The synthesis of potential new heterocyclic medicinal agents for dopaminergic and serotonergic systems

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The Synthesis of Potential New Heterocyclic Medicinal Agents for Dopaminergic and Serotonergic Systems

A thesis submitted in fulfilment of the requirements for the award of the degree of

DOCTOR OF PHILOSOPHY

from

University of Wollongong

By

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Department of Chemistry
January 1997
In memory of my grandfather
Gholamreza Rezaie
Author's Statement

This thesis contains no material which has been accepted for the award of any higher degree or graduate diploma in any tertiary institution and that, to the best of my knowledge and belief, the thesis contains no material previously published or written by another person, except when due reference is made in the text of the thesis.

Robert Rezaie
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The following abbreviation are used throughout this thesis:

- **AIBN**: azobisisobutyronitrile
- **BBB**: blood brain barrier
- **(Boc)₂O**: di-tert-butyl dicarbonate
- **CI**: chemical ionisation
- **CNS**: central nervous system
- **DCM**: dichloromethane
- **DMF**: N,N-dimethylformamide
- **DPAC**: dipropyl aminochroman
- **DPAT**: dipropyl aminotetralin
- **EI**: electron impact
- **EPSP**: excitatory postsynaptic potential
- **Et₃N**: triethylamine
- **EtOAc**: ethyl acetate
- **EtOH**: ethanol
- **5-HT**: 5 hydroxytryptamine (serotonin)
- **IPSP**: inhibitory postsynaptic potential
- **LP**: light petroleum (bp 60-80°C)
- **MAO**: monoamine oxidase
- **MeOH**: methanol
- **NaH**: sodium hydride
- **NBS**: N-bromosuccinimide
- **(Tf)₂O**: triflic anhydride
- **THF**: tetrahydrofuran
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Abstract

The general aim of the work was to explore the design and synthesis of new ligands which could have potential to mimic the action of neurotransmitters at the dopaminergic or serotonergic receptor sites.

The first part of the project involved studies on the design and development of medium-ring cyclophane-based potential prodrugs which could be ultimately converted to an endogenous ligand, dopamine. A photochemical route to the \( m \)-cyclophane lactams was improved and extended. New chloroacetamides and derivatives were prepared for photochemical investigation. Photolysis of (40) gave rise to a new \( m \)-cyclophane analogue (64) in good yield whose structure was confirmed by X-ray crystallography. In addition, a range of other \( m \)-cyclophanes (65), (66) and (67) were obtained from the photolysis of chloroacetamides (42), (44) and (46) respectively. Photolysis of other new chloroacetamide derivatives (52), (53), (54), (57), (58), (59), (60), (61) and (63), however, did not result in the formation of \( m \)-cyclophane lactams. Benzazepinone analogues or non-heterocyclic products were obtained instead. Mechanistic pathways for the products were indicated.

The usefulness of the photochemical approach to medium ring heterocycles was further extended. Photolysis of \( N \)-chloroacetamide derivatives, 3-chloroacetyl-7,8-dimethoxy-4,5-dihydro-1\( H \)-3-benzazepin-2(3\( H \))-one (86) in aqueous acetonitrile gave 11a-hydroxy-8,9-dimethoxy-5,6,11,11a-tetrahydrooxazolo[2,3-\( b \)][3]benzazepin-2-(2\( H \))-one (87) in good yield. This representative of a new heterocyclic system could be converted into the 11a-ethoxy derivative (88) by recrystallization from ethanol. The structure of (88) was confirmed by X-ray crystallography.
Work was also conducted to develop methods to modify the bridging chain of the m-cyclophane derivatives as part of the potential prodrug studies. Further to this effort, some new chemistry associated with approaches to fused indole systems from the m-cyclophane precursors was uncovered. Reaction of cyclophane lactams (8) and (64) with N-bromosuccinimide in the presence of a catalytic amount of azobisisobutyronitrile led to new seven membered ring fused indolic derivatives (104-112) via C-N intramolecular cyclisation. The reaction, however, did not proceed with N-protected lactam functionality in the bridging ring. Alternative C-C cyclisation in (8) by using boron tribromide gave the previously reported imine (102) which, in turn, was used to prepare the new tricyclic chloroacetamide derivatives (119), (120) and (121) for photochemical investigation. Ultraviolet irradiation of the silylated enamide (121) afforded a benzopyran chloroacetamide derivative (122) in low yield.

The second part of this project was involved with the design and development of non-natural ligands for serotonergic sites and was carried out under a scientific exchange program at the Université of Orléans (France). A new series of 3,4-dihydro-3-amino-2H-benzopyran derivatives with various C5-substituents, (146), (143), (145), (137), (158), (159), (160), (141) and (178) were successfully prepared. The substituents were introduced via palladium-mediated cross-coupling reactions. The effect of these different groups in the 5-position on the interactions with 5HT1A- and 5HT7-subtype receptors was evaluated. In vitro studies, carried out by the pharmaceutical company SERVIER indicated that these derivatives are very active agonists while the ketones (145) and (160) are more potent than the lead compounds at the serotonergic receptor sites. In an extension of this work,
an azido derivative, (69) was also synthesised for future photo-affinity labelling of the above receptors.
CHAPTER 1

General Introduction

1.1 Background

It has been shown, by histological studies, that there is always a gap between the nerve ending and the target tissue, and if a signal from the nerve is to reach the target this gap must be crossed.\textsuperscript{1,3} Observations of the effects of poisons on animals led to the idea that nerves may communicate with other cells by releasing small quantities of chemicals at their junction\textsuperscript{1} and, in fact, this is how a signal is transferred from one cell to another.

The first evidence for the actual release of a chemical in response to activation of nerves was provided by Otto Loewi.\textsuperscript{1} He showed that when the vagus nerve to the heart of a frog was stimulated a substance was released into the perfusion fluid and the heart was slowed. If the perfusion fluid was passed into a second heart which was free of nervous stimulation, then this heart also was slowed. He concluded that a chemical which was released, after stimulation of the vagus nerve, slowed the heart. This chemical passed into the perfusion fluid and acted to slow the second heart. To demonstrate this process in many organs and tissues, more refined techniques were subsequently introduced. The process has been called neurochemical transmission, and the chemicals released have been named neurotransmitters.

Neurotransmitters act at targets close to the nerve from which they are released. Neurotransmitters and hormones (which may also act at sites quite distant from the site of release) are classes of information known as primary messengers. These messengers are recognised by target cells via a specialised mechanisms which allow transferring the message from the
outer surface of the cell, into the cell. The recognition site is called the receptor.

Receptors are, in fact, proteins found in the membrane which can selectively bind messenger molecules and transduce the chemical signal into a response in the target cell.

There are two types of precursor which are used as sources of neurotransmitters. A transmitter may be synthesised in the nerve terminal from which it is released. There is an active transport mechanism in the cell membrane which carries the precursor from the extracellular space into the nerve. Tryptophan uptake into 5-hydroxytryptamine neurones is an example of such a precursor-uptake system. Increased precursor availability is the basis of some forms of therapy. In some neurones, the transmitter is not synthesised in the nerve terminal. A larger precursor may be synthesised in the nerve-cell body and then carried by axonal transport to the nerve terminal. At the nerve terminal, there is an enzymatic process which causes the large precursor to break down into a smaller molecule which is then released. It has been reported that peptides are brought to nerve terminals via this mechanism. The only drugs which can modify the availability of these precursors are actually the inhibitors of the axonal transport.

The following criteria by which it is established that a substance can act as a neurotransmitter have been reported.¹

1) The substance must be synthesised and stored within the neurone from which it is released. Enzymes and substances must be present in the neurone.

2) Calcium-dependent release must be shown to occur, with all transmitters, following physiological stimulation of the appropriate neuronal pathway.
3) A synthetic neurotransmitter applied exogenously must mimic the actions of the true transmitter in response to physiological or electrical stimulation. It must behave identically in every other regard to the endogenous neurotransmitter.

4) There must be a rapid termination of the action of a released neurotransmitter. The exogenously applied substance must be inactivated by the same mechanism as the true neurotransmitter.

1.2 Neurochemical Transmission

A neurone is the basic unit of the nervous system and can be divided structurally into three parts (1) the dendrites and the cell body, (2) the axon, and (3) the axon terminals. The junction between two nerve cells is called a synapse.

Neurones can be divided into three classes: Afferent neurones, efferent neurones and interneurones. Afferent and efferent neurones lie largely outside the skull or vertebral column while interneurones lie within the CNS.

The process of transferring information from one end of a neurone to the other end (synaptic cleft) is electrical. The peripheral endings of the afferent neurones have receptors. They are either specialised peripheral endings of afferent neurones or separate cells intimately connected to afferent neurone endings that convert the energy presented by the environment into the electrochemical energy of an action potential.

When the receptor is activated by a stimulus (Figure 1), the permeability properties of the receptor membrane changes to permit the movement of ions across the membrane. With the increased permeability sodium ions move into the cell and potassium ions from inside the cell
move out to the plasma. This is because the concentration of potassium in intra-cellular fluid is higher and the concentration of the sodium is lower than in the extracellular fluid.

The effect of this increased membrane permeability is a net diffusion of a small number of potassium ions and the simultaneous movement of a large number of sodium ions. This is probably because the sodium is a smaller ion than the potassium. The result is the movement of positive charges into the cell leading to a decrease in membrane potential or depolarisation\(^2\), since the inside of a resting neurone is about 70 mV negative with respect to the outside.

The depolarisation initiates an action potential which then propagates along the neurone axon to the axon terminal (presynaptic axon), which is in conjunction with the interneurones cell body (postsynaptic cell). This is where a synaptic transmission takes place (Figure 1.1). The information carried by the action potential is then transmitted across the synaptic cleft by means of a chemical agent.

When an action potential in the presynaptic neurone reaches the axon terminal and depolarises the synaptic knob, small quantities of chemical transmitters are released from the synaptic knob into the synaptic cleft. These chemical transmitters are identified largely by histochemical fluorescence techniques, as well as by electron microscopy and spectrophotofluorometry\(^3\).

The transmitter then diffuses across the synaptic cleft and combines with the reactive site of the postsynaptic cell lying right under the subsynaptic membrane, and changes its permeability properties. Here the effect of the chemical transmitter-reactive site combination is to increase the permeability of the subsynaptic membrane to positively charged ions. The
net movement of positive ions is into the neurone and that depolarises the postsynaptic cell. This potential change is called the excitatory postsynaptic potential (EPSP).

![Diagram of a synapse]

**Figure 1.1 A synapse**

However, some chemical transmitters can combine with the receptor site of the postsynaptic neurone, causing an increase in the permeability of the subsynaptic membrane to potassium and chloride ions, but the sodium ion permeability is not affected. Potassium ions, as discussed, diffuse into the extracellular fluid. The inside of the neurone then becomes more negative with respect to the outside. This increased negativity (hyperpolarisation) is an inhibitory postsynaptic potential (IPSP). The transmittance of the concerned information is then inhibited as a result of feed back originating primarily from an increased effect of EPSP.

This type of feed back, in which the increased output of a system leads to an inhibitory effect, is known as negative feed back (Figure 1.2).
1.3 Ligands to Mimic the Action of Neurotransmitters

Transfer of information from the neurone to a neuro-effector tissue, as discussed so far, is achieved by means of release of chemicals from the nerve terminal. The chemical diffuses across the synaptic cleft between the nerve terminal and the neuro-effector tissue and combines with the recognition site (the receptor). This process of chemical neurotransmission is susceptible to the action of drugs at several stages of the sequence and the synthesis of such potential medicinal agents is the subject of this thesis.

1.3.1 Endogenous Ligand Derived from an Administered Precursor

During the past few decades, it has been repeatedly reported that the commonly used processes of delivering therapeutic agents to the sites of their action within the body are generally inefficient and unreliable. Much attention has been focussed on approaches which aim at enhancing the efficacy and reducing the toxicity and unwanted effects of drugs by
controlling their absorption, blood levels, metabolism, distribution and cellular uptake.

Prodrug design comprises an area of drug delivery and consequently an improvement in drug efficacy.\textsuperscript{4} This implies an efficient and selective delivery and transport of a drug substance to the site of action. A prodrug is a pharmacologically inactive compound which undergoes biotransformation, facilitated by enzymes specific to an area, in order to release the active drug.\textsuperscript{4}

Levodopa (L-Dopa) (2) is an example of a natural precursor of dopamine (1) (an endogenous ligand at dopaminergic receptor sites) and is currently a widely used prodrug for dopamine.

![Dopamine (1) and Levodopa (2)](image)

Deficiencies of dopamine\textsuperscript{3,5,6} in the brain are believed to be associated with a number of the symptoms of Parkinson’s disease (PD). In the last few decades, a considerable number of investigations have been conducted for increasing brain dopamine levels in patients suffering from this debilitating disease.

Dopamine is believed to act as a neurotransmitter at certain corpus striatal synapses that are concerned with inhibitory effects in the nigrostriatal pathway in the central nervous system (CNS)\textsuperscript{3}.

Compound (1) itself cannot be administered as it is incapable of crossing the lipid-like blood-brain barrier (BBB). It exists primarily in its protonated form under physiological conditions and that gives rise to the
observed high polarity of the molecule. The pKₐ values³ for the hydroxyl and amine functionalities are 8.9 and 10.6 respectively. The other reason why it cannot be used is due to the "first pass" effect⁵ which results in the loss of the compound due to the metabolism of the drug in the gastrointestinal tract or liver in its initial passage.

It is currently believed that acetylcholine, unlike dopamine, is an excitatory transmitter for neurones running between the substantia nigra, the pallidum and corpus striatum in the brain. In Parkinsonism there is an imbalance between the two transmitters, dopamine and acetylcholine. The dopaminergic input to the corpus striatum is deficient whereas the cholinergic input (level of acetylcholine) remains the same. This imbalance explains³ any apparent increased effect of acetylcholine and rationalises the former empirical use of anticholinergics in parkinsonism.

It is worthwhile to note here that there are three mechanisms³ by which some drugs cause a relative dopamine- acetylcholine imbalance in the CNS. These are believed to be:

1. (1) by depletion of dopamine from intraneuronal stores as is the case with reserpine
2. (2) by rendering the dopamine receptor less accessible to dopamine, as with the neuroleptic agents such as the butyrophenones
3. (3) by increasing acetylcholine levels as occurs with the cholinesterase inhibitor physostigmine.

1.3.1.1 Pro-drugs for Dopamine

The pro-drug approach has a number of advantages over using the active compounds directly. Among these are the more aesthetic reasons such as taste and patient acceptance of the treatment. Other more
physiologically important reasons include the optimisation of drug delivery and consequently an improvement in drug efficacy as discussed earlier.

Levodopa, as pointed out in Section 1.2, is an example of prodrug for dopamine and is used in the treatment of Parkinson's disease. Levodopa has the ability to cross the BBB by the active transport mechanism for amino acids. Dopamine is then formed from Levodopa by the cytoplasmic enzyme aromatic L-amino acid decarboxylase. However, in man, dopa decarboxylase activity is greater in the liver, heart, lungs and kidneys than in brain\(^5\). This fact necessitates the co-administration of peripheral decarboxylase inhibitors such as carbidopa (3), benserazide hydrochloride (4) and MAO (mono amine oxidase) inhibitors. This consequently increases the proportion of Levodopa that crosses the BBB.

![Chemical structures](image)

L-Dopa treatment can have a number of undesirable side-effects associated with it, both in the long term and short term\(^7\). It has been found that one of the most common side effects of L-Dopa therapy is gastric upset with nausea and vomiting\(^3,8\). Also the effectiveness of the treatment in controlling the symptoms of Parkinson's disease decreases with time\(^9\).
One approach which is widely used\textsuperscript{10} is the combination of the pro-drug, L-dopa with an agonist treatment such as bromocriptine. This allows for smaller amounts of L-dopa to be administered which can lead to a reduction of the long term side effects.

Overall, there is still a need for other compounds which can act as precursors of dopamine after uptake into the CNS. Another approach which is being investigated is the development of slow release dopamine pro-drugs.\textsuperscript{11} Most of these pro-drugs have large ester or amide groups which increase lipid solubility, for example in (5) and (6). The compounds then become capable of entering the brain and there are biotransformed ultimately to dopamine (1). It was reported\textsuperscript{11} that (6) produced prolonged brain dopamine levels due to lipophilic absorption followed by slow release of L-dopa. Direct evidence for the brain-specific delivery of dopamine from the redox chemical delivery system (5) was also reported.\textsuperscript{11}

\begin{align*}
\text{(5)} \\
\text{(6)}
\end{align*}

One of the problems associated with having large groups on the prodrugs is that upon the enzymatic hydrolysis large fragments are released.
at the site of actions which are undesirable. Reducing the size of amide or ester group in a way that the lipid solubility of the prodrug molecule would not be dramatically decreased was thus of interest.

Work carried out from the late 1960's in relation to the synthesis of ten membered ring lactams (cyclophane type) from haloacetamides (7 for example) led to the idea that these compounds (eg. 8) might have potential to be used for developing slow release pro-drugs for dopamine. The isomers (9), (10) and (11) were also obtained from the photolysis of (7) (Scheme 1.1).

Demethylation of compound (8) to give the hydroxy cyclophane (12) has also been reported.

\[ \text{Scheme 1.1} \]
An alternative route to (12) was via demethylation of silyloxy cyclophane (14) which, in turn, was obtained via the photolysis of \(N\)-[2-(4-\text{t-butyldimethyl}silyloxy-3-methoxyphenyl)ethyl] chloroacetamide (13) as shown in Scheme 1.2.\(^{17}\)

It is proposed that the cyclophane-based compound (12) might be able to cross the blood-brain barrier, since (compared to that of dopamine) the lipophilicity of the molecule would be significantly increased by blocking protonation of the nitrogen functionality and ionisation of one hydroxyl group. The amine and one phenolic hydroxyl groups are tied up as an amide and ether group respectively by the use of the common bridging chain. The basicity of the amine functionality is greatly reduced by being part of a lactam and at the same time the phenolic ether derivative formed would be less polar than the hydroxyl group. At the site of action, the
compound may then be converted to dopamine as a consequence of ring cleavage by enzymatic processes.

To test this hypothesis, preliminary investigations were carried out indicating that this cyclic lactam (12) appeared to be stable when subjected to basic or enzymatic hydrolysis (amidase). It was thus proposed that if the bridging chain was modified by introducing certain substituents, a two stage cleavage process might be possible resulting ultimately in dopamine (1). The first stage was to include ester hydrolysis via an esterase, and ring opening of the resultant ketal to afford an amide, which now not being part of the ring, may be more readily hydrolysed enzymatically in the second stage to give (1). For example, introducing an acyloxy group in the chain adjacent to the ether oxygen, probably via a photochemical approach, could give access to developing a new potential pro-drug for dopamine as shown in Scheme 1.3.

\[
\text{esterase} \\
\begin{align*}
(H_3C)_2C_2 & \rightarrow H_2O \\
\text{RO} & \quad \text{H} \\
\text{RO} & \quad \text{NH}, \\
R=H & \quad \text{dopamine (1)}
\end{align*}
\]
1.3.2 Design and Development of Non-Natural Ligands

There are a considerable number of exogenously applied substances which can mimic the action of neurotransmitters and initiate a response in the neuroeffector tissues. They are referred to as agonists. Tissues generally have a maximal response which cannot be exceeded; substances which can initiate the maximal response are known as full agonists. A substance which can initiate a response in the tissue but which cannot initiate the maximal response is known as a partial agonist or stimulant. Substances which prevent an agonist from initiating a response are known as antagonists or blockers. Some antagonists have a limited capacity to initiate a biological response. This property of antagonists is referred to as partial agonist activity.

1.3.2.1 Dopamine Receptor Agonists

Direct stimulation of dopamine receptors by some agonists has been used in the treatment of Parkinson's disease. The drugs used for stimulating the dopamine receptor directly have a potential advantage over Levodopa, in that their effect is independent of striatonigral degeneration; Levodopa depends on the remaining neurones to decarboxylate Levodopa to dopamine. This realisation led to the development of dopamine agonists.

Dopamine has a neuronal inhibitory effect by binding to the receptor site of the receiving neurone (postsynaptic neurone). The molecular configuration of the receptor site allows only a particular transmitter molecule to fit the receptor precisely. Therefore receptors embedded in the cell membrane are selective in their ability to bind to the transmitter for which they are designed.
If a drug has a molecular configuration complementary to that of an endogenous neurotransmitter, it may be able to bind to the membrane receptor and substitute for the neurotransmitter's action. Such drugs, as discussed earlier are known as receptor agonists. An example of a drug in this group is apomorphine (15).3,8

In apomorphine, ring A and atoms 1, 2 and 3 produce a substructure similar to that of dopamine and it is this part of the molecule which is thought to interact with the dopamine receptor.

Bromocriptine is another example of a drug in this class and it is widely used in the treatment of Parkinson's disease. There are number of advantages to the agonist approach, such as high receptor selectivity, small dosage required and the ability to by-pass the damaged pre-synaptic neurone. However, rapid introduction causes nausea and vomiting10. Postural hypotension is also produced in many patients as a result of bromomcriptine treatment.

It is notable that stimulation of dopamine release may be possible by using agents such as amantadine (16) that can release dopamine from peripheral neuronal storage sites.3 Amantadine is a primary amine with a pKₐ of 10.8, more basic than the amine group of dopamine (pKₐ 10.6).
Therefore at physiological pH (7.3) it would be in the protonated form, but it is believed that the cage-like structure of amantadine increases, its lipophilicity, enabling it to pass through the barrier.

Furthermore, with regard to treatment of Parkinson's disease, attempts have been made to increase the central anticholinergic effects by using a number of naturally occurring and synthetic anticholinergic agents. Examples of naturally occurring agents are atropine and scopolamine. Benztropine mesylate (Cogentive) and biperiden hydrochloride (Akineton) are examples of the synthetic agents. Unfortunately there are troublesome side effects such as dry mouth, blurred vision, constipation and urinary retention.

1.3.2.2 Serotonin Receptor Agonists

Serotonin (5-Hydroxytryptamine, 5HT) is a neurotransmitter in the central nervous system and in the plexus of the gut. It is found in high concentration in the enterochromafin cells in the lining of the alimentary canal and in the blood platelets. 5-HT is a monoamine and many features of its synthesis, storage, release and inactivation are similar to the processes occurring in tissues which synthesise the other monoamines such as dopamine, noradrenaline and adrenaline.

5HT (19) is made from the aromatic amino acid 5-hydroxytryptaphan (5-HTP) (18) which, in turn, is derived from hydroxylation of the L-
tryptophan (17) by the enzyme tryptophan hydroxylase as shown in Scheme 1.4.

![Scheme 1.4](image)

The dysfunction in serotoninergic systems of the brain has been found to be a most probable cause of illnesses such as anxiety, depression and panic disorders. Therefore, compounds with selective actions on different serotonergic receptors may prove to have clinical utility, besides their use as important pharmacological tools. Apart from serotonin itself, several other compounds have served as templates for the design of potential new drugs.

It is important here to briefly review 5HT receptors prior to discussing the use of serotonin agonists. 5-HT receptor classification has been reviewed several times over the years since the first attempt by Gaddum and Picarelli. The pharmacology, molecular biology and medicinal chemistry
of 5HT receptors have also been extensively reviewed.\textsuperscript{25-31} Until now, classification of receptor subtypes has been made by differentiation of the action of more or less selective drugs. The amino acid sequences of most of the previously known receptor subtypes have been determined and cloned.

The 5-HT receptors can first be divided into the two superfamilies, G-protein coupled receptors and ligand gated ion channels. The G-protein coupled 5-HT receptors include the subtypes of the 5HT\textsubscript{1}, 5HT\textsubscript{2}, 5HT\textsubscript{4}, 5HT\textsubscript{5}, 5HT\textsubscript{6} and 5HT\textsubscript{7} receptors. The 5HT\textsubscript{3} receptor is a ligand gated ion channel.

8-Hydroxy-\textit{N,N}-dipropyl-2-aminotetralin (8-OH-DPAT) (20), whose synthesis was reported by Arvidsson and co-worker\textsuperscript{32} in 1981, has been found to induce the 5HT behavioural syndrome and decrease the cerebral 5HT synthesis in the rat, indicative of central 5-HT receptor agonist properties.

![8-OH-DPAT (20)](image)

It has been demonstrated\textsuperscript{33,34} by \textit{in vitro} radioligand binding studies, that 8-OH-DPAT is a potent and selective agonist at the 5HT\textsubscript{1} subtype receptor, 5HT\textsubscript{1A}. This was supported by \textit{in vivo} studies.\textsuperscript{37,38} The cloning \textsuperscript{35,36} of this receptor indicated that the protein is a single subunit and consists of 421 amino acids arranged with seven transmembrane helices.\textsuperscript{35}

Hacksell and co-workers\textsuperscript{39} have prepared a series of 2-(dipropylamino)tetralin derivatives (DPAT) in which the C8 substituent is varied. They pharmacologically evaluated and explored the importance of
the C8 substituent in the interaction of 2-aminotetralin-based ligands with serotonin (5-HT₁A) receptors. Examples of substituents that they introduced are triflate, acetyl, phenyl, phenyl carboxy, butyl carboxy, methyl, methy ester, carboxylic acid, primary amide, and cyano groups. The affinity of these compounds for the 5HT₁A receptor was evaluated by competition experiments with [³H]-8-OH-DPAT in rat hippocampal and cortical tissue. In addition, the compounds were evaluated for central 5-HT and dopamine receptor stimulating activity in vivo by use of biochemical and behavioural assays in rats. They concluded that a number of derivatives have moderate to high affinities (Kᵢ values range from 0.7 to 130 nM) for 5HT₁A, with no apparent dopaminergic activity. This group of compounds, being similar in profile to the 8-OH-DPAT, were described as agonists. They produced a full-blown 5-HT syndrome in normal as well as in reserpine-treated animals, inhibit the cage-leaving response, and decreased body temperature and 5-HT turnover.

In recent years, there has been interest in various non-benzodiazepine-based treatments of anxiety. Buspirone (21), for example, has been found to be a potent ligand at 5-HT₁A subtype receptor⁴⁰, but with rather low selectivity verses D₂ receptors. However, more selective ligands such as gepirone (22) and ipsapirone (23) have been obtained.⁴¹-⁴⁴
Development of such therapeutic agents that exhibit weak or moderate activity at D$_2$ receptor binding sites and display high affinity for 5-HT$_{1A}$ receptor sites has been pursued further which led to synthesis of 3,4-dihydro-3-amino-2H-1-benzopyran derivatives.$^{45-47}$ Amongst them, 5-MeO-DPAC [5-methoxy-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran] (24), which is closely related to 8-OH-DPAT (20), acts in the nanomolar range at 5HT$_{1A}$ receptor sites and very poorly recognises D$_2$ receptor sites in rat brain membranes.
Studies on the modification of amino substituents and the length of the alkyl side chains of this compound have been conducted also by Podona and coworkers. They found that the best compounds (25, 26, 27, 28) possess imido or sulfonamideo functional groups with a preferential length of four methylenes for the side chain.

\[ \text{OCH}_3 \quad \text{N} \quad \text{(CH}_2)_n \quad \text{O} \]

- n=4 (25)
- n=3 (26)

\[ \text{OCH}_3 \quad \text{N} \quad \text{(CH}_2)_n \quad \text{S} \quad \text{O} \]

- n=4 (27)
- n=2 (28)

These compounds proved to be full agonists, with (25) being the most potent and selective ligand at the 5HT$_{1A}$ subtype receptor.

### 1.4 Aims of the project

The aims of this project were to investigate the design and synthesis of new ligands which could have potential to mimic the action of neurotransmitters at receptor sites. In particular, the first aim was to develop new compounds which could be ultimately converted to an endogenous ligand, dopamine. Medium ring cyclophane-based potential pro-drugs derived from the photolysis of aromatic chloroacetamides, as discussed in Subsection 1.3.1.1, were the focus of the investigation. The specific aim for this part of the project was, thus, to investigate the
preparation of new chloroacetamide derivatives and their photochemical conversion to m-cyclophanes. It was also planned to study the chemistry of m-cyclophanes in order to develop methods to modify the bridging chain.

The second major aim of the project was to design and develop selective non-natural ligands for serotonergic sites. As described earlier, in recent years attention has been focused on using non-benzodiazepine compounds as agonists at serotonin receptor sites. Structurally related benzopyran derivatives (24), (25) have attracted much interest in this area. The aim of the work described in the second part of this thesis was to study the effect of various C5 substituents of (24) and (25) on interactions with the 5HT receptors (5HT$_{1A}$ and 5HT$_7$ subtypes). Furthermore, the intention was to synthesise a DPAC-based ligand for photo-affinity binding of these receptors.
CHAPTER 2

Synthesis of Medium Ring Lactam-Containing \textit{m}-Cyclophanes

2.1 Introduction

2.1.1 General Points

In the first part of this introduction a review of the synthesis of different size bridged \textit{m}-cyclophanes will be presented. Several examples of classical methods previously described in the literature are given. Attention is then focused on the synthesis of ten-membered ring \textit{m}-cyclophanes via the photochemical approach. It was expected that the photolysis of new aromatic chloroacetamides would afford, as indeed had been the case, the analogous ten-membered lactam-containing \textit{m}-cyclophanes.

In the second part, structural modifications to induce pharmacological activity will be discussed. Furthermore, it was hoped that a judicious choice of substituents for the aromatic chloroacetamide derivatives would facilitate a high-yield photocyclisation entry to the target medium-ring heterocycles.

2.1.2 Historical Aspects

Notable progress has been made in the last few decades in the synthesis and properties of compounds containing a benzene ring bridged at the \textit{m}-or \textit{p}-position ([n]\textit{metacyclophanes} and [n]\textit{paracyclophanes}). A variety of routes to prepare \textit{m}-cyclophanes have been described in the literature. For example, the coupling of Grignard reagents with dihalo-aromatic compounds in the presence of a catalytic nickel-phosphane complex afforded nine to thirteen and fifteen-membered ring \textit{m}-cyclophanes as shown in Scheme 2.1\textsuperscript{48}.
The short bridged [5]-m-cyclophane (30) was obtained from (29) by the following elimination rearrangement route (Scheme 2.2).\textsuperscript{48}

As shown in Scheme 2.3, [7]-m-cyclophane (32) has also been generated by treatment of [7]-p-cyclophane (31) with fluorosulfonic acid and \( p \)-toluenesulfonic acid in benzene.\textsuperscript{49}

Märkl has reported the rearrangement of [10]-o-cyclophanes that afforded [10]-m-cyclophanes (Scheme 2.4, \( R=\text{alkyl groups} \)).\textsuperscript{50}
To date the shortest bridge in a 1,3-position, represented by the [4]pyrrolophane (34), has been achieved from the thermal rearrangement of (33) (Scheme 2.5) as reported\textsuperscript{51} by Patterson and co-workers.

Furthermore, reaction of dithia compounds with dihalogenated arene-containing compounds (eg. 35) gave ten to sixteen-membered ring m-cyclophanes as described\textsuperscript{52,53,48} by Vögtle and co-workers (Scheme 2.6).
The ten-membered ring cyclophane, n=3 above, was originally obtained, quite unexpectedly, in 18% yield by adding the dibromide (35) to a solution of the bis-dithiane (36) and n-butyllithium in tetrahydrofuran.\textsuperscript{54}

Ten-membered lactam-containing \textit{m}-cyclophanes, which are of particular interest in this work, have been prepared via a photochemical approach. Witkop and co-workers\textsuperscript{14} reported the isolation of the \textit{m}-cyclophane derivative (8) in low yield (12%) from the photolysis of \(N\)-[2-(3,4-dimethoxyphenyl)ethyl]chloroacetamide (7); analogous products were also obtained in generally low yield from other related photolyses as noted in the review by Sundberg.\textsuperscript{12} However, the silylated \textit{m}-cyclophane (14) derived from the photolysis of the chloroacetamide (13) was isolated in a better yield (31%).\textsuperscript{17,55}
2.1.3 Structural Modifications

Cyclophanes (bridged aromatic compounds) represent an important class of synthetic receptor (hosts) in molecular recognition. All types of substrates (guests) from inorganic and organic cations to neutral molecules have been complexed by tailor-made cyclophanes. In these association processes, all known modes of intermolecular binding interactions have been used. A majority of the crown ethers and cryptands and all of the spherands and cavitands for cation complexation are cyclophanes. In a variety of studies on biomimetic research, the nature of weak non-covalent interactions in biological systems and mechanistic details of enzymatic reactions have also been modelled by using cyclophanes without any receptor properties.

m-Cyclophanes, have been used not only for modelling of biological interactions and processes but also they are of continuing interest with regard to structure modifications for inducing pharmacological activity. It is notable that some m-cyclophanes are naturally occurring compounds. One of the simplest natural phanes is (37) which is also available by synthesis.

As the search for biological properties of m-cyclophanes continues, approaches to design some m-cyclophanes which might have potential as pro-drugs for dopamine were pursued (See Subsection 1.3.1.1).
On the basis that the lactam-containing $m$-cyclophane skeleton may be utilised for developing new potential pro-drugs, it was decided to seek ways to increase the photochemical yield of this system from chloroacetamide precursors.

A further aim of the work presented in this chapter was to investigate the power of the photochemical approach to synthesise new lactam-containing ten-membered ring $m$-cyclophanes with different substituents in the bridging chain, including the 7, 6, 4 and 3 positions (compound 8). For example, introducing an acyloxy group at the 3 position, via a photochemical approach, could ultimately give access to a new potential pro-drug for dopamine as shown in Scheme 1.3 (Subsection 1.3.1.1). Hence, a wider range of N-chloroacetamides and derivatives needed to be investigated for photolysis.

2.2 Synthesis of Precursors for Photolyses

For the purposes discussed above, a number of different N-monochloroacetamides, di and trichloroacetamides, azidoacetamides, fluoro and bromoacetamides were successfully prepared in generally high yields for later photochemical investigation.

2.2.1 Preparation of N-Chloroacetamide Derivatives

2.2.1.1 Preparation of Methyl 2-chloroacetamido-3-(3,4-dimethylphenyl) propanoate (40)

Introducing a methyl ester group at the 7 position of the lactam-containing $m$-cyclophanes would provide an essential skeleton for these compounds to be used for designing potential pro-drugs for L-dopa, the
natural precursor of dopamine. Hence, it was necessary to synthesise (40) for photochemical investigation. The effect of the methyl ester substituent in the amide chain of the chloroacetamide on the photochemical yield of the ten-membered cyclophane system was also to be studied.

The chloroacetamide (40) was derived from commercially available L-dopa. The L-dopa was first esterified using methanol and hydrogen chloride gas to afford (38) (See Scheme 2.7). The methyl ester was then reacted with chloroacetyl chloride, using triethylamine as a base, to give the dihydroxy chloroacetamide derivative (39). The methylation of (39) with diazomethane in a mixture of methanol and diethyl ether led to formation of the dimethoxy chloroacetamide derivative (40) in good yield (75%).

The structures of both chloroacetamides (39 and 40) were confirmed spectroscopically. A distinctive feature in the $^1$H-nmr spectrum of (39) was a two-proton singlet at $\delta$ 4.06 assigned to the hydrogen atoms of the methylene group adjacent to the chlorine atom. In the $^1$H-nmr spectrum of (40), in contrast, a geminal coupling ascribable to the protons of the corresponding
methylene group was observed. The two sets of doublets, as a result of the geminal coupling, were centred at δ 4.02 and 4.06 with a coupling constant of 15.2 Hz. The mass spectrum confirmed the presence of one chlorine atom. The composition of (40) was further supported by elemental microanalysis.

2.2.1.2 Preparation of N-[2-(3,4-Diethoxyphenyl)ethyl]chloroacetamide (42)

It was also desirable to study the effect of the 3-substituent of chloroacetamides on photocyclisation process. It was hoped that the irradiation of a chloroacetamide derivative with an ethoxy instead of a methoxy group at the 3-position would result in the formation of a more stable radical (see Subsection 2.3.2). Hence, a higher yield of the m-cyclophane with a 3-methyl substituent might be obtained. Therefore, chloroacetamides (42) and (44) (See Subsection 2.2.1.3) were also synthesised. Scheme 2.8 shows the synthetic steps involved to prepare the diethoxychloroacetamide (42).

Scheme 2.8
Boron tribromide proved to be an efficient reagent to demethylate $N$-[2-(3,4-dimethoxyphenyl)ethyl]chloroacetamide (7), resulting in the dihydroxychloroacetamide (41). This latter compound could also be obtained from the reaction of dopamine with chloroacetyl chloride in tetrahydrofuran using sodium hydroxide (2M) as a base. The diethylation of (41) was carried out in good yield using diethyl sulphate in refluxing methyl ethyl ketone.

The most salient features of the $^1$H-nmr spectrum of (42) were the two sets of three-proton triplets centred at $\delta$ 1.43 and 1.46 indicating the incorporation of aromatic ethoxy groups. In addition, two-proton quartets, centred at $\delta$ 4.06 and 4.09, were ascribed to the methylene hydrogens adjacent to the methyl groups. Both the $^{13}$C-nmr and mass spectra were consistent with the proposed structure. Furthermore, elemental microanalysis for this compound supported its formula.

2.2.1.3 Preparation of $N$-[2-(3-Ethoxy-4-methoxyphenyl)ethyl]chloroacetamide (44)

For the same reason described above the synthesis of (44) was also undertaken. This compound was obtained from the ethylation of $N$-[2-(3-hydroxy-4-methoxyphenyl)ethyl]chloroacetamide (43) with diethyl sulphate in refluxing methyl ethyl ketone (Scheme 2.9). The amide (43), in turn, was prepared from a standard reaction of $N$-2-(3-hydroxy-4-methoxyphenyl)ethylamine (43a)$^{64,65}$ with chloroacetyl chloride in a mixture of aqueous solution of sodium hydroxide and tetrahydrofuran.

In the $^1$H-nmr spectrum of (44), a three-proton triplet and a two-proton quartet, centred at $\delta$ 1.46 and 4.09, respectively were ascribed to the methyl and the neighbouring methylene groups respectively.
2.2.1.4 Preparation of $N$-Methyl-$[2-(3,4$-dimethoxyphenyl)ethyl]$ chloroacetamide (46)

To study the effect of an $N$-methyl group on the photochemical yield of the $m$-cyclophane system, the title compound (46) was synthesised. A new 6-substituted lactam-containing $m$-cyclophane could therefore be obtained as a result of the photocyclisation of (46). Following the general procedure for the preparation of chloroacetamides, the secondary amine, $N$-methyl homoveratrylamine (45), was reacted with chloroacetyl chloride to afford (46) in good yield (Scheme 2.10).
In the $^1$H-nmr spectrum of (46), the two singlets at $\delta$ 2.95 and 3.01, which integrated overall for three protons, were attributed to the methyl group on the nitrogen, the observation of two $N$-methyl signals being the result of hindered rotation about the amide bond. The mass spectrum of (46) confirmed the presence of one chlorine atom.

2.2.1.5 Preparation of $N$-[2-(3-Pivalylcarbonyloxymethoxy-4-methoxyphenyl)ethyl]chloroacetamide (52)

As described in the introduction, preparation of an (acyloxy)alkyl ether group in the chloroacetamide precursor was quite desirable. This would further expand the study of the effect of the 3-substituent on the photocyclisation of chloroacetamides. (Acyloxy) alkyl $\alpha$-ethers of phenols have been reported to be formed in good yield by alkylation with (acyloxy)alkyl $\alpha$-chlorides or iodides in acetone in the presence of potassium carbonate.$^{57-59}$ Either partial or complete acylation rather than alkylation on oxygen can take place if the iodo compound is not used.

Complete acylation was indeed the case when (43) was reacted with commercially available chloromethyl pivalate resulting in (47) (Scheme 2.11).
MINDO/3SCF MO calculations, reported by Border and coworkers,\textsuperscript{57} on the carbocation \(48a\) generated from the ionization of the representative halide \(48\) showed that significantly more positive charge was found to reside on the carbonyl atom than on the alkyl halide carbon atom.

\[
\begin{align*}
\text{H}_3\text{C}-\overset{\text{O}}{-\overset{\text{C}}{\text{O}}}-\text{CH}_2\text{Cl} & \xrightarrow{-\text{Cl}^-} \text{H}_3\text{C}-\overset{\text{O}}{-\overset{\text{O}}{\text{C}}}-\text{CH}_2^+ \\
& \overset{\delta^+}{\text{O}} & \overset{\delta^+}{\text{O}} & \overset{\delta^+}{\text{O}} & \overset{\delta^+}{\text{O}} & \overset{\delta^+}{\text{O}} \\
\text{(48)} & \text{(48a)} & \text{(48b)}
\end{align*}
\]

Based on this observation, it was not surprising that the acylated \(47\) rather than an alkylated product was isolated from the reaction of the phenol \(43\) with chloromethyl pivalate. According to Border and co-workers, an excellent yield of the desired alkylated product should be achievable when the leaving group is changed to iodide. However, when \(43\) was treated with iodomethyl pivalate, partial acylation occurred with the alkylated and acylated products distributed in a ratio of approximately 3:2.

It was thought that the iodide leaving group, after release from the iodomethyl pivalate, may act as a nucleophile which displaces the chlorine atom of the chloroacetamide \(52\), setting up an equilibrium (Scheme 2.12). The release of chloride ions could subsequently result in formation of chloromethyl pivalate also at equilibrium, as shown in Scheme 2.12. The presence of a small amount of chloromethyl pivalate in the reaction mixture could, in turn, lead to formation of some of the acylated chloroacetamide product \(47\).
It is notable that the acylation on the phenolic group of the chloroacetamide seemed to proceed at a much faster rate (as observed by thin layer chromatographic analysis of the reaction mixture during the course of the reaction) than alkylation. As this causes further release of chloride ions, the concentration of chloromethyl pivalate is therefore retained by re-establishing the equilibrium.

Efforts to trap the iodide ions by silver nitrate did not improve the yield of the alkylated product. All the products including the acylated iodoacetamide (49) were isolated and characterised by their nmr and mass spectra (see later in this Subsection).
Though there are other factors involved in the product distribution obtained from the reaction of (acetyloxy)alkyl α-halides with phenols such as the nucleophilicity of the phenoxide and the ability of the electrophile to stabilize a carbocation, it was decided to carry out the reaction of (43) in a chloride ion free environment. This indeed prevented the acylation since no chloromethyl pivalate could be formed and only the alkylated product was obtained (See Scheme 2.13).

The above was accomplished by converting (43) to the iodoacetamide (50) in the presence of sodium iodide in acetone followed by a reaction with iodomethyl pivalate which gave the alkylated product (51) in good yield as shown in Scheme 2.13. Conversion of (51) to the required chloroacetamide (52) was then achieved using a large excess of lithium chloride and one equivalent of silver nitrate in acetone.
The most noticeable feature of the $^1$H-nmr spectrum of the alkylated product (52) was a two-proton singlet at $\delta$ 5.77, assigned to the hydrogen atoms of the OCH$_2$O moiety whereas this did not appear in the $^1$H-nmr spectrum of the (47) or (49) arising from acylation. The two-proton singlet at $\delta$ 3.78 and the nine-proton singlet at $\delta$ 1.20 were attributed to the methylene group adjacent to the iodine atom and the tertiary butyl group respectively. Evidence for the displacement of iodine with chlorine was a relative downfield shift in resonance frequency of adjacent protons compared to that of the starting iodoacetamide. The signal generated by the methylene protons adjacent to chlorine was downfield by 0.24 ppm. The structural assignment was further supported by mass spectrometry. This spectrum confirmed the presence of a chlorine atom. In addition, the molecular composition, C$_{17}$H$_{24}$NO$_5^{35}$Cl, was established from high resolution mass spectrometry.

2.2.1.6 Preparation of N-[2-(3-Methoxymethylmethoxy-4-methoxyphenyl)ethyl]chloroacetamide (53)

The investigation of the effect of the 3-substituent of chloroacetamides on the photocyclisation process was expanded by preparing (53). The alkylation of (43) with chloromethyl methyl ether was found to proceed in good yield (94%) using sodium hydride as a base in tetrahydrofuran (Scheme 2.14).
The extra two-proton and three-proton singlets in the $^1$H-nmr spectrum of (53), compared to that of the starting chloroacetamide, at $\delta$ 5.22 and 3.51 respectively, was indicative of the incorporation of a methylene ether and an aliphatic methoxy group respectively. The $^{13}$C-nmr spectrum was consistent with the proposed structure, and the methylene ether carbon resonance appeared at $\delta$ 56.1.

2.2.1.7 Preparation of cis and trans isomers of the ester/amide (54)

As introducing various functional groups on the bridging chain of the lactam-containing $m$-cyclophanes, particularly at the 3-position, was desirable, it was decided to also synthesise an enol ether chloroacetamide derivative (54) for photochemical study.

The reaction of (43) with methyl propiolate in the presence of sodium hydride led to formation of the desired product in moderate yield (Scheme 2.15).

![Scheme 2.15](image)

This Michael addition resulted in cis and trans isomers in an approximately 1:1 ratio as shown by their proton spectra. These two spectra were discriminated based on coupling constants of 7.2 and 12.4 Hz for the cis and trans vinyl hydrogens respectively. Both $^{13}$C-nmr and mass spectra provided further evidence for the proposed structure. In the $^{13}$C-nmr
spectrum, the aliphatic methoxy group, the amide and ester carbonyl groups resonated at δ 51.3, 165.8 and 167.7 respectively. The mass spectrum confirmed the presence of one chlorine atom.

2.2.2 Preparation of Di- and Trichloroacetamide Derivatives

The low yield of the desired m-cyclolactams previously obtained from the monochloroacetamides was a limitation for further synthetic transformation. Therefore, the synthesis of di- and trichloroacetamides as precursors for photolysis was investigated. The one or two additional chlorine atoms would provide built-in functionality at the 4-position in the m-cyclophane photoproducts and this functionality could be used for further modifications.

Di- and trichloroacetamide derivatives (55-59) were readily accessible (Scheme 2.16) using dichloro or trichloroacetyl chloride in the same manner as described in Subsection 2.2.1.1, followed by a reaction with diazomethane in a mixture of methanol and diethyl ether to O-methylate when needed.

The structural assignment of these compounds was made by comparison with the spectra of the monochloroacetamides. In the $^1$H-nmr spectra of the dichloroacetamides, the additional chlorine atom resulted in a number of shifts in resonance frequencies of adjacent or nearby nuclei. The signal generated by the methine proton adjacent to the chlorine atoms was moved downfield by 2.0-2.7 ppm. Other signals arising from atoms in the amide chain also exhibited downfield shifts, though not as strongly.
2.2.3 Preparation of Azidoacetamide Derivatives

It was thought that upon the photocyclisation of some aromatic azidoacetamides, an extra nitrogen atom may be incorporated within the ring moiety of the lactam-containing \( m \)-cyclophanes giving scope for further manipulation. Therefore, it was decided to synthesise \( 60 \) and \( 61 \) (\( \text{cis} \) and \( \text{trans} \) isomers).
The substitution of the chlorine atom of (7) and (54) by the azido group took place quite successfully using sodium azide in refluxing methyl ethyl ketone or acetonitrile. The structures of products (60) and (61) were readily ascertained from the spectroscopic data. An upfield shift of around 0.04 ppm in resonance frequency generated by the methylene hydrogens adjacent to the azido group was apparent compared to that of the starting chloroacetamides. In the infrared spectrum of the azidoacetamide compound (60), an absorption band at 2112 cm\(^{-1}\) was attributed to the azide group.

### 2.2.4 Preparation of Miscellaneous N-Substituted Acetamide Derivatives

It was planned that by replacing the chlorine atom with fluorine or bromine, a study of the leaving group effect upon the formation of the cyclolactam could be conducted. The procedure used to synthesise the bromoacetamide (62) involved the addition of a slight excess of bromoacetyl bromide to commercially available homoveratrylamine in dichloromethane. The bromoacetamide was then treated with cesium fluoride in refluxing acetonitrile to afford the fluoroacetamide (63) (Scheme 2.17).
In the $^1$H-nmr spectrum of (62), an upfield shift of 0.15 ppm for a signal generated by the methylene group adjacent to the bromine atom was observed compared to that of the corresponding chloroacetamide. The mass spectrum showed bromine-isotope-containing molecular ion peaks, confirming the presence of one bromine atom. In the $^1$H-nmr spectrum of the (63) the two-proton doublet centred at $\delta$ 4.75, with a large coupling constant of 47.4 Hz due to the interaction with the fluorine atom, was attributed to the methylene group adjacent to the fluorine atom. Both $^{13}$C-nmr and mass spectra gave further evidence for the consistency of the structural assignment. In the $^{13}$C-nmr spectrum, the resonance for the amidomethylene carbon showed coupling with the fluorine atom and appeared as a doublet, centred at $\delta$ 80.2, with a coupling constant of 184 Hz. This interaction with fluorine was also observed for the carbonyl group. It appeared as a doublet which resonated at $\delta$ 167.4 with a coupling constant of 17 Hz.

2.3 Photolysis of Chloroacetamide Derivatives

2.3.1 Introduction to Mechanistic Aspects

Photolyses of the chloroacetamides were generally conducted in benzene using a 16 or 250 W mercury lamp and a vycor filter sleeve, allowing transmission of wavelengths greater than 210 nm. The compound (8), as shown in Section 2.1, was isolated in 24% yield, which was an improvement on the yield (12%) obtained previously in THF. The reason is thought to be an increased effectiveness of the solvent cage in the slightly more viscous solvent benzene. The low polarity of the solvent is also believed to contribute to the higher yield of (8) obtained, since it retards
the formation of the other radical ion derived-products such as 7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one (9),\footnote{14} which was isolated in only 6.5% yield. The possible formation of other isomers such as (10) in benzene was suspected but not isolated.

The mechanism leading to the benzazepin-2-one isomers is thought to involve electron transfer. The first step in this mechanism is believed to be the photoionization which requires two photons. The first is to excite an electron to the singlet state and the second to eject the electron from the aromatic ring to the carbonyl group. This is then followed by chloride ionization and ultimately aromatization.\footnote{12} Therefore, a more polar solvent such as tetrahydrofuran or a mixture of tetrahydrofuran and water should favour this mechanism and give rise to higher yields of the isomers (9) and (10). Alternatively, some of the benzazepin-2-one could conceivably also arise from direct attack on the aromatic ring by the amidomethylene radical from C-Cl homolysis, particularly in benzene, followed by hydrogen abstraction and re-aromatization.
The mechanism leading to products (8) and (14) (Section 2.1) most probably also involves homolytic cleavage of the C-Cl bond,\textsuperscript{78,17} affording a chlorine radical and an amidomethylene radical. The chlorine radical may then abstract a hydrogen atom from the methoxy group (A\textsubscript{8,14}) to form a diradical intermediate. Subsequently, the intra-molecular combination of the diradical (B\textsubscript{8,14}) forms the cyclolactams (8) and (14). It is possible that the t-butyldimethylsilyloxy group at the 4 position in (13) (See Section 2.1) has an effect upon the conformation of the methoxy group at the 3 position. This sterically demanding group may orient the 3-methoxy group a little closer to the chloroacetyl group resulting in more hydrogen abstraction from the methoxy group and subsequently formation of (14) in a higher yield; the bulky silyloxy group may also slow radical diffusion from the solvent cage. Furthermore, with (13) the possible problem of competitive hydrogen abstraction from a saturated C-H group adjacent to oxygen at the 4-position is removed.

2.3.2 Results and Discussion

Based on the above observations, it was thought that with the photocyclisation of the new chloroacetamides described earlier, bridging chain-substituted \textit{m}-cyclophanes could be obtained. Indeed, the ultraviolet irradiation of (40) afforded the new 7-substituted \textit{m}-cyclophane derivative (64) in 30\% yield or 60\% based on the recovered starting material (Scheme 2.18).
Distinguishing signals in the $^1$H-nmr spectrum of the lactam (64) were produced by the oxymethylene, aromatic and aliphatic methoxy groups. A two-proton multiplet at $\delta$ 4.28-4.30 was assigned to the oxymethylene group. The aromatic and aliphatic methoxy groups appeared as singlets at $\delta$ 3.88 and 3.81 respectively (Figure 2.2), while ortho coupling was observed for the 10, 11- aromatic hydrogens ($J=8.0$ Hz) and meta coupling for the 10, 13-aromatic hydrogens ($J=2.0$ Hz). Resonances at $\delta$ 170.9 and 172.1 in the $^{13}$C-nmr spectrum were assigned to the lactam carbonyl and carbonyl of the ester group respectively. The structure of (64) was also confirmed unequivocally by X-ray crystallography (Assoc. Prof. A. H. White, University of Western Australia). The structure obtained is shown in Figure 2.1 and non-hydrogen atom co-ordinates and equivalent isotropic thermal parameters are given in the appendix 1. It is notable from the figure 2.1 that the lactam moiety is transoid with the carbonyl group pointing towards the aromatic ring.

A COSY experiment indicated the coupling patterns for the methylene hydrogens as well as their chemical shift values. Figure 2.3 shows the geminal coupling of the methylene hydrogens. The coupling patterns are also observed for all the neighbouring methylene hydrogens. Characteristically, the methylene hydrogens next to the carbonyl group (4a and 4b) resonated far apart from each other (centred at $\delta$ 2.30 and 2.69),
Figure 2.1 Molecular projection of the cyclophane (64) normal to the phenyl ring; 20% thermal ellipsoids are shown for the non-hydrogen atoms, together with skeletal ring numbering. Hydrogen atoms have arbitrary radii of 0.1 Å.
Figure 2.2 (top). Proton nmr spectrum of 64 in deuterochloroform.

Figure 2.3 (bottom). COSY spectrum of 64 in deuterochloroform.
probably because one is influenced more than the other by the shielding effect of the carbonyl group. Similarly the benzylic methylene hydrogens generated resonances centred at $\delta$ 2.54 and 3.22.

It was proposed that if the oxymethylene radical (B8,14), formed via photolysis, was further stabilized, a better yield of the resulting $m$-cyclophane might be obtained. Representation (A42,44) below, shows the diradical intermediate which would be formed from the photolysis of (42) and (44) (Subsections 2.2.1.2 and 2.2.1.3). The secondary carbon radical produced should be more stable allowing greater intramolecular diradical coupling.

![Diagram A42,44]

The ultraviolet irradiation of the these chloroacetamides in benzene (Scheme 2.19) afforded the new 3-substituted $m$-cyclophanes (65) and (66) in low yields (10-12%). On the other hand, the isomeric benzazepin-2-ones (67 and 68 derived from photolysis of 42, and 69 and 70 from photolysis of 44) were isolated in considerably higher combined yields of 28-31% compared to those of the analogous dimethoxy $m$-cyclophanes.
The reason for the low yield of products (65) and (66) is thought to be most probably due to a steric hindrance effect of the methyl group on the secondary carbon radical. Hence, the intramolecular diradical combination would be retarded and the direct attack on the aromatic ring by the amidomethylene radical (as represented by A42,44) might become more favourable, affording higher yields of the seven-membered ring benzazepin-2-ones.

The structures of (65) and (66) were based on the spectroscopic data. The same complex coupling pattern in the $^1$H-nmr spectra, as described for (64), was observed for (65) and (66). The most salient feature of these spectra was a three-proton doublet at $\delta$ 1.46 ascribable to the methyl substituent at the 3 position in the bridging chain; this was not present in the $^1$H-nmr spectra of the $m$-cyclophanes with the unsubstituted bridging chain (8 or 14).
The signal assigned to the carbonyl group appeared at δ 171.8 in the 13C-nmr spectrum of (65).

It was decided to investigate the effect of the N-methyl substituent in the chloroacetamide derivative (46) on the orientation of the amide-containing chain. If the amidomethylene group is placed a little closer to the 3-methoxy group, the photolysis of the compound (46) might result in more hydrogen abstraction from the methoxy group at 3 the position and also more intramolecular combination of the diradical (as shown by B8,14 page 43) affording a higher yield of m-cyclophane. For this reason, the photolysis of (46) in benzene was conducted with a view to extending the usefulness of the photocyclisation approach to lactam-containing m-cyclophanes with a new substituted bridging chain. Irradiation of (46) in benzene afforded the corresponding 6-substituted m-cyclophane derivative (71) in 18% yield based on the recovered starting material (Scheme 2.20). Despite the assumption that more H-abstraction by the chlorine atom from the 3-methoxy group may have been favourable due to the orientation of the amide-containing chain, no improvement in yield was observed compared to the cyclophane with the unsubstituted bridging chain. The corresponding benzazepin-2-one isomers (72) and (73) (Scheme 2.20) were isolated in a combined yield of 22%.

It is notable that the reaction proceeded slowly as 62% of the starting material was recovered after 19 hours of irradiation. Hindered rotation about the amide bond, as confirmed by the proton spectrum of this compound, might be a contributing factor to the slow photochemical process. The slow inter-conversion of conformers probably retards the photochemical reaction as one conformer might be less favourable for photocyclisation than the other one. The two conformers may be represented by (46a) and (46b), below.
Hindered rotation about the secondary amide bond in the compound (7) was not observed, due to less double bond character in the nitrogen-carbon (carbon of the carbonyl group) bond resulting in a lower energy barrier to rotation.

A distinguishing feature in the $^1$H-nmr spectrum of the $m$-cyclophane product (71) was a three-proton singlet at $\delta$ 3.15 which was assigned to the N-methyl group.

The incorporation of an (acyloxy) alkyl $\alpha$ ether substituent at the 3 position of the $m$-cyclophane bridging chain was also desirable as described earlier (Subsections 2.1.3 and 2.2.1.5). However, the irradiation of (52) in
benzene using 16 W or 250 W mercury lamps fitted in a vycor sleeve failed to give the desired result. The products obtained arose from i) a photorearrangement affording (74) and ii) fragmentation/substitution to give (75), (77), and (43) (Scheme 2.21).

The assignment of structures to these photolysis products was supported by analytical and spectroscopic data. The salient feature in the $^1$H-nmr of (74) was two sets of one-proton doublets centred at $\delta$ 6.75 and 6.82 ascribable to aromatic protons, indicating the incorporation of an acyl group on the aromatic ring. This was further supported by a nine-proton singlet at $\delta$ 1.20 and the absence of a signal which is generated by the methylene group in the $^1$H-nmr of the starting chloroacetamide (52). The mass spectrum confirmed the presence of one chlorine atom.
Scheme 2.21

The $^1$H-nmr of (75) was also quite distinctive. An extra five-proton multiplet at $\delta$ 7.17-7.32 was attributed to the incorporated phenyl ring. An upfield shift of 0.48 ppm in the resonance frequency generated by the methylene hydrogens next to the carbonyl group was observed compared to that of the starting chloroacetamide. Similarly, the $^1$H-nmr of (77) exhibited a multiplet resonating at $\delta$ 7.17-7.32 which was ascribed to the phenyl group.
The spectroscopic data obtained for (43) were identical to those previously described (Subsection 2.2.1.3).

The molecular compositions, C_{16}H_{22}NO_{4}^{35}Cl, C_{23}H_{29}NO_{5} and C_{17}H_{19}NO_{3} of (74), (75) and (77) respectively, were established from high resolution mass spectrometry.

The mechanism leading to (74) probably involves homolytic cleavage of the C-O bond of the ether group to give the intermediate shown by (74a) (Scheme 2.22), followed by loss of formaldehyde. The acyl radical could then add to the benzene ring and re-aromatization would give the product (74).

The conversion of compound (52) to (43) may conceivably proceed by acidic ester hydrolysis followed by loss of the formaldehyde group. The hydrogen chloride required to cleave the ester bond may arise as a result of chlorine atom displacement by the phenyl group which also leads to formation of (75) and (77).
The photolysis of (52) was also conducted in tetrahydrofuran. The change of solvent prevented the formation of products obtained in benzene. Nevertheless, no \( m \)-cyclophane formation was observed. Instead, the product (78) was isolated in 43% converted yield (Scheme 2.23) most probably arising from hydrogen abstraction by the amidomethylene radical from the solvent.
The structure of (78) was readily ascertained from spectroscopic data. A singlet resonating at δ 1.95 in the $^1$H-nmr spectrum of this compound was attributed to the methyl group of the acetamide chain, while the $^{13}$C-nmr exhibited a resonance at δ 23.1 ascribable to this methyl group.

Due to the multi-product formation observed upon the photolysis of (52) in benzene, it was decided to approach the synthesis of 3-alkyloxy substituted $m$-cyclophanes from a simpler system. The photolysis of (53) was therefore investigated. The irradiation of this compound in benzene gave the products (76) and (77), which were spectroscopically identical to those isolated from the photolysis of (52), together with a new benzazepin-2-one derivative (79) (Scheme 2.24); no $m$-cyclophane formation was observed.
In support of the proposed structure (79), the proton $^1$H-nmr of this compound exhibited a one-proton triplet and two-proton doublet centred at δ 3.19 and 4.90, ascribable to the aliphatic hydroxyl group and the adjacent methylene group respectively. The methylene next to the carbonyl group appeared as a two-proton singlet at δ 3.78 ppm. The molecular composition, C$_{12}$H$_{15}$NO$_4$, was established from high resolution mass spectrometry.

The course of the reaction appears to be similar to that observed in the photolysis of (52). However in this case, the photocyclisation forms a seven-membered benzazepin-2-one (79). The formaldehyde expelled, most probably via the same mechanism as described in Scheme 2.22, could add to the nitrogen of the amide resulting in formation of the acylated amino alcohol (79).
Condensation of amides with formaldehyde under neutral, acidic or basic conditions to give methylolamides has been reported previously.\(^6\)

\[
\text{RCONH}_2 + \text{CH}_2\text{O} \quad \rightleftharpoons \quad 
\text{RCONHCH}_2\text{OH}
\]

\(N\text{-methylolamide}\)

Amides (and imides) as shown above, react reversibly with formaldehyde. The reaction is catalysed by either acid or base over a relatively wide \(pH\) range (2-12), and the activation energy of the reverse reaction remains greater than that of the forward process by about 5 Kcal/mol.\(^6\) Although the equilibrium favouring the \(N\text{-methylolamide}\) is unaffected by \(pH\), elevated temperatures tend to favour the dissociation reaction which has a higher activation energy. For this reason the isolation of products often must be carried out at or near room temperature, and purifications by recrystallisation is conducted with a minimum of heating.\(^6\)

In the light of the results from the photolyses of (52) and (53), further work on the photochemical approach to 3 acyl/alkyloxy-substituted \(m\)-cyclophanes was not pursued further.

Further efforts to introduce a functional group at the 3-position of the \(m\)-cyclophane system involved the photolysis of (54). It was anticipated that the ultraviolet irradiation of this compound (Subsection 2.2.1.7) might afford a new \(m\)-cyclophane via a possible addition of the amidomethylene radical to either carbon of the double bond. Although not specifically covered by Baldwin's Rules\(^{10}\), \(10\text{-Exo-Tris}\) ring closure would appear to be favourable. However, in the event, the irradiation of (54) gave a seven-membered ring benzazepin-2-one analogue (80) together with the phenolic derivative (43) (Scheme 2.25) as the main products. The yield of the photochemical formation of (80) was optimized by using acetonitrile as a solvent (34%). The
hydrolysis of the ester most probably occurs during the work up of the reaction mixture. The conversion of the *trans* isomer (54) to the *cis* isomer was observed when the photolysis was conducted in benzene.

![Reaction Diagram](image)

Scheme 2.25

The spectroscopic data for these compounds was consistent with the proposed structures. In the $^1$H-nmr of (80), the methylene hydrogens adjacent to the carbonyl group appeared as a singlet at $\delta$ 4.05. The disappearance of the resonance corresponding to the aliphatic methoxy group was indicative of ester hydrolysis resulting in formation of the carboxylic group. The spectroscopic data for (43) was identical to that previously described (Subsection 2.2.1.3).
Overall, the photochemical approach to the 3 substituted ten-membered lactam-containing \( m \)-cyclodaphanes proved to be quite difficult, with the exception of the methyl substituted (65) and (66) described earlier in this Chapter. It appears that a chloroacetamide must possess an alkoxy such as methoxy or ethoxy in order for intramolecular photocyclisation to proceed satisfactorily. However, formation of the 7-and 6-substituted \( m \)-cyclodaphanes was achievable. The 7-methyl ester substituted \( m \)-cyclodaphane was obtained in good photochemical yield (60\%, based on the recovered starting material) and no formation of benzazepin-2-ones isomers was observed.

As described earlier, a silyloxy group at the 4 position of a chloroacetamide also increases the photochemical yield of the ten-membered \( m \)-cyclodaphane system. In the future, designing a compound as shown below (81), would seem to be of interest for photochemical investigations in benzene. It might give access to higher yields of the corresponding ten-membered lactam-containing \( m \)-cyclodaphane.

\[
\begin{align*}
\text{H}_3\text{CON}^\| & \text{NHCOCH}_2\text{Cl} \\
\text{J} & \text{J} \\
\text{COOCH}_3 & \text{H}_3\text{SiCl}(\text{CH}_3)_2 \\
\end{align*}
\]

(81)

2.4 Photolysis of Di- and Trichloroacetamides

2.4.1 Results

The photolysis of the dichloroacetamide (57, Subsection 2.2.2) in benzene resulted in a complicated product mixture as analysed by thin layer chromatography. However, benzazepin-2-one isomers (82) and (83) were obtained as a result of the irradiation of (57) (Subsection 2.2.2). The
distinguishing feature of the $^1$H-nmr spectra of these compounds was a singlet at $\delta$ 4.3 generated by the methine group next to the chlorine atom. The mass spectra of these compounds exhibited chlorine-isotope-containing molecular ion peaks confirming the presence of one chlorine atom.

![Diagram](attachment:image.png)

To further explore the effect of the acetamide moiety on the photocyclisation process to $m$-cyclophanes, the photolysis of trichloroacetamides was also investigated. Ultraviolet irradiation of (56) (Subsection 2.2.2) in benzene failed, however, to give any cyclised products in particular the $m$-cyclophane system. A carboxylic acid (84) was isolated instead, as shown in Scheme 2.26.

![Scheme 2.26](attachment:scheme.png)

2.4.2 Discussion

As shown in Scheme 2.27, the mechanism leading to (84) most probably involves photo-assisted solvolysis in the presence of adventitious water to afford an intermediate, (84a), followed by the formation of the acid
halide (84b) which in turn is converted to the carboxylic acid (84), possibly during the work up. No dark reaction was observed when a solution of (56) in benzene was stirred at 30-35°C.

Scheme 2.27

2.5 Photolysis of Azidoacetamide Derivatives

The irradiation of azidoacetamides (60) and (61) in benzene failed to give any evidence of m-cyclophane products. A glyoxylamide (85) was isolated from the photolysis of (60) (Scheme 2.28), and a good yield of 51% was obtained when a mixture of acetonitrile and water in a ratio of 1:1 was used as the solvent.

Scheme 2.28

Mechanistically, as shown in Scheme 2.29, a possible sequence for the conversion of the azidoacetamide (60) to (85) could involve formation of a
nitrene intermediate (85a) followed by intramolecular C-H insertion to afford the imine-amide (85b). Hydrolysis of the imine to afford the hydroxylamine intermediate (85c), followed by deamination, could then give rise to the glyoxylamide (85).

Scheme 2.29

The only change observed upon the irradiation of the azidoacetamide (61) (Subsection 2.2.3) in benzene was the conversion of the cis to the trans isomer. No formation of cyclic products was observed.

2.6 Photolysis of Miscellaneous N-Substituted Acetamide Derivatives

When the fluoroacetamide (63) was irradiated in benzene through vycor under nitrogen for 4 hours, very little change was observed on monitoring by thin layer chromatography. No m-cyclophane was observed and it appeared that only some polymeric material may have been formed. The photolysis of the bromoacetamide (62) gave rise to a mixture of products from which the m-cyclophane (8) was isolated in low yield (11%).
2.7 Photochemical Study on the Benzazepin-2-one Derivative (86)

A photochemical approach to fused heterocycles from benzazepin-2-ones was thought to be possible, and this was investigated briefly in order to explore the further synthetic usefulness of the photocyclisation of chloroacetamides. Hence, 7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one (6) was allowed to react with chloroacetyl chloride affording the new aromatic chloroacetamide (86) in good yield (Scheme 2.30). The structure of this compound was readily ascertained from analytical and spectroscopic data. The salient feature in the $^1$H-nmr spectrum of this compound was a singlet at $\delta$ 4.01 which was attributed to the methylene group next to the chlorine atom. In the $^{13}$C-nmr spectrum, this carbon resonated at $\delta$ 41.3. The mass spectrum of (86) confirmed the presence of one chlorine atom and the structure was further supported by the elemental microanalysis.

When (86) was irradiated for 3 hours in a mixture of acetonitrile and water, using a 16 W mercury lamp, a new fused heterocycle, the oxazolo[2,3-
b][3]benzazepinone (87) was formed in good yield (Scheme 2.31). The assignment of the structure was based on spectroscopic data and chemical transformation. In the $^1$H-nmr, the benzylic methylene hydrogens next to the carbon bearing the hydroxyl substituent appeared as a pair of doublets, centred at $\delta$ 3.15 and 3.26 with a coupling constant of 14.4 Hz as a result of the geminal coupling. The methylene hydrogens adjacent to the carbonyl group (together with the hydroxy group) generated a multiplet at $\delta$ 4.10-4.25. In the $^{13}$C-nmr spectrum of this compound, the most distinguishing feature was a resonance at $\delta$ 110.3 generated by the quaternary carbon next to the hydroxyl group. In addition, the loss of a chlorine atom as a result of photocyclisation was confirmed by mass spectrometry. The elemental microanalysis supported the formula of this compound.

![Scheme 2.31](image)

The mechanism leading to (87), as shown in Scheme 2.31, most probably involves photo-assisted solvolysis as a major initial step.\textsuperscript{88-89} This would result in formation of the hydroxy derivative (87a), which could then undergo intramolecular cyclisation to afford (87). To support this
mechanism, a solution of (86) in a mixture of acetonitrile and water was refluxed for one hour in the absence of light. The major product isolated was (9) as a result of hydrolysis of the chloroacetamide (86). Nevertheless, a small quantity of (87) was also observed on thin layer chromatographic analysis of the reaction mixture, suggesting the formation of the intermediate hydroxy compound (87a). No dark reaction was observed when (86) was stirred in a mixture of acetonitrile and water at the temperature of the photolysis (30-35°C).

When (87) was dissolved in hot ethanol the hydroxyl group was displaced to afford the ethoxy analogue (88). The structure of this ethoxy substituted oxazolobenzazepinone derivative was confirmed by spectroscopic data including high resolution mass spectrometry and by X-ray crystallography. The structure obtained is shown in Figure 2.4; non-hydrogen atom co-ordinates and equivalent isotropic thermal parameters are given in appendix 2.

![Structure of (88)](image)

2.8 Some Non-Photochemical Approaches to Lactam-Containing \( m \)-Cyclophanes

In view of the difficulties with the photochemical approaches, it was decided to study lactam-containing \( m \)-cyclophane formation via a non-photochemical route. The possibility of the idoacetamide (50) (Subsection 2.2.1.5) undergoing intramolecular nucleophilic substitution was therefore investigated. When (50) was treated with sodium hydride in tetrahydrofuran in low concentration (6.7 mM), the only product isolated
Figure 2.4. Molecular projection of 88, showing the folding of the molecule; 20% thermal ellipsoids are shown for the non-hydrogen atoms, together with skeletal ring numbering. Hydrogen atoms have arbitrary radii of 0.1 Å.
was an 18-membered ring bridged derivative (89) in 61% yield (Scheme 2.32). The assignment of the structure of this symmetrical dimer was supported by analytical and spectroscopic data. The most salient feature of the ¹H-nmr spectrum of this compound was a singlet at δ 4.52, which integrated for four protons, ascribable to the hydrogens of the two methylene groups next to the carbonyls. The mass spectrum provided further evidence for the dimeric structure as it exhibited a molecular ion peak at m/z 414. The molecular composition of C₂₂H₂₆O₆N₂ was consistent with the elemental microanalysis.

Attempts at intramolecular cyclisation on the extended amide-containing chain compound (90), failed to give an alternative route to the ten-membered ring m-cyclophane (8). The main product isolated was the elimination product (91). No intramolecular Michael addition was observed.
when (91) was treated further with the base sodium hydride, presumably due to steric and entropic constraints.

In addition, it was decided to examine an aza-Witting cyclisation approach to the lactam-containing \( m \)-cyclophanes. The intramolecular version of the aza-Witting reactions has been described by Eguchi and co-workers\(^{66,67} \); it has considerable potential for the synthesis of nitrogen-containing heterocycles. For example a 2-substituted oxazole (93) has been prepared via this approach, by reacting (92) with triethyl phosphite (Scheme 2.33).\(^{66} \)

\[
\begin{align*}
\text{(92)} & \quad \text{P(OEt)}_3 \\
\text{O} & \quad \text{N} \quad \text{P(OEt)}_3 \\
\text{N} & \quad \text{O} \quad \text{R}
\end{align*}
\]

Therefore, it seemed worthwhile to assess whether 3-(acetyloxy) azidoacetamide (95) could be induced to undergo the intramolecular aza-Witting reaction to afford a ring enlarged diaza \( m \)-cyclophane as shown in the Scheme 2.34. Compound (95) was obtained from the acetylation of (94)
which, in turn, was derived from (43) via a nucleophilic substitution of the chlorine atom by the azide ion (Scheme 2.34). Refluxing (95) with triethyl phosphite in cyclohexane afforded the product (96). According to Eguchi and co-workers this type of ylide is the intermediate which would be formed prior to cyclisation. However, compound (96) did not undergo intramolecular reaction when refluxed in cyclohexane or toluene for 48 hours.

It is thought that because the amidomethylene substituent is oriented far from the acetyloxy group, the nitrogen cannot attack the carbonyl group which is required for cyclisation to proceed.
CHAPTER 3
Chemistry of Lactam-Containing \textit{m}-Cylophanes

3.1 Introduction

3.1.2 General points

In the first part of this introduction some examples of \textit{m}-cyclophane transformations will be given. In the second part the reactivity of the bridging chain of lactam-containing \textit{m}-cylophanes towards introducing functional groups will be discussed. This proved difficult due to some interactions between the bridge and the aromatic ring. The constraint that the aromatic nucleus exerts on the bridge by its being the anchor point of attachment, as well as the presence of the $\pi$-electron system transannular to many of the bridge substituents, rendered these interactions more likely. Efforts were therefore focused on functionalising the bridging chain, in order to sensitise the lactam moiety for hydrolysis.

3.1.2 Examples of Chemical Transformation

\textit{Meta}-cyclophanes have been reported to undergo chemical transformation via ring openings, introduction of intra-annular functional groups and ring closures. For example, 1,3-bridged naphthalenophanes (97) can undergo a ring opening when treated with hydrogen bromide resulting in formation of (98) (Scheme 3.1).\textsuperscript{68}
A large number of \([n]metacyclophanes\) with specific intra-annular lithiated \([n]\) metacyclophane groups can be prepared from the intra-annular lithiated \([n]\)metacyclophane as exemplified by Scheme 3.2.\(^{69}\)

Irradiation of 2-chloro\([6](1,3)\)naphthalenophane (99) leads to transannular cyclisation affording compound (100) and (101) (Scheme 3.3).\(^{70}\)
The ten-membered lactam-containing \textit{m}-cyclophane (8), of particular interest in this work, has been reported to undergo a ring closure and demethylation upon treatment with hydrobromic acid to give (102) (Scheme 3.4).\textsuperscript{14}

3.2 Functionalisation of the Bridging Chain

As the search for approaches associated with the formation of functionalised bridging chains via photocyclisation of chloroacetamide derivatives faced some degree of limitation, it was decided to study some reactions on lactam-containing \textit{m}-cyclophanes in order to find methods to functionalise their bridging chain. Appropriate functional groups such as
an acyloxy group at the 3-position, would theoretically provide the \( m \)-cyclophanes with an essential feature to undergo ring cleavage enzymatically (Subsection 2.1.3).

Treatment of lactam-containing \( m \)-cyclophanes with boron tribromide and \( N \)-bromosuccinimide resulted in ring closure involving C-C and C-N cyclisation respectively, the latter providing access to new fused indolic systems. The C-C cyclisation induced by boron tribromide gave the imine (102) which, in turn, was used to prepare new chloroacetamide derivatives for photochemical investigation.

In order to introduce a carbon-carbon double bond adjacent to the lactam carbonyl group, the reaction of the \( N \)-protected \( m \)-cyclophane (103) with lithium diisopropylamide and benzeneselenyl bromide was investigated. In the event, an \( \alpha,\beta \)-unsaturated amide was obtained successfully. However, a side process also occurred which resulted in a ring cleavage.

![Diagram of Compound 103]

### 3.2.1 C-N Cyclization

#### 3.2.1.1 Reaction of Methoxy Cyclolactam (8) With \( N \)-Bromosuccinimide

It was envisaged that the reaction of \( N \)-bromosuccinimide (NBS) with \( m \)-cyclophanes may result in bromination at the \( \alpha \) position to the oxygen in the ring moiety, providing a handle for the later introduction of an acyloxy substituent. In the event, however, this reagent led to intramolecular
reactions and bromination at the benzylic position forming representatives of a new tricyclic system.

When the methoxy cyclolactam (8) was treated with N-bromosuccinimide and azobisisobutyronitrile (AIBN) in refluxing carbon tetrachloride for 30 minutes the result was C-N cyclisation forming the new seven-membered fused indolic derivative (104) as the major product. Other minor products (105)-(108) were also formed (Scheme 3.5). Intramolecular cyclisation, bromination at the benzylic position and subsequent dehydrobromination resulted in compound (106). The aromatic bromination products (107) and (108), which were discriminated on the basis of NOESY experiments, and (105), probably arise from the dihydroindole derivative (104).

![Scheme 3.5](image)
The assignment of structures to these compounds rested on spectroscopic data. The most significant feature of the $^1$H-nmr spectrum of (106) was two sets of one-proton doublet at $\delta$ 6.63 and 7.79 ascribed to indolic hydrogens. In the $^1$H-nmr spectrum of (104), the benzylic methylene hydrogens together with the methylene group adjacent to the carbonyl group appeared as a multiplet at $\delta$ 3.03-3.10. The molecular compositions, C$_{12}$H$_{11}$NO$_3$ and C$_{12}$H$_{13}$NO$_3$ of (106) and (104) respectively, were established from high resolution mass spectrometry.

3.2.1.2 Reaction of Methyl Ester Cyclolactam (64) With NBS

The m-cyclophane ester derivative (64) was also treated with N-bromosuccinimide under the same conditions as for (8) but for double the time. This resulted in the indole analogues (109-112), with no dihydro indole derivatives being isolated (Scheme 3.6). The reason for not obtaining this latter derivative appears to be the stronger driving force to form the indole ring in this case as a more conjugated system would result. In addition, the reaction was run for a longer period of time. Hence, there was a greater possibility of bromination at the benzylic position and the subsequent dehydrobromination.
Mechanistically as shown in Scheme 3.7, a plausible sequence could involve formation of traces of hypobromous acid from N-bromosuccinimide\textsuperscript{71} or bromine and adventitious water, followed by the formation of N-bromolactam and water on reaction of the hypobromous acid with the lactam. The N-bromolactam could then possibly cyclise directly (with overall loss of hydrogen bromide) or via thermal lactam radical formation.

Amidyl radical cyclisation on to aromatic rings has been proposed in the photolysis or thermolysis of N-iodoacetamides generated in turn from amide precursors in the presence of strong base (potassium-\textit{t}-butoxide).\textsuperscript{72,73}
In general support of these mechanistic considerations, cyclisation also resulted from reaction of (8) with excess bromine in refluxing carbon tetrachloride (30 minutes) to give the 9,10-dibromo derivative of (106) in moderate yield. Furthermore, when (8) was refluxed in benzene (1 hour) in the presence of one equivalent of benzoyl peroxide (conditions conducive to amidyl radical formation), the fused dihydroindole (104) was obtained in 35% yield. In contrast, however, when the simpler model compound N-[2-(3,4-dimethoxyphenyl)ethyl]acetamide (113) was reacted with N-bromosuccinimide in refluxing carbon tetrachloride and in the presence of AIBN, aromatic bromination took precedence at the electronically activated and sterically favoured 2-position to afford the known non-cyclised compound, (114) (Scheme 3.8). This bromo derivative has been cyclised to 1-acetyl-2,3-dihydro-5,6-dimethoxy-1H-indole but only after treatment with sodium hydride and copper (I) bromide.
When the secondary lactam functionality in the bridging ring was protected with a N-\textit{t}-butoxycarbonyl group (compound 103), cyclisation was prevented and a single brominated product (115) was isolated (Scheme 3.9) from standard bromination at the benzylic position. Dehydrobromination does not occur since the driving force to form an indolic system is removed by preventing \textit{N}-bromination and subsequent formation of the amidyl radical for cyclisation.

On the basis of this work, a new route to fused indole derivatives based on \textit{m}-cyclophanic lactams has been developed. This work also provides an alternative strategy towards the synthesis of the indolic 6,7-dialkylxy dihydro indoles and indoles, since hydrolysis of the indolic \textit{N}-acyl moiety should be easily achieved. A previously described approach to these latter derivatives involves the reductive cyclisation of 2,6-dinitrostyrene
derivatives with ammonium formate in the presence of a catalytic amount of palladium on carbon in refluxing methanol.\textsuperscript{75}

Analogous compounds, the six membered ring fused dihydroindole derivatives exemplified by (116)\textsuperscript{79a,b} and (117)\textsuperscript{80}, have been reported to show fungicidal properties. Other fluorinated alkyl derivatives have shown antihypertensive activity.\textsuperscript{81a,b} Synthesis of (116) has been carried out by reacting the 7-hydroxy substituted dihydroindole derivative with haloacetyl halide.\textsuperscript{79a}

There have been, however, no reports on the preparation and properties of the analogous seven membered 1,4-oxazepino ring fused derivatives as described in this Subsection, while the azepino analogue (118) has only recently been described\textsuperscript{82} as the basis for a structurally novel tricyclic dipeptide mimetic.
3.2.2 C-C Cyclization and Reactions of the Resulting Imine (102)

Boron tribromide was found to be a mild alternative reagent to refluxing hydrobromic acid\textsuperscript{14}, for demethylation and cyclisation of (8). The reaction was carried out at -78°C to afford (102) in good yield (Scheme 3.10).

\[ \text{Scheme 3.10} \]

The spectroscopic details of (102) were identical to those previously reported. The imine (102) was then reacted with chloroacetyl chloride to afford (119). Since it was decided to investigate the photolysis of the chloroacetamide (119), it was necessary to protect the hydroxy group of this compound. This was carried out by silylation with tert-butylidimethylsilyl chloride. The ultraviolet irradiation of the resulting silylated compound (121) afforded a benzopyran chloroacetamide derivative (122) in low yield (Scheme 3.11).
The assignment of structures was based on spectroscopic data and elemental microanalysis. In the $^1$H-nmr spectrum of (119), the most salient feature was a two-proton doublet centred at $\delta$ 5.04 ascribable to the methylene group adjacent to the ether oxygen. In the $^{13}$C-spectrum, this methylene carbon resonated at $\delta$ 66.3. In the $^1$H-nmr spectrum of (121) the two singlets at $\delta$ 0.18 and 1.00, which were assigned to the methyl groups on the silicon atom and the tertiary butyl group respectively, were indicative of incorporation of the silyl group. A singlet at $\delta$ 4.31 in this spectrum, was ascribed to the methylene protons adjacent to the chlorine atom. In the $^1$H-nmr of (122) the methylene protons of the chloromethyl group resonated further upfield ($\delta$ 4.00) indicating that the nitrogen of the amidomethylene group was now part of the straight chain ethylacetamide. The methylene
hydrogens adjacent to the carbonyl group of the benzopyranone ring appeared as a triplet centred at δ 3.21 which integrated for two protons. The methylene hydrogens next to the oxygen in this ring were assigned by a two-proton triplet which resonated at δ 4.61. The proposed structure was supported by mass spectrometry.

The mechanism leading to the formation of the benzopyranone (122) most probably involves the photohydration of the eneamide (121) to give the intermediate (122a) which can then rearrange to afford (122) by ring cleavage and solvolysis (Scheme 3.12). While no dark reaction on (121) was carried out, it was observed to be stable on chromatography on silica gel presumably with traces of water present.

Scheme 3.12

An azidoacetamide derivative (120) was also prepared in these studies by reaction of (119) with sodium azide in refluxing acetonitrile. The structure of this compound was confirmed by spectroscopic data and elemental microanalysis. It was thought that (120) might cyclise via thermal nitrene formation to possibly form compound (120a). However, in the event, no change was observed when this compound was refluxed in toluene for 6 hours.
The carbon-nitrogen double bond of (102) was also reduced using lithium aluminium hydride to give a secondary amine (123) (Scheme 3.13) which was assessed for receptor binding in a broad screen (NovaScreen, USA). However, no particularly strong binding properties were observed in a range of receptors including dopaminergic D₁, D₂, and serotonergic 5HT₁ and 5HT₂ receptors as shown in appendix 3.

A distinguishing feature of the ¹H-nmr spectrum of (123) was an extra signal which appeared as a multiplet at δ 4.07-4.12 and was ascribed to the methine hydrogen. In the ¹³C-nmr spectrum of (123), the benzylic carbon next to nitrogen atom was ascribed to the signal at δ 51.6.

3.2.3 Reaction of the N-Protected Cyclophane (103) with Benzenselenyl Bromide

It is worthwhile to stress here that a pro-drug is a compound which undergoes biotransformation prior to exhibiting a pharmacological effect⁴. This transformation may be enzymatically or non-enzymatically induced, and the latter instance can include acid or base-induced reactions.
Treatment of the methoxycyclolactam (8) with a refluxing solution of sodium hydroxide did not result in ring cleavage. The lactam was also resistant to amidase-induced hydrolysis at pH 7 at room temperature. These observations justified the efforts directed towards seeking methodologies to functionalise the bridging chain, particularly at the 3 position, of the lactam-containing \( m \)-cyclophanes. A suitably functionalised bridge might be expected to be more susceptible to hydrolytic cleavage.

Hence, introducing a carbon-carbon double bond adjacent to the carbonyl group was desirable since it could possibly undergo slow hydrolysis under physiological conditions as shown by Scheme 3.14a.

![Scheme 3.14a](image)

Syntheses of \( \alpha,\beta \)-unsaturated ketones and esters have been described in the literature using organoselenium reagents.\(^{76,77}\) In each case, the penultimate step involves oxidation of an \( \alpha \)-phenylselenocarbonyl
compound to the corresponding selenoxide which eliminates at room temperature to the desired olefin (Scheme 3.14).

![Scheme 3.14]

Compound (8) was first protected using di-tert-butyl dicarbonate and triethylamine and 4-(dimethylamino)pyridine as the base. Reaction of the N-protected cyclophane (103) with lithium diisopropylamide and benzeneselenyl bromide resulted in ring cleavage. However, the benzeneselenyl group was also incorporated leading to (124) (Scheme 3.15).

![Scheme 3.15]
The incorporation of the benzeneselenyl and diisopropylamino groups in (124) was confirmed by the $^1$H-nmr and mass spectra. The phenyl group in the $^1$H-nmr spectrum gave rise to two-proton and three-proton multiplets at $\delta$ 7.61-7.64 and 7.22-7.29 respectively. In this spectrum, the two sets of doublets, centred at $\delta$ 0.92 and 0.94, were ascribed to the methyls of the isopropyl groups and integrated for twelve protons overall.

It appeared that lithium diisopropylamide, in the first step acted as a nucleophile to attack the carbonyl group cleaving the ring to afford the intermediate (124a) (Scheme 3.16). In the second step, as a base, it deprotonated the carbon adjacent to the carbonyl group. The carbanion formed could either attack the benzeneselenyl bromide forming $\alpha$-phenylselenocarbonyl (124) or undergo elimination to afford (125) (Scheme 3.17).
In general support of the fragmentation shown in Scheme 3.17, when the unprotected methoxy cyclophane (8) was reacted with sodium hydride and methyl iodide in order to methylate the nitrogen, ring cleavage and O-methylation occurred giving compound (126) as shown in Scheme 3.17a.

The phenylselenyl derivative (124) was then oxidised using hydrogen peroxide in acetic acid and subsequently eliminated to the corresponding α,β-unsaturated carbonyl compound (127) (Scheme 3.18). The side product (125) most probably arises from (127) as a result of acidic hydrolysis. The structural assignment of (127) rested on spectroscopic data. The trans vinylic hydrogens in the $^1$H-nmr appeared as two one-proton doublets ($J=12.9$ Hz) centred at $\delta 6.05$ and 7.86.
The related vinylogous ester analogues of (127) can also be synthesised alternatively by reacting appropriate phenols, such as (128), with methyl propiolate. The Michael addition of (128) to methyl propiolate resulted in the formation of compounds (129) and (130). Intramolecular cyclisation of (129) and/or (130) gave (131) (Scheme 3.19).

Scheme 3.18

Scheme 3.19
3.3 **Conclusion**

While a number of new compounds including those which are representative of new heterocyclic systems were produced, appropriately substituted \( m \)-cyclophane lactams for assessment as potential dopamine pro-drugs could not be synthesised.
CHAPTER 4
Synthesis of New Benzopyran Derivatives

4.1 Introduction

4.1.1 General points

The work in this chapter, which was carried out under a scientific exchange program, represents a different class of heterocycles (benzopyrans) which were investigated with respect to activity at serotonin receptors.

Some compounds based on the benzopyran skeleton for future photo-affinity labelling of serotonergic sub-type receptors were also designed continuing the theme of photochemistry in drug design and development.

4.1.2 Synthetic Background

Several benzopyran derivatives act as agonists at serotonin receptors. Amongst them, Guillaumet and co-workers have reported the synthesis of 5-methoxy-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran (137) (Scheme 4.1) and the analogous 5-hydroxy compound (138). Amongst them, Guillaumet and co-workers have reported the synthesis of 5-methoxy-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran (137) (Scheme 4.1) and the analogous 5-hydroxy compound (138).

Commercially substituted 2-hydroxybenzaldehyde (132) was treated with nitroethene in the presence of di-n-butylamine in chloroform to afford the nitro derivative (133). The unsaturated compound was then reacted with sodium borohydride in the presence of silica gel in a mixture of chloroform and isopropyl alcohol to give the saturated nitro compound (134). This product was then converted to the corresponding amino derivative (135) by means of a procedure that involved using hydrazine in the presence of Raney nickel. The amine (135) was then reacted with allyl bromide in toluene in the presence of a saturated aqueous solution of potassium carbonate to afford (136). Catalytic hydrogenation in ethyl acetate
in the presence of palladium on carbon and triethylamine then resulted in formation of (137) which was demethylated with hydrobromic acid to afford (138).

The alkylation on the nitrogen in (135) was carried out alternatively using iodopropane and potassium carbonate in N,N-dimethylformamide at 60°C.

\[
\begin{align*}
\text{(132)} & \quad \text{O}_2\text{NCH}=\text{CH}_2/\text{nBu}_2\text{NH, CHCl}_3 \\
\text{(133)} & \quad \text{NaBH}_4, \text{SiO}_2, \text{CHCl}_3, \text{iPrOH} \\
\text{(135)} & \quad \text{Raney Ni, H}_2\text{N-NH}_2, \text{EtOH} \\
\text{(134)} & \quad \text{BrCH}_2\text{CH}=\text{CH}_2, \text{K}_2\text{CO}_3, \text{PhCH}_3 \\
\text{(136)} & \quad \text{H}_2, \text{Pd/C, AcOEt, Et}_3\text{N} \\
\text{(137)} & \quad \text{HBr, AcOH} \\
\text{(138)} & 
\end{align*}
\]

Scheme 4.1
Preparation of the 8-azaspiro[4.5]decane-7,9-dione analogue (140a) has been described by Pondona and co-workers as shown in Scheme 4.2.\textsuperscript{46} Reductive amination\textsuperscript{83} of ketone (139)\textsuperscript{84}, which in turn was obtained from 2-hydroxy-6-methoxybenzaldehyde according to a procedure described by Wise and co-workers\textsuperscript{85} with 8-(4-aminobutyl)-8-azaspiro[4.5]decane-7,9-dione hydrochloride\textsuperscript{86,87}, afforded (140a).

![Scheme 4.2](image)

An alternative route to compound (140a) has also been reported\textsuperscript{45} that involved direct alkylation of 3,4-dihydro-3-amino-2H-1-benzopyran (135) using appropriate alkylation agents as shown in Scheme 4.3.
4.1.3 Structural Modification

Compounds (137), (138) and (140a) proved to have the necessary structural requirements for good affinity to 5-HT$_1$A receptors and high selectivity versus other receptors. Modifications in these compounds of the extracyclic amino substituents involving the length of the alkyl side chains and their substituents have been explored previously. The most potent compounds possessed imido or sulfonamido functional groups with a preferential length of four methylenes for the side chain. It is notable that after resolution, the dextrorotatory enantiomers showed better affinity and selectivity for the 5H$_1$A receptor. These compounds have been shown to be full agonists.

The aim of the work presented in this chapter, was to investigate the effect of C5-substituents in 3,4-dihydro-3-amino-2H-1-benzopyran derivatives on interactions with the serotonergic receptor subtypes, 5H$_1$A and 5HT$_7$. Therefore, new substituents needed to be incorporated at the 5 position. It must be noted that the cloning and characterisation of the novel
serotonin receptor, designated as 5HT7, have been conducted only recently\(^8^8,^8^9\). This receptor has unique pharmacological profiles that redefines the agonist and antagonist classification of ligands previously thought to be selective.

An appropriate azido group containing ligand also needed to be prepared for later photo-affinity labelling of the above receptors.

4.2 Results and Discussion

4.2.1 Synthesis of 5-methoxy-3,4-dihydro-3-di-N-propylamino-2H-1-bezopyran (5-MeO-DPAC) Derivatives

Various substituents were introduced in generally high yields at the 5 position, via well documented\(^9^5,^9^6\) palladium-mediated cross-coupling reactions. The compound (137) (5-MeO-DPAC) was demethylated using hydrogen bromide in acetic acid at 140\(^\circ\)C to afford the corresponding hydroxy compound which was then reacted with triflic anydride in dichloromethane in the presence of pyridine to give the 5-triflate analogue (141) (Scheme 4.4).

\[
egin{align*}
\text{OCH}_3 & \quad 1) \text{HBr/CH}_3\text{COOH} \quad 140^\circ\text{C}, 90\% \\
& \quad 2) (\text{Tf})_2\text{O/pyridine/CH}_2\text{Cl}_2 \quad 72\%
\end{align*}
\]

\textit{Scheme 4.4}

The compound (141) was coupled with vinyltributyltin using a palladium (II) complex in \(N,N\)-dimethylformamide at 90\(^\circ\)C to afford the 5-vinyl analogue (142) in good yield (Scheme 4.5). In order to remove the
excess of tin reagent and the tributyltin hydride, the compound (142) was isolated as its hydrochloride salt. The compound (142) was then hydrogenated using a palladium on carbon catalyst to give the target compound (143) (Scheme 4.5).

The assignment of structures was supported by elemental microanalyses and spectroscopic data. In the $^1$H-nmr spectrum of (142) the vinyl hydrogens appeared as three sets of doublets of doublets centred at δ 5.32, 5.65 and 6.87. The disappearance of these resonances in the T-H-nmr spectrum of compound (143) was indicative of the reduction of the carbon-carbon double bond.

In order to prepare the 5-acetyl derivative (145), (141) was reacted with (1-ethoxyvinyl)tributyltin to afford the intermediate (144) which was then treated with hydrochloric acid (10%) to give the amino ketone (145) after basification of the reaction mixture (Scheme 4.6).
The structure of (145) was readily ascertained from the spectroscopic data. A characteristic signal in the $^1$H-nmr spectrum was a three-proton singlet at $\delta$ 2.60 which was assigned to the acetyl methyl group. In the $^{13}$C-nmr spectrum this carbonyl group resonated at $\delta$ 205.0. Mass spectrometry and elemental microanalysis further supported the structure.

The 5-phenyl benzopyran derivative (146) was obtained in good yield via a Suzuki coupling, as shown in Scheme 4.7.
The substitution of the triflate with the phenyl group was confirmed by elemental microanalysis and the spectroscopic data. In the $^1$H-nmr spectrum of (146) a multiplet at $\delta$ 7.33-7.48 was assigned to the incorporated phenyl ring. In addition, the structure was further supported by mass spectrometry.

It was desirable to prepare the 5-cyano derivative (147) since the study of the effect of this electron withdrawing substituent on interaction with serotonergic receptors was also of interest. Furthermore, the cyano derivative would also serve as a good starting material to further diversify functional groups at the 5 position. The cyano group was therefore introduced in good yield using tetrakis(triphenylphosphine)palladium(0) and zinc cyanide in $N,N$-dimethylformamide at 90°C (Scheme 4.8). The infrared spectrum of (147) showed an absorption band at 2228 cm$^{-1}$ consistent with the presence of a cyano group.

![Scheme 4.8](image)
The reaction mechanism for palladium-mediated cyanation of the aryl triflates is dissimilar to that of the so-called cross-coupling reaction\textsuperscript{97} as one equivalent of the palladium complex is required for the reaction to proceed in good yield. The process cannot construct a catalytic cycle because of the deposition of metallic palladium.\textsuperscript{97}

The 5-cyano derivative (147) was reduced with lithium aluminium hydride in absolute ethanol to afford the amine (149). The structural assignment of this compound rested on spectroscopic data. In the \textsuperscript{1}H-nmr spectrum, the methylene hydrogens adjacent to the primary amino group appeared as a singlet at $\delta$ 3.86.

An attempt to hydrolyse the nitrile (147) by refluxing in a solution of sodium hydroxide in a mixture of ethanol and water resulted in formation of a primary amide (148). The spectroscopic data of this compound was consistent with the proposed structure. In the \textsuperscript{1}H-nmr spectrum, a singlet at $\delta$ 7.22 was assigned to the hydrogens of the primary amide group. In the \textsuperscript{13}C-nmr spectrum the amide carbonyl group resonated at $\delta$ 171.7. The infrared spectrum showed absorption bands at 3202 and 3392 cm\textsuperscript{-1} which were attributed to the amide hydrogens.

4.2.2 Synthesis of 8-[4-N-propyl-N-(5-methoxy-3,4-dihydro-2H-1-benzopyran-3-yl)amino-propyl]-8-azaspiro[4.5]decane-7,9-dione

Previous investigations have shown that an imide-containing side chain on the nitrogen increases the potency of benzopyran derivatives at the 5HT\textsubscript{1A} receptor. Hence, there was a need to also vary the substituent at the 5 position of these compounds in order study their effects on the interaction with the receptors.
The same methodology as described in Subsection 4.2.1 was used to introduce different groups at the 5 position. Since the imide-containing side chain was likely to be unstable in acidic or basic conditions, it was decided to incorporate this group after the palladium-catalysed cross-coupling reactions. The starting material for this sequence was the N-protected triflate (152) prepared in turn from (135). This methoxy derivative was demethylated using hydrogen bromide and acetic acid to afford (150) which was then reacted with di-tert-butyl dicarbonate giving (151) (Scheme 4.9). Treatment of (151) with triflic anhydride in the presence of pyridine led to formation of (152) in good yield (Scheme 4.9).

Scheme 4.9

Compound (152) was then utilised to perform the coupling reactions to introduce phenyl, ethyl, and acetyl groups, at the 5 position. Scheme 4.10 gives the conditions used, as described earlier, to obtain the respective compounds (156), (154) and (157).
These Boc-protected products were deprotected in high yields using trifluoroacetic acid in dichloromethane (Scheme 4.11). Alkylations on the nitrogen were carried out using appropriate alkylation agents and potassium carbonate in N,N-dimethylformamide in moderate to high yields. The unprotected primary amines were reacted with 8-(4-bromobutyl)-8-azaspiro[4.5]decane-7,9-dione to afford secondary amines which, in turn, were reacted with iodopropane to obtain the target tertiary amines (158), (159) and (160) (Scheme 4.11).
The structural assignment of these compounds was based on spectroscopic data and elemental microanalysis. In the $^1$H-nmr spectrum of compound (158), the aromatic protons in the phenyl group at the 5 position appeared as multiplets at $\delta$ 7.33-7.48. In the $^1$H-nmr spectrum of (159), a three-proton triplet at $\delta$ 1.25 was assigned to the methyl of the ethyl group. The $^1$H-nmr spectrum of (160) showed a three-proton singlet at $\delta$ 2.58 which was consistent with the presence of an acetyl group.

Under the above alkylation conditions a carbamate side product, arising from the carbonylation of nitrogen, was isolated (24-56%) during each
alkylation step. Compounds (161), (162) and (163), which were obtained in the first alkylation step, were isolated using column chromatography.

During the second alkylation step, compounds (164), (165) and (166) were formed as side products. The separation of each carbamate from the corresponding tertiary amine was carried out by oxalate formation. The assignment of structures was supported by both the nmr and mass spectral data.

The carbonylation of primary and secondary amines has been reported previously under these conditions. It was proposed that the carbamate esters were derived from the alkylation of an intermediate carbamate anion generated by the reaction of the amine with carbon dioxide (Scheme 4.12). In turn, it was hypothesised that the carbon dioxide was
generated *in situ* from neutralisation of potassium carbonate (Scheme 4.13). The reaction was solvent dependent, as no carbamate ester formation was observed in either acetonitrile or tetrahydrofuran. However, the rate of the required alkylation reactions were reduced when these alternative solvents were used.

\[
\text{R—NH}_2 + \text{CO}_2 \rightarrow \text{R—N}^{\text{H}}^+ \xrightarrow{\text{H}^+} \text{R—N}^{\text{H}} \xrightarrow{\text{CO}_2} \text{R—N}^{\text{H}} \xrightarrow{\text{CH}_2\text{R'}} \text{O—CH}_2\text{R'}
\]

Scheme 4.12

\[
\text{R—NH}_2 + 1/2 \text{K}_2\text{CO}_3 \xrightarrow{\text{RH}_2\text{C—I}} \text{R—N}^{\text{CH}_2\text{R'}} + \text{KI} + 1/2\text{H}_2\text{O} + 1/2\text{CO}_2
\]

Scheme 4.13

4.3 Synthesis of the 5-Azidophenyl Derivative As a Potential Photoaffinity Ligand

Among the many proteins that respond to 5-hydroxytryptamine, the 5HT$_1$A receptor is distinguished by both ligand-binding and functional characteristics.$^{92}$

Photolabile aryl azide groups have previously been appended to some high-affinity ligands for photoaffinity labelling of the 5HT$_1$A receptor. Ransom and co-workers have photolysed $[^3\text{H}]$-1-[(p-azidophenyl)ethyl]-4-[(trifluoromethyl)-phenyl]piperazine ($[^3\text{H}]p$-N$_3$PAPP) in bovine cortical membranes and obtained$^{93}$ binding to a 55-KDa protein that shows characteristics of a 5HT$_1$A binding protein. Emerit and co-workers have
used 8-methoxy-2-[N-n-propyl-N-[3-[(p-azidophenyl)amino]-propyl]amino]-1,2,3,4-tetrahydronaphthalene to obtain 55-60% irreversible inhibition of [3H]-8-OH-DPAT binding. However, there is still a need for more selective photo-affinity labels to probe in greater detail the molecular basis of ligand-receptor binding.

The moderate selectivity and nanomolar affinity of the agonist 5-phenyl benzopyrane (146) for the 5HT7 receptor, as discussed in Section 4.4, has made this the ligand of choice to label this receptor. Hence, it was decided to prepare a new photo-affinity ligand based on the 5-phenyl benzopyran skeleton. It was therefore necessary to seek ways to incorporate an azidophenyl group at the 5 position as the resulting azido compound would most likely have the structural requirements necessary for photo-affinity labelling via aryl nitrene formation.

Palladium-catalysed cross-coupling reactions on the triflate derivative (141), using commercially available m-nitrophenyl boronic acid or m-aminophenyl boronic acid, seemed to be a judicious choice. Reactions were carried out according to the procedures described earlier in Subsections 4.2.1 and 4.2.2 (Scheme 4.14). The nitrophenyl derivative (167) obtained was reduced using activated zinc power in dichloromethane in the presence of acetic acid to afford the 5-aminophenyl analogue (168). It was also possible to perform the coupling reaction on (141) using m-aminophenyl boronic acid to obtain the 5-aminophenyl derivative (168) directly (Scheme 4.14).
The amine (168) was then converted to the 5-azidophenyl analogue via diazonium salt formation (intermediate 168a) as shown in Scheme 4.15.
The structural assignment of compound (169) and the starting materials (167) and (168) was based on spectroscopic data. In the infrared spectrum of the azidophenyl compound (169), a strong absorption band at 2102 cm\(^{-1}\) was attributed to the azide group.

Time constraints prevented photo-affinity labelling studies to be undertaken.

4.4 Pharmacological Studies

Drugs interacting with the 5-HT\(_{1\alpha}\)-subtype of serotonin (5-HT) receptors are of potential clinical interest in the treatment of anxiety and depression,\(^{18,19}\) and 5-methoxy-3,4-dihydro-3-(di-\(n\)-propylamino)-2H-1-benzopyran (137) and the analogue 8-[4-N-propyl-N-(5-methoxy-3,4-dihydro-2H-1-benzopyran-3-yl)amino-propyl]-8-azaspiro[4.5]decane-7,9-dione (141) are probably amongst the most thoroughly examined 5-HT\(_{1\alpha}\) receptor agonists.\(^{45}\)

As shown in Table 4.1, most of the new derivatives have moderate to high affinity for the 5-HT\(_{1\alpha}\) receptor; this testing was done by the pharmaceutical company SERVIER in France. In fact, (145) and (160) are more potent in this respect than the previously described lead compounds (141) and (137). The derivative substituted with an ethyl group at the 5 position (159, an analogue of 141) exhibits high affinity for the 5-HT\(_{1\alpha}\) receptor. Compounds (146), (143) and (178) are less potent, whereas (158) (the phenyl analogue of 141) displays intermediate affinity.

Compound (160) is also more potent than the previously reported compounds (137) and (141) at the 5-HT\(_7\) subtype receptor site. It is believed that (146) and (158) should serve as new lead compounds for conducting further work to explore the development of medicinal agents which act as selective agonists at the 5-HT\(_7\) receptor sub-type. Such agents would be of
value in the treatment of illnesses such as depression, anxiety, and panic disorders.

Table 4.1 IC$_{50}$ (nM) values in the binding tests

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<th>5HT$_7$</th>
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<td>Ph</td>
<td>62</td>
<td>107</td>
</tr>
<tr>
<td>143</td>
<td>CH$_3$CH$_2$</td>
<td>30.7</td>
<td>157</td>
</tr>
<tr>
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<td>CH$_3$CO</td>
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<td>50</td>
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</tr>
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<td>2</td>
<td>12</td>
</tr>
<tr>
<td>160</td>
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<td>CH$_3$O</td>
<td>190</td>
<td>1100</td>
</tr>
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</table>
4.5 Synthesis of Benzopyran Chloroacetamide Derivatives for Photochemical Investigation

Photolysis of chloroacetamide derivatives, as presented in Chapter 2, proved to be a useful method for ring constructions. The work here presents attempts that were made to photocyclise the benzopyran chloroacetamides (170) and (175) which, in turn, were prepared from the standard chloroacetylation of primary amines (135) and (149) respectively. The intention of this aspect of the work was to try and prepare tricyclic benzopyran derivatives for pharmacological evaluation.

Photolysis of (170) in benzene afforded the reduced product (171) (Scheme 4.16) as a result of hydrogen abstraction by the intermediate amidomethylene radical. The solvent, benzene, is not a good hydrogen donor so it is most likely that the hydrogen is abstracted from the benzylic position of this benzopyran derivative.
Ultraviolet irradiation of compound (170) in a mixture of acetonitrile and water, to promote e-transfer, afforded the hydroxy derivative (172) (Scheme 4.16) which is believed to arise via photo-assisted solvolysis; no cyclisation to the methoxy group was observed.

It was thought that the photolysis of (175) may result in the structurally novel six-and/or seven-membered ring fused heterocycles (173) and (174) as shown below.

![Chemical structures of (173) and (174)]

However, ultraviolet irradiation of (149) failed to give any ring construction products, and the only product isolated in low yield was (176) resulting from amidomethylene radical attack on benzene (Scheme 4.17).
4.6 Conclusion

New desired DPAC derivatives were successfully synthesised. The effect of various substituents in the 5-position of these compounds on interactions with \(5\text{HT}_{1\text{A}}\) and \(5\text{HT}_{7}\) subtype receptors was studied. In general, the acetyl and ethyl groups gave rise to improvement in the receptor binding. Furthermore, a new DPAC-based ligand for future photo-affinity binding of these receptors was prepared.
Chapter 5
Experimental

General Procedures:

All melting points were determined using a Reichert hot stage or Gallenkamp Melting Point apparatus and are uncorrected. The infrared spectra were recorded using a Digilab FTS-7 spectrophotometer and NaCl disks on mulls in nujol or hexachloro-1,3-butadiene (HCB). The peak positions were recorded in wave numbers (cm⁻¹). The ¹H nuclear magnetic resonance spectra (nmr) were determined at 300 or 400 MHz with a Varian Unity-300 or 400 spectrometer. ¹³C nmr spectra were recorded using the same instruments at 75 or 100 MHz. Unless otherwise stated, the spectra were obtained on solutions in CDCl₃ and referenced to TMS. Chemical shifts of the outer peaks are given for specified multiplet patterns in the ¹H-nmr spectra. Ultra-violet/visible spectra were recorded on a Shimadzu UV-visible 160 spectrophotometer. Mass spectra (EI) were obtained using Vacuum General 12-12, Vacuum General - Quattro, or MAT-44 spectrometers and the direct insertion technique, with an electron beam energy of 70 eV and a source temperature of 200°C. The peak intensities, in parentheses, are expressed as the percentage abundance. In the CI mass spectra, methane was used as the ionising gas. High resolution mass spectra were run in the Research School of Chemistry, Australian National University, by Dr. J.K. MacLeod using a VG 70-70 double focussing mass spectrometer, in the Central Science Laboratory, University of Tasmania by Dr. N. Davies using a Kratos Concept ISQ or a VG 7070F mass spectrometer or in the Department of Chemistry, University of Wollongong, by Mr. Larry Hick using a Fisons/VG Austospec-OA-TOF Mass Spectrometer. The optical rotation was determined on a JASCO digital polarimeter, Model DIP-370.
Elemental microanalyses of samples were carried out at the Australian National University and the University of Queensland or in SERVIER (French pharmaceutical company); analytical values are given as percentages. Analytical thin layer chromatography (tlc) was performed on Merck Kieselgel 60PF254 silica on aluminium sheets. $R_f$ values were recorded from the centre of spots. All chromatographic solvent proportions are volume for volume. Column chromatography was performed using Merck silica gel under medium pressure. Dry DMF was distilled from BaO, and dry THF was distilled from sodium metal and benzophenone. Light petroleum had a boiling point range of 60-80°C. Solvents were removed under reduced pressure by rotary evaporation, and organic solvent extracts were dried with anhydrous Na$_2$SO$_4$.

The 5-HT receptor binding tests were carried out by SERVIER. Tests for various other receptors including dopaminergic and also serotonergic sites were conducted by NOVASCREEN (a division of Oceanix Biosciences Corporation, USA)

**General Information for the Photolyses:**

The photolyses were conducted in a large quartz immersion well reactor (model RQ 400) supplied by Photochemical Reactors Ltd., U.K. The lamp was housed internally in a vycor glass sleeve (transmission $>210$ nm) and the solution was saturated with N$_2$ before and during photolysis. The lamp used was a 16 W mercury lamp unless otherwise stated.
5.1 Experimental for Chapter 2

Preparation of L-dopa Methyl Ester Hydrochloride (38)

Hydrogen chloride was bubbled into a refluxing solution of L-dopa (1.0 g, 5.07 mmol) in methanol (40 ml) for 5.5 h. The solvent was then removed \textit{in vacuo} and the residue was dried under high vacuum to give L-dopa methylester hydrochloride\textsuperscript{17} (38) (1.1 g, 90%) as colourless hygroscopic crystals. \textsuperscript{1}H-Nmr (D\textsubscript{2}O) $\delta$: 2.94 (dd, J=14.0, J=6.8 Hz, 1H, CHAr), 3.10 (dd, J=14.0, J=5.6 Hz, 1H, CHAr), 3.68 (s, 3H, COOCH\textsubscript{3}), 4.15-4.21 (m, 1H, CHNH\textsubscript{2}), 6.53 (dd, J=8.0, J=2.0 Hz, 1H, 6-H\textsubscript{arom}), 6.62 (d, J=2.0 Hz, 1H, 2-H\textsubscript{arom}), 6.74 (d, J=8.0 Hz, 1H, 5-H\textsubscript{arom}).

Preparation of Methyl 2-Chloroacetamido-3-(3,4-dihydroxyphenyl) propanoate (39)

To a solution of (38) (810 g, 3.27 mmol) in dry THF (40 ml) were added triethylamine (0.91 ml, 6.54 mmol) and chloroacetyl chloride (0.388 g, 0.28 ml, 3.50 mmol). The solution was then stirred at room temperature for 48 h. Water (20 ml) was then added and the solution was extracted with DCM (3 x 40 ml). The combined organic extracts were washed with water (3 x 10 ml) and then dried. The organic solvent was removed to give a yellow oil. The oil was chromatographed (MeOH : DCM, 4 : 96) to give 2-chloroacetamido-3-(3,4-dihydroxyphenyl)propanoate (39) as a pale yellow oil (799 mg, 85%); $R_f$ 0.20 (MeOH : DCM, 4 : 96). \textsuperscript{1}H-Nmr (CDCl\textsubscript{3}) $\delta$: 2.97 (dd, J=14.0, J=6.8 Hz, 1H,
CHAr), 3.06 (dd, J=14.0, J=5.6 Hz, 1H, CHAr), 3.74 (s, 3H, COOCH₃), 4.06 (s, 2H, CH₂Cl), 4.78-4.83 (m, 1H, CHNH), 6.50 (dd, J=8.0, J=2.0, Hz, 1H, 6-Harom), 6.65 (d, J=2.0 Hz, 1H, 2-Harom), 6.75 (d, J=8.0 Hz, 1H, 5-Harom), 7.12 (d, J=8.4 Hz, 1H, NH). ¹³C-Nmr (CDCl₃) δ: 37.2 (CH₂Ar), 42.3 (CH₂Cl), 52.7 (COOCH₃), 53.7 (CHNH), 115.4 (ArC-H), 116.0 (ArC-H), 121.4 (ArC-H), 127.4 (ArC-CH₂), 143.4 (ArC-OH), 144.1 (ArC-OH), 166.5 (COCH₂), 171.6 (COOCH₃). Ms (EI) m/z (%): 287 (1, M⁺; accurate mass 287.0571, C₁₂H₁₄NO₅³⁵Cl requires 287.0561), 228 (2, M⁺+1), 194 (50), 163 (15), 123 (100).

Preparation of Methyl 2-Chloroacetamido-3-(3,4-dimethoxyphenyl) propanoate (40)

\[ \text{NHCOCH₂Cl} \]

To a solution of (39) (800 mg, 2.78 mmol) in MeOH (10 ml) was added diazomethane in ether (30 ml). The solution was kept at 1°C for 10 h and then at room temperature for 40 h. The organic solvent was then removed by rotary evaporation and then further MeOH (10 ml) and diazomethane (in excess) in ether (30 ml) was added. The solution was kept at 1°C overnight. The organic solvent was evaporated in vacuo to give a colourless solid. The solid was recrystallized from ethanol/ether to give methyl 2-chloroacetamido-3-(3,4-dimethoxyphenyl)propanoate (40) (660 mg, 75%) as colourless crystals; mp 106-107°C. ¹H-Nmr (CDCl₃) δ: 3.10 (d, J=6.0 Hz, 2H, CH₂Ar), 3.75 (s, 3H, COOCH₃), 3.856 (s, 3H, Ar-OCH₃), 3.861 (s, 3H, Ar-OCH₃), 4.02 (d, J=15.2 Hz, 1H, CHCl), 4.06 (d, J=15.2 Hz, 1H, CHCl), 4.83-4.87 (m, 1H, CHNH), 6.64 (dd, J=5.6, J=2.0 Hz, 1H, 6-Harom), 6.68 (d, J=2.4 Hz, 1H, 2-Harom), 6.80 (d, J=8.0 Hz, 1H, 5-Harom), 7.02 (d, J=8.0 Hz, 1H, NH). ¹³C-Nmr (CDCl₃) δ:
37.2 (CH$_2$Ar), 42.3 (CH$_2$Cl), 52.4 (COOC$_2$H$_3$), 53.3 (CHNH), 55.7 (Ar-OCH$_3$), 111.1 (Ar-C-H), 112.1 (Ar-C-H), 121.2 (Ar-C-H), 127.6 (Ar-C-C$_2$H$_2$), 148.1 (Ar-C-OCH$_3$), 165.4 (COCH$_2$Cl), 171.2 (COOCH$_3$). Ms (EI) m/z (%): 315 (2, M$^+$, 35Cl), 222 (35), 191 (5), 151 (100), 137 (5). Anal. Calcd for C$_{14}$H$_{18}$N$_{10}$O$_5$Cl: C, 53.25; H, 5.75; N, 4.44. Found: C, 53.27; H, 5.85; N, 4.34.

**Photolysis of Methyl 2-Chloroacetamido-3-(3,4-dimethoxyphenyl)propanoate (64)**

(i) A solution of (40) (200 mg, 0.634 mmol) in benzene (300 ml) was irradiated for 5 h. The organic solvent was evaporated in vacuo to give a pale yellow oil. The oil was then chromatographed (ethyl acetate : hexane, 70 : 30) to give two fractions after solvent evaporation. The first fraction was the starting material (130 mg, 65%). The second fraction was recrystallized from ethanol to give (64) (37 mg, 21%; 60% based on recovered starting material) as colourless needle-like crystals; mp 234-236°C; $[\alpha]_D^{20} = +105.0^\circ$ (c, 1g/100ml, CHCl$_3$). $^1$H-Nmr (CDCl$_3$) $\delta$: 2.28-2.33 (m, 1H, CHCO), 2.54 (dd, J=13.0, J=11.6 Hz, 1H, CHAr), 2.65-2.72 (ddd, J=13.6, J=9.6, J=4.0 Hz, 1H, CHCO), 3.22 (dd, J=13.0, J=3.2 Hz, 1H, CHAr), 3.81 (s, 3H, COOCH$_3$), 3.88 (s, 3H, ArOCH$_3$), 4.28-4.30 (m, 2H, CH$_2$O), 4.35 (dt, J=11.2, J=3.6 Hz, 1H, CHNH), 5.96 (d, J=10.8, 1H, NH), 6.88 (d, J=8.0 Hz, 1H, 11-H$_{arom}$), 6.97(d, J=2.0 Hz, 13-H$_{arom}$), 7.00 (dd, J=8.0, J=2.0 Hz, 1H, 10-H$_{arom}$). $^{13}$C-Nmr (CDCl$_3$) $\delta$: 39.6 (CH$_2$CO), 41.8 (CH$_2$Ar), 52.6 (CHNH), 55.9 (COOC$_2$H$_3$), 57.3 (CH$_3$OAr), 71.7 (CH$_2$O), 133.6 (ArC-H), 125.3 (ArC-H), 128.3 (ArC-H), 128.6 (ArC-C$_2$H$_2$), 146.3 (ArC-OCH$_3$), 151.5 (ArC-OCH$_2$), 170.9 (COCH$_2$), 172.1 (COOCH$_3$). Ms (EI) m/z (%): 279 (10, M$^+$), 262 (5), 220 (5), 223 (46), 192 (45), 164 (100), 149 (46), 137 (50), 121 (20), 108 (70). Anal. Calcd for C$_{14}$H$_{17}$NO$_5$: C, 60.21; H, 6.14; N, 5.02. Found: C, 60.45; H, 6.33; N, 4.86.
(ii) A solution of (40) (150 mg, 0.475 mmol) in benzene (300 ml) was irradiated for 10 h. The organic solvent was evaporated in vacuo to give a pale yellow oil. The oil was chromatographed as above to give the starting material (40 mg, 11%) and (64) (40 mg, 30%; 39% based on recovered starting material) after recrystallization from ethanol.

Preparation of \( N-[2-(3,4\text{-Dihydroxyphenol})\text{ethyl}]\text{chloacetamide (41)} \)

To a stirred solution of \( N-[2-(3,4\text{-dimethoxyphenyl})\text{ethyl}]\text{chloacetamide (7) (0.2 g, 0.77 mmol) in dry DCM (5 ml), under N}_2/, at -78\text{°C was added boron tribromide (0.2 ml, 2.12 mmol). The solution was allowed to stir at this temperature for 0.5 h and then at room temperature overnight. A saturated solution of ammonium chloride (1 ml) was added and the pH was adjusted to 7 (NaOH, 1M). A small amount of sodium chloride was then added and the solution was extracted with EtOAc (3 x 40 ml). The combined extracts were dried, evaporated and chromatographed (DCM : MeOH, 96 : 4) to give \( N-[2-(3,4\text{-dihydroxyphenol})\text{ethyl}]\text{chloacetamide (41)} \) (150 mg, 84%) as a colourless oil. \(^1\text{H} \text{(CD}_3\text{OD, 400 MHz) } \delta: 2.65 \text{ (t, } J=7.2 \text{ Hz, 2H, CH}_2\text{Ar), 3.37 (t, } J=7.2 \text{ Hz, 2H, CH}_2\text{NH), 4.00 (s, 2H, CH}_2\text{Cl), 6.52 (dd, } J=8.0, J=2.4 \text{ Hz, 1H}_\text{arom), 6.64 (d, } J=2.4 \text{ Hz, 1H}_\text{arom), 6.67 (d, } J=8.0 \text{ Hz, 1H}_\text{arom). Ms (Cl) m/z
Preparation of N-[2-(3,4-Diethoxyphenyl)ethyl]chloroacetamide (42)

A mixture of N-[2-(3,4-dihydroxyphenyl)ethyl]chloroacetamide (41) (200 mg, 1.0307 mmol), potassium carbonate (300 mg, 2.171 mmol) and diethyl sulfate (0.42 ml) in methyl ethyl ketone (10 ml) was refluxed overnight. Water (15 ml) and a saturated solution of ammonium chloride (2 ml) were then added and the mixture was extracted with DCM (3 x 20 ml). The combined extracts were washed, dried, evaporated and chromatographed (DCM : MeOH, 99 : 1) to give N-[2-(3,4-diethoxyphenyl)ethyl]chloroacetamide (42) (328 mg, 88%) as colourless crystals, mp 89-90°C (DCM/MeOH). 1H-Nmr (CDCl₃, 400 MHz) δ: 1.43 (t, J=4.0 Hz, 3H, CH₃CH₂O), 1.46 (t, J=4.0 Hz, 3H, CH₃CH₂O), 2.77 (t, J=6.8 Hz, 2H, CH₂Ar), 3.53 (q, J=6.8 Hz, CH₂NH), 4.02 (s, 2H, CH₂Cl), 4.06 (q, J=4.0 Hz, 2H, CH₃CH₂O), 4.09 (q, J=4.0 Hz, 2H, CH₃CH₂O), 6.64 (s, 1H, NH), 6.70-6.84 (m, 3H_ arom). 13C-Nmr (CDCl₃, 100 MHz) δ: 14.8 (2 x CH₃CH₂O), 34.9 (CH₂Ar), 41.0 (CH₂NH), 42.6 (CH₂Cl), 64.4 (CH₃CH₂O), 64.5 (CH₃CH₂O), 113.7 (ArC-H), 113.9 (ArC-H), 120.7 (ArC-H), 130.8 (ArC-CH₂), 147.4 (ArC-O), 148.8 (ArC-O), 165.7 (CO). Ms (EI) m/z (%): 287 (0.2, M⁺, 37Cl), 285 (0.6, M⁺, 35Cl), 236 (0.1), 226 (0.1), 222 (0.4), 192 (100), 179 (20), 164 (38), 151 (34), 136 (50), 123 (71). Anal. Calcd for C₁₄H₂₀O₃N₃5Cl: C, 58.92; H, 7.07; N, 4.91. Found: C, 58.54; H, 7.10; N, 4.79.
Photolysis of \(N\)-[2-(3,4-Diethoxyphenyl)ethyl]chloroacetamide (42)

A solution of (42) (270 mg, 0.946 mmol) in benzene (350 ml) was irradiated at room temperature for 4 h. The solvent was then evaporated and the residue was chromatographed (EtOAc : hexane, 70 : 30 and then DCM : MeOH, 98.5 : 1.5) to give three fractions. The first fraction was starting material (100 mg, 35%). The second fraction was rechromatographed (same conditions as above) to give 12-ethoxy-3-methyl-2-oxa-6-azabicyclo[7.3.1.]trideca-1(13),9,11-trien-5-one (65) (26 mg, 11%) as a pale yellow gum after evaporation. \(^1\)H-Nmr (CDCl\(_3\), 400 MHz) \(\delta\): 1.43 (t, \(J=6.8\) Hz, 3H, CH\(_3\)CH\(_2\)OAr), 1.46 (d, \(J=6.8\)Hz, 3H, CH\(_3\)CHOAr), 2.35-2.37 (m, 1H, CHCO), 2.38-2.50 (m, 2H, CH\(_2\)Ar), 2.78-2.84 (m, 1H, CHCO), 3.08-3.12 (m, 1H, CHNH), 3.36-3.44 (m, 1H, CHNH), 4.03-4.17 (m, 2H, CH\(_3\)CH\(_2\)OAr), 4.42-4.50 (m, 1H, CH\(_3\)CHOAr), 4.98 (d, 1H, NH), 6.82 (d, \(J=2.0\) Hz, 1H\(_{arom}\)), 6.86 (d, \(J=8.0\) Hz, 1H\(_{arom}\)), 6.91 (dd, \(J=8.0, J=2.0\) Hz, 1H\(_{arom}\)). \(^1\)C-Nmr (CDCl\(_3\), 100 MHz) \(\delta\): 15.0 (CH\(_3\)CH\(_2\)OAr), 22.1 (CH\(_3\)CHOAr), 38.4 (CH\(_2\)Ar), 44.0 (CH\(_2\)NH), (CH\(_2\)CO), 46.4 (CH\(_2\)CO), 53.4 (CH\(_3\)CH\(_2\)OAr), 78.7 (CH\(_3\)CHOAr), 115.2 (ArC-H), 124.4 (ArC-H), 128.4 (ArC-H), 123.0 (ArC-C\(_2\)), 146.4 (ArC-O), 150.6 (ArC-O), 171.8 (CO). Ms (EI) m/z (%): 249 (27, M\(^+\); accurate mass 249.1379, C\(_{14}\)H\(_{19}\)NO\(_3\) requires 249.1365), 220 (3), 206 (9), 192 (11), 177 (5), 164 (100), 151 (17), 149 (37), 136 (38), 123 (30). The third fraction was a mixture of 7,8-diethoxy-1,2,4,5-tetrahydro-2H-3-benzazepin-2-one (67) and 8,9-diethoxy-1,2,4,5-tetrahydro-3H-3-benzazepin-2-one (68) (72 mg, 31%) as a pale yellow oil. \(^1\)H-Nmr (CDCl\(_3\), 400 MHz) \(\delta\): 1.38-1.45 (m, 12H, 4 x CH\(_3\)CH\(_2\)O), 2.99-3.07 (m, 4H, 2 x CH\(_2\)CH\(_2\)NH), 3.49-3.58 (m, 4H, 2 x CH\(_2\)CH\(_2\)NH), 3.74 (s, 2H, COCH\(_2\)), 3.94 (s, 2H, COCH\(_2\)), 3.99-4.08 (m, 8H, 4 x CH\(_3\)CH\(_2\)O), 6.27 (s, 1H, NH), 2.45 (s, 1H, NH), 6.61 (s, 1H\(_{arom}\)), 6.63 (s, 1H\(_{arom}\)), 6.74 (d, \(J=8.0\) Hz, 1H\(_{arom}\)), 6.79 (d, \(J=8.0\) Hz, 1H\(_{arom}\)). Ms (EI) m/z (%): 249 (65, M\(^+\)), 234 (4), 221 (14), 220 (18), 206 (8), 193 (11), 192
Preparation of N-[2-(3-Hydroxy-4-methoxyphenyl)ethyl]chloroacetamide (43)

To a stirred solution of N-2-(3-hydroxy-4-methoxyphenyl)ethylamine hydrochloride\(^{64,65}\) (200 mg, 0.98 mmol) in THF (20 ml), under N\(_2\), was added an aqueous sodium hydroxide solution (3.5 ml, 5M). The solution was then allowed to cool in an ice bath. Chloroacetyl chloride was added dropwise until a white precipitate was observed. The mixture was allowed to stir for 1 h. It was basified to pH 9 (1M NaOH) and then acidified to pH 6.5 (1M HCl). This solution was then extracted with DCM (3 x 30 ml). The combined organic extracts were washed with water (15 ml), dried and evaporated to give a yellow oil. The oil was then chromatographed. Elution with EtOAc : hexane, 45 : 55 gave N-[2-(3-hydroxy-4-methoxyphenyl)ethyl]chloroacetamide (43) as a colourless oil (210 mg, 88 %). \(^1\)H-Nmr (CDCl\(_3\), 400 MHz) \(\delta: 2.75\) (t, J=7.2 Hz, 2H, CH\(_2\)Ar), 3.53 (q, J=7.2 Hz, 2H, CH\(_2\)NH), 3.88 (s, 3H, CH\(_3\)O), 4.02 (s, 2H, CH\(_2\)Cl), 6.61 (s, 1H, NH), 6.68 (dd, J=8.0, J=2.0 Hz, 1H\(_{\text{arom}}\)), 6.78 (d, J=2.0, 1H\(_{\text{arom}}\)), 6.80 (d, J=8.0 Hz, 1H\(_{\text{arom}}\)). Ms (Cl) m/z (%): 246 (4, M\(^{+}+1\), \(^{37}\)Cl), 244
(11, $M^+ + 1$, $^{35}\text{Cl}$), 150 (93), 137 (100), 135 (48); (EI) m/z: accurate mass 243.0658, $C_{11}H_{14}NO_3^{35}\text{Cl}$ requires 243.0662.

**Preparation of $N$-[2-(3-Ethoxy-4-methoxyphenyl)ethyl]chloroacetamide (44)**

![Chemical Structure](image)

A mixture of $N$-[2-(3-hydroxy-4-methoxyphenyl)ethyl]chloroacetamide (43) (210 mg, 0.863 mmol), potassium carbonate (200 mg, 1.447 mmol) and diethyl sulfate (0.3 ml) in methyl ethyl ketone (8 ml) was refluxed for 3 h. The mixture was placed in an ultrasonic bath for 10 min to make a homogeneous suspension and then it was allowed to continue refluxing overnight. Water (10 ml) and a saturated ammonium chloride solution (2 ml) were added and the mixture was extracted with DCM (3 x 20 ml). The combined extracts were dried, evaporated and chromatographed (EtOAc : hexane, 40 : 60) to give $N$-[2-(3-ethoxy-4-methoxyphenyl)ethyl]chloroacetamide (44) (165 mg, 55%) as colourless crystals, mp 80-82°C (EtOAc/hexane). $^1$H-Nmr (CDCl$_3$, 300 MHz) $\delta$: 1.46 (t, J=6.0 Hz, 3H, CH$_3$CH$_2$O), 2.77 (t, J=6.9 Hz, 2H, CH$_2$Ar), 3.53 (q, J=6.9 Hz, 2H, CH$_2$NH), 3.85 (s, 3H, CH$_3$O), 4.01 (s, 2H, CH$_2$Cl), 4.09 (q, J=6.0 Hz, CH$_3$CH$_2$O), 6.69 (s, 1H, NH), 6.72-6.84 (m, 3H$_{arom}$). $^{13}$C-Nmr (CDCl$_3$, 75 MHz) $\delta$: 14.7 (CH$_3$CH$_2$O), 34.9 (CH$_2$Ar), 40.9 (CH$_2$NH), 42.5 (CH$_2$Cl), 55.9 (CH$_3$O), 64.2 (CH$_3$CH$_2$O), 11.8 (ArC-H), 113.4 (ArC-H), 120.6 (ArC-H), 130.7 (ArC-CH$_2$), 148.1 (ArC-O), 148.3 (Ar-O), 165.6 (CO). Ms (EI) m/z (%): 273 (3, $M^+$, $^{37}\text{Cl}$), 271 (9, $M^+$, $^{35}\text{Cl}$), 179 (17), 178 (100), 165 (46), 150 (46), 150 (37), 137 (40), 135 (25), 122 (12). Anal. Calcd for $\text{Cl}_{13}\text{H}_{18}\text{O}_3\text{N}^{35}\text{Cl}$: C, 57.54; H, 6.69; N, 5.17. Found: C, 57.73; H, 6.76; N, 4.94.
Photolysis of $N$-[2-(3-Ethoxy-4-methoxyphenyl)ethyl]chloroacetamide (44)

A solution of (44) (270 mg, 1.006 mmol) in benzene (350 ml) was irradiated at room temperature for 4 h. The solvent was then evaporated and the residue was chromatographed (EtOAc : hexane, 70 : 30 and then DCM : MeOH, 98.5 : 1.5) to give three fractions. The first fraction was stating material (98 mg, 36%). The second fraction was rechromatographed to give 12-methoxy-3-methyl-2-oxa-6-azabicyclo[7.3.1]trideca-1(13),9,11-trien-5-one (66) (28 mg, 12%) as a pale yellow gum after evaporation. $^1$H-Nmr (CDCl$_3$, 400 MHz) δ: 1.45 (d, J=6.8Hz, 3H, CH$_3$CHOAr), 2.35-2.37 (m, 1H, CHCO), 2.38-2.50 (m, 2H, CH$_2$Ar), 2.78-2.84 (m, 1H, CHCO), 3.08-3.12 (m, 1H, CH$_2$NH), 3.36-3.44 (m, 1H, CH$_2$NH), 3.88 (s, 3H, CH$_3$O), 4.42-4.51 (m, 1H, CH$_3$CHOAr), 4.97 (d, 1H, NH), 6.81 (d, J=2.0 Hz, 1H$_{arom}$), 6.85 (d, J=8.0 Hz, 1H$_{arom}$), 6.90 (dd, J=8.0, J=2.0 Hz, 1H$_{arom}$). Ms (EI) m/z (%) 235 (30, M$^+$; accurate mass 235.1193, C$_{13}$H$_{17}$NO$_3$ requires 235.1208), 164 (100), 151 (17). The third fraction was a mixture of 7-ethoxy-8-methoxy-1,2,4,5-tetrahydro-2H-3-benzazepin-2-one (69) and 8-methoxy-9-ethoxy-1,2,4,5-tetrahydro-3H-3-benzazepin-2-one (70) (76 mg, 32%). $^1$H-Nmr (CDCl$_3$, 400 MHz) δ: 1.37-1.44 (m, 6H, 2 x CH$_3$CH$_2$O), 2.99-3.08 (m, 4H, 2 x CH$_2$CH$_2$NH), 3.48-3.58 (m, 4H, 2 x CH$_2$CH$_2$NH), 3.74 (s, 2H, COCH$_2$), 3.94 (s, 2H, COCH$_2$), 3.88 (s, 3H, CH$_3$O), 3.89 (s, 3H, CH$_3$O), 3.99-4.08 (m, 4H, 2 x CH$_3$CH$_2$O), 6.28 (s, 1H, NH), 2.44 (s, 1H, NH), 6.61 (s, 1H$_{arom}$), 6.64 (s, 1H$_{arom}$), 6.75 (d, J=8.0 Hz, 1H$_{arom}$), 6.78 (d, J=8.0 Hz, 1H$_{arom}$).
Preparation of N-[2-(3-Hydroxy-4-methoxyphenyl)ethyl]iodoacetamide (50)

A mixture of (43) (200 mg, 0.821 mmol) and sodium iodide (410 mg, 2.73 mmol) in acetone (10 ml) was allowed to stir overnight. The solvent was then evaporated and the crude residue was chromatographed. Elution with EtOAc : hexane, 50 : 50 gave N-[2-(3-hydroxy-4-methoxyphenyl)ethyl]iodoacetamide (50) (262 mg, 95%) as a colourless crystalline solid after evaporation, mp 131-133°C. 

\[ ^1H-Nmr \quad (CDCl_3, 400 MHz) \delta: 2.73 \quad (t, J=9.6 \text{ Hz}, 2H, \text{CH}_2\text{Ar}), 3.49 \quad (q, J=9.6 \text{ Hz}, 2H, \text{CH}_2\text{NH}), 3.65 \quad (s, 2H, \text{CH}_2\text{I}), 3.88 \quad (s, 3H, \text{CH}_3\text{O}), 5.61 \quad (s, 1H, \text{OH}), 6.01 \quad (s, 1H, \text{NH}), 6.68 \quad (dd, J=12.0, J=3.4 \text{ Hz}, 1\text{H}_{\text{arom}}), 6.78 \quad (d, J=3.4 \text{ Hz}, 1\text{H}_{\text{arom}}), 6.80 \quad (d, J=12.0 \text{ Hz}, 1\text{H}_{\text{arom}}). \]

Ms (Cl) m/z (%): 336 (40, M+1), 208 (10), 191 (12), 151 (80), 150 (100), 137 (100), 135 (61); (EI) m/z: accurate mass 335.0003, C_{11}H_{14}NO_3I requires 335.0018.

Preparation of N-[2-(3-Pivalylcarbonyloxymethoxy-4-methoxyphenyl)ethyl]iodoacetamide (51)

A mixture of (50) (700 mg, 2.09 mmol), iodomethyl pivalate\textsuperscript{57} (0.6 ml) and potassium carbonate (520 mg, 3.77 mmol) in acetone (15 ml) was allowed to stir overnight under N\textsubscript{2}. The solvent was then evaporated and the crude residue was chromatographed. Elution with EtOAc : hexane, 45 : 55, afforded two fractions. The solvent in the first fraction was evaporated to give N-[2-
(3-pivalylcarbonyloxymethoxy-4-methoxyphenyl)ethyl]iodoacetamide (51) (591 mg, 63 %, 72 % based on recovered starting material) as a pale yellow oil. 

$^1$H-Nmr (CDCl$_3$, 400 MHz) δ: 1.20 (s, 9H, (CH$_3$)$_3$C), 2.78 (t, J=7.0 Hz, 2H, CH$_2$Ar), 3.52 (q, J=7.0 Hz, 2H, CH$_2$NH), 3.78 (s, 2H, CH$_2$I), 3.85 (s, 3H, CH$_3$O), 5.77 (s, 2H, OCH$_2$O), 6.68 (s, 1H, NH), 6.87-6.91 (m, 3H arom). Ms (EI) m/z (%): 449 (20, M$^+$; accurate mass 449.0697, C$_{17}$H$_{24}$N$_2$O$_5$I requires 449.0699), 150 (100), 137 (100). The second fraction contained the starting material (86 mg, 12 %).

Preparation of N-[2-(3-Pivalylcarbonyloxymethoxy-4-methoxyphenyl)ethyl] chloroacetamide (52)

A mixture of (51) (590 mg, 1.65 mmol), lithium chloride (355 mg, 8.35 mmol) and silver nitrate (384 mg, 2.26 mmol) in acetone (10 ml) was allowed to stir for 48 h. The solvent was then evaporated and the crude residue was extracted with DCM (50 ml). The extract was washed with water (2 x 10 ml), dried and evaporated to give N-[2-(3-pivalylcarbonyloxymethoxy-4-methoxyphenyl)ethyl] chloroacetamide (52) (537 mg, 91%) as a pale yellow oil. $^1$H-Nmr (CDCl$_3$, 400 MHz) δ: 1.20 (s, 9H, (CH$_3$)$_3$C), 2.78 (t, 7.0 Hz, 2H, CH$_2$Ar), 3.52 (q, J=7.0 Hz, 2H, CH$_2$NH), 3.85 (s, 1H, NH), 4.02 (s, 2H, CH$_2$I), 5.77 (s, 2H, OCH$_2$O), 6.68 (s, 1H, NH), 6.87-6.91 (m, 3H arom). $^{13}$C-Nmr (CDCl$_3$, 100 MHz) 26.8 ((CH$_3$)$_3$C), 27.2 ((CH$_3$)$_3$C), 34.7 (CH$_2$Ar), 40.9 (CH$_2$NH), 42.5 (CH$_2$I), 55.8 (CH$_3$O), 86.9 (OCH$_2$O), 112.0 (ArC-H), 118.1 (ArC-H), 123.7 (ArC-H), 130.7 (ArC-CH$_2$), 145.9 (ArC-O), 148.9 (ArC-O), 165.7 (COCH$_2$Cl), 177.2 ((CH$_3$)$_3$CCO). Ms (EI) m/z (%): 357 (0.7, M$^+$, $^{35}$Cl; accurate mass 357.1335,
C\textsubscript{17}H\textsubscript{24}N\textsubscript{5}O\textsubscript{5}\textsuperscript{35}Cl requires 357.1343), 327 (1), 256 (2), 235 (41), 234 (7), 233 (2), 226 (2).

**Reaction of N-[2-(3-Hydroxy-4-methoxyphenyl)ethyl]chloroacetamide (43) with Chloromethyl Pivalate**

A mixture of (43) (0.206 mg, 0.846 mmol), chloromethyl pivalate (0.25 ml) and potassium carbonate (140 mg, 1.013 mmol) in acetone (5 ml) was allowed to stir overnight under N\textsubscript{2}. The solvent was then evaporated and the crude residue was chromatographed. Elution with EtOAc : hexane, 45 : 55, afforded N-[2-(3-pivalylcarbonyloxy-4-methoxyphenyl)ethyl]chloroacetamide (47) as a pale yellow oil. \textsuperscript{1}H-Nmr (CDCl\textsubscript{3}, 400 MHz) \( \delta \): 1.19 (s, 9H, (CH\textsubscript{3})\textsubscript{3}C), 2.77 (t, 7.0 Hz, 2H, CH\textsubscript{2}Ar), 3.54 (q, \textit{J}=7.0 Hz, 2H, CH\textsubscript{2}NH), 3.84 (s, 1H, NH), 4.02 (s, 2H, CH\textsubscript{2}Cl), 5.77 6.68 (s, 1H, NH), 6.86-6.91 (m, 3H\textsubscript{arom}). Ms (EI) \textit{m/z} (%): 327 (2, M\textsuperscript{+}, \textsuperscript{35}Cl; accurate mass 327.1235, C\textsubscript{16}H\textsubscript{22}N\textsubscript{4}O\textsubscript{4}\textsuperscript{35}Cl requires 327.1237), 256 (3), 235 (40).

![Structure of 47](image)

**Reaction of N-[2-(3-Hydroxy-4-methoxyphenyl)ethyl]chloroacetamide (43) with Iodomethyl Pivalate**

A mixture of (43) (0.201 mg, 0.825 mmol), chloromethyl pivalate (0.25 ml) and potassium carbonate (140 mg, 1.013 mmol) in acetone (5 ml) was allowed to stir overnight under N\textsubscript{2}. The solvent was then evaporated and the crude residue was chromatographed. Elution with EtOAc : hexane, 45 : 55, afforded two fractions. The first fraction contained (47) and (52) (121 mg),
in a ratio of 2:3 respectively, as a pale yellow oil. The second fraction was evaporated to give (49) and (51) (149 mg), in a ratio of approximately 2:3, as a pale yellow oil. The oil was rechromatographed to give N-[2-(3-pivalylcarbonyloxoy-4-methoxyphenyl)ethyl] chloroacetamide (49) (50 mg, 15%) as a pale yellow oil. $^1$H-Nmr (CDCl$_3$, 400 MHz) δ: 1.21 (s, 9H, (CH$_3$)$_3$C), 2.78 (t, 7.0 Hz, 2H, CH$_2$Ar), 3.53 (q, J=7.0 Hz, 2H, CH$_2$NH), 3.84 (s, 1H, NH), 3.78 (s, 2H, CH$_2$I), 5.77 6.68 (s, 1H, NH), 6.85-6.91 (m, 3H$_{arom}$). Ms (EI) m/z (%): 419 (3, M$^+$; accurate mass 419.2594, C$_{16}$H$_{22}$N$O$_4$I requires 419.2595), 235 (45).

Photolysis of N-[2-(3-Pivalylcarbonyloxymethoxy-4-methoxyphenyl)ethyl] chloroacetamide (52) in Benzene

A solution of (52) (140 mg, 0.392 mmol) in benzene (350 ml) was irradiated for 4 h at room temperature. The organic solvent was evaporated in vacuo and the residual oil was dissolved in EtOAc (80 ml). The extract was washed with brine (3 x 15 ml), dried, evaporated and chromatographed (DCM : MeOH, 98 : 2) to leave a yellow oil. The oil was then rechromatographed. Elution with EtOAc : hexane, 45 : 55 gave five fractions. The first fraction contained the starting material (52) (25 mg, 18 %). The solvent in the second fraction was evaporated to give (74) (20 mg, 16 %) as a pale yellow oil. $^1$H-Nmr (CDCl$_3$, 400 MHz) δ: 1.25 (s, 9H, (CH$_3$)$_3$C), 2.58 (t, J=6.4 Hz, 2H, CH$_2$Ar), 3.47 (q, J=6.4 Hz, 2H, CH$_2$NH), 3.90 (s, 3H, CH$_3$O), 4.00 (s,
2H, CH₂Cl), 5.76 (s, 1H, OH), 6.75 (d, J=8.4 Hz, 1Hₐrom), 6.82 (d, J=8.4 Hz, 1Hₐrom). ¹³C-Nmr (CDCl₃, 100 MHz) δ: 26.9 ((CH₃)₃C), 27.4 ((CH₃)₃C), 31.9 (CH₂Ar), 41.5 (CH₂NH), 42.6 (CH₂Cl), 59.1 (CH₃O), 110.9 (Ar-C-H), 121.0 (Ar-C-H), 127.3 (Ar-C-CH₂), 129.1 (Ar-C-CO), 129.4 (Ar-C-O), 141.0 (Ar-C-O), 166.3 (COCH₂Cl), 182.9 (COC(CH₃)₃). Ms (EI) m/z (%): 327 (2, M⁺, ³⁵Cl; accurate mass 327.1248, CI₆H₂₂N₀₄³⁵Cl requires 327.1237), 270 (10), 252 (2), 234 (10), 193 (13), 165 (8), 150 (13), 137 (17). The third fraction was evaporated to give (75) (15 mg, 10%) as a pale yellow oil. ¹H-Nmr (CDCl₃, 400 MHz) δ: 1.18 (s, 9H, (CH₃)₃C), 2.65 (t, J=7.2 Hz, 2H, CH₂Ar), 3.42 (q, J=7.2 Hz, 2H, CH₂NH), 3.54 (s, 2H, CH₂Ph), 3.84 (s, 3H, CH₃O), 5.73 (s, 2H, OCH₂O), 6.67-6.81 (m, 3Hₐrom), 7.17-7.32 (m, 5Hₐrom). Ms (EI) m/z (%): 399 (0.5, M⁺), 369 (0.5), 298 (1.2), 297 (1), 285 (0.5), 264 (2), 234 (6). The fourth fraction was (43) (20 mg, 21%). The solvent in the fifth fraction was evaporated to give (77) (10 mg, 9%) as a pale yellow oil. ¹H-Nmr (CDCl₃, 400 MHz) δ: 2.63 (t, J=6.8 Hz, 2H, CH₂Ar), 3.41 (q, J=6.8 Hz, 2H, CH₂NH), 3.54 (s, 2H, CH₂Ph), 3.87 (s, 3H, CH₃O), 5.34 (s, 1H, NH), 5.60 (s, 1H, OH), 6.50 (dd, J=8.0, J=2.0 Hz, 1Hₐrom), 6.63 (d, J=2.0 Hz, 1Hₐrom), 6.70 (d, J=8.4 Hz, 1Hₐrom), 7.17-7.33 (m, 5Hₐrom). Ms (EI) m/z (%): 285 (1, M⁺; accurate mass 285.1359, C₁₇H₁₉NÖ₃ requires 285.1365), 271 (0.8), 255 (0.2), 219 (0.8), 194 (1), 150 (100), 137 (34), 135 (30), 91 (81).

![Chemical Structures](image-url)
Photolysis of N-[2-(3-Pivalylcarbonyloxymethoxy-4-methoxyphenyl)ethyl] chloroacetamide (52) in THF

A solution of (52) (390 mg, 1.09 mmol) in THF was photolysed for 4 h at room temperature. The solvent was evaporated in vacuo and the crude residue was chromatographed. The first elution with EtOAc : hexane, 50 : 50 gave the starting material (160 mg, 41%). The second elution with DCM : MeOH, 98 : 2, gave N-[2-(3-pivalylcarbonyloxymethoxy-4-methoxyphenyl)ethyl]acetamide (78) (90 mg, 25%, 43% based on recovered starting material) as a pale yellow oil. ¹H-Nmr (CDCl₃, 300 MHz) δ: 1.19 (s, 9H, (CH₃)₃C), 1.95 (s, 3H, COCH₃), 2.09 (s, 1H, NH), 2.74 (t, J=9.4 Hz, 2H, CH₂Ar), 3.46 (q, J=9.4 Hz, 2H, CH₂NH), 3.85 (s, 3H, CH₃O), 5.77 (s, 2H, OCH₂O), 6.86-6.90 (m, 3H arom). ¹³C-Nmr (CDCl₃, 75 MHz) δ: 23.1 (COCH₃), 26.9 ((CH₃)₃C), 34.8 (CH₂Ar), 40.6 (CH₂NH), 55.9 (CH₃O), 87.0 (OCH₂O), 112.3 (Ar-C-H), 118.5 (Ar-C-H), 123.9 (Ar-C-H), 131.4 (Ar-C-CH₂), 145.8 (Ar-C-O), 170.0 (COCH₃), 177.3 ((CH₃)₃CCO). Ms (EI) m/z (%): 323 (3, M⁺, accurate mass 323.1738, C₁₇H₂₅NO₅ requires 323.1733), 293 (2), 264 (4), 234 (40), 222 (2), 192 (10), 180 (5), 163 (5), 150 (100), 137 (13), 135 (12).
Preparation of \(N-[2-(3\text{-methoxymethylmethoxy-4-methoxyphenyl})\text{ethyl}]\) chloroacetamide (53)

\[
\begin{align*}
\text{H}_3\text{CO} & \quad \text{O} \\
\text{H}_3\text{CO} & \quad \text{N} \\
& \quad \text{CH}_2\text{Cl}
\end{align*}
\]

A stirred solution of \(N-[2-(3\text{-hydroxy-4-methoxyphenyl})\text{ethyl}]\) chloroacetamide (43) (91 mg, 0.374 mmol) in THF (5 ml), under \(\text{N}_2\), was cooled in an ice bath. To this solution was added sodium hydride (35 mg, 60%, 0.87 mmol). After 5 min, chloromethyl methyl ether (0.05 ml, 4.27 mmol) was then added. The solution was allowed to stir for 3 h and then filtered through a filter aid (Celite). Solvent was evaporated and the remaining residue was chromatographed. Elution with EtOAc : hexane, 50 : 50 gave \(N-[2-(3\text{-methoxymethylmethoxy-4-methoxyphenyl})\text{ethyl}]\) chloroacetamide (53) (100 mg, 94%) as a colourless oil after evaporation. 1H-Nmr (CDCl\(_3\), 400 MHz) \(\delta\): 2.77 (t, \(J=6.8\ \text{Hz}\), CH\(_2\)Ar), 3.51 (s, 3H, CH\(_2\)OCH\(_3\)), 3.53 (q, \(J=6.8\), CH\(_2\)NH), 3.86 (s, 3H, CH\(_3\)O-Ar), 4.02 (s, 2H, CH\(_2\)Cl), 5.22 (s, 2H, OCH\(_2\)O), 6.72 (s, 1H, NH), 6.80-6.86 (m, 3H\(_\text{arom}\)). 13C-Nmr (CDCl\(_3\), 100 MHz) \(\delta\): 34.6 (CH\(_2\)Ar), 40.9 (CH\(_2\)NH), 42.5 (CH\(_2\)Cl), 55.8 (CH\(_3\)O-Ar), 56.1 (CH\(_2\)OCH\(_3\)), 95.3 (OCH\(_2\)O), 111.8 (ArC-H), 122.2 (ArC-H), 130.8 (ArC-CH2), 146.3 (ArC-O), 148.3 (ArC-O), 165.7 (CO). Ms (EI) m/z (%): 287 (2, M\(^+\), \(^{35}\text{Cl}\); accurate mass 287.0922, \(\text{C}_{13}\text{H}_{18}\text{NO}_{4}{^{35}}\text{Cl}\) requires 287.0924), 255 (2), 220 (1), 194 (14), 181 (14), 181 (3), 164 (12), 150 (7), 137 (5).

Photolysis of \(N-[2-(3\text{-methoxymethylmethoxy-4-methoxyphenyl})\text{ethyl}]\) chloroacetamide (53)

A solution of (53) (100 mg, 0.348 mmol) in benzene (350 ml) was irradiated for 3.5 h at room temperature. Solvent was evaporated \textit{in vacuo}
and the remaining crude residue was chromatographed. Elution with DCM : MeOH : 98 : 2, gave four fractions. The first fraction was (43) (20 mg, 24%), obtained as a pale yellow oil after evaporation. The solvent in the second fraction was evaporated to give (77) (15 mg, 15%) as a pale yellow crystalline solid. The third fraction was unidentified. The fourth fraction was rechromatographed. Elution with DCM : MeOH, 98 : 2, gave \(N\)-methylenehydroxy-7-hydroxy-8-methoxy-1,2,4,5-tetrahydro-2H-3-benzazepin-2-one (79) as a pale yellow crystalline solid (15 mg, 18%) after evaporation, mp 144-147°C (DCM/MeOH). \(^1\)H-Nmr (CDCl\(_3\), 400 MHz) \(\delta\): 3.09 (t, J=6.0, 2H, CH\(_2\)CH\(_2\)N), 3.19 (t, J=8.0 Hz, 1H, CH\(_2\)OH), 3.78 (s, 2H, COCH\(_2\)), 3.82 (t, J=6.0, 2H, CH\(_2\)CH\(_2\)N), 3.86 (s, 3H, CH\(_3\)O), 4.90 (d, J=8.0 Hz, 2H, CH\(_2\)OH), 5.51 (s, 1H, ArOH), 6.59 (s, 1H\_arom), 6.67 (s, 1H\_arom). Ms (EI) m/z (%): 237 (7.5, M\(^+\)), 219 (3), 207 (16), 193 (5), 178 (2.5), 163 (7), 151 (57), 150 (67), 137 (20), 136 (18), 135 (32); (CI) m/z: accurate mass 238.1065 (MH\(^+\)), 238.1065, C\(_{12}\)H\(_{16}\)NO\(_4\) requires 238.1079.

![Chemical structure of 79](image)

Preparation of \(N\)-[2-[[3-((E)-2'-Methoxycarbonylthienyloxy)-4-methoxyphenyl]ethyl]chloroacetamide (54, cis and trans isomers)

To a stirred solution of \(N\)-[2-(3-hydroxy-4-methoxyphenyl)ethyl] chloroacetamide (43) (390 mg, 1.602 mmol) in dry THF (20 ml), under N\(_2\),
added sodium hydride (120 mg, 60%, 3.00 mmol). Methyl propiolate (0.2 ml, 2.38 mmol) was then added. The solution was allowed to stir overnight. The solvent was then evaporated and the crude residue was extracted with DCM (30 ml). The extract was washed with water (2 x 10 ml), dried, evaporated and chromatographed on aluminium oxide, neutral activity I. Elution with EtOAc : hexane, 35 : 65, gave \( \text{N-}\{2-[(E)-2'-methoxycarbonyl]ethoxyloxy}-4\text{-methoxyphenylethyl}\text{chloroacetamide (54)} \) (105 mg, 20%) as a colourless crystalline solid after evaporation, mp 77-79°C (EtOAc/hexane). \(^1\)H-Nmr (CDCl\(_3\), 400 MHz) 8: 2.79 (t, J=7.2 Hz, 2H, CH\(_2\)Ar), 3.53 (q, J=7.2 Hz, 2H, CH\(_2\)NH), 3.71 (s, 3H, COOCH\(_3\)), 3.85 (s, 3H, CH\(_3\)OAr), 4.04 (s, 2H, CH\(_2\)Cl), 5.43 (d, J=12.4 Hz, 1H, COCH\(_2\)CH), 6.60 (s, 1H, NH), 6.90 (d, J=2.0 Hz, 1H\(_{\text{arom}}\)), 6.92 (d, J=8.4 Hz, 1H\(_{\text{arom}}\)), 7.01 (dd, J=8.4, J=2.0 Hz, 1H\(_{\text{arom}}\)), 7.11 (d, J=12.4 Hz, COCH\(_2\)CH). \(^{13}\)C-Nmr (CDCl\(_3\), 75 MHz) 8: 34.6 (CH\(_2\)Ar), 40.9 (CH\(_2\)NH), 52.6 (COOCH\(_3\)), 56.1 (CH\(_3\)OAr), 100.8 (ArC-H), 113.2 (ArC-H), 120.7 (ArC-H), 126.3 (COCH\(_2\)CH), 131.4 (ArC-CH\(_2\)), 144.4 (ArC-O), 149.2 (ArC-O), 160.7 (COCH\(_2\)CH), 165.8 (COCH\(_2\)Cl), 167.7 (COOCH\(_3\)). Ms (El) m/z (%): 329 (1.3, M\(^+\), 37Cl), 327 (4, M\(^+\), 35Cl; accurate mass 327.0870, C\(_{15}\)H\(_{18}\)NO\(_5\)\(^{35}\)Cl requires 327.0874), 234 (100), 221 (8), 203 (11), 175 (8), 147 (7), 135 (35), 134 (18). Further elution with DCM : MeOH, 98 : 2, gave \( \text{N-}\{2-[(Z)-2'-methoxycarbonyl]ethoxyloxy}-4\text{-methoxyphenylethyl}\text{chloroacetamide (54)} \) (90 mg, 17%) as a colourless oil. \(^1\)H-Nmr (CDCl\(_3\), 400 MHz), 2.79 (t, J=7.2 Hz, 2H, CH\(_2\)Ar), 3.53 (q, J=7.2 Hz, 2H, CH\(_2\)NH), 3.75 (s, 3H, COOCH\(_3\)), 3.84 (s, 3H, CH\(_3\)OAr), 4.03 (s, 2H, CH\(_2\)Cl), 5.11 (d, J=7.2 Hz, 1H, COCH\(_2\)CH), 6.65 (s, 1H, NH), 6.75 (d, J=7.2 Hz, 1H, COCH\(_2\)CH), 6.91 (d, J=8.0 Hz, 1H\(_{\text{arom}}\)), 6.97 (d, J=2.0 Hz, 1H\(_{\text{arom}}\)), 6.98 (dd, J=8.0, J=2.0 Hz, 1H\(_{\text{arom}}\)). Ms (El) m/z (%): 329 (1.6, M\(^+\), 37Cl), 327 (5, M\(^+\), 35Cl), 234 (100), 221 (12), 203 (17), 175 (13), 135 (69), 134 (41).
Photolysis of N-{2-[3-((E)-2'-Methoxycarbonylethenyloxy)-4-methoxyphenyl]ethyl}chloroacetamide (54) in Acetonitrile

A solution of (54) (trans isomer) (70 mg, 0.214 mmol) in acetonitrile (350 ml) was irradiated for 3 h at room temperature using. Potassium carbonate (150 mg, 1.09 mmol) was then added and the solvent was evaporated in vacuo. The crude residue was extracted with DCM (40 ml). The extract was washed with water (2 x 10 ml), dried and evaporated to give a yellow oil. The oil was chromatographed (EtOAc : hexane, 65 : 35 and then DCM : MeOH, 98.5 : 1.5) to give two fractions. The first fraction was (43) (18 mg, 35%). The second fraction was evaporated to give 7-((E)-2-hydroxycarbonylethenyloxy)-8-methoxy-1,2,4,5-tetrahydro-2H-3-benzazepin-2-one (80) (20 mg, 34%) as a pale yellow solid, mp 145-148°C (DCM/MeOH).

$^1$H-Nmr (CDCl$_3$, 300 MHz) δ: 3.03 (t, $J$=7.2 Hz, 2H, CH$_2$CH$_2$NH), 3.49 (q, $J$=7.2 Hz, 2H, CH$_2$CH$_2$NH), 3.94 (s, 3H, CH$_3$O), 4.05 (s, 2H, COCH$_2$), 6.48 (d, $J$=9.9 Hz, 1H, COCHCH), 6.76 (s, 1H, NH), 7.03 (s, 1H, NH), 8.05 (d, $J$=9.9 Hz, 1H, COCHCH). Ms (EI) m/z (%): 277 (5, M$^+$; accurate mass 277.0948, C$_{14}$H$_{15}$NO$_5$ requires 277.0950), 135 (30).

![Compound 80](image)

Photolysis of N-{2-[3-((E)-2'-Methoxycarbonylethenyloxy)-4-methoxyphenyl]ethyl}chloroacetamide (54) in Benzene

A solution of (54) (trans isomer) (70 mg, 0.214 mmol) in benzene (350 ml) was irradiated for 3 h at room temperature using 16W mercury lamp. The solvent was evaporated and the remaining crude was chromatographed
(EtOAc : hexane, 65 : 35, and then DCM : MeOH, 98.5 : 1.5 to give two factions. The first fraction was (54) (cis isomer) (15 mg, 21%). The second fraction consisted (80) (16 mg, 27%).

**Preparation of N-Methyl-[2-(3,4-dimethoxyphenyl)ethyl]chloroacetamide (46)**

![Chemical structure of N-Methyl-[2-(3,4-dimethoxyphenyl)ethyl]chloroacetamide (46)](https://example.com/structure.png)

A mixture of N-methylhomoveratrylamine (510 mg, 2.61 mmol) and sodium carbonate (310 mg, 292 mmol) in dry DCM (8 ml) was added chloroacetyl chloride (0.3 ml, 3.762 mmol). The mixture was allowed to stir overnight. Water (10 ml) was added and the two layers were separated. The aqueous layer was extracted with further DCM (2 x 15 ml) and the combined extracts were washed with water (2 x 10 ml), evaporated and chromatographed. Elution with DCM : MeOH, 99 : 1, gave N-methyl-[2-(3,4-dimethoxyphenyl)ethyl]chloroacetamide (46) (666 mg, 94%) as a colourless crystalline solid after evaporation, mp 53-55°C (DCM/MeOH).

**1H-Nmr (CDCl3, 400 MHz)**: 2.80-2.86 (m, 2H, CH2Ar), 2.95 (s, 3/2H, 1/2 x CH3N), 3.01 (s, 3/2H, 1/2 x CH3N), 3.54-3.60 (m, 2H, CH2N), 3.69 (s, 1H, 1/2 x CH2Cl), 3.86 (s, 3/2H, 1/2 x CH3O), 3.87 (s, 3/2H, 1/2 x CH3O), 3.87 (s, 3/2H, 1/2 x CH3O), 3.88 (s, 3/2H, 1/2 x CH3O), 4.06 (s, 1H, 1/2 x CH2Cl), 6.65-6.83 (m, 3Harom).  

**Ms (CI) m/z (%):** 273 (18, M++1, 37Cl), 271 (5, M++1, 35Cl; accurate mass 271.0980 C13H18NO335Cl requires 271.0975), 235 (10), 165 (75), 164 (100), 152 (30), 151 (100), 149 (63).
Photolysis of N-methyl-[2-(3,4-dimethoxyphenyl)ethyl]chloroacetamide (46)

A solution N-methyl-[2-(3,4-dimethoxyphenyl)ethyl]chloroacetamide (46) (1.94 g, 7.145 mmol) in benzene (350 ml) was irradiated at room temperature for 19 h using a 180W mercury lamp. The solvent was evaporated and the residue was chromatographed (EtOAc : hexane, 70 : 30, 80 : 20, and then 90 : 10) to give four fractions. The first fraction was the starting material (1.2 g, 62%). The solvent in the second fraction was evaporated to give (72) (50 mg, 3%, 8% based on recovered starting material) as a pale yellow oil. ¹H-Nmr (CDCl₃, 300 MHz) δ: 2.99 (s, 3H, CH₃N), 3.08 (t, J=6.4 Hz, 2H, CH₂CH₂N), 3.64 (t, J=6.4 Hz, 2H, CH₂CH₂N), 3.81 (s, 3H, CH₃O), 3.84 (s, 3H, CH₃O), 3.97 (s, 2H, CH₂CO), 6.76 (d, J=9.4 Hz, 1Hₜₐₗ), 6.83 (d, J=9.4 Hz, 1Hₜₐₗ). The third fraction consisted of (73) (90 mg, 5%, 14% based on recovered starting material) as pale yellow oil after evaporation. ¹H-Nmr (CDCl₃, 300 MHz) δ: 3.03 (s, 3H, CH₃N), 3.06 (t, J=6.8 Hz, 2H, CH₂CH₂N), 3.71 (t, J=6.8 Hz, 2H, CH₂CH₂N), 3.840 (s, 3H, CH₃O), 3.843 (s, 3H, CH₃O), 3.88 (s, CH₂CO), 6.58 (s, 1Hₜₐₗ), 6.62 (s, 1Hₜₐₗ). The fourth fraction rechromatographed (DCM : MeOH, 98.5 : 1.5) to give N-methyl-12-methoxy-2-oxa-6-azabicyclo[7.3.1.]trideca-1(13),9,11-trien-5-one (71) (112 mg, 7%, 18% based on recovered starting material) as a pale yellow oil. ¹H-Nmr (CDCl₃, 300 MHz) δ: 2.57-2.59 (m, 1H, CHCO), 2.61-2.63 (m, 1H, CHAr), 2.71-2.75 (m, 1H, CHAr), 2.77-2.81 (m, 1H, CHCO), 2.86-2.88 (m, 1H, CHNCH₃), 2.90-2.93 (m, 1H, CHNCH₃), 3.15 (s, 3H, CH₃N), 3.89 (s, 3H, CH₃O), 4.13-4.16 (m, 2H, CH₂O), 6.91-6.92 (m, 3Hₜₐₗ). Ms (EI): 235 (22, M⁺; accurate mass 235.1191, C₁₃H₁₇NO₃ requires 235.1208), 22 (2), 192 (6), 164 (40), 151 (10), 150 (10).
Preparation of Methyl 2,2-Dichloroacetamido-3-(3,4-dihydroxyphenyl) propanoate (55)

To a solution of L-dopa methyl ester hydrochloride (38) (0.5 g, 2.02 mmol) in dry THF (25 ml) under N₂ were added triethylamine (0.56 ml, 4.04 mmol) and dichloroacetyl chloride (0.195 ml, 2.02 mmol). The solution was allowed to stir for 48 h at room temperature. Water (20 ml) was then added and the mixture was extracted with DCM (3 x 30 ml). The combined extracts were washed with water (7 x 10 ml). The combined wash solutions were extracted with DCM (20 ml) and then the combined organic extracts were dried, evaporated and chromatographed. Elution with DCM: MeOH, 97:3, gave methyl 2,2-dichloroacetamido-3-(3,4-dihydroxyphenyl) propanoate (55) (480 mg, 74%) as a pale yellow crystalline solid after evaporation, mp 134-136°C (DCM/MeOH). ¹H-Nmr (CDCl₃, 400 MHz) δ: 3.01 (dd, J=14.8, J=6.4 Hz, 1H, CHAr), 3.06 (dd, J=14.8, J=14.8, J=6.4, 1H, CHAr), 3.76 (s, 3H, COOCH₃), 4.73-4.76 (m, 1H, CHNH), 6.00 (s, 1H, CH₂Cl), 6.49 (dd, J=8.0, J=2.0 Hz, 1H, CH₂Ar), 6.61 (d, J=2.0 Hz, 1H, CH₂Ar), 6.75 (d, J=8.0 Hz, 1H, CH₂Ar). ¹³C-Nmr (CDCl₃, 100 MHz) δ: 36.7 (CH₂Ar), 52.5 (COOCH₃), 53.9 (CHNH), 65.9 (CH₂Cl), 115.1 (Ar-C-H), 115.8 (Ar-C-H), 120.9 (Ar-C-H), 126.7 (Ar-C-CH₂), 143.6
(ArC-O), 144.4 (ArC-O), 164.0 (COCHCl2), 171.2 (COOCH3). Ms (EI) m/z (%): 323 (0.45, M+, 37Cl), 321 (0.52, M+, 35Cl, accurate mass 321.0174, C12H13NO535Cl2 requires 321.0171), 262 (0.46), 238 (0.47), 222 (0.35), 194 (17), 123 (100).

Preparation of Methyl 2,2-Dichloroacetamido-3-(3,4-dimethoxyphenyl)propanoate (58)

To a solution (55) (500 mg, 1.553 mmol) in MeOH (10 ml) was added excess of diazomethane in ether (30 ml). The solution was kept at 1°C for 20 h. The solvent was then evaporated in vacuo to give a yellow solid. The solid was recrystallised from ethanol/diethylether to give methyl 2,2-dichloroacetamido-3-(3,4-dimethoxyphenyl)propanoate (58) (460 mg, 85%) as colourless crystals, mp 93-94°C (EtOH/Et2O). 1H-Nmr (CDCl3, 400 MHz) δ: 3.14-3.15 (m, 2H, CH2Ar), 3.78 (s, 3H, COOCH3), 3.85 (s, 3H, CH3OAr), 3.86 (s, 3H, CH3OAr), 5.94 (s, 1H, CHCl2), 4.81-4.85 (m, 1H, CHNH), 6.65 (dd, J=8.0, J=2.0 Hz, 1H arom), 6.66 (d, J=2.0 Hz, 1H arom), 6.80 (d, J=8.0 Hz, 1H arom), 7.01 (d, J=8.0 Hz, 1H, NH). 13C-Nmr (CDCl3, 100 MHz) δ: 37.0 (CH2Ar), 52.6 (COOCH3), 53.8 (CHNH), 55.8 (2 x CH3OAr), 66.0 (CHCl2), 111.2 (ArC-H), 112.2 (ArC-H), 121.4 (ArC-H), 127.3 (ArC-CH2), 148.3 (ArC-O), 148.8 (ArC-O), 163.4 (COCHCl2), 170.9 (COOCH3). Ms (EI) m/z (%): 351 (0.52, M+, 37Cl), 349 (0.96, M+, 35Cl, accurate mass 349.0494, C14H17NO535Cl2 requires 349.0484), 318 (0.12), 292 (0.2), 290 (0.32), 266 (0.44), 236 (2), 222 (13), 151 (100).
Photolysis of Methyl 2,2-Dichloroacetamido-3-(3,4-dimethoxyphenyl)propanoate (58)

A solution of (58) (200 mg, 0.685 mmol) in benzene (350 ml) was irradiated at room temperature for 2 h. The solvent was evaporated to give a yellow oil. The structures of the products remains undetermined.

Preparation of N-[2-(3,4-Dimethoxyphenyl)ethyl]dichloroacetamide (57)

\[
\begin{align*}
\text{H}_3\text{CO} & \quad \text{NHCOCHCl}_2 \\
\text{H}_3\text{CO} & \quad \text{H}_2\text{NH}
\end{align*}
\]

A solution of homoveratrylamine (2.0 g, 11.0 mmol) and a finely divided anhydrous sodium carbonate (2.33 g, 22.0 mmol) in DCM (40 ml) was stirred vigorously at 3°C while dichloroacetyl chloride (1.23 ml, 12.1 mmol) was added dropwise during 10 min. The mixture was allowed to stir for further 1 h. Sodium carbonate was then removed by filtration and washed with dichloromethane (25 ml). The combined organic phases were washed with water (3 x 20 ml), dried and evaporated to give N-[2-(3,4-dimethoxyphenyl)ethyl]dichloroacetamide (57) (2.221 g, 69%) as pale yellow oil. \(^1\text{H-Nmr} \) (CDCl\textsubscript{3}, 400 MHz) \(\delta: 2.82 \text{ (t, } J=7.6, 2\text{H, CH}_2\text{Ar}), 3.57 \text{ (q, } J=7.6 \text{ Hz, } 2\text{H, CH}_2\text{NH}), 3.88 \text{ (s, } 3\text{H, CH}_3\text{O}), 3.89 \text{ (s, } 3\text{H, CH}_3\text{O}), 5.91 \text{ (s, } 1\text{H, CHCl}_2), 6.72 \text{ (d, } J=2.0, 1\text{H}_{\text{arom}}), 6.76 \text{ (dd, } J=8.0, J=2.0 \text{ Hz, } 1\text{H}_{\text{arom}}), 6.83 \text{ (d, } J=8.0 \text{ Hz, } 1\text{H}_{\text{arom}}).\)

Photolysis of N-[2-(3,4-Dimethoxyphenyl)ethyl]dichloroacetamide (57)

A solution of (57) (200 mg, 0.685 mmol) in benzene (350 ml) was irradiated at room temperature for 2 h. The solvent was evaporated and the residue was chromatographed (DCM : MeOH, 97 : 3 ) to give a fraction which
consisted of a mixture of the benzazepin-2-one isomers (82) and (83). Ms (El) m/z (%): 357 (20, M+, \(^{37}\)Cl), 355 (61, M+, \(^{35}\)Cl).

**Preparation of Methyl 2,2,2-Trichloroacetamido-3-(3,4-dihydroxyphenyl) propanoate (56)**

\[
\begin{align*}
\text{HO} & \quad \text{NHCOC}_{\text{Cl}} \quad \text{COOCH}_{3} \\
\text{HO} & \quad \text{H} \\
\end{align*}
\]

To a solution of L-dopa methylester (38) (300 mg, 1.211 mmol) in dry THF (20 ml) under N\(_2\) were added triethylamine (0.34 ml, 2.42 mmol) and trichloroacetyl chloride (0.135 ml, 1.21 mmol). The solution was allowed to stir at room temperature for 48 h. Water (15 ml) was then added and the mixture was extracted with DCM (3 x 25 ml). The combined extracts were washed with water (3 x 10 ml). The combined wash solutions were extracted with EtOAc (2 x 20 ml) and then the combined organic extracts were dried and evaporated to give methyl 2,2,2-trichloroacetamido-3-(3,4-dihydroxyphenyl) propanoate (56) (415 mg, 96%) as a yellow oil. \(^1\)H-Nmr (CDCl\(_3\), 400 MHz) \(\delta\): 3.06 (dd, \(J=14.0, J=5.6\) Hz, 1H, CHAr), 3.14 (dd, \(J=14.0, J=5.6\) Hz, 1H, CHAr), 3.79 (s, 3H, COOCH\(_3\)), 4.75-4.79 (m, 1H, CHNH), 6.51 (dd, \(J=8.0, J=2.0\) Hz, 1Harom), 6.65 (d, \(J=2.0\) Hz, 1Harom), 6.77 (d, \(J=8.0\) Hz, 1Harom), 7.25 (d, \(J=7.2\) Hz, 1H, NH).

**Preparation of Methyl 2,2,2-Trichloroacetamido-3-(3,4-dimethoxyphenyl) propanoate (59)**

\[
\begin{align*}
\text{CH}_3\text{O} & \quad \text{H}_3\text{CO} & \quad \text{NHCOC}_{\text{Cl}} \quad \text{COOCH}_{3} \\
\text{H}_3\text{CO} & \quad \text{H} \\
\end{align*}
\]
To a solution (56) (500 mg, 1.403 mmol) in MeOH (10 ml) was added excess of diazomethane in ether (30 ml). The solution was kept at 1°C for 20 h. The solvent was then evaporated in vacuo to give a yellow solid. The solid was recrystallised from ethanol/diethylether to give methyl 2,2,2-trichloroacetamido-3-(3,4-dimethoxyphenyl)propanoate (59) (465 mg, 87%) as pale yellow oil. 

\[ \text{\textsuperscript{1}H-Nmr (CDCl\textsubscript{3}, 400 MHz)} \delta: 3.12-3.22 (m, 2H, CH\textsubscript{2}Ar), 3.78 (s, 3H, COOCH\textsubscript{3}), 3.83 (s, 3H, CH\textsubscript{3}OAr), 3.84 (s, 3H, CH\textsubscript{3}OAr), 4.78-4.82 (m, 1H, CH\textsubscript{NH}), 6.61 (dd, J=8.0, J=2.0 Hz, 1H\textsubscript{arom}), 6.64 (d, J=2.0 Hz, 1H\textsubscript{arom}), 6.78 (d, J=8.0 Hz, 1H\textsubscript{arom}), 7.20 (d, J=8.0 Hz, 1H, NH). \text{\textsuperscript{13}C-Nmr (CDCl\textsubscript{3}, 100 MHz)} \delta: 36.4 (CH\textsubscript{2}Ar), 52.4 (COOCH\textsubscript{3}), 54.5 (CH\textsubscript{NH}), 55.4 (2 \times CH\textsubscript{3}OAr), 110.8 (ArC-H), 111.8 (ArC-H), 121.0 (ArC-H), 126.7 (ArC-CH\textsubscript{2}), 134.0 (CCl\textsubscript{3}), 148.0 (ArC-O), 148.5 (ArC-O), 160.6 (COOCH\textsubscript{3}), 170.2 (COOCH\textsubscript{3}).

**Photolysis of Methyl 2,2,2-Trichloroacetamido-3-(3,4-dimethoxyphenyl)propanoate (59)**

A solution of (59) (200 mg, 0.522 mmol) in benzene (350 ml) was irradiated at room temperature for 2 h. The solvent was evaporated and the residue was chromatographed (DCM : MeOH, 97 : 3) to give N-\{3-(3,4-dimethoxyphenyl)-1-methoxycarbonyl\}propyloxamic acid (84) (45 mg, 28%) as a pale yellow oil. 

\[ \text{\textsuperscript{1}H-Nmr (CDCl\textsubscript{3}, 300 MHz)} \delta: 4.14 (d, J=5.4 Hz, 2H, CH\textsubscript{2}Ar), 3.76 (s, 3H, COOCH\textsubscript{3}), 3.84 (s, 3H, CH\textsubscript{3}OAr), 3.85 (s, 3H, CH\textsubscript{3}OAr), 4.79 (dt, J=7.5, J=5.4 Hz, 1H, CH\textsubscript{NH}), 6.66-6.77 (m, 3H\textsubscript{arom}), 7.40 (d, J=7.5 Hz, 1H, NH). \text{\textsuperscript{13}C-Nmr (CDCl\textsubscript{3}, 75 MHz)} \delta: 36.9 (CH\textsubscript{2}Ar), 52.5 (COOCH\textsubscript{3}), 54.9 (CH\textsubscript{NH}), 55.86 (CH\textsubscript{3}OAr), 55.89 (CH\textsubscript{3}OAr), 111.3 (ArC-H), 112.6 (ArC-H), 121.5 (ArC-H), 127.5 (ArC-CH\textsubscript{2}), 148.4 (ArC-O), 149.0 (ArC-O), 161.4 (COCOOH), 170.8 (COOCH\textsubscript{3}), 189.8 (CO\textsubscript{2}COOH). \text{Ms (EI) m/z (%): 311 (2, M*, accurate mass.
Preparation of N-{2-[3-((E)-2'-methoxycarbonylethenyloxy)-4-methoxyphenyl]ethyl}azidoacetamide (61, cis and trans isomers)

A mixture of 54 (cis isomer) (115 mg) and sodium azide (115 mg, 1.771 mmol) in acetonitrile (25 ml) was refluxed for 11h. The solvent was then evaporated and the residue was chromatographed (EtOAc : hexane, 55 : 45 and then DCM : MeOH, 98 : 2) to give two fractions. The solvent in first fraction was evaporated to give N-{2-[3-((E)-2'-methoxycarbonylethenyloxy)-4-methoxyphenyl]ethyl}azidoacetamide (61 trans) (53 mg, 45%) as a pale yellow gum. ¹H-Nmr (CDCl₃, 300 MHz) δ: 2.78 (t, J=8.0 Hz, 2H, CH₂Ar), 3.52 (q, J=8.0 Hz, 2H, CH₂ NH), 3.72 (s, 3H, COOCH₃), 3.85 (s, 3H, CH₃OAr), 3.97 (s, 1H, CH₂N₃), 5.43 (d, J=12.2 Hz, COCHCH), 6.89 (d, J=1.8, 1Harom), 6.93 (d, J=8.1 Hz, 1Harom), 7.01 (dd, J=8.1, J=1.8 Hz, 1Harom), 7.72 (d, J=12.2 Hz, COCHCH).

The second was N-{2-[3-((Z)-2'-methoxycarbonylethenyloxy)-4-methoxyphenyl]ethyl}azidoacetamide (61, cis) (48 mg, 41%) as pale yellow oil after evaporation. ¹H-Nmr (CDCl₃, 300 MHz) δ: 2.77 (t, J=8.0 Hz, 2H, CH₂Ar), 3.51 (q, J=8.0 Hz, 2H, CH₂NH), 3.75 (s, 3H, COOCH₃), 3.85 (s, 3H, CH₃OAr), 3.94 (s, 2H, CH₂N₃), 5.10 (d, J=7.2 Hz, 1H, COCHCH), 6.74 (d, J=7.2 Hz, 1H,
COCHCH), 6.89-6.99 (m, 3H\text{arom}). Ms (EI) (%): 334 (5, M\text{+}, accurate mass 357.1280, C_{15}H_{18}N_{4}O_{5} requires 334.1277), 250 (9), 234 (76), 221 (9), 203 (10), 175 (5), 150 (100), 137 (56), 135 (45).

**Preparation of N-[2-(3,4-Dimethoxyphenyl)ethyl]azidoacetamide (60)**

![Diagram of N-[2-(3,4-Dimethoxyphenyl)ethyl]azidoacetamide](image)

A mixture of N-[2-(3,4-dimethoxyphenyl)ethyl]chloroacetamide and sodium azide (402 mg, 6.188 mmol) in methyl ethyl ketone (20 ml) was refluxed for 24h. To the resulting mixture was added water (25 ml) and the solution was then extracted with EtOAc (3 x 25 ml). The combined extracts were washed with water (15 ml), dried and evaporated \textit{in vacuo} to give pale brown residue. The residue was then chromatographed. Elution with DCM : MeOH, 99.5 : 0.5, gave N-[2-(3,4-dimethoxyphenyl)ethyl]azidoacetamide (60) (179 mg, 74%) as colourless crystals, mp 72-74°C. \textsuperscript{1}H-Nmr (CDCl\textsubscript{3}, 400 MHz) \delta: 2.81 (t, J=8.5 Hz, 2H, CH\textsubscript{2}Ar), 3.47 (q, J=8.5 Hz, CH\textsubscript{2}NH), 3.90 (s, 3H, CH\textsubscript{3}O), 3.91 (s, 3H, CH\textsubscript{3}O), 3.99 (s, 2H, CH\textsubscript{2}N\textsubscript{3}), 6.34 (s, 1H, NH), 6.72-6.87 (m, 3H\text{arom}). Ms (EI) m/z (%): 264 (5, M\text{+}, accurate mass 264.1224, C\textsubscript{12}H\textsubscript{16}N\textsubscript{4}O\textsubscript{3} requires 264.1222), 164 (100), 151 (55), 135 (4), 121 (5), 107 (12). Ir (Nujol) \nu\textsubscript{max}: 3205 (NH), 2900 (Ar-H), 2112 (N\textsubscript{3}), 1653 (CO) cm\textsuperscript{-1}.

**Photolysis of N-[2-(3,4-Dimethoxyphenyl)ethyl]azidoacetamide (60)**

![Diagram of Photolysis of N-[2-(3,4-Dimethoxyphenyl)ethyl]azidoacetamide](image)

(85)
A solution of (60) (200 mg, 758 mmol) in acetonitrile and water (50:50) was irradiated for 3.5 h at room temperature. The solvent was evaporated in vacuo and the yellow residual oil was chromatographed. Elution with DCM : MeOH, 98 : 2, gave N-[2-(3,4-dimethoxyphenyl)ethyl]glyoxylamide (85) (91 mg, 51%) as a yellow oil after evaporation. \[1H-Nmr \ (CDCl_3, 400 MHz) \delta: 2.82 (t, J=7.0 Hz, CH_2Ar), 3.59 (q, J=7.0 Hz, 2H, CH_2NH), 3.870 (s, 3H, CH_3O), 3.874 (s 3H, CH_3O), 6.70-6.83 (m, 3H_arom), 9.22 (s, 1H, CHO). \] \[13C-Nmr \ (CDCl_3, 100 MHz) \delta: 34.6 (CH_2Ar), 40.9 (CH_2NH), 56.0 (2x CH_3O), 111.8 (ArC-H), 112.0 (ArC-H), 121.0 (ArC-H), 130.8 (ArC-CH_2), 148.0 (ArC-OCH_3), 149.5 (ArC-OCH_3), 160.1 (CO-CHO), 188.8 (CO-CHO). \] Ms (Cl) m/z (%): 238 (10, M*+1), 220 (12), 208 (15), 192 (12), 165 (65), 164 (93), 151 (100); (EI) m/z: accurate mass 219.0891, C_{12}H_{13}NO_3 requires 219.0895. Ir (Nujol) v_max: 1732 (CO), 1656 (CO).

Preparation of N-[2-(3,4-Dimethoxyphenyl)ethyl]bromoacetamide (62)

To a stirred mixture of homoveratrylamine (5.0 g, 27.6 mmol) and sodium carbonate (2.29 g, 27.6 mmol) in dry DCM (30 ml) was added bromoacetyl bromide (2.61 ml, 30.0 mmol). The mixture was then allowed to stir overnight. Water (30 ml) was added and the two layers were separated. The aqueous layer was extracted with further DCM (30 ml). The combined organic extracts were dried and evaporated to give a solid crude residue. The solid was recrystallised from EtOH/diethyl ether to give N-[2-(3,4-dimethoxyphenyl)ethyl]bromoacetamide (62) (5.18, 62%) as colourless crystals, mp 115-117°C (EtOH/Et_2O). \[1H-Nmr \ (CDCl_3, 300 MHz) \delta: 2.77 (t,
J=7.0 Hz, 2H, CH₂Ar), 3.54 (q, J=7.0 Hz, 2H, CH₂NH), 3.84 (s, 3H, CH₃O), 3.85 (s, 3H, CH₃O), 3.87 (s, 2H, CH₂Br), 6.50 (s, 1H, NH), 6.76-6.80 (m, 3H_arom). Ms (Cl) m/z (%): 304 (20, M^+1, ^81Br), 302 (20, M^+1, ^79Br), 258 (100), 222 (16), 221 (16), 205 (30), 165 (100), 164 (100), 152 (100), 151 (100), 149 (80).

Photolysis of N-[2-(3,4-Dimethoxyphenyl)ethyl]bromoacetamide (62)

A solution of (57) (200 mg, 0.664 mmol) in benzene (350 ml) was irradiated at room temperature for 3 h. The solvent was evaporated and the residue was chromatographed (DCM : MeOH, 97 : 3 ) to give a fraction which consisted of (8) (22 mg, 15 %).

Preparation of N-[2-(3,4-Dimethoxyphenyl)ethyl]fluoroacetamide (63)

A mixture of N-[2-(3,4-dimethoxyphenyl)ethyl]bromoacetamide (62) (44 mg, 1.457 mmol) and cesium fluoride (1.07 g, 7.086 mmol) in acetonitrile (25 ml) was refluxed overnight. The solvent was then evaporated and the crude was extracted with DCM (40 ml). The extract was washed with water (3 x 10 ml), dried and evaporated to give N-[2-(3,4-dimethoxyphenyl)ethyl]fluoroacetamide (63) (340 mg, 97%) as a colourless crystalline solid, mp 89-90°C. ¹H-Nmr (CDCl₃, 300 MHz) δ: 2.78 (t, J=7.2 Hz, 2H, CH₂Ar), 3.55 (q, J=7.2 Hz, 2H, CH₂NH), 3.84 (s, 3H, CH₃O), 3.85 (s, 3H, CH₃O), 4.75 (d, J=47.4 Hz, 2H, CH₂F), 6.38 (s, 1H, NH), 6.70-6.81 (m, 3H_arom). ¹³C-Nmr (CDCl₃, 75 MHz) δ: 35.1 (CH₂Ar), 40.0 (CH₂NH), 55.78 (CH₃O), 55.80 (CH₃O), 80.2 (d, J=184 Hz, CH₂F), 115.5 (ArC-H), 111.8 (ArC-H), 120.5 (ArC-H), 130.8 (ArC-CH₂), 147.8
Photolysis of N-[2-(3,4-Dimethoxyphenyl)ethyl]fluoroacetamide (63)

A solution of (57) (200 mg, 0.830 mmol) in benzene (350 ml) was irradiated at room temperature for 6 h. The solvent was evaporated and the residue was chromatographed (DCM : MeOH, 97 : 3) to give a fraction which consisted the starting material (190 mg, 95%).

Preparation of 3-Chloroacetyl-7,8-dimethoxy-1,3,4,5-tetrahydro-1H-3-benzazepin-2-one (86)

To a stirred mixture of 7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one (9)\(^{14,17}\) (100 mg, 0.452 mmol) and potassium carbonate (85 mg, 0.615 mmol) in dry DCM (5 ml) was added chloroacetyl chloride (0.075 ml, 0.940 mmol). The mixture was allowed to stir overnight. Water (10 ml) was then added and the two layers were separated. The aqueous layer was extracted with DCM (3 x 10 ml). The combined extracts were dried and evaporated to give solid residue. Recrystallisation from EtOAc/hexane gave 3-chloroacetyl-7,8-dimethoxy-4,5-dihydro-1H-3-benzazepin-2(3H)-one (86) (110 mg, 82%) as colourless crystals, mp 155-157°C (EtOAc/hexane). \(^{1}H\)-Nmr (CDCl\(_3\), 300 MHz) \(\delta\): 3.15 (t, J=6.0 Hz, 2H, CH\(_2\)CH\(_2\)N), 3.84 (s, 3H, CH\(_3\)O), 3.86 (s, 3H, CH\(_3\)O), 4.01 (s, 2H, CH\(_2\)Cl), 4.38 (t, J=6.0 Hz, CH\(_2\)CH\(_2\)N), 4.73 (s, 2H, ArCH\(_2\)CO), 6.57 (s, 1H\(_{arom}\)), 6.58 (s, 1H\(_{arom}\)). \(^{13}C\)-Nmr (CDCl\(_3\), 75 MHz) \(\delta\): 31.9 (CH\(_2\)CH\(_2\)N), 41.3 (CH\(_2\)Cl), 44.3 (CH\(_2\)CH\(_2\)N), 47.3 (ArCH\(_2\)CO), 55.7 (CH\(_3\)O),
55.64 (CH₃O), 112.9 (Ar-C-H), 113.7 (Ar-C-H), 120.2 (Ar-C-CH₂), 126.5 (Ar-C-CH₂), 147.2 (Ar-C-O), 148.4 (Ar-C-O), 168.5 (COCH₂Cl), 173.1 (ArCH₂CO). Ms (EI) m/z (%): 299 (13, M⁺, 37Cl), 297 (40, M⁺, 35Cl), 261 (21), 246 (15), 204 (60), 191 (30), 177 (100), 164 (59), 149 (21), 146 (22). Anal. Calcd for C₁₄H₁₆NO₄⁺Cl: C, 56.55; H, 5.43; N, 4.71. Found: C, 56.48; H, 5.46; N, 4.45.

Photolysis of 3-Chloroacetyl-7,8-dimethoxy-4,5-dihydro-1H-3-benzazepin-2(3H)-one (86)

A solution of 3-chloroacetyl-7,8-dimethoxy-4,5-dihydro-1H-3-benzazepin-2(3H)-one (86) (100 mg, 0.336) in water and acetonitrile (350 ml, 50:50, v/v) was irradiated for 5 h using 16 W mercury lamp and a vycor filter. The solvent was then evaporated and the residue was chromatographed (EtOAc : hexane : MeOH, 75 : 22.5 : 2.5) to give 11a-hydroxy-8,9-dimethoxy-5,6,11,11a-tetrahydrooxazolo[2,3-b][3]benzazepin-3(2H)-one (87) (76 mg, 81%) as a colourless crystalline solid after evaporation; mp 136.5-138.5 °C. ¹H (acetone-d₆, 300 MHz) δ: 2.83-2.89 (m, 4H, CH₂CH₂N), 3.15 (d, J=14.4 Hz, 1H, ArCHC-OH), 3.26 (d, J=14.4 Hz, 1H, ArCHC-OH), 3.78 (s, 6H, 2 x CH₃O), 4.10-4.25 (m, 3H, CH₂O and OH), 6.79 (s, 1H arom), 6.82 (s, 1H arom). ¹³C-Nmr (acetone-d₆, 75 MHz) δ: 34.9 (CH₂CH₂N), 38.8 (CH₂CH₂N), 46.7 (ArCH₂C-OH), 56.3 (CH₃O), 56.4 (CH₃O), 66.8 (CH₂CO), 110.3 (ArCH₂C-OH), 114.9 (Ar-C-H), 116.9 (Ar-C-H), 128.3 (Ar-C-CH₂), 134.3 (Ar-C-CH₂), 148.8 (Ar-C-O), 149.8 (Ar-C-O), 169.0 (CO). Ms (Es -ve) m/z (%): 278.3 (100, M⁺-1). Ms (EI) m/z (%): 279 (18), 261 (8), 246 (6), 221 (3), 204 (5), 178 (13), 165 (100), 151 (8). Anal. Calcd for C₁₄H₁₇NO₅⁺Cl: C, 60.19; H, 6.14; N, 5.02. Found: C, 60.07; H, 6.19; N, 5.03.
Recrystallisation from EtOH gave 11α-ethoxy-8,9-dimethoxy-5,6,11,11α-tetrahydrooxazolo[2,3-b][3]benzazepin-3(2H)-one (88) as colourless crystals, mp 125-127 °C. \( ^1H (\text{CDCl}_3, 300 \text{ MHz}) \delta: 1.11 (t, J=6.9 \text{ Hz}, 3\text{H}, \text{CH}_3\text{CH}_2\text{O}), 2.84-2.90 (m, 4\text{H}, \text{CH}_2\text{CH}_2\text{N}), 3.22-3.31 (m, 2\text{H}, \text{ArCH}_2\text{C-OH}), 3.86 (s, 3\text{H}, \text{CH}_3\text{O}), 3.87 (s, 3\text{H}, \text{CH}_3\text{O}), 4.21-4.38 (m, 2\text{H}, \text{CH}_2\text{CO}), 6.65 (s, 1\text{H}_{\text{arom}}), 6.70 (s, 1\text{H}_{\text{arom}}). \)

Ms (EI) (%): 307 (M+, 37), 278 (72), 262 (43), 246 (17), 179 (58), 178 (57), 162 (34); (CI) m/z: M^+1 accurate mass 308.1498, C_{16}H_{22}N_2O_5 requires 308.1498.

Reaction of N-[2-(3-Hydroxy-4-methoxyphenyl)ethyl]iodoacetamide (50) with Sodium Hydride

To a solution on N-[2-(3-hydroxy-4-methoxyphenyl)ethyl] iodoacetamide (50) (45 mg, 0.134 mmol) in dry THF (20 ml) under N\(_2\) was added sodium hydride (58 mg, 60 %, 1.45 mmol). The solution was allowed to stir overnight. Water (15 ml) was then added and the mixture was extracted with DCM (3 x 20 ml). The combined extracts were dried, evaporated and chromatographed (DCM : MeOH, 96 : 4) to give a solid residue. The residue was then crystallised from EtOH to give (89) (17 mg, 61%) as colourless crystals; mp 263-265 °C. \( ^1H\text{-Nmr (CDCl}_3, 400 \text{ MHz}) \delta: 2.73 (t, J=6.0 \text{ Hz}, 4\text{H}, 2 \times \text{CH}_2\text{Ar}), 3.53 (q, J=6.0, 4\text{H}, 2 \times \text{CH}_2\text{NH}), 3.85 (s, 6\text{H}, 2 \times \text{CH}_3\text{O}). \)
CH₃O), 4.52 (s, 4H, 2 x COCH₂), 6.48 (s, 2H, 2 x NH), 6.50 (d, J=2.0 Hz, 2 x 1H_arom), 6.73 (d, J=8.4 Hz, 2 x 1H_arom), 6.77 (dd, J=8.4, J=2.0 Hz, 2 x 1H_arom). Ms (EI) m/z (%): 414 (5, M⁺), 382 (2), 207 (47), 176 (11), 136 (6), 150 (20), 137 (8), 135 (10). Anal. Calcd for C₂₂H₂₆O₆N₂: C, 63.76; H, 6.32; N, 6.72. Found: C, 63.26; H, 6.36; N, 6.47.

Reaction of N-2-(3-Hydroxy-4-methoxyphenyl)ethylamine Hydrochloride with 3-Chloropropionyl Chloride

To a solution of N-2-(3-hydroxy-4-methoxyphenyl)ethylamine hydrochloride₆₄,₆₅ (120 mg, 0.59 mmol) in THF (5 ml), under N₂, was added NaOH (0.5 ml, 5M). The solution was then cooled in an ice bath. 3-Chloropropionyl chloride was added dropwise until a white precipitate was observed. Stirring was allowed to continue for 1 h. Water (5 ml) was then added and the mixture was extracted with DCM (3 x 15 ml). The combined extracts were dried and evaporated. The crude was dissolved in MeOH (5 ml), potassium carbonate was then added and the mixture was allowed to stir for 0.5 h. Water (5 ml) was added, the pH was adjusted to 7 (HCl, 1M) and the solution was extracted with DCM (3 x 15 ml). The combined extracts were dried and evaporated to give a yellow oil. The oil was then chromatographed. Elution with EtOAc : hexane, 45 : 55, gave two fractions. The solvent in the first fraction was evaporated to give (90) (50 mg, 33%) as
pale yellow oil. $^1$H-Nmr (CDCl$_3$, 400 MHz) $\delta$: 2.57 (t, J=6.4 Hz, 2H, COCH$_2$), 2.74 (t, J=6.8 Hz, 2H, CH$_2$Ar), 3.51 (q, J=6.8 Hz, 2H, CH$_2$NH), 3.79 (t, 6.4 Hz, 2H, CH$_2$Cl), 3.88 (s, 3H, CH$_3$O), 5.57 (s, 1H, NH), 5.64 (s, 1H, OH), 6.68 (dd, J=8.4, 2.0 Hz, 1H$_{arom}$), 6.78 (d, J=2.0 Hz, 1H$_{arom}$), 6.80 (d, J=8.4 Hz, 1H$_{arom}$). Ms (EI) m/z (%): 259 (0.6, M+, 37Cl), 257 (1.8, M+, 35Cl), 247 (0.6), 232 (2), 221 (0.6), 204 (2), 181 (1.9), 178 (3), 167 (2), 150 (100), 137 (30), 135 (35). The second fraction consisted of (91) (50 mg, 38%) as a pale yellow oil after evaporation. $^1$H-Nmr (CDCl$_3$, 400 MHz) $\delta$: 2.76 (t, J=6.8 Hz, 2H, CH$_2$Ar), 3.57 (q, J=6.8 Hz, 2H, CH$_2$NH), 3.88 (s, 3H, CH$_3$O), 5.53 (s, 1H, NH), 5.618 (dd, J=10.4, J=1.4 Hz, 1H, COCH$_2$CH$_2$), 5.619 (s, 1H, OH), 6.02 (dd, J=17.2, J=10.4 Hz, 1H, COCHCH$_2$), 6.26 (dd, J=17.2, J=1.4 Hz, 1H, COCHCH), 6.68 (dd, J=8.4, J=2.0 Hz, 1H$_{arom}$), 6.78 (d, J=2.0 Hz, 1H$_{arom}$), 6.80 (d, J=8.4 Hz, 1H$_{arom}$). Ms (EI) m/z (%): 221 (37, M+), 167 (12), 151 (100), 149 (84), 138 (47), 137 (100), 135 (100), 122 (100).

**Preparation of N-[2-(3-Hydroxy-4-methoxyphenyl)ethyl]azidoacetaamide (94)**

A mixture of N-[2-(3-hydroxy-4-methoxyphenyl)]chloroacetamide (43) (200 mg, 0.821 mmol) and sodium azide (267 mg, 4.105 mmol) in methyl ethyl ketone (15 ml) was refluxed for 28 h. Water (20 ml) was added and the mixture was then extracted with DCM (3 x 20 ml). The combined extracts were dried, evaporated and chromatographed. Elution with EtOAc : hexane, 50 : 50 gave a fraction which was evaporated to give N-[2-(3-Hydroxy-4-
methoxy phenyl) ethyl] azidoacetamide (94) (150 mg, 73%) as a colourless crystalline solid, mp 67-69°C. \(^1\)H-Nmr (CDCl\(_3\), 300 MHz) \(\delta\): 2.74 (t, \(J=6.6\) Hz, 2H, CH\(_2\)Ar), 3.51 (q, \(J=6.6\) Hz, 2H, CH\(_2\)NH), 3.89 (s, 3H, CH\(_3\)O), 3.95 (s, 2H, CH\(_2\)N\(_3\)), 5.78 (s, 1H, OH), 6.35 (s, 1H, NH), 6.67 (dd, \(J=8.4, J=2.1\) Hz, 1H\(_{arom}\)), 6.77 (d, \(J=2.1\) Hz, 1H\(_{arom}\)), 6.80 (d, \(J=8.4\) Hz, 1H\(_{arom}\)). \(^1\)C-Nmr (CDCl\(_3\), 75 MHz) \(\delta\): 34.8 (CH\(_2\)Ar), 40.5 (CH\(_2\)NH), 52.7 (CH\(_2\)N\(_3\)), 56.0 (CH\(_3\)O), 110.9 (ArC-H), 114.8 (ArC-H), 120.1 (ArC-H), 131.6 (ArC-CH\(_2\)), 145.4 (ArC-O), 145.8 (ArC-O), 166.5 (CO).

Preparation of N-[2-(3-Acetyloxy-4-methoxyphenyl)ethyl]azidoacetamide (95)

\[
\begin{align*}
\text{CH}_3 & \quad \text{C} & \quad \text{O} & \quad \text{O} \\
\text{O} & \quad \text{N} & \quad \text{CH}_2\text{N}_{3} \\
& \quad \text{H} & \quad \text{CH}_3
\end{align*}
\]

To a stirred solution of N-[2-(3-hydroxy-4-methoxyphenyl)] azidoacetamide (94) (170 mg, 0.68 mmol) in THF (7 ml) under N\(_2\), cooled in an ice bath, was added sodium hydride (41 mg, 60%, 1.03 mg). After 5 min acetyl chloride (0.06 ml, 0.84 mmol) was added and the mixture was allowed to stir for 3 h. The solvent was then evaporated and the crude was extracted with DCM (30 ml). The extract was washed with water (2 x 10 ml), dried, evaporated and chromatographed. Elution with EtOAc : hexane, 60 : 40 gave a fraction which was evaporated to give N-[2-(3-acetyloxy-4-methoxyphenyl)ethyl]azidoacetamide (95) (175 mg, 88%) as a colourless crystalline solid, 52-54°C. \(^1\)H-Nmr (CDCl\(_3\), 300 MHz) \(\delta\): 2.32 (s, 3H, COCH\(_3\)), 2.77 (t, \(J=6.9\) Hz, 2H, CH\(_2\)Ar), 3.51 (q, \(J=6.9\) Hz, 2H, CH\(_2\)NH), 3.82 (s, 3H, CH\(_3\)O), 3.94 (s, 2H, CH\(_2\)N\(_3\)), 6.37 (s, 1H, NH), 6.88 (d, \(J=1.8\) Hz, 1H\(_{arom}\)), 6.92 (d, \(J=8.1\) Hz, 1H\(_{arom}\)), 7.03 (dd, \(J=8.1, 1.8\) Hz, 1H\(_{arom}\)). \(^1\)C-Nmr (CDCl\(_3\), 75 MHz) \(\delta\): 20.6 (COCH\(_3\)), 34.5
(CH$_2$Ar), 40.0 (CH$_2$NH), 52.7 (CH$_2$N), 55.9 (CH$_3$O), 112.6 (ArC-H), 123.1 (ArC-H), 126.8 (ArC-H), 130.9 (ArC-CH$_2$), 139.7 (ArC-O), 149.8 (ArC-O), 166.5 (COCH$_2$Cl), 169.0 (COCH$_3$).

**Reaction of N-[2-(3-Acetyloxy-4-methoxyphenyl)ethyl]azidoacetamide (95) with Triethylphosphite**

A mixture of N-[2-(3-acetyloxy-4-methoxyphenyl)ethyl]azidoacetamide (95) (150 mg, 0.514 mmol) and triethylphosphite (0.88 ml, 5.14 mmol) was refluxed in cyclohexane (25 ml) 5 h. The solvent was evaporated and the residue was refluxed in toluene (25 ml) for 48 h. The organic solvent was then evaporated and the crude residue was extracted with DCM (20 ml). The extract was washed with water (2 x 5 ml), dried and evaporated to give (96) (208 mg, 94%) as a pale yellow oil. $^1$H-Nmr (CDCl$_3$, 300 MHz) $\delta$: 1.30 (t, J=6.6 Hz, 9H, 3 x OCH$_2$CH$_3$), 2.32 (s, 3H, COCH$_3$), 2.77 (t, J=6.9 Hz, 2H, CH$_2$Ar), 3.53 (q, J=6.9 Hz, 2H, CH$_2$NH), 3.81 (s, 3H, CH$_3$O), 4.0-4.07 (m, 8H, CH$_2$N, 3 x OCH$_2$CH$_3$), 6.75 (s, 1H, NH), 6.86-7.04 (m, 3H$_{arom}$). Ms (EI) m/z (%): 430 (15, M$^+$), 356 (20), 293 (15), 239 (100), 180 (85).

\[ \begin{array}{c}
\text{H}_3\text{C} \\
\text{O} \\
\text{H}_3\text{CO} \\
\text{N} \\
\text{CH}_2\text{N} = \text{P(OEt)}_3 \\
\end{array}\]

\[ \text{(96)} \]

5.2 **Experimental for Chapter 3**

**Reaction of 12-Methoxy-2-oxa-6-azabicyclo[7.3.1.]trideca-1(13),9,11-trien-5-one (8) with N-Bromosuccinimide**

To a stirred solution of 12-methoxy-2-oxa-6-azabicyclo[7.3.1.]trideca-1(13),9,11-trien-5-one (8) (68 mg, 0.308) in CCl$_4$ (5 ml) was added N-
bromosuccinimide (55 mg, 0.308 mmol) and AIBN (3 mg, 18.3 mmol). The mixture was allowed to reflux under N₂ for 30 min. The solvent was then evaporated and the crude residue was chromatographed (EtOAc : hexane, 30 : 70 and then 75 : 25) to give five fractions. The solvent in the first fraction was evaporated to give 9-bromo-10-methoxy-2,3-dihydro-4H-pyrrolo[1,2,3-e,f][1,4]benzoxazepin-4-one (107) (6 mg, 7%) as a colourless crystalline solid, mp 116-118°C (EtOAc/hexane). ¹H-Nmr (CDCl₃, 300 MHz) δ: 3.33 (t, J=4.8 Hz, 2H, CH₂CO), 3.89 (s, 3H, CH₃O), 4.52 (t, J=4.8 Hz, 2H, CH₂O), 6.60 (d, J=3.9 Hz, CHCHN), 7.40 (s, 1H arom), 7.85 (d, J=3.9 Hz, CHCHN). Ms (EI) m/z (%): 297 (28, M⁺, 81Br), 295 (28, M⁺, 79Br), 281 (10), 280 (11), 243 (5), 241 (6), 228 (7), 226 (7), 55 (100). The second fraction was 8-bromo-10-methoxy-2,3-dihydro-4H-pyrrolo[1,2,3-e,f][1,4]benzoxazepin-4-one (108) (3 mg, 3%) as a colourless crystalline solid, mp 142-144°C (EtOAc/hexane). ¹H-Nmr (CDCl₃, 300 MHz) δ: 3.30 (t, J=4.5 Hz, 2H, CH₂CO), 3.93 (s, 3H, CH₃O), 4.50 (t, J=4.5 Hz, 2H, CH₂O), 6.69 (d, J=3.9 Hz, 1H, CHCHN), 7.09 (s, 1H arom), 7.83 (d, J=3.9 Hz, 1H, CHCHN). The third fraction consisted of 10-methoxy-2,3-dihydro-4H-pyrrolo[1,2,3-e,f][1,4]benzoxazepin-4-one (106) (11 mg, 16%) as a colourless crystalline solid, mp 97-98°C (EtOAc/hexane). ¹H-Nmr (CDCl₃, 300 MHz) δ: 3.31 (t, J=4.8 Hz, 2H, CH₂CO), 3.95 (s, 3H, CH₃O), 4.52 (t, J=4.8 Hz, 2H, CH₂O), 6.63 (d, J=3.9 Hz, 1H, CHCHN), 6.94 (d, J=8.1 Hz, 1H arom), 7.14 (d, J=8.1 Hz, 1H arom), 7.79 (d, J=3.9 Hz, 1H, CHCHN). ¹³C-Nmr (CDCl₃, 300 MHz) δ: 40.7 (CH₂CON), 57.1 (CH₃O), 63.6 (CH₂O), 109.4 (CHCHN), 110.0 (ArC-H), 113.7 (ArC-H), 123.3 (ArC-CH), 124.5 (CHCHN), 127.7 (ArC-N), 136.5 (ArC-O), 146.7 (ArC-O), 169.0 (CO). Ms (EI) m/z (%): 217 (53, M⁺, accurate mass 217.0738, C₁₂H₁₁NO₃ requires 217.0739), 202 (9), 163 (22), 148 (20), 134 (4), 55 (100). The fourth fraction gave 9-bromo-10-methoxy-2,3,6,7-tetrahydro-4H-pyrrolo[1,2,3-e,f][1,4]benzoxazepin-4-one (105) (10 mg, 11%) as a colourless solid, mp 84-86°C (EtOAc/hexane).
\(^{1}\text{H-Nmr (CDCl}_3,\ 300\ \text{MHz)}\ \delta: 3.01-3.11\ (m, 4H, CH}_2\text{Ar and CH}_2\text{CO), 3.83\ (s, 3H, CH}_3\text{O), 4.14\ (t, J=8.7 Hz, CH}_2\text{N), 4.32-4.36\ (m, 2H, CH}_2\text{O), 7.19\ (s, 1H}_\text{arom}).\)

\(^{\text{Ms (EI) m/z (%)}}: 299\ (95, M^+, \text{ }^{81}\text{Br}), 297\ (100, M^+, \text{ }^{79}\text{Br}), 244\ (80), 243\ (83), 163\ (20), 148\ (24).\) The fifth fraction afforded \(10\)-methoxy-\(2,3,6,7\)-tetrahydro-\(4\text{H-pyrrolo[1,2,3-e,f][1,4]benzoxazepin-4-one (104)}\) (32 mg, 47%) as a colourless crystalline solid after evaporation, mp 121-123°C (EtOAc/hexane). \(^{1}\text{H-Nmr (CDCl}_3,\ 300\ \text{MHz)}\ \delta: 3.03-3.10\ (m, 4H, CH}_2\text{Ar and CH}_2\text{CO), 4.14\ (t, J=8.7 Hz, CH}_2\text{N), 4.37\ (t, J=4.8 Hz, 2H, CH}_2\text{O), 6.58\ (d, 8.1 Hz, 1H}_\text{arom), 6.78\ (d, J=8.1, 1H}_\text{arom}).\)

\(^{13}\text{C-Nmr (CDCl}_3,\ 300\ \text{MHz)}\ \delta: 26.1\ (\text{CH}_2\text{Ar), 39.9\ (CH}_2\text{CO), 48.2\ (CH}_2\text{N), 64.2\ (CH}_2\text{O), 107.1\ (ArC-H), 117.4\ (ArC-H), 127.0\ (ArC-N), 128.5\ (ArC}-\text{CH}_2\text{), 136.6\ (ArC-O), 149.4\ (ArC-O), 170.2\ (CO).\) \(^{\text{Ms (EI) m/z (%)}}: 219\ (13, M^+, \text{ accurate mass 219.0901, C}_{12}\text{H}_{13}\text{NO}_3\text{ requires 219.0895, 165}\ (19), 149\ (2), 132\ (4), 99\ (100), 56\ (100).\)
Reaction of 12-Methoxy-2-oxa-6-azabicyclo[7.3.1.]trideca-1(13),9,11-trien-5-one (8) with Bromine

To a solution of 12-methoxy-2-oxa-6-azabicyclo[7.3.1.]trideca-1(13),9,11-trien-5-one (8) (20 mg, 0.9 mmol) in CCl₄ (5 ml) was added excess of bromine. The solution was refluxed for 1 h. The solvent was evaporated and the crude residue was chromatographed (EtOAc/hexane, 35:65) to give the 9,10-dibromo derivative of (106) (13 mg, 39%) as a pale yellow gum. ^1H-Nmr (CDCl₃, 300 MHz) δ: 3.30 (t, J=4.8 Hz, 2H, CH₂CO), 3.98 (s, 3H, CH₃O), 4.51 (t, J=4.8 Hz, 2H, CH₂O), 6.62 (d, J=3.9 Hz, 1H, CHCHN), 7.80 (d, J=3.9 Hz, 1H, CHCHN).

Reaction of 12-Methoxy-2-oxa-6-azabicyclo[7.3.1.]trideca-1(13),9,11-trien-5-one (8) with Benzoyl Peroxide

A mixture of 12-methoxy-2-oxa-6-azabicyclo[7.3.1.]trideca-1(13),9,11-trien-5-one (8) (20 mg, 0.09 mol) and benzoyl peroxide (22 mg, 0.09) in benzene (5 ml) was refluxed for 1 h. The solvent was evaporated and the residue was chromatographed (EtOAc/hexane, 50:50 and then 80:20) to give (104) (7 mg, 35%).

Reaction of N-[2-(3,4-Dimethoxyphenyl)ethyl]chloroacetamide (113) with N-Bromosuccinimide

A mixture of N-[2-(3,4-dimethoxyphenyl)ethyl]acetamide (500, 2.24 mmol) and N-bromosuccinimde (399 mg, 224 mmol) and AIBN (10 mg, 0.05 mmol) in CCl₄ (35 ml) was refluxed for 30 min. The solvent was then evaporated. The crude residue was extracted with DCM (30 ml). The organic extract was washed with water (2 x 10 ml), dried and evaporated to give N-[2-
(2-bromo-4,5-dimethoxyphenyl)ethyl)acetamide (114) (474 mg, 70%) as a colourless solid, mp 101-103°C (lit. 102-103°C).

Reaction of 12-Methoxy-2-oxa-6-azabicyclo[7.3.1]trideca-1(13),9,11-trien-5-one (8) with Sodium Hydride and Iodomethane

To a solution of 12-methoxy-2-oxa-6-azabicyclo[7.3.1]trideca-1(13),9,11-trien-5-one (8) (50 mg, 0.226 mmol) in THF (5 ml) was added sodium hydride (10 mg, 0.249 mmol) and iodomethane (0.02 ml, 0.226 mmol). The solution was allowed to stir overnight. The solvent was evaporated and the crude residue was extracted with DCM (20 ml). The extract was washed with water (2 x 5 ml), dried, evaporated and chromatographed (EtOAc:hexane, 50:50) to give (126) (32 mg, 61%) as a pale yellow oil. $^1$H-Nmr (CDCl$_3$, 400 MHz) δ: 2.80 (t, J=7.2 Hz, 2H, CH$_2$Ar), 3.57 (q, J=7.2 Hz, 2H, CH$_2$NH), 3.86 (s, 6H, 2 x CH$_3$O), 5.62 (dd, J=10.4, 1.6 Hz, 1H, COCHCH$_2$), 5.89 (s, 1H, NH), 6.06 (dd, J=17.2, J=10.4 Hz, 1H, COCHCH), 6.26 (dd, J=17.2, J=1.6 Hz, 1H, COCHCH), 6.78 (3H arom). $^{13}$C-Nmr (CDCl$_3$, 100 MHz) δ: 35.01 (CH$_2$Ar), 40.7 (CH$_2$N), 55.7 (CH$_3$O), 111.2 (COCHCH$_2$), 111.8 (COCHCH$_2$), 120.5 (Ar-C-H), 126.3 (Ar-C-H), 130.8 (Ar-C-H), 131.2 (Ar-C-CH$_2$), 147.5 (Ar-C-CH$_2$), 148.9 (Ar-C-OCH$_3$), 165.5 (CO).
Reaction of 12-Methoxy-2-oxa-6-azabicyclo[7.3.1.]trideca-1(13),9,11-trien-5-one (8) with a Solution of Sodium Hydroxide

A solution of 12-methoxy-2-oxa-6-azabicyclo[7.3.1.]trideca-1(13),9,11-trien-5-one (8) (50 mg, 0.226 mmol) in sodium hydroxide (5 ml) was refluxed for a week. No change was observed as reaction was monitored by t.l.c. and $^1$H-Nmr spectrometry.

Reaction of 12-Methoxy-2-oxa-6-azabicyclo[7.3.1.]trideca-1(13),9,11-trien-5-one (8) with an Acylase

A solution of 12-methoxy-2-oxa-6-azabicyclo[7.3.1.]trideca-1(13),9,11-trien-5-one (8) (25 mg, 0.113 mmol) and acylase I (1 mg) (Grade I, from Porcine kidney) in phosphate buffer solution (pH near 7) was stirred for 72 h. No change was observed as the reaction was monitored by t.l.c. and $^1$H-Nmr spectrometry.

Preparation of N-Protected 12-Methoxy-2-oxa-6-azabicyclo[7.3.1.]trideca-1(13),9,11-trien-5-one (103)

To a solution of 12-methoxy-2-oxa-6-azabicyclo[7.3.1.]trideca-1(13),9,11-trien-5-one (8) (50 mg, 0.226 mmol) in DCM (2 ml) was added triethylamine (0.04 ml, 0.289 mmol), 4-(dimethylamino) pyridine (27.6 mg, 0.226 mmol) and di-tert-butyldimethylidicarbamate (78.6 mg, 0.452 mmol). The mixture was allowed to stir overnight and then chromatographed (EtOAc : hexane, 55
156 : 45 and then DCM : MeOH, 98 : 2) to give two fractions. The solvent in first fraction was evaporated to give (103) (20 mg, 28%, 69% based on recovered starting material) as pale yellow oil. \(^1\)H-Nmr (CDCl\(_3\), 300 MHz) \(\delta\): 1.59 (s, 9H, (CH\(_3\))\(_3\)C), 2.55 (dd, J=16.8, J=5.4 Hz, 1H, CHCO), 2.63 (dt, J=13.2, J=2.4 Hz, 1H, CHAr), 2.87 (dt, J=13.2, J=4.5 Hz, 1H, CHAr), 3.53 (ddd, J=16.8, J=10.5, J=1.8 Hz, 1H, CHCO), 3.60 (dd, J=7.8, J=2.4 Hz, 1H, CHN), 3.66 (dt, J=7.8, J=4.5 Hz, 1H, CHN), 3.88 (s, 3H, CH\(_3\)O), 4.27 (t, J=10.5 Hz, 1H, CHO), 4.41 (ddd, J=10.5, 5.4, 1.8 Hz, 1H, CHO), 6.81-6.90 (m, 3Harom). Ms (Es +ve) m/z (%): 344.3 (85, M\(^+\)+23), 322.3 (2, M\(^+\)+1), 266.3 (3), 248.2 (11), 244.2 (12).

Reaction of (103) with N-Bromosuccinimide

To a solution of (103) (10 mg, 0.031 mmol) in CCl\(_4\) (2 ml) was added N-bromosuccinimide (10 mg, 0.056 mmol) and AIBN (0.4 mg, 0.0024 mmol). The mixture was allowed to reflux for 10 h. The solvent was then evaporated and the crude residue was chromatographed (EtOAc : hexane, 20 : 80) to give (115) (9.5 mg, 76%) as colourless crystals, mp 108-109\(^\circ\)C (EtOAc/hexane). \(^1\)H-Nmr (CDCl\(_3\), 300 MHz) \(\delta\): 2.48 (dd, J=16.5, J=5.4 Hz, 1H, CHCO), 3.37 (ddd, J=16.5, 10.5, 1.8 Hz, 1H, CHCO), 3.67 (dd, J=19.2, J=10.8 Hz, 1H, CHN), 3.79 (dd, J=19.2, J=3.6 Hz, 1H, CHN), 3.88 (s, 3H, CH\(_3\)O), 4.18 (t, 10.5 Hz, 1H, CHO), 4.31 (ddd, J=10.5, 5.4, 1.8 Hz, 1H, CHO), 4.91 (dd, J=10.8, 3.6 Hz, 1H, BrCHAr), 6.67 (d, J=2.1 Hz, 1Harom), 6.92 (d, 8.4 Hz, 1Harom), 7.31 (dd, J=8.4, J=2.1 Hz, 1Harom). \(^1\)C-Nmr (CDCl\(_3\), 300 MHz) \(\delta\): 15.3 ((CH\(_3\))\(_3\)C), 28.1 ((CH\(_3\))\(_3\)C), 41.7 (CH\(_2\)CO), 49.3 (CH\(_2\)N), 56.1 (CH\(_3\)O), 72.7 (CH\(_2\)O), 84.1 (BrCHAr), 114.6 (ArC-H), 123.2 (ArC-H), 129.5 (ArC-H), 146.7 (ArC-CHBr), 152.1 (ArC-O), 153.1 (ArC-O), 173.7 (CO). Ms (EI): 401 (2, M\(^+\), \(^{81}\)Br), 399 (1.7, M\(^+\), accurate mass 399.0677, C\(_{17}\)H\(_{22}\)\(^{79}\)BrNO\(_5\) requires 399.0681), 300 (3), 298 (3), 272 (2), 270 (2), 220 (15), 191 (7), 164 (12).
Reaction of (64) with N-Bromosuccinimide

To a stirred solution of (64) (50 mg, 0.179 mmol) in CDCl₃ (5 ml) was added N-bromosuccinimide (32 mg, 0.179 mmol) and AIBN (1.5 mg, 0.0091 mmol). The mixture was allowed to reflux for 1 h. The solvent was then evaporated and the crude residue was chromatographed (EtOAc, hexane, 30 : 70, and 40 : 60, and then 100 : 0) to give five fractions. The solvent in the first fraction was evaporated to give methyl 8-bromo-10-methoxy-4-oxo-2,3-dihydro-4H-pyrrolo[1,2,3-e,f][1,4]benzoxazepine-6-carboxylate (110) (3 mg, 5%, 9% based on recovered starting material) as a yellow gum. ¹H-Nmr (CDCl₃, 300 MHz) δ: 3.34 (t, J=5.1 Hz, 2H, CH₂CO), 3.90 (s, 3H, COOCH₃), 3.91 (s, 3H, CH₃OAr), 4.63 (t, J=5.1 Hz, 2H, CH₂O), 7.06 (s, 1H, CHC-N), 7.43 (s, 1H₂arom). Ms (EI) m/z (%): 355 (2.5, M⁺, ⁸¹Br), 353 (2.5, M⁺, ⁷⁹Br), 301 (2.5), 299 (2.5), 172 (1), 172 (2). The second fraction consisted of methyl 9-bromo-10-methoxy-4-oxo-2,3-dihydro-4H-pyrrolo[1,2,3-e,f][1,4] benzoxazepine-6-carboxylate (111) (6 mg, 9%, 17% based on recovered starting material) as a pale yellow gum. ¹H-Nmr (CDCl₃, 300 MHz) δ: 3.25 (t, J=4.8 Hz, 2H, CH₂CO), 3.85 (s, 3H, COOH₃), 3.88 (s, 3H, CH₃OAr), 4.56 (t, J=4.8 Hz, 2H, CH₂O), 7.04 (s, 1H, CHC-N), 7.12 (s, 1H₂arom). Ms (EI) m/z (%): 355 (3, M⁺, ⁸¹Br), 353 (3, M⁺, ⁷⁹Br). The third fraction was methyl 10-methoxy-4-oxo-2,3-dihydro-4H-pyrrolo[1,2,3-e,f][1,4]benzoxazepine-6-carboxylate (109) (11 mg, 22%, 40% based on recovered starting material) as a pale yellow gum after evaporation. ¹H-Nmr
(CDCl₃, 300 MHz) δ: 3.25 (t, J=5.1 Hz, 2H, CH₂CO), 3.84 (s, 3H, COOH₃), 3.89 (s, 3H, CH₃OAr), 4.58 (t, J=5.1 Hz, 2H, CH₂O), 6.90 (d, 8.4 Hz, 1Hₐrom), 7.07 (s, 1H, CHC-N), 7.11 (d, J=8.4 Hz, 1Hₐrom). ¹³C-Nmr (CDCl₃, 75 MHz) δ: 40.1 (CH₂CO), 52.5 (COOCH₃), 57.1 (CH₃OAr), 64.0 (CH₂O), 110.1 (CHC-N), 115.2 (ArC-H), 118.0 (ArC-H), 124.6 (ArC-CH), 125.6 (CHC-N), 131.1 (ArC-N), 136.1 (ArC-O), 148.4 (ArC-O), 162.2 (COOCH₃), 170.1 (CH₂CO). Ms (EI) m/z (%): 276.3 (100, M⁺+1), 244.4 (27); (EI) m/z: accurate mass 275.0808, C₁₄H₁₃NO₅ requires 275.0794. The fourth fraction was (112) (4 mg, 6%, 11% based on recovered starting material) as a colourless crystalline solid, mp 294-296°C (EtOAc/hexane). Ms (EI) m/z (%): 357 (4, M⁺, ⁸¹Br), 355 (4, M⁺, ⁷⁹Br), 272 (14), 270 (14), 216 (20), 163 (100). The sixth fraction was the starting material (22 mg, 44%).

![Chemical Structures](111, 110, 109, 112)
Preparation of 2,3,5,6-Tetrahydropyran[2,3,4-ij]isoquinolin-9-ol (102)

To a solution of 12-methoxy-2-oxa-6-azabicyclo[7.3.1]trideca-1(13),9,11-trien-5-one (8) (100 mg, 0.453 mmol) in dry DCM (3 ml) under N₂ was added boron tribromide (3.0 ml, 1M, 3.0 mmol) at -78°C. The solution was allowed to stir for 6 h. It was then cooled in an ice bath and saturated solution of sodium bicarbonate was added (pH 7.5). The resulting mixture was extracted with DCM (40 ml) and EtOAc (2 x 30 ml). The combined extracts were dried, evaporated and chromatographed (DCM : MeOH, 95 : 5) to give 2,3,5,6-tetrahydropyran[2,3,4-ij]isoquinolin-9-ol (102) (70 mg, 82%) as a yellow crystalline solid, mp 202-204°C (lit. 204°C). ¹H-Nmr (acetone-d₆, 300 MHz) δ: 2.58 (t, J=7.2 Hz, 2H, CH₂Ar), 2.70 (t, J=6.0 Hz, 2H, OCH₂CH₂), 3.65 (t, J=7.2 Hz, 2H, CH₂N), 4.41 (t, J=6.0 Hz, 2H, OCH₂CH₂), 6.59 (d, J=7.8 Hz, 1Hₐrom), 6.83 (d, J=7.8 Hz, 1Hₐrom). Ms (EI) m/z (%): 189 (100, M⁺), 173 (5), 172 (5), 161 (16).

Preparation of 2,3,3a,4,5,6-Hexahydropyran[2,3,4-ij]isoquinolin-9-ol (123)

To a solution of 2,3,5,6-tetrahydropyran[2,3,4-ij]isoquinolin-9-ol (102) (65 mg, 0.344 mmol) in EtOH (5 ml) was added sodium borohydride (40 mg, 0.86 mmol). The mixture was allowed to stir for 30 min. Saturated solution
of ammonium chloride (2 ml) was then added. The mixture was evaporated and the remaining crude residue was chromatographed (DCM : MeOH, 85 : 15) to give \(2,3,3a,4,5,6\)-hexahydropyrano[2,3,4-ij]isoquinolin-9-ol (123) (45 mg, 69\%) as a colourless crystalline solid, mp 166-168°C (DCM/MeOH). \(^1\)H-Nmr (CD\(_3\)OD, 300 MHz) \(\delta\): 1.88-2.02 (m, 1H, OCH\(_2\)CH), 2.20-2.28 (m, 1H, OCH\(_2\)CH), 2.78-2.86 (m, 1H, ArCH\(_2\)CH\(_2\)NH), 2.88-3.00 (m, 1H, ArCH\(_2\)CH\(_2\)NH), 3.13-3.23 (ArCH\(_2\)CHNH), 3.56-3.42 (m, 1H, ArCH\(_2\)CH\(_2\)NH), 4.07-4.12 (m, 1H, NHCH\(_2\)Ar), 4.19-4.28 (m, 1H, OCH\(_2\)CH\(_2\)), 4.47-4.53 (m, 1H, OCH\(_2\)CH\(_2\)), 6.52 (d, \(J=8.4\) Hz, 1H\(_{arom}\)), 6.68 (d, \(J=8.4\) Hz, 1H\(_{arom}\)). 13\(^C\)-Nmr (CD\(_3\)OD, 75 MHz) \(\delta\): 26.7 (OCH\(_2\)CH\(_2\)), 28.4 (CH\(_2\)Ar), 43.9 (CH\(_2\)NH), 51.6 (NHCH\(_2\)Ar), 116.3 (ArC-H), 119.9 (ArC=CH\(_2\)), 120.9 (ArC-H), 124.4 (ArC=CH), 142.4 (ArC-O), 144.5 (ArC-O). Ms (EI) m/z (%): 191 (40, M\(^+\)), 163 (100), 162 (61), 149 (23), 149 (23), 134 (18).

**Preparation of 4-Chloroacetyl-5,6-dihydropyrano[2,3,4-ij]isoquinolin-9-ol (119)**

To a stirred mixture of (102) (70 mg, 0.370), potassium carbonate (56 mg, 0.405 mmol) in DCM (8 ml), under N\(_2\), was added chloroacetyl chloride (0.032 ml, 0.401 mmol). The mixture was placed in ultrasonic bath for 15 min and then was allowed to stir overnight. The solvent was evaporated and the residue was chromatographed (EtOAc : hexane, 38 : 62) to give two fractions. The solvent in the first fraction was evaporated to give 9-chloroacetoxy-4-chloroacetyl-5,6-dihydropyrano[2,3,4-ij]isoquinoline (119a).
(20 mg, 16%) as a yellow crystalline solid. \(^1\)H-Nmr (CDCl\(_3\), 300 MHz) \(\delta\): 2.88 (t, J=5.7 Hz, 2H, CH\(_2\)Ar), 3.97 (t, J=5.7 Hz, 2H, CH\(_2\)N), 4.30 (s, 2H, NCOCH\(_2\)Cl), 4.33 (s, 2H, OCOCH\(_2\)Cl), 5.01 (d, J=3.6 Hz, OCH\(_2\)), 5.80 (broad s, 1H, OCH\(_2\)CH) 6.70 (d, J=8.4 Hz, 1H\(_{arom}\)), 6.91 (d, J=8.4 Hz, 1H\(_{arom}\)). The second fraction consisted of 4-chloroacetyl-5,6-dihydropyrano[2,3,4-ij]isoquinoline-9-ol (119) (78 mg, 79%) as a colourless crystalline solid after evaporation, mp 55-57°C (EtOAc/hexane). \(^1\)H-Nmr (CDCl\(_3\), 300 MHz) \(\delta\): 2.82 (t, 5.7 Hz, 2H, CH\(_2\)Ar), 3.94 (t, J=5.7 Hz, 2H, CH\(_2\)N), 4.31 (s, 2H, CH\(_2\)Cl), 5.04 (d, J=3.9 Hz, 2H, OCH\(_2\)), 5.80 (broad s, 1H, OCH\(_2\)CH), 6.60 (d, J=8.1 Hz, 1H\(_{arom}\)), 6.81 (d, J=8.1 Hz, 1H\(_{arom}\)). \(^13\)C-Nmr (acetone-d\(_6\), 75 MHz) \(\delta\): 28.5 (CH\(_2\)Ar), 43.1 (CH\(_2\)Cl), 44.0 (CH\(_2\)N), 66.3 (OCH\(_2\)), 111.9 (OCH\(_2\)CH), 117.6 (ArC-H), 118.0 (ArC-CH\(_2\)), 121.3 (ArC-H), 124.7 (ArC= C), 132.5 (OCH\(_2\)CH\(_3\)), 142.0 (ArC-O), 144.3 (ArC-O), 166.1 (CO). Ms (EI) m/z (%): 267 (12, M\(^+\), 37Cl), 265 (37, M\(^+\), 35Cl), 230 (100), 202 (8), 180 (100), 160 (17).

Preparation of 4-Azidoacetyl-5,6-dihydropyrano[2,3,4-ij]isoquinolin-9-ol (120)

\[
\begin{align*}
\text{O} & \text{CH}_{2}\text{N}_{3} \\
\text{O} & \text{N} \\
\text{HO}
\end{align*}
\]

A mixture of (119) (110 mg, 0.414 mmol), sodium azide (135 mg, 2.077 mmol) in acetonitrile, under N\(_2\), (55 ml) was refluxed for 2.5 h. The solvent was then evaporated and the residue was chromatographed (EtOAc : hexane, 37 : 63) to give 4-azidoacetyl-5,6-dihydropyrano[2,3,4-ij]isoquinolin-9-ol (120) (79 mg, 78%) as a colourless crystalline solid, mp 159-161°C (EtOAc/hexane). \(^1\)H-Nmr (CDCl\(_3\), 300 MHz) \(\delta\): 2.81 (t, J=6.0 Hz, 2H, CH\(_2\)Ar), 3.92 (t, J=6.0 Hz,
2H, CH2N), 4.11 (s, 2H, CH2Cl), 5.02 (d, J=3.6 Hz, 2H, OCH2), 5.55 (broad s, 1H, OCH2CH), 6.59 (d, J=8.4 Hz, 1H arom), 6.80 (d, J=8.4 Hz, 1H arom). 13C-Nmr (CDCl3, 75 MHz) δ: 42.4 (CH2Ar), 51.0 (CH2N), 60.4 (CH2N3), 66.0 (OCH2), 110.1 (OCH2CH), 116.3 (ArC-CH2), 116.5 (ArC-H), 121.0 (ArC-H), 124.0 (ArC-C), 131.8 (OCH2CHC), 140.2 (ArC-O), 142.4 (ArC-O), 166.5 (CO). Ms (ES +ve) m/z (%): 295.4 (100, M++23), 265.5 (50), 218.7 (50). Ms (EI) m/z (%): 244 (41), 222 (23), 215 (52), 188 (76), 173 (20), 164 (36), 151 (82). Anal. Cald for C13H12O3N4: C, 57.33; H, 4.44; N, 20.59. Found: C, 57.55; H, 4.48; N, 20.46.

Preparation of 9-(t-Butyldimethylsilyloxy)-4-chloroacetyl-5,6-dihydropyrano[2,3,4-ij]isoquinoline (121)

A mixture of (119) (67 mg, 0.252 mmol), imidazole (26 mg, 0.382 mmol), tert-butyldimethylsilyl chloride (114 mg, 0.756 mmol) in DMF (1 ml) was allowed to stir overnight. The solvent was evaporated under high vacuum and the crude residue was chromatographed (EtOAc : hexane, 20 : 80) to give 9-(t-butyldimethylsilyloxy)-4-chloroacetyl-5,6-dihydropyrano[2,3,4-ij]isoquinoline (121) (44 mg, 46%) as a colourless crystalline solid, mp 101-103°C (EtOAc/hexane). 1H-Nmr (CDCl3, 300 MHz) δ: 0.18 (s, 6H, Si(CH3)2), 1.00 (s, 9H, (CH3)3CSi), 2.82 (t, J=6.0 Hz, 2H, CH2Ar), 3.95 (t, J=6.0 Hz, CH2N), 4.31 (s, 2H, CH2Cl), 4.96 (d, J=3.9 Hz, 2H, OCH2), 5.75 (broad s, 1H, OCH2CH), 6.55 (d, J=8.4 Hz, 1H arom), 6.72 (d, J=8.4 Hz, 1H arom). 13C-Nmr (CDCl3, 75 MHz) δ: -4.6 (2 x Si(CH3)2), 18.4 ((CH3)3CSi), 25.7 (3 x (CH3)3CSi), 27.8 (CH2Ar),
41.3 (CH₂N), 42.6 (CH₂Cl), 65.3 (OCH₂CH), 110.7 (OCH₂CH), 117.5 (ArC-CH₂), 120.6 (ArC-H), 122.5 (ArC-H), 125.3 (ArC-C), 132.3 (OCH₂CHC), 141.8 (ArC-O), 144.6 (ArC-O), 165.4 (CO). Ms (EI) m/z (%): 381 (1, M⁺, 37Cl), 379 (3, M⁺, 35Cl), 344 (2), 322 (53), 288 (3), 246 (100), 231 (3), 216 (6), 186 (4).

Photolysis of 9-(t-Butyldimethylsilyloxy)-4-chloroacetyl-5,6-dihydropyrano[2,3,4-ij]isoquinoline (121)

A solution of (121) (40 mg, 0.105) in acetonitrile and water (50 : 50) was irradiated for 4.5 h at room temperature. The solvent was then evaporated and the residue was chromatographed (EtOAc : hexane : MeOH, 65 : 33 : 2) to give (122) (8 mg, 27%) as a pale yellow oil. ¹H-Nmr (CDCl₃, 300 MHz) δ: 2.88 (t, J=6.6 Hz, 2H, CH₂Ar), 3.21 (t, J=6.6 Hz, 2H, CH₂COAr), 3.53 (q, J=6.6 Hz, 2H, CH₂NH), 4.00 (s, 2H, CH₂Cl), 4.61 (t, J=6.6 Hz, OCH₂), 5.53 (s, 1H, OH), 6.74 (d, J=8.1 Hz, 1H aröm), 6.87 (s, 1H, NH), 7.05 (d, J=8.1 Hz, 1H aröm). Ms (Es -ve) m/z (%): 282.3 (100, M⁺-1, 35Cl). Ms (Es +ve) m/z (%): 308.0 (35, M⁺+23, 37Cl), 306.0 (100, M⁺+23, 35Cl), 284.6 (70, M⁺+1, 35Cl). Ms (EI) m/z (%): 285 (1, M⁺, 37Cl), 283 (3, M⁺, 35Cl), 221 (10), 190 (50), 189 (32), 178 (18), 164 (14), 150 (42).

Reaction of (103) with Lithium Diisopropylamide and Benzeneselenyl Bromide

A solution of lithium diisopropylamide (0.286 mmol) (prepared from 0.04 ml of diisopropylamine and 0.16 ml of 1.8 M of butyllithium in hexane) in THF (3 ml) was prepared under N₂ at -78°C and (103) (45.7 mg, 0.143 mmol) in THF (2 ml) was added dropwise. The solution was stirred for 15
min and benzeneselenyl bromide (0.143 mmol) (prepared by addition of 0.004 ml of bromine to 22.3 mg of diphenyl diselenide in 0.3 ml of THF) was added dropwise. The solution was allowed to stir overnight. Water (5ml) was then added and the mixture was extracted with DCM (3 x 10 ml). The combined organic extracts were dried, evaporated and chromatographed (EtOAc : hexane, 20 : 80 and then 30 : 70) to give two fractions. The solvent in the first fraction was evaporated to give (124) (32mg, 38%) as a pale yellow oil. $^1$H-Nmr (CDCl$_3$, 300 MHz) $\delta$: 0.92 (d, J=4.2 Hz, 6H, CH(CH$_3$)$_2$), 0.94 (d, J=3.9 Hz, 6H, CH(CH$_3$)$_2$), 1.46 (s, 9H, OC(CH$_3$)$_3$), 2.66 (t, J=7.8 Hz, 2H, CH$_2$Ar), 2.87-2.99 (m, 2H, CH$_2$NH), 3.15 (dd, J=10.2, J=9.9 Hz, 1H, CHSePh), 3.72-3.79 (m, 2H, CH$_2$O), 3.86 (s, 3H, CH$_3$O), 6.67-6.78 (m, 3H$_{arom}$), 7.22-7.29 (m, 3H$_{arom}$), 7.61-7.64 (m, 2H$_{arom}$). The second fraction was (125) as pale yellow crystals, mp 89-91°C (EtOAc/hexane). $^1$H-Nmr (CDCl$_3$, 300 MHz) $\delta$: 1.44 (s, 9H, OC(CH$_3$)$_3$), 2.70 (t, J=7.2 Hz, 2H, CH$_2$Ar), 3.34 (q, J=7.2 Hz, 2H, CH$_2$NH), 3.87 (s, 3H, CH$_3$O), 4.54 (s, 1H, NH), 5.64 (s, 1H, OH), 6.67 (dd, J=8.1, J=2.1 Hz, 1H$_{arom}$), 6.77 (d, J=2.1 Hz, 1H$_{arom}$), 6.79 (d, J=8.1 Hz, 1H$_{arom}$). Ms (EI) m/z (%): 267 (3, M$^+$), 211 (32), 194 (10), 150 (100), 137 (78).
Oxidation of (124) with Hydrogen Peroxide in the Presence of Acetic Acid

To a stirred solution of (124) (15 mg, 0.026 mmol) in THF (2 ml) was added water (0.1 ml), acetic acid (0.01 ml) and hydrogen peroxide (70 mg, 30%). The solution was allowed to stir for 30 min. More water (5 ml) was then added and the mixture was extracted with DCM (3 x 15 ml). The combined extracts were dried, evaporated and chromatographed (EtOAc : hexane, 25 : 75) to give two fractions. The first fraction was (125). The solvent in the second fraction was evaporated to give (127) as pale yellow oil.

\[ \text{1H-Nmr (CDCl}_3, 300 MHz) \delta: 0.82-0.91 \text{ (m, 12H, } 2 \times \text{CH(CH}_3)_2\text{), 1.56} \text{ (s, 9H, OC(CH}_3)_3\text{), 2.04 \text{ (m, 2H, CH}_2\text{Ar), 2.78 \text{ (m, 2H, CH}_2\text{NH), 3.86 \text{ (s, 3H, CH}_3\text{O), 6.05 \text{ (d, J=12.9 Hz, OCHCH), 6.75-6.83 \text{ (m, 3H}_\text{arom), 7.86 \text{ (d, J=12.9 Hz, OCHCH). Ms (EI) m/z (%): 420 (1, M}^+\text{), 320 (1), 305 (1), 263 (2), 215 (6), 196 (6), 183 (13), 171 (6), 154 (100).} \]

Reaction of N-Protected Dopamine (128) with Methyl Propiolate

To a stirred solution of N-protected dopamine (128)\(^57\) (340 mg, 1.344 mmol) in dry THF (25 ml), under N\(_2\), were added NaH (135 mg, 60%, 3.375 mmol) and then methyl propiolate (0.24 ml, 2.698 mmol). The mixture was allowed to stir for 3 h. Water (15 ml) was then added and the mixture was extracted with DCM (2 x 30 ml) and (2 x 30 ml). The combined extracts were dried, evaporated and chromatographed (DCM : MeOH, 98.5 : 1.5) to give two fractions. The solvent in the first fraction was evaporated to give (129) (30}
mg, 7%) as a pale yellow oil. $^1$H-Nmr (CDCl$_3$, 400 MHz) $\delta$: 1.44 (OC(CH$_3$)$_3$), 2.70 (t, J=7.2 Hz, 2H, CH$_2$Ar), 2.98 (d, J=5.2, 2H, OCHCH$_2$), 3.32 (q, J=7.2 Hz, 2H, CH$_2$NH), 3.77 (s, 3H, CH$_3$O), 4.56 (s, 1H, NH), 6.51 (t, J=5.2 Hz, 1H, OCHCH$_2$), 6.62-6.73 (m, 3H$_{arom}$). $^{13}$C-Nmr (CDCl$_3$, 400 MHz) $\delta$: 28.3 (OC(CH$_3$)$_3$), 40.0 (CH$_2$Ar), 52.1 (CH$_2$NH). Ms (EI) m/z (%): 337 (8, M$^+$), 281 (18), 264 (11), 220 (90), 207 (30), 190 (15), 175 (50). The second fraction was rechromatographed (DCM : hexane : MeOH, 90.9 : 9 : 0.1) to give two fractions. The first fraction was (130) (120 mg, 27%) as a pale yellow oil. $^1$H-Nmr (CDCl$_3$, 400 MHz) $\delta$: 1.44 (s, 9H, OC(CH$_3$)$_3$), 2.71 (t, J=7.5 Hz, 2H, CH$_2$Ar), 3.33 (q, J=7.5 Hz, 2H, CH$_2$NH), 3.73 (s, 3H, CH$_3$O), 4.62 (s, 1H, NH), 5.56 (d, J=12.0 Hz, 1H, OCHCH), 6.19 (s, 1H, OH), 6.84-6.93 (m, 3H$_{arom}$), 7.74 (d, J=12.0 Hz, OCHCH). $^{13}$C-Nmr (CDCl$_3$, 400 MHz) $\delta$: 28.3 (OC(CH$_3$)$_3$), 35.3 (OC(CH$_3$)$_3$), 51.4 (COOCH$_3$), 67.9 (CH$_2$NH), 102.1 (OCHCH), 117.0 (ArC-H), 118.6 (ArC-H), 126.3 (ArC-H), 131.6 (ArC-CH$_2$), 142.7 (ArC-O), 145.0 (ArC-O), 156.0 (NHCO), 159.3 (OCHCH), 167.4 (COOCH$_3$). Ms (EI) m/z (%): 337 (4, M$^+$), 281 (17), 264 (8), 232 (3), 220 (50), 208 (18), 188 (31), 175 (32). The second fraction was (131) (170 mg, 38%) as a pale yellow oil. $^1$H-Nmr (CDCl$_3$, 400 MHz) $\delta$: 1.44 (s, 9H, OC(CH$_3$)$_3$), 2.73 (t, J=6.8 Hz, 2H, CH$_2$Ar), 3.35 (q, J=6.8 Hz, 2H, CH$_2$NH), 3.72 (s, 3H, CH$_3$O), 4.63 (s, 1H, NH), 5.54 (d, J=12.0 Hz, 1H, OCHCH), 6.35 (s, 1H, OH), 6.68-6.95 (m, 3H$_{arom}$), 7.74 (d, J=12.0 Hz, OCHCH). $^{13}$C-Nmr (CDCl$_3$, 400 MHz) $\delta$: 28.3 (OC(CH$_3$)$_3$), 35.6 (OC(CH$_3$)$_3$), 41.6 (CH$_2$Ar), 51.4 (COOCH$_3$), 60.4 (CH$_2$NH), 101.7 (OCHCH), 117.2 (ArC-CH$_2$), 141.4 (ArC-O), 146.6 (ArC-O), 159.7 (OCHCH), 156.1 (NHCO), 167.5 (COOCH$_3$). Ms (EI) m/z (%): 337 (2, M$^+$), 281 (12), 264 (5), 249 (6), 232 (5), 220 (40), 208 (16), 188 (33), 175 (26).
5.3 Experimental for Chapter 4

Preparation of 5-Triflate-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran (141)*

To a stirred solution of 5-hydroxy-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran45 (2.225 g, 8.94 mmol) in DCM (50 ml) under argon at -30°C were added pyridine (1.37 ml, 16.99 mmol) and then trifluoromethanesulfonic anhydride (1.83 ml, 11.17 mmol). The solution was stirred at -20°C for 2 h and then allowed to reach the ambient temperature. It was then washed with a saturated solution of NaHCO₃ (30 ml) and water (20 ml), dried and evaporated to give a yellow residue. The crude residue was then chromatographed (Lp:EtOAc, 94:6) to give 5-triflate-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran (141) (2.447 g, 72%) as a pale yellow oil. $^1$H-Nmr (CDCl₃) $\delta$: 0.91 (t, J=7.4 Hz, 6H, 2 x CH₂CH₃), 1.41-1.56 (m, 4H, 2 x CH₂CH₃), 2.54 (t, J=6.9 Hz, 2H, NCH₂), 2.55 (t, J=7.0 Hz, 2H,
NCH2), 2.75 (dd, J=16.4, J=10.6 Hz, 1H, CHAr), 2.98 (ddd, J=16.4, J=5.2, J=1.8 Hz, 1H, CHAr), 3.12-3.24 (m, 1H, CHN), 3.88 (t, J=10.3 Hz, 1H, CHO), 4.30-4.36 (m, 1H, CHO), 6.86 (2d, J=8.3 Hz, 2H arom), 7.17 (t, J=8.3 Hz, 1H arom).

13C-Nmr (CDCl3) δ: 11.7 (2 x CH2CH3), 21.9 (2 x CH2CH3), 23.1 (CH2Ar), 52.4 (CHN), 54.7 (2 x CH2N), 68.1 (CH2O), 112.9 (ArC-H), 116.2 (ArC), 116.6 (ArC-H), 121.3 (CF3), 127.7 (ArC-H), 148.6 (ArC), 156.2 (ArC).

Ms (Cl) m/z (%): 382 (20, M+1), 250 (10), 149 (5), 102 (35).

Preparation of 5-Vinyl-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran (142)

To a mixture of (141) (2.50 g, 6.56 mmol), LiCl (836 mg, 16.676 mmol), Bis (triphenylphosphine)-palladium (II) chloride, containing 15% pd, (230 mg, 0.328 mmol) in DMF (30 ml) under argon was added vinyltributyltin (2.30 ml, 7.87 mmol). The stirred solution was heated at 90°C for 5 h. The solvent was then removed in vacuo and the remaining residue was chromatographed (Lp:EtOAc, 90:10, v/v) to give a pale yellow oil. The oil was then treated with etheral hydrochloric acid to afford 5-vinyl-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran hydrochloride (142.HCl) (1.483 g, 76%) as colourless crystals.

1H-Nmr (CDCl3) δ: 0.75 (t, J=7.5 Hz, 6H, 2 x CH2CH3), 1.40-1.54 (m, 4H, 2 x CH2CH3), 2.51 (t, 7.0 Hz, 2H, CH2N), 2.53 (t, 7.0 Hz, 2H, CH2N), 2.70 (dd, J=16.0, J=10.0 Hz, 1H, CHAr), 2.88 (ddd, J=16.0, J=6.0, J=2.0 Hz, 1H, CHAr), 3.10-3.24 (m, 1H, CHN), 3.65 (t, J=10.2 Hz, 1H, CHO), 4.25-4.32 (m, 1H, CHO), 5.32 (dd, J=11.2, J=1.4 Hz, 1H, Ar-CHCH2), 5.65 (dd, J=17.7,
J=1.4 Hz, 1H, Ar-CHCH), 6.76 (t, J=6.0 Hz, 1H arom), 6.87 (dd, J=17.7, 11.2 Hz, 1H, Ar-CHCH), 7.08 (2d, J=6.0 Hz, 2H arom). $^{13}$C-Nmr (CDCl$_3$) δ: 11.8 (2 x CH$_2$CH$_3$), 22.0 (2 x CH$_2$CH$_3$), 26.0 (CH$_2$Ar), 52.8 (2 x CH$_2$N), 53.5 (CHN), 67.4 (CH$_2$O), 116.0 (Ar-CHCH$_2$), 116.1 (ArC-H), 117.9 (ArC-H), 119.7 (ArC), 126.9 (ArC-H), 134.0 (Ar-CHCH$_2$), 138.3 (ArC), 154.6 (ArC). Ms (Cl) m/z (%): 260 (67, M+1), 230 (4), 159 (3).

Preparation of 5-Ethyl-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran (143)

A solution of (142) (532 mg, 2.05 mmol) in ethanol (10 ml) was hydrogenated at 50 p.s.i. at room temperature for 6 h in the presence of palladium on carbon (10% pd). The resulting solution was filtered through celite, evaporated and the remaining crude residue was chromatographed (LP:EtOAc, 90:10) to give 5-ethyl-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran (143) (461 mg, 86%) as a colourless oil. $^1$H-Nmr (CDCl$_3$) δ: 1.06 (t, J=7.4 Hz, 6H, 2 x NCH$_2$CH$_2$CH$_3$), 1.39 (t, J=7.5 Hz, 3H, Ar-CH$_2$CH$_3$), 1.57-1.71 (m, 4H, 2 x NCH$_2$CH$_2$CH$_3$), 2.61-2.88 (m, 7H, N(CH$_2$)$_2$, Ar-CHCH, ArCH$_2$CH$_3$), 2.99 (ddd, J=16.4, J=5.2, J=1.8 Hz, 1H, CHAr), 3.28-3.40 (m, 1H, CHN), 3.93 (t, J=10.3 Hz, 1H, CHO), 4.42-4.49 (m, 1H, CHO), 6.85 (d, J=8.1 Hz, 1H arom), 6.94 (d, J=8.1 Hz, 1H arom), 7.22 (t, J=8.1 Hz, 1H arom). $^{13}$C-Nmr (CDCl$_3$) δ: 18.9 (2 x NCH$_2$CH$_2$CH$_3$), 21.2 (Ar-CH$_2$CH$_3$), 29.1 (2 x CH$_2$CH$_2$CH$_3$), 32.5 (CH$_2$Ar), 32.7 (CH$_2$Ar), 59.8 (2 x CH$_2$N), 60.5 (CHN), 74.3 (CH$_2$O), 121.3 (ArC-H), 127.0 (ArC-H), 127.1 (ArC), 133.9 (ArC-H), 150.8 (ArC), 161.6 (ArC). Ms (Cl) m/z (%): 262
Preparation of 5-Phenyl-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran (146)

To a stirred solution of (141) (800 mg, 2.10 mmol) in toluene (40 ml) under argon was added tetrakis (triphenylphosphine) palladium (0) (122 mg, 0.105 mmol). The mixture was allowed to stir for 30 min at ambient temperature. Phenylboronic acid (384 mg, 3.15 mmol) was then added, followed immediately by saturated solution of NaHCO$_3$ (15 ml). This biphasic solution was thereafter refluxed for 5 h. Brine solution was then added, the two layers formed were separated and the aqueous phase was extracted with DCM (3 x 30 ml). The combined organic extracts were dried, evaporated and chromatographed (LP:EtOAc, 95:5, v/v) to give 5-phenyl-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran (146) (580 mg, 89%) as colourless crystals, mp 69-71°C (EtOAc/Lp). $^1$H-Nmr (CDCl$_3$) δ: 0.85 (t, J=7.4 Hz, 6H, 2 x CH$_2$CH$_3$), 1.34-1.49 (m, 4H, 2 x CH$_2$CH$_3$), 2.46 (t, J=7.6 Hz, 4H, 2 x CH$_2$N), 2.59-2.81 (m, 2H, CH$_2$Ar), 3.04-3.16 (m, 1H, CHN), 3.90 (t, J=10.2 Hz, 1H, CHO), 4.30-4.36 (m, 1H, CHO), 6.85 (d, J=7.4 Hz, 1H$_{arom}$), 6.87 (d, J=7.4 Hz, 1H$_{arom}$), 7.18 (t, J=7.4 Hz, 1H$_{arom}$), 7.33-7.48 (m, 5H$_{arom}$). $^{13}$C-Nmr (CDCl$_3$) δ: 12.1 (2 x CH$_2$CH$_3$), 22.3 (2 x CH$_2$CH$_3$), 27.9 (CH$_2$Ar), 53.1 (2 x CH$_2$N), 54.1 (2 x CHN), 68.2 (CH$_2$O), 116.0 (ArC-H), 120.1 (ArC), 122.5 (ArC-H), 127.3 (ArC-H),
127.4 (ArC-H), 128.6 (2 x ArC-H), 129.4 (2 x ArC-H), 141.4 (ArC), 143.8 (ArC), 155.0 (ArC). Ms (CI) m/z (%): 310 (95, M+1), 280 (5), 209 (4), 128 (4). Anal. Calcd for C_{21}H_{27}NO: C, 81.51; H, 8.79; N, 4.53. Found: C, 80.88; H, 8.74; N, 4.40.

Preparation of 5-Acetyl-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran (145)

To a mixture of (141) (1.30 g, 3.41 mmol), LiCl (435 mg, 10.24 mmol), Bis(tiphenylphosphine)-palladium (II) chloride containing 15% pd (120 mg, 0.171 mmol) in DMF (20 ml) under argon was added (1-ethoxyvinyl)tributyltin (1.38 ml, 4.094 mmol). The stirred solution was heated at 90 °C for 3.5 h. The solvent was then removed in vacuo and the crude residue was chromatographed (Lp:EtOAc, 90:10) to give a pale yellow oil. The oil was then treated with hydrochloric acid (10%) at room temperature for 1 h. Potassium carbonate was added to adjust the pH to 9. The solution was then extracted with DCM (3 x 20 ml). The combined organic extracts were dried, evaporated and treated with etheral hydrochloric acid to afford 5-acetyl-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran hydrochloride (145.HCl) (940 mg, 88%). \(^1\)H-Nmr (D_{2}O) δ: 0.89-0.96 (m, 6H, 2 x CH_{2}CH_{3}), 1.59-1.84 (m, 4H, 2 x CH_{2}CH_{3}), 2.60 (s, 3H, COCH_{3}), 3.10-3.25 (m, 4H, 2 x CH_{2}N), 3.31-3.55 (m, 2H, CH_{2}Ar), 3.91-4.00 (m, 1H, CHN), 4.35-4.50 (m, 2H, CH_{2}O), 7.12 (d, J=7.4 Hz, 1H_{arom}), 7.33 (t, J=7.4 Hz, 1H_{arom}), 7.59 (d, J=7.4 Hz, 1H_{arom}). \(^{13}\)C-Nmr (D_{2}O) δ: 9.4 (2 x CH_{2}CH_{3}), 16.7 (COCH_{3}), 24.1 (2 x CH_{2}CH_{3}), 28.3 (CH_{2}Ar), 52.0 (2 x CH_{2}N), 54.6 (CHN), 62.6 (CH_{2}O), 117.2 (ArC), 120.9
Preparation of 5-(3-Nitrophenyl)-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran (167)

As described for (146). 5-(3-Nitrophenyl)-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran (167) (7%, 51% based on the recovered starting material) was obtained as yellow crystals, mp 83-85 °C (EtOAc/LP). 

$^1$H-Nmr (CDCl$_3$) δ: 0.85 (t, J=7.4 Hz, 6H, 2 x CH$_2$CH$_3$), 1.35-1.46 (m, 4H, 2 x CH$_2$CH$_3$), 2.46 (t, J=7.5 Hz, 4H, 2 x CH$_2$N), 2.50-2.60 (m, 1H, CHAr), 2.70-2.81 (m, 1H, CHAr), 3.07-3.18 (m, 1H, CHAr), 3.92 (t, J=10.2 Hz, CHO), 4.32-4.37 (m, 1H, CHO), 6.84 (d, J=7.4 Hz, 1H$_{arom}$), 6.92 (d, J=7.4 Hz, 1H$_{arom}$), 7.21 (t, J=7.4 Hz, 1H$_{arom}$), 7.59-7.72 (m, 2 H$_{arom}$), 8.24-8.27 (m, 2H$_{arom}$). 

$^{13}$C-Nmr (CDCl$_3$) δ: 11.7 (2 x CH$_2$CH$_3$), 21.8 (2 x CH$_2$CH$_3$), 27.5 (CH$_2$Ar), 52.7 (2 x CH$_2$N), 53.5 (CHN), 67.6 (CH$_2$O), 116.7 (ArC-H), 119.5 (ArC), 121.9 (ArC-H), 122.1 (ArC-H), 124.0 (ArC-H), 127.3 (ArC-H), 129.2 (ArC-H), 135.2 (ArC-H), 140.7 (ArC), 142.7 (ArC), 148.1 (ArC), 154.8 (ArC). Ms (Cl) m/z (%): 355 (95, M+1), 325 (10), 234 (10).

Starting material recovered was 1.3 g from 1.5 g, 87%.

Preparation of 5-(3-Aminophenyl)-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran (168)
i) As described for (146). 5-(3-aminophenyl)-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran (168) (10%, 25% based on the recovered starting material) was obtained as a pale yellow oil. Starting material recovered was 467 mg from 767 mg, 61%. (Note: the aminophenylboronic acid was dissolved in ethanol before addition)

ii) To a stirred solution of (167) (91 mg, 0.257 mmol) were added glacial acetic acid (0.5 ml) and zinc powder (85 mg, 1.32 mmol) at room temperature. The solution was then allowed to continue stirring for 2h. The pH was then adjusted to 6 by addition of dilute solution of NaOH and the solution was extracted with DCM (3 x 10 ml). The combined organic extracts were dried, evaporated and chromatographed (LP: EtOAc, 65:35 v/v) to give 5-(3-aminophenyl)-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran (168) (30 mg, 36%). \( ^1H\text{-Nmr (CDCl}_3 \delta: 0.86 \text{ (t, } J=7.4 \text{ Hz, } 6H, 2 \times \text{CH}_2\text{CH}_3), 1.38-1.47 \text{ (m, } 4H, 2 \times \text{CH}_2\text{CH}_3), 2.47 \text{ (t, } J=7.6 \text{ Hz, } 4H, 2 \times \text{CH}_2\text{N}), 2.70-2.74 \text{ (m, } 2H, \text{CH}_2\text{Ar), 3.05-3.17 \text{ (m, } 1H, \text{CHN), 3.73 \text{ (s, } 2H, \text{NH}_2), 3.89 \text{ (t, } J=10.1 \text{ Hz, } 1H, \text{CHO), 4.29-4.34 \text{ (m, } 1H, \text{CHO), 6.66-6.86 \text{ (m, } 5H_{\text{arom}), 7.12-7.25 \text{ (m, } 2H_{\text{arom)).}}\)

\( ^{13}C\text{-Nmr (CDCl}_3 \delta: 11.7 \text{ (2} \times \text{CH}_2\text{CH}_3), 21.8 \text{ (2} \times \text{CH}_2\text{CH}_3), 27.3 \text{ (CH}_2\text{Ar), 52.7 \text{ (2} \times \text{CH}_2\text{N), 53.7 (CHN), 67.8 (CH}_2\text{O), 113.8 (ArC-H), 115.4 (ArC-H), 115.8 (ArC-H), 119.5 (ArC-H), 119.9 (ArC), 121.9 (ArC-H), 126.8 (ArC-H), 129.0 (ArC-H), 142.2 (ArC), 143.6 (ArC), 146.2 (ArC), 154.5 (ArC). Ms (CI) m/z (%): 325 (68, M+1), 283 (4), 224 (3).
Preparation of 5-(3-Azidophenyl)-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran (169)

(168) (63 mg, 0.195) was dissolved in water (2 ml) and 7 drops of sulphuric acid and was then placed in an ice bath. To this stirred solution was added a solution of NaNO₂ (15 mg, 0.214 mmol) in water (2 ml). The solution was then allowed to continue stirring for 30 min. A solution of NaN₃ (23 mg, 0.351 mmol) in water (2 ml) was added thereafter. The solution was stirred for further 40 min. The pH was adjusted to 10 by addition of dilute solution NaOH and the resulting solution was extracted with DCM (5 x 10 ml). The combined organic extracts were dried, evaporated and chromatographed (LP:EtOAc, 90:10, v/v) to give 5-(3-azidophenyl)-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran (169) (38 mg, 56%) as pale yellow solid, mp 60-61°C (EtOAc/LP). ¹H-Nmr (CDCl₃) δ: 0.86 (t, J=7.4 Hz, 6H, 2 x CH₂CH₃), 1.35-1.50 (m, 4H, 2 x CH₂CH₃), 2.46 (t, J=7.5 Hz, 4H, 2 x CH₂N), 2.60 (ddd, J=18.2, J=5.6, J=2.0 Hz, 1H, CHAr), 2.73 (dd, J=18.2, J=10.4 Hz, 1H, CHAr), 3.04-3.16 (m, 1H, CHN), 3.90 (t, J=10.2 Hz, 1H, CHO), 4.30-4.36 (m, 1H, CHO), 6.80-6.90 (m, 2H arom), 7.01-7.29 (m, 4H arom), 7.42 (t, J=7.8 Hz, 1H arom). ¹³C-Nmr (CDCl₃) δ: 11.7 (2 x CH₂CH₃), 21.9 (2 x CH₂CH₃), 27.5 (CH₂Ar), 52.7 (2 x NCH₂), 53.6 (CHN), 67.7 (CH₂O), 116.0 (ArC-H), 117.7 (ArC-H), 119.5 (ArC), 119.6 (ArC-H), 121.8 (ArC-H), 125.7 (ArC-H), 127.0 (ArC-H), 129.5 (ArC-H), 139.9 (ArC), 142.3 (ArC), 142.8 (ArC), 154.6 (ArC). Ir (Neat)νmax: 2102 (N₃) cm⁻¹.
Preparation of 5-Cyano-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran (147)

A stirred mixture of (141) (845 mg, 2.218 mmol), tetrakis (triphenylphosphine)palladium (0) (2.563 g, 2.218 mmol) and zinc cyanide (156 mg, 1.331 mmol) in DMF (20 ml) under argon was heated at 90°C overnight. The solvent was removed in vacuo and the residue was extracted with DCM (40 ml). The organic phase was then washed with saturated solution of NaHCO₃ (2 x 10 ml), dried, evaporated and chromatographed (LP: EtOAc, 95:5 and then 90:10) to give 5-cyano-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran (147) (406 mg, 71%) as a colourless oil. ¹H-Nmr (CDCl₃) δ: 0.92 (t, J=7.4 Hz, 6H, 2 x CH₂CH₃), 1.42-1.56 (m, 4H, 2 x CH₂CH₃), 2.46-2.64 (m, 4H, 2 x CH₂N), 2.93 (dd, J=16.6, J=10.7 Hz, 1H, CHAr), 3.11 (ddd, J=16.6, J=5.1, J=1.9 Hz, 1H, CHAr), 3.15-3.27 (m, 1H, CHN), 3.88 (t, J=10.3 Hz, 1H, CHO), 4.30-4.37 (m, 1H, CHO), 7.04 (dd, J=7.9, J=1.6 Hz, 1H, CHAr), 7.18 (t, J=7.9 Hz, 1H, CHO), 7.24 (dd, J=7.9, J=1.6 Hz, 1H, CHAr). ¹³C-Nmr (CDCl₃) δ: 11.7 (2 x CH₂CH₃), 21.9 (2 x CH₂CH₃), 26.8 (CH₂Ar), 52.5 (CHN), 52.7 (2 x CH₂N), 68.3 (CH₂O), 113.5 (CN), 117.5 (ArC), 121.3 (ArC-H), 125.0 (ArC-H), 125.5 (ArC), 127.7 (ArC-H), 155.0 (ArC). Ms (CI) m/z (%): 259 (95, M+1), 244 (80), 222 (60), 217 (85). Ir (Neat) νmax: 2228 (CN)cm⁻¹.

Preparation of 5-Amido-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran (148)
A stirred solution of (147) (50 mg, 0.194 mmol) and NaOH (9 pellets) in a mixture of ethanol and water (4 ml, 1:1) was refluxed overnight. The pH was adjusted to 6 by addition of hydrochloric acid (2M) and the solution was then extracted with DCM (3 x 10 ml). The combined organic extracts were dried and evaporated to give 5-amido-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran (148) (40 mg, 75%) as a pale yellow oil. \( ^1H\)-Nmr (CDCl\textsubscript{3}) \( \delta \): 0.91 (t, \( J=7.4 \) Hz, 6H, 2 x CH\textsubscript{2}CH\textsubscript{3}), 1.44-1.59 (m, 4H, 2 x CH\textsubscript{2}CH\textsubscript{3}), 2.56-2.67 (m, 4H, 2 x CH\textsubscript{2}N), 3.07-3.11 (m, 2H, CH\textsubscript{2}Ar), 3.18-3.28 (m, 1H, CHN), 3.94 (t, \( J=10.1 \) Hz, 1H, CHO), 4.31-4.37 (m, 1H, CHO), 6.93 (dd, \( J=8.0, J=1.4 \) Hz, 1Harom), 7.06 (dd, \( J=8.0, J=1.4 \) Hz, 1Harom), 7.15 (t, \( J=8.0 \) Hz, 1Harom), 7.22 (s, 2H, NH\textsubscript{2}). \( ^{13}C\)-Nmr (CDCl\textsubscript{3}) \( \delta \): 11.7 (2 x CH\textsubscript{2}CH\textsubscript{3}), 21.3 (2 x CH\textsubscript{2}CH\textsubscript{3}), 52.5 (2 x CH\textsubscript{2}N), 53.2 (CHN), 67.6 (CH\textsubscript{2}O), 119.1 (ArC-H), 119.2 (ArC-H), 120.3 (ArC), 127.1 (ArC-H), 136.1 (ArC), 155.0 (ArC), 171.9 (CO). Ms (Cl) m/z (%): 227 (95, M+1), 259 (8), 176 (4). Ir (Neat) \( \nu_{\text{max}} \): 3392 (NH), 3202 (NH), 1646 (CO) cm\textsuperscript{-1}.

**Preparation of 5-Aminomethyl-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran (149)**
To a stirred solution of (147) (355 mg, 1.376 mmol) in absolute ethanol (10 ml) was added lithium aluminium hydride (209 mg, 5.504 mmol). The solution was stirred for 5 h at room temperature. Water (15 ml) was then added and the solution was extracted with ethyl acetate (4 x 20 ml). The combined organic extracts were dried, evaporated to give 5-aminomethyl-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran (149) (342 mg, 95%) as a pale yellow oil. \( ^1H\)-Nmr (CDCl₃) \( \delta \): 0.92 (t, \( J=7.4 \) Hz, 6H, 2 x CH₂(CH₃), 1.43-1.57 (m, 4H, 2 x CH₂CH₃), 2.41 (s, 2H, NH₂), 2.57 (t, \( J=7.8 \) Hz, 2H, CH₂N), 2.58 (t, \( J=7.8 \) Hz, 2H, CH₂N), 2.67-2.89 (m, 2H, CHCH₂Ar), 3.18-3.24 (m, 2H, CH₂NH₂), 3.78-3.83 (m, 1H, CHO), 3.86 (s, 2H, CH₂NH₂), 4.29-4.36 (m, 1H, CHO), 6.76 (d, \( J=8.6 \) Hz, 1Hₐrom), 6.94 (d, \( J=8.6 \) Hz, 1Hₐrom), 7.13 (t, \( J=8.6 \) Hz, 1Hₐrom). \( ^{13}C\)-Nmr (CDCl₃) \( \delta \): 11.8 (2 x CH₂CH₃), 22.0 (2 x CH₂CH₃), 25.2 (CHCH₂Ar), 43.2 (CH₂NH₂), 52.7 (2 x CH₂N), 53.4 (CHN), 67.3 (CH₂O), 115.4 (ArC-H), 119.1 (ArC-H), 119.7 (ArC), 127.1 (ArC-H), 142.2 (ArC), 154.7 (ArC-H). Ms (Cl) m/z (%): 263 (95, M+1), 243 (4).

Preparation of 5-Chloroacetamidomethyl-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran (175)
To a stirred solution of (149) (336 mg, 1.282 mmol) in DCM (8 ml) under argon, in an ice bath, were added potassium carbonate (195 mg, 1.41 mmol) and then chloromethylchloride (0.11 ml, 1.41 mmol). The solution was then stirred overnight. Water (20 ml) was added and the two phase were separated. The aqueous phase was extracted with further DCM (2 x 20 ml) and the combined extracts were dried, evaporated and chromatographed (EtOAc: LP, 40:60, v/v) to give 5-chloroacetamidomethyl-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran (175) (290 mg, 67%) as colourless crystals, mp 78-80°C (EtOAc/LP). 1H-Nmr (CDCl₃) δ: 0.91 (t, J=7.4 Hz, 6H, 2 x CH₂CH₃), 1.41-1.56 (m, 4H, 2 x CH₂CH₃), 2.54 (t, J=6.9 Hz, 2H, CH₂N), 2.55 (t, J=6.9 Hz, 2H, CH₂N), 2.69 (dd, J=16.2, 10.8 Hz, 1H, CHCHAr), 2.84 (ddd, J=16.2, J=5.8, J=1.8 Hz, 1H, CHCHAr), 3.15-3.27 (m, 1H, CHN), 3.82 (t, J=10.3 Hz, 1H, CHO), 4.41 (s, 2H, CH₂Cl), 4.29-4.36 (m, 1H, CHO), 4.48 (dd, J=21.4, J=15.1 Hz, 1H, CHNH), 4.50 (dd, J=21.4, J=15.1 Hz, 1H, CHNH), 6.83 (d, J=8.0 Hz, 1H, CHN), 6.86 (d, J=8.0 Hz, 1H, CHN), 7.13 (t, J=8.0 Hz, 1H, CHN). 13C-Nmr (CDCl₃) δ: 11.7 (2 x CH₂CH₃), 21.9 (2 x CH₂CH₃), 25.4 (CHCH₂Ar), 41.4 (CH₂NH), 42.6 (CH₂Cl), 52.7 (2 x CH₂N), 53.2 (CHN), 67.5 (CH₂O), 116.6 (ArC-H), 120.3 (ArC-H), 120.5 (ArC), 127.3 (ArC-H), 136.2 (ArC), 155.0 (ArC), 165.6 (CO). Ms (Cl) m/z (%): 341 (32, M+1, ³⁷Cl), 339 (95, M+1, ³⁵Cl), 305 (33), 263 (2), 204 (2). Ir (Near)ν max: 3264 (NH), 1654 (CO) cm⁻¹.

Photolysis of 5-Chloroacetamidomethyl-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran (175)
A solution of (175) (135 mg, 0.399 mmol) in benzene (350 ml) was irradiated for 30 min at room temperature using 500 W mercury lamp. The solvent was then evaporated and the remaining crude residue was chromatographed (LP:EtOAc, 50:50 and then 20:80, v/v) to give (176) (11 mg, 7%) as a pale yellow solid. mp 93-95°C (EtOAc/LP). \(^1\)H-Nmr (CDCl\(_3\)) \(\delta\): 0.91 (t, \(J=7.3\) Hz, 6H, 2 x CH\(_2\)CH\(_3\)), 1.40-1.55 (m, 4H, 2 x CH\(_2\)CH\(_3\)), 2.50 (t, \(J=6.8\) Hz, 2H, CH\(_2\)N), 2.51 (t, \(J=6.8\) Hz, 2H, CH\(_2\)N), 2.57-2.80 (m, 2H, CHCH\(_2\)Ar), 3.10-3.21 (m, 1H, CHN), 3.67 (s, 2H, COCH\(_2\)Ar), 3.76 (t, \(J=10.3\) Hz, 1H, CHO), 4.25-4.32 (m, 1H, CHO), 4.34-4.48 (m, 2H, CH\(_2\)NH), 5.55 (s, 1H, NH), 6.70 (d, \(J=7.5\) Hz, 1H\(_\text{arom}\)), 6.77 (d, \(J=7.5\) Hz, 1H\(_\text{arom}\)), 7.06 (t, \(J=7.5\) Hz, 1H\(_\text{arom}\)), 7.31-7.42 (m, 5H\(_\text{arom}\)). \(^{13}\)C-Nmr (CDCl\(_3\)) \(\delta\): 11.7 (2 x CH\(_2\)CH\(_3\)), 21.9 (2 x CH\(_2\)CH\(_3\)), 25.1 (CHCH\(_2\)Ar), 41.2 (CH\(_2\)NH), 43.9 (COCH\(_2\)Ar), 52.7 (2 x CH\(_2\)N), 53.2 (CHN), 67.5 (CH\(_2\)O), 116.1 (ArC-H), 119.8 (ArC-H), 120.5 (ArC), 127.1 (ArC-H), 127.5 (ArC-H), 129.1 (2 x ArC-H), 129.4 (ArC-H), 134.7 (ArC), 137.1 (ArC), 154.8 (ArC), 170.7 (CO). Ms (Cl) m/z (%): 381 (95, M+1), 303 (35).

Preparation of 5-Hydroxy-3,4-dihydro-3-amino-2H-1-benzopyran (150)
A solution of 5-methoxy-3,4-dihydro-3-amino-2H-1-benzopyran \(^{(135)}\) (2.145 g, 9.954 mmol) in hydrobromic acid (48\%, 13 ml) and acetic acid (glacial, 20 ml) was heated at 138°C for 6 h. The solution was then evaporated to give *5-hydroxy-3,4-dihydro-3-amino-2H-1-benzopyran hydrobromide* \((150\cdot\text{HCl})\) (2.28 g, 100\%) as yellow crystals, mp 256-258°C (H₂O).

\(^{1}\)H-Nmr (D₂O) \(~\delta: 2.82-2.91\ (m, 1H, CH₂Ar), 3.12 \ (dd, J=18.0, J=5.8 Hz, 1H, CH₂Ar), 4.04-4.07 \ (m, 1H, CHN), 4.19-4.40 \ (m, 2H, CH₂O), 6.55 \ (d, J=8.3 Hz, 1H, CH₂Ar), 6.60 \ (d, 8.3 Hz, 1H arom), 7.13 \ (t, J=8.3 Hz, 1H arom). \(^{13}\)C-Nmr (D₂O) \(~\delta: 23.4 \ (CH₂Ar), 44.2 \ (CH₂N), 65.6 \ (CH₂O), 106.3 \ (ArC), 108.5 \ (ArC-H), 109.0 \ (ArC-H), 128.7 \ (ArC-H), 154.4 \ (ArC), 155.2 \ (ArC).\)

M$\text{S}$ (Cl) m/z (%): 166 (95, M+1), 148 (5).

**Preparation of 5-Hydroxy-3,4-dihydro-3-(tert-butoxycarbonylamino)-2H-1-benzopyran (151)**

To a solution of \((150)\) (1.9 g, 7.72 mmol) in THF (20 ml) were added a solution NaOH (1M, 18 ml) and (Boc)\(_{2}\)O (97\%, 2.122 g, 9.43 mmol). The solution was stirred overnight and the two phases were then separated. The pH of the aqueous phase was adjusted to 7 by addition of HCl (1M) and the solution was then extracted with DCM (3 x 20 ml). The combined organic extracts were dried, evaporated and chromatographed (LP:EtOAc, 77:23, v/v)
to give 5-hydroxy-3,4-dihydro-3-(tert-butoxycarbonylamino)-2H-1-benzopyran (151) (2.0 g, 98%) as a colourless solid, mp 158-160°C (EtOAc/LP). 

\[^1H\text{Nmr} \text{(CDCl}_3\text{)}\]: \(\delta\): 1.44 (s, 9H, C(CH\text{3})\text{3}), 2.64-2.75 (m, 1H, CHAr), 2.90 (dd, \(\text{J}=7.6\) Hz, 1H, NH), 6.05 (s, 1H, OH), 6.42 (d, \(\text{J}=7.4\) Hz, 1H\text{arom}), 6.46 (d, \(\text{J}=7.4\) Hz, 1H\text{arom}), 6.97 (t, \(\text{J}=7.4\) Hz, 1H\text{arom}). \[^{13}\text{C-Nmr} \text{(CDCl}_3\text{)}\]: \(\delta\): 26.0 (CH\text{2Ar}), 28.4 (C(C\text{H}_3)\text{3}), 43.0 (CHN), 68.0 (CH\text{2O}), 107.4 (2 x Ar\text{C-H}), 108.9 (ArC), 127.4 (ArC-H), 155.0 (2 x ArC), 155.6 (CO). Ms (CI) m/z (%): 266 (5, M+1), 227 (12), 210 (95), 195 (5), 166 (60), 148 (8).

Preparation of 5-Triflate-3,4-dihydro-3-(tert-butoxycarbonylamino)-2H-1-benzopyran (152)

![Formula Image]

As described for (141). The crude product was chromatographed (LP:EtOAc, 90:10, v/v) to give 5-triflate-3,4-dihydro-3-(tert-butoxycarbonylamino)-2H-1-benzopyran (152) (93% from 4.615 g of starting material) as colourless crystals, mp 82-84°C (EtOAc/LP). \[^1H\text{Nmr} \text{(CDCl}_3\text{)}\]: \(\delta\): 1.43 (s, 9H, C(CH\text{3})\text{3}), 2.84 (dd, \(\text{J}=18.4\), 4.9 Hz, 1H, CHAr), 3.07 (dd, \(\text{J}=18.4\), 4.9 Hz, 1H, CHAr), 4.13-4.26 (m, 3H, CHN, CH\text{2O}), 4.85 (d, \(\text{J}=7.6\) Hz, 1H, NH), 6.89 (2d, \(\text{J}=8.5\) Hz, 2H\text{arom}), 7.19 (t, \(\text{J}=8.5\) Hz, 1H\text{arom}). \[^{13}\text{C-Nmr} \text{(CDCl}_3\text{)}\]: \(\delta\): 26.5 (CH\text{2Ar}), 28.3 (C(C\text{H}_3)\text{3}), 42.3 (CHN), 68.3 (CH\text{2O}), 113.6 (ArC-H), 113.9 (ArC), 117.0 (ArC-H), 121.1 (CF\text{3}), 128.1 (ArC-H), 148.6 (ArC), 155.1 (ArC), 155.4 (CO). Ms (CI) m/z (%): 398 (3, M+1), 359 (96), 342 (32), 298 (94).
Preparation of 5-Vinyl-3,4-dihydro-3-(tert-butoxycarbonylamino)-2H-1-benzopyran (153)

As described for (142). The crude residue was chromatographed (Lp:EtOAc, 85:15, v/v) to give 5-vinyl-3,4-dihydro-3-(tert-butoxycarbonylamino)-2H-1-benzopyran (153) (75% from 3.0 g of starting material) as colourless crystals, mp 106-108°C (EtOAc/LP). ¹H-Nmr (CDCl₃) δ: 1.47 (s, 9H, C(CH₃)), 2.75-2.83 (m, 1H, CHAr), 3.06 (dd, J=16.9, J=5.6 Hz, 1H, CHAr), 4.11-4.27 (m, 3H, CHN, CH₂O), 4.93 (d, J=7.6 Hz, 1H, NH), 5.35 (dd, J=11.0, J=1.3 Hz, 1H, Ar-CHCH₂), 5.67 (dd, J=17.4, J=1.3 Hz, 1H, Ar-CHCH), 6.76-6.87 (m, 2H, Ar-CHCH, 1H₂arom), 7.11-7.19 (m, 2H₂arom). ¹³C-Nmr (CDCl₃) δ: 28.4 (C(CH₃)), 29.2 (CH₂Ar), 43.3 (CH₂N), 67.8 (CH₂O), 116.3 (Ar-CHCH₂), 116.5 (ArC-H), 117.3 (ArC), 118.6 (ArC-H), 127.3 (ArC-H), 133.5 (ArCHCH₂), 138.6 (ArC), 154.0 (ArC), 155.4 (CO). Ms (Cl) m/z (%): 276 (5, M+1), 237 (35), 220 (95), 176 (45).

Preparation of 5-Ethyl-3,4-dihydro-3-(tert-butoxycarbonylamino)-2H-1-benzopyran (154)

As described for (143). 5-Ethyl-3,4-dihydro-3-(tert-butoxycarbonylamino)-2H-1-benzopyran (154) was obtained as colourless crystals (87% from 1.53 g of starting material), mp 98-99°C (EtOAc/LP). ¹H-Nmr (CDCl₃) δ: 1.20 (t, J=8.4 Hz, 3H, CH₂CH₃), 1.42 (s, 9H, C(CH₃)₃), 2.54 (q,
J=8.4 Hz, 2H, CH₂CH₃), 2.66-2.77 (m, 1H, CHCH₂Ar), 2.96 (dd, J=16.8, J=5.9 Hz, 1H, CHCH₂Ar), 4.04-4.25 (m, CHN, CH₂O), 5.97 (d, J=7.6 Hz, 1H, NH), 6.72 (d, J=8.3 Hz, 1H arom), 6.81 (d, J=8.3 Hz, 1H arom), 7.08 (t, J=8.3 Hz, 1H arom). ¹³C-Nmr (CDCl₃) δ: 14.2 (CH₂CH₃), 25.3 (CH₂CH₃), 28.4 (C(CH₃)₃), 28.6 (CHCH₂Ar), 43.4 (CH₂N), 67.9 (CH₂O), 114.6 (Ar-C-H), 117.7 (Ar-C), 120.7 (Ar-C-H), 127.3 (Ar-C-H), 144.2 (Ar-C), 154.0 (Ar-C), 155.3 (CO). Ms (Cl) m/z (%): 278 (8, M+1), 239 (20), 222 (95), 178 (45).

Preparation of 5-ethyl-3,4-dihydro-3-amino-2H-1-benzopyran (159a)

To a stirred solution of (154) (1.23 g, 4.62 mmol) in DCM (5 ml), under argon, was added trifluoroacetic acid (4 ml). The solution was allowed to continue stirring for 1 h. The solvent was then evaporated and the crude was extracted with DCM (40 ml). The organic phase was washed with saturated solution of NaHCO₃ (2 x 10 ml). The combined wash layers were extracted with EtOAc (30 ml). The combined organic extracts were dried and evaporated to give 5-ethyl-3,4-dihydro-3-amino-2H-1-benzopyran (159a) (735 mg, 90%) as a colourless oil. ¹H-Nmr (CDCl₃) δ: 1.24 (t, J=7.6 Hz, 3H, CH₂CH₃), 1.43 (s, 2H, NH₂), 2.50 (dd, J=16.3, J=7.3 Hz, 1H, CHCH₂Ar), 2.60 (q, J=7.6 Hz, 2H, CH₂CH₃), 3.04 (dd, J=16.3, J=4.7 Hz, 1H, CHCH₂Ar), 3.36-3.42 (m, 1H, CHNH₂), 3.79 (ddd, J=10.4, J=7.4, J=0.7 Hz, 1H, CHO), 4.15 (ddd, J=10.4, J=3.0, J=1.6 Hz, 1H, CHO), 6.74 (d, J=8.1 Hz, 1H arom), 6.82 (d, J=8.1 Hz, 1H arom), 7.10 (t, J=8.1 Hz, 1H arom). ¹³C-Nmr (CDCl₃) δ: 14.2 (CH₂CH₃), 25.4 (CH₂CH₃), 32.0 (CHCH₂Ar), 44.4 (CHNH₂), 114.3 (Ar-C-H), 118.5 (Ar-C), 120.3 (Ar-C-H), 127.1 (Ar-C-H), 143.8 (Ar-C), 154.0 (Ar-C). Ms (Cl) m/z (%): 178 (95, M+1).
Preparation of 8-[N-(5-Ethyl-3,4-dihydro-2H-1-benzopyran-3-yl)amino-propyl]-8-azaspiro[4.5]decane-7,9-dione (159b)

To a stirred solution of (159a) (556 mg, 3.41 mmol) in DMF (13 ml), under argon, were added a solution of 8-(4-bromobutyl)-8-azaspiro[4.5]decane-7,9-dione (948 mg, 3.41 mmol) in DMF (2 ml), potassium carbonate (868 mg, 6.28 mmol) and then a catalytic amount of sodium iodide. The mixture was allowed to continue stirring at 35°C for 24 h. The solvent was then removed and the crude residue was extracted with DCM (30 ml). The extract was washed with water (2 x 10 ml), dried, evaporated and chromatographed (MeOH:EtOAc, 3: 97 and then 15:85) to give three fractions. The first fraction was rechromatographed (EtOAc: Lp, 35:65, v/v) to give (162) (246 mg, 18%, 24% based on the recovered starting material) as a colourless gum. 1H-Nmr (CDCl3) δ: 1.22 (t, J=7.6 Hz, 3H, CH2CH3), 1.48-1.76 (m, 12H, 6 x CH2), 2.53-2.60 (m, 6H, CH3CH2Ar, 2 x CH2CO), 2.70-2.80 (m, 1H, NCHCHAr), 3.01 (dd, J=16.8, J=5.5 Hz, 1H, NCHCHAr), 3.80 (t, J=6.0 Hz, 2H, CH2NCO), 4.05-4.16 (m, 4H, 2 x CH2O), 4.22-4.33 (m, 1H, CHNH), 5.10 (d, J=7.6 Hz, 1H, NH), 6.75 (d, J=8.1 Hz, 1H), 6.83 (d, J=8.1 Hz, 1H), 7.11 (t, J=8.1 Hz, 1H). Ms (Cl) m/z (%): 443 (14,
The solvent in the second fraction was evaporated to give 8-[N-(5-ethyl-3,4-dihydro-2H-1-benzopyran-3-yl)amino-propyl]-8-azaspiro[4.5]decane-7,9-dione (159b) (648 mg, 52%, 70% based on the recovered starting material) as a colourless oil. $^1$H-Nmr (CDCl$_3$) δ: 1.20 (t, $J$=7.3 Hz, 3H, CH$_2$CH$_3$), 1.46-1.74 (m, 12H, 6 x CH$_2$), 2.48-2.61 (m, 7H, CH$_3$CH$_2$Ar, CHCHAr, 2 x CH$_2$CO), 2.75 (t, $J$=7.0 Hz, 2H, CH$_2$NH), 2.94 (dd, $J$=15.6 Hz, $J$=5.2 Hz, 1H, CHCHAr), 3.07-3.17 (m, 1H, NH), 3.73-3.85 (m, 3H, CH$_2$NCO, CHO), 4.15-4.22 (m, 1H, CHO), 6.69 (d, $J$=7.8 Hz, 1H$_{arom}$), 6.77 (d, $J$=7.8 Hz, 1H$_{arom}$), 7.05 (t, $J$=7.8 Hz, 1H$_{arom}$). Ms (Cl) m/z (%): 399 (45, M+1).

The third fraction was the starting material (142 mg, 26%).

Preparation of 8-[4-N-Propyl-N-(5-ethyl-3,4-dihydro-2H-1-benzopyran-3-yl)amino-propyl]-8-azaspiro[4.5]decane-7,9-dione (159)

To a stirred solution of (159b) (600 mg, 1.508 mmol) in DMF (10 ml), under argon, were added potassium carbonate (569 mg, 4.117 mmol) and then iodopropane (0.4 ml, 4.10 mmol). The mixture was allowed to stir at
60°C overnight. The solvent was then evaporated and the crude residue was extracted with DCM (40 ml). The extract was washed with water (2 x 15 ml), dried, evaporated and chromatographed (EtOAc: LP, 25:75 and then EtOAc:MeOH, 99:1, v/v) to give two fractions. The solvent in the first fraction was evaporated and the remaining oil was treated with ethereal oxalic acid. Crystals were collected and then treated with saturated solution of NaHCO₃. Extraction with DCM, followed by evaporation gave 8-[4-N-propyl-N-(5-ethyl-3,4-dihydro-2H-1-benzopyran-3-yl)amino-propyl]-8-azaspiro[4.5]decane-7,9-dione (159) (220 mg, 33%, 49% based on recovered starting material) as a colourless oil. ¹H-Nmr (CDCl₃) δ: 0.91 (t, J=7.4 Hz, 3H, CH₃CH₂CH₂N), 1.25 (t, 7.6 Hz, 3H, CH₃CH₂H₂Ar), 1.44-1.75 (m, 14H, 7 x CH₂), 2.51-2.71 (m, 11H, 2 x CH₂CO, 2 x CH₂N, CHCHAr, CH₃CH₂Ar), 2.90 (dd, J=15.6, J= 5.2 Hz, 1H, CHCHAr), 3.10-3.22 (m, 1H, CHN), 3.73-3.83 (m, 3H, CH₂NCO, CHO), 4.27-4.31 (m, 1H, CHO), 6.70 (d, J=8.1 Hz, 1Hₐrom), 6.79 (d, J=8.1 Hz, 1Hₐrom), 7.07 (t, J=8.1 Hz, 1Hₐrom). Ms (CI) m/z (%): 441 (95, M⁺1, 399 (3), 381 (5), 232 (8). Anal. Calcd for C₂₇H₄₀N₂O₃.C₂H₂O₄: C, 65.64; H, 7.98; N, 5.28. Found: C, 65.50; H, 7.99; N, 5.32. The mother liquor was evaporated to give (165) (138 mg, 19%, 26% based on the recovered starting material). ¹H-Nmr (CDCl₃) δ: 0.95 (t, J=7.6 Hz, 3H, CH₂CH₂CH₃), 1.22 (t, J=7.4 Hz, 3H, ArCH₂CH₃), 1.42-1.73 (m, 14H, 7 x CH₂), 2.51-2.62 (m, 6H, CH₃CH₂Ar, 2 x CH₂CO), 2.82-2.98 (m, 2H, CHCH₂Ar), 3.24 (t, J=6.4 Hz, 2H, CH₂NCO), 3.73 (t, J=6.4 Hz, 2H, CH₂N(CO)₂), 4.04 (t, J=6.8 Hz, 2H, CH₂OCO), 4.13-4.20 (m, 3H, CH₂OAr, CHN), 6.71 (d, J=7.7 Hz, 1Hₐrom), 6.79 (d, J=7.7 Hz, 1Hₐrom), 7.07 (t, J=7.7 Hz, 1Hₐrom). Ms (CI) m/z (%): 485 (11, M⁺1). The second fraction was the starting material (155 mg, 26%).
Preparation of 5-Acetyl-3,4-dihydro-3-(tert-butoxycarbonylamino)-2H-1-benzopyran (157)

As described for (145). The crude product was chromatographed (EtOAc:LP, 10:90 and then 25:75, v/v) to give 5-acetyl-3,4-dihydro-3-(tert-butoxycarbonylamino)-2H-1-benzopyran (157) (1.164 g from 2.0 g of the starting material, 79%), mp 106-107 (EtOAc/LP). $^1$H-Nmr (CDCl$_3$) $\delta$: 1.46 (s, 9H, C(CH$_3$)), 2.59 (s, 3H, COCH$_3$), 3.01 (dd, $J$=18.1, $J$=5.0 Hz, 1H, CHAr), 3.34 (dd, $J$=18.1, $J$=5.5 Hz, 1H, CHAr), 4.40-4.19 (m, 3H, CH$_2$O, CHNH), 4.75 (d, $J$=7.6 Hz, 1H, NH), 7.04 (dd, $J$=8.2, $J$=1.2 Hz, 1H$_{arom}$), 7.23 (t, $J$=8.2 Hz, 1H$_{arom}$), 7.40 (dd, $J$=8.2 Hz, $J$=1.2 Hz, 1H$_{arom}$). $^{13}$C-Nmr (CDCl$_3$) $\delta$: 28.4 (s, C(CH$_3$)$_3$), 29.5 (COCH$_3$), 30.6 (CH$_2$Ar), 43.2 (CHNH), 68.0 (CH$_2$O), 119.9 (ArC-H), 121.0 (ArC-H), 122.9 (ArC), 127.1 (ArC-H), 138.5 (ArC), 154.8 (ArC), 155.1 (NHCO), 200.9 (COCH$_3$). Ms (CI) m/z (%): 292 (3), 253 (30), 236 (60), 192 (95). Ir (Neat)$\nu_{max}$: 3366 (NH), 1688 (CO) cm$^{-1}$.

Preparation of 5-Acetyl-3,4-dihydro-3-amino-2H-1-benzopyran (160a)

As described for (159a). 5-Acetyl-3,4-dihydro-3-amino-2H-1-benzopyran (160a) was obtained as a colourless oil (703 mg from 1.107 g of starting material, 97%). $^1$H-Nmr (CDCl$_3$) $\delta$: 1.47 (s, 2H, NH$_2$), 2.57 (s, 3H,
CH₃), 2.82 (dd, J=18.8, J=9.0 Hz, 1H, CHAr), 3.25-3.36 (m, 2H, CHAr, CHNH₂),
3.80-3.89 (m, 1H, CHO), 4.15 (ddd, J=10.8, J=2.5, J=2.5 Hz, 1H, CHO), 7.01 (dd,
J=8.1, J=1.0 Hz, 1Hₐrₐm), 7.19 (t, J=8.1 Hz, 1Hₐrₐm), 7.35 (dd, J=8.1, J=1.0 Hz,
1Hₐrₐm). ¹³C-Nmr (CDCl₃) δ: 31.1 (COCH₃), 35.3 (CH₂Ar), 45.3 (CHNH₂), 72.3
(CH₂O), 122.1 (ArC-H), 124.0 (ArC-H), 128.3 (ArC-H), 131.8 (ArC), 139.9 (ArC),
156.2 (ArC), 202.7 (CO). Ms (CI) m/z (%): 192 (95, M+1), 150 (11).

Preparation of 8-[N-(5-Acetyl-3,4-dihydro-2H-1-benzopyran-3-yl)amino-
propyl]-8-azaspiro[4.5]decane-7,9-dione (160b)

Method i) As described for (159b). Reaction was carried out at 60°C. The crude product was chromatographed (EtOAc:MeOH, 97:3, v/v) to give three fractions. The solvent in the first fraction was evaporated to give (163) (240 mg from 294 mg starting material, 34%, 55% based on the recovered starting material) as a colourless gum. ¹H-Nmr (CDCl₃) δ: 1.49-1.76 (m, 12H,
2 x CH₂), 2.597 (s, 4H, 2 x CH₂CO), 2.604 (s, 3H, COCH₃), 3.02 (dd, J=18.7, J=4.4
Hz, 1H, CHAr), 3.37 (J=18.7, J=5.3 Hz, 1H, CHAr), 3.79 (t, J=6.2 Hz, 2H,
CH₂N(CO)₂), 4.05-4.23 (m, 5H, 2 x CH₂O, CHNH), 4.93 (d, J=7.8 Hz, NH), 7.05
(dd, J=7.6, J=1.2 Hz, 1Hₐrₐm), 7.24 (t, J=7.6 Hz, 1Hₐrₐm), 7.41 (dd, J=7.6, J=1.2 Hz,
The second fraction contained 8-\[N-(5-acetyl-3,4-dihydro-2H-1-benzopyran-3-yl)amino-propyl]-8-azaspiro[4.5]decane-7,9-dione (160b) (135 mg from 294 mg starting material, 21%, 35% based on the recovered starting material) as a pale yellow oil after evaporation of the solvent. $^1$H-Nmr (CDCl$_3$) δ: 1.46-1.74 (m, 12H, 6 x CH$_2$), 2.57 (s, 3H, COCH$_3$), 2.58 (s, 4H, 2 x CH$_2$CO), 2.73 (t, J=6.5 Hz, 2H, CH$_2$NH), 2.87 (dd, J=17.3, J=7.3 Hz, 1H, CHAr), 3.08 (m, 1H, CHNH), 3.27 (dd, J=17.3, J=4.8 Hz, 1H, CHAr), 3.76 (t, J=7.3 Hz, 2H, CH$_2$N(CO)$_2$), 3.88 (dd, J=10.6, J=7.3 Hz, 1H, CHO), 4.20 (ddd, J=10.6, J=1.9, J=1.9, 1H, CHO), 6.99 (d, J=7.8 Hz, 1H$_{arom}$), 7.18 (t, J=7.8 Hz, 1H$_{arom}$), 7.34 (d, J=7.8 Hz, 1H$_{arom}$). Ms(CI) m/z (%): 413 (95, M+1), 371 (10).

Method ii) To a solution of (160a) (416, 2.178 mmol) in acetonitrile (20 ml) under argon were added potassium carbonate (903 mg, 6.53 mg), a solution of 8-(4-bromobutyl)-8-azaspiro[4.5]decane-7,9-dione (720 mg, 2.38 mmol) in acetonitrile (2 ml) and a catalytic amount of sodium iodide. The mixture was refluxed for 48 h. The solvent was then evaporated and the residue was extracted with DCM (40 ml). The organic extract was washed with water (10 ml), dried, evaporated and chromatographed (EtOAc: MeOH, 97:3, v/v) to give (160b) (368 mg, 41%) as a pale yellow oil.

Preparation of 8-[4-N-Propyl-N-(5-acetyl-3,4-dihydro-2H-1-benzopyran-3-yl)amino-propyl]-8-azaspiro[4.5]decane-7,9-dione (160)
Method i) As described for (159). 8-[4-N-Propyl-N-(5-acetyl-3,4-dihydro-2H-1-benzopyran-3-yl)amino-propyl]-8-azaspiro[4.5]decane-7,9-dione (160) was obtained as a pale yellow oil (50 mg from 125 mg of starting material, 36%) after column chromatography (EtOAc: LP, 35:65, v/v). \(^{1}\)H-Nmr (CDCl\(_3\)) \(\delta\): 0.88 (t, J=7.3 Hz, 3H, CH\(_2\)CH\(_3\)), 1.40-1.75 (m, 14H, 7 x CH\(_2\)), 2.46-2.68 (m, 11H, 2 x CH\(_2\)CO, 2 x CH\(_2\)N, COCH\(_3\)), 2.99-3.12 (m, 3H, CH\(_2\)Ar, CHN), 3.75-3.88 (m, 3H, CH\(_2\)N(CO)\(_2\), CHO), 4.25-4.30 (m, 1H, CHO), 6.98 (d, J=7.8 Hz, 1H\(_{arom}\)), 7.18 (t, J=7.8 Hz, 1H\(_{arom}\)), 7.31 (d, J=7.8 Hz, 1H\(_{arom}\)). Ms (Cl) m/z (%): 455 (96, M+1). Anal. Calcd for C\(_{27}\)H\(_{38}\)N\(_2\)O\(_4\).C\(_2\)H\(_2\)O\(_4\): C, 63.95; H, 7.40; N, 5.14. Found: C, 63.32; H, 7.20; N, 5.13. Compound (166) was a colourless gum (80 mg from 125 mg of starting material, 53%). \(^{1}\)H-Nmr (CDCl\(_3\)) \(\delta\): 0.96 (t, J=7.3 Hz, 3H, CHCH\(_3\)), 1.45-1.75 (m, 14H, 7 x CH\(_2\)), 2.59 (s, 3H, COCH\(_3\)), 2.61 (s, 4H, 2 x CH\(_2\)CO), 3.13-3.41 (m, 4H, CH\(_2\)NCO, CH\(_2\)Ar), 3.77 (t, J=6.8 Hz, 2H, CH\(_2\)N(CO)\(_2\)), 4.07 (t, J=6.7 Hz, 2H, CH\(_2\)OCHO), 4.17-4.25 (m, 3H, CHN, CH\(_2\)OAr), 7.03 (d, J=7.8 Hz, 1H\(_{arom}\)), 7.24 (t, J=7.8 Hz, 1H\(_{arom}\)), 7.39 (d, J=7.8 Hz, 1H\(_{arom}\)). Ms (Cl) m/z (%): 498 (94, M+1), 546 (6).

Method ii) To a stirred solution of (160b) (360 mg, 0.874 mmol) in acetonitrile (10), under argon, were added potassium carbonate (362 mg, 2.62 mmol) and idodopropane (0.26 ml, 2.62 mmol). The mixture was allowed to
reflux for overnight. The solvent was then evaporated and the remaining residue was extracted with DCM. The organic extract was dried, evaporated and chromatographed (EtOAc:LP, 35:65) to give (160) (151 mg, 35%) as a pale yellow oil.

**Preparation of (177)**

To a stirred solution of 5-hydroxy-3,4-dihydro-3-amino-2H-1-benzopyran (370 mg, 2.07 mmol) in DMF (20 ml), under argon, were added potassium carbonate (858 mg, 6.21 mmol) and 8-(4-bromobutyl)-8-azaspiro[4.5]decane-7,9-dione (625 mg, 2.07 mmol). The mixture was then allowed to continue stirring at 60°C overnight. Iodopropane (0.61 ml, 6.21 mmol) was added thereafter and the mixture was stirred for further 24 h at this temperature. The solvent was removed *in vacuo* and the remaining residue was extracted with DCM (30 ml). The organic extract was washed with water (2 x 10 ml), dried, evaporated and chromatographed (EtOAc:LP, 40:60, v/v) to give two fractions. The first fraction was (141) (389 mg, 43%). The solvent in the second fraction was evaporated to give (177) (302 mg, 33%) as a colourless solid, hygroscopic. $^1$H-Nmr (CDCl$_3$) δ: 1.49-1.74 (m, 12H, 6 x CH$_2$), 2.58 (s, 4H, 2 x CH$_2$CO), 2.70 (dd, J=17.3, J=2.7 Hz, 1H, CHAr), 2.89 (dd,
J=17.3, J=5.6 Hz, 1H, CHAr), 3.75-3.82 (m, 5H, CH$_3$O, CH$_2$N(CO)$_2$), 4.04-4.21 (m, 5H, 2 x CH$_2$O, CHNH), 5.08 (d, J=7.9 Hz, 1H, NH), 6.45 (d, J=8.2 Hz, 1H$_{arom}$), 6.50 (d, J=8.2 Hz, 1H$_{arom}$), 7.08 (t, J=8.2 Hz, 1H$_{arom}$). Ms (CI) m/z (%): 445 (48, M+1), 240 (95), 206 (74).

**Preparation of 5-Phenyl-3,4-dihydro-3-(tert-butoxycarbonylamino)-2H-1-benzopyran (156)**

As described for (146) (Note: The phenyl bromic acid was dissolved in ethanol before addition; the solution was refluxed for overnight). The crude product was chromatographed (LP:EtOAc, 95:5 and then 80:20) to give a solid residue. This was then recrystallised from EtOAc/LP to give 5-phenyl-3,4-dihydro-3-(tert-butoxycarbonylamino)-2H-1-benzopyran (156) (1.30 g, from 2.485 of the starting material, 64%, 80% based on the recovered starting material), mp 116-118°C (EtOAc/LP). $^1$H-Nmr (CDCl$_3$) δ: 1.44 (s, 9H, C(CH$_3$)$_3$), 2.58 (dd, J=16.9, J=4.3 Hz, 1H, CHAr), 3.01 (dd, J=16.9, J=4.3 Hz, CHAr), 4.14-4.21 (m, 3H, CH$_2$O, CHNH), 4.80 (s, 1H, NH), 6.87-6.92 (m, 2H$_{arom}$), 7.22 (t, J=7.6 Hz, 1H$_{arom}$), 7.29-7.47 (m, 5H$_{arom}$). $^{13}$C-Nmr (CDCl$_3$) δ: 28.3 (C(CH$_3$)$_3$), 30.4 (CH$_2$Ar), 43.3 (CHNH), 68.1 (CH$_2$O), 116.0 (ArC-H), 117.2 (ArC), 122.6 (ArC-H), 127.2 (ArC-H), 127.3 (ArC-H), 128.2 (2 x ArC-H), 129.0 (2 x ArC-H), 140.5 (ArC), 143.7 (ArC), 154.1 (ArC), 155.1 (CO). Ms (CI) m/z (%): 326 (10, M+1), 270 (95), 226 (27). The mother liquor was evaporated to give the starting material (0.5 g, 20%).
Preparation of 5-phenyl-3,4-dihydro-3-amino-2H-1-benzopyran (158a)

As described for (159a). 5-Phenyl-3,4-dihydro-3-amino-2H-1-benzopyran (158a) was obtained as a colourless oil (0.80 g from 1.1159 g of the starting material, 100%). ¹H-Nmr (CDCl₃) δ: 2.47 (dd, J=16.5, J=6.9 Hz, 1H, CHAr), 2.84-2.93 (m, 1H, CHAr), 3.26-3.38 (m, 1H, CHNH₂), 3.85 (dd, J=10.1, 7.2 Hz, 1H, CHO), 4.19 (d, J=10.1 Hz, 1H, CHO), 6.84-6.89 (m, 2Hₐrom), 7.22 (t, J=7.8 Hz, 1Hₐrom), 7.29-7.46 (m, 5Hₐrom). ¹³C-Nmr (CDCl₃) δ: 30.9 (CH₂Ar), 44.1 (CH₂NH₂), 71.2 (CH₂O), 115.6 (ArC-H), 118.0 (ArC-H), 122.2 (ArC-H), 125.9 (ArC), 127.1 (ArC-H), 128.1 (2 x ArC-H), 129.1 (2 x ArC-H), 140.8 (ArC), 143.5 (ArC), 154.0 (ArC). Ms (Cl) m/z (%): 226 (95, M+1).

Preparation of 8-[N-(5-phenyl-3,4-dihydro-2H-1-benzopyran-3-yl)amino-propyl]-8-azaspiro[4.5]decane-7,9-dione (158b)
As described for (159b). Reaction was carried out at 60°C. The crude product was chromatographed (EtOAc:Lp, 60: 40 and then 100:0) to give two fractions. The solvent in the first fraction was evaporated to give (161) (390 mg, 23%) as a colourless gum. \(^1\)H-Nmr (CDCl\(_3\)) \(\delta\): 1.42-1.73 (m, 12H, 6 x CH\(_2\)), 2.49-2.60 (m, 5H, 2 x CH\(_2\)CO, CHAr), 2.98 (dd, J=18.8, J=7.3 Hz, 1H, CHAr), 3.76 (t, J=6.0 Hz, 2H, CH\(_2\)N(CO\(_2\))), 4.00-4.18 (m, 5H, CHNH, 2 x CH\(_2\)O), 5.03 (d, J=8.0 Hz, NH), 6.79-6.88 (m, 2H\(_{\text{arom}}\)), 7.18 (t, J=8.0 Hz, 1H\(_{\text{arom}}\)), 7.26-7.45 (m, 5H\(_{\text{arom}}\)). The second fraction contained 8-[N-(5-phenyl-3,4-dihydro-2H-1-benzopyran-3-yl)amino-propyl]-8-azaspiro[4.5]decane-7,9-dione (158b) (870 mg, 57%) as a colourless oil. \(^1\)H-Nmr (CDCl\(_3\)) \(\delta\): 1.42-1.75 (m, 12H, 6 x CH\(_2\)), 2.50-2.72 (m, 7H, 2 x CH\(_2\)CO, CH\(_2\)NH, CHAr), 2.80 (dd, J=17.2, J=6.3 Hz, 1H, CHAr), 3.00-3.05 (m, CHNH), 3.67-3.92 (m, 3H, CH\(_2\)N(CO\(_2\)), CHO), 4.23-4.28 (m, 1H, CHO), 6.83-6.88 (m, 2H\(_{\text{arom}}\)), 7.17 (t, J=7.6 Hz, 1H\(_{\text{arom}}\)), 7.29-7.46 (m, 5H\(_{\text{arom}}\)). Ms (Cl) m/z (%): 448 (75, M+1), 280 (25), 240 (95).

Preparation of 8-[4-N-Propyl-N-(5-phenyl-3,4-dihydro-2H-1-benzopyran-3-yl)amino-propyl]-8-azaspiro[4.5]decane-7,9-dione (158)
As described for (159); chromatography was performed using EtOAc:LP, 40:60, v/v. 8-[4-N-Propyl-N-(5-phenyl-3,4-dihydro-2H-1-benzopyran-3-yl)amino-propyl]-8-azaspiro[4.5]decane-7,9-dione (158) was obtained as a colourless oil (471 mg from 775 mg of starting material, 53%). 

\[ \text{H-Nmr (CDCl}_3\text{)} \delta: 0.83 (t, J=7.3 \text{ Hz, } 3\text{H, CH}_3), 1.29-1.76 (m, 12\text{H, } 6 \times \text{CH}_2), 2.33-2.78 (m, 8\text{H, CH}_2\text{N}, 2 \times \text{CH}_2\text{CO, CH}_2\text{Ar}), 3.02-3.13 (m, 1\text{H, CHN}), 3.75 (t, J=7.2 \text{ Hz, } 2\text{H, CH}_2\text{N(CO)}_2), 3.88 (t, J=10.2 \text{ Hz, } 1\text{H, CHO}), 4.30 (ddd, J=10.2, J=3.2, J=2.0 \text{ Hz, } 1\text{H, CHO}), 6.84 (d, J=7.8 \text{ Hz, } 1\text{H}_{\text{arom}}), 6.85 (d, J=7.8 \text{ Hz, } 1\text{H}_{\text{arom}}), 7.17 (t, J=7.8 \text{ Hz, } 1\text{H}_{\text{arom}}), 7.33-7.48 (m, 5\text{H}_{\text{arom}}). \]

\[
\text{Ms (Cl) m/z (%): 489 (77, M+1), 268 (95).}\]

\[
\text{Anal. Calcd for } C_{31}H_{40}N_2O_3: C, 68.49; H, 7.31; N, 4.84. \text{ Found: C, 67.86; H, 7.23; N, 4.84; H}_2\text{O, 1.20. (164) was obtained as a colourless gum (130 mg, 14%) after evaporation of solvent.} \]

\[ \text{H-Nmr (CDCl}_3\text{)} \delta: 0.93 (t, J=7.4 \text{ Hz), 1.34-1.72 (m, 14\text{H, } 7 \times \text{CH}_2), 2.40-2.71 (m, 5\text{H, } 2 \times \text{CH}_2\text{CO, CHAr}), 3.00-3.20 (m, 3\text{H, CHAr, CH}_2\text{NCO}), 3.70-3.78 (m, 2\text{H, CH}_2\text{N(CO)}_2), 3.99-4.26 (m, 5\text{H, CHN, } 2 \times \text{CH}_2\text{O), 6.81-6.88 (m, 2\text{H}_{\text{arom}}), 7.16 (dd, J=7.6 \text{ Hz, } 1\text{H}_{\text{arom}}), 7.29-7.47 (m, 5\text{H}_{\text{arom}}).} \]

Preparation of 5-Methoxy-3,4-dihydro-3-chloroacetamido-2H-1-benzopyran (170)
To a stirred solution of 5-methoxy-3,4-dihydro-3-amino-2H-1-benzopyran (135) \( \text{g, } 6.00 \text{ mmol} \) in DCM (30 ml), in an ice bath and under argon, was added chloroacetyl chloride (0.54 ml, 6.741 mmol). The solution was allowed to continue stirring overnight. Water (30 ml) was then added and the two layers were separated. The aqueous phase was extracted with further DCM (3 x 20 ml). The combined organic extracts were dried and evaporated to give 5-methoxy-3,4-dihydro-3-chloroacetamido-2H-1-benzopyran (170) (1.504 g, 98%) as a pale yellow solid. \( ^1 \text{H-Nmr (CDCl}_3 \delta: 2.77 (d, J=17.6, J=2.4 \text{ Hz}, 1\text{H, CHAr}), 2.96 (d, J=17.6, J=5.75 \text{ Hz}, 1\text{H, CHAr}), 3.84 (s, 3\text{H, OCH}_3), 4.06 (s, 2\text{H, CH}_2\text{Cl}), 4.12-4.16 (m, 2\text{H, CH}_2\text{O}), 4.49-4.55 (m, 1\text{H, CHNH}), 6.50 (d, J=8.1 \text{ Hz}, 1\text{H}_\text{arom}), 6.56 (d, J=8.1 \text{ Hz}, 1\text{H}_\text{arom}), 6.82 (\text{broad s, 1H, NH}), 7.14 (t, J=8.1 \text{ Hz}, 1\text{H}_\text{arom}). \)

Photolysis of 5-Methoxy-3,4-dihydro-3-chloroacetamido-2H-1-benzopyran (170) in Benzene

A solution of (170) (500 mg, 1.966 mmol) in benzene (350 ml) was irradiated for 3 h using 500 W mercury lamp. The solvent was then evaporated and the remaining crude residue was chromatographed (EtOAc:LP, 75:25 and then EtOAc:LP:MeOH, 75:23:2, v/v) to give two fractions. The first fraction was the starting material (110 mg, 22%). The solvent in the second fraction was evaporated to give 5-methoxy-3,4-dihydro-3-acetamido-2H-1-benzopyran (171) (110 mg, 26%) as a pale yellow oil. \( ^1 \text{H-Nmr (CDCl}_3 \delta: 1.99 (s, 3\text{H, COCH}_3), 2.75 (d, J=17.5 \text{ Hz}, 1\text{H, CHAr}), 2.89 (d, J=17.5, J=5.5 \text{ Hz}, 1\text{H, CHAr}), 3.83 (s, 3\text{H, CH}_3\text{O}), 4.03-4.19 (m, \text{CH}_2\text{O}), 4.50-4.55 (m, \text{CHNH}), 5.88 (\text{broad s, 1H, NH}), 6.49 (d, J=8.2 \text{ Hz}, 1\text{H}_\text{arom}), 6.54 (d, J=8.2 \text{ Hz}, 1\text{H}_\text{arom}), 7.13 (t, J=8.2 \text{ Hz}, 1\text{H}_\text{arom}). \)
OCH

Photolysis of 5-Methoxy-3,4-dihydro-3-chloroacetamido-2H-1-benzopyran (170) in a Mixture of Acetonitrile and Water

A solution of (170) (627 mg, 2.454 mmol) in a mixture of acetonitrile and water was irradiated for 2 h using 500 W mercury lamp. The solvent was then evaporated and the remaining crude residue was extracted with DCM (30 ml). The extract was washed with water (10 ml), dried, evaporated and chromatographed (EtOAc:LP, 80:20 and then 100:0) to give 5-methoxy-3,4-dihydro-3-hydroxyacetamido-2H-1-benzopyran (172) (116 mg, 20%) as a pale yellow oil. $^1$H-Nmr (CDCl$_3$) δ: 2.72 (dd, J=17.4, J=3.4, 1H, CHAr), 2.92 (dd, J=17.4, J=7.0 Hz), 3.80 (s, 3H, CH$_3$O), 4.03 (s, 2H, CH$_2$OH), 4.07-4.10 (m, 2H, CH$_2$O), 4.45-4.49 (m, 1H, CHNH), 6.47 (d, J=8.0 Hz, 1H$_{arom}$), 6.51 (d, J=8.0 Hz, 1H$_{arom}$), 7.01 (d, J=7.9 Hz, 1H, NH), 7.09 (t, J=8.0 Hz, 1H$_{arom}$).

OCH$_3$
(172)

Equipments and Methods for Bindings to 5HT$_7$ Receptors

Products to be tested or reference compounds (eleven concentrations, 10$^{-5}$ M to 10$^{-12}$ M) were incubated with membrane preparation. Radioligand, non specific binding, cloned receptors, reference products, protein
concentration, buffer, incubation time and temperature are indicated in the table below.

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Radioligand</th>
<th>Non-specific binding</th>
<th>Cloned receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>5HT₇</td>
<td>[3H]-Lysergic acid diethylamide</td>
<td>10⁻⁵M Methiothepin</td>
<td>Human 5HT₇ Biosignal batch 692203 cloned receptor</td>
</tr>
<tr>
<td></td>
<td>NEN batch 3235-049 S.A. = 88 Ci/mmol 3.3 nM</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reference products</th>
<th>Prot. ml⁻¹</th>
<th>Binding buffer</th>
<th>Incubation time, temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metergoline</td>
<td>16 µg</td>
<td>Tris HCl 50mM pH 7.4 + MgSO₄ 10mM + EDTA 0.5 mM</td>
<td>120 minutes 27°C</td>
</tr>
<tr>
<td>Methiothepin</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Methiothepin was from Tocris Cookson (Langford, Bristol U.K.) and Metergoline from Virbac (Carros, Nice Fr).

-Competition experiments were analysed using the interactive non linear least-squares curve fitting program, "inplot4, graphed". Kᵢ were determined using the method of Cheng and Prussof.

Equipments and Methods for Bindings to 5HT₁A Receptors

Products to be tested or reference compounds (eleven concentrations, 10⁻⁵ M to 10⁻¹¹ M) were incubated with membrane preparation. Radioligand, non specific binding, structure, reference products, protein concentration, buffer, incubation time and temperature are indicated in the table below.
<table>
<thead>
<tr>
<th>Receptor</th>
<th>Radioligand</th>
<th>Non-specific binding</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>5HT$_{1A}$</td>
<td>[3H]-8-OH-DPAT NEN batch 2923-137 S.A.= 143.8 Ci/mol 0.5 nM + 0.1% ascorbic acid</td>
<td>$10^{-5}$M Buspirone</td>
<td>Bovine Hippocampus</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reference products</th>
<th>Prot. ml$^{-1}$</th>
<th>Binding buffer</th>
<th>Incubation time, temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buspirone</td>
<td>0.6 mg</td>
<td>Tris HCl 50mM pH 7.4 + CaCl$_2$ 4mM + Pargyl 10 μg</td>
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<tr>
<td>WB4101</td>
<td></td>
<td></td>
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</table>

Buspirone was from Sigma (St Louis, MO) and WB4101 from R.B.I. (Natick, MA).

- Competition experiments were analysed using the interactive non linear least-squares curve fitting program, “inplot4, graphed”. $K_i$ were determined using the method of Cheng and Prussof.
References


13. Beck, A.L., Mascal, M., Moody, C.J., Slawin, A.M.Z., Williams, D.J.; Coates,


37. Tricklebank, M.D. Br. J. Pharmacol. 1984, 81, 26P.


   31, 2219.


   York 1967; p78.


78. Murov, S.I. 'Handbook of Photochemistry', p. 85 (Marcel Dekker, New 


   1980, 93, 239264 b) Aldrich, P.E.; Berezin, G.H., Belgian Patent, 1979, 

83. Emerson, W.S. *Org. React.*, **1948**, 4, 175-244.


Appendix 1

Non-hydrogen atom coordinates and equivalent isotropic thermal parameters of the cyclophane (64). y(c(1)) defines the origin.

<table>
<thead>
<tr>
<th>Atom</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>$10^2U_{eq}$Å²</th>
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<tr>
<td>C(1)</td>
<td>0.039(2)</td>
<td>1.0(-)</td>
<td>0.8501(5)</td>
<td>0.041(4)</td>
</tr>
<tr>
<td>O(2)</td>
<td>0.087(1)</td>
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<td>0.9282(3)</td>
<td>0.050(3)</td>
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<td>0.9379(5)</td>
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<td>0.052(2)</td>
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<td>0.044(3)</td>
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<td>0.643(2)</td>
<td>0.7979(5)</td>
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<tr>
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<td>0.662(1)</td>
<td>0.7816(3)</td>
<td>0.044(2)</td>
</tr>
<tr>
<td>N(6)</td>
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<td>0.616(1)</td>
<td>0.7429(4)</td>
<td>0.035(3)</td>
</tr>
<tr>
<td>C(7)</td>
<td>0.079(2)</td>
<td>0.674(2)</td>
<td>0.6598(5)</td>
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<td>C(71)</td>
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<td>0.5958(6)</td>
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<tr>
<td>O(71)</td>
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<tr>
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<td>0.6215(4)</td>
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<td>0.5612(6)</td>
<td>0.103(6)</td>
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<td>0.6477(5)</td>
<td>0.042(4)</td>
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<td>0.6897(5)</td>
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</tr>
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<td>C(11)</td>
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<td>O(12)</td>
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<td>C(121)</td>
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<td>0.8824(6)</td>
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<td>C(13)</td>
<td>0.191(2)</td>
<td>0.938(1)</td>
<td>0.7896(5)</td>
<td>0.036(3)</td>
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</table>
Appendix 2

Non-hydrogen positional and isotropic displacement parameters of the oxazolobenzazepinone (88).

<table>
<thead>
<tr>
<th>atom</th>
<th>x/a</th>
<th>y/b</th>
<th>z/c</th>
<th>U(eq)</th>
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<tbody>
<tr>
<td>O(1)</td>
<td>0.66213</td>
<td>0.8901(4)</td>
<td>0.35882</td>
<td>0.059(1)</td>
</tr>
<tr>
<td>C(2)</td>
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<td>0.7441(7)</td>
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</tr>
<tr>
<td>C(3)</td>
<td>0.6040(3)</td>
<td>0.6160(6)</td>
<td>0.3581(4)</td>
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</tr>
<tr>
<td>O(3)</td>
<td>0.5671(3)</td>
<td>0.4775(5)</td>
<td>0.3267(4)</td>
<td>0.083(2)</td>
</tr>
<tr>
<td>N(4)</td>
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<td>0.6829(4)</td>
<td>0.4621(4)</td>
<td>0.051(1)</td>
</tr>
<tr>
<td>C(5)</td>
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<td>0.6017(7)</td>
<td>0.5532(5)</td>
<td>0.062(2)</td>
</tr>
<tr>
<td>C(6)</td>
<td>0.5577(4)</td>
<td>0.7149(9)</td>
<td>0.5918(5)</td>
<td>0.073(2)</td>
</tr>
<tr>
<td>C(6a)</td>
<td>0.5000(3)</td>
<td>0.8334(6)</td>
<td>0.5000(4)</td>
<td>0.053(2)</td>
</tr>
<tr>
<td>C(7)</td>
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<td>0.8048(7)</td>
<td>0.4572(4)</td>
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</tr>
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<td>C(8)</td>
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<td>0.9142(5)</td>
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</tr>
<tr>
<td>O(8)</td>
<td>0.2799(2)</td>
<td>0.8984(4)</td>
<td>0.3309(3)</td>
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</tr>
<tr>
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<td>0.750(1)</td>
<td>0.3656(8)</td>
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</tr>
<tr>
<td>C(9)</td>
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<td>1.0607(5)</td>
<td>0.3388(4)</td>
<td>0.048(2)</td>
</tr>
<tr>
<td>O(9)</td>
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<td>1.1648(4)</td>
<td>0.2617(4)</td>
<td>0.067(1)</td>
</tr>
<tr>
<td>C(9a)</td>
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<td>1.3214(9)</td>
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<tr>
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<td>C(11a)</td>
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<td>O(11a)</td>
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<td>0.8607(4)</td>
<td>0.5451(3)</td>
<td>0.061(1)</td>
</tr>
<tr>
<td>C(1')</td>
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<td>0.7331(8)</td>
<td>0.5247(6)</td>
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</tr>
<tr>
<td>C(2')</td>
<td>0.8874(4)</td>
<td>0.764(1)</td>
<td>0.6023(7)</td>
<td>0.082(3)</td>
</tr>
</tbody>
</table>
Appendix 3

NOVASCREEN receptor selectivity report on the hexahydropyrano isoquinoline (123).

<table>
<thead>
<tr>
<th>Receptor/Selectivity</th>
<th>Reference Compound</th>
<th>Reference Ki(nM)</th>
<th>Initial Inhibition (Average; N=2)</th>
<th>Verification Inhibition (Average; N=2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>10^-5M</td>
<td>10^-6M</td>
</tr>
<tr>
<td>Neurotransmitters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenosine</td>
<td>NECA</td>
<td>7.25</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>Alpha 1</td>
<td>Prazosin</td>
<td>14.15</td>
<td>5.5</td>
<td></td>
</tr>
<tr>
<td>Alpha 2</td>
<td>RX 821002</td>
<td>12.42</td>
<td>4.4</td>
<td></td>
</tr>
<tr>
<td>Beta</td>
<td>Alprenolol</td>
<td>12.42</td>
<td>4.3</td>
<td></td>
</tr>
<tr>
<td>Dopamine 1</td>
<td>SCH 23390</td>
<td>4.59</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Dopamine 2</td>
<td>Sulpiride</td>
<td>7.53</td>
<td>24.5</td>
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</tr>
<tr>
<td>GABA_&lt;A&gt;</td>
<td>Muscimol</td>
<td>6.56</td>
<td>4.9</td>
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<tr>
<td>GABA_&lt;B&gt;</td>
<td>Baclofen</td>
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<td>2.1</td>
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<td>Methysergide</td>
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<td>NMDA</td>
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<td>Kainic Acid DME</td>
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<td>Quisqualic Acid</td>
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<td>1.9</td>
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<td>Strychnine Nitrate</td>
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<td>Regulatory Sites</td>
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<td>Brain/Gut Peptides</td>
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<td>-5.8</td>
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</table>

Values are expressed as the percent inhibition of specific binding and represent the average of duplicate tubes at each of the concentrations tested. Bolded values represent inhibition of fifty percent or greater (see attached Verification Report).
<table>
<thead>
<tr>
<th>Receptor/Selectivity</th>
<th>Reference Compound</th>
<th>Reference Ki(nM)</th>
<th>Initial Percent Inhibition (Average; N=2)</th>
<th>Verification Percent Inhibition (Average; N=2)</th>
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<td><strong>Brain/Gut Peptides</strong></td>
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<td>Substance K</td>
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<tr>
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<td>PDBU</td>
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<td>Inositol Triphosphate</td>
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<tr>
<td><strong>Uptake Sites</strong></td>
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<td></td>
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<tr>
<td>Dopamine Reuptake</td>
<td>RS Bupropion</td>
<td>513.81</td>
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<tr>
<td>Norepinephrine Uptake</td>
<td>Desmethylinipramine</td>
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<td>24.4</td>
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<tr>
<td>Serotonin Uptake</td>
<td>Imipramine</td>
<td>32.81</td>
<td>18.4</td>
<td></td>
</tr>
<tr>
<td>Choline Uptake</td>
<td>Choline</td>
<td>1938.73</td>
<td>20.7</td>
<td></td>
</tr>
</tbody>
</table>

Values are expressed as the percent inhibition of specific binding and represent the average of duplicate tubes at each of the concentrations tested. Bolded values represent inhibition of fifty percent or greater (see attached Verification Report).
List of Publications


4) Robert Rezaie, Benoit Joseph, John B. Bremner, Gérald Guillaumet, 'The Studies of the Effect of the C-5 Substituent of the 3,4-Dihydro-3-amino-2H-1-benzopyran Derivatives on Interactions with 5-HT\textsubscript{1A} and 5-HT\textsubscript{7} Subtype Receptors', to be published.