SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF N-4 SUBSTITUTED DIHYDRO-2-ACENAPHTHYLENYL PIPERAZINES AND SUBSTITUTED PIPERAZINYL INDOLYL PROPANONES AS MODULATORS OF 5-HYDROXYTRYPTAMINE RECEPTOR

THESIS

Submitted in partial fulfilment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

BY

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Under the supervision of

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CERTIFICATE

This is to certify that the thesis entitled **"SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF N-4 SUBSTITUTED DIHYDRO-2-ACENAPHTHYLENYL PIPERAZINES AND SUBSTITUTED PIPERAZINYL INDOLYL PROPANONES AS MODULATORS OF 5-HYDROXYTRYPTAMINE RECEPTOR"** and submitted by **P.SRINIVAS**, ID.No. **92PHXF003** for the award of the **Ph.D.** degree of the Institute, embodies the original work done by him under my supervision.

Date. 13th May 1998

Signature in full of the supervisor

(Dr. Addepalli Veeranjaneyulu)
Associate Professor
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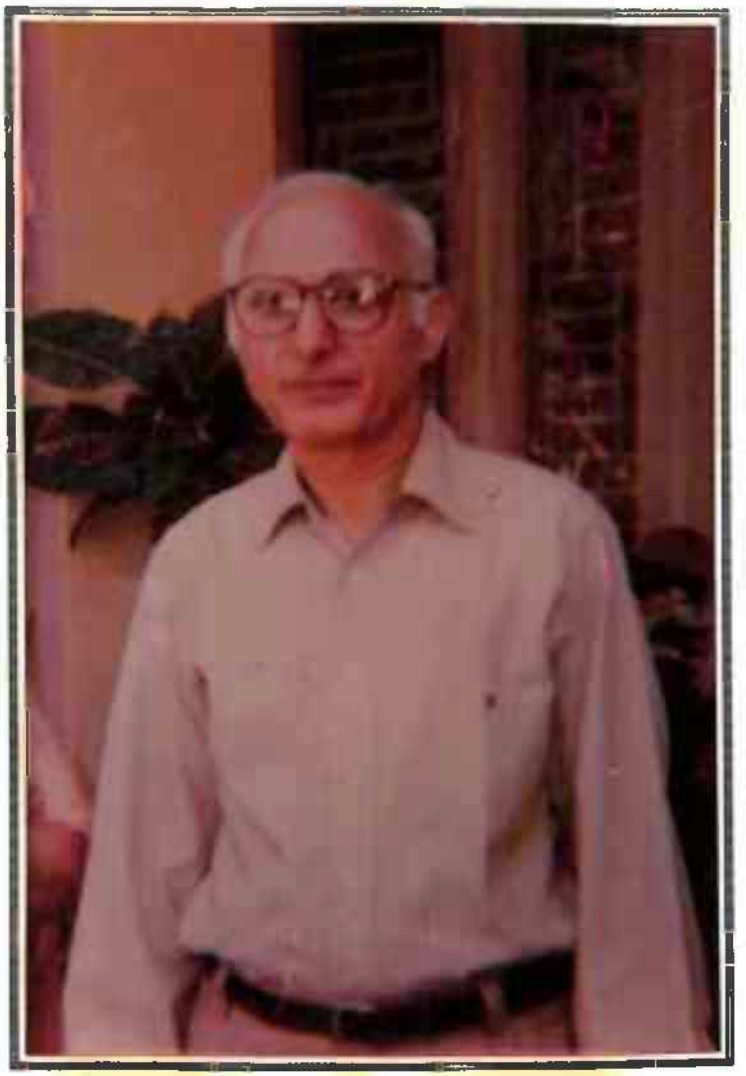
DEDICATED TO



DR. P. PARIMOO

06.11.1938 - 07.03.1998

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PREFACE

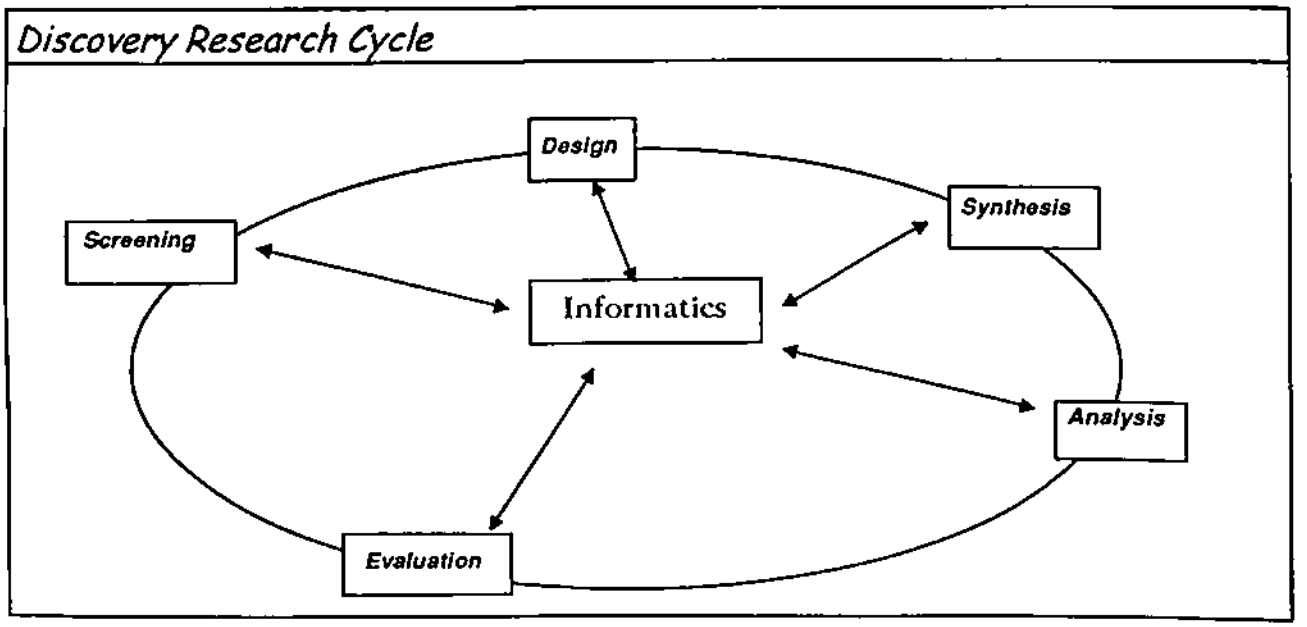
Medicinal chemistry is a science whose roots lie in all branches of chemistry and biology dealing with the discovery or design of new chemicals and their development as potential therapeutic agents. It also concerns with the understanding and explanation of the mechanisms of the actions of drugs. It revolves around the synthesis of new compounds, investigations of the relationships between the structure of natural and/or synthetic compounds and their biological activities, elucidation's of their interactions with receptors of various kinds including enzymes and DNA. It involves the determination of their absorption, transport and distribution properties, and studies of the metabolic transformations of these chemicals into other chemicals. It also attempts to link biodynamic behavior to the chemical reactivity and physical properties of the therapeutic agents. Thus, medicinal chemistry provides the chemical basis for the interdisciplinary field of therapeutics.

The earliest drug discoveries were made by random sampling of higher plants. Herbal drug discovery continues to be a potential source. Although many natural products are used in pharmaceuticals in their original chemical structures, successful efforts have been made to improve their pharmaceutical and therapeutic properties by structural modifications.

Another approach to improve therapeutic properties is to identify the selective portion of a natural molecule responsible for its biological activity and synthesise new molecules on that structural basis. As a result of advances made in synthesis and separation methods and in biochemical techniques since late 1940's, a rational approach to drug discovery has been possible, namely, one which involves the element of *design.*

Modern drug design, as compared with, *Let's make a change on an existing compound or synthesise a new structure and see what happens*, is a fairly recent discipline. It is still in infancy based on modern chemical techniques utilizing recent knowledge of disease mechanisms and receptor properties.

In general, clinically used drugs are not discovered. What is more likely discovered is known as a *lead compound*. The *lead* is a prototype compound that has the desired biological or pharmacological activity, but may have many other undesirable characteristics, for example, high toxicity, other biological activities, insolubility, or metabolism problems. All these characteristics form a basis of *Informatics*, in a typical drug discovery research cycle.



The structure of the lead compound is then modified by further design and synthesis to specify the desired activity and to minimise or eliminate the unwanted properties, the follow-up of which leads to further directions in a drug discovery process.

This will make the processes as rational as possible to avoid - redundant synthetic work and biological screening covering the extensive pharmacological aspects in picking new drug molecules.

The present thesis work describes the synthesis and pharmacological evaluation of two series of molecules based on the arylpiperazine structure for their modulatory effects at the 5-Hydroxytryptamine Receptor.

In the first series of compounds an attempt has been made to discover a new arylpiperazine, and the second series is an attempt to structurally modify 5-Hydroxytryptamine itself, which has led to the synthesis of N-4-Substituted-1,2-dihydro-

2-acenaphthylenyl piperazines and Substituted Piperazinyl Indolyl Propanones respectively.

The thesis consists of different chapters, an Introduction- which gives an overview of all important serotonergic molecules acting at various 5-HT receptor subtypes, Statement of Problem- which encompasses the basic framework analysis and reasoning for the design of the target molecules, Experimental Reaction Scheme and Experimental-which gives the synthetic routes adopted and description of the experimental procedures, Results and Discussion, Conclusions and References.

The Serotonin Club Nomenclature Committee of IUPHAR has permitted the usage of either 5-HT or Serotonin to denote 5-Hydroxytryptamine interchangeably. The same has been adopted in this thesis.

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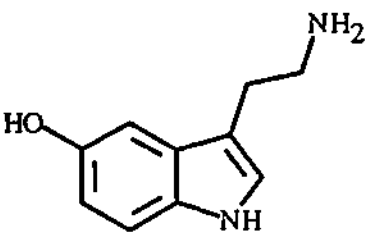
Chapter - 1

INTRODUCTION

Serotonin (5-hydroxytryptamine, 5-HT) (1) is widely distributed in animals and plants, occurring in vertebrates, fruits, nuts, and venoms. Serotonin was first isolated from blood serum, but is found in many other cells including neurons and has been shown to constrict smooth muscle tissue. Even more interesting is serotonin's neuromodulatory action on neuronal excitability. While only 1-2% of all serotonin is located in the brain, it is thought to play an important role in mediating behavior and moods.

A number of congeners of serotonin are also found in nature and have been shown to possess a variety of peripheral and central nervous system activities. Of particular interest over the years is the psychotomimetic activity displayed by several serotonin-related compounds such as N,N-dimethyltryptamine, 5-hydroxy-N,N-dimethyltryptamine (bufotenine), and 4-phosphoryloxy-N,N-dimethyl-tryptamine (psilocybin).



(1)

Although serotonin may be obtained from a variety of dietary sources, endogenous 5-HT is synthesized *insitu* from tryptophan through the actions of the enzymes tryptophan hydroxylase and aromatic L-amino acid decarboxylase. Both dietary and endogenous 5-HT are rapidly metabolized and inactivated by monoamine oxidase and aldehyde dehydrogenase to the major metabolite, 5-hydroxyindoleacetic acid (5-HIAA).

Of the chemical neurotransmitter substances, serotonin is perhaps the most implicated in the etiology or treatment of various disorders, particularly those of the central nervous system, including anxiety, depression, obsessive-compulsive disorder, schizophrenia, stroke, obesity, pain, hypertension, vascular disorders, migraine and nausea. The most important factor in our understanding of the role of 5-HT in these disorders is the rapid advance made in understanding the physiological role of various serotonin receptor subtypes in recent years.[1]

In 1948, Page and coworkers[2] isolated serotonin from blood for the first time and was later reported to be present in the central nervous system. Like most neurotransmitters, serotonin has a relatively simple chemical structure but displays complex pharmacological properties. Based on the similarity of its structure to the structures of norepinephrine and dopamine, it is not surprising that serotonin, like its catecholamine counterparts, possesses a diversity of pharmacological effects, both centrally and peripherally. It is found in three main areas of the body: the intestinal wall (where it causes increased gastrointestinal motility); blood vessels (where large vessels are constricted); and the central nervous system (CNS).[3]

The most widely studied effects of serotonin have been those on the central nervous system. The functions of serotonin are numerous and appear to involve control of appetite, sleep, memory and learning, temperature regulation, mood, behavior (including sexual and hallucinogenic behavior), cardiovascular function, muscle contraction, endocrine regulation and depression. Peripherally, serotonin appears to play a major role in platelet homeostasis, motility of the gastrointestinal tract, and carcinoid tumor secretion. This represents quite a broad spectrum of pharmacological and psychological effects, considering the fact that the average turn over in human adult is only about 10 mg of 5-HT.[4] Page and coworkers have also stated that there is no physiological substance known to possesses such diverse actions in the body as 5-HT.[2]

Chemical neurotransmitters (CNT's) produce their effects as a consequence of interactions with appropriate receptors. Serotonin like other chemical neurotransmitters is synthesized in brain neurons and stored in vesicles. Upon a nerve impulse, it is released into the synaptic cleft, where it interacts with various postsynaptic receptors.[5]

The actions of 5-HT are terminated by three major mechanisms: diffusion; metabolism; and uptake back into the synaptic cleft through the actions of specific amine membrane transporter systems.[3] These events are summarized in Figure 1.

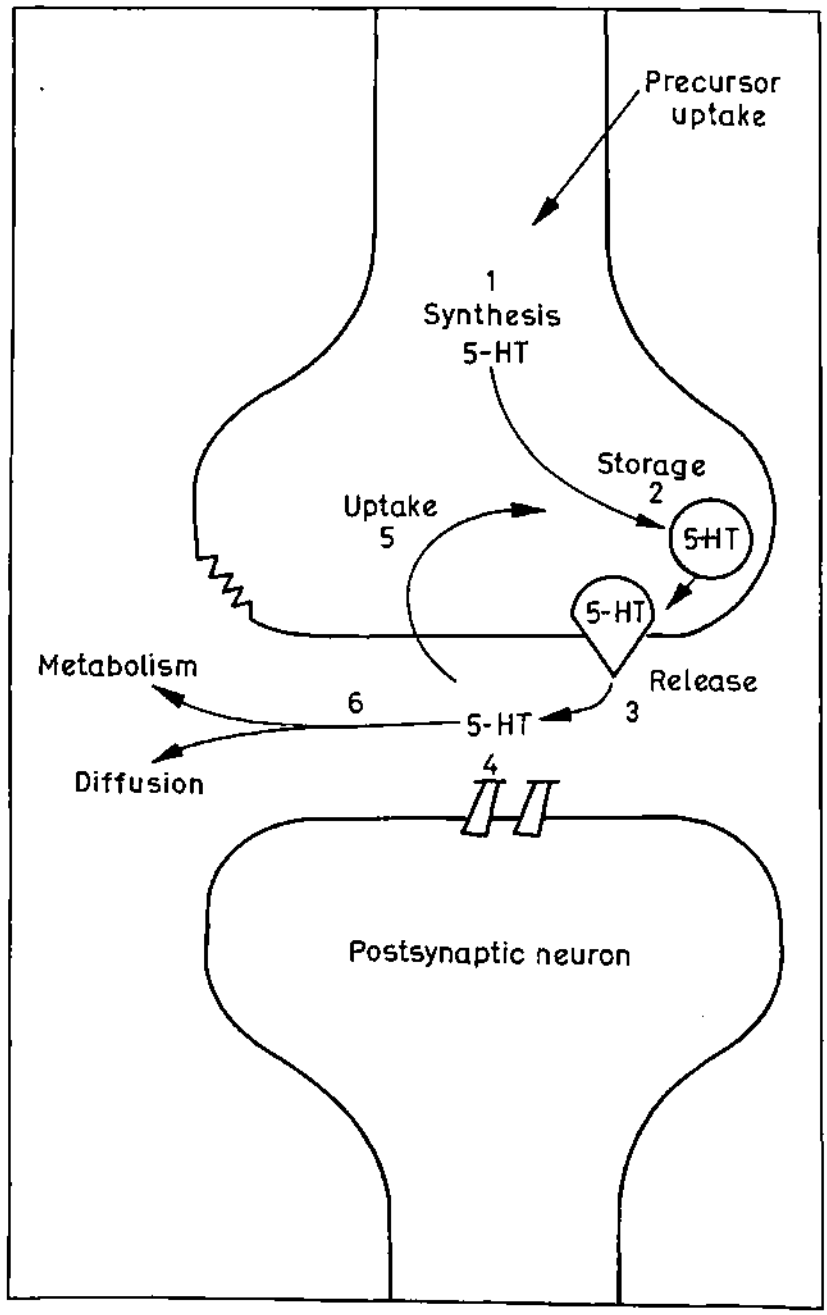


Figure 1. Actions of 5-Hydroxytryptamine

Thus, the actions of 5-HT can be theoretically modulated by, Step1: Agents that stimulate or inhibit its biosynthesis; Step 2: Agents that block its storage; Step 3: Agents that stimulate or inhibit its release; Step 4: Agents that mimic or inhibit its actions at its various postsynaptic receptors; Step 5: Agents that inhibit its uptake back into the nerve terminal; Step 6: Agents that affect its metabolism.

Of all the chemical neurotransmitters, 5-HT presents the most perplexing array of receptor interactions. In 1957, Gaddum suggested that 5-HT interacted on two different receptors in isolated tissues, one on smooth muscle and the other one on nervous tissue.[6] Since, dibenzyline selectively antagonized smooth muscle, and morphine was selective for nervous tissue, these receptors were named "D" and "M" receptors, respectively. Since 1948, and especially in the past decade, there has been a great progress in 5-HT receptor identification. In 1986, Bradley and coworkers suggested a more formal definition of 5-HT receptors.[7] A 5-HT_x system of nomenclature has been proposed for the classification of 5-HT receptors. They proposed that there are three main groups of 5-HT receptors, *viz.*, 5-HT_1, 5-HT_2 and 5-HT_3 receptors.

The current approach for classifying 5-HT receptors and their characterization is based on the "finger print" criteria required to characterize a particular receptor. The three main criteria are operational (i.e., drug-related characteristics), transductional (receptor-effect coupling events), and structural (gene and receptor structural sequences for their nucleotide and amino acid components) respectively.[8]

It now appears that there are at least four populations of receptors for serotonin: 5-HT_1, 5-HT_2, 5-HT_3 and 5-HT_4. Recent cloning studies suggest the existence of 5-HT_5, 5-HT_6 and 5-HT_7 subtypes as well, but the receptors are yet to be fully characterized operationally and transductionally in intact tissues, and as such their appellations must be considered provisional.

This classification has become furthermore complicated because, evidence has been presented that seven distinct subtypes of the 5-HT_1 (5-HT $_{1A,1B,1D,\ 1E,\ 1F,\ 1P\ \&\ 1S}$), three subtypes of the 5-HT_2 (one of which was formerly named the 5-HT_{1C} receptor, a name that still appears in the literature) and two subtypes of the 5-HT_5 receptors exist.[3]

The physiological function of each receptor subtype has not been established and is currently the subject of intensive investigation. With the exception of the 5-HT_3 receptor, which is a ligand-gated ion channel[9] related to N-methyl-D-aspartic acid (NMDA), γ-amino butyric acid (GABA) and nicotinic receptors, all of the 5-HT receptor subtypes belong to the group of G-protein linked receptors,[10] which in turn belong to the family of seven transmembrane (7TM) receptors, coupled to their intracellular effectors via

guanine nucleotide binding proteins (G-proteins). The evolution of 5-HT receptor and classification is given in Table 1.

A brief summarization of our understanding of the main function of the most widely studied 5-HT receptors is given below followed by an insight into reported drug molecules / compounds for individual receptors and their subtypes.

5-HT_1 receptors

These receptors appear to be involved in the processes of smooth muscle relaxation, contraction of some cardiac and vascular smooth muscle, rejunctional inhibition of neurotransmitter release and effects in the central nervous system. Seven subtypes have been proposed (5-$HT_{1A,1B,1C,1D,\ 1E,\ 1F\ \&\ 1P(cripheral)}$, four of which appear to play a major role in humans:

5-HT_{1A}

This represents perhaps the most widely studied 5-HT receptor subtype. These receptors are located primarily in the central nervous system. Agonists facilitate male sexual behavior in rats, hypotension, increase food intake, produce hypothermia, and act as anxiolytics. This receptor has also been widely implicated in depression.

5-HT_{1B}

These may serve as autoreceptors; thus, activation causes an inhibition of neurotransmitter release. Agonists inhibit aggressive behavior and food intake in rodents. These receptors, which have been identified only in rodents and are apparently absent in humans, are thus only of theoretical interest at present. These receptors may be the counterpart of the 5-HT_{1D} receptor found in other species.

5-HT_{1C}

These receptors belong to the same receptor subfamily as the 5-HT_2 receptor and have been recently renamed as 5-HT_{2C} receptors. This receptor is located in high density in the choroid plexus and regulates cerebrospinal fluid production and cerebral circulation. This subtype is speculated to be involved in the regulation of analgesia, sleep and cardiovascular function.

Table 1

EVOLUTION OF 5-HT RECEPTOR AND CLASSIFICATION

1957 Gaddum & Picarelli	D		M			
1979 Peroutka & Snyder	$5HT_1$	$5HT_2$				
1986 Bradley et al	$5HT_1$-like	$5HT_2$	$5HT_3$			
1986 - 1992 E. Zifa et.al.	$5HT_{1A}$ $5HT_{1B}$ $5HT_{1C}$ $5HT_{1D}$ $5HT_{1E}$ $5HT_{1P(eripheral)}$	$5HT_2$	$5HT_3$	$5HT_4$		
1992- Hoyer et. al.	ORPHAN / RECOMBINANT RECEPTORS				$5HT_{5\alpha}$ $5HT_{5\beta}$	$5ht_6$ ---- $5ht_7$ ----
1997- Hoyer & Martin	$5HT_{1A}$ $5HT_{1B}$ $5HT_{1C}$ $5HT_{1D\alpha}$ $5HT_{1D\beta}$ $5HT_{1E}$ $5HT_{1F}$ $5HT_{1F\beta}$	$5HT_{2A}$ $5HT_{2B}$ $5HT_{2C}$	$5HT_3$	$5HT_{4S}$ $5HT_{4L}$	$5HT_{5A}$ $5HT_{5B}$	$5HT_6$ --- $5HT_7$ ---

5-HT$_{1D}$

This receptor is reported to be located primarily in the central nervous system and plays a role as a presynaptic heteroreceptor or as a terminal autoreceptor, being thus involved in the inhibition of neurotransmitter release by mediating a negative feedback effect on transmitter release. This subtype is the most abundant 5-HT$_1$ receptor in the central nervous system, but is also found in vascular smooth muscle mediating contraction. While the role of activation of this receptor subtype is not fully understood, agonists at this site are effective in treating acute migraine headaches. The development of selective antagonists of this receptor would clarify the functional role of 5-HT$_{1D}$ receptors in the central nervous system.

5-HT$_2$ receptors

The 5-HT$_2$ family includes 5-HT$_{2A}$,5-HT$_{2B}$ and 5-HT$_{2C}$ receptor subtypes. These are located in the vascular smooth muscle, platelets, lung, central nervous system, and the gastrointestinal tract. These subtypes appear to be involved in gastrointestinal and vascular smooth muscle contraction, platelet aggregation, hypertension, migraine, and neuronal depolarization. Their antagonists have potential use as antipsychotic agents. Since, these receptors belong to the same receptor subfamily as the former 5-HT$_{1C}$ receptors, they have been recently renamed as 5-HT$_{2A}$ receptors.

5-HT$_3$ receptors

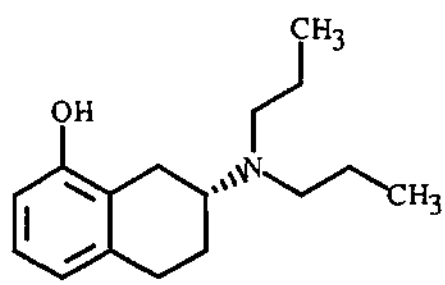
The classical M receptors (5-HT$_M$ receptors) are now termed 5-HT$_3$ receptors and are located in peripheral and central neurons. These receptors appear to be involved in the depolarization of peripheral neurons, pain and the emesis reflex. Potential uses of agents acting at this site include migraine, anxiety, and cognitive and psychotic disorders.

5-HT$_4$ receptors

These receptors are found in the central nervous system, the heart, and the gastro intestinal tract. Their activation produces an increase in cyclic adenosine monophosphate (cAMP) and appears to involve activation of neurotransmitter release. The gastric prokinetic activity of metoclopramide has been attributed, in part, to its ability to activate 5-HT$_4$ receptors.

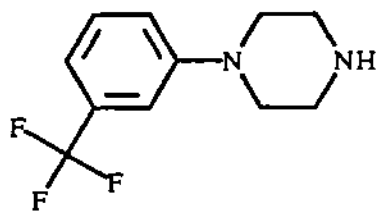
Research in the area of serotonin has continued at a rapid pace. Never before has a single neurotransmitter been implicated in the etiology or treatment of so many medical problems. The ability to treat distinctive disease states arises from differential drug interactions at multiple 5-HT receptor subtypes. Great strides are being made in the elucidation of the physiological components linked to these multiple receptor subtypes. The challenge or forefront of 5-HT research today involves the search for agents that selectively interact with one receptor subtype.[11]

The 5-HT_1 receptor is reported to be a high affinity-binding site, while its subtypes exert different functions at both the cellular and behavioral levels.[12] The 5-HT_{1A} receptor is broadly distributed in the central nervous system, occurring as a somatodendritic autoreceptor on 5-HT neurons located in the raphe nuclei and postsynaptically in the other areas such as the hippocampus.[13,14] Several classes of agents are known to bind at 5-HT_1 receptor sites, *viz.*, aminotetralins, indolylalkylamines, aryloxyalkylamines, alkyl piperidines, arylpiperazines, phenylalkylamines, ergolines and (aryloxy)propanamines. Arylpiperazines are the most notable class of agents that bind at the various 5-HT_1 sites.[15] The 5-HT_{1A} receptor subtype has been widely implicated in anxiety and depression.[16,17]
It has been reported that 8-hydroxy-2-di-n-propyl amino tetralin [8-OH-DPAT] (2) is a prototypical 5-HT_{1A} agonist and in its radiolabelled form is used to characterize the 5-HT_{1A} receptor. It binds specifically to the 5-HT_{1A} receptor subtype and at low dose levels has been reported to have preferential action on serotonin autoreceptors, whereas at high dose levels it acts at postsynaptic receptors.[18-20]



(2)

A large amount of data indicates that compounds in the arylpiperazine class have anxiolytic and antidepressant properties in man. Two arylpiperazine derivatives 1-[3-(trifluoromethyl) phenyl] piperazine, [TFMPP] (3) and its chloro analogue (m-chlorophenyl) piperazine, [mCPP] (4) have been extensively investigated. These two compounds have shown affinity to 5-HT_{1A} receptors. Further, 1-(4-chlorophenyl) piperazine [pCPP] (5) and 6-chloro-2-(1-piperazinyl) pyrazine, [MK-212] (6) have been reported to produce a dose dependent suppression of spontaneous ambulatory behaviour in rats.[21]



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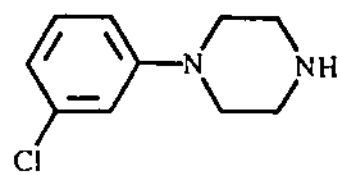

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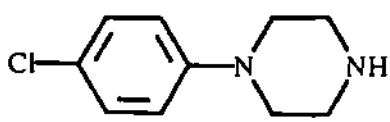

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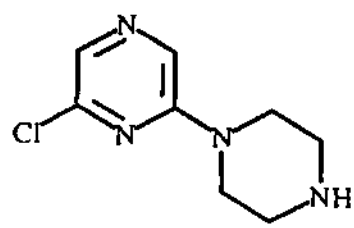
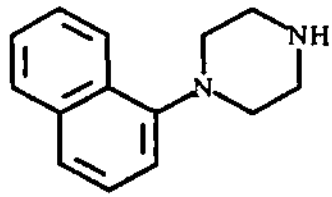
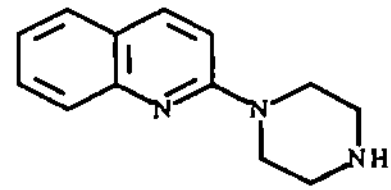


(6)

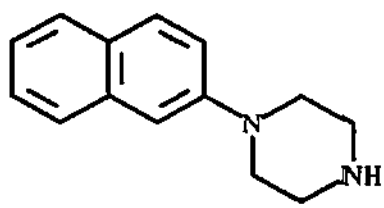
Sills and coworkers have reported that TFMPP (3) and mCPP (4) possess 30-70 fold selectivity for 5-HT_{1B} sites.[19] 1-Naphthyl piperazine, [1-NP] (7) has been reported by Dourish and coworkers, to be a 5-HT_1 antagonist at peripheral smooth muscles.[22] Sills and coworkers have also reported that, 1-NP (7), mCPP (4) and TFMPP (3) are $5HT_{1B}$ agonists.[19] Glennon and coworkers have described, Quipazine [2-(1-piperazinyl) quinoline] (8), as a non-indolic serotonergic agent having affinity towards 5-HT_1, 5-HT_2 and $5HT_3$ sites.[23]

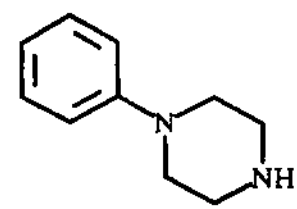




(7) (8)

On removal of quinoline nitrogen atom from quipazine, 2-naphthyl piperazine, [2-NP] (9) having enhanced affinity for 5-HT_2 sites rather than 5-HT_1 sites was obtained. Further, removal of the fused phenyl ring from 2-NP (9) afforded 1-phenyl piperazine (10), a compound which has a very high affinity for 5-HT_1 sites comparable to that of 1-NP (7).[24]

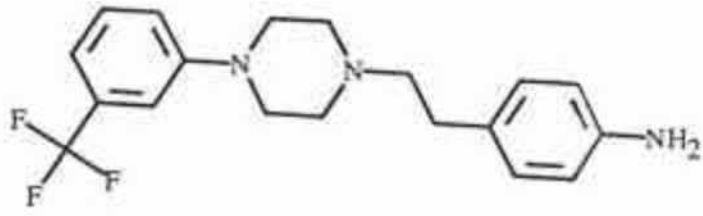




(9) (10)

A novel piperazine derivative, 1-(m-Trifluoromethyl phenyl)-4-(p-aminophenyl ethyl) piperazine, [PAPP] (11), based on the chemical structure of TFMPP (3) has been reported to be a central serotonin agonist whose neurochemical and behavioral evidence for its agonist action at central 5-HT receptors, has been reported by Hutson and coworkers.[25] The binding of PAPP (11) to 5-HT_{1A} sites, provided a clear cut example of a shift in the selectivity pattern of 5-HT receptor substrate towards 5-HT_{1A} activity from 5-HT_{1B} which is exhibited by TFMPP, as a result of N-substitution.[26]

Another arylpiperazine, 2-methoxy phenyl piperazine (12) has been reported to bind to 5-HT_{1A} sites with an affinity equal to that of 1-phenyl piperazine (10). Both have been reported to show a several-fold activity for 5-HT_{1A} versus 5-HT_{1B} sites.[27]



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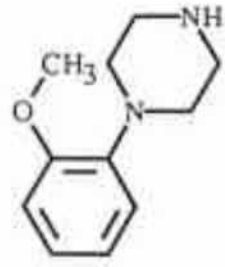
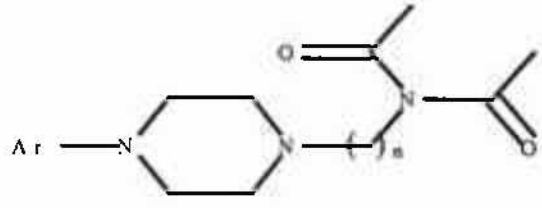


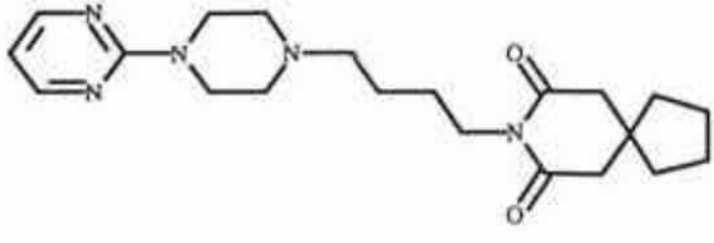
(12)

A new class of novel compounds i.e., the azapirones, with the general structure (13), have been recently developed as anxiolytics. The main point of distinction is that, this class of compounds are non-benzodiazepine derivatives. These comprise of an arylpiperazine moiety and do not interact with the benzodiazepine-GABA Chloride Channel ionophore complex.[28] Further, their behavioral effects are not blocked by benzodiazepine antagonists.[29]



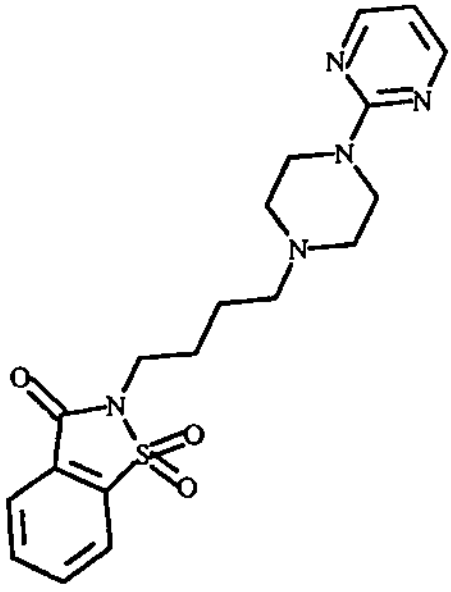
(13)

The azapirones are hence classified as "Second Generation Anxiolytics" (SGA's). The second-generation anxiolytic (SGA) buspirone (14) is an arylpiperazine and has been reported by Peroutka[30] and Titler and coworkers[31] to bind with high affinity and selectivity for 5-HT_{1A} sites.



(14)

Taylor and coworkers,[32] proposed a dopaminergic mechanism of action for buspirone due to its interaction with pre and post synaptic dopamine receptors apart from its affinity for the 5-HT_{1A} receptor. Buspirone was therefore, considered to be a partial agonist at the 5-HT_{1A} receptor and this opened up venues for further research for full agonists at the 5-HT_{1A} receptor so that affinity and selectivity could be enhanced accordingly. Ipsapirone (15) [TVX Q7821], and gepirone (16) are structurally related compounds and both these compounds, unlike buspirone, are reported to lack direct interaction with dopamine receptors but bind like buspirone with high affinity to 5-HT_{1A} sites.[33,34]



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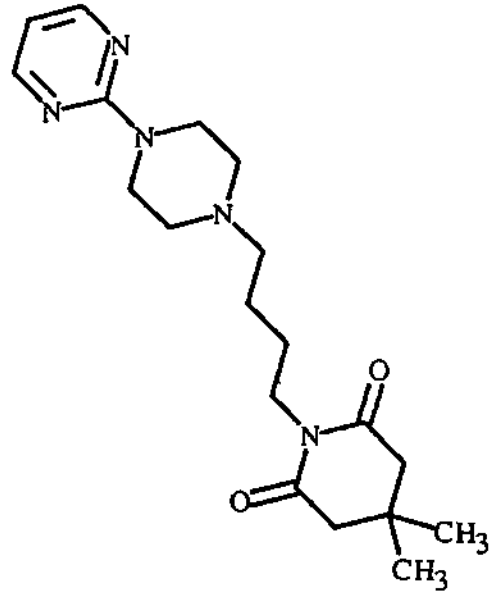
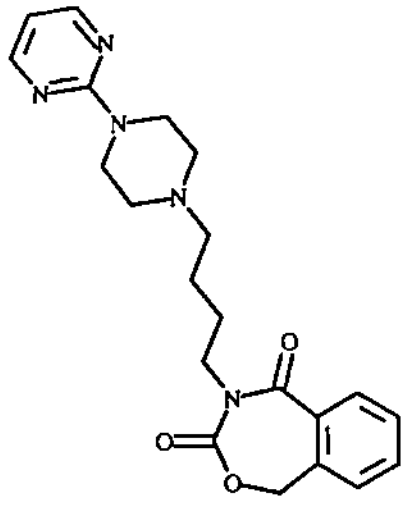


(16)

Kuribara has reported SUN 8399 (17), to be highly selective towards 5-HT_{1A} receptors and has also been reported to display some dopamine (D_2) and alpha adrenergic activity *in vivo*.[35] Umespirone, [KC-9172] (18) was reported by Krijer and Krahling, to have an anxiolytic potency superior or equal to diazepam or buspirone and antipsychotic potential superior or equal to clozapine.[36]



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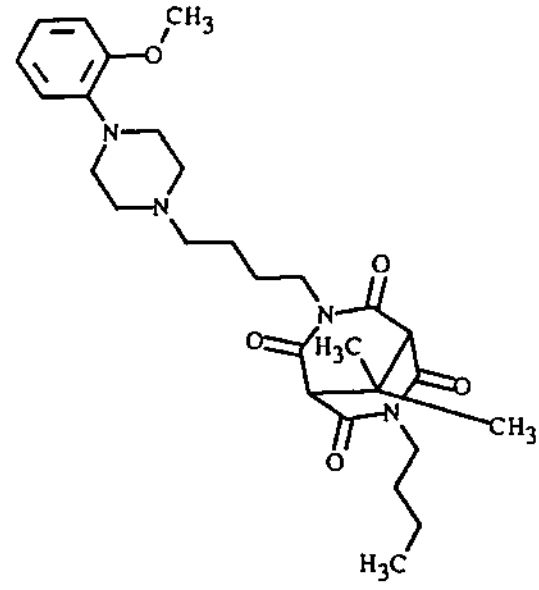
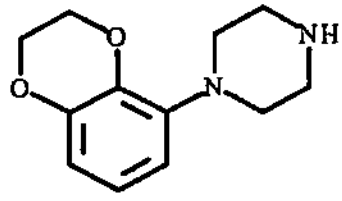


(18)

Hibert and coworkers have described that, all these long chain aryl piperazines have two structural features necessary for recognition of ligands by the 5-HT_{1A} sites, an aromatic ring and a strongly basic nitrogen atom at a distance of 5.2-5.6 angstroms.[37]

In order to find clinically useful antidepressants and anxiolytics, evaluation of compounds belonging to another class of arylpiperazines led to the discovery of eltoprazine (19), its benzofuranyl analogue (20), befiperide (21) and flesinoxan (22). Van Steen and coworkers have reported, all of them to be highly selective for the 5-HT_{1A} site[38] and flesinoxan[39] (22) is described to be a highly selective and full agonist for the 5-HT_{1A} site.



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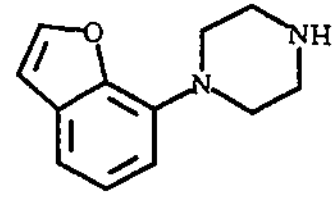

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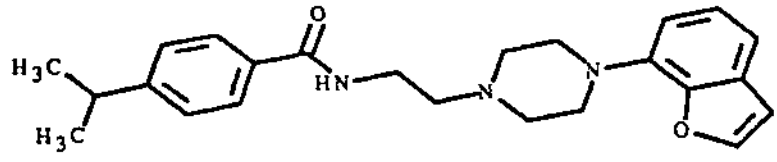

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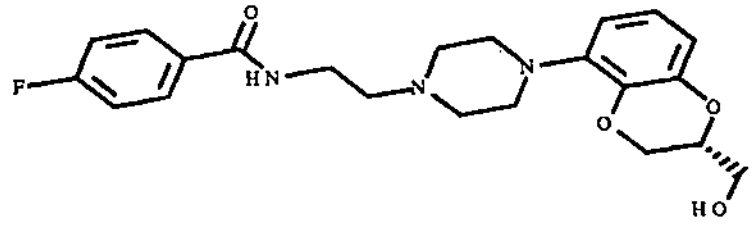
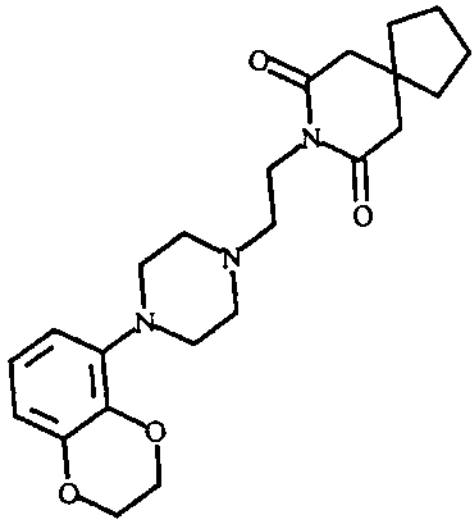


(22)

Van Steen and coworkers also synthesized a series of N4-Imidoethyl derivatives of 1-(2,3-Dihydro-1,4-benzdioxin-5-yl) piperazine (eltoprazine) in order to establish their affinity for the 5-HT_{1A} receptor, among them, the azaspiro decane dione analog (23) has shown the highest affinity for the 5-HT_{1A} receptor.[40]

The naphthyl piperazine, S-14671 (24) was reported by Hirotsu and coworkers as a potent agonist at 5-HT_{1A} receptors having a selectivity of 30 fold over 5-HT_{1C} and 5-HT_2 receptors, where it is an antagonist.[41]

While the selective 5-HT_{1A} antagonists have remained elusive, the most commonly used 5-HT_{1A} antagonists are spiperone, propranolol and (–)pindolol, though they lack selectivity. They have been reported to block various effects produced by the 5-HT_{1A}-selective agonist 8-OH-DPAT (2). Glennon and coworkers have reported that NAN-190, 1-(2-methoxy phenyl)-4-[4-(2-phthalimido) butyl] piperazine (25) binds with high affinity at 5-HT_{1A} sites, as a useful 5-HT_{1A} antagonist.[42]



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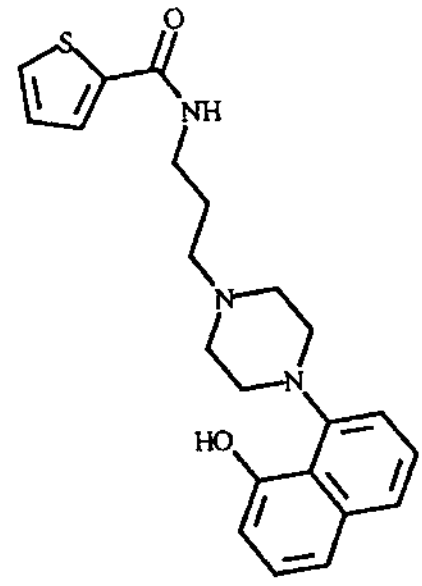

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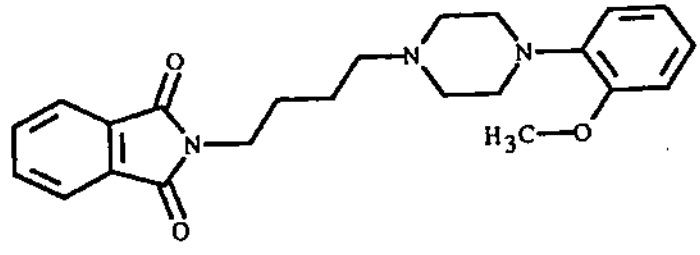
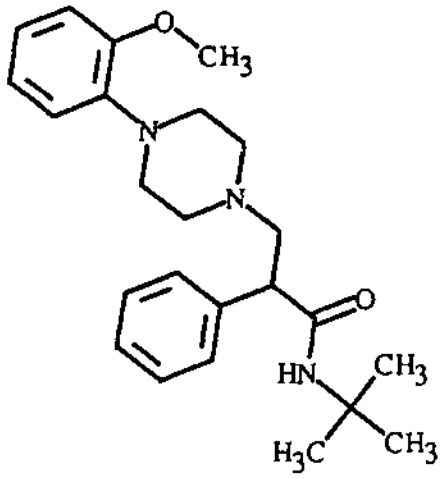


(25)

Wozniak and coworkers have reported WAY 100135 (26) as the first selective anxiolytic to act as an antagonist in both pre- and post-synaptic receptor models.[43] Fletcher and coworkers reported that the antagonist RK-153 (27) binds at 5-HT_{1A} receptors with 160 fold selectivity compared to alpha-1-adrenergic receptors.[44]

A series of indolyl butyl piperazines have been reported by Perregaard and coworkers, as being 5-HT_{1A} receptor antagonists of which LU-27079 (28) was the first compound, which showed only a seven fold selectivity for 5-HT_{1A} binding sites compared to alpha and dopamine (D_2) sites.[45]



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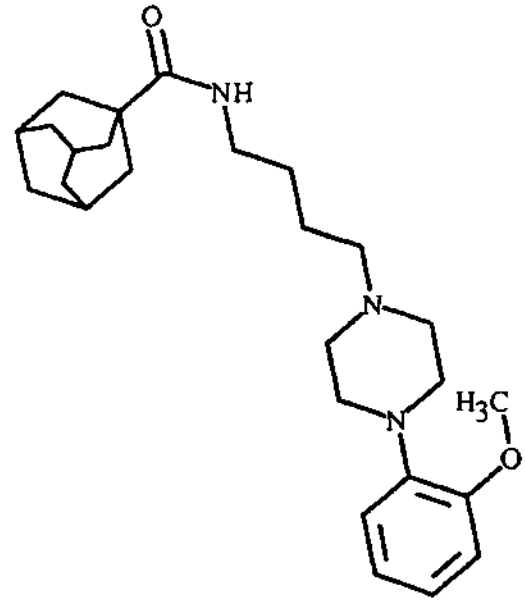
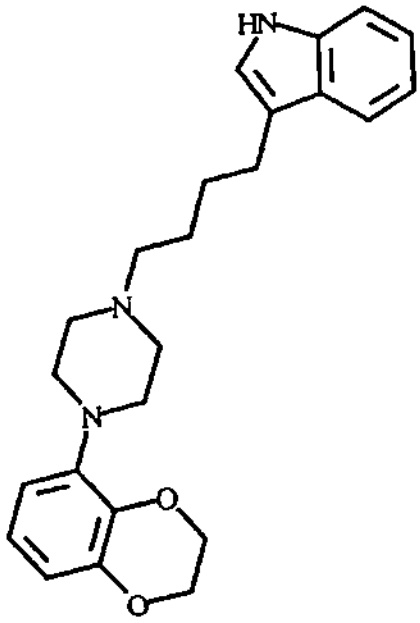


(27)

Perrone and coworkers have reported a new model of 4-alkyl-1-arylpiperazines containing a terminal dihydronaphthalene fragment on the alkyl chain, 4-[3-(1,2-dihydro-6-methoxynaphthalene-4-yl)-n-propyl]-1-(2-methoxyphenyl)piperazine (29) which shows nanomolar affinity for 5-HT_{1A}, D_2 and low affinity for 5-HT_2 receptors.[46]

Mokrosz and coworkers have reported 4-allyl-1-(*o*-methoxy phenyl) piperazine containing a terminal benzotriazole moiety, 4-[3-[(benzotriazol-1-yl) propyl]-1-(2-methoxy phenyl) piperazine (30) as a new potent 5-HT_{1A} antagonist.[47]

Orjales and coworkers have reported that 2-(methoxy phenyl) piperazine derivatives (31) containing a terminal cycloalkyl amide fragment increases the affinity towards 5-HT_{1A} sites. These derivatives bind at 5-HT_{1A} site with 2-10 fold higher affinity than NAN-190 and are devoid of antagonistic activity at α-1 and adrenergic receptors.[48]



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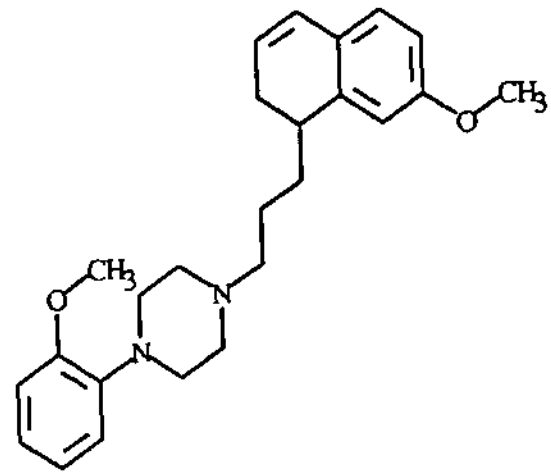

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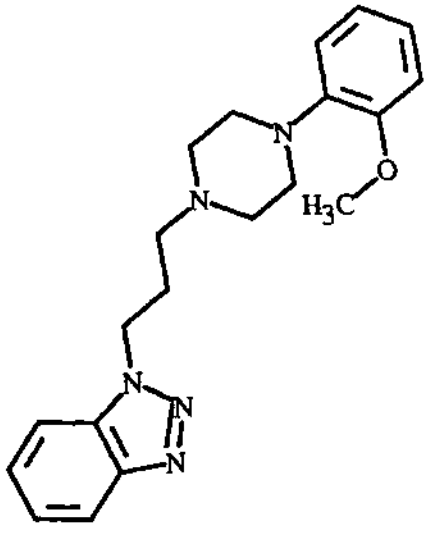

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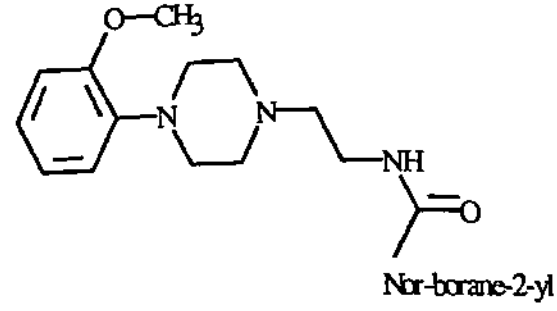
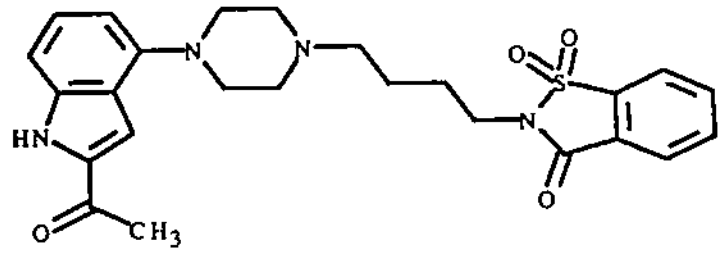


(31)

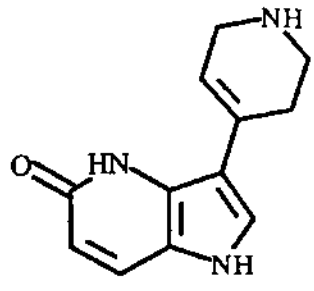
Fletcher and coworkers have suggested that for effective management of central nervous system and relative disorders, the silent 5-HT_{1A} receptor antagonists can be used as vital research tools for new drug research.[49] The discovery of SDZ-216525 (32) by Hoyer and coworkers[50] and WAY-100135 (26) by Fletcher and coworkers, opened up new research in the area of silent 5-HT_{1A} receptor antagonists.[51]



(32)

Although the 5-HT_{1B} receptor is found in rats and mice, its presence has not been demonstrated in humans,[52] where the 5-HT_{1D} receptor, which is found in similar brain locations in man, has been proposed to have an analogous function. Hoyer and Schoeffter, have reported TFMPP (3) & mCPP (4) to display less than three-fold selectivity for 5-HT_{1B} sites and are frequently used as selective ligands.[53]

Although only few selective ligands are available, the recently described agonist, CP - 93129 (34) a tetrahydropyridine, does appear to be 5-HT_{1B} selective.[53] Macor and coworkers have reported CGS-12066B (35) a pyrrolo[1,2-a]quinoxaline derivative, as the only compound to be 5-HT_{1B} selective, as an agonist.[54]



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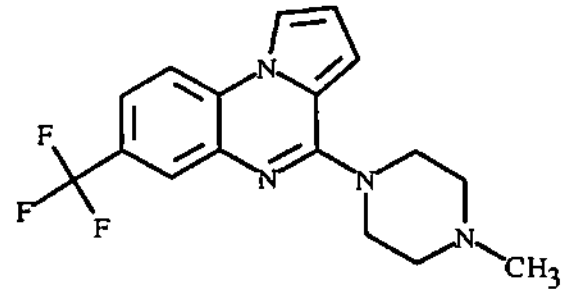
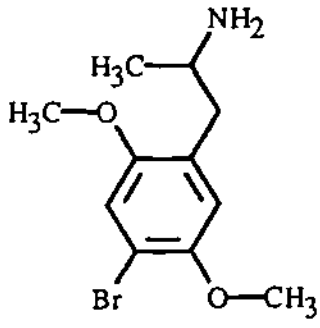


(35)

At the same time, no good selective antagonists are reported to be available, however some indole β-adrenoceptor antagonists are potent 5-HT_{1B} receptor antagonists, but their potency at 5-HT_{1A} receptor has also been reported to be similar.

It has been found that most agents that bind at 5-HT_{1C} receptors also bind at 5-HT_2 receptors, because the 5-HT_{1C} receptor is coupled to the same second messenger system as the 5-HT_2 receptor. Quipazine (8) and mCPP (4) have been utilized as 5-HT_{1C}

agonists, yet are far from being selective.[55] Middlemiss and coworkers reported bromo and iodo derivatives of 1-(2,5-Dimethoxy) phenyl -2-amino propanes, DOB (36) and DOI (37) as probable 5-HT_{1C} agonists, but also as prototypical 5-HT_2 receptor ligands.[56] The literature does not describe any selective ligand for 5-HT_{1C} receptor sites.



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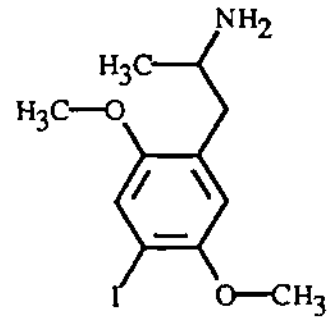
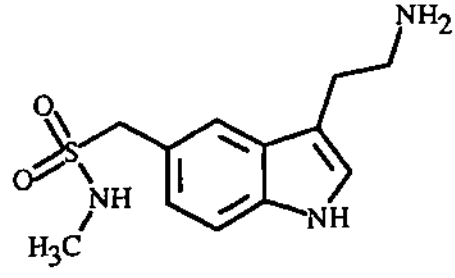


(37)

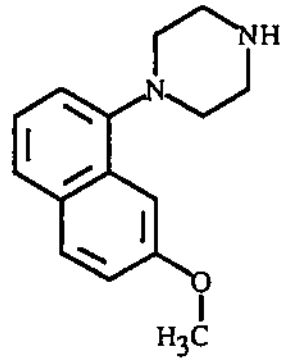
In the late 1980's, Heuring and Peroutka[57] were the first to report 5-HT_{1D} receptors. The high potencies of the 5-HT agonist 5-carboxamido tryptamine and the antagonist methiothepin justified classification of these receptors as 5-HT_1-like.[57] To date, there are no reported selective 5-HT_{1D} receptor ligands. The only agent that has received considerate attention is sumatriptan (38). Sumatriptan (GR-43175) has been shown to be clinically effective in the treatment of acute migraine.[14] Peroutka and McCarthy have reported that sumatriptan binds at 5-HT_{1D} receptors with high affinity but with limited selectivity.[58]



(38)

The affinity of arylpiperazines for the 5-HT_{1D} receptor has been reported to depend on the nature of the N4-substituent. Phenyl piperazine (10) binds with low affinity whereas 1-naphthyl piperazine [1-NP] (7) binds with a significantly high affinity.[59] Boulenguez

and coworkers, have reported newer naphthylpiperazines (39) and (40) to show a split in affinity for 5-HT_{1D} receptor[60] and also reported that the naphthylpiperazine derivative (39) binds with very high affinity.



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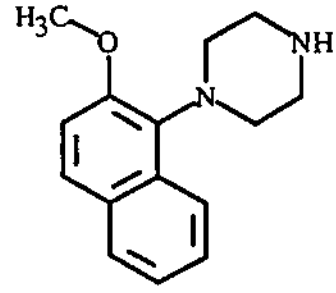
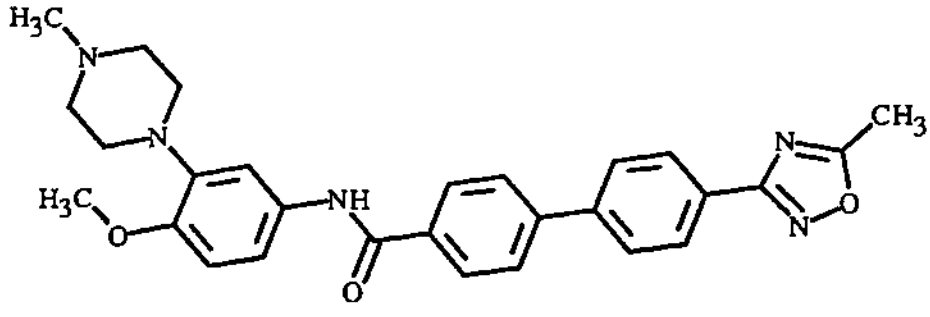


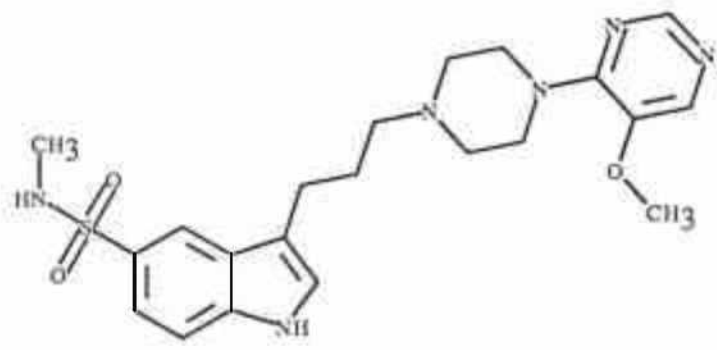
(40)

Skingle and coworkers have identified, N-[4-Methoxy-3-(4-methyl-1-piperazinyl) phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-[1,1-biphenyl]-4-carboxamide,[GR 127935] (41) as a very potent and the only selective 5-HT_{1D} receptor antagonist.[61]



(41)

Recently, Avitriptan (42), [BMS-180048] has been reported to be a new 5-$HT_{1B/1D}$ receptor agonist, in experimental models predictive of antimigraine activity and coronary side-effect potential.[62]

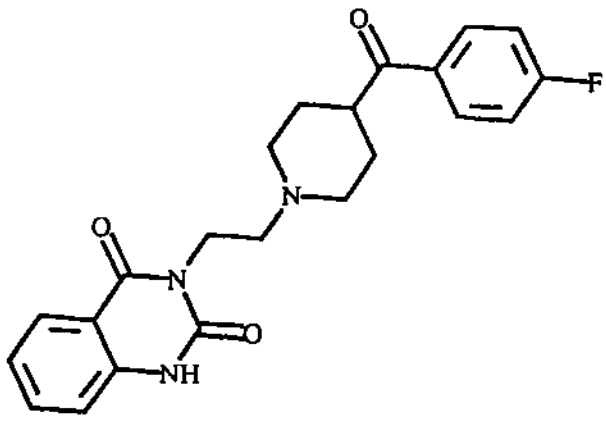


(42)

The 5-HT_2 receptor has been more completely characterized than some of the other types of 5-HT receptors, due to the availability of selective 5-HT_2 antagonists. The 5-HT_2 receptor is reported to mediate a variety of pharmacological effects.[14] Agonists at 5-HT_2 receptors in mice produce head twitches and selective 5-HT_2 antagonists block this effect. Clinically, 5-HT_2 agonists have been associated with hallucinogenic events and antagonists are indicated in the prophylactic treatment of migraine.[63]

In general, agents that display a high affinity for 5-HT_2 sites are those that are usually considered as being serotonin antagonists. Classical 5-HT agonists, on the other hand, commonly display a relatively low affinity for 5-HT_2 sites.[14]

The most prototypical 5-HT_2 receptor agonists reported are DOB (36) and DOI (37). Though they are not selective, DOI (37) has equal affinity, for 5-HT_2 and 5-HT_{1C} receptors.[64] Glennon has also reported that quipazine (8), the non-indolic serotonin agonist, binds both to the 5-HT_1 and 5-HT_2 sites, and that some of its effects are mainly due to its action at the 5-HT_2 receptors.[65] Ketanserin (43) has been reported to be a prototypical 5-HT_2 antagonist, though not selective. Van Nueten and coworkers have reported that, ketanserin is an antagonist at alpha-1 adrenoceptors.[66] Barret has reported, Irindalone (44), a piperazinyl aryl indan derivative, acting as a 5-HT_2 receptor antagonist and is currently under development as an antihypertensive agent.[67]



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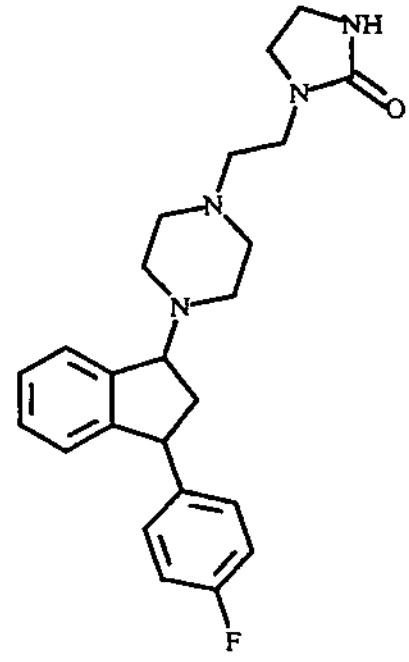
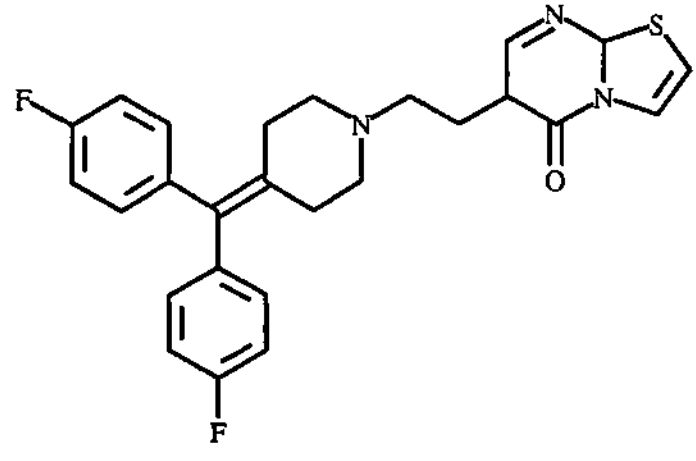


(44)

Owens and coworkers have reported, Ritanserin (45) to be a more selective 5-HT_2 receptor antagonist and to produce only modest behavioral and biochemical effects in man. These include increasing the release of dopamine (DA) and 5-HT in the nucleus accumbens, thus implying potential use as an antipsychotic. They have also suggested a mixed D_2/5-HT_2 blocking effect to contribute to the clinical efficacy of atypical antipsychotics.[68,69]

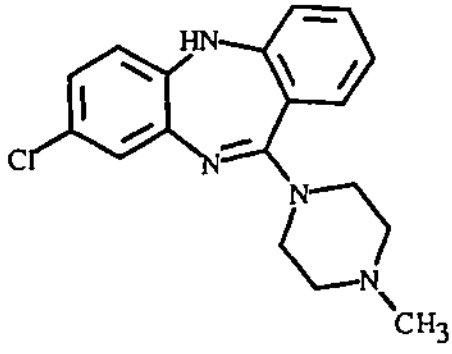


(45)

The 1990's promise to be an interesting decade in both the clinical and preclinical development of new antipsychotics, showing significantly divergent characteristics, including effects upon negative symptoms and a low level of extrapyramidal side effects (EPS) which are observed in conventional antipsychotics which are D_2 receptor antagonists. One of the most revolutionary events in the research on new antipsychotics is the recognition of the antipsychotic effects of clozapine (46). Clozapine has provided a hope that it is possible to develop new antipsychotics with a profile of low D_2 receptor blockade and antagonism of other receptor types such as D_1 and D_4. Gerlach and Casey, have described the importance of 5-HT_2 receptors particularly, because there has been an emphasis of a specific role for serotonin in psychosis and drug side effects.[70]

Kinon and Lieberman have described various criteria used to define atypical antipsychotics which include: (i) decrease, or absence of the capacity to cause acute extra pyramidal side effects (acute EPS) and tardive dyskinesia (TD); (ii) increased therapeutic efficacy reflected by improvement in positive, negative, or cognitive symptoms; (iii) and a decrease, or absence of the capacity to increase prolactin levels.[71]
The pharmacological basis of atypical antipsychotic drug activity has been the target of intensive study. Three notions have been utilized conceptually to explain the distinction between atypical versus typical antipsychotic drugs: (i) dose-response separation between particular pharmacologic functions; (ii) anatomic specificity of particular pharmacologic activities; (iii) neurotransmitter receptor interactions and pharmacodynamics.[71]

Many of the established "New" antipsychotics are reported to have the first two qualities of the criteria used to define atypicality; though to a lesser degree. This is true of sulpiride (47) and risperidone (48).[72] However, in the relatively high doses required to treat some severe psychoses, lose their potential advantages in relation to extra pyramidal side effects (EPS) and negative symptoms and thus act like traditional D_2 antagonists.[70]



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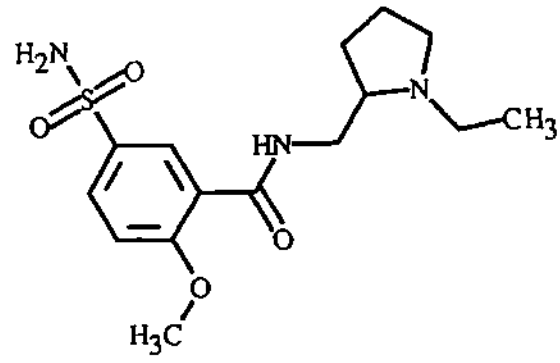
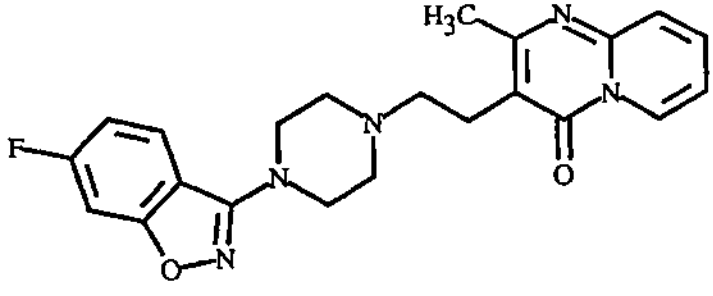


(47)

Newer antipsychotic agents like olanzapine (49), seroquel (50) and sertindole (51) are reported to have a relatively low blockade of D_2 receptors, which is the first requirement for a significantly lower risk of both acute and tardive extra pyramidal side effects (EPS).[73-75]



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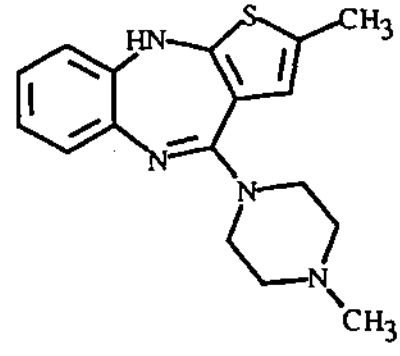
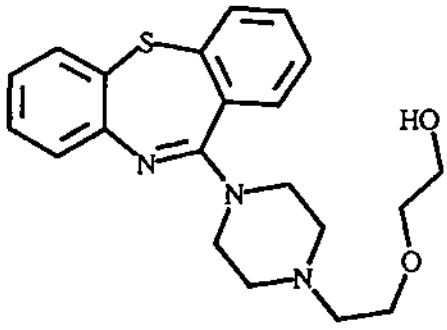
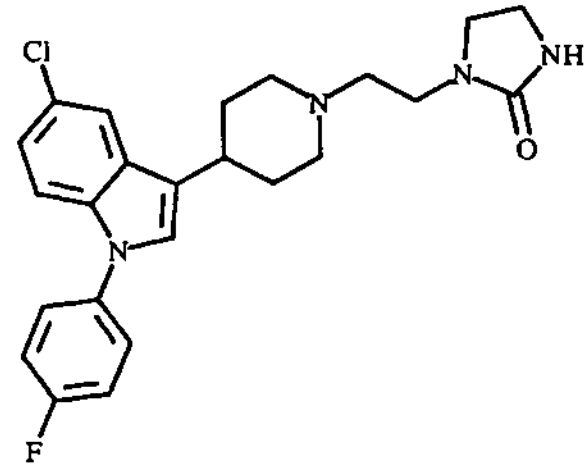


(49)

Some arylpiperazines have also been reported to be potential atypical antipsychotics. Davis and coworkers have reported HRP-392 (52) , a benzisoxazole derivative, to display a preclinical profile of an atypical antipsychotic. This compound comprises the arylpiperazine moiety.[76]

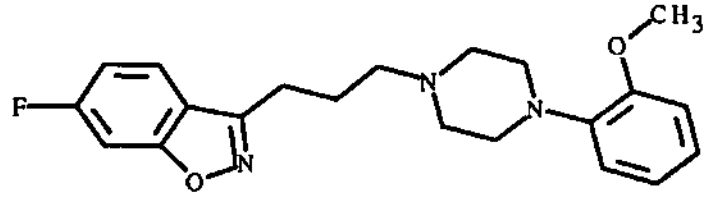
The benzisothiazolyl piperazine moiety is also a common pharmacophore in several new combined D_2/5-HT_2 antagonists. Thus, tiospirone (53) has been reported to be a mixed antagonist, but with comparatively less antagonism for 5-HT_2 receptor as result of which it does cause negative symptoms.





(50) (51)

Howard and coworkers have reported Ziprasidone (54), to show a high affinity and selectivity for 5-HT_2 vs D_2 receptors.[77] A series of benzimidazolones (55) have also been described by Damour and coworkers, to be selective for 5-HT_2 antagonism.[78]



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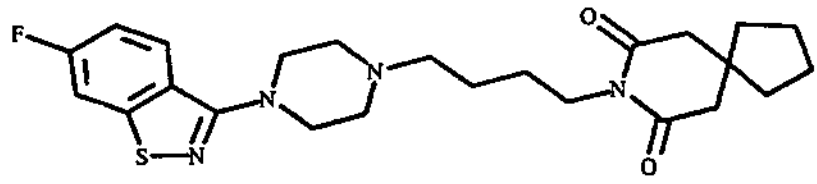

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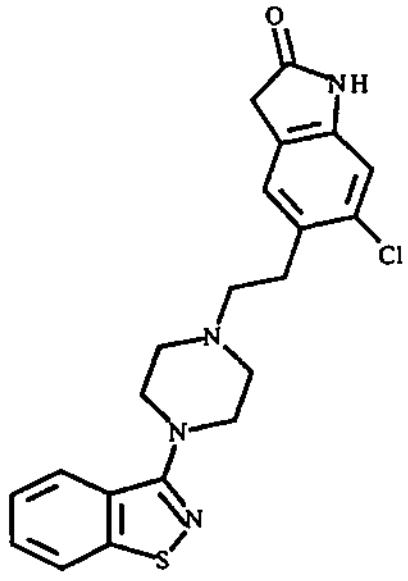

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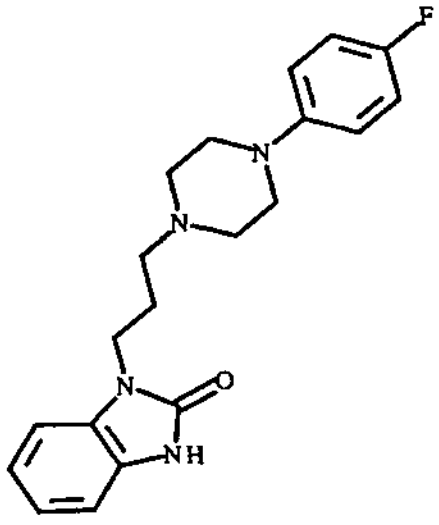
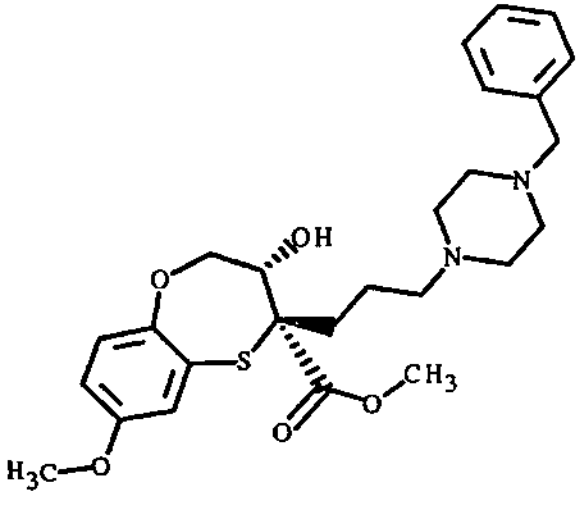


(55)

Newer 5-HT_2 receptor antagonists reported are (+) CV-5197 (56) by Devaud and Hulligsworth, and a naphthosultam [RP-62203] (57) by Janssen and coworkers, wherein both have shown potent affinity for the 5-HT_2 receptor and also possess long lasting 5-HT_2 antagonism.[79,80]



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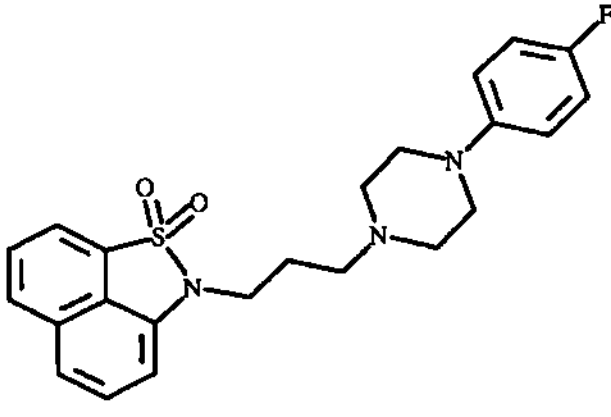
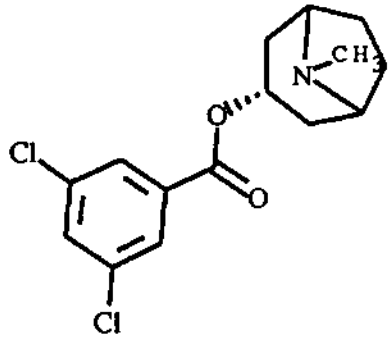


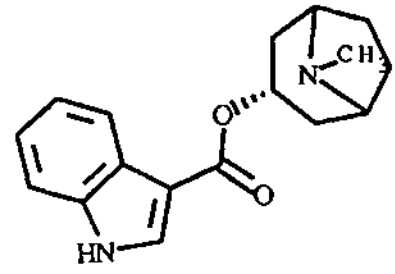
(57)

5-HT_3 receptors are found to be exclusively associated with neurones of both central[81] and peripheral[82] origin. The majority of putative indications for 5-HT_3 receptor compounds include anxiety,[83] migraine,[84]schizophrenia[85] and cognition disorders.[86]

Many 5-HT_3 receptor antagonists also have affinity for the 5-HT_4 receptor. A large number of compounds have been prepared which bind at the 5-HT_3 receptor as antagonists, many of them are clinically effective in reducing the nausea caused by radiation and chemotherapy in cancer treatment.[87,88] These compounds are structurally unique compared to agents with high affinity for the other 5-HT receptor subtypes. Most analogs fall into two general structural classes, the tropine-like (bridged bicyclic amines) and the imidazole-containing compounds. The two early examples, MDL-72222 (58) and tropisetron [ICS-205930] (59), were reported by Marty and coworkers, to have anti-emetic properties.[89] In addition (59) also possesses affinity for 5-HT_4 receptor and is currently available as a 5-HT_4 antagonist.



(58)



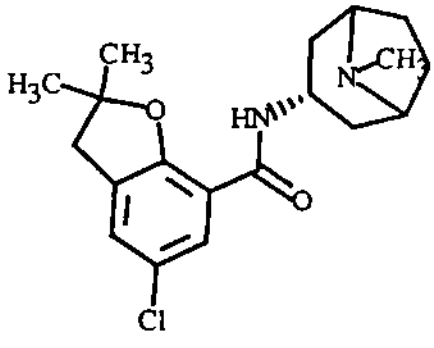
(59)

The main focus of interest in the 5-HT_3 mediated models of emesis inhibition is due to interest in developing drugs as conjuncts to cancer chemotherapy. Cancer radiation and cancer chemotherapy increase the level of 5-HT in the area postrema as well as activating sensory fibers in the gut, leading to nausea.[90] The anti-nausea effect of these 5-HT_3 antagonists is believed to be due to their antagonist activity at both peripheral and central 5-HT_3 receptors. Peripherally, it is thought to be the result of blocking the sensory input at the sites of sensory nerve endings in the gut. The central nervous system effect is due to the blockade of 5-HT_3 receptors in the area postrema.

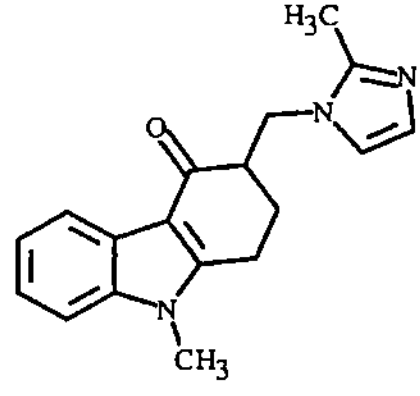
Zatosetron (60) [LY-277359], has been reported by Higgins and coworkers, as a highly selective 5-HT_3 antagonist and has been shown to inhibit emesis in dogs without causing any effect on gastric emptying.[91] Ondansetron (61) [GR-38032] has been shown to be

clinically effective in blocking radiation and cancer chemotherapy induced nausea, and suggested to involve activation of 5-HT_3 receptors in the area postrema. Rasmussen and coworkers have also reported Ondansetron, to possess anxiolytic and antipsychotic actions.[92]

It is to be noted that the presently available 5-HT_3 antagonists *viz.*, zatosetron (60), ondansetron (61) etc., have some drawbacks, i.e., they are effective only for a short period and the activity usually decreases rather rapidly to a degree insufficient for treating a delayed response emesis effectively.[93]



(60)



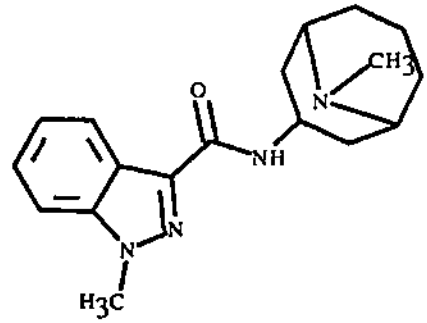
(61)

The key pharmacophoric elements of 5-HT_3 antagonists generally include an aromatic moiety, a linking acyl group, and a basic amine,[94] as are present in the case of drugs like MDL-72222 (58), tropisetron (59) or ondansetron (61). King and Sanger have reported Granisetron (62), [BRL-43694], an indazole derivative to be a potent and highly selective 5HT_3 receptor antagonist.[95] Other 5-HT_3 antagonists include a thiazole ring between the aromatic and basic moieties, and it has been suggested that the nitrogen atom in the thiazole ring may represent a bioisostere equivalent to the carbonyl group.[96,97] In addition, compounds such as quipazine (8) and other arylpiperazines, which bind with high affinity to 5-HT_3 receptors, do not share the above mentioned common structural requirements.

Arylpiperazines, depending upon the presence and location of pendant substituent groups are known to bind at 5-HT_1 and 5-HT_2 sites.[15] With regard to the 5-HT_3 sites, it was hence better to understand the structure-affinity relationships of these aryl piperazines before any rational drug design can be attempted. Glennon and coworkers have

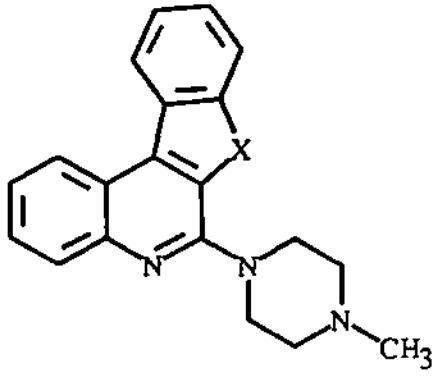
investigated and reported the binding affinities of a series of aryl piperazine derivatives at central 5-HT_3 sites.[98]

Features determined to be important for binding of aryl piperazines include the N-4 piperazine nitrogen atom (but not the N-1 piperazine nitrogen atom). In general, the quinoline nucleus of quipazine imparts a higher affinity than that noted for any of the monocyclic derivatives, and the quinoline nitrogen atom, though not essential, is important for binding.



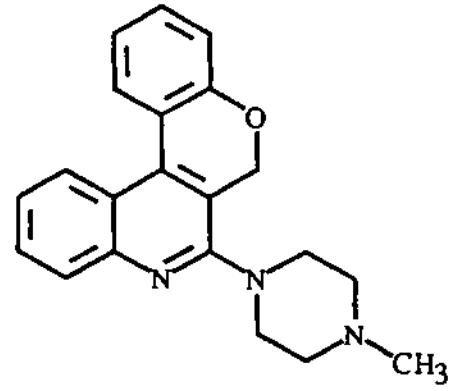
(62)

Quipazine (8), in spite of its high affinity for 5-HT_3 receptors, has not generally been used as a lead for the synthesis of more selective 5-HT_3 antagonists; the reason being its ability to interact with other 5-HT receptor subtypes. As a result, newer research programs were initiated for the discovery of new quipazine derivatives, wherein modifications of the heteroaromatic portion of quipazine (8), such as indeno fusion, reported by Anzini and coworkers, at the *c*-face to yield indenoquipazines (63) and (64). These two derivatives have shown high affinity and selectivity for 5-HT_3 receptors.[99] The affinity and the selectivity for 5-HT_3 sites for the indenoquipazine derivatives (63) and (64) could be modulated by changes in the structure of the heteroaromatic portion. These modifications lead to the discovery of the benzopyrano-[3,4-c]-quinoline derivative (65), also by Anzini and coworkers, which displayed an affinity reported for quipazine (8) along with an improved selectivity, or rather 5-HT_3 receptor antagonism, with potencies in the same range as the best known 5-HT_3 antagonists ondansetron (61), tropisetron (59) etc.[100]



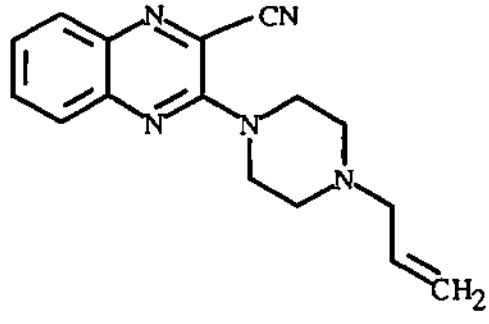
(63) X : C=O

(64) X : CH_2



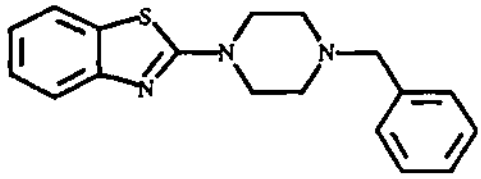
(65)

A series of piperazinyl quinoxaline derivatives were synthesized by Monge and coworkers, and their 5-HT_3 receptor antagonism has been evaluated.[101] Of these, VC-605 (66) a piperazinyl cyanoquinoxaline was evaluated to be approximately three orders of magnitude more potent than ondansetron (61).[102]



(66)

2-Piperazinyl benzothiazole derivative (67) and 2-piperazinyl benzoxazole derivative (68), have also been reported by Monge and coworkers to antagonize the effect of 5-HT at the longitudinal muscle myenteric plexus (LMMP) preparation of the guinea pig ileum.[103]



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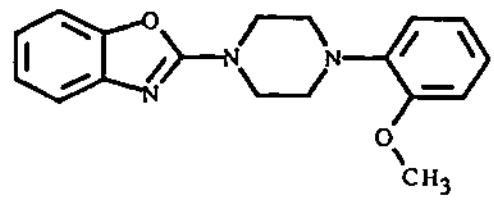
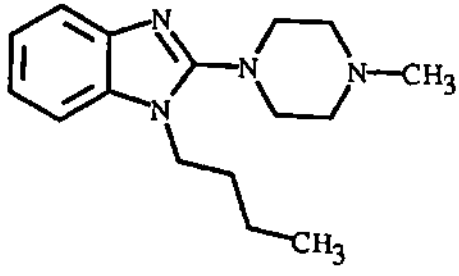
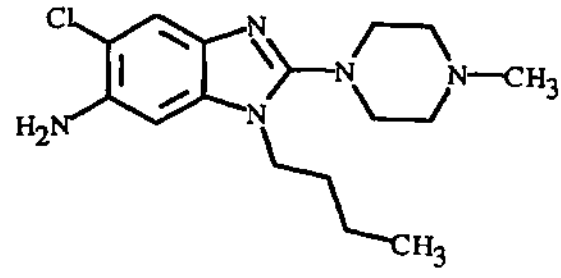


(68)

A series of 2-piperazinyl benzimidazoles were synthesised by Ohtaka and Fujita, and evaluated for their 5-HT_3 antagonism.[104] The antagonism of 2-piperazinyl benzimidazole (69) was reported to be comparable to that of ondansetron (61). Since this particular compound also showed potent histamine H_1-antagonistic activity,[105] the 2-piperazinyl benzimidazole structure was taken as the prototype and structural optimization of the prototype was carried out to make the activity more selective for 5-HT_3 antagonism and increase its potency.[104] Structural optimization of (69) was carried out with the aid of quantitative structure-activity relationship studies (QSAR) and as a result, one of the compounds KB-6933 (70), was found to be the most potent 5-HT_3 antagonist with the lowest toxicity and showed the longest duration as well as the best bioavailability indices among compounds such as ondansetron (61) etc., which were taken as positive control.[104]

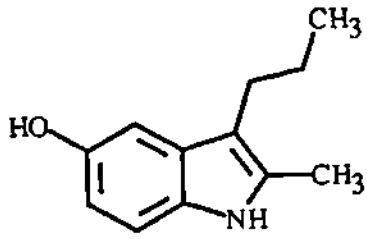


(69)



(70)

While all information on 5-HT_3 antagonists is available, there is little known information on specific 5-HT_3 agonists and their therapeutic potential. The list of the available selective and potent agonists is limited than that for the antagonists, the most frequently mentioned derivatives being the 2-methyl-5-hydroxytryptamine (71), the (m-chloro phenyl) biguanide (mCPBG) [106] (72) and the Quipazine (8).



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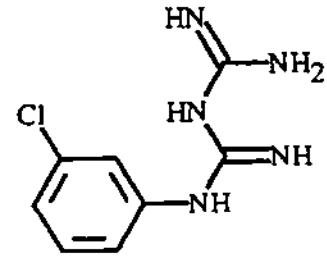
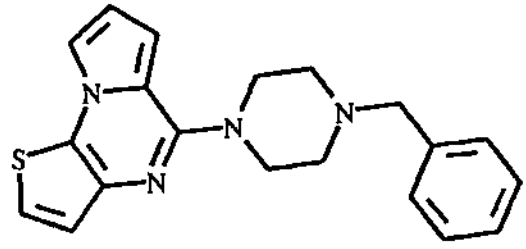


(72)

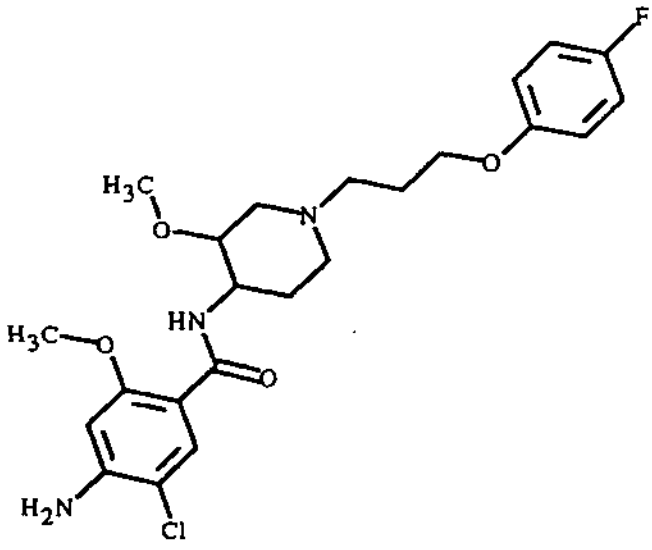
Recently, a series of piperazinopyrrolothienopyrazines (PPTP) were reported by Rault and coworkers as a first attempt towards novel selective and partial agonists of 5-HT_3 receptors.[107] One of the compounds characterized as a partial agonist (73) has shown *in vivo* a potent anxiolytic-like activity at a very low dose.



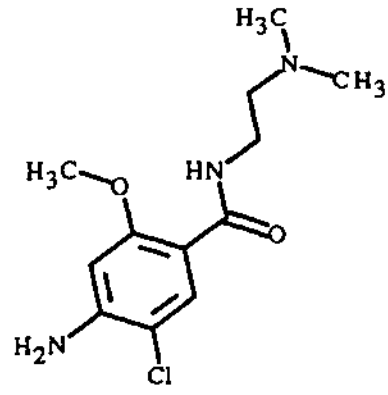
(73)

Receptors of the 5-HT_4 type have been identified both peripherally and centrally.[108,109] Agonists at the 5-HT_4 receptors are reported to cause contractions of the guinea pig ileum and colon , mediated by activation of the cholinergic system, enhancements of "twitch" responses in electrically stimulated guinea pig ileum, and relaxation of the muscularis mucosae preparation. They have also been implicated in certain cardiac effects[110] and in the release of corticotropin-releasing factor (CRF).[111] In the central nervous system 5-HT_4 agonists have been shown to activate adenylate cyclase[109] and induce an increase in electroencephalograph (EEG) energy.[112] The design of potent and selective ligands for the 5-HT_4 receptor opens up avenues to new therapies for gastrointestinal as well as central nervous system disorders. The activity of prokinetic agents of the benzamide class *viz.*, cisapride (74), metoclopramide (75) etc., is attributed to agonism at the 5-HT_4 receptor.[113]

Recently, 2-[1-(4-piperonyl) piperazinyl] benzothiazole, (VB20B7) (76) was reported by Ramirez and coworkers as a novel 5-HT-ergic agent with gastrokinetic activity. It showed a weak affinity for 5-HT_3 receptors like cisapride (74) and lacked affinity at other 5-HT receptors or at dopaminergic D_2 receptor and behaved as a 5-HT_4 receptor agonist.[114]

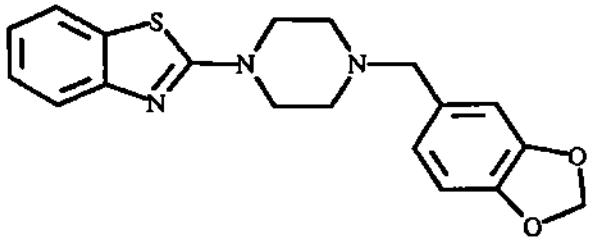


(74)



(75)

A new series of piperazinyl quinoxaline derivatives were synthesized recently, as agents with affinity for peripheral 5-HT_3 and 5-HT_4 receptors. Of these, JB-25 (77) has shown weak antagonism at the 5-HT_3 receptor and prominent 5-HT_4 agonism. The agonistic property of JB-25 (77) is reported to be comparable to that of cisapride (74). The gastro-prokinetic effect of JB-25 (77) has been reported to be mediated through the 5-HT_4 receptor.[115-117]



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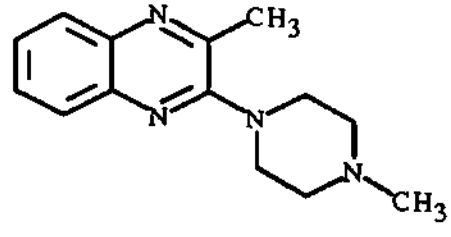
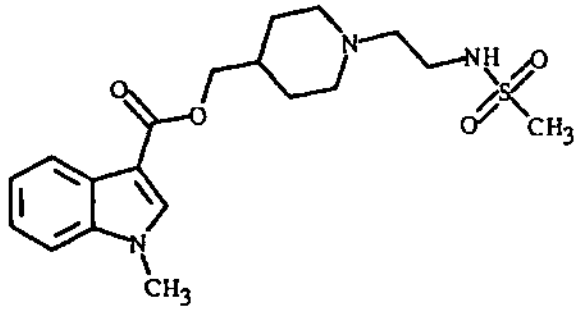


(77)

The possibility of different pathophysiological roles for the 5-HT_4 receptor would seem to conflict with the absence of clear 5-HT_4 receptor-related side-effects that are associated with the widespread use of partial 5-HT_4 receptor agonists, cisapride (74) and metoclopramide (75) in the correction of gut gastroparesis (reflux oesophagitis, dyspepsia, constipation). The physiology of the 5-HT_4 receptor is now being explored with the newly identified, selective 5-HT_4 receptor antagonists.[118] A significant advance in the search for 5-HT_4 receptor antagonists has come with the discovery of GR-113808 (78), which was claimed to be highly potent and selective. The most potent and selective 5-HT_4 receptor antagonist reported so far is SB-204070 (79).[119]



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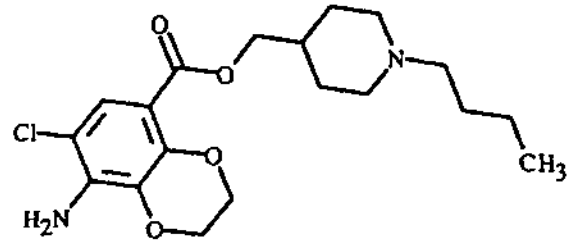


(79)

Putative indications for 5-HT_4 receptor antagonists include transient and prolonged activities, with reference to central nervous system; gastrointestinal tract involving neurogastroenterology, functional bowel disorders and emesis; urinary bladder; cardiovascular effects and on aldosterone secretion.[120] The compounds like GR-113808 (78) and SB-204070 (79) will no doubt help to further refine the characterization of this receptor, but more importantly they will be useful to define the ultimate therapeutic potential for this class of agents.[119]

The design of specific agonists and antagonists for each receptor system offers much promise for new drug development. The various representative agonists and antagonists acting at 5-HT receptor subtypes launched and under clinical trials is given in Table 2. The therapeutic potential of agonists and antagonists at 5-HT receptor subtypes as described in current literature and patents is presented in Table 3.

Table 2. Agonists and antagonists at 5-HT receptor subtypes launched (year of Introduction) and under clinical trials.

5-HT$_{1A}$ Agonists/Partial Agonists	*5-HT$_2$ Antagonists*
Buspirone HCl (1985)-Bristol-Myers Squibb	Amperozide* - Ferrosan
Flesinoxan hydrochloride - Duphar	ICI-204636* - Zeneca
Gepirone hydrochloride - Bristol-Myers Squibb	Ketanserin (1988) - Janssen
Ipsapirone hydrochloride - Bayer	Risperidone* - Janssen
Lesopitron hydrochloride - Esteve	Ritanserin - Janssen
Tandospirone citrate - Pfizer	RP-62203 - Rhone-Poulenc Rorer
Zalospirone hydrochloride - Wyeth-Ayerst	Sertindole* - Lundbeck
	Ziprasidone* - Pfizer
5-HT$_{1A}$ Silent Antagonists	
SDZ-216525 - Sandoz	*5-HT$_{1D}$ Agonists*
WAY - 100135 - American Home Products	Sumatriptan succinate (1991)- Glaxo
5-HT$_3$ Antagonists	*5-HT$_4$ Agonists (also 5-HT$_3$ Antagonists)*
Alosetron hydrochloride - Glaxo	Cisapride hydrate (1988) - Janssen
Azasetron hydrochloride - Yoshitomi	FK-1052 - Fujisawa
BRL-46470A - SmithKline Beecham	Metoclopramide (1964) - Delagrange
DAU-6215 - Boehringer Ingelheim	Renzapride HCl - SmithKline Beecham
Dolasetron Mesylate - Marion Merrell Dow	
Granisetron HCl (1991) - SmithKline Beecham	*5-HT$_4$ Antagonists*
Ondansetron hydrochloride (1990) - Glaxo	GR-113808 - Glaxo
Tropisetron (1992) - Sandoz	SB-204070 - SmithKline Beecham
WAY-100289 - American Home Products	
YM-060 - Yamanouchi	
Zacopride - Delalande	
Zatosetron Maleate - Lily	

* Also dopamine D_2 antagonist

Table 3. Therapeutic applications of agonists and antagonists at 5-HT receptor subtypes, as described in current literature and patents.

5-HT$_{1A}$ Agonists	***5-HT$_2$ Antagonists***
Anxiety	Anxiety
Depression	Depression
Obsessive compulsive behavior	Psychoses
Alcohol abuse	Migraine
Cognition disorders	Alcohol abuse
Eating disorders	Drug dependency
Sexual dysfunction	Cognition disorders
Sleep apnea	Eating disorders
Hypertension	Sexual dysfunction
Congestive Heart Failure	Sleep disorders
Gastric Ulcer	Hypertension
	Thrombosis
5-HT$_{1A}$ Antagonists	
Anxiety	***5-HT$_3$ Antagonists***
	Emesis secondary to cytotoxic drugs
5-HT$_{1B}$ Agonists	Anxiety
Obesity	Psychoses
	Depression
5-HT$_{1C}$ Antagonists	Migraine
Sleep disorders	Cognition disorders
Anxiety	Irritable bowel syndrome
Migraine	Visceral pain
Depression	
	5-HT$_4$ Agonists
5-HT$_{1D}$ Agonists	Gastrointestinal motility disorders
Migraine	
	5-HT$_4$ Antagonists
5-HT$_{1D}$ Antagonists	Gastrointestinal disorders
Depression	CNS & CVS disorders
	Urinary Bladder disorders

Serotonergic ligands belong to relatively few chemical families (Table 4). However, (a) a significant amount of bioisosteric replacement is allowed, and (b) substituent groups (specific groups and spacer lengths) can dramatically alter potency (agonist or antagonist potency), intrinsic activity, affinity and selectivity. This has resulted in an enormous number of serotonergic agents that now number in the hundreds, if not thousands. The classification given in Table 4 encompasses most major classes of serotonergic ligands; however, many bioisosteres are not listed separately but are considered here as belonging to the category with which they are bioisosteric. In addition, too little is known about selective ligands for certain types of serotonin receptors (e.g. 5-HT_5, 5-HT_6 and 5-HT_7) making chemical classification of agents for these receptors premature at this time.

One of the newest, and certainly one of the least investigated, is the 5-HT_5 population. Plassat and coworkers first described the mouse 5-HT_5 receptors and it was demonstrated soon thereafter that there are two different members of the 5-HT_5 family: 5-HT_{5A} and 5-HT_{5B} receptors.[121,122] It has been speculated that 5-HT_5 receptors may be involved in brain development[122] and non-neuronally, the regulation of gliosis. Because disruption of serotonergic neuronal-glial interactions is thought to play a role in several CNS pathologies, including Alzheimer's disease, Down's syndrome and drug-induced developmental deficits, 5-HT_5 receptor ligands might represent a novel class of potentially useful psychotherapeutic agents.[123] 5-HT_{5A} receptors are positively coupled to adenyl cyclase , whereas the 5-HT_{5B} receptors are G-protein coupled,but not coupled to adenyl cyclase or phospholipase C.[124] To date, no 5-HT_5 selective agents have been reported. 5-HT binds only with modest affinity at 5-HT_{5A} receptors. Development of selective agents generally requires one of the two approaches: (a) screening of a large number of agents, or (b) application of structure affinity relationships to specifically design novel agents. No structure affinity investigations have been reported for 5-HT_{5A} and 5-HT_{5B} binding.

Unlike the classic 5-HT receptors, the 5-HT_6 receptor was first discovered by cloning from rat striatal cDNA but had not been previously identified as a pharmacological entity in physiological or radioligand binding experiments.

Table 4. Chemical Classification of Serotonergic Agents

5-HT$_{1A}$ Ligands	(a) Indolealkylamines	Tryptamines	
		Ergolines	
		Partial ergolines	
		Other indolealkylamines	
	(b) 2-Aminotetralins		
	(c) Arylpiperazines	Simple arylpiperazines	
		Long-chain arylpiperazines	
	(d) Aryloxyalkylamines		
	(e) N-Alkylpiperidines		
	(f) Miscellaneous		
5-HT$_{1B}$ Ligands	(a) Indolealkylamines		
	(b) Simple arylpiperazines		
5-HT$_{1D}$ Ligands	(a) Indolealkylamines		
	(b) Miscellaneous agents		
5-HT$_2$/5-HT$_{1C}$ Ligands	(a) Indolealkylamines	Tryptamines	
		Ergolines	
		Others	
	(b) N-Alkylpiperidines	Acylpiperidines	
		Piperidine methanols	
	(c) Arylpiperazines		
	(d) Phenylalkylamines		
	(e) Tricyclic analogues		
	(f) Miscellaneous agents		
5-HT$_3$ Ligands	(a) Indolealkylamines		
	(b) Arylpiperazines		
	(c) Arylbiguanides		
	(d) Keto compounds	Benzoic acids derivatives	
			Benzoates
			Benzamides
		Ketoindoles	
			Indolecarboxylic esters
			Indolecarboxamides
			Benzimidazoles
			γ-Carbolines
			Carbazoles
		Ureas and carbamates	
		Heteroaryl acid derivatives	
	(e) Miscellaneous agents		
5-HT$_4$ Ligands	(a) Ketocompounds		
		Benzamides	
	(b) Arylpiperazines		
	(c) Heteroaryl acid derivatives		
	(d) Miscellaneous agents		

The 5-HT_6 receptors are positively coupled to adenyl cyclase and may be involved in modulation of acetylcholine release in the brain. Many nonselective compounds, such as tricyclic antidepressant drugs and a large number of antipsychotic agents, tryptamine, and ergoline derivatives, interact with the 5-HT_6 receptor. Because no selective ligands are available, identification of functional 5-HT_6 receptors in physiological preparations can be only tentative.[125]

The recently cloned 5-HT_7 receptor seems to be a suitable candidate for responses mediated by the atypical, sumatriptan-insensitive 5-HT_1-like receptors. 5-HT_7 receptors are positively coupled to adenyl cyclase and may be involved in sleep/wake rhythms. Todate, no selective 5-HT_7 receptor ligands have been reported.[126]

The tremendous recent interest and advances in serotonin receptors, coupled with the intensive research programs in industry and academia for selective agonists and antagonists at the various 5-HT receptors and its subtypes, offer great promise for the development of important new therapeutic agents.

Chapter - 2

STATEMENT

OF

PROBLEM

The neurotransmitter serotonin has been implicated to play a vital role in the control of appetite, memory, thermoregulation, sleep, sexual behavior, anxiety, depression and hallucinogenic behavior. The exact role of serotonin i.e., primary or modulatory in nature is yet to be established; nevertheless, it does seem to be involved in numerous actions that would be difficult to explain on the basis of the interactions of a single neurotransmitter with a single type of receptor. The recent discovery of multiple populations of central serotonin binding sites has brought about a renewed interest in this neurotransmitter, particularly in the light of the possibility that its interaction with different types of central sites might explain its various actions. There has been a spillover effect in that there is also increased interest in peripheral serotonergic systems.

The entire issue of central serotonin binding sites is relatively new, fraught with controversy, and still in the developmental stage. New binding sites are being reported, multiple-state binding and regulatory processes are being examined, and the functional significance of these sites is being explored. This is probably the most exciting period that serotonin has enjoyed since the pioneering days of serotonin research in the late 1950s and early 1960s.

One of the most significant problems facing serotonin research today is a lack of site-selective agonists and antagonists; a continued lack of such tools surely has retarded further advances in this field. Investigations of functional correlates of central binding, are highly dependent upon the availability of these tools; i.e., site-selective agonists and antagonists.

In general, the chemical neurotransmitter amines by themselves act as agonists at the respective receptor. These chemical neurotransmitter amines have such common structural elements as an aromatic ring and an aminoethyl side chain. The specific pharmacology which the neurotransmitter amine, serotonin displays, is related to the specific physicochemical characteristics of the aromatic moiety. The binding specificity of the aromatic moiety could be controlled by the hydrogen-bond formation and electrostatic functionalities on or within the aromatic ring in addition to the hydrophobic bonding of the entire ring structures with counterparts on receptors. The side chain amino

group, which exists in a protonated form under physiological conditions, will interact with anionic sites of receptors, the characteristics of which depend upon the aromatic structures in individual amines.

Analogs of neurotransmitter amines "properly" modified at the aromatic and/or side-chain moieties are expected to interact with the receptor sites in manners very similar to endogenous agonists and to retain respective agonistic activities. This means that, even if the structures belonging to a certain agonist class seem to be miscellaneous, there should be topographical arrangements of functional moieties (pharmacophores) in nearly common manners essential for the interactions with corresponding receptor sites. Structural modifications such as those resulting in distortions of physicochemical features of the pharmacophore, introduction of unnecessary substructural elements and elimination of essential functional groups are expected to lead to antagonists.

The current interest involves the study of modulatory role of central serotonergic receptors. Arylpiperazines and Indolylalkylamines are the prominent structural classes of compounds (Table 4) with affinity for all of the 5-HT receptor subtypes. Selectivity for a particular 5-HT receptor subtype is normally achieved by the incorporation of appropriate substituent groups on the piperazinyl nitrogen. The lipophilicity of the aryl group in arylpiperazines plays an important role in determining the central nervous system activity.

Considerable interest has been generated in the study of indole-containing compounds in biological systems. The prominent indole derivatives aimed at central nervous system activities include indoleacetamides, glyoxamides and tryptamines; all of them could be directly or indirectly belong to the parent class of indolylalkylamines. The central nervous system activities associated with the above categories of indoles and other miscellaneous indole derivatives include behavior, potentiation of hexobarbital-induced sleep, inhibition of motor activity, antagonism of bufotenine induced pawing, potentiation of antagonism of a number of agents and *invitro* inhibition of enzymes. In addition, various other derivatives of indole have been tested and reported to have

diuretic, hypotensive, pharmacodynamic, anti-inflammatory, hypoglycemic, uterine relaxant and antifertility properties.

In lieu of the promising central nervous system activities, which the indole moiety is capable of exhibiting, the incorporation of a suitable arylpiperazine as the amine in an indolylalkylamine offers scope for the discovery of new chemical substances with serotonin-modulatory effects for prospective central nervous system activities.

Hence, the initial attempt was to synthesize a ***new arylpiperazine***, and its substitution products for central nervous system activities as the first series in this investigation. The second series in this investigation involves the synthesis of suitable ***indolylalkylamines***, incorporating known arylpiperazines as the amine component as serotonin modulators for prospective central nervous system activities.

Most arylpiperazines reported todate comprise an aromatic phenyl; substituted phenyl (2,3 and 4-chloro and methoxy; 4-fluoro; 3-trifluoromethyl etc.,); benzfused phenyl (1&2-naphthyl; 1-indanyl etc.,); heteroaryl (2-pyridyl and pyrimidinyl etc.,); benzfused heteroaryl (2-quinolinyl; -quinoxalinyl; -quinazolinyl; -benzimidazolyl; -benzoxazolyl; -benzothiazolyl etc.,) groups attached to one of the piperazinyl nitrogen atom. All such arylpiperazines have been reported to have peripheral actions along with anticipated central serotonergic modulatory effects.

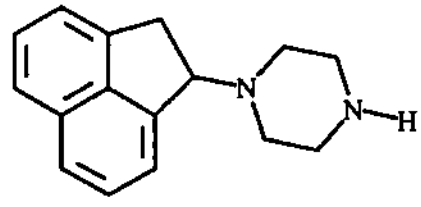
In order to target an ***arylpiperazine*** for specific action on the central nervous system, lipophilicity of the aryl group was chosen as the main criteria and the fact that, carbocyclic systems offer a higher lipophilic potential than heterocyclic systems, was kept in mind while searching for a new arylpiperazine with potential central nervous system activities.

Carbocyclic systems such as 1-Naphthyl piperazine (7) and 2-Naphthyl piperazine (9) have been reported to have affinities at the 5-HT_1 and 5-HT_2 sites respectively, which are the predominant 5-HT receptor subtypes in the central nervous system.[22,24]

The antagonists of the 5-HT_2 receptors have been reported to have potential use as antipsychotic agents.[127,128]

RP-62202 (57), a naphthosultam derivative, comprising a 4-fluorophenyl piperazine moiety, has been reported to have potent affinity for the 5-HT_2 receptor with long lasting antagonism,[80] indicating that the naphthosultam moiety plays a major role in determining the affinity for the 5-HT_2 receptor type.

The carbocyclic bioisostere of naphthosultam, i.e., 1,2-dihydroacenaphthylene was therefore chosen as the aryl component, which would offer high lipophilicity onto which the incorporation of the piperazine moiety could be brought about to afford a new arylpiperazine - 1,2-dihydro-2-acenaphthylenyl piperazine.

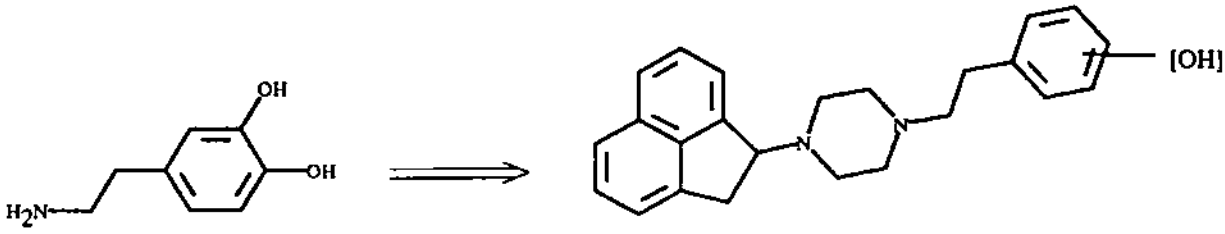


The first stage in the present investigation was to establish a method to synthesize, characterize and to evaluate the new aryl piperazine, i.e., 1,2-dihydro-2-acenaphthylenyl piperazine and its substitution products [Type I and II] as serotonin modulators for prospective central nervous system activities.

Majority of clinically effective antipsychotic agents have been reported to have characteristically high affinity for Dopamine (D_2) sites and produce extrapyramidal side-effects (EPS). It has also been suggested that properly balanced D_1/D_2 receptor interactions in combination with 5-HT_2 receptor blockade favour an atypical antipsychotic profile,[129] having greater clinical efficacy, and/or reduced liability to produce EPS. The combination of dopaminergic and serotonergic antagonistic activity necessary for antipsychotic activity with minimum EPS liability offers the prospect of a novel "atypical" antipsychotic agent.

The strategy adopted to achieve incorporation of the requisite dopamine-blocking activity into the serotonergic 1,2-dihydro-2-acenaphthylenyl piperazine nucleus is based on the concepts established by Ariens.[130] Briefly, this approach involves modification of

the structure of a receptor agonist, i.e., dopamine, with a large serotonergic lipophilic group on the amino position, which binds to the *accessory binding site* adjacent to the agonist binding site and transforms the agonist into an antagonist. With 1,2-dihydro-2-acenaphthylenyl piperazine as the serotonergic lipophilic group connected to the basic amine, the modification shown below can be envisaged.



Dopamine, agonist *Dopamine antagonist*

It was of our interest to test the hypothesis that whether hydrogen-bonding (donating or receiving) group is necessary to mimic the catechol group of dopamine. This hypothesis is based on studies of the β_2 adrenergic receptor, which show a pair of serine residues that coordinates with the catechol group of noradrenaline.[131] A similar pair of serine residues is present in the analogous position in the sequence determined for the cloned dopamine (D_2) receptor gene.[132]

In the case of 1,2-dihydro-2-acenaphthylenyl piperazine moiety (bound at the accessory binding site), an appropriate hydrogen-bonding group could be held by a phenethyl side chain so as to reach these serine residues, as shown in the depiction of D_2 receptor in figure 2.

In this figure, which is based on a published model of the β-adrenergic receptor,[133] the trans-membrane helices which comprise the ligand binding domain of the receptor are viewed end-on from above the plane of the membrane and are arranged in analogy to the structure found from low-resolution X-ray studies of rhodopsin.[134] The residues that interact with dopamine are then depicted as projecting from their respective helices, and the proposed accessory binding site is depicted at one end of the ligand binding site where only antagonists can reach it.

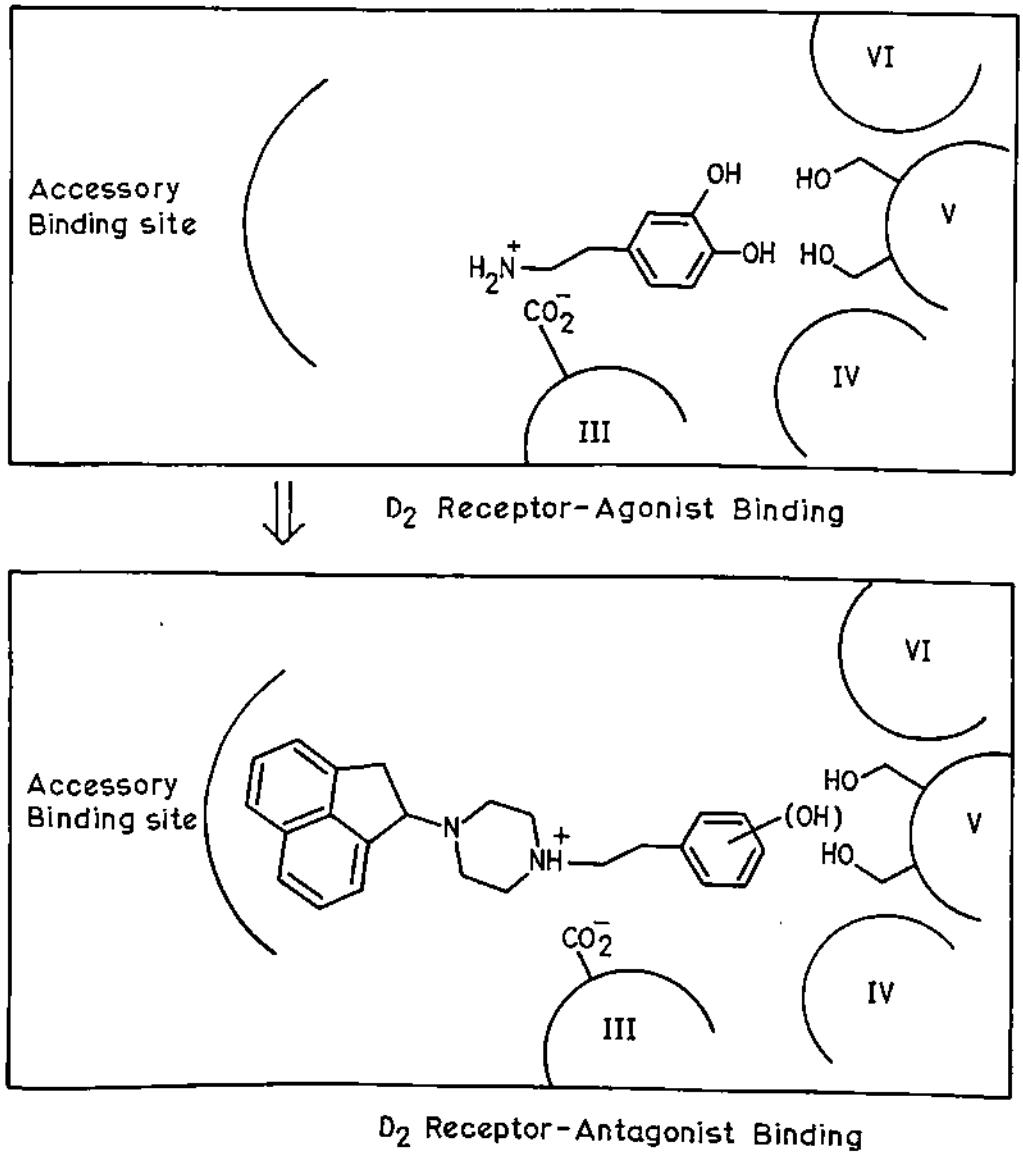


Figure 2. Model of D_2 Receptor, based on studies of the β-adrenergic receptor, showing proposed agonist and antagonist binding sites in Receptor antagonist design.

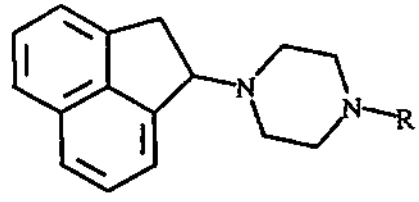
Therefore, heterocyclic groups, both fused and appended to the phenethyl side chain were selected, which would offer various modes of hydrogen-bonding interactions with the D_2 receptor serine residues. There is considerable literature precedent for the molecules of the appended type [Type III] (heterocyclic groups appended to the phenethyl side chain)[135] and fused type [Type IV] (heterocyclic groups fused to the phenethyl side

chain)[136] as ligands for the dopamine D_2 receptor, which suggests that the interactions being envisaged are reasonable.

Based on literature reports,[135,136] 2- and -5- substituted thiazoles were chosen which were appended to the phenethyl moiety and 5-(2-chloroethyl)-1,3- and-6-substituted-2,3-dihydro-1*H*-indole-2-ones and an isosteric 6-(2-bromoethyl)-benzoxazol-2(3*H*)-one, were chosen as the fused heterocyclic groups, that would offer various modes of hydrogen-bond interactions with the D_2 receptor serine residues.

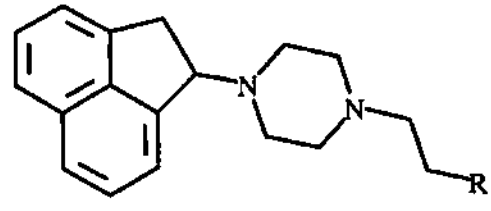
The molecules proposed for synthesis in this series are

Type I



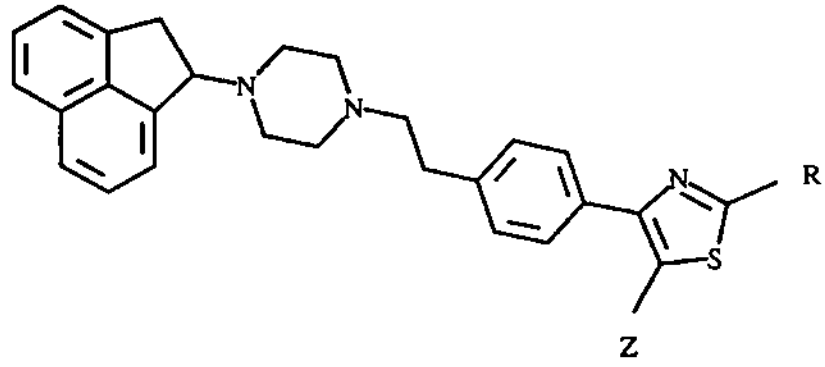
Where, R = methyl, ethyl, n-propyl, isopropyl, n-allyl and n-butyl
phenyl, 3-chlorophenyl, 4-chlorophenyl, 4-fluorophenyl, 2-methoxy phenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3-trifluoromethyl phenyl, 2-pyridyl, 2-pyrimidinyl, benzoyl, 4-fluorobenzoyl and piperonyl

Type II



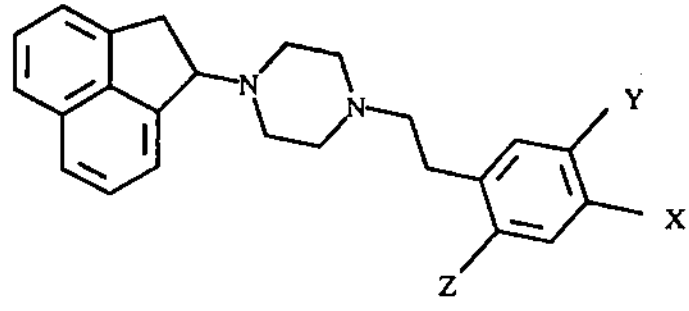
Where, R = hydroxy, amino, dimethylamino, diethylamino, pyrrolidinyl, piperidinyl, morpholinyl and phenyl

Type III



Where,		
	$R = NH_2$	$Z = H$
	$R = CH_3$	$Z = H$
	$R = NH_2$	$Z = CH_3$
	$R = NH\text{-}CH_3$	$Z = H$
	$R = NH\text{-}CH_2\text{-}CH{=}CH_2$	$Z = H$
	$R = OH$	$Z = H$

Type IV



Where,	----X--------Y----	Z
	$NH\text{-}CO\text{-}CH_2$	H
	$N(CH_3)\text{-}CO\text{-}CH_2$	H
	$NH\text{-}CO\text{-}CH(CH_3)$	H
	$N(CH_3)\text{-}CO\text{-}CH(CH_3)$	H
	$N(C_2H_5)\text{-}CO\text{-}CH_2$	H
	$NH\text{-}CO\text{-}CH_2$	Cl
	$NH\text{-}CO\text{-}CH_2$	F
	O-CO-NH	H

The second series of molecules involved the synthesis of various piperazinyl indolyl propanones (an indolylalkylamine in which the amine is a substituted piperazine) to evaluate their affinity at the 5-HT receptor mediated central nervous system effects.

5-HT [3-(β-aminoethyl)-5-hydroxy indole] itself is an indolyalkylamine. Numerous synthetic or naturally occuring congeners of 5-HT have varying degrees of peripheral and central serotonergic activity. The second series of the study consists of the basic structural class of compounds - the ***indolylalkylamines***.
The major structural features of indolylalkylamines which are to be considered are, *(a)* the terminal amine function, *(b)* the side chain, *(c)* the indole-1 position, and *(d)* other substituents.

Offermeier and Ariens,[137] suggested that the terminal amine group of 5-HT interacts with the receptor in an electrostatic manner. As a result, steric bulk of the amine group plays an important role in determining affinity. These authors have also determined that the terminal amine is a prerequisite function in order to possess an affinity for 5-HT receptors. They have reported that decreasing the length of the side chain from two to one methylene unit decreases the affinity. Increasing the length of the side chain from two to three or four methylene units shows varying affinity for the 5-HT receptor, depending on the other substituents present.

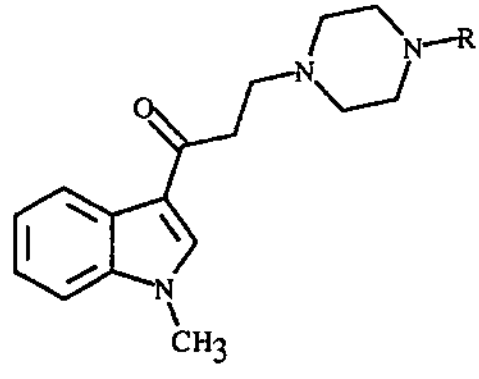
The first position on the indole (NH), is a vital component in determining the affinities for the 5-HT receptor. Depending on the substituent present on the indolyl nitrogen, selectivity can be achieved for a particular 5-HT receptor subtype. The other structural features, which can be considered, include a hydroxyl group at the 5^{th} position, which is a vital component of 5-HT itself. Various indole derivatives have been reported, as already described in first chapter, for their affinity at the 5-HT receptor, which lack the hydroxyl group at the 5^{th} position. Thus, primarily the structural modifications possible are at *(a)* the terminal amine, *(b)* the side-chain and at *(c)* the indolyl nitrogen.

In the present investigation, the primary amine of 5-HT is to be replaced with known substituted arylpiperazines, the reason being the well-known fact that arylpiperazines constitute one of the important structural templates for 5-HT receptor affinities.

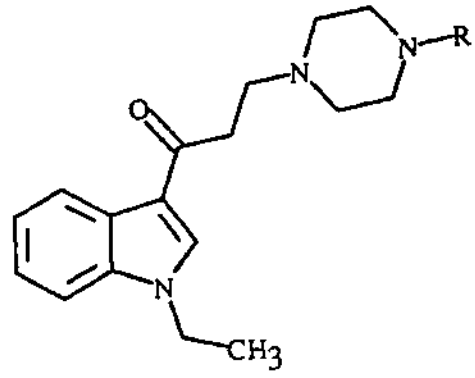
The side-chain length was increased to three methylene units. This is to be brought about by the incorporation of a propionyl group at the 3rd position of the indole nucleus. In this case, the carbon atom attached to the indole nucleus, bears a doubly bonded oxygen atom to provide a carbonyl function in the place of one of the three methylenes - the propionyl side-chain in anticipation that the carbonyl functionality in the sidechain would result in antagonists rather than agonists. The substituent on the indolyl nitrogen determines affinity for 5-HT receptor in a large way and also determines selectivity for a particular 5-HT receptor subtype. Most of the compounds which have an affinity for the 5-HT receptor carry a small alkyl group on the indolyl nitrogen, i.e., a methyl group as in the case of *Ondansetron (61)*, which is a 5-HT_3 antagonist, or a substituted aryl group i.e., 4-fluoro phenyl group as in the case of *Sertindole (51)*, which is an antagonist at the 5-HT_2 receptor and is used as an atypical antipsychotic. This concept of varying the substituent on the indolyl nitrogen (NH) gives varying affinities at different 5-HT receptor subtypes, thereby increasing the therapeutic applications of the molecules. Hence, the substituents proposed, in this investigation are methyl [Type V], ethyl [Type VI], 4-fluoro phenyl [Type VII] and 4-fluoro benzoyl [Type VIII] groups for the indolyl nitrogen.

The molecules proposed for synthesis in this series are

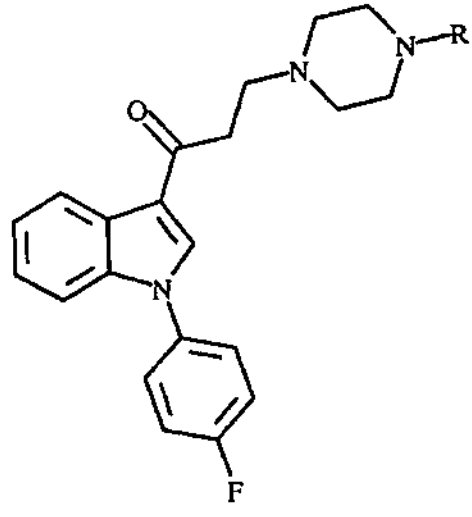
Type V



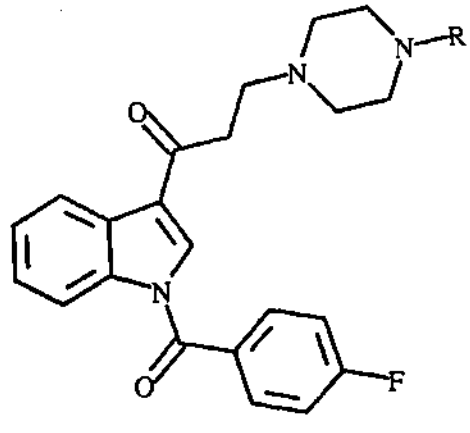
Type VI



Type VII



Type VIII



Where, R = phenyl, 3-chlorophenyl, 4-chlorophenyl, 4-fluorophenyl, 2-methoxy phenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3-trifluoromethyl phenyl, 2-pyridyl and 2-pyrimidinyl

Thus, the specific goal of the present study was :

Series I

(i) To identify and synthesize a new arylpiperazine that would bind at 5-HT sites, with a scope for the development of new molecules with potent central nervous system activities.

(ii) To structurally modify this arylpiperazine by incorporating various substituents at the N-4 nitrogen atom of the piperazine and study the effect of the substitutions for 5-HT sites.

(iii) Evaluation of the new arylpiperazine and its substitution products for 5-HT receptor modulatory activity and it's comparison with standard drug substances available.

(iv) Pharmacological characterization of the new arylpiperazine and its potent substitution products for their affinity at specific 5-HT receptor subtypes and other receptors if any, and their therapeutic application.

Series II

(i) To identify and synthesize a novel indolyl substrate interms of generating an indolylalkylamine.

(ii) To incorporate various substitutions on the indolyl nitrogen, inorder to study their modulatory effects on the 5-HT receptor.

(iii) To incorporate a suitable sidechain with the required number of methylene units on the indolyl substrate identified above.

(iv) To bring about the incorporation of a substituted arylpiperazine moiety as the terminal amine portion at the end of the alkyl side chain.

(v) Evaluation of the new indolyl piperazines for 5-HT receptor modulatory activity and comparison with standard drug substances available.

(vi) Pharmacological characterization of the potent indolyl piperazines for their affinity at specific 5-HT receptors and other receptors if any, and their therapeutic application.

Chapter - 3

EXPERIMENTAL

REACTION

SCHEME

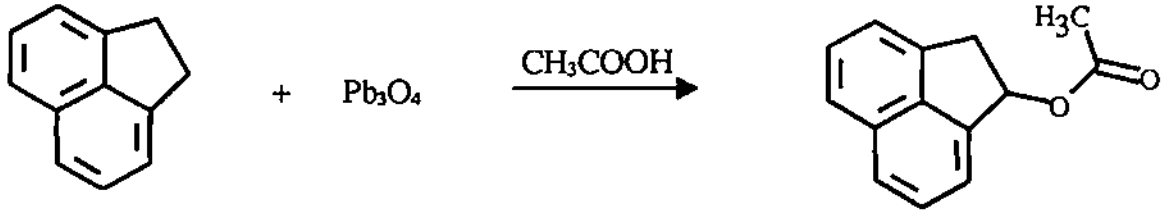
&

EXPERIMENTAL

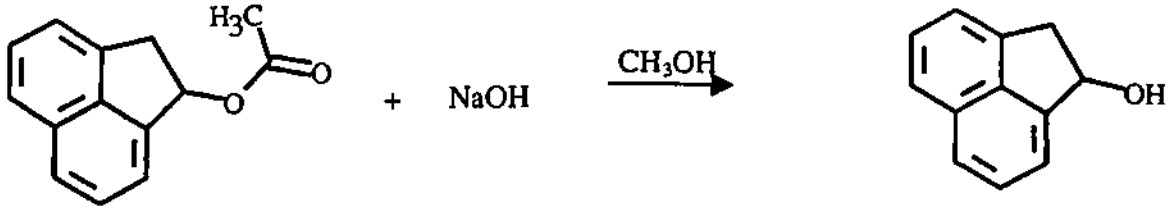
The reaction schemes given below describe the preparation by which the syntheses of the proposed compounds were achieved in this work.

Series – I

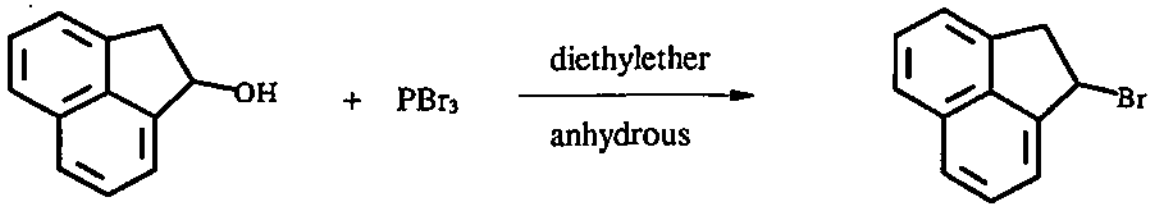
1. Synthesis of 1,2-dihydro-2-acenaphthylenyl acetate



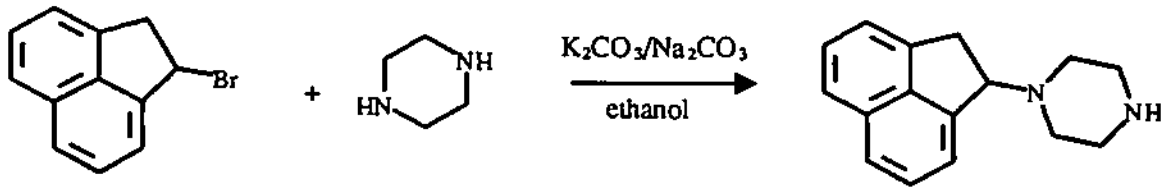
2. Synthesis of 1,2-dihydro-2-acenaphthylenol



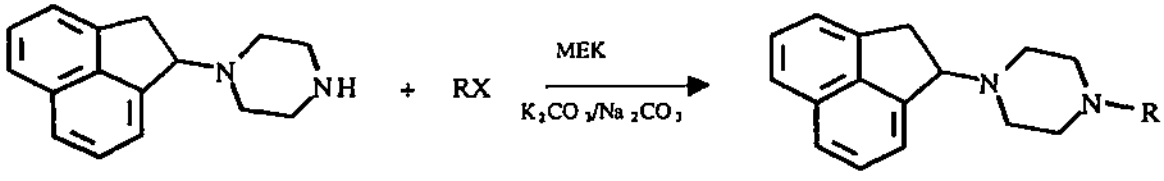
3. Synthesis of 2-Bromo-1,2-dihydroacenaphthylene



4. Synthesis of 1-(1,2-dihydro-2-acenaphthylenyl) piperazine

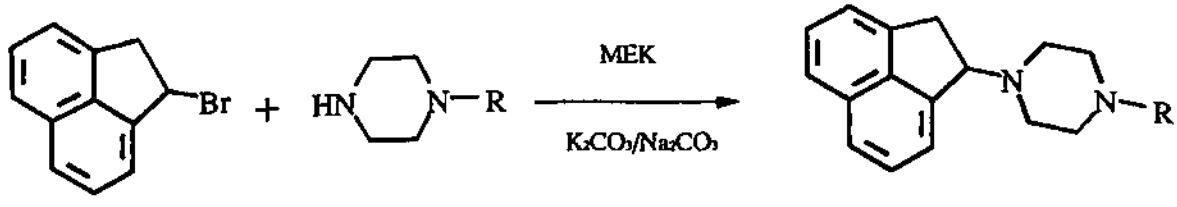


5. Synthesis of N4-Substituted-1-(1,2-dihydro-2-acenaphthylenyl) piperazine



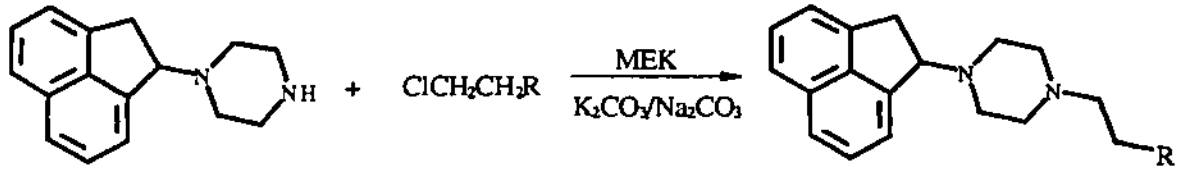
where, R = ethyl
i-propyl
n-propyl
n-butyl
allyl

6. Synthesis of N4-Substituted-1-(1,2-dihydro-2-acenaphthylenyl) piperazines



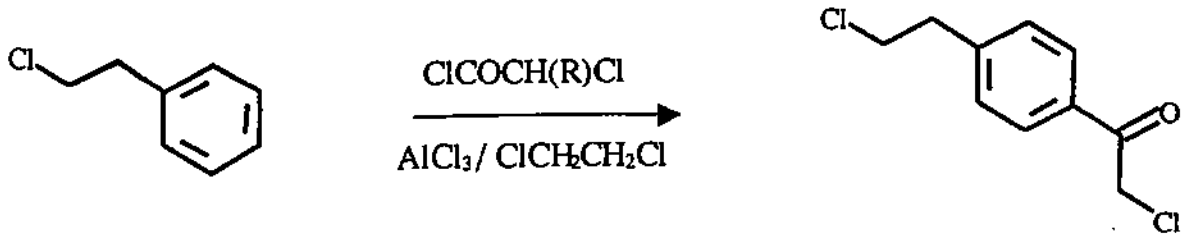
where, R = methyl
phenyl
1-(3-chlorophenyl)
1-(4-chlorophenyl)
1-(4-fluorophenyl)
1-(2-methoxyphenyl)
1-(3-methoxyphenyl)
1-(4-methoxyphenyl)
1-(3-trifluoromethyl) phenyl
1-(2-pyridyl)
1-(2-pyrimidinyl)
benzoyl
1-(4-fluorobenzoyl)
piperonyl

7. Synthesis of 1-(1,2-dihydro-2-acenaphthylenyl)-4-[(2-substituted) ethyl]-piperazines



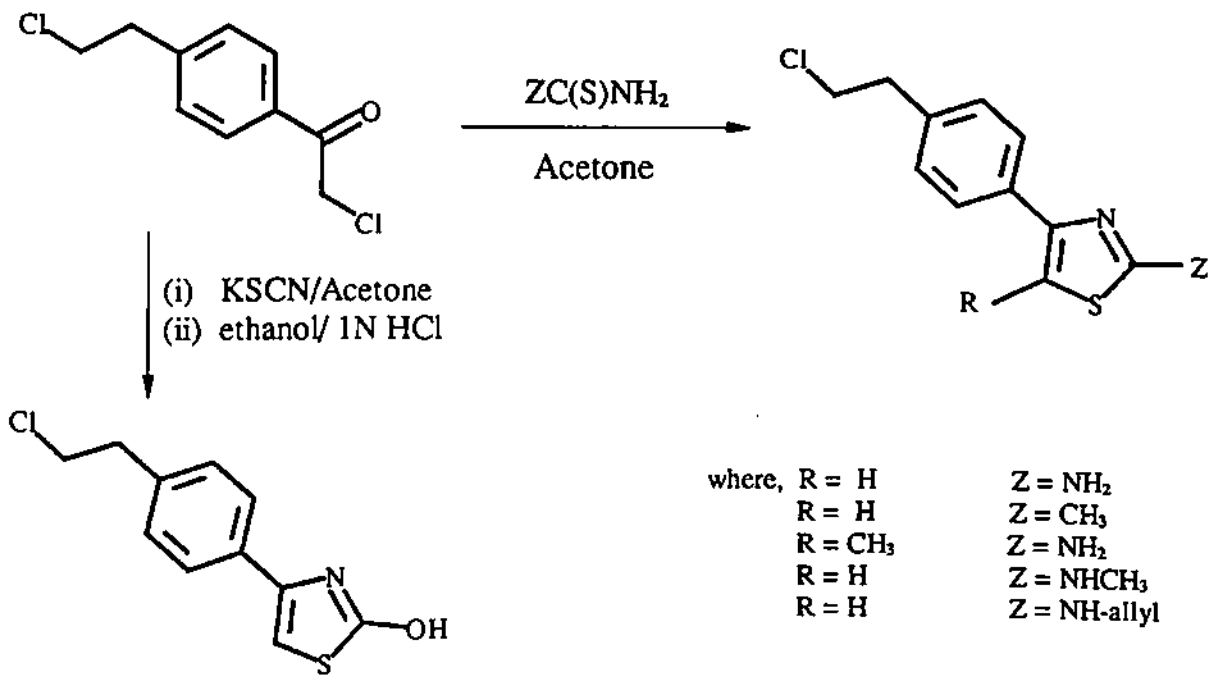
where R = hydroxy
amino
dimethylamino
diethylamino
pyrrolidinyl
piperidinyl
morpholinyl
phenyl

8. Synthesis of 4-(2-Chloroacetyl)-1-(2-chloroethyl) benzenes



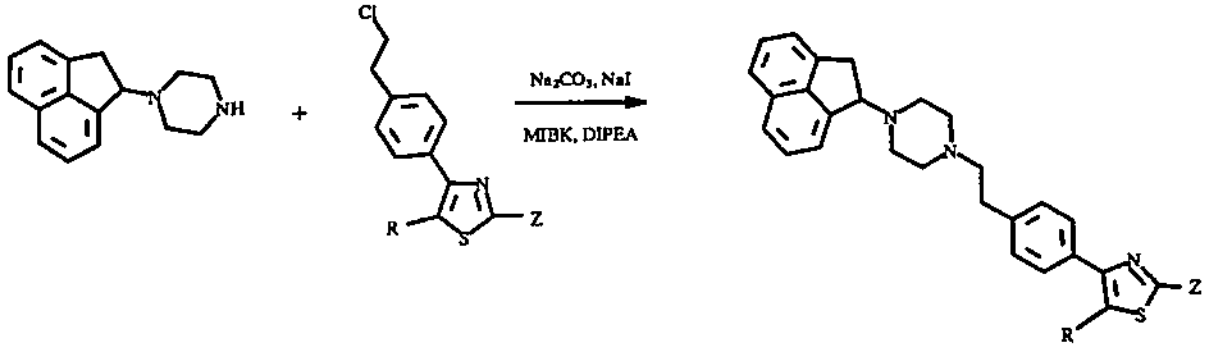
where, R = H
methyl

9. Synthesis of 4-[4-(2-Chloroethyl)phenyl]-2- and -5-substituted thiazoles



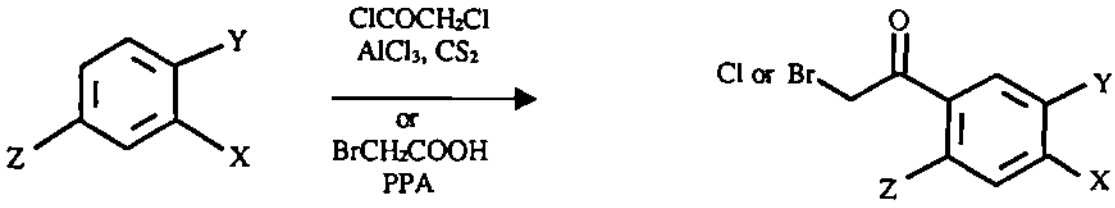
where, R = H Z = NH_2
R = H Z = CH_3
R = CH_3 Z = NH_2
R = H Z = $NHCH_3$
R = H Z = NH-allyl

10. Synthesis of 4-(4-{2-[4-(1,2-dihydro-2-acenaphthylenyl) piperazin-1-yl] ethyl} phenyl)-2- and -5- substituted thiazoles

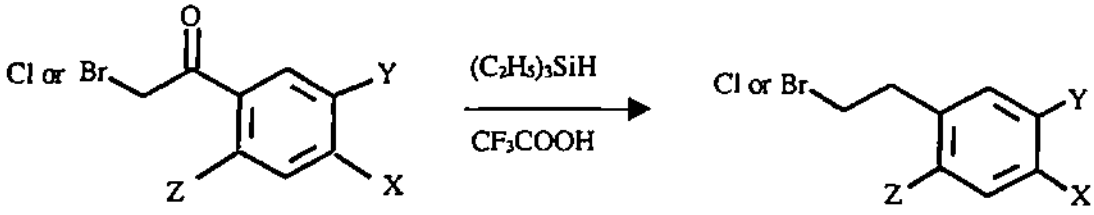


where, R = H Z = NH_2
R = H Z = CH_3
R = CH_3 Z = NH_2
R = H Z = $NHCH_3$
R = H Z = NH-allyl
R = H Z = OH

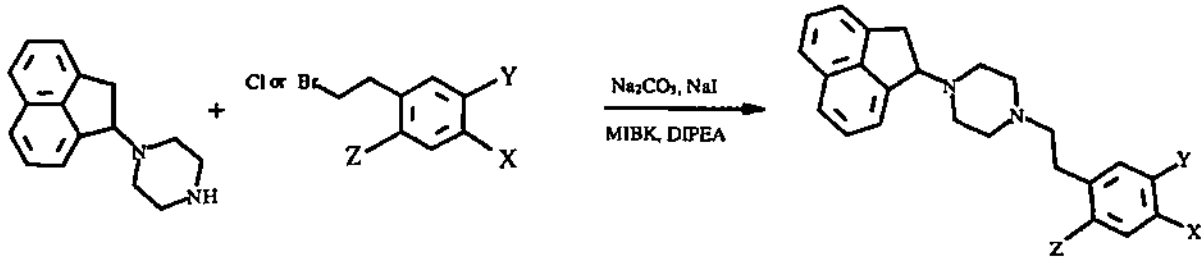
11. Synthesis of 5-(2-Chloroacetyl)-1,3- and -6-substituted-2,3-dihydro-1*H*-indol-2-ones and 6-(2-Bromoacetyl)-benzoxazolin-2(3*H*)-one.



12. Synthesis of 5-(2-Chloroethyl)-1,3-and -6-substituted -2,3-dihydro-1*H*-indol-2-ones and 6-(2-Bromoethyl)-benzoxazolin-2(3*H*)-one.



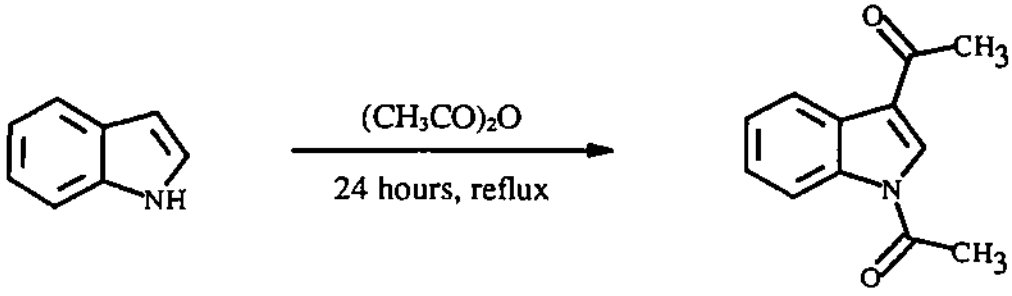
13. Synthesis of 5-{2-[4-(1,2-dihydro-2-acenaphthylenyl) piperazin-1-yl] ethyl}-1,3- and -6-substituted-2,3-dihydro-1*H*-indol-2-ones and 6-{2-[4-(1,2-dihydro-2-acenaphthylenyl) piperazin-1-yl] ethyl}-benzoxazolin-2(3*H*)-one.



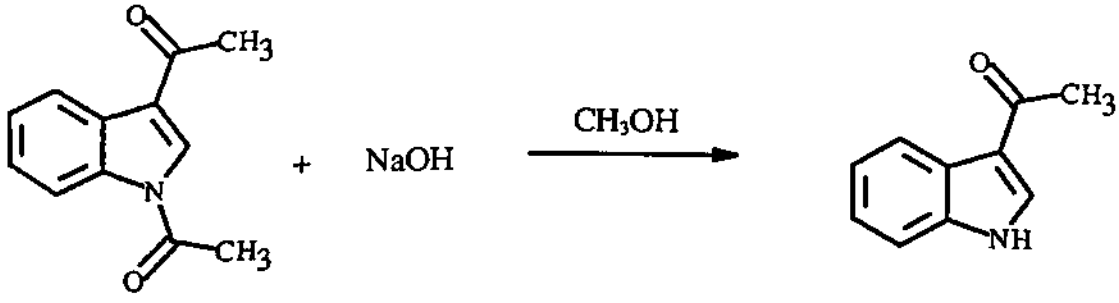
where,	---X---Y---	Z
	NH-CO-CH_2	H
	N(CH_3)-CO-CH_2	H
	NH-CO-CH(CH_3)	H
	N(CH_3)-CO-CH(CH_3)	H
	N(C_2H_5)-CO-CH_2	H
	NH-CO-CH_2	Cl
	NH-CO-CH_2	F
	O-CO-NH	H

Series – II

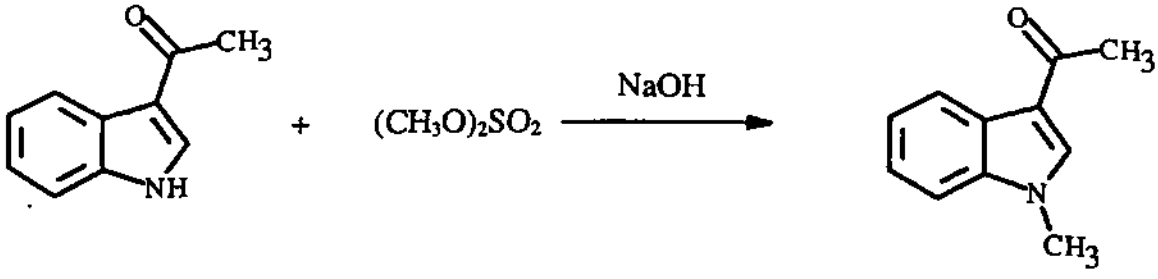
1. Synthesis of 1,3-diacetyl indole



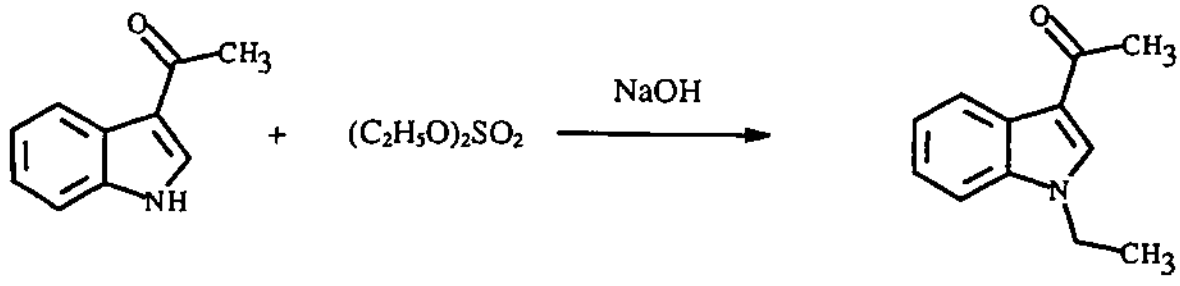
2. Synthesis of 3-acetyl indole



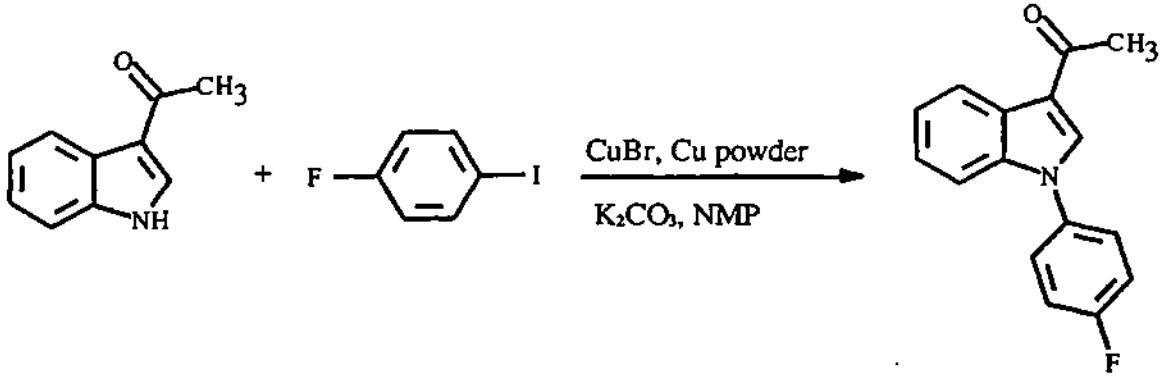
3. Synthesis of N-methyl-3-acetyl indole



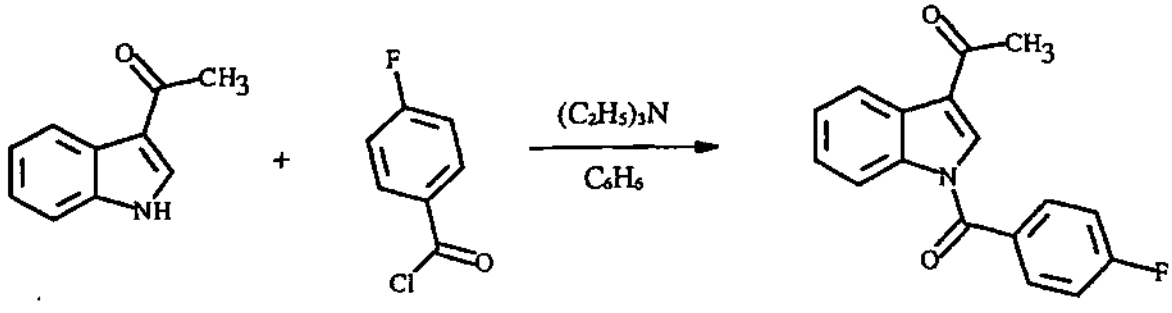
4. Synthesis of N-ethyl-3-acetyl indole



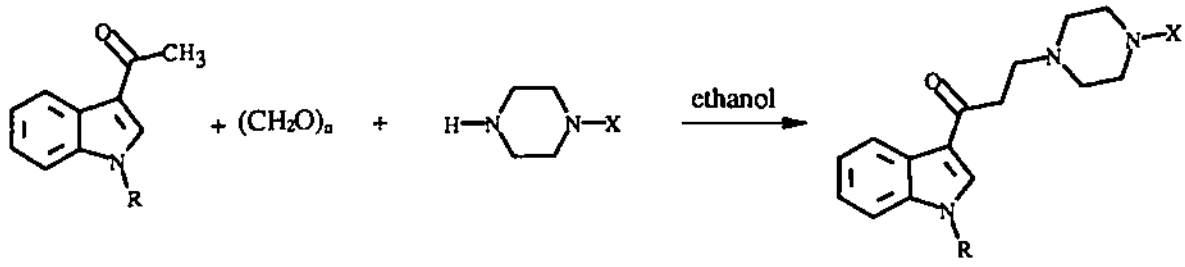
5. Synthesis of N-(4-fluoro phenyl)-3-acetyl indole



6. Synthesis of N-(4-Fluoro benzoyl)-3-acetyl indole



7. Synthesis of (4-substituted piperazin-1-yl) mannich products of N-substituted-3-acetyl indoles



where, R = methyl
ethyl
4-fluorophenyl
4-fluorobenzoyl

X = phenyl
1-(3-chlorophenyl)
1-(4-chlorophenyl)
1-(4-fluorophenyl)
1-(2-methoxyphenyl)
1-(3-methoxyphenyl)
1-(4-methoxyphenyl)
1-(3-trifluoromethyl) phenyl
1-(2-pyridyl)
1-(2-pyrimidinyl)

All melting points were determined on a Buchi model 530 melting point apparatus and are uncorrected. Infrared spectra were recorded on JASCO IR Report-100 Infrared spectrophotometer and are given in cm^{-1} and were recorded as a mull, unless specified. The ^1H NMR spectra, were recorded using Varian EM-390 - 90 MHz NMR spectrophotometer or Brucker AC 300F NMR spectrophotometer or Jeol GSX 400 NMR spectrophotometer and are reported in δ units (ppm) relative to tetramethylsilane as internal standard. Mass spectra were recorded on a Finnigan MAT 8230 spectrophotometer. Elemental analyses are indicated by the symbols of the elements and were within ± 0.45% of the theoretical values.

SERIES – I

1,2-dihydro-2-acenaphthylenyl acetate (80)

The procedure described by Feiser and Cason was adopted for this preparation.[138,139] A solution of 1,2-dihydro-2-acenaphthylene, 154 gm (1 mol) in 1100 ml of glacial acetic acid, was stirred at 60 - 70°C, at which point the source of heat was removed and treated with 820 gm of red lead, added in 50 gm portions as soon as the colour due to the previous portion had been discharged. During this operation, which required 30-40 minutes, the temperature was maintained at 60-70°C by external cooling. Shortly after each addition of red lead, the presence of lead tetra acetate was detected with moistened starch-iodide paper. The reaction was complete when a portion of the solution gave no test for lead tetra acetate. The dark syrupy solution (which contained a few suspended particles of red lead and lead di oxide) was poured into 2 litres of water. An oily product which separated was first extracted with a 350 ml portion of ether and then with a 250 ml portion, respectively. The total extract was washed first with 100 ml of water and then with 300 ml of saturated sodium chloride solution. The extract was finally dried over anhydrous sodium sulphate. The ether was evaporated and the residual oil was distilled under reduced pressure to give 170-175 gm (80-82%) of the acetate which distilled almost entirely at 166-168°C/5mm, as a yellow oil which had a density of 1.21 gm / ml (lit.b.p. 169 °C/5mm).

IR(cm^{-1}) [Neat] :1725 (C=O); 1230 (C-O); 1617,1600 (Aromatic); 800, 775 (1,2,3-trisubstituted benzene)

1,2-dihydro-2-acenaphthylenol (81)

The method described by Feiser and Cason, was adopted for this preparation.[138,139] The acetate (80) was dissolved in 275 ml of methanol in a 2 litre round bottom flask and a solution of 40 gm (1.2 equiv.) of NaOH in 400 ml of water was added. The reaction mixture was refluxed for 2 hours and then cooled below 20°C. The yellow crystalline acenaphthylenol was filtered and washed well with water. The crude product was air-

dried (142 gm) and then dissolved in boiling benzene. The solution was treated with activated charcoal and filtered. The orange red filtrate was concentrated to about one fourth of the initial volume and was allowed to crystallize which gave about 119 gms (70%) of the 1,2-dihydro-2-acenaphthylenol as colourless needles, melting at 144.5-145.5°C.

IR(cm^{-1}): 3225 (C-OH); 1600,1617 (Aromatic); 800, 775 (1,2,3-trisubstituted benzene). ^1H NMR($CDCl_3$):7.72-7.19 (m,6H,Ar-H); 5.63 (d,1H,CH); 3.65 (d, 2H,CH_2); 2.10 (s,1H, CH). Anal. Calcd. for $C_{12}H_{10}O$. Calcd. C = 84.70 ; H = 5.88; Found. C= 84.97; H = 5.95.

2-Bromo-1,2-dihydroacenaphthylene (82)

The procedure described by Bachmann and Sheenan, was adopted for this preparation.[140] To a cooled solution of 6 gm (0.025 mol) of 1,2-dihydro-2-acenaphthylenol (81) in 50 ml of anhydrous ether was added 1.23 ml (0.012 mol) of phosphorus tribromide. After standing for one and half-hour, the mixture was hydrolyzed by the addition of a small quantity of water. The ethereal layer was washed with water, sodium bicarbonate solution and again with water. The ethereal layer was dried over anhydrous sodium sulphate and evaporated. The residual oil solidified immediately. The solid was recrystallised from petroleum ether (40 - 60°C) and cooled, where upon yellowish leaflets of 2-bromo-1,2-dihydroacenaphthylene were obtained, melting at 70-71°C, (lit. m.p. 72.5°C) in 89% yield. Since, 2-bromo-1,2-dihydroacenaphthylene is not stable, it was prepared when required and used immediately .

1-(1,2-dihydro-2-acenaphthylenyl) piperazine (83)

The following procedure was devised for this preparation. A mixture of 23.3 gms (0.1 mol) of 2-bromo-1,2-dihydroacenaphthylene (82), 17.23 gms (0.2 mol) of anhydrous piperazine and 8.5 gms of anhydrous sodium bicarbonate in 100 ml of 95% ethanol was refluxed for 6 hours. The sodium bicarbonate was filtered off in a hot condition and the filterate was concentrated under reduced pressure to give an oily substance. This oil was taken up in 75 ml diethyl ether and washed with three portions of distilled water. The ether solution was dried over anhydrous sodium sulphate and evaporated, to give an oil (d=1.179 gm/ml), which gave a semisolid substance on prolonged cooling in a refrigerator. This substance on trituration with diisopropyl ether afforded 15.47gm (65%) of 1-(1,2-dihydro-2-acenaphthylenyl) piperazine as a pale yellow crystalline substance, melting at 66°C. A small quantity of the product was converted into its hydrochloride (dihydrochloride) melting at 254°C; and it's mono fumarate melting at 108°C.

IR(cm^{-1}): 2470($^+NHCl^-$); 1600 (Aromatic); 1560 (C-N); 800,775 (1,2,3-trisubstituted benzene). Mass: 238 (M^+, $C_{16}H_{18}N_2$); 223 ($C_{16}H_{17}N$); 182 ($C_{14}H_{14}$); 153 ($C_{12}H_9$); 127

($C_{10}H_7$); 85 ($C_4H_9N_2$) ; 56 ($C_2H_4N_2$). ^{1}H NMR (D_2O): 7.79-7.30 (m,6H, Ar-H); 5.16 (s,1H, C-H); 3.55-3.23 (m,10H, methylenes); 3.01 (s,1H, N-H). Anal.Calcd. for $C_{16}H_{18}N_2$.C= 80.67 %; H=7.61%; N=11.76%. Found.C=80.93%; H=7.64%; N=11.79 %.

1-(1,2-Dihydro-2-acenaphthylenyl)-4-methyl piperazine (84)

The following procedure was devised for its preparation. A mixture of 1.16 gms (0.005 mol) of 2-bromo-1,2-dihydroacenaphthylene (82), 0.748 ml (0.005 mol) of N-methyl piperazine and 1.5 gms of anhydrous potassium carbonate was placed in 20 ml of methyl ethyl ketone (MEK) and refluxed for 8 hours. The potassium carbonate was filtered while hot and the solvent was removed under reduced pressure. An oily substance was obtained which could not be crystallised. The oily substance was converted into its hydrochloride in acetone. The hydrochloride obtained was recrystallised from ethanol-ether, to give 1.10 gm (60%) of the product, melting at 244°C.

IR(cm^{-1}):2650 (CH_3-N); 2470 ($^+$NHCl$^-$); 1600 (Aromatic); 1560 (C-N); 800,775 (1,2,3-trisubstituted benzene). ^{1}H NMR(D_2O) : 7.75 (m,6H, Ar-H); 5.40(s,1H,CH); 3.8 (m,10H, methylenes); 3.20 (s, 3H, CH_3). Anal. Calcd. for $C_{17}H_{20}N_2$.2HCl. N= 8.61%. Found. N= 8.64%

1-(1,2-Dihydro-2-acenaphthylenyl)-4-ethyl piperazine (85)

A mixture of 2.38 gms (0.01 mol) of 1-(1,2-dihydro-2-acenaphthylenyl) piperazine (83), 0.81 ml (0.01 mol) of Ethyl iodide and 2 gms of anhydrous potassium carbonate was placed in 20 ml of MEK and refluxed for 8 hours. The potassium carbonate was filtered while hot and the solvent was removed under reduced pressure. An oily substance was obtained which was converted into its hydrochloride in acetone. The hydrochloride obtained was recrystallised from ethanol- ether, to give 1.762 gm (52%) of the product, melting at 244°C.

IR(cm^{-1}):2470 ($^+$NHCl$^-$); 1600 (Aromatic); 1160,1080 (C-N); 800,775 (1,2,3-trisubstituted benzene); 720 (CH_2). ^{1}H NMR (D_2O): 7.75-7.60 (m,6H, Ar-H); 5.48 (s,3H, CH, CH_3); 3.71-3.51(m,8H, piperazinyl methylenes); 1.29 (s,3H,CH_3). Anal. Calcd. for $C_{18}H_{22}$ N_2.2HCl. N= 8.25%. Found. N= 8.28%.

1-(1,2-Dihydro-2-acenaphthylenyl)-4-n-propyl piperazine (86)

A mixture of 2.38 gms (0.01 mol) of 1-(1,2-dihydro-2-acenaphthylenyl) piperazine (83), 0.938 ml (0.01 mol) of *n*-propyl bromide, 2 gms of anhydrous potassium carbonate and 2mg of potassium iodide was placed in 25 ml of MEK and prepared according to the procedure described for (85). The oily substance obtained was converted into its hydrochloride in acetone.The hydrochloride obtained was recrystallised from ethanol-ether, to give 1.063 gm (31%) of the product, melting at 263°C.

IR(cm^{-1}):2400 ($^{+}NHCl^{-}$); 1600 (Aromatic); 1020 (C-N); 800, 775 (1,2,3-trisubstituted benzene); 720 (CH_2). ^1H NMR (D_2O): 7.54 (m,6H,Ar-H); 5.54(d,1H,CH); 3.62 (m,8H, piperazinyl methylenes); 3.24 (m,2H,CH_2); 1.77 (m,2H,CH_2); 1.00 (t,3H, CH_3). Anal. Calcd. for $C_{19}H_{24}N_2.2HCl$. N= 7.93 %. Found. N= 7.96 %.

1-(1,2-Dihydro-2-acenaphthylenyl)-4-allyl piperazine (87)

A mixture of 2.38 gms (0.01 mol) of 1-(1,2-dihydro-2-acenaphthylenyl) piperazine (83), 0.84 ml (0.01 mol) of allyl bromide, 2 gms of anhydrous potassium carbonate and 2mg of potassium iodide was placed in 25 ml of MEK and prepared according to the procedure described for (85). The oily substance obtained was converted into its hydrochloride in acetone. The hydrochloride obtained was recrystallised from ethanol-ether, to give 1.29 gm (38%) of the product, melting at 267°C.

IR(cm^{-1}):2400,2475 ($^{+}NHCl^{-}$); 1600 (Aromatic); 1025 (C-N); 800 (1,2,3-trisubstituted benzene); 1290, 925, 900 (allyl). ^1H NMR (D_2O): 7.50 (m,6H,Ar-H); 6.00 (m,1H,CH); 5.52 (d,2H,CH_2); 3.52 (m,8H, piperazinyl methylenes); 3.27 (m,2H,CH_2); 1.77 (m,2H, CH_2); 1.00 (t,3H,CH_3). Anal. Calcd. for $C_{19}H_{22}N_2.2HCl$. N= 7.97 %. Found. N= 7.94 %.

1-(1,2-Dihydro-2-acenaphthylenyl)-4-isopropyl piperazine (88)

A mixture of 2.38 gms (0.01 mol) of 1-(1,2-dihydro-2-acenaphthylenyl) piperazine (83), 0.938 ml (0.01 mol) of *i*-propyl bromide, 2 gms of anhydrous potassium carbonate and 2mg of potassium iodide was placed in 25 ml of MEK and prepared according to the procedure described for (85). An oily substance was obtained which was converted into its hydrochloride in acetone. The hydrochloride obtained was recrystallised from ethanol-ether, to give 1.40gm (41%) of the product, melting at 232°C.

IR(cm^{-1}): 2425 ($^{+}NHCl^{-}$); 1600 (Aromatic); 1140,1175 (skeletal *i*-propyl); 1075 (C-N); 800, 775 (1,2,3-trisubstituted benzene). ^1H NMR (D_2O): 7.60 (m,6H,Ar-H); 5.54 (d,1H, CH);3.34(m,8H,piperazinylmethylenes);3.24 (m,CH_2); 1.37 (s,3H,CH_3); 1.35 (s,3H,CH_3). Anal.Calcd. for $C_{19}H_{24}N_2.2HCl$. N= 7.93 %. Found.N= 7.96 %.

1-(1,2-Dihydro-2-acenaphthylenyl)-4-n-butyl piperazine (89)

A mixture of 2.38 gms (0.01 mol) of 1-(1,2-dihydro-2-acenaphthylenyl) piperazine (83), 1.078 ml (0.01 mol) of *n*-butyl bromide, 2 gms of anhydrous potassium carbonate and 2mg of potassium iodide was placed in 25 ml of MEK and prepared according to the procedure described for (85). The oily substance obtained was converted into its hydrochloride in acetone.The hydrochloride obtained was recrystallised from ethanol-ether, to give 1.43 gm (39%) of the product, melting at 260°C.

IR(cm^{-1}):2400 ($^{+}NHCl^{-}$); 1600 (Aromatic); 1280 (C-N); 800, 775 (1,2,3-trisubstituted benzene); 720 (CH_2). ^1H NMR (D_2O): 8.02-7.46 (m,6H,Ar-H); 5.63 (d,1H,CH); 3.70 (m,8H, piperazinyl methylenes); 3.22 (t, 2H, CH_2); 1.68 (m, 2H, CH_2); 1.36 (m,2H,CH_2); 0.90 (t, 3H,CH_3). Anal. Calcd. for $C_{20}H_{26}N_2.2HCl$. N= 7.62 %. Found. N= 7.65%.

1-(1,2-Dihydro-2-acenaphthylenyl)-4-phenyl piperazine (90)

A mixture of 1.16 gms (0.005 mol) of 2-bromo-1,2-dihydroacenaphthylene (82), 0.760 ml (0.005 mol) of 1- phenyl piperazine and 1.38 gms of anhydrous potassium carbonate was placed in 25 ml of MEK and prepared according to the procedure described for (84). The oily substance obtained was converted into its hydrochloride in acetone. The hydrochloride obtained was recrystallised from ethanol- ether, to give 0.737 gm (47%) of the product, melting at 210°C.

IR(cm^{-1}): 2400,2350 ($^{+}NHCl^{-}$); 1595 (Aromatic);1180 (C-N); 820, 795 (1,2,3-trisubstituted benzene); 695 (monosubstituted benzene). ^1H NMR (DMSO-d_6): 8.20-6.72 (m,11H,Ar-H); 5.66 (d,2H,CH_2); 3.80 (t,1H,CH); 3.44 (m,8H, piperazinyl methylenes). Anal. Calcd. for $C_{22}H_{22}N_2.2HCl$. N= 7.23 %. Found.N= 7.25 %.

1-(3-Chloro phenyl)-4-(1,2-Dihydro-2-acenaphthylenyl) piperazine (91)

A mixture of 1.16 gms (0.005 mol) of 2-bromo-1,2-dihydroacenaphthylene (82), 1.1657 gms (0.005 mol) of 1-(3-chlorophenyl) piperazine hydrochloride and 1.5 gms of anhydrous sodium carbonate was placed in 25 ml of MEK and prepared according to the procedure described for (84). The oily substance obtained was converted into its hydrochloride in acetone.The hydrochloride obtained was recrystallised from ethanol-ether, to give 1.08 gm (62%) of the product, melting at 199°C.

IR(cm^{-1}):2200-2400 ($^{+}NHCl^{-}$); 1595 (Aromatic); 1025 (C-Cl); 810 (1,2,3-trisubstituted benzene); 780 (1,3disubstituted benzene). ^1H NMR (DMSO-d $_6$): 8.23-7.19 (m,10H, Ar-H); 5.61 (d,1H,CH); 4.51 (t,1H, CH); 4.30 (t,1H, CH); 4.00-3.56 (m,8H,piperazinyl methylenes). Anal. Calcd. for $C_{22}H_{21}N_2Cl.2HCl$. N= 6.64 %. Found. N= 6.66 %.

1-(4-Chloro phenyl)-4-(1,2-Dihydro-2-acenaphthylenyl) piperazine (92)

A mixture of 1.16 gms (0.005 mol) of 2-bromo-1,2-dihydroacenaphthylene (82), 1.1657 gms (0.005 mol) of 1-(4-chlorophenyl) piperazine hydrochloride and 1.5 gms of anhydrous sodium carbonate was placed in 25 ml of MEK and prepared according to the procedure described for (84). An oily substance was obtained which crystallised on standing. The product was recrystallised from acetone to give 0.90 gm (54%) of the product as the free base, melting at 156°C.

IR(cm^{-1}): 1595 (Aromatic); 1495 (C-N); 1010 (C-Cl) ; 800 (1,2,3-trisubstituted benzene); 815 (1,4-disubstituted benzene). ^1H NMR (DMSO-d $_6$): 7.71-6.77 (m,10H,Ar-H); 4.98 (m,1H,CH); 3.49 (d,2H,CH_2); 3.18-2.55 (m,8H, piperazinyl methylenes). Anal.Calcd. for $C_{22}H_{21}N_2Cl$. N= 8.03 %. Found. N= 8.06%.

1-(1,2-Dihydro-2-acenaphthylenyl)-4-(2-methoxy phenyl) piperazine (93)

A mixture of 1.16 gms (0.005 mol) of 2-bromo-1,2-dihydroacenaphthylene (82), 1.143 gms (0.005 mol) of 1-(2-methoxyphenyl) piperazine monohydrochloride and 1.59 gms (0.015 mol) of anhydrous sodium carbonate was placed in 25 ml of MEK and prepared according to the procedure described for (84). The oily substance obtained was converted into its hydrochloride. The hydrochloride obtained was recrystallised from methanol, to give 1.32 gm (65%) of the product, melting at 219°C.

IR(cm^{-1}): 2350 ($^+NHCl^-$); 1600 (Aromatic); 1257 (Arom-O-CH_3); 1020 (C-N); 810 (1,2,3-trisubstituted benzene); 745 (1,2-disubstituted benzene). ^1H NMR (DMSO-d_6): 8.30-6.93 (m,10H,Ar-H); 5.55 (d,2H,CH_2); 3.81 (t,3H,Ar-O-CH_3); 3.36-3.15 (m,8H, piperazinyl methylenes). Anal. Calcd. for $C_{23}H_{24}N_2O.2HCl$. N=6.17%. Found.N=6.16 %.

1-(1,2-Dihydro-2-acenaphthylenyl)-4-(3-methoxy phenyl) piperazine (94)

A mixture of 1.16 gms (0.005 mol) of 2-bromo-1,2-dihydroacenaphthylene (82), 1.32 gms (0.005 mol) of 1-(3-methoxyphenyl) piperazine dihydrochloride and 2.0 gms (0.02 mol) of anhydrous sodium carbonate was placed in 25 ml of MEK and prepared according to the procedure described for (84). The oily substance obtained was converted into its hydrochloride in acetone.The hydrochloride obtained was recrystallised from methanol, to give 1.41 gm (68%) of the product, melting at 208°C.

IR(cm^{-1}): 2350 ($^+NHCl^-$); 1610 (Aromatic); 1260 (Arom-O- CH_3); 1024 (C-N); 815 (1,2,3-trisubstituted benzene);770 (1,3- disubstituted benzene). ^1H NMR (DMSO-d_6): 7.89-6.82 (m,10H,Ar-H); 5.58 (d,2H,CH_2); 4.04 (t,3H,Ar-O-CH_3); 3.90-3.52(m,8H, piperazinylmethylenes).Anal. Calcd. for $C_{23}H_{24}N_2O.2HCl$. N= 6.17%. Found. N= 6.19%.

1-(1,2-Dihydro-2-acenaphthylenyl)-4-(4-methoxy phenyl) piperazine (95)

A mixture of 0.842 gms (0.0036 mol) of 2-bromo-1,2-dihydroacenaphthylene (82), 0.959 gms (0.0036 mol) of 1-(4-methoxyphenyl) piperazine dihydrochloride and 1.11 gms (0.0105 mol) of anhydrous sodium carbonate was placed in 15 ml of MEK and prepared according to the procedure described for (84). An oily substance was obtained which crystallised on standing. The product was recrystallised from acetone to give 0.940 gm (55%) of a crystalline substance melting at 129°C.

IR(cm^{-1}):1595 (Aromatic); 1040,1240 (Arom-O- CH_3); 1038 (C-N); 810 (1,2,3-trisubstituted benzene); 780 (1,4-disubstituted benzene). ^1H NMR (DMSO-d_6): 7.71-6.79 (m,10H,Ar-H); 4.99 (q,1H,CH); 3.75 (s,3H,Ar-O-CH_3); 3.52 (q,2H,CH_2); 3.10-2.57 (m, 8H,piperazinyl methylenes). Anal. Calcd. for $C_{23}H_{24}N_2O$. N= 8.13%. Found. N= 8.14%.

1-(1,2-Dihydro-2-acenaphthylenyl)-4-(4-fluoro phenyl) piperazine (96)

A mixture of 0.58 gms (0.0025 mol) of 2-bromo-1,2-dihydroacenaphthylene (82), 0.63 gms (0.0025 mol) of 1-(4-fluorophenyl) piperazine dihydrochloride and 2.0 gms (0.02 mol) of anhydrous sodium carbonate was placed in 15 ml of MEK and prepared according to the procedure described for (84). The oily substance obtained was converted into its hydrochloride in acetone. The hydrochloride obtained was recrystallised from methanol-ether, to give 1.062 gm (64%) of the product, melting at 233°C.

IR(cm^{-1}):2300 ($^+NHCl^-$); 1610 (Aromatic); 1725, 1230(monofluorobenzene); 800 (1,2,3-trisubstituted benzene);780 (1,4-disubstituted benzene). ^1H NMR (DMSO-d_6): 8.23-7.06 (m,10H,Ar-H);5.57(d,1H,CH);4.52 (s,2H,CH_2); 4.05-3.17 (m,8H,piperazinylmethylenes). Anal. Calcd. for $C_{22}H_{21}N_2F.2HCl$. N= 6.91%. Found. N= 6.94%.

1- (1,2-Dihydro-2-acenaphthylenyl)-4-(3-trifluoromethyl phenyl) piperazine (97)

A mixture of 0.58 gms (0.0025 mol) of 2-bromo-1,2-dihydroacenaphthylene (82), 0.5675 gms (0.0025 mol) of 1-(3-trifluoromethyl phenyl) piperazine and 1.59 gms (0.015 mol) of anhydrous sodium carbonate was placed in 15 ml of MEK and prepared according to the procedure described for (84). The oily substance obtained was converted into its hydrochloride in acetone. The hydrochloride obtained was recrystallised from ethanol, to give 1.42 gm (63%) of the product, melting at 223°C.

IR(cm^{-1}): 2390-2360 ($^+NHCl^-$); 1600 (Aromatic); 1120 (CF_3); 1495 (C-N); 800 (1,2,3-trisubstituted benzene); 778 (1,3-disubstituted benzene). ^1H NMR (DMSO-d_6): 8.12-6.99 (m,10H,Ar-H);5.51(s,1H,CH); 4.52 (s,2H,CH_2); 4.05-3.17 (m,8H,piperazinyl methylene). Anal. Calcd. for $C_{23}H_{21}N_2F_3.2HCl$. N=6.15%. Found. N= 6.19%.

1-(1,2-Dihydro-2-acenaphthylenyl)-4-(2-pyridyl) piperazine (98)

A mixture of 0.812 gms (0.0035 mol) of 2-bromo-1,2-dihydroacenaphthylene (82), 0.826 gms (0.0035 mol) of 1-(2-pyridyl) piperazine dihydrochloride and 1.11 gms (0.0105 mol) of anhydrous sodium carbonate was placed in 15 ml of MEK and prepared according to the procedure described for (84). The oily substance obtained was converted into its hydrochloride salt in acetone. The hydrochloride obtained was recrystallised from ethanol- acetone, to give 1.34 gm (69%) of the product, melting at 262°C.

IR(cm^{-1}): 2650-2275 ($^{+}NHCl^{-}$); 1610 (Aromatic); 1540 (C=N); 1495 (C-N); 795 (1,2,3-trisubstituted benzene);755 (2-pyridyl). ^{1}H NMR (DMSO-d_6): 8.10-6.94 (m,10H,Ar-H); 5.58(s,1H,CH);4.44-2.59(m,10H,methylenes).Anal.Calcd.for $C_{21}H_{21}N_3.2HCl$.N=10.82%. Found. N=10.86%.

1-(1,2-Dihydro-2-acenaphthylenyl)-4-(2-pyrimidinyl) piperazine (99)

A mixture of 1.16 gms (0.005 mol) of 2-bromo-1,2-dihydroacenaphthylene (82), 0.82 gms (0.005 mol) of 1-(2-pyrimidinyl) piperazine dihydrochloride and 1.06 gms (0.01 mol) of anhydrous sodium carbonate was placed in 25 ml of MEK and prepared according to the procedure described for (84). The oily substance obtained was converted into its hydrochloride in acetone. The hydrochloride obtained was recrystallised from ethanol, to give 1.26 gm (65%) of the product, melting at 248°C.

IR(cm^{-1}): 2490-2390 ($^{+}NHCl^{-}$); 1605 (Aromatic); 1542 (C=N); 1495 (C-N); 805 (1,2,3-trisubstituted benzene). ^{1}H NMR (DMSO-d_6): 8.35-6.56 (m,9H,Ar-H); 5.43 (s,1H,CH); 4.89(t,2H,CH_2);4.00-3.00(m,8H,piperazinylmethylenes).Anal. Calcd.for $C_{20}H_{20}N_4.2HCl$. N=14.39%. Found. N=14.43%.

1-Benzoyl-4-(1,2-Dihydro-2-acenaphthylenyl) piperazine (100)

A mixture of 0.58 gms (0.0025 mol) of 2-bromo-1,2-dihydroacenaphthylene (82), 0.6575 gms (0.005 mol) of 1-Benzoyl piperazine dihydrochloride [the procedure described by Cymerman-craig and co-workers [141] was followed, and was prepared from piperazine hexahydrate and benzoyl chloride] and 1.11 gms (0.0105 mol) of anhydrous sodium carbonate was placed in 15 ml of MEK and prepared according to the procedure described for (84). The oily substance obtained was converted into its hydrochloride in acetone. The hydrochloride obtained was recrystallised from ethanol, to give 1.289 gm (62%) of the product, melting at 254°C.

IR(cm^{-1}): 2375 ($^{+}NHCl^{-}$); 1610 (Aromatic); 1700 (C=O); 1495 (C-N);800(1,2,3-trisubstituted benzene); 710 (monosubstituted benzene). ^{1}H NMR (DMSO-d_6): 8.12-7.35 (m,11H,Ar-H); 5.50 (d,1H,CH); 3.95-3.80 (m,10H, methylenes). Anal. Calcd. for $C_{23}H_{22}N_2O.2HCl$. N=6.74%. Found. N= 6.75%.

1-(1,2-Dihydro-2-acenaphthylenyl)-4-(4-fluoro benzoyl) piperazine (101)

A mixture of 0.435 gms (0.00187 mol) of 2-bromo-1,2-dihydroacenaphthylene (82), 0.525 gms (0.005 mol) of 1-(4-fluoro benzoyl) piperazine dihydrochloride [the procedure described by Cymerman-craig and co-workers [141] was followed with minor modifications, and was prepared from piperazine hexahydrate and 4-fluoro benzoyl chloride instead of benzoyl chloride] and 1.11 gms (0.0105 mol) of anhydrous sodium carbonate was placed in 15 ml of MEK and prepared according to the procedure

described for (84). The oily substance obtained was converted into its hydrochloride in acetone. The hydrochloride obtained was recrystallised from methanol, to give 1.69 gm (67%) of the product, melting at 248°C.

IR(cm^{-1}): 2375 ($^+NHCl^-$); 1610 (Aromatic); 1700(C=O); 1495(C-N); 800(1,2,3-trisubstituted benzene); 710 (monosubstituted benzene). ^1H NMR (DMSO-d_6): 8.16-7.06 (m,10H,Ar-H); 5.51(d,1H,CH); 3.96-3.20 (m,10H,methylenes). Anal. Calcd. for $C_{23}H_{21}N_2FO.2HCl$. N=6.46%. Found. N=6.51%.

1-(1,2-Dihydro-2-acenaphthylenyl)-4-(1-piperonyl) piperazine (102)

A mixture of 0.425 gms (0.00183 mol) of 2-bromo-1,2-dihydroacenaphthylene (82), 0.420 gms (0.005 mol) of 1-piperonyl piperazine and 1.11 gms (0.0105 mol) of anhydrous sodium carbonate was placed in 15 ml of MEK and prepared according to the procedure described for (84). The oily substance obtained was converted into its hydrochloride in acetone.The hydrochloride obtained was recrystallised from ethanol, to give 1.57 gm (69%) of the product, melting at 262°C.

IR(cm^{-1}): 2375 ($^+NHCl^-$); 1610 (Aromatic); 1495(C-N); 1025 (5-membered cyclic ether) ; 800 (1,2,3-trisubstituted benzene);710 (monosubstituted benzene). ^1H NMR (DMSO-d_6): 7.83-6.78 (m,9H,Ar-H); 5.50 (d,1H,CH); 3.91 (s,2H,CH_2); 3.79-3.70 (m,8H, piperazinyl methylenes);3.52(s,2H,CH_2). Anal. Calcd. For $C_{24}H_{24}N_2O_2.2HCl$. N= 6.29%. Found. N= 6.34%.

1-(1,2-Dihydro-2-acenaphthylenyl)-4-(2-hydroxy ethyl) piperazine (103)

The procedure described by Van Steen and co-workers, was adopted for this preparation.[40] A mixture of 2.38 gms (0.01 mol) of 1-(1,2-dihydro-2-acenaphthylenyl) piperazine (83), 1.2 ml (0.015 mol) of 2-chloroethanol, 2 gms of anhydrous potassium carbonate, 2 ml of diisopropyl ethyl amine (DIPEA) and 2mg of potassium iodide was placed in 25 ml of acetonitrile and refluxed for 8 hours. The potassium carbonate was filtered while hot and the solvent was removed under reduced pressure. An oily substance was obtained which could not be crystallised and was hence converted into its hydrochloride in acetone. The hydrochloride obtained was recrystallised from ethanol-ether, to give 1.63 gm (46%) of the product, melting at 270°C.

IR(cm^{-1}): 3625, 3425 (free OH); 2380 ($^+NHCl^-$); 1600 (Aromatic); 1495 (C-N); 800 (1,2,3-trisubstituted benzene). ^1H NMR (D_2O): 7.73-7.47 (m,6H,Ar-H); 5.50 (d,1H,CH); 3.91-3.47 (m,8H,piperazinyl methylenes); 3.37-3.22 (m,4H,methylenes). Anal. Calcd. for $C_{18}H_{22}N_2O.2HCl$. N=7.88%. Found. N=7.94%.

1-(1,2-Dihydro-2-acenaphthylenyl)-4-(2-amino ethyl) piperazine (104)

The procedure described by Van Steen and co-workers, was modified and adopted for this preparation.[40]A mixture of 2.38 gms(0.01 mol) of 1-(1,2-dihydro-2-acenaphthylenyl) piperazine (83), 1.16 gm (0.015 mol) of 2-chloroethyl amine hydrochloride, 2 gms of anhydrous potassium carbonate, 2 ml of DIPEA and 2mg of potassium iodide was placed in 25 ml of MEK and refluxed for 8 hours. The potassium carbonate was filtered while hot and the solvent was removed under reduced pressure. An oily substance was obtained which was taken up in hot acetone and refrigerated for 2 days, where upon yellow crystals separated. The crystalline substance was filtered through a sintered glass funnel. The product, 1.06 gm (38%), so obtained was further recrystallised from hot acetone, to give the product melting at 164°C.

IR(cm^{-1}):3250 (amino); 1600(Aromatic); 1180 (C-N); 795 (1,2,3-trisubstituted benzene) ; 720 (CH_2). ^1H NMR (DMSO-d_6): 7.91-7.45 (m,6H,Ar-H); 5.56 (s,1H,CH); 3.69-3.52 (m,12H,methylenes). Anal.Calcd. for $C_{18}H_{23}N_3$. N=14.93%. Found.N=15.01%.

1-(1,2-Dihydro-2-acenaphthylenyl)-4-(2-Dimethyl amino ethyl) piperazine (105)

The method described for (103) was modified and adopted for this preparation. A mixture of 2.38 gms (0.01 mol) of 1-(1,2-dihydro-2-acenaphthylenyl) piperazine (83), 1.2 gm (0.01 mol) of dimethylaminoethylchloride, 2 gms of anhydrous potassium carbonate, 2 ml of DIPEA and 2mg of potassium iodide was placed in 25 ml of MEK and refluxed for 8 hours. The potassium carbonate was filtered while hot and the solvent was removed under reduced pressure. An oily substance was obtained which could not be crystallised. The oily substance was taken up in n-butanol and an equimolar quantity of fumaric acid was added and dissolved by warming and then cooled in ice. The mono fumarate was precipitated out from the solution by the addition of *n*-hexane. The solid obtained was filtered on a sintered funnel and washed with *n*-hexane. It was dried and recrystallised from hot methanol to give 1.52 gm (47%) of the product, melting at 186°C.

IR(cm^{-1}):1725,1655 (C=O); 1575 (carboxylateion); 1600(Aromatic); 1180(C-N); 795 (1,2,3-trisubstituted benzene); 720 (CH_2). ^1H NMR (D_2O): 8.02 (d,2H,fumarate); 7.85-7.50(m,6H,Ar-H);5.49(d,1H,CH);3.88(q,2H,CH_2);3.73-3.29(m,8H,piperazinylmethylene) 3.25 (q,4H,methylenes); 2.98(q,3H,CH_3); 2.87(q,3H,CH_3). Anal. Calcd. for $C_{20}H_{27}N_3.C_4H_4O_4$. N= 9.88%. Found. N= 9.94%.

1-(1,2-Dihydro-2-acenaphthylenyl)-4-(2-Diethyl amino ethyl) piperazine (106)

A mixture of 1.19 gms (0.005 mol) of 1-(1,2-dihydro-2-acenaphthylenyl) piperazine (83), 0.678 gm (0.005 mol) of diethylaminoethylchloride, 2 gms of anhydrous potassium carbonate, 2 ml of DIPEA and 2mg of potassium iodide was placed in 25 ml of MEK

and prepared according to the method described for (105). The mono fumarate obtained was recrystallised from hot methanol to give 0.906 gm (40%) of the product, melting at 174°C.

IR(cm^{-1}):1725,1645 (C=O); 1575 (carboxylate); 1600 (Aromatic); 1180(C-N); 795 (1,2,3 -trisubstituted benzene); 720 (CH_2). ^1H NMR (D_2O): 7.99 (d,2H,fumarate); 7.82-7.47 (m,6H,Ar-H); 5.46 (d,1H,CH); 3.89-3.21 (m,8H,piperazinyl methylenes); 2.79(t,2H,CH_2) 2.2 (t,2H,CH_2); 1.23 (m,6H,CH_3). Anal. Calcd. for $C_{22}H_{31}N_3.C_4H_4O_4$.N=9.27%. Found. N= 9.34%.

1-(1,2-Dihydro-2-acenaphthylenyl)-4-(2-pyrrolidino ethyl) piperazine (107)

A mixture of 1.19 gms (0.005 mol) of 1-(1,2-dihydro-2-acenaphthylenyl) piperazine (83), 0.6675 gm (0.005 mol) of pyrrolidinoethylchloride, 2 gms of anhydrous potassium carbonate, 2 ml of DIPEA and 2mg of potassium iodide was placed in 25 ml of MEK and prepared according to the method described for (105). The mono fumarate obtained was recrystallised from hot ethanol to give 1.17 gm (52%) of the product, melting at 188°C.

IR(cm^{-1}):1725,1650 (C=O); 1575 (carboxylate ion); 1600 (Aromatic); 1180 (C-N); 795 (1,2,3-trisubstituted benzene); 720 (CH_2). ^1H NMR (D_2O): 7.99 (d,2H,fumarate); 7.82-7.46 (m,6H,Ar-H); 5.45 (d,1H,CH); 3.87-2.77 (m,16H, piperazinyl & pyrrolidinyl methylenes); 2.20(t,4H,CH_2-CH_2). Anal. Calcd. for $C_{22}H_{29}N_3.C_4H_4O_4$.N= 9.31%. Found. N= 9.34%.

1-(1,2-Dihydro-2-acenaphthylenyl)-4-(2-piperidino ethyl) piperazine (108)

A mixture of 1.19 gms (0.005 mol) of 1-(1,2-dihydro-2-acenaphthylenyl) piperazine (83), 0.7375 gm (0.005 mol) of piperidinoethylchloride, 2 gms of anhydrous potassium carbonate, 2 ml of DIPEA and 2mg of potassium iodide was placed in 25 ml of MEK and prepared according to the method described for (105). The mono fumarate obtained was recrystallised from ethanol to give 1.27 gm (55%) of the product, melting at 190°C.

IR(cm^{-1}):1725, 1650 (C=O); 1575 (carboxylate ion); 1600 (Aromatic);1180 (C-N); 795 (1,2,3-trisubstituted benzene); 720 (CH_2). ^1H NMR (D_2O): 8.41 (d,2H,fumarate); 7.82-7.46 (m,6H,Ar-H); 6.88 (d,1H,CH); 5.34-4.24 (m,18H, piperazinyl & piperidinyl methylenes); 3.33(t,4H,methylenes). Anal. Calcd. for $C_{23}H_{31}N_3.C_4H_4O_4$.N= 9.03%. Found. N=9.04%.

1-(1,2-Dihydro-2-acenaphthylenyl)-4-(2-morpholino ethyl) piperazine (109)

A mixture of 1.19 gms (0.005 mol) of 1-(1,2-dihydro-2-acenaphthylenyl) piperazine (83), 0.7475 gm (0.005 mol) of morpholinoethylchloride, 2 gms of anhydrous potassium

carbonate, 2 ml of DIPEA and 2mg of potassium iodide was placed in 25 ml of MEK and prepared according to the method described for (105). The mono fumarate obtained was recrystallised from ethanol to give 1.28 gm (55%) of the product, melting at 196°C.

IR(cm^{-1}):1715,1655 (C=O); 1575 (carboxylate ion); 1600 (Aromatic); 1180 (C-N); 795 (1,2,3-trisubstituted benzene); 720 (CH_2). ^1H NMR (D_2O): 8.08 (d,2H,fumarate); 7.91-7.56 (m,6H,Ar-H); 5.56 (d,1H,CH); 4.17-3.33 (m,16H,piperazinyl & morpholinyl methylenes); 2.99 (t,4H,CH_2-CH_2). Anal. Calcd. for $C_{22}H_{29}N_3O.C_4H_4O_4$ .N= 8.99%. Found. N=9.04%.

Synthesis of 1-(1,2-Dihydro-2-acenaphthylenyl)-4-phenethyl piperazine (110)

A mixture of 2.38 gms (0.01 mol) of 1-(1,2-dihydro-2-acenaphthylenyl) piperazine (83), 2.12 gm (0.015 mol) of phenethylchloride (2-chloro ethyl benzene), 2ml of DIPEA, 2 gm of anhydrous potassium carbonate and 2mg of potassium iodide was placed in 25 ml of MEK and prepared according to the method described for (85). The oily substance obtained was converted into its hydrochloride in acetone. The hydrochloride obtained was recrystallised from methanol, to give 2.57 gm (64%) of the product, melting at 238°C.

IR(cm^{-1}) 2428 ($^+NHCl^-$); 1600 (Aromatic); 1180 (C-N); 800(1,2,3-trisubstituted benzene); 690 (monosubstituted benzene). ^1H NMR (DMSO-d_6): 7.77-7.21 (m,10H,Ar-H); 5.06 (d,1H,CH); 3.68-3.34 (m,8H, piperazinyl methylenes); 3.15-2.58 (m,6H,CH_2). Anal. Calcd. for $C_{24}H_{31}N_2.2HCl$ .N= 6.66%. Found. N= 6.72%.

4-(4-{2-[4-(1,2-dihydro-2-acenaphthylenyl) piperazinyl]ethyl} phenyl) -2-amino thiazole

4-(2-Chloro acetyl) phenethyl chloride (111)

The procedure described by Greber and Egle, was modified and adopted for this preparation.[142] In a 250 ml round bottom flask equipped with a pressure equalising dropping funnel was placed 13.3 gms (0.1 mol) of finely powdered anhydrous aluminium chloride and 3.98 ml (0.05 mol) of chloroacetyl chloride in 50 ml of ethylene chloride. Phenethyl chloride, 6.57 ml (0.05 mol) in 50 ml of ethylene chloride was placed in the dropping funnel and was added dropwise with continuous stirring. The reaction mixture was stirred for one hour and the brownish black solution was poured into ice cold water containing 5 ml of hydrochloric acid. The organic layer was separated and washed with sodium bicarbonate solution, followed by brine solution and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure to give an oily residue, which solidified on standing for prolonged periods of time (more than a week),

to give 8.67 gm (80%) of the 4-chloroacetyl phenethyl chloride, melting at 44 °C. The oily product was therefore used directly in subsequent reactions without further purification.

IR(cm^{-1}) (Neat):2975,1600 (aromatic); 1700 (C=O); 817 (1,4-disubstituted benzene); 725 (C-Cl).

4-[4-(2-Chloroethyl)phenyl]-2-amino thiazole (112)

The procedure described by John A. Lowe and co-workers, was modified and adopted for this preparation.[77,143] In a 100 ml round bottom flask equipped with a reflux condenser was placed 10.84 gm (0.05 mol) 4-(2-Chloroacetyl) phenethyl chloride (111) prepared as above, in 50 ml of dry acetone and 3.81 gm (0.05 mol) of thiourea was added to it. The mixture was refluxed for 3 hours, with continuous stirring. The solution was then cooled in a refrigerator, where upon, a yellowish solid separated. The solid was filtered and recrystallised from methanol to give 8.2 gm (60%) of 4-[4-(2-Chloroethyl) phenyl]-2-amino thiazole, as the hydrochloride, melting at 228°C.

IR(cm^{-1}):2375 ($^{+}NHCl^{-}$); 1700,1300 (C-S); 1618 (aromatic); 825 (1,4-disubstituted benzene); 720 (C-Cl). ^{1}H NMR (D_2O): 7.59-6.93 (m,5H,Ar-H); 4.64 (s,2H,CH_2); 3.84 (q,2H,NH_2); 3.11 (s,2H,CH_2).

4-(4-[2-[4-(1,2-dihydro-2-acenaphthylenyl)piperazinyl]ethyl]phenyl)-2-amino thiazole (113)

The procedure described by John A. Lowe and co-workers, was adopted for this preparation.[77,143] In a 100 ml round-bottomed flask equipped with a reflux condenser and N_2 inlet were placed 0.952 gm (0.00346 mol) of 4-[4-(2-Chloroethyl) phenyl]-2-amino thiazole (112), 0.825 gm (0.00346 mol) of 1-(1,2-dihydro-2-acenaphthylenyl) piperazine (83), 0.733 gm (0.0103 mol) of anhydrous sodium carbonate, 2mg of sodium iodide, 1.79 ml (0.0103 mol) of DIPEA and 15 ml of methyl isobutyl ketone (MIBK). The reaction mixture was refluxed for 2 days, cooled and filtered. The filterate was purified by treatment with activated charcoal and filtered again to remove the charcoal. The solvent was removed under reduced pressure to give yellowish oil, which was converted into its hydrochloride in acetone-ether mixture. The hydrochloride obtained was recrystallised from methanol, to give 0.990 gm (52%) of the product, melting at 227°C.

IR(cm^{-1}):3400 (amino); 2395 ($^{+}NHCl^{-}$); 1700,1300 (C-S); 1620 (aromatic); 810 (1,2,3-trisubstituted benzene). ^{1}H NMR (DMSO-d_6): 8.05-7.31 (m,11H,Ar-H); 5.33 (d,1H,CH); 3.84 (s,2H,CH_2); 3.70-3.33 (m,8H,piperazinylmethylenes); 3.12-2.97 (q,4H, methylenes).

Anal. Calcd. for $C_{27}H_{28}N_4S.3HCl$. N=10.19%. Found. N=10.16%.

4-(4-{2-[4-(1,2-dihydro-2-acenaphthylenyl)piperazinyl]ethyl}phenyl)-2-methyl thiazole

4-[4-(2-Chloroethyl)phenyl]-2-methyl thiazole (114)

The procedure described for (112) was modified and adopted for this preparation. In a 100 ml round bottom flask equipped with a reflux condenser was placed 10.84 gm (0.05 mol) 4-(2-Chloroacetyl) phenethyl chloride (111), in 50 ml of dry acetone and 3.76 gm (0.05 mol) of thioacetamide was added to it. The mixture was refluxed for 3 hours, with continuous stirring. The solution was then cooled in a refrigerator, where upon, a yellowish solid separated. The solid was filtered and recrystallised from acetone to give 8.9 gm (65%) of 4-[4-(2-Chloroethyl) phenyl]-2-methyl thiazole, as the hydrochloride, melting at 226°C.

IR(cm^{-1}):2375 ($^{+}NHCl^{-}$); 1660,1330 (C-S); 1600 (aromatic); 820 (1,4-disubstituted benzene); 720 (C-Cl). ^1H NMR (DMSO-d_6): 7.96-7.34 (m,5H,Ar-H); 5.71 (d,4H,CH_2); 2.74 (s,3H,CH_3).

4-(4-{2-[4-(1,2-dihydro-2-acenaphthylenyl)piperazinyl]ethyl}phenyl)-2-methyl thiazole (115)

The procedure described for (113) was adopted for this preparation. In a 100 ml round-bottomed flask equipped with a reflux condenser and N_2 inlet were placed 0.9516 gm (0.00346 mol) of 4-[4-(2-Chloroethyl) phenyl]-2-methyl thiazole (114), 0.825 gm (0.00346 mol) of 1-(1,2-dihydro-2-acenaphthylenyl) piperazine (83), 0.733 gm (0.0103 mol) of anhydrous sodium carbonate, 2mg of sodium iodide, 1.79 ml (0.0103 mol) of DIPEA and 15 ml of MIBK. The mixture was refluxed for 2 days, cooled and filtered. The filterate was purified by treatment with activated charcoal and filtered again to remove the charcoal. The solvent was removed under reduced pressure to give an oily substance, which crystallised on standing. The product was recrystallised from acetone to give 1.045 gm (55%) of the free base, melting at 78°C.

IR(cm^{-1}):1680 (C-S); 1600 (aromatic); 780(1,2,3-trisubstituted benzene); 740 (1,4-disubstituted benzene). ^1H NMR (DMSO-d_6): 7.96-7.31 (m,11H,Ar-H); 5.33 (d,1H,CH); 4.79 (d,2H,CH_2); 3.82-3.33 (m,8H,piperazinylmethylenes); 3.12-3.01 (q, 4H, methylenes) 2.91 (s,3H,CH_3). Anal. Calcd. for $C_{28}H_{29}N_3S.3HCl$. N=9.56%. Found. N=9.60%.

4-(4-{2-[4-(1,2-dihydro-2-acenaphthylenyl) piperazinyl]ethyl} phenyl) -2-amino- 5-methyl thiazole

4-[4-(2-Chloroethyl)phenyl]-2-amino-5-methyl thiazole (116)

The procedure described for (112) was modified suitably and adopted for this preparation. 4-(2-bromopropionyl) phenethyl chloride was prepared as described for (111), where 5.04 ml (0.05 mol) of 2-bromopropionyl chloride was used instead of chloroacetyl chloride. The solvent after evaporation under vacuo gave 10.96 gm (80%) of 4-(2-bromopropionyl) phenethyl chloride as an yellow oil .

In a 100 ml round bottom flask equipped with a reflux condenser was placed 13.71 gm (0.05 mol) 4-(2-bromo propionyl) phenethyl chloride obtained above, in 50 ml of dry acetone and 3.81 gm (0.05 mol) of thiourea was added to it. The mixture was refluxed for 3 hours, with continuous stirring. The solution was then cooled in a refrigerator, where upon, a yellowish solid separated. The solid was filtered and recrystallised from ethanol-ether to give 9.96 gm (60%) of 4-[4-(2-Chloroethyl)phenyl]-2-amino-5-methylthiazole, as the hydrobromide, melting at 278°C.

IR(cm^{-1}):2375 ($^{+}NHCl^{-}$); 1700,1300 (C-S); 1618 (aromatic); 825 (1,4-disubstituted benzene); 720 (C-Cl). ^{1}H NMR (DMSO-d_6): 7.35(q,4H,Ar-H);3.54(s,2H,NH_2);2.87(q,2H, CH_2); 1.94 (d,3H,CH_3).

***4-(4-{2-[4-(1,2-dihydro-2-acenaphthylenyl)piperazinyl]ethyl}phenyl)-2-amino-5-methyl thiazole* (117)**

In a 100 ml round-bottomed flask equipped with a reflux condenser and N_2 inlet were placed 1.1513 gm (0.00346 mol) of 4-[4-(2-Chloroethyl)phenyl]-2-amino-5-methyl thiazole (116), 0.825 gm (0.00346 mol) of 1-(1,2-dihydro-2-acenaphthylenyl) piperazine (83), 0.733 gm (0.0103 mol) of anhydrous sodium carbonate, 2mg of sodium iodide, 1.79 ml (0.0103 mol) of DIPEA and 25 ml of MIBK. The reaction mixture was refluxed for 2 days and worked up according to the procedure described for (113) to give the hydrochloride. The hydrochloride obtained was recrystallised from ethanol-ether, to give 1.21 gm (62%) of the product, melting at 258°C.

IR(cm^{-1}):3400 (amino); 2415 ($^{+}NHCl^{-}$); 1700,1300 (C-S); 1615,1600 (aromatic); 810 (1,2,3-trisubstituted benzene); 780 (1,4-disubstituted benzene). ^{1}H NMR (DMSO-d_6): 7.35-6.76 (m,10H,Ar-H); 5.62 (d,1H,CH); 4.24 (d,2H,CH_2) ; 3.51(s,2H,NH_2); 3.42-3.03 (m,8H, piperazinyl methylenes); 1.97 (s,3H,CH_3). Anal. Calcd. for $C_{29}H_{30}N_4S.3HCl$. N= 9.73%. Found. N=9.72%.

4-(4-{2-[4-(1,2-dihydro-2-acenaphthylenyl)piperazinyl]ethyl}phenyl)-2-methyl amino thiazole

4-[4-(2-Chloroethyl)phenyll-2-methyl amino thiazole (118)

The procedure described for (112) was modified and adopted for this preparation. In a 100 ml round bottom flask equipped with a reflux condenser was placed 10.84 gm (0.05 mol) 4-(2-Chloroacetyl) phenethyl chloride (111), in 50 ml of dry acetone and 4.00 gm (0.05 mol) of N-methyl thiourea was added to it. The mixture was refluxed for 3 hours, with continuous stirring. The solution was then cooled in a refrigerator, where upon, a yellowish white solid separated. The solid was filtered and recrystallised from methanol to give 9.39 gm (65%) of 4-[4-(2-Chloroethyl) phenyl]-2-methyl amino thiazole, as the hydrochloride, melting at 107°C.

IR(cm^{-1}):2355 ($^{+}NHCl^{-}$); 1700,1300 (C-S); 1624 (aromatic); 820 (1,4-disubstituted benzene); 720 (C-Cl). ^{1}H NMR ($CDCl_3$): 7.28-6.52 (m,5H,Ar-H); 3.91 (s,4H,CH_2); 3.37 (s,1H,NH); 2.68 (t,3H,CH_3).

***4-(4-{2-[4-(1,2-dihydro-2-acenaphthylenyl)piperazinyl]ethyl}phenyl)-2-methyl amino thiazole* (119)**

In a 100 ml round-bottomed flask equipped with a reflux condenser and N_2 inlet were placed 1.00 gm (0.00346 mol) of 4-[4-(2-Chloroethyl) phenyl]-2-methylamino thiazole (118), 0.825 gm (0.00346 mol) of 1-(1,2-dihydro-2-acenaphthylenyl) piperazine (83), 0.733 gm (0.0103 mol) of anhydrous sodium carbonate, 2mg of sodium iodide, 1.79 ml (0.0103 mol) of DIPEA and 15 ml of MIBK. The reaction mixture was refluxed for 2 days and worked up according to the procedure described for (113) to give a hydrochloride. The hydrochloride obtained was recrystallised from methanol, to give 1.11 gm (57%) of the product, melting at 226°C.

IR(cm^{-1}): 2515, 2475 ($^{+}NHCl^{-}$); 1700 (C-S); 1620 (aromatic); 1495 (C-N); 825 (1,2,3-trisubstituted benzene); 720 (1,4-disubstituted benzene). ^{1}H NMR (DMSO-d_6): 7.29-6.62 (m,11H,Ar-H); 5.41 (d,1H,CH); 3.98 (d,4H,CH_2); 3.51(s,1H,NH); 3.22-3.03 (m,8H, piperazinyl methylenes); 2.24 (s,3H,CH_3). Anal. Calcd. for $C_{28}H_{30}N_4S.3HCl$. N= 9.93%. Found. N=9.98%.

4-(4-{2-[4-(1,2-dihydro-2-acenaphthylenyl)piperazinyl]ethyl}phenyl)-2-allylamino thiazole

4-[4-(2-Chloroethyl)phenyll-2-allylamino thiazole (120)

The procedure described for (112) was modified and adopted for this preparation. In a 100 ml round bottom flask equipped with a reflux condenser was placed 10.84 gm (0.05

mol) 4-(2-Chloroacetyl) phenethyl chloride (111), in 50 ml of dry acetone and 5.81 gm (0.05 mol) of N-allyl thiourea was added to it. The mixture was refluxed for 3 hours, with continuous stirring. The solution was then cooled in a refrigerator, where upon, a red solid separated. The solid was filtered and recrystallised from acetone to give 9.39 gm (65%) of 4-[4-(2-Chloroethyl)phenyl]-2-allylaminothiazole, as the hydrochloride, melting at 53°C. This hydrochloride salt was unstable and was hence used immediately in the next step.

IR(cm^{-1}):2375 ($^+NHCl^-$); 1700,1300 (C-S); 1618 (aromatic); 825 (1,4-disubstituted benzene);720(C-Cl).^{1}H NMR (DMSO-d_6): 7.79-7.24 (m,5H,Ar-H);5.95(m,1H,CH-vinyl); 5.35 (q,2H,CH_2); 4.76-4.10 (m,5H,CH_2); 3.48 (t,1H,NH).

4-(4-{2-[4-(1,2-dihydro-2-acenaphthylenyl)piperazinyl]ethyl}phenyl)-2-allylamino thiazole (121)

In a 100 ml round-bottomed flask equipped with a reflux condenser and N inlet were placed 1.0938 gm (0.00346 mol) of 4-[4-(2-Chloroethyl) phenyl]-2-allylamino thiazole (120), 0.825 gm (0.00346 mol) of 1-(1,2-dihydro-2-acenaphthylenyl) piperazine (83), 0.733 gm (0.0103 mol) of anhydrous sodium carbonate, 2mg of sodium iodide, 1.79 ml (0.0103 mol) of DIPEA and 20 ml of MIBK. The reaction mixture was refluxed for 2 days and processed according to the procedure described for (113) to give a hydrochloride. The hydrochloride obtained was recrystallised from methanol-ether, to give 0.614 gm(30%) of the product, melting at 278°C.

IR(cm^{-1}):2505, 2380 ($^+NHCl^-$); 1690 (C-S); 1600 (aromatic); 1075 (C-N); 925 (vinyl); 870 (1,2,3-trisubstituted benzene); 780 (1,4-disubstituted benzene).^{1}H NMR(DMSO-d_6): 8.07-7.26 (m,11,Ar-H); 5.37 (d,1H,CH); 5.35 (q,2H,CH_2); 5.15 (m,1H,CH-vinyl); 4.76-4.10(m,8H,CH_2); 3.91-3.73 (m,8H,piperazinyl methylenes); 3.48 (t,1H,NH). Anal. Calcd. for $C_{30}H_{32}N_4S.3HCl$. N=9.49%. Found. N=9.44%.

4-(4-{2-[4-(1,2-dihydro-2-acenaphthylenyl)piperazinyl]ethyl}phenyl)-thiazole-2(3H)-one

4-[4-(2-Chloroethyl)phenyl]thiazole-2-one (122)

The procedure described by deStevens and co-workers, was modified and adopted for this preparation.[144] In a 100 ml round bottom flask equipped with a reflux condenser was placed 10.84 gm (0.05 mol) 4-(2-Chloroacetyl) phenethyl chloride (111), in 50 ml of dry acetone and 4.9 gm (0.05 mol) of potassium thiocyanate. The reaction mixture was stirred at room temperature for 3 hours. The precipitate obtained was filtered off and the filterate was evaporated under reduced pressure in a rotary evaporator. The residue was taken up in ethyl acetate and washed with water, brine and dried over anhydrous sodium

sulfate and evaporated to a solid. The solid was then taken up in 100 ml of boiling ethanol and treated slowly with 83 ml of 1 N hydrochloric acid and refluxed for 14 hours. The reaction mixture was cooled in a refrigerator and the product obtained was filtered and washed with water and recrystallised from ethanol to give 14.29 gm (55%) of 4-[4-(2-Chloroethyl) phenyl] thiazole-2-one as a white crystalline solid, melting at 162 °C (lit. m.p. 164.5 °C).

IR(cm^{-1}):1710 (C-S); 1670 (C=O); 1600 (aromatic); 825 (1,4-disubstituted benzene); 720 (C-Cl). ^1H NMR (DMSO-d_6): 11.74 (d,1H,OH(enolised); 7.98-7.61 (m,5H,Ar-H); 3.15 (t, 2H,CH_2); 3.06 (t,2H,CH_2).

4-(4-[2-[4-(1,2-dihydro-2-acenaphthylenyl)piperazinyl]ethyl]phenyl)thiazole-2(3H)-one (123)

In a 100 ml round-bottomed flask equipped with a reflux condenser and N inlet were placed 0.829 gm (0.00346 mol) of 4-[4-(2-Chloroethyl) phenyl] thiazole-2-one (122), 0.825 gm (0.00346 mol) of 1-(1,2-dihydro-2-acenaphthylenyl) piperazine (83), 0.733 gm (0.0103 mol) of anhydrous sodium carbonate, 2mg of sodium iodide, 1.79 ml (0.0103 mol) of DIPEA and 15 ml of MIBK. The reaction mixture was refluxed for 2 days and worked up according to the procedure described for (113) to give a hydrochloride. The hydrochloride obtained was recrystallised from methanol, to give 0.57 gm (32%) of the product, melting at 218°C.

IR(cm^{-1}):3400 (OH); 2395 ($^+NHCl^-$); 1680 (C-S); 1600 (aromatic); 805 (1,2,3-trisubstituted benzene); 780 (1,4-disubstituted benzene). ^1H NMR (DMSO-d_6): 11.74 (d,1H,OH (enolised);8.21-7.26(m,11,Ar-H);5.44(d,1H,CH);4.16-3.74(m,8H,piperazinylmethylenes) 3.35 (d,2H,CH_2); 3.15 (t,2H,CH_2); 3.06 (t,2H,CH_2). Anal. Calcd. for $C_{27}H_{27}N_3OS.3HCl$. N=7.62%. Found. N= 7.69 %.

5-{2-[4-(1,2-dihydro-2-acenaphthylenyl)piperazinyl]ethyl}-2,3-dihydro-1*H*-indol-2-one

2,3-dihydro-1*H*-indol-2-one (124)

The method described by Domanig was adopted for this preparation.[145] In a round bottom flask equipped with a mercury sealed stirrer, a pressure equalising dropping funnel and a reflux condenser was placed 23 ml (0.25 mol) of freshly distilled aniline and 100 ml of benzene. Chloroacetyl chloride, 20 ml (0.25 mol) was placed in the pressure equalising dropping funnel and was added drop wise to the solution with continuous stirring at 5-10°C. When the addition of the chloroacetyl chloride was completed, the reaction mixture was refluxed for 30 min. on a steam bath to ensure completion of the reaction and then cooled. A white solid product separated out which

was filtered, washed with cold benzene and then dried to give 39.80 gm (95%) of α-Chloroacetanilide, melting at 132°C (lit. m.p. 134-137°C). About 6.65 gm (0.05 mol) of this α-Chloroacetanilide was mixed with 20 gms (0.15 mol) of finely powdered anhydrous aluminium chloride in a round bottom flask and heated in an oil bath at 150°C for 14 hours. The reaction mixture was transferred slowly into a beaker containing ice-water mixture and a few ml of hydrochloric acid with continuous stirring. A solid substance separated which was filtered and the aqueous filterate was extracted exhaustively with dichloromethane. The dichloromethane extracts were combined, washed with water followed by brine solution and then dried over anhydrous sodium sulphate. The extract was treated with activated charcoal and filtered again to remove the charcoal. The solvent was removed under reduced pressure to give pale yellow oil, which crystallised on standing. The product was recrystallised from ethanol to give 1.73 gm (33%) of 2,3-dihydro-1*H*-indol-2-one, melting at 125°C (lit. m.p. 127°C).

IR(cm^{-1}):3255 (N-H); 1705 (C=O: amide); 1620 (Aromatic); 745 (1,2-disubstituted benzene). ^1H NMR ($CDCl_3$): 9.75 (s,1H,NH); 7.10-6.75 (m,4H,Ar-H); 3.45 (s,2H,CH_2).

5-(2-Chloroacetyl)-2,3-dihydro-1*H*-indol-2-one (125)

The method described by Caignard and co-workers, was modified and adopted for this preparation.[146] In a 250 ml round bottom flask equipped with a reflux condenser, a pressure equalising dropping funnel and N_2 inlet were placed 15.4 gm (0.0011 mol) of finely powdered anhydrous aluminium chloride, 100 ml of dried carbon disulphide, and 2.5 gm (0.0018 mol) of 2,3-dihydro-1*H*-indol-2-one (124). Chloroacetyl chloride, 2 ml (0.0024 mol) was taken in the dropping funnel and added to the reaction mixture drop wise with continuous stirring. The reaction mixture was stirred and the thick gummy deposit formed was then refluxed for 3 hours and cooled. The solvent was decanted and crushed ice-water mixture was added to the gummy residue with vigorous stirring, until it became a solid suspension. The solid product was filtered, washed with water, and dried. It was then recrystallised from ethanol to give 3.54 gms (90%) of product, melting at 229°C.

IR(cm^{-1}):3200 (N-H); 1705 (C=O: amide); 1670 (C=O); 1610 (Aromatic). ^1H NMR (DMSO-d_6): 7.89-6.93 (m,3H,Ar-H); 5.07 (s,2H,CH_2); 3.56 (s,2H,CH_2).

5-(2-Chloroethyl)-2,3-dihydro-1*H*-indol-2-one (126)

The method described by Vaccher-Ledein and co-workers , was modified and adopted for this preparation.[147] In a 125ml round-bottomed flask equipped with a dropping funnel and N_2 inlet was placed 3.83 gm (0.017 mol) of 5-(2-Chloroacetyl)-2,3-dihydro-1*H*-indol-2-one (125) and 13.45 ml (0.17 mol) of trifluoroacetic acid. The solution was

cooled to 0°C and 6.41 ml (0.040 mol) of triethylsilane was added drop wise over 2 minutes. The reaction mixture was stirred at room temperature for 40 hours. It was then poured into crushed ice water, layered with hexane, stirred vigourously and filtered. The product was washed with hexane and dried to give 2.29 gms (65%) of a light brown solid, melting at 171°C.

IR(cm^{-1}) :3200 (N-H) ; 1690 (C=O) ; 1620 (Aromatic)

5-[2-[4-(1,2-dihydro-2-acenaphthylenyl)piperazinyl]ethyl]-2,3-dihydro-1H-indol-2-one (127)

In a 100 ml round-bottomed flask equipped with a reflux condenser and N_2 inlet were placed 0.750 gm (0.00383 mol) of 5-(2-Chloroethyl)-2,3-dihydro-1*H*-indol-2-one (126), 0.911 gm (0.00383 mol) of 1-(1,2-dihydro-2-acenaphthylenyl) piperazine (83), 0.733 gm (0.0103 mol) of anhydrous sodium carbonate, 2mg of sodium iodide, 1.79 ml (0.0103 mol) of DIPEA and 15 ml of MIBK. The reaction mixture was refluxed for 2 days and worked up according to the procedure described for (113) to give a hydrochloride. The hydrochloride obtained was recrystallised from ethanol-ether, to give 1.15 gm (64%) of the product, melting at 236°C.

IR(cm^{-1}):3200 (N-H); 2400 ($^{+}$NHCl^{-}); 1695 (C=O: amide); 1620 (Aromatic); 1482 (C-N); 810 (1,2,3-trisubstituted benzene). ^{1}H NMR (DMSO-d_6): 8.14-7.79 (m,3H,Ar-H {oxindolyl}); 7.68-6.79(m,6H,Ar-H); 5.42(d,1H,CH); 3.94-3.75(m,8H,piperazinylmethy-lenes); 3.47 (t,4H,CH_2); 3.16 (bs,2H,CH_2). Anal. Calcd. for $C_{26}H_{27}N_3O.2HCl$. N= 8.93%. Found. N= 8.99%.

5-{2-[4-(1,2-dihydro-2-acenaphthylenyl)piperazinyl]ethyl}-1-methyl-2,3-dihydro-1*H*-indol-2-one

1-methyl-2,3-dihydro-1*H*-indol-2-one (128)

In a round bottom flask equipped with a mercury sealed stirrer, a pressure equalising dropping funnel and a reflux condenser was placed 27.70 ml (0.25 mol) of freshly distilled N-methyl aniline and 100 ml of benzene. Chloroacetyl chloride, 20 ml (0.25 mol) of was placed in the pressure equalising dropping funnel and added drop wise to the solution with continuous stirring at 5-10°C. The reaction mixture was worked up according to the procedure described for (124) to give 43 gm (93%) of α-Chloro-N-methyl acetanilide, melting at 57°C, which was further cyclised as described for (124) to give 1-methyl-2,3-dihydro-1*H*-indol-2-one (38%). The product was recrystallised from ethanol, melting at 88°C. (lit.m.p.89°C).

IR(cm^{-1}):1720(C=O,amide);1605(aromatic); 1495(C-N); 740 (1,2-disubstituted benzene). ^1H NMR (DMSO-d_6): 7.30-6.70 (m,4H,Ar-H); 3.45 (s,2H,CH_2); 3.15(s,3H,CH_3).

5-(2-Chloroacetyl)-1-methyl-2,3-dihydro-1*H*-indol-2-one (129)

In a 250 ml round bottom flask equipped with a reflux condenser, a pressure equalising dropping funnel and N_2 inlet were placed 15.4 gm (0.0011 mol) of finely powdered anhydrous aluminium chloride, 100 ml of dried carbon disulphide, and 2.0 gm (0.0018 mol) of 1-methyl-2,3-dihydro-1*H*-indol-2-one (128) . Chloroacetyl chloride, 2 ml (0.0024 mol) was taken in the dropping funnel and added to the reaction mixture drop wise with continuous stirring. The product was isolated according to procedure described for (125) to give 2.85 gms (90%) of product, which was recrystallised from ethanol, melting at 202°C.

IR(cm^{-1}):1710 (C=O, amide); 1685 (C=O); 1605 (aromatic); 710 (C-Cl). ^1H NMR (DMSO-d_6):7.80-7.12 (m,3H,Ar-H); 5.11 (s, 2H,CH_2); 3.63 (s,2H,CH_2); 3.16 (s,3H,CH_3).

5-(2-Chloroethyl)-1-methyl-2,3-dihydro-1*H*-indol-2-one (130)

In a 125ml round-bottomed flask equipped with a dropping funnel and N_2 inlet was placed 4.07 gm (0.017 mol) of 5-(2-Chloroacetyl)-1-methyl-2,3-dihydro-1*H*-indol-2-one (129) and 13.45 ml (0.17 mol) of trifluoroacetic acid. The solution was cooled to 0°C and 6.41 ml (0.040 mol) of triethylsilane was added drop wise over 2 minutes. The product was isolated according to the procedure described for (126) to give 1.00 gm (54%) of a brown solid, melting at 135°C.

IR(cm^{-1}) : 1700 (C=O, amide) ; 1610 (aromatic) ; 710 (C-Cl)

***5-[2-[4-(1,2-dihydro-2-acenaphthylenyl)piperazinyl]ethyl]-1-methyl-2,3-dihydro-1H-indol-2-one* (131)**

In a 100 ml round-bottomed flask equipped with a reflux condenser and N_2 inlet were placed 0.7919 gm (0.00378 mol) of 5-(2-Chloroethyl)-1-methyl-2,3-dihydro-1*H*-indol-2-one (130), 0.825 gm (0.00346 mol) of 1-(1,2-dihydro-2-acenaphthylenyl) piperazine (83), 0.733 gm (0.0103 mol) of anhydrous sodium carbonate, 2mg of sodium iodide, 1.79 ml (0.0103 mol) of DIPEA and 15 ml of MIBK. The reaction mixture was refluxed for 2 days and processed according to the procedure described for (113) to give a hydrochloride. The hydrochloride obtained was recrystallised from methanol- ether, to give 0.905 gm (54%) of the product, melting at 247°C.

IR(cm^{-1}):2400 ($^+NHCl^-$); 1695 (C=O, amide); 1610 (aromatic); 815 (1,2,3-trisubstituted benzene). ^1H NMR (DMSO-d_6): 8.15-7.86 (m,3H,Ar-H {oxindolyl});7.72-6.82 (m,6H,Ar-H); 5.62 (d,1H,CH); 3.78-3.60 (m,8H,piperazinyl methylenes); 3.46 (s,3H,N-CH_3); 3.38

(t,2H,CH_2); 3.15-3.06 (q,4H,methylenes). Anal. Calcd. for $C_{27}H_{29}N_3O.2HCl$. N= 8.59 %. Found. N= 8.67 %.

5-{2-[4-(1,2-dihydro-2-acenaphthylenyl)piperazinyl]ethyl}-3-methyl-2,3-dihydro-1*H*-indol-2-one

3-methyl-2,3-dihydro-1*H*-indol-2-one (132)

In a round bottom flask equipped with a mercury sealed stirrer, a pressure equalising dropping funnel and a reflux condenser was placed 22.70 ml (0.25 mol) of freshly distilled aniline and 100 ml of benzene. 2-Chloropropionyl chloride, 24.60 ml (0.25 mol) of was placed in the pressure equalising dropping funnel and added drop wise to the solution with continuous stirring at 5-10°C. The reaction mixture was worked up according to the procedure described for (124) to give 43.5 gm (96%) of α-Chloro-α-methyl acetanilide, melting at 73°C, which was further cyclised as described for (124) to give 3-methyl-2,3-dihydro-1*H*-indol-2-one (42%). The product was recrystallised from ethanol, melting at 120°C (lit.m.p.123-4°C).

IR(cm^{-1}): 3250 (N-H); 2950,1460 (methyl); 1710 (C=O, amide); 1610 (aromatic); 740 (1,2-disubstituted benzene). ^1H NMR ($CDCl_3$): 9.40 (s,1H,NH); 7.20-6.81 (q,4H,Ar-H); 3.4 (d,1H,CH); 1.45 (d,3H,CH_3).

5-(2-Chloroacetyl)-3-methyl-2,3-dihydro-1*H*-indol-2-one (133)

In a 250 ml round bottom flask equipped with a reflux condenser, a pressure equalising dropping funnel and N_2 inlet were placed 15.4 gm (0.0011 mol) of finely powdered anhydrous aluminium chloride, 100 ml of dried carbon disulphide, and 2.0 gm (0.0018 mol) of 3-methyl-2,3-dihydro-1*H*-indol-2-one (132). Chloroacetyl chloride, 2 ml (0.0024 mol) was taken in the dropping funnel and added to the reaction mixture drop wise with continuous stirring. The product was isolated according to procedure described for (125) to give 2.72 gms (90%) of product, which was recrystallised from ethanol, melting at 204°C.

IR(cm^{-1}): 3225 (NH); 1710 (C=O,amide); 1680 (C=O); 1605 (aromatic); 720 (C-Cl). ^1H NMR (DMSO-d_6): 7.78-6.90 (m,3H,Ar-H); 4.55 (s,2H,CH_2); 2.51(q,1H,NH); 1.49 (s,3H,CH_3).

5-(2-Chloroethyl)-3-methyl-2,3-dihydro-1*H*-indol-2-one (134)

In a 125ml round-bottomed flask equipped with a dropping funnel and N_2 inlet was placed 4.07 gm (0.017 mol) of 5-(2-Chloroacetyl)-3-methyl-2,3-dihydro-1*H*-indol-2-one (133) and 13.45 ml (0.17 mol) of trifluoroacetic acid. The solution was cooled to 0°C and 6.41 ml (0.040 mol) of triethylsilane was added drop wise over 2 minutes. The product

was isolated according to the procedure described for [126] to give 1.50 gm (41%) of a yellowish brown solid, melting at 143°C.

IR(cm^{-1}): 3200 (NH); 1710 (C=O, amide); 1620 (aromatic); 719 (C-Cl).

***5-{2-[4-(1,2-dihydro-2-acenaphthylenyl)piperazinyl]ethyl}-3-methyl-2,3-dihydro-1H-indol-2-one* (135)**

In a 100 ml round-bottomed flask equipped with a reflux condenser and N_2 inlet were placed 0.7919 gm (0.00378 mol) of 5-(2-Chloroethyl)-3-methyl-2,3-dihydro-1*H*-indol-2-one (134), 0.825 gm (0.00346 mol) of 1-(1,2-dihydro-2-acenaphthylenyl) piperazine (83), 0.733 gm (0.0103 mol) of anhydrous sodium carbonate, 2mg of sodium iodide, 1.79 ml (0.0103 mol) of DIPEA and 15 ml of MIBK. The reaction mixture was refluxed for 2 days and processed according to the procedure described for (113) to give a hydrochloride. The hydrochloride obtained was recrystallised from methanol-ether, to give 0.883 gm (62%) of the product, melting at 103°C.

IR(cm^{-1}) :3200 (NH); 2400 ($^+$NHCl$^-$); 1705 (C=O); 1620 (aromatic); 710 (C-Cl). ^{1}H NMR (DMSO-d_6): 8.09-7.78 (m,3H,Ar-H{oxindolyl}); 7.70-7.01 (m,6H,Ar-H); 5.46 (d,1H,CH); 3.92-3.69 (m,8H, piperazinyl methylenes); 3.38 (t,2H,CH_2); 3.15-3.06 (q,4H,methylenes); 2.59 (s,3H,CH_3); 2.51 (q,1H,NH). Anal. Calcd. for $C_{27}H_{29}N_3O.2HCl$. N= 8.64%. Found. N= 8.71%.

5-{2-[4-(1,2-dihydro-2-acenaphthylenyl)piperazinyl]ethyl}-1,3-dimethyl-2,3-dihydro-1*H*-indol-2-one

1,3-dimethyl-2,3-dihydro-1*H*-indol-2-one (136)

In a round bottom flask equipped with a mercury sealed stirrer, a pressure equalising dropping funnel and a reflux condenser was placed 27.70 ml (0.25 mol) of freshly distilled N-methyl aniline and 100 ml of benzene. 2-Chloropropionyl chloride, 24.60 ml (0.25 mol) of was placed in the pressure equalising dropping funnel and added drop wise to the solution with continuous stirring at 5-10°C. The reaction mixture was worked up according to the procedure described for (124) to give 45 gm (92%) of α-Chloro-α-methyl-N-methyl acetanilide, melting at 44°C, which was further cyclised as described for (124) to give 1,3-dimethyl-2,3-dihydro-1*H*-indol-2-one as a thick oil, which crystallised on standing and recrystallised from ethanol to give a product melting at 53°C. (lit. m.p. 55°C).

IR(cm^{-1}) (Neat): 2950,1460 (methyl); 1710 (C=O, amide); 1600 (aromatic); 740 (1,2-disubstituted). ^{1}H NMR (CDCl$_3$): 7.80-7.12 (m,4H,Ar-H); 3.40 (d,1H,CH); 3.21 (s,3H, CH_3); 1.40 (s,3H,CH_3).

5-(2-Chloroacetyl)-1,3-dimethyl-2,3-dihydro-1*H*-indol-2-one (137)

In a 250 ml round bottom flask equipped with a reflux condenser, a pressure equalising dropping funnel and N_2 inlet were placed 15.4 gm (0.0011 mol) of finely powdered anhydrous aluminium chloride, 100 ml of dried carbon disulphide, and 2.89 gm (0.0018 mol) of 1,3-dimethyl-2,3-dihydro-1*H*-indol-2-one (136). Chloroacetyl chloride, 2 ml (0.0024 mol) was taken in the dropping funnel and added to the reaction mixture drop wise with continuous stirring. The product was isolated according to procedure described for (125) to give 3.97 gms (90%) of product, which was recrystallised from ethanol, melting at 162°C.

IR(cm^{-1}) : 1710 (C=O, amide); 1680 (C=O); 1600 (aromatic); 840 (1,2,4-trisubstituted benzene). ^1H NMR ($CDCl_3$): 7.70-6.75 (m,3H,Ar-H); 4.55 (s,2H,CH_2); 3.40 (d,1H,CH); 3.21 (s,3H, CH_3); 1.40 (s,3H,CH_3).

5-(2-Chloroethyl)-1,3-dimethyl-2,3-dihydro-1*H*-indol-2-one (138)

In a 125ml round-bottomed flask equipped with a dropping funnel and N_2 inlet was placed 4.07 gm (0.017 mol) of 5-(2-Chloroacetyl)-1,3-methyl-2,3-dihydro-1*H*-indol-2-one (137) and 13.45 ml (0.17 mol) of trifluoroacetic acid. The solution was cooled to 0°C and 6.41 ml (0.040 mol) of triethylsilane was added drop wise over 2 minutes. The product was isolated according to the procedure described for (126) to give 1.50 gm (41%) of a pale yellow solid, melting at 57°C.

IR(cm^{-1}) : 1710 (C=O, amide); 1610 (aromatic); 840 (1,2,4-trisubstituted benzene).

5-{2-[4-(1,2-dihydro-2-acenaphthylenyl)piperazinyl]ethyl}-1,3-dimethyl-2,3-dihydro-1H-indol-2-one (139)

In a 100 ml round-bottomed flask equipped with a reflux condenser and N_2 inlet were placed 0.8448 gm (0.00378 mol) of 5-(2-Chloroethyl)-1,3-dimethyl-2,3-dihydro-1*H*-indol-2-one (138), 0.825 gm (0.00346 mol) of 1-(1,2-dihydro-2-acenaphthylenyl) piperazine (83), 0.733 gm (0.0103 mol) of anhydrous sodium carbonate, 2mg of sodium iodide, 1.79 ml (0.0103 mol) of DIPEA and 15 ml of MIBK. The reaction mixture was refluxed for 2 days and worked up according to the method described for (113) to give a hydrochloride. The hydrochloride obtained was recrystallised from methanol-acetone, to give 0.828 gm (48%) of the product, melting at 235°C.

IR(cm^{-1}) :2400 ($^+NHCl^-$); 1700 (C=O); 1610 (aromatic); 1495 (C-N); 810 (1,2,3-trisubstituted benzene). ^1H NMR (DMSO-d_6): 8.17-7.64 (m,3H,Ar-H{oxindolyl});7.61-6.71(m,6H,Ar-H); 5.54 (d,1H,CH); 4.16(d,2H,CH_2); 3.93-3.53 (m,8H,piperazinyl methylenes); 3.37 (t,2H,CH_2); 3.26 (d,2H,CH_2); 3.01 (s,3H,N-CH_3); 1.51 (d,3H,CH_3).

Anal. Calcd. for $C_{28}H_{31}N_3O.2HCl$. N= 8.43%. Found. N= 8.51%.

5-{2-[4-(1,2-dihydro-2-acenaphthylenyl)piperazinyl]ethyl}-1-ethyl-2,3-dihydro-1*H*-indol-2-one

1-ethyl-2,3-dihydro-1*H*-indol-2-one (140)

In a round bottom flask equipped with a mercury sealed stirrer, a pressure equalising dropping funnel and a reflux condenser was placed 31.70 ml (0.25 mol) of freshly distilled N-ethyl aniline and 100 ml of benzene. Chloroacetyl chloride, 20 ml (0.25 mol) of was placed in the pressure equalising dropping funnel and added drop wise to the solution with continuous stirring at 5-10°C. The reaction mixture was worked up according to the procedure described for (124) to give 47 gm (96%) of α-Chloro-N-ethyl acetanilide, melting at 49°C, which was further cyclised as described for (124) to give 1-ethyl-2,3-dihydro-1*H*-indol-2-one (38%). The product was recrystallised from ethanol, melting at 95°C. (lit. m.p. 97°C).

IR(cm^{-1}) :1710 (C=O, amide); 1610 (aromatic); 740 (1,2-disubstituted).^{1}H NMR ($CDCl_3$) 7.80-7.12 (m,4H, Ar-H); 3.40 (d,1H,CH); 3.21 (s,2H,CH_2); 1.40 (s,3H,CH_3).

5-(2-Chloroacetyl)-1-ethyl-2,3-dihydro-1*H*-indol-2-one (141)

In a 250 ml round bottom flask equipped with a reflux condenser, a pressure equalising dropping funnel and N_2 inlet were placed 15.4 gm (0.0011 mol) of finely powdered anhydrous aluminium chloride, 100 ml of dried carbon disulphide, and 2.99 gm (0.0018 mol) of 1-ethyl-2,3-dihydro-1*H*-indol-2-one (140). Chloroacetyl chloride, 2 ml (0.0024 mol) was taken in the dropping funnel and added to the reaction mixture drop wise with continuous stirring. The product was isolated according to procedure described for (125) to give 3.91 gms (85%) of product, which was recrystallised from ethanol, melting at 231°C.

IR(cm^{-1}): 1710 (C=O, amide); 1670 (C=O); 1610 (aromatic). ^{1}H NMR ($CDCl_3$):7.80-7.12 (m,4H,Ar-H); 3.98 (d,2H,CH_2); 3.40 (d,2H,CH_2); 3.21 (s,2H,CH_2); 1.40 (s,3H,CH_3)

5-(2-Chloroethyl)-1-ethyl-2,3-dihydro-1*H*-indol-2-one (142)

In a 125ml round-bottomed flask equipped with a dropping funnel and N_2 inlet was placed 4.32 gm (0.017 mol) of 5-(2-Chloroacetyl)-1-ethyl-2,3-dihydro-1*H*-indol-2-one (141) and 13.45 ml (0.17 mol) of trifluoroacetic acid. The solution was cooled to 0°C and 6.41 ml (0.040 mol) of triethylsilane was added drop wise over 2 minutes. The product was isolated according to the procedure described for (126) to give 2.03 gm (52%) of a tan solid, melting at 154°C.

IR(cm^{-1}) 1690 (C=O) ; 1620 (aromatic) ; 1495 (C-N) 720 (methylene)

5-{2-[4-(1,2-dihydro-2-acenaphthylenyl)piperazinyl]ethyl}-1-ethyl-2,3-dihydro-1H-indol-2-one **(143)**

In a 100 ml round-bottomed flask equipped with a reflux condenser and N_2 inlet were placed 0.8448 gm (0.00378 mol) of 5-(2-Chloroethyl)-1-ethyl-2,3-dihydro-1*H*-indol-2-one (142), 0.825 gm (0.00346 mol) of 1-(1,2-dihydro-2-acenaphthylenyl) piperazine (83), 0.733 gm (0.0103 mol) of anhydrous sodium carbonate, 2mg of sodium iodide, 1.79 ml (0.0103 mol) of DIPEA and 15 ml of MIBK. The reaction mixture was refluxed for 2 days and worked up according to the procedure described for (113) to give a hydrochloride. The hydrochloride obtained was recrystallised from ethanol, to give 0.80 gm (42%) of the product, melting at 245°C.

IR(cm^{-1}) : 2400(⁺NHCl⁻); 1695(C=O); 1620 (aromatic); 1495(C-N); 810(1,2,3-trisubstituted benzene). ^{1}H NMR (DMSO-d_6): 8.15-7.69 (m,3H,Ar-H[oxindolyl]); 7.64-6.79 (m,6H,Ar-H); 5.43 (d,1H,CH); 3.96 (d,2H,N-CH_2); 3.77 (q,4H,methylenes); 3.48-3.01 (m,8H,piperazinyl methylenes); 2.30 (d,2H,CH); 1.25 (d,3H,CH_3). Anal. Calcd. for $C_{28}H_{31}N_3O.2HCl$. N=8.43%. Found. N= 8.41%.

6-Chloro-5-{2-[4-(1,2-dihydro-2-acenaphthylenyl)piperazinyl]ethyl}-2,3-dihydro-1H-indol-2-one

6-Chloro-2,3-dihydro-1*H*-indol-2-one (144)

In a round bottom flask equipped with a mercury sealed stirrer, a pressure equalising dropping funnel and a reflux condenser was placed 26.80 ml (0.25 mol) of freshly distilled 3-chloro aniline and 100 ml of benzene. Chloroacetyl chloride, 20 ml (0.25 mol) of was placed in the pressure equalising dropping funnel and added drop wise to the solution with continuous stirring at 5-10°C. The reaction mixture was worked up according to the procedure described for (124) to give 46.4 gm (92%) of α-Chloro-(3-chloro phenyl) acetamide, melting at 115°C, which was further cyclised as described for (124) to give 6-chloro-2,3-dihydro-1*H*-indol-2-one(42%). The product was recrystallised from ethanol, melting at 103°C.

IR(cm^{-1}): 3300 (N-H); 1705 (C=O); 1620 (aromatic); 800 (1,2,4-trisubstituted benzene). ^{1}H NMR ($CDCl_3$): 7.92-7.12 (m,3H, Ar-H); 3.40 (d,1H, NH) ; 3.21 (d,2H,CH_2).

6-Chloro-5-(2-Chloroacetyl)-2,3-dihydro-1*H*-indol-2-one (145)

In a 250 ml round bottom flask equipped with a reflux condenser, a pressure equalising dropping funnel and N_2 inlet were placed 15.4 gm (0.0011 mol) of finely powdered anhydrous aluminium chloride, 100 ml of dried carbon disulphide, and 3.114 gm (0.0018

mol) of 6-chloro-2,3-dihydro-1*H*-indol-2-one (144). Chloroacetyl chloride, 2 ml (0.0024 mol) was taken in the dropping funnel and added to the reaction mixture drop wise with continuous stirring. The product was isolated according to procedure described for (125) to give 3.10 gms (69%) of product, which was recrystallised from benzene-petroleum ether, melting at 190°C.

IR(cm^{-1}) : 3300 (N-H); 1705 (C=O,amide); 1675 (C=O); 1620 (aromatic). ^1H NMR ($CDCl_3$): 7.92-7.12 (m,3H,Ar-H); 3.40 (d,1H,NH); 3.21 (d,2H,CH_2); 3.11(s,2H,CH_2).

6-Chloro-5-(2-Chloroethyl)-2,3-dihydro-1*H*-indol-2-one (146)

In a 125ml round-bottomed flask equipped with a dropping funnel and N_2 inlet was placed 4.28 gm (0.017 mol) of 6-chloro-5-(2-Chloroacetyl)-2,3-dihydro-1*H*-indol-2-one (145) and 13.45 ml (0.17 mol) of trifluoroacetic acid. The solution was cooled to 0°C and 6.41 ml (0.040 mol) of triethylsilane was added drop wise over 2 minutes. The product was isolated according to the procedure described for (126) to give 2.10 gm (53%) of a reddish brown solid, melting at 158°C.

IR(cm^{-1}) : 3300 (N-H); 1705 (C=O,amide); 1620 (aromatic); 720 (methylene). ^1H NMR ($CDCl_3$): 7.92-7.12 (m,3H,Ar-H); 3.40 (d,1H,NH); 3.21 (q,4H,CH_2); 3.11 (s,2H,CH_2).

***6-Chloro-5-[2-[4-(1,2-dihydro-2-acenaphthylenyl)piperazinyl]ethyl]-2,3-dihydro-1H-indol-2-one* (147)**

In a 100 ml round-bottomed flask equipped with a reflux condenser and N_2 inlet were placed 0.7733 gm (0.00346 mol) of 6-chloro-5-(2-Chloroethyl)-2,3-dihydro-1*H*-indol-2-one (146), 0.825 gm (0.00346 mol) of 1-(1,2-dihydro-2-acenaphthylenyl) piperazine (83), 0.733 gm (0.0103 mol) of anhydrous sodium carbonate, 2mg of sodium iodide, 1.79 ml (0.0103 mol) of DIPEA and 15 ml of MIBK. The reaction mixture was refluxed for 2 days and worked up according to the procedure described for (113) to give a hydrochloride. The hydrochloride obtained was recrystallised from ethanol-ether, to give 0.70 gm (40%) of the product, melting at 228°C.

IR(cm^{-1}) : 3400 (N-H); 1695 (C=O); 1598 (aromatic); 1525 (C-N); 800(1,2,3-trisubstituted benzene). ^1H NMR (DMSO-d_6): 7.83-7.70 (m,2H,Ar-H{oxindolyl}); 7.67-6.74 (m,6H,Ar-H); 5.48 (d,1H,CH); 3.98-3.59 (m,8H,piperazinyl methylenes); 3.53-3.44 (m,4H,CH_2); 3.17 (q,2H,CH_2). Anal. Calcd. for $C_{26}H_{26}N_3OCl.2HCl$. N= 8.32%. Found. N= 8.39%.

6-Fluoro-5-{2-[4-(1,2-dihydro-2-acenaphthylenyl)piperazinyl]ethyl}-2,3-dihydro-1*H*-indol-2-one

6-Fluoro-2,3-dihydro-1*H*-indol-2-one (148)

In a round bottom flask equipped with a mercury sealed stirrer, a pressure equalising dropping funnel and a reflux condenser was placed 26.80 ml (0.25 mol) of freshly distilled 3-fluoro aniline and 100 ml of benzene. Chloroacetyl chloride, 20 ml (0.25 mol) of was placed in the pressure equalising dropping funnel and added drop wise to the solution with continuous stirring at 5-10°C. The reaction mixture was worked up according to the procedure described for (124) to give 44.4 gm (92%) of α-Chloro-(3-fluoro phenyl) acetamide, melting at 125°C, which was further cyclised as described for (124) to give 6-fluoro-2,3-dihydro-1*H*-indol-2-one (35%).The product was recrystallised from ethanol, melting at 109°C.

IR(cm^{-1}) : 3300 (N-H);1700 (C=O); 1620 (aromatic); 1200 (C-F). ^{1}H NMR ($CDCl_3$): 7.12-6.85 (m,3H,Ar-H); 3.55 (d,1H,NH); 3.11 (d,2H,CH_2).

5-(2-Chloroacetyl)-6-Fluoro-2,3-dihydro-1*H*-indol-2-one (149)

In a 250 ml round bottom flask equipped with a reflux condenser, a pressure equalising dropping funnel and N_2 inlet were placed 15.4 gm (0.0011 mol) of finely powdered anhydrous aluminium chloride, 100 ml of dried carbon disulphide, and 2.81 gm (0.0018 mol) of 6-fluoro-2,3-dihydro-1*H*-indol-2-one (148). Chloroacetyl chloride, 2 ml (0.0024 mol) was taken in the dropping funnel and added to the reaction mixture drop wise with continuous stirring. The product was isolated according to procedure described for (125) to give 3.60 gms (85%) of product, which was recrystallised from ethanol, melting at 203°C.

IR(cm^{-1}) : 3200 (N-H); 1710 (C=O,amide); 1690 (C=O); 1605 (aromatic); 1200 (C-F). ^{1}H NMR ($CDCl_3$): 7.12-6.19 (d,2H,Ar-H); 3.55 (d,1H,NH); 3.11 (d,2H,CH_2); 2.95 (s,2H, CH_2).

5-(2-Chloroethyl)-6-Fluoro-2,3-dihydro-1*H*-indol-2-one (150)

In a 125ml round-bottomed flask equipped with a dropping funnel and N_2 inlet was placed 3.97 gm (0.017 mol) of 5-(2-Chloroacetyl)-6-fluoro-2,3-dihydro-1*H*-indol-2-one (149) and 13.45 ml (0.17 mol) of trifluoroacetic acid. The solution was cooled to 0°C and 6.41 ml (0.040 mol) of triethylsilane was added drop wise over 2 minutes. The product was isolated according to the procedure described for (126) to give 1.94 gm (51%) of a reddish brown solid, melting at 185°C.

IR(cm^{-1}) : 3200 (N-H); 1700 (C=O); 1630 (aromatic); 1200 (C-F); 720(methylene).

6-Fluoro-5-{ 2-[4-(1,2-dihydro-2-acenaphthylenyl)piperazinyl]ethyl }-2,3-dihydro-1H-indol-2-one **(151)**

In a 100 ml round-bottomed flask equipped with a reflux condenser and N_2 inlet were placed 0.7387 gm (0.00346 mol) of 5-(2-Chloroethyl)-6-fluoro-2,3-dihydro-1*H*-indol-2-one (150), 0.825 gm (0.00346 mol) of 1-(1,2-dihydro-2-acenaphthylenyl) piperazine (83), 0.733 gm (0.0103 mol) of anhydrous sodium carbonate, 2mg of sodium iodide, 1.79 ml (0.0103 mol) of DIPEA and 15 ml of MIBK. The reaction mixture was refluxed for 2 days and worked up according to the procedure described for (113) to give a hydrochloride. The hydrochloride obtained was recrystallised from ethanol- ether, to give 0.760 gm (45%) of the product, melting at 248°C.

IR(cm^{-1}) : 3190 (N-H); 2400 ($^+$NHCl$^-$); 1700 (C=O); 1622 (aromatic); 1480 (C-N); 810 (1,2,3-trisubstituted benzene). ^{1}H NMR (DMSO-d_6): 8.11-7.78 (m,2H,Ar-H{oxindolyl}); 7.68-6.60 (m,6H,Ar-H); 5.47 (d,1H,CH); 3.92-3.72 (m,8H,piperazinyl methylenes); 3.55-3.30 (m,4H,CH_2); 3.19 (q,2H,CH_2). Anal.Calcd. for $C_{26}H_{26}N_3OF.2HCl$. N=8.60%. Found. N=8.69%.

6-{2-[4-(1,2-dihydro-2-acenaphthylenyl)piperazinyl]ethyl}-benzoxazol-2(3*H*)-one

6-(2-Bromoacetyl)benzoxazol-2(3*H*)-one (152)

The method described by Caignard and co-workers, was adopted for this preparation.[146] In a 500 ml three necked round bottomed flask equipped with a mechanical stirrer and N_2 inlet were placed 200 gm of polyphosphoric acid, 13.51 gm (0.1mol)of benzoxazolone and 13.89 gm (0.1 mol) of bromoacetic acid. The reaction mixture was heated with stirring at 115°C for 2.5 hours and then poured into 1 kg of ice. The mixture was stirred mechanically for 1 hour to form a purple solid, which was then filtered and washed with water. The solid was slurried with acetone for 30 min, a small amount of insoluble purple solid was filtered, and the brown filterate evaporated. The resulting dark brown gummy product was taken up in 150 ml of ethanol and stirred for 30 minutes. The brown insoluble solid was filtered and washed with ethanol. This solid melted at 218°C (lit.[132] m.p. 228°C) and was used directly without further purification.

IR(cm^{-1}) : 3250 (N-H); 1780 (C=O:amide); 1725 (C=O); 1620 (Aromatic). ^{1}H NMR (DMSO-d_6): 12.13 (d,1H,enolised); 7.89-7.24 (m,3H,Ar-H); 2.56 (s,2H,CH_2).

6-(2-Bromoethyl)benzoxazol-2(3*H*)-one (153)

In a 125ml round-bottomed flask equipped with a dropping funnel and N_2 inlet was placed 0.4335 gm (0.0017 mol) of 6-(2-Bromoacetyl) benzoxazol-2(3H)-one (152) and 13.45 ml (0.0017 mol) of trifluoroacetic acid. The solution was cooled to 0°C and 6.41ml

(0.0040 mol) of triethylsilane was added drop wise over 2 minutes. The product was isolated according to the procedure described for (126) to give 0.15 gm (11%) of a tan coloured solid, melting at 134°C (lit. m.p.142°C).[132]

IR(cm^{-1}) : 3250 (N-H); 1760 (C=O:amide); 1620 (Aromatic); 700 (CH_2).

6-[2-[4-(1,2-dihydro-2-acenaphthylenyl) piperazinyl] ethyl]- benzoxazol-2(3-H)-one (154)

In a 100 ml round-bottomed flask equipped with a reflux condenser and N_2 inlet were placed 0.839 gm (0.00347 mol) of 6-(2-Bromoethyl) benzoxazol-2(3*H*)-one (153), 0.825 gm (0.00347 mol) of 1-(1,2-dihydro-2-acenaphthylenyl) piperazine (83), 0.733 gm (0.0103 mol) of anhydrous sodium carbonate, 2mg of sodium iodide, 1.79 ml (0.0103 mol) of DIPEA and 15 ml of MIBK. The reaction mixture was refluxed for 2 days and processed according to the procedure described for (113) to give a hydrochloride salt. The hydrochloride obtained was recrystallised from ethanol-ether, to give 1.07 gm (40%) of the product, melting at 255°C.

IR(cm^{-1}) : 3450 (N-H); 2400 ($^+NHCl^-$); 1760 (C=O:amide); 1620 (Aromatic); 810 (1,2,3-trisubstituted benzene). ^1H NMR (DMSO-d_6) : 8.13-6.90 (m,9H,Ar-H); 5.42 (d,1H,CH); 4.01-3.76 (m,8H,piperazinyl methylenes); 3.38-3.01(m,6H,CH_2). Anal. Calcd. for $C_{25}H_{25}N_3O_2.2HCl$. N=8.80%. Found. N=8.76%.

SERIES – II

1,3-Diacetyl Indole (155)

The method described by Saxton was adopted for this preparation.[148] In a 500 ml round bottom flask equipped with a reflux condenser and N_2 inlet were placed, Indole 23.43 gm (0.2 mol), acetic acid glacial 24 gm (0.4 mol), acetic anhydride 221 gm (2.2 mol) and the reaction mixture was refluxed for 24 hours. The solvent was removed by distillation under reduced pressure and the crude residue (22 gm, 55%), was recrystallised from ethanol. 1,3-Diacetyl indole, 13 gm (32%) of pure material was obtained as colourless needles, melting at 150-151°C (lit.m.p.151°C). The susbtance could also be recrystallised from benzene.

IR (cm^{-1}) : 1700,1650 (C=O); 1600 (aromatic); 745 (1,2-disubstituted benzene). ^1H NMR ($CDCl_3$): 8.32-7.24(m,5H,Ar-H); 2.71(s,3H,CH_3); 2.57(s,3H,CH_3).Anal. Calcd. for $C_{12}H_{11}NO_2$. C=71.63%; H=5.51%; N=6.96%. Found. C=71.78%; H=5.53%; N=6.99 %.

3-Acetyl indole (156)

The method described by Saxton was adopted for this preparation.[148] In a 500 ml round bottom flask, were placed a mixture of 1,3-diacetyl indole (155) 30 gm (0.15 mol), ethanol 225 ml, sodium hydroxide solution 75 ml (2N) and stirred until the solution of the diacetyl indole was completed. A by-product [1,1-di-(1-acetyl-3-indolyl)ethylene, about 3 gms] remained as an insoluble crystalline powder and was removed by filteration and washed with warm ethanol. Thereafter, 3-acetyl indole was precipitated from the combined filterates on dilution with water. The product was recrystallised from ethanol to give 18 gm (76%) of 3-acetyl indole as long, colourless prisms, melting at 191°C (lit. m.p. 190.5-191.5°C).

IR (cm^{-1}) : 3400 (N-H); 1650 (C=O); 1605 (aromatic); 745(1,2-disubstituted benzene). ^1H NMR ($CDCl_3$-DMSO-d_6) : 7.99-6.81 (m,6H,Ar-H); 2.20 (s,3H,CH_3). Anal. Calcd. for $C_{10}H_9N$ O. C=75.38%; H=5.65% ; N=8.79%. Found. C=75.45%; H=5.70%; N=8.81%.

1-Methyl-3-acetyl indole (157)

The method described by Baskakov and Mel'nikov was adopted for this preparation.[149] In a 1 litre flat bottom flask equipped with a pressure equalising dropping funnel were placed, 14 gm (0.088 mol) of 3-acetyl indole (156) and 30 gm sodium hydroxide in 300 ml of water. Dimethyl sulphate, 63 gm (0.5 mol) was placed in the dropping funnel and was added drop wise to the solution with continuous stirring over one hour at 80 - 85 °C. The reaction mixture was stirred for 4 hours and allowed to stand overnight in a refrigerator. The reaction mixture was filtered and the product was washed free of alkali and taken up in hot benzene. The solution on cooling in a refrigerator gave a pink crystalline substance which was filtered and dried at room temperature, to give 14 gm (95%) of the product, melting at 95°C.

IR(cm^{-1}):1630(C=O); 1605(aromatic); 1180(C-N); 740(1,2-disubstituted benzene).^1H NMR ($CDCl_3$): 8.37-7.21(m,5H,Ar-H); 3.76(t,3H,CH_3); 2.42(t,3H,CH_3). Anal. Calcd. for $C_{11}H_{11}NO$. C=76.21%; H=6.40%; N=8.09%. Found. C=76.44%; H=6.42%; N=8.12%.

1-(1-Methyl-1*H*-3-indolyl)-3-(4-phenyl piperazin-1-yl)-1- propanone (158)

The method described by Szmuskovicz was modified and adopted for this preparation.[150] In a 50 ml round bottom flask equipped with a reflux condenser and N_2 inlet were placed 0.4787 gm (0.0027 mol) of 1-methyl-3-acetyl indole (157), 0.124 gm (0.0041 mol) of paraformaldehyde, 0.6976 gm (0.0027 mol) of 1-phenyl piperazine and 15 ml of absolute ethanol. The pH was adjusted to 4 and the mixture was refluxed for 19 hours. The solvent was evaporated to dryness under reduced pressure, to give a semisolid residue. The residue was dissolved in dried acetone by warming. The resulting solution on cooling

gave the product as its hydrochloride, which was not stable. The hydrochloride was dissolved in water and the aqueous solution was basified with a 10% solution of potassium hydroxide. The solution was then extracted with three 25-ml portions of diethyl ether. The combined ether extracts were dried over anhydrous sodium sulphate and evaporated to give the free base as an oily product, which was converted into its monofumarate in *n*-butanol-hexane. The monofumarate was recrystallised from isopropyl alcohol to give 1.24 gm (59%) of the product, melting at 220°C.

IR (cm^{-1})[Neat]: 1655 (C=O); 1600 (aromatic); 1160 (C-N); 755 (1,2-disubstituted benzene); 705 (monosubstituted benzene). ^1H NMR (DMSO-d_6): 8.47-6.84 (m,10H,Ar-H); 4.25-3.20 (m,12H,methylenes); 2.51 (s,3H,CH_3). Anal. Calcd. for $C_{22}H_{25}N_3O$. $C_4H_4O_4$. N=9.07%. Found. N=9.05%.

3-[4-(3-Chloro phenyl) piperazin-1-yl]-1-(1-methyl-1*H*-3-indolyl)-1-propanone (159)

The method described for (158) was adopted for its preparation. In a 50 ml round bottom flask equipped with a reflux condenser and N_2 inlet were placed 0.866 gm (0.005 mol) of 1-methyl-3-acetyl indole (157), 0.225 gm (0.0075 mol) of paraformaldehyde and 1.1657 gm (0.005 mol) of 1-(3-chlorophenyl) piperazine hydrochloride and 15 ml of absolute ethanol. The mixture was refluxed for 19 hours. The solvent was evaporated to dryness under reduced pressure to give a semisolid residue. The residue was dissolved in dried acetone by warming. The resulting solution on cooling gave a solid substance, which was recrystallised from methanol-ether to give 1.17 gm (51%) of the product as its hydrochloride, melting at 241°C.

IR (cm^{-1}): 2425 ($^+NHCl^-$); 1645 (C=O); 1600 (aromatic); 1540,1080 (C-N); 790 (1,3-disubstituted benzene); 760 (1,2-disubstituted benzene). ^1H NMR(D_2O): 8.29-7.02 (m,9H,Ar-H); 4.69 (d,2H,CH_2); 3.92-3.35(m,10H,methylenes); 2.21 (s,3H,CH_3). Anal. Calcd. for $C_{22}H_{24}N_3OCl.2HCl$. N=9.24%. Found. N=9.13%.

3-[4-(4-Chloro phenyl) piperazin-1-yl]-1-(1-methyl-1*H*-3-indolyl)-1-propanone (160)

In a 50 ml round bottom flask equipped with a reflux condenser and N_2 inlet were placed 0.866 gm (0.005 mol) of 1-methyl-3-acetyl indole (157), 0.225 gm (0.0075 mol) of paraformaldehyde, 1.1657 gm (0.005 mol) of 1-(4-chlorophenyl)piperazine hydrochloride and 15 ml of absolute ethanol and refluxed for 19 hours. The reaction mixture was worked up according to the procedure described for (159), to give a solid substance, which was recrystallised from methanol-ether to give 1.31 gm (57%) of the product as it's hydrochloride, melting at 249°C.

IR (cm^{-1}): 2325 ($^+NHCl^-$); 1660 (C=O); 1620 (aromatic); 1500,1520 (C-N); 780 (1,3-disubstituted benzene); 752 (1,2-disubstituted benzene). ^1H NMR (DMSO-d_6): 7.45-6.84

(m,8H,Ar-H); 3.38 (d,8H,methylenes); 3.20 (q,4H,methylenes); 2.43 (s,3H,CH_3). Anal. Calcd. for $C_{22}H_{24}N_3OCl.2HCl$. N= 9.24%. Found. N=9.11%.

3-[4-(4-Fluoro phenyl) piperazin-1-yl]-1-(1-methyl-1*H*-3-indolyl)-1-propanone (161)

In a 50 ml round bottom flask equipped with a reflux condenser and N_2 inlet were placed 0.866 gm (0.005 mol) of 1-methyl-3-acetyl indole (157), 0.225 gm (0.0075 mol) of paraformaldehyde, 0.9011 gm (0.005 mol) of 1-(4-fluorophenyl) piperazine and 15 ml of absolute ethanol. The pH was adjusted to 4 and the mixture was refluxed for 19 hours. The reaction mixture was worked up according to the procedure described for (159), to give a solid substance, which was recrystallised from methanol-ether to give 0.895 gm (41%) of the product as it's hydrochloride, melting at 237°C.

IR (cm^{-1}): 2550 ($^+NHCl^-$); 1635 (C=O); 1600 (aromatic); 1320 (Ar-F); 1180(C-N); 795 (1,4-disubstituted benzene); 760 (1,2-disubstituted benzene). ^1H NMR (D_2O): 7.33-7.18 (m,8H,Ar-H) ; 3.62-3.54 (m,12H,methylenes) ; 2.20 (s,3H,CH_3). Anal. Calcd. for $C_{22}H_{24}N_3OF.2HCl$. N= 9.57%. Found. N= 9.61%.

3-[4-(2-Methoxy phenyl) piperazin-1-yl]-1-(1-methyl-1*H*-3-indolyl)-1-propanone (162)

In a 50 ml round bottom flask equipped with a reflux condenser and N_2 inlet were placed 0.866 gm (0.005 mol) of 1-methyl-3-acetyl indole (157), 0.225 gm (0.0075 mol) of paraformaldehyde, 1.1436gm (0.005 mol) of 1-(2-methoxyphenyl) piperazine hydrochloride and 15 ml of absolute ethanol and refluxed for 19 hours. The reaction mixture was worked up according to the procedure described for (159), to give a solid substance, which was recrystallised from methanol-ether to give 1.10 gm (49%) of the product as it's hydrochloride, melting at 210°C.

IR (cm^{-1}): 2475 ($^+NHCl^-$); 1640 (C=O); 1595 (aromatic); 1520,1180 (C-N); 1245 (Ar-O-CH_3); 737 (1,2-disubstituted benzene). ^1H NMR (DMSO-d_6): 7.20-6.66 (m,9H,Ar-H); 3.66 (s,3H, Ar-O-CH_3); 3.48 (d,2H,CH_2); 3.20(m,10H,methylenes);1.04 (s,3H,CH_3). Anal. Calcd. for $C_{23}H_{27}N_3O_2.2HCl$. N= 9.32%. Found. N=9.28%.

3-[4-(3-Methoxy phenyl) piperazin-1-yl]-1-(1-methyl-1*H*-3-indolyl)-1-propanone (163)

In a 50 ml round bottom flask equipped with a reflux condenser and N_2 inlet were placed 0.866 gm (0.005 mol) of 1-methyl-3-acetyl indole (157), 0.225 gm (0.0075 mol) of paraformaldehyde, 1.3259 gm (0.005 mol) of 1-(3-methoxyphenyl) piperazine dihydrochloride and 15 ml of absolute ethanol and refluxed for 19 hours. The reaction mixture was worked up according to the procedure described for (158) and recrystallised

from isopropyl alcohol, to give 0.808 gm (43%) of the product as it's mono fumarate, melting at 215°C.

IR (cm^{-1}):1635 (C=O); 1610 (aromatic); 1510 (C-N); 1260,1245 (Ar-O-CH_3);790 (1,3-disubstituted benzene); 745 (1,2-disubstituted benzene). ^1H NMR (DMSO-d_6); 8.43-6.45 (m,9H,Ar-H); 3.85-3.13 (m,12H,methylenes); 3.07 (s,3H,Ar-O-CH_3); 2.58(s,3H,CH_3). Anal. Calcd. for $C_{23}H_{27}N_3O_2.C_4H_4O_4$ .N=8.50%. Found. N= 8.53%.

3-[4-(4-Methoxy phenyl) piperazin-1-yl]-1-(1-methyl-1*H*-3-indolyl)-1-propanone (164)

In a 50 ml round bottom flask equipped with a reflux condenser and N_2 inlet were placed 0.866 gm (0.005 mol) of 1-methyl-3-acetyl indole (157), 0.225 gm (0.0075 mol) of paraformaldehyde, 1.3259 gm (0.005 mol) of 1-(4-Methoxyphenyl) piperazine dihydrochloride and 15 ml of absolute ethanol and refluxed for 19 hours. The reaction mixture was worked up according to the procedure described for (159) to give a solid substance, which was recrystallised from methanol-ether to give 0.900 gm (48%) of the product as it's hydrochloride, melting at 253°C.

IR (cm^{-1}): 2350 ($^+NHCl^-$); 1620 (C=O); 1605 (aromatic); 1495 (C-N); 1245,1035 (Ar-O-CH_3);780(1,4-disubstituted benzene);740(1,2-disubstituted benzene). ^1H NMR(DMSO-d_6) 7.20-6.91 (m,8H,Ar-H); 4.49 (bs,10H,methylenes); 3.70 (d,2H,CH_2); 3.44 (s,3H,Ar-O-CH_3); 3.32 (s,3H,CH_3). Anal. Calcd. for $C_{23}H_{27}N_3O_2.2HCl$. N=9.32%. Found.N=9.37%.

1-(1-Methyl-1*H*-3-indolyl)-3-[4-(3-trifluoromethylphenyl)piperazin-1-yl]-1-propanone (165)

In a 50 ml round bottom flask equipped with a reflux condenser and N_2 inlet were placed 0.866 gm (0.005 mol) of 1-methyl-3-acetyl indole (157), 0.225 gm (0.0075 mol) of paraformaldehyde, 1.1511 gm (0.005 mol) of 1-(3-trifluoromethyl phenyl) piperazine and 15 ml of absolute ethanol. The pH was adjusted to 4 and the mixture was refluxed for 19 hours. The reaction mixture was worked up according to the procedure described for (159) to give a solid substance, which was recrystallised from methanol-ether to give 0.949 gm (39%) of the product as it's hydrochloride, melting at 224°C.

IR (cm^{-1}): 2485 ($^+NHCl^-$); 1660 (C=O); 1600 (aromatic); 1495 (C-N); 1120(C-F_3);790 (1,3-disubstituted benzene); 740 (1,2-disubstituted benzene). ^1H NMR (DMSO-d_6):8.13-7.33 (m,9H,Ar-H); 3.23-3.03 (m,10H,methylenes); 2.63 (d,2H,CH_2); 1.57 (t,3H,CH_3). Anal. Calcd. for $C_{23}H_{24}N_3OF_3.2HCl$. N=8.60%. Found. N=8.69%.

1-(1-Methyl-1*H*-3-indolyl)-3-[4-(2-pyridyl) piperazin-1-yl]-1- propanone (166)

Ino a 50 ml round bottom flask equipped with a reflux condenser and N_2 inlet were placed 0.866 gm (0.005 mol) of 1-methyl-3-acetyl indole (157), 0.225 gm (0.0075 mol) of paraformaldehyde, 0.8161 gm (0.005 mol) of 1-(2-pyridyl) piperazine and 15 ml of absolute ethanol. The pH was adjusted to 4 and the mixture was refluxed for 19 hours. The reaction mixture was worked up according to the procedure described for (159) to give a solid substance, which was recrystallised from methanol-ether to give 1.15 gm (58%) of the product as it's hydrochloride, melting at 258°C.

IR (cm^{-1}): 2425 ($^+NHCl^-$); 1655 (C=O); 1595 (aromatic); 1525,1510 (C=N); 1180 (C-N); 749 (1,2-disubstituted benzene). ^1H NMR (D_2O) :8.16-7.11(m,9H,Ar-H) ;4.8-3.47 (m,12H,methylenes);2.21 (s,3H,CH_3). Anal. Calcd.for $C_{21}H_{24}N_4O.2HCl$. N=13.28%. Found. N=13.33%.

1-(1-Methyl-1*H*-3-indolyl)-3-[4-(2-pyrimidinyl) piperazin-1-yl]-1- propanone (167)

In a 50 ml round bottom flask equipped with a reflux condenser and N_2 inlet were placed 0.866 gm (0.005 mol) of 1-methyl-3-acetyl indole (157), 0.225 gm (0.0075 mol) of paraformaldehyde, 1.1856 gm (0.005 mol) of 1-(2-pyrimidinyl) piperazine dihydrochloride and 15 ml of absolute ethanol and refluxed for 19 hours. The reaction mixture was worked up according to the procedure described for (159) to give a solid substance, which was recrystallised from methanol-ether to give 1.26 gm (61%) of the product as it's hydrochloride, melting at 225°C.

IR (cm^{-1}): 2475 ($^+NHCl^-$); 1655 (C=O); 1595 (aromatic); 1530, 1520 (C=N); 1160(C-N); 742 (1,2-disubstituted benzene). ^1H NMR (D_2O): 8.39-6.79 (m,8H,Ar-H); 3.99-3.32 (m,12H,methylenes); 2.20 (s,3H,CH_3). Anal. Calcd. for $C_{20}H_{23}N_5O.2HCl$. N=16.57%. Found. N=16.59%.

1-Ethyl-3-acetyl indole (168)

The method described by Baskakov and Mel'nikov, was adopted for this preparation.[149] In a 1 litre flat bottom flask equipped with a pressure equalising dropping funnel were placed, 14 gm (0.088 mol) of 3-acetyl indole (156) and 30 gm sodium hydroxide in 300 ml of water. Diethyl sulphate, 43.55 ml (0.5 mol) of was placed in the dropping funnel and was added drop wise to the solution with continuous stirring over one hour at 80-85°C. The reaction mixture was stirred for 4 hours and allowed to stand overnight in a refrigerator. The reaction mixture was filtered and the product was washed free of alkali and taken up in hot benzene. The solution on cooling in a refrigerator gave a light brown crystalline substance, which was filtered and dried at room temperature, to give 12.50 gm (76%) of the product, melting at 88°C.

IR (cm^{-1}): 1630 (C=O);1605 (aromatic); 1180 (C-N); 740 (1,2-disubstituted benzene). ^1H NMR ($CDCl_3$): 8.35-7.19 (m,5H,Ar-H); 4.20 (q,2H,CH_2); 3.76 (t,3H,CH_3); 2.42(t, 3H,CH_3).Anal.Calcd.for $C_{12}H_{13}NO$.C=76.90%; H=6.94%; N=7.47%. Found. C=76.98%; H=6.94%; N=7.48%.

1-(1-Ethyl-1*H*-3-indolyl)-3-(4-phenyl piperazin-1-yl)-1- propanone (169)

In a 50 ml round bottom flask equipped with a reflux condenser and N_2 inlet were placed 0.69 gm (0.0037 mol) of 1-ethyl-3-acetyl indole (168), 0.222 gm (0.0074 mol) of paraformaldehyde, 0.597 gm (0.0037 mol) of 1-phenyl piperazine and 15 ml of absolute ethanol. The pH was adjusted to 4 and the mixture was refluxed for 19 hours. The reaction mixture was worked up according to the procedure described for (159), to give a solid substance, which was recrystallised from methanol-ether to give 1.06 gm (49%) of the product as it's hydrochloride, melting at 201°C.

IR (cm^{-1}): 2510 ($^+NHCl^-$);1655 (C=O); 1600 (aromatic); 1160 (C-N); 745 (1,2-disubstituted benzene); 695 (monosubstituted benzene). ^1H NMR (DMSO-d_6): 7.65-6.84 (m,10H,Ar-H); 4.37 (q,2H,NCH_2); 3.93-2.51 (m,12H,methylenes); 1.49 (q,3H,CH_3). Anal. Calcd. for $C_{23}H_{27}N_3O.2HCl$. N= 9.67%. Found. N= 9.65%.

3-[4-(3-Chloro phenyl) piperazin-1-yl]-1-(1-ethyl-1*H*-3-indolyl)-1-propanone (170)

In a 50 ml round bottom flask equipped with a reflux condenser and N_2 inlet were placed 0.9362 gm (0.005 mol) of 1-ethyl-3-acetyl indole [168], 0.300 gm (0.010 mol) of paraformaldehyde, 1.3988 gm (0.006 mol) of 1-(3-chlorophenyl) piperazine hydrochloride and 15 ml of absolute ethanol and refluxed for 19 hours. The reaction mixture was worked up according to the procedure described for (159) to give a solid substance, which was recrystallised from methanol-ether to give 0.861 gm (35%) of the product as it's hydrochloride, melting at 202°C.

IR (cm^{-1}): 2505 ($^+NHCl^-$); 1660 (C=O); 1600 (aromatic); 1495 (C-N); 1040 (C-Cl); 780 (1,3-disubstituted benzene); 747 (1,2-disubstituted benzene). ^1H NMR(DMSO-d_6): 7.65-6.84 (m,9H,Ar-H); 4.02 (q,2H,NCH_2); 3.46-3.14 (m,10H,methylenes); 2.51 (s,2H,CH_2); 1.45 (t,3H,CH_3). Anal. Calcd. for $C_{23}H_{26}N_3OCl.2HCl$. N=8.95%. Found. N=8.89%.

3-[4-(4-Chloro phenyl) piperazin-1-yl]-1-(1-ethyl-1*H*-3-indolyl)-1-propanone (171)

In a 50 ml round bottom flask equipped with a reflux condenser and N_2 inlet were placed 0.9362 gm (0.005 mol) of 1-ethyl-3-acetyl indole (168), 0.300 gm (0.010 mol) of paraformaldehyde, 1.3988 gm (0.006 mol) of 1-(4-chlorophenyl) piperazine hydrochloride and 15 ml of absolute ethanol and was refluxed for 19 hours. The reaction mixture was worked up according to the procedure described for (159) to give a solid

substance, which was recrystallised from methanol-ether to give 0.961 gm (41%) of the product as it's hydrochloride, melting at 220°C.

IR (cm^{-1}): 2435 ($^{+}NHCl^{-}$); 1630 (C=O); 1595 (aromatic); 1520 (C-N); 1020 (C-Cl); 795 (1,4-disubstituted benzene); 743 (1,2-disubstituted benzene). ^{1}H NMR (DMSO-d_6):8.22-6.59 (m,9H,Ar-H); 4.36 (q,2H,NCH_2); 3.58-3.38 (m,10H,methylenes); 3.21(t,2H,CH_2); 1.49 (t,3H,CH_3). Anal. Calcd. for $C_{23}H_{26}N_3OCl.2HCl$. N=8.95%. Found. N=8.89%.

1-(1-Ethyl-1*H*-3-indolyl)-3-[4-(4-fluoro phenyl) piperazin-1-yl]- 1-propanone (172)
In a 50 ml round bottom flask equipped with a reflux condenser and N_2 inlet were placed 0.9362 gm (0.005 mol) of 1-ethyl-3-acetyl indole (168), 0.300 gm (0.010 mol) of paraformaldehyde, 1.0814 gm (0.006 mol) of 1-(4-fluorophenyl) piperazine and 15 ml of absolute ethanol. The pH was adjusted to 4 and the mixture was refluxed for 19 hours. The reaction mixture was worked up according to the procedure described for (159) to give a solid substance, which was recrystallised from methanol-ether to give 0.972 gm (43%) of the product as it's hydrochloride, melting at 227°C.

IR (cm^{-1}): 2350 ($^{+}NHCl^{-}$); 1630 (C=O); 1590 (aromatic); 1510 (C-N); 1720(C-F); 780 (1,4-disubstituted benzene); 760(1,2-disubstituted benzene). ^{1}H NMR (DMSO-d_6):8.49-6.15 (m,9H,Ar-H); 4.64 (q,2H,NCH_2); 3.91-2.44 (m,12H,methylenes); 1.23 (t,3H,CH_3). Anal. Calcd.for $C_{23}H_{26}N_3OF.2HCl$. N=9.28%. Found. N=9.31%.

1-(1-Ethyl-1*H*-3-indolyl)-3-[4-(2-methoxy phenyl) piperazin-1-yl]- 1-propanone (173)
In a 50 ml round bottom flask equipped with a reflux condenser and N_2 inlet were placed 0.9362 gm (0.005 mol) of 1-ethyl-3-acetyl indole (168), 0.300 gm (0.010 mol) of paraformaldehyde, 1.3723 gm (0.006 mol) of 1-(2-methoxyphenyl) piperazine hydrochloride and 15 ml of absolute ethanol and refluxed for 19 hours. The reaction mixture was worked up according to the procedure described for (159) to give a solid substance, which was recrystallised from methanol-ether to give 0.907 gm (39%) of the product as it's hydrochloride, melting at 217°C.

IR (cm^{-1}): 2475 ($^{+}NHCl^{-}$); 1640 (C=O); 1603 (aromatic); 1520,1180 (C-N); 1260 (Ar-O-CH_3); 750 (1,2-disubstituted benzene). ^{1}H NMR (DMSO-d_6): 8.26-7.06 (m,9H,Ar-H); 4.22 (q,2H,NCH_2); 3.63-3.23 (m,10H,methylenes); 3.15 (s,3H,Ar-O-CH_3); 2.72 (t,2H, CH_2); 1.62 (t,3H,CH_3). Anal. Calcd. for $C_{24}H_{29}N_3O_2.2HCl$. N=9.04%. Found. N=9.06%.

1-(1-Ethyl-1*H*-3-indolyl)-3-[4-(3-methoxyphenyl) piperazin-1-yl]-1-propanone (174)
In a 50 ml round bottom flask equipped with a reflux condenser and N_2 inlet were placed 0.9362 gm (0.005 mol) of 1-ethyl-3-acetyl indole (168), 0.300 gm (0.010 mol) of

paraformaldehyde, 1.591 gm (0.006 mol) of 1-(3-methoxyphenyl) piperazine dihydrochloride and 15 ml of absolute ethanol and refluxed for 19 hours. The reaction mixture was worked up according to the procedure described for (159). The hydrochloride obtained was not stable and was hence dissolved in water. The aqueous solution was basified with a 10% solution of potassium hydroxide, to give a crude product, which was recrystallised from ethanol-petroleum ether, to give 1.093 gm (48%) of the product as the free base melting at 111°C.

IR (cm^{-1}): 1640 (C=O); 1603 (aromatic); 1520,1180 (C-N); 1260 (Ar-O-CH_3); 775 (1,3-disubstituted benzene); 740 (1,2-disubstituted benzene). ^1H NMR ($CDCl_3$): 8.18-6.97 (m,9H,Ar-H); 4.36 (q,2H,NCH_2); 3.83-3.37 (m,10H,methylenes); 3.20 (s,3H,Ar-O-CH_3); 2.5(t,2H,CH_2);1.49(t,3H,CH_3).Anal.Calcd.for $C_{24}H_{29}N_3O_2$.N=10.74%.Found.N=10.79%.

1-(1-Ethyl-1*H*-3-indolyl)-3-[4-(4-methoxy phenyl) piperazin-1-yl]- 1-propanone (175)

In a 50 ml round bottom flask equipped with a reflux condenser and N_2 inlet were placed 0.9362 gm (0.005 mol) of 1-ethyl-3-acetyl indole (168), 0.300 gm (0.010 mol) of paraformaldehyde, 1.3723 gm (0.006 mol) of 1-(4-methoxyphenyl) piperazine hydrochloride and 15 ml of absolute ethanol and refluxed for 19 hours. The reaction mixture was worked up according to the procedure described for (159) to give a solid substance, which was recrystallised from methanol-ether to give 1.12 gm (50%) of the product as it's hydrochloride, melting at 251°C.

IR (cm^{-1}): 2325 ($^+NHCl^-$); 1640 (C=O); 1600 (aromatic); 1510,1040 (C-N); 1200 (Ar-O-CH_3); 780 (1,3-disubstituted benzene); 750 (1,2-disubstituted benzene). ^1H NMR (DMSO-d_6):8.19-6.87 (m,9H,Ar-H); 4.37 (q,2H,NCH_2); 3.84-3.54 (m,10H, methylenes); 3.33(s,3H,Ar-O-CH_3);2.51(t,2H,CH_2);1.49(t,3H,CH_3).Anal.Calcd. for $C_{24}H_{29}N_3O_2$ .2HCl. N=9.05%. Found. N=9.02%.

1-(1-Ethyl-1*H*-3-indolyl)-3-[4-(3-trifluoromethylphenyl)piperazin-1-yl]-1-propanone (176)

In a 50 ml round bottom flask equipped with a reflux condenser and N_2 inlet were placed 0.9362 gm (0.005 mol) of 1-ethyl-3-acetyl indole (168), 0.300 gm (0.010 mol) of paraformaldehyde, 1.3813 gm (0.006 mol) of 1-(3-trifluoromethyl phenyl) piperazine and 15 ml of absolute ethanol. The pH was adjusted to 4 and the mixture was refluxed for 19 hours. The reaction mixture was worked up according to the procedure described for (159) to give a solid substance, which was recrystallised from methanol-ether to give 0.956 gm (38%) of the product as it's hydrochloride, melting at 218°C.

IR (cm^{-1}): 2525 ($^+NHCl^-$); 1640 (C=O); 1595 (aromatic); 1520,1070 (C-N); 1120 (CF_3); 790 (1,3-disubstituted benzene); 740 (1,2-disubstituted benzene). ^1H NMR (DMSO-d_6): 8.23-7.13 (m,9H,Ar-H); 4.37 (q,2H,NCH_2); 3.55-3.20 (m,10H,methylenes);2.52 (d,2H,CH_2); 1.49 (t,3H,CH_3). Anal. Calcd. for $C_{24}H_{26}N_3OF_3.2HCl$. N=8.36%. Found. N=8.42%.

1-(1-Ethyl-1*H*-3-indolyl)-3-[4-(2-pyridyl) piperazin-1-yl]-1- propanone (177)

In a 50 ml round bottom flask equipped with a reflux condenser and N_2 inlet were placed 0.9362 gm (0.005 mol) of 1-ethyl-3-acetyl indole (168), 0.300 gm (0.010 mol) of paraformaldehyde, 0.9793 gm (0.006 mol) of 1-(2-pyridyl) piperazine and 15 ml of absolute ethanol . The pH was adjusted to 4 and the mixture was refluxed for 19 hours. The reaction mixture was worked up according to the procedure described for (159) to give a solid substance, which was recrystallised from methanol-ether to give 1.01 gm (51%) of the product as it's hydrochloride, melting at 259°C.

IR (cm^{-1}): 2550 ($^+NHCl^-$); 1637 (C=O); 1600 (aromatic); 1540,1520 (C=N); 1140 (C-N); 757 (1,2-disubstituted benzene). ^1H NMR (DMSO-d_6): 8.55-6.96 (m,9H,Ar-H); 4.54 (q,2H,NCH_2); 3.97-2.48(m,12H,methylenes);1.45(t,3H,CH_3). Anal.Calcd.for $C_{22}H_{26}N_4O.2HCl$. N=12.87%. Found. N=12.91%.

1-(1-Ethyl-1*H*-3-indolyl)-3-[4-(2-pyrimidinyl) piperazin-1-yl]-1- propanone (178)

In a 50 ml round bottom flask equipped with a reflux condenser and N_2 inlet were placed 0.9362 gm (0.005 mol) of 1-ethyl-3-acetyl indole (168), 0.300 gm (0.010 mol) of paraformaldehyde, 1.4227 gm (0.006 mol) of 1-(2-pyrimidinyl) piperazine dihydrochloride and 15 ml of absolute ethanol and refluxed for 19 hours. The reaction mixture was worked up according to the procedure described for (159) to give a solid substance, which was recrystallised from methanol-ether to give 1.03 gm (48%) of the product as it's hydrochloride, melting at 231°C.

IR (cm^{-1}): 2515 ($^+NHCl^-$); 1640 (C=O); 1603 (aromatic); 1543,1520 (C=N); 1110 (C-N); 760 (1,2-disubstituted benzene). ^1H NMR (DMSO-d_6): 8.55-6.73 (m,9H,Ar-H); 4.76 (q,2H,NCH_2); 4.00-3.13 (m,12H, methylenes); 1.49 (t,3H,CH_3). Anal. Calcd. for $C_{21}H_{25}N_5O.2HCl$. N=16.05%. Found. N=16.12%.

1-(4-Fluoro phenyl)-3-acetyl indole (179)

The following procedure was devised for its preparation based on the procedures described by Perregaard and co-workers.[151,152,153] In a 100 ml round bottom flask equipped with a reflux condenser and N_2 inlet were placed 3.98 gm (0.025 mol) of 3-acetyl indole, 4.18 ml (0.036 mol) of 4- fluoroiodobenzene, 2.08 gm (0.014 mol) of copper bromide, 100 mg of activated copper metal powder, 5.78 gm (0.034 mol) of

anhydrous potassium carbonate in 35 ml of N-methyl-2-pyrrolidone (NMP) and heated at 180°C in an oil bath for 4 hours. The mixture was cooled to room temperature and poured into 150 ml of a dilute solution of hydrochloric acid, where upon a yellowish brown solid substance separated out. The solid was filtered and washed thoroughly with water and dried at 100°C. The dried solid was repeatedly digested with 25 ml portions of boiling dichloromethane. A small amount of insoluble residue was left, which was removed by filteration. The filterate was treated with activated charcoal and filtered to remove the charcoal. The extract was then washed with water followed by brine solution to remove traces of acidic impurities and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to dryness, where upon a brown solid substance was obtained. This crude substance was recrystallised from hot absolute alcohol to give 3.48 gm (55%) of the product as a pale yellow crystalline substance, melting at 140-141°C.

IR (cm^{-1}): 1630 (C=O); 1600 (aromatic); 1520 (C-N); 810 (1,4-disubstituted benzene); 740 (1,2-disubstituted benzene). ^1H NMR ($CDCl_3$): 8.47(q,1H,Ar-H);7.88-6.89(m,8H,Ar -H); 2.57 (s,3H,CH_3). Anal. Calcd. for $C_{16}H_{12}NOF$. C=75.88%; H=4.78%; N=5.53 %. Found. C=76.17%; H=4.80%; N=5.54%.

1-[1-(4-Fluorophenyl)-1*H*-3-indolyl]-3-(4-phenyl piperazin-1-yl)-1-propanone (180)

In a 50 ml round bottom flask equipped with a reflux condenser and N_2 inlet were placed 0.7595 gm (0.0029 mol) of 1-(4-fluoro phenyl) -3-acetyl indole (179), 0.135 gm (0.0045 mol) of paraformaldehyde, 0.3196 gm (0.0029 mol) of 1-phenyl piperazine and 15 ml of absolute ethanol. The pH was adjusted to 4 and the reaction mixture was refluxed for 19 hours. The reaction mixture was worked up according to the procedure described for (158) and recrystalised from isopropyl alcohol, to give 0.847 gm (52%) of the product as it's monofumarate, melting at 178°C.

IR (cm^{-1}): 1640 (C=O); 1595 (aromatic); 1575 (carboxylate); 1160 (C-N); 759(1,2-disubstituted benzene); 695 (monosubstituted benzene). ^1H NMR (DMSO-d_6): 7.28-6.46 (m,14H,Ar-H); 3.76-3.12(m,10H,methylenes); 2.51 (s,2H,CH_2). Anal. Calcd. for $C_{27}H_{26}N_3OF.C_4H_4O_4$ .N=7.73%. Found. N=7.75%.

3-[4-(3-Chlorophenyl)piperazin-1-yl]-1-[1-(4-fluorophenyl)-1*H*-3-indolyl]-1-propanone (181)

In a 50 ml round bottom flask equipped with a reflux condenser and N_2 inlet were placed 1.01 gm (0.004 mol) of 1-(4-fluoro phenyl) -3-acetyl indole (179), 0.18 gm (0.006 mol) of paraformaldehyde, 0.932 gm (0.004 mol) of 1-(3-chloro phenyl) piperazine hydrochloride and 15 ml of absolute ethanol and the reaction mixture was refluxed for 19 hours. The reaction mixture was worked up according to the procedure described for

(159) to give a solid substance, which was recrystallised from methanol-ether to give 0.865 gm (47%) of the product as its hydrochloride, melting at 145°C.

IR (cm^{-1}): 2495 ($^{+}NHCl^{-}$); 1640(C=O); 1595 (aromatic); 1550,1180 (C-N); 1050 (C-Cl); 770 (1,4-disubstituted benzene); 756 (1,3-disubstituted benzene); 740 (1,2-disubstituted benzene). ^{1}H NMR (DMSO-d_6):8.30-6.73 (m,13H,Ar-H); 3.76-2.84(m,10H,methylenes); 2.57 (s,2H,CH_2). Anal. Calcd. for $C_{27}H_{25}N_3OFCl.2HCl$. N=7.85%. Found. N=7.92%.

3-[4-(4-Chlorophenyl)piperazin-1-yl]-1-[1-(4-fluorophenyl)-1*H*-3-indolyl]-1-propanone (182)

In a 50 ml round bottom flask equipped with a reflux condenser and N_2 inlet were placed 0.7595 gm (0.0029 mol) of 1-(4-fluoro phenyl) -3-acetyl indole (179), 0.135 gm (0.0045 mol) of paraformaldehyde, 0.699 gm (0.0029 mol) of 1-(4-chloro phenyl) piperazine dihydrochloride and 15 ml of absolute ethanol and the reaction mixture was refluxed for 19 hours. The reaction mixture was worked up according to the procedure described for (159) to give a solid substance, which was recrystallised from methanol-ether to give 0.865 gm (47%) of the product as its hydrochloride, melting at 210°C.

IR (cm^{-1}): 2495 ($^{+}NHCl^{-}$); 1640(C=O); 1595 (aromatic); 1540,1180 (C-N); 1050 (C-Cl); 770 (1,4-disubstituted benzene); 740 (1,2-disubstituted benzene). ^{1}H NMR (DMSO-d_6): 8.29-6.57 (m,13H,Ar-H); 3.99-2.90(m,10H,methylenes); 2.60 (s,2H,CH_2). Anal. Calcd. for $C_{27}H_{25}N_3OFCl.2HCl$. N=7.85%. Found. N=7.79%.

1-[1-(4-Fluorophenyl)-1*H*-3-indolyl]-3-(4-(4-fluorophenyl)piperazin-1-yl)-1-propanone [183]

In a 50 ml round bottom flask equipped with a reflux condenser and N_2 inlet were placed 0.7595 gm (0.0029 mol) of 1-(4-fluoro phenyl) -3-acetyl indole (179), 0.135 gm (0.0045 mol) of paraformaldehyde, 0.766 gm (0.0029 mol) of 1-(4-fluoro phenyl) piperazine dihydrochloride and 15 ml of absolute ethanol and the reaction mixture was refluxed for 19 hours. The reaction mixture was worked up according to the procedure described for (159) to give a solid substance, which was recrystallised from methanol-ether to give 0.606 gm (39%) of the product as its hydrochloride, melting at 175°C.

IR (cm^{-1}): 2475 ($^{+}NHCl^{-}$); 1640(C=O); 1605 (aromatic); 1520, 1180 (C-N); 770 (1,4-disubstituted benzene); 740 (1,2-disubstituted benzene). ^{1}H NMR (DMSO-d_6):8.32-7.05 (m,13H,Ar-H); 3.77-3.16(m,10H,methylenes); 2.52 (s,2H,CH_2). Anal. Calcd. for $C_{27}H_{25}N_3OF_2.2HCl$. N=8.10%. Found. N=8.06%.

1-[1-(4-Fluorophenyl)-1*H*-3-indolyl]-3-[4-(2-methoxyphenyl)piperazin-1-yl]-1-propanone (184)

In a 50 ml round bottom flask equipped with a reflux condenser and N_2 inlet were placed 0.7595 gm (0.0029 mol) of 1-(4-fluoro phenyl) -3-acetyl indole (179), 0.135 gm (0.0045 mol) of paraformaldehyde, 0.686 gm (0.0029 mol) of 1-(2-methoxy phenyl) piperazine hydrochloride and 15 ml of absolute ethanol and the reaction mixture was refluxed for 19 hours. The reaction mixture was worked up according to the procedure described for (159) to give a solid substance, which was recrystallised from methanol-ether to give 0.7314 gm (46%) of the product as its hydrochloride, melting at 135°C.

IR (cm^{-1}): 2475 ($^+NHCl^-$); 1650(C=O); 1595 (aromatic); 1530,1180 (C-N); 1235 (Ar-O-CH_3); 770 (1,4-disubstituted benzene); 740 (1,2-disubstituted benzene). ^1H NMR (DMSO-d_6): 8.32-6.93 (m,13H,Ar-H); 3.80-3.31(m,10H,methylenes); 3.20 (s,3H,Ar-O-CH_3); 2.52 (s,2H,CH_2). Anal. Calcd. for $C_{28}H_{28}N_3O_2F.2HCl$. N=7.92%. Found.N=7.99%.

1-[1-(4-Fluorophenyl)-1*H*-3-indolyl]-3-[4-(3-methoxyphenyl)piperazin-1-yl]-1-propanone (185)

In a 50 ml round bottom flask equipped with a reflux condenser and N_2 inlet were placed 0.7595 gm (0.0029 mol) of 1-(4-fluoro phenyl) -3-acetyl indole (179), 0.135 gm (0.0045 mol) of paraformaldehyde, 0.795 gm (0.0029 mol) of 1-(3-methoxy phenyl) piperazine dihydrochloride and 15 ml of absolute ethanol and the reaction mixture was refluxed for 19 hours. The reaction mixture was worked up according to the procedure described for (159). The hydrochloride obtained was not stable and was hence dissolved in water. The aqueous solution was basified with a 10% solution of potassium hydroxide, to give a crude product which was recrystallised from ethanol-petroleum ether, to give 0.672 gm (49%) of the product as its free base, melting at 90°C.

IR (cm^{-1}): 1660(C=O); 1600 (aromatic); 1520, 1180 (C-N); 1260 (Ar-O-CH_3); 770 (1,4-disubstituted benzene); 760 (1,3-disubstituted benzene); 740 (1,2-disubstituted benzene). ^1H NMR (DMSO-d_6): 8.47-6.38 (m,13H,Ar-H); 3.99-3.49(m,10H,methylenes); 3.07 (s,3H,Ar-O-CH_3); 2.58 (s,2H,CH_2). Anal. Calcd. for $C_{28}H_{28}N_3O_2F$ .N=9.18%. Found. N=9.26%.

1-[1-(4-Fluorophenyl)-1*H*-3-indolyl]-3-[4-(4-methoxyphenyl)piperazin-1-yl]-1-propanone (186)

In a 50 ml round bottom flask equipped with a reflux condenser and N_2 inlet were placed 0.7595 gm (0.0029 mol) of 1-(4-fluoro phenyl) -3-acetyl indole (179), 0.135 gm (0.0045 mol) of paraformaldehyde, 0.686 gm (0.0029 mol) of 1-(4-methoxy phenyl) piperazine hydrochloride and 15 ml of absolute ethanol and the reaction mixture was refluxed for 19

hours. The reaction mixture was worked up according to the procedure described for (159) to give a solid substance, which was recrystallised from methanol-ether to give 0.8585 gm (54%) of the product as its hydrochloride, melting at 151°C.

IR (cm^{-1}): 2350 ($^{+}NHCl^{-}$);1645(C=O); 1600 (aromatic); 1510,1180 (C-N); 1210 (Ar-O-CH_3); 770 (1,4-disubstituted benzene); 735 (1,2-disubstituted benzene). ^1H NMR (DMSO-d_6): 8.31-6.83 (m,13H,Ar-H); 3.69-3.36(m,10H, methylenes);3.22(s,3H,Ar-O-CH_3);2.52 (s,2H,CH_2). Anal. Calcd. for $C_{28}H_{28}N_3O_2F.2HCl$. N=7.92%. Found. N=7.84%.

1-[1-(4-Fluorophenyl)-1*H*-3-indolyl]-3-[4-(3-trifluoromethyl phenyl) piperazin-1-yl]-1-propanone (187)

In a 50 ml round bottom flask equipped with a reflux condenser and N_2 inlet were placed 0.50 gm (0.0019 mol) of 1-(4-fluoro phenyl)-3-acetyl indole (179), 0.088 gm (0.0029 mol) of paraformaldehyde, 0.454 gm (0.0019 mol) of 1-(3-trifluoromethyl phenyl) piperazine and 15 ml of absolute ethanol. The pH was adjusted to 4 and the reaction mixture was refluxed for 19 hours. The reaction mixture was worked up according to the procedure described for (159) to give a solid substance, which was recrystallised from methanol-ether to give 0.436 gm (39%) of the product as its hydrochloride, melting at 220°C.

IR (cm^{-1}): 2525 ($^{+}NHCl^{-}$); 1650(C=O); 1590 (aromatic); 1540,1175 (C-N); 1120 (CF_3); 790 (1,4-disubstituted benzene); 772 (1,3-disubstituted benzene);740 (1,2-disubstituted benzene).^1H NMR (DMSO-d_6): 8.33-7.10 (m,13H,Ar-H); 3.99-3.03(m,10H, methylenes); 2.51 (s,2H,CH_2). Anal. Calcd. for $C_{28}H_{25}N_3OF_4.2HCl$, N=7.39%. Found. N=7.41%.

1-[1-(4-Fluorophenyl)-1*H*-3-indolyl]-3-[4-(2-pyridyl)piperazin-1-yl]-1-propanone (188)

In a 50 ml round bottom flask equipped with a reflux condenser and N_2 inlet were placed 0.7595 gm (0.0029 mol) of 1-(4-fluoro phenyl) -3-acetyl indole [179], 0.135 gm (0.0045 mol) of paraformaldehyde, 0.708 gm (0.0029 mol) of 1-(2-pyridyl) piperazine dihydrochloride and 15 ml of absolute ethanol and the reaction mixture was refluxed for 19 hours. The reaction mixture was worked up according to the procedure described for (159) to give a solid substance, which was recrystallised from methanol-ether to give 0.887 gm (59%) of the product as its hydrochloride, melting at 265°C.

IR (cm^{-1}): 2475 ($^{+}NHCl^{-}$);1640(C=O); 1590 (aromatic); 1530,1180 (C-N); 1545(C=N); 770 (1,4-disubstituted benzene); 740 (1,2-disubstituted benzene). ^1H NMR (DMSO-d_6): 8.27-6.99 (m,13H,Ar-H); 3.93-3.27(m,10H, methylenes);2.53 (s,2H,CH_2). Anal. Calcd. for $C_{26}H_{25}N_4OF.2HCl$. N=11.17%. Found. N=11.24%.

1-[1-(4-Fluorophenyl)-1*H*-3-indolyl]-3-[4-(2-pyrimidinyl)piperazin-1-yl]-1-propanone (189)

In a 50 ml round bottom flask equipped with a reflux condenser and N_2 inlet were placed 0.7595 gm (0.0029 mol) of 1-(4-fluoro phenyl) -3-acetyl indole (179), 0.135 gm (0.0045 mol) of paraformaldehyde, 0.711 gm (0.0029 mol) of 1-(2-pyrimidinyl) piperazine dihydrochloride and 15 ml of absolute ethanol and the reaction mixture was refluxed for 19 hours. The reaction mixture was worked up according to the procedure described for (159) to give a solid substance, which was recrystallised from methanol-ether to give 0.919 gm (61%) of the product as its hydrochloride, melting at 235°C.

IR (cm^{-1}): 2510 ($^+NHCl^-$);1630(C=O); 1590 (aromatic); 1530,1180 (C-N); 1565 (C=N) ; 770 (1,4-disubstituted benzene); 740 (1,2-disubstituted benzene). ^1H NMR (DMSO-d_6): 8.47-6.73 (m,12H,Ar-H); 4.00-3.15(m,10H, methylenes); 2.65 (s,2H,CH_2). Anal. Calcd. for $C_{25}H_{24}N_5OF.2HCl$. N=13.94%. Found. N=14.01%.

1-(4-Fluoro benzoyl)-3-acetyl indole (190)

The following procedure was devised for its preparation. In a 100 ml round bottom flask equipped with a reflux condenser were placed, 3 gm (0.0188 mol) of 3-acetyl indole and 2.989 ml (0.025 mol) of 4-Fluoro benzoyl chloride in 35 ml of benzene. Triethylamine (anhydrous), 2.6167 ml (0.0188 mol) was added drop wise to the solution with continuous stirring and the reaction mixture was refluxed for 7 hours. The solution was cooled and the solid substance that separated was filtered. The filterate was washed with water and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to give a yellow coloured solid. The solid was recrystallised from ethanol to give 2 gm (63%) of a fawn coloured crystalline product, melting at 154°C.

IR (cm^{-1}): 1700,1655 (C=O); 1595 (aromatic); 800 (1,4-disubstituted benzene); 750 (1,2-disubstituted benzene). ^1H NMR ($CDCl_3$): 8.37-7.18 (m,9H,Ar-H); 2.47 (t,3H,CH_3). Anal. Calcd. for $C_{17}H_{12}NO_2F$. C=72.59%; H=4.30%; N=4.98%. Found. C=72.65%; H=4.37%; N=5.02%.

1-(1-(4-Fluorobenzoyl)-1*H*-3-indolyl)-3-(4-phenyl piperazin-1-yl)-1-propanone (191)

In a 50 ml round bottom flask equipped with a reflux condenser and N_2 inlet were placed 0.6829 gm (0.0024 mol) of 1-(4-fluoro benzoyl)-3-acetyl indole (190), 0.108 gm (0.0036 mol) of paraformaldehyde, 0.3929 gm (0.0024 mol) of 1-phenyl piperazine and 15 ml of absolute ethanol. The pH was adjusted to 4 and the mixture was refluxed for 19 hours. The reaction mixture was worked up according to the procedure described for (159). The hydrochloride obtained was not stable and was hence dissolved in water. The aqueous solution was basified with a 10% solution of potassium hydroxide, to give a crude

product, which was recrystallised from ethanol-hexane, to give 0.455 gm (41%) of the product as its free base, melting at 94°C.

IR (cm^{-1}): 1695, 1640 (C=O); 1595 (aromatic); 1180 (C-N); 795 (1,4-disubstituted benzene); 755 (1,2-disubstituted benzene); 700 (monosubstituted benzene). ^1H NMR (DMSO-d_6):9.42-6.91(m,14H,Ar-H);3.72-3.46(m,8H,methylenes);3.22(bs,4H,methylene) Anal. Calcd. for $C_{28}H_{26}N_3O_2F$. N=9.23%. Found. N=9.29%.

3-[4-(3-Chlorophenyl)piperazin-1-yl)-1-(1-(4-fluorobenzoyl)-1*H*-3-indolyl)-1-propanone (192)

In a 50 ml round bottom flask equipped with a reflux condenser and N_2 inlet were placed 1.4064 gm (0.005 mol) of 1-(4-fluoro benzoyl)-3-acetyl indole (190), 0.300 gm (0.010 mol) of paraformaldehyde, 1.3988 gm (0.006 mol) of 1-(3-chloro phenyl) piperazine hydrochloride and 15 ml of absolute ethanol and the reaction mixture was refluxed for 19 hours. The reaction mixture was worked up according to the procedure described for (159) to give a solid substance, which was recrystallised from methanol-ether to give 1.60 gm (57%) of the product as its hydrochloride, melting at 191°C.

IR (cm^{-1}): 2495 ($^+NHCl^-$); 1695, 1640 (C=O); 1580 (aromatic); 1175 (C-N); 790 (1,4-disubstituted benzene); 770 (1,3-disubstituted benzene); 755 (1,2-disubstituted benzene). ^1H NMR (DMSO-d_6): 9.61-6.82 (m,13H,Ar-H); 3.53-3.40 (m,8H,piperazinylmethylenes) 3.14(bs,4H,methylenes).Anal.Calcd.for $C_{28}H_{25}N_3O_2FCl.2HCl$.N=7.46%.Found.N=7.51%

3-[4-(4-Chlorophenyl)piperazin-1-yl)-1-(1-(4-fluorobenzoyl)-1*H*-3-indolyl)-1-propanone (193)

In a 50 ml round bottom flask equipped with a reflux condenser and N_2 inlet were placed 1.4064 gm (0.005 mol) of 1-(4-fluoro benzoyl)-3-acetyl indole (190), 0.300 gm (0.010 mol) of paraformaldehyde, 1.3988 gm (0.006 mol) of 1-(4-chloro phenyl) piperazine hydrochloride and 15 ml of absolute ethanol and the reaction mixture was refluxed for 19 hours. The reaction mixture was worked up according to the procedure described for (159) to give a solid substance, which was recrystallised from methanol-ether to give 1.66 gm (59%) of the product as it's hydrochloride, melting at 249°C.

IR (cm^{-1}): 2500 ($^+NHCl^-$);1695,1640 (C=O); 1595 (aromatic); 1175 (C-N); 805 (1,4-disubstituted benzene); 743 (1,2-disubstituted benzene). ^1H NMR (DMSO-d_6): 9.53-6.96 (m,13H,Ar-H); 3.52-3.38 (m,8H,piperazinyl methylenes); 3.16 (bs,4H,methylenes). Anal. Calcd. for $C_{28}H_{25}N_3O_2FCl.2HCl$. N=7.46%. Found. N=7.49%.

1-(1-(4-Fluorobenzoyl)-1*H*-3-indolyl)- 3-[4-(4-fluorophenyl) piperazin-1-yl]- 1-propanone (194)

In a 50 ml round bottom flask equipped with a reflux condenser and N_2 inlet were placed 1.4064 gm (0.005 mol) of 1-(4-fluoro benzoyl)-3-acetyl indole (190), 0.300 gm (0.010 mol) of paraformaldehyde, 1.0814 gm (0.006 mol) of 1-(4-fluoro phenyl) piperazine and 15 ml of absolute ethanol. The pH was adjusted to 4 and the reaction mixture was refluxed for 19 hours. The reaction mixture was worked up according to the procedure described for (159) to give a solid substance, which was recrystallised from methanol-ether to give 0.901 gm (33%) of the product as it's hydrochloride, melting at 230°C.

IR (cm^{-1}): 2300 w ($^+NHCl^-$); 1695,1640 (C=O); 1605 (aromatic); 1180(C-N); 800 (1,4-disubstituted benzene); 760 (1,2-disubstituted benzene). ^1H NMR (DMSO-d_6):9.46-6.98 (m,13H,Ar-H); 3.32-3.29 (m,8H,piperazinyl methylenes); 3.18 (bs,4H,methylenes). Anal. Calcd. for $C_{28}H_{25}N_3O_2F_2.2HCl$. N=7.68%. Found. N=7.73%.

1-(1-(4-Fluorobenzoyl)-1*H*-3-indolyl)- 3-[4-(2-methoxyphenyl) piperazin-1-yl]- 1-propanone (195)

In a 50 ml round bottom flask equipped with a reflux condenser and N_2 inlet were placed 1.4064 gm (0.005 mol) of 1-(4-fluoro benzoyl)-3-acetyl indole (190), 0.300 gm (0.010 mol) of paraformaldehyde, 1.3723 gm (0.006 mol) of 1-(2-methoxy phenyl) piperazine hydrochloride and 15 ml of absolute ethanol and the reaction mixture was refluxed for 19 hours. The reaction mixture was worked up according to the procedure described for (159) to give a solid substance, which was recrystallised from methanol-ether to give 1.14 gm (41%) of the product as it's hydrochloride, melting at 203°C.

IR (cm^{-1}): 2510 ($^+NHCl^-$); 1700,1655 (C=O); 1600 (aromatic); 1255 (Ar-O-CH_3);1180 (C-N);800(1,4-disubstituted benzene);740(1,2-disubstituted benzene).^1H NMR(DMSO-d_6): 9.38-6.15 (m,13H,Ar-H); 3.91 (s,3H,Ar-O-CH_3); 3.53-3.38(m,8H,piperazinyl methylenes); 3.18 (s,4H,methylenes). Anal. Calcd. for $C_{29}H_{28}N_3O_3F.2HCl$. N=7.52%. Found. N=7.62%.

1-(1-(4-Fluorobenzoyl)-1*H*-3-indolyl)- 3-[4-(3-methoxyphenyl) piperazin-1-yl]- 1-propanone (196)

In a 50 ml round bottom flask equipped with a reflux condenser and N_2 inlet were placed 1.4064 gm (0.005 mol) of 1-(4-fluoro benzoyl)-3-acetyl indole (190), 0.300 gm (0.010 mol) of paraformaldehyde, 1.3723 gm (0.006 mol) of 1-(3-methoxy phenyl) piperazine dihydrochloride and 15 ml of absolute ethanol and the reaction e mixture was refluxed for 19 hours. The reaction mixture was worked up according to the procedure described for (159). The hydrochloride obtained was not stable and was hence dissolved in water. The aqueous solution was basified with a 10% solution of potassium hydroxide, to give a

crude product, which was recrystallised from ethanol-petroleum ether, to give 0.898 gm (37%) of the product as its free base, melting at 124°C.

IR (cm^{-1}): 1700,1655 (C=O); 1600 (aromatic); 1257 (Ar-O-CH_3); 1180 (C-N); 800 (1,4-disubstituted benzene); 780 (1,3-disubstituted benzene); 750(1,2-disubstituted benzene). ^1H NMR (DMSO-d_6): 9.34-6.40(m,13H,Ar-H); 3.74(s,3H,Ar-O-CH_3); 3.69-3.49(m,8H, piperazinylmethylenes); 3.34(d,4H,methylenes). Anal. Calcd. for $C_{29}H_{28}N_3O_3F$. N=8.65%. Found. N=8.71%.

1-(1-(4-Fluorobenzoyl)-1*H*-3-indolyl)- 3-[4-(4-methoxyphenyl) piperazin-1-yl]- 1-propanone (197)

In a 50 ml round bottom flask equipped with a reflux condenser and N_2 inlet were placed 1.4064 gm (0.005 mol) of 1-(4-fluoro benzoyl)-3-acetyl indole (190), 0.300 gm (0.010 mol) of paraformaldehyde, 1.3723 gm (0.006 mol) of 1-(4-methoxy phenyl) piperazine hydrochloride and 15 ml of absolute ethanol and the reaction mixture was refluxed for 19 hours. The reaction mixture was worked up according to the procedure described for (159) to give a solid substance, which was recrystallised from methanol-ether to give 1.19 gm (43%) of the product as it's hydrochloride, melting at 251°C.

IR (cm^{-1}): 2475 ($^+NHCl^-$); 1695,1655 (C=O); 1595 (aromatic); 1230 (Ar-O-CH_3); 1120 (C-N); 805 (1,4-disubstituted benzene); 753 (1,2-disubstituted benzene). ^1H NMR (DMSO-d_6): 9.54-6.88 (m,13H,Ar-H); 3.70 (d,3H,Ar-O-CH_3); 3.46-3.29(m,12H, methylenes). Anal. Calcd. for $C_{29}H_{28}N_3O_3F.2HCl$. N=7.51%. Found. N=7.56%.

1-(1-(4-Fluorobenzoyl)-1*H*-3-indolyl)- 3-[4-(3-trifluoromethyl phenyl) piperazin-1-yl]- 1-propanone (198)

In a 50 ml round bottom flask equipped with a reflux condenser and N_2 inlet were placed 1.4064 gm (0.005 mol) of 1-(4-fluoro benzoyl)-3-acetyl indole (190), 0.300 gm (0.010 mol) of paraformaldehyde, 1.0814 gm (0.006 mol) of 1-(3-trifluoromethyl phenyl) piperazine and 15 ml of absolute ethanol. The pH was adjusted to 4 and the reaction mixture was refluxed for 19 hours. The reaction mixture was worked up according to the procedure described for (159) to give a solid substance, which was recrystallised from methanol-ether to give 0.911 gm (31%) of the product as it's hydrochloride, melting at 224°C.

IR (cm^{-1}): 2485 ($^+NHCl^-$); 1695,1650 (C=O); 1580 (aromatic); 1170 (C-N); 800 (1,4-disubstituted benzene); 780 (1,3-disubstituted benzene); 750 (1,2-disubstituted benzene). ^1H NMR (DMSO-d_6): 9.58-6.98 (m,13H,Ar-H); 3.98-3.41 (m,8H,piperazinylmethylenes); 3.23(d,4H,methylenes).Anal. Calcd. for $C_{29}H_{25}N_3O_2F_4.2HCl$. N=7.04%. Found.N=7.14%

1-(1-(4-Fluorobenzoyl)-1*H*-3-indolyl)- 3-[4-(2-pyridyl) piperazin-1-yl]- 1-propanone (199)

In a 50 ml round bottom flask equipped with a reflux condenser and N_2 inlet were placed 1.4064 gm (0.005 mol) of 1-(4-fluoro benzoyl)-3-acetyl indole (190), 0.300 gm (0.010 mol) of paraformaldehyde, 0.9793 gm (0.006 mol) of 1-(2-pyridyl) piperazine dihydrochloride and 15 ml of absolute ethanol and the reaction the mixture was refluxed for 19 hours. The reaction mixture was worked up according to the procedure described for (159) to give a solid substance, which was recrystallised from methanol-ether to give 1.29 gm (49%) of the product as it's hydrochloride, melting at 175°C.

IR (cm^{-1}): 2425 ($^+NHCl^-$); 1705,1640 (C=O); 1600 (aromatic); 1520 (C=N); 1175 (C-N); 805 (1,4-disubstituted benzene); 760 (1,2-disubstituted benzene). ^1H NMR(DMSO-d_6): 9.51-6.66(m,12H,Ar-H);3.76-3.31(m,8H,piperazinylmethylenes);3.21(d,4H,methylenes). Anal. Calcd. for $C_{27}H_{25}N_4O_2F.2HCl$. N=10.57%. Found. N=10.63%.

1-(1-(4-Fluorobenzoyl)-1*H*-3-indolyl)- 3-[4-(2-pyrimidinyl) piperazin-1-yl]- 1-propanone (200)

In a 50 ml round bottom flask equipped with a reflux condenser and N_2 inlet were placed 1.4064 gm (0.005 mol) of 1-(4-fluoro benzoyl)-3-acetyl indole (190), 0.300 gm (0.010 mol) of paraformaldehyde and 0.9793 gm (0.006 mol) of 1-(2-pyrimidinyl) piperazine dihydrochloride and 15 ml of absolute ethanol and the reaction the mixture was refluxed for 19 hours. The reaction mixture was worked up according to the procedure described for (159) to give a solid substance, which was recrystallised from methanol-ether to give 1.40 gm (53%) of the product as it's hydrochloride, melting at 243°C.

IR (cm^{-1}): 2450 ($^+NHCl^-$); 1695,1620 (C=O); 1595 (aromatic); 1560 (C=N);1180 (C-N); 795 (1,4-disubstituted benzene); 755 (1,2-disubstituted benzene). ^1H NMR (DMSO-d_6): 9.59-6.73(m,12H,Ar-H);3.99-3.54 (m,8H,piperazinylmethylenes);3.18 (t,4H,methylenes). Anal. Calcd. for $C_{26}H_{24}N_5O_2F.2HCl$. N=13.19%. Found. N=13.26%.

Chapter - 4

PHARMACOLOGY

Substantial biochemical, pharmacological and histochemical evidence has been accumulated in support of the role of serotonin as a neurotransmitter, neuromodulator and hormone. The identification of selective agonists and antagonists of 5-HT receptor subtypes has allowed the discovery of several therapeutic substances. Receptor binding studies have demonstrated that many compounds display high affinity for 5-HT receptors, but only a few of them are selective for one of the 5-HT receptor subtypes. Amongst the agents that bind at various 5-HT sites, arylpiperazines are the most notable.

The new arylpiperazines synthesized in this study were evaluated for their peripheral as well as central serotonergic activity and further pharmacological activity profile of the "lead" compounds were investigated.

The investigations were taken up as stated below :

1. To evaluate the *serotonergic activity* in the guinea pig ileum and compare it with the most potent 5-HT_3 antagonist Ondansetron.
2. To evaluate the antipsychotic effects in mice and compare it with Haloperidol.
3. To detect the atypicality of the antipsychotic activity, the molecules were screened for 5-HT_2 antagonism by evaluating their ability to reverse the catalepsy induced by haloperidol.

MATERIALS

I. Animals

Guinea pigs (400-500 gm) and male albino mice (20-30 gm) were used throughout this investigation. The animals received food and water *ad libitum.*

II. Physiological Salt Solutions :

a) Tyrode solution

Composition in mM, NaCl (136), KCl (2.7), $CaCl_2$ (1.8), $MgCl_2$ (1.05), NaH_2PO_4 (0.42), $NaHCO_3$ (11.9), and Glucose (5.5) (pH7.4)

III. Drugs and Chemicals

a) Drugs: The following drugs were used in this study

5-Hydroxytryptamine Creatinine sulphate	Sigma labs, St.Louis M.O., U.S.A.
Apomorphine HCl	RBI Inc., U.S.A.
Ondansetron HCl & Haloperidol	Torrent Pharmaceuticals Ltd., Ahmedabad, India

b) Equipment:

Student physiograph [Biodevices, India (Force Transducer T-305)]

METHODS

Isolated longitudinal muscle-myenteric plexus preparation of guinea pig ileum (LMMP)

The new arylpiperazine derivatives synthesized in this investigation were intially tested on the longitudinal muscle-myenteric plexus preparation of the guinea pig ileum, where the typical 5-HT_3 antagonist Ondansetron (10^{-5} M), inhibited about 69% of the contractions induced by serotonin (10^{-5} M). Even though the contractile response to 5-HT in this preparation can be elicited by activation of other 5-HT receptors different from the 5-HT_3 subtype, this was considered to be a reliable initial screening test , the reason being 5-HT_3 receptors are preferentially involved in the contractile response to high 5-HT concentration. All known 5-HT_3 antagonists clearly block this response.

Guinea pigs (400-500 gm) of either sex fasted overnight were stunned by a blow to the head and bled. The abdomen was opened, the caecum lifted and the caecoileal junction was located. A length of 10 cm of ileum was cut off and a suitable length of adjoining ileum was excised out and placed in warm (37°C) aerated Tyrode solution. The mesenteric attachments were slowly trimmed away and pieces of approximately 2 cm length were removed. The lumen of the tissue was cleaned by gently passing warm aerated Tyrode solution. Longitudinal muscle strips with the myenteric plexus attached (LMMP) were prepared.[154] The strips were mounted into an organ bath of 20 ml

capacity. The tissue was maintained in Tyrode solution at 37 ± 0.5°C with constant aeration at resting tension of 500 mg.

Evaluation of 5-HT antagonism in guinea pig ileum longitudinal muscle myenteric plexus

The tissue was mounted in the organ bath as described above. Following a 30 minute equilibrium period, tissues were stimulated with increasing concentrations of 5-HT from 10^{-8} to 10^{-4} M. A fixed concentration of 10^{-5} M, approximately the ED_{50} of ondansetron was used for subsequent antagonism studies. The response to 10 μM 5-HT is expressed as 100%. After 30 minutes incubation with the test compound (10^{-5}M), serotonin was added to the bath and the response measured. The antagonistic effect of the compound is expressed as a percentage of the previous response to 5-HT and the results are given in Tables 19 to 22.

Apomorphine-induced cage climbing behavior in male mice

Male albino mice weighing 20-30 gm were used. They were allowed food and water *ad libitum*. Animals were randomly distributed into groups of 4 animals each. Each animal was used only once. All observations were made between 10 a.m. and 4 p.m. at 27- 35°C in a noiseless, diffusely illuminated room. During the experiments, animals were placed in individual cages made of wire netting, measuring 25x20x15 cm, 30 minutes before drug treatment to allow adaptation to the new environment. Observations were made blind with respect to treatments used. All drug solutions were prepared fresh just before the experiment.

Evaluation of Apomorphine-induced cage climbing behavior in male mice

The effect of pretreatment with 30 mg/kg doses of the test compounds on apomorphine (0.5 mg/kg)-induced cage climbing behavior was studied by the method of Costall and coworkers.[155] Animals received test compound and distilled water (ip) followed 30 minutes later by apomorphine. They were individually tested for climbing behavior taking the percentage of time spent climbing during 30 min period after the first climb as

a measure of climbing (climbing index) Further, the maximum time spent (min) in a single climb throughout the duration of the apomorphine effect was also recorded. The results are given in Tables 23 to 26. Haloperidol, 1.0 mg/kg (ip) was used as control as it completely inhibited the climbing induced by apomorphine.

Catalepsy Testing

Male albino mice were tested for catalepsy according to the method of Ahtee and Buncombe[156] by placing both front paws of the animal over a 5 cm high wooden block and measuring the time (sec) that the animal maintained this imposed posture. Animals were tested for catalepsy 30, 60, 120 and 180 minutes after haloperidol (0.25 mg/kg) injection. Catalepsy score (immobility time in sec) of each animal in the group, at the respective testing time interval, was taken to compute the mean value of the group for that particular timing. Catalpesy was scored in a manner similar to that described by Costall and Naylor[157] and Shore and Dorris.[158] Animals were tested for the presence of catalepsy by placing both front limbs over a horizontal bar placed 5 cm above the bench surface, a cataleptic animal maintaining this position for a period of time dependent upon the degree of catalepsy. If the animal maintained the imposed posture for atleast twenty seconds it was said to be cataleptic and given one point. For every further twenty seconds it continued to maintain the cataleptic posture, one extra point was given, thus the animal was given a score of two points if it maintained the posture for forty seconds, three points for sixty seconds, upto a maximum of six points.

Evaluation of Reversal of Haloperidol-induced Catalepsy

The test compounds (30 mg/kg) were injected 30 minutes before the injection of haloperidol (0.25 mg/kg). The catalepsy score was recorded at 30, 60, 120 and 180 minutes after haloperidol administration. The percentage reversal is calculated as a percentage of the difference between the total points obtained between control and test drugs. The results are given in Table 27.

Reversal of apomorphine-induced stereotypy[143]

Male mice weighing 18-20 gm were placed two to a cage and injected with the test drug. At time intervals of 1,3 and 5 hours, each animal received an s.c. injection of apomorphine. The animals were observed for stereotypic behavior at 10 min. intervals upto 50 min. and rated according to the following scale : 0, no movement; 1, moving around cage or discontinuous sniffing; 2, continous sniffing; 3, discontinuous oral movements (licking, chewing or biting); 4, continuous chewing and biting. Haloperidol 0.5 mg/kg (ip) and apomorphine 5 mg/kg (sc) were used as control.

Chapter - 5

RESULTS

&

DISCUSSION

Chemistry

This thesis describes the synthesis and pharmacological evaluation of a series of N-4 substituted-1,2-dihydro-2-acenaphthylenyl piperazines and Substituted Indolyl Propanones as modulators of 5-Hydroxytryptaminergic receptor.

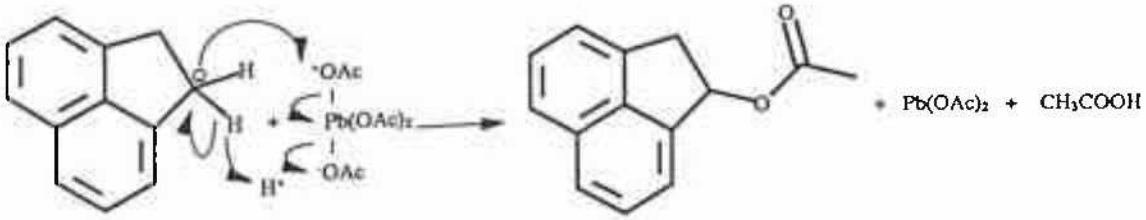
The quest to identify and synthesize a novel arylpiperazine has led to the synthesis of ,2-dihydro-2-acenaphthylenyl piperazine and its various derivatives to evaluate their nodulatory effects at the 5-HT receptors.

1,2-Dihydro-2-acenaphthylenyl piperazine was synthesized, starting from the hydrocarbon 1,2-dihydro-acenaphthylene (acenaphthene). The best possible method of introducing the piperazine moiety into the 1,2-dihydro acenaphthylene, was to bring in a fairly reactive halogen atom onto the 2nd position of the hydrocarbon ,i.e. the alicyclic ring and then introduce the piperazine moiety through conventional nucleophilic substitution. For the present work, 1,2-dihydro-2-acenaphthylenol was required as the starting material.

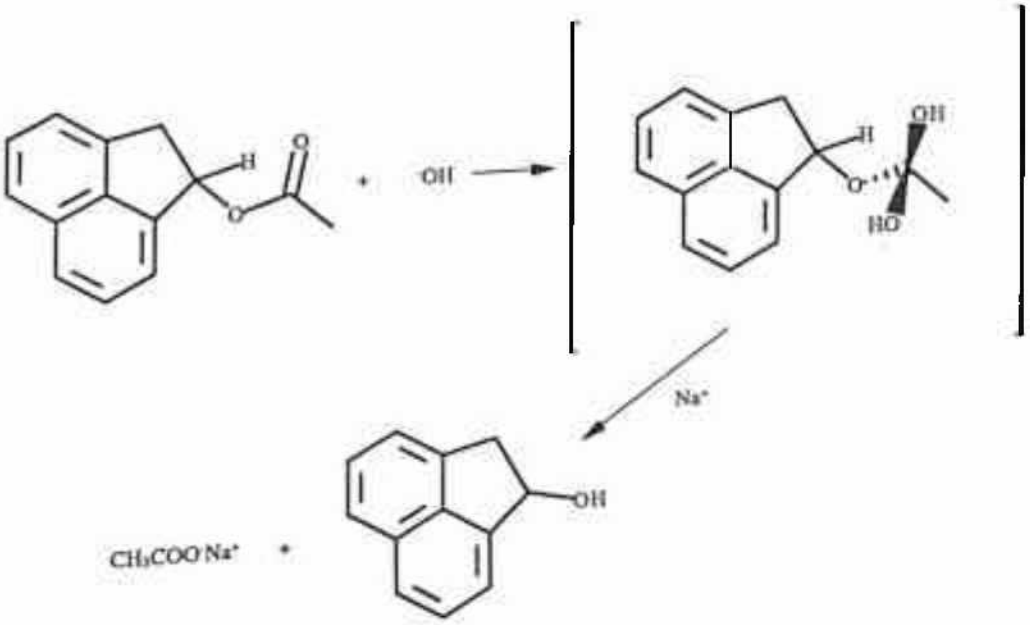
Marquis[159] observed that 1,2-dihydro-2-acenaphthylenol is obtained in low yield in the form of the acetate by the oxidation of 1,2-dihydro-acenaphthylene with lead dioxide in acetic acid, during a study of the action of lead tetraacetate on other hydrocarbons. Feiser and Hershberg[160] reported that 1,2-dihydro-2-acenaphthylenyl acetate can be obtained using lead tetraacetate. Lead tetraacetate, as a reagent is not stable and is required to be prepared as and when required and used immediately or should be generated *in situ*. A practical procedure for conducting the oxidation was employed in the present investigation. The method of treating quantities of red lead with acetic acid for the preparation of a reagent for use in this solvent (acetic acid) suggested that this operation could be dispensed with, and indeed it was found that 1,2-dihydro-acenaphthylene can be converted freely into the 2-acetoxy compound with red lead and acetic acid. The acetate is a liquid and is not easily freed from traces of the hydrocarbon, but pure crystalline 1,2-dihydro-2-acenaphthylenol was readily obtained in good yield on saponification.[138]

The basic mechanism for the conversion of 1,2-dihydro-acenaphthylene to 1,2-dihydro-2-acenaphthylenyl acetate, using red lead and acetic acid can be envisaged as follows :

$$Pb_3O_4 + 8CH_3COOH \longrightarrow Pb(OAc)_4 + 2Pb(OAc)_2 + 4H_2O$$



The conversion of the acetoxy compound, i.e., 1,2-dihydro-2-acenaphthylenyl acetate to the crystalline hydroxy compound, i.e., 1,2-dihydro-2-acenaphthylenol by saponification using sodium hydroxide in methanol can be envisaged to occur as follows :

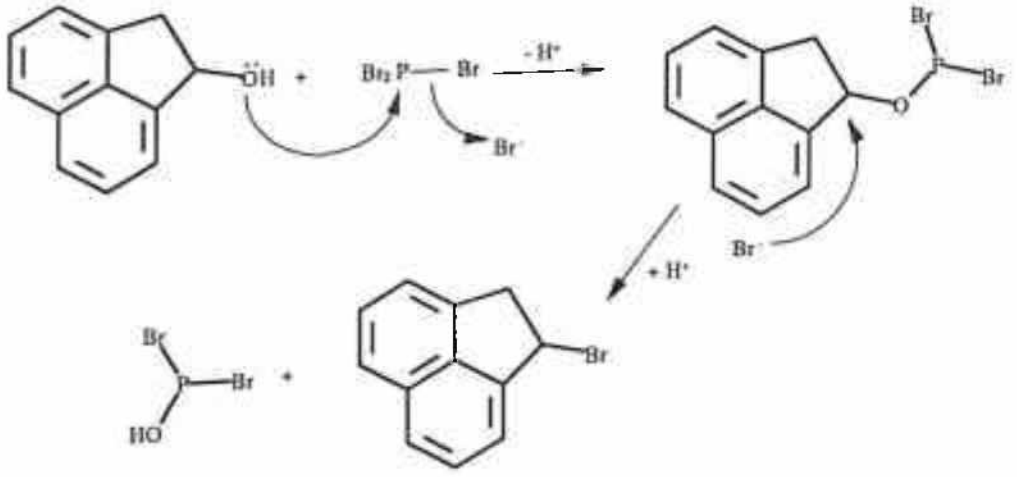


The next step involved the synthesis of 2-bromo-1,2-dihydro acenaphthylene from the hydroxy compound. This conversion follows the S_N^2 displacement mechanism, whereby greater regio-selectivity is achieved. This conversion may be brought about by the addition of liquid bromine to a warm suspension of purified red phosphorus in the hydroxy compound. This reaction is of a general application for the bromination of

alcohols, particularly secondary alcohols and is to be preferred to the direct use (rather than the *in-situ* generation) of phosphorus tribromide.[161]

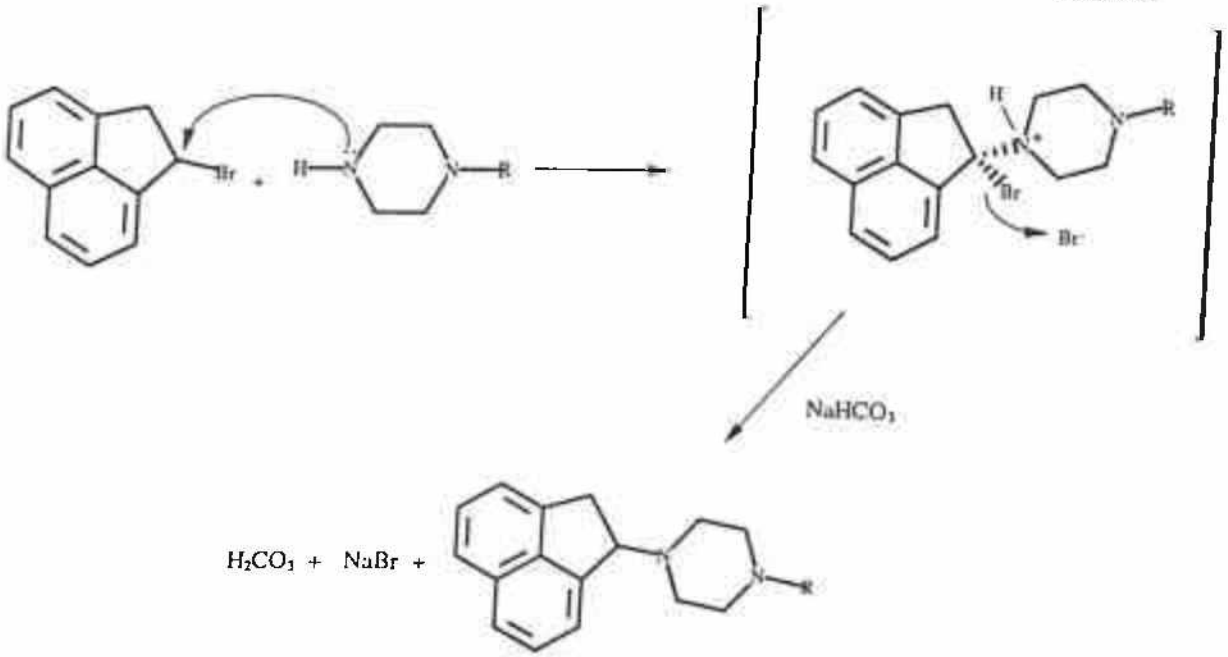
This is conventionally true for most secondary alcohols. Since, it was difficult to make a suspension of purified red phosphorus with 1,2-dihydro-2-acenaphthylenol, to bring about the bromination, the only other option was to use phosphorus tribromide directly, in a non-polar solvent like diethyl ether, in which the 1,2-dihydro-2-acenaphthylenol was also freely soluble. The reaction between 1,2-dihydro-2-acenaphthylenol and phosphorus tribromide was rapid and occurred readily at room temperature.

The tribromide was hydrolysed followed by evaporation of the washed (water, saturated sodium-bi-carbonate solution, brine) ether layer to give a thick oil which readily solidified, to give the bromo derivative, i.e., 2-bromo-1,2-dihydroacenaphthylene. The outline mechanism may be represented as :



Nucleophilic substitution of 2-bromo-1,2-dihydroacenaphthylene was carried out with anhydrous piperazine in ethanol, using excess sodium bicarbonate as the base. The molar proportion of the brominated acenaphthylene and anhydrous piperazine had to be optimized based on the yield of the product obtained. When used in equimolar quantities, the yield of the product was only 43%. When the proportion of anhydrous piperazine was doubled, i.e., one mole of brominated acenaphthylene and two moles of anhydrous piperazine, the product was obtained in 65% yield. Further increase in the molar proportion of anhydrous piperazine or increase in reaction time did not improve the yield

of the product. Excess of sodium bicarbonate was taken, on the basis that one mole was consumed in the neutralization of the HBr evolved and the rest was to facilitate the nucleophilic reaction. The possible mechanism involved in this reaction is as follows :



where, R = H / alkyl / aryl / substituted aryl / aralkyl

The 1,2-dihydro-2-acenaphthylenyl piperazine was initially obtained as an oily substance, which solidified on cooling over a prolonged period. The free base could be obtained as a yellow crystalline substance, melting at 64°C. Two different salts were prepared for characterization purposes and for further evaluation of the compound. The dihydrochloride was obtained readily as pale yellow flakes in acetone and melted at 254°C. The monofumarate was prepared using *n*-butanol-hexane, to give a pale pink crystalline substance, melting at 108°C. The solvent system was changed from ethanol to methyl ethyl ketone, when substitutions were desired at the N-4-nitrogen atom of 1,2-dihydro-2-acenaphthylenyl piperazine, and when a N-4-substituted piperazine was employed, with the advantage that the isolation of the products was not hindered by the polarity of the solvent which affected the yield of the products significantly. In order to ascertain the effects of various substitutions at the N-4 nitrogen atom of 1,2-dihydro-2-acenaphthylenyl piperazine,- alkyl, aryl, substituted aryl, aralkyl and heteroaralkyl groups were incorporated. The physical properties of the N-4-alkyl, -aryl, -substituted aryl, -

aralkyl and -heteroaralkyl-1-(1,2-dihydro-2-acenaphthylenyl) piperazines, are shown in Tables 5, 6 and 7 respectively. Similarly, the solvent system was also changed from ethanol for various other substitutions carried out on the N-4-nitrogen atom of 1,2-dihydro-2-acenaphthylenyl piperazine. Ethanol had to be used as a solvent for the preparation of 1,2-dihydro-2-acenaphthylenyl piperazine, the reason being that reactions involving the use of anhydrous piperazine, require a protic solvent for optimum yield.

This aryl piperazine i.e., 1,2-dihydro-2-acenaphthylenyl piperazine is totally a new chemical component/entity (NCE), and hence its characterization was of importance, before further modifications, in terms of adding various side chain moieties which carried vital pharmacophores, could be done.

The elemental analysis obtained for this compound was well within the prescribed limit of ± 0.45 %. Deuterated water was used as the solvent for recording the ^{1}H NMR spectra of this compound, the reason being the hydrochloride salt of 1,2-dihydro-2-acenaphthylenyl piperazine was freely soluble in water. The ^{1}H NMR spectra showed characteristic peaks in the region δ 7.79-7.30, which is indicative of the six aromatic protons (integral 1.0). The methylene of the acenaphthylene is observed along with the piperazinyl methylenes in the region δ 3.55-3.01 as a multiplet. The N-H proton of the piperazine is observed as a doublet at δ 3.01, totalling to 11 protons (integral 1.832). The benzylic proton of the acenaphthylene is observed at δ 5.16 (integral 0.16).

The mass spectrum of 1-(1,2-dihydro-2-acenaphthylenyl) piperazine was found to be very neat and followed a very simple pattern. It showed a M^+ peak at 238 which corresponded to the molecular formula of $C_{16}H_{18}N_2$, which conforms to the Nitrogen rule. The fragmentation showed peaks at 233 and 182 indicating that there was loss of NH (m/e 15) and $^+$CH=CH=NH (m/e 41) respectively. The peak at 153 had 100% intensity and corresponds to $C_{12}H_9$ which is the molecular ion of 1,2-dihydro-2-acenaphthylene. However, there were additional peaks at 127, 85 and 56. The peak at 85 corresponds to the molecular ion of piperazine while the peak at 127 evidently can be formed from 1,2-dihydro-2-acenaphthylene via loss of CH ≡ CH (m/e 26).

The infrared spectrum showed characteristic aromatic peak at 1600 cm^{-1}, the NH peak at 3250 cm^{-1} and the piperazinyl C-N stretching at 1560 cm^{-1}. The peaks at 800 and 775 cm^{-1} were indicative of 1,2,3-trisubstituted benzene, the two benzene components present in the acenaphthylene nucleus.

Other important properties of 1,2-dihydro-2-acenaphthylenyl piperazine were to be considered, before any further structural modification by incorporating substituents at the N-4-nitrogen atom could be performed, in order to make way for candidate drug molecules. Physicochemical parameters are of prime interest because, these parameters play a vital role in the binding profile of any candidate drug molecule, with the respective receptors. Various physicochemical parameters for 1,2-dihydro-2-acenaphthylenyl piperazine were determined using available software.[162]

Of these, the parameter involving partition coefficient logP, which accounts for the lipophilicity was taken into consideration. The reason for this being, that lipophilicity of a molecule would help in specifying whether the molecule would be active centrally or peripherally. The calculated logP (clogP) value for 1,2-dihydro-2-acenaphthylenyl piperazine was found to be 3.04 ± 0.59. As this clogP value was considerably high, the effort was to concentrate on the structural modifications on the N-4-nitrogen atom of 1,2-dihydro-2-acenaphthylenyl piperazine, which would result in enhanced activities, for the treatment of central nervous system disorders, like, anxiety, depression, psychoses, migraine, drug abuse, sleep and cognition disorders.

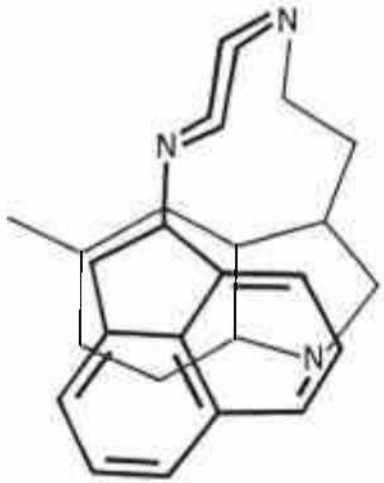
Before any attempt to perform structural modifications at the N-4-nitrogen atom could be achieved, it was first necessary to establish the serotonergic potential of 1,2-dihydro-2-acenaphthylenyl piperazine. All known or reported aryl piperazines have been established to have a serotonergic potential, atleast at one of the 5-HT receptor subtypes.
To start with, an orientation for the interaction of the 1,2-dihydro-2-acenaphthylenyl piperazine with 5-HT binding sites had to be envisaged. One possibility is that, in which the five-membered cyclopentyl ring, the six-membered aromatic ring and the terminal amines of 5-HT and 1,2-dihydro-2-acenaphthylenyl piperazine are overlayed (figure 3). Another possibility is that the cyclopentyl portion of the 1,2-dihydro-2-acenaphthylenyl

piperazine occupies a site on the receptor, which the pyrrole portion of 5-HT normally interacts. In both the cases, one of the aromatic rings of 1,2-dihydro-2-acenaphthylenyl piperazine overlaps either with the 5-membered pyrrole portion or with the 6-membered aromatic portion of 5-HT. This type of overlapping has been used by Glennon and co-workers for the orientation of the binding of phenyl piperazines with 5-HT.[163]

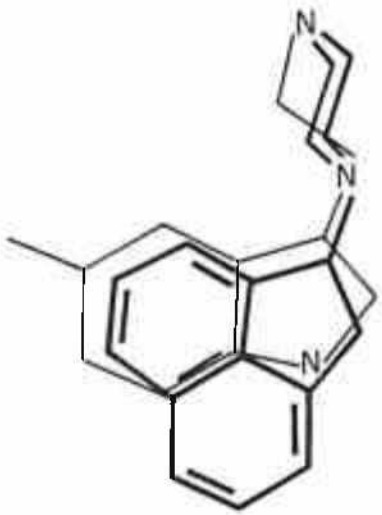
The next step was to evaluate the serotonergic potential of 1,2-dihydro-2-acenaphthylenyl piperazine, in an experimental model. The preliminary pharmacological evaluation of 1,2-dihydro-2-acenaphthylenyl piperazine has shown promising serotonergic activity without any histaminic activity.[164]

This approach made it mandatory to briefly study the physiology involved in the central nervous system disorders. In this regard, an important distinction is to be made among the central nervous system disorders, between the psychoses and the less severe conditions commonly referred to as neuroses. The psychoses are among the most severe psychiatric disorders, in which there is not only a marked impairment of behavior but a serious inability to think coherently to comprehend reality or to gain insight into these abnormalities. Psychotic disorders include organic conditions (notably, delirium and dementia), which typically are associated with definable toxic, metabolic or neuropathologic changes and are characterized by confusion, disorientation and memory disturbances as well as behavioral disorganisation. Other psychotic conditions are designated as idiopathic (or functional disorders), for which underlying causes, remain obscure. The latter are characterized by the retention of orientation and memory in the presence of severely disordered thought or reasoning, emotion and behavior. Those primary disorders, characterized by abnormal emotion or mood, are called major affective or maniac depressive disorders.[127] Antipsychotic drugs exert beneficial effects in virtually all classes of psychotic illness.

On the other hand, the less pervasive psychiatric disorders include notably the neuroses. Neuroses may be acute and transient or more commonly persistent or recurrent. Their symptoms may include mood changes (anxiety, panic, dysphoria) or limited abnormalities of thought or of behavior. In such disorders, drugs may have some beneficial effects, particularly by modifying associated anxiety and depression.[128]



(A)



(B)

Figure 3. Two representations for the possible overlap of the structures of 1,2-dihydro-2-acenaphthylenyl piperazine (heavy lines) and serotonin at serotonin binding sites. The cyclopentyl portion of the 1,2-dihydro-2-acenaphthylenyl piperazine may be congruent with the benzene ring (A) or the pyrrole portion (B) of serotonin.

The search for newer drug molecules for effective management/treatment of psychoses, offers newer avenues for drug research.

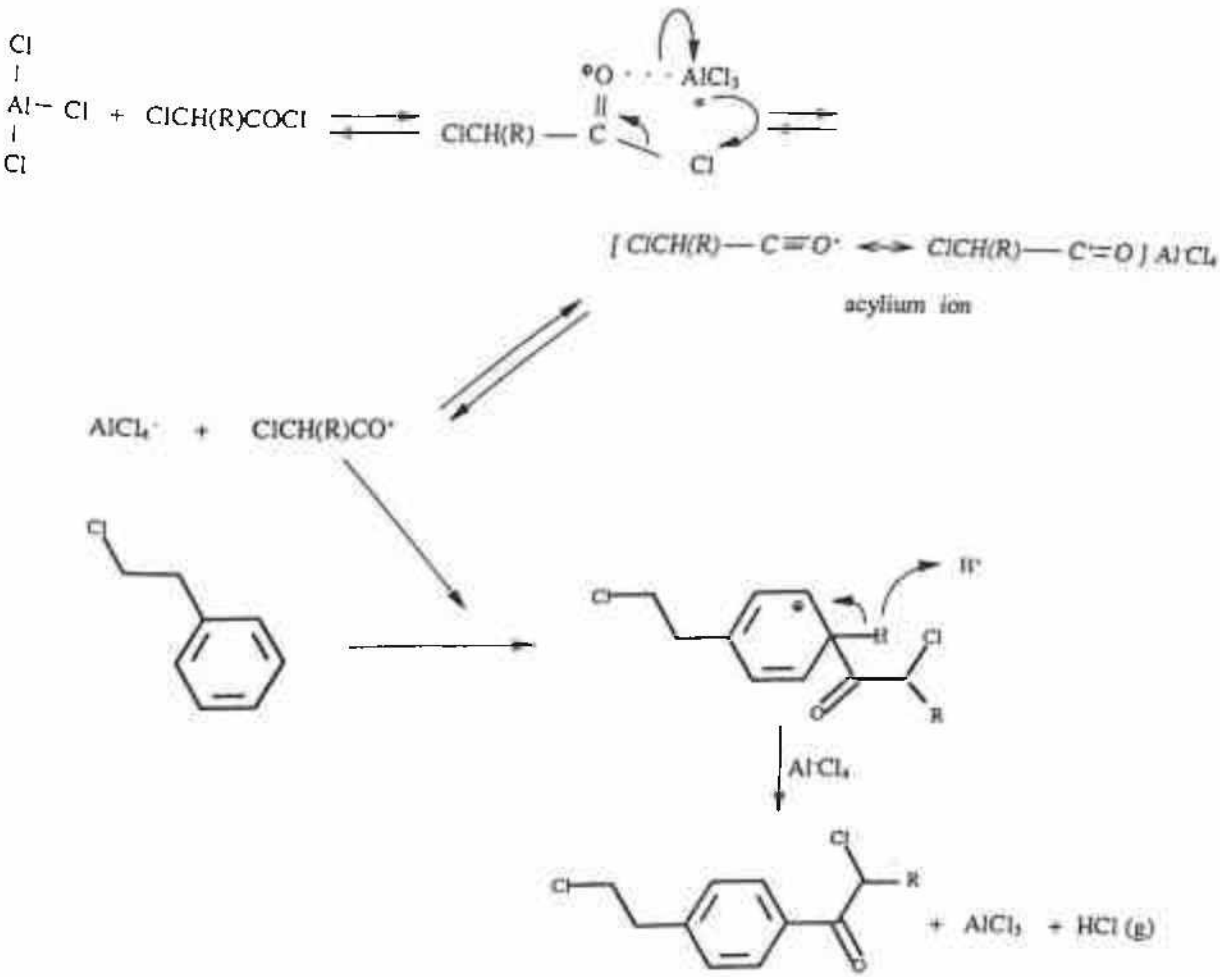
Based on literature reports,[135,136] 2- and -5- substituted thiazoles were chosen which were appended to the phenethyl moiety and 1,3- and -6-substituted-5-(2-chloroethyl) oxindoles and one of its isostere 6-(2-bromoethyl) benzoxazol-2(3*H*)-one, were chosen as the fused heterocyclic groups, that would offer various modes of hydrogen-bond interactions with the D_2 receptor serine residues for the requisite D_2 affinities.

In the preparation of the thiazoles, i.e., 4-[4-(2-Chloro ethyl)phenyl]-2- and -5-substituted thiazoles, the first step involved Friedel-Craft's acylation of phenethyl chloride. Literature methods[144] suggest acylation of the phenethyl chloride using acetyl chloride in the presence of anhydrous aluminium chloride and ethylene chloride as the solvent at room temperature or directly starting with the 4-(2-chloroethyl) acetophenone, followed by bromination using liquid bromine in acetic acid inorder to generate α-halo carbonyl compounds which react efficiently with various thioamides to form thiazoles. The reaction between thioamides and α-halo carbonyl compouds is one of the general synthetic routes developed for thiazoles.[165]

In the present study, chloro acetyl chloride was used instead of acetyl chloride in the presence of anhydrous aluminium chloride and ethylene chloride was used as the solvent, to give 4-(2-chloroacetyl) phenethyl chloride in a single step. This reaction was also carried out at room temperature. Phenethyl chloride was added dropwise to a suspension of anhydrous aluminium chloride and chloroacetyl chloride in ethylene chloride with continuous stirring at room temperature. The reaction mixture after hydrolysis and solvent removal gave 4-(2-chloroacetyl) phenethyl chloride as an oil which solidified on standing for prolonged periods of time. The possible mechanism involved in the formation of 4-(2-chloro acetyl) phenethyl chloride can be envisaged as given below. The product formed was characterized and used immediately in the next step for the synthesis of 4-[4-(2-Chloro ethyl)phenyl]-2- and -5-substituted thiazoles.

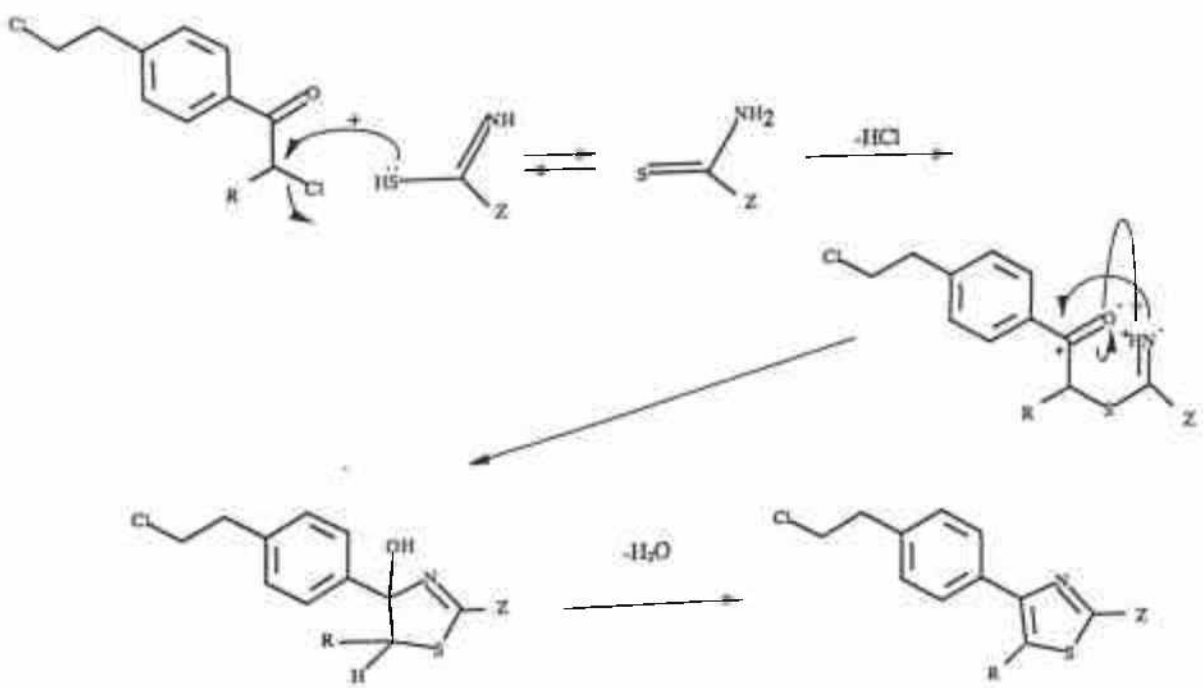
The synthesis of 4-[4-(2-Chloro ethyl) phenyl]-2- and -5-substituted thiazoles involved the reaction of thioamides *viz.*, thiourea, thioacetamide and *N*-substituted thioureas, with the α-halo carbonyl compound i.e., 4-(2-chloroacetyl) phenethyl chloride, in acetone. Acetone was used as the solvent, because both the thioamides and the 4-(2-Chloroacetyl)

phenethyl chloride were readily soluble in it and the removal of a molecule of water was facilitated by its use.



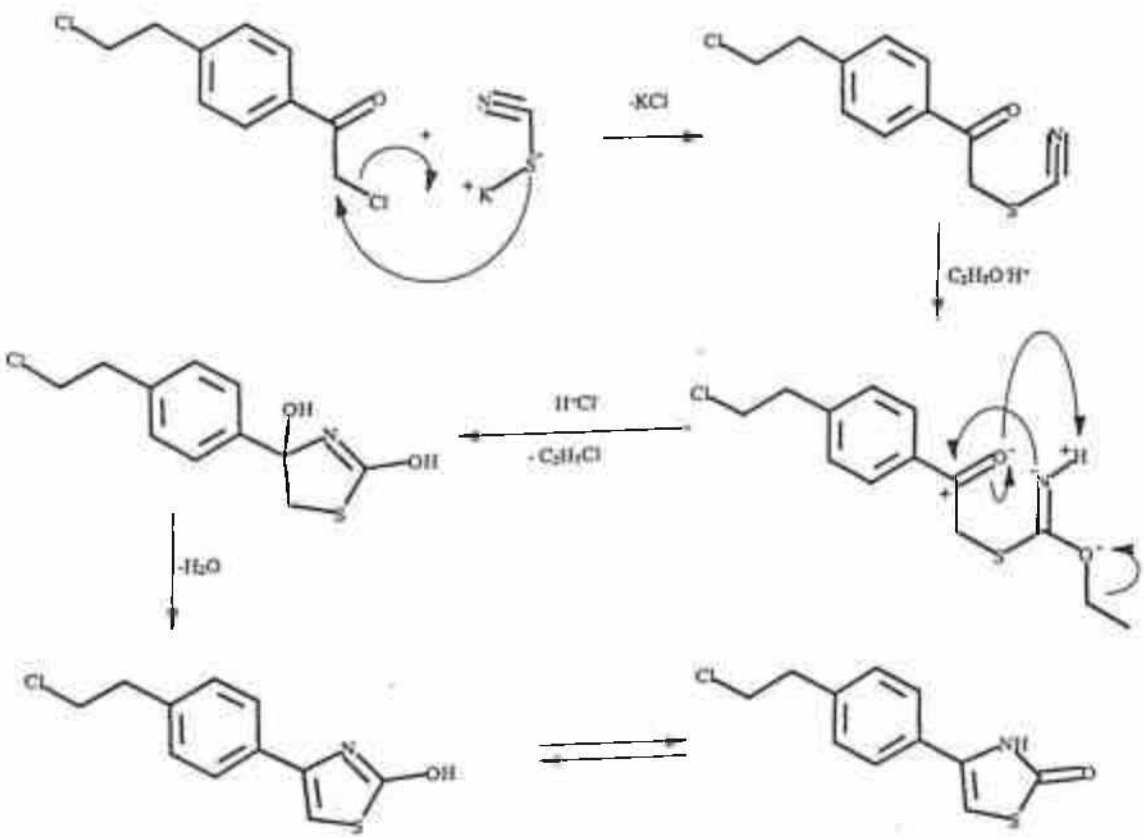
The mixture was refluxed for 3 hours, during which time the product precipitated out as the hydrochloride. By this method 2-amino, 2-methyl, 2-methyl amino and 2-allylamino thiazole side-chain moieties were prepared using thiourea, thioacetamide, N-methyl thiourea and N-allylthiourea (thiosinamine) respectively. The products were obtained as their hydrochlorides in fairly good yields, about 60-65%. Where a substitution at the 5th position of the thiazole was required, the respective acid chloride was used in the chloroacetylation of the phenethyl chloride. 2-Chloro propionyl chloride was used instead of chloroacetyl chloride, for a methyl substituent at the 5th position of the 2-amino thiazole moiety. All the hydrochlorides were stable except for the N-allylamino thiazole derivative, which was hygroscopic and low melting. The direct use of N-methyl thiourea and N-allylthiourea was preferred rather than trying to perform substitutions on the 2-

amino thiazole product, because it has been reported that alkylation of 2-amino thiazoles gave exclusively the 3-alkyl derivatives and not the substitution products on the amino nitrogen.[166,167] The reaction mechanism involved in the formation of the thiazoles is as follows :



There has been an outline critique of thiazole chemistry, with a particular emphasis on the scope and limitations of the subject.[168] Although a number of diverse substituted thiazoles have been prepared by various routes, investigations in the field of 2-hydroxy thiazoles are limited. Klein and Prijs,[169] suggested that the structure of the 2-hydroxy thiazole, exists predominantly in the keto form, which is why the terminology thiazole-2-one is used to the hydroxy thiazole. 4-(2-Chloroacetyl)phenethyl chloride was first refluxed with potassium thiocyanate in acetone resulting in the formation of the α-thiocyano ketone. The precipitated potassium chloride was removed by filteration followed by removal of the solvent. The residue was extracted with ethyl acetate and the solvent was removed under reduced pressure to give a solid which was then taken in boiling ethanol to form the ethyl imidate. This was then treated with 1 N HCl and refluxed. Based on mechanisms reported for the formation of various types of thiazole-2-

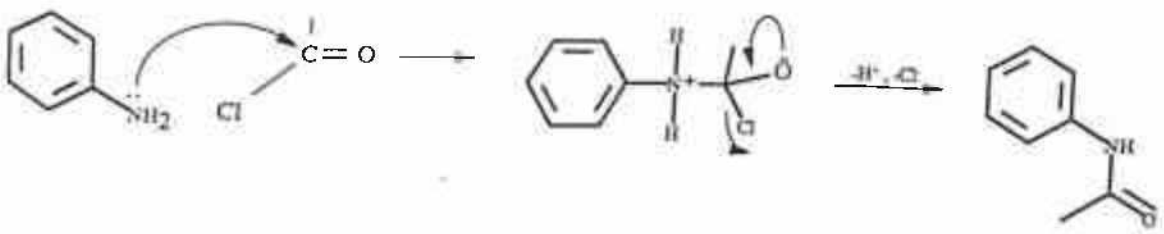
ones.[166]The mechanism involved in the synthesis of 4-[4-(2-Chloroethyl)phenyl]thiazole-2-one can be envisaged as follows :



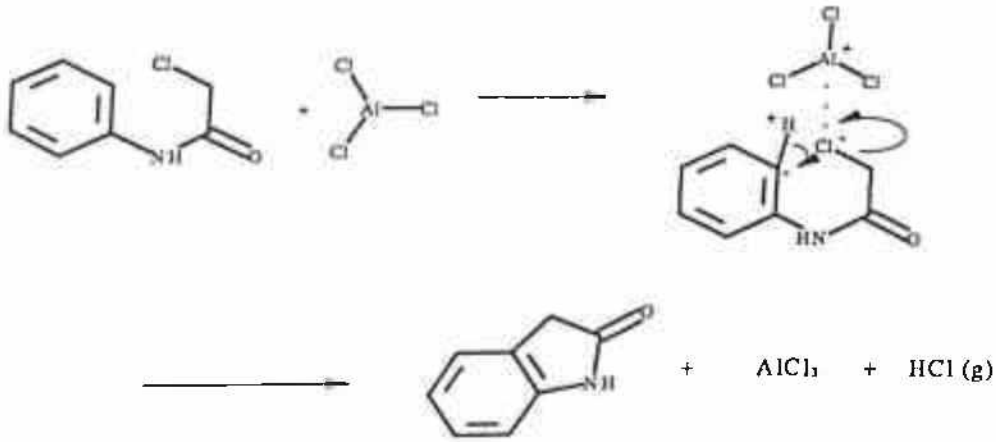
This process cyclised the thiazole-2-one by dehydration. The reaction mixture was refrigerated overnight to give the thiazole-2-one as a crystalline solid in 55% yield. The physical properties of 4-[4-(2-Chloro ethyl)-2- and -5- substituted thiazoles are shown in Table 8.

In the next series, involving the generation of fused systems, i.e., heterocyclic groups fused to the phenethyl side-chain, a series of 2,3-dihydro-1*H*-indol-2-ones substituted at the 1,3 and 6 positions were synthesized. The starting material used here was the substituted or unsubstituted aniline, which was treated with α-chloro acid chloride, depending on the substitution desired at the 3rd position of the indole-2-one. Aniline, N-methyl aniline, N-ethyl aniline, m-chloro aniline and m-fluoro aniline were treated with chloroacetyl chloride to give the intermediate amide. 2-Chloro propionyl chloride was used as the acid chloride, when a methyl substituent was desired at the 3rd position of the

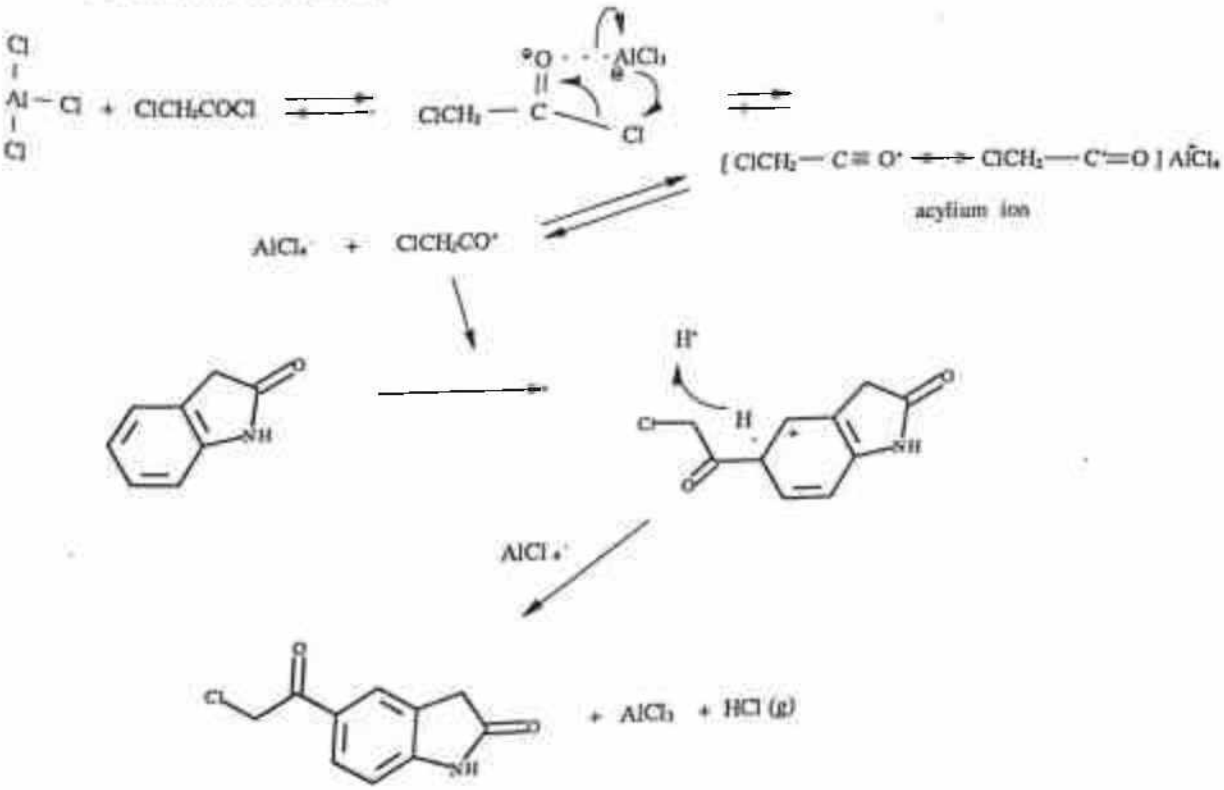
indole-2-one. In this case, advantage is taken of the fact that a carbonyl group attached to a group capable of departing with the covalent bonding-pair is susceptible to substitution by nitrogen nucleophiles. The outline mechanism involved in the formation of the amides is:



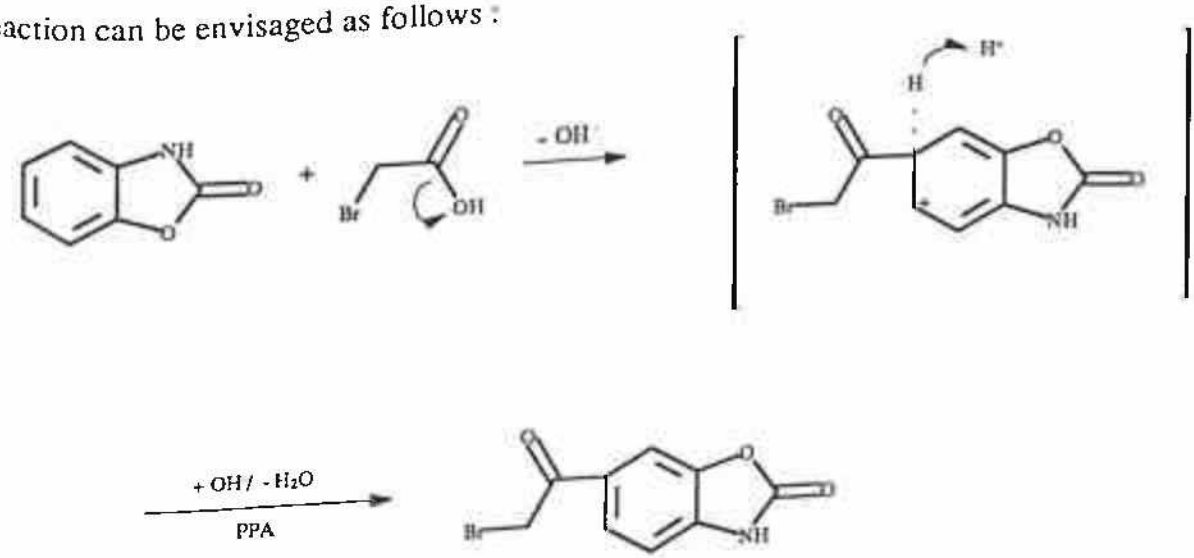
The next step involved the cyclisation of the α-haloacyl anilides / α-halogenoalkyl amides to the respective substituted indol-2-ones. Stolle cyclization forms the basis for this reaction.[170] Various literature reports are available based on the stolle cyclisation, wherein the α-haloacyl anilides / α-halogenoalkyl amides were cyclised to the respective substituted 2,3-dihydro-1*H*-indol-2-ones.[171-175] This cyclisation is carried out by mixing the α-halogenoalkylamides with anhydrous aluminium chloride taken in excess and gently heated at first in an oil bath with stirring. As the temperature was increased the mixture foamed as HCl was evolved. The reaction mixture was then heated to 160-175°C after the evolution of HCl had ceased. The time duration for each α-halogenoalkylamide for cyclisation was determined by monitoring the reaction for completion at periodic intervals. The substituted 2,3-dihydro-1*H*-indol-2-ones were obtained in yields of 33-42%, in accordance with literature reports for this type of cyclisation. The physical properties of substituted indol-2-ones are shown in Table 9. The mechanism involved in this cyclisation is as follows :



The next step involved the introduction of the chloro ethyl component at the 5th position of the 2,3-dihydro-1*H*-indol-2-ones. The option available was to introduce a chloro acetyl group and then selectively reduce the carbonyl to methylene affording the haloethyl derivative. Friedel-Craft's acylation of the substituted 2,3-dihydro-1*H*-indol-2-ones was carried out using chloroacetyl chloride in the presence of aluminium chloride using carbon disulfide as the solvent. 5-(2-Chloroacetylated)-1,3- and 6-substituted-2,3-dihydro-1*H*-indol-2-ones were obtained in good yields by this process. The mechanism involved in this chloroacetylation is as follows:



In order to study the effect of isosterism in the heterocyclic component fused to th phenethyl side-chain, isosteric replacement of the methylene group of 2,3-dihydro-1*H* indol-2-one with a nitrogen atom and replacement of the indolyl nitrogen with an oxygen atom – benzoxazolin-2(3*H*)-one was used as the starting material. The usual Friedel-Crafts technique utilizing an acid chloride in conjunction with anhydrous aluminium chloride as a catalyst invariably results in total or partial ether cleavage when the acyl function enters the molecule.[176] The ether linkage in benzoxazolinone is prone to such a cleavage. On the contrary, benzoxazole, gets readily chloroacetylated in the absence of aluminium chloride, at the 2nd position to give 2-chloroacetyl-benzoxazole. Inorder to retain the integrity of the oxazolinone ring, an alternative procedure for haloacetylation of the benzoxazolin-2(3*H*)-one at the sixth position, was followed. Polyphosphoric acid [PPA] has been reported to be an efficient catalyst, to bring about Friedel-Crafts acylation and alkylation.[177] Polyphosphoric acid, even though an acid catalyst, when compared with aluminium chloride, which is used in most of the Friedel-Crafts reactions, does not break the integrity of the oxazolinone moiety. The mechanism involved in this reaction can be envisaged as follows :



Bromoacetic acid was used as the acylating agent in the presence of polyphosphoric acid, which brings about bromoacetylation with removal of a molecule of water to give the 6-(2-bromoacetyl) benzoxazolin-2(3*H*)-one as a dark coloured solid. The physical properties of the 5-(2-chloroacetyl)-1,3-and –6-substituted-2,3-dihydro-1*H*-indol-2-ones and the 6-(2-bromoacetyl) benzoxazolin-2(3*H*)-one are shown in Table 10.

The next step involved the selective reduction of the carbonyl function on the aliphatic side chain. The reduction of the carbonyl group of aldehydes and ketones to methylene has enjoyed wide applications in organic synthesis. Of the reductive methods that have been employed, the Clemmensen[178] and Wolff-Kishner[179-183] reactions have exhibited the most general utility. Other methods, including catalytic hydrogenation,[184-186] reductions using Raney nickel in hydroxide media[187,188] and trichlorosilane - trialkylamine[189,190] and metal hydride reductions,[191-193] have been successfully applied more specifically to aryl aldehydes and ketones.

Kursanov and co-workers have recently reported the reduction of the carbonyl group of benzophenone, acetophenone and 2,4,6-trimethyl benzaldehyde to methylene using triethylsilane in trifluoroacetic acid media.[194-196] Because of the good yields reported for these silane reductions and the reported ability of silanes to undergo hydride transfer to relatively stable carbenium ions,[197,198] it was expected that silane reductions of aldehydes and ketones would represent a selective, convenient and synthetically useful method for transforming a carbonyl group to methylene.

The yields of arylhydrocarbon products from triethylsilane reductions of the corresponding carbonyl compounds is appreciative, the reason being the reductions occur readily at room temperature and no formation of interfering side-products in complex-forms is involved, which makes isolation of the reduced product tedious.

In general, the reaction between the carbonyl compound and triethylsilane can be envisaged to occur as per the following equation:

$$Ar\text{-}CO\text{-}R + 2\,(Et)_3SiH + 2\,CF_3COOH \longrightarrow Ar\text{-}CH_2\text{-}R + 2\,(Et)_3\text{-}SiOOCCF_3 + H_2O$$

Where, R = H or alkyl or aryl

In general, two equivalents of the silane are required for the reduction of one equivalent of the carbonyl compound to the methylene product in trifluoroacetic acid. The silane products are the triethylsilyltrifluoroacetate and hexaethyldisiloxane in amounts that vary with the reaction conditions.

Trifluoroacetic acid was chosen as the solvent for these reactions because of its acidity and good solvating properties. Other acids, including sulfuric acid reacted with triethylsilane.[199] Aqueous acids are not used because of the insolubility of the silane and

the carbonyl compounds in these media. When the silane was rapidly added to a trifluoroacetic acid solution containing the carbonyl compound, a reaction occured that was visibly exothermic. Hence, the silane was added, while the temperature of the reaction mixture was being maintained at 0°C.

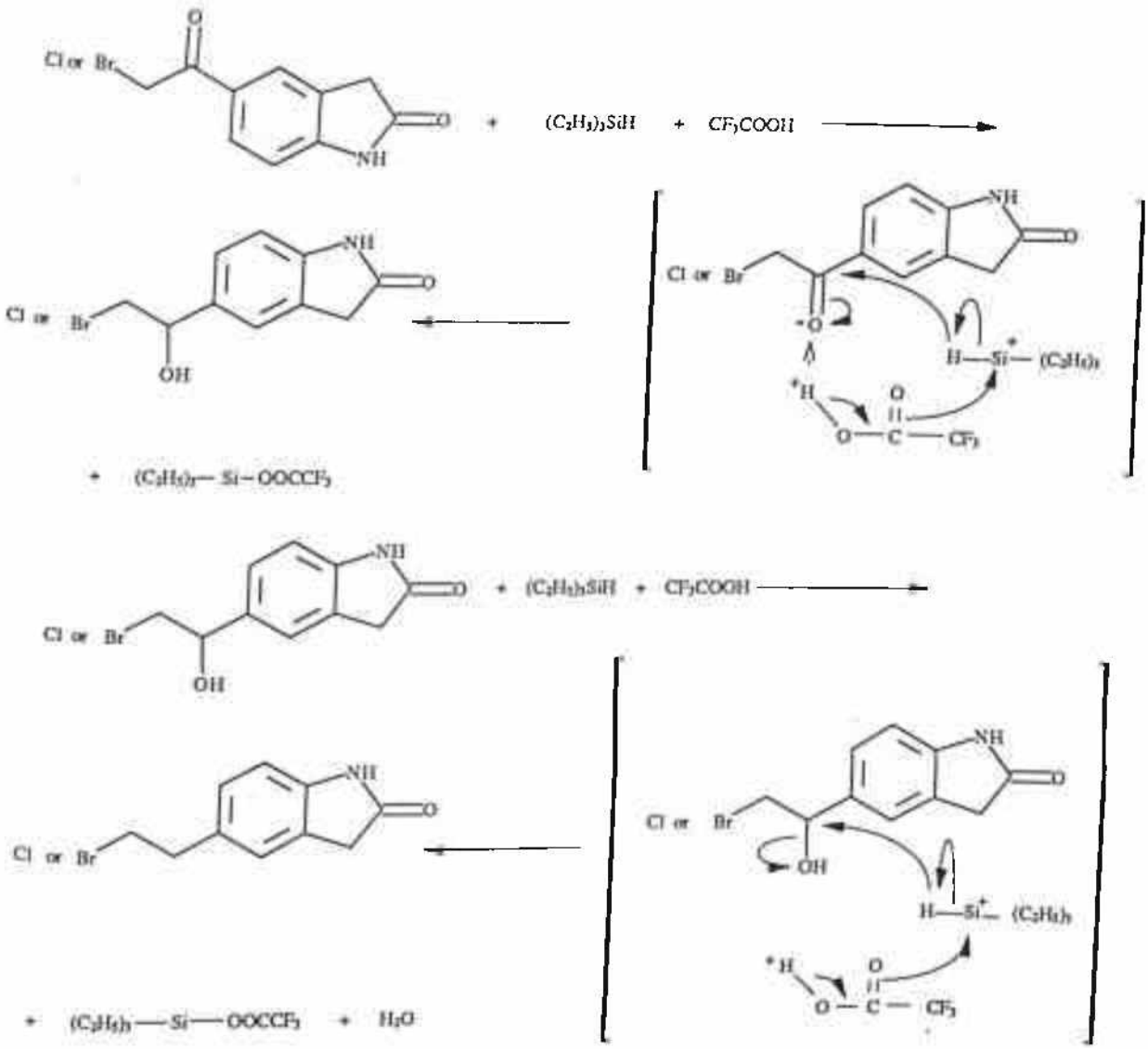
Compared with other trialkylsilanes, *viz.*, tri-n-propylsilane, tri-n-butylsilane and tri-n-hexylsilane, triethylsilane has been reported suitable for compounds whose reduced products had a boiling point greater than 300°C.[200]

With carbonyl compounds containing carboxylate, cyano, or nitro functional groups, among others, which include the amide groups, only the carbonyl group is reduced in trifluoroacetic acid media. Silane reductions of the carbonyl group to methylene are specific for aryl carbonyl compounds.

The reductions of the carbonyl group to methylene, in this case 5-(2-chloroacetyl)-1,3-and-6-substituted-2,3-dihydro-1*H*-indol-2-ones to 5-(2-chloroethyl)-1,3-and-6-substituted -2,3-dihydro-1*H*-indol-2-ones by triethylsilane can be viewed as occuring in two steps : reduction of the carbonyl group to the primary alcohol or alcohol derivative followed by the reduction of the intermediate alcohol or alcohol derivative. The mechanism involved may be envisaged as given below for the reduction of 5-(2-chloroacetyl)-2,3-dihydro-1*H*-indol-2-one to 5-(2-chloroethyl)-2,3-dihydro-1*H*-indol-2-ones. The same mechanism of reduction holds good for the reduction of the 6-(2-bromo acetyl) benzoxazolin-2(3*H*)-one to 6-(2-bromoethyl) benzoxazolin-2(3*H*)-one. The physical properties of the 5-(2-chloroethyl)-1,3- and –6-substituted-2,3-dihydro-1*H*-indol-2-ones and the 6-(2-bromo ethyl) benzoxazolin-2(3*H*)-one are shown in Table 11.

The next step involved the nucleophilic substitution of the hetero appended and fused phenethyl chlorides to the parent 1,2-dihydro-2-acenaphthylenyl piperazine. This reaction was slow, because the side chain is comparatively large in terms of size and other functionalities present in it. The reaction was carried out in the presence of anhydrous sodium carbonate and a few milligram of sodium iodide. In this reaction diisopropylethylamine (*DIPEA*), also referred to as Hunig's base, which is a hindered non-nucleophilic base, was used as a catalyst in a definite molar proportion. The use of diisopropylethylamine as a basic catalyst has been reported in such type of condensations involving a nucleophilic attack.[77,143] The reaction was carried out for two days using

methylisobutyl ketone (MIBK) as the solvent. As mentioned earlier the reaction was slow, but it proceeded to completion after two days. Reactions of this type have been reported to take upto 5 days for completion.[77,143]



The sodium carbonate was filtered off and the solvent was removed under reduced pressure to dryness to give the product, which was isolated in the form of hydrochloride wherever the free base was not obtainable as a stable solid. The physical properties of the hetero appended phenethyl chlorides, i.e., 4-(4-{2-[4-(-1,2-dihydro-2-acenaphthylenyl) piperazin-1-yl] ethyl} phenyl)-2- and -5-substituted thiazoles are shown in Table 12 and the hetero fused phenethyl chlorides, i.e., 5-{2-[4-(1,2-dihydro-2-acenaphthylenyl) piperazinyl]ethyl}-1-,-3-and-6-substituted-2,3-dihydro-1*H*-indole-2-ones and the isosteric

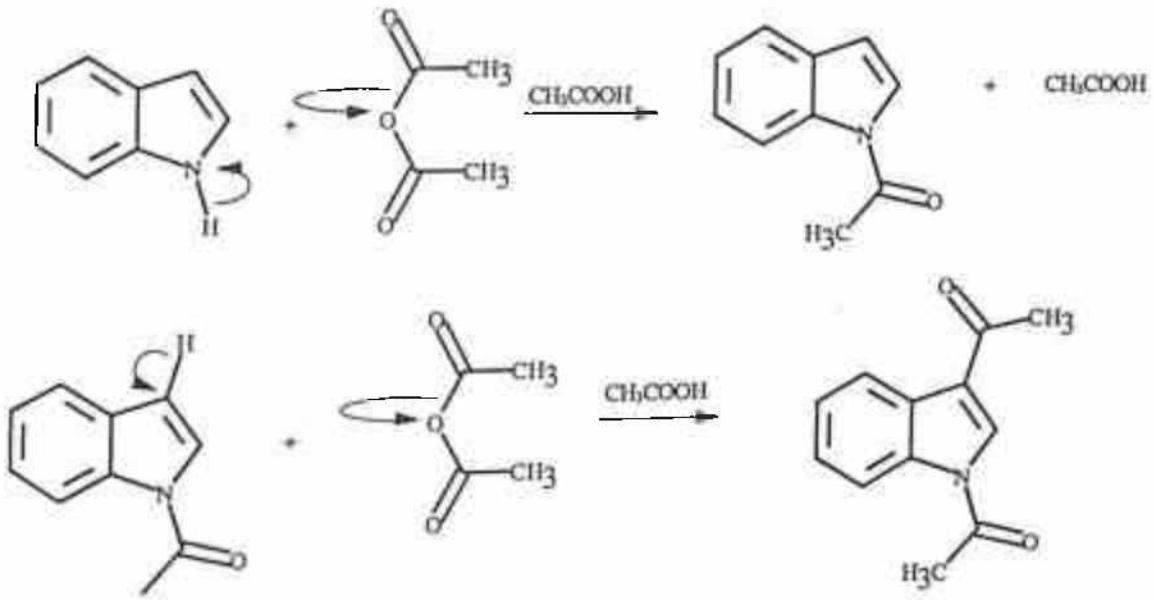
6-{2-[4-(1,2-dihydro-2-acenaphthylenyl)piperazinyl]ethyl}benzoxazolin-2-(3*H*)-one are shown in Table 13.

The second series of molecules involved the synthesis of various piperazinyl indolyl propanones to evaluate their affinity at the 5-HT receptor.

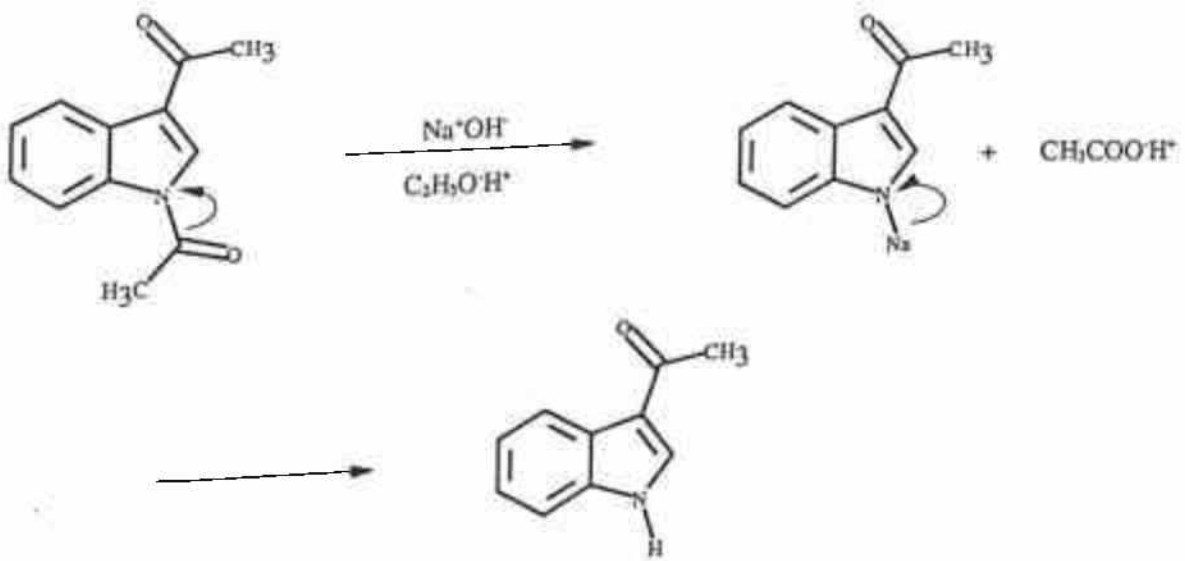
The synthetic route involved the generation of a substituted indole system followed by the incorporation of the aryl piperazine moiety in the side-chain. The substrate used in this investigation is a substituted 3-acetyl indole on to which the aryl piperazine moiety was incorporated through a *Mannich reaction*, which resulted in increasing the side-chain length, by one methylene unit and the incorporation of the substituted aryl piperazine moiety.

The synthetic approach involved the generation of the 3-acetyl indole in the first step. The principal methods which have been used for the preparation of this compound are the reaction of indole with acetic anhydride at 180-200°C[201-203] and of indolyl magnesium halides with chloroacetyl chloride[204-206] which gave varying yields of a mixture of mono- and di-acetyl indoles. However, their yields are not satisfactory. For this reason, the reaction of indole with acetic anhydride was preferred as a preparative method, but it cannot be easily adopted owing to the conditions used i.e., 180-200°C. In addition, the dark product had to be crystallized several times in order to obtain pure diacetyl indole. Accordingly, the reaction was carried out at 147°C for periods of 24-48 hours. Pure acetic anhydride gave an oil, which on crystallization gave a low yield of diacetyl indole, but the addition of 10 % of acetic acid to the reaction mixture gave after 24 hours a product which crystallized readily during the removal of the solvent under reduced pressure and on further crystallization gave 55-60% yields of pure diacetyl indole. The mechanism involved in the formation of diacetyl indole can be envisaged as

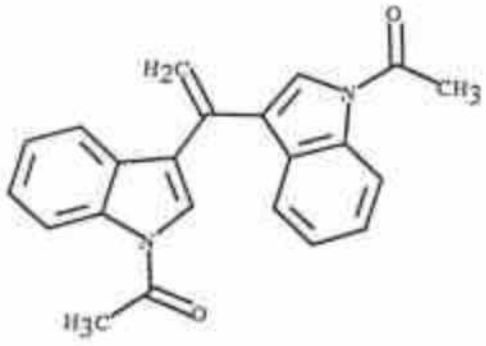
follows:



The N-acetyl group of this diacetyl indole was removed quantitatively at room temperature by aqueous-alcoholic sodium hydroxide. The mechanism involved in the hydrolytic process is as follows :



The crude diacetyl indole was contaminated by 5-10% of a by-product 1,1-di-(1-acetyl-3-indolyl) ethylene, which is a dimer.



The structure of this by-product is known.[207,208] This by-product was left as an insoluble residue after the first crystallization of the crude diacetyl indole. Complete separation of the diacetyl indole from the by-product by fractional crystallization resulted in substantial losses of material. In order to ensure an optimum yield of 3-acetyl indole, the by-product was removed in the hydrolysis stage by taking excess of ethanol and sodium hydroxide, warming the solution slightly, and then filtering the insoluble residue. The next step involved substitutions on the indolyl nitrogen, with methyl, ethyl, 4-fluoro phenyl and 4-fluoro benzoyl groups. Methyl and ethyl substitutions on the indolyl nitrogen were carried out by the addition of the respective dialkyl sulphates to a suspension of 3-acetyl indole in excess of aqueous sodium hydroxide (10% solution). This reaction is a neutralisation reaction, which occurs simultaneously along with alkylation. The addition of the dialkyl sulphates was carried out between 80-85°C. The reaction being highly exothermic, the addition of the dialkyl sulphate was made in a controlled manner, so as to maintain 85°C as the maximum temperature of the reaction mixture. N-methyl-3-acetyl indole and N-ethyl-3-acetyl indole were obtained in yields of 95% and 76% respectively. This method was preferred to the method described by Potts and Saxton[209] and Gary,[210] for unsubstituted indoles, which involved the use of sodamide or sodium hydride followed by alkyl iodide on indole at elevated temperatures.

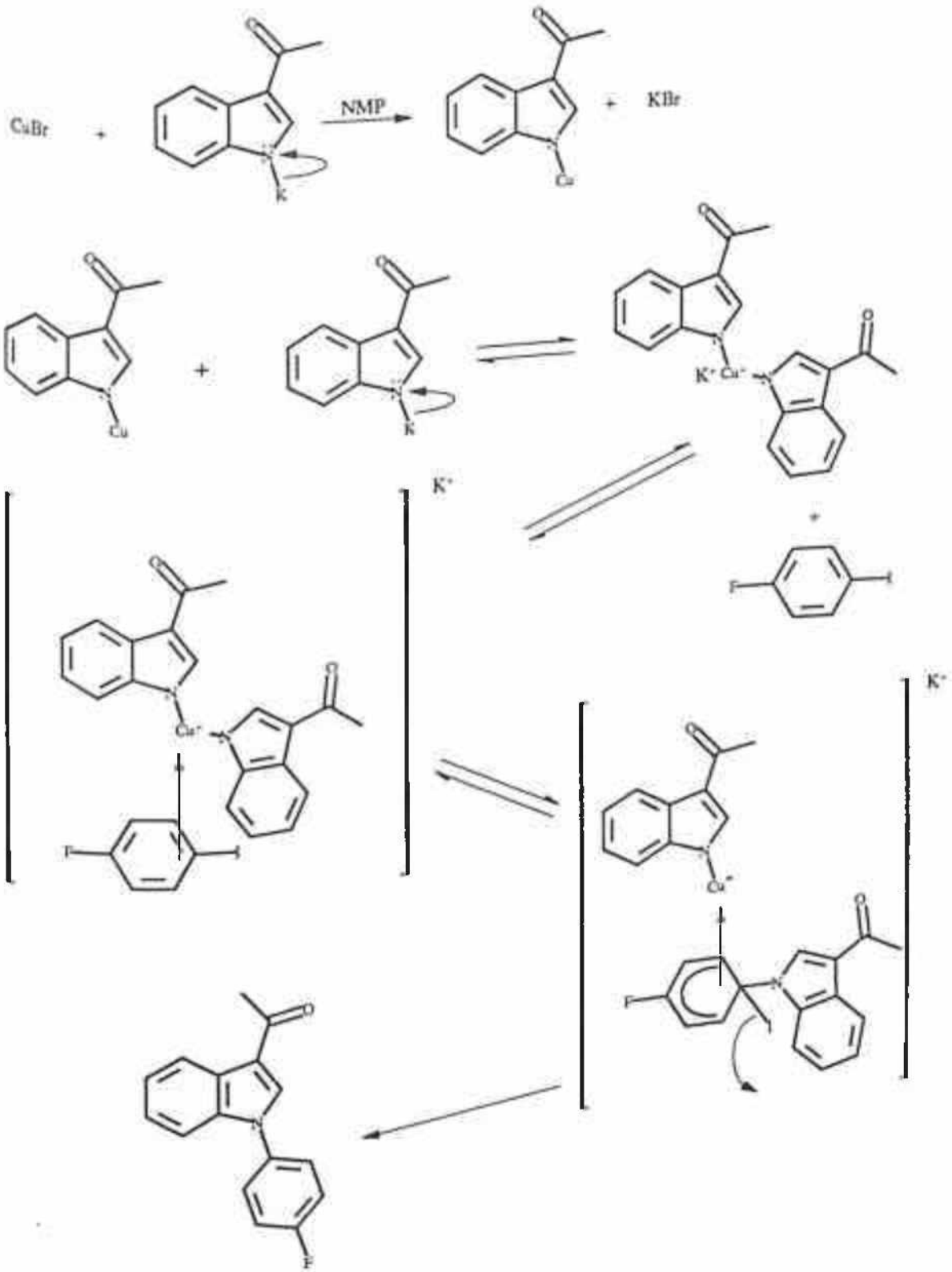
In the synthesis of N-4-fluorophenyl-3-acetyl indole a modified *Ulmann condensation* procedure was devised. The condensation of five-membered heteroaromatic compounds

containing a free NH group with aryl halides in the presence of a copper catalyst is related to analogous *Ulmann condensation*.[211-213] Some N-aryl heteroaromatic compounds have been previously reported by conducting such condensations in nitrobenzene[214-217] and pyridine.[218] A high boiling polar aprotic solvent was required to bring about the condensation of the heteroaromatic compound containing a free NH group with aryl halides. This is a type of a nucleophilic substitution and is catalyzed by copper and / or copper salts at around 150-200°C. Intermediates such as copper oxide and aryl copper have been postulated to take part in all types of *Ulmann reactions*. Some azoles (benzimidazole, imidazole etc.,) are known to form complexes with copper salts.[219-221] It is likely that such an intermediate is also responsible for arylation under *Ulmann conditions*.

In the present study, 3-acetyl indole was treated with 4-fluoroiodo benzene in the presence of anhydrous potassium carbonate in N-methyl-2-pyrrolidone (NMP). Copper bromide and activated copper metal powder were used as catalysts in this reaction.

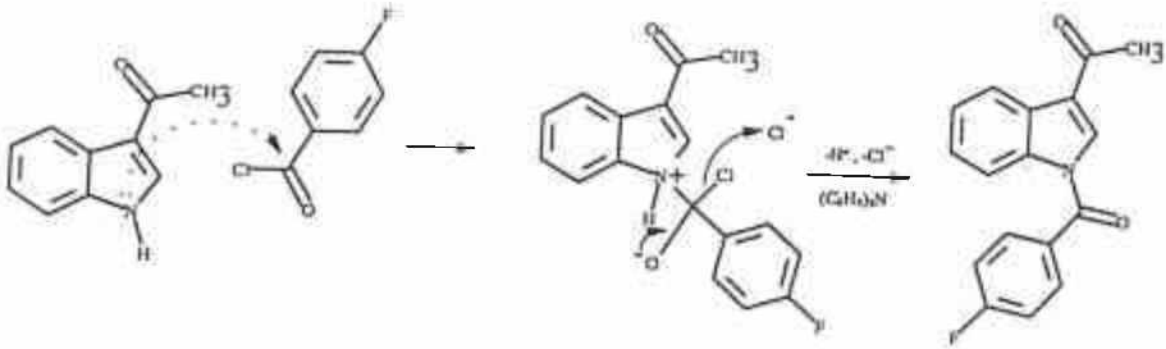
In this reaction, 3-acetyl indole reacts as its anion in a copper-catalyzed nucleophilic substitution on the aryl halide,[222,223] i.e., 4-fluoroiodo benzene to give 1-(4-fluorophenyl)-3-acetyl indole. A copper complex is first obtained which is hydrolysed by addition of dilute HCl, followed by extraction with dichloromethane. Reactions of this type using N-methyl-2-pyrrolidone (NMP) as the solvent, in an analogous *Ulmann reaction* have been reported for N-arylation of various indoles. The mechanism involved in this reaction can be envisaged as given below.

In order to increase the distance between the aryl group, i.e., 4-fluoro phenyl group and the indolyl nitrogen by a methylene unit, to study the modulatory effects of such a modification at the 5-HT receptor, 4-fluoro benzoyl substitution was performed at the indolyl nitrogen to give 1-(4-fluorobenzoyl)-3-acetyl indole. The other alternative would be to bring about the introduction of a 4-fluorobenzyl group, instead of the 4-fluorobenzoyl group at the indolyl nitrogen. Introduction of a 4-fluoro benzoyl group was done in this study, the reason being that the group could be easily and readily introduced in the form of an acid chloride, i.e., 4-fluorobenzoyl chloride. The reaction is a simple reaction for the formation of amides.



The acid chloride, i.e., 4-fluorobenzoyl chloride was added to a solution of 3-acetyl indole in benzene. The hydrogen chloride evolved was trapped by using anhydrous

triethylamine in the reaction. The mechanism involved in this reaction is the formation of an amide at the indolyl nitrogen of 3-acetyl indole to give 1-(4-fluoro benzoyl)-3-acetyl indole. The mechanism involved can be envisaged as follows :



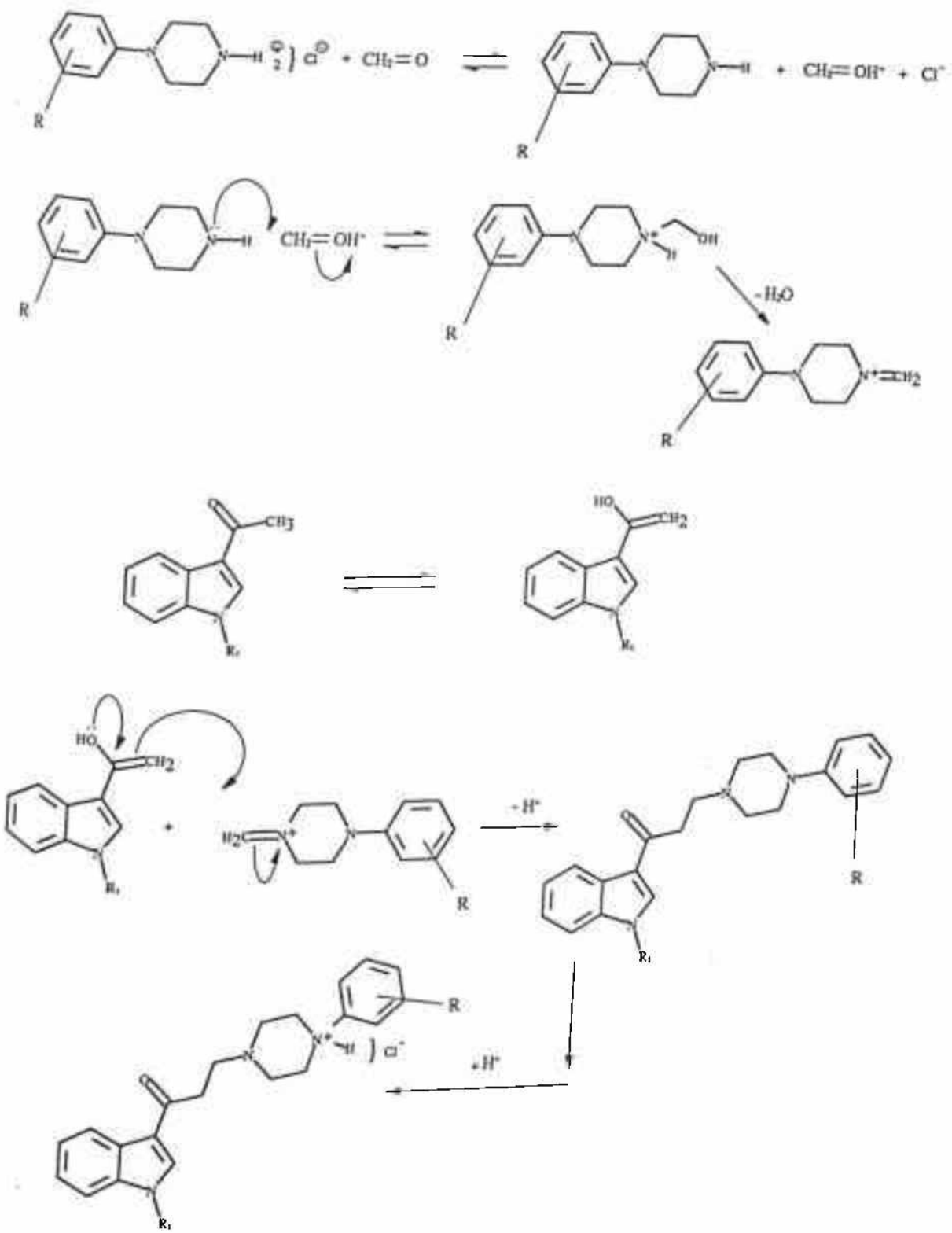
The physical properties of the N-substituted-3-acetyl indoles are shown in Table 14. The next step in all the four series of molecules, i.e., methyl, ethyl, 4-fluorophenyl and 4-fluoro benzoyl substituents on the indolyl nitrogen, involved the incorporation of a substituted phenyl piperazine at the terminal amine portion and also to increase the length of the side chain from two methylene units to three methylene units. In these series of compounds, the presence of an active methylene, in the form of an acetyl group at the 3rd postion of the indole, offers an advantage that the incorporation of a methylene group and the terminal amine could be brought about simultaneously.

As a result, the *Mannich reaction*[224,225] offered the best alternative, for increasing the sidechain length of the 3-acetyl indole by one methylene unit and the incorporation of a substituted phenyl piperazine which could be achieved in one step.

In the *Mannich reaction* formaldehyde or paraformaldehyde reacts with a ketone and a secondary amine in the presence of a trace of acid to give the aminoalkylated ketone, which is otherwise referred to as the mannich base. The mechanism of this reaction involves the initial reaction of formaldehyde/paraformaldehyde with the substituted phenyl piperazine, which serves as the secondary amine to form an iminium ion, through elimination of water, functioning as the active aminomethylating agent. This ion then reacts with the enol from of the active methylene compound to form the mannich base, as

the product. The mannich reactions were carried out in ethanol and the time duration for the mannich reaction was determined experimentally, in terms of the yield of the product obtained. The mannich products were directly obtained as stable hydrochloride salts except in few cases where the hydrochlorides were not stable.

The time required for the mannich reaction was 19 hours for an optimum yield of the product. Increase in the reaction time upto 42 hours, did not show any further increase in the yields of the products considerably. The physical properties of the N-methyl, ethyl, 4-fluoro phenyl and 4-fluoro benzoyl-3-acetyl indole mannich bases are shown in Tables 15, 16, 17 and 18 respectively. The mechanism involved in the mannich reaction of N-substituted-3-acetyl indoles with substituted phenyl piperazines is as follows :

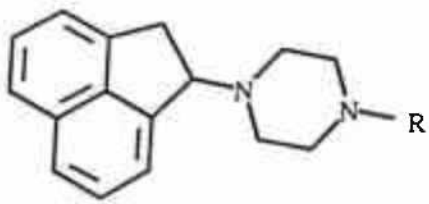


where, R_1 = methyl, ethyl, 4-fluorophenyl and 4-fluorobenzoyl

R = phenyl, 3-chlorophenyl, 4-chlorophenyl, 4-fluorophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3-trifluoromethyl phenyl, 2-pyridyl and 2-pyrimidinyl.

All the compounds synthesized, were characterized by elemental analysis, infrared spectra, and the ^1H NMR spectra. All values and spectras obtained were as expected for the respective functionalities present in the compounds.

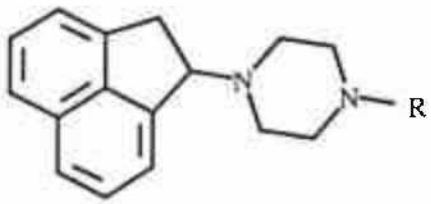
Table 5. *Physical Properties of N-4- alkyl substituted- 1-(1,2-dihydro-2-acenaphthylenyl)piperazines*



Compound No.	R	M.P. (°C)	Yield (%)	Recryst. Solv.	Mol. Formula
83	H	66	67	A	$C_{16}H_{18}N_2$
84	CH_3	244	60	B - C	$C_{17}H_{20}N_2.2HCl$
85	C_2H_5	205	52	B - C	$C_{18}H_{22}N_2.2HCl$
86	n-C_3H_7	263	31	B - C	$C_{19}H_{24}N_2.2HCl$
87	Allyl	267	38	B - C	$C_{19}H_{22}N_2.2HCl$
88	i-C_3H_7	232	41	B - C	$C_{19}H_{24}N_2.2HCl$
89	n-C_4H_9	260	39	B - C	$C_{20}H_{26}N_2.2HCl$

A - Diisopropyl ether ; B - Ethanol ; C - Diethyl ether

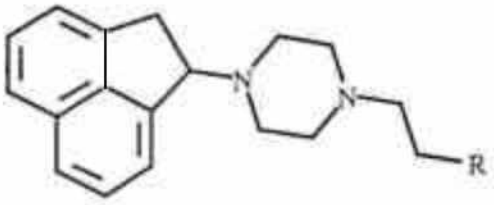
Table 6. Physical Properties of N-4- aryl, -substituted aryl, and -aralkyl - 1-(1,2-dihydro-2-acenaphthylenyl)piperazines



Compound No.	R	M.P. (°C)	Yield (%)	Recryst. Solv.	Mol. Formula
90	Phenyl	210	40	A - B	$C_{22}H_{22}N_2.2HCl$
91	3-Chloro phenyl	199	62	A - B	$C_{22}H_{21}N_2Cl.2HCl$
92	4-Chloro phenyl	156	54	C	$C_{22}H_{21}N_2Cl$
93	2-Methoxy phenyl	219	65	D	$C_{23}H_{24}N_2O.2HCl$
94	3-Methoxy phenyl	208	68	D	$C_{23}H_{24}N_2O.2HCl$
95	4-Methoxy phenyl	129	55	C	$C_{23}H_{24}N_2O$
96	4-Fluoro phenyl	233	64	D - B	$C_{22}H_{21}N_2F.2HCl$
97	3-Trifluoro methyl phenyl	223	63	A	$C_{23}H_{21}N_2F_3.2HCl$
98	2-Pyridyl	262	69	A - C	$C_{21}H_{21}N_3.2HCl$
99	2-Pyrimidinyl	248	65	A	$C_{20}H_{20}N$-4 2HCl
100	Benzoyl	254	62	A	$C_{23}H_{22}N_2O.2HCl$
101	4-Fluoro Benzoyl	248	67	D	$C_{23}H_{21}N_2OF.2HCl$
102	Piperonyl	262	69	A	$C_{24}H_{24}N_2O_2.2HCl$

A - Ethanol ; B - Diethyl ether ; C - Acetone ; D - Methanol

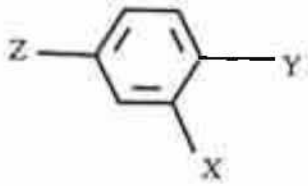
7. Physical Properties of N-4- (2- substituted ethyl) - 1-(1,2-dihydro-2-acenaphthylenyl)piperazines



Compound No.	R	M.P. (°C)	Yield (%)	Recryst. Solv.	Mol. Formula
103	OH	270	46	A - B	$C_{18}H_{22}N_2O.2HCl$
104	NH_2	164	38	C	$C_{18}H_{23}N_3$
105	$N(CH_3)_2$	186	47	D	$C_{20}H_{27}N_3.C_4H_4O_4$
106	$N(C_2H_5)_2$	174	40	D	$C_{22}H_{31}N_3.C_4H_4O_4$
107	Pyrrolidinyl	188	52	A	$C_{22}H_{29}N_3.C_4H_4O_4$
108	Piperidinyl	190	55	A	$C_{23}H_{31}N_3.C_4H_4O_4$
109	Morpholinyl	196	55	A	$C_{22}H_{29}N_3O.C_4H_4O_4$
110	Phenyl	238	64	D	$C_{24}H_{31}N_2.2HCl$

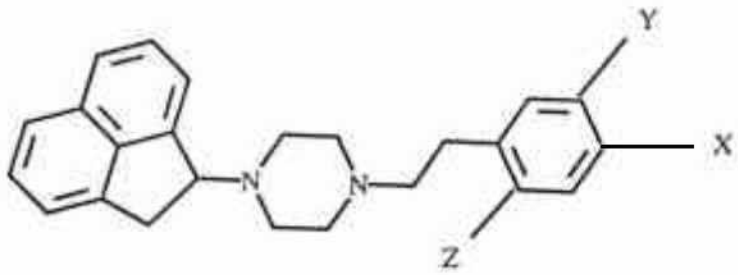
A - Ethanol ; B - Diethyl ether ; C - Acetone ; D - Methanol

Table 9. Physical Properties of 1,3 & 6 substituted-2,3-dihydro-1*H*-indol-2-ones



Compound No.	--- X --- Y ---	Z	M.P. (°C)	Yield (%)	Recryst. Solvent
124	NH-CO-CH_2	H	125	33	Ethanol
128	N(CH_3)-CO-CH_2	H	88	38	Ethanol
132	NH-CO-CH(CH_3)	H	120	42	Ethanol
136	N(CH_3)-CO-CH(CH_3)	H	53	49	Ethanol
140	N(C_2H_5)-CO-CH_2	H	95	38	Ethanol
144	NH-CO-CH_2	6-Cl	103	42	Ethanol
148	NH-CO-CH_2	6-F	109	35	Ethanol

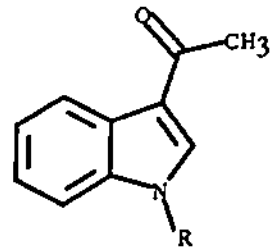
Table 13. Physical Properties of 5-{2-[4-(1,2-dihydro-2-acenaphthylenyl) piperazinyl] ethyl}-1,3- and -6-substituted-2,3-dihydro-1H-indol-2-ones And 6-{2-[4-(1,2-dihydro-2-acenaphthylenyl) piperazinyl] ethyl} benzoxazolin -2(3H)-one



Compound No.	--- X --- Y ---	Z	M.P. (°C)	Yield (%)	Recryst. Solvent	Mol. Formula
127	NH-CO-CH_2	H	236	64	A - B	$C_{26}H_{27}N_3O.2HCl$
131	N(CH_3)-CO-CH_2	H	247	54	C - B	$C_{27}H_{29}N_3O.2HCl$
135	NH-CO-CH(CH_3)	H	98	62	C - B	$C_{27}H_{29}N_3O.2HCl$
139	N(CH_3)-CO-CH(CH_3)	H	235	48	C - D	$C_{28}H_{31}N_3O.2HCl$
143	N(C_2H_5)-CO-CH_2	H	245	48	A	$C_{28}H_{31}N_3O.2HCl$
147	NH-CO-CH_2	6-Cl	228	45	A - B	$C_{26}H_{26}N_3OCl.2HCl$
151	NH-CO-CH_2	6-F	256	40	A - B	$C_{26}H_{26}N_3OF.2HCl$
154	O-CO-NH	H	256	23	A - B	$C_{25}H_{25}N_3O_2.2HCl$

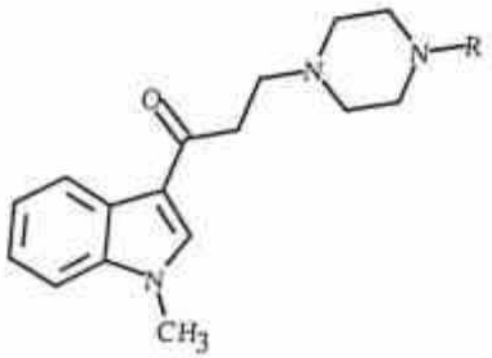
A - Ethanol ; B - Diethyl ether ; C - Methanol ; D - Acetone

Table 14. Physical Properties of N- substituted-3-acetyl indoles



Compound No.	R	M.P. (°C)	Yield (%)	Recryst. Solvent
157	Methyl	95	95	Benzene
168	Ethyl	88	76	Benzene
179	4-Fluoro phenyl	140-41	55	Ethanol
190	4-Fluoro benzoyl	154	63	Ethanol

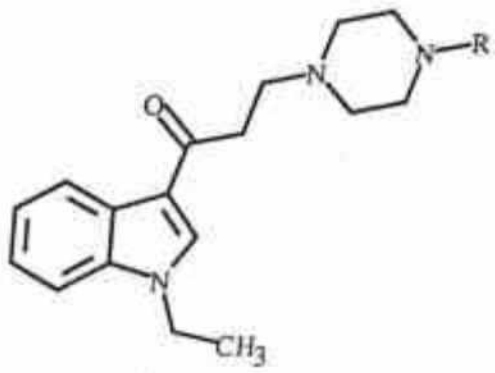
Table 15. Physical Properties of N-methyl -indol-3-yl-(4-substituted piperazin-1-yl) propanones



Compound No.	R	M.P. (°C)	Yield (%)	Recryst. Solv.	Mol. Formula
158	Phenyl	220	48	A	$C_{22}H_{25}N_3O.C_4H_4O_4$
159	3-Chloro phenyl	241	51	B - C	$C_{22}H_{24}N_3OCl.2HCl$
160	4-Chloro phenyl	249	57	B - C	$C_{22}H_{24}N_3OCl.2HCl$
161	4- Fluoro phenyl	237	41	B - C	$C_{22}H_{24}N_3OF.2HCl$
162	2-Methoxy phenyl	210	49	B - C	$C_{23}H_{27}N_3O_2.2HCl$
163	3-Methoxy phenyl	215	43	A	$C_{23}H_{27}N_3O_2.C_4H_4O_4$
164	4-Methoxy phenyl	253	48	B - C	$C_{23}H_{27}N_3O_2.2HCl$
165	3-Trifluoromethyl phenyl	224	39	B - C	$C_{23}H_{24}N_3OF_3.2HCl$
166	2-Pyridyl	258	58	B - C	$C_{21}H_{24}N$-4O.2HCl
167	2-Pyrimidinyl	225	61	B - C	$C_{20}H_{23}N_5O.2HCl$

A - Isopropyl alcohol ; B - Methanol ; C - Diethyl ether

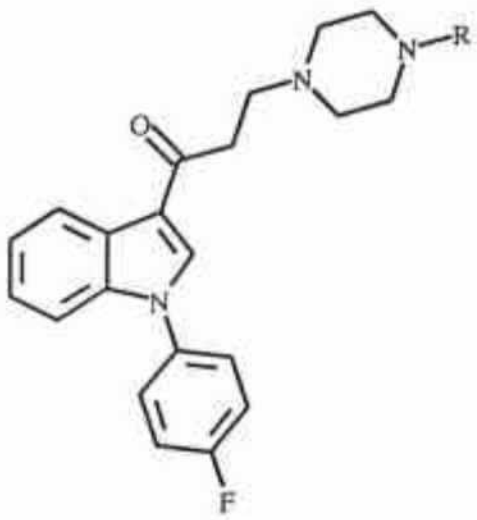
Table 16. Physical Properties of N-ethyl -indol-3-yl-(4-substituted piperazin-1-yl) propanones



Compound No.	R	M.P. (°C)	Yield (%)	Recryst. Solv.	Mol. Formula
169	Phenyl	201	49	A - B	$C_{23}H_{27}N_3O.2HCl$
170	3-Chloro phenyl	202	35	A - B	$C_{23}H_{26}N_3OCl.2HCl$
171	4-Chloro phenyl	220	41	A - B	$C_{23}H_{26}N_3OCl.2HCl$
172	4- Fluoro phenyl	227	43	A - B	$C_{23}H_{26}N_3OF.2HCl$
173	2-Methoxy phenyl	217	39	A - B	$C_{24}H_{29}N_3O_2.2HCl$
174	3-Methoxy phenyl	111	48	C - D	$C_{24}H_{29}N_3O_2.$
175	4-Methoxy phenyl	251	50	A - B	$C_{24}H_{29}N_3O_2.2HCl$
176	3-Trifluoromethyl phenyl	218	38	A - B	$C_{24}H_{26}N_3OF_3.2HCl$
177	2-Pyridyl	259	51	A - B	$C_{22}H_{26}N$-4O.2HCl
178	2-Pyrimidinyl	231	48	A - B	$C_{21}H_{25}N_5O.2HCl$

A - Methanol ; B - Diethyl ether ; C - Ethanol ; D - Petroleum ether (60-80°C)

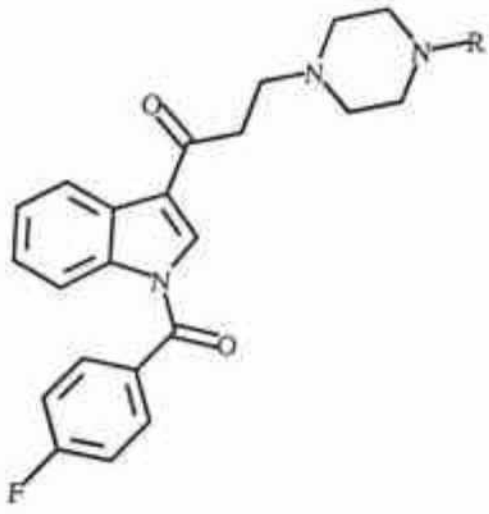
Table 17. Physical Properties of N-(4-fluorophenyl) -indol-3-yl-(4-substituted piperazin-1-yl) propanones



Compound No.	R	M.P. (°C)	Yield (%)	Recryst. Solv.	Mol. Formula
180	Phenyl	178	52	A	$C_{27}H_{26}N_3OF.C_4H_4O_4$
181	3-Chloro phenyl	145	47	B - C	$C_{27}H_{25}N_3OClF.2HCl$
182	4-Chloro phenyl	210	47	B - C	$C_{27}H_{25}N_3OClF.2HCl$
183	4- Fluoro phenyl	175	39	B - C	$C_{27}H_{25}N_3OF_2.2HCl$
184	2-Methoxy phenyl	135	46	B - C	$C_{28}H_{28}N_3FO_2.2HCl$
185	3-Methoxy phenyl	90	49	D - E	$C_{28}H_{28}N_3FO_2$
186	4-Methoxy phenyl	252	54	B - C	$C_{28}H_{28}N_3FO_2.2HCl$
187	3-Trifluoromethyl phenyl	220	39	B - C	$C_{28}H_{25}N_3OF_4.2HCl$
188	2-Pyridyl	265	59	B - C	$C_{26}H_{25}N\text{-}4OF.2HCl$
189	2-Pyrimidinyl	235	61	B - C	$C_{25}H_{24}N_5OF.2HCl$

A - Isopropyl alcohol ; B - Methanol ; C - Diethyl ether ; D - Ethanol ;
E - Petroleum ether (60-80°C)

Table 18. Physical Properties of N-(4-fluorobenzoyl) -indol-3-yl-(4-substituted piperazin-1-yl) propanones



Compound No.	R	M.P. (°C)	Yield (%)	Recryst. Solv.	Mol. Formula
191	Phenyl	94	41	A - D	$C_{28}H_{26}N_3O_2F$
192	3-Chloro phenyl	191	57	B - C	$C_{28}H_{25}N_3O_2ClF.2HCl$
193	4-Chloro phenyl	249	59	B - C	$C_{28}H_{25}N_3O_2ClF.2HCl$
194	4- Fluoro phenyl	230	33	B - C	$C_{28}H_{25}N_3O_2F_2.2HCl$
195	2-Methoxy phenyl	203	41	B - C	$C_{29}H_{28}N_3FO_3.2HCl$
196	3-Methoxy phenyl	124	37	A - E	$C_{29}H_{28}N_3FO_3$
197	4-Methoxy phenyl	251	43	B - C	$C_{29}H_{28}N_3FO_3.2HCl$
198	3-Trifluoromethyl phenyl	224	31	B - C	$C_{29}H_{25}N_3O_2F_4.2HCl$
199	2-Pyridyl	175	49	B - C	$C_{27}H_{25}N\text{-}4O_2F.2HCl$
200	2-Pyrimidinyl	243	53	B - C	$C_{26}H_{24}N_5O_2F.2HCl$

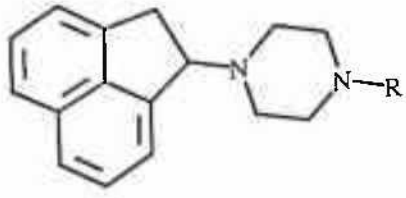
A - Ethanol ; B - Methanol ; C - Diethyl ether ; D - Hexane ; E - Petroleum ether (60-80°C)

Pharmacology

5-HT_3 Antagonistic Activity

In compounds of Type - I, the N-4 alkyl substituted-1-(1,2-dihydro-2-acenaphthylenyl) piperazines, which were evaluated for their antagonism at the 5-HT_3 receptor in the guinea pig ileum LMMP, compound (88) showed antagonism comparable to that of Ondansetron, a 5-HT_3 antagonist, which is used as a reference standard for our study. Compounds (83) and (89) also showed antagonism, but they were half as potent as Ondansetron. (Table 19)

Table 19. Results of N-4-alkyl substituted -1-(1,2-dihydro-2-acenaphthylenyl) piperazines for their 5-HT_3 receptor antagonism in the guinea pig ileum.



Compound No.	R	% Inhibition Mean ± S.E.
83	H	39.86 ± 4.3*
84	CH_3	16.77 ± 3.8
85	C_2H_5	N.S.
86	n-C_3H_7	N.S.
87	Allyl	N.S.
88	i-C_3H_7	67.13 ± 4.6*
89	n-C_4H_9	32.3 ± 5.4
Ondansetron	-	69.46 ± 2.7

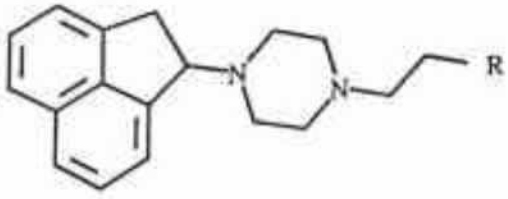
N.S. Not Significant -- Inhibition less than 10%

$P < 0.05$

In compounds of Type - II, N-4-(2-substituted) ethyl-1-(1,2-dihydro-2-acenaphthylenyl) piperazines, which were evaluated for their antagonism at the 5-HT_3 receptor in the

guinea pig ileum LMMP, only compound (105) showed antagonism comparable to that of Ondansetron and compound (106) was found to be half as potent as Ondansetron. The antagonistic effect of other compounds in this series was not found to be significant. (Table 20)

Table 20. Results of N-4-(2-Substituted) ethyl –1-(1,2-dihydro-2-acenaphthylenyl) piperazines for their 5-HT_3 receptor antagonism in the guinea pig ileum.



Compound No.	R	% Inhibition Mean ± S.E.
103	OH	N.S.
104	NH_2	N.S.
105	$N(CH_3)_2$	54.08 ± 5.3*
106	$N(C_2H_5)_2$	31.23 ± 4.7
107	Pyrrolidinyl	16.86 ± 3.8
108	piperidinyl	N.S.
109	Morpholinyl	N.S.
Ondansetron	-	69.46 ± 2.7

N.S. Not Significant -- Inhibition less than 10%

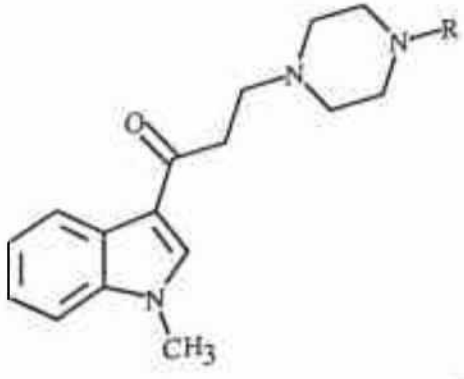
$P \leq 0.05$

Among the compounds of Type-I [N-4 alkyl substituted-1-(1,2-dihydro-2-acenaphthylenyl) piperazines] and Type-II [N-4-(2-substituted) ethyl-1-(1,2-dihydro-2-acenaphthylenyl) piperazines], evaluated for their peripheral serotonergic antagonism, compound (88) showed the maximum potency. On the other hand, compound (86), which possesses an n-propyl substituent at the N-4 piperazine, showed no significant activity, indicating that a bulky isopropyl group is contributing to the activity. Furthermore, the compound (105), which possess a dimethylaminoethyl substituent on the N-4 piperazine, has showed significant antagonism. This is an indication that a

dimethyl substituent at the terminal position imparts antagonistic activity. This aspect is also supported by our observation that an unsubstituted free terminal amino group, as in compound (104) or any higher substituent on the terminal nitrogen, as in compounds (106-109) is detrimental to antagonistic activity.

In compounds of Type - V, the substituted-piperazinyl indol-(1-methyl)-3-yl propanones, which were evaluated for their peripheral serotonergic activity, only compound (165) showed significant antagonism at the 5-HT_3 receptor. Compounds (166) and (167) were found to be possess lesser degree of antagonism. (Table 21)

Table 21. Antagonism by N-methyl substituted-piperazinyl indol-3-yl propanones of the response to 5-HT in the guinea pig ileum (Longitudinal muscle myenteric plexus).



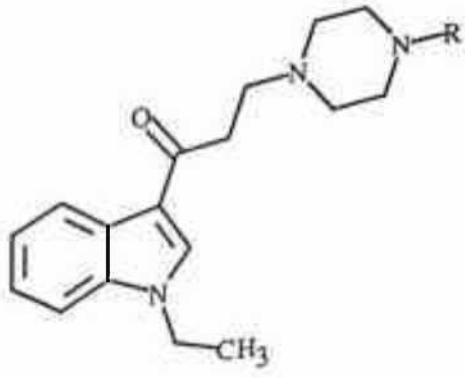
Compound No.	R	% Inhibition Mean ± S.E.
158	Phenyl	N.S.
159	3-Chlorophenyl	N.S.
160	4-Chlorophenyl	N.S.
161	4-Fluorophenyl	13.33 ± 5.4
162	2-Methoxyphenyl	8.33 ± 2.6
163	3-Methoxyphenyl	N.S.
164	4-Methoxyphenyl	N.S.
165	3-Trifluoromethyl phenyl	46.66 ± 5.6*
166	2-Pyridyl	30.76 ± 7.8*
167	2-Pyrimidinyl	32.36 ± 3.3*
Ondansetron	-	65.84 ± 4.6

N.S. Not Significant -- Inhibition less than 5%

$P < 0.05$

In compounds of Type - VI, the substituted-piperazinyl indol-(1-ethyl)-3-yl propanones, which were evaluated for their peripheral serotonergic activity, only compound (176) showed significant antagonism at the 5-HT_3 receptor. (Table 22)

Table 22. Antagonism by N-ethyl substituted-piperazinyl indol-3-yl propanones of the response to 5-HT in the guinea pig ileum (Longitudinal muscle myenteric plexus).



Compound No.	R	% Inhibition Mean ± S.E.
169	Phenyl	N.S.
170	3-Chlorophenyl	N.S.
171	4-Chlorophenyl	N.S.
172	4-Fluorophenyl	11.22 ± 2.6
173	2-Methoxyphenyl	6.50 ± 7.8
174	3-Methoxyphenyl	N.S.
175	4-Methoxyphenyl	N.S.
176	3-Trifluoromethyl phenyl	41.68 ± 6.3*
177	2-Pyridyl	28.92 ± 2.7*
178	2-Pyrimidinyl	30.97 ± 4.6*
Ondansetron	-	65.84 ± 4.6

N.S. Not Significant -- Inhibition less than 5%

$P < 0.05$

Among compounds of Type-V [substituted-piperazinyl indol-(1-methyl)-3-yl propanones] and Type-VI [substituted-piperazinyl indol-(1-ethyl)-3-yl propanones], compound (165) has shown significant antagonism. Further increase in the chain length on the indolyl nitrogen, as in compound (176) has shown to decrease the antagonistic

activity. This observation is consistent with the reported 5-HT_3 antagonists, which possesses a methyl substituent on the indolyl nitrogen, where replacement of the methyl group with an ethyl group has lead to significant loss of activity.

Inhibition of Apomorphine induced climbing behavior and Reversal of Haloperidol induced Catalepsy

The compounds of Type-III, IV,VII & VIII synthesized in this work are targeted, for *atypicality in antipsychotic activity*, on the basis described in Chapter-2.

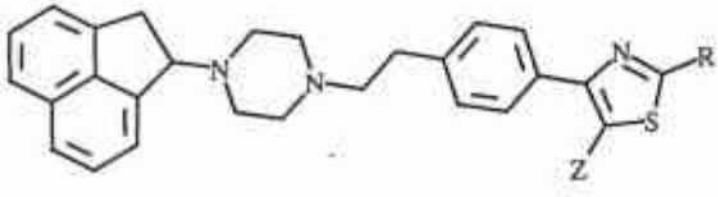
The study initiated by Kostowski and coworkers[226] and followed by the findings of Meltzer,[227,228] led to the the concept of combined 5-HT_2 and D_2 antagonism. It has been the focus of scientific investigation and pharmaceutical development. The uniqueness of clozapine and the recent reports of reduced extrapyramidal side effects (EPS) due to risperidone are often construed as benefits of 5-HT_2/D_2 antagonism. The clinical gains of these new drugs has been unequivocally attributed to their 5-HT_2 antagonism. It is hypothesized that the addition of 5-HT_2 antagonism delays the onset or diminishes the severity of the extrapyramidal symptoms associated with a given dose of a D_2 antagonist. Neuroleptic induced catalepsy in rodents serves as a model of human EPS and has been used to examine the effect of 5-HT_2 antagonists.[229] The EPS protection afforded by 5-HT_2 blockade is conditional.[230] When D_2 antagonism is just above the EPS threshold, the concomitant 5-HT_2 blockade may delay the onset of EPS. If the dose of the D_2 antagonism is increased further, the 5-HT_2 occupancy may reduce the severity of EPS. However, if the level of D_2 occupancy is increased still further, the protective effect of 5-HT_2 blockade may be overwhelmed. This view is supported by several findings. First, neurochemical studies in animals show that 5-HT_2 antagonism enhances dopaminergic activity in the striatum, but only in the face of moderate D_2 block, not with supramaximal D_2 block.[231] Second, animal studies with risperidone and olanzapine show that these drugs do induce catalepsy.[232] However, they do so at a much higher dose relative to typical neuroleptics, suggesting that the 5-HT_2 component functions to delay, not obviate, the onset of EPS. Third, Bligh-Glover and coworkers[233] have recently shown that while

ritanserin is able to reverse catalepsy induced with 0.25 mg/kg, it is unable to reverse catalepsy induced by 0.75 mg/kg haloperidol.

Hence, the prime options among the outline methods of evaluating the compounds for atypicality in the antipsychotic activity, were to evaluate their D_2 antagonism, in terms of the compounds ability to antagonize the actions of Apomorphine, a D_2/D_1 agonist and to evaluate the compounds ability to reverse catalepsy induced by the typical antipsychotic haloperidol, which is a non-selective dopamine antagonist.

Among the compounds of Type-III [4-(4-{2-[4-(1,2-dihydro-2-acenaphthylenyl) piperazin-1-yl] ethyl} phenyl)-2- and -5-substituted thiazoles] evaluated, compounds (117), (121) and (123) have shown significant inhibition of the climbing induced by the D_2/D_1 agonist apomorphine. These compounds have shown 62%, 42% and 53% inhibition of this climbing behavior respectively, indicating that these compounds show a significant anitpsychotic profile. (Table 23)

Table 23. Results of 4-(4-{2-[4-(1,2-dihydro-2-acenaphthylenyl) piperazin-1-yl] ethyl} phenyl)-2- and –5-substituted thiazoles for their inhibition of apomorphine induced climbing behavior in mice



Compound No.	R	Z	% Inhibition Mean ± S.E.
113	NH_2	H	N.S.
115	CH_3	H	N.S.
117	NH_2	CH_3	61.1 ± 6.4 *
119	$NHCH_3$	H	11.1 ± 5.8
121	NH-Allyl	H	41.6 ± 7.9 *
123	OH	H	52.4 ± 4.8
Haloperidol	-	-	100

N.S.- Not Significant -- Inhibition less than 10%

$P < 0.05$

These selected compounds were further evaluated for their *atypicality* in antipsychotic activity by their ability to reverse the catalepsy induced by Haloperidol, a non-selective Dopamine antagonist which has a high incidence of extra pyramidal side-effects. These three selected compounds, were found to reverse catalepsy by 6.25%, 80% and 40% respectively. Of these compounds, compound (121) showed a maximum reversal of catalepsy indicating probable antagonism at the 5-HT_2 receptors, which is a prime requirement for *atypicality* in antipsychotic activity in terms of EPS benefits. (Table 27)

Among the compounds of Type-III [4-(4-{2-[4-(1,2-dihydro-2-acenaphthylenyl) piperazin-1-yl] ethyl} phenyl)-2- and -5-substituted thiazoles] compounds carrying a substituted amino group at the 2nd position of the thiazole ring, showed increasing D_2 antagonism depending on the size of the substituent. This is evident from our observations that a free amino group (113) at the said position has insignificant activity, whereas the incorporation of a methyl group on the nitrogen (119), has increased the antagonism to a lesser extent. Further increase in the size to an allyl group (121), enhances the antagonistic activity significantly. Compound (117) on the other hand even though carries a free amino group at the 2nd position, the presence of a methyl substituent at the 5th position has increased the antagonism significantly. Compound (123), which carries a keto function at the 2nd position, has also shown a high incidence of antagonism.

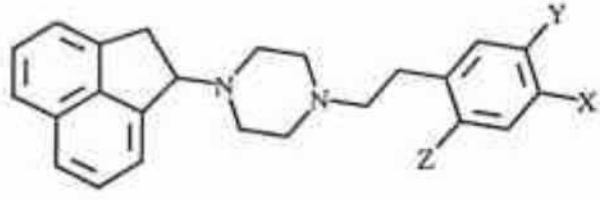
The effect of the allyl substituted amino group (121) and a free amino group with a 5-methyl substituent (117) and a keto group (123) at the 2nd position on the 5-HT2 antagonism was evaluated for their atypicality in antipsychotic profile by estimating their reversal of catalepsy induced by haloperidol. Among these, compound (117) brought about a minimal reversal of catalepsy. Compound (121) showed an ideal atypical antipsychotic profile, by exhibiting a very high level of reversal of catalepsy and compound (123) was comparatively lower in potency.

Hence, compound (121) promises to be a good candidate for an atypical antipsychotic agent.

Among the compounds of Type-IV [5-{2-[4-(1,2-dihydro-2-acenaphthylenyl) piperazin-1-yl] ethyl}-1,3- and -6-substituted-2,3-dihydro-1*H*-indole-2-ones] and 6-{2-[4-(1,2-dihydro-2-acenaphthylenyl) piperazin-1-yl] ethyl}-benzoxazolin-2(3*H*)-one evaluated, only compounds (127), (131), (151) & (154) showed a minimal inhibition of the climbing induced by the D_2/D_1 agonist apomorphine.

These compounds have shown around 16-28% inhibition of this climbing behavior, indicating that these compounds could be promising candidates for atypical antipsychotics, the reason being a low incidence of dopamine antagonism, which in turn is a prime requirement for atypicality. (Table 24)

Table 24. Results of 5-{2-[4-(1,2-dihydro-2-acenaphthylenyl) piperazin-1-yl] ethyl} –1,3- and –6-substituted-2,3-dihydro-1*H*-indole-2-ones and 6-{2-[4-(1,2-dihydro-2-acenaphthylenyl) piperazin-1-yl] ethyl}-benzoxazolin-2(3*H*)-one for their inhibition of apomorphine induced climbing behavior in mice



Compound No.	---X---Y---	Z	% Inhibition Mean ± S.E.
127	$NH\text{-}CO\text{-}CH_2$	H	16.6 ± 7.8
131	$N(CH_3)\text{-}CO\text{-}CH_2$	H	22.2 ± 5.6 *
135	$NH\text{-}CO\text{-}CH(CH_3)$	H	N.S.
139	$N(CH_3)\text{-}CO\text{-}CH(CH_3)$	H	N.S.
143	$N(C_2H_5)\text{-}CO\text{-}CH_2$	H	N.S.
147	$NH\text{-}CO\text{-}CH_2$	Cl	N.S.
151	$NH\text{-}CO\text{-}CH_2$	F	27.7 ± 7.3 *
154	O-CO-NH	H	11.1 ± 5.7
Haloperidol	-	-	100

N.S.- Not Significant -- Inhibition less than 10%

$P < 0.05$

These compounds were then evaluated for their *atypicality* in antipsychotic activity by their ability to reverse the catalepsy induced by Haloperidol. These compounds were

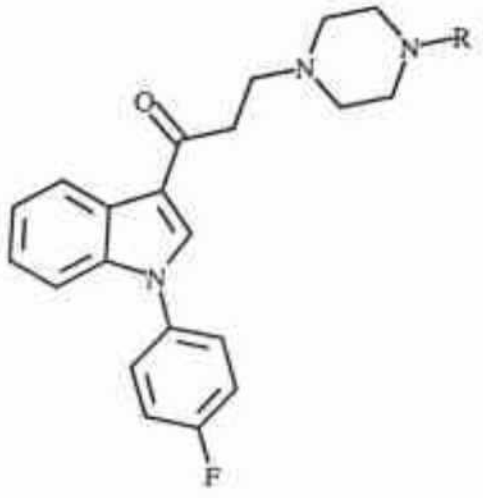
found to reverse catalepsy by 84%, 6.25%, 65% and 8% respectively. Of these compounds, compound (127) showed a maximum reversal of catalepsy indicating probable antagonism at 5-HT_2 receptors, which is a prime requirement for *atypicality* in antipsychotic activity. (Table 27)

Among compounds of Type-IV [5-{2-[4-(1,2-dihydro-2-acenaphthylenyl) piperazin-1-yl] ethyl}-1,3- and -6-substituted-2,3-dihydro-1*H*-indole-2-ones] and 6-{2-[4-(1,2-dihydro-2-acenaphthylenyl) piperazin-1-yl] ethyl}-benzoxazolin-2(3*H*)-one, compounds possessing a free hydrogen atom on the amide nitrogen and a free methylene at the 3rd position of the indol-2-one (127) have been found to be essential for D_2 antagonism. Compound (131) having a methyl substituent on the amide nitrogen and compound (135) possessing a methyl substituent at the 3rd position have shown lesser antagonism. Compound (127) mimics both the position and acidity of one of the phenol groups in dopamine and gratifyingly possessess the desired antagonism. Furthermore, compounds (147) and (151), which possess an electronegative halogen atom at the 6th position of the indol-2-one (which carries a free amide nitrogen and a free methylene at the 3rd postion) have been found to be active. This activity is further dependent on the steric bulk of the electronegative atom, where compound (147) carrying a chlorine atom is insignificant, while (151) carrying a fluorine atom shows enhanced antagonism.
These compounds were then evaluated for their atypicality in antipsychotic profile by estimating their reversal of catalepsy induced by haloperidol. Among these compounds, (127) having a free amide nitrogen as well as a free methylene at the 3rd position of the indol-2-one and (151) having a fluorine atom at the 6th position in addition to the free amide nitrogen and the methylene group have significantly reversed the catalepsy.
Of these two compounds (127) promises to be an ideal candidate for an atypical antipsychotic agent.

Among the compounds of Type-VII [substituted-piperazinyl indol-(1-{4-fluorophenyl}-3-yl) propanones] evaluated for their central activity at the D_2 receptors, only compounds (180), (181), (182), (187) and (188) showed a significant inhibition of the climbing induced by the D_2/D_1 agonist apomorphine. These compounds have shown around

25-75% inhibition of this climbing behavior, indicating that these compounds show a significant anitpsychotic profile. (Table 25)

Table 25. Results of N-(4-fluorophenyl)- piperazinyl indolyl propanones for their inhibition of apomorphine induced climbing behavior in mice.



Compound No.	R	% Inhibition Mean ± S.E.
180	Phenyl	36.4 ± 6.3*
181	3-Chlorophenyl	58.3 ± 5.9*
182	4-Chlorophenyl	25.4 ± 6.3
183	4-Fluorophenyl	N.S.
184	2-Methoxyphenyl	N.S.
185	3-Methoxyphenyl	24.6 ± 7.9
186	4-Methoxyphenyl	N.S.
187	3-Trifluoromethyl phenyl	69.5 ± 8.5*
188	2-Pyridyl	72.6 ± 5.3*
189	2-Pyrimidinyl	25.6 ± 6.4
Haloperidol	-	100

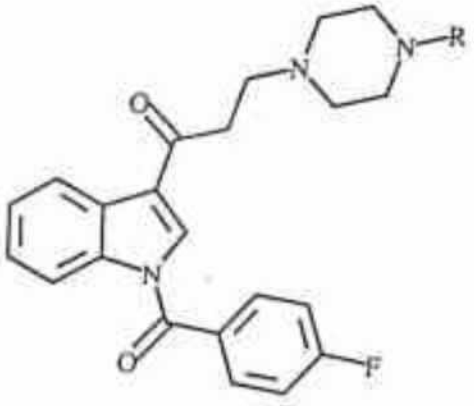
N.S.- Not Significant

$P < 0.05$

These compounds were then evaluated for their *atypicality* in antipsychotic activity by their ability to reverse the catalepsy induced by Haloperidol. These compounds were found to reverse catalepsy by around 20-40%. This data suggests that the test compounds probably possess 5-HT_2 antagonism towards antipsychotic activity. (Table 27)

Among the compounds of Type-VIII [substituted-piperazinyl indol-(1-{4-fluorobenzoyl}-3-yl) propanones] evaluated, compounds (194), (195) & (197) showed significant inhibition of the climbing induced by the D_2/D_1 agonist apomorphine. (Table 26)

Table 26. Results of N-(4-fluorobenzoyl)- piperazinyl indolyl propanones for their inhibition of apomorphine induced climbing behavior in mice.



Compound No.	R	% Inhibition Mean ± S.E.
191	Phenyl	N.S.
192	3-Chlorophenyl	19.4 ± 6.8
193	4-Chlorophenyl	16.6 ± 7.3
194	4-Fluorophenyl	44.4 ± 5.8 *
195	2-Methoxyphenyl	63.8 ± 6.5 *
196	3-Methoxyphenyl	N.S.
197	4-Methoxyphenyl	27.7 ± 7.4
198	3-Trifluoromethyl phenyl	N.S.
199	2-Pyridyl	13.8 ± 8.3
200	2-Pyrimidinyl	N.S.
Haloperidol	-	100

N.S.- Not Significant

These compounds have shown 45%, 64% & 28% inhibition of this climbing behavior respectively, indicating that compounds (194) and (195) could be showing a profile similar to those of typical antipsychotics exhibiting higher levels of dopamine

antagonism. Compound (197) on the other hand shows a lower dopamine antagonism, which could be a promising candidate for atypicality in antipsychotic activity.

These compounds were then evaluated for their *atypicality* in antipsychotic activity by their ability to reverse the catalepsy induced by Haloperidol. The compound (194) showed insignificant reversal of catalepsy, indicating that it could only act as a conventional antipsychotic with dopamine antagonism. On the other hand, compounds (195) & (197) have shown 19% and 60% reversal of catalepsy respectively. Compound (197) shows significant reversal indicating antagonism at 5-HT_2 receptors, inaddition to minimal dopamine antagonism, thereby satisfying requirements for an atypical antipsychotic. (Table 27)

Table 27. Results of Reversal of Haloperidol-induced Catalepsy for selected promising compounds

Compound No.	% Reversal Mean ± S.E.
83	75.40 ± 7.3 *
117	6.25 ± 2.4
121	79.16 ± 6.4 *
123	39.58 ± 5.7
127	83.30 ± 7.4 *
131	6.25 ± 3.4
151	64.58 ± 8.9 *
180	10.41 ± 4.6
181	18.75 ± 6.3
182	N.S.
187	20.83 ± 5.8
188	33.33 ± 5.7
194	N.S.
195	18.75 ± 5.6
197	60.41 ± 6.7 *
Haloperidol	Nil

N.S.- Not Significant -- Inhibition less than 5%

$P < 0.05$

Among the compounds of Type-VII [substituted-piperazinyl indol-(1-{4-fluorophenyl}-3-yl) propanones] which comprise of various aryl and substituted aryl groups at the N-4 piperazine, compounds (180), (181), (182), (187) and (188) were found to have a high level of dopamine antagonism. All these compounds however, failed to reverse the catalepsy induced by haloperidol, indicating a probable lack of 5-HT_2 antagonism, ruling out atypical behavior. (Table 27)

Further structural modification, in terms of incorporating a 4-fluorobenzoyl function in place of the 4-fluorophenyl function on the indolyl nitrogen led to the synthesis of compounds of Type-VIII [substituted-piperazinyl indol-(1-{4-fluorobenzoyl}-3-yl) propanones].

Of these, compounds (194), (195) and (197) have shown moderate to high dopamine antagonism. Compound (197) has significantly reversed the catalepsy, whereas the other two have shown no significance in the reversal of catalepsy. (Table 27)

Hence, Compound (197) promises to be a good candidate for an atypical antipsychotic agent.

These findings are in agreement with those of Kostowski and coworkers[226] *and suggest that the central serotonergic system has an inhibitory influence on the central dopaminergic system and that the cataleptogenic effect of neuroleptics apparently depends on the balance between the two systems.*

Inhibition of Apomorphine induced stereotypic behavior

In order to ascertain the balance required between the 5-HT_2/D_2 receptors, specificity of the antagonism at the D_2 receptor was a prime criteria. Few of the promising molecules were evaluated for their ability to inhibit the stereotypic behavior induced by apomorphine in mice, which is characteristic of antagonism at the D_2 receptor.

Compounds (83), (121), (127) & (197) were selected for this evaluation in order to ascertain the specificity for antagonism at the D_2 receptor.

Among these, compounds (83), (121) & (127) had no significant inhibition in the stereotypic behavior induced by apomorphine at a dose of 30 mg/kg & 60 mg/kg (ip), further it was observed that a dose of 100 mg/kg was found to be lethal.

Compound (197) at a dose of 60 mg/kg, showed 14.8 ± 2.5% inhibition of apomorphine induced stereotypic behavior. It was further noticed that a dose of 100mg/kg was lethal.

On the other hand haloperidol which is a non-selective dopamine antagonist, inhibits 17.5 ± 2.1% of the stereotypic behavior induced by apomorphine at a dose of 0.5mg/kg (ip).

The low D_2 antagonism exhibited provides a strong point towards the atypical behavior in antipsychotic activity of these selected promising molecules.

In view of the involvement of D_1 receptor antagonism (in inhibition of apomorphine induced climbing behavior) and possible role of 5-HT_2 antagonism (in haloperidol induced catalepsy reversal) and also an indicative role of D_2 antagonism (exhibited by the inhibition of apomorphine induced stereotypic behavior), the present study needs further pharmacological investigations to selectively suggest the specific modulatory role of 5-HT_2 / D_2 / D_1 receptors in the atypical behavior of the promising compounds in their antipsychotic activity.

Chapter - 6

SUMMARY

1. A new arylpiperazine, 1-(1,2-dihydro-2-acenaphthylenyl) piperazine as a *new lead molecule* and its various substitution products as the first series and a second series involving the concept of *lead modification*, N-substituted-3-acetyl indole derivatives (Piperazinyl indolyl propanones) incorporating known arylpiperazines for 5-HT receptor modulator activity were synthesized.
   (a) New arylpiperazines based on the structure of 1,2-dihydro-2-acenaphthylenyl piperazine were synthesized and their pharmacological evaluation was carried out.
   (b) New N-substituted-3-acetyl indole derivatives (mannich products incorporating known aryl piperazines)- Piperazinyl Indolyl Propanones were synthesized and their pharmacological evaluation was carried out.
2. All chemical intermediates which were synthesized were used in the synthesis of the various compounds involved in both the series of compounds.
3. (a) The first series in this thesis work has resulted in the ***synthesis of a new arylpiperazine***, i.e., 1-(1,2-dihydro-2-acenaphthylenyl) piperazine (83), followed by structural modifications in terms of bringing in suitable pharmacophoric moieties at N4 of the piperazine for beneficial activities.
   (b) The new arylpiperazine (83) was synthesized from 1,2-dihydro acenaphthylene through a series of reactions involving electrophilic and nucleophilic substitution reactions in good yield and purity.
4. Compound (83), the new arylpiperazine exhibited 5-HT_3 antagonistic activity in the longitudinal muscle myenteric plexus preparation of guinea pig ileum (LMMP) and showed a maximal reversal of catalepsy induced by haloperidol, which is a characteristic feature of all reported arylpiperazines.
5. (a) Of the N-4 substituted derivatives of (1,2-dihydro-2-acenaphthylenyl) piperazines, the series containing linear side chain groups, compounds of Type-I & Type-II were evaluated on the LMMP of guinea pig ileum and showed varying degree of 5-HT_3 antagonistic activity.
   (b) Compound (88) (Type-I), 1-(1,2-dihydro-2-acenaphthylenyl)-4-isopropyl piperazine and compound (105) (Type-II), 1-(1,2-dihydro-2-acenaphthylenyl)-4-(2-dimethyl amino ethyl) piperazine showed

antagonism comparable to that of the standard 5-HT_3 antagonist Ondansetron.

6. (a) The N-4 substituted derivatives of (1,2-dihydro-2-acenaphthylenyl) piperazines, of Type-III and Type-IV which were substituted onto the N-4 of the piperazine, specifically designed and synthesized for atypical antipsychotic activity, were evaluated for their potential antipsychotic activity.

   (b) These compounds showed antagonism to D_2/D_1 receptors in the evaluation of apomorphine induced climbing behavior in mice. Compounds that have shown D_2/D_1 antagonism were evaluated for their 5-HT_2 antagonism in reversing the catalepsy induced by the neuroleptic drug-haloperidol, which was consistent with the design parameters involved.

7. (a) Compounds (117), (121) and (123) (Type-III), showed antagonism to apomorphine induced climbing behavior. Compound (121) 4-(4-{2-[4-(1,2-dihydro-2-acenaphthylenyl) piperazinyl] ethyl} phenyl)-2-allylamino thiazole, showed a maximum reversal of catalepsy induced by haloperidol indicating probable antagonism at 5-HT_2 receptors.

   (b) Compounds (127), (131), (151) and (154) (Type-IV), showed minimal antagonism to apomorphine induced climbing behavior. Compound (127) 5-{2-[4-(1,2-dihydro-2-acenaphthylenyl) piperazinyl] ethyl}-2,3-dihydro-1*H*-indol-2-one, showed a maximum reversal of catalepsy induced by haloperidol indicating probable antagonism at 5-HT_2 receptors, which is a prime requirement for *atypicality* in antipsychotic activity in terms of EPS benefits.

8. The methodology adopted in the syntheses of chemical intermediates for compounds of Type-III & Type-IV, involved newer approaches that are different from those of in the literature in terms of reducing the number of steps, required to synthesize an intermediate.

9. In the second series of Substituted Piperazinyl Indolyl propanones, compounds of Type-V and Type-VI were evaluated for their serotonergic activity on the LMMP of guinea pig ileum and exhibited varying degree of antagonistic activity.

10. Compounds (165) (Type-V) and (176) (Type-VI) showed antagonism at the 5-HT_3 receptor compared to the standard 5-HT_3 receptor antagonist-Ondansetron.
11. The compounds of Type-VII and Type-VIII were evaluated for ability to inhibit the climbing behavior induced by D_2/D_1 agonist apomorphine and reverse catalepsy induced by haloperidol, consistent with the presence of the aromatic substituent on the indolyl nitrogen.
12. The starting material for the compounds of Type-VII, N-(4-Fluorophenyl)-3-acetyl indole (179) is ***new chemical entity*** (NCE) and its synthesis was accomplished through an *analogous Ulmann condensation* procedure using 3-acetyl indole and 4-fluoroiodo benzene.
13. The starting material for the compounds of Type-VIII, involved the structural modification of N-(4-Fluorophenyl)-3-acetyl indole, in terms of increasing the distance between the indolyl nitrogen and the 4-fluorobenzene moiety by one carbon atom. This was best achieved by bringing in the 4-fluorobenzene as an acid chloride (4-fluorobenzoyl chloride) to result in the formation of an amide on the indolyl nitrogen, leading to N-(4-Fluorobenzoyl)-3-acetyl indole (190), which is also a ***new chemical entity*** (NCE).
14. Compounds of Type-VII showed significant inhibition of the climbing behavior induced by apomorphine, but failed to reverse the catalepsy induced by haloperidol to a significant extent, indicating that these compounds would probably act as antipsychotics.
15. The compounds of Type-VIII showed both D_2/D_1 antagonism and 5-HT_2 antagonism.
16. Compounds (194) and (195) (Type-VIII) showed a profile of a *typical* antipsychotic. Whereas compound (197), 1-(1-(4-Fluoro benzoyl)-1*H*-3-indolyl)-3-[4-(4-methoxyphenyl) piperazin-1-yl]-1-propanone, on the other hand showed minimal D_2 antagonism combined with maximal 5-HT_2 antagonism, indicative of a promising *atypical* antipsychotic nature.

Chapter - 7

CONCLUSIONS

1. The present thesis work has led to suggest the new arylpiperazines, compound (88), 1-(1,2-dihydro-2-acenaphthylenyl)-4-isopropyl piperazine & (105), 1-(1,2-dihydro-2-acenaphthylenyl)-4-(2-dimethylaminoethyl) piperazine exhibited 5-HT_3 antagonistic activity while compounds (121), 4-(4-{2-[4-(1,2-dihydro-2-acenaphthylenyl) piperazinyl] ethyl}phenyl)-2-allylamino thiazole & (127) 5-{2-[4-(1,2-dihydro-2-acenaphthylenyl) piperazinyl] ethyl}-2,3-dihydro-1*H*-indol-2-one showed significant 5-HT_2 antagonistic activity towards their antipsychotic nature.
2. Compound (197), 1-(1-(4-fluorobenzoyl)-1*H*-3-indolyl)-3-[4-(4-methoxy phenyl) piperazin-1-yl]-1-propanone exhibited both 5-HT_2 and D_2 antagonistic activity, which is a prime criteria for the atypical profile of antipsychotic agents.
3. As the present synthetic work has shown promising leads of arylpiperazines, further *in vitro* binding studies would characterize selective 5-HT modulatory role (as 5-HT_3 and 5-HT_2 combined with D_1/D_2 modulation) for these compounds.

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