shown in **Figure 2.64**. Benzydamine **244** is marketed as Difflam™ and is a locally acting analgesic and anti-inflammatory used in treatment of painful inflammatory conditions of the mouth and throat. Bendazac **245** is an NSAID used topically for joint and muscular pain. Bindarit **246** is being investigated for its anti-inflammatory effects against a variety of conditions such as arthritis and lonidamine **247** is an anti-cancer therapeutic agent.[75]

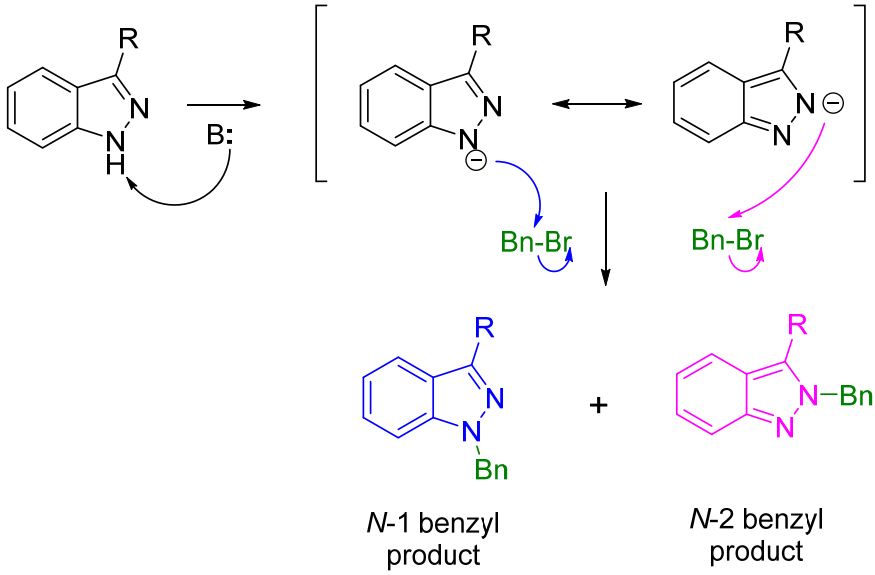


244 **245** **246** **247**

Figure 2.64 *Benzylated indazole derivatives displaying therapeutic activities*

In general, 1-alkyl isomers are thermodynamically more stable whereas the 2-alkyl derivatives are kinetically favoured. Benzylation under basic conditions is less selective and usually provides equimolar regioisomeric products, however, the ratio of the isomers is influenced by electronic and steric effects.

Indazole benzylation proceeds under basic conditions *via* an ambident indazolyl anion to provide a mixture of two distinct isomeric products to a mixture of 1-benzyl-1*H*- and 1-benzyl-2*H*-indazoles (**Scheme 2.55**).



Scheme 2.55

This section describes the synthetic routes utilised to provide a range of novel benzylated derivatives to send for biological evaluation.

2.8.1 Initial benzylation reactions[65,76]

The 1*H*-indazole derivatives prepared in **Section 2.7** were used as substrates in the alkylation reaction as illustrated in **Figure 2.65**. A mixture of *N*-1 and *N*-2 products were separated to provide a range of novel benzylated compounds in combined yields of 44-59% after column chromatography on silica gel.

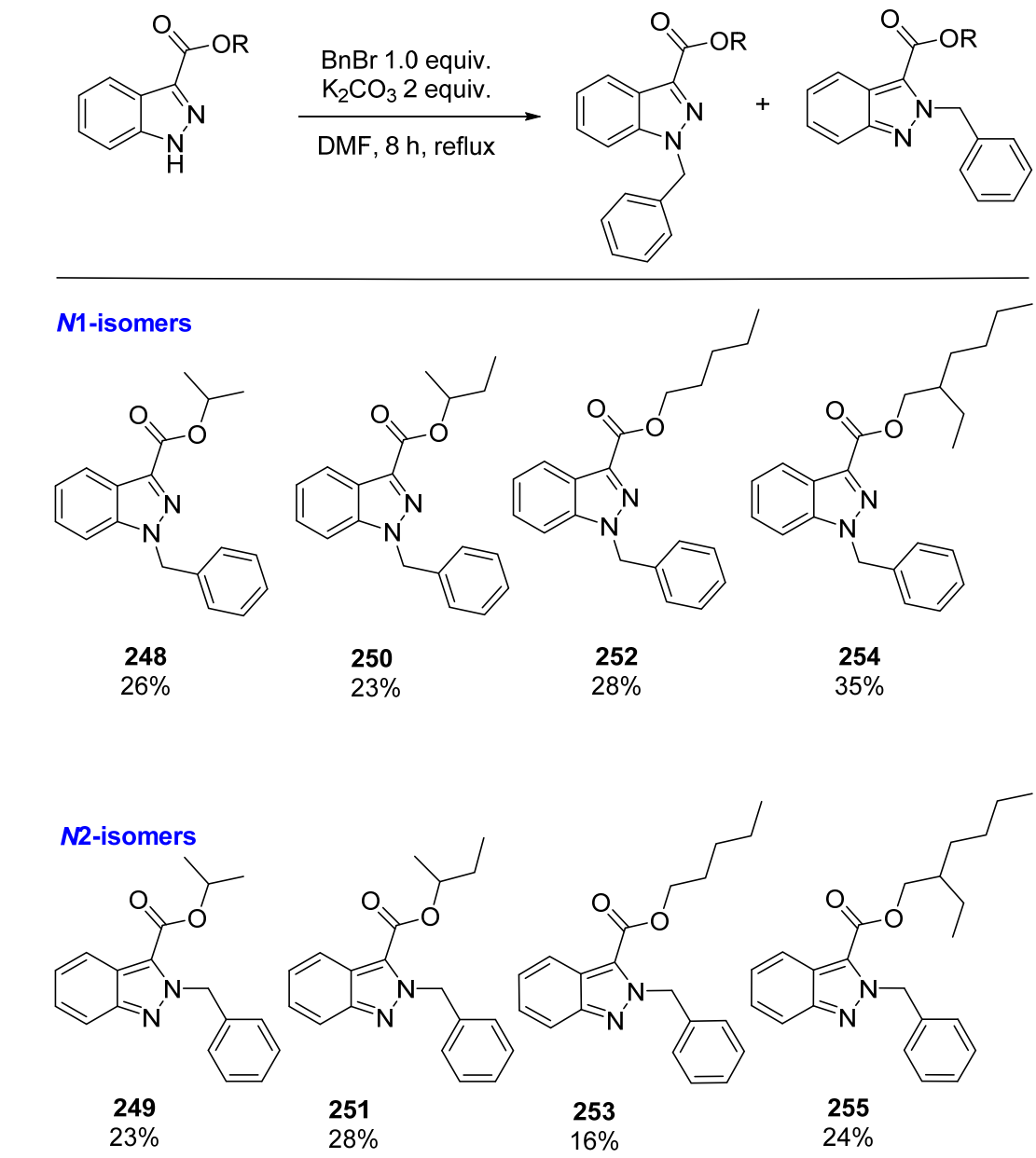


Figure 2.65 *First series of benzylation products*

In all cases the *N*-2 isomer was eluted first followed by the *N*-1 isomer in combined yields of 44-59%. The separate structures of the *N-1* and *N-2* derivatives are confirmed by analogy to similar derivatives in the literature (**Figure 2.66**).[66,65] For example, the *N*-1 isomer, H-7 in the ^{1}H NMR spectra of both derivatives **256** and **248** are doublet signals at δ_H 8.21 ppm with the same *J* value coupling constant and the benzyl CH_2 singlet is *ca.* δ_H 5.7 ppm for both compounds. For the *N*-2 isomer, H-7 in the ^{1}H NMR spectra of both derivatives **257** and **249** are doublet-type signals in the range δ_H 7.81-7.93 ppm with similar *J*

value coupling constants and the benzyl CH_2 singlet is between δ_H 6.11-6.20 ppm for both compounds.

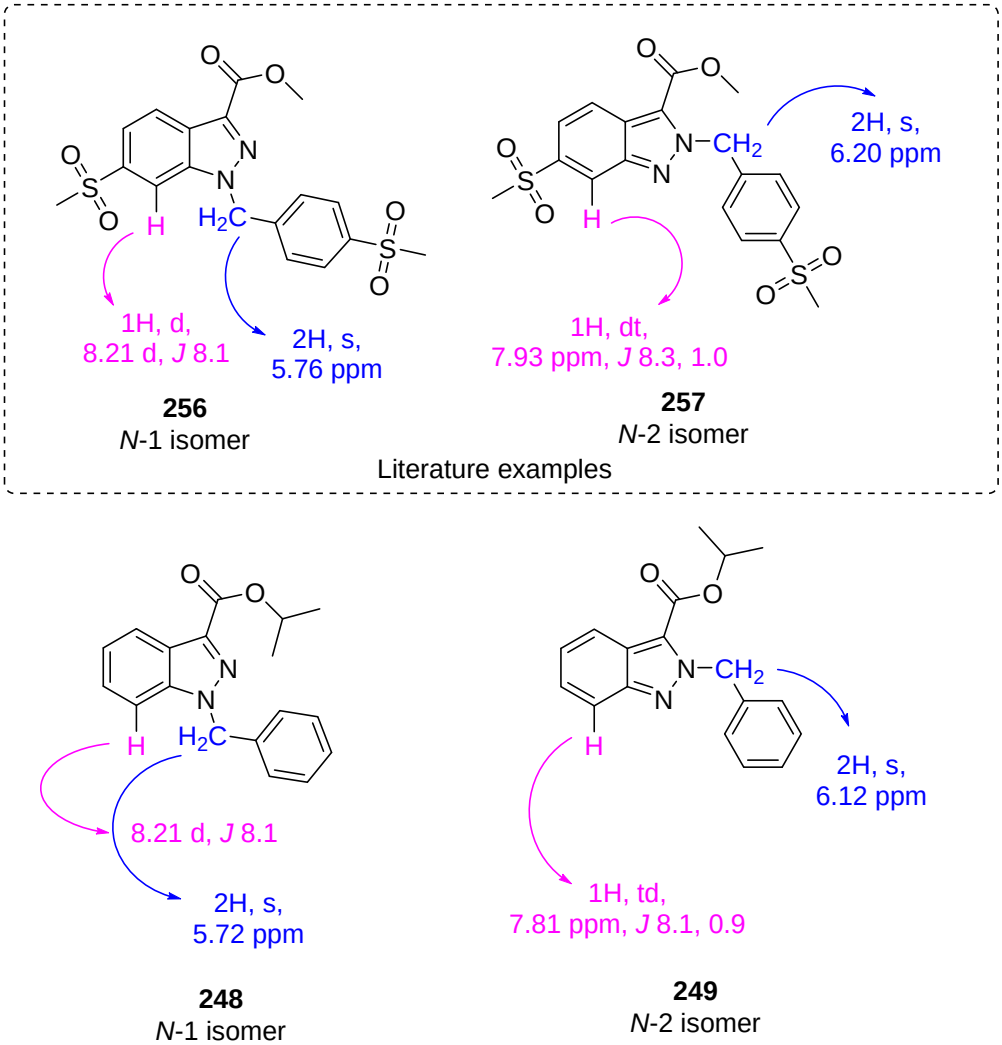


Figure 2.66 *Literature comparison of N-1 and N-2 benzylated isomers*

The isomers are easily differentiated by their ^{1}H NMR spectra in the aromatic region where the *N-1*-isomer always has a 1H doublet between δ_H 8.18-8.21 ppm and an 8H multiplet more upfield between δ_H 7.20-7.38 ppm; the *N-2*-isomer always has two doublet-type signals at δ_H 8.02-8.03 ppm, δ_H 7.81-7.82 ppm and a 7H multiplet between δ_H 7.23-7.45 ppm. The benzyl CH_2 group appears at δ_H 5.71/5.72 ppm in the *N-1* isomer and at δ_H 6.12/6.13 ppm in the *N-2* isomer. Representative examples of the ^{1}H NMR of *N*-1 isomer **252** and *N*-2 isomer **253** are shown in **Figure 2.67**.

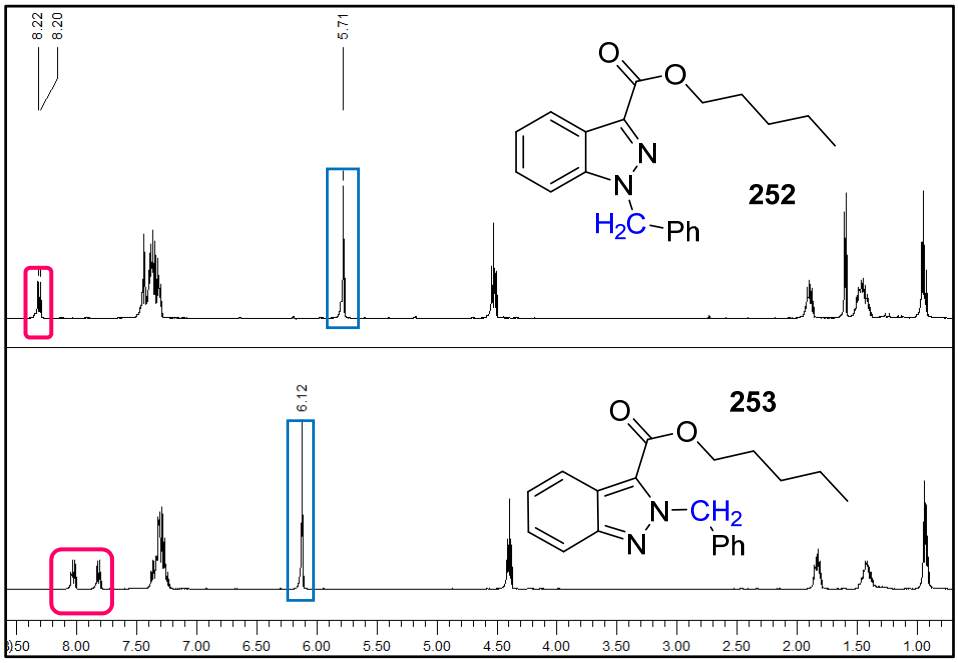
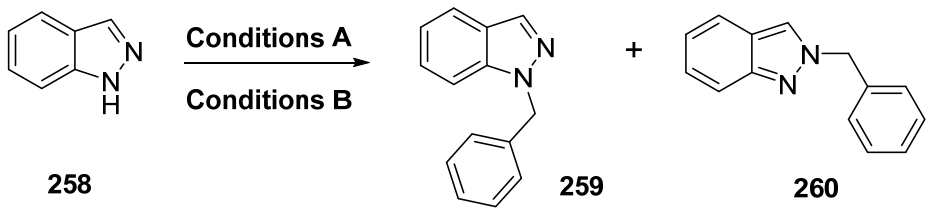


Figure 2.67 *^{1}H NMR spectra comparison N-1 vs N-2 isomers*

In the ^{13}C NMR spectra the benzyl CH_2 of the *N-1* isomer appears at δ_C 54.1 ppm in all cases and at δ_C 56.5 or 56.6 ppm for the *N-2* isomer. In the IR spectrum, broad stretches from ν_{max} 3269-3281cm^{-1} for the primary amine NH starting material are not present and the ester carbonyl stretches are in the very narrow range of ν_{max} 1707-1709 cm^{-1} for these eight derivatives.

The ratios of the *N*-1:*N*-2 isomers can be influenced by the ester side chains slightly preferentially forming the less sterically hindered product and there are methods reported in the literature to induce the formation of one isomer over another.[77,78] For example, performing the reaction under phase transfer conditions at different temperatures considerably affects the ratio of isomers formed (**Scheme 2.56**).



Conditions A: BnCl, K_2CO_3,KOH, 5% TBAC, xylene, 160°C, 16 h

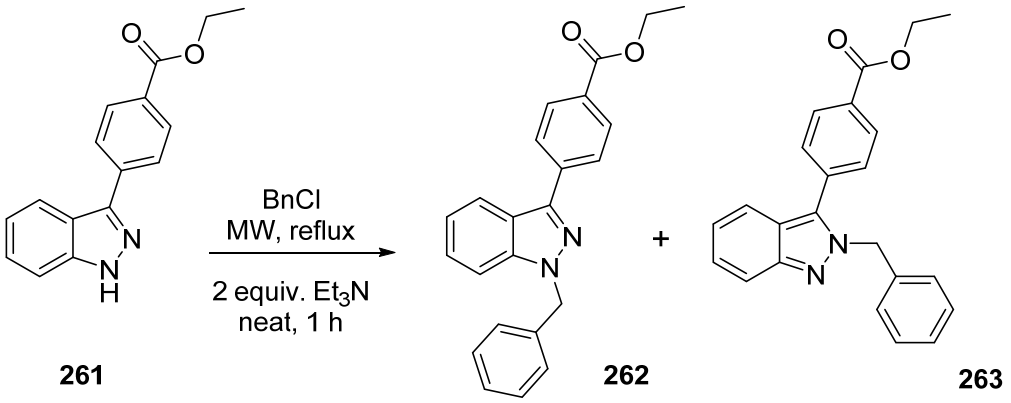
Conditions B: BnCl, K_2CO_3, KOH, 5% 18-Crown-6, CCl_4, 25°C, 6 h

Conditions A
ratio
60.5 : 39.5
86%

Conditions B
ratio
38.7: 61.3
72%

Scheme 2.56

Chromatographic separation on silica gel was used in this project to isolate both isomers as investigation of biological activity of both derivatives was desired. However, methods to form exclusively one isomer over the other were not applied here but could be looked at in the future as a more attractive route to the compounds. The yields of these reactions could be improved upon and future work will involve using microwave conditions in the alkylation reactions as a reported method in the literature shows similar reactions forming product in up to 82% yields in 15 mins under these conditions, favouring the *N*-2 isomer (**Scheme 2.57**).[78]



Scheme 2.57

No correlation in melting point values were observed across our range of isomers although literature precedence indicates the *N-1* isomers usually melt at a lower point than their *N-2* counterparts. For example, *N*-1 isomer **252** is a yellow oil while *N*-2 isomer **253** is a white solid with a melting point of 69-70°C.

2.8.2 Benzylation reactions of substituted indazole derivatives

The following series of compounds prepared have difluoro- and dimethyl-substitution on the indazole core structure and incorporate an isopropyl ester side chain. These compounds were chosen as their *N*-acyl precursors (2 steps previous in **Section 2.5.3.2**) gave encouraging biological results which will be discussed in **Section 2.10**. By introducing a benzyl group in the 1-or 2-positions it was hoped to increase this observed activity based on compounds currently on the market. Again, for these derivatives the *N*-2 isomer was eluted first followed by the *N*-1 isomer in combined yields of 27-28% (**Figure 2.68**).

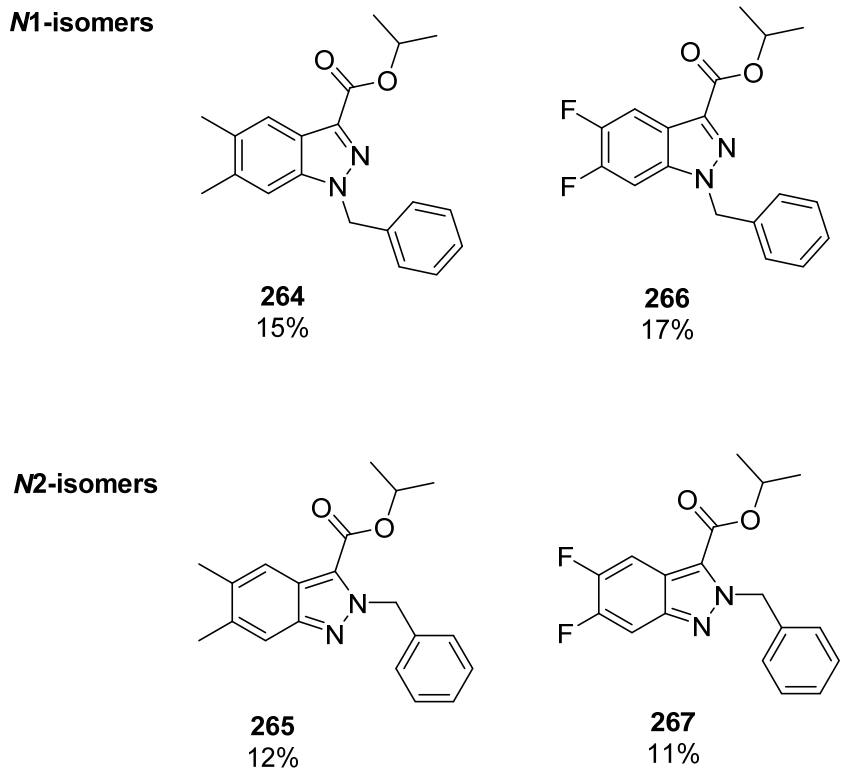


Figure 2.68 *Substituted N-benzyl derivatives*

Dimethyl derivatives

The substituted *N*-1 and *N*-2 benzylated isomers **264** and **265** were easily differentiated by their ^{1}H NMR spectra in the aromatic region where the *N-1*-isomer contains two 1H singlets at δ_H 7.08 and 7.94 ppm and 2H and 3H multiplets in between those signals; the *N-2*-isomer has two singlets at δ_H 7.55 and 7.75 ppm and a 5H multiplet upfield of those. The benzyl CH_2 group appears at δ_H 5.66 ppm in the *N-1* isomer and at δ_H 6.06 ppm in the *N-2* isomer (**Figure 2.69**).

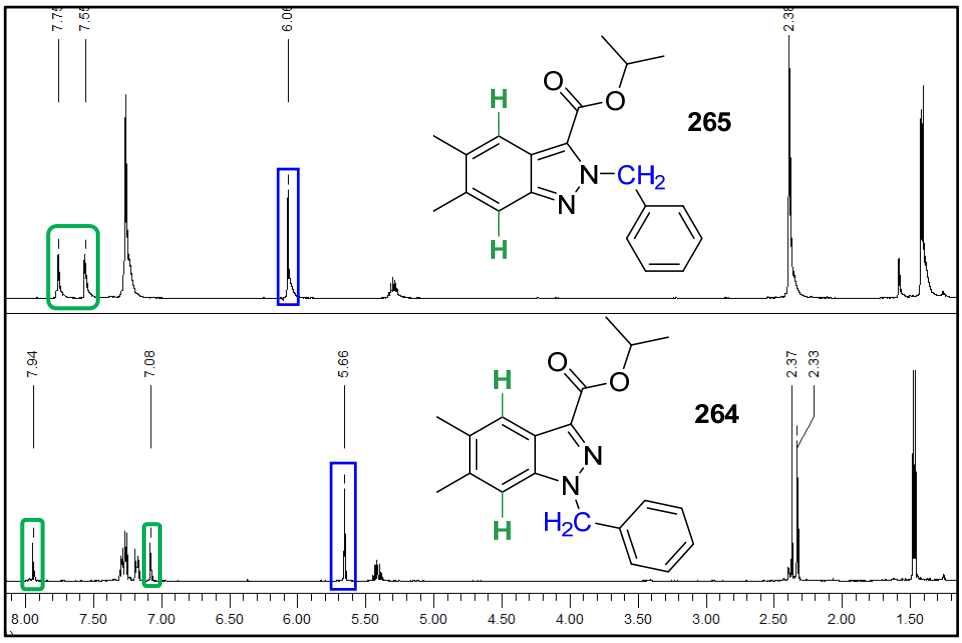


Figure 2.69 *^{1}H NMR spectra comparison N-1 vs N-2 isomers*

In the ^{13}C NMR spectra, the benzyl CH_2 of the *N-1* isomer appears at δ_C 53.9 ppm and at δ_C 56.4 ppm for the *N-2* isomer. In the IR spectrum, the broad stretches from ν_{max} 3269-3281 cm^{-1} for the amine NH starting material are not present and the ester carbonyl stretches are observed at ν_{max} 1709 and 1726 cm^{-1} for the *N-1* and *N-2* derivatives respectively.

Difluoro derivatives

These *N*-1 and *N*-2 isomers are also easily differentiated by their ^{1}H NMR spectra in the aromatic region where the *N-1*-isomer has two 1H doublet of doublet signals at δ_H 7.05 and 7.94 ppm and then a 2H and 3H multiplet in between those signals and the *N-2*-isomer has two 1H doublet of doublet signals at δ_H 7.50 and 7.71 ppm, then a 5H multiplet upfield of those. The benzyl CH_2 groups appear at

the same chemical shift values as the dimethyl derivatives at δ_H 5.66 ppm for the *N-1* isomer and at δ_H 6.06 ppm for the *N-2* isomer (**Figure 2.70**).

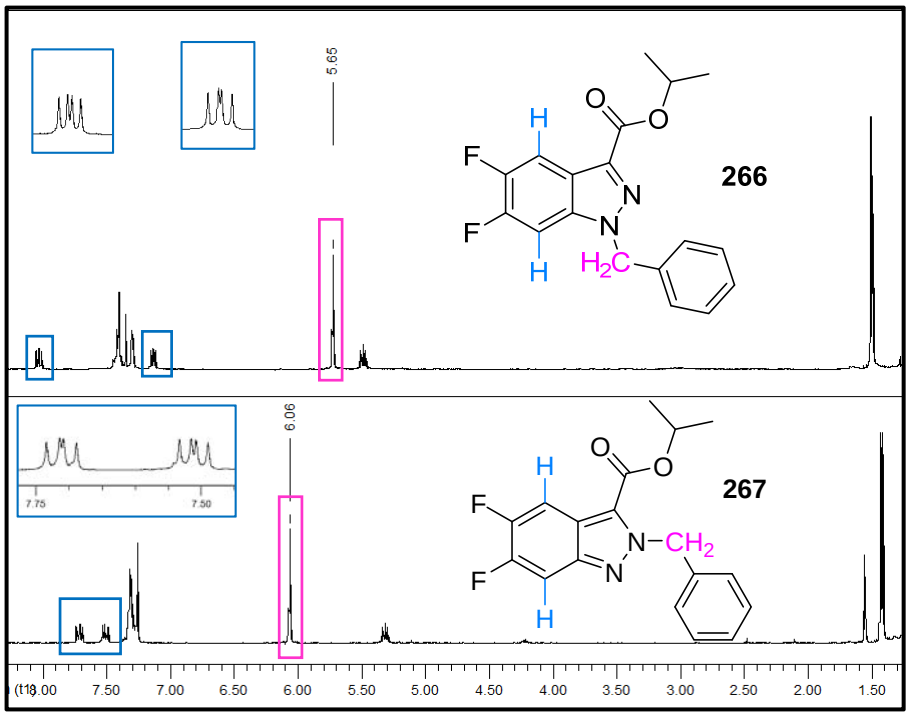


Figure 2.70 *^{1}H NMR spectra of **266** and **267***

In the ^{13}C NMR spectra, the benzyl CH_2 of the *N-1* isomer appears at δ_C 54.6 ppm and at δ_C 56.7 ppm for the *N-2* isomer (**Figure 2.71**).

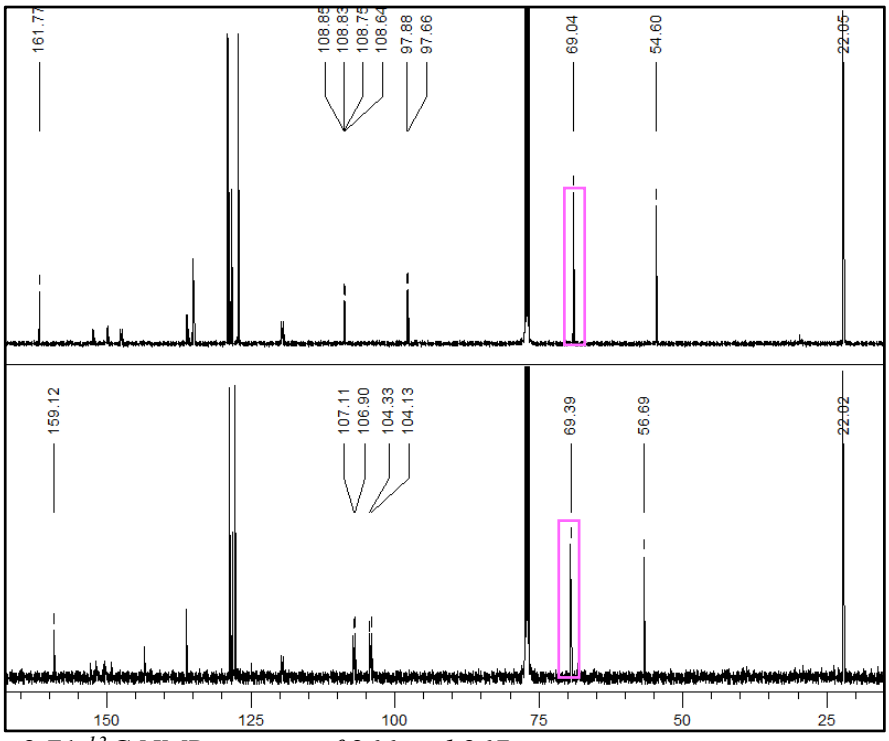


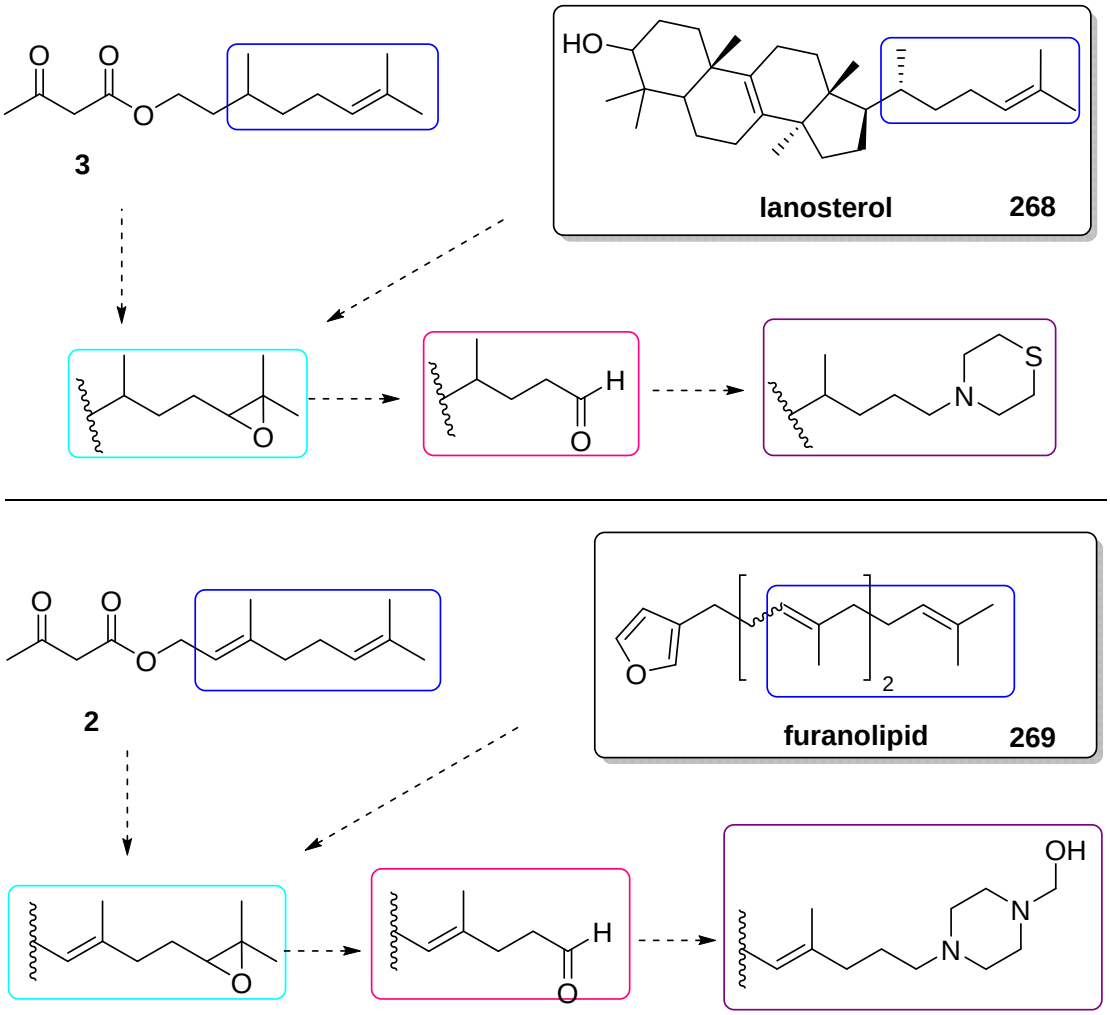
Figure 2.71 *^{13}C NMR spectra of **266** and **267***

In the IR spectrum, broad stretches from ν_{max} 3269-3281 cm^{-1} for the amine NH starting material are not present and the ester carbonyl stretches appear at ν_{max} 1720 and 1711 cm^{-1} for the *N-1* and *N-2* derivatives respectively.

Access to 12 novel *N-1* and *N-2* indazole compounds was described herein. Most notable is the further scope for the preparation of a wide range of novel indazole derivatives, made possible merely by changing the alkylating reagent. Substituted benzyl groups, long alkyl chain derivatives and long chain alkyl halides will be the next alkyl groups to be targeted as their involvement in similar structures has greatly increased the biological activity of our compounds.

2.9 Side-chain transformations

Following on from the long side-chained and functionalised α-diazo-β-ketoesters in **Section 2.2.3**, the preparation of a range of novel β-ketoesters and their diazocarbonyl derivatives is described in the following section. Performing side chain transformations on the functionalisable esters to give more diverse side chains in the range of indazoles is an attractive route to explore. Focus was placed on the synthesis of tertiary amine compounds synthesised *via* epoxide and aldehyde derivatives as shown in **Scheme 2.58**.



Scheme 2.58

These derivatives were chosen as the side-chain of the citronellol ester **2** is similar to the side-chain of lanosterol-type steroids **268** and the geraniol ester **3** is similar to the side-chain of furanolipid-type derivatives **269** .These compounds have previously been transformed to tertiary amines and investigated within the research group, showing excellent cytotoxic and apoptotic anti-cancer activity

potential in U937 model cell lines[79] and positive growth inhibition across the NCI 60 cell line panel at both one- and five-dose testing levels.

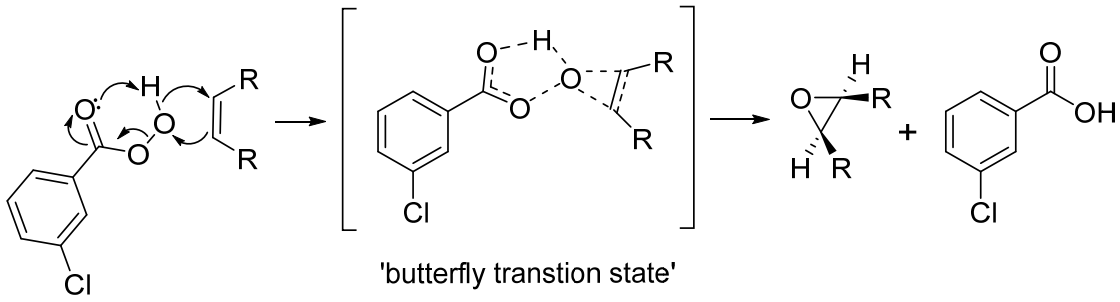
The alkene present in the side chain of the esters enables the formation of epoxide derivatives which in turn allow oxidative cleavage to an aldehyde intermediate which can then be used to introduce amine functionality *via* reductive amination under mild conditions. Using the methodology towards the preparation of tertiary amine derivatives also provides interesting novel epoxide and aldehyde derivatives.

For the above transformations three potential options for introducing the various functional groups were available: after the ester formation, diazo transfer or indazole formation stage. The results of these transformations and reactions are discussed below.

2.9.1 Epoxidations of alkene-containing derivatives

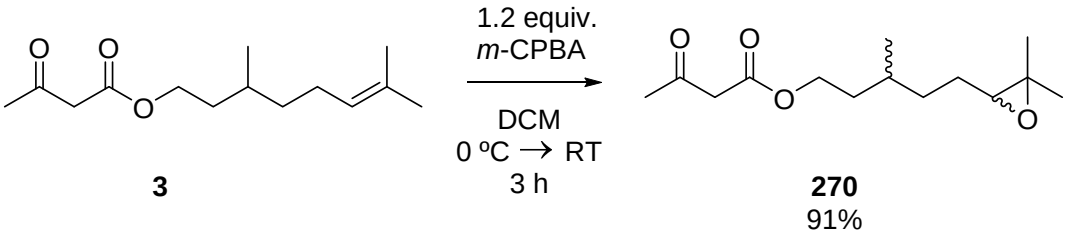
Epoxides are versatile building blocks in organic synthesis and are present in several bioactive compounds. Epoxide formation was successfully achieved in this project using commercially available *m*-CPBA as the oxidising agent and the standard associated reaction conditions to convert the alkene moiety to an oxirane ring.[80] Use of *m*-CPBA in laboratories is preferred over other peroxy acids due to its ease of handling (present as a powder and can be stored in a refrigerator), versatile applicability (such as epoxidation of alkenes, oxidation of sulphides to sulfoxides and sulfones, Baeyer Villiger oxidation of aldehydes and ketones to esters, etc.), higher reactivity (due to the oxygen-oxygen bond being quite weak) and selectivity (stereochemistry is always retained).

The reaction proceeds *via* what is commonly known as the 'Butterfly mechanism' as the transition state in which oxygen is added and proton shifted simultaneously resembles a butterfly. The peroxide is viewed as an electrophile, and the alkene a nucleophile (**Scheme 2.59**).



Scheme 2.59

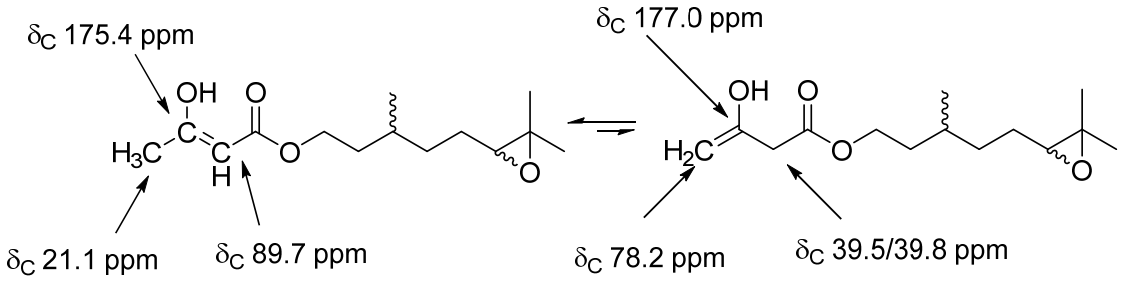
The initial reaction was carried out on the citronellol ester **3** in the presence of 1.2 equivalents of *m*-CPBA. This reaction involved the addition of the first half of the *m*-CPBA at 0 ºC (using an ice bath) and the second half was added as the reaction was allowed to warm to room temperature.[81] The epoxide was obtained as an orange oil in 91% yield, which was pure by ^{1}H NMR spectroscopy **(Scheme 2.60)**.



Scheme 2.60

The most distinctive feature for the epoxide in the ^{1}H NMR spectrum is the disappearance of the 1H triplet at δ_H 5.03 ppm corresponding to the 1H of the alkene and the appearance of a 1H triplet at δ_H 2.69 ppm (*J* 6.0) for the oxirane CH. In the ^{13}C NMR spectrum, the alkene peaks at δ_C 124.7 ppm for the alkene CH and δ_C 131.9 ppm for the quaternary alkene carbon were absent with the appearance of a new signal at δ_C 64.4 ppm corresponding to the oxirane CH. The IR spectra of both compounds shows ester and ketone carbonyl group bands which appeared at ν_{max} 1739 and 1736 cm^{-1}. Although not visible in the ^{1}H NMR spectrum, the ^{13}C NMR spectrum of **270** contained a duplication of signals for diastereoisomers which could not be distinguished from each other.

Similar to its β-ketoester precursor **3**, this epoxide derivative **270** also exhibited keto-enol tautomerisation which was visible in the ^{13}C NMR spectrum. From NMR analysis, both enol forms are believed to be present here.

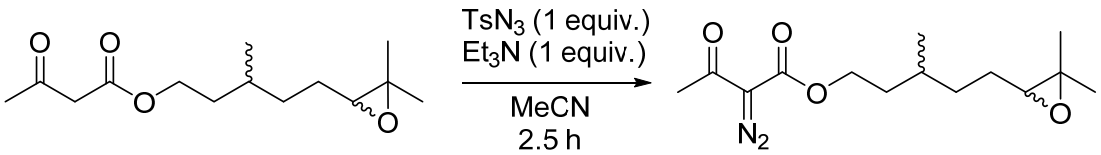


271 **272**

Figure 2.72 *Evidence of both enol forms in 13C NMR spectrum*

The enol-form of **271** is characterised by the enolic *C*H and *C*OH signals at δ_C 89.7 and 175.4 ppm respectively and also the ester carbonyl signal at δ_C 172.6 ppm in the ^{13}C NMR spectrum. The trace amount of the more unusual enol-form **272** is characterised by the alkenyl *C*H_2 signal at δ_C 78.2 ppm and also the α-CH_2 at δ_C 39.5/39.8 ppm (**Figure 2.72**).

With the epoxide **270** in hand, the next step was the diazo transfer reaction. It was initially thought that this reaction involving triethylamine base and potassium hydroxide work-up could be problematic due to the labile nature of epoxides, however, successful diazo transfer to the epoxide was achieved in 77% yield with no adverse effects to the epoxide product isolated **273** (**Scheme 2.61**).



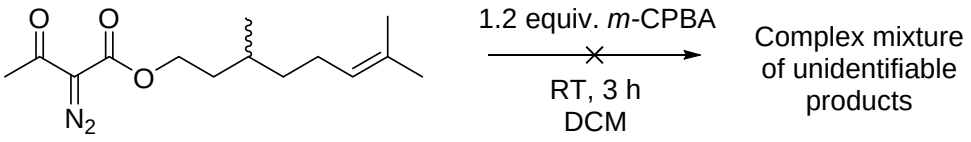
270 **273** 77%

Scheme 2.61

Similar to the other diazocarbonyl compounds synthesised in this project, the disappearance of the 2H singlet at δ_H 3.45 ppm was evidence for successful diazo transfer. The methyl ketone CH_3 singlet was seen to shift from δ_H 2.27 ppm

to δ_H 2.47 ppm and the IR spectrum shows absorptions at ν_{max} 2149 cm^{-1} for the diazo (C=N_2) group. The carbonyl group of the ketone was seen to shift from δ_C 200.5 ppm to δ_C 190.1 ppm in the ^{13}C NMR spectrum.

Previous work on the above investigations explored the possibility of carrying out an epoxidation on the citronellol diazocarbonyl compound **27** as shown in **Scheme 2.62**. However, no identifiable products were recovered from the reaction. It is thought that reaction with the *m*-CPBA led to decomposition of the diazocarbonyl compound as the ^1H NMR spectrum showed no evidence of any starting material or any epoxide signals.

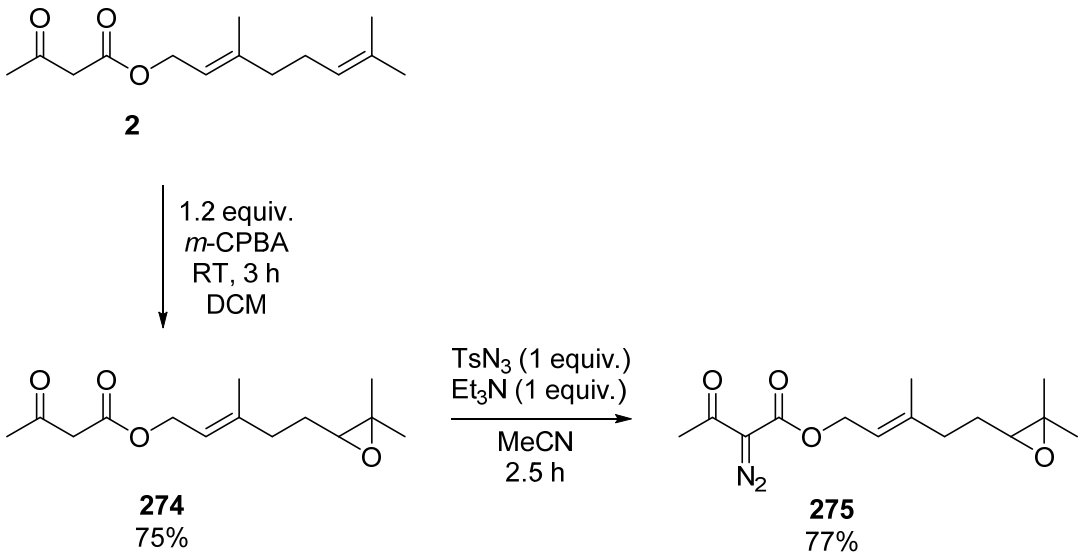


27

Scheme 2.62

Because of this, it was decided to bring the ester epoxide derivative **270** through the side chain transformation reactions to form the aldehyde and then tertiary amine derivatives and then subsequently prepare the diazo derivatives of each of those steps, as described in the following pages.

Another epoxide derivative **274** and diazo compound **275** were prepared in the same way as above using a geraniol ester **2** as illustrated in **Scheme 2.63**. The more sterically accessible alkene was selectively epoxidised to provide **274** in good yield and without requiring further purification.



Scheme 2.63

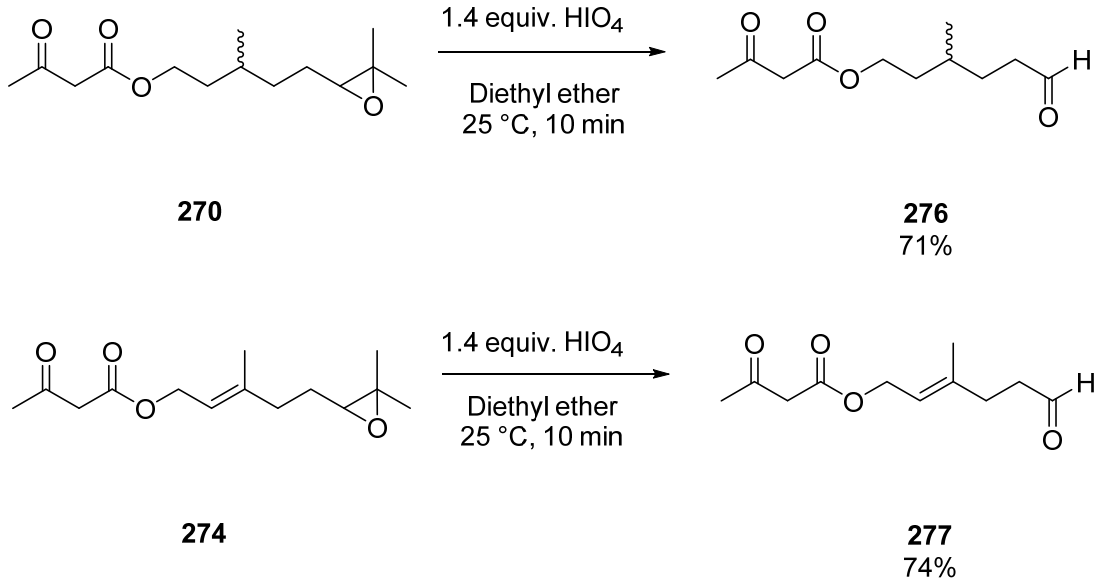
Again, the most distinctive feature for the epoxide in the ^{1}H NMR spectrum is the disappearance of the 1H triplet at δ_H 5.07 ppm corresponding to the 1H of the alkene and the appearance of a 1H triplet at δ_H 2.70 ppm for the oxirane CH. In the ^{13}C NMR spectrum, the alkene peaks at δ_C 123.6 ppm for the alkene CH and δ_C 131.8 ppm for the quaternary alkene carbon are absent with the appearance of a new signal at δ_C 63.7 ppm corresponding to the oxirane CH. The IR spectra of both compounds show ester and ketone carbonyl group bands which appear at ν_{max} 1725 and 1743 cm^{-1}.

As with the citronellol derivative, evidence of the enol form is observed in the ^{13}C NMR spectra, but in this case, only the more substituted enol. Some characteristic signals of the enol form include the enolic *C*H and *C*OH signals at δ_C 89.7 and 175.5 ppm respectively and also the ester carbonyl signal at δ_C 172.5 ppm in the ^{13}C NMR spectrum. The disappearance of the 2H singlet for **275** at δ_H 3.45 ppm was evidence for successful diazo transfer. The methyl ketone CH_3 singlet was seen to shift from δ_H 2.26 ppm to δ_H 2.48 ppm and the IR spectrum showed absorptions at ν_{max} 2141 cm^{-1} for the diazo ($C{=}N_2$) group. The carbonyl group of the ketone was seen to shift from δ_C 200.5 ppm to δ_C 190.1 ppm in the ^{13}C NMR spectrum also. The epoxides were stable in storage at room temperature over a period of many months and would be used in a cycloaddition reaction with benzyne **50** which will be described in **Section 2.9.4**.

2.9.2 Oxidative cleavage of epoxide derivatives

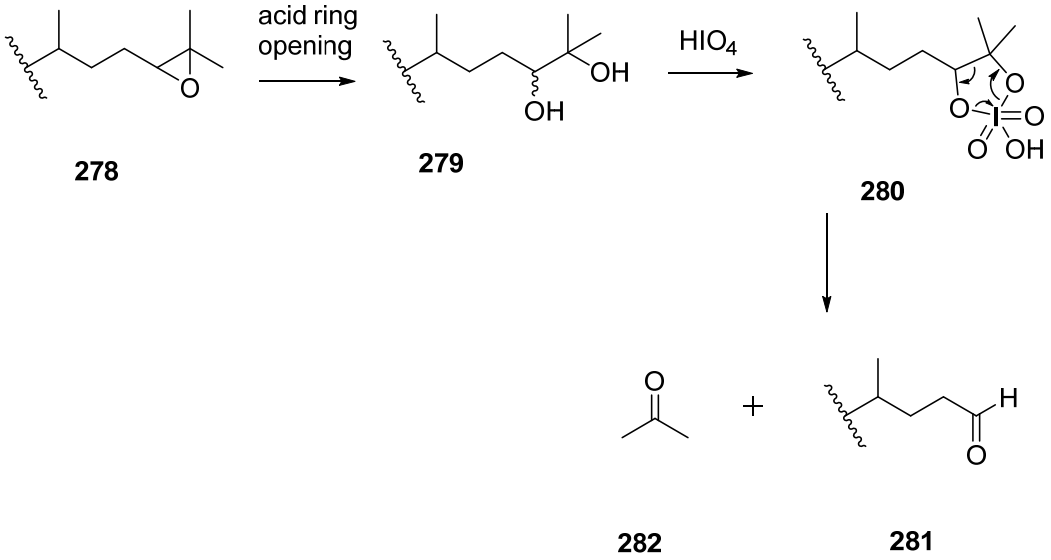
The next transformations investigated involved novel aldehyde derivatives, synthesised *via* the epoxide esters **270** and **274**. Oxidative cleavage of the C-C bond in epoxides serves as a chemoselective alternative to ozonolysis, a process that can be dangerous on larger scales. This method was used in this project to access novel aldehyde derivatives which could subsequently be used in the synthesis of tertiary amines. The aldehydes themselves were not necessarily designed to be biologically evaluated as derivatives synthesised within the research group previously containing aldehyde functionality were not accepted as candidates for biological testing, implying that the aldehyde group may be an unfavourable feature when submitting compounds to be screened. Rather, the formation of the aldehyde derivatives were used as a route to tertiary amines *via* reductive amination which will be discussed further in **Section 2.9.3**.

Due to the apparent instability of diazo **27** in the epoxidation reactions using *m*-CPBA, it was decided to carry out the initial oxidative cleavage reaction on the ester derivative **270** and perform diazo transfer on the aldehyde derivative **276** subsequently. The aldehydes were prepared using periodic acid in diethyl ether at 25 ºC as shown in **Scheme 2.64**.[82,83]



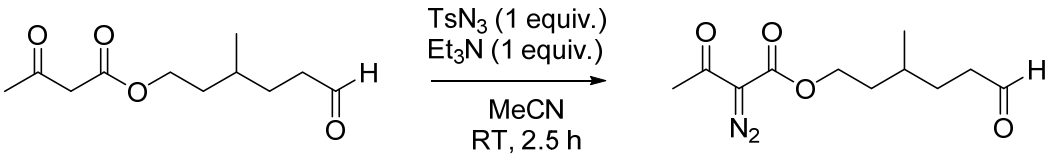
Scheme 2.64

Mechanistically, this reaction proceeds *via* initial acid ring opening of the epoxide **278** to form a vicinal diol **279**. The periodic acid then forms a five membered cyclic periodate intermediate with the diol **280**, and the concerted collapse of this intermediate leads to the formation of the aldehyde product **281** and acetone **282** (**Scheme 2.65**).



Scheme 2.65

There are a few points to note for this reaction. The first is that the reaction must be stirred vigorously to ensure the periodic acid, which is insoluble in diethyl ether, is sufficiently mixed in the solution. The second is that the temperature must be maintained at 25 ºC using an oil bath and reflux condenser to facilitate 100% conversion to the aldehyde. The aldehydes are characterised in the ^{1}H NMR spectrum by a 1H triplet at δ_H 9.77-9.79 ppm as well as the disappearance of the 1H triplet of the oxirane at δ_H 2.69 or 2.70 ppm and the presence of the carbonyl CH of the aldehyde at δ_C 201.6 or 202.3 ppm in the ^{13}C NMR spectrum. In contrast to the epoxides, the aldehydes are found to be very unstable unless used immediately, even when stored in the freezer under nitrogen. Successful diazo transfer to the aldehyde **276** was achieved as illustrated in **Scheme 2.66** to provide **283** in good yield.

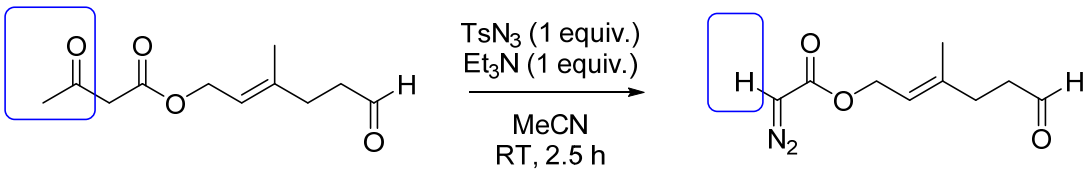


276 **283** 75%

Scheme 2.66

The diazocarbonyl product was obtained as a bright yellow oil and again the characteristic signals included the disappearance of the CH_2 singlet at δ_H 3.45 ppm and the methyl ketone CH_3 singlet was seen to shift from δ_H 2.27 ppm to δ_H 2.47 ppm. The IR spectrum showed the diazo group ($C{=}N_2$) absorption at ν_{max} 2143 cm^{-1} and the carbonyl group of the aldehyde was seen to shift from δ_C 202.3 ppm to δ_C 190.0 ppm in the ^{13}C NMR spectrum also.

For the geraniol derived aldehyde **277** an interesting result was obtained. The reaction was carried out using the standard reaction conditions and the ^1H NMR spectrum of the crude reaction mixture showed the formation of the desired compound. However the major product obtained after the work-up and purification was acyl cleavage product **284** which was obtained as a bright yellow oil as illustrated in **Scheme 2.67**.



277 **284** 88%

Scheme 2.67

α-Diazo β-ketoesters have been known to undergo alkaline acyl cleavage in aqueous conditions as reported in the literature[84-86] but acyl cleavage was not expected using the routine 9% potassium hydroxide wash as it was not previously observed, even for similar substrates. This compound was characterised by the 1H singlet at δ_H 4.74 ppm for the proton attached to the diazo carbon and the lack of

a full methyl ketone CH_3 singlet at δ_H 2.48 ppm (**Figure 2.73**). ^{13}C NMR analysis also showed the absence of the ketone carbonyl and methyl ketone CH_3 at *ca*. δ_C 30 and 190 ppm.

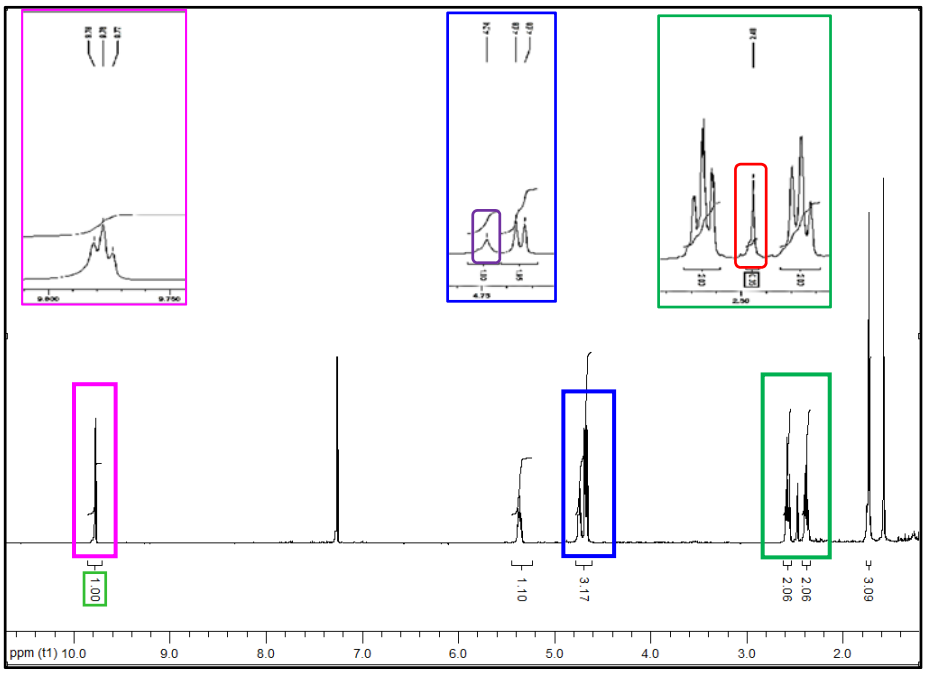
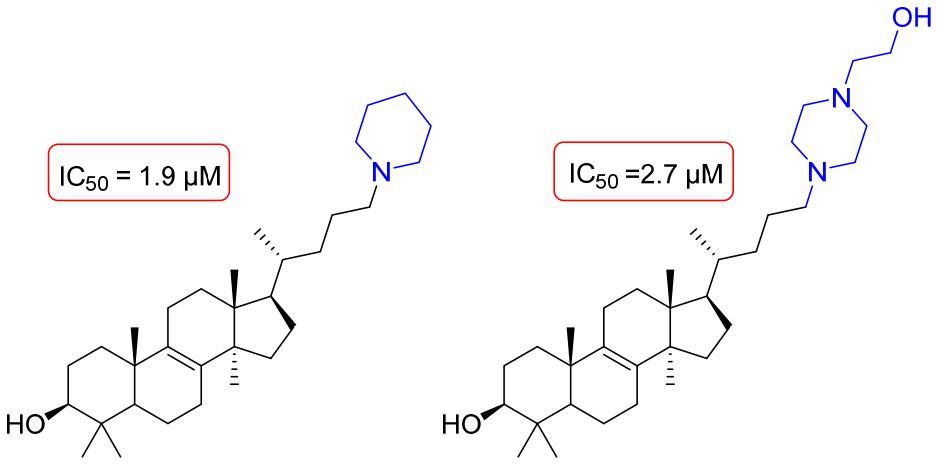


Figure 2.73 *^1H NMR spectrum of **284***

2.9.3 Reductive amination of aldehyde derivatives

The final derivatives investigated in this project were tertiary amines which were formed *via* the aldehyde. Collins reported recently on the synthesis and evaluation of a range of novel lanostane derivatives in U937 cell lines for their cytotoxic and apoptotic potential.[79] Excellent IC_{50} values were observed for the tertiary amine functionalised derivatives **285** and **286** as shown in **Figure 2.74**. Since an important part of this project involves structural derivatisation of indazole compounds, reductive amination seemed like a fantastic avenue to explore in the development of novel compounds for biological testing.



285 **286**

Figure 2.74 *Aminolanostane derivatives showing low IC_{50} values*

The amine group is one of the most frequently found functional groups in today's armoury of commercially available drugs. Amine based pharmaceutical drugs are used therapeutically for a range of causes such as allergies (diphenhydramine **287**), pain (codeine **288**), malaria (quinine **289**), bacterial infections (tetracycline **290**) and in tissue numbing for certain procedures (lidocaine **291**), to name a few (**Figure 2.75**). The amine functionality is the most common functional group found in drug molecules (>85%). The primary physicochemical property of importance in the drug chemistry of the amino group is its basicity. Because most amines are basic, salt forms can be generated to facilitate water solubility or solubility in other vehicles for drug administration.

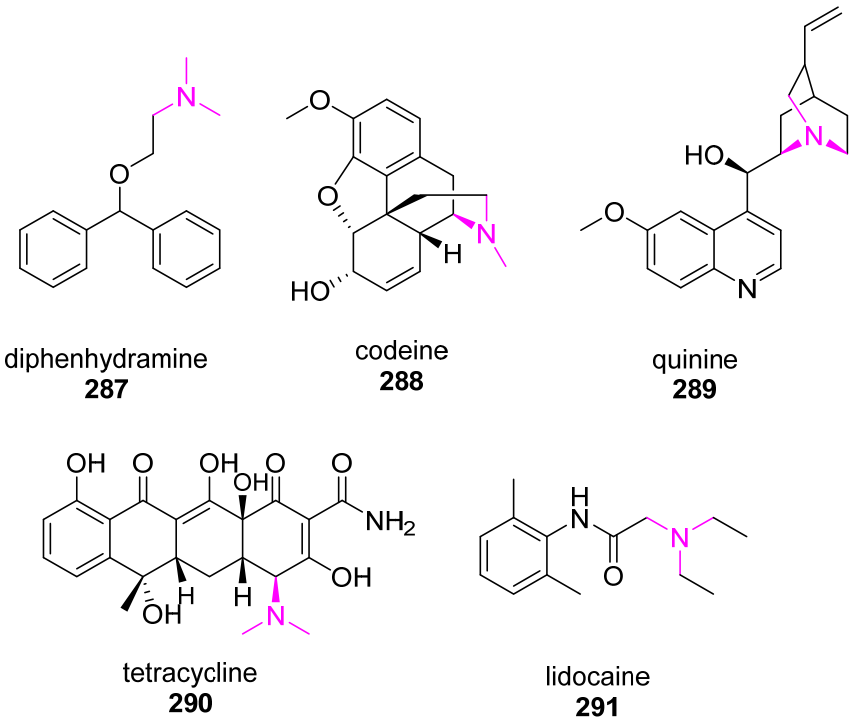
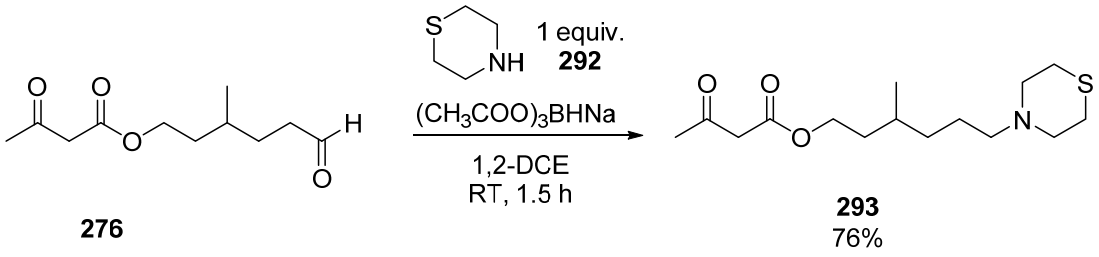


Figure 2.75 *Pharmaceutical drugs containing an amine group*

Reductive amination is an important tool in organic synthesis for introducing amine functionality into an organic compound containing an aldehyde or ketone. These carbonyl compounds react with ammonia, primary or secondary amines to form primary, secondary or tertiary amines respectively.[87-90]

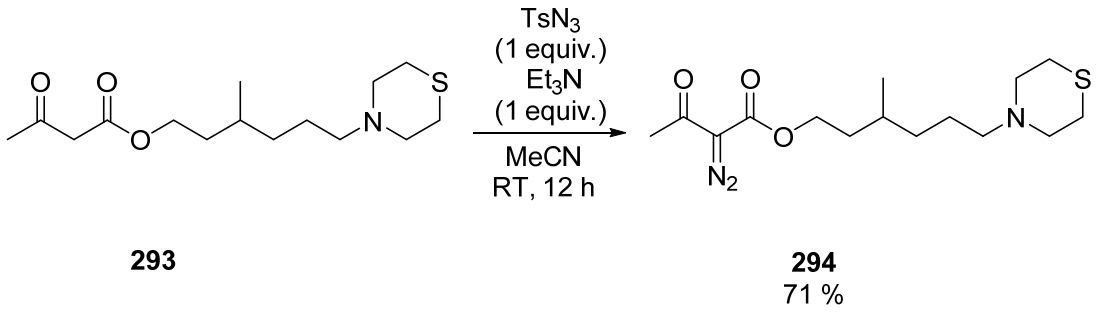
The first reaction undertaken in this project, was carried out following an established protocol, comprehensively cited in the literature, by Abdel and co-workers. Citronellol derived aldehyde **276** was converted into its corresponding novel amine **293** in 76% yield following treatment with 1 equivalent of thiomorpholine **292** in the presence of sodium triacetoxyborohydride in dry 1,2-dichlorethane at room temperature under an inert nitrogen atmosphere as shown in **Scheme 2.68**. The reducing agent exhibits remarkable selectivity, as no reduction of the aldehyde to form an alcohol is observed. The steric and electron-withdrawing effects of the three acetoxy groups stabilise the boron-hydrogen bond resulting in the mild reducing properties of the substance.



Scheme 2.68

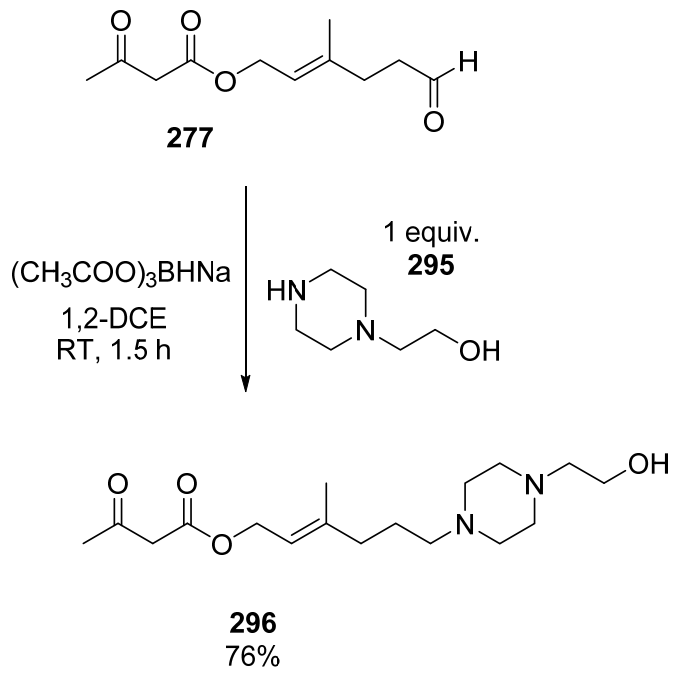
The ester was characterised in the ^{1}H NMR spectrum by the disappearance of the aldehyde triplet at δ_H 9.78 ppm and the distinctive peaks of the thiomorpholine ring which appeared between δ_H 2.66-2.72 ppm as an 8H multiplet corresponding to the four CH_2 groups in the ring. The ^{13}C NMR spectrum showed the two SCH_2 groups at δ_C 27.4 ppm and the two NCH_2 groups at δ_C 54.7 ppm of the thiomorpholine ring. The IR spectrum showed the usual ester and ketone carbonyl absorptions at ν_{max} 1743 and 1715 cm^{-1}.

Successful diazo transfer to the ester **293** gave the novel diazocarbonyl **294** as a bright yellow oil in 71% yield (**Scheme 2.69**). Again the characteristic signals included the disappearance of the CH_2 singlet at δ_H 3.44 ppm and the methyl ketone CH_3 singlet was seen to shift from δ_H 2.27 ppm to δ_H 2.48 ppm. The IR spectrum showed the diazo group ($C{=}N_2$) absorption at ν_{max} 2141 cm^{-1} and the carbonyl group of the ketone was seen to shift from δ_C 200.5 ppm to δ_C 190.1 ppm in the ^{13}C NMR spectrum.



Scheme 2.69

The next reaction was carried out with the geraniol derived aldehyde **277** using 2-(piperazin-1-yl)ethan-1-ol **295** as the tertiary amine yielding the novel amine **296** in 76% yield as shown in **Scheme 2.70**.



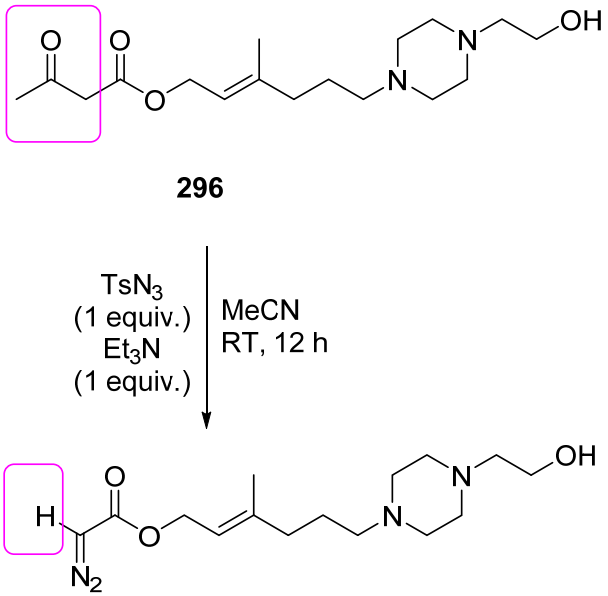
Scheme 2.70

The ester was characterised in the ^{1}H NMR spectrum by the disappearance of the aldehyde triplet at δ_H 9.77 ppm and the distinctive peaks of the piperazine ring which appeared between δ_H 2.48 and 2.62 ppm as an 11H multiplet corresponding to the four NCH_2 groups in the ring along with the NCH_2 and OH of the ethanol group. The ^{13}C NMR spectrum showed the NCH_2 groups of the ring at δ_C 52.8 and 53.2 ppm.

The diazo transfer reaction took place using ester **296** to give another interesting result where the acyl cleavage derivative **297** was obtained as the major product (**Scheme 2.71**) similar to the diazo aldehyde with the same geraniol scaffold **284**.

This compound was characterised in the same way as **284** by the 1H singlet at δ_H 4.67 ppm for the proton attached to the diazo carbon and the lack of a "full" methyl ketone CH_3 singlet at δ_H 2.40 ppm.

The ^{1}H NMR spectrum showed the presence of impurities which were not removed by repeated column chromatography on silica gel and the ^{1}H and ^{13}C NMR spectra were assigned with the presence of these impurities.

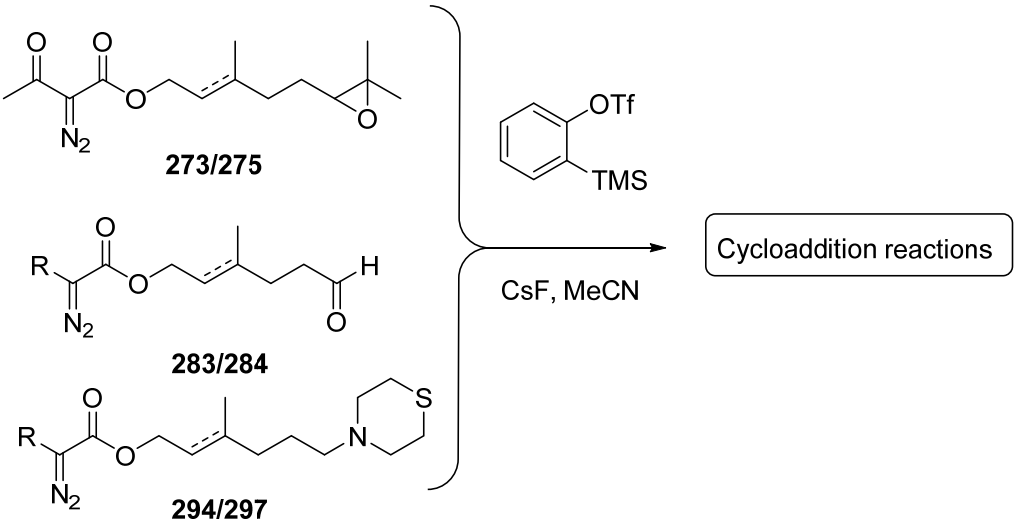


Scheme 2.71

In total, 2 epoxide **273** and **275**, 2 aldehyde **283** and **284**, and 2 tertiary amine **294** and **297** derivatised diazo dipole compounds were synthesised and brought forward to the cycloaddition stage with the benzyne precursor **49** which is described in **Section 2.9.4**.

2.9.4 Indazole cycloaddition reactions with diazo dipoles of epoxide, aldehyde and tertiary amine derivatives

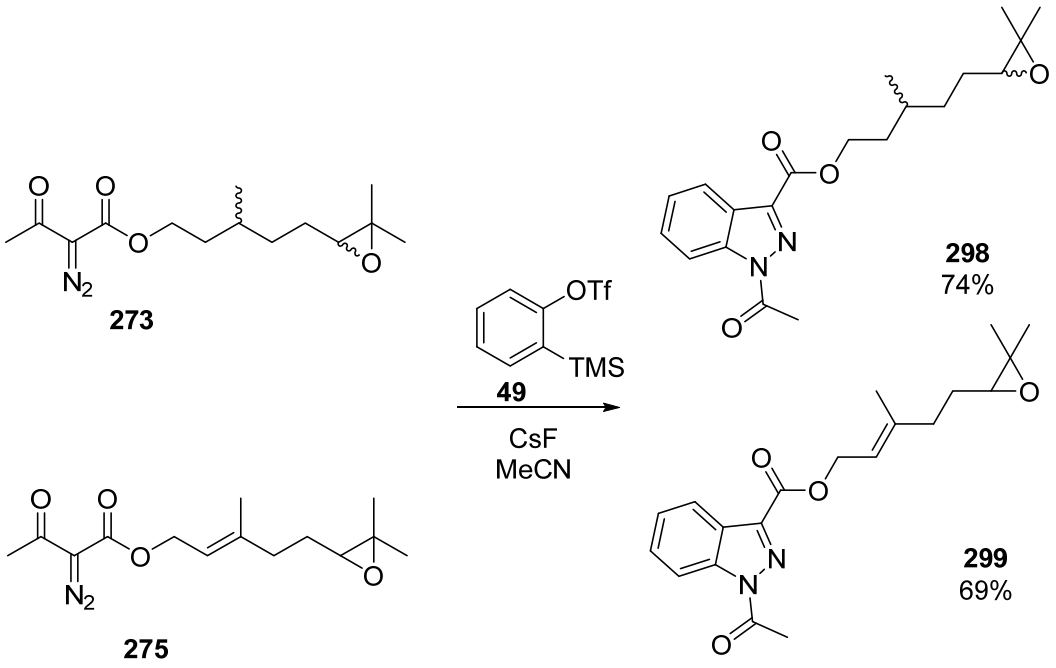
Aryne cycloaddition reactions were performed with the epoxide diazo derivatives **273** and **275**, and attempted with aldehydes **283** and **284** and tertiary amines **294** and **297** diazo derivatives as described below (**Scheme 2.72**).



Scheme 2.72

Epoxides

With two novel epoxide-containing diazo derivatives **273** and **275** in hand, work could begin on the cycloaddition reactions with the aryne to generate novel epoxide-containing indazole compounds. Although apprehensive about these diazo dipoles not performing well (as the alkene-containing diazo of the starting material ester **25** and **27** derivatives had not given pure product in the reactions with the triflate aryne precursor in **Section 2.4.2.1**), we are delighted to report that indazole derivatives with an epoxide moiety in the side chain were successfully isolated in good yields and high purity (**Scheme 2.73**).



Scheme 2.73

Comparative ^{1}H NMR spectra for diazo **273** and indazole **298** are shown in **Figure 2.76**.

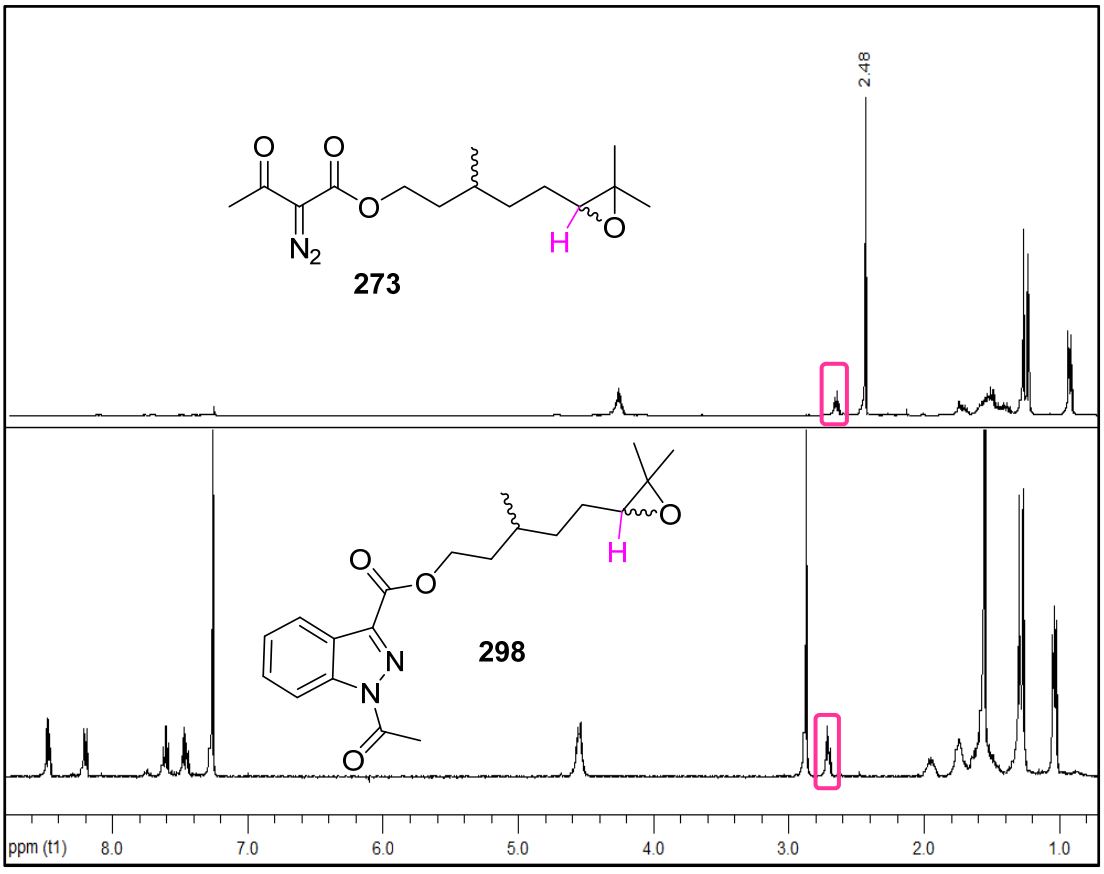
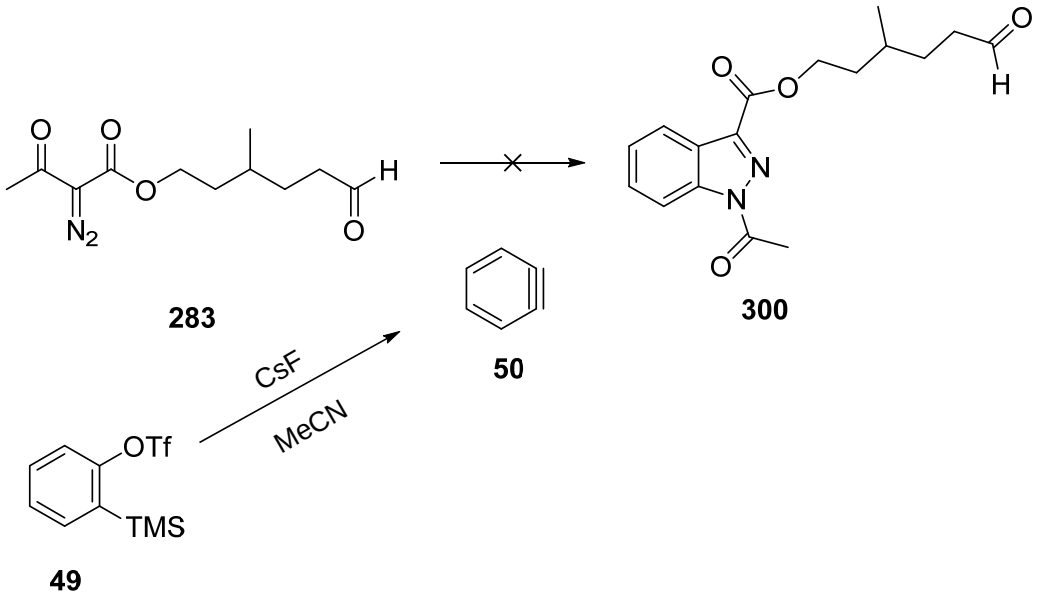


Figure 2.76 *^{1}H NMR* spectra *of diazo **273** and corresponding indazole **298***

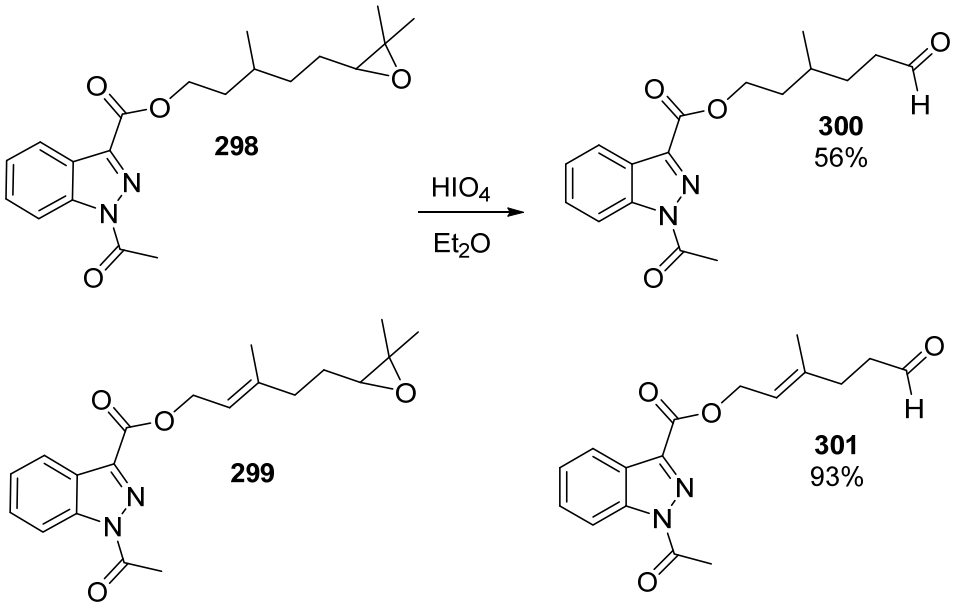
Oxidative decomposition

In the aldehyde forming reactions, initial attempts were made to form indazole **300** using the diazo 1,3-dipoles of the aldehyde derivative **283** (**Scheme 2.74**), however, there was limited success with these routes.



Scheme 2.74

The epoxide derivatives of the indazole **298** and **299** were brought through the synthetic route instead (**Scheme 2.75**).

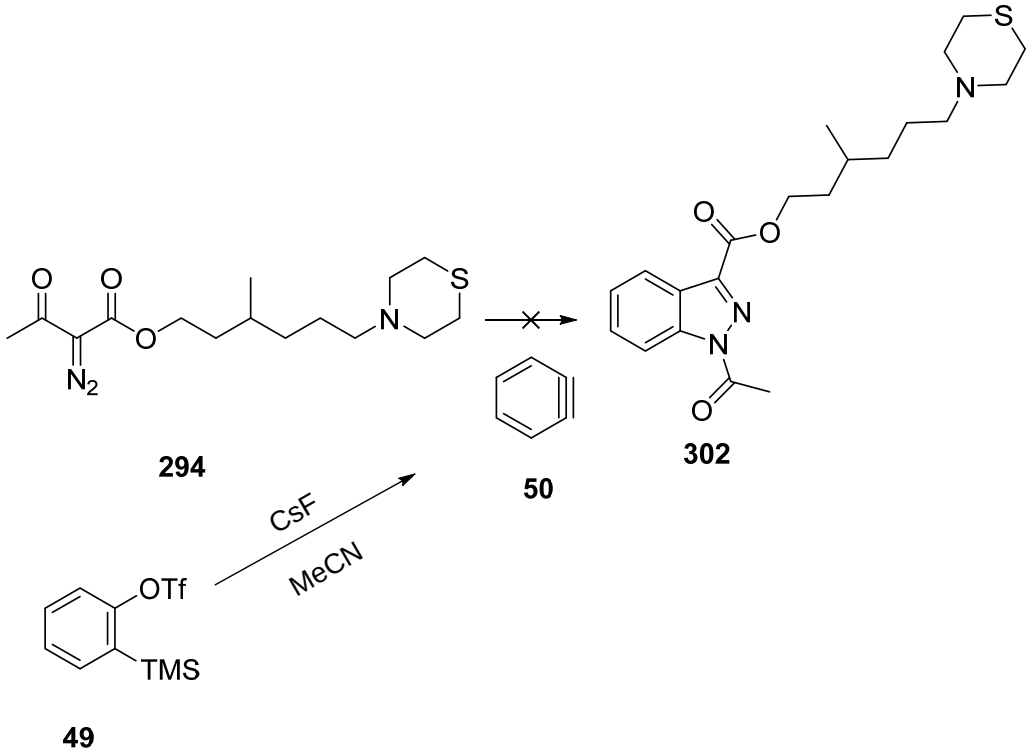


Scheme 2.75

It was found that the reactions in **Scheme 2.75** did not go to completion; even when excess periodic acid was used and when the reaction times were extended. A pure sample of the aldehydes **300** and **301** were not isolated despite repeated purification attempts using column chromatography on silica gel so the impure aldehyde derivatives **300** and **301** were brought forward to the reductive amination step.

Reductive amination

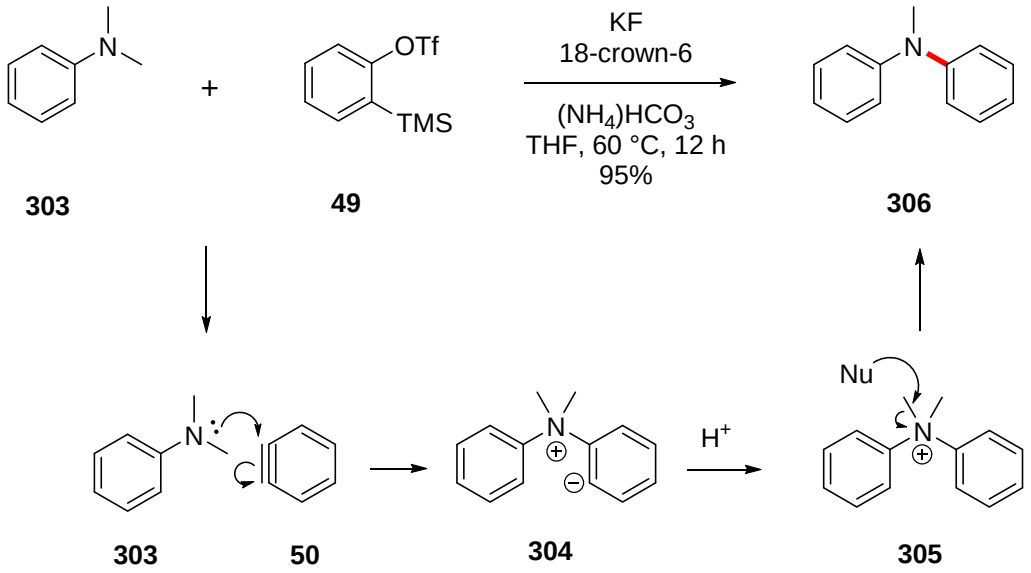
Initial attempts were made to form the indazole cycloadduct using the diazo 1,3-dipoles of the tertiary amine derivatives with no success (**Scheme 2.76**).



Scheme 2.76

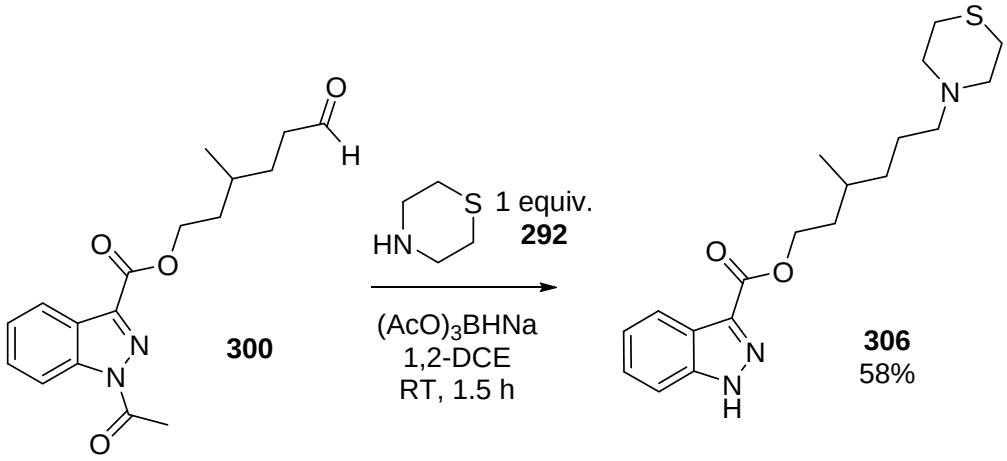
A subsequent search of the literature showed that arynes can also react readily with tertiary amines. One example reported in 2013 by Bhogude and co-workers is shown in **Scheme 2.77** where *N*-arylation of aromatic tertiary amines occurs readily in high yields. The authors proposed a plausible mechanistic route whereby the reaction is initiated by fluoride-induced aryne generation from **49** and then nucleophilic addition of dimethylaniline **303** to the aryne **50**, generating a zwitterionic intermediate **304** which is protonated to form the dimethyl diphenyl

ammonium salt **305**. Demethylation induced by the fluoride ion or the basic reaction medium provides *N*-aryl product **306**.[91,92]



Scheme 2.77

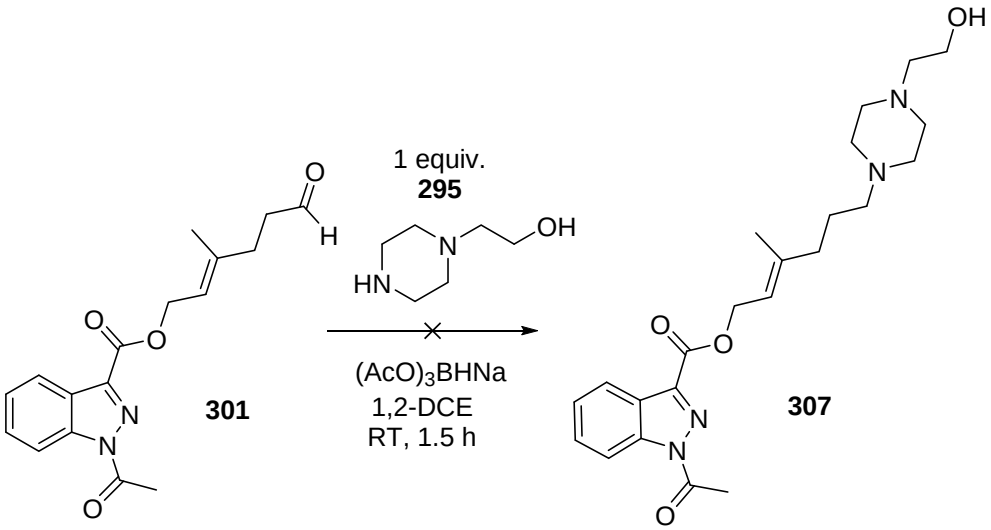
Instead, the aldehyde derivative of the indazole **300** was carried through the synthesis (**Scheme 2.78**). These reactions were less than ideal as the aldehyde starting materials contained irremovable starting material and the sodium triacetoxyborohydride was also involved in cleaving the acetyl group (preferable in the one-pot preparation of 1*H*-indazoles). Although pleased to report successful reductive amination of the aldehyde **300** with thiomorpholine **292**, the major product was the deacylated **306**. However, after repeated column chromatography on silica gel a fully pure sample of this could not be obtained (95% purity).



Scheme 2.78

The key characteristic signal in the ^{1}H NMR spectra to show the incorporated thiomorpholine ring was the 8H multiplet at δ_H 2.64-2.75 ppm. In the ^{13}C NMR spectra, the thiomorpholine CH_2 signals appeared at δ_C 27.8 and 54.9 ppm and evidence of deacylation was that the amide carbonyl signal and methyl ketone CH_3 were not present.

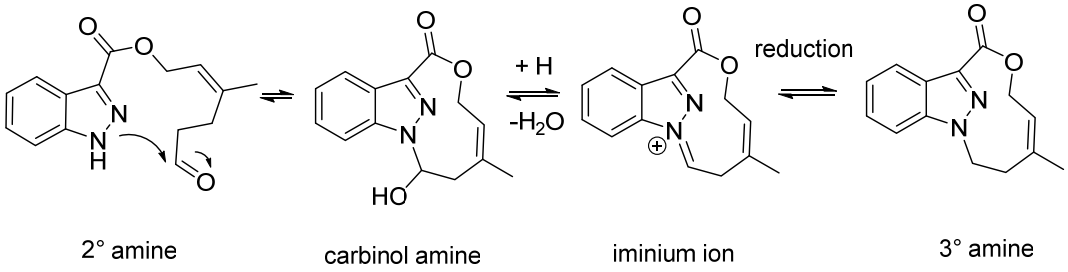
Next the aldehyde **301** was used in a reductive amination reaction with piperazine ethanol **295** (**Scheme 2.79**), however no evidence of product formation in the ^{1}H NMR spectra of the crude material was observed. After purification attempts using column chromatography on silica gel, only the aldehyde starting material **301** and deacylated **301** were observed.



Scheme 2.79

Throughout the project, derivatives of geraniol were found to be poor substrates in a range of indazole reactions. Increasing the equivalents of piperazine ethanol **295** in this reaction may aid in the future success of this reaction as **295** is a viscous liquid that is difficult to handle and measure accurately.

It is also possible that for this compound, when the *N*-1 position is deacylated by the reducing agent it would be possible that the aldehyde side chain and the newly formed secondary amine of the indazole would react to further complicate this reaction and crude ^{1}H NMR spectrum (**Scheme 2.80**).



Scheme 2.80

Overall, the side-chain transformations performed in this project were successful in that a range of novel ester and diazo derivatives could be prepared with epoxide, aldehyde and tertiary amine functionality. Although the initial indazole forming reactions with the epoxide side chain worked well, as a whole, the aldehyde and tertiary amine indazoles were not as successful. The synthesis of tertiary amine indazole derivative **306** was a notable result and further work on optimisation of this route and alteration of the secondary amine starting material should isolate more novel tertiary amine indazole derivatives. Future work in this area will involve the investigation other reductive amination routes, using simpler tertiary amines and perhaps using a shorter isopent-2-ene side-chain ester for the transformations. In general, the geraniol side chain has proven problematic throughout the project in indazole forming reactions.

2.10 Biological Evaluation

2.10.1 Introduction

The 1*H*-indazole nucleus is an effective pharmocophore in medicinal chemistry and shows diverse biological and pharmacological activity.[75] A major aim in this project was to synthesise a range of novel indazole compounds containing varying functionalisation throughout the structure and then to evaluate these for their biological activity.

By making modifications to the indazole core it was hoped to first identify the structural features that enhance or diminish the biological action of the indazole derivative and then use this knowledge to direct synthesis to particular structural features of compounds that might return promising biological results.

Collaboration with the National Cancer Institute (NCI) allowed assessment of the chemotherapeutic potential of synthesised novel indazole derivatives. Over four rounds of testing so far, 40 novel derivatives have been sent forward to be tested and 21 of those were accepted and screened for one-dose testing.

Participation in an open global initiative for discovery and development of new drugs against superbugs with the Community for Antimicrobial Drug Discovery (CO-ADD) was undertaken. 19 novel indazole compounds have been sent to the Queensland University Bioscience Precinct in New Zealand for these microbial tests, and results for these are currently pending at the time of writing.

2.10.2 National Cancer Institute Testing

2.10.2.1 Development Therapeutic Programme

The U.S. NCI's Developmental Therapeutics Programme (DTP) is the drug discovery and developmental arm of the NCI. It plans, conducts and facilitates development of therapeutic agents for the treatment of cancer and AIDS.[93] In 1955, the NCI set up the DTP, originally known as the Cancer Chemotherapy National Service Center (CCNSC), to act as a public screening centre for anticancer activity in compounds submitted by external institutions and companies. It operates a series of *in vitro* and *in vivo* anticancer compound screening programmes with the aim of identifying novel compound leads and their biological mechanisms of action.[94]

Since its establishment, the DTP has been involved in the discovery or development of more than 40 U.S. licenced chemotherapeutic agents, which translates to >70% of the anticancer drugs on the market today.[95-97] Some examples of anti-cancer agents developed with DTP involvement are shown in **Table 2.1**.

Table 2.1: *Anti-cancer agents developed with DTP involvement**

Year	Drug	Year	Drug	Year	Drug
2015	*Dinutuximab*	**1989**	*Carboplatin*	**1973**	*Bleomycin*
2010	*Eribulin*	**1988**	*Ifosamide*	**1970**	*Mitramycin*
2009	*Romidepsin*	**1987**	*Mitoxantrone*	**1969**	*Procarbazine*
2004	*Erbitux*	**1983**	*Etoposide*	**1967**	*Hydroxyurea*
2003	*Velcade*	**1982**	*Streptozotocin*	**1966**	*Thioguanine*
1998	*Ontax*	**1979**	*Daunorubicin*	**1964**	*Actinomycin*
1996	*Topotecan*	**1978**	*Cisplatin*	**1963**	*Vincristine*
1995	*All-t-retinoic acid*	**1977**	*Carmustine*	**1962**	*Fluorouracil*
1992	*Taxol*	**1976**	*Lomustine*	**1961**	*Vinblastine*
1991	*Pentostatin*	**1975**	*Dacarbazine*	**1959**	*Cyclophosphamide*
1990	*Hevamisole*	**1974**	*Adriamycin*	**1957**	*Chloroambucil*

*Table adapted from NCI website

Notably, the above list contains Paclitaxel (Taxol®) **308** is one of the most widely prescribed anti-cancer drugs on the market (**Table 2.1**). It is a natural product isolated from the bark of the Pacific yew tree. It was first discovered by researchers working under a joint U.S. Department of Agriculture-National Cancer Institute grant and a DTP contractor formulated the drug for clinical trials. Paclitaxel is a mitotic inhibitor and is used today in cancer chemotherapy for the treatment of lung, ovarian, breast, head and neck cancer, and advanced forms of Kaposi's sarcoma. Paclitaxel is also used for the prevention of restenosis (**Figure 2.77**).

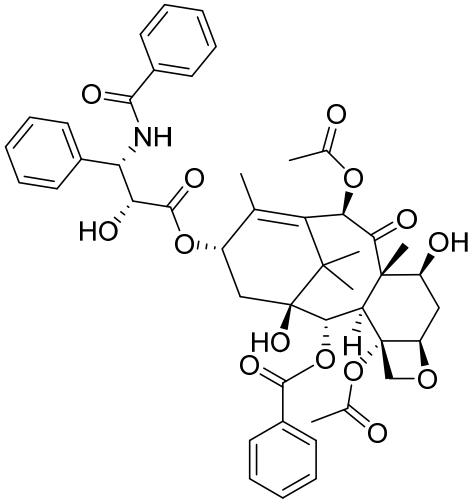


Figure 2.77 *Paclitaxel (Taxol®)* ***308***

Bortezomib **309** is another DTP success story which was screened and formulated by the DTP in cooperation with its commercial sponsor. It was approved by the Food and Drug Administration (FDA) in 2003 and was the first treatment in more than a decade to be approved for patients with multiple myeloma. It took only 8 years from initial NCI-60 hit identification of the novel proteasome inhibitor bortezomib agent **309** in 1995 to full FDA approval (**Figure 2.78**).

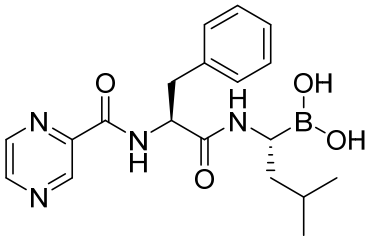


Figure 2.78 *Bortezomib (Velcade®)* ***309***

The DTP functions as a valuable service that aids the academic and private sectors in overcoming various financial and technical barriers associated with drug discovery and that consequently keep the delivery of promising therapeutic agents from reaching patients. Particularly, the DTP has been a vital service in its support of high risk projects and therapeutic development for rare cancers.[98,99]

2.10.2.2 Introduction to NCI-60 Cancer Cell-line Screen Programme

The NCI-DTP is a 60 human tumour cell line service, developed in the late 1980s as a strategic high-throughput screening tool for *in vitro* anti-cancer drug activity.[99] Cytotoxicity data for more than 100,000 compounds across diverse cancer lines have been classified following this approach. The project is designed to screen up to 3,000 compounds per year for potential anticancer activity using 60 different human tumour cell lines representing nine human cancers: leukaemia, melanoma, and cancers of the lung, colon, brain, ovaries, breast, prostate and kidney. The aim is to identify synthetic compounds or natural product samples showing selective growth inhibition or cell killing of particular tumour cell lines for further evaluation.

The screening is a two-stage process beginning with an initial evaluation involving a single dose of 10 μM cytotoxicity screen of the compound with the 60 cell line assay, known as a one-dose NCI-60 screen. *In vitro* activity of each compound in the human tumour cell line is displayed as a 'mean graph' (**Figure 2.79**), consisting of a series of horizontal bar graphs representing units of nominal growth percent, deviating from the arithmetic mean growth for the entire 60 cell line panel ('0'). The value reported is growth relative to the no-drug control, and relative to the time zero number of cells. This allows detection of both growth inhibition and lethality.

In each case, graphs which extend to the right (values less than 0) signify more selective cytotoxicity or positive growth inhibition while those which extend to the left of centre line (values between 0 and 100) indicate a chemotherapeutic or non-cytotoxic effect on individual cell lines. For example, a value of 100 means no growth inhibition. A value of 40 would mean 60% growth inhibition. A value of 0 means no net growth over the course of the experiment. A value of -40 would mean 40% lethality. A value of -100 means all cells are dead.

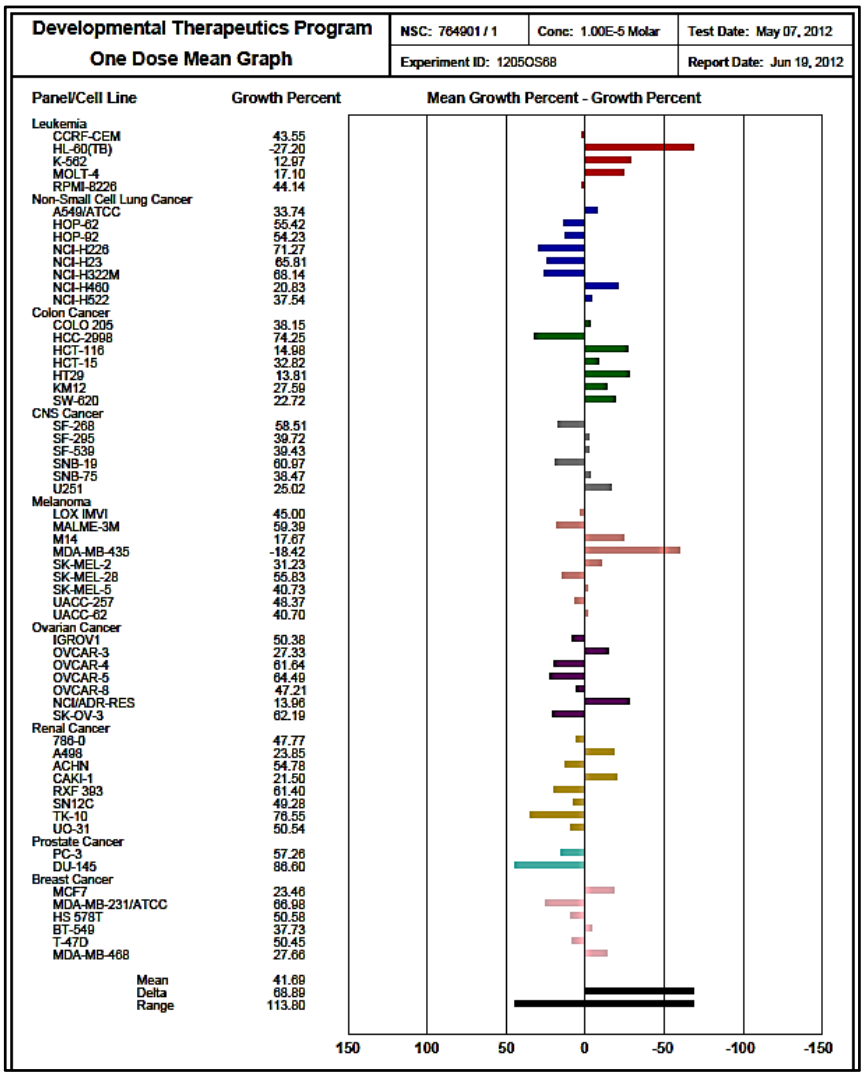


Figure 2.79 *NCI-60 One-dose 'mean graph'*

Compounds that exhibit significant growth inhibition and satisfy the threshold inhibition criteria mean value of ≥ 50% across all 60 cell lines fit the necessary NCI-60 criteria for five dose screening and are then evaluated at five concentration levels, known as a 5-dose NCI-60 screen. Patterns of total panel activity can be correlated with those of over 100,000 compounds within an NCI-60 database to reveal key mechanisms of action using the COMPARE programme.

Following initial NCI-60 screening, compounds exhibiting interesting patterns of inhibition are evaluated by the Data Review Committee, prior to a five-dose investigation. This screen is performed by a 5 × 10 fold serial dilution of a

100μM stock solution at the same time as the one-dose sample. The results are displayed on a graph (**Figure 2.80**) showing the three response parameters; GI_{50}, TGI and LC_{50}.

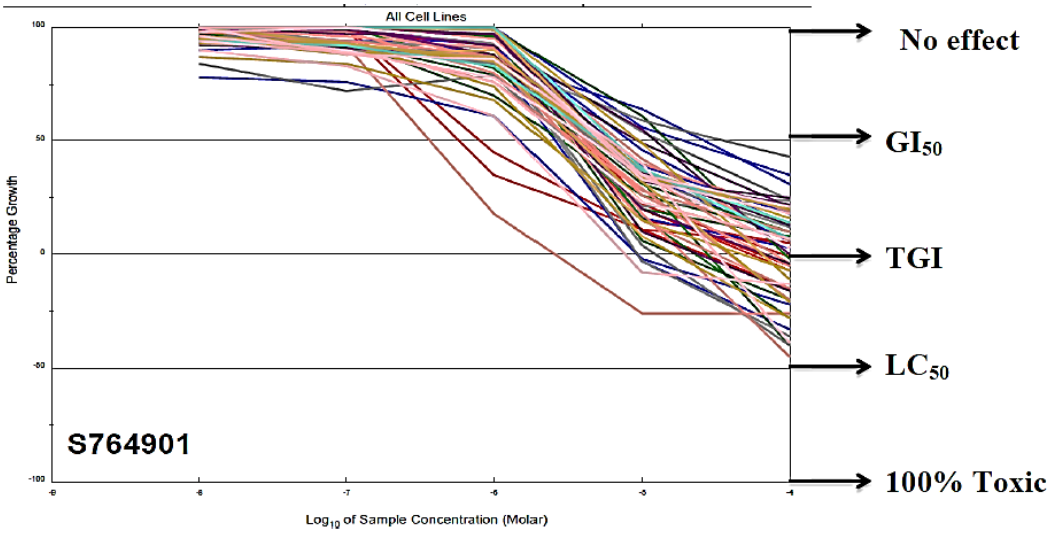


Figure 2.80 *NCI-60 'five-dose graph/dose response curve' for all cancer cell lines*

Following recommendation by the Biological Review Committee, compounds which exhibit useful activity profiles may progress to *in vivo* hollow-fibre testing in mouse models and further xenograft assays, with successful drug candidates eventually authorised by Drug Development Group to enter NCI clinical development.

2.10.2.3 NCI-60 one-dose screen results

An initial selection of novel 1,3-disubstituted indazole compounds prepared in this project were submitted for biological evaluation to the NCI as the indazole core structure is present in a range of anti-cancer therapeutic agents on the market. The first round of compounds evaluated were unsubstituted on the benzene ring of the indazole and had a variety of acyl groups in the *N*-1 position and the 3-position contained a range of alkyl ester side chain lengths and functionality as shown in **Figure 2.81**. It was envisioned that the selection of novel derivatives would provide alternative types of binding and steric interactions that could enhance or alter the biological activity by varying the ester side chain to include groups such as a bulky *t*-butyl group in **106**, a lipophilic decyl group in **113** and an extra aromatic ring in **110** Also, it was thought that altering the *N*-acetyl side chain to a longer *N*-acyl group such as in **119** or having a fluorinated benzoyl group could have an interesting impact on the biological activity.

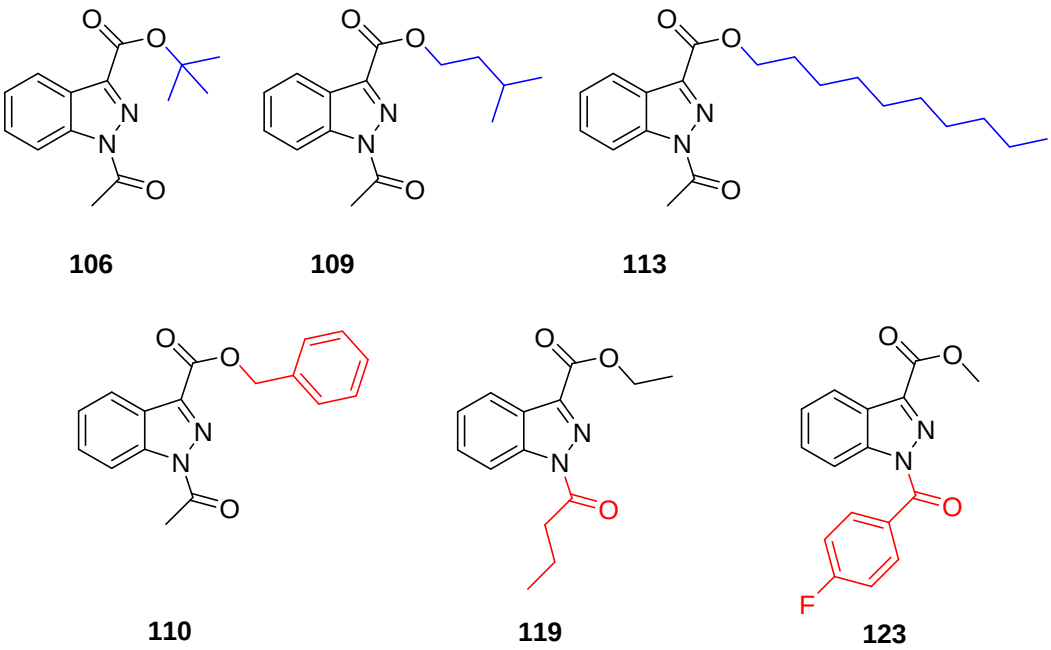


Figure 2.81 *Initial series of N-acyl indazole derivatives submitted to DTP for NCI-60 cell line screening*

The indazole derivatives in **Figure 2.81** were investigated for initial NCI-60 one-dose tumour cell line activity and the one-dose mean graphs for each of the compounds depicted are presented in ***Appendix II***. The pattern of quantifiable

growth inhibition of these agents on the NCI-60 human cell line panel is outlined below. Evaluation of these one-dose mean graphs revealed that compound **123** (contains a *p*-fluorobenzoyl group in the *N*-1 position) showed the greatest overall biological activity when compared to the other compounds tested in this series.

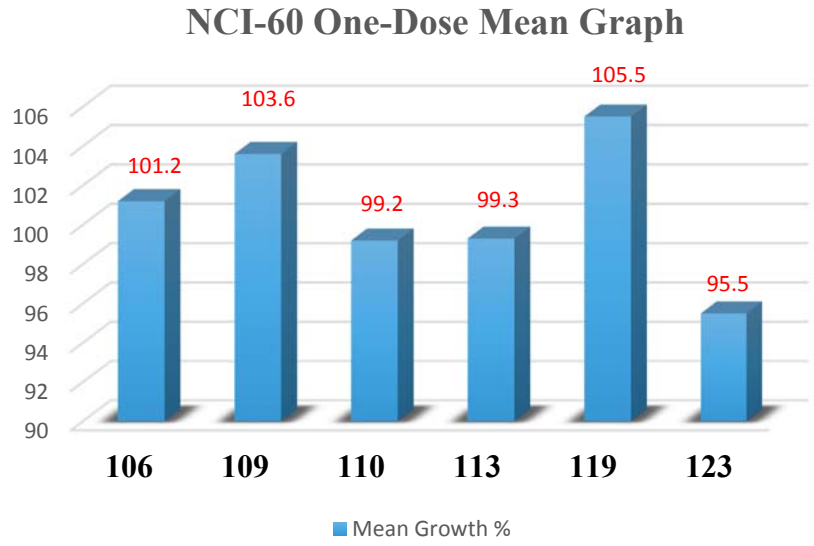


Figure 2.82 *Illustration of NCI-60 mean growth percent for our initial derivatives*

While none of the initial indazole derivatives exhibited the necessary biological activity across the 60 cell lines required for five-dose screening by the NCI (<50% mean growth), an interesting trend could be seen to emerge in activity against non-small cell lung cancer cell lines by altering the length or bulkiness of the side chain esters (**Figure 2.83**).

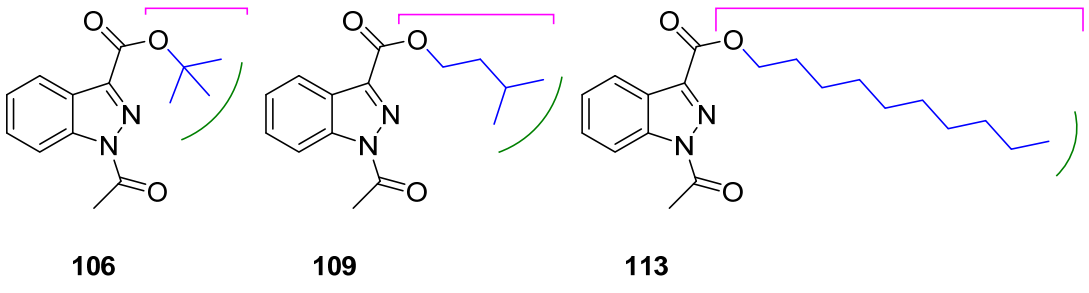


Figure 2.83 *Altering ester side-chain length/bulkiness*

The indazole derivative containing the *t*-butyl ester group **106** exhibits better growth inhibition (88.9%) of the NCI-H226 lung cancer cell line (represents

squamous cell carcinoma and mesothelioma cancers) in comparison to the slightly less bulky isopentyl containing ester group **109** (90.16%) and activity against this particular cell line is completely switched off when the ester alkyl side chain contains the straight chain decyl group **113**, showing no measurable growth inhibition on this cell line (100.36%).

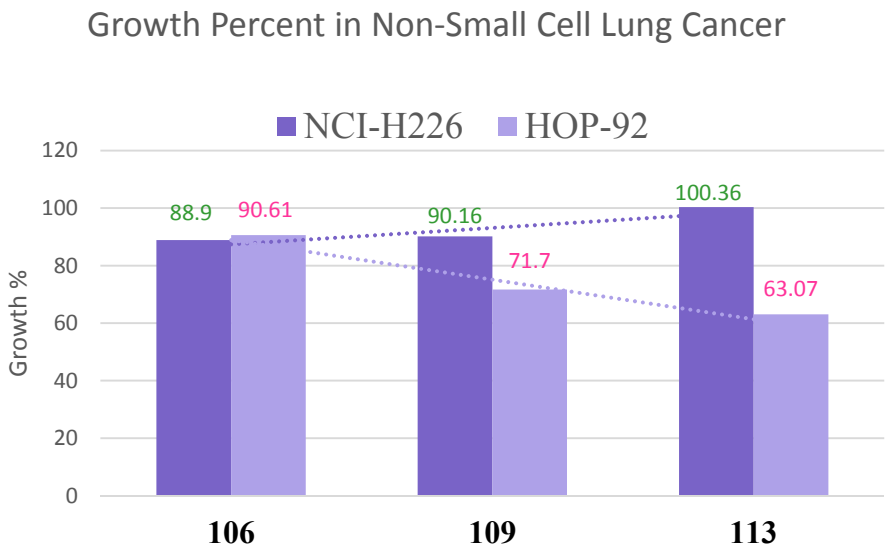


Figure 2.84 *Activity against particular lung cancer cell lines*

Contrastingly, on analysis of the HOP-92 lung cancer cell line (represents undifferentiated large cell lung cancers), as the ester side chain increases in length, the growth inhibition increases from 90.61% for *t*-butyl **106** to 71.7% for isopentyl **109** to 63.07% for the decyl group containing derivative **113** (**Figure 2.84**).

The indazole derivative containing the *t*-butyl ester side chain **106** also shows most inhibition against some particular renal cancer cell lines including the CAKI-1 cell line (71.19%) (clear cell carcinoma) and UO-31 cell line (81.78%) (carcinoma) in comparison to the isopentyl containing indazole analogue **109** which showed its highest growth inhibition against the 786-O cell line (88.91%) (renal cell adenocarcinoma). The decyl ester-containing indazole derivative **113** showed its highest inhibition against the CAKI-1 cell line (86.65%) (**Figure 2.85**).

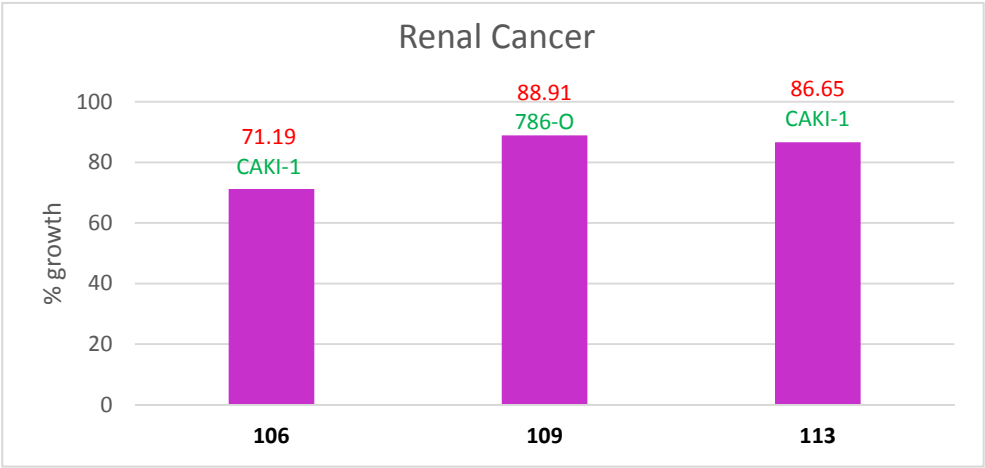
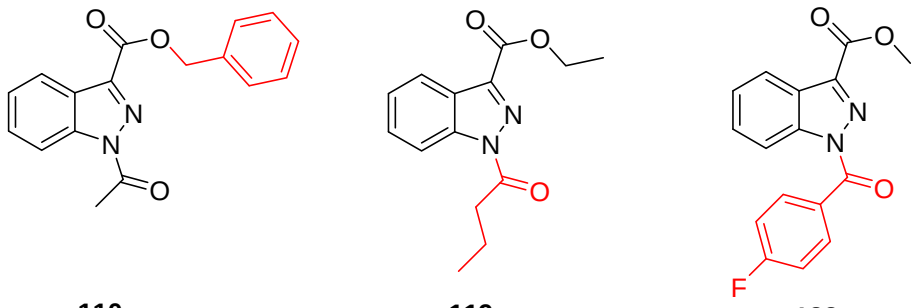


Figure 2.85 *Activity against particular renal cancer cell lines*

Analysis of the more functionalised indazoles **110**, **119** and **123** provided information on the biological activity of derivatives incorporating a benzyl ester side chain and modified *N*-acyl groups (**Figure 2.86**).



110 **119** **123**

Figure 2.86 *Indazoles containing other functionality*

In comparison to aliphatic side chain ester containing indazoles in **Figure 2.83**, benzyl containing indazole **110** exhibited some increased activity against similar cell lines discussed above, such as lung cancer cell line NCI-H226 (80.51%), renal cancer cell lines CAKI-1 (79.63%) and UO-31 (78.33%). Increased activity against breast cancer cell line MCF7 (adenocarcinoma) is observed for **110** (75.35%) in comparison to 86-97% for aliphatic ester side chain indazoles **106**, **109** and **113**. Interestingly, the elongation of the *N*-acyl group in **119** did not provide any increase in activity against any of the cell lines in comparison to *N*-acetyl derivatives **106**, **109**, **110** and **113** and, in fact, it can be said that this derivative is biologically inactive across the 60 cell lines. The greatest selective inhibition exhibited by **119** was 90.75% against breast cancer cell line

MCF7, slightly better than the previously mentioned *N*-acetyl aliphatic side chain ester-containing indazoles which showed 91.52-96.95% growth inhibition on the same cell line.

The most active indazole derivative across the 60 cell lines in the initial round of testing was **123**. Contrary to the most active derivatives in this section, **123** contains the shortest ester side chain so the fluorinated benzoyl *N*-acyl group could be playing a significant role in increasing its activity. Elevated selective activity against the HOP-92 non-small cell lung cancer cell line (61.38%) and UO-31 renal cancer cell line (77.19%) is observed in comparison to the other initial indazole derivatives **106**, **109**, **110**, **113** and **119**. Selective activity is also seen against the PC-3 prostate cancer cell line (represents grade 4 adenocarcinoma) at 72.53% growth inhibition.

Surprisingly, none of the 1*H*-indazole derivatives as described in **Section 2.7** were selected to be screened by the NCI, as a search of their database can identify a number of *in vivo* biologically active indazole derivatives with a hydrogen in the 1-position. However, they may be accepted on resubmission in the future following favourable results for similar compounds.

The next indazole derivatives selected to be assessed were disubstituted on the aryl ring with a methylenedioxy group **154** and **158**, and methyl groups **168** and **169** (**Figure 2.87**). These compounds were targeted as the previous NCI-60 results seemed to suggest indazole derivatives containing bulkier/longer side chain ester groups in the 3-position would return more favourable results. All derivatives contain an acetyl group in the 1-position. Assessment of the effect of having two resonance electron-donating groups of the methylenedioxy group versus the effect of two inductively electron-donating methyl groups on the aryl ring was also possible.

These compounds were investigated for initial NCI-60 one-dose tumour cell line activity and evaluation of the one-dose mean graphs revealed a number of interesting and distinctive patterns. The activity of the methylene-dioxy bridge-containing indazoles was of particular interest as this moiety is present in a wide

range of biologically active compounds.[57] The one-dose mean graphs for each of the compounds depicted in **Figure 2.87** are presented in ***Appendix II***.

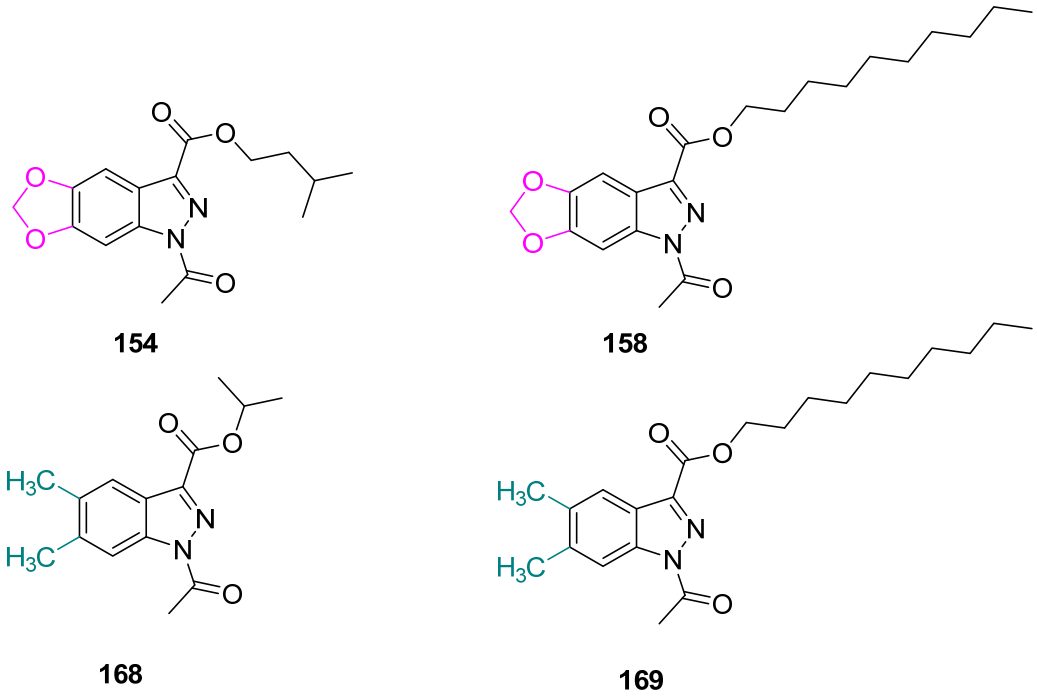


Figure 2.87 *Series of substituted indazole derivatives submitted to DTP for NCI-60 testing*

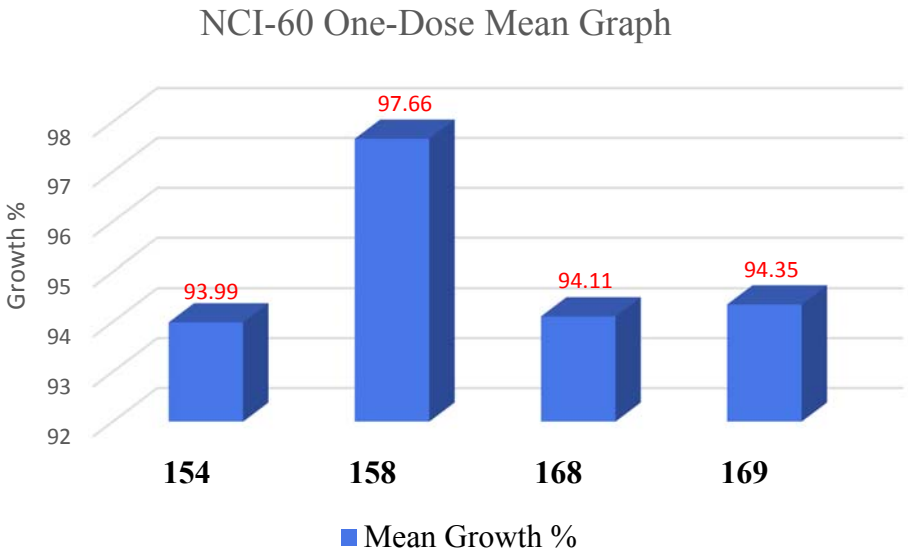


Figure 2.88 *Illustration of NCI-60 mean growth percent for substituted derivatives*

In comparison to the unsubstituted aryl ring indazole derivatives, the activity of these compounds is increased across the 60 cell lines (**Figure 2.88**) and further analysis of the one-dose mean graphs revealed some excellent selective inhibition of certain cell lines.

These substituted derivatives can be observed to give an increased growth inhibition across the lung (HOP-92 cell line), renal (TK-10, UO-31, A498 and 786-O cell lines, representing renal cell and spindle cell carcinomas) and prostate (PC-3 cell line) cancer cell lines, in particular, in comparison to the unsubstituted indazoles (**Figure 2.89**). The methylenedioxy-substituted indazole **154** shows more selective growth inhibition (41.1%) on the HOP-92 lung cancer cell line in comparison to when the isopentyl ester in the 3-position is changed to a decyl group **158** (27.2%). However, on analysis of renal cancer lines, it is the decyl derivative **158** that shows more inhibition (27.1%) in comparison to isopentyl derivative **154** (19.1%), albeit on different cell lines: A498 which represents adenocarcinoma and 786-D which represents renal cell adenocarcinoma respectively.

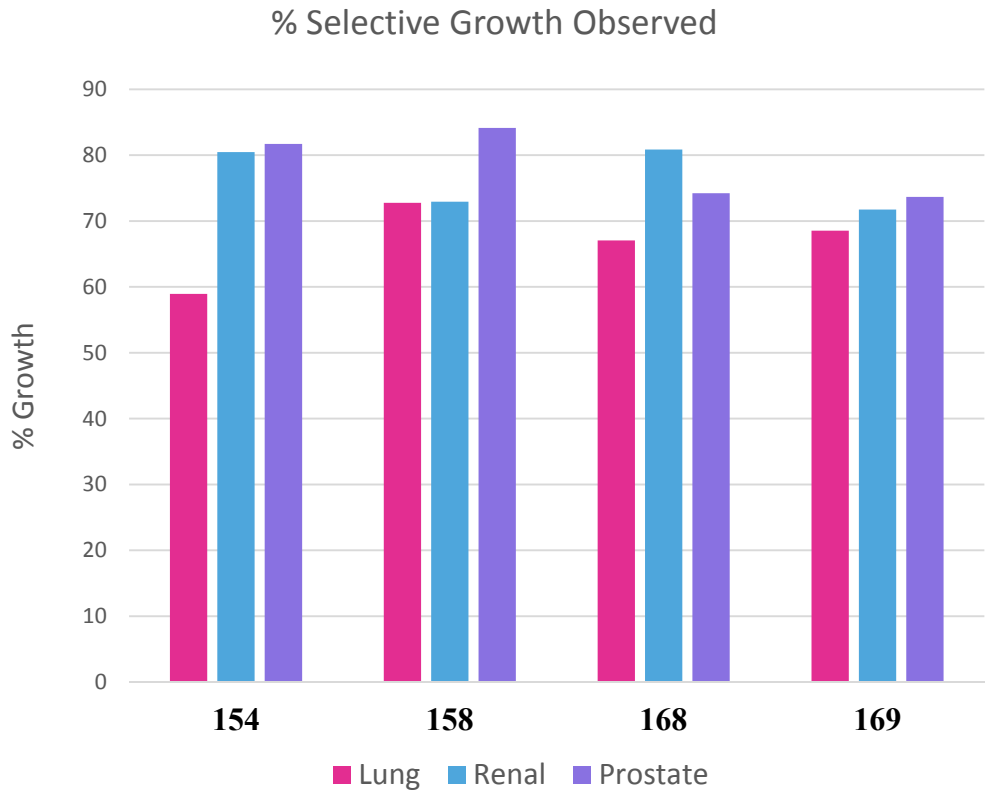


Figure 2.89 *Illustration of mean growth% in lung, renal and prostate cancer cell lines*

Some moderate selective inhibition is also observed against breast cancer cell lines, in particular the T-47D cell line, as observed in **Figure 2.90**. The inhibitory effect is most pronounced when the cell line is treated with methylenedioxy-containing indazole derivatives **154** and **158**, producing a growth inhibition of 22 and 18% respectively.

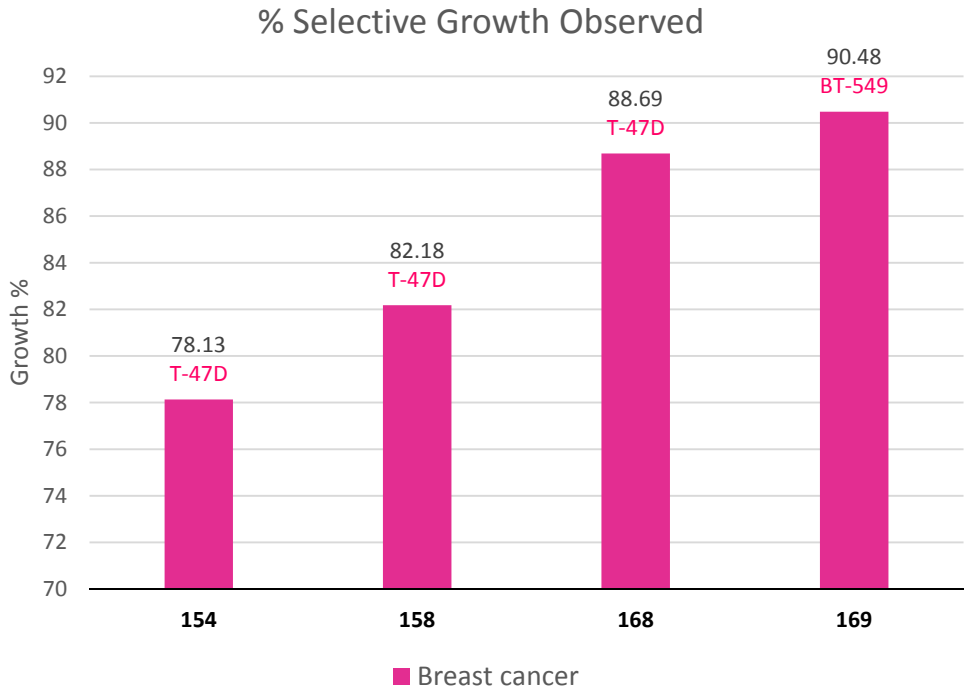


Figure 2.90 *% Selective Growth Observed in Breast Cancer cell lines*

We are delighted to report our most significant selective growth inhibition up until this point for these derivatives which was found in the dimethyl indazole analogues, and for the first time with an ovarian cancer cell line. When treated with the dimethyl substituted indazole derivatives **169** and **168**, a particular ovarian cancer cell line, OVCAR-4, exhibited just 0.47 and 2.77 growth percent, respectively (**Figure 2.91**). The OVCAR-4 cell line was developed from an ovarian cancer patient with clinical resistance to platinum-based chemotherapy.

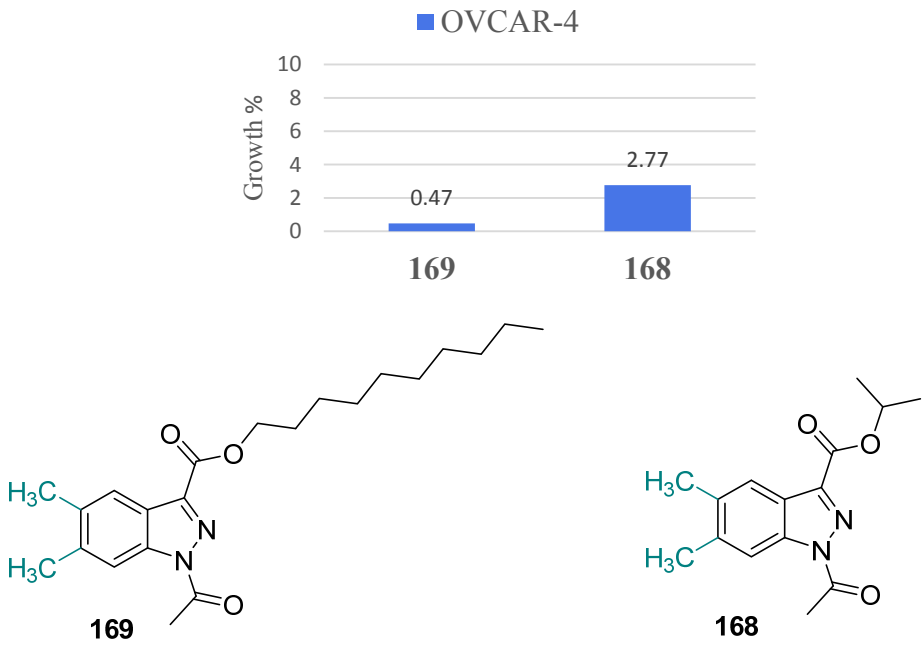


Figure 2.91 *Illustration of mean growth % in ovarian cancer cell lines*

There is a considerable difference observed on the activity against the OVCAR-4 cell line on comparison of unsubstituted decyl indazole **113** (106.19% growth) and dimethyl substituted indazole analogue **169** (0.47%), suggesting the presence of the methyl groups on the aryl ring enhances the biological activity of the indazole derivatives.

The next derivatives selected for biological evaluation contained two fluorine substitutents on the aryl ring of the indazole. A total of seven of these analogues were tested, five compounds contain a long or bulky aliphatic ester group, one contains a benzyl group and one derivative incorporates an amide in the 3-position, all analogues include an *N*-acetyl group in the 1-position (**Figure 2.92**). Assessment of the effect of having two electron-withdrawing fluorine atoms versus the effect of two electron-donating methyl groups on the aryl ring is also possible.

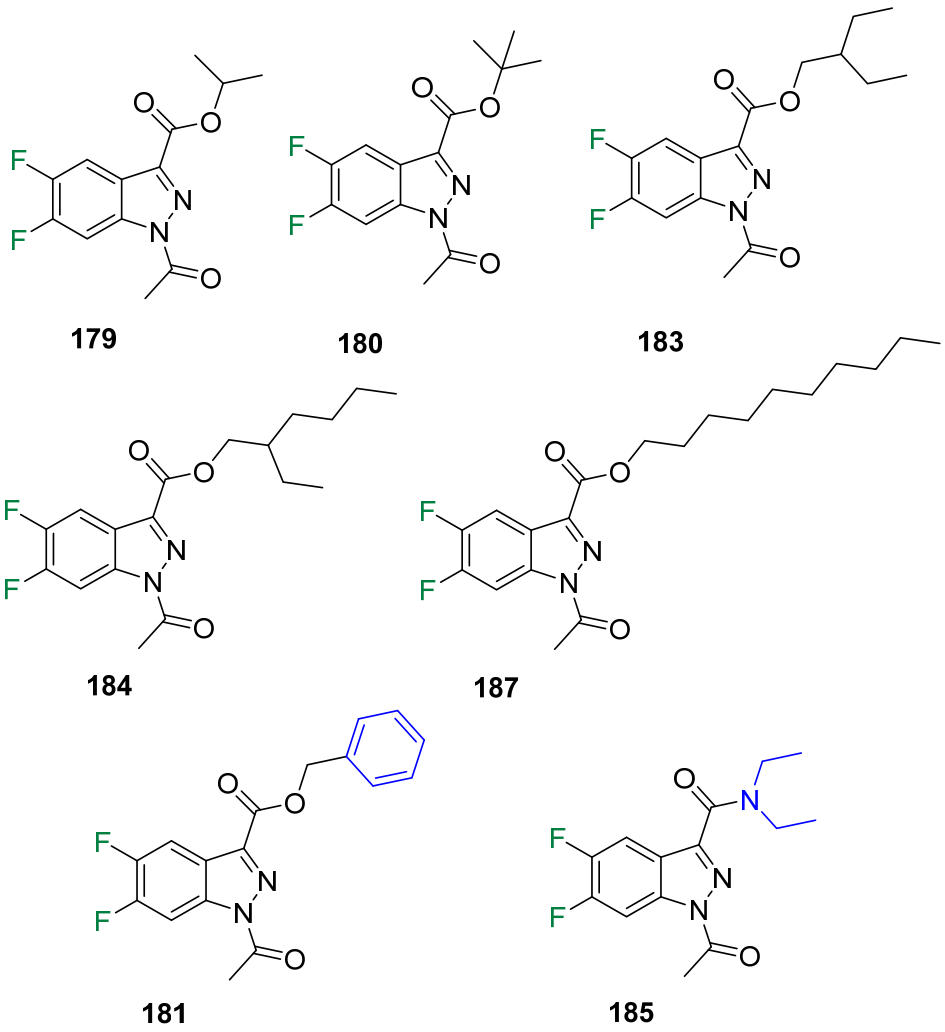


Figure 2.92 *Selection of difluoro substituted indazoles evaluated*

These compounds were investigated for initial NCI-60 one-dose tumour cell line activity but the activity profile required for five-dose testing across all 60 cell lines was not present. Again, however, some interesting and characteristic selective growth inhibitory effects can be observed on evaluation of the one-dose mean graphs. The distinctive pattern of growth inhibition for these agents is outlined below (**Figure 2.93**) and the one-dose mean graphs for each of the compounds depicted in **Figure 2.92** are presented in ***Appendix II***.

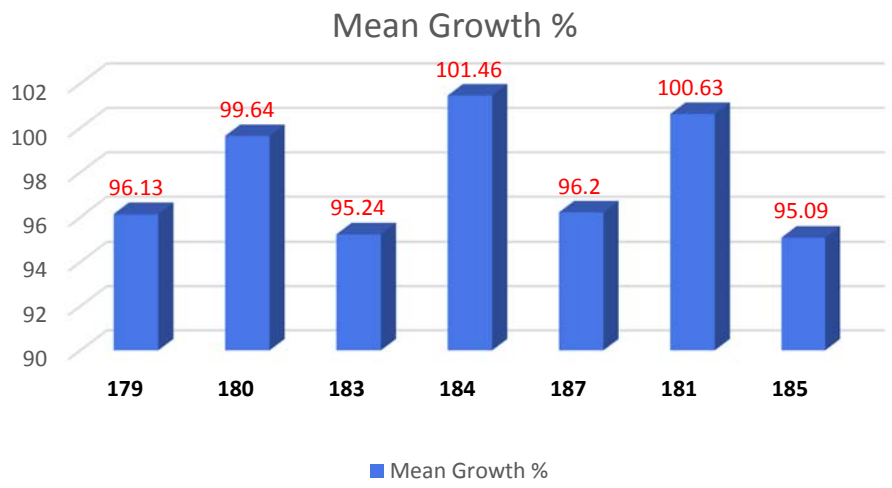


Figure 2.93 *Mean growth% for difluoro substituted indazoles*

The isopropyl ester-containing indazole **179** shows the most selective growth inhibition 42.43% observed for these compounds on the HOP-92 lung cancer cell line and **179** also shows activity against the CNS SNB-75 cell line (72.14%), which is an *in vitro* model for astrocytoma-type brain cancer. The *t*-butyl derivative **180** shows slightly decreased similar selective inhibition against the same CNS cell line (80.16%) and the melanoma UACC-62 cell line (80.34%).

The bulky 2-ethylbutyl ester-containing indazole **183** shows an elevated mean growth % inhibition in comparison to aryl unsubstituted indazoles containing a bulky ester side chain while also showing an impressive 43.1% growth inhibition on the T-47D breast cancer cell line. The amide-containing derivative **185** exhibits the most active mean growth percent while also showing higher selective activity against the lung (68.03%), renal (67.7%) and prostate (68.93%) cell lines in comparison to its ester analogues. The benzyl ester-containing indazole **181** shows some selectivity against the colon cancer KM12 cell line (87.73%) and the breast cancer MDA-MB-231 cell line (85.5%). All derivatives show some selective activity against lung, renal, prostate and breast cancer cell lines as illustrated in **Figure 2.94**.

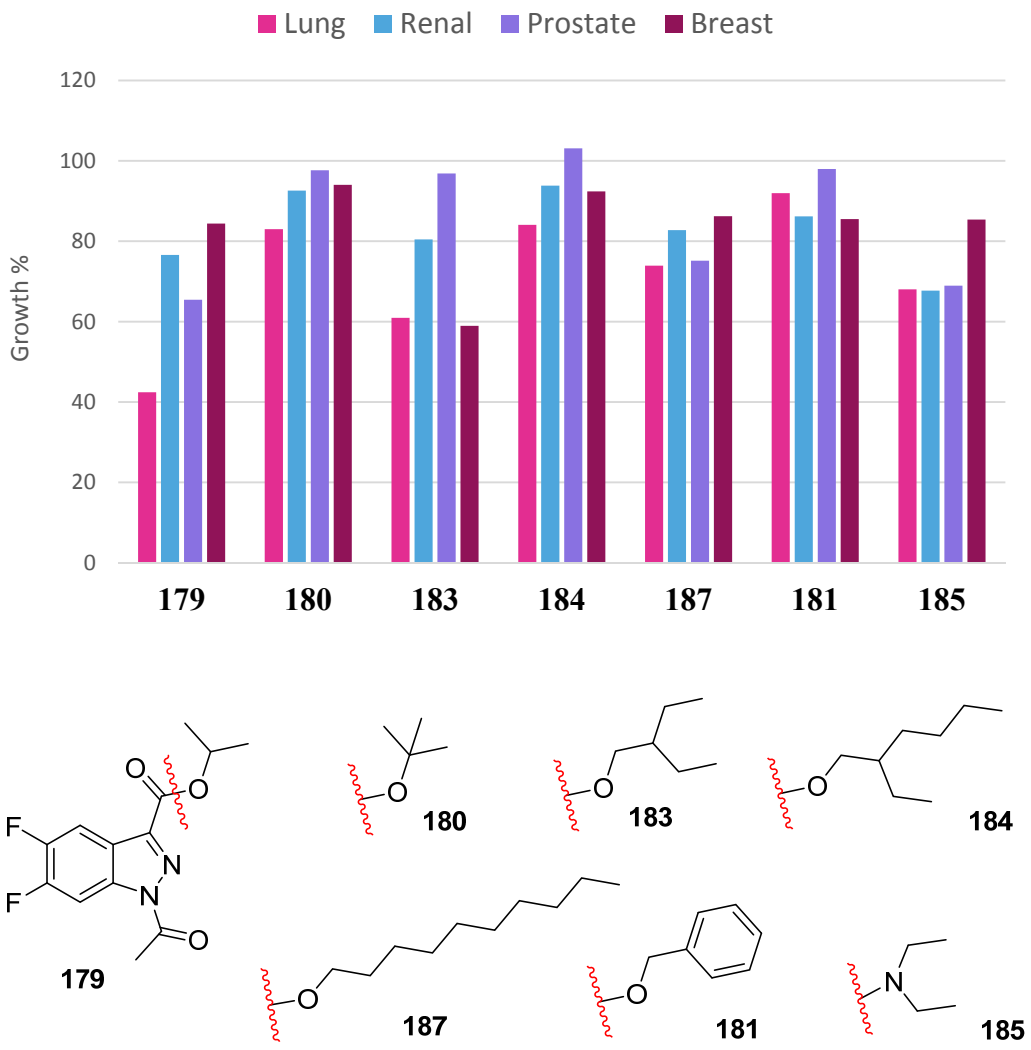


Figure 2.94 *Altering side chain of difluoro derivatives*

On comparison of the dimethyl-substituted indazole derivatives **168** and **169** to difluoro-substituted indazole derivatives **179** and **187**, it is clear that the methyl groups on the aryl ring have a dramatic effect on the growth inhibition of the OVCAR-4 ovarian cancer cell line but when the methyl groups are replaced by fluorines, the effect on the OVCAR-4 cell line is completely switched off (**Figure 2.95**).

The difluoro indazole **179** has a more potent effect on the HOP-92 lung cancer cell line (42.43%) than its dimethyl analogue **168** (67.06%) suggesting that the isopropyl group is beneficial to activity against this particular cell line and that difluoro substitution is favoured for this selective inhibition. The isopropyl group

also has a favourable effect on the activity against the SNB-75 CNS cancer cell line and again difluoro substitution is slightly more active (72.14%) than dimethyl substitution (80.71%).

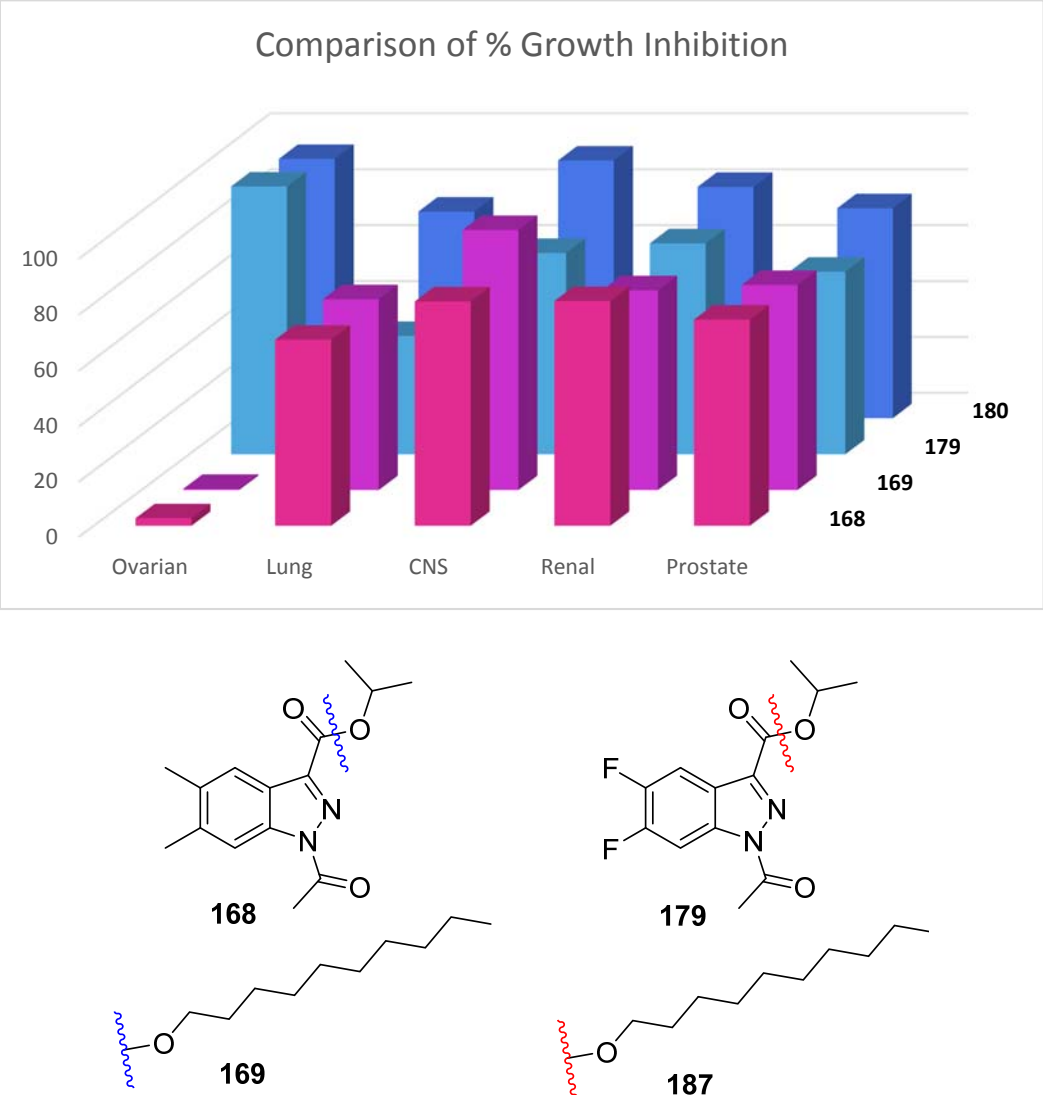


Figure 2.95 *Comparison of dimethyl and difluoro indazoles*

With previous results in mind, the next series of compounds sent for biological evaluation consisted of methyl- and fluoro-disubstituted indazole rings, containing isopropyl side chain esters in the 3-position. We were keen to evaluate our novel derivatives benzylated in the *N-1* position due to their similarity to drug compounds on the market and compare them to their or *N-2* analogues (**Figure 2.96**). These compounds **264-267** were successfully investigated for initial NCI-60 one-dose tumour cell line activity.

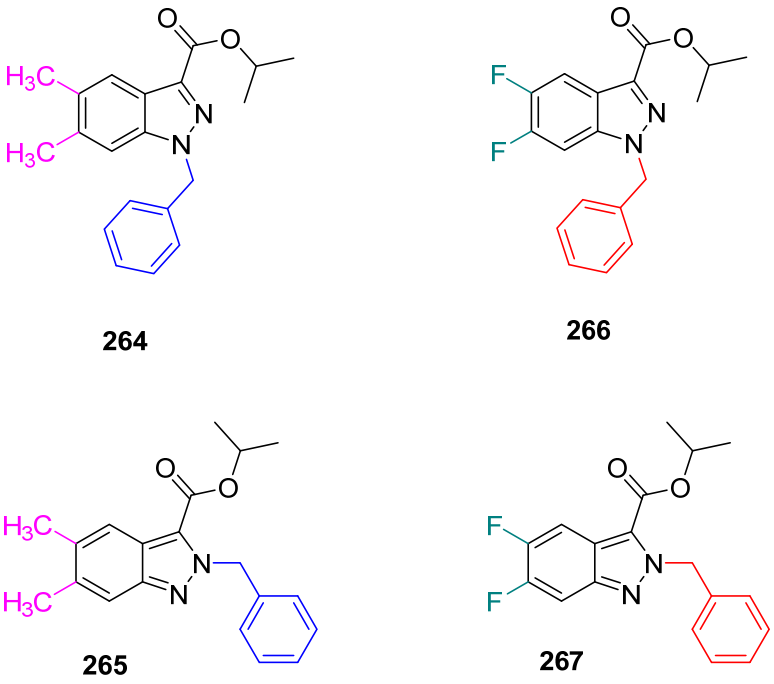


Figure 2.96 *N-Benzyl indazole derivatives*

An account of the growth inhibition for these agents is outlined below and the one-dose mean graphs for each of the compounds depicted in **Figure 2.96** are presented in ***Appendix II***. The highest mean % growth across all 60 cancer cell lines in this project was observed for *N*-1 benzylated difluoro-indazole **266** (**Figure 2.97**).

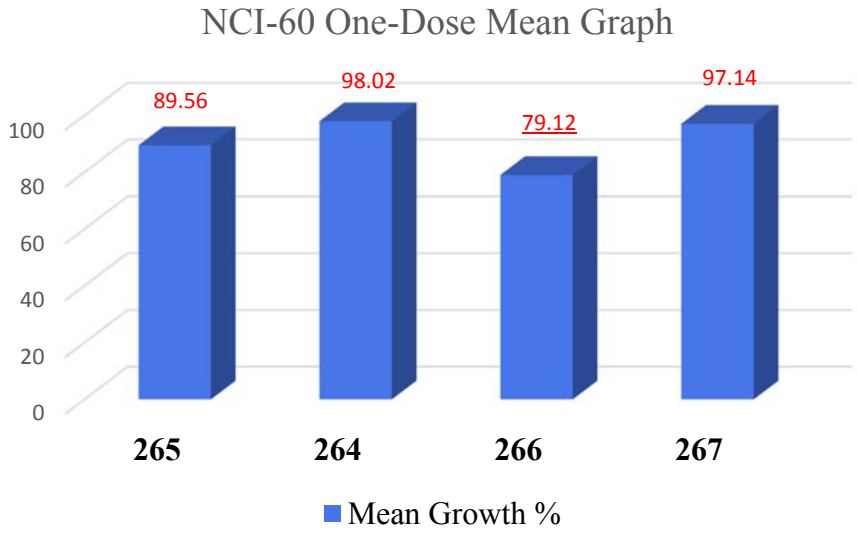


Figure 2.97 *Illustration of NCI-60 mean growth percent for N-benzyl substituted derivatives*

On examination of the one-dose mean graphs, some interesting selectivity for inhibition of particular cell lines could be observed. It was found that by altering the benzyl substitution position from the 1-position to the 2-position of the indazole results in contrasting activity and selectivity across the 60 cell line panel.

For difluoro derivatives **266** and **267** the *N*-1 benzyl indazole **266** performed best in terms of activity across the 60 cell line panel and also in selectivity and growth inhibition against certain cell lines in comparison to *N*-2 benzyl indazole **267**. As shown in **Figure 2.98**, *N*-1 benzyl derivative **266** is a much more potent agent for inhibition of a number of cell lines in comparison to the *N*-2 analogue. Other selective activity not shown below includes growth inhibition of the K-562 leukaemia cell line (68.09%), the NCI-H522 lung cancer cell line (51.91%), the HT29 colon cancer cell line (58.88%), the CAKI-1 renal cancer cell line (58.78%) and the MCF7 breast cancer cell line (65.08%).

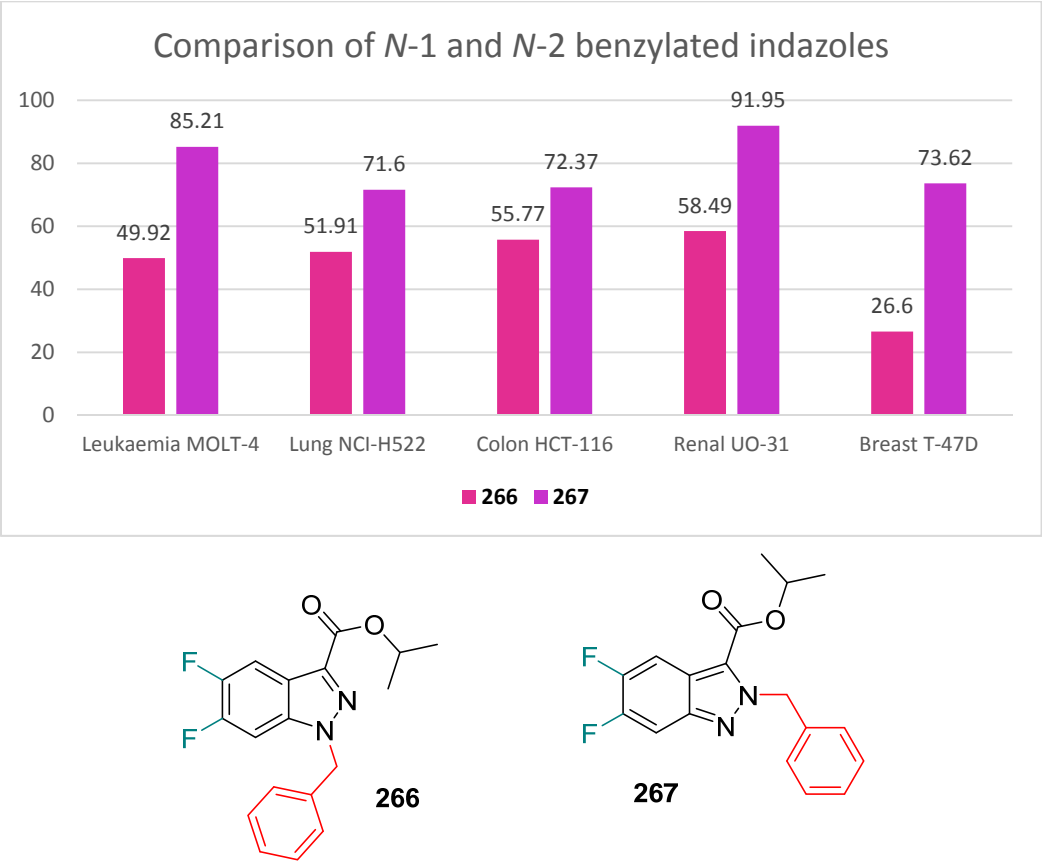


Figure 2.98 *Illustration of selective growth % for N-benzyl substituted derivatives*

In contrast to the difluoro derivatives **266** and **267**, the *N*-2 dimethyl indazole **265** exhibits slightly increased activity across the 60 cell lines in comparison to the *N*-1 indazole **264**. However, the *N*-1 benzyl indazole displays a more selective growth inhibition profile.

On inspection of the one-dose mean graphs, we can see that when treated with **264**, the growth of the RPM-8228 leukaemia cell line (*in vitro* model of plasmacytoma and myeloma) is inhibited to 27.73% growth, a significant difference when compared to the *N*-2 analogue **265** (85.4%). The *N*-2 analogue, however, displays an increased activity profile against lung, colon and breast cancer cell lines in comparison to the corresponding *N*-1 benzyl indazole (**Figure 2.99**).

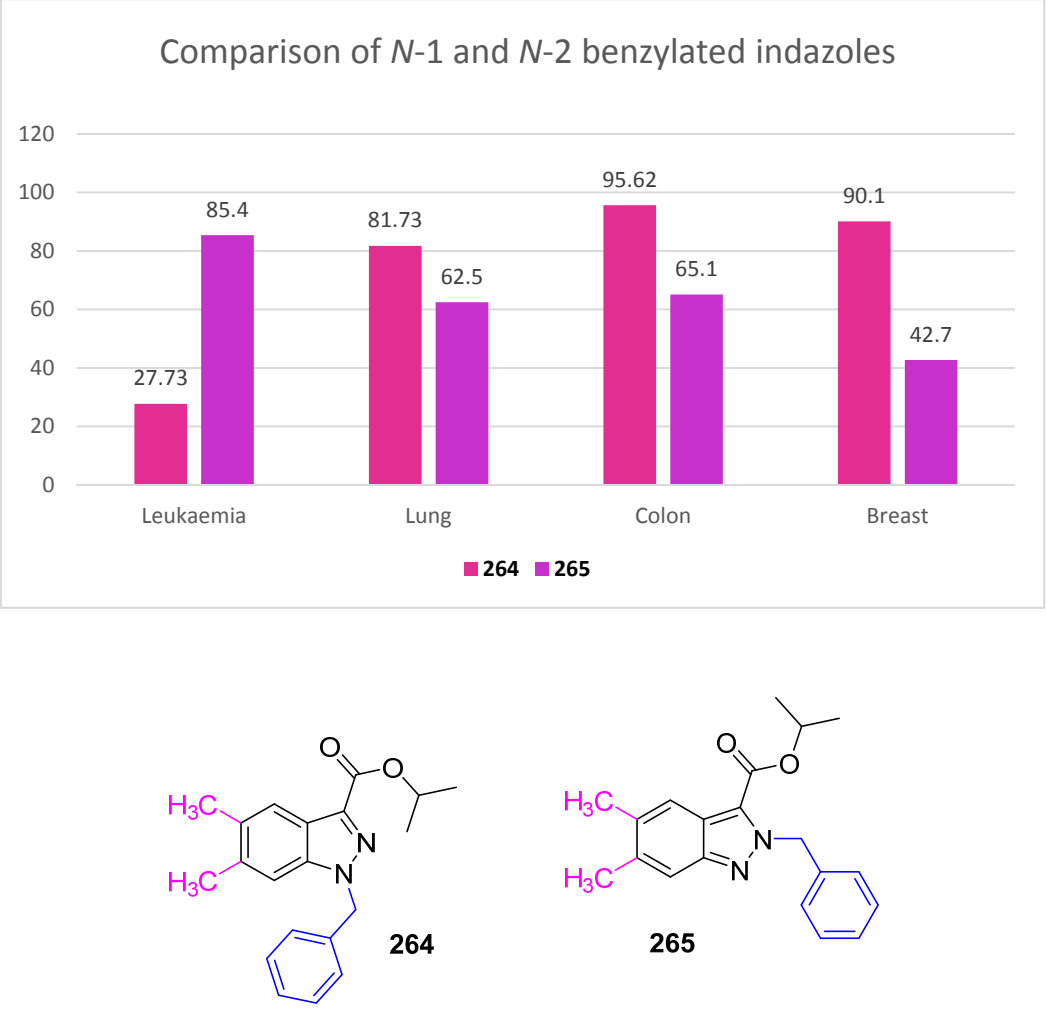


Figure 2.99 *Illustration of selective growth % for N-benzyl substituted derivatives*

2.10.2.3 COMPARE analysis

The NCI COMPARE programme is an online database and comparison tool which can analyse one-dose and five-dose cytotoxicity data for the 60 cell line panel for similar activity profiles with compounds screened previously by the DTP. The COMPARE algorithm was developed by the NCI to help predict a biochemical mechanism of action from the *in vitro* anti-tumour screen.[100] Comparison of the mean graph cytotoxicity profile for a certain anti-cancer agent having a known mechanism of action with those of single compounds not previously characterised allows the identification of new agents with similar cytotoxicity profiles to that of the 'seed' compound, which may share the same mechanism of action.[101] A high correlation of cytotoxicity with compounds of known biological activity can predict the compounds mechanism of action. It can also tell if the compound has any unique response of the drug in comparison to the known compounds.

COMPARE analysis was carried out for a number of our most active derivatives **168**, **169**, **265** and **267** to see if their mechanisms of action were similar, even after changing substitution patterns. Derivatives **168** and **169** were investigated initially as they were observed to show the greatest activity on the OVCAR-4 ovarian cancer cell line at one-dose levels, exhibiting selective growth inhibition of 97.23 and 99.53% respectively.

It was found that derivatives **168** and **169** have a definite correlation value of 0.81 at the one-dose concentration level, indicating the existence of a similar biological mode of action despite alteration of the alkyl group of the ester in the 3-position from an isopropyl group to a decyl group as would be expected (**Figure 2.100**).

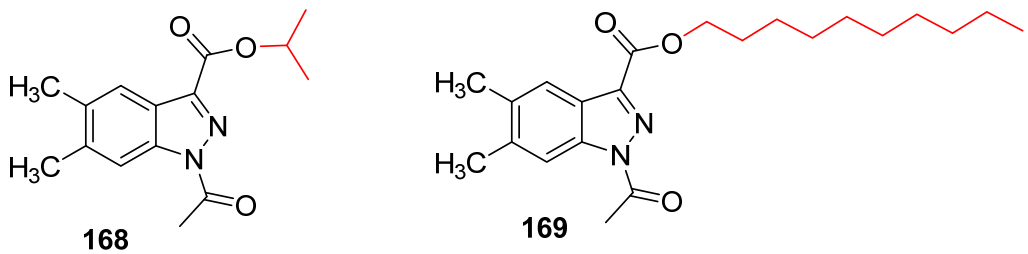


Figure 2.100 *Derivatives with high correlation value possibly sharing mechanism of action*

The *N*-2 benzyl substituted dimethyl **265** and difluoro indazoles **267** were found to have a high correlation between the analogues of 0.74, again indicating a similar biological mechanism of action in spite of **265** containing two electron donating methyl groups on the aryl ring and **267** having two electron withdrawing fluorines present (**Figure 2.101**).

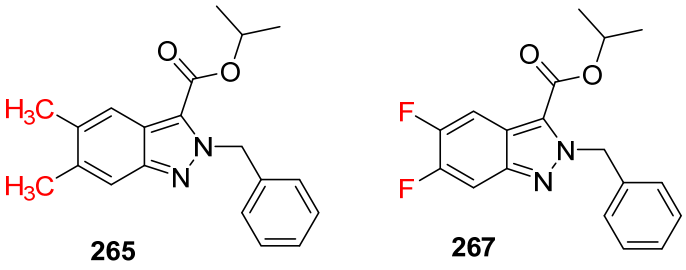


Figure 2.101 *Derivatives possibly sharing mechanism of action*

Both derivatives had been found to be highly potent against a number of cell lines as illustrated in **Figure 2.102**. The difluoro analogue **267** exhibits an increased inhibitory effect against the particular cell lines in comparison to dimethyl derivative **265**.

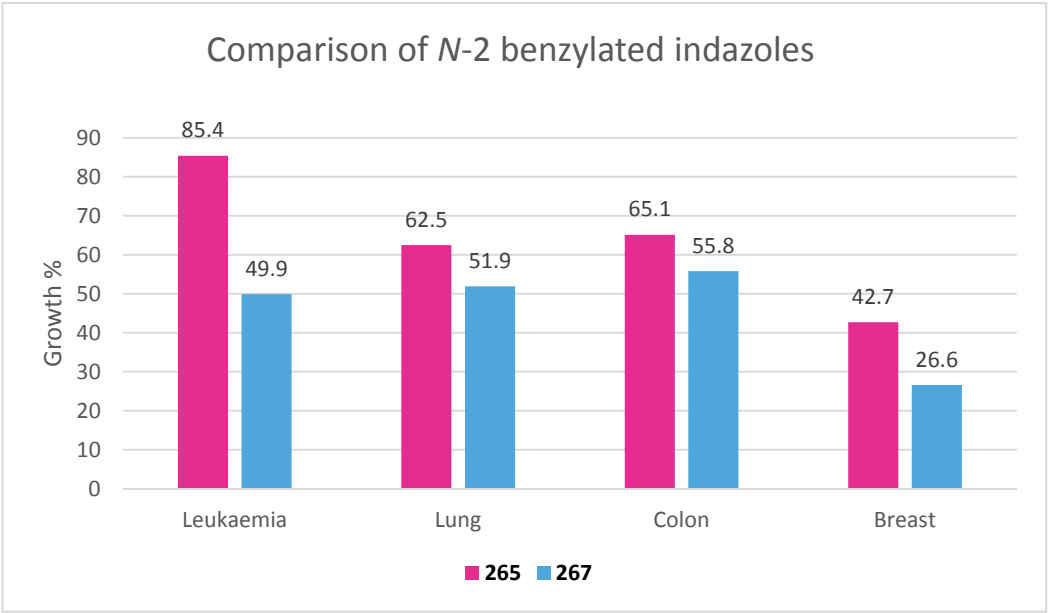


Figure 2.102 *Comparison of dimethyl and difluoro N-2 benzylated analogues*

2.10.3 Introduction to CO-ADD antimicrobial testing

A new not-for-profit initiative was launched in March 2015 where compounds could be screened for antibiotic activity by "The Community for Antimicrobial Drug Discovery" (CO-ADD) in a worldwide search for the next big antibiotic.[102] The CO-ADD reached out to chemists in academia and research organisations who have synthesised novel compounds for other projects and would not otherwise be screened for antimicrobial activity. They believe there is untapped diversity in the scale of >36 million compounds contained in the laboratories of academic and small biotech companies, with thousands of chemists discovering and synthesising more every day.

These compounds are screened at no cost against a key panel of drug-resistant bacterial strains and researchers who get positive results from initial screening have the option to proceed to further development using the CO-ADD's resources. Samples are screened primarily against 5-7 ESKAPE bacterial pathogens and two fungal/yeast pathogens and if active, will be brought further through the screening stages.[103]

This organisation's integrated capabilities can help fast track hit compounds from the early stages to identification of a new drug candidate.

This unique opportunity allows the worldwide community of researchers to submit novel compounds for free and readily accessible antimicrobial testing of compounds that otherwise would not have been investigated for their antibiotic activity.

Figure 2.103 shows the range of indazole deriatives sent for antimicrobial testing. By sending a large range of diverse compounds it was hoped to see a trend emerge to direct the project towards altering the structures so that antibiotic activity would be increased.

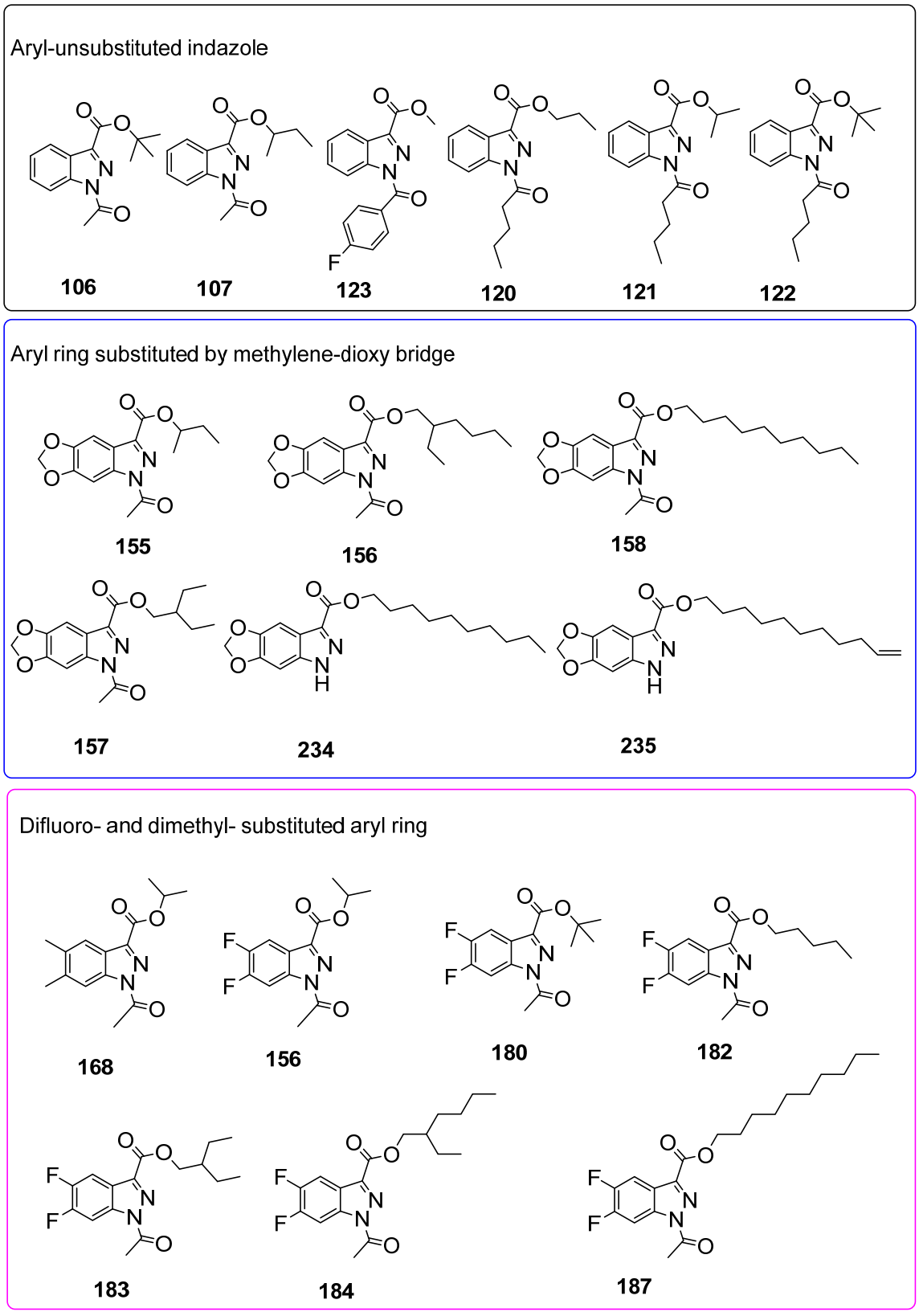


Figure 2.103 *19 compounds submitted to CO-ADD for antimicrobial screening*

2.10.4 Conclusion to biological testing

From the 40 compounds submitted to the NCI for biological screening to date, 21 were accepted and assessed for their anticancer activity. The initial one-dose screening was extremely useful in identifying which structural features to target in future submissions and in future synthesis of novel indazole compounds in this project. Future synthetic studies within the research group will look at further exploring the *N*-alkyl derivatives by using substituted benzyl groups and long chain alkyl halides as potential alkylating agents for these compounds.

Derivatives having undergone side-chain transformations like the epoxide and tertiary amine indazole derivatives will be sent for testing in the future. Previously, a 1*H*-indazole with the epoxide side chain was not accepted for testing but perhaps substitution in the 1-position would increase the chances of being accepted. Surprisingly, no *N*-1 unsubstituted indazole derivatives were accepted for testing. Work within the group has also discovered that structures containing aldehydes are not usually accepted to the NCI for assessment.

The one-dose screening results have shown that the initial aryl-unsubstituted indazole deriatives do not show significant biological action against the NCI-60 cell array but increased selectivity was seen in growth inhibition of particular cancer cell lines in the presence of our substituted derivatives. For example, our most active derivatives showed remarkable inhibition across ovarian cancer cell lines (**168** and **169**), lung cancer cell lines (**179**), leukaemia cell lines (**264**) and breast cancer cell lines (**266**) (**Figure 2.104**).

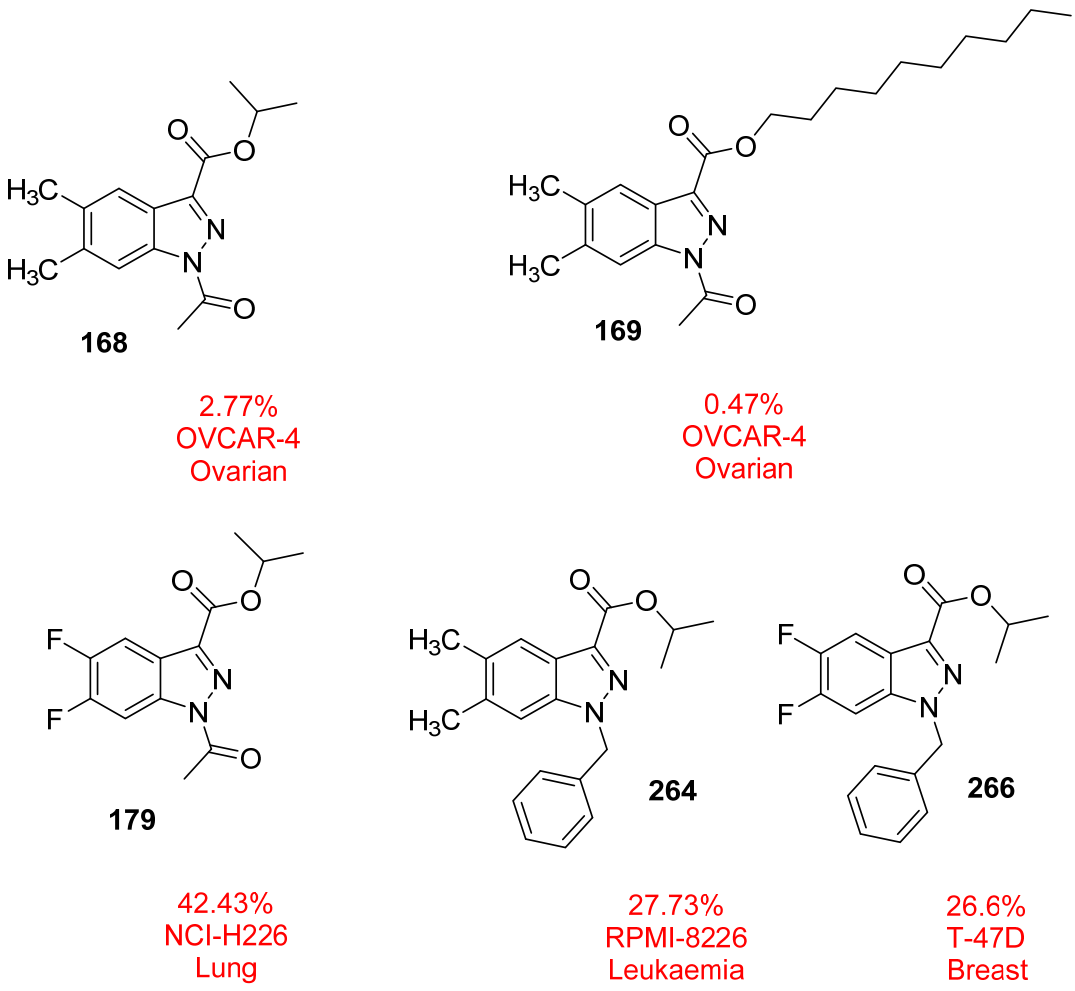


Figure 2.104 *Most active compounds in NCI evaluation*

To conclude, it is evident from these investigations that indazole-containing derivatives are an important class of heterocyclic compounds which, through some structural modification and biological evaluation, possess unique bioactivity and much potential for the development of novel anticancer agents. Antimicrobial test results from the CO-ADD are pending.

2.11 Concluding remarks

The overall synthetic achievement of this project was the successful synthesis of a range of novel compounds (>160) and specifically, indazole derivatives (>100), through a number of tailored and modified synthetic routes in high purities and good yields. This initial project has great potential for expansion as most routes explored so far have more novelty to be further investigated. Following on from the synthetic strategies put in place during the course of this work, a number of potential target molecules could be identified for future synthesis.

The initial indazole formation cycloaddition reactions were accomplished using an established method that uses aryne precursors as the dipolarophile and diazocarbonyl compounds as the 1,3-dipole, both of which were prepared in the laboratory. We were able to easily diversify the indazole derivatives formed by altering the diazo and/or aryne precursor starting materials. This method used 2-trimethylsilylphenyltriflate derivatives and caesium fluoride to generate the aryne *in situ.*

During the project, a newer and less exploited method of aryne generation was discovered that had not been fully taken advantage of yet in indazole formation before our research. Tailoring this method to suit our chemical syntheses provided a new method that was more cost effective and limited the formation of by-products in comparison to the more established method used previously. This method generated a 2-trimethylsilylphenylnonaflate which subsequently formed the aryne *in situ* in a one-pot reaction.

Initial studies into using the nonaflate method for the generation of pyridyne intermediates were initially investigated. Two novel pyridyne precursors were prepared in the laboratory but unfortunately with no success with these in cycloaddition reactions so far. There is much scope for the expansion and improvement of this foundation work.

A route to a mild and general deacylation method of *N*-acyl indazoles was established in this project. This gave rise to a number of novel indazoles being synthesised and the potential for derivatisation at the *N*-1 position.

A method for successful alkylation of the 1*H*-indazoles was identified that gave rise to the formation of both *N-1*- and *N-2*-benzylated isomers which were separable by column chromatography on silica gel producing compounds similar in structure to some indazole derivatives on the market.

Initial investigations into side chain transformations of the functionalisable ester group of some indazole derivatives were performed, giving rise to even more structurally varied indazole derivatives and a range of novel functionalised derivatives.

Four rounds of biological testing involving 21 novel derivatives took place at the NCI where some structural-activity patterns were identified and encouraging anti-cancer activity was observed for some derivatives.

An antimicrobial screen was performed by CO-ADD on 19 novel indazole derivatives in an initiative to find the next antibiotic with results pending.

2.12 References

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Chapter Three

Experimental

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3.1 General Procedures

Solvents were distilled prior to use as follows: dichloromethane (DCM) was distilled from phosphorus pentoxide,[1] ethyl acetate was distilled from potassium carbonate,[2,3] hexane was stored and distilled prior to use, tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl, dimethylformamide (DMF) was stored for 24 h over calcium hydride then distilled under reduced pressure and stored over 4Å molecular sieves. 3-Chloroperoxybenzoic acid (70%) was supplied by Aldrich and used without purification. Caesium fluoride was supplied by Aldrich and stored in a desiccator. Organic phases were dried using anhydrous magnesium sulphate. All commercial reagents were used without further purification unless otherwise stated.

Proton (300 MHz) and carbon (75.5 MHz) NMR spectra were recorded on a Bruker Avance 300 MHz NMR spectrometer. Proton (400 MHz), carbon (100 MHz) and fluorine (376 MHz) NMR spectra were recorded on a Bruker Avance 400 MHz NMR spectrometer. All spectra were recorded at room temperature (~20 ºC) in deuterated chloroform ($CDCl_3$) unless otherwise stated using tetramethylsilane (TMS) as internal standard. Chemical shifts (δ_H and δ_C) are reported in parts per million (ppm) relative to TMS and coupling constants are expressed in Hertz (Hz). Splitting patterns in ^1H spectra are designated as s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), ddd (doublet of doublets of doublets), dt (doublet of triplets), dq (doublet of quartets) and m (multiplet). ^{13}C NMR spectra were assigned with the aid of DEPT experiments. Compounds which were assigned with the aid of DEPT experiments were assigned by identifying the carbon type (CH_3, CH_2, CH or C).

Infra red spectra were recorded as thin films on sodium chloride (NaCl) plates, as potassium bromide (KBr) discs for solids or as solution spectra in $CDCl_3$ on a Perkin Elmer Paragon 1000 FT-IR spectrometer. Melting points were measured on a Uni-Melt Thomas Hoover capillary melting point apptus and are uncorrected. Flash chromatography was performed using Kieselgel silica gel 60, 0.040-0.063 mm (Merck). Thin layer chromatography (TLC) was carried out on

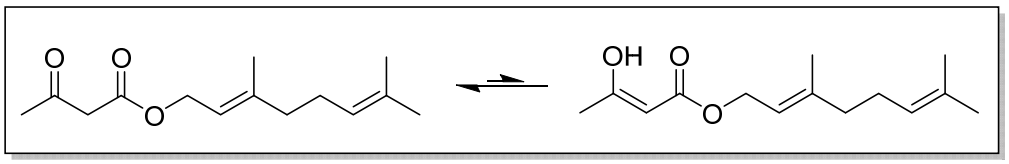
pre-coated silica gel plates (Merck 60 PF_{254}). Visualisation was achieved by UV (254 nm) light detection and vanillin staining.

Elemental analyses were performed by the Microanalysis Laboratory, National University Ireland, Cork using Perkin-Elmer 240 and Exeter Analytical CE440 elemental analysers. Nominal mass spectra were recorded on a Waters Quattro Micro triple quadrupole spectrometer in electrospray ionisation (ESI) mode using 50% water/acetonitrile containing 0.1% formic acid as eluent; samples were made up in acetonitrile. High resolution mass spectra (HRMS) were recorded on a Waters LCT Premier Time of Flight spectrometer in electrospray ionisation (ESI) mode using 50% water/acetonitrile containing 0.1% formic acid as eluent; samples were made up in acetonitrile.

3.2 Synthesis of α-diazocarbonyl compounds

3.2.1 Preparation of ester derivatives by transesterification[4]

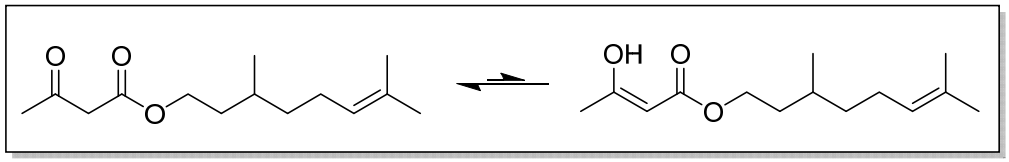
3,7-Dimethylocta-2,6-dienyl 3-oxobutanoate 2



Geraniol **310** (1.54 g, 10.0 mmol, 1.0 equiv.) was added to a stirred solution of ethyl acetoacetate **311** (1.30 g, 10.0 mmol, 1.0 equiv.) in toluene (40 mL). 3-nitrophenylboranic acid **1** (42 mg, 250 μmol, 2.5 mol%) was then added as catalyst. The reaction was heated under reflux (150 °C) with the toluene-ethanol azetrope continuously removed from the reaction using a Dean-stark distillation apptus. TLC analysis after 5 h indicated complete consumption of the ethyl acetoacetate **311** starting material and, after cooling, the toluene was removed under reduced pressure to yield 3,7-dimethylocta-2,6-dienyl 3-oxobutanoate **2** as a yellow oil (0.78 g, 66%), which was used without further purification. The ^{13}C NMR spectra were assigned to the keto and enol forms as listed below. **Keto form:** δ_H($CDCl_3$, 300 MHz): 1.61 (3H, s, C*H*$_3$), 1.68 (3H, s, C*H*$_3$), 1.71 (3H, s, C*H*$_3$), 2.01-2.13 (4H, m, 2 × C*H*$_2$), 2.27 [3H, s, C(O)C*H*$_3$], 3.46 [2H, s, C(O)C*H*$_2$C(O)], 4.65 (2H, d, *J* 7.2, OC*H*$_2$), 5.07 [1H, t, *J* 7.2, C*H*=C(CH$_3$)$_2$], 5.35 [1H, t, *J* 7.2, OCH$_2$C*H*=C(CH$_3$)]; δ_C($CDCl_3$, 100 MHz): 16.4 (*C*H$_3$), 17.6 (*C*H$_3$), 25.6 (*C*H$_3$), 26.2 (*C*H$_2$), 30.0 [C(O)*C*H$_3$], 39.5 (*C*H$_2$), 50.1 [C(O)*C*H$_2$C(O)], 62.2 (O*C*H$_2$), 117.7 (*C*H) alkene, 123.6 (*C*H) alkene, 131.8 [*C*$_q$(CH$_3$)$_2$], 143.0 (*C*$_q$) alkene, 167.1 (*C*=O) ester, 200.5 (*C*=O) ketone; ν_{max} (film)/cm^{-1} 1742, 1719, 1649, 1152; *m/z* (ESI$^+$) 238 [M]$^+$ (10%) 162 (100).

Enol form: δ_C($CDCl_3$, 100 MHz): 14.0 (*C*H$_3$), 16.2 (*C*H$_3$), 21.1 (*C*H$_3$COH), 26.4 (*C*H$_2$), 30.0 (*C*H$_3$), 39.5 (*C*H$_2$), 59.3 (O*C*H$_2$), 89.7 (*C*H) alkene, 123.5 (*C*H) alkene, 123.9 (*C*H) alkene, 139.4 [*C*$_q$(CH$_3$)$_2$], 142.3 (*C*$_q$) alkene, 172.5 (*C*=O), 175.3 (*C*OH). Spectral details are in agreement with those reported in the literature.[5]

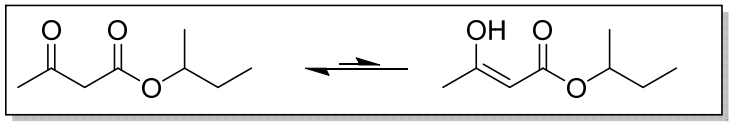
3,7-Dimethyloct-6-enyl 3-oxobutanoate 3



The title compound was prepared following the same procedure as 3,7-dimethylocta-2,6-dienyl 3-oxobutanoate **2** using citronellol **312** (2.39 g, 15.4 mmol), ethyl acetoacetate **311** (2.01 g, 15.4 mmol) in toluene (50 mL) and 3-nitrophenylboranic acid **1** (64 mg, 384 μmmol, 2.5 mol%). After 5 h the toluene was removed under reduced pressure to yield 3,7-dimethyloct-6-enyl 3-oxobutanoate **3** as a yellow oil (3.48 g, 94%) as a mixture of diastereoisomers which were indistinguishable in the ^{1}H NMR spectrum and was used without further purification. δ_H($CDCl_3$, 400 MHz): 0.91 (3H, d, *J* 6.3, CHC*H*$_3$), 1.12-1.79 [11H, m, containing C*H*, 2 × C*H*$_2$, 1.61 (3H, s, C*H*$_3$) and 1.68 (3H, s, C*H*$_3$)], 1.92-2.15 (2H, m, OCH$_2$C*H*$_2$), 2.27 [3H, s, C(O)C*H*$_3$], 3.45 [2H, s, C(O)C*H*$_2$C(O)], 4.12-4.30 (2H, m, OC*H*$_2$), 5.08 [1H, t, *J* 7.1, C*H*=C(CH$_3$)$_2$]; δ_C($CDCl_3$, 100 MHz): 17.6 (*C*H$_3$), 19.3 (*C*H$_3$), 25.3 (*C*H$_2$), 25.7 (*C*H$_3$), 29.4 [C(O)*C*H$_3$], 30.1 (*C*H), 35.3 (*C*H$_2$), 36.9 (*C*H$_2$), 50.2 [C(O)*C*H$_2$C(O)], 64.0 (O*C*H$_2$), 124.5 (*C*H) alkene, 131.4 (*C*$_q$) alkene, 167.2 (*C*=O) ester, 200.5 (*C*=O) ketone. ν_{max} (film)/cm^{-1} 1749, 1718, 1654; *m/z* (ESI$^+$) 241 [M + H]$^+$ (7%); HRMS (ESI$^+$): exact mass calculated for $C_{14}H_{25}O_3$ [M + H]$^+$ 241.1804. Found 241.1803.

Note: Trace amount of enol form visible in ^{13}C NMR spectrum with characteristic peaks at δ_C(ppm) 21.2 (*C*H$_3$COH), 89.8 (*C*H) alkene, 172.5 (*C*=O) ester, 175.4 (*C*OH). Spectral details are in agreement with those reported in the literature.[6]

***sec*-Butyl 3-oxobutanoate 4**

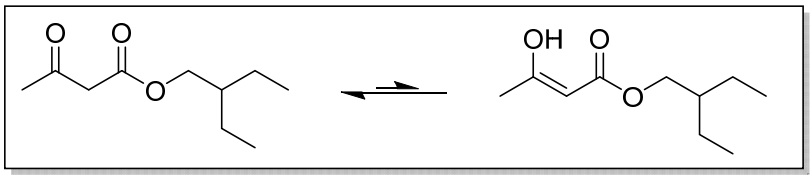


The title compound was prepared following the procedure described for 3,7-dimethyloct-6-enyl 3-oxobutanoate **2** using butan-2-ol **313** (1.79 g, 23.1 mmol), ethyl acetoacetate **311** (2.00 g, 23.1 mmol) and 3-nitrophenylboranic acid **1** (95

mg, 576 μmmol, 2.5 mol%) in toluene (50 mL). After 5 h the toluene was removed under reduced pressure to yield the reaction mixture as a pale yellow oil. Following purification of the crude product by column chromatography on silica gel using hexane:ethyl acetate (95:5) as eluent, *sec*-butyl 3-oxobutanoate **4** was isolated as a pale orange oil (1.97 g, 54%). δ_H($CDCl_3$, 400 MHz): 0.91 (3H, t, *J* 7.4, CH_2CH_3), 1.23 (3H, d, *J* 6.3, $CHCH_3$), 1.48-1.70 (2H, m, CH_2CH_3), 2.26 [3H, s, $C(O)CH_3$], 3.43 [2H, s, $C(O)CH_2C(O)$], 4.85-4.95 (1H, m, OCH); δ_C($CDCl_3$, 100 MHz): 9.5 (CH_2CH_3), 19.3 ($CHCH_3$), 28.6 (CH_2CH_3), 30.0 [$C(O)CH_3$], 50.4 [$C(O)CH_2C(O)$], 73.5 (OCH), 166.7 (*C*=O) ester, 200.6 (*C*=O) ketone; ν_{max} (film)/cm^{-1} 1741, 1716; HRMS (ESI^+): exact mass calculated for $C_8H_{15}O_3$ $[M + H]^+$ 159.1021. Found 159.1023.

Note: Trace amount of enol form visible in ^{13}C NMR spectrum with characteristic peaks at δ_C(ppm) 21.1 (CH_3COH), 90.1 (*C*H) alkene, 172.4 (*C*=O) ester, 175.2 (*C*OH). Spectral details are in agreement with those reported in the literature.[7]

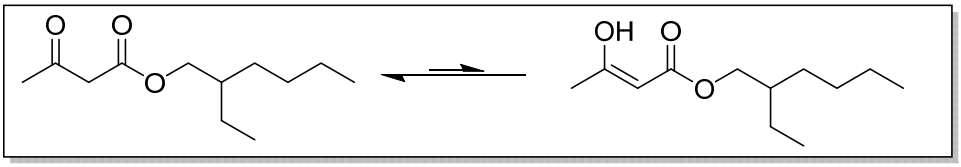
2-Ethylbutyl 3-oxobutanoate 5



The title compound was prepared following the procedure described for 3,7-dimethyloct-6-enyl 3-oxobutanoate **2** using 2-ethylbutan-1-ol **314** (2.35 g, 15.4 mmol), ethyl acetoacetate **311** (3.01 g, 15.4 mmol) and 3-nitrophenylboranic acid **1** (64 mg, 384 μmmol, 2.5 mol%) in toluene (50 mL). After 5 h the toluene was removed under reduced pressure to yield 2-ethylbutyl 3-oxobutanoate **5** as a colourless oil (2.68 g, 95%), which was used without further purification. δ_H($CDCl_3$, 300 MHz): 0.89 (6H, t, *J* 7.5, 2 × CH_3), 1.31-1.41 (4H, m, 2 × CH_2CH_3), 1.47-1.60 (1H, m, CH), 2.27 [3H, s, $C(O)CH_3$], 3.47 [2H, s, $C(O)CH_2C(O)$], 4.07 (2H, d, *J* 6.0, OCH_2); δ_C($CDCl_3$, 100 MHz): 10.8 (2 × CH_3), 22.8 (2 × CH_2), 30.0 [$C(O)CH_3$], 40.2 (CH), 50.2 [$C(O)CH_2C(O)$], 67.5 (OCH_2), 167.2 (*C*=O) ester, 200.5 (*C*=O) ketone; ν_{max} (film)/cm^{-1} 1745, 1716; *m/z* (ESI^+) 186 $[M]^+$ (100%).

Note: Trace amount of enol form visible in ^{13}C NMR spectrum with characteristic peaks at δ_C(ppm) 21.1 (*C*H$_3$COH), 89.7 (*C*H) alkene, 172.8 (*C*=O) ester, 175.3 (*C*OH). Spectral details are in agreement with those reported in the literature.[8]

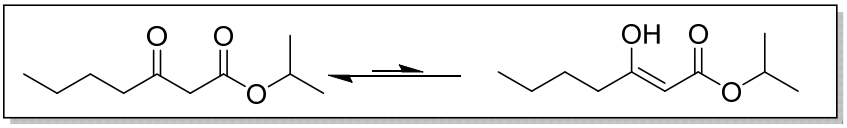
2-Ethylhexyl 3-oxobutanoate 6



The title compound was prepared following the procedure described for 3,7-dimethyloct-6-enyl 3-oxobutanoate **2** using 2-ethyl-1-hexanol **315** (2.40 g, 15.4 mmol), ethyl acetoacetate **311** (2.04 g, 15.4 mmol) and 3-nitrophenylboranic acid **1** (64 mg, 384 μmmol, 2.5 mol%) in toluene (50 mL). After 5 h the toluene removed under reduced pressure to yield 2-ethylhexyl 3-oxobutanoate **6** as a colourless oil (3.09 g, 94%), which was used without further purification. δ_H(CDCl$_3$, 300 MHz): 0.86-0.91 (6H, m, 2 × C*H*$_3$), 1.20-1.45 (8H, m, 4 × C*H*$_2$), 1.52-1.62 (1H, m, C*H*), 2.27 [3H, s, C(O)C*H*$_3$], 3.43 [2H, s, C(O)C*H*$_2$C(O)], 4.07 (2H, d, *J* 5.8, OC*H*$_2$); δ_C(CDCl$_3$, 100 MHz): 10.9 (*C*H$_3$), 14.1 (*C*H$_3$), 22.7 (*C*H$_2$), 23.1 (*C*H$_2$), 28.8 (*C*H$_2$), [C(O)*C*H$_3$], 30.3 (*C*H$_2$), 38.7 (*C*H), 50.0 [C(O)*C*H$_2$C(O)], 67.7 (O*C*H$_2$), 167.3 (*C*=O) ester, 200.5 (*C*=O) ketone; ν_{max} (film)/cm^{-1} 1742, 1717; *m/z* (ESI$^+$) 215 [M + H]$^+$ (5%); HRMS (ESI$^+$): exact mass calculated for C$_{12}$H$_{23}$O$_3$ [M + H]$^+$ 215.1647. Found 215.1645.

Note: Trace amount of enol form visible in ^{13}C NMR spectrum with characteristic peaks at δ_C(ppm) 21.1 (*C*H$_3$COH), 89.7 (*C*H) alkene, 172.8 (*C*=O) ester, 175.3 (*C*OH). Spectral details are in agreement with those reported in the literature.[9]

Isopropyl 3-oxoheptanoate 7

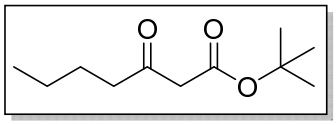


The title compound was prepared following the procedure described for 3,7-dimethyloct-6-enyl 3-oxobutanoate **2** using isopropanol **316** (0.75 g, 12.6 mmol), methyl 3-oxoheptanoate **317** (2.03 g, 12.6 mmol) and 3-

nitrophenylboronic acid (52 mg, 316 μmol, 2.5 mol%) in toluene (50 mL). After 5 h the toluene was removed to give the reaction mixture as a yellow oil. Following purification of the crude product by chromatography on silica gel, using hexane:ethyl acetate (80:20) as eluent, isopropyl 3-oxoheptanoate **7** (1.65 g, 70%) was isolated as an orange oil. δ_H($CDCl_3$, 400 MHz): 0.92 (3H, t, *J* 7.3, C*H*$_3$), 1.27-1.39 {8H, m containing [1.27 (6H, d, *J* 6.3, 2 × C*H*$_3$) and C*H*$_2$]}, 1.52-1.61 (2H, m, C*H*$_2$), 2.51 [2H, t, *J* 7.4, C(O)C*H*$_2$], 3.49 [2H, s, C(O)C*H*$_2$C(O)], 5.06 (1H, septet, *J* 6.2, OC*H*); δ_C($CDCl_3$, 100 MHz): 13.7 (*C*H$_3$), 21.7 (2 × *C*H$_3$), 22.1 (*C*H$_2$), 25.5 (*C*H$_2$), 42.6 (*C*H$_2$), 49.6 [C(O)*C*H$_2$C(O)], 68.9 (O*C*H), 166.8 (*C*=O) ester, 203.0 (*C*=O) ketone. ν_{max} (film)/cm^{-1} 1734, 1718. *m/z* (ESI$^+$) 187 [M + H]$^+$ (22%), 185 (100); HRMS (ESI$^+$): exact mass calculated for $C_{10}H_{19}O_3$ [M + H]$^+$ 187.1334. Found 187.1308. Spectral details are in agreement with those reported in the literature.[10]

Note: Trace amount of enol form visible in ^{13}C NMR spectrum with characteristic peaks at δ_C(ppm) 89.3 (*C*H) alkene, 172.4 (*C*=O) ester, 178.8 (*C*OH).

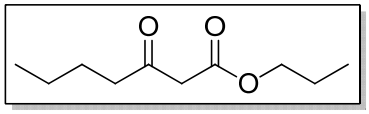
***t*-Butyl 3-oxoheptanoate 8**



The title compound was prepared following the procedure described for 3,7-dimethyloct-6-enyl 3-oxobutanoate **2** using *t*-butanol **318** (0.94 g, 12.7 mmol), methyl 3-oxoheptanoate **317** (2.01 g, 12.7 mmol) and 3-nitrophenylboranic acid **1** (52 mg, 316 μmol, 2.5 mol%) in toluene (40 mL). After 5 h the toluene was removed to give the reaction mixture as a yellow oil. Following purification of the crude product by chromatography on silica gel using hexane:ethyl acetate (70:30) as eluent, *t*-butyl 3-oxoheptanoate **8** was isolated as a light brown oil (1.45 g, 57%). δ_H($CDCl_3$, 400 MHz): 0.91 (3H, t, *J* 7.2, CH_2CH_3), 1.29-1.37 (2H, m, C*H*$_2$), 1.47 (9H, s, 3 × C*H*$_3$), 1.52-1.62 (2H, m, C*H*$_2$), 2.53 [2H, t, *J* 7.2, C(O)C*H*$_2$CH$_2$], 3.34 [2H, s, C(O)C*H*$_2$C(O)]; δ_C($CDCl_3$, 100 MHz): 13.8 (*C*H$_3$), 22.2 (*C*H$_2$), 25.6 (*C*H$_2$), 27.9 (3 × *C*H$_3$), 42.6 [C(O)*C*H$_2$CH$_2$], 50.7 [C(O)*C*H$_2$C(O)], 81.8 (O*C*$_q$), 166.6 (*C*=O) ester, 203.5 (*C*=O) ketone; ν_{max} (film)/cm^{-1} 1747, 1720, 1323; *m/z* (ESI$^-$) 200 M$^+$ (5%), 241 (100); HRMS (ESI$^+$):

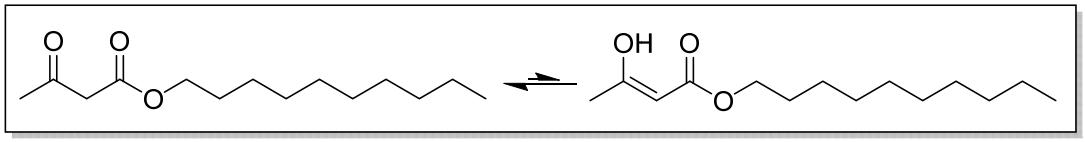
exact mass calculated for $C_{11}H_{21}O_3$ $[M + H]^+$ 201.1491. Found 201.1477. Spectral details are in agreement with those reported in the literature.[11]

Propyl 3-oxoheptanoate 9



The title compound was prepared following the procedure described for 3,7-dimethyloct-6-enyl 3-oxobutanoate **2** using *n*-propanol **319** (0.76 g, 12.7 mmol), methyl 3-oxoheptanoate **317** (2.02 g, 12.7 mmol) and 3-nitrophenylboronic acid **1** (52 mg, 316 μmol, 2.5 mol%) in toluene (50 mL). After 5 h the toluene was removed to give the reaction mixture as a yellow oil. Following purification of the crude product by chromatography on silica gel, using hexane:ethyl acetate (80:20) as eluent, propyl 3-oxoheptanoate **9** was isolated as an orange oil (1.98 g, 84%). δ_H($CDCl_3$, 300 MHz): 0.91-0.99 [6H, m, containing 0.91 (3H, t, *J* 7.2, C*H*$_3$) and 0.94 (3H, t, *J* 7.2, C*H*$_3$)], 1.26-1.38 (2H, m, C*H*$_2$), 1.52-1.72 (4H, m, 2 × C*H*$_2$), 2.53 [2H, t, *J* 7.2, C(O)C*H*$_2$CH$_2$], 3.44 [2H, s, C(O)C*H*$_2$C(O)], 4.09 (2H, t, *J* 6.8, OC*H*$_2$); δ_C($CDCl_3$, 100 MHz): 10.3 (*C*H$_3$), 13.8 (*C*H$_3$), 21.9 (*C*H$_2$), 22.1 (*C*H$_2$), 25.5 (*C*H$_2$), 42.7 [C(O)*C*H$_2$CH$_2$], 49.3 [C(O)*C*H$_2$C(O)], 66.9 (O*C*H$_2$), 167.4 (*C*=O) ester, 202.9 (*C*=O) ketone; ν_{max} (film)/cm^{-1} 1748, 1717; *m/z* (ESI$^+$) 187 $[M + H]^+$ (100%), 209 (88); HRMS (ESI$^+$): exact mass calculated for $C_{10}H_{19}O_3$ $[M + H]^+$ 187.1326. Found 187.1334.

Decyl 3-oxobutanoate 10

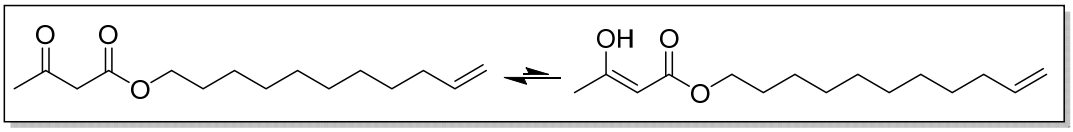


The title compound was prepared following the procedure described for 3,7-dimethyloct-6-enyl 3-oxobutanoate **2** using decanol **320** (2.92 g, 15.4 mmol), ethyl acetoacetate **311** (2.01 g, 15.4 mmol) and 3-nitrophenylboranic acid **1** (64 mg, 384 μmmol, 2.5 mol%) in toluene (45 mL). After 5 h the toluene was removed under reduced pressure and decyl 3-oxobutanoate **10** was isolated as colourless oil (3.32 g, 89%) and was used without further purification. The ^{13}C NMR spectra

were assigned to the keto and enol forms as listed below. δ_H($CDCl_3$, 300 MHz): 0.86 (3H, t, *J* 7.2, C*H*$_3$), 1.15-1.45 (14H, m, 7 × C*H*$_2$), 1.50-1.73 (2H, m, C*H*$_2$), 2.27 [3H, s, C(O)C*H*$_3$], 3.45 [2H, s, C(O)C*H*$_2$C(O)], 4.13 (2H, t, *J* 7.2, OC*H*$_2$); δ_C($CDCl_3$, 100 MHz): 14.0 (*C*H$_3$), 22.6 (*C*H$_2$), 25.7 (*C*H$_2$), 28.4 (*C*H$_2$), 29.1 (*C*H$_2$), 29.2 (*C*H$_2$), 29.45 (*C*H$_2$), 29.47 (*C*H$_2$), 30.0 [C(O)*C*H$_3$], 31.8 (*C*H$_2$), 50.1 [C(O)*C*H$_2$C(O)], 65.5 (O*C*H$_2$), 167.2 (*C*=O) ester, 200.5 (*C*=O) ketone; ν_{max} (film)/cm^{-1} 1734, 1718; *m/z* (ESI$^-$) 241 [M - H]$^-$ (50%); HRMS (ESI$^+$): exact mass calculated for $C_{14}H_{27}O_3$ [M + H]$^+$ 243.1960. Found 243.1956.

Enol form: δ_C($CDCl_3$, 100 MHz): 14.0 (*C*H$_3$), 21.1 (*C*H$_3$COH), 25.7 (*C*H$_2$), 28.9 (*C*H$_2$), 29.2 (*C*H$_2$), 29.3 (*C*H$_2$), 29.4 (*C*H$_2$), 29.5 (*C*H$_2$), 29.6 (*C*H$_3$), 30.1 (*C*H$_2$), 63.0 [*C*H$_2$C(O)], 64.1 (O*C*H$_2$), 89.8 (*C*H) alkene, 172.5 (*C*=O) ester, 175.3 (*C*OH). Spectral details are in agreement with those reported in the literature.[12]

Undec-10-en-1-yl 3-oxobutanoate 11



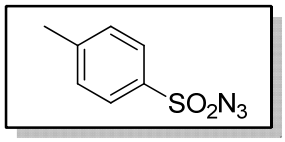
The title compound was prepared following the procedure described for 3,7-dimethyloct-6-enyl 3-oxobutanoate **2** using undec-10-en-1-ol **321** (2.41 g, 15.4 mmol), ethyl acetoacetate **311** (2.00 g, 15.4 mmol) and 3-nitrophenylboranic acid **1** (64 mg, 384 μmmol, 2.5 mol%) in toluene (50 mL). After 5 h the toluene was removed under reduced pressure to yield undec-10-en-1-yl 3-oxobutanoate **11** as a colourless oil (3.78 g, 97%), which was used without further purification. The ^{13}C NMR spectra were assigned to the keto and enol forms as listed below. δ_H($CDCl_3$, 400 MHz): 1.21-1.45 (12H, m, 6 × C*H*$_2$), 1.59-1.70 (2H, m, C*H*$_2$), 2.01-2.07 (2H, m, C*H*$_2$), 2.26 [3H, s, C(O)C*H*$_3$], 3.45 [2H, s, C(O)C*H*$_2$C(O)], 4.13 (2H, t, *J* 6.7, OC*H*$_2$), 4.90-5.02 (2H, m, CH=C*H*$_2$), 5.74-5.87 (1H, m, C*H*=CH$_2$); δ_C($CDCl_3$, 100 MHz): 25.7 (*C*H$_2$), 28.4 (*C*H$_2$), 28.8 (*C*H$_2$), 29.0 (*C*H$_2$), 29.1 (*C*H$_2$), 29.3 (*C*H$_2$), 29.3 [C(O)*C*H$_3$], 33.7 (*C*H$_2$), 50.0 [C(O)*C*H$_2$C(O)], 65.4 (O*C*H$_2$), 114.1 (*C*H$_2$) alkene, 139.0 (*C*H) alkene, 167.1 (*C*=O) ester, 200.5 (*C*=O) ketone; ν_{max} (film)/cm^{-1} 1734, 1718, 1640; *m/z* (ESI$^+$) 255 [M + H]$^+$ (8%); HRMS (ESI$^+$): exact mass calculated for $C_{15}H_{27}O_3$ [M + H]$^+$ 255.1960. Found 255.1962.

Enol form: δ_C($CDCl_3$, 100 MHz): 21.1 (*C*H_3COH), 25.9 (*C*H_2), 28.7 (*C*H_2), 29.0 (*C*H_2), 29.1 (*C*H_2), 29.2 (*C*H_2), 29.3 (*C*H_2), 32.8 (*C*H_2), 63.0 [*C*H_2C(O)], 64.1 (O*C*H_2), 89.7 (*C*H) alkene, 172.7 (*C*=O) ester, 175.3 (*C*OH). Spectral details are in agreement with those reported in the literature.[13]

3.2.2 Preparation of diazo transfer reagent

Caution: Diazo transfer reagents are potentially hazardous reagents and extreme care should be taken in their use[14-16]. They are shock sensitive and in the case of *p*-toluenesulfonyl azide **13** (tosyl azide **13**), which is a solid below room temperature, it should not be scraped out of its container as it may explode. Instead, tosyl azide **13** should be allowed to warm to its melting point (*ca.* 20 °C) and then be pipetted from its container using a clean Pasteur pipette which has no sharp edges. The preparation or concentration of solutions containing diazo transfer reagents was carried out in a well-ventilated fumehood behind a safety shield. For safety reasons only one batch of tosyl azide **13** was made and stored in the laboratory at any one time. Tosyl azide **13** was stored in a freezer.

4-Toluenesulfonyl azide 13



A solution of *p*-toluenesulfonyl chloride **14** (13.00 g, 63.0 mmol) in acetone (30 mL) was added dropwise over 15 min to a stirred solution of sodium azide **15** (4.34 g, 67.0 mmol) in water (15 mL) and acetone (30 mL) in an ice bath at 0°C. Once the addition was complete, the reaction mixture was stirred at ambient temperature for 2 h after which time the acetone was removed under reduced pressure. The aqueous solution was extracted with DCM (30 mL) and the organic layer was then washed with water (2 × 20 mL) and brine (2 × 20 mL). The organic layer was dried with $MgSO_4$ and concentrated under reduced pressure without heating the water bath, to yield pure *p*-toluenesulfonyl azide **13** as a colourless oil which crystallised to a white solid on refrigeration (12.22 g, 98%). δ_H($CDCl_3$, 400 MHz) 2.48 (3H, s, C*H*$_3$), 7.41 (2H, d, *J* 8.0, 2 × ArC*H*), 7.82-7.85 (2H, m, 2 × ArC*H*); ν_{max}

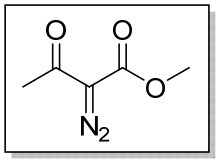
(film)/cm^{-1} 2129, 1595, 1371, 1172. Spectral details are in agreement with those reported in the literature.[17]

3.2.3 Diazo transfer reactions to β-ketoesters

Room temperature addition of tosyl azide 13 and work-up as described by Regitz[18-21]

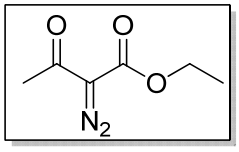
Variation of ester side-chain

Methyl 2-diazo-3-oxobutanoate 18



Triethylamine (1.45 mL, 10.4 mmol) was added to a stirred solution of methyl acetoacetate **17** (2.07 g, 10.4 mmol) in acetonitrile (25 mL). After 2 min a solution of *p*-toluenesulfonyl azide **13** (2.05 g, 10.4 mmol) in acetonitrile (25 mL) was added dropwise at room temperature over 15 min to yield a bright yellow solution. The reaction was stirred for 18 h under a nitrogen atmosphere. After 18 h, TLC analysis showed complete consumption of the ester starting material and the reaction mixture was concentrated under reduced pressure. The resulting cream residue was dissolved in diethyl ether (40 mL) and washed with 9% KOH (2 × 50 mL) followed by water (50 mL). The organic layer was dried with $MgSO_4$ and concentrated under reduced pressure to yield methyl 2-diazo-3-oxobutanoate **18** as a bright yellow oil (1.93 g, 80%), which was used without further purification. δ_H($CDCl_3$, 300 MHz): 2.49 [3H, s, C(O)CH_3], 3.85 (3H, s, OCH_3); δ_C($CDCl_3$, 100 MHz): 28.1 [C(O)CH_3], 52.2 (OCH_3), 161.8 (*C*=O) ester, 190.0 (*C*=O) ketone, no signal observed for (*C*=N_2); *m/z* (ESI$^+$) 143 [M + H]$^+$ (26%), 74 (100), 144 (12); ν_{max} (film)/cm^{-1} 2144, 1726, 1660, 1317. Spectral details are in agreement with those reported in the literature.[22]

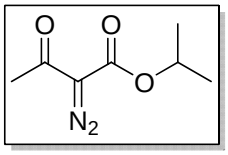
Ethyl 2-diazo-3-oxobutanoate 19



The title compound was prepared following the procedure described for methyl 2-diazo-3-oxobutanoate **18** using triethylamine (2.15 mL, 15.4 mmol), ethyl acetoacetate **311** (2.01 g, 15.4 mmol) in acetonitrile (25 mL) and *p*-toluenesulfonyl azide **13** (3.03 g, 15.4 mmol) dissolved in acetonitrile (25 mL). The reaction was stirred at room temperature under a nitrogen atmosphere for 18 h. Following the work-up,ethyl 2-

diazo-3-oxobutanoate **19** was obtained as a bright yellow oil (2.06 g, 86%), which was used without further purification. δ_H($CDCl_3$, 300 MHz): 1.33 (3H, t, *J* 7.2 OCH_2CH_3), 2.48 [3H, s, C(O)CH_3], 4.32 (2H, q, *J* 7.2, OCH_2CH_3); δ_C($CDCl_3$, 75.5 MHz): 14.3 (CH_3), 28.3 [C(O)CH_3], 61.5 (OCH_2), 161.4 (*C*=O) ester, 190.3 (*C*=O) ketone, no signal observed for (*C*=N_2); ν_{max} (film)/cm^{-1} 2141, 1723, 1661; *m/z* (ESI^+) 157 $[M + H]^+$ (5%), 64 (100). Spectral details are in agreement with those reported in the literature.[23]

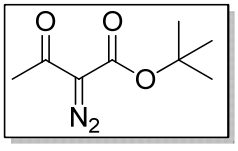
Isopropyl 2-diazo-3-oxobutanoate 20



The title compound was prepared following the procedure described for methyl 2-diazo-3-oxobutanoate **18** using triethylamine (1.91 mL, 13.89 mmol), isopropyl acetoacetate **322** (2.00 g, 13.89 mmol) in acetonitrile (25 mL) and *p*-toluenesulfonyl azide **13** (2.74 g, 13.89 mmol) dissolved in acetonitrile (25 mL). The reaction was stirred at room temperature under a nitrogen atmosphere for 18 h. Following the work-up, isopropyl 2-diazo-3-oxobutanoate **20** was obtained as a bright yellow oil (1.99 g, 84%), which was used without further purification. δ_H($CDCl_3$, 300 MHz): 1.31 (6H, d, *J* 6.3, 2 × CH_3), 2.49 [3H, s, C(O)CH_3], 5.18 (1H, septet, *J* 6.3, C*H*); δ_C($CDCl_3$, 100 MHz): 21.9 (2 × CH_3), 28.5 [C(O)CH_3], 69.7 (*C*H), 161.3 (*C*=O) ester, 190.6 (*C*=O) ketone, no signal observed for (*C*=N_2); ν_{max} (film)/cm^{-1} 2142, 1715, 1660, 1368; *m/z* (ESI^+)171 $[M + H]^+$ (5%), 102 (100). Spectral details are in agreement with those reported in the literature.[24]

Note: The ^{1}H NMR spectrum showed 3% unreacted tosyl azide **13** starting material after work-up.

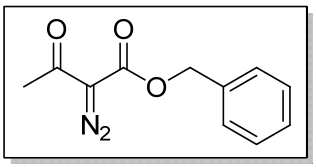
***t*-Butyl 2-diazo-3-oxobutanoate 21**



The title compound was prepared following the procedure described for methyl 2-diazo-3-oxobutanoate **18** using triethylamine (1.82 mL, 12.64 mmol), *t*-butyl acetoacetate **323** (2.00 g, 12.64 mmol) in acetonitrile (25 mL), *p*-toluenesulfonyl azide **13** (2.51 g, 12.64 mmol) dissolved in acetonitrile (25 mL). The reaction was stirred for 18

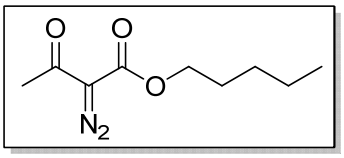
h under a nitrogen atmosphere. Following the work-up, *t*-butyl 2-diazo-3-oxobutanoate **21** was obtained as a bright yellow oil (2.21 g, 95%), which was used without further purification. δ_H($CDCl_3$, 400 MHz): 1.52 (9H, s, 3 × C*H*$_3$ of *t*-butyl), 2.45 [3H, s, C(O)C*H*$_3$]; δ_C($CDCl_3$, 100 MHz): 27.9 [C(O)*C*H$_3$], 28.2 (3 ×*C*H$_3$), 83.1 (*C*$_q$), 160.5 (*C*=O) ester, 190.5 (*C*=O) ketone, no signal observed for C=N$_2$; ν_{max} (film)/cm^{-1} 2134, 1715, 1660, 1311; *m/z* (ESI$^+$) 185 $[M + H]^+$ (40%), 129 (100). Spectral details are in agreement with those reported in the literature.[25]

Benzyl 2-diazo-3-oxobutanoate 22



The title compound was prepared following the procedure described for methyl 2-diazo-3-oxobutanoate **18** using triethylamine (1.45 mL, 10.4 mmol), benzyl acetoacetate **326** (2.00 g, 10.4 mmol) in acetonitrile (25 mL) and *p*-toluenesulfonyl azide **13** (2.03 g, 10.4 mmol) dissolved in acetonitrile (25 mL). The reaction was stirred at room temperature under a nitrogen atmosphere for 18 h. Following the work-up, benzyl 2-diazo-3-oxobutanoate **22** was obtained as a bright yellow oil (2.1 g, 93%), which was used without further purification. δ_H($CDCl_3$, 400 MHz): 2.48 [3H, s, C(O)C*H*$_3$], 5.29 (2H, s, OC*H*$_2$C$_6$H$_5$), 7.32-7.44 (5H, m, 5 × ArC*H*); δ_C($CDCl_3$, 100 MHz): 28.3 [C(O)*C*H$_3$], 67.0 (O*C*H$_2$), 128.4 (Ar*C*H), 128.7 (2 × Ar*C*H), 128.8 (2 × Ar*C*H), 161.3 (*C*=O) ester, 190.1 (*C*=O) ketone, no signal observed for (*C*=N$_2$); ν_{max} (film)/cm^{-1} 2144, 1712, 1651, 1328; *m/z* (ESI$^+$) 219 $[M + H]^+$ (10%), 459 (100). Spectral details are in agreement with those reported in the literature.[26]

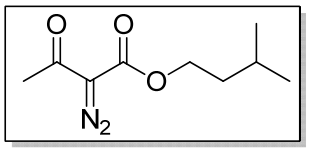
Pentyl 2-diazo-3-oxobutanoate 23



The title compound was prepared following the procedure described for methyl 2-diazo-3-oxobutanoate **18** using triethylamine (1.62 mL, 11.6 mmol), pentyl 3-oxobutanoate **324** (2.05 g, 11.6 mmol) in acetonitrile (25 mL) and *p*-toluenesulfonyl azide **13** (2.28 g, 11.6 mmol) dissolved in acetonitrile (25 mL). The reaction was stirred at room temperature under a nitrogen atmosphere for 18 h. Following the work-up, pentyl 2-diazo-3-oxobutanoate **23** was obtained as a bright yellow oil (2.1 g, 92%), which was used without further purification.

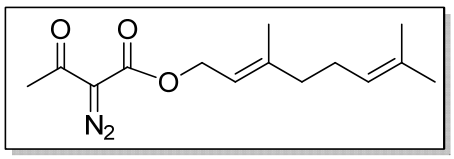
δ_H($CDCl_3$, 400 MHz): 0.92 (3H, t, *J* 6.9, CH_2CH_3), 1.31-1.39 (4H, m, 2 × CH_2), 1.65-1.74 (2H, m, CH_2), 2.48 [3H, s, $C(O)CH_3$], 4.24 (2H, t, *J* 6.9, OCH_2CH_2); δ_C($CDCl_3$, 100 MHz): 13.9 (CH_3), 22.2 (CH_2), 27.9 (CH_2), 28.4 (CH_2), 28.3 [$C(O)CH_3$], 65.5 (OCH_2), 161.5 (*C*=O) ester, 190.2 (*C*=O) ketone, no signal observed for (*C*=N_2); ν_{max} (film)/cm^{-1} 2141, 1719, 1663, 1365; *m/z* (ESI^+) 199 [M + H]$^+$ (30%), 116 (100); HRMS (ESI^+): exact mass calculated for $C_9H_{14}O_3N_2$ [M + H]$^+$ 199.1083. Found 199.1088.

Isopentyl 2-diazo-3-oxobutanoate 24



The title compound was prepared following the procedure described for methyl 2-diazo-3-oxobutanoate **18** using triethylamine (1.65 mL, 11.61 mmol), isopentyl 3-oxobutanoate **325** (2.00 g, 11.61 mmol) in acetonitrile (25 mL) and *p*-toluenesulfonyl azide **13** (2.31 g, 11.62 mmol) dissolved in acetonitrile (25 mL). The reaction was stirred at room temperature under a nitrogen atmosphere for 18 h. Following the work-up, isopentyl 2-diazo-3-oxobutanoate **24** was obtained as a bright yellow oil (2.02 g, 88%), which was used without further purification. δ_H($CDCl_3$, 400 MHz): 0.94 (6H, d, *J* 6.6, 2 × CH_3), 1.54-1.76 [3H, m, OCH_2CH_2 and $CH(CH_3)_2$], 2.48 [3H, s, $C(O)CH_3$], 4.27 (2H, t, *J* 6.6, OCH_2CH_2); δ_C($CDCl_3$, 100 MHz): 22.4 (2 × CH_3), 25.1 (*C*H), 28.2 [$C(O)CH_3$], 37.3 (CH_2), 64.1 (OCH_2), 161.5 (*C*=O) ester, 190.2 (*C*=O) ketone, no signal observed for (*C*=N_2); ν_{max} (film)/cm^{-1} 2141, 1716, 1662, 1316; *m/z* (ESI^+) 199 [M + H]$^+$ (5%), 102 (100). Spectral details are in agreement with those reported in the literature.[24]

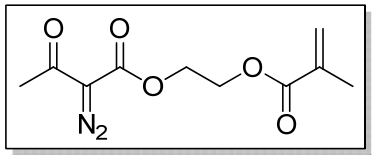
3,7-Dimethylocta-2,6-dienyl 2-diazo-3-oxobutanoate 25



The title compound was prepared following the procedure described for methyl 2-diazo-3-oxobutanoate **18** using triethylamine (1.17 mL, 8.4 mmol), 3,7-dimethylocta-2,6-dienyl 3-oxobutanoate **2** (2.12 g, 8.4 mmol) in acetonitrile (25 mL) and *p*-toluenesulfonyl azide **13** (1.65 g, 8.4 mmol) dissolved in acetonitrile (25 mL). The reaction was stirred at room temperature

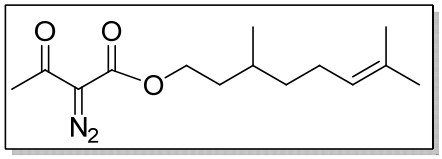
under a nitrogen atmosphere for 18 h. Following the work-up, the residue was purified by column chromatography on silica gel using hexane:ethyl acetate (90:10) as eluent to yield 3,7-dimethylocta-2,6-dienyl 2-diazo-3-oxobutanoate **25** as a yellow oil (1.91 g, 86%). δ_H($CDCl_3$, 400 MHz): 1.58 (3H, s, C*H*$_3$), 1.66 (3H, s, C*H*$_3$), 1.71 (3H, s, C*H*$_3$), 2.02-2.13 (4H, td, *J* 12.1, 6.4, 2 × C*H*$_2$), 2.46 [3H, s, C(O)C*H*$_3$], 4.73 (2H, d, *J* 7.2, OC*H*$_2$), 5.05 [1H, t, *J* 5.9, C*H*=C(CH$_3$)$_2$], 5.34 [1H, t, *J* 7.0, OCH$_2$C*H*=C(CH$_3$)]; δ_C($CDCl_3$, 100 MHz): 16.5 (*C*H$_3$), 17.7 (*C*H$_3$), 25.6 (*C*H$_3$), 26.2 (*C*H$_2$), 28.2 [C(O)*C*H$_3$], 39.5 (*C*H$_2$), 62.1 (O*C*H$_2$), 117.6 (*C*H) alkene, 123.5 (*C*H) alkene, 131.9 (*C*$_q$) alkene, 143.4 (*C*$_q$) alkene, 161.4 (*C*=O) ester, 190.2 (*C*=O) ketone, no signal observed for (*C*=N$_2$); ν_{max} (film)/cm^{-1} 2141, 1719, 1660, 1312; *m/z* (ESI$^+$) 264 [M]$^+$ 238 (100); HRMS (ESI$^+$): exact mass calculated for $C_{14}H_{21}O_3N_2$ [M + H]$^+$ 265.1552. Found 265.1556. Spectral details are in agreement with those reported in the literature.[27]

2-(Methacryloyloxy) ethyl 2-diazo-3-oxobutanoate 26



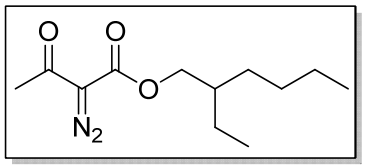
The title compound was prepared following the procedure described for methyl 2-diazo-3-oxobutanoate **18** using triethylamine (0.94 mL, 9.33 mmol), 2-(methacryloyloxy)ethyl 3-oxobutanoate **327** (2.01 g, 9.33 mmol) in acetonitrile (25 mL) and *p*-toluenesulfonyl azide **13** (1.84 g, 9.33 mmol) dissolved in acetonitrile (25 mL). The reaction was stirred at room temperature under a nitrogen atmosphere for 18 h. Following the work-up, the residue was purified by column chromatography on silica gel using hexane:ethyl acetate (90:10) as eluent to yield 2-(methacryloyloxy) ethyl 2-diazo-3-oxobutanoate **26** as a yellow oil (1.78 g, 79%). δ_H($CDCl_3$, 400 MHz): 1.95 (3H, dd, *J* 1.5, 1.0, C*H*$_3$), 2.48 [3H, s, C(O)C*H*$_3$], 4.40-4.44 (2H, m, OC*H*$_2$), 4.48-4.53 (2H, m, OC*H*$_2$), 5.61-5.64 (1H, m, one of alkene C*H*$_2$), 6.12-6.14 (1H, m, one of alkene C*H*$_2$); δ_C($CDCl_3$, 100 MHz): 18.2 (*C*H$_3$), 28.2 [C(O)*C*H$_3$], 62.0 (O*C*H$_2$), 62.9 (O*C*H$_2$), 126.2 (*C*H$_2$) alkene, 135.8 (*C*$_q$) alkene, 161.1 (*C*=O) α-diazo ester, 166.9 (*C*=O) methacrylate ester, 189.7 (*C*=O) ketone, no signal observed for (*C*=N$_2$); ν_{max} (film)/cm^{-1} 2144, 1719, 1656, 1313; HRMS (ESI$^+$): exact mass calculated for $C_{10}H_{13}O_5N_2$ [M + H]$^+$ 241.0824. Found 241.0829.

3,7-Dimethyloct-6-enyl 2-diazo-3-oxobutanoate 27



The title compound was prepared following the procedure described for methyl 2-diazo-3-oxobutanoate **18** using triethylamine (1.21 mL, 8.37 mmol), 3,7-dimethyloct-6-enyl 3-oxobutanoate **3** (2.01 g, 8.37 mmol) in acetonitrile (25 mL) and *p*-toluenesulfonyl azide **13** (1.64 g, 8.37 mmol) dissolved in acetonitrile (25 mL). The reaction was stirred at room temperature under a nitrogen atmosphere for 18 h. Following the work-up, the residue was purified by column chromatography on silica gel using hexane:ethyl acetate (90:10) as eluent to yield 3,7-dimethylocta-6-enyl 2-diazo-3-oxobutanoate **27** as a yellow oil (1.52 g, 68%). δ_H($CDCl_3$, 400 MHz): 0.93 (3H, d, *J* 6.3, CHC*H*$_3$), 1.14-1.82 [11H, m, containing CH_2C*H*, (2 × C*H*$_2$), 1.61 (3H, s, C*H*$_3$) and 1.68 (3H, s, C*H*$_3$)], 1.89-2.08 (2H, m, C*H*$_2$), 2.47 [3H, s, C(O)C*H*$_3$], 4.02-4.34 (2H, m, OC*H*$_2$), 5.07 [1H, t, *J* 6.9, C*H*=C(CH_3)$_2$]; δ_C($CDCl_3$, 100 MHz): 17.6 (*C*H_3), 19.3 (*C*H_3), 25.3 (*C*H_2), 25.6 (*C*H_3), 28.1 [C(O)*C*H_3], 29.4 (*C*H), 35.4 (*C*H_2), 36.8 (*C*H_2), 63.9 (O*C*H_2), 124.3 (*C*H) alkene, 131.5 (C_q) alkene, 161.4 (*C*=O) ester, 190.2 (*C*=O) ketone, no signal observed for (*C*=N_2); ν_{max} (film)/cm^{-1} 2141, 1721, 1662, 1316; HRMS (ESI^+): exact mass calculated for $C_{14}H_{23}O_3N_2$ $[M + H]^+$ 267.1709. Found 267.1712.

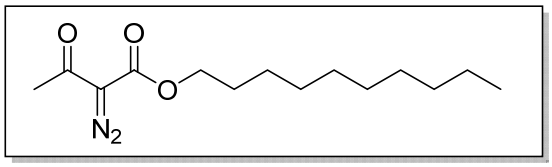
2-Ethylhexyl 2-diazo-3-oxobutanoate 28



The title compound was prepared following the procedure described for methyl 2-diazo-3-oxobutanoate **18** using triethylamine (1.34 mL, 9.3 mmol), 2-ethylhexyl 3-oxobutanoate **6** (2.06 g, 9.3 mmol) in acetonitrile (25 mL) and *p*-toluenesulfonyl azide **13** (1.84 g, 9.3 mmol) dissolved in acetonitrile (25 mL). The reaction was stirred at room temperature under a nitrogen atmosphere for 18 h. Following the work-up, the residue was purified using column chromatography on silica gel using hexane:ethyl acetate (95:5) to yield 2-ethylhexyl 2-diazo-3-oxobutanoate **28** as a bright yellow oil (1.60 g, 78%. δ_H($CDCl_3$, 300 MHz): 0.90 (6H, m, 2 × C*H*$_3$), 1.25-1.43 (8H, m, 4 × C*H*$_2$), 1.59-1.68 (1H, m, C*H*), 2.47 [3H, s, C(O)C*H*$_3$], 4.17 (2H, d, *J* 5.6, OC*H*$_2$); δ_C($CDCl_3$, 100 MHz): 10.9 (*C*H_3), 14.0 (*C*H_3), 22.9 (*C*H_2), 23.1 (*C*H_2), 28.9 (*C*H_2), 30.1 (*C*H_2), 30.3 [C(O)*C*H_3], 38.7 (*C*H), 67.7 (O*C*H_2), 161.5 (*C*=O), 190.1 (*C*=O),

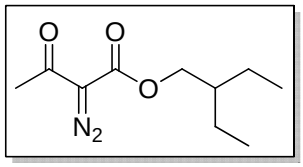
no signal observed for (*C*=N_2); ν_{max} (film)/cm^{-1} 2960, 2143, 1711, 1656, 1315; *m/z* (ESI^+) 241 $[M + H]^+$ (8%), 118 (100).

Decyl 2-diazo-3-oxobutanoate 29



The title compound was prepared following the procedure described for methyl 2-diazo-3-oxobutanoate **18** using triethylamine (0.42 mL, 4.1 mmol), decyl 3-oxobutanoate **10** (1.01 g, 4.1 mmol) in acetonitrile (25 mL) and *p*-toluenesulfonyl azide **13** (0.81 g, 4.1 mmol) dissolved in acetonitrile (25 mL). The reaction was stirred at room temperature under a nitrogen atmosphere for 18 h. Following the work-up, decyl 2-diazo-3-oxobutanoate **29** (0.88 g, 80%) was isolated as a bright yellow oil which was used without further purification. δ_H($CDCl_3$, 400 MHz): 0.88 (3H, t, *J* 6.9, C*H*$_3$), 1.20-1.41 (14H, m, 7 × C*H*$_2$), 1.62-1.72 (2H, m, C*H*$_2$), 2.48 [3H, s, C(O)C*H*$_3$], 4.23 (2H, t, *J* 6.7, OC*H*$_2$); δ_C($CDCl_3$, 100 MHz): 14.1 (*C*H$_3$), 22.7 (*C*H$_2$), 25.8 (*C*H$_2$), 28.2 (*C*H$_2$), 28.6 [C(O)*C*H$_3$], 29.2 (*C*H$_2$), 29.3 (*C*H$_2$), 29.5 (*C*H$_2$), 29.5 (*C*H$_2$), 31.9 (*C*H$_2$), 65.6 (O*C*H$_2$), 161.5 (*C*=O) ester, 190.2 (*C*=O) ketone, no signal observed for (*C*=N_2); ν_{max} (film)/cm^{-1} 2139, 1721, 1664, 1314; HRMS (ESI^+): exact mass calculated for $C_{14}H_{25}O_3N_2$ $[M + H]^+$ 269.1865. Found 269.1871. Spectral details are in agreement with those reported in the literature.[27]

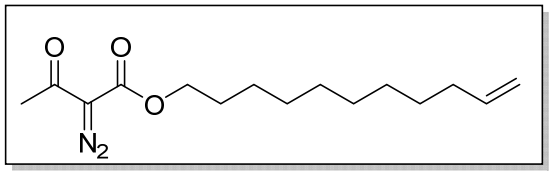
2-Ethylbutyl 2-diazo-3-oxobutanoate 30



The title compound was prepared following the procedure described for methyl 2-diazo-3-oxobutanoate **18** using triethylamine (1.84 mL, 9.3 mmol), 2-ethylbutyl 3-oxobutanoate **5** (2.01 g, 9.3 mmol) in acetonitrile (25 mL) and *p*-toluenesulfonyl azide **13** (1.84 g, 9.3 mmol) dissolved in acetonitrile (25 mL). The reaction was stirred at room temperature under a nitrogen atmosphere for 18 h. Following the work-up, 2-ethylbutyl 2-diazo-3oxobutanoate **30** was isolated as a bright yellow oil (1.54 g, 78%), which was used without further purification. δ_H($CDCl_3$, 400 MHz): 0.92 (6H, t, *J* 7.5, 2 × C*H*$_3$), 1.31-1.43 (4H, m, 2 × C*H*$_2$), 1.52-1.64 (1H, m, C*H*), 2.48 [3H, s, C(O)C*H*$_3$], 4.19 (2H, d, *J* 6.0, OC*H*$_2$);

δ_C($CDCl_3$, 100 MHz): 10.7 (2 × *C*H_3), 22.8 (2 × *C*H_2), 28.1 [C(O)*C*H_3], 40.4 (*C*H), 67.3 (O*C*H_2), 161.5 (*C*=O) ester, 190.0 (*C*=O) ketone, no signal observed for (*C*=N_2); ν_{max} (film)/cm^{-1} 2140, 1717, 1662, 1312; *m/z* (ESI^+) 213 $[M + H]^+$ (30%), 102 (100), 118 (80).

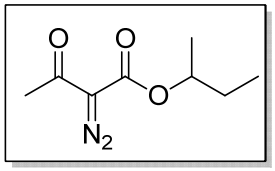
Undec-10-en-1-yl 2-diazo-3-oxobutanoate 31



The title compound was prepared following the procedure described for methyl 2-diazo-3-oxobutanoate **18** using triethylamine (1.20 mL, 11.8 mmol), dodec-11-en-1-yl 3-oxobutanoate **11** (3.06 g, 11.5 mmol) in acetonitrile (30 mL) and *p*-toluenesulfonyl azide **13** (2.33 g, 11.8 mmol) dissolved in acetonitrile (30 mL). The reaction was stirred at room temperature under a nitrogen atmosphere for 18 h. Following the work-up, the residue was purified by column chromatography on silica gel using hexane:ethyl acetate (90:10) as eluent to yield undec-10-en-1-yl 2-diazo-3-oxobutanoate **31** as a yellow oil (1.78 g, 78%). δ_H($CDCl_3$, 400 MHz): 1.22-1.43 (12H, m, 6 × C*H*$_2$), 1.64-1.75 (2H, m, C*H*$_2$), 1.99-2.09 (2H, m, C*H*$_2$), 2.47 [3H, s, C(O)C*H*$_3$], 4.23 (2H, t, *J* 6.6, OC*H*$_2$), 4.90-5.01 (2H, m, CH=C*H*$_2$), 5.74-5.87 (1H, m, C*H*=CH_2); δ_C($CDCl_3$, 100 MHz): 25.7 (*C*H_2), 28.2 [C(O)*C*H_3], 28.6 (*C*H_2), 28.8 (*C*H_2), 29.0 (*C*H_2), 29.1 (*C*H_2), 29.3 (*C*H_2), 29.4 (*C*H_2), 33.7 (*C*H_2), 65.5 (O*C*H_2), 114.1 (*C*H_2) alkene, 139.1 (*C*H) alkene, 161.5 (*C*=O) ester, 190.2 (*C*=O) ketone, no signal observed for (*C*=N_2); ν_{max} (film)/cm^{-1} 2140, 1721, 1660, 1315; HRMS (ESI^+): exact mass calculated for $C_{15}H_{25}O_3N_2$ $[M + H]^+$ 281.1865. Found 281.1867.

***sec*-Butyl 2-diazo-3-oxobutanoate 32**

The title compound was prepared following the procedure described for methyl 2-

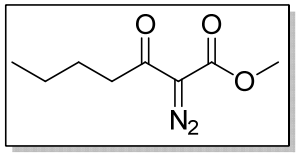


diazo-3-oxobutanoate **18** using triethylamine (0.29 mL, 2.05 mmol), *sec*-butyl 3-oxobutanoate **4** (0.320 g, 2.05 mmol) in acetonitrile (10 mL) and *p*-toluenesulfonyl azide **13** (0.401 g, 2.05 mmol) dissolved in acetonitrile (10 mL). The reaction was stirred at room temperature under a nitrogen atmosphere for 18 h. Following the work-up, *sec*-butyl 2-diazo-3-oxoanoate **32** was isolated as a bright yellow oil (0.293 g,

78%), which was used without further purification. δ_H($CDCl_3$, 400 MHz): 0.94 (3H, t, *J* 7.5, C*H*$_3$), 1.29 (3H, d, *J* 6.3, C*H*$_3$), 1.56-1.73 (2H, m, C*H*$_2$CH$_3$), 2.48 [3H, s, C(O)C*H*$_3$], 4.96-5.04 (1H, m, OC*H*); δ_C($CDCl_3$, 100 MHz): 9.5 (*C*H$_3$), 19.5 (*C*H$_3$), 28.2 [C(O)*C*H$_3$], 28.8 (*C*H$_2$), 73.9 (O*C*H), 161.1 (*C*=O) ketone, 190.3 (*C*=O) ester, no signal observed for C=N$_2$; ν_{max} (film)/cm^{-1} 2141, 1725, 1719, 1662; *m/z* (ESI$^+$) 185 [M + H]$^+$ (10%), 255 (100). Spectral details are in agreement with those reported in the literature.[24]

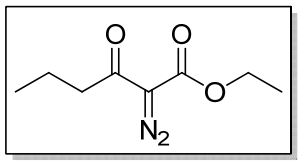
Variation of ketone side-chain

Methyl 2-diazo-3-oxoheptanoate 33



The title compound was prepared following the procedure described for methyl 2-diazo-3-oxobutanoate **18** using triethylamine (0.91 mL, 6.32 mmol), methyl 3-oxoheptanoate **317** (1.04 g, 6.32 mmol) in acetonitrile (25 mL) and *p*-toluenesulfonyl azide **13** (1.26 g, 6.32 mmol) dissolved in acetonitrile (25 mL). The reaction was stirred at room temperature under a nitrogen atmosphere for 18 h. Following the work-up, methyl 2-diazo-3-oxoheptanoate **33** was obtained as a bright yellow oil (0.84 g, 72%), which was used without further purification. δ_H($CDCl_3$, 400 MHz): 0.93 (3H, t, *J* 7.2, CH$_2$C*H*$_3$), 1.33-1.42 (2H, m, C*H*$_2$), 1.58-1.65 (2H, m, C*H*$_2$), 2.85 [2H, t, *J* 7.6, C(O)C*H*$_2$], 3.84 (3H, s, OC*H*$_3$); δ_C($CDCl_3$, 100 MHz): 13.6 (*C*H$_3$), 22.2 (*C*H$_2$), 26.3 (*C*H$_2$), 39.7 [C(O)*C*H$_2$], 51.9 (O*C*H$_3$), 75.4 (*C*=N$_2$), 161.6 (*C*=O) ester, 192.6 (*C*=O) ketone; ν_{max} (film)/cm^{-1} 2137, 1726, 1660, 1312; *m/z* (ESI$^+$) 185 [M + H]$^+$ (58%). HRMS (ESI$^+$): exact mass calculated for $C_8H_{13}O_3N_2$ [M + H]$^+$ 185.0926. Found 185.0918. Spectral details are in agreement with those reported in the literature.[29]

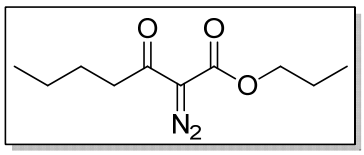
Ethyl 2-diazo-3-oxohexanoate 34



The title compound was prepared following the procedure described for methyl 2-diazo-3-oxobutanoate **18** using triethylamine (1.28 mL, 12.66 mmol), ethyl 3-oxohexanoate **327** (2.01 g, 12.66 mmol) in acetonitrile (25 mL) and *p*-toluenesulfonyl azide **13** (2.51 g, 12.66 mmol) dissolved in

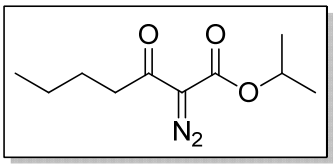
acetonitrile (25 mL). The reaction was stirred at room temperature under a nitrogen atmosphere for 18 h. Following the work-up, ethyl 2-diazo-3-oxohexanoate **34** was obtained as a bright yellow oil (2.22 g, 95%), which was used without further purification. δ_H($CDCl_3$, 400 MHz): 0.96 (3H, t, *J* 7.5, C*H*$_3$), 1.34 (3H, t, *J* 7.2, OCH$_2$C*H*$_3$), 1.62-1.71 [2H, m, C(O)CH$_2$C*H*$_2$], 2.83 [2H, t, *J* 7.2, C(O)C*H*$_2$CH$_2$], 4.31 (2H, q, *J* 7.2, OC*H*$_2$CH$_3$); δ_C($CDCl_3$, 100 MHz): 13.7 (*C*H$_3$), 14.3 (*C*H$_3$), 17.8 (*C*H$_2$), 42.0 [C(O)*C*H$_2$], 61.3 (O*C*H$_2$), 161.3 (*C*=O) ester, 192.8 (*C*=O) ketone, no signal observed for (*C*=N$_2$); ν_{max} (film)/cm^{-1} 2135, 1721, 1659, 1302; *m/z* (ESI$^+$) 185 [M + H]$^+$ (58%), 102 (100). HRMS (ESI$^+$): exact mass calculated for $C_8H_{13}O_3N_2$ [M + H]$^+$ 185.0926. Found 185.0903. Spectral details are in agreement with those reported in the literature.[30]

Propyl 2-diazo-3-oxoheptanoate 35



The title compound was prepared following the procedure described for methyl 2-diazo-3-oxobutanoate **18** using triethylamine (0.54 mL, 5.37 mmol), propyl 3-oxoheptanoate **9** (1.06 g, 5.37 mmol) in acetonitrile (25 mL) and *p*-toluenesulfonyl azide **13** (1.06 g, 5.37 mmol) dissolved in acetonitrile (25 mL). The reaction was stirred at room temperature under a nitrogen atmosphere for 18 h. Following the work-up, the residue was purified by column chromatography on silica gel, using hexane:ethyl acetate (90:10) as eluent to yield propyl 2-diazo-3-oxoheptanoate **35** as a bright yellow oil (615 mg, 71%). δ_H($CDCl_3$, 400 MHz): 0.81-1.00 [6H, m, containing 0.94 (3H, t, *J* 7.3, C*H*$_3$) and 0.97 (3H, t, *J* 7.4, C*H*$_3$)], 1.33-1.42 (2H, m, C*H*$_2$), 1.58-1.70 (4H, m, 2 × C*H*$_2$), 2.82 [2H, t, *J* 7.8, C(O)C*H*$_2$], 4.12 (2H, t, *J* 6.7, OC*H*$_2$); δ_C($CDCl_3$, 100 MHz): 10.2 (*C*H$_3$), 13.8 (*C*H$_3$), 21.8 (*C*H$_2$), 22.3 (*C*H$_2$), 26.6 (*C*H$_2$), 39.9 [C(O)*C*H$_2$], 66.8 (O*C*H$_2$), 75.8 (*C*=N$_2$), 161.4 (*C*=O) ester, 192.9 (*C*=O) ketone; ν_{max} (film)/cm^{-1} 2135, 1719, 1660, 1394; *m/z* (ESI$^+$) 213 [M + H]$^+$ (80%), 214 (13) 338 (100). HRMS (ESI$^+$): exact mass calculated for $C_{10}H_{17}O_3N_2$ [M + H]$^+$ 213.1239. Found 213.1234. Spectral details are in agreement with those reported in the literature.[24]

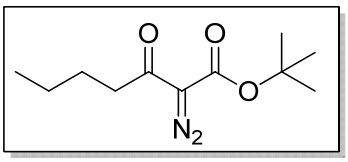
Isopropyl 2-diazo-3-oxoheptanoate 36



The title compound was prepared following the procedure described for methyl 2-diazo-3-oxobutanoate **18** using triethylamine (0.31 mL, 2.15 mmol), isopropyl 3-oxoheptanoate **7** (0.4 g, 2.15 mmol) in acetonitrile (10 mL) and *p*-toluenesulfonyl azide **13** (0.42 g, 2.15 mmol) dissolved in acetonitrile (5 mL). The reaction was stirred at room temperature under a nitrogen atmosphere for 18 h. Following the work-up, the residue was purified by column chromatography on silica gel, using hexane:ethyl acetate (90:10) as eluent to yield isopropyl 2-diazo-3-oxoheptanoate **36** as a bright yellow oil (317 mg, 68%). δ_H($CDCl_3$, 400 MHz): 0.92 (3H, t, *J* 7.2, C*H*$_3$), 1.25-1.45 [1.32 (6H, d, *J* 6.4, 2 × C*H*$_3$) and C*H*$_2$], 1.57-1.65 (2H, m, C*H*$_2$), 2.81 (2H, t, *J* 7.2, C(O)C*H*$_2$), 5.11-5.20 (1H, m, C*H*). δ_C(CDCl3, 100 MHz): 13.8 (*C*H$_3$), 21.9 (2 × CH_3), 22.3 (CH_3*C*H$_2$), 26.5 (CH_3CH_2*C*H$_2$), 39.9 (CO*C*H$_2$), 69.2 (O*C*H(CH_3)$_2$), 161.0 (*C*=O) ester, 193.1 (*C*=O) ketone, no signal observed for (*C*=N_2); ν_{max} (film)/cm^{-1} 2135, 1716, 1660, 1299; *m/z* (ESI^+) 213 $[M + H]^+$ (100%), 214 (10); HRMS (ESI^+): exact mass calculated for $C_{10}H_{17}O_3N_2$ $[M + H]^+$ 213.1239. Found 213.1239.

Note: The ^{1}H NMR spectrum showed the product was contaminated with 6% ethyl 2-diazo-3-oxobutanoate **19** which was brought forward through the synthesis and removed completely at a later stage.

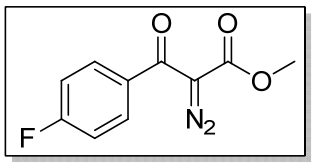
***t*-Butyl 2-diazo-3-oxoheptanoate 37**



The title compound was prepared following the procedure described for methyl 2-diazo-3-oxobutanoate **18** using triethylamine (1.44 mL, 9.98 mmol), *t*-butyl 3-oxoheptanoate **8** (2.01 g, 9.98 mmol) in acetonitrile (25 mL) and *p*-toluenesulfonyl azide **13** (1.97 g, 9.98 mmol) dissolved in acetonitrile (25 mL). The reaction was stirred at room temperature under a nitrogen atmosphere for 18 h. Following the work-up, the residue was purified by column chromatography on silica gel using hexane:ethyl acetate (95:5) to yield *t*-butyl 2-diazo-3-oxoheptanoate **37** as a bright yellow oil (1.59 g, 69%). δ_H($CDCl_3$, 400 MHz): 0.92 (3H, t, *J* 7.2, C*H*$_3$), 1.28-1.41 (2H, m, CH_2), [11H, m containing C*H*$_2$ and 1.52

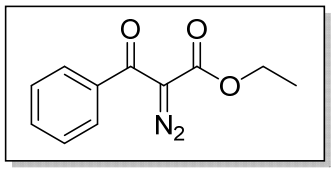
(9H, s, 3 × C*H*$_3$ of *t*-butyl), 2.82 [2H, t, *J* 7.6, C(O)C*H*$_2$]; δ_C(CDCl$_3$, 100 MHz): 13.9 (*C*H$_3$), 22.3 (*C*H$_2$), 26.4 (*C*H$_2$), 28.3 (3 × *C*H$_3$ of *t*-butyl), 39.9 [*C*(O)CH$_2$], 83.0 (*C*$_q$), 160.6 (*C*=O) ester, 193.3 (*C*=O) ketone, no signal observed for (*C*=N$_2$); ν_{max} (film)/cm^{-1} 2960, 2131, 1713, 1652, 1313; *m/z* (ESI$^+$) 213 [M + H]$^+$ (100%), 214 (10) HRMS (ESI$^+$): exact mass calculated for $C_{11}H_{18}O_3N_2$ [M + H]$^+$ 227.1396 Found 227.1390.

Methyl 2-diazo-3-(4-fluorophenyl)-3-oxopropanoate 38



The title compound was prepared following the procedure described for methyl 2-diazo-3-oxobutanoate **18** using triethylamine (0.06 mL, 0.41 mmol), methyl 3-(4-fluorophenyl)-3-oxopropanoate **328** (0.08 g, 0.41 mmol) in acetonitrile (4 mL) and *p*-toluenesulfonyl azide **13** (0.16 g, 0.82 mmol) dissolved in acetonitrile (0.5 mL). The reaction was stirred at room temperature under a nitrogen atmosphere for 18 h. Following the work-up, methyl 2-diazo-3-(4-fluorophenyl)-3-oxopropanoate **38** was obtained as a bright yellow oil (78 mg, 85%), which was used without further purification. δ_H(CDCl$_3$, 300 MHz): 3.79 (3H, s, OC*H*$_3$), 7.08-7.42 (2H, m, 2 × ArC*H*), 7.66-7.70 (2H, m, 2 × ArC*H*); δ_C(CDCl$_3$, 100 MHz): 52.4 (O*C*H$_3$), 115.1 (d, $^2J_{CF}$ 22.0, 2 × Ar*C*H), 131.2 (d, $^3J_{CF}$ 9.1, 2 × Ar*C*H), 133.0 (d, $^4J_{CF}$ 3.2, Ar*C*$_q$), 161.3 (*C*=O) ester, 165.2 (d, $^1J_{CF}$ 251, Ar*C*F), 185.4 (*C*=O) ketone, no signal observed for (*C*=N$_2$); ν_{max} (film)/cm^{-1} 2985, 2145, 1725, 1692, 1630, 1322; *m/z* (ESI$^+$) 245.3 [M + Na]$^+$(30%). Spectral details are in agreement with those reported in the literature.[31]

Ethyl 2-diazo-3-oxo-3-phenylpropanoate 39

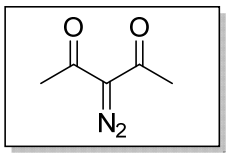


The title compound was prepared following the procedure described for methyl 2-diazo-3-oxobutanoate **18** using triethylamine (0.73 mL, 5.2 mmol), ethyl 3-phenyl-3-oxopropanoate **329** (1.0 g, 5.2 mmol) in acetonitrile (15 mL) and *p*-toluenesulfonyl azide **13** (1.03 g, 5.2 mmol) dissolved in acetonitrile (20 mL). The reaction was stirred at room temperature under a nitrogen atmosphere for 18 h. Following the work-up, methyl 2-diazo-3-phenyl-3-oxopropanoate **39** was obtained as a bright yellow oil (0.7 g, 61%), which was

used without further purification. δ_H($CDCl_3$, 300 MHz): 1.25 (3H, t, *J* 7.1, CH_2CH_3), 4.24 (2H, q, *J* 7.1, OCH_2CH_3), 7.41 (2H, ddd, *J* 6.7, 4.5, 1.2, 2 × Ar*CH*), 7.49-7.56 (1H, m, Ar*CH*) 7.60-7.65 (2H, m, 2 × Ar*CH*); δ_C($CDCl_3$, 100 MHz): 14.2 (CH_3), 60.9 (*C*=N_2); 61.6 (OCH_2CH_3), 127.9 (2 × Ar*C*H), 128.4 (2 × Ar*C*H), 132.3 (Ar*C*H), 137.1 (ArC_q), 161.0 (*C*=O) ester, 186.9 (*C*=O) ketone; ν_{max} (film)/cm^{-1} 2145, 1726, 1630, 1308; *m/z* (ESI^+) 218 $[M]^+$, 223 (100%). Spectral details are in agreement with those reported in the literature.[32]

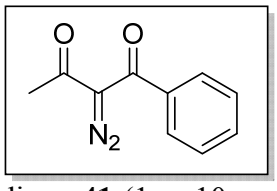
3.2.4 Diazo transfer to β-diketones

3-Diazopentane-2,4-dione 42



The title compound was prepared following the procedure described for methyl 2-diazo-3-oxobutanoate **18** using triethylamine (1.4 mL, 10 mmol), acetylacetone **40** (1 g, 10 mmol) in DCM (15 mL) and *p*-toluenesulfonyl azide **13** (1.97 g, 10 mmol) in DCM (25 mL). The reaction was stirred at room temperature for 18 h under a atmosphere. The reaction mixture was washed with 9% KOH (2 × 50 mL) followed by water (1 × 50 mL). The organic layer was dried with $MgSO_4$ and concentrated under reduced pressure Following the work-up, 3-diazopentane-2,4-dione **42** was obtained as a yellow oil and used without further purification (0.99 g, 79%). δ_H($CDCl_3$, 400 MHz): 2.44 (6H, s, 2 × CH_3); δ_C($CDCl_3$, 100 MHz): 28.4 (2 × CH_3), 84.6 (*C*=N_2), 188.2 (2 × *C*=O); *m/z* (ESI^+) 127 $[M + H]^+$ (10%) 141 (100); HRMS (ESI^+): exact mass calculated for $C_5H_7O_2N_2$ $[M + H]^+$ 127.0508. Found 127.0511; ν_{max} (film)/cm^{-1} 2130, 1666, 1308. Spectral details are in agreement with those reported in the literature.[33]

2-Diazo-1-phenylbutane-1,3-dione 43



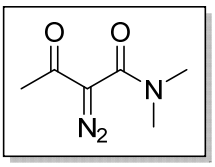
The title compound was prepared following the procedure described for methyl 2-diazo-3-oxobutanoate **18** using triethylamine (1.4 mL, 10 mmol), 1-phenylbutane-1,3-dione **41** (1 g, 10 mmol) in acetonitrile (15 mL) and *p*-toluenesulfonyl azide **13** (1.97 g, 10 mmol) in acetonitrile (25 mL). The reaction was stirred at room temperature for 18 h under a atmosphere. Following the work-up, 2-diazo-1-

phenylbutane-1,3-dione **43** was obtained as a yellow solid and used without further purification (1.54 g, 82%), m.p. 77-80 ºC, (Lit.[34] 78-81 ºC). δ_H (400 MHz, $CDCl_3$): 2.57 [3H, s, C(O)*C*H$_3$], 7.46-7.52 (2H, m, 2 × ArC*H*), 7.55-7.61 (1H, m, ArC*H*), 7.62-7.66 (2H, m, ArC*H*); δ_C($CDCl_3$, 100 MHz): 29.1 [C(O)*C*H$_3$], 83.7 (*C*=N$_2$), 127.3 (2 × Ar*C*H), 128.9 (2 × Ar*C*H), 132.7 (Ar*C*H), 137.3 (ArC_q), 185.0 (Ph*C*O), 190.7 (CH$_3$*C*O); (Found: C 63.52; H 4.30; N 14.82; $C_{10}H_8O_2N_2$ requires C 63.83; H 4.29; N 14.89%); *m/z* (ESI$^+$) 161 $[M + H - N_2]^+$ (10%); HRMS (ESI$^+$): exact mass calculated for $C_{10}H_9O_2N_2$ $[M + H]^+$ 189.0664. Found 189.0661; ν_{max} (KBr)/cm^{-1} 2120, 1659, 1646, 1578, 1362. Spectral details are in agreement with those reported in the literature.[34]

3.2.5 Diazo transfer reactions to β-ketoamides

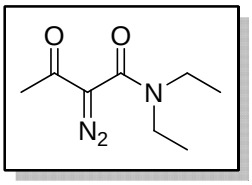
Note: The α-diazo-β-ketoamide derivatives were often difficult to yield in high purity even after repeated column chromatography on silica gel and were carried forward to the next stage.

2-Diazo-*N*,*N*-dimethyl-3-oxobutanamide 44



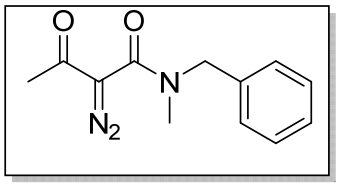
Triethylamine (0.7 mL, 5 mmol) was added to a stirred solution of *N*,*N*-dimethylacetoacetamide **330** (0.79 g, 5 mmol, 80% solution in water) in acetonitrile (15 mL). After 2 min a solution of *p*-toluenesulfonyl azide **13** (0.99 g, 5 mmol) in acetonitrile (10 mL) was added dropwise at room temperature over 15 min to yield a bright yellow solution. The reaction was stirred for 18 h under a nitrogen atmosphere. After 18 h the acetonitrile was removed under reduced pressure. The resulting yellow residue was dissolved in DCM (40 mL), washed with brine (2 × 50 mL) and water (50 mL). The organic layer was extracted, dried with $MgSO_4$ and concentrated under reduced pressure and the residue obtained was purified by column chromatography on silica gel using chloroform as eluent to yield diazo-*N*,*N*-dimethyl-3-oxobutanamide **44** as a bright yellow oil (0.65 g, 84%). δ_H($CDCl_3$, 400 MHz): 2.36 [3H, s, C(O)*C*H$_3$], 3.02 (6H, s, 2 × C*H*$_3$); δ_C($CDCl_3$, 100 MHz): 27.3 (*C*H$_3$), 37.5 [N(*C*H$_3$)$_2$], 161.4 (*C*=O) amide, 201.6 (*C*=O) ketone, no signal observed for (*C*=N$_2$); *m/z* (ESI$^+$) 155 $[M]^+$(100%); ν_{max} (film)/cm^{-1} 2931, 2108, 1658, 1651. Spectral details are in agreement with those reported in the literature.[35]

2-Diazo-*N*,*N*-diethyl-3-oxobutanamide 45



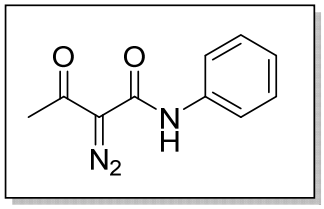
The title compound was prepared following the procedure described for 2-diazo-*N*,*N*-dimethyl-3-oxobutanamide **44** using triethylamine (0.7 mL, 5 mmol), *N*,*N*-diethylacetoacetamide **331** (1.0 mL, 5 mmol) in acetonitrile (10 mL) and *p*-toluenesulfonyl azide **13** (0.96 g, 5 mmol) in acetonitrile (25 mL). The reaction was stirred under a nitrogen atmosphere for 18 h. Following the work-up, the residue was purified by column chromatography on silica gel using hexane:ethyl acetate (65:35) as eluent to yield 2-diazo-*N*,*N*-diethyl-3-oxobutanamide **45** as a bright yellow oil (0.60 g, 65%). δ_H($CDCl_3$, 400 MHz): 1.15 (6H, t, *J* 7.1, 2 × CH_2CH_3), 2.29 [3H, s, C(O)CH_3], 3.34 (4H, q, *J* 7.1, 2 × CH_2CH_3); δ_C($CDCl_3$, 100 MHz): 13.1 (2 × CH_3), 27.3 [C(O)CH_3], 41.9 (2 × CH_2), 72.4 (*C*=N_2), 160.4 (*C*=O) amide, 190.1 (*C*=O) ketone; ν_{max} (film)/cm^{-1} 2106, 1652, 1607; *m/z* (ESI^+) 184 [M + H]$^+$ (6%). Spectral details are in agreement with those reported in the literature.[36]

***N*-Benzyl-2-diazo-*N*-methyl-3-oxobutanamide 46**



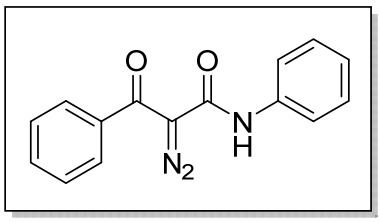
The title compound was prepared following the procedure described for 2-diazo-*N*,*N*-dimethyl-3-oxobutanamide **44** using triethylamine (0.7 mL, 4.9 mmol), *N*-benzyl-*N*-methyl-3-oxobutanamide **332** (1.0 g, 4.9 mmol) in acetonitrile (10 mL) and *p*-toluenesulfonyl azide **13** (0.97 g, 4.9 mmol) in acetonitrile (25 mL). The reaction was stirred under a nitrogen atmosphere for 18 h. Following the work-up, the residue was purified by column chromatography on silica gel using hexane:ethyl acetate (65:35) as eluent to yield *N*-benzyl-2-diazo-*N*-methyl-3-oxobutanamide **46** as a bright yellow oil (0.79 g, 70%). δ_H($CDCl_3$, 400 MHz): 2.41 [3H, s, C(O)CH_3], 2.90 (3H, s, NCH_3), 4.62 (2H, s, CH_2), 7.20-7.41 (5H, m , 5 × Ar*C*H); δ_C($CDCl_3$, 100 MHz): 27.4 [C(O)CH_3], 35.8 (NCH_3), 52.9 (CH_2), 73.5 (*C*=N_2), 127.7 (2 × Ar*C*H), 127.8 (Ar*C*H), 128.9 (2 × Ar*C*H), 136.0 (ArC_q), 161.7 (*C*=O) amide, 189.4 (*C*=O) ketone; ν_{max} (film)/cm^{-1} 2925, 2108, 1657, 1641, 1631; *m/z* (ESI^+) 231 [M]$^+$ (10%), 212 (100). HRMS $(ESI)^+$: Exact mass calculated for $C_{12}H_{14}N_3O_2$ [M + H]$^+$ 232.1086. Found: 232.1072.

2-Diazo-3-oxo-*N*-phenylbutanamide 47



The title compound was prepared following the procedure described for 2-diazo-*N*,*N*-dimethyl-3-oxobutanamide **44** using triethylamine (1.8 mL, 4.0 mmol), 3-oxo-*N*-phenylbutanamide **333** (0.35 g, 2.0 mmol) in acetonitrile (10 mL) and *p*-toluenesulfonyl azide **13** (0.43 g, 2.2 mmol, 1.1 equiv.) in acetonitrile (20 mL). The reaction was stirred under a nitrogen atmosphere for 18 h. The acetonitrile was removed under reduced pressure. The resulting yellow residue was dissolved in DCM (40 mL) and washed with water (3 × 50 mL), dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using hexane:ethyl acetate (85:15) as eluent to yield 2-diazo-3-oxo-*N*-phenylbutanamide **47** as a yellow solid (0.33 g, 82%), m.p. 117-120 ºC, (Lit.[37] 118-120 ºC). δ_H($CDCl_3$, 400 MHz): 2.42 [3H, s, C(O)*C*H_3], 7.10-7.14 (1H, m, ArC*H*), 7.31-7.35 (2H, m, 2 × ArC*H*), 7.58 (2H, dd, *J* 8.6, 1.0, 2 × ArC*H*) 10.17 (1H, br s, N*H*); δ_C($CDCl_3$, 100 MHz): 26.8 [C(O)*C*H_3], 120.1 (2 × Ar*C*H), 124.5 (1 × Ar*C*H), 129.1 (2 × Ar*C*H), 137.8 (ArC_q), 158.2 (*C*=O) amide, 189.9 (*C*=O) ketone, no signal observed for (*C*=N_2);. ν_{max} (KBr)/cm^{-1} 2130, 1676, 1598, 1553; *m/z* (ESI$^-$) 202 [M - H]$^-$ (19%) 201 (60), 324 (100). Spectral details are in agreement with those reported in the literature.[37]

2-Diazo-3-oxo-*N*,3-diphenylpropanamide 48



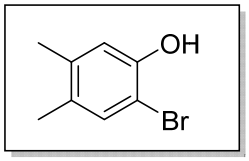
The title compound was prepared following the procedure described for 2-diazo-*N*,*N*-dimethyl-3-oxobutanamide **44** using triethylamine (1.1 mL, 8.0 mmol), 3-oxo-*N*,3-diphenylpropanamide **334** (0.96 g, 4.0 mmol) in acetonitrile (10 mL) and *p*-toluenesulfonyl azide **13** (0.87 g, 4.4 mmol) in acetonitrile (25 mL). The reaction was stirred under a nitrogen atmosphere for 3 h. The acetonitrile was removed under reduced pressure. The resulting yellow residue was dissolved in DCM (40 mL) and washed with water (3 × 50 mL), dried with $MgSO_4$ and concentrated under reduced pressure. The

residue was purified by column chromatography on silica gel using hexane:ethyl acetate (65:35) as eluent to yield 2-diazo-3-oxo-*N*,3-diphenylpropanamide **48** as a yellow solid (0.78 g, 74%), m.p. 97-100 ºC, (Lit.[38] 95-98 ºC). δ_H($CDCl_3$, 400 MHz): 7.13 (1H, t, *J* 7.4, ArC*H*), 7.35 (2H, t, *J* 8.0, 2 × ArC*H*), 7.52 (2H, t, *J* 7.4, 2 × ArC*H*), 7.57-7.74 (5H, m, 5 × ArC*H*), 10.45 (1H, br s, N*H*); δ_C($CDCl_3$, 100 MHz): 120.2 (2 × Ar*C*H), 124.5 (Ar*C*H), 127.1 (2 × Ar*C*H), 129.1 (4 × Ar*C*H), 132.8 (Ar*C*H), 136.6 (ArC_qNH), 137.9 (ArC_qCO), 158.6 (*C*=O) amide, 188.1 (*C*=O) ketone, no signal observed for (*C*=N_2); ν_{max} (KBr)/cm^{-1} 3256, 2130, 1674, 1594, 1542; *m/z* (ESI^+) 266 $[M + H]^+$ (100%); HRMS (ESI^+): exact mass calculated for $C_{15}H_{12}N_3O_2$ $[M + H]^+$ 266.0930. Found 266.0932. Spectral details are in agreement with those reported in the literature.[38]

3.3 Synthesis of 2-trimethylsilyl aryl triflates/nonaflates as aryne precursors

3.3.1 Bromination of phenol derivatives

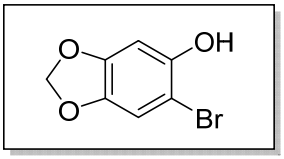
2-Bromo-4,5-dimethylphenol 62



N-Bromosuccinimide **338** (1.46 g, 8.2 mmol) in acetonitrile (10 mL) was added to 3,4-dimethylphenol **61** (1 g, 8.2 mmol) in acetonitrile (10 mL) at 0 °C *via* an addition funnel. After 10 min the reaction was quenched with water and extracted with DCM which was then washed with water (3 × 50 mL), dried with magnesium sulfate and concentrated under reduced pressure. The residue obtained was purified by column chromatography on silica gel using hexane:ethyl acetate (98:2) as eluent to yield 2-bromo-4,5-dimethylphenol **62** as a white solid, (1.43 g, 90%), m.p. 75-78 ºC, (Lit.[43] 80 ºC). δ_H($CDCl_3$, 400 MHz): 2.15 (3H, s, C*H*$_3$), 2.17 (3H, s, C*H*$_3$), 5.28 (1H, br s, O*H*), 6.80 (1H, s, ArC*H*), 7.18 (1H, s, ArC*H*); δ_C($CDCl_3$, 100 MHz): 18.6 (ArC*C*H$_3$), 19.5 (ArC*C*H$_3$), 106.5 (Ar*C*Br), 117.1 (Ar*C*H), 130.2 (Ar*C*CH$_3$), 132.2 (Ar*C*H), 137.9 (Ar*C*CH$_3$), 150.0 (Ar*C*OH); HRMS (ESI^+): exact mass calculated for $C_8H_{10}{}^{79}BrO$ $[M + H]^+$ 200.9915. Found 200.9908 $[(C_8H_{10}{}^{79}BrO)]^+$; ν_{max} (film)/cm^{-1} 3319, 2944, 1604, 1406, 1193. Spectral details are in agreement with those reported in the literature.[43]

Note: After repeated column chromatography the sample still contained 5% starting material visible in the ^1H NMR spectrum that could not be removed and was carried forward through the synthesis where it was removed completely, at a later stage.

6-Bromobenzo[*d*][1,3]dioxol-5-ol 60

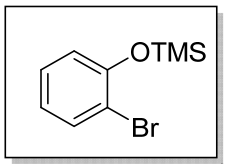


The title compound was prepared in the same manner as 2-bromo-4,5-dimethylphenol **62** using *N*-bromosuccinimide **338** (3.2 g, 18 mmol) in acetonitrile (20 mL), 5-benzodioxolol **59** (2.5 g, 18 mmol) in acetonitrile (20 mL). Following the work-up, the solvent was removed under reduced pressure to provide the product 6-bromobenzo[*d*][1,3]dioxol-5-ol **60** as a green/black solid (3.30 g, 85%)

m.p. 85-88 ºC, (Lit.[45] 87-88 ºC), which contained 10% starting material, was used without further purification. δ_H($CDCl_3$, 400 MHz): 5.23 (1H, br s, O*H*), 5.93 (2H, s, OC*H*$_2$O), 6.59 (1H, s, ArC*H*), 6.89 (1H, s, ArC*H*); δ_C($CDCl_3$, 100 MHz): 98.1 (Ar*C*H), 99.2 (Ar*C*Br), 101.7 (O*C*H$_2$O), 110.6 (Ar*C*H), 142.0 (Ar*C*O), 147.4 (Ar*C*OH), 148.3 (Ar*C*O); *m/z* (ESI$^-$) 215.9[($C_7H_5O_2{}^{79}Br)^+$, 6%], 217.9[($C_7H_5O_2{}^{81}Br)^+$, 6%], 81 (100), 79 (95); ν_{max} (KBr)/cm^{-1} 3393, 2959, 1502, 1486, 1253, 1184. Spectral details are in agreement with those reported in the literature.[45]

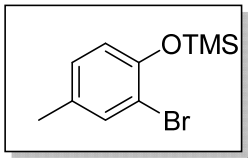
3.3.2 Silylation of bromophenol derivatives

(2-Bromophenoxy)trimethylsilane 63



A mixture of 2-bromophenol **53** (0.79 g, 3.64 mmol) and hexamethyldisilazane (HMDS) **334** (0.5 ml, 3.64 mmol) in THF (10 mL) was stirred under reflux for 2 h in a flask fitted with a condenser and a $CaCl_2$ tube. Excess NH_3 and unreacted HMDS were removed under reduced pressure to provide (2-bromophenoxy)trimethylsilane **63** as a yellow oil (0.8 g, quantitative) which was used without further purification. δ_H($CDCl_3$, 400 MHz): 0.24 [9H, s, Si(C*H*$_3$)$_3$], 6.73-6.83 (2H, m, 2 × ArC*H*), 7.10 (1H, ddd, *J* 8.0, 7.3, 1.6, ArC*H*), 7.45 (1H, dd, *J* 8.0, 1.6, ArC*H*); δ_C($CDCl_3$, 100 MHz): 0.34 [Si(*C*H$_3$)$_3$], 115.6 (Ar*C*Br), 120.7 (Ar*C*H), 122.7 (Ar*C*H), 128.3 (Ar*C*H), 133.3 (Ar*C*H), 152.4 (Ar*C*O); *m/z* (ESI$^+$) 243[($C_9H_{13}OSi^{79}Br)^+$, 50%], 245[($C_9H_{13}OSi^{81}Br)^+$, 50%]; ν_{max} (film)/cm^{-1} 2960, 1584, 1477, 1255. Spectral details are in agreement with those reported in the literature.[39]

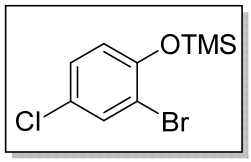
(2-Bromo-4-methylphenoxy)trimethylsilane 64



The title compound was prepared using the procedure described for (2-bromophenoxy)trimethylsilane **54** using 2-bromo-4-methylphenol **335** (1.21 mL, 10 mmol) and HMDS **334** (1.24 mL, 6.0 mmol) in the absence of solvent at 80 ºC for 45 min in a flask protected with a $CaCl_2$ tube. Excess NH_3 and unreacted HMDS were removed under reduced pressure to provide (2-bromo-4-methylphenoxy)trimethylsilane **64** in high purity as a colourless oil (2.59 g, quantitative). δ_H($CDCl_3$, 400 MHz): 0.23 [9H, s,

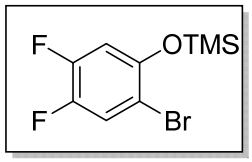
Si(CH_3)$_3$], 2.20 (3H, s, CH_3), 6.70 (1H, d, *J* 8.2, ArCH), 6.90 (1H, ddd, *J* 8.2, 2.1, 0.6, ArCH), 7.28 (1H, d, *J* 1.6, ArCH); δ_C($CDCl_3$, 100 MHz): 0.4 [Si(*C*H_3)$_3$], 20.3 (*C*H_3), 115.1 (Ar*C*-Br), 120.4 (Ar*C*H), 128.9 (Ar*C*H), 132.4 (Ar*C*CH_3), 133.6 (Ar*C*H), 150.1 [Ar*C*OSi$(CH_3)_3$]; ν_{max} (film)/cm^{-1} 2958, 1599, 1486, 1247; *m/z* (ESI^+) 258[$(C_9H_{12}OSiCl^{79}Br + H)^+$, 8%], 260[$(C_9H_{12}OSiCl^{81}Br + H)^+$, 4%]. Spectral details are in agreement with those reported in the literature.[41]

(2-Bromo-4-chlorophenoxy)trimethylsilane 65



The title compound was prepared using the procedure described for (2-bromophenoxy)trimethylsilane **54** using 2-bromo-4-chlorophenol **336** (0.64 g, 3.08 mmol) and HMDS **334** (0.7 ml, 3.39 mmol) in THF (10 mL). Excess NH_3 and unreacted HMDS were removed under reduced pressure to provide (2-bromo-4-chlorophenoxy)trimethylsilane **65** in high purity as a colourless oil (0.86 g, quantitative) which was used without further purification. δ_H($CDCl_3$, 400 MHz): 0.30 [9H, s, Si(CH_3)$_3$], 6.74 (1H, d, *J* 8.6, ArC*H*), 7.09 (1H, d, *J* 8.6, ArC*H*), 7.46 (1H, s, ArCH); δ_C($CDCl_3$, 100 MHz): 0.4 [Si(*C*H_3)$_3$], 116.1 (Ar*C*Br), 121.3 (Ar*C*H), 126.9 (Ar*C*-Cl), 128.0 (Ar*C*H), 132.8 (Ar*C*H), 151.5 [Ar*C*OSi$(CH_3)_3$]; ν_{max} (film)/cm^{-1} 2960, 1458, 1422, 1215; *m/z* (ESI^+) 279[$(C_9H_{12}OSi^{79}BrCl)^+$, 4%], 281[$(C_9H_{12}OSi^{81}BrCl)^+$, 5%],163 (12), 81 (22), 79 (20). Spectral details are in agreement with those reported in the literature.[41]

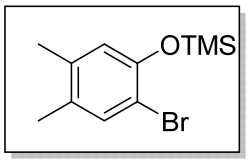
(2-Bromo-4,5-difluorophenoxy)trimethylsilane 67



The title compound was prepared using the procedure described for (2-bromophenoxy)trimethylsilane **54** using 2-bromo-4,5-difluorophenol **337** (0.34 g, 3 mmol) and HMDS **334** (0.68 ml, 3.3 mmol) in THF (10 mL). Excess NH_3 and unreacted HMDS were removed under reduced pressure to provide (2-bromo-4,5-difluorophenoxy)trimethylsilane **67** in high purity as a colourless oil (0.8 g, quantitative). δ_H($CDCl_3$, 400 MHz): 0.30 [9H, s, Si(CH_3)$_3$], 6.80-6.90 (1H, m, ArC*H*), 7.05-7.09 (1H, m, ArC*H*); δ_C($CDCl_3$, 100 MHz): 0.5 [Si(*C*H_3)$_3$], 109.3 (dd, $^3J_{CF}$ 7.1, $^4J_{CF}$ 3.9, *C*Br), 109.7 (d, $^2J_{CF}$ 19.1, Ar*C*H), 121.3 (d, $^2J_{CF}$ 20.7,

Ar*C*H), 145.5 (dd. $^{1}J_{CF}$ 245.7, $^{2}J_{CF}$ 13.5, Ar*C*F), 149.2 [dd, $^{2}J_{CF}$ 8.8, $^{3}J_{CF}$ 3.0, Ar*C*O Si$(CH_3)_3$], 149.7 (dd, $^{1}J_{CF}$ 249.3, $^{2}J_{CF}$ 13.5, Ar*C*F); ν_{max} (film)/cm^{-1} 2962, 1599, 1499, 1105; *m/z* (ESI$^+$) 281 {[($C_9H_{11}OSi^{79}BrF_2$) + H]$^+$, 12%}. Spectral details are in agreement with those reported in the literature.[41]

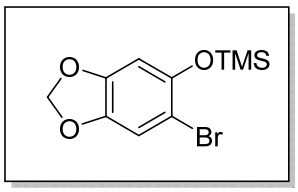
(2-Bromo-4,5-dimethylphenoxy)trimethylsilane[44] 66



The title compound was prepared using the procedure described for (2-bromophenoxy)trimethylsilane **54** using 2-bromo-4,5-dimethylphenol **62** (1 g, 5.0 mmol) and HMDS **334** (1.1 ml, 5.0 mmol) in THF (10 mL). Excess NH_3 and unreacted HMDS were removed under reduced pressure to yield (2-bromo-4,5-dimethylphenoxy)trimethylsilane **66** as a colourless oil (1.27 g, 94%). δ_H($CDCl_3$, 400 MHz): 0.37 [9H, s, Si(C*H*$_3$)$_3$], 2.24 (6H, s, 2 × C*H*$_3$), 6.75 (1H, s, ArC*H*), 7.34 (1H, s, ArC*H*); δ_C($CDCl_3$, 100 MHz): 0.36 [Si(*C*H$_3$)$_3$], 18.6 (Ar*C*H$_3$), 19.5 (Ar*C*H$_3$), 111.7 (Ar*C*Br), 121.9 (Ar*C*H), 131.1 (Ar*C*CH$_3$), 133.6 (Ar*C*H), 136.7 (Ar*C*CH$_3$), 150.1 (Ar*C*OH); ν_{max} (film)/cm^{-1} 2960, 1491, 1288, 850; *m/z* (ESI$^+$) 272 [($C_{11}H_{18}SiO^{79}Br$)+, 5%], 274 [$C_{11}H_{18}SiO^{81}Br)^+$, 5%]. Spectral details are in agreement with those reported in the literature.

Note: The sample contained 5% starting material carried forward from the previous step that could not be removed and was carried forward to the next step.

{(6-Bromobenzo[d][1,3]dioxol-5-yl)oxy}trimethylsilane 68

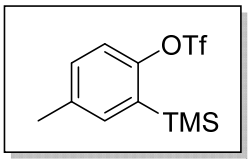


The title compound was prepared using the procedure described for (2-bromophenoxy)trimethylsilane **54** using 6-bromobenzo[*d*][1,3]dioxol-5-ol **60** (0.79 g, 3.64 mmol) and HMDS **334** (0.5 ml, 3.64 mmol) in THF (10 mL). Excess NH_3 and unreacted HMDS were removed under reduced pressure to yield [(6-bromobenzo[d][1,3]dioxol-5-yl)oxy]trimethylsilane **68** in high purity as a dark oil (0.8 g, quantitative). δ_H($CDCl_3$, 400 MHz): 0.27 [9H, s, Si(C*H*$_3$)$_3$], 5.93

(2H, s, OCH_2O), 6.44 (1H, s, ArC*H*), 6.95 (1H, s, ArC*H*); Spectral details are in agreement with those reported in the literature.[46]

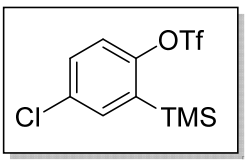
3.3.3 Preparation of 2-(trimethylsilyl)phenyltriflate derivatives

4-Methyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate 73



(2-Bromo-4-methylphenoxy)trimethylsilane **64** (2.59 g, 10 mmol) was dissolved in THF (50 mL), the solution cooled to -100 ºC and *n*-BuLi (4.8 mL, 2.5M in hexanes, 12 mmol, 1.2 equiv.) was added dropwise. The mixture was stirred for 20 min while the temperature reached -80 ºC. The mixture was again cooled to -100 ºC and triflic anhydride (2.1 mL, 12.5 mmol, 1.2 equiv.) was added dropwise and stirred was continued for 20 min while the temperature reached -80˚C. Cold saturated sodium bicarbonate was added, the phases separated and the aqueous layer extracted with diethyl ether (3 × 20 mL). The combined organic layers dried with $MgSO_4$, filtered and concentrated under reduced pressure. The residue obtained was purified by column chromatography on silica gel using hexane as eluent to provide 4-methyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **73** as a colourless oil (1.86 g, 60%). δ_H($CDCl_3$, 400 MHz): 0.36 [9H, s, Si(C*H*$_3$)$_3$], 2.36 (3H, s, C*H*$_3$), 7.21 (2H, d, *J* 1.6, 2 × ArC*H*), 7.30 (1H, s, ArC*H*); δ_C($CDCl_3$, 100 MHz): 0.4 [Si(*C*H$_3$)$_3$], 22.0 (*C*H$_3$), 117.6 (q, $^1J_{CF}$ 320.2, *C*F$_3$) 120.5 (Ar*C*H), 132.8, (Ar*C*H), 133.4, (Ar*C*CH$_3$)$_3$), 137.9 (Ar*C*H), 138.4 (Ar*C*CH$_3$), 154.3 (Ar*C*OTf); ν_{max} (film)/cm^{-1} 2960, 1468, 1421, 1254, 1213. Spectral details are in agreement with those reported in the literature.[41]

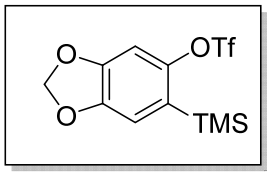
4-Chloro-2-(trimethylsilyl)phenyl trifluoromethanesulfonate 74



The title compound was prepared using the procedure described for 4-methyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **73** using (2-bromo-4-chlorophenoxy)trimethylsilane **65** (0.86 g, 3.1 mmol) in THF (10 mL), *n*-BuLi (1.5 mL, 2.5M in hexanes, 3.7 mmol) and triflic anhydride (0.67 mL, 4.0 mmol). Following the work-up, the residue was purified by column chromatography on silica gel and using hexane as eluent to afford 4-chloro-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **74** as a colourless oil (0.78 g, 76%). δ_H($CDCl_3$, 400

MHz): 0.37 [9H, s, Si(C*H*$_3$)$_3$], 7.26 (1H, d, *J* 1.4, ArC*H*), 7.39 (1H, dd, *J* 8.8, 2.6, ArC*H*), 7.45 (1H, d, *J* 2.6, ArC*H*); δ_C(CDCl$_3$, 100 MHz): -1.0 [Si(*C*H$_3$)$_3$], 116.3 (q, $^1J_{CF}$ 320.1, *C*F$_3$), 121.0 (Ar*C*H), 131.0 (Ar*C*H), 133.5 (Ar*C*Cl), 135.3 (Ar*C*Si), 135.8, (Ar*C*H), 153.1 (Ar*C*OTf); ν_{max} (film)/cm^{-1} 2959, 1580, 1474, 1278, 1184; *m/z* (ESI$^+$) 332 [M$^+$] (2%). Spectral details are in agreement with those reported in the literature.[41]

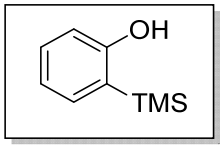
6-(Trimethylsilyl)benzo[d][1,3]dioxol-5-yl trifluoromethanesulfonate 75



The title compound was prepared using the procedure described for 4-methyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **68** using {(6-bromobenzo[*d*][1,3]dioxol-5-yl)oxy}trimethylsilane **68** (0.80 g, 3.6 mmol), *n*-BuLi (1.7 mL, 2.5M in hexanes, 4.3 mmol) and triflic anhydride (0.7 mL, 4.3 mmol, 1.2 equiv.) Following the work-up, the residue was purified by column chromatography on silica gel and using hexane as eluent to afford 6-(trimethylsilyl)benzo[*d*][1,3]dioxol-5-yl trifluoromethanesulfonate **75** as a colourless oil (34%, 0.323 g). δ_H(CDCl$_3$, 400 MHz): 0.33 [s, 9H, Si(C*H*$_3$)$_3$], 6.03 (s, 1H, OC*H*$_2$O), 6.86 (d, *J* 14.1, 2H, ArC*H*); δ_C(CDCl$_3$, 100 MHz): -0.35 [Si(*C*H$_3$)$_3$], 102.7 (O*C*H$_2$O), 113.5 (Ar*C*H), 116.7 (q, $^1J_{CF}$ 320.4, *C*F$_3$), 120.9 (Ar*C*Si), 125.3 (Ar*C*H), 147.2 (Ar*C*O), 149.0 (Ar*C*O), 149.9 (Ar*C*OTf); ν_{max} (film)/cm^{-1} 1217, 1248, 1507, 2960. Spectral details are in agreement with those reported in the literature.[43]

3.3.4 Preparation of 2-(trimethylsilyl)phenol derivatives and nonaflated aryne precursor

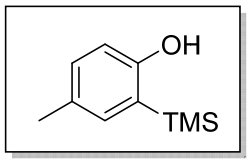
2-(Trimethylsilyl)phenol 58



An oven dried flask was charged with (2-bromophenoxy)trimethylsilane **63** (3.69 g, 11 mmol) and THF (15 mL) and the mixture was cooled to -78 ºC. *n*-BuLi (4.8 mL, 2.5M in hexanes, 12 mmol) was added dropwise and the reaction was allowed to warm to room temperature. A saturated aqueous solution of ammonium chloride was added to the mixture to quench and the mixture was extracted with ethyl

acetate (3 × 20 mL). The combined organic extracts were dried with $MgSO_4$, and concentrated under reduced pressure. The residue obtained was purified by column chromatography on silica gel hexane:ethyl acetate (10:1) to provide 2-(trimethylsilyl)phenol **58** as a colourless oil (2.17 g, 77%). δ_H($CDCl_3$, 400 MHz): 0.31 [1H, s, 9H, Si(*C*H_3)], 4.80 (1H, br s, O*H*), 6.66 (1H, dd, *J* 8.0, 0.6, ArC*H*), 6.91(1H, dt, *J* 7.3, 0.9, ArC*H*), 7.19-7.24 (1H, m, ArC*H*), 7.36 (dd, *J* 7.2, 1.7, ArC*H*). δ_C($CDCl_3$, 100 MHz): 0.35 [Si(*C*H_3)$_3$], 115.4 (Ar*C*H), 121.5 (Ar*C*H), 126.3 (Ar*C*Si), 131.6 (Ar*C*H), 136.2 (Ar*C*H), 161.3 (Ar*C*OH); ν_{max} (film)/cm^{-1} 3560, 2957, 1700, 1587, 1474, 1249. *m/z* (ESI^+) 167 $[M + H]^+$ (12%). Spectral details are in agreement with those reported in the literature.[40]

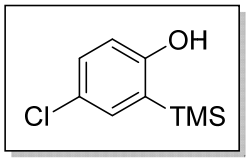
4-Methyl-2-(trimethylsilyl)phenol 76



The title compound was prepared using the procedure described for 2-(trimethylsilyl)phenol **58** using (2-bromo-4-methylphenoxy)trimethylsilane **64** (7.54 g, 29 mmol) in THF (30 mL) and *n*-BuLi (12.8 mL, 2.5M in hexanes, 32 mmol) Following the work-up, the residue obtained was purified by column chromatography on silica gel using hexane:ethyl acetate (95:5) to yield 4-methyl-2-(trimethylsilyl)phenol **76** as a colourless oil (4.01 g, 76%). δ_H($CDCl_3$, 400 MHz): 0.30 [9H, s, Si(C*H*$_3$)$_3$], 2.27 (3H, s, C*H*$_3$), 4.63 (1H, br s, O*H*), 6.56 (1H, d, *J* 8.1, ArC*H*), 7.02 (1H, dd, *J* 8.1, 1.8, ArC*H*), 7.14 (1H, d, *J* 1.8, ArC*H*); δ_C($CDCl_3$, 100 MHz): -0.93 [Si(*C*H$_3$)$_3$], 20.5 (*C*H$_3$), 114.4 (Ar*C*H), 125.1 (Ar*C*Si), 129.4 (Ar*C*CH$_3$), 131.1 (Ar*C*H), 135.7 (Ar*C*H), 158.1 (Ar*C*OH); *m/z* (ESI^-) 179 $[M - H]^-$ (100%), 180 (20); HRMS (ESI^+): exact mass calculated for $C_{10}H_{15}OSi$ $[M - H]^-$ 179.0892. Found 179.0888; ν_{max} (film)/cm^{-1} 3540, 2958, 1486, 1247. Spectral details are in agreement with those reported in the literature.[42]

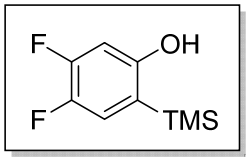
Note: Sample contained 5% starting material and was carried forward to the next step where it was completely removed.

4-Chloro-2-(Trimethylsilyl)phenol 77



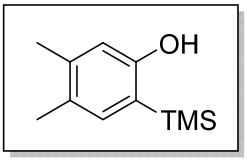
The title compound was prepared using the procedure described for 2-(trimethylsilyl)phenol **58** using (2-bromo-4-chlorophenoxy)trimethylsilane **65** (1.68 g, 6.0 mmol) in THF (20 mL) and *n*-BuLi (2.64 mL, 2.5M in hexanes, 6.6 mmol) Following the work-up, the residue was purified by column chromatography on silica gel using hexane:ethyl acetate (10:1) to yield 4-chloro-2-(trimethylsilyl)phenol **77** as a colourless solid (150 mg, 13%), m.p. 24-26 ºC, (Lit. 25-27 ºC). δ_H($CDCl_3$, 400 MHz): 0.30 [9H, s, Si(CH_3)$_3$], 4.95 (1H, br s, O*H*), 6.61 (1H, d, *J* 8.5, ArC*H*), 7.16 (1H, dd, *J* 8.5, 2.5, ArC*H*), 7.26 (1H, d, *J* 2.5, ArC*H*); δ_C($CDCl_3$, 100 MHz): -1.2 [Si(*C*H_3)$_3$], 115.8 (Ar*C*H), 125.7 (ArCCl), 128.1 (Ar*C*Si), 130.1 (Ar*C*H), 134.7 (Ar*C*H), 158.7 (Ar*C*OH); ν_{max} (KBr)/cm^{-1} 3562, 2957, 1382, 1249; *m/z* (ESI^-) 199 $[M - H]^-$ (60%), 201 (25). Spectral details are in agreement with those reported in the literature.[40]

4,5-Difluoro-2-(trimethylsilyl)phenol 78



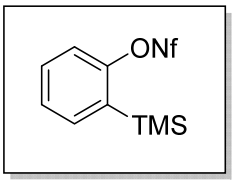
The title compound was prepared using the procedure described for 2-(trimethylsilyl)phenol **58** using (2-bromo-4,5-difluorophenoxy)trimethylsilane **74** (6.7 g, 24 mmol) in THF (20 mL) and *n*-BuLi (10.6 mL, 2.5M in hexanes, 26 mmol). Following the work-up, the residue was purified by column chromatography on silica gel hexane:ethyl acetate (16:1) to provide 4,5-difluoro-2-(trimethylsilyl)phenol **78** as a colourless oil (2.12 g, 44%). δ_H($CDCl_3$, 400 MHz): 0.30 [1H, s, 9H, Si(CH_3)$_3$], 5.56 (1H, br s, O*H*), 6.54 (1H, dd, $^2J_{HF}$ 11.4, $^3J_{HF}$ 5.9, ArC*H*), 7.09 (1H, t, $^2J_{HF}$ 10.1, ArC*H*); δ_C($CDCl_3$, 100 MHz): -1.2 [Si(*C*H_3)$_3$], 104.2 (d, $^2J_{CF}$ 18.9, Ar*C*H), 121.9 (dd, $^3J_{CF}$ 3.8, $^4J_{CF}$ 1.8, Ar*C*Si), 122.6 (dd, $^2J_{CF}$ 16.3, $^3J_{CF}$ 1.5 Ar*C*H), 145.0 (dd. $^1J_{CF}$ 241.2, $^2J_{CF}$ 11.9, Ar*C*F), 150.9 (dd, $^1J_{CF}$ 249.4, $^2J_{CF}$ 14.3, Ar*C*F), 156.2 (dd, $^3J_{CF}$ 8.0, $^4J_{CF}$ 2.0, Ar*C*OH); ν_{max} (film)/cm^{-1} 3603, 3403, 2959, 1614, 1513, 1436; *m/z* (ESI^-) 201 $[M - H]^-$ (100%), 202 (12). Spectral details are in agreement with those reported in the literature.[40]

4,5-Dimethyl-2-(trimethylsilyl)phenol 79



The title compound was prepared using the procedure described for 2-(trimethylsilyl)phenol **58** using (2-bromo-3,4-dimethylphenoxy)trimethylsilane **66** (1.15 g, 4.2 mmol) in THF and *n*-BuLi (1.8 mL, 2.5 M in hexanes, 4.6 mmol). Following the work-up, the residue was purified by column chromatography on silica gel hexane:ethyl acetate (10:1) to yield 4,5-dimethyl-2-(trimethylsilyl)phenol **79** as a colourless oil (0.64 mg, 79%). δ_H($CDCl_3$, 400 MHz): 0.36 [9H, s, Si(C*H*$_3$)$_3$], 2.25 (6H, s, 2 × C*H*$_3$), 5.01 (1H, br s, O*H*) 6.54 (1H, s, ArC*H*), 7.15 (1H, s, ArC*H*); δ_C($CDCl_3$, 100 MHz): -0.86 [Si(C*H*$_3$)$_3$], 18.6 (*C*H$_3$), 19.7 (*C*H$_3$), 115.9 (Ar*C*H), 121.9 (Ar*C*Si), 128.0 (Ar*C*CH$_3$), 136.2 (Ar*C*H), 139.2 (Ar*C*CH$_3$), 158.6 (Ar*C*OH); ν_{max} (film)/cm^{-1} 3521, 2954, 1607, 1498, 1192; *m/z* (ESI$^-$) 193 [M - H]$^-$ (100%), 194 [M]$^+$(20). Spectral details are in agreement with those reported in the literature.[40]

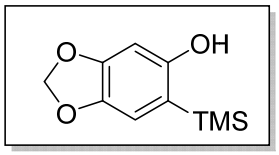
2-(Trimethylsilyl)phenyl nonaflate 72



A mixture of 2-trimethylsilyl phenol **58** (100 mg, 0.6 mmol), NfF (0.43 mL, 2.4 mmol) and NaH (55% in mineral oil, 79 mg, 1.8 mmol) in acetonitrile (6.0 mL) were stirred under a nitrogen atmosphere for 4.5 h at 60 ºC. A saturated aqueous solution of ammonium chloride was added to the mixture to quench and the mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried with $MgSO_4$ and concentrated under reduced pressure. The residue obtained was purified by column chromatography on silica gel using hexane as eluent to provide 2-(trimethylsilyl)phenyl nonaflate **72** as a colourless oil (239 mg, 89%). δ_H($CDCl_3$, 400 MHz): 0.37 [9H, s, Si(C*H*$_3$)$_3$], 7.31-7.37 (2H, s, 2 × ArC*H*), 7.42-7.48 (1H, m, ArC*H*), 7.54 (1H, dd, *J* 7.6, 1.8, ArC*H*); δ_C($CDCl_3$, 100 MHz): -0.9 [Si(*C*H$_3$)$_3$], 119.7 (Ar*C*H), 127.5 (Ar*C*H), 131.3 (Ar*C*H), 132.6 [Ar*C*Si(CH$_3$)$_3$], 136.2 (Ar*C*H), 155.4 (Ar*C*ONf), signals for *C*F$_2$*C*F$_2$*C*F$_2$*C*F$_3$ not visible; *m/z* (ESI$^+$) 448 M$^+$ (12%). Spectral details are in agreement with those reported in the literature.[40]

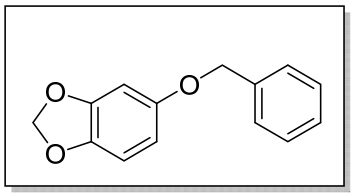
3.3.5 Attempted synthesis of 6-(trimethylsilyl)benzo[d][1,3]dioxol-5-ol

6-(Trimethylsilyl)benzo[d][1,3]dioxol-5-ol 80



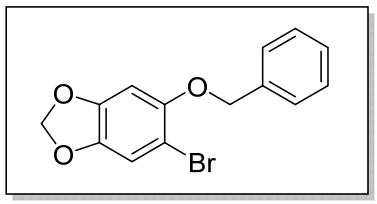
Using the procedure described for 2-(trimethylsilyl)phenol **58**, *n*-BuLi (1.0 mL, 2.5M in hexanes, 2.5 mmol, 1.1 equiv.) was added to {(6-bromobenzo[d][1,3]dioxol-5-yl)oxy}trimethylsilane **68** (665 mg, 2.3 mmol) in THF (10 mL). Following the work-up, purification was attempted using column chromatography on silica gel hexane:ethyl acetate (16:1) but the reaction was deemed unsuccessful and the ^{1}H NMR spectrum showed a complex mixture of unidentifiable material.

5-(Benzyloxy)benzo[d][1,3]dioxole 83



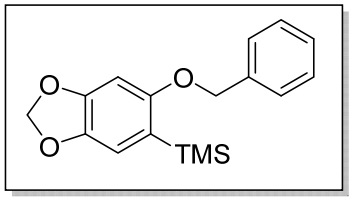
5-Benzodioxolol (200 mg, 1.45 mmol), potassium carbonate (200 mg, 1.45 mmol) and benzylbromide **339** (0.172 mL, 1.45 mmol) were stirred in acetone (50 mL) for 3 h at 60 ºC. The residue was purified using column chromatography in silica gel hexane:ethyl acetate (98:2) to yield 5-(benzyloxy)benzo[d][1,3]dioxole **83** (230 mg, 70%). δ_H($CDCl_3$, 400 MHz): 4.98 (2H, s, C*H*$_2$ benzyl), 5.90 (2H, s, OC*H*$_2$O), 6.39 (1H, dd, *J* 8.5, 2.5, ArC*H*), 6.56 (1H, d, *J* 2.5, ArC*H*), 6.69 (1H, d, *J* 8.5, ArC*H*), 7.28-7.42 (5H, m, 5 × ArC*H* benzyl). Spectral details are in agreement with those reported in the literature.[47]

5-(Benzyloxy)-6-bromobenzo[d][1,3]dioxole 81



The title compound was prepared in the same manner as 6-bromobenzo[*d*][1,3]dioxol-5-ol **60** using *N*-bromosuccinimide **338** (93 mg, 0.52 mmol) in 20 mL acetonitrile and 5-(benzyloxy)benzo[*d*][1,3]dioxole **83** (119 mg, 0.52 mmol) in acetonitrile (20 mL). Following the work-up,5-(benzyloxy)-6-bromobenzo[d][1,3]dioxole **81** was obtained in high purity (159 mg, quantitative). δ_H($CDCl_3$, 400 MHz): 5.06 (1H, s, C*H*$_2$), 5.92 (2H, s, OC*H*$_2$O), 6.56 (1H, s, ArC*H*), 7.00 (1H, s, ArC*H*), 7.27-7.54 (5H, m, 5 × ArC*H* benzyl). Spectral details are in agreement with those reported in the literature.[48]

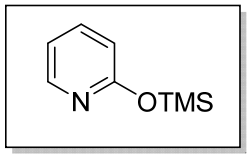
Attempted synthesis of {6-(Benzyloxy)benzo[*d*][1,3]dioxol-5-yl}trimethylsilane 82



n-BuLi (0.31 mL, 2.5M in hexanes, 0.77 mmol) was added to a solution of 5-(benzyloxy)-6-bromobenzo[d][1,3]dioxole (215 mg, 0.7 mmol) **340** in dry THF (5 mL) at -78 ºC. After 15 min trimethylsilylchloride (0.1 mL, 0.77 mmol) was added dropwise. After 5 minutes, the cold bath was removed and the reaction mixture was allowed to warm to room temperature. After 15 minutes, the mixture was quenched with saturated aqueous ammonium chloride (5 mL). The aqueous layer was extracted with Et_2O (3 × 5 mL). The organic layers were combined, dried with $MgSO_4$ andconcentrated under reduced pressure. Following the work-up, purification was attempted with column chromatography on silica gel using hexane:ethyl acetate (10:1) as eluent but the reaction was deemed to be unsuccessful and the ^{1}H NMR spectrum showed a complex mixture of unidentifiable material.[43]

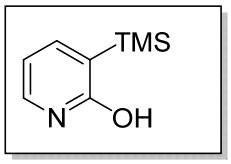
3.3.6 Synthesis of pyridyne precursors

2-[(Trimethylsilyl)oxy]pyridine 90



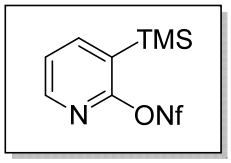
The title compound was prepared using the procedure described for (2-bromophenoxy)trimethylsilane **54** using 2-hydroxypyridine **89** (1.0 g, 10.4 mmol) and HMDS **334** (2.2 ml, 10.4 mmol) in THF (10 mL). Excess NH_3 and unreacted HMDS were removed under reduced pressure to yield 2-[(trimethylsilyl)oxy]pyridine **90** in high purity as a colourless oil (1.75 g, quantitative). δ_H($CDCl_3$, 400 MHz): 0.29 [9H, s, Si(C*H*$_3$)$_3$], 6.61 (1H, d, *J* 8.2, ArC*H*), 6.78 (1H, dd, *J* 6.6, 5.4, ArC*H*), 7.45-7.51 (1H, m, ArC*H*), 8.04 (1H, dd, *J* 4.8, 1.5, ArC*H*); δ_C($CDCl_3$, 100 MHz): 0.46 [Si(*C*H$_3$)$_3$], 112.8 (Ar*C*H), 116.7 (Ar*C*H), 138.8 (Ar*C*H), 147.3 (Ar*C*H), 162.6 [Ar*C*OSi(C*H*$_3$)$_3$]; ν_{max} (film)/cm^{-1} 2964, 1642, 1496, 1274; *m/z* (ESI$^+$) 191 [M + H + Na]$^+$ (26%); Spectral details are in agreement with those reported in the literature.[49]

3-(Trimethylsilyl)pyridin-2-ol 91



A solution of *n*-BuLi (4.2 mL, 2.5M in hexanes, 10.5 mmol) was added to freshly distilled diisopropylamine **341** (1.54 mL, 10.5 mmol) in dry THF (5 mL) at -78 ºC and stirred for 15 mins under a nitrogen atmosphere. A solution of 2-[(trimethylsilyl)oxy]pyridine **90** (1.75 g, 10.4 mmol) in dry THF (10 mL) was added to the flask at -78 ºC and the temperature was then allowed to increase slowly to room temperature. The mixture was poured into a 5% sodium bicarbonate solution (20 mL), extracted with DCM (3 × 20 mL) and dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue obtained was purified by chromatography hexane:ethyl acetate (70:30-50:50) to yield 3-(trimethylsilyl)pyridin-2-ol **91** as a white solid (0.65 g, 37%), m.p. 99-102 ºC, (Lit.[50] 101-102 ºC). δ_H($CDCl_3$, 400 MHz): 0.28 [9H, s, $Si(CH_3)_3$], 6.23 (1H, t, *J* 6.4, ArC*H*), 7.36 (1H, dd, *J* 6.4, 2.2, ArC*H*), 7.55 (1H, dd, *J* 6.4, 2.1, ArC*H*), 13.01 (1H, br s, O*H*); δ_C($CDCl_3$, 100 MHz): -1.8 [$Si(CH_3)_3$], 106.5 (Ar*C*H), 131.5 (Ar*C*Si), 135.6 (Ar*C*H), 147.3 (Ar*C*H), 167.9 (Ar*C*OH); ν_{max} (KBr)/cm^{-1} 3074, 2956, 1630, 1465, 1244; *m/z* (ESI^+) 168 $[M + H]^+$ (100%) 169 (10); HRMS (ESI^+): exact mass calculated for $C_8H_{14}NOSi$ $[M + H]^+$ 168.0845. Found 168.0839. Spectral details are in agreement with those reported in the literature.[50]

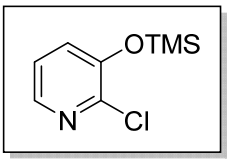
3-(Trimethylsilyl)pyridin-2-yl-nonaflate 92



A mixture of 3-(trimethylsilyl)pyridin-2-ol **91** (60 mg, 0.36 mmol), NfF (0.26 mL, 1.44 mmol) and NaH (55% in mineral oil, 47 mg, 1.1 mmol) in acetonitrile (4.0 mL) were stirred under a nitrogen atmosphere for 6.5 h. A saturated aqueous solution of ammonium chloride was added to the reaction and it was extracted with DCM (3 × 10 mL). The crude product was purified by column chromatography on silica gel using hexane:ethyl acetate (98:2) as eluent to provide 3-(trimethylsilyl)pyridin-2-yl nonaflate **92** as a colourless oil (239 mg, 89%). δ_H($CDCl_3$, 400 MHz): 0.38 [9H, s, $Si(CH_3)_3$], 7.32 (1H, dd, *J* 6.8, 5.1, ArC*H*), 7.93 (1H, d, *J* 7.0, ArC*H*), 8.34 (1H, d, *J* 3.5, ArC*H*); δ_C($CDCl_3$, 100 MHz): -1.2 [$Si(CH_3)_3$], 110.7-119.0 (4C, m, $SO_2CF_2CF_2CF_2CF_3$) 123.7 (Ar*C*H), 125.9 (Ar*C*Si), 147.2 (Ar*C*H), 149.2 (Ar*C*H), 161.3 (Ar*C*ONf); δ_F($CDCl_3$, 376.5 MHz): -125.72 (2F, ddd, *J* 14.5, 6.1, 3.1, CF_2),

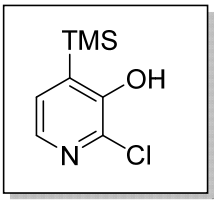
-120.94 (2F, d, *J* 6.5, C*F*$_2$), -107.93 (2F, t, *J* 13.8, C*F*$_2$), -80.70 (3F, t, *J* 9.7, C*F*$_3$); ν_{max} (film)/cm^{-1} 2908, 1571, 1508, 1417; *m/z* (ESI)$^+$ 450 [M + H]$^+$ (20%) 305 (100), 323 (90). HRMS (ESI$^+$): exact mass calculated for $C_{12}H_{13}F_9NO_3SSi$ [M + H]$^+$ 450.0242. Found 450.0234.

2-Chloro-3-[(trimethylsilyl)oxy]pyridine 94



The title compound was prepared using the procedure described for (2-bromophenoxy)trimethylsilane **54** using 2-chloro-3-hydroxypyridine **93** (1.42 g, 11 mmol) and HMDS **334** (1.4 ml, 6.59 mmol) in THF (10 mL). Excess NH_3 and unreacted HMDS were removed under reduced pressure to yield 2-chloro-3-[(trimethylsilyl)oxy]pyridine **94** in high purity as an orange oil (2.22 g, quantitative). δ_H($CDCl_3$, 400 MHz): 0.28 [9H, s, Si(C*H*$_3$)$_3$], 7.10 (1H, dd, *J* 8.2, 4.5, ArC*H*), 7.15 (1H, dd, *J* 7.9, 1.5, ArC*H*), 7.98 (1H, dd, *J* 4.4, 1.5, ArC*H*); δ_C($CDCl_3$, 100 MHz): 0.16 [Si(*C*H$_3$)$_3$], 123.0 (Ar*C*H), 128.1 (Ar*C*H), 141.7 (Ar*C*H), 143.8 (Ar*C*Cl), 147.9 (Ar*C*OSi); *m/z* (ESI$^+$) 202 [M + H]$^+$ (100%) 204 (30); HRMS (ESI$^+$): exact mass calculated for $C_8H_{13}NOSiCl$ [M + H]$^+$ 202.0455. Found 202.0453; ν_{max} (film)/cm^{-1} 1657, 1568, 1312. Spectral details are in agreement with those reported in the literature.[51]

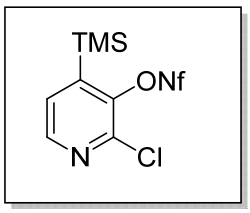
2-Chloro-4-(trimethylsilyl)pyridin-3-ol 95



A solution of *n*-BuLi (4.3 mL, 2.5M in hexanes, 10.7 mmol) was added to freshly distilled diisopropylamine **341** (1.7 mL, 11.6 mmol) in dry THF (5 mL) at -78 ºC and stirred for 15 mins under a nitrogen atmosphere. A solution of 2-chloro-3-[(trimethylsilyl)oxy]pyridine **94** (1.66 g, 10.4 mmol) in dry THF (20 mL) was added to the flask at -78 ºC and the temperature was then allowed to increase slowly to room temperature. The mixture was poured into a 5% sodium bicarbonate solution (20 mL), extracted with DCM (3 × 20 mL), dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue obtained was purified by column chromatography on silica gel using hexane:ethyl acetate (70:30-50:50) as eluent to yield 2-chloro-4-(trimethylsilyl)pyridin-3-ol **95** as a white solid (1.20 g, 56%), m.p. 103-106 ºC, (Lit. 104-106 ºC). δ_H($CDCl_3$, 400

MHz): 0.33 [9H, s, Si(C*H*$_3$)$_3$], 5.79 (1H, br s, O*H*), 7.19 (1H, d, *J* 4.5, ArC*H*), 7.93 (1H, d, *J* 4.5, ArC*H*); δ_C(CDCl$_3$, 100 MHz): -1.4 [Si(*C*H$_3$)$_3$], 129.1 (Ar*C*H), 137.1 (Ar*C*Cl), 137.9 (Ar*C*Si), 140.9 (Ar*C*H), 152.2 (Ar*C*OH); ν_{max} (KBr)/cm^{-1} 3526, 3060, 1572, 1392, 1125; *m/z* (ESI$^+$) 202 [M + H]$^+$ (45%); HRMS (ESI$^+$): exact mass calculated for $C_8H_{13}NOSiCl$ [M + H]$^+$ 202.0455. Found 202.0446. Spectral details are in agreement with those reported in the literature.[51]

2-Chloro-4-(trimethylsilyl)pyridin-3-yl nonaflate 96



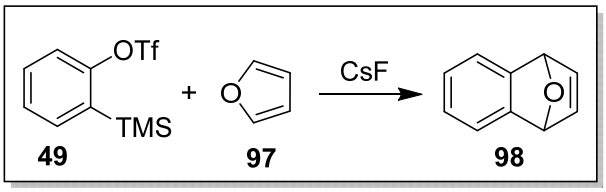
The title compound was prepared using the procedure described for 3-(trimethylsilyl)pyridin-2-yl nonaflate **92** using 2-chloro-4-(trimethylsilyl)pyridin-3-ol **95** (100 mg, 0.5 mmol), NfF (604 mg, 2 mmol) and NaH (55% in mineral oil, 36 mg, 1.5 mmol) in acetonitrile (6 mL) were stirred under a nitrogen atmosphere for 6.5 h. Following the work-up, crude product was purified by column chromatography on silica gel using hexane:ethyl acetate (98:2) as eluent to provide 2-chloro-4-(trimethylsilyl)pyridin-3-yl nonaflate **96** as a colourless oil (220 mg, 91%). δ_H(CDCl$_3$, 400 MHz): 0.43 [9H, s, Si(C*H*$_3$)$_3$], 7.40 (1H, d, *J* 4.6, ArC*H*), 8.36 (1H, d, *J* 4.6, ArC*H*); δ_C(CDCl$_3$, 100 MHz): -0.29 [Si(*C*H$_3$)$_3$], 109.6-118.7 (4C, m, SO$_2$*C*F$_2$*C*F$_2$*C*F$_2$*C*F$_3$), 129.8 (Ar*C*H), 145.2 (Ar*C*Cl), 145.4 (Ar*C*Si), 148.0 (Ar*C*H), 149.0 (Ar*C*ONf); δ_F(CDCl$_3$, 376.5 MHz): -125.7 (2F, ddd, *J* 14.5, 5.9, 3.0, C*F*$_2$), -120.5 (2F, dd, *J* 8.0, 4.5, C*F*$_2$), -107.3 (2F, t, *J* 14.0, C*F*$_2$), -80.7 (3F, t, *J* 9.7, C*F*$_3$); ν_{max} (KBr)/cm^{-1} 2962, 1417, 1357, 1205, 1144; *m/z* (ESI)$^+$ 484 [M + H]$^+$ (80%), 454 (60), 413 (50), 102 (100); HRMS (ESI$^+$): exact mass calculated for $C_{12}H_{11}ClF_9NO_3SSi$ [M + H]$^+$ 483.9852. Found 483.9843.

3.4 Synthesis of 1-acyl-1*H*-indazole compounds Method 1

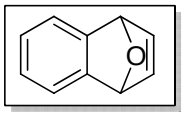
3.4.1 Generation of aryne and trapping with furan

Method 1:

Using 2-(trimethylsilyl)phenyl-trifluoromethanesulfonate[52,53]49



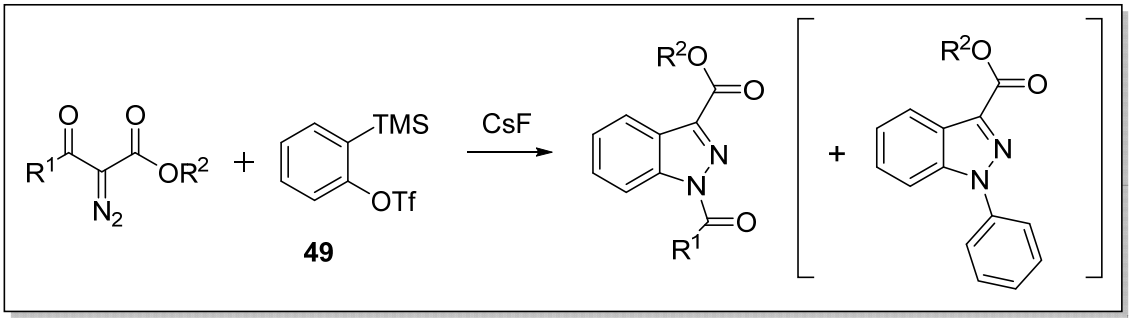
1,4-Dihydro-1,4-epoxynaphthalene 98



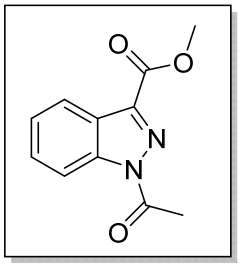
Caesium fluoride (102 mg, 0.68 mmol) was added to 2-(trimethylsilyl)phenyl-trifluoromethanesulfonate **49** (100 mg, 0.34 mmol), furan **97** (18 mg, 0.27 mmol) and acetonitrile (4 mL). The reaction mixture was stirred at reflux for 24 h, under a nitrogen atmosphere. The mixture was diluted with brine (4 mL) and the organic layer was extracted with diethyl ether (3 × 5 mL). The combined organic extracts were dried with $MgSO_4$, concentrated under reduced pressure and purified by column chromatography on silica gel using hexane:ethyl acetate (70:30) as eluent, to yield 1,4-dihydro-1,4-epoxynaphthalene **98** as a white solid (26 mg, 67%), m.p. 53-56 ºC, (Lit.[54] 54-56 ºC). δ_H($CDCl_3$, 400 MHz): 5.71 (2H, s, 2 × C=C*H*), 6.96 [2H, dd, *J* 5.0, 3.0, 2 × C(O)*H*], 7.03 (2H, s, 2 × ArC*H*), 7.25 (2H, dd, *J* 4.8, 2.8, 2 × ArC*H*); δ_C($CDCl_3$, 100 MHz): 82.33 (2 × *C*O), 120.26 (2 × Ar*C*H), 125.00 (2 × Ar*C*H), 143.02 (*C*=*C*), 149.00 (2 × C_q); ν_{max} (KBr)/cm^{-1} 2924, 2342, 1457; *m/z* (ESI^-) 143 $[M - H]^-$ (100%). Spectral details are in agreement with those reported in the literature.[54]

3.4.2 Synthesis of 1-acyl-1*H*-indazole-3-carboxylate compounds

Method 1[52,53]**:**

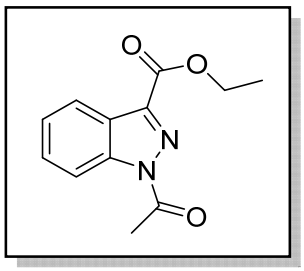


Methyl 1-acetyl-1*H*-indazole-3-carboxylate 104



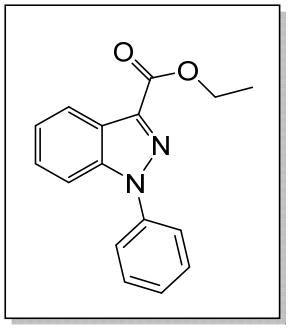
Caesium fluoride (91 mg, 0.6 mmol) was added to a stirred solution of 2-(trimethylsilyl)phenyl-trifluoromethanesulfonate **49** (104 mg, 0.35 mmol), and methyl 2-diazo-3-oxo-butanoate **18** (43 mg, 0.3 mmol) in acetonitrile (4 mL). The reaction was stirred at room temperature under a nitrogen atmosphere for 24 h. The solution obtained was diluted with brine (20 mL) and extracted with ethyl acetate (3 × 20 mL). The residue obtained was purified by column chromatography on silica gel using DCM:ethyl acetate eluent (95:5) to yield methyl 1-acetyl-1*H*-indazole-3-carboxylate **104** as light pink crystals (45 mg, 69%), m.p. 106-109 ºC, (Lit.[55] 111-112 ºC). δ_H($CDCl_3$, 300 MHz): 2.88 [3H, s, C(O)C*H*$_3$], 4.07 (3H, s, OC*H*$_3$), 7.47 (1H, ddd, *J* 8.0, 7.0, 1.0, ArC*H*), 7.61 (1H, ddd, *J* 8.0, 7.0, 1.0, ArC*H*), 8.23 (1H, td, *J* 8.0, 1.0, ArC*H*), 8.47 (1H, td, *J* 8.5, 1.0, ArC*H*). δ_C($CDCl_3$, 100 MHz): 23.1 [C(O)*C*H$_3$], 52.7 (O*C*H$_3$), 115.6 (Ar*C*H), 122.2 (Ar*C*H), 124.7 (Ar*C*$_q$) 125.8 (Ar*C*H), 130.0 (Ar*C*H), 140.3 (*C*=N), 145.5 (Ar*C*N), 162.3 (*C*=O) ester, 171.3 (*C*=O) amide; ν_{max} (KBr)/cm^{-1} 1727, 1505, 1324; *m/z* (ESI$^+$) 219 [M + H]$^+$ (5%), 141 (100); HRMS (ESI)$^+$: Exact mass calculated for $C_{11}H_{11}N_2O_3$ [M + H]$^+$ 219.0770. Found 219.0763. Spectral details are in agreement with those reported in the literature.[55]

Ethyl 1-acetyl-1*H*-indazole-3-carboxylate 99



The title compound was prepared following the procedure described for methyl 1-acetyl-1*H*-indazole-3-carboxylate **104** using caesium fluoride (91 mg, 0.6 mmol), 2-(trimethylsilyl)phenyl-trifluoromethanesulfonate **49** (104 mg, 0.35 mmol) and ethyl 2-diazo-3-oxo-butanoate **19** (47 mg, 0.3 mmol) in acetonitrile (4 mL). Following the work-up, the crude ^{1}H NMR showed the presence of ethyl 1-phenyl-1*H*-indazole-3-carboxylate **117** which could not be separated from ethyl 1-acetyl-1*H*-indazole-3-carboxylate **99** after chromatography. The residue was purified by column chromatography on silica gel using DCM:ethyl acetate eluent (95:5) to yield ethyl 1-acetyl-1*H*-indazole-3-carboxylate **99** and ethyl 1-phenyl-1*H*-indazole-3-carboxylate **117** as a white solid in a 5:1 ratio (65 mg, 91%), m.p. 93-96 ºC, (Lit.[52] 93 ºC). δ_H($CDCl_3$, 400 MHz): 1.49 (3H, t, *J* 7.1, $OCH_2C\mathit{H}_3$), 2.88 [3H, s, C(O)CH_3], 4.56 (2H, q, *J* 7.2, OCH_2CH_3), 7.45 (1H, td, *J* 7.1, 0.9, ArC*H*), 7.60 (1H, td, *J* 8.4, 1.2, ArC*H*,), 8.15 (1H, dt, *J* 8.1, 0.9, ArC*H*), 8.48 (1H, dt, *J* 8.1, 0.9, ArC*H*); δ_C($CDCl_3$, 100 MHz): 14.3 ($CH_2\mathit{C}H_3$), 23.1 [C(O)$\mathit{C}H_3$], 61.9 ($\mathit{C}H_2CH_3$), 115.6 (Ar*C*H), 122.3 (Ar*C*H), 124.7 (ArC_q), 125.7 (Ar*C*H), 129.9 (Ar*C*H), 140.9 (*C*=N), 141.7 (Ar*C*N), 161.8 (*C*=O) ester, 171.5 (*C*=O) ketone; ν_{max} (KBr)/cm^{-1}: 2859, 1726, 1622; HRMS (ESI$^+$): exact mass calculated for $C_{12}H_{13}N_2O_3$ [M + H]$^+$ 233.0926. Found 233.0917. Spectral details are in agreement with those reported in the literature.[52]

Ethyl 1-phenyl-1*H*-indazole-3-carboxylate 117

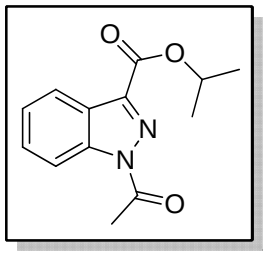


Note: Characteristic signals of the *N*-arylated by-product observed in the ^{1}H NMR spectrum occurred at δ_H(ppm): 7.70-7.79 (3H, m, 3 × ArC*H*) and 8.32 (1H, d, *J* 8.1, ArC*H*).

A sample of ethyl 1-phenyl-1*H*-indazole-3-carboxylate **117** could be isolated after deacylation of ethyl 1-acetyl-1*H*-indazole-3-carboxylate and subsequent purification of the 1-phenyl- and 1-*H*-

derivatives by column chromatography on silica gel. See *N*-Deacylation experimental on page 87 for more information.[52]

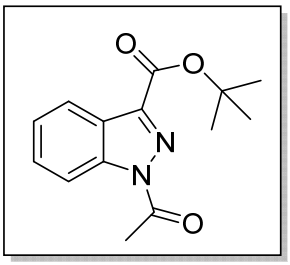
Isopropyl 1-acetyl-1*H*-indazole-3-carboxylate 105



The title compound was prepared following the procedure described for methyl 1-acetyl-1*H*-indazole-3-carboxylate **104** using 2-(trimethylsilyl)phenyl-trifluoromethanesulfonate **49** (104 mg, 0.35 mmol), isopropyl 2-diazo-3-oxo-butanoate **20** (51 mg, 0.3 mmol) in acetonitrile (4 mL) and caesium fluoride (91 mg, 0.6 mmol). Following the work-up, isopropyl 1-acetyl-1*H*-indazole-3-carboxylate **105** was obtained as light pink crystals (68 mg, 92%). δ_H($CDCl_3$, 400 MHz): 1.49 (6H, d, *J* 6.3, 2 × C*H*$_3$), 2.88 [3H, s, C(O)C*H*$_3$], 5.43 (1H, septet, *J* 6.3, C*H*), 7.46 (1H, ddd, *J* 8.1, 7.2, 0.9, ArC*H*), 7.60 (1H, ddd, *J* 8.4, 7.1, 1.2, ArC*H*), 8.19 (1H, td, *J* 8.1, 1.0, ArC*H*), 8.46 (1H, dd, *J* 4.7, 3.8, ArC*H*). δ_C($CDCl_3$, 100 MHz): 22.9 (2 × *C*H_3), 24.0 [C(O)*C*H_3], 70.6 (O*C*H), 116.4 (Ar*C*H), 123.1 (Ar*C*H), 125.4 (ArC_q), 126.5 (Ar*C*H), 130.7 (Ar*C*H), 141.1 (*C*=N), 142.1 (Ar*C*N), 160.8 (*C*=O) ester, 171.6 (*C*=O) amide; ν_{max} (KBr)/cm^{-1} 1716, 1644, 1378; HRMS $(ESI)^+$: Exact mass calculated for $C_{13}H_{15}N_2O_3$ $[M + H]^+$ 247.1083. Found 247.1071; (Found C, 63.5; H, 5.71; N 10.91. $C_{14}H_{16}O_3N_2$ requires C, 63.4; H, 5.73; N, 11.38%).

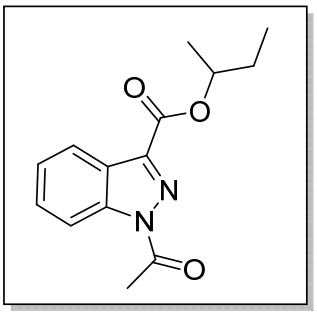
Note: 4% of the *N*-arylated by-product was observed in the ^{1}H NMR spectrum which could not be separated from the 1-acyl compound after column chromatography on silica gel.

_t_-Butyl 1-acetyl-1*H*-indazole-3-carboxylate 106



The title compound was prepared following the procedure described for methyl 1-acetyl-1*H*-indazole-3-carboxylate **104** using 2-(trimethylsilyl)phenyl-trifluoromethanesulfonate **49** (100 mg, 0.34 mmol), *t*-butyl 2-diazo-3-oxo-butanoate **21** (66 mg, 0.36 mmol, 1.1 equiv.) in acetonitrile (4 mL) and caesium fluoride (91 mg, 0.6 mmol). The reaction was stirred at room temperature under a nitrogen atmosphere for 24 h. Following the work-up, *t*-butyl 1-acetyl-1*H*-indazole-3-carboxylate **106** was obtained as light pink crystals (75.7 mg, 97%). δ_H($CDCl_3$, 300 MHz): 1.72 (9H, s, 3 × C*H*$_3$ of *t*-butyl), 2.87 [3H, s, C(O)C*H*$_3$], 7.44 (1H, ddd, *J* 8.1, 7.2, 0.9, ArC*H*), 7.59 (1H, ddd, *J* 8.4, 7.1, 1.2, ArC*H*), 8.15 (1H, td, *J* 8.1, 1.0, ArC*H*), 8.47 (1H, td, *J* 8.5, 0.8, ArC*H*); δ_C($CDCl_3$, 100 MHz): 23.1 [C(O)*C*H$_3$], 28.3 (3 × *C*H$_3$ of *t*-butyl), 83.3 [*C*(CH$_3$)$_3$], 115.5 (Ar*C*H), 122.3 (Ar*C*H), 124.5 (ArC_q), 125.5 (Ar*C*H), 129.7 (Ar*C*H), 140.4 (*C*=N), 142.1 (Ar*C*N), 160.8 (*C*=O) ester, 171.6 (*C*=O) amide; ν_{max} (KBr)/cm^{-1} 1713, 1501 1141; HRMS (ESI)$^+$: Exact mass calculated for $C_{14}H_{17}N_2O_3$ $[M + H]^+$ 261.1239. Found 261.1232.

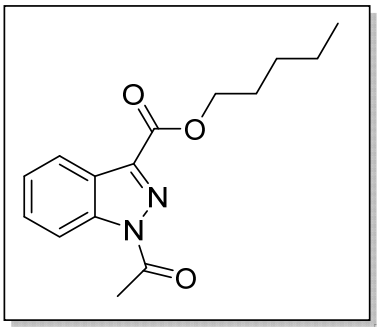
sec-Butyl 1-acetyl-1*H*-indazole-3-carboxylate 107



The title compound was prepared following the procedure described for methyl 1-acetyl-1*H*-indazole-3-carboxylate **104** using 2-(trimethylsilyl)phenyl-trifluoromethanesulfonate **49** (100 mg, 0.34 mmol), *sec*-butyl 2-diazo-3-oxobutanoate **32** (66 mg, 0.36 mmol, 1.1 equiv.) in acetonitrile (4 mL) and caesium fluoride (91 mg, 0.6 mmol). Following the work-up, the residue was purified by column chromatography on silica gel using DCM:ethyl acetate eluent (95:5) to yield pure *sec*-butyl 1-acetyl-1*H*-indazole-3-carboxylate **107** as a yellow oil. (57 mg, 73%). δ_H($CDCl_3$, 400 MHz): 1.04 (3H, t, , *J* 7.5, C*H*$_3$), 1.46 (3H, d, *J* 6.3, C*H*$_3$), 1.74-1.94 (2H, m, C*H*$_2$), 2.88 [3H, s, C(O)C*H*$_3$], 5.24-5.32 (1H, m, OC*H*), 7.43-7.48 (1H, m, ArC*H*), 7.57-7.63 (1H, m, ArC*H*), 8.19 (1H, d, *J* 8.1, ArC*H*),

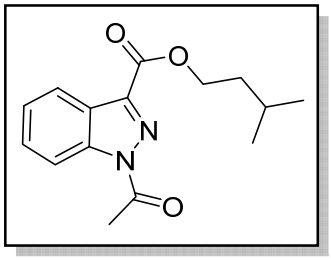
8.47 (1H, d, *J* 8.5, ArC*H*); δ_C(CDCl$_3$, 100 MHz): 9.8 (CH_2CH_3), 19.6 ($CHCH_3$), 23.1 [C(O)CH_3], 28.9 (CH_2), 74.3 (O*C*H), 115.6 (Ar*C*H), 122.2 (Ar*C*H), 124.6 (ArC_q), 125.6 (Ar*C*H), 129.8 (Ar*C*H), 140.3 (*C*=N), 141.2 (Ar*C*N), 161.5 (*C*=O) ester, 171.6 (*C*=O) amide; ν_{max} (film)/cm^{-1} 1732, 1501, 1194; HRMS (ESI$^+$): exact mass calculated for $C_{14}H_{17}N_2O_3$ $[M + H]^+$ 261.1239. Found 261.1237.

Pentyl 1-acetyl-1*H*-indazole-3-carboxylate 108



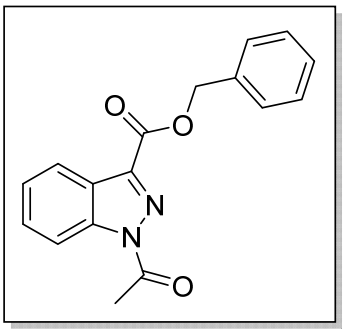
The title compound was prepared following the procedure described for methyl 1-acetyl-1*H*-indazole-3-carboxylate **104** using 2-(trimethylsilyl)phenyl-trifluoromethanesulfonate **49** (100 mg, 0.34 mmol), pentyl 2-diazo-3-oxo-butanoate **23** (71 mg, 0.36 mmol, 1.1 equiv.) in acetonitrile (4 mL) and caesium fluoride (91 mg, 0.6 mmol) was added. The reaction was stirred at room temperature under a nitrogen atmosphere for 24 h. Following the work-up, the residue was purified by column chromatography on silica gel using DCM:ethyl acetate eluent (95:5) and to yield pentyl 1-acetyl-1*H*-indazole-3-carboxylate **108** (65 mg, 79%) as a yellow oil. δ_H(CDCl$_3$, 400 MHz): 0.93 (3H, t, *J* 7.1, CH_2CH_3), 1.36-1.48 (4H, m, 2 × CH_2), 1.85-1.92 (2H, m, CH_2), 2.88 (3H, s, C(O)CH_3), 4.50 (2H, t, *J* 6.8, OCH_2), 7.44-7.49 (1H, m, ArC*H*), 7.55-7.65 (1H, ddd, *J* 8.4, 7.1, 1.1, ArC*H*), 8.20 (1H, d, *J* 8.1, ArC*H*), 8.47 (1H, d, *J* 8.5, ArC*H*); δ_C(CDCl$_3$, 100 MHz): 14.0 (CH_3), 22.3 (CH_2), 23.1 [C(O)CH_3], 28.1 (CH_2), 28.3 (CH_2), 66.0 (OCH_2), 115.6 (Ar*C*H), 122.2 (Ar*C*H), 124.6 (ArC_q), 125.7 (Ar*C*H), 129.9 (Ar*C*H), 140.3 (*C*=N), 140.9 (Ar*C*N), 161.9 (*C*=O) ester, 171.6 (*C*=O) amide; ν_{max} (film)/cm^{-1} 1722, 1644; HRMS (ESI$^+$): exact mass calculated for $C_{15}H_{19}N_2O_3$ $[M + H]^+$ 273.1396. Found 273.1388; (Found C, 65.77; H, 6.67; N 8.14. $C_{15}H_{18}O_3N_2$ requires C, 65.68; H, 6.61; N, 10.21%).

Isopentyl-1*H*-indazole-3-carboxylate 109



The title compound was prepared following the procedure described for methyl 1-acetyl-1*H*-indazole-3-carboxylate **104** using 2-(trimethylsilyl)phenyl-trifluoromethanesulfonate **49** (100 mg, 0.34 mmol), isopentyl 2-diazo-3-oxo-butanoate **24** (71 mg, 0.36 mmol, 1.1 equiv.) in acetonitrile (4 mL) and caesium fluoride (91 mg, 0.6 mmol). The reaction was stirred at room temperature under a nitrogen atmosphere for 24 h. Following the work-up, the residue was purified by column chromatography on silica gel using DCM: ethyl acetate eluent (95:5) and isopentyl-1*H*-indazole-3-carboxylate **109** was obtained as light pink crystals (62 mg, 76%). δ_H($CDCl_3$, 400 MHz): 1.00 (6H, d, *J* 6.4, 2 × C*H*$_3$), 1.70-1.89 [3H, m, containing OCH_2CH_2 and $CH(CH_3)_2$], 2.87 [3H, s, C(O)C*H*$_3$], 4.53 (2H, t, *J* 6.8, OC*H*$_2$), 7.46 (1H, ddd, *J* 8.1, 0.9, ArC*H*), 7.60 (1H, ddd, *J* 7.1, 1.2, ArC*H*), 8.20 (1H, td, *J* 8.1, 1.0, ArC*H*), 8.47 (1H, td, *J* 8.5, 0.9, ArC*H*); δ_C($CDCl_3$, 100 MHz): 22.5 (2 × *C*H$_3$), 23.1 (*C*H), 25.3 [C(O)*C*H$_3$], 37.3 (*C*H$_2$), 64.6 (O*C*H$_2$), 115.6 (Ar*C*H), 122.2 (Ar*C*H), 124.6 (Ar*C*$_q$), 125.7 (Ar*C*H), 129.9 (Ar*C*H), 140.3 (*C*=N), 140.8 (Ar*C*N), 161.9 (*C*=O) ester, 171.5 (*C*=O) amide; ν_{max} (KBr)/cm^{-1} 2959, 1722, 1646, 1124; *m/z* (ESI$^+$) 274 [M]$^+$; HRMS (ESI)$^+$: Exact mass calculated for $C_{15}H_{19}N_2O_3$ [M + H]$^+$ 275.1396. Found 275.1388.

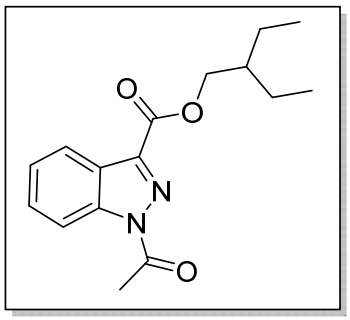
Benzyl 1-acetyl-1*H*-indazole-3-carboxylate 110



The title compound was prepared following the procedure described for methyl 1-acetyl-1*H*-indazole-3-carboxylate **104** using 2-(trimethylsilyl)phenyl-trifluoromethanesulfonate **49** (100 mg, 0.34 mmol), benzyl 2-diazo-3-oxo-butanoate **22** (68 mg, 0.36 mmol, 1.1 equiv.) in acetonitrile (4 mL) and caesium fluoride (91 mg, 0.6 mmol). The reaction was stirred at room temperature under a nitrogen atmosphere for 24 h. Following the work-up, the residue was purified by column chromatography on silica gel using

DCM:ethyl acetate eluent (95:5) to yield benzyl-1*H*-indazole-3-carboxylate **110** as light pink crystals (64.7 mg, 73%). δ_H($CDCl_3$, 400 MHz): 2.88 (3H, s, C(O)C*H*$_3$), 5.53 (2H, s, OC*H*$_2$C$_6$H$_5$), 7.34-7.46 (4H, m, 3 × ArC*H* benzyl and 1 × ArC*H* indazole), 7.51-7.55 (2H, m, 2 × ArC*H* benzyl), 7.60 (1H, ddd, *J* 8.4, 7.1, 1.1, ArC*H*), 8.18 (1H, d, *J* 8.1, ArC*H*), 8.47 (1H, d, *J* 8.48, ArC*H*); δ_C($CDCl_3$, 100 MHz): 23.1 [C(O)*C*H$_3$], 67.4 (O*C*H$_2$C$_6$H$_5$), 115.6 (Ar*C*H indazole), 122.2 (Ar*C*H indazole), 123.8 (Ar*C*$_q$ benzyl), 123.9 (Ar*C*$_q$ indazole), 125.8 (Ar*C*H indazole), 128.6 (2 × Ar*C*H benzyl), 128.6 (Ar*C*H benzyl), 128.8 (2 × Ar*C*H benzyl), 129.9 (Ar*C*H indazole), 135.3 (*C*$_q$ benzyl), 140.3 (*C*=N), 140.5 (Ar*C*N), 161.7 (*C*=O) ester, 171.5 (*C*=O) amide; ν_{max} (KBr)/cm^{-1} 1718, 1646, 1498, 1324; HRMS (ESI)$^+$: Exact mass calculated for $C_{17}H_{15}N_2O_3$ $[M + H]^+$ 295.1083. Found 295.1082.

2-Ethylbutyl 1-acetyl-1*H*-indazole-3-carboxylate 111

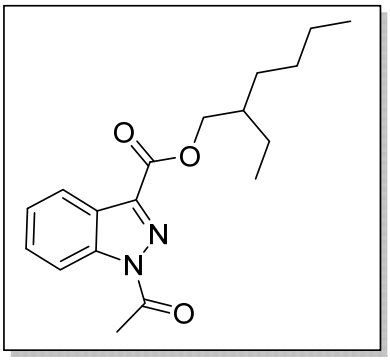


The title compound was prepared following the procedure described for methyl 1-acetyl-1*H*-indazole-3-carboxylate **104** using 2-(trimethylsilyl)phenyl-trifluoromethanesulfonate **49** (104 mg, 0.35 mmol), 2-ethylbutyl 2-diazo-3oxobutanoate **30** (0.0636 g, 0.3 mmol) in acetonitrile (4 mL) and caesium fluoride (91 mg, 0.6 mmol). Following the work-up, the residue was purified by column chromatography on silica gel using DCM:ethyl acetate eluent (95:5) to yield 2-ethylbutyl 1-acetyl-1*H*-indazole-3-carboxylate **111** as a yellow oil (58.8 mg, 68%). δ_H($CDCl_3$, 400 MHz): 0.99 (6H, t, *J* 7.5, 2 × C*H*$_3$), 1.46-1.57 (4H, m, 2 × C*H*$_2$), 1.78 (td, *J* 12.5, 6.2, C*H*), 2.87 [3H, s, C(O)C*H*$_3$], 4.44 (2H, d, *J* 5.8, OC*H*$_2$), 7.46 (1H, ddd, *J* 8.1, 7.1, 1.0, ArC*H*), 7.60 (1H, ddd, *J* 8.4, 7.1, 1.2, ArC*H*), 8.18 (1H, td, *J* 8.1, 1.0, ArC*H*), 8.47 (1H, td, *J* 8.5, 0.9, ArC*H*); δ_C($CDCl_3$, 100 MHz): 11.1 (2 × *C*H$_3$), 23.1 [C(O)*C*H$_3$], 23.5 (2 × *C*H$_2$), 40.5 (*C*H), 67.8 (O*C*H$_2$), 115.6 (Ar*C*H), 122.1 (Ar*C*H), 124.6 (Ar*C*$_q$), 125.7 (Ar*C*H), 129.8 (Ar*C*H), 140.3 (*C*=N), 140.9 (Ar*C*N), 162.0 (*C*=O) ester, 171.5 (*C*=O) amide; ν_{max} (film)/cm^{-1} 2964, 1733, 1500, 1325; *m/z* (ESI$^-$) 245

[M - $COCH_3$]$^-$ (60%), 262 (100), 263 (12), 246 (10); HRMS (ESI^+): exact mass calculated for $C_{16}H_{21}N_2O_3$ [M + H]$^+$ 289.1552. Found 289.1548.

Note: 4% of the *N*-arylated by-product was observed in the ^1H NMR spectrum which could not be separated from the 1-acyl compound after column chromatography on silica gel.

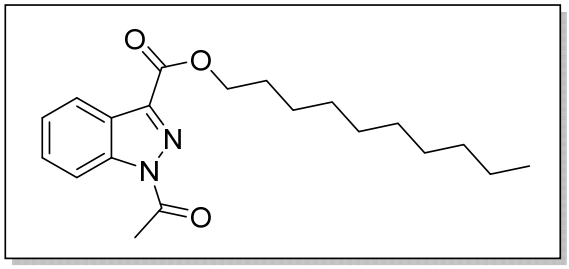
2-Ethylhexyl 1-acetyl-1*H*-indazole-3-carboxylate 112



The title compound was prepared following the procedure described for methyl 1-acetyl-1*H*-indazole-3-carboxylate **104** using 2-(trimethylsilyl)phenyl-trifluoromethanesulfonate **49** (104 mg, 0.35 mmol), 2-ethylhexyl 2-diazo-3-oxobutanoate **28** (0.072 g, 0.3 mmol) in acetonitrile (4 mL) and caesium fluoride (91 mg, 0.6 mmol). Following the work-up, the residue was purified by column chromatography on silica gel using DCM:ethyl acetate eluent (95:5) to yield 2-ethylhexyl 1-acetyl-1*H*-indazole-3-carboxylate **112** as a yellow oil (63.6 mg, 67%). δ_H($CDCl_3$, 400 MHz): 0.88-1.03 [6H, m, containing 0.91 (3H, t, *J* 7.1, C*H*$_3$) and 0.99 (3H, t, *J* 7.5, C*H*$_3$)], 1.21-1.56 (8H, m, 4 × C*H*$_2$), 1.83 (1H, td, *J* 12.3, 6.1, C*H*), 2.87 [3H, s, C(O)C*H*$_3$], 4.42 (2H, d, *J* 5.8, OC*H*$_2$), 7.46 (1H, ddd, *J* 8.1, 7.1, 0.9, ArC*H*), 7.62 (1H, ddd, *J* 8.4, 7.1, 1.1, ArC*H*), 8.17-8.21 (1H, m, ArC*H*), 8.47 (1H, td, *J* 8.5, 0.8, ArC*H*); δ_C($CDCl_3$, 100 MHz): 11.1 (*C*H$_3$), 14.0 (*C*H$_3$), 23.0 (*C*H$_2$), 23.0 [C(O)*C*H$_3$], 24.0 (*C*H$_2$), 29.0 (*C*H$_2$), 30.6 (*C*H$_2$), 38.9 (*C*H), 68.2 (O*C*H$_2$), 115.6 (Ar*C*H), 122.1 (Ar*C*H), 124.6 (ArC_q), 125.7 (Ar*C*H), 129.8 (Ar*C*H), 140.3 (*C*=N), 140.9 (Ar*C*N), 162.0 (*C*=O) ester, 171.5 (*C*=O) amide. ν_{max} (film)/cm^{-1} 2955, 1735, 1730, 1670, 1254; *m/z* (ESI^-) 316 [M]$^+$ (18%), 113 (100). HRMS (ESI^+): exact mass calculated for $C_{18}H_{25}N_2O_3$ [M + H]$^+$ 317.1865. Found 317.1855.

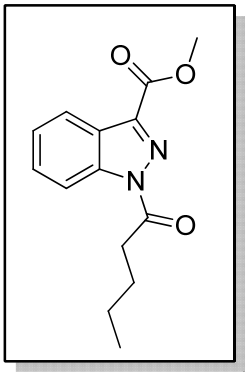
Note: 8% of the *N*-arylated by-product was observed in the ^{1}H NMR spectrum which could not be separated from the 1-acyl compound after column chromatography on silica gel.

Decyl 1-acetyl-1*H*-indazole-3-carboxylate 113



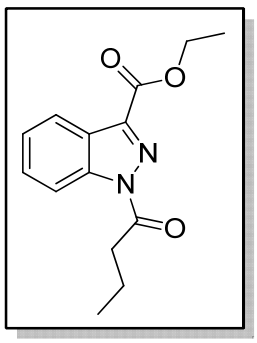
The title compound was prepared following the procedure described for methyl 1-acetyl-1*H*-indazole-3-carboxylate **104** using 2-(trimethylsilyl)phenyltrifluoromethanesulfonate **49** (100 mg, 0.34 mmol), decyl 2-diazo-3-oxobutanoate **29** (67 mg, 0.34 mmol) in acetonitrile (4 mL) and caesium fluoride (91 mg, 0.6 mmol). The reaction was stirred at room temperature under a nitrogen atmosphere for 24 h. Following the work-up, the residue was purified by column chromatography on silica gel using DCM:ethyl acetate eluent (95:5) to yield decyl 1-acetyl-1*H*-indazole-3-carboxylate **113** as light pink crystals (89 mg, 86%), m.p. 47-49 ºC. δ_H($CDCl_3$, 400 MHz): 0.93 (3H, t, *J* 6.7, C*H*$_3$), 1.20-1.47 (14H, m, 7 × C*H*$_2$), 1.84-1.91 (2H, m, OCH$_2$C*H*$_2$), 2.88 [3H, s, C(O)C*H*$_3$], 4.49 (2H, t, *J* 6.9, OC*H*$_2$), 7.43 (1H, t, *J* 8.3, ArC*H*), 7.60 (1H, t, *J* 8.3, ArC*H*), 8.20 (1H, d, *J* 8.3, ArC*H*), 8.47 (1H, d, *J* 8.3, ArC*H*); δ_C($CDCl_3$, 100 MHz): 14.1 (CH$_2$C*H*$_3$), 22.7 [C(O)*C*H$_3$], 23.1 (C*H*$_2$), 25.9 (C*H*$_2$), 28.7 (C*H*$_2$), 29.2 (C*H*$_2$), 29.3 (C*H*$_2$), 29.5 (2 × C*H*$_2$), 31.9 (OCH$_2$*C*H$_2$), 65.9 (OC*H*$_2$), 115.6 (Ar*C*H), 122.2 (Ar*C*H), 124.7 (*C*$_q$), 125.7 (Ar*C*H), 129.8 (Ar*C*H), 140.3 (*C*=N), 140.9 (Ar*C*N), 161.9 (*C*=O) ester, 171.5 (*C*=O) amide; *m/z* (ESI$^+$) 345 [M + H]$^+$ (38%), 346 (10), 42 (100). Exact mass calculated for $C_{20}H_{29}N_2O_3$ [M + H]$^+$ 345.2178. Found 345.2179; ν_{max} (KBr)/cm^{-1} 2926, 1736, 1501, 1195; (Found: C, 70.61; H, 8.36; N, 7.65. $C_{20}H_{28}N_2O_3$ requires C, 69.74; H, 8.19; N, 8.13%).

Methyl 1-pentanoyl-1*H*-indazole-3-carboxylate 118



The title compound was prepared following the procedure described for methyl 1-acetyl-1*H*-indazole-3-carboxylate **104** using 2-(trimethylsilyl)phenyl-trifluoromethanesulfonate **49** (100 mg, 0.34 mmol), methyl 2-diazo-3-oxoheptanoate **33** (67 mg, 0.36 mmol) in acetonitrile (4 mL) and caesium fluoride (91 mg, 0.6 mmol). The reaction was stirred at room temperature under a nitrogen atmosphere for 24 h. Following the work-up, the residue was purified by column chromatography on silica gel using DCM:ethyl acetate eluent (95:5) to yield methyl 1-pentanoyl-1*H*-indazole-3-carboxylate **118** as light pink crystals (65 mg, 83%). δ_H($CDCl_3$, 400 MHz): 0.99 (3H, t, *J* 7.3, CH_2CH_3), 1.43-1.55 (2H, m, CH_2), 1.79-1.89 (2H, m, CH_2), 3.31 (2H, t, *J* 7.5, $C(O)CH_2$), 4.1 (3H, s, OCH_3), 7.44 (1H, ddd, *J* 8.04, 7.2, 0.9, ArC*H*), 7.59 (1H, ddd, *J* 8.4, 7.1, 1.2, ArC*H*), 8.22 (1H, td, *J* 8.1, 1.0, 1.0, ArC*H*), 8.46 (1H, td, *J* 8.5, 0.8, 0.8, ArC*H*); δ_C($CDCl_3$, 100 MHz): 14.7 (CH_3), 23.1 (CH_2CH_3), 27.2 ($CH_2CH_2CH_3$), 35.5 [$C(O)CH_2$], 53.4 (OCH_3), 116.4 (ArCH), 123.0 (ArCH), 125.5 (ArC_q), 126.5 (ArCH), 130.7 (ArCH), 141.1 (C=N), 141.2 (ArCN), 163.1 (C=O) ester, 175.1 (C=O) amide; ν_{max} (KBr)/cm^{-1} 1722, 1645; *m/z* (ESI^+) 261 [M + H]$^+$ (60%), 262 (8), 177 (100); HRMS $(ESI)^+$: Exact mass calculated for $C_{14}H_{17}N_2O_3$ [M + H]$^+$, 261.1239. Found 261.1229; (Found: C, 64.93; H, 6.36; N, 10.45. $C_{14}H_{16}N_2O_3$ requires C, 64.60; H, 6.2; N, 10.76%).

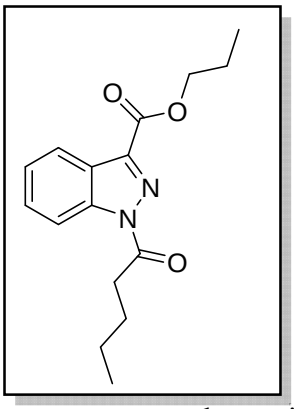
Ethyl 1-butyryl-1*H*-indazole-3-carboxylate 119



The title compound was prepared following the procedure described for methyl 1-acetyl-1*H*-indazole-3-carboxylate **104** using 2-(trimethylsilyl)phenyl-trifluoromethanesulfonate **49** (100 mg, 0.34 mmol), ethyl 2-diazo-3-oxohexanoate **34**, (67 mg, 0.36 mmol) in acetonitrile (4 mL) and caesium fluoride (91 mg, 0.6 mmol). The reaction was stirred at room temperature under a nitrogen atmosphere for 24 h. Following the work-up, the residue was purified by column chromatography

on silica gel using DCM:ethyl acetate eluent (95:5) to yield ethyl 1-butyryl-1*H*-indazole-3-carboxylate **119** as light pink crystals (72 mg, 92%). δ_H($CDCl_3$, 400 MHz): 1.08 (3H, t, *J* 7.4, CH_2CH_3), 1.51 (3H, t, *J* 7.1, OCH_2CH_3), 1.84-1.94 (2H, m, $CH_2CH_2CH_3$), 3.30 (2H, t, *J* 7.4, C(O)CH_2), 4.56 (2H, q, *J* 7.1, OCH_2CH_3), 7.42-7.47 (1H, m, ArC*H*), 7.59 (1H, ddd, *J* 8.4, 7.1, 1.1, ArC*H*), 8.21 (1H, d, *J* 8.1, ArC*H*), 8.48 (1H, d, *J* 8.5, ArC*H*); δ_C($CDCl_3$, 100 MHz): 14.3 ($CH_3CH_2CH_2$), 14.5 (CH_3CH_2O), 17.8 ($CH_3CH_2CH_2$), 36.7 [$CH_3CH_2CH_2C(O)$], 61.8 (OCH_2CH_3), 115.5 (ArCH), 122.2 (ArCH), 124.0 (ArC_q), 125.6 (ArCH), 129.8 (ArCH, 140.4 (C=N), 140.6 (ArCN), 161.9 (C=O) ester, 174.2 (C=O) amide; ν_{max} (KBr)/cm^{-1} 1652, 1646, 1373; *m/z* (ESI^+) 261 $[M + H]^+$ (100%), 191 (100); HRMS $(ESI)^+$: Exact mass calculated for $C_{14}H_{17}N_2O_3$ $[M + H]^+$ 261.1239. Found 261.1237.

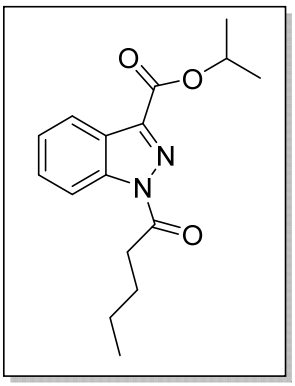
Propyl 1-pentanoyl-1*H*-indazole-3-carboxylate 120



The title compound was prepared following the procedure described for methyl 1-acetyl-1*H*-indazole-3-carboxylate **104** using 2-(trimethylsilyl)phenyl-trifluoromethanesulfonate **49** (100 mg, 0.34 mmol), propyl 2-diazo-3-oxoheptanoate butanoate **35** (67 mg, 0.36 mmol) in acetonitrile (4 mL) and caesium fluoride (91 mg, 0.6 mmol). The reaction was stirred at room temperature under a nitrogen atmosphere for 24 h. Following the work-up, the crude residue was purified by column chromatography on silica gel using DCM:ethyl acetate eluent (95:5) to isolate propyl 1-pentanoyl-1*H*-indazole-3-carboxylate **120** as a yellow solid (58 mg, 67%) m.p. 40-42 °C. δ_H($CDCl_3$, 400 MHz): 0.99 (3H, t, *J* 7.3, CH_3), 1.09 (3H, t, *J* 7.4, CH_3), 1.44-1.52 (2H, m, CH_2), 1.58-1.84 (4H, m, 2 × CH_2), 3.32 [2H, t, *J* 7.8, C(O)CH_2], 4.46 (2H, t, *J* 6.7, OCH_2), 7.45 (1H, t, *J* 8.0, ArC*H*), 7.59 (1H, t, *J* 8.0, ArC*H*), 8.19 (1H, d, *J* 8.0, ArC*H*), 8.48 (1H, d, *J* 8.0, ArC*H*); δ_C($CDCl_3$, 100 MHz): 10.5 (CH_3 ester), 13.9 (CH_3) amide, 22.1 (CH_2), 22.3 (CH_2), 26.5 (CH_2), 34.7 (CH_2), 67.3 (OCH_2), 115.6 (ArCH), 122.1 (ArCH), 124.6 (ArC_q), 125.6 (ArCH), 129.8 (ArCH), 140.4 (C=N),

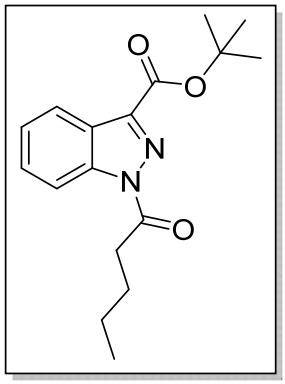
140.6 (Ar*C*N), 162.0 (*C*=O) ester, 174.4 (*C*=O) amide; ν_{max} (KBr)/cm^{-1} 2919, 1734, 1718, 1507; *m/z* (ESI$^+$) 289 [M + H]$^+$ (100%), 290 (42), 287 (10); HRMS (ESI)$^+$: Exact mass calculated for $C_{16}H_{21}N_2O_3$ [M + H]$^+$ 289.1552; Found 289.1546; (Found: C, 66.65; H, 6.99; N, 9.72. $C_{16}H_{20}N_2O_3$ requires C, 66.65; H, 6.99; N, 9.52%).

Isopropyl 1-pentanoyl-1*H*-indazole-3-carboxylate 121



The title compound was prepared following the procedure described for methyl 1-acetyl-1*H*-indazole-3-carboxylate **104** using 2-(trimethylsilyl)phenyl-trifluoromethanesulfonate **49** (100 mg, 0.34 mmol), isopropyl 2-diazo-3-oxoheptanoate **36** (67 mg, 0.36 mmol) in acetonitrile (4 mL) and caesium fluoride (91 mg, 0.6 mmol). The reaction was stirred at room temperature under a nitrogen atmosphere for 24 h. Following the work-up, the crude residue was purified by column chromatography on silica gel using DCM:ethyl acetate eluent (95:5) to isolate isopropyl 1-pentanoyl-1*H*-indazole-3-carboxylate **121** as a yellow oil (55.4 mg, 64%). δ_H($CDCl_3$, 400 MHz): 0.99 (3H, t, *J* 7.3, C*H*$_3$), 1.44-1.56 (8H, m, *J* 6.3, 2 × CH_3 and CH_2), 1.84 (2H, td, *J* 15.1, 7.5, C*H*$_2$), 3.32 (2H, t, *J* 7.5, C*H*$_2$), 5.42 (1H, sept, *J* 6.3, C*H* of isopropyl), 7.42-7.47 (1H, m, ArC*H*), 7.59 (1H, ddd, *J* 8.4, 7.1, 1.1, ArC*H*), 8.18 (1H, d, *J* 8.1, ArC*H*), 8.48 (1H, d, *J* 8.5, ArC*H*); δ_C($CDCl_3$, 100 MHz): 13.9 (*C*H$_3$), 22.2 (2 × *C*H$_3$), 22.3 (*C*H$_2$), 26.4 (*C*H$_2$), 34.6 (*C*H$_2$), 69.7 [*C*H(CH$_3$)$_2$], 115.5 (Ar*C*H), 122.2 (Ar*C*H), 124.5 (Ar*C*$_q$), 125.5 (Ar*C*H), 129.7 (Ar*C*H), 140.4 (*C*=N), 141.0 (Ar*C*N), 161.4 (*C*=O) ester, 174.4 (*C*=O) amide. ν_{max} (film)/cm^{-1} 2934, 2131, 1777, 1728, 1693, 1163; *m/z* (ESI$^+$) 289 [M + H]$^+$ (10%), 493 (100); HRMS (ESI$^+$): exact mass calculated for $C_{16}H_{21}O_3N_2$ [M + H]$^+$ 289.1552. Found 289.1542; (Found: C, 67.07; H, 7.18. $C_{16}H_{20}N_2O_3$ requires C, 66.65; H, 6.99%).

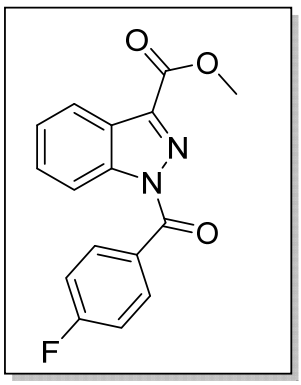
_t_-Butyl 1-pentanoyl-1*H*-indazole-3-carboxylate 122



The title compound was prepared following the procedure described for methyl 1-acetyl-1*H*-indazole-3-carboxylate **104** using 2-(trimethylsilyl)phenyl-trifluoromethanesulfonate **49** (100 mg, 0.34 mmol), *t*-butyl 2-diazo-3-oxoheptanoate **37** (67 mg, 0.36 mmol) in acetonitrile (4 mL) and caesium fluoride **(**91 mg, 0.6 mmol). The reaction was stirred at room temperature under a nitrogen atmosphere for 24 h. Following the work-up, the residue was purified by column chromatography on silica gel using DCM:ethyl acetate eluent (95:5) to yield *t*-butyl 1-pentanoyl-1*H*-indazole-3-carboxylate **122** as light pink crystals (41 mg, 72%). δ_H($CDCl_3$, 400 MHz): 0.99 (3H, t, C*H*$_3$, *J* 7.3), 1.42-1.55 (2H, m, C*H*$_2$), 1.72 (9H, s, 3 × C*H*$_3$), 1.83 (2H, ddd, C*H*$_2$, *J* 13.2, 8.5, 6.5), 3.32 [2H, t, *J* 7.5, C(O)C*H*$_2$], 7.44 (1H, ddd, *J* 8.0, 7.2, 0.9, ArC*H*), 7.59 (1H, ddd, *J* 8.4, 7.1, 1.2, ArC*H*), 8.15 (1H, td, *J* 8.1, 0.9, ArC*H*), 8.46 (1H, d, *J* 8.5, ArCH). δ_C($CDCl_3$, 100 MHz): 13.9 (*C*H$_3$), 22.3 (*C*H$_2$), 26.5 (*C*H$_2$), 28.3 (3 × *C*H$_3$), 34.7 [*C*(O)*C*H$_2$], 83.2 [*C*(CH$_3$)$_3$], 115.6 (Ar*C*H), 122.3 (Ar*C*H), 124.0 (Ar*C*$_q$), 125.4 (Ar*C*H), 129.6 (Ar*C*H), 140.5 (*C*=N), 141.9 (Ar*C*N), 165.0 (*C*=O) ester, 174.5 (*C*=O) amide; ν_{max} (KBr)/cm^{-1} 1737, 1710, 1611. *m/z* (ESI$^+$) 303 $[M + H]^+$ (100%), 302 (4), 57 (52); HRMS (ESI$^+$): exact mass calculated for $C_{17}H_{23}O_3N_2$ $[M + H]^+$ 303.1709. Found 303.1711.

Aryl ketone side chain

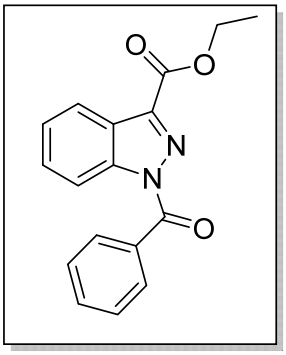
Methyl 1-(4-fluorobenzoyl)-1*H*-indazole-3-carboxylate 123



The title compound was prepared following the procedure described for methyl 1-acetyl-1*H*-indazole-3-carboxylate **104** using 2-(trimethylsilyl)phenyl-trifluoromethanesulfonate **49** (100 mg, 0.34 mmol), methyl 2-diazo-3-(4-fluorophenyl)-3-oxopropanoate **38** (80 mg, 0.36 mmol) in acetonitrile (4 mL) and caesium fluoride (91 mg, 0.6 mmol). The reaction was stirred at

room temperature under a nitrogen atmosphere for 24 h. Following the work-up, the residue was purified by column chromatography on silica gel using DCM:ethyl acetate eluent (95:5) to provide methyl 1-(4-fluorobenzoyl)-1*H*-indazole-3-carboxylate **123** as a yellow solid (69 mg, 68%), m.p. 96-99˚C. δ_H($CDCl_3$, 400 MHz): 4.06 (3H, s, OC*H*$_3$), 7.20-7.25 (2H, m, 2 × ArC*H* phenyl), 7.52 (1H, ddd, *J* 8.0, 7.2, 0.9, ArC*H* indazole), 7.67 (1H, ddd *J* 8.4, 7.1, 1.2, ArC*H* indazole) 8.20-8.26 (2H, m, 2 × ArC*H* phenyl), 8.30 (1H, td, *J* 8.1, 0.9, ArC*H* indazole), 8.56 (1H, d, *J* 8.5, ArC*H* indazole); δ_C($CDCl_3$, 100 MHz): 52.61 (O*C*H$_3$), 115.7 (Ar*C*H indazole*)*, 115.6 (d, $^2J_{CF}$, 31.8, 2 × Ar*C*H phenyl), 122.2 (Ar*C*H indazole), 124.5 (ArC_q indazole), 126.1 (Ar*C*H), 129.5 (d, $^4J_{CF}$, 4.0, ArC_q), 130.0 (Ar*C*H), 134.5 (d, $^3J_{CF}$, 9.3, 2 × Ar*C*H phenyl), 140.9 (*C*=N), 141.5 (Ar*C*N), 162.2 (C=O) amide, 165.4 (*C*F, d, $^1J_{CF}$ 214.9), 167.4 (*C*=O) ester; ν_{max} (KBr)/cm^{-1} 1720, 1602, 1499; *m/z* (ESI$^+$) 299 $[M + H]^+$ (80%); HRMS (ESI$^+$): exact mass calculated for $C_{16}H_{12}O_3N_2F$ $[M + H]^+$ 299.0832. Found 299.0829.

Ethyl 1-benzoyl-1*H*-indazole-3-carboxylate 124

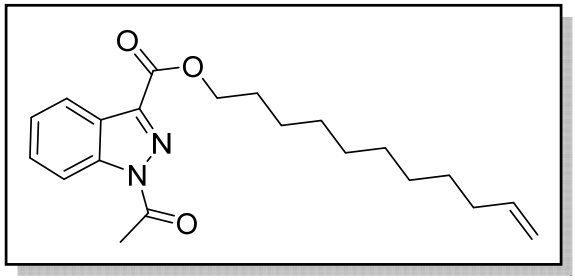


The title compound was prepared following the procedure described for methyl 1-acetyl-1*H*-indazole-3-carboxylate **104** using 2-(trimethylsilyl)phenyl-trifluoromethanesulfonate **49** (100 mg, 0.34 mmol), ethyl 2-diazo-3-oxo-3-phenylpropanoate (74 mg, 0.36 mmol) in acetonitrile (4 mL) and caesium fluoride (91 mg, 0.6 mmol). The reaction was stirred at room temperature under a nitrogen atmosphere for 24 h. Following the work-up, the residue was purified by column chromatography on silica gel using DCM:ethyl acetate eluent (95:5) to yield ethyl 1-phenyl-1*H*-indazole-3-carboxylate **124** as a light pink solid (62.4 mg, 71%), m.p. 118-121 ºC, (Lit.[56] 123 ºC). δ_H($CDCl_3$, 400 MHz): 1.48 (3H, t, *J* 7.13, C*H*$_3$), 4.53 (2H, q, *J* 7.13, OC*H*$_2$), 7.48-7.56 (3H, m, containing ArC*H* indazole and 2 × ArC*H* phenyl), 7.60-7.69 (2H, m, containing ArC*H* indazole and ArC*H* phenyl), 8.14-8.18 (2H, m, 2 × ArC*H* phenyl), 8.27 (1H, td, *J* 8.18, 1.0, ArC*H* indazole), 8.57 (1H, td, *J* 8.5, 1.0, ArC*H* indazole); δ_C($CDCl_3$, 100 MHz): 14.3 (*C*H$_3$), 61.8 (*C*H$_2$), 115.8 (Ar*C*H indazole), 122.2 (Ar*C*H indazole), 124.5

(ArC_q indazole), 125.9 (Ar*C*H indazole), 128.1 (2 × Ar*C*H phenyl), 129.8 (Ar*C*H indazole), 131.7 (2 × Ar*C*H phenyl), 132.2 (ArC_q phenyl), 133.0 (Ar*C*H phenyl), 141.5 (*C*=N), 141.5 (Ar*C*N), 161.8 (*C*=O) ester, 168.2 (*C*=O) amide; ν_{max} (KBr)/cm^{-1} 1734, 1717, 1700, 1684, 1328, 1151; *m/z* (ESI$^+$) 294 M$^+$ (5%), 276 (50), 219 (100), 163 (65), 46 (100). Spectral details not reported in literature.[56]

Functionalisable ester side chain

Undec-10-en-1-yl 1-acetyl-1*H*-indazole-3-carboxylate 126

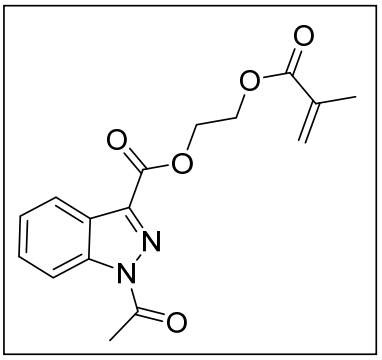


The title compound was prepared following the procedure described for methyl 1-acetyl-1*H*-indazole-3-carboxylate **104** using 2-(trimethylsilyl)phenyl-trifluoromethanesulfonate **49** (100 mg, 0.34 mmol), undec-10-en-1-yl 2-diazo-3-oxobutanoate butanoate **31** (71 mg, 0.36 mmol) in acetonitrile (4 mL) and caesium fluoride (91 mg, 0.6 mmol). The reaction was stirred at room temperature under a nitrogen atmosphere for 24 h. Following the work-up, the residue was purified by column chromatography on silica gel using DCM:ethyl acetate eluent (95:5) to yield undec-10-en-1-yl 1-acetyl-1*H*-indazole-3-carboxylate **126** as light pink crystals (84 mg, 79%). δ_H($CDCl_3$, 400 MHz): 1.31-1.65 (12H, m, 6 × C*H*$_2$), 1.84-1.91 (2H, m, C*H*$_2$), 1.91-2.06 (2H, m, C*H*$_2$), 2.88 [3H, s, C(O)C*H*$_3$], 4.49 (2H, t, *J* 7.0, OC*H*$_2$), 4.91-5.01 (2H, m, CH=C*H*$_2$), 5.75-5.86 (1H, m, C*H*=CH$_2$), 7.46 (1H, t, *J* 8.0, ArC*H*), 7.60 (1H, t, *J* 8.0, ArC*H*), 8.21 (1H, d, *J* 8.0, ArC*H*), 8.47 (1H, d, *J* 8.0, ArC*H*); ν_{max} (KBr)/cm^{-1} 2928, 1934, 1919, 1507; *m/z* (ESI$^+$) 357 [M + H]$^+$ (22%), 267 (100); HRMS (ESI)$^+$: Exact mass calculated for $C_{21}H_{29}N_2O_3$ [M + H]$^+$ 357.2178. Found 357.2176.

Note: ^{13}C NMR analysis was run on an impure sample and contained some peaks belonging to impurities. δ_C($CDCl_3$, 100 MHz): 23.1 (*C*H$_2$), 26.0 [C(O)*C*H$_3$], 28.6 (*C*H$_2$), 28.9 (*C*H$_2$), 29.1 (*C*H$_2$), 29.2 (*C*H$_2$), 29.4 (*C*H$_2$), 29.4 (*C*H$_2$), 33.7 (*C*H$_2$), 66.0 (O*C*H$_2$), 114.2 (*C*H$_2$) alkene, 115.6 (Ar*C*H), 122.2 (Ar*C*H), 123.9

(ArC_q),125.5 (Ar*C*H), 129.8 (Ar*C*H), 139.2 (*C*H) alkene, 140.3 (*C*=N), 140.6 (ArCN), 161.8 (*C*=O) ester, 171.5 (*C*=O) amide.

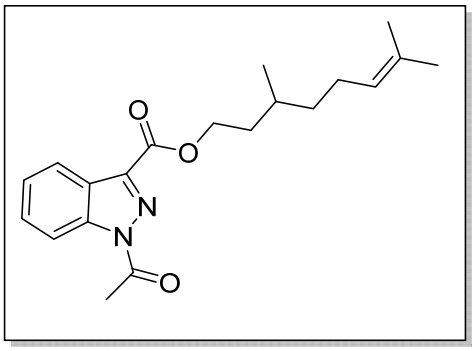
2-(Methacryloyloxy)ethyl 1-acetyl-1*H*-indazole-3-carboxylate 125



The title compound was prepared following the procedure described for methyl 1-acetyl-1*H*-indazole-3-carboxylate **104** using 2-(trimethylsilyl)phenyl-trifluoromethanesulfonate **49** (104 mg, 0.35 mmol), 2-(methacryloyloxy)ethyl 2-diazo-3-oxo-3-phenylpropanoate **26** (65 mg, 0.3 mmol) in acetonitrile (4 mL) and caesium fluoride (91 mg, 0.6 mmol). The reaction was stirred at room temperature under a nitrogen atmosphere for 24 h. Following the work-up, the crude ^{1}H NMR showed the presence of the *N*-arylated by-product 2-(methacryloyloxy)ethyl 1-phenyl-1*H*-indazole-3-carboxylate **227** which could not be separated from 2-(methacryloyloxy)ethyl 1-acetyl-1*H*-indazole-3-carboxylate **125** after column chromatography on silica gel. The residue was purified by column chromatography on silica gel using DCM:ethyl acetate eluent (95:5) to yield 2-(methacryloyloxy)ethyl 1-acetyl-1*H*-indazole-3-carboxylate **125** as a brown oil (62 mg, 65%). δ_H($CDCl_3$, 400 MHz): 1.96 (3H, d, C*H*$_3$, *J* 1.5), 2.88 [3H, s, C(O)C*H*$_3$], 4.57-4.61 (2H, m, OC*H*$_2$), 4.74-4.77 (2H, m, OC*H*$_2$), 5.61 (1H, d, *J* 1.4, one of alkene C*H*$_2$), 6.18 (1H, s, one of alkene C*H*$_2$), 7.42-7.48 (1H, m, ArC*H*), 7.61 (1H, ddd, *J* 8.5, 7.2, 1.1, ArC*H*), 8.18 (1H, dd, *J* 8.5, 0.9, ArC*H*), 8.47 (1H, dd, *J* 8.5, 0.9, ArC*H*); δ_C($CDCl_3$, 100 MHz): 18.3 (*C*H$_3$), 23.1 [C(O)*C*H$_3$], 62.2 (O*C*H$_2$), 63.2 (O*C*H$_2$), 115.6 (Ar*C*H), 122.1 (Ar*C*H), 123.9 (*C*$_q$) alkene, 124.6 (Ar*C*$_q$), 125.8 (Ar*C*H), 126.3 (*C*H$_2$ alkene), 130.0 (Ar*C*H), 135.9 (*C*=N), 140.3 (Ar*C*N), 161.5 (*C*=O) ester, 167.1 (*C*=O) ester, 171.5 (*C*=O) amide; ν_{max} (film)/cm^{-1} 2999, 1723, 1498, 1323, 1146; *m/z* (ESI$^+$) 317 [M + H]$^+$ (5%), 339 (10), 196 (60); HRMS (ESI$^+$): exact mass calculated for $C_{16}H_{17}O_5N_2$ [M + H]$^+$ 317.1137. Found 317.1135.

Note: 10% of the *N*-arylated by-product was observed in the ^{1}H NMR spectrum which could not be separated from the 1-acyl compound after chromatography.

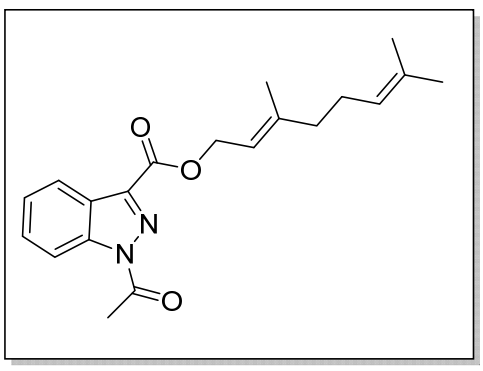
3,7-Dimethyloct-6-en-1-yl 1-acetyl-1*H*-indazole-3-carboxylate 128



The title compound was prepared following the procedure described for methyl 1-acetyl-1*H*-indazole-3-carboxylate **104** using 2-(trimethylsilyl)phenyl-trifluoromethanesulfonate **49** (104 mg, 0.35 mmol), 3,7-dimethyloct-6-enyl 2-diazo-3-oxobutanoate **27** (59 mg, 0.3 mmol) in acetonitrile (4 mL) and caesium fluoride (91 mg, 0.6 mmol). The reaction was stirred at room temperature under a nitrogen atmosphere for 24 h. The ^{1}H NMR spectrum of the crude reaction mixture showed the presence of the desired compound along with other impurities and by-products. Attempts to purify the residue by column chromatography on silica gel using DCM:ethyl acetate eluent (95:5) and by preparative TLC were unsuccessful in isolating the desired compound from this mixture.

^{1}H NMR peaks for 3,**7**-dimethyloct-6-en-1-yl 1-acetyl-1*H*-indazole-3-carboxylate **128** were extracted as follows: δ_H($CDCl_3$, 300 MHz): 1.01 (3H, d, *J* 6.3, CHC*H*$_3$), 1.14-1.26 (1H, m, CH_3C*H*), 1.30-1.42 (2H, m, C*H*$_2$), 1.44-1.57 (2H, m, C*H*$_2$), 1.61 (3H, s, C*H*$_3$), 1.68 (3H, s, C*H*$_3$), 2.08-2.38 (2H, m, C*H*$_2$), 2.87 [3H, s, C(O)C*H*$_3$], 4.42-4.53 (2H, m, OC*H*$_2$), 5.78 [1H, t, *J* 6.9, C*H*=C(CH_3)$_2$], 7.46 (1H, t, *J* 7.5, ArC*H*), 7.60 (1H, t, *J* 7.5, ArC*H*), 8.20 (1H, d, *J* 8.1, ArC*H*), 8.47 (1H, d, *J* 8.1, ArC*H*).

3,7-Dimethylocta-2,6-dien-1-yl 1-acetyl-1*H*-indazole-3-carboxylate 127



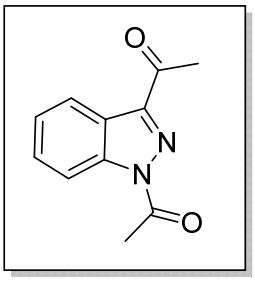
The title compound was prepared following the procedure described for methyl 1-acetyl-1*H*-indazole-3-carboxylate **104** using 2-(trimethylsilyl)phenyl-trifluoromethanesulfonate **49** (104 mg, 0.35 mmol), 3,7-dimethylocta-2,6-dienyl 2-diazo-3-oxobutanoate **25** (59 mg, 0.3 mmol) in acetonitrile (4 mL) and caesium

fluoride (91 mg, 0.6 mmol). The reaction was stirred at room temperature under a nitrogen atmosphere for 24 h. The ^{1}H NMR spectrum of the crude reaction mixture showed the presence of the desired compound along with other impurities and by-products. Attempts to purify the residue by column chromatography on silica gel using DCM:ethyl acetate eluent (95:5) and by preparative TLC were unsuccessful in isolating the desired compound from this mixture.

^{1}H NMR peaks for 3,7-dimethylocta-2,6-dien-1-yl 1-acetyl-1*H*-indazole-3-carboxylate **127** were extracted as follows: δ_H($CDCl_3$, 300 MHz): 1.61 (3H, s, C*H*$_3$), 1.68 (3H, s, C*H*$_3$), 1.73 (3H, s, C*H*$_3$), 2.02-2.13 (4H, m, 2 × C*H*$_2$), 2.88 [3H, s, C(O)C*H*$_3$], 5.01 (2H, d, *J* 7.2, OC*H*$_2$), 5.07 [1H, t, *J* 7.2, C*H*=C(CH$_3$)$_2$], 5.56 [1H, m, OCH$_2$C*H*=C(CH$_3$)], 7.46 (1H, t, *J* 8.1, ArC*H*), 7.56 (1H, t, *J* 7.5, ArC*H*), 8.20 (1H, d, *J* 8.1, ArC*H*), 8.47 (1H, d, *J* 8.1, ArC*H*).

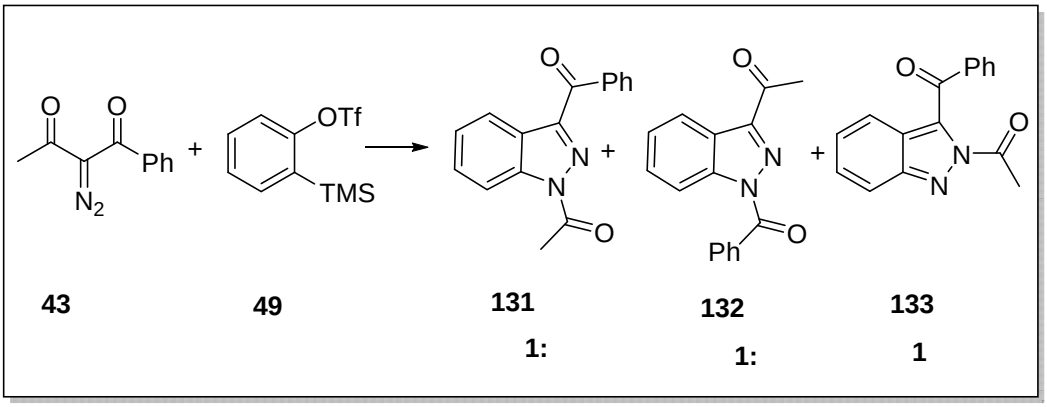
3.4.3 Synthesis of β-diketone indazole derivatives

1,1'-(1*H*-Indazole-1,3-diyl)bis(ethan-1-one) 130



The title compound was prepared following the procedure described for methyl 1-acetyl-1*H*-indazole-3-carboxylate **104** using 2-(trimethylsilyl)phenyl-trifluoromethanesulfonate **49** (100 mg, 0.3 mmol), 2-diazo acetylacetone **42** (65 mg, 0.3 mmol) in acetonitrile (4 mL) and caesium fluoride (91 mg, 0.6 mmol). The reaction was stirred at room temperature under a nitrogen atmosphere for 24 h. Following the work-up, the residue was purified by column chromatography on silica gel using hexane:ethyl acetate eluent (95:5) to yield 1,1'-(1*H*-indazole-1,3-diyl)bis(ethan-1-one) **130** as an off white solid (38 mg, 62%), m.p. 114-117ºC, (Lit.[52] 114-117 ºC). δ_H($CDCl_3$, 400 MHz): 2.77 [3H, s, C(O)*C*H$_3$ ketone], 2.87 [3H, s, C(O)*C*H$_3$ amide], 7.46 (1H, t, *J* 7.6, ArC*H*), 7.59 (1H, t, *J* 7.8 ArC*H*), 8.36 (1H, d, *J* 8.0, ArC*H*), 8.44 (1H, d, *J* 8.5, ArC*H*); δ_C($CDCl_3$, 100 MHz): 22.9 [C(O)*C*H$_3$] ketone, 26.9 [C(O)*C*H$_3$] amide, 115.3 (Ar*C*H), 122.9 (Ar*C*H), 123.9 (Ar*C*$_q$), 126.1 (Ar*C*H), 129.9 (Ar*C*H), 140.4 (*C*=N), 146.3 (Ar*C*N), 171.3 (*C*=O) ester, 195.1 (*C*=O) amide. ν_{max} (KBr)/cm^{-1} 1727, 1686, 1485, 1320, 1166, 1139; HRMS (ESI$^+$): exact mass calculated for $C_{11}H_{11}O_2N_2$ $[M + H]^+$ 203.0821. Found 203.0812. Spectral details are in agreement with those reported in the literature.[52]

1-(3-Benzoyl-1*H*-indazol-1-yl)ethan-1-one 131, 1-(1-benzoyl-1*H*-indazol-3-yl)ethan-1-one 132 and 1-(3-benzoyl-2*H*-indazol-2-yl)ethan-1-one 133



Following the procedure described for methyl 1-acetyl-1*H*-indazole-3-carboxylate **104**, 2-(trimethylsilyl)phenyl-trifluoromethanesulfonate **49** (100 mg, 0.34 mmol), 2-diazo-1-phenylbutane-1,3-dione **43** (63 mg, 0.34 mmol) in acetonitrile (4 mL) and caesium fluoride (103 mg, 0.6 mmol). The reaction was stirred at room temperature under a nitrogen atmosphere for 24 h. Following the work-up, the ^{1}H NMR spectrum of the crude reaction mixture showed the presence of three distinct products. The residue was purified by column chromatography on silica gel using hexane:ethyl acetate eluent (95:5). The ^{1}H NMR spectrum showed an inseparable mixture of 3 products from the reaction in a 1:1:1 ratio. Acyl peaks that could be identified with the compounds are assigned as follows:

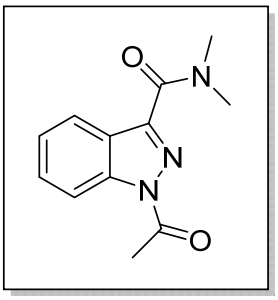
1-(1-Benzoyl-1*H*-indazol-3-yl)ethan-1-one 131: δ_H($CDCl_3$, 400 MHz): 2.87 [3H, s, C(O)*C*H$_3$ amide].

1-(3-Benzoyl-1*H*-indazol-1-yl)ethan-1-one 132: δ_H($CDCl_3$, 400 MHz): 2.77 [3H, s, C(O)*C*H$_3$ ketone].

1-(3-Benzoyl-2*H*-indazol-2-yl)ethan-1-one 133: δ_H($CDCl_3$, 400 MHz): 2.70 [3H, s, C(O)*C*H$_3$ amide].

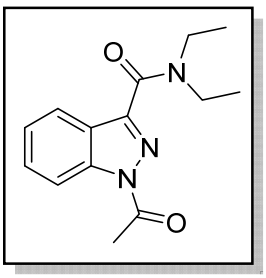
3.4.4 Synthesis of 1-acetyl-*N*,*N*-disubstituted-1*H*-indazole-3-carboxamide derivatives

1-Acetyl-*N*,*N*-dimethyl-1*H*-indazole-3-carboxamide 140



Caesium fluoride (91 mg, 0.6 mmol) was added to a stirred solution of 2-(trimethylsilyl)phenyl-trifluoromethanesulfonate **49** (100 mg, 0.34 mmol), and 2-diazo-*N*,*N*-dimethyl-3-oxobutanamide **44** (56 mg, 0.36 mmol) in acetonitrile (4 mL). The reaction was stirred at room temperature under a nitrogen atmosphere for 24 h. The solution obtained was diluted with brine (20 mL) and extracted with ethyl acetate (3 × 20 mL). The residue obtained was purified by column chromatography on silica gel using DCM:ethyl acetate eluent (95:5) followed by chloroform-methanol (99:1) and 1-acetyl-*N*,*N*-dimethyl-1*H*-indazole-3-carboxamide **140** was obtained as yellow crystals (66 mg, 84%). δ_H($CDCl_3$, 400 MHz): 2.78 [3H, s, C(O)*C*H_3], 3.23 (3H, s, NC*H*$_3$), 3.36 (3H, s, NC*H*$_3$), 7.41 (1H, ddd, *J* 8.1, 7.2, 0.9, ArC*H*), 7.59 (1H, ddd, *J* 8.1, 7.2, 1.2, ArC*H*), 8.06 (1H, td, *J* 8.1, 1.0, ArC*H*), 8.44 (1H, td, *J* 8.4, 0.8, ArC*H*); δ_C($CDCl_3$, 100 MHz): 23.0 [CO(*C*H_3)], 36.0 (N*C*H_3), 38.9 (N*C*H_3), 115.3 (Ar*C*H), 122.3 (Ar*C*H). 125.3 (Ar*C*H), 125.6 (ArC_q), 129.9 (Ar*C*H), 139.5 (*C*=N), 144.4 (Ar*C*N), 162.8 [$(CH_3)_2$N*C*O], 171.1 (*C*=O) *N*-acyl; ν_{max} (KBr)/cm^{-1} 2934, 1724, 1634, 1500; *m/z* (ESI^+) 255 $[M + H + Na]^+$ (21%); HRMS (ESI^+): exact mass calculated for $C_{12}H_{14}N_3O_2$ $[M + H]^+$ 232.1086. Found 232.1076.

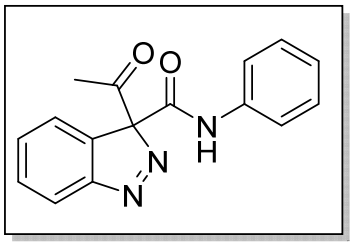
1-Acetyl-*N*,*N*-diethyl-1*H*-indazole-3-carboxamide 141



The title compound was prepared following the procedure described for 1-acetyl-*N*,*N*-dimethyl-1*H*-indazole-3-carboxamide **140** using 2-(trimethylsilyl)phenyl-trifluoromethanesulfonate **49** (100 mg, 0.34 mmol), 2-diazo-*N*,*N*-diethyl-3-oxobutanamide **45** (71 mg, 0.36 mmol) in acetonitrile (4 mL) and caesium fluoride (91 mg, 0.6 mmol). The reaction was stirred at room temperature under a nitrogen atmosphere for 24 h.

Following the work-up, the residue was purified by column chromatography on silica gel using DCM:ethyl acetate eluent (95:5) followed by chloroform-methanol (99:1) to yield 1-acetyl-*N*,*N*-diethyl-1*H*-indazole-3-carboxamide **141** as yellow crystals (84 mg, 95%). δ_H($CDCl_3$, 400 MHz): 1.29 [6H, t (overlapping), *J* 8.1, 2 × C*H*$_3$CH$_2$], 2.79 [3H, s, C(O)*C*H$_3$], 3.65 [4H, q × 2 (overlapping), *J* 8.1, 2 × CH$_3$C*H*$_2$], 7.46 (1H, t, *J* 8.1, ArC*H*), 7.56 (1H, t, *J* 8.1, ArC*H*), 8.06 (1H, d, *J* 8.1, ArC*H*), 8.44 (1H, d, *J* 8.1, ArC*H*); δ_C($CDCl_3$, 100 MHz): 12.9 (*C*H$_3$), 14.7 (*C*H$_3$), 23.0 [CO(*C*H$_3$)], 40.9 (NCH$_2$), 43.5 (NCH$_2$), 115.2 (Ar*C*H), 122.3 (Ar*C*H). 125.2 (Ar*C*H), 125.8 (ArC_q), 129.9 (Ar*C*H), 139.5 (*C*=N), 144.7 (Ar*C*N), 162.2 [(CH$_3$CH$_2$)$_2$N*C*O], 171.1 (*C*=O) *N*-acyl; ν_{max} (KBr)/cm^{-1} 2978, 1726, 1631, 1381, 1137; *m/z* (ESI$^+$) 260 [M + H]$^+$ (30%); HRMS (ESI$^+$): exact mass calculated for $C_{14}H_{18}O_2N_3$ [M + H]$^+$ 260.1399. Found 260.1395.

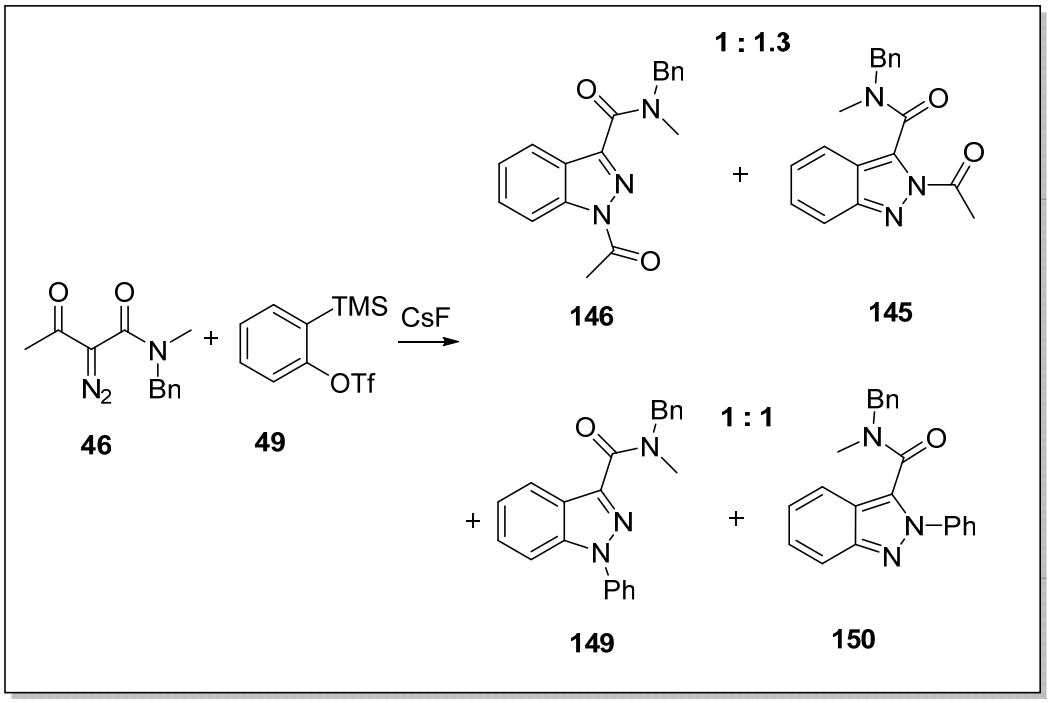
3-Acetyl-*N*-phenyl-3*H*-indazole-3-carboxamide 151



The title compound was prepared following the procedure described for 1-acetyl-*N*,*N*-dimethyl-1*H*-indazole-3-carboxamide **140** using 2-(trimethylsilyl)phenyl-trifluoromethanesulfonate **49** (100 mg, 0.33 mmol), 2-diazo-3-oxo-*N*-phenylbutanamide **47** (61 mg, 0.3 mmol) in acetonitrile (4 mL) and caesium fluoride (91 mg, 0.6 mmol). The reaction was stirred at room temperature under a nitrogen atmosphere for 24 h. Following the work-up, the residue was purified by column chromatography on silica gel using DCM:ethyl acetate eluent (95:5) followed by chloroform-methanol (99:1) to yield 1-acetyl-*N*,*N*-diethyl-1*H*-indazole-3-carboxamide **151** as yellow crystals (27 mg, 32%), m.p. 134-136 ºC. δ_H($CDCl_3$, 400 MHz): 2.65 [3H, s, C(O)C*H*$_3$], 6.89-6.93 (2H, m, 2 × Ar*CH* phenyl), 7.10-7.16 (1H, m, Ar*CH* phenyl), 7.28-7.34 (2H, m, 2 × Ar*CH* indazole), 7.46-7.54 (3H, m, containing 2 × Ar*CH* and N*H*), 7.67 (2H, dd, *J* 8.3, 1.6, 2 × Ar*CH* phenyl); δ_C($CDCl_3$, 100 MHz): 27.7 [CO(*C*H$_3$)], 96.9 [(CO)$_2$*C*], 115.9 (Ar*C*H), 123.2 (Ar*C*H). 124.5 (Ar*C*H), 126.5 (ArC_q indazole) 129.6 (Ar*C*H), 129.6 (2 × Ar*CH*), 129.8 (Ar*CH*), 129.9 (2 × Ar*CH*), 134.2 (C_q phenyl), 151.5 (tentative Ar*C*N), 156.1 (*C*=O) amide, 191.1 (*C*=O) ketone; ν_{max} (KBr)/cm^{-1}:

2144, 1724, 1692, 1298; *m/z* (ESI+) 279 M^+ (8%), 46 (100); HRMS (ESI^+): exact mass calculated for $C_{16}H_{14}O_2N_3$ $[M + H]^+$ 280.1086. Found 280.1088.

1-Acetyl-*N*-benzyl-*N*-methyl-1*H*-indazole-3-carboxamide 146 and 2-acetyl-*N*-benzyl-*N*-methyl-2*H*-indazole-3-carboxamide 145 (1:1.3)



Following the procedure described for 1-acetyl-*N*,*N*-dimethyl-1*H*-indazole-3-carboxamide **140**, 2-(trimethylsilyl)phenyl-trifluoromethanesulfonate **49** (100 mg, 0.34 mmol), *N*-benzyl-2-diazo-*N*-methyl-3-oxobutanamide **46** (90 mg, 0.3 mmol) in acetonitrile (4 mL) and caesium fluoride (91 mg, 0.6 mmol) was allowed to stir at room temperature under a nitrogen atmosphere for 24 h. Following the work-up, the crude ^1H NMR showed a mixture of products. The residue was purified by column chromatography on silica gel using DCM:ethyl acetate eluent (95:5) followed by chloroform:methanol (99:1) to yield the mixture of products **146** and **145** in a 1.3:1 ratio of 1,3-disubstituted regioisomers: 2,3-disubstitued regioisomers as a brown oil (60 mg, 58%); and **149** and **150** *N*-arylated by-products (4 mg, 3.9%), which were further separated using from the *N*-acyl products using column chromatography on silica gel using hexane:ethyl acetate eluent (80:20). ν_{max} (film)/cm^{-1}: 1726, 1637, 1375; *m/z* (ESI^+) 330 $[M + Na]^+$ (20%), 308 (8); HRMS (ESI^+): exact mass calculated for $C_{18}H_{18}O_2N_3$ $[M + H]^+$ 308.1399. Found 308.1394.

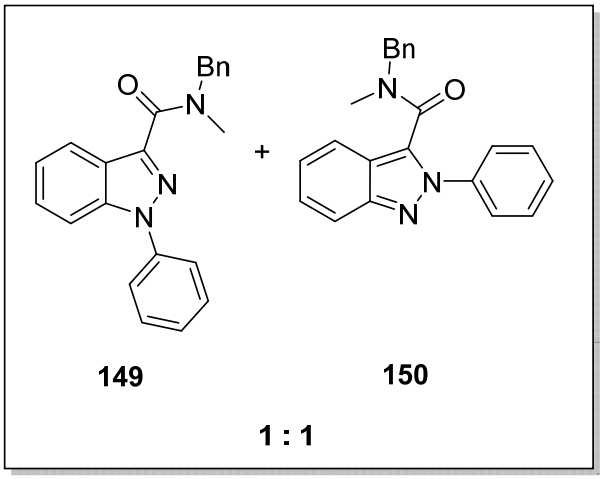
Major isomer: **2-Acetyl-*N*-benzyl-*N*-methyl-2*H*-indazole-3-carboxamide 145**

δ_H($CDCl_3$, 400 MHz): 2.53 [3H, s, C-C(O)C*H*$_3$], 3.15 [3H, s, C(O)NC*H*$_3$], 4.97 (2H, s, C*H*$_2$), 7.29-7.46 (6H, m, containing 5 × ArC*H* benzyl and ArC*H* indazole), 7.56-7.62 (1H, m, ArC*H* indazole), 8.13 (1H, dd *J* 13.6, 8.1, ArCH indazole), 8.43 (1H, dd *J* 12.4, 8.5, ArC*H* indazole); δ_C($CDCl_3$, 100 MHz): 22.8 [C(O)*C*H$_3$], 33.8 (N*C*H$_3$), 54.7 (N*C*H$_2$), 115.2 (Ar*C*H), 122.4 (Ar*C*H), 125.3 (Ar*C*H), 125.8 (ArC_q), 127.2 (2 × Ar*C*H), 127.6 (Ar*C*H), 128.3 (Ar*C*H), 128.7 (2 × Ar*C*H), 136.8 (ArC_q phenyl), 139.6 (*C*=N), 143.9 (Ar*C*N), 163.2 [*C*(O)NMe], 171.1 [*C*(O)CH$_3$].

Minor isomer: **1-Acetyl-*N*-benzyl-*N*-methyl-1*H*-indazole-3-carboxamide 146**

δ_H($CDCl_3$, 400 MHz): 2.78 (3H, s, NC(O)C*H*$_3$), 3.28 (3H, s, NC*H*$_3$), 4.87 (2H, s, C*H*$_2$), 7.29-7.46 (6H, m, containing 5 × ArCH benzyl and ArCH indazole), 7.56-7.62 (1H, m, ArCH indazole), 8.13 (1H, dd *J* 13.6, 8.1, ArCH indazole), 8.43 (1H, dd, *J* 12.4, 8.5, ArCH indazole); δ_C($CDCl_3$, 100 MHz): 23.0 [CO(*C*H$_3$)], 36.5 (N*C*H$_3$), 51.6 (N*C*H$_2$), 115.3 (Ar*C*H), 122.3 (Ar*C*H), 125.3 (Ar*C*H), 125.8 (ArC_q), 127.2 (2 × Ar*C*H), 127.7 (Ar*C*H), 128.3 (Ar*C*H), 128.8 (2 × Ar*C*H), 136.6 (ArC_q phenyl), 139.5 (Ar*C*N), 144.4 (*C*=N), 162.9 [*C*(O)NMe], 171.1 (CH$_3$*C*=O);

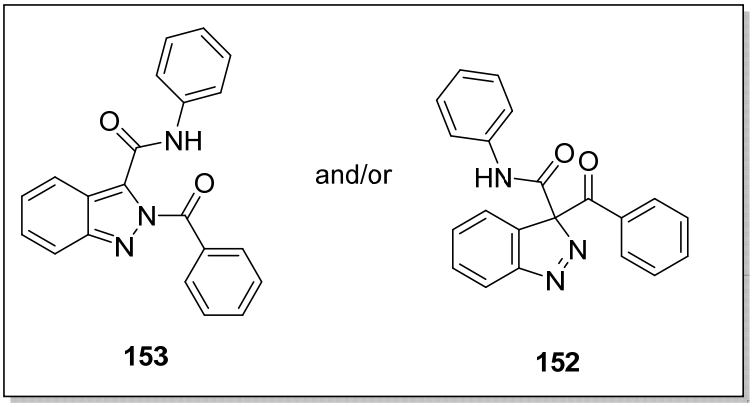
***N*-benzyl-*N*-methyl-1-phenyl-1*H*-indazole-3-carboxamide 149 and *N*-benzyl-*N*-methyl-2-phenyl-2*H*-indazole-3-carboxamide 150**



δ_H($CDCl_3$, 400 MHz): 3.13 and 3.41 (2 × 3H, s, NC*H*$_3$), 4.89 and 5.20 (2 × 2H, s, C*H*$_2$), 7.26-7.64 (22H, m, 22 × ArC*H*), 7.74 (2 × 2H, t, *J* 7.1, 4 × ArC*H* indazole), 8.31 (2 × 1H, t, *J* 7.5, ArC*H* indazole).

****Note:** Further investigation into these compounds have suggested the duplication of signals is due to the presence of two rotameric forms of the 1,3-disubstituted derivatives **146** and **149**.

Tentative assignment of 2-benzoyl-*N*-phenyl-2*H*-indazole-3-carboxamide 153 and/or 3-benzoyl-*N*-phenyl-3*H*-indazole-3-carboxamide 152

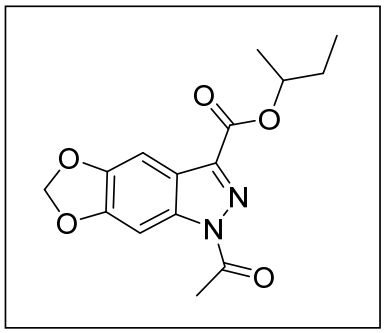


153 **152**

The title compounds were prepared following the procedure described for 1-acetyl-*N*,*N*-dimethyl-1*H*-indazole-3-carboxamide **140** using 2-(trimethylsilyl)phenyl-trifluoromethanesulfonate **49** (104 mg, 0.35 mmol), 2-diazo-3-oxo-*N*,3-diphenylpropanamide **48** (59 mg, 0.3 mmol) in acetonitrile (4 mL) and caesium fluoride (91 mg, 0.6 mmol). The reaction was stirred at room temperature under a nitrogen atmosphere for 24 h. Following the work-up, the residue was purified by column chromatography on silica gel using hexane:ethyl acetate eluent (90:10-80:20) to yield 2-benzoyl-*N*-phenyl-2H-indazole-3-carboxamide **153** and/or 3-benzoyl-*N*-phenyl-3H-indazole-3-carboxamide **152** as yellow crystals (74 mg, 95%), m.p. 157-160 ºC. δ_H($CDCl_3$, 400 MHz): 3.22 (1H, br s, N*H*), 7.20-7.25 (1H, m, ArC*H*), 7.27-7.39 (5H, m, 5 × ArC*H*), 7.45-7.39 (4H, m, 4 × ArC*H*), 7.60 (2H, t, *J* 7.8, 2 × ArC*H*), 7.93 (2H, dd, *J* 8.6, 1.2, 2 × ArC*H*); δ_C($CDCl_3$, 100 MHz: 70.3 [C_q(CO)$_2$ of **152** tentative], 117.0 (Ar*C*H indazole), 121.5 (2 × ArC*H*), 125.7 (Ar*C*H indazole), 126.5 (2 × ArC*H*), 127.5 (Ar*C*H indazole), 128.2 (2 × ArC*H* phenyl), 128.8 (ArC*H* phenyl), 129.6 (Ar*C*H indazole), 129.7 (2 × ArC*H* phenyl), 130.7 (ArC*H* phenyl), 133.8 (COC_q phenyl), 135.2 (ArCN), 145.4 (*C*=O) amide, 149.3 [N(CO)Ph of **153** tentative]; ν_{max} (KBr)/cm^{-1}: 3282, 2966, 1718, 1616, 1276; *m/z* (ESI^+) 341 M^+ (10%), 46 (100); HRMS (ESI^+): exact mass calculated for $C_{21}H_{16}O_2N_3$ $[M + H]^+$ 342.1243. Found 342.1232.

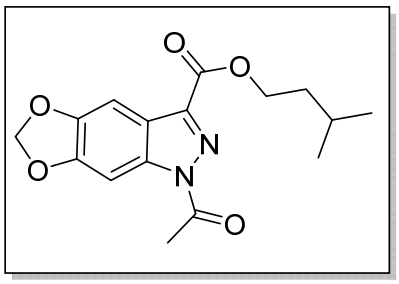
3.4.5 Synthesis of 1-acyl-1*H*-[1,3]dioxolo[4,5-f]indazole-3-carboxylate compounds

sec-Butyl 1-acetyl-1*H*-[1,3]dioxolo[4,5-f]indazole-3-carboxylate 155



Caesium fluoride (91 mg, 0.6 mmol) was added to a stirred solution of 6-(trimethylsilyl)benzo[d][1,3]dioxol-5-yl trifluoromethanesulfonate **75** (100 mg, 0.29 mmol), and *sec*-butyl 2-diazo-3-oxobutanoate **32** (80 mg, 0.44 mmol, 1.5 equiv.) in acetonitrile (4 mL). The reaction was stirred at room temperature under a nitrogen atmosphere for 24 h. The solution obtained was diluted with brine (20 mL) and extracted with ethyl acetate (3 × 20 mL). The residue obtained was purified by column chromatography on silica gel using DCM:ethyl acetate eluent (95:5) to yield pure *sec*-butyl 1-acetyl-1*H*-[1,3]dioxolo[4,5-f]indazole-3-carboxylate **156**5as a yellow solid (41 mg, 47%), m.p. 169-170°C. δ_H($CDCl_3$, 400 MHz): 1.02 (3H, t, C*H*$_3$, *J* 7.5), 1.43 (3H, d, *J* 6.3, C*H*$_3$), 1.70-1.91 (2H, m, CH_2), 2.84 [3H, s, C(O)C*H*$_3$], 5.20-5.28 (1H, m, OC*H*), 6.11 (2H, s, OC*H*$_2$O), 7.44 (1H, s, ArC*H*), 7.88 (1H, s, ArC*H*). δ_C($CDCl_3$, 100 MHz): 9.8 (CH_2CH_3), 19.6 ($CHCH_3$), 23.0 [C(O)*C*H$_3$], 28.9 (*C*H$_2$), 74.2 (O*C*H), 95.7 (Ar*C*H), 99.4 (Ar*C*H), 102.3 (O*C*H$_2$O), 119.7 (Ar*C*$_q$), 137.1 (*C*=N), 140.7 (Ar*C*N), 147.3 (Ar*C*OCH$_2$), 150.9 (Ar*C*OCH$_2$), 161.6 (*C*=O) ester, 171.6 (*C*=O) amide; ν_{max} (KBr)/cm^{-1} 2974, 1727, 1644, 1491, 1459; *m/z* (ESI$^+$) 305 $[M + H]^+$ (56%), 249 (8); HRMS (ESI$^+$): exact mass calculated for $C_{15}H_{17}N_2O_5$ $[M + H]^+$ 305.1137. Found 305.1124.

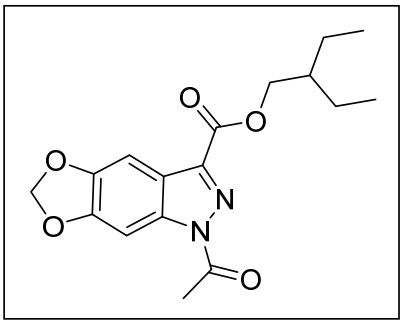
Isopentyl 1-acetyl-1*H*-[1,3]dioxolo[4,5-f]indazole-3-carboxylate 154



The title compound was prepared following the procedure described for *sec*-butyl 1-acetyl-1*H*-[1,3]dioxolo[4,5-f]indazole-3-carboxylate **156** using 6-(trimethylsilyl)benzo[d][1,3]dioxol-5-yl trifluoromethanesulfonate **75** (100 mg, 0.28 mmol), isopentyl 2-diazo-3-oxo-butanoate **24** (59 mg, 0.3 mmol) in acetonitrile (4

mL) and caesium fluoride (91 mg, 0.6 mmol). The reaction was stirred at room temperature under a nitrogen atmosphere for 24 h. Following the work-up, the residue was purified by column chromatography on silica gel using DCM: ethyl acetate eluent (95:5) to yield isopentyl 1-acetyl-1*H*-[1,3]dioxolo[4,5-f]indazole-3-carboxylate **154** as an orange oil (66 mg, 72%). δ_H($CDCl_3$, 400 MHz): 1.00 (6H, d, *J* 6.4, 2 × C*H*$_3$), 1.72-1.86 [3H, m, containing OCH$_2$C*H*$_2$ and C*H*(CH$_3$)$_2$], 2.87 [3H, s, C(O)C*H*$_3$], 4.49 (2H, t, *J* 6.8, OC*H*$_2$), 6.11 (2H, s, OC*H*$_2$O), 7.46 (1H, s, ArC*H*), 7.88 (1H, s, ArC*H*); δ_C($CDCl_3$, 100 MHz): 22.5 (2 × *C*H$_3$), 23.0 [C(O)*C*H$_3$], 25.3 (*C*H), 37.3 (*C*H$_2$), 64.5 (O*C*H$_2$), 95.7 (Ar*C*H), 99.3 (Ar*C*H), 102.3 (O*C*H$_2$O), 119.8 (Ar*C*$_q$), 137.1 (*C*=N), 140.3 (Ar*C*N), 147.3 (Ar*C*OCH$_2$), 151.0 (Ar*C*OCH$_2$), 162.0 (*C*=O) ester, 171.6 (*C*=O) amide; ν_{max} (film)/cm^{-1} 2958, 1730, 1478, 1210, 1149; *m/z* (ESI$^+$) 319 [M + H]$^+$ (10%); HRMS (ESI)$^+$: Exact mass calculated for $C_{16}H_{18}N_2O_5$ [M + H]$^+$ 319.1294. Found 319.1283.

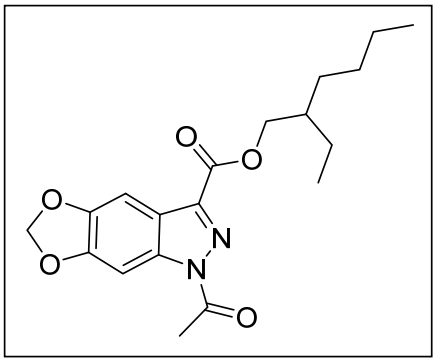
2-Ethylbutyl 1-acetyl-1*H*-[1,3]dioxolo[4,5-f]indazole-3-carboxylate 157



The title compound was prepared following the procedure described for *sec*-butyl 1-acetyl-1*H*-[1,3]dioxolo[4,5-f]indazole-3-carboxylate **156** using 6-(trimethylsilyl)benzo[d][1,3]dioxol-5-yl trifluoromethanesulfonate **75** (100 mg, 0.29 mmol), 2-ethylbutyl 2-diazo-3-oxo-butanoate **30** (59 mg, 0.3 mmol) in acetonitrile (4 mL) and caesium fluoride (91 mg, 0.6 mmol). The reaction was stirred at room temperature under a nitrogen atmosphere for 24 h. Following the work-up, the residue was purified by column chromatography on silica gel using DCM: ethyl acetate eluent (95:5) to yield 2-ethylbutyl 1-acetyl-1*H*-[1,3]dioxolo[4,5-f]indazole-3-carboxylate **157** as a white solid (65 mg, 68%), m.p. 105-107°C. δ_H($CDCl_3$, 400 MHz): 0.98 (6H, t, *J* 7.5, 2 × C*H*$_3$), 1.45-1.54 (4H, m, 2 × C*H*$_2$), 1.76 (1H, td, *J* 12.5, 6.3, C*H*), 2.84 (3H, s, C(O)C*H*$_3$), 4.40 (2H, d, *J* 5.9, OC*H*$_2$), 6.11 (2H, s, OC*H*$_2$O), 7.44 (1H, s, ArC*H*), 7.88 (1H, s, ArC*H*); δ_C($CDCl_3$, 100 MHz): 11.1 (2 × *C*H$_3$), 22.9 [C(O)*C*H$_3$], 23.5 (2 × *C*H$_2$), 40.4 (*C*H), 67.8 (O*C*H$_2$), 95.7 (Ar*C*H), 99.3 (Ar*C*H), 102.3 (O*C*H$_2$O), 119.7 (Ar*C*$_q$), 137.1 (*C*=N), 140.4 (Ar*C*N), 147.3 (Ar*C*OCH$_2$), 150.9 (Ar*C*OCH$_2$), 162.1 (*C*=O) ester,

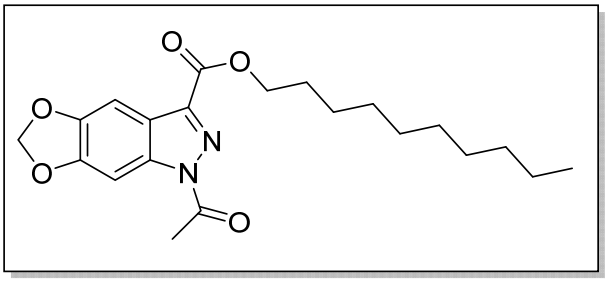
171.6 (*C*=O) amide; ν_{max} (KBr)/cm^{-1} 2963, 1729, 1648, 1462, 1388. *m/z* (ESI$^+$) 333 [M + H]$^+$ (100%); HRMS (ESI)$^+$: Exact mass calculated for $C_{17}H_{21}N_2O_5$ [M + H]$^+$ 333.1450. Found 333.1450; (Found: C, 60.03; H, 5.94; N, 7.78. $C_{17}H_{20}N_2O_5$ requires C, 61.44; H, 6.07; N, 8.43%).

2-Ethylhexyl 1-acetyl-1*H*-[1,3]dioxolo[4,5-f]indazole-3-carboxylate 156



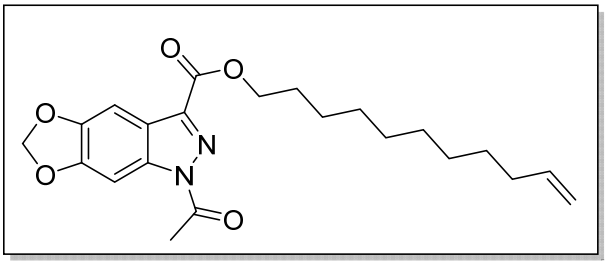
The title compound was prepared following the procedure described for *sec*-butyl 1-acetyl-1*H*-[1,3]dioxolo[4,5-f]indazole-3-carboxylate **156** using 6-(trimethylsilyl)benzo[d][1,3]dioxol-5-yl trifluoromethanesulfonate **75** (100 mg, 0.29 mmol), 2-ethylhexyl 2-diazo-3-oxo-butanoate **28** (80 mg, 0.3 mmol) in acetonitrile (4 mL) and caesium fluoride (91 mg, 0.6 mmol). The reaction was stirred at room temperature under a nitrogen atmosphere for 24 h. Following the work-up, the residue was purified by column chromatography on silica gel using hexane:ethyl acetate eluent (90:10) to yield 2-ethylhexyl 1-acetyl-1*H*-[1,3]dioxolo[4,5-f]indazole-3-carboxylate **156** as a white solid (58 mg, 56%), m.p. 84-85°C. δ_H($CDCl_3$, 400 MHz): 0.91 (3H, t, *J* 7.1, C*H*$_3$), 0.98 (3H, t, *J* 7.5, C*H*$_3$)], 1.30-1.54 (8H, m, 4 × C*H*$_2$), 1.70-1.90 (1H, m, C*H*), 2.84 [3H, s, C(O)C*H*$_3$], 4.39 (2H, d, *J* 5.8, OC*H*$_2$), 6.11 (2H, s, OC*H*$_2$O), 7.45 (1H, s, ArC*H*), 7.89 (1H, s, ArC*H*); δ_C($CDCl_3$, 100 MHz): 11.1 (*C*H$_3$), 14.1 (*C*H$_3$), 22.9 (*C*H$_2$), 23.0 [C(O)*C*H$_3$], 24.0 (*C*H$_2$), 28.9 (*C*H$_2$), 30.6 (*C*H$_2$), 38.9 (*C*H) 68.1 (O*C*H$_2$), 95.7 (Ar*C*H), 99.3 (Ar*C*H), 102.3 (O*C*H$_2$O), 119.7 (Ar*C*$_q$), 137.1 (*C*=N), 140.4 (Ar*C*N), 147.3 (Ar*C*OCH$_2$), 150.9 (Ar*C*OCH$_2$), 162.1 (*C*=O) ester, 171.6 (*C*=O) amide; ν_{max} (KBr)/cm^{-1} 2960, 1731, 1650, 1462, 1317, 1062; *m/z* (ESI$^+$) 361 [M + H]$^+$ (100%), 249 (8). HRMS (ESI$^+$): exact mass calculated for $C_{19}H_{25}N_2O_5$ [M + H]$^+$ 361.1763. Found 361.1765; (Found: C, 62.97; H, 6.70; N, 7.57. $C_{19}H_{24}N_2O_5$ requires C, 63.32; H, 6.71; N, 7.77%).

Decyl 1-acetyl-1*H*-[1,3]dioxolo[4,5-f]indazole-3-carboxylate 158



The title compound was prepared following the procedure described for *sec*-butyl 1-acetyl-1*H*-[1,3]dioxolo[4,5-f]indazole-3-carboxylate **156** using 6-(trimethylsilyl)benzo[d][1,3]dioxol-5-yl trifluoromethanesulfonate **75** (95 mg, 0.28 mmol), decyl 2-diazo-3-oxo-butanoate **29** (108 mg, 0.28 mmol) in acetonitrile (4 mL) and caesium fluoride (91 mg, 0.6 mmol). The reaction was stirred at room temperature under a nitrogen atmosphere for 24 h. Following the work-up, the residue was purified by column chromatography on silica gel using DCM:ethyl acetate eluent (95:5) and decyl 1-acetyl-1*H*-[1,3]dioxolo[4,5-f]indazole-3-carboxylate **158** was obtained as a white solid (74 mg, 66%), m.p. 84-85°C. δ_H($CDCl_3$, 400 MHz): 0.88 (3H, t, *J* 6.8, C*H*$_3$), 1.20-1.51 (14H, m, 7 × C*H*$_2$), 1.80-1.90 (2H, m, C*H*$_2$), 2.84 [3H, s, C(O)C*H*$_3$], 4.45 (2H, t, *J* 6.9, OC*H*$_2$), 6.11 (2H, s, OC*H*$_2$O), 7.47 (1H, s, ArC*H*), 7.89 (1H, s, ArC*H*); δ_C($CDCl_3$, 100 MHz): 14.1 (CH_2CH_3), 22.7 (*C*H$_2$), 23.0 [C(O)*C*H$_3$], 26.0 (*C*H$_2$), 28.6 (*C*H$_2$), 29.2 (*C*H$_2$), 29.3 (CH_2), 29.5 (2 × *C*H$_2$), 31.9 (OCH_2CH_2), 65.9 (OC*H*$_2$), 95.7 (Ar*C*H), 99.4 (Ar*C*H), 102.3 (O*C*H$_2$O), 119.8 (Ar*C*$_q$), 137.1 (*C*=N), 140.3 (Ar*C*N), 147.3 (Ar*C*OCH$_2$), 151.0 (Ar*C*OCH$_2$), 162.0 (*C*=O) ester, 171.6 (*C*=O) amide; *m/z* (ESI^+) 389 $[M + H]^+$ (100%); HRMS $(ESI)^+$: Exact mass calculated for $C_{21}H_{29}N_2O_5$ $[M + H]^+$ 389.2076. Found 389.2069; ν_{max} (KBr)/cm^{-1} 2924, 1720, 1651, 1295; (Found: C, 67.36; H, 7.55; N, 7.10. $C_{21}H_{28}N_2O_5$ requires C, 64.93; H, 7.27; N, 7.21%).

Undec-10-en-1-yl 1-acetyl-1*H*-[1,3]dioxolo[4,5-f]indazole-3-carboxylate 159



The title compound was prepared following the procedure described for *sec*-butyl 1-acetyl-1*H*-[1,3]dioxolo[4,5-f]indazole-3-carboxylate **156** using 6-(trimethylsilyl)benzo[d][1,3]dioxol-5-yl trifluoromethanesulfonate **75** (100 mg,

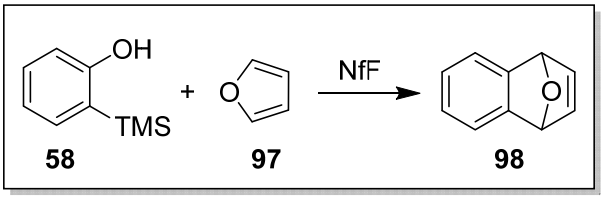
0.33 mmol), undec-10-en-1-yl 2-diazo-3-oxobutanoate **31** (59 mg, 0.3 mmol) in acetonitrile (4 mL) and caesium fluoride (91 mg, 0.6 mmol). The reaction was stirred at room temperature under a nitrogen atmosphere for 24 h. Following the work-up, the residue was purified by column chromatography on silica gel using hexane:ethyl acetate eluent (95:5) to yield undec-10-en-1-yl 1-acetyl-1*H*-[1,3]dioxolo[4,5-f]indazole-3-carboxylate **159** as a white solid (80 mg, 67%), m.p. 75-76 °C. δ_H($CDCl_3$, 400 MHz): 1.27-1.50 (12H, m, 6 × C*H*$_2$), 1.80-1.90 (2H, m, C*H*$_2$), 2.00-2.08 (2H, m, C*H*$_2$), 2.84 [3H, s, C(O)C*H*$_3$], 4.45 (2H, t, *J* 7.0, OC*H*$_2$), 4.90-5.03 (2H, m, CH=C*H*$_2$), 5.75-5.87 (1H, m, C*H*=CH$_2$), 6.11 (2H, s, OC*H*$_2$O), 7.47 (1H, s, ArC*H*), 7.89 (1H, s, ArC*H*); δ_C($CDCl_3$, 100 MHz): 23.0 (*C*H$_2$), 25.9 (*C*H$_3$), 28.6 (*C*H$_2$), 28.9 (*C*H$_2$), 29.1 (*C*H$_2$), 29.2 (*C*H$_2$), 29.4 (*C*H$_2$), 29.4 (*C*H$_2$), 33.8 (*C*H$_2$), 65.9 (OCH$_2$), 95.7 (Ar*C*H), 99.4 (Ar*C*H), 102.3 (OCH$_2$O), 114.2 (*C*H$_2$) alkene, 119.8 (ArC_q), 137.1 (*C*=N), 139.2 (*C*H) alkene, 139.2 (Ar*C*N), 147.3 (Ar*C*OCH$_2$), 150.9 (Ar*C*OCH$_2$), 162.1 (*C*=O) ester, 171.6 (*C*=O) amide; ν_{max} (KBr)/cm^{-1} 2926, 1721, 1493, 1475, 1296, 1159; HRMS $(ESI)^+$: Exact mass calculated for $C_{22}H_{29}N_2O_5$ $[M + H]^+$ 401.2076. Found 401.2072.

3.5 Synthesis of 1-acyl-1*H*-indazole derivatives Method 2

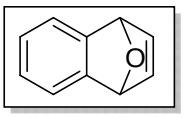
3.5.1 Generation of aryne and trapping with furan

Method 2:

Using 2-(trimethylsilyl)phenol 58 and nonafluorobutanesulfonyl fluoride[40]



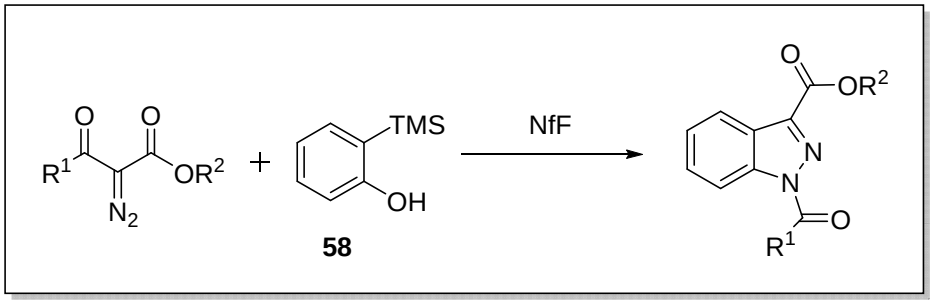
1,4-Dihydro-1,4-epoxynaphthalene[54] 98



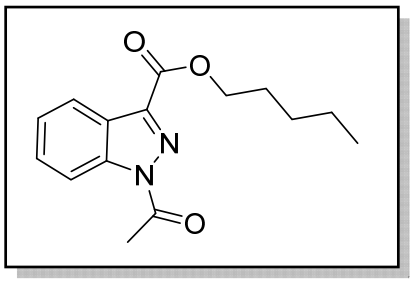
2-(Trimethylsilyl)phenol **58** (0.05 g, 0.3 mmol) was added to a flask evacuated and filled with nitrogen followed by caesium carbonate (0.1466 g, 0.45 mmol) in acetonitrile (3 ml) and caesium fluoride (23 mg, 0.15 mmol). Furan **97** (0.065 ml, 0.9 mmol) and nonafluorobutanesulfonyl fluoride (81 μL, 0.45 mmol) were added by syringe. The reaction was stirred at 60 °C under a nitrogen atmosphere for 8 h. The reaction mixture was diluted with brine (20 mL) and extracted with ethyl acetate (20 mL). The organic layer was dried with $MgSO_4$ and analysis of the crude residue identified the characteristic peaks of 1,4-dihydro-1,4-epoxynaphthalene **98** as assigned on page 46 **(Section 3.4.2)**.

3.5.2 Synthesis of 1-acyl-1*H*-indazole derivatives using 2-(trimethylsilyl)phenol 58 and nonafluorobutanesulfonyl fluoride

Method 2[40]:

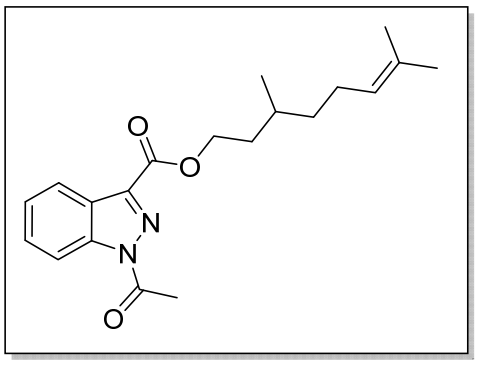


Pentyl 1-acetyl-1*H*-indazole-3-carboxylate 108



Caesium fluoride (45.6 mg, 0.3 mmol) and nonafluorobutanesulfonyl fluoride (0.272 g, 0.9 mmol) was added to a stirred solution of 2-(trimethylsilyl)phenol **58** (100 mg, 0.6 mmol), caesium carbonate (293 mg, 0.9 mmol) and *n*-pentyl 2-diazo-3-oxobutanoate **23** (351 mg, 1.8 mmol) in acetonitrile (6 mL). The reaction was stirred at 60 °C under a nitrogen atmosphere for 8 h. The reaction mixture was diluted with brine (20 mL) and extracted with ethyl acetate (20 mL). The organic layer was dried with $MgSO_4$ and concentrated under reduced pressure, the residue was purified by column chromatography on silica gel using DCM:ethyl acetate eluent (95:5) to yield *n*-pentyl 1-acetyl-1*H*-indazole-3-carboxylate **108** as a yellow oil (143 mg, 87%). δ_H(CDCl3, 400 MHz): 0.93 (3H, t, *J* 7.1, CH_2CH_3), 1.36-1.48 (4H, m, 2 × CH_2), 1.85-1.92 (2H, m, CH_2), 2.88 [3H, s, C(O)CH_3], 4.50 (2H, t, *J* 6.8, OCH_2), 7.44-7.49 (1H, m, ArC*H*), 7.55-7.65 (1H, ddd, *J* 8.4, 7.1, 1.1, ArC*H*), 8.20 (1H, d, *J* 8.1, ArC*H*), 8.47 (1H, d, *J* 8.5, ArC*H*). Spectral details as described previously on page 51 (**Section 3.4.2.1).**

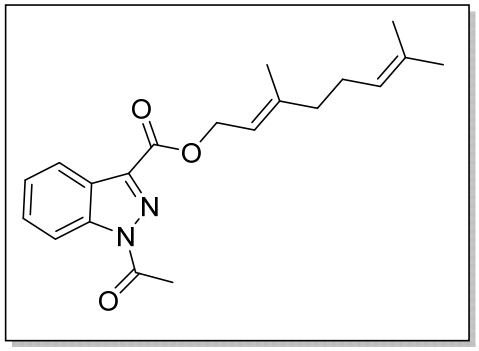
3,7-Dimethyloct-6-en-1-yl 1-acetyl-1*H*-indazole-3-carboxylate 128



The title compound was prepared following the procedure described for pentyl 1-acetyl-1*H*-indazole-3-carboxylate **108** using caesium fluoride (45.6 mg, 0.3 mmol), nonafluorobutanesulfonyl fluoride (0.272 g, 0.9 mmol), 2 (trimethylsilyl)phenol **58** (100 mg, 0.35 mmol), 3 ,7-dimethyloct-6-enyl 2-diazo-3-oxobutanoate (59 mg, 0.3 mmol) and caesium carbonate (293 mg, 0.9 mmol) in acetonitrile (6 mL). The reaction was stirred at 60 °C under a nitrogen atmosphere for 8 h. After work-up, the residue obtained was purified by column chromatography on silica gel using hexane:ethyl acetate (3:1) and then DCM:hexane (5:1) to yield 3,7-dimethyloct-6-en-1-yl 1-acetyl-1*H*-indazole-3-carboxylate **128** as a colourless oil (48 mg, 40%).

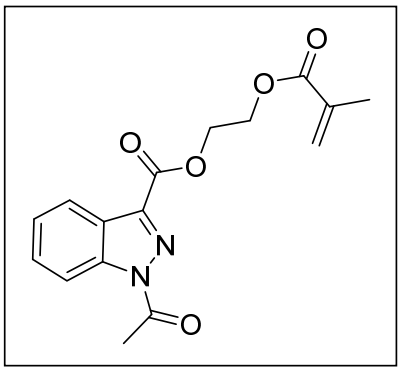
δ_H($CDCl_3$, 400 MHz): 1.01 (3H, d, *J* 6.2, CHC*H*$_3$), 1.22-1.50 (2H, m, C*H*$_2$), 1.56-1.75 [8H, m, containing 1.61 (3H, s, C*H*$_3$), 1.66 (3H, s, C*H*$_3$) and C*H*$_2$], 1.85-2.11 (3H, m, containing C*H*$_2$ and CH_3C*H*), 2.88 [3H, s, C(O)C*H*$_3$], 4.50-4.59 (2H, m, OC*H*$_2$), 5.10 [1H, t, *J* 6.8, C*H*=C(CH_3)$_2$], 7.46 (1H, t, *J* 7.6, ArC*H*), 7.60 (1H, t, *J* 7.8, ArC*H*), 8.20 (1H, d, *J* 7.9, ArC*H*), 8.47 (1H, d, *J* 8.4, ArC*H*); δ_C($CDCl_3$, 100 MHz): 17.7 (*C*H_3), 19.5 (*C*H_3), 23.1 (*C*H_2), 25.4 (*C*H_3), 25.7 (*C*H_3), 29.7 (*C*H), 35.5 (*C*H_2), 37.0 (*C*H_2), 64.5 (O*C*H_2), 115.6 (Ar*C*H), 122.2 (Ar*C*H), 124.5 (Ar*C*H), 124.6 (Ar*C*$_q$), 125.7 (*C*H) alkene 129.9 (Ar*C*H), 131.5 (*C*$_q$) alkene, 140.3 (*C*=N), 142.9 (Ar*C*N), 161.9 (*C*=O) ester, 171.5 (*C*=O) amide; ν_{max} (KBr)/cm^{-1} 2960, 2924, 1731, 1499; *m/z* (ESI$^+$) 365 $[M + Na]^+$ (40%); HRMS (ESI$^+$): exact mass calculated for $C_{20}H_{27}N_2O_3$ $[M + H]^+$ 330.2022. Found 330.2020.

3,7-Dimethylocta-2,6-dien-1-yl 1-acetyl-1*H*-indazole-3-carboxylate 127



The title compound was prepared following the procedure described for pentyl 1-acetyl-1*H*-indazole-3-carboxylate **108** using caesium fluoride (45.6 mg, 0.3 mmol), nonafluorobutanesulfonyl fluoride (0.272 g, 0.9 mmol), 2-(trimethylsilyl)phenol **58** (100 mg, 0.35 mmol), 3,7-dimethylocta-2,6-dienyl 2-diazo-3-oxobutanoate **25** (177 mg, 1.1 mmol) in acetonitrile (4 mL) and caesium fluoride (91 mg, 0.6 mmol). The reaction was stirred at room temperature under a nitrogen atmosphere for 8 h. Following the work-up, attempts were made to purify the residue by column chromatography on silica gel using hexane:ethyl acetate (3:1) and then DCM: hexane (5:1) to yield 3,7-dimethylocta-2,6-dien-1-yl 1-acetyl-1*H*-indazole-3-carboxylate **127** contaminated with 6% impurities which could not be removed by repeated column chromatography on silica gel (19 mg, 16%). δ_H($CDCl_3$, 300 MHz): 1.61 (3H, s, C*H*$_3$), 1.68 (3H, s, C*H*$_3$), 1.73 (3H, s, C*H*$_3$), 2.02-2.13 (4H, m, 2 × C*H*$_2$), 2.88 [3H, s, C(O)C*H*$_3$], 5.01 (2H, d, *J* 7.2, OC*H*$_2$), 5.07 [1H, t, *J* 7.2, C*H*=C(CH_3)$_2$], 5.56 [1H, m, OCH_2C*H*=C(CH_3)], 7.46 (1H, t, *J* 8.1, ArC*H*), 7.56 (1H, t, *J* 7.5, ArC*H*), 8.20 (1H, d, *J* 8.1, ArC*H*), 8.47 (1H, d, *J* 8.1, ArC*H*).

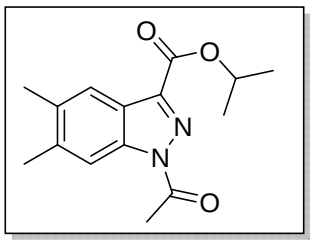
2-(Methacryloyloxy)ethyl 1-acetyl-1*H*-indazole-3-carboxylate 125



The title compound was prepared following the procedure described for pentyl 1-acetyl-1*H*-indazole-3-carboxylate **108** using caesium fluoride (45.6 mg, 0.3 mmol), nonafluorobutanesulfonyl fluoride (0.272 g, 0.9 mmol), 2-(trimethylsilyl)phenol **58** (100 mg, 0.35 mmol), 2-(methacryloyloxy)ethyl 2-diazo-3-oxo-3-phenylpropanoate **26** (195 mg, 0.9 mmol) and caesium carbonate (293 mg, 0.9 mmol) in acetonitrile (6 mL). The reaction was stirred at 60 °C under a nitrogen atmosphere for 8 h. Following the work-up, the residue obtained was purified by column chromatography on silica gel using DCM:ethyl acetate (3:1) and then preparative TLC using hexane:ethyl acetate (65:35) to yield 2-(methacryloyloxy)ethyl 1-acetyl-1*H*-indazole-3-carboxylate **125** as a white solid (22 mg, 20%), m.p. 295-299 ºC. δ_H($CDCl_3$, 400 MHz): 1.96 (3H, d, *J* 1.5, C*H*$_3$), 2.88 [3H, s, C(O)C*H*$_3$], 4.57-4.61 (2H, m, OC*H*$_2$), 4.74-4.77 (2H, m, OC*H*$_2$), 5.60 (1H, d, *J* 1.4, one of alkene C*H*$_2$), 6.18 (1H, s, one of alkene C*H*$_2$), 7.42-7.48 (1H, m, ArC*H*), 7.61 (1H, ddd, *J* 8.5, 7.2, 1.1, ArC*H*), 8.18 (1H, dd, *J* 8.5, 0.9, ArC*H*), 8.47 (1H, dd, *J* 8.5, 0.9, ArC*H*); δ_C($CDCl_3$, 100 MHz): 18.3 (*C*H$_3$), 23.1 [C(O)*C*H$_3$], 62.2 (O*C*H$_2$), 63.2 (O*C*H$_2$), 115.6 (Ar*C*H), 122.1 (Ar*C*H), 123.9 (*C*$_q$)alkene, 124.6 (Ar*C*$_q$), 125.8 (Ar*C*H), 126.3 (*C*H$_2$ alkene), 130.0 (Ar*C*H), 135.9 (*C*=N), 140.3 (Ar*C*N), 161.5 (*C*=O) ester, 167.1 (*C*=O) methacrylate ester, 171.5 (*C*=O) amide; Spectral details as described on page 61 (**Section 3.4.2.1)**.

3.5.3 Synthesis of 5,6-dimethyl-1*H*-indazole-3-carboxylate compounds

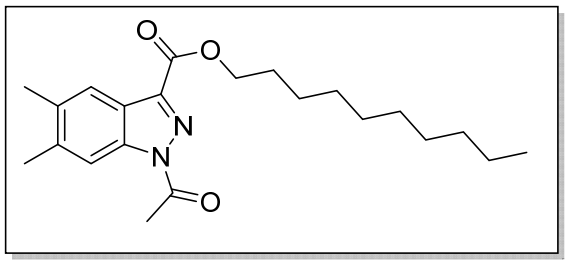
Isopropyl 1-acetyl-5,6-dimethyl-1*H*-indazole-3-carboxylate 168



Caesium fluoride (45.6 mg, 0.3 mmol) and nonafluorobutanesulfonyl fluoride (0.272 g, 0.9 mmol) were added to a stirred solution of 4,5-dimethyl-2-(trimethylsilyl)phenol **79** (100 mg, 0.6 mmol), caesium carbonate (293 mg, 0.9 mmol) and isopropyl 2-diazo-3-oxobutanoate **20** (351 mg, 1.8 mmol) in acetonitrile (6 mL). The reaction was

stirred at 60 °C under a nitrogen atmosphere for 8 h. The solution obtained was diluted with brine (20 mL) and extracted with ethyl acetate (20 mL). The organic layer was dried with $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel using DCM:ethyl acetate eluent (95:5) to yield isopropyl 1-acetyl-1*H*-indazole- 3-carboxylate **168** as a white solid (62 mg, 76%), m.p. 78-83 ºC. δ_H($CDCl_3$, 400 MHz): 1.49 (6H, d, *J* 6.3, 2 × C*H*$_3$), 2.40 (3H, s, ArC*H*$_3$), 2.43 (3H, s, ArC*H*$_3$), 2.85 [3H, s, C(O)C*H*$_3$], 5.41 (1H, sep, *J* 6.2, OC*H*), 7.90 (1H, s, ArC*H*), 8.23 (1H, s, ArC*H*); δ_C($CDCl_3$, 100 MHz): 20.3 (Ar*C*H$_3$), 20.9 (Ar*C*H$_3$), 21.9 (2 × *C*H$_3$), 23.0 [C(O)*C*H$_3$], 69.6 (*C*H), 115.5 (Ar*C*H), 121.6 (Ar*C*H), 123.3 (C_q), 135.1 (Ar*C*CH$_3$), 139.5 (*C*=N), 140.1 (Ar*C*CH$_3$), 140.8 (Ar*C*N), 161.6 (*C*=O) ester, 171.5 (*C*=O) amide; ν_{max} (KBr)/cm^{-1} 2984, 1716, 1644, 1496, 1467, 1378; HRMS (ESI^+): exact mass calculated for $C_{15}H_{19}N_2O_3$ $[M + H]^+$ 275.1396. Found 275.1393.

Decyl 1-acetyl-5,6-dimethyl-1*H*-indazole-3-carboxylate 169

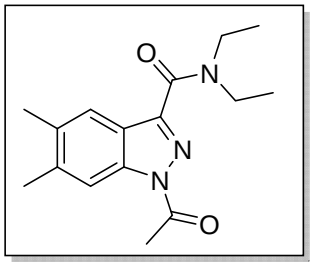


The title compound was prepared using the procedure described for pentyl 1-acetyl-1*H*-indazole-3-carboxylate **108** using caesium fluoride (38 mg, 0.25 mmol), nonafluorobutanesulfonyl fluoride (224 mg, 0.74 mmol), 4,5-dimethyl-2-(trimethylsilyl)phenol **79** (100 mg, 0.5 mmol), caesium carbonate (293 mg, 0.74 mmol) and decyl 2-diazo-3-oxobutanoate (314 mg, 1.5 mmol) in acetonitrile (6 mL). The reaction was stirred at 60 °C under a nitrogen atmosphere for 8 h. Following the work-up, the residue was purified using column chromatography on silica gel using hexane:ethyl acetate eluent (98:2) and then preparative TLC using DCM as eluent to yield decyl 1-acetyl-5,6-dimethyl-1*H*-indazole-3-carboxylate **169** as a yellow solid (38 mg, 41%), m.p. 54-59 ºC. δ_H($CDCl_3$, 400 MHz): 0.88 (3H, t, *J* 6.6, C*H*$_3$), 1.25-1.60 (14H, m, 7 × C*H*$_2$), 1.81-1.91 (2H, m, C*H*$_2$), 2.41 (3H, s, ArC*H*$_3$), 2.44 (3H, s, ArC*H*$_3$), 2.85 [3H, s, C(O)C*H*$_3$], 4.48 (2H, t, *J* 6.9, OC*H*$_2$), 7.92 (1H, s, ArC*H*), 8.25 (1H, s, ArC*H*); ν_{max} (KBr)/cm^{-1} 2985, 2928,

1716, 1644, 1496, 1415, 1104; *m/z* (ESI$^+$) 373 [M + H]$^+$ (32%); HRMS (ESI$^+$): exact mass calculated for $C_{22}H_{33}N_2O_3$ [M + H]$^+$ 372.2491. Found 373.2480.

Note: ^{13}C analysis was run on an impure sample and contained some peaks belonging to impurities. δ_C($CDCl_3$, 100 MHz): 14.1 (CH_2CH_3), 20.3 (ArCH_3), 20.9 (ArCH_3), 22.7 (CH_2), 23.0 [C(O)CH_3], 26.0 (CH_2), 28.7 (CH_2), 29.3 (2 × CH_2), 29.5 (2 × CH_2), 31.9 (OCH_2CH_2), 65.9 (OCH_2), 115.5 (ArCH), 121.6 (ArCH), 123.3 (ArC_q), 135.2 (ArCCH$_3$), 139.5 (C=N), 140.2 (ArCCH$_3$), 140.5 (ArCN), 162.2 (C=O) ester, 171.5 (C=O) amide.

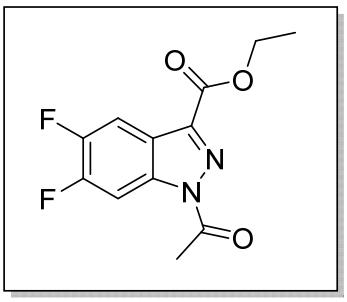
1-Acetyl-*N*,*N*-diethyl-5,6-dimethyl-1*H*-indazole-3-carboxamide 170



The title compound was prepared using the procedure described for pentyl 1-acetyl-1*H*-indazole-3-carboxylate **108** using caesium fluoride (59 mg, 0.39 mmol), nonafluorobutanesulfonyl fluoride (362 mg, 1.2 mmol), 4,5-dimethyl-2-(trimethylsilyl)phenol **79** (150 mg, 0.77 mmol), caesium carbonate (391 mg, 1.2 mmol) and 2-diazo-*N*,*N*-diethyl-3-oxobutanamide **45** (421 mg, 2.3 mmol) in acetonitrile (8 mL). The reaction was stirred at 60 °C under a nitrogen atmosphere for 8 h. Following the work-up, the residue was purified using column chromatography on silica gel using hexane:ethyl acetate eluent (70:30) to yield 1-acetyl-*N*,*N*-diethyl-5,6-dimethyl-1*H*-indazole-3-carboxamide **170** as an orange solid (68 mg, 30%), m.p. 67-69 ºC. δ_H($CDCl_3$, 400 MHz): δ_H($CDCl_3$, 400 MHz): 1.32 (6H, dt, *J* 2.3, 6.3, 2 × NCH_2CH_3), 2.37 (3H, s, ArCH_3), 2.43 (3H, s, ArCH_3), 2.75 (3H, s, C(O)CH_3), 3.59-3.70 (4H, m, 2 × NCH_2), 7.79 (1H, s, ArCH), 8.21 (1H, s, ArCH). δ_C($CDCl_3$, 100 MHz): 12.9 (CH_3), 14.7 (CH_3), 20.1 (ArCH_3), 20.9 (ArCH_3), 23.0 [CO(CH_3)], 40.9 (NCH_2), 43.5 (NCH_2), 115.2 (ArCH), 121.7 (ArCH), 124.3 (ArC_q), 134.7 (ArCCH$_3$), 138.6 (C=N), 140.1 (ArCCH$_3$), 144.3 (ArCN), 162.5 [NC(O)(CH_3CH_2)$_2$], 171.1 [NC(O)CH_3]; ν_{max} (KBr)/cm^{-1} 2974, 1635, 1382, 1175; *m/z* (ESI$^+$) 310 [M + Na]$^+$ (100%), 288 [M + H]$^+$(4); HRMS (ESI$^+$): exact mass calculated for $C_{16}H_{22}N_3O_2$ [M + H]$^+$ 288.1712. Found 2881711.

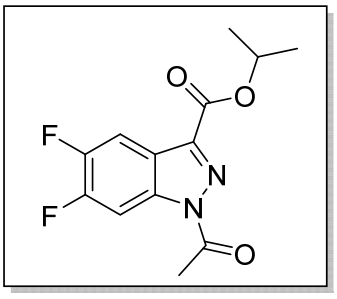
3.5.4 Synthesis of 5,6-difluoro-1*H*-indazole-3-carboxylate compounds

Ethyl 1-acetyl-5,6-difluoro-1H-indazole-3-carboxylate 178



The title compound was prepared using the procedure described for pentyl 1-acetyl-1*H*-indazole-3-carboxylate **108** using caesium fluoride (38 mg, 0.25 mmol), nonafluorobutanesulfonyl fluoride (224 mg, 0.74 mmol), 4,5-difluoro-2-(trimethylsilyl)phenol **78** (100 mg, 0.5 mmol), caesium carbonate (241 mg, 0.74 mmol) and ethyl 2-diazo-3-oxobutanoate **19** (222 mg, 1.5 mmol) in acetonitrile (6 mL). The reaction was stirred at 60 °C under a nitrogen atmosphere for 24 h. Following the work-up, the residue was purified using column chromatography on silica gel using DCM: hexane (80:20) to yield ethyl 1-acetyl-5,6-difluoro-1*H*-indazole-3-carboxylate **178** as a white solid (68 mg, 51%), m.p. 116-118 ºC. δ_H ($CDCl_3$, 400MHz): 1.51 (3H, t, *J* 7.1, CH_2CH_3), 2.87 [3H, s, C(O)CH_3], 4.56 (2H, q, *J* 7.1, OCH_2), 7.98 (1H, dd, $^3J_{HF}$ 9.1, $^4J_{HF}$ 7.8, ArC*H*), 8.31 (1H, dd, $^3J_{HF}$ 9.9, $^4J_{HF}$ 6.8, ArC*H*); δ_C($CDCl_3$, 100 MHz): 14.3 (CH_2CH_3), 22.8 [C(O)CH_3], 62.2 (OCH_2), 104.1 (d, $^2J_{CF}$ 24.1, Ar*C*H), 109.1 (dd, $^2J_{CF}$ 20.6, $^3J_{CF}$ 1.2, Ar*C*H), 120.4 (dd, $^3J_{CF}$ 8.7, $^4J_{CF}$ 1.1, ArC_q), 135.9 (d, $^3J_{CF}$ 10.6, Ar*C*N), 140.4 (d, $^4J_{CF}$ 4.4, *C*=N), 149.6 (dd, $^1J_{CF}$ 249.5, $^2J_{CF}$ 15.3, Ar*C*F), 152.6 (dd, $^1J_{CF}$ 253.9, $^2J_{CF}$ 15.8, Ar*C*F), 161.3 (*C*=O) ester, 171.2 (*C*=O) amide; ν_{max} (KBr)/cm^{-1} 2986, 1722, 1505, 1319, 1159; *m/z* (ESI^+) 291 $[M + Na]^+$ (5%); HRMS (ESI^+): exact mass calculated for $C_{12}H_{11}N_2O_3F_2$ $[M + H]^+$ 269.0738. Found 269.0747.

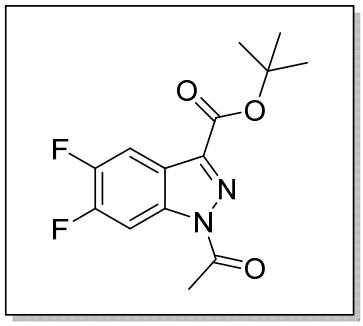
Isopropyl 1-acetyl-5,6-difluoro-1*H*-indazole-3-carboxylate 179



The title compound was prepared using the procedure described for pentyl 1-acetyl-1*H*-indazole-3-carboxylate **108** using caesium fluoride (38 mg, 0.25 mmol), nonafluorobutanesulfonyl fluoride (224 mg, 0.74 mmol), 4,5-difluoro-2-(trimethylsilyl)phenol **78** (100 mg, 0.5 mmol), caesium carbonate (241 mg, 0.74 mmol) and isopropyl 2-diazo-3-oxobutanoate **20** (255 mg, 1.5 mmol) in acetonitrile (6 mL). The reaction was stirred at 60 °C under

a nitrogen atmosphere for 24 h. Following the work-up, the residue was purified using column chromatography on silica gel using DCM: hexane (80:20) to yield isopropyl 1-acetyl-5,6-difluoro-1*H*-indazole-3-carboxylate **179** as a white solid (80 mg, 57%), m.p. 134-139 ºC. δ_H ($CDCl_3$, 400MHz): 1.49 (6H, d, *J* 6.3, 2 × C*H*$_3$), 2.86 [3H, s, C(O)C*H*$_3$], 5.35-5.46 (1H, m, OC*H*), 7.94 (1H, dd, $^3J_{HF}$ 9.3, $^4J_{HF}$ 7.7, ArC*H*), 8.30 (1H, dd, $^3J_{HF}$ 10.0, $^4J_{HF}$ 6.8, ArC*H*); δ_C($CDCl_3$, 100 MHz): 21.9 (2 × *C*H$_3$), 22.8 [C(O)*C*H$_3$], 70.2 (O*C*H), 104.0 (d, $^2J_{CF}$ 23.8, Ar*C*H), 109.1 (d, $^2J_{CF}$ 20.6, Ar*C*H), 120.3 (d, $^3J_{CF}$ 8.8, *C*$_q$), 135.9 (d, $^3J_{CF}$ 11.1, Ar*C*N), 140.8 (dd, $^4J_{CF}$ 4.4, $^5J_{CF}$ 1.5, *C*=N), 149.6 (dd, $^1J_{CF}$ 249.7, $^2J_{CF}$ 14.8, Ar*C*F), 152.5 (dd, $^1J_{CF}$ 254.0, $^2J_{CF}$ 15.7, Ar*C*F), 160.8 (*C*=O) ester, 171.2 (*C*=O) amide; ν_{max} (KBr)/cm^{-1} 2984, 1737, 1711, 1317, 1167; *m/z* (ESI$^+$) 282 M$^+$ (20%), 263 (60); HRMS (ESI$^+$): exact mass calculated for $C_{13}H_{13}F_2N_2O_3$ [M + H]$^+$ 283.1083. Found 283.1077.

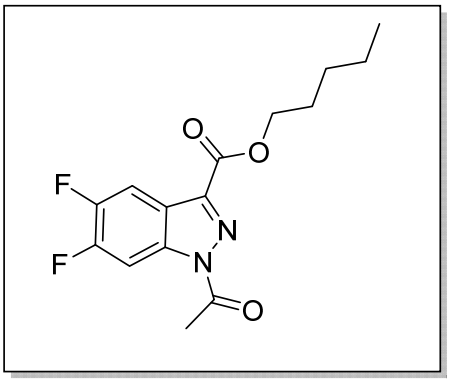
_t_-Butyl 1-acetyl-5,6-difluoro-1*H*-indazole-3-carboxylate 180



The title compound was prepared using the procedure described for pentyl 1-acetyl-1*H*-indazole-3-carboxylate **108** using caesium fluoride (38 mg, 0.25 mmol), nonafluorobutanesulfonyl fluoride (224 mg, 0.74 mmol), 4,5-difluoro-2-(trimethylsilyl)phenol **78** (100 mg, 0.5 mmol), caesium carbonate (241 mg, 0.74 mmol) and *t*-butyl 2-diazo-3-oxobutanoate **21** (276 mg, 1.5 mmol) in acetonitrile (6 mL). The reaction was stirred at 60 °C under a nitrogen atmosphere for 24 h. Following the work-up, the residue was purified using column chromatography on silica gel using DCM: hexane (80:20) to yield *t*-butyl 1-acetyl-5,6-difluoro-1*H*-indazole-3-carboxylate **180** as a white solid (68 mg, 46%), m.p. 144-146˚C. δ_H ($CDCl_3$, 400MHz): 1.70 (9H, s, 3 × C*H*$_3$), 2.85 [3H, s, C(O)C*H*$_3$], 7.90 (1H, dd, $^3J_{HF}$ 9.2, $^4J_{HF}$ 7.8, ArC*H*), 8.30 (1H, dd, $^3J_{HF}$ 10.0, $^4J_{HF}$ 6.8, ArC*H*); δ_C($CDCl_3$, 100 MHz): 22.7 [C(O)*C*H$_3$], 28.2 (3 × *C*H$_3$ of *t*-butyl), 83.8 [*C*(CH$_3$)$_3$], 104.0 (d, $^2J_{CF}$ 24.2, Ar*C*H), 109.1 (dd, $^2J_{CF}$ 20.6, $^3J_{CF}$ 1.4, Ar*C*H), 120.2 (dd, $^3J_{CF}$ 5.3, $^4J_{CF}$ 1.5, Ar*C*$_q$), 136.0 (d, $^3J_{CF}$ 11.3, Ar*C*N), 140.1 (*C*=N), 141.6-152.1 (m, 2 × Ar*C*F), 160.2 (*C*=O) ester, 171.3 (*C*=O) amide; ν_{max}

(KBr)/cm^{-1} 2935, 1723, 1499, 1146; *m/z* (ESI$^-$) 318 [M - H + Na]$^+$ (10%). HRMS (ESI$^-$): exact mass calculated for $C_{14}H_{13}N_2O_4F_2$ [M - H]$^-$ 295.0894. Found 295.0883.

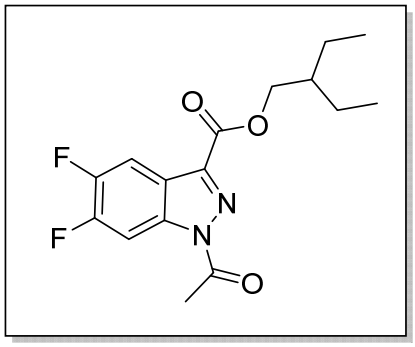
Pentyl 1-acetyl-5,6-difluoro-1*H*-indazole-3-carboxylate 182



The title compound was prepared using the procedure described for pentyl 1-acetyl-1*H*-indazole-3-carboxylate **108** using caesium fluoride (38 mg, 0.25 mmol), nonafluorobutanesulfonyl fluoride (224 mg, 0.74 mmol), 4,5-difluoro-2-(trimethylsilyl)phenol **78** (100 mg, 0.5 mmol), caesium carbonate (293 mg, 0.74 mmol) and pentyl 2-diazo-3-oxobutanoate **23** (297 mg, 1.5 mmol) in acetonitrile (6 mL). The reaction was stirred at 60 °C under a nitrogen atmosphere for 24 h. Following the work-up, the residue was purified using column chromatography on silica gel using DCM:hexane (80:20) to yield pentyl 1-acetyl-5,6-difluoro-1*H*-indazole-3-carboxylate **182** as a yellow oil (55 mg, 35%). δ_H($CDCl_3$, 400 MHz): 0.95 (3H, t, *J* 7.0, C*H*$_3$), 1.40-1.70 (4H, m, 2 × C*H*$_2$), 1.83-1.91 (2H, m, C*H*$_2$), 2.86 [3H, s, C(O)C*H*$_3$], 4.48 (2H, t, *J* 6.8, OC*H*$_2$), 7.96 (1H, dd, $^3J_{HF}$ 9.2, $^4J_{HF}$ 7.7, ArC*H*), 8.31 (1H, dd, $^3J_{HF}$ 10.0, $^4J_{HF}$ 6.8, ArC*H*); δ_C($CDCl_3$, 100 MHz): 13.9 (*C*H$_3$), 22.3 (*C*H$_2$), 22.8 [C(O)*C*H$_3$], 28.1 (*C*H$_2$), 28.3 (*C*H$_2$), 66.2 (O*C*H$_2$), 104.1 (d, $^2J_{CF}$ 23.9, Ar*C*H), 109.0 (d, $^2J_{CF}$ 20.6, Ar*C*H), 120.4 (dd, $^3J_{CF}$ 6.5, $^4J_{CF}$ 3.8, Ar*C*$_q$), 135.9 (d, $^3J_{CF}$ 11.2, Ar*C*N), 140.5 (d, $^4J_{CF}$ 3.1, *C*=N), 148.3-157.7 (m, 2 × Ar*C*F), 161.3 (*C*=O) ester, 171.2 (*C*=O) amide; ν_{max} (film)/cm^{-1} 2922, 1734, 1509, 1317, 1159; *m/z* (ESI$^-$) 309 [M - H]$^-$ (25%), 311 (25); HRMS (ESI$^+$): exact mass calculated for $C_{15}H_{17}N_2O_3F_2$ [M + H]$^+$ 311.1207. Found 311.1198.

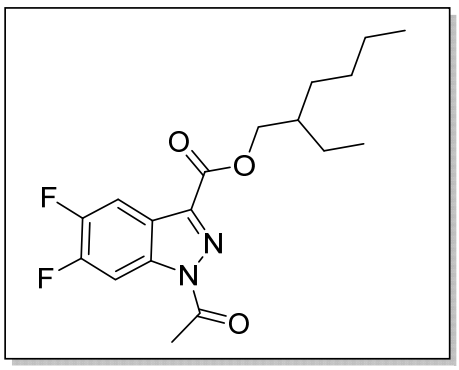
Note: Significant amounts of 4,5-difluoro-2-(trimethylsilyl)phenol (20 mg) **78** was recovered unreacted after column chromatography.

2-Ethylbutyl 1-acetyl-5,6-difluoro-1*H*-indazole-3-carboxylate 183



The title compound was prepared using the procedure described for pentyl 1-acetyl-1*H*-indazole-3-carboxylate **108** using caesium fluoride (38 mg, 0.25 mmol), nonafluorobutanesulfonyl fluoride (224 mg, 0.74 mmol), 4,5-difluoro-2-(trimethylsilyl)phenol **78** (100 mg, 0.5 mmol), caesium carbonate (293 mg, 0.74 mmol) and 2-ethylbutyl 2-diazo-3-oxobutanoate **30** (314 mg, 1.5 mmol) in acetonitrile (6 mL). The reaction was stirred at 60 °C under a nitrogen atmosphere for 24 h. Following the work-up, the residue was purified using column chromatography on silica gel using DCM:hexane (80:20) to yield 2-ethylbutyl 1-acetyl-5,6-difluoro-1*H*-indazole-3-carboxylate **183** as a white solid, (64 mg, 39%), m.p. 78-81 ºC. δ_H($CDCl_3$, 400 MHz): 0.99 (6H, t, *J* 7.5, 2 × C*H*$_3$), 1.50 (4H, m, 2 × C*H*$_2$), 1.77 [1H, td, *J* 12.5, 6.2, C*H*(CH_3)$_2$], 2.86 [3H, s, C(O)C*H*$_3$], 4.42 (2H, t, *J* 5.9, OC*H*$_2$), 7.94 (1H, dd, $^3J_{HF}$ 9.3, $^4J_{HF}$ 7.6, ArC*H*), 8.30 (1H, dd, $^3J_{HF}$ 10.0, $^4J_{HF}$ 6.8, ArC*H*); δ_C($CDCl_3$, 100 MHz): 11.0 (2 × *C*H_3), 22.7 [C(O)*C*H_3], 23.5 (2 × *C*H_2), 40.5 (*C*H), 68.1 (O*C*H_2), 104.1 (d, $^2J_{CF}$ 23.9, Ar*C*H), 108.9 (dd, $^2J_{CF}$ 20.7, $^3J_{CF}$ 1.5, Ar*C*H), 120.3 (dd, $^3J_{CF}$ 20.7, $^4J_{CF}$ 1.5, ArC_q), 135.9 (d, $^3J_{CF}$ 10.7, Ar*C*N), 140.5 (dd, $^4J_{CF}$ 4.4, $^5J_{CF}$ 1.5, *C*=N), 149.6 (dd, $^1J_{CF}$ 249.3, $^2J_{CF}$ 5.2, Ar*C*F), 152.5 (dd, $^1J_{CF}$ 254.1, $^2J_{CF}$ 15.7, Ar*C*F), 161.4 (*C*=O) ester, 171.2 (*C*=O) amide; ν_{max} (KBr)/cm^{-1} 2962, 1733, 1507, 1319, 1157; HRMS (ESI^+): exact mass calculated for $C_{16}H_{19}F_2N_2O_3$ $[M + H]^+$ 325.1364. Found 325.1367.

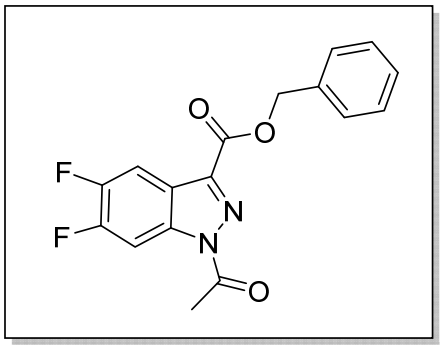
2-Ethylhexyl 1-acetyl-5,6-difluoro-1*H*-indazole-3-carboxylate 184



The title compound was prepared using the procedure described for pentyl 1-acetyl-1*H*-indazole-3-carboxylate **108** using caesium fluoride (38 mg, 0.25 mmol), nonafluorobutanesulfonyl fluoride (224 mg, 0.74 mmol), 4,5-difluoro-2-(trimethylsilyl)phenol **78** (100 mg, 0.5

mmol), caesium carbonate (293 mg, 0.74 mmol) and 2-ethylhexyl 2-diazo-3-oxobutanoate **28** (360 mg, 1.5 mmol) in acetonitrile (6 mL). The reaction was stirred at 60 °C under a nitrogen atmosphere for 24 h. Following the work-up, the residue was purified using column chromatography on silica gel using DCM: hexane (80:20) to yield 2-ethylhexyl 1-acetyl-5,6-difluoro-1*H*-indazole-3-carboxylate **184** as a white solid (70 mg, 40%), m.p. 72-73 ºC. δ_H($CDCl_3$, 400 MHz): 0.92 (3H, t, *J* 6.9, C*H*$_3$), 0.99 (3H, t, *J* 7.5, C*H*$_3$), 1.30-1.52 (8H, m, 4 × C*H*$_2$), 1.82 (1H, td, *J* 12.3, 6.0, C*H*), 2.86 [3H, s, C(O)C*H*$_3$], 4.41 (2H, d, *J* 5.9, OC*H*$_2$), 7.94 (1H, dd, $^3J_{HF}$ 9.2, $^4J_{HF}$ 7.7, ArC*H*), 8.31 (1H, dd, $^3J_{HF}$ 10.0, $^4J_{HF}$ 6.8, ArC*H*); δ_C($CDCl_3$, 100 MHz): 11.0 (*C*H$_3$), 14.0 (*C*H$_3$), 22.7 (*C*H$_2$), 22.9 [C(O)*C*H$_3$], 24.0 (*C*H$_2$), 28.9 (*C*H$_2$), 30.6 (*C*H$_2$), 38.9 (*C*H), 68.5 (O*C*H$_2$), 104.1 (d, $^2J_{CF}$ 24.0, Ar*C*H), 108.9 (dd, $^2J_{CF}$ 20.7, $^3J_{CF}$ 1.5, Ar*C*H), 120.3 (d, $^3J_{CF}$ 8.9, Ar*C*$_q$), 135.9 (d, $^3J_{CF}$ 11.1, Ar*C*N), 140.5 (dd, $^4J_{CF}$ 4.5, $^5J_{CF}$ 1.5, *C*=N), 149.6 (dd, $^1J_{CF}$ 249.4, $^2J_{CF}$ 15.3, Ar*C*F), 152.5 (dd, $^1J_{CF}$ 254.2, $^2J_{CF}$ 15.7, Ar*C*F), 161.4 (*C*=O) ester, 171.2 (*C*=O) amide; ν_{max} (KBr)/cm^{-1} 2928, 1726, 1509, 1319, 1156; *m/z* (ESI$^-$) 309 [M - H - $COCH_3$]$^+$ (20%), 315 (100); HRMS (ESI$^+$): exact mass calculated for $C_{18}H_{23}F_2N_2O_3$ [M + H]$^+$ 353.1853. Found 353.1864.

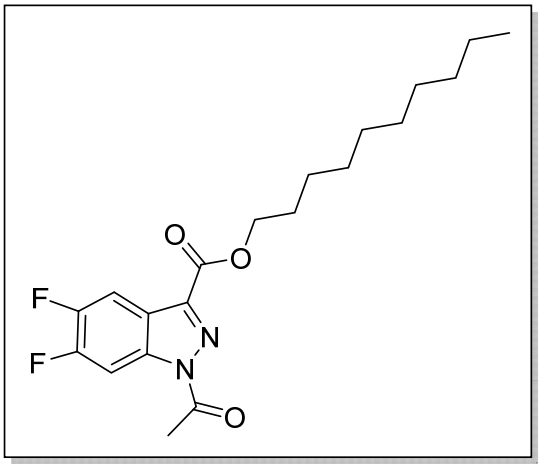
Benzyl 1-acetyl-5,6-difluoro-1*H*-indazole-3-carboxylate 181



The title compound was prepared using the procedure described for pentyl 1-acetyl-1*H*-indazole-3-carboxylate **108** using caesium fluoride (38 mg, 0.25 mmol), nonafluorobutanesulfonyl fluoride (224 mg, 0.74 mmol), 4,5-difluoro-2-(trimethylsilyl)phenol **78** (100 mg, 0.5 mmol), caesium carbonate (241 mg, 0.74 mmol) and benzyl 2-diazo-3-oxobutanoate **22** (327 mg, 1.5 mmol) in acetonitrile (6 mL). The reaction was stirred at 60 °C under a nitrogen atmosphere for 24 h. Following the work-up, the residue was purified using column chromatography on silica gel using DCM: hexane (80:20) to yield benzyl 1-acetyl-5,6-difluoro-1*H*-indazole-3-carboxylate **181** as a white solid (65 mg, 39%), m.p. 119-121 ºC. δ_H ($CDCl_3$, 400MHz): 2.85

[3H, s, C(O)CH_3], 5.52 (2H, s, OCH_2C$_6$H$_5$), 7.26-7.64 (5H, m, 5 × ArC*H*), 7.94 (1H, dd, $^3J_{HF}$ 9.1, $^4J_{HF}$ 7.7, ArC*H*), 8.30 (1H, dd, $^3J_{HF}$ 9.8, $^4J_{HF}$ 6.7, ArC*H*); δ_C(CDCl$_3$, 100 MHz): 22.8 [C(O)*C*H$_3$], 67.6 (O*C*H$_2$C$_6$H$_5$), 104.1 (d, $^2J_{CF}$ 24.2, Ar*C*H), 109.0 (dd, $^2J_{CF}$ 21.2, $^3J_{CF}$ 1.6, Ar*C*H), 120.1 (d, $^3J_{CF}$ 54.0, ArC_q), 128.6 (2 × Ar*C*H benzyl), 128.8 (Ar*C*H benzyl), 128.8 (2 × Ar*C*H benzyl), 135.0 (ArC_q benzyl), 161.1 (*C*=O) ester, 171.2 (*C*=O) amide, Ar*C*N, *C*=N and 2 × *C*F too close to baseline to detect. ν_{max} (KBr)/cm^{-1} 2926, 1722, 1504, 1311, 1153; *m/z* (ESI$^+$) 330 [M]$^+$ (40%), 331 (10); HRMS (ESI$^+$): exact mass calculated for C$_{17}$H$_{13}$F$_2$N$_2$O$_3$ [M + H]$^+$ 331.0910. Found 331.0903.

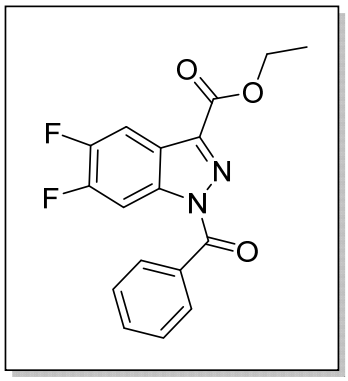
Decyl 1-acetyl-5,6-difluoro-1*H*-indazole-3-carboxylate 187



The title compound was prepared using the procedure described for pentyl 1-acetyl-1*H*-indazole-3-carboxylate **108** using caesium fluoride (38 mg, 0.25 mmol), nonafluorobutanesulfonyl fluoride (224 mg, 0.74 mmol), 4,5-difluoro-2-(trimethylsilyl)phenol **78** (100 mg, 0.5 mmol), caesium carbonate (241 mg, 0.74 mmol) and decyl 2-diazo-3-oxobutanoate **29** (402 mg, 1.5 mmol) in acetonitrile (6 mL). The reaction was stirred at 60 °C under a nitrogen atmosphere for 24 h. Following the work-up, the residue was purified using column chromatography on silica gel using DCM: hexane (80:20) to yield decyl 1-acetyl-5,6-difluoro-1*H*-indazole-3-carboxylate **187** as a yellow solid (60 mg, 32%), m.p. 59-61 ºC. δ_H (CDCl$_3$, 400MHz): 0.88 (3H, t, *J* 6.8, C*H*$_3$), 1.22-1.37 (14H, m, 7 × C*H*$_2$), 1.80-1.90 (2H, m, C*H*$_2$), 2.86 [3H, s, C(O)C*H*$_3$], 4.48 (2H, t, *J* 6.8, OC*H*$_2$), 7.96 (1H, dd, $^3J_{HF}$ 9.3, $^4J_{HF}$ 7.6, ArC*H*), 8.31 (1H, dd, $^3J_{HF}$ 10.0, $^4J_{HF}$ 6.8, ArC*H*); δ_C(CDCl$_3$, 100 MHz): 14.1 (CH$_2$C*H*$_3$), 22.7 [C(O)*C*H$_3$], 22.8 (C*H*$_2$), 25.9 (C*H*$_2$), 28.6 (C*H*$_2$), 29.2 (C*H*$_2$), 29.3 (C*H*$_2$), 29.5 (2 × C*H*$_2$), 31.9 (OCH$_2$*C*H$_2$), 66.2 (OC*H*$_2$), 104.1 (d, $^2J_{CF}$ 24.0, Ar*C*H), 109.0 (d, $^2J_{CF}$ 20.5, Ar*C*H), 120.4 (d, $^3J_{CF}$ 8.8, ArC_q), 135.9 (d, $^3J_{CF}$ 11.6, Ar*C*N),

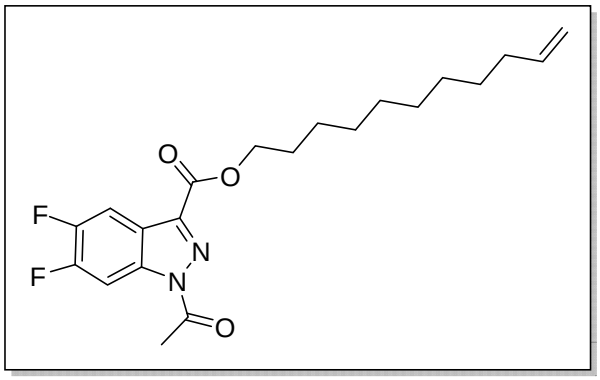
140.5 (d, $^{4}J_{CF}$ 4.2, *C*=N), 149.7 (dd, $^{1}J_{CF}$ 270.0, $^{2}J_{CF}$ 20.8, Ar*C*F), 152.6 (dd, $^{1}J_{CF}$ 243.3, $^{2}J_{CF}$ 7.6, Ar*C*F), 161.3 (*C*=O) ester, 171.2 (*C*=O) amide; ν_{max} (KBr)/cm^{-1} 2922, 2854, 1734, 1509, 1317, 1158; HRMS (ESI^{+}): exact mass calculated for $C_{20}H_{27}F_2N_2O_3$ [M + H]$^{+}$ 381.1990. Found 381.2005.

Ethyl 1-benzoyl-5,6-difluoro-1*H*-indazole-3-carboxylate 186



The title compound was prepared using the procedure described for pentyl 1-acetyl-1*H*-indazole-3-carboxylate **108** using caesium fluoride (38 mg, 0.25 mmol), nonafluorobutanesulfonyl fluoride (224 mg, 0.74 mmol), 4,5-difluoro-2-(trimethylsilyl)phenol **78** (100 mg, 0.5 mmol), caesium carbonate (241 mg, 0.74 mmol) and ethyl 2-diazo-3-oxo-3-phenylpropanoate **39** (327 mg, 1.5 mmol) in acetonitrile (6 mL). The reaction was stirred at 60 °C under a nitrogen atmosphere for 24 h. Following the work-up, the residue was purified using column chromatography on silica gel using DCM: hexane (80:20) to yield ethyl 1-benzoyl-5,6-difluoro-1*H*-indazole-3-carboxylate **186** as a white solid, (45 mg, 27%), m.p. 119-120 ° C. δ_H ($CDCl_3$, 400MHz): 1.50 (3H, t, *J* 7.1, C*H*$_3$), 4.55 (2H, q, *J* 7.1, C*H*$_2$), 7.26-7.50 (5H, m, 5 × ArC*H*), 7.55-7.61 (1H, m, ArC*H*), 8.07 (1H, dd, $^{3}J_{HF}$ 9.4, $^{4}J_{HF}$ 7.7, ArC*H*); δ_C($CDCl_3$, 100 MHz): 14.4 (CH_2CH_3), 61.7 (OCH_2), 98.4 (d, $^{2}J_{CF}$ 23.5 Ar*C*H indazole), 109.2 (dd, $^{2}J_{CF}$ 20.1, $^{3}J_{CF}$ 1.4, Ar*C*H indazole), 113.6 (Ar*C*H phenyl), 113.8 (Ar*C*H phenyl), 118.2 (Ar*C*H phenyl), 118.4 (Ar*C*H phenyl), 119.5 (ArC_q phenyl), 119.6 (Ar*C*H phenyl), 120.0 (d, $^{3}J_{CF}$ 8.2, ArC_q indazole), 135.0 (d, $^{3}J_{CF}$ 2.7, Ar*C*N), 135.9 (*C*=N), 139.0-151.0 (m, 2 × Ar*C*F), 161.8 (*C*=O) ester, 164.1 (*C*=O) amide; ν_{max} (KBr)/cm^{-1} 1726, 1645, 1521, 1496, 115; *m/z* (ESI^{+}) 331 [M + H]$^{+}$ (10%), 330 (40); HRMS (ESI^{+}): exact mass calculated for $C_{17}H_{13}F_2N_2O_3$ [M + H]$^{+}$ 331.0894. Found 331.0903.

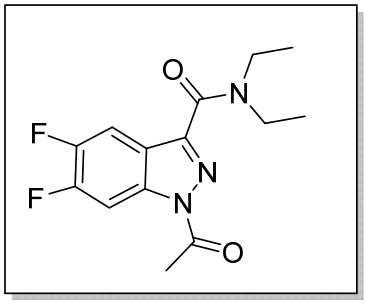
Undec-10-en-1-yl 1-acetyl-5,6-difluoro-1*H*-indazole-3-carboxylate 188



The title compound was prepared using the procedure described for pentyl 1-acetyl-1*H*-indazole-3-carboxylate **108** using caesium fluoride (38 mg, 0.25 mmol), nonafluorobutanesulfonyl fluoride (224 mg, 0.74 mmol), 4,5-difluoro-2-(trimethylsilyl)phenol **78** (100 mg, 0.5 mmol), caesium carbonate (241 mg, 0.74 mmol) and undec-10-en-1-yl 2-diazo-3-oxobutanoate **31** (420 mg, 1.5 mmol) in acetonitrile (6 mL). The reaction was stirred at 60 °C under a nitrogen atmosphere for 24 h. Following the work-up, the residue was purified using column chromatography on silica gel using DCM: hexane (80:20) to yield undec-10-en-1-yl 1-acetyl-5,6-difluoro-1*H*-indazole-3-carboxylate **188** as an off white solid (45 mg, 23%), m.p. 59-61 ºC. δ_H ($CDCl_3$, 400MHz): 1.24-1.50 (12H, m, 6 × C*H*$_2$), 1.80-1.91 (2H, m, C*H*$_2$), 2.04 (2H, dd, *J* 13.4, 6.3, C*H*$_2$), 2.87 [3H, s, C(O)C*H*$_3$], 4.48 (2H, t, *J* 6.3, OC*H*$_2$), 4.96 (2H, dd, *J* 23.7, 13.7, CH=C*H*$_2$), 5.81 (1H, tdd, *J* 13.3, 10.1, 6.7, C*H*=CH$_2$), 7.96 (1H, dd, $^3J_{HF}$ 9.0, $^4J_{HF}$ 7.9, ArC*H*), 8.31 (1H, dd, $^3J_{HF}$ 9.9, $^4J_{HF}$ 6.8, ArC*H*); δ_C($CDCl_3$, 100 MHz): 22.8 [C(O)*C*H$_3$], 25.9 (*C*H$_2$), 28.6 (*C*H$_2$), 28.9 (*C*H$_2$), 29.1 (*C*H$_2$), 29.2 (*C*H$_2$), 29.4 (*C*H$_2$), 29.4 (*C*H$_2$), 33.8 (*C*H$_2$), 66.3 (O*C*H$_2$), 104.1 (d, $^2J_{CF}$ 23.8, Ar*C*H), 109.0 (d, $^2J_{CF}$ 20.8, Ar*C*H), 114.2 (*C*H$_2$) alkene, 120.4 (d, $^3J_{CF}$ 8.5, Ar*C*$_q$), 135.9 (d, $^3J_{CF}$ 11.6, Ar*C*N), 139.2 (*C*H) alkene, 140.5 (dd, $^4J_{CF}$ 4.1, $^5J_{CF}$ 1.4, *C*=N), 149.6 (d, $^1J_{CF}$ 264.5, Ar*C*F), 152.6 (d, $^1J_{CF}$ 254.0, Ar*C*F), 161.3 (*C*=O) ester, 171.2 (*C*=O) amide; ν_{max} (KBr)/cm^{-1}: 2928, 2849, 1716, 1643, 1317, 1148; HRMS (ESI$^+$): exact mass calculated for $C_{20}H_{27}F_2N_2O_3$ $[M + H]^+$ 381.1051. Found 330.1065.

Note: The sample contained 3% starting material after column chromatography on silica gel.

1-Acetyl-*N*,*N*-diethyl-5,6-difluoro-1*H*-indazole-3-carboxamide 185



The title compound was prepared using the procedure described for pentyl 1-acetyl-1*H*-indazole-3-carboxylate **108** using caesium fluoride (38 mg, 0.25 mmol), nonafluorobutanesulfonyl fluoride (224 mg, 0.74 mmol), 4,5-difluoro-2-(trimethylsilyl)phenol **78** (100 mg, 0.5 mmol), caesium carbonate (241 mg, 0.74 mmol) and 2-diazo-*N*,*N*-diethyl-3-oxobutanamide **45** (275 mg, 1.5 mmol) in acetonitrile (6 mL). The reaction was stirred at 60 °C under a nitrogen atmosphere for 24 h. Following the work-up, the residue was purified using column chromatography on silica gel using DCM: hexane (80:20) to yield 1-acetyl-*N*,*N*-diethyl-5,6-difluoro-1*H*-indazole-3-carboxamide **185** as a low melting brown solid (47 mg, 32%). δ_H ($CDCl_3$, 400MHz): 1.28-1.39 [6H, m, containing 1.31 (3H, t, *J* 7.1, C*H*$_3$) and 1.36 (3H, t, *J* 7.0, C*H*$_3$)], 2.77 [3H, s, C(O)CH_3], 3.62 (2H, q, *J* 7.2, NC*H*$_2$), 3.75 (2H, q, *J* 7.0, NC*H*$_2$), 7.94 (1H, dd, $^3J_{HF}$ 9.3, $^4J_{HF}$ 7.8, ArC*H*), 8.25 (1H, dd, $^3J_{HF}$ 10.0, $^4J_{HF}$ 6.8, ArC*H*); δ_C($CDCl_3$, 100 MHz):12.8 (*C*H_3), 14.7 (*C*H_3), 22.6 [C(O)*C*H_3], 41.3 (*C*H_2), 43.5 (*C*H_2), 103.6 (d, $^2J_{CF}$ 23.9, Ar*C*H), 109.6 (dd, $^2J_{CF}$ 20.5, $^3J_{CF}$ 1.5, Ar*C*H), 122.7 (dd, $^3J_{CF}$ 8.5, $^4J_{CF}$ 1.1, ArC_q), 135.1 (d, $^3J_{CF}$ 11.1, Ar*C*N), 144.0 (dd, $^4J_{CF}$ 4.3, $^5J_{CF}$ 1.4, *C*=N), 149.2 (dd, $^1J_{CF}$ 248.5, $^2J_{CF}$ 15.2, Ar*C*F), 152.5 (dd, $^1J_{CF}$ 253.5, $^2J_{CF}$ 15.7, Ar*C*F), 161.3 (*C*=O) ester, 170.7 (*C*=O) amide; ν_{max} (KBr)/cm^{-1} 2981, 1734, 1629, 1430; *m/z* (ESI$^+$) 318 $[M + Na]^+$ (70%), 296 (10); HRMS (ESI$^+$): exact mass calculated for $C_{14}H_{16}N_3O_2F_2$ $[M + H]^+$ 296.1211. Found 296.1205.

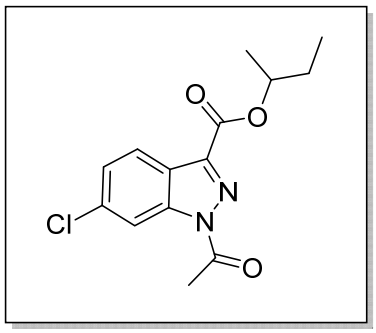
Note: The ^{1}H and ^{13}C NMR spectra showed 2% unreacted starting material after column chromatography.

3.5.5 Synthesis of 5/6-substituted indazole compounds using unsymmetrical aryne precursors

sec-Butyl 1-acetyl-6-chloro-1*H*-indazole-3-carboxylate 189 and _sec_-butyl 1-acetyl-5-chloro-1*H*-indazole-3-carboxylate 190 70:30

Using the procedure described for pentyl 1-acetyl-1*H*-indazole-3-carboxylate **108**, caesium fluoride (46 mg, 0.3 mmol), nonafluorobutanesulfonyl fluoride (269 mg, 0.89 mmol), 4-chloro-2-(trimethylsilyl)phenol **77** (120 mg, 0.60 mmol), caesium carbonate (289 mg, 0.89 mmol) and *sec*-butyl 2-diazo-3-oxobutanoate **32** (331 mg, 1.8 mmol) in acetonitrile (6 mL) were stirred at 60 °C under a nitrogen atmosphere for 8 h. Following the work-up, the residue was purified using column chromatography on silica gel using DCM: hexane (80:20) to yield a 70:30 mixture of regioisomers as a colourless oil (83 mg, 47%). ν_{max} (KBr)/cm^{-1} 2975, 1736, 1497, 1162; *m/z* (ESI$^+$) 317 [M + Na]$^+$ (20%); HRMS (ESI$^+$): exact mass calculated for $C_{14}H_{16}ClN_2O_3$ [M + H]$^+$ 295.0849. Found 295.0845.

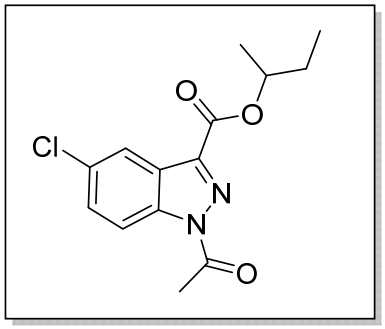
Major isomer: **_sec_-Butyl 1-acetyl-6-chloro-1*H*-indazole-3-carboxylate 189**



δ_H($CDCl_3$, 400 MHz): 1.03 (3H, t, C*H*$_3$, *J* 7.4), 1.45 (3H, d, *J* 6.3, C*H*$_3$), 1.70-1.93 (2H, m), 2.86 [3H, s, C(O)C*H*$_3$], 5.21-5.31 (1H, m, OC*H*), 7.42 (1H, dd, *J* 8.6, 1.7, ArC*H*), 8.10 (1H, d, *J* 8.6, ArC*H*), 8.51 (1H, d, *J* 1.4, ArC*H*);

Tentative ^{13}C NMR assignment: δ_C($CDCl_3$, 100 MHz): 9.8 (CH_2CH_3), 19.5 ($CHCH_3$), 23.0 [C(O)CH_3], 28.9 (CH_2), 74.5 (O*C*H), 115.6 (Ar*C*H), 123.1 (Ar*C*H), 123.2 (ArC_q), 126.7 (Ar*C*H), 131.5 (Ar*C*-Cl), 136.4 (*C*=N), 140.6 (Ar*C*N), 161.1 (*C*=O) ester, 171.4 (*C*=O) amide.

Minor isomer: ***sec*-Butyl 1-acetyl-5-chloro-1*H*-indazole-3-carboxylate 190**



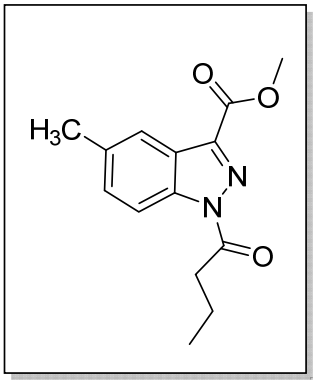
δ_H($CDCl_3$, 400 MHz): 1.04 (3H, t, , *J* 7.4, C*H*$_3$), 1.46 (3H, d, *J* 6.3, C*H*$_3$), 1.70-1.93 (2H, m), 2.87 [3H, s, C(O)C*H*$_3$], 5.21-5.31 (1H, m, OC*H*), 7.55 (1H, dd, *J* 8.9, 2.0, ArC*H*), 8.16 (1H, d, *J* 1.7, ArC*H*), 8.40 (1H, d, *J* 8.9, ArC*H*);

Tentative ^{13}C NMR assignment: δ_C($CDCl_3$, 100 MHz): 9.8, (CH_2CH_3) 19.6 ($CHCH_3$), 22.9 [C(O)CH_3], 28.9 (CH_2), 74.6 (O*C*H), 116.6 (Ar*C*H), 121.7 (Ar*C*H), 121.7 (ArC_q), 125.7 (ArC_q), 127.1 (Ar*C*-Cl), 130.4 (Ar*C*H), 138.7 (*C*=N), 141.0 (Ar*C*N), 161.1 (*C*=O) ester, 171.3 (*C*=O) amide.

Methyl 5-methyl-1-pentanoyl-1*H*-indazole-3-carboxylate 193 and methyl 6-methyl-1-pentanoyl-1*H*-indazole-3-carboxylate 194 1:1

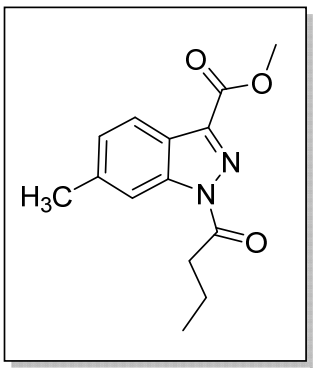
Using the procedure described for pentyl 1-acetyl-1*H*-indazole-3-carboxylate **108** using caesium fluoride (43 mg, 0.28 mmol), nonafluorobutanesulfonyl fluoride (269 mg, 0.89 mmol), 4-methyl-2-(trimethylsilyl)phenol **76** (100 mg, 0.55 mmol), caesium carbonate (290 mg, 0.89 mmol) and methyl 2-diazo-3-oxobutanoate **33** (306 mg, 1.68 mmol) in acetonitrile (6 mL) were stirred at 60 °C under a nitrogen atmosphere for 8 h. Following the work-up, the residue was purified using column chromatography on silica gel using DCM: hexane (80:20) to yield a 50:50 mixture of regioisomers (99 mg, 65%) as a colourless oil. δ_C($CDCl_3$, 100 MHz): 13.9 (CH_2CH_3), 21.5 and 22.1 (ArCH_3), 22.3 and 26.4 (CH_2CH_3), 34.5 and 34.7 [C(O)CH_2], 52.6 (OCH_3), 115.1 and 115.3 (Ar*C*H), 121.3 and 121.6 (Ar*C*H), 125.0 (ArC_q), 127.6 (Ar*C*H), 131.7 (Ar*C*CH_3), 135.7 (*C*=N), 140.8 (Ar*C*N), 162.4 (*C*=O) ester, 174.2 (*C*=O) amide.

***Methyl 5-methyl-1-pentanoyl-1H-indazole-3-carboxylate* 193**



δ_H ($CDCl_3$, 400MHz): 0.99 (3H, t, *J* 7.3, CH_2CH_3), 1.43-1.55 (2H, m, CH_2), 1.77-1.87 (2H, m, CH_2), 2.54 (3H, s, $ArCH_3$), 3.30 (2H, t, *J* 7.4, $C(O)CH_2$), 4.08 (3H, s, OCH_3), 7.42 (1H, d, *J* 8.3, ArC*H*), 8.08 (1H, d, *J* 8.3, ArCH), 8.30 (1H, s, ArC*H*).

***Methyl 6-methyl-1-pentanoyl-1H-indazole-3-carboxylate* 194**



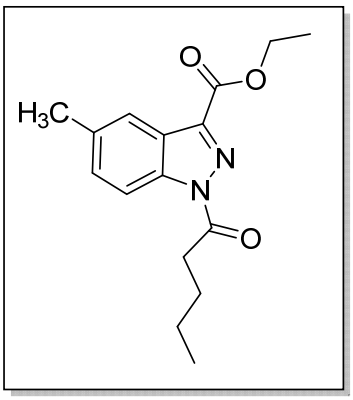
δ_H ($CDCl_3$, 400MHz): 0.99 (3H, t, *J* 7.3, CH_2CH_3), 1.43-1.55 (2H, m, CH_2), 1.77-1.87 (2H, m, CH_2), 2.52 (3H, s, $ArCH_3$), 3.30 [2H, t, *J* 7.4, $C(O)CH_2$], 4.07 (3H, s, OCH_3), 7.28 (1H, d, *J* 8.6, ArCH), 8.00 (1H, s, ArCH), 8.35 (1H, d, *J* 8.6, ArC*H*).

Ethyl 5-ethyl-1-butyryl-1*H*-indazole-3-carboxylate 195 and ethyl 6-methyl-1-butyryl-1*H*-indazole-3-carboxylate 196 1:1

Using the procedure described for pentyl 1-acetyl-1*H*-indazole-3-carboxylate **108**, caesium fluoride (43 mg, 0.28 mmol), nonafluorobutanesulfonyl fluoride (251 mg, 0.83 mmol), 4-methyl-2-(trimethylsilyl)phenol **58** (100 mg, 0.56 mmol), caesium carbonate (271 mg, 0.83 mmol) and ethyl 2-diazo-3-oxohexanoate **34** (309 mg, 1.68 mmol) in acetonitrile (6 mL) were stirred at 60 ºC for 8 h. Following the work-up, the residue was purified using column chromatography on silica gel using DCM: hexane (80:20) to yield a 50:50 mixture of regioisomers as a yellow solid (65 mg, 66%), m.p. 104-107 ºC which could not be separated by column chromatography on silica gel. ν_{max} (KBr)/cm^{-1} 2924, 1712, 1480, 1280; *m/z* (ESI^-) 175 $[M - H]^-$ (100%), 176 $[M^+]$ (10); δ_C($CDCl_3$, 100 MHz): 13.7 [$CH_3CH_2CH_2C(O)$], 14.4 (CH_3CH_2O), 17.8 [$CH_3CH_2CH_2C(O)$], 21.5 ($ArCH_3$), 22.1 ($ArCH_3$), 36.6 and 36.8 [$CH_3CH_2CH_2C(O)$], 61.8 (CH_3CH_2O),

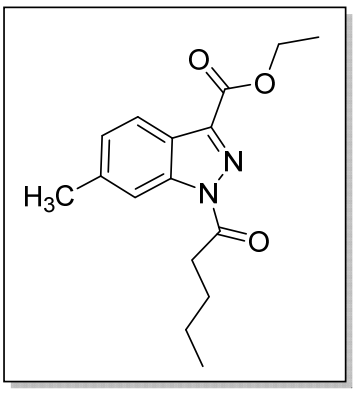
115.5 and 115.3 (Ar*C*H), 121.4 and 121.6 (Ar*C*H), 122.7 and 125.0 (ArC_q), 127.5 (Ar*C*H), 131.6 (Ar*C*H), 135.6 and 140.7 (Ar*C*CH_3), 138.9 and 140.2 (*C*=N), 140.5 and 140.9 (Ar*C*N), 162.0 and 162.1 (*C*=O) ester, 174.1 and 174.3 (*C*=O) amide; HRMS (ESI^+): exact mass calculated for $C_{16}H_{20}N_2O_3$ $[M + H]^+$ 289.2379. Found 289.2383.

Ethyl 5-ethyl-1-butyryl-1*H*-indazole-3-carboxylate 195



δ_H ($CDCl_3$, 400MHz): 1.08 [3H, t, *J* 7.4, C(O)$CH_2CH_2CH_3$], 1.50 (3H, dt, *J* 2.5, 7.1, OCH_2CH_3), 1.88 [2H, dd, *J* 7.4, 4.8, C(O)$CH_2CH_2CH_3$], 2.54 (3H, s, ArCH_3), 3.29 [2H, t *J* ,7.3, C(O)$CH_2CH_2CH_3$], 4.55 (2H, dq, *J* 3.8, 7.1, OCH_2CH_3), 7.42 (1H, d, *J* 8.2, Ar*C*H), 8.06 (1H, d, *J* 8.2, Ar*C*H), 8.30 (1H, s, Ar*C*H).

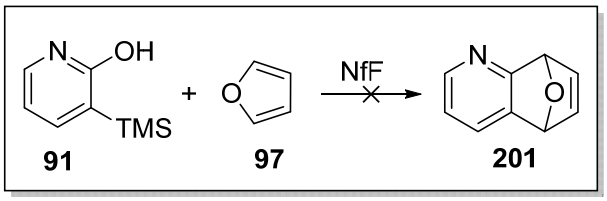
Ethyl 6-methyl-1-butyryl-1*H*-indazole-3-carboxylate 196



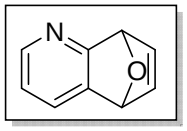
δ_H ($CDCl_3$, 400MHz): 1.08 [3H, t, *J* 7.4, C(O)$CH_2CH_2CH_3$], 1.50 (3H, dt, *J* 2.5, 7.1, OCH_2CH_3), 1.88 [2H, dd, *J* 7.4, 4.8, C(O)$CH_2CH_2CH_3$], 2.52 (3H, s, ArCH_3), 3.29 [2H, t *J* ,7.3, C(O)$CH_2CH_2CH_3$], 4.55 (2H, dq, *J* 3.8, 7.1, OCH_2CH_3), 7.27 (1H, d, *J* 8.1, Ar*C*H), 7.98 (1H, s, Ar*C*H), 8.35 (1H, d, *J* 8.1, Ar*C*H).

3.6 Attempted Syntheses of Azaindazole derivatives

3.6.1 Attempted generation of pyridyne and trapping with furan



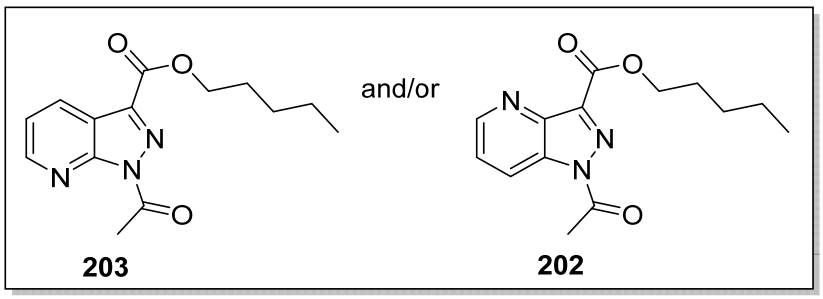
5,8-Dihydro-5,8-epoxyquinoline[57] 201



Using the procedure described for pentyl 1-acetyl-1*H*-indazole-3-carboxylate **108**, 3-(trimethylsilyl)pyridin-2-ol **58** (0.05 g, 0.3 mmol, caesium carbonate (0.147 g, 0.45 mmol) in acetonitrile (3 ml), caesium fluoride (23 mg, 0.15 mmol), furan **97** (0.065 ml, 0.9 mmol) and nonafluorobutanesulfonyl fluoride (81 μL, 0.45 mmol) were stirred at 60 °C under a nitrogen atmosphere. TLC analysis after 24 h indicated the presence of starting material only in the reaction mixture. After a further 24 h, water (10 mL) was added to the reaction flask and the layers separated. The aqueous layer was extracted with diethyl ether (3 × 10 mL), the organic layers combined, dried with $MgSO_4$ and concentrated under reduced pressure. The ^1H NMR spectrum of the crude material showed no evidence of product formation with only unreacted starting material recovered.

3.6.2 Attempted Syntheses of Azaindazole derivatives

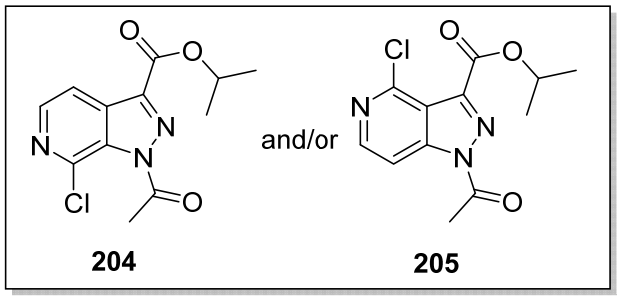
Pentyl 1-acetyl-1*H*-pyrazolo[3,4-b]pyridine-3-carboxylate 203 and/or pentyl 1-acetyl-1*H*-pyrazolo[4,3-b]pyridine-3-carboxylate 202



Using the procedure described for pentyl 1-acetyl-1*H*-indazole-3-carboxylate **108,** 3-(trimethylsilyl)pyridin-2-ol **58** (100 mg, 0.6 mmol), caesium carbonate (174 mg, 0.9 mmol) in acetonitrile (6 ml), caesium fluoride (46 mg, 0.3

mmol), pentyl 2-diazo-3-oxobutanoate **23** (238 mg, 1.2 mmol) and nonafluorobutanesulfonyl fluoride (272 mg, 0.9 mmol) were stirred at 60 °C under a nitrogen atmosphere. TLC analysis after 24 h indicated the presence of starting material only in the reaction mixture. After a further 24 h, water (10 mL) was added to the reaction flask and the layers separated. The aqueous layer was extracted with diethyl ether (3 × 10 mL), the organic layers combined, dried with $MgSO_4$ and concentrated under reduced pressure. The ^1H NMR spectrum of the crude material showed no evidence of product formation with only unreacted starting material recovered.

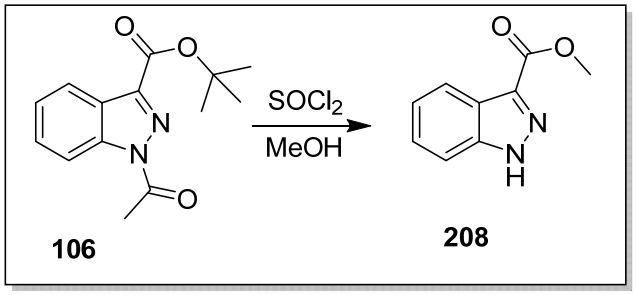
Isopropyl 1-acetyl-4-chloro-1*H*-pyrazolo[4,3-c]pyridine-3-carboxylate 205 and/or isopropyl 1-acetyl-7-chloro-1*H*-pyrazolo[3,4-c]pyridine-3-carboxylate 204



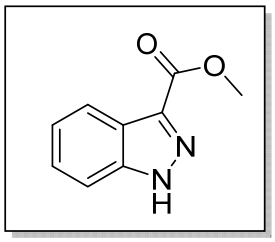
Using the procedure described for pentyl 1-acetyl-1*H*-indazole-3-carboxylate **108,** 3-(trimethylsilyl)pyridin-2-ol **58** (100 mg, 0.5 mmol), caesium carbonate (245 mg, 0.75 mmol) in acetonitrile (6 ml), caesium fluoride (38 mg, 0.25 mmol), isopropyl 2-diazo-3-oxobutanoate **20** (93.5 mg, 0.6 mmol) and nonafluorobutanesulfonyl fluoride (227 mg, 0.75 mmol) were stirred at 60 °C under a nitrogen atmosphere. TLC analysis after 24 h indicated the presence of starting material only in the reaction mixture. After a further 24 h, water (10 mL) was added to the reaction flask and the layers separated. The aqueous layer was extracted with diethyl ether (3 × 10 mL), the organic layers combined, dried with $MgSO_4$ and concentrated under reduced pressure. The ^1H NMR spectrum of the crude material showed no evidence of product formation with only unreacted starting material recovered.

3.7 *N*-Deacylation of 1-acyl indazoles

Method 1: Using thionyl chloride in methanol[58]



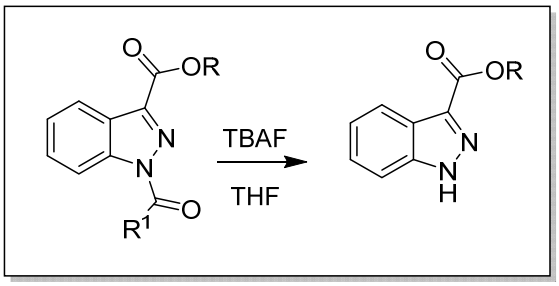
Methyl 1*H*-indazole-3-carboxylate 208



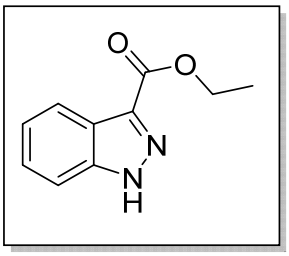
Thionyl chloride (0.04 mL, 0.36 mmol) was added to *t*-butyl 1-acetyl-1*H*-indazole-3-carboxylate **106** (78 mg, 0.36 mmol) in methanol (5 mL) at 0 ºC and the mixture was then stirred at reflux for 1.5 h. The reaction mixture was concentrated under reduced pressure and a solution of saturated sodium bicarbonate (10 mL) was added to the residue. The crude mixture was extracted with diethyl ether (2 × 10 mL), dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified using column chromatography on silica gel using hexane:ethyl acetate (3:1-1:3) to yield methyl 1*H*-indazole-3-carboxylate **208** as a white solid (31 mg, 49%), m.p. 159-162 ºC, (Lit.[52] 162-163 ºC). ^{1}H NMR analysis showed *N*-deacylation but also transesterification of the ester side chain, from *t*-butyl to methyl. δ_H ($CDCl_3$, 400MHz): 4.08 (1H, s, COC*H*$_3$), 7.35 (1H, t, *J* 7.6, ArCH), 7.48 (1H, t, *J* 7.6, ArCH*)*, 7.70 (1H, d, *J* 8.5, ArCH), 8.24 (1H, d, *J* 8.2, ArCH), 11.82 (1H, br s, N*H*); δ_C($CDCl_3$, 100 MHz): 52.1 (O*C*H$_3$), 110.8 (Ar*C*H), 121.8 (Ar*C*H), 122.5 (ArC_q), 123.4 (Ar*C*H), 127.5 (Ar*C*H), 136.4 (*C*=N), 141.2 (Ar*C*N), 163.3 (*C*=O); ν_{max} (KBr)/cm^{-1} 3430, 2954, 1727, 1474, 1148; *m/z* (ESI$^+$) 177 $[M + H]^+$ (40%); HRMS (ESI$^+$): exact mass calculated for $C_9H_9N_2O_2$ $[M + H]^+$ 177.0664. Found 177.0658. Spectral details are in agreement with those reported in the literature.[52]

Note: This reaction was repeated using DCM as solvent but was unsuccessful and only recovered unreacted starting material.

Method 2: Using TBAF in THF

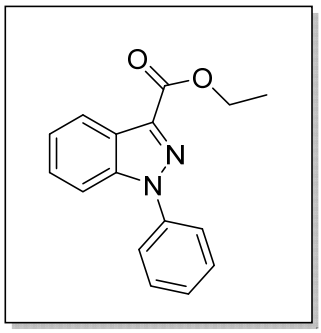


Ethyl 1*H*-indazole-3-carboxylate 211



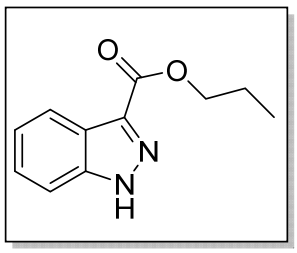
A solution of ethyl 1-acetyl 1*H*-indazole-3-carboxylate **99** (54 mg, 0.23 mmol), ethyl 1-phenyl-1*H*-indazole-3-carboxylate **117** (11 mg, 0.04 mmol) (inseparable) in THF (10 mL) and TBAF (1M in THF, 0.92 mL, 0.92 mmol, 4 equiv.) was stirred at room temperature for 1 h. The solution obtained was diluted with water (10 mL) and extracted with diethyl ether (2 × 10 mL). This solution was washed with water (5 × 20 mL) to remove excess TBAF. Column chromatography on silica gel using hexane:ethyl acetate (3:1) isolated ethyl 1-phenyl-1*H*-indazole-3-carboxylate **117** as a white solid (8 mg, 73%), m.p. 109-112 ºC, (Lit.[52] 112-114 ºC) and hexane:ethyl acetate (1:3) isolated ethyl 1*H*-indazole-3-carboxylate **211** as a white solid (11 mg, 26%), m.p. 127-129 ºC, (Lit.[59] 130 ºC). δ_H ($CDCl_3$, 400MHz): 1.50 (3H, t, *J* 7.1, CH_2CH_3), 4.54 (2H, q, *J* 7.2, OCH_2), 7.35 (1H, t, *J* 7.6, ArC*H*), 7.47 (1H, t, *J* 7.7, ArC*H),* 7.60 (1H, d, *J* 8.3, ArC*H*), 8.25 (1H, d, *J* 8.0, ArC*H*), 10.85 (1H, br s, N*H*); δ_C($CDCl_3$, 100 MHz): 14.4 (CH_2CH_3), 61.1 (OCH_2), 110.3 (Ar*C*H), 122.1 (Ar*C*H), 122.6 (ArC_q), 123.3 (Ar*C*H), 127.5 (Ar*C*H), 135.2 (*C*=N), 141.5 (Ar*C*N), 162.7 (*C*=O); ν_{max} (KBr)/cm^{-1} 2984, 1730, 1500, 1194; *m/z* (ESI$^+$) 213 $[M + Na]^+$ (100%), 191 $[M + H]^+$ (10); HRMS (ESI$^+$): exact mass calculated for $C_{10}H_{11}N_2O_2$ $[M + H]^+$ 191.0821. Found 191.0820. Spectral details are in agreement with those reported in the literature.[59]

Ethyl 1-phenyl-1*H*-indazole-3-carboxylate 225



δ_H ($CDCl_3$, 400MHz): 1.51 (3H, t, *J* 7.1, CH_2CH_3), 4.56 (2H, q, *J* 7.1, OCH_2), 7.36-7.61 (5H, m, 5 × ArC*H*), 7.70-7.79 (3H, m, 3 × ArC*H*), 8.32 (1H, d, *J* 8.1, ArC*H*); δ_C($CDCl_3$, 100 MHz): 14.5 (CH_2CH_3), 61.2 (OCH_2), 110.9 (ArCH), 122.5 (ArCH), 123.7 (ArC_q indazole), 124.0 (2 × ArCH), 124.5 (ArCH), 127.6 (ArCH), 128.0 (ArCH), 129.5 (2 × ArCH), signals for (ArC_q phenyl), (ArCN), (C=N) and (C=O) too close to the baseline to detect; ν_{max} (KBr)/cm^{-1} 2967, 1708, 1598, 1476, 1189; *m/z* (ESI^+) 267 $[M + H]^+$ (14%); HRMS (ESI^+): exact mass calculated for $C_{16}H_{15}N_2O_2$ $[M + H]^+$ 267.1134. Found 267.1121. Spectral details are in agreement with those reported in the literature.[52]

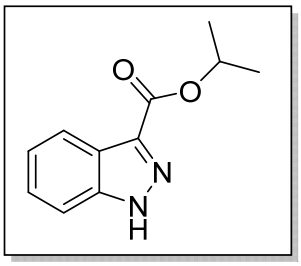
Propyl 1*H*-indazole-3-carboxylate 223



A solution of propyl 1-pentanoyl 1*H*-indazole-3-carboxylate **120** (20 mg, 76.5 μmol) and TBAF (1M in THF, 0.31 mL, 0.31 mmol, 4 equiv.) was stirred in THF (6 mL) at room temperature for 1 h. The solution obtained was diluted with water (10 mL) and extracted with diethyl ether (2 × 10 mL). This solution was washed with water (5 × 20 mL) to remove excess TBAF. The reaction mixture was concentrated under reduced pressure for an extended period of time to remove the pentanoyl fluoride deacylation by-product and propyl 1*H*-indazole-3-carboxylate **223** was isolated as a white solid with no further purification required (14.0 mg, 84%), m.p. 133-135 ºC, (Lit. value not reported). δ_H($CDCl_3$, 400 MHz): 1.08 (3H, t, *J* 7.4, CH_3), 1.84-1.94 (2H, m, CH_2), 4.46 (2H, t, *J* 6.7, OCH_2, 7.34 (1H, ddd, *J* 7.9, 6.9, 0.8, ArC*H*), 7.47 (1H, ddd, *J* 8.4, 6.9, 1.1, ArC*H*), 7.71 (1H, d, *J* 8.5, ArC*H*), 8.22 (1H, d, *J* 8.2, ArC*H*), 12.50 (1H, br s, NH); δ_C($CDCl_3$, 100 MHz): 10.6 (CH_3), 22.2 (CH_2), 66.7 (OCH_2), 111.4 (ArCH), 121.7 (ArCH), 122.4 (ArC_q), 123.2 (ArCH), 127.2 (ArCH), 136.6 (C=N), 141.5 (ArCN), 163.3 (C=O); ν_{max} (KBr)/cm^{-1}: 3278, 2969,

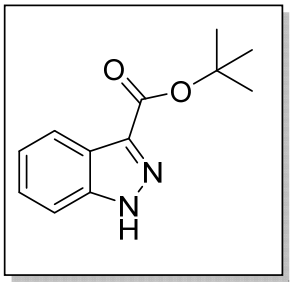
1719, 1421, 1139; *m/z* (ESI$^+$) 205 [M + H]$^+$ (4%); HRMS (ESI)$^+$: Exact mass calculated for $C_{11}H_{13}N_2O_2$ [M + H]$^+$ 205.0977. Found 205.0971.
Compound reported in literature without spectral details.[60]

Isopropyl 1*H*-indazole-3-carboxylate 212



The title compound was prepared in the same manner as propyl 1*H*-indazole-3-carboxylate **223** using isopropyl 1-acetyl 1*H*-indazole-3-carboxylate **105** (20 mg, 81.2 μmol) and TBAF (1M in THF, 0.32 mL, 0.32 mmol) in THF (6 mL). Following the work-up, isopropyl 1*H*-indazole-3-carboxylate **212** was isolated as a white solid with no further purification required (12.8 mg, 79%), m.p. 127-130 ºC, (Lit. value not reported). δ_H($CDCl_3$, 400 MHz): 1.47 [6H, d, *J* 6.3, CH(C*H*$_3$)$_2$], 5.45 [1H, sept, *J* 6.3, C*H*(CH$_3$)$_2$], 7.29-7.36 (1H, m, ArC*H*), 7.46 (1H, ddd, *J* 8.3, 6.9, 1.1, ArC*H*), 7.72 (1H, d, *J* 9.1, ArCH), 8.22 (1H, d, *J* 8.2, ArCH), 11.87 (1H, br s, N*H*); δ_C($CDCl_3$, 100 MHz): 22.1 (2 × *C*H$_3$), 68.8 [*C*(CH$_3$)$_2$], 111.1 (Ar*C*H), 121.9 (Ar*C*H), 123.2 (Ar*C*H), 122.4 (ArC_q), 127.2 (Ar*C*H), 137.0 (*C*=N), 141.4 (Ar*C*N), 162.6 (*C*=O); ν_{max} (KBr)/cm^{-1} 3260, 2980, 1715, 1472, 1104; *m/z* (ESI$^-$) 203 [M - H]$^-$ (100%), 204 [M$^+$] (18); HRMS (ESI$^+$): exact mass calculated for $C_{11}H_{13}N_2O_2$ [M + H]$^+$ 205.0977. Found 205.0970. Compound reported in literature without spectral details.[60]

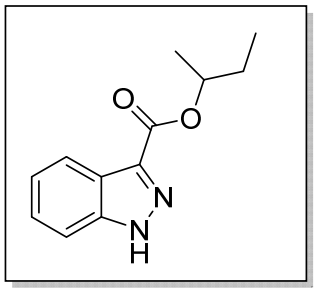
***t*-Butyl 1*H*-indazole-3-carboxylate 213**



The title compound was prepared in the same manner as propyl 1*H*-indazole-3-carboxylate **223** using *t*-butyl 1-acetyl 1*H*-indazole-3-carboxylate **106** (20 mg, 76.5 μmol) and TBAF (1M in THF, 0.306 mmol, 0.31 mL) in THF (6 mL). Following the work-up, *t*-butyl 1*H*-indazole-3-carboxylate **213** was isolated as a white solid with no further purification required (14.0 mg, 84%), m.p. 137-139 ºC, (Lit. value not reported). δ_H($CDCl_3$, 400 MHz):

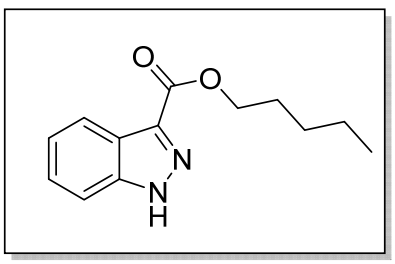
1.71 [9H, s, (CH_3)$_3$], 7.29-7.35 (1H, m, ArC*H*), 7.45 (1H, t, *J* 7.5, ArC*H*), 7.57 (1H, d, *J* 8.4, ArC*H*), 8.21 (1H, d, *J* 8.1, ArC*H*), 10.61 (1H, br s, N*H*); δ_C($CDCl_3$, 100 MHz): 28.4 (3 × *C*H_3), 82.0 (Ar*C*H), 122.2 (Ar*C*H), 123.1 (Ar*C*H), 127.3 (Ar*C*H), (ArC_q), (Ar*C*N), (*C*=N) and (*C*=O) not detected; ν_{max} (KBr)/cm^{-1} 3269, 2954, 1722, 1467, 1141; *m/z* (ESI$^+$) 241 [M + Na]$^+$ (100%), 242 (15). Spectral details are in agreement with those reported in the literature.[53]

sec-Butyl 1*H*-indazole-3-carboxylate 214



The title compound was prepared in the same manner as propyl 1*H*-indazole-3-carboxylate **223** using *sec*-butyl 1-acetyl 1*H*-indazole-3-carboxylate **107** (20 mg, 76.8 μmol) and TBAF (1M in THF, 0.3 mmol, 0.3 mL) in THF (6 mL). Following the work-up, *sec*-butyl 1*H*-indazole-3-carboxylate **214** was isolated as a yellow solid with no further purification required (8 mg, 51%), m.p. 115-117 ºC. δ_H ($CDCl_3$, 400 MHz): 1.04 (3H, t, *J* 7.5, CH_3), 1.45 (3H, d, *J* 6.3, CH_3), 1.70-1.93 (2H, m, CH_2), 5.27-5.36 (1H, m, OC*H*), 7.29-7.35 (1H, m, ArC*H*), 7.46 (1H, ddd, *J* 8.3, 7.0, 1.0, ArC*H*), 7.78 (1H, d, *J* 8.5, ArC*H*), 8.20 (1H, d, *J* 8.2, ArC*H*), 12.47 (1H, br s, N*H*); δ_C($CDCl_3$, 100 MHz): 9.9 (*C*H_3), 19.8 (*C*H_3), 29.1 (*C*H_2), 73.3 (*C*H), 111.4 (Ar*C*H), 121.8 (Ar*C*H), 122.3 (ArC_q), 123.1 (Ar*C*H), 127.1 (Ar*C*H), 136.9 (*C*=N), 141.5 (Ar*C*N), 162.9 (*C*=O); ν_{max} (KBr)/cm^{-1}: 3264, 2972, 2934, 1717, 1622, 1471, 1151; *m/z* (ESI$^+$) 219 [M + H]$^+$ (3%), 186 (100); HRMS (ESI)$^+$: Exact mass calculated for $C_{12}H_{15}N_2O_2$ [M + H]$^+$ 219.1134. Found 219.1136.

Pentyl 1*H*-indazole-3-carboxylate 215

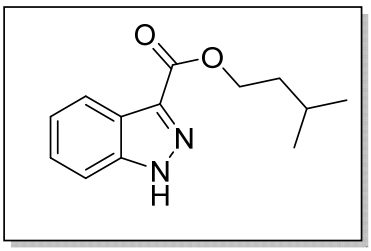


The title compound was prepared in the same manner as propyl 1*H*-indazole-3-carboxylate **223** using pentyl 1-acetyl 1*H*-indazole-3-carboxylate **108** (73 μmol, 20 mg) and TBAF (1M in THF, 0.03 mmol, 0.03 mL) in THF (6 mL). Following the work-up, the residue was purified using column chromatography on silica gel

using hexane:ethyl acetate (3:1-1:3) to yield pentyl 1*H*-indazole-3-carboxylate **215** as a yellow solid (10.5 mg, 62%), m.p. 76-79 ºC. δ_H($CDCl_3$, 400 MHz): 0.92 (3H, t, *J* 7.2, CH_2CH_3), 1.35-1.50 (4H, m, 2 × CH_2), 1.81-1.90 (2H, m, CH_2), 4.50 (2H, t, *J* 6.8, OCH_2), 7.33 (1H, ddd *J* 7.9, 6.9, 0.8, ArC*H*), 7.46 (1H, ddd, *J* 8.4, 6.9, 1.1, ArC*H*), 7.77 (1H, d, *J* 8.5, ArC*H*), 8.21 (1H, td, *J* 8.5, 0.9, ArC*H*), 12.37 (1H, br s, N*H*); δ_C($CDCl_3$, 100 MHz): 13.9 (CH_3), 22.4 (CH_2), 28.2 (CH_2), 28.5 (CH_2), 65.3 (OCH_2), 111.3 (ArCH), 121.8 (ArCH), 122.4 (ArC_q), 123.2 (ArCH), 127.2 (ArCH), 136.6 (ArCN), 141.4 (C=N), 163.2 (C=O); ν_{max} (KBr)/cm^{-1} 3283, 2960, 1718, 1670, 1624, 1476, 1147; *m/z* (ESI^-) 231 $[M - H]^-$ (10%), 149 (20); HRMS (ESI^+): exact mass calculated for $C_{13}H_{17}N_2O_2$ $[M + H]^+$ 233.1290. Found 233.1280.

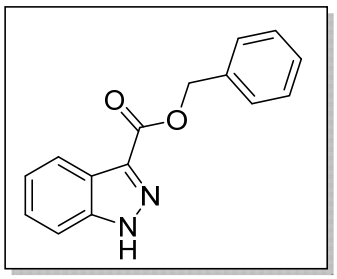
Note: The ^{1}H NMR spectrum showed the presence of 2% unreacted starting material after chromatography.

Isopentyl 1H-indazole-3-carboxylate 216



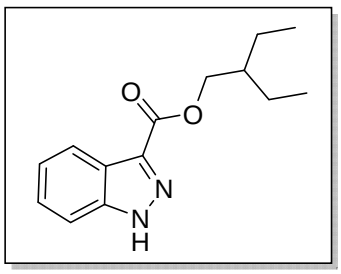
The title compound was prepared in the same manner as propyl 1*H*-indazole-3-carboxylate **223** using isopentyl 1-acetyl 1*H*-indazole-3-carboxylate **109** and and TBAF (1M in THF, 0.23 mmol, 0.23 mL) in THF (6 mL). Following the work-up, isopentyl 1*H*-indazole-3-carboxylate **216** was isolated as a yellow solid with no further purification required (8.8 mg, 52%) m.p. 68-70 °C. δ_H($CDCl_3$, 400 MHz): 1.00 (6H, d, *J* 6.4, 2 × CH_3), 1.70-1.90 [3H, m, containing OCH_2CH_2 and $CH(CH_3)_2$], 4.52 (2H, t, *J* 6.8, OCH_2), 7.38 (1H, t, *J* 7.6, ArC*H*), 7.60 (1H, t, *J* 7.6, ArC*H*), 7.67 (1H, d, *J* 8.4, ArC*H*), 8.22 (1H, d, *J* 8.2, ArC*H*), 11.48 (1H, br d, N*H*); δ_C($CDCl_3$, 100 MHz): 22.5 (2 × CH_3), 25.2 (CH), 37.5 (CH_2), 63.8 (OCH_2), 110.7 (ArCH), 121.9 (ArCH), 122.5 (ArC_q), 123.3 (ArCH), 127.4 (ArCH), 136.9 (C=N), 141.2 (ArCN), 163.0 (C=O); ν_{max} (KBr)/cm^{-1} 2959, 1721, 1472, 1148; *m/z* (ESI^-) 231 $[M - H]^-$ (50%), 232 $[M^+]$ (8); HRMS (ESI^+): exact mass calculated for $C_{13}H_{17}N_2O_2$ $[M + H]^+$ 233.1290. Found 233.1283.

Benzyl 1*H*-indazole-3-carboxylate 217



The title compound was prepared in the same manner as propyl 1*H*-indazole-3-carboxylate **223** using benzyl 1-acetyl 1*H*-indazole-3-carboxylate (10 mg, 0.034 mmol) **110** and TBAF (1M in THF, 0.12 mmol, 0.12 mL) in THF (4 mL). Following the work-up, benzyl 1*H*-indazole-3-carboxylate **217** was isolated as a yellow solid with no further purification required (4 mg, 47%), m.p. 136-138 ºC, (Lit. value not reported). δ_H($CDCl_3$, 400 MHz): 5.54 (2H, s, OC*H*$_2$), 7.24-7.60 (7H, m, 5 × ArC*H* phenyl and 2 × ArC*H* indazole), 7.71 (1H, d, *J* 8.5, ArC*H*), 8.17 (1H, d, *J* 8.2, ArC*H*), 12.51 (1H, br s, N*H*); δ_C($CDCl_3$, 100 MHz): 66.8 (O*C*H$_2$C$_6$H$_5$), 111.2 (Ar*C*H indazole), 121.7 (Ar*C*H indazole), 123.4 (Ar*C*$_q$ indazole), 123.3 (Ar*C*H indazole), 127.3 (Ar*C*H indazole), 128.4 (Ar*C*H benzyl), 128.4 (2 × Ar*C*H benzyl), 128.7 (2 × Ar*C*H benzyl), 135.8 (*C*$_q$) benzyl, 136.3 (*C*=N), 141.4 (Ar*C*N), 162.9 (*C*=O); ν_{max} (KBr)/cm^{-1} 3256, 2924, 1723, 1470, 1146; *m/z* (ESI$^+$) 253 [M + H]$^+$ (8%), 242 (100). Spectral details are in agreement with those reported in the literature.[61]

2-Ethylbutyl 1*H*-indazole-3-carboxylate 218

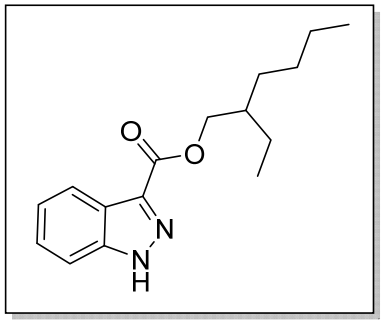


The title compound was prepared in the same manner as propyl 1*H*-indazole-3-carboxylate **223** using 2-ethylbutyl 1-acetyl 1*H*-indazole-3-carboxylate **111** (20 mg, 69.2 μmol) and TBAF (1M in THF, 0.277 mmol, 0.28 mL) in THF (6 mL). Following the work-up, 2-ethylbutyl 1*H*-indazole-3-carboxylate **218** was isolated as a low melting white solid with no further purification required (87%, 13 mg). δ_H($CDCl_3$, 400 MHz): 0.98 (6H, t, *J* 7.5, 2 × CH_3), 1.52 (4H, m, 2 × CH_2), 1.78 (1H, td, *J* 12.4, 6.2, C*H*), 4.42 (2H, d, *J* 5.9, OC*H*$_2$), 7.34 (1H, ddd, *J* 7.9, 6.9, 0.9, ArC*H*), 7.46 (1H, ddd, *J* 8.4, 6.9, 1.1, ArC*H*), 7.68 (1H, dd, *J* 8.4, 0.8, ArC*H*), 8.2 (1H, td, *J* 8.2, 1.0, ArC*H*), 11.43 (1H, bs, N*H*); δ_C($CDCl_3$, 100 MHz): 11.1 (2 × *C*H_3), 23.5 (2 × *C*H_2), 40.5 (*C*H), 67.1 (O*C*H$_2$), 110.7 (Ar*C*H), 121.86 (Ar*C*H), 122.5 (Ar*C*$_q$),

123.3 (Ar*C*H), 127.3 (Ar*C*H), 137.0 (*C*=N), 141.3 (Ar*C*N), 163.1 (*C*=O); υ_{max} (film)/cm^{-1} 2956, 1728, 1711, 1255; *m/z* (ESI$^-$) 245 [M - H]$^-$ (50%), 246 (8); HRMS (ESI)$^+$: Exact mass calculated for $C_{14}H_{19}N_2O_2$ [M + H]$^+$ 247.1447. Found 247.1436.

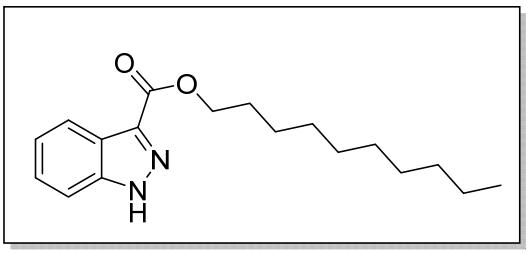
Note: The ^{1}H NMR spectrum showed the presence of 4% *N*-aryl by-product from the 2-ethylbutyl 1-acetyl 1*H*-indazole-3-carboxylate **111** starting material.

2-Ethylhexyl 1*H*-indazole-3-carboxylate 219



The title compound was prepared in the same manner as propyl 1*H*-indazole-3-carboxylate **223** using 2-ethylhexyl 1-acetyl-1*H*-indazole-3-carboxylate **112** (63.2 μmol, 20 mg) and TBAF (1M in THF, 0.25 mmol, 0.25 mL) was stirred in THF (6 mL). Following the work-up, 2-ethylhexyl 1*H*-indazole-3-carboxylate **219** was isolated as a yellow oil with no further purification required (51%, 10 mg). δ_H ($CDCl_3$, 400 MHz): 0.88-1.0 [6H, m, containing 0.90 (3H, t, *J* 7.1, C*H*$_3$) and 0.97 (3H, t, *J* 7.5, C*H*$_3$)], 1.29-1.60 (8H, m, 4 × C*H*$_2$), 1.82 (1H, td, *J* 12.3, 6.1, C*H*), 4.43 (2H, dd, *J* 5.8, 2.5, OC*H*$_2$), 7.34 (1H, ddd, *J* 8.0, 6.9, 0.8, ArC*H*), 7.44-7.49 (1H, m, ArC*H*), 7.75 (d, *J* 8.5, ArC*H*), 8.2 (dd, *J* 8.2, 0.8, ArC*H*), 11.99 (1H, s, N*H*); δ_C($CDCl_3$, 100 MHz): 11.0 (*C*H$_3$), 14.0 (*C*H$_3$), 23.0 (*C*H$_2$), 24.0 (*C*H$_2$), 29.0 (*C*H$_2$), 30.5 (*C*H$_2$), 39.0 (*C*H), 67.5 (O*C*H$_2$), 111.1 (Ar*C*H), 121.8 (Ar*C*H), 122.4 (Ar*C*$_q$), 123.2 (Ar*C*H), 127.3 (Ar*C*H), 136.8 (*C*=N), 141.4 (Ar*C*N), 163.3 (*C*=O); ν_{max} (KBr)/cm^{-1} 2957, 2928, 1722, 1471, 1148; *m/z* (ESI$^+$) 275 [M + H]$^+$ (10%), 298 (20), 297 (100); HRMS (ESI$^+$): exact mass calculated for $C_{16}H_{23}N_2O_2$ [M + H]$^+$ 275.1760. Found 275.1758.

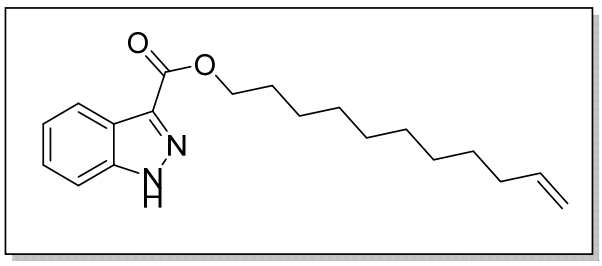
Decyl 1*H*-indazole-3-carboxylate 220



The title compound was prepared in the same manner as propyl 1*H*-indazole-3-carboxylate **223** using decyl 1-acetyl-1*H*-indazole-3-carboxylate **113** (20 mg, 58.06 μmol) and TBAF (1M in THF, 0.23 mmol, 0.23 mL) in THF (6 mL). Following the work-up, decyl 1*H*-indazole-3-carboxylate **220** was isolated as a low melting solid with no further purification required (12 mg, 72%). δ_H($CDCl_3$, 400 MHz): 0.87 (3H, t, *J* 6.9, C*H*$_3$), 1.24-1.53 (14H, m, 7 × C*H*$_2$), 1.81-1.90 (2H, m, C*H*$_2$), 4.48 (2H, t, *J* 6.8, OC*H*$_2$), 7.33 (1H, ddd, *J* 7.9, 6.9, 0.8, ArC*H*), 7.45 (1H, ddd, *J* 8.3, 6.9, 1.1 ArC*H*), 7.65 (1H, d, *J* 8.5, ArC*H*), 8.21 (1H, td, *J* 8.2, 0.9, ArC*H*), 11.99 (1H, br s, N*H*); δ_C($CDCl_3$, 75.5 MHz): 14.1 (*C*H$_3$), 22.7 (*C*H$_2$), 26.0 (*C*H$_2$), 28.8 (*C*H$_2$), 29.3 (*C*H$_2$), 29.3 (*C*H$_2$), 29.5 (*C*H$_2$), 29.5 (*C*H$_2$), 31.9 (*C*H$_2$), 65.3 (O*C*H$_2$), 111.23 (Ar*C*H), 121.8 (Ar*C*H), 122.4 (ArC_q), 123.2 (Ar*C*H), 127.2 (Ar*C*H), 136.6 (*C*=N), 141.4 (Ar*C*N), 163.2 (*C*=O); ν_{max} (KBr)/cm^{-1} 1718, 1474, 1232, 1147; *m/z* (ESI$^-$) 301 [M - H]$^-$ (20%), 302 (5), 277 (100); HRMS (ESI$^+$): exact mass calculated for $C_{18}H_{27}N_2O_2$ [M + H]$^+$ 303.2073. Found 303.2063.

Note: The ^{1}H NMR spectrum showed the presence of 4% *N*-aryl by-product from the decyl 1-acetyl-1*H*-indazole-3-carboxylate **113** starting material.

Undec-10-en-1-yl 1*H*-indazole-3-carboxylate 221

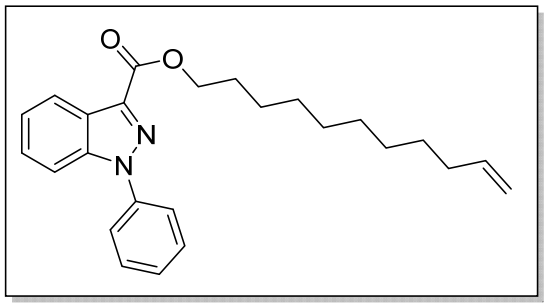


The title compound was prepared in the same manner as propyl 1*H*-indazole-3-carboxylate **223** using undec-10-en-1-yl 1-acetyl 1*H*-indazole-3-carboxylate (15 mg, 0.04 mmol) **126** and TBAF (1M in THF, 0.16 mmol, 0.16 mL) in THF (6 mL). Following the work-up, the residue was purified by column

chromatography on silica gel using hexane:ethyl acetate (3:1-1:3) to isolate undec-10-en-1-yl 1*H*-indazole-3-carboxylate **221** as a yellow oil (8 mg, 62%). δ_H($CDCl_3$, 400 MHz): 1.25-1.53 (12H, m, 6 × C*H*$_2$), 1.82-1.90 (2H, m, C*H*$_2$), 2.03 (2H, dd, *J* 13.8, 7.2, C*H*$_2$), 4.48 (2H, t, *J* 6.8, OC*H*$_2$), 4.90-5.03 (2H, m, CH=C*H*$_2$), 5.81 (1H, m, C*H*=CH$_2$), 7.31-7.37 (1H, m, ArC*H*), 7.47 (1H, dd, *J* 8.2, 7.2, ArC*H*), 7.67 (1H, d, *J* 8.4, ArC*H*), 8.23 (1H, d, *J* 8.2, ArC*H*), 11.50 (1H, br s, N*H*); δ_C($CDCl_3$, 100 MHz): 26.0 (*C*H$_2$), 28.8, (*C*H$_2$), 28.9 (*C*H$_2$), 29.1 (*C*H$_2$), 29.3 (*C*H$_2$), 29.4 (*C*H$_2$), 29.5 (*C*H$_2$), 33.8 (*C*H$_2$), 65.3 (O*C*H$_2$), 110.7 (Ar*C*H), 114.1 (*C*H$_2$) alkene, 121.9 (Ar*C*H), 122.5 (Ar*C*$_q$), 123.3 (Ar*C*H), 127.4 (Ar*C*H), 136.6 (*C*=N), 139.2 (*C*H) alkene, 141.4 (Ar*C*N), 163.0 (*C*=O); ν_{max} (film)/cm^{-1} 3193, 2926, 2855, 1724, 1471, 1299, 1143; *m/z* (ESI$^-$) 313 [M - H]$^-$ (100%), 314 (22); HRMS (ESI)$^+$: Exact mass calculated for $C_{19}H_{27}N_2O_2$ [M + H]$^+$ 315.2073. Found 315.2058.

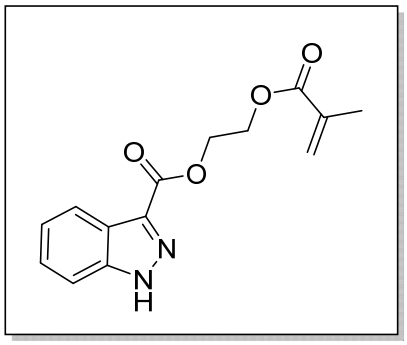
Note: The undec-10-en-1-yl 1-acetyl 1*H*-indazole-3-carboxylate **223** starting material contained trace amounts of the *N*-arylated by-product which was isolated here as a yellow oil (1 mg).

Undec-10-en-1-yl 1-phenyl 1*H*-indazole-3-carboxylate 226



δ_H($CDCl_3$, 400 MHz): 1.25-1.40 (12H, m, 6 × C*H*$_2$), 1.84-1.92 (2H, m, C*H*$_2$), 2.00-2.07 (2H, m, C*H*$_2$), 4.49 (2H, t, *J* 6.9, OC*H*$_2$), 4.90-5.03 (2H, m, CH=C*H*$_2$), 5.75-5.85 (1H, m, C*H*=CH$_2$), 7.31-7.59 (5H, m, 5 × ArC*H*), 7.69-7.80 (3H, m, 3 × ArC*H*), 8.28-8.35 (1H, m, ArC*H*).

2-(Methacryloyloxy)ethyl 1*H*-indazole-3-carboxylate 222

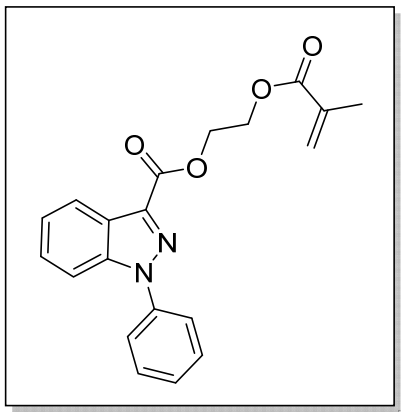


The title compound was prepared in the same manner as propyl 1*H*-indazole-3-carboxylate **223** using 2-(methacryloyloxy)ethyl 1-acetyl 1*H*-indazole-3-carboxylate **125** (20 mg, 58 μmol) and TBAF (1M in THF, 0.23 mmol, 0.23 mL) in THF (6 mL). Following the work-up, the residue was purified by column chromatography on silica gel using hexane:ethyl acetate (3:1-1:3) to isolate 2-(methacryloyloxy)ethyl 1*H*-indazole-3-carboxylate **222** as a yellow solid (12 mg, 72%), m.p. 69-75 ºC. δ_H($CDCl_3$, 400 MHz): 1.95 (3H, s, C*H*$_3$), 4.59 (2H, dd, *J* 5.7, 3.8, OC*H*$_2$), 4.74-4.77 (2H, m, OC*H*$_2$), 5.58 (1H, s, one of alkene C*H*$_2$), 6.16 (1H, s, one of alkene C*H*$_2$), 7.33 (1H, t, *J* 7.6, ArC*H*), 7.48 (1H, t, *J* 7.6, ArC*H*), 7.72 (1H, d, *J* 8.4, ArC*H*), 8.20 (1H, d, *J* 8.2, ArC*H*), 11.98 (1H, br s, N*H*); δ_C($CDCl_3$, 100 MHz): 18.3 (*C*H$_3$), 62.5 (O*C*H$_2$), 62.7 (O*C*H$_2$), 111.0 (Ar*C*H), 121.8 (Ar*C*H), 122.5 (Ar*C*$_q$), 123.4 (Ar*C*H), 126.3 (*C*H$_2$ alkene), 127.5 (Ar*C*H), 135.9 (*C*$_q$) alkene, 136.2 (*C*=N), 141.3 (Ar*C*N), 162.7 (*C*=O) ester, 167.2 (*C*=O) methacrylate ester; ν_{max} (KBr)/cm^{-1} 3270, 2957, 1723, 1147; *m/z* (ESI$^+$) 275 [M + H]$^+$ (72%), 196 (40), 113 (100); HRMS (ESI$^+$): exact mass calculated for $C_{14}H_{15}O_4N_2$ [M + H]$^+$ 275.1032. Found 275.1035.

Note 1: The ^{1}H NMR spectrum still showed the presence of 6% 1-acyl starting material after chromatography

Note 2: The 2-(methacryloyloxy)ethyl 1-acetyl 1*H*-indazole-3-carboxylate starting material contained 10% of the *N*-arylated by-product **227** which was isolated here (1 mg).

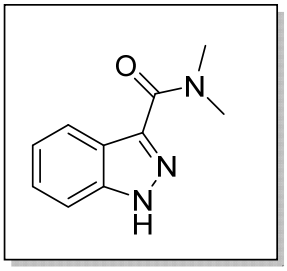
2-(Methacryloyloxy)ethyl 1-phenyl-1*H*-indazole-3-carboxylate 227



δ_H($CDCl_3$, 400 MHz): 1.97 (3H, s, C*H*$_3$), 4.57-4.61 (2H, m, OC*H*$_2$), 4.74-4.78 (2H, m, OC*H*$_2$), 5.60 (1H, s, one of alkene C*H*$_2$), 6.18 (1H, s, one of alkene C*H*$_2$), 7.34-7.67 (5H, m, 5 × ArC*H*), 7.70-7.81 (3H, m, 3 × ArC*H*), 8.28 (1H, d, *J* 8.1, ArC*H*); δ_C($CDCl_3$, 100 MHz): 18.3 (*C*H$_3$), 62.5 (O*C*H$_2$), 62.6 (O*C*H$_2$), 123.9 (2 × Ar*C*H) and 129.6 (2 × Ar*C*H) were the only characteristic signals visible.

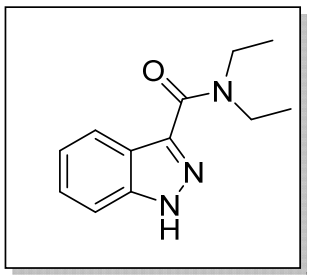
Amide side chain

***N,N*-Dimethyl-1*H*-indazole-3-carboxamide 228**



The title compound was prepared in the same manner as propyl 1*H*-indazole-3-carboxylate **223** using *N,N*-dimethyl 1*H*-indazole-3-carboxamide **140** (20 mg, 0.09 mmol) and TBAF (1M in THF, 0.35 mmol, 0.35 mL) in THF (6 mL). Following the work-up, *N,N*-dimethyl-1*H*-indazole-3-carboxamide **228** was isolated as a white solid with no further purification required (8 mg, 49%), m.p. 186-189 ºC, (Lit.[62] 187-189 ºC). δ_H($CDCl_3$, 400 MHz): 3.21 (3H, s, NC*H*$_3$), 3.41 (3H, s, NC*H*$_3$), 7.26 (1H, t, *J* 7.7, ArC*H*), 7.42 (1H, t, *J* 7.5, ArC*H*), 7.49 (1H, dd, *J* 8.4, 0.9, ArC*H*), 8.16 (1H, td, *J* 8.2, 0.9, ArC*H*), 10.23 (N*H*); δ_C($CDCl_3$, 100 MHz): 39.0 (2 × NCH$_3$), 109.5 (Ar*C*H), 122.4 (Ar*C*H), 122.48 (ArC_q), 122.50 (Ar*C*H), 127.3 (Ar*C*H), 140.4 (*C*=N), 142.2 (Ar*C*N), 164.1 (*C*=O); *m/z* (ESI$^+$) 212 $[M + Na]^+$ (100%), 190 (10); HRMS (ESI$^+$): exact mass calculated for $C_{10}H_{12}O_2N_3$ $[M + H]^+$ 190.0980. Found 190.0979; ν_{max} (KBr)/cm^{-1} 3430, 2978, 2934, 1629, 1381. Spectral details are in agreement with those reported in the literature.[62]

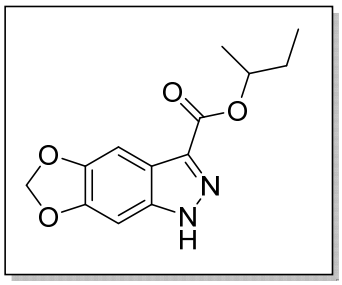
_N_,_N_-Diethyl-1_H_-indazole-3-carboxamide 229



The title compound was prepared in the same manner as propyl 1*H*-indazole-3-carboxylate **223** using *N*,*N*-diethyl 1-acetyl 1*H*-indazole-3-carboxamide **141** (20 mg, 0.08 mmol) and TBAF (1M in THF, 0.31 mmol, 0.31 mL) in THF (6 mL). Following the work-up, *N*,*N*-diethyl-1*H*-indazole-3-carboxamide **229** isolated as a white solid with no further purification required (10 mg, 55%), m.p. 170-172 ºC, (Lit.[63] 172.5-174 ˚C). δ_H($CDCl_3$, 400 MHz): 1.27 (6H, t, *J* 7.0, 2 × C*H*$_3$), 3.64 (2H, q, *J* 6.6, C*H*$_2$), 3.79 (2H, q, *J* 6.7, C*H*$_2$) 7.26 (1H, dd, *J* 6.8, 1.0, ArC*H*), 7.39-7.44 (1H, m, ArC*H*), 7.49 (1H, d, *J* 8.4, ArC*H*), 8.17 (1H, d, *J* 8.2, ArC*H*), 10.16 (1H, br s, N*H*); δ_C($CDCl_3$, 100 MHz): 13.0 (*C*H$_3$), 14.7 (*C*H$_3$), 40.8 (N*C*H$_2$), 43.1 (N*C*H$_2$), 109.4 (Ar*C*H), 122.2 (Ar*C*H). 122.5 (Ar*C*$_q$), 122.6 (Ar*C*H), 127.2 (Ar*C*H), 139.2 (*C*=N), 140.4 (Ar*C*N), 163.4 (*C*=O); ν_{max} (KBr)/cm^{-1} 3148, 2850, 1684, 1597, 1579, 1495, 1242; *m/z* (ESI$^+$) 256 [M + Na]$^+$ (12%).Spectral details are in agreement with those reported in the literature.[63]

Methylene dioxy substituted aryl ring

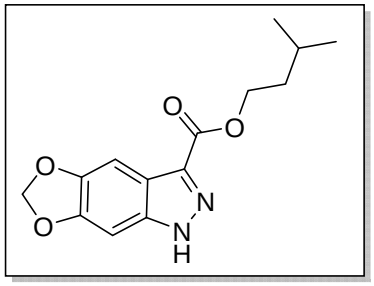
sec-Butyl 1_H_-[1,3]dioxolo[4,5-f] indazole-3-carboxylate 230



The title compound was prepared in the same manner as propyl 1*H*-indazole-3-carboxylate **223** using *sec*-butyl 1-acetyl-1*H*-[1,3]dioxolo[4,5-f]indazole-3-carboxylate **156** (20 mg, 0.07 mmol) and TBAF (1M in THF, 0.26 mmol, 0.26 mL) in THF (6 mL). Following the work-up, *sec*-butyl 1*H*-[1,3]dioxolo[4,5-f] indazole-3-carboxylate **230** was isolated with no further purification required (12 mg, 67%), m.p. 92-93 ºC. δ_H($CDCl_3$, 400 MHz): 1.02 (3H, t, *J* 7.5, C*H*$_3$), 1.42 (3H, d, *J* 6.4, C*H*$_3$), 1.70-1.89 (2H, m, C*H*$_2$), 5.20-5.30 (1H, m, *J* 6.9, OC*H*), 6.05 (2H, s, OC*H*$_2$O), 7.07 (1H, s, ArC*H*), 7.45 (1H, s, ArC*H*), 11.76 (1H, br s, N*H*); δ_C($CDCl_3$, 100 MHz): 9.9 (CH$_2$*C*H$_3$), 19.7 (CH*C*H$_3$), 29.0 (*C*H$_2$), 73.2 (O*C*H), 90.6 (Ar*C*H), 98.5 (Ar*C*H), 101.7 (O*C*H$_2$O), 117.8 (Ar*C*$_q$), 135.9 (*C*=N), 138.8 (Ar*C*N), 146.4

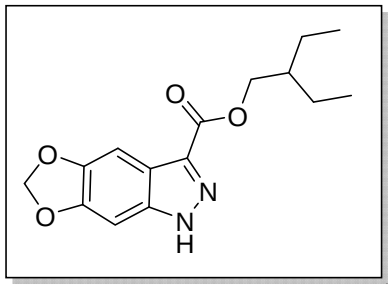
(Ar*C*OCH$_2$), 149.4 (Ar*C*OCH$_2$), 162.6 (*C*=O); ν_{max} (film)/cm^{-1} 3455, 2959, 1736, 1485; *m/z* (ESI$^+$) 285 [M + Na]$^+$ (10%); HRMS (ESI$^+$): exact mass calculated for $C_{13}H_{15}N_2O_4$ [M + H]$^+$ 262.1032. Found 263.1024.

Isopentyl 1*H*-[1,3]dioxolo[4,5-f]indazole-3-carboxylate 231



The title compound was prepared in the same manner as propyl 1*H*-indazole-3-carboxylate **223** using isopentyl 1-acetyl-1*H*-[1,3]dioxolo[4,5-f]indazole-3-carboxylate **24** (20 mg, 0.06 mmol) and TBAF (1M in THF, 0.25 mmol, 0.25 mL) in THF (6 mL). Following the work-up, isopentyl 1*H*-[1,3]dioxolo[4,5-f]indazole-3-carboxylate **231** was isolated as a white solid with no further purification required (13 mg, 78%), m.p. 90-91 ºC. δ_H(CDCl$_3$, 400 MHz): 0.99 (6H, d, *J* 8.5, 2 × C*H*$_3$), 1.65-1.90 [3H, m, containing 1.74 (2H, dd, OCH$_2$C*H*$_2$) and C*H*(CH$_3$)$_2$], 4.49 (2H, t, *J* 6.8, OC*H*$_2$), 6.05 (2H, s, OC*H*$_2$O), 7.07 (1H, s, ArC*H*), 7.44 (1H, s, ArC*H*) 11.41 (1H, br s, N*H*); δ_C(CDCl$_3$, 100 MHz): 22.5 (2 × *C*H$_3$), 25.2 (*C*H), 37.5 (*C*H$_2$), 63.7 (O*C*H$_2$), 90.5 (Ar*C*H), 98.4 (Ar*C*H), 101.7 (O*C*H$_2$O), 117.8 (Ar*C*$_q$), 138.7 (*C*=N), 138.8 (Ar*C*N), 146.4 (Ar*C*OCH$_2$), 149.5 (Ar*C*OCH$_2$), 163.0 (*C*=O); ν_{max} (film)/cm^{-1} 3407, 2956, 1732, 1484, 1262; *m/z* (ESI$^+$) 277 [M + H]$^+$ (74%), 243 (4); HRMS (ESI)$^+$: Exact mass calculated for $C_{14}H_{17}N_2O_4$ [M + H]$^+$ 277.1188. Found 277.1184.

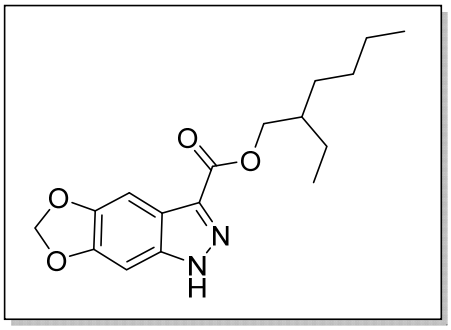
2-Ethylbutyl 1*H*-[1,3]dioxolo[4,5-f]indazole-3-carboxylate 232



The title compound was prepared in the same manner as propyl 1*H*-indazole-3-carboxylate **223** using 2-ethylbutyl 1-acetyl-1*H*-[1,3]dioxolo[4,5-f]indazole-3-carboxylate **157** (20 mg, 0.06 mmol) and TBAF (1M in THF, 0.24 mmol, 0.24 mL) in THF (6 mL). Following the work-up, 2-ethylbutyl 1*H*-[1,3]dioxolo[4,5-f]indazole-3-carboxylate **232** was isolated as a white solid with no further purification required (14 mg, 82%), m.p. 113-114 ºC. δ_H(CDCl$_3$, 400 MHz): 0.97

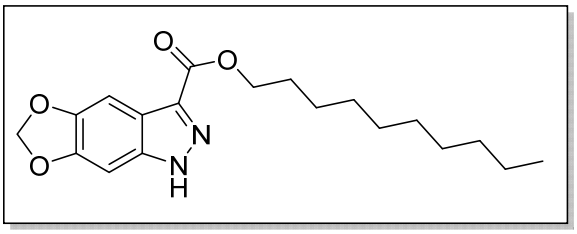
(6H, t, *J* 7.5, 2 × C*H*$_3$), 1.46-1.54 (4H, m, 2 × C*H*$_2$), 1.75 [1H, td, *J* 12.4, 6.2, C*H*(CH$_2$)$_2$], 4.40 (2H, d, *J* 5.8, OC*H*$_2$), 6.05 (2H, s, OC*H*$_2$O), 7.12 (1H, s, ArC*H*), 7.42 (1H, s, ArC*H*), N*H* signal not visible; δ_C(CDCl$_3$, 100 MHz): 11.1 (2 × *C*H$_3$), 23.5 (2 × *C*H$_2$), 40.5 (*C*H), 67.0 (O*C*H$_2$), 90.8 (Ar*C*H), 98.3 (Ar*C*H), 101.7 (O*C*H$_2$O), 117.7 (Ar*C*$_q$), 135.6 (*C*=N), 138.8 (Ar*C*N), 146.4 (Ar*C*OCH$_2$), 149.4 (Ar*C*OCH$_2$), 163.1 (C=O); ν_{max} (KBr)/cm^{-1} 3429, 2955, 2934, 2861, 1729, 1137; *m/z* (ESI$^+$) 291 [M + H]$^+$ (5%), 242 (100); HRMS (ESI)$^+$: Exact mass calculated for $C_{15}H_{19}N_2O_4$ [M + H]$^+$ 291.1345. Found 291.1341.

2-Ethylhexyl 1*H*-[1,3]dioxolo[4,5-f]indazole-3-carboxylate 233



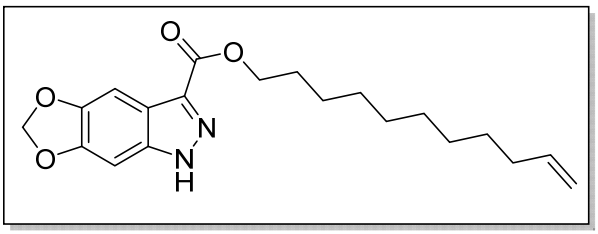
The title compound was prepared in the same manner as propyl 1*H*-indazole-3-carboxylate **223** using 2-ethylhexyl 1-acetyl-1*H*-[1,3]dioxolo[4,5-f]indazole-3-carboxylate **156** (20 mg, 0.06 mmol) and TBAF (1M in THF, 0.25 mmol, 0.25 mL) in THF (6 mL). Following the work-up, 2-ethylhexyl 1*H*-[1,3]dioxolo[4,5-f]indazole-3-carboxylate **233** was isolated as a white solid with no further purification required (74%, 14 mg), m.p. 83-86 ºC. δ_H(CDCl$_3$, 400 MHz) : 0.80-1.00 [6H, m, containing 0.90 (3H, t, *J* 7.1, C*H*$_3$) and 0.96 (3H, t, *J* 7.5, C*H*$_3$)], 1.22-1.90 [9H, m, containing 4 × C*H*$_2$ and 1.80 (1H, td, *J* 12.3, 6.2, C*H*)], 4.38 (2H, dd, *J* 5.8, 2.7, OC*H*$_2$), 6.06 (2H, s, OC*H*$_2$O), 7.09 (1H, s, ArC*H*), 7.43 (1H, s, ArC*H*), 11.74 (1H, br s, N*H*); δ_C(CDCl$_3$, 100 MHz): 11.0 (*C*H$_3$), 14.0 (*C*H$_3$), 22.9 (*C*H$_2$), 23.9 (*C*H$_2$), 28.9 (*C*H$_2$), 30.5 (*C*H$_2$), 38.9 (*C*H), 67.4 (O*C*H$_2$), 90.7 (O*C*H$_2$O), 98.3 (Ar*C*H), 101.7 (Ar*C*H), 117.8 (Ar*C*$_q$), 136.4 (*C*=N), 138.8 (Ar*C*N), 146.5 (Ar*C*OCH$_2$), 149.5 (Ar*C*OCH$_2$), 163.0 (*C*=O) ester; ν_{max} (KBr)/cm^{-1} 3423, 2928, 1727, 1463, 1138; *m/z* (ESI$^+$) 319 [M + H]$^+$ (100%), 277 (25); HRMS (ESI)$^+$: Exact mass calculated for $C_{17}H_{23}N_2O_4$ [M + H]$^+$ 319.1658. Found 319.1646.

Decyl 1*H*-[1,3]dioxolo[4,5-f]indazole-3-carboxylate 234



The title compound was prepared in the same manner as propyl 1*H*-indazole-3-carboxylate **223** using decyl 1-acetyl-1*H*-[1,3]dioxolo[4,5-f]indazole-3-carboxylate **158** (20 mg, 0.05 mmol) and TBAF (1M in THF, 0.21 mmol, 0.21 mL) in THF (6 mL). Following the work-up, decyl 1*H*-[1,3]dioxolo[4,5-f]indazole-3-carboxylate **234** was isolated as a white solid with no further purification required (15 mg, 88%), m.p. 104-105 ºC. δ_H($CDCl_3$, 400 MHz): 0.87 (3H, t, *J* 6.9, C*H*$_3$), 1.20-1.32 (12H, m, 6 × C*H*$_2$), 1.40-1.51 (2H, m, C*H*$_2$), 1.79-1.87 (2H, m, C*H*$_2$), 4.45 (2H, t, *J* 6.8, OC*H*$_2$), 6.05 (2H, s, OC*H*$_2$O), 7.12 (1H, s, ArC*H*), 7.44 (1H, s, ArC*H*), 12.11 (1H, br s, N*H*); δ_C($CDCl_3$, 100 MHz): 14.1 (CH_2CH_3), 22.7 (C*H*$_2$), 26.0 (C*H*$_2$), 28.8 (C*H*$_2$), 29.3 (C*H*$_2$), 29.5 (C*H*$_2$), 29.52 (2 × C*H*$_2$), 31.9 (OCH_2CH_2), 65.2 (OC*H*$_2$), 90.7 (Ar*C*H), 98.4 (Ar*C*H), 101.7 (O*C*H$_2$O), 117.8 (ArC_q), 135.7 (*C*=N), 138.7 (Ar*C*N), 146.4 (Ar*C*OCH$_2$), 149.5 (Ar*C*OCH$_2$), 163.0 (*C*=O); ν_{max} (film)/cm^{-1} 3382, 2956, 1732, 1484, 1262; *m/z* (ESI$^+$) 347 [M + H]$^+$ (100%); HRMS (ESI)$^+$: Exact mass calculated for $C_{19}H_{27}N_2O_4$[M + H]$^+$ 347.1971. Found 347.1971.

Undec-10-en-1-yl 1*H*-[1,3]dioxolo[4,5-f]indazole-3-carboxylate 235

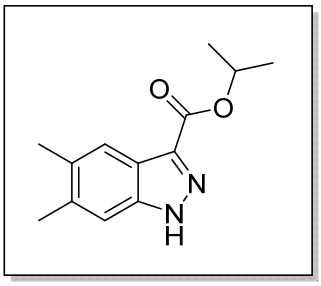


The title compound was prepared in the same manner as propyl 1*H*-indazole-3-carboxylate **223** using undec-10-en-1-yl 1-acetyl-1*H*-[1,3]dioxolo[4,5-f]indazole-3-carboxylate **159** (20 mg, 0.08 mmol) and TBAF in THF 1M 0.31 mmol, 0.31 mL) in THF (6 mL). Following the work-up, undec-10-en-1-yl 1*H*-[1,3]dioxolo[4,5-f]indazole-3-carboxylate **235** was isolated as a cream solid with no further purification required (15 mg, 83%), m.p. 128-129 ºC. δ_H($CDCl_3$, 400 MHz): 1.26-1.50 (12H, m, 6 × C*H*$_2$), 1.79-1.88 (2H, m, C*H*$_2$), 2.03 (2H, dd, *J* 13.9, 7.3, C*H*$_2$), 4.43 (2H, t, *J* 6.8, OC*H*$_2$), 4.95 (2H, m, CH=C*H*$_2$), 5.81 (1H, tdd, *J* 17.0, 10.2, 6.7, C*H*=CH$_2$), 6.05 (2H, s, OC*H*$_2$O), 6.99 (1H, s, ArC*H*), 7.46 (1H, s, ArC*H*), N*H* signal not visible; δ_C($CDCl_3$, 100 MHz): 26.0 (*C*H$_2$), 28.8

(CH_2), 28.9 (CH_2), 29.1 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 33.8 (CH_2), 65.2 (OCH_2), 90.2 (Ar*C*H), 98.5 (Ar*C*H), 101.8 (OCH_2O), 114.1 (CH_2) alkene, 139.2 (*C*H) alkene, 146.5 (Ar*C*OCH_2), 149.6 (Ar*C*OCH_2), 162.7 (*C*=O), ArC_q, Ar*C*N and *C*=N not detected; ν_{max} (KBr)/cm^{-1} 3193, 2926, 2855, 1724, 1471, 1299, 1143; *m/z* (ESI$^+$) 359 $[M + H]^+$ (50%); HRMS (ESI)$^+$: Exact mass calculated for $C_{20}H_{27}N_2O_4[M + H]^+$ 359.1971. Found 359.1962.

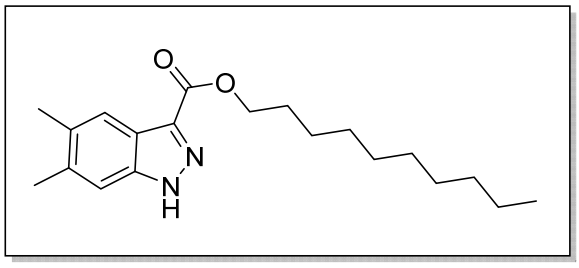
Dimethyl substituted aryl ring

Isopropyl 5,6-dimethyl-1*H*-indazole-3-carboxylate 236



The title compound was prepared in the same manner as propyl 1*H*-indazole-3-carboxylate **223** using isopropyl 1-acetyl-1*H*-5,6-dimethylindazole-3-carboxylate **168** (20 mg, 0.07 mmol) and TBAF (1M in THF, 0.29 mL, 0.29 mmol) in THF (6 mL). Following the work-up, isopropyl 5,6-dimethyl-1*H*-indazole-3-carboxylate **236** was isolated as a yellow solid with no further purification required (69%, 11 mg), m.p. 148-150 ºC. δ_H($CDCl_3$, 400 MHz): 1.46 (6H, t, *J* 6.1, 2 × C*H*$_3$), 2.40 (6H, s, 2 × ArC*H*$_3$), 5.38-5.46 (1H, m, OC*H*), 7.40 (1H, s, ArC*H*), 7.94 (1H, s, ArC*H*), 11.38 (1H, br s, N*H*); δ_C($CDCl_3$, 100 MHz): 20.4 (Ar*C*H_3), 20.9 (Ar*C*H_3), 22.1 (2 × *C*H_3), 68.6 (*C*H), 110.4 (Ar*C*H), 121.1 (Ar*C*H), 121.3 (ArC_q), 132.8 (Ar*C*CH_3), 136.2 (*C*=N), 137.4 (Ar*C*CH_3), 140.7 (Ar*C*N), 162.8 (*C*=O); ν_{max} (KBr)/cm^{-1} 3267, 2978, 1718, 1105; *m/z* (ESI$^+$) 255 $[M + Na]^+$ (80%), 256 (20); HRMS (ESI)$^+$: Exact mass calculated for $C_{13}H_{17}N_2O_2[M + H]^+$ 233.1290. Found 233.1282.

Decyl 5,6-dimethyl-1*H*-indazole-3-carboxylate 237

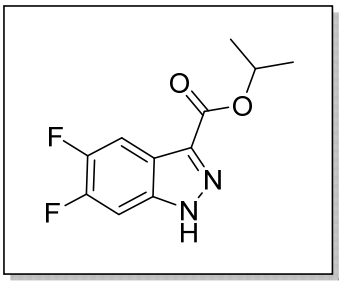


The title compound was prepared in the same manner as propyl 1*H*-indazole-3-carboxylate **223** using decyl 1-acetyl-1*H*-5,6-dimethyl indazole-3-carboxylate **169** (20 mg, 0.07 mmol) and TBAF (1M in THF, 0.29 mL, 0.29 mmol) in THF (6 mL). Following the work-up, decyl 5,6-dimethyl-1*H*-indazole-3-carboxylate **237** was

isolated as a white solid with no further purification required (57%, 13 mg), m.p. 79-80 ºC. δ_H($CDCl_3$, 400 MHz): 0.87 (3H, t, *J* 6.6, C*H*$_3$), 1.22-1.30 (12H, m, 6 × C*H*$_2$), 1.41-1.51 (2H, m, C*H*$_2$), 1.78-1.88 (2H, m, C*H*$_2$), 2.40 (2 × Ar*C*H$_3$), 4.47 (2H, t, *J* 6.8, OC*H*$_2$), 7.47 (1H, s, ArC*H*), 7.93 (1H, s, ArC*H*), 12.18 (1H, br s, N*H*); δ_C($CDCl_3$, 75.5 MHz): 14.1 (CH_2CH_3), 20.4 (Ar*C*H$_3$), 20.9 (Ar*C*H$_3$), 22.7 (C*H*$_2$), 26.1 (C*H*$_2$), 28.8 (C*H*$_2$), 29.3 (2 × C*H*$_2$), 29.5 (2 × C*H*$_2$), 31.9 (OCH_2CH_2), 65.1 (OC*H*$_2$), 110.8 (Ar*C*H), 120.9 (Ar*C*H), 121.3 (Ar*C*$_q$), 132.8 (Ar*C*CH$_3$), 135.7 (*C*=N), 137.3 (Ar*C*CH$_3$), 140.8 (Ar*C*N), 163.4 (*C*=O); ν_{max} (KBr)/cm^{-1} 3382, 2956, 1732, 1484, 1213; *m/z* (ESI$^+$) 353 $[M + Na]^+$ (100%), 304 (30); HRMS (ESI)$^+$: Exact mass calculated for $C_{20}H_{31}N_2O_2$ $[M + H]^+$ 331.2386. Found 331.2374.

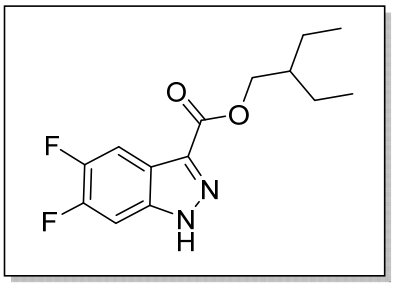
Difluoro substituted aryl ring

Isopropyl 5,6-difluoro-1*H*-indazole-3-carboxylate 238



The title compound was prepared in the same manner as propyl 1*H*-indazole-3-carboxylate **223** using isopropyl 1-acetyl-1*H*-5,6-difluoroindazole-3-carboxylate **179** (20 mg, 0.07 mmol) and TBAF (1M in THF, 0.29 mL, 0.29 mmol) in THF (6 mL). Following the work-up, isopropyl 5,6-difluoro-1*H*-indazole-3-carboxylate **238** was isolated as a white solid with no further purification required (12 mg, 73%), m.p. 239-241 ºC. δ_H($CDCl_3$, 400 MHz): 1.51 (6H, t, *J* 6.2, 2 × C*H*$_3$), 5.42-5.51 (1H, m, C*H*), 7.66 (1H, dd, $^1J_{HF}$ 9.5, $^1J_{HF}$ 6.6, ArC*H*), 7.92 (1H, dd, $^1J_{HF}$ 9.0, $^1J_{HF}$ 8.1, ArC*H*), 12.37 (1H, br s, N*H*); δ_C($CDCl_3$, 75.5 MHz): 22.1 (2 × *C*H$_3$), 69.4 (O*C*H), 99.2 (d, $^1J_{HF}$ 22.0, Ar*C*H), 108.0 (d, $^1J_{HF}$ 18.8, Ar*C*H), 117.7 (d, $^1J_{HF}$ 9.6, Ar*C*$_q$), [137.2 (d, $^1J_{HF}$ 6.9) and 137.3 (d, $^1J_{HF}$ 6.1), Ar*C*N and *C*=N], 148.8 (d, $^1J_{HF}$ 261.8, Ar*C*F), 151.5 (d, $^1J_{HF}$ 251.1, Ar*C*F), 162.2 (*C*=O); ν_{max} (KBr)/cm^{-1} 3212, 1726, 1489, 1441, 1146; *m/z* (ESI$^-$) 239 $[M - H]^-$ (100%), 240 (12); HRMS (ESI)$^+$: Exact mass calculated for $C_{11}H_{11}N_2F_2O_2$ $[M + H]^+$ 241.0789. Found 241.0781.

2-Ethylbutyl 5,6-difluoro-1*H*-indazole-3-carboxylate 239



The title compound was prepared in the same manner as propyl 1*H*-indazole-3-carboxylate **223** using 2-ethylbutyl 1-acetyl-1*H*-5,6-difluoroindazole-3-carboxylate **183** (20 mg, 0.07 mmol) and TBAF (1M in THF, 0.29 mL, 0.29 mmol) in THF (6 mL). Following the work-up, 2-ethylbutyl 5,6-difluoro-1*H*-indazole-3-carboxylate **239** was isolated with no further purification required as a white solid (14 mg, 71%), m.p. 195-197 ºC. δ_H($CDCl_3$, 400 MHz): 1.01 (6H, t, *J* 7.3, 2 × C*H*$_3$), 1.49-1.59 (4H, m, 2 × C*H*$_2$), 1.78 (1H, dt, *J* 6.4, 12.1, C*H*), 4.50 (2H, d, *J* 5.6, OC*H*$_2$), 7.84 (2H, m, 2 × ArC*H*), 13.35 (1H, br s, N*H*); δ_C($CDCl_3$, 100 MHz): 11.1 (2 × *C*H$_3$), 23.6 (2 × *C*H$_2$), 40.7 (*C*H), 67.5 (O*C*H$_2$), 99.95 (d, $^2J_{CF}$ 22.6, Ar*C*H), 107.5 (d, $^2J_{CF}$ 20.6, Ar*C*H), 117.5 (d, $^3J_{CF}$ 9.0, Ar*C*$_q$), 136.8 (d, $^4J_{CF}$ 5.9, *C*=N), 137.5 (d, $^3J_{CF}$ 11.0 Ar*C*N), 149.0 (dd, $^1J_{CF}$ 261.1, $^2J_{CF}$ 17.2, Ar*C*F), 150.3 (dd, $^1J_{CF}$ 250.4, $^2J_{CF}$ 16.5, Ar*C*F), 163.1 (*C*=O); ν_{max} (KBr)/cm^{-1} 3647, 2962, 1733, 1507, 1319, 1157; *m/z* (ESI$^-$) 281 [M - H]$^-$ (100%), 113 (6); HRMS (ESI)$^+$: Exact mass calculated for $C_{14}H_{17}N_2F_2O_2$ [M + H]$^+$ 283.1258. Found 283.1251.

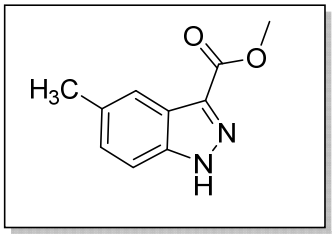
5/6-Substituted aryl ring

Methyl-5-methyl-1*H*-indazole-3-carboxylate 240 and methyl-6-methyl 1*H*-indazole-3-carboxylate 241 1:1

The title compounds were prepared in the same manner as propyl 1*H*-indazole-3-carboxylate **223** using methyl-5/6-methyl-1-pentanoyl 1*H*-indazole-3-carboxylate **193/194** (20 mg, 0.07 mmol) and TBAF (1M in THF, 0.29 mL, 0.29 mmol) in THF (6 mL). Following the work-up, the residue was purified using column chromatography on silica gel using hexane:ethyl acetate (3:1-1:3) as eluent and the 50:50 mixture of regioisomers were isolated as a white solid (8 mg, 62%), m.p. 91-92 ºC. δ_C($CDCl_3$, 100 MHz): 21.5 and 22.0 (Ar*C*H$_3$), 52.0 (O*C*H$_3$), 110.1 and 110.6 (Ar*C*H), 120.7 and 121.3 (Ar*C*H), 120.8 and 122.9 (Ar*C*$_q$), 125.7 and 129.6 (Ar*C*H), 133.1 and 137.8 (Ar*C*CH$_3$), 135.7 and 140.0 (*C*=N), 136.3 and 141.9 (Ar*C*N), 163.4 and 163.5 (*C*=O); ν_{max} (KBr)/cm^{-1} 3269, 2954, 1722, 1467, 1141;

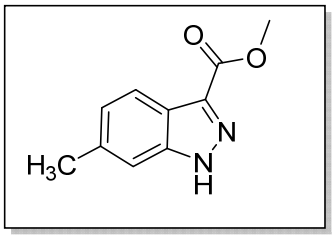
m/z (ESI$^+$) 191 [M + H]$^+$ (65%); HRMS (ESI$^+$): exact mass calculated for $C_{10}H_{11}N_2O_2$ [M + H]$^+$ 191.0821. Found 191.0814.

Methyl-5-methyl-1*H*-indazole-3-carboxylate 240



δ_H ($CDCl_3$, 400MHz): 2.52 (3H, s, ArC*H*$_3$), 4.05 or 4.06 (3H, s, OC*H*$_3$), 7.30 (1H, d, *J* 8.5, ArC*H*), 7.58 (1H, d, *J* 8.6, ArC*H*), 8.09 (1H, d, *J* 8.4, ArC*H*), 11.7 (1H, br s, N*H*).

Methyl-6-methyl 1*H*-indazole-3-carboxylate 241

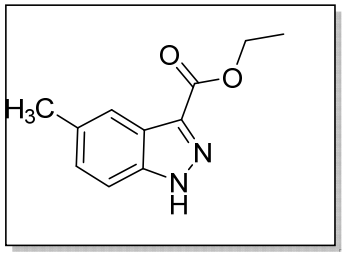


δ_H ($CDCl_3$, 400MHz): 2.52 (3H, s, ArC*H*$_3$), 4.05 or 4.06 (3H, s, OC*H*$_3$) 7.17 (1H, d, *J* 8.4, ArC*H*), 7.44 (1H, s, ArC*H*), 8.00 (1H, s, ArC*H*), 11.7 (1H, br s, N*H*).

Ethyl 5-methyl-1*H*-indazole-3-carboxylate 242 and ethyl 6-methyl-1*H*-indazole-3-carboxylate 243

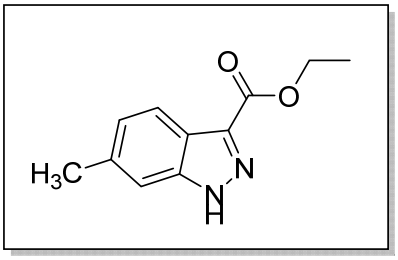
The title compounds were prepared in the same manner as propyl 1*H*-indazole-3-carboxylate **223** using ethyl-5/6-methyl-1-butyryl 1*H*-indazole-3-carboxylate **195/196** (20 mg, 0.07 mmol) and TBAF (1M in THF, 0.29 mL, 0.29 mmol) in THF (6 mL). Following the work-up, the 50:50 mixture of regioisomers were isolated as a yellow oil with no further purification required (11 mg, 80%). δ_C($CDCl_3$, 100 MHz): 14.4 (*C*$H_3$$CH_2$O), 21.6 and 21.9 (Ar*C*$H_3$), 61.0 ($CH_3$*C*$H_2$O), 110.1 and 110.5 (Ar*C*H), 120.8 and 121.4 (Ar*C*H), 121.4 and 123.0 (ArC_q), 125.6 and 129.5 (Ar*C*H), 133.0 and 137.8 (Ar*C*CH_3), 136.0 and 141.9 (*C*=N), 136.6 and 140.0 (Ar*C*N), 163.0 and 163.1 (*C*=O); ν_{max} (film)/cm^{-1} 3287, 2924, 1712, 1480, 1420, 1280.

Ethyl 5-methyl-1*H*-indazole-3-carboxylate 242



δ_H ($CDCl_3$, 400MHz): 1.47 (3H, dt, *J* 7.0, 1.3, OCH_2CH_3), 2.51 (3H, s, $ArCH_3$), 4.54 (2H, dq, *J* 3.7, 7.1, OCH_2CH_3), 7.29 (1H, d, *J* 8.9, ArC*H*), 7.43 (1H, s, ArC*H*), 8.00 (1H, s, ArC*H*), 11.63 (1H, br s, N*H*).

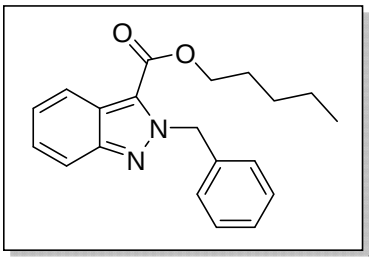
Ethyl 6-methyl-1*H*-indazole-3-carboxylate 243



δ_H ($CDCl_3$, 400MHz): 1.47 (3H, dt, *J* 7.0, 1.3, OCH_2CH_3), 2.51 (3H, s, $ArCH_3$), 4.54 (2H, dq, *J* 3.7, 7.1, OCH_2CH_3), 7.16 (1H, d, *J* 8.4, ArC*H*), 7.57 (1H, d, *J* 8.6, ArC*H*), 8.08 (1H, d, *J* 8.3, ArC*H*), 11.63 (1H, br s, N*H*).

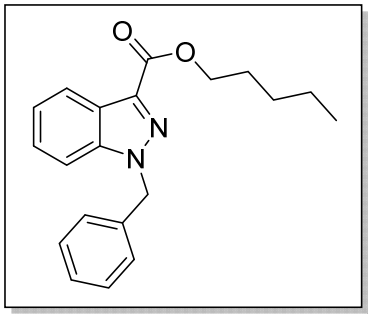
3.8 Alkylations of 1-*H*-indazole derivatives to yield *N*-1 and *N*-2 isomers[64,65]

Pentyl 2-benzyl-2*H*-indazole-3-carboxylate 253



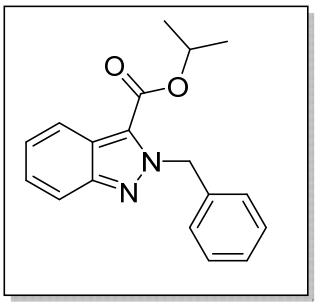
A solution containing pentyl 1*H*-indazole-3-carboxylate **215** (50 mg, 0.2 mmol), benzylbromide **339** (25 μL, 0.2 mmol) and potassium carbonate (55 mg, 0.4 mmol) in DMF (5 mL) was stirred under nitrogen at 80 ºC. After 8 h, the reaction solution was diluted with brine (10 mL), extracted with methyl *t*-butyl ether (3 × 10 mL), washed with water (3 × 10 mL), dried with $MgSO_4$ and concentrated under reduced pressure to yield a residue which was further purified by column chromatography on silica gel using hexane:ethyl acetate (95:5) initially to yield pure *N*-2 benzylated isomer **253** (10 mg, 16%), m.p. 69-70 ºC and then hexane:ethyl acetate (70:30) to isolate pure *N*-1 benzylated isomer **252** (18 mg, 28%) as a yellow oil. δ_H($CDCl_3$, 400 MHz): 0.93 (3H, t, *J* 7.1, C*H*$_3$), 1.35-1.49 (4H, m, 2 × C*H*$_2$), 1.78-1.87 (2H, m, C*H*$_2$), 4.40 (2H, t, *J* 6.7, OC*H*$_2$), 6.12 (2H, s, benzyl C*H*$_2$), 7.23-7.39 (7H, m, containing 5 × ArC*H* benzyl and 2 × ArC*H* of indazole), 7.82 (1H, dd, *J* 8.1, 0.9, ArC*H*), 8.02 (1H, td, *J* 8.4, 1.0, ArC*H*); δ_C($CDCl_3$, 100 MHz): 13.9 (*C*H$_3$), 22.3 (*C*H$_2$), 28.2 (*C*H$_2$), 28.4 (*C*H$_2$), 56.6 (benzyl *C*H$_2$), 65.2 (O*C*H$_2$), 118.4 (Ar*C*H), 121.5 (Ar*C*H), 123.7 (Ar*C*$_q$ indazole), 123.8 (Ar*C*$_q$ phenyl), 125.1 (Ar*C*H), 126.4 (Ar*C*H), 127.8 (2 × Ar*C*H), 127.9 (*p*-Ar*C*H), 128.6 (2 × Ar*C*H), 136.5 (Ar*C*N), 147.7 (*C*=N), 160.3 (*C*=O); ν_{max} (film)/cm^{-1} 2957, 1709, 1465, 1206; HRMS (ESI$^+$): exact mass calculated for $C_{20}H_{22}N_2O_2$ $[M + H]^+$ 323.1760. Found 323.1753.

Pentyl 1-benzyl-1*H*-indazole-3-carboxylate 252



δ_H($CDCl_3$, 400 MHz): 0.94 (3H, t. *J* 7.1, C*H*$_3$), 1.36-1.52 (4H, m, 2 × C*H*$_2$), 1.84-1.92 (2H, m, C*H*$_2$), 4.47 (2H, t, *J* 6.9, OC*H*$_2$), 5.71 (2H, s, benzyl C*H*$_2$), 7.20-7.38 (8H, m, containing 5 × ArC*H* benzyl and 3 × ArC*H* indazole), 8.21 (1H, d, *J* 8.1, ArC*H*); δ_C($CDCl_3$, 100 MHz): 14.0 (*C*H$_3$), 22.4 (*C*H$_2$), 28.2 (*C*H$_2$), 28.6 (*C*H$_2$), 54.1 (benzyl *C*H$_2$), 65.2 (O*C*H$_2$), 110.1 (Ar*C*H), 122.4 (Ar*C*H), 123.1 (Ar*C*H), 124.0 (Ar*C*$_q$ indazole), 126.9 (Ar*C*H), 127.3 (2 × Ar*C*H), 128.1 (*p*-Ar*C*H), 128.8 (2 × Ar*C*H), 135.4 (Ar*C*$_q$ phenyl), 135.7 (Ar*C*N), 140.6 (*C*=N), 162.8 (*C*=O); ν_{max} (film)/cm^{-1} 2935, 2865, 1710, 1497, 1277, 1085; *m/z* (ESI$^+$) 322 $[M + H]^+$ (100%) 324 (22) 325 (4); HRMS (ESI$^+$): exact mass calculated for $C_{20}H_{22}N_2O_2$ $[M + H]^+$ 323.1760. Found 323.1758.

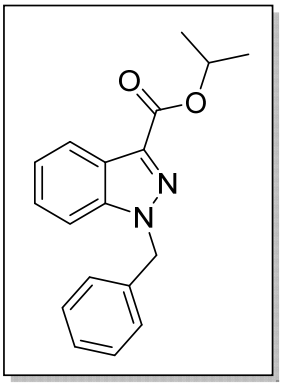
Isopropyl 2-benzyl-2*H*-indazole-3-carboxylate 249



Using the procedure described for pentyl 1-benzyl-1*H*-indazole-3-carboxylate **252** and pentyl 2-benzyl-1*H*-indazole-3-carboxylate **253**, a solution containing isopropyl 1*H*-indazole-3-carboxylate **212** (52 mg, 0.25 mmol), benzylbromide **339** (30 μL, 0.25 mmol) and potassium carbonate (69 mg, 0.5 mmol) in DMF (5 mL) was stirred for 8 h under nitrogen at 80 ºC. Following the work-up, the residue was further purified by column chromatography on silica gel using hexane:ethyl acetate (95:5) to yield pure *N*-2 benzylated isomer **249** as a yellow oil (17 mg, 23%) followed by hexane:ethyl acetate (70:30) to isolate pure *N*-1 benzylated isomer **248** as a yellow solid (19 mg, 26%), m.p. 63-64 ºC. δ_H($CDCl_3$, 400 MHz): 1.42 (6H, d, *J* 6.3, 2 × C*H*$_3$), 5.27-5.38 (1H, m, OC*H*), 6.12 (2H, s, benzyl C*H*$_2$), 7.27-7.38 (7H, m, containing 5 × ArC*H* benzyl and 2 × ArC*H* indazole), 7.81 (1H, td, *J* 8.6, 0.9, ArC*H*, indazole), 8.03 (1H, td, *J* 8.4, 1.0, ArC*H*, indazole); δ_C($CDCl_3$, 100 MHz): 22.1 (2 × *C*H$_3$), 56.5 (*C*H$_2$ benzyl), 68.9 (O*C*H), 118.4 (ArCH), 121.6 (Ar*C*H), 125.0 (Ar*C*H), 126.4 (Ar*C*$_q$ indazole and Ar*C*H), 127.7 (2

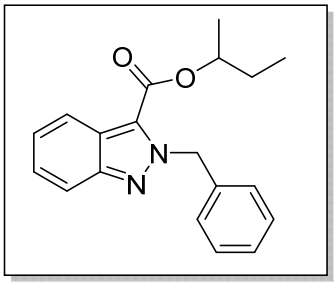
× ArCH), 127.9 (*p*-ArCH), 128.0 (2 × ArCH), 128.6 (C_q benzyl), 136.6 (*C*-N), 147.7 (ArC=N), 159.7 (*C*=O); ν_{max} (KBr)/cm^{-1} 2981, 1707, 1465, 1081; *m/z* (ESI^+) 295 $[M + H]^+$ (100%) 296 (20); HRMS (ESI^+): exact mass calculated for $C_{18}H_{19}N_2O_2$ $[M + H]^+$ 295.1447. Found 295.1447.

Isopropyl 1-benzyl-1*H*-indazole-3-carboxylate 248



δ_H($CDCl_3$, 400 MHz): 1.48 (6H, d, *J* 6.3, 2 × C*H*$_3$), 5.38-5.48 (1H, m, C*H*), 5.72 (2H, s, benzyl C*H*$_2$), 7.20-7.38 (8H, m, containing 5 × ArC*H* phenyl and 3 × ArC*H* indazole), 8.21 (1H, d, *J* 8.1, ArC*H*, indazole); δ_C($CDCl_3$, 100 MHz): 22.1 (2 × *C*H_3), 54.1 (*C*H_2 benzyl), 68.6 (O*C*H), 110.1 (Ar*C*H), 122.5 (Ar*C*H), 123.0 (Ar*C*H), 124.0 (Ar*C*H), 126.9 (ArC_q indazole), 127.3 (2 × Ar*C*H), 128.0 (*p*-Ar*C*H), 128.8 (2 × Ar*C*H), 135.7 (ArC_q benzyl), 135.8 (Ar*C*N), 140.6 (*C*=N), 162.4 (*C*=O); ν_{max} (KBr)/cm^{-1} 2980, 1709, 1477, 1166; *m/z* (ESI^+) 294 $[M + H]^+$ (100%) 296 (22); HRMS (ESI^+): exact mass calculated for $C_{18}H_{19}N_2O_2$ $[M + H]^+$ 295.1447. Found 295.1440.

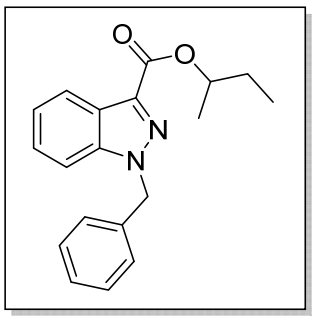
***sec*-Butyl 2-benzyl-2*H*-indazole-3-carboxylate 251**



Using the procedure described for pentyl 1-benzyl-1*H*-indazole-3-carboxylate **252** and pentyl 2-benzyl-1*H*-indazole-3-carboxylate **253**, a solution containing *sec*-butyl 1*H*-indazole-3-carboxylate **214** (15 mg, 0.069 mmol), benzylbromide **339** (8 µL, 0.069 mmol) and potassium carbonate (19 mg, 0.138 mmol) in DMF (5 mL) was stirred for 8 h under nitrogen at 80 ºC. Following the work-up, the residue was further purified by column chromatography on silica gel using hexane:ethyl acetate (95:5) initially to yield pure *N*-2 benzylated isomer **251** as a white solid (6 mg, 28%), m.p. 166-169 ºC followed by hexane:ethyl acetate (70:30) to isolate pure *N*-1 benzylated isomer **250** as a yellow oil (5 mg, 23%). δ_H($CDCl_3$, 400 MHz): 0.98 (3H, t, *J* 7.5, C*H*$_3$), 1.38 (3H, d, *J* 6.3, C*H*$_3$), 1.66-1.90 (2H, m, C*H*$_2$),

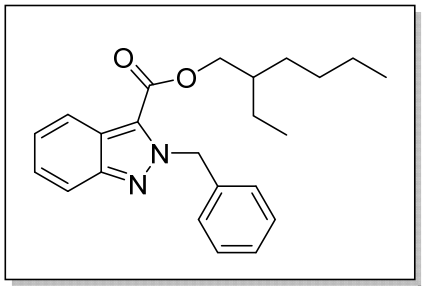
5.18 (1H, dd, *J* 12.6, 6.5, OC*H*), 6.13 (2H, s, benzyl CH_2), 7.26-7.38 (7H, m, containing 5H × ArC*H* phenyl and 2 × ArC*H* indazole), 7.81 (1H, d, *J* 8.1, ArC*H*), 8.03 (1H, d, *J* 8.4, ArC*H*); δ_C($CDCl_3$, 100 MHz): 9.8, (CH_2CH_3) 19.7 ($CHCH_3$), 29.0 (CH_2), 56.5 (CH_2 benzyl), 73.4 (O*C*H), 118.4 (Ar*C*H), 121.6 (Ar*C*H), 125.0 (Ar*C*H), 126.4 (Ar*C*H), 126.4 (ArC_q indazole), 127.7 (2 × Ar*C*H), 127.9 (*p*-Ar*C*H), 128.6 (2 × Ar*C*H) and ArC_q benzyl), 136.6 (*C*-N), 147.6 (Ar*C*=N), 162.2 (*C*=O); ν_{max} (KBr)/cm^{-1} 2981, 1707, 1465, 1081; *m/z* (ESI^+) 309 $[M + H]^+$ (34%); HRMS (ESI^+): exact mass calculated for $C_{19}H_{21}N_2O_2$ $[M + H]^+$ 309.1603. Found 309.1599.

sec-Butyl 1-benzyl-1*H*-indazole-3-carboxylate 250



δ_H($CDCl_3$, 400 MHz): 1.04 (3H, t, CH_3, *J* 7.4), 1.45 (3H, d, *J* 6.2, CH_3), 1.67-1.93 (2H, m, CH_2), 5.25-5.31 (1H, m, OC*H*), 5.72 (2H, s, benzyl CH_2), 7.20-7.37 (8H, m, containing 5 × ArC*H* phenyl and 3 × ArC*H* indazole), 8.20 (1H, d, *J* 8.1, ArC*H* indazole); δ_C($CDCl_3$, 100 MHz): 10.0 (CH_2CH_3), 19.8 ($CHCH_3$), 29.0 (CH_2), 54.1 (CH_2 benzyl), 73.2 (O*C*H), 110.1 (Ar*C*H), 122.4 (Ar*C*H), 123.1 (Ar*C*H), 124.0 (ArC_q indazole), 126.9 (Ar*C*H), 127.3 (2 × Ar*C*H), 128.1 (*p*-Ar*C*H), 128.8 (2 × Ar*C*H), 135.7 (ArC_q benzyl), 135.8 (Ar*C*N), 140.6 (*C*=N), 162.6 (*C*=O); ν_{max} (KBr)/cm^{-1} 2980, 1709, 1477, 1166; *m/z* (ESI^+) 331 $[M + Na]^+$ (60%), 332 (12); HRMS (ESI^+): exact mass calculated for $C_{19}H_{21}N_2O_2$ $[M + H]^+$ 309.1603. Found 309.1591.

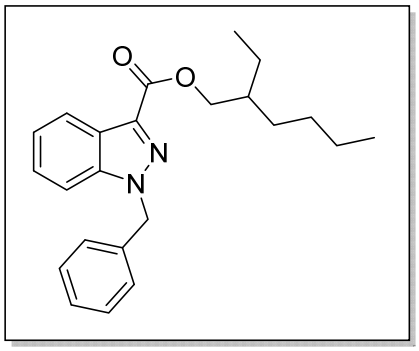
2-Ethylhexyl 2-benzyl-2*H*-indazole-3-carboxylate 255



Using the procedure described for pentyl 1-benzyl-1*H*-indazole-3-carboxylate **252** and pentyl 2-benzyl-1*H*-indazole-3-carboxylate **253**, a solution containing 2-ethyl-butyl 1*H*-indazole-3-carboxylate **219** (15 mg, 0.069 mmol), benzylbromide **339** (8 μL, 0.069 mmol) and potassium carbonate (19 mg,

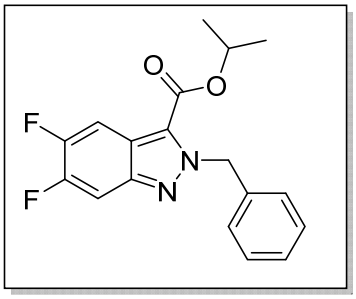
0.138 mmol) in DMF (5 mL) was stirred for 8 h under nitrogen at 80 ºC. Following the work-up, the residue was further purified by column chromatography on silica gel using hexane:ethyl acetate (95:5) to yield pure *N*-2 isomer **255** (6 mg, 24%) followed hexane:ethyl acetate (70:30) to isolate pure *N*-1 benzylated isomer **254** (9 mg, 35%) as colourless oils. δ_H($CDCl_3$, 400 MHz): 0.89-0.96 {6H, m, containing [0.90 (3H, t, *J* 7.0, C*H*$_3$) and 0.95 (3H, t, *J* 7.4, C*H*$_3$)]}, 1.22-1.65 (8H, m, 4 × C*H*$_2$), 1.77 (1H, td, *J* 12.2, 6.1, C*H*), 4.34 (2H, d, *J* 5.6, OC*H*$_2$), 6.13 (2H, s, benzyl *C*H$_2$), 7.24-7.45 (7H, m, containing 5 × ArC*H* benzyl and 2 × ArC*H* indazole), 7.82 (1H, d, *J* 8.6, ArC*H*), 8.02 (1H, d, *J* 6.4, ArC*H*); δ_C($CDCl_3$, 100 MHz): 11.0 (*C*H$_3$), 14.0 (*C*H$_3$), 22.9 (*C*H$_2$), 24.0 (*C*H$_2$), 28.9 (*C*H$_2$), 30.6 (*C*H$_2$), 39.0 (*C*H), 56.6 (*C*H$_2$ benzyl), 67.3 (O*C*H$_2$), 118.4 (Ar*C*H), 121.4 (Ar*C*H), 125.1 (Ar*C*H), 126.4 (Ar*C*H and Ar*C*$_q$ indazole), 127.7 (2 × Ar*C*H), 128.0 (*p*-Ar*C*H), 128.6 (2 × Ar*C*H), 128.9 (Ar*C*$_q$ benzyl), 136.5 (*C*-N), 147.7 (Ar*C*=N), 160.5 (*C*=O); ν_{max} (KBr)/cm^{-1} 2958, 2928, 1709, 1465, 1204; *m/z* (ESI$^+$) 365 $[M + H]^+$ (100%), 328 (5); HRMS (ESI$^+$): exact mass calculated for $C_{23}H_{29}N_2O_2$ $[M + H]^+$ 365.2229. Found 365.2245.

2-Ethylhexyl 1-benzyl-1*H*-indazole-3-carboxylate 254



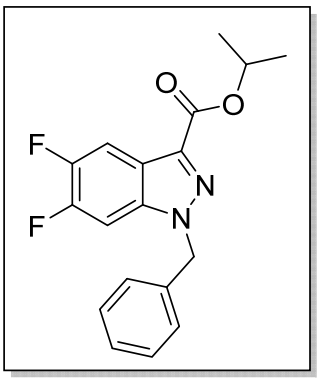
δ_H($CDCl_3$, 400 MHz): 0.90 (3H, t, *J* 7.0, *C*H$_3$), 0.98 (3H, t, *J* 7.5, C*H*$_3$), 1.30-1.65 (8H, m, 4 × C*H*$_2$), 1.81-1.89 (1H, m, C*H*), 4.40 (2H, d, *J* 5.9, OC*H*$_2$), 5.71 (2H, s, benzyl C*H*$_2$), 7.21-7.37 (8H, m, containing 5 × ArC*H* phenyl and 3 × ArC*H* indazole), 8.18 (1H, d, *J* 8.1, ArCH, indazole); δ_C($CDCl_3$, 100 MHz): 11.0 (*C*H$_3$), 14.0 (*C*H$_3$), 23.0 (*C*H$_2$), 24.0 (*C*H$_2$), 29.0 (*C*H$_2$), 30.6 (*C*H$_2$), 39.0 (*C*H), 54.1 (*C*H$_2$ benzyl) 67.5 (O*C*H$_2$), 110.1 (Ar*C*H), 122.3 (Ar*C*H), 123.1 (Ar*C*H), 123.9 (Ar*C*H), 126.8 (Ar*C*$_q$ indazole), 127.3 (2 × Ar*C*H), 128.1 (*p*-Ar*C*H), 128.8 (2 × Ar*C*H), 135.5 (Ar*C*$_q$ benzyl), 135.7 (Ar*C*N), 140.6 (*C*=N), 163.0 (*C*=O); ν_{max} (KBr)/cm^{-1} 2959, 2930, 1708, 1639, 1163; *m/z* (ESI$^+$) 365 $[M + H]^+$ (100%), 328 (20), 275 (11); HRMS (ESI$^+$): exact mass calculated for $C_{23}H_{29}N_2O_2$ $[M + H]^+$ 365.2229. Found 365.2227.

Isopropyl 2-benzyl-2*H*-indazole-3-carboxylate 266



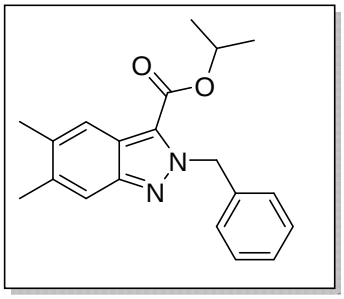
Using the procedure described for pentyl 1-benzyl-1*H*-indazole-3-carboxylate **252** and pentyl 2-benzyl-1*H*-indazole-3-carboxylate **253**, a solution isopropyl 1-*H*-5,6-difluoro-1H-indazole-3-carboxylate **238** (26 mg, 0.11 mmol), benzylbromide **339** (13 μL, 0.11 mmol) and potassium carbonate (30 mg, 0.22 mmol) in DMF (5 mL) was stirred for 8 h under nitrogen at 80 ºC. Following the work-up, the residue was further purified by column chromatography on silica gel using hexane:ethyl acetate (90:10) to yield isopropyl 2-benzyl-2*H*-indazole-3-carboxylate **266** (4 mg, 11%), m.p. 80-81 ºC followed by hexane:ethyl acetate (50:50) to isolate isopropyl 1-benzyl-5,6-difluoro-1*H*-indazole-3-carboxylate **267** (6 mg, 17%), m.p. 67-68 ºC. δ_H($CDCl_3$, 400 MHz): 1.42 (6H, d, *J* 6.3, 2 × C*H*$_3$), 5.27-5.35 (1H, m, OC*H*), 6.06 (2H, s, benzyl C*H*$_2$), 7.27-7.34 (5H, m, 5 × ArC*H* phenyl), 7.50 (1H, dd, $^2J_{HF}$ 10.1, $^3J_{HF}$ 7.1, ArC*H* indazole), 7.71 (1H, dd, $^2J_{HF}$ 10.2, $^3J_{HF}$ 7.9, ArC*H*, indazole); δ_C($CDCl_3$, 100 MHz): 22.0 (2 × *C*H$_3$), 56.7 (*C*H$_2$ benzyl), 69.4 (O*C*H), 104.2 (d, $^2J_{CF}$ 19.9, Ar*C*H), 107.0 (d, $^2J_{CF}$ 21.4, Ar*C*H), 119.5 (d, $^3J_{CF}$ 10.4, ArC_q indazole), 124.9 (d, $^4J_{CF}$ 6.0, *C*-N indazole), 127.8 (2 × Ar*C*H phenyl), 128.1 (*p*-Ar*C*H phenyl), 128.7 (2 × Ar*C*H phenyl), 136.2 (ArC_q phenyl), 143.4 (d, $^3J_{CF}$ 11.1, Ar*C*=N), 150.1 (dd, $^1J_{CF}$, 248.6, $^2J_{CF}$ 89.0, Ar*C*F), 151.5 (d, $^1J_{CF}$ 268.0, Ar*C*F), 159.1 (*C*=O); ν_{max} (KBr)/cm^{-1} 2981, 1711, 1485, 1178; *m/z* (ESI$^+$) 331 $[M + H]^+$ (74%); HRMS (ESI$^+$): exact mass calculated for $C_{18}H_{17}N_2O_2F_2$ $[M + H]^+$ 331.1258. Found 331.1252.

Isopropyl 1-benzyl-5,6-difluoro-1*H*-indazole-3-carboxylate 266



δ_H($CDCl_3$, 400 MHz): 1.48 (6H, d, *J* 6.3, 2 × C*H*$_3$), 5.37-5.47 (1H, m, OC*H*), 5.66 (2H, s, benzyl C*H*$_2$), 7.05 (1H, dd, $^2J_{HF}$ 9.5, $^3J_{HF}$ 6.3, ArC*H* indazole), 7.19-7.23 (2H, m, 2 × ArC*H* phenyl), 7.31-7.34 (3H, m, 3 × phenyl ArC*H*), 7.94 (1H, dd, $^2J_{HF}$ 9.7, $^3J_{HF}$ 7.7, ArC*H*, indazole); δ_C($CDCl_3$, 100 MHz): 22.0 (2 × *C*H$_3$), 54.6 (*C*H$_2$ benzyl), 69.0 (O*C*H), 97.8 (d, $^2J_{CF}$ 22.2, Ar*C*H), 108.7 (dd, $^2J_{CF}$ 20.4, $^3J_{CF}$ 1.4, Ar*C*H), 119.5 (d, $^3J_{CF}$ 8.9, Ar*C*$_q$ indazole), 127.2 (2 × Ar*C*H phenyl), 128.4 (*p*-Ar*C*H phenyl), 129.0 (2 × Ar*C*H phenyl), 135.0 (Ar*C*$_q$ phenyl), 135.9 (dd, $^4J_{CF}$ 5.3, $^5J_{CF}$ 1.4, *C*=N), 136.2 (d, $^3J_{CF}$ 10.0, Ar*C*N indazole), 148.6 (dd, $^1J_{CF}$ 239.1, $^2J_{CF}$ 8.6, Ar*C*F), 151.1 (dd, $^1J_{CF}$ 244.9, $^2J_{CF}$ 10.1, Ar*C*F), 161.8 (*C*=O); ; ν_{max} (KBr)/cm^{-1} 2982, 1720, 1492, 1146; *m/z* (ESI$^+$) 353 $[M + Na]^+$ (100%), 331 (4); HRMS (ESI$^+$): exact mass calculated for $C_{18}H_{17}N_2O_2F_2$ $[M + H]^+$ 331.1258. Found 331.1250.

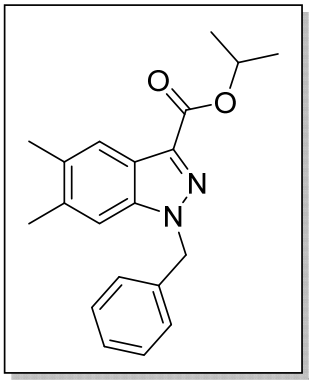
Isopropyl 2-benzyl-5,6-dimethyl-2*H*-indazole-3-carboxylate 265



Using the procedure described for pentyl 1-benzyl-1*H*-indazole-3-carboxylate **252** and pentyl 2-benzyl-1*H*-indazole-3-carboxylate **253**, a solution containing isopropyl 5,6-dimethyl-1*H*-indazole-3-carboxylate **236** (70 mg, 0.3 mmol), benzylbromide **339** (36 µL, 0.3 mmol) and potassium carbonate (83 mg, 0.6 mmol) in DMF (8 mL) was stirred for 8 h under nitrogen at 80 ºC. Following the work-up, the residue was further purified by column chromatography on silica gel using hexane:ethyl acetate (95:5) to yield pure *N*-2 benzylated isomer isopropyl 2-benzyl-5,6-dimethyl-2*H*-indazole-3-carboxylate **265** as a colourless oil (12 mg, 12%) and then hexane:ethyl acetate (70:30) to isolate pure *N*-1 benzylated isomer isopropyl 1-benzyl-5,6-dimethyl-1*H*-indazole-3-carboxylate **264** (15 mg, 15%), m.p. 103-104 ºC. δ_H($CDCl_3$, 400 MHz): 1.41 (6H, d, *J* 6.2, 2 × C*H*$_3$), 2.38 (6H, s, 2 × ArC*H*$_3$), 5.24-5.33 (1H, m, OC*H*), 6.06 (2H, s, benzyl C*H*$_2$), 7.20-7.29 (5H,

m, 5 × ArC*H* phenyl), 7.55 (1H, s, ArC*H* indazole), 7.75 (1H, s, ArC*H*, indazole); δ_C($CDCl_3$, 100 MHz): 20.8 (Ar*C*H_3), 20.9 (Ar*C*H_3), 22.0 (2 × *C*H_3), 56.4 (*C*H_2 benzyl), 68.7 (O*C*H), 117.2 (Ar*C*H), 120.2 (Ar*C*H), 122.9 (ArC_q indazole), 123.1 (C_q phenyl), 127.5 (2 × Ar*C*H), 127.7 (*p*-Ar*C*H), 128.5 (2 × Ar*C*H), 135.3 (Ar*C*H_3), 136.6 (Ar*C*H_3), 136.9 (*C*-N), 147.4 (Ar*C*=N), 159.8 (*C*=O); ν_{max} (KBr)/cm^{-1} 2994, 1726, 1489, 1146; *m/z* (ESI^+) 323 $[M + H]^+$ (100%), 345 $[M + Na]^+$ (15); HRMS (ESI^+): exact mass calculated for $C_{20}H_{23}N_2O_2$ $[M + H]^+$ 323.1760. Found 323.1744.

Isopropyl 1-benzyl-5,6-dimethyl-1*H*-indazole-3-carboxylate 264

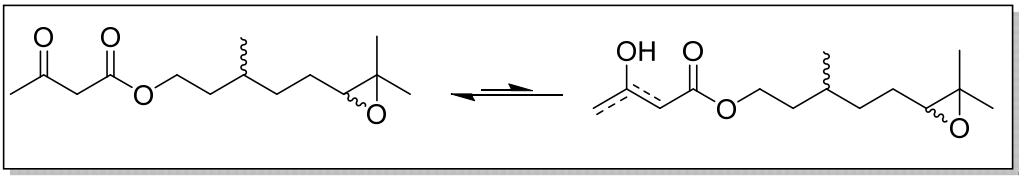


δ_H($CDCl_3$, 400 MHz): 1.48 (6H, d, *J* 6.3, 2 × C*H*$_3$), 2.33 (3H, s, ArC*H*$_3$), 2.37 (3H, s, ArC*H*$_3$), 5.36-5.48 (1H, m, C*H*), 5.66 (2H, s, benzyl C*H*$_2$), 7.08 (1H, s, ArC*H*, indazole), 7.15-7.20 (2H, m, 2 × phenyl ArC*H*), 7.24-7.32 (3H, m, 3 × phenyl ArC*H*), 7.94 (1H, s, ArC*H*, indazole); δ_C($CDCl_3$, 100 MHz): 20.4 (Ar*C*H_3), 21.0 (Ar*C*H_3), 22.2 (2 × *C*H_3), 53.9 (*C*H_2 benzyl), 68.6 (O*C*H), 109.8 (Ar*C*H), 121.7 (Ar*C*H), 123.0 (ArC_q indazole), 127.2 (2 × Ar*C*H), 128.0 (*p*-Ar*C*H), 128.9 (2 × Ar*C*H), 132.8 (Ar*C*H_3), 135.0 (C_q phenyl), 136.2 (Ar*C*H_3), 137.1 (Ar*C*N), 140.1 (*C*=N), 162.7 (*C*=O); ν_{max} (film)/cm^{-1} 2980, 1709, 1477, 1166; *m/z* (ESI^+) 345 $[M + Na]^+$ (8); 323 $[M + H]^+$ (8%); HRMS (ESI^+): exact mass calculated for $C_{20}H_{23}N_2O_2$ $[M + H]^+$ 323.1760. Found 323.1745.

3.9 Side-chain transformations

3.9.1 Epoxidations of alkene-containing derivatives [66]

5-(3,3-Dimethyloxiran-2-yl)-3-methylpentyl 3-oxobutanoate 270



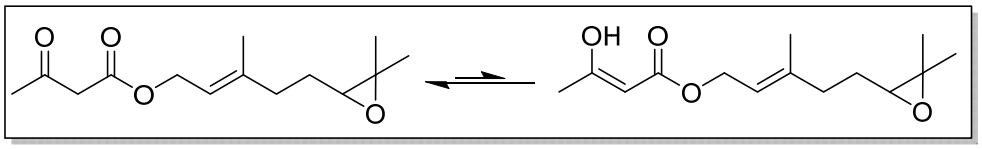
3,7-Dimethyloct-6-enyl 3-oxobutanoate **3** (103 mg, 0.42 mmol) was dissolved in DCM (4.0 mL) and the mixture was cooled to 0 °C in an ice-bath. *m*-Chloroperoxybenzoic acid (111 mg, 0.64 mmol, 70%, 1.5 equiv.) was dissolved in DCM (4.0 mL) and the first half added to the ester **3** dropwise at 0 °C. The second half was added as the reaction mixture was allowed to warm to room temperature. The reaction was stirred under a nitrogen atmosphere at room temperature. TLC analysis after 3 h showed complete consumption of the ester starting material. The crude reaction mixture was washed with saturated sodium bicarbonate solution (2 × 30 mL), water (30 mL) and brine (30 mL). The organic layer was dried with $MgSO_4$ and concentrated under reduced pressure to yield 5-(3,3-dimethyloxiran-2-yl)-3-methylpentyl 3-oxobutanoate **270** as an orange oil (95 mg, 91%) which was used with no further purification required. δ_H($CDCl_3$, 400 MHz): 0.93 (3H, d, *J* 6.6, CHC*H*$_3$), 1.10-1.76 [13H, m, containing 1.27 (3H, s, C*H*$_3$), 1.31 (3H, s, C*H*$_3$), 3 × C*H*$_2$ and C*H*], 2.27 [3H, s, C(O)C*H*$_3$], 2.69 (1H, t, *J* 6.0, C*H* of epoxide), 3.45 [2H, s, C(O)C*H*$_2$C(O)], 4.12-4.26 (2H, m, OC*H*$_2$); ν_{max} (film)/cm^{-1} 2961, 2927, 1739, 1736, 1248; *m/z* (ESI$^+$) 257 $[M + H]^+$ (22%), 155 (35), 141 (70); HRMS (ESI$^+$): exact mass calculated for $C_{14}H_{25}O_4$ $[M + H]^+$ 257.1753. Found 257.1744.

Note 1: Trace amount of both enol forms visible in ^{13}C NMR spectrum with characteristic peaks at δ_C(ppm) 21.1 (*C*H$_3$COH), 39.5 and 39.8 (*C*H$_2$-COH), 53.4 (*C*$_q$), 89.7 (*C*H) alkene, 168.3 (*C*=O) ester, 175.4 (*C*OH).

Note 2: The ^{13}C NMR spectrum also contained a duplication of signals for diastereoisomers of **270** which could not be distinguished from each other: δ_C($CDCl_3$, 100 MHz): 18.6 and 18.7 (*C*H$_3$CH), 19.2 and 19.3 [(*C*H$_3$)$_2$C$_q$], 24.8 [C(O)C*H*$_3$], 26.2 and 26.3 (*C*H$_2$), 29.6 and 30.1 (d, *C*H), 33.4 and 33.5 (*C*H$_2$), 35.1

and 35.3 (CH_2), 50.1 [C(O)CH_2C(O)], 58.2 and 58.3 (C_q), 63.7 (d, OCH_2), 64.4 (d, *C*H) epoxide, 167.1 (*C*=O) ester, 200.5 (*C*=O) ketone.

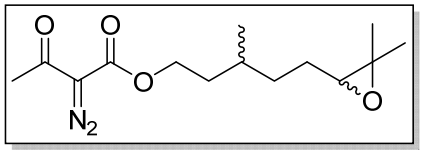
5-(3,3-Dimethyloxiran-2-yl)-3-methylpent-2-en-1-yl 3-oxobutanoate 274



The title compound was prepared following the procedure described for 5-(3,3-dimethyloxiran-2-yl)-3-methylpentyl 3-oxobutanoate **270** using 3,7-dimethylocta-2,6-dienyl 3-oxobutanoate **2** (103 mg, 0.42 mmol) in DCM (4.0 mL), *m*-chloroperoxybenzoic acid (111 mg, 0.64 mmol) in DCM (4.0 mL) at 0 °C. The reaction was stirred under a nitrogen atmosphere and allowed to warm to room temperature. TLC analysis after 3 h showed complete consumption of the ester starting material. Following the work-up, the organic layer was dried with $MgSO_4$ and concentrated under reduced pressure to yield 5-(3,3-dimethyloxiran-2-yl)-3-methylpent-2-en-1-yl 3-oxobutanoate **274** as a yellow oil (80 mg, 75%) which was used without further purification. δ_H($CDCl_3$, 400 MHz): 1.26 (3H, s, CH_3), 1.30 (3H, s, CH_3), 1.66 (2H, td, *J* 14.0, 7.0, CH_2CH), 1.74 (3H, s, CH_3), 2.10-2.26 {3H, m, containing CH_2 and 2.26 [3H, s, C(O)CH_3]}, 2.70 (1H, t, *J* 6.0, C*H* of epoxide), 3.45 [2H, s, C(O)CH_2C(O)], 4.67 (2H, d, *J* 7.0 OCH_2), 5.36-5.42 (1H, m, C*H* alkene); δ_C($CDCl_3$, 100 MHz): 16.4 (*C*H_3), 18.7 (*C*H_3), 24.8 (*C*H_3), 27.0 (*C*H_2), 30.1 [C(O)*C*H_3], 36.1 (*C*H_2), 50.1 [C(O)*C*H_2C(O)], 58.3 (O*C*H_2), 62.0 [*C*$(CH_3)_2$], 63.7 (*C*H) epoxide, 118.3 (C=*C*H), 142.0 (C=*C*CH_3) 167.1 (*C*=O) ester, 200.5 (*C*=O) ketone; ν_{max} (film)/cm^{-1} 2965, 2930, 1725, 1743, 1314, 960; *m/z* (ESI^+) 254 $[M + H]^+$ (4%), 253 (14), 153 (72); HRMS (ESI^+): exact mass calculated for $C_{14}H_{23}O_4$ $[M + H]^+$ 255.1596. Found 255.1584.

Note: Trace amount of enol form visible in ^{13}C NMR spectrum with characteristic peaks at δ_C(ppm) 21.1 (*C*H_3COH), 89.7 (*C*H) enol alkene), 118.9 (OCH_2*C*H) alkene, 141.4 (C=*C*CH_3), 172.5 (*C*=O) ester, 175.5 (*C*OH).

5-(3,3-Dimethyloxiran-2-yl)-3-methylpentyl 2-diazo-3-oxobutanoate 273

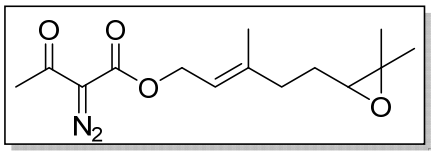


Triethylamine (0.034 mL, 0.24 mmol) was added to a stirred solution of 5-(3,3-dimethyloxiran-2-yl)-3-methylpentyl 3-oxobutanoate **270** (60 mg, 0.24 mmol) in acetonitrile (5.0 mL). After 2 min a solution of *p*-toluenesulfonyl azide **13** (46 mg, 0.24 mmol) in acetonitrile (5 mL) was carefully added dropwise, at room temperature, to yield a bright yellow solution. The reaction was stirred at room temperature under a nitrogen atmosphere. TLC analysis after 2.5 h showed complete consumption of the starting material and the acetonitrile was removed under reduced pressure, keeping the temperature of the water bath below 30 °C. The resulting yellow oil was dissolved in diethyl ether (15 mL) and washed with 9% KOH (2 × 25 mL), water (25 mL), dried with $MgSO_4$ and concentrated under reduced pressure. The residue obtained was purified by column chromatography on silica gel using hexane:ethyl acetate (90:10) to yield 5-(3,3-dimethyloxiran-2-yl)-3-methylpentyl 2-diazo-3-oxobutanoate **273** as a yellow oil (254 mg, 77%). δ_H($CDCl_3$, 400 MHz): 0.96 (3H, d, *J* 6.3, CHC*H*$_3$), 1.27 (3H, s, C*H*$_3$), 1.30 (3H, s, C*H*$_3$), 1.37-1.65 (5H, m, containing C*H* and 2 × C*H*$_2$), 1.67-1.81 (2H, m, C*H*$_2$), 2.47 [3H, s, C(O)C*H*$_3$], 2.68 (1H, t, *J* 6.3, C*H* of epoxide), 4.22-4.36 (2H, m, OC*H*$_2$); ν_{max} (film)/cm^{-1} 2149, 1772, 1642; *m/z* (ESI^-) 281 $[M - H]^-$ (10%), 255 (20); HRMS (ESI^+): exact mass calculated for $C_{14}H_{23}N_2O_4$ $[M + H]^+$ 283.1658. Found 283.1654.

Note 1: The ^{13}C NMR spectrum contained a duplication of signals for diastereoisomers of **273**:

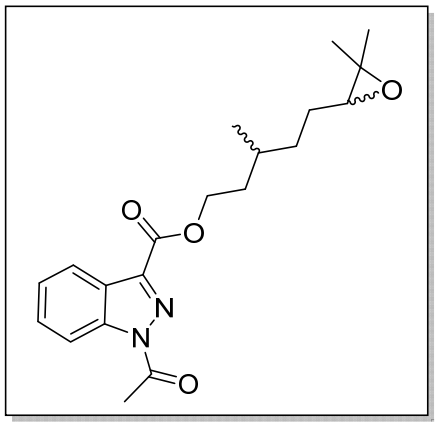
δ_C($CDCl_3$, 100 MHz): 18.7 (d, *C*H$_3$), 19.3 and 19.4 (*C*H$_3$), 24.8 (*C*H$_3$), 26.2 and 26.4 (*C*H$_2$), 28.2 (*C*H), 29.7 and 29.8 [C(O)*C*H$_3$], 33.5 and 33.6 (*C*H$_2$), 35.3 and 35.6 (*C*H$_2$), 58.1 and 58.2 [*C*(CH$_3$)$_2$], 63.7 (O*C*H$_2$), 64.3 and 64.4 (*C*H) epoxide, 161.4 (*C*=O) ester, 190.1 (*C*=O) ketone, no signal observed for *C*=N$_2$.

5-(3,3-Dimethyloxiran-2-yl)-3-methylpent-2-en-1-yl 2-diazo-3-oxobutanoate 275



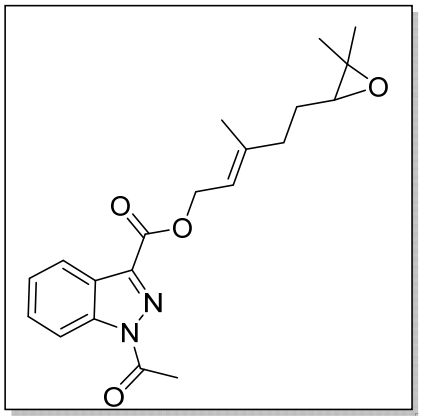
The title compound was prepared following the procedure described for 5-(3,3-dimethyloxiran-2-yl)-3-methylpentyl 2-diazo-3-oxobutanoate **273** using triethylamine (0.034 mL, 0.24 mmol, 5-(3,3-dimethyloxiran-2-yl)-3-methylpent-2-en-1-yl 3-oxobutanoate **274** (60 mg, 0.24 mmol in acetonitrile (5.0 mL) and *p*-toluenesulfonyl azide **13** (46 mg, 0.24 mmol in acetonitrile (5 mL). The reaction was stirred at room temperature under a nitrogen atmosphere. TLC analysis after 2.5 h showed complete consumption of the starting material and the acetonitrile was removed under reduced pressure, keeping the temperature of the water bath below 30 °C. The resulting yellow oil was dissolved in diethyl ether (15 mL) and washed with 9% KOH (2 × 25 mL), water (25 mL), dried with $MgSO_4$ and concentrated under reduced pressure. The residue obtained was purified by column chromatography on silica gel using hexane:ethyl acetate (90:10) to yield 5-(3,3-dimethyloxiran-2-yl)-3-methylpent-2-en-1-yl 2-diazo-3-oxobutanoate **275** as a yellow oil (254 mg, 77%). δ_H($CDCl_3$, 400 MHz): 1.27 (3H, s, C*H*$_3$), 1.31 (3H, s, C*H*$_3$), 1.63-1.71 (2H, m, C*H*$_2$CH), 1.77 (3H, s, C*H*$_3$C=C), 2.13-2.30 (2H, m, C*H*$_2$C=C), 2.48 [3H, s, C(O)C*H*$_3$], 2.70 (1H, t, C*H* of epoxide, *J* 6.2), 4.76 (2H, d, *J* 7.1, OC*H*$_2$), 5.42 (1H, dt, *J* 7.1, 1.2, C*H* alkene); δ_C($CDCl_3$, 100 MHz): 16.5 (*C*H$_3$C=C), 18.7 (*C*H$_3$CO), 24.8 (*C*H$_3$), 27.0 (*C*H$_2$), 28.2 [C(O)*C*H$_3$], 36.2 (*C*H$_2$), 58.3 [C_q(CH_3)$_2$], 62.0 (O*C*H$_2$), 63.7 (*C*H) epoxide, 118.3 (*C*H) alkene, 142.2 (C_q) alkene, 161.4 (*C*=O) ester, 190.1 (*C*=O) ketone; ν_{max} (film)/cm^{-1} 2141, 1715, 1659, 1309; HRMS (ESI$^+$): exact mass calculated for $C_{14}H_{21}N_2O_4$ $[M + H]^+$ 281.1501. Found 281.1501.

5-(3,3-Dimethyloxiran-2-yl)-3-methylpent-2-en-1-yl 1-acetyl-1*H*-indazole-3-carboxylate 298



The title compound was prepared following the procedure described for methyl 1-acetyl-1*H*-indazole-3-carboxylate **104** using 2-(trimethylsilyl)phenyl-trifluoromethanesulfonate **49** (100 mg, 0.33 mmol), 5-(3,3-dimethyloxiran-2-yl)-3-methylpentyl 2-diazo-3-oxobutanoate **273** (51 mg, 0.3 mmol) in acetonitrile (4 mL) and caesium fluoride (103 mg, 0.6 mmol). The reaction was stirred at room temperature under a nitrogen atmosphere for 24 h. Following the work-up, the residue was purified by column chromatography on silica gel using hexane:ethyl acetate (90:10) as eluent to yield 5-(3,3-dimethyloxiran-2-yl)-3-methylpent-2-en-1-yl 1-acetyl-1*H*-indazole-3-carboxylate **298** as an orange oil (80 mg, 74%). δ_H($CDCl_3$, 400 MHz): 1.03 (3H, d, *J* 6.3, CHC*H*$_3$), 1.27 (3H, d, *J* 1.4, C*H*$_3$), 1.30 (3H, d, *J* 1.3, C*H*$_3$), 1.42-1.68 (4H, m, 2 × C*H*$_2$), 1.70-1.80 (2H, m, C*H*$_2$), 1.90-1.99 (1H, m, C*H*), 2.71(1H, t, *J* 5.9, C*H* of epoxide), 2.87 [3H, s, C(O)C*H*$_3$], 4.51-4.58 (2H, m, OC*H*$_2$), 7.46 (1H, dd, *J* 8.4, 0.8, ArC*H*), 7.61 (1H, ddd, *J* 8.4, 7.1, 1.1, ArC*H*), 8.20 (1H, dd, *J* 8.0, 0.8, ArC*H*), 8.48 (1H, dd, *J* 8.4, 0.8, ArC*H*); δ_C($CDCl_3$, 100 MHz): 18.7 (*C*H$_3$CH), 19.5 [C(O)*C*H$_3$], 23.1 (*C*H$_3$CO), 24.9 (*C*H$_3$CO), 26.3 (*C*H$_2$CH), 29.9 (*C*HCH$_3$), 33.6 (*C*H$_2$), 35.3 (*C*H$_2$), 35.6 (*C*H$_2$), 58.2 (*C*$_q$ epoxide), 64.2 (O*C*H$_2$), 64.4 (*C*H epoxide), 115.6 (Ar*C*H), 122.2 (Ar*C*H), 125.7 (Ar*C*H), 125.9 (Ar*C*$_q$), 129.9 (Ar*C*H), 140.3 (*C*=N), 140.8 (Ar*C*N), 161.9 (*C*=O) ester, 172.2 (*C*=O) amide; ν_{max} (film)/cm^{-1} 2959, 1731, 1375, 1193; HRMS (ESI^+): exact mass calculated for $C_{20}H_{27}N_2O_4$ $[M + H]^+$ 359.1971. Found 359.1960

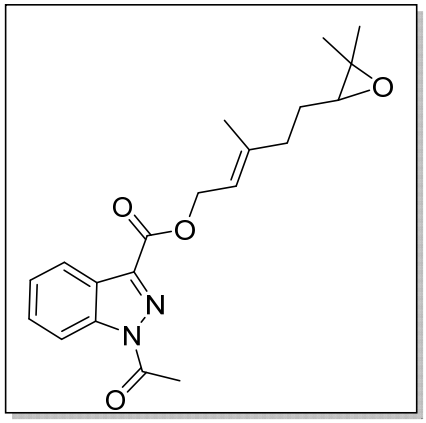
5-(3,3-Dimethyloxiran-2-yl)-3-methylpentyl 1-acetyl-1*H*-indazole-3-carboxylate 299



The title compound was prepared following the procedure described for methyl 1-acetyl-1*H*-indazole-3-carboxylate **104** using 2-(trimethylsilyl)phenyl-trifluoromethanesulfonate **49** (100 mg, 0.33 mmol), 5-(3,3-dimethyloxiran-2-yl)-3-methylpent-2-en-1-yl 2-diazo-3-oxobutanoate **275** (51 mg, 0.3 mmol) in acetonitrile (4 mL) and caesium fluoride (103 mg, 0.6 mmol). The reaction was stirred at room temperature under a nitrogen atmosphere for 24 h. Following the work-up, the residue was purified by column chromatography on silica gel using hexane:ethyl acetate eluent (90:10) and then DCM:ethyl acetate eluent (95:5) and 5-(3,3-dimethyloxiran-2-yl)-3-methylpentyl 1-acetyl-1*H*-indazole-3-carboxylate **299** was obtained as an orange oil (74 mg, 69%). δ_H($CDCl_3$, 400 MHz): 1.29 (6H, d, *J* 10.9, 2 × C*H*$_3$), 1.71 (2H, td, *J* 14.0, 7.1, C*H*$_2$CH), 1.85 (3H, s, C*H*$_3$), 2.19-2.32 (2H, m, C*H*$_2$C=C), 2.73 (1H, t, *J* 6.2, C*H* of epoxide), 2.87 [3H, s, C(O)C*H*$_3$], 5.02 (2H, d, *J* 7.1, OC*H*$_2$), 5.61 (1H, t, *J* 7.1, C*H* alkene), 7.43-7.48 (1H, m, ArC*H*), 7.60 (1H, ddd, *J* 8.3, 7.2, 1.1, ArC*H*), 8.21 (1H, d, *J* 8.1, ArC*H*), 8.47 (1H, d, *J* 8.5, ArC*H*); δ_C($CDCl_3$, 100 MHz): 16.7 (*C*H$_3$C=C), 18.8 [C(O)*C*H$_3$], 23.1 (*C*H$_3$CO), 24.8 (*C*H$_3$CO), 27.1 (*C*H$_2$CH), 36.3 (*C*H$_2$C=C), 58.4 [C_q(CH_3)$_2$], 62.5 (O*C*H$_2$), 63.9 (*C*H epoxide), 115.5 (Ar*C*H), 118.4 (*C*H) alkene, 122.2 (Ar*C*H), 123.9 (ArC_q), 125.7 (Ar*C*H), 129.9 (Ar*C*H), 140.3 (*C*=N), 140.81 (Ar*C*N), 142.4 (C=C_q), 161.8 (C=O) ester, 171.5 (*C*=O) amide; ν_{max} (film)/cm^{-1} 2959, 1731, 1616, 1193; HRMS (ESI$^+$): exact mass calculated for $C_{20}H_{25}N_2O_4$ $[M + H]^+$ 357.1814. Found 357.1810

Note: 6% of the *N*-acyl by-product was formed in this reaction which could not be removed by column chromatography on silica gel.

5-(3,3-Dimethyloxiran-2-yl)-3-methylpentyl 1-acetyl-1*H*-indazole-3-carboxylate 299



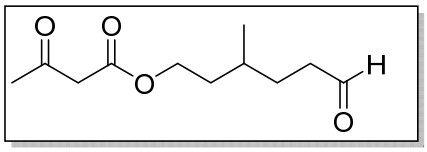
The title compound was prepared following the procedure described for pentyl 1-acetyl-1*H*-indazole-3-carboxylate **108** using caesium fluoride (76 mg, 0.5 mmol), nonafluorobutanesulfonyl fluoride (453 mg, 1.5 mmol), 2-(trimethylsilyl)phenol **58** (166 mg, 1 mmol), 5-(3,3-dimethyloxiran-2-yl)-3-methylpent-2-en-1-yl 2-diazo-3-oxobutanoate **275** (338 mg, 1.2 mmol) and caesium carbonate (500 mg, 1.5 mmol) in acetonitrile (10 mL). The reaction was stirred at 60 °C under a nitrogen atmosphere for 24 h. After work-up, the residue obtained was purified by column chromatography on silica gel using hexane:ethyl acetate (95:5) to yield 5-(3,3-dimethyloxiran-2-yl)-3-methylpentyl 1-acetyl-1*H*-indazole-3-carboxylate **299.**
as a colourless oil. Spectral details as described previously.

Note: Due to insufficient diazo starting material, only 1.2 equiv. was present in comparison to the preferred 3 equiv. in the reaction, therefore, 10% of the *N*-acyl by-product was formed which could not be removed by column chromatography on silica gel. Characteristic signals at δ_H(ppm) 7.73 (3H, dd, *J* 10.4, 8.3, 3 × ArC*H*) and 8.31 (1H, d, *J* 8.1, ArC*H*).

3.9.2 Oxidative cleavage of epoxide derivatives and subsequent diazo transfer reactions[67]

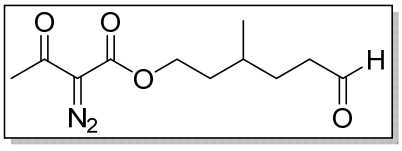
Note: All aldehyde derivatives were found to be unstable for short periods even when stored in the freezer.

3-Methyl-6-oxohexyl 3-oxobutanoate 276



Periodic acid(107 mg, 0.56 mmol, 1.4 equiv.) was stirred in diethyl ether (10.0 mL) in a two-neck round-bottomed flask. The reaction temperature was maintained at 25 °C using an oil bath and reflux condenser under a nitrogen atmosphere. The epoxide 5-(3,3-dimethyloxiran-2-yl)-3-methylpentyl 3-oxobutanoate **270** (100 mg, 0.39 mmol) dissolved in diethyl ether (5.0 mL) was added dropwise and the reaction was stirred vigorously at 25 °C for ten min. The reaction was quenched using water (20 mL). The organic layer was separated and washed with water (2 × 50 mL), dried with $MgSO_4$ and concentrated under reduced pressure to yield 3-methyl-6-oxohexyl 3-oxobutanoate **276** as an orange oil (58 mg, 71%). δ_H($CDCl_3$, 400 MHz): 0.93 (3H, d, *J* 6.0, CHC*H*$_3$), 1.42-1.77 (5H, m, containing C*H* and 2 × C*H*$_2$), 2.27 [3H, s, C(O)C*H*$_3$], 2.42-2.45 [2H, m, C*H*$_2$C(O)H], 3.45 [2H, s, C(O)C*H*$_2$C(O)], 4.12-4.26 (2H, m, OC*H*$_2$), 9.78 [1H, t, *J* 6.0, CH$_2$C(O)*H*]; δ_C($CDCl_3$, 100 MHz): 19.1 (*C*H$_3$), 28.6 (*C*H), 29.4 (*C*H$_2$), 30.2 [C(O)*C*H$_3$], 35.1 (*C*H$_2$), 41.4 (*C*H$_2$), 50.1 [C(O)*C*H$_2$C(O)], 63.5 (O*C*H$_2$), 167.1 (*C*=O) ester, 202.3 (*C*=O) ketone and (*C*=O) aldehyde; ν_{max} (film)/cm^{-1} 2958, 1755, 1640, 1304; HRMS (ESI$^+$): exact mass calculated for $C_{11}H_{19}O_4$ $[M + H]^+$ 215.1283. Found 215.1277.

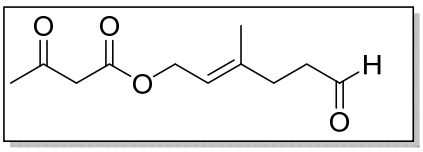
3-Methyl-6-oxohexyl 2-diazo-3-oxobutanoate 283



The title compound was prepared following the procedure described for 5-(3,3-dimethyloxiran-2-yl)-3-methylpentyl 2-diazo-3-oxobutanoate **273** using triethylamine (0.034 mL, 0.24 mmol), 3-methyl-6-oxohexyl 3-oxobutanoate **276** (60 mg, 0.24 mmol) in acetonitrile (5.0 mL) and *p*-toluenesulfonyl azide **13** (46 mg, 0.24 mmol) in acetonitrile (5.0 mL). TLC

analysis after 2.5 h showed complete consumption of the starting material and Following the work-up,the residue was concentrated under reduced pressure and purified using column chromoatography on silica gel using hexane:ethyl acetate (90:10-80:20) to yield 3-methyl-6-oxohexyl 2-diazo-3-oxobutanoate **283** as a yellow oil (124 mg, 75%). δ_H($CDCl_3$, 400 MHz): 0.95 (3H, d, *J* 6.4, C*H*$_3$), 1.46-1.61 (3H, m, containing C*H* and C*H*$_2$), 1.69-1.77 (2H, m, C*H*$_2$), 2.41-2.53 {5H, m, containing C*H*$_2$C(O)H and 2.47 [3H, s, C(O)C*H*$_3$]}, 4.25-4.33 (2H, m, OC*H*$_2$), 9.79 [1H, t, *J* 6.0, CH$_2$C(O)*H*]; δ_C($CDCl_3$, 100 MHz): 19.1 (*C*H$_3$), 28.2 (*C*H), 28.5 (*C*H$_2$), 29.4 [C(O)*C*H$_3$], 35.3 (*C*H$_2$), 41.3 (*C*H$_2$), 63.5 (O*C*H$_2$), 161.4 (*C*=O) ester, 190.0 (*C*=O) ketone, 202.1 (*C*=O) aldehyde, no signal observed for *C*=N$_2$; *m/z* (ESI$^+$) 263 [M + Na]$^+$(40%), 240 (4), (239) (10); ν_{max} (film)/cm^{-1} 2961, 2932, 2143, 1711, 1656, 1156; HRMS (ESI$^+$): exact mass calculated for $C_{11}H_{17}N_2O_4$ [M + H]$^+$ 241.1188. Found 241.1180.

3-Methyl-6-oxohex-2-en-1-yl 3-oxobutanoate 277

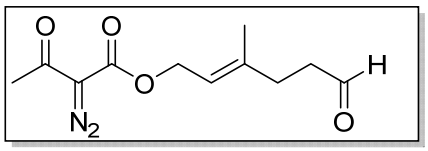


The title compound was prepared following the procedure described for 3-methyl-6-oxohexyl 3-oxobutanoate **276** using periodic acid(107 mg, 0.56 mmol) in diethyl ether (10.0 mL) and the epoxide 5-(3,3-dimethyloxiran-2-yl)-3-methylpentyl 3-oxobutanoate **274** (100 mg, 0.39 mmol) in diethyl ether (5.0 mL). Following the work-up, the organic layers were concentrated under reduced pressure to yield 3-methyl-6-oxohex-2-en-1-yl 3-oxobutanoate **277** as an orange oil (62 mg, 74%). δ_H($CDCl_3$, 400 MHz): 1.73 (3H, s, CHC*H*$_3$), 2.27 [3H, s, C(O)C*H*$_3$], 2.38 [2H, t, *J* 7.4, C*H*$_2$C(O)H], 2.58 (2H, dt, *J* 7.5, 1.5, C*H*$_2$), 3.45 [2H, s, C(O)C*H*$_2$C(O)], 4.65 (2H, d, *J* 7.0, OC*H*$_2$), 5.34-5.41 (1H, m, C*H* alkene), 9.77 [1H, t, *J* 1.5, CH$_2$C(O)*H*]; ν_{max} (film)/cm^{-1} 2950, 1747, 1664; HRMS (ESI$^+$): exact mass calculated for $C_{11}H_{17}O_4$ [M + H]$^+$ 213.1127. Found 213.1124.

Note 1: Some peaks belonging to the epoxide starting material could be seen in the ^{13}C NMR spectrum. δ_C($CDCl_3$, 100 MHz): 16.6 (*C*H$_3$), 30.1 [C(O)*C*H$_3$], 31.4 (*C*H$_2$), 41.7 (*C*H$_2$CHO), 50.0 [C(O)*C*H$_2$C(O)], 61.9 (O*C*H$_2$), 118.7 (*C*H) alkene, 140.8 (*C*$_q$) alkene, 167.1 (*C*=O) ester, 200.5 (*C*=O) ketone, 201.6 (*C*=O) aldehyde;

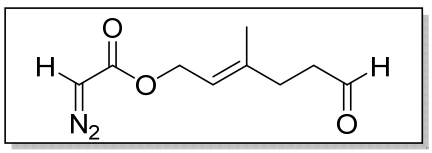
Note 2: Trace amount of enol form visible in ^{13}C NMR spectrum with characteristic peaks at δ_C(ppm) 89.7 (*C*H) alkene, 175.6 (*C*OH).

Attempted synthesis of 3-methyl-6-oxohex-2-en-1-yl 2-diazo-3-oxobutanoate 342



The title compound was prepared following the procedure described for 5-(3,3-dimethyloxiran-2-yl)-3-methylpentyl 2-diazo-3-oxobutanoate **273** using triethylamine (0.034 mL, 0.24 mmol), 3-methyl-6-oxohexyl 3-oxobutanoate **277** (51 mg, 0.24 mmol) in acetonitrile (5.0 mL) and *p*-toluenesulfonyl azide **13** (46 mg, 0.24 mmol) in acetonitrile (5.0 mL). TLC analysis after 2.5 h showed complete consumption of the starting material and ^1H NMR analysis of the crude reaction mixture showed the presence of the desired compound. The residue obtained after concentration under reduced pressure was purified by column chromatography on silica gel using hexane:ethyl acetate (90:10) to yield 3-methyl-6-oxohex-2-en-1-yl 2-diazoacetate **284** as a yellow oil (40 mg, 85%) as the major product with 10% of the desired compound as an inseparable mixture. δ_H($CDCl_3$, 400 MHz): 1.73 (3H, s, CHC*H*$_3$), 2.38 [2H, t, *J* 7.5, C*H*$_2$C(O)H], 2.48 [3H, s, C(O)C*H*$_3$], 2.55-2.61 (2H, m, C*H*$_2$), 4.67 (2H, d, *J* 7.0, OC*H*$_2$), 5.34-5.39 (1H, m, C*H* alkene), 9.78 [1H, t, *J* 1.6, CH$_2$C(O)*H*].

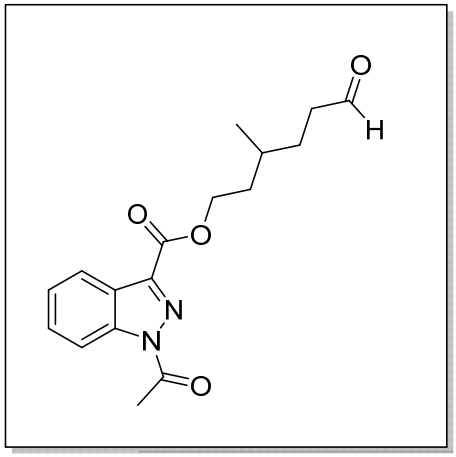
3-Methyl-6-oxohex-2-en-1-yl 2-diazoacetate 284



δ_H($CDCl_3$, 400 MHz): 1.73 (3H, s, CHC*H*$_3$), 2.38 [2H, t, *J* 7.5, C*H*$_2$C(O)H], 2.55-2.61 (2H, m, C*H*$_2$), 4.67 (2H, d, *J* 7.0, OC*H*$_2$), 4.74 (1H, s, C*H*), 5.34-5.39 (1H, m, C*H* alkene), 9.78 [1H, t, *J* 1.6, CH$_2$C(O)*H*]; δ_C($CDCl_3$, 100 MHz): 16.6 (*C*H$_3$), 31.5 (*C*H$_2$), 41.7 (*C*H$_2$CHO), 61.4 (O*C*H$_2$), 119.3 (*C*H) alkene, 140.3 (C_q) alkene, 171.1 (*C*=O) ester, (*C*=O) aldehyde; ν_{max} (film)/cm^{-1}: 2966, 2140, 1717, 1662, 1312; HRMS (ESI$^-$): exact mass calculated for $C_9H_{11}N_2O_3$ $[M + H]^+$ 197.0803. Found 197.0809.

*****Initial attempts were made to form the indazole cycloadduct using the diazo 1,3-dipoles of the aldehyde and tertiary amine derivatives, however, little success was achieved with these routes and therefore the epoxide derivative of the indazole was carried through the synthesis instead*****

3-Methyl-6-oxohexyl 1-acetyl-1*H*-indazole-3-carboxylate 300

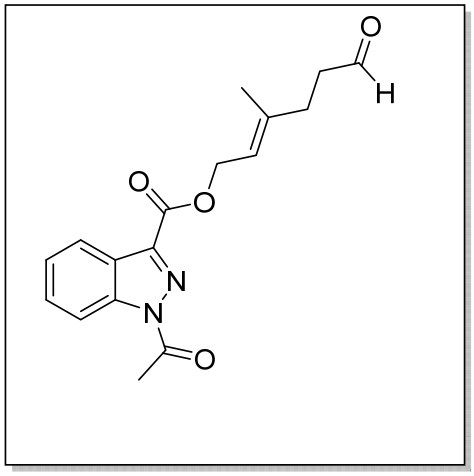


The title compound was prepared following the procedure described for 3-methyl-6-oxohexyl 3-oxobutanoate **276** using periodic acid(53 mg, 0.28 mmol) in diethyl ether (5 mL) and the epoxide 5-(3,3-dimethyloxiran-2-yl)-3-methylpentyl 1*H*-indazole-3-carboxylate **298** (67 mg, 0.19 mmol) dissolved in diethyl ether (5.0 mL). Following the work-up, the organic layers were concentrated under reduced pressure to yield 3-methyl-6-oxohexyl 1-acetyl-1*H*-indazole-3-carboxylate **300** as an orange oil (33 mg, 56%). δ_H($CDCl_3$, 400 MHz): 1.09 (3H, d, *J* 6.9, CHC*H*$_3$), 1.48-2.00 (5H, m, C*H* and 2 × C*H*$_2$), 2.49-2.54 (2H, m, C*H*$_2$CHO), 2.87 [3H, s, C(O)C*H*$_3$], 4.55 (2H, dd, *J* 11.9, 5.0, OC*H*$_2$), 7.47 (1H, dt, *J* 7.6, 0.7, ArC*H*), 7.61 (1H, ddd, *J* 8.4, 7.2, 1.1, ArC*H*), 8.19 (1H, dd, *J* 1.0, 8.1, ArC*H*), 8.47 (1H, d, *J* 8.5, ArC*H*), 9.80 [1H, t, *J* 1.6, CH$_2$C(O)*H*]; δ_C($CDCl_3$, 100 MHz): 19.0 (*C*H$_3$), 28.6 (*C*H), 29.3 (*C*H$_2$), 30.1 [C(O)*C*H$_3$], 35.1 (*C*H$_2$), 41.4 (*C*H$_2$), 50.0 [C(O)*C*H$_2$C(O)], 63.5 (O*C*H$_2$), 115.6 (Ar*C*H), 122.2 (Ar*C*H), 124.7 (Ar*C*$_q$), 125.7 (Ar*C*H), 129.9 (Ar*C*H), 167.1 (*C*=O) ester, 200.5 (*C*=O) ketone, 202.3 (*C*=O) aldehyde; ν_{max} (film)/cm^{-1} 2977, 1741, 1716, 1646, 1456; *m/z* (ESI$^+$) 315 [M - H]$^-$ (100%), M$^+$ (20); HRMS (ESI$^+$): exact mass calculated for $C_{17}H_{21}N_2O_4$ [M + H]$^+$ 317.1841. Found 317.1853.

Note 1: Significant impurity peaks visible in ^{13}C NMR spectrum, possibly for decomposition products.

Note 2: This reaction did not reach completion, despite many attempts at increasing periodic acid equiv. and length of reaction time.

3-Methyl-6-oxohex-2-en-1-yl 1-acetyl-1*H*-indazole-3-carboxylate 301



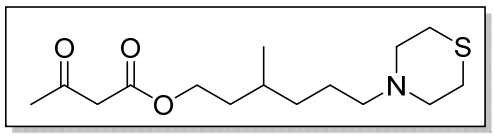
The title compound was prepared following the procedure described for 3-methyl-6-oxohexyl 3-oxobutanoate **276** using periodic acid(45 mg, 0.2 mmol) in diethyl ether (5 mL) and the epoxide 5-(3,3-dimethyloxiran-2-yl)-3-methylpentyl 1-acetyl-1*H*-indazole-3-carboxylate **299** (47 mg, 0.13 mmol) dissolved in diethyl ether (5.0 mL). Following the work-up, the organic layers were concentrated under reduced pressure to yield 3-methyl-6-oxohex-2-en-1-yl 1-acetyl-1*H*-indazole-3-carboxylate **301** as a colourless oil (57 mg, 93%). δ_H($CDCl_3$, 400 MHz): 1.84 (3H, s, C=CC*H*$_3$), 2.43 (2H, t, *J* 7.5, C*H*$_2$), 2.62 (2H, ddd, *J* 8.9, 7.8, 0.6, C*H*$_2$), 2.87 [3H, s, C(O)C*H*$_3$], 5.00 (2H, d, *J* 7.1, OC*H*$_2$), 5.57 (dt, *J* 7.1, 1.3, C*H* alkene), 7.45 (1H, t, *J* 7.6, ArC*H*), 7.56-7.62 (1H, m, ArC*H*), 8.19 (1H, d, *J* 8.1, ArC*H*), 8.46 (1H, dd, *J* 8.5, 0.7, ArC*H*), 9.79 [1H, t, *J* 1.5, CH_2C(O)*H*].

Note 1: The epoxide starting material used for this reaction contained 10% of the *N*-aryl-by-product which was converted to the aldehyde.

Note 2: This reaction contained 4% starting material epoxide after repeated column chromoatography.

3.9.3 Reductive amination of aldehyde derivatives[68]

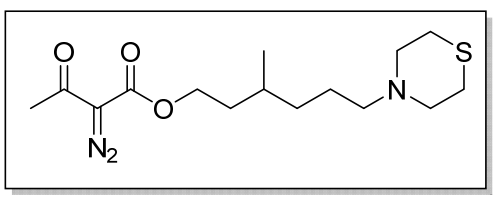
3-Methyl-6-thiomorpholinohexyl 3-oxobutanoate 293



Sodium triacetoxyborohydride (0.48 g, 2.28 mmol) was added to a stirred solution of the aldehyde, 3-methyl-6-oxohexyl 3-oxobutanoate **276**, (0.35 g, 1.63 mmol) and thiomorpholine **292** (0.14 mL, 1.63 mmol) in 1,2-dichloroethane (15.0 mL) under a nitrogen atmosphere at room temperature. TLC analysis after 1.5 h showed complete consumption of the aldehyde starting material and the reaction was quenched using saturated sodium bicarbonate solution (15.0 mL). The organic layer was extracted with ethyl acetate (2 × 15 mL) and washed with water (2 × 15 mL) followed by brine (15 mL). The organic layer was dried with $MgSO_4$ and concentrated under reduced pressure to yield the crude product which was purified using column chromatography on silica gel using hexane:ethyl acetate (90:10) to yield 3-methyl-6-thiomorpholinohexyl 3-oxobutanoate **293** as an orange oil (0.35 g, 76%). δ_H($CDCl_3$, 400 MHz): 0.91 (3H, d, CHC*H*$_3$, *J* 6.5), 1.09-1.36 (2H, m, C*H*$_2$), 1.40-1.60 (4H, m, containing 2 × C*H*$_2$), 1.62-1.74 (1H, m, C*H*CH_3), 2.27-2.35 {5H, m, containing 2.27 [3H, s, C(O)C*H*$_3$] and NC*H*$_2$}, 2.66-2.72 (8H, m, containing 2 × NC*H*$_2$ and 2 × SC*H*$_2$), 3.44 [2H, s, C(O)C*H*$_2$C(O)], 4.13-4.21 (2H, m, OC*H*$_2$); δ_C($CDCl_3$, 100 MHz): 19.4 (*C*H_3), 23.2 (*C*H_2), 27.4 (2 × S*C*H_2), 29.7 (*C*H), 30.2 [C(O)*C*H_3], 34.5 (*C*H_2), 35.3 (CH_2), 50.1 (*C*H_2), 54.7 (2 × N*C*H_2), 59.2 [C(O)*C*H_2C(O)], 63.8 (O*C*H_2), 167.2 (*C*=O) ester, 200.5 (*C*=O) ketone; ν_{max} (film)/cm^{-1} 2951, 1743, 1715, 1305; *m/z* (ESI^+) 302 $[M + H]^+$ (100%), 303 (20), 304 (10); HRMS (ESI^+): exact mass calculated for $C_{15}H_{27}NO_3S$ $[M + H]^+$ 302.1790 Found 302.1791.

Note: Trace amount of enol form visible in ^{13}C NMR spectrum with characteristic peaks at δ_C(ppm) 89.7 (*C*H) alkene, 172.7 (*C*=O) ester, 175.4 (*C*OH).

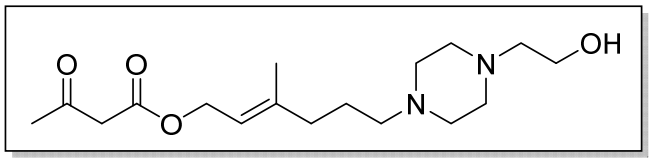
3-Methyl-6-thiomorpholinohexyl 2-diazo-3-oxobutanoate 294



The title compound was prepared following the procedure described for 5-(3,3-dimethyloxiran-2-yl)-3-methylpentyl 2-diazo-3-oxobutanoate

273 using triethylamine (0.16 mL, 1.12 mmol), 3-methyl-6-thiomorpholinohexyl 3-oxobutanoate **293** (0.32 g, 1.12 mmol) in acetonitrile (8.0 mL) and *p*-toluenesulfonyl azide **13** (0.22 g, 1.12 mmol) in acetonitrile (4.0 mL). The reaction was stirred for 18 h under a nitrogen atmosphere, after which time TLC analysis showed complete consumption of the ester starting material. Following the work-up, the residue obtained was purified using column chromatography on silica gel using hexane:ethyl acetate (90:10-50:50) to isolate 3-methyl-6-thiomorpholinohexyl 2-diazo-3-oxobutanoate **294** as a red oil (260 mg, 71%). δ_H($CDCl_3$, 400 MHz): 0.93 (3H, d, *J* 6.6, CHC*H*$_3$), 1.08-1.80 (7H, m, containing 3 × C*H*$_2$ and C*H*), 2.30-2.38 (2H, m, NC*H*$_2$), 2.48 [3H, s, C(O)C*H*$_3$], 2.66-2.75 (8H, m, containing 2 × NC*H*$_2$ and 2 × SC*H*$_2$), 4.24-4.31 (2H, m, OC*H*$_2$); δ_C($CDCl_3$, 75.5 MHz): 19.4 (*C*H$_3$), 23.8 (*C*H$_2$), 27.9 (2 × SCH$_2$), 28.2 (*C*H), 29.8 [C(O)*C*H$_3$], 34.5 (*C*H$_2$), 35.5 (*C*H$_2$), 55.0 (2 × NCH$_2$), 59.5 (NCH$_2$), 63.9 (OCH$_2$), 161.5 (*C*=O) ester, 190.1 (*C*=O) ketone; ν_{max} (film)/cm^{-1} 2952, 2141, 1718, 1651, 1309; *m/z* (ESI$^+$) 328 [M + H]$^+$ (100%), 300 (5); HRMS (ESI$^+$): exact mass calculated for $C_{15}H_{26}N_3O_3S$ [M + H]$^+$ 328.1695. Found 328.1690.

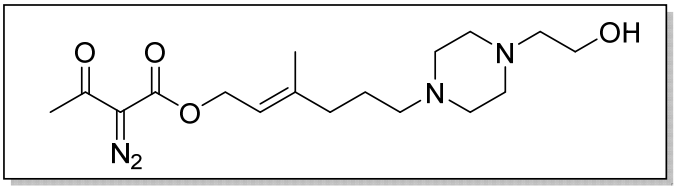
6-(4-(2-Hydroxyethyl)piperazin-1-yl)-3-methylhex-2-en-1-yl 3-oxobutanoate 296



The title compound was prepared following the procedure described for 3-methyl-6-thiomorpholinohexyl 3-oxobutanoate **293** using sodium triacetoxyborohydride (0.48 g, 2.28 mmol), 3-methyl-6-oxohex-2-en-1-yl 3-oxobutanoate **277**, (0.35 g, 1.63 mmol) and 2-(piperazin-1-yl)ethan-1-ol **295** (0.14 mL, 1.63 mmol) in 1,2-dichloroethane (15.0 mL). TLC analysis after 1.5 h showed complete consumption of the aldehyde starting material and the reaction was quenched using saturated sodium bicarbonate solution (15.0 mL). Following the work-up, the organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. The residue obtained was purified using column chromatography on silica gel chloroform:methanol (95:5) to yield 6-(4-(2-hydroxyethyl)piperazin-1-yl)-3-methylhex-2-en-1-yl 3-oxobutanoate **296** as a yellow oil (0.35 g, 76%). δ_H($CDCl_3$, 400 MHz): 1.58-1.71 [5H, m, containing C*H*$_2$

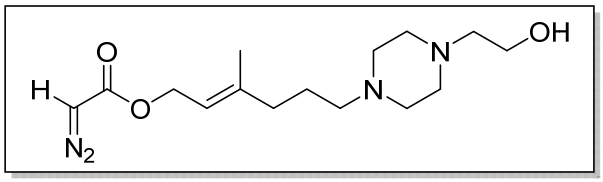
and 1.71 (3H, s, CH_3)], 2.02-2.08 (2H, m, CH_2), 2.30-2.35 {5H, m, containing 2.27 [3H, s, C(O)CH_3], and NCH_2}, 2.48-2.62 (11H, m, containing 5 × NCH_2 and OH), 3.45 [2H, s, C(O)CH_2C(O)], 3.61-3.66 (2H, m, CH_2OH), 4.66 (2H, d, *J* 7.1, OCH_2), 5.35 (1H, ddd, *J* 7.1, 2.4, 1.2, CH alkene); δ_C($CDCl_3$, 100 MHz): 16.4 (*C*H_3), 24.7 (*C*H_2), 30.1 [C(O)*C*H_3], 37.2 (*C*H_2), 50.1 [C(O)*C*H_2C(O)], 52.8 (2 × N*C*H_2), 53.2 (2 × N*C*H_2), 57.7 (*C*H_2OH), 58.0 (N*C*H_2CH_2OH), 59.3 (N*C*H_2), 62.2 (O*C*H_2), 118.5 (*C*H) alkene, 142.2 (C_q) alkene, 161.4 (*C*=O) ester; ν_{max} (film)/cm^{-1} 2955, 2834, 1740, 1722, 1651, 1309; *m/z* (ESI^+) 327 $[M + H]^+$ (100%), 328 (20), 329 (4). HRMS (ESI^+): exact mass calculated for $C_{17}H_{31}N_2O_4$ $[M + H]^+$ 327.2284. Found 327.2282.

Attempted synthesis of 3-methyl-6-(piperazin-1-yl)hex-2-en-1-yl 2-diazo-3-oxobutanoate 343



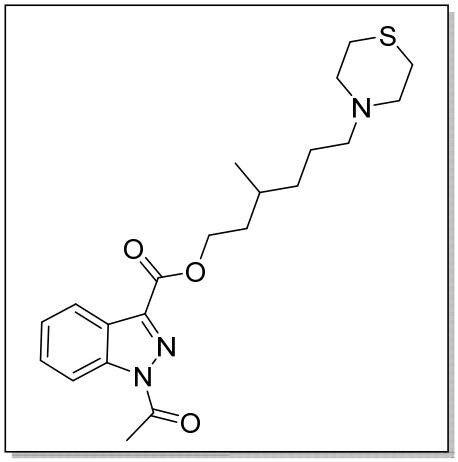
The title compound was prepared following the procedure described for 5-(3,3-dimethyloxiran-2-yl)-3-methylpentyl 2-diazo-3-oxobutanoate **273** using triethylamine (0.068 mL, 0.48 mmol), 3-methyl-6-piperazine-hexyl 3-oxobutanoate **296** (60 mg, 0.24 mmol) in acetonitrile (5.0 mL) and *p*-toluenesulfonyl azide **13** (46 mg, 0.24 mmol) in acetonitrile (5.0 mL). 1H NMR analysis of the crude mixture showed the presence of **297** as the major product with trace amounts of the desired product. Attempted purification of the residue by column chromatography on silica gel using hexane:ethyl acetate (90:10-50:50) isolated **297** as the major product still contaminated by a large amount of impurities and starting material. The only characteristic signal differing from major product below: δ_H($CDCl_3$, 400 MHz): 2.40 [3H, s, C(O)CH_3].

6-(4-(2-hydroxyethyl)piperazin-1-yl)-3-methylhex-2-en-1-yl 2-diazoacetate 297



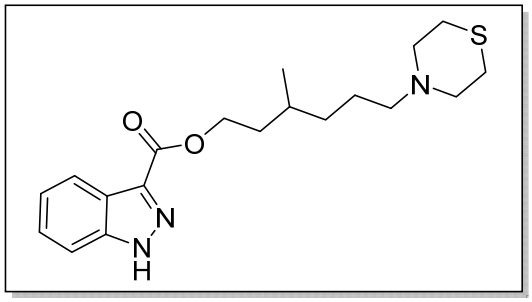
δ_H($CDCl_3$, 400 MHz): 1.50-1.70 [5H, m, containing C*H*$_2$ and 1.71 (3H, s, C*H*$_3$)], 1.94-2.00 (2H, m, C*H*$_2$), 2.20-2.26 (2H, m, C*H*$_2$), 2.37-2.51 (11H, m, 5 × NH_2 and O*H*], 3.54 (2H, t, *J* 10.7, C*H*$_2$OH), 4.06 (2H, d, *J* 7.1, OC*H*$_2$), 4.67 (1H, br s, C*H*), 5.29 (1H, t, *J* 7.1, C*H* alkene); δ_C($CDCl_3$, 100 MHz): 16.4 (*C*H_3), 24.8 (*C*H_2), 37.3 (*C*H_2), 52.9 (2 × N*C*H_2), 53.3 (2 × N*C*H_2), 57.7 (*C*H_2OH), 58.1 (N*C*H_2CH_2OH), 59.2 (N*C*H_2), 61.7 (O*C*H_2), 118.0 (*C*H) alkene, 142.7 (C_q) alkene, 167.1 (*C*=O) ester.

Attempted synthesis of 3-methyl-6-thiomorpholinohexyl 1-acetyl-1*H*-indazole-3-carboxylate 344



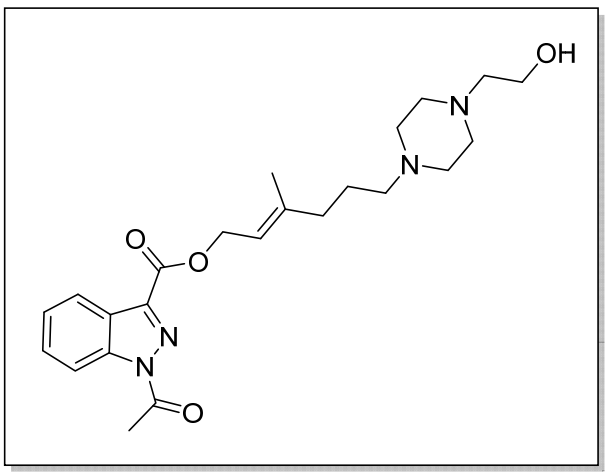
Following the procedure described for 3-methyl-6-thiomorpholinohexyl 3-oxobutanoate **293**, sodium triacetoxyborohydride (82 mg, 0.39 mmol), the aldehyde, 3-methyl-6-oxohexyl 1-acetyl-1*H*-indazole-3-carboxylate **300**, (89 mg, 0.28 mmol) and thiomorpholine **292** (45 µL, 0.45 mmol) were stirred in 1,2-dichloroethane (5.0 mL) at room temperature. TLC analysis after 1.5 h showed complete consumption of the aldehyde starting material. Following the work-up, the crude product was further purified using column chromatography on silica gel using hexane:ethyl acetate (90:10) eluent to yield 3-methyl-6-thiomorpholinohexyl 1*H*-indazole-3-carboxylate **306** as an orange oil (0.06 g, 58%) rather than the expected 1-acyl derivative **344**, as described below.

3-Methyl-6-thiomorpholinohexyl 1*H*-indazole-3-carboxylate 306



δ_H($CDCl_3$, 400 MHz): 0.99 (3H, d *J* 6.4, CHC*H*$_3$), 1.09-2.00 (7H, m, containing 3 × C*H*$_2$ and C*H*CH$_3$), 2.38 (2H, t, *J* 7.6, NC*H*$_2$), 2.64-2.75 (8H, m, containing 2 × NC*H*$_2$ and 2 × SC*H*$_2$), 4.45-4.68 (2H, m, OC*H*$_2$), 7.30-7.35 (1H, m, ArCH), 7.46 (1H, dd, *J* 8.1, 7.2, ArCH), 7.67 (1H, d, *J* 8.4, ArCH), 8.21 (1H, d, *J* 8.2, ArCH), no signal for N*H* observed; δ_C($CDCl_3$, 100 MHz): 19.6 (*C*H$_3$), 23.5 (*C*H$_2$), 27.8 (2 × SCH$_2$), 29.9 (*C*H), 34.6 (*C*H$_2$), 35.5 (CH$_2$), 54.9 (2 × NCH$_2$), 59.4 (NCH$_2$), 63.5 (OCH$_2$), 110.7 (Ar*C*H), 121.9 (Ar*C*H), 122.5 (ArC_q), 123.3 (Ar*C*H), 127.3 (Ar*C*H), 136.7 (*C*=N), 141.3 (*ArCN*), 163.0 (*C*=O) ester; ν_{max} (film)/cm^{-1} 3200, 2926, 1713; *m/z* (ESI$^+$) 362 $[M + H]^+$ (100%) 363 (20) 364 (10). HRMS (ESI$^+$): exact mass calculated for $C_{19}H_{28}N_3O_2S$ $[M + H]^+$ 362.1902. Found 362.1905.

Attempted synthesis of 6-(4-(2-hydroxyethyl)piperazin-1-yl)-3-methylhexyl 1-acetyl-1*H*-indazole-3-carboxylate 307



The title compound was prepared following the procedure described for 3-methyl-6-thiomorpholinohexyl 3-oxobutanoate **293** using sodium triacetoxyborohydride (62 mg, 0.29 mmol), the aldehyde, 3-methyl-6-oxohex-2-en-1-yl 1-acetyl-1*H*-indazole-3-carboxylate **301**, (66 mg, 0.21 mmol) and 2-(piperazin-1-yl)ethan-1-ol **295** (44 mg, 0.34 mmol) in 1,2-dichloroethane (5.0 mL) under a nitrogen atmosphere. The reaction was stirred at room temperature for 18 h and following the work-up, the ^{1}H NMR of the crude residue showed no evidence of the desired product formation. The residue was further purified using column chromatography on

silica gel using hexane:ethyl acetate (90:10 to 100% ethyl acetate) to see if any trace of the compound could be identified, but to no avail.

3.10 References

1. Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*, 1st ed.; Pergamon: Oxford, U.K., 1966.
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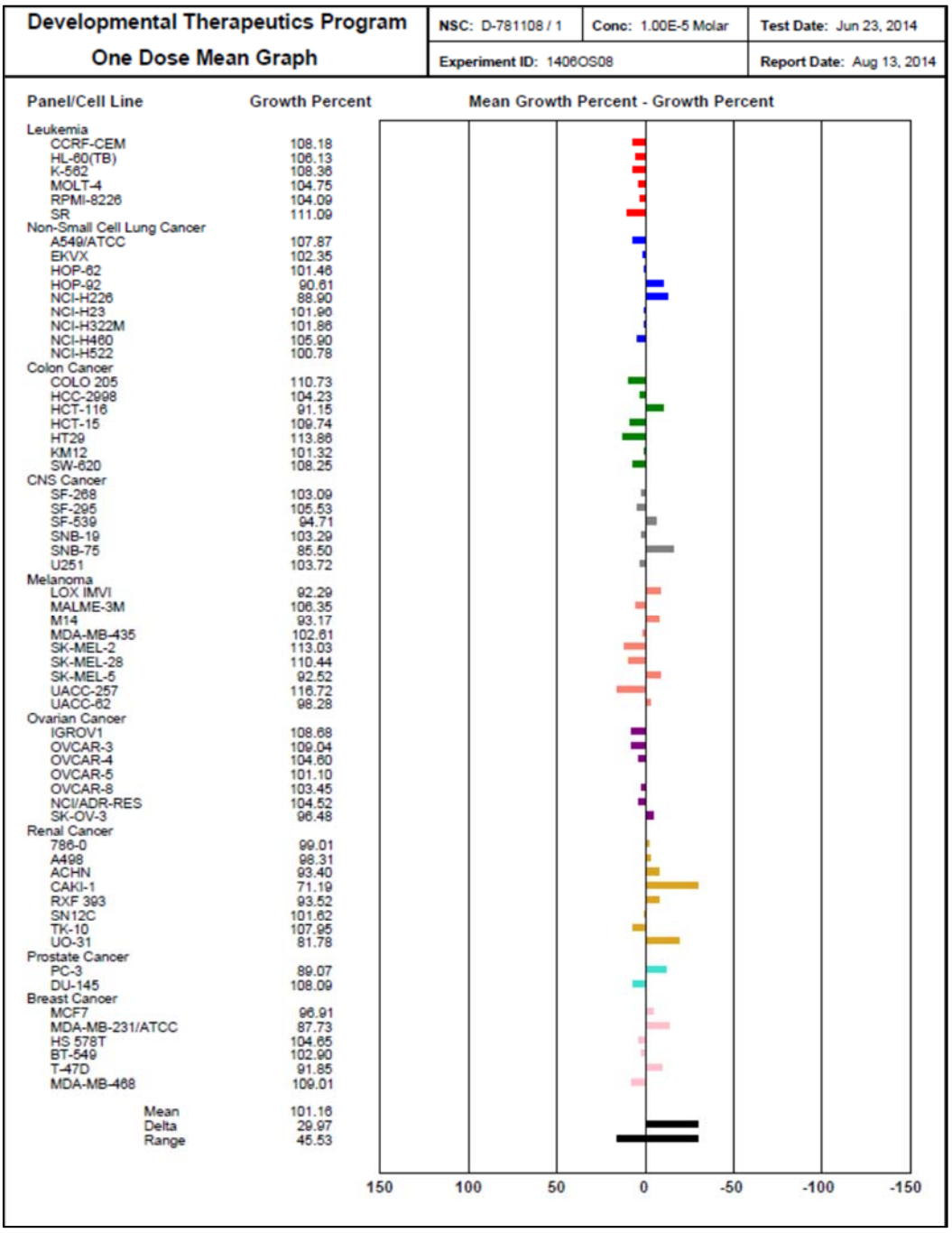
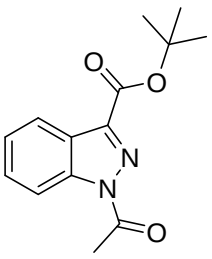
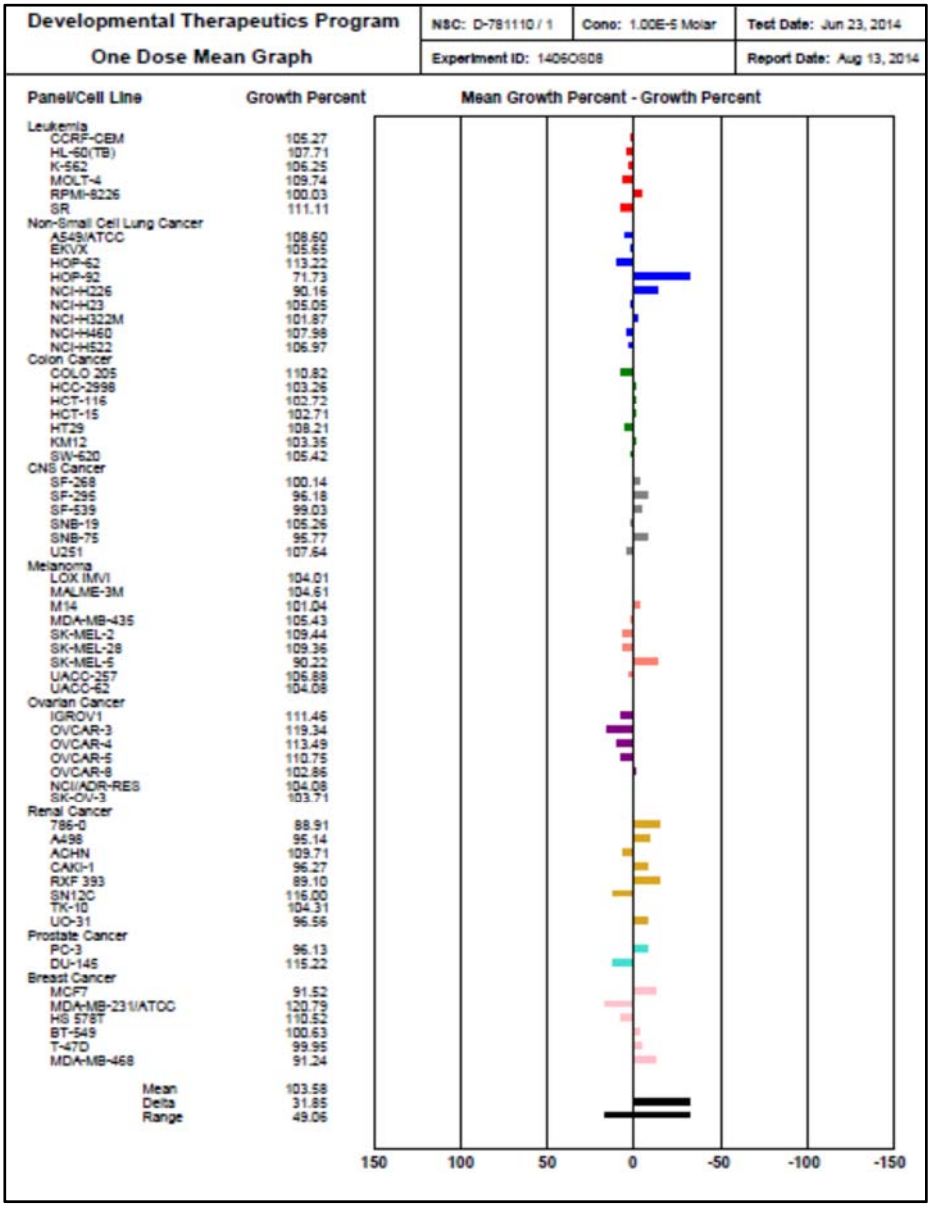
Appendix

NCI-60 One-Dose Mean Graphs





tert-butyl 1-acetyl-1*H*-indazole-3-carboxylate **106**

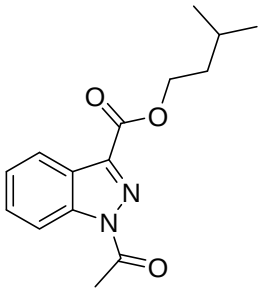


Developmental Therapeutics Program	NSC: D-781110 / 1	Conc: 1.00E-5 Molar	Test Date: Jun 23, 2014
One Dose Mean Graph	Experiment ID: 1406OS08		Report Date: Aug 13, 2014

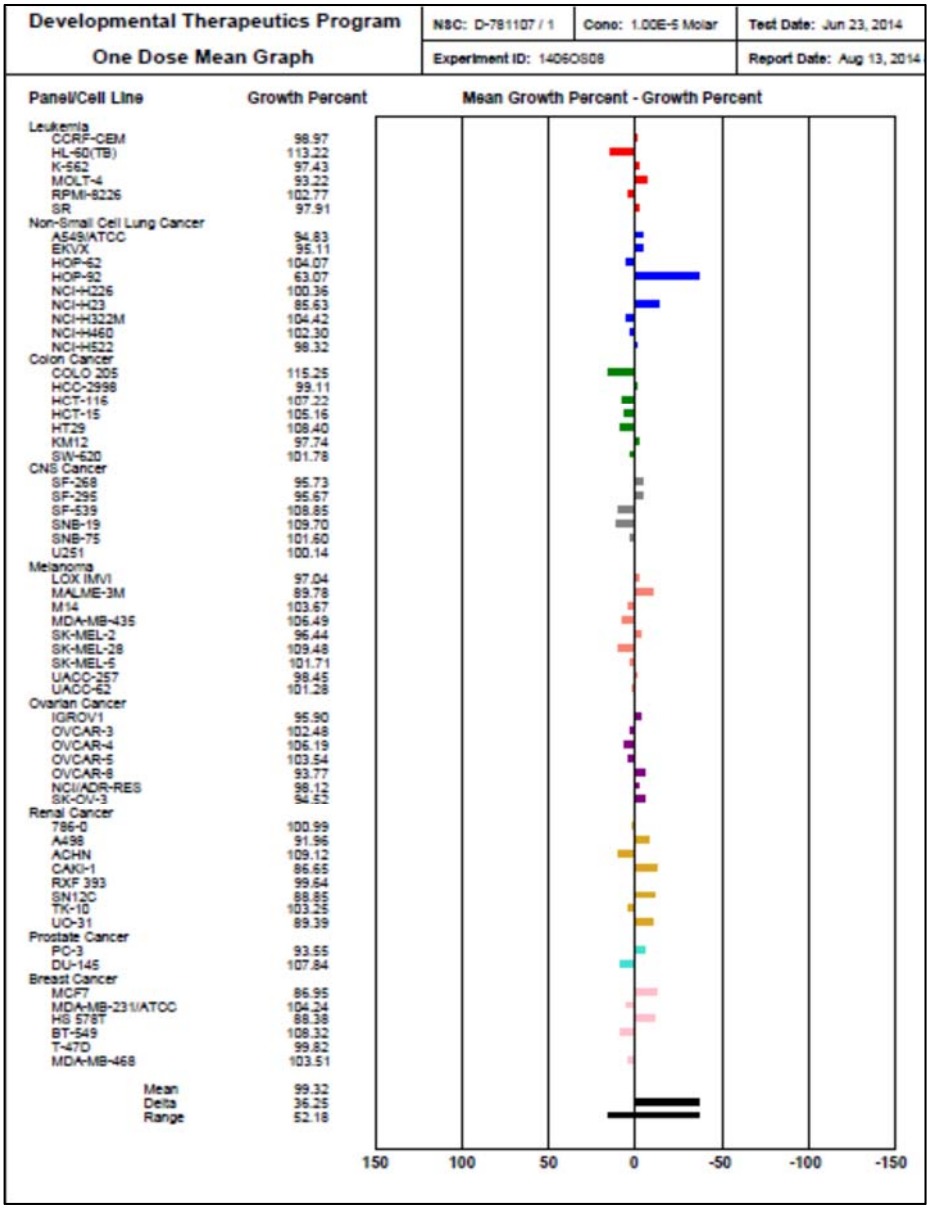
Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	105.27
HL-60(TB)	107.71
K-562	106.25
MOLT-4	109.74
RPMI-8226	100.03
SR	111.11
Non-Small Cell Lung Cancer	
A549/ATCC	108.60
EKVX	105.65
HOP-62	113.22
HOP-92	71.73
NCI-H226	90.16
NCI-H23	105.05
NCI-H322M	101.87
NCI-H460	107.98
NCI-H522	106.97
Colon Cancer	
COLO 205	110.82
HCC-2998	103.26
HCT-116	102.72
HCT-15	102.71
HT29	108.21
KM12	103.35
SW-620	105.42
CNS Cancer	
SF-268	100.14
SF-295	96.18
SF-539	99.03
SNB-19	105.26
SNB-75	95.77
U251	107.64
Melanoma	
LOX IMVI	104.01
MALME-3M	104.61
M14	101.04
MDA-MB-435	105.43
SK-MEL-2	109.44
SK-MEL-28	109.36
SK-MEL-5	90.22
UACC-257	106.88
UACC-62	104.08
Ovarian Cancer	
IGROV1	111.46
OVCAR-3	119.34
OVCAR-4	113.49
OVCAR-5	110.75
OVCAR-8	102.86
NCI/ADR-RES	104.08
SK-OV-3	103.71
Renal Cancer	
786-0	88.91
A498	95.14
ACHN	109.71
CAKI-1	96.27
RXF 393	89.10
SN12C	116.00
TK-10	104.31
UO-31	96.56
Prostate Cancer	
PC-3	96.13
DU-145	115.22
Breast Cancer	
MCF7	91.52
MDA-MB-231/ATCC	120.79
HS 578T	110.52
BT-549	100.63
T-47D	99.95
MDA-MB-468	91.24
Mean	103.58
Delta	31.85
Range	49.06

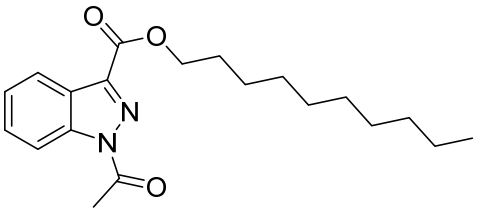
Mean Growth Percent - Growth Percent

150 100 50 0 -50 -100 -150



isopentyl 1-acetyl-1*H*-indazole-3-carboxylate **109**





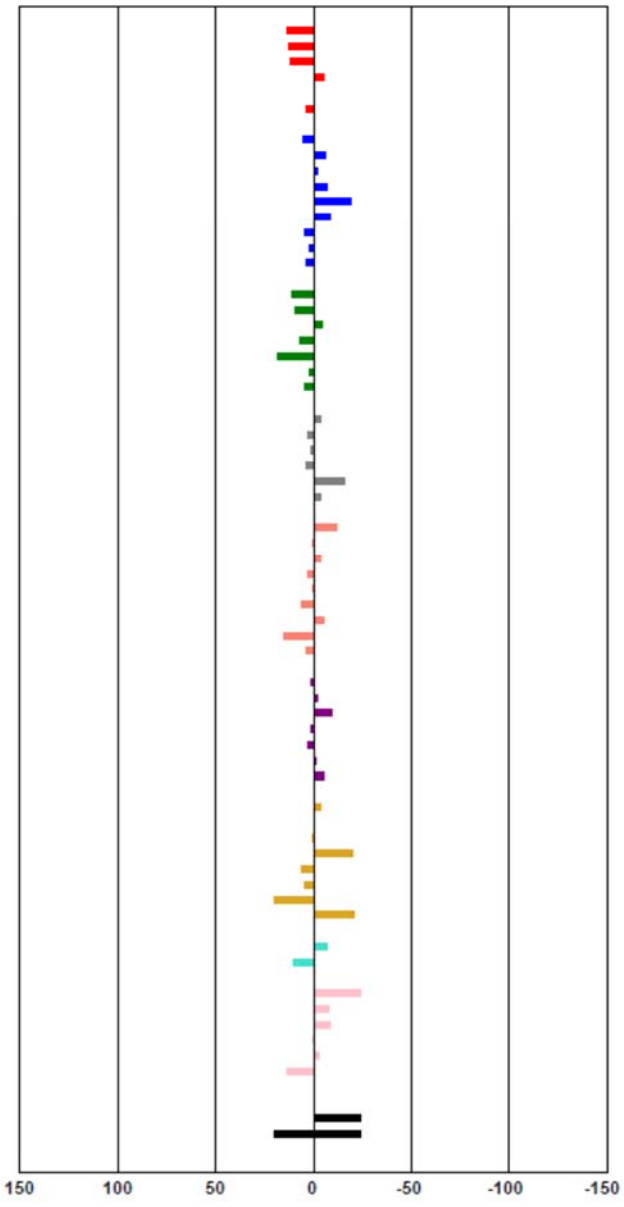
decyl 1-acetyl-1*H*-indazole-3-carboxylate **113**

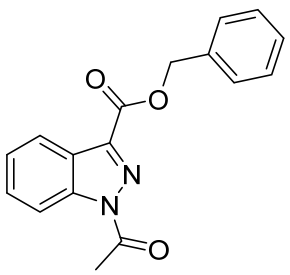
Developmental Therapeutics Program
One Dose Mean Graph

NSC: D-781109 / 1	Conc: 1.00E-5 Molar	Test Date: Jun 23, 2014
Experiment ID: 1406OS08		Report Date: Aug 13, 2014

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	113.02
HL-60(TB)	111.62
K-562	110.84
MOLT-4	94.35
RPMI-8226	98.83
SR	102.91
Non-Small Cell Lung Cancer	
A549/ATCC	104.58
EKVX	92.90
HOP-62	97.60
HOP-92	92.15
NCI-H226	80.51
NCI-H23	90.97
NCI-H322M	103.79
NCI-H460	101.53
NCI-H522	102.70
Colon Cancer	
COLO 205	110.13
HCC-2998	108.63
HCT-116	94.98
HCT-15	106.13
HT29	117.44
KM12	101.06
SW-620	104.10
CNS Cancer	
SF-268	95.37
SF-295	101.82
SF-539	100.65
SNB-19	102.83
SNB-75	83.57
U251	95.45
Melanoma	
LOX IMVI	87.28
MALME-3M	99.49
M14	95.91
MDA-MB-435	102.49
SK-MEL-2	99.73
SK-MEL-28	105.28
SK-MEL-5	94.25
UACC-257	114.55
UACC-62	102.67
Ovarian Cancer	
IGROV1	100.37
OVCAR-3	97.31
OVCAR-4	89.85
OVCAR-5	100.34
OVCAR-8	102.43
NCI/ADR-RES	98.24
SK-OV-3	93.64
Renal Cancer	
786-0	95.63
A498	99.02
ACHN	99.52
CAKI-1	79.63
RXF 393	105.59
SN12C	103.82
TK-10	118.90
UO-31	78.33
Prostate Cancer	
PC-3	92.02
DU-145	109.49
Breast Cancer	
MCF7	75.35
MDA-MB-231/ATCC	91.90
HS 578T	91.04
BT-549	99.46
T-47D	96.63
MDA-MB-468	112.96
Mean	99.23
Delta	23.88
Range	43.55

Mean Growth Percent - Growth Percent





benzyl 1-acetyl-1*H*-indazole-3-carboxylate **110**

Developmental Therapeutics Program

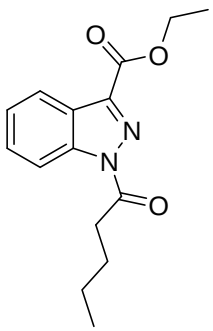
One Dose Mean Graph

NSC: D-781106 / 1	Conc: 1.00E-5 Molar	Test Date: Jun 23, 2014
Experiment ID: 1406OS08		Report Date: Aug 13, 2014

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	97.41
HL-60(TB)	99.34
K-562	106.08
MOLT-4	103.40
RPMI-8226	97.68
SR	105.82
Non-Small Cell Lung Cancer	
A549/ATCC	103.35
EKVX	104.35
HOP-62	109.02
HOP-92	98.97
NCI-H226	103.27
NCI-H23	93.75
NCI-H322M	105.32
NCI-H460	108.98
NCI-H522	102.49
Colon Cancer	
COLO 205	116.41
HCC-2998	94.73
HCT-116	102.08
HCT-15	104.07
HT29	106.93
KM12	105.63
SW-620	107.42
CNS Cancer	
SF-268	101.00
SF-295	99.95
SF-539	109.59
SNB-19	106.59
SNB-75	111.35
U251	103.88
Melanoma	
LOX IMVI	99.37
MALME-3M	104.58
M14	104.09
MDA-MB-435	109.89
SK-MEL-2	107.60
SK-MEL-28	119.20
SK-MEL-5	102.36
UACC-257	112.48
UACC-62	107.45
Ovarian Cancer	
IGROV1	109.75
OVCAR-3	119.44
OVCAR-4	122.42
OVCAR-5	113.91
OVCAR-8	108.80
NCI/ADR-RES	99.93
SK-OV-3	110.43
Renal Cancer	
786-0	101.55
A498	108.02
ACHN	109.30
CAKI-1	99.25
RXF 393	108.23
SN12C	111.30
TK-10	100.94
UO-31	92.01
Prostate Cancer	
PC-3	98.32
DU-145	108.47
Breast Cancer	
MCF7	90.75
MDA-MB-231/ATCC	113.45
HS 578T	110.69
BT-549	112.08
T-47D	103.57
MDA-MB-468	103.11
Mean	105.53
Delta	14.78
Range	31.67

Mean Growth Percent - Growth Percent

150 100 50 0 -50 -100 -150



ethyl 1-pentanoyl-1*H*-indazole-3-carboxylate **119**

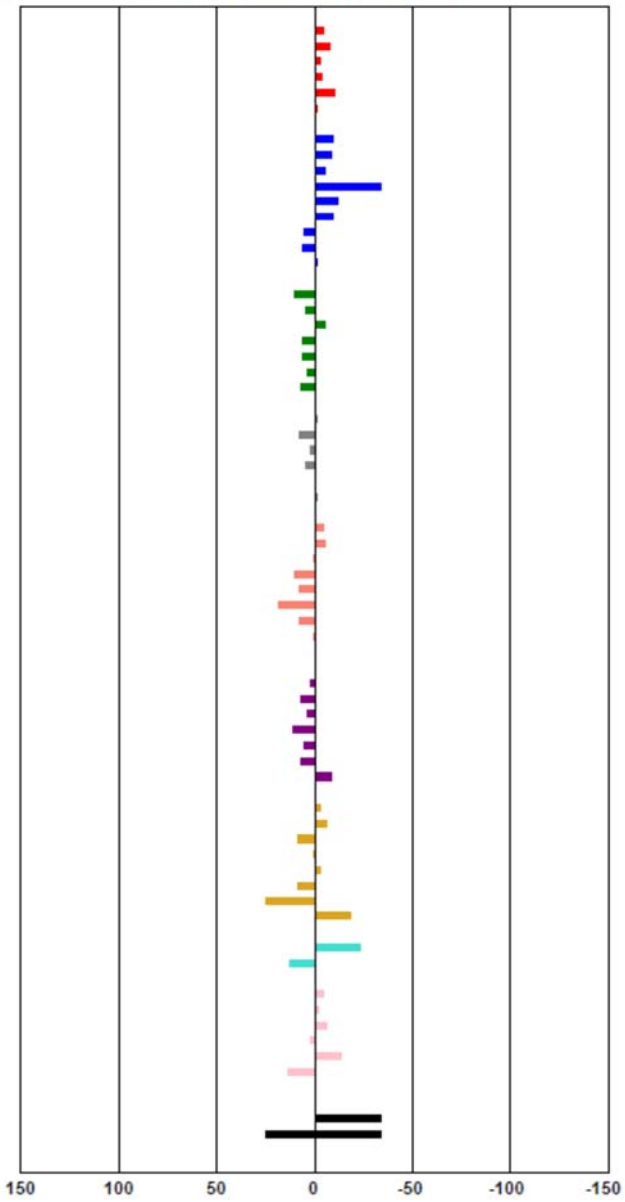
Developmental Therapeutics Program

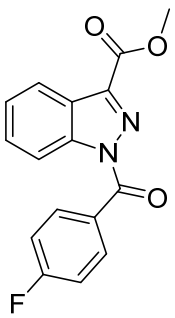
One Dose Mean Graph

NSC: D-784823 / 1	Conc: 1.00E-5 Molar	Test Date: Jun 15, 2015
Experiment ID: 1506OS04		Report Date: Jul 03, 2015

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	91.47
HL-60(TB)	87.83
K-562	92.70
MOLT-4	91.53
RPMI-8226	85.30
SR	94.27
Non-Small Cell Lung Cancer	
A549/ATCC	86.44
EKVX	86.76
HOP-62	90.02
HOP-92	61.38
NCI-H226	83.49
NCI-H23	86.36
NCI-H322M	100.72
NCI-H460	101.29
NCI-H522	94.18
Colon Cancer	
COLO 205	106.08
HCC-2998	100.38
HCT-116	89.92
HCT-15	101.47
HT29	101.96
KM12	99.27
SW-620	102.09
CNS Cancer	
SF-268	94.61
SF-295	103.11
SF-539	97.50
SNB-19	100.23
SNB-75	95.09
U251	94.62
Melanoma	
LOX IMVI	91.17
MALME-3M	90.02
M14	95.57
MDA-MB-435	105.68
SK-MEL-2	103.04
SK-MEL-28	113.75
SK-MEL-5	103.08
UACC-257	96.23
UACC-62	95.09
Ovarian Cancer	
IGROV1	97.74
OVCAR-3	102.68
OVCAR-4	99.56
OVCAR-5	106.54
OVCAR-8	100.98
NCI/ADR-RES	102.12
SK-OV-3	86.80
Renal Cancer	
786-0	92.73
A498	89.84
ACHN	103.80
CAKI-1	96.06
RXF 393	93.01
SN12C	104.21
TK-10	120.49
UO-31	77.19
Prostate Cancer	
PC-3	72.53
DU-145	108.10
Breast Cancer	
MCF7	91.07
MDA-MB-231/ATCC	93.17
HS 578T	89.19
BT-549	97.96
T-47D	82.22
MDA-MB-468	108.87
Mean	95.51
Delta	34.13
Range	59.11

Mean Growth Percent - Growth Percent





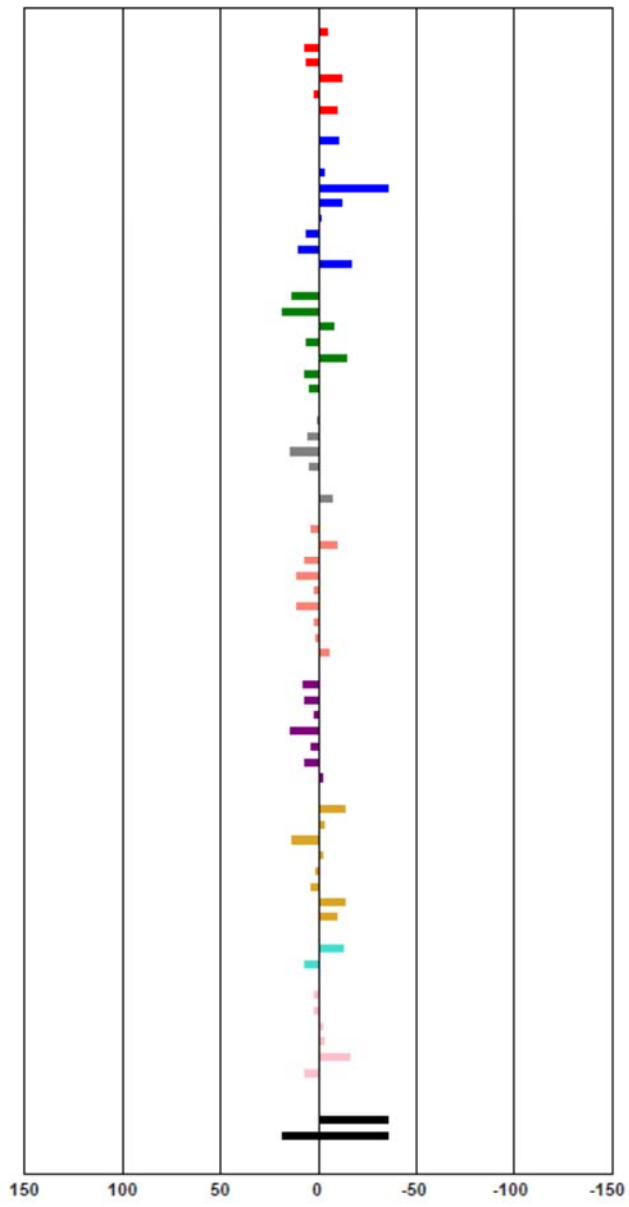
methyl 1-(4-fluorobenzoyl)-1*H*-indazole-3-carboxylate **123**

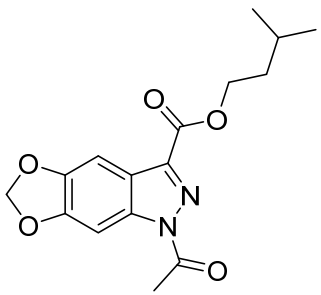
Developmental Therapeutics Program
One Dose Mean Graph

NSC: D-784825 / 1	Conc: 1.00E-5 Molar	Test Date: Jun 15, 2015
Experiment ID: 1506OS04		Report Date: Jul 03, 2015

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	89.67
HL-60(TB)	101.19
K-562	99.99
MOLT-4	81.82
RPMI-8226	96.15
SR	85.06
Non-Small Cell Lung Cancer	
A549/ATCC	83.60
EKVX	93.59
HOP-62	91.44
HOP-92	58.93
NCI-H226	82.10
NCI-H23	92.64
NCI-H322M	100.51
NCI-H460	104.20
NCI-H522	77.63
Colon Cancer	
COLO 205	107.86
HCC-2998	112.20
HCT-116	85.89
HCT-15	100.45
HT29	79.62
KM12	101.29
SW-620	98.22
CNS Cancer	
SF-268	94.35
SF-295	99.10
SF-539	108.20
SNB-19	98.86
SNB-75	93.77
U251	87.01
Melanoma	
LOX IMVI	97.53
MALME-3M	84.29
M14	100.70
MDA-MB-435	105.23
SK-MEL-2	96.05
SK-MEL-28	105.28
SK-MEL-5	96.27
UACC-257	95.09
UACC-62	89.06
Ovarian Cancer	
IGROV1	102.16
OVCAR-3	101.28
OVCAR-4	95.75
OVCAR-5	108.25
OVCAR-8	97.58
NCI/ADR-RES	101.05
SK-OV-3	92.02
Renal Cancer	
786-0	80.84
A498	90.93
ACHN	107.85
CAKI-1	92.12
RXF 393	95.56
SN12C	97.82
TK-10	80.47
UO-31	84.73
Prostate Cancer	
PC-3	81.72
DU-145	100.65
Breast Cancer	
MCF7	95.97
MDA-MB-231/ATCC	96.22
HS 578T	91.87
BT-549	90.87
T-47D	78.13
MDA-MB-468	100.60
Mean	93.99
Delta	35.06
Range	53.27

Mean Growth Percent - Growth Percent





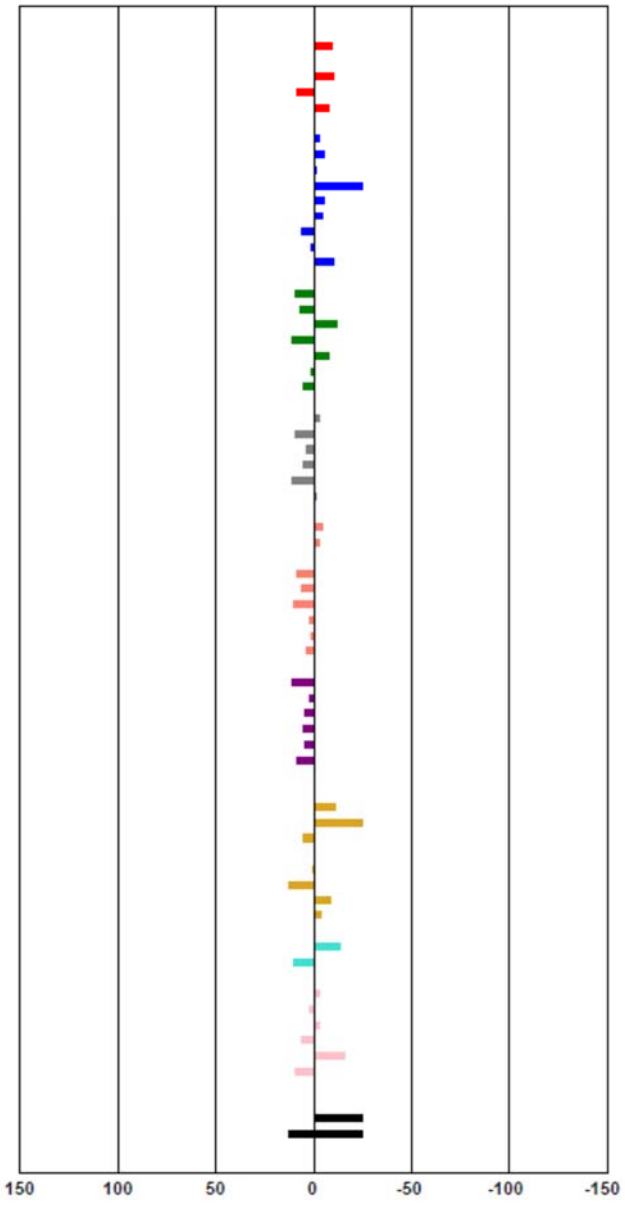
isopentyl 1-acetyl-1*H*-[1,3]dioxolo[4,5-*f*]indazole-3-carboxylate **154**

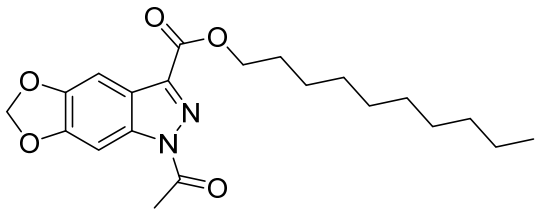
Developmental Therapeutics Program
One Dose Mean Graph

NSC: D-784824 / 1	Conc: 1.00E-5 Molar	Test Date: Jun 15, 2015
Experiment ID: 1506OS04		Report Date: Jul 03, 2015

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	97.27
HL-60(TB)	88.31
K-562	97.45
MOLT-4	87.61
RPMI-8226	106.10
SR	90.13
Non-Small Cell Lung Cancer	
A549/ATCC	94.91
EKVX	92.39
HOP-62	96.17
HOP-92	72.76
NCI-H226	92.59
NCI-H23	93.51
NCI-H322M	103.64
NCI-H460	98.93
NCI-H522	87.76
Colon Cancer	
COLO 205	107.07
HCC-2998	104.35
HCT-116	85.66
HCT-15	108.41
HT29	90.23
KM12	99.16
SW-620	102.83
CNS Cancer	
SF-268	94.98
SF-295	107.42
SF-539	101.33
SNB-19	103.02
SNB-75	108.80
U251	96.15
Melanoma	
LOX IMVI	93.31
MALME-3M	95.21
M14	97.40
MDA-MB-435	105.89
SK-MEL-2	103.44
SK-MEL-28	108.19
SK-MEL-5	99.87
UACC-257	98.88
UACC-62	101.20
Ovarian Cancer	
IGROV1	108.60
OVCAR-3	100.00
OVCAR-4	102.50
OVCAR-5	102.66
OVCAR-8	102.49
NCI/ADR-RES	106.20
SK-OV-3	97.68
Renal Cancer	
786-0	86.71
A498	72.94
ACHN	102.73
CAKI-1	97.40
RXF 393	98.36
SN12C	110.59
TK-10	89.49
UO-31	94.18
Prostate Cancer	
PC-3	84.14
DU-145	107.68
Breast Cancer	
MCF7	94.57
MDA-MB-231/ATCC	100.07
HS 578T	95.10
BT-549	103.81
T-47D	82.18
MDA-MB-468	107.18
Mean	97.66
Delta	24.90
Range	37.83

Mean Growth Percent - Growth Percent





decyl 1-acetyl-1*H*-[1,3]dioxolo[4,5-*f*]indazole-3-carboxylate **158**

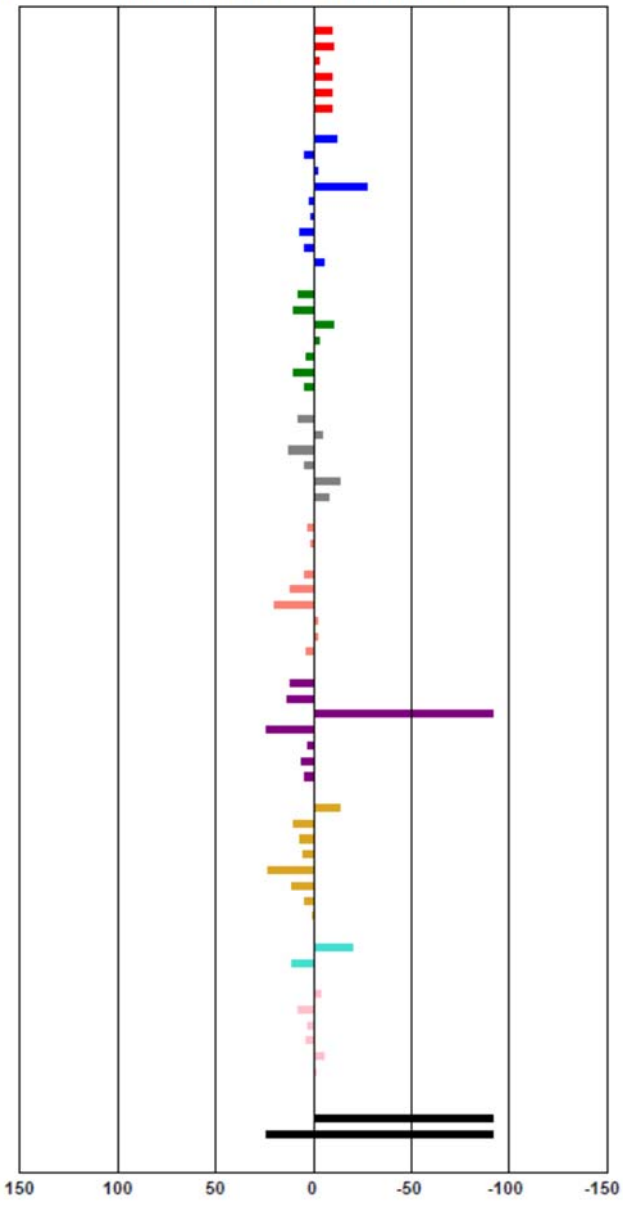
Developmental Therapeutics Program

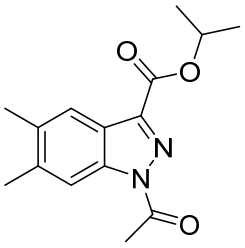
One Dose Mean Graph

NSC: D-784826 / 1	Conc: 1.00E-5 Molar	Test Date: Jun 15, 2015
Experiment ID: 1506OS04		Report Date: Jul 03, 2015

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	84.67
HL-60(TB)	83.68
K-562	91.08
MOLT-4	84.85
RPMI-8226	84.99
SR	84.62
Non-Small Cell Lung Cancer	
A549/ATCC	82.22
EKVX	98.97
HOP-62	92.12
HOP-92	67.06
NCI-H226	96.37
NCI-H23	95.20
NCI-H322M	101.23
NCI-H460	98.71
NCI-H522	88.82
Colon Cancer	
COLO 205	102.01
HCC-2998	104.63
HCT-116	83.84
HCT-15	90.92
HT29	97.78
KM12	104.53
SW-620	98.75
CNS Cancer	
SF-268	101.95
SF-295	89.82
SF-539	106.94
SNB-19	98.48
SNB-75	80.71
U251	86.33
Melanoma	
LOX IMVI	96.99
MALME-3M	95.01
M14	93.74
MDA-MB-435	98.59
SK-MEL-2	105.82
SK-MEL-28	113.82
SK-MEL-5	92.01
UACC-257	92.28
UACC-62	97.57
Ovarian Cancer	
IGROV1	105.85
OVCAR-3	107.85
OVCAR-4	2.77
OVCAR-5	118.38
OVCAR-8	96.83
NCI/ADR-RES	100.57
SK-OV-3	98.61
Renal Cancer	
786-0	80.87
A498	104.37
ACHN	100.72
CAKI-1	99.25
RXF 393	117.66
SN12C	104.74
TK-10	98.63
UO-31	94.38
Prostate Cancer	
PC-3	74.23
DU-145	104.90
Breast Cancer	
MCF7	90.84
MDA-MB-231/ATCC	101.69
HS 578T	96.59
BT-549	98.17
T-47D	88.69
MDA-MB-468	92.88
Mean	94.11
Delta	91.34
Range	115.61

Mean Growth Percent - Growth Percent





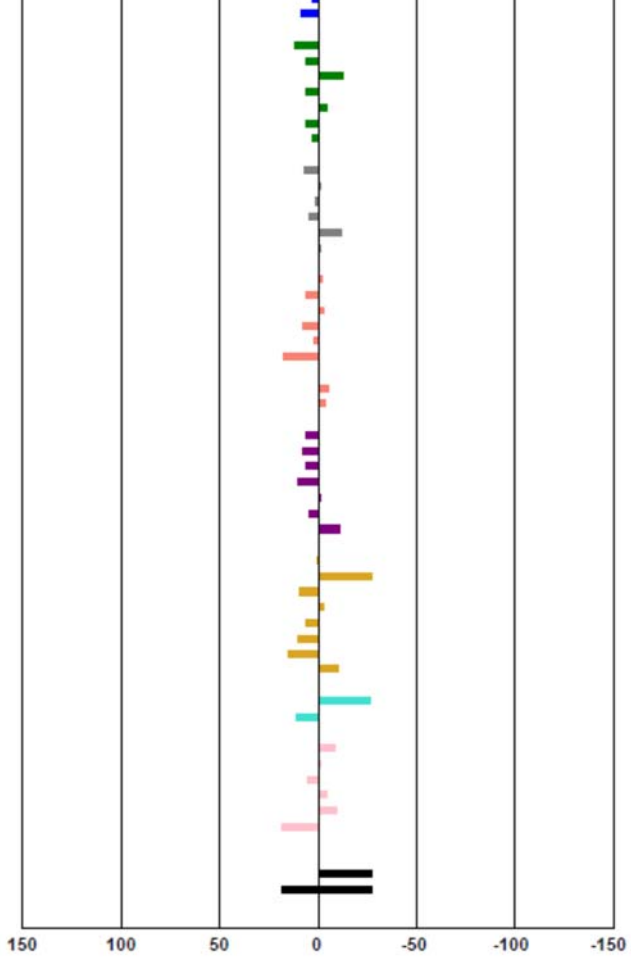
isopropyl 1-acetyl-5,6-dimethyl-1*H*-indazole-3-carboxylate **168**

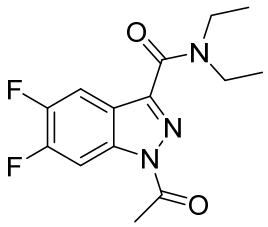
Developmental Therapeutics Program

One Dose Mean Graph

NSC: D-784828 / 1	Conc: 1.00E-5 Molar	Test Date: Jun 15, 2015
Experiment ID: 1506OS04		Report Date: Jul 03, 2015

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	93.82
HL-60(TB)	94.32
K-562	87.75
MOLT-4	90.45
RPMI-8226	93.70
SR	95.73
Non-Small Cell Lung Cancer	
A549/ATCC	83.76
EKVX	95.16
HOP-62	92.62
HOP-92	68.03
NCI-H226	88.51
NCI-H23	99.68
NCI-H322M	109.35
NCI-H460	98.33
NCI-H522	103.56
Colon Cancer	
COLO 205	107.29
HCC-2998	101.33
HCT-116	82.86
HCT-15	101.41
HT29	90.79
KM12	101.21
SW-620	97.78
CNS Cancer	
SF-268	101.70
SF-295	93.71
SF-539	96.29
SNB-19	99.89
SNB-75	83.11
U251	94.02
Melanoma	
LOX IMVI	93.12
MALME-3M	101.60
M14	92.11
MDA-MB-435	102.64
SK-MEL-2	97.56
SK-MEL-28	112.77
SK-MEL-5	94.55
UACC-257	90.06
UACC-62	91.51
Ovarian Cancer	
IGROV1	101.10
OVCAR-3	102.47
OVCAR-4	101.19
OVCAR-5	104.99
OVCAR-8	94.04
NCI/ADR-RES	99.82
SK-OV-3	84.00
Renal Cancer	
786-0	95.90
A498	67.70
ACHN	104.26
CAKI-1	91.89
RXF 393	101.09
SN12C	105.64
TK-10	110.20
UO-31	85.34
Prostate Cancer	
PC-3	68.93
DU-145	105.85
Breast Cancer	
MCF7	86.36
MDA-MB-231/ATCC	93.74
HS 578T	100.06
BT-549	90.30
T-47D	85.42
MDA-MB-468	113.08
Mean	95.09
Delta	27.39
Range	45.38





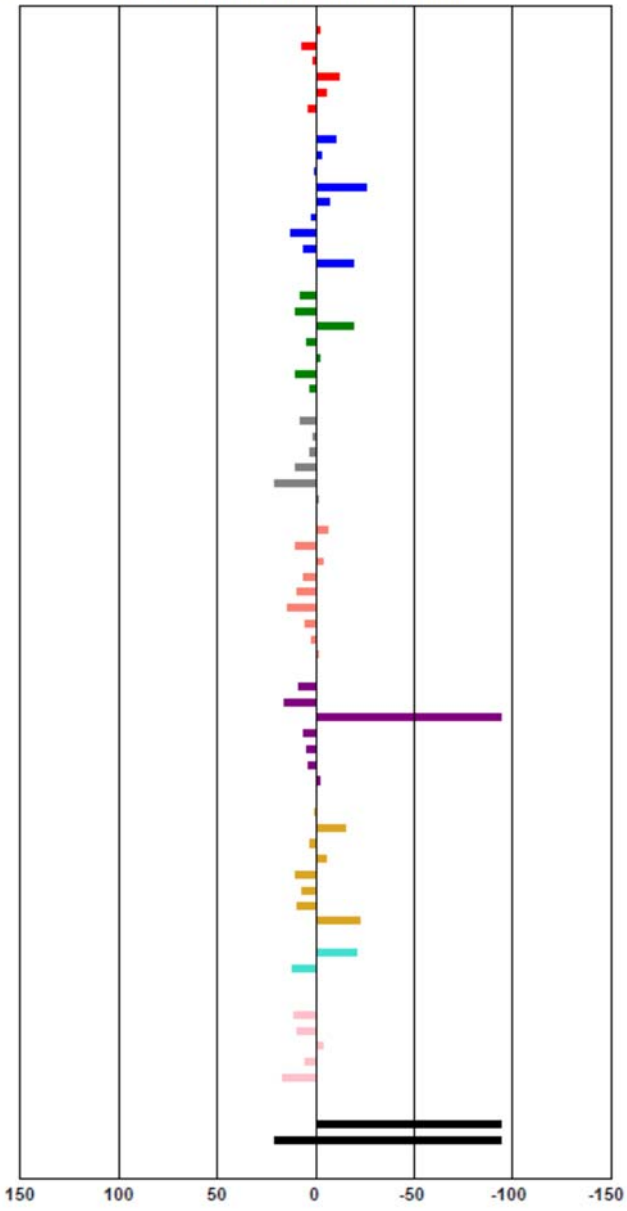
1-acetyl-*N*,*N*-diethyl-5,6-difluoro-1*H*-indazole-3-carboxamide **185**

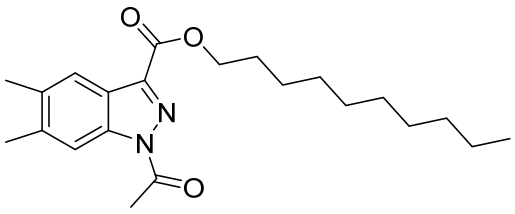
Developmental Therapeutics Program

One Dose Mean Graph

NSC: D-784827 / 1	Conc: 1.00E-5 Molar	Test Date: Jun 15, 2015
Experiment ID: 1506OS04		Report Date: Jul 03, 2015

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	92.24
HL-60(TB)	101.00
K-562	95.20
MOLT-4	82.74
RPMI-8226	88.91
SR	98.15
Non-Small Cell Lung Cancer	
A549/ATCC	83.85
EKVX	91.56
HOP-62	94.50
HOP-92	68.54
NCI-H226	87.81
NCI-H23	96.30
NCI-H322M	106.90
NCI-H460	100.90
NCI-H522	75.10
Colon Cancer	
COLO 205	102.03
HCC-2998	104.74
HCT-116	75.42
HCT-15	98.85
HT29	92.14
KM12	104.42
SW-620	97.33
CNS Cancer	
SF-268	102.21
SF-295	95.95
SF-539	97.58
SNB-19	104.84
SNB-75	115.38
U251	93.30
Melanoma	
LOX IMVI	87.90
MALME-3M	104.47
M14	90.72
MDA-MB-435	100.14
SK-MEL-2	103.95
SK-MEL-28	108.66
SK-MEL-5	99.55
UACC-257	96.27
UACC-62	93.32
Ovarian Cancer	
IGROV1	102.96
OVCAR-3	110.52
OVCAR-4	0.47
OVCAR-5	100.32
OVCAR-8	98.49
NCI/ADR-RES	98.10
SK-OV-3	92.27
Renal Cancer	
786-0	94.58
A498	79.12
ACHN	97.11
CAKI-1	88.81
RXF 393	104.20
SN12C	101.56
TK-10	103.99
UO-31	71.75
Prostate Cancer	
PC-3	73.66
DU-145	105.91
Breast Cancer	
MCF7	93.98
MDA-MB-231/ATCC	105.33
HS 578T	104.12
BT-549	90.48
T-47D	99.73
MDA-MB-468	110.82
Mean	94.35
Delta	93.88
Range	114.91





decyl 1-acetyl-5,6-dimethyl-1*H*-indazole-3-carboxylate **169**

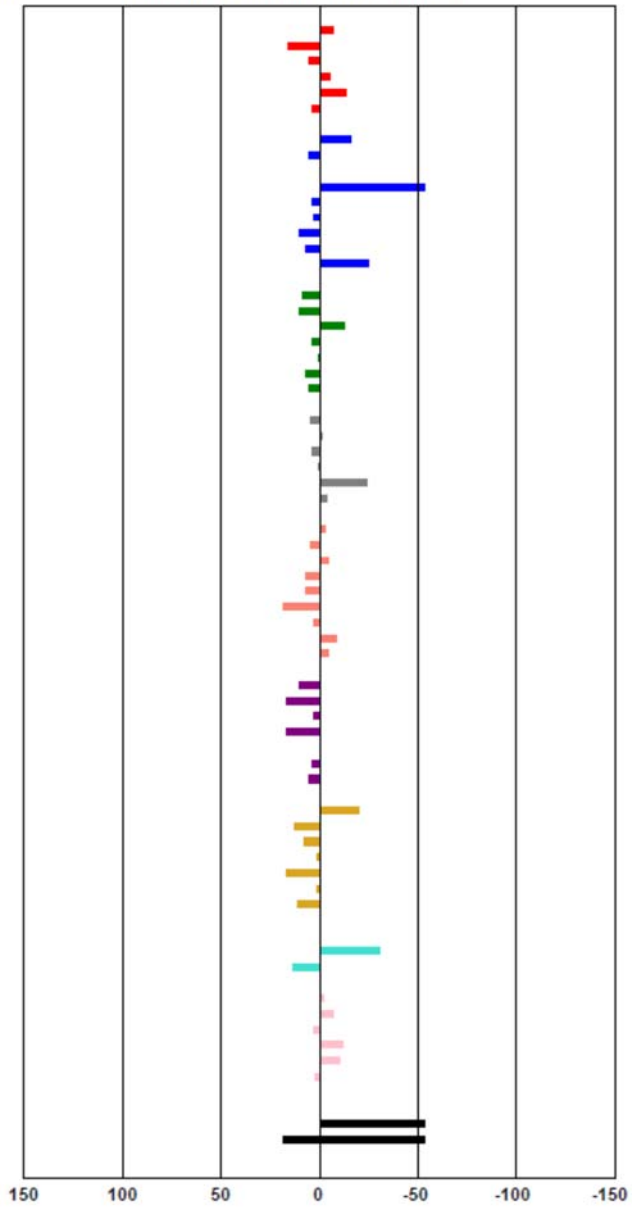
Developmental Therapeutics Program

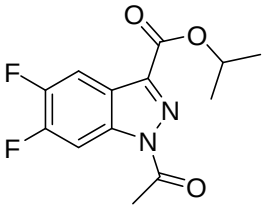
One Dose Mean Graph

NSC: D-784830 / 1	Conc: 1.00E-5 Molar	Test Date: Jun 15, 2015
Experiment ID: 1506OS04		Report Date: Jul 03, 2015

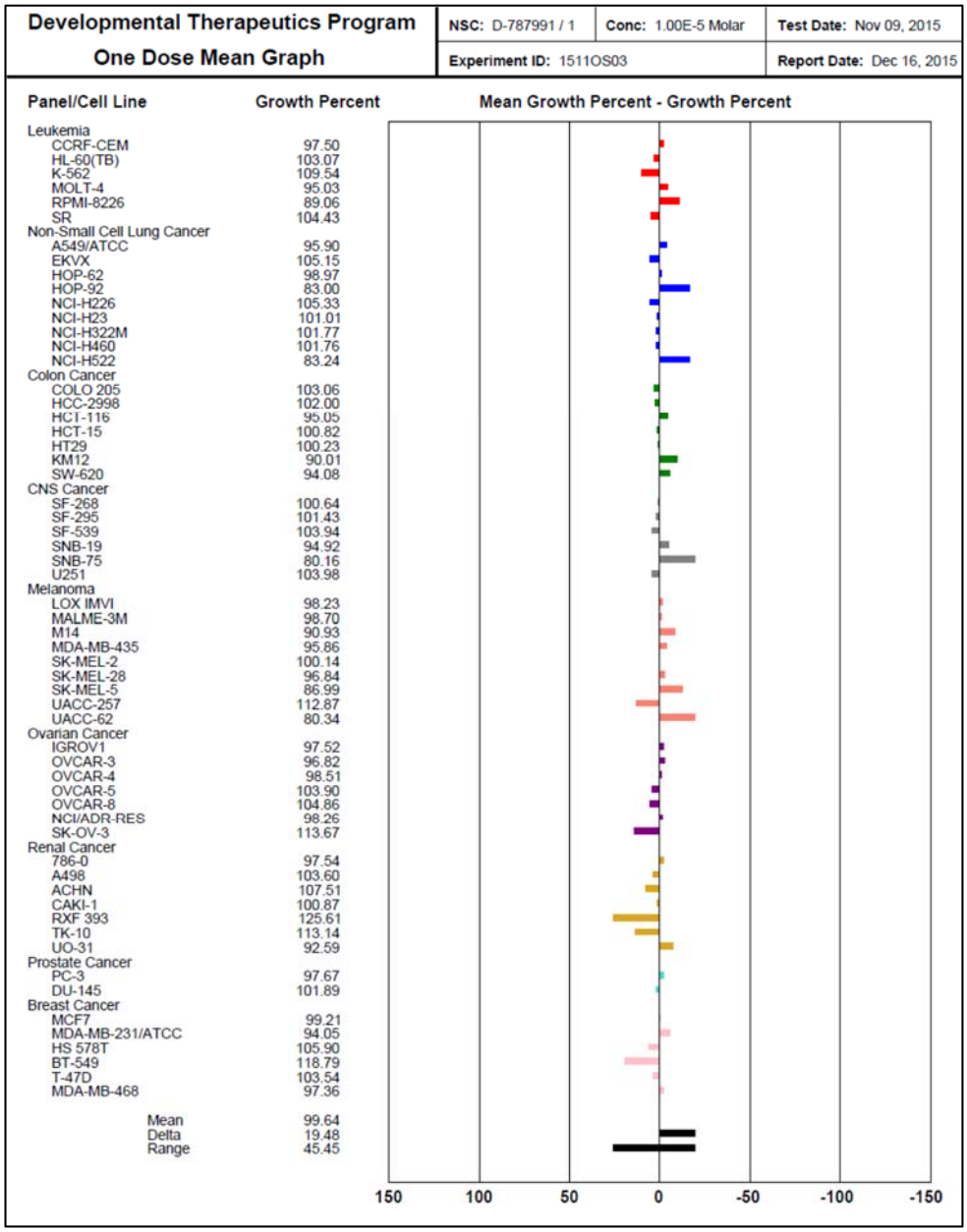
Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	89.42
HL-60(TB)	112.28
K-562	101.08
MOLT-4	91.01
RPMI-8226	82.94
SR	99.90
Non-Small Cell Lung Cancer	
A549/ATCC	80.11
EKVX	101.68
HOP-62	95.98
HOP-92	42.43
NCI-H226	100.13
NCI-H23	98.80
NCI-H322M	106.34
NCI-H460	103.11
NCI-H522	71.51
Colon Cancer	
COLO 205	104.92
HCC-2998	106.27
HCT-116	83.22
HCT-15	99.75
HT29	96.45
KM12	103.07
SW-620	101.23
CNS Cancer	
SF-268	100.39
SF-295	95.21
SF-539	99.45
SNB-19	96.45
SNB-75	72.14
U251	92.72
Melanoma	
LOX IMVI	93.17
MALME-3M	100.87
M14	91.95
MDA-MB-435	102.76
SK-MEL-2	103.43
SK-MEL-28	114.37
SK-MEL-5	99.26
UACC-257	87.68
UACC-62	91.97
Ovarian Cancer	
IGROV1	106.42
OVCAR-3	112.54
OVCAR-4	99.37
OVCAR-5	113.22
OVCAR-8	95.91
NCI/ADR-RES	99.98
SK-OV-3	101.86
Renal Cancer	
786-0	76.57
A498	109.12
ACHN	103.90
CAKI-1	96.98
RXF 393	113.01
SN12C	97.36
TK-10	106.86
UO-31	95.51
Prostate Cancer	
PC-3	65.42
DU-145	109.43
Breast Cancer	
MCF7	94.46
MDA-MB-231/ATCC	89.40
HS 578T	98.91
BT-549	84.40
T-47D	85.79
MDA-MB-468	98.00
Mean	96.13
Delta	53.70
Range	71.94

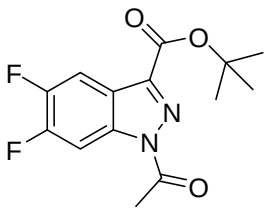
Mean Growth Percent - Growth Percent



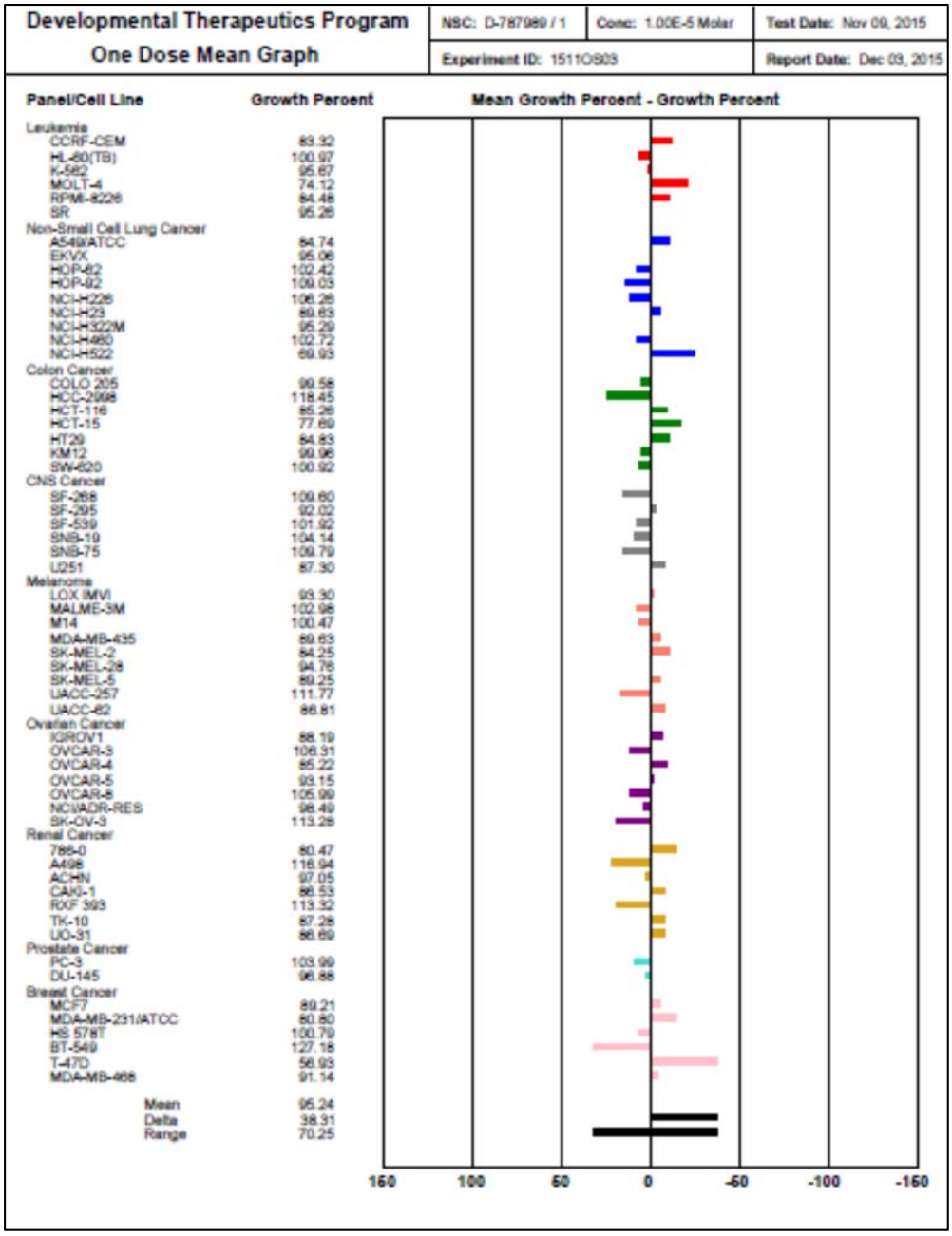


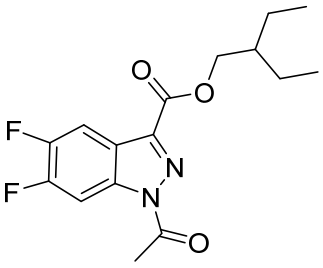
isopropyl 1-acetyl-5,6-difluoro-1*H*-indazole-3-carboxylate **179**





tert-butyl 1-acetyl-5,6-difluoro-1*H*-indazole-3-carboxylate **180**





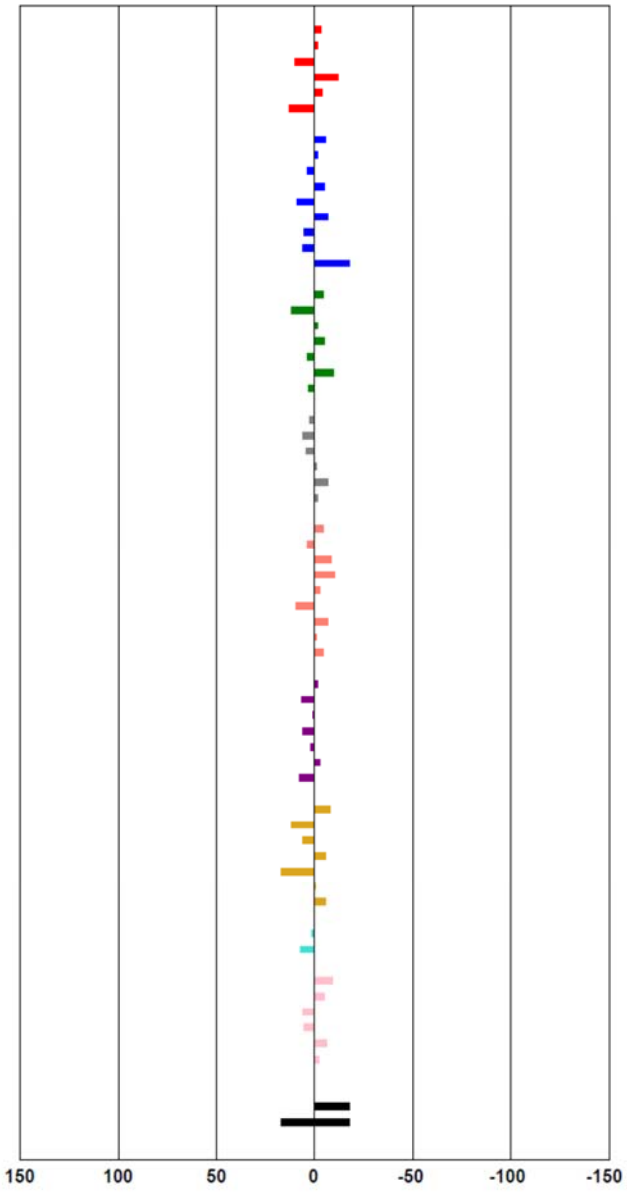
2-ethylbutyl 1-acetyl-5,6-difluoro-1*H*-indazole-3-carboxylate **183**

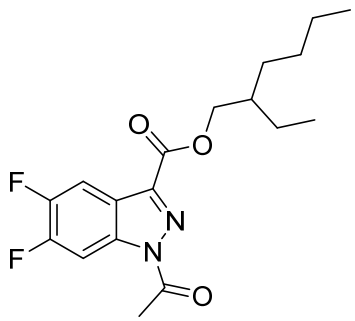
Developmental Therapeutics Program
One Dose Mean Graph

NSC: D-787990 / 1	Conc: 1.00E-5 Molar	Test Date: Nov 09, 2015
Experiment ID: 1511OS03		Report Date: Dec 16, 2015

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	98.20
HL-60(TB)	100.18
K-562	111.31
MOLT-4	89.34
RPMI-8226	97.47
SR	114.26
Non-Small Cell Lung Cancer	
A549/ATCC	95.83
EKVX	100.19
HOP-62	105.45
HOP-92	96.65
NCI-H226	110.24
NCI-H23	94.78
NCI-H322M	107.19
NCI-H460	107.48
NCI-H522	84.07
Colon Cancer	
COLO 205	97.03
HCC-2998	113.14
HCT-116	100.13
HCT-15	96.43
HT29	104.93
KM12	91.67
SW-620	104.36
CNS Cancer	
SF-268	104.12
SF-295	107.37
SF-539	105.61
SNB-19	100.43
SNB-75	94.92
U251	99.92
Melanoma	
LOX IMVI	97.13
MALME-3M	105.05
M14	92.78
MDA-MB-435	91.12
SK-MEL-2	98.98
SK-MEL-28	110.83
SK-MEL-5	95.00
UACC-257	100.37
UACC-62	97.14
Ovarian Cancer	
IGROV1	99.98
OVCAR-3	108.09
OVCAR-4	102.56
OVCAR-5	107.57
OVCAR-8	103.64
NCI/ADR-RES	98.90
SK-OV-3	109.03
Renal Cancer	
786-0	93.83
A498	113.24
ACHN	107.37
CAKI-1	95.64
RXF 393	118.64
TK-10	100.95
UO-31	95.77
Prostate Cancer	
PC-3	103.10
DU-145	108.71
Breast Cancer	
MCF7	92.42
MDA-MB-231/ATCC	96.25
HS 578T	107.77
BT-549	106.73
T-47D	95.12
MDA-MB-468	99.66
Mean	101.46
Delta	17.39
Range	34.57

Mean Growth Percent - Growth Percent





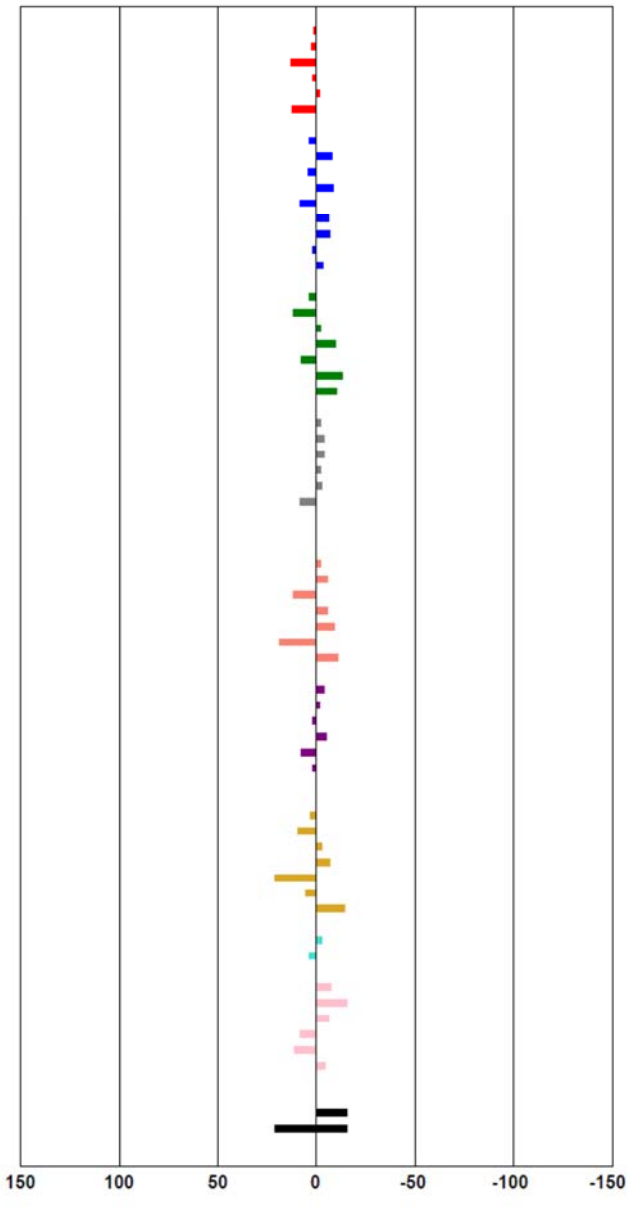
2-ethylhexyl 1-acetyl-5,6-difluoro-1*H*-indazole-3-carboxylate **184**

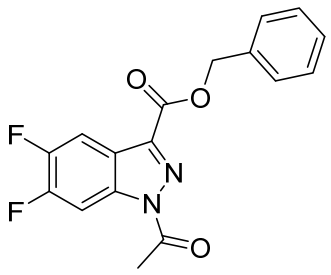
Developmental Therapeutics Program
One Dose Mean Graph

NSC: D-787992 / 1	Conc: 1.00E-5 Molar	Test Date: Nov 09, 2015
Experiment ID: 1511OS03		Report Date: Dec 16, 2015

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	102.09
HL-60(TB)	102.94
K-562	113.48
MOLT-4	102.75
RPMI-8226	98.98
SR	112.83
Non-Small Cell Lung Cancer	
A549/ATCC	104.56
EKVX	92.64
HOP-62	104.65
HOP-92	91.96
NCI-H226	108.77
NCI-H23	94.28
NCI-H322M	93.80
NCI-H460	102.68
NCI-H522	97.36
Colon Cancer	
COLO 205	104.32
HCC-2998	112.63
HCT-116	98.29
HCT-15	90.84
HT29	108.16
KM12	87.73
SW-620	90.55
CNS Cancer	
SF-268	98.76
SF-295	97.08
SF-539	96.71
SNB-19	98.85
SNB-75	98.01
U251	108.98
Melanoma	
LOX IMVI	100.70
MALME-3M	100.90
M14	98.59
MDA-MB-435	95.01
SK-MEL-2	112.29
SK-MEL-28	94.85
SK-MEL-5	91.62
UACC-257	119.38
UACC-62	89.95
Ovarian Cancer	
IGROV1	97.04
OVCAR-3	99.28
OVCAR-4	102.44
OVCAR-5	95.63
OVCAR-8	108.53
NCI/ADR-RES	102.58
SK-OV-3	100.95
Renal Cancer	
786-0	103.73
A498	110.08
ACHN	97.85
CAKI-1	93.75
RXF 393	121.81
TK-10	106.23
UO-31	86.17
Prostate Cancer	
PC-3	97.97
DU-145	104.53
Breast Cancer	
MCF7	93.22
MDA-MB-231/ATCC	85.50
HS 578T	94.29
BT-549	109.19
T-47D	112.09
MDA-MB-468	96.09
Mean	100.63
Delta	15.13
Range	36.31

Mean Growth Percent - Growth Percent





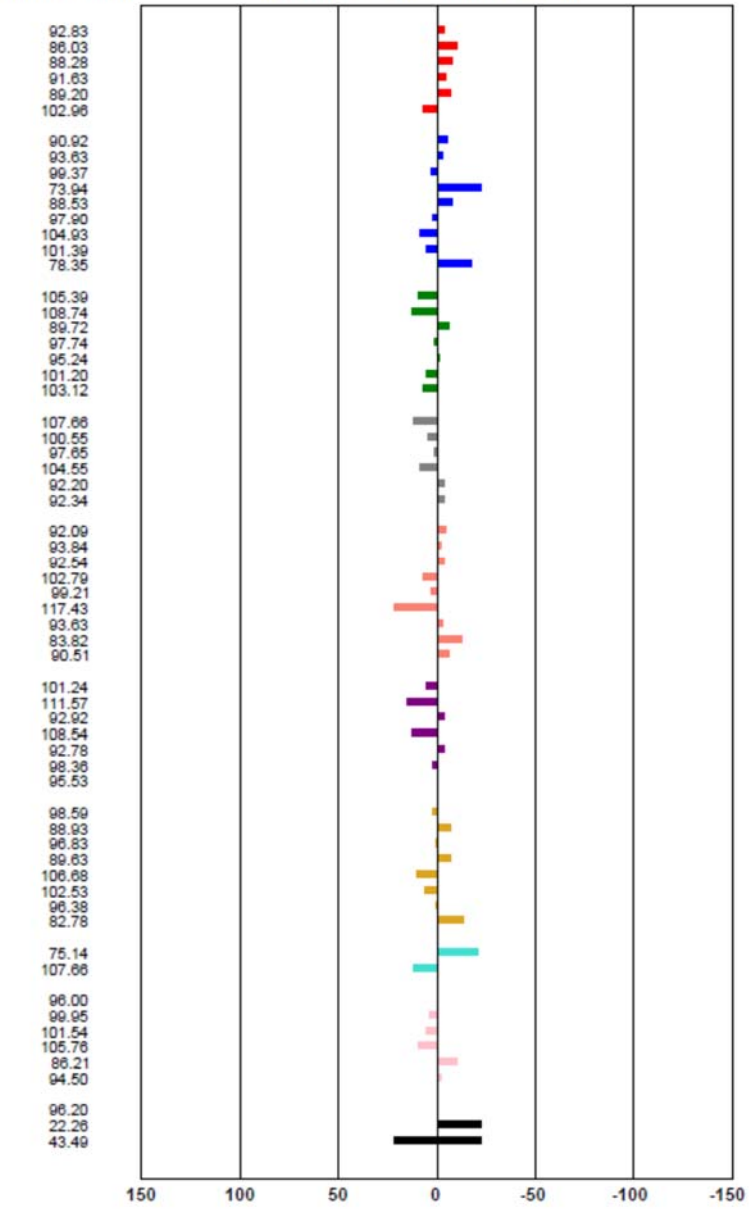
benzyl 1-acetyl-5,6-difluoro-1*H*-indazole-3-carboxylate **181**

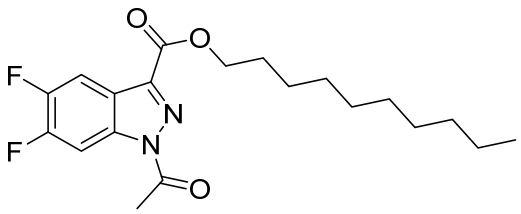
Developmental Therapeutics Program

One Dose Mean Graph

NSC: D-784829 / 1	Conc: 1.00E-5 Molar	Test Date: Jun 15, 2015
Experiment ID: 1506OS04		Report Date: Jul 03, 2015

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	92.83
HL-60(TB)	86.03
K-562	88.28
MOLT-4	91.63
RPMI-8226	89.20
SR	102.96
Non-Small Cell Lung Cancer	
A549/ATCC	90.92
EKVX	93.63
HOP-62	99.37
HOP-92	73.94
NCI-H226	88.53
NCI-H23	97.90
NCI-H322M	104.93
NCI-H460	101.39
NCI-H522	78.35
Colon Cancer	
COLO 205	105.39
HCC-2998	108.74
HCT-116	89.72
HCT-15	97.74
HT29	95.24
KM12	101.20
SW-620	103.12
CNS Cancer	
SF-268	107.66
SF-295	100.55
SF-539	97.65
SNB-19	104.55
SNB-75	92.20
U251	92.34
Melanoma	
LOX IMVI	92.09
MALME-3M	93.84
M14	92.54
MDA-MB-435	102.79
SK-MEL-2	99.21
SK-MEL-28	117.43
SK-MEL-5	93.63
UACC-257	83.82
UACC-62	90.51
Ovarian Cancer	
IGROV1	101.24
OVCAR-3	111.57
OVCAR-4	92.92
OVCAR-5	108.54
OVCAR-8	92.78
NCI/ADR-RES	98.36
SK-OV-3	95.53
Renal Cancer	
786-0	98.59
A498	88.93
ACHN	96.83
CAKI-1	89.63
RXF 393	106.68
SN12C	102.53
TK-10	96.38
UO-31	82.78
Prostate Cancer	
PC-3	75.14
DU-145	107.66
Breast Cancer	
MCF7	96.00
MDA-MB-231/ATCC	99.95
HS 578T	101.54
BT-549	105.76
T-47D	86.21
MDA-MB-468	94.50
Mean	96.20
Delta	22.26
Range	43.49





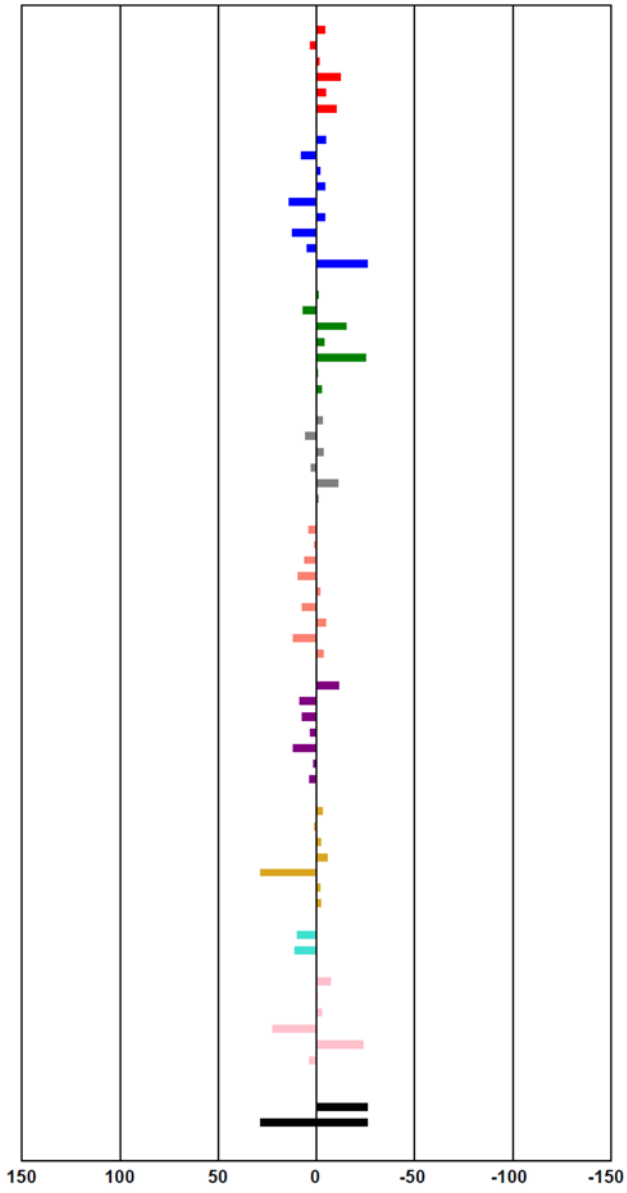
decyl 1-acetyl-5,6-difluoro-1*H*-indazole-3-carboxylate **187**

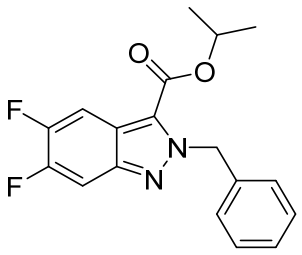
Developmental Therapeutics Program
One Dose Mean Graph

NSC: D-787985 / 1	Conc: 1.00E-5 Molar	Test Date: Nov 09, 2015
Experiment ID: 1511OS03		Report Date: Dec 03, 2015

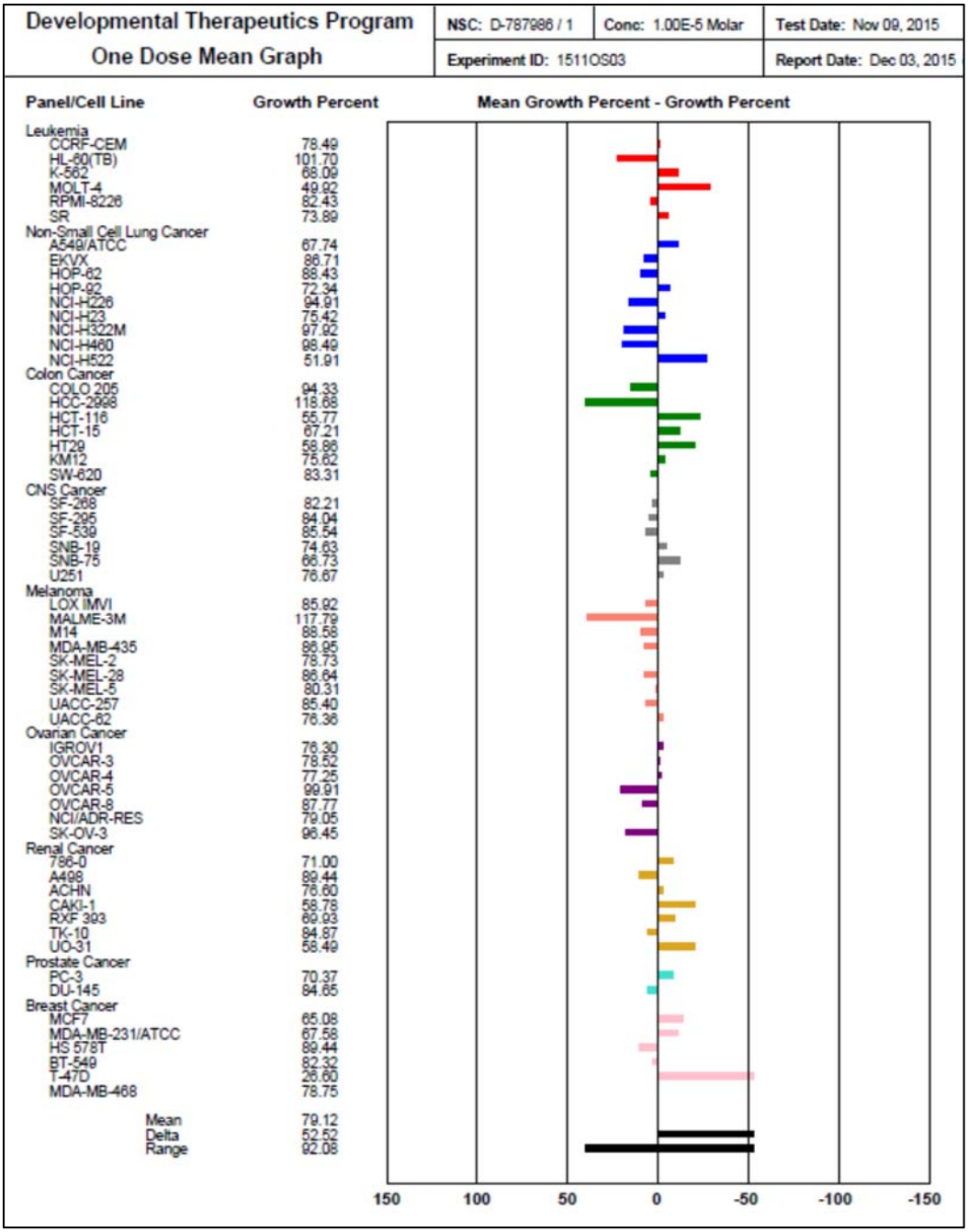
Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	92.94
HL-60(TB)	100.03
K-562	96.10
MOLT-4	85.21
RPMI-8226	92.47
SR	87.07
Non-Small Cell Lung Cancer	
A549/ATCC	92.66
EKVX	104.59
HOP-62	95.38
HOP-92	93.25
NCI-H226	111.08
NCI-H23	93.00
NCI-H322M	109.37
NCI-H460	101.59
NCI-H522	71.60
Colon Cancer	
COLO 205	96.18
HCC-2998	103.95
HCT-116	82.21
HCT-15	93.36
HT29	72.37
KM12	96.83
SW-620	94.62
CNS Cancer	
SF-268	94.18
SF-295	102.75
SF-539	93.69
SNB-19	99.61
SNB-75	86.60
U251	96.28
Melanoma	
LOX IMVI	100.90
MALME-3M	98.22
M14	102.83
MDA-MB-435	106.31
SK-MEL-2	95.62
SK-MEL-28	104.30
SK-MEL-5	92.71
UACC-257	108.72
UACC-62	93.89
Ovarian Cancer	
IGROV1	85.94
OVCAR-3	105.54
OVCAR-4	104.41
OVCAR-5	100.27
OVCAR-8	108.75
NCI/ADR-RES	98.26
SK-OV-3	100.40
Renal Cancer	
786-0	94.18
A498	97.89
ACHN	95.24
CAKI-1	91.95
RXF 393	125.65
TK-10	95.55
UO-31	95.32
Prostate Cancer	
PC-3	106.83
DU-145	107.90
Breast Cancer	
MCF7	90.20
MDA-MB-231/ATCC	96.66
HS 578T	94.72
BT-549	119.05
T-47D	73.62
MDA-MB-468	100.68
Mean	97.14
Delta	25.54
Range	54.05

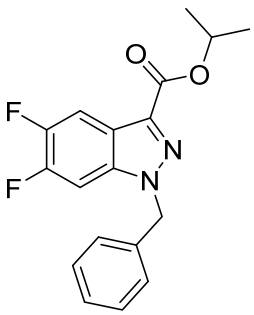
Mean Growth Percent - Growth Percent





isopropyl 2-benzyl-5,6-difluoro-2*H*-indazole-3-carboxylate **267**



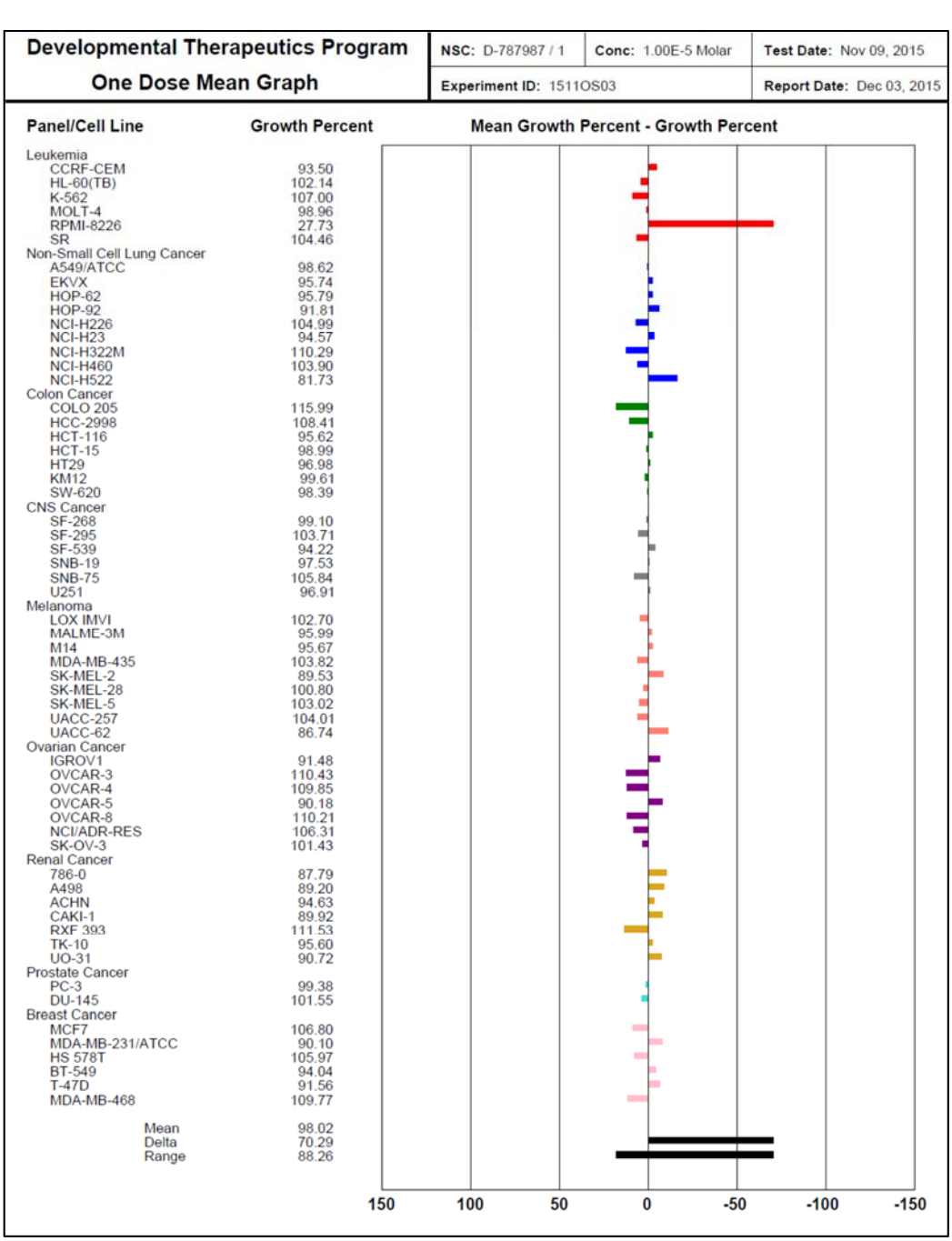


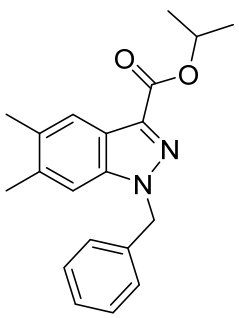
isopropyl 1-benzyl-5,6-difluoro-1*H*-indazole-3-carboxylate **266**

Developmental Therapeutics Program
One Dose Mean Graph

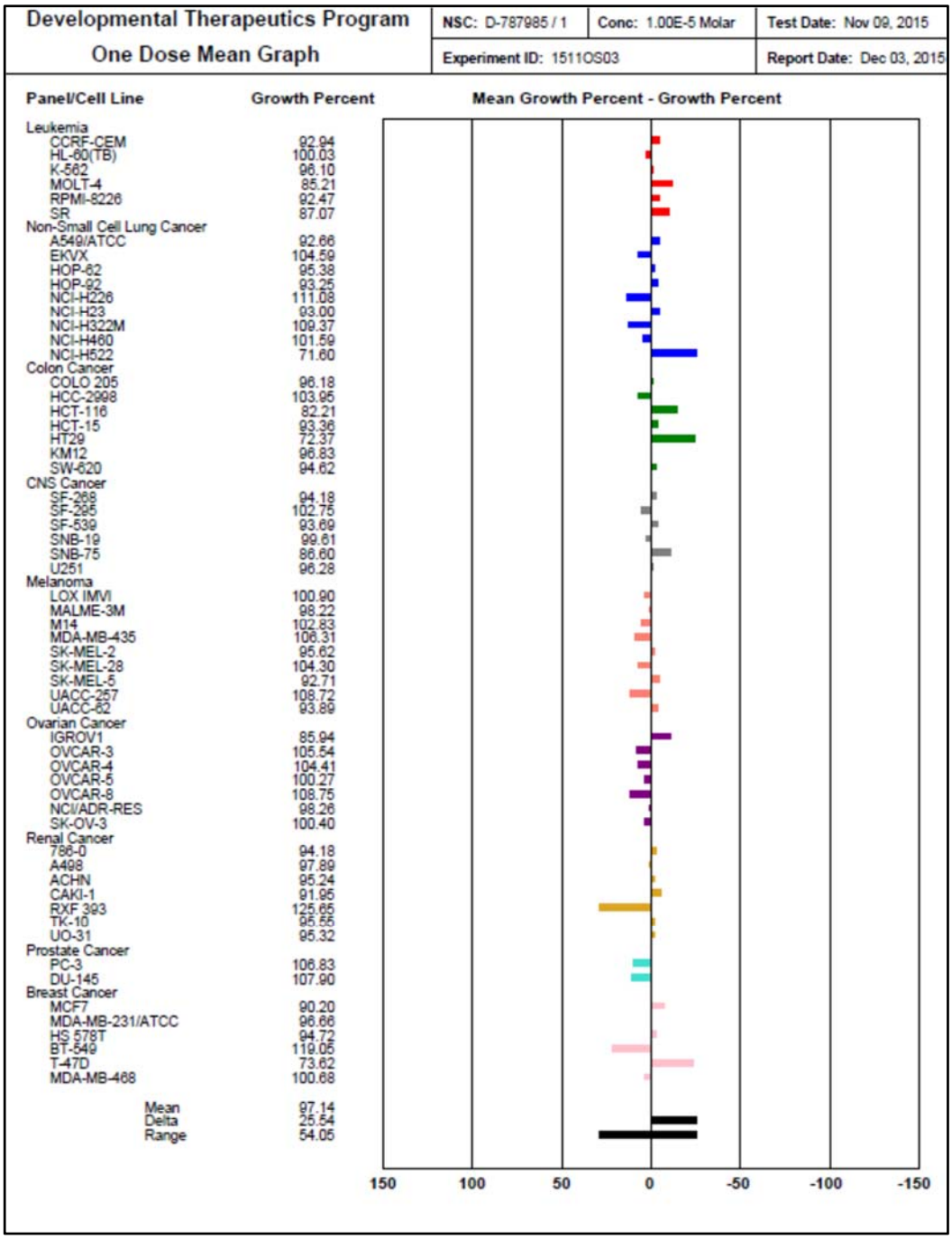
NSC: D-787987 / 1	Conc: 1.00E-5 Molar	Test Date: Nov 09, 2015
Experiment ID: 1511OS03		Report Date: Dec 03, 2015

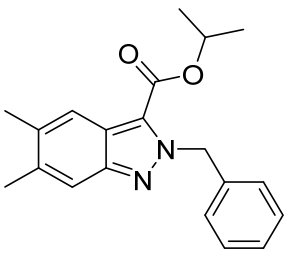
Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	93.50
HL-60(TB)	102.14
K-562	107.00
MOLT-4	98.96
RPMI-8226	27.73
SR	104.46
Non-Small Cell Lung Cancer	
A549/ATCC	98.62
EKVX	95.74
HOP-62	95.79
HOP-92	91.81
NCI-H226	104.99
NCI-H23	94.57
NCI-H322M	110.29
NCI-H460	103.90
NCI-H522	81.73
Colon Cancer	
COLO 205	115.99
HCC-2998	108.41
HCT-116	95.62
HCT-15	98.99
HT29	96.98
KM12	99.61
SW-620	98.39
CNS Cancer	
SF-268	99.10
SF-295	103.71
SF-539	94.22
SNB-19	97.53
SNB-75	105.84
U251	96.91
Melanoma	
LOX IMVI	102.70
MALME-3M	95.99
M14	95.67
MDA-MB-435	103.82
SK-MEL-2	89.53
SK-MEL-28	100.80
SK-MEL-5	103.02
UACC-257	104.01
UACC-62	86.74
Ovarian Cancer	
IGROV1	91.48
OVCAR-3	110.43
OVCAR-4	109.85
OVCAR-5	90.18
OVCAR-8	110.21
NCI/ADR-RES	106.31
SK-OV-3	101.43
Renal Cancer	
786-0	87.79
A498	89.20
ACHN	94.63
CAKI-1	89.92
RXF 393	111.53
TK-10	95.60
UO-31	90.72
Prostate Cancer	
PC-3	99.38
DU-145	101.55
Breast Cancer	
MCF7	106.80
MDA-MB-231/ATCC	90.10
HS 578T	105.97
BT-549	94.04
T-47D	91.56
MDA-MB-468	109.77
Mean	98.02
Delta	70.29
Range	88.26





isopropyl 1-benzyl-5,6-dimethyl-1*H*-indazole-3-carboxylate **264**





isopropyl 2-benzyl-5,6-dimethyl-2*H*-indazole-3-carboxylate **265**