Studies in Benzimidazo[2,1-*a*]isoquinoline Chemistry

Michael John Donaghy, B. Sc. (Hons.)

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This thesis is dedicated to my late father

John Joseph Donaghy

Born 21st January 1939

Died 17th November 1995

And to all the members of my family past and present.

" For you all, I did it "

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ABSTRACT

Studies in Benzimidazo[2,1-*a*]isoquinoline Chemistry

by

Michael John Donaghy B. Sc. (Hons.)

Ellipticine, a member of the pyrido[4,3-*b*]carbazole alkaloid family first isolated in 1959 from the leaves of the plant *Ochrosia Elliptica* has been shown to possess anti-cancer activity against various tumours. Ellipticine is thought to undergo biological oxidation to give the more active 9-hydroxyellipticine that is subsequently converted to a highly reactive quinone-imine intermediate. The quinone-imine is then thought to interact with bionucleophiles in the body promoting cell death.

The aim of the project was to synthesise a series of benzimidazo[2,1-*a*]isoquinolines. The benzimidazo[2,1-*a*]isoquinolines were similar in general structure to ellipticines and should therefore undergo similar biological reactions. The target benzimidazo[2,1-*a*]isoquinolines have been screened to evaluate their ability to inhibit the enzyme topoisomerase II that is involved in DNA replication and ultimately cell reproduction. The target compounds have also been evaluated by the American National Cancer Institute.

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CHAPTER 1

INTRODUCTION

Introduction

1.0

Cancer is one of the plagues of the twentieth century and is on the increase in society today, despite man's efforts to find a cure for this disease it still remains a killer.

Cancer is a collection of different life threatening diseases characterised by uncontrolled growth of cells, leading to invasion of surrounding tissue and often spreading to other parts of the body.

1.1.0 Cancer Initiation

Altered DNA bases (mutations) are the basis for the cellular change that cause cancer. This can involve chemical alteration of individual bases or the order in which bases occur. Many chemicals are known to cause cancer by damaging DNA, but cancer can also be initiated by exposure of cells to radiation or a virus, or a combination of all these factors.

The biggest single contributor to deaths from cancer is tobacco.[1] When smoked tobacco releases a myriad of chemicals that contain well known carcinogens such as polycyclic aromatic hydrocarbons, aza arenes, aromatic amines, nicotine and phenols.[2] These chemicals cause cancer of the lung, upper respiratory tract, oesophagus, bladder, pancreas, stomach, liver and kidneys. Diet is another major contributor to cancer deaths, some saturated animal fat from red meat are well known to cause cancer of the colon, rectum and prostate. Environmental carcinogens that are naturally occurring such as ultra violet radiation from the sun and radon gas[3] (which

when inhaled decays by alpha emission) both directly harm DNA but account for only a small number of deaths. Man made environmental carcinogens such as the chemical cocktail released by vehicle exhaust emissions (particularly diesel particulates[4] and benzene[5]) play a major role in the development of cancers.

1.1.1 Cancer Development

For a cancer to flourish in the body two important gene classes must be mutated by external factors. These gene classes are **Protooncogenes** and **Tumour suppresor genes**.[6]

Protooncogenes in their normal configuration choreograph the life cycle of a cell (*i.e.* the intricate sequence of events by which a cell enlarges and divides). They are situated in a cell's cytoplasm and are activated by receptors on the cell's exterior which receive growth stimulatory signals from neighbouring cells. The protooncogenes relay the growth signals from the cell interior deep into the nucleus activating a cohort of genes that help usher the cell through its growth cycle. The growth of a cell becomes deregulated when a mutation in one of its protooncogenes energises a critical growth stimulatory pathway keeping the cell active in terms of cell division when it should be dormant.

Tumour suppressor genes work in the opposite way to protooncogenes, they are specifically designed to inhibit cell growth. The tumour suppressor genes are activated by receptors to relay messages to the cell nucleus to stop reproducing. In cancer cells these genes are mutated thereby enabling the cell to ignore normally potent inhibitory signals.

If a mutation occurs in the gene classes then a healthy cell has a back up system or "apoptosis" to allow it to self terminate. Apoptosis induced by widespread mutations to cell DNA is circumvented by cancerous cells by production of a protein Bcl-2 which wards off cell suicide by suppressing protein p53 (a protein produced by cells with severely damaged DNA to trigger the process of apoptosis). Once all back up systems have been safely negotiated the cancer is free to grow.

Initial evasion of cell defence mechanisms allows cancer to develop and progress over a period of 10-20 years. Following the initiation of a cancer cell, the cell and its progeny over this period are then exposed to further mutations that increase the growth rate of the cancer. The affected cells eventually grow large enough in size to form a visible tumour.[7] If the tumour has not broken any of the tissue boundaries surrounding it then it is termed "in situ" cancer and can be usually removed by surgery. If genetic changes to the tumour allow it to begin invading tissue boundaries and shed its mutated cells into the bloodstream or lymph then the tumour is said to have "metastasised" and the mutant cells are now free in the body to establish new sites for uncontrolled growth.

1.1.2 Cancer Metastasis [8]

For a cancer to metastasise successfully cells have to detach from their original location, invade a blood or lymphatic vessel, travel in the circulation to a distant site and establish a new cellular colony. At every one of these steps they must escape many of the controls that in effect keep normal cells in place. In normal tissue, cells adhere to both one another *via* a protein called *E-Cadherin*. Cancer cells are deficient in *E-Cadherin* so therefore have the ability to break free of their neighbouring cells

and invade other areas. For cells to reproduce they need to bind to a surface as well as each other; this is a phenomenon called "anchorage". The extracellular matrix between cells is saturated with molecules known as integrins that allow the anchored cells the stability they require to reproduce. Healthy cells, if not anchored to the extracellular matrix will cease proliferation because the nuclear protein *cyclin E-CDK2* (an integrin) which regulates growth when anchored does not function when outside its own extra cellular matrix. Cancer cells bypass this control by keeping the *cyclin CDK2* complex active whilst being completely anchorage independent.

Once free of the cell-cell interactions a cancer cell then has to successfully negotiate its way through several membranes to enter the bloodstream or lymph. Cancer cells achieve this by using enzymes called metalloproteinases which dissolve basement membranes and other cellular matrices allowing the cells passage through into the bloodstream or lymph.

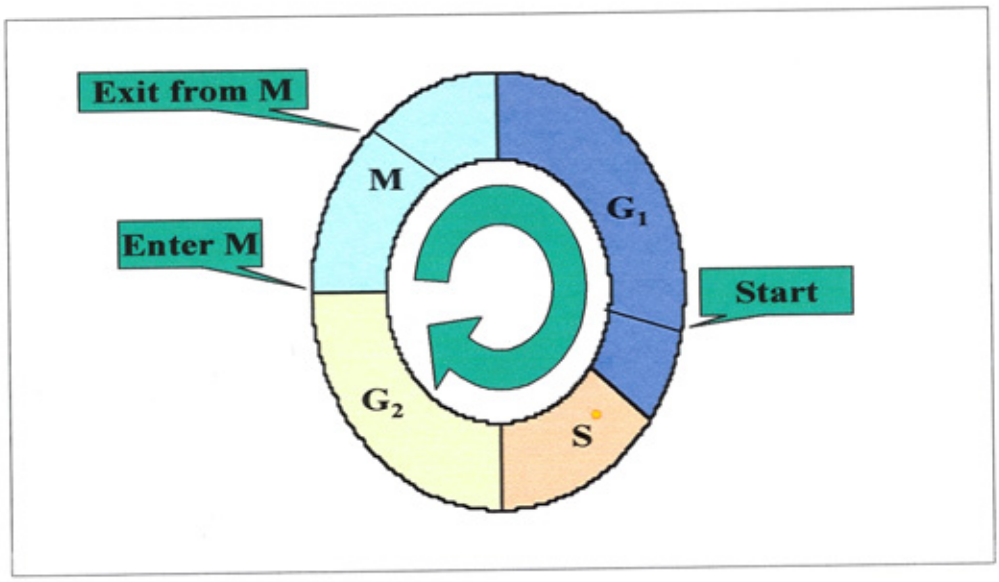
Cancer cells when entering the bloodstream are at their most vulnerable, in fact fewer that 1 in 10,000 cells that make it into the circulation survive to form a new tumour at a distant site. For a cancer cell to form a new tumour at a distant site it must attach itself to the inner lining of a blood vessel further downstream penetrating the basement membrane at this new location, and then it must invade the tissue beyond and establish a new colony. There are many proposed theories as to why cancer cells do not survive this, such as defence mechanisms that keep cells in the right places, new tasks the cells have not faced before in a new environment, incomplete anchorage independence of tumour cells and many others. Whatever the reasons it is well established that a small amount of cells overcome all these defence mechanisms and go on to form new colonies at new sites eventually reaching major organs in the body leading to disfunctioning of the organs and ultimately death.

1.1.3 Cancer Treatment

Cancer once developed and metastasised is not completely curable but can be treated in several ways.[9]

Radiotherapy is the bombardment of cancer cells using electromagnetic radiation obtained *via* radioactive decay of metals (*i.e.* ^{60}Co), usually given in the dose range 10-100 Gy$^{\phi}$. Radiotherapy is usually administered in the G_2 phase of a cell cycle (Scheme 1);[10] this is the gap before cell division and is the point where the cells have least resistance to radioactive bombardment thus making the treatment most effective. The exposure to radiation causes a cascade of energy transfer that ionises and excites biological molecules (*i.e.* DNA, RNA and proteins) within the cell. The radiation can damage DNA in several ways such as inducing single or double strand breaks in the sugar-phosphate backbone of the molecule, alteration or loss of bases, formation of cross links between DNA strands or between DNA and chromosomal proteins. The results of the excitation lead to irreparable damage of the DNA and ultimately death of cells.

$^{\phi}$Gy = Grays = energy absorbed per unit mass (joules/gram).



Scheme 1 : Cell Cycle

G_1 is "gap" phase between the completion of mitosis and the beginning of DNA synthesis.

S is "synthesis" where DNA is replicated.

G_2 is "gap" phase between synthesis of DNA and the beginning of mitosis.

M is "mitosis" where cell division occurs.

Start point for the triggering of the cells replication machinery.

Enter M is the triggering point of the mitosis machinery.

Exit from M is the triggering point for the exit from mitosis to proceed through the metaphase-anaphase transition.

A side product of the radiation process is the production of chemically reactive species such as free radicals. The hydroxyl radical an oxidising agent is known to be extremely damaging to DNA. When cells are exposed to these radicals the resultant damage inevitably leads to all cell death.

Other cell death mechanisms are induced at low doses of radiation (<1Gy). One such defect is chromosomal aberrations that are detectable in cells exposed to low dose radiation. Also at low doses the continued reproductivity of a cell is impaired so that when reproducing the cells progeny are lethally damaged and undergo immediate apoptosis disappearing from the population and regulating a cancer's growth.

Recent developments in radiotherapy have improved the effectiveness of the technique. Certain cancerous cells known as "hypoxic" cells represent a radiation resistant sub population in tumours that does not exist in healthy cells. If oxygen is administered in conjunction with radiotherapy then the effect the hypoxic cells have on the tumour is suppressed allowing the treatment to be much more successful. Sensitisers are now also widely used in conjunction with radiotherapy. Sensitisers are activated when exposed to radiation, and administration of the sensitiser followed by selective irradiation of the tumour cells, results predominantly in cell death specific to the cancer.

1.1.4 Cancer Chemotherapy

The first documented clinical use of chemotherapy as a method to combat cancer was in 1942,[11] and since then many drugs have been developed and tested for their potential clinical activity. For a drug to be termed "anti-cancer" it must in some way destroy tumour cells, including stem cells at the heart of the tumour.

One of the major problems to be overcome when finding the right drug is the cell cycle phase specificity. It is well known certain drugs are more effective at certain phases of the cells cycle (Scheme 1). A tumour exists as a multitude of cells at different stages in the cell cycle and so administration of a drug will be lethal to cells

only in the part of the cycle that the drug is active. As a result of this regulation of drug administration is critically important, as the body needs time to recover from each drug dosage.

Another problem associated with chemotherapy is the drug sensitivity of specific cells. Sensitivity to drugs may differ not only between cell populations, but also amongst cells in a single population. This factor seriously limits the efficacy of clinical chemotherapy as drug resistant cells in a single population survive chemotherapy to become the dominant cell population in the tumour resulting in a tumour which is completely resistant to the drug administered.

1.1.5 Side effects of treatment

The major problem associated with all chemotherapy is the toxicity of drugs to healthy cells. This limits both the dose and frequency of drug administration. Many drugs cause toxic side effects because of their preferential activity against rapidly dividing cells.

New bone marrow cells in adults are rapidly proliferating and so are prime targets for chemotherapeutic drugs. The resultant death of new bone marrow cells leads to a depletion in blood count around 8-10 days after drug administration (depletion time is drug dependant), and so full recovery of bone marrow after treatment takes between 3-6 weeks. As a result the effect of chemotherapy on bone marrow is a major determinant of the interval between drug courses. If a drug is administered when blood counts are low this can delay recovery increasing the chance of bleeding and infection. In conjunction to this there is a high chance of depleting the stem cell population leading to irreversible damage to the bone marrow.[12]

Mucosal ulceration may also occur after drug treatment as new growing cells in the intestinal mucosa are proliferating rapidly, this is a situation which can be worsened when drugs are used in combination.

Partial or complete hair loss is common after treatment with many anti-cancer drugs and is due to the lethal effects against proliferating cells in hair follicles.

Drug treatment on mature adults affects the reproduction systems of both men and women. Men who receive chemotherapy often have decreased production of sperm leading to infertility. Premenopausal women have temporary or permanent cessation of menstrual periods leading to menopausal symptoms.

Nausea and vomiting are common side effects during the first few hours after treatment with many chemotherapeutic drugs. Drug induced vomiting is thought to occur because of direct stimulation of chemoreceptors in the brain stem that emit signals *via* connecting nerves to a neighbouring vomit centre, not *via* direct effect on intestinal mucosa.

One of the more macabre side effects of chemotherapeutic drugs is that they induce direct damage of DNA and chromosomes in an attempt to kill cancerous cells. If this damage does not result in the death of the cell, then the now even more mutated cell could possibly undergo further proliferation giving rise to secondary malignancies in long surviving patients.

1.2.0 Mechanisms of action of chemotherapeutic drugs

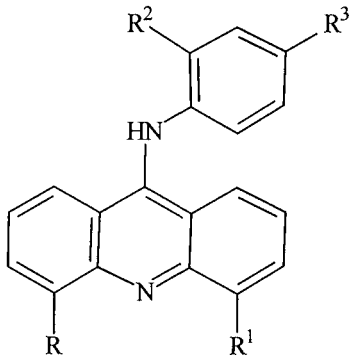
Mechanisms and action of anti-tumour drugs are open to speculation, however some drugs are well defined and certain aspects of these interactions within the body have been elucidated. It is fair to say that some of the compounds below are placed in a particular category, this however does not eliminate them from other mechanistic pathways as their mode of action.

1.2.1 DNA Intercalators

Flat aromatic or heteroaromatic molecules are known to bind to DNA by inserting and stacking between the base pairs of the double helix; this process is known as intercalation. Intercalation is a non covalent interaction in which the drug is held rigidly perpendicular to the helix axis causing base pairs to separate vertically distorting the sugar phosphate backbone and decreasing the pitch of the helix. This destroys the regular helical structure unwinding the DNA at the site of binding. As a result of this all subsequent actions of DNA binding enzymes (*i.e.* DNA topoisomerases) are affected. This implies that intercalation, although involved, is not the sole mechanism responsible for cell death.[13]

Selected examples of intercalators:-

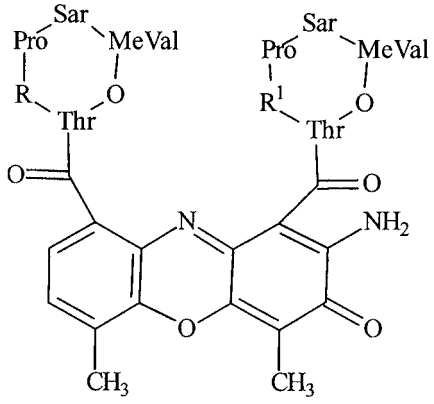
Amsacrine, an acridine,[14] structure **1**



1

	R	R^1	R^2	R^3
1	H	$NHSO_2CH_3$	CH_3O	$NHSO_2CH_3$

Dactinomycin, an actinomycin,[15] a chromopeptide antibiotic of structure **2**

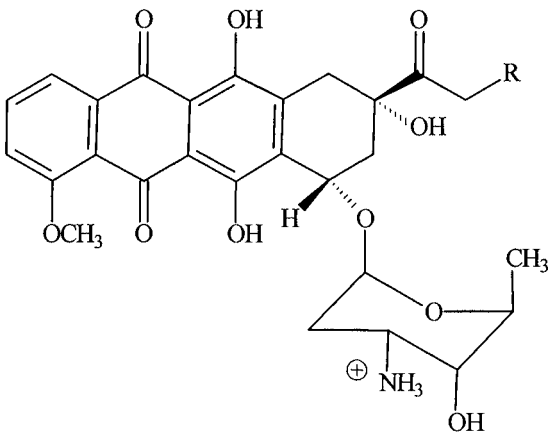


2

R and R^1 are D-Valine

Pro = L-proline, sar = sarcosine, MeVal = L-N-methylvaline, Thr = L-threonine

Doxorubicin and Daunorubicin, anthracyclines,[16] antibiotics of structure **3**



3

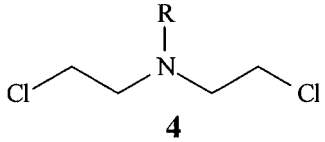
R is OH = Doxorubicin, R is H = Daunorubicin

1.2.2 DNA Alkylators

DNA alkylators include drugs that undergo direct nucleophilic substitution reactions or are transformed *via* reduction in the body to give electron deficient species that undergo Michael type addition reactions with nucleophiles in the body.[17] The major nucleophilic sites in cells are DNA bases, and alkylation of these bases results in cell death *via* cross linking or breaks in the DNA strands.

Selected examples of alkylators:-

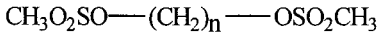
Mechlorethamine, a Nitrogen Mustard,[18] structure **4**



4

R is CH_3

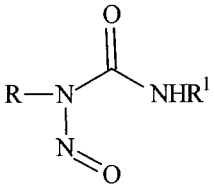
Busulfan, a methanesulfonate,[19] structure **5**



5

n is 4

Carmustine, a nitrosourea,[20] structure **6**



6

R and R^1 is CH_2CH_2Cl

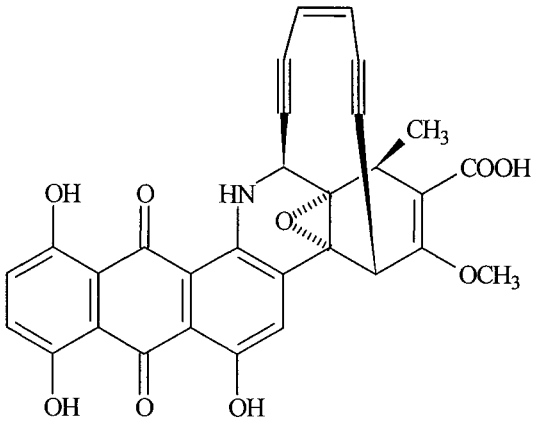
1.2.3 DNA Strand Breakers

Drugs that are known as DNA strand breakers initially intercalate into the DNA and then react further to form radical species. These radicals can then react directly with DNA causing damage to DNA strands or they can react with other molecules present to form more harmful radicals that will then directly attack DNA.

Selected examples of DNA strand breakers:-

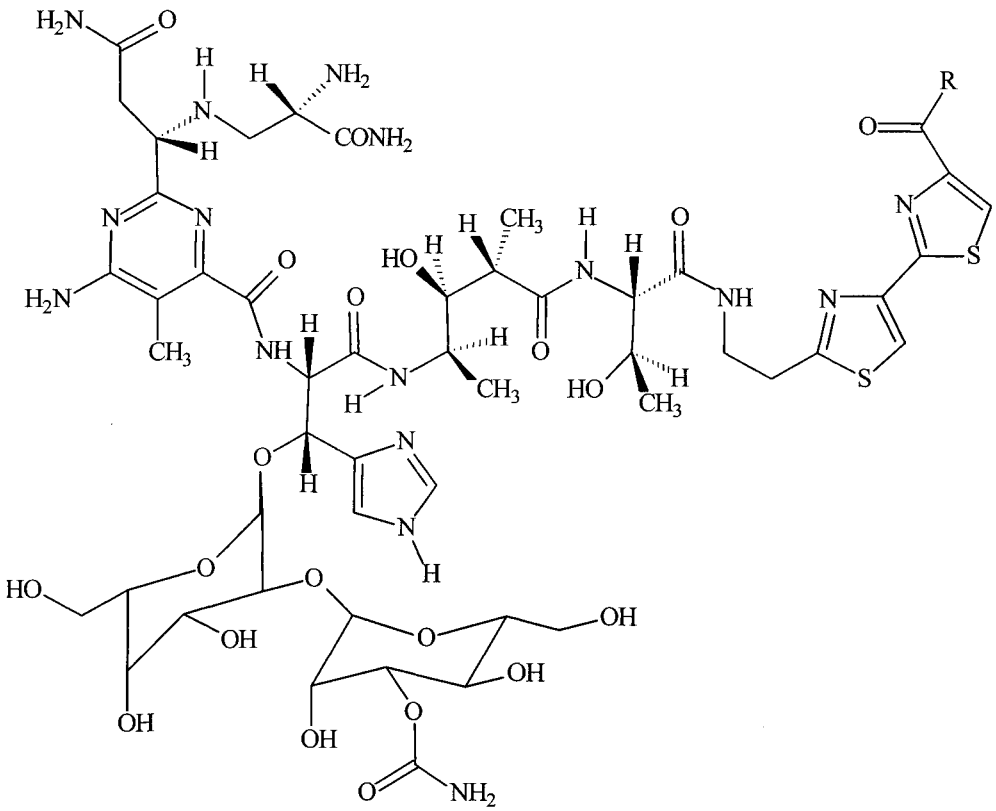
Doxorubicin and Daunorubicin, anthracyclines,[22] structure **3**

Dynemycin A, an enediyne antibiotic,[23] structure **7**



7

Bleomycin A_2, a glycopeptide antibiotic,[24] structure **8**



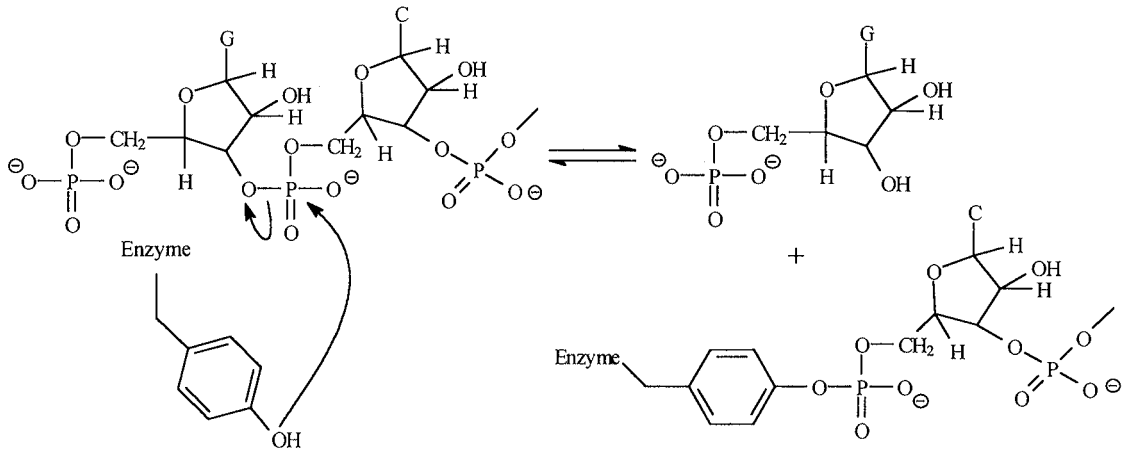
8

R is $NHCH_2CH_2CH_2S^+(CH_3)_2$

1.3.0 DNA Topoisomerases – Targets for anti-cancer drugs

To replicate itself a cell undergoes a series of complex transitions before it can split into two new cells. One of these transitions is the replication of DNA to duplicate precisely its complement of chromosomes. DNA in the cell nucleus exists in a highly ordered coiled state making replication difficult. To overcome this a nuclear enzyme (topoisomerase) is used to help facilitate replication by catalysing the breaking and rejoining of the DNA strands and allowing separation of daughter DNA molecules. The topoisomerases achieve this by scising the DNA strand or strands whilst binding themselves simultaneously to both of the cut ends creating a linkage which facilitates unwinding of the DNA coil allowing strand replication. The enzyme mechanism involves an active tyrosine site.[10]

The active tyrosine site of the enzyme covalently binds to the DNA *via* breakage of the DNA phosphodiester bond to form a phosphotyrosine linkage (Scheme 2).[25] The energy retained by the phosphotyrosine linkage promotes the rejoining of the phosphodiester bond making the process reversible freeing the replicated DNA and the enzyme.



Scheme 2

G = Guanine C = Cytosine

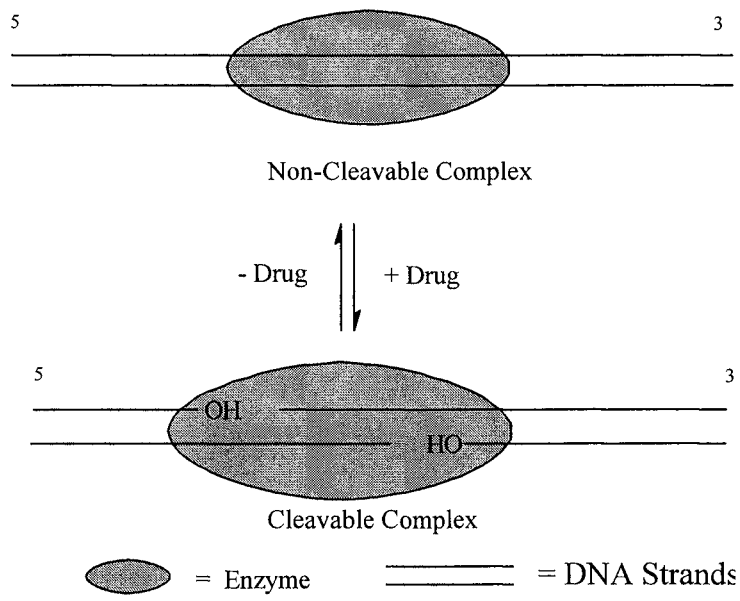
The two major forms of topoisomerase enzymes present in cells are called topoisomerase I and topoisomerase II. Topoisomerase I is characterised by its ability to break and reseal one DNA strand. The complex formed with the DNA allows the unbroken strand to pass through it with the topoisomerase linked to the 3-phosphoryl groups on the DNA strand. Topoisomerase II is characterised by its ability to break and reseal both DNA strands and catalyse ATP (adenosine 5'-triphosphate) dependant strand passing.[26] It has 3 major roles in cell replication

1) The ability to remove complex knots from topologically constrained DNA.
2) The ability to remove or create supercoiling in topologically constrained DNA.
3) The ability to reversibly catenate double strand DNA.

Cleavable complex

In the replication process a key intermediate termed the "non-cleavable" complex exists in equilibrium with the "cleavable" complex,[27, 28] the equilibrium being in favour of the non-cleavable complex (Scheme 3). When a drug is administered into

the system the equilibrium is then shifted in favour of the cleavable complex. Evidence for this has been illustrated by the addition of a strong protein denaturant to the system trapping the cleavable complex. Isolation and structural determination shows a covalent linking of topoisomerase polypeptide to the broken end of the DNA strand.[28] An accumulation of the cleavable complex within the cell is perceived by the cell machinery as damage and the cell arrests.[29, 30]

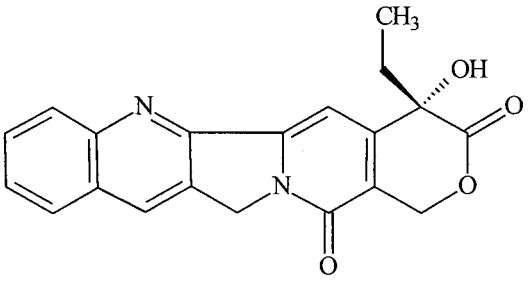


Scheme 3

Investigation of the topoisomerases led to the discovery of drugs that interact with topoisomerases resulting in the shifting of the equilibrium in favour of the cleavable complex inducing cell death.

Topoisomerase I poisons

Camptothecin **9**, a plant alkaloid was first isolated from the stem wood of the tree *Camptotheca acuminata* by Wall *et al.* in 1966 and its structure was determined.[31] Camptothecin's activity against a wide range of experimental tumours was quickly established although the mechanism of action remains speculative. However it is believed that inhibition of the synthesis of DNA and RNA and fragmentation of DNA are putative mechanisms involved in cell death.

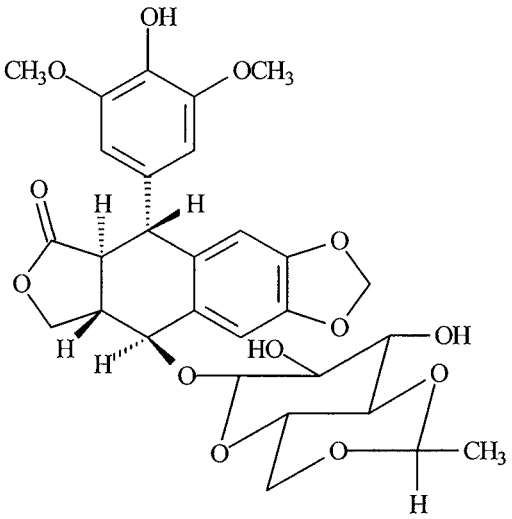


9

It was determined that camptothecin does not directly interfere with DNA yet somehow induces single strand breaks.[32] Evidence *via* trapping for the formation of the topoisomerase I cleavable complex explained the single strand breaks observed in the DNA and renewed interest in the development of topoisomerase I poisons.[33] A direct link was established between the production of the topoisomerase I cleavable complex and cytotoxic potency of the drug when present in the system.[34] Evidence also suggested camptothecin cell cytotoxicity to be phase specific showing drugs administered in the S phase of the cell cycle (Scheme 1) to be much more effective than in the G phases.[35]

Topoisomerase II poisons

Initial studies on drug dosed (4-demethylepipodophyllotoxin ethylidene-β-D-glucoside **10**) pure DNA system proved direct DNA cleavage by the drug unsuccessful, [36] and so it was hypothesised that one of the nuclear enzymes was responsible for drug induced DNA damage. Further investigation on a drug dosed non pure DNA system isolated an etoposide (an epipodophyllotoxin) topoisomerase II cleavable complex in the presence of a strong alkali. This isolation showed the protein bound covalently to both ends of the broken DNA strands indicating the importance of the role topoisomerase II plays in cell damage.[37]



10

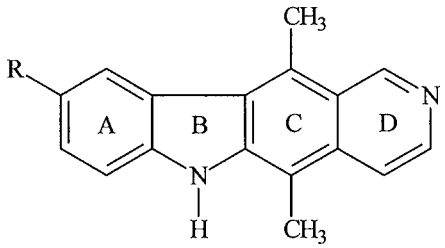
DNA topoisomerase II is much more widely recognised as a target for anti-cancer drugs than topoisomerase I and it is widely thought that the activity of this enzyme is higher in malignant cells than normal cells. Families of drugs such as the intercalating acridines, ellipticines, actinomycins and anthracyclines all target topoisomerase II, as do the non intercalating epipodophyllotoxins. The mechanism of action of these drugs remains speculative. One theory is that unwinding of the DNA during intercalation causes the broken DNA strands to become misaligned or disjointed resulting in an

inability to reseal the strands leading to cell death.[27] This explanation is valid only for intercalative drugs, however non intercalators are also biologically active and this suggests other mechanisms are present. Mechanisms of action may be speculative but it is widely known that topoisomerase II poisons exhibit cellular damage by causing an increase in chromosomal aberrations, sister chromatid exchanges and inhibition of both DNA and RNA synthesis. Evidence suggests that administration of topoisomerase II drugs is phase specific as greater chromatid aberrations and sister chromatid exchanges are present with drugs administered in the G_2 and G_1-S phase of the cell cycle.[38] Whereas DNA and RNA inhibition occurs predominantly in the late S or G_2 phase of the cycle [39] (Scheme 1).

Ellipticines

1.4.0 Ellipticine and related analogues

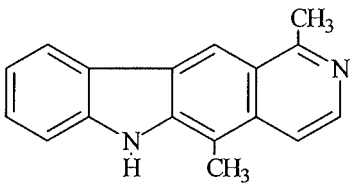
Ellipticine **11** a member of the pyrido[4,3-*b*]carbazole alkaloid family was first isolated from the leaves of the plant *Ochrosia Elliptica* in 1959; from this the structure was assigned and a total synthesis was established.[40] Following the discovery of ellipticine's anti-tumour activity, other members of the pyrido[4,3-*b*]carbazole family were synthesised *e.g.* Olivacine **14**.



11 R is H = Ellipticine

12 R is OCH_3 = 9-Methoxyellipticine

13 R is OH = 9-Hydroxyellipticine

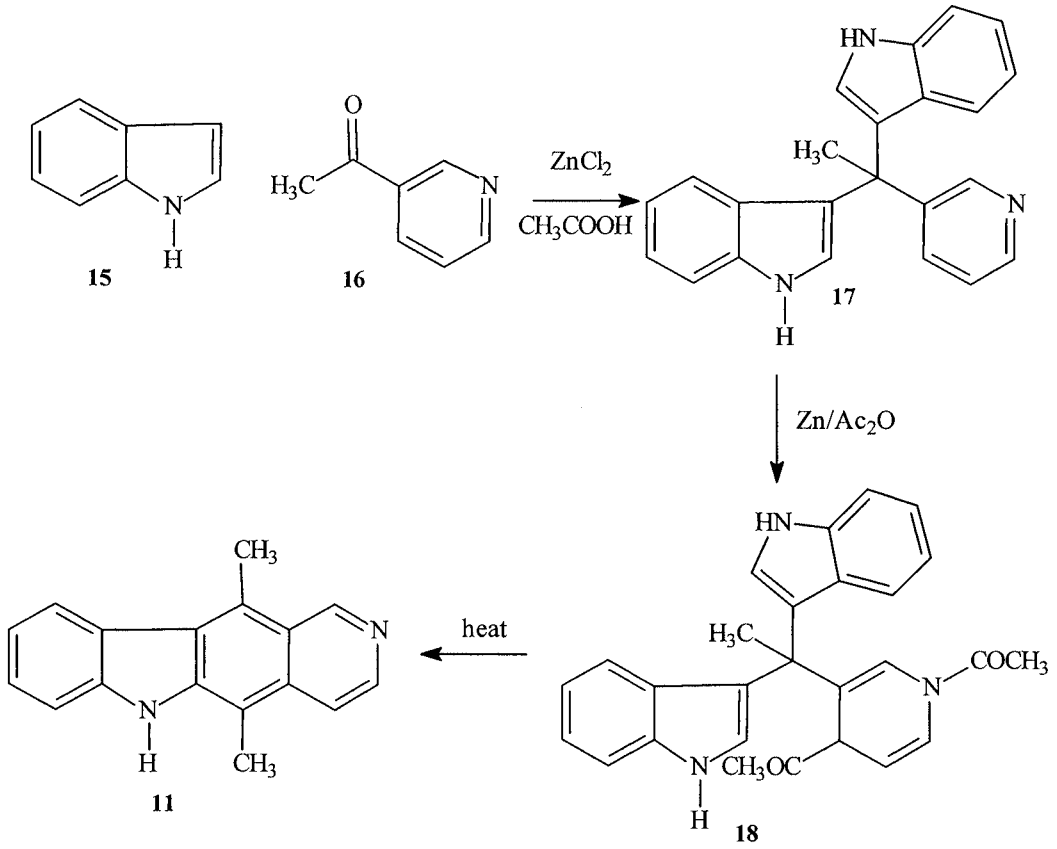


14 = Olivacine

1.5.0 Review of synthetic strategies to production of Ellipticine and its analogues

This section will highlight synthetic investigations into the pyrido[4,3-*b*]carbazole family of compounds from 1959 to the present. This will not be a complete review as work carried out is already immense, however it will show the major synthetic developments that have been achieved over the last 40 years. This section will concentrate predominantly on ellipticine synthesis, but it should be noted that the routes shown could be manipulated to produce the ellipticine analogue required.

Woodward *et al.* [40] carried out the first synthesis of ellipticine (Scheme 4) by the condensation of indole **15** with 3-acetylpyridine **16** in acetic acid with a zinc chloride catalyst. Reduction of the resulting 1,1-bis-(3-indolyl)-1-(3-pyridyl)ethane **17** by zinc in acetic anhydride gave **18** which on pyrolysis gave ellipticine **11** (2 % yield from starting material) as yellow crystals.

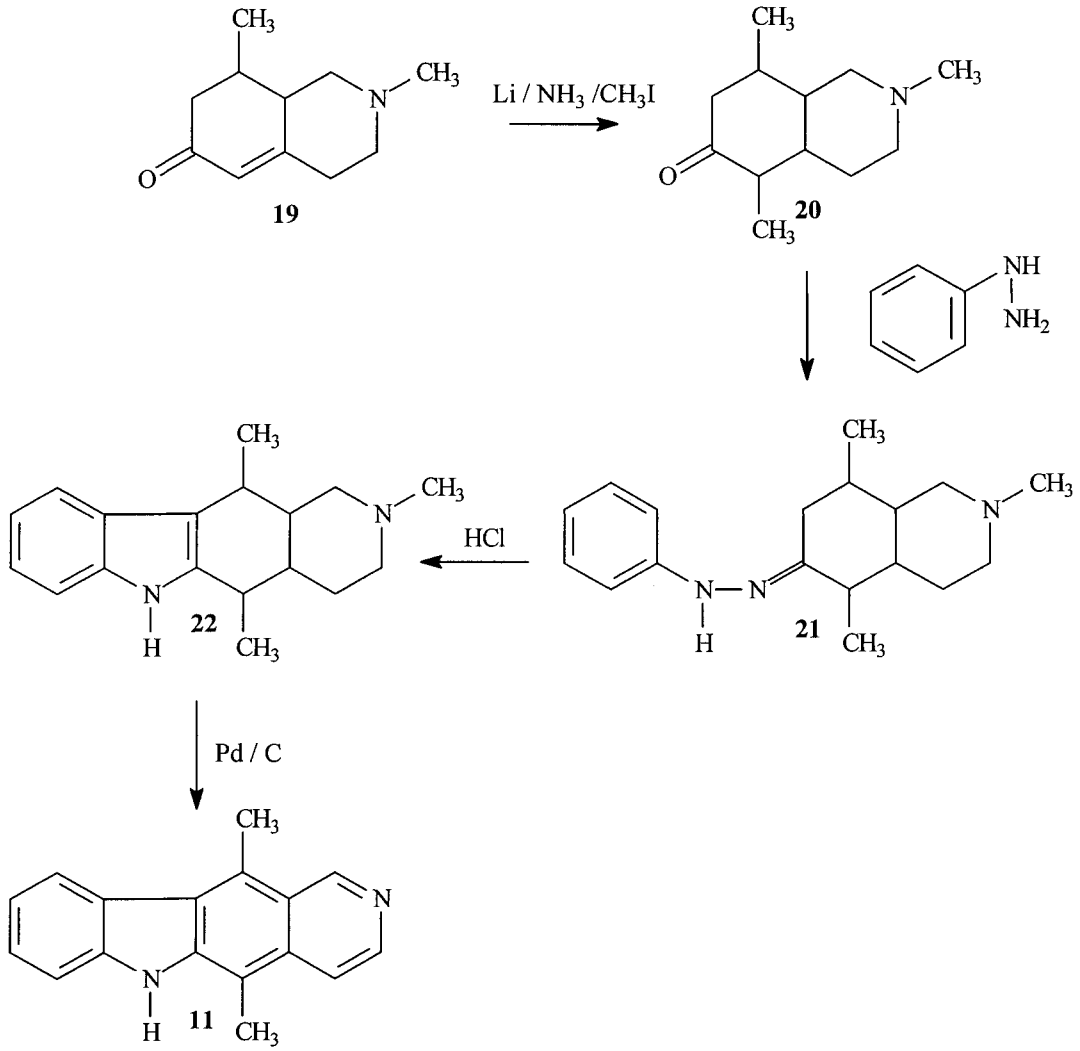


Scheme 4

Subsequent attempts to synthesise the pyrido[4,3-*b*]carbazole between 1959 and 1982 were reviewed by Sainsbury [41] and Shannon *et al.* [42] who classified them by construction of the last ring system [ordered A,B,C and D, see structure **11**]. Subsequent reviews by Kansal [43] and Gribble [44] target synthetic strategies from 1982-1990.

1.5.1 *B-type syntheses*

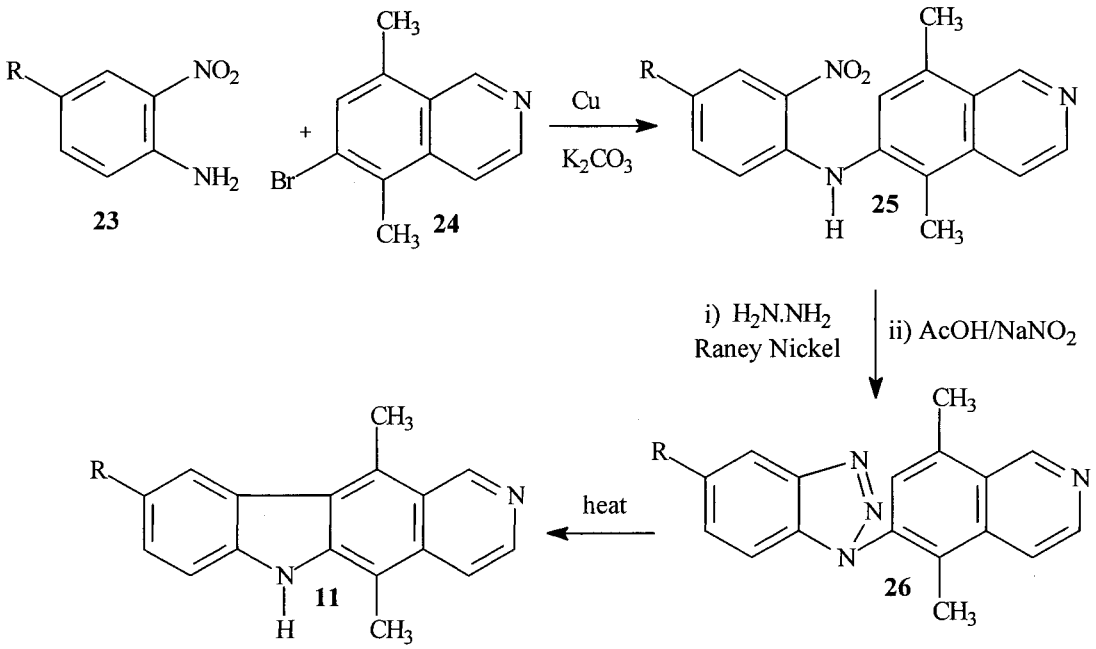
Stilwell and Woodward [45] devised a Fischer indolisation type synthesis (Scheme 5). Reaction of 1-methyl-4-piperidone with 3-penten-2-one giving **19** was followed by a reductive Stork alkylation in liquid ammonia affording the octahydroisoquinolone derivative **20**. Reaction with the desired phenyhydrazone in a Fischer indolisation through derivative **21** yielded the hydrogenated ellipticine **22**. On heating with palladium on carbon dehydration occurred giving ellipticine **11** (0.3 % yield from starting material).



Scheme 5

Miller and Moock [46] developed a route that involved a Goldberg modification of the Ullmann coupling reaction of the substituted acetanilide with the required bromoisoquinoline to produce the diarylamide. Subsequent acidic hydrolysis gave the diarylamine **25** (90 % yield) that underwent cyclisation using palladium acetate in a trifluoroacetic acid/acetic acid solvent giving ellipticine **11** (15 % yield from **25**).

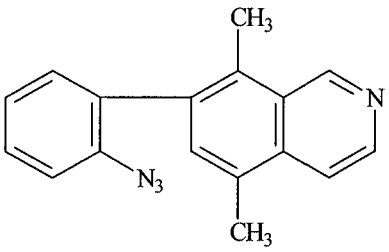
Subsequent work by Miller and Stowell [47] (Scheme 6) incorporated the same Goldberg coupling of substituted nitroaniline **23** with the required bromoisoquinoline **24** to give the diarylamine **25**. Reduction of the nitro group with Raney-Nickel followed by diazotisation gave the benzotriazole **26** which then underwent pyrolytic decomposition (500°C) to give ellipticine **11** (69 % yield from **26**).



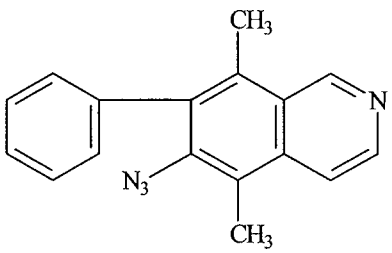
Scheme 6

Further work by Miller *et al.* [48, 49] involved the intramolecular cyclisation of isoquinoline azides to produce ellipticines. In the first paper the isoquinoline azide **27** was heated (180-200°C) in dodecane to give ellipticine **11** (20 % yield from **27**). In the second paper the isoquinoline azide **28** was synthesised switching the position of the azido group from C_2' to C_6 on the isoquinoline skeleton. Cyclisation in boiling

dodecane gave ellipticine **11** in higher yield (41 % yield from **28**) making a more efficient route.

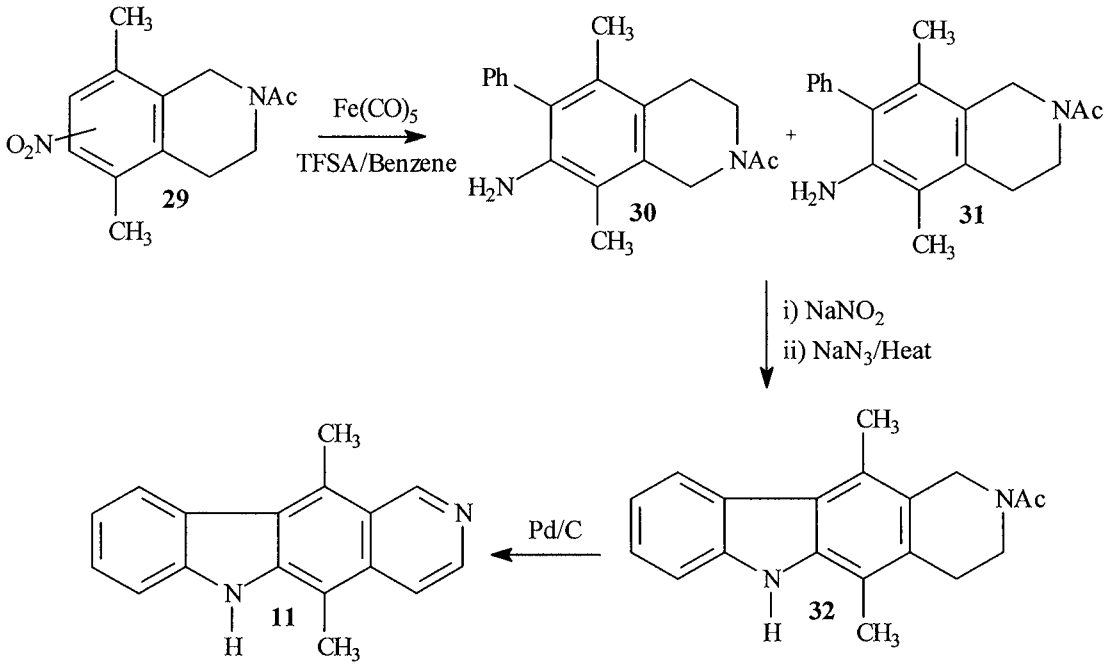


27



28

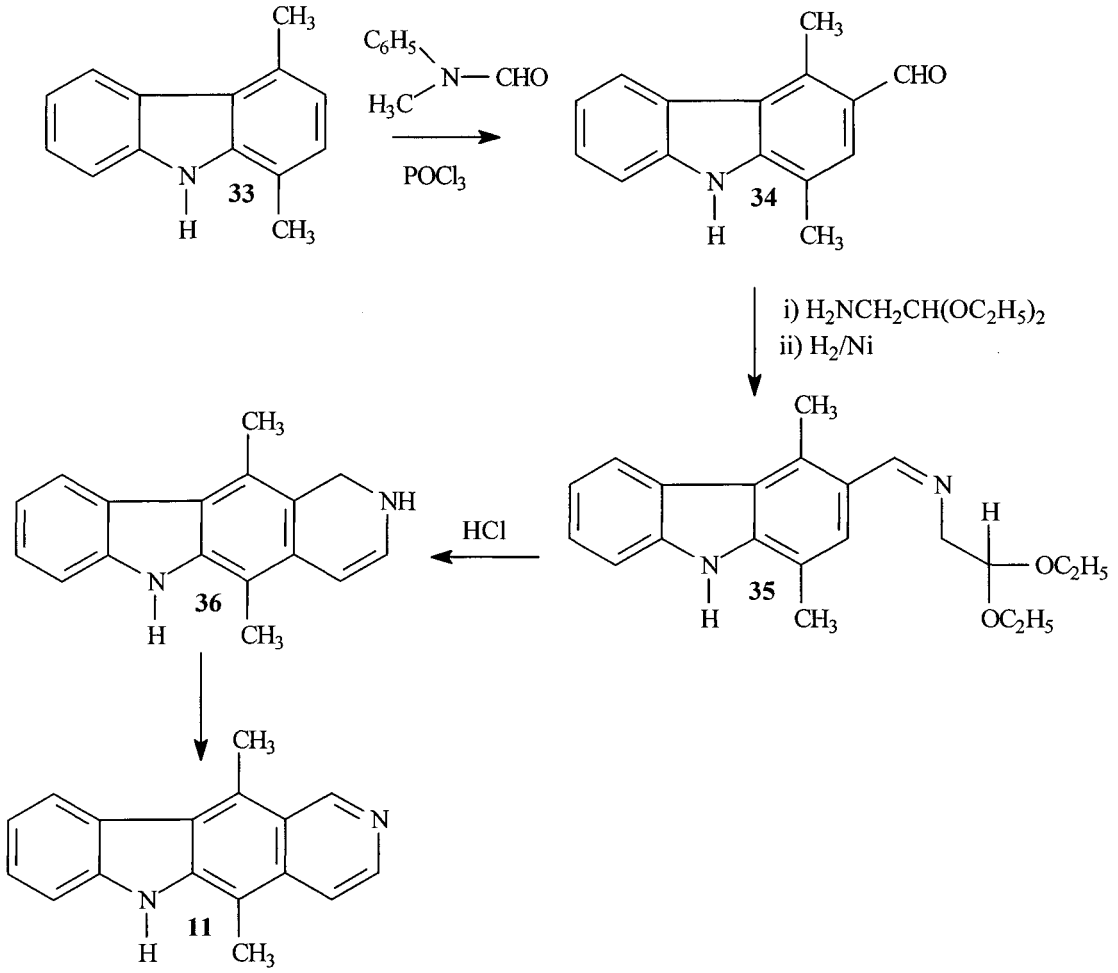
Miyake *et al.* [50] developed a synthesis *via* the reductive phenylation of nitroarenes (Scheme 7). Reductive phenylation of an inseparable mixture of 2-acetyl-1,2,3,4-tetrahydro-5,8-dimethyl-6- and 7-nitroisoquinoline **29** using iron pentacarbonyl, trifluoromethanesulphonic acid (TFSA) in benzene gave a 2:1 mixture of phenyl-aminotetrahydroisoquinolines **30** and **31**. The desired isomer **31** was separated using chromatography before diazotisation and conversion to its corresponding azide that underwent cyclisation on heating to give **32**. Subsequent dehydrogenation of **32** with palladium on carbon yielded ellipticine **11** (9 % yield from starting material).



Scheme 7

1.5.2 *D-type syntheses* - Synthesis from Carbazole Derivatives

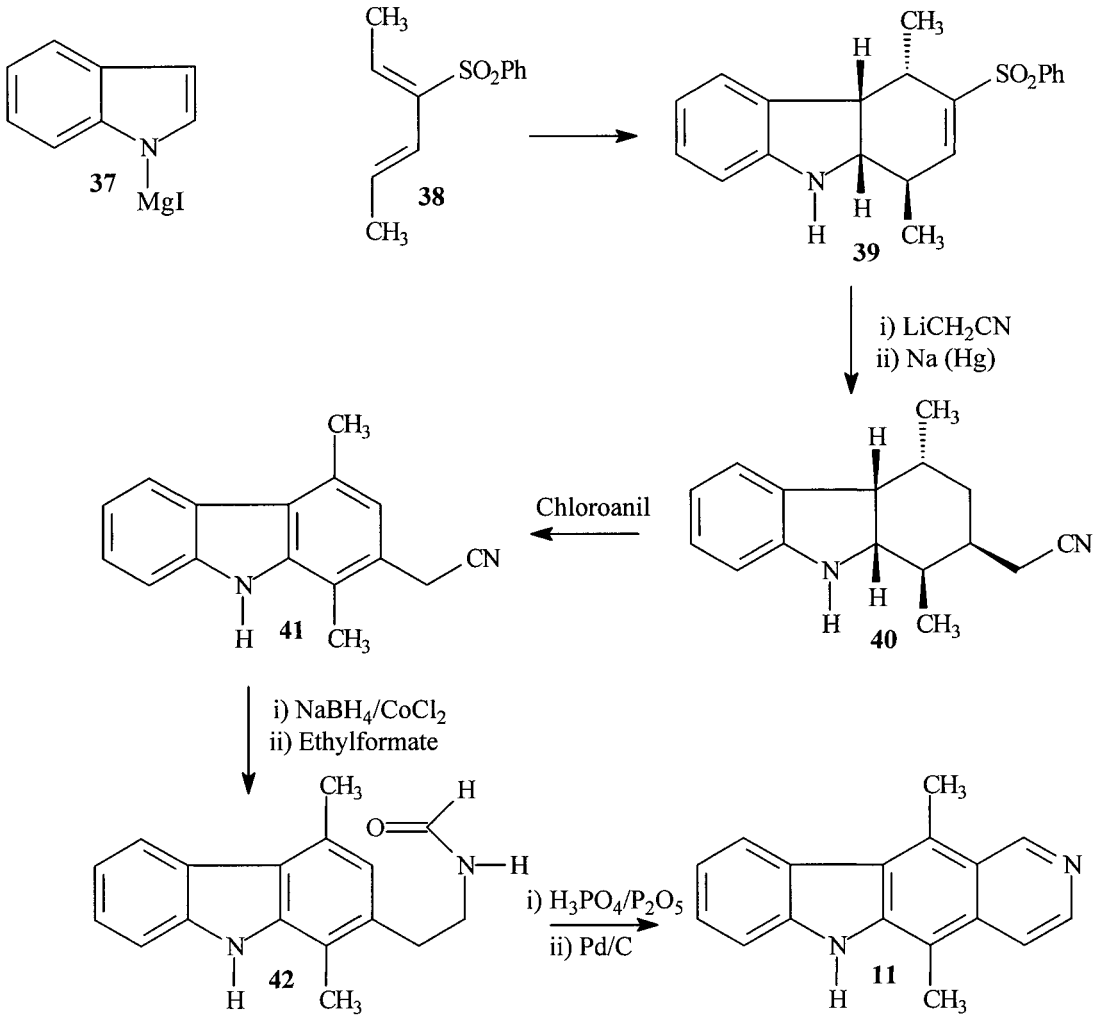
Several synthetic attempts have been made to synthesise ellipticines *via* a carbazole ring system the most successful and versatile being the synthesis devised by Cranwell and Saxton [51] (Scheme 8). Initial treatment of indole with 2,5-hexanedione gave the 1,5-dimethylcarbazole **33** that was formylated under Vilsmeier conditions to give 1,5-dimethylcarbazole aldehyde **34**. Condensation with 2,2-diethoxyethylamine followed by hydrogenation yielded the saturated acetal **35**, which underwent cyclisation in HCl to give the dihydroellipticine **36**. Dehydrogenation of the dihydroellipticine with Pd/C gave ellipticine **11** (1.5 % yield from starting material).



Scheme 8

Subsequent modifications of Cranwell and Saxton's initial synthesis have improved both yields and diversity of ellipticine derivatives [52], however the synthetic route is still far from efficient.

Backvall and Plobeck [53] developed a synthetic route (Scheme 9) to ellipticine by cycloaddition of 2-phenylsulphonyl-1,3-dienes to indole. A Diels-Alder reaction of 3-(phenylsulphonyl)-2,4-hexadiene **38** with indolylmagnesium iodide **37** gave the tetrahydrocarbazole **39**. Subsequent Michael addition of the lithium salt of acetonitrile to ring C followed by elimination of the sulphone gave compound **40** that underwent aromatisation with chloroanil to give compound **41**. Reduction of the nitrile using cobalt chloride/$NaBH_4$ was followed by formylation with ethyl formate, then subsequent Bischler-Napieralski cyclisation gave the dihydroellipticine **42**. Subsequent dehydrogenation using Pd/C gave ellipticine **11** (77 % yield from **42**).


37
MgI
38
39
i) LiCH2CN
ii) Na (Hg)
40
Chloroanil
41
i) NaBH4/CoCl2
ii) Ethylformate
42
i) H3PO4/P2O5
ii) Pd/C
11

Scheme 9

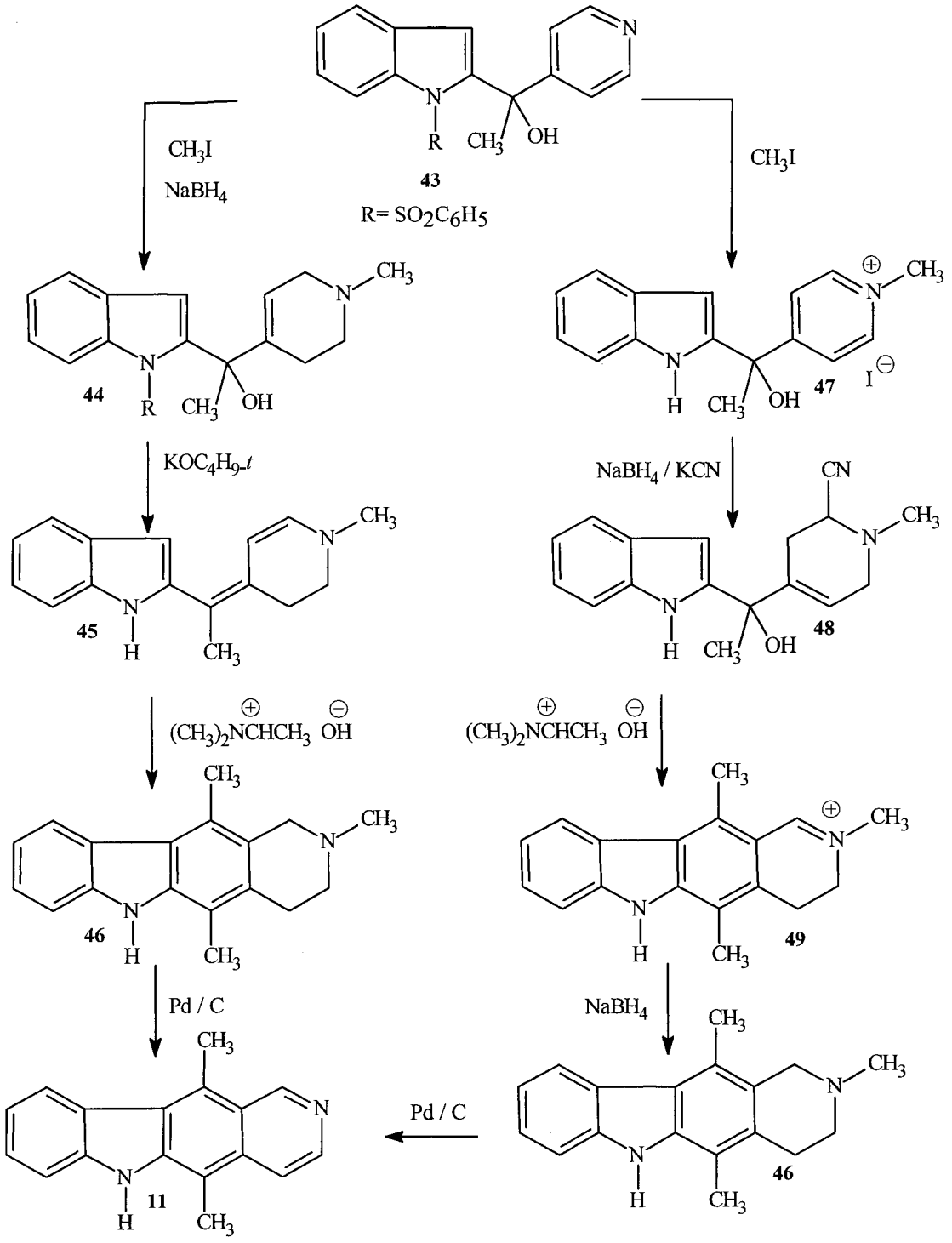
1.5.2 *C-type syntheses* - Synthesis from Indole Precursors

Investigations into versatile routes to ellipticines *via* indole precursors have been widely investigated.

Potier *et al.* [54] developed a synthetic route to ellipticine that was thought in some way to mimic the biosynthesis of the natural alkaloid. Initial condensation of 2-lithio-1-benzenesulphonylindole with 4-acetylpyridine yielded **43**, and this compound was then converted to ellipticine *via* the two routes shown in Scheme 10.

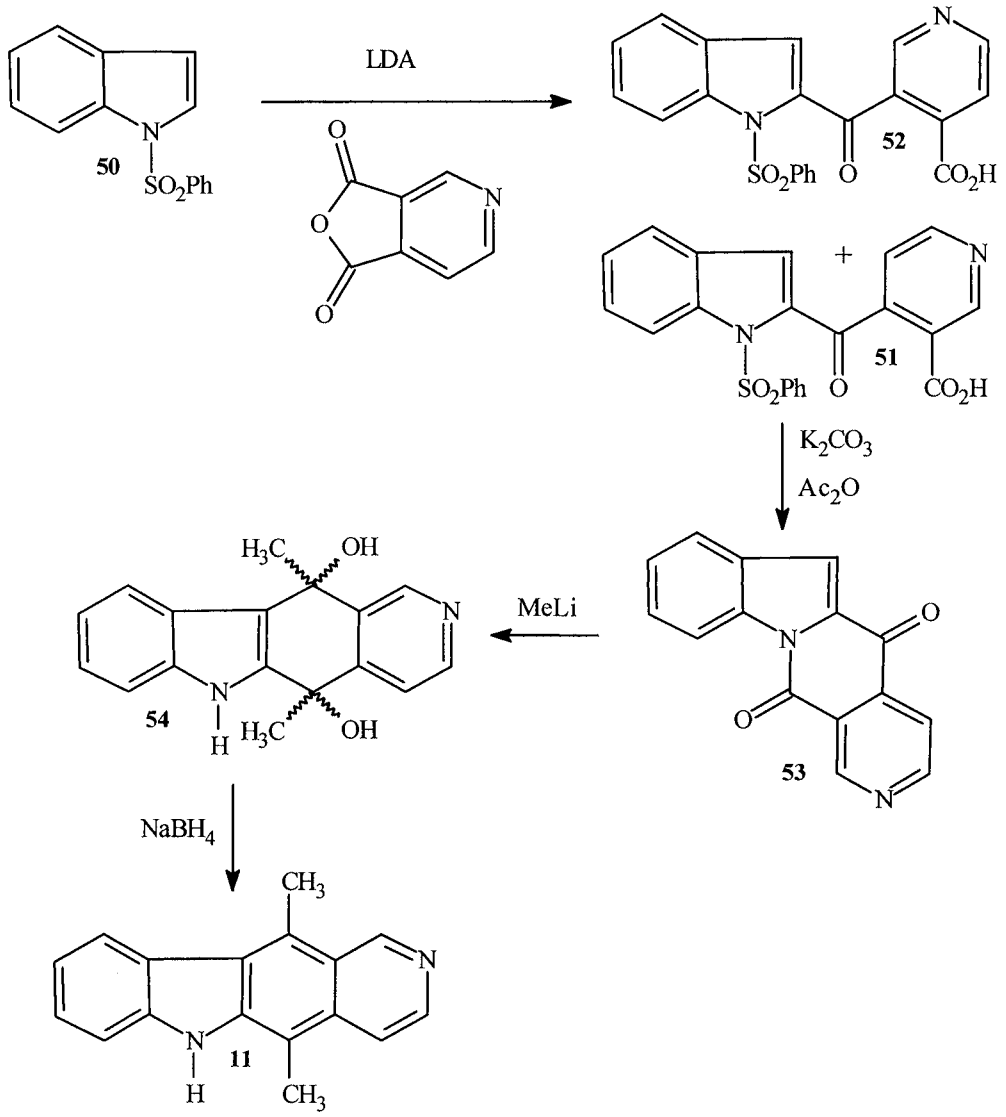
Route 1 involved iodomethylation of **43** with methyl iodide followed by reduction to the tetrahydropyridine **44** with sodium borohydride. Subsequent reaction with potassium *tert*-butoxide gave the dieneamine **45** that was then converted under Mannich conditions to the *N*-methyl-1,2,3,4-tetrahydroellipticine **46**. The final demethylation and dehydrogenation using palladium on carbon yielded ellipticine **11** (< 2 % yield from **44**).

Route 2 involved hydrolysis of compound **43** to the parent indole followed by iodomethylation to give compound **47**. Reduction with sodium borohydride and cyanation with potassium cyanide gave compound **48**. Subsequent Mannich reaction gave the imminium salt **49** which was reduced by sodium borohydride to the *N*-methyl-1,2,3,4-tetrahydroellipticine **46** which then underwent demethylation and dehydrogenation with palladium on carbon to yield ellipticine **11** (8 % yield from **49**).


CH3I
NaBH4
43
R= SO2C6H5
CH3I
44
47
I
KOC4H9-t
NaBH4 / KCN
CN
45
48
(CH3)2NCHCH3 OH
(CH3)2NCHCH3 OH
46
49
Pd / C
NaBH4
Pd / C
11
46

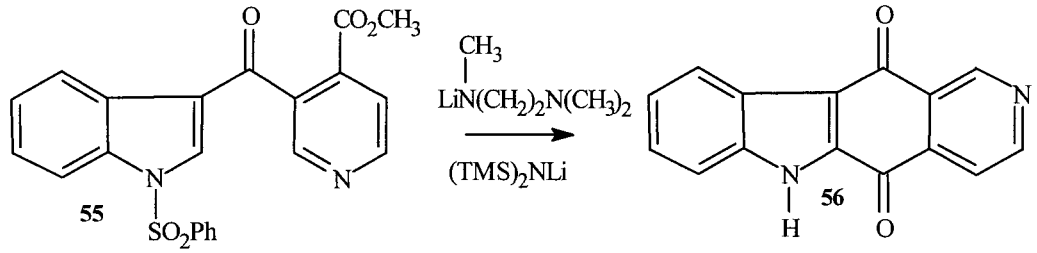
Scheme 10

Gribble *et al.* [55] developed an efficient high yielding route to ellipticine using 1-(phenylsulphonyl)indole (Scheme 11). Initial generation of the indole anion of **50** using LDA at -100°C was followed by reaction with cinchomeronic anhydride to give a mixture of keto acids (**51** and **52**, ratio 92:8). Subsequent hydrolysis of **51** by methanolic potassium carbonate followed by reaction in hot acetic anhydride yielded ketolactam **53** which underwent conversion to a diastereomeric mixture of diols **54** with 2 equivalents of methyllithium. Dehydration and subsequent reduction of the diol **54** with sodium borohydride gave ellipticine **11** (54 % yield from **50**).



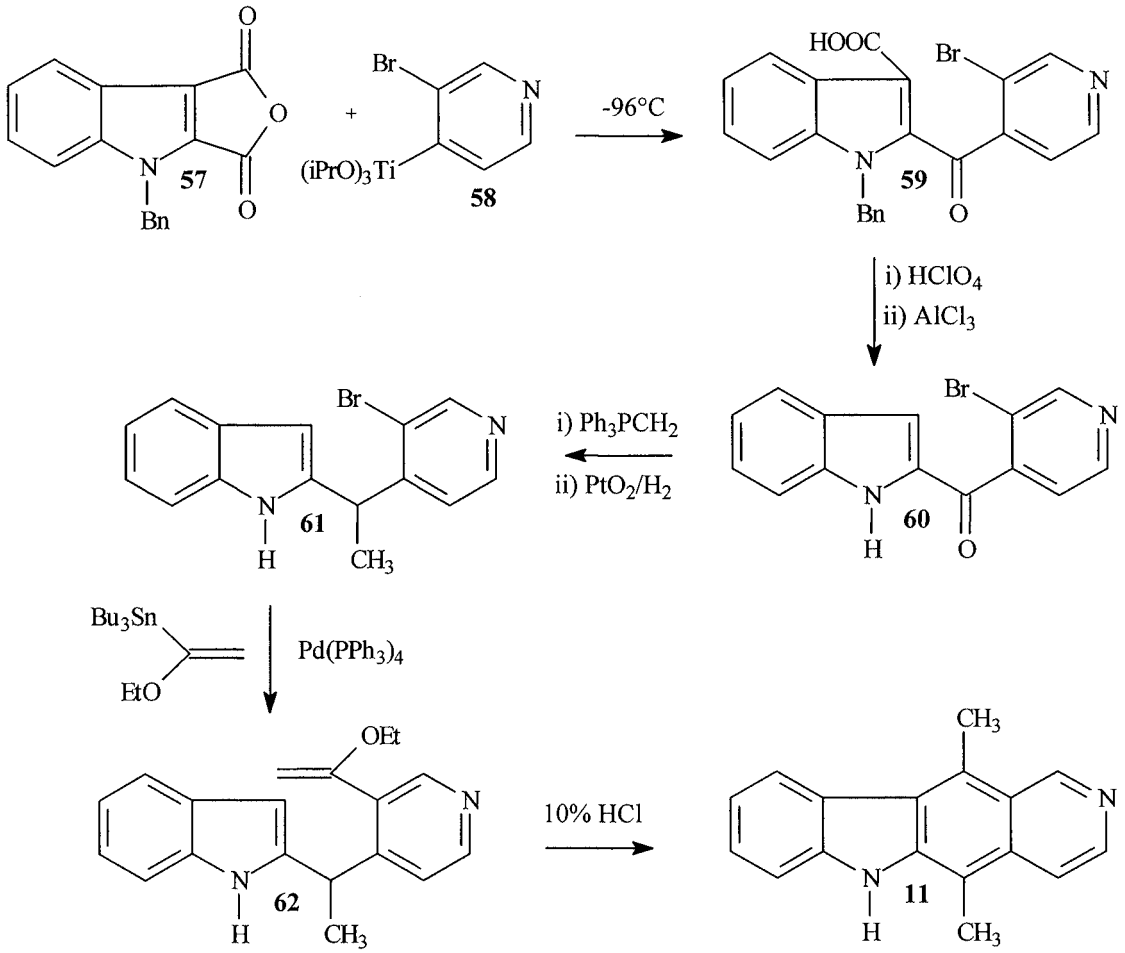
Scheme 11

Gribble *et al.* [56] have extended the above work using a Friedel-Crafts acylation reaction of **50** so as to improve regioselectivity. Treatment of cinchomeronic anhydride with sodium methoxide/methanol in THF followed by aqueous hydrochloric acid gave its mono-ester, which was then converted to its acid chloride by heating with thionyl chloride. Friedel-Crafts reaction with the 1-(phenylsulphonyl)indole gave the ketoester **55**. Cyclisation to the quinone **56** was achieved using *N, N, N*-trimethylethylenediamine followed by treatment with lithium bis(trimethylsilyl)amide. The quinone was then converted (Scheme 12) by treatment with methyl lithium/sodium borohydride into ellipticine **11** (13 % yield from **50**). Further work on this synthetic route by Gribble [57] has significantly improved yields of ellipticines.



Scheme 12

Miki *et al.* [58] have reported novel synthetic routes to ellipticines using *N*-benzylindole-2,3-dicarboxylic anhydride. In one of the routes (Scheme 13) *N*-benzylindole-2,3-dicarboxylic anhydride **57** was reacted with a 3-bromo-4-pyridyltitanium complex **58** to give the 2-acylindole-3-carboxylic acid **59**. Subsequent decarboxylation and debenzylation gave the ketone **60** which underwent a Wittig reaction followed by catalytic reduction to the 1-(3-bromo-4-pyridyl)-1-(2-indolyl)ethane **61**. Treatment with (1-ethoxyvinyl)tributyltin in the presence of a palladium(0) complex gave the ethoxyvinyl derivative **62** which was converted to ellipticine **11** (87 % yield from **62**) in 10% hydrochloric acid.

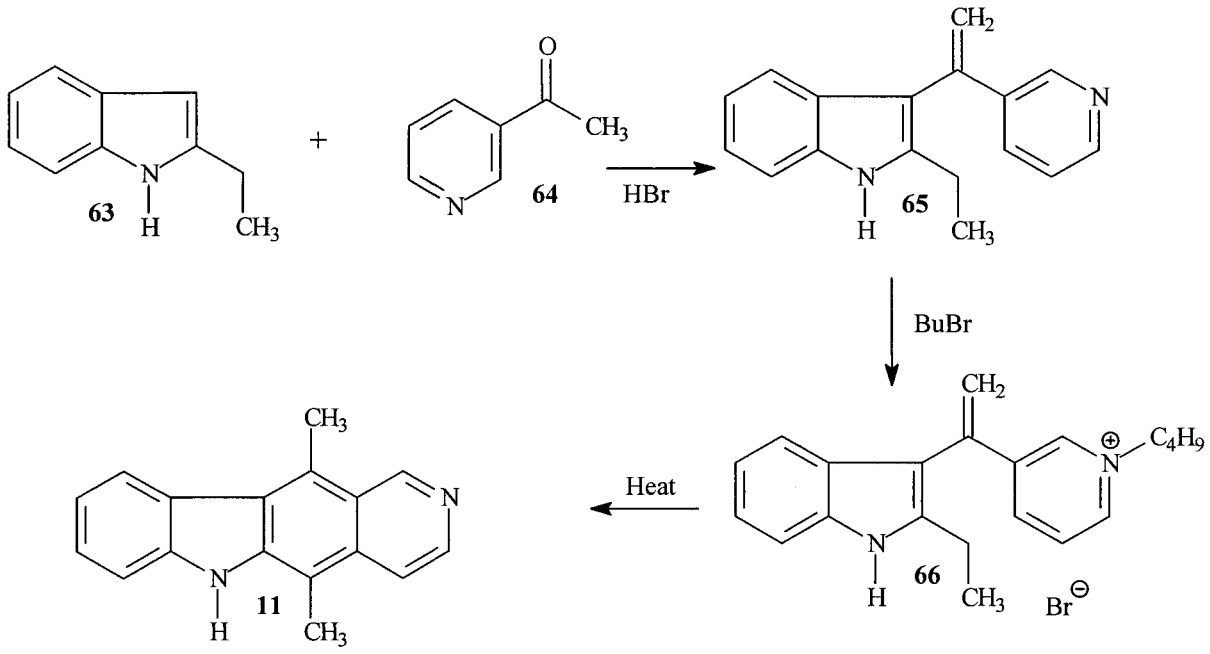


Scheme 13

1.5.2.1 Thermal and Photochemical ring closures

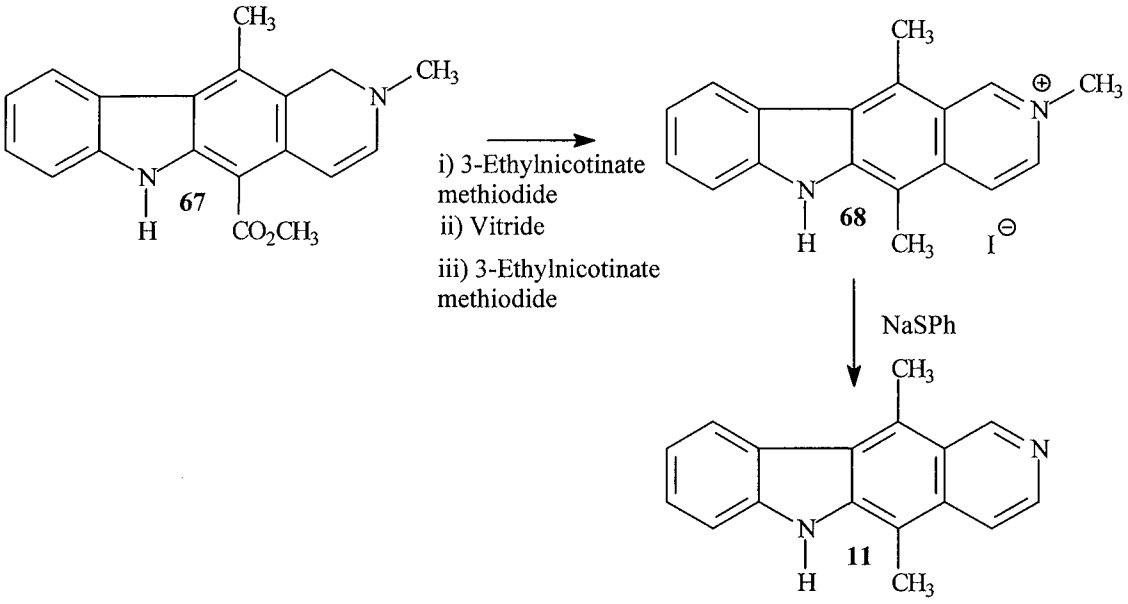
Improvements on initial synthetic routes have been developed to synthesise intermediates which when exposed to energy in the form of heat or light undergo intramolecular cyclisations to give ellipticine or its derivatives.

Bergmann *et al.* [59] developed an improved synthetic route (Scheme 14) based on Woodward's initial synthesis. Initial reaction of 2-ethylindole **63** and 3-acetylpyridine **64** in methanolic HBr afforded substituted indole **65** in high yield; subsequent *N*-alkylation of the pyridine ring system with butyl bromide gave salt **66**, which upon slow heating gave ellipticine **11** (72 % yield from **66**).



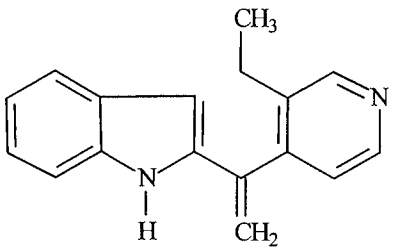
Scheme 14

Weller *et al.* [60] developed a synthetic route (Scheme 15) that is similar to Bergmann's approach.[59] 2-(Carboxymethyl)indole was condensed with 3-acetylpyridine in methanolic HBr. Subsequent quarternisation of the pyridinium nitrogen with methyl iodide was followed by cyclisation upon heating with sodium methoxide in methanol to yield the dihydroellipticine **67**. Oxidation of **67** with 3-ethylnicotinate methiodide was followed by reduction of the ester group with vitride in hot xylene. Immediate oxidation with 3-ethylnicotinate methiodide yields *N*-2-methylellipticinium iodide **68**. Subsequent demethylation with sodium thiophenoxide yielded ellipticine **11** (91 % yield from **68**).



Scheme 15

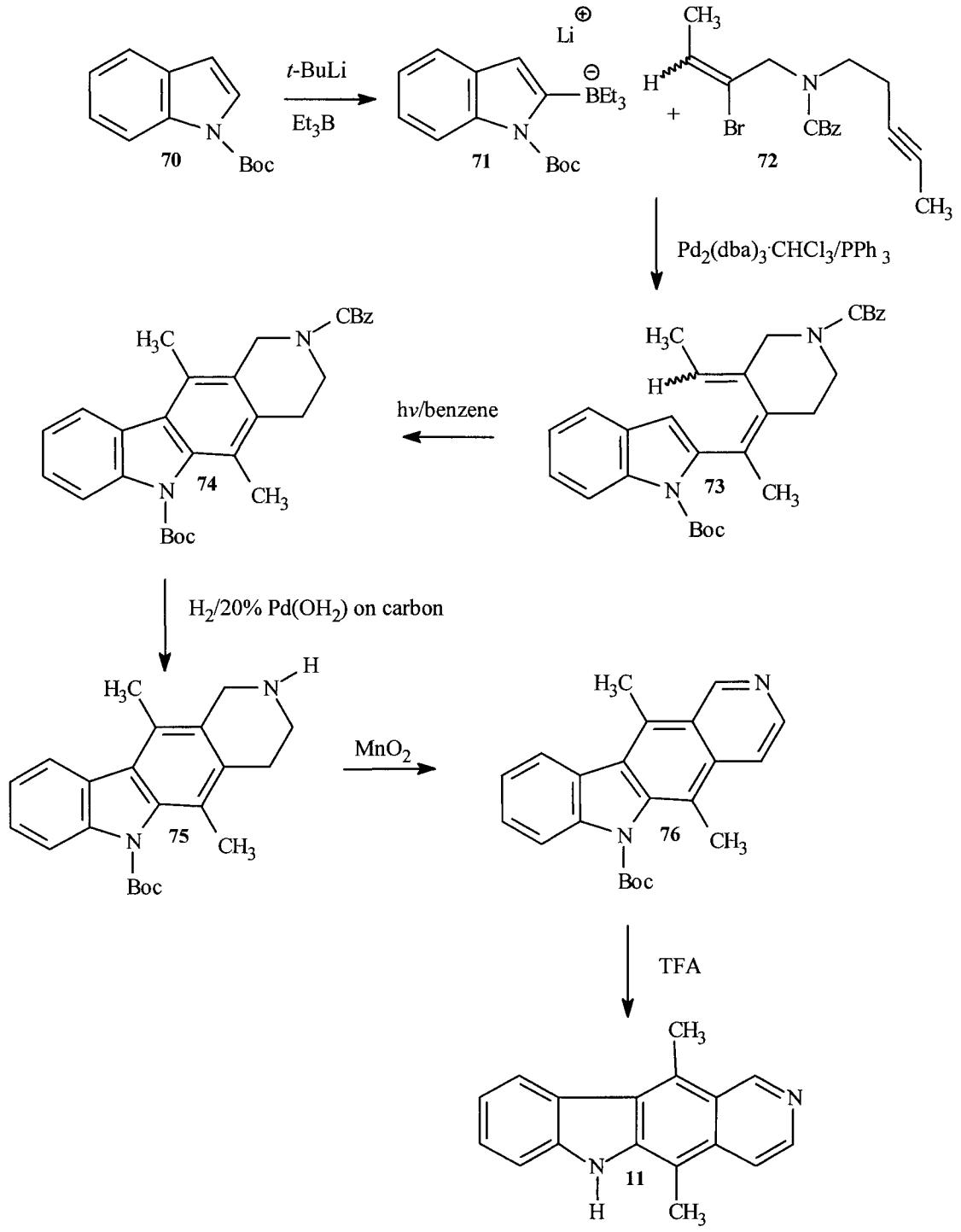
Hibino and Sugino [61] developed a synthetic route to ellipticines *via* a thermal electrocyclic reaction of a conjugated hexatriene system. Condensation of *N*-benzylsulphonylindole with an acetylpyridine (3-ethyl-4-acetylpyridine in the case of ellipticine) afforded the 2-alkenylindole **69** which was heated to 500°C for 3 minutes to yield ellipticine **11** (37 % yield from **69**).



69

Ishikura *et al.* [62] developed several synthetic routes to ellipticines *via* photochemical ring closure of hexatriene systems. One route (Scheme 16) involved the reaction of the Boc protected indole **70** with triethylborate and *tert*-butyl-lithium gave 1-(*tert*-butoxycarbonyl)indolylborate **71**. *In situ* reaction with **72** gave hexatriene **73** that underwent photochemical cyclisation to pyridocarbazole **74**. Subsequent

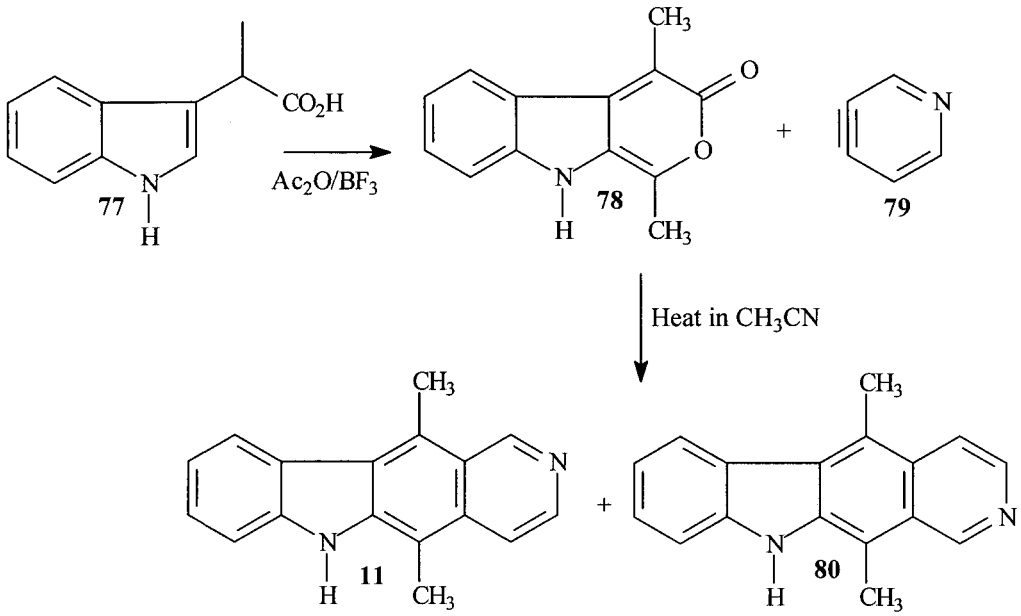
hydrogenation using palladium hydroxide cleaved the benzyl group giving **75**. Dehydrogenation using potassium permanganate gave **76** which was then converted to ellipticine **11** (49 % yield from **74**) using trifluoroacetic acid.



Scheme 16

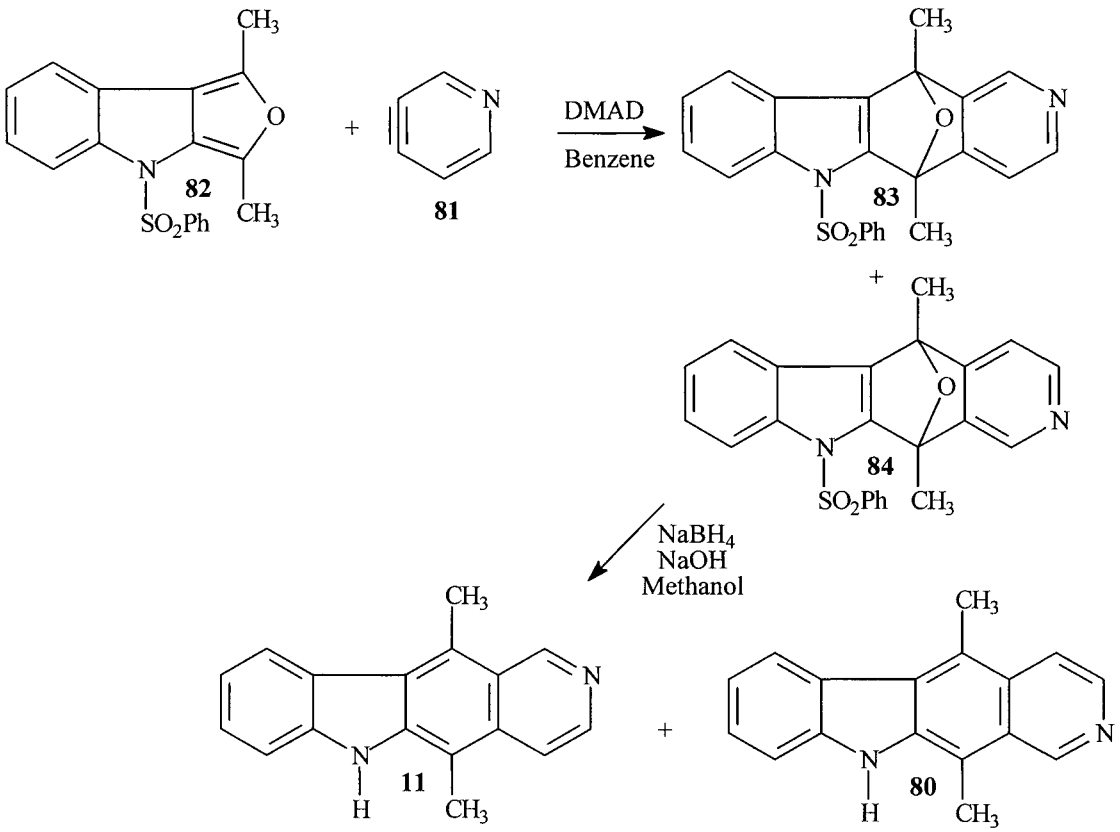
1.5.2.0 Diels-Alder type reactions

Moody *et al.* [63] developed a novel approach to the synthesis of ellipticines *via* a Diels-Alder type reaction (Scheme 17). The diene precursor **78** was prepared by the reaction of α-methylindole-3-acetic acid **77** in acetic anhydride with a trace of boron trifluoride. Subsequent reaction of the diene with the dienophile **79** obtained from heating 3-(3,3-dimethyltriazen-1-yl)pyridine-4-carboxylic acid gave ellipticine **11** (20 % yield from **77**) and isoellipticine **80** (20% yield from **77**).



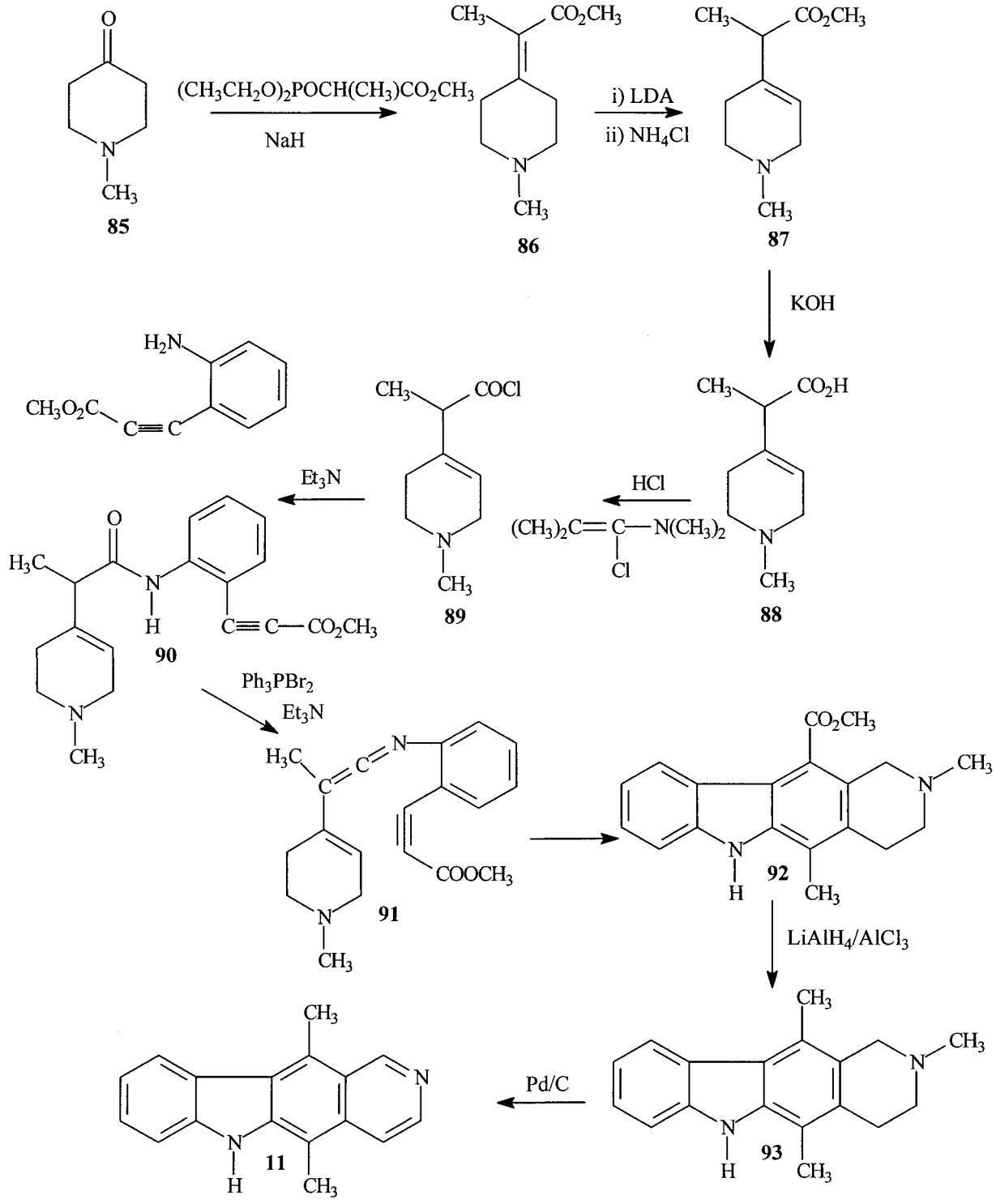
Scheme 17

Gribble *et al.* [64] developed a similar Diels-Alder approach (Scheme 18) by reacting 3,4-pyridyne **81** with 1,3-dimethyl-4-(phenylsulphonyl)-4*H*-furo[3,4-*b*]indole **82** giving a mixture of diastereoisomers **83** & **84**. Subsequent oxygen bridge extrusion using a basic methanolic sodium borohydride solution yielded ellipticine **11** (23 % yield from **82**) and isoellipticine **80** (29 % yield from **84**). Gribble *et al.* [65, 66] and Castedo *et al.* [67] have furthered this area of research to improve both regioselectivity and yield of ellipticines.



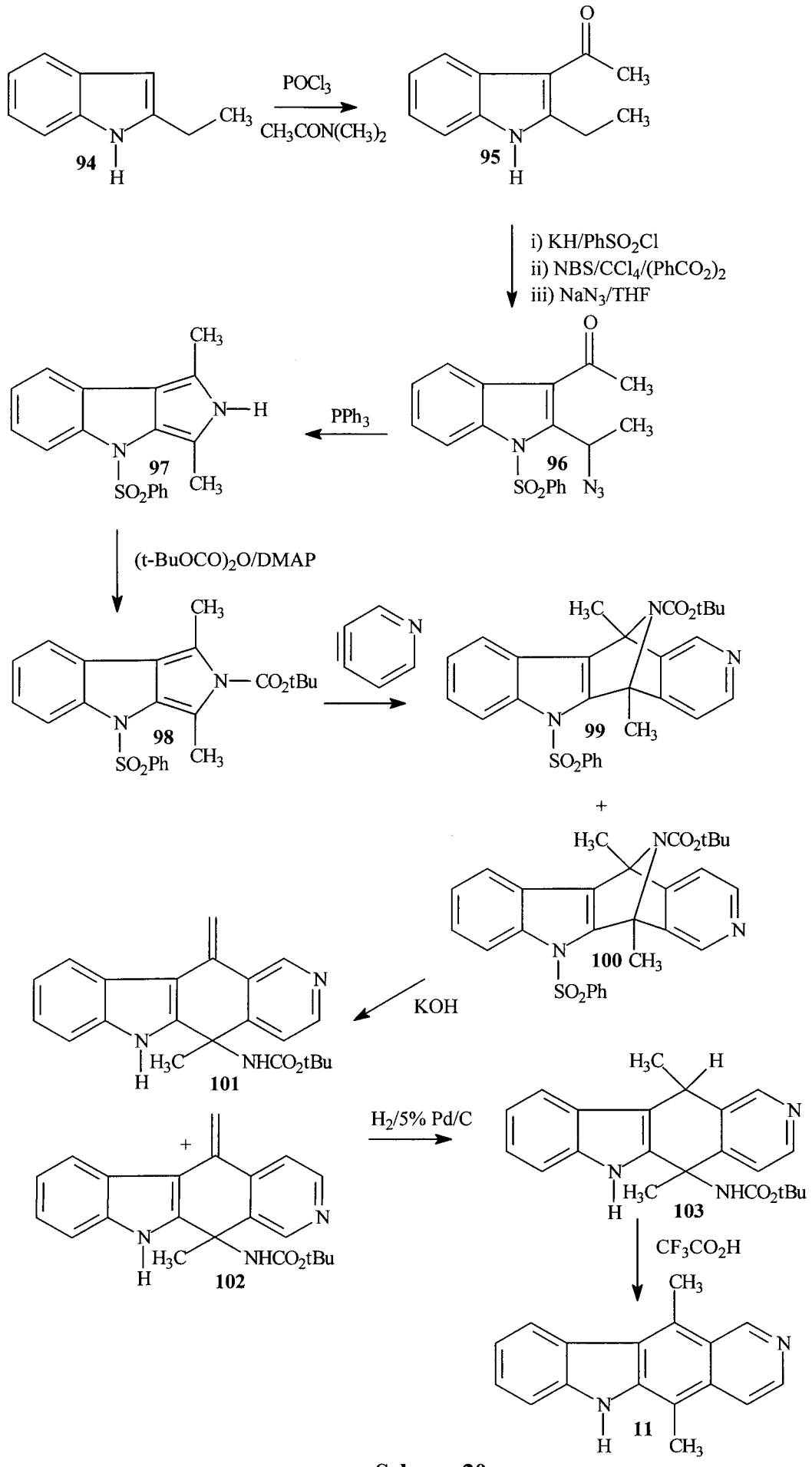
Scheme 18

Differding and Ghosez [68] developed an intramolecular Diels-Alder cycloaddition route to ellipticine (Scheme 19). Piperidone **85** underwent conversion to its unsaturated ester **86** followed by deconjugation **87** and saponification to give the acid **88**. Subsequent conversion to the acid chloride **89** then reaction with substituted aniline gave the amide **90** that is converted *in situ* to the vinylketenimine **91**. The vinylketenimine underwent an intramolecular Diels-Alder reaction to give **92**; subsequent reduction of the ester group gave *N*-methyl-tetrahydroellipticine **93**. Dehydrogenation and demethylation with Pd/C gave ellipticine **11** (5 % yield from **85**).


(CH3CH2O)2POCH(CH3)CO2CH3
NaH
i) LDA
ii) NH4Cl
KOH
HCl
Et3N
Ph3PBr2
Et3N
LiAlH4/AlCl3
Pd/C
85
86
87
88
89
90
91
92
93
11

Scheme 19

Sha and Yang [69] developed a total synthesis of ellipticine (Scheme 20) *via* an intramolecular Diels-Alder cyclisation. Initial acetylation of 2-ethylindole **94** with dimethylacetamide and phosphorus oxychloride gave **95**, that underwent *N*-phenylsulphonation using potassium hydride and phenylsulphonyl chloride. Subsequent bromination using *N*-bromosuccinimide followed by conversion to azide using sodium azide gave compound **96**. A Staudinger reaction with triphenylphosphine gave **97**, that was followed by reaction with di-*tert*-butyl dicarbonate to give diene **98**. Reaction of diene with dienophile 3,4-pyridyne (obtained from reaction of 1-aminotriazolo[4,5-*c*]pyridine with lead tetraacetate) gave a mixture of cycloadducts **99** and **100**. Treatment with potassium hydroxide and separation of isomers **101** & **102** was followed by hydrogenation with 5% palladium on carbon giving **103**. Subsequent stirring in trifluoroacetic acid gave ellipticine **11** (10 % yield from **94**).


POCl3
CH3CON(CH3)2
94
95
i) KH/PhSO2Cl
ii) NBS/CCl4/(PhCO2)2
iii) NaN3/THF
PPh3
96
97
(t-BuOCO)2O/DMAP
98
99
100
KOH
101
102
H2/5% Pd/C
103
CF3CO2H
11

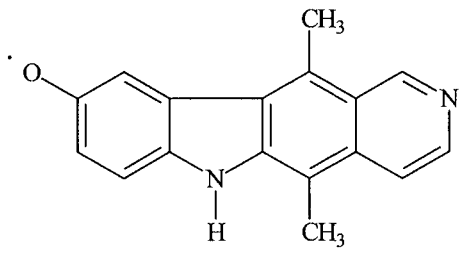
Scheme 20

1.6.0 Proposed mechanisms of action of Ellipticines

The mechanism of action of ellipticines still remains speculative, however recent studies have gone a long way to proposing a new and clear understanding as to how these drugs act when they are placed in cellular situations.

Initial work established ellipticines as intercalating agents [70] by measuring binding affinity of the drugs for DNA by direct competition with ethidium bromide, a known intercalating agent. Further work [71] establishing intercalation measured the effect of the drugs on viscocity and sedimentation of linear, nicked and closed circular DNA by comparing results with known intercalating drugs. It was established that when ellipticine is placed *in vivo* it undergoes biogenic oxidation to 9-hydroxyellipticine [72] which has been shown to be 40 times more active than ellipticine. This increased activity was thought to be a result of increased binding affinity of 9-hydroxyellipticine for DNA.[73] However certain ellipticine derivatives (9-aminoellipticine and 9-fluoroellipticine) possesing similar binding affinities did not display similar drug activity suggesting that intercalation was not the sole mechanism responsible for activity.

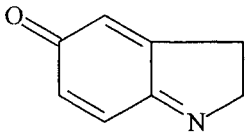
One of the proposed further mechanisms is the formation of phenoxy radicals **104** which is an intermediate thought to be generated during the formation of quinone-imines.



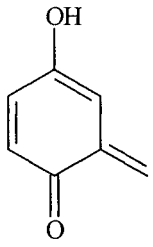
104

It is thought that phenoxy radicals are formed *in vivo* by reduction of molecular oxygen to superoxide ions. Phenoxy radicals are very stable and are not thought to directly attack DNA, however the superoxide ions formed during phenoxy radical production can react with water to give hydroxyl radicals which can directly damage DNA.[74]

Phenoxy radicals are formed by a one electron oxidation, however a two electron oxidation *in vivo* gives the highly reactive quinone-imine species [75] of general structure **105**.



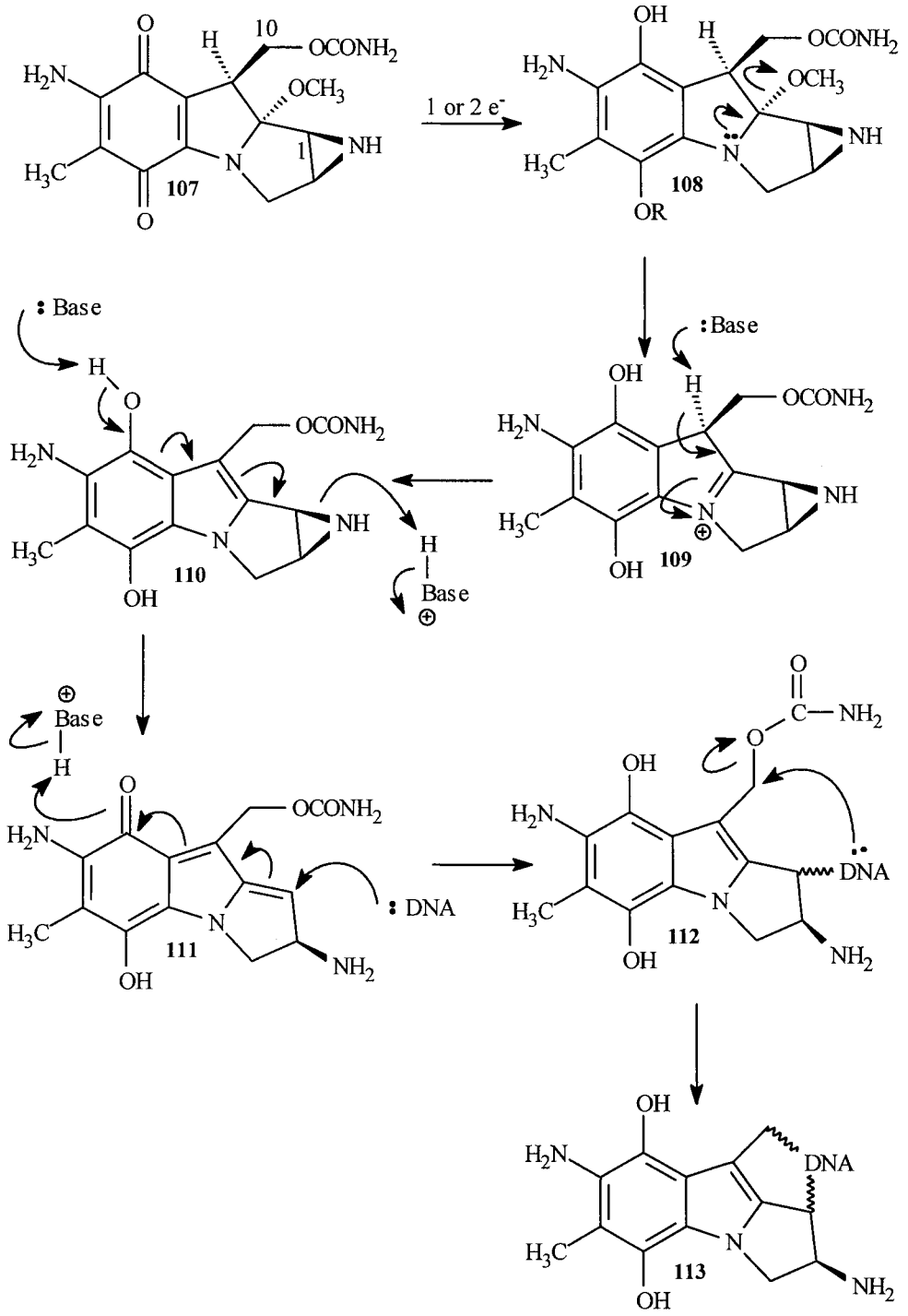
105



106

Quinone-imines are analogous to quinone-methides that have been proposed as models for biological activity.[17] Quinone-methides of general structure **106** are produced by the initial reduction of corresponding quinones by the enzyme nicotinamide adenine dinucleotide phosphate (NADPH). Reduction of the quinone by NADPH is enhanced in hypoxic oxygen deficient cells deep inside the tumour thus increasing selectivity of these drugs over conventional radiation treatment. The quinone-methides are known to undergo Michael addition reactions *in vivo* and it is this type of bioalkylation that is thought to be responsible for their mode of action.[76] Several anti-tumour agents are thought to undergo bioreduction yielding quinone-methides such as Mitomycin C and the anthracycline antibiotics Doxorubicin and Daunorubicin.

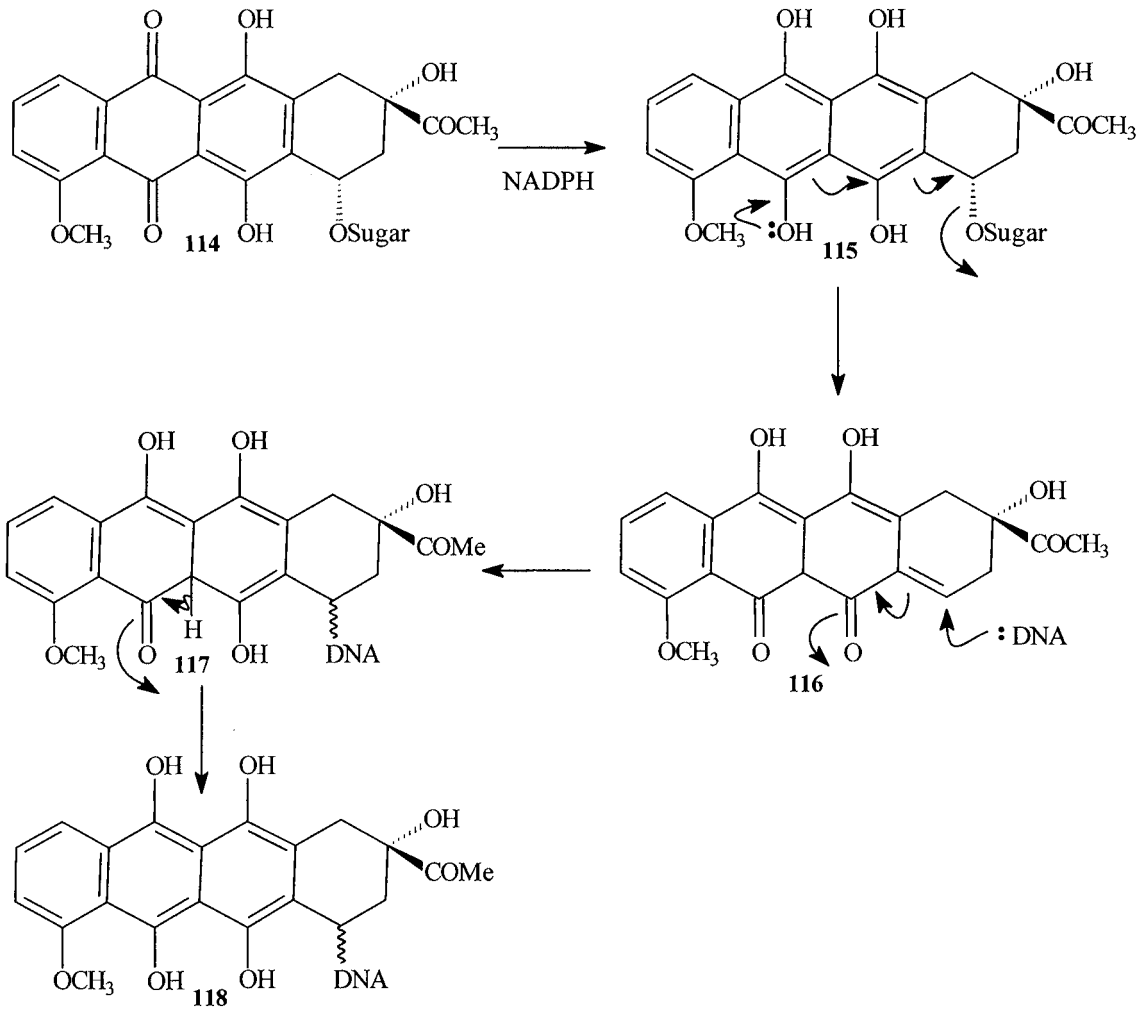
Mitomycin C **107** is an antineoplastic antibiotic in which several key functional groups are deployed within the drug. It has been established that Mitomycin C functions as a bioreductive alkylating agent with both carbons 1 and 10 being likely DNA binding sites.[77] The carcinostatic functional groups quinone, aziridine and carbamate have important roles to play in the mechanistic action of the drug. The proposed mechanism (Scheme 21) involves the one or two electron reduction of the quinone **107** converting the heterocyclic nitrogen from a vinylogous amide nitrogen to an amine nitrogen that can eliminate a β-methoxide ion to give **109**. Tautomerisation of **109** gives **110** that can undergo aziridine ring opening giving the quinone-methide **111**. This activates electrophilic C_1 alkylating DNA giving **112**. A subsequent reaction of DNA at C_{10} displaces the carbamate function resulting in cross-linking of the DNA giving **113** leading to irreparable damage and cell death.



Scheme 22

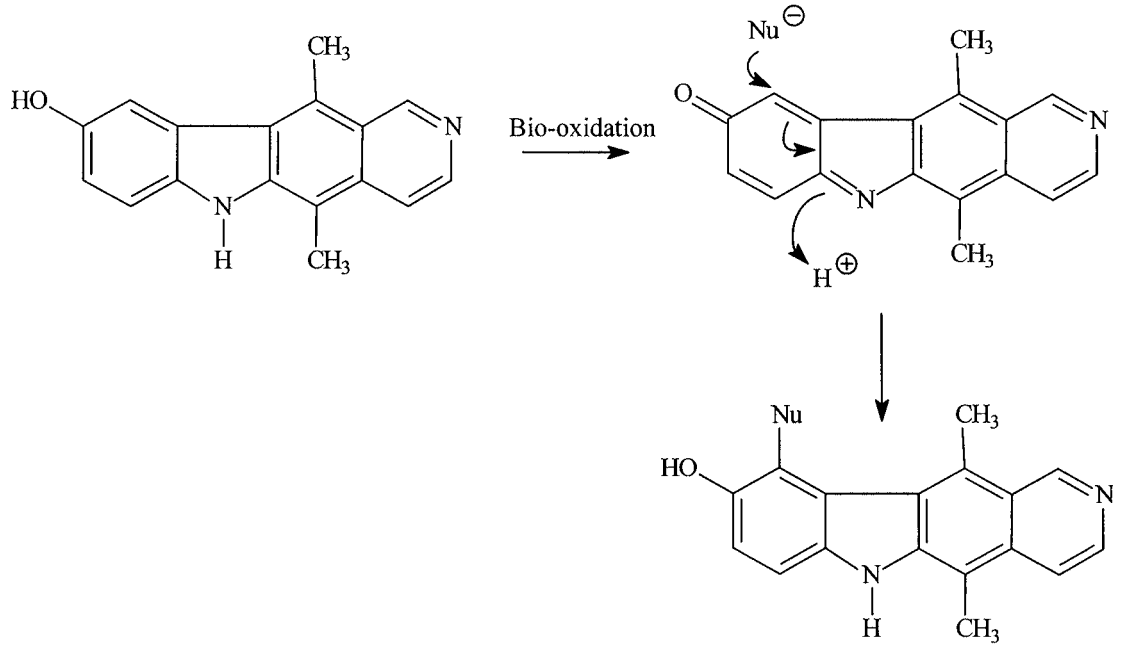
The anthracycline antibiotics Doxorubicin and Daunorubicin are thought also to act as bioreductive alkylating agents (Scheme 23).[78] A two electron reduction of **114** forms the bishydroquinone **115**. Subsequent elimination of the glycosyloxy sugar moiety results in the formation of the quinone-methide entity **116**. This species is thought to

react by alkylating DNA giving **118**, promoting the cell death mechanisms associated with this.



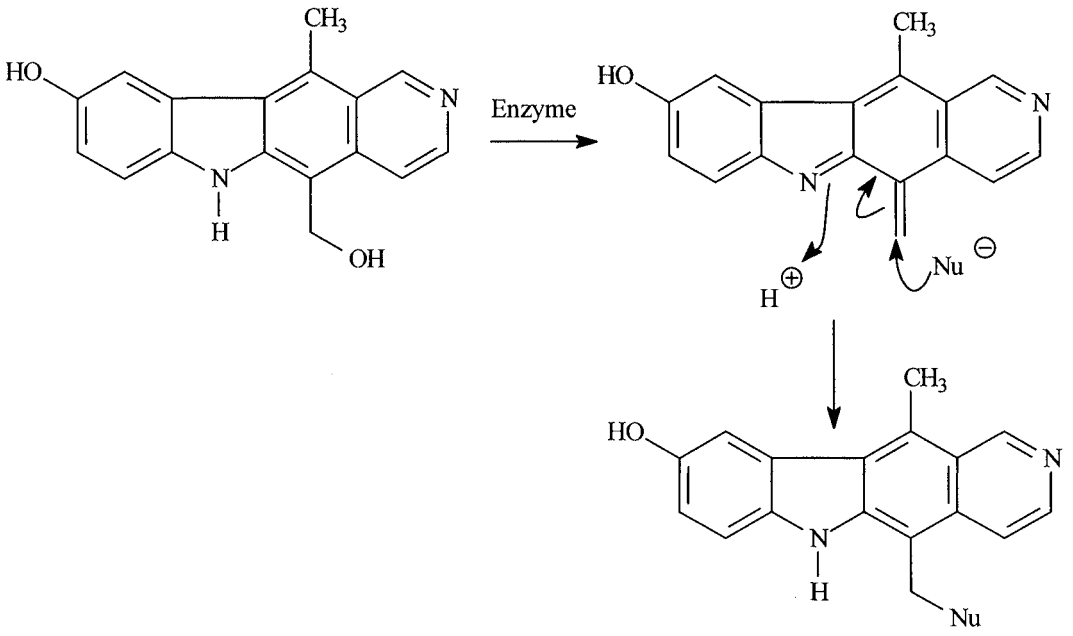
Scheme 23

Hydroxylation of ellipticine at the 9 position is followed by oxidation to the quinone-imine (Scheme 24). Quinone-imines like quinone-methides are a highly reactive electrophilic species that undergo similar Michael addition reactions with bionucleophiles *in vivo*. The resulting bioalkylation is thought to play a major role in the mechanistic action of these drugs.



Scheme 24

Archer *et al.* [79] have shown an alternative mechanism to Scheme 24 as the formation of a vinylogous imine (Scheme 25). Initially ellipticine undergoes bio-oxidation to 9-hydroxyellipticine. The 5-methyl group of 9-hydroxyellipticine is initially enzymically oxidised to the carbinol. The carbinol then undergoes further enzymical oxidation to its phosphate or sulphate ester (a potent leaving group). Subsequent elimination of the ester group forms the vinylogous imine that should undergo Michael addition reactions to yield the alkylated adduct.



Scheme 25

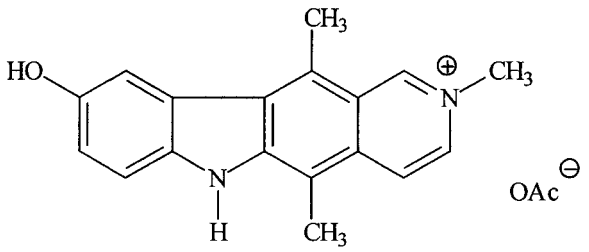
Potier *et al.* [80, 81] have investigated the reaction of pyrido[4,3-*b*]carbazoles with oxygen bearing nucleophiles such as methanol, ethylene glycol and ribonucleosides, under oxidative conditions. They have shown the formation of a ketalic linkage between C_{10} of the pyrido[4,3-*b*]carbazole ring and the oxygen of ribonucleosides. This reaction could be an important feature of cell death mechanisms associated with these compounds as alkylation of the terminal end of t-RNAs stop formation of key RNA intermediates and interaction with mRNA could inhibit the biosynthesis of proteins essential for replication.

Pyrido[4,3-*b*]carbazoles and their oxidation products are thought to directly interfere with enzymes that play an important role in DNA replication, in particular topoisomerase II. Fermandjian *et al.* [82] have shown using polyacrylamide gel electrophoresis a double strand cleavage of DNA by topoisomerase II in an ellipticine drug dosed system. It was postulated that the drug acts by inhibition or induction of the topoisomerase-DNA cleavable complex irrespective of direct intercalation into the minor groove of DNA. This results in formation of a ternary complex that is unable to

reseal the DNA strands leading to cell death. The mechanism by which the ternary complex is produced has been investigated by Osheroff *et al.* [83] Osheroff has shown that protonated and deprotonated forms of ellipticine exist in equilibrium at neutral pH. The protonated form intercalates in free DNA whilst the deprotonated form binds to topoisomerase II in the absence of DNA. The fact that ellipticine can bind to the enzyme alone raises the potential for multiple pathways to ternary complex formation and suggests that interaction of the drug with the cleavable complex may not be correct.

Although the mechanisms of action of ellipticines are still not completely understood their anti-tumour properties are widely accepted. Analogues of ellipticine have been tested for their antitumoural activity against mouse L 1210 leukaemia and have been shown to possess cytotoxic effects.[84] 9-Hydroxyellipticine was shown to be the most cytotoxic and 9-bromoellipticine the least cytotoxic.

Elliptinium **119** has successfully completed phase I clinical trials for the treatment of non-Hodgkin's lymphoma, breast cancer and nasopharyngeal carcinoma.[44]



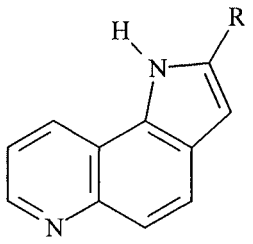
119

The success of ellipticine and its derivatives as anti-tumour agents has instigated global interest in the synthesis of compounds that are structurally similar in the hope that they will exhibit anti-tumour activity.

1.7.0 Synthesis of compounds structurally similar to Ellipticines

1.7.1 Quinoline and Isoquinoline derivatives

2-Substituted 1H-Pyrrolo[2,3-f] quinolines and isoquinolines [85]

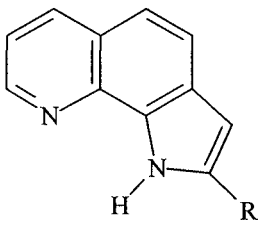


120

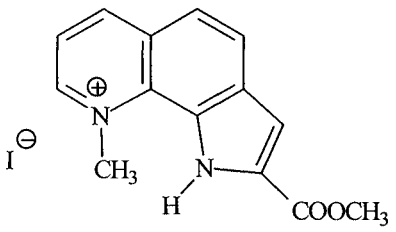
R= H, CH_3, COOH, $COOCH_3$, CH_2OH

Quinolinyl and isoquinolinyl derivatives of **120** were screened for biological activity and all were shown to exhibit intercalation between base pairs of DNA. Testing was also carried out to determine ability to inhibit DNA synthesis. Relatively good antiproliferative activity was found in 5 of 8 of compounds tested showing no preference for nature of substituent at 2-position or position of nitrogen in aromatic ring.

2-Substituted 1H-Pyrrolo[3,2-h] Quinolines [86]



121

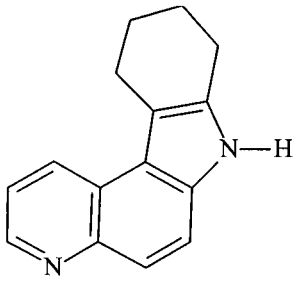


122

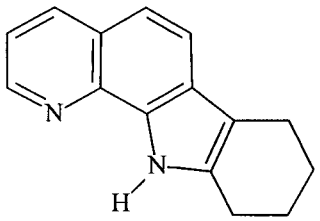
Where R = H, COOH, $COOCH_3$, CH_2OH

Derivatives of **121** and **122** were screened for biological activity and compared directly with ellipticine. Results showed all compounds tested were capable of inhibiting DNA synthesis and inducing breaks in DNA strands leading to antiproliferative activity, although all were less active than ellipticine.

1.7.2 Pyrido-tetrahydrocarbazole derivatives [87]



123



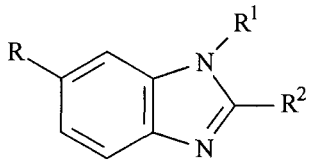
124

Compounds **124** have nitrogen at varying positions of the pyridyl ring.

Compounds **123-124** were screened for biological activity to obtain an understanding of their mechanism of action. Studies showed that these compounds have the ability to intercalate into base pairs of DNA, inhibit DNA synthesis, form double strand breaks and DNA-protein cross-links. In all the above tests compound **124** with the nitrogen at the 2 position in the quinoline ring proved to be the most active. A simple test against T2 bacteriophage (a virus particle consisting of a DNA molecule that is inactivated upon direct drug interaction) showed no virus inactivation suggesting that like ellipticine these compounds have a more complex mechanism of action than just direct interference with DNA.

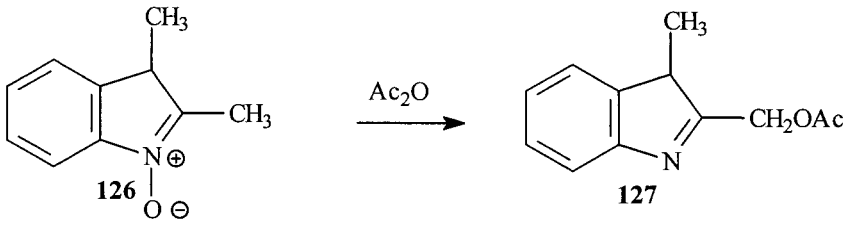
1.7.3 Synthesis of Benzimidazoles

Benzimidazoles of general structure **125** can be chemically manipulated to give compounds that are structurally similar to ellipticines.



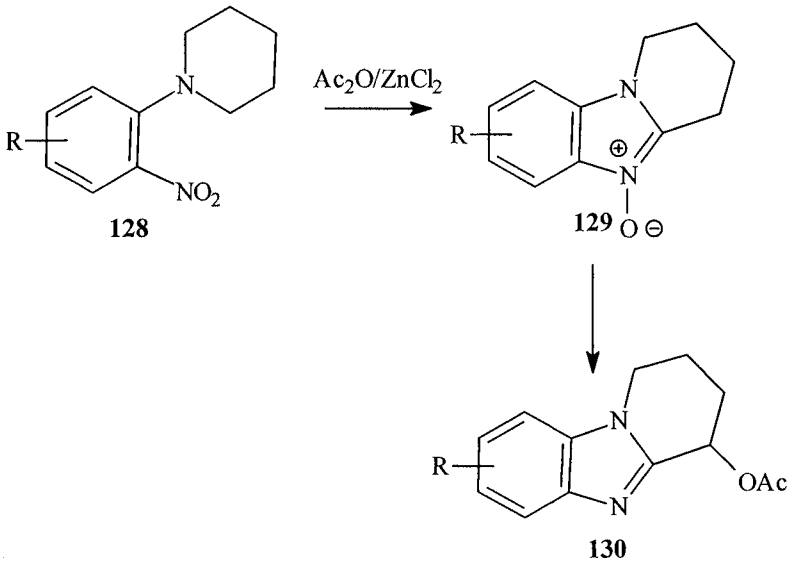
125

Takahashi and Kano[88] have shown the treatment of benzimidazole *N*-oxides **126** with acetic anhydride deoxygenates the *N*-oxide system to yield the 2-acetoxymethyl-1-benzimidazole **127**.



Scheme 26

Grantham and Meth-Cohn [89] examined the action of refluxing acetic anhydride and zinc chloride on cyclic tertiary anilines to produce substituted benzimidazoles (Scheme 27).



Scheme 27

In formulae **128-130**

	R
a	H
b	NO_2
c	CH_3CO

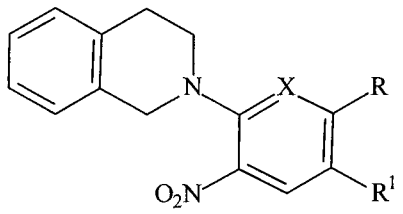
The reaction of **128** was thought to proceed through the benzimidazole *N*-oxide **129**; this was subsequently trapped by the acetic anhydride to give the product **130**. To prove the *N*-oxide theory efforts were made to isolate the *N*-oxide by carrying out the reaction using zinc chloride in an inert solvent, however this proved unsuccessful.

T-amino effect [90, 91]

Subsequent investigations by Suschitsky *et al.* into this area lead to the discovery of the t-amino effect which states that tertiary anilines bearing an *ortho* substituent can undergo intramolecular cyclisation reactions. An example of this reaction was the formation of the *N*-oxide **129** (Scheme 27). This chemistry has been applied to reactions to produce molecules with five, six and eight membered ring systems with a host of substituents attached to them. This chemistry has also been applied to *N*-aryl-1,2,3,4-tetrahydroisoquinoline derivatives to produce the benzimidazo[2,1-*a*]isoquinoline ring system.

1.7.4 Synthesis of Benzimidazo[2,1-*a*]isoquinoline *N*-oxides

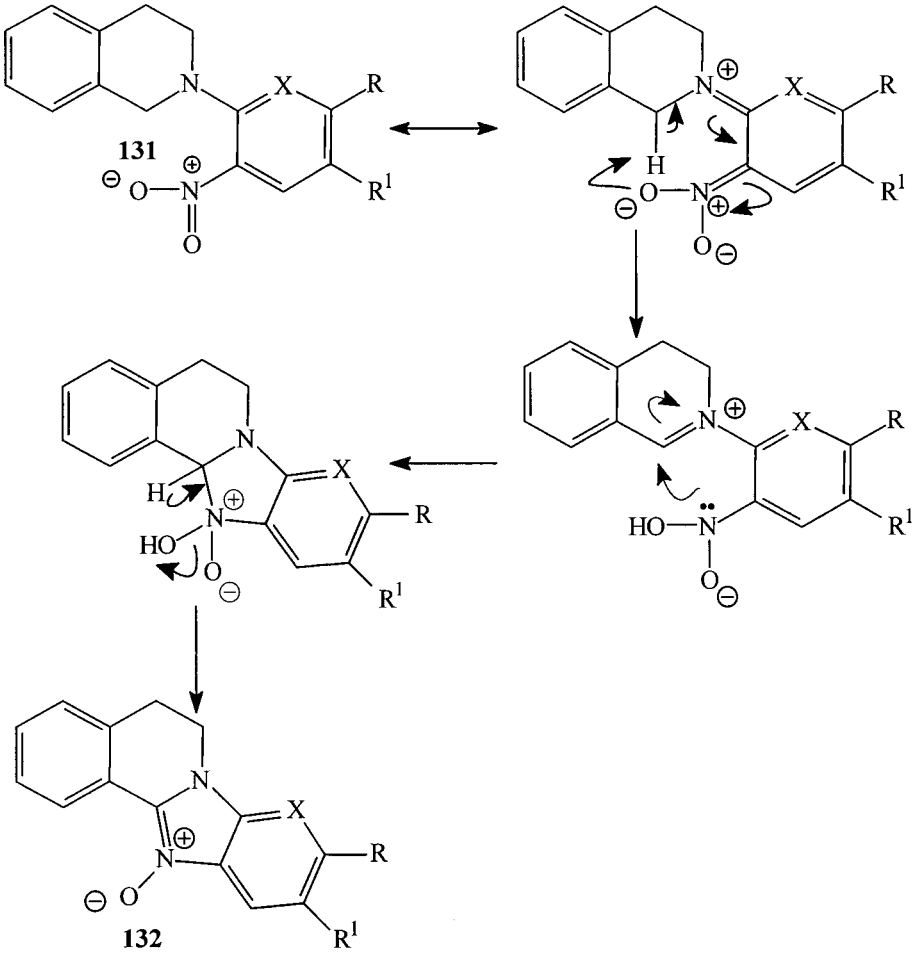
Stanforth and Hedley [92] have recently synthesised a series of *N*-aryl-1,2,3,4-tetra hydroisoquinoline derivatives of general structure **131** by the reaction of 1,2,3,4-tetrahydroisoquinoline with the corresponding chloro or fluoronitroaryl compounds.



131

X = CH or N
R = H, F or OCH_3
R^1 = H, NO_2, OCH_3, F or Br

Subsequent cyclisation of compounds **131** *via* the t-amino effect [93] was carried out in glacial acetic or propionic acid to yield the corresponding benzimidazo[2,1-*a*]isoquinoline *N*-oxides **132** *via* mechanism shown in Scheme 28.



Scheme 28

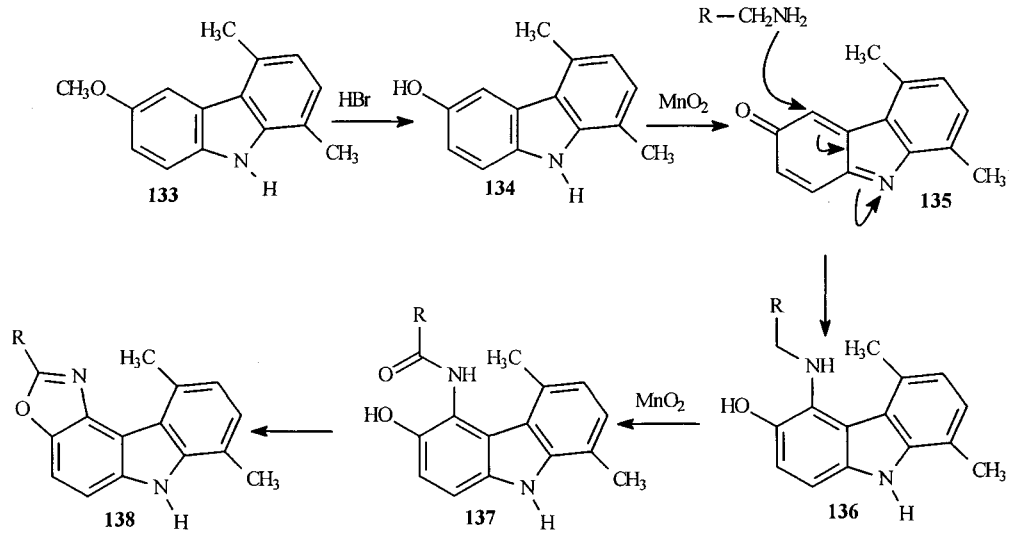
CHAPTER 2

DISCUSSION

Discussion

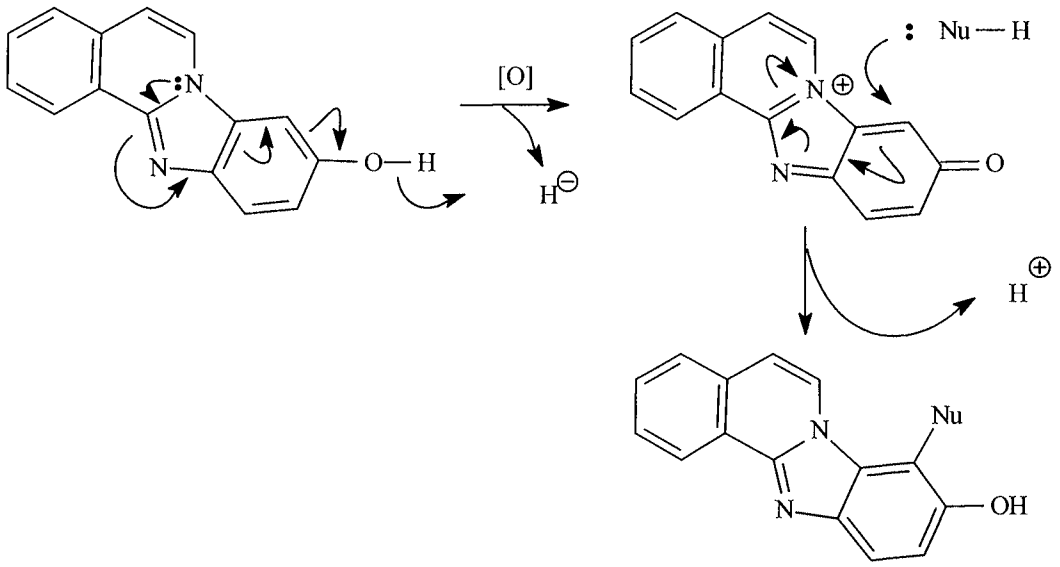
2.0 Research proposals

Potier *et al.* [94] investigated the sequential chemical oxidation and addition of amine nucleophiles to the carbazole ring system in an attempt to understand the mechanistic aspects of *in vivo* oxidation and subsequent bioalkylation of compounds related to ellipticine. The reaction involved the addition of the nucleophile, in this case a primary amine, to 1,4-dimethyl-6-hydroxycarbazole **134** (Scheme 29) or 9-hydroxyellipticine **13** in the presence of active manganese dioxide as the oxidising agent. Compound **134** was oxidised in the presence of manganese dioxide to the quinone-imine **135** that underwent nucleophilic attack by the amine giving **136**. Further oxidation resulted in formation of amide **137** that underwent cyclisation giving oxazole **138**. The results of this investigation suggested that the compounds **134** & **13** should covalently bind to bionucleophiles in the body *via* a quinone-imine intermediate.



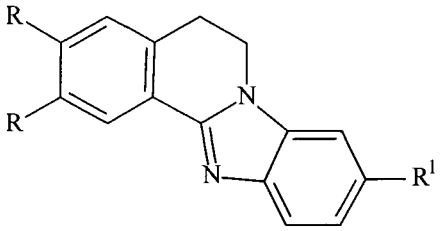
Scheme 29

The benzimidazo[2,1-*a*]isoquinoline ring system is structurally related to the pyridocarbazole ring system and may undergo similar bioalkylation reactions. Biooxidation of the benzimidazo[2,1-*a*]isoquinoline ring system to its hydroxylated adduct followed by one electron oxidation could facilitate radical formation and the cell death mechanisms associated with it. Two electron oxidation could result in the formation of a quinone-imine intermediate that could undergo bioalkylation (Scheme 30) promoting cell death.

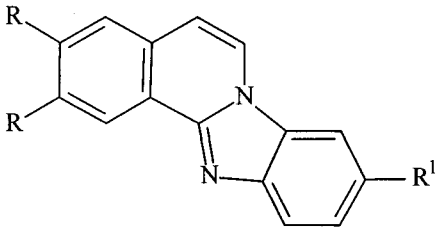


Scheme 30

The aim of the research project was to synthesise a series of 3,4-dihydro-benzimidazo[2,1-*a*]isoquinolines and benzimidazo[2,1-*a*]isoquinolines of general structure **139** & **140** respectively and investigate the oxidation and addition of nucleophiles to these compounds.



139

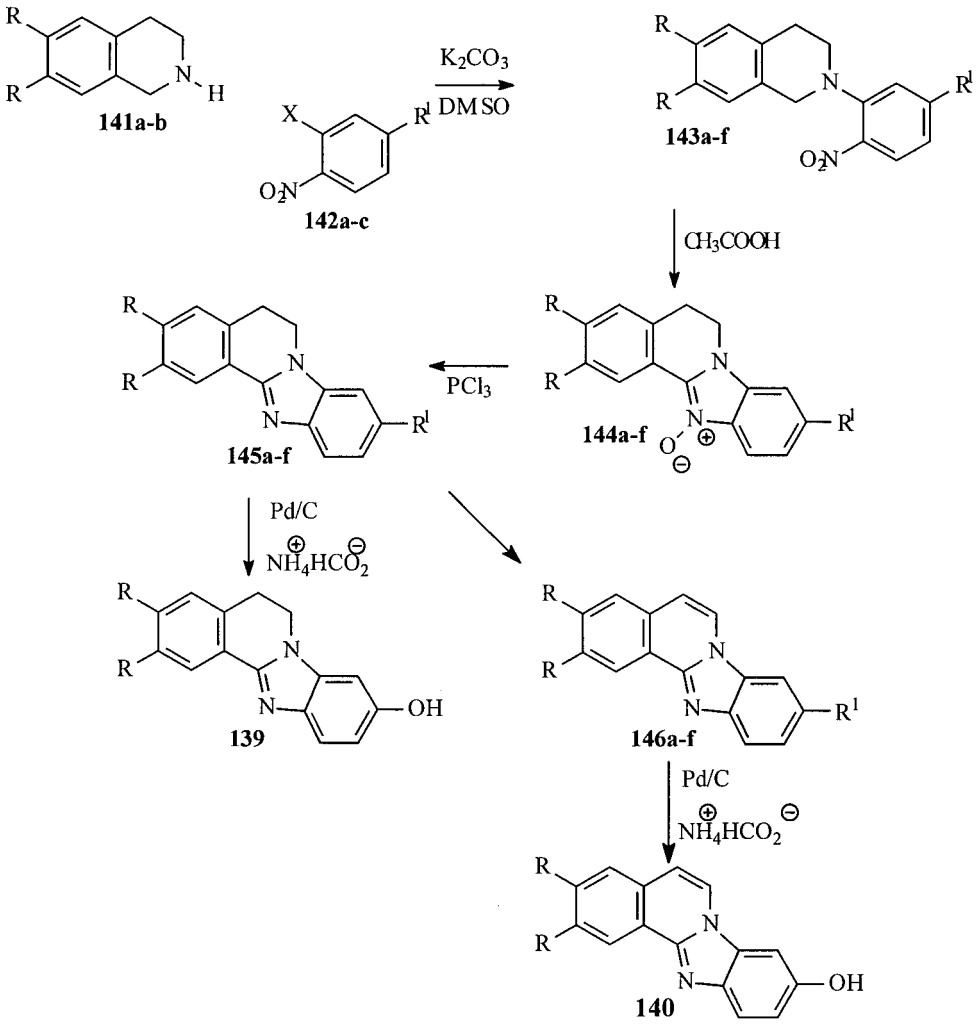


140

R = H or OCH_3 ; R^1 = OH

The strategy (Scheme 31) was to prepare compound **139** (where R is H or OCH_3 and R^1 is OH); subsequent dehydrogenation of compound **139** would give heterocycle **140**.

2.1 Synthetic Strategy-Part A



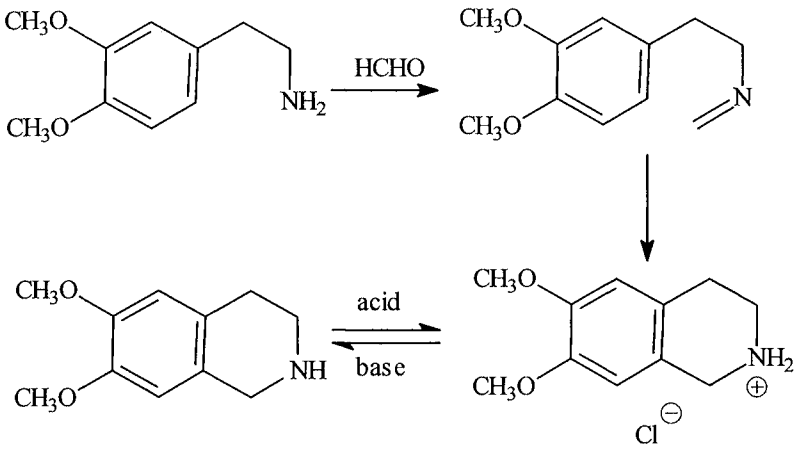
In formulae **143-146**

					R	R^1		
141a	R = H	**142a**	R^1 = H	**a**	H	H	**139**	R = H
141b	R = OCH_3	**142b**	R^1 = OCH_3	**b**	H	OCH_3	**140**	R = OCH_3
		142c	R^1 = OCH_2Ph	**c**	H	OCH_2Ph		
				d	OCH_3	H		
				e	OCH_3	OCH_3		
				f	OCH_3	OCH_2Ph		

Scheme 31

2.1.1 Synthesis of starting compounds 141b, 142b and 142c

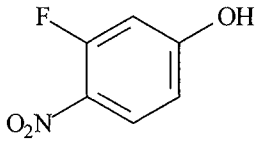
6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride [95] **141b** was prepared using the Pictet-Spengler method for the synthesis of isoquinolines (Scheme 32). 2-(3,4-Dimethoxy)phenylethylamine was heated in aqueous formaldehyde solution and a dichloromethane solution of the imine intermediate was isolated. Freshly prepared hydrogen chloride gas was bubbled through the imine solution affecting cyclisation yielding the hydrochloride salt (12 % yield) isolated as yellow plates following recrystallisation from ethanol. The free base **141b** of the hydrochloride salt was liberated in subsequent reactions.



141b

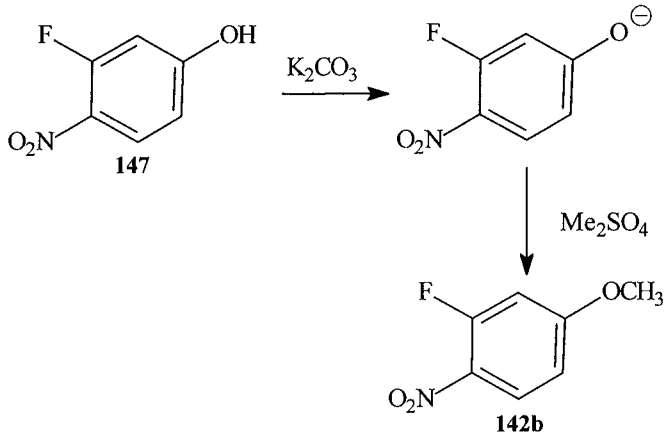
Scheme 32

3-Fluoro-4-nitrophenol **147** cannot be directly reacted with the isoquinoline derivatives **141a** & **b** due to the presence of the acidic hydroxyl group. Protection of the hydroxyl group *via* transformation into an ether was carried out before it was reacted.



147

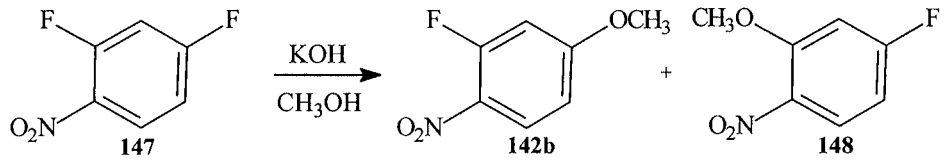
3-Fluoro-4-nitroanisole **142b** was prepared using two methods. The initial method involved methylation of 3-fluoro-4-nitrophenol **147** using dimethylsulphate (Scheme 33).[96]



Scheme 33

3-Fluoro-4-nitrophenol **147** was dissolved in acetone and the phenoxide anion was generated by the addition of solid potassium carbonate. Subsequent addition of dimethylsulphate and heating to reflux yielded product **142b** which was isolated as yellow crystals (93 % yield) from ethanol.[97]

The second method involved methoxylation of 2,4-difluoronitrobenzene **148** (Scheme 34).[98]

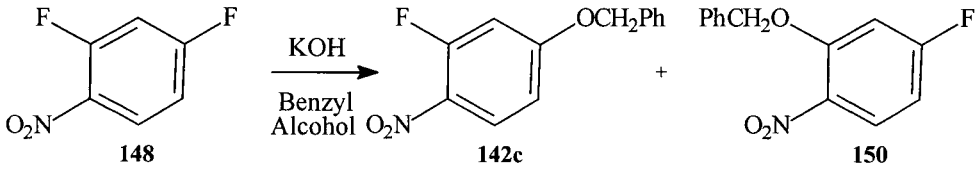


Scheme 34

The reaction of alkoxides with alkyl halides (Williamson synthesis) is a popular and well established method for the formation of mixed ethers. 2,4-Difluoronitrobenzene **148** was dissolved in methanol and to this was added dropwise a solution of potassium hydroxide in methanol. After evaporation of methanol the resulting oil was distilled under pressure to yield fraction enriched in one structural isomer. ^{1}H-nmr spectroscopy showed the second fraction (6 mm Hg, b.p. 116-122°C) was enriched in the desired isomer **142b** in a 3:1 ratio (40.3 % yield). The first fraction (6mm Hg, b.p. 78-116°C) was predominantly low boiling point material and the third fraction (6mm Hg, b.p. 122-124°C) contained a 50:50 mixture of both isomers **142b** and **149**.

2-Fluoro-4-benzyloxynitrobenzene **142c** was prepared using two methods. The initial method involved benzylation of 3-fluoro-4-nitrophenol **147** using benzyl bromide. 3-Fluoro-4-nitrophenol **147** was dissolved in anhydrous tetrahydrofuran and the phenoxide anion generated by the addition of solid potassium carbonate. Subsequent addition of benzyl bromide and a few crystals of sodium iodide followed by heating to reflux yielded product **142c** isolated as yellow crystals (16 % yield) from ethanol.

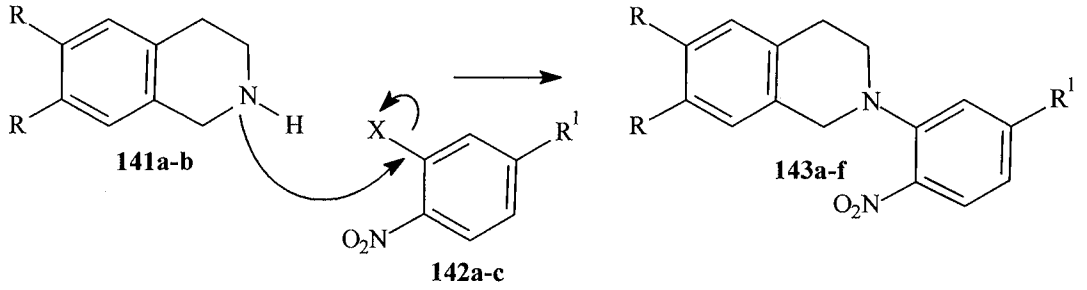
The second method involved oxybenzylation of 2,4-difluoronitrobenzene **148** (Scheme 35). [98]



Scheme 35

2,4-Difluoronitrobenzene **148** was dissolved in benzyl alcohol and to this was added dropwise a solution of potassium hydroxide in benzyl alcohol. The resulting oil was distilled under pressure using a Kugel-Rohr apparatus (3mm Hg, b.p. 158-160°C) removing firstly the excess benzyl alcohol, and then fractions enriched in one structural isomer. ^{1}H-nmr spectroscopy showed the second fraction was enriched in the desired isomer **142c** in a 1:0.8 ratio. The final fraction contained predominantly the undesired isomer **150**. The second fraction crystallised upon cooling and was recrystallised from ethanol to give yellow needle crystals of desired isomer **142c** (25.7 % yield).

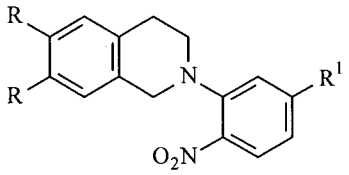
2.1.2 Synthesis of compounds 143a-k



Scheme 36

The general nucleophilic substitution reaction mechanism of tetrahydroisoquinolines **141a-b** with aryl halides **142a-c** is shown in Scheme 36.[92] Reactions were carried out using potassium carbonate as the base in dimethylsulphoxide giving yields (40-93%) at 100°C. Initial reaction was carried out using compounds **141a** and **142a** as a model system. The general data for compounds **143a-f** are shown in Table 1. The structures of compounds **143a-f** were confirmed using ^{1}H-nmr spectroscopy, elemental analysis, infra-red spectroscopy and high resolution mass spectrometry.

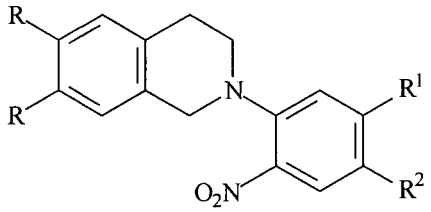
Compound	Appearance	Yield	Mass Spec. m/z	Melting Pt. °C
143a	Orange Crystals	60%	-	100-102
143b	Orange oil	91%	284.1133	-
143c	Yellow Crystals	79%	-	95-98
143d	Orange Crystals	40%	-	131-133
143e	Orange Crystals	93%	-	128-131
143f	Yellow Crystals	86%	-	156-159



	R	R^1
143a	H	H
143b	H	OCH_3
143c	H	OCH_2Ph
143d	OCH_3	H
143e	OCH_3	OCH_3
143f	OCH_3	OCH_2Ph

Table 1: General data for compounds **143a-f**

Compounds **143g-k** were prepared using different methods and starting materials to compounds **143a-f**.

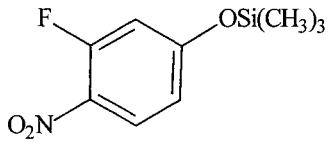


143

In formulae **143g-k**

	R	R^1	R^2
g	H	OH	H
h	H	$OCOCH_3$	H
i	H	OCOPh	H
j	H	2-(1,2,3,4-THIQ)$^{\phi}$	H
k	H	2-(1,2,3,4-THIQ)$^{\phi}$	NO_2

$^{\phi}$ THIQ = tetrahydroisoquinolyl



151

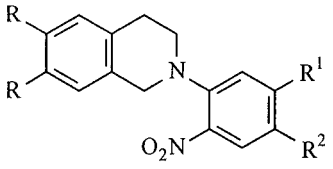
Silyl groups are commonly used in the protection of alcohols [99] and are easily cleaved in mild acidic conditions. Moreau *et al.* [100] have shown that trimethylsilylchloride in the presence of base protects phenolic groups. 3-Fluoro-4-nitrophenol **147** was reacted with trimethylsilylchloride in toluene with heating in the presence of triethylamine. The resultant silyl ether was not isolated but reacted directly with 1,2,3,4-tetrahydroisoquinoline **141a** and triethylamine. Subsequent acidic work up cleaved the trimethylsilyl protecting group yielding compound **143g** that was isolated as orange crystals (16 % yield) after recrystallisation from ethanol.

Compounds **143h-i** were synthesised by stirring compound **143g** in acetic anhydride/triethylamine and benzoyl chloride/triethylamine respectively.[101] Subsequent isolation and crystallisation gave both **143h-i** as orange crystals.

Compounds **143j-k** were synthesised by reaction of 1,2,3,4-tetrahydroisoquinoline with 2,4-difluoronitrobenzene and 1,3-difluoro-4,6-dinitrobenzene respectively. Reactions were carried out as Scheme 36 using a potassium carbonate base with dimethylsulphoxide as solvent. Subsequent isolation and crystallisation gave compounds **143j-k** as orange crystals.

The general data for compounds **143g-k** are shown in Table 2. The structures of compounds **143g-k** were confirmed using ^{1}H-nmr spectroscopy, elemental analysis, infra-red spectroscopy and high resolution mass spectrometry.

Compound	Appearance	Yield	Mass Spec. m/z	Melting Pt. °C
143g	Orange Crystals	16%	270.1014	153-156
143h	Orange Crystals	87%	-	79-81
143i	Orange Crystals	85%	-	95-98
143j	Orange Crystals	82%	385.1771	131-133
143k	Orange Crystals	60%	-	-

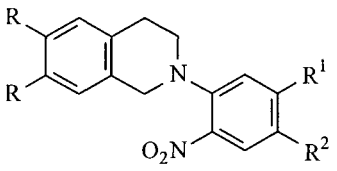


	R	R^1	R^2
143g	H	OH	H
143h	H	$OCOCH_3$	H
143i	H	OCOPh	H
143j	OCH_3	2-(1,2,3,4-THIQ)	H
143k	OCH_3	2-(1,2,3,4-THIQ)	NO_2

Table 2: General data for compounds **143g-k**

The general features of the ^{1}H-nmr spectral data for compounds **143a-k** are presented in Table 3. The signals observed in the spectra are typical of compounds **143a-k** with only slight variations in chemical shifts, multiplicity and coupling constants for members of this series of compounds. Additional signals are present for substituents R and R^1 in compounds **143b-k**, but these are not shown in Table 3. General signals that identify these compounds are triplets at δ3.40-3.45 and δ2.95-3.00 that are assigned to the C_3 and C_4 CH_2 protons and the singlet at δ4.30-4.35 that is assigned to the C_1 CH_2 protons of the isoquinoline ring.

Chemical Shift δ (ppm)	Number of Protons and Multiplicity	Coupling Constants J (Hz)	Assignment
7.80-8.00	dd, 1H	8.0-9.0	Ar-H
6.85-7.55	m, 7H	-	Ar-H
4.30-4.35	s, 2H	-	CH_2-N
3.40-3.45	t, 2H	8.0-9.0	N-CH_2-CH_2
2.95-3.00	t, 2H	8.0-9.0	N-CH_2-CH_2



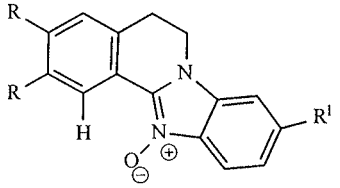
	R	R^1	R^2		R	R^1	R^2
143a	H	H	H	**143g**	H	OH	H
143b	H	OCH_3	H	**143h**	H	$OCOCH_3$	H
143c	H	OCH_2Ph	H	**143i**	H	OCOPh	H
143d	OCH_3	H	H	**143j**	OCH_3	2-(1,2,3,4-THIQ)	H
143e	OCH_3	OCH_3	H	**143k**	OCH_3	2-(1,2,3,4-THIQ)	NO_2
143f	OCH_3	OCH_2Ph	H				

Table 3: General features of ^{1}H-nmr spectral data for compounds **143a-k**

2.1.3 Synthesis of compounds 144-a-f

Cyclisation *via* the *t*-amino effect (Scheme 28) of compounds **143a-f** was achieved by heating in glacial acetic or propionic acid at reflux to yield compounds **144a-f** (50-90 % yields). Compounds **143g-i** showed no presence of the desired product when heated in acetic acid. The evidence for this is the lack of signal present in their ^{1}H-nmr spectra at a chemical shift δ 9.30-9.50 that is indicative of the *N*-oxides **144a-f**. This indicates that hydroxyl, acetoxy and benzoyl substituents have not cyclised successfully. Compound **143j-k** when cyclised shows trace amounts of *N*-oxide present indicating cyclisation but the reaction was inefficient. The general data for compounds **144a-f** are shown in Table 4. The structures of compounds **144a-f** were confirmed using ^{1}H-nmr spectroscopy, elemental analysis, infra-red spectroscopy and high resolution mass spectrometry.

Compound	Appearance	Yield	Mass Spec. m/z	Melting Pt. °C
144a	Yellow Crystals	94%	-	205-208
144b	Brown Crystals	68%	-	204-206
144c	Brown Crystals	54%	342.1357	187-189
144d	Yellow Crystals	73%		229-231
144e	White Crystals	50%	326.1267	231-233
144f	Brown Crystals	72%	402.1581	236-240

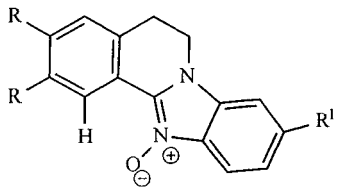


	R	R^1
144a	H	H
144b	H	OCH_3
144c	H	OCH_2Ph
144d	OCH_3	H
144e	OCH_3	OCH_3
144f	OCH_3	OCH_2Ph

Table 4: General data for compounds **144a-f**

Identification of *N*-oxides using ^{1}H-nmr spectroscopy often proved difficult in $CDCl_3$ solution due to the insolubility in this common solvent. The general features of the ^{1}H-nmr spectral data using deuterated dimethylsulphoxide as solvent for compounds **144a-f** are presented in Table 5. The signals observed in the spectra are typical of compounds **144a-f** with only slight variations in chemical shifts, multiplicity and coupling constants for members of this series of compounds. Additional signals are present for substituents R and R^1 in compounds **144b-f**, but these are not shown in Table 5. General signals that identifies compounds **144a-f** are the doublets at δ9.30-9.50 that represent the aromatic C_1 proton of the benzimidazo[2,1-*a*]isoquinoline ring system that are shifted downfield due to the proximity of the *N*-oxide group. The loss of the isoquinoline ring systems C_1 CH_2 singlet present in compounds **143a-k** also indicated cyclisation had occurred.

Chemical Shift δ (ppm)	**Number of Protons and Multiplicity**	**Coupling Constants J (Hz)**	**Assignment**
9.30-9.50	d, 1H	6.0-8.0	Ar-H
8.00-8.05	d, 1H	6.0-8.0	Ar-H
7.20-7.50	m, 6H	-	Ar-H
4.30-4.35	t, 2H	8.0-9.0	N-CH_2-CH_2
3.20-3.30	t, 2H	8.0-9.0	N-CH_2-CH_2

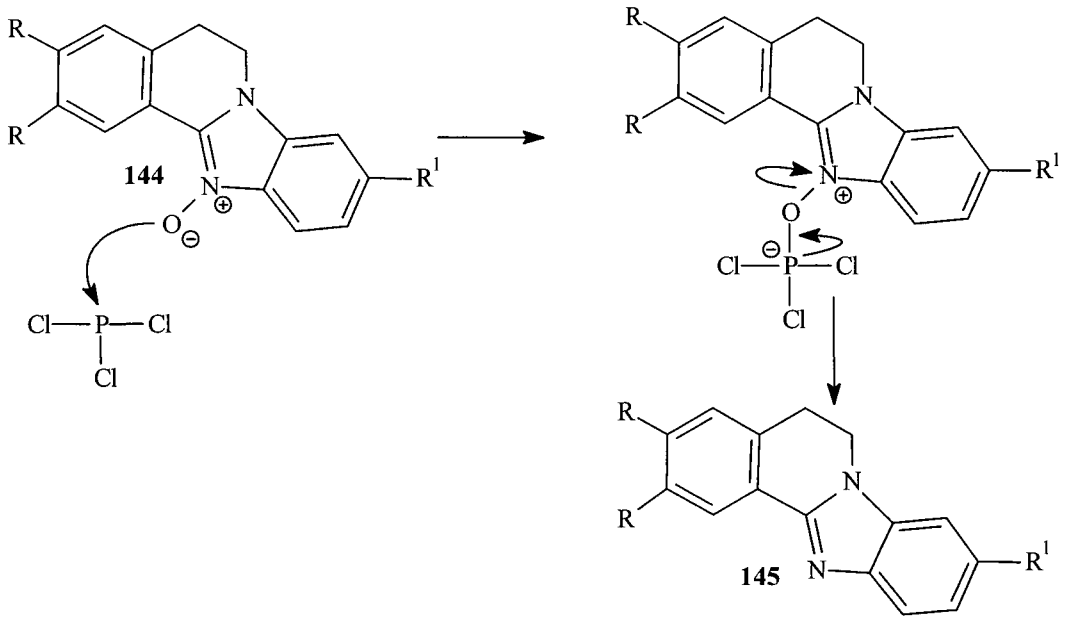


	R	R^1
144a	H	H
144b	H	OCH_3
144c	H	OCH_2Ph
144d	OCH_3	H
144e	OCH_3	OCH_3
144f	OCH_3	OCH_2Ph

Table 5: General features of ^{1}H-nmr spectral data for compounds **144a-f**

2.1.4 Synthesis of compounds 145a-f

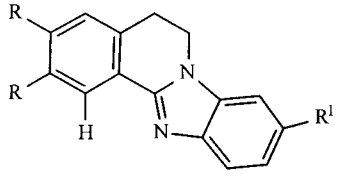
Deoxygenation of **144a-f** using phosphorus trichloride in boiling chloroform [88] afforded heterocycles **145a-f** *via* the general mechanism shown in Scheme 37.



Scheme 37

The general data for compounds **145a-f** are shown in Table 6. The structures of compounds **145a-f** were confirmed using ^{1}H-nmr spectroscopy, elemental analysis, infra-red spectroscopy and high resolution mass spectrometry.

Compound	Appearance	Yield	Mass Spec. m/z	Melting Pt. °C
145a	Yellow Crystals	97%	-	207-209
145b	Brown Crystals	61%	266.1068	201-205
145c	Brown Crystals	62%	-	151-152
145d	Orange Crystals	41%	-	190-192
145e	White Plates	78%	310.1315	243-245
145f	Orange Crystals	14%	386.1619	160-162

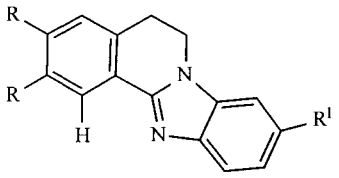


	R	R^1
145a	H	H
145b	H	OCH_3
145c	H	OCH_2Ph
145d	OCH_3	H
145e	OCH_3	OCH_3
145f	OCH_3	OCH_2Ph

Table 6: General data for compounds **145a-f**

The general features of the ^{1}H-nmr spectral data for compounds **145a-f** are presented in Table 7. The signals observed in the spectra are typical of compounds **145a-f** with only slight variations in chemical shifts, multiplicity and coupling constants for members of this series of compounds. Additional signals are present for the substituents R and R^1 groups in compounds **145b-f**, but these are not shown in Table 7. General signals that identifies compounds **145a-f** are the peaks at δ8.30-8.60 which represent the aromatic C_1 proton of the benzimidazo[2,1-*a*]isoquinoline ring system that are shifted downfield due to its proximity to the nitrogen of the imidazole ring.

Chemical Shift δ (ppm)	**Number of Protons and Multiplicity**	**Coupling Constants J (Hz)**	**Assignment**
8.30-8.60	.m, 1H	-	Ar-H
7.85-8.05	d, 1H	9.0	Ar-H
7.10-7.50	m, 6H	-	Ar-H
4.30-4.35	t, 2H	10.0	N-CH_2-CH_2
3.20-3.25	t, 2H	10.0	N-CH_2-CH_2

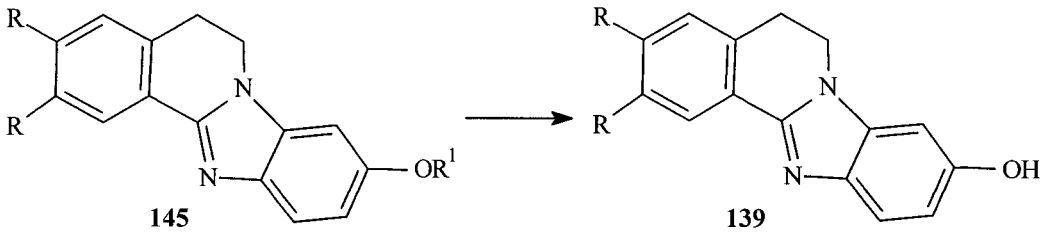


	R	R^1
145a	H	H
145b	H	OCH_3
145c	H	OCH_2Ph
145d	OCH_3	H
145e	OCH_3	OCH_3
145f	OCH_3	OCH_2Ph

Table 7: General features of ^{1}H-nmr spectral data for compounds **145a-f**

2.1.5 Deprotection of ether groups to give hydroxy derivatives

Cleavage of the ether groups (Scheme 38) to give the phenolic compounds should give increased biological activity. Various methods were attempted to cleave the methyl and benzyl ethers with limited success.



145 **139**

Scheme 38

In formulae **145b-c**

	R	R^1
b	H	CH_3
c	H	CH_2Ph
f	OCH_3	CH_2Ph

In formulae **139a-b**

	R
a	H
b	OCH_3

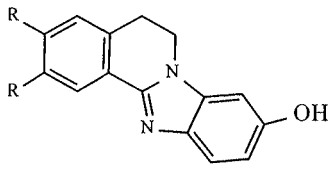
Refluxing in hydroiodic acid using acetic acid as a co-solvent is a well known method of cleaving methyl ethers.[102] Compound **145b** was heated to reflux in hydroiodic acid/acetic acid for six hours. Subsequent work up and analysis using ^{1}H-nmr spectroscopy showed only starting material to be present.

Initial cleavage of the benzyl ether was attempted using *N*-bromosuccinimide in carbon tetrachloride. Subsequent work up and analysis using ^{1}H-nmr spectroscopy showed only starting material to be present. Hydrogenolysis is a mild convenient method for the cleavage of benzyl ethers.[102] The general conditions involve the use of a palladium catalyst with some form of hydrogen donor. Compound **145c** was refluxed under standard conditions using 5% palladium on carbon in cyclohexene (a known hydrogen donor) with a small amount of ethanol. Subsequent work up and

analysis using ^{1}H-nmr spectroscopy showed the reaction was unsuccessful as only starting material was present. This reaction was re-attempted using boiling decalin as the solvent, again without success. Bieg and Szeja [103] have shown the cleavage of benzyl ethers can be achieved using ammonium formate as a hydrogen donor. Compounds **145c** and **145f** were hydrogenated to their corresponding phenolic derivatives using 5% palladium on carbon in methanol with ammonium formate.

Compounds **139a-b** whose general data are shown in Table 8 were isolated and their structures were confirmed, however this route was discarded due to poor yields (13-14%). The structures of compounds **139a-b** were confirmed using ^{1}H-nmr spectroscopy, elemental analysis, infra-red spectroscopy and high resolution mass spectrometry.

Compound	Appearance	Yield	Mass Spec. m/z	Melting Pt. °C
139a	Brown oil	14%	-	-
139b	Brown Crystals	13%	296.1162	266-269

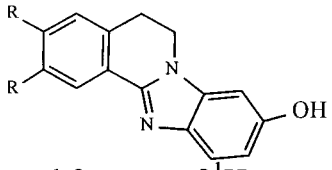


	R
139a	H
139b	OCH_3

Table 8: General data for compounds **139a-b**

The general features of the ^{1}H-nmr spectral data for compounds **139a-b** are presented in Table 9. The signals observed in the spectra are typical of compounds **139a-b** with only slight variations in chemical shifts, multiplicity and coupling constants for members of this series of compounds. Additional signals are present for the substituents R in compound **139b**. The loss of benzyl ether singlet at δ5.15-5.20 present in the ^{1}H-nmr spectra of compounds **145c** and **145f** indicates success of reaction.

Chemical Shift δ (ppm)	**Number of Protons and Multiplicity**	**Coupling Constants J (Hz)**	**Assignment**
8.20-8.24	m, 1H	-	Ar-H
7.60-7.65	d, 1H	9.0	Ar-H
7.20-7.40	m, 3H	-	Ar-H
6.75-6.80	m, 2H	-	Ar-H
4.20-4.25	t, 2H	7.0-8.0	N-CH_2-CH_2
3.20-3.25	t, 2H	7.0-8.0	N-CH_2-CH_2

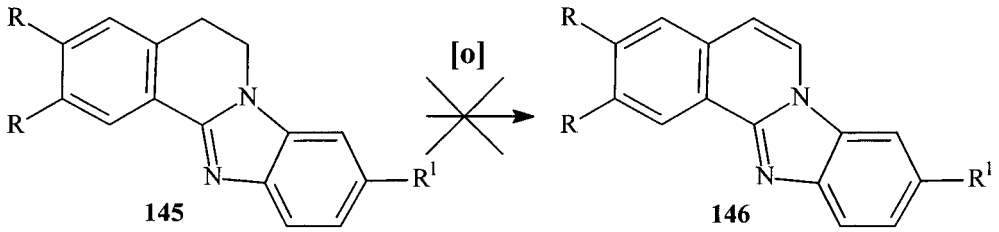


	R
139a	H
139b	OCH_3

Table 9: General features of ^{1}H-nmr spectral data for compound **139a-b**

2.1.6 Dehydrogenation reactions of compounds 145a and 145e

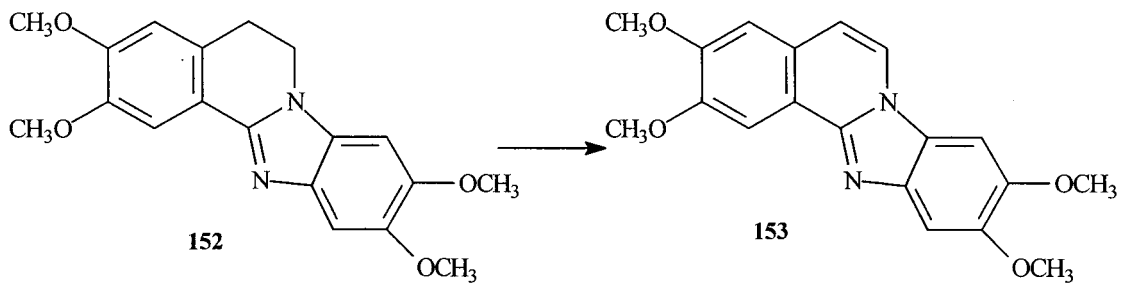
Attempts were made to aromatise the 5,6-dihydrobenzimidazo[2,1-*a*]isoquinoline ring **145** system giving the benzimidazo[2,1-*a*]isoquinoline ring system **146** (Scheme 39). This would give planar molecules that might have increased DNA intercalating ability. A comprehensive review of dehydrogenation of polycyclic hydroaromatic compounds has been published by Harvey and Fu.[104] This review covers a range of methods, several were selected and applied to compounds **145a** and **145e**.



Scheme 39

Catalytic dehydrogenation

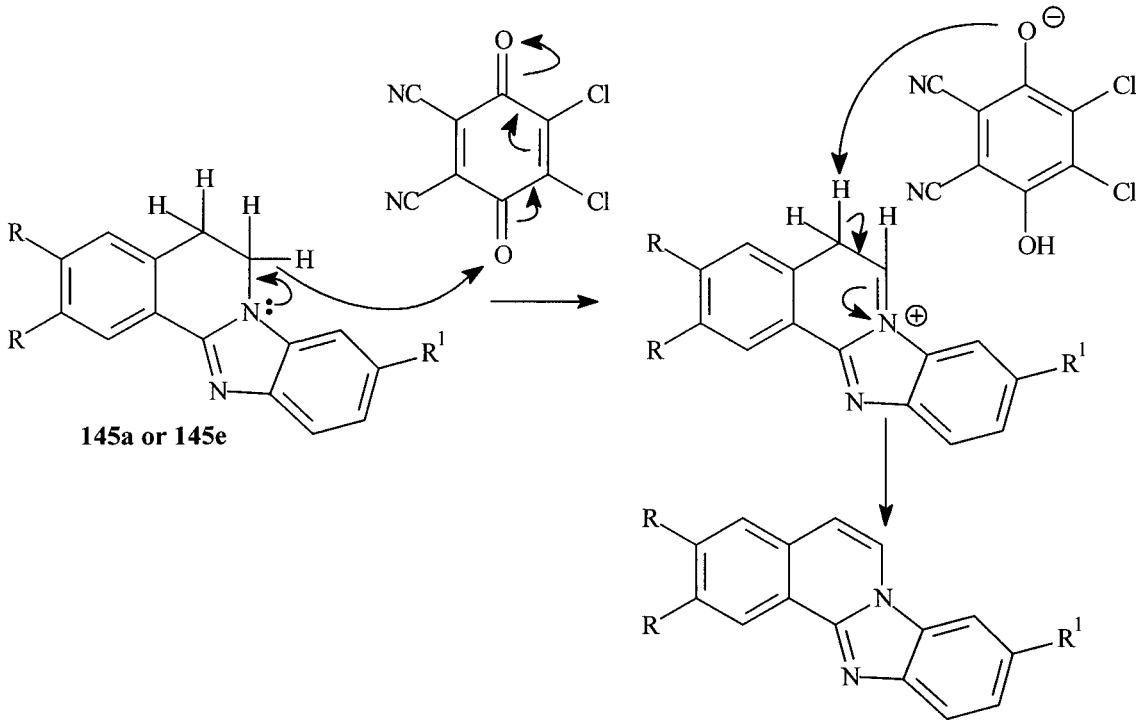
Kametani *et al.* [105] dehydrogenated compound **152** using 40% palladium on carbon to give the fully aromatic system **153** (Scheme 40). The reaction took 24 hours in boiling decalin under nitrogen giving a yield of 10% based on recovery of 20% starting material. The conditions required were extremely severe giving a poor yield. This reaction was carried out on compound **145a** using a large excess of 5% palladium on carbon in boiling cymene for 4 hours. Subsequent reaction work up and analysis using ^{1}H-nmr spectroscopy showed predominantly starting material present (triplets present at δ 4.30-4.35 and δ 3.20-3.25).



Scheme 40

Hydride transfer using DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone)

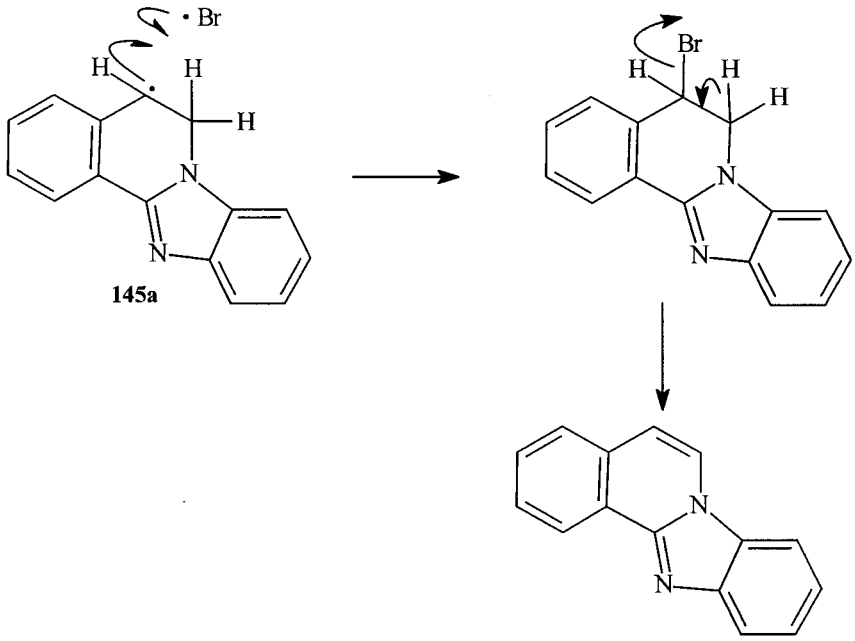
Quinones can be reduced to their corresponding hydroquinones whilst simultaneously oxidising compounds which are present in the same system. DDQ is used to dehydrogenate complex substrates in anhydrous solvents under relatively mild conditions.[106] It was envisaged that heating **145a** or **145e** in anhydrous 1,4-dioxan or toluene with DDQ present would oxidise the ring system by the mechanism shown (Scheme 41). Another possible mechanism involves initial hydride extraction of one of the benzylic protons reducing DDQ in a similar manner to that shown (Scheme 41). Subsequent reaction work up and analysis using ^{1}H-nmr spectroscopy showed predominantly starting material present (triplets present at δ 4.30-4.35 and δ 3.20-3.25).



Scheme 41

Radical bromination

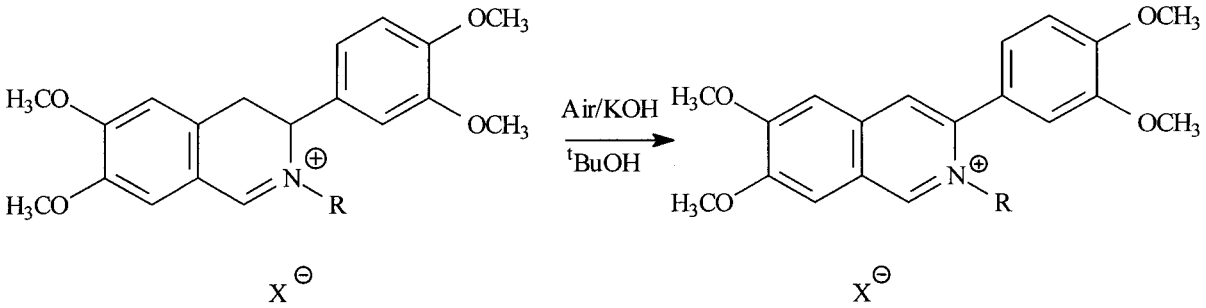
N-Bromosuccinimide when heated is a source of bromine radicals obtained from the homolysis of the nitrogen-bromine bond. These bromine radicals initiate benzylic bromination with hydroaromatic compounds.[104] Stanforth *et al.* [92] have shown that benzylic bromination occurs in the 1,2,3,4-tetrahydroisoquinoline ring system. It was envisaged that heating **145a** with *N*-bromosuccinimide (Scheme 42) in DCM or CCl_4 with a radical initiator such as benzoyl peroxide would give the brominated adduct which could then undergo elimination of HBr giving the aromatised ring system. Subsequent reaction work up and analysis using ^{1}H-nmr spectroscopy showed predominantly starting material present (triplets present at δ 4.30-4.35 and δ 3.20-3.25).



Scheme 42

Oxidation using molecular oxygen

Sotomayor *et al.* [107] have oxidised 2-fuctionalised 3-aryldihydroisoquinolines using molecular oxygen in the presence of potassium hydroxide (Scheme 43).

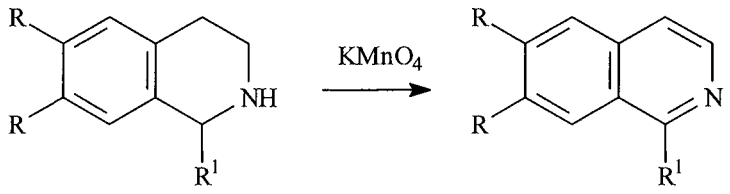


Scheme 43

Compounds **145a** and **145e** were stirred vigorously in a solution of dimethylsulphoxide and powdered potassium hydroxide at 50-55°C for 12-18 hours. Reaction work up gave a yellow oil. Subsequent analysis using ^{1}H-nmr spectroscopy showed predominantly starting material present (triplets present at δ 4.30-4.35 and δ 3.20-3.25).

Oxidation using Potassium Permanganate

Venkov *et al.* [108] have shown the complete dehydrogenation of tetrahydroisoquinoline using potassium permanganate can be achieved (Scheme 44). Work was concentrated on attempting to control this rate of this reaction. The reaction was carried out in dichloromethane using a phase transfer catalyst such as 18-crown-6 ether and cooled in an attempt to selectively dehydrogenate the tetrahydroisoquinoline system. This route was applied to the dehydrogenation of the benzimidazo[2,1-*a*]isoquinoline ring system.

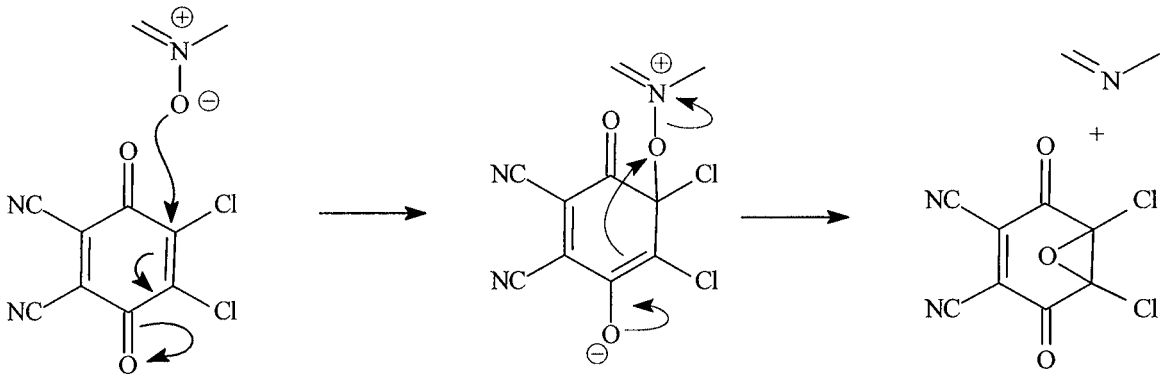


Scheme 44

Compound **145a** was reacted with potassium permanganate and 18-crown-6 ether in dichloromethane at room temperature. Reaction work up by washing with sodium metabisulphite gave a brown oil. Subsequent analysis using ^{1}H-nmr spectroscopy showed predominantly starting material present (triplets present at δ 4.30-4.35 and δ 3.20-3.25).

2.1.7 Attempted dehydrogenation of *N*-oxides 144a,b and e

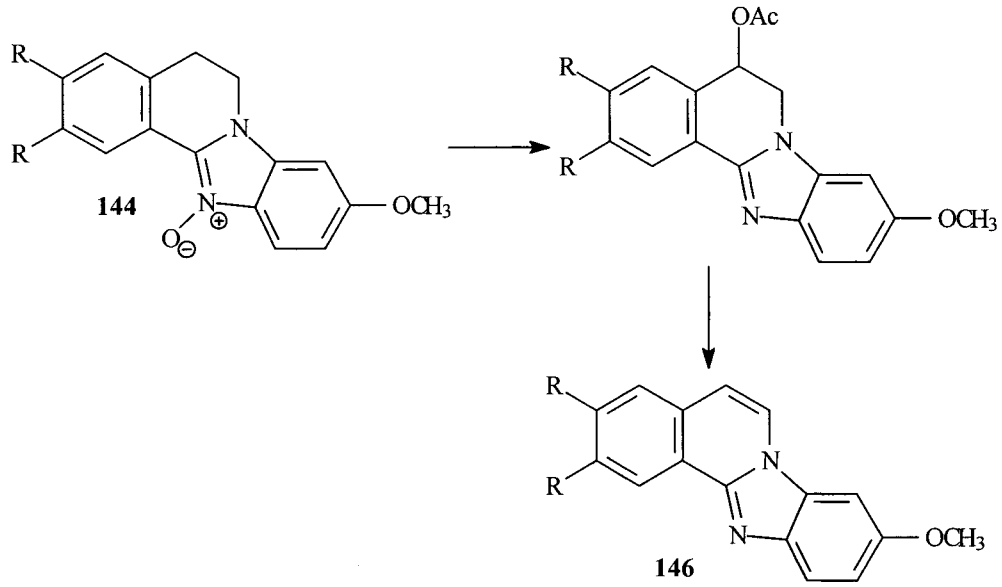
Attempts were made to unsaturate the 5,6-position of the *N*-oxide ring system with DDQ. Treatment of the *N*-oxides **144a,b** & **e** with DDQ did not give the desired 5,6-dihydro derivative, instead it gave the deoxygenated adducts **145a,b** & **e** in 45-70% yield. The fate of DDQ in this reaction has not been determined, however a speculative mechanism for this reaction is epoxidation *via* a Michael type addition followed by elimination shown (Scheme 45).



Scheme 45

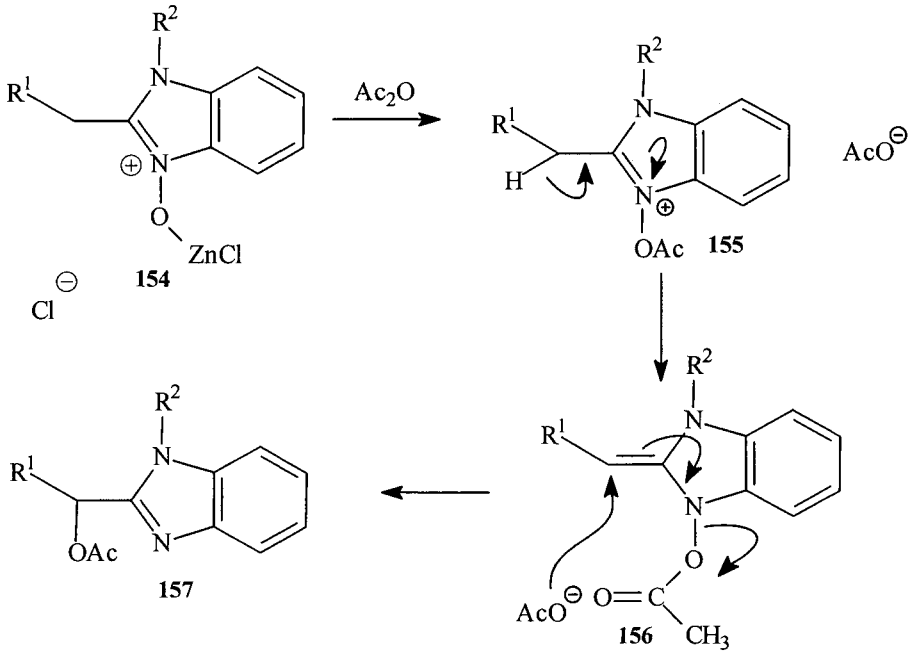
2.1.8 Conversion of *N*-oxides 144b and 144e to acetates 158a-b

A new strategic approach to dehydrogenation was attempted (Scheme 46) by reacting the 5,6-dihydro position of the benzimidazo[2,1-*a*]isoquinoline *N*-oxides **144** with the acetate nucleophile. Subsequent elimination of acetic acid could aromatise the system giving compounds **146**.



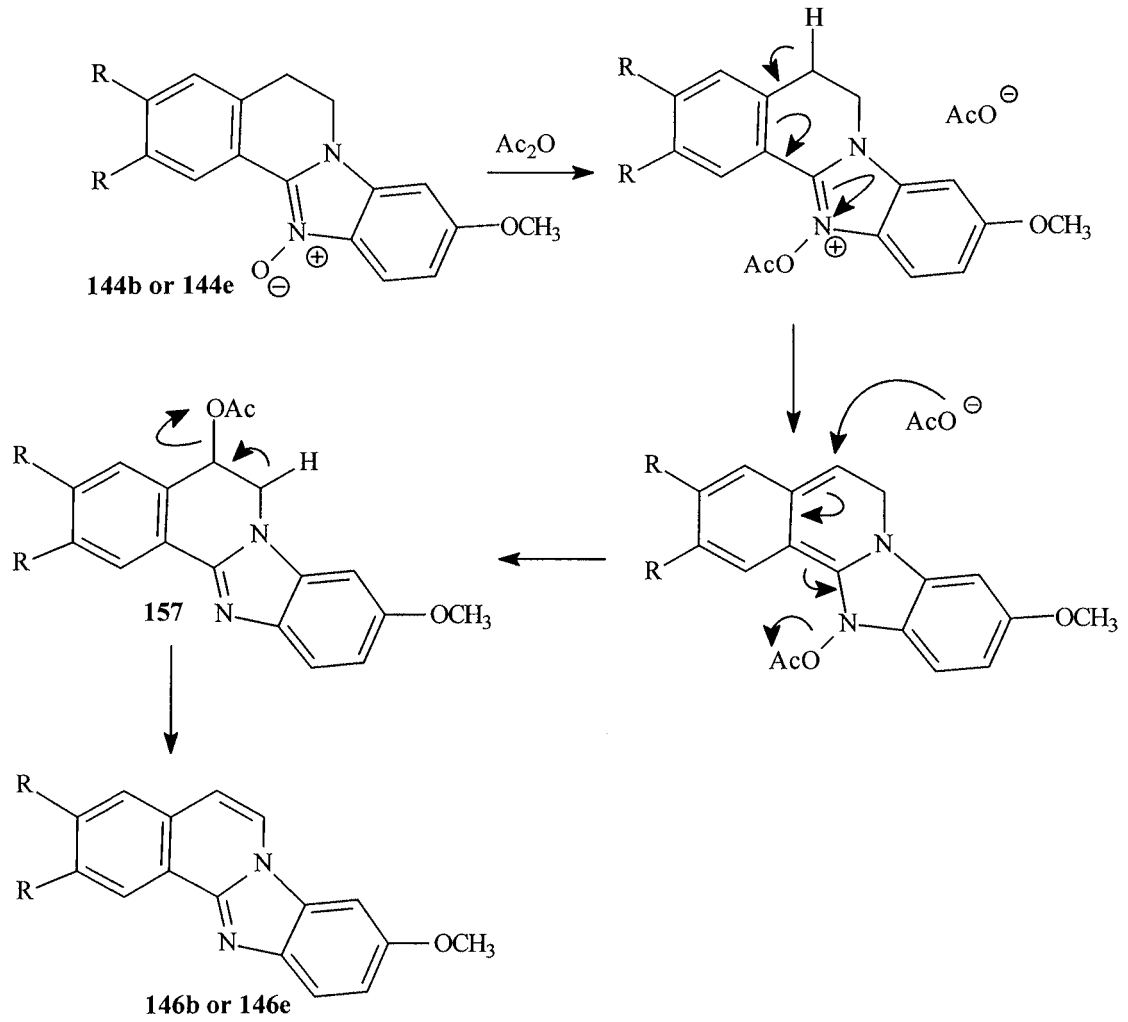
Scheme 46

Grantham and Meth-Cohn [89] have shown that benzimidazole *N*-oxides of general structure **154** shown can be transformed into the acetates **155** by heating in the presence of acetic anhydride (Scheme 47). Subsequent attack of **156** by acetate nucleophile results in elimination of acetic acid giving the product **157**.



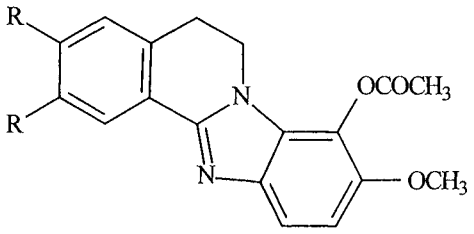
Scheme 47

It was envisaged that a fully aromatised benzimidazo[2,1-*a*]isoquinoline system may obtained in a similar reaction of *N*-oxides **144b** and **144e**. Transformation of **144b** and **144e** (Scheme 48) might yield the acetoxy derivatives **157** from which elimination of acetic acid would yield the fully conjugated systems **146b** and **146e**.



Scheme 48

When *N*-oxides **144b** and **144e** were heated with a mixture of acetic anhydride and sodium acetate, acetoxy derivatives **158a** (40% yield) and **158b** (15% yield) were unexpectedly isolated.

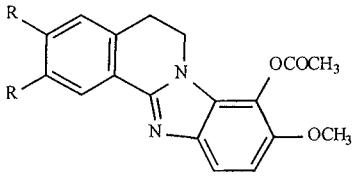


In formulae **158a-b**

	R
a	H
b	OCH_3

The general data for compounds **158a-b** are shown in Table 10. The structures of compounds **158a-b** were confirmed using ^{1}H-nmr spectroscopy, elemental analysis, infra-red spectroscopy and high resolution mass spectrometry.

Compound	Appearance	Yield	Mass Spec. m/z	Melting Pt. °C
158a	Brown Crystals	50%	308.1147	137-138
158b	Brown Crystals	20%	368.1378	254-256

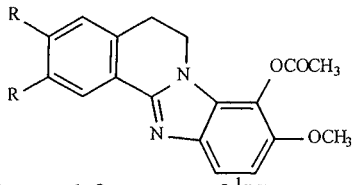


	R
158a	H
158b	OCH_3

Table 10: General data for compounds **158a-b**

The general features of the ^{1}H-nmr spectral data for compounds **158a-b** are presented in Table 11. The signals observed in the spectra are typical of compounds **158a-b** with only slight variations in chemical shifts, multiplicity and coupling constants for members of this series of compounds. Additional signals are present for the substituents R in compound **158b**. The signal that identifies these compounds is the singlet at δ2.40-2.42 that corresponds to the CH_3 of the acetoxy group.

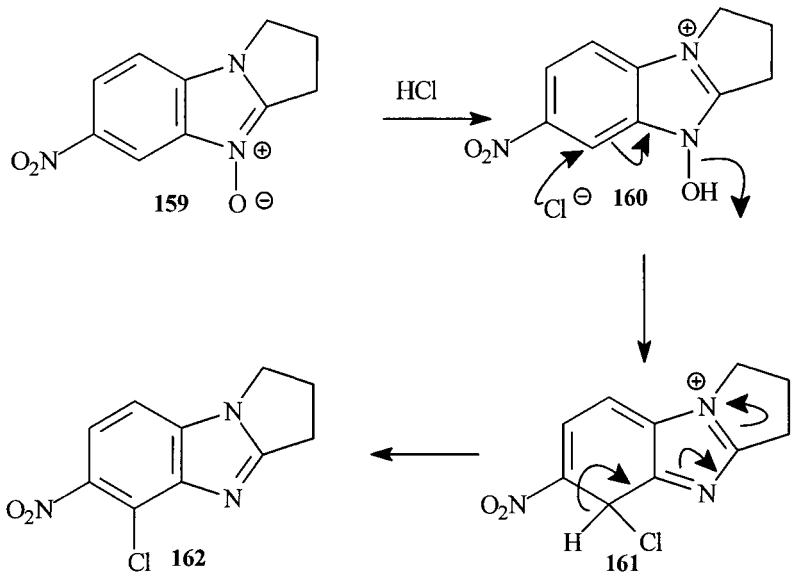
Chemical Shift δ (ppm)	Number of Protons and Multiplicity	Coupling Constants J (Hz)	Assignment
8.20-8.24	m, 1H	-	Ar-H
7.60-7.65	Dd, 1H	6.0 & 1.0	Ar-H
7.25-7.45	m, 3H	-	Ar-H
6.98-7.02	Dd, 1H	6.0 & 1.0	Ar-H
4.20-4.25	t, 2H	7.0-8.0	$N-CH_2-CH_2$
3.90-3.92	s, 3H	-	$O-CH_3$
3.20-3.25	t, 2H	7.0-8.0	$N-CH_2-CH_2$
2.40-2.42	s, 3H	-	$CO-CH_3$



	R
158a	H
158b	OCH_3

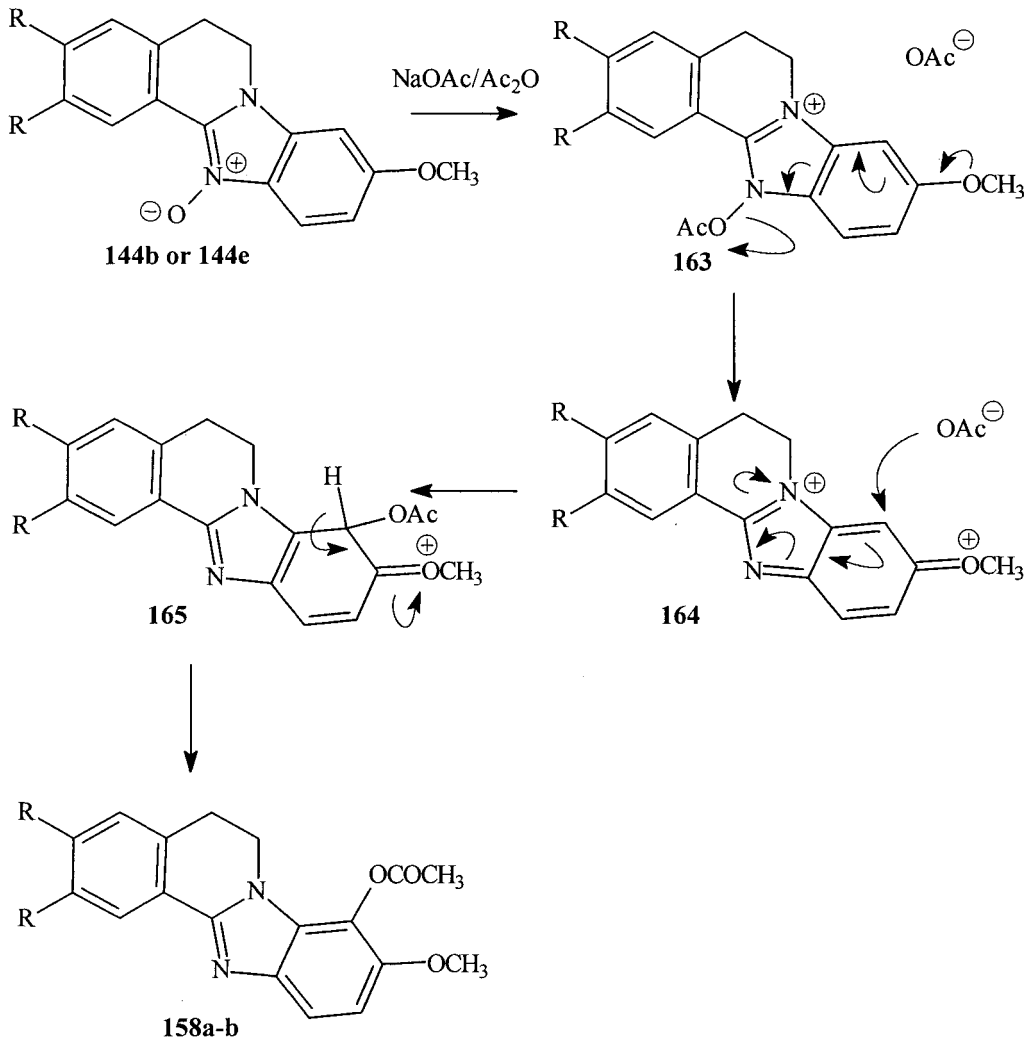
Table 11: General features of ^{1}H-nmr spectral data for compounds **158a-b**

Suschitzky *et al.* [109] have shown nucleophilic attack on benzimidazole-*N*-oxides by chloride ion (Scheme 49) gave chlorinated benzimidazoles **162**. The mechanism of this reaction involves conversion of the *N*-oxide oxygen in **159** with hydrochloric acid into a potential leaving group (in this case hydroxy) to give **160**. Subsequent attack by the chloride nucleophile causes elimination of the hydroxyl group to give **161**. Loss of a proton leads to re-aromatisation yielding the chlorinated benzimidazole **162**.



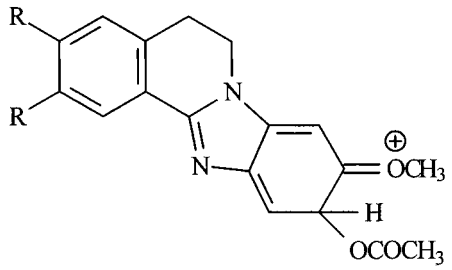
Scheme 49

The rational for the formation of compounds **158a-b** is depicted in Scheme 50 and bears similarities to the mechanism proposed by Suschitzky. Initial nucleophilic attack of the *N*-oxide **144b** or **144e** on acetic anhydride gives intermediate **163**. Elimination of acetate results in formation of quinone-imine intermediate **164**. The quinone-imine intermediate undergoes nucleophilic attack by the acetate nucleophile *via* a Michael type addition to give **165**. Subsequent loss of a proton results in re-aromatisation and yields the acetoxy adduct **158a-b**.



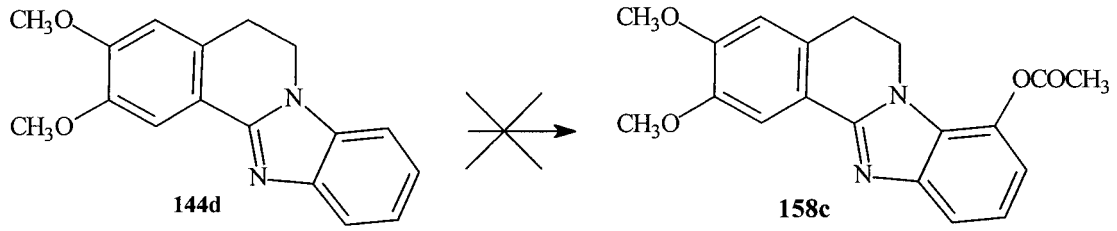
Scheme 50

The mechanism shown in Scheme 50 also accounts for the regioselectivity of the reaction. When the acetate is added at the 8-position the resulting intermediates **165** posses aromatic imidazole fragments. If the addition were to occur at the 10-position giving structures **166**, an aromatic imidazole moiety cannot be drawn. This is confirmed in the ^{1}H-nmr spectrum; if the acetate attacked at the 10 position we would expect to see two singlets for the benzimidazole aromatic ring. The fact we see two doublets for the aromatic ring indicates addition of the acetate nucleophile at the 8 position. This reaction mimics one of the biological mechanisms of action proposed for these compounds (see Scheme 30).



166

The presence of a methoxy group was thought to be essential in the formation of compounds **158a-b**. The key quinone-imine intermediate **164** cannot be formed without the methoxy group, and subsequently reaction with the acetate nucleophile cannot take place. To illustrate this compound **144d** was reacted using identical conditions (Scheme 51). Subsequent reaction work up and analysis using ^{1}H-nmr spectroscopy showed no evidence of **158c** and only starting material was observed.

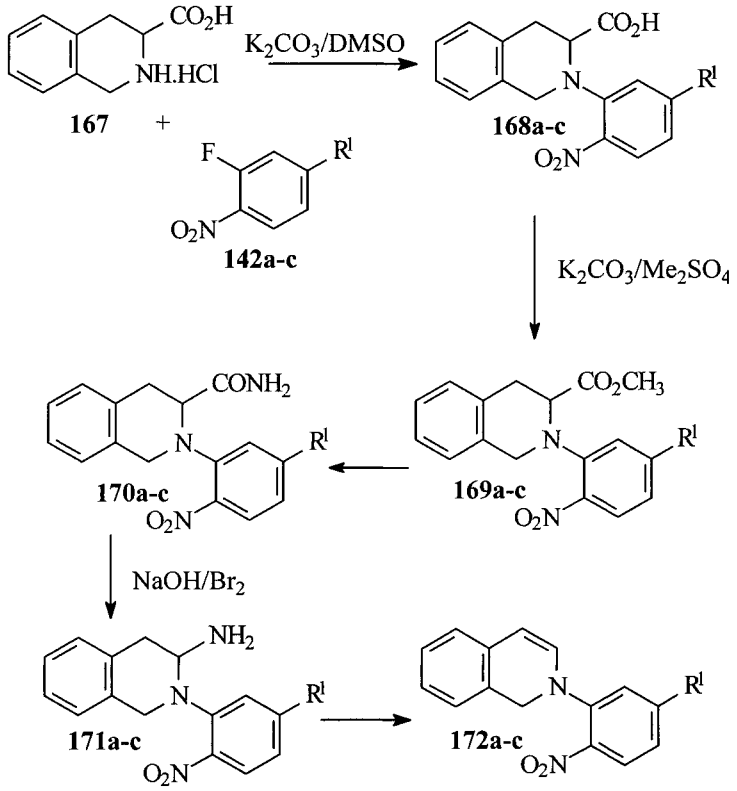


144d **158c**

Scheme 51

2.2 Synthetic strategy-Part B

Due to unsuccessful attempts at dehydrogenation, compounds were synthesised with the ultimate goal of elimination of functionalities to affect complete aromatisation of the benzimidazo[2,1-*a*]isoquinoline ring system (Scheme 52). The strategy was to synthesise 1,2,3,4-tetrahydroisoquinoline carboxylic acid hydrochloride **167** and then react this with fluoronitroaryl compounds **142a-c** to give compounds **168a-c**. Compounds **168a-c** would then be converted to carboxylic esters **169a-c**. Subsequent conversion of esters **169a-c** to amides **170a-c** would be followed by a Hoffmann rearrangement (Scheme 53) to give amines **171a-c** which could allow elimination of ammonia group to give aromatised compounds **172a-c**.



Scheme 52

In formulae **168-172a-c**

	R^1
a	H
b	OCH_3
c	OCH_2Ph

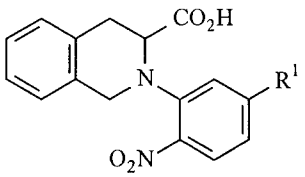
2.2.1 Synthesis of compounds 168a-c

1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid hydrochloride **167** was prepared *via* a Pictet-Spengler type cyclisation reaction.[110] DL-phenylalanine was dissolved in concentrated HCl to which was added formaldehyde. The solution was heated to 95°C for 4 hours and the white crystalline product filtered under pressure and washed with water/acetone to give **167** as white solid (84 % yield).

The reactions to give **168a-c** follow the same nucleophilic substitution mechanism as shown (Scheme 36) and involves halonitroaryl compounds **142a-c**. Initially all chemistry was carried out using 1-fluoro-4-nitrobenzene as a test system and the chemistry was then transferred to compounds **142a-c**.

The general data for compounds **168a-c** are shown in Table 12. The structures of compounds **168a-c** were confirmed using ^{1}H-nmr spectroscopy, elemental analysis, infra-red spectroscopy and high resolution mass spectrometry.

Compound	Appearance	Yield	Melting Pt. °C
168a	Orange Crystals	87%	141-143
168b	Orange oil	88%	-
168c	Orange oil	54%	-

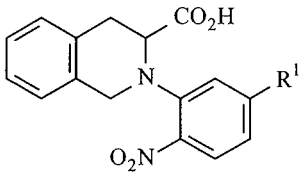


	R^1
168a	H
168b	OCH_3
168c	OCH_2Ph

Table 12: General data for compounds **168a-c**

The general features of the ^{1}H-nmr spectral data for compounds **168a-c** are presented in Table 13. The signals observed in the spectra are typical of compounds **168a-c** with only slight variations in chemical shifts, multiplicity and coupling constants for members of this series of compounds. Additional signals not shown in Table 13 are present for the substituents R^1 in compound **168b-c**. The introduction of a chiral centre in the molecule introduced complex splitting patterns in the ^{1}H-nmr spectra. The protons of the isoquinoline system were split by hydrogens on the same carbon atom as well as hydrogens on adjacent carbon atoms. General signals that identify compounds **168a-c** are the characteristic doublets at δ4.70-4.80 and δ4.05-4.15 that represents the C_1 CH_2 group. The double doublets at δ3.45-3.60 and δ3.30-3.40 represent the C_4 CH_2 group. The final double doublet at δ4.30-4.35 represents the C_3 CH group.

Chemical Shift δ (ppm)	Number of Protons and Multiplicity	Coupling Constants J (Hz)	Assignment
7.80-8.05	dd, 1H	6.0-8.0 & 1.0-3.0	Ar-H
7.00-7.50	m, 7H	-	Ar-H
4.70-4.80	d, 1H	8.0-9.0	CH_2-N-CH
4.30-4.35	dd, 1H	4.0-5.0 & 1.0-2.0	CH_2-CH-CO_2H
4.05-4.15	d, 1H	8.0-9.0	CH_2-N-CH
3.45-3.60	dd, 1H	8.0-9.0 & 1.0-3.0	N-CH-CH_2-
3.30-3.40	dd, 1H	8.0-9.0 & 1.0-3.0	N-CH-CH_2-



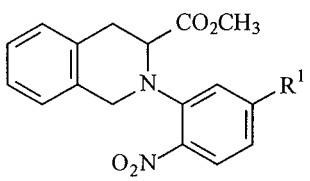
	R^1
168a	H
168b	OCH_3
168c	OCH_2Ph

Table 13: General features of ^{1}H-nmr spectral data for compound **168a-c**

2.2.2 Synthesis of compounds 169a-c

Pattenden *et al.* [111] have shown dimethyl sulfate allows the methylation of sterically hindered carboxylic acid groups. Compounds **168a-c** were converted to their corresponding methyl esters **169a-c** by reaction with potassium carbonate and dimethyl sulphate in acetone. The general data for compounds **169a-c** are shown in Table 14.

Compound	Appearance	Yield	Melting Pt. °C
169a	Yellow Crystals	52%	111-112
169b	Yellow Crystals	69%	108-111
169c	Yellow Crystals	47%	111-114



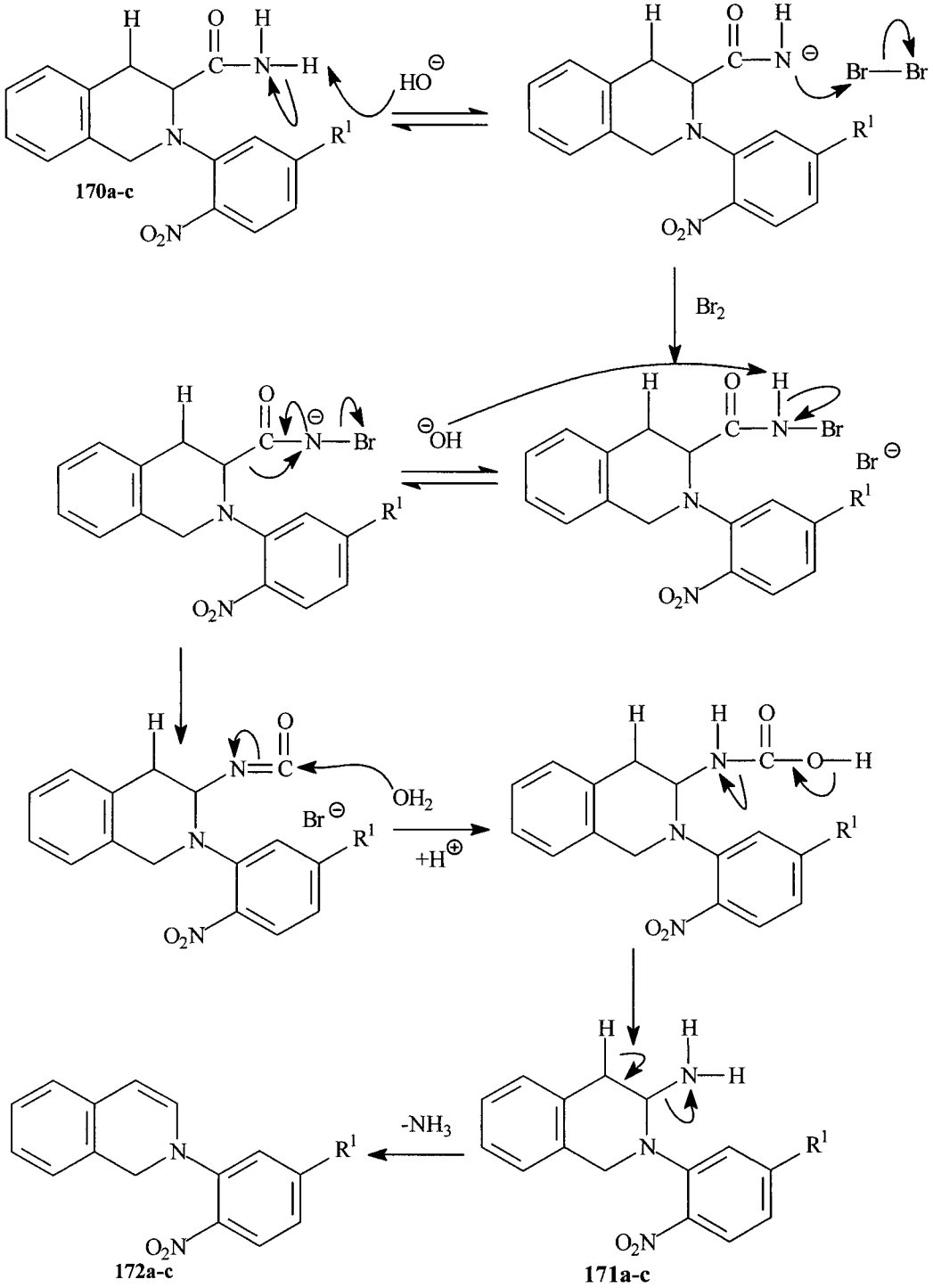
	R^1
169a	H
169b	OCH_3
169c	OCH_2Ph

Table 14: General data for compounds **169a-c**

The structures of compounds **169a-c** were confirmed using ^{1}H-nmr spectroscopy, elemental analysis, infra-red spectroscopy and high resolution mass spectrometry. Esters **169a-c** have similar ^{1}H-nmr spectra to their corresponding acids in Table 13 with the added singlet at chemical shift δ 3.57-3.59 that corresponds to the ester methyl group.

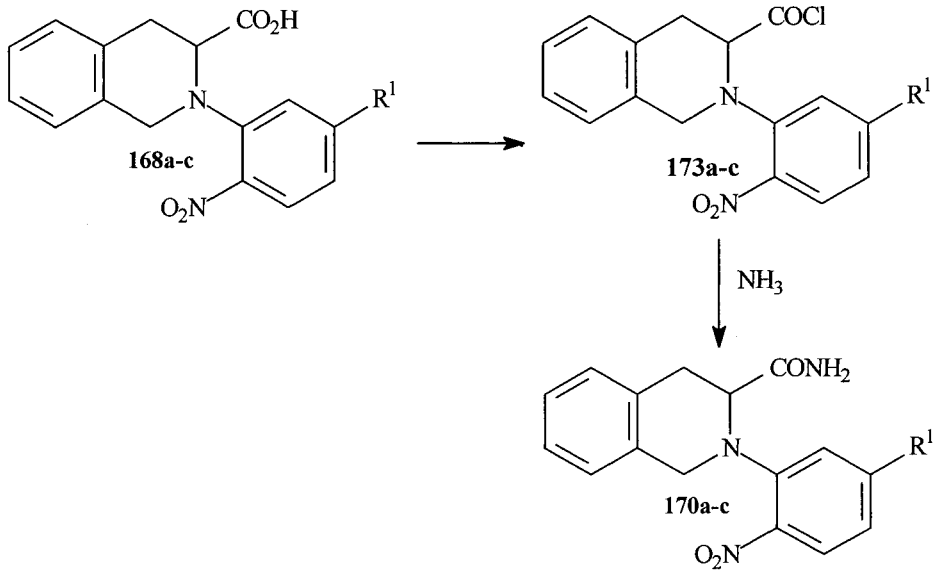
Unsuccessful attempts were made to affect cyclisation of **168a** and **169a** using conditions as those in Scheme 28. Analysis of the cyclisation reaction of **168a** using ^{1}H-nmr spectroscopy proved inconclusive due to insolubility in common ^{1}H-nmr solvents. Analysis of the cyclisation reaction of **169a** using ^{1}H-nmr spectroscopy showed complex mixture of starting material and decomposition products with no evidence of characteristic *N*-oxide proton signal at δ 9.30-9.50.

It was envisaged that conversion of the acid/ester function to its corresponding amides **170a-c** followed by a Hoffmann rearrangement (Scheme 53) would replace the acid/ester functionality with an amine group. Subsequent elimination of ammonia would lead to aromatisation of the ring system to give **172a-c**. Cyclisation to the *N*-oxide could then be re-attempted.



Scheme 53

Initial investigations centred around the conversion of the acid function of compounds **168a-c** to its acid chloride **173a-c**, subsequent reaction with ammonia was expected to yield amide **170a-c** (Scheme 54).

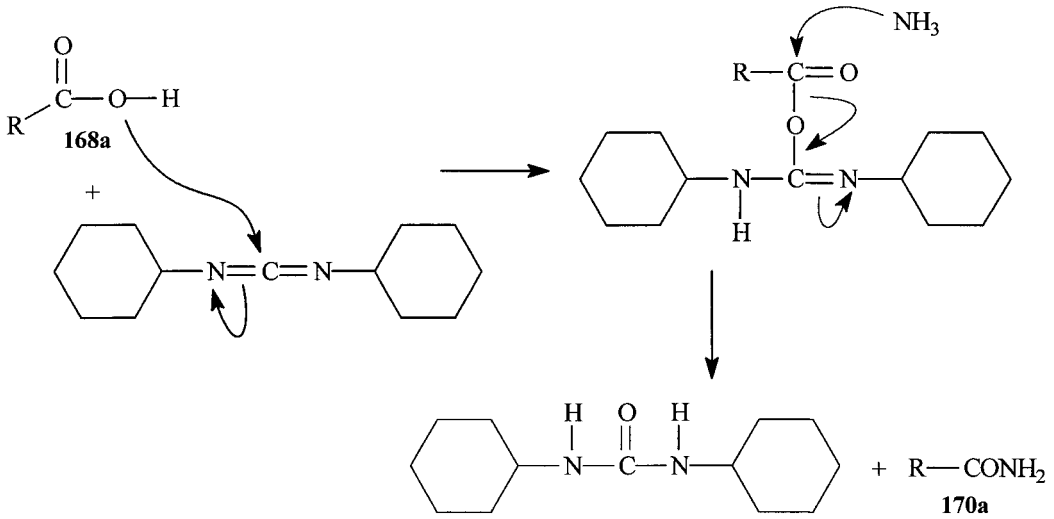


Scheme 54

Phosphorous trichloride is commonly used for the conversion of carboxylic acid groups to its corresponding acid chloride.[112] Compound **168a**, phosphorous trichloride and pyridine was heated to reflux for 2 hours in chloroform. Subsequent addition of ammonia solution and work up gave a brown oil. Analysis using ^{1}H-nmr spectroscopy showed complex mixture containing little or no product.

Attempts were made to convert the acid to its acid chloride using thionyl chloride.[113] Compound **168a** was heated to reflux for 2 hours in thionyl chloride, excess thionyl chloride was then removed by distillation under reduced pressure. The acid chloride was isolated as a red oil and was then carefully added to a solution of ammonia/ammonium carbonate. The resultant product was isolated as a red solid. Subsequent analysis using ^{1}H-nmr spectroscopy showed complex mixture containing no product.

Dicyclohexylcarbodiimide (DCCI) has been shown as a milder method for conversion of acids to amides (Scheme 55).[114]

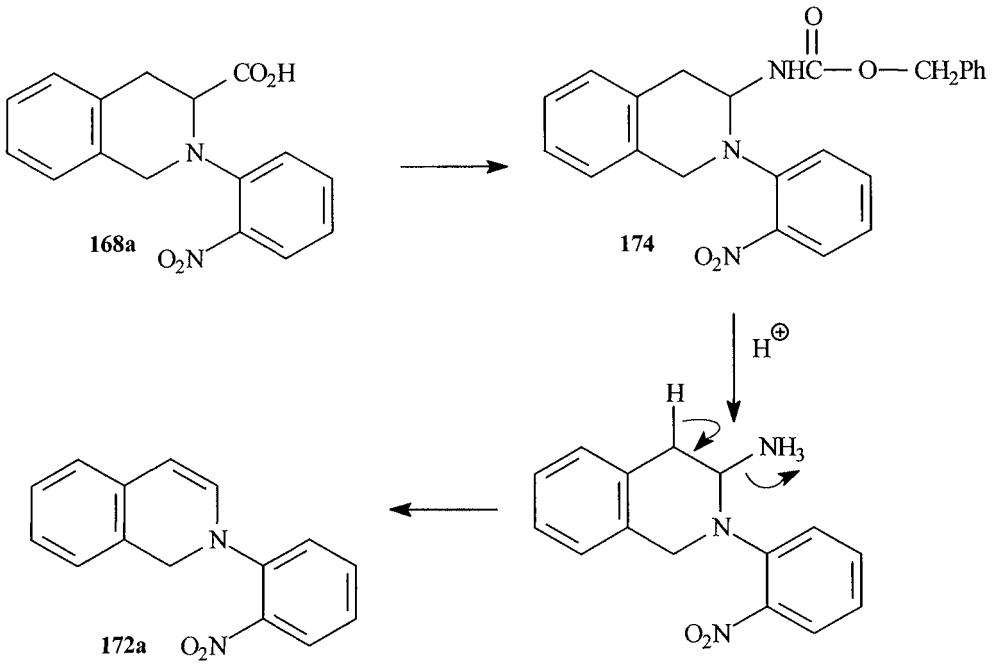


Scheme 55

To compound **168a** and ammonia in dichloromethane, a dichloromethane solution of DCCI was added carefully and the resultant solution stirred at room temperature for 18 hours. The resultant product was isolated as a orange oil. Subsequent analysis using ^{1}H-nmr spectroscopy showed predominantly starting material.

Conversion of acid function to urethane (modified Curtius reaction)

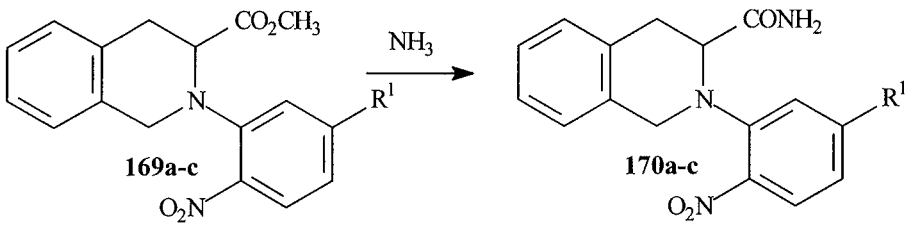
Diphenylphosphoryl azide (DPPA) is a mild convenient method of converting carboxylic acid functions through its urethane to its corresponding amine (Scheme 56).[115] The reaction involves the refluxing of the carboxylic acid, triethylamine and DPPA in the presence of the hydroxyl component. Treatment of the urethane **174** with acid converts it to the amine that could then eliminate ammonia to give **172**. Compound **168a** was heated in the above conditions using t-butanol as both hydroxyl component and solvent. Subsequent work up by distillation of excess t-butanol and washing with base solution gave crude mixture that showed evidence of product urethane **174** but reaction was inefficient.



Scheme 56

Attempted conversion of ester to amide

Attempts were made to convert esters **169a-c** to its amide **170a-c** (Scheme 57).



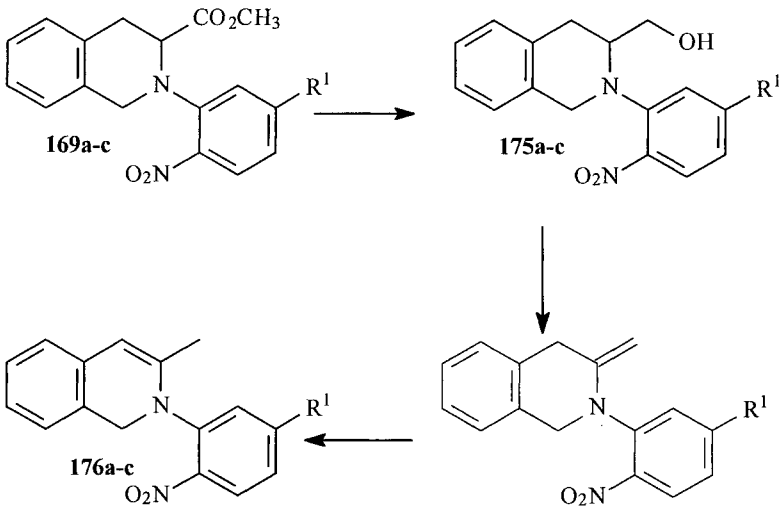
Scheme 57

Compound **169a** was stirred in ammonia solution for 18 hours. Subsequent analysis using ^{1}H-nmr spectroscopy showed predominantly starting material.

Compound **169a** in ammonia/ammonium carbonate/methanol solution was heated to 125°C in a bomb for 3 hours. Subsequent work up gave a brown oil that was fractionated by column chromatography. Analysis using ^{1}H-nmr spectroscopy showed presence of a product but the reaction was inefficient.

2.3 Synthetic strategy-Part C

A further strategy (Scheme 58) involved the conversion of the ester functionality in compounds **169a-c** into a potent leaving group giving compounds **175a-c**. Subsequent conversion or elimination of leaving group should give aromatised compounds **176a-c**.



Scheme 58

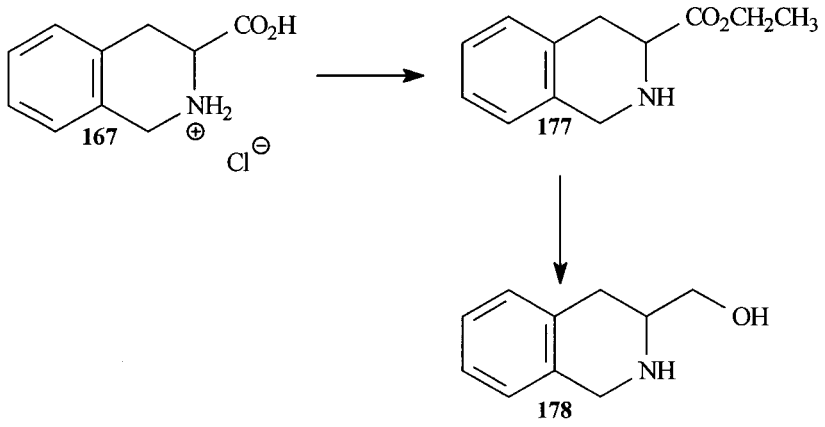
In formulae **175-176a-c**

	R^1
a	H
b	OCH_3
c	OCH_2Ph

Conversion of the ester functionality by reduction to its corresponding alcohol gave a reactive nucleophilic species on the molecule. The nucleophilic hydroxyl can then undergo further reaction placing functional groups upon the molecule that can be easily eliminated. Reduction of the ester group in compounds **169a-c** to its corresponding alcohol would prove difficult using standard reducing agents due to the presence of the nitro group that is essential for cyclisation.

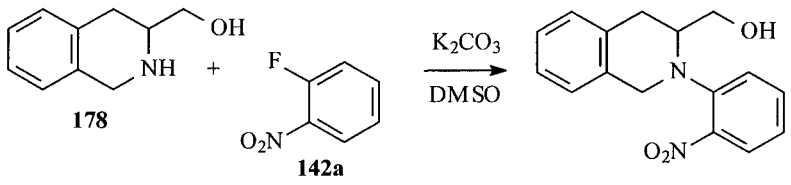
2.3.1 Synthesis of compounds 175a-c

Initial chemistry centred on the reduction of the ester function before reaction with the halonitroaryl compounds (Scheme 59).



Scheme 59

Archer [116] has shown conversion of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid hydrochloride **167** to its ethyl ester **177** can be achieved by dissolving the acid in boiling ethanol and bubbling fresh HCl gas through the refluxing solution for six hours. Reaction and subsequent isolation of product by distillation gave the ester as a yellow oil (23 % yield). Reduction of the ester was carried out with lithium aluminium hydride [117] in refluxing tetrahydrofuran to give the alcohol **178** as an orange oil (63 % yield).

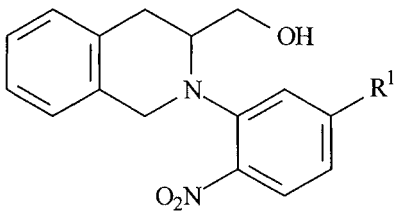


Scheme 60

Attempted reaction of compound **178** and **142a** (Scheme 60) proved unsuccessful. Analysis of reaction mixture using ^{1}H-nmr spectroscopy showed a small amount of product. The major component isolated after purification using column chromatography and analysis using ^{1}H-nmr spectroscopy was thought to be 2-nitrophenol. A further attempt involved protection of the hydroxy group in **178** with trimethylsilyl chloride (as with compound **151**). Subsequent reaction of the silyl ether protected isoquinoline with **142a** in triethylamine was followed by acidic work up. Purification using column chromatography on silica gave an orange solid (12 % yield). Analysis of orange solid using ^{1}H-nmr spectroscopy showed complex mixture with no evidence of product. This type of coupling reaction investigation was pursued no further.

Brown and Narasimhan [118] have shown that lithium borohydride in the presence of certain catalysts can selectively reduce ester groups in the presence of other functional groups such as chloro and nitro. General reaction conditions involve the dissolving of reagents in anhydrous ether and heating together under an inert atmosphere with a 0.1 mole % equivalence of catalyst.

Compounds **169a-c** were reacted with lithium borohydride with a trimethylborate catalyst yielding compounds **175a-c**.

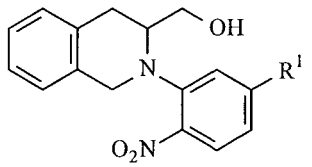


In formulae **175a-c**

	R^1
a	H
b	OCH_3
c	OCH_2Ph

The general data for compounds **175a-c** are shown in Table 15. The structures of compounds **175a-c** were confirmed using ^{1}H-nmr spectroscopy, elemental analysis, infra-red spectroscopy and high resolution mass spectrometry.

Compound	Appearance	Yield	Mass Spec. m/z
175a	Orange oil	66%	-
175b	Orange oil	72%	314.126
175c	Orange oil	87%	390.161

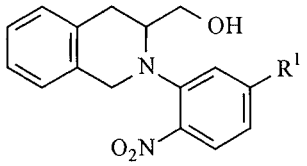


	R^1
175a	H
175b	OCH_3
175c	OCH_2Ph

Table 15: General data for compounds **175a-c**

The general features of the ^{1}H-nmr spectral data for compounds **175a-c** are presented in Table 16. The signals observed in the spectra are typical of compounds **175a-c** with only slight variations in chemical shifts, multiplicity and coupling constants for members of this series of compounds. Additional signals are present for substituents R^1 in compounds **175b-c**, but these are not shown in Table 16. General peaks that identify compounds **175a-c** are the characteristic doublets at δ3.70-3.80 and δ3.60-3.65 that represents the CH_2 group of the reduced ester.

Chemical Shift δ (ppm)	Number of Protons and Multiplicity	Coupling Constants J (Hz)	Assignment
7.80-8.00	d, 1H	8.0-9.0	Ar-H
7.15 -7.45	m, 5H	-	Ar-H
6.90-7.00	m, 2H	-	Ar-H
4.55-4.65	d, 1H	15.0-16.0	CH_2-N-
4.05-4.15	m, 1H	-	N-CH-CH_2-
3.70-3.80	m, 2H	-	CH_2-N & CH_2-OH
3.60-3.65	dd, 1H	10.0-12.0 & 4.0-6.0	CH_2-OH
3.25-3.30	dd, 1H	15.0-16.0 & 4.0-5.0	N-CH-CH_2-
2.70-2.80	dd, 1H	15.0-16.0 & 3.0-4.0	N-CH-CH_2-

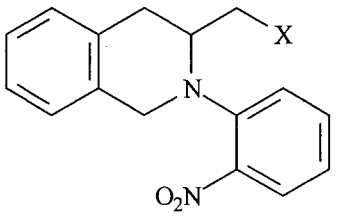


	R^1
175a	H
175b	OCH_3
175c	OCH_2Ph

Table 16: General features of ^{1}H-nmr spectral data for compounds **175a-c**

2.3.2 Derivatisation of hydroxyl group on compounds 175a-c

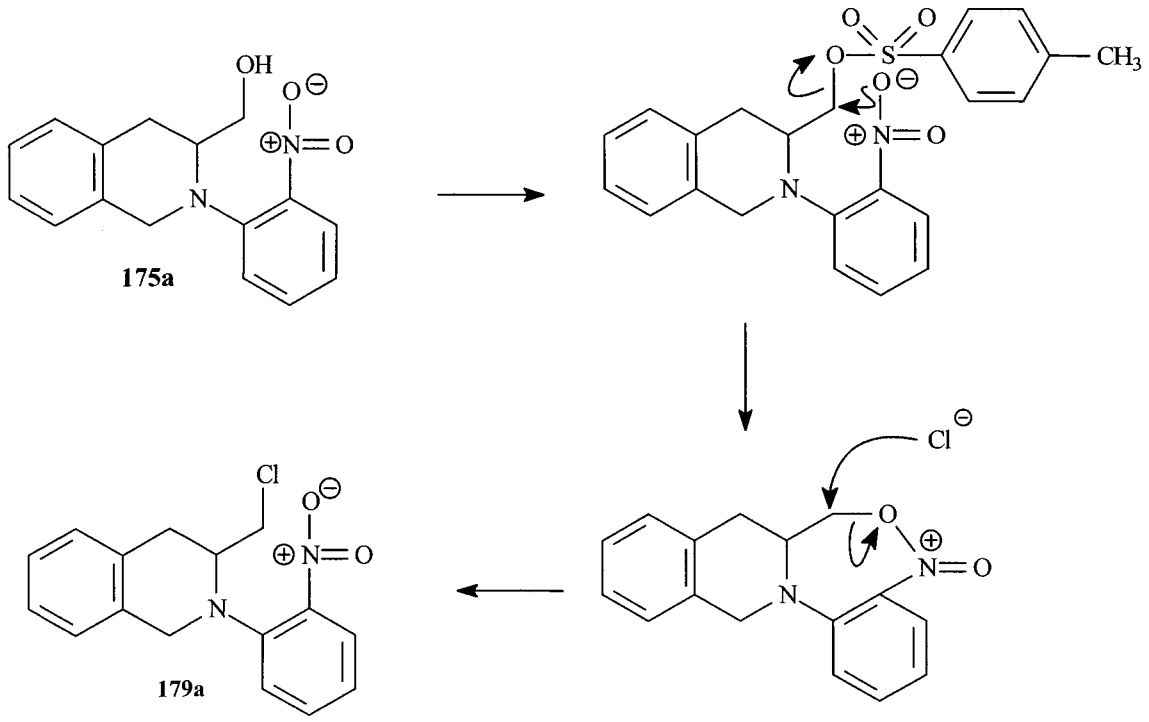
The hydroxyl group in compounds **175a** was reacted further to attempt to give different functionalities at this position giving compounds **179a-d**.



In formulae **179a-d**

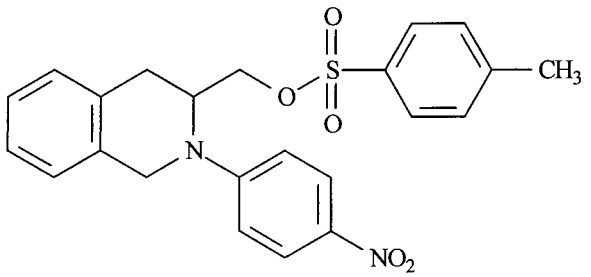
	X
a	Cl
b	Br
c	SPh
d	OTosyl

Gibson *et al.* [119] have shown that treatment of primary alcohols with tosyl chloride and triethylamine in anhydrous dichloromethane affects tosylation of the hydroxy group followed by *in situ* elimination to give the alkene system. This reaction was attempted with **175a** in the above conditions to synthesise *in situ* **179d**, subsequent work up and analysis using ^{1}H-nmr spectroscopy showed no evidence of desired product. The structure of the product obtained was identified as **179a**. It was thought that chlorination occurs *via* the mechanism shown in Scheme 61 as a result of the nitro group attacking the tosyl group. Application of Baldwin's Rules for ring closure [120] shows the process to be a favoured 7-Exo-Tet (7-Exocyclic-Tetrahedral) process.



Scheme 61

To confirm this theory the isomeric compound **183** was synthesised through intermediates **180-182** using established procedures from Schemes 52 and 58. This compound was perfectly stable.



183

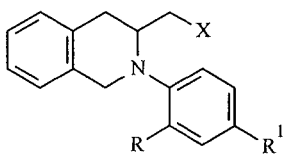
An authentic sample of **179a** was made using conventional methods [121] by reaction of **175a** with carbon tetrachloride and triphenyphosphine in anhydrous dichloromethane.

Compound **179b** was synthesised in the same way as the authentic sample of **179a** [121] using tetrabromoethane as the bromine source. Subsequent work up and analysis using ^{1}H-nmr spectroscopy showed the reaction was successful.

Attempts were made to synthesise compound **179c** *via* a standard nucleophilic substitution reaction of thiophenol with **179b** in anhydrous tetrahydrofuran. Subsequent work up and analysis using ^{1}H-nmr spectroscopy showed only starting material present.

The general data for compounds **179a-b & 183** are shown in Table 17. The structures of compounds **179a-b & 183** were confirmed using ^{1}H-nmr spectroscopy, elemental analysis, infra-red spectroscopy and high resolution mass spectrometry.

Compound	Appearance	Yield	Mass Spec. m/z	Melting Pt. °C
179a	Yellow Crystals	34%	302.0826	100-103
179b	Orange oil	32%	346.0299	-
183	Orange Crystals	42%	-	160-162

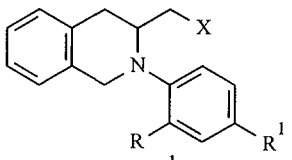


	R	R^1	X
179a	NO_2	H	Cl
179b	NO_2	H	Br
183	H	NO_2	OTs

Table 17: General data for compounds **179a-b & 183**

The general features of the ^{1}H-nmr spectral data for compounds **179a-b & 183** are presented in Table 18. The signals observed in the spectra are typical of compounds **179a-b & 183** with slight variations in chemical shifts, multiplicity and coupling constants for members of this series of compounds. Additional signals are present for substituents X in compound **183**, but these are not shown in Table 18. General signals that identify compounds **179a-b & 183** are the characteristic signals at δ3.55-3.90 and δ3.35-3.60 that represents the CH_2 group of the carbon adjacent to the leaving group X. These signals occur at varying chemical shifts dependant on the substituent X.

Chemical Shift δ (ppm)	**Number of Protons and Multiplicity**	**Coupling Constants J (Hz)**	**Assignment**
7.80-7.85	d, 1H	8.0-9.0	Ar-H
7.45-7.47	t, 1H	8.0-9.0	Ar-H
7.00-7.25	m, 6H	-	Ar-H
4.57-4.58	d, 1H	15.0-16.0	CH_2-N-
4.09-4.11	d, 1H	15.0-16.0	CH_2-N-
3.90-3.92	m, 1H	-	N-CH-CH_2-
3.65-3.67	m, 1H	-	CH_2-Cl
3.44-3.46	dd, 1H	5.0-6.0 & 5.0-6.0	CH_2-Cl
3.42-3.44	dd, 1H	15.0-16.0 & 4.0-5.0	N-CH-CH_2-
2.90-2.92	dd, 1H	15.0-16.0 & 1.0-2.0	N-CH-CH_2-

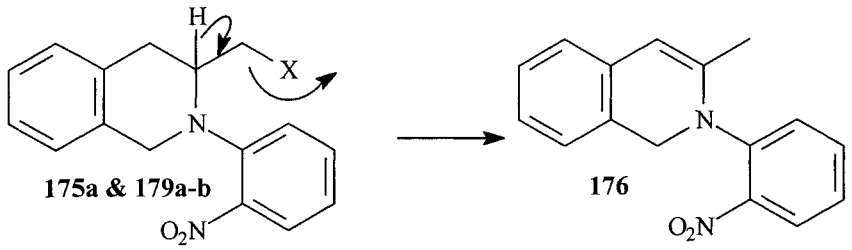


	R	R^1	X
179a	NO_2	H	Cl
179b	NO_2	H	Br
183	H	NO_2	OTs

Table 18: General features of ^{1}H-nmr spectral data for compound **179a-b & 183**

2.3.3 Elimination Reactions

Attempts were made to eliminate functional groups to achieve aromatisation of the isoquinoline ring system (Scheme 62) all without success.



Scheme 62

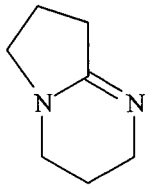
Concentrated sulphuric acid is a popular method of dehydrating alcohols to alkenes.[101] This reaction is carried in extreme conditions at high temperatures leading to degradation of starting materials giving increased impurities. Compound **175a** was heated at reflux for 12 hours in a mixture of acetic acid and sulphuric acid. Subsequent work up gave a brown oil that was purified using column chromatography on silica. Analysis of fractions using ^{1}H-nmr spectroscopy showed cyclisation and deoxygenated adducts but no presence of desired product.

Phosphorus pentoxide is also commonly used in the dehydration of alcohols to alkenes.[122] The reaction is carried out at high temperature using a high boiling solvent with a large excess of phosphorus pentoxide. Compound **175a** was refluxed in xylene with a 400% mole excess of phosphorus pentoxide. Subsequent work up by distillation of xylene and analysis using ^{1}H-nmr spectroscopy showed predominantly starting material present.

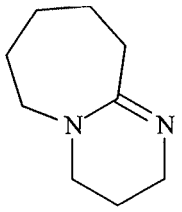
Elimination of Chloride and Bromide

The introduction of double bonds into a system *via* the elimination of hydrogen halides can be achieved using organic bases.

Bicyclic amidines such as 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) are commonly used organic bases in dehydrohalogenation reactions.[123]



DBN



DBU

Compounds **179a-b** were stirred with DBU at room temperature in anhydrous THF for 18 hours. Subsequent work up gave an orange oil which when analysed using ^{1}H-nmr spectroscopy showed predominantly starting material present.

The base potassium *tert*-butoxide is also used in dehydrohalogenation reactions, particularly elimination of HBr.[124] Compound **179b** and potassium *tert*-butoxide was stirred in anhydrous THF for 18 hours and the reaction monitored by TLC. Subsequent work up gave an orange oil which when analysed using ^{1}H-nmr spectroscopy showed predominantly starting material present.

2.4 Conclusions

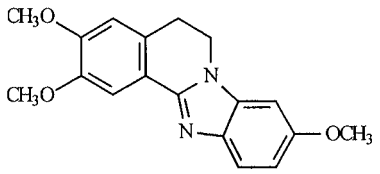
The research studies involved the synthesis of a range of benzimidazo[2,1-*a*]isoquinoline derivatives that are structurally similar to that of the known anti-cancer agent ellipticine. Several compounds were submitted for biological evaluation (see section 2.5).

9-Hydroxyelliticine is shown to be forty times more active than ellipticine *in vivo*. The initial target was therefore the synthesis of the hydroxy derivatives **139a-b** that should have increased biological activity. This was achieved, however the synthetic route was far from efficient and resulted in low yields of products.

By analogy with ellipticines, it was envisaged that these benzimidazo[2,1-*a*]isoquinolines compounds could undergo biological oxidation to give a reactive quinone-imine intermediate that subsequently could react with bionucleophiles in the body yielding the bioalkyated adduct. The alkylation of the benzimidazo[2,1-*a*]isoquinoline *N*-oxides **144b** and **144e** with the acetate nucleophile mimics the bioalkyation reaction of ellipticine and the work by Potier *et al.* on the carbazole ring system (Scheme 29). This indicates the possible formation of the reactive quinone-imine species in our compounds.

The application of Baldwin's rules to the peculiar 7-Exo-Tet process in the synthesis of **179a** (Scheme 60) illustrates the interaction of the nitro group at the 2-position of the ring and the tosyl group when in close proximity. This interaction was not present when the nitro group was at the 4-position of the ring as shown by formation of compound **183**.

2.5 Results of Testing



145e

Compound **145e** was submitted to Dr Caroline Austin and her colleagues at the University of Newcastle, Department of Biochemistry and Genetics. It was screened for its ability to interact with the enzyme topoisomerase II.

Human cells contain 2 (iso) forms of type II topoisomerases, α and β. A test system was used in which human topoisomerase IIβ could be expressed in yeast cells in such a way as to allow the survival of yeast cells that carry a non functional yeast topoisomerase II. The yeast cells have a temperature sensitive mutation in their own topoisomerase II gene rendering it non functional at a growth temperature of 35°C. At this non permissive growth temperature these cells cannot survive unless they are given a piece of DNA in the form of a plasmid that encodes a functional yeast topoisomerase II or either of the human topoisomerases α and β allowing them to survive at 35°C. The yeast cells possessing the "plasmid borne" topoisomerases can be treated with known concentrations of compound **145e** and their survival measured by counting the number of colonies that are still able to grow after exposure. From the results an inhibitory concentration for 50% cell death (IC_{50}) in μg/ml was obtained. Results for IC_{50} of **145e** was compared to ellipticine and is shown in Table 19.

Yeast Type	IC_{50}(μg/ml) 400e	IC_{50}(μg/ml) Ellipticine
Yeast topo. II	49	78
Human topo. IIα	49	12
Human topo. IIβ	56	72

Table 19: Results of testing of Compound **145e** against topoisomerase II

The results showed that compound **145e** had similar activity against the types of topoisomerase II shown. It was more active against human topoisomerase IIα than ellipticine and was slightly less active than ellipticine against topoisomerase II and human topoisomerase IIβ. These initial results were encouraging and merited further investigation into this compound.

Compound **145e** was submitted to the National Cancer Institute based in Maryland, USA. Initial screening was evaluated in the 3-cell line, one dose primary anticancer assay. The three cell lines consist of MCF7 (breast), NCI-H460 (lung) and SF-268 (CNS). The procedure involves inoculation and preincubation of the cell line on a microtitre plate. Compound **145e** was added and the culture incubated for 48 hours. End point determination was made using sulforhodamine B, a protein-binding dye. Results for the test are recorded as the percent of growth of the treated cells when compared to the untreated control cells. Compounds that reduce the growth of any one of the cell lines to 32% or less are then submitted for evaluation against 60 cell lines. The results for compound **145e** are shown in Table 20.

Compound	Breast (%growth) MCF7	Lung (%growth) NCI-H460	CNS (%growth) SF-268
145e	17	20	55

Table 20: Results for compound **145e** in 3-cell line anticancer assay

Preliminary results showed compound **145e** to be active in both breast and lung cell lines, so the compound was submitted for testing against the 60-cell lines.

After subsequent screening of **145e** against 60 cell lines the NCI decided that the results did not merit further investigation into this compound.

CHAPTER 3

EXPERIMENTAL

3.0 Index of Reactions

3.1 Experimental

General: ^{1}H-nmr spectra were recorded on either a Jeol 90Q or a Jeol GX270 instrument. All proton chemical shifts are quoted in ppm relative to tetramethylsilane (TMS) as internal standard in deterio-trichloromethane and dimethylsulphoxide. All chemical shifts are reported as follows: δ_H δ value in ppm (number of protons, multiplicity, coupling constant in Hz and assignments). The multiplicity of signals is expressed as follows: s, singlet; d, doublet; t, triplet; q, quartet; dd, double doublet and m, multiplet.

Elemental analysis and high resolution mass spectra were performed by the Department of Chemistry, University of Newcastle upon Tyne. Melting points are reported as uncorrected as determined on a Stuart SMP1. Infra-red spectra were obtained using KBr discs for solids and liquid films for oils using a Perkin Elmer Paragon 1000 spectrophotometer.

Chromatography: Thin layer chromatography (tlc) was performed on Merck plastic foil plates pre-coated with silica gel 60 F_{254}, running in suitable solvents. Reaction components were visualised by U.V. (254 or 366 nm). Silica gel for column chromatography was Merck silica gel 60 with appropriate fractions being combined on the basis of their tlc behaviour.

Materials: Unless otherwise indicated, all reagents were obtained from commercial suppliers and used without further purification. Tetrahydrofuran and 1,4 dioxan were dried by distillation from sodium hydride. Toluene and diethylether were dried using

sodium. Reactions involving air and/or moisture sensitive reagents were conducted under an atmosphere of dry nitrogen and glassware was oven dried (110-120°C).

3.1.1 Experimental for strategy A

Preparation of 6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride **141b**[93]

Formaldehyde (100ml) in water (200ml) was cooled in ice bath to 0°C. To this was added 2-(3,4-dimethoxyphenyl)ethylamine (100g, 551.0mmol) and the mixture heated to 50°C (2 hours) with stirring. After cooling the layers were separated and the oily layer dissolved in dichloromethane. The organic layer was washed with water and dried ($MgSO_4$). Freshly prepared HCl gas was bubbled through the solution yielding **141b** (15.14g, 12%) as yellow crystals, m.p. 261-263°C (ethanol), lit. m.p.[93] 263-265°C. The free base was obtained by washing a solution of the hydrochloride salt in dichloromethane with sodium bicarbonate solution. δ 6.60 (1H, s, Ar-H), 6.48 (1H, s, Ar-H), 3.95 (2H, s, CH_2-N-), 3.80 (6H, s, 2 x O-CH_3) 3.10 (2H, t, J 8Hz, N-CH_2-CH_2-), 2.70 (2H, t, J 8Hz, N-CH_2-CH_2-).

Preparation of 3-Fluoro-4-nitroanisole **142b** (*Method a*)[95]

To 3-fluoro-4-nitrophenol **147** (2.00g, 12.7mmol) and K_2CO_3 (2.60g, 18.8mmol) in acetone (25ml), was added dimethylsulphate (1.19ml, 32.5mmol) and the mixture was heated under reflux (2 hours) with stirring. After cooling the mixture was poured on to water and extracted with dichloromethane. The organic layer was washed with water, dried ($MgSO_4$) and evaporated yielding **142b** (1.90g, 93%) as yellow crystals, m.p. 59-60°C (ethanol) lit. m.p.[95] 56-56.5°C. $\nu_{max.}$ 1609, 1510, 1337, 1282 and 1091 cm^{-1}. δ 8.10 (1H, m, Ar-H), 6.80-6.65 (2H, m, Ar-H), 3.90 (3H, s, O-CH_3).

Preparation of 3-Fluoro-4-nitroanisole **142b** (*Method b*)

To 2,4-difluoronitrobenzene **148** (60.0g, 377.2mmol) in methanol (50ml) was added dropwise a solution of potassium hydroxide (21.2g, 377.8mmol) in methanol (100ml). The mixture was stirred (2 hours) at room temperature. The excess methanol was removed by evaporation washed with water and extracted with dichloromethane. The resultant brown oil was distilled under vacuum (6mm Hg, b.p. 116-122°C) giving second fraction enriched in **142b** 3:1 ratio **142b:149** (26.0g, 40%) as yellow oil, identical with an authentic sample. δ 8.10 (1H, m, Ar-H), 6.80-6.65 (2H, m, Ar-H), 3.90 (3H, s, O-CH_3). The first fraction (6mm Hg, b.p. 78-116°C) was predominantly low boiling point material. The third fraction fraction (6mm Hg, b.p. 122-124°C) contained a 50:50 mixture of **142b** and **149**.

Preparation of 2-Fluoro-4-benzyloxynitrobenzene **142c** (*Method a*)

To 3-fluoro-4-nitrophenol **147** (4.90g, 31.2mmol) and K_2CO_3 (6.46g, 46.7mmol) in tetrahydrofuran (75ml), was added benzyl bromide (5.04ml, 32.5mmol) and sodium iodide (few crystals) and the mixture heated under reflux (2 hours) with stirring. After cooling the mixture was poured into water and extracted with dichloromethane. The organic layer was washed with water, dried ($MgSO_4$) and evaporated yielding brown oil which was fractionated by column chromatography (silica gel, eluent petroleum ether b.p. 60-80°C : ethyl acetate 2:1) giving compound **142c** (1.18g, 16%) as creamy yellow crystals, m.p. 72-73°C (ethanol). [Found: C,63.18; H,4.01; N,5.73 $C_{13}H_{10}NO_3F$ requires C,63.16; H,4.08; N,5.67%]. $\nu_{max.}$ 1609, 1512, 1331, 1274 and 1091 cm^{-1}. δ 8.10 (1H, m, Ar-H), 7.45-7.35 (5H, s, Ar-H), 6.85-6.75 (2H, m, Ar-H), 5.15 (2H, s, O-CH_2-Ph).

Preparation of 2-Fluoro-4-benzyloxynitrobenzene **142c** (*Method b*)

To 2,4-difluoronitrobenzene **148** (10.0g, 62.9mmol) in benzyl alcohol (20ml) was added dropwise a solution of potassium hydroxide (21.2g, 377.9mmol) in benzyl alcohol (20ml). The mixture was stirred (2 hours) at room temperature. The resultant brown oil distilled under vacuum using Kugel-Rohr apparatus (3mm Hg, b.p. 158-160°C) giving second fraction enriched in **142c** 1:0.8 ratio **142c:150**. Product was recrystallised form ethanol to give **142c** (2.57g, 16%) as yellow crystals m.p. 72-73°C identical with authentic sample. δ 8.10 (1H, m, Ar-H), 7.45-7.35 (5H, s, Ar-H), 6.85-6.75 (2H, m, Ar-H), 5.15 (2H, s, O-CH_2-Ph). The first fraction contained benzyl alcohol. The third fraction contained a 1:4 mixture of **142c** and **150**.

Preparation of Compounds **143a-f** General Method.

A mixture of 1,2,3,4-tetrahydroisoquinoline (THIQ) **141a** or 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **141b**, K_2CO_3/Na_2CO_3 and the appropriate halonitroaryl compound **142a-c** were heated (100°C) in dimethylsulphoxide (DMSO) 50-100mls with stirring (4 hours). The mixture was poured into water and the product was extracted into dichloromethane. The organic layer was washed several times with water, dried ($MgSO_4$) and evaporated yielding the product. By this method the following compounds were prepared.

Preparation of *N*-(2-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline **143a**[90]

1,2,3,4-THIQ **141a** (15.0g, 112.6mmol), Na_2CO_3 (17.9g, 168.8mmol) and 1-fluoro-2-nitrobenzene **142a** (15.8g, 112.0mmol) gave compound **143a** (17.15g, 60%) as orange crystals, m.p. 100-102°C (ethanol), lit. m.p.[90] 100-102°C. $\nu_{max.}$ 1608, 1513, and 1332 cm^{-1}. δ 7.80 (1H, dd, J 8Hz and 1Hz, Ar-H), 7.55-6.85 (7H, m, Ar-H), 4.30 (2H, s, CH_2-N-), 3.40 (2H, t, J 8Hz, N-CH_2-CH_2-), 3.00 (2H, t, J 8Hz, N-CH_2-CH_2-).

Preparation of *N*-(2-nitro-5-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline **143b**[90]

1,2,3,4-THIQ **141a** (4.12g, 30.9mmol) , Na_2CO_3 (4.93g, 46.5mmol) and 3-fluoro-4-nitroanisole **142b** (5.37g, 31.4mmol) gave compound **143b** (8.05g, 91%) as orange oil, identical with authentic sample.[90] [Found: C,67.54; H,5.91; N,9.83, m/z 284.1133 $C_{16}H_{16}N_2O_3$ requires C,67.59; H,5.67; N,9.85%, M, 284.1133].$\nu_{max.}$ 1607, 1505, 1251, and 1091 cm^{-1}(liquid film). δ 7.96 (1H, d, J 9Hz, Ar-H), 7.20-7.00 (4H, m, Ar-H), 6.60 (1H, d, J 1Hz, Ar-H), 6.46 (1H, dd, J 7 and 1Hz, Ar-H), 4.30 (2H, s, CH_2-N), 3.86 (3H, s, O- CH_3), 3.41 (2H, t, J 6Hz, N-CH_2-CH_2-), 3.03 (2H, t, J 5Hz, N-CH_2-CH_2-).

Preparation of *N*-(2-nitro-5-benzyloxyphenyl)-1,2,3,4-tetrahydroisoquinoline **143c**

1,2,3,4-THIQ **141a** (1.52g, 11.4mmol), Na_2CO_3 (1.72g, 16.2mmol) and 2-fluoro-4-benzyloxynitrobenzene **142c** (2.57g, 10.8mmol) gave compound **143c** (2.97g, 79%) as yellow crystals, m.p. 95-98°C (ethanol). [Found: C,73.17; H,5.45; N,7.74 $C_{22}H_{20}N_2O_3$ requires C,73.32; H,5.59; N,7.77%]. $\nu_{max.}$ 1618, 1484, 1288, 1174 and 1139 cm^{-1}. δ 7.96 (1H, d, J 8Hz, Ar-H), 7.42-7.30 (5H, m, Ar-H), 7.18-7.00 (4H, m, Ar-H), 6.70 (1H, d, J 1Hz, Ar-H), 6.55 (1H, dd, J 8 and 1Hz, Ar-H), 5.10 (2H, s, O-CH_2-Ph), 4.28 (2H, s, CH_2-N-), 3.38 (2H, t, J 7Hz, N-CH_2-CH_2-), 3.02 (2H, t, J 7Hz, N-CH_2-CH_2-).

Preparation of 6,7-Dimethoxy-*N*-(2-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline **143d**

6,7-Dimethoxy-1,2,3,4-THIQ **141b** (3.50g, 18.0mmol), Na_2CO_3 (2.84g, 26.8mmol) and 1-fluoro-2-nitrobenzene **142a** (2.78g, 19.7mmol) gave compound **143d** (2.45g, 40%) as orange crystals, m.p. 131-133°C (ethanol). [Found: C,62.7; H,5.65; N,7.90 $C_{17}H_{18}N_2O_4$ requires C,62.7; H,5.85; N,8.10%]. $\nu_{max.}$ 1604, 1519, 1342, and 1115 cm^{-1}. δ 7.80 (1H, dd, J 8 and 1Hz, Ar-H), 7.50-6.85 (4H, m, Ar-H), 6.60 (1H, dd, J 8 and 1Hz, Ar-H), 4.20 (2H, s, CH_2-N-), 3.80 (6H, s, 2 x O-CH_3), 3.35 (2H, t, J 8Hz, N-CH_2-CH_2-), 2.90 (2H, t, J 8Hz, N-CH_2-CH_2-).

Preparation of 6,7-Dimethoxy-*N*-(2-nitro-5-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline **143e**

6,7-Dimethoxy-1,2,3,4-THIQ **141b** (6.64g, 34.2mmol), Na_2CO_3 (6.91g, 65.2mmol) and 3-fluoro-4-nitroanisole **142b** (5.10g, 29.8mmol) gave compound **143e** (10.1g, 93%) as orange crystals, m.p. 128-131°C (ethanol). [Found: C,62.66; H,5.69; N,8.05 $C_{18}H_{20}N_2O_5$ requires C,62.78; H,5.85; N,8.13%]. $\nu_{max.}$ 1610, 1518, 1301, 1175 and 1114 cm^{-1}. δ 7.95 (1H, d, J 8Hz, Ar-H), 6.70-6.35 (4H, m, Ar-H), 4.20 (2H, s, CH_2-N-), 3.80 (9H, s, 3 x O-CH_3), 3.30 (2H, t, J 8Hz, N-CH_2-CH_2-), 2.90 (2H, t, J 8Hz, N-CH_2-CH_2-).

Preparation of 6,7-Dimethoxy-*N*-(2-nitro-5-benzyloxyphenyl)-1,2,3,4-tetrahydro-isoquinoline **143f**

6,7-Dimethoxy-1,2,3,4-THIQ **141b** (1.59g, 8.2mmol), Na_2CO_3 (1.65g, 15.6mmol) and 2-fluoro-4-benzyloxynitrobenzene **142c** (1.85g, 7.8mmol) gave compound **143f** (4.02g, 86%) as yellow crystals, m.p. 156-159°C (ethanol). [Found: C,68.36; H,5.65; N,6.51 $C_{24}H_{24}N_2O_5$ requires C,68.56; H,5.75; N,6.66%]. $\nu_{max.}$ 1603, 1520, 1331, 1251 and 1117 cm^{-1}. δ 7.98 (1H, d, J 4Hz, Ar-H), 7.45-7.30 (5H, m, Ar-H), 6.65 (2H, d, J 2Hz, Ar-H), 6.59 (1H, s, Ar-H), 6.56 (1H, dd, J 3 and 1Hz, Ar-H), 5.10 (2H, s, O-CH_2-Ph), 4.20 (2H, s, CH_2-N-), 3.82 (6H, d, J 8Hz, 2 x O-CH_3), 3.37 (2H, t, J 6Hz, N-CH_2-CH_2-), 2.94 (2H, t, J 6Hz, N-CH_2-CH_2-).

Preparation of *N*-(2-nitro-5-hydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline **143g**

To 3-fluoro-4-nitrophenol **147** (4.00g, 25.5mmol) and triethylamine (3ml, 21.5mmol) in toluene (75ml), was added trimethylsilyl chloride (3.38ml, 26.6mmol) and the mixture heated to 80°C (18 hours) with stirring giving compound **151**. To compound **151** and triethylamine (3ml, 21.5mmol) was added 1,2,3,4-tetrahydroisoquinoline **141a** (3.56g, 26.7mmol) and the mixture refluxed for 4 hours with stirring. After cooling the mixture was poured into dil. HCl and extracted with ethyl acetate. The organic layer was washed with water dried ($MgSO_4$) and evaporated yielding **143g** (1.07g, 16%) as an orange solid, m.p. 153-156°C (ethanol). [Found: C,66.47; H,5.37; N,10.34, m/z 270.1014 $C_{15}H_{14}N_2O_3$ requires C,66.66; H,5.22; N,10.36%, M, 270.1004]. $\nu_{max.}$ 3500-3200 (broad), 1614, 1514, 1307, 1182 and 1088 cm^{-1}. δ 7.92 (1H, d, J 5Hz, Ar-H), 7.40-7.00 (4H, m, Ar-H), 6.90 (1H, d, J 1Hz, Ar-H), 6.40 (1H, dd, J 3 and 1Hz, Ar-H), 4.28 (2H, s, CH_2-N), 3.36 (2H, t, J 5Hz, N-CH_2-CH_2-), 3.02 (2H, t, J 5Hz, N-CH_2-CH_2-).

Preparation of *N*-(2-nitro-5-acetoxyphenyl)-1,2,3,4-tetrahydroisoquinoline **143h**

To compound **143g** (2.0g, 7.4mmol) in triethylamine (20ml), was added acetic anhydride (1ml, 11.2mmol) and the mixture stirred (24 hours) at room temperature. The mixture was poured onto water and extracted into dichloromethane. The organic layer was dried ($MgSO_4$) and evaporated yielding **143h** (2.01g, 87%) as orange crystals, m.p. 79-81°C (ethanol). [Found: C,65.41; H,4.92; N,8.88, $C_{17}H_{16}N_2O_4$ requires C,65.38; H,5.16; N,8.97%]. $\nu_{max.}$ 1753, 1621, 1502, 1282 1216 and 1171 cm^{-1}. δ 7.90 (1H, d, J 9Hz, Ar-H), 7.25-7.00 (4H, m, Ar-H), 6.92 (1H, d, J 1Hz, Ar-H), 6.69 (1H, dd, J 9 and 1Hz, Ar-H), 4.28 (2H, s, CH_2-N), 3.40 (2H, t, J 6Hz, N-CH_2-CH_2-), 3.00 (2H, t, J 6Hz, N-CH_2-CH_2-).

Preparation of *N*-(2-nitro-5-benzoylphenyl)-1,2,3,4-tetrahydroisoquinoline **143i**

To compound **143g** (1.0g, 3.7mmol) in triethylamine (10ml), was added benzoyl chloride (0.5ml, 4.3mmol) and the mixture stirred (24 hours) at room temperature. The mixture was poured onto dil. HCl and extracted into dichloromethane. The organic layer was washed with water, dried ($MgSO_4$), evaporated and washed with ethanol yielding **143i** (1.18g, 85%) as orange crystals, m.p. 95-98°C. δ 8.27 (2H, d, J 9Hz, Ar-H), 7.99 (1H, d, J 9Hz, Ar-H), 7.67 (1H, m, Ar-H), 7.56 (2H, m, Ar-H), 7.25-7.03 (4H, m, Ar-H), 7.01 (1H, d, J 1Hz, Ar-H), 6.83 (1H, dd, J 9 and 1Hz, Ar-H), 4.31 (2H, s, CH_2-N), 3.41 (2H, t, J 6Hz, N-CH_2-CH_2-), 3.03 (2H, t, J 6Hz, N-CH_2-CH_2-).

Preparation of *N*-(2-nitro-5-tetrahydroisoquinolinylphenyl)-1,2,3,4-tetrahydroisoquinoline **143j**

1,2,3,4-THIQ **141a** (3.51g, 26.4mmol), K_2CO_3 (2.59g, 18.7mmol) and 2,4-difluoronitrobenzene **148** (2.00g, 12.6mmol) gave compound **143j** (3.94, 82%) as orange crystals, m.p.131-133°C (ethanol/dichloromethane). [Found: C,74.14; H,6.06; N,10.81, m/z 385.1771 $C_{24}H_{23}N_3O_2$ requires C,74.78; H,6.01; N,10.90%, M, 385.1790]. $\nu_{max.}$ 1596, 1471, 1241, and 1181cm^{-1}. δ 8.12 (1H, d, J 9Hz, Ar-H), 7.25-7.10 (8H, m, Ar-H), 6.42 (1H, dd, J 9 and 1Hz, Ar-H), 6.36 (1H, d, J 1Hz, Ar-H), 4.52 (2H, s, CH_2-N-), 4.35 (2H, s, CH_2-N-), 3.65 (2H, t, J 6Hz, N-CH_2-CH_2-), 3.39 (2H, t, J 6Hz, N-CH_2-CH_2-), 3.07 (2H, t, J 6Hz, N-CH_2-CH_2-), 2.99 (2H, t, J 6Hz, N-CH_2-CH_2-).

Preparation of *N*-(2,4-dinitro-(5-tetrahydroisoquinolinyl)phenyl)-1,2,3,4-tetrahydroisoquinoline **143k**

1,2,3,4-THIQ **141a** (1.37g, 10.3mmol), K_2CO_3 (1.01g, 7.3mmol) and 1,3-difluoro-4,6-dinitrobenzene (1.00g, 4.9mmol) gave compound **143k** (2.63, 60%) as orange crystals. δ 8.73 (1H, s, Ar-H), 7.26-7.10 (8H, m, Ar-H), 6.49 (1H, s, Ar-H), 4.36 (4H, s, 2 x CH_2-N-), 3.48 (4H, t, J 6Hz, 2 x N-CH_2-CH_2-), 3.04 (4H, t, J 6Hz, 2 x N-CH_2-CH_2-).

Preparation of Compounds **144a-f** General Method.

Compounds **143a-f** in either acetic or propionic acid were heated at reflux. After cooling the mixture was poured onto ice/sodium hydroxide solution (until alkaline) and the product extracted into dichloromethane. The organic layer was washed several times with water, dried ($MgSO_4$) and evaporated yielding the product. By this method the following compounds were prepared.

Preparation of 5,6-Dihydrobenzimidazo[2,1-*a*]isoquinoline *N*-oxide **144a**

Compound **143a** (17.0g, 70.8mmol) in propionic acid (150ml) was refluxed (48 hours) with stirring yielding compound **144a** (14.9g, 94%) as yellow crystals m.p. 205-208°C (acetone). $\nu_{max.}$ 1654, 1488, 1307, 1240 and 1190 cm^{-1}. δ 9.50 (1H, d, J 6Hz, Ar-H), 8.00 (1H, d, J 6Hz, Ar-H), 7.55-7.20 (6H, m, Ar-H), 4.32 (2H, t, J 6Hz, N-CH_2-CH_2-), 3.35 (2H, t, J 6Hz, N-CH_2-CH_2-).

Preparation of 9-Methoxy-5,6-dihydrobenzimidazo[2,1-*a*]isoquinoline *N*-oxide **144b**

Compound **143a** (3.30g, 12.2mmol) in acetic acid (75ml) was refluxed (20 hours) with stirring yielding compound **144b** (2.09g, 68%) as brown crystals m.p. 204-206°C (acetone). [Found: C,69.25; H,5.45; N,10.00 $C_{16}H_{14}N_2O_2.0.75H_2O$ requires C,72.1; H,5.30; N,10.50%]. $\nu_{max.}$ 1622, 1490, 1240 and 1136 cm^{-1}. δ 9.45 (1H, dd, J 4 and 1Hz, Ar-H), 7.93 (1H, d, J 4Hz, Ar-H), 7.55-7.30 (3H, m, Ar-H), 7.00 (1H, dd, J 4 and 1Hz, Ar-H), 6.80 (1H, d, J 1Hz, Ar-H), 4.30 (2H, t, J 6Hz, N-CH_2-CH_2-), 3.90 (3H, s, O-CH_3), 3.35 (2H, t, J 6Hz, N-CH_2-CH_2-).

Preparation of 9-Benzyloxy-5,6-dihydrobenzimidazo[2,1-*a*]isoquinoline *N*-oxide **144c**

Compound **143c** (2.63g, 7.5mmol) in acetic acid (100ml) was refluxed (24 hours) with stirring yielding compound **144c** (1.39g, 54%) as brown crystals m.p. 187-189°C (acetone/ethanol). [Found: C,75.82; H,5.09; N,7.93, m/z 342.1357 $C_{22}H_{18}N_2O_2.0.5H_2O$ requires C,77.17; H,5.30; N,8.18%, M, 342.1368]. $\nu_{max.}$ 1618, 1484, 1234 and 1174 cm^{-1}. δ 9.47 (1H, dd, J 7 and 1Hz, Ar-H), 7.95 (1H, d, J 8Hz, Ar-H), 7.55-7.30 (8H, m, Ar-H), 7.10 (1H, dd, J 8 and 1Hz, Ar-H), 6.90 (1H, d, J 1Hz, Ar-H), 5.15 (2H, s,O-CH_2-Ph), 4.30 (2H, t, J 7Hz, N-CH_2-CH_2-), 3.30 (2H, t, J 7Hz, N-CH_2-CH_2-).

Preparation of 2,3-Dimethoxy 5,6-dihydrobenzimidazo[2,1-*a*]isoquinoline *N*-oxide **144d**

Compound **143d** (3.09g, 10.3mmol) in propionic acid (75ml) was refluxed (12 hours) with stirring yielding compound **144d** (2.13g, 73%) as creamy yellow crystals, m.p. 229-231°C (acetone). $\nu_{max.}$ 1609, 1498, 1257 and 1147 cm^{-1}. δ 9.20 (1H, s, Ar-H), 7.95 (1H, m, Ar-H), 7.43-7.30 (3H, m, Ar-H), 6.83 (1H, d, J 1Hz, Ar-H), 4.30 (2H, t, J 8Hz, N-CH_2-CH_2-), 4.03 (3H, d, J 1Hz, O-CH_3), 3.95 (3H, d, J 1Hz, O-CH_3), 3.23 (2H, t, J 8Hz, N-CH_2-CH_2-).

Preparation of 2,3,9-Trimethoxy-5,6-dihydrobenzimidazo[2,1-*a*]isoquinoline *N*-oxide **144e**

Compound **143e** (10.0g, 30.4mmol) in acetic acid (150ml) was refluxed (24 hours) with stirring yielding compound **144e** (5.29g, 50%) as white crystals m.p. 231-233°C (acetone/ethanol). [Found: C,59.63; H,6.26; N,7.66, m/z 326.1267 $C_{18}H_{18}N_2O_4.2H_2O$ requires C,66.25; H,5.56; N,8.58%, M, 326.1267]. $\nu_{max.}$ 1620, 1496, 1245 and 1147 cm^{-1}. δ 9.20 (1H, s, Ar-H), 7.85 (1H, d, J 10Hz, Ar-H), 7.00 (1H, dd, J 9 and 1Hz, Ar-H), 6.82-6.70 (2H, m, Ar-H), 4.20 (2H, t, J 7Hz, N-CH_2-CH_2-), 4.00 (3H, s, O-CH_3), 3.80 (6H, d, J 9Hz, 2 x O-CH_3), 3.20 (2H, t, J 8Hz, N-CH_2-CH_2-).

Preparation of 2,3-Dimethoxy-9-benzyloxy-5,6-dihydrobenzimidazo[2,1-*a*]isoquinoline *N*-oxide **144f**

Compound **143f** (4.02g, 9.8mmol) in acetic acid (75ml) was refluxed (24 hours) with stirring yielding compound **144f** (2.81g, 72 %) as brown crystals m.p. 236-240°C (acetone/ethanol). [Found: C,65.79; H,5.73; N,6.36, m/z 402.1581 $C_{24}H_{22}N_2O_4.2H_2O$ requires C,71.63; H,5.51; N,6.96%, M, 402.1580].$\nu_{max.}$ 1622, 1495, 1220 and 1152 cm^{-1}. δ 9.18 (1H, s, Ar-H), 7.85 (1H, d, J 7Hz, Ar-H), 7.55-7.30 (5H, m, Ar-H), 7.05 (1H, dd, J 7 and 1Hz, Ar-H), 6.86 (1H, d, J 1Hz, Ar-H), 6.80 (1H, s, Ar-H), 5.15 (2H, s, O-CH_2-Ph), 4.22 (2H, t, J 7Hz, N-CH_2-CH_2-), 4.05 (3H, d, J 1Hz, O-CH_3), 3.95 (3H, d, J 1Hz, O-CH_3), 3.20 (2H, t, J 8Hz, N-CH_2-CH_2-).

Attempted cyclisation of compounds **143g-k**.

Attempts were made to cyclise compounds **143g-k** using established procedure. Analysis using ^{1}H-nmr spectroscopy showed no presence of product in compounds **143g-i** and trace amounts of product in **143j-k**, however isolation of products was difficult due to the poor conversion.

Preparation of Compounds **145a-f** *(General Method a)*

Deoxygenation of compounds was achieved by dissolving the appropriate *N*-oxide in chloroform to which was added phosphorus trichloride and the resultant mixture heated under reflux for 2 hours with stirring. The mixture was poured onto ice/sodium hydroxide solution and the product extracted into dichloromethane. The organic layer was washed several times with water, dried ($MgSO_4$) and evaporated yielding the product. By this method the following compounds were prepared.

Preparation of 5,6-Dihydrobenzimidazo[2,1-*a*]isoquinoline **145a**

N-Oxide **144a** (19.33g, 81.9mmol) and PCl_3 (8.48ml, 97.2mmol) gave compound **145a** (17.23g, 97%) as yellow crystals m.p. 207-209°C (ethanol). $\nu_{max.}$ 1653, 1458, 1229 and 1156 cm^{-1}. δ 8.22 (1H, m, Ar-H), 7.75 (1H, m, Ar-H), 7.35-7.10 (6H, m, Ar-H), 4.23 (2H, t, J 7Hz, N-CH_2-CH_2-), 3.20 (2H, t, J 7Hz, N-CH_2-CH_2-).

Preparation of 9-Methoxy-5,6-dihydrobenzimidazo[2,1-*a*]isoquinoline **145b**

N-Oxide **144b** (2.00g, 7.5mmol) and PCl_3 (0.79ml, 9.1mmol) gave compound **131** (1.14g, 61%) as brown crystals, m.p. 201-205°C (acetone). [Found: C,67.60; H,5.45; N,9.75, m/z 266.1068 $C_{16}H_{14}N_2O.2H_2O$ requires C, 76.70; H,5.60; N,11.20%, M, 266.1055]. $\nu_{max.}$ 1624, 1493, 1245 and 1176 cm^{-1}. δ 8.20 (1H, m, Ar-H), 7.90 (1H, d, J 9Hz, Ar-H), 7.50-7.30 (3H, m, Ar-H), 7.00-6.80 (2H, m, Ar-H), 4.30 (2H, t, J 10Hz, N-CH_2-CH_2-), 3.90 (3H, s, O-CH_3), 3.30 (2H, t, J 10Hz, N-CH_2-CH_2-).

Preparation of 9-Benzyloxy-5,6-dihydrobenzimidazo[2,1-*a*]isoquinoline **145c**

N-Oxide **144c** (1.39g, 4.1mmol) and PCl_3 (0.42ml, 4.8mmol) gave compound **145c** (0.81g, 62%) as brown crystals, m.p. 151-152°C (ethanol). [Found: C,80.90; H,5.59; N,8.51. $C_{22}H_{18}N_2O$ requires C,80.96; H,5.56; N,8.58%]. $\nu_{max.}$ 1623, 1481, 1237 and 1165 cm^{-1}. δ 8.25 (1H, d, J 5Hz, Ar-H), 7.75 (1H, d, J 9Hz, Ar-H), 7.55-7.35 (9H, m, Ar-H), 7.00 (1H, dd, J 10 and 1Hz, Ar-H), 6.90 (1H, d, J 1Hz, Ar-H), 5.15 (2H, s, O-CH_2-Ph), 4.30 (2H, t, J 10Hz, N-CH_2-CH_2-), 3.30 (2H, t, J 10Hz, N-CH_2-CH_2-).

Preparation of 2,3-Dimethoxy 5,6-dihydrobenzimidazo[2,1-*a*]isoquinoline **145d**

N-Oxide **144d** (0.50g, 1.7mmol) and PCl_3 (0.17ml, 1.9mmol) gave compound **145d** (0.19g, 41%) as orange crystals m.p. 190-192°C (ethanol). [Found: C,72.23; H,5.75; N,9.84 $C_{17}H_{16}N_2O_2$ requires C,72.84; H,5.75; N,9.99 %]. $\nu_{max.}$ 1623, 1481, 1237 and 1165 cm^{-1}. δ 7.82 (2H, m, Ar-H), 7.36-7.24 (3H, m, Ar-H), 6.80 (1H, s, Ar-H), 4.32 (2H, t, J 7Hz, N-CH_2-CH_2-), 4.01 (3H, s, O-CH_3), 3.95 (3H, s, O-CH_3), 3.23 (2H, t, J 7Hz, N-CH_2-CH_2-).

Preparation of 2,3,9-Trimethoxy-5,6-dihydrobenzimidazo[2,1-*a*]isoquinoline **145e**

N-Oxide **144e** (4.00g, 12.2mmol) and PCl_3 (1.27ml, 14.5mmol) gave compound **145e** (2.96g, 78%) as creamy white plates, m.p. 243-245°C (ethanol). [Found: C,58.15; H,5.55; N,7.45, m/z 310.1315 $C_{18}H_{18}N_2O_3.3H_2O$ requires C,69.60; H,5.80; N,9.00%, M, 310.1317]. $\nu_{max.}$ 1621, 1510, 1254 and 1177 cm^{-1}. δ 7.90 (1H, s, Ar-H), 7.70 (1H, d, J 10Hz, Ar-H), 7.00-6.70 (3H, m, Ar-H), 4.30 (2H, t, J 10Hz, N-CH_2-CH_2-), 4.00 (3H, s, O-CH_3), 3.90 (6H, d, J 10Hz, 2 x O-CH_3), 3.20 (2H, t, J 10Hz, N-CH_2-CH_2-).

Preparation of 2,3-Dimethoxy-9-benzyloxy-5,6-dihydrobenzimidazo[2,1-*a*]isoquinoline **145f**

N-Oxide **144f** (2.80g, 6.9mmol) and PCl_3 (0.72ml, 8.3mmol) gave compound **145f** (0.37g, 14%) as orange crystals, m.p. 160-162°C (ethanol). [Found: C,74.60; H,5.74; N,7.25, m/z 386.1619 $C_{24}H_{22}N_2O_3$ requires C,72.88; H,5.67; N,7.06%, M, 386.1630]. $\nu_{max.}$ 1627, 1483, 1236 and 1135 cm^{-1}. δ 7.75 (1H, s, Ar-H), 7.65 (1H, d, J 10Hz, Ar-H), 7.50-7.30 (5H, m, Ar-H), 7.00 (1H, dd, J 7 and 1Hz, Ar-H), 6.90 (1H, d, J 1Hz, Ar-H), 6.80 (1H, s, Ar-H), 5.15 (2H, s, O-CH_2-Ph), 4.22 (2H, t, J 8Hz, N-CH_2-CH_2-), 4.00 (3H, s, O-CH_3), 3.90 (3H, s, O-CH_3), 3.20 (2H, t, J 8Hz, N-CH_2-CH_2-).

Preparation of Compounds **145a,b & e** *(General Method b)*

Deoxygenation of compounds was achieved by dissolving the appropriate *N*-oxide in anhydrous dichloromethane to which was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (2 equivalents) and the resultant mixture heated to reflux for 18 hours with stirring. The mixture was poured onto sodium hydroxide solution and extracted with further dichloromethane. The organic layer was washed several times with water, dried ($MgSO_4$) and evaporated yielding the product. By this method the following compounds were prepared.

Preparation of 5,6-Dihydrobenzimidazo[2,1-*a*]isoquinoline **145a**

N-Oxide **144a** (0.20g, 0.9mmol) and DDQ (0.38g, 1.7mmol) gave compound **145a** (0.12g, 66%) as yellow oil, identical with an authentic sample. δ 8.24 (1H, m, Ar-H), δ 7.80 (1H, m, Ar-H), 7.40-7.15 (6H, m, Ar-H), 4.23 (2H, t, J 7Hz, N-CH_2-CH_2-), 3.22 (2H, t, J 7Hz, N-CH_2-CH_2-).

Preparation of 9-Methoxy-5,6-dihydrobenzimidazo[2,1-*a*]isoquinoline **145b**

N-Oxide **144b** (0.02g, 0.07mmol) and DDQ (0.04g, 0.18mmol) gave compound **145b** (0.01g, 55%) as orange oil, identical with an authentic sample. δ 8.22 (1H, dd, J 9 and 1Hz, Ar-H), 7.69 (1H, d, J 9Hz, Ar-H), 7.43-7.28 (3H, m, Ar-H), 6.91 (1H, dd, J 9 and 1Hz, Ar-H), 6.81 (1H, d, J 1Hz, Ar-H), 4.28 (2H, t, J 9Hz, N-CH_2-CH_2-), 3.89 (3H, s, O-CH_3), 3.28 (2H, t, J 9Hz, N-CH_2-CH_2-).

Preparation of 2,3,9-Trimethoxy-5,6-dihydrobenzimidazo[2,1-*a*]isoquinoline **145e**

N-Oxide **144e** (0.10g, 0.3mmol) and DDQ (0.14g, 0.6mmol) gave compound **145e** (0.04g, 47%) as brown oil, identical with an authentic sample. δ 7.71 (1H, s, Ar-H), 7.68 (1H, d, J 9Hz, Ar-H), 6.90 (1H,dd, J 9 and 2Hz, Ar-H), 6.78 (1H,d, J 2Hz, Ar-H), 6.76 (1H,s, Ar-H), 4.23 (2H, t, J 9Hz, N-CH_2-CH_2-), 4.00 (3H, d, J 1Hz, O-CH_3), 3.93 (3H, d, J 1Hz, O-CH_3), 3.87 (3H, d, J 1Hz, O-CH_3), 3.19 (2H, t, J 9Hz, N-CH_2-CH_2-).

Preparation of compounds **139a-b**

Preparation of 9-Hydroxy-5,6-dihydrobenzimidazo[2,1-*a*]isoquinoline **139a** *(method a)*

To compound **145b** (0.10g, 0.4mmol) in acetic acid (10ml), was added hydroiodic acid (0.12ml, 1.6mmol) and the mixture heated under reflux (6 hours) with stirring. After cooling sodium hydroxide solution was added to neutralise the brown mixture which was then extracted with dichloromethane. The organic layer was washed with water and dried ($MgSO_4$). Analysis using ^{1}H-nmr spectroscopy showed only starting material to be present.

Preparation of 9-Hydroxy-5,6-dihydrobenzimidazo[2,1-*a*]isoquinoline **139a** *(method b)*

To compound **145c** (0.15g, 0.45mmol) in carbon tetrachloride (10ml), was added *N*-bromosuccinimide (0.08g, 0.45mmol) and the mixture heated under reflux (4 hours) with stirring. After cooling the mixture was poured onto sodium hydroxide solution and extracted with dichloromethane. The organic layer was washed with water and dried ($MgSO_4$). Analysis using ^{1}H-nmr spectroscopy shows predominantly starting material to be present.

Preparation of 9-Hydroxy-5,6-dihydrobenzimidazo[2,1-*a*]isoquinoline **139a** *(method c)*

To compound **145c** (0.10g, 0.31mmol) in cyclohexene (10ml) and ethanol (1ml), was added 5% palladium on carbon (0.08g, 0.04mmol) and the mixture heated under reflux (72 hours) with stirring. After cooling the mixture was filtered and washed through with dichloromethane. The organic layer was washed with water and dried ($MgSO_4$) yielding brown oil which was fractionated by column chromatography (silica gel, eluent petroleum ether b.p. 60-80°C : ethyl acetate 2:1). Analysis using ^{1}H-nmr spectroscopy was inconclusive due to insolubility in common solvents.

Preparation of 9-Hydroxy-5,6-dihydrobenzimidazo[2,1-*a*]isoquinoline **139a** *(method d)*

To compound **145c** (0.10g, 0.31mmol) and ammonium formate (0.02g, 0.21mmol) in methanol (10ml), was added 5% palladium on carbon (0.05g, 0.02mmol) and the mixture heated under reflux (4 hours) with stirring. After cooling the mixture was filtered, poured onto sodium hydroxide solution, neutralised using dil. HCl then extracted with dichloromethane. The organic layer was washed with water, dried ($MgSO_4$) and evaporated yielding **139a** (0.01g, 14%) as brown oil. δ 8.22 (1H, m, Ar-H), 7.60 (1H, d, J 9Hz, Ar-H), 7.40-7.20 (3H, m, Ar-H), 6.80-6.75 (2H, m, Ar-H), 4.23 (2H, t, J 8Hz, N-CH_2-CH_2-), 3.23 (2H, t, J 8Hz, N-CH_2-CH_2-).

Preparation of 2,3-Dimethoxy-9-hydroxy-5,6-dihydrobenzimidazo[2,1-*a*]isoquinoline **139b**

To compound **145f** (0.50g, 1.5mmol) and ammonium formate (0.16g, 2.5mmol) in methanol (50ml), was added 5% palladium on carbon (0.50g, 0.23mmol) and the mixture heated under reflux (5 hours) with stirring. After cooling the mixture was filtered, poured onto sodium hydroxide solution, neutralised using dil. HCl then extracted with dichloromethane. The organic layer was washed with water, dried ($MgSO_4$) and evaporated yielding **139b** (0.05g, 13%) as brown crystals m.p. 266-269°C (ethanol). [Found: C,66.95; H,5.27; N,8.98 m/z 296.1162 $C_{17}H_{16}N_2O_3.0.5H_2O$ requires C,68.91; H,5.44; N,9.45%, M, 296.1161]. $\nu_{max.}$ 1616, 1477, 1280, 1234 and 1171 cm^{-1}. δ 7.73 (1H, s, Ar-H), 7.61 (1H, d, J 9Hz, Ar-H), 6.79 (3H, m, Ar-H), 4.23 (2H, t, J 7Hz, N-CH_2-CH_2-), 3.97 (3H, d, J 1Hz, O-CH_3), 3.94 (3H, d, J 1Hz, O-CH_3), 3.20 (2H, t, J 7Hz, N-CH_2-CH_2-).

Attempted preparation of compounds **146a** and **146e**

Attempted preparation of Benzimidazo[2,1-*a*]isoquinoline **146a** *(method a)*

To compound **145a** (0.10g, 0.45mmol) in p-cymene (10ml), was added 5% palladium on carbon (0.25g, 0.12mmol) and the mixture heated under reflux (2 hours) with stirring. After cooling the mixture was filtered, distilled under pressure to remove p-cymene and extracted with dichloromethane. The organic layer was washed with water and dried ($MgSO_4$). Analysis using ^{1}H-nmr spectroscopy and GC-mass spectrometry showed only starting material to be present.

Attempted preparation of Benzimidazo[2,1-*a*]isoquinoline **146a** *(method b)*

To compound **145a** (0.10g, 0.45mmol) in anhydrous toluene (20ml), was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.10g, 0.44mmol) and the mixture heated under reflux (4 hours) with stirring. After cooling the mixture was poured onto sodium hydroxide solution and extracted with dichloromethane. The organic layer was washed with water and dried ($MgSO_4$). Analysis using ^{1}H-nmr spectroscopy showed only starting material to be present.

Attempted preparation of 2,3,9-Trimethoxybenzimidazo[2,1-*a*]isoquinoline **146e** *(method b)*

To compound **145e** (0.10g, 0.32mmol) in anhydrous 1,4-dioxan (15ml), was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.07g, 0.31mmol) and the mixture heated under reflux (4 hours) with stirring. After cooling the mixture was poured onto sodium hydroxide solution and extracted with dichloromethane. The organic layer was washed with water and dried ($MgSO_4$) yielding brown oil which was fractionated by column chromatography (silica gel, eluent chloroform : methanol 10:1). Analysis of column fractions by ^{1}H-nmr spectroscopy showed only starting material to be present.

Attempted preparation of Benzimidazo[2,1-*a*]isoquinoline **146a** *(method c)*

To compound **145a** (0.10g, 0.45mmol) in dichloromethane or carbon tetrachloride (20ml), was added *N*-bromosuccinimide (0.09g, 0.54mmol) and the mixture heated under reflux (3 hours) with stirring. After cooling the mixture was poured onto sodium hydroxide solution and extracted with dichloromethane. The organic layer was washed with water and dried ($MgSO_4$). Analysis using ^{1}H-nmr spectroscopy showed only starting material to be present.

Attempted preparation of Benzimidazo[2,1-*a*]isoquinoline **146a** *(method d)*

To compound **145a** (0.10g, 0.45mmol) in DMSO (20ml), was added potassium hydroxide (0.05g, 0.89mmol) and the mixture warmed to 50°C (12 hours) with stirring. After cooling the mixture was poured onto water and extracted with dichloromethane. The organic layer was washed with water and dried ($MgSO_4$). Analysis using ^{1}H-nmr spectroscopy showed only starting material to be present.

Attempted preparation of 2,3-Trimethoxybenzimidazo[2,1-*a*]isoquinoline **146e** *(method d)*

To compound **145e** (0.10g, 0.32mmol) in DMSO (10ml), was added potassium hydroxide (0.04g, 0.71mmol) and the mixture warmed to 50°C (4 hours) with stirring. After cooling the mixture was poured onto water and extracted with dichloromethane. The organic layer was washed with water and dried ($MgSO_4$). Analysis using ^{1}H-nmr spectroscopy showed only starting material to be present.

Attempted preparation of Benzimidazo[2,1-*a*]isoquinoline **146a** *(method e)*

To compound **145a** (0.10g, 0.45mmol) in dichloromethane (10ml) and 18-crown-6 (0.02g) cooled in ice, was added potassium permanganate (0.14g, 1.8mmol) and the mixture stirred at room temperature (24 hours). The mixture was poured onto sodium metabisulphite solution and extracted with dichloromethane. The organic layer was washed with water and dried ($MgSO_4$). Analysis using ^{1}H-nmr spectroscopy showed only starting material to be present.

Preparation of Compounds **158a-b** General Method.

Compounds **144a,b & e** in acetic anhydride with sodium acetate were heated at reflux. After cooling the mixture was stirred overnight in sodium hydroxide solution and the product extracted into dichloromethane (dichloromethane). The organic layer was washed several times with water, dried ($MgSO_4$) and evaporated yielding the product. By this method the following compounds were prepared.

Preparation of 9-Methoxy-8-acetoxy-5,6-dihydrobenzimidazo[2,1-*a*]isoquinoline **158a**

Compound **144b** (0.50g, 1.9mmol) in acetic anhydride (20ml) and sodium acetate (0.30g, 3.7mmol) was heated under reflux (4 hours) with stirring yielding compound **158a** (0.28g, 50 %) as brown crystals, m.p. 137-138°C (ethanol). [Found: C,67.01; H,5.54; N,8.73, m/z 308.1147 $C_{18}H_{16}N_2O_3.0.75H_2O$ requires C,70.12; H,5.23; N,9.09%, M, 308.1161]. $\nu_{max.}$ 1762, 1638, 1263, 1174 and 1094 cm^{-1}. δ 8.22 (1H, m, Ar-H), 7.60 (1H, dd, J 6 and 1Hz, Ar-H), 7.44-7.25 (3H, m, Ar-H), 7.00 (1H, dd, J 6 and 1Hz, Ar-H), 4.43 (2H, t, J 7Hz, N-CH_2-CH_2-), 3.90 (3H, s, O-CH_3), 3.23 (2H, t, J 7Hz, N-CH_2-CH_2-), 2.41 (3H, s, CO-CH_3).

Preparation of 2,3,9-Trimethoxy-8-acetoxy-5,6-dihydrobenzimidazo[2,1-*a*]isoquinoline **158b**

Compound **144e** (0.10g, 0.3mmol) in acetic anhydride (5ml) and sodium acetate (0.05g, 0.6mmol) was refluxed (4 hours) with stirring yielding compound **158b** (0.02g, 20%) as brown crystals, m.p. 254-256°C (ethanol). [Found: C,65.00; H,5.21; N,7.34, m/z 368.1378 $C_{20}H_{20}N_2O_5$ requires C,65.21; H,5.47; N,7.60%, M, 368.1373]. $\nu_{max.}$ 1764, 1638, 1264, 1163 and 1097 cm^{-1}. δ 7.75 (1H, s, Ar-H), 7.62 (1H, d, J 6Hz, Ar-H), 7.00 (1H, d, J 6Hz, Ar-H), 6.78 (1H, s, Ar-H), 4.48 (2H, t, J 7Hz, N-CH_2-CH_2-), 4.00 (3H, s, O-CH_3), 3.95 (3H, s, O-CH_3), 3.90 (3H, s, O-CH_3), 3.20 (2H, t, J 7Hz, N-CH_2-CH_2-), 2.41 (3H, s, CO-CH_3).

Attempted preparation of 2,3-Dimethoxy-8-acetoxy-5,6-dihydrobenzimidazo[2,1-*a*]isoquinoline **158c**

Compound **144d** (0.25g, 0.8mmol) in acetic anhydride (20ml) and sodium acetate (0.15g, 1.8mmol) was refluxed (4 hours) with stirring yielding brown solid (0.19g). Analysis using ^{1}H-nmr spectroscopy showed only starting material to be present.

3.1.2 Experimental for strategy B

Preparation of 1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid hydrochloride **167**[108]

To DL-phenylalanine (20.0g, 121mmol) in conc. HCl (155ml) was added formaldehyde (46ml) and the white mixture heated to 95-100°C (4 hours) with stirring. After cooling overnight solid was filtered under pressure, washed with water and cold acetone yielding **167** (21.6g, 84%) as white solid, m.p. > 300°C, lit. m.p.[108] > 280°C.

Compounds **168a-c** were synthesised using same methodology as compounds **143a-f**

Preparation of *N*-(2-Nitrophenyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid **168a**

1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid **167** (4.00g, 22.7mmol), K_2CO_3 (5.60g, 40.7mmol) and 2-fluoronitrobenzene **142a** (3.36g, 23.8mmol) gave compound **168a** (5.89g, 87%) as orange crystals, m.p.141-143°C (ethanol). $\nu_{max.}$ 1699, 1602, 1508, 1334 and 1235cm^{-1}. δ 7.82 (1H, dd, J 6 and 1Hz, Ar-H), 7.55-7.00 (7H, m, Ar-H), 4.80 (1H, d, J 9Hz, CH_2-N-CH-), 4.35 (1H, dd, J 4 and 1Hz, CH_2-CH-CO_2H), 4.10 (1H, d, J 9Hz, CH_2-N-CH-), 3.49 (1H, dd, J 9 and 3Hz, N-CH-CH_2-), 3.35 (1H, dd, J 9 and 1Hz, N-CH-CH_2-).

Preparation of *N*-(2-Nitro-5-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid **168b**

1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid **167** (2.19g, 12.5mmol), K_2CO_3 (2.44g, 17.7mmol) and 3-fluoro-4-nitroanisole **142b** (2.03g, 11.9mmol) gave compound **168b** (3.39g, 88%) as an orange oil. $\nu_{max.}$ 1709, 1605, 1514, 1331, 1235 and 1160cm^{-1}. δ 8.02 (1H, d, J 6Hz, Ar-H), 7.20-7.00 (4H, m, Ar-H), 6.74 (1H, d, J 1Hz, Ar-H), 6.59 (1H, dd, J 7 and 1Hz, Ar-H), 4.76 (1H, d, J 9Hz, CH_2-N-CH-), 4.33 (1H, dd, J 2 and 1Hz, CH_2-CH-CO_2H), 4.12 (1H, d, J 9Hz, CH_2-N-CH-), 3.85 (3H, s, O-CH_3), 3.55 (1H, dd, J 13 and 4Hz, N-CH-CH_2-), 3.35 (1H, dd, J 12 and 1Hz, N-CH-CH_2-).

Preparation of Compounds **169a-c** General Method.

A mixture of the appropriate 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid precursor **168a-c**, K_2CO_3 and dimethylsulphate were heated under reflux (2 hours) with stirring in acetone. The mixture was poured into water and the product was extracted into dichloromethane (dichloromethane). The organic layer was washed several times with water, dried ($MgSO_4$) and evaporated yielding the product. By this method the following compounds were prepared.

Preparation of Methyl *N*-(2-Nitrophenyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **169a**

Compound **168a** (5.89g, 19.8mmol), K_2CO_3 (4.00g, 28.9mmol) and dimethylsulphate (2.00ml, 21.2mmol) gave compound **169a** (3.08g, 52%) as yellow crystals, m.p.111-112°C (ethanol). [Found: C,65.38; H,5.16; N,8.97, $C_{17}H_{16}N_2O_4$ requires C,65.40; H,4.60; N,8.85%]. $\nu_{max.}$ 1727, 1606, 1524, 1342, 1203 and 1164 cm^{-1}. δ 7.84 (1H, d, J 8Hz, Ar-H), 7.57-7.44 (2H, m, Ar-H), 7.19-7.06 (5H, m, Ar-H), 4.92 (1H, d, J 15Hz, CH_2-N-CH-), 4.31 (1H, dd, J 4 and 1Hz, CH_2-CH- CO_2CH_3), 4.16 (1H, d, J 15Hz, CH_2-N-CH-), 3.57 (3H, s, CO_2- CH_3), 3.58 (1H, dd, J 16 and 4Hz, N-CH-CH_2-), 3.25 (1H, dd, J 16 and 1Hz, N-CH-CH_2-).

Preparation of Methyl *N*-(2-Nitro-5-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **169b**

Compound **168b** (3.39g, 10.7mmol), K_2CO_3 (2.13g, 15.4mmol) and dimethylsulphate (1.01ml, 10.7mmol) gave compound **169b** (2.39g, 69%) as yellow crystals, m.p.108-111°C (ethanol). [Found: C,63.28; H,5.09; N,8.05, $C_{18}H_{18}N_2O_5$ requires C,63.15; H,5.30; N,8.18%]. $\nu_{max.}$ 1736, 1604, 1505, 1325, 1202 and 1088 cm^{-1}. δ 8.02 (1H, d, J 9Hz, Ar-H), 7.19-7.07 (4H, m, Ar-H), 6.86 (1H, d, J 1Hz, Ar-H), 6.56 (1H, dd, J 9 and 1Hz, Ar-H), 4.89 (1H, d, J 15Hz, CH_2-N-CH-), 4.31 (1H, dd, J 6 and 2Hz, CH_2-CH- CO_2CH_3), 4.22 (1H, d, J 15Hz, CH_2-N-CH-), 3.90 (3H, s, O- CH_3), 3.65 (1H, dd, J 16 and 6Hz, N-CH-CH_2-), 3.57 (3H, s, CO_2- CH_3), 3.25 (1H, dd, J 17 and 2Hz, N-CH-CH_2-).

Preparation of Methyl *N*-(2-Nitro-5-benzyloxyphenyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **169c**

1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid **167** (1.94g, 11.0mmol), K_2CO_3 (2.17g, 15.7mmol) and 2-fluoro-4-benzyloxy nitrobenzene **142c** (2.50g, 10.5mmol) gave compound **168c** (2.29g, 54%) as orange oil. Due to insolubility in common solvents Analysis using ^{1}H-nmr spectroscopy proved inconclusive. Compound **168c** (2.29g, 5.9mmol), K_2CO_3 (1.17g, 8.5mmol) and dimethylsulphate (0.56ml, 5.9mmol) gave compound **169c** (1.13g, 47%) as yellow crystals, m.p.111-114°C (ethanol). [Found: C,69.02; H,5.12; N,6.46, $C_{24}H_{22}N_2O_5$ requires C,68.89; H,5.30; N,6.69%]. $\nu_{max.}$ 1741, 1610, 1509, 1340, 1198 and 1095 cm^{-1}. δ 8.02 (1H, d, J 9Hz, Ar-H), 7.46-7.35 (5H, m, Ar-H), 7.19-7.05 (4H, m, Ar-H), 6.93 (1H, d, J 2Hz, Ar-H), 6.63 (1H, dd, J 10 and 2Hz, Ar-H), 5.15 (2H, s, O-CH_2-Ph), 4.85 (1H, d, J 15Hz, CH_2-N-CH-), 4.30 (1H, dd, J 6 and 2Hz, CH_2-CH- CO_2CH_3), 4.15 (1H, d, J 15Hz, CH_2-N-CH-), 3.65 (1H, dd, J 17 and 6Hz, N-CH-CH_2-), 3.55 (3H, s, CO_2- CH_3), 3.25 (1H, dd, J 17 and 2Hz, N-CH-CH_2-).

Attempted cyclisation of compounds **168a** and **169a**

Attempts were made to cyclise compounds **168a** and **169a** using established procedure. Analysis using ^{1}H-nmr spectroscopy showed no presence of product in complex reaction mixtures.

Attempted preparation of compound **170a**

Attempted preparation of *N*-(2-Nitrophenyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide **170a** (*method a*)

Compound **168a** (0.1g, 0.3mmol), pyridine (2ml) and phosphorus trichloride (0.03ml, 0.3mmol) in chloroform (5ml) was refluxed (2 hours) with stirring. After cooling 0.880 ammonia solution (25ml) was added and the mixture stirred (5 minutes) at room temperature. The reaction mixture was washed with water and extracted into dichloromethane. Evaporation of dichloromethane gave red solid (0.12g) that was dried in a dessicator over Conc. H_2SO_4 to remove traces of pyridine. Analysis using ^{1}H-nmr spectroscopy showed complex mixture.

Attempted preparation of *N*-(2-Nitrophenyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide **170a** (*method b*)

Compound **168a** (1.50g, 5.0mmol) in thionyl chloride (5ml, 25.6mmol) was refluxed (2 hours) with stirring. After cooling the mixture was distilled under pressure to remove excess thionyl chloride yielding **173a** as red oil (1.78g, 112 % crude). To 0.880 ammonia solution (75ml) and ammonium carbonate (0.25g, 0.8mmol), compound **173a** (1.78g) was added and the mixture stirred (5 minutes) at room temperature, yielding a red solid (1.25g, 83 %) which was dried over phosphorus pentoxide. Analysis using ^{1}H-nmr spectroscopy showed complex mixture.

Attempted preparation of *N*-(2-Nitrophenyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide **170a** *(method c)*

To compound **168a** (0.25g, 0.8mmol) in 0.880 ammonia solution (5ml)/dichloromethane (25ml), was added dicyclohexyldicarboimidazole (0.18g, 0.9mmol) and the mixture stirred (18 hours) at room temperature. The mixture was poured onto water and extracted with dichloromethane. The organic layer was washed with water and dried ($MgSO_4$). Analysis using ^{1}H-nmr spectroscopy showed only starting material to be present.

Attempted preparation of *N*-(2-Nitrophenyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide **170a** *(method d)*

Compound **168a** (0.25g, 0.8mmol) in t-butanol (10ml) and triethylamine (0.14ml, 1.9mmol), was added diphenylphosphorylazide (0.18ml, 0.8mmol) and the mixture heated under reflux (4 hours) with stirring. After distillation of the t-butanol the mixture was poured onto sodium hydroxide solution and extracted with dichloromethane. The organic layer was washed with water and dried ($MgSO_4$). Analysis using ^{1}H-nmr spectroscopy showed only starting material to be present.

Attempted preparation of *N*-(2-Nitrophenyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide **170a** *(method e)*

Compound **169a** (4.47g, 14.3mmol) in 0.880 ammonia solution (75ml) was stoppered and stirred at room temperature (18 hours). After stopper removal left for 2 hours then the mixture was poured onto water and extracted with dichloromethane. The organic layer was washed with water and dried ($MgSO_4$). Analysis using ^{1}H-nmr spectroscopy showed only starting material to be present.

Attempted preparation of *N*-(2-Nitrophenyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide **170a** *(method f)*

Compound **169a** (3.56g, 12.7mmol) in 0.880 ammonia/methanol solution (60ml) and ammonium carbonate (2.00g, 20.8mmol) was placed in a bomb at 125°C (3 hours) with stirring. After cooling the mixture was poured onto water and extracted with dichloromethane. The organic layer was washed with water and dried ($MgSO_4$) yielding brown oil that was fractionated by column chromatography (silica gel, eluent dichloromethane). Analysis of fractions by ^{1}H-nmr spectroscopy showed presence of product. δ 7.82 (1H, dd, J 8 and 1Hz, Ar-H), 7.43-7.10 (4H, m, Ar-H), 7.02 (1H, t, J 7Hz, Ar-H), 6.97 (1H, d, J 7Hz, Ar-H), 4.61 (1H, d, J 16Hz, CH_2-N-), 4.45 (1H, t, J 7Hz, N-CH-CH_2-), 3.80 (1H, d, J 16Hz, CH_2-N-), 3.40-3.20 (2H, m, N-CH-CH_2-).

3.1.3 Experimental for strategy C

Preparation of Ethyl 1,2,3,4-Tetrahydroisoquinoline-3-carboxylate **177**

Compound **167** (10.0g, 56.8mmol) in ethanol (500ml) was heated under reflux while HCl gas was bubbled through (6 hours) with stirring. After cooling to room temperature the mixture was poured onto potassium carbonate solution and extracted with diethylether. The organic layer was washed with water and dried ($MgSO_4$). The resultant brown oil was distilled (134°C, 2mm Hg) yielding **177** (2.20g, 23%) as a yellow oil[114]. δ 7.16-7.01 (4H, m, Ar-H), 4.22 (2H, q, J 8Hz, O-CH_2-CH_3), 4.10 (2H, m, CH_2-N-), 3.73 (1H, m, N-CH-CH_2-), 3.11 (1H, dd, J 16 and 4Hz, N-CH-CH_2-), 2.98 (1H, d, J 10Hz, N-CH-CH_2-), 1.30 (3H, t, J 7Hz, O-CH_2-CH_3).

Preparation of 3-Hydroxymethyl-1,2,3,4-tetrahydroisoquinoline **178**

To compound **177** (2.00g, 9.8mmol) in anhydrous tetrahydrofuran (100ml), lithium aluminium hydride (1.86g, 49.0mmol) was added and the mixture heated under reflux (2 hours) with stirring. After cooling the mixture was carefully poured onto water/ethyl acetate and extracted with EtOAc. The organic layer was washed with water, dried ($MgSO_4$) and evaporated yielding **178** (1.00g, 63%) as orange oil[115]. δ 7.08-7.98 (4H, m, Ar-H), 4.05 (2H, d, J 1Hz, CH_2-OH), 3.77 (1H, d, J 16Hz, CH_2-N-), 3.55 (1H, d, J 16Hz, CH_2-N-), 3.10 (1H, m, N-CH-CH_2-), 2.70 (1H, dd, J 12 and 3Hz, N-CH-CH_2-), 2.58 (1H, d, J 10Hz, N-CH-CH_2-).

Attempted preparation of 3-Hydroxymethyl-*N*-(2-nitrophenyl)-1,2,3,4-tetrahydro-isoquinoline **175a** using standard conditions as used in synthesis of **143a-k**.

Attempted preparation of 3-Hydroxymethyl-*N*-(2-nitrophenyl)-1,2,3,4-tetrahydro-isoquinoline **175a** (*method a*)

To compound **178** (0.10g, 0.6mmol) and K_2CO_3 (0.13g, 0.9mmol) in DMSO (10ml), was added 2-fluoronitro-benzene **142a** (0.09g, 0.6mmol) and the mixture warmed to 100°C (4 hours) with stirring. After cooling the mixture was poured onto water and extracted with dichloromethane. The organic layer was washed with water and dried ($MgSO_4$). Analysis using ^{1}H-nmr spectroscopy showed trace amount of product to be present, mixture predominantly 2-nitrophenol.

Attempted Preparation of 3-Hydroxymethyl-*N*-(2-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline **175a** (*method b*)

To compound **178** (0.10g, 0.6mmol) in toluene (10ml) and triethylamine (0.17ml, 1.2mmol), was added trimethylsilylchloride (0.16ml, 0.6mmol) and the mixture warmed to 80°C (18 hours) with stirring. To the mixture triethylamine (0.08ml, 0.6mmol) and 2-fluoronitrobenzene **142a** (0.09g, 0.6mmol) was added and the mixture stirred (4 hours) at 80°C. After cooling the mixture was carefully poured onto dil. HCl and extracted with EtOAc. The organic layer was washed with water and dried ($MgSO_4$). Analysis using ^{1}H-nmr spectroscopy showed only starting material to be present.

Preparation of Compounds **175a-c** General *Method* (carried out under N_2)

A mixture of trimethylborate, lithium borohydride and the appropriate isoquinoline ester **169a-c** were heated to reflux in anhydrous ether (4 hours) with stirring. The mixture was carefully poured into water and the product was extracted into ether. The organic layer was washed several times with water, dried ($MgSO_4$) and evaporated yielding the product. By this method the following compounds were prepared.

Preparation of 3-Hydroxymethyl-*N*-(2-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline **175a**

To compound **169a** (0.50g, 1.6mmol) in anhydrous ether (20ml) and trimethylborate (0.02ml, 0.16mmol), was added lithium borohydride (0.04g, 1.8mmol) and the mixture heated under reflux (4 hours) with stirring. After cooling the mixture was carefully poured onto water and extracted with Et_2O. The organic layer was washed with water, dried ($MgSO_4$) and evaporated yielding **175a** (0.30g, 66%) as an orange oil. $\nu_{max.}$ 3500-3200(broad), 1603, 1512, 1345 and 1045 cm^{-1} δ 7.82 (1H, d, J 7Hz, Ar-H), 7.40 (1H, t, J 7Hz, Ar-H), 7.22-710 (4H, m, Ar-H), 7.00-6.90 (2H, m, Ar-H), 4.58 (1H, d, J 16Hz, CH_2-N-), 4.10 (1H, m, N-CH-CH_2-), 3.77 (1H, d, J 16Hz, CH_2-N-), 3.70 (1H, dd, J 12 and 2Hz, CH_2-OH), 3.60 (1H, dd, J 12 and 5Hz, CH_2-OH), 3.25 (1H, dd, J 16 and 6Hz, N-CH-CH_2-), 2.58 (1H, dd, J 16 and 2Hz, N-CH-CH_2-).

Preparation of 3-Hydroxymethyl-*N*-(2-nitro-5-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline **175b**

Compound **169b** (2.00g, 5.8mmol), $LiBH_4$ (0.14g, 6.5mmol) and trimethylborate (0.06ml, 0.53mmol) gave compound **175b** (1.31g, 72%) as an orange oil. [Found: C,64.53; H,6.56; N,8.59, m/z 314.1287 $C_{17}H_{18}N_2O_4$ requires C,64.96; H,5.77; N,8.91%, M 314.1267] $\nu_{max.}$ 3500-3200(broad), 1605, 1503, 1333 and 1092 cm^{-1}. δ 7.93 (1H, d, J 9Hz, Ar-H), 7.19-6.99 (4H, m, Ar-H), 6.60 (1H, d, J 2Hz, Ar-H), 6.48 (1H, dd, J 9 and 2Hz, Ar-H), 4.62 (1H, d, J 16Hz, CH_2-N-), 4.10 (1H, m, N-CH-CH_2-), 3.81 (3H, s, O-CH_3), 3.78-3.70 (2H, m, CH_2-N-and CH_2-OH), 3.61 (1H, dd, J 12 and 5Hz, CH_2-OH), 3.34 (1H, dd, J 16 and 4Hz, N-CH-CH_2-), 2.76 (1H, dd, J 16 and 3Hz, N-CH-CH_2-).

Preparation of 3-Hydroxymethyl-*N*-(2-nitro-5-benzyloxyphenyl)-1,2,3,4-tetrahydro-isoquinoline **175c**

Compound **169c** (1.00g, 2.4mmol), $LiBH_4$ (0.06g, 2.8mmol) and trimethylborate (0.03ml, 0.27mmol) gave compound **175c** (0.81g, 87%) as an orange oil. [Found: C,70.81; H,6.41; N,6.74, m/z 390.1590 $C_{23}H_{22}N_2O_4$ requires C,70.76; H,5.68; N,7.18%, M 390.1610] $\nu_{max.}$ 3500-3200(broad), 1605, 1498, 1332 and 1091 cm^{-1}. δ 7.92 (1H, d, J 9Hz, Ar-H), 7.41-7.32 (5H, m, Ar-H), 7.18-6.98 (4H, m, Ar-H), 6.66 (1H, d, J 2Hz, Ar-H), 6.54 (1H, dd, J 9 and 3Hz, Ar-H), 5.06 (2H, s, O-CH_2-Ph), 4.60 (1H, d, J 16Hz, CH_2-N-), 4.08 (1H, m, N-CH-CH_2-), 3.80-3.68 (2H, m, CH_2-N-and CH_2-OH), 3.58 (1H, dd, J 12 and 5Hz, CH_2-OH), 3.32 (1H, dd, J 16 and 4Hz, N-CH-CH_2-), 2.74 (1H, dd, J 16 and 3Hz, N-CH-CH_2-).

Attempted preparation using standard procedures[117] of 3-Methyl-*p*-toluenesulphonyl-oxy-*N*-2-nitrophenyl-1,2,3,4-tetrahydroisoquinoline resulted in the formation of compound **179a**.

Preparation of 3-Chloromethyl-*N*-(2-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline **179a** (*method a*)

To compound **175a** (0.50g, 1.8mmol) in anhydrous dichloromethane (25ml) and triethylamine (0.62ml, 4.4mmol) cooled to 0°C, was added p-toluene sulphonyl chloride (0.42g, 2.2mmol) and the mixture heated under reflux (2 hours) with stirring. After cooling the mixture was poured onto dil. HCl and extracted with dichloromethane. The organic layer was washed with water and dried ($MgSO_4$) and evaporated yielding brown oil (0.67g), which was fractionated by column chromatography (silica gel, eluent petroleum ether b.p. 60-80°C: ethyl acetate 20:1) and evaporated yielding **179a** (0.18g, 34%) as yellow crystals, m.p. 100-103°C (ethanol). [Found: C,63.55; H,4.67; N,9.14, m/z 302.0826 $C_{16}H_{15}N_2O_2Cl$ requires C,63.48; H,4.99; N,9.25%, M 302.0822]. $\nu_{max.}$ 1604, 1518, 1342, 1236, 1162 and 751 cm^{-1}. δ 7.81 (1H, d, J 9Hz, Ar-H), 7.47 (1H, t, J 8Hz, Ar-H), 7.25-7.00 (6H, m, Ar-H), 4.58 (1H, d, J 16Hz, CH_2-N-), 4.10 (1H, d, CH_2-N-), 3.92 (1H, m, N-CH-CH_2-), 3.67 (1H, m, CH_2-Cl), 3.46 (1H, dd, J 6 and 6Hz, CH_2-Cl), 3.44 (1H, dd, J 16 and 5Hz, N-CH-CH_2-), 2.90 (1H, dd, J 16 and 2Hz, N-CH-CH_2-).

Preparation of 3-Chloromethyl-*N*-(2-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline **179a** (*method b*).

To compound **175a** (0.25g, 0.9mmol) in anhydrous dichloromethane (10ml) and triphenylphosphine (0.30g, 0.9mmol), was added CCl_4 (0.27g, 1.7mmol) and the mixture heated under reflux (4 hours) with stirring. After cooling the mixture was poured onto water and extracted with dichloromethane. The organic layer was washed with water, dried ($MgSO_4$), yielding orange oil (0.21g) which was fractionated by column chromatography (silica gel, eluent petroleum ether b.p. 60-80°C: ethyl acetate 20:1) and evaporated yielding **179a** (0.07g, 27%) as yellow crystals, m.p. 102-103°C (ethanol), identical with authentic sample. $\nu_{max.}$ 1604, 1518, 1342, 1236, 1162 and 751 cm^{-1}. δ 7.81 (1H, d, J 9Hz, Ar-H), 7.47 (1H, t, J 8Hz, Ar-H), 7.25-7.00 (6H, m, Ar-H), 4.58 (1H, d, J 16Hz, CH_2-N-), 4.10 (1H, d, J 16Hz, CH_2-N-), 3.92 (1H, m, N-CH-CH_2-), 3.67 (1H, dd, J 6 and 6Hz, CH_2-Cl), 3.46 (1H, dd, J 16 and 6Hz, CH_2-Cl), 3.44 (1H, dd, J 16 and 5Hz, N-CH-CH_2-), 2.90 (1H, dd, J 16 and 2Hz, N-CH-CH_2-).

Preparation of 3-Bromomethyl-*N*-(2-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline **179b**

To compound **175a** (0.50g, 1.8mmol) in anhydrous dichloromethane (25ml) and triphenylphosphine (0.60g, 2.3mmol), was added CBr_4 (1.21g, 3.5mmol) and the mixture heated under reflux (4 hours) with stirring. After cooling the mixture was poured onto water and extracted with dichloromethane. The organic layer was washed with water, dried ($MgSO_4$) yielding brown oil (2.07g) which was fractionated by column chromatography (silica gel, eluent petroleum ether b.p. 60-80°C: ethyl acetate 10:1) and evaporated yielding **179b** (0.19g, 32%) as an orange oil. [Found: C,56.27; H,4.32; N,8.11, m/z 346.0299 $C_{16}H_{15}N_2O_2Br$ requires C,55.35; H,4.35; N,8.07%, M 346.0316]. $\nu_{max.}$ 1602, 1514, 1456, 1343, 1236, 1136 and 745 cm^{-1}. δ 7.81 (1H, d, J 9Hz, Ar-H), 7.46 (1H, t, J 8Hz, Ar-H), 7.25-7.00 (6H, m, Ar-H), 4.58 (1H, d, J 16Hz, CH_2-N-), 4.07 (1H, d, J 16Hz, CH_2-N-), 3.95 (1H, m, N-CH-CH_2-), 3.54 (1H, dd, J 6 and 6Hz, CH_2-Br), 3.46 (1H, dd, J 16 and 5Hz, N-CH-CH_2-), 3.36 (1H, t, J 8Hz, CH_2-Br), 2.99 (1H, dd, J 16 and 2Hz, N-CH-CH_2-).

Preparation of 3-Methyl-p-toluenesulphonyloxy-*N*-(4-nitrophenyl)-1,2,3,4-tetrahydro-isoquinoline **183**

1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid **167** (5.00g, 28.3mmol), K_2CO_3 (7.00g, 50.6mmol) and 4-fluoronitrobenzene (3.98g, 28.3mmol) gave compound **180** (*N*-(4-Nitrophenyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid) (3.73g, 53%) as orange crystals, m.p.193-195°C (ethanol). $\nu_{max.}$ 1715, 1597, 1484, 1317 and 1112cm^{-1}. δ 8.20 (2H, d, J 6Hz, Ar-H), 7.30-7.15 (4H, m, Ar-H), 6.82 (2H, d, J 6Hz, Ar-H), 4.90 (1H, dd, J 4 and 1Hz, CH_2-CH-CO_2H), δ 4.70 (1H, d, J 12Hz, CH_2-N-CH-), 4.58 (1H, d, J 12Hz, CH_2-N-CH-), 3.42 (1H, dd, J 10 and 1Hz, N-CH-CH_2-), 3.35 (1H, dd, J 10 and 3Hz, N-CH-CH_2-). Compound **180** (1.00g, 5.2mmol), K_2CO_3 (0.7g, 5.1mmol) and dimethylsulphate (0.35ml, 3.7mmol) gave compound **181** (*N*-(4-Nitrophenyl)-

1,2,3,4-tetrahydroisoquinoline-3-carboxylate) (0.9g, 87%) as yellow crystals, m.p.149°C (ethanol/methanol). $\nu_{max.}$ 1743, 1601, 1488, 1347, 1200 and 1179 cm^{-1}. δ 8.18 (2H, d, J 7Hz, Ar-H), 7.30-7.15 (4H, m, Ar-H), 6.80 (2H, d, Ar-H), 4.91 (1H, dd, J 4 and 1Hz, CH_2-CH-CO_2CH_3), 4.73 (1H, d, J 12Hz, CH_2-N-CH-), 4.60 (1H, d, J 12Hz, CH_2-N-CH-), 3.59 (3H, s, CO_2- CH_3), 3.40 (1H, dd, J 12 and 1Hz, N-CH-CH_2-), 3.32 (1H, dd, J 10 and 3Hz, N-CH-CH_2-). Compound **181** (0.15g, 0.5mmol), $LiBH_4$ (0.01g, 0.5mmol) and trimethylborate (0.01ml, 0.08mmol) gave compound **182** (3-Hydroxymethyl-*N*-(4-Nitrophenyl)-1,2,3,4-tetrahydroisoquinoline) (0.10g, 74%) as a yellow oil. $\nu_{max.}$ 3500-3200(broad), 1596, 1486, 1314 and 1112 cm^{-1}. δ 8.18 (2H, d, J 10Hz, Ar-H), 7.29-7.20 (4H, m, Ar-H), 6.92 (2H, d, J 10Hz, Ar-H), 4.58 (1H, d, J 16Hz, CH_2-N-), 4.43 (1H, d, CH_2-N-), 4.42 (1H, m, N-CH-CH_2-), 3.60 (1H, m, N-CH-CH_2-), 3.40 (1H, m, N-CH-CH_2-), 3.12 (2H, d, J 6Hz, CH_2-OH). To compound **182** (0.10g, 0.4mmol) in anhydrous dichloromethane (10ml) and triethylamine (0.12ml, 0.9mmol) cooled to 0°C, was added p-toluene sulphonyl chloride (0.08g, 0.42mmol) and the mixture heated under reflux (4 hours) with stirring. After cooling the mixture was poured onto dil. HCl and extracted into dichloromethane. The organic layer was washed with water, dried ($MgSO_4$) yielding an orange oil (0.22g) which was fractionated by column chromatography (silica gel, eluent petroleum ether b.p. 60-80°C: ethyl acetate 20:1) and evaporated yielding **183** (0.16g, 42%) as orange crystals, m.p.160-162°C (ethanol). [Found: C,63.10; H,5.23; N,6.36 $C_{23}H_{22}N_2O_5S$ requires C,63.00; H,5.05; N,6.39%] $\nu_{max.}$ 1596, 1502, 1324, 1173, 1096 and 975 cm^{-1}. δ 8.13 (2H, d, J 9Hz, Ar-H), 7.65 (2H, d, J 9Hz, Ar-H), 7.30-7.12 (6H, m, Ar-H), 6.79 (2H, d, J 10Hz, Ar-H), 4.52 (1H, m, N-CH-CH_2-), 4.48 (1H, d, J 16Hz, CH_2-N-), 4.29 (1H, d, J 16Hz, CH_2-N-), 3.92 (1H, m, N-CH-CH_2-), 3.90 (1H, dd, J 6 and 6Hz, CH_2-S-), 3.61 (1H, t, J 6Hz, CH_2-S-), 3.11 (2H, m, N-CH-CH_2-).

Preparation of 3-Thiophenyl-*N*-(2-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline **179c**

To compound **176a** (0.06g, 0.2mmol) in anhydrous THF (10ml), thiophenol (0.05g, 0.4mmol) was added and the mixture heated under reflux (48 hours) with stirring. After cooling the mixture was poured onto water and extracted with dichloromethane. The organic layer was washed with water and dried ($MgSO_4$). Analysis using ^{1}H-nmr spectroscopy showed only starting material to be present.

Attempted preparation of compounds **176a-c**.

Preparation of 3-Methyl-*N*-(2-Nitrophenyl)isoquinoline **176a** *(method a)*

To compound **175a** (0.25g, 0.89mmol) in acetic acid (10ml), concentrated sulphuric acid (1ml) was added and the mixture heated under reflux (18 hours) with stirring. After cooling the mixture was poured onto sodium hydroxide solution and extracted into dichloromethane. The organic layer was washed with water and dried ($MgSO_4$) and evaporated yielding brown oil (0.13g) which was fractionated by column chromatography (silica gel, eluent chloroform : methanol 20:1). Analysis of fractions by ^{1}H-nmr spectroscopy showed a complex mixture.

Preparation of 3-Methyl-*N*-(2-Nitrophenyl)isoquinoline **176a** *(method b)*

To compound **175a** (0.10g, 0.4mmol) in xylene (10ml), phosphorus pentoxide (0.20g, 1.4mmol) was added and the mixture heated under reflux (6 hours) with stirring. Xylene was removed by distilling under pressure and the residue washed with water and extracted with dichloromethane. The organic layer was washed with water and dried ($MgSO_4$) and evaporated yielding brown oil (0.07g). Analysis using ^{1}H-nmr spectroscopy showed a complex mixture.

Preparation of 3-Methyl-*N*-(2-Nitrophenyl)isoquinoline **176a** *(method c)*

To compound **179a** (0.10g, 0.3mmol) in tetrahydrofuran (10ml), 1,8-diazabicyclo[5.4.0] hep-7-undecene (0.15g, 1.0mmol) was added and the mixture stirred (18 hours) at room temperature. The mixture was poured onto water and extracted with dichloromethane. The organic layer was washed with water and dried ($MgSO_4$) and evaporated yielding orange oil (0.028g). Analysis using ^{1}H-nmr spectroscopy showed only starting material to be present.

Preparation of 3-Methyl-*N*-(2-Nitrophenyl)isoquinoline **176a** *(method c)*

To compound **179b** (0.10g, 0.3mmol) in tetrahydrofuran (10ml), 1,8-diazabicyclo[5.4.0] hep-7-undecene (0.13g, 0.9mmol) was added and the mixture stirred (18 hours) at room temperature. The mixture was poured onto and extracted with dichloromethane. The organic layer was washed with water and dried ($MgSO_4$) and evaporated yielding orange oil (0.06g). Analysis using ^{1}H-nmr spectroscopy showed only starting material to be present.

Preparation of 3-Methyl-*N*-(2-Nitrophenyl)isoquinoline **176a** *(method d)*

To compound **179b** (0.10g, 0.3mmol) in tetrahydrofuran (10ml), potassium tertiary butoxide (0.07g, 0.6mmol) was added and the mixture heated under reflux (6 hours) under nitrogen with stirring. After cooling the mixture was poured onto water and extracted with dichloromethane. The organic layer was washed with water and dried ($MgSO_4$) and evaporated yielding orange oil (0.07g). Analysis using ^{1}H-nmr spectroscopy showed a complex mixture.

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TETRAHEDRON

Nucleophilic Additions to Fused Benzimidazole *N*-Oxides

Michael J. Donaghy and Stephen P. Stanforth*

Department of Chemical and Life Sciences, University of Northumbria at Newcastle, Newcastle upon Tyne, NE1 8ST UK.

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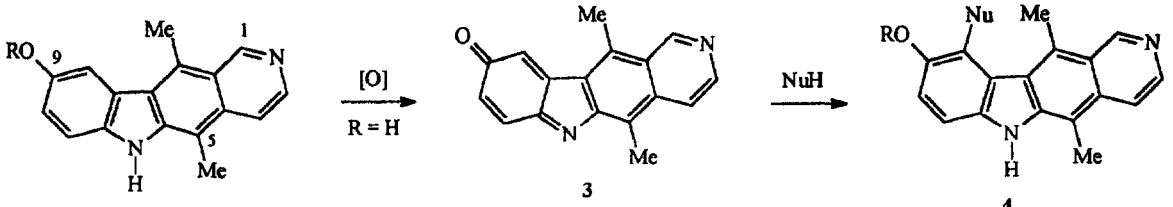
Abstract: The benzimidazoles **16a-f** have been prepared from *N*-oxides **15a-d**. Treatment of *N*-oxides **15c** and **15d** with a mixture of acetic anhydride and sodium acetate gave the corresponding acetoxy derivatives **26** and **27** *via* a regiospecific nucleophilic substitution reaction. *N*-Oxides **15c** and **15d** were also deoxygenated by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ).

Ellipticine, and its 9-oxygenated derivatives such as 9-hydroxyellipticine **1** and 9-methoxyellipticine **2** have attracted considerable attention as potential anti-cancer agents.[1-4] Several modes of anti-cancer action have been proposed for ellipticine and its derivatives; for example they have been described as bioalkylating agents, intercalating agents, inhibitors of the enzyme topoisomerase II and in the case of 9-hydroxyellipticine **1**, the corresponding phenoxy radical has been suggested to cause DNA damage either directly or indirectly by reduction of molecular oxygen to superoxide ions.



1 R = H
2 R = Me

3

4

Scheme 1

Two broad mechanisms[1] by which ellipticine and its derivatives can act as bioalkylating agents have been proposed. In the first mechanism (Scheme 1), 9-hydroxyellipticine **1** (which may be formed *in vivo* by oxidation of ellipticine or demethylation[5,6] of 9-methoxyellipticine **2**) is oxidised to the quinone-imine **3** which then undergoes regiospecific Michael-type addition of bionucleophiles at the 10-position yielding the products **4**. Adducts of general structure **4**, and other compounds derived from these primary adducts, have been

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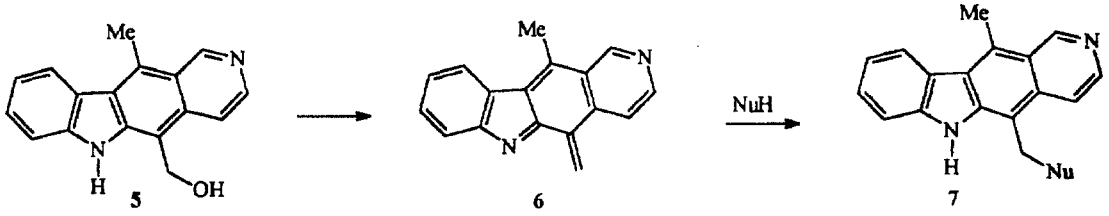
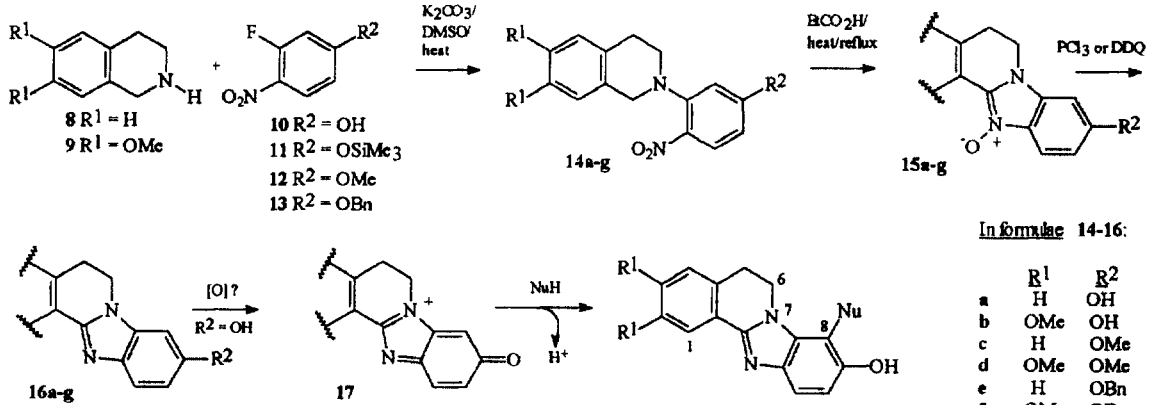
chemically prepared by oxidation of 9-hydroxyellipticine **1** in the presence of nucleophiles by both Potier's[7-9] and Meunier's[10-12] research groups. In an alternative mechanism[13] (Scheme 2), Archer's research group has provided evidence that the 5-methyl group of ellipticine derivatives is oxidised to the alcohol **5** which (as its sulfate or phosphate ester) acts as the precursor to the vinylogous imine intermediate **6**. Michael-type addition of bionucleophiles to this vinylogous imine **6** then yields products **7**.



Scheme 2

We have been interested in identifying and synthesising novel heterocyclic compounds which might act as precursors for quinone-imine intermediates similar in structure to **3** with the objective of developing novel bioalkylating agents. In this paper we report our work on the synthesis of the derivatives of 5,6-dihydro-9-hydroxybenzimidazo[2,1-*a*]isoquinoline **16a-f** which we reasoned might be a suitable precursor to the quinone-imines of general structure **17** and hence adducts **18** after Michael-type addition to nucleophiles (Scheme 3)

The synthetic route chosen to the target heterocycles **16** is shown in Scheme 3. The cyclodehydration of *N,N*-disubstituted 2-nitroaniline derivatives giving benzimidazole *N*-oxides is well-known (the *t*-amino effect)[14] and we have previously used this reaction to prepare substituted 5,6-dihydrobenzimidazo[2,1-*a*]isoquinoline *N*-oxides.[15] We therefore envisaged a similar route to the 9-oxygenated 5,6-dihydrobenzimidazo[2,1-*a*]isoquinoline *N*-oxides **15a-f** by a similar cyclodehydration of the nitro-compounds **14a-f** respectively from which heterocycles **16a-f** might then be obtained by deoxygenation.



Scheme 3

The preparation of nitro-compound **14a** was firstly investigated. Commercially available 3-fluoro-4-nitrophenol **10** was treated with a mixture of triethylamine and trimethylsilyl chloride to yield the silylated

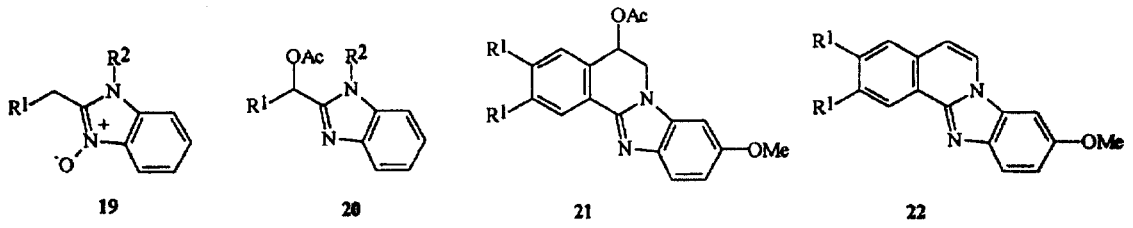
derivative **11** which was not isolated but was reacted directly with 1,2,3,4-tetrahydroisoquinoline **8** under basic conditions giving, after an acidic work-up, the nitrophenol derivative **14a** in low (16 %) yield. However, when compound **14a** was heated in propionic acid at reflux a complex mixture was produced and no compound **15a** was obtained. We therefore turned our attention to the synthesis of the *O*-protected derivatives **14c** and **14e** of compound **14a**. Both compounds **14c** and **14e** were readily prepared in excellent yields by heating a mixture of heterocycle **8** and fluoro-compounds **12** and **13** respectively under basic conditions. When these two compounds were heated in boiling propionic acid the required *N*-oxide derivatives **15c** (68 % yield) and **15e** (54 % yield) respectively were produced. Similarly prepared were the 6,7-dimethoxy analogues **14d** (93 % yield) and **14f** (86 % yield) from 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **9** and fluoro-compounds **12** and **13** respectively. Nitro-compounds **14d** and **14f** gave the corresponding *N*-oxides **15d** (50 % yield) and **15f** (72 % yield) as expected. In view of the failure to obtain compound **15a**, the synthesis of the dimethoxy derivative **15b** *via* its precursor **14b** was not attempted.

Deoxygenation of compounds **15c-f** afforded heterocycles **16c-f** respectively and was achieved with phosphorus trichloride in boiling chloroform. Heterocycles **16c-e** were obtained in good yield (61–78 %) but compound **16f** was only isolated in poor yield (14 %). Hydrogenation of heterocycles **16e** and **16f** then gave the phenolic derivatives **16a** and **16b** respectively, but disappointingly in low yield (13-14 %). Although compounds **16e** and **16f** have been successfully prepared, in view of their low yields, this avenue was not pursued further and their chemistry was not investigated.

We were also interested in preparing benzimidazo[2,1-*a*]isoquinolines and benzimidazo[2,1-*a*]isoquinoline *N*-oxides in which the 5,6-positions are unsaturated. Literature precedent[16] suggested that dehydrogenation of benzimidazo[2,1-*a*]isoquinolines would not provide a satisfactory method of preparing these compounds because 2,3,9,10-tetramethoxybenzimidazo[2,1-*a*]isoquinoline had only been obtained in 10% yield by Pd/C mediated dehydrogenation of its corresponding 5,6-dihydro derivative. We therefore attempted two alternative methods of dehydrogenating benzimidazo[2,1-*a*]isoquinoline *N*-oxides as described below.

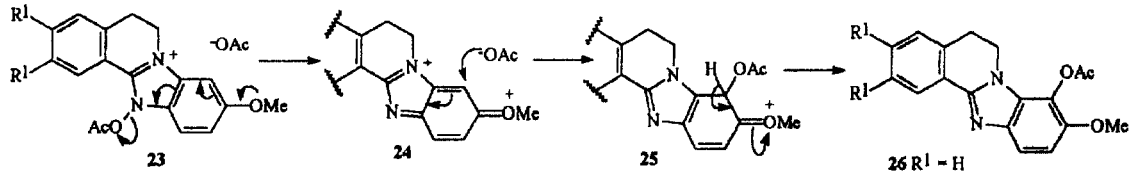
Treatment of *N*-oxide **15c** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) gave a product which was not the corresponding 5,6-dihydro derivative but was the deoxygenation product **16c** (55 % yield). The fate of the DDQ in this reaction has not been determined but it is possibly epoxidised *via* a Michael-type addition followed by an elimination process. Similarly, *N*-oxide **15d** afforded heterocycle **16d** in 47 % yield when treated with DDQ.

Benzimidazole *N*-oxides of general structure **19** can be transformed into the acetates **20** by heating in the presence of acetic anhydride.[17] We envisaged that fully conjugated benzimidazo[2,1-*a*]isoquinolines **22** (R^1 = H, OMe) might be obtained in a similar reaction from *N*-oxides **15c** and **15d**. Thus, a vinylogous equivalent of the transformation **19** → **20** might yield acetates **21** (R^1 = H, OMe) from which compounds **22** (R^1 = H, OMe) would be obtained by elimination of acetic acid.



19 20 21 22

When the *N*-oxides **15c** and **15d** were heated with a mixture of acetic anhydride and sodium acetate, the acetoxy derivatives **26** (40 % yield) and **27** (15 % yield) were unexpectedly isolated. We have rationalised the formation of these compounds by the mechanism depicted in Scheme 4. Thus, reaction of acetic anhydride at the *N*-oxide substituent gives intermediates **23** which then expel acetate giving the quinone-imine intermediates **24**. A regiospecific Michael-type addition at the 8-position of compounds **24** with acetate then yields the structures **25** from which the products are derived by loss of a proton. The C-9 methoxy group is an essential structural requirement for this reaction since the lone pair of electrons associated with this methoxy group is necessary to assist the departure of acetate (arrows, structure **23**). In support of this argument, the *N*-oxide **15g** did not react under similar conditions.

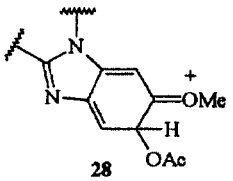


23 24 25 26 R¹ = H, 27 R¹ = OMe

Scheme 4

Nucleophilic substitution in benzimidazole *N*-oxides was reported by Takahashi and Kano in 1966[18] and further investigated in 1973 by Kielden, Meth-Cohn and Suschitzky.[19] In these nucleophilic substitutions, the *N*-oxide group is firstly transformed into a potential leaving group before the nucleophile attacks by an S_N2' mechanism. The reaction shown in Scheme 4 is unusual since it is believed to occur by an elimination-addition process and requires an appropriately positioned electron-rich substituent, in this case a methoxy group.

The mechanism shown in Scheme 4 also accounts for the regioselectivity of the reaction. When acetate is added at the 8-position, the resulting intermediates **25** possess aromatic imidazole fragments. If the addition of acetate were to occur at the 10-position giving structures **28**, an aromatic imidazole moiety cannot be drawn.



28

The unexpected nucleophilic substitution reactions of the *N*-oxides described above has been rationalised in terms of the quinone-imine intermediates **24** or their equivalents. These quinone-imines are in fact the methylated analogues of the compounds **17** that we had originally intended to investigate. Our studies of the reaction of the benzimidazo[2,1-*a*]isoquinoline *N*-oxides with acetic anhydride reported in this paper have therefore produced the desired nucleophilic substitution reactions.

Experimental

^{1}H-nmr spectra (60 or 270 MHz) were determined in $CDCl_3$ solution unless otherwise stated. Infra-red spectra were recorded as KBr discs unless otherwise stated.

4-Benzyloxy-2-fluoronitrobenzene **13**

To 3-fluoro-4-nitrophenol (4.90 g, 31.2 mmol) and K_2CO_3 (6.46 g, 46.8 mmol) in tetrahydrofuran (75 ml) was added benzyl bromide (5.04 ml, 32.7 mmol) and sodium iodide (few crystals) and the mixture was heated under reflux for 2 hours with stirring. After cooling the mixture was poured into water and extracted several times with DCM. The combined organic layers were washed with water, dried ($MgSO_4$) and evaporated yielding brown oil which was fractionated by column chromatography (silica gel, eluent petroleum ether b.p. 60-80°C : ethyl acetate 2:1) giving compound **13** (1.18 g, 15 %) as pale yellow crystals, m.p. 72-73 °C (ethanol). [Found: C, 63.2; H, 4.1; N, 5.7. $C_{13}H_{10}FNO_3$ requires C, 63.2; H, 4.0; N, 5.7 %]. $\nu_{max.}$ 1609, 1512, 1331, 1274 and 1091 cm^{-1}. δ 8.10 (1H, m, Ar-H), 7.45-7.35 (5H, s, Ar-H), 6.85-6.75 (2H, m, Ar-H), 5.15 (2H, s, -OCH_2Ph).

N-(5-Hydroxy-2-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline **14a**

Trimethylsilyl chloride (3.38 ml, 26.6 mmol) was added to a mixture of 3-fluoro-4-nitrophenol (4.00 g, 25.5 mmol), toluene (75 ml) and triethylamine (3 ml, 21.5 mmol). The mixture was heated at 80 °C overnight with stirring under a nitrogen atmosphere and then allowed to cool to room temperature. Triethylamine (3 ml, 21.5 mmol) and 1,2,3,4-tetrahydroisoquinoline (3.56 g, 26.7 mmol) were added and the mixture was refluxed for 4 hours with stirring. After cooling to room temperature the mixture was poured into dilute hydrochloric acid and extracted several times with with ethyl acetate. The combined organic layers were washed with water, dried ($MgSO_4$) and evaporated yielding compound **14a** (1.07 g, 16 %) as an orange solid, m.p. 152-155 °C (ethanol). [Found: C, 66.5; H, 5.4; N, 10.3; M$^+$, 270.1015. $C_{15}H_{14}N_2O_3$ requires C, 66.7; H, 5.2; N, 10.4 %; M, 270.1004]. $\nu_{max.}$ 3500-3200 (broad), 1614, 1514, 1307, 1182 and 1088 cm^{-1}. δ 7.92 (1H, d, *J* 9 Hz, Ar-H), 7.25-7.00 (4H, m, Ar-H), 6.58 (1H, d, *J* 2 Hz, Ar-H), 6.40 (1H, dd, *J* 9 and 2 Hz, Ar-H), 4.28 (2H, s, -CH_2-), 3.36 (2H, t, *J* 6 Hz, C(5)H_2) and 3.02 (2H, t, *J* 6 Hz, C(6)H_2). The –OH proton was too broad to be located.

Compounds **14c-g**. *General Method*.

A mixture of 1,2,3,4-tetrahydroisoquinoline (THIQ) or 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, K_2CO_3 and the appropriate halonitroaryl compound were heated (100 °C) in DMSO (4 hours) with stirring. The mixture was poured into water and the product was extracted several times with DCM. The combined organic layers were washed several times with water, dried ($MgSO_4$) and evaporated yielding the product. The following compounds were prepared.

N-(5-Methoxy-2-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline **14c**

THIQ (4.12 g, 30.9 mmol), K_2CO_3 (4.93 g, 46.4 mmol) and 3-fluoro-4-nitroanisole[20] (5.37 g, 31.4 mmol) gave compound **14c** (8.05g, 91 %) as an orange oil. [Found: C ,67.5; H ,5.9; N, 9.8; M$^+$, 267.1141. $C_{16}H_{16}N_2O_3$ requires C, 67.6; H, 5.7; N, 9.9 %; M, 267.1134].$\nu_{max.}$ 1607, 1505, 1251, and 1091 cm^{-1}(liquid film). δ 7.96 (1H, d, *J* 9 Hz, Ar-H), 7.20-7.00 (4H, m, Ar-H), 6.60 (1H, d, *J* 2 Hz, Ar-H), 6.46 (1H, dd, *J* 7 and 2 Hz, Ar-H), 4.30 (2H, s, -CH_2-), 3.86 (3H, s, -OCH_3), 3.41 (2H, t, *J* 6 Hz, C(5)H_2) and 3.03 (2H, t, *J* 6 Hz, C(6)H_2).

6,7-Dimethoxy-N-(5-methoxy-2-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline **14d**

6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline (6.64 g, 31.3 mmol), K_2CO_3 (6.91 g, 44.7 mmol) and 3-fluoro-4-nitroanisole[20] (5.10 g, 29.8 mmol) gave compound **14d** (10.1 g, 93 %) as orange crystals, m.p. 130-132 °C (ethanol). [Found: C, 62.7; H, 5.7; N, 8.05. $C_{18}H_{20}N_2O_5$ requires C, 62.8; H, 5.85; N, 8.1 %]. $\nu_{max.}$ 1610, 1518, 1301, 1175 and 1114 cm^{-1}. δ 7.95 (1H, d, *J* 8 Hz, Ar-H), 6.70-6.35 (4H, m, Ar-H), 4.20 (2H, s, -CH_2-), 3.80 (9H, s, 3 x -OCH_3), 3.30 (2H, t, *J* 8 Hz, C(5)H_2) and 2.90 (2H, t, *J* 8 Hz, C(6)H_2).

N-(5-Benzyloxy-2-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline **14e**

THIQ (1.52 g, 11.4 mmol), K_2CO_3 (1.72 g, 17.1 mmol) and 4-benzyloxy-2-fluoronitrobenzene (2.57 g, 10.8 mmol) gave compound **14e** (2.97 g, 79 %) as yellow crystals, m.p. 96-97 °C (ethanol). [Found: C, 73.2; H, 5.45; N,7.7. $C_{22}H_{20}N_2O_3$ requires C, 73.3; H, 5.6; N, 7.8 %]. $\nu_{max.}$ 1618, 1484, 1288, 1174 and 1139 cm^{-1}. δ 7.96 (1H, d, *J* 8 Hz, Ar-H), 7.42-7.30 (5H, m, Ar-H), 7.18-7.00 (4H, m, Ar-H), 6.70 (1H, d, *J* 1 Hz, Ar-H), 6.55 (1H, dd, *J* 8 and 1 Hz, Ar-H), 5.10 (2H, s, -OCH_2Ph), 4.28 (2H, s, -CH_2-), 3.38 (2H, t, *J* 7 Hz, C(5)H_2) and 3.02 (2H, t, *J* 7 Hz, C(6)H_2).

N-(5-Benzyloxy-2-nitrophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **14f**

6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline (1.59 g, 8.19 mmol), K_2CO_3 (1.62 g, 11.7 mmol) and 4-benzyloxy-2-fluoronitrobenzene (1.85 g, 7.81 mmol) gave compound **14f** (4.02 g, 86 %) as yellow crystals, m.p. 156-158 °C (ethanol). [Found: C, 68.4; H, 5.65; N, 6.5. $C_{24}H_{24}N_2O_5$ requires C, 68.6; H, 5.75; N, 6.7%]. $\nu_{max.}$ 1603, 1520, 1331, 1251 and 1117 cm^{-1}. δ 7.98 (1H, d, *J* 4 Hz, Ar-H), 7.45-7.30 (5H, m, Ar-H), 6.65 (2H, d, *J* 2 Hz, Ar-H), 6.59 (1H, s, Ar-H), 6.56 (1H, dd, *J* 3 and 1 Hz, Ar-H), 5.10 (2H, s, -OCH_2Ph), 4.20 (2H, s, -CH_2-), 3.82 (6H, s, 2 x -OCH_3), 3.37 (2H, t, *J* 6Hz, C(5)H_2) and 2.94 (2H, t, *J* 6 Hz, C(6)H_2).

6,7-Dimethoxy-N-(2-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline **14g**

6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline (3.50 g, 17.9 mmol), K_2CO_3 (3.71 g, 26.8 mmol) and 1-fluoro-2-nitrobenzene (2.78 g, 19.7 mmol) gave compound **14g** (2.45 g, 40%) as orange crystals, m.p. 132 °C (ethanol). [Found: C, 62.7; H, 5.65; N, 7.90. $C_{17}H_{18}N_2O_4$ requires C, 62.7; H, 5.85; N, 8.1 %]. $\nu_{max.}$ 1604, 1519, 1342, and 1115 cm^{-1}. δ 7.80 (1H, dd, *J* 8 and 1 Hz, Ar-H), 7.50-6.85 (4H, m, Ar-H), 6.60 (1H, dd, *J* 8 and 1 Hz, Ar-H), 4.20 (2H, s, -CH_2-), 3.80 (6H, s, 2 x -OCH_3), 3.35 (2H, t, *J* 8 Hz, C(5)H_2) and 2.90 (2H, t, *J* 8 Hz, C(6)H_2).

Compounds **15c-g**. *General Method*.

Compounds **14c-g** in either acetic or propionic acid were heated at reflux (20 – 24 hours) with stirring. After cooling to room temperature, the mixture was poured onto a mixture of ice and dilute sodium hydroxide solution (until alkaline) and the product was extracted into DCM. The organic layer was washed several times with water, dried ($MgSO_4$) and evaporated yielding the product. The following compounds were prepared:

5,6-Dihydro-9-methoxybenzimidazo[2,1-a]isoquinoline N-oxide **15c**

Compound **14c** (3.30 g, 11.6 mmol) in acetic acid (75 ml) yielded compound **15c** (2.09 g, 68 %) as brown crystals, m.p. 204-207 °C (acetone). [Found: M^+, 266.1052. $C_{16}H_{14}N_2O_2$ requires M, 266.1055]. $\nu_{max.}$ 1622, 1490, 1240 and 1136 cm^{-1}. δ 9.45 (1H, dd, *J* 4 and 1 Hz, Ar-H), 7.93 (1H, d, *J* 4 Hz, Ar-H), 7.55-7.30 (3H, m, Ar-H), 7.00 (1H, dd, *J* 4 and 1 Hz, Ar-H), 6.80 (1H, d, *J* 1 Hz, Ar-H), 4.30 (2H, t, *J* 6 Hz, C(5)H_2), 3.90 (3H, s, -OCH_3) and 3.35 (2H, t, *J* 6 Hz, C(6)H_2).

5,6-Dihydro-2,3,9-trimethoxybenzimidazo[2,1-a]isoquinoline N-oxide **15d**

Compound **14d** (10.0 g, 30.3 mmol) in acetic acid (150 ml) yielded compound **15d** (5.29 g, 50 %) as off white crystals, m.p. 229-232 °C (acetone/ethanol). [Found: C, 59.6; H, 6.3; N, 7.7; M^+, 326.1268. $C_{18}H_{18}N_2O_4.2H_2O$ requires C, 59.7; H, 6.1; N, 7.7 %; M, 326.1267]. $\nu_{max.}$ 1620, 1496, 1245 and 1147 cm^{-1}. δ 9.20 (1H, s, Ar-H), 7.85 (1H, d, *J* 10 Hz, Ar-H), 7.00 (1H, dd, *J* 9 and 1 Hz, Ar-H), 6.82-6.70 (2H, m, Ar-H), 4.20 (2H, t, *J* 7 Hz, C(5)H_2), 4.00 (3H, s, -OCH_3), 3.80 (6H, d, *J* 9 Hz, 2 x -OCH_3) and 3.20 (2H, t, *J* 8 Hz, C(6)H_2).

5,6-Dihydro-9-benzyloxybenzimidazo[2,1-a]isoquinoline N-oxide **15e**

Compound **14e** (2.63 g, 7.51 mmol) in acetic acid (100 ml) yielded compound **15e** (1.39 g, 54 %) as brown crystals m.p. 185-189 °C (acetone/ethanol). [Found: M^+, 342.1358. $C_{22}H_{18}N_2O_2$ requires M, 342.1368]. $\nu_{max.}$ 1618, 1484, 1234 and 1174 cm^{-1}. δ 9.47 (1H, dd, *J* 7 and 1 Hz, Ar-H), 7.95 (1H, d, *J* 8 Hz, Ar-H), 7.55-7.30 (8H, m, Ar-H), 7.10 (1H, dd, *J* 8 and 1 Hz, Ar-H), 6.90 (1H, d, *J* 1 Hz, Ar-H), 5.15 (2H, s, -OCH_2Ph), 4.30 (2H, t, *J* 7 Hz, C(5)H_2) and 3.30 (2H, t, *J* 7 Hz, C(6)H_2).

9-Benzyloxy-5,6-dihydro-2,3-dimethoxybenzimidazo[2,1-a]isoquinoline N-oxide **15f**

Compound **14f** (4.02 g, 9.56 mmol) in acetic acid (75 ml) yielded compound **15f** (2.81 g, 72 %) as brown crystals, m.p. 237-240 °C (acetone/ethanol). [Found: C, 65.8; H, 5.7; N, 6.4; M^+, 402.1581. $C_{24}H_{22}N_2O_4.2H_2O$ requires C, 65.8; H, 6.0; N, 6.4 %; M, 402.1580]. $\nu_{max.}$ 1622, 1495, 1220 and 1152 cm^{-1}. δ 9.18 (1H, s, Ar-H), 7.85 (1H, d, *J* 7 Hz, Ar-H), 7.55-7.30 (5H, m, Ar-H), 7.05 (1H, dd, *J* 7 and 1 Hz, Ar-H), 6.86 (1H, d, *J* 1 Hz, Ar-H), 6.80 (1H, s, Ar-H), 5.15 (2H, s, -OCH_2Ph), 4.22 (2H, t, *J* 7 Hz, C(5)H_2), 4.05 (3H, s, -OCH_3), 3.95 (3H, s, -OCH_3) and 3.20 (2H, t, *J* 8 Hz, C(6)H_2).

5,6-Dihydro-2,3-dimethoxybenzimidazo[2,1-a]isoquinoline N-oxide **15g**

Compound **14g** (3.09 g, 9.82 mmol) in propionic acid (75 ml) yielded compound **15g** (2.13 g, 73 %) as creamy yellow crystals, m.p. 230 °C (acetone). $\nu_{max.}$ 1609, 1498, 1257 and 1147 cm^{-1}. δ 9.20 (1H, s, Ar-H), 7.95 (1H, m, Ar-H), 7.43-7.30 (3H, m, Ar-H), 6.83 (1H, d, *J* 1 Hz, Ar-H), 4.30 (2H, t, *J* 8Hz, C(5)H_2), 4.03 (3H, s, -OCH_3), 3.95 (3H, s, -OCH_3) and 3.23 (2H, t, *J* 8 Hz, C(6)H_2). This compound was characterised as its deoxygenated derivative, compound **16g**.

5,6-Dihydro-9-hydroxybenzimidazo[2,1-a]isoquinoline **16a**

A mixture of compound **16e** (0.10 g, 0.30 mmol), ammonium formate (0.02 g, 0.33 mmol), 5% palladium on carbon (0.05 g, 0.02 mmol) and methanol (10 ml) was heated under reflux (4 hours) with stirring. After cooling to room temperature the mixture was filtered, poured onto sodium hydroxide solution, neutralised with dilute hydrochloric acid and then extracted several times with dichloromethane (DCM). The combined organic layers were washed with water, dried ($MgSO_4$) and evaporated yielding **16a** (0.01 g, 14%) as brown oil. δ 8.22 (1H, m, Ar-H), 7.60 (1H, d, *J* 9 Hz, Ar-H), 7.40-7.20 (3H, m, Ar-H), 6.80-6.75 (2H, m, Ar-H), 4.23 (2H, t, *J* 8 Hz, C(5)H_2) and 3.23 (2H, t, *J* 8 Hz, C(6)H_2). The –OH proton was too broad to be located. In view of the low yield, this compound was not characterised further.

5,6-Dihydro-9-hydroxy-2,3-dimethoxybenzimidazo[2,1-a]isoquinoline **16b**

Following the procedure described above for the preparation of compound **16a**, compound **16f** (0.50 g) yielded compound **16b** (0.05g, 13 %) as brown crystals m.p. 267 °C (ethanol). [Found: M^+, 296.1162. $C_{17}H_{16}N_2O_3$ requires M, 296.1161]. $\nu_{max.}$ 1616, 1477, 1280, 1234 and 1171 cm^{-1}. δ 7.73 (1H, s, Ar-H), 7.61 (1H, d, *J* 9 Hz, Ar-H), 6.79 (3H, m, Ar-H), 4.23 (2H, t, *J* 7 Hz, C(5)H_2), 3.97 (3H, s, -OCH_3), 3.94 (3H, s, -OCH_3) and 3.20 (2H, t, *J* 7 Hz, C(6)H_2). The –OH proton was too broad to be located.

Compounds **16c-g**. *Method A*.

The appropriate *N*-oxide was dissolved in chloroform. Phosphorus trichloride was then added and the resulting mixture heated at reflux for 2 hours with stirring. The mixture was poured into a mixture of ice and dilute sodium hydroxide solution and the product extracted into DCM. The organic layer was washed several times with water, dried ($MgSO_4$) and evaporated yielding the product. The following compounds were prepared:

5,6-Dihydro-9-methoxybenzimidazo[2,1-a]isoquinoline **16c**

N-Oxide **15c** (2.00 g, 7.51 mmol) and PCl_3 (0.79 ml, 9.01 mmol) gave compound **16c** (1.14 g, 61 %) as brown crystals, m.p. 203-206 °C (acetone). [Found: M^+, 250.1096. $C_{16}H_{14}N_2O$ requires M, 250.1106]. $\nu_{max.}$ 1624, 1493, 1245 and 1176 cm^{-1}. δ 8.20 (1H, m, Ar-H), 7.90 (1H, d, *J* 9 Hz, Ar-H), 7.50-7.30 (3H, m, Ar-H), 7.00-6.80 (2H, m, Ar-H), 4.30 (2H, t, *J* 9 Hz, C(5)H_2), 3.90 (3H, s, -OCH_3) and 3.30 (2H, t, *J* 9 Hz, C(6)H_2).

5,6-Dihydrobenzimidazo-2,3,9-trimethoxy[2,1-a]isoquinoline **16d**

N-Oxide **15d** (4.00 g, 12.3 mmol) and PCl_3 (3.15 ml, 14.7 mmol) gave compound **16d** (2.96 g, 78 %) as white plates, m.p. 244-246 °C (ethanol). [Found: M^+, 310.1315. $C_{18}H_{18}N_2O_3$ requires M, 310.1317]. $\nu_{max.}$ 1621, 1510, 1254 and 1177 cm^{-1}. δ 7.90 (1H, s, Ar-H), 7.70 (1H, d, *J* 10 Hz, Ar-H), 7.00-6.70 (3H, m, Ar-H), 4.30 (2H, t, *J* 9 Hz, C(5)H_2), 4.00 (3H, s, -OCH_3), 3.90 (6H, s, 2 x -OCH_3) and 3.20 (2H, t, *J* 9 Hz, C(6)H_2).

9-Benzyloxy-5,6-dihydrobenzimidazo[2,1-a]isoquinoline **16e**

N-Oxide **15e** (1.39 g, 4.06 mmol) and PCl_3 (0.42 ml, 4.87 mmol) gave compound **16e** (0.81 g, 62%) as brown crystals, m.p. 150-153 °C (ethanol). [Found: C, 80.9; H, 5.6; N, 8.5. $C_{22}H_{18}N_2O$ requires C, 81.0; H, 5.6; N, 8.6 %]. $\nu_{max.}$ 1623, 1481, 1237 and 1165 cm^{-1}. δ 8.25 (1H, d, *J* 5 Hz, Ar-H), 7.75 (1H, d, *J* 9 Hz, Ar-H), 7.55-7.35 (8H, m, Ar-H), 7.00 (1H, dd, *J* 9 and 1 Hz, Ar-H), 6.90 (1H, d, *J* 1 Hz, Ar-H), 5.15 (2H, s, -OCH_2Ph), 4.30 (2H, t, *J* 9 Hz, C(5)H_2) and 3.30 (2H, t, *J* 9 Hz, C(6)H_2).

9-Benzyloxy-5,6-dihydrobenzimidazo-2,3-dimethoxy[2,1-a]isoquinoline **16f**

N-Oxide **15f** (2.80 g, 6.96 mmol) and PCl_3 (0.72 ml, 8.35 mmol) gave compound **16f** (0.37 g, 14%) as orange crystals, m.p. 160-162 °C (ethanol). [Found: M^+, 386.1619. $C_{24}H_{22}N_2O_3$ requires M, 386.1630]. $\nu_{max.}$ 1627, 1483, 1236 and 1135 cm^{-1}. δ 7.75 (1H, s, Ar-H), 7.65 (1H, d, *J* 10 Hz, Ar-H), 7.50-7.30 (5H, m, Ar-H), 7.00 (1H, dd, *J* 7 and 2 Hz, Ar-H), 6.90 (1H, d, *J* 2 Hz, Ar-H), 6.80 (1H, s, Ar-H), 5.15 (2H, s, -OCH_2Ph), 4.22 (2H, t, *J* 8 Hz, C(5)H_2), 4.00 (3H, s, -OCH_3), 3.90 (3H, s, -OCH_3) and 3.20 (2H, t, *J* 8 Hz, C(6)H_2).

5,6-Dihydro-2,3-dimethoxybenzimidazo[2,1-a]isoquinoline **16g**

N-oxide **15g** (0.50 g, 1.69 mmol) and PCl_3 (0.17 ml, 2.02 mmol) gave compound **16g** (0.19g, 41%) as orange crystals m.p. 191 °C (ethanol). [Found: C, 72.2; H, 5.75; N, 9.8. $C_{17}H_{16}N_2O_2$ requires C, 72.8; H, 5.75; N, 10.0 %]. $\nu_{max.}$ 1623, 1481, 1237 and 1165 cm^{-1}. δ 7.82 (2H, m, Ar-H), 7.36-7.24 (3H, m, Ar-H), 6.80 (1H, s, Ar-H), 4.32 (2H, t, *J* 7 Hz, C(5)H_2), 4.01 (3H, s, -OCH_3), 3.95 (3H, s, -OCH_3) and 3.23 (2H, t, *J* 7 Hz, C(6)H_2).

Compounds **16c** *and* **16d**. *Method B*.

A mixture of the appropriate *N*-oxide and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and anhydrous DCM was heated at reflux for 18 hours with stirring. The mixture was allowed to cool to room temperature

and was poured into dilute sodium hydroxide solution. The organic layer was separated and washed several times with water, dried ($MgSO_4$) and evaporated yielding the product. By this method *N*-oxide **15c** (0.02 g, 0.08 mmol) and DDQ (0.04 g, 0.15 mmol) gave compound **16c** (0.01 g, 55 %), identical with an authentic sample and *N*-oxide **15d** (0.10 g, 0.31 mmol) and DDQ (0.14 g, 0.61 mmol) gave compound **16d** (0.047 g, 47 %), identical with an authentic sample.

Compounds **26** *and* **27** *General Method*.

A mixture of the appropriate *N*-oxide, acetic anhydride and sodium acetate were heated at reflux (4 hours). After cooling to room temperature the mixture was poured into sodium hydroxide solution. After stirring overnight the mixture was extracted several times with DCM, the combined organic layers were washed several times with water, dried ($MgSO_4$) and evaporated yielding the product. By this method the following compounds were prepared.

8-Acetoxy-5,6-dihydro-9-methoxybenzimidazo[2,1-a]isoquinoline **26**

Compound **15c** (0.50 g, 1.88 mmol) in acetic anhydride (20 ml) and sodium acetate (0.30 g, 3.76 mmol) yielded compound **26** (0.28 g, 50 %) as brown crystals, m.p. 136–139 °C (ethanol). [Found: C, 67.0; H, 5.5; N, 8.7; M^+, 308.1147. $C_{18}H_{16}N_2O_3.0.8H_2O$ requires C, 67.05; H, 5.5; N, 8.7 %; M, 308.1161]. $\nu_{max.}$ 1762, 1638, 1263, 1174 and 1094 cm^{-1}. δ 8.22 (1H, m, Ar-H), 7.60 (1H, dd, *J* 6 and 1 Hz, Ar-H), 7.44-7.25 (3H, m, Ar-H), 7.00 (1H, dd, *J* 6 and 1 Hz, Ar-H), 4.43 (2H, t, *J* 7 Hz, C(5)H_2), 3.90 (3H, s, -OCH_3), 3.23 (2H, t, *J* 7 Hz, C(6)H_2) and 2.41 (3H, s, -$COCH_3$).

8-Acetoxy-5,6-dihydro-2,3,9-trimethoxybenzimidazo[2,1-a]isoquinoline **27**

Compound **15d** (0.10 g, 0.31 mmol), acetic anhydride (5.0 ml) and sodium acetate (0.049 g, 0.61 mmol) yielded compound **27** (0.023 g, 20 %) as brown crystals, m.p. 254-257 °C (ethanol). [Found: C, 65.0; H, 5.2; N, 7.3. $C_{20}H_{20}N_2O_5$ requires C, 65.2; H, 5.5; N, 7.6 %]. $\nu_{max.}$ 1764, 1638, 1264, 1163 and 1097 cm^{-1}. δ 7.75 (1H, s, Ar-H), 7.62 (1H, d, *J* 6 Hz, Ar-H), 7.00 (1H, d, *J* 6 Hz, Ar-H), 6.78 (1H, s, Ar-H), 4.48 (2H, t, *J* 7 Hz, C(5)H_2), 4.00 (3H, s, -OCH_3), 3.95 (3H, s, -OCH_3), 3.90 (3H, s, -OCH_3) and 3.20 (2H, t, *J* 7 Hz, C(6)H_2), 2.41 (3H, s, -$COCH_3$).

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