Asymmetric Synthesis and Histamine Receptor Activity of New H_1-Receptor Agonists and Conformationally Restricted H_3-Receptor Antagonists

Dissertation

zur Erlangung des Doktorgrades der Naturwissenschaften

Dr. rer. nat.

an der Fakultät für Chemie und Pharmazie

der Universität Regensburg

vorgelegt von

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Borgaon (Indien)

Regensburg 2006

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Promotionsgesuch eingereicht am:	11. Mai 2006	
Promotionskolloquium am:	30. Mai 2006	
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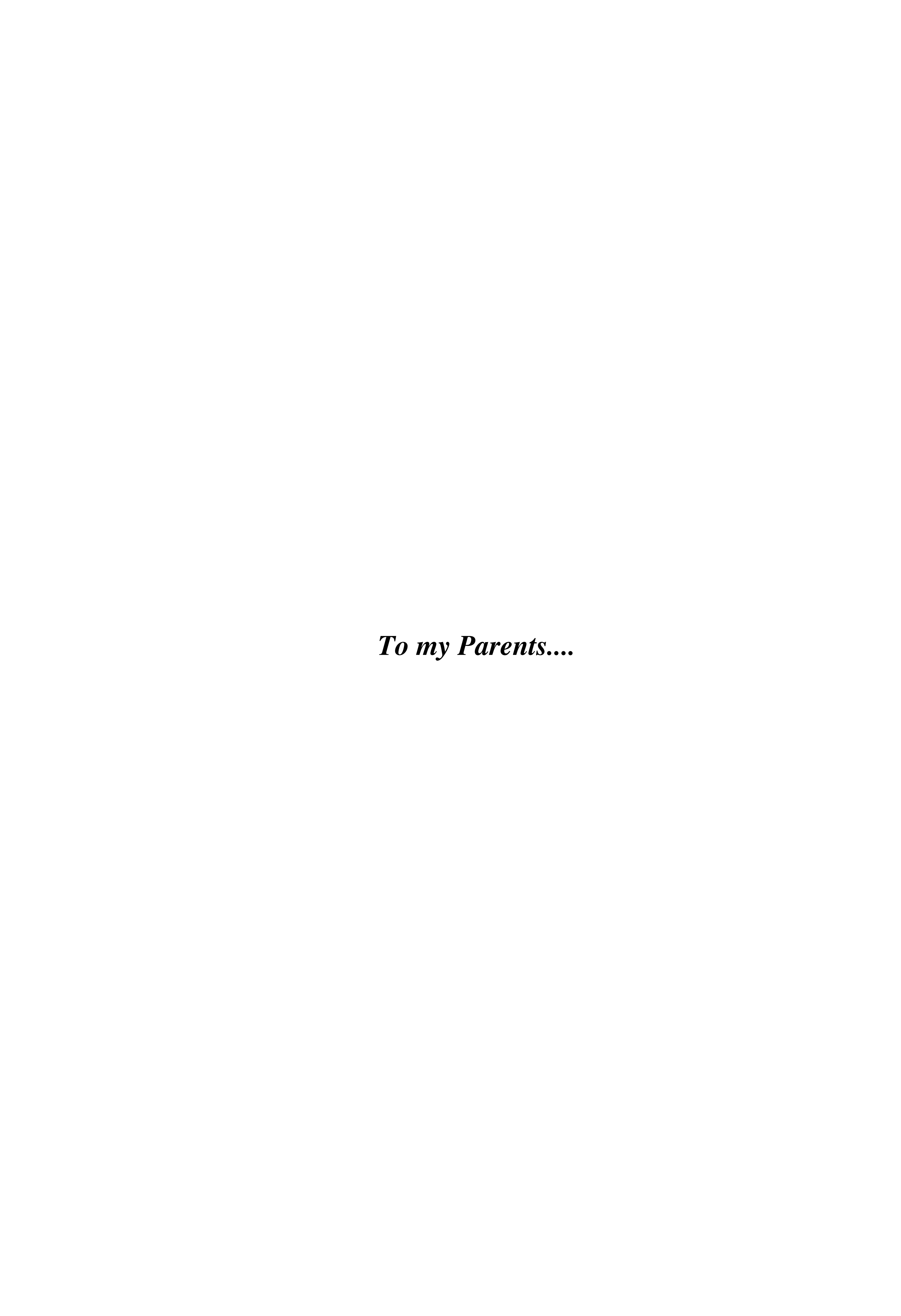
Die vorliegende Arbeit wurde in der Zeit von Oktober 2002 bis Mai 2006 am Institut für Organische Chemie der Universität Regensburg unter der Leitung von Prof. Dr. O. Reiser angefertigt. Die pharmakologischen Testreihen wurden von Herrn Prof. Dr. Sigurd Elz am Institut für Pharmazeutische/Medizinische Chemie I der Universität Regensburg durchgeführt.

Herrn Prof. Dr. Oliver Reiser möchte ich herzlich für die Überlassung des äußerst interessanten Themas, die anregenden Diskussionen und seine stete Unterstützung während der Durchführung dieser Arbeit danken.



To my Parents....

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Abbreviations

abs.	Absolute
Ac	Acetyl
ACN	Acetonitrile
Ar	Aromatic
Bn	Benzyl
Boc	*t*- Butyloxycarbonyl
Bu	Butyl
BuLi	Butyl lithium
Cbz	Carbobenzyloxy
m-CPBA	meta-Chloroperbenzioc acid
DIBAL-H	Diisobutylaluminium Hydride
DMAP	Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxyde
ee	Enantiomeric Excess
Et	Ethyl
EI	Electrom Impact (MS)
EtOH	Ethanol
eqv.	Equivalents
h	hours
Imi	Imidazole
IPA	Isopronanol
IR	Infrared Spectroscopy
LAH	Lithium Aluminium Hydride
LDA	Lithium Diisopropylamide
Me	Methyl
MEM	β-Methoxyethoxymethyl
MeOH	Methanol
min.	Minutes
MS	Mass Spectroscopy
NaH	Sodium Hydride
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
PG	Protecting Group
^{i}Pr	Isopropyl
Ph	Phenyl
ppm	Parts Per Milion
Py	Pyridine
R_f	Retention Factior
RT	Room Temperature
sat.	Saturated
TBAF	Tetra-*n*-butylammonium fluoride
TBDMS	t-Butyldimethylsilyl
TEA	Triethylamine
tert	Tertary
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TFA	Trifluoro acetic acid
TMS	Tetramethylsilane
UV	Ultraviolet

Amino Acids

Amino acids	One-letter code	Three-letter code
Alanine	A	Ala
Arginine	R	Arg
Aspargine	N	Asn
Aspartic acid	D	Asp
Cysteine	C	Cys
Glutamine	Q	Gln
Glutamic acid	E	Glu
Glycine	G	Gly
Histidine	H	His
Isoleucine	I	Ile
Leucine	L	Leu
Lysine	K	Lys
Methionine	M	Met
Phenylalanine	F	Phe
Proline	P	Pro
Serine	S	Ser
Threonine	T	Thr
Tryptophan	W	Trp
Tyrosine	Y	Tyr
Valine	V	Val

1. Histamine and its receptors

1.1 Histamine

Histamine[1] (2-(1H-imidazol-4-yl)ethanamine), is a biogenic amine formed from L-histidine by the enzyme called histidine decarboxylase or an ubiquitous L-amino acid decarboxylase. Histamine is present in many plants and found in nearly all animal tissues where it was detected in different cell types including mast cells, basophils, platelets, endothelial and neuronal cells.[2] Highest concentration of histamine is found in lungs, skin, and the gastrointestinal tract. Histamine plays a role as chemical messenger and transfers signals from one cell to another. As such histamine is also able to induce numerous physiological and pathophysiological effects like contraction of smooth muscle, stimulation of hormone release, modulation of immune responses, gastric acid secretion, induction of sleep and cognitive processes.

Figure 1.1 Tautomeric forms of histamine

Histamine exists in two tautomeric forms, termed N^{τ}H and N^{π}H (Fig. 1.1). The ratio between the tautomers, N^{τ}H and N^{π}H is approximately 4:1 in an aqueous environment. Histamine is basic and the pK_a of the α-amino group and the imidazole moiety is 9.7 and 5.9 respectively. Therefore histamine can exist as a dication whereby stabilizing protonated moieties through the delocalization of the positive charge. At physiological pH only the primary amino group is protonated.

1.2 Metabolism of histamine

The histamine N-methyltransferase (*HNMT*) plays an important role in metabolism of histamine within the human airways and gut. It is the only enzyme responsible for the termination of neurotransmitter actions.[3] The *HNMT* inactivates histamine by transferring a methyl group from S-adenosyl-L-methionine to the imidazole ring. Inactive N^{τ}-methylhistamine is excreted in urine or can be further oxidized by diamine oxidase (*DAO*) or

monoamine oxidase (*MAO*) into N^{τ}-methyl-imidazole-aldehyde, which can be further oxidized into its corresponding acid (Fig. 1.2). The histamine metabolism pathway starting with *DAO* is only relevant in Peripheral Nervous System (PNS).

CNS PNS

HNMT *DAO*

N^{τ}-Methylhistamine

2-(1*H*-imidazol-4-yl)acetaldehyde

DAO/MAO

Aldehyde Dehydrogenase

2-(1-methyl-1*H*-imidazol-4-yl)acetaldehyde

2-(1*H*-imidazol-4-yl)acetic acid

Aldehyde Dehydrogenase

Ribosyl Transferase

2-(1-methyl-1*H*-imidazol-4-yl)acetic acid

N^{τ}-ribosyl-imidazoleacetic acid

Figure 1.2 Metabolism of histamine

1.3 Classification of ligands

Ligands can be classified mainly into agonists, partial agonists, antagonists and inverse agonists based on the biological response they provoke.

Agonists: An agonist is a substance that binds to a receptor and triggers a response in the cell.

Partial agonists: Partial agonists are compounds that have a submaximal tissue response even if they fully occupy the receptor.

Antagonists: A ligand that binds to a receptor without causing activation but impending agonist binding has been termed as antagonist.

Inverse agonists: Inverse agonists are ligands that reduce the constitutive or basal activity.

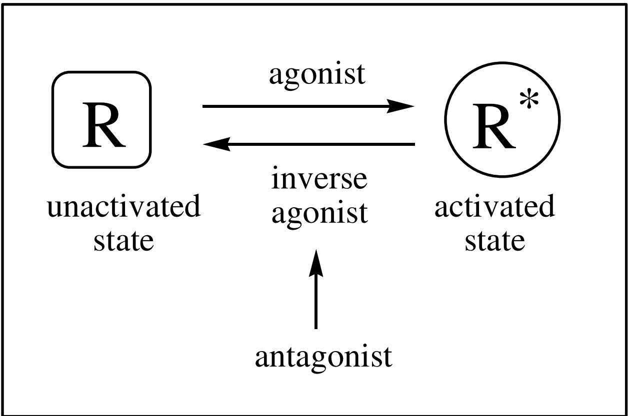


Figure 1.3 Two state receptor activation model of receptors

Figure 1.3 represents the classical two-state receptor model, however currently this model is discussed controversially, as there is evidence for different coexisting receptor conformations.

1.4 Histamine H_1-Receptors

Table 1.1 A short overview on histamine H_1-Receptors (H_1Rs)

Family	G-protein coupled receptors (GPCRs)
Protein sequence	487 aa (human), 486 (rat), 489 (mouse)
Homology to other receptors	hH_2R (40% in TM domains), hH_3R (20%), hH_4R (20%)
Molecular functions	Contraction of smooth muscles in ileum, bronchi and uterus Increase in the permeability of the capillaries Stimulation of hormone release (adrenal medulla) Vasoconstriction via receptors at vascular smooth muscles Vasodilation via NO release from endothelial cells. CNS: regulation of wakefulness.
Potential therapeutic applications	Agonists: Therapeutic applications for agonists have not yet been established, are potential diagnostic tools Antagonists: Play a prominent role in the symptomatic treatment of allergy, motion sickness and vertigo and can also be used as mild sedatives.
Isoforms	No isoforms known so far
Species differences	Marked differences in the potency of antagonists for species homologues of the H_1R
Signal transduction	The primary mechanism by which H_1 receptors produce functional responses is via $G_{q/11}$-mediated activation of phospholipase C (PLC) and Ca^{2+} mobilization

Histamine exerts its pharmacological effects via four different receptor subtypes H_1-H_4.[4,5] Dale and Laidlaw in 1910 observed the stimulation of the smooth muscles and vasodilation by histamine.[6] Later, Ash and Schild in 1966 identified this receptor and named as histamine H_1R.[7] The H_1Rs, located on chromosome 3 of human genome are coupled via $G_{q/11}$ proteins. In the CNS, H_1Rs are expressed in the thalamus, hippocampus, cortex, amygdala, and the basal forebrain. Outside the CNS, the H_1Rs are widely expressed in tissue such as ileum, smooth muscles of airways and vasculature, and heart. A short overview on histamine H_1R is given in Table 1.1, for detailed information see chapter 2.1.

1.5 Histamine H_2-Receptor

Histamine H_2-Receptor (H_2R)[8] was pharmacologically characterized by Black *et al.* in 1972. H_2R is widely distributed in the brain; highest densities are found in basal ganglia, hippocampus, amygdala and cerebral cortex.[9] It is also found with lower densities in cerebellum and hypothalamus.[9] In the periphery H_2R was found in gastric cells, cardiac tissue, airway, uterine and the vascular smooth muscle.[4] The important features of histamine H_2R are given in Table 1.2.

Table 1.2 A short overview on histamine H_2-Receptors (H_2Rs)

Family	G-protein coupled receptors (GPCRs)
Protein sequence	359 aa (human, mouse) 358 (rat)
Homology to other receptors	hH_1R (41% in TM domains), hH_3R (22%), hH_4R (20%)
Molecular functions	Stimulation of gastric acid secretion Positive inotropic and chronotropic effects on the heart Vasodilation Stimulation of adenylyl cyclase activity in guinea-pig hippocampal membranes Cardiac stimulation (increase of rate and output of heart action)
Potential therapeutic applications	Agonists: Congestive heart failure Antagonist: Treatment of gastric and duodenal ulcer
Isoforms	No isoforms known so far
Species differences	Significant differences in the potency of antagonists for species homologues of the H_1R
Signal transduction	Coupled positively to adenylyl cyclase via Gs, leading to the formation of cAMP which is responsible for other effects like activation of H^+/K^+ -ATPase in the cytosole of the parietal cell resulting in the stimulation of gastric acid secretion.

1.6 Histamine H_3-Receptor s

The discovery of a third receptor subtype came in 1983 when Arrang *et al.* found that the histamine inhibits its own release from the depolarized slices of rat cerebral cortex by an action mediated by another receptor subtype which is pharmacologically different from the H_1 and H_2 receptors. This novel receptor was named H_3R,[10] subsequently characterized[11] in 1987 and recently cloned[12] in 1999 by Lovenberg *et al.* A short overview on histamine H_3-Receptor (H_3R) is given in Table 1.3, detailed information is given in chapter 3.1.

Table 1.3 A short overview on histamine H_3-Receptors (H_3Rs)

Family	G-protein coupled receptors (GPCRs)
Protein sequence	445 aa (human H_3R)
Homology to other receptors	hH_1R (20%), hH_2R (22%), hH_4R (37%, 58% in TM-domains) and other biogenic aminergic receptors (20-27%)
Gene organization	Most likely three exons and two introns.
Histamine affinity	p*Ki* = 7.8 (human H_3R)
Molecular functions	Autoreceptor: Inhibition of histamine synthesis Heteroreceptor: In CNS, modulation of release of dopamine, noradrenaline, serotonin, GABA, glutamate In peripheral nervous system, acetylcholine, neuropeptides.
Potential therapeutic applications	Agonists: Insomnia, antinociceptive, myocardial ischaemic arrhythmias (via modulation of noradrenaline liberation) Antagonists: In the treatment of obesity, narcolepsy, attention deficient hyperactivity disorder (ADHD), schizophrenia, Alzheimer's disease, and nasal congestion (in combination with H_1R antagonists).
Splice variants	More than 20 isoforms known in four different parts of receptor gene. With a shortened amino terminal end. With a partial deletion of TM2 and E_1loop. With a variable length of E_3 loop and finally With an elongated C-terminal end.
Species differences	More than 92% sequence conservation in human, mouse, rat, guinea-pig and monkey H_3Rs. Comparable profiles for agonists but different pharmacological profile for inverse agonists/antagonists.
Signal transduction	Coupling to $G_{i/o}$ and inhibition of adenylyl cyclase → cAMP ↓ Other probable pathways include MAP kinase via βγ subunits, modulation of Ca^{2+} levels (agonists → Ca^{2+} ↓ → neurotransmitter release↓)

1.7 Histamine H_4-Receptor s

The histamine H_4-Receptor (H_4R)[13] is less widely expressed than other histamine receptors. In CNS, H_4R is found mainly in the cerebellum and at much lower levels in the hippocampus.[14] Outside the CNS H_4R is found in medullary and peripheral hematopoetic cells such as eosinophils, neutrophils, and $CD4^+$ T-cells, suggesting an important role for the H_4R in the immune system. A short overview on histamine H_4R is given in Table 1.4.

Table 1.4 A short overview on histamine H_4 receptor (H_4R)

Family	G-protein coupled receptors (GPCRs)
Protein sequence	390 amino acids (human H_4R)
Homology to other receptors	hH_1R (20%, 26% in TM-domains), hH_2R (20%, 27% in TM-domains), hH_3R (37%, 58% in TM-domains)
Histamine affinity	p*Ki* = 7.8 - 8.4
Gene organization	Contains two introns and three exons.
Molecular functions	Involved in various brain functions. Chemotaxis of eosinophils of mast cells to histamine; control of IL-16 release from $CD8^+$ T-cells It can play a role in inflammatory response.
Potential therapeutic applications	Antiinflammatory, allergic rhinitis (via mast cells), asthma (via mast cells, eosinophils and T-cells) atopic dermatitis. Autoimmune diseases like rheumatoid arthritis, multiple sclerosis, type I diabetes and systemic lupus erythematous (via dendritic or T-cells.)
Splice variants	No splice variants known so far.
Species differences	Has been cloned from different species including, rat, mouse, pig and guinea-pig and share only 65-72% homology Similar expression patterns but pharmacological profiles and signal transduction responses are dissimilar.
Signal transduction	Coupling to $G_{i/o}$ and inhibition of adenylyl cyclase $\rightarrow$ cAMP $\downarrow$ In mast cells probably linked to PLC $\rightarrow$ release of Ca^{2+} from ER

2. Side-chain modified analogues of histaprodifen: Asymmetric synthesis and histamine H_1-Receptor activity

2.1 Introduction

Histamine[1] is known to exert its pharmacological effects via four different receptor subtypes, H_1-H_4 receptors.[4,15] Dale and Laidlaw described the stimulation of smooth muscles and vasodilation by histamine for the first time in 1910.[6] Later in 1966, Ash and Schild identified the histamine H_1-Receptor (H_1R).[7] The H_1R is widely distributed in different mammalian tissues including brain, smooth muscles from airways, gastrointestinal tract, genitourinary system, the cardiovascular system, adrenal medulla, endothelial cells and lymphocytes.[2] H_1R antagonists have been used in the therapy of many allergic diseases, including urticaria, allergic rhinitis, pollenosis, and bronchial asthma. Nowadays H_1R antagonists play a prominent role in the symptomatic treatment of allergies, motion sickness, and vertigo, and are also used as mild sedatives.[16] On the other hand therapeutic applications for H_1R agonists have not yet been established. There are different reasons responsible for this, mainly that H_1Rs are involved in pathological processes and knowledge of H_1R mediated physiological and pathophysiological functions is still limited, especially in the central nervous system (CNS). Until recently, highly potent and selective H_1R agonists were not available. To review the most promising aspects of receptor activations, the development of potent and selective H_1R agonists is highly demanding.

2.1.1 Molecular architecture of histamine H_1Rs

The histamine H_1R belongs to the super family of G-protein coupled receptors. Identification of H_1R came in 1966 when Ash and Schild[7] found the specific antagonism of some actions of histamine by low concentrations of antihistamine drugs. The human histamine H_1R protein consists of 487 amino acids and is predicted to have seven transmembrane (TM) domains along with a helix VIII (Fig. 2.1.1), which is supposed to be perpendicular to the TM domains. Histamine H_1Rs possess a large third intracellular loop (197 amino acids) and a short carboxyl terminal, which are common characteristics among Ca^{2+}-mobilizing receptors.[17] The genomic cloning of H_1Rs from cattle,[18] rats,[19] guinea-pig[20,21] and human[22] has led to valuable knowledge regarding the pharmacochemistry of the H_1R. Overall, homology among the different H_1Rs is more than 60%. Moreover, in TM domains it is more than 90%. The residue Asp 107 in TM-III is one of the most crucial amino acids for the binding of H_1R agonists and antagonists.[23,24] Other binding sites include Asp 73 in TM-II,

Asp 124 and Arg 125 as cationic and anionic sites, respectively, at the cytoplasmic border of TM-III and the ten amino acid residues Leu 455 to Pro 464 in the seventh TM domain.

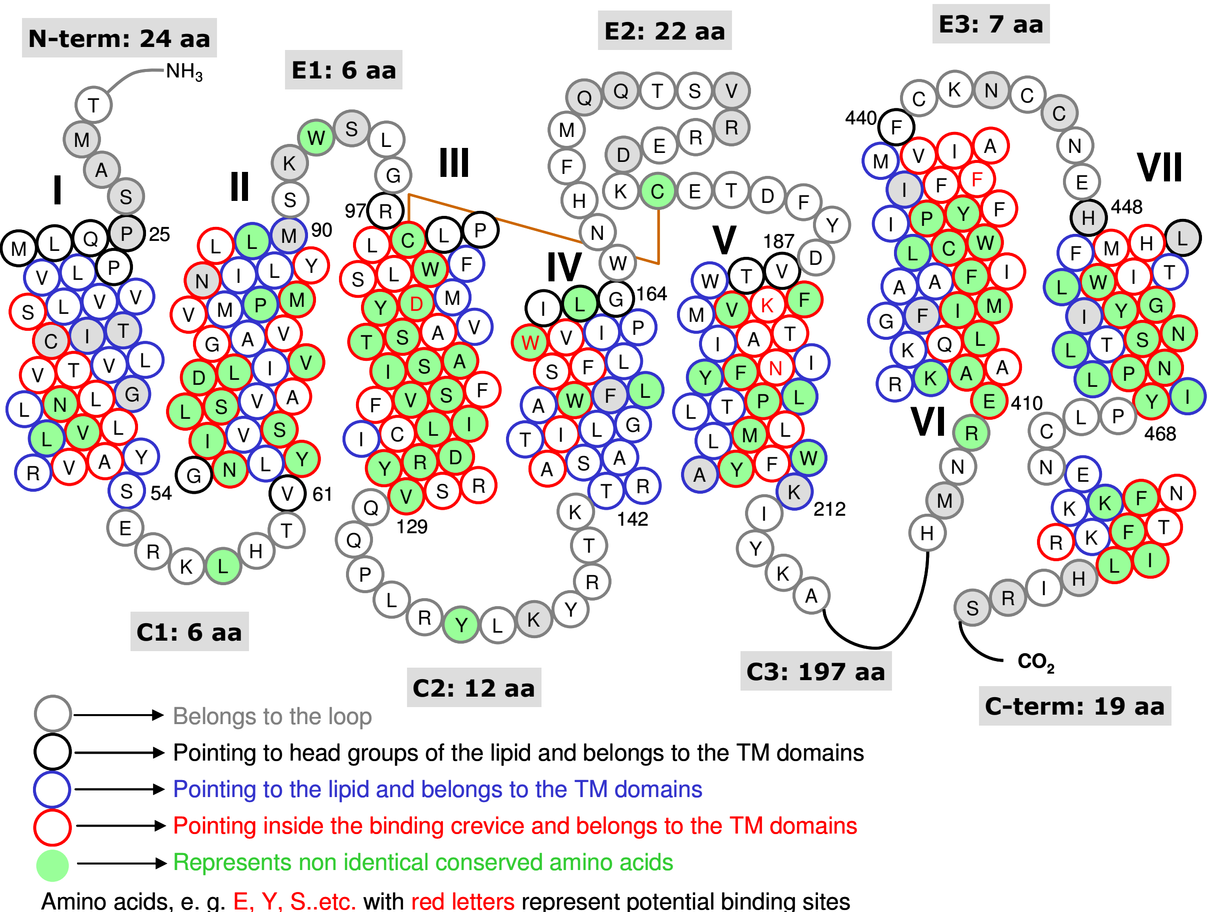


Figure 2.1.1 Snake plot of human histamine H$_1$R protein

Amino acids represented in gray circles belong to the intra and extracellular loop of the receptor protein. Amino acids shown in black bold circles point to the head groups of the lipids and belong to the TM domains. Blue circles represent the amino acids that point to the lipid and belong to the TM domains. Amino acids pointing inside the binding crevice are shown with red circles and also belong to the TM domain. Amino acids with gray background represent the most conserved amino acids. Amino acids designated with red letters represent the potential binding sites.

2.1.2 Signal transduction pathways for histamine H$_1$Rs

The histamine H$_1$Rs are coupled to G-proteins in the region of the second and third intracellular loop (Fig. 2.2.2). On activation with H$_1$R agonists, the receptor subsequently stimulates the connected phospholipase C (PLPC) in the cytoplasmic membrane.[25] The PLPC catalyzes the inositol-phosphate-cycle leading to the formation of inositol 1,4,5-trisphospate

(IP_3) and 1,2-diacylglycerol (DAG).[26] IP_3 interacts with its own receptors and releases Ca^{2+} into the cytosole under participation of ion channels.[27] Free Ca^{2+} ions bind to the calmodulin (CaM) and stimulate the NO synthesis (NOS)[28] leading to the enzymatic nitric oxide production[29] and subsequently to the stimulation of guanylylcyclase (GC) and thus to the formation of cGMP from GTP.[30] Ca^{2+} ions also activate phosphorylase which leads to the glycogenic response. Significantly H_1R stimulation is connected with an influx of extracellular Ca^{2+} ions.[31] The possible mechanisms for this effect are the opening of voltage-dependent Ca^{2+}-chanals (VDC) or receptor-operated Ca^{2+}-channels (ROC).

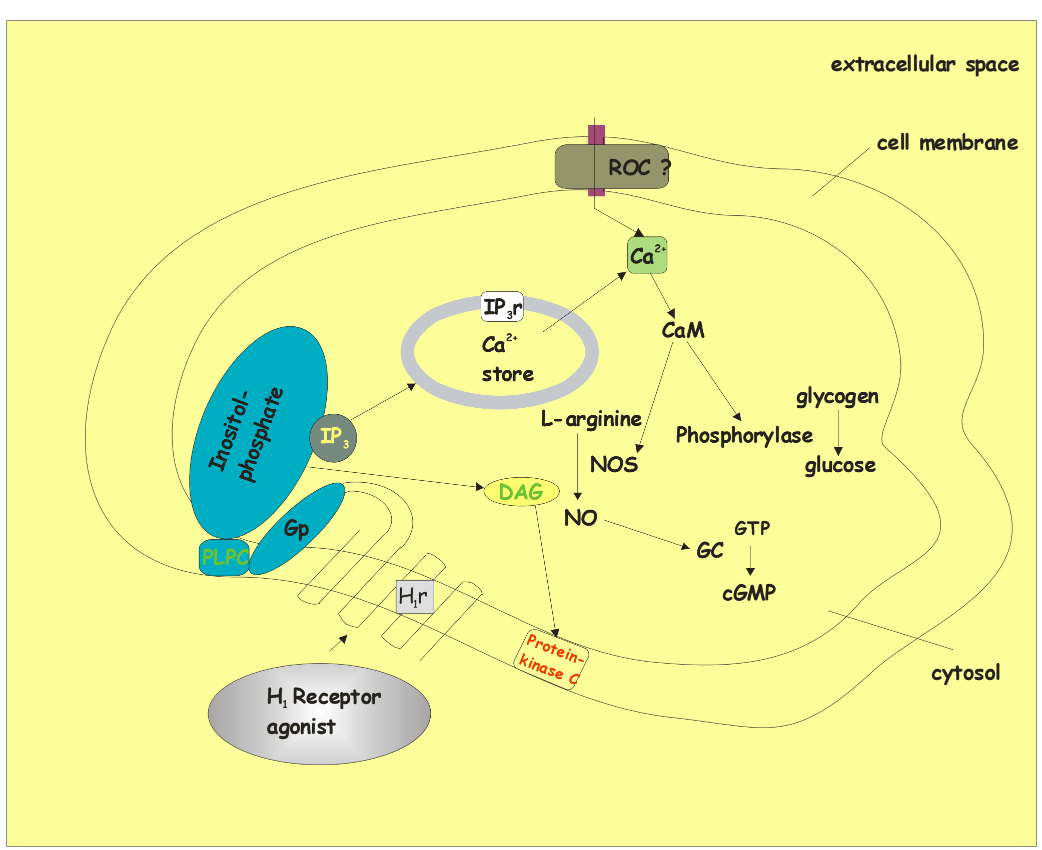


Figure 2.1.2 Signal transduction pathways for histamine H_1R

2.1.3 Histamine H_1-Receptor agonists

Since the identification of histamine H_1R by Ash and Schild,[7] histamine H_1R agonists have gained significant importance for the investigation of H_1R mediated effects, such as neuroregulation of arousal,[32-34] allergy, modulation of cardiovascular parameters,[35,36] and release of endothelium derived relaxing factor.[35,37,38] Studies of these effects have always been hampered by the lack of highly potent and selective histamine H_1R agonists. In contrast, for the histamine H_2 and H_3 receptors, highly potent agonists have been described which

exceed the potency of the endogenous ligand histamine by a factor of 10 to 100.[11,39-41] The use of the endogenous ligand histamine is not helpful because it often requires the concomitant presence of H_2 and H_3 receptor blockers, as histamine is able to activate H_2 and H_3 receptors. The search for the potent and high affinity H_1R agonists has been an arduous task for several decades.[4,42]

2.1.4 Developments in histamine H_1R agonists

Since the first chemical synthesis of histamine[1] by Windaus *et al.* in early 1900's, numerous derivatives were synthesized, possessing the imidazole as a common feature. The year 1941 can be considered as the "year of the birth of H_1R agonists" when Walter *et al.*[43] synthesized a series of pyridylalkanamines and recognized that 2-(pyridine-2-yl)ethanamine (**17**) possesses H_1-histaminergic effects. Since then numerous heterocyclic analogues of histamine have been synthesized and screened for histamine H_1R agonist activity.[44]

Het–CH2CH2–NH2

1 histamine 100%

2 inactive; **3** 0.1%; **4** 0.1%; **5** 0.2%; **6** inactive

7 1.2%; **8** 13%; **9** inactive; **10** inactive

11 0.5%; **12** 11-45%; **13** 0.01%; **14** 2%; **15** 8%; **16** 48%

Figure 2.1.3 Five-membered heterocyclic analogues of histamine

Pharmacological data of some five membered heterocyclic analogues of histamine are summarized in Figure 2.1.3. Among five membered heterocyclic analogues **3**, **4** and **5** were able to stimulate H_1R and showed very weak agonism.[45] Triazole analogues like **7** and **8** were

weak agonists but **9** and **10** were inactive. Heterocyclic analogues **12**, **15** and **16** with two hetero atoms were relatively more potent H_1R agonists.[46] But histamine derivative **2** with ethylamine side chain connected to imidazole nitrogen was found to be inactive.[47]

Figure 2.1.4 Six-membered heterocyclic analogues of histamine

Replacement of the imidazole ring with six membered nitrogen heterocycles did not increase the agonistic activity. Compounds **17** and **21** in which the ethylamine side chain is attached to the ortho position to a heterocyclic nitrogen atom elicit histaminergic response.[46] From the data obtained from five and six membered heterocyclic analogues it can be concluded that replacing the 4-sustituted imidazole by other azole, di- or triazole, isoxazole, or six membered heterocycles, such as azine, diazine or by benzene nuclei reduces H_1R agonistic potency. However, these data also indicate that imidazole nucleus is not compulsory for the H_1R agonistic activity.

2.1.5 Search for selective H_1R agonists

From the historical perspective the work on methylated histamines is very significant.[48,49] Further improvement of the selectivity for one of the three receptor subtypes was possible by methylation (Fig. 2.1.5). Durant *et al.*[49] carried out the methylation of histamine at different positions. Methylation at C2 position of histamine led to 2-methylhistamine (**27**, Fig. 2.1.6), which is a selective H_1R agonist. On the other hand, methylation at the C5 position of histamine led to 5-methylhistamine (**32**),[10] which is a selective agonist for the histamine H_2R. Later, in 1987 Arrang *et al.*[11] found that the α-methylhistamine is a very selective agonists for the histamine H_3R. Looking at this trend, the development of selective agonist for the newly found histamine H_4R could also be achieved[50] by incorporating the methyl group at specific positions of histamine.

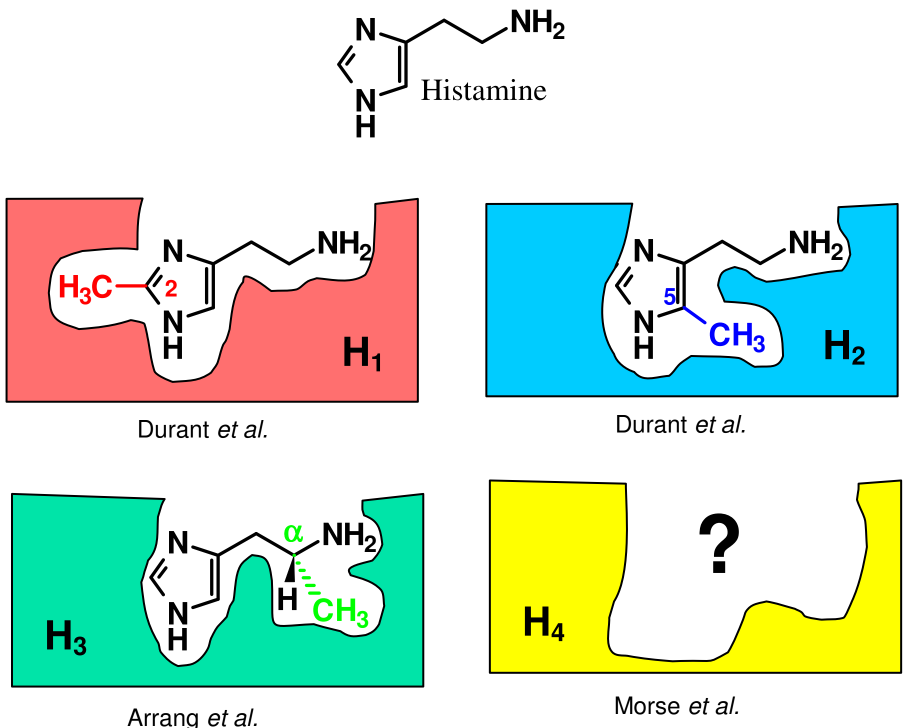


Figure 2.1.5 Methylhistamines, selective keys for single locks

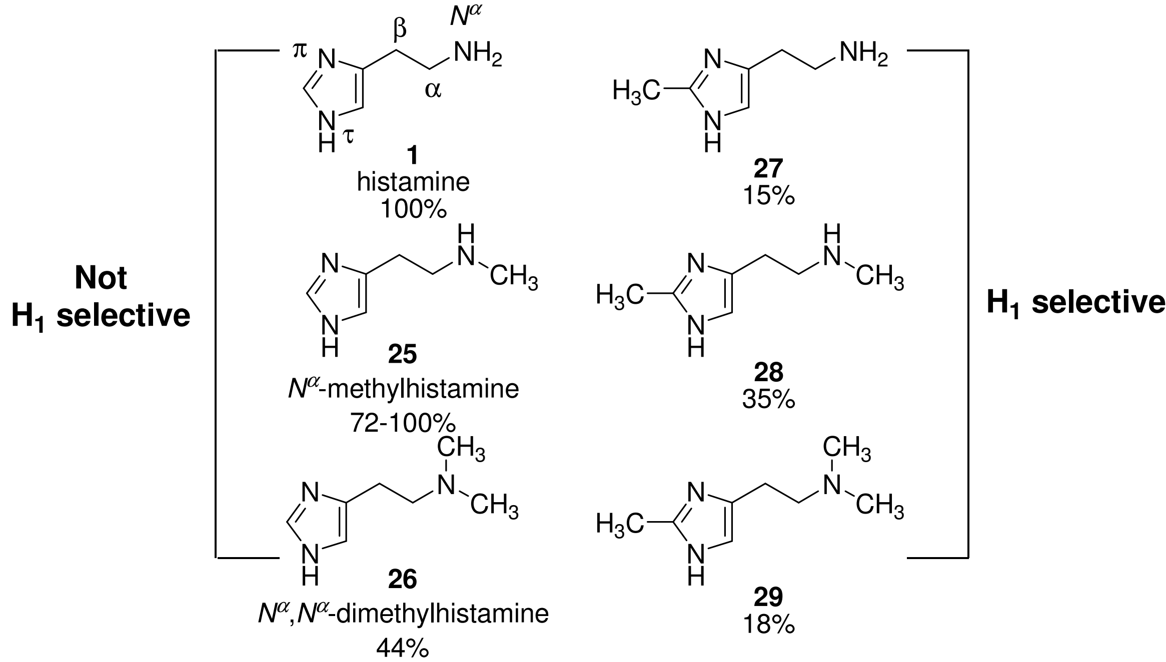


Figure 2.1.6 Methyl substituents in histamine

Incorporation of methyl groups at different positions of the histamine molecule yielded many different analogues[10] and among them 2-substituted analogues were found to be H_1 selective (Fig. 2.1.6). N^{α}-methyl analogue **25** was equipotent with histamine but was not H_1 selective, however compound **28** showed quite good activity and selectivity. Unfortunately, none of the compounds showed more activity than histamine itself. Table 2.1.1 elaborates in details the effect of methyl group on H_1R agonistic activity of histamine.

Table 2.1.1 Effect of methyl group on H_1R agonistic activity of histamine

Comp.	Position of methyl group	Rel. Pot. (E_{max})	Comp.	Position of methyl group	Rel. Pot. (E_{max})
30	π	inactive	**37**	5, N^{α}	0.2-1 %
31	τ	0.5 %	**38**	5, α	0.1 %
32	5	0.2-1 %	**39**	β, β	inactive
33	α	0.4 %	**40**	α, α	-
34	β	0.8 %	**41**	α N^{α}	0.7 %
35	2, 5	0.3 %	**42**	5, N^{α}, N^{α}	0.1 %
36	τ, N^{α}	0.7 %	**43**	N^{α}, N^{α}, N^{α}	1 %

Methylation at C2 and C5 led to the selective agonists for H_1 and H_2 receptors respectively, and these properties remain unchanged in the case of mono- (**28**) and dimethylation (**29**) of the N^{α}-atom of **27**. Methylation at other positions in histamine did not increase H_1-agonistic activity (Table 2.1.1). Moreover ring methylation led to a significant loss of activity in the case of N^{τ}-methylhistamine (**31**), the main metabolite of histamine, and complete loss of activity in the case of N^{π}-methylhistamine (**30**).

2.1.6 Histamine derivatives modified at C2 position

Inspired from the results of 2-methylated histamines, many derivatives having a variety of substituents were synthesized and screened for histamine H_1-agonistic activity (Table 2.1.2). Introduction of polar groups such as -OH (**44**), -SH (**45**) or –NH_2 (**46**) at the C2 position of histamine led to inactive or very weakly active compounds. Efforts were also made towards compounds having longer alkyl chains in C2 position resulting in the synthesis of many compounds such as **49-55**, but only compound **54** with lipophilic substituents showed moderate activity. Compounds with ring systems like cyclopropane (**58**) or cyclopentane (**59**) were found to be also very weak agonists. 2-Phenyl histamine (**61**) was proved to be relatively potent but increasing the distance between the phenyl ring and the imidazole moiety lowers the agonist activity significantly, as compounds **71-73** were weak

antagonists. In spite of the vast structural diversity none of the compounds showed more activity than histamine. Only 2-phenyl histamine (**61**) proved to be relatively potent and was consequently selected for further exploration of structure activity relationships (SARs).

Table 2.1.2 SARs of 2-substituted histamine derivatives

Comp.	R	Rel. Pot. (E_{max})	Comp.	R	Rel. Pot. (E_{max})
1	**H**	**100% (100)**	**59**	—$(CH_2)_2$–	3% (65)
44	OH	inactive (0)	**60**	—$(CH_2)_2$–	pA_2 5.3 (0)
45	SH	inactive (0)	**61**	**Ph-**	**31% (100)**
46	NH_2	2% (100)	**62**	$PhCH_2$-	2.5% (90)
47	**CH_3**	**15% (100)**	**63**	H_3COCH_2-	20% (100)
48	CF_3	7% (100)	**64**	H_3CSCH_2-	<0.4% (60)
49	C_2H_5	7% (100)	**65**	$PhOCH_2$-	1.4% (100)
50	C_3H_7	0.5% (80)	**66**	$PhSCH_2$-	19% (100)
51	C_4H_9	0.5% (100)	**67**	H_3C—SCH_2–	13% (100)
52	$(CH_3)_2CH$-	0.6% (90)	**68**	$PhCH_3CH$-	1.5% (80)
53	H_3C, H_3C —$(CH_2)_2$–	2.4% (100)	**69**	$Ph(CH_2)_2$-	3.2% (90)
54	**H_3C, H_3C, H_3C —$(CH_2)_2$–**	**19% (100)**	**70**	$Ph(CH_2)_3$-	1.2 (44)
55	H_3C, H_3C —$(CH_2)_3$–	0.8% (53)	**71**	$Ph(CH_2)_4$-	pA_2 4.9 (0)
56	H_3C, Ph —$(CH_2)_2$–	7.6% (96)	**72**	$Ph(CH_2)_5$-	pA_2 5.1 (0)
57	C_2H_5, Ph —$(CH_2)_2$–	7.4% (76)	**73**	$Ph(CH_2)_6$-	pA_2 5.6 (0)
58	—CH_2–	5% (98)	**74**	—CH_2–	pA_2 5.7 (10)

2.1.7 SARs of 2-phenyl histamines

From the SARs of 2-phenyl histamine (**61**), it is observed that the majority of the derivatives possess moderate to strong H_1R agonist activity (Table 2.1.3). Substitution in ortho-position seems to be unfavorable for agonistic activity as ortho substituted analogues **75** and **76** lead to a decrease in H_1R agonist activity. Among para-substituted compounds only the fluoro (**89**) and the hydroxyl derivative (**93**) possess more than 10% of potency of histamine. Bulkier groups at para-position lead to a drastic decrease of H_1R agonist activity. Interestingly, meta-substitution of the phenyl ring leads to a remarkable improvement of the histaminergic potency at H_1R. Most of the meta-substituted compounds show full intrinsic activity (E_{max}) with moderate to strong agonistic activity. Independent of the electronical features, the substituents in meta-position are well tolerated. The compounds with high agonist potency are **77-81**. Among halogenated derivatives, the bromo compound (**79**) is the most potent H_1R agonist. Compound **81** with trifluoromethyl substitution at meta position was found to be the most potent H_1R agonist in this series.

Table 2.1.3 SARs of 2-phenyl histamine derivatives

Comp.	R	Rel. Pot. (E_{max})	Comp.	R	Rel. Pot. (E_{max})
61	H	31% (100)	**84**	3-OC_2H_5	1%(70)
75	2-Cl	2% (90)	**85**	3-OCF_3	54%(100)
76	2-CF_3	1% (30)	**86**	3-OH	6%(100)
77	3-F	85% (100)	**87**	3-NH_2	7% (100)
78	3-Cl	96% (100)	**88**	3-NO_2	40% (100)
79	**3-Br**	**112% (100)**	**89**	4-F	14% (100)
80	3-I	96% (100)	**90**	4-Cl	0.5% (100)
81	**3-CF_3**	**128% (100)**	**91**	4-CF_3	0.7% (100)
82	3-CH_3	15% (100)	**92**	2-CH_3	0.4% (100)
83	3-OCH_3	42%(100)	**93**	2-OH	16% (100)

Further studies of the most potent 2-phenyl histamine derivative **81** was carried out with different alkyl groups on the primary amine (Table 2.1.4). Mono-methylation of **81** produced compound **94** with even better potency than the parent compound. Using bigger

alkyl groups led to the compounds **96** and **97** with decrease in the agonistic as well as intrinsic activity. Di-methylated analogue **95** was found to be equipotent with histamine.

Table 2.1.4 Effect of N^{α}-substitution on H_1R agonistic potency

Comp.	R^1	R^2	Rel. Pot. (E_{max})
81	H	H	128% (100)
94	**H**	**CH_3**	**174% (97)**
95	CH_3	CH_3	95% (88)
96	H	C_2H_5	30% (63)
97	H		28% (36)

Table 2.1.5 Effect of heterocyclic moieties at C2 position on H_1R agonistic potency

Comp.	Heterocycle	Rel. Pot. (E_{max})	Comp.	Heterocycle	Rel. Pot. (E_{max})
98		47% (100)	**103**		1% (78)
99		14% (93)	**104**		11% (100)
100		46% (100)	**105**		9% (85)
101		**66% (100)**	**106**		**70% (100)**
102		26% (100)			

2.1.8 Effect of heterocyclic moieties at C2 position on H_1R agonistic potency

Studies were also carried out involving different heterocyclic moieties at C2 position of histamine (Table 2.1.5). With five membered heterocycles, such as furan, pyrrole or thiophen, only weak to moderate H_1R agonistic activity was observed. Even using the pyridine heterocycle attached at ortho, meta or para position did not led to the good activity. Only the compound with a bromo substituent (**106**) on the pyridine ring showed moderate activity.

2.1.9 The discovery of histaprodifens

Table 2.1.6 Effect of lipophilic moieties at C2 position on H_1R agonistic potency

N $(CH_2)_X$—NH_2
R—
N
H

Comp.	R	n	x	Rel. Pot. (E_{max})
107	$(CH_2)_n$—	0	2	8% (28)
108		1	2	0.5% (50)
109		**2**	**2**	**111% (100)**
110		3	2	pA_2 5.9 (2)
111		4	2	pA_2 6.2 (0)
112		4	3	pA_2 4.5 (0)
113	$(CH_2)_n$—	1	2	pA_2 4.5 (0)
114		2	2	8% (26)
115	$n(H_2C)$ $(CH_2)_2$—	1	2	pA_2 5.9 (0)
116		2	2	pA_2 6.2 (0)
117	N—$(CH_2)_2$—	-	2	2.5% (34)

The discovery of histaprodifen[51] came very recently while attempting to get more potent and selective histamine H_1R agonists. The design of histaprodifen had its origin in the idea to attach a hydrophobic moiety at the C2 position of histamine. Moreover a diphenylalkyl substituent is a common feature of therapeutically used high affinity H_1R antagonists such as diphenydramine, oxatomide, cetirizine, and fexofenadine. It has been thought that the high affinity might be provided by the two phenyl rings and efficacy by the histamine moiety.

2.1.10 SAR of histaprodifen analogues

Attachment of large lipophilic substituents at the 2-position of the imidazole ring of histamine was investigated (Table 2.1.6). The attachment of a diphenylmethyl or a diphenylethyl group as in **107** and **108** resulted in weak partial agonism of low efficacy. Compounds such as **110** and **111** with increased distance between the diphenyl and imidazole moiety led to the low affinity antagonists. Moreover, increasing the distance between the imidazole moiety and the basic amino group also led to an antagonist with low affinity (**112**). In contrast, using a diphenylpropyl substituent yielded a potent H_1R agonist, histaprodifen (**109**). Histaprodifen was found to be more potent than histamine and behaved as a full agonist in guinea-pig ileum tissues. Efforts to increase the potency by increasing the distance between the two phenyl moieties were unsuccessful as it led to compounds with partial agonism (**114**) or weak antagonism (**113**). Introducing rigidity in the diphenyl part did not help as compounds **115** and **116** were found to be weak antagonists. Compound **117** with the nitrogen linker to the diphenyl group was also found to be an agonist with weak intrinsic activity. From these data it can be concluded that the diphenylpropyl moiety with ethylamine side chains is optimal for the H_1R agonistic potency.

Like in 2-phenyl histamine (**62**), histaprodifen (**109**) was chosen for further SARs studies, and it was of special interest to see the effect of halogen substituents on the phenyl moieties along with N^{α}-methyl substitution in the ethylamine side chain. Many compounds with different substituents on the phenyl rings were synthesized along with heterocyclic analogues with five and six membered rings and screened for histamine H_1R agonistic activity. Table 2.1.7 explains the detailed SARs of these classes of compounds.

Unlike the trend observed for 2-phenylhistamines, substitution of one of the phenyl ring with halogens did not improve agonistic activity, and in some cases it dropped drastically. Trifluoromethyl substitution had produced the most potent agonists **81** and **94** in the 2-phenylhistamine series but applying the same strategy in **109** was not successful as it yielded the compound **129** with very weak agonistic activity. Changing one of the phenyl

rings by heterocycles also did not improve the activity; only compound **133** with a 2-thienyl heterocycle showed moderate activity and was a full agonist. In contrast, N^{α}-methyl substitution led to the methylhistaprodifen (**118**) with higher potency. Moreover, the di-methylated analogue **119** was also found to be potent. 3-Fluoro substitution of methylhistaprodifen led to the most potent analogue **122** which exceeded the potency of the endogenous ligand histamine by a factor of 5.

Table 2.1.7 SARs of histaprodifen analogues

Comp.	X	R	R^1	R^2	Rel. Pot. (E_{max})
109	**Ph**	**H**	**H**	**H**	**111% (100)**
118	**Ph**	**H**	**H**	**CH_3**	**343% (100)**
119	**Ph**	**H**	**CH_3**	**CH_3**	**242% (100)**
120	Ph	2-F	H	H	9% (86)
121	Ph	3-F	H	H	92% (98)
122	**Ph**	**3-F**	**H**	**CH_3**	**522% (100)**
123	Ph	4-F	H	H	43% (85)
124	Ph	2-Cl	H	H	30% (89)
125	Ph	3-Cl	H	H	89% (93)
126	Ph	4-Cl	H	H	10% (58)
127	Ph	3-Br	H	H	52% (87)
128	Ph	3-CH_3	H	H	20% (88)
129	Ph	3-CF_3	H	H	4% (62)
130	2-Pyridyl	H	H	H	8% (89)
131	3-Pyridyl	H	H	H	18% (100)
132	4-Pyridyl	H	H	H	5% (77)
133	2-Thienyl	H	H	H	63% (100)
134	3-Thienyl	H	H	H	51% (97)

2.1.11 Molecular dynamic simulation of histaprodifens

Histaprodifens possess high agonist activity and enhanced receptor affinity compared with histamine. The common feature of these compounds is a space filling substituent in the C2 position of imidazole ring. For a better understanding of SARs, interaction of **109** within the TM domains of the human histamine H_1R were studied by Elz *et al.* using molecular dynamic (MD) simulations. The complex of **109** and the TM region of human H_1R is shown in Figure 2.1.7. The carboxyl oxygen of the Asn 198 side chain is able to form two hydrogen bonds with the N^{τ}H-atom of the imidazole moiety and the hydroxyl group of Tyr 108 and at the same time N^{π}H-atom of imidazole forms the stable hydrogen bond with Tyr 431. The imidazole ring of **109** is located near Phe-435 and Tyr-108. Phenyl rings are located in a deep hydrophobic pocket built by Phe-199, Pro-202, Phe-432, Trp-428, Trp-158, Ile-115 and Tyr-108. Both phenyl rings fill out the space of receptor pocket, and no space is available for the substituents on the ring. This observation is well supported by the experimental fact that efforts to increase the potency of **109** by benzyl substitution failed[52] (Table 2.1.7).

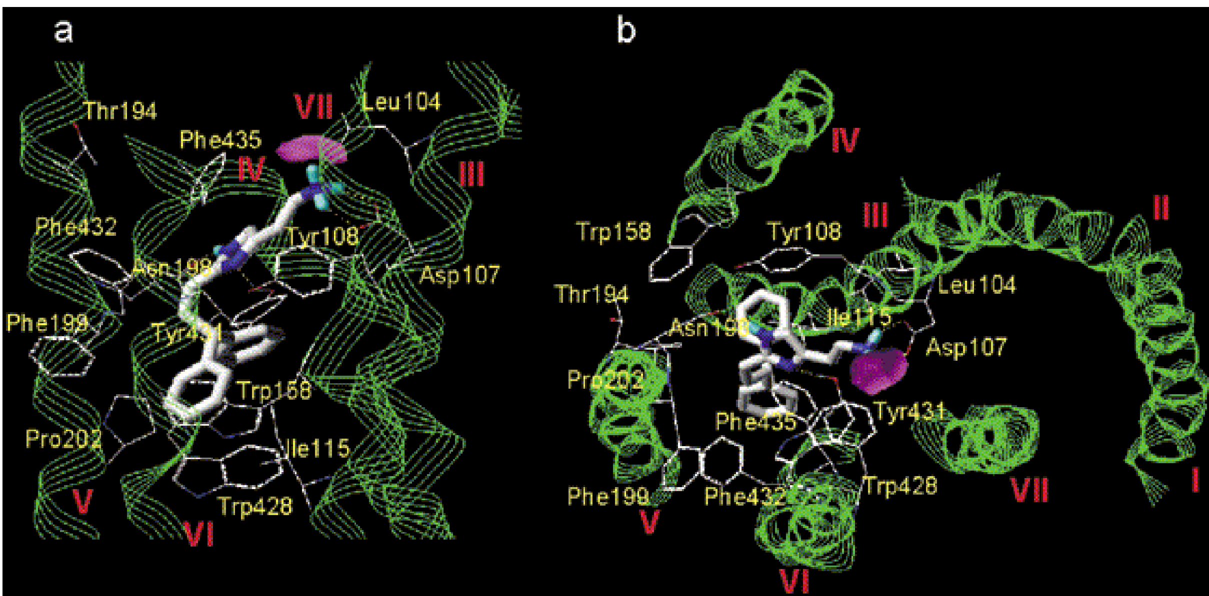


Figure 2.1.6 Binding model of histaprodifen

2.1.11 SAR of suprahistaprodifen analogues

Histaprodifen (**109**) has been a lead structure for the development of potent H_1R agonists. For a long time now, interest has focused on the structural modification of the diphenyl part of the **109**. Structural modification of the ethylamine side chain, specially

attaching different polar groups with the help of methylene linkers led to the discovery of suprahistaprodifen (**136**).

Table 2.1.8 SARs of suprahistaprodifen analogues

136
Suprahistaprodifen

$(CH_2)n$-R

Comp.	R	n	Rel. Pot. (E_{max})
135	H_2N—	2	n.d. (19)
136	N, HN	**2**	**3630% (96)**
137	N	2	923% (92)
138	O—	2	pA_2 6.4 (0)
139	HN—	2	pA_2 5.9 (0)
140	H_2N—	3	6% (81)
141	O—	3	251% (47)
142	H N—	4	148% (45)
143	H_2N—	4	6% (87)
144		4	955% (49)
145	**N**	**4**	**2856% (89)**
146	S	4	433% (43)
147	S	4	1016% (52)
148	NO_2	4	130% (43)
149	O_2N—	4	91% (57)
150	H_2N—	4	779% (49)
151	H_2N—	5	14% (92)

Suprahistaprodifen (**136**) shows extremely high potency in guinea-pig ileum and is the most potent H_1R agonists known so far. Efforts were also made to further improve the agonistic activity. Replacement of imidazole moiety with pyridine as in **137** leads to an agonist with moderate activity. With the exception of compounds **138** and **139,** which were found to be weak antagonists, all other compounds showed moderate to very good activity but most of the compounds were partial agonists. Compound **147** with pyridine heterocycle also showed very high activity but replacement with other heterocycles **147**-**151** led to moderate to good activity.

Many potent and relatively selective H_1R agonists have been developed by academic research groups. Histaprodifen and suprahistaprodifen class of compounds are still the most potent H_1R agonists in guinea-pig ileum and are the lead structures for the development of highly potent H_1R agonists. With increasing understanding of histamine H_1R and the mediated effects, H_1R agonist may become important “future drugs or diagnostic tools.”

2.2 Aim of the work

Since the identification of the histamine H_1-Receptor by Ash and Schild,[7] histamine H_1R agonists have gained significant importance for the investigation of H_1R mediated effects, such as neuroregulation of arousal,[32-34] allergy, modulation of cardiovascular parameters,[35,36] and release of endothelium derived relaxing factor.[35,37,38] The study of these effects has always been hampered by the lack of highly potent and selective histamine H_1R agonists. The search for highly potent and subtype-selective H_1R agonists has been an arduous task for several years,[53] and many derivatives have arisen from the class of 2-substituted histamines,[54] which display improved potency and selectivity.[55,56]

NHR
Ph
Ph
NH_2
1
Histamine
pEC_{50} = 6.70
136 Suprahistaprodifen, R =
109 Histaprodifen, R = H
pEC_{50} = 6.74

Figure 2.2.1

Recently histaprodifen (**109**, Fig. 2.2.1)[57] has been identified as a potent and selective histamine H_1R agonist offering a starting point for the systematic development of highly potent and selective histamine H_1R agonists. The main aim of the present study was to develop analogues of **109** as shown in Figure 2.2.2 to get additional information about structure-activity relationships (SARs) of histamine H_1R agonists. In particular, the effects of polar groups attached to ethylamine side-chain should also be investigated, posing the additional challenge to introduce such groups in a regio-, diastereo- and enantioselective manner. A general retrosynthetic approach is given in Figure 2.2.2. As a suitable starting material toward side-chain modified derivatives of **1** and **109**, commercially available *trans* urocanic acid (**162**) and the 3,3-diphenyl propionic acid (**170**) were envisioned. The coupling of two fragments should give the desired substrates and the required amino group in β-position to the imidazole moiety could be introduced *via* an asymmetric aminohydroxylation (AA) reaction.

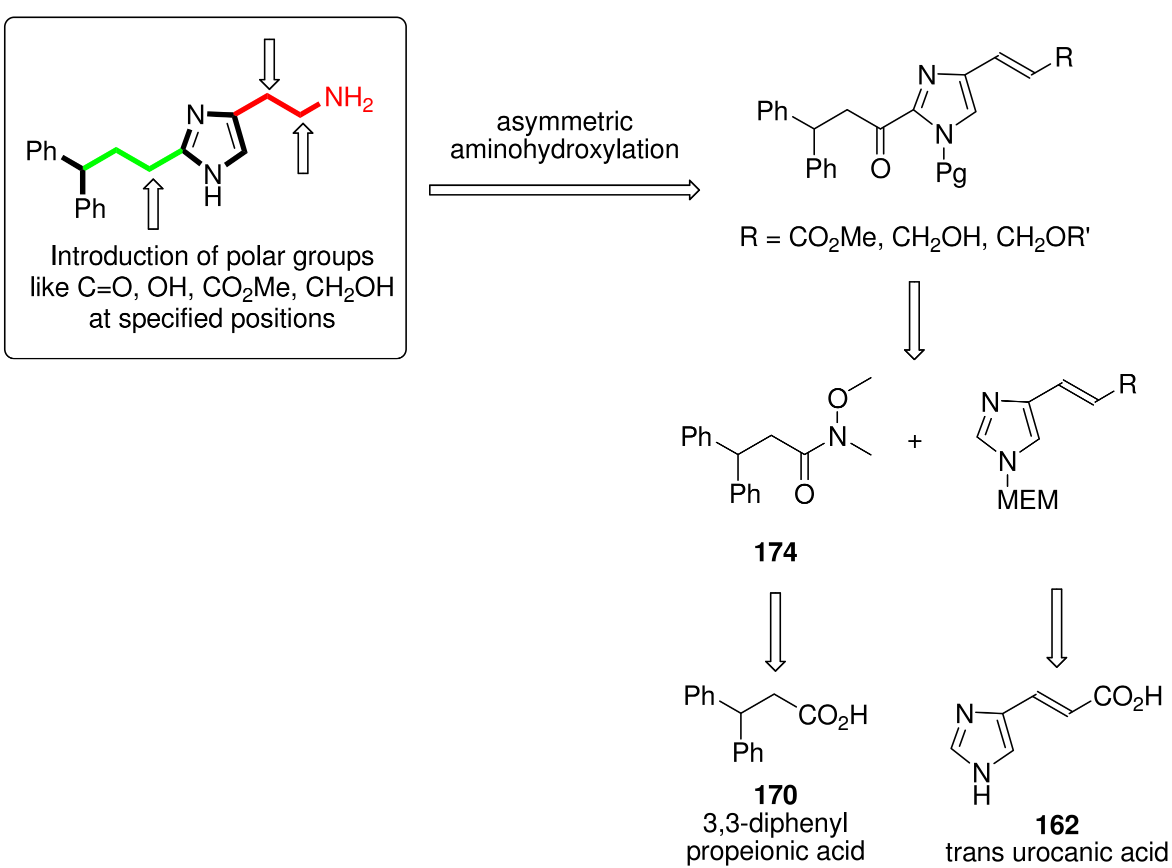


Figure 2.2.2 General retrosynthetic approach

2.3 Synthesis of side-chain modified histaprodifen analogues

2.3.1 Attempted AA reaction on imidazole derivatives

As stated previously, AA reaction was envisoned as one of the key steps, which has proved to be especially effective with cinnamates as substrates. On the other hand the AA reaction is also known to be problematic in presence of nitrogen containing heterocycles. Indeed, it has been reported by Dong *et al.*[58] that the various imidazole urocanic acid methyl esters (**152-155**) failed completely to give the AA reaction despite its structural similarity with cinnamic acid ester (Scheme 2.3.1).

CO_2Me

152, X = H
153, X = Tr
154, X = Cbz
155, X = Ts

AA → No reaction

Scheme 2.3.1 Attempted AA reaction on urocanic acid methyl esters by Dong *et al.*[58]

The possible chelation of the imidazole with osmium (VIII) was assumed to be the reason for these failed attempts.[59] Moreover competition studies were also performed to explore this assumption. Using equal equivalents of 4-benzyloxy methyl cinnamate along with compounds **152** and **154**, desired products were not detected. In a separate experiment, when a reaction of **154** was conducted in the presence of a stoichiometric amount of osmium reagent, no consumption of the substrates was observed.

A similar trend was earlier observed for pyridylacrylates.[60] The direct AA reaction on pyridylacrylates **156(a-c)** was unsuccessful (Scheme 2.3.2), the possible and again the chelation of the pyridine nitrogen with osmium (VIII) could be the reason for these failed attempts. However, *N*-oxides **159(a-c)** with the blocked nitrogen functionalities readily underwent the AA reaction furnishing the regioisomers **160(a-c)** and **161(a-c)** (Scheme 2.3.2). A similar strategy was also envisioned for imidazole derivatives, and consequently *N*-oxide imidazole acrylate was synthesized (Scheme 2.3.3). Starting from *trans* urocanic acid (**162**), esterification[61] and *N*-methylation[62] was achieved by known procedures. Finally **163**, on exposure to *m*-CPBA, *N*-oxide **164** was generated, nevertheless in low yield. On the other hand, attempts to utilize the *N*-oxide **164** for AA reaction, which in case of the pyridylacrylates proved to be the method of choice to achieve asymmetric amino- and dihydroxylations, were not successful.

AA
156a - 156c
ortho, meta, para
157a - 157c
158a - 158c
159a - 159c
ortho, meta, para
160a - 160c
161a - 161c

Scheme 2.3.2 AA reaction of *N*-oxide pyridylacrylates by Reiser and co-workers[60]

162 152 163 164 165
AD mix β

Scheme 2.3.3 Attempted AD reaction on imidazole *N*-oxides.; Reagents and conditions: (a) MeOH, H_2SO_4 (cat), reflux, 30 h, 91%; (b) DMS, K_2CO_3, acetone, RT, 10 h, 38%; (c) *m*-CPBA(75%), EtOAc, RT, 24 h, 12-15%.

2.3.2 Successful asymmetric dihydroxylation reaction on imidazole derivatives

In an important contribution from Pyne and coworkers (Scheme 2.3.4) it was demonstrated that *N*-protected urocanic ethers having an acetyl group in 2-position of imidazole moiety are amenable toward osmium-catalyzed asymmetric dihydroxylation (AD).[63] Looking at the similarity between AD and AA reactions and keeping the side chain in 2-position of histaprodifen in mind, novel 2-keto-substituted imidazole derivatives as a starting point for AA reaction were envisioned.

AD mix-β

AD mix-α

166 R = TBDMS
167 R = H

168a R = TBDMS (65%, ee 99%)
169a R = H (79 %, ee 95%)

168b R = TBDMS (56%, ee 98%)
169b R = H (76 %, ee 90%)

Scheme 2.3.4 AD reaction of 2-acyl imidazole derivatives reported by Pyne and co-workers[63]

152 → a) → **171** (90) : **172** (10)

170 → b) → **173** → c) → **174**

Scheme 2.3.5 Reagents and conditions: (a) NaH, MEM-Cl, DMSO, 0-80 °C, 6 h, 86 % [90:10 mixture of **171**:**172**]; (b) $SOCl_2$, reflux 3 h, 72 %; (c) C_6H_5N, $CHCl_3$, 0 °C → RT, 16 h, 98 %.

2.3.3 Synthesis of substrates for AA reaction

Treatment of **152** with 2-methoxyethoxymethyl chloride (MEM-Cl) and NaH afforded a 90:10 mixture of *N*-alkylated regioisomers **171** and **172**, from which **171** being the major product could be separated by careful column chromatography, while the minor isomer **172** was difficult to isolate. The synthesis of acid chloride **173** was achieved from 3,3-diphenylpropionic acid (**170**) by known procedures.[64] Acid chloride **173**, was treated with

N,*O*-dimethylhydroxylamine hydrochloride and pyridine in ethanol free chloroform[65] to generate Weinreb amide **174** quantitatively (Scheme 2.3.5).

Scheme 2.3.6 Reagents and conditions: (a) LDA, THF, 0 °C → RT, 2 h, 36-52 %

Subsequently, metallation of **171** with LDA and trapping with the Weinreb amide **174** gave rise to **175** in moderate yield (Scheme 2.3.6). To overcome the problems in the separation of regioisomers (Scheme 2.3.5), the LDA mediated coupling was performed with the mixture of regioisomers (**171**, **172**). Metallation of mixture of **171** and **172** with LDA and trapping with the Weinreb amide **174** gave rise to a mixture of **175** and **176**, readily separated by column chromatography. The structures of **175** and **176** were confirmed by X-ray crystallographic analysis (Fig. 2.3.3 and 2.3.4).

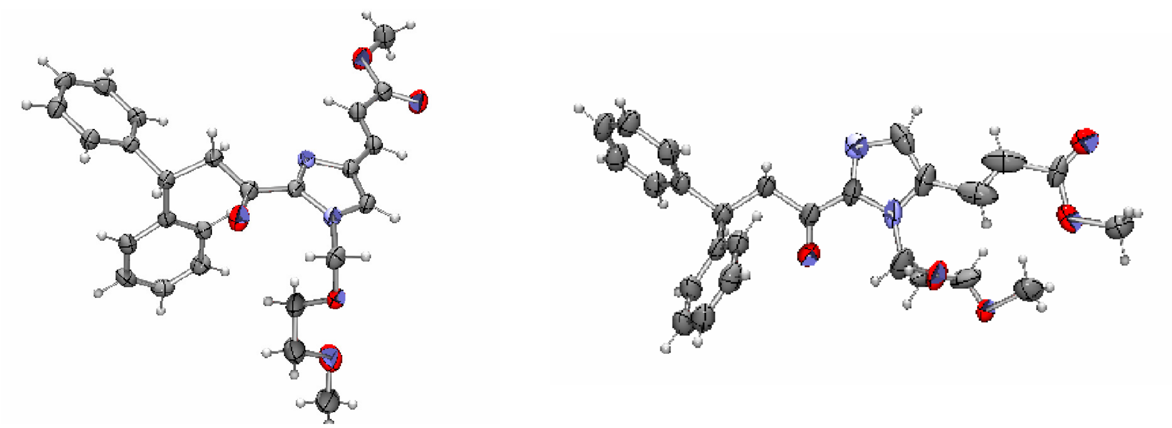


Figure 2.3.3 X-ray structure of **175** **Figure 2.3.4** X-ray structure of **176**

Scheme 2.3.7 Reagents and conditions: (a) DIBAL-H, CH_2Cl_2, 0 °C → RT, 12 h, 86%; (b) NaH, Benzyl bromide, DMF, 0 °C → RT, 16 h, 82%; (c) *n*-BuLi, THF, -78 °C, 1 h, **174**, 1 h, then, RT, 1 h, 67%.

Scheme 2.3.8 Reagents and conditions (a) TBDMS-Cl, imidazole, DMF, 0 °C → RT, 1 h, 96%; (b) *n*-BuLi, THF, -78 °C, 1 h, **174**, 1 h, then, RT, 1 h, 69%; (c) TBAF, THF, 0 °C → RT, 1 h, 91%

The synthesis of substrate **179** for AA reaction is highlighted in Scheme 2.3.7. DIBAL-H reduction of **171** furnished the desired allyl alcohol **177** in 86% yield, which was subsequently treated with sodium hydride and benzyl bromide to furnish the benzyl ether **178** in 85% yield. Finally, metallation of **178** with *n*-BuLi and trapping with Weinreb amide **174** at -78 ^{o}C, afforded **179** in 67 % yield. Similarly TBDMS protection of allyl alcohol **177** followed by subsequent metallation with *n*-BuLi and trapping with Weinreb amide **174** at -78 ^{o}C, afforded **181** in 69 % yield. Finally TBDMS group was removed using TBAF to generate the allyl alcohol **182** in excellent yield (Scheme 2.3.8).

2.3.4 Asymmetric aminohydroxylation of imidazolyl derivatives

Table 2.3.1 Asymmetric aminohydroxylation of imidazolyl derivatives[a]

AA → A + B

175 R = CO_2Me
179 R = CH_2OBn
182 R = CH_2OH

183 R = CO_2Me
185 R = CH_2OBn
187 R = CH_2OH

184 R = CO_2Me
186 R = CH_2OBn
188 R = CH_2OH

Entry	Substrate	Ligand	Solvent	Reaction time [h]	Ratio of regioisomers[b]	Yield[c] [%]	% ee[d] A B
1	**175**	$(DHQ)_2$PHAL	*n*-PrOH/H_2O (1.5:1)	30	**183:184** 1:3	52	56 53
2	**175**	$(DHQD)_2$AQN	*n*-PrOH/H_2O (1.5:1)	30	**183:184** 1:1	56	54 52
3	**175**	$(DHQD)_2$AQN	MeCN/H_2O (3:1)	4	**183:184** 1:1	72	75 87
4	**179**	$(DHQ)_2$PHAL	*n*-PrOH/H_2O (1.5:1)	1	**185:186** 1:3.3	56	nd nd
5	**179**	$(DHQD)_2$AQN	*n*-PrOH/H_2O (1.5:1)	1	**185:186** 1:3	65	nd nd
6	**179**	$(DHQD)_2$AQN	MeCN/H_2O (3:1)	1	**185:186** 1:1.5	67	48[e] nd
7	**182**	$(DHQD)_2$AQN	MeCN/H_2O (1.5:1)	1	**187:188** 1:3	63	0 nd

[a] Reagents and conditions: $K_2OsO_2(OH)_4$ (4 mol %), ligand (5 mol %), BnOC(O)NNaCl (5 mol %) at 25 °C.
[b] Ratio determined by ^{1}H NMR, for substrate **179** and **182** ratio determined after *N*-Cbz to *N*-Boc conversion.
[c] Isolated yields as a mixture of regioisomers.
[d] Determined by HPLC on Chiracel™ OD/ODH (nd, not determined)
[e] Determined after conversion to **194** by HPLC on Chiracel™ OD/ODH

Indeed, **175**, **179** and **182** could be utilized as substrate for the osmium-catalyzed aminohydroxylation (Table 2.3.1) with moderate results, nevertheless, succeeding for the first time with imidazole derivatives in this transformation. In agreement with the general trend observed in AA reactions with aromatic substrate, in the presence of $(DHQ)_2$PHAL the amino group is preferentially introduced in the benzylic position (regioisomers **B**, entries 1, 7). To obtain a better ratio of regioisomers with respect to the desired histamine analogues, the pseudoenantiomeric ligand $(DHQD)_2$AQN was employed. Although the ratio of regioisomers

could not be reversed as it is known in the case of cinnamates, at least the formation of desired regioisomer **A** was somewhat improved (Table 2.3.1, entries 2, 3, and 7).

Changing the solvent from *n*-propyl alcohol/water to acetonitrile/water considerably improved the yield of the reaction with **175**, as well as the enantioselectivity of the products (Table 2.3.1, entries 2, 3). Surprisingly the allyl ether **178** and allyl alcohol **182** were considerably more reactive than the ester **175**, however with the former substrate the undesired regioisomer was always favored, even when the AQN ligand was employed. Moreover, only racemic products were obtained with the allyl alcohol **182** (Table 2.3.1, entry 7). Preparatively most useful appeared to be the formation of **183** and **184** mediated by $(DHQD)_2AQN$ (Table 2.3.1, entry 3), giving useful yields and selectivities that allowed to arrive at regio- and enantiomerically pure products at the next stage in the reaction sequence.

2.3.5 Separation of regioisomers in AA reaction

OH NHCbz Ph N N MEM Ph O CO_2Me **183** + NHCbz OH Ph N N MEM Ph O CO_2Me **184**

a)

OH NHBoc Ph N N MEM Ph O CO_2Me **189** + NHBoc OH Ph N N MEM Ph O CO_2Me **190**

189 b) → OH NH_2 Ph N N H Ph O CO_2Me • 2HCl **191**

Scheme 2.3.9 Reagents and conditions: (a) 10% Pd/C, H_2, MeOH, $(Boc)_2O$, RT, 3 h 96%; (b) i) Conc. HCl:MeOH:H_20 (1:1:1), reflux, 1 h, ii) H_2SO_4(cat.), MeOH, reflux 30 h, 75% (over two steps).

One of the most common limitations in AA reaction is the separation of regioisomers. In the reaction sequence the regioisomers were very difficult to separate, and were separated using preparative column chromatography (**183**, **184**) and in some cases were inseparable (**185**, **186** and **187**, **188**) by column chromatography. On the other hand single-step exchange[66] of the nitrogen protecting group on the mixture of **183** and **184** from Cbz to Boc allowed the facile separation of desired isomer **183** by column chromatography, which was obtained enantiomerically pure in 40% yield after recrystallization (28% yield starting from **175**) along with the corresponding regioisomer being obtained in 48% yield.

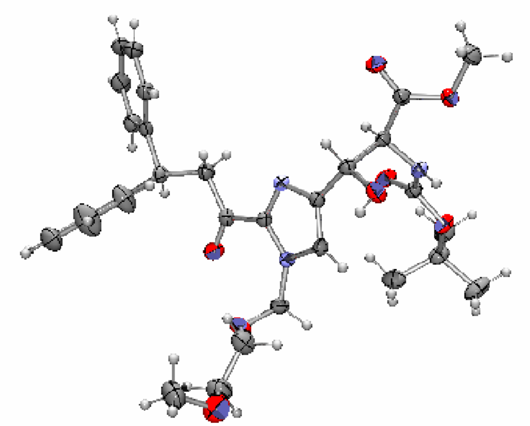


Figure 2.3.6 X-ray structure of **189**

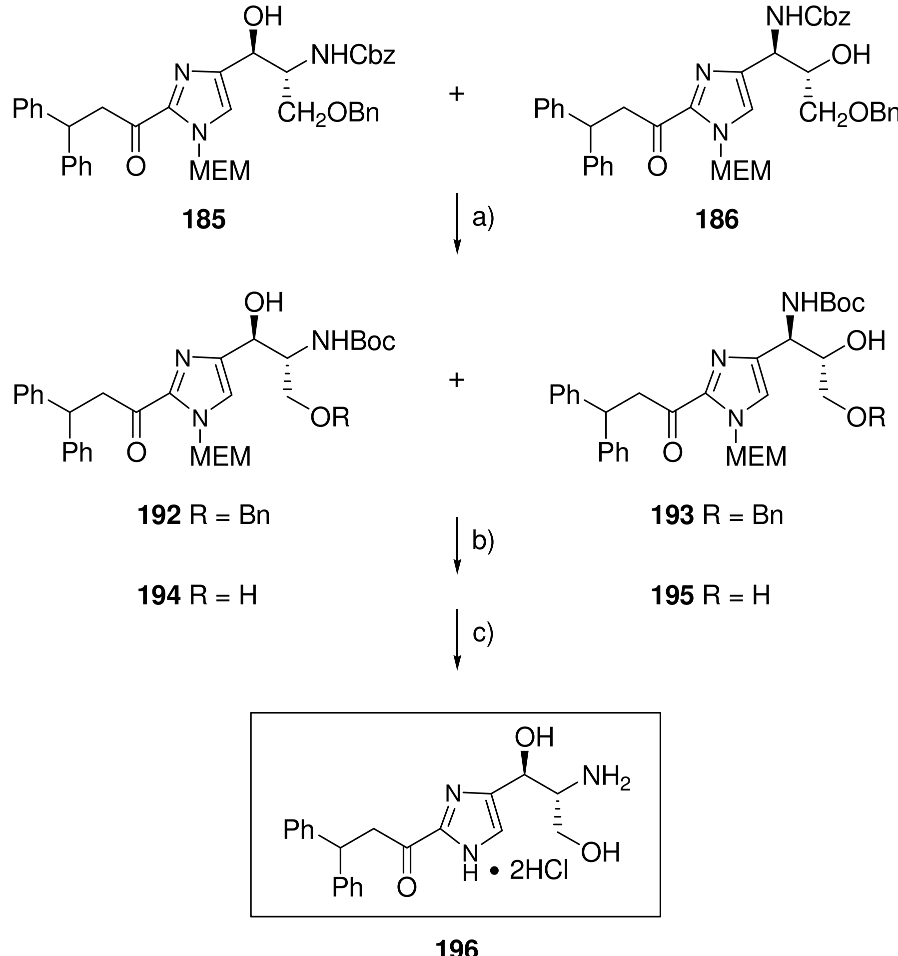
The structure of **189** was confirmed by X-ray analysis (Fig. 2.3.6) and the absolute configuration (*S*, *S*) was assigned by an analogy to the Sharpless ligands. Finally deprotection of **189** was achieved by treatment with aqueous HCl in methanol (using ethanol as a solvent resulted in transesterification products), resulting also in partial cleavage of methyl ester, which was subsequently remedied by acid catalyzed reesterification with abs. MeOH to give rise to **191** (Scheme 2.3.9).

(*rac*)-**183** —a)→ b) R = MEM, **183-a** → R = H, (*rac*)-**191**

Scheme 2.3.10 Reagents and conditions: (a) 10% Pd/C, H_2, MeOH, RT, 3 h 78%; (b) i) Conc. HCl:MeOH:H_20 (1:1:1), reflux, 1 h, ii) H_2SO_4(cat.), MeOH, reflux 30 h, 75% (over two steps).

The synthesis of (*rac*)-**191** was achieved by mixing the (*S*,*S*) and (*R*,*R*)-**183** followed by the Cbz deprotection to form the amine **183-a**. Finally MEM group was deprotected by refluxing (**183-a**) with aqueous HCl in methanol, resulting also in partial cleavage of methyl ester, which was subsequently remedied by acid catalyzed reesterification with abs. MeOH to give rise to (*rac*)-**191** (Scheme 2.3.10).

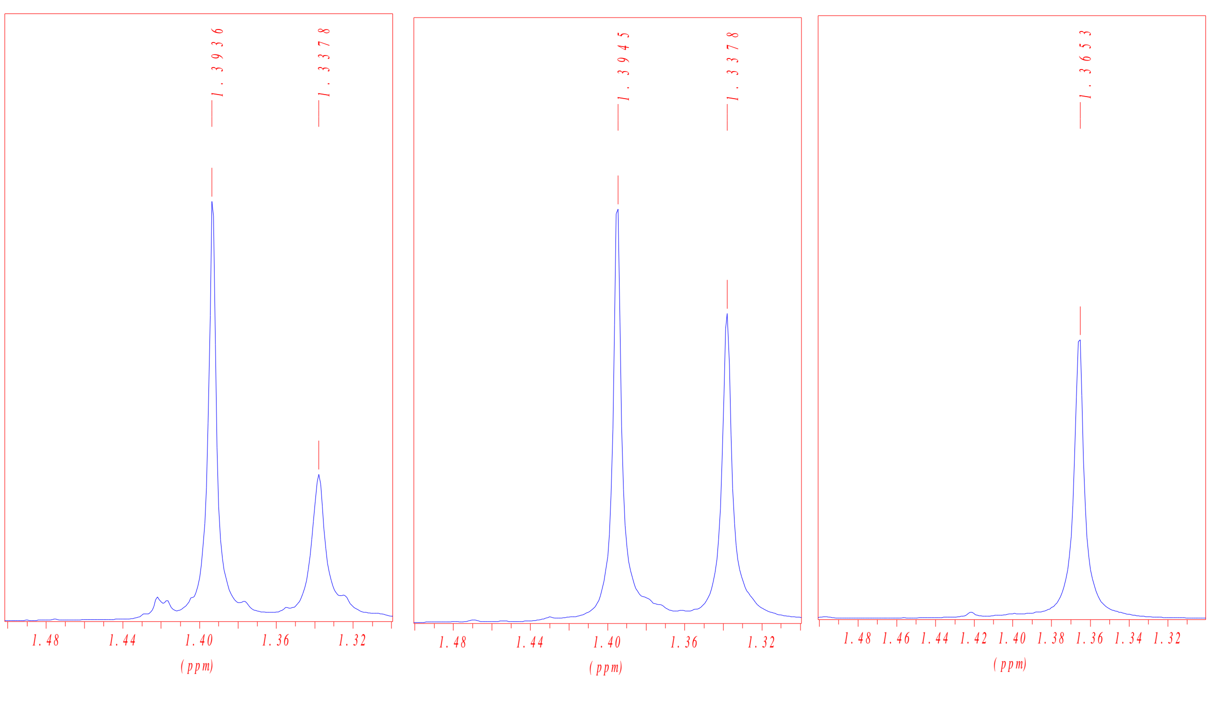
Similarly, the mixture of **185** and **186** was converted to the *N*-Boc derivatives **192** and **193** (94% yield). The reaction was followed carefully as extended reaction time led to the *O*-debenzylation in minor quantity. Moreover, *O*-debenzylation being very slow, one pot debenzylation and *N*-Cbz to *N*-Boc exchange was not possible. Even though the two regioisomers **192** and **193** were not separable by chromatography, nor could be the major isomer defined at this stage, we nevertheless proceeded forward in the hope of achieving the separation in the later stage.



Scheme 2.3.11 Reagents and conditions: (a) 10% Pd/C, H_2, MeOH, Boc_2O, RT, 3 h, 94%; (b) 10% Pd/C, H_2, THF, 40 bar, 40 °C, 48 h, 62%; (c) i) $NaIO_4$, 1,4-dioxane, H_2O, RT, 2.5 h, 87% based on **192**; ii) concd. HCl:MeOH:H_20 (1:1:1), reflux, 1 h, 95%.

Thus, debenzylation of the mixture **192** and **193**, with Pd-C/H_2 in THF led to the mixture of 1,2- and 1,3-diols **194** and **195** in 62% yield. In contrast, with EtOAc as a solvent the reaction yields were low and side-products were formed. In all attempts complete conversion of starting material was not observed. After the debenzylation, the mixture of 1,2 and 1,3-diols was treated with $NaIO_4$ to cleave the 1,2-diol in undesired regioisomer **195** (Scheme 2.3.11). This way **194** could be obtained as single distereomer and hence it was possible to determine the enantiomeric excess (48% *ee*). Finally MEM and Boc protecting groups were removed under acidic condition in one pot reaction to leave **196** as a hydrochloride salt.

Initially, it was thought that the major isomers in the AA reaction on **179** as well as **182** were **185** and **187**. Later chemical analysis based on the reaction of regioisomers **194** and **195** with $NaIO_4$, which reacted only with 1,2-diol leaving 1,3-diol unaffected, revealed that the major isomers were undesired **186** and **188**. It is evident from the investigation of ^{1}H NMR (Fig. 2.3.7). After 20 minutes the resonance of Boc group in the 1,2-diol **195** was found to be decreasing and vanished completely after 2.5 h (Fig. 2.3.7), suggesting that the major isomer was 1,2-diol and hence it was concluded that the major isomers in AA reaction on **179** and **182** were **186** and **188** respectively (Table2.3.1 entries 4- 7)



^{1}H NMR before reaction ^{1}H NMR after 20 minutes ^{1}H NMR after 2.5 hours

Figure 2.3.7

2.3.6 Synthesis of keto-histaprodifen

As the missing link to allow a meaningful assessment of the influence of the modified ethylamine side chain in **191** and **196** with respect to **109**, histaprodifen analogue **201** being acylated instead of alkylated was thought to be synthesized using Curtius reaction as a key step. Starting from acrylate **175**, hydrogenation with Pd-C/H_2 followed by saponification of the methyl ester afforded acid **198** in very good yield. Initially, attempts to utilize acid **198** for the corresponding acyl azide transformation using ethyl chloroformate and sodium azide were not satisfactory, giving very low yield of the acyl azide. On the other hand, acid activation with oxalyl chloride followed by treatment with TMS-azide proved to be the method of choice. Subsequently, the azide was immediately subjected to the modified Curtius rearrangement, which proceeded well to furnish Cbz protected amine **199** in high yield (Scheme 2.3.12). The Cbz group was removed by hydrogenation and finally the MEM group was deprotected with HCl to give **201** as a dihydrochloride salt in 97% yield.

Ph Ph O N N MEM CO_2Me **175** a) → Ph Ph O N N MEM CO_2Me **197** b) →

Ph Ph O N N MEM CO_2H **198** c) → Ph Ph O N N MEM NHCbz **199** d) →

Ph Ph O N N MEM NH_2 **200** e) → Ph Ph O N N H NH_2 • 2HCl **201**

Scheme 2.3.12 Reagents and conditions: (a) 10% Pd/C, H_2, MeOH, RT, 16 h, 96%; (b) LiOH, THF:MeOH:H_2O (3:1:1) 0 °C → RT, 6 h, 95%; (c) i) $(COCl)_2$, CH_2Cl_2, 0 °C → RT, 3 h; ii) TMS-N_3, CH_2Cl_2, 0 °C → RT, 5 h; iii) BnOH, toluene, reflux, 18 h, 87% (over three steps); (d) 10% Pd/C, H_2, MeOH, RT, 16 h, 86%; (e) Conc. HCl:MeOH:H_20 (1:1:1), reflux, 1.5 h, 97%.

Scheme 2.3.13 Reagents and conditions (a) i) $(COCl)_2$, CH_2Cl_2, 0 °C → RT, 3 h; ii) TMS-N_3, CH_2Cl_2, 0 °C → RT, 5 h; (b) H_2O, toluene, reflux, 18 h; (c) Conc. HCl:MeOH:$H_2$0 (1:1:1), reflux, 1.5 h, 92%.

In an attempt to achieve a direct conversion of **198** to the free amine **200**, by the Curtius reaction, the intermediate isocyanate **202** was hydrolyzed using H_2O, and interestingly, the urea derivative **201** was isolated. The possible attack of amine **200**, which is formed by the partial hydrolysis of isocyanate **202** on the intermediate isocyanate itself, could be the reason for the formation of this interesting urea derivative **203** (Scheme 2.3.13). Later MEM group was removed under usual acidic condition followed by the basic work-up to obtain **204**, a suprahistaprodifen type of compound as a free base.

The minor isomer **176**, obtained previously from the LDA mediated coupling (Scheme 2.3.6) could be utilized for further transformations and would result to similar products as obtained from major isomers. With this in mind, building block **207** was synthesized in a straightforward way (Scheme 2.3.14) using similar routs used for the major isomer **199**.

Scheme 2.3.14 Reagents and conditions: (a) 10% Pd/C, H_2, MeOH, RT, 16 h, 92% (b) LiOH, THF:MeOH:H2O (3:1:1) 0 °C → RT, 6 h, 96 %; (c) i) $(COCl)_2$, CH_2Cl_2, 0 °C → RT, 3 h; ii) TMS-N_3, CH_2Cl_2, 0 °C → RT, 5 h; iii) BnOH, toluene, reflux, 18 h 78 % (over three steps); (d) 10% Pd/C, H_2, MeOH, Boc_2O, RT, 3 h, 89%.

Scheme2.3.15 Reagents and conditions: (a) $NaBH_4$, IPA, 0 °C → RT, 16 h, 94%; (b) Conc. HCl:MeOH:H_20 (1:1:1), reflux, 1.5 h, quantitative; (c) Ph_3PCH_2I, *t*BuOK, THF 24 h.

For the synthesis of polar derivatives of histaprodifen, being one of the main aims of the present study, our attention was turned towards the hydroxyl derivative of keto-histaprodifen (**201**). However, the attempts to utilize **208** were not as successful as anticipated. Sodium boro hydride reduction of **208** yielded alcohol **209** in 94% yields.

However, treatment of **209** under usual MEM deprotection condition led only to Boc deprotection, leaving MEM group intact (Scheme 2.3.15). Furthermore the effect of the polar carbonyl functionality should be compared with lipophilic moieties such as alkene, which has of more or less the same size. However, **208** did not undergo the Wittig transformation (Scheme 2.3.15).

Scheme 2.3.16 Reagents and conditions: (a) Ph_3PCH_2I, *t*BuOK, THF 0 °C → RT, 3 h 92%; (b) Ph_3PCH_2I, *t*BuOK, THF 0 °C → RT, 5 h 95 %.

Scheme 2.3.17 Reagents and conditions: (a) 10% Pd/C, H_2, MeOH, RT, 16 h, 96%; (b) Conc. HCl, reflux, 16 h, quantitative; (c) Conc. HCl:MeOH:$H_2$0 (1:1:1), reflux, 1.5 h, (quantitative, crude).

To verify the reason for this failed attempt, the Wittig reaction was performed on the similar substrate **197**. Using 2 equivalents of Wittig reagent the ketone **197** underwent the

Wittig reaction successfully and gave rise to the alkene **211** in excellent yield. Also **212** was found to be amenable towards the Wittig reaction (Scheme 2.3.16), implying that in **208** steric factors could be the reasons for the failed Wittig reaction.

2.3.7 Manipulation of carbonyl group

Having accomplished the successful Wittig reaction on **212**, the alkene **213** was hydrogenated with Pd-C/H_2 to the methyl compound **214**. On the other hand, $NaBH_4$ reduction of **213** generated corresponding alcohol **217** in excellent yield. Disappointingly, however in all compounds **213**, **214** and **217**, only deprotection of Boc protecting group was accomplished under strongly acidic conditions (6N HCl), leaving MEM group intact (Scheme 2.3.15, 2.3.16 and 2.3.17). Moreover, upon refluxing **213** with concentrated HCl for 16 hours, the MEM group was not deprotected completely and compound **215** was obtained (Scheme 2.3.17). So far, it has been observed that, MEM deprotection from imidazole derivatives is only possible for compounds having a 2-acyl moiety, suggesting the possible involvement of the carbonyl moiety during the acid catalyzed deprotection of MEM group. This unfortunate outcome has not been recognized before and requires further investigations.

NHBoc N Ph N Ph O MEM **212** —a)→ NHBoc N Ph N Ph OH MEM **217**

—b)→ NH_2 N Ph N • HCl Ph OH MEM **218**

Scheme 2.3.18 Reagents and conditions: (a) $NaBH_4$, IPA, 0 °C → RT, 10 h, 92 %; (b) Conc. HCl:MeOH:$H_2$0 (1:1:1), reflux, 1.5 h, quantitative.

Ph, Ph, O, N, N H, NH_2, • 2HCl, **201**, a), **219**, NHBoc, b), **220**, OH, c), **221**

Scheme 2.3.19 Reagents and conditions: (a) NaOH, $(Boc)_2O$, RT, 30 min. 91%; (b) $NaBH_4$, IPA, 0 °C → RT, 16 h, 96%; (c) Sat. HCl in ether 0 °C → RT, 16 h, quantitative.

After facing these unexpected problems of MEM deprotection, another strategy for the synthesis of hydroxyl derivative **221** of histaprodifen was planed and carried out successfully (Scheme 2.3.19). Starting from dihydrochloride salt **201**, the free amine functionality was selectively protected using $(Boc)_2O$ to achieve the required lipophilicity, which allowed the facile isolation of reduced product **220** after hydride treatment. Finally the Boc group was removed under acidic conditions to afford **221** as a hydrochloride salt. On the other hand, use of MEM deprotected building block **219** was not successful as **219** did not undergo a routine Wittig transformation even after refluxing in THF for 24 hours (Scheme 2.3.20).

Ph, Ph, O, N, N H, NHBoc, **219**, a), CH_2, **222**

Scheme 2.3.20 Reagents and conditions: (a) Ph_3PCH_2I, *t*BuOK, THF 0 °C → RT, 2 h, then reflux, 24 h.

2.3.8 Attempted synthesis of the N^{α}-methylated analogue of keto-histaprodifen

N^{α}-methylated analogues of histaprodifen are known to be more potent than the histaprodifen itself.[51] To achieve a better potency, the synthesis of the N^{α}-methylated analogue of **201** was of a great interest. As a suitable starting material towards the N^{α}-methylated analogue of **201**, the Boc protected amine **208** was envisioned. However, on

treatment of **208** with methyl iodide and bases such as, NaH or *t*BuOK, along with N^{α}-methylation, α-methylation to the carbonyl group was always observed (Scheme 2.3.21).

Scheme 2.3.21 Reagents and conditions: (a) NaH, MeI, 0 °C → RT, 2 h, 83%; (b) Conc. HCl:MeOH:$H_2$0 (1:1:1), reflux, 1.5 h, quantitative.

Several attempts to achieve selective N^{α}-methylation were failed. Methylation of **208** was faster when NaH was employed as a base, However, the reaction time was longer with *t*BuOK. In all attempts the only product formed was **223**. Moreover using one equivalent of methyl iodide, mixture of products along with starting material **208** were observed and were not possible to separate by column chromatography. On the other hand, similar problem was observed when the methylation was performed with **212**. Moreover, attempts to use protected carbonyl group were failed as silyl enol ether **225** was not found to be very stable and hence could not be utilized. Finally treatment of **223** with 6N HCl, the MEM and Boc protecting groups were removed in one pot reaction. Interestingly, this time the reaction proceeded in a usual manner (Scheme 2.3.21), making the argument stronger that MEM group deprotection on imidazole is amenable only in the presence of 2-acyl substituents under these conditions.

An alternative strategy was employed to synthesize the N^{α}-methylated analogue of **201**, in which the crucial N^{α}-methylation step was envisioned before the base mediated coupling (Fig. 2.3.8). The synthon **234** was envisioned to be obtained from **232** which in turn

should be easily accessible from **171** by hydrogenation, saponification followed by modified Curtius reaction.

Figure 2.3.8 Alternative retrosynthetic approach for *N*-methylated analogue **234**

Scheme 2.3.22 Reagents and conditions: (a) LiOH, THF:MeOH:H2O (3:1:1) 0 °C → RT, 6 h, 84%; (b) 10% Pd/C, H_2, MeOH, RT, 16 h, 93%; (c) i) $(COCl)_2$, CH_2Cl_2, 0 °C → RT, 3 h; ii) TMS-N_3, CH_2Cl_2, 0 °C → RT, 5 h; iii) BnOH, toluene, reflux, 18 h, 72% (over three steps); (d) 10% Pd/C, H_2, MeOH, Boc_2O, RT, 3 h, 83% of **232**.

As described in Figure 2.3.8, starting with the mixture of regioisomers **171** and **172**, upon treatment of this mixture with LiOH in THF:H_2O:MeOH mixture a white solid was obtained as a non-separable mixture of regioisomers **226** and **227**. The regioisomers were not separable even after the recrystallization as both were crystallized together. Upon hydrogenation with 10% Pd-C, a mixture of regioisomers **228** and **229** was obtained. At this stage the regioisomers were still not separable. Subsequently the mixture of acids was subjected to a modified Curtius protocol (Scheme 2.3.11) to obtain the Cbz protected mixture of regioisomers **230** and **231**. At this stage, the separation of regioisomers was still not possible. On the other hand single step exchange of the nitrogen protecting group on the mixture of **230** and **231** from Cbz to Boc allowed the facile separation of desired isomer **232** by column chromatography (Scheme 2.3.22). However attempts to convert **232** into **234** were unsuccessful (Scheme 2.3.23), probably also leading to the ring methylation of imidazole nitrogen.

Scheme 2.3.23: Attempted N^{α}-methylation of **232**

2.4.2 Conclusion

In the race toward the highly potent and selective histamine H_1R agonists, the asymmetric aminohydroxylation was performed successfully for the first time on imidazolyl derivatives and many polar analogues of histaprodifen were synthesized, in some cases also in enantiopure form. A convenient and straightforward synthesis of a keto derivative of **109**, a *keto-histaprodifen* (**201**) was developed using the Curtius reaction as a key step. Moreover along with **201**, its racemic hydroxy derivative **221** was also synthesized in an efficient way. All newly synthesized compounds were screened in vitro for functional interaction with guinea-pig ileum and have enlarged the knowledge about SARs of histamine H_1R agonists.

2.4 Pharmacology

2.4.1 Histamine H_1R agonist activity

All newly synthesized compounds were screened in vitro for functional interaction with histamine H_1Rs of guinea-pig ileum according to standard procedures (see 2.5 pharmacological methods). Table 2.4.1 summarizes all the pharmacological data.

Table 2.4.1 Interaction with histamine H_1Rs (guinea-pig ileum)[a]

Comp.	Agonism			Affinity[b]	N[c]
	E_{max} ± SEM	pEC_{50} ± SEM	Rel. Pot. [%]	pD'_2 ± SEM	
1	100	6.70 ± 0.02	100	-	>95
109	100	6.74 ± 0.02	111	6.04 ± 0.05[d]	34[e]
(*rac*)-**191**	0	-	-	3.80 ± 0.09	7
191	0	-	-	4.61 ± 0.12	9
196	0	-	-	4.08 ± 0.14	6
200	0	-	-	5.05 ± 0.12	4
201	**75 ± 3**	**5.78 ± 0.08**	**12**	**nd**	**9**
204	0	-	-	6.04 ± 0.07	13
221	**66± 2**	**5.00 ± 0.09**	**2**	**4.03 ± 0.10**[d]	**7**
224	0	-	-	4.18 ± 0.09	7
Mepyramine[f]	0	-	-	9.07 ±0.03[g]	34

[a] Experimental protocol and definition of parameters see (2.5 pharmacological methods)

[b] Determined at 10-100 µM unless otherwise indicated.

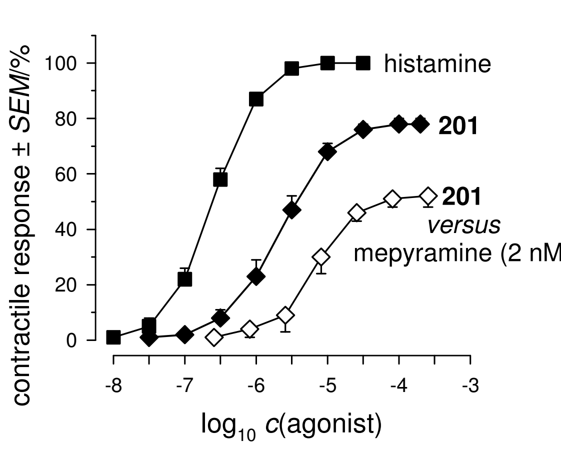
[c] Number of experiments for agonism or affinity determination.

[d] pK_p value, determined at 3-30 µM (**109**) and 200 µM (**221**)

[e] $N = 12$ for affinity measurement.

[f] Data from Ref.[57]

[g] pA_2 value, determined at 0.3-100 µM.



201

Partial Agonism:
pEC_{50} = 5.78 ± 0.08 (histamine: 6.70)
Rel. Potency: 12% (8 – 19)
E_{max} = 75 ± 3% (N = 7, 2 animals)

Sensitivity *vs* Mepyramine:
pA_2 = 9.03 ± 0.18 (N = 3)

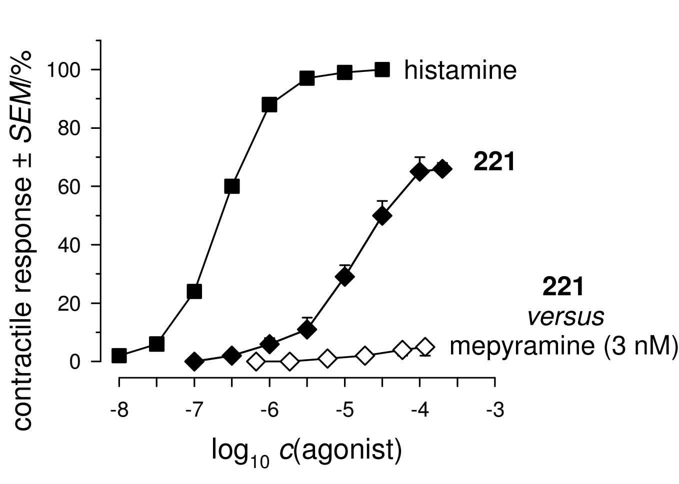
Figure 2.4.1 Partial H_1R Agonism of 201 (keto-histaprodifen): Contraction of guinea-pig ileum by histamine (**1**) (■, N = 9) and **201** in the absence (♦, E_{max} = 75 ± 3%, N = 9) and presence (◊, 47 ± 4%, N = 5) of mepyramine (2 nM). Rel. Pot. of **201** was 12% (95% conf limits 9-17%), pA_2 of mepyramine was 9.08 ± 0.11. These data were obtained from three animals. For protocol, see Ref.[57]

Neither (*rac*)-**191** nor the enantiopure **191** showed any elicited ileal contractions (Table 2.4.1). Moreover, the diastereomerically pure **196** behaved similarly like **191**. Only at higher concentrations (30-100 μM), these compounds depressed the effect of histamine (**1**) without producing a rightward shift of the agonist curve. Thus, in contrast to the potent reference antagonist mepyramine (nanomolar affinity, pA_2 = 9.07), these compounds have to be classified as weak non-competitive H_1R blockers ($pD'_2 < 5$).

Compared with the lead compound histaprodifen (**109**), the new compounds **191** and **196** are endowed with several chemical modifications. It was of a special interest to understand the effect of the carbonyl group attached to C2 of imidazole, since 2-acyl histamine derivatives have never been studied so far. Moreover, several modifications at once in histaprodifen (**109**) led the new compounds to behave as weak H_1R antagonists. Therefore the synthesis of **201** was sought and carried out in a straightforward way (Scheme 2.3.11). Surprisingly compound **201**, a *´keto-histaprodifen`* turned out to be a moderate partial H_1R agonists, displaying approximately 12% relative potency compared with its parent compound **109**. The contractile effect was mediated by H_1Rs since mepyramine (2 nM), a reference H_1R antagonist, successfully blocked the effect of **201** (Fig. 2.4.1) with the expected nanomolar

affinity. However its N^{τ}-protected precursor **200** failed completely to stimulate the H_1Rs which is well in agreement with the current concept of SARs of histamine H_1R agonists.[67]

The symmetric histaprodifen urea hybrid **204** did not stimulate the histamine H_1Rs despite its structural similarity with potent histaprodifen dimer (3,3-Diphenylpropyl derivative of **136**, Rel. Pot. = 1680, histamine = 100) and turned out to be weak antagonist (pD'_2 = 6.04, Table 2.4.1).



221

Partial Agonism:
pEC_{50} = 5.00 ± 0.09 (histamine: 6.70)
Rel. Potency: 2.0% (1.1 – 3.5)
E_{max} = 66 ± 2% (N = 7, 3 animals)
Affinity: pK_P = 4.03 ± 0.10 (N = 7)

Sensitivity *vs* Mepyramine:
Strong sensitivity (N = 4)

Figure 2.4.2 Partial H_1R Agonism of 221 (Hydroxy-histaprodifen): Contraction of guinea-pig ileum by histamine (**1**) (■, N = 7) and **221** in the absence (♦, E_{max} = 66 ± 2%, N = 7) and presence (◊, 5 ± 3%, N = 4) of mepyramine (3 nM). Rel. Pot. of **221** was 2.0% (95% conf limits 1.1 – 3.5%), pA_2 of mepyramine could not be calculated due to the strong depression of the **221**-induced response. The affinity of **221** was estimated as pK_P value by competition of 200 µM **221** (incubation time 3 min) with histamine at the end of each single agonist experiment (curve not shown). All data were obtained from three animals. For protocol, see Ref.[57]

As several modifications at once did not produce the desired effect, the focus was turned on one modification at a time. One of the first modifications was to convert the carbonyl to alcohol functionality, which was thought to be easily obtained either from **208** or **212**. However, because of problems in the MEM deprotection, the desired analogue **221** was obtained by an alternative strategy (Scheme 2.3.18). In addition, the compound **221**, a hydroxyl analogue of keto-histaprodifen (**201**) also turned out to be a partial H_1R agonist

displaying about 2 % potency compared with histamine (**1**). The contractile effect was mediated by H_1Rs since mepyramine (2 nM), a reference H_1R antagonist, successfully blocked the effect of **201** (Fig. 2.4.2) with the expected nanomolar affinity.

Another modification was the N^{α}-methylation to have an analogue of methyl histaprodifen. However, because of competing reactions, it was not possible to obtain the desired isomer (**234**). On the other hand a compound having additional methyl substituent α-to the carbonyl group (**223**) was synthesized and screened for H_1R agonistic activity. Surprisingly, **223** was not able to stimulate the H_1Rs and behaved as weak antagonist (Figure 2.4.3). This behaviour indicates that even a small substituent is not tolerated in the diphenyl side-chain of the keto-histaprodifen (**201**). So far it has been observed that agonistic activity could be obtained by carrying out some modifications at the carbonyl position in the side-chain of **201**. On the other hand, all other positions seem to be very sensitive.

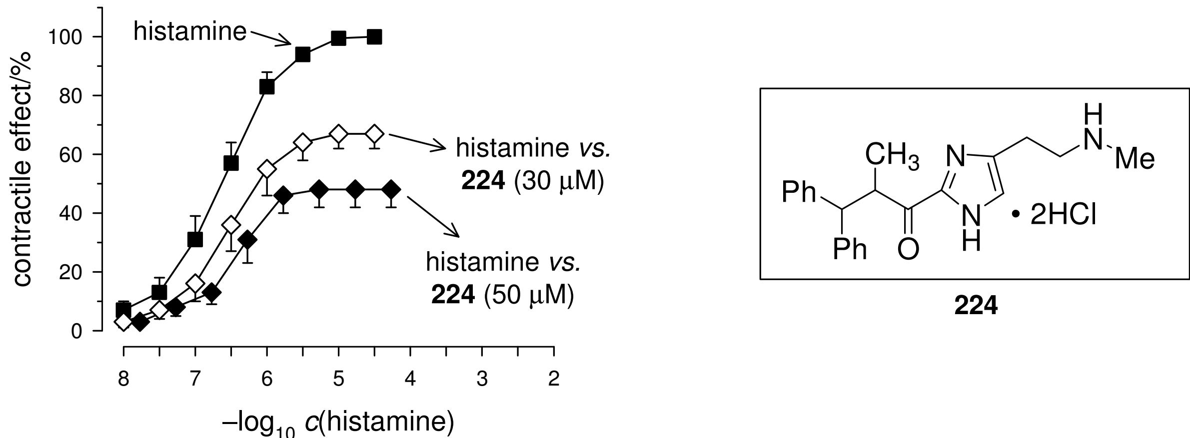


Figure 2.4.3 Nonsurmountable H_1R Antagonism of Compound 223 (α-Methylketo-histaprodifen): Contraction of guinea-pig ileum by histamine (**1**) in the absence (■, N = 5) and in the presence of **223** [µM]: 30 (◊, E_{max} = 67 ± 5%, N = 5) and 50 (♦, E_{max} = 48 ± 6%, N = 2). Incubation time was 10 min. The rightward shift of the histamine curves amounted to less than 0.3 log units (0.15 ± 0.07, P > 0.05 for 30 µM **223** (N = 5), and 0.23 ± 0.11 for 50 µM **223** (N = 2). Therefore, affinity was calculated as pD'_2 = 4.18 ± 0.09 (95% conf limits 3.92 – 4.44, N = 7). All data were obtained from three animals.

Considering this fact, attempts were also made to convert carbonyl into more lipophilic moieties, but because of deprotection problem of MEM protecting group, desired compounds were not obtained and compounds such as **215** and **216** were not screened for the

H_1R activity.It is also clear from the fact that N^{τ}-protected histamine derivatives are not able to stimulate the H_1Rs. Moreover, because of the similar reasons compounds such as **211** and **218** were also not screened.

2.4.2 Conclusion

In is concluded that the lack of H_1R agonist activity observed for aminohydroxylated products structurally related to **109** [(*rac*)-**191**, **191**, **196**] is due to the additional oxygen-containing polar functionalities attached to ethylamine side chain of **109**. The keto derivative **201** is the first 2-acyl derivative of **1** reported so far. This finding may be of importance since 2-acyl congeners of histamine (**1**) are available much more efficiently than their 2-alkyl counterparts. Moreover, agonistic activity of hydroxyl analogue **221** indicates that the carbonyl position in the side chain of keto-histaprodifen has potential for the further modifications.

2.5 Pharmacological methods

2.5.1 Pharmacology, data handling and pharmacological parameters

Data are presented as mean ± *SEM* or *SE* or with 95% confidence limits (cl) unless otherwise indicated. Agonist potencies are given in percent or are expressed as pEC_{50} values (negative decadic logarithm of the molar concentration of the agonist producing 50% of the maximal response) and were corrected according to the long term mean value of the reference agonist histamine in our laboratory (guinea-pig ileum (H_1): $pEC_{50} = 6.70$ for histamine). Maximal responses are expressed as E_{max} values (percentage of the maximal response to a reference compound). Antagonist affinities are expressed as either an apparent pA_2 or a full pA_2 value. The apparent pA_2 value was calculated from the following equation: $pA_2 = -\log c(B) + \log(r - 1)$, where $c(B)$ is the molar concentration of antagonist and r the ratio of agonist EC_{50} measured in the presence and absence of antagonist.[68] The full pA_2 value was determined according to the method of Arunlakshana and Schild[69] using antagonist concentrations over 1-2 log units. Noncompetitive antagonists are characterized by estimation of a pD'_2 value according to the equation: $pD'_2 = -\log c(B) + \log(100/E_{max} - 1)$.[70] Partial agonist affinity was estimated according to the method of Marano and Kaumann.[71] The equilibrium dissociation constant K_P for the partial agonist/receptor complex was estimated by comparing equiactive molar concentrations of the full agonist A (histamine) in the absence and presence of the partial agonist P in the same tissue according to the equation $c(A) = m \cdot c(A)^* + b$ with $m = 1/[1 + (1 - \varepsilon_P/\varepsilon_A) \cdot c(P)/K_P]$, where $c(A)$ is the molar concentration of A in the absence of P, $c(A)^*$ the molar concentration of A in the presence of P, m the slope of a weighted regression line of $c(A)$ *versus* $c(A)^*$, b the ordinate intercept, and $c(P)$ the molar concentration of P. ε_A and ε_P represent the intrinsic efficacies of A and P, respectively. Weights were calculated according to Lit.[71] If $\varepsilon_P \ll \varepsilon_A$, $pK_P = -\log K_P$ can be calculated from $\log[(1/m) - 1] = \log c(P) - \log K_P$. Where appropriate, differences between means were determined by Student's *t*-test, after checking the homogeneity of the variances; P values < 0.05 were considered to indicate a significant difference between the mean values being compared.

2.5.2 Histamine H_1R assay on the isolated guinea-pig ileum

Guinea-pigs of either sex (250-500 g) were stunned by a blow on the neck and exsanguinated. The ileum was rapidly removed, rinsed and cut into segments of 1.5-2 cm length. The tissues were mounted isotonically (preload of 5 mN) in a jacketed 20-mL organ bath that was filled with Tyrode's solution of the following composition [mM]: NaCl 137, KCl 2.7, $CaCl_2$ 1.8, $MgCl_2$ 1.0, NaH_2PO_4 0.4, $NaHCO_3$ 11.9, and glucose 5.0. The solution additionally contained atropine to block cholinergic M receptors at a concentration not affecting H_1Rs (0.05 µM). The solution was aerated with 95% O_2-5% CO_2 and warmed to a constant temperature of 37 °C. During an equilibration period of 80 min, the tissues were stimulated three times with histamine (1 µM, then 10 µM) followed by washout. *Full and partial agonists:* Each preparation was used to establish a cumulative concentration-effect curve for histamine (0.01-30 µM) followed by a second curve for a new agonist either in the absence or presence of mepyramine (1-100 nM, incubation time 10-15 min). For the determination of pK_P, the partial agonist was not washed out and incubated for a defined period of time. A final cumulative curve for histamine was then constructed. pEC_{50} differences were not corrected since up to four successive curves for histamine were superimposable ($n > 10$). *Antagonists:* Up to four cumulative concentration-response curves were determined on each tissue: a first to histamine (0.01-30 µM), and the 2nd – 4th to histamine in the presence of increasing concentrations of antagonist (incubation time 10–15 min). pEC_{50} differences were not corrected since four successive curves for histamine were superimposable ($n > 10$).

2.6 Experimental part

2.6.1 General Remarks

Where indicated, reactions were carried out under a dry, oxygen-free atmosphere of N_2 using Schlenk-technique or under argon atmosphere. Commercially available reagents were used as received. DMF, CH_3CN and CH_2Cl_2 were distilled over P_4O_{10} and stored under N_2 over molecular sieves 3Å. EtOH and MeOH were dried over Mg and stored under N_2. THF and Et_2O were distilled over Na and stored over Na wire under N_2. EtOAc, petroleum ether (60/40), $CHCl_3$, CH_2Cl_2, MeOH and hexane for chromatographic separations were distilled before use.

Thin Layer Chromatography (TLC): Silica gel 60 F_{254} on aluminum sheets of Merck Co. Ltd., (layer thickness: 0.2 mm) was used. The UV-light (λ = 254 nm) was adopted for the detection, Mostain, Vanillin sulfuric acid, Molybdato phosphoric acid (5% in EtOH), and Iodine were further used for development.

Column Chromatography: Silica gel Geduran SI 60 (70-230 mesh) or Flash silica gel 60 (230-400 mesh) purchased from Merck. Each experimental procedure gives more detailed information about the eluents.

^{1}H-NMRs: were recorded on Bruker Avance 300 (300 MHz), Bruker Avance 400 (400 MHz) and Bruker Avance 600 (600 MHz). The chemical shift (δ) is referred in ppm, which was calibrated on $CDCl_3$ (7.26 ppm), DMSO-d_6 (2.50 ppm), CD_3OD (3.31 ppm), or Tetramethylsilane (0.00 ppm) as internal standard. The coupling constant *J* are given in Hz. The abbreviations for spin-spin splitting patterns: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, ddd = doublet of doublet of doublet, dt = doublet of triplet.

^{13}C-NMRs: were recorded on Bruker Avance 300 (75.5 MHz), Bruker Avance 400 (100.6 MHz), Bruker ARX 400 (100.6 MHz), and Bruker Avance 600 (150.9 MHz). The chemical shifts are given in δ (ppm), were calibrated on $CDCl_3$ (77.16 ppm), DMSO-d_6 (39.52 ppm), CD_3OD (49.00 ppm), or Tetramethylsilane (0.00 ppm) as internal standard. The coupling constant *J* are given in Hz and the abbreviations for spin-spin splitting patterns are similar as used for ^{1}H-NMRs. The multiplicities of signals were assigned by DEPT 90 and 135 (DEPT; distortionless enhancement by polarization transfer), and the notations were allotted as follow: + = primary and tertiary C-atoms (positive DEPT 135 signal; tertiary C-atoms: DEPT 90 signal), - = secondary C-atoms (negative DEPT signal), quart = quarternary C-atoms (DEPT

signal intensity zero). In some cases the COSY, HSQC, HMBC, and NOESY signals were investigated for the exact assignment of the structure.

Melting points: were measured using the Buchi 510 or Buchi SMP 20 and are uncorrected.

IR spectra: were recorded on Bio-Rad Excalibur Series FT-IR or Mattson Genesis Series FT-IR.

Mass spectra: were measured by Thermoquest Finnigan TSQ 7000 at the Central Analytical Laboratory University of Regensburg. The percentage in the bracket referes to the relative intensity of the peak compared to base peak (I = 100 %). For HRMS, the theoretical molecular formula and weight were calculated by ChemDraw® software, the practical measured figures were accepted in having a range of ± 3 ppm accuracy.

Optical Rotation: was measured by Perkin-Elmer 241 MC polarimeter using 1.0 dm or 0.1 dm measuring cell with 589 nm wavelength of Na-D-Line as light source. The concentration was noted in [g/100ml] unit.

X-ray analysis: was performed by the Crystallography Laboratory (University of Regensburg, M. Zabel, S. Stempfhuber).

HPLC-measurement: was achieved by using Chiracel OD / OD-H RH.

2.6.2 Experimental procedures and analysis of spectral data

(E)-methyl 3-(1*H*-Imidazol-4-yl)acrylate (152)

Trans urocanic acid (42 g 304, 1 mmol) and anhydrous Na_2SO_4 (6.0 g) were added to 450 mL of anhydrous methanol. Concentrated sulfuric acid (24 mL) was added to the reaction mixture, which was heated at reflux for 30 h. The solid Na_2SO_4 was filtered off, and the solvent was removed in vacuo. The remaining white solid was dissolved in a small amount of water and neutralized with saturated aq. $NaHCO_3$ until no gas was evolved. The cloudy aqueous solution was extracted with ethyl acetate (2 × 400 mL). The organic layer was dried over Na_2SO_4, and the solvent was removed in vacuo. A white solid remained (44.56 g, 96%). **m.p.** = 92-94 °C. All data were consistent with literature.[72]

(E)-methyl 3-(1-methyl-1H-imidazol-4-yl)acrylate (163):

Dimethyl sulfate (3.4 mL) was added slowly to a stirred solution of **152** (2.9 g) in dry acetone (170 mL) and anhydrous potassium carbonate (10.2 g) and the mixture stirred at RT for a further 10 h. Filtration and removal of the solvent from the filtrate gave a viscous oil which was purified by column chromatography ($CHCl_3$/EtOH, 10:1) gave the ester **163** (1.2 g 38%) which was used further without any purification. All data were consistent with literature.[62]

(E)-methyl 3-(1-methyl-1H-imidazol-4-yl)acrylate (164):

To a solution of **163** (240 mg, 1.45 mmol) in EtOAc (10 mL) was added *m*-CPBA (299.3 mg, 1.74 mmol). The reaction mixture was stirred at RT for 24 h. Water (10 mL) was added and the reaction mixture was extracted in ethyl acetate (4 10 mL). Organic phases were combined and washed with brine (10 mL) and dried over Na_2SO_4. Filtration and evaporation gave a crude solid which was purified by column chromatography (CH_2Cl_2/MeOH, 10:2) to obtain **164** (45 mg, 17%).

R_f (SiO_2, CH_2Cl_2/MeOH, 8:2) = 0.17; **^{1}H NMR** (300 MHz CD_3OD): δ 3.74 (s, 3 H, OCH_3), 3.75 (s, 3 H, NCH_3), 6.91 (d, J = 16.26 Hz, 1 H, =C*H*CO_2), 7.56 (d, J = 16.26 Hz, 1 H, =C*H*), 7.54 (bs, 1 H, Imi-*C*5), 8.33 (bs, 1 H, Imi-*C*2); **^{13}C NMR** (75.4 MHz CD_3OD): δ = 36.2 (+, N*C*H_3), 66.9 (+, O*C*H_3), 120.31 (+, =*C*HCO_2Me), 121.2 (+, CH, Imi-*C*5), 129.3 (+, =*C*H), 129.8 (+, C_{quat}, Imi-*C*4), 131.2 (+, CH, Imi-*C*2), 167.8 (+, C_{quat}, *C*O); **MS** (EI, 70 eV): *m/z* (%) = 182.1 (49.8) [$M^{+\bullet}$], 166.1, (66.5) [M - O], 151.1 (17.2), 135.1 (100), 123.1 (42.9), 111.1 (34.5).

(E)-methyl 3-(1-((2methoxyethoxy)methyl)1*H*-Imidazol-4-yl)acrylate (171):

To a suspensation of NaH (5.8 g 144.6 mmol) in DMSO (40 mL) was added dropwise a solution of methyl urocanate (**152**) (20 g 131.5 mmol) at 0 °C. The reaction mixture was stirred at 80 °C until no gas evolved (Ca. 2 h). MEM-chloride (18 g 144.6 mmol) in DMSO (20 mL) was added dropwise and the solution was stirred for further 12 h at 80 °C, excess of DMSO was distilled under reduced pressure to leave black oil. 5% aqueous solution of $NaHCO_3$ (300 mL) was added and extracted with 1:1 mixture of CH_2Cl_2:Et_2O (3×300 mL). The combined extracts were dried and concentrated to leave a black oil which was purified by short path column chromatography (EtOAc/hexanes 9:1) to give a mixture of regioisomers (**171:172**) as brown oil (25 g 86 %) the ratio of **171** and **172** was 90:10 as determined by ^{1}H NMR. The major isomer **171** could be separated by careful column chromatography (white solid, 72 %).

R_f (SiO_2, EtOAc) = 0.17; **m.p.** = 74-75 °C; **^{1}H NMR** (300 MHz $CDCl_3$): δ 3.37 (s, 3 H OCH_3), 3.50-3.58 (m, 4 H, OC*H*$_2$C*H*$_2$O), 3.77 (s, 3 H, CO_2CH_3), 5.36 (s, 2 H, NC*H*$_2$O), 6.59 (d, J = 15.6 Hz 1 H, =C*H*CO_2), 7.25 (bs, 1 H, Imi-5*H*), 7.56 (d, J = 15.6 Hz 1 H, =C*H*), 7.64

(bs, 1 H, Imi-2*H*); **^{13}C NMR** (75.4 MHz $CDCl_3$): δ = 51.4 (+, CO_2CH_3), 58.9 (+, OCH_3), 67.8 (-, CH_2O), 71.5 (-, CH_2O), 76.7 (-, NCH_2O), 116.2 (+, *C*H, Imi-*C*5), 121.2 (+, *C*HCO_2), 135.9 (+, =*C*H), 138.7 (+, CH, Imi-*C*2), 138.8 (+, C_{quat}, Imi-*C*4), 167.8 (+, C_{quat}, *C*O); **IR** (KBr): ṽ = 3190, 2866, 2586, 1719, 1651, 1541, 1504, 1431, 1300, 1215, 1168, 1097, 852, 788, 740, 618, 512 cm^{-1}; **MS** (DCI, NH_3): *m/z* (%) = 241.2 (100) [M + H^+], 481.1, (0.52) [2 M + H^+]; **Elemental analysis** calcd (%) for $C_{11}H_{16}N_2O_4$ (240.11) C 54.99, H 6.71, N 11.66; found C 54.86, H 6.16, N 11.58.

***N*-methoxy-*N*-methyl-3,3-diphenylpropanamide (174):**

To a solution of acid chloride (**173**)[64] (11.63 g 47.5 mmol) and N,O-dimethylhydroxylamine hydrochloride (5.1 g 52.3 mmol) in $CHCl_3$ (ethanol free)[65] at 0 °C was added dropwise pyridine (8.5 mL 104.5 mmol). The reaction mixture was stirred at the same temperature for 30 min. and then reacted overnight at ambient temperature. Evaporated to dryness, water (100 mL) was added and aqueous phase was extracted in hexane (300 mL) washed with aqueous saturated $NaHCO_3$ (100 mL) and brine (100 mL). Dried over $MgSO_4$, Solvent was evaporated in rotary evaporator to leave oil, which was purified by column chromatography to obtain the product as white solid (98%).

R_f (SiO_2, hexanes/EtOAc 7:3) = 0.24; **m.p.** = 48-49 °C; ^{1}H NMR (300 MHz $CDCl_3$): δ 3.09 (s, 3 H, NCH_3), 3.18 (d, *J* = 7.68 Hz, 2 H, CH_2CO), 3.55 (s, 3 H, OCH3), 4.68 (t, *J* = 7.68 Hz, 1 H, C*H*CH_2), 7.30-7.13 (m, 10 H, aromatic); **^{13}C NMR** (CDCl3): δ = 32.3 (+, NCH_3), 38.0 (-, CH_2), 46.5 (+, *C*HCH_2), 61.4 (+, OCH_3), 126.4 (+, CH, *aromatic*), 128.0 (+, CH, *aromatic*), 128.6 (+, CH, *aromatic*), 144.3 (+, C_{quat}, *aromatic*), 172.5 (+, C_{quat}, *C*O); **IR** (KBr): ṽ = 3026, 2966, 1663, 1491, 1460, 1412, 1381, 1172, 1078, 1029, 987, 952, 777, 754, 695 cm^{-1}; **MS** (DCI, NH_3): *m/z* (%) = 270.3 (100) [M + H^+], 287.3, (66) [M + NH_4^+], 539.2, (6.7) [2 M + H^+]; **Elemental analysis** calcd for $C_{17}H_{19}NO_2$ (269.14), C 75.81, H 7.11, N 5.20; found C 75.68, H 6.40, N 5.05.

(E)-methyl3-(1-((2methoxyethoxy)methyl)-2-(3,3-diphenylpropanoyl)-1*H*-Imidazol-4-yl)acrylate (175) and (E)-methyl 3-(1-((2-methoxyethoxy)methyl)-2-(3,3-diphenylpropanoyl)-1H-imidazol-5-yl)acrylate (176):

175 **176**

A mixture of **171** (700 mg, 2.914 mmol) and Weinreb amide **174** (863 mg, 3.205 mmol) in dry THF (15 mL) was set to stir under N_2 at 0 °C. LDA (2 equiv. 5.828 mmol) in THF (7 mL) was added slowly, dropwise over a period of 4-7 min. The reaction mixture was sired at the same temperature for 1 h and allowed to warm up to RT and stirred for further 30 min. H_2O (xx mL) was added and mixture was extracted in CH_2Cl_2 (3 × 20 mL), washed with 5% aqueous $NaHCO_3$ (10 mL), Brine (10 mL), dried and concentrated to give a brown oil. Purification of this oil by column chromatography (EtOAc/Hexanes 3/7) gave **175** as white solid (48%). Recrystallization from Ether/hexanes (1:2), **175** was dissolved in ether and hexane was added slowly until precipitation, warmed up to 40 °C and kept at RT. Crystals were grown in 2 days and were suitable for the X-ray analysis. A similar reaction can also be performed on the mixture of **171** and **172** to obtain the mixture of **175** and **176** in 51% yield.

Data for **175**; $\mathbf{R}_f$ (SiO_2, hexanes/EtOAc 7:3) = 0.16; **m.p.** = 78-80 °C; **^{1}H NMR** (300 MHz $CDCl_3$): δ 3.31 (s, 3 H OCH_3), 3.36-3.42 (m, 4 H, OCH_2CH_2O), 3.80 (s, 3 H CO_2CH_3), 3,93 (d, *J* = 7.8 Hz, 2 H, $CHCH_2$), 4.79 (t, *J* = 7.8 Hz, 1 H, $=CHCH_2$), 5.70 (s, 2 H, NCH_2O), 6.70 (d, *J* = 15.64 Hz, 1 H, $CHCO_2$), 7.12-7.31 (m, 10 H, *aromatic*), 7.44 (bs, 1 H, Imi-5*H*), 7.57 (d, *J* = 15.64 Hz 1 H, =C*H*); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 45.0 (-, $CHCH_2$), 46.4 (+, $CHCH_2$), 51.7 (+, CO_2CH_3), 59.0 (+, OCH_3), 68.6 (-, OCH_2), 71.3 (-, OCH_2), 77.6 (-, NCH_2O), 118.2 (+, CH, Imi-*C*5), 125.9 (+, $=CHCO_2$), 126.4 (+, CH, *aromatic*), 127.9 (+, CH, *aromatic*), 128.6 (+, CH, *aromatic*), 135.5 (+, =*C*H), 137.9 (+, C_{quat}, Imi-*C*4), 143.3 (+, C_{quat}, Imi-*C*2), 143.8 (+, C_{quat}, *aromatic*), 167.6 (+, C_{quat}, CO_2CH_3), 191.6 (+, C_{quat}, *C*O); **IR** (KBr): $\tilde{\nu}$ = 3122, 3026, 2941, 2883, 1718, 1676, 1650, 1456, 1377, 1296, 1240, 1195, 1163, 1082, 1021, 817, 746, 727, 698, 650, 619, 575, 531 cm^{-1}; **MS** (ESI, CH_2Cl_2/MeOH/NH_4Ac): *m/z* (%) = 449.2 (100) [M + H^+], 447.0 (100) [M - H^+]; **Elemental analysis** calcd (%) for $C_{26}H_{28}N_2O_5$ (448.2): calc. C 69.63, H 6.29, N 6.25; found C 69.37, H 5.82, N 6.06.

Data for **176**; $\mathbf{R}_f$ (SiO_2, hexanes/EtOAc 7:3) = 0.18; **m.p.** = 104-105 °C; **^{1}H NMR** (300 MHz $CDCl_3$): δ 3.29 (s, 3 H OCH_3), 3.30-3.35 (m, 4 H, OCH_2CH_2O), 3.79 (s, 3 H CO_2CH_3), 3,92 (d, *J* = 7.96 Hz, 2 H, $CHCH_2$), 4.79 (t, *J* = 7.96 Hz, 1 H, $=CHCH_2$), 5.88 (s, 2 H, NCH_2O), 6.48 (d, *J* = 16.19 Hz, 1 H, $CHCO_2$), 7.11-7.16 (m, 2 H, *aromatic*), 7.21-7.31 (m, 2 H, *aromatic*), 7.53 (bs, 1 H, Imi-5*H*), 7.62 (d, *J* = 16.19 Hz 1 H, =C*H*); **^{13}C NMR** (75.5 MHz,

$CDCl_3$): δ = 45.4 (-, CH*C*H_2), 46.6 (+, *C*HCH_2), 52.0 (+, CO_2*C*H_3), 59.0 (+, O*C*H_3), 67.9 (-, O*C*H_2), 71.3 (-, O*C*H_2), 73.8 (-, NCH_2O), 121.3 (+, CH, Imi-*C*4), 129.2 (+, =*C*HCO_2), 126.5 (+, CH, *aromatic*), 127.9 (+, CH, *aromatic*), 128.6 (+, CH, *aromatic*), 131.2 (+, =*C*H), 134.1 (+, C_{quat}, Imi-*C*5), 143.7 (+, C_{quat}, *aromatic*), 144.7 (+, C_{quat}, Imi-*C*2), 166.5 (+, C_{quat}, *C*O_2CH_3), 191.6 (+, C_{quat}, *C*O); **IR** (KBr): ṽ = 2882, 2828, 1701, 1679, 1644, 1492, 1439, 1275, 1248, 1198, 1156, 1133, 1107, 1083, 1030, 851, 746, 704, 648 cm^{-1}; **MS** (CI, NH_3): *m/z* (%) = 449.3 (100) [M + H^+], 359.2 (2.3) [M - MEM], 167.1 (3.04) [$CHPh_2$], 165.1 (2.9).

benzyl(1*S*,2*S*)-1-(methoxycarbonyl)-2-(1-((2-methoxyethoxy)methyl)-2-(3,3-diphenylpropanoyl)-1*H*-imidazol-4-yl)-2-hydroxyethylcarbamate (183):
benzyl(1R,2S)-2-(methoxycarbonyl)-1-(1-((2-methoxyethoxy)methyl)-2-(3,3-diphenylpropanoyl)-1H-imidazol-4-yl)-2-hydroxyethylcarbamate (184):

A procedure for asymmetric aminohydroxylation: A 25 mL round-bottomed flask was charged with benzyl carbamate (397 mg, 2.626 mmol) and CH_3CN (4 mL). To this stirred solution was added a freshly prepared aqueous solution of NaOH (103.34 g, 2.583 mmol in 3 mL water), followed by *tert*-butyl hypochlorite (0.30 mL 280.5 mg 2.583 mmol). After 5 min a solution of $(DHQD)_2AQN$ (13 mg 0.038 mmol 5 mol %) and acrylate **175** (380 mg, 0.847 mmol) in CH_3CN (5 mL) was added in one portion followed by $K_2OsO_2(OH)_4$ (13 mg 0.034 mmol 4 mol %). The reaction mixture was stirred at 25 °C for 4 hours. Ethyl acetate (10 mL) was added and reaction mixture was extracted (3×20 mL) washes with broine (20 mL) Dried over $MgSO_4$, Solvent was evaporated in rotary evaporator to leave oil which was purified by column chromatography to obtain the mixture of regioisomers (72%).

Data for **183**; $\mathbf{R_f}$ (SiO_2, hexanes/EtOAc 7:3) = 0.14; thick oil; $[\alpha]_D^{20}$ = - 4.7 (c = 0.4, $CHCl_3$) for 75% ee; **^{1}H NMR** (300 MHz $CDCl_3$): δ = 3.30 (s, 3 H O*C*H_3), 3.34-3.37 (m, 4 H, OCH_2CH_2O), 3.54 (bs, 1 H, O*H*), 3.77 (dd, *J* = 16.40, 7.93 Hz, 1 H, CH*H*CH), 3.79 (s, 3 H CO_2CH_3), 3.87 (dd, *J* = 16.40, 7.93 Hz, 1 H, C*H*HCH), 4.75 (t, *J* = 7.93 Hz, 1 H, C*H*CH_2), 4.79 (dd, *J* = 2.59, 9.30 Hz, 1 H, C*H*NH), 5.07 (s, 2 H, CH_2, benzyl), 5.23 (bs, 1 H, C*H*OH),

5.64 (dd, *J* = 14.03, 10.36 Hz, 2 H, NCH_2O), 5.79 (d, *J* = 9.30 Hz, 1 H, N*H*), 7.10-7.17 (m, 2 H, *aromatic* + Imi-5*H*), 720-7.29 (m, 14 H, *aromatic*); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 45.1 (-, $CHCH_2$), 46.5 (+, $CHCH_2$), 52.9 (+, CO_2CH_3), 58.0 (+, *C*HNH), 59.2 (+, OCH_3), 67.2 (-, CH_2OCO), 68.4 (-, OCH_2), 68.8 (+, *C*HOH), 71.4 (-, OCH_2), 77.5 (-, NCH_2O), 121.9 (+, CH, Imi-*C*5), 126.5 (+, CH, *aromatic*), 127.9 (+, CH, *aromatic*), 128.1 (+, CH, *aromatic*), 128.3 (+, CH, *aromatic*), 128.6 (+, CH, *aromatic*), 136.2 (+, C_{quat}, Imi-*C*4), 141.5 (+, C_{quat}, *aromatic*), 141.9 (+, C_{quat}, *aromatic*), 143.8 (+, C_{quat}, Imi-*C*2), 156.4 (+, C_{quat}, $NHCO_2$), 171.2 (+, C_{quat}, CO_2CH_3), 191.1 (+, C_{quat}, *C*O); **IR** (Film): $\tilde{\nu}$ = 3423, 3061, 3030, 2927, 1726, 1681, 1599, 1516, 1455, 1339, 1213, 1056, 983, 909, 847, 736, 701 cm^{-1}; **MS** (EI, 70 eV): *m/z* (%) = 615.0 (3.53) [$M^{+\bullet}$], 507.0 (7.2) 448.(3.2) 393.1 (100) [M - (MEM + Cbz)] 303 (12.5), 207 (16.9), 167 (41.1), 165 (15.8), 108 (15.7), 91.0 (32.5), 89.0 (56.7), 59.0 (28.1); **HRMS** calcd for $C_{34}H_{37}N_{23}O_8$, 615.2581. Found 615.2579.

Data for **184**; **R_f** (SiO_2, hexanes/EtOAc 7:3) = 0.15; thick oil; $[\alpha]_D^{20}$ = - 18.5 (c = 0.4, $CHCl_3$) for 87% *ee*; **^{1}H NMR** (300 MHz $CDCl_3$): δ = 3.26 (s, 3 H, OCH_3), 3.30-3.39 (m, 4 H, OCH_2CH_2O), 3.68-384 (m, 5 H, CH_2CH + $COCH_3$), 4.63 (dd, *J* = 11.06, 5.50 Hz, 1 H, C*H*OH), 4.67 (t, *J* = 7.68 Hz, 1 H, $CHCH_2$), 5.05 (s, 2 H, CH_2, benzyl), 5.20 (dd, *J* = 1.95, 9.33 Hz, 1 H, C*H*NH), 5.53-5.65 (m, 2 H, NCH_2O), 5.70 (d, *J* = 9.43 Hz 1 H, N*H*), 7.07-7.28 (m, 16 H, *aromatic* + Imi-5*H*); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 45.1 (-, $CHCH_2$), 46.5 (+, $CHCH_2$), 51.4 (+, *C*HNH), 53.0 (+, CO_2CH_3), 59.1 (+, OCH_3), 67.3 (-, CH_2OCO), 68.6 (-, OCH_2), 71.4 (-, OCH_2), 72.5 (+, *C*HOH), 77.5 (-, NCH_2O), 122.7 (+, CH, Imi-*C*5), 126.5 (+, CH, *aromatic*), 127.9 (+, CH, *aromatic*), 128.0 (+, CH, *aromatic*), 128.3 (+, CH, *aromatic*), 128.3 (+, CH, *aromatic*), 128.4 (+, CH, *aromatic*), 128.6 (+, CH, *aromatic*), 128.7 (+, CH, *aromatic*), 136.3 (+, C_{quat}, Imi-*C*4), 142.4 (+, C_{quat}, *aromatic*), 143.8 (+, C_{quat}, Imi-*C*2), 143.8 (+, C_{quat}, *aromatic*), 155.9 (+, C_{quat}, $NHCO_2$), 172.7 (+, C_{quat}, CO_2CH_3), 191.1 (+, C_{quat}, *C*O); **IR** (Film): $\tilde{\nu}$ = 3329 (broad), 3139, 3061, 3029, 2926, 1724, 1682, 1600, 1532, 1496, 1455, 1397, 1253, 1107, 1049, 1027, 984, 918, 845, 753, 701 cm^{-1}; **MS** (ESI, CH_2Cl_2/MeOH/NH_4Ac): *m/z* = 616.2 [M + H^+], 1231.6 [2M + H^+], 1253.6 [2M + NH_4^+].

methyl 3-(1-((2-methoxyethoxy)methyl)-2-(3,3-diphenylpropanoyl)-1H-imidazol-4-yl)-2-amino-3-hydroxypropanoate (183-a)

To a solution of **183** (racemic) (80 mg 0.13 mmol) in ethanol (5 mL) was added Pd/C (8 mg, 10% wt) and purged with the atmosphere of hydrogen via balloon and stirred for 3 h, filtered through a small pad of Celite, washed with MeOH (10 mL), concentrated and purified by column chromatography (MeOH/EtOAc) to obtain the pail yellow product as a thick oil.

$\mathbf{R}_f$ (SiO_2, MeOH/EtOAc 2:8) = 0.23; thick oil; **^{1}H NMR** (300 MHz $CDCl_3$): δ = 1.74 (bs, 2 H, NH_2 exchangeable with D_2O), 3.31 (s, 3 H, OCH_3), 3.38-3.40 (m, 4 H, OCH_2CH_2O), 3.78 (s, 3 H CO_2CH_3), 3.86 (d, *J* = 7.86 Hz, 1 H, C*H*HCH), 4.05 (d, *J* = 3.16 Hz, 1 H, C*H*NH_2), 4.76 (t, *J* = 7.86 Hz, 1 H, C*H*CH_2), 5.04 (d, *J* = 3.16, Hz, 1 H, C*H*OH), 5.68 (d, *J* = 10.39 Hz, 1 H, NCH*H*O), 5.73 (d, *J* = 10.39 Hz, 1 H, NC*H*HO), 7.12-7.18 (m, 2 H, *aromatic*), 721-7.30 (m, 8 H, *aromatic*),7.31 (bs, 1 H, Imi-5*H*); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 44.9 (-, CH*C*H_2), 46.6 (+, *C*HCH_2), 52.6 (+, CO_2*C*H_3), 58.2 (+, *C*HNH_2), 59.1 (+, O*C*H_3), 68.5 (-, O*C*H_2), 69.4 (+, *C*HOH), 71.5 (-, O*C*H_2), 77.4 (-, NCH_2O), 122.9 (+, CH, Imi-*C*5), 126.5 (+, CH, *aromatic*), 128.0 (+, CH, *aromatic*), 128.1, (+, CH, *aromatic*), 128.6 (+, CH, *aromatic*), 128.6 (+, CH, *aromatic*), 142.3 (+, C_{quat}, Imi-*C*4), 143.3 (+, C_{quat}, Imi-*C*2), 143.9 (+, C_{quat}, *aromatic*), 144.0 (+, C_{quat}, *aromatic*), 173.7 (+, C_{quat}, *C*O_2CH_3), 191.3 (+, C_{quat}, *C*O); **IR** (Film): $\tilde{\nu}$ = 3400-3354 (broad), 3026, 2929, 2882, 1745, 1680, 1600, 1493, 1249, 1201, 1101, 981, 848, 754, 702, 667 cm^{-1}; **MS** (ESI, CH_2Cl_2/MeOH/NH_4Ac): *m/z* (%) = 482.2 (100) [M + H^+]; **HRMS** (EI, 70 eV) calcd for $C_{26}H_{31}N_3O_6$, 481.2291. Found 481.2284.

tert-butyl (1S,2S)-1-(methoxycarbonyl)-2-(1-((2-methoxyethoxy)methyl)-2-(3,3-diphenylpropanoyl)-1H-imidazol-4-yl)-2-hydroxyethylcarbamate (189):

To a solution of **183** (80 mg 0.13 mmol) and $(Boc)_2O$ (37 mg 0.17 mmol) in MeOH (6 mL) was added Pd/C (8 mg, 10 % wt) and purged with the atmosphere of hydrogen via balloon and stirred for 1 h, filtered through a small pad of Celite, washed with EtOAc (15 mL), concentrated and purified by column chromatography (hexanes/EtOAc 6:4) to obtain the pure product (96 %). The same reaction can also be performed on the mixture of regioisomers **183** and **184** to yield the mixture of **189** and **190**, which is readily separated by column chromatography.

R_f (SiO_2, hexanes/EtOAc 6:4) = 0.25; **m.p.** = 89-90 °C; $[\alpha]_D^{20}$ = + 7.15 (c = 1, $CHCl_3$) for 99.9 % *ee*; **^{1}H NMR** (300 MHz $CDCl_3$): δ = 1.40 (s, 9 H, NHC*Me*$_3$), 3.31 (s, 3 H, OC*H*$_3$), 3.36-3.39 (m, 4 H, OC*H*$_2$C*H*$_2$O), 3.57 (bs, 1 H, O*H*), 3.80 (dd, *J* = 16.42, 7.92 Hz, 1 H, CH*H*CH), 3.78 (s, 3 H, CO_2C*H*$_3$), 3.90 (dd, *J* = 16.42, 7.92 Hz, 1 H, C*H*HCH), 4.70 (dd, *J* = 3.05, 9.06 Hz, 1 H, C*H*NH), 4.76 (t, *J* = 7.92 Hz, 1 H, C*H*CH_2), 5.19 (dd, 1 H, *J* = 3.05, 5.32 Hz C*H*OH), 5.57 (d, *J* = 9.05 Hz, 1 H, N*H*), 5.66 (d, *J* = 10.56 Hz, 1 H, NCH*H*O), 5.70 (d, *J* = 10.56 Hz, 1 H, NC*H*HO), 7.12-7.18 (m, 2 H, *aromatic* + Imi-5*H*), 722-7.29 (m, 10 H, *aromatic* + Imi-2*H*), **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 45.1 (-, CH*C*H_2), 46.6 (+, *C*HCH_2), 52.8 (+, CO_2*C*H_3), 57.6 (+, *C*HNH), 59.1 (+, O*C*H_3), 68.5 (-, O*C*H_2), 68.9 (+, *C*HOH), 71.4 (- , O*C*H_2), 77.5 (-, NCH_2O), 80.3 (+, C_{quat}, *C*Me_3), 122.0 (+, CH, Imi-*C*5), 126.5 (+, CH, *aromatic*), 127.9 (+, CH, *aromatic*), 128.0, (+, CH, *aromatic*), 128.6 (+, CH, *aromatic*), 141.8 (+, C_{quat}, Imi-*C*4), 142.0 (+, C_{quat}, Imi-*C*2), 143.8 (+, C_{quat}, *aromatic*), 143.9 (+, C_{quat}, *aromatic*), 155.9 (+, C_{quat}, NH*C*O_2), 171.5 (+, C_{quat}, *C*O_2CH_3), 191.1 (+, C_{quat}, *C*O); **IR** (Film): ṽ = 3400, 2930, 2890, 1724 1692, 1512, 1500, 1454, 1363, 1285, 1163, 1106, 1057, 1017, 1000, 857, 784, 754, 729, 705, 615 cm^{-1}; **MS** (EI, 70 eV): *m/z* (%) = 581.3 [$M^{+\bullet}$], 508.0 (5.5), 448.(3.2) 393.2 (100) [M – (MEM + Boc)], 303 (3.9), 207 (8.9), 167 (41.1), 167 (49.7), 133 (10.3), 89.1 (91.6), 59.0 (50.1); **HRMS** calcd for $C_{31}H_{39}N_3O_8$, 581.2737. Found 581.2728.

(2*S*,3*S*)-methyl3-(2-(3,3-diphenylpropanoyl)-1*H*-imidazol-4-yl)-2-amino-3 hydroxypropanoatedihydrochloride (191):

To a solution of **189** (40 mg 0.069 mmol) in 1:1 mixture of MeOH:H_2O (2 mL) was added conc. HCl (1 mL) and the reaction mixture was refluxed for 1.5 h, cooled to RT and excess of solvent was removed using rotary evaporator and remaining yellowish solid was kept under high vacuum for 3-4 hours at 60 °C. The solid was dissolved in dry MeOH (4 mL) and Na_2SO_4 (40 mg) was added. Concentrated sulfuric acid (2 drops) was added to the reaction mixture, which was heated at reflux for 30 h. The solid Na_2SO_4 was filtered off, and the solvent was removed in vacuo. Brine (5 mL) was added and the reaction mixture was

extracted in CH_2Cl_2 (4×7 mL) dried over Na_2SO_4. After evaporation of solvent the white solid was obtained (75% over two steps).

R*f* (SiO_2, MeOH/EtOAc 3:7) = 0.16; white solid, **m.p.** = 147-154 °C; $[\alpha]_D^{20}$ = − 14.3 (c = 0.6, CH_2Cl_2); **^{1}H NMR** (300 MHz CD_3OD): δ = 3.73 (s, 3 H, COC*H*$_3$), 3.79 (dd, *J* = 1.89, 7.82 Hz, 2 H, C*H*$_2$CO), 3.87 (d, 1 H, *J* = 3.60 Hz, 1 H, C*H*NH$_2$), 4.75 (t, *J* = 7.82 Hz, 1 H, C*H*CH$_2$), 5.11 (dd, *J* = 0.72, 3.60 Hz, 1 H, C*H*OH), 7.09-7.31 (m, 10 H, *aromatic* + Imi-5*H*), **^{13}C NMR** (75.5 MHz, CD_3OD): δ = 44.5 (-, CH*C*H$_2$), 47.6 (+, *C*HCH$_2$), 52.8 (+, CO$_2$*C*H$_3$), 60.3 (+, *C*HNH$_2$), 70.3 (+, *C*HOH), 118.0 (+, CH, Imi-*C*5), 127.4 (+, CH, *aromatic*), 128.9 (+, CH, *aromatic*), 129.0 (+, CH, *aromatic*), 129.5 (+, CH, *aromatic*), 145.5 (+, C_{quat}, Imi-*C*4), 145.6 (+, C_{quat}, *aromatic*), 146.3 (+, C_{quat}, Imi-*C*2), 174.5 (+, C_{quat}, *C*O$_2$CH$_3$), 190.4 (+, C_{quat}, *C*O); **IR** (neat): $\tilde{\nu}$ = 3300-2500 (broad), 1754, 1715, 1599, 1495, 1219, 1163, 1039, 1017, 754, 698, 613 cm^{-1}; **MS** (ESI, CH_2Cl_2/MeOH/NH_4Ac): *m/z* = 394.1 [M + H^+], 787.5 [2M + H^+]; **HRMS** (EI, 70 eV) calcd for $C_{22}H_{23}N_3O_4$, 393.1689. Found 393.1688. **Elemental analysis** calcd (%) for $C_{22}H_{25}Cl_2N_3O_4$ (466.3576): calc. C, 56.66; H, 5.40; Cl, 15.20; N, 9.01; found C 56.71, H 5.68, N 8.60.

(E)- 3-(1-((2-methoxyethoxy)methyl)-1*H*-Imidazol-4-yl)prop-2-en-1-ol (177):

N OH
N
MEM

Compound **171** (2 g, 8.32 mmol) was dissolved in CH_2Cl_2 (40 mL) under N_2 and cooled to 0 °C. DIBAL-H (1 M in CH_2Cl_2, 25.8 mL, 25.8 mmol) was added dropwise. The mixture was allowed to warm up to RT slowly and stirred further for 6-8 h and cooled to 0 °C again, H_2O (9 mL) was added slowly, followed by NaOH (2N, 8 mL) and H_2O (9 mL). The mixture was filtered through Celite and washed with CH_2Cl_2 several times. The organic layer of the filtrate was separated. Water phase was extracted with CH_2Cl_2 (8×30 mL). The combined organic phase was dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and the residue was subjected to column chromatography (90/10, EtOAc/MeOH) to afford **177** as colorless thick oil (1.52 g 86%).

R*f* (SiO_2, EtOAc/MeOH) = 0.29; thick oil; **^{1}H NMR** (300 MHz $CDCl_3$): δ = 3.32 (s, 3 H OC*H*$_3$), 3.44-3.51 (m, 4 H, OC*H*$_2$C*H*$_2$O), 3.73 (bs, 1 H, OH), 4.17-4.28 (m, 2 H, C*H*$_2$OH), 5.26 (s, 2 H, NC*H*$_2$O), 6.42 (dd, *J* = 15.85, 3.74 Hz, 1 H, =C*H*CH$_2$OH), 6.48 (dd, *J* = 15.85,

3.74 Hz 1 H, =C*H*), 6.94 (d, *J* = 1.17 Hz, 1 H, Imi-5*H*), 7.52 (d, *J* = 1.17 Hz, 1 H, Imi-2*H*); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 59.1 (+, O*C*H_3), 63.1 (-, *C*H_2OH), 67.7 (-, *C*H_2O), 71.6 (-, *C*H_2O), 76.7 (-, N*C*H_2O), 116.2 (+, CH, Imi-*C*5), 121.8 (+, =C*H*), 128.7 (+, =*C*HCH_2), 137.7 (+, CH, Imi-*C*2), 140.8 (+, C_{quat}, Imi-*C*4); **IR** (Film): ṽ = 3358-3262 (broad), 3126, 2924, 2881, 1501, 1458, 1359, 1228, 1200, 1096, 1037, 969, 848, 775, 739, 628 cm^{-1}; **MS** (EI, 70 eV): *m/z* (%) = 212.1 (41.2) [$M^{+\bullet}$], 183.1, (84.6) [M^+ - C_2H_5] 123.0 (45.2) [M^+ - MEM], 89.1 (33.1), 59.1 (100), 45.1 (7.33); **HRMS** (EI, 70 eV) calcd for $C_{10}H_{16}N_2O_3$, 212.1161. Found 212.1162.

1-((2-methoxyethoxy)methyl)-4-((E)- 3-(benzyloxy)prop-1-enyl)-1*H*-Imidazole (178):

A round bottom flask charged with NaH (151 mg 60% dispersion 3.76 mmol), was added dropwise a solution of alcohol **177** in DMF (4 mL) at RT and the reaction mixture was stirred at RT for 1 h. Benzyl bromide (643 mg, 3.76 mmol, 0.48 mL) was added slowly and the reaction mixture was stirred at RT for 16 h. Water (10 mL) was added and the reaction mixture was extracted in ether (20 mL), washed with brine(10 mL) and dried ($MgSO_4$). Filtration and evaporation of the solvent afforded the crude product which was purified by column chromatography (hexanes/EtOAc) (82%).

R_f (SiO_2, EtOAc) = 0.21 Thick oil; **^{1}H NMR** (300 MHz $CDCl_3$): δ 3.35 (s, 3 H OC*H_3*), 3.46-3.53 (m, 4 H, OC*H_2*C*H_2*O), 4.17 (d, *J* = 4.80 Hz, 2 H, =CHC*H_2*), 4.55 (s, 2 H, C*H_2*O), 5.27 (s, 2 H, NC*H_2*O), 6.46 (dt, *J* = 4.84, 15.75 Hz, =C*H*CH_2), 6.54 (d, *J* = 15.81 Hz, 1 H, =C*H*), 6.98 (d, *J* = 0.95 Hz, 1 H, Imi-5*H*), 7.23-7.38 (m, 5 H, *aromatic*), 7.54 (d, *J* = 0.95 Hz, 1 H, Imi-2*H*); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 59.0 (+, O*C*H_3), 67.6 (-, *C*H_2O), 70.5 (-, *C*H_2O), 71.5 (-, *C*H_2O), 71.8 (-, O*C*H_2), 76.5 (-, N*C*H_2O), 116.3 (+, CH, Imi-*C*5), 123.9 (+, =C*H*), 125.0 (+, =*C*HCH_2), 127.5 (+, CH, *aromatic*), 127.6 (+, CH, *aromatic*), 128.3 (+, CH, *aromatic*), 137.6 (+, CH, Imi-*C*2), 138.4 (+, C_{quat}, *aromatic*), 140.8 (+, C_{quat}, Imi-*C*4); **IR** (film): ṽ = 3128, 2926, 2879, 1668, 1540, 1497, 1454, 1360, 1304, 1242, 1200, 1102, 1037, 970, 847, 746, 700, 623 cm^{-1}; **MS** (EI, 70 eV): *m/z* (%) = 302.1 (20.2) [$M^{+\bullet}$], 211.0 (24.8) [M – C_7H_7], 183.1, (46.6) [M - (Bn + C_2H_5)] 107.0 (18.3), 89.1 (64.2), 59.1 (100), 31.1 (12.3); **HRMS** (EI, 70 eV) calcd for $C_{17}H_{22}N_2O_3$, 302.1630. Found 302.1628.

1-(1-((2methoxyethoxy)methyl)4-((E)-3-(benzyloxy)prop-1-enyl)-1*H*-Imidazol -2-yl)3,3-diphenylpropan-1-one (179):

To a solution of alkene (250 mg, 0.827 mmol) in THF (2 mL) at -78 °C was added drop wise solution of n-BuLi (0.62 mL 0.992 mmol,15% sol in *n*-hexane) and the black solution was stirred at the same temperature for 1 h. Weinreb amide **174** (245 mg, 0.909 mmol) in THF (2 mL) was added slowly at -78 °C and reaction mixture was stirred at the same temperature for further 1 h and warmed up to RT and stirred for further 1.5 h. The mixture was diluted with CH_2Cl_2 (10 mL) washed with 5% aqueous Na_2CO_3 (5 mL) dried ($MgSO_4$) filtration and evaporation gave the oil which was purified by column chromatography (EtOAc/hexanes 3:7) gave **179** as a tan oil (67-69%).

$\mathbf{R_f}$ (SiO_2, hexanes/EtOAc 7:3) = 0.23; Thick oil; **^{1}H NMR** (300 MHz $CDCl_3$): δ = 3.30 (s, 3 H, OC*H*$_3$), 3.32-3.38 (m, 4 H, OC*H*$_2$C*H*$_2$O), 3.92 (d, *J* = 7.89 Hz, 2 H, C*H*$_2$CH), 4.20 (dd, *J* = 1.97 Hz, =CHC*H*$_2$O), 4.58 (s, 2 H, OC*H*$_2$Ph), 4.80 (t, *J* = 7.89 Hz, 1 H, CH$_2$C*H*), 5.68 (s, 2 H, NC*H*$_2$O), 6.50-6.61 (m, 2 H, C*H*=C*H*), 7.10-7.40 (m, 16 H, *aromatic* + Imi-5*H*), **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 45.0 (-, CH*C*H$_2$), 46.4 (+, *C*HCH$_2$), 59.0 (+, O*C*H$_3$), 68.2 (-, O*C*H$_2$), 70.4 (-, *C*H$_2$OBn), 71.3 (-, O*C*H$_2$), 72.3 (-, O*C*H$_2$Ph), 77.2 (-, NCH$_2$O), 122.3 (+, CH, Imi-*C*5), 123.4 (+, =*C*H), 126.4 (+, CH, *aromatic*), 127.2 (+, =*C*HCH$_2$), 127.7 (+, CH, *aromatic*), 127.8 (+, CH, *aromatic*), 128.0 (+, CH, *aromatic*), 128.4 (+, CH, *aromatic*), 128.5 (+, CH, *aromatic*), 138.3 (+, C_{quat}, Imi-*C*4), 140.2 (+, C_{quat}, *aromatic*), 142.5 (+, C_{quat}, Imi-*C*2), 144.0 (+, C_{quat}, *aromatic*), 191.4 (+, C_{quat}, CO); **IR** (Film): ṽ = 3059, 3028, 2924, 2874, 1678, 1493, 1454, 1427, 1361, 1303, 1245, 1200, 1105, 980, 847, 815, 733, 700, 608 cm^{-1}; **MS** (ESI): *m/z* (%) = 511.2 (100) [M + H^+]; **HRMS** (EI, 70 eV) calcd for $C_{32}H_{34}N_2O_4$, 510.2519. Found 510.2518.

Compound (180):

To a solution of allyl alcohol **177** (1 g 4.72 mmol) and TBDMS-Cl (854 mg 5.66 mmol) in DMF (2 mL) was added imidazole (803 mg 11.8 mmol). The reaction mixture was stirred at RT for 1 h. Water (10 mL) was added and the reaction mixture was extracted in ether (2×20 mL), washed with brine (10 mL) and dried ($MgSO_4$). Filtration and evaporation of the solvent afforded the crude product which was purified by column chromatography (hexanes/EtOAc 1:9) to obtain the product as thick oil (96%).

***R*f** (SiO_2, EtOAc) = 0.26; thick oil; **^{1}H NMR** (300 MHz $CDCl_3$): δ = 0.08 (s, 6 H, Si*Me*$_2$), 0.91 (s, 9 H, SiC*Me*$_3$), 3.35 (s, 3 H OC*H*$_3$), 3.47-3.54 (m, 4 H, OC*H*$_2$C*H*$_2$O), 4.32 (d, *J* = 3.50 Hz, 2 H, C*H*$_2$O), 5.29 (s, 2 H, NC*H*$_2$O), 6.41 (dt, *J* = 15.68, 4.12 Hz, 1 H, =C*H*CH_2O), 6.48 (d, *J* = 15.68 Hz 1 H, =C*H*), 6.95 (d, *J* = 0.92 Hz, 1 H, Imi-5*H*), 7.53 (d, *J* = 0.92 Hz, 1 H, Imi-2*H*); **^{13}C NMR** ($CDCl_3$): δ = – 5.1 (+, Si*Me*$_2$), 18.6 (+, C_{quat}, Si*C*Me_3), 26.1 (+, SiC*Me*$_3$), 59.2 (+, O*C*H_3), 63.7 (-, *C*H_2O), 67.7 (-, *C*H_2O), 71.7 (-, *C*H_2O), 76.7 (-, N*C*H_2O), 116.0 (+, CH, Imi-*C*5), 120.8 (+, =C*H*), 128.4 (+, =*C*HCH_2), 137.6 (+, CH, Imi-*C*2), 141.2 (+, C_{quat}, Imi-*C*4); **IR** (neat): ṽ = 2953, 2929, 2884, 2856, 1690, 1541, 1499, 1462, 1359, 1252, 1098, 1061, 1040, 966, 834, 775, 625 cm^{-1}; **MS** (EI, 70 eV): *m/z* (%) = 326.4 (78.8) [$M^{+\bullet}$], 311.3, (10.7) [M - CH_4] 269.3 (35.3) [M - C_4H_{10}], 237.2 (100) [M^+ - MEM], 193.2 (32.5), 119.1 (41.7), 89.1 (40.7), 75.1 (38.9), 59.1 (77.8); **HRMS** (EI, 70 eV) calcd for $C_{16}H_{30}N_2SiO_3$, 326.2026. Found 326.2025.

Compound (181):

To a solution of alkene **180** (760 mg, 2.33 mmol) in THF (5 mL) at -78 °C was added drop wise solution of *n*-BuLi (1.75 mL 2.80 mmol, 15% sol in *n*-hexane) and the black solution was stirred at the same temperature for 1 h. Weinreb amide **174** (690 mg, 2.5 mmol) in THF (5 mL) was added slowly at -78 °C and reaction mixture was stirred at the same temperature for further 1 h and warmed up to RT and stirred for further 1.5 h. The mixture was diluted with diethyl ether (20 mL) washed with 5% aqueous Na_2CO_3 (5 mL) dried ($MgSO_4$) filtration and evaporation gave the oil which was purified by column chromatography (EtOAc/hexanes 3/7) gave **181** (69%).

R*f* (SiO_2, hexanes/EtOAc 7:3) = 0.25; **m.p.** = 56.57 °C; **^{1}H NMR** (300 MHz $CDCl_3$): δ = 0.12 (s, 6 H, Si*Me*$_2$), 0.95 (s, 9 H, SiC*Me*$_3$), 3.31 (s, 3 H OC*H*$_3$), 3.34-3.40 (m, 4 H, OC*H*$_2$C*H*$_2$O), 3.93 (d, *J* = 7.86 Hz, 2 H, CHC*H*$_2$), 4.31-4.42 (m, 2 H, C*H*$_2$O), 4.81 (t, *J* = 7.86 Hz, 1 H, C*H*CH$_2$), 5.71 (s, 2 H, NC*H*$_2$O), 6.41 (dt, *J* = 15.68, 4.12 Hz, 1 H, =C*H*CH$_2$O), 6.47-6.59 (m, 2 H, *H*C=C*H*), 7.12-7.32 (m, 11 H, aromatic + Imi-5*H*); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = − 5.1 (+, Si*Me*$_2$), 18.6 (+, C_{quat}, Si*C*Me$_3$), 26.1 (+, SiC*Me*$_3$), 45.1 (-, *C*H$_2$CH), 46.4 (+, CH$_2$*C*H), 59.1 (+, O*C*H$_3$), 63.6 (-, *C*H$_2$O), 68.2 (-, *C*H$_2$O), 71.4 (-, *C*H$_2$O), 77.2 (-, N*C*H$_2$O), 120.4 (+, CH, Imi-*C*5), 122.0 (+, =*C*H), 126.4 (+, CH, *aromatic*), 128.1 (+, CH, *aromatic*), 128.6 (+, CH, *aromatic*), 130.5 (+, =*C*HCH$_2$), 140.7 (+, C_{quat}, Imi-*C*4) 142.5 (+, C_{quat}, Imi-*C*2), 144.1 (+,C_{quat}, *aromatic*), 191.5 (+, C_{quat}, CO); **IR** (neat): $\tilde{\nu}$ = 3119, 2927, 2857, 2856, 1685, 1493, 1452, 1359, 1274, 1125, 1082, 1066, 1022, 1006, 943, 836, 810, 769, 728, 698, 669 cm^{-1}; **MS** (EI, 70 eV): *m/z* (%) = 534.4 (59.8) [$M^{+•}$], 506.2 (12.4) [M - C_2H_6], 479.4, (22.8), 447.4 (12.2), 313.3 (29.9), 207.2 (12.1), 181.2 (12.0), 167.2 (100), 89.1 (37.6), 59.1 (54.2); **HRMS** (EI, 70 eV) calcd for $C_{31}H_{42}N_2SiO_4$, 534.2914. Found 534.2909.

1-(1-((2-methoxyethoxy)methyl)-4-((E)-3-hydroxyprop-1-enyl)-1H-imidazol-2-yl)-3,3-diphenylpropan-1-one (182):

To a solution of **181** (200 mg 0.374 mmol) in THF (5 mL) at 0 °C was added TBAF (130 mg 0.415 mmol) and the reaction mixture was stirred at RT for 1.5 h. Water (5 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (2×20 mL) and dried over $MgSO_4$. Filtration and evaporation of the solvent afforded the crude product which was purified by column chromatography (hexanes/EtOAc 3:7) to obtain the product as thick oil (91%).

R*f* (SiO_2, hexanes/EtOAc 3:7) = 0.29; thick oil; **^{1}H NMR** (300 MHz $CDCl_3$): δ = 1.60 (bs, 1 H, O*H*), 3.31 (s, 3 H, OC*H*$_3$), 3.35-3.40 (m, 4 H, OC*H*$_2$C*H*$_2$O), 3.93 (d, *J* = 7.89 Hz, 2 H, CHC*H*$_2$), 4.34 (d, 2 H, *J* = 3.36 Hz, C*H*$_2$O), 4.80 (t, *J* = 7.89 Hz, 1 H, C*H*CH$_2$), 5.71 (s, 2 H, NC*H*$_2$O), 6.51-6.66 (m, 2 H, *H*C=C*H*), 7.12-7.31 (m, 11 H, aromatic + Imi-5*H*); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 45.1 (-, *C*H$_2$CH), 46.4 (+,CH$_2$*C*H), 59.1 (+, O*C*H$_3$), 63.5 (-, *C*H$_2$O), 68.4 (-, *C*H$_2$O), 71.5 (-, *C*H$_2$O), 77.2 (-, N*C*H$_2$O), 122.1 (+, CH, Imi-*C*5), 122.3 (+, =*C*H), 126.5 (+, CH, *aromatic*), 128.1 (+, CH, *aromatic*), 128.6 (+, CH, *aromatic*), 129.9 (+,

$=C$HCH$_2$), 140.2 (+, C_{quat}, Imi-*C*4) 142.6 (+, C_{quat}, Imi-*C*2), 144.0 (+, C_{quat}, *aromatic*), 191.5 (+, C_{quat}, *C*O); **IR** (neat): $\tilde{\nu}$ = 2923, 2856, 1674, 1493, 1451, 1426, 1301, 1198, 1082, 1089, 1029, 979, 813, 750, 729, 699, 613 cm^{-1}; **MS** (EI, 70 eV): *m/z* (%) = 420.4 (56.8) [$M^{+\bullet}$], 392.4 (12.4) 331.3 [M – MEM], 301.3, (25.7), 253.2 (31.7), 211.2 (25.3), 207.2 (34.6), 167.2 (100), 138.2 (56.7), 124.1 (25.2), 89.1 (25.1), 59.1 (55.6); **HRMS** (EI, 70 eV) calcd for $C_{25}H_{28}N_2O_4$, 420.2049. Found 420.2050.

Compounds 185 and 186

185 **186**

Procedure for asymmetric aminohydroxylation: A 25 mL round-bottomed flask was charged with NaOH (49.22 mg, 1.23 mmol) in water (2 mL) and to the clear solution benzyl carbamate (189.03 mg, 1.25 mmol) was added followed by CH_3CN (1.5 mL). At this stage the solution should be homogeneous. To this stirred solution was added a freshly prepared *tert*-butyl hypochlorite (0.142 mL 133.6 mg 1.53 mmol). After 5 min a solution of $(DHQD)_2AQN$ (15.8 mg 0.021 mmol 5 mol %) and **179** (206 mg, 0.4034 mmol) in CH_3CN (4 mL) was added in one portion followed by $K_2OsO_2(OH)_4$ (5.95 mg 0.016 mmol 4 mol %). The reaction mixture was stirred at 25 °C for 1 h. Ethyl acetate (10 mL) and water (5 mL)was added and reaction mixture was extracted in EtOAc (3×10 mL) washed with brine (10 mL) and dried over $MgSO_4$. Solvent was evaporated in rotary evaporator to leave oil which was purified by column chromatography (hexanes/EtOAc 1:1) to obtain the product as mixture of regioisomers (65-67%). The regioisomers were not separable and used as such for the next reaction.

$\mathbf{R}_f$ (SiO_2, hexanes/EtOAc 7:3) = 0.17; thick oil; **MS** (ESI, CH_2Cl_2/MeOH/NH_4Ac): *m/z* = 678.4 [$M + H^+$], 712.3 [$M + Cl^-$], 736.4 [$M + CH_3CO_2^-$].

Compounds 192 and 193:

To a solution of mixture of regioisomers **185** and **186** (81 mg 0.12 mmol) and $(Boc)_2O$ (34 mg 0.15 mmol) in MeOH (3 mL) was added Pd/C (8 mg, 10% wt) and purged with the atmosphere of hydrogen via balloon and stirred for 1 h, filtered through a small pad of Celite, washed with EtOAc (15 mL), concentrated and purified by column chromatography (hexanes/EtOAc 6:4) to obtain non-separable mixture of regioisomers (92%).
R$_f$ (SiO_2, hexanes/EtOAc 7:3) = 0.19; thick oil.

Compounds 194 and 195

To a solution of mixture of regioisomers **192** and **193** (400 mg 0.621 mmol) in THF (15 mL) was added Pd/C (40 mg, 10% wt) and stirred under the atmosphere of hydrogen (40 bar 40 °C) for 48 h, filtered through a small pad of Celite, washed with MeOH (30 mL), concentrated and purified by column chromatography (hexanes/EtOAc 8:2) to obtain non-separable mixture of regioisomers (62%).
Separation of regioisomers 194 and 195: To a solution of mixture of 1,3-(**194**) and 1,2-diol (**195**) (250 mg 0.45 mmol) in dioxane:water (3:1 42 mL) at RT was added solid $NaIO_4$ (483 mg 2.25 mmol) in portions over a period of 5 min. The reaction mixture was stirred at RT for 2.5 h. Water (15 mL) was added and the reaction mixture was extracted in EtOAc (4×15 mL). The combined organic phase was washed with brine (10 mL), dried over $MgSO_4$. Filtration and evaporation gave a mixture of aldehyde and unreacted 1,3-diol. 1,3-diol (**194**) was isolated by column chromatography (hexanes/EtOAc 8:2).

Compound 194:

R*f* (SiO$_2$, EtOAc) = 0.26; thick oil; $[\alpha]_D^{20}$ = − 2.18 (c = 0.55, CHCl$_3$) for 48 % ee; **^{1}H NMR** (300 MHz CDCl$_3$): δ = 1.34 (s, 9 H, NHC*Me*$_3$), 3.24 (s, 3 H OC*H*$_3$), 3.29-3.35 (m, 4 H, OC*H*$_2$C*H*$_2$O), 3.65-3.87 (m, 5 H, CHC*H*$_2$, C*H*$_2$OH, C*H*NH), 4.68 (t, *J* = 7.62 Hz, 1 H, C*H*CH$_2$), 4.96 (d, 1 H, *J* = 3.12 Hz, C*H*OH), 5.42 (d, 1 H, *J* = 7.37 Hz, N*H*Boc), 5.63 (s, 2 H, NC*H*$_2$O), 6.51-6.66 (m, 2 H, *H*C=C*H*), 7.05-7.10 (m, 2 H, *aromatic*), 7.15-7.23 (m, 8 H, *aromatic*), 7.26 (bs, 1 H, Imi-5*H*); **^{13}C NMR** (75.5 MHz, CDCl$_3$): δ = 28.3 (+, C*Me*$_3$), 45.0 (-, *C*H$_2$CH), 46.6 (+,*C*HCH$_2$), 56.0 (+, *C*HNH), 59.0 (+, O*C*H$_3$), 63.4 (-, *C*H$_2$OH), 68.4 (-, *C*H$_2$O), 70.1 (+, *C*HOH), 71.4 (-, *C*H$_2$O), 77.4 (-, N*C*H$_2$O), 80.0 (+, C$_{quat}$, *C*Me$_3$), 122.4 (+, CH, Imi-*C*5), 126.6 (+, CH, *aromatic*), 127.9 (+, CH, *aromatic*), 128.0 (+, CH, *aromatic*), 128.5 (+, CH, *aromatic*), 142.0 (+, C$_{quat}$, Imi-*C*4), 142.7 (+, C$_{quat}$, Imi-*C*2), 143.7 (+, C$_{quat}$, *aromatic*), 143.8 (+, C$_{quat}$, *aromatic*), 156.7 (+, C$_{quat}$, NH*C*O), 191.0 (+, C$_{quat}$, *C*O); **IR** (neat): ṽ = 3400 (broad), 3000, 1720, 1682, 1494, 1454, 1366, 1249, 1165, 1103, 1050, 1030, 983, 702, 682, 672 cm^{-1}; **MS** (EI, 70 eV): *m/z* (%) = 554.4 [M + H$^+$], 393.1 (37.7), 227.1, 167.0 (34.9), 89.1 (100), 59.1 (94.2); **HRMS** (EI, 70 eV) calcd for $C_{30}H_{39}N_3O_7$, 533.2788. Found 533.2789.

1-(4-((1*S*,2*R*)-2-amino-1,3-dihydroxypropyl)-1*H*-imidazol-2-yl)3,3-diphenylpropan-1-onedihydrochloride (196):

To a solution of 1,3-diol **194** (40 mg 0.072 mmol)in 1:1 mixture of MeOH:H$_2$O (3 mL) was added concentrated HCl (1.5 mL) and refluxed for 1.5 h, evaporated to dryness on rotary evaporator and dried under high vacuum at 55 °C for 4 h to yield a glassy solid (97 %).

R*f* (SiO$_2$, CH$_2$Cl$_2$/MeOH/NH$_3$. 7:3:0.2) = 0.27; **m.p.** = 122-127 °C; $[\alpha]_D^{20}$ = -4.8 (*c* 0.6, MeOH); **^{1}H NMR** (600 MHz DMSO): δ = 3.43 (dd, *J* = 5.97, 11.10 Hz, 1 H, C*H*HOH), 3.47

(m, 1 H, C*H*NH_3), 3.55 (dd, *J* = 3.93, 11.10 Hz, 1 H, CH*H*OH), 3.87 (dd, *J* = 7.77, 17.15 Hz, 1 H, C*H*HCO), 3.93 (dd, *J* = 7.77, 17.15 Hz, 1 H, CH*H*CO), 4.68 (dd, *J* = 7.77, 7.77 Hz, 1 H, C*H*CH_2), 4.85 (d, *J* = 6.98 Hz, 1 H, C*H*OH), 4.98 (s, very broad, 2 H, imidazole N*H* and CH_2O*H*), 7.12-7.35 (m 10 H, *aromatic*), 7.51 (s 1 H, Imi-5*H*), 8.06 (bs, 3 H, CHNH_3); **^{13}C NMR** (150.9 MHz, DMSO): δ = 43.2 (–, *C*H_2CH), 45.4 (+, *C*HCH_2), 56.5 (+, *C*HNH_2), 58.3 (*C*H_2OH), 63.2 (+, *C*HOH), 121.0 (+, CH, Imi-*C*5, broad) 126.1 (+, CH, *aromatic*), 127.5 (+, CH, *aromatic*), 128.3 (+, CH, *aromatic*), 139.9 (+, C_{quat}, Imi-*C*4) 142.5 (+, C_{quat}, Imi-*C*2), 144.0 (+, C_{quat}, *aromatic*), 187.2 (+, C_{quat}, *C*O); **IR** neat: $\tilde{\nu}$ = 3400-3020 (broad), 2890, 1703, 1676, 1599, 1493, 1396, 1223, 1044, 1022, 990, 731, 699, 613 cm^{-1}; **MS** (EI, 70 eV): *m/z* (%) = 365.2 [$M^{+\bullet}$], 166.9 (18.6), 139.0 (65.0), 60.0 (12.0), 28.1 (100); **HRMS**: calcd for $C_{21}H_{23}N_3O_3$: 365.1739. Found: 365.1732.

methyl3-(1-((2methoxyethoxy)methyl)-2-(3,3-diphenylpropanoyl)-1*H*-Imidazol-4 yl)propanoate (197):

A solution of **175** (610 mg 1.36 mmol) in MeOH (20 mL) was treated with 10 wt % Pd/C (61 mg) and purged with a atmosphere of hydrogen followed by vigorous stirring in an atmosphere of hydrogen (via balloon) for 16 h. The reaction mixture was filtered through a pad of Celite, washed with MeOH (20 mL). The solvent was removed in vacuo to obtain quantitative yield of the product which was used for the next step without any purification.
R*f* (SiO_2, hexanes/EtOAc 7:3) = 0.16; thick oil; **^{1}H NMR** (300 MHz $CDCl_3$): δ = 2.73 (t, *J* = 7.39 Hz, 2 H, C*H*$_2$CO), 2.94 (t, *J* = 7.39 Hz, 2 H, C*H*$_2$$CH_2$), 3.30 (s, 3 H, OC*H*$_3$), 3.32-3.39 (m, 4 H, OC*H*$_2$C*H*$_2$O), 3.68 (s, 3 H, CO_2C*H*$_3$), 3,87 (d, *J* = 7.86 Hz, 2 H, CHC*H*$_2$), 4.78 (t, *J* = 7.86 Hz, 1 H, C*H*CH_2), 5.67 (s, 2 H, NC*H*$_2$O), 7.05 (s, 1 H, Imi-5*H*), 7.10-7.16 (m, 2 H, *aromatic*), 7.21-7.30 (m, 8 H, *aromatic*); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 23.5 (-, *C*H_2CO), 33.5 (-, CH_2*C*H_2), 44.9 (-, CH*C*H_2), 46.5 (+, *C*HCH_2), 51.7 (+, CO_2*C*H_3), 59.0 (+, O*C*H_3), 68.1 (-, O*C*H_2), 71.4 (-, O*C*H_2), 77.0 (-, NCH_2O), 122.1 (+, CH, Imi-*C*5), 126.4 (+, CH, *aromatic*), 128.0 (+, CH, *aromatic*), 128.5 (+, CH, *aromatic*), 141.9 (+, C_{quat}, Imi-*C*4), 142.2 (+, C_{quat}, Imi-*C*2), 144.0 (+, C_{quat}, *aromatic*), 173.4 (+, C_{quat}, *C*O_2CH_3), 191.2 (+, C_{quat}, *C*O); **IR** (Film): $\tilde{\nu}$ = 3027, 2927, 2890, 1738, 1673, 1600, 1489, 1430, 1365, 1260, 1200, 1129,

1099, 753, 703 cm^{-1}; **MS** (CI, NH_3): *m/z* (%) = 451.3 (100) [M + H^+], 422.2 (1.53), 167.1 (2.12);

3-(1-((2methoxyethoxy)methyl)-2-(3,3-diphenylpropanoyl)-1*H*-Imidazol-4-yl)propanoicacid (198):

A solution of **197** (530 mg, 1.17 mmol) in THF-MeOH-H_2O (3:1:1, 25 mL) at 0 °C was treated with 1 N LiOH (1.765 mmol) and the mixture was allowed to come to RT and stirred for 8 h. After most of the THF and MeOH were evaporated, the aqueous phase was acidified with the addition of 1 N HCl and extracted with CH_2Cl_2 (4×40 mL). Combined organic layers were washed with brine (20 mL), dried ($MgSO_4$) filtration and evaporation gave the corresponding acid as thick oil.

R_f (SiO_2, EtOAc) = 0.17; thick oil; **^{1}H NMR** (300 MHz $CDCl_3$): δ = 2.76 (t, *J* = 6.96 Hz, 2 H, CH_2CO), 2.94 (t, *J* = 6.96 Hz, 2 H, CH_2CH_2), 3.31 (s, 3 H, OCH_3), 3.34-3.40 (m, 4 H, OCH_2CH_2O), 3,87 (d, *J* = 7.82 Hz, 2 H, $CHCH_2$), 4.76 (t, *J* = 7.82 Hz, 1 H, $CHCH_2$), 5.67 (s, 2 H, NCH_2O), 7.07 (s, 1 H, Imi-5*H*), 7.10-7.16 (m, 2 H, *aromatic*), 7.21-7.31 (m, 8 H, *aromatic*) 9.68 (bs; 1 H, CO_2H); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 23.0 (-, CH_2CO), 33.8 (-, CH_2CH_2), 45.0 (-, $CHCH_2$), 46.5 (+, $CHCH_2$), 59.1 (+, OCH_3), 68.3 (-, OCH_2), 71.4 (-, OCH_2), 77.2 (-, NCH_2O), 122.0 (+, CH, Imi-*C*5), 126.4 (+, CH, *aromatic*), 128.0 (+, CH, *aromatic*), 128.6 (+, CH, *aromatic*), 141.6 (+, C_{quat}, Imi-*C*4), 141.9 (+, C_{quat}, Imi-*C*2), 143.9 (+, C_{quat}, *aromatic*), 177.3 (+, C_{quat}, CO_2H), 190.9 (+, C_{quat}, *C*O); **IR** (Film): $\tilde{\nu}$ = 3325 (broad), 3027, 2927, 1726, 1678, 1491, 1454, 1103, 984, 848, 751, 702 cm^{-1}; **MS** (EI, 70 eV): *m/z* (%) = 436.1 (66.6) [$M^{+\bullet}$], 349.1 (45.8) [M^+ - MEM], 269.1 (22.5), 179.1 (24.5), 154.0 (100)123.0 (13.5), 89.0 (10.7), 59.0 (36.1); **HRMS** calcd for $C_{25}H_{28}N_2O_5$ 436.1998. Found 436.1998.

benzyl2-(1-((2methoxyethoxy)methyl)-2-(3,3-diphenylpropanoyl)-1*H*-imidazol-4-yl)ethylcarbamate (199):

To a suspensation of acid **198** (300 mg, 687 mmol) in CH_2Cl_2 (4 mL) at 0 °C was slowly added Oxalyl chloride (175 mg, 1.37 mmol) and reaction mixture was stirred at room temperature for 3 h. N_2 was bubbled to remove the excess of Oxalyl chloride. CH_2Cl_2 (4 mL) was added and evaporated by bobbling N_2 and dried under high vacuum (30 min.) to remove any traces of Oxalyl chloride. Again CH_2Cl_2 (4 mL) was added followed by TMS-azide (159 mg, 1.375 mmol) and the reaction mixture was stirred at room temperature for 4 h. N_2 was bubbled and dried under high vacuum (30 min.) to leave the corresponding azide as a pale yellow oil which was used for the rearrangement without any further purification.

Rearrangement: To a solution of azide in toluene (5 mL) was added benzyl alcohol (0.5 mL) and the reaction mixture was refluxed for 18 h. The solvent was removed in vacuo. The residue was purified by chromatography on silica (hexanes/EtOAc 1:1) to obtain **199** (86%).

R_f (SiO_2, hexanes/EtOAc 1:1) = 0.27; thick oil; **^{1}H NMR** (300 MHz $CDCl_3$): δ = 2.79 (t, *J* = 6.38 Hz, 2 H, CH_2CCH_2), 3.29 (s, 3 H, OCH_3), 3.35-3.37 (m, 4 H, OCH_2CH_2O), 3.52-3.59 (m, 2 H, CH_2NH), 3,86 (d, *J* = 7.96 Hz, 2 H, $CHCH_2$), 4.76 (t, *J* = 7.96 Hz, 1 H, $CHCH_2$), 5.10 (s, 2 H, CH_2OBn), 5.46 (t, *J* = 6.38 Hz, 1 H, N*H*), 5.66 (s, 2 H, NCH_2O), 7.04 (s, 1 H, Imi-5*H*), 7.09-7.14 (m, 2 H, *aromatic*), 7.18-7.32 (m, 13 H, *aromatic*); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 28.1 (-, CH_2CH_2), 33.8 (-, CH_2NH), 44.9 (-, $CHCH_2$), 46.6 (+, $CHCH_2$), 59.0 (+, OCH_3), 66.7 (-, CH_2OCO), 68.3 (-, OCH_2), 71.4 (-, OCH_2), 77.1 (-, NCH_2O), 122.5 (+, CH, Imi-*C*5), 126.4 (+, CH, *aromatic*), 128.0 (+, CH, *aromatic*), 128.2 (+, CH, *aromatic*), 128.5 (+, CH, *aromatic*), 128.6 (+, CH, *aromatic*), 136.7 (+, C_{quat}, *aromatic*), 140.7 (+, C_{quat}, Imi-*C*4), 142.4 (+, C_{quat}, Imi-*C*2), 143.9 (+, C_{quat}, *aromatic*), 156.4 (+, C_{quat}, CO_2Bn), 191.1 (+, C_{quat}, *C*O); **IR** (Film): $\tilde{\nu}$ = 3344 (broad), 3061, 3029, 2929, 1717, 1677, 1521, 1454, 1364, 1249, 1132, 1103, 983, 910, 848, 733, 700 cm^{-1}; **MS** (ESI,CH_2Cl_2/MeOH/NH_4Ac): *m/z* = 542.4 [M + H^+].

1-(1-((2methoxyethoxy)methyl)-4-(2-aminoethyl)-1*H*-Imidazolyl)-3,3-diphenylpropan-1-one (200):

A solution of the **199** (80 mg, 0.148 mmol) in MeOH (4 mL) was treated with 10 % Pd/C (8 mg) and purged with hydrogen followed by vigorous stirring in an atmosphere of hydrogen (via balloon) for 2 h. The reaction mixture was filtered through a pad of Celite, washed with MeOH. The solvent was removed in vacuo. The residue was purified by chromatography on silica (CH_2Cl_2/MeOH/NH_3 19:1:0.5).

R*f* (SiO_2, CH_2Cl_2/MeOH 8:2:) = 0.32; thick oil; **^{1}H NMR** (300 MHz $CDCl_3$): δ = 2.18 (bs, 2 H, N*H*$_2$), 2.83 (t, *J* = 6.48 Hz, 2 H, C*H*$_2$CH$_2$), 2.93-2.98 (m, 2 H, C*H*$_2$NH$_2$), 3.28-3.40 (m, 7 H, OC*H*$_3$ + OC*H*$_2$C*H*$_2$O), 3.88 (d, *J* = 7.82 Hz, 2 H, CHC*H*$_2$), 4.78 (t, *J* = 7.82 Hz, 1 H, C*H*CH$_2$), 5.69 (s, 2 H, NC*H*$_2$O), 7.08 (s, 1 H, Imi-5*H*), 7.12-7.17 (m, 2 H, *aromatic*), 7.22-7.31 (m, 8 H, *aromatic*); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 27.9 (-, *C*H$_2$CH$_2$), 45.0 (-, CH*C*H$_2$), 46.6 (+, *C*HCH$_2$), 51.0 (-, *C*H$_2$NH), 59.1 (+, O*C*H$_3$), 68.3 (-, O*C*H$_2$), 71.5 (-, O*C*H$_2$), 77.2 (-, NCH$_2$O), 122.5 (+, CH, Imi-*C*5), 126.5 (+, CH, *aromatic*), 128.1 (+, CH, *aromatic*), 128.6 (+, CH, *aromatic*), 141.4 (+, C_{quat}, Imi-*C*4), 142.4 (+, C_{quat}, Imi-*C*2), 144.0 (+, C_{quat}, *aromatic*), 191.2 (+, C_{quat}, *C*O); **IR** (Film): ṽ = 3381, 2925, 2819, 1674, 1599, 1550, 1454, 1247, 1199, 1101, 948, 848, 797, 752, 703 cm^{-1}; **MS** (CI, NH_3) *m/z* (%) = 408.3 (5.9) [MH^+], 360.2 (96.2), 346.2 (100).

1-(4-(2-aminoethyl)-1*H*-Imidazolyl)-3,3-diphenylpropan-1-onedihydrochloride (201):

To a solution of **200** (60 mg, 0.147 mmol) in MeOH:H_20 1:1 (3 mL) was added Conc. HCl (1.5 mL) and reaction mixture was refluxed for 2 h. The solvent was removed in vacuo to leave a white solid as a hydrochloride salt (97%).

R*f* (SiO_2, CH_2Cl_2/MeOH/NH_3 10:1:0.2) = 0.13; **m.p.** = 180-182 °C; **^{1}H NMR** (300 MHz, DMSO): δ = 2.97 (t, *J* = 7.25 Hz, 2 H, C*H*$_2$CH$_2$N), 3.13 (tq, *J* = 7.25, 6.03 Hz, 2 H, C*H*$_2$NH$_3$), 3.93 (d, *J* = 7.68 Hz, C*H*$_2$CO), 4.68 (t, *J* = 7.68 Hz, 2 H, C*H*CH$_2$CO), 5.1-6.5 (s, very broad, Imi-N*H*), 7.12-7.41 (m, 10 H, *aromatic*), 7.54 (s, 1 H, Imi-5-*H*), 8.24 (s, broad 3 H, CH$_2$N*H*$_3$); **^{13}C NMR** (75.5 MHz, DMSO) δ: 23.5 (-, *C*H$_2$CH$_2$), 37.6 (-, CH*C*H$_2$), 43.51 (-, CH*C*H$_2$), 45.31 (+, *C*HCH$_2$), 121.5 (+, CH, Imi-*C*5, broad), 126.3 (+, CH, *aromatic*), 127.6 (+, CH, *aromatic*), 128.4 (+, CH, *aromatic*), 135.1 (+, C_{quat}, Imi-*C*4, broad), 141.4 (+, C_{quat}, Imi-*C*2, broad), 144.1 (+, C_{quat}, *aromatic*), 186.33(+, C_{quat}, *C*O); **IR** (KBr): $\tilde{\nu}$ = 3448, 3029, 1699, 1495, 1213, 1034, 749, 702 , 567, cm^{-1}; **HRMS**: Calcd for $C_{20}H_{21}N_3O$: 319.1685. Found: 319.1685.

1,3-bis(2-(1-((2methoxyethoxy)methyl)-2-(3,3-diphenylpropanoyl)-1*H*-imidazol-4-yl)ethyl)urea (203):

Ph Ph N H N H N N O O O N N MEM MEM Ph Ph

To a suspensation of acid **198** (300 mg, 687 mmol) in CH_2Cl_2 (4 mL) at 0 °C was slowly added Oxalyl chloride (175 mg, 1.37 mmol) and reaction mixture was stirred at room temperature for 3 h. N_2 was bubbled to remove the excess of Oxalyl chloride. CH_2Cl_2 (4 mL) was added and evaporated by bobbling N_2 and dried under high vacuum (30 min.) to remove any traces of Oxalyl chloride. Again CH_2Cl_2 (4 mL) was added followed by TMS-azide (159 mg, 1.375 mmol) and the reaction mixture was stirred at room temperature for 4 h. N_2 was bubbled and dried under high vacuum (30 min.) to leave the corresponding azide as a pale yellow oil. To a solution of azide in toluene (5 mL) was added to a flask pre heated to 80 °C and heated to 100 °C for 3 h. H_2O (3 mL) was added and the reaction mixture was refluxed for 16 h. The solvent was removed in vacuo. The residue was purified by chromatography on silica (CH_2Cl_2/MeOH 95:5)

R*f* (SiO_2, CH_2Cl_2/MeOH 95:5) = 0.16; thick oil; **^{1}H NMR** (300 MHz CDCl$_3$): δ = 2.75 (t, *J* = 6.59 Hz, 4 H, C*H*$_2$CH$_2$), 3.29 (s, 6 H, OC*H*$_3$), 3.32-3.39 (m, 8 H, OC*H*$_2$C*H*$_2$O), 3.42-3.52 (m, 4 H, C*H*$_2$NH), 3,85 (d, *J* = 7.96 Hz, 4 H, CHC*H*$_2$), 4.76 (t, *J* = 7.96 Hz, 2 H, C*H*CH$_2$), 5.00 (bs, 2 H, N*H*), 5.65 (s, 2 H, NC*H*$_2$O), 7.04 (s, 2 H, Imi-5*H*), 7.09-7.15 (m, 4 H, *aromatic*), 7.19-7.28 (m, 20 H, *aromatic*); **^{13}C NMR** (75.5 MHz, CDCl$_3$): δ = 28.6 (-, *C*H$_2$CH$_2$), 40.1 (-,

CH_2CON), 45.0 (-, CHCH_2), 46.5 (+, *C*HCH_2), 59.1 (+, OCH_3), 68.3 (-, OCH_2), 71.5 (-, OCH_2), 77.2 (-, NCH_2O), 122.6 (+, CH, Imi-*C*5), 126.4 (+, CH, *aromatic*), 128.0 (+, CH, *aromatic*), 128.6 (+, CH, *aromatic*), 141.0 (+, C_{quat}, Imi-*C*4), 142.3 (+, C_{quat}, Imi-*C*2), 144.0 (+, C_{quat}, *aromatic*), 158.3 (+, C_{quat}, *C*ONH), 191.0 (+, C_{quat}, *C*O); **IR** (film): ṽ = 3365, 3129, 3061, 2926, 1676, 1556, 1491, 1454, 1364, 1249, 1099, 1029, 982, 850, 796, 757, 702, 665, 607 cm^{-1}; **MS** (ESI,CH_2Cl_2/MeOH/NH_4Ac): *m/z* (%) = 841.6 [M + H^+].

1,3-bis(2-(2-(3,3-diphenylpropanoyl)-1*H*-imidazol-4-yl)ethyl)urea (204):

To a solution of **203** (170 mg, 0.42 mmol) in EtOH:H_20 1:1 (8 mL) was added conc. HCl (4 mL) and reaction mixture was refluxed for 1.5 h. After most of the EtOH was evaporated in vacuo, aqueous phase was made strongly basic by the addition of solid K_2CO_3 and extracted in CH_2Cl_2:MeOH 9:1 (4×20 mL) dried ($MgSO_4$) filtration and evaporation gave the free base as a white solid (92%).

R_f (SiO_2, CH_2Cl_2/MeOH 9:1) = 0.33; **m.p.** = 109-110 °C; **^{1}H NMR** (300 MHz CD_3OD): δ = 2.76 (t, *J* = 6.82 Hz, 4 H, C$H_2$$CH_2$), 3.36 (t, *J* = 6.82 Hz, 4 H, CH_2NH), 3.76 (d, *J* = 7.72 Hz, 4 H, CHCH_2), 4.74 (t, *J* = 7.72 Hz, 2 H, C*H*CH_2), 7.02 (s, 2 H, Imi-5*H*), 7.08-7.13 (m, 4 H, *aromatic*), 7.18-7.29 (m, 16 H, *aromatic*); **^{13}C NMR** (75.5 MHz, CD_3OD): δ = 28.3 (-, CH_2CH_2, broad), 40.5 (-, CH_2CON), 47.4 (+, CHCH_2), 124.8 (+, CH, Imi-*C*5, broad), 127.3 (+, CH, *aromatic*), 128.9 (+, CH, *aromatic*), 129.5 (+, CH, *aromatic*), 145.5 (+, C_{quat}, Imi-*C*4), 145.5 (+, C_{quat}, *aromatic*), 146.0 (+, C_{quat}, Imi-*C*2), 160.9 (+, C_{quat}, *C*ONH), 189.8 (+, C_{quat}, *C*O); **IR** (neat): ṽ = 3026, 1676, 1650, 1456, 1562, 1492, 1428, 1400, 1267, 1069, 1032, 966, 753, 734, 699, 666 cm^{-1}; **MS** (ESI,CH_2Cl_2/MeOH/NH_4Ac): *m/z* = 665.5 [M + H^+], 1330.9 [2M + H^+]; **Elemental analysis** calcd (%) for $C_{41}H_{40}N_6O_3$ (664.32) C 74.07, H 6.706, N 12.64; found C 73.26, H 5.64, N 12.40.

tert-butyl 2-(1-((2-methoxyethoxy)methyl)-2-(3,3-diphenylpropanoyl)-1H-imidazol-4-yl)ethylcarbamate (212):

To a solution of the **199** (1.1 g, 2.031 mmol) and $(Boc)_2O$ (532 mg 2.43 mmol) in MeOH (20 mL) was treated with 10 % Pd/C (110 mg) and purged with hydrogen followed by vigorous stirring in an atmosphere of hydrogen (via balloon) for 1 h. The reaction mixture was filtered through a pad of Celite, washed with MeOH (30 mL). The solvent was removed in vacuo. The residue was purified by chromatography on silica (EtOAc/hexanes1:1) to obtain **212** (94 %).
R_f (SiO_2, hexanes/EtOAc 6:4) = 0.33; thick oil; **^{1}H NMR** (300 MHz $CDCl_3$): δ = 1.44 (s, 9 H, C*Me*$_3$), 2.77 (t, *J* = 6.59 Hz, 2 H, C*H*$_2$CCH$_2$), 3.30 (s, 3 H, OC*H*$_3$), 3.33-3.39 (m, 4 H, OC*H*$_2$C*H*$_2$O), 3.42-3.48 (m, 2 H, C*H*$_2$NH), 3,89 (d, *J* = 7.86 Hz, 2 H, CHC*H*$_2$), 4.77 (t, *J* = 7.86 Hz, 1 H, C*H*CH$_2$), 5.30 (bs, 1 H, N*H*), 5.67 (s, 2 H, NC*H*$_2$O), 7.06 (s, 1 H, Imi-5*H*), 7.10-7.15 (m, 2 H, *aromatic*), 7.20-7.32 (m, 8 H, *aromatic*); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 28.1 (-, *C*H$_2$CH$_2$), 28.5 (+, C*Me*$_3$), 40.0 (-, *C*H$_2$NH), 44.8 (-, CH*C*H$_2$), 46.5 (+, *C*HCH$_2$), 58.9 (+, O*C*H$_3$), 68.2 (-, O*C*H$_2$), 71.3 (-, O*C*H$_2$), 77.0 (-, NCH$_2$O), 79.1 (+, C_{quat}, *C*Me$_3$), 122.4 (+, CH, Imi-*C*5), 126.3 (+, CH, *aromatic*), 127.9 (+, CH, *aromatic*), 128.5 (+, CH, *aromatic*), 140.9 (+, C_{quat}, Imi-*C*4), 142.2 (+, C_{quat}, Imi-*C*2), 143.9 (+, C_{quat}, *aromatic*), 156.4 (+, C_{quat}, *C*O$_2$Bn), 191.1 (+, C_{quat}, *C*O); **IR** (KBr): ṽ = 3362, 3061, 3026, 2977, 2928, 1730, 1679, 1512, 1455, 1392, 1366, 1250, 1169, 1105, 1050, 982, 853, 791, 751, 702 cm^{-1}; **MS** (CI, NH_3) *m/z* (%) = 508.3 (100) [MH^+], 509.4 (21.2).

tert-butyl 2-(1-((2-methoxyethoxy)methyl)-2-(1-hydroxy-3,3-diphenylpropyl)-1H-imidazol-4-yl)ethylcarbamate (217):

To a solution of **212** (65 mg 0.128 mmol) in isopropanol (2 mL) was added $NaBH_4$ (12.2 mg 0.32 mmol). The reaction mixture was stirred for 6-8 h at room temperature. The reaction

mixture was cooled to 0 °C, aqueous sat. ammonium chloride (4 mL) was added and the reaction mixture was extracted in CH_2Cl_2 (3×10 mL), washed with brine (8 mL), dried over $MgSO_4$ and concentrated in vacuo to leave an oil which was purified by column chromatography (EtOAc/hexanes 8:2) and the alcohol **217** was obtained (92 %).

R_f (SiO_2, EtOAc) = 0.30; thick oil; **^{1}H NMR** (300 MHz $CDCl_3$): δ = 1.42 (s, 9 H, C*Me*$_3$), 2.59-2.76 (m, 4 H, C*H*$_2$CH$_2$ + C*H*$_2$CH), 3.28 (s, 3 H, OC*H*$_3$), 3.31-3.44 (m, 6 H, OC*H*$_2$C*H*$_2$O + C*H*$_2$NH), 4.15 (bs, 1 H, OH), 4.23 (dd, *J* = 9.14, 6.81 Hz, 1 H, CHC*H*$_2$), 4.55 (dd, *J* = 8.26, 5.59 Hz, 1 H, C*H*OH), 4.99 (d, *J* = 10.81 Hz NC*H*HO), 5.05 (d, *J* = 10.81 Hz NCH*H*O), 5.22 (bs, 1 H, N*H*), 6.67 (s, 1 H, Imi-5*H*), 7.12-7.29 (m, 10 H, *aromatic*); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 28.0 (-, *C*H$_2$CH$_2$), 28.5 (+, C*Me*$_3$), 40.2 (-, *C*H$_2$NH), 41.5 (-, CH*C*H$_2$), 47.1 (+, *C*HCH$_2$), 59.0 (+, O*C*H$_3$), 63.9 (+, *C*HOH), 67.5 (-, O*C*H$_2$), 71.4 (-, O*C*H$_2$), 75.4 (-, NCH$_2$O), 79.1 (+, C_{quat}, *C*Me$_3$), 117.2 (+, CH, Imi-*C*5), 126.3 (+, CH, *aromatic*), 126.4 (+, CH, *aromatic*), 127.9 (+, CH, *aromatic*), 128.2 (+, CH, *aromatic*), 128.5 (+, CH, *aromatic*), 128.6 (+, CH, *aromatic*), 138.0 (+, C_{quat}, Imi-*C*4), 144.0 (+, C_{quat}, *aromatic*), 144.6 (+, C_{quat}, *aromatic*), 149.7 (+, C_{quat}, Imi-*C*2), 156.1 (+, C_{quat}, *C*O); **IR** (Film): $\tilde{\nu}$ = 3353 (broad), 3060, 2976, 2930, 1703, 1496, 1452, 1392, 1364, 1252, 1169, 1095, 1028, 736, 702 cm^{-1}; **MS** (ESI,CH_2Cl_2/MeOH/NH_4Ac): *m/z* = 510.4 [M + H^+].

1-(1-((2-methoxyethoxy)methyl)-4-(2-aminoethyl)-1H-imidazol-2-yl)-3,3-diphenylpropan-1-ol hydrochloride (218)

To a solution of **217** (40 mg, 0.0785 mmol) in MeOH:H$_2$0 1:1 (2 mL) was added Conc. HCl (1 mL) and reaction mixture was refluxed for 2 h. The solvent was removed in vacuo to leave a residue as a hydrochloride salt (quantitative).

Rf (SiO_2, CH_2Cl_2/MeOH 8:2) = 0.28; thick oil; **^{1}H NMR** (300 MHz CD_3OD): δ = 2.51-2.60 (m, 1 H, C*H*HCHOH), 2.75-2.85 (m, 1 H, CH*H*CHOH), 3.04 (t, *J* = 7.48 Hz, 2 H, C*H*$_2$CH$_2$), 3.22-3.25 (m, 2 H, C*H*$_2$NH$_2$), 3.29 (s, 3 H, OC*H*$_3$), 3.46-3.57 (m, 2 H, OC*H*$_2$CH$_2$O), 3.69 (*J* = 4.32 Hz, 2 H, OC*H*$_2$CH$_2$O), 4.93 (dd, *J* = 10.41, 5.20 Hz, 1 H, CHC*H*$_2$), 4.97 (dd, *J* = 9.07, 3.58 Hz, 1 H, C*H*OH), 5.42 (d, *J* = 10.94 Hz NC*H*HO), 5.47 (d, *J* = 10.94 Hz NCH*H*O), 7.12-7.41 (m, 10 H, *aromatic*), 7.51 (s, 1 H, Imi-5*H*); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 23.5 (-,

CH_2CH_2), 39.0 (-, *C*H_2NH_2), 42.2 (-, CH*C*H_2), 47.8 (+, *C*HCH_2), 59.2 (+, O*C*H_3), 64.2 (+, *C*HOH), 70.4 (-, O*C*H_2), 72.6 (-, O*C*H_2), 78.7 (-, NCH_2O), 121.7 (+, CH, Imi-*C*5), 127.4 (+, CH, *aromatic*), 127.7 (+, CH, *aromatic*), 128.6 (+, CH, *aromatic*), 129.2 (+, C_{quat}, Imi-*C*4), 129.3 (+, CH, *aromatic*), 129.6 (+, CH, *aromatic*), 129.8 (+, CH, *aromatic*), 144.5 (+, C_{quat}, *aromatic*), 144.6 (+, C_{quat}, *aromatic*), 152.2 (+, C_{quat}, Imi-*C*2); **IR** (KBr): ṽ = 3304 (broad), 2932, 2836, 2628, 1627, 1520, 1494, 1449, 1411, 1329, 1137, 1095, 1025, 847, 739, 699, cm^{-1}; **MS** (CI, NH_3) *m/z* (%) = 410.3 (100) [M + H^+], 392.2 (3.0), 380.2 (3.5), 200.1 (1.1).

tert-butyl 2-(1-((2-methoxyethoxy)methyl)-2-(4,4-diphenylbut-1-en-2-yl)-1H-imidazol-4-yl)ethylcarbamate (213):

To a suspension of Ph_3PCH_3I (210.3 mg 0.394 mmol) in THF (4 mL) at 0 °C was added *t*-BuOK (44.2 mg 0.394 mmol) and pail yellow reaction mixture was stirred for 10 min. and warmed to RT and stirred further for 1 h. The reaction mixture was cooled to 0 °C again and ketone **212** (100 mg 0.197 mmol) in THF (4 mL) was added. The reaction mixture was allowed to come to RT and stirred further for 2-3 h. Water (x mL) was added and the reaction mixture was extracted in ether (3×10 mL). Organic layers were combined and washed with brine (10 mL), dried over $MgSO_4$ and concentrated in vacuo to leave an oil which was purified by column chromatography (EtOAc/hexanes 4:6) to obtain **213** (95 %)

$\mathbf{R}_f$ (SiO_2, hexanes/EtOAc 6:4) = 0.30; thick oil; ^{1}**H NMR** (300 MHz $CDCl_3$): δ = 1.42 (s, 9 H, C*Me*$_3$), 2.75 (t, *J* = 6.48 Hz, 2 H, C*H*$_2CH_2$), 3.33 (s, 3 H, OC*H*$_3$), 3.37 (d, *J* = 8.37 Hz, 2 H, C*H*$_2$CH), 3.42-3.48 (m, 6 H, OC*H*$_2$C*H*$_2$O + C*H*$_2$NH), 4.17 (t, *J* = 8.37 Hz, 1 H, C*H*CH_2), 4.66 (s, 2 H, NC*H*$_2$O), 5.35 (bs, 3 H, =C*H*$_2$ + N*H*), 6.71 (s, 1 H, Imi-5*H*), 7.08-7.23 (m, 10 H, *aromatic*); ^{13}**C NMR** (75.5 MHz, $CDCl_3$): δ = 28.0 (-, *C*H_2CH_2), 28.5 (+, C*Me*$_3$), 40.4 (-, *C*H_2NH), 42.0 (-, CH*C*H_2), 50.1 (+, *C*HCH_2), 59.1 (+, O*C*H_3), 67.7 (-, O*C*H_2), 71.6 (-, O*C*H_2), 75.5 (-, NCH_2O), 79.0 (+, C_{quat}, *C*Me_3), 117.7 (+, CH, Imi-*C*5), 120.4 (-, =*C*H_2), 126.2 (+, CH, *aromatic*), 128.1 (+, CH, *aromatic*), 128.3 (+, CH, *aromatic*), 136.4 (+, C_{quat}, Imi-*C*4), 138.7 (+, C_{quat}, Imi-*C*2), 143.9 (+, C_{quat}, *aromatic*), 148.0 (+, C_{quat}, *C*=CH_2), 156.1 (+, C_{quat}, *C*O); **IR** (KBr): ṽ = 3352 (broad), 3059, 2972, 2828, 1710, 1454, 1389, 1366, 1251, 1170, 1088, 740, 703 cm^{-1}; **MS** (CI, NH_3) *m/z* (%) = 506.3 (100) [M + H^+], 340.2 (4.9), 167.0 (1.0).

tert-butyl 2-(1-((2-methoxyethoxy)methyl)-2-(4,4-diphenylbutan-2-yl)-1H-imidazol-4-yl)ethylcarbamate (214):

A solution of Comp. **213** (40 mg 0.079 mmol) in MeOH (2 mL) was treated with 10 wt % Pd/C (5 mg) and purged with a atmosphere of hydrogen followed by vigorous stirring in an atmosphere of hydrogen (via balloon) for 16 h. The reaction mixture was filtered through a pad of Celite, washed with MeOH (10 mL). The solvent was removed in vacuo to obtain quantitative yield of the product.

R_f (SiO_2, hexanes/EtOAc 1:1) = 0.25; thick oil; **^{1}H NMR** (300 MHz $CDCl_3$): δ = 1.30 (d, *J* = 6.86 Hz, C*H*$_3$CH), 1.41 (s, 9 H, C*Me*$_3$), 2.31-2.41 (m, 1 H, C*H*HCH), 2.61-2.69 (m, 1 H, CH*H*CH), 2.71-2.83 (m, 3 H, C*H*$_2$CH$_2$ + C*H*CH$_3$), 3.28-3.31 (m, 5 H, C*H*$_2$NH + OC*H*$_3$), 3.34-3.48 (m, 4 H, OC*H*$_2$C*H*$_2$O), 3.82 (dd, *J* = 9.05, 7.13 Hz, 1 H, C*H*CH$_2$), 4.59 (d, *J* = 10.98 Hz, 1 H, NCH*H*O), 4.76 (d, *J* = 10.98 Hz, 1 H, NC*H*HO), 5.27 (bs, 1 H, N*H*), 6.60 (s, 1 H, Imi-5*H*), 7.10-7.27 (m, 10 H, *aromatic*); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 20.9 (+, *C*H$_3$CH), 28.0 (-, *C*H$_2$CH$_2$), 28.5 (+, C*Me*$_3$), 29.2 (+ *C*HCH$_3$), 40.4 (-, *C*H$_2$NH$_2$), 41.8 (-, CH*C*H$_2$), 49.0 (+, *C*H*C*H$_2$), 58.1 (+, O*C*H$_3$), 67.4 (-, O*C*H$_2$), 71.5 (-, O*C*H$_2$), 74.9 (-, NCH$_2$O), 78.9 (+, C_{quat}, *C*Me$_3$), 115.8 (+, CH, Imi-*C*5), 126.2 (+, CH, *aromatic*), 126.5 (+, CH, *aromatic*), 127.8 (+, CH, *aromatic*), 128.1 (+, CH, *aromatic*), 128.4 (+, CH, *aromatic*), 128.6 (+, CH, *aromatic*), 137.9 (+, C_{quat}, Imi-*C*4), 152.3 (+, C_{quat}, Imi-*C*2), 143.9 (+, C_{quat}, *aromatic*), 144.6 (+, C_{quat}, *aromatic*), 156.1 (+, C_{quat}, *C*O); **IR** (KBr): ṽ = 3346 (broad), 2974, 2930, 1690, 1495, 1454, 1366, 1251, 1169, 1090, 853, 739, 702 cm^{-1}; **MS** (CI, NH_3) *m/z* (%) = 508.4 (100) [M + H^+], 524.2 (1.3) [M + NH_3^+].

2-((4-(2-aminoethyl)-2-(4,4-diphenylbut-1-en-2-yl)-1H-imidazol-1-yl)methoxy)ethanol hydrochloride (215))

R$_f$ (SiO_2, MeOH/EtOAc 6:4) = 0.27; thick oil; **^{1}H NMR** (300 MHz CD_3OD): δ = 3.09 (t, *J* = 7.44 Hz, 2 H, CH_2CH_2), 3.28-3.40 (m, 2 H, NH_2), 3.49 (d, *J* = 8.13 Hz, 2 H, CH_2CH), 3.65 (s, 4 H, OCH_2CH_2O), 4.13 (t, *J* = 8.13 Hz, 1 H, $CHCH_2$), 5.12 (s, 2 H, NCH_2O), 5.91-5.99 (m, 2 H, $=CH_2$), 7.13-7.19 (m, 2 H, *aromatic*), 7.23-7.31 (m, 8 H, *aromatic*) 7.59 (s, 1 H, Imi-5*H*); **^{13}C NMR** (75.5 MHz, CD_3OD): δ = 23.6 (-, CH_2CH_2), 39.0 (-, CH_2NH), 41.7 (-, $CHCH_2$), 52.0 (+, $CHCH_2$), 61.8 (-, CH_2OH), 72.8 (-, OCH_2), 78.9 (-, NCH_2O), 122.1 (+, CH, Imi-*C*5), 127.8 (+, CH, *aromatic*), 128.9 (+, CH, *aromatic*), 129.7 (+, CH, *aromatic*), 130.3 (-, $=CH_2$), 132.2 (+, C_{quat}, Imi-*C*4),144.5 (+, C_{quat}, *aromatic*), 144.7 (+, C_{quat}, Imi-*C*2), 147.5 (+, C_{quat}, $C=CH_2$); **IR** (KBr): $\tilde{\nu}$ = 3382 (broad), 2918, 1628, 1491, 1453, 1366, 1238, 1163, 1125, 1078, 1032, 955, 746, 704 cm^{-1}; **MS** (CI, NH_3) *m/z* (%) = 392.3 (53.1) [$M + H^+$], 318.2 (11.1), 226.2 (100).

methyl 3-(1-((2-methoxyethoxy)methyl)-2-(4,4-diphenylbut-1-en-2-yl)-1H-imidazol-4-yl)propanoate (211):

To a suspension of Ph_3PCH_3I (558 mg 1.043 mmol) in THF (5 mL) at 0 °C was added *t*-BuOK (117.1 mg 1.043 mmol) and pail yellow reaction mixture was stirred for 10 min. and warmed to RT and stirred further for 1 h. The reaction mixture was cooled to 0 °C again and ketone **197** (235 mg 0.522 mmol) in THF (5 mL) was added. The reaction mixture was allowed to come to RT and stirred further for 1 h. Water (x mL) was added and the reaction mixture was extracted in ether (3×10 mL), washed with brine (10 mL), dried over $MgSO_4$ and concentrated in vacuo to leave an oil which was purified by column chromatography (EtOAc/hexanes 4:6) to obtain **211** (92 %)

R$_f$ (SiO_2, hexanes/EtOAc 7:3) = 0.15; thick oil; **^{1}H NMR** (300 MHz $CDCl_3$): δ = 2.73 (t, *J* = 7.38 Hz, 2 H, CH_2CO), 2.92 (t, *J* = 7.38 Hz, 2 H, CH_2CH_2), 3.31 (s, 3 H, OCH_3), 3,35 (d, *J* = 8.30 Hz, 2 H, $CHCH_2$), 3.40-3.47 (m, 4 H, OCH_2CH_2O), 3.65 (s, 3 H, CO_2CH_3), 4.10 (t, *J* = 8.30 Hz, 1 H, $CHCH_2$), 4.61 (s, 2 H, NCH_2O), 5.29-5.31 (m, 2 H, $=CH_2$), 6.69 (s, 1 H, Imi-5*H*), 7.08-7.22 (m, 10 H, *aromatic*); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 23.5 (-, CH_2CO), 33.8 (-, CH_2CH_2), 42.0 (-, $CHCH_2$), 49.6 (+, $CHCH_2$), 51.5 (+, CO_2CH_3), 59.0 (+, OCH_3), 67.6 (-, OCH_2), 71.5 (-, OCH_2), 75.4 (-, NCH_2O), 117.1 (+, CH, Imi-*C*5), 120.0 (-, $=CH_2$), 126.1 (+,

CH, *aromatic*), 128.0 (+, CH, *aromatic*), 128.2 (+, CH, *aromatic*), 136.5 (+, C_{quat}, Imi-*C*4), 139.7 (+, C_{quat}, *C*=CH_2), 144.0, (+, C_{quat}, *aromatic*), 147.8 (+, C_{quat}, Imi-*C*2), 173.7 (+, C_{quat}, *C*O_2CH_3).

methyl 3-(1-((2-methoxyethoxy)methyl)-2-(3,3-diphenylpropanoyl)-1H-imidazol-5-yl)propanoate (205):

A solution of compound **176** (2.4 g 5.35 mmol) in MeOH (60 mL) was treated with 10 wt % Pd/C (250 mg) and purged with hydrogen followed by vigorous stirring in an atmosphere of hydrogen (via balloon) for 10 h. The reaction mixture was filtered through a pad of Celite, washed with MeOH (40 mL). The solvent was removed in vacuo to obtain quantitative yield of the product which was used for the next step without any purification.

R_f (SiO_2, hexanes/EtOAc 7:3) = 0.14; thick oil; **^{1}H NMR** (300 MHz $CDCl_3$): δ = 2.71 (t, J = 7.38 Hz, 2 H, CH_2CO), 2.98 (t, J = 7.38 Hz, 2 H, C$H_2$$CH_2$), 3.24-3.32 (m, 7 H, OC$H_2CH_2$O + OC$H_3$), 3.68 (s, 3 H, CO_2CH_3), 3,90 (d, J = 7.92 Hz, 2 H, CHCH_2), 4.78 (t, J = 7.92 Hz, 1 H, C*H*CH_2), 5.82 (s, 2 H, NCH_2O), 6.98 (s, 1 H, Imi-5*H*), 7.10-7.31 (m, 10 H, *aromatic*); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 19.5 (-, *C*H_2CO), 32.4 (-, CH_2*C*H_2), 44.9 (-, CH*C*H_2), 46.5 (+, *C*HCH_2), 51.9 (+, CO_2*C*H_3), 58.9 (+, O*C*H_3), 67.3 (-, O*C*H_2), 71.2 (-, O*C*H_2), 73.6 (-, NCH_2O), 126.3 (+, CH, *aromatic*), 127.9 (+, CH, *aromatic*), 128.0 (+, CH, Imi-*C*4), 128.5 (+, CH, *aromatic*), 138.0 (+, C_{quat}, Imi-*C*5), 143.4 (+, C_{quat}, Imi-*C*2), 144.0 (+, C_{quat}, *aromatic*), 172.5 (+, C_{quat}, *C*O_2CH_3), 191.2 (+, C_{quat}, *C*O); with calibration **IR** (neat): $\tilde{\nu}$ = 2927, 2884, 1737, 1672, 1429, 1261, 1199, 1169, 1089, 1030, 995, 924, 846, 733, 699 cm^{-1}; **MS** (CI, NH_3): *m/z* (%) = 451.2 (100) [M + H^+], 243.1 (2.65), 94.2 (1.63);

3-(1-((2-methoxyethoxy)methyl)-2-(3,3-diphenylpropanoyl)-1H-imidazol-5-yl)propanoic acid (206):

Prepared following the similar procedure for **170** (96 % yield); **R_f** (SiO_2, EtOAc) = 0.17; white solid **m.p.** = 132-133 °C; **^{1}H NMR** (300 MHz $CDCl_3$): δ = 2.75 (t, *J* = 7.31 Hz, 2 H, CH_2CO), 2.98 (t, *J* = 7.31 Hz, 2 H, CH_2CH_2), 3.26-3.32 (m, 7 H, OCH_2CH_2O + OCH_3), 3,91 (d, *J* = 7.79 Hz, 2 H, $CHCH_2$), 4.77 (t, *J* = 7.79 Hz, 1 H, $CHCH_2$), 5.82 (s, 2 H, NCH_2O), 7.07 (s, 1 H, Imi-5*H*), 7.11-7.15 (m, 2 H, *aromatic*), 7.21-7.32 (m, 8 H, *aromatic*); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 19.4 (-, CH_2CO), 32.4 (-, CH_2CH_2), 45.0 (-, $CHCH_2$), 46.4 (+, $CHCH_2$), 58.9 (+, OCH_3), 67.4 (-, OCH_2), 71.2 (-, OCH_2), 73.6 (-, NCH_2O), 126.4 (+, CH, *aromatic*), 127.7 (+, CH, Imi-*C*4), 127.9 (+, CH, *aromatic*), 128.5 (+, CH, *aromatic*), 138.0 (+, C_{quat}, Imi-*C*5), 142.9 (+, C_{quat}, Imi-*C*2), 143.9 (+, C_{quat}, *aromatic*), 176.2 (+, C_{quat}, CO_2H), 190.9 (+, C_{quat}, *C*O); **IR** (neat): ṽ = 2921, 1722, 1674, 1457, 1394, 1362, 1249, 1207, 1181, 1125, 1075, 1052, 1033, 976, 954, 862, 842, 794, 775, 750, 733, 701 cm^{-1}; **MS** (ESI, CH_2Cl_2/MeOH/NH_4Ac): *m/z* = 437.3 [M + H^+], 459.3 [M + Na^+], 391.4 [M - EtOH].

benzyl 2-(1-((2-methoxyethoxy)methyl)-2-(3,3-diphenylpropanoyl)-1H-imidazol-5-yl)ethylcarbamate (207):

Ph Ph O N N MEM NHCbz

prepared following the similr procedure for **199** (78 % yield)

R_f (SiO_2, hexanes/EtOAc 1:1) = 0.26; thick oil; **^{1}H NMR** (300 MHz $CDCl_3$): δ = 2.85 (t, *J* = 6.69 Hz, 2 H, CH_2CH_2), 3.19 (s, 3 H, OCH_3), 3.25-3.27 (m, 4 H, OCH_2CH_2O), 3.42-3.49 (m, 2 H CH_2NH), 3,90 (d, *J* = 7.92 Hz, 2 H, $CHCH_2$), 4.78 (t, *J* = 7.92 Hz, 1 H, $CHCH_2$), 4.07 (s, 2 H, CH_2OCO), 5.44 (t, *J* = 7.92 Hz, 1 H, N*H*), 5.75 (s, 2 H, NCH_2O), 6.99 (s, 1 H, Imi-5*H*), 7.08-7.13 (m, 2 H, *aromatic*), 7.18-7.31 (m, 8 H, *aromatic*); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 24.5 (-, CH_2CH_2), 39.5 (-, CH_2NH), 44.8 (-, $CHCH_2$), 46.4 (+, $CHCH_2$), 58.6 (+, OCH_3), 66.6 (-, CH_2OCO), 67.1 (-, OCH_2), 71.1 (-, OCH_2), 73.2 (-, NCH_2O), 127.9 (+, CH, *aromatic*), 128.0 (+, CH, *aromatic*), 128.1 (+, CH, *aromatic*),128.4 (+, CH, *aromatic*), 128.5 1(+, CH, *aromatic*), 29.2 (+, CH, Imi-*C*5), 136.4 (+, C_{quat}, *aromatic*), 136.5 (+, C_{quat}, Imi-*C*4), 143.4 (+, C_{quat}, Imi-*C*2), 143.9 (+, C_{quat}, *aromatic*), 156.4 (+, C_{quat}, NH*C*O), 191.1 (+, C_{quat}, *C*O); **IR** (neat): ṽ = 3356 (broad), 2927, 1717, 1672, 1529, 1494, 1450, 1426, 1242, 1133, 1085, 995, 845, 776, 735, 698 cm^{-1}; **MS** (CI, NH_3): *m/z* (%) = 542.3 (100) [M + H^+], 434.2 (6.5), 408.3 (9.6), 334.2 (6.9), 167.0 (2.4), 108.1 (3.6);

tert-butyl 2-(1-((2-methoxyethoxy)methyl)-2-(3,3-diphenylpropanoyl)-1H-imidazol-5-yl)ethylcarbamate (208)

Prepared following the similar procedure for **212** (95 % yield); **R_f** (SiO_2, hexanes/EtOAc 1:1) = 0.27; thick oil; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.43 (s, 9 H, CMe_3), 2.86 (t, *J* = 6.76 Hz, 2 H, CH_2CH_2), 3.25 (s, 3 H, OCH_3), 3.26-3.31 (m, 4 H, OCH_2CH_2O), 3.37-3.44 (m, 2 H, CH_2NH), 3,91 (d, *J* = 7.96 Hz, 2 H, $CHCH_2$), 4.79 (t, *J* = 7.96 Hz, 1 H, $CHCH_2$), 4.99 (bs, 1 H, N*H*), 5.79 (s, 2 H, NCH_2O), 7.02 (s, 1 H, Imi-5*H*), 7.09-7.15 (m, 2 H, *aromatic*), 7.20-7.31 (m, 8 H, *aromatic*); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 24.6 (-, CH_2CH_2), 28.4 (+, CMe_3), 39.1 (-, CH_2NH), 44.8 (-, $CHCH_2$), 46.5 (+, $CHCH_2$), 58.7 (+, OCH_3), 67.2 (-, OCH_2), 71.2 (-, OCH_2), 73.4 (-, NCH_2O), 79.4 (+, C_{quat}, CMe_3), 126.3 (+, CH, *aromatic*), 127.9 (+, CH, *aromatic*), 128.5 (+, CH, *aromatic*), 129.2 (+, CH, Imi-*C*5), 136.7 (+, C_{quat}, Imi-*C*4), 143.4 (+, C_{quat}, Imi-*C*2), 143.9 (+, C_{quat}, *aromatic*), 155.9 (+, C_{quat}, NH*C*O), 191.1 (+, C_{quat}, *C*O); **IR** (neat): ṽ = 3348 (broad), 3027, 2976, 2930, 1708, 1676, 1600, 1515, 1494, 1427, 1392, 1366, 1265, 1170, 1136, 1087, 1031, 847, 736, 702 cm^{-1}; **MS** (CI, NH_3): *m/z* (%) = 508.3 (100) [M + H^+], 300.2 (7.2), 228.1 (1.1), 94.1 (1.1);

tert-butyl 2-(1-((2-methoxyethoxy)methyl)-2-(1-hydroxy-3,3-diphenylpropyl)-1H-imidazol-5-yl)ethylcarbamate (209):

Prepared following the similar procedure for **217** (94 % yield); **R_f** (SiO2, EtOAc) = 0.30; thick oil; **^{1}H NMR** (300 MHz $CDCl_3$): δ = 1.43 (s, 9 H, CMe_3), 2.61-2.70 (m, 4 H, CH_2CH_2 + CH_2CH), 3.26 (s, 3 H, OCH_3), 3.24-3.35 (m, 6 H, OCH_2CH_2O + CH_2NH), 4.25 (t, *J* = 7.96 Hz, 1 H, $CHCH_2$), 4.48 (t, *J* = 6.99 Hz, 1 H, C*H*OH), 4.92 (t, *J* = 5.76 Hz, 1 H, N*H*) 4.95 (d, *J* = 10.98 Hz NC*H*HO), 5.10 (d, *J* = 10.98 Hz NCH*H*O), 6.67 (s, 1 H, Imi-5*H*), 7.12-7.26 (m, 10 H, *aromatic*); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 23.7 (-, CH_2CH_2), 27.5 (+, CMe_3), 38.5 (-, CH_2NH), 40.3 (-, $CHCH_2$), 46.1 (+, $CHCH_2$), 57.9 (+, OCH_3), 62.9 (+, *C*HOH), 66.1 (-,

OCH_2), 70.4 (-, OCH_2), 71.5 (-, NCH_2O), 78.4 (+, C_{quat}, *C*Me_3), 124.4 (+, CH, Imi-*C*5), 125.2 (+, CH, *aromatic*), 125.3 (+, CH, *aromatic*), 126.9 (+, CH, *aromatic*), 127.2 (+, CH, *aromatic*), 127.5 (+, CH, *aromatic*), 127.6 (+, CH, *aromatic*), 129.0 (+, C_{quat}, Imi-*C*4), 143.3 (+, C_{quat}, *aromatic*), 143.6 (+, C_{quat}, *aromatic*), 149.4 (+, C_{quat}, Imi-*C*2), 155.0 (+, C_{quat}, *C*O); **IR** (neat): ṽ = 3340 (broad), 3027, 2978, 2929, 1702, 1494, 1451, 1391, 1365, 1266, 1250, 1168, 1081, 1031, 892, 734, 629 cm^{-1}; **MS** (CI, NH_3) *m/z* (%) = 510.2 (100) [M + H^+], 405.2 (3.9), 300.1 (4.8), 228 (3.7).

tert-butyl 2-(1-((2-methoxyethoxy)methyl)-2-(2-methyl-3,3-diphenylpropanoyl)-1H-imidazol-5-yl)ethylmethylcarbamate (223):

To a solution of **208** (105 mg 0.207 mmol) in DMF (2 mL) at 0 °C was added NaH (60 % dispersion in oil)(15.56 mg 414 mmol) and the reaction mixture was warmed up to RT and stirred further for 2 h. Diethyl ether (5 mL) was added followed by water (4 mL). The reaction mixture was extracted in 2:1 mixture of ether and CH_2Cl_2 (3×10 mL), washed with brine (10 mL), dried over $MgSO_4$ and concentrated in vacuo to leave an oil which was purified by column chromatography (EtOAc/hexanes 1:1) to obtain **223** (83 %).

R*f* (SiO_2, hexanes/EtOAc 1:1) = 0.28; thick oil; **^{1}H NMR** (300 MHz $CDCl_3$): δ = 1.13 (d, *J* = 6.83 Hz, 3 H, C*H*$_3$CH), 1.43 (bs, 9 H, C*Me*$_3$), 2.78-2-89 (m, 6 H, NC*H*$_3$ + C*H*$_2$O + C*H*HCH_2), 3.02-3.09 (m,1 H, CH*H*CH_2), 3.14-3.24 (m, 2 H, C*H*$_2$O), 3.27 (s, 3 H, OC*H*$_3$), 3.48 (bs, 2 H, C*H*$_2$NH), 4.28 (d, *J* = 11.87 Hz, 1 H, C*H*CHCH_3), 4.93-5.04 (m, 1 H, C*H*CH_3), 5.59 (d, *J* = 10.94 Hz, NC*H*HO), 6.02 (d, *J* = 10.94 Hz, NC*H*HO), 6.96-7.18 (m, 5 H, *aromatic*), 7.24-7.40 (m, 6 H, *aromatic* + Imi-4*H*); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 17.9 (+, *C*H_3CH), 22.5-22.9 (-, *C*H_2CH_2, rotamer), 28.4 (+, C*Me*$_3$), 34.4-34.7 (+, N*C*H_3, rotamer), 45.2 (+, *C*H*C*H_2), 47.3-47.9 (-, *C*H_2NH, rotamer), 54.8 (+, *C*HCHCH_3), 58.9 (+, O*C*H_3), 66.9 (-, O*C*H_2), 71.1 (-, O*C*H_2), 73.4 (-, NCH_2O), 79.8 (+, *C*Me_3), 126.0 (+, CH, *aromatic*), 126.5 (+, CH, *aromatic*), 128.0 (+, CH, *aromatic*), 128.3 (+, CH, *aromatic*), 128.4 (+, CH, *aromatic*), 128.6 (+, CH, *aromatic*), 128.9-129.0 (+, CH, Imi-*C*4, rotamer), 136.9 (+, C_{quat}, Imi-*C*5), 143.0 (+, C_{quat}, Imi-*C*2), 143.1 (+, C_{quat}, *aromatic*), 143.8 (+, C_{quat}, *aromatic*), 155.4-155.6 (+,C_{quat}, NH*C*O, roramer), 196.4 (+, C_{quat}, *C*O); **IR** (KBr): ṽ = 2974, 2930, 1694, 1678, 1453, 1422, 1393,

1366, 1146, 1104, 993, 847, 744, 702 cm^{-1}; **MS** (ESI,CH_2Cl_2/MeOH/NH_4Ac): *m/z* = 536.5 [M + H^+].

2-methyl-1-(4-(2-(methylamino)ethyl)-1H-imidazol-2-yl)-3,3-diphenylpropan-1-one dihydrochloride (224):

To a solution of **223** (60 mg, 0.112 mmol) in MeOH:$H_2$0 1:1 (3 mL) was added Conc. HCl (1.5 mL) and reaction mixture was refluxed for 2 h. The solvent was removed in vacuo to leave a white solid as a hydrochloride salt.

$\mathbf{R_f}$ (SiO_2, = 0.33; white solid **m.p.** = 238-240 °C; **^{1}H NMR** (300 MHz CD_3OD): δ = 1.22 (d, *J* = 6.72 Hz, 3 H, C*H*$_3$CH), 2.77 (s, 3 H, NC*H*$_3$), 3.20 (t, *J* = 6.80 Hz, 2 H, C*H*$_2$CH$_2$), 3.36-3.41 (m, 2 H, C*H*$_2$NH), 4.25 (d, *J* = 11.42 Hz, 1 H, C*H*CHCH$_3$), 4.63-4.73 (m, 1 H, C*H*CH$_3$), 7.10-7.15 (m, 2 H, *aromatic*), 7.00-7.20 (m, 4 H, *aromatic*); 7.33-7.38 (m, 4 H, *aromatic*), 750-752 (m, 2 H, *aromatic*), 7.62 (s, 1 H, Imi-5*H*); **^{13}C NMR** (75.5 MHz, CD_3OD): δ = 17.1 (+, *C*H$_3$CH), 22.9 (-, *C*H$_2$CH$_2$), 33.7 (+, N*C*H$_3$), 47.6 (+, *C*H*C*H$_2$), 56.8 (+, *C*HCHCH$_3$), 122.0 (+, CH, Imi-*C*5), 127.8 (+, CH, *aromatic*), 128.0 (+, CH, *aromatic*), 129.1 (+, CH, *aromatic*), 129.4 (+, CH, *aromatic*), 129.7 (+, CH, *aromatic*), 129.9 (+, CH, *aromatic*), 134.1 (+, C_{quat}, Imi-*C*4), 141.2 (+, C_{quat}, Imi-*C*2), 143.1 (+, C_{quat}, *aromatic*), 144.0 (+, C_{quat}, *aromatic*), 190.7 (+, C_{quat}, *C*O); **IR** (KBr): ṽ = 3434 (broad), 2932, 2770, 2730, 1697, 1494, 1452, 1426, 1376, 1339, 1221, 1082, 1047, 947, 749, 704, 635, 592 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%) = 347.3 (1) [$M^{+\bullet}$], 304.2 (37.8) [M – C_2H_5N], 167.0 (38.9) [$CHPh_2^+$], 91.1 (8.9), 44.1 (100), 32.1 (12.5). **HRMS**: Calcd for $C_{22}H_{25}N_3O$: 347.1998. Found: 347.1994.

tert-butyl 2-(2-(3,3-diphenylpropanoyl)-1H-imidazol-4-yl)ethylcarbamate(219):

To a solution of dihydrochloride salt **201** (230 mg 0.586 mmol) and $(Boc)_2O$ (166 mg 0.762 mmol) in water (4 mL) was added dropwise a solution of NaOH (70 mg 1.759 mmol) in water (2 mL). The reaction mixture was stirred at RT for 30 min. and extracted in extracted in 6:4 mixture of ether and CH_2Cl_2 (3×10 mL). Organic phases were combined and washed with brine (10 mL), dried over $MgSO_4$ and concentrated in vacuo to leave an oil which was purified by column chromatography (EtOAc/hexanes 1:1) to obtain **219** (91 %)

R_f (SiO_2, hexanes/EtOAc 4:6) = 0.27; white solid; **m.p.** =78-80 °C; **^{1}H NMR** (300 MHz $CDCl_3$): δ = 1.42 (s, 9 H, C*Me*$_3$), 2.77 (t, *J* = 6.89 Hz, 2 H, C*H*$_2$CH$_2$), 3.39 (bs, 2 H, C*H*$_2$NH), 3,89 (d, *J* = 7.68 Hz, 2 H, CHC*H*$_2$), 4.79 (t, *J* = 7.68 Hz, 1 H, C*H*CH$_2$), 525 (bs, 1 H, N*H*, very broad), 6.93 (bs, 1 H, Imi-5*H*), 7.11-7.16 (m, 2 H, *aromatic*), 7.20-7.30 (m, 8 H, *aromatic*),11.15 (bs, 1 H Imi-N*H*); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 26.8 (-, *C*H$_2$CH$_2$ very broad), 28.5 (+, C*Me*$_3$), 39.9 (-, *C*H$_2$NH, broad), 43.5 (-, CH*C*H$_2$), 46.0 (+, *C*HCH$_2$), 79.6 (+,C_{quat}, *C*Me$_3$), 118.2 (+, CH, Imi-*C*5 broad), 126.4 (+, CH, *aromatic*), 127.8 (+, CH, *aromatic*), 128.5 (+, CH, *aromatic*), 142.0 (+, C_{quat}, Imi-*C*4, broad), 144.0 (+, C_{quat}, *aromatic*),144.6 (+, C_{quat}, Imi-*C*2), 156.2 (+, C_{quat}, NH*C*O), 189.9 (+, C_{quat}, *C*O); **IR** (Film): $\tilde{\nu}$ = 3270 (broad), 3022, 2976, 1690. 1674, 1393, 1366, 1250, 1169, 1069, 959, 849, 753, 701 cm^{-1}; **MS** (CI, NH_3) *m/z* (%) = 420.2 (100) [M + H^+], 254.1 (5.0).

tert-butyl 2-(2-(1-hydroxy-3,3-diphenylpropyl)-1H-imidazol-4-yl)ethylcarbamate (220):

To a solution of **219** (46 mg 0.11 mmol) in isopropanol (2 mL) was added $NaBH_4$ (12 mg 0.33 mmol). The reaction mixture was stirred for 6-8 h at room temperature. The reaction mixture was cooled to 0 °C, aqueous sat. ammonium chloride (4 mL) was added and the reaction mixture was extracted in CH_2Cl_2 (3×10 mL), washed with brine (8 mL), dried over $MgSO_4$ and concentrated in vacuo to leave an oil which was purified by column chromatography (EtOAc/hexanes 8:2).

R_f (SiO_2, EtOAc) = 0.23; white solid; **m.p.** =135-137 °C; **^{1}H NMR** (300 MHz $CDCl_3$): δ = 1.41 (s, 9 H, C*Me*$_3$), 2.35-2.45 (m, 1 H, CH*H*CH), 2.54 (t, 2 H, C*H*$_2$CH$_2$), 2.61 (dd, *J* = 9.71, 4.22 Hz, 1 H, CH*H*CH), 3.19 (dd, *J* = 12.73, 6.55 Hz, 2 H, C*H*$_2$NH), 4.21 (dd, *J* = 9.71, 5.69 Hz, 1 H, C*H*CH$_2$), 4.47 (dd, *J* = 8.78, 4.22 Hz, 1 H, C*H*OH), 5.09 (t, *J* = 6.55 Hz,1 H, N*H*),

6.44 (s, 1 H, Imi-5*H*), 7.09-7.23 (m, 10 H, *aromatic*); ^{13}**C NMR** (75.5 MHz, $CDCl_3$): δ = 27.4 (-, *C*H_2CH_2), 28.5 (+, C*Me*$_3$), 40.2 (-, *C*H_2NH), 42.2 (-, CH*C*H_2), 46.9 (+, *C*H*C*H_2), 65.8 (+, *C*HOH), 79.5 (+,C_{quat}, *C*Me_3), 116.7 (+, CH, Imi-*C*5, broad), 126.2 (+, CH, *aromatic*), 126.4 (+, CH, *aromatic*), 127.9 (+, CH, *aromatic*), 128.3 (+, CH, *aromatic*), 128.5 (+, CH, *aromatic*), 128.6 (+, CH, *aromatic*), 134.3 (+, C_{quat}, Imi-*C*4, broad), 143.7 (+, C_{quat}, *aromatic*), 144.9 (+, C_{quat}, *aromatic*), 150.7 (+, C_{quat}, Imi-*C*2), 156.2 (+, C_{quat}, *C*O); **IR** (KBr): $\tilde{\nu}$ = 3356 (broad), 3027, 2977, 2931, 1690, 1451, 1392, 1366, 1275, 1253, 1169, 1056, 753, 702 cm^{-1}; **MS** (CI, NH_3) *m/z* (%) = 422.2 (100) [M + H^+], 348.1 (2.0), 254 (3.0), 228.9 (10.2), 212.1 (3.4).

1-(4-(2-aminoethyl)-1H-imidazol-2-yl)-3,3-diphenylpropan-1-ol dihydrochloride (221):

To a solution of **00** (40 mg, 0.095 mmol) in ether (2 mL) was added a solution of saturated HCl in ether (2 mL) and reaction mixture was stirred for 16 h. The solvent was removed in vacuo to leave a white solid as a hydrochloride salt (quantitative).

R*f* (SiO_2, CH_2Cl_2/MeOH/NH_3 10:3:0.2) = 0.17; white solid; **m.p.** = 195-197 °C; ^{1}**H NMR** (300 MHz DMSO): δ = 2.36 (ddd, *J* = 14.11, 9.82, 4.56 Hz, C*H*HCH), 2.89-2.97 (m, 3 H, CH*H*CH + C*H*$_2CH_2$), 3.05-3.16 (m, 2 H, C*H*$_2$NH), 3.58 (bs, 1 H, OH), 4.31 (dd, *J* = 10.70, 4.56 Hz, 1 H, C*H*CH_2), 4.62 (dd *J* = 9.81, 2.85 Hz, 1 H, C*H*OH), 6.58 (bs, 1 H, Imi-5*H*), 7.12-7.36 (m, 8 H, *aromatic*), 7.44-7.47 (m, 2 H, *aromatic*), 8.32 (bs, 3 H, N*H*$_3$), 14.22 (bs, I H, Imi-N*H*), 14.58 (bs, 1 H, Imi-N^+*H*). ^{13}**C NMR** (75.5 MHz, DMSO): δ = 22.3 (-, *C*H_2CH_2), 37.1 (-, *C*H_2NH), 40.3 (-, *C*H_2CH), 46.0 (+, *C*H*C*H_2), 62.9 (+, *C*HOH), 116.2 (+, CH, Imi-*C*5), 126.1 (+, CH, *aromatic*), 126.3 (+, CH, *aromatic*), 127.4 (+, CH, *aromatic*), 128.1 (+, CH, *aromatic*), 128.4 (+, CH, *aromatic*), 128.4 (+, C_{quat}, Imi-*C*4),128.5 (+, CH, *aromatic*), 142.9 (+, C_{quat}, *aromatic*), 144.9 (+, C_{quat}, *aromatic*), 149.6 (+, C_{quat}, Imi-*C*2); **IR** (KBr): $\tilde{\nu}$ = 3375 (broad), 2924, 1638, 1600, 1494, 1448, 1227, 1082, 1031, 947, 846, 753, 702 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%) = 321.1 (3.6) [$M^{+\bullet}$], 292.2 (71.8) [M – CH_2NH_3], 217.2 (70.7), 167.0 (100) [$CHPh_2$], 141.1 (47.8), 107.1 (80.8), 81.1 (11.6). **HRMS**: Calcd for $C_{20}H_{23}N_3O$: 321.1841. Found: 321.1842.

Compounds (226) and (227):

226 227

A 92:8 mixture of **171** and **172** (3.2 g, 13.32 mmol) was dissolved in THF-MeOH-H_2O (3:1:1, 65 mL) and cooled to 0 °C and treated with LiOH (19.98 mmol) dissolved in water (15 mL). The reaction mixture was allowed to come to RT and stirred for 8 h. After most of the THF and MeOH were evaporated, the aqueous phase was acidified (p*H* = 4) with the addition of 2 N HCl and extracted with CH_2Cl_2 (6×40 mL). Combined organic layers were washed with brine (20 mL), dried ($MgSO_4$) filtration and evaporation gave a nonseparable mixture (93:7) of acids **226** and **227** (84%).

Compounds (228) and (229):

228 229

A solution of mixture of **226** and **227** (2.7 g 11.935 mmol) in MeOH (80 mL) was treated with 10 wt % Pd/C (270 mg) and purged with an atmosphere of hydrogen followed by vigorous stirring in an atmosphere of hydrogen (via balloon) for 12 h. The reaction mixture was filtered through a pad of Celite, washed with MeOH (60 mL). The solvent was removed in vacuo to obtain a mixture of **228** and **229** (93 %) which was used for the next step without any purification.

Compounds (230) and (231):

230 231

To a suspensation of mixture of acids **228** and **229** (1.8 g, 7.89 mmol) in CH_2Cl_2 (25 mL) at 0 °C was slowly added Oxalyl chloride (2.0 g, 1.35 mL, 15.78 mmol) and reaction mixture was stirred at room temperature for 3 h. N_2 was bubbled to remove the excess of Oxalyl chloride. CH_2Cl_2 (10 mL) was added and evaporated by bobbling N_2 and dried under high vacuum (30 min.) to remove any traces of Oxalyl chloride. Again CH_2Cl_2 (25 mL) was added followed by TMS-azide (1.82 g, 2.06 mL, 15.78 mmol) and the reaction mixture was stirred at room temperature for 4 h. N_2 was bubbled and dried under high vacuum (30 min.) to leave the corresponding azide as a pale yellow oil which was used for the rearrangement without any further purification.

Rearrangement: To a solution of azide in toluene (30 mL) was added benzyl alcohol (5.5 mL) and the reaction mixture was refluxed for 18 h. The solvent was removed in vacuo. The residue was purified by chromatography on silica (hexanes/EtOAc 1:1) to obtain a nonseparable mixture of **230** and **231** (72 %).

tert-butyl 2-(1-((2-methoxyethoxy)methyl)-1H-imidazol-4-yl)ethylcarbamate (232):

To a solution of the mixture of **230** and **231** (358 mg, 1.075 mmol) and $(Boc)_2O$ (281 mg 2.43 mmol) in MeOH (10 mL) was treated with 10 % Pd/C (40 mg) and purged with hydrogen followed by vigorous stirring in an atmosphere of hydrogen (via balloon) for 1 h. The reaction mixture was filtered through a pad of Celite, washed with MeOH (20 mL). The solvent was removed in vacuo. The residue was purified by chromatography on silica (EtOAc/hexanes1:1) to obtain a mixture of **232** and **233**. However at this stage regioisomers could be separated by column chromatography and **232** was obtained (83 %).

R*f* (SiO_2, EtOAc) = 0.22; thick oil; **^{1}H NMR** (300 MHz $CDCl_3$): δ = 1.39 (s, 9 H, C*Me*$_3$), 2.71 (t, *J* = 6.62 Hz, 2 H, C*H*$_2$CH$_2$), 3.32 (s, 3 H OC*H*$_3$), 3.34-3.40 (m, 2 H, C*H*$_2$NH), 3.45-3.52 (m, 4 H, OC*H*$_2$C*H*$_2$O), 3,89 (d, *J* = 7.86 Hz, 2 H, CHC*H*$_2$), 4.77 (t, *J* = 7.86 Hz, 1 H, C*H*CH$_2$), 5.15 (bs, 1 H, N*H*), 5.26 (s, 2 H, NC*H*$_2$O), 6.81 (s, 1 H, Imi-5*H*), 7.53 (s, 1 H, Imi-2*H*); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 28.4 (-, *C*H$_2$CH$_2$), 28.5 (+, C*Me*$_3$), 40.2 (-, *C*H$_2$NH), 59.1 (+, O*C*H$_3$), 67.7 (-, O*C*H$_2$), 71.6 (-, O*C*H$_2$), 76.6 (-, NCH$_2$O), 79.0 (+,C_{quat}, *C*Me$_3$), 115.6 (+, CH, Imi-*C*5), 137.1 (+, CH, Imi-*C*2), 140.9 (+, C_{quat}, Imi-*C*4), 156.1 (+, C_{quat}, NH*C*O); **IR**

(KBr): $\tilde{\nu}$ = 3541, 3356, 2974, 2928, 2881, 1711, 1452, 1392, 1364, 1177, 1089, 1035, 984, 956, 922, 853, 758, 623 cm^{-1}; **MS** (CI, NH_3) *m/z* (%) = 300.1 (100) [$M + H^+$].

3. Synthesis of conformationaly restricted analogs of FUB-372 and proxyfan: Interaction with histamine H_3-Receptor

3.1 Introduction

Drugs targeting G-protein coupled receptors (GPCRs) represent one of the most successful classes of pharmaceutical remedies known. It was estimated that at present more than 50% of all available drugs act directly via stimulating or blocking GPCRs.[73] Histamine has proven to exert tremendous influence over a variety of physiological processes including inflammatory triple response and gastric acid secretion. The importance of histamine H_1 and H_2 receptor agonists and specially antagonists is unquestioned to the human health. Antagonists that target histamine H_1 or H_2 receptors and are used in the treatment of allergic conditions such as rhinitis and gastric acid release disorders have been 'blockbuster' drugs for many years[74] and proved to be financially profitable for the pharmaceutical industry. Recently, following the completion of Human Genome Project, the family of histamine receptors has been extended to include four different GPCRs, H_1, H_2, H_3 and H_4 receptors.[75] In the view of blockbuster status of the histamine H_1 and H_2 receptor antagonists, current expectations for the therapeutic potential of drugs that target the H_3 and H_4 receptors are high.

3.1.1 Discovery of histamine H_3Rs

Histamine is known to act on target cells in the mammalian brain via stimulation of two classes of receptor H_1 and H_2 previously characterized in peripheral organs.[7,8] It is well established that several neurotransmitters affect neuronal activity in the central nervous system (CNS) through the stimulation of not only post, but also presynaptically located receptors, often displaying distinct pharmacological specificity by which they may control their own release. Such autoreceptors have been found in the case of noradrenaline, dopamine, serotonin, acetylcholine and γ-aminobutyric acid (GABA) neutrons[76,77] but not in case of histamine. In 1983 Arrang *et al.* found that histamine inhibits its own release from depolarized slices of rat cerebral cortex by an action apparently mediated by another receptor subtype which is pharmacologically distinct from H_1 and H_2 receptors. This novel presynaptically located autoreceptor was named as histamine H_3R, and subsequently definitively characterized[11] in 1987.

The H_3R, primarily located on nerve terminals and in the central nervous system (CNS), modulates the production and release of histamine.[15,32] The pharmacological blockade of H_3R enhances the release of histamine and other neurotransmitters[74,78-80] and has been

shown to enhance the vigilance or alertness.[81,82] Consequently, H_3R antagonists are thought to have a potential as drug therapies for attention-deficit hyperactivity disorder (ADHD), Alzheimer's disease, Parkinson's disease, Epilepsy, and sleep related disorders.[83-85] Recently, the role of histamine neurotransmission in the CNS was extensively reviewed by Panula and Haas.[86] Histaminergic neurons are localized in the tuberomammillary nucleus of the hypothalamus, projects to all major areas of the brain and are involved in many functions, including the regulation of sleep/wakefulness, feeding and memory processes. Although the H_3R can also be found in the periphery (mainly, but not exclusively, on neurons), the CNS contains the great majority.[12,87,88]

3.1.2 Molecular Architecture of H_3R gene and its isoforms

Although H_3R was identified more than a couple of decades, its molecular architecture was unknown until 1999. For the past few years, the histamine H_3R has been the target of cloning and purification attempts, yet its molecular identity was remained an enigma. Lovenberg *et al.* using molecular cloning technique showed that like H_1 and H_2 receptors,[18,89] the H_3R also belongs to the large super-family of GPCRs.[12] The human H_3R shows very low sequence similarity with other GPCRs. Overall similarity between the H_3R and other biogenic amine receptors is 20 - 27%. Its also show very low homology with H_1 (22%) and H_2 (20%) receptors. Because of this remarkable divergence H_3R gene was not cloned by similarity screening with H_1 or H_2 receptor-specific probes. On the other hand it shows the greatest degree of homology at 37% with human histamine H_4R. Moreover their homology in the transmembrane domain is 58% and both H_3 and H_4 receptors have a long third intracellular loop

Unlike other histamine receptors the analysis of H_3R gene revealed the presence of several splice variants. The histamine H_4R has a similar genomic structure to the H_3R in that it contains two introns and three exons but so far no splice variants of H_4R have been reported. The human H_3R gene has been suggested to consist of either three exons and two introns,[90,91] or four exons and three introns.[92,93] The various H_3R isoforms that are derived from alternative splicing of H_3R gene differ in four different parts of the receptor protein. In the region between N-terminus and TM-I alternative splicing results H_3R with a shortened amino-terminal domain. Alternative splicing might also occur in region of TM-II which results in the partial deletion of second TM domain and first extracellular loop. In the long intracellular loop between TM-V and TM-VI which has 132 amino acids, alternative splicing occurs most extensively and yields H_3R isoforms with a third intracellular loop of variable length or

putative H$_3$R proteins. Finally, alternative splicing at the C-terminus results H$_3$R protein with additional eight amino acids. At present a full characterization is available for only a limited number of isoforms. The H$_3$R$_{445}$ isoform[12] described by Lovenberg *et al.* is currently the best characterized H$_3$R isoform. Isoforms of the H$_3$R are not limited to human but are also found in other species including guinea pig, and mice.[94] Interestingly, rat H$_3$R isoforms with deletion in the third intracellular loop differ in their effectiveness to activate cAMP-response element (CRE)-dependent transcription or MAPK activation. The role of the activation of PKB/GSK3β by the H$_3$R in the brain is currently less clear, but the disregulation of GSK3 is linked to several prevalent pathological conditions, like diabetes and/or insulin resistance, and Alzheimer's disease.[95]

3.1.3 Potential binding sites for the H$_3$R ligands

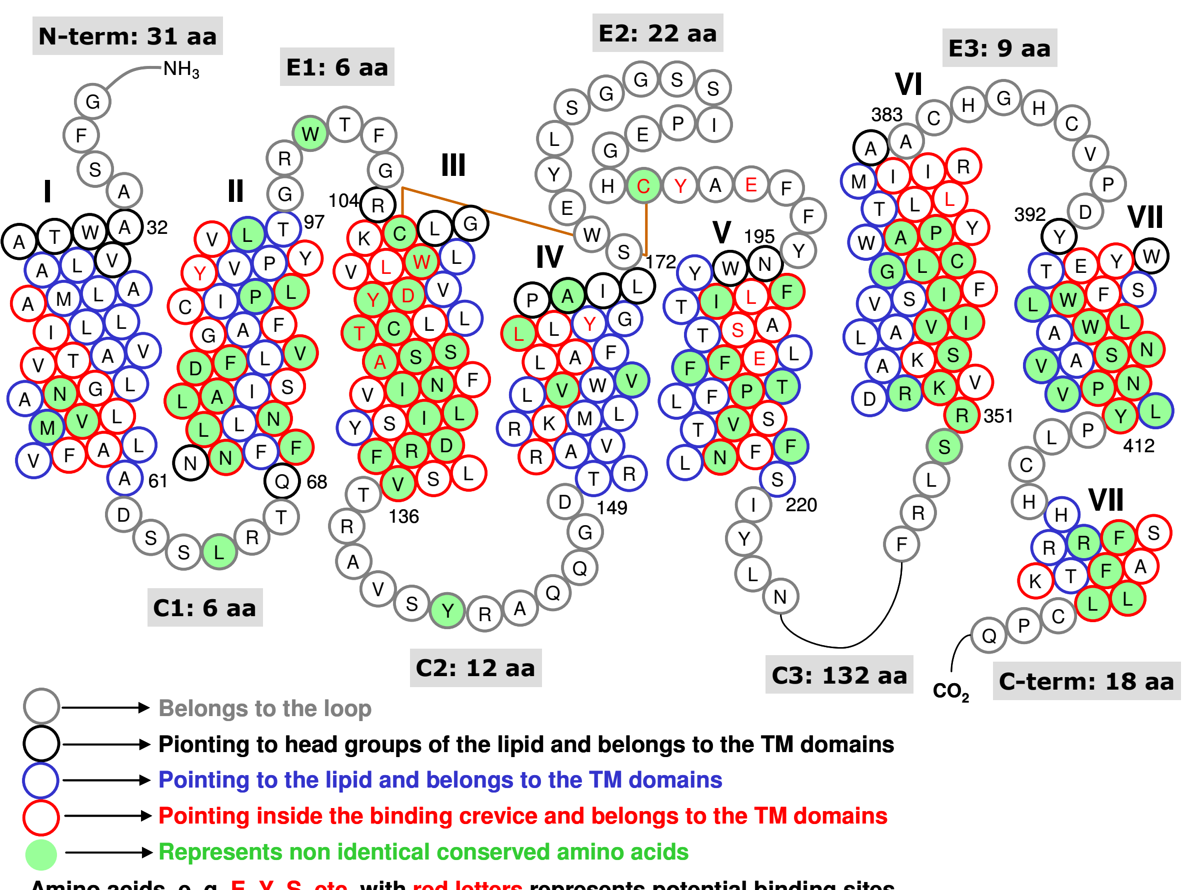


Fig 3.1.1 The snake plot of human histamine H$_3$R protein

The human histamine H$_3$R protein consists of 445 amino acids and is predicted to have seven transmembrane (TM) domains along with a helix VIII (Fig. 2.1.1). Helix VIII is referred as only helix and not as transmembrane and is supposed to be perpendicular to the

TM domains. Amino acids represented in gray circles belong to the intra and extracellular loop of the receptor protein. Amino acids shown in black bold circles point to the head groups of the lipids and belong to the TM domain. Blue circles represent the amino acids point to the lipid and belong to the TM domain. Amino acids pointing inside the binding crevice are shown with red circles and also belong to the TM domain. Amino acids with gray background represent the most conserved amino acids. Amino acids designated with red letters are supposed to be the important binding sites.

Overall homology between histamine H_3R of human and rat is more than 90% and differ by only five amino acids in TM domain region. The strong binding of endogenous ligand histamine at both species makes it more evident. In contrast discrepancy in binding has been found for some antagonists suggesting the different possible binding sites in the receptor. Structural identification of bovine rhodopsin,[96] resolved by X-ray crystallographic analysis, has given a major breakthrough in the understanding of GPCRs. Stark *et al.* used molecular modeling studies to generate a computational model[97] of human and rat histamine H_3Rs which shows close resemblance to the crystal structure of rhodopsin. Like rhodopsin the H_3R is also stabilized by an intramolecular disulfide bridge between Cys 107 and 188 (Fig. 2.1.1). This bridge is also supposed to be responsible for the deep folding of the extracellular loop into the binding pocket. Recently, Schlegel *et al*[98]. has performed molecular modeling studies very extensively and some of the features from Stark (mainly on imidazole containing H_3R antagonists) and Schlegel (mainly on non-imidazole containing H_3R antagonists) are summarized below.

From the molecular modeling experiments which have been studied using different ligands to form ligand-receptor complexes it can be seen that there are several different binding sites found for variety of agonistic and antagonistic ligands, glutamate 206 is one of the most important amino acids involved in the binding.

Ligand to receptor interactions can be briefly divided into two main types

1. Polar interactions like hydrogen binding or ionic interaction.
2. Non-polar interactions like aromatic or lipophilic interaction.

3.1.4 Polar Interactions:

In a receptor-ligand complex model involving ciproxifan **246** with the human H_3R the possible interaction of amino acids involved in the binding can be explained. The imidazole ring of ligand was located in a polar pocket formed by many residues like Tyr 115, Glu 191, Glu 206, Ser 203 and Thr 375 capable of forming hydrogen bonds. Especially Glu 206 which

is one of the most important amino acids located on TM-V and Glu 191 located on second extracellular loop which fold deeply in the binding pocket can make hydrogen bond interactions with the imidazole ring. Moreover, the tautomerism of the imidazole ring allows the molecule to interact with both glutamate 191 and 206 residues. Schlegel *et al*[98] in their recent studies showed that protonated heterocyclic moieties like piperidine, piperazine, pyrrolidine as well as imidazoles are able to interact with Asp 114. The side chain of Asp 114 is flexible allowing the carboxylate group to interact with different linker of H_3R antagonists residues. Thr 119 and Ala 122 (human H_3R) and Ala 119 and Val 122 (rat H_3R) are located in close proximity to Glu206 and Tyr 115 and influences the geometry of the binding pocket. Both residues have been shown to be important for the species selectivity of the investigated compounds.[99]

3.1.5 Non-polar Interactions:

The hydrophobic part of the binding pocket is constituted by several aromatic and aliphatic amino acid residues like Tyr 91, Trp 110, Leu 111, Cys 188, Phe 398 and Tyr 402. These amino acids interact with aliphatic chains of the lipophilic part of antagonists. In receptor complex studies involving compound SCH79687 (**252**) it is observed that aromatic ring systems in the linker moieties are expected to be oriented orthogonal to the membrane plane. It is also thought that the aromatic system lies parallel displaced to Tyr 189 from second extracellular loop and at the same time a T-shaped interaction could be formed with Tyr 267. De Esch *et al.*[100] suggested two lipophilic binding pockets for inverse agonist binding located between TM-III, IV and TM-V and TM-V and VI.

3.1.6 The signal transduction pathways of H_3R protein

The signal transduction pathways for H_3R are very well explained by Leurs *et al.* as shown in the figure 3.1.2. H_3R can activate the members of the $G_{i/o}$ protein family and the activated $G_{i/o}$ proteins inhibits adenylyl cyclase (AC), the enzyme responsible for the induction of cyclic AMP, which in turn results in the activation of protein kinase A (PKA) and consequently cAMP responsive element binding protein (CREB) to modulate gene transcription. Other effective pathways of H_3R-mediated activation of $G_{i/o}$ proteins include mitogen-activated protein kinase (MAPK) and phosphatidyl-inositol 3-kinase (PI3K). H_3R mediated activation of $G_{i/o}$ proteins might also lead to the activation of phospholipase A_2(PLA_2) which includes the release of arachidonic acid as well as the inhibition of Na^+/H^+ exchange and the lowering of intracellular Ca^{2+} levels. The subsequent activation of the

AMPK and PI3K pathways results in the phosphorylation of extracellular signal-regulated kinases (ERKs) and protein kinase B (PKB) respectively. Activated PKB will subsequently phosphorylate and thereby inhibit the action of glycogen synthase kinase 3β (GS3Kb).

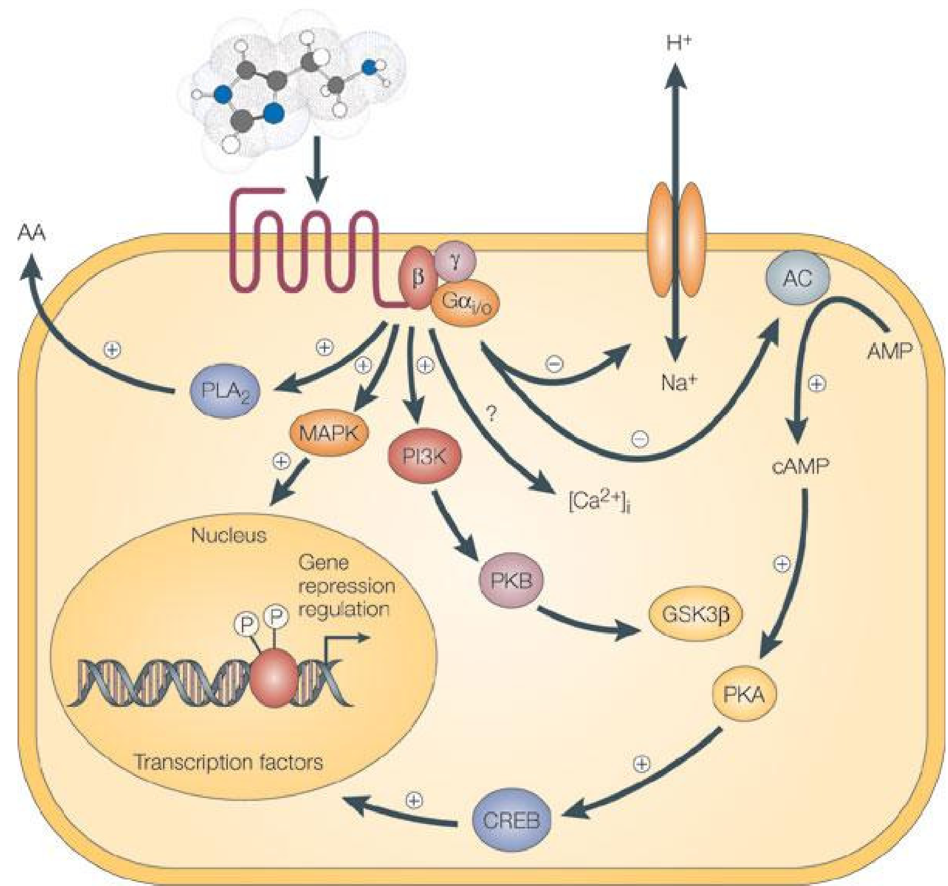


Figure 3.1.2 Diverse signaling pathways of H_3R activation. *Reproduced with permission from Nature Reviews Drug Discovery*[79] *copyright (**2005**) Macmillan Magazines Ltd.*

3.1.7 The structure activity relationships (SARs) of histamine H_3R agonists

Structurally diverse H_3R agonists having different chain length, rigidity and different polar groups are shown in Fig. 3.1.3. All known H_3R agonists contain the imidazole heterocycle. The initial attempts for the development of H_3R ligands were mainly focused on the endogenous ligand histamine, probably because of its high affinity to the human H_3R (pK_i, 7.8). So far all H_3R agonists closely resemble histamine and contain 4(5)-substituted imidazole moieties.

The stepwise chemical modification of histamine lead to the variety of different molecules but the efforts to replace imidazole heterocyclic moieties have so far been

unsuccessful,[101,102] prompting speculations that the capacity of imidazole to tautomerise might be of importance in the receptor activation. There is also evidence that histamine could bind to the human H_3R in its di-protonated state. Additional substituents on the imidazole ring eliminate H_3R activity,[101] but surprisingly, small structural modifications of side chains resulted in very potent and selective H_3R agonists. The methylation of histamine at different position is known to produce the selective analogues for different subtypes among histamine receptors. Methylation of side chain at α and β position is allowed. Moreover monomethylation of the primary amine enhances the activity but dimethylation results in significant loss of agonistic activity. Introducing relatively bigger groups like ethyl or propyl eliminates the activity significantly, probably indicating that the space in the agonistic binding site is very limited.[102]

1 Histamine $pK_i(h)$ 7.8

25 N^{α}–methylhistamine $pK_i(h)$ 8.6

33 (*R*)- α-methylhistamine $pK_i(h)$ 8.4

235 BP 2-94

236 (R)α,(R)β-cyclopropyl histamine $pK_i(r)$ 8.7

237 SCH50971 $pK_i(gp)$ 8.6

238 Immepip $pK_i(h)$ 8.8

239 Immethridine $pK_i(h)$ 9.1

240 imetit $pK_i(h)$ 9.2

241 Impentamine $pK_i(h)$ 8.3

242 FUB 475 $pK_i(r, gp)$ 7.6, 7.4

243 cmp 12 $pK_i(r)$ 8.4

Figure 3.1.3 Imidazole containing H_3R agonists, pK_i values are given for human (h), rat (r) and guinea-pig (gp) receptors

Stereoisomers also play an important role in the binding, suggesting specific conformational aspects of the receptor. (*R*)-α-methylhistamine (RAMH; Fig. 3.1.3) shows very high activity at human H_3R (pK_i, 8.4)[11] and has been used in many pharmacological studies together with its less active (*S*)-isomer. Its high basicity, hydrophilicity, extensive metabolism and low bioavailability limit its *in vitro* use. By applying a Prodrug concept Schunack *et al.* prepared its hydrophobic derivative BP 2-94 (**235** Fig 2.1.3).[103] This prodrug has significantly improved oral bioavailability and pharmacokinetic properties.[104] In humans the administration of BP 2-94 results in a 100-fold increase in the plasma RAMH.

3.1.8 The potential therapeutic applications of H_3R agonists

Unlike histamine receptor antagonists/inverse agonists, the therapeutic applications for agonists are limited as can be seen for both H_1 and H_2 receptors. Nevertheless, H_3R agonists might be of therapeutic use for the treatment of insomnia, myocardial ischaemic arrhythmias or could also be antinociceptive. Since the CNS contains the great majority of H_3Rs which are also found in the periphery (mainly, but not exclusively, on neurons), H_3R agonists might be of therapeutic use in both CNS as well as peripheral nervous system. Histaminergic neurons mainly located in the hypothalamus are thought to have an important role in the regulation of sleep and wakefulness.[105] The H_3R activation in CNS results in the lower hypothalamic histamine release, suggesting the potential use of H_3R agonists against insomnia.[105] Moreover studies in various preclinical model with the prodrug BP 2-94 and SCH50971 ,[106] (Fig. 2.1.3), also confirmed that sleep is induced by H_3R agonists. The H_3R activation also modulates ischaemic noradrenaline release in animal as well as human models of protected myocardial ischaemia. The excessive nonadrenaline is regarded as an important cause for cardiac arrhythmias in human. The H_3R agonists could provide an attractive new approach for preventing and treating myocardial ischaemic arrhythmias.[107] Finally H_3R agonists such as BP 2-94 and SCH50791 are reported to inhibit neurogenic inflammatory processes in various tissues, including the lungs and dura matter.[104,106,108,109] These observations indicate a potential use of H_3R agonists in inflammation, asthma and migraine.

3.1.9 Histamine H_3R antagonists

The H_3R is known to modulate various neurotransmitter systems in the brain. In rodent and/or in human brains, the H_3R activation inhibits presynaptically the release of many important neurotransmitters. Despite this interesting feature the drugs that target H_3R have until 1999 been mainly developed by academic research groups. Since the identification of

H_3R at molecular level,[5] many pharmaceutical companies have put considerable recourses into the development of H_3R antagonists because of its potential therapeutic applications, as can be judged from the recent literature. Currently, many pharmaceutical companies are active in this field which includes Abbott Laboratories, Boehringer Ingelheim, De Novo Pharmaceutical, Eli Lilly, GlaxoSmithKline, Johnson & Johnson PRD/Ortho-McNeil, Merck, NovoNordisk, Pfizer, Sanofi-Synthelabo, Schering-Plough and UCB Pharma. The development of H_3R antagonists has recently been extensively reviewed.[110-112]

244 Thioperamid pK_i (r, h) 8.4, 7.2

245 Clobenpropit pK_i (r, h) 9.4, 9.2

246 Ciproxifan pK_i (r, h) 8.4, 7.3

247 Proxyfan pK_i (r, h) 8.5, 8.6

248 Iodoproxyfan

249 FUB 372

250 GT 2331 pK_i (r, h) 9.9, 8.4

251 Imoproxyfan

252 SCH79687 pK_i (r) 8.7

253 SCHpat pK_i (gp) 7.7

254 VUF 5228 pK_i (r) 9.3

255 pK_i (r) 8.5

Figure 3.1.4 Imidazole containing H_3R antagonists, pK_i values are given for human (h), rat (r) and guinea pig (gp) receptors

3.1.10 Classification of H_3R antagonists

Histamine H_3R antagonists can be briefly classified into two types

1. Imidazole containing H_3R antagonists
2. Non-imidazole H_3R antagonists

3.1.11 Imidazole containing H_3R antagonists

Thioperamide **244** (Fig. 3.1.4) was the first potent H_3R antagonist described in the literature that lacked H_1 and H_2 receptor activity.[11,113] More recently, this and many other compounds that were initially classified as H_3R antagonist have had to be reclassified as inverse H_3R agonists. Thioperamide **244** has been used as a reference H_3R antagonist for almost twenty years, and many preclinical studies have been carried out with this compound. **244** shows high affinity for rat H_3R (pK_i, 7.2).[114] At the same time **244** shows high activity at human H_4R (pK_i, 7.3), the rat 5-HT_3 receptor (pK_i 5.6) and α_{2A} receptor (pK_i 6.9), and the human α_{2C} receptor (pK_i = 6.5).[115]

3.1.12 SARs of imidazole containing H_3R antagonists

Clobenpropit **245** (Fig. 3.1.4),[116] is one of the early imidazole containing H_3R antagonists that has been extensively used to characterize H_3R. **245** (pK_i, 9.2, human H_3R) can be considered as a imetit analogue (Fig. 3.1.4) and illustrates a trend in the SARs for the H_3R antagonists. One of the strategies in the design of imidazole containing inverse agonist is increasing the distance between the basic moieties observed in the agonists. For example, by increasing the distance between histamine and/or the attachment of larger lipophilic moieties in the side chain, potent H_3R antagonists can be obtained. Attachment of lipophilic groups to the linker moiety can increase the inverse agonistic activity and large aromatic as well as aliphatic groups are shown to be well tolerated. The basic moieties in the imidazole side chain can however be omitted, as shown by compounds of the proxyfan class. Proxyfan (Fig. 3.1.4) has recently been identified as a neutral H_3R antagonist (pK_i, 8.0, rat H_3R).[117] However the proxyfan is a particular H_3R ligand, because it shows both H_3R agonistic (partial), neutral H_3R antagonistic and inverse H_3R agonistic properties, depending on the signaling assay used.[118,119]

The linker moiety can have a great structural diversity and thus can play an important role. There are many compounds known with different linker groups; some of the potent, structurally diverse H_3R antagonists are shown in figure 3.1.4. Many compounds contain linkers like, ethers (e.g. proxyfan **247** and ciproxifan **246**), thioethers, ketones, carbamates,

esters, urea, thiourea (e.g. thioperamide **244**), isothiourea (e.g. clobenpropit **245**), sulfoxides, sulphonamides, sulphamide, amine, amide, amidine and guanidine. Linkers are not limited to polar groups, some nonpolar linkers are also known like methylene units, phenyl rings (e.g. SCH79687 **252**), unsaturated hydrocarbons and heterocyclic ring systems. In the proxyfan class of compounds the replacement of ether functionality by other functional groups like carbamates, esters and amides[120] and even simple methylene units was achieved without loosing its H_3R activity.[121,122] **246** (Fig. 3.1.4) has also been extensively used in various *in vitro* studies but show only moderate affinity for human H_3R (pK_i, 7.2). Inspired by the results from proxyfan **247** Stark *et al.* examined the SARs of a series of proxyfan and found that the para-substituted 4-(3-(phenoxy)propyl)-1H-imidazoles show nanomolar activities which led to the compound FUB-372 **249**.[123] Later Sasse *et al.* synthesized its oxime derivative imoproxyfan **251** (Fig. 3.1.4) which displays even more potency *in vitro* as well as *in vivo* H_3R assays.[124]

256 FUB373 pK_i (m) 8.9 *partial agonist*

257 FUB407 pK_i (m) 9.4 *partial agonist*

258 FUB373 pK_i (m) 9.2 *inverse agonist*

259 FUB335 pK_i (m) 8.6 *inverse agonist*

260 VUF 5300 pK_i (h) 8.0 *full agonist*

261 VUF 5207 pK_i (h) 7.8 *partial agonist*

262 VUF 4904 pK_i (h) 7.9 *neutral antagonist*

263 VUF 4903 pK_i (h) 8.0 *inverse agonist*

Figure 3.1.5 Influence of small structural changes on the activity

However in the FUB series it is observed that small structural changes can greatly influence the pharmacological profile (Fig. 3.1.5). Compounds FUB373 and FUB407 show partial agonism while, similar compounds like FUB335 and FUB397 were found to be inverse

agonist. A similar kind of relationship was also observed for the class of VUF series (Fig. 3.1.5), where small structural changes in the side chain can shift the activity from full agonism to the inverse agonism.

3.1.13 Non-imidazole H_3R antagonist

264 FUB836 pK_i(h) 10.0
265 NNC-cmp2d pK_i(h) 8.5
266 A-304121 pK_i(h,r) 6.1, 8.6
267 FUB 833 pK_i(h) 9.5
268 Cmp19 pK_i(gp) 9.0
269 NNcmp1 pK_i(h) 9.4
270 JNJ-10181457 pK_i(h) 9.1
271 NNC-0038-0000-1202 pK_i(h) 8.3
272 A-331440 pK_i(h) 8.6
273 JNJ-5207852 pK_i(h) 9.5
274 SCHcmp1 pK_i(gp) 7.4
275 ABT-239 pK_i(h) 9.3
276 VUF5391 pK_i(r) 8.2
277 A-349821 pK_i(h,r) 9.3, 8.8
278 A-923 pK_i(r) 8.9

Figure 3.1.6 Structurally diverse non-imidazole H_3R antagonist

One potential liability of imidazole based drug candidates like **244**, clobenpropit **245** and ciproxifan **246** is their possibility for mechanism based inhibition of hepatic CYPs (cytochrome P_{450}).[125,126] This inhibition is known to be caused by the imidazole nitrogen complexation to heme iron in the active site of enzyme.[127] Since these enzymes are a major

route of clearance for most medicines, drugs that are cytochrome P_{450} inhibitors perpetrate drug-drug interaction by reducing or preventing the clearance of co-administered medicines. Additionally, the inhibition of CYPs by imidazole based H_3R antagonists can interfere with adrenal steroids[126] synthesis via inhibition of heme containing enzymes. As such interactions are unwanted in drug development, many research groups have also been developing non-imidazole H_3R antagonists. In the last 5-6 years many new classes of compounds have appeared good show good activity; some of them are depicted in Fig. 3.1.6. Compared to the imidazole containing H_3R antagonists the structural diversity among non imidazole H_3R antagonists is higher. But on the other hand such type of interaction needs higher dowses of compounds, and at nanomolar level these interaction can be minimized.

3.1.14 Radiolabeled H_3R ligands

Radioligands are useful tools to localize and characterize the functions of receptors. The available H_3R radioligands were either tritiated agonists like [^{3}H]-N^{α}-methylhistamine[128,129] and its more selective analogue [^{3}H]-(*R*)-α-methylhistamine[11,130] (Fig. 3.1.7) or the [^{125}I]-iodinated antagonist iodophenpropit[131,132] (Fig. 3.1.7). The agonists have been useful for demonstrating the G-protein coupling of H_3R and their distribution in brain. Despite these facts, agonistic tritiated ligands have problems as their binding is more complex than that of antagonists, and they are not allowing a sensitive receptor detection. Moreover low sensitivity of the tritium limits their use because the density of the H_3Rs in the brain is lower than that of the many other aminergic receptors. On the other hand [^{125}I]-iodophenpropit, being a antagonist overcomes these problems but unfortunately has some other limitations.[133]

279 [^{3}H](*R*)-α-Methylhistamine

280 [^{125}I]-Iodoproxifan

281 [^{3}H]N^{α}-Methylhistamine

282 [^{125}I]-Iodophenpropit

Figure 3.1.7 Radiolabeled H_3R ligands

To overcome these problems Stark *et al.* in 1996 developed a H_3R antagonist radioligand [^{125}I]-iodoproxyfan **280** (Fig. 3.1.7) which displays extremely high affinity and selectivity for H_3R. The developed ligand has been successfully used for binding assay as well as for autoradiographic studies.[133] Introduction of rigidity by incorporating the cyclopropane ring in iodoproxyfan **248** could lead to more potent analogues and can be further converted to their corresponding radioligand which will be helpful to understand the functions of H_3R in more details.

3.1.15 Why rigid H_3R antagonists?

Many research groups have been trying to make more rigid H_3 R antagonists to increase their druglikeness. Ali S. M. *et al.* incorporated cyclopropane rings and acetylene moieties. The resulting compound GT2331 **250** (Fig. 3.1.4) showed very high affinity (pK_i, 9.9, rat H_3R) and contains a imidazole heterocycle along with a very rigid and lipophilic side chain.[134] Recently, some controversy over its absolute configuration has emerged. The absolute configuration (*1R*, *2R*) which was assigned by the developers was reassigned to (*1S*,*2S*) by Abbott scientist after re-synthesis and X-ray crystallographic analysis.[135] This compound shows somewhat lower affinity at human H_3R (pK_i, 8.4), demonstrating the species differences like other imidazole containing compounds. Schering-Plough also developed relatively more rigid and lipophilic H_3R antagonist by incorporation of phenyl rings into the side chain that resulted in the lead compound SCH79687 **252**[136] (Fig. 3.1.4, pK_i, 8.7, rat H_3R). Looking at the extensive history of SARs of H_3R antagonists rigid antagonists like **250** and **252** fulfils many criteria, display very high potency and have apparently reached clinical studies. Therefore rigid analogues of other lead structures (Fig. 3.1.4) consequently could also result in more potent compounds, lead to interesting activity and will also help to understand the SARs of imidazole containing rigid H_3R antagonists.

3.1.16 The therapeutic utility of H_3R antagonist

Unlike H_3R agonists, antagonists or inverse agonists provides a broader spectrum of potential therapeutic applications due to their implication in the regulation of body weight, arousal and sleep or wakefulness. But on the other hand due to the potential liability of imidazole containing H_3R antagonists to interact with cytochrome P_{450}, many research groups are trying to develop non-imidazole H_3R antagonists, and in last 5-7 years and many different classes of H_3R antagonists have appeared.[111] Despite the large number of non-imidazole antagonists only a few reports of their preclinical use have so far been made. To review most

promising applications for H_3R antagonists, one still has to rely to a large extent on the observed effects of the early imidazole-containing H_3R antagonists.

3.1.17 H_3R antagonists a potential drug target for obesity:

The need for the development of anti-obesity drugs is rapidly growing with the increasing incidence of obesity, diabetes and associated health risks specially in the modern western society.[137] The role of neuronal histamine in food intake has been established for many years,[110,138] and the blockade of its action at hypothalamic H_1R has been indicated as mechanistic action of weight gain after therapy with various antipsychotics.[139] In brain, the H_3R is implicated in the regulation of histamine release in the hypothalamus. Moreover, recent *in situ* hybridization studies revealed H_3R mRNA expression in rat brown adipose tissue,[140] indicating H_3R ligands might (peripherally) regulate thermogenesis. These observations reveals that H_3R antagonists elevate hypothalamic histamine level in the CNS.[141,142] That is the reason why H_3R antagonists have gained considerable attention for anti-obesity. A study with compounds like **244** or **246** (imidazole containing H_3R antagonists) also provides evidence for the modulatory role of H_3R in feeding behaviour. Moreover H_3R antagonists have been reported to be effective in various models of acute food intake.[110]

On the basis of data obtained from the preclinical models, it is clear that H_3R blockers reduce weight gain, lower plasma ghrelin and leptin levels, and seem to be well tolerated. The blockade of H_3R by selective antagonists or inverse H_3R agonists might be an attractive mechanism of action for anti-obesity compounds. Clinical data on human obesity from H_3R antagonists is eagerly awaited, but, unfortunately at present no clinical trials in this area have been announced.

3.1.18 Therapeutic use of H_3R antagonists in sleep and cognitive disorders

It is often considered that indirect modulation of brain functions by H_3R antagonists might be a means to modulate attention and memory processes. On the other hand the H_3R agonists are shown to induce sleep in preclinical animal models. **244** increases wakefulness in wild type mice, but has no effect on sleep/wakefulness in $H_3R^{-/-}$ mice.[143] These data indicate that the H_3R antagonists promote wakefulness. Therefore, the H_3R antagonists might be useful in sleep-related disorders like narcolepsy. Recently, modafinyl (novel wakefulness-promoting drug for the treatment of narcolepsy) has shown to increase hypothalamic histamine release,[144] and studies using the classic Doberman model of narcolepsy with GT2331 **250** showed that H_3R antagonists reduce the number of narcoleptic attacks and its

duration. In many neuropsychiatric conditions like ADHD, schizophrenia and Alzheimer's disease, cognitive deficits are an integral part of the disease. It is therefore of a great interest that a variety of the H_3R antagonists can improve cognitive performance in various animal models.[145] In addition imidazole-containing H_3R antagonists like **246** and **250** improve acquisition in an inhibitory avoidance model with rat pups.[81] On the basis of these observations compound **250** has reached clinical trials.[146] However, the development of this drug for the treatment of ADHD has been halted in Phase II for unknown reasons.

Many potent and relatively selective H_3R antagonists and inverse agonists have been developed by many academic and industrial scientists. For both H_3R agonists and H_3R antagonists/inverse agonists, many interesting activities in several preclinical models of important human diseases have been reported. Results from the clinical trials are eagerly awaited and will be the next step in the process of moving from knowledge of the gene encoding H_3R to the development of drugs for a range of indications. The preclinical finding indicates that the H_3R antagonists might become future '*wonder drugs*'.

3.2. Aim of the work

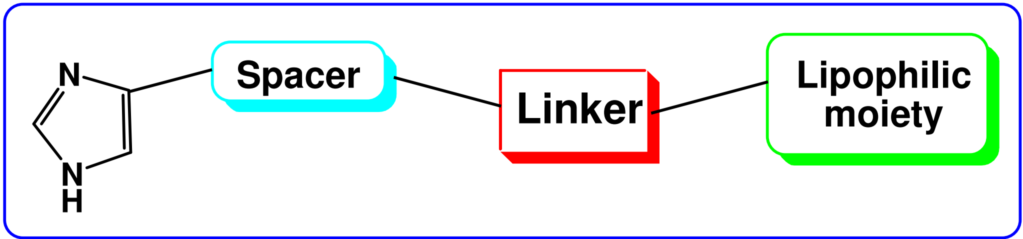


Figure 3.2.1 General structural pattern of imidazole containing H_3R antagonists

Recent developments in the medicinal chemistry field of H_3R antagonists have generated numerous compounds that are highly active *in vitro* and also *in vivo*. Although these compounds possess different functionalities, they all have more or less in common, the 4(5)-substituted imidazole heterocycle connected by a spacer (commonly aliphatic carbon chain) with a linker (polar groups), being optionally connected to a lipophilic moiety (aromatic or aliphatic) (Fig. 3.2.1). The aim of the present study was to develop compounds, structurally related to FUB-372, proxyfan and iodoproxyfan (Fig. 3.1.14) with more rigidity to achieve druglikeness. The required rigidity could either be obtained by introducing different spacer groups such as, *cis* and/or *trans* double bonds, triple bonds or cyclopropane rings. Moreover, the use the basic pharmacophores present in the lead compounds (Fig. 3.1.14), can be used to develop novel histamine H_3R antagonists with nanomolar affinities. By keeping this goal in mind the novel compounds shown in figure 3.1.2 were targeted for the synthesis.

X = H, CH_3, I, Br, CN, CF_3.....

Figure 3.2.2. Target structures for imidazole containing H_3R antagonists

In formulating a general synthetic approach for the synthesis of variety of conformationally restricted analogues (Fig. 3.1.2), allyl alcohol **284** was recognized as a key intermediate which is readily accessible from commercially available *trans* urocanic acid (**162**) by known procedures.[61,147] Ether formation for FUB-372 and proxyfan analogues were sought to accomplish by Mitsunobu type reactions and/or by nucleophilic substitution. For the Cyclopropane analogues the Simon-Smith reaction of **284** was envisioned, in which the ether formations can be performed either before or after the cyclopropanation.

Figure 3.2.3 General retrosynthetic strategy for the imidazole containing H_3R antagonists: EWG (electron withdrawing groups), EDG (electron donating groups)

3.3 Synthesis of conformationally restricted histamine H_3R antagonists

3.3.1 Synthesis of the key intermediate

The campaign was began with *trans* urocanic acid (**162**), esterification was achieved by known procedure,[61] followed by trityl protection.[148] The ester functionality was then reduced to the corresponding allyl alcohol using DIBAL-H with slight modification of the literature procedure,[147] and the key intermediate (E)-3-(1-trityl-1*H*-imidazol-4-yl)prop-2-en-1-ol (**284**) was obtained in high yield (Scheme 3.3.1).

Scheme 3.3.1 Reagents and conditions: (a) MeOH, H_2SO_4 (cat.), reflux, 36 h, 95%; (b) Tr-Cl, TEA, DMF, RT, 1 h, 92%; (c) DIBAL-H, CH_2Cl_2, 0 °C → RT, 12 h, 82%.

Scheme 3.3.2 Reagents and conditions: (a) PPh_3, DEAD, 4-hydroxy acetophenone, THF, 0 °C → RT, 4 h, 42% of **285** and 12-15% of **286**; (b) 2N HCl, acetone, reflux 1.5 h 75%.

Ether formation was achieved by a Mitsunobu type reaction[149] with 4-hydroxyacetophenone as a nucleophile. During the course of the reaction, along with the desired isomer **285**, being obtained as a major product formation of the minor isomer **286** was always observed (Fig. 3.3.2). All attempts to completely suppress the formation of **286** were unsuccessful. Finally deprotection[123] of the trityl group under acidic condition furnished **287**, a *trans* olefinic analogue of FUB-372.

Figure 3.3.1 Transition state for the ether formation

3.3.2 Synthesis of alkyne analogue of FUB-372

Fig. 3.3.2 Retrosynthetic strategy for olefinic/alkyne analogue of FUB-372

From the retrosynthetic analysis the target compounds can be assembled as shown in Figure 3.3.2. The Sonogashira coupling was envisioned as a key step in which the coupling products can also be utilized further for the formation of *cis* olefinic analogue **295** of FUB 372. Synthons, such as *N*-protected 4-iodoimidazole can be obtained from imidazole, and alkyne **290**, could be easily obtained from propargyl alcohol *via* Mitsunobu type reactions.

3.3.3 Sonogashira coupling

The synthesis of the precursor **289** for the Sonogashira coupling was achieved by sequential iodination and deiodination of imidazole followed by trityl protection following known procedures.[150,151] The alkyne precursor **290** was obtained *via* Mitsunobu type reaction using 4-hydroxyacetophenone and propargyl alcohol in quantitative yield (Scheme 3.3.4).

Scheme 3.3.4 Reagents and conditions: (a) PPh_3, DEAD, THF, 0 °C → RT, 3 h, 98%.

Palladium catalyzed Sonogashira coupling, the reaction of a terminal alkyne with a variety of organic halides, has been one of the most powerful tools for the C-C bond formation.[152,153] The coupling of trityl protected 4-iodoimidazole **289** with alkyne **290** was carried out using 1 mol % of $PdCl_2(Ph_3P)_2$ catalyst in conjunction with 10 mol % of CuI (Table 3.3.1). Initially, with DMF as a solvent bases such as, K_2CO_3 or TEA the reaction yields were low and also led to the dimerization product of alkyne **290** in small amounts. Moreover, it has been reported that Sonogashira reactions proceed more efficiently when carried out with an excess amine.[154] However, the use of an excess diisopropylamine (DIPA) led to very bad solubility of the starting materials and hence could not be used. Nevertheless, a THF:DIPA mixture proved to be the method of choice, furnishing moderate yields of the desired product. Other attempts to improve the yield of the reaction failed.

Scheme 3.3.5 Reagents and conditions: (a) 2N HCl, acetone, reflux 1.5 h, 82%.

Table 3.3.1 Sonogashira coupling

Entry	Base	Solvent	Time	Temp.	Yield
1	K_2CO_3	DMF	3 h	70 °C	28 %
2	TEA	DMF	6 h	RT	10 %
3	TEA	THF	16 h	RT	15 %
4	Excess TEA	THF	6 h	RT	25 %
5	**Excess DIPA**	**THF**	**6 h**	**RT**	**52 %**

3.3.4 Synthesis of oximes

Scheme 3.3.6 Reagents and conditions: (a) Na_2CO_3, $NH_2OH.HCl$, EtOH, reflux, 2 h, 82%; (b) Na_2CO_3, $NH_2OH.HCl$, EtOH, reflux, 1 h, 94%

Oximes are known to be more potent H_3R antagonist than their parent ketones.[124] Both, *trans* olefinic and alkyne ketones **287** and **292** were converted to their corresponding oximes **293** and **294** respectively by refluxing with hydroxylamine hydrochloride and sodium carbonate as a base in ethanol (Scheme 3.3.6).

3.3.5 Structure elucidation of oxime 294

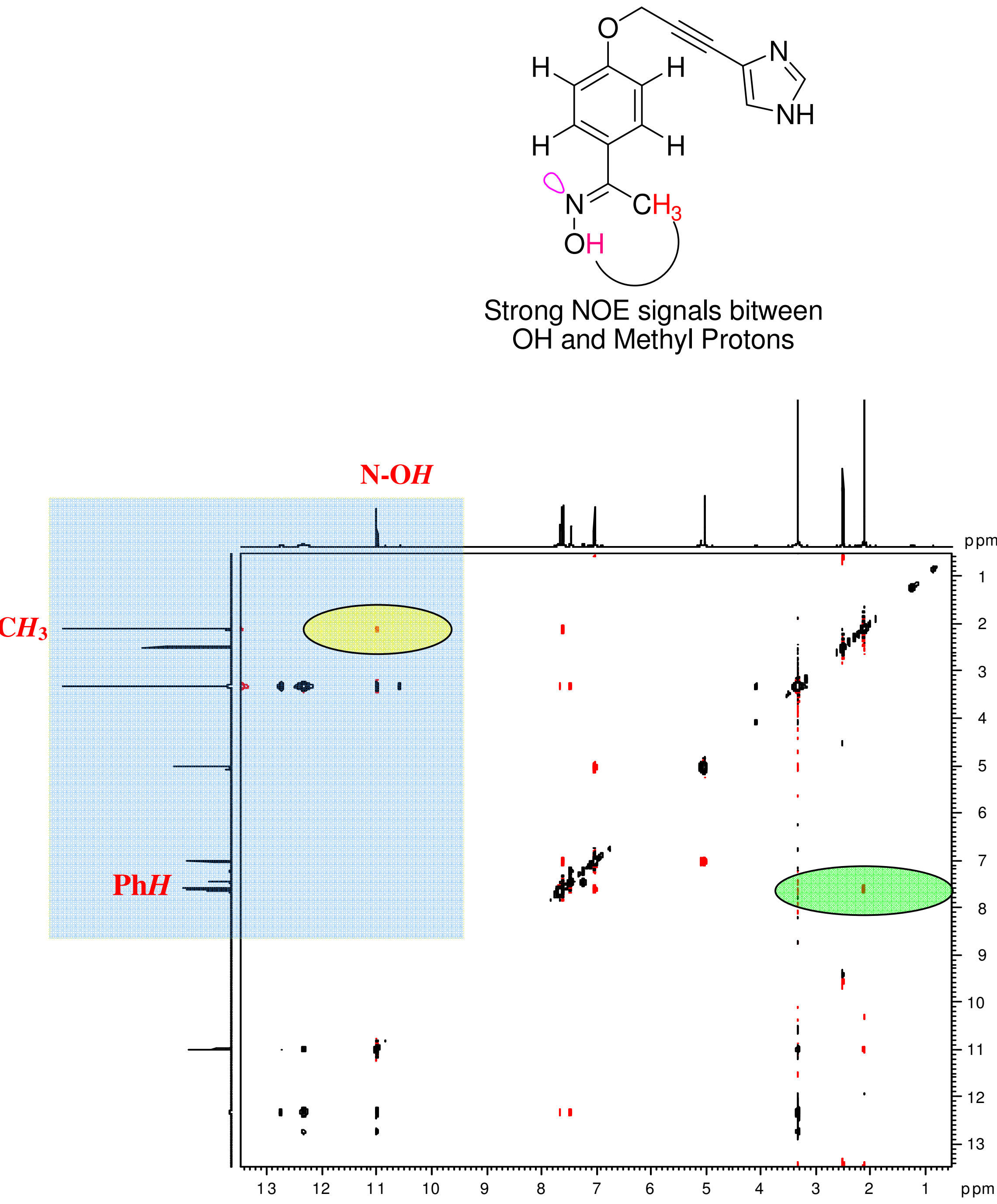


Figure 3.3.3 NOE spectrum of oxime **294**

For the structure elucidation of **294**, the main concern was the geometry of the oxime. X-ray analysis would be one of the best choices to confirm the geometry, and moreover, Stark and co-workers have confirmed the geometry of its saturated analogue imoproxyfan **251** (Fig. 3.1.4) by X-ray analysis.[124] Unfortunately, our attempts to grow suitable crystals were not successful to carry out a X-ray. However, the geometry of the oxime was confirmed by NOE experiments in which the *cis* stereochemistry between hydroxyl proton at 11.01 ppm and the methyl protons at 2.12 ppm (a cross peak highlighted in yellow eclipse, Fig. 3.3.3). On the other hand the methyl protons also show a cross peak to ortho protons of the aromatic group (highlighted in green eclipse), where as there was no signal corresponding to a cross peak of the aromatic protons with the oxime proton.

3.3.6 Synthesis of the *cis* olefinic analogue 295 of FUB-372

292 **295**

Scheme 3.3.8 Reagents and conditions: (a) Pd-$BaSO_4$, H_2, RT, 16 h, 92%

To get the more information regarding the binding of the novel ligand and in order to compare the effects of conformationaly restricted analogues with respect to the known ligand such as FUB-372, it was necessary to synthesize the cis olefinic analogue **295**. The synthesis of **65** was achieved *via* controlled hydrogenation of **292** using $BaSO_4$ poisoned Pd (Lindlar's catalyst). On the other hand, the analogous transformation with the trityl protected substrate **291** was not successful.

3.3.7 Synthesis of cyclopropyl building block

The importance of the cyclopropyl moiety for the H_3R antagonist activity is evident from the highly active cyclopropyl derivative GT 2331 (**250**, Fig 3.1.4). To incorporate the cyclopropane ring into FUB 372 or into the proxyfan class of compounds was one of the main aims of the present study to enhance the activity. The ester **296** was obtained by refluxing **152** with 2-butanol and catalytic H_2SO_4 in a Dean-stark apparatus. The yield of **296** was improved by changing the work-up procedures reported by Liu *et al.*[135] The cyclopropyl ester **297** was

obtained by trityl protection of **296** followed by cyclopropanation using sulphur ylides following known procedures.[135] Finally LAH reduction of **297** afforded the corresponding alcohol **298**, a key intermediate for many novel H_3R antagonists in high yield.

Scheme 3.3.9 Reagents and conditions: (a), (b) Lit[135] (c) LAH, ether, 0 °C → RT, 30 min, 96%.

3.3.8 Attempted synthesis of cyclopropanated analogue of FUB-372

Scheme 3.3.10 Reagents and conditions: (a) PPh_3, DEAD, THF, 0 °C → RT, 4 h, 65%; (b) 2 N HCl, acetone, reflux 1.5 h, 82%.

Initially, the synthesis of the cyclopropanated analogue **300** of FUB-372 was envisioned using a Simon-Smith reaction. However, treatment of **285** with excess of

diiodomethane and diethyl zinc at room temperature did not led to the product formation. On the other hand, refluxing the mixture in toluene led to the decomposition of starting material **285**. Moreover, the reaction of detrytilated compound **287** under similar conditions, only starting materials were recovered.

A second strategy was envisioned using a Mitsunobu type reaction as a key step. Unfortunately, the Mitsunobu type reaction of alcohol **298** using 4-hydroxy acetophenone failed to give desired product **299** and surprisingly led to the formation of ring opened product **71**, even though the alcohol **298** is known to undergo Mitsunobu type reaction using pthalamide as a nucleophile.[155] The possible mechanism for the formation of the unexpected product is given in Figure 3.3.4. Later the trityl group of **301** was removed under acidic condition to achieve the compound **302** which could be screened for the H_3R antagonist activity.

Ph3P
COOEt
N=N
EtOOC
H
O
O
Ph3P
COOEt
N–N
EtOOC
H
R
O
H
Ph3P
COOEt
N–N
EtOOC
H
EtOOC
Ph3P
N
N
H
COOEt
R
O
H
R
O
PPh3
O
O
R
O
PPh3
O
O
R
301
N
N
CPh3
= R

Figure 3.3.4 Probable mechanism for ring opened product **301**

3.3.9 Synthesis of iodoproxyfan and its *trans* olefinic analogue

Scheme 3.3.10 Reagents and conditions: (a) Ref.[120]; (b) NaH, 4-iodobenzylbromide, DMF, overnight 70%; (c) 2N HCl, MeOH, reflux, 1.5 h, 68%; (d) NaH, 4-iodobenzylbromide, DMF, overnight 75%; (e) 2N HCl, MeOH, reflux, 1.5 h, 87%.

The key intermediate **303** for the synthesis of iodoproxyfan **248** was obtained following known procedures.[120] Starting from urocanic methyl ester **152**, hydrogenation with Pd-C/H_2 and protection of the imidazole ring by trityl chloride afforded a compound with increased lipophilicity and in turn facilitated the easy isolation of **303** after reduction with complex hydrides. The intermediate alcohol **303** was then successfully used to form the benzyl ether **304** on treatment with sodium hydride and 4-iodobenzyl bromide in DMF. The deprotection could be easily performed by refluxing **304** in 2N HCl and methanol for 1.5 hours to form **248** in good yield (Scheme 3.1.11). Similarly allyl the alcohol **284** was converted to **306**, a *trans* olefinic analogue of iodoproxyfan.

3.3.10 Synthesis of cyclopropanated analogues of proxyfan with oxygen linker

Cyclopropane derivatives **314-320** were synthesized from the **298** by reacting it with different 4-substituted benzylbromides and sodium hydride in DMF, followed by the deprotection of trityl group. Yields of benzyl ethers were good with the exception of compound **313**, in this case the maximum isolated yield was 34 %. Deprotection of the trityl group was achieved by refluxing the corresponding ethers in 2N HCl and methanol. For cyano compound **320** mild conditions could be used: the deprotection was carried out at ambient

temperature using 2N HCl and ethanol as a solvent. All compounds were isolated as free base while the exception of the only cyano compound **320** that was isolated as a hydrochloride salt.

307 R = H (87%)
308 R = CH_3 (80%)
309 R = CF_3 (79%)
310 R = OCF_3 (84%)
311 R = I (94%)
312 R = Br (91%)
313 R =CN (34%)

314 R = H (91%)
315 R = CH_3 (88%)
316 R = CF_3 (86%)
317 R = OCF_3 (89%)
318 R = I (66%)
319 R = Br (78%)
320 R =CN (92%)

Scheme 3.3.14 Reagents and conditions: (a) NaH, 4-substituted benzylbromides, DMF, overnight 34-94 %; (b) 2 N HCl, MeOH, reflux, 1.5 h, 66-91 %.

In an attempt to achieve more lipophilicity, which will help the ligands to cross the blood brain barrier (BBB), analogues **322** was envisioned to synthesize. Starting from **298** the benzyl ether **321** was obtained in a straightforward way (Scheme 3.3.15), nevertheless in moderate yield, which is probably because of steric effects of the methyl substituents on the aromatic ring. On usual treatment with 2N HCl, all the starting material was consumed but the desired product **322** was not isolated and ^{1}H NMR revealed the presence of **323** in the reaction mixture. Moreover, by changing the reaction conditions from 2N HCl to trifluoroacetic acid (TFA) at room temperature or even at 0 °C did not improve the outcome of the reaction.

Product not stable

Scheme 3.3.15 Reagents and conditions: (a) NaH, 4-iodobenzylbromide, DMF, overnight 38%; (b) i) 2 N HCl, MeOH, reflux, 1.5 h; or ii) TFA, CH_2Cl_2, 0 °C or RT.

3.3.11 Synthesis of cyclopropyl analogues of proxyfan with nitrogen linker

Scheme 3.3.16 Reagents and conditions: (a), (b) Lit.[155], (c) PhCHO, $MgSO_4$, CH_2Cl_2, $NaBH_4$, MeOH, 0 °C → RT 24 h 36%; (d) 2 N HCl, MeOH, reflux, 1.5 h, 96%.

To evaluate the effect of a polar linker the cyclopropyl derivative **327** with a nitrogen bridge was envisioned. Cyclopropyl alcohol **298** was succefully converted to cyclopropyl amine **325** by known procedures[155] *via* Mitsunobu reaction using pthalamide as a nucleophile, followed by refluxing **324** with hydrazine hydrate. Reductive amination of **325** was successfully carried out even though in bad yields using *in situ* imine formation with freshly distilled benzaldehyde followed by the reduction with $NaBH_4$ in methanol. Finally the trityl group was removed with 2N HCl in methanol to obtain **327** as a dihydrochloride salt.

In conclusion, many diverse, conformationally restricted compounds have been developed. Moreover, the synthesis of a series of cyclopropanated analogues with different linker has been described in an efficient way. All novel compounds are currently screened for histamine H3R antagonistic activity on guinea-pig. Moreover, these compounds will also be screened for H1R as well as Muscarinic receptor (M_3R) activity to study the selectivity.

3.4 Pharmacology

All novel, conformationally restricted imidazole containing compounds were screened in vitro for functional interactions with histamine H_3Rs of guinea-pig ileum according to standard procedures. Moreover, compounds were also screened in vitro for functional interactions with muscarinic M_3-Receptors (M_3R) to identify suitable concentration that could be tested in the H_3R assay. Some compounds were also studied at histamine H_1R of guinea-pig ileum with regard to subtype selectivity (Table 3.4.1). Cyclopropanated analogues will also be studied at histamine H_1Rs of guinea-pig ileum in near future.

The H_3R antagonistic activity of the new compounds structurally related to FUB-372 was not found to be as good as it was anticipated. Nevertheless, most of the compounds showed moderate to good H_3R antagonistic activity. The compound **287** a *trans* olefinic analogue of FUB-372 showed 2 orders of magnitude lower activity (pA_2 = 5.92 ± 0.08) than its parent one (pA_2 = 7.8 ± 0.1, Table 3.4.1). To view the difference in binding, the *cis* olefinic compound **295** was also synthesized and screened for the H_3R activity. The compound **295** did not show any significant deviation (pA_2 = 6.06 ± 0.06) in the activity and also behaved similarly like the *trans* analogue (**287**). On the other hand alkyne analogue **292** which is more rigid, did not show any significant antagonism (pA_2 < 5.5) when screened against R-alpha-methyl histamine (RAMH).

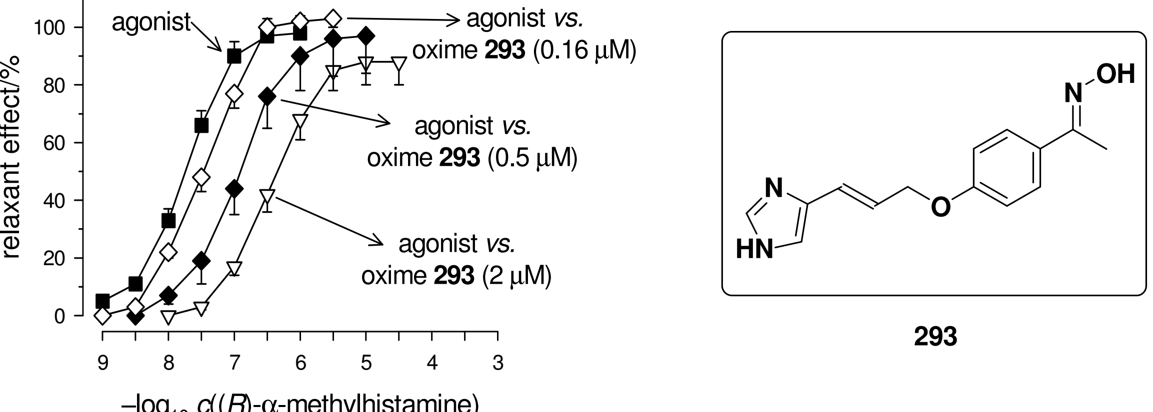


Figure 3.4.1: Concentration response curve for 293

Table 3.4.1 H_1 and H_3R activity of FUB-372 analogues[a]

Comp. Nu.	Structure	H_3R antagonism ($pA_2 \pm$ SEM; N[b])	H_1R activity
249		7.8 ± 0.1	$pEC_{50} = 4.7 \pm 0.1$ $pK_P = 4.2 \pm 0.1$
287		5.92 ± 0.08 (12)	$pD'_2 = 4.3 \pm 0.2$
295		6.06 ± 0.06 (6)	$pD'_2 < 4.5 \pm 0.2$
292		< 5.5 (5)	$pD'_2 = 4.2 \pm 0.2$
302		< 6 (2)	nd[c]
293		**7.06 ± 0.06 (14)**	**$pD'_2 < 4.2 \pm 0.2$**
294		< 5.7 (4)	$pD'_2 < 4.5 \pm 0.2$

[a] Experimental protocol and definition of parameters see (3.5, pharmacological methods)

[b] Number of experiments for affinity determination.

[c] pD'_2 value not determined

Table 3.4.2 H_3R activity of cyclopropanated analogues[a]

Comp.	Structure	H_3R antagonism (pA_2 ± SEM; N[b])	Relaxant effect (%) (± SEM)
314		7.29 ± 0.03 (5)	0
315		7.21 ± 0.06 (6)	24 ± 4
316		7.36 ± 0.09 (4)	39 ± 5
317		7.34 ± 0.14 (4)	38 ± 4
318		7.44 ± 0.08 (8)	62 ± 6
319		7.40 ± 0.07 (4)	56 ± 8
320		6.82 ± 0.05 (6)	0
327		6.58 ± 0.11 (4)	0

[a] Experimental protocol and definition of parameters see (3.5, pharmacological methods)

[b] Number of experiments for agonism or determination.

It is well known in the literature that the oximes are more potent H_3R antagonists than their parent ketones.[124] In order to achieve more potency, the oximes were synthesized from corresponding ketones (Scheme 3.3.6). The oxime **294** of alkyne analogue **292** did not show any significant antagonism (pA_2 = < 5.7) On the other hand oxime derivative **293** was found to be more potent (pA_2 = 7.06 ± 0.06) than the parent ketone (**287**) which is well in agreement with the current concept of SARs of histamine H_3R antagonists. A concentration response curve for most active compound (**293**) is shown in Fig. 3.4.1. Apart from this a new class of structural isomer **302** of FUB-372 was also screed, but showed no detectable antagonism verses RAMH (pA_2 < 6).

In cyclopropanated series, mostly independent of the nature of substituents at the para position of the phenyl ring, the H_3R antagonism was found in the range of 0.03-0.1 μmol/L. The compounds **314-319** showed good antagonistic activity (pA_2 = 7.2-7.4). Compound **318** was found to be the most active among the cyclopropanated analogues (Fig. 3.4.2). On the other hand amino analogue **327** of ether **314** was found to be less potent. Several compounds, after addition to the organ bath produced a relaxant response which was not related to the M_3R antagonism because the applied concentration of the antagonist was too low.

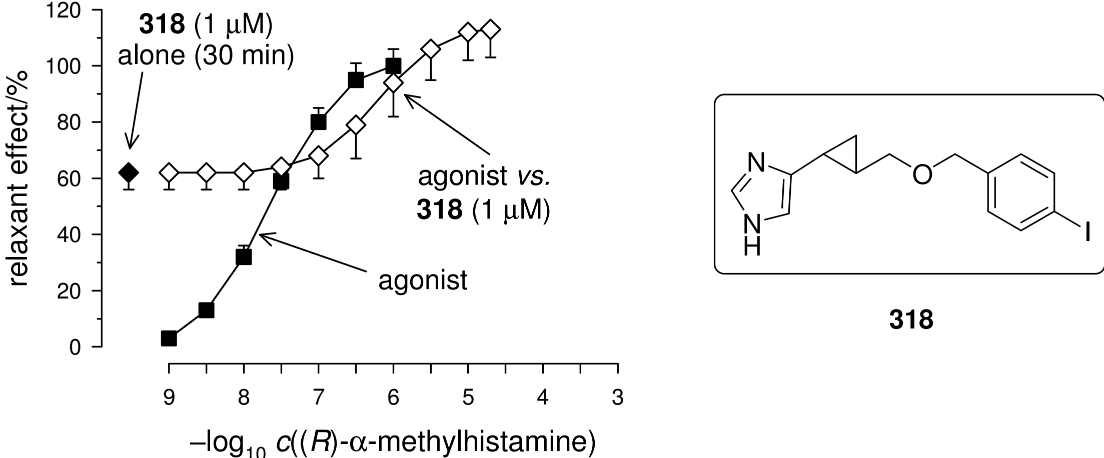


Figure 3.4.2: Concentration response curve for 318

Interestingly, in preliminary experiments for **318** it was shown that this pseudo-H_3R agonism was not sensitive to the presence of H_3R antagonist such as FUB-372 of ciproxifan (data not shown), and therefore, this effect has to be related to a different mechanism, may be an interaction with ion channels.

Table 3.4.2 H_3R activity of iodoproxyfan and its trans olefinic analogue[a]

Comp. Nu.	Structure	H_3R antagonism (pA_2 ± SEM; N[b])	Relaxant effect (%) (± SEM)
248		9.0[c]	-
307		6.64 ± (6)	46 ± 3

[a] Experimental protocol and definition of parameters see (3.5, pharmacological methods)

[b] Number of experiments for agonism or affinity determination.

[c] pA_2values was calculated from pK_B value given in Lit.[133].

Finally compound **307** a trans configurated olefinic analogue of iodoproxyfan (**248**) display only 1% relative affinity compared with the potent lead **248**.

As a conclusion, it has been shown that all attempts to rigidize flexible H_3R antagonists, such as FUB-372 and/or iodoproxyfan, have ultimately led to more or less severe attenuation of H_3R affinity.

3.5 Pharmacological methods

For pharmacology, data handling and pharmacological parameters and histamine H_1R assay on the isolated guinea-pig ileum, see (2.5 and 2.5.1, chapter 2) and references cited therein

3.5.1 Histamine H_3-Receptor assay on electrically stimulated guinea-pig ileum longitudinal muscle with adhering myenteric plexus.

Strips of guinea-pig ileal longitudinal muscle, with adhering myenteric plexus of approximately 2 cm length and proximal to the ileocaecal junction, were prepared as previously described.[156,157] The strips were mounted isometrically under an initial tension of approximately 7.5 mN in a jacketed 20-mL organ bath of filled with modified Krebs-Henseleit solution of the following composition [mM]: NaCl 117.9, KCl 5.6, $CaCl_2$ 2.5, $MgSO_4$ 1.2, NaH_2PO_4 1.3, $NaHCO_3$ 25.0, glucose 5.5, and choline chloride 0.001. The solution was aerated with 95% O_2-5% CO_2 and warmed to a constant temperature of 37 °C. After an equilibration period of 1 h with washings every 15 min, the preparations were stimulated for 30 min with rectangular pulses of 15 V and 0.5 ms at a frequency of 0.1 Hz. Viability of the muscle strips was monitored by addition of the histamine H_3-Receptor agonist (*R*)-α-methylhistamine (100 nM). The agonist caused a relaxation of the twitch response of more than 50% up to 100%. After washout, reequilibration and 30 min field-stimulation, a cumulative concentration-response curve to (*R*)-α-methylhistamine (1-1000 nM) was constructed. Subsequently, the preparations were washed intensively and reequilibrated for 20-30 min. During the incubation period of the antagonist under study, the strips were stimulated continuously for 30 min. Finally, a second concentration-response curve to (*R*)-α-methylhistamine was obtained. The rightward displacement of the curve to the histamine H_3-Receptor agonist evoked by the antagonist under study was corrected with the mean shift monitored by daily control preparations in the absence of antagonist. New antagonists were tested at concentrations that did not block ileal cholinergic M_3Rs. Mepyramine (1 μM) and cimetidine (30 μM) were present throughout the experiments to block H_1 and H_2 receptors, respectively.

3.5.2 Acetylcholine M_3-Receptor assay on the isolated guinea-pig ileum.

Guinea-pigs of either sex were stunned by a blow on the head and exsanguinated. The ileum was removed, and whole segments (1.5-2 cm) were mounted isotonically (preload 0.5 g) at 37 °C in Tyrode's solution,[158] aerated with 95% O_2-5% CO_2, in the continuous presence of 1–3 µM mepyramine, a concentration not affecting M_3Rs. During an equilibration period of *ca.* 80 min, the organs were stimulated three times with carbachol (1 and 10 µM) followed by washout. Each preparation was used to establish a cumulative concentration-effect curve for carbachol (0.003-10 µM) followed by up to three curves for carbachol in the presence of increasing concentrations of antagonist (incubation time 10-15 min). The pEC_{50} difference was not corrected since four successive curves for carbachol were superimposable ($n > 10$). In most cases, it was sufficient to determine a range of concentrations for the new compounds where there was no apparent interaction with the carbachol response. Such concentrations were then chosen to be used during the H_3R experiments. For most of the new compounds, a precise M_3-Receptor affinity was not determined to avoid the loss of compound.

3.6 Experimental part

For general remarks see (2.6.1 experimental part chapter 2)

3.6.1 Experimental procedures and analysis of data

(E)-methyl3-(1-trityl-1*H*-imidazol-4-yl)acrylate (283):

To a solution of methyl urocanate(**152**) (6 g, 39.43 mmol) and triethylamine (13.7 mL, 98.57 mmol) in dry DMF (40 mL) was added dropwise a solution of triphenylmethyl chloride (12.1 g, 43.38 mmol) in dry DMF (12 mL) at RT. After stirring at RT for 4 h the reaction mixture was poured into ice water (300 g). The precipitates were collected and dried to give **283** (15.5 g, quantitative), which was essentially pure for the next step.

R*f* (SiO_2, MeOH/CH_2Cl_2 2:98) = 0.25; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 3.74 (s, 3 H, CO_2CH_3), 6.55 (d, *J* = 15.6 Hz, 1 H, =C*H*CO), 7.03 (d, *J* = 1.2, Hz, 1 H, Imi-5*H*), 7.09-7.17 (m, 6 H, *aromatic*), 7.32-7.36 (m, 9 H, *aromatic*), 7.45 (d, *J* = 1.2, Hz, 1 H, Imi-2*H*), 7.51 (d, *J* = 15.6 Hz, 1 H =C*H*); **^{13}C NMR** (75.5 MHz $CDCl_3$): δ = 51.5 (+, CO_2CH_3), 75.8 (+, C_{quat}, *C*Ph_3), 115.8 (+, CH, Imi-*C*5), 124.2 (+, =*C*HCO), 128.3 (+, CH, *aromatic*) 128.4 (+, CH, *aromatic*) 129.7 (+, CH, *aromatic*) 136.5 (+, =*C*H), 137.1 (+, C_{quat}, Imi-*C*4) 140.4 (+, CH, Imi-*C*2) 141.9 (+, C_{quat}, *aromatic*), 168.0 (+, C_{quat}, *C*O). All other data was in good agreement with the literature.[159]

(E)-3-(1-trityl-1*H*-imidazol-4-yl)prop-2-en-1-ol (284):

Methyl ester **283** (3.94 g, 10 mmol) was dissolved in CH_2Cl_2 (100 mL) under N_2 and cooled to 0 °C. DIBAL-H (1 M in CH_2Cl_2, 30 mL, 30 mmol) was added dropwise. The mixture was

allowed to warm up to RT slowly and stirred for 6-8 h and cooled to 0 °C again. Water (10 mL) was added slowly, followed by NaOH (2N, 10 mL) and H_2O (10 mL). The mixture was filtered through Celite and washed several times with CH_2Cl_2. The organic layer of the filtrate was separated. Aqueous phase was extracted with CH_2Cl_2 (4×50 mL). The combined organic phase was dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and the residue was subjected to column chromatography (95/5, EtOAc/MeOH) to afford allyl alcohol **284** (2.72 g, 75 %) as a white solid.

R_f (SiO_2, MeOH/EtOAc 5:95) = 0.28; **^{1}H NMR** (300 MHz CD_3OD): δ 4.15 (d, *J* = 5.0 Hz, 2 H C*H*$_2$OH), 6.31 (dt, *J* = 15.9, 5.0 Hz, 1 H, =C*H*CH$_2$), 6.41 (d, *J* = 15.9 Hz, 1H =C*H*), 6.87 (d, *J* = 1.2 Hz, 1 H, Imi-5*H*), 7.11-7.17 (m, 6 H, *aromatic* C*H*), 7.34-7.38 (m, 9 H, *aromatic* C*H*), 7.41 (d, *J* = 1.2 Hz, 1 H, Imi-2*H*); **^{13}C NMR** (75.5 MHz CD_3OD): δ = 63.5 (-, *C*H$_2$OH), 76.9 (+, C_{quat}, *C*Ph$_3$), 120.8 (+, =*C*H), 122.7 (+, CH Imi-*C*5) 129.2 (+, =*C*HCH$_2$) 129.3 (+, CH, *aromatic*) 129.4 (+, CH, *aromatic*) 130.8 (+, CH, *aromatic*) 139.9 (+, C_{quat}, Imi-*C*4) 140.1 (+, CH, Imi-*C*2) 143.5 (+, C_{quat}, *aromatic*). All other data was in good agreement with the literature.[160]

1-(4-((E)-3-(1-trityl-1*H*-imidazol-4-yl)allyloxy)phenyl)ethanone (285):

Triphenylphospine (1.57 g, 6 mmol) was dissolved in THF (30 mL) together with allyl alcohol **284** (1.83 g, 5mmol) and 4-hydroxyacetophenone (817 mg, 6 mmol) and cooled to an ice bath. Diethyl azodicarboxylate (DEAD) (0.95 mL, 6 mmol) was added slowly followed by additional stirring for 4 h at ambient temperature. THF was removed and diethyl ether (40 mL) was added washed with H_2O (20 mL) and brine (20 mL). Filtration and evaporation of the solvent gave a residue which was purified by column chromatography (EtOAc/hexanes 1:1) and the **285** was obtained as white solid (42%) along with the minor isomer **286** (≈ 15 %) **R_f** (SiO_2, hexanes/EtOAc 1:1) = 0.21; **m.p.** = 187-189 °C; **^{1}H NMR** (*spectra is not first order*). (300 MHz $CDCl_3$): δ = 2.54 (s, 3 H, COC*H*$_3$), 4.72 (d, *J* = 4.94 Hz, 2 H, OC*H*$_2$), 6.51 (dt, *J* = 4.94, 15.92 Hz, 1 H, =C*H*CH$_2$), 6.58 (d, *J* = 15.92 Hz, =C*H*), 6.79 (d, *J* = 1.23 Hz, Imi-5*H*), 6.93-6.97 (m, 2 H, *aromatic*), 7.10-7.16 (m, 6 H, *aromatic*), 7.30-7.35 (m, 9 H,

aromatic), 7.42 (d, *J* = 1.23 Hz, Imi-2*H*), 7.89-7.93 (m, 2 H, *aromatic*); **^{13}C NMR** (75.5 MHz $CDCl_3$): δ = 26.5 (+, CO*C*H_3), 68.7 (-, *C*H_2O), 75.5 (+, C_{quat}, *C*Ph_3), 114.5 (+, CH, *aromatic*), 120.1 (+, =*C*H), 121.9 (+, CH, Imi-*C*5), 125.3 (+, CH, *aromatic*), 128.2 (+, CH, *aromatic*), 128.2 (+, CH, *aromatic*), 129.8 (+, =*C*HCH_2), 130.3 (+, C_{quat}, Imi-*C*4), 130.7 (+, CH, *aromatic*), 138.2 (+, C_{quat}, *aromatic*), 139.4 (+, CH, Imi-*C*2) , 142.3 (+, C_{quat}, *aromatic*), 162.7 (+, C_{quat}, *aromatic*), 196.9 (+, C_{quat}, *C*O); **IR** (KBr): ṽ = 3059, 2928, 1732, 1672, 1597, 1491, 1445, 1358, 1272, 1242, 1171, 1127, 981, 928, 834, 748, 702 cm^{-1}; **MS** (ESI, CH_2Cl_2/MeOH/NH_4Ac): *m/z* = 485.2 [M + H^+], 969.6 [2 M + H^+].

1-(4-((E)-3-(1*H*-imidazol-4-yl)allyloxy)phenyl)ethanone (287):

To a solution of **285** (150 mg, 0.31 mmol) in acetone (3 mL) was added 2M solution of HCl (3 mL) and reaction mixture was refluxed for 1.5 h. most of the acetone was evaporated in vacuo and aqueous phase was made strongly basic by adding solid K_2CO_3 and extracted in CH_2Cl_2:MeOH 9:1 (4×10 mL) dried ($MgSO_4$). The solvent was removed in vacuo. The residue was purified by chromatography on silica (CH_2Cl_2/MeOH/NH_3 50:1:0.5) to get the product as a cream white solid (56 mg, 74.6 %).

R_f (SiO_2, MeOH/CH_2Cl_2 5:95) = 0.20; **m.p.** = 160-161 °C; **^{1}H NMR** (300 MHz DMSO): δ = 2.51 (s, 3 H, COC*H*$_3$), 4.77 (dd, *J* = 1.20, 6.11, Hz, 2 H, C*H*$_2$O), 6.28 (dt, *J* = 15.81, 6.11, Hz, 1 H, =C*H*CH_2), 6.63 (d, *J* = 15.81, Hz, 1 H, =C*H*), 7.04-7.09 (m, 2 H, *aromatic*), 7.11 (bs, Imi-5*H*), 7.62 (bs, Imi-2*H*), 7.89-7.94 (m, 2 H, *aromatic*), 12.15 (bs, Imi-N*H*); **^{13}C NMR** (75.5 MHz DMSO): δ = 26.4 (+, CO*C*H_3), 68.4 (-, *C*H_2OH), 114.6 (+, CH, *aromatic*), 120.4, (+, =*CH*CH_2), 120.4 (+, CH, *aromatic*), 124.8 (+, CH, Imi-*C*5, broad), 129.8 (+, C_{quat}, Imi-*C*4), 130.5 (+, CH, *aromatic*), 136.3 (+, CH, Imi-*C*2 and vinyl, broad), 162.2 (+, C_{quat}, *aromatic*), 196.3 (+, C_{quat}, *C*O); **IR** (KBr): ṽ = 3101, 3070, 2970, 2922, 2806, 2602, 1662, 1598, 1571, 1506, 1461, 1420, 1381, 1353, 1306, 1251, 1176, 1112, 996, 854, 832, 631, 590 cm^{-1};**MS** (EI, 70 eV): *m/z* (%) = 242.1 (3) [M^+], 136 (4.8) [phenoxy acetyl], 121 (13.6), 107 (100), 80 (41.6), 53 (15.7); **HRMS** calcd for $C_{14}H_{14}N_2O_2$, 242.1055. Found 242.1053.

1-(4-((E)-3-(1H-imidazol-4-yl)allyloxy)phenyl)ethanone oxime (293)

To a solution of ketone **287** (110 mg, 0.45 mmol) and hydroxylamine hydrochloride (69.49 mg, 0.91 mmol) in dry EtOH (5 mL) was added Na_2CO_3 (106 mg, 0.91 mmol). The reaction mixture was heated to reflux for 2 h. After the filtration of inorganic salts, the solvent was evaporated under reduced pressure. The product was purified by column chromatography (CH_2Cl_2/MeOH 90/10) to obtain a cream white solid (96 mg 82 %).

R*f* (SiO_2, MeOH/ CH_2Cl_2 10:90) = 0.4; **m.p.** = 178-180 °C and start to become brown from 172 °C; **^{1}H NMR** (300 MHz CD_3OD): δ = 2.19 (s, 3 H, COC*H*$_3$), 4.68 (dd, *J* = 1.42, 5.78, Hz, 2 H, C*H*$_2$O), 6.36 (dt, *J* = 15.96, 5.78, Hz, 1 H, =C*H*CH$_2$), 6.65 (d, *J* = 15.96, Hz, 1 H, =C*H*), 6.93-6.98 (m, 2H, *aromatic*), 7.06 (bs, Imi-5*H*), 7.55-7.60 (m, 2H, *aromatic*), 7.63 (bs, Imi-2*H*); **^{13}C NMR** (75.5 MHz CD_3OD): δ = 12.1 (+, CO*C*H$_3$), 69.5 (-, *C*H$_2$OH), 115.6 (+, CH, *aromatic*), 115.6 (+, CH, *aromatic*), 116.7 (+, CH, Imi-*C*5), 123.6, (+, =*CH*CH$_2$), 128.4 (+, CH, *aromatic*), 129.6 (+, C_{quat}, Imi-*C*4), 131.1 (+, C_{quat}, *aromatic*), 137.2 (+, CH, Imi-*C*2 and *vinyl*, broad), 155.8, (+, C_{quat}, *C*NOH), 160.8 (+, C_{quat}, *aromatic*); **IR** (neat): ṽ = 3350-3200 (broad), 2850, 1602, 1511, 1303, 1243, 1177, 1002, 921, 831 cm^{-1}; **MS** (EI-MS,70 eV): *m/z* (%) = 257.1 (7 %) [M $^{+\cdot}$], 107 (100 %); **HRMS** calcd for $C_{14}H_{14}N_2O_2$, 257.1164. Found 257.1166.

1-(4-(prop-2-ynyloxy)phenyl)ethanone (290):

Triphenylphospine (13.17 g, 48 mmol) was dissolved in THF (70 mL) together with propargyl alcohol (2.5 mL, 43.64 mmol) and 4-hydroxyacetophenone (6.54 g, 48 mmol) and cooled to an ice bath. DEAD (8.74 mL, 48 mmol) was added slowly followed by additional stirring for 6 h at ambient temperature. THF was removed and diethyl ether (200 mL) was

added washed with H_2O (2×75 mL). Filtration and evaporation of the solvent gave a residue which was purified by column chromatography (EtOAc/hexanes 2:8) to get the product as white solid. (7.56, 99%)

R_f (SiO_2, hexanes/EtOAc 8:2) = 0.3; **m.p.** = 72-73 °C; **^{1}H NMR** (300 MHz $CDCl_3$): δ = 2.54 (s, 3 H, COC*H_3*), 2.55 (t, *J* = 2.5 Hz, 1 H, C*H*, *acetylynic*), 4.73 (d, *J* = 2.5 Hz, 2 H, C*H_2*O), 7.02-7.26 (m, 2 H, *aromatic*), 7.90-7.95 (m, 2 H, *aromatic*); **^{13}C NMR** (75.5 MHz CDCl3): δ = 26.5 (+, CO*C*H_3), 55.9 (-, *C*H_2O), 76.3 (+, CH, *acetylynic*), 77.8, (+, C_{quat}, *acetylynic*), 114.6 (+, CH *aromatic*), 130.6 (+, CH *aromatic*), 131.1 (+, C_{quat}, *aromatic*), 161.3 (+, C_{quat}, *aromatic*), 196.8 (+, C_{quat}, *C*O); **IR** (KBr): ṽ = 3225, 2923, 2871, 2117, 1611, 1603, 1573, 1421, 1377, 1355, 1277, 1244, 1182, 1018, 959, 827, 756, 696 cm^{-1}; **MS** (EI +VE): *m/z* (%) = 174.1 (40.84) [M^+], 159.1, (100) [M^+ - CH_3], 131.1 (44.8) [M^+ - $COCH_3$]; **Elemental analysis** calcd (%) for $C_{11}H_{10}O_2$ (174.07) C 75.84, H 5.79; found C 75.76, H 5.66.

1-(4-(3-(1-trityl-1*H*-imidazol-4-yl)prop-2-ynyloxy)phenyl)ethanone (291):

To a (1:1) mixture of Diisopropyl amine and THF (12 ml), degased with N_2 for 10 min., was added 4-iodo-1-trityl-imidazole (437 mg, 1 mmol), CuI (19mg, 0.1 mmol), $PdCl_2(Ph_3P)_2$ (7 mg, 0.01 mmol) and acetyline **290** (174 mg, 1 mmol) and stirred at ambient temprature for 6 h. Diethyl ehter (20 mL) was added and reaction mixture was filtered through a small pad of celite, washed with H_2O (10 mL) and dryed over $MgSO_4$. Filtration and evaporation of the solvent gave a residue which was purified by column chromatography (EtOAc/hexanes 1:1) to get the product as pale yellow solid (252 mg, 52 %).

R_f (SiO_2, hexanes/EtOAc 1:1) = 0.28; **m.p.** = 194-196 °C; **^{1}H NMR** (300 MHz $CDCl_3$): δ 2.53 (s, 3 H, COC*H_3*), 4.93 (bs, 2 H, C*H_2*O), 7.00-7.13 (m, 9 H, *aromatic*), 7.30-7.35 (m, 9 H, *aromatic* and Imi-5*H*), 7.39 (bs 1 H, Imi-2*H*), 7.90-7.95 (m, 2 H, *aromatic*); **^{13}C NMR** (75.5 MHz $CDCl_3$): δ = 26.4 (+, CO*C*H_3), 56.8 (-, *C*H_2O), 75.9 (+, C_{quat}, *C*Ph_3), 81.8 (+, C_{quat}, *acetylinic*), 83.4 (+, C_{quat}, *acetylynic*), 114.6 (+, CH, *aromatic*), 122.3 (+, C_{quat}, Imi-*C*4, broad), 126.5 (+, CH, Imi-*C*5, broad), 128.3 (+, CH, *aromatic*), 128.4 (+, CH, *aromatic*), 129.7 (+, CH, *aromatic*), 130.6 (+, CH, *aromatic*), 130.8 (+, C_{quat}, *aromatic*), 139.2 (+, CH, Imi-*C*2, broad), 141.9 (+, C_{quat}, *aromatic*), 161.6 (+, C_{quat}, *aromatic*), 196.8 (+, C_{quat}, *C*O); **IR** (neat): ṽ = 3130, 2238, 1680, 1596, 1443, 1356, 1249, 1168, 1139, 1044, 956, 825, 749, 703

cm^{-1}; **MS** (70 eV, EI): *m/z* (%) = 482.3 [$M^{+\bullet}$], 243.2 (100) [CPh_3^+], 165.1 (52.8) [CPh_2^+], 121.0 (9.8), 105.0 (8.2).

1-(4-(3-(1*H*-imidazol-4-yl)prop-2-ynyloxy)phenyl)ethanone (292):

To a solution of **291** (240 mg, 0.49 mmol) in acetone (5 mL) was added 2M solution of HCl (5 mL) and reaction mixture was refluxed for 1 h. most of the acetone was evaporated in vacuo and aqueous phase was made strongly basic by adding solid K_2CO_3 and extracted in CH_2Cl_2:MeOH 9:1 (4×10 mL) dried ($MgSO_4$).The solvent was removed in vacuo. The residue was purified by chromatography on silica (CH_2Cl_2/MeOH/NH_3 50:1:0.5) to get the product as a cream white solid. (98 mg, 82%)

R_f (SiO_2, MeOH/CH_2Cl_2 5:95) = 0.28; **m.p.** = 165-166 °C; **^{1}H NMR** (300 MHz DMSO): δ = 2.55 (s, 3 H, COC*H*$_3$), 5.04 (s, 2 H, C*H*$_2$O), 7.08-7.13 (m, 2 H, *aromatic*), 7.30 (bs, Imi-5*H*), 7.65 (bs, Imi-2*H*), 7.96-8.01 (m, 2 H, *aromatic*); **^{13}C NMR** (75.5 MHz DMSO): δ = 26.4 (+, CO*C*H$_3$), 57.4 (-, *C*H$_2$O), 81.7 (+, C_{quat}, *acetylinic*, broad), 85.5 (+, C_{quat}, *acetylinic*, broad), 115.8 (+, CH, *aromatic*), 124.8 (+,CH, Imi-*C*5, broad), 131.7 (+, CH, *aromatic*), 131.8 (+, C_{quat}, Imi-*C*4), 137.2 (+, CH, Imi-*C*2), 163.4 (+, C_{quat}, *aromatic*), 196.4 (+, C_{quat}, *C*O); **IR** (KBr): ṽ = 3122, 2918, 2852, 2245, 1680, 1601, 1511, 1454, 1420, 1377, 1307, 1252, 1043, 1009, 956, 827, 766 cm^{-1}; **MS** (EI-MS, 70 eV): *m/z* (%) = 240.0 (3.5) [M^+], 197 (3) [M^+ - $COCH_3$],105 (100 %) [M^+ - phenoxy acetyl], 51.1 (11); **HRMS** calcd for $C_{14}H_{12}N_2O_2$, 240.0899. Found 240.0900; **Elemental analysis** calcd (%) for $C_{14}H_{12}N_2O_2$ (240.09): calc. C 69.99, H 5.03, N 11.66; found C 68.51, H 5.00, N 11.49.

1-(4-(3-(1*H*-imidazol-4-yl)prop-2-ynyloxy)phenyl)ethanone (294)

To a solution of ketone **291** (20 mg, 0.083 mmol) and hydroxylamine hydrochloride (23.11 mg, 0.33 mmol) in dry EtOH (4 mL) was added Na_2CO_3 (35.25 mg, 0.33 mmol). The reaction

mixture was heated to reflux for 1 h. After the filtration of inorganic salts, the solvent was evaporated under reduced pressure to obtain a cream white solid. H_2O was added and the precipitate was filtered and washed with H_2O and dried (20 mg 94 %).Structure was determined by NOE experiments.

R_f (SiO_2, MeOH/CH_2Cl_2 5:95) = 0.23; **m.p.** = 180-182 °C **^{1}H NMR** (300 MHz DMSO): δ = 2.12 (s, 3 H, COC*H_3*), 5.04 (s, 2 H, C*H_2*O), 7.00-7.05 (m, 2 H, *aromatic*), 7.44 (bs, Imi-5*H*), 7.58-7.63 (m, 2 H, *aromatic*), 7.67 (bs, Imi-2*H*), 11.01 (s, NO*H*), 12.34 (bs, 1 H, Imi-N*H*); **^{13}C NMR** (150.9 MHz DMSO): δ = 11.4 (+, CN*C*H_3), 56.1 (-, *C*H_2O), 82.1 (+, C_{quat}, *acetylinic*), 83.3 (+, C_{quat}, *acetylinic*), 114.6 (+, CH, *aromatic*), 121.4 (+, C_{quat}, Imi-*C*4), 121.6 (+, CH, Imi-*C*5), 126.8 (+, CH, *aromatic*), 130.0 (+, CH, *aromatic*), 136.1 (+, CH, Imi-*C*2), 152.3 (+, C_{quat}, *C*=NOH, 157.7 (+, C_{quat}, *aromatic*); **IR** (neat): $\tilde{\nu}$ = 3250-3100 (broad), 2320, 2242, 1604, 1512, 1449, 1373,1306, 1221, 1037, 1002, 831, 754, 656 cm^{-1}; **MS** (EI-MS, 70 eV): *m/z* (%) = 255.1 (9 %) [M $^{+\cdot}$], 238.1 (12 %) [M^+ - OH], 105.0 (100 %) [M^+ - phenoxy oxime]; **HRMS** calcd for $C_{14}H_{14}N_2O_2$, 255.1008. Found 255.1009; **Elemental analysis** calcd (%) for $C_{14}H_{14}N_2O_2$ (255.10): C 65.87, H 5.13, N 16.46; found C 65.21, H 5.32, N 16.59.

1-(4-((Z)-3-(1*H*-imidazol-4-yl)allyloxy)phenyl)ethanone (295):

ketone **292** (30 mg 0.125 mmol) was dissolved in MeOH (3 mL) and was treated with 10 wt %Pd-$BaSO_4$ (5 mg) and purged with a atmosphere of hydrogen followed by vigorous stirring in an atmosphere of hydrogen (via balloon) for 16 h. The reaction mixture was filtered through a pad of Celite, washed with MeOH (10 mL). The solvent was removed in vacuo to leave the oil which was precipitated by ether. Finally ether was decanted to leave the pail brown (92 %).

R_f (SiO_2, MeOH/ CH_2Cl_2 5:95) = 0.19; **m.p.** = 170-173 °C; **^{1}H NMR** (300 MHz CD_3OD): δ = 2.55 (s, 3 H, COC*H_3*), 4.94 (dd, *J* = 1.27, 5.56 Hz, 2 H, C*H_2*O), 6.26 (dt, *J* = 11.97, 5.55 Hz, 1 H, =C*H*CH_2), 6.57 (dt, *J* = 11.96, 1.26 Hz, 1 H, =C*H*), 7.03-7.06 (m, 2 H, *aromatic*), 7.63 (bs, Imi-5*H*), 7.96-7.99 (m, 2 H, *aromatic*), 8.83 (bs, Imi-2*H*); with calibration **^{13}C NMR** (75.5 MHz CD_3OD): δ = 26.4 (+, CO*C*H_3), 66.3 (-, *C*H_2O), 115.6 (+, CH, *aromatic*), 117.5 (+, *C*H=CHCH_2), 119 1 (+, CH, Imi-*C*5), 131.8 (+, C_{quat}, Imi-*C*4), 131.9 (+, CH, *aromatic*), 132.8 (+, =*C*HCH_2), 135.5 (+, CH, Imi-*C*2), 163.8 (+, C_{quat}, *aromatic*), 199.3 (+, C_{quat}, *C*O);

IR (KBr): ṽ = 3101, 3070, 2970, 2922, 2806, 2602, 1662, 1598, 1571, 1506, 1461, 1420, 1381, 1353, 1306, 1251, 1176, 1112, 996, 854, 832, 631, 590 cm^{-1}; **MS** (EI, 70 eV): *m/z* (%) = 242.1 (3) [M^+], 136 (4.8) [M^+ -] 121 (13.6), 107 (100) 80 (41.6), 53 (15.7); **HRMS** calcd for $C_{14}H_{14}N_2O_2$, 242.1055. Found 242.1053.

1-(4-(1-(1-trityl-1*H*-imidazol-4-yl)but-3-enyloxy)phenyl)ethanone (301):

O
O
N
N
Ph_3C

Triphenylphospine (288 mg, 1.1 mmol) was dissolved in THF (10 mL) together with cyclopropyl alcohol **298** (381 mg, 1 mmol) and 4-hydroxyacetophenone (150 mg, 1.1 mmol) and cooled to an ice bath. DEAD (0.19 mL, 1.2 mmol) was added and stirred for 1 h, slowly followed by additional stirring for 2 h at ambient temperature. THF was removed and diethyl ether (20 mL) was added washed with H_2O (10 mL) and brine (20 mL). Filtration and evaporation of the solvent gave a residue which was purified by column chromatography (EtOAc/hexanes 1:1) to get the product as a white solid (324 mg 65%).
$\mathbf{R}_f$ (SiO_2, hexanes/EtOAc 1:1) = 0.21; **m.p.** = 125-126 °C; **^{1}H NMR** (300 MHz $CDCl_3$): δ = 2.54 (s, 3 H, COC*H*$_3$), 2.81 (t, *J* = 6.35 Hz, 2 H, C*H*$_2$CO), 5.04-5.13 (m, 2 H, =C*H*$_2$), 5.35 (t, *J* = 6.35 Hz, CH_2OC*H*), 5.85 (ddt, *J* = 17.33, 10.19, 6.93 Hz, 1 H, C*H*=CH_2), 6.66 (d, *J* = 1.23 Hz, Imi-5*H*), 6.90-6.95 (m, 2 H, *aromatic*), 7.02-7.06 (m, 6 H, *aromatic*), 7.22-7.32 (m, 9 H, *aromatic*), 7.41 (d, *J* = 1.37 Hz, Imi-2*H*), 7.82-7.87 (m, 2 H, *aromatic*); **^{13}C NMR** (75.5 MHz $CDCl_3$): δ = 26.4 (+, CO*C*H_3), 40.2 (-, *C*H_2CO), 75.3 (+, CH, O*C*HCH_2), 75.4 (+, C_{quat}, *C*Ph_3), 115.8 (+, CH, *aromatic*), 117.8 (-, =*C*H_2), 119.9 (+, CH, Imi-C5), 128.0 (+, CH, *aromatic*), 128.1 (+, CH, *aromatic*), 129.7 (+, CH, *aromatic*), 130.2 (+, C_{quat}, Imi-*C*4), 130.3 (+, CH, *aromatic*), 133.7 (+, CH, *aromatic*), 138.5 (+, CH, Imi-*C*2), 140.3 (+, C_{quat}, *aromatic*), 142.1 (+, C_{quat}, *aromatic*), 162.1 (+, C_{quat}, *aromatic*), 196.8 (+, C_{quat}, *C*O); **IR** (KBr): ṽ = 3332, 3146, 3061, 2921, 1729, 1674, 1597, 1493, 1445, 1420, 1358, 1306, 1249, 1171, 1130, 1037, 1001, 956, 914, 835, 754, 702 cm^{-1}; **MS** (ESI, CH_2Cl_2/MeOH/NH_4Ac): *m/z* = 499.3 [$M^+ + H^+$], 997.7 [$2M^+ + H^+$], 243.1 [Ph_3C^+].

1-(4-(1-(1*H*-imidazol-4-yl)but-3-enyloxy)phenyl)ethanone (302):

To a solution of **301** (150 mg, 0.30 mmol) in acetone (3 mL) was added 2M solution of HCl (3 mL) and reaction mixture was refluxed for 1 h. most of the acetone was evaporated in vacuo and aqueous phase was made strongly basic by adding solid K_2CO_3 and extracted in CH_2Cl_2 (4×6 mL), dried ($MgSO_4$) and solvent was removed in vacuo. The residue was purified by chromatography on silica (CH_2Cl_2/MeOH/NH_3 50:1:0.5) to get the product as a cream white solid (68 mg, 88 %).

R_f (SiO_2, MeOH/CH_2Cl_2 1:9) = 0.42; **m.p.** = 116-117 °C; **^{1}H NMR** (300 MHz $CDCl_3$): δ = 2.48 (s, 3 H, COC*H*$_3$), 2.78 (ddd, *J* = 6.94, 14.42, 28.24 Hz, 2 H, C*H*$_2$CH=CH$_2$), 5.04-5.13 (m, 2 H, =C*H*$_2$ terminal), 5.39 (t, *J* = 6.69 Hz, CH$_2$OC*H*), 5.81 (ddt, *J* = 17.10, 10.20, 6.90 Hz, 1 H, C*H*=CH$_2$), 6.89-6.92 (m, 2 H, *aromatic*), 6.99 (bs, 1 H, Imi-5*H*), 7.63 (bs, 1 H, Imi-2*H*), 7.78-7.82 (m, 2 H, *aromatic*), 9.88 (bs, 1 H, Imi-N*H*); **^{13}C NMR** (75.5 MHz $CDCl_3$): δ = 26.4 (+, CO*C*H$_3$), 40.4 (-, *C*H$_2$CO), 74.5 (+, CH, O*C*HCH$_2$), 115.5 (+, CH, *aromatic*), 114.6 (+, CH, Imi-*C*5), 118.1 (-, =*C*H$_2$), 130.3, (+, C_{quat}, *aromatic*), 130.5 (+, CH, *aromatic*), 133.5 (+, CH, *aromatic*), 135.3 (+, CH, Imi-*C*2), 138.6 (+, C_{quat}, Imi-*C*4), 162.2 (+, C_{quat}, *aromatic*), 197.3 (+, C_{quat}, *C*O); **IR** (KBr): $\tilde{\nu}$ = 3306, 3085, 2986, 2858, 2738, 2670, 2631, 1662, 1598, 1573, 1504, 1468, 1422, 1386, 1308, 1281, 1251, 1178, 1111, 996, 974, 914, 836, 631, 589 cm^{-1}; **MS** (EI, 70 eV): *m/z* (%) = 256.3 (<1) [$M^{+\bullet}$], 218.2 (2.7), 136.2 (9.3) [phenoxy acetyl], 122.2 (7.8), 121.2 (100), 94.2 (14.9), 81.2 (6.0), 65.2 (10.3) 44.2 (18.4); **HRMS** calcd for $C_{15}H_{16}N_2O_2$, 256.1219. Found 256.1212.

4-(3-(4-iodobenzyloxy)propyl)-1-trityl-1*H*-imidazole (304):

A solution of alcohol **303** (709 mg 1.923 mmol) and 4-iodobenzylbromide (600 mg 2.02 mmol) in DMF (5 mL) was cooled to 0 °C and treated with NaH (60% in oil) (84.5 mg 2.11 mmol). The reaction mixture was allowed to come to room temperature and stirred overnight. Water (10 mL) was added and the reaction mixture was extracted with ether (3×15 mL). The combined organic phase was dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and the residue was subjected to column chromatography (95/5, EtOAc/MeOH) to afford **304** (787 mg, 70 %) as a white solid.

$\mathbf{R}_f$ (SiO_2, hexanes/EtOAc 1:1) = 0.29; thick oil; **^{1}H NMR** (300 MHz $CDCl_3$): δ = 1.88-1.98 (m, 2 H $CH_2C\mathit{H}_2CH_2$), 2.63 (t, *J* = 7.67, Hz 1 H, $C\mathit{H}_2CH_2$), 3.46 (t, *J* = 6.41, Hz 2 H, $CH_2C\mathit{H}_2O$), 4.38 (s, 2 H, $C\mathit{H}_2O$), 6.51 (bs,1 H, Imi-*C*5), 7.01-7.05 (m, 2 H, *aromatic*), 7.09-7.16 (m, 6 H, *aromatic*), 7.27-7.34 (m, 9 H, *aromatic*), 7.35 (d, *J* = 1.40, 1 H, Imi-*C*2), 7.59-7.64 (m, 2 H, *aromatic*); **^{13}C NMR** (75.5 MHz $CDCl_3$): δ = 25.1 (-, $CH_2\mathit{C}H_2CH_2$), 29.4 (-, $\mathit{C}H_2CH_2$,), 69.9 (-, $CH_2\mathit{C}H_2O$), 72.2 (-, $\mathit{C}H_2O$), 75.2 (+, C_{quat}, $\mathit{C}Ph_3$), 92.9 (+, C_{quat}, *C*-I), 118.1 (+, CH, Imi-*C*5), 128.0 (+, CH, *aromatic*), 128.1 (+, CH, *aromatic*), 129.5 (+, CH, *aromatic*), 129.9 (+, CH, *aromatic*), 137.5 (+, CH, *aromatic*), 138.4 (+, CH, Imi-*C*2), 138.5 (+, C_{quat}, Imi-*C*4), 141.2 (+, C_{quat}, *aromatic*), 142.6 (+, C_{quat}, *aromatic*); **IR** (Film): $\tilde{\nu}$ = 3058, 2926, 2856, 1713, 1586, 1485, 1446, 1393, 1266, 1236, 1156, 1126, 1099, 1036, 1005, 746, 701, 658 cm^{-1}; **MS** (ESI,CH_2Cl_2/MeOH/NH_4Ac): *m/z* = 585 [M + H^+], 243.1 [CPh_3^+].

4-(3-(4-iodobenzyloxy)propyl)-1*H*-imidazole (248):

To a solution of **304** (600 mg, 1.03 mmol) in MeOH (10 mL) was added 2M solution of HCl (10 mL) and reaction mixture was refluxed for 1.5 h. Most of the MeOH was evaporated in vacuo and aqueous phase was made strongly basic by adding solid K_2CO_3 and extracted in CH_2Cl_2 (4×15 mL), dried ($MgSO_4$) and solvent was removed in vacuo. The residue was purified by chromatography on silica (CH_2Cl_2/MeOH 9:1) to get the product as a cream white solid (243 mg, 69 %).

$\mathbf{R}_f$ (SiO_2, MeOH/CH_2Cl_2 1:9) = 0.18; **m.p.** = 65-66 °C, free base, (Lit.[120] 123-124 °C as a hydrogen maleate); **^{1}H NMR** (300 MHz $CDCl_3$): δ = 1.89-1.98 (m, 2 H $CH_2C\mathit{H}_2CH_2$), 2.71 (t, *J* = 7.58, Hz 1 H, $C\mathit{H}_2CH_2$), 3.49 (t, *J* = 6.23 Hz, 2 H, $CH_2C\mathit{H}_2O$), 4.41 (s, 2 H, $C\mathit{H}_2O$), 6.76 (bs, 1 H, Imi-C5), 7.03-7.07 (m, 2 H, *aromatic*), 7.55 (bs, 1 H, Imi-2*H*), 7.61-7.65 (m, 2 H,

aromatic), 11.56 (bs,1 H, Imi-N*H*); **^{13}C NMR** (75.5 MHz $CDCl_3$): δ = 23.4 (-, CH_2*C*H_2CH_2), 29.4 (-, *C*H_2CH_2,), 69.9 (-, *C*H_2O), 72.3 (-, *C*H_2O), 93.1 (+, C_{quat}, *C*-I), 117.9 (+, CH, Imi-*C*5), 129.6 (+, CH, *aromatic*), 134.4 (+, CH, Imi-*C*2), 136.1 (+, C_{quat}, Imi-*C*4), 137.5 (+, CH, *aromatic*), 138.2 (+, C_{quat}, *aromatic*); **IR** (KBr): ṽ = 3436, 3113, 3074, 2943, 2851, 2731, 2619, 1585, 1470, 1386, 1356, 1262, 1234, 1199, 1170, 1097, 1058, 1026, 1005, 943, 878, 842, 788, 666, 627 cm^{-1}; **MS** (EI +VE): *m/z* (%) = 342.2 (2.5) [$M^{\bullet+}$], 217.1 (19.4), 125.2 (49.2), 110.2 (51.1), 95.2 (37.2), 82.2 (100), 68.3 (4.2); **HRMS** calcd for $C_{13}H_{15}IN_2O$, 342.0229. Found 342.0226.

4-((*E*)-3-(4-iodobenzyloxy)prop-1-enyl)-1-trityl-1*H*-imidazole (305):

A solution of alcohol **284** (71 mg 0.194 mmol) and 4-iodobenzylbromide (63.3 mg 0.213 mmol) in DMF (2 mL) was cooled to 0 °C and treated with NaH (60% in oil) (8.5 mg 0.213 mmol). The reaction mixture was allowed to come to room temperature and stirred overnight. Water (5 mL) was added and the reaction mixture was extracted with ether (3×8 mL). The combined organic phase was dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and the residue was subjected to column chromatography (EtOAc/hexanes 1/1) to afford **305** (85 mg, 75 %) as a white solid.

R_f (SiO_2, hexanes /EtOAc1:1) = 0.28; **m.p.** = 170-171 °C; **^{1}H NMR** (300 MHz $CDCl_3$): δ = 4.15 (d, *J* = 4.67, Hz 2 H, CHC*H*$_2$O), 4.48 (s, 2 H, C*H*$_2$O), 6.42 (dt, *J* = 15.91, 4.67, Hz 1 H, =C*H*CH_2), 6.49 (d, *J* = 15.91, Hz 1 H, =C*H*), 6.78 (d, *J* = 1.13 Hz, 1 H, Imi-5 *H*), 7.08-7.10 (m, 2 H, *aromatic*), 7.13-7.17 (m, 6 H, *aromatic*), 7.31-7.35 (m, 9 H, *aromatic*), 7.43 (d, *J* = 1.13 Hz, 1 H, Imi-2 *H*), 7.62-7.66 (m, 2 H, *aromatic*), **^{13}C NMR** (75.5 MHz $CDCl_3$): δ = 70.8 (-, CH*C*H_2O), 71.2 (-, *C*H_2O), 75.5 (+, C_{quat}, *C*Ph_3), 92.9 (+, C_{quat}, *C*-I), 119.6 (+, CH, Imi-*C*5), 124.4 (+, CH, =*C*HCH_2 and =*C*H), 128.2 (+, CH, *aromatic*), 128.2 (+, CH, *aromatic*), 129.6 (+, CH, *aromatic*), 129.8 (+, CH, *aromatic*), 137.5 (+, CH, *aromatic*), 138.3 (+, C_{quat}, *aromatic*), 138.5 (+, C_{quat}, Imi-*C*4), 139.2 (+, CH, Imi-*C*2), 142.2 (+, C_{quat}, *aromatic*), **IR** (KBr): ṽ = 3057, 3028, 2917, 2848, 1591, 1484, 1444, 1394, 1355, 1292, 1216, 1185, 1156, 1110, 1038, 1004, 949, 829, 791, 747, 701, 656 cm^{-1}; **MS** (ESI): *m/z* (%) = 495.2 [M + H^+], 243.0 [CPh_3^+], 1165.6 [2M + H^+].

4-((E)-3-(4-iodobenzyloxy)prop-1-enyl)-1H-imidazole (306):

Prepared by following the same procedure used for **304**, (87% yield); **R_f** (SiO_2, $MeOH/CH_2Cl_2$ 1:9) = 0.19; thick oil; **^{1}H NMR** (300 MHz $CDCl_3$): δ = 4.08 (dd, 2 H, J = 6.00, 1.26 Hz =CHC*H*$_2$), 4.50 (s, 2 H, OC*H*$_2$), 6.22 (dd, 1 H, J = 15.91, 6.00 Hz, =C*H*CH_2), 6.50 (dt, 1 H, J = 15.91, 1.26 Hz, =C*H*), 6.99 (bs, Imi-5*H*), 7.05-7.08 (m, 2 H, *aromatic*), 7.61 (bs, Imi-2*H*), 7.62-7.66 (m, 2 H, *aromatic*) 9.91 (bs, 1 H, Imi-N*H*); **^{13}C NMR** (75.5 MHz CDCl3): δ = 69.7 (-, =CHCH_2), 70.4 (-, OCH_2), 92.2 (+, C_{quat}, *C*-I), 117.9 (+, CH, Imi-*C*5), 121.6 (+, =*C*HCH_2), 123.5 (+, =*C*H), 128.7 (+, CH, *aromatic*), 134.1 (+, C_{quat},. Imi-*C*4), 134.7 (+, CH, Imi-*C*2), 136.6 (+, CH *aromatic*), 137.0 (+, C_{quat},. *aromatic*); **IR** (Film): ṽ = 3063, 2852, 16641, 1481, 1357, 1303, 1247, 1106, 1007, 965, 908, 829, 798, 731, cm^{-1}; **MS** (EI +VE): *m/z* (%) = 341.0/340.0 (3.5/16.0) [$M^{\bullet+}$], 311.0 (9.8) 297.0, (13.6) 218.0/217.0 (3.2/42.8) 124/123.0 (3.5/58.8), 95.0 (100), 68.0 (12.2); **HRMS** calcd for $C_{13}H_{13}IN_2O$, 340.0073. Found 340.0068.

(E)-1-(1*H*-imidazol-4-yl)-4-methylhex-1-en-3-one (296):

Trans urocanic acid **162** (4 g, 28.95 mmol) and 2-butanol (30 mL) were added to benzene (15 mL). H_2SO4 (2 mL) was added and the reaction refluxed (96 °C) using a Dean-Stark trap for 24 hours. The reaction mixture was cooled to room temperature and concentrated in vacuo. The aqueous layer was slowly neutralized with 10% NaOH and extracted with EtOAc (3 × 30 mL), combined organic layers were washed with H_2O (2 × 20 mL) dried over $MgSO_4$. Filtration and evaporation of the solvent afforded the ester as thick pail yellow oil (5.07 g, 98%). All data were in good agreement with the literature.[135]

(2-(1-trityl-1*H*-imidazol-4-yl)cyclopropyl)methanol (298):

To a suspension of $LiAlH_4$ (291.5 mg, 7.68 mmol) in ether (10 mL) at 0 °C was added dropwise a solution of ester **297** (1.73 g, 3,84 mmol) in ether (15mL). The reaction mixture was allowed to come to RT and stirred for 30 min. 0.1 M NaOH (35 mL) was added slowly and mixture was extracted with $CHCl_3$ (4 × 25 mL). Combined organic layers were washed with saturated aq $NaHCO_3$ (25 mL) and brine (25 mL) dried over $MgSO_4$. Filtration and evaporation of the solvent afforded the corresponding alcohol as a white solid (1.41 g, 96%). All data were in agreement with the literature.[135]

General procedure for preparation of cyclopropanated benzyl ethers: To a suspension of NaH (1.2 eq.) in DMF at 0 °C was added the solution of alcohol **298** (1 equv.) and the corresponding benzyl bromide (1.2 equv.). The reaction mixture was stirred at ambient temperature for 3-12 h. A (2:1) mixture of ether and CH_2Cl_2 (15 mL) was added, washed with H_2O twice and dried over $MgSO_4$. Filtration and evaporation of the solvent afforded the benzyl ethers which were purified by column chromatography (EtOAc/hexanes 1:1).

4-(2-((benzyloxy)methyl)cyclopropyl)-1-trityl-1*H*-imidazole (307):

Stirred for 12 h, (87% yield); $\mathbf{R_f}$ (EtOAc/hexanes 1:1) = 0.30; **m.p.** = 141-143 °C; **^{1}H NMR** (300 MHz $CDCl_3$): δ = 0.75-0.82 (m, 1 H, CH*H*, *cyclopropane*), 0.99-1.05 (m, 1 H, C*H*H, *cyclopropane*), 1.47-1.57 (m, 1 H, C*H*CH_2O), 1.68-1.74 (m, 1 H, CHC*H*CH_2), 3.38 (dd, *J* = 10.42, 6.96 Hz, 1 H, CHCH_2O), 3.53 (dd, *J* = 10.42, 6.38 Hz, 1 H, CHCH_2O), 4.53 (s, 2 H, CH_2O), 6.54 (d, *J* = 1.37 Hz, Imi-5 *H*), 7.09-7.16 (m, 6 H, *aromatic*), 7.28-7.32 (m, 16 H, *aromatic*); **^{13}C NMR** (75.5 MHz $CDCl_3$): δ = 12.5 (-, CH_2, *cyclopropane*), 15.2 (+, CH, *cyclopropane*), 20.5 (+, CH, *cyclopropane*), 72.4 (-, *C*H_2O), 73.5 (-, *C*H_2O), 75.2 (+, C_{quat},

CPh_3), 116.9 (+, CH, Imi-*C*5), 127.5 (+, CH, *aromatic*), 127.8 (+, CH, *aromatic*), 128.0 (+, CH, *aromatic*), 128.4 (+, CH, *aromatic*), 129.9 (+, CH, *aromatic*), 138.3 (+, CH, Imi-*C*2), 138.6 (+, C_{quat}, Imi-*C*4), 142.2 (+, C_{quat}, *aromatic*), 142.6 (+, C_{quat}, *aromatic*); **IR** (neat): $\tilde{\nu}$ = 3050, 3223, 1492, 1445, 1359, 1229, 1130, 1102, 1001, 821, 749, 701, 656 cm^{-1}; **MS** (EI +VE): *m/z* (%) = 470.4 [$M^{\bullet+}$], 243.2, (100) [CPh_3^+], 241.2 (14.6) , 228.2 (10.2), 165.1 (65.2), 91.1 (22.2); **HRMS** calcd for $C_{33}H_{30}N_2O$, 470.2358. Found 470.2359.

4-(2-((4-(methyl)benzyloxy)methyl)cyclopropyl)-1-trityl-1*H*-imidazole (308):

Stirred for 12 h, (80% yield); $\mathbf{R_f}$ (EtOAc/hexanes 1:1) = 0.33; **m.p. =** 141-142 °C; **^{1}H NMR** (300 MHz $CDCl_3$): δ = 0.78 (ddd, 1 H, *J* = 8.77, 5.32, 4.50 Hz CH*H*, *cyclopropane*), 0.98-1.04 (m, 1 H, C*H*H, *cyclopropane*), 1.46-1.56 (m, 1 H, C*H*CH_2O), 1.68-1.74(m, 1 H, CHC*H*CH_2), 2.32(s, 3 H, CH_3), 3.35 (dd, *J* = 10.36, 6.89, Hz, 1 H, CHCH_2O), 3.50 (dd, *J* = 10.36, 6.39, Hz, 1 H, CHCH_2O), 4.49 (s, 2 H, CH_2O), 6.54 (d, *J* = 1.37 Hz, Imi-5 *H*), 7.09-7.15 (m, 8 H, *aromatic*), 7.19-7.22 (m, 2 H, *aromatic*), 7.28-7.33 (m, 10 H, *aromatic*); **^{13}C NMR** (75.5 MHz $CDCl_3$): δ = 12.5 (-, CH_2, *cyclopropane*), 15.1 (+, CH, *cyclopropane*), 20.6 (+, CH, *cyclopropane*), 21.2 (+, *C*H_3), 72.3 (-, CH*C*H_2O), 73.2 (-, *C*H_2O), 75.2 (+, C_{quat}, *C*Ph_3), 116.9 (+, CH, Imi-*C*5), 127.9 (+, CH, *aromatic*), 128.1 (+, CH, *aromatic*), 129.1 (+, CH, *aromatic*), 129.9 (+, CH, *aromatic*), 135.5 (+, C_{quat}, *aromatic*), 137.2 (+, CH, Imi-*C*2), 138.2 (+, C_{quat}, Imi-*C*4), 142.1 (+, C_{quat}, *aromatic*), 142.5 (+, C_{quat}, *aromatic*); **IR** (neat): $\tilde{\nu}$ = 3010, 2820, 1491, 1445, 1360, 1224, 1085, 1005, 805, 746, 700, 656 cm^{-1}; **MS** (EI +VE): *m/z* (%) = 484.3 [$M^{\bullet+}$], 244.2 (16.5), 243.1, (100) [CPh_3^+], 241.0 (7.7) , 228.1 (4.5), 165.0 (33.7), 105.0 (13.2); **HRMS** calcd for $C_{34}H_{32}N_2O$, 484.2515. Found 484.2514.

4-(2-((4-(trifluoromethyl)benzyloxy)methyl)cyclopropyl)-1-trityl-1*H*-imidazole (309):

Stirred for 16 h, (79% yield); **R*f*** (EtOAc/hexanes 1:1) = 0.32; **m.p.** = 127-129 °C; **^{1}H NMR** (300 MHz $CDCl_3$): δ = 0.77-0.83 (m, 1 H, CH*H*, *cyclopropane*), 1.00-1.07 (m, 1 H, C*H*H, *cyclopropane*), 1.47-1.58 (m, 1 H, C*H*CH_2O), 1.70-1.76 (m, 1 H, CHC*H*CH_2), 3.42 (dd, *J* = 10.42, 6.89, Hz, 1 H, CHCH_2O), 3.54 (dd, *J* = 10.42, 6.48, Hz, 1 H, CHCH_2O), 4.59 (s, 2 H, CH_2O), 6.55 (d, *J* = 1.37 Hz, Imi-5 *H*), 7.10-7.16 (m, 6 H, *aromatic*), 7.29-7.34 (m, 10 H, *aromatic*), 7.42-7.45 (m, 2 H, *aromatic*), 7.56-7.58 (m, 2 H, *aromatic*); **^{13}C NMR** (75.5 MHz $CDCl_3$): δ = 12.4 (-, CH_2, *cyclopropane*), 15.3 (+, CH, *cyclopropane*), 20.5 (+, CH, *cyclopropane*), 71.6 (-, CH*C*H_2O), 73.9 (-, *C*H_2O), 75.2 (+, C_{quat}, *C*Ph_3), 117.0 (+, CH, Imi-*C*5), 124.3 (+, q, *j* = 271.97 *C*F_3,), 125.4 (+, q, *j* = 3.81 *C*HC-CF_3), 127.6 (+, CH, *aromatic*), 128.0 (+, CH, *aromatic* + C_{quat}, *C*CF_3), 129.9 (+, CH, *aromatic*), 138.3 (+, C_{quat}, Imi-*C*4), 138.4 (+, CH, Imi-*C*2), 142.0 (+, C_{quat}, *aromatic*), 142.6 (+, C_{quat} *aromatic*), 142.9 (+, C_{quat}, *aromatic*); **IR** (neat): ṽ = 2825, 1490, 1443, 1325, 1223,1165, 1121, 1089, 1065, 823, 749, 699, 657 cm^{-1}; **MS** (EI +VE): *m/z* (%) = 538.4 [$M^{\bullet+}$], 244.2 (36.5), 243.2, (100) [CPh_3^+], 242.2 (10.0) , 241.1 (12.8), 165.0 (61.3), 159.1 (10.4), 122.1 (5.3); **HRMS** calcd for $C_{34}H_{29}F_3N_2O$, 538.2232. Found 538.2227.

4-(2-((4-(trifluoromethoxy)benzyloxy)methyl)cyclopropyl)-1-trityl-1*H*-imidazole (310):

Stirred for 16 h, (79% yield); **R*f*** (EtOAc/hexanes 1:1) = 0.29; **m.p.** = 85-87 °C; **^{1}H NMR** (300 MHz $CDCl_3$): δ = 0.77-0.83 (m, 1 H, CH*H*, *cyclopropane*), 1.01-1.07 (m, 1 H, C*H*H, *cyclopropane*), 1.47-1.58 (m, 1 H, C*H*CH_2O), 1.70-1.76(m, 1 H, CHC*H*CH_2), 3.41 (dd, *J* = 10.46, 6.96, Hz, 1 H, CHCH_2O), 3.55 (dd, *J* = 10.46, 6.44, Hz, 1 H, CHCH_2O), 4.53 (s, 2 H, CH_2O), 6.56 (d, *J* = 1.37 Hz, Imi-5 *H*), 7.10-7.18 (m, 8 H, *aromatic*), 7.29-7. 37 (m, 12 H, *aromatic*); **^{13}C NMR** (75.5 MHz $CDCl_3$): δ = 12.4 (-, CH_2, *cyclopropane*), 15.3 (+, CH, *cyclopropane*), 20.5 (+, CH, *cyclopropane*), 71.5 (-, CH*C*H_2O), 73.2 (-, *C*H_2O), 75.2 (+, C_{quat}, *C*Ph_3), 117.1 (+, CH, Imi-*C*5), 120.5 (+ q, *J* = 256.9, C*H*, *aromatic*), 121.0 (+, q, *J* = 0.92, O*C*F_3), 128.1 (+, CH, *aromatic*), 129.0 (+, CH, *aromatic*), 129.8 (+, CH, *aromatic*), 137.5 (+, C_{quat}, Imi-*C*4), 138.6 (+, CH, Imi-*C*2), 142.1 (+, C_{quat}, *aromatic*), 142.5 (+, C_{quat}, *aromatic*), 148.64 (+, q, *J* = 0.92, C_{quat}, *C*OCF_3); **IR** (neat): ṽ = 3050, 3223, 1492, 1445, 1359, 1229, 1130, 1102, 1001, 821, 749, 701, 656 cm^{-1}; **MS** (EI +VE): *m/z* (%) = 470.4 [$M^{\bullet+}$], 243.2,

(100) [CPh_3^+], 241.2 (14.6) , 228.2 (10.2), 165.1 (65.2), 91.1 (22.2); **HRMS** calcd for $C_{33}H_{30}N_2O$, 470.2358. Found 470.2359.

4-(2-((2,4,6-trimethyl)benzyloxy)methyl)cyclopropyl)-1-trityl-1*H*-imidazole (321):

Stirred for 16 h, (38% yield); $\mathbf{R}_f$ (EtOAc/hexanes 4:6) = 0.30; **m.p.** = 119-120 °C; **^{1}H NMR** (300 MHz $CDCl_3$): δ = 0.77 (ddd, 1 H, *J* = 8.78, 5.23, 4.57 Hz CH*H*, *cyclopropane*), 0.98-1.05 (m, 1 H, C*H*H, *cyclopropane*), 1.48-1.58 (m, 1 H, C*H*CH_2O), 1.68-1.74 (m, 1 H, CHC*H*CH_2), 2.23 (s, 3 H, CH_3), 2.31 (s, 6 H, CH_3), 3.40 (dd, *J* = 10.43, 6.91, Hz, 1 H, CHCH_2O), 3.52 (dd, *J* = 10.43, 6.62, Hz, 1 H, CHCH_2O), 4.49 (dd, *J* = 12.45, 10.43 Hz 2 H, CH_2O), 6.53 (d, *J* = 1.37 Hz, Imi-5 *H*), 6.81 (bs, 2 H, *aromatic*), 7.09-7.15 (m, 6 H, *aromatic*) 7.27 (d, *J* = 1.37 Hz, Imi-2 *H*), 7.28-7.32 (m, 9 H, *aromatic*); **^{13}C NMR** (75.5 MHz $CDCl_3$): δ = 12.4 (-, CH_2, *cyclopropane*), 15.2 (+, CH, *cyclopropane*), 19.5 (+, CH_3), 20.5 (+, CH, *cyclopropane*), 20.9 (+, CH_3), 66.3 (-, CH_2O), 73.5(-, CHCH_2O), 75.1 (+, C_{quat}, CPh_3), 116.8 (+, CH, Imi-*C*5), 127.9 (+, CH *aromatic*), 127.9 (+, CH, *aromatic*), 128.8 (+, CH, *aromatic*), 129.8 (+, CH, *aromatic*), 131.4 (+, C_{quat}, *aromatic*), 137.4 (+, C_{quat}, Imi-*C*4), 137.8 (+, C_{quat}, *aromatic*), 138.2 (+, CH, Imi-*C*2), 142.1 (+, C_{quat}, *aromatic*), 142.5 (+, C_{quat}, *aromatic*); **IR** (neat): ṽ = 3012, 2923, 2822, 2811, 1572, 1491, 1442, 1354, 1223, 1130, 1087, 1050, 1033, 1004, 934, 851,819, 746, 697, 655, 638 cm^{-1}; **MS** (EI +VE): *m/z* (%) = 512.1 (1.1) [$M^{\bullet+}$], 270.3 (1.3) [$M^{\bullet}$ - CPh_3^+], 243.0, (100) [CPh_3^+], 227.9 (3.9), 165.0 (14.6), 132.9 (13.4), 121.0 (4.9), 28.1 (13.9); **HRMS** calcd for $C_{36}H_{36}N_2O$, 512.2828. Found 512.2827.

4-(2-((4-bromobenzyloxy)methyl)cyclopropyl)-1-trityl-1*H*-imidazole (312):

Stirred for 16 h, (79% yield); $\mathbf{R}_f$ (EtOAc/hexanes 1:1) = 0.31; **m.p.** = 139-141 °C; **^{1}H NMR** (300 MHz $CDCl_3$): δ = 0.77 (ddd, 1 H, *J* = 8.74, 5.28, 4.63 Hz CH*H*, *cyclopropane*), 0.98-

1.04 (m, 1 H, C*H*H, *cyclopropane*), 1.45-1.55 (m, 1 H, C*H*CH_2O), 1.68-1.74(m, 1 H, CHC*H*CH_2), 3.38 (dd, *J* = 10.44, 6.91, Hz, 1 H, CHCH_2O), 3.50 (dd, *J* = 10.44, 6.46, Hz, 1 H, CHCH_2O), 4.48 (s, 2 H, CH_2O), 6.54 (d, *J* = 1.37 Hz, Imi-5 *H*), 7.09-7.15 (m, 6 H, *aromatic*), 7.17-7.21 (m, 2 H, *aromatic*), 7.27-7.33 (m, 10 H, *aromatic*), 7.41-7.45 (m, 2 H, *aromatic*); **^{13}C NMR** (75.5 MHz $CDCl_3$): δ = 12.4 (-, CH_2, *cyclopropane*), 15.3 (+, CH, *cyclopropane*), 20.4 (+, CH, *cyclopropane*), 71.6 (-, CH*C*H_2O), 73.6 (-, *C*H_2O), 75.2 (+, C_{quat}, *C*Ph_3), 117.0 (+, CH, Imi-*C*5), 121.4 (+, C_{quat}, *C*-Br), 128.1 (+, CH, *aromatic*), 129.4 (+, CH, *aromatic*), 129.9 (+, CH, *aromatic*), 131.5 (+, CH, *aromatic*), 137.7 (+, C_{quat}, Imi-*C*4), 138.4 (+, CH, Imi-*C*2), 142.1 (+, C_{quat}, *aromatic*), 142.6 (+, C_{quat}, *aromatic*); **IR** (neat): ṽ = 3010, 2820, 1491, 1445, 1360, 1224, 1085, 1005, 805, 746, 700, 656 cm^{-1}; **MS** (EI +VE): *m/z* (%) = 548.3 [$M^{\bullet+}$], 244.2 (16.5), 243.1, (100) [CPh_3^+], 241.0 (7.7), 228.1 (4.5), 165.0 (33.7), 105.0 (13.2); **HRMS** calcd for $C_{33}H_{29}BrN_2O$, 548.1463. Found 548.1456.

4-(2-((4-iodobenzyloxy)methyl)cyclopropyl)-1-trityl-1*H*-imidazole (311):

Stirred for 16 h, (79% yield); **R_f** = (EtOAc/hexanes 1:1) 0.32; **m.p.** = 159-161 °C; **^{1}H NMR** (300 MHz $CDCl_3$): δ = 0.77 (ddd, 1 H, *J* = 8.75, 5.29, 4.67 Hz, CH*H*, *cyclopropane*), 0.98-1.04 (m, 1 H, C*H*H, *cyclopropane*), 1.44-1.54 (m, 1 H, C*H*CH_2O), 1.68-1.74(m, 1 H, CHC*H*CH_2), 3.38 (dd, *J* = 10.46, 6.82, Hz, 1 H, CHCH_2O), 3.49 (dd, *J* = 10.46, 6.55 Hz, 1 H, CHCH_2O), 4.48 (s, 2 H, CH_2O), 6.53 (d, *J* = 1.37 Hz, Imi-5*H*), 7.05-7.09 (m, 2 H, *aromatic*), 7.11-7.15 (m, 6 H, *aromatic*), 7.27 (d, *J* = 1.37 Hz, Imi-2*H*), 7.29-7.34 (m, 9 H, *aromatic*), 7.62-7.66 (m, 2 H, *aromatic*); **^{13}C NMR** (75.5 MHz $CDCl_3$): δ = 12.4 (-, CH_2, *cyclopropane*), 15.3 (+, CH, *cyclopropane*), 20.4 (+, CH, *cyclopropane*), 71.7 (-, CH*C*H_2O), 73.6 (-, *C*H_2O), 75.2 (+, C_{quat}, *C*Ph_3), 93.0 (+, *C*$_{quat}$, *C*-I), 117.0 (+, CH, Imi-*C*5), 128.1 (+, CH, *aromatic*), 129.6 (+, CH, *aromatic*), 129.9 (+, CH, *aromatic*), 137.5 (+, C_{quat}, *aromatic*), 138.4 (+, C_{quat}, Imi-*C*4), 138.4 (+, CH, Imi-*C*2), 142.1 (+, C_{quat}, *aromatic*), 142.6 (+, C_{quat}, *aromatic*); **IR** (neat): ṽ = 3012, 2853, 1483, 1442, 1343, 1276, 1224, 1127, 1081, 1036, 1006, 823, 792, 750, 699, 657, 638 cm^{-1}; **MS** (EI +VE): *m/z* (%) = 596.0 [$M^{\bullet+}$], 243.1, (100) [CPh_3^+], 239.1 (10.1), 228.1 (7.7), 165.0 (48.5), 127.9 (3.8), 91.0 (2.7); **HRMS** calcd for $C_{33}H_{29}IN_2O$, 596.1325. Found 596.1322.

4-(((2-(1-trityl-1H-imidazol-4-yl)cyclopropyl)methoxy)methyl)benzonitrile (313):

Stirred for 16 h, (34% yield); **R_f** (EtOAc/hexanes 7:3) = 0.27; **m.p.** = 48-50 °C, (pail yellow foam); **^{1}H NMR** (300 MHz $CDCl_3$): δ = 0.77-0.83 (m, 1 H CH*H*, *cyclopropane*), 1.00-1.07 (m, 1 H, C*H*H, *cyclopropane*), 1.47-1.57 (m, 1 H, C*H*CH_2O), 1.71-1.77(m, 1 H, CHC*H*CH_2), 3.44 (dd, *J* = 10.46, 6.82, Hz, 1 H, CHCH_2O), 3.55 (dd, *J* = 10.46, 6.51, Hz, 1 H, CHCH_2O), 4.59 (s, 2 H, CH_2O), 6.55 (d, *J* = 1.26 Hz, Imi-5*H*), 7.11-7.14 (m, 6 H, *aromatic*), 7.30-7.33 (m, 10 H, *aromatic*), 7.42-7.48 (m, 2 H, *aromatic*), 7.59-7.62 (m, 2 H, *aromatic*); **^{13}C NMR** (75.5 MHz $CDCl_3$): δ = 12.3 (-, CH_2, *cyclopropane*), 15.3 (+, CH, *cyclopropane*), 20.4 (+, CH, *cyclopropane*), 71.4 (-, *C*H_2O), 74.1 (-, *C*H_2O), 75.3 (+, C_{quat}, *C*Ph_3), 111.2 (+, C_{quat}, *aromatic*), 117.0 (+, CH, Imi-*C*5), 119.0 (+, C_{quat}, *C*N), 127.7 (+, CH, *aromatic*), 128.1 (+, CH, *aromatic*), 129.9 (+, CH, *aromatic*), 132.2 (+, CH, *aromatic*), 138.4 (+, CH, Imi-*C*2), 141.9 (+, C_{quat}, Imi-*C*4), 142.5 (+, C_{quat}, *aromatic*), 144.4 (+, C_{quat}, *aromatic*); **IR** (neat): ṽ = 3057, 2859, 2228, 1492, 1445, 1362, 1267, 1224, 1157, 1086, 1035, 819, 735, 700, 657 cm^{-1}; **MS** (EI +VE): *m/z* (%) = 495.2 [$M^{•+}$], 253.1 (1.3) [M- CPh_3] 244.1, (40.3) 243.1 (100) [CPh_3^+], 241.1 (16.9), 239.1 (11.9), 228.2 (10.2), 165.1 (54.9), 152.1 (3.4), 116.0 (4.7), 94 (3.3); **HRMS** calcd for $C_{34}H_{29}N_3O$, 495.2311. Found 495.2306;

General procedure for trityl deprotection of cyclopropanated ethers: To a solution of benzyl ether (0.25 mmol) in MeOH (2 mL) was added 2 M solution of HCl (2 mL) and reaction mixture was refluxed for 1.5 h. Most of the MeOH was evaporated in vacuo and aqueous phase was made strongly basic by adding solid K_2CO_3 and extracted in CH_2Cl_2 (4×8 mL) dried ($MgSO_4$). The solvent was removed in vacuo to leave the pure products as oils.

4-(2-((benzyloxy)methyl)cyclopropyl)-1*H*-imidazole (314):

(91% yield); **R*f*** (SiO_2, MeOH/EtOAc 1:9) = 0.32; thick oil; **^{1}H NMR** (300 MHz $CDCl_3$): δ = 0.76-0.82 (m, 1 H, CH*H*, *cyclopropane*), 0.94-1.00 (m, 1 H, C*H*H, *cyclopropane*), 1.39-1.50 (m, 1 H, C*H*CH_2O), 1.73-1.79 (m, 1 H, CHC*H*CH_2), 3.40 (dd, *J* = 10.33, 6.96, Hz, 1 H, CHCH_2O), 3.46 (dd, *J* = 10.33, 6.55, Hz, 1 H, CHCH_2O), 4.52 (s, 2 H, CH_2O), 6.67 (bs, Imi-5*H*), 7.22-7.32 (m, 5 H, *aromatic*), 7.41 (bs, 1 H, Imi-2*H*), 9.76 (bs, 1 H, Imi-N*H*); **^{13}C NMR** (75.5 MHz $CDCl_3$): δ = 12.0 (-, CH_2, *cyclopropane*), 14.1 (+, CH, *cyclopropane*), 20.5 (+, CH, *cyclopropane*), 72.6 (-, CH*C*H_2O), 73.5 (-, *C*H_2O), 115.3 (+, CH, Imi-*C*5), 127.7 (+, CH, *aromatic*), 127.8 (+, CH, *aromatic*), 128.5 (+, CH, *aromatic*), 134.5 (+, CH, Imi-*C*2), 138.3 (+, C_{quat}, *aromatic*), 138.7 (+, C_{quat}, Imi-*C*4); **IR** (neat): ṽ = 3050, 3030, 2856, 1572, 1453, 1361, 1210, 1071, 1027, 819, 734, 697, 660, 625 cm^{-1}; **MS** (EI +VE): *m/z* (%) = 228.2 (15.4) [$M^{\bullet+}$], 198.2 (3.2), 187.2 (3.9), 137.1 (30.1), 122.1 (37.9), 107.1 (60.1), 94.1 (37.1), 91.1, (100) [$C_7H_7^+$], 80.1 (32.7) **HRMS** calcd for $C_{14}H_{16}N_2O$, 228.1263. Found 228.1266.

4-(2-((4-(methyl)benzyloxy)methyl)cyclopropyl)-1*H*-imidazole (315):

N
N
H
O
CH_3

(88% yield)**;** **R*f*** (SiO_2, MeOH/EtOAc 1:9) = 0.28; thick oil; **^{1}H NMR** (300 MHz $CDCl_3$): δ = 0.76-0.83 (m, 1 H, CH*H*, *cyclopropane*), 0.94-1.00 (m, 1 H, C*H*H, *cyclopropane*), 1.39-1.49 (m, 1 H, C*H*CH_2O), 1.73-1.79 (m, 1 H, CHC*H*CH_2), 2.33 (s, 3 H, CH_3), 3.39 (dd, *J* = 10.29, 6.93, Hz, 1 H, CHCH_2O), 3.47 (dd, *J* = 10.29, 6.48, Hz, 1 H, CHCH_2O), 4.50 (s, 2 H, CH_2O), 6.67 (bs, Imi-5*H*), 7.12-7.23 (m, 4 H, *aromatic*), 7.43 (bs, 1 H, Imi-2*H*), 9.22 (bs, 1 H, Imi-N*H*); **^{13}C NMR** (75.5 MHz $CDCl_3$): δ = 12.0 (-, CH_2, *cyclopropane*), 14.1 (+, CH, *cyclopropane*), 20.5 (+, CH, *cyclopropane*), 21.2 (+, *C*H_3), 72.6 (-, CH*C*H_2O), 73.4 (-, *C*H_2O), 115.5 (+, CH, Imi-*C*5, broad), 128.0 (+, CH, *aromatic*), 129.2 (+, CH, *aromatic*), 134.5 (+, CH, Imi-*C*2, broad), 135.3 (+, C_{quat}, *aromatic*), 137.4 (+, C_{quat}, *aromatic*) 138.7 (+, C_{quat}, Imi-*C*4, broad); **IR** (neat): ṽ = 3055, 3035, 2855, 1572, 1450, 1359, 1213, 1075, 939, 803, 754, 659, 626 cm^{-1}; **MS** (EI +VE): *m/z* (%) = 242.2 (15.4) [$M^{\bullet+}$], 201.0 (4.02), 212.2 (5.9), 137.1 (21.6), 122.1 (35.8), 105.0 (100) [$C_8H_9^+$] 93.9 (18.3), 77.0, (15.2), **HRMS** calcd for $C_{15}H_{18}N_2O$, 242.1419. Found 242.1420;

4-(2-((4-(trifluoromethyl)benzyloxy)methyl)cyclopropyl)-1*H*-imidazole (316):

(86% yield); **R*f*** (SiO_2, MeOH/EtOAc 1:9) = 0.30; thick oil; **^{1}H NMR** (300 MHz $CDCl_3$): δ = 0.79-0.85 (m, 1 H, CH*H*, *cyclopropane*), 0.97 - 1.03 (m, 1 H, C*H*H, *cyclopropane*), 1.42-1.53 (m, 1 H, C*H*CH_2O), 1.77-1.84 (m, 1 H, CHC*H*CH_2), 3.43 (dd, *J* = 10.29, 6.79, Hz, 1 H, CHCH_2O), 3.49 (dd, *J* = 10.29, 6.55, Hz, 1 H, CHCH_2O), 4.57 (s, 2 H, CH_2O), 6.74 (bs, Imi-5*H*), 7.40-7.43 (m, 2 H, *aromatic*), 7.49 (bs, 1 H, Imi-2*H*), 7.55-7.57 (m, 2 H, *aromatic*), 10.76 (bs, 1 H, Imi-N*H*); **^{13}C NMR** (75.5 MHz $CDCl_3$): δ = 12.1 (-, CH_2, *cyclopropane*), 14.2 (+, CH, *cyclopropane*), 20.5 (+, CH, *cyclopropane*), 71.7 (-, CH*C*H_2O), 73.8 (-, *C*H_2O), 115.2 (+, CH, Imi-*C*5, broad), 124.2 (+, q, *J* = 272.0, *C*F_3), 125.3 (+, q *J* = 3.9, *C*HC-CF_3, *aromatic*), 127.6 (+, CH, *aromatic*), 129.7 (+, q *J* = 32.2, *C*-CF_3), 134.4 (+, CH, Imi-*C*2, broad), 138.9 (+, C_{quat}, Imi-*C*4, broad), 142.6 (+, C_{quat}, *aromatic*); **IR** (neat): ṽ = 3058, 3038, 2857, 1620, 1415, 1313, 1161, 1112, 1064, 1017, 943, 819, 757, 627 cm^{-1}; **MS** (EI +VE): *m/z* (%) = 297.2/296.2 (5.4/33.6) [$M^{\bullet+}$], 277.2 (4.5) [$M^{\bullet+}$-F], 174.1/173.1 (4.7/13.0), 159.1 (100) [$C_8H_9^+$], 137.1 (29.7), 122.1 (67.6), 119.1 (40.3), 107.1, (87.5), 94.1 (86.), 80.1 (49.6) **HRMS** calcd for $C_{15}H_{15}F_3N_2O$, 296.1136. Found 296.1134;

4-(2-((4-(trifluoromethoxy)benzyloxy)methyl)cyclopropyl) -1*H*-imidazole (317):

(89% yield); **R*f*** (SiO_2, MeOH/EtOAc 1:9) = 0.30; thick oil; **^{1}H NMR** (300 MHz $CDCl_3$): δ = 0.79-0.85 (m, 1 H, CH*H*, *cyclopropane*), 0.97-1.03 (m, 1 H, C*H*H, *cyclopropane*), 1.42-1.53 (m, 1 H, C*H*CH_2O), 1.76-1.82 (m, 1 H, CHC*H*CH_2), 3.43 (dd, *J* = 10.24, 6.84, Hz, 1 H, CHCH_2O), 3.49 (dd, *J* = 10.24, 6.60, Hz, 1 H, CHCH_2O), 4.53 (s, 2 H, CH_2O), 6.74 (bs, Imi-5*H*), 7.16-7.18 (m, 2 H, *aromatic*), 7.33-7.36 (m, 2 H, *aromatic*), 7.49 (bs, 1 H, Imi-2*H*), 8.68 (bs, 1 H, Imi-N*H*); **^{13}C NMR** (75.5 MHz $CDCl_3$): δ = 12.1 (-, CH_2, *cyclopropane*), 14.2 (+, CH, *cyclopropane*), 20.5 (+, CH, *cyclopropane*), 71.7 (-, CH*C*H_2O), 73.7 (-, *C*H_2O), 115.1 (+, CH, Imi-*C*5, broad), 120.5 (+, C_{quat}, q, *J* = 256.9 Hz, *C*F_3), 120.9 (+, q, *J* = 0.92, *C*HC-CF_3,

aromatic), 121.1 (+, C_{quat}, q, J = 0.92, *C*-CF_3), 134.5 (+, CH, Imi-*C*2, broad), 137.3 (+, C_{quat}, *aromatic*), 139.1 (+, C_{quat}, Imi-*C*4 broad), 148.7 (+, C_{quat}, q, J = 1.96 Hz, *C*OCF_3); **IR** (neat): ṽ = 3061, 3042, 2862, 1721, 1508, 1254, 1217, 1159, 1097, 1018, 815, 767, 708, 621 cm^{-1}; **MS** (EI +VE): *m/z* (%) = 313.3/312.2 (2.8/18.8) [$M^{\bullet+}$], 190.1/189.1 (3.4/7.0), 175.1 (100) [$C_8H_6F_3^+$], 137.1 (28.4) [$M^{\bullet+}$ - $C_8H_6F_3^+$] 122.1 (46.5), 119.1 (20.3), 109.1, (26.7), 107 (56.2), 94.1 (36.0.), 80.1 (26.5) **HRMS** calcd for $C_{15}H_{15}F_3N_2O_2$, 312.1086. Found 312.1084.

4-(2-((4-iodobenzyloxy)methyl)cyclopropyl)-1*H*-imidazole (312)

(66% yield); R_f (SiO_2, MeOH/EtOAc 1:9) = 0.23; thick oil; **^{1}H NMR** (300 MHz $CDCl_3$): δ = 0.77-0.83 (m, 1 H, CH*H*, *cyclopropane*), 0.95-1.01 (m, 1 H, C*H*H, *cyclopropane*), 1.39-1.50 (m, 1 H, C*H*CH_2O), 1.74-1.80 (m, 1 H, CHC*H*CH_2), 2.33 (s, 3 H, CH_3), 3.39 (dd, J = 10.33, 6.86, Hz, 1 H, CHCH_2O), 3.46 (dd, J = 10.33, 6.51 Hz, 1 H, CHCH_2O), 4.47 (s, 2 H, CH_2O), 6.71 (bs, Imi-5*H*), 7.04-7.08 (m, 2 H, *aromatic*), 7.46 (bs, 1 H, Imi-2*H*), 7.62-7.66 (m, 2 H, *aromatic*), 9.23 (bs, 1 H, Imi-N*H*); **^{13}C NMR** (75.5 MHz $CDCl_3$): δ = 10.9 (-, CH_2, *cyclopropane*), 13.0 (+, CH, *cyclopropane*), 19.4 (+, CH, *cyclopropane*), 70.8 (-, CH*C*H_2O), 72.5 (-, *C*H_2O), 92.0 (+, C_{quat}, *C*-I), 114.1 (+, CH, Imi-*C*5 broad), 129.6 (+, CH, *aromatic*), 137.5 (+, CH, *aromatic*), 133.4 (+, CH, Imi-*C*2 broad), 137.1 (+, C_{quat}, *aromatic*), 137.8 (+, C_{quat}, Imi-*C*4 broad); **IR** (neat): ṽ = 3052, 2856, 1719, 1586, 1484, 1364, 1261, 1221, 1165, 1088, 1007, 803, 749, 702, 659 cm^{-1}; **MS** (EI +VE): *m/z* (%) = 354.0 (4.9) [$M^{\bullet+}$], 227.1 (5.9), 216.9 (55.6), 137.1 (34.3), 122.1 (100), 107.0 (66.6) [$C_8H_9^+$] 93.1 (12.3), 80.1, (23.9); **HRMS** calcd for $C_{14}H_{15}IN_2O$, 354.0229. Found 354.0233.

4-(2-((4-bromobenzyloxy)methyl)cyclopropyl)-1*H*-imidazole (319):

(78% yield); R_f (SiO_2, MeOH/EtOAc 1:9) = 0.25; thick oil; **^{1}H NMR** (300 MHz $CDCl_3$): δ = 0.77-0.83 (m, 1 H, CH*H*, *cyclopropane*), 0.96-1.02 (m, 1 H, C*H*H, *cyclopropane*), 1.39-1.50

(m, 1 H, C*H*CH_2O), 1.74-1.80 (m, 1 H, CHC*H*CH_2), 3.39 (dd, *J* = 10.36, 6.89 Hz, 1 H, CHCH_2O), 3.47 (dd, *J* = 10.36, 6.52 Hz, 1 H, CHCH_2O), 4.47 (s, 2 H, CH_2O), 6.72 (bs, Imi-5*H*), 7.17-7.21 (m, 2 H, *aromatic*), 7.41-7.45 (m, 2 H, *aromatic*), 7.46 (bs, 1 H, Imi-2*H*), 8.89 (bs, 1 H, Imi-N*H*); **^{13}C NMR** (75.5 MHz $CDCl_3$): δ = 12.0 (-, CH_2, *cyclopropane*), 14.1 (+, CH, *cyclopropane*), 20.5 (+, CH, *cyclopropane*), 71.8 (-, CH*C*H_2O), 73.6 (-, *C*H_2O), 115.2 (+, CH, Imi-*C*5, broad), 121.5 (+, C_{quat}, *C*-Br), 129.4 (+, CH, *aromatic*), 131.5 (+, CH, *aromatic*), 134.5 (+, CH, Imi-*C*2, broad), 137.5 (+, C_{quat}, *aromatic*), 138.9 (+, C_{quat}, Imi-*C*4, broad); **IR** (neat): ṽ = 3060, 2854, 1722, 1592, 1486, 1402, 1211, 1088, 1069,1011, 941, 795, 757, 657, 625 cm^{-1}; **MS** (EI +VE): *m/z* (%) = 308.1/306.1 (4.6/4.8) [$M^{\bullet+}$], 227.1 (8.5), 170.9/169.0 (62.5/62.0), 137.1 (48.8), 122.1 (92.6), 107.1 (100) [$C_8H_9^+$] 94.1 (57.8), 80.1, (45.6), 53.1 (14.6); **HRMS** calcd for $C_{14}H_{15}BrN_2O$, 306.0368. Found 306.0362.

4-(((2-(1H-imidazol-4-yl)cyclopropyl)methoxy)methyl)benzonitrile hydrochloride (320):

To a solution of **313** (45 mg 0.091 mmol) in EtOH (2 mL) at 0 °C was slowly added 2N HCl (2 mL). The reaction mixture was allowed to come to RT and stirred for 12 h. Ether (6 mL) was added and the reaction mixture was extracted in the (3 × 6 mL). The aqueous layer was concentrated to leave a hydrochloride salt as a white solid (92 %).

R_f (SiO_2, MeOH/EtOAc/NH_3 1:9:0.2) = 0.25; **m.p.** = 158-159 °C; **^{1}H NMR** (300 MHz CD_3OD): δ = 1.01-1.11 (m, 2 H, CH_2, *cyclopropane*), 1.51-1.62 (m, 1 H, C*H*CH_2O), 1.94-1.99 (m, 1 H, CHC*H*CH_2), 3.49 (dd, *J* = 10.36, 6.86 Hz, 1 H, CHCH_2O), 3.66 (dd, *J* = 10.36, 5.90 Hz, 1 H, CHCH_2O), 4.64 (s, 2 H, CH_2O), 7.26 (d, *J* = 1.33 Hz, Imi-5*H*), 7.52-7.55 (m, 2 H, *aromatic*), 7.69-7.72 (m, 2 H, *aromatic*), 8.74 (d, *J* = 1.33 Hz, Imi-2*H*); **^{13}C NMR** (75.5 MHz CD_3OD): δ = 12.0 (+, CH, *cyclopropane*), 12.5 (-, CH_2, *cyclopropane*), 22.2 (+, CH, *cyclopropane*), 72.8 (-, CH*C*H_2O), 73.9 (-, *C*H_2O), 112.3 (+, C_{quat}, *C*CN), 115.8 (+, CH, Imi-*C*5), 119.7 (+, C_{quat}, *C*N), 129.2 (+, CH, *aromatic*), 133.4 (+, CH, *aromatic*), 134.4 (+, CH, Imi-*C*2), 136.9 (+, C_{quat}, Imi-*C*4), 145.8 (+, C_{quat}, *aromatic*); **IR** (neat): ṽ = 3144, 3092, 3006, 2941, 2763, 2227, 1730, 1618, 1474, 1450, 1403, 1369, 1277, 1203, 1171, 1014, 840, 813, 626 cm^{-1}; **MS** (EI +VE): *m/z* (%) = 253.2 (25.5) [$M^{\bullet+}$], 137.1 (30.6) [$M^{\bullet+}$ – NC-C_6H_4-$CH_2^{\bullet}$], 122.1, (68.5), 116.1 (76.8) [NC-$C_6H_4CH_2^+$], 107.1 (100) [$C_6H_7N_2^+$, imidazole cyclopropyl],

94.1 (95.1), 80.0 (60.7), 53.0 (21.9); **HRMS** calcd for $C_{15}H_{15}N_3O$, 253.1215. Found 253.1216.

Phenyl-*N*-((2-(1-trityl1*H*-imidazol-4-yl)cyclopropyl)methyl)methanamine (326):

To a solution of **325** (100 mg 0.263 mmol) together with powdered activated molecular sieves (100 mg) was added freshly distilled benzaldehyde (30.76 mg, 29.5 µL, 0.290 mmol). The reaction mixture was stirred overnight filtered and dissolved in MeOH (5 mL). The reaction mixture was cooled to 0 °C and $NaBH_4$ (24.9 0.657 mmol) was added. The reaction mixture was allowed to come to RT and stirred further for 12 h. quenched with sat. ammonium chloride and the reaction mixture was extracted with CH_2Cl_2 (4 × 8 mL). Combined organic layers were washed with saturated aq $NaHCO_3$ (5 mL) and brine (5 mL) dried over $MgSO_4$. Filtration and evaporation of the solvent afforded the crude product was purified by column chromatography (CH_2Cl_2/MeOH 95:5) to obtain **326** (45 mg, 36%).

R_f (SiO_2, EtOAc/hexanes 7:3) = 0.23; thick oil; **^{1}H NMR** (300 MHz $CDCl_3$): δ = 0.68-0.75 (m, 1 H, CH*H*, *cyclopropane*), 0.92-0.98 (m, 1 H, C*H*H, *cyclopropane*), 1.34-1.44 (m, 1 H, C*H*CH_2O), 1.64-1.70 (m, 1 H, CHC*H*CH_2), 2.66 (d, J = 6.96 Hz, 2 H, CHCH_2N), 4.87 (bs, 3 H, CH_2N + NH), 6.51 (d, J = 1.30 Hz, Imi-5*H*), 7.08-7.15 (m, 6 H, *aromatic*), 7.24-7.37 (m, 15 H, *aromatic* + Imi-2*H*); **^{13}C NMR** (75.5 MHz $CDCl_3$): δ = 12.9(-, CH_2, *cyclopropane*), 16.0 (+, CH, *cyclopropane*), 20.4 (+, CH, *cyclopropane*), 52.6 (-, *C*H_2N), 52.8 (-, *C*H_2N), 75.2 (+, C_{quat}, *C*Ph_3), 116.9 (+, CH, Imi-*C*5), 127.4 (+, CH, *aromatic*), 128.0 (+, CH, *aromatic*), 128.1 (+, CH, *aromatic*), 128.6 (+, CH, *aromatic*), 128.7 (+, CH, *aromatic*), 129.9 (+, CH, *aromatic*), 138.3 (+, CH, Imi-*C*2), 138.5 (+, C_{quat}, Imi-*C*4), 142.2 (+, C_{quat}, *aromatic*), 142.5 (+, C_{quat}, *aromatic*); **IR** (neat): $\tilde{\nu}$ = 3359, 3061, 2927, 1468, 1489, 1445, 1285, 1223, 1156, 1128, 1084, 1034, 907, 870, 825, 749, 700, 658 cm^{-1}; **MS** (CI, NH_3): *m/z* (%) = 470.2 (100) [M + H^+], 386.0 (5.0), 243.1 (70.3) [CPh_3^+], 228.1 (53.4).

(2-(1H-imidazol-4-yl)cyclopropyl)-N-benzylmethanamine dihydrochloride (327):

To a solution of **326** (60 mg 0.128 mmol) in MeOH (2 mL) was added 2N HCl (2 mL). The reaction mixture was refluxed for 1.5 h. cooled to RT Ether (6 mL) was added and the reaction mixture was extracted in ether (3 × 6 mL). The aqueous layer was separated and concentrated to leave a hydrochloride salt as a white solid (96 %).

R*f* (SiO_2, MeOH/EtOAc/NH_3 3:7:0.3) = 0.23; thick oil (hygroscopic); **^{1}H NMR** (300 MHz CD_3OD): δ = 1.25 (m, 2 H, C*H*$_2$, *cyclopropane*, broad), 1.67 (m, 1 H, C*H*CH_2O, broad), 2.22 (m, 1 H, CHC*H*CH_2, broad), 3.19 (m, 2 H, CHC*H*$_2$O, broad), 4.28 (m, 2 H, C*H*$_2$O, broad), 7.37 (bs, 1 H, Imi-5*H*), 7.44 (m, 3 H, *aromatic*, broad), 7.59 (m, 2 H, *aromatic*, broad), 8.79 (bs, 1 H, Imi-2*H*); **^{13}C NMR** (75.5 MHz CD_3OD): δ = 13.6 (+, CH, *cyclopropane*), 13.8 (-, CH_2, *cyclopropane*), 18.3 (+, CH, *cyclopropane*), 51.9 (-, CH*C*H_2O), 52.6 (-, *C*H_2O), 116.9 (+, CH, Imi-*C*5), 130.4 (+, CH, *aromatic*), 130.8 (+, CH, *aromatic*), 131.4 (+, CH, *aromatic*), 132.6 (+, C_{quat}, Imi-*C*4), 134.9 (+, CH, Imi-*C*2), 135.6 (+, C_{quat}, *aromatic*); **IR** (Film): $\tilde{\nu}$ = 3382 (broad), 3099, 3003, 2957, 2798, 2612, 1625, 1494, 1454, 1206, 1175, 1085, 1019, 830, 752, 700 cm^{-1}; **MS** (EI +VE): *m/z* (%) = 227.1 (2.7) [$M^{\bullet +}$], 186.1 (14.6), 146.1 (6.6), 132.1 (11.8), 122.1 (34.8) [M - C_7H_7N], 108.0 (10.9) [M - C_6H_9N], 106.0 (14.1), 95.0 (28.9), 91.0, (100) [$C_7H_7^+$], 65.0 (13.1) **HRMS** calcd for $C_{14}H_{17}N_3$, 227.1422. Found 227.1421.

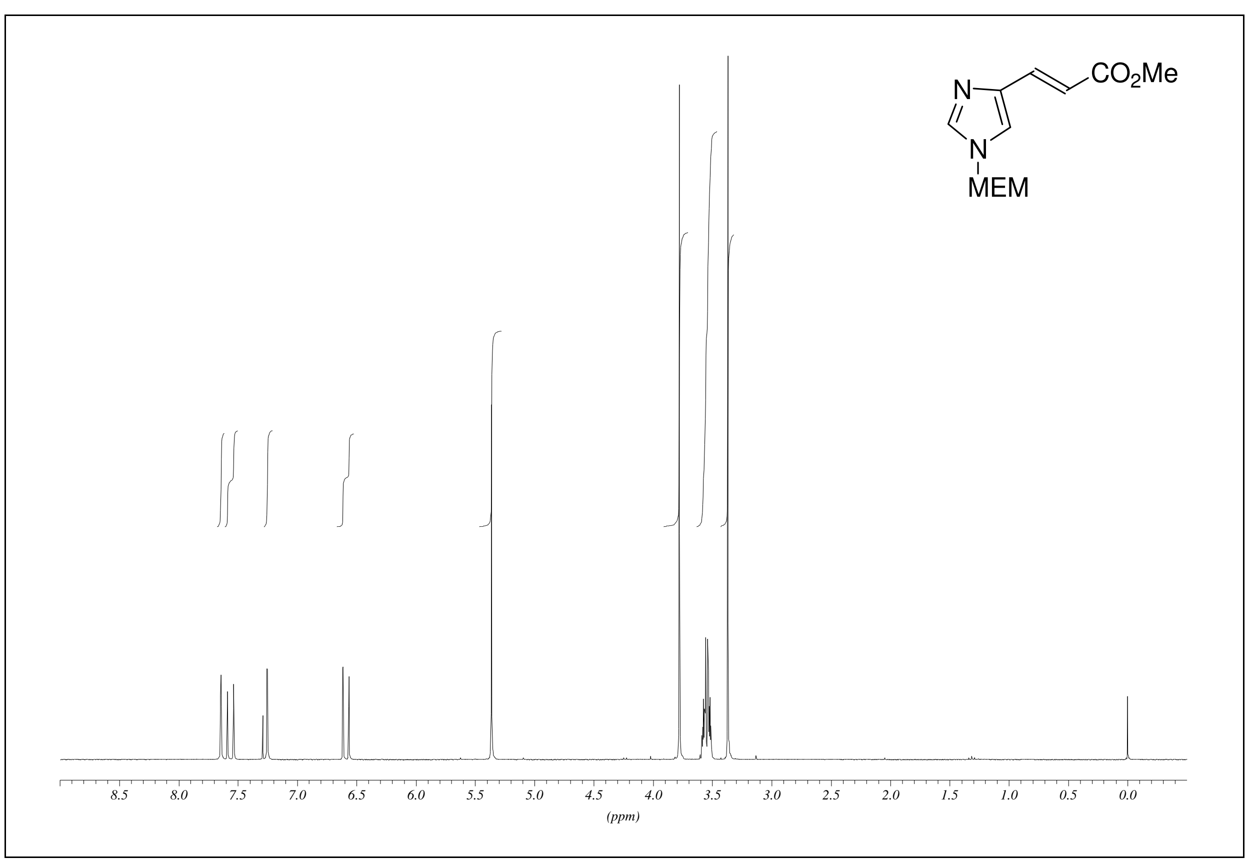
4 Appendix of NMR and X-ray data

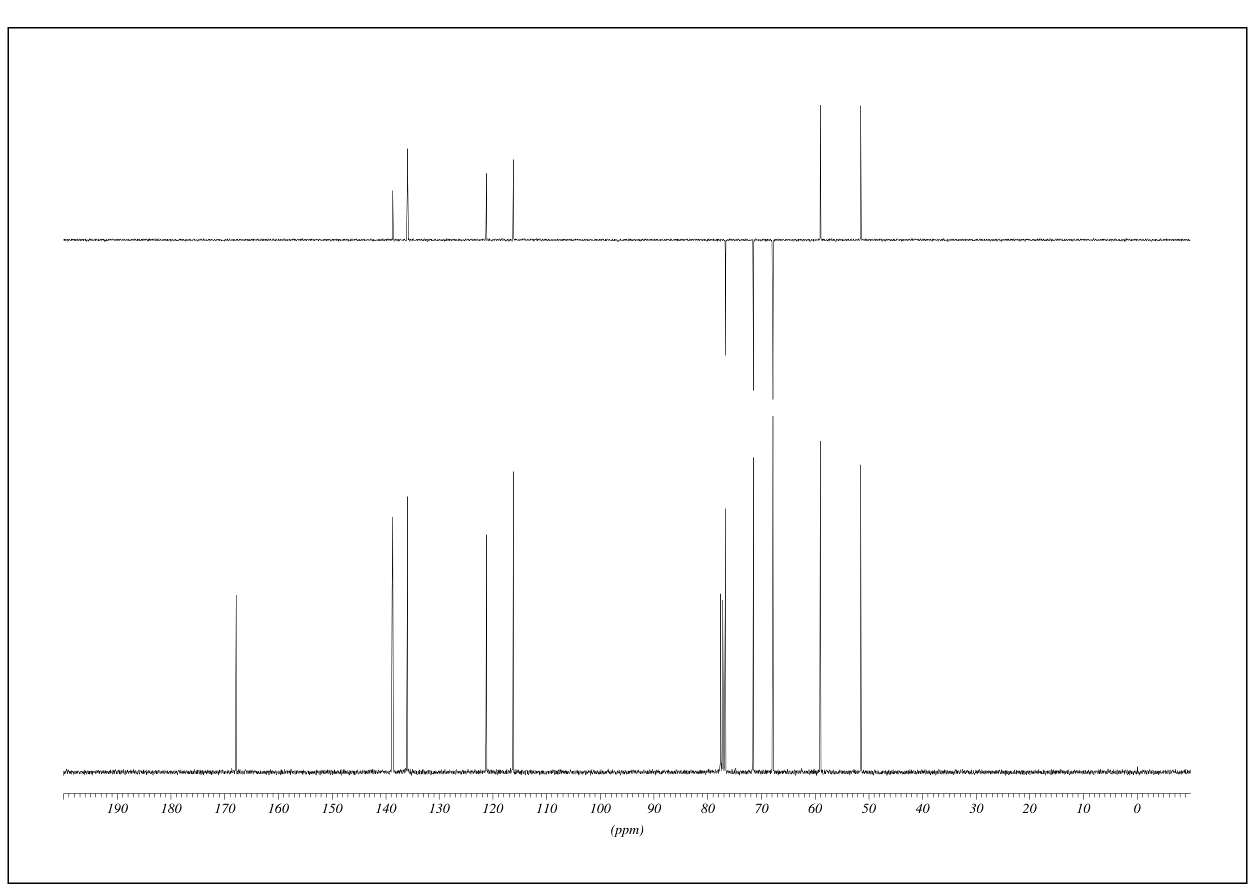
4.1 NMRs

^{1}HNMR-Spectra (top of the page)

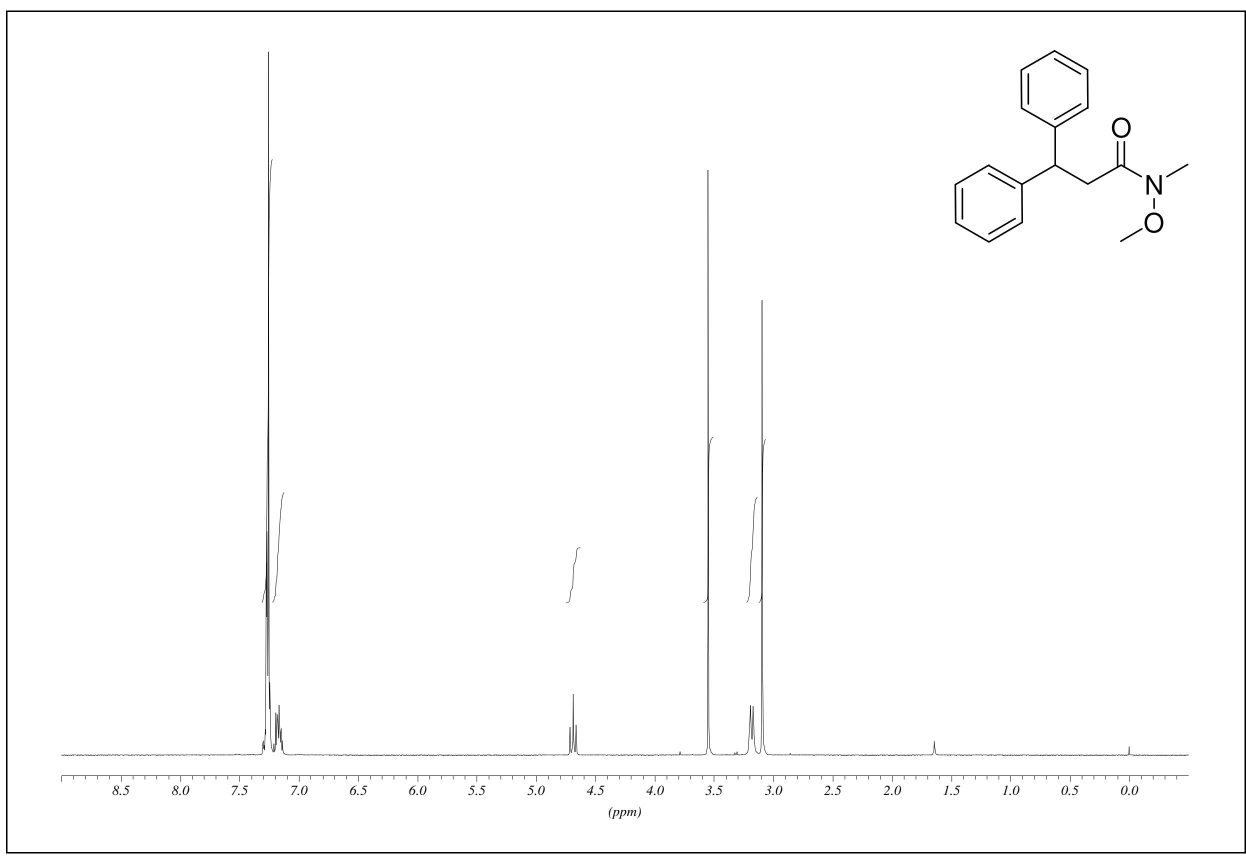
^{13}CNMR-Spectra (bottom of the page)

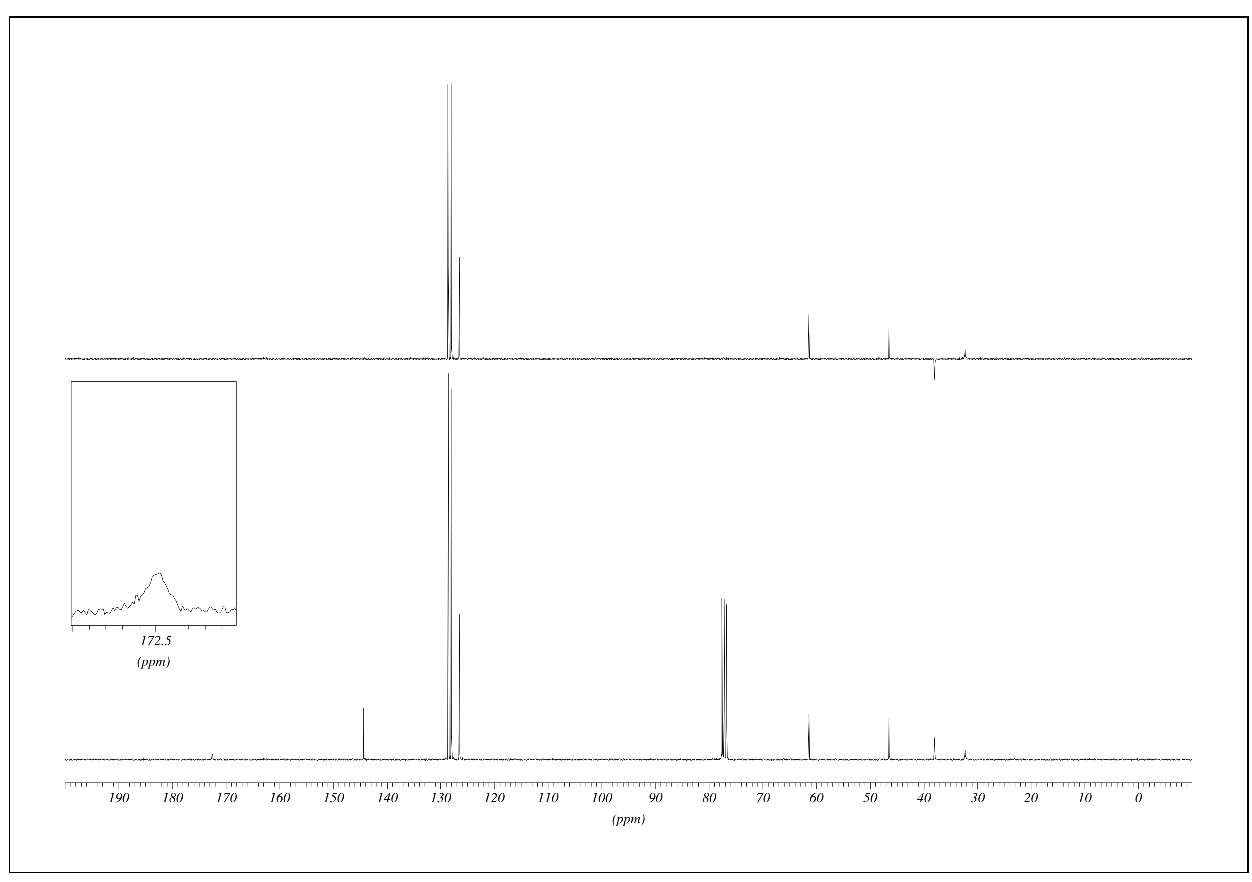
(E)-methyl 3-(1-((2methoxyethoxy)methyl)1*H*-Imidazol-4-yl)acrylate (171)



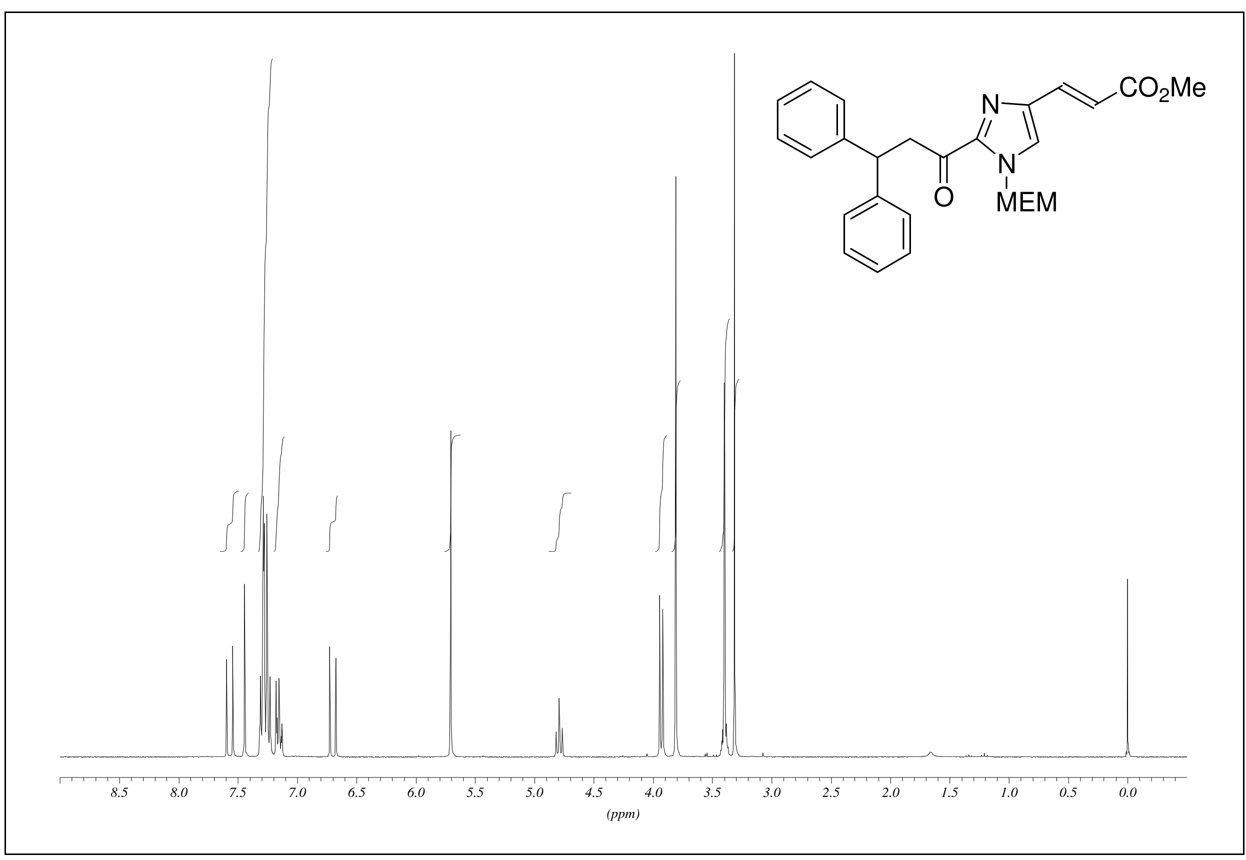


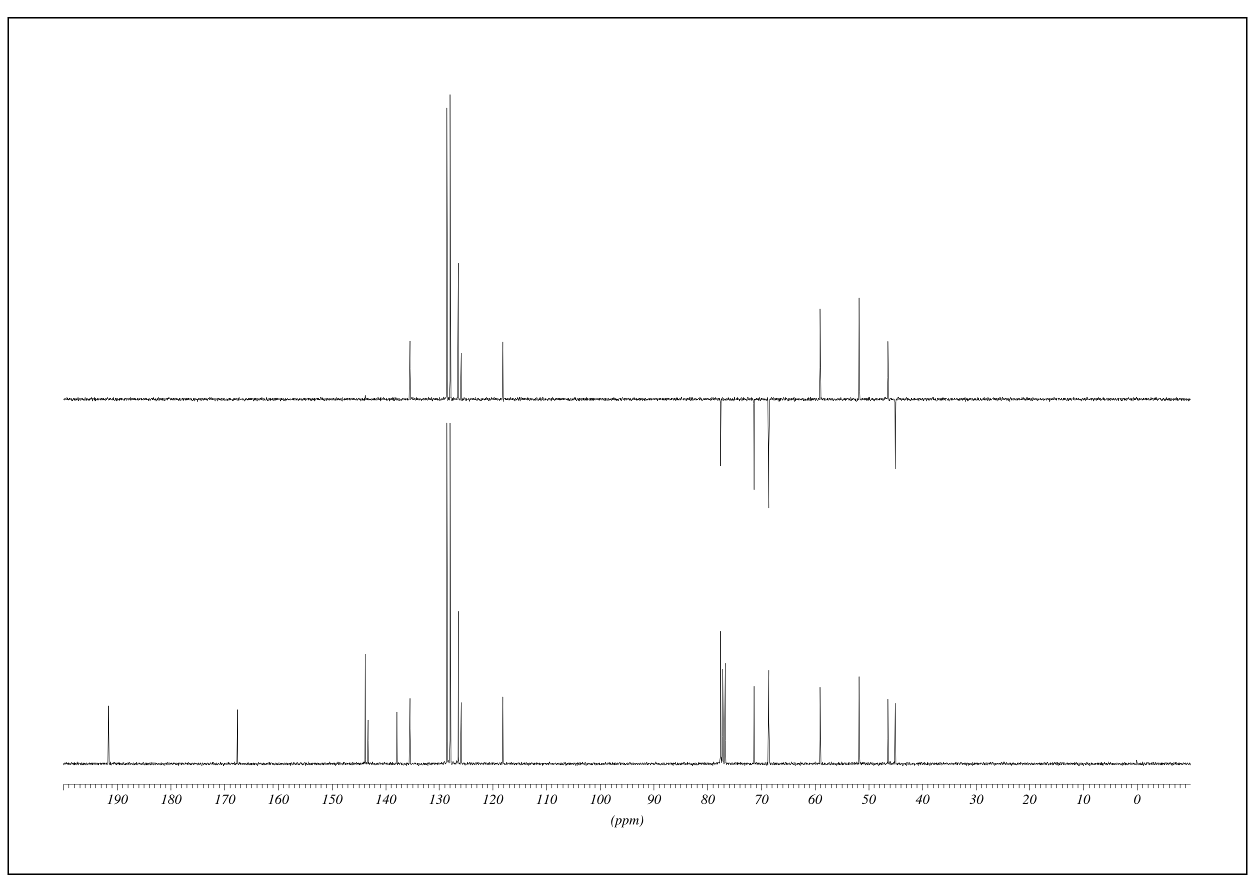
_N_-methoxy-_N_-methyl-3,3-diphenylpropanamide (174)



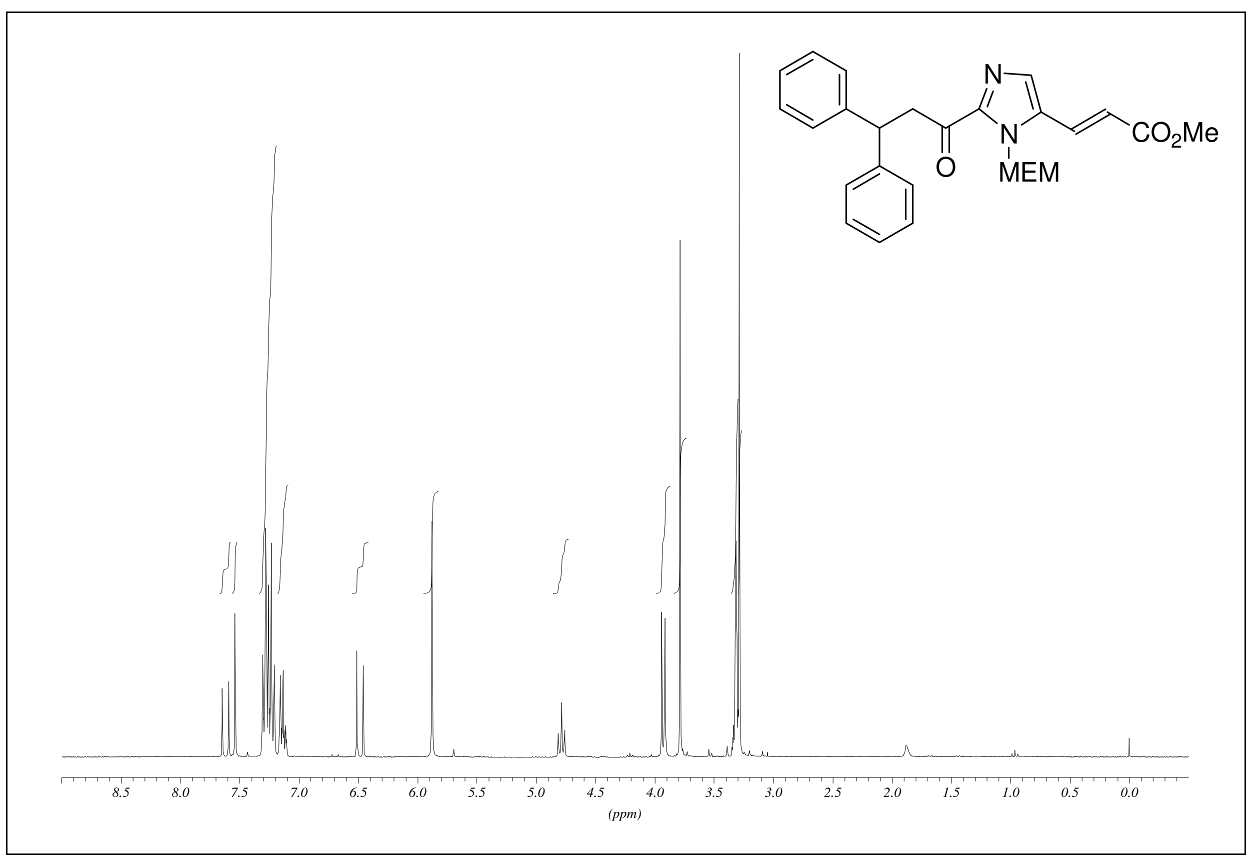


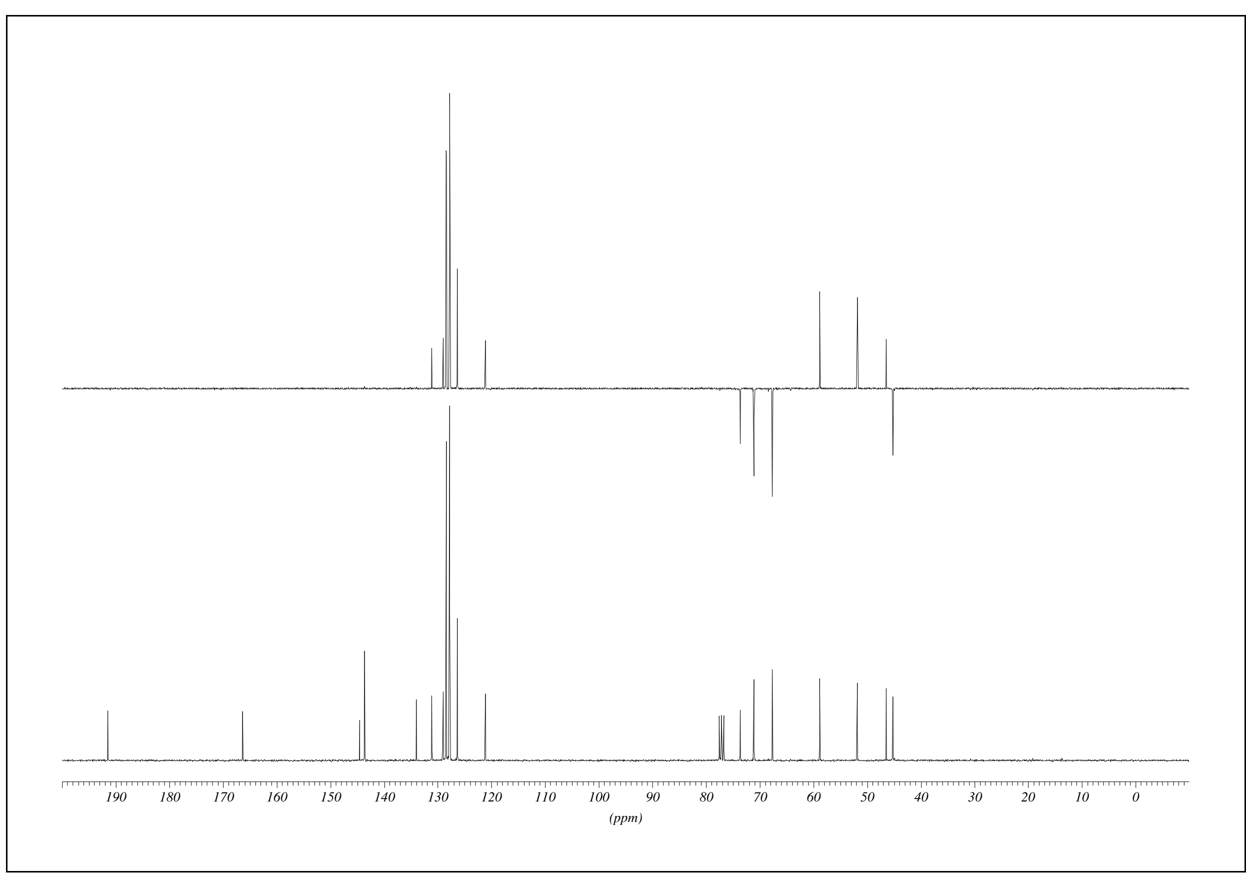
(E)-methyl3-(1-((2methoxyethoxy)methyl)-2-(3,3-diphenylpropanoyl)-1*H*-Imidazol-4-yl)acrylate (175)



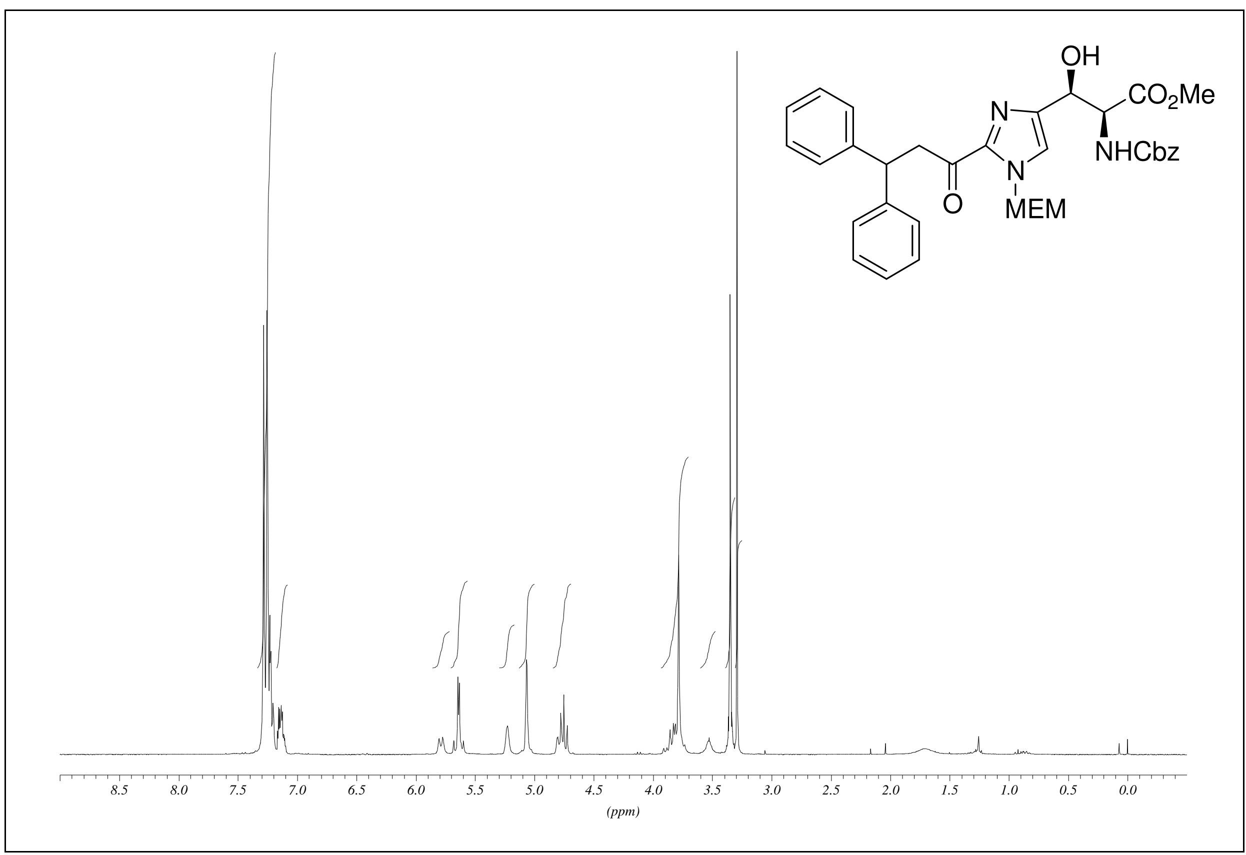


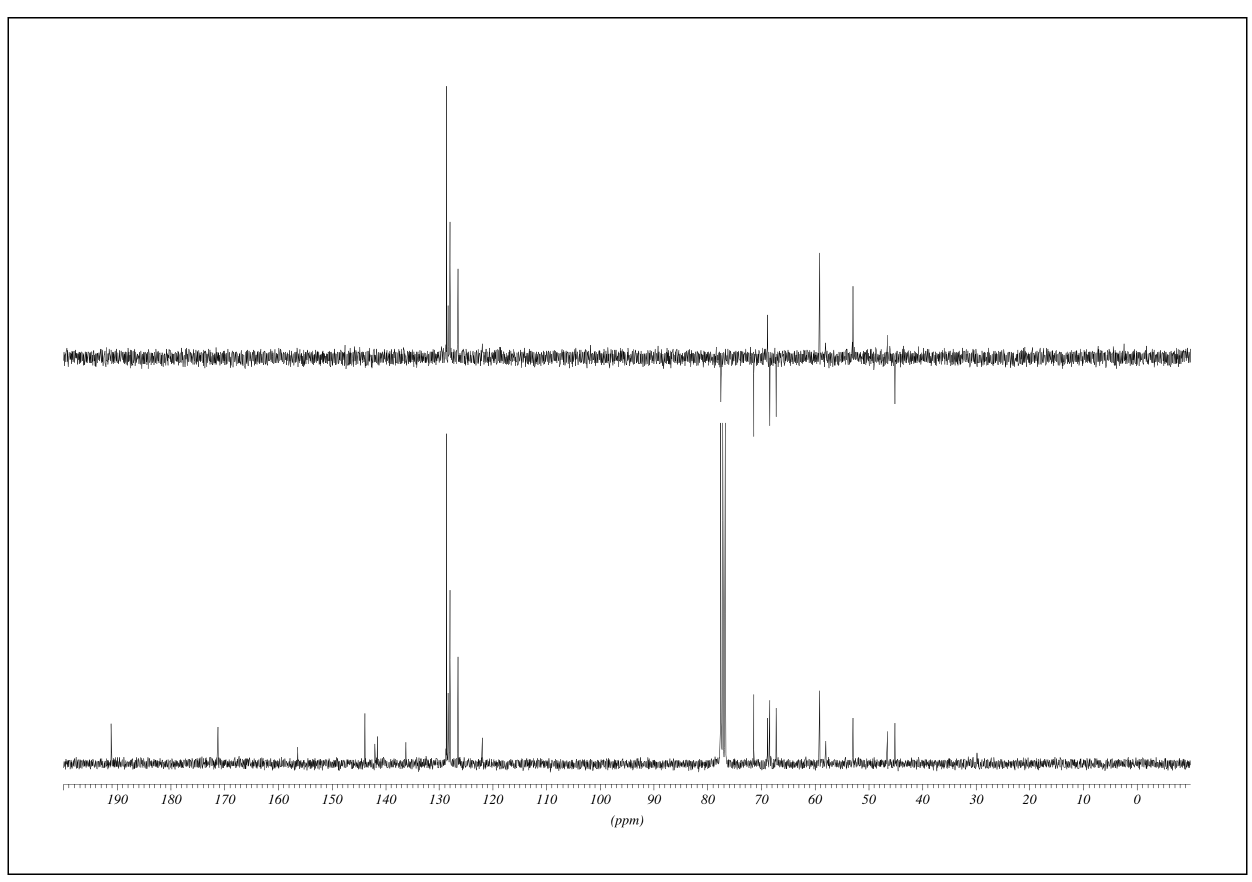
(E)-methyl 3-(1-((2-methoxyethoxy)methyl)-2-(3,3-diphenylpropanoyl)-1H-imidazol-5-yl)acrylate (176)



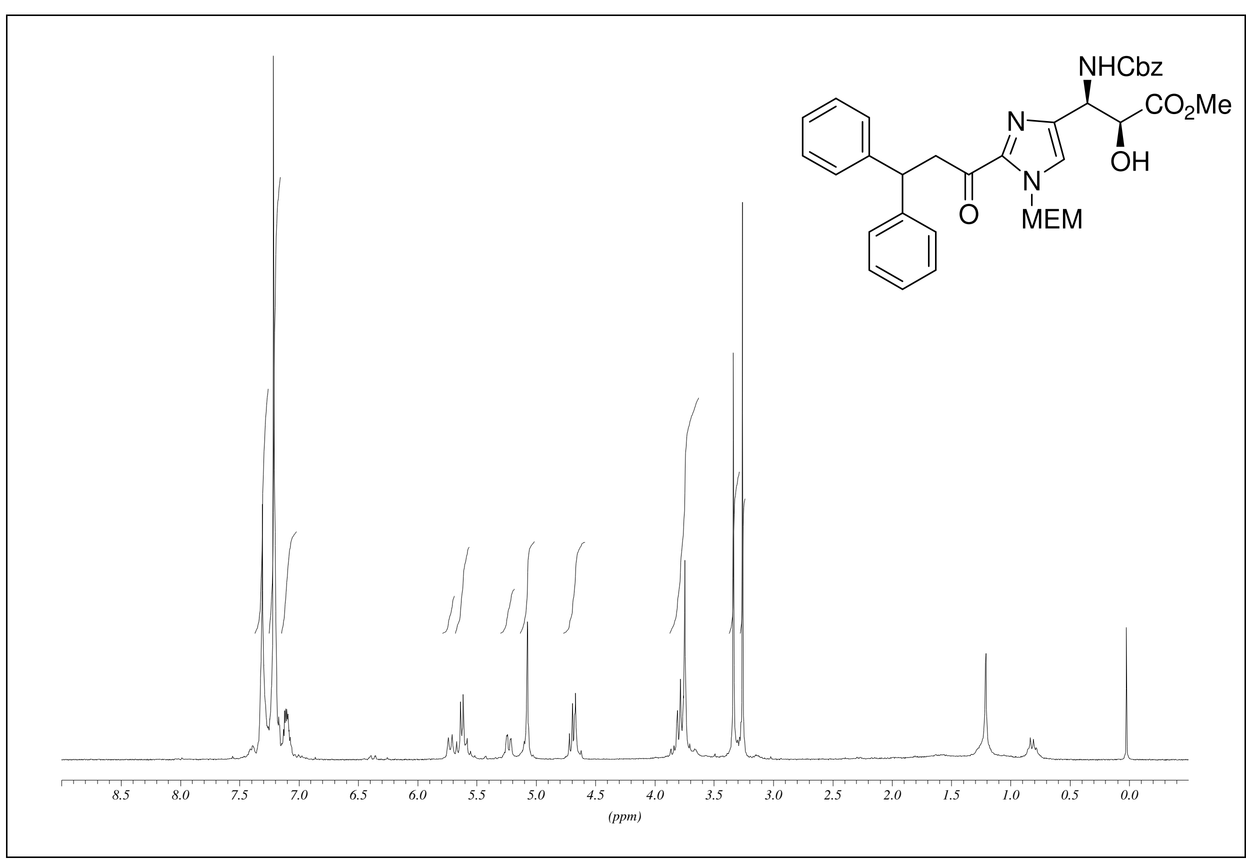


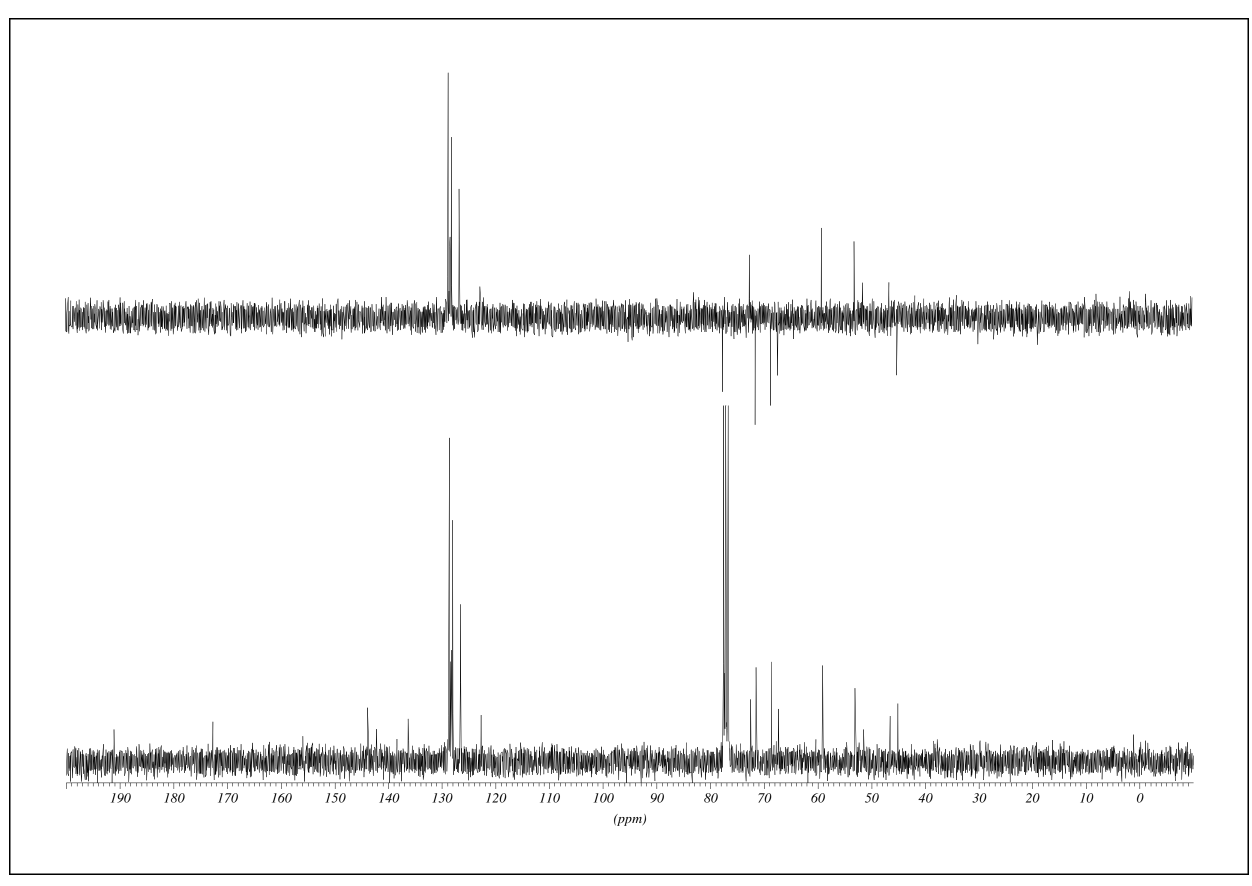
Benzyl(1*S*,2*S*)-1-(methoxycarbonyl)-2-(1-((2-methoxyethoxy)methyl)-2-(3,3-diphenylpropanoyl)-1*H*-imidazol-4-yl)-2-hydroxyethylcarbamate (183)



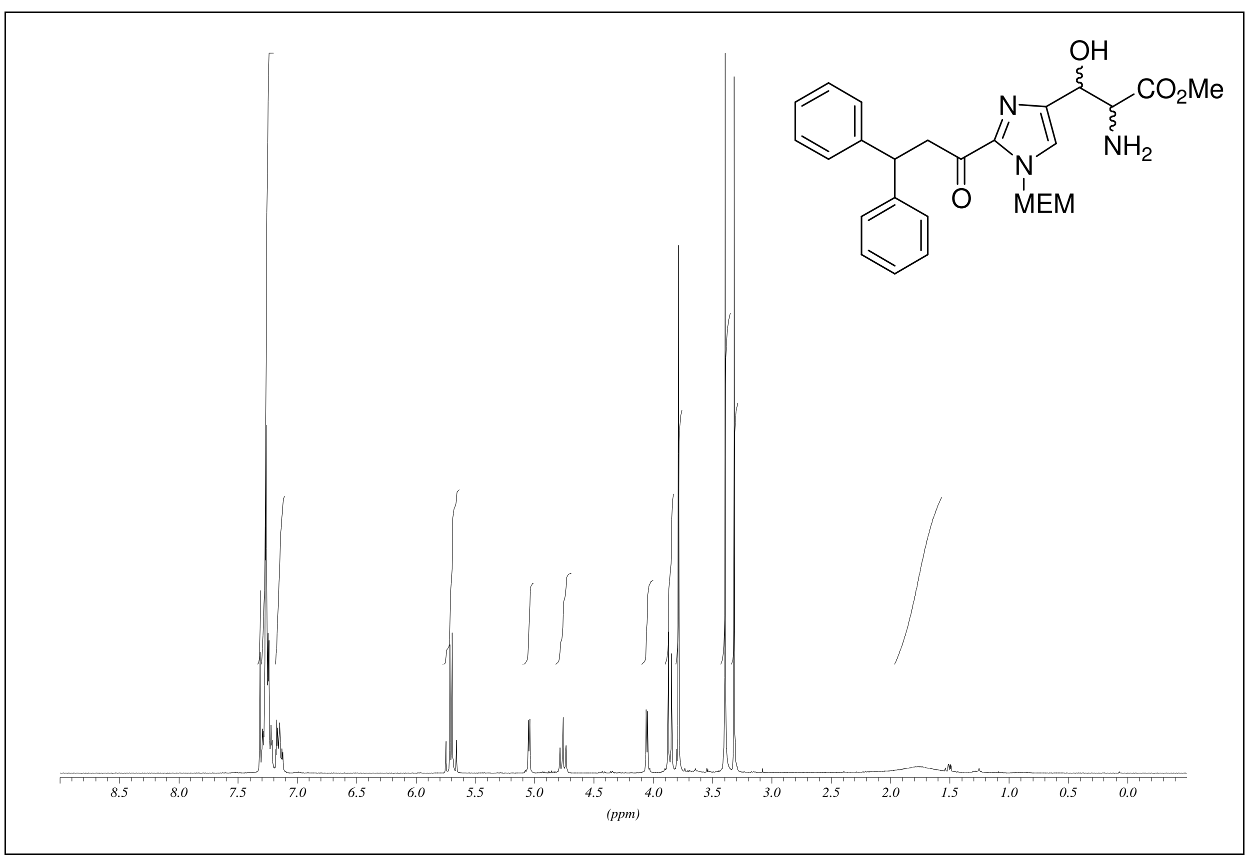


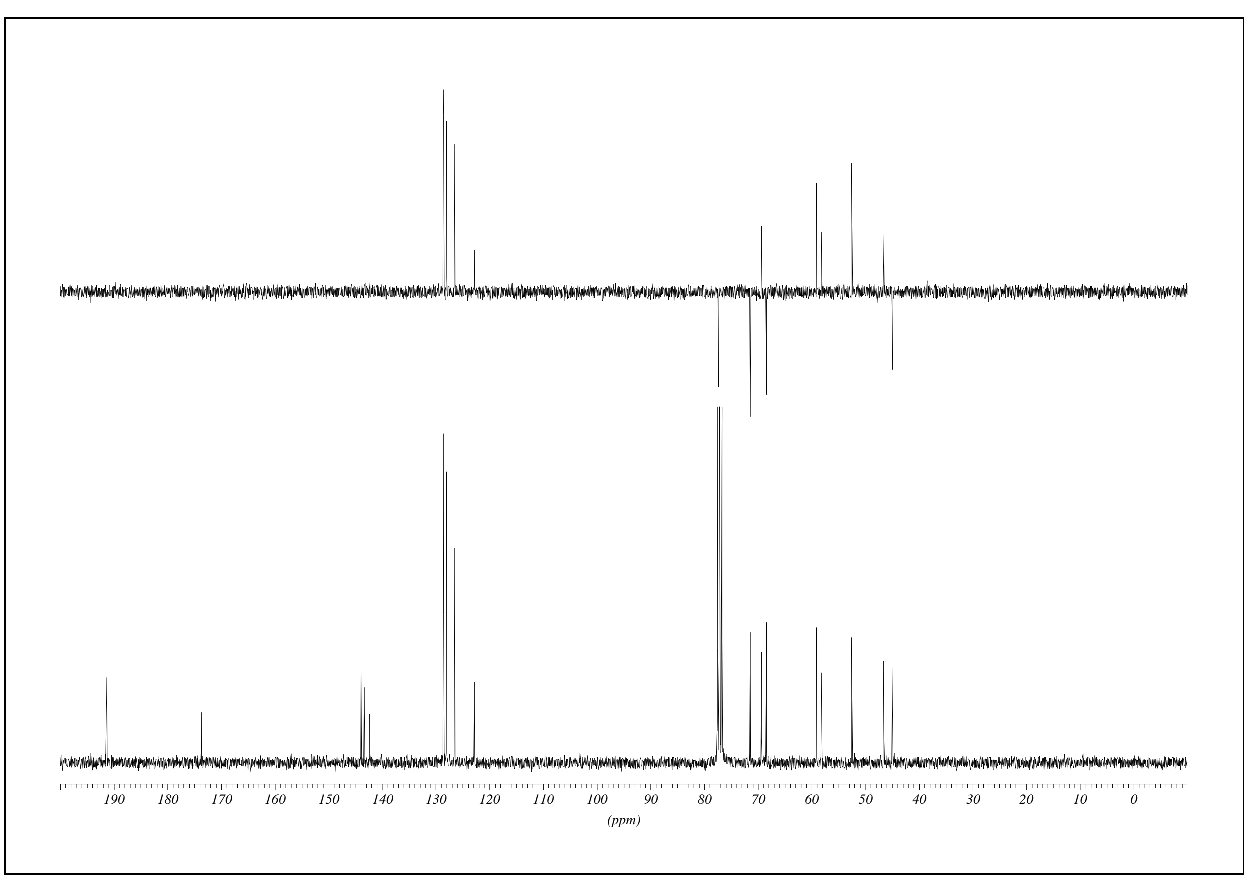
Benzyl (1R,2S)-2-(methoxycarbonyl)-1-(1-((2-methoxyethoxy)methyl)-2-(3,3-diphenylpropanoyl)-1H-imidazol-4-yl)-2-hydroxyethylcarbamate (184)



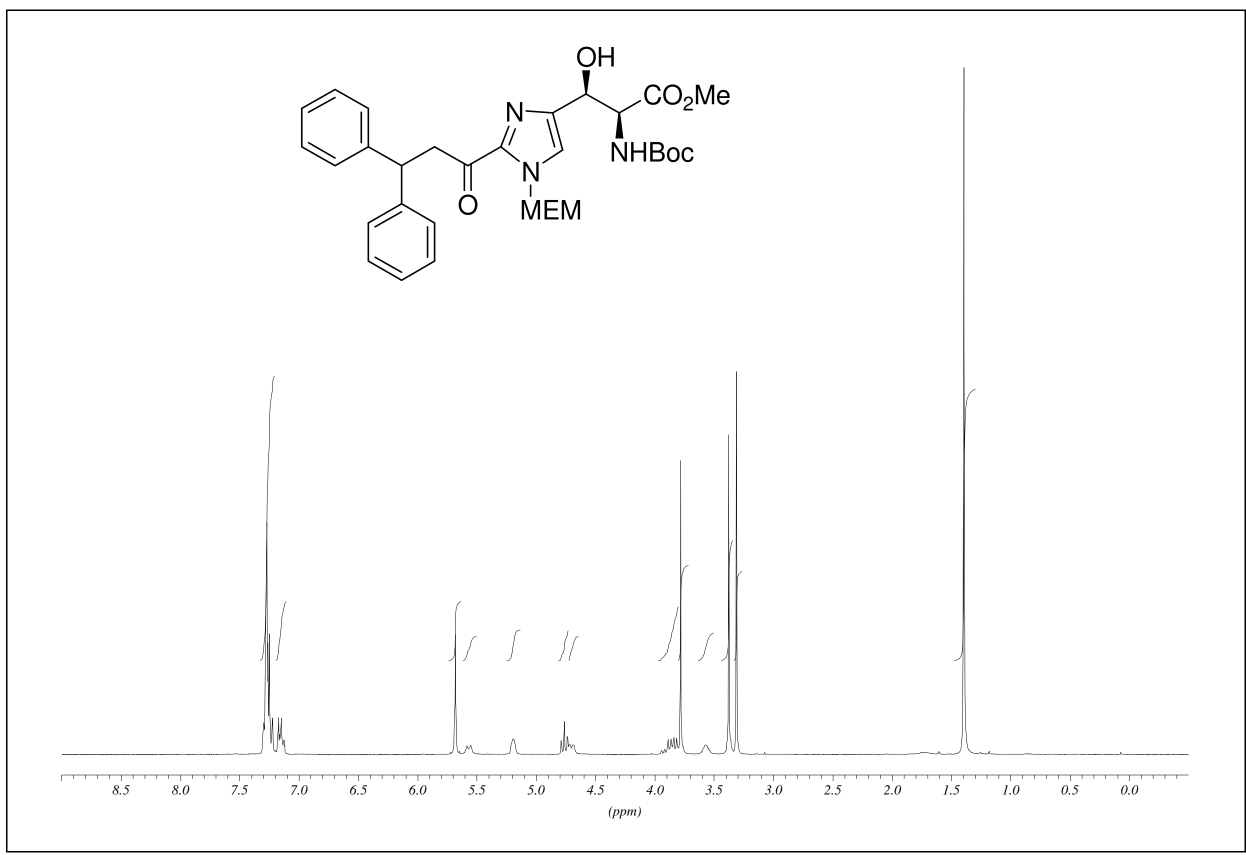


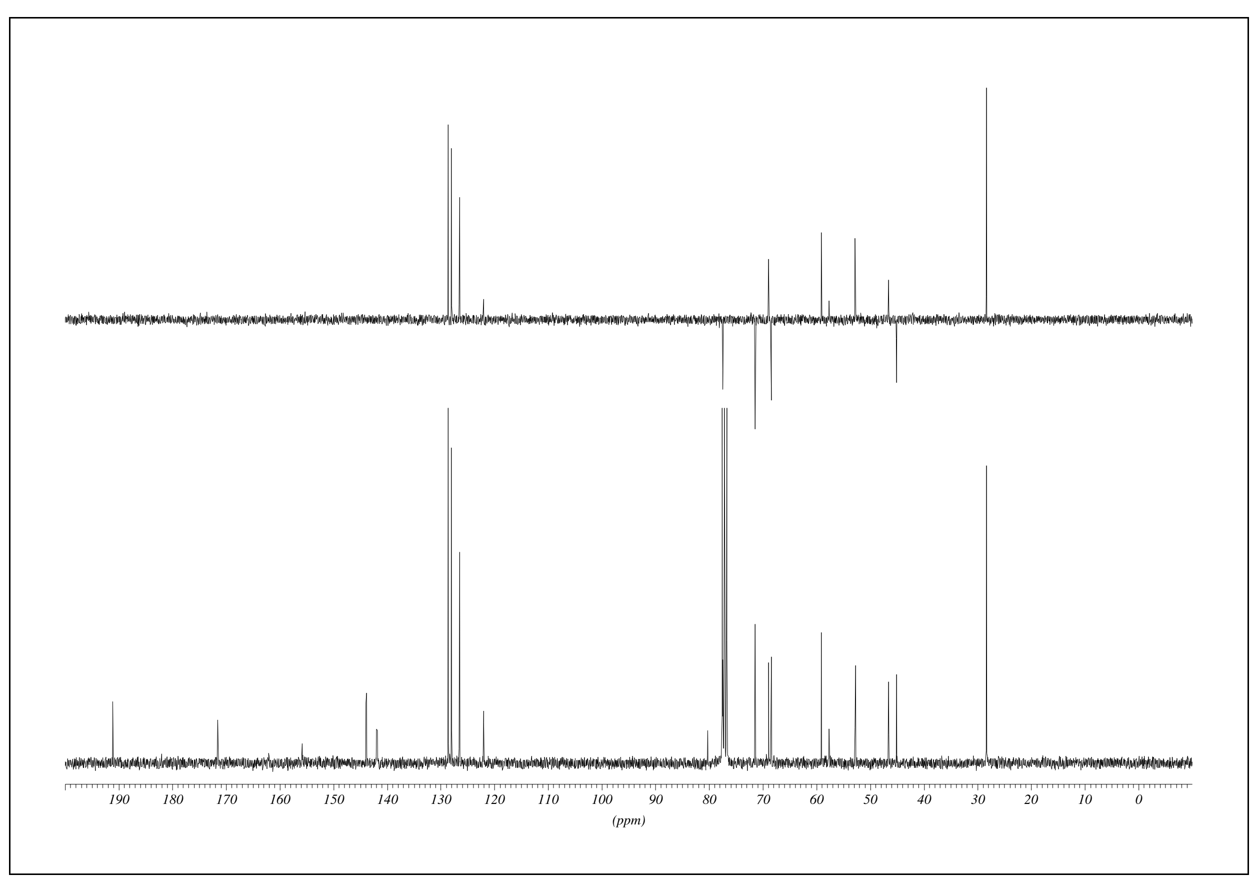
Methyl3-(1-((2-methoxyethoxy)methyl)-2-(3,3-diphenylpropanoyl)-1*H*-imidazol-4-yl)-2-amino-3-hydroxypropanoate (183-a)



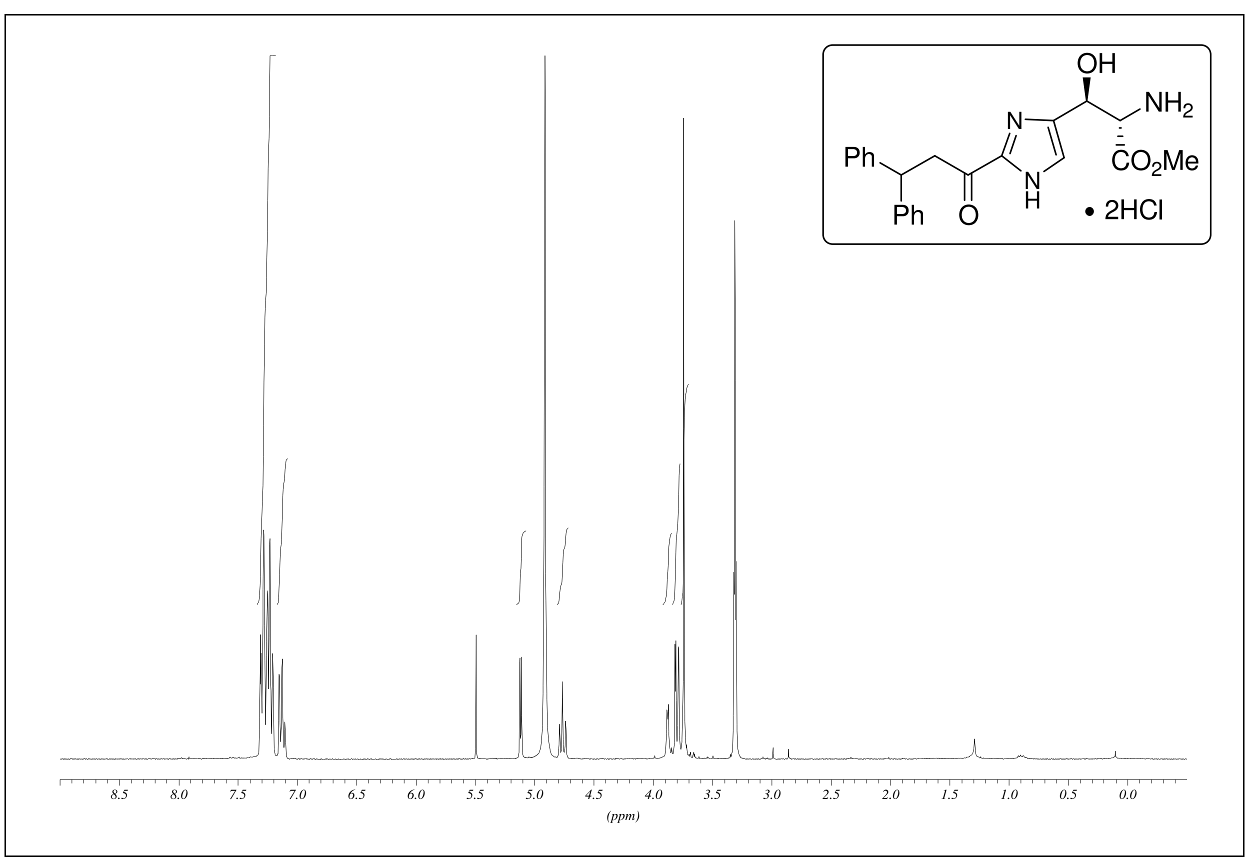


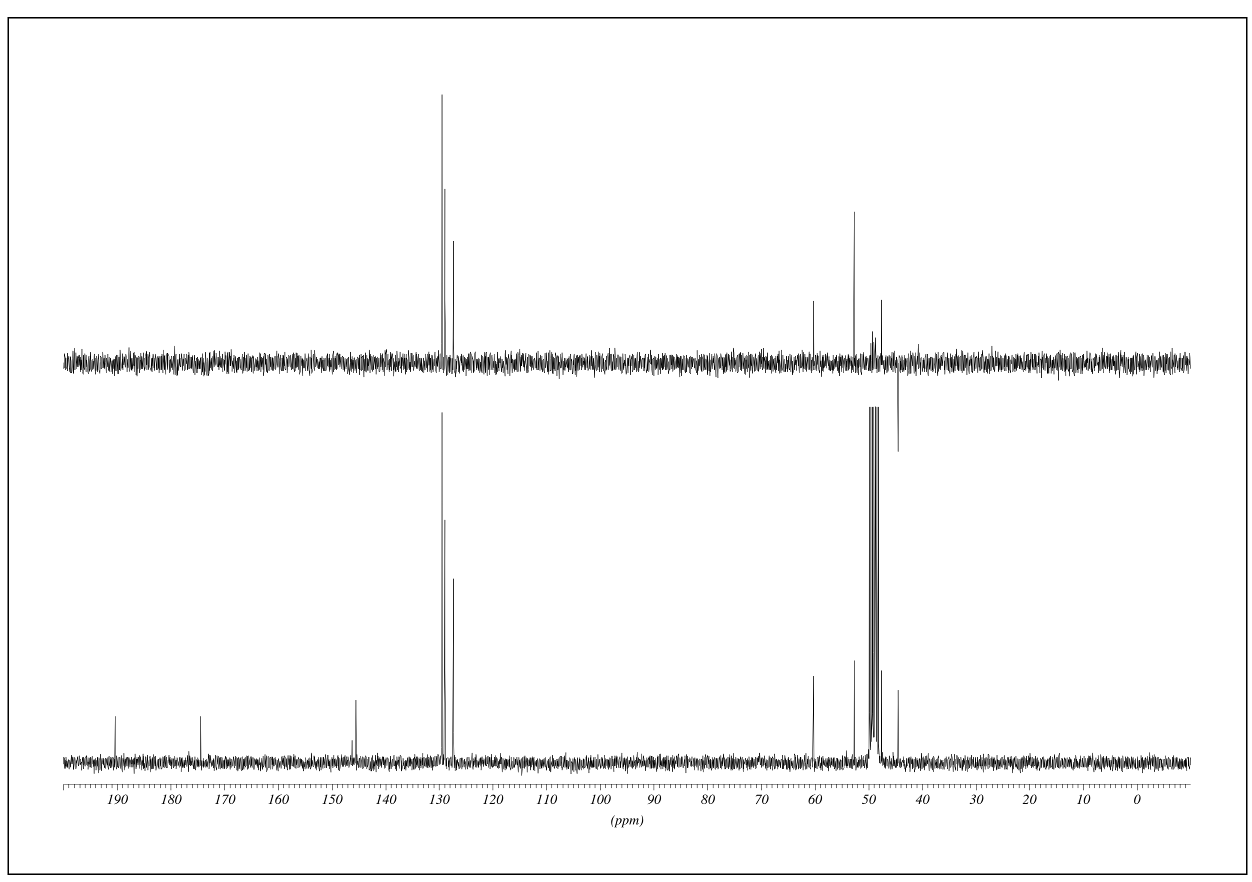
Tert-butyl (1S,2S)-1-(methoxycarbonyl)-2-(1-((2-methoxyethoxy)methyl)-2-(3,3-diphenylpropanoyl)-1H-imidazol-4-yl)-2-hydroxyethylcarbamate (189)



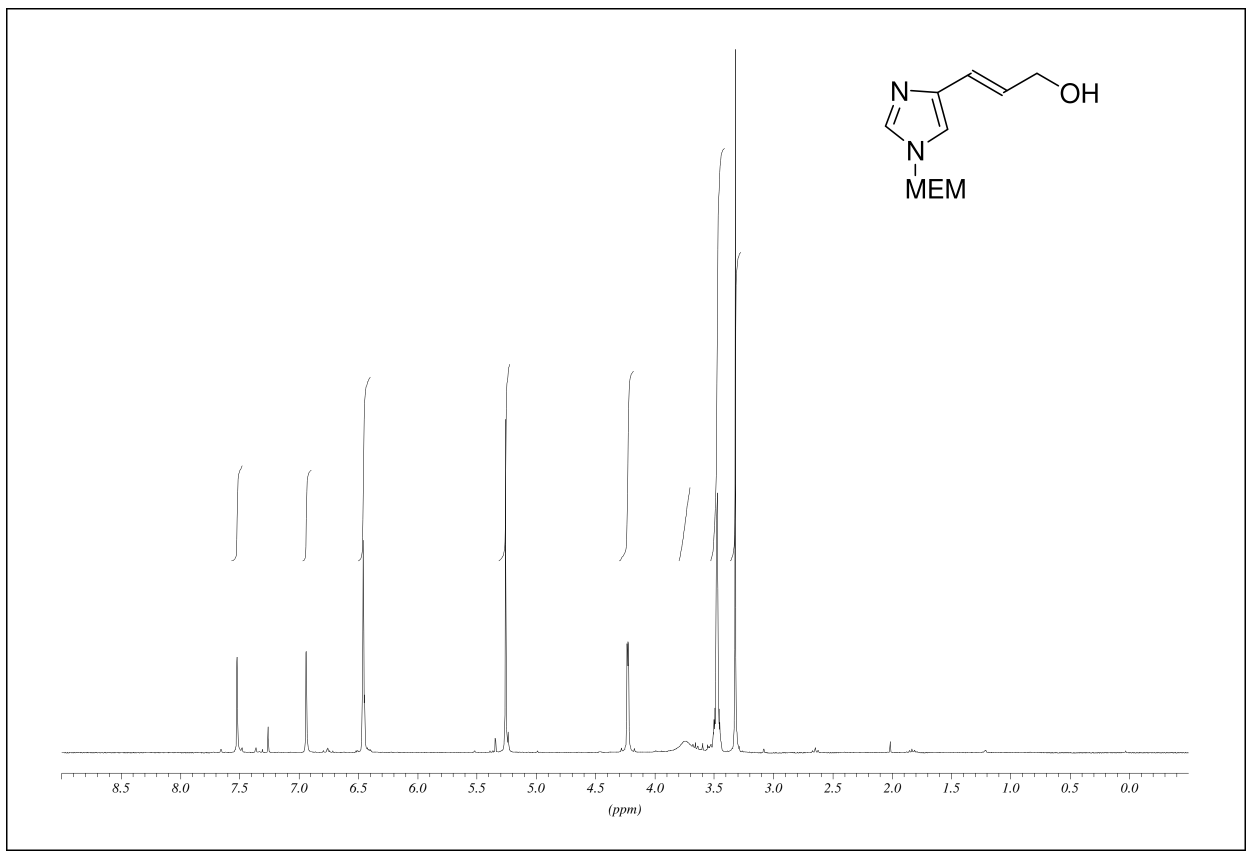


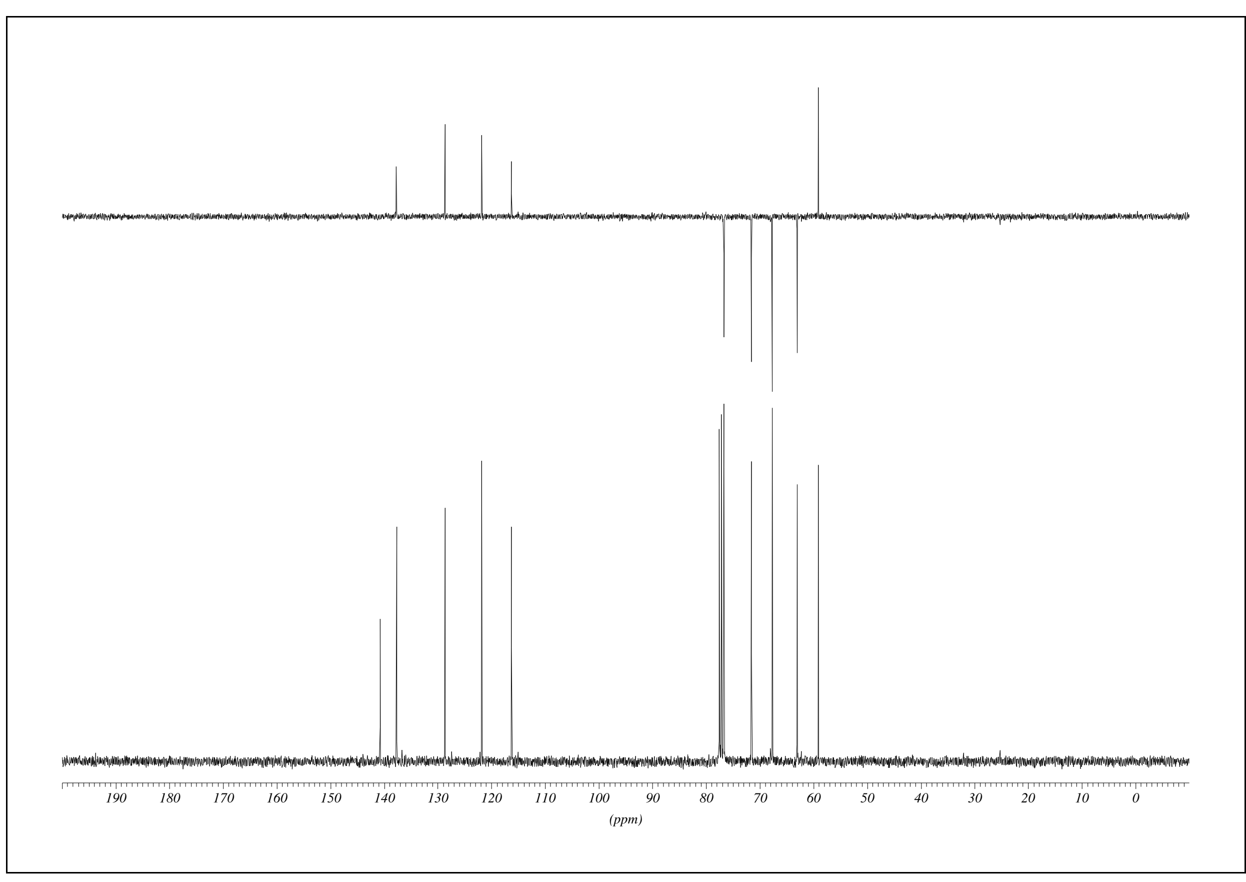
(2*S*,3*S*)-methyl3-(2-(3,3-diphenylpropanoyl)-1*H*-imidazol-4-yl)-2-amino-3-hydroxypropanoatedihydrochloride (191)



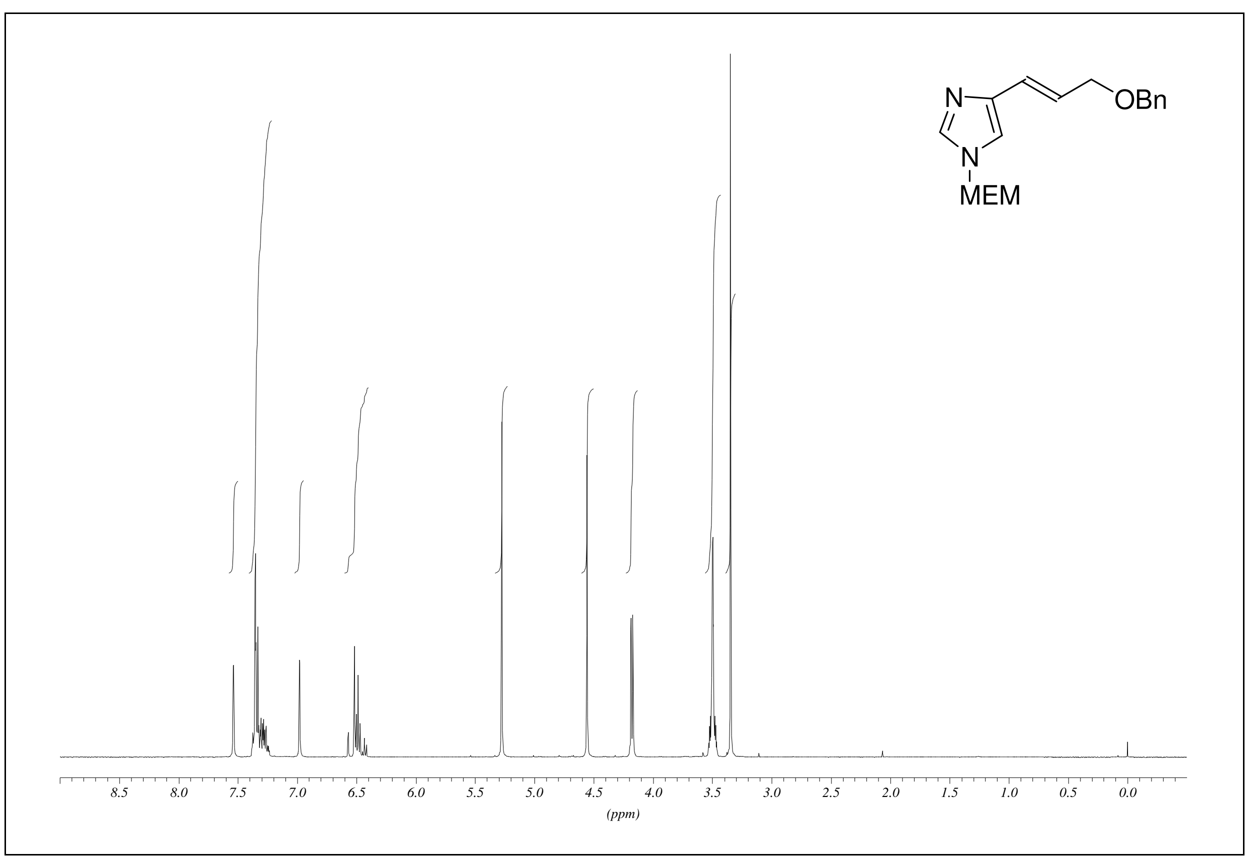


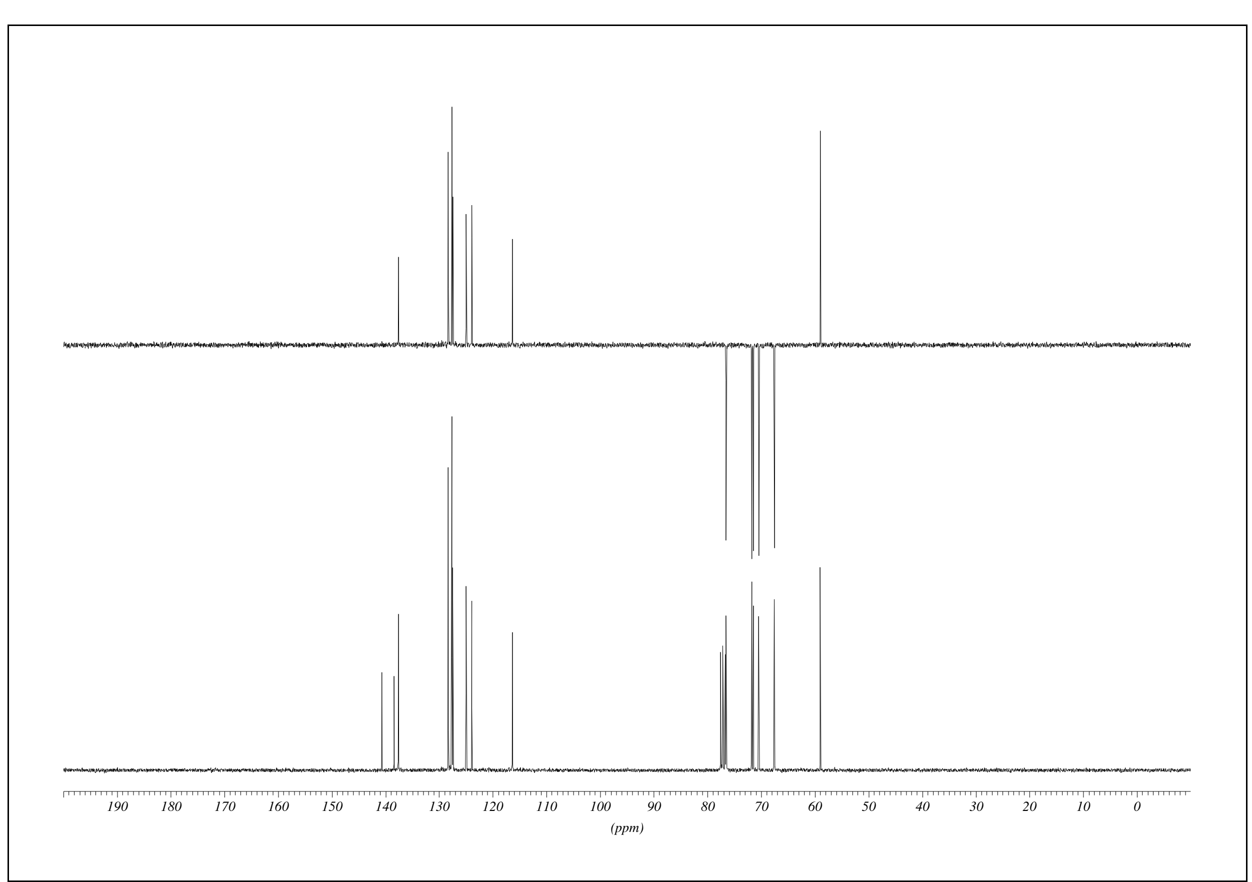
(E)- 3-(1-((2-methoxyethoxy)methyl)-1*H*-Imidazol-4-yl)prop-2-en-1-ol (177)



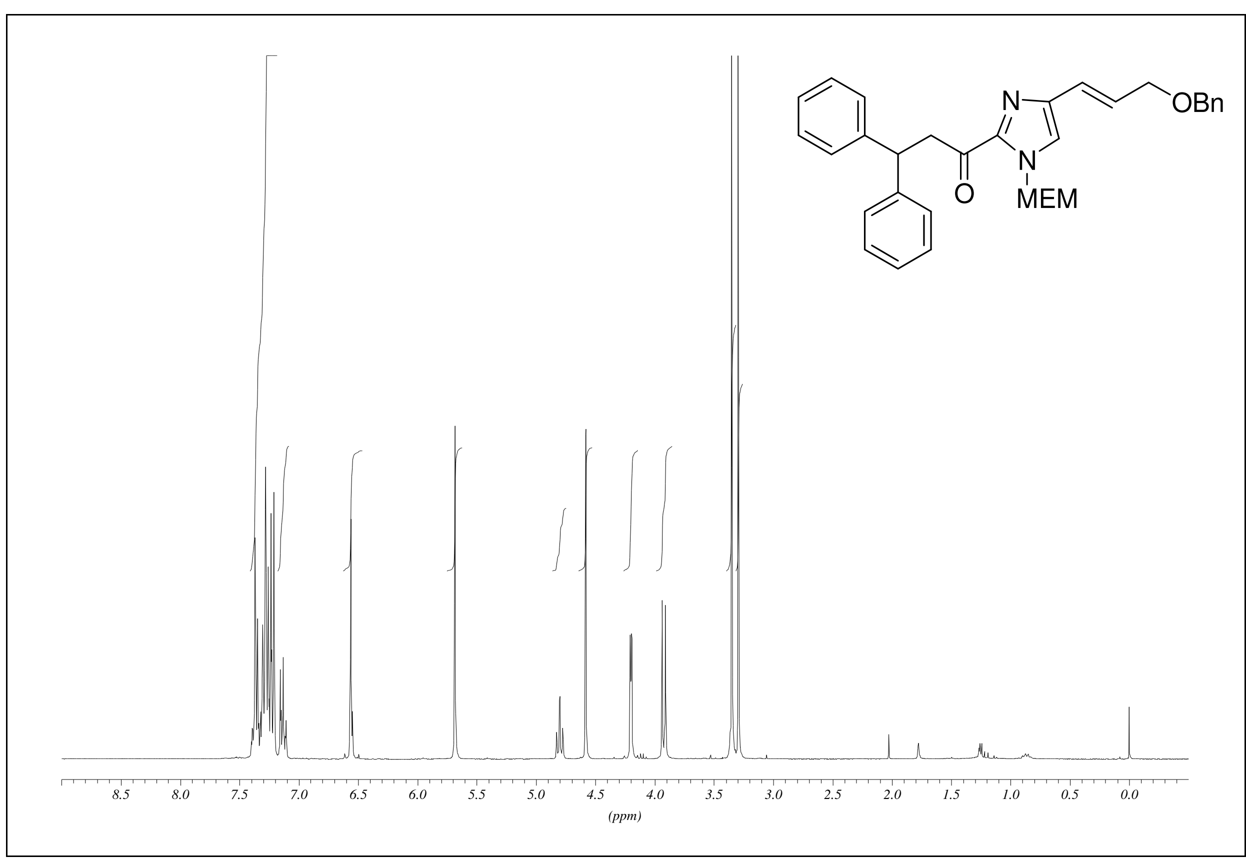


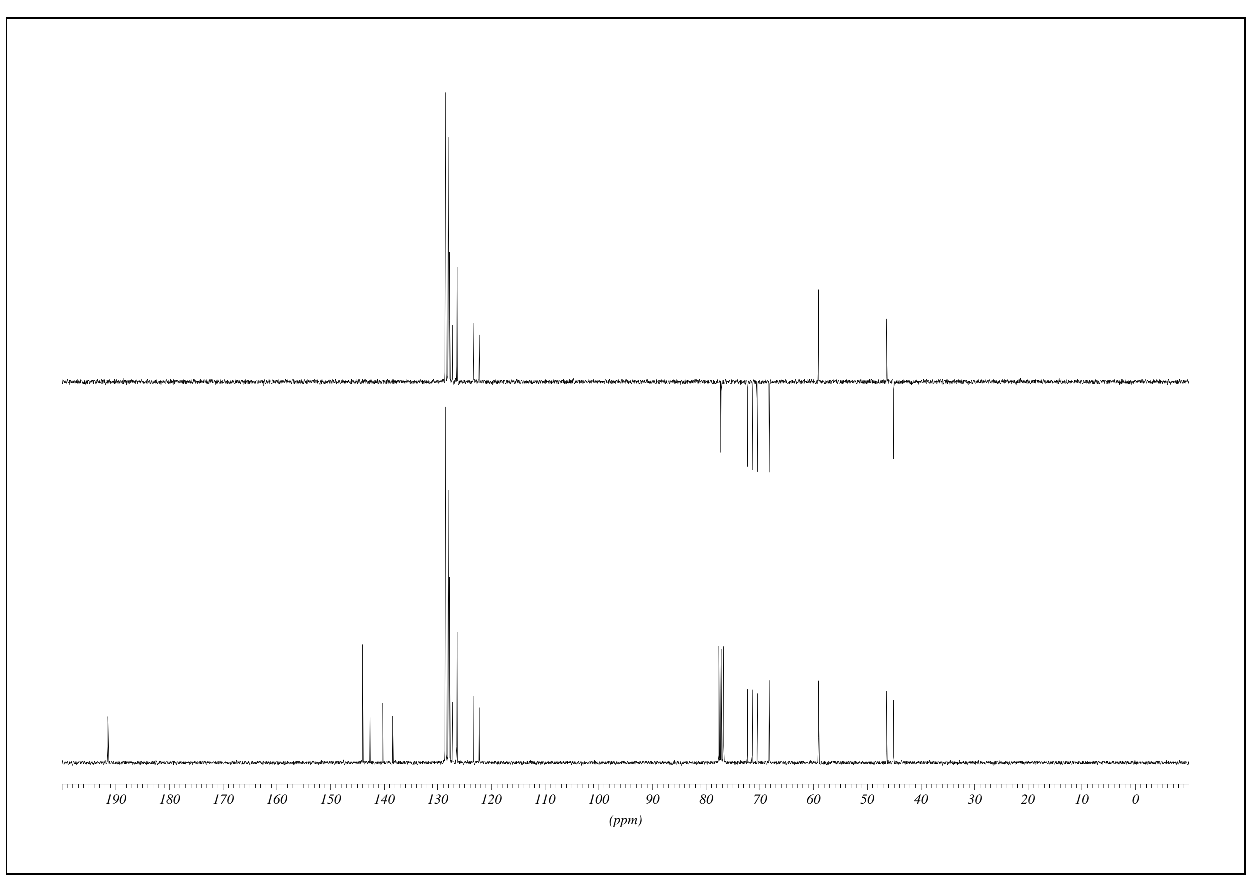
1-((2-methoxyethoxy)methyl)-4-((E)- 3-(benzyloxy)prop-1-enyl)-1*H*-Imidazole (178)



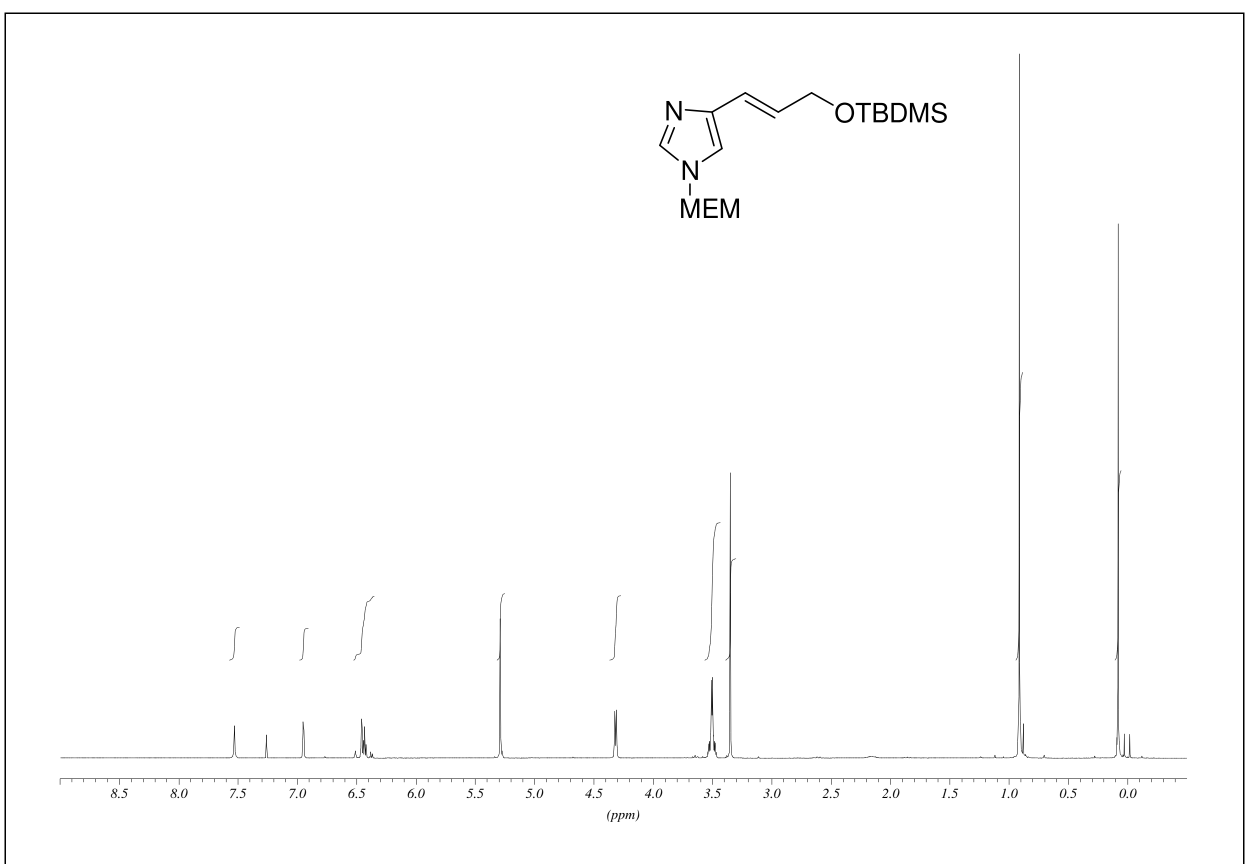


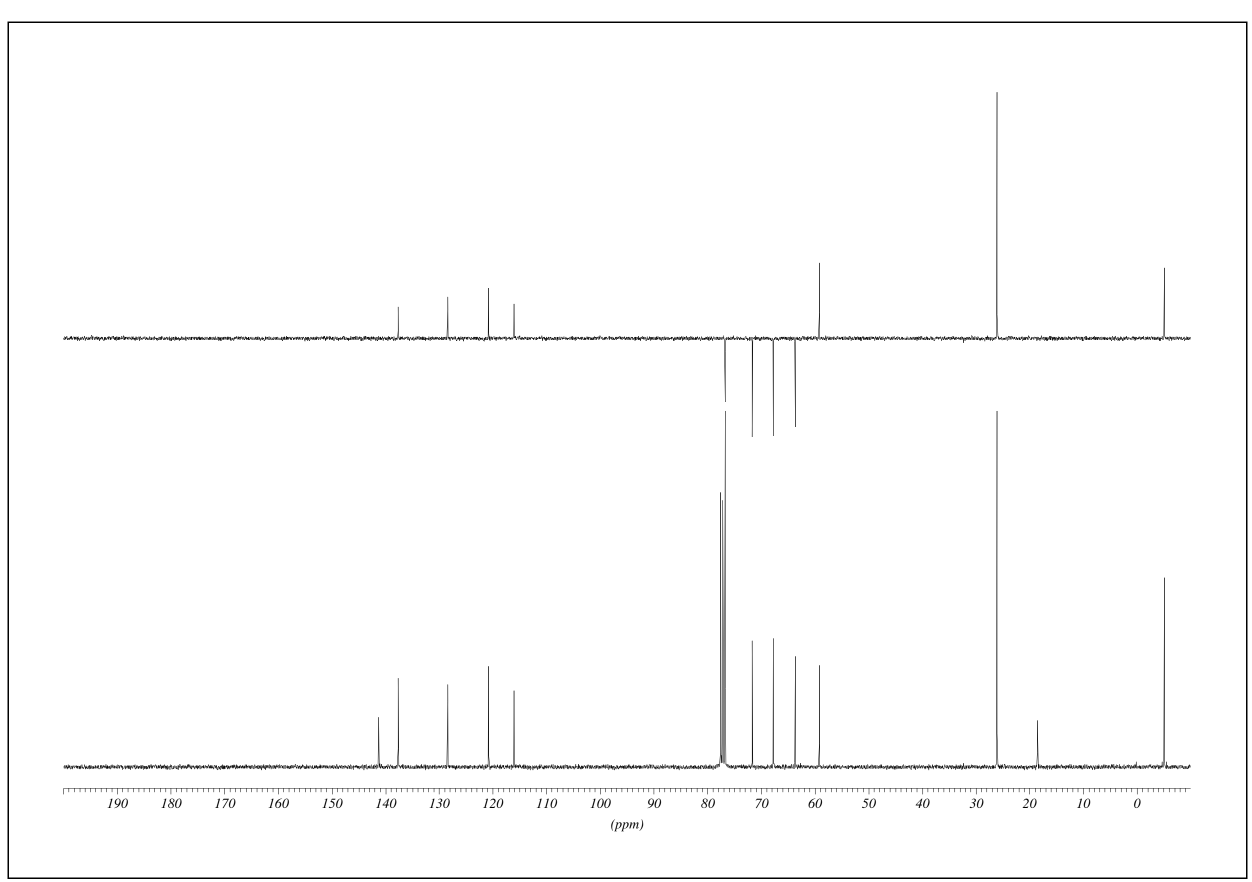
1-(1-((2methoxyethoxy)methyl)4-((E)-3-(benzyloxy)prop-1-enyl)-1*H*-Imidazol -2-yl)3,3-diphenylpropan-1-one (179)



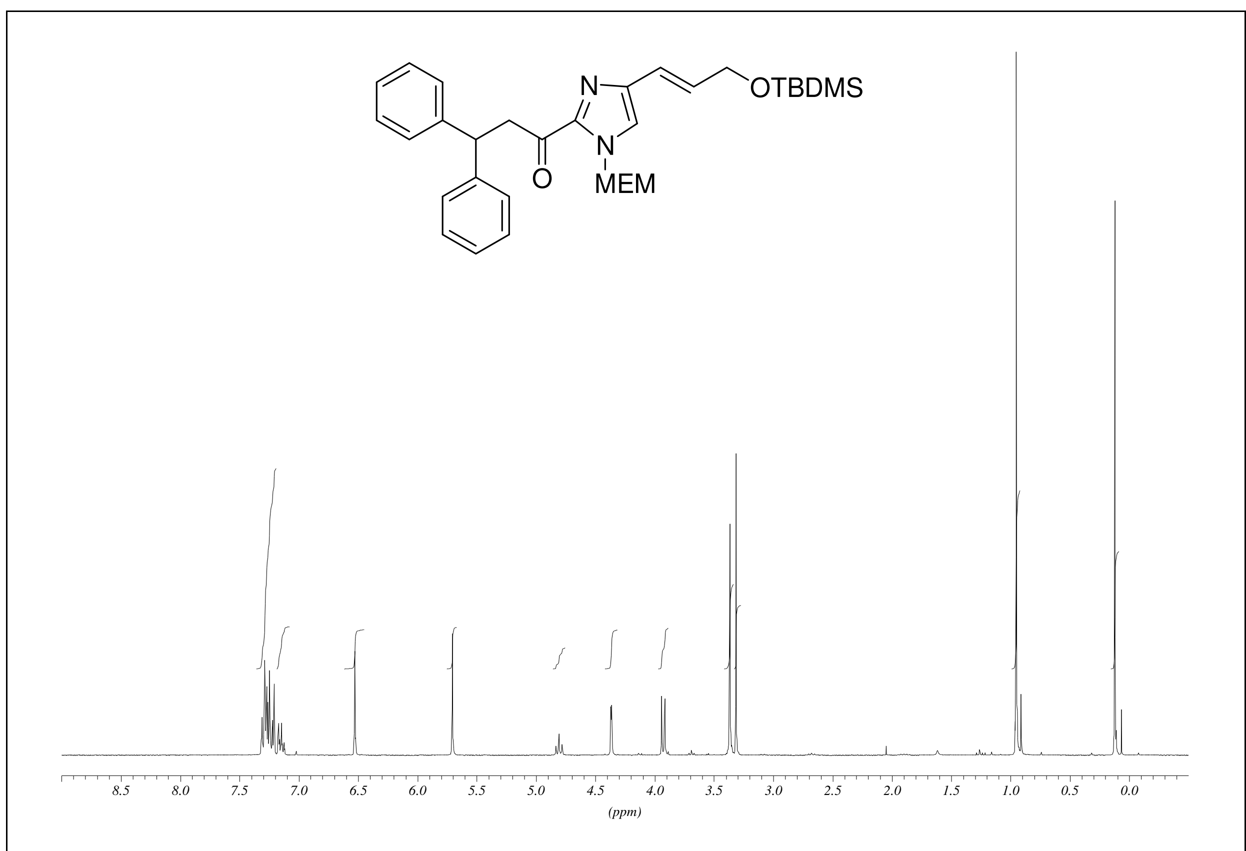


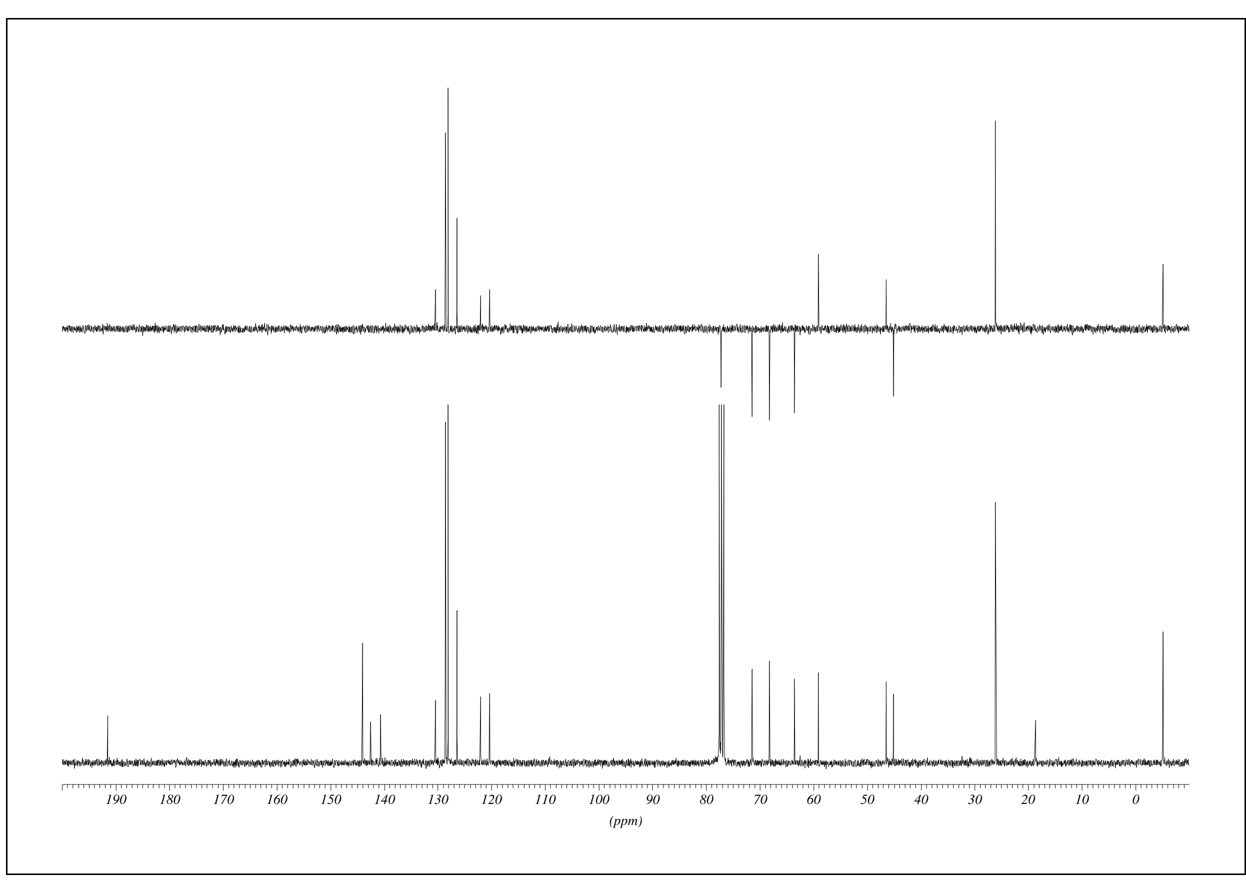
Compound (180)



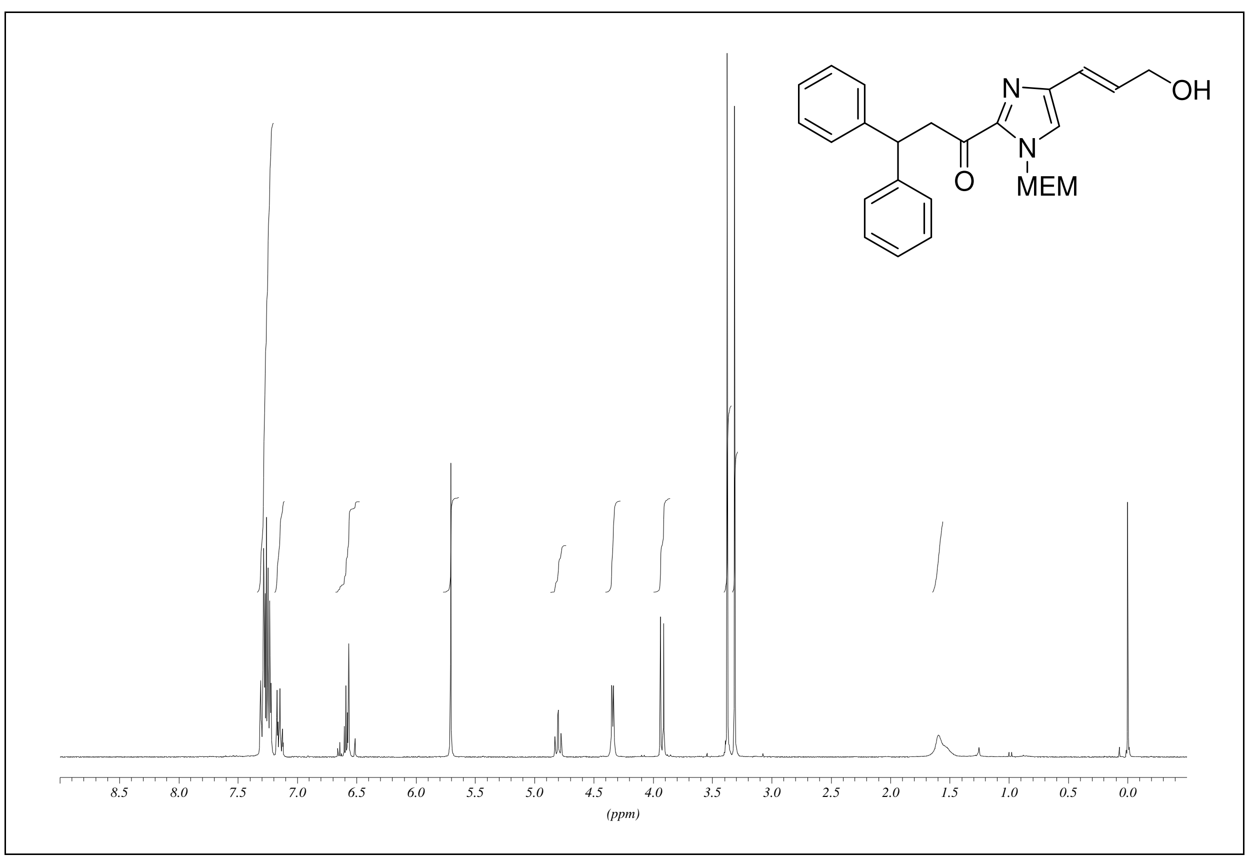


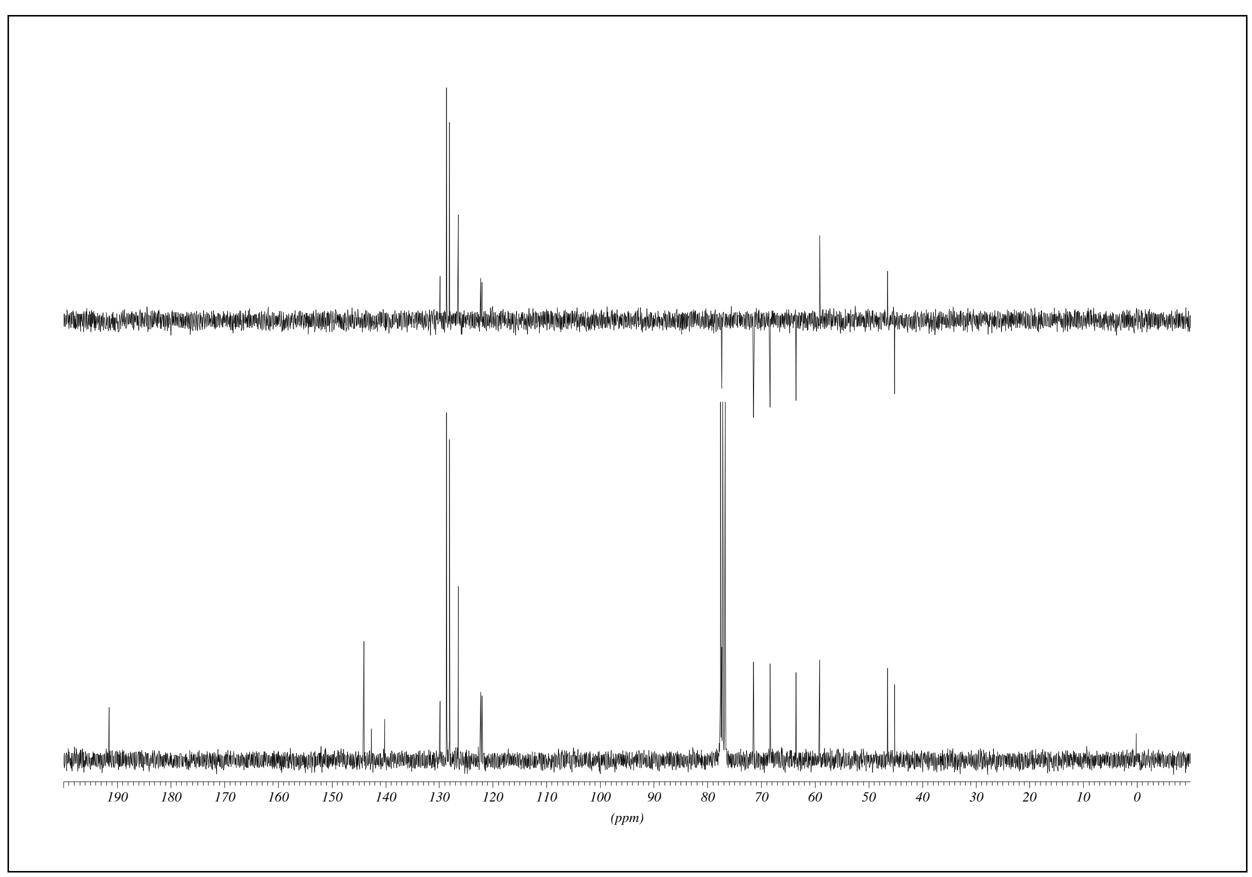
Compound (181)



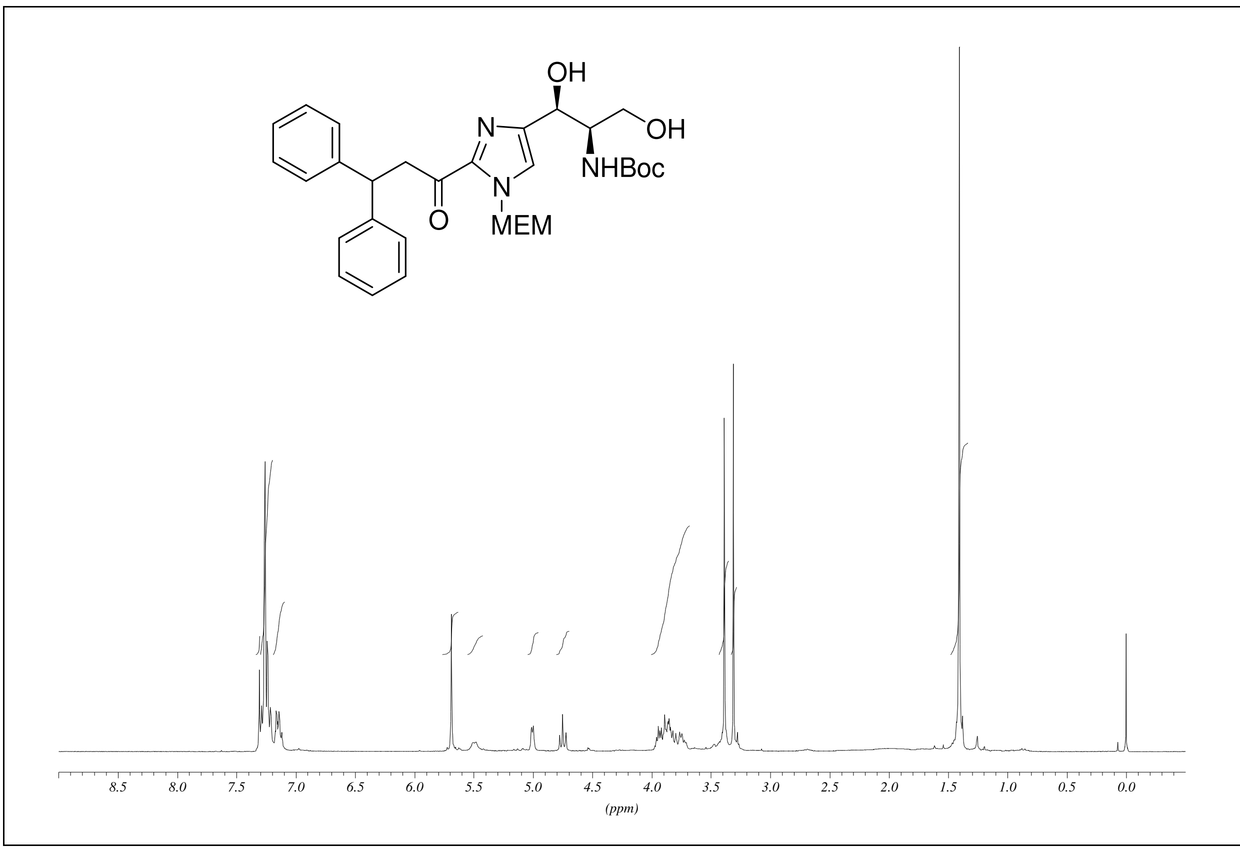


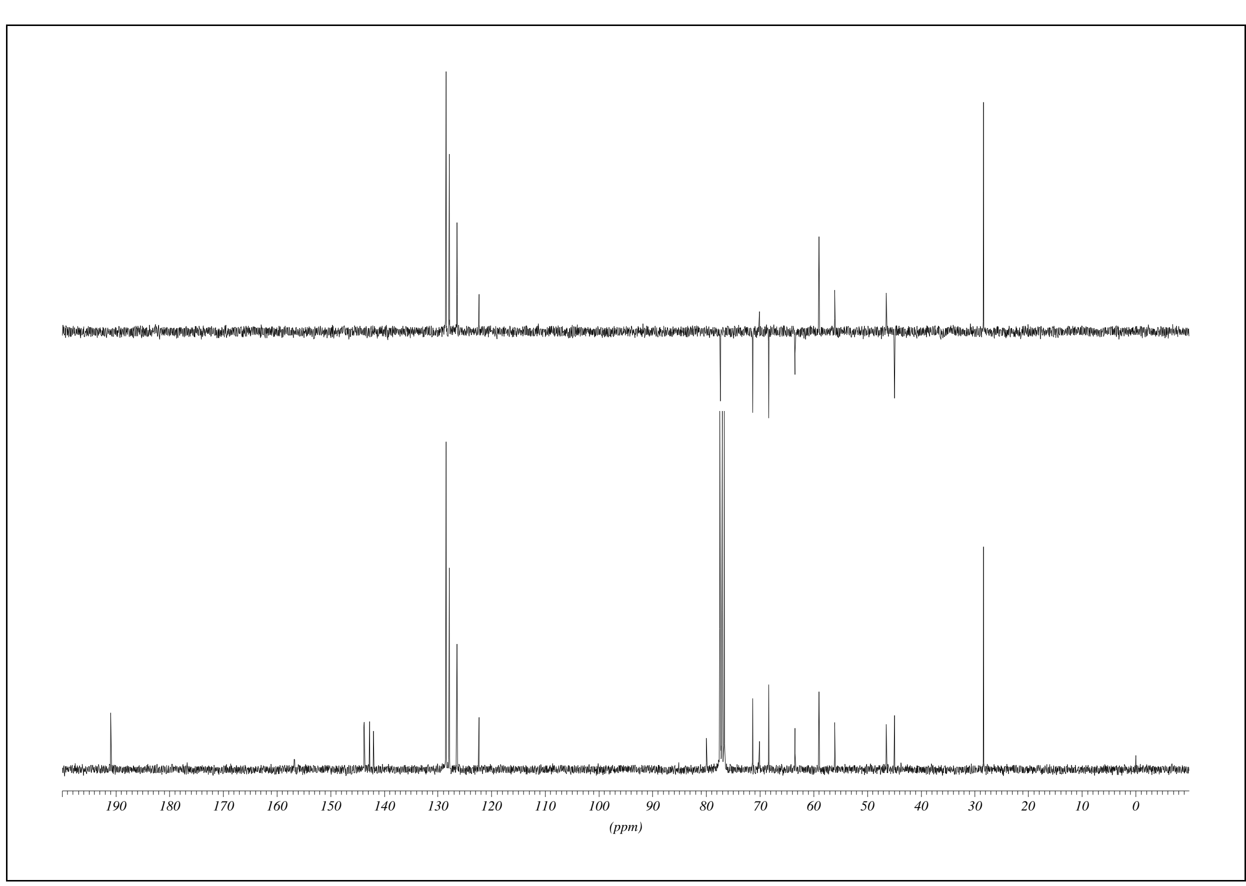
1-(1-((2-methoxyethoxy)methyl)-4-((E)-3-hydroxyprop-1-enyl)-1H-imidazol-2-yl)-3,3 diphenylpropan-1-one (182)



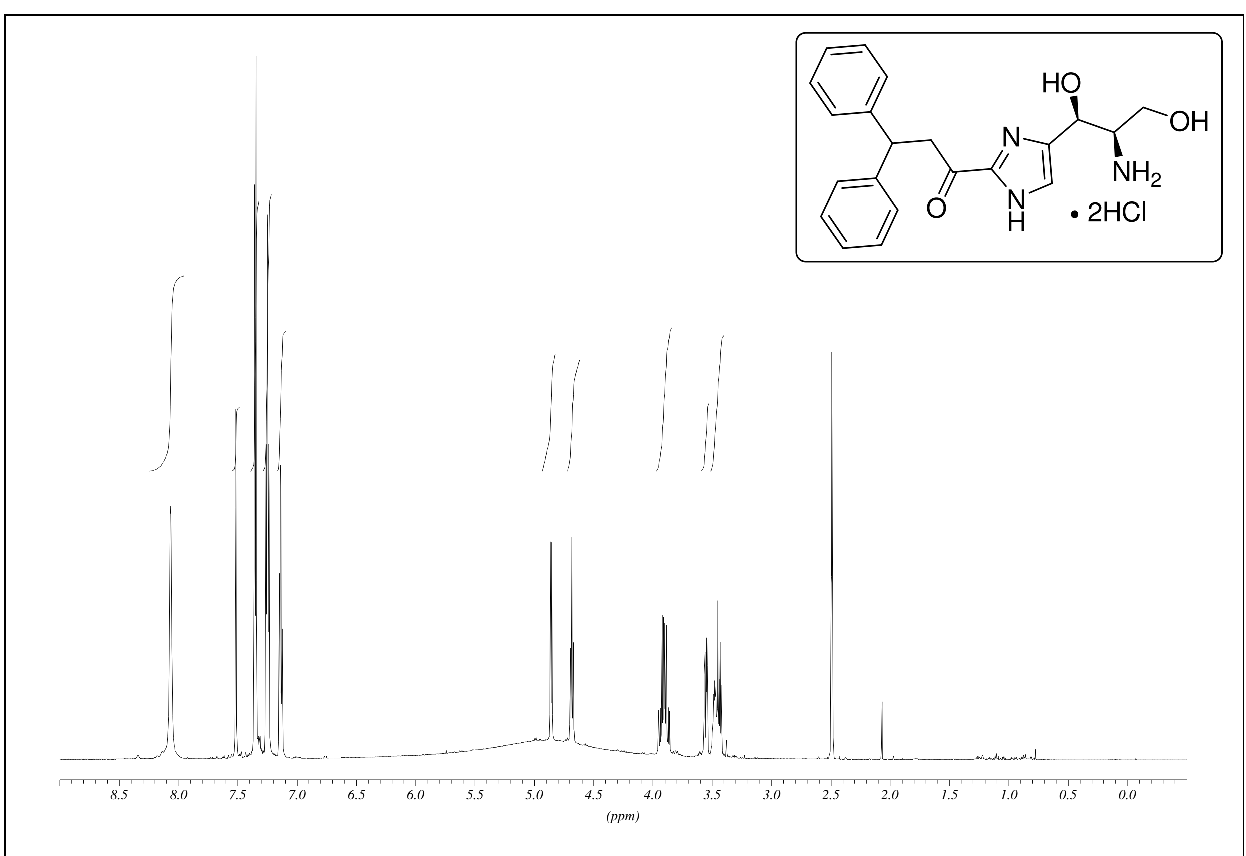


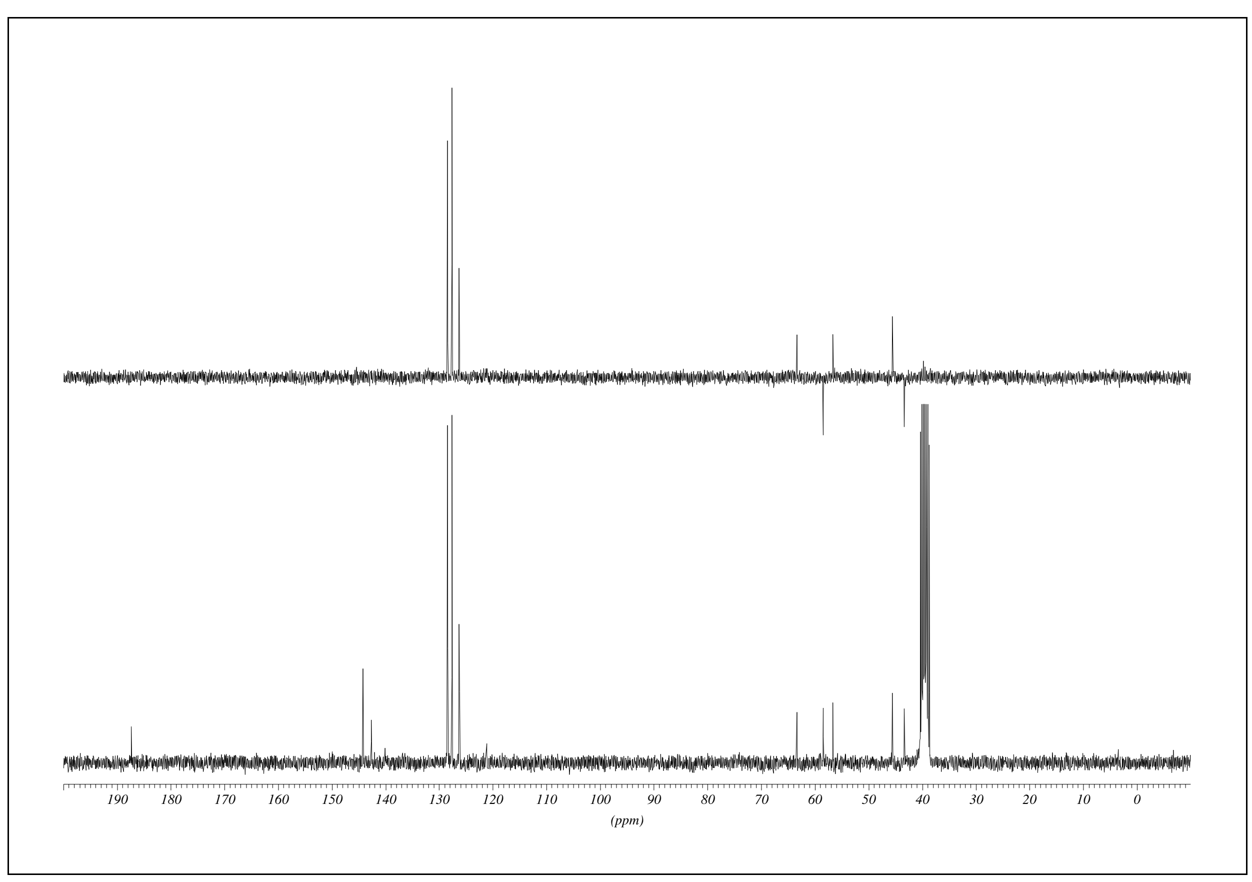
Compound (194)



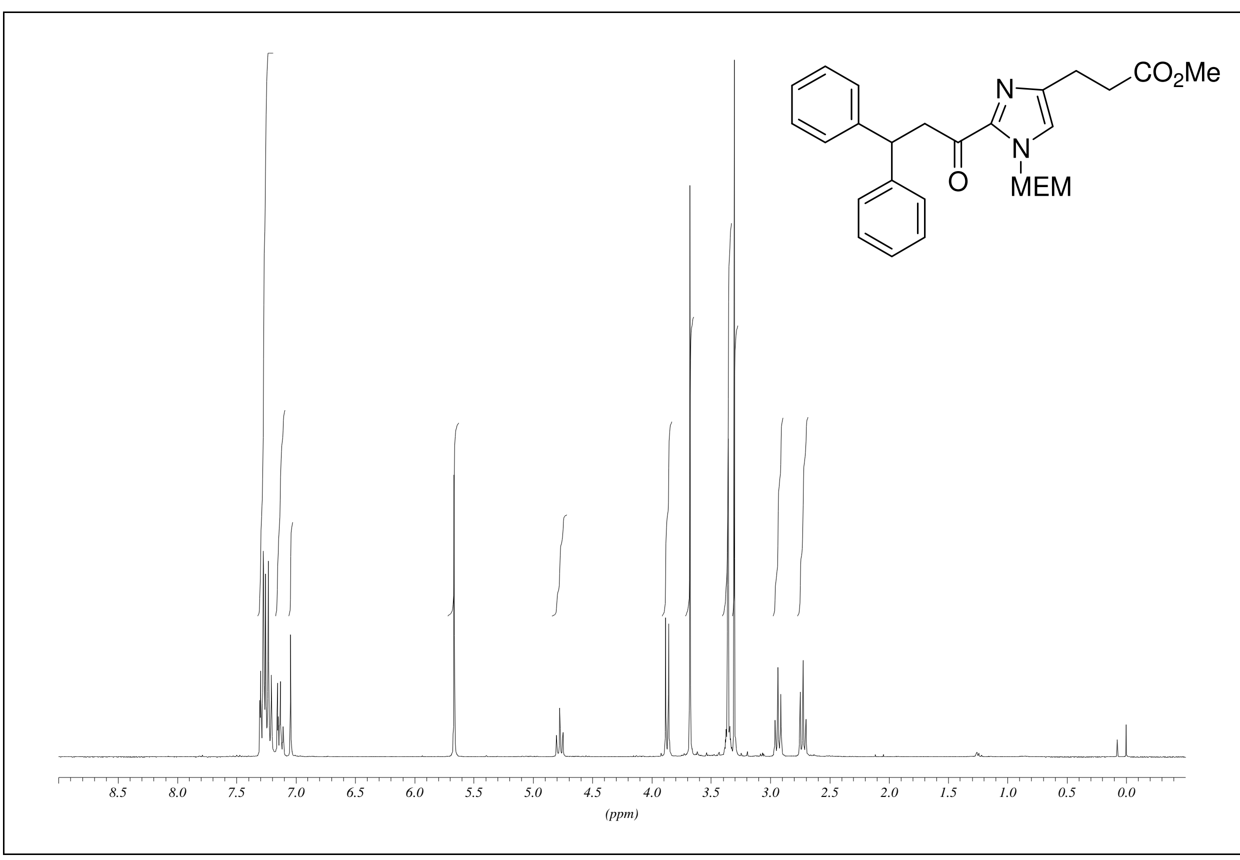


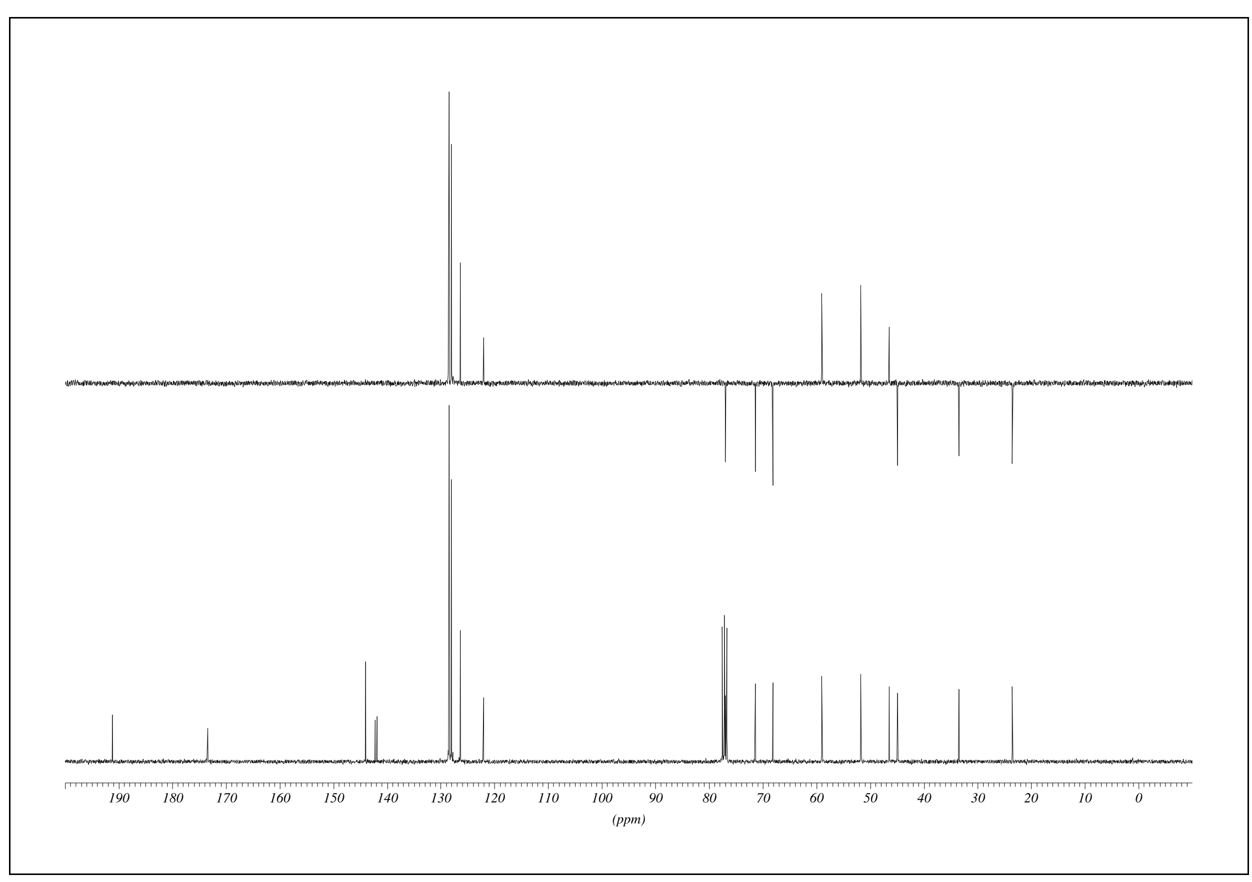
1-(4-((1*S*,2*R*)-2-amino-1,3-dihydroxypropyl)-1*H*-imidazol-2-yl)3,3-diphenylpropan-1-onedihydrochloride (196)



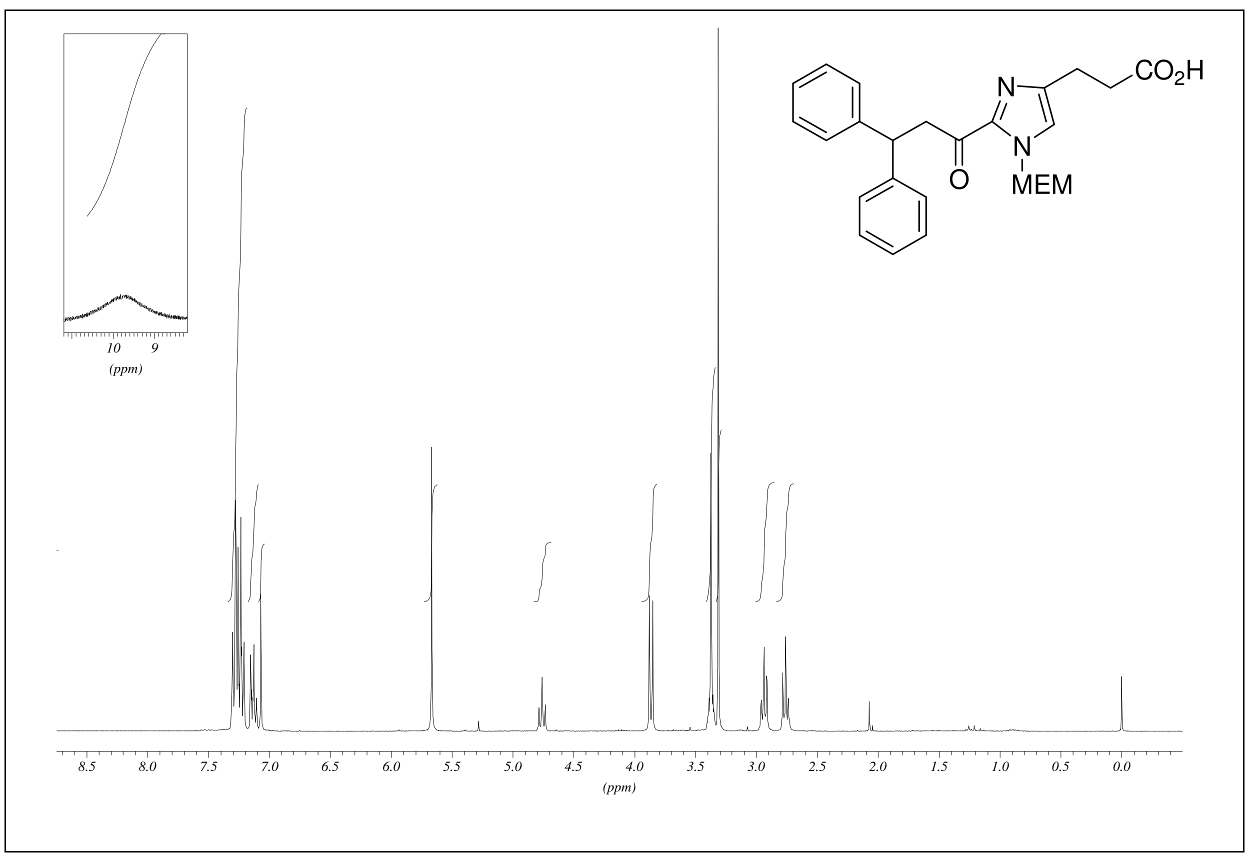


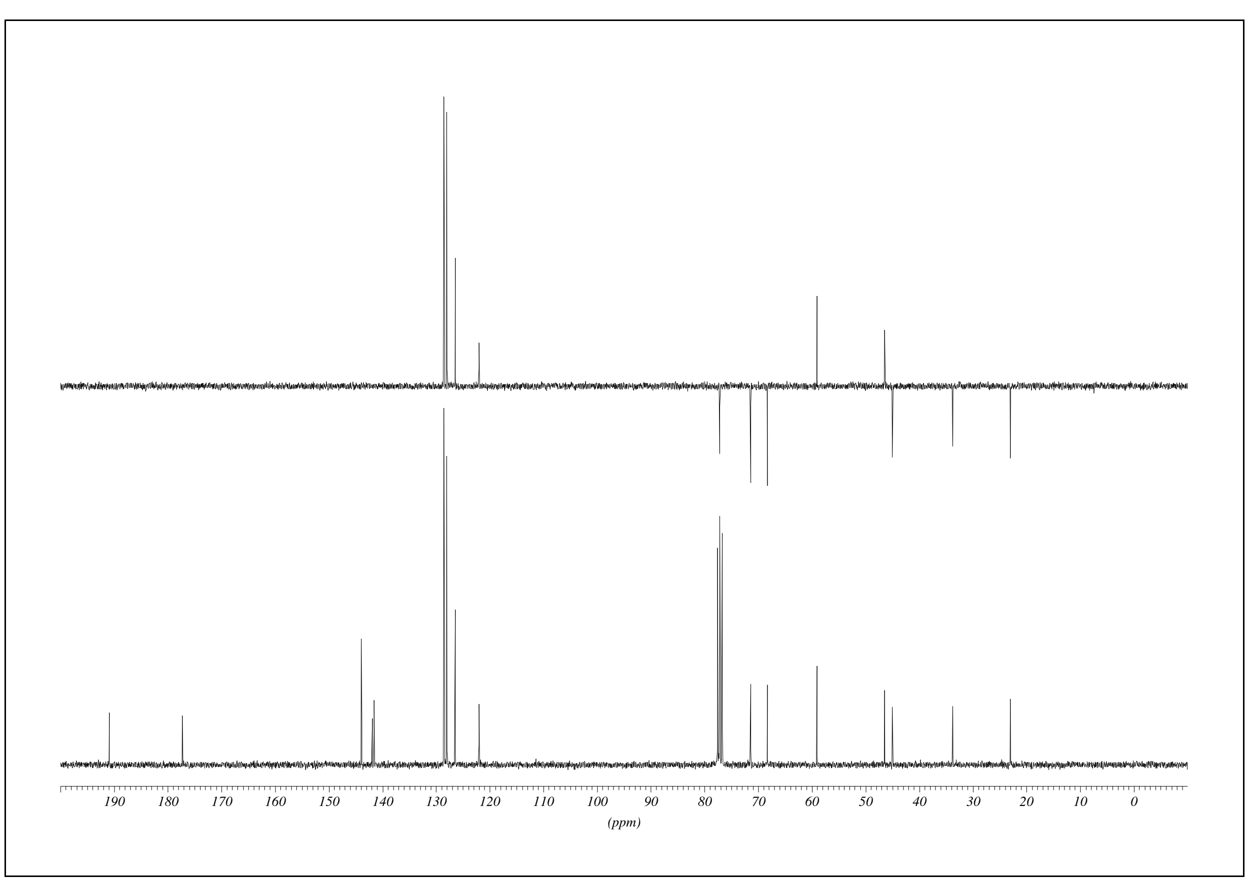
methyl3-(1-((2methoxyethoxy)methyl)-2-(3,3-diphenylpropanoyl)-1*H*-Imidazol-4 yl)propanoate (197)



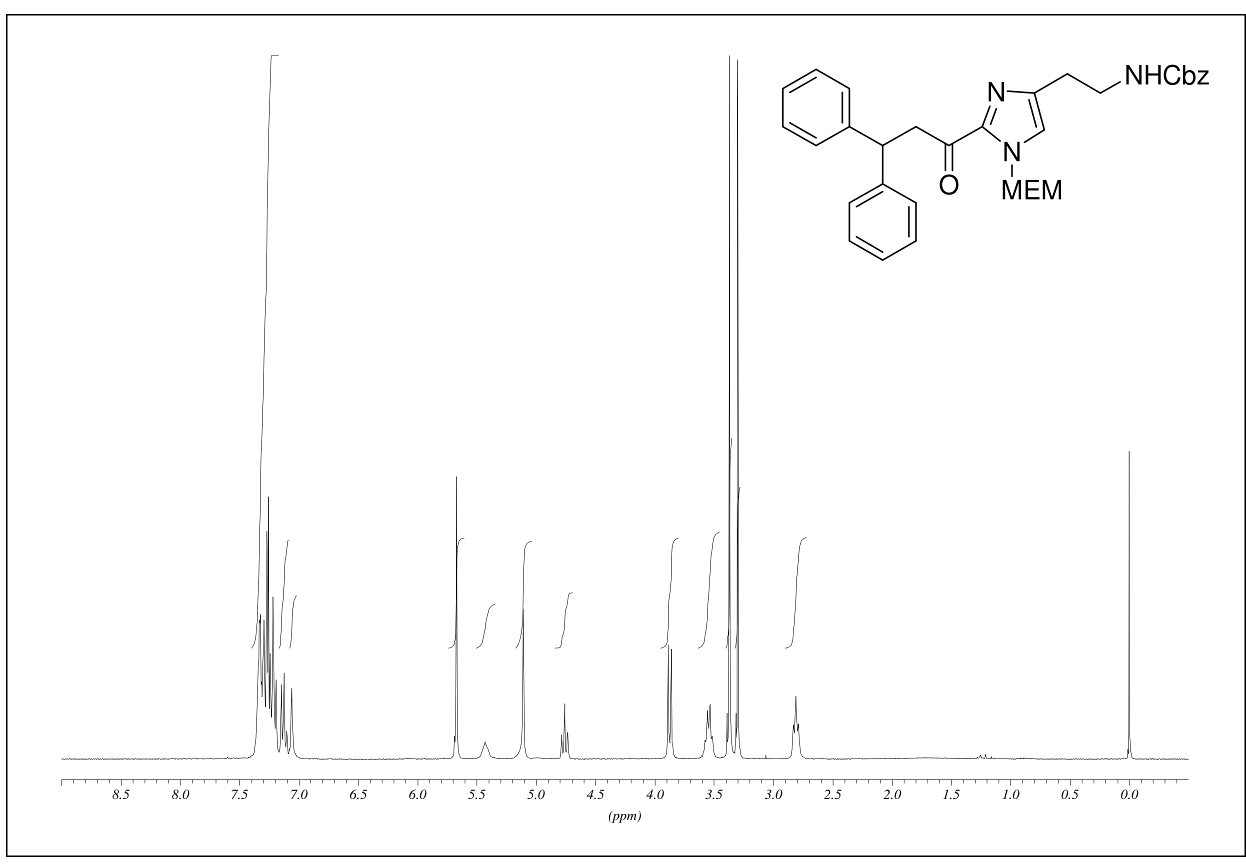


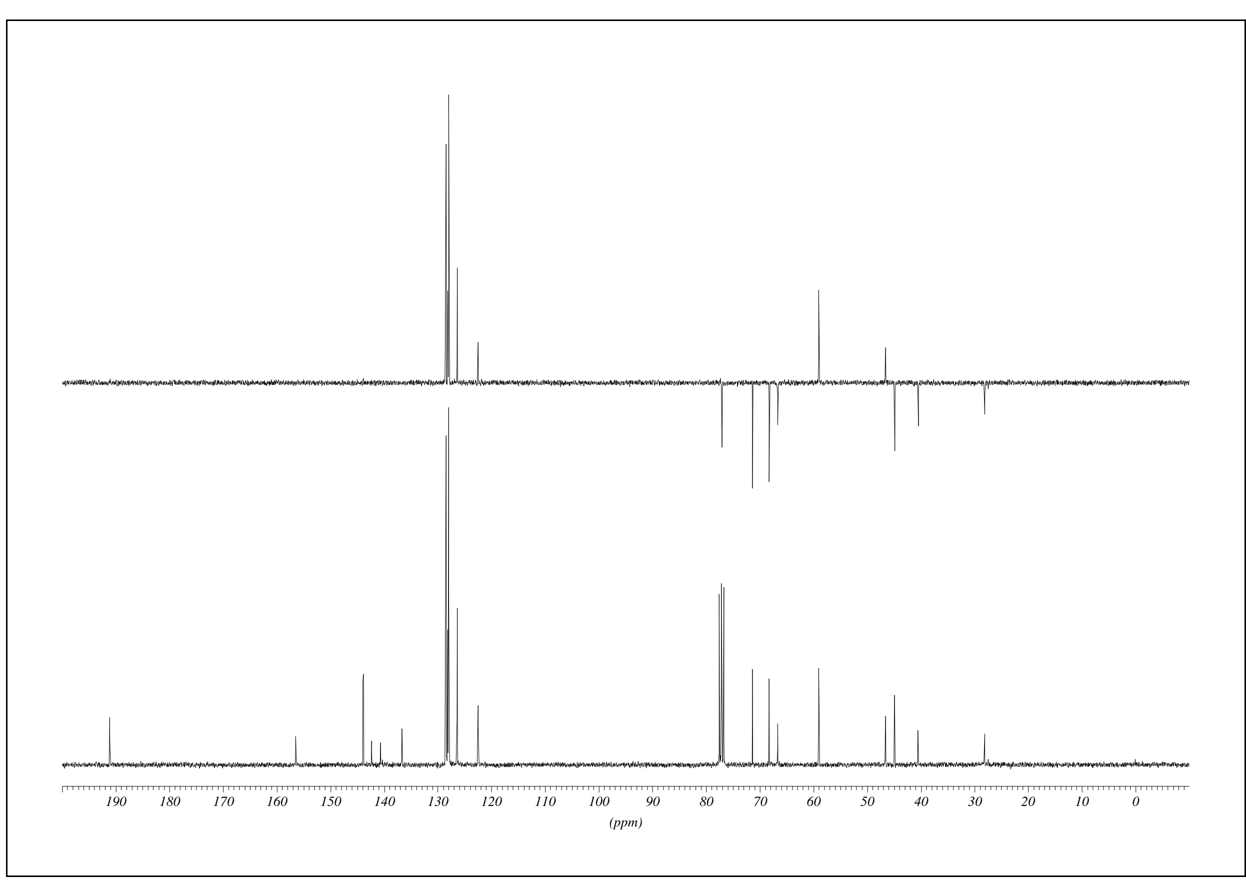
3-(1-((2methoxyethoxy)methyl)-2-(3,3-diphenylpropanoyl)-1*H*-Imidazol-4-yl)propanoicacid (198)



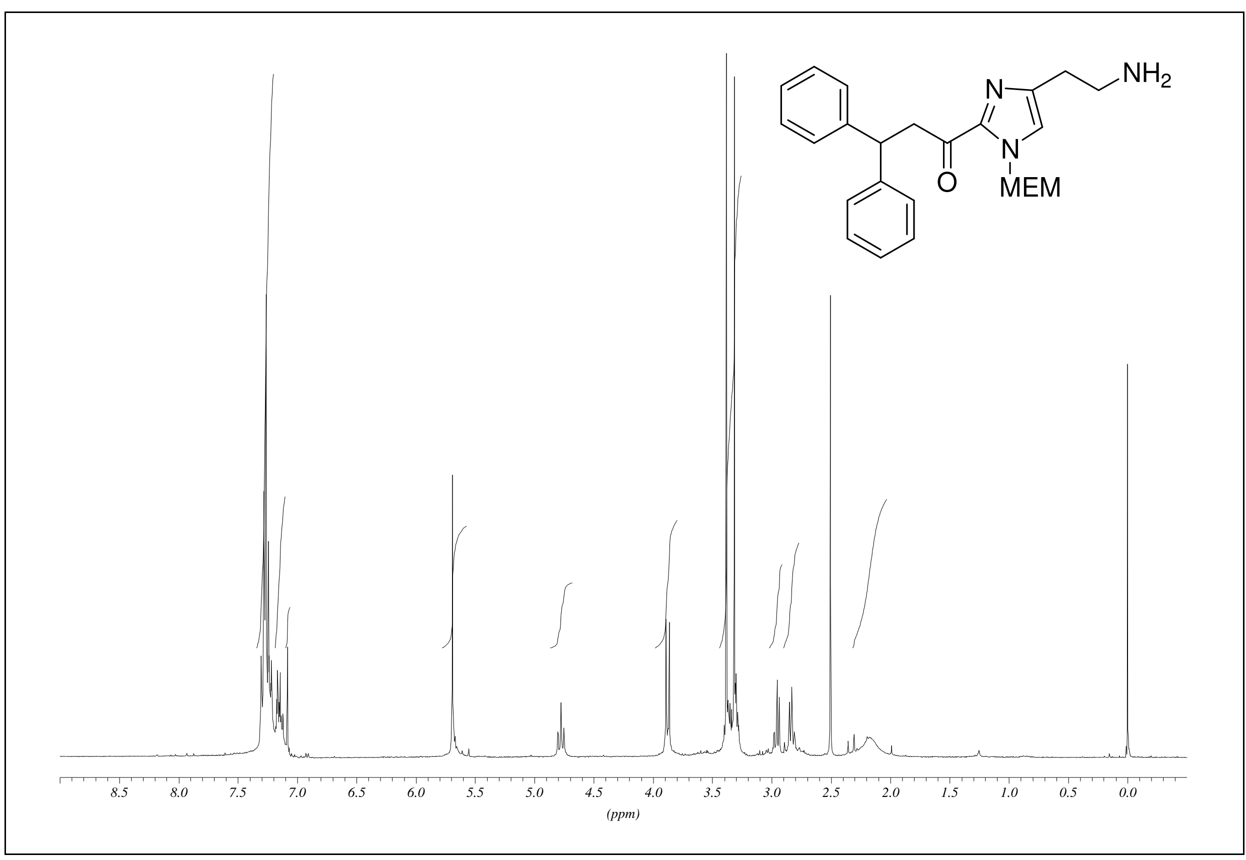


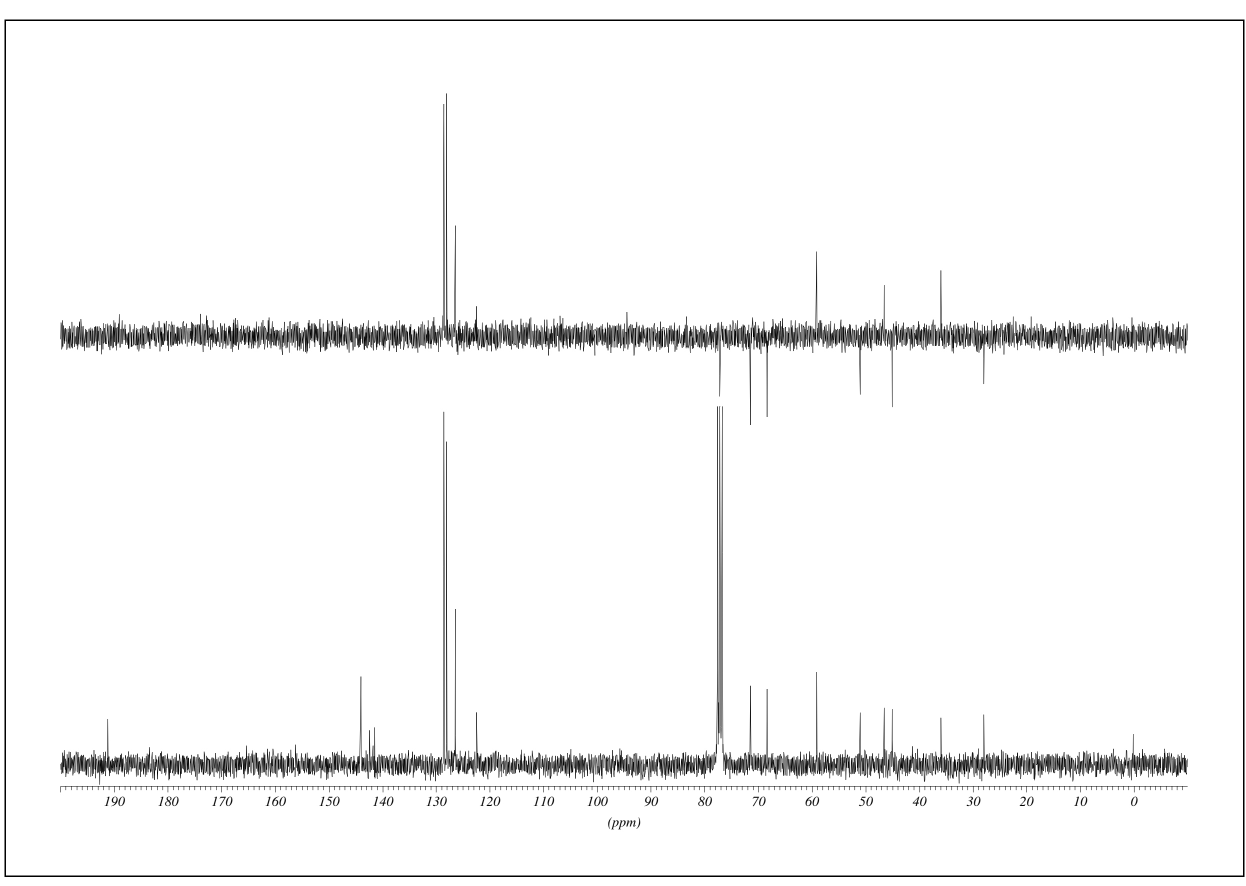
benzyl2-(1-((2methoxyethoxy)methyl)-2-(3,3-diphenylpropanoyl)-1*H*-imidazol-4-yl)ethylcarbamate (199)



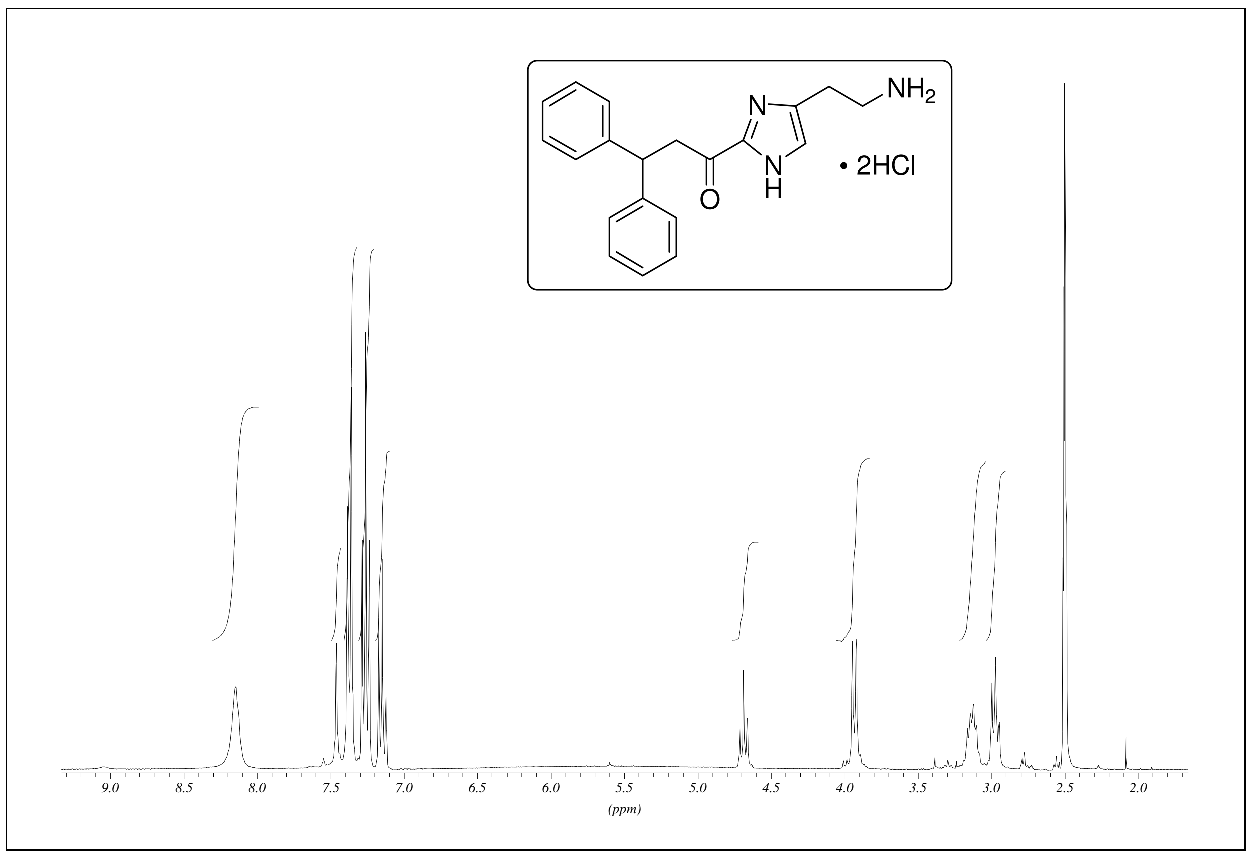


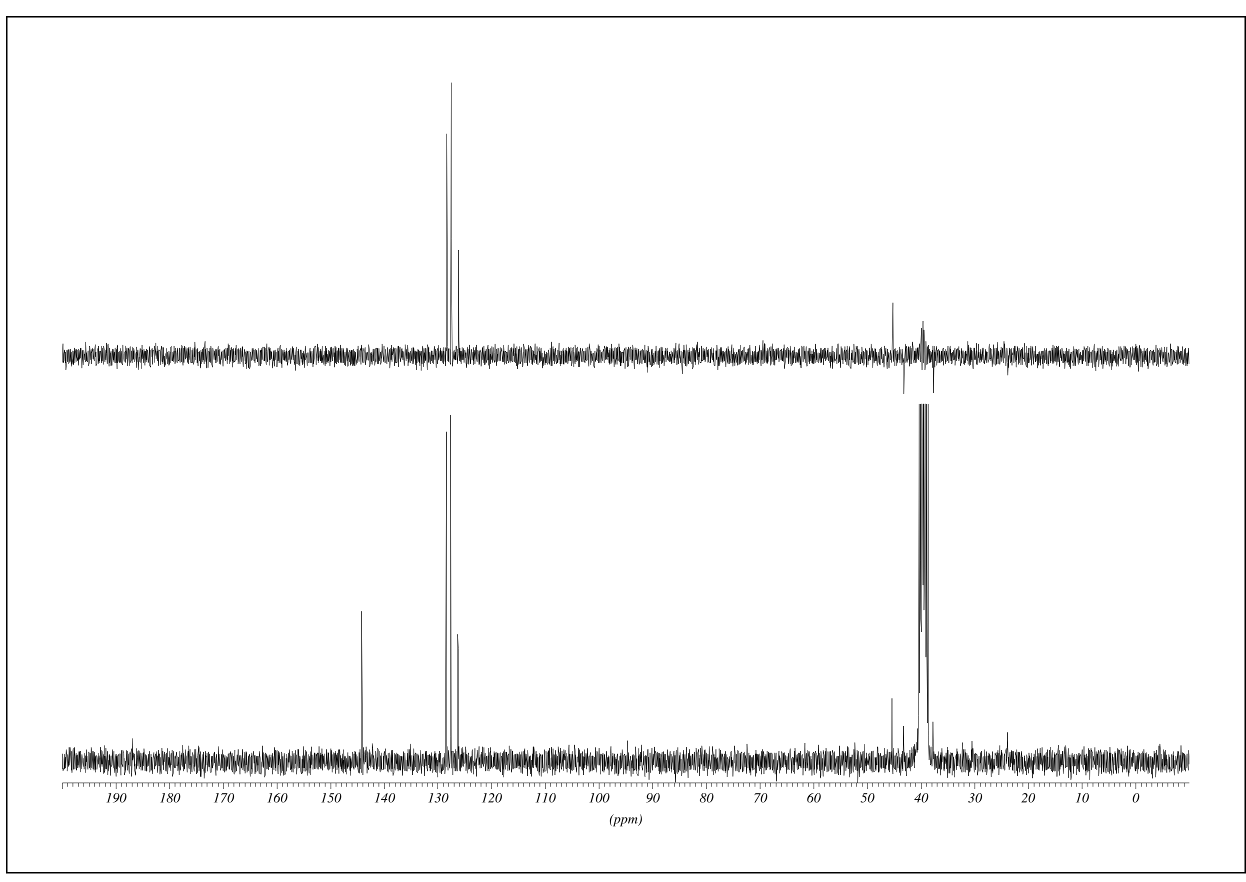
1-(1-((2methoxyethoxy)methyl)-4-(2-aminoethyl)-1*H*-Imidazolyl)-3,3-diphenylpropan-1-one (200)



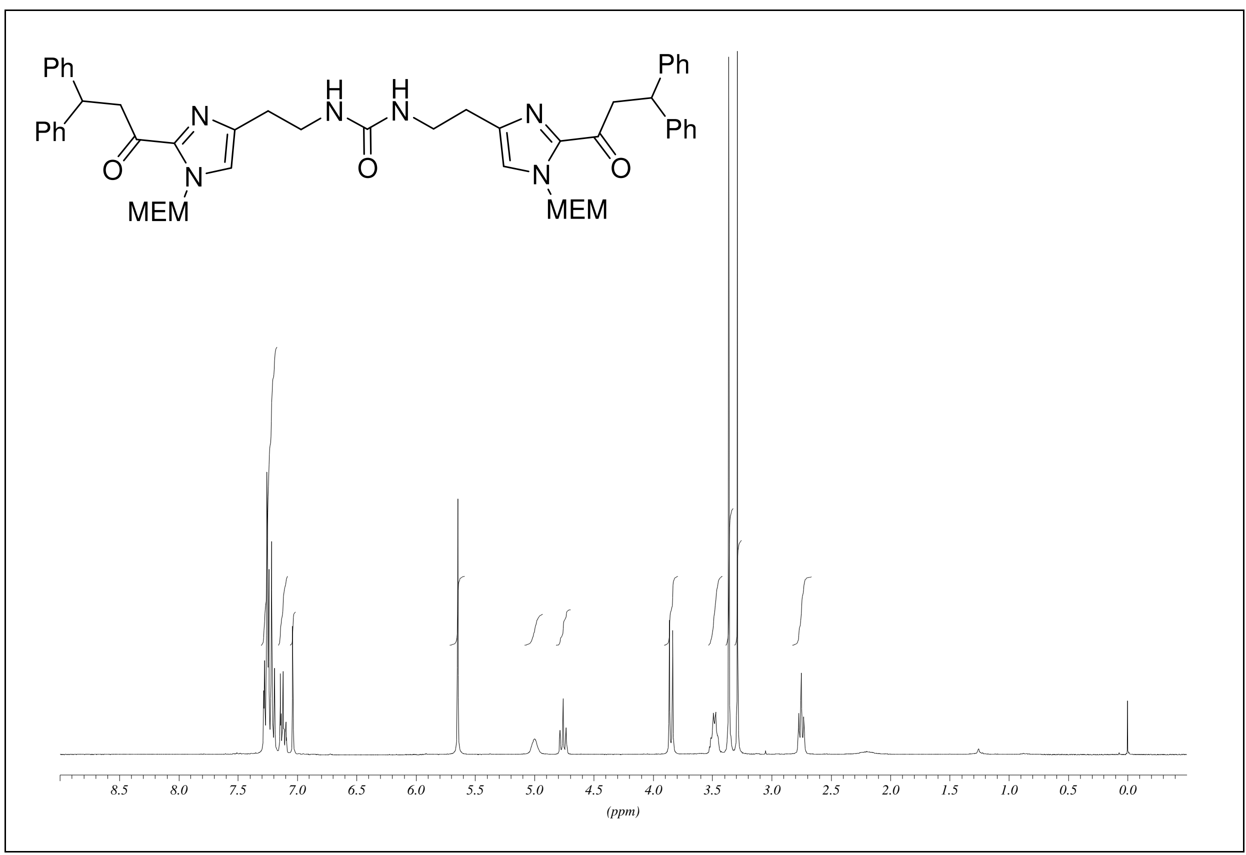


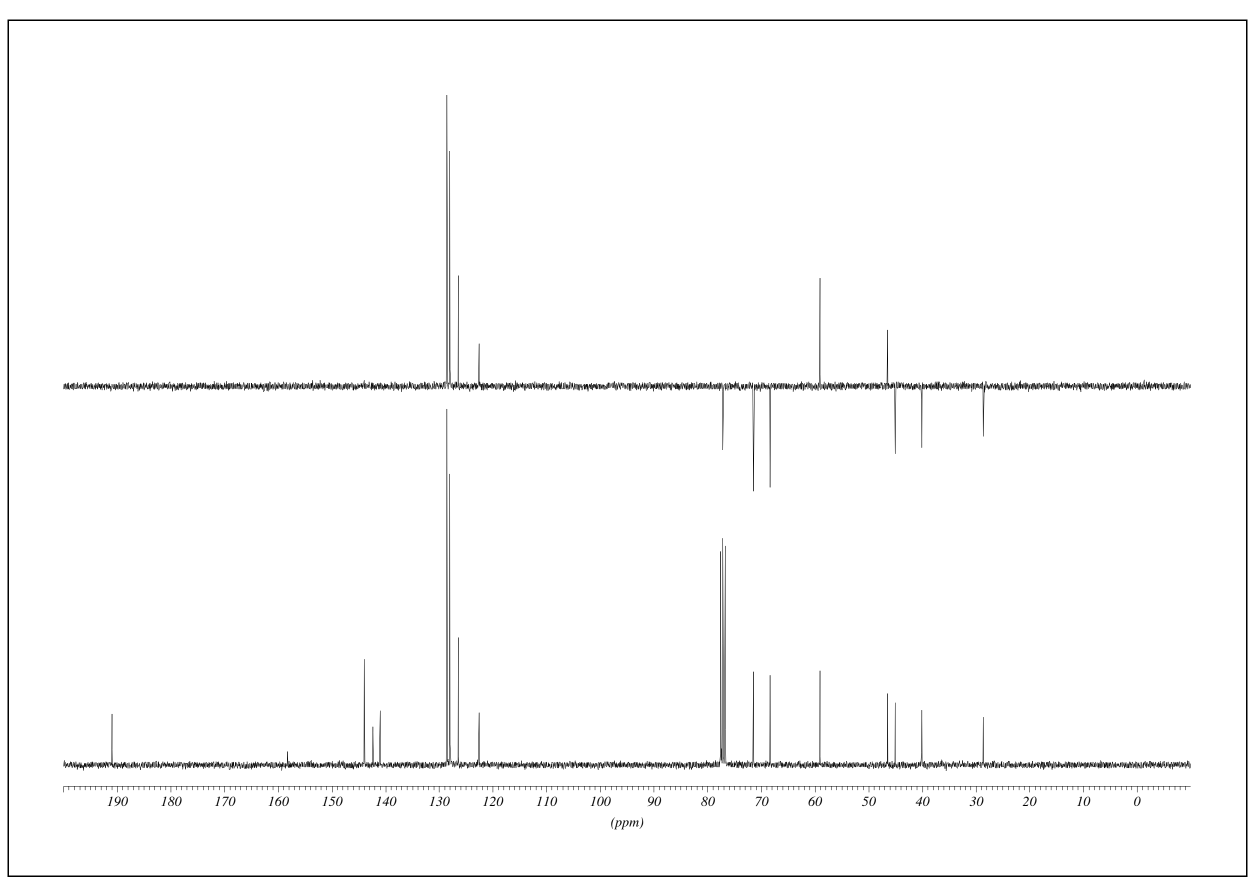
1-(4-(2-aminoethyl)-1*H*-Imidazolyl)-3,3-diphenylpropan-1-onedihydrochloride (201)



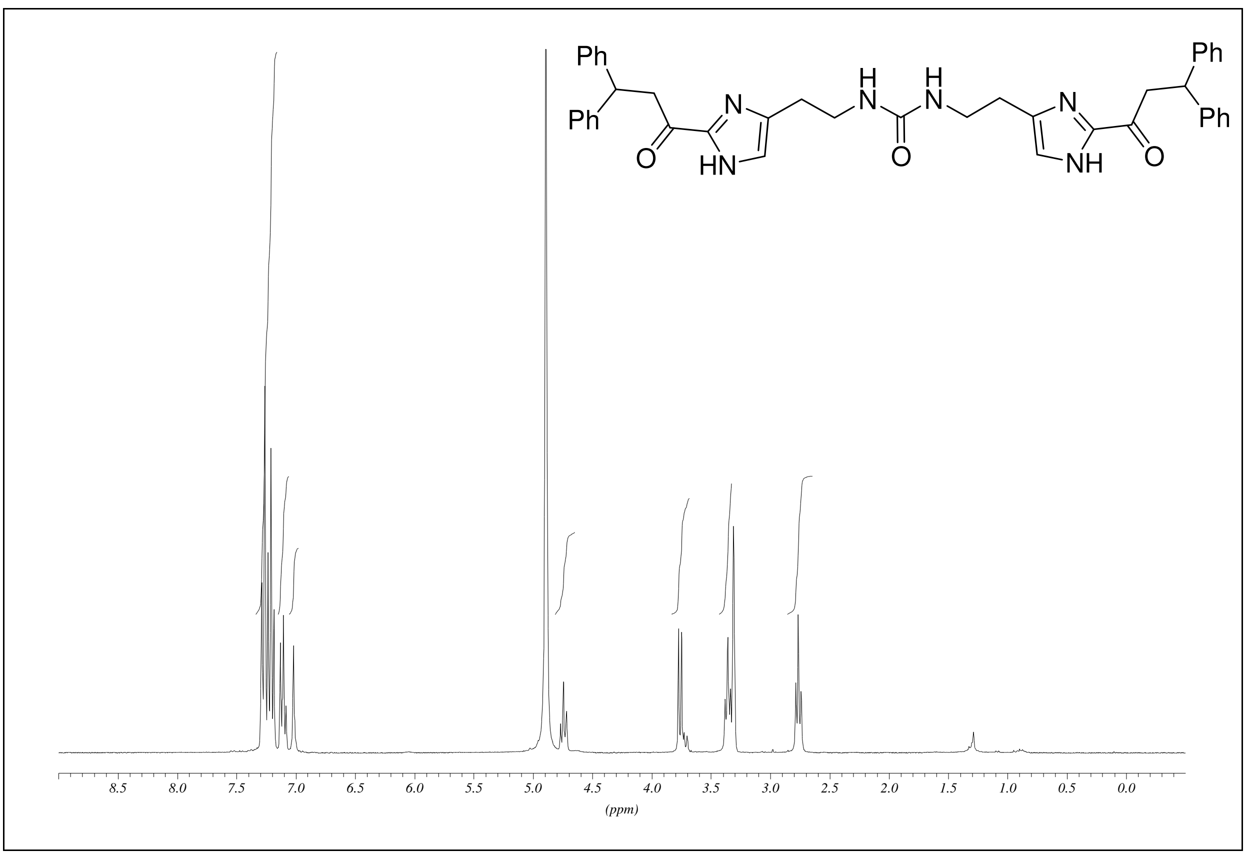


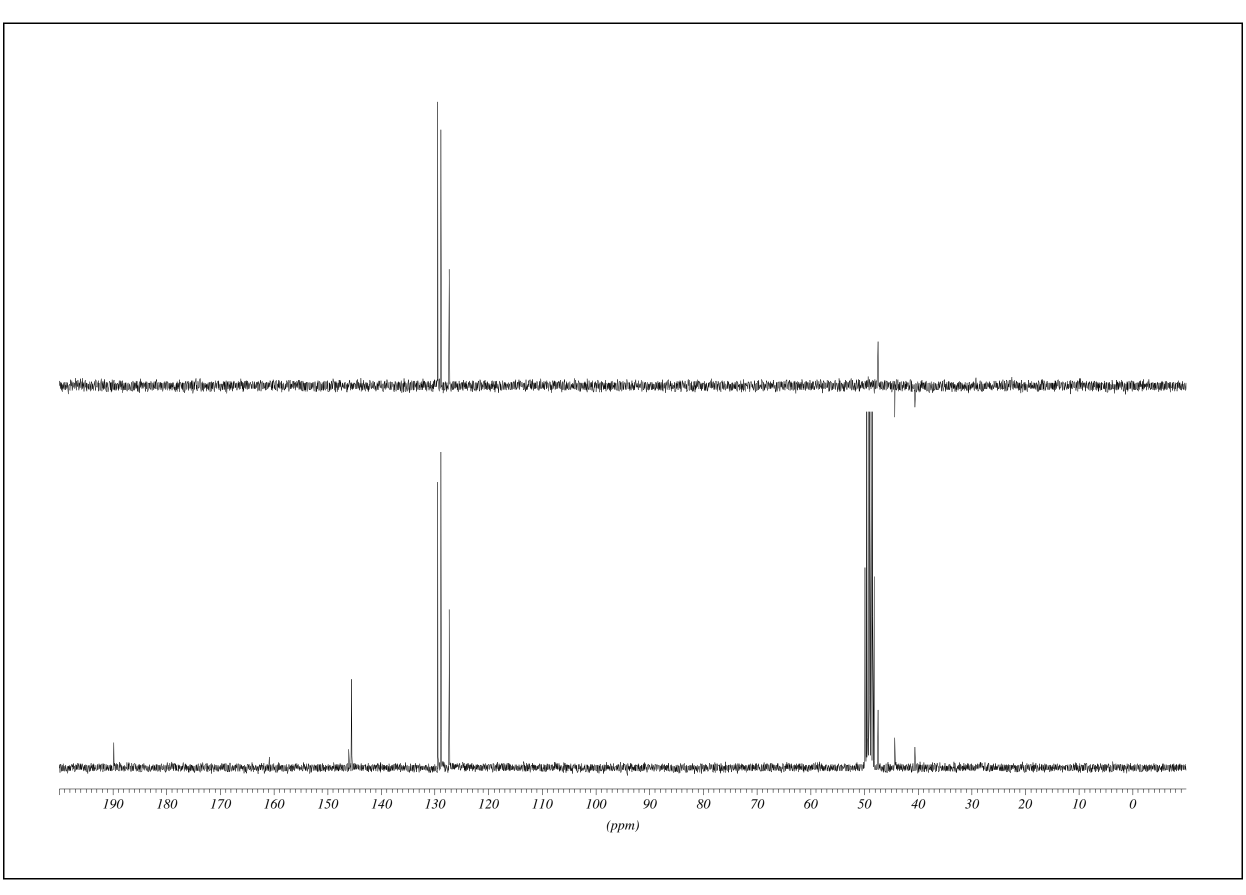
1,3-bis(2-(1-((2methoxyethoxy)methyl)-2-(3,3-diphenylpropanoyl)-1*H*-imidazol-4-yl)ethyl)urea (203)



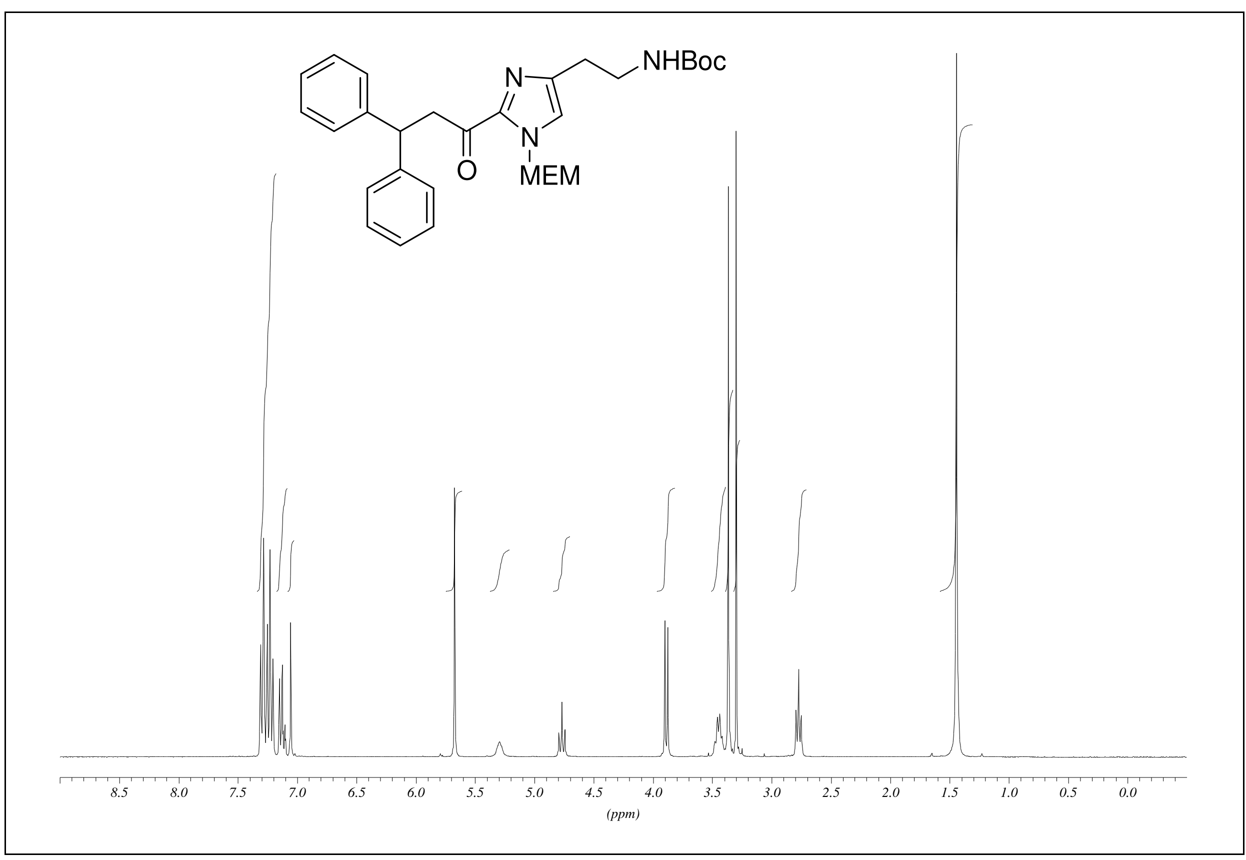


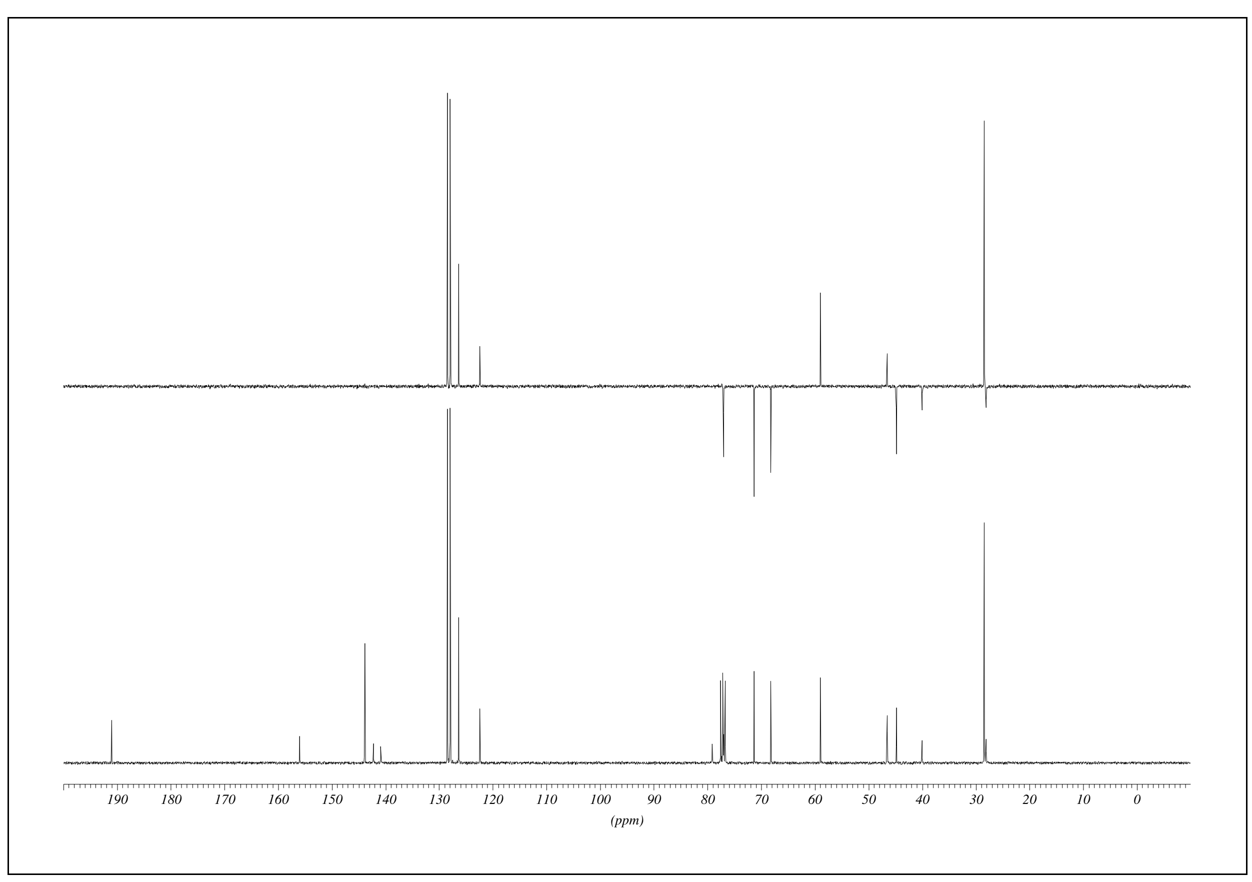
1,3-bis(2-(2-(3,3-diphenylpropanoyl)-1*H*-imidazol-4-yl)ethyl)urea (204)



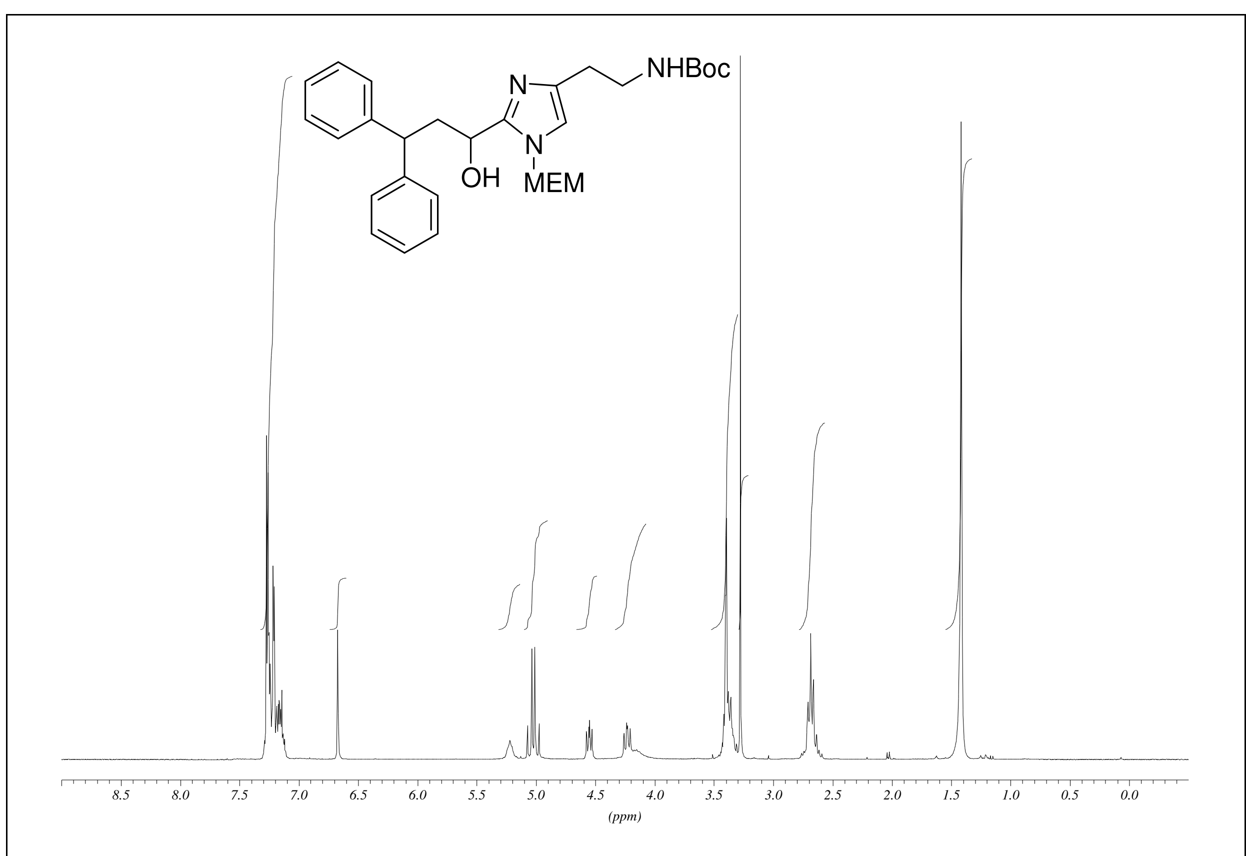


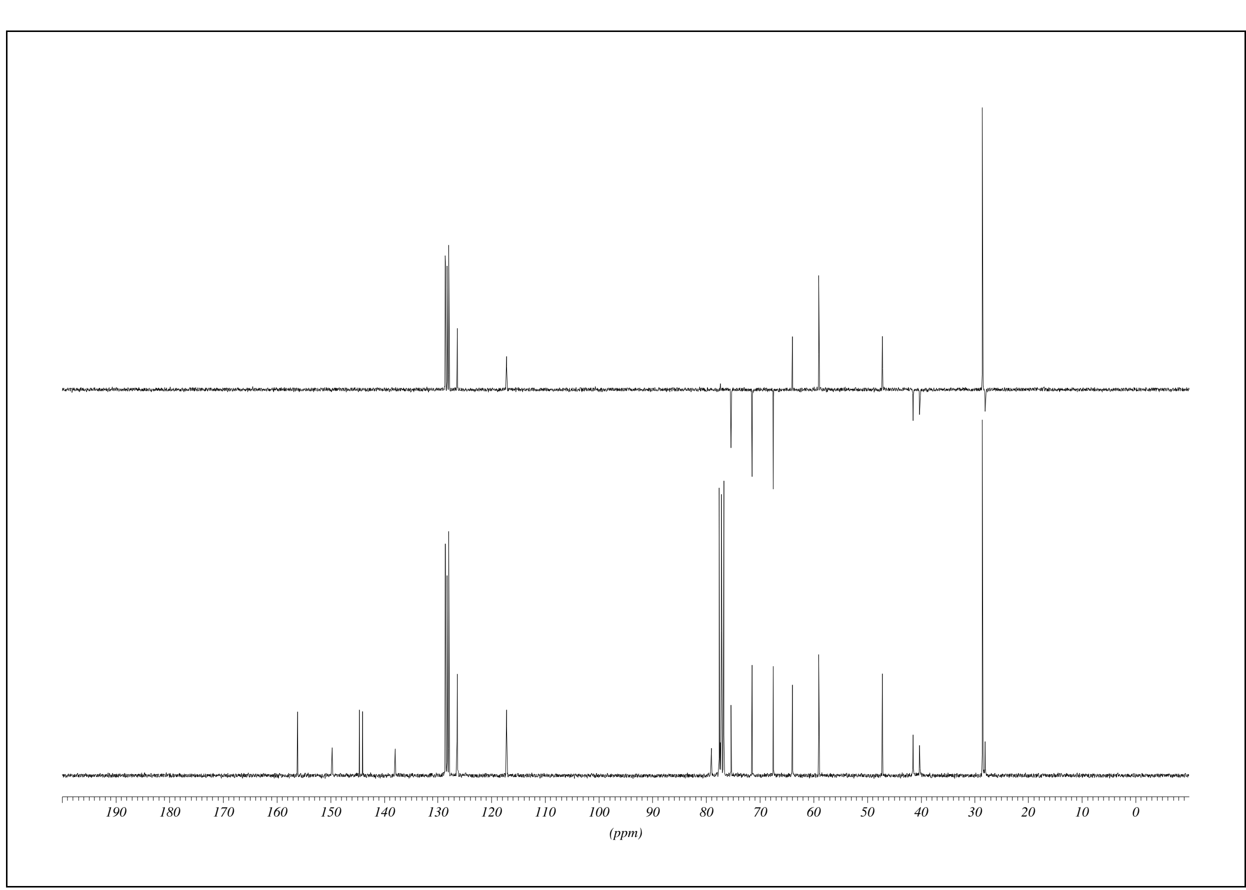
tert-butyl 2-(1-((2-methoxyethoxy)methyl)-2-(3,3-diphenylpropanoyl)-1H-imidazol-4-yl)ethylcarbamate (212)



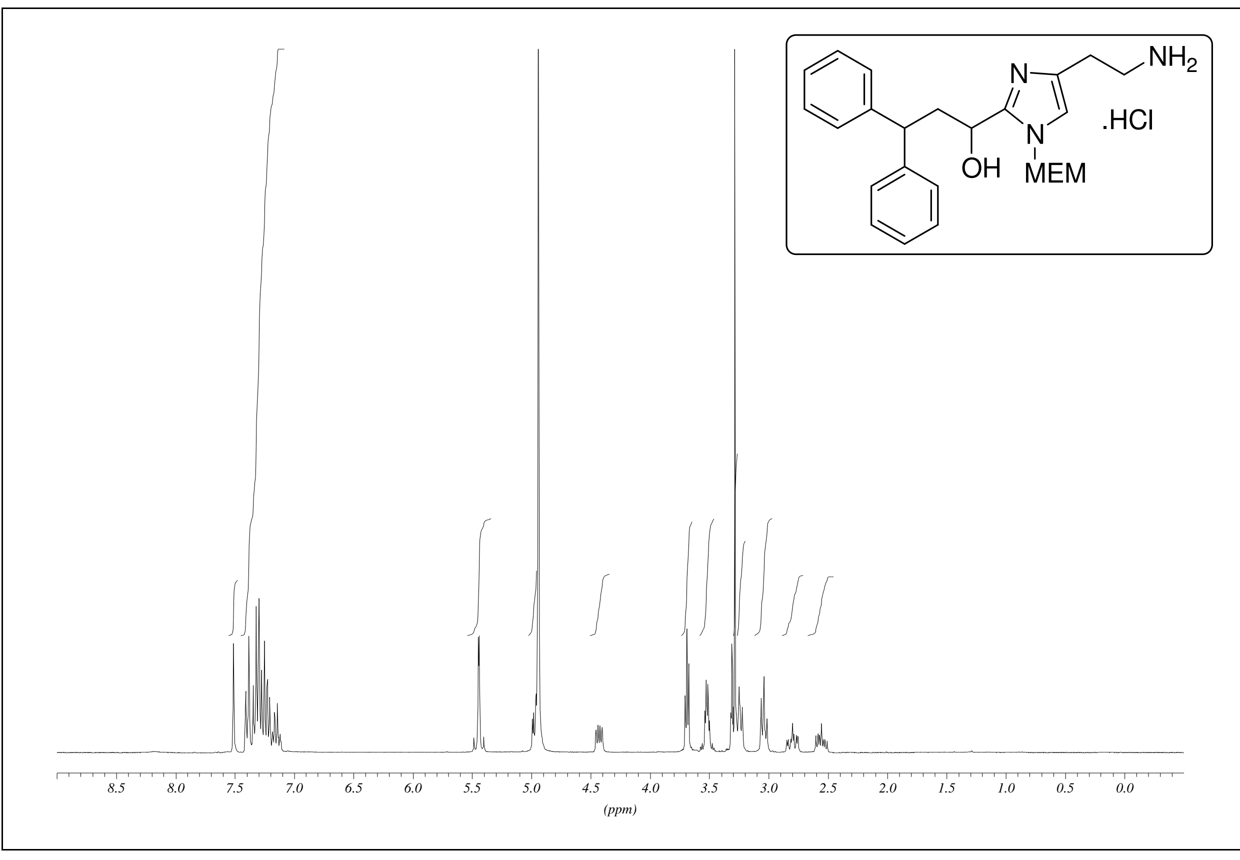


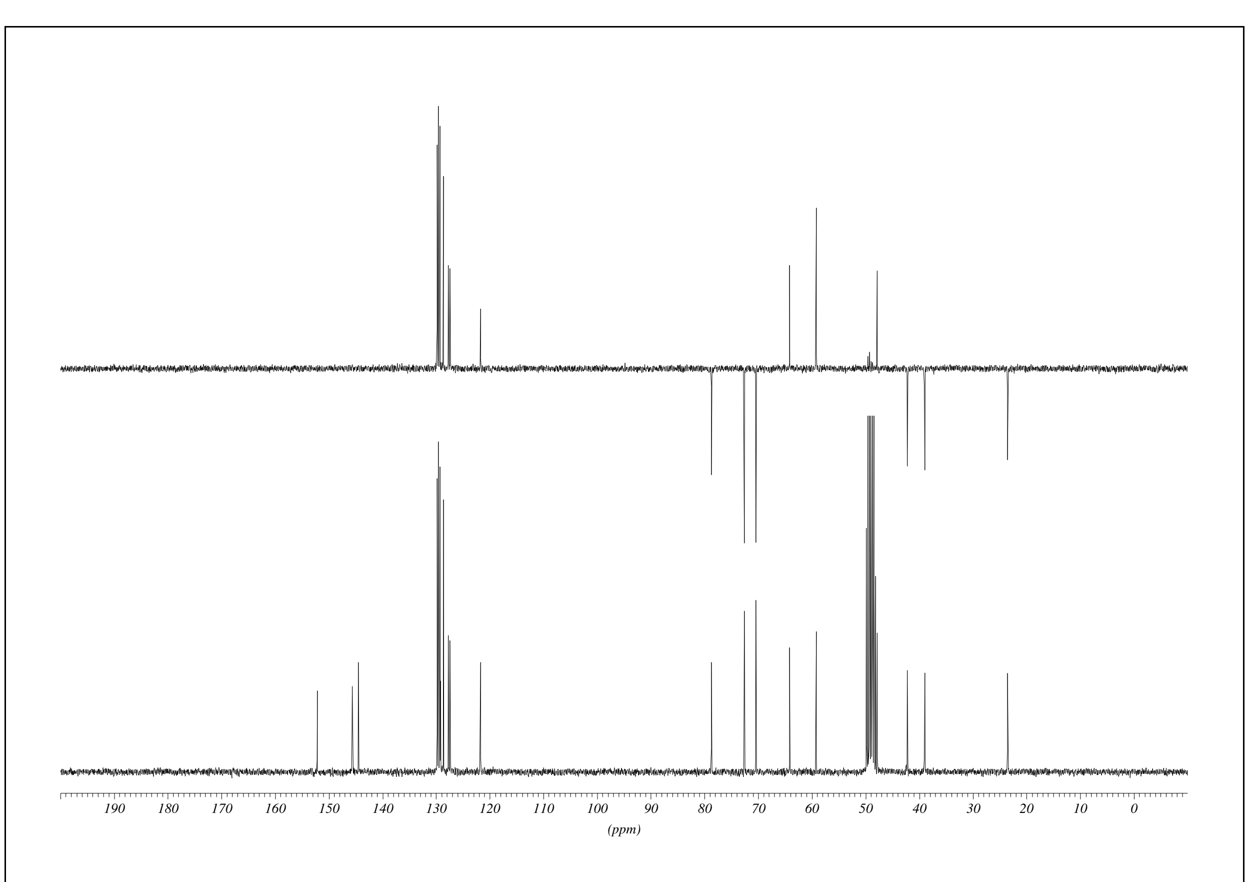
tert-butyl 2-(1-((2-methoxyethoxy)methyl)-2-(1-hydroxy-3,3-diphenylpropyl)-1H-imidazol-4-yl)ethylcarbamate (217)



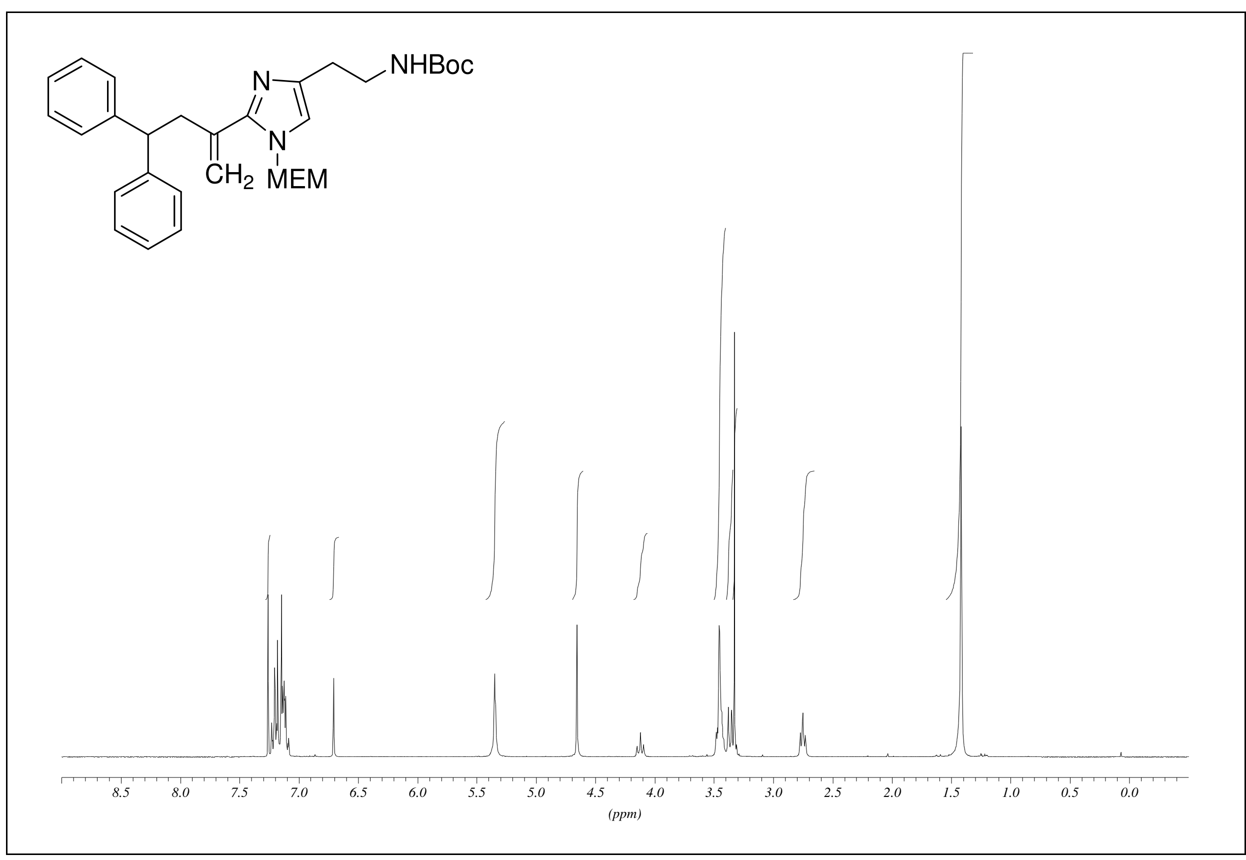


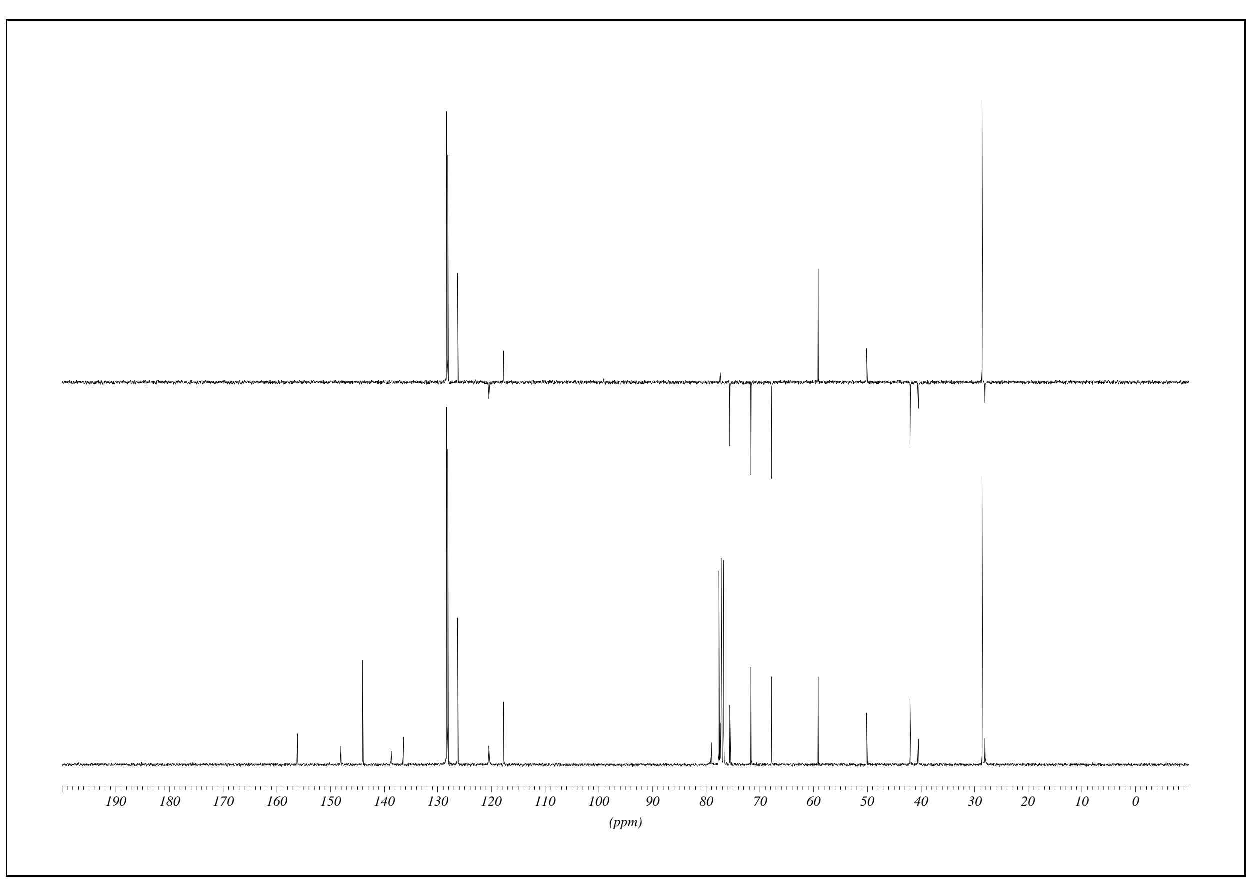
1-(1-((2-methoxyethoxy)methyl)-4-(2-aminoethyl)-1H-imidazol-2-yl)-3,3-diphenylpropan-1-ol hydrochloride (218)



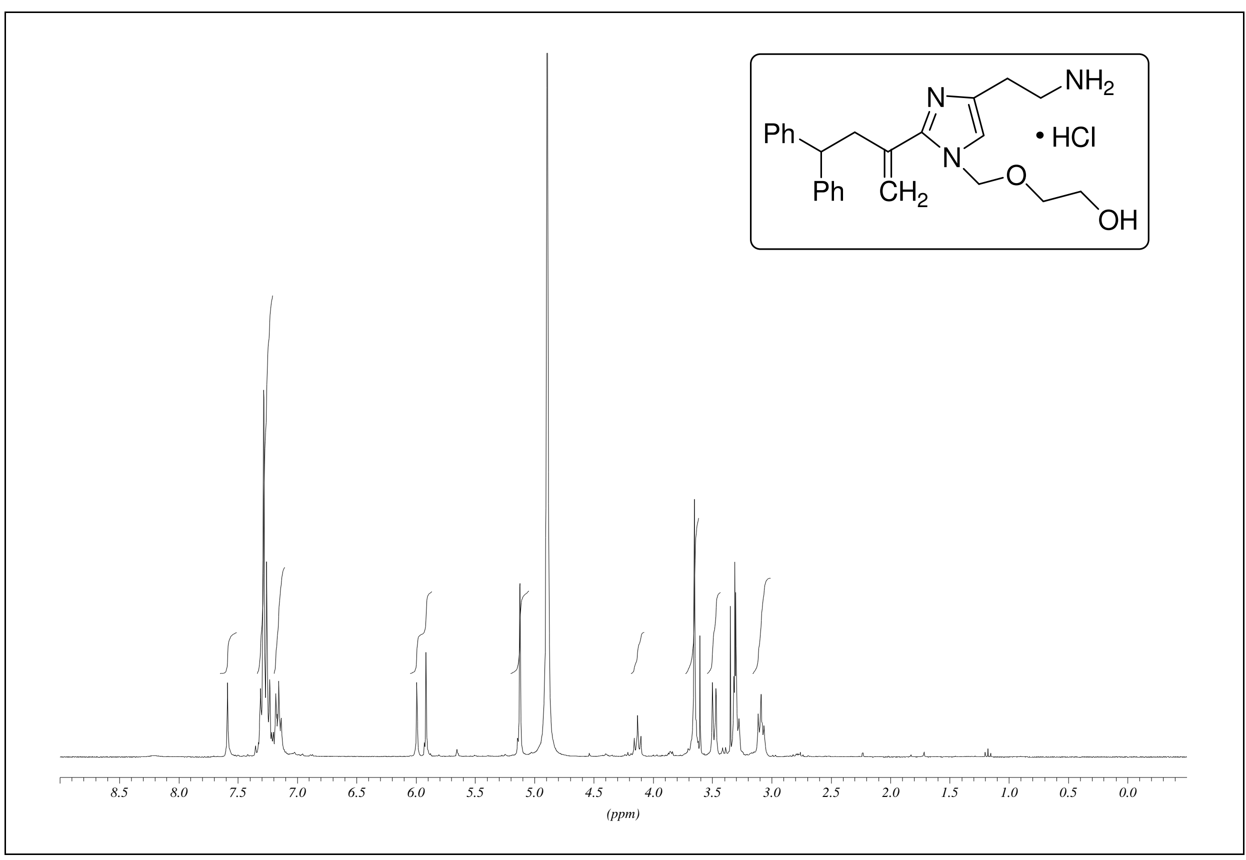


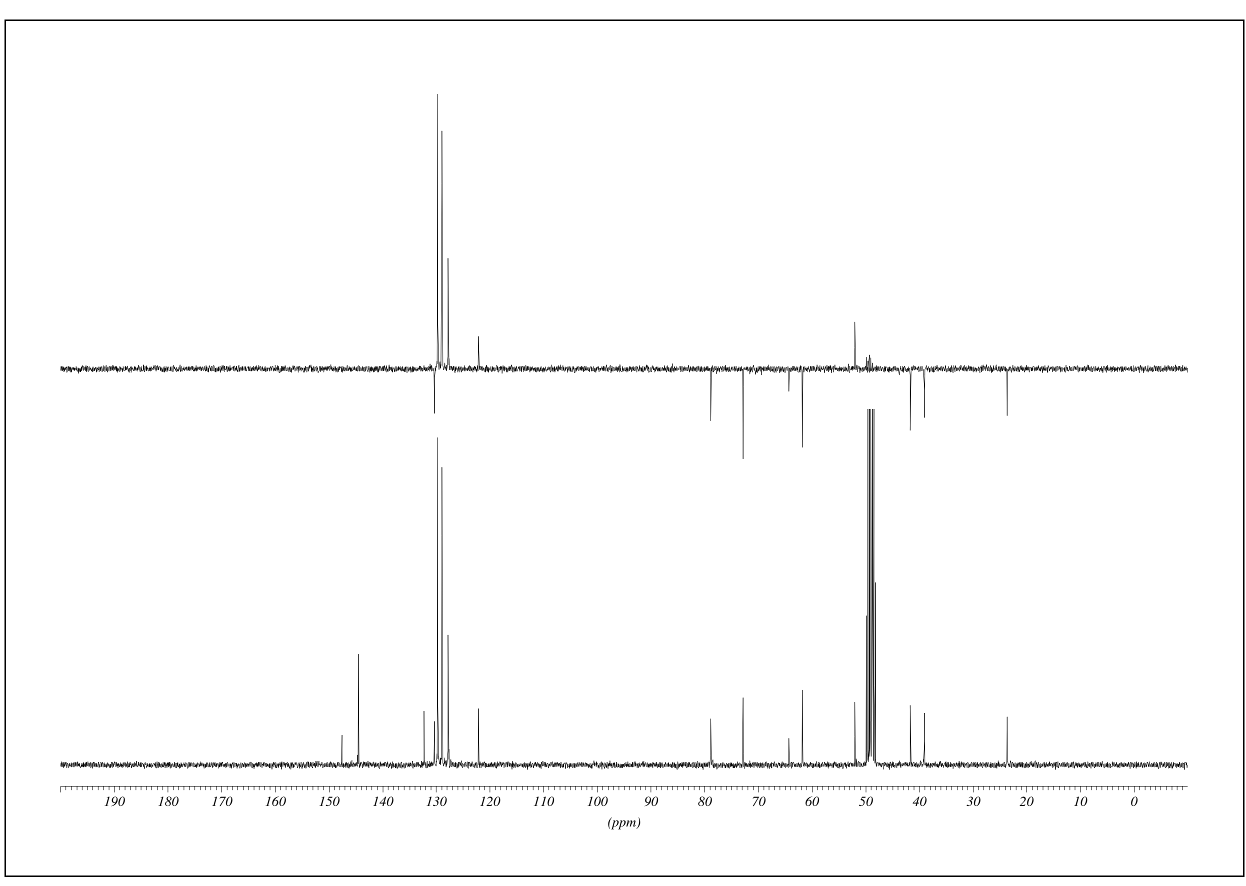
tert-butyl 2-(1-((2-methoxyethoxy)methyl)-2-(4,4-diphenylbut-1-en-2-yl)-1H-imidazol-4-yl)ethylcarbamate (213)



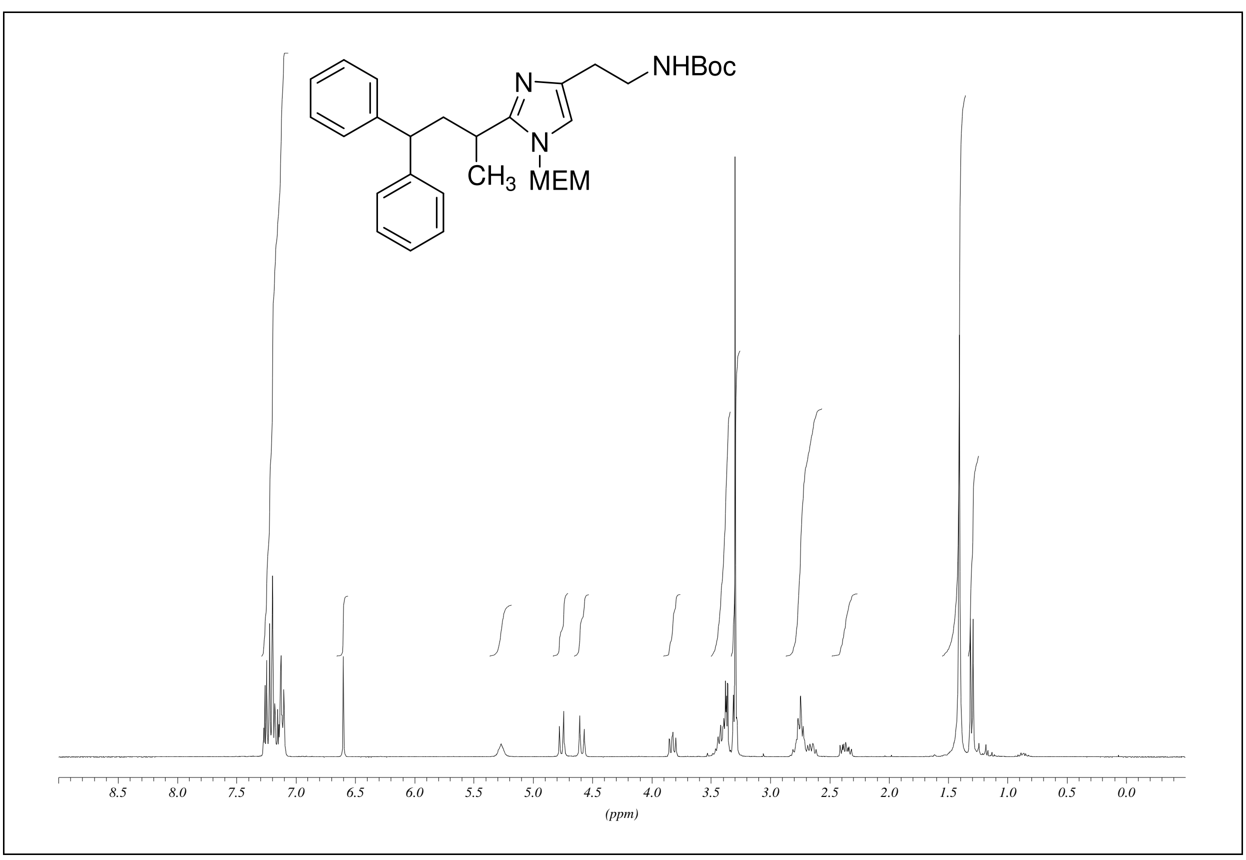


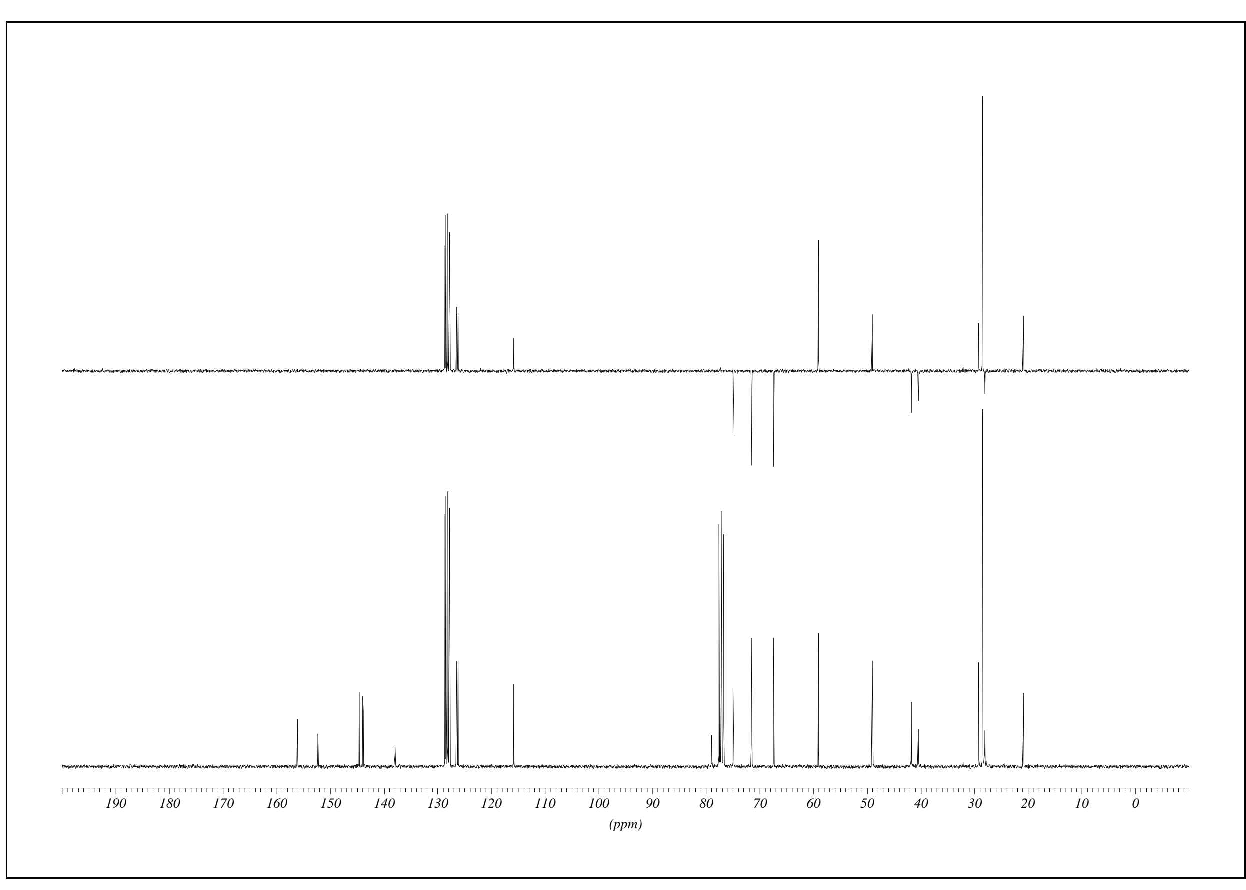
2-((4-(2-aminoethyl)-2-(4,4-diphenylbut-1-en-2-yl)-1H-imidazol-1-yl)methoxy)ethanol hydrochloride (215))



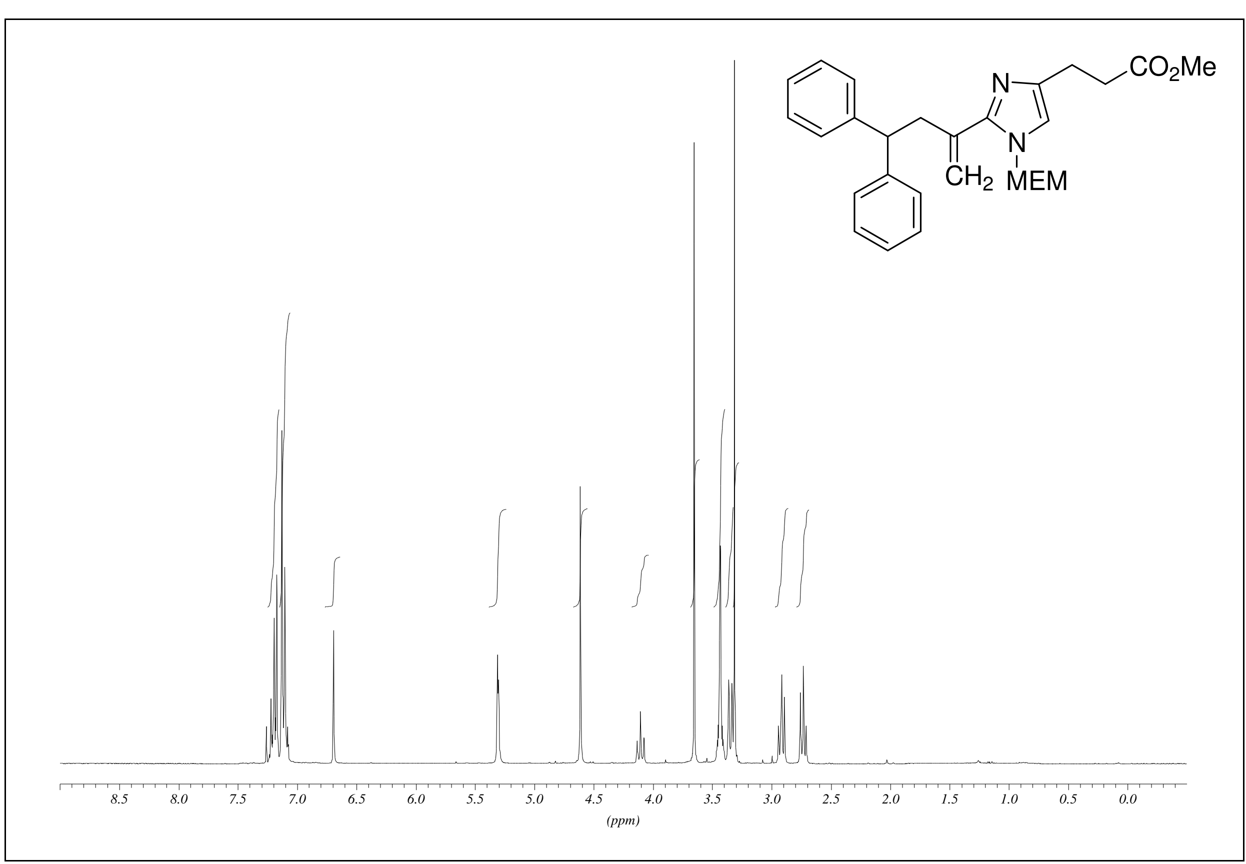


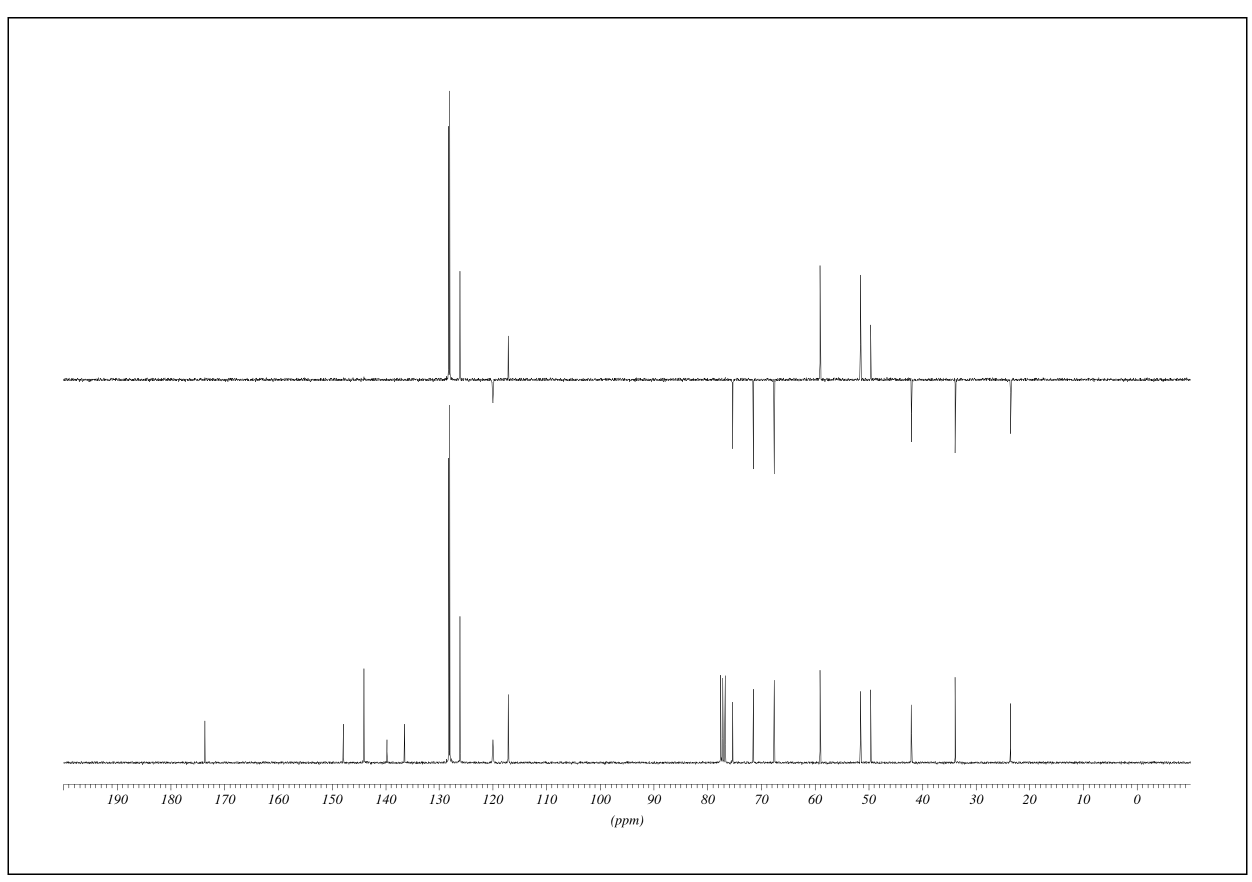
tert-butyl 2-(1-((2-methoxyethoxy)methyl)-2-(4,4-diphenylbutan-2-yl)-1H-imidazol-4-yl)ethylcarbamate (214)



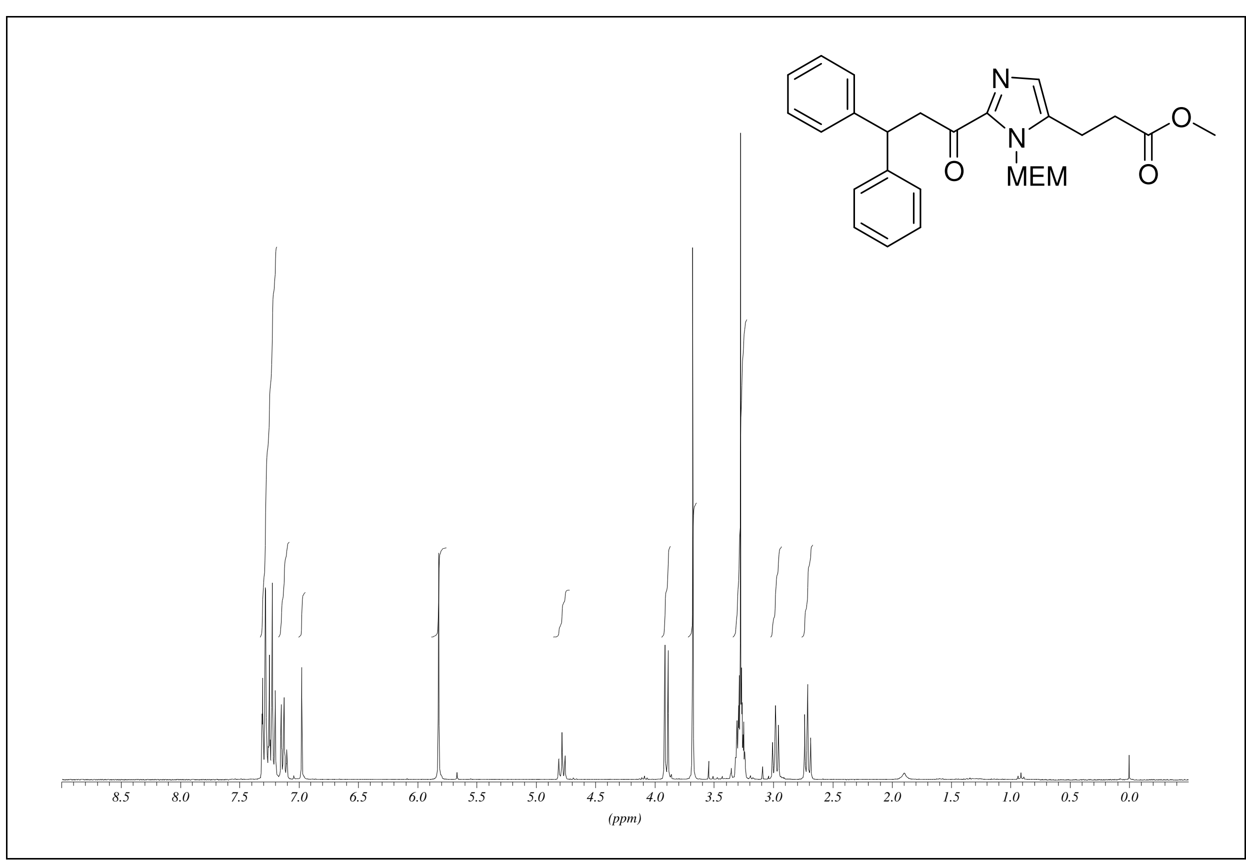


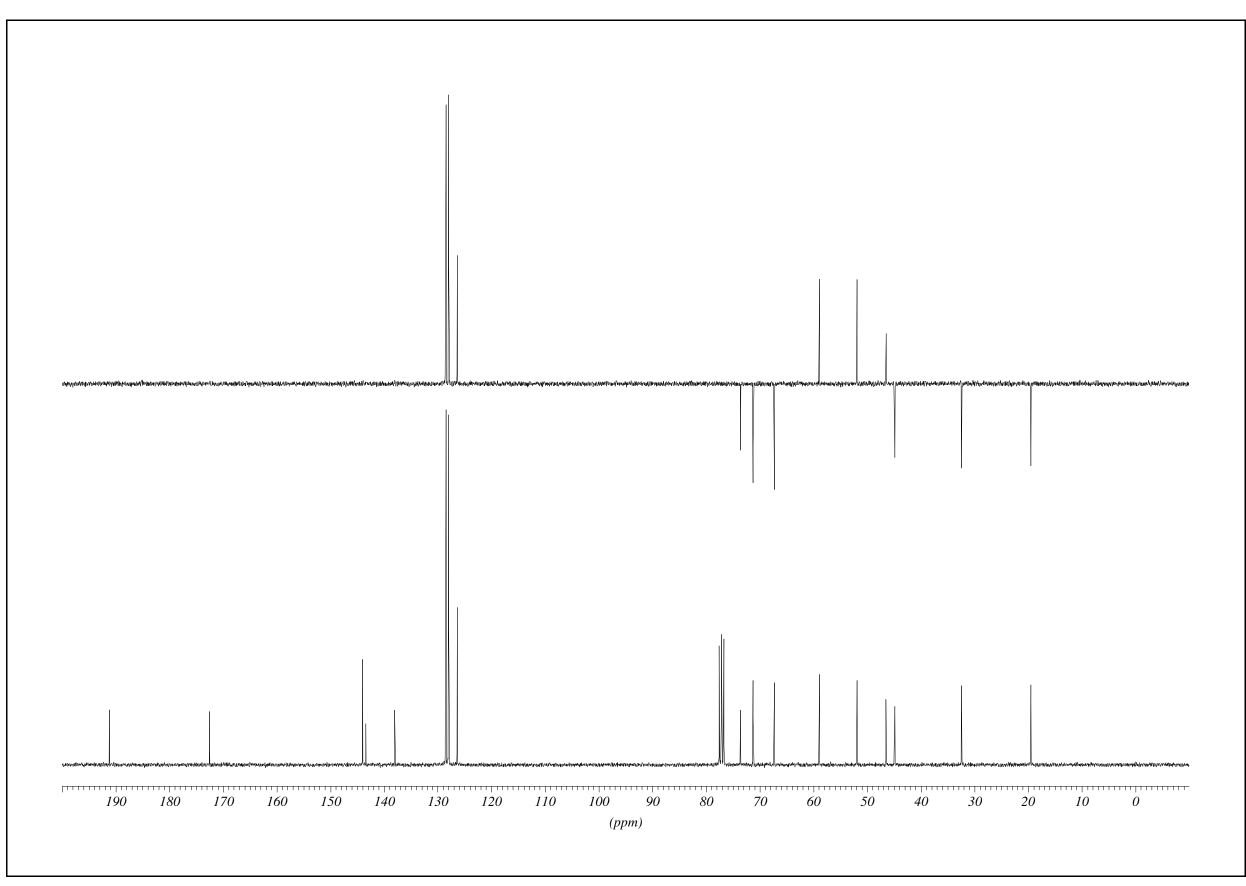
methyl 3-(1-((2-methoxyethoxy)methyl)-2-(4,4-diphenylbut-1-en-2-yl)-1H-imidazol-4-yl)propanoate (211)



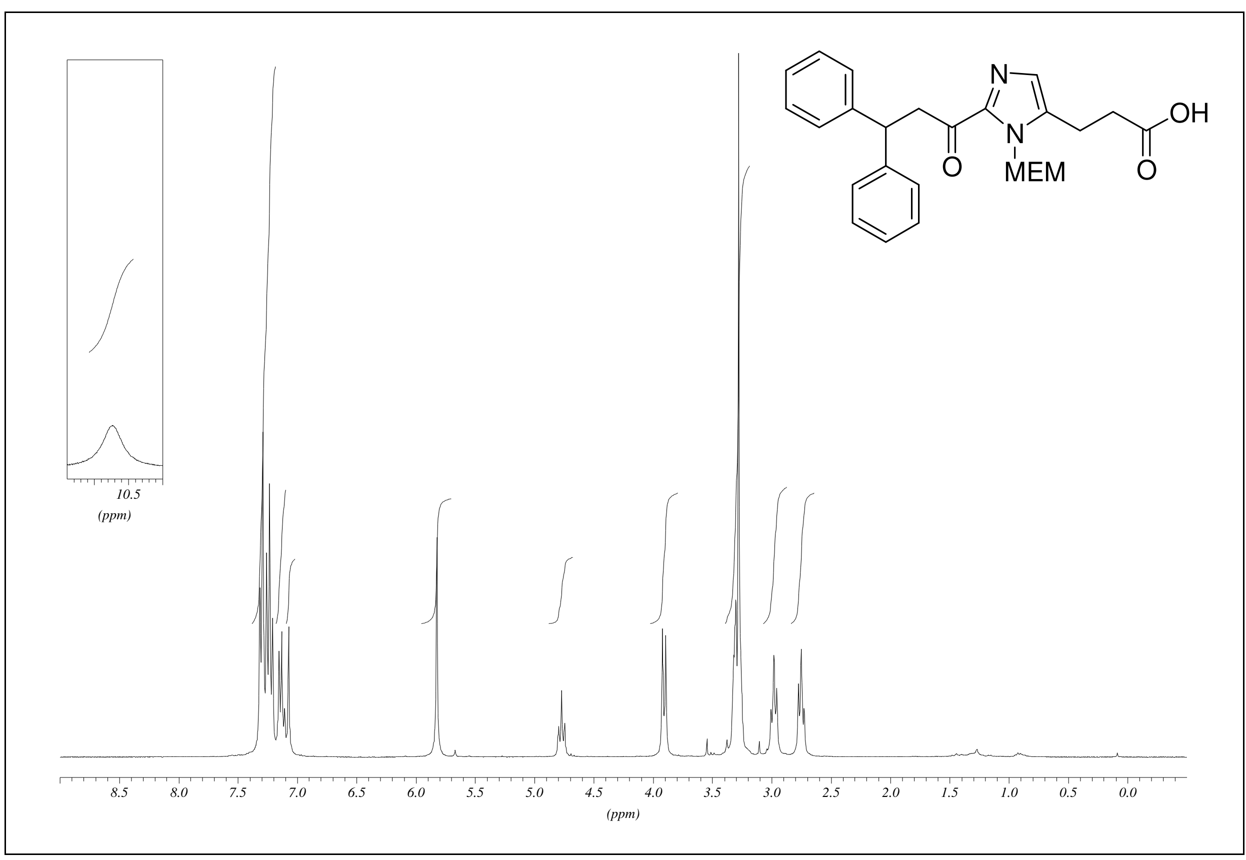


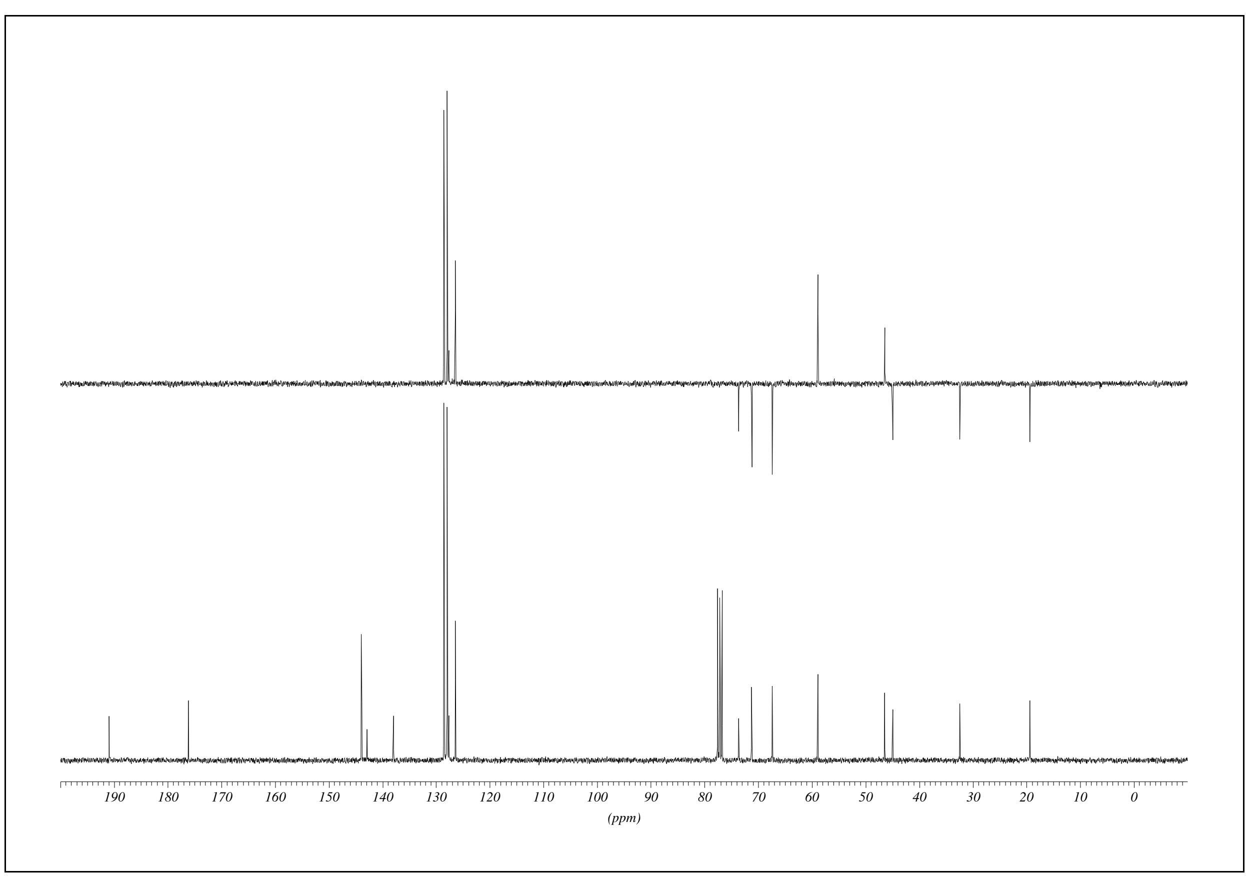
methyl 3-(1-((2-methoxyethoxy)methyl)-2-(3,3-diphenylpropanoyl)-1H-imidazol-5-yl)propanoate (205)



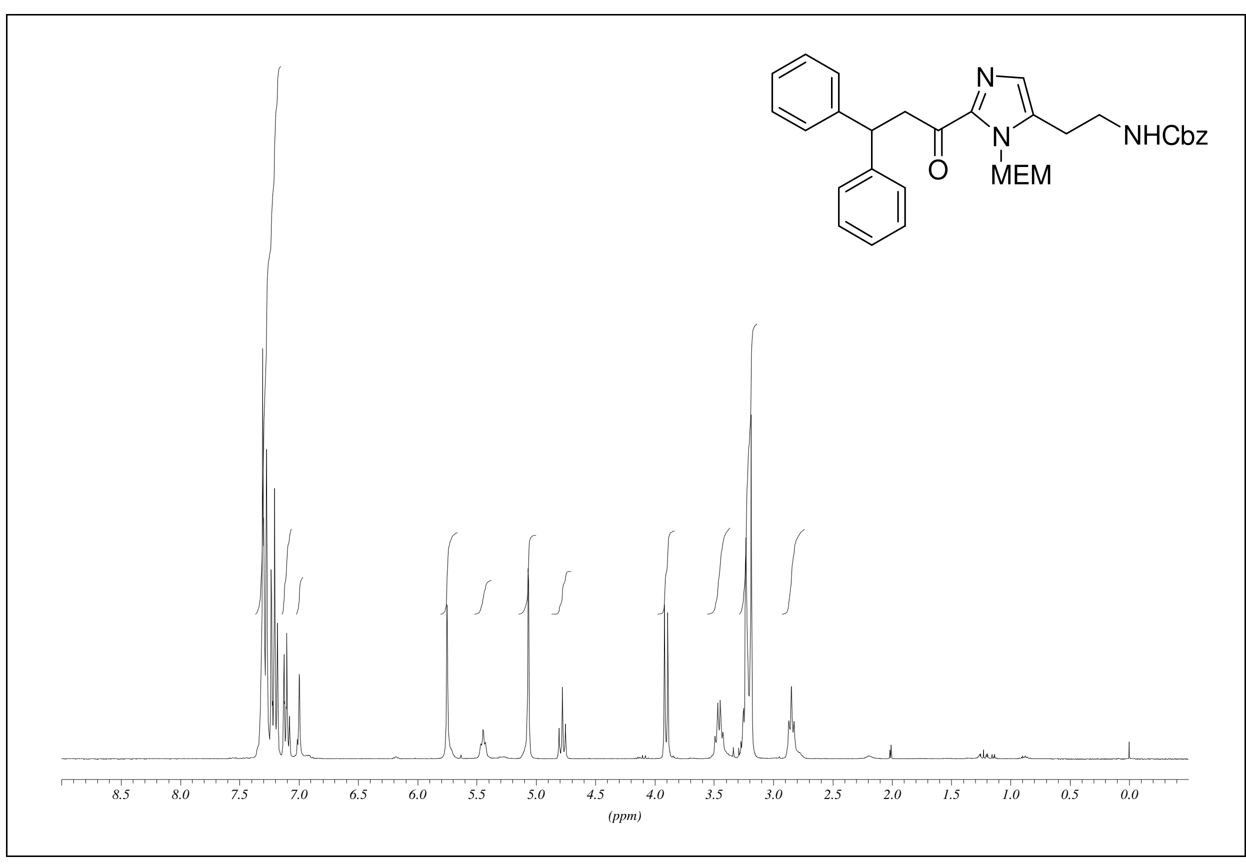


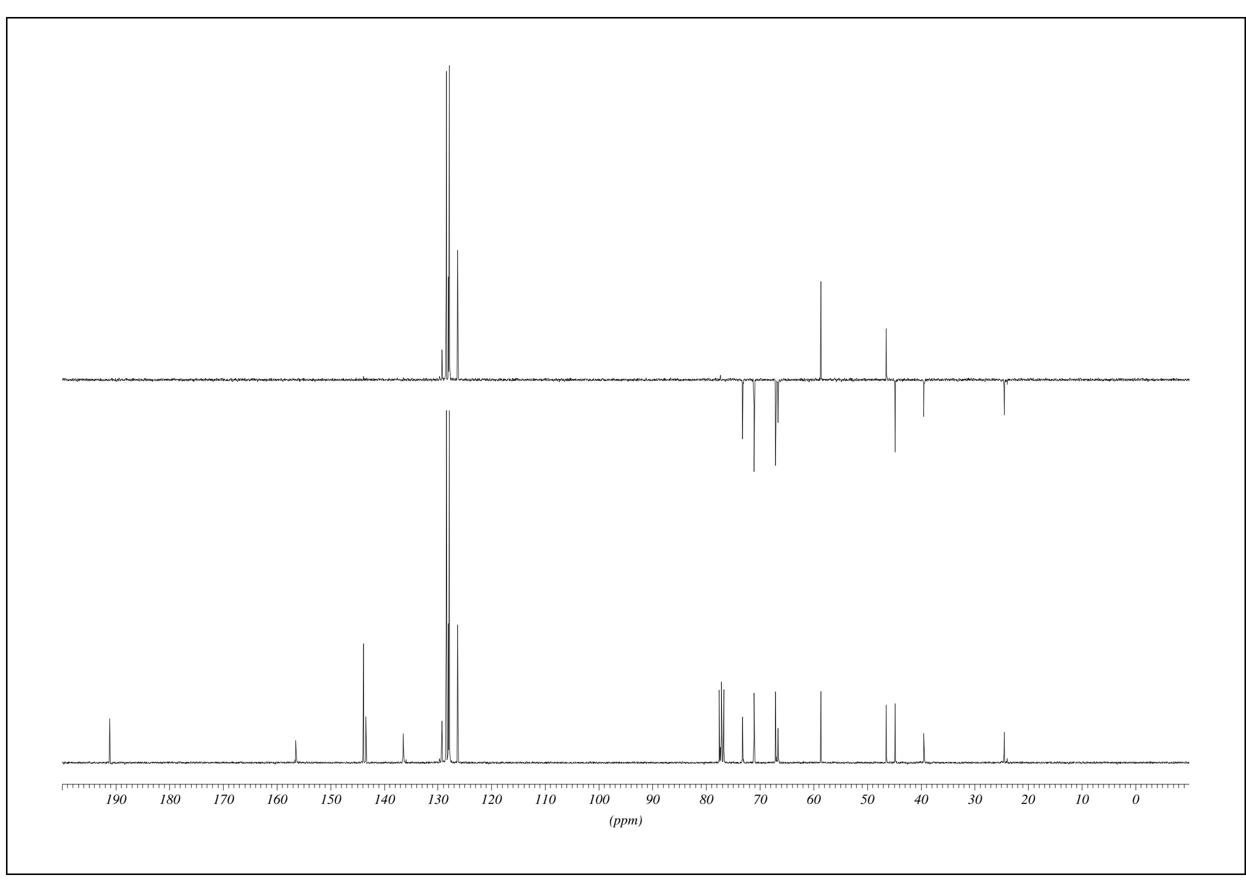
3-(1-((2-methoxyethoxy)methyl)-2-(3,3-diphenylpropanoyl)-1H-imidazol-5-yl)propanoic acid (206)



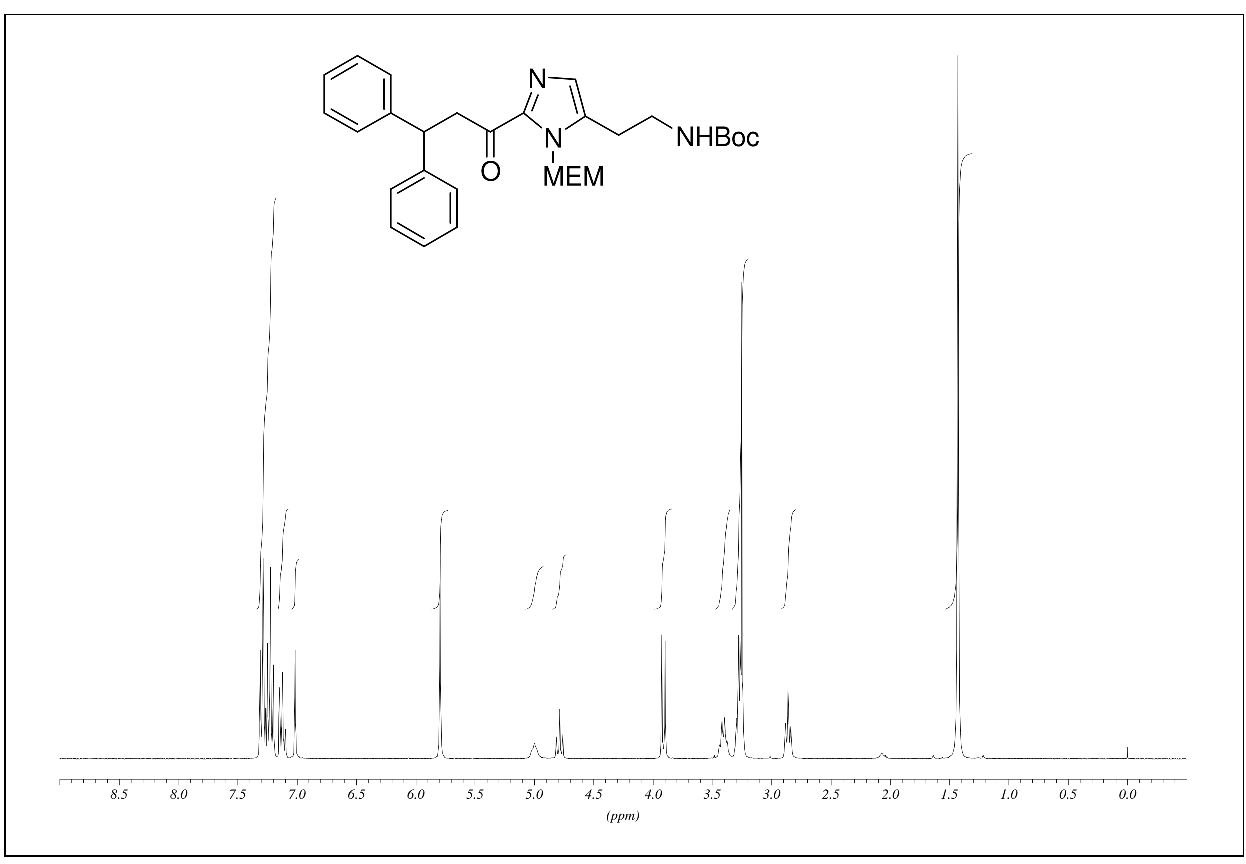


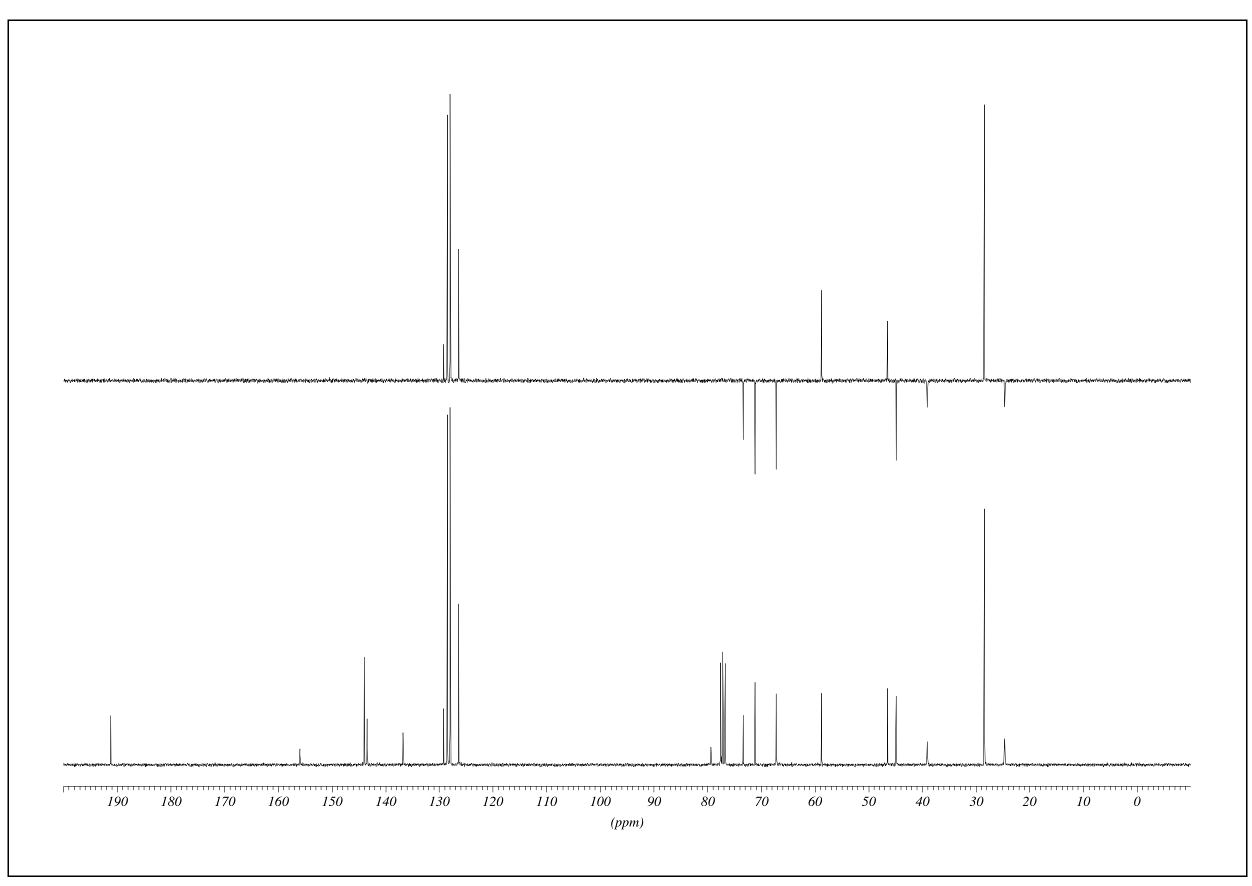
benzyl 2-(1-((2-methoxyethoxy)methyl)-2-(3,3-diphenylpropanoyl)-1H-imidazol-5-yl)ethylcarbamate (207)



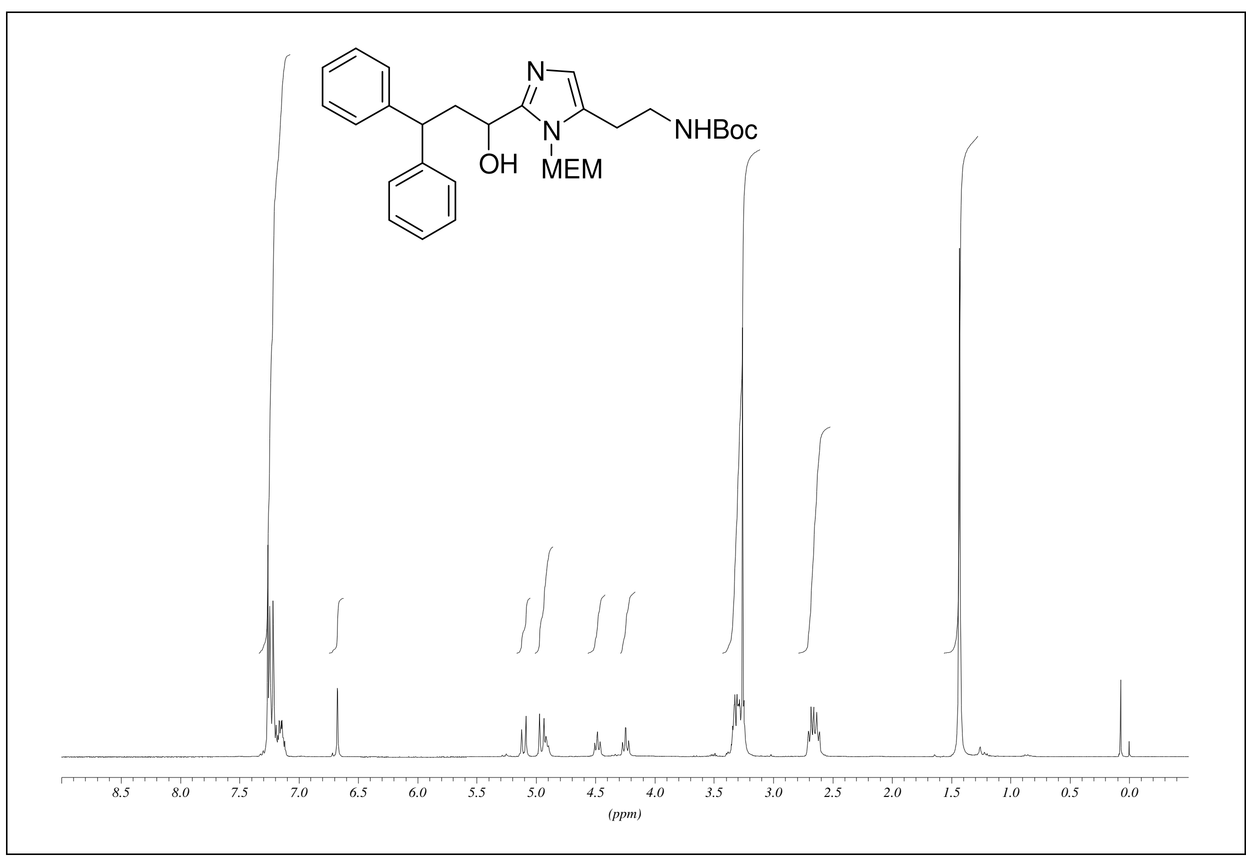


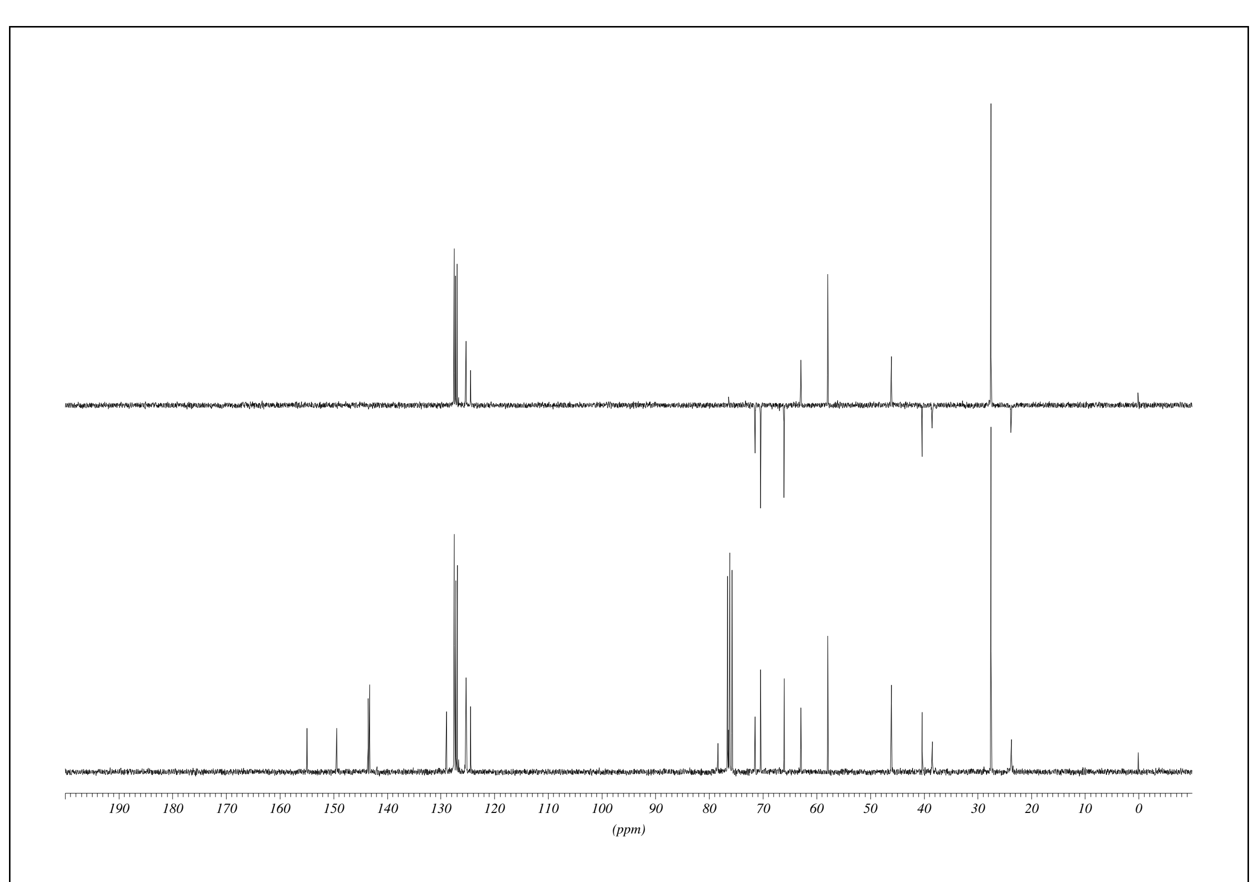
tert-butyl 2-(1-((2-methoxyethoxy)methyl)-2-(3,3-diphenylpropanoyl)-1H-imidazol-5-yl)ethylcarbamate (208)



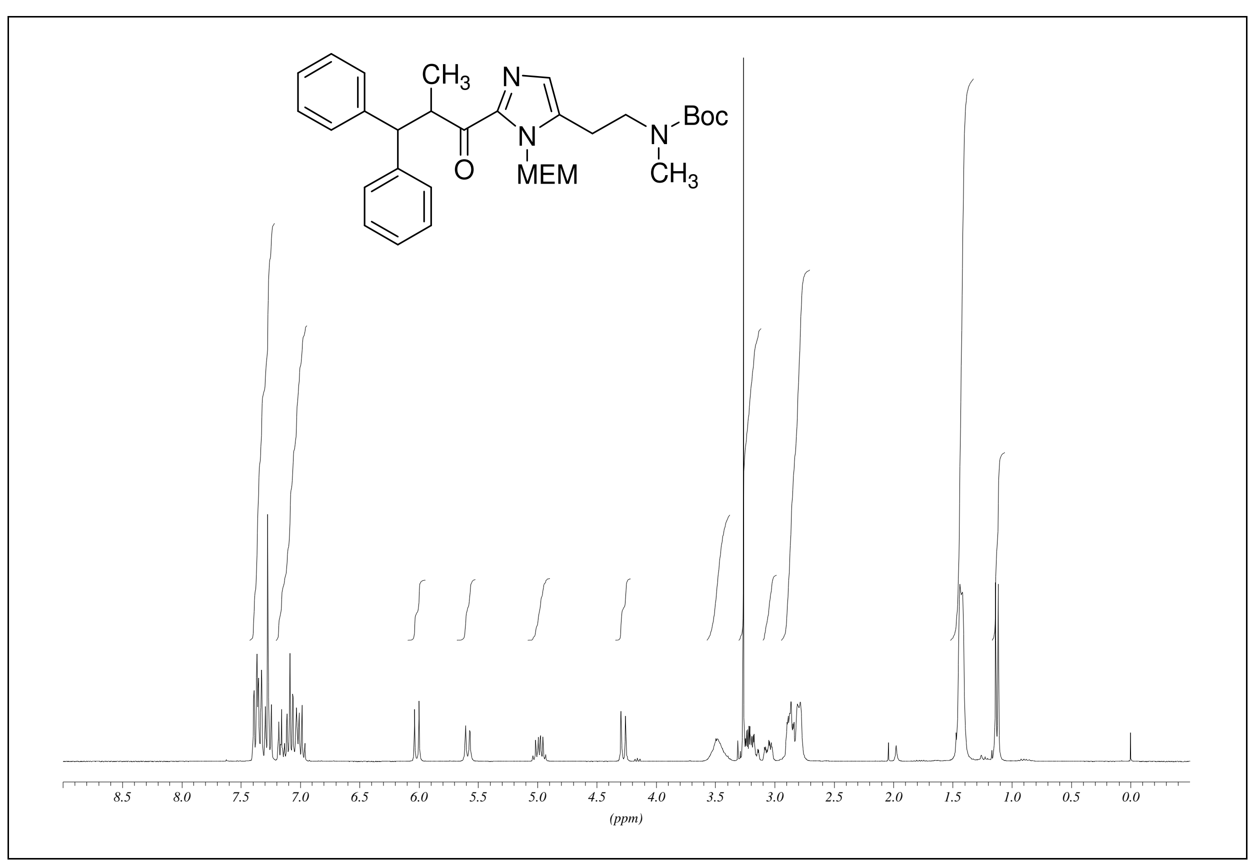


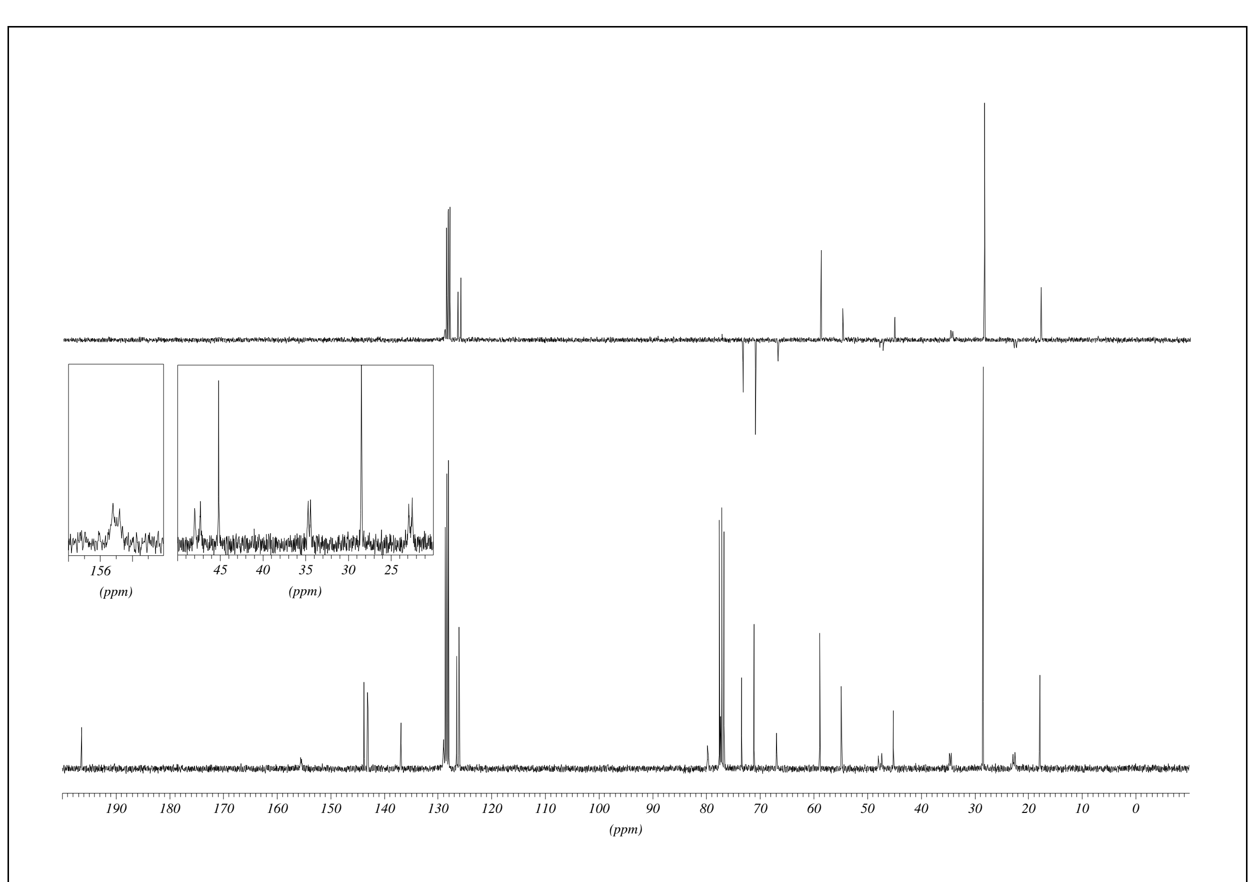
tert-butyl 2-(1-((2-methoxyethoxy)methyl)-2-(1-hydroxy-3,3-diphenylpropyl)-1H-imidazol-5-yl)ethylcarbamate (209)



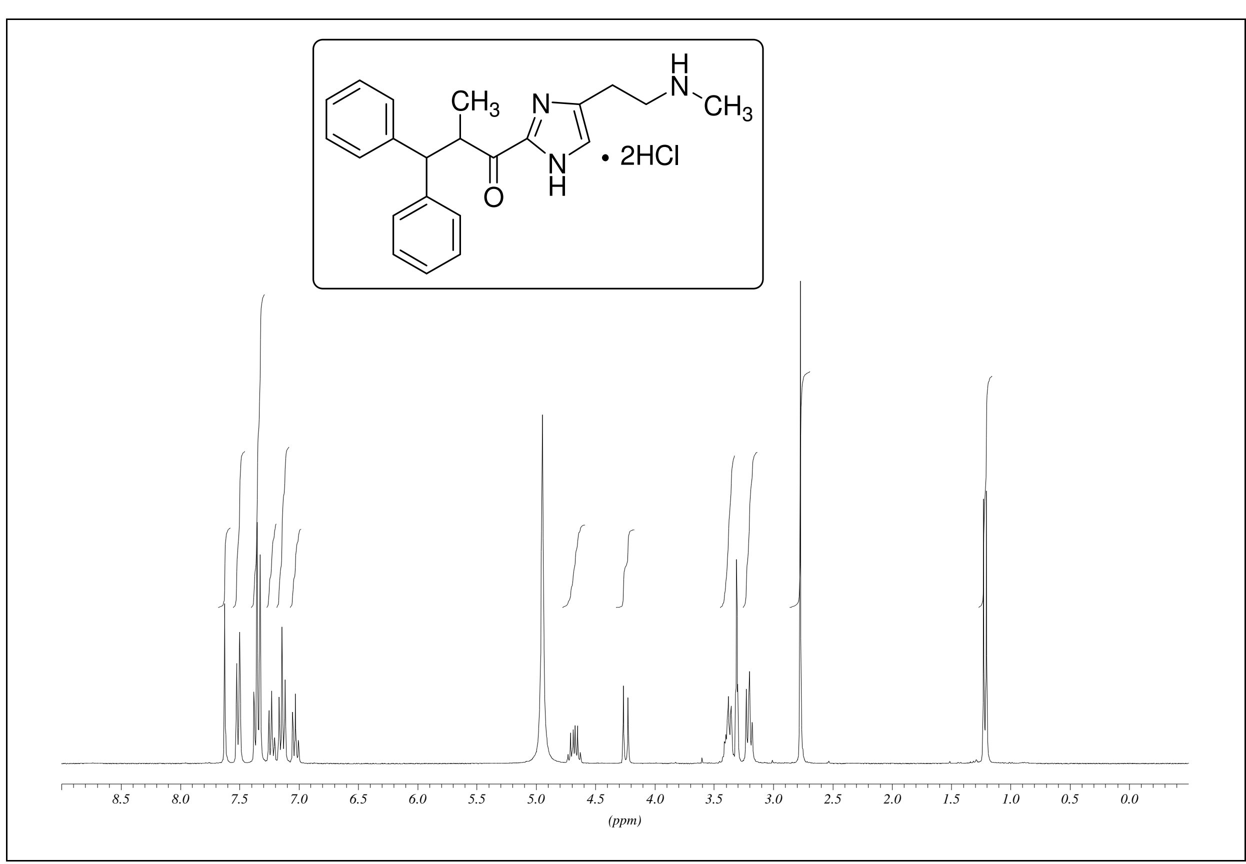


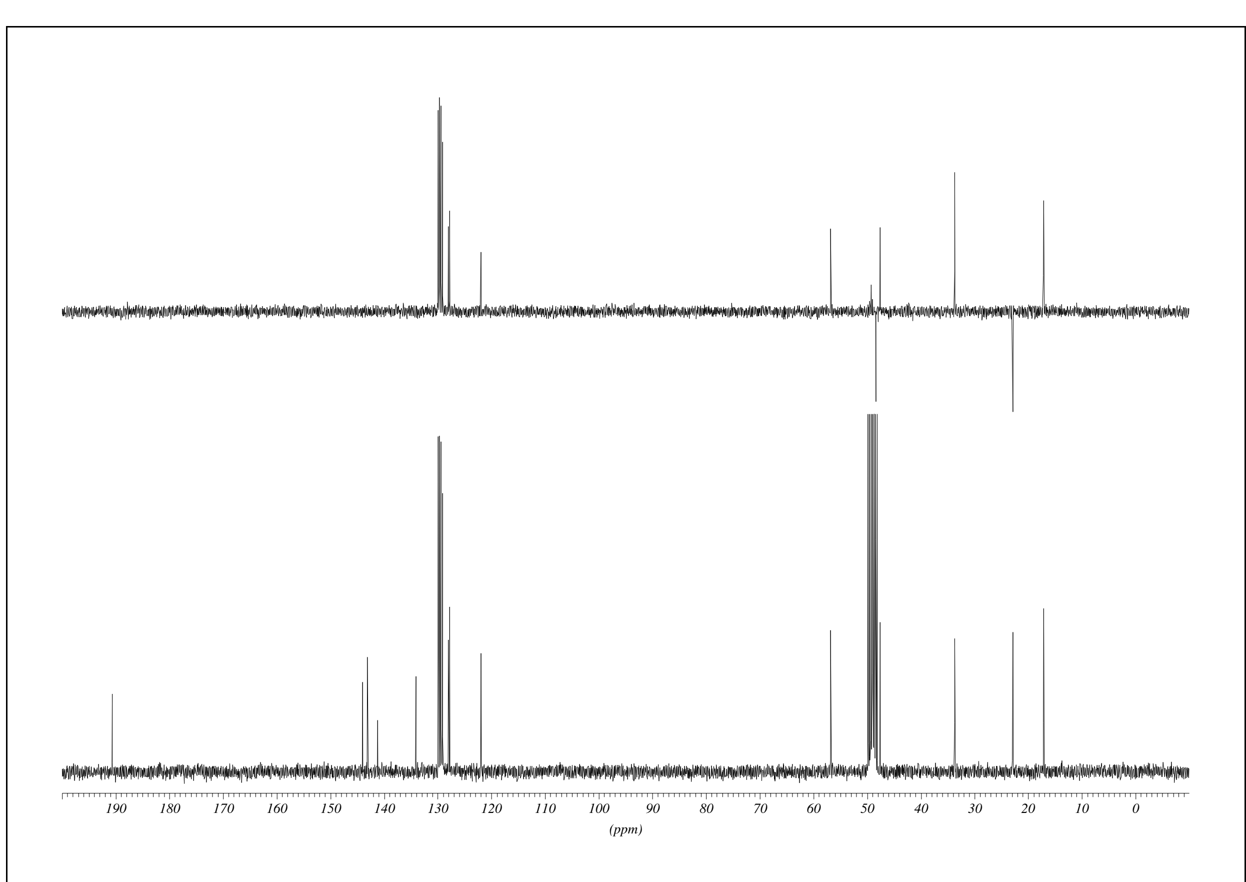
tert-butyl 2-(1-((2-methoxyethoxy)methyl)-2-(2-methyl-3,3-diphenylpropanoyl)-1H-imidazol-5-yl)ethylmethylcarbamate (223)



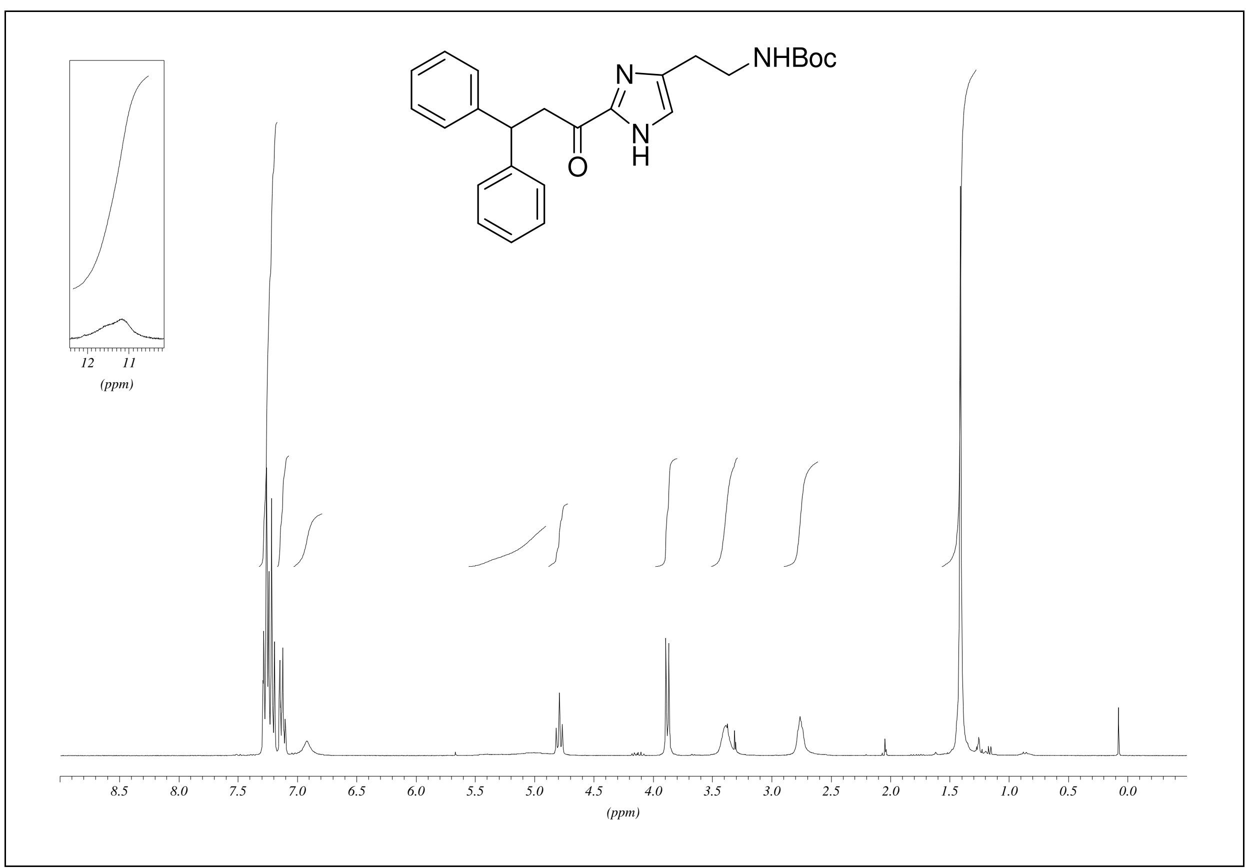


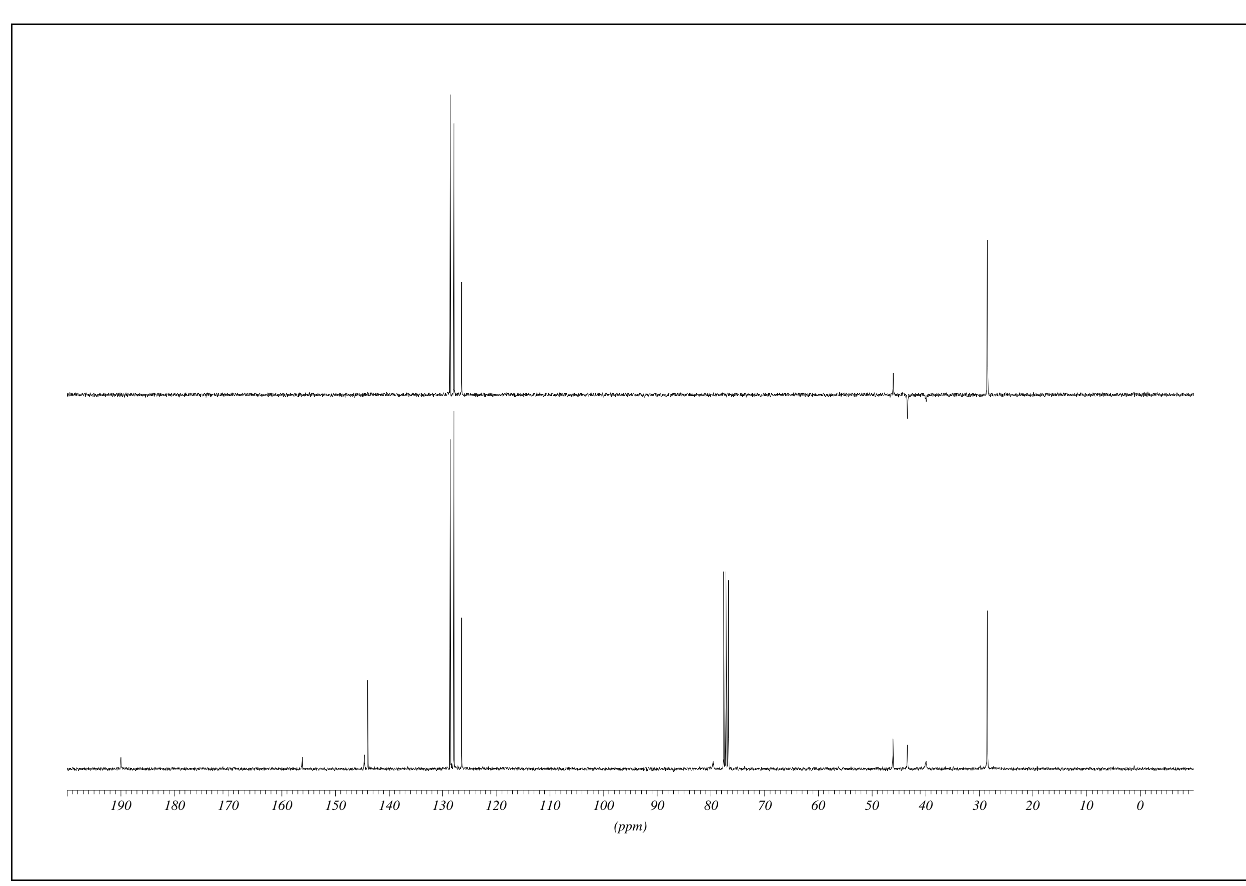
2-methyl-1-(4-(2-(methylamino)ethyl)-1H-imidazol-2-yl)-3,3-diphenylpropan-1-one dihydrochloride (224)



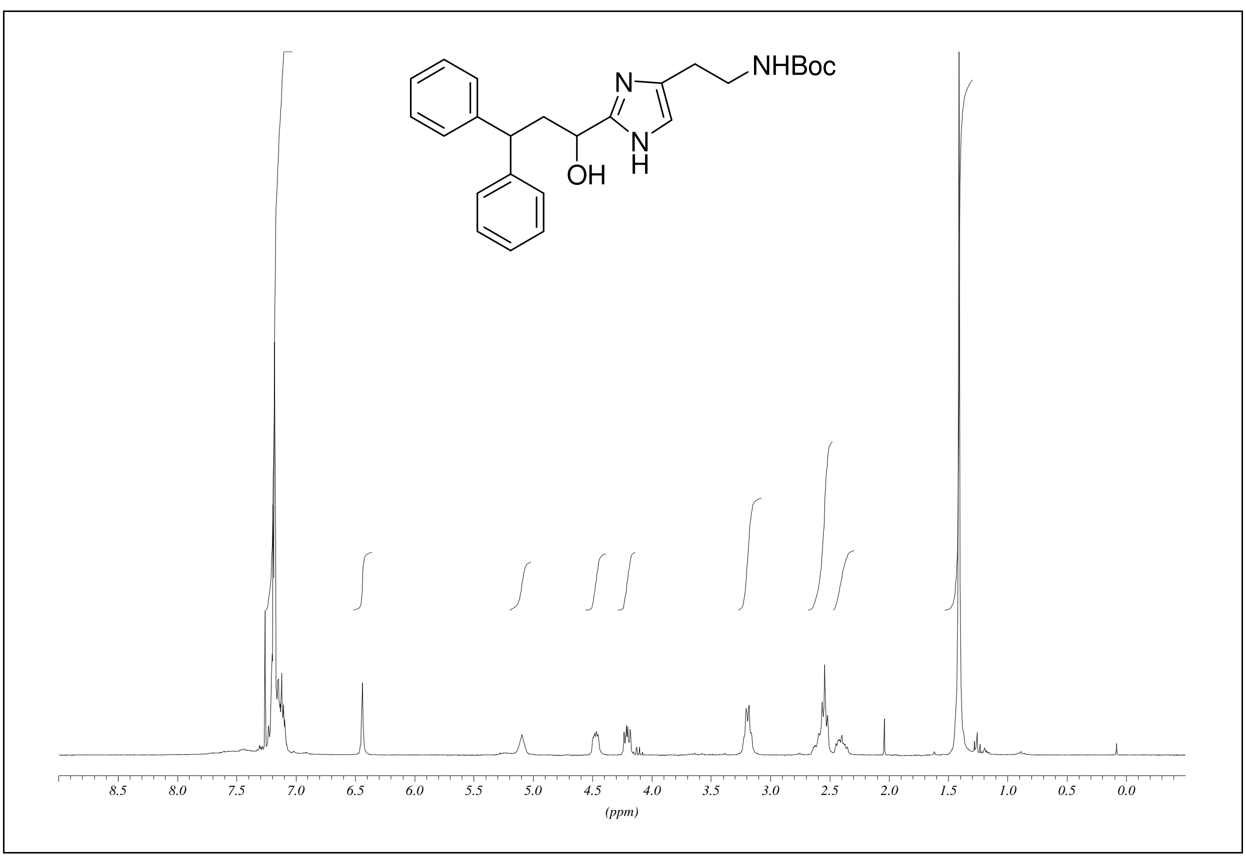


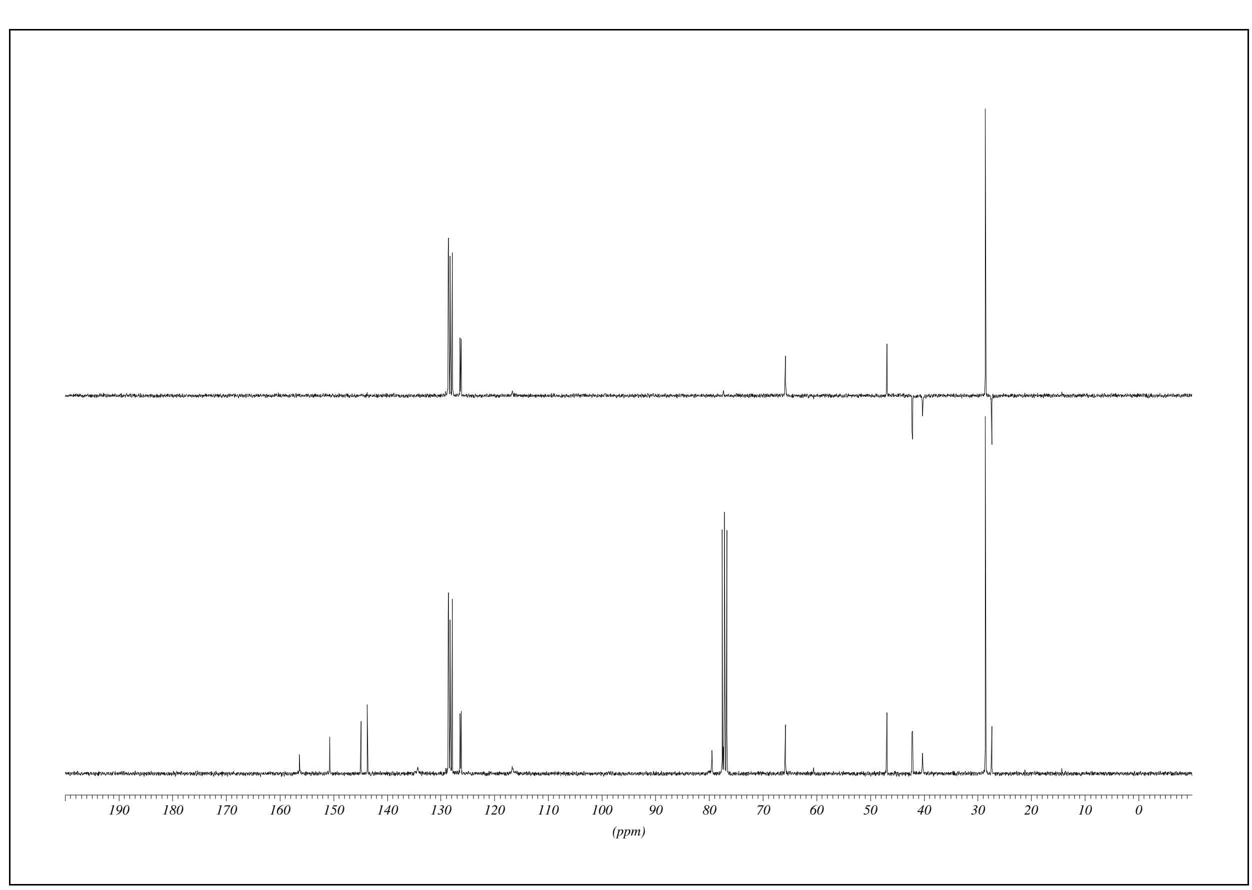
tert-butyl 2-(2-(3,3-diphenylpropanoyl)-1H-imidazol-4-yl)ethylcarbamate(219)



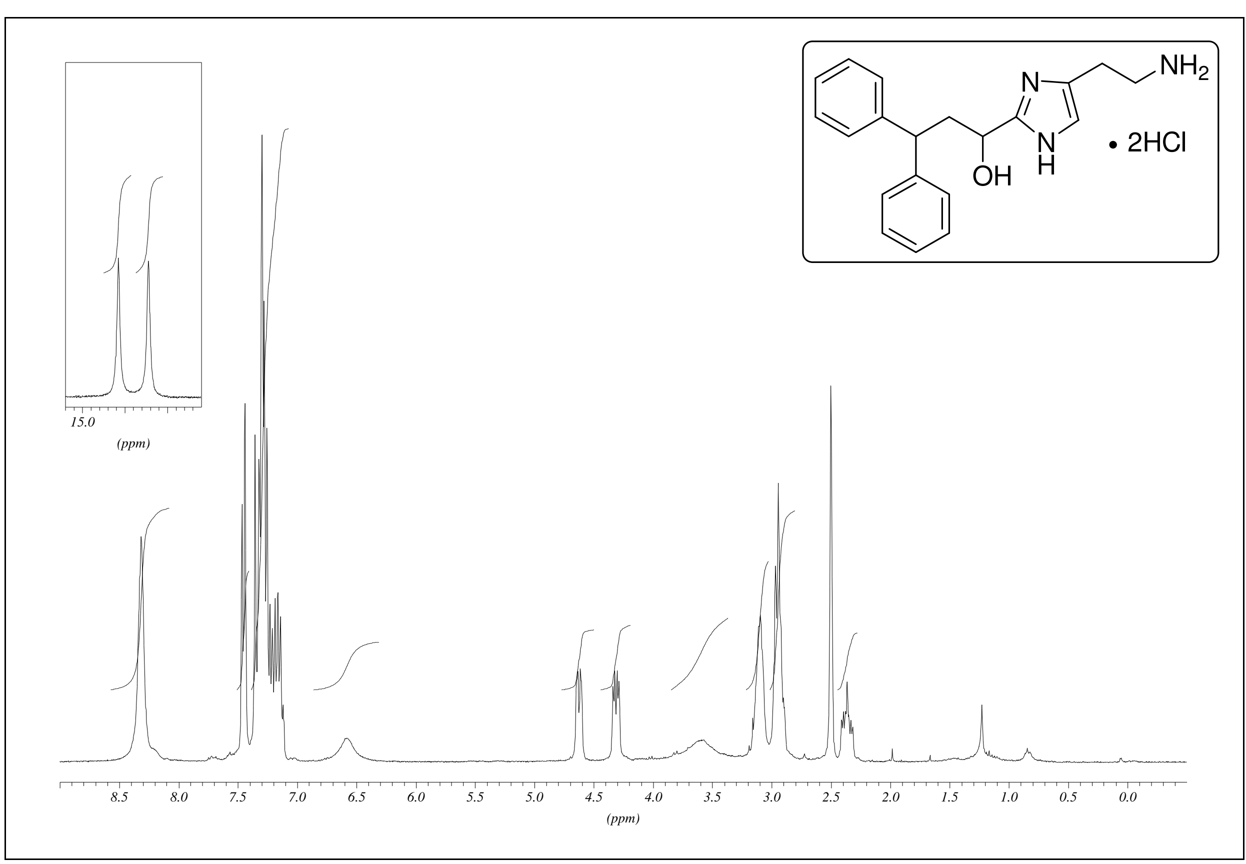


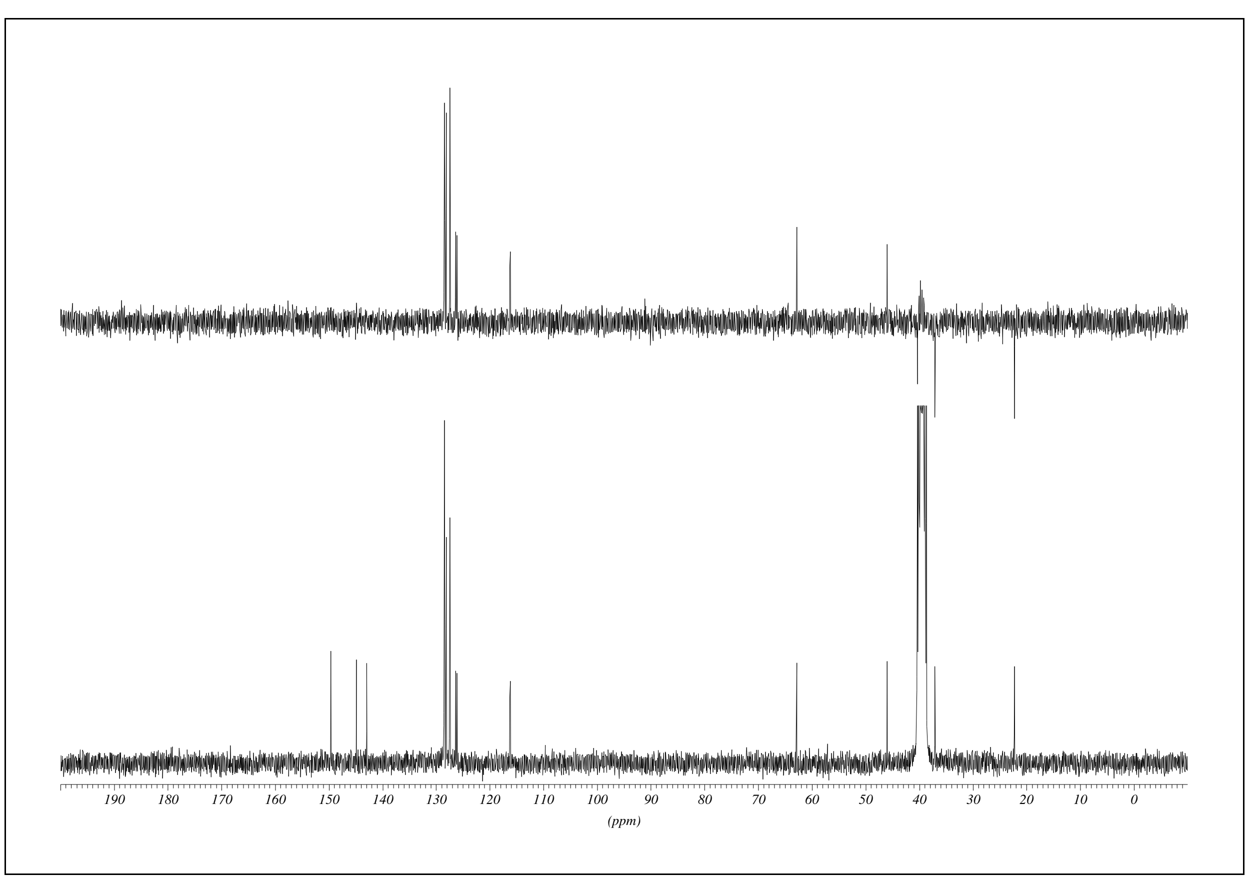
tert-butyl 2-(2-(1-hydroxy-3,3-diphenylpropyl)-1H-imidazol-4-yl)ethylcarbamate (220)



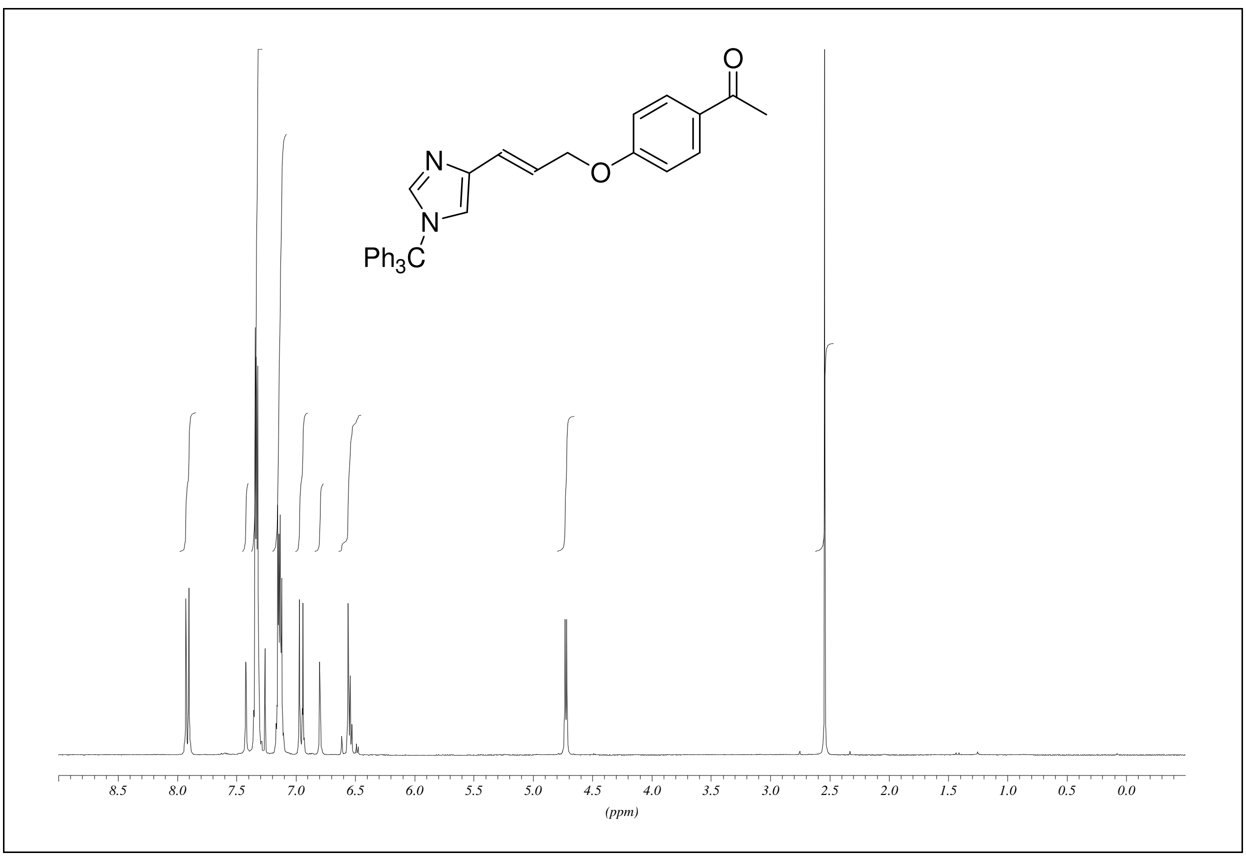


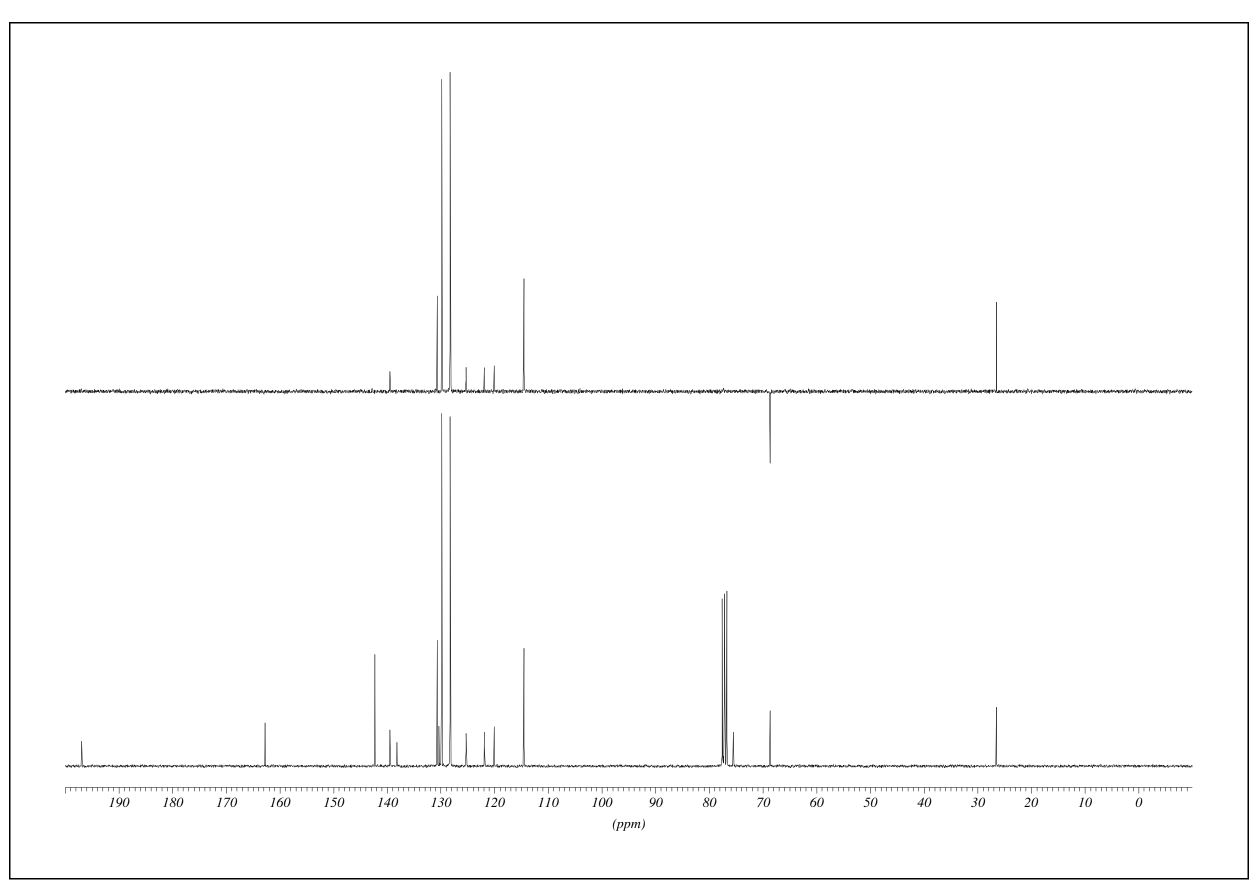
1-(4-(2-aminoethyl)-1H-imidazol-2-yl)-3,3-diphenylpropan-1-ol dihydrochloride (221)



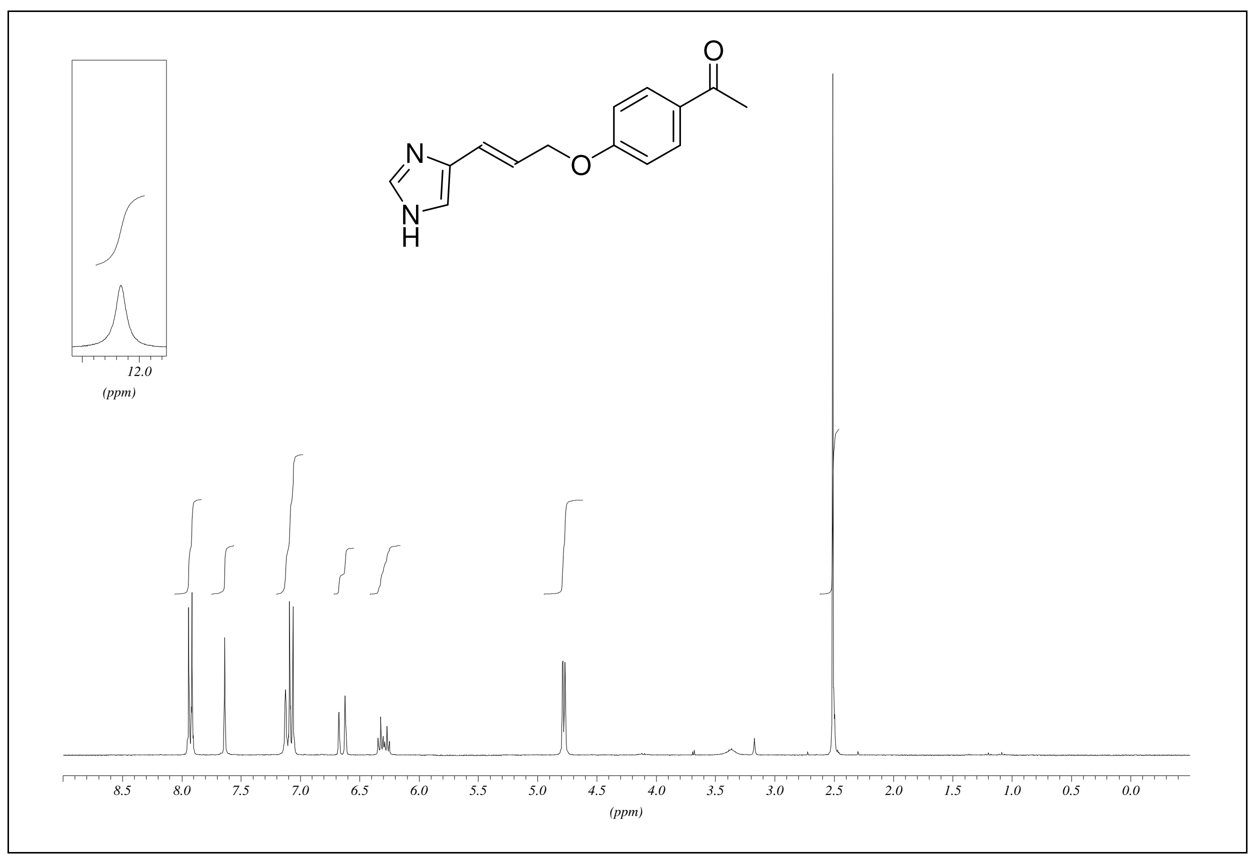


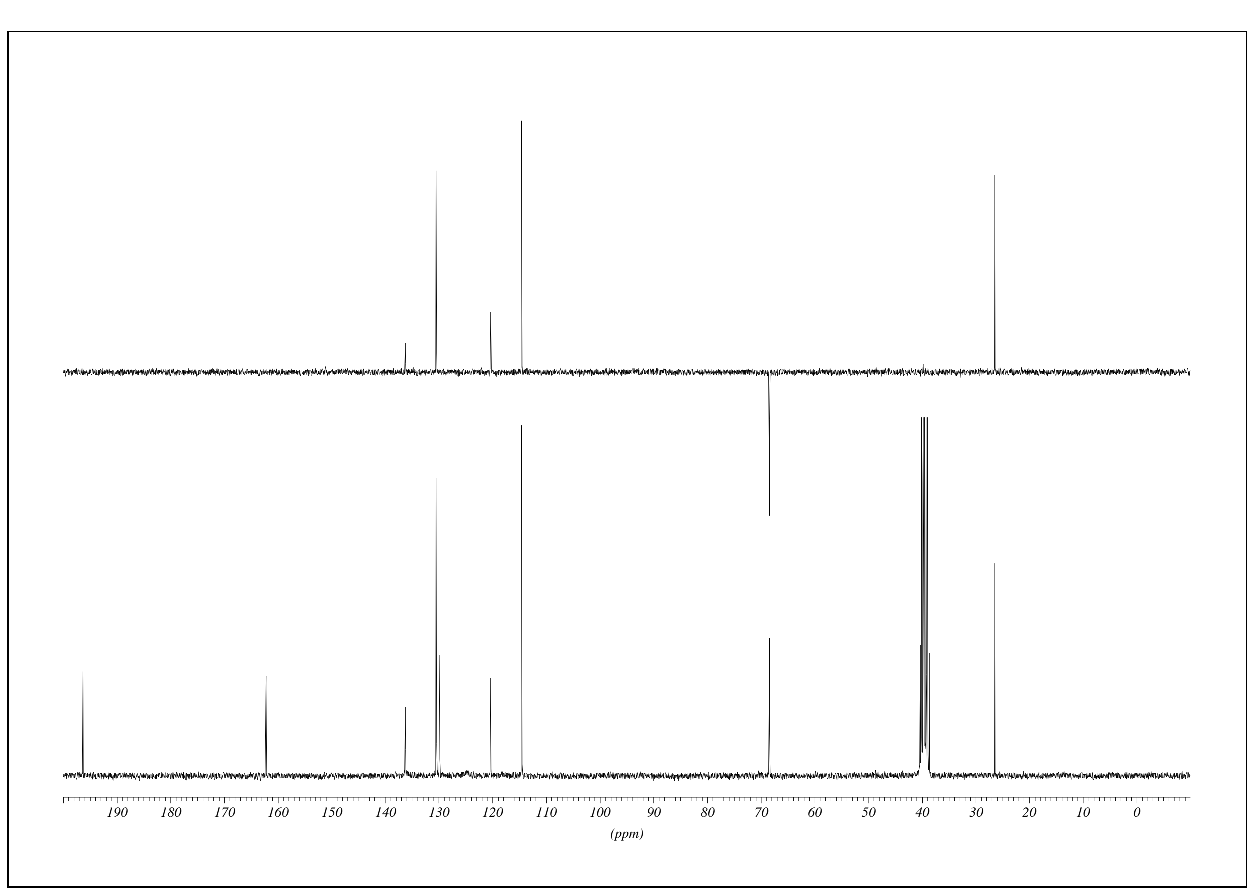
1-(4-((E)-3-(1-trityl-1*H*-imidazol-4-yl)allyloxy)phenyl)ethanone (285)



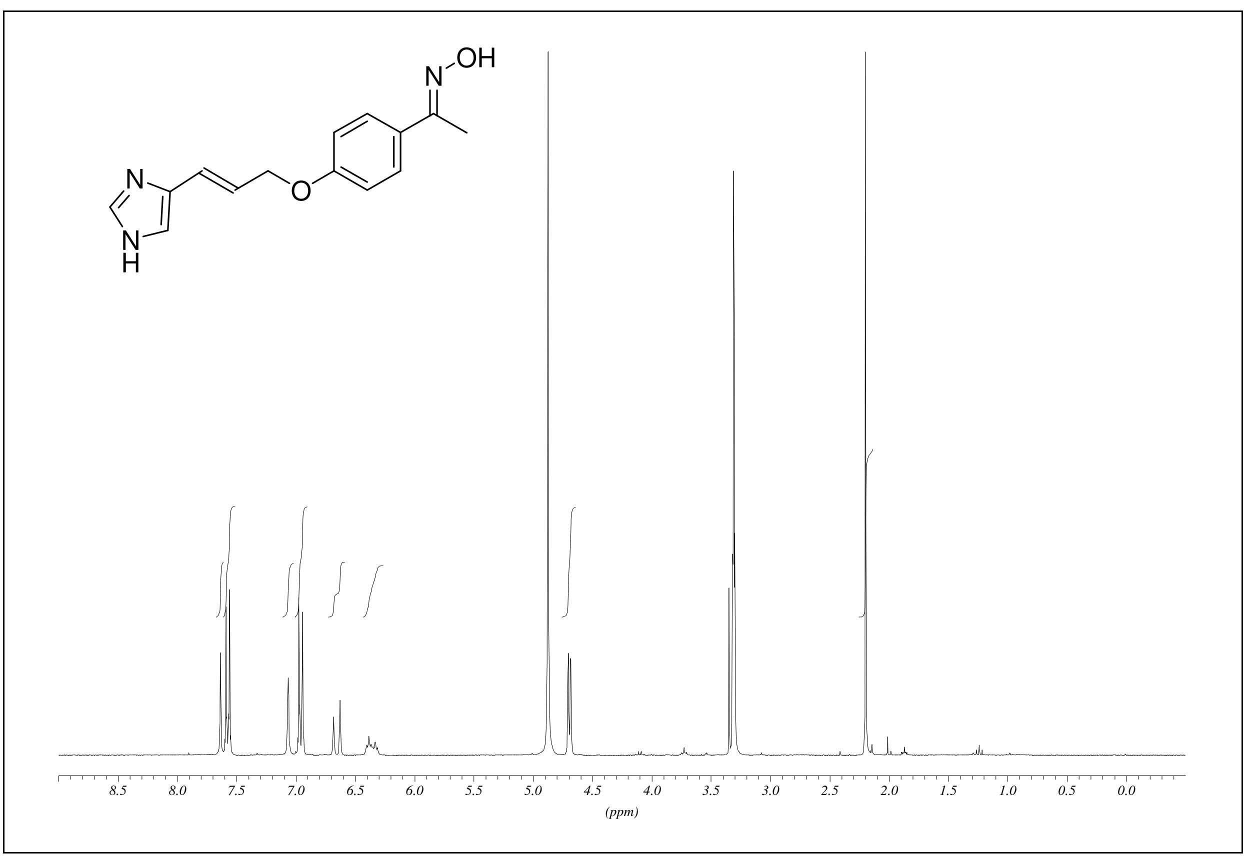


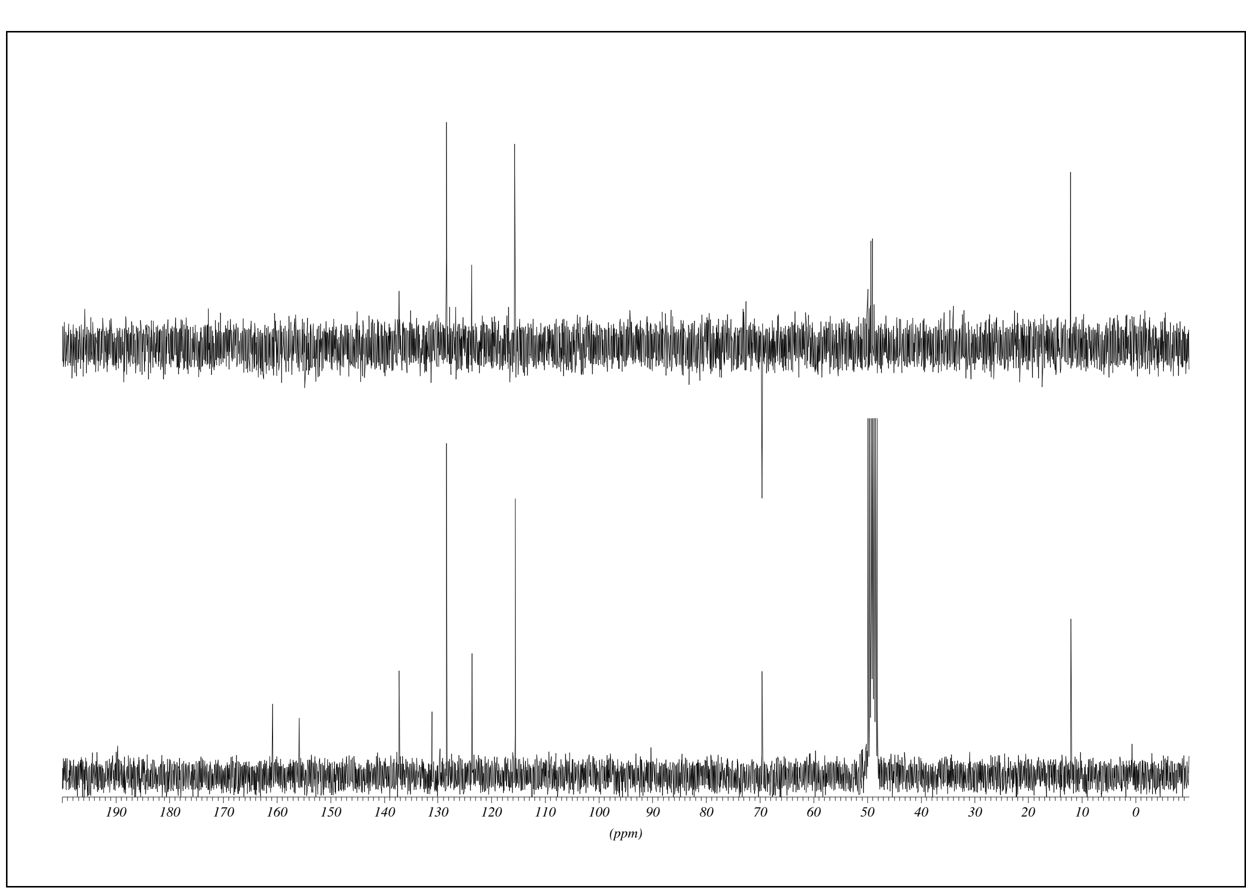
1-(4-((E)-3-(1*H*-imidazol-4-yl)allyloxy)phenyl)ethanone (287)



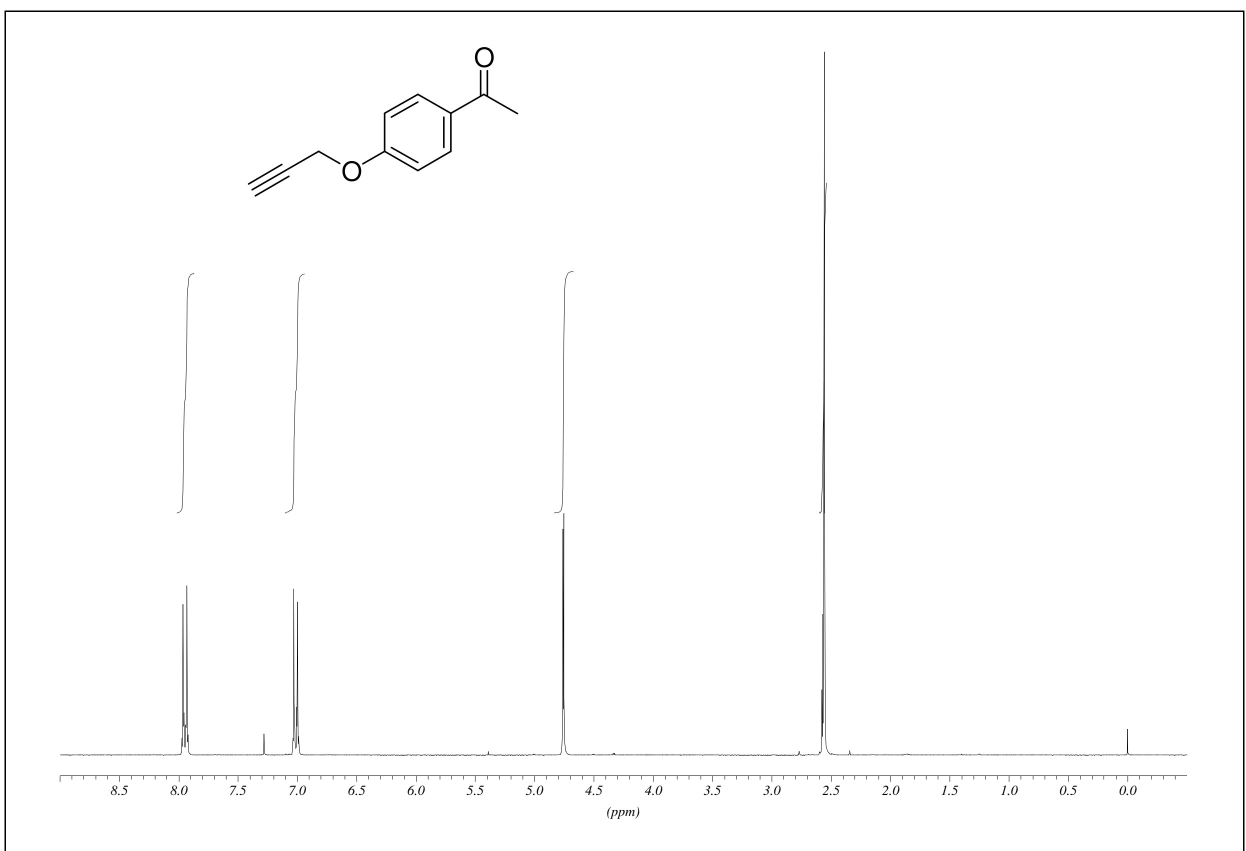


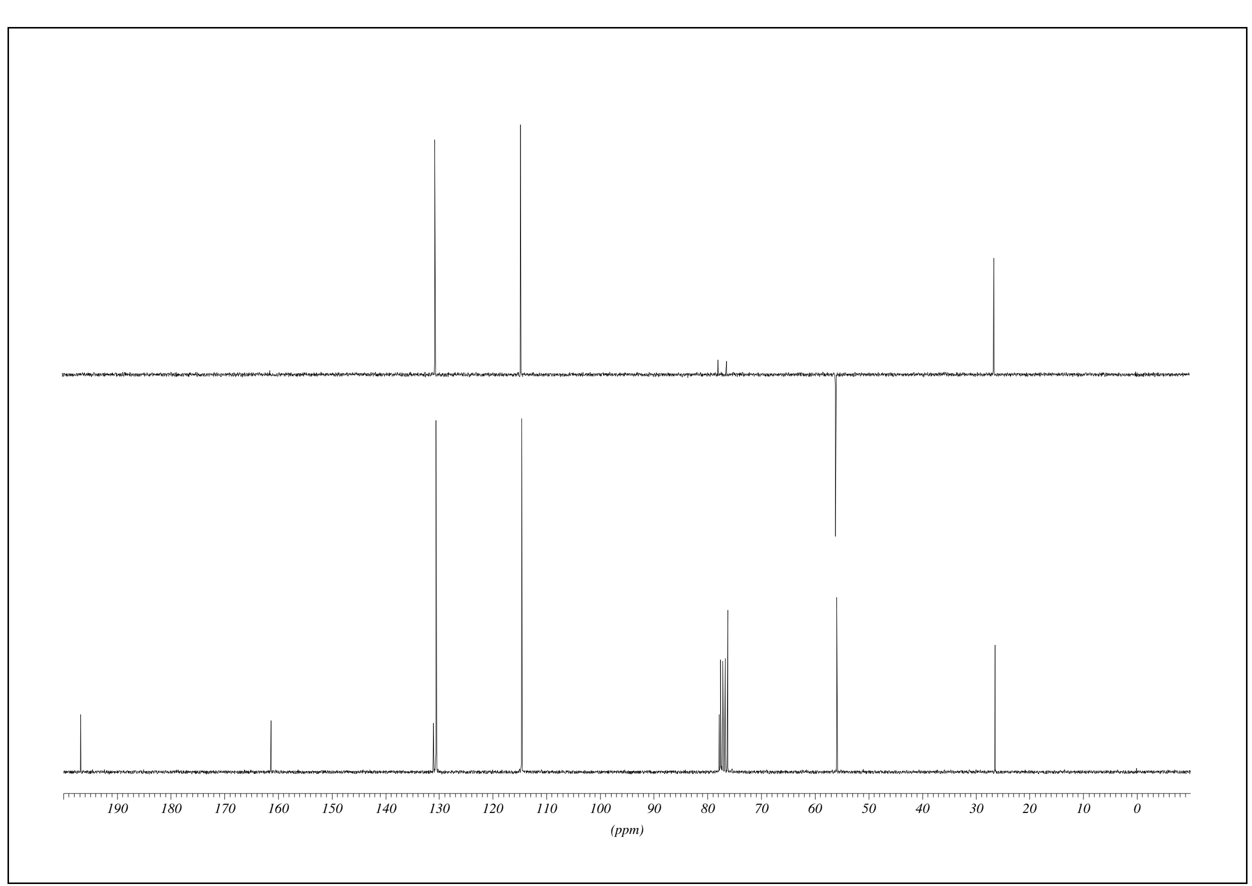
1-(4-((E)-3-(1H-imidazol-4-yl)allyloxy)phenyl)ethanone oxime (293)



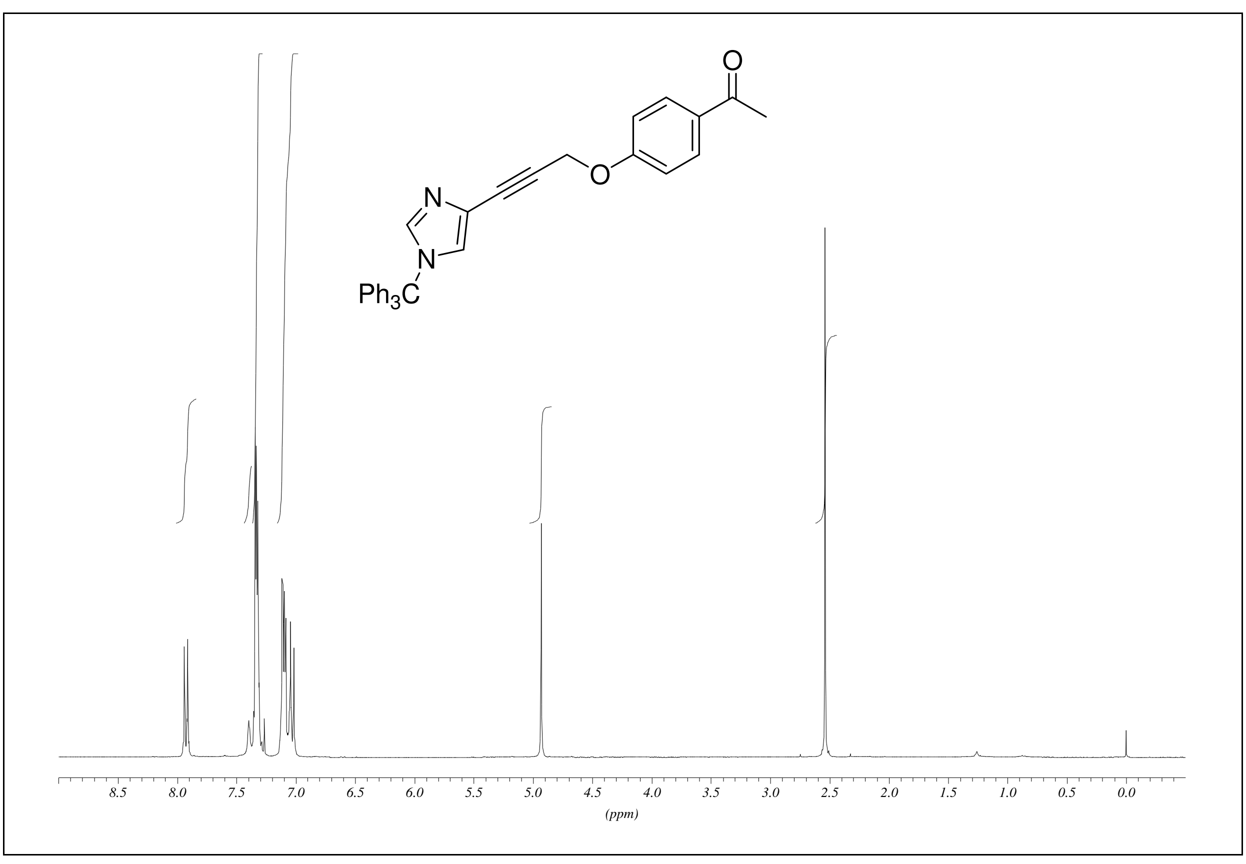


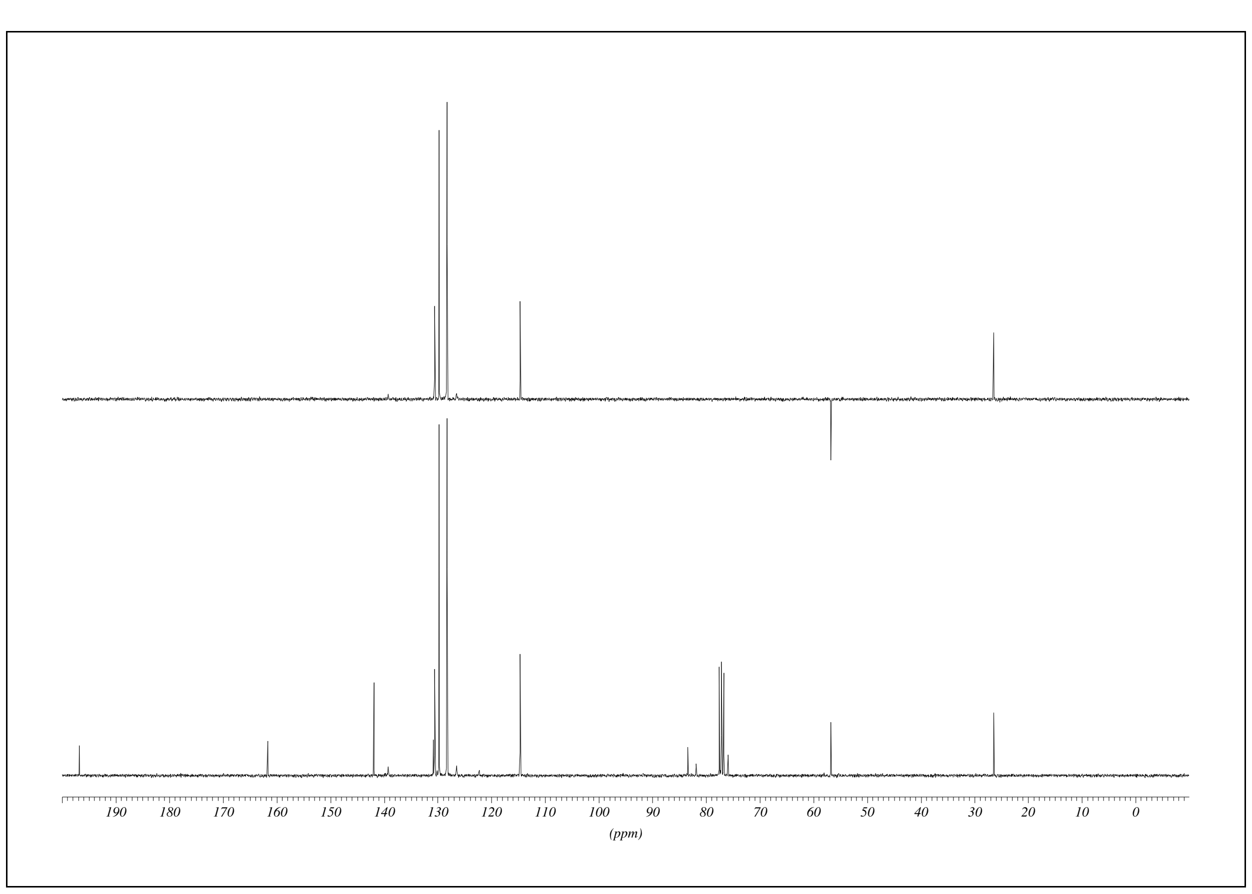
1-(4-(prop-2-ynyloxy)phenyl)ethanone (290)



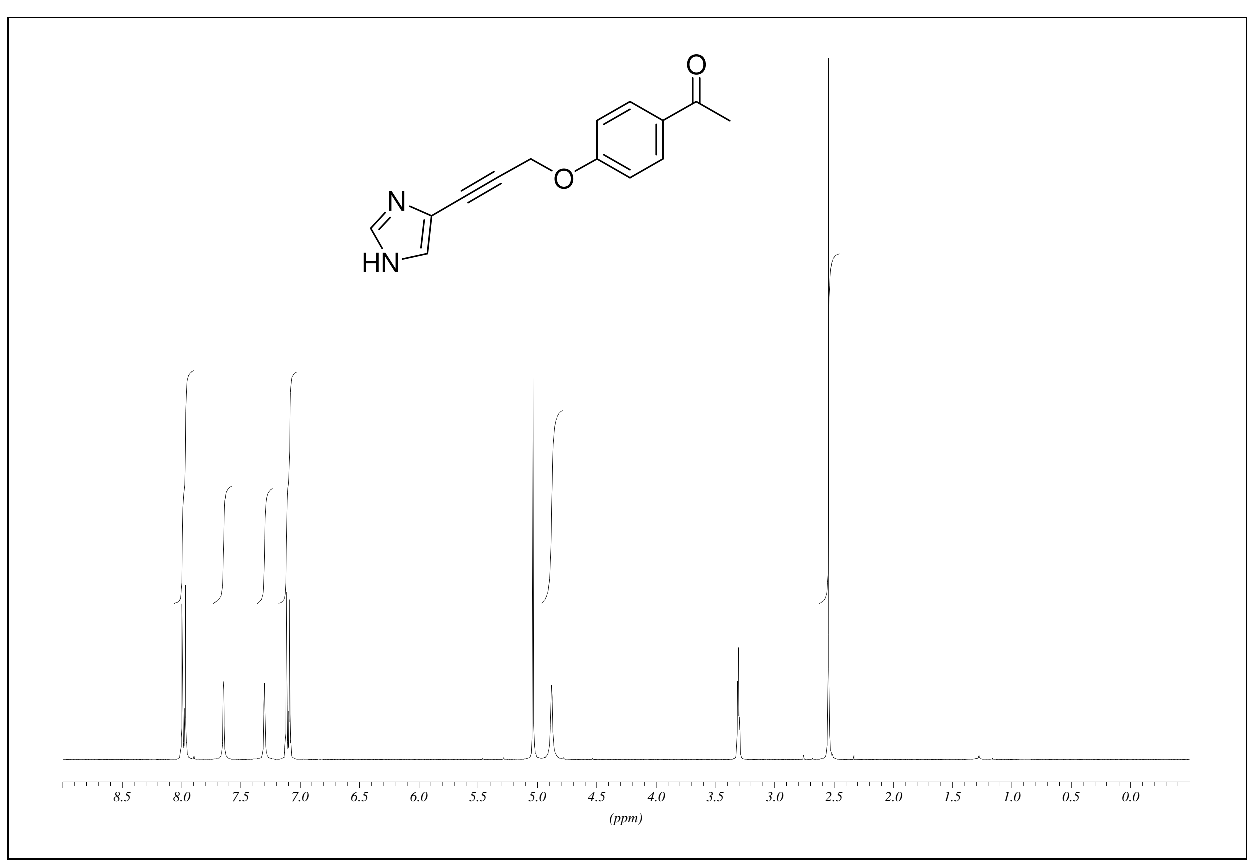


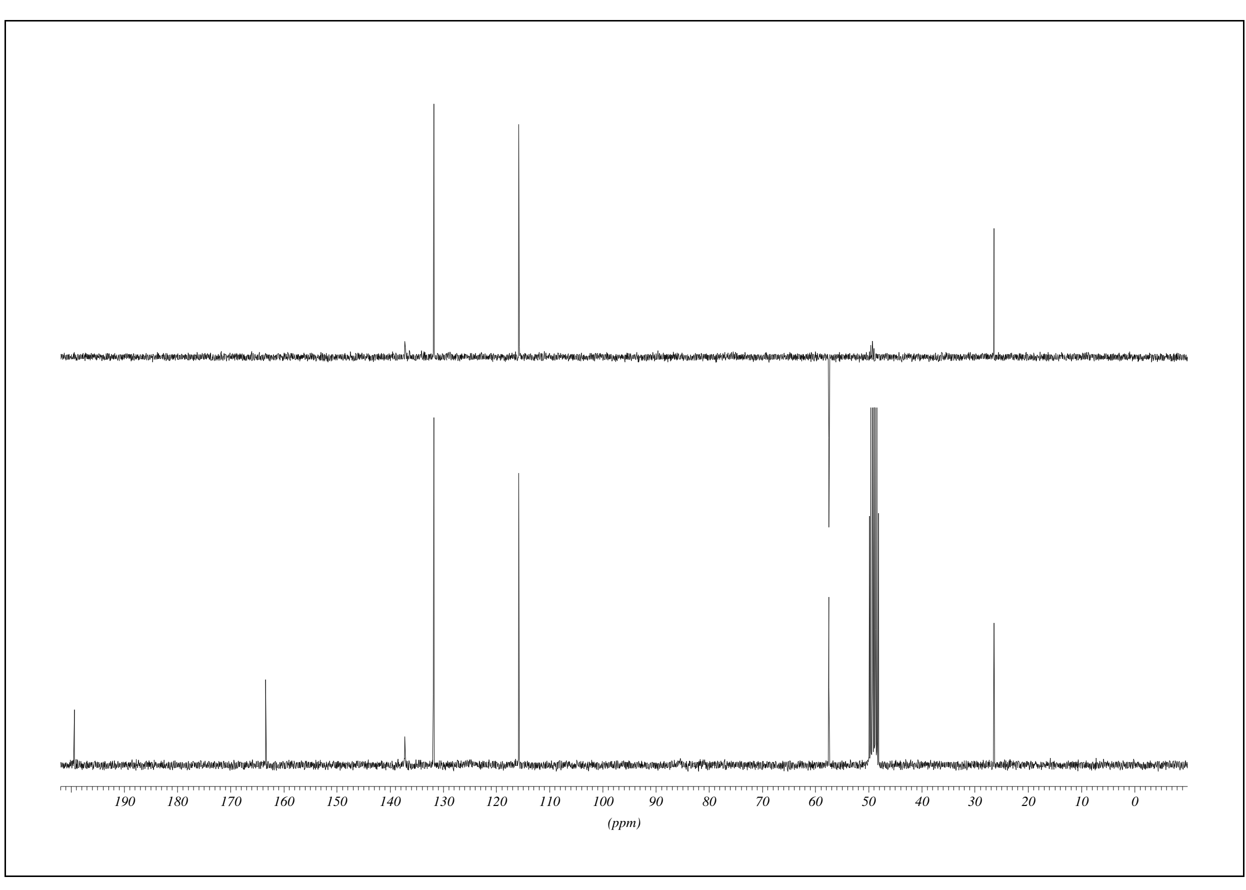
1-(4-(3-(1-trityl-1*H*-imidazol-4-yl)prop-2-ynyloxy)phenyl)ethanone (291)



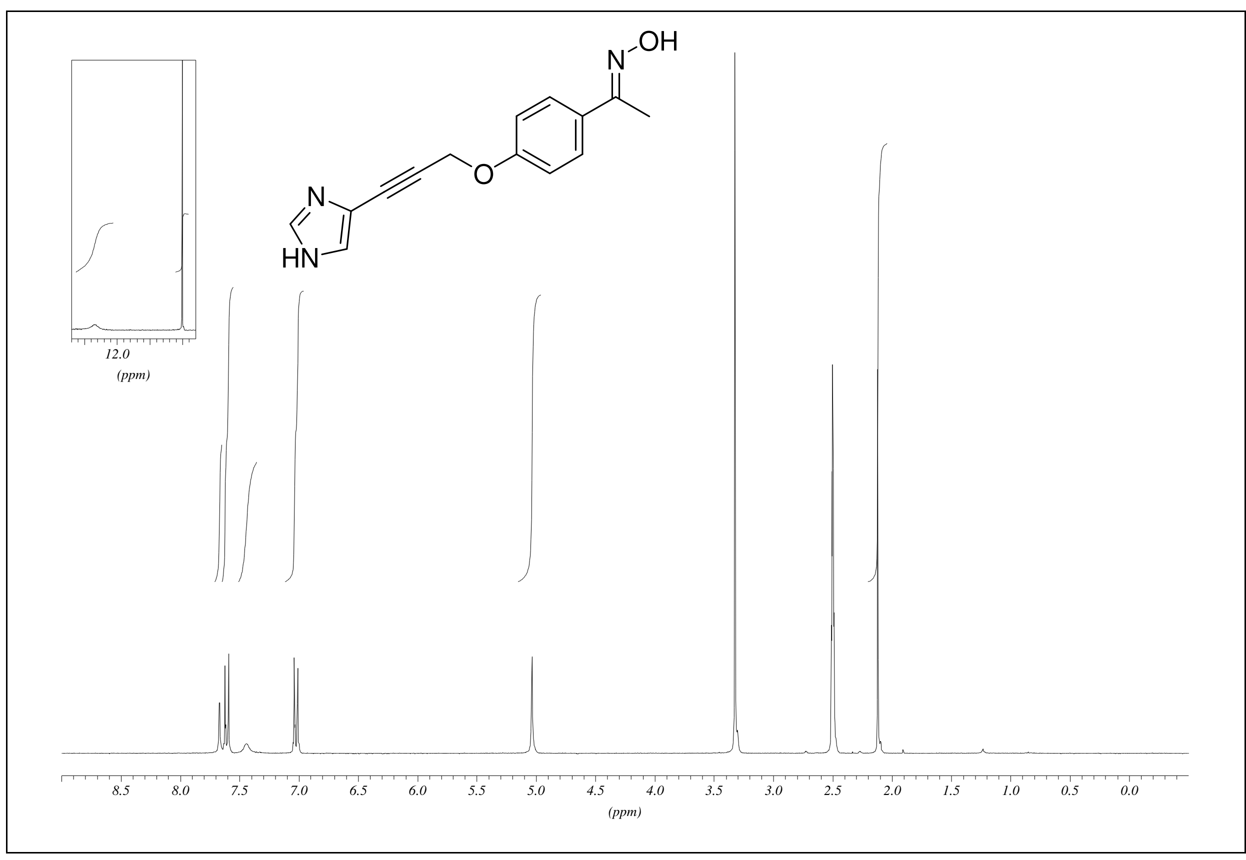


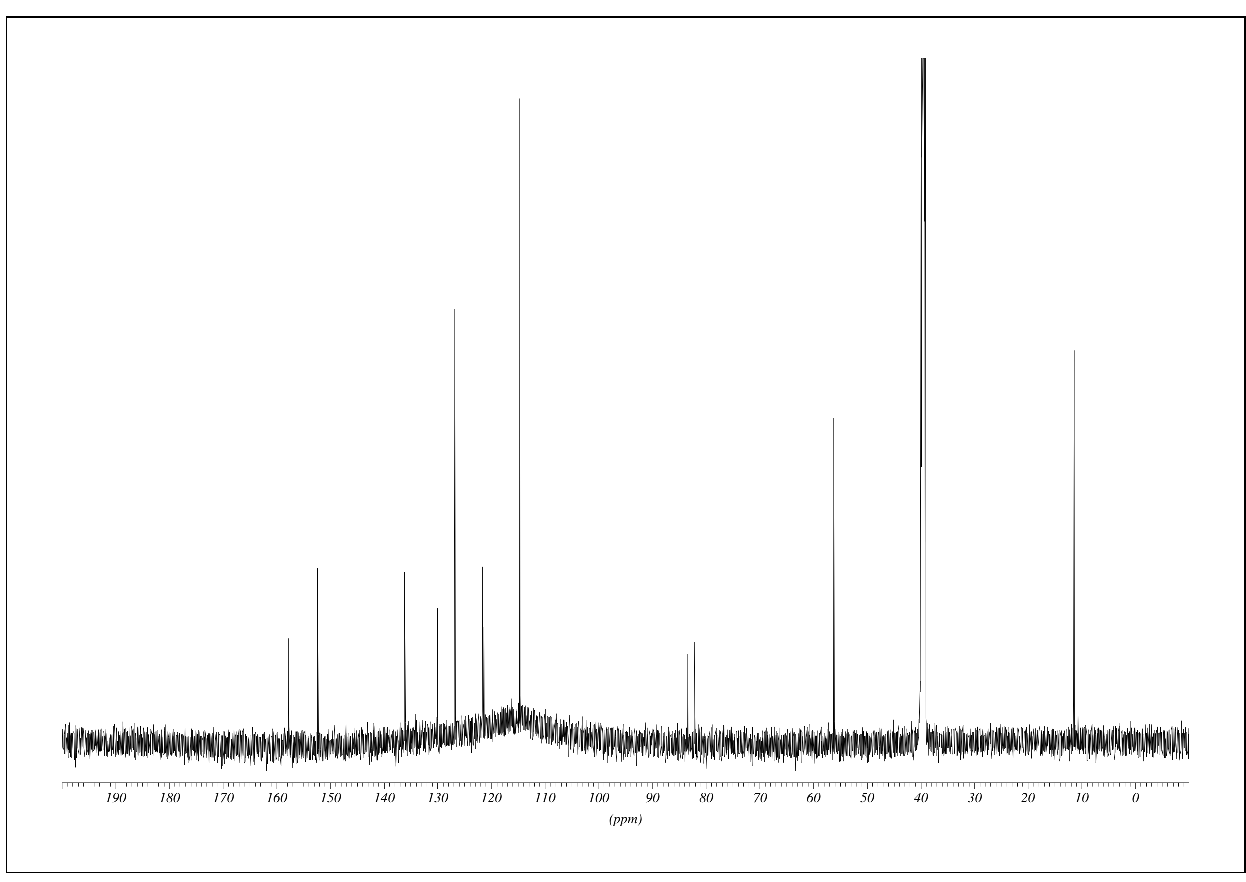
1-(4-(3-(1*H*-imidazol-4-yl)prop-2-ynyloxy)phenyl)ethanone (292)



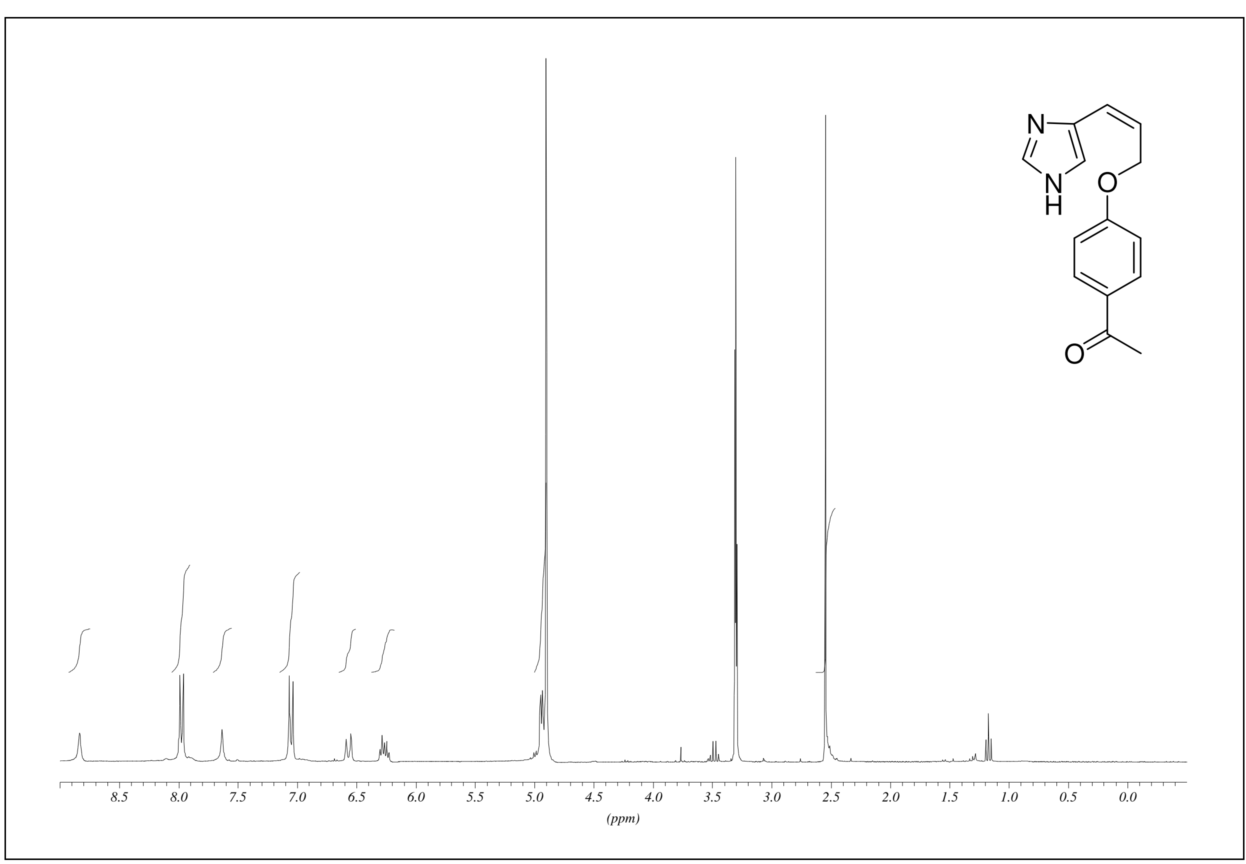


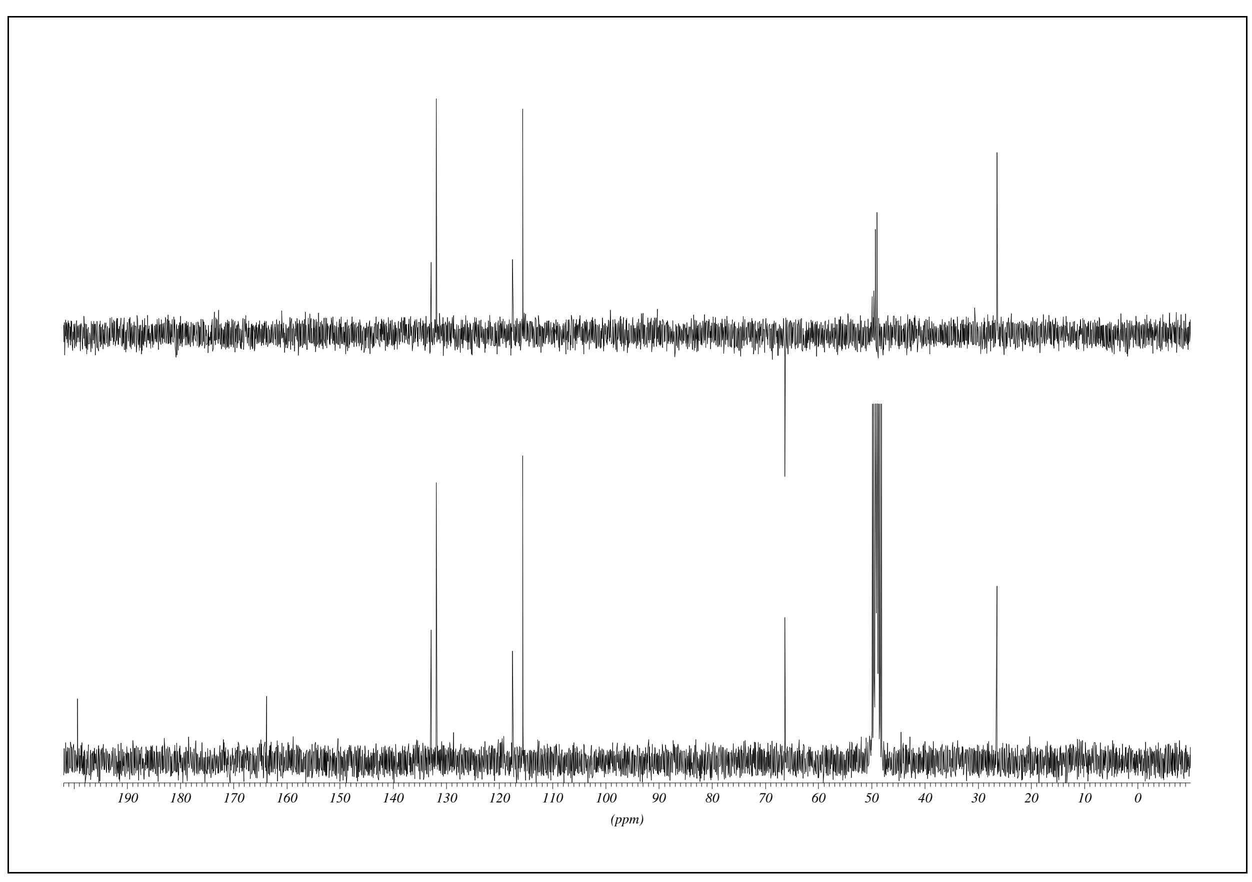
1-(4-(3-(1*H*-imidazol-4-yl)prop-2-ynyloxy)phenyl)ethanone (294)



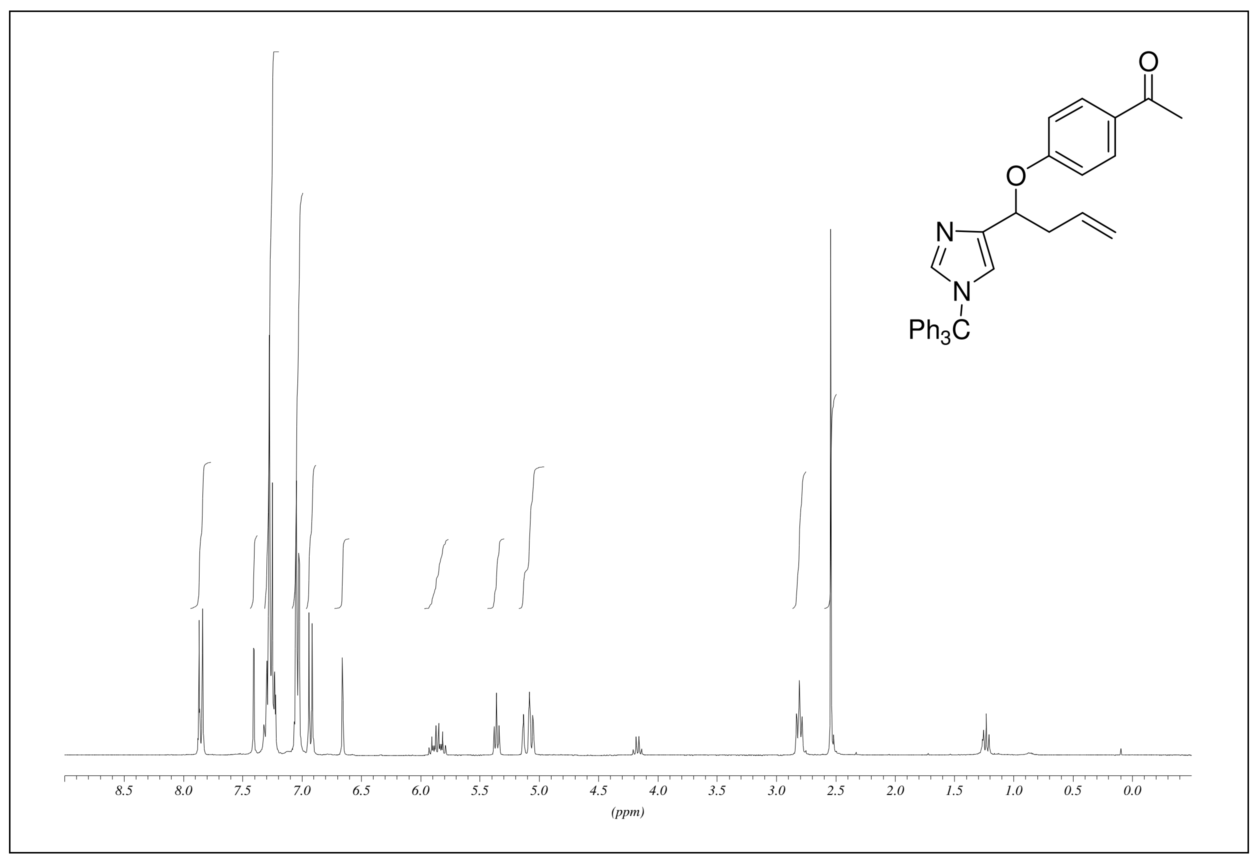


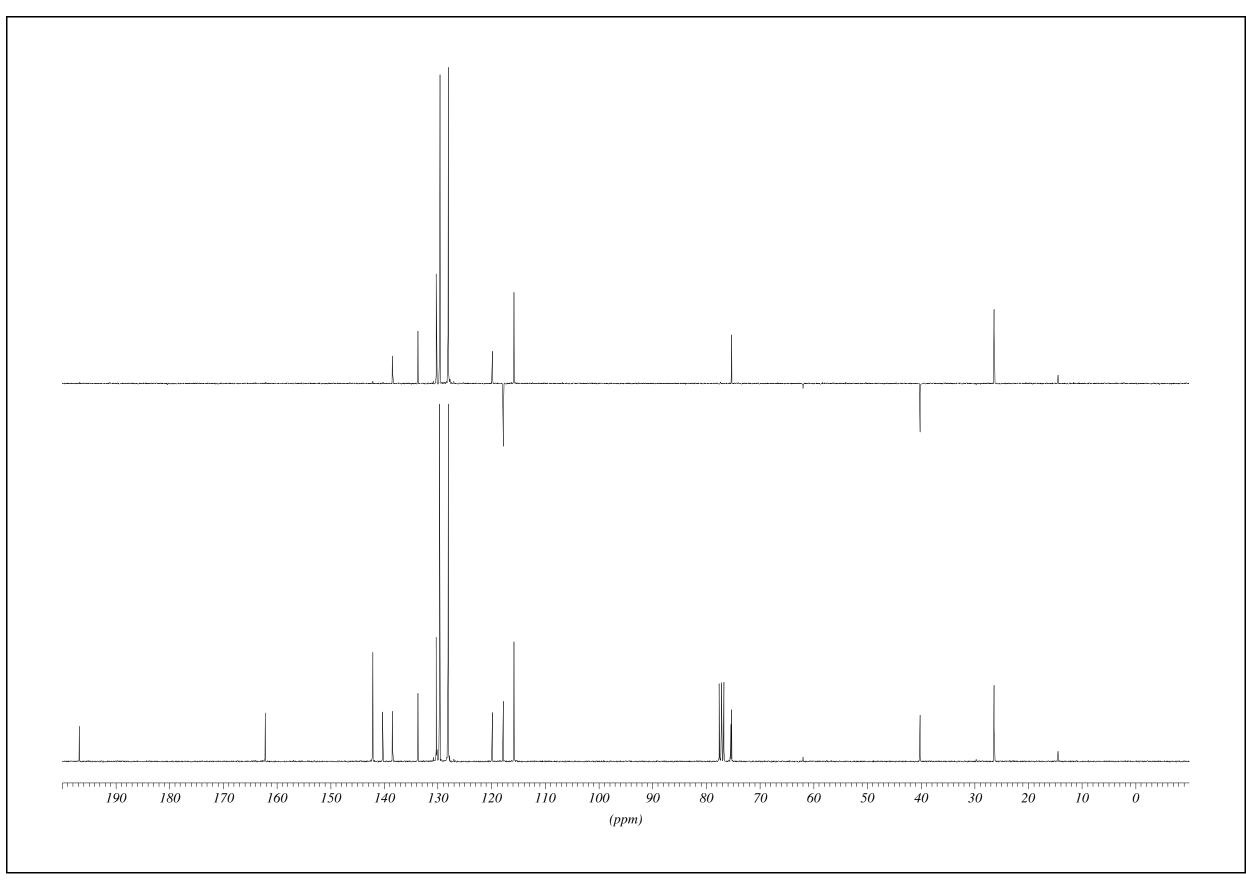
1-(4-((Z)-3-(1*H*-imidazol-4-yl)allyloxy)phenyl)ethanone (295)



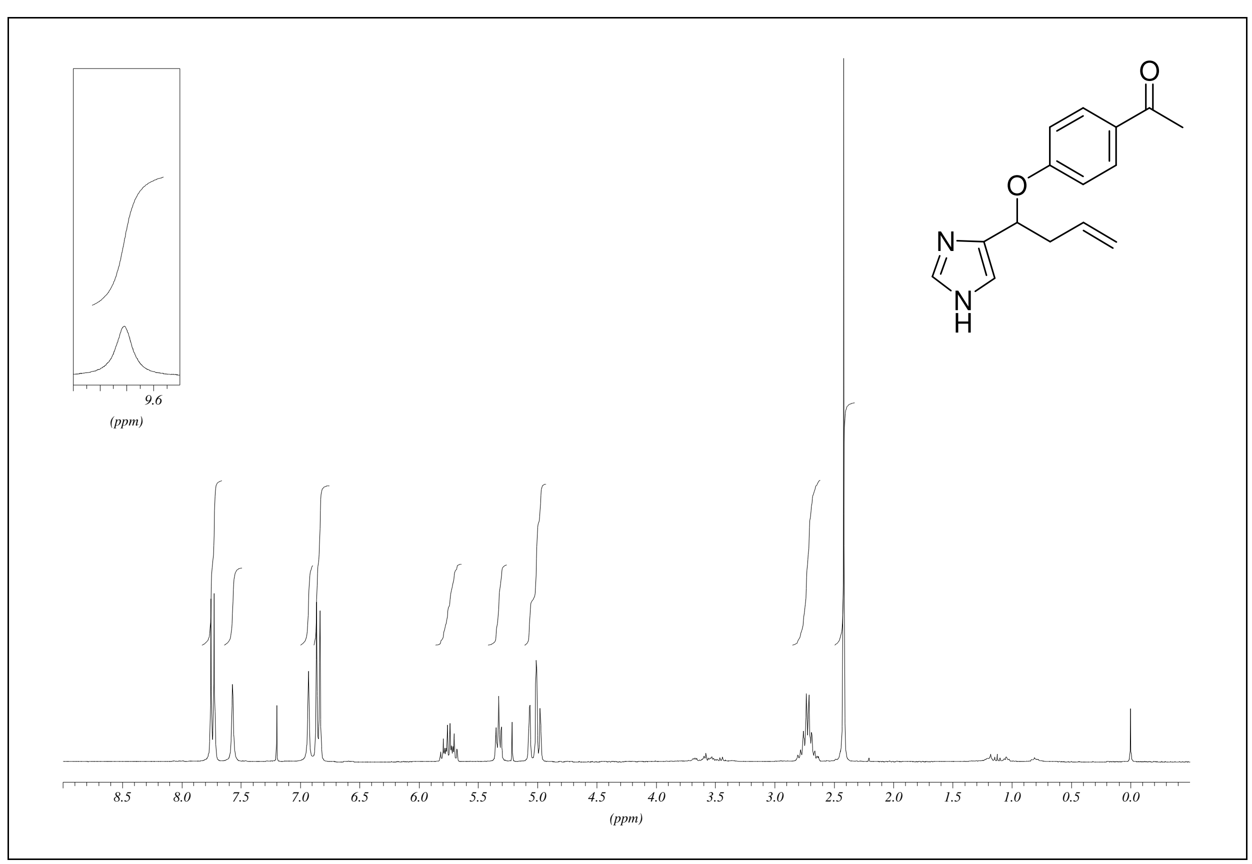


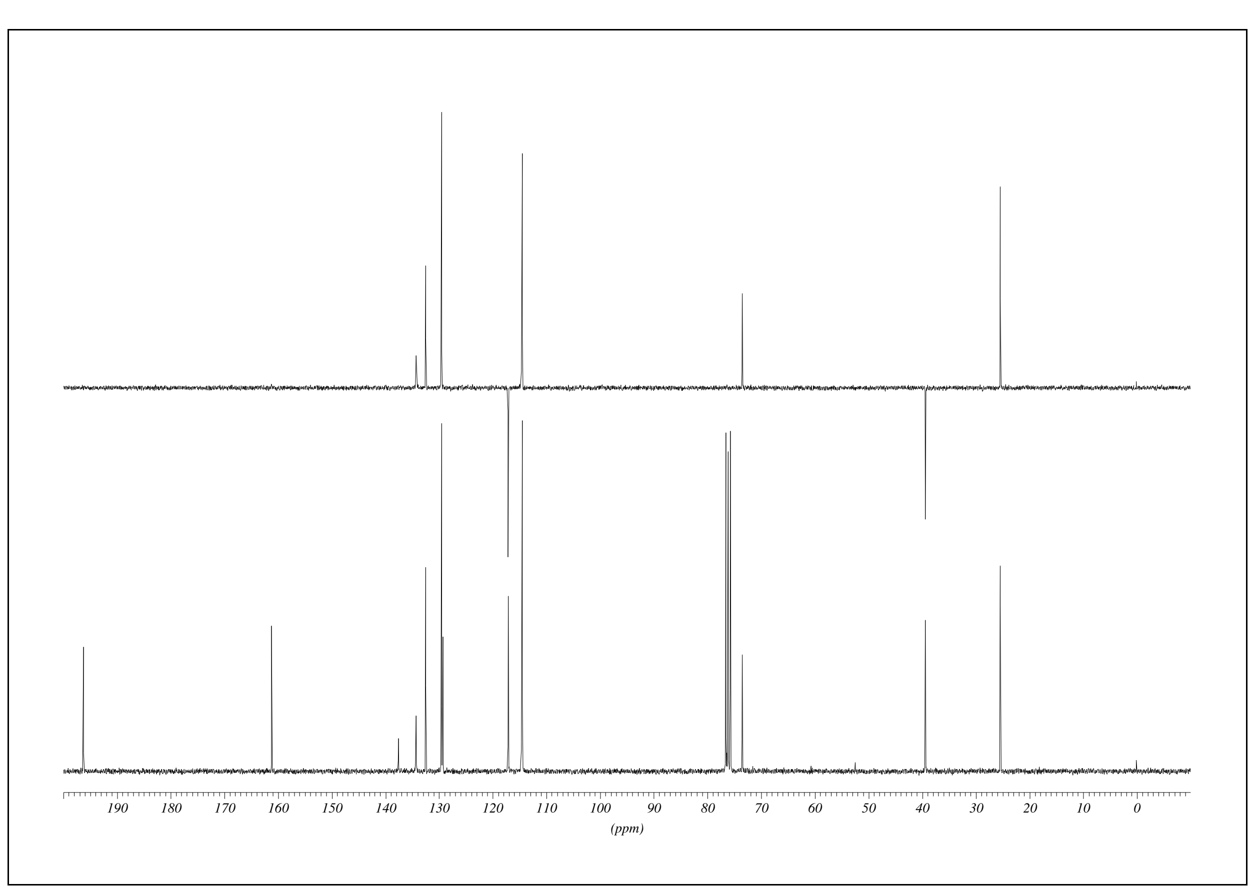
1-(4-(1-(1-trityl-1*H*-imidazol-4-yl)but-3-enyloxy)phenyl)ethanone (301)



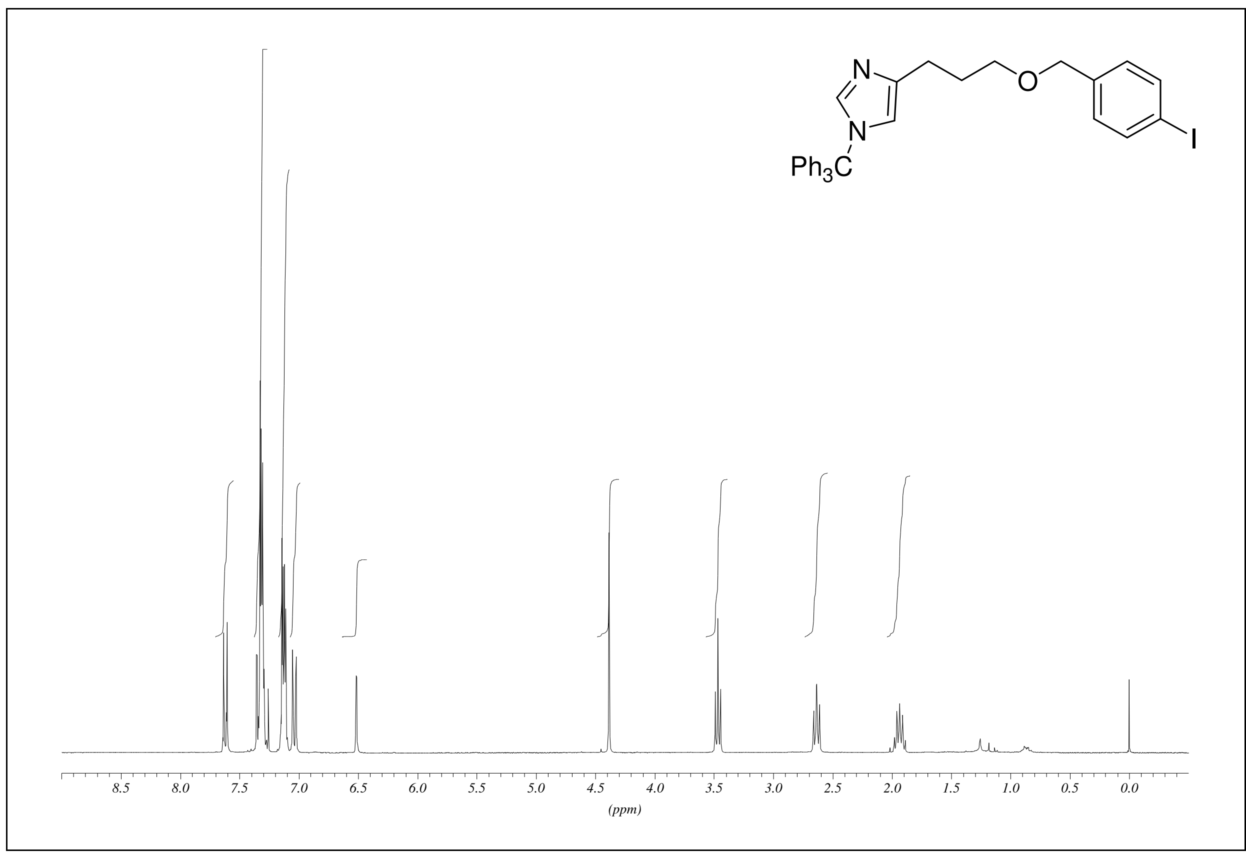


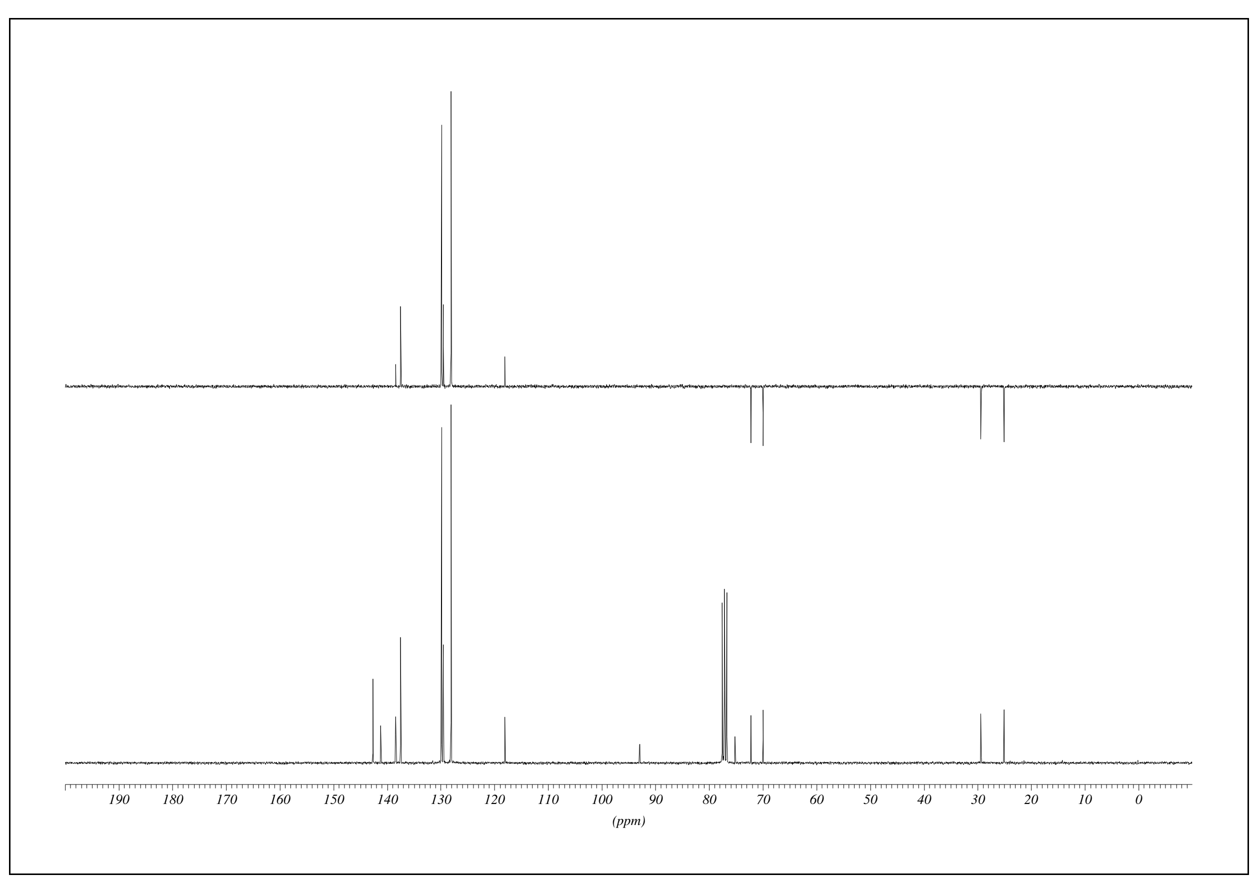
1-(4-(1-(1*H*-imidazol-4-yl)but-3-enyloxy)phenyl)ethanone (302)



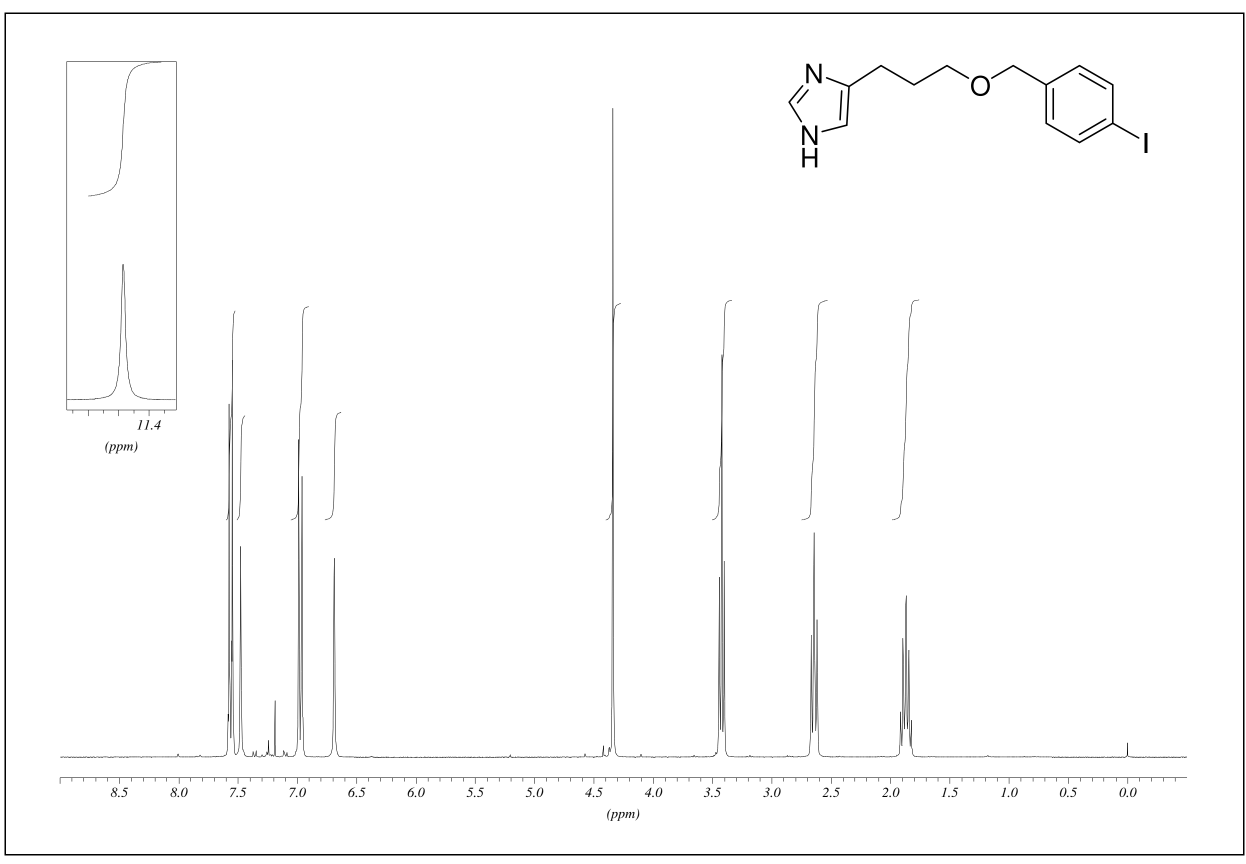


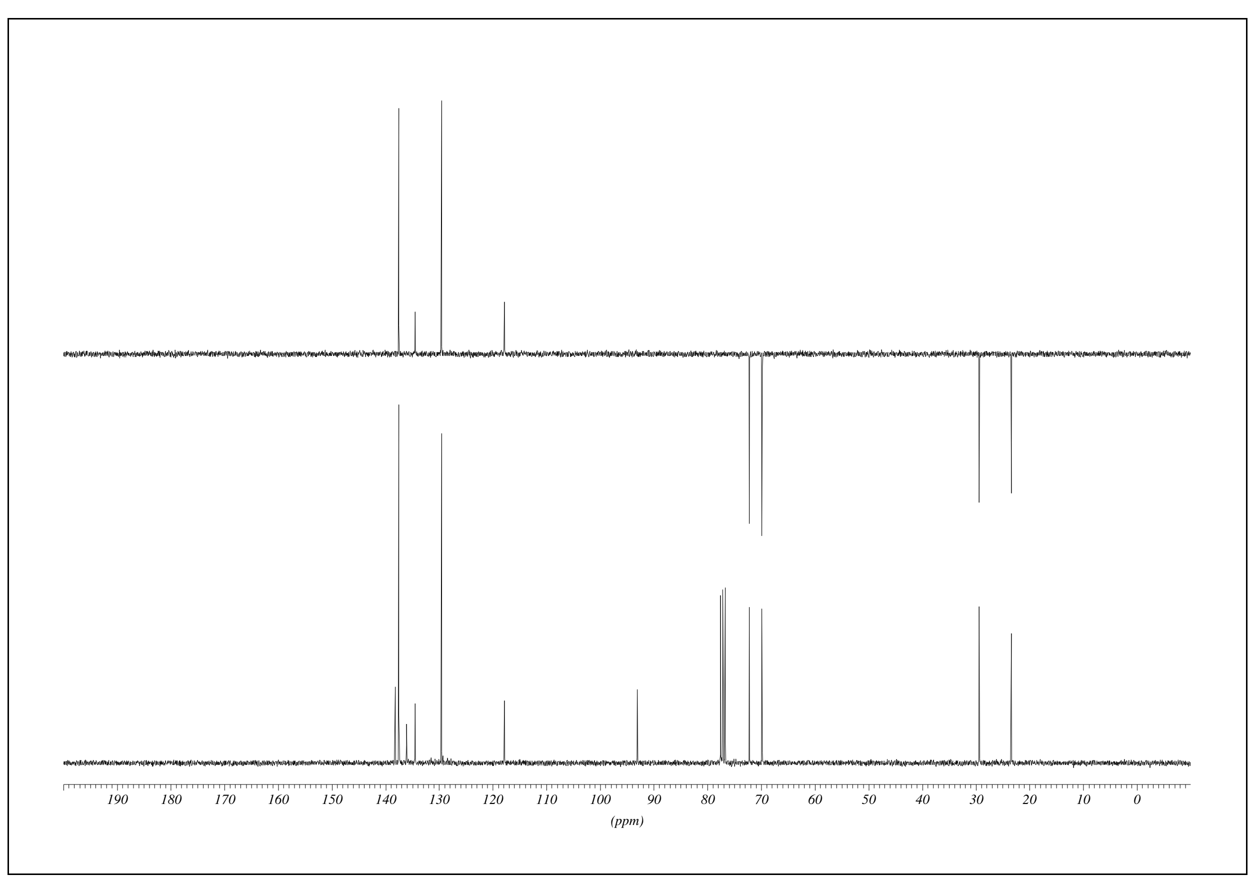
4-(3-(4-iodobenzyloxy)propyl)-1-trityl-1*H*-imidazole (304)



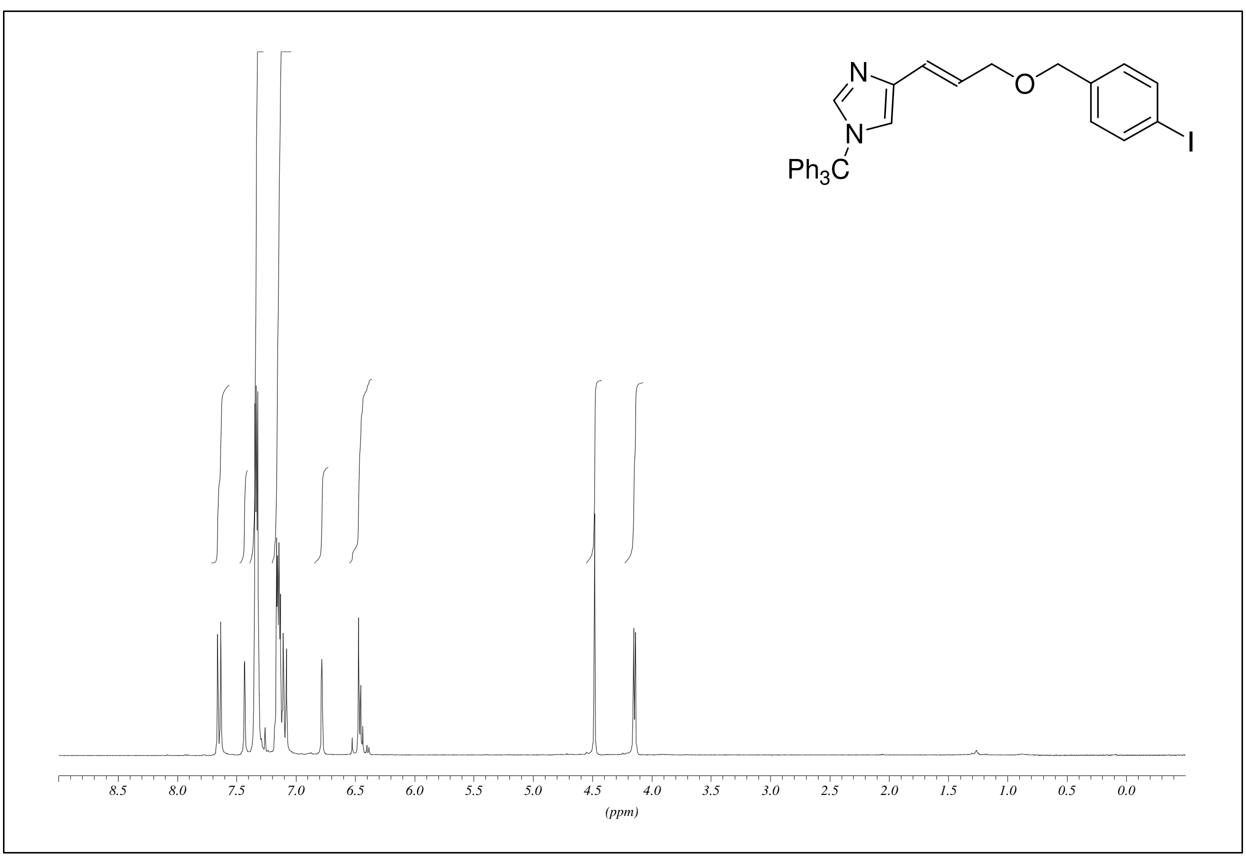


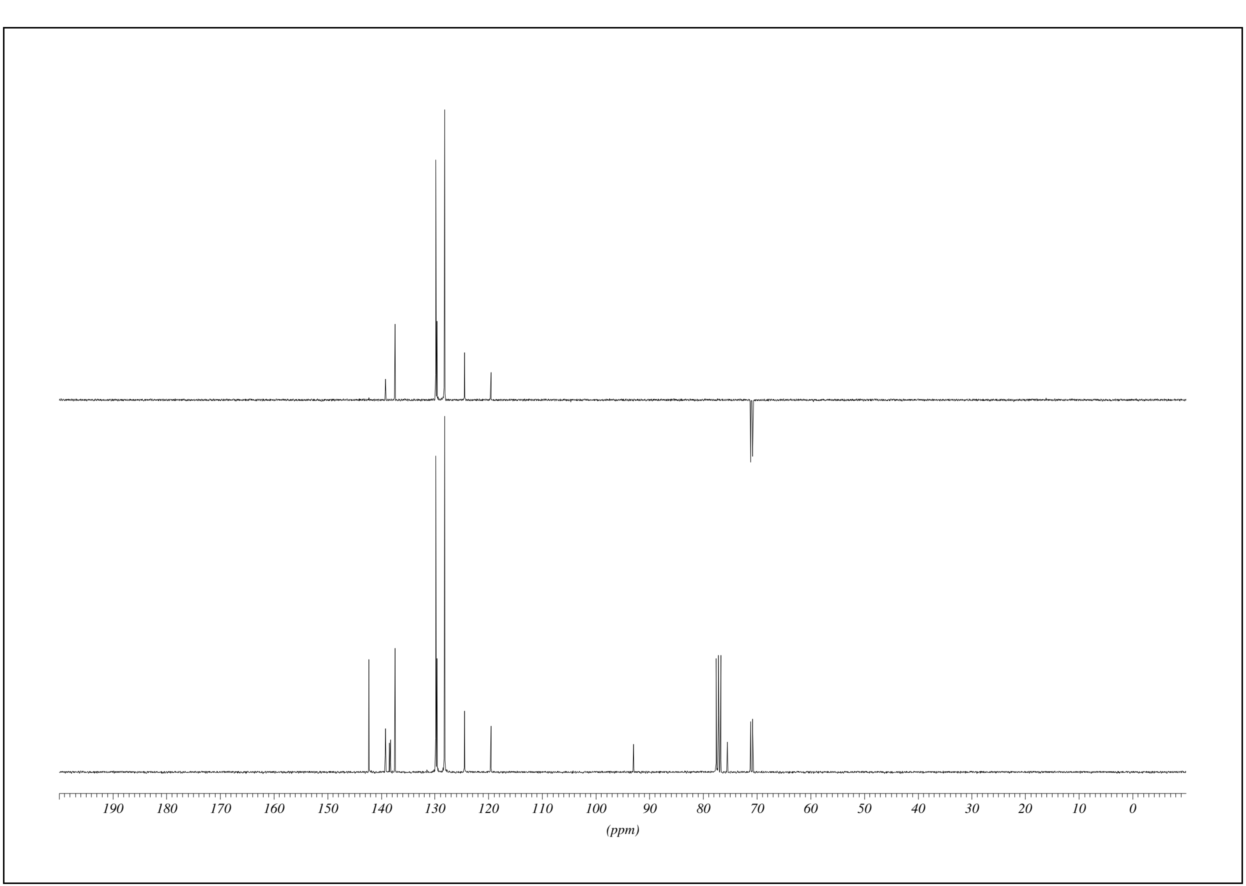
4-(3-(4-iodobenzyloxy)propyl)-1*H*-imidazole or (*iodoproxyfan*)(248)



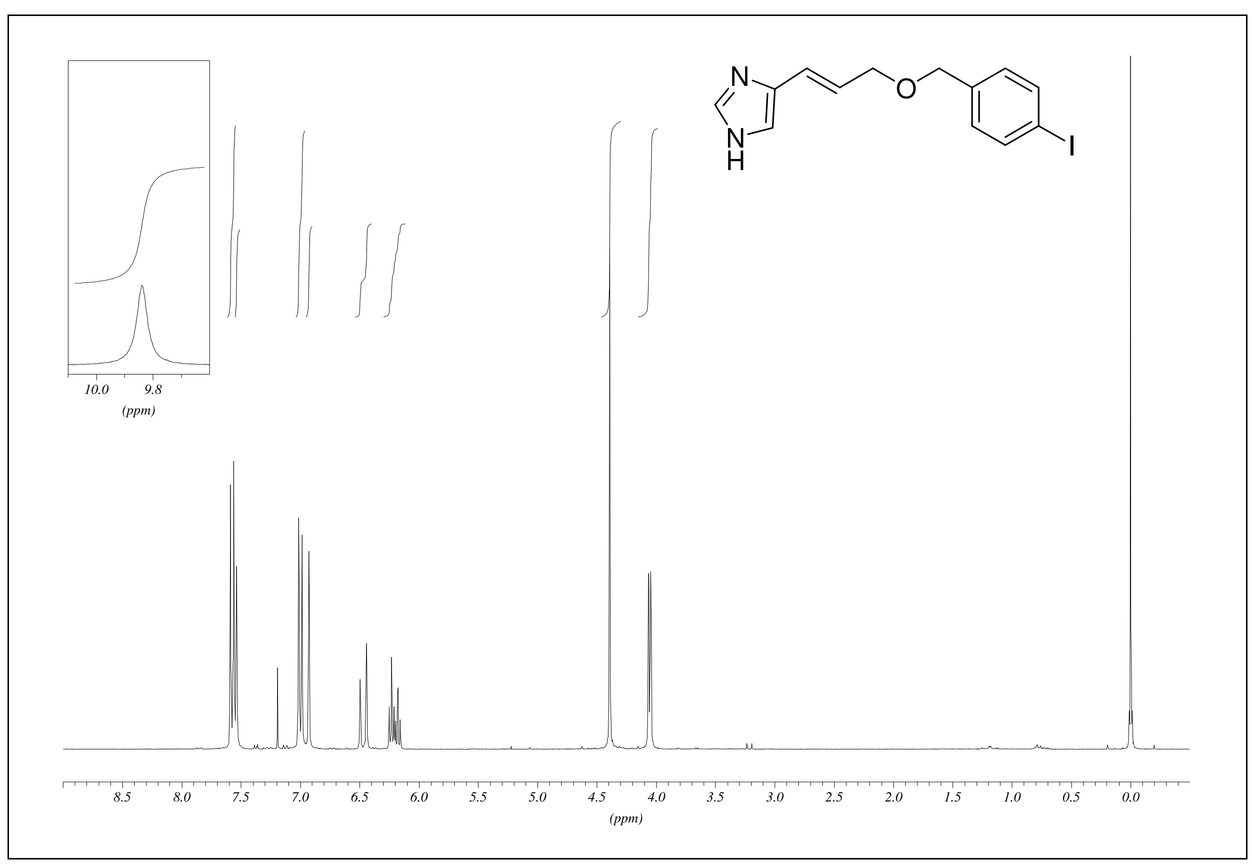


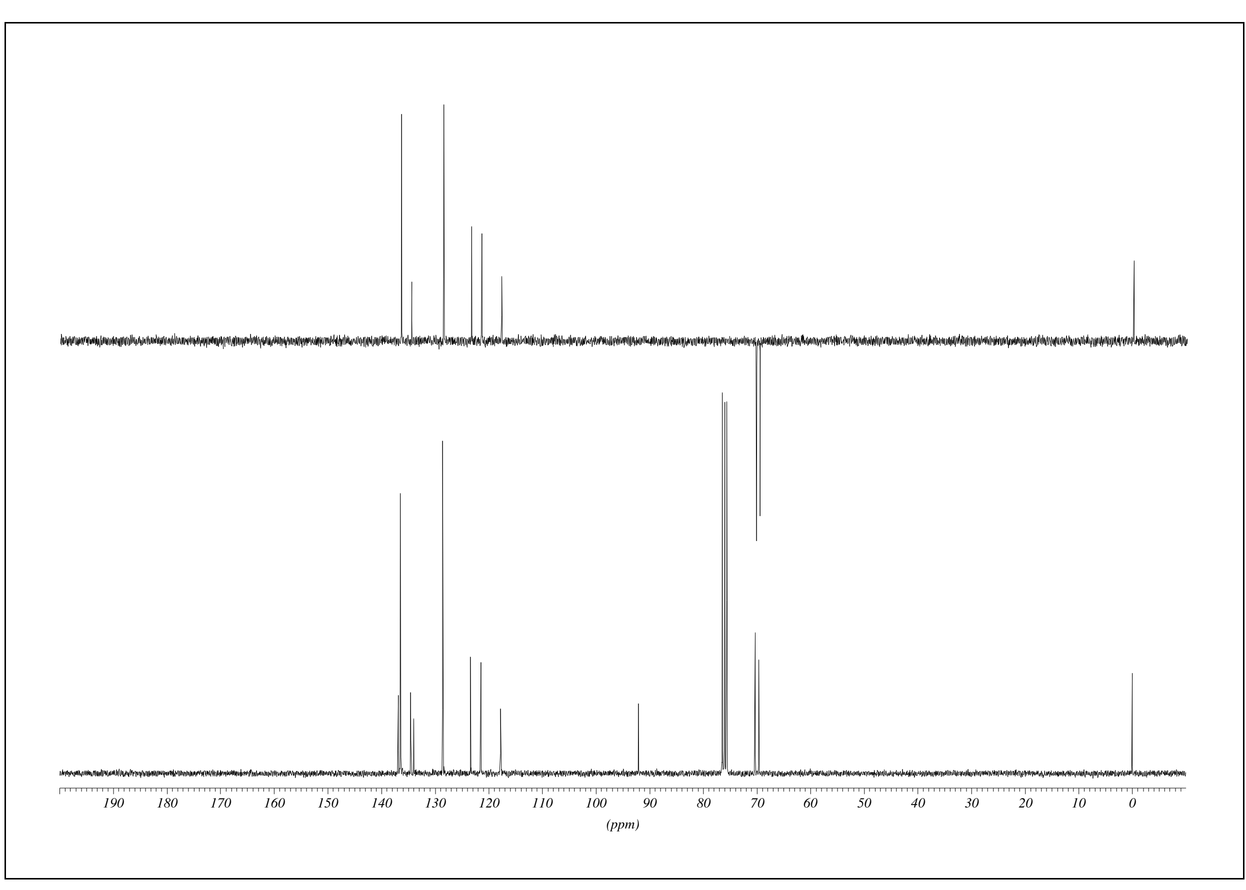
4-((*E*)-3-(4-iodobenzyloxy)prop-1-enyl)-1-trityl-1*H*-imidazole (305)



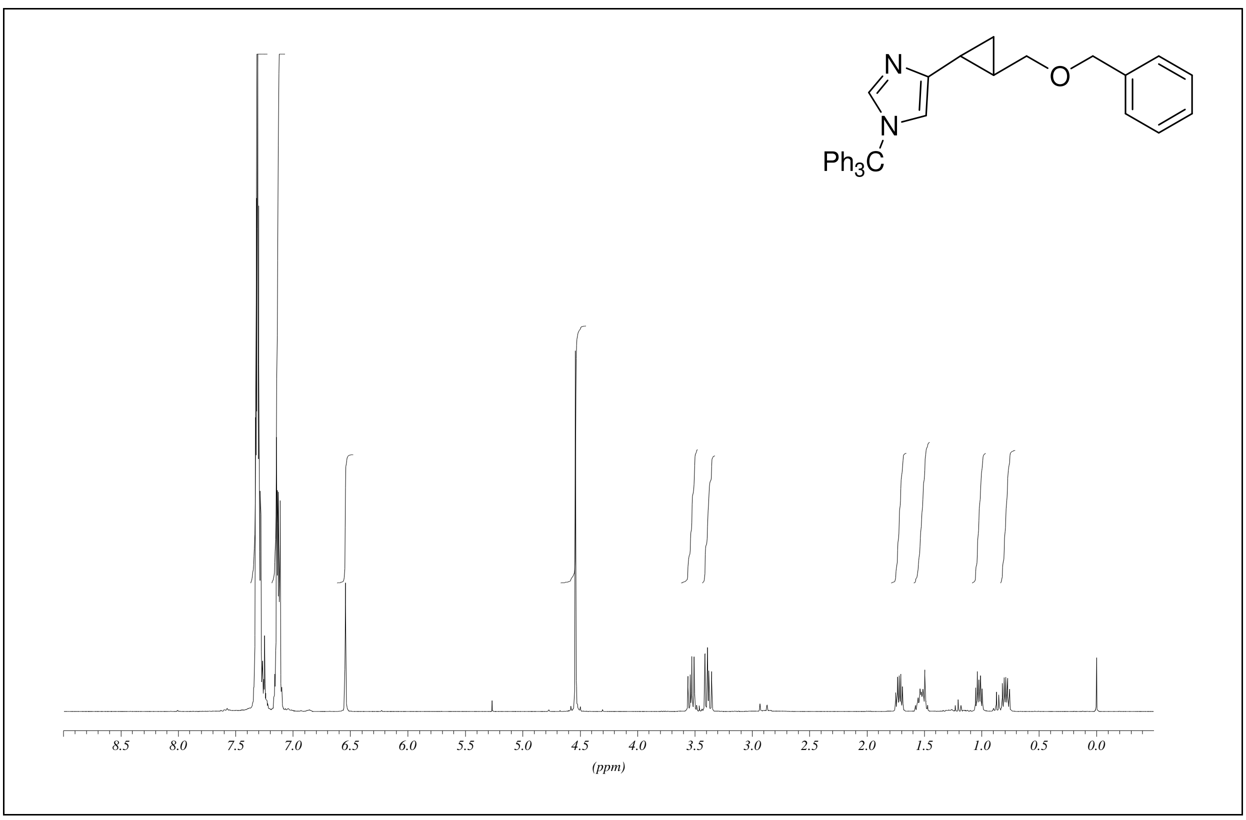


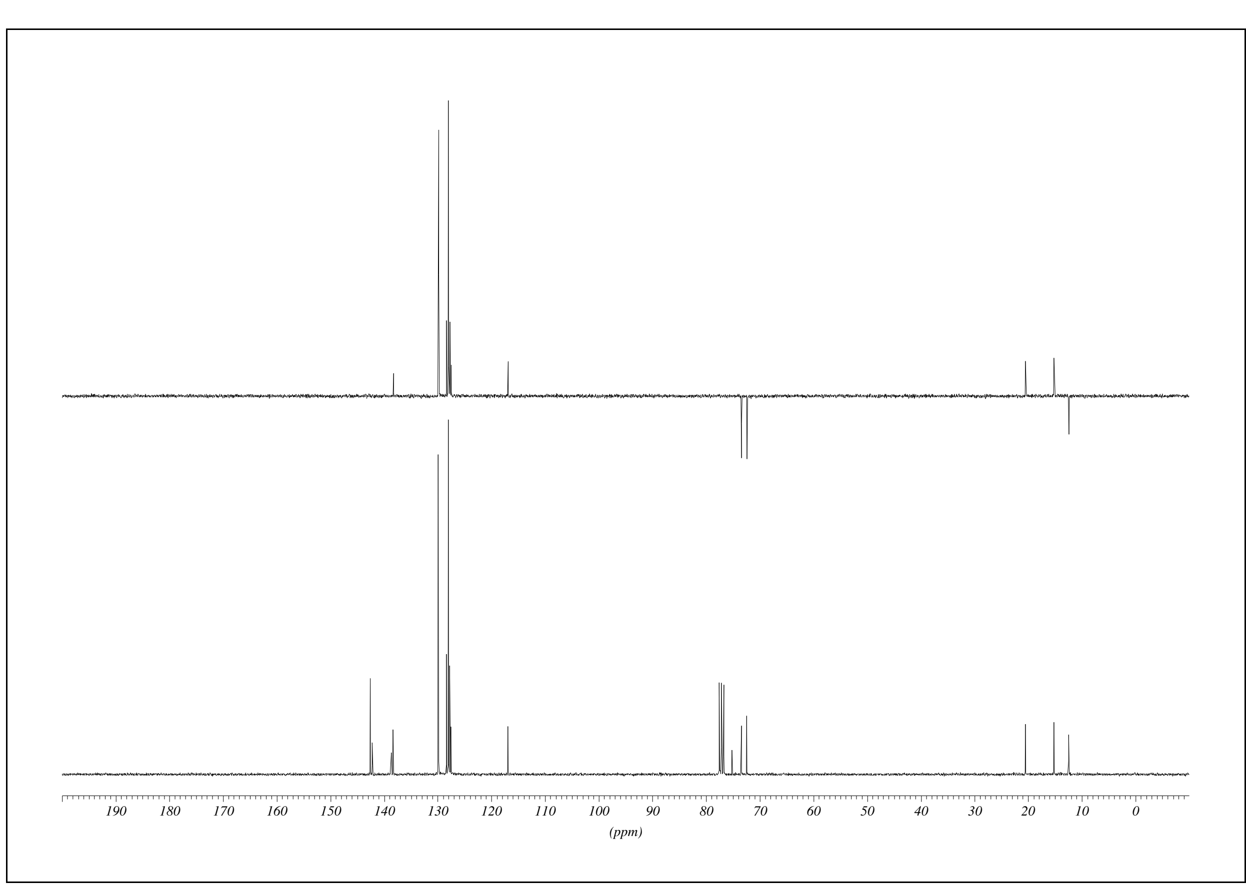
4-((E)-3-(4-iodobenzyloxy)prop-1-enyl)-1H-imidazole (306)



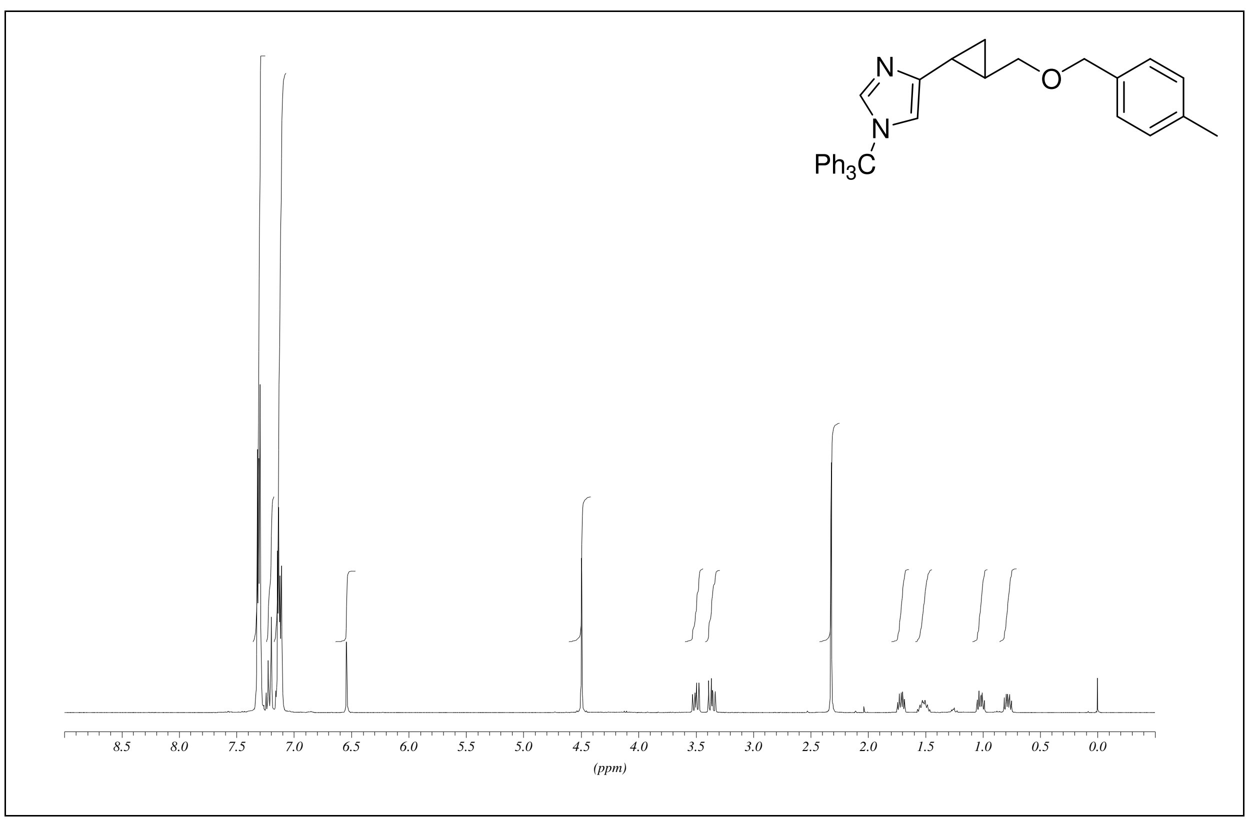


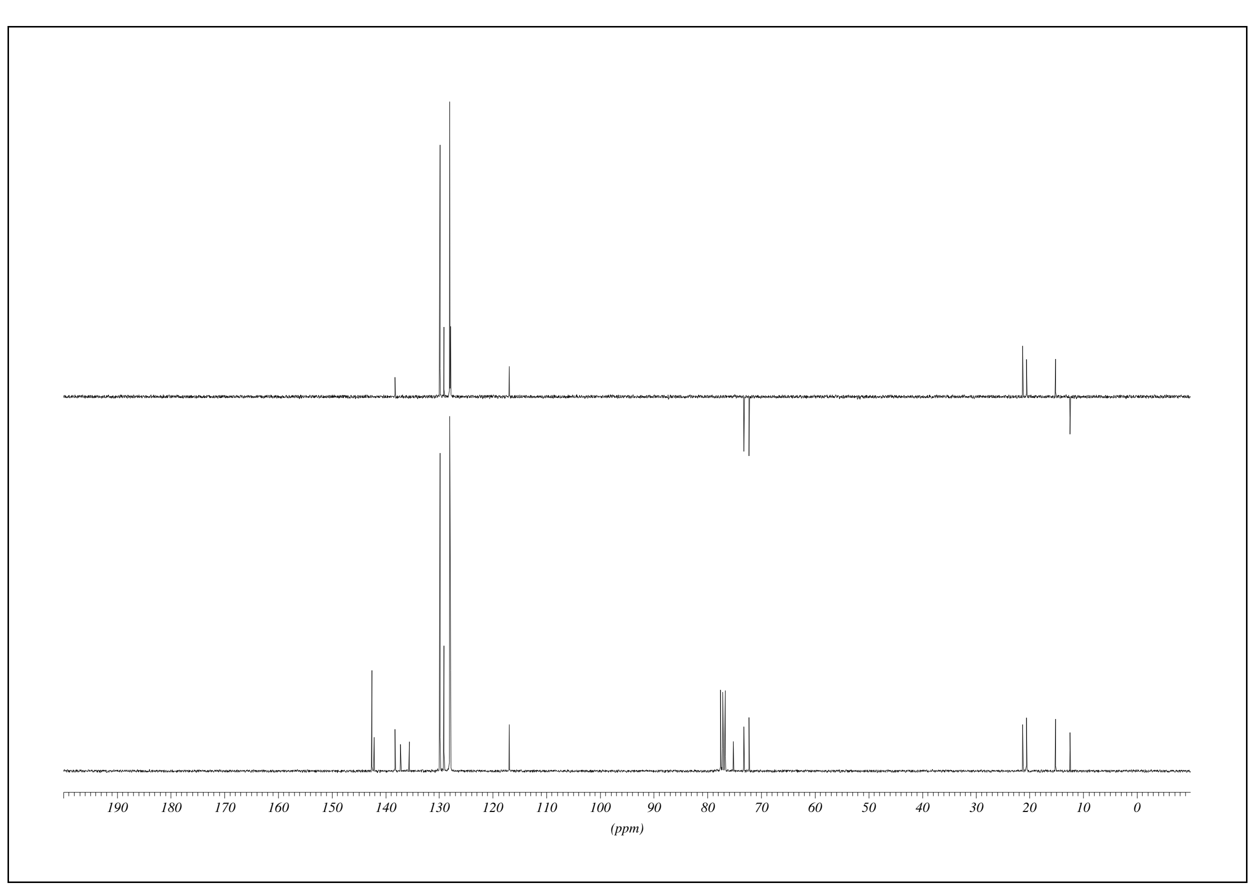
4-(2-((benzyloxy)methyl)cyclopropyl)-1-trityl-1*H*-imidazole (307)



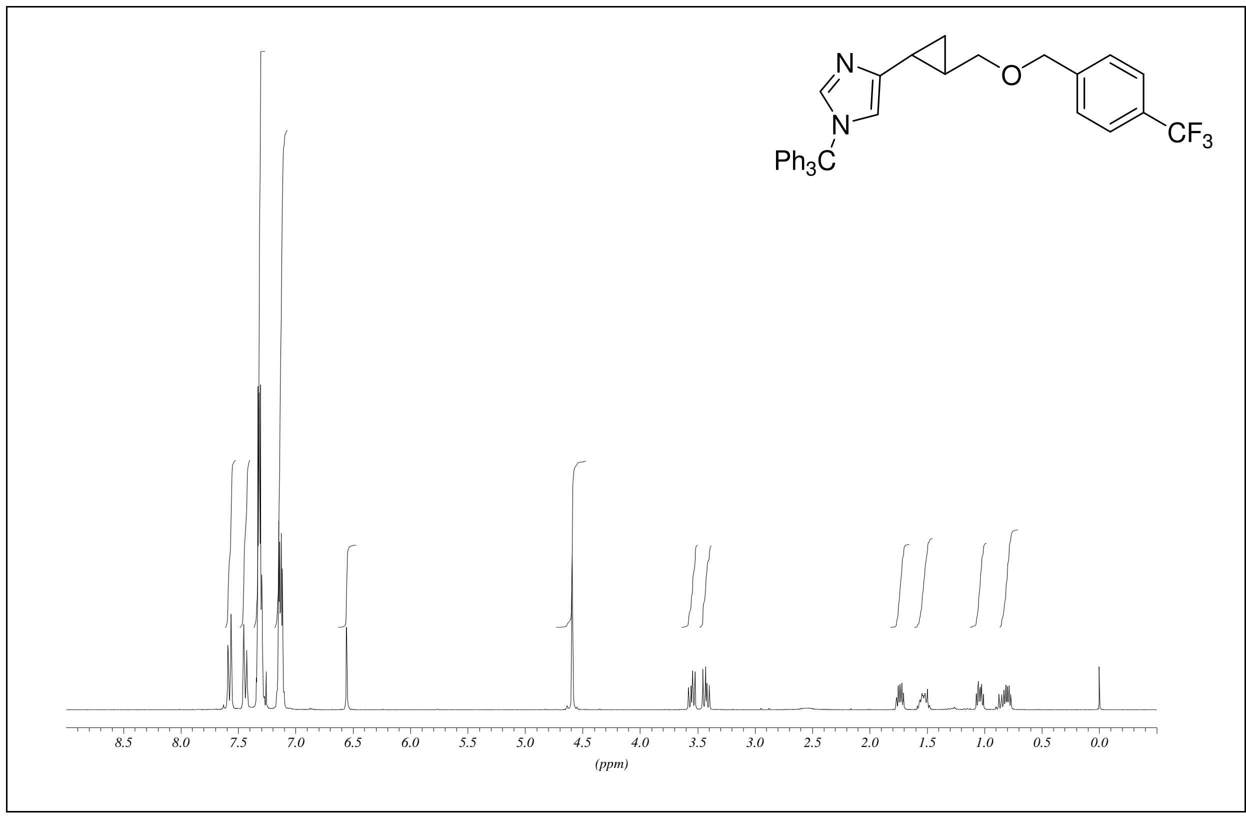


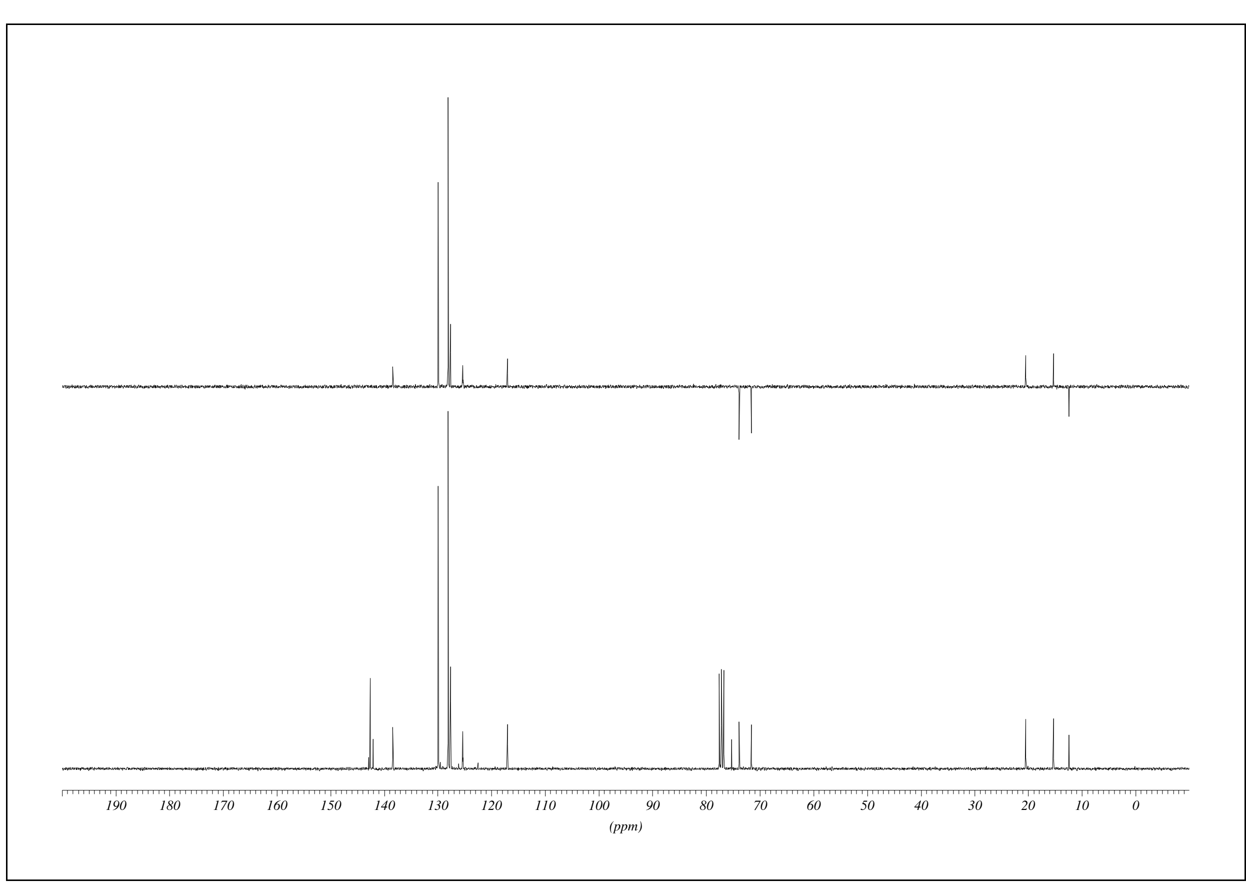
4-(2-((4-(methyl)benzyloxy)methyl)cyclopropyl)-1-trityl-1*H*-imidazole (308)



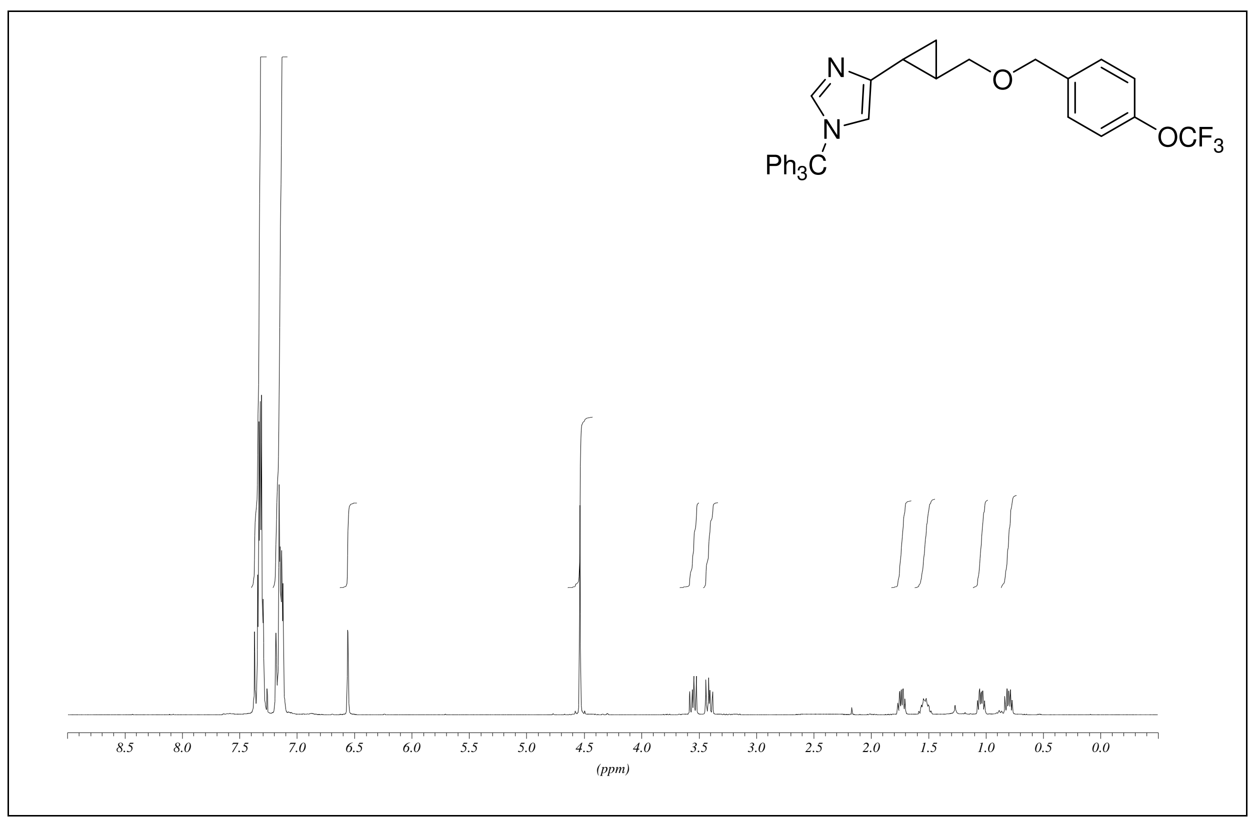


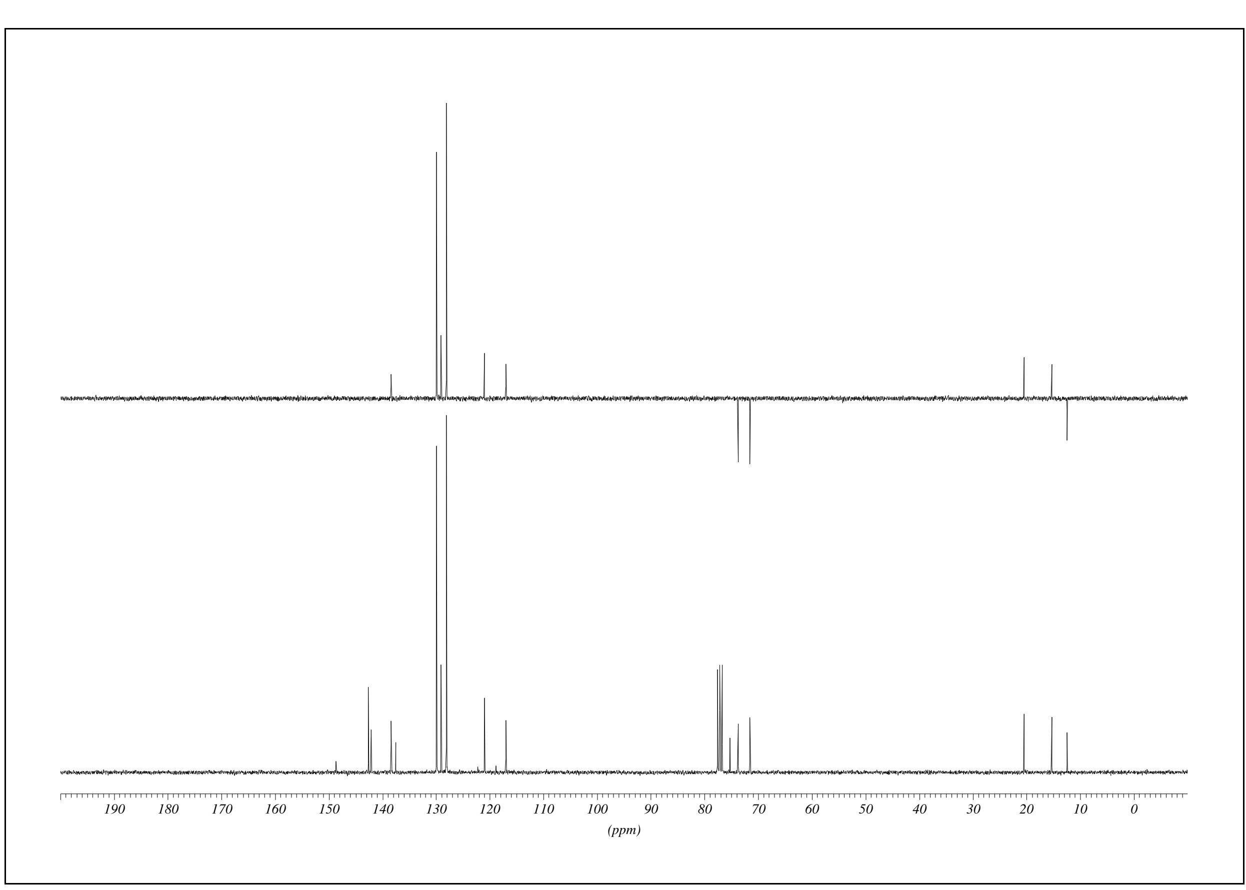
4-(2-((4-(trifluoromethyl)benzyloxy)methyl)cyclopropyl)-1-trityl-1*H*-imidazole (309)



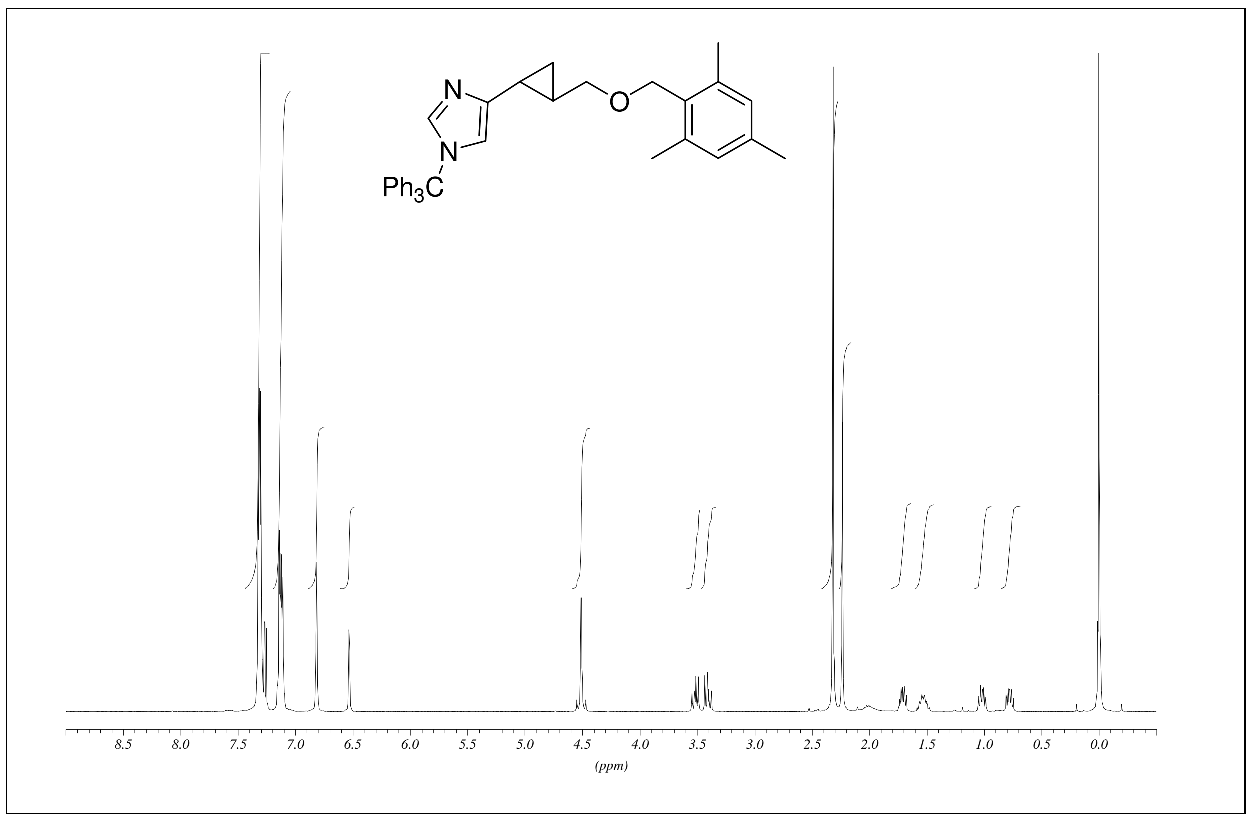


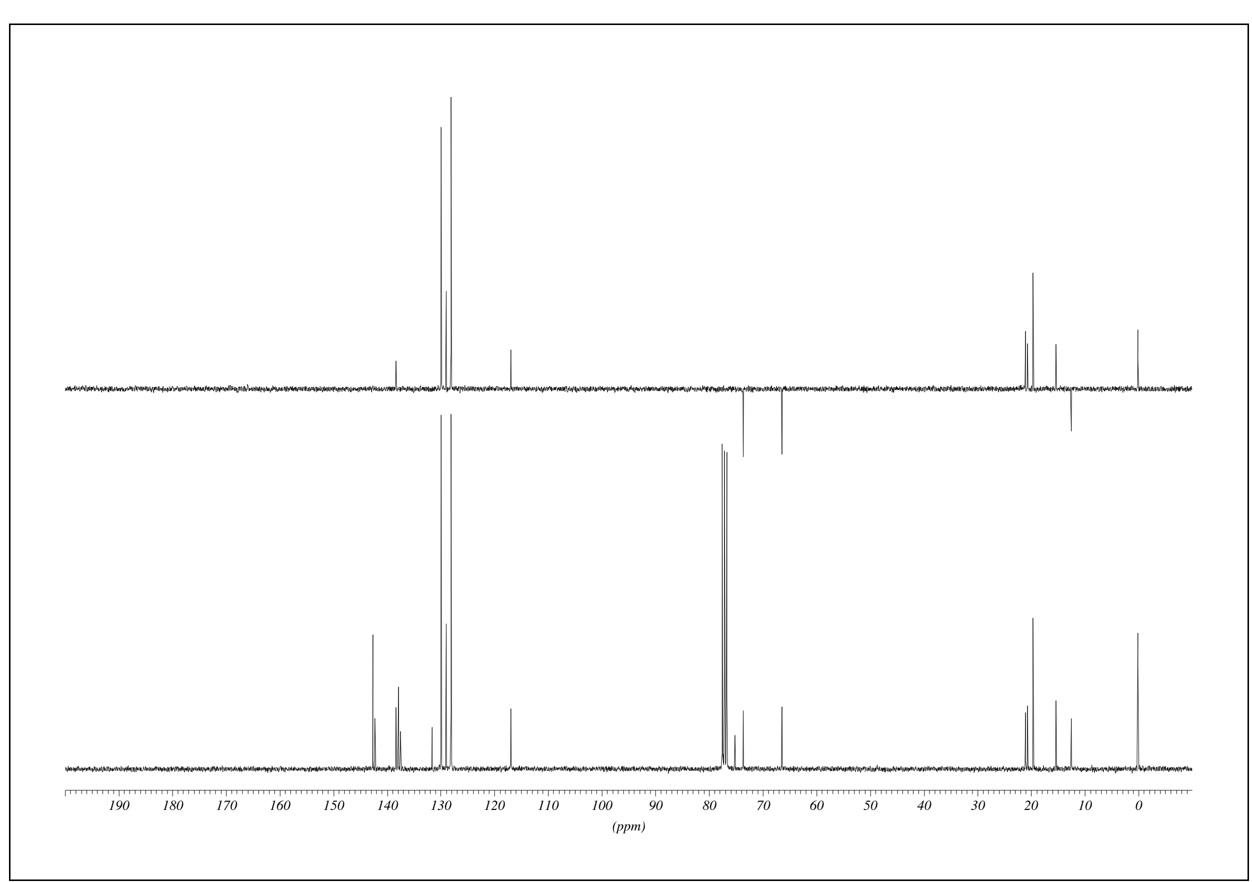
4-(2-((4-(trifluoromethoxy)benzyloxy)methyl)cyclopropyl)-1-trityl-1*H*-imidazole (310)



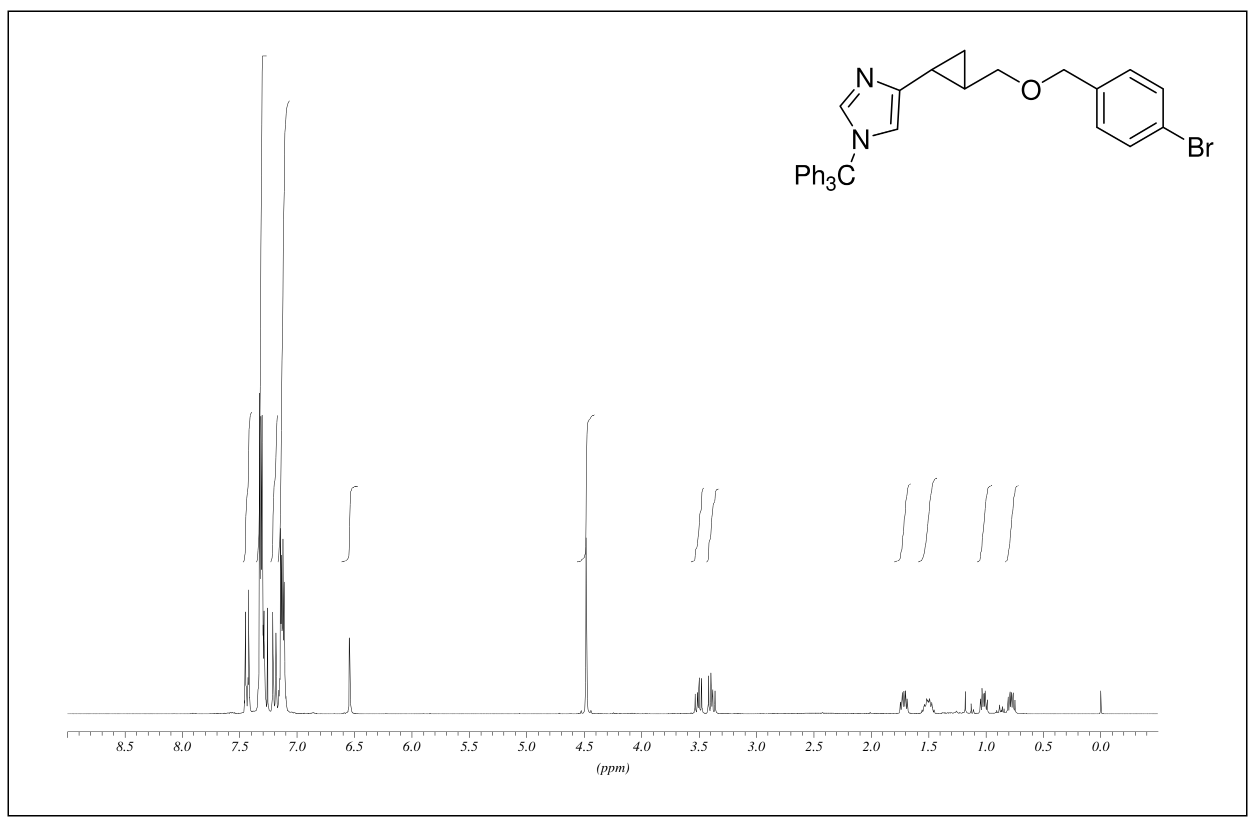


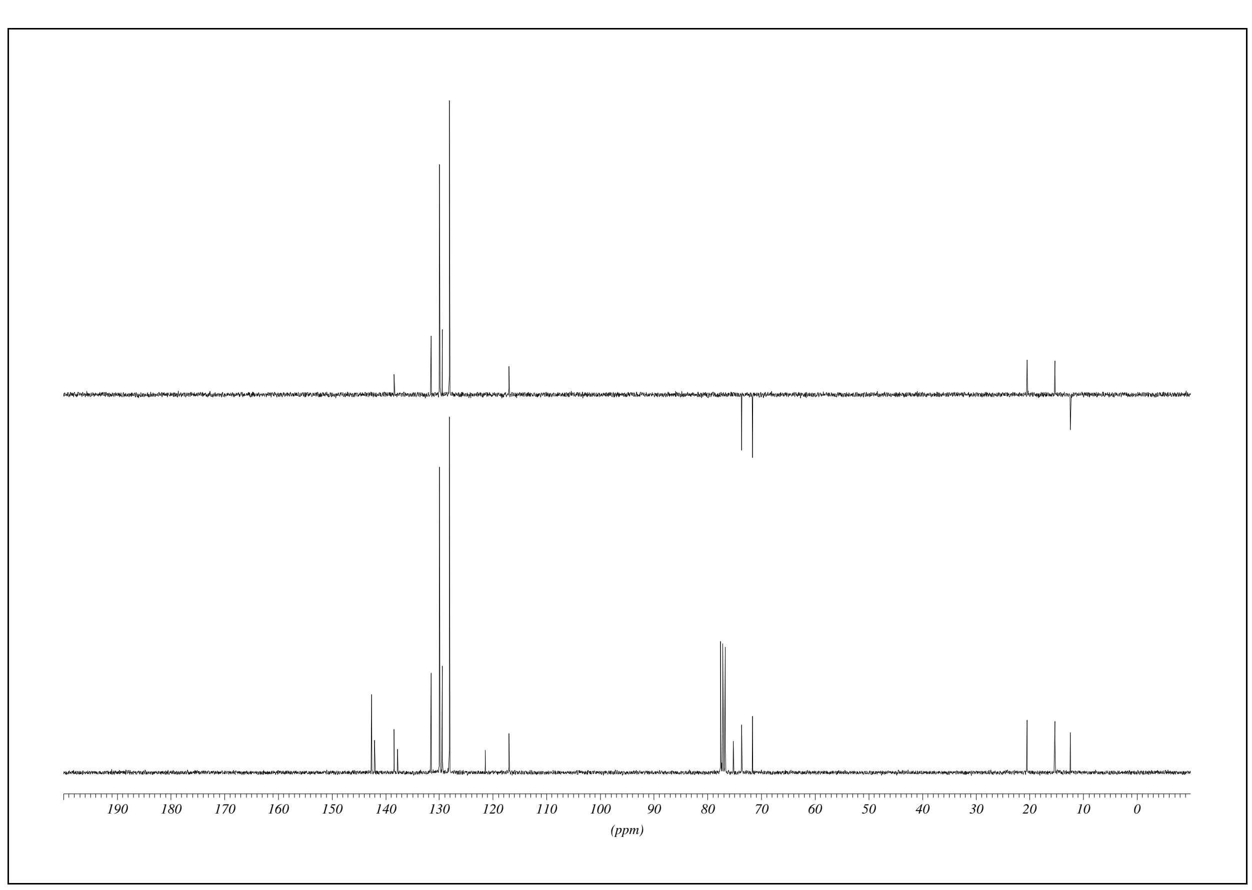
4-(2-((2,4,6-trimethyl)benzyloxy)methyl)cyclopropyl)-1-trityl-1*H*-imidazole (321)



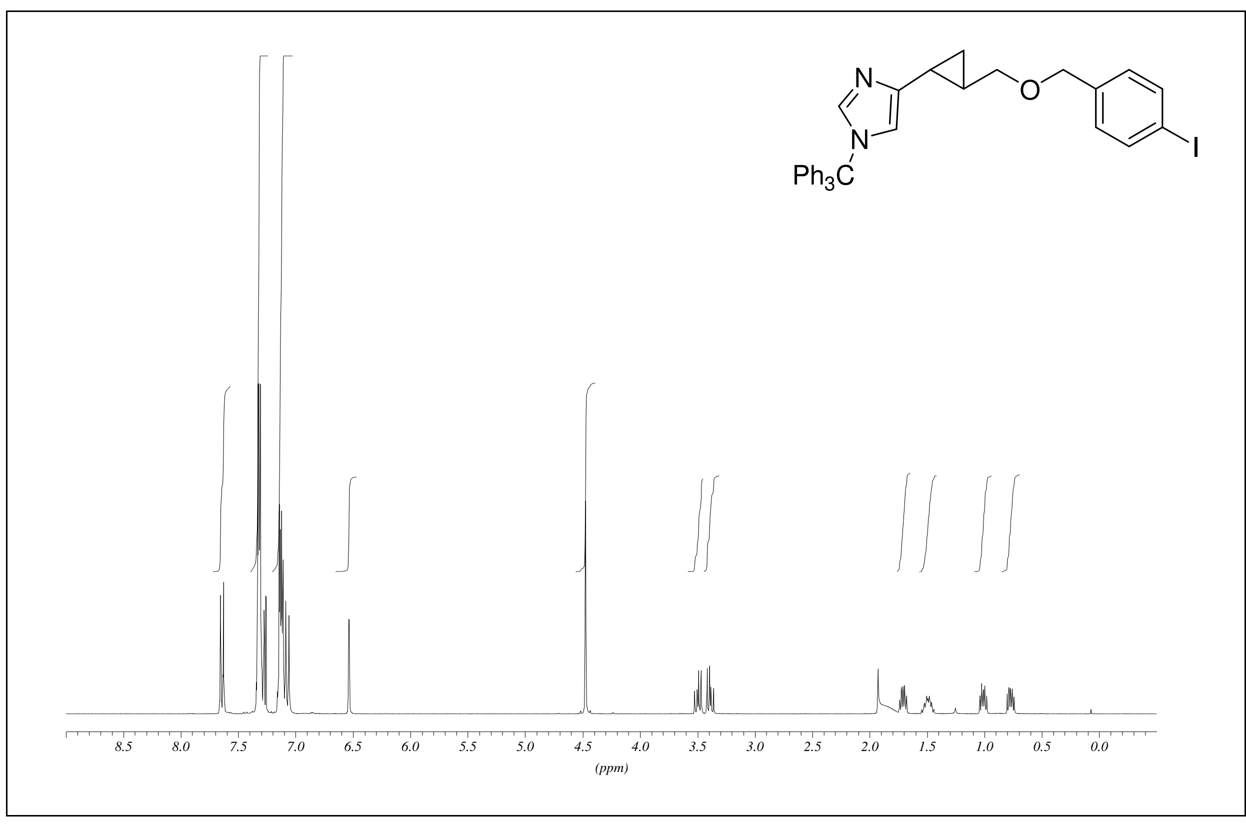


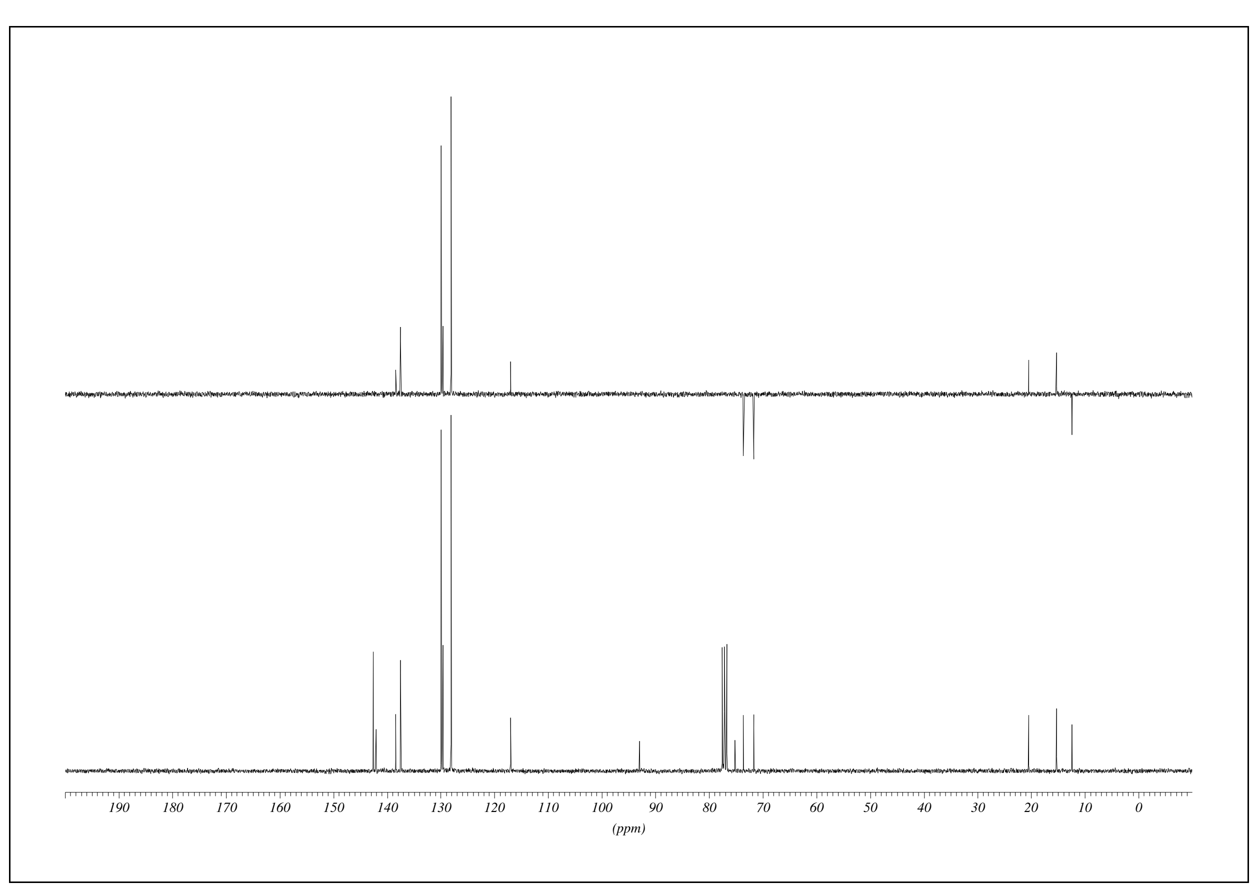
4-(2-((4-bromobenzyloxy)methyl)cyclopropyl)-1-trityl-1*H*-imidazole (312)



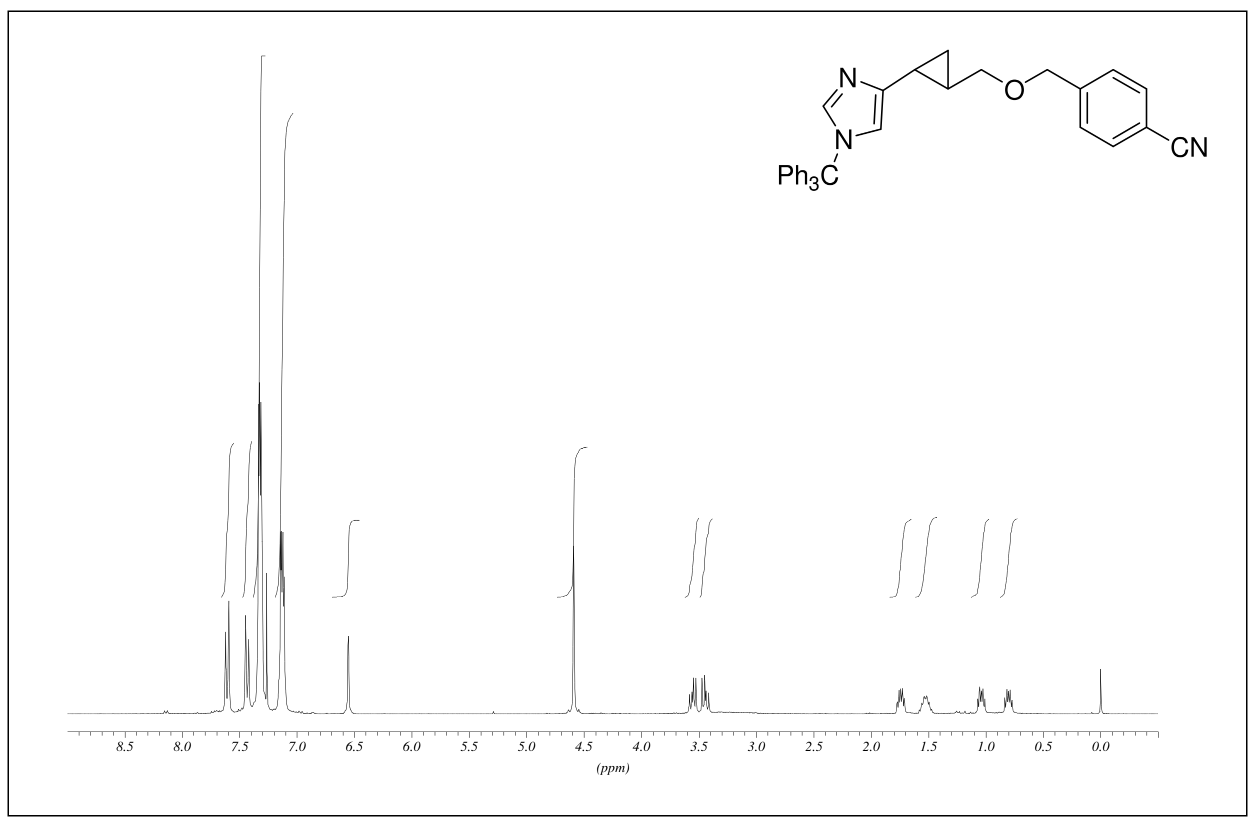


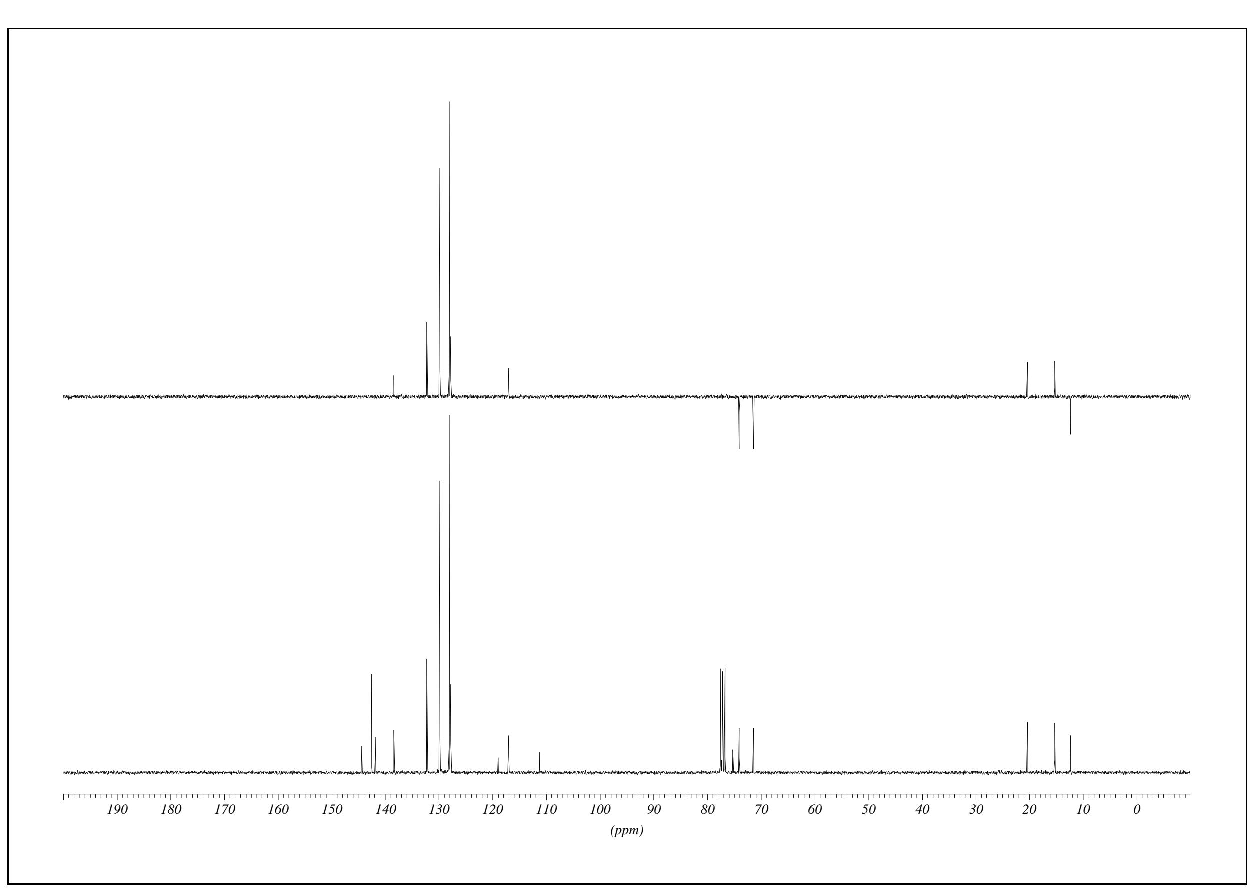
4-(2-((4-iodobenzyloxy)methyl)cyclopropyl)-1-trityl-1*H*-imidazole (311)



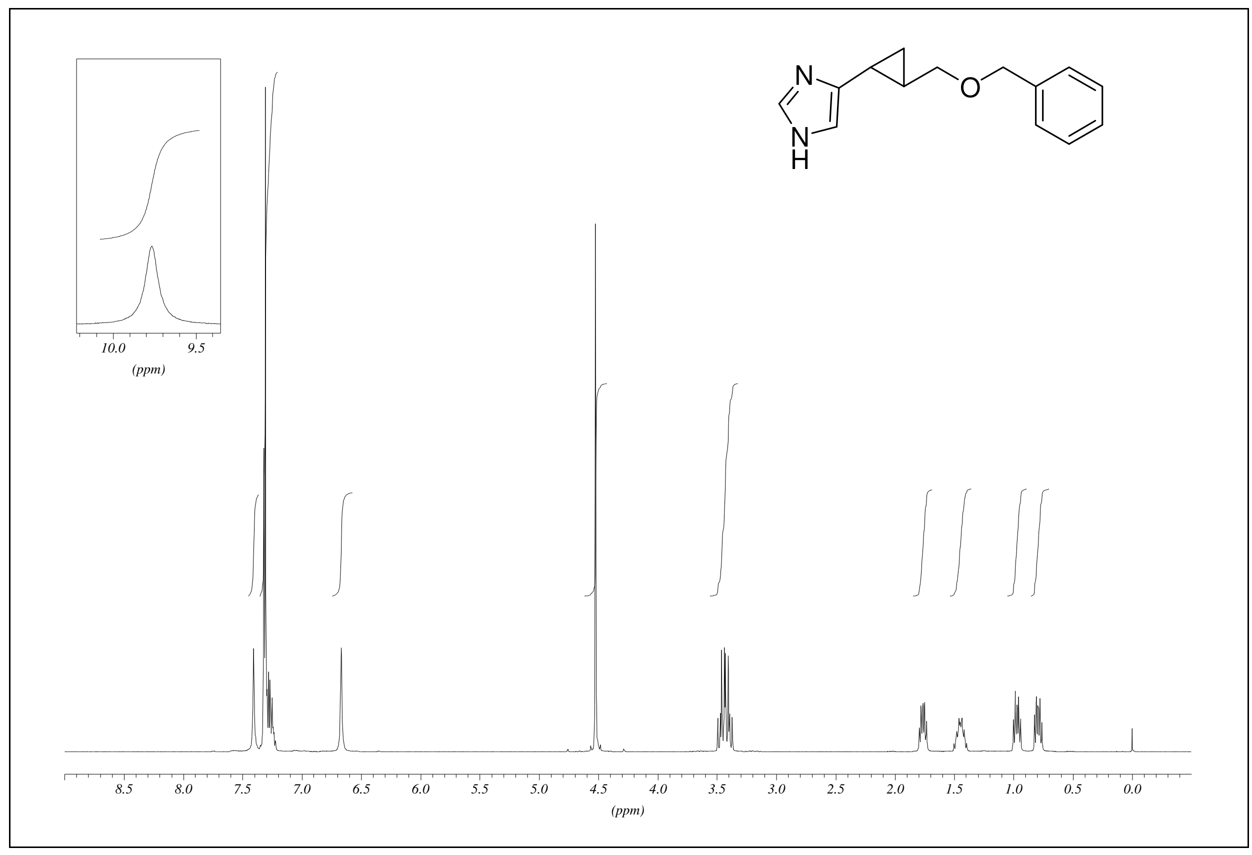


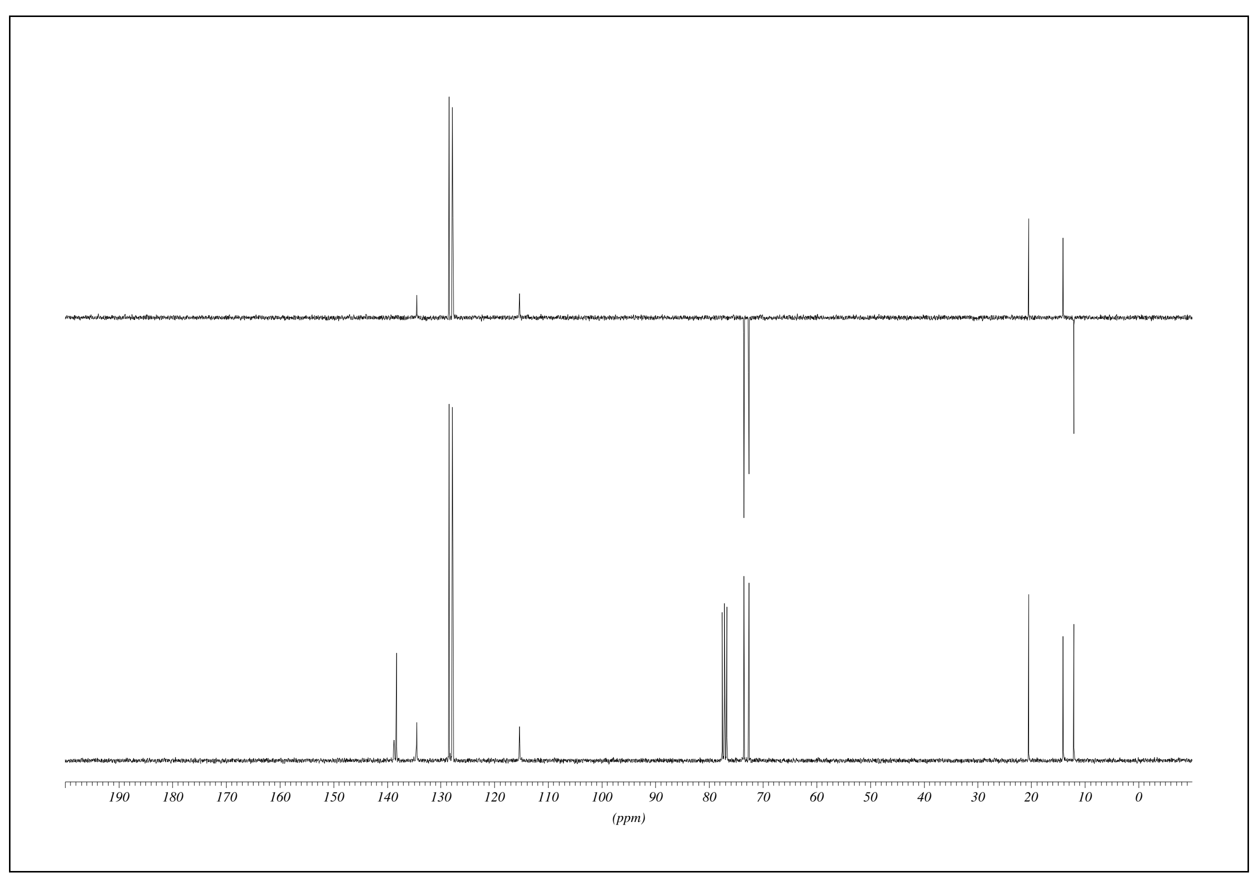
4-(((2-(1-trityl-1H-imidazol-4-yl)cyclopropyl)methoxy)methyl)benzonitrile (313)



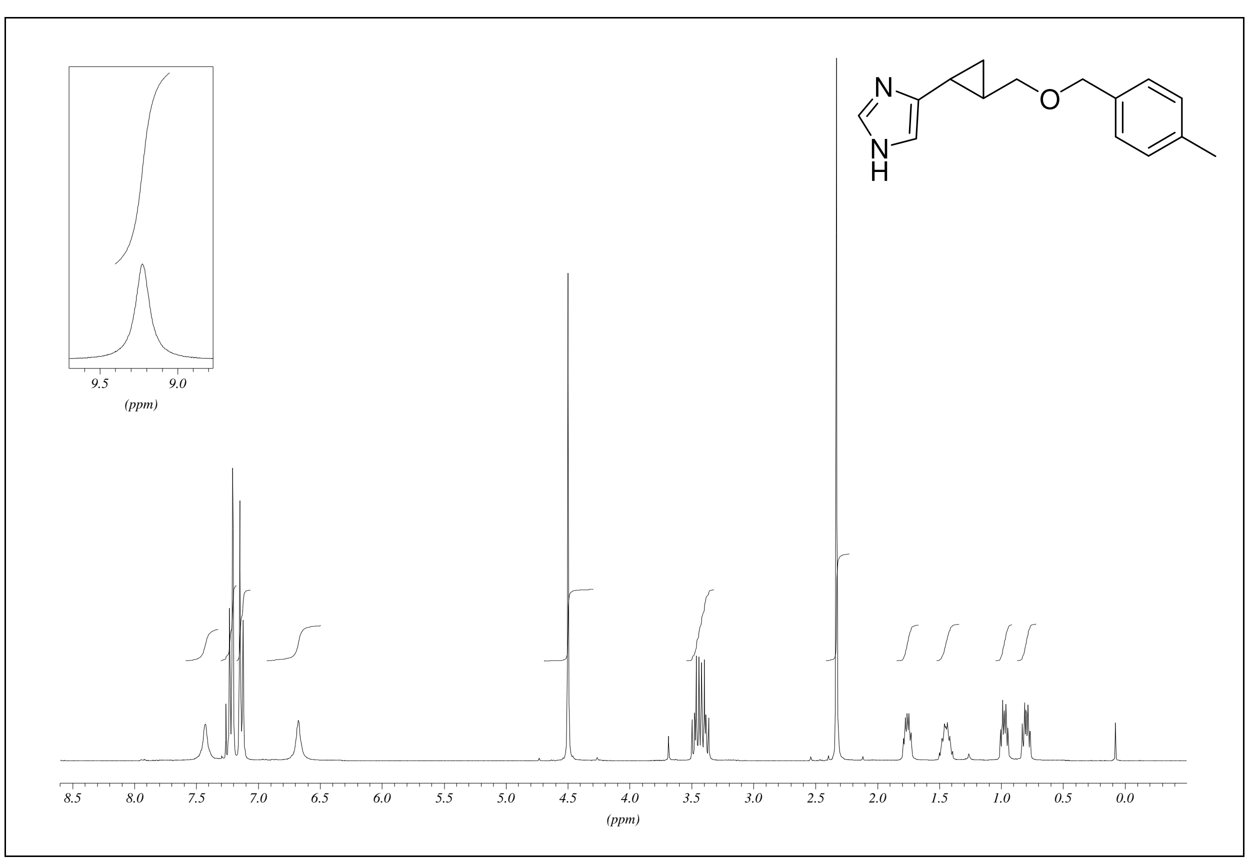


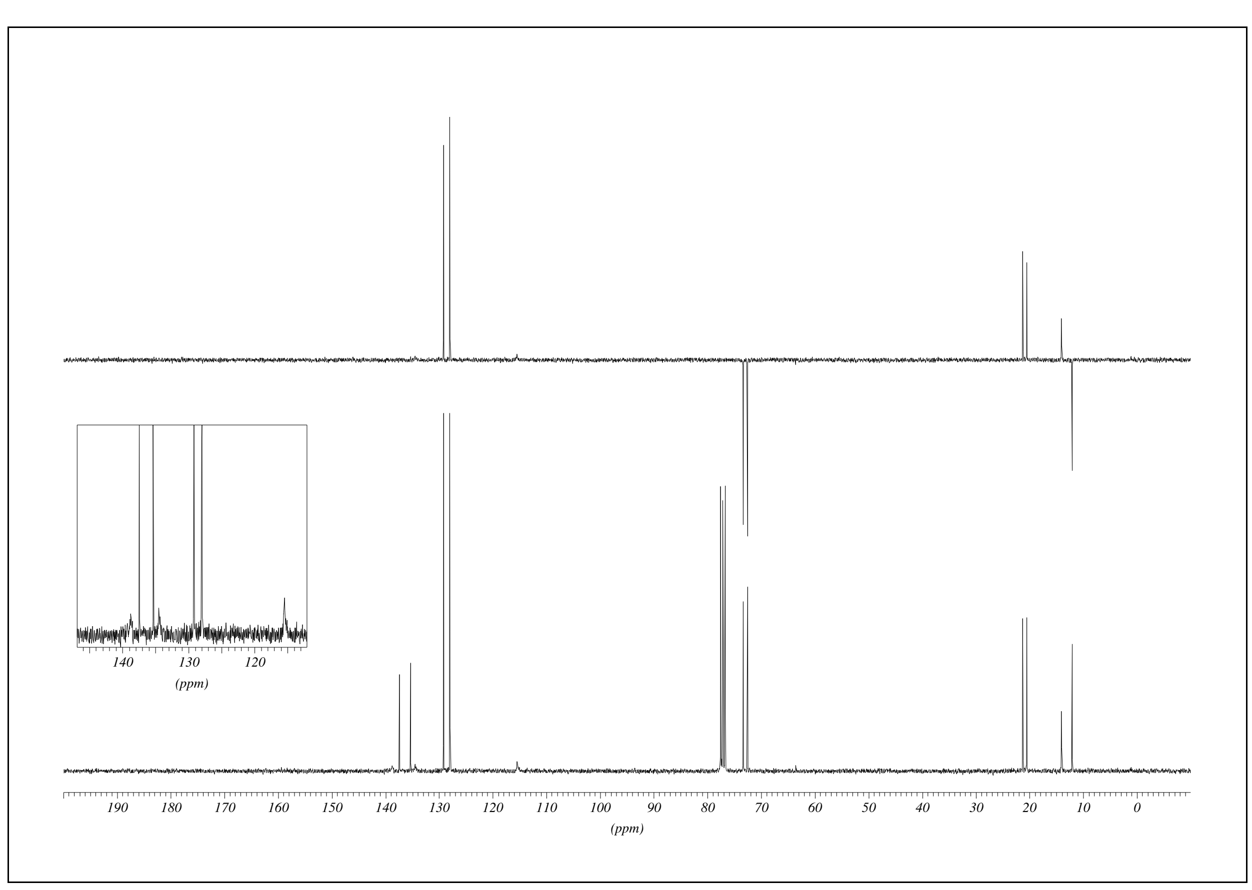
4-(2-((benzyloxy)methyl)cyclopropyl)-1*H*-imidazole (314)



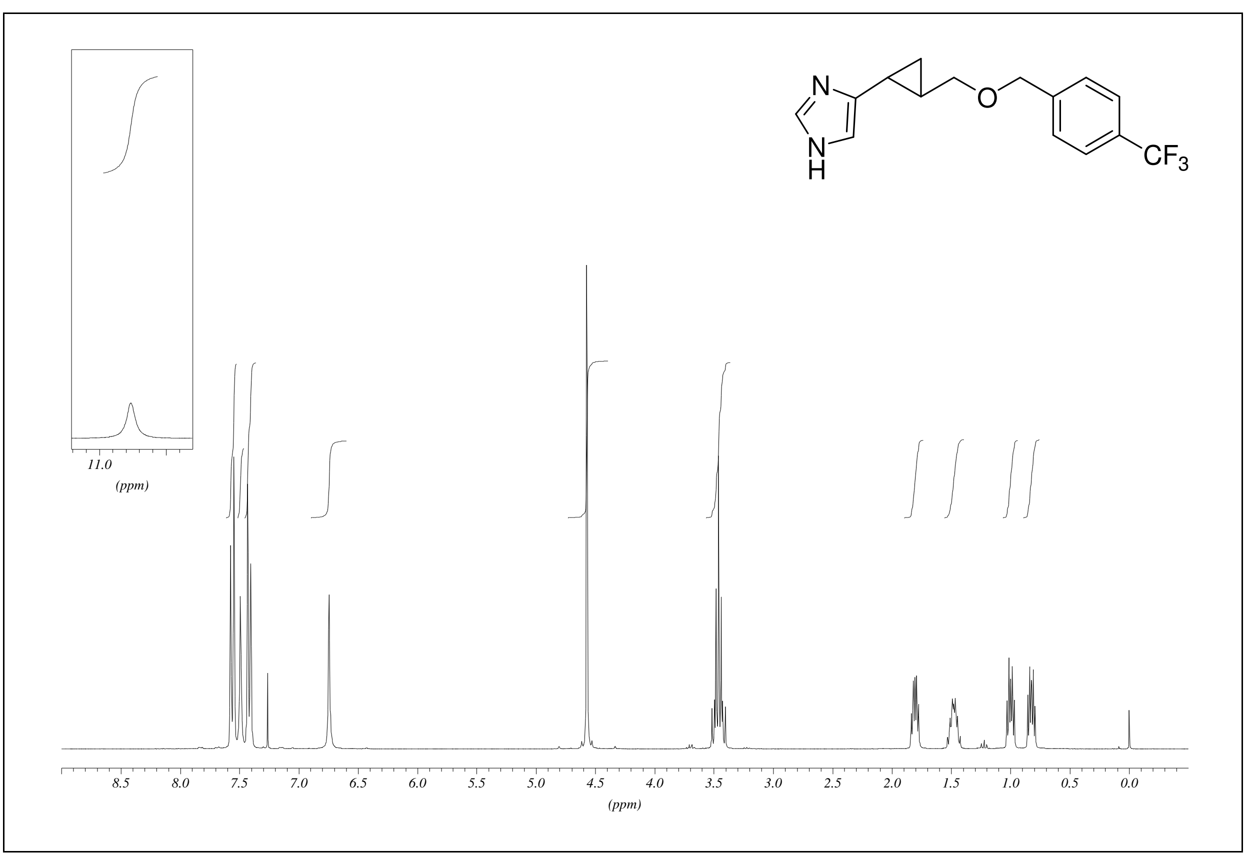


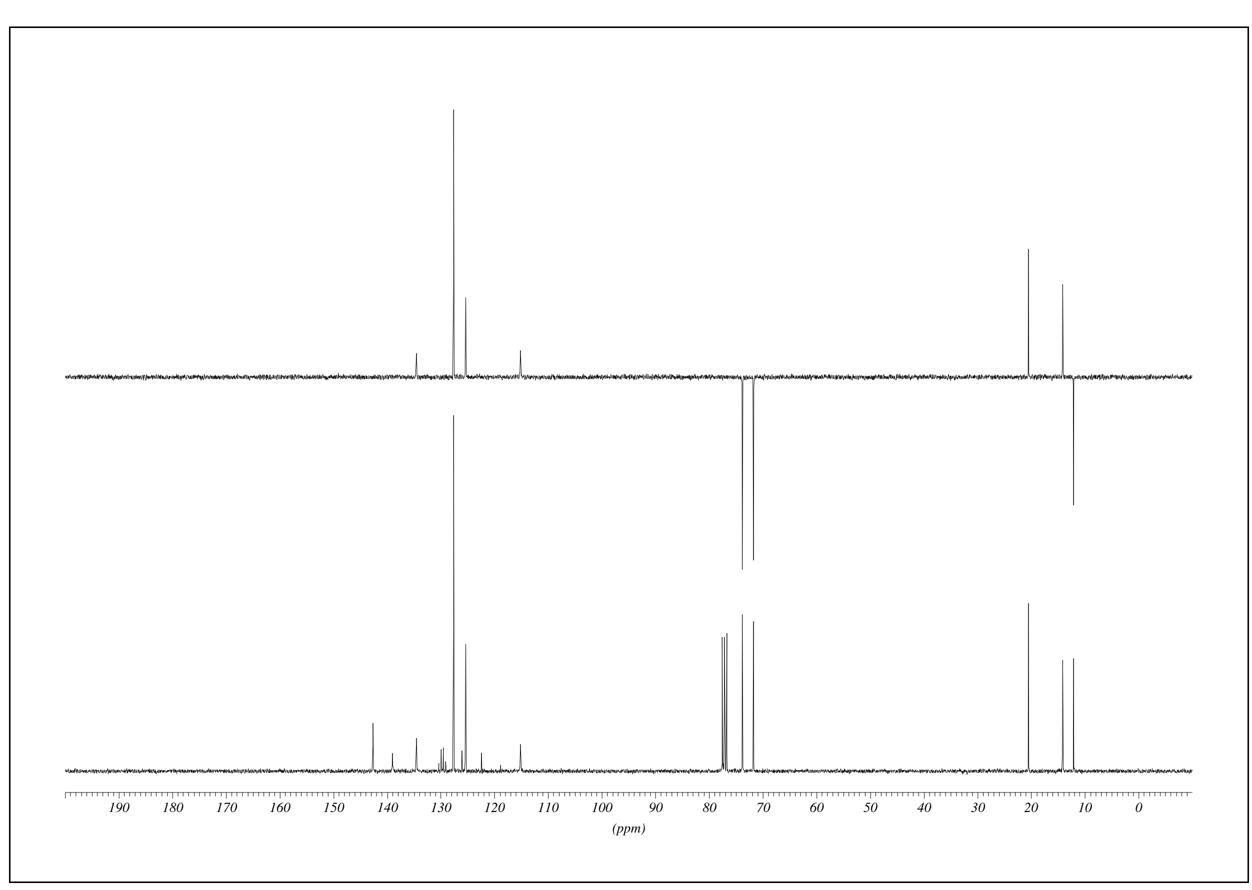
4-(2-((benzyloxy)methyl)cyclopropyl)-1*H*-imidazole (314)



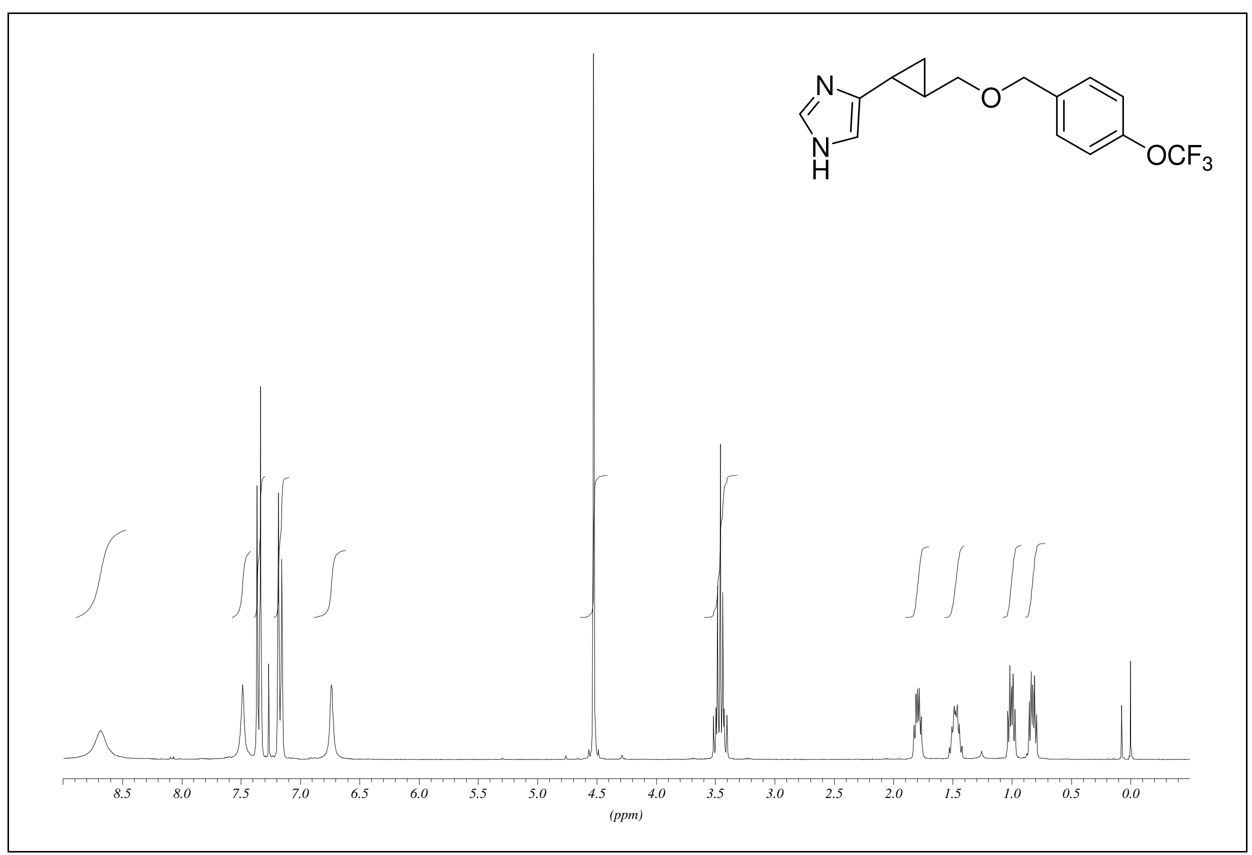


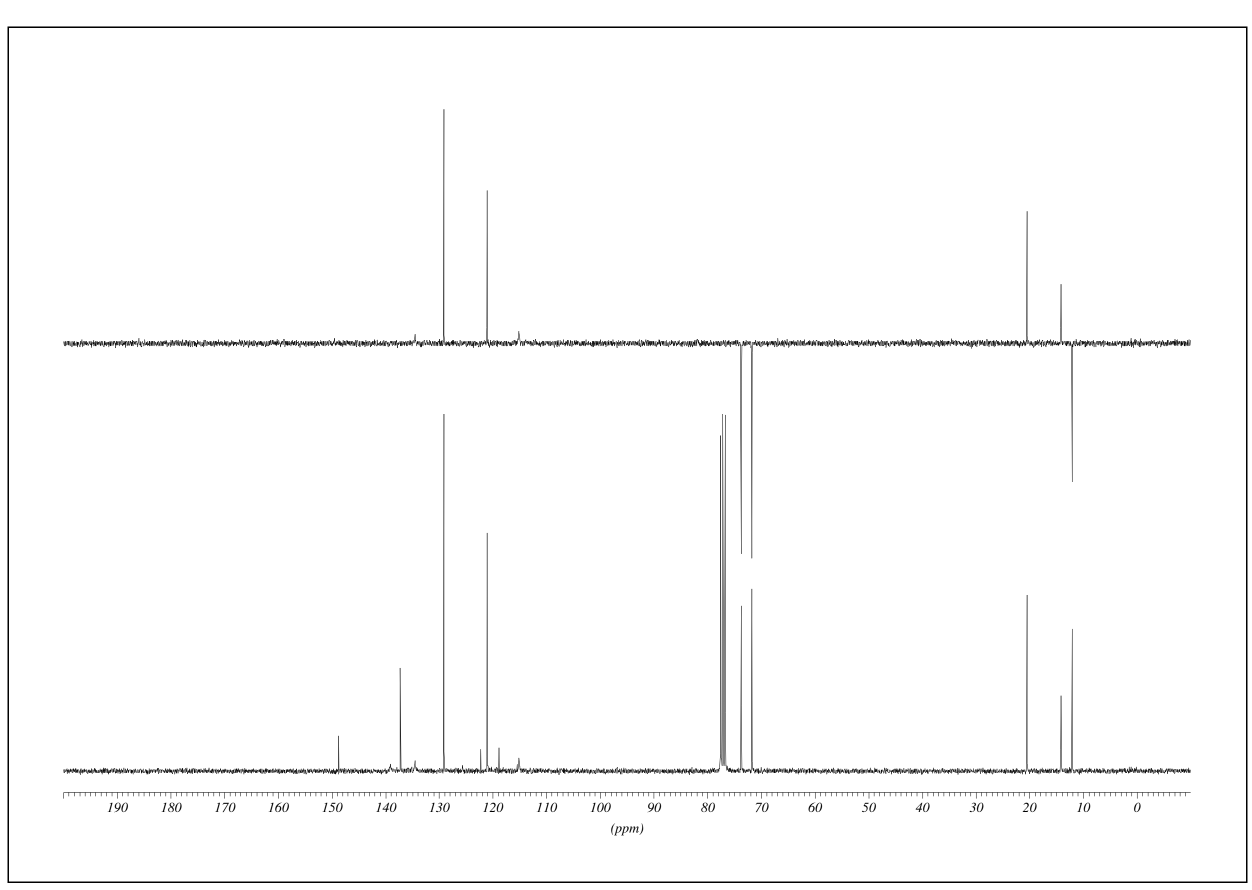
4-(2-((4-(trifluoromethyl)benzyloxy)methyl)cyclopropyl)-1*H*-imidazole (316)



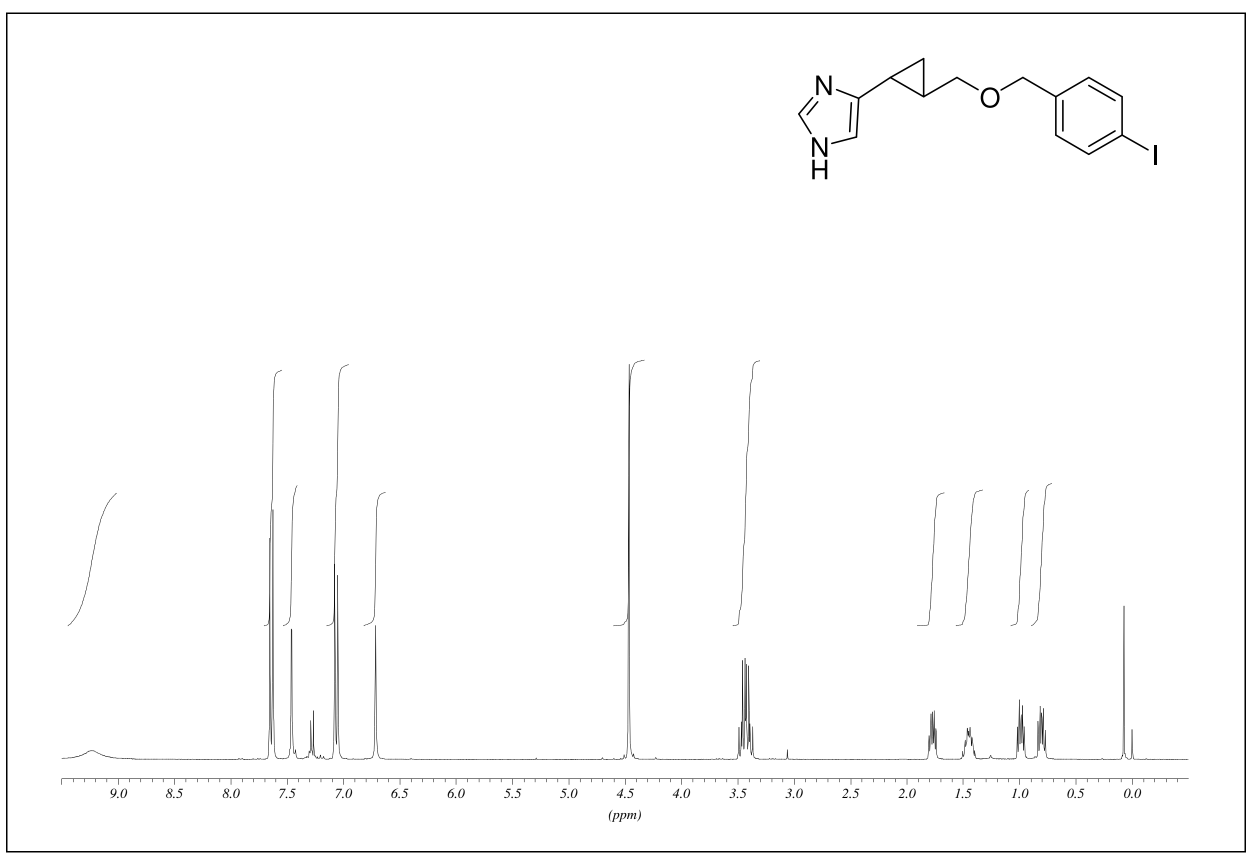


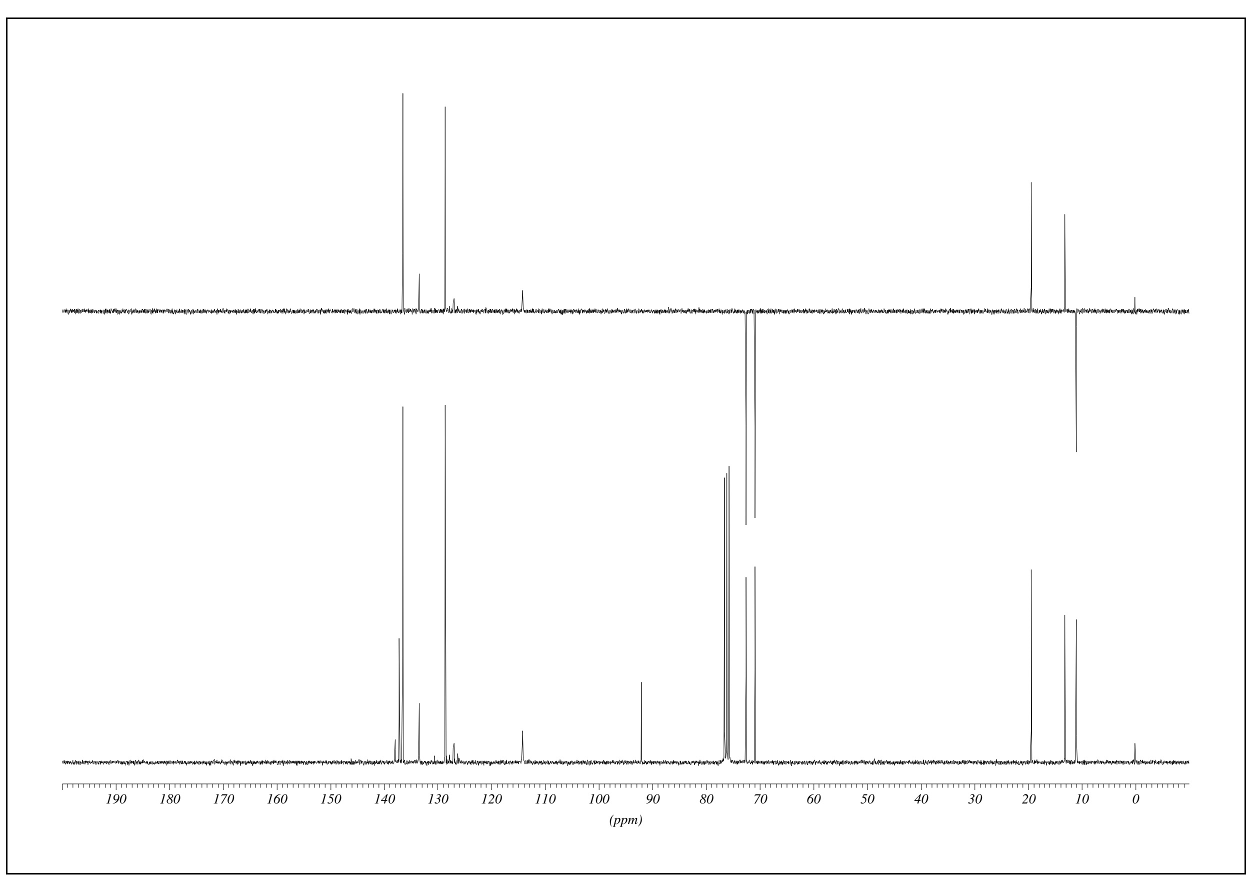
4-(2-((4-(trifluoromethoxy)benzyloxy)methyl)cyclopropyl) -1*H*-imidazole (317)



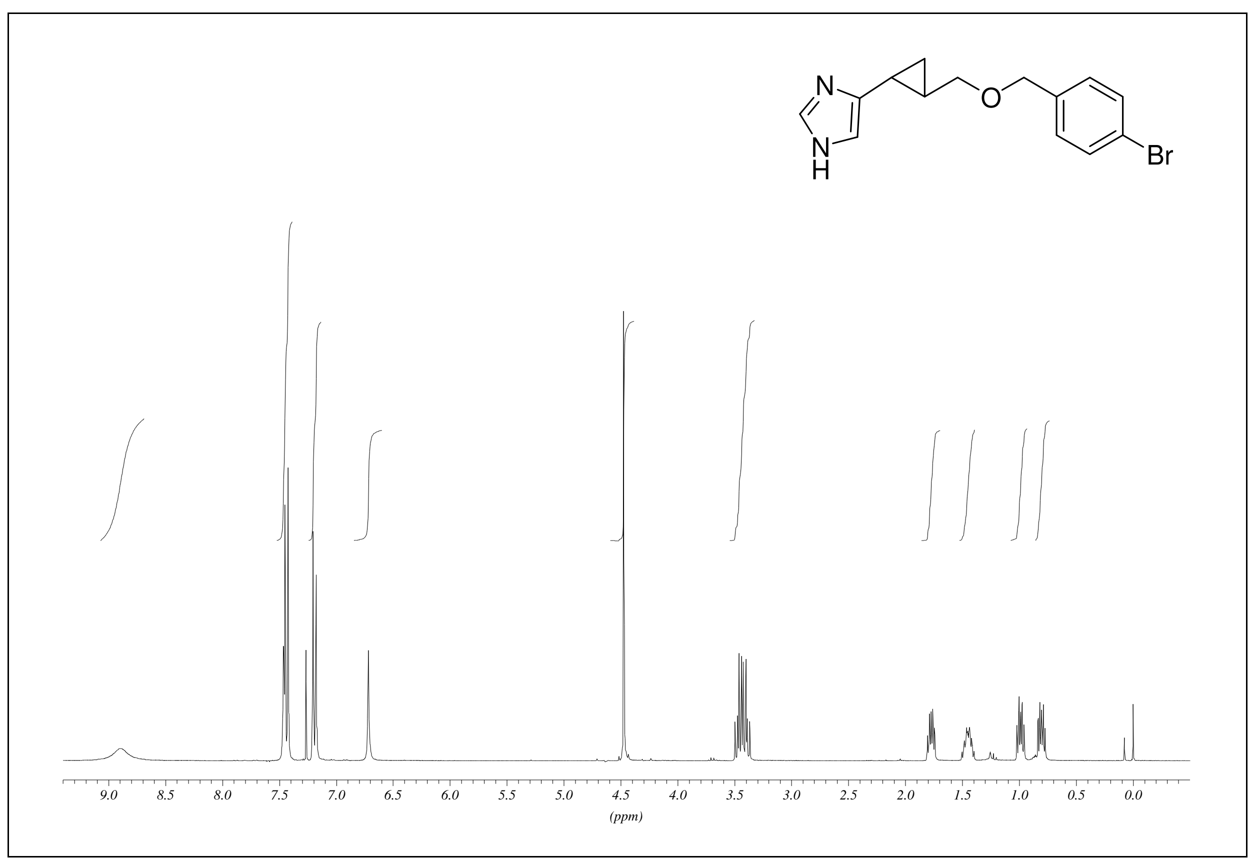


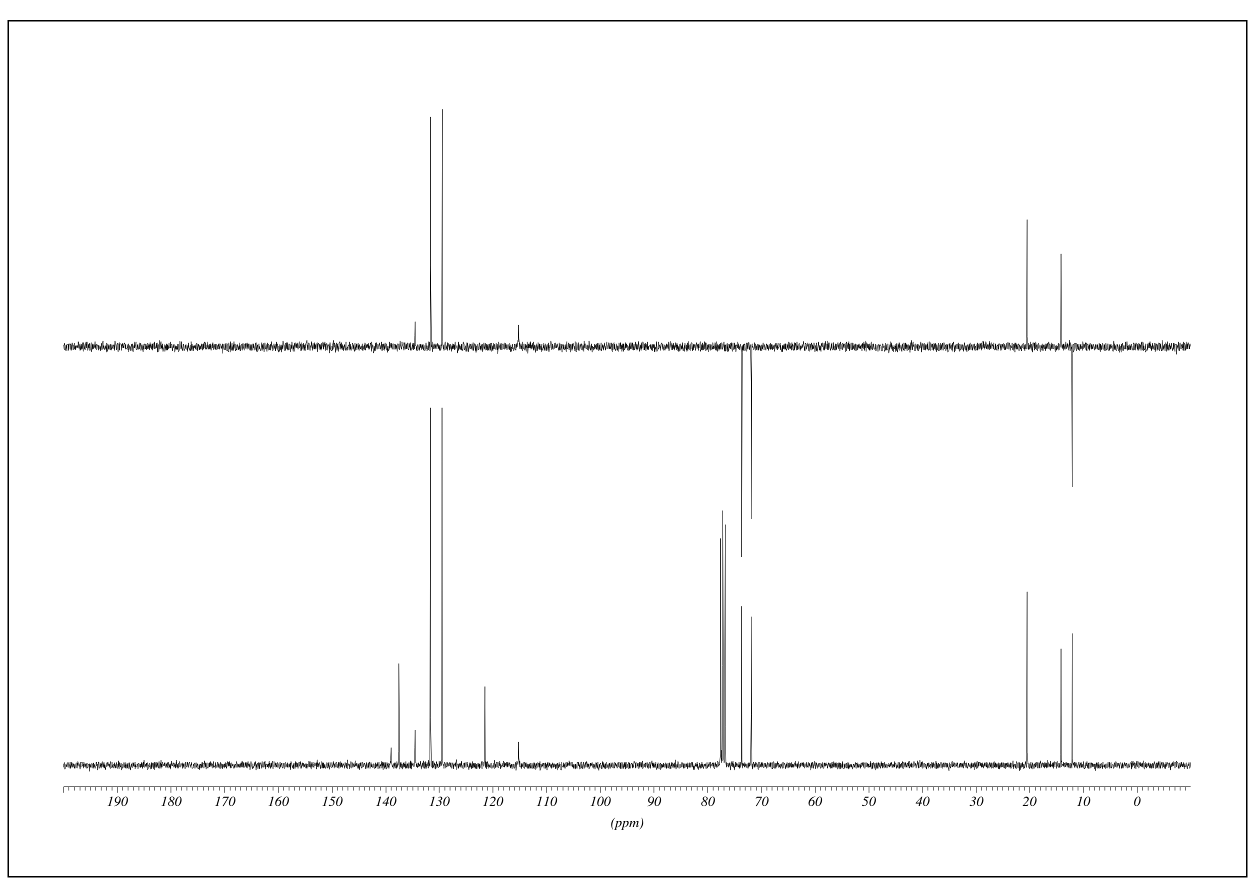
4-(2-((4-iodobenzyloxy)methyl)cyclopropyl)-1*H*-imidazole (312)



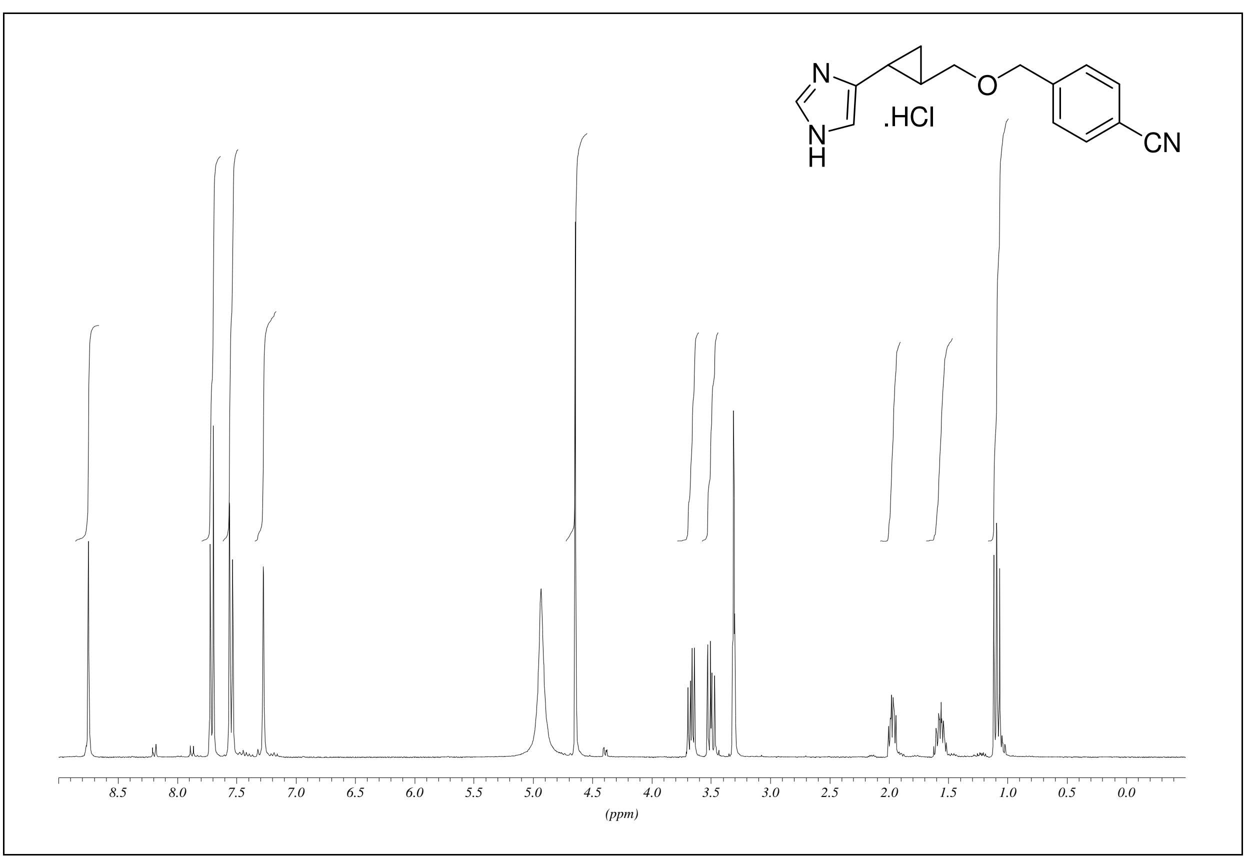


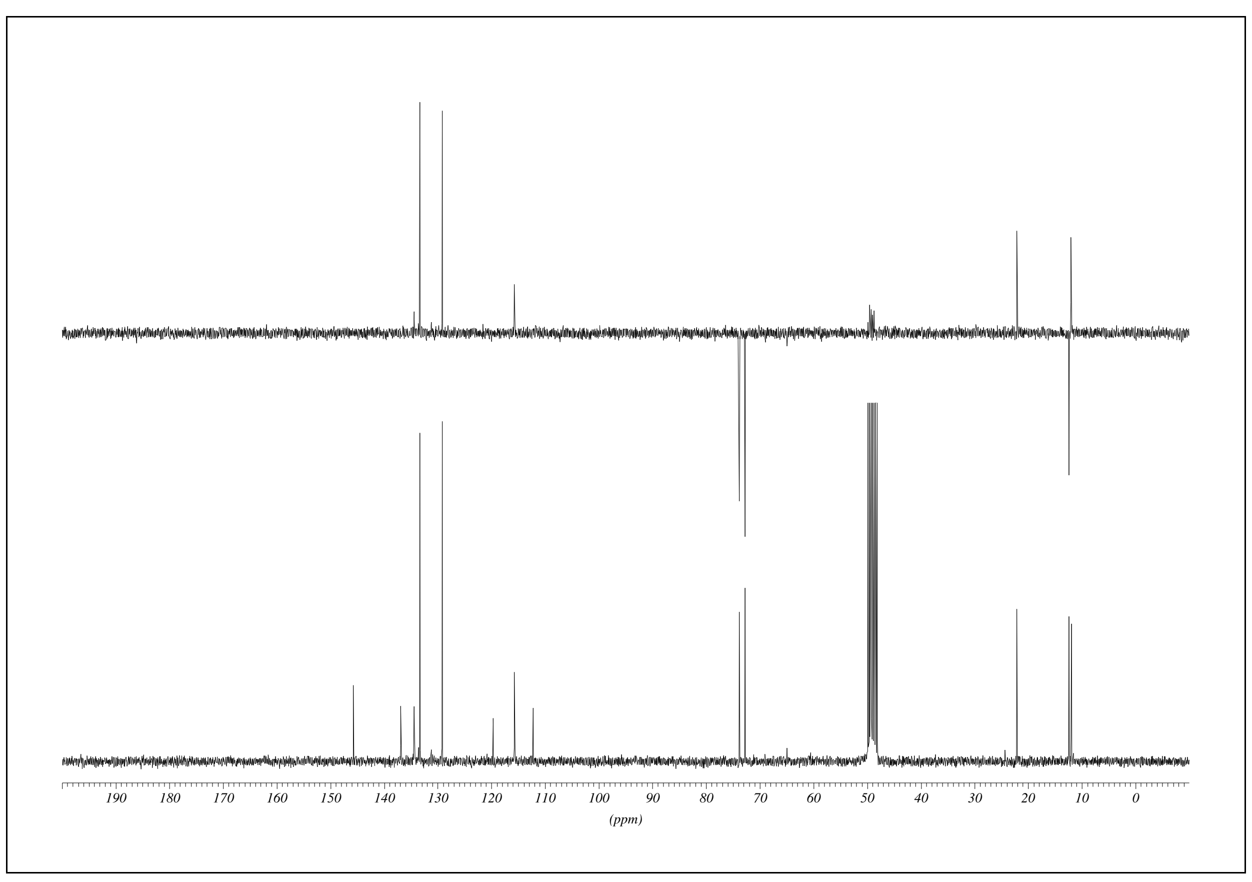
4-(2-((4-bromobenzyloxy)methyl)cyclopropyl)-1*H*-imidazole (319)



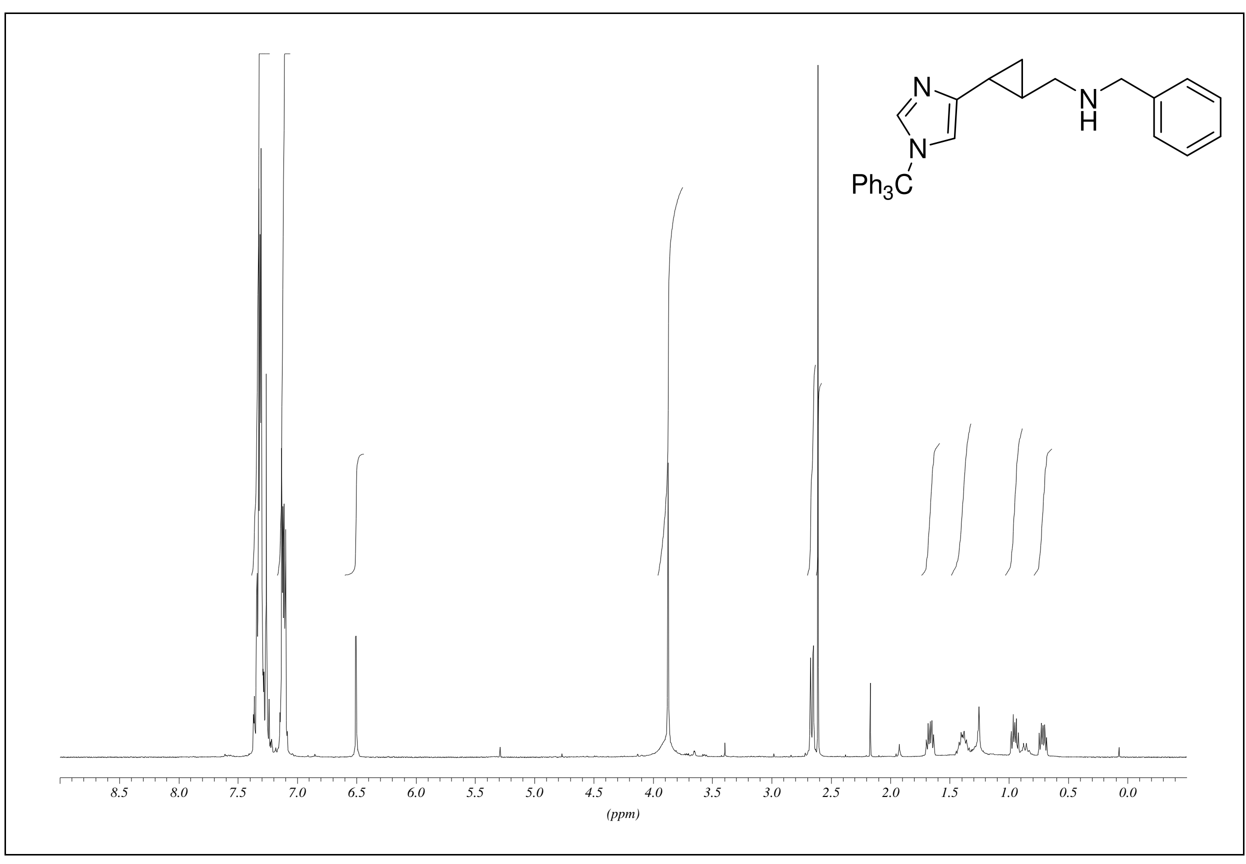


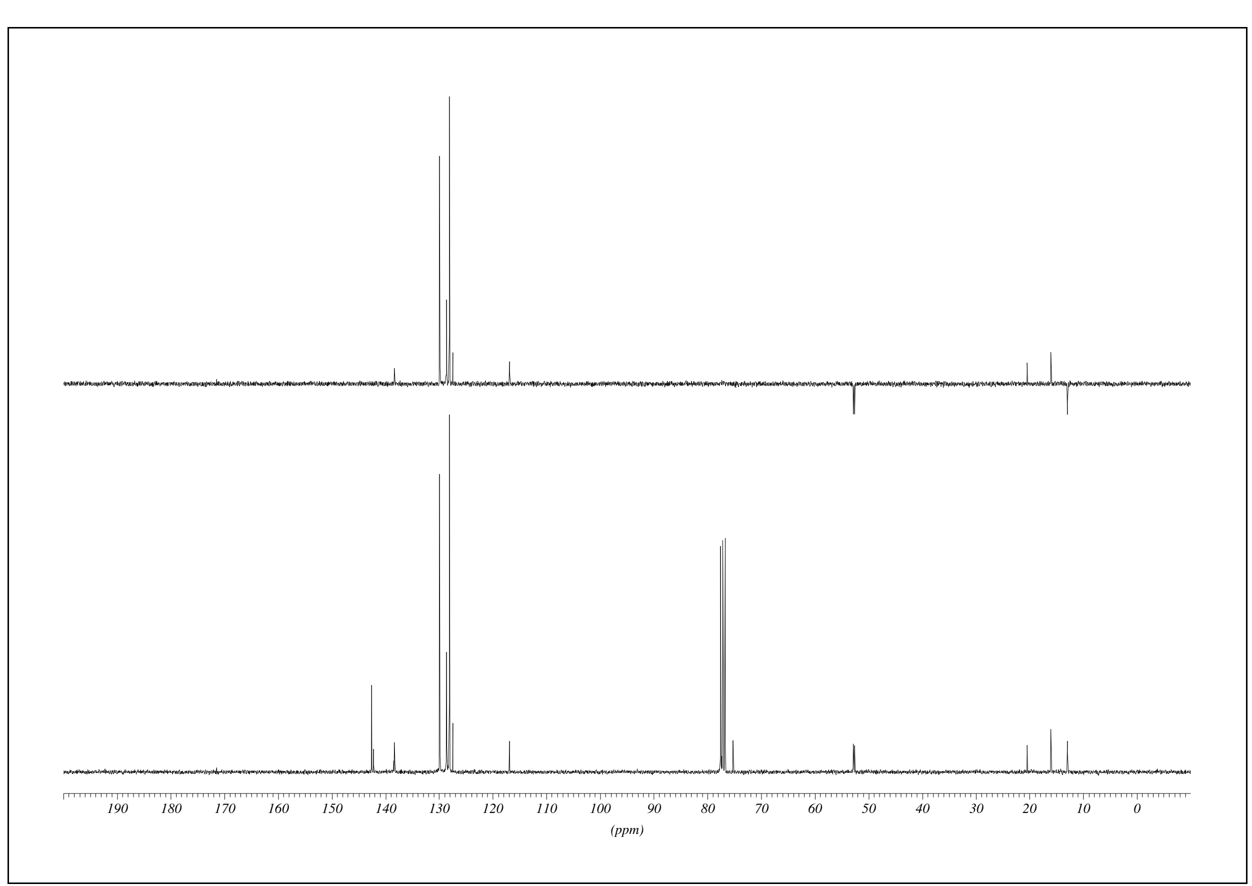
4-(((2-(1H-imidazol-4-yl)cyclopropyl)methoxy)methyl)benzonitrile hydrochloride (320)



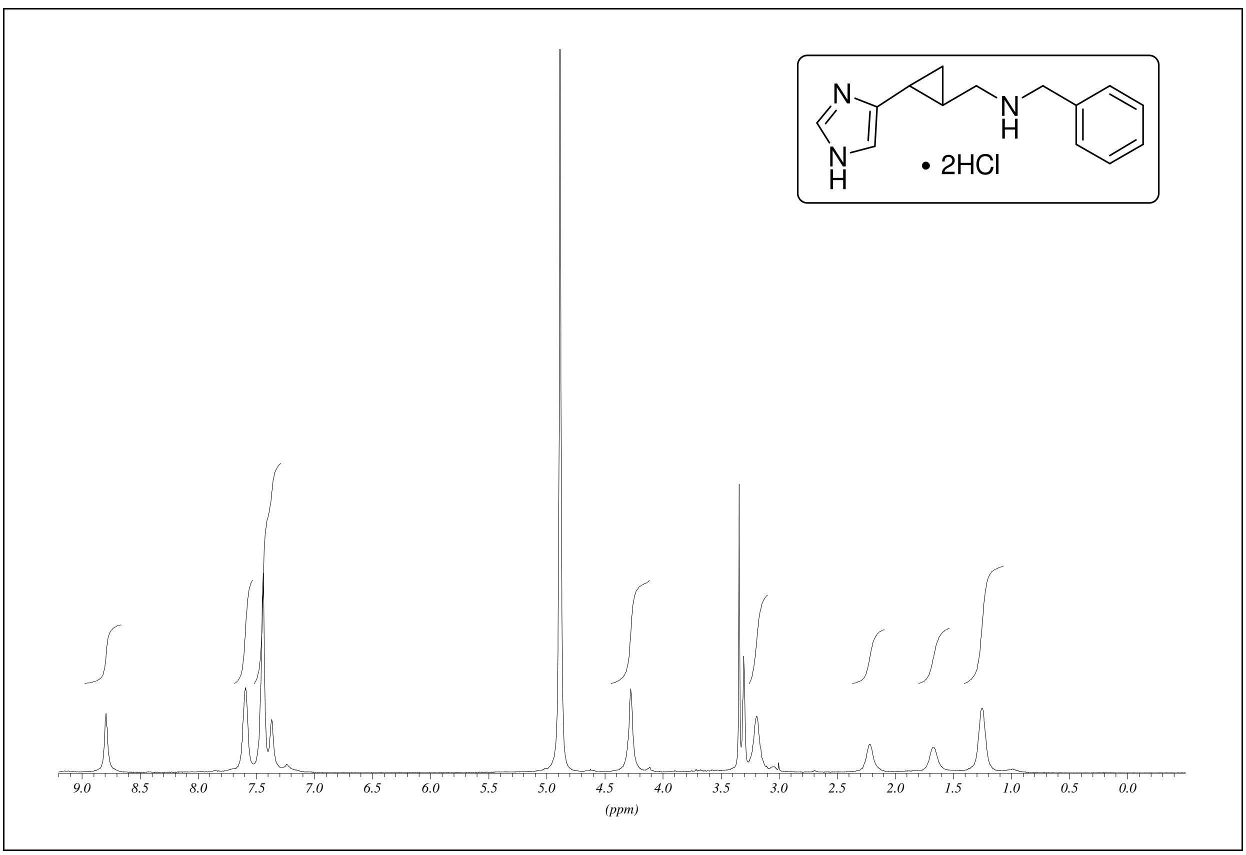


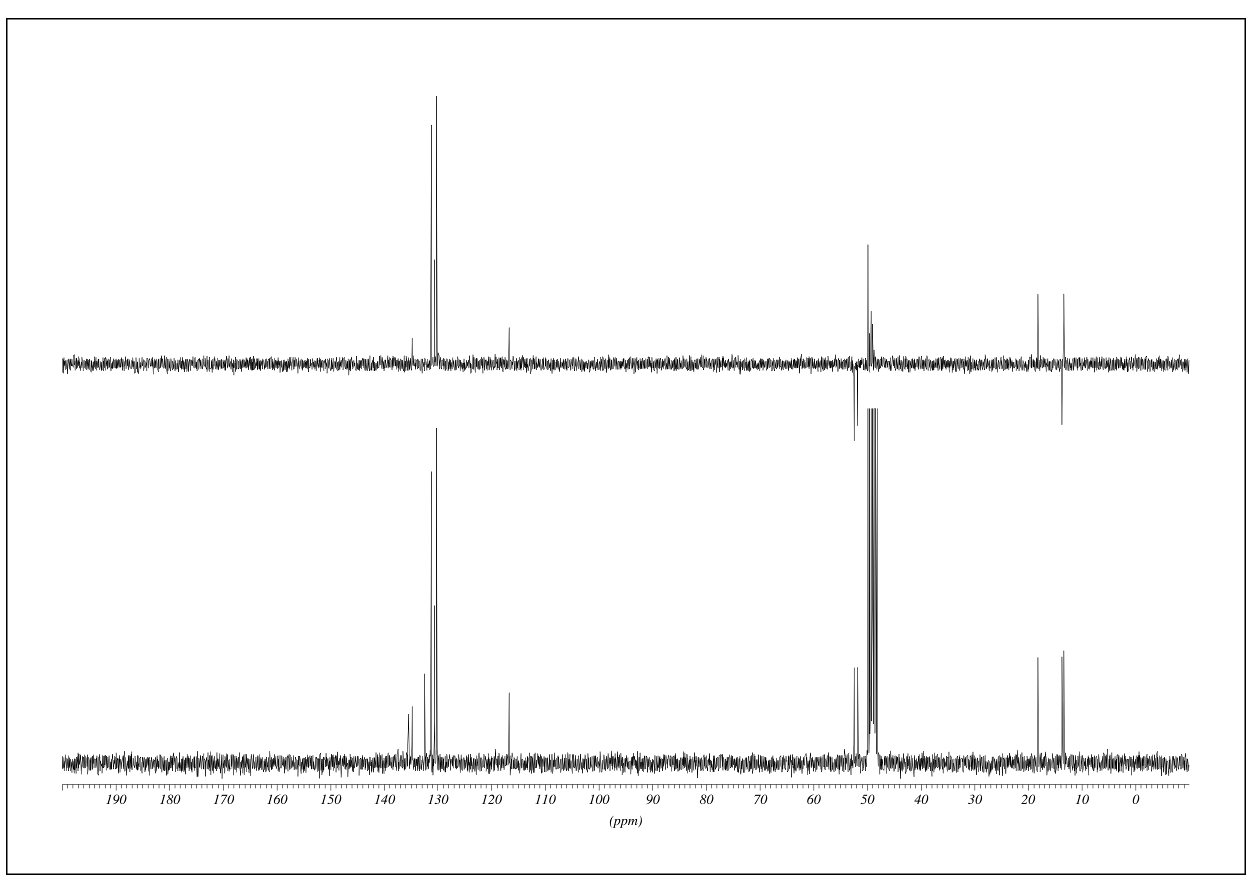
Phenyl-*N*-((2-(1-trityl1*H*-imidazol-4-yl)cyclopropyl)methyl)methanamine (326)



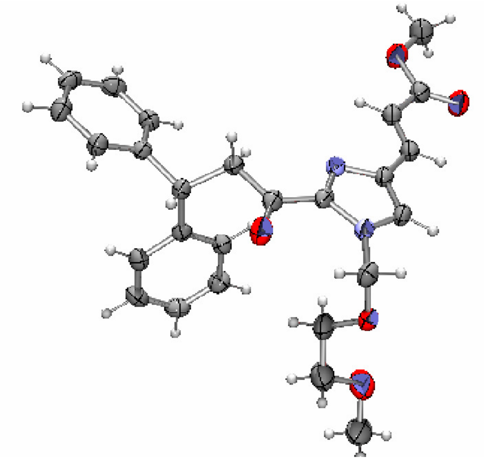


(2-(1H-imidazol-4-yl)cyclopropyl)-N-benzylmethanamine dihydrochloride (327)



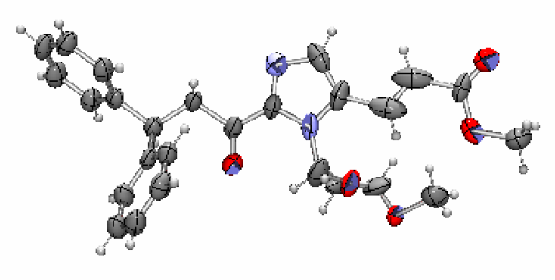


4.2 X-ray crystallographic data



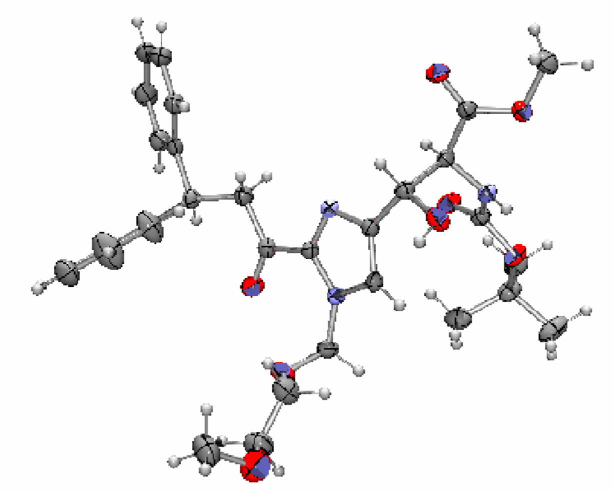
(E)-methyl3-(1-((2methoxyethoxy)methyl)-2-(3,3-diphenylpropanoyl)-1*H*-Imidazol-4-yl)acrylate (**175**):

CCDC 606450



(E)-methyl 3-(1-((2-methoxyethoxy)methyl)-2-(3,3-diphenylpropanoyl)-1H-imidazol-5-yl)acrylate (**176**):

CCDC 606449



tert-butyl (1S,2S)-1-(methoxycarbonyl)-2-(1-((2-methoxyethoxy)methyl)-2-(3,3-diphenylpropanoyl)-1H-imidazol-4-yl)-2-hydroxyethylcarbamate (**189**):

CCDC 286008

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Curriculum Vitae

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- "Side-Chain Modified Analogues of Histaprodifen: Asymmetric Synthesis and Histamine H_1-Receptor Activity." **Patil, R.**; Elz, S.; Reiser O. *Bioorg. Med. Chem. Lett.* **2006**, *6*, 672-676.
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Poster Presentations

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- "Conformationaly Restricted Analogues of FUB 372 and Proxyfan: Synthesis and Interaction with Histamine H_3-Receptor." **Patil, R.**; Elz, S.; Reiser, O.; *Evaluation of GRK 760,* Regensburg, Germany, January 2006.
- "New Side-Chain Modified Histamine Derivatives as Ligands for Histamine H_1-Receptors." Elz, S.; Paraschiv, G.-I., **Patil, R.**; Kunze, M.; Striegl, B.; Sunel, V.; Cecal, A.; Buschauer, A.; Reiser, O.; *46th Spring Meeting of German Society of Experimental and Clinical Pharmacology* (DGPT)*,* Mainz, March 2005.
- "Histaprodifen Derivatives: Synthesis of Side-Chain Modified Analogues and Interaction with H_1-Receptors." **Patil, R.**; Elz, S.; Buschauer, A.; Reiser, O.; *2nd Summer School Medicinal chemisty,* Regensburg, Germany, October 2004.
- "Synthesis and Pharmacological Investigation of Side-Chain Functionalised Histaprodifen Analogues" **Patil, R.**; Elz, S.; Buschauer, A.; Reiser, O.; *Jahrestagung-Joint Meeting GDPH*, Regensburg, Germany, October 2004.

Acknowledgements

First and foremost I would like to thank Prof. Dr. Oliver Reiser, for providing me an interesting project as well as for his insistent enthusiasm and his many valuable suggestions to this work.

I am equally grateful to Prof. Dr. Sigurd Elz for carrying out the biological investigations of my compounds personally and also for his valuable suggestions regarding the structure activity relationships. Although as a Ph.D. thesis, this work is necessarily authored by me alone, most of the views that are expressed in this work have been jointly developed along with Prof. Dr. Oliver Reiser and Prof. Dr. Sigurd Elz.

I would like to acknowledge GRK 760, supported by Deutsche Forschungsgemeinschaft (DFG) for providing financial support during my research work.

Many thanks to Dr. Peter Kreitmeier for his regular help in solving all the technical problems in the lab through out my stay in the working group. I also express thanks to Dr. Kirsten Zeitler for her precious suggesations during the synthesis of histamine analogues.

Ms. Andrea Roithmeier, Mr. Georg Adolin, Mr. Klaus Döring, and Mr. Robert Tomahogh are also thanked for their consistent help in various aspects during my experimental work.

I am also obliged to Dr. Burgermeister for his kind help in the structural assignment of a few complicated spectra. Similarly, Mr. Kastner and Ms. Stülher are recognized for the NMR measurements. I appreciate the help from Dr. Zabel and his co-workers for their in X-ray crystallographic analysis. I thank Dr. Mayer, Mr. Kiermaier, and Mr. Söllner for the mass spectrometry and Mr. Wandinger and his co-workers for elemental analysis.

I would like to thank Prof. Dr. Stefan Dove and Dr. Andrea Straßer for important suggestions concerning the snake plots of histamine H_1 and H_3-Receptors.

I am grateful to my lab collogues Dr. Eva Jezek, Mr. Yogesh Shinde and Mr. Florian Sahr for maintaining lively atmosphere in and outside (*Gleiche kneippe*) the lab.

A special thanks to Mrs. Rotermund, Ms. Ohli and Dr. Hirtreiter for their constant help in all the administrative work.

I am grateful to all the former and current members of the work group of Prof. Dr. Reiser for their healthy discussion during the seminars.

I thank Prof. Dr. Armin Buschauer and all the members of GRK 760 for their advices and ideas during the GRK-presentations.

My Indian friends Mr. Prantik, Dr. Prasanta, Mr. Yogesh, Dr. Rakeshwar, Dr. Shobi, Dr. Suneel, Ms. Anu, Mr. Srinivas, Mr. Ramesh, Mr. Chinna and Mr. Bansal are greatly acknowledged for making the life much easier during my stay in Regensburg.

They may be far away by distance from here, I specially remember Dr. Arun, Bandya and Mr. Mohan who inspired me all the time and initiated my carrier in Science.

Words are not enough to express my gratitude towards my friends Dr. Vinod, Mr. Nagendra, Mr. Shiram, and Mr. Kulbhushan who encouraged me all the time in my life ever since I met them. I am equally grateful to Mr. Laxman, Mr. Awadut, Mr. Namdev Mr. Amol, Mr. Pandurang, Mr. Balaji, Dr. Santosh and Mr. Bhagwat.

I would like to thank Archana, my wife and Aditya, my son for their love, affection and constant support extended to me during most of my work.

Finally, I wish to thank my parents for their unconditional love, constant encouragement and faith in my ability to make this work.