Chapter I

Introduction
1.0. Introduction

Organic and medicinal chemistry becoming very essential chemistry explores role of organic chemists towards isolation, characterization and synthesis of new compounds that can be used as medicine for the prevention, treatment and cure of certain diseases. Medicinal chemistry manifests chemical basis of the interdisciplinary field of therapeutics. The main concern of an organic chemist normally lies in conceiving an ideal structure of needed drug with negligible or very minimal adverse effect usually based on theoretical consideration and in constructing a plausible way for a strategically synthesis towards that target drug. Hence chemists, having specific reason for synthesizing a particular compound, have to work backward starting from the structure of the compound i.e., to adopt retro-synthetic approach. One of the major factors leading to rational approach to new drugs has provided insight of biological mechanism.

Finding the novel drug is a complex process. Historically, the main source of biologically active compounds used in drug discovery programs has been natural products, isolated from plant, animal or fermentation sources. The process of drug discovery involves the identification of candidates, synthesis, characterization, screening, and assays for therapeutic efficacy. Once a compound has shown its value in these tests, it will begin the process of drug development prior to clinical trials.

Despite advances in technology and understanding of biological systems, drug discovery is still a long process with low rate of new therapeutic discovery. Information on the human genome, its sequence and what it encodes has been hailed as a potential windfall for drug discovery, promising to virtually eliminate the bottleneck in therapeutic targets that has been one limiting factor on the rate of therapeutic discovery [1]. However, data indicates that "new targets" as opposed to "established targets" are
more prone to drug discovery project failure in general [2]. This data corroborates some thinking underlying a pharmaceutical industry trend beginning at the turn of the twenty-first century and continuing today which finds more risk aversion in target selection among multi-national Combinatorial chemistry involves the rapid synthesis or the computer simulation of a large number of different but structurally related molecules.

Combinatorial chemistry is one of the important new methodologies developed by researchers in the pharmaceutical industry to reduce the time and costs associated with producing effective and competitive new drugs. By accelerating the process of chemical synthesis, this method is having a profound effect on all branches of chemistry, but especially on drug discovery. Through the rapidly evolving technology of combi-chemistry, it is now possible to produce compound libraries to screen for novel bioactivities. This powerful new technology has begun to help pharmaceutical companies to find new drug candidates quickly, save significant money in preclinical development costs and ultimately change their fundamental approach to drug discovery.

The payoff of combinatorial chemistry to drug discovery is already becoming obvious to the industry in terms of a significant increase in the number of drug candidates and of decreases in time from target identification to drug candidates and manpower employed per drug candidate. Similar benefits are beginning to emerge in process chemistry, catalyst discovery and material science, where combinatorial chemistry techniques have also been implemented.

The design and discovery of new drugs requires a team effort. This is not only involves chemists but also workers from a wide range of discipline more particularly pharmacologists and biochemists, amongst others. The pharmacologists design and operate model system for detecting and evaluating the activity of compounds for
control of diseases. It is a big task of finding a potent drug, which does not have side effects in some individuals. A detailed study of absorption, distribution, metabolism and excretion of drug is an essential part of pharmacology. Kinetics of this process after intravenous and oral administration of the drug constitutes rational drug therapy. Besides concentrating in synthesis of new compounds as well as isolating and characterization of natural products, interest will also be shown in the complex relationship between chemical structure and biological activities (structure-activity relationship) by an organic chemist. The search for a chemical structure which exhibits physiological activity is a difficult goal of organic chemical approach. The search for a chemical structure which exhibits physiological activity is a difficult goal of organic chemical approach. Observed biological and pharmacological actions upon screening often open new vistas of additional chemical research.

A majority of the compounds produced by nature have heterocyclic rings as part of their structures. Many heterocyclic rings are found as key components in biological systems. Significant numbers of compounds synthesized in the industrial sector each year are heterocyclic in nature. Of the more than 20 million chemical compounds currently registered, about one half contain heterocyclic systems. Heterocycles are among the most frequently encountered scaffolds in drugs and pharmaceutically relevant substances. Because of the drug-like character and considerable range of structural diversity, large collections or libraries of diverse heterocycles are routinely employed in high-throughput screening at early stages of drug discovery programs. Furthermore, a heterocyclic core is propitious for variations of substitution patterns during structure-activity relationship (SAR) studies. Consequently, relatively small (< 300 membered) focused libraries of heterocycles are frequently generated for SAR studies during the development and optimization of lead structures [3].
Heterocyclic chemistry is a vast and expanding area of chemistry, because of the obvious applications of compounds derived from heterocyclic rings in pharmacy, medicine, agriculture and other fields. Heterocycles count among their number many natural products, such as vitamins, antibiotics, alkaloids, as well as Pharmaceuticals, herbicides, dyes, and other products of technical importance (corrosion inhibitors, antiaging drugs, sensitizers, stabilizing agents, etc.).

Many compounds from many sources, both natural and synthetic, are tested for effectiveness against many types of medical problems. Once a compound is found to be an effective medicinal agent, then it is the lead compound. New compounds are synthesized in the laboratory in order to find perhaps a better medicine or one with less toxicity. The process takes many years of intense work. Scientists then follow up on the lead compounds and attempt to synthesize better compounds.

1.1. Introduction to Homopiperazine

Seven-membered heterocycles with two heteroatoms in the 1,4-position are well known because of their unique pharmacological activity towards the central nervous system as observed in the case of 1,4-benzodiazepines [4]. These properties strongly depend on the nature of the heterocyclic core, particularly on the relative positions of the two nitrogen atoms and the type of ring fused to the seven-membered ring. This ring system has demonstrated considerable utility in drug design, with derivatives demonstrating a wide range of biological activities. As a consequence [5], there is an abiding interest in developing a deeper understanding of conformational preferences associated with 1,4-diazepines that permits more effective control of conformer populations with a view to broadening the potential applications. The clinical importance and commercial success associated with the 1,4-benzodiazepine class of central nervous system (CNS)-active agents and the utility of 1,4-diazepines as
peptidomimetic scaffolds have led to their recognition by the medicinal chemistry community as privileged structures. This ring system has demonstrated considerable utility in drug design, with derivatives demonstrating a wide range of biological activities. In recent years a variety of 1,4-diazepines was reported for inhibition of platelet aggregation [6], peptidoglycan synthesis inhibition [7], 5-HT antagonists [8,9], H3 receptor antagonists [10], as peptidomimetic scaffolds [11], biological tools [12], protein kinase inhibitors [13], matrix metalloproteinase inhibitors [14] (MMPs), and anti-HIV agents [15]. The DNA strand breaking activity was reported [16] for diaryl diazepine. In concert with this, the development of new synthetic approaches to the 1,4-diazepine ring system and their further elaboration have provided access to a broad range of functionalized derivatives that have contributed to advances in understanding the underlying principles of structure and reactivity.

1,4-Diazepane (Homopiperazine) is often used as a building block, which is incorporated into the templates through substitution reaction [16]. Little information on the direct synthesis of ring-substituted diazipinones [17] and homopiperazines [18] could be found in the recent literature [20]. To accommodate future hetero libraries syntheses around these templates, the synthetic strategy was designed to facilitate large scale, ambient temperature reactions requiring little or no purification for each step of the current reaction sequence (Schem 1). Commercially available 4-piperidone hydrochloride 1 was Boc-protected and treated with hydroxylamine hydrochloride in the presence of DABCO to yield the desired oxime 3 (77 %, two steps) [21]. Aza-ring expansion was effected by the activation of 3 with p-toluenesulfonyl chloride followed by the hydrolysis of the resulting imine to afford 5 (98 %), which is the product of Beckmann rearrangement in quantitative yield. An attempt to reduce amide bond of 5 by the two-step reaction sequence utilizing triethylxonium fluoroborate/sodium
borohydride did not lead to the corresponding amine 6. It was also disappointing that
direct transformation of oximes 3 or 4 to the rearranged secondary amine 6, was not
successful in the refluxing DIBAL-H solution. However, the reduction of amide bond
[22] of 5 was performed smoothly in refluxing borane/THF to give another scaffold-
homopiperazine 6 which can be further derivatized with various electrophiles.

\[
\begin{align*}
\text{(1)} & \quad \text{NH}_2\text{OH.HCl} \\
\text{(2)} & \quad \text{DABACO,rt} \\
\text{(3)} & \quad \text{Pyridine} \\
\text{(4)} & \quad \text{H}_2\text{O} \\
\text{(5)} & \quad \text{THF} \\
\text{(6)} & \quad \text{BH}_3
\end{align*}
\]

Scheme 1. Synthetic route to the homopiperazine diazepinone

\(N,N\)-Disubstituted homopiperazine derivatives have been discovered as CC-
chemokine receptor 2b (CCR2b) inhibitors with submicromolar activity in the CCR2b
binding assay [23]. A 4-substituted benzyl group on one homopiperazine nitrogen was
an important moiety for binding affinity to the CCR2b receptor. The SAR for CCR2b
binding affinity correlated inversely with the \(\sigma\) factor of the functional group on this
benzyl moiety. Introduction of hydroxy groups to appropriate positions in the 3,3-
diphen-ylpropyl group on the other homopiperazine nitrogen increased CCR2b binding
activity.
Within the \(N-(3,3\text{-diphenylpropyl})-N-(\text{benzyl})\text{homopiperazine series}\) 7, electron-withdrawing groups in the 4-position of the benzyl moiety such as the methylsulfonyl and the nitro substituents are favored, while electron-donating groups decrease activity. Furthermore, introduction of a hydroxyl group to the methyne carbon of the benzhydryl group as well as 3-position of one phenyl ring increased the activity of the compounds.

ML-7 (5-iodonaphthalene-1-sulfonyle) homopiperazine 8, is commonly employed as a myosin light chain kinase (MLCK) inhibitor. Keita Odani., et al., [24] demonstrated that ML-7 affects the superoxide (\(O_2^-\))-producing system of human neutrophils in an MLCK-independent manner. ML-7 inhibited extracellular release, but not intracellular production of \(O_2^-\) in the stimulated cells.

Fluorescence microscopy revealed the generation of \(O_2^-\) at intracellular compartments in the stimulated cells exposed to ML-7. ML-7 strongly inhibited the association of the oxidant-producing intracellular compartments with the plasma membrane. Furthermore, the upregulation of alkaline phosphatase activity, a marker enzyme of the oxidant producing intracellular compartments, was also inhibited by ML-7. These findings indicate that ML-7 inhibits the fusion of the oxidant producing intracellular compartments to the plasma membrane resulting in the inhibition of the extracellular release of \(O_2^-\) in PMA-stimulated human neutrophils in an MLCK-independent manner.
ML-7 has been widely employed to elucidate the function of MLCK and its role in the exocytotic mechanisms in various types of cells. Choi et al., [25] demonstrated that the phosphorylation of myosin light chains by protein kinase C causes Ca\(^{2+}\)-dependent exocytosis of granules from basophilic RBL-2H3 cells, and that the secretion is blocked by ML-7. This agent also inhibits Ca\(^{2+}\)-induced catecholamine secretion in bovine adrenal chromaffin cells [26] and prevents Ca\(^{2+}\)/calmodulin-dependent inhibition of rennin secretion from rat renal cortical cells [27]. The evidence at hand thus shows that ML-7 affects exocytosis in a Ca\(^{2+}\)-dependent fashion. ML-7 is generally considered to be an inhibitor of the MLCK activity [28].

Compounds with homopiperazine skeleton are designed to find a potent DPP-IV inhibitor without inhibiting CYP. In recent past, many reports on use of small molecules as inhibitors of DPP-IV are available in the literature [29]. Merck described a series of structurally novel \(\beta\)-amino amide derivatives, and among them, Januvia (MK-0431) 9 was launched into the market in 2006 [30]. Also, Merck has developed 1,4-diazepine-2-one derivative (A) 10 as a potential back-up candidate [31].
Jin Hee Ahn., et al., [32] were reported the synthesis and biological evaluation of a series of β-aminoacyl-containing homopiperazine derivatives as DPP-IV inhibitors. The sequence of reaction steps involved in synthesis is shown in Scheme 2. Cbz-protected homopiperazine 11 was reacted with β-amino acid 12 in presence of EDCI to provide the coupled product 13. It is on reduction with 10% palladium on carbon in hydrogen atmosphere to provide a key intermediate 14, followed by boc-deprotection using 4 M HCl to result corresponding HCl salt 15. The compound 14 is also derivatized with diverse electrophiles to obtain compounds 16, followed by deprotection to give compound 17.
**Scheme 2**

**Reagents and conditions:** (a) (R)-3-BocNH-4-(2,4,5-trifluorophenyl)butanoic acid (12), EDCI, Et₃N, CH₂Cl₂, room temperature, 12 h; (b) 10% Pd/C, H₂ balloon, MeOH, room temperature, 12 h; (c) 4 M HCl, ethyl acetate, room temperature, 12 h; (d) electrophile, CH₂Cl₂, TEA, room temperature.

Several homopiperazine derivatives with acid moiety were found to be potent inhibitors of DPP-IV with no CYP 3A4 inhibition. The compound 18 showed submicromolar activity with no CYP inhibition towards five subtypes, and is a prototype for further derivatization. Based on the results, Jin Hee Ahn., et al., identified 19 and 20, which showed good in vitro activity, no CYP inhibition and good selectivity. Further studies are underway to optimize this compound class for the treatment of diabetes.
Han Ying., et al., [33] show that fasudil [1-(5-isoquinolinesulfonyl)-homopiperazine] 21, an orally available inhibitor of Rho kinases, and its metabolite 1-(hydroxy-5-isoquinoline sulfonyl-homopiperazine) (fasudil-OH) 22 modify tumor cell morphology and inhibit tumor cell migration and anchorage-independent growth. In addition, we show that fasudil inhibited tumor progression in three independent animal models. In the MM1 peritoneal dissemination model, tumor burden and ascites production were reduced by >50% (P < 0.05).
Fasudil 21 is a well-described orally available Rho kinase inhibitor, which has been shown to modify myosin light chain phosphorylation in smooth muscle cells and thereby to regulate vasodilation [34,35]. It has been approved in Japan for the treatment of cerebral vasospasm following surgery for subarachnoid hemorrhage and associated cerebral ischemic symptoms [36]. Following p.o. administration, fasudil is converted into the active metabolite 1-(hydroxy-5-isoquinoline sulfonyl-homopiperazine) (fasudil-OH) 22. In patients, fasudil is well tolerated without any severe adverse reactions [37]. Recently, H. Yamaguchi, et., [38] showed that fasudil interacts with the phosphate-binding loop of Rho kinase and induces conformational changes that increases the surface complimentarity to the inhibitor, resulting in changes in catalytic activity of Rho kinase. Previous studies have provided a rationale for us to test the activity of fasudil on the peritoneal dissemination model that uses the rat hepatoma cell line MM1 and on the lung metastasis model using the human fibrosarcoma cell line HT1080. In addition, it has been shown that Rho proteins, such as RhoA, are overexpressed in breast cancer [39, 40, 41], which gives a rationale for selecting MDA-MB-231 for our studies.

Protein kinases are implicated in various physiological processes. They are known to play an important role for cellular signal transduction and regulation of a variety of cellular events [42]. Targeting of these enzymes is a relatively recent activity
for medicinal chemists. Consequently, selective inhibitors of particular protein kinases may have therapeutic value in a wide range of diseases, such as cancer, diabetes, arthritis and hypertension [43]. Among these inhibitors, Fasudil has been shown to inhibit Rho-kinase activity in a manner competitive with ATP [44, 45].

Chemical modifications of the structure of Fasudil have been carried out in order to specify structure-activity relationships and eventually to improve the pharmacological profile of this compound [46]. These modifications affected the isoquinolinyl heterocycle and the sulfonyl group which could be involved in ionic and/or hydrogen bonds with the ATP binding site of Rho-kinase. With the aim of evaluating the selectivity level of these compounds that showed a Rho-kinase inhibitory effect, they were also tested on another protein-kinase: protein-kinase C (PKC).

Most of the chemical modifications result in a loss of activity showing that interactions of Fasudil with the catalytic domain of Rho-kinase seem to be particularly definite and sensitive to structural variations. The presence of an isoquinolinyl nitrogen and a basic aminogroup separated by a spacer bearing a sulfonamide function are of utmost importance. Only the tetrahydroisoquinoline analogue shows the same activity as Fasudil. Moreover, this compound is unable to inhibit PKC biological activity contrary to Fasudil. The loss of the aromatic property could increase the selectivity level in favour of compound 23.
Dilazep (3,3'-{(1,4-diazepane-1,4-diyl)b-is(propane-3,1-diyl)b-is(3,4,5-trimethoxy benzoate) 24, an antiplatelet agent, is generally used as an antithrombotic drug in clinical practice. Dilazep is also known to exert cytoprotective and antioxidant effects on endothelial cells. However, its effect on the endothelial or monocyte procoagulant activity is unknown. The effect of dilazep on the expression of tissue factor (TF) in human umbilical vein endothelial cells (HUVECs) after the stimulation with tumor necrosis factor-α (TNF), thrombin or phorbol 12-myristate 13-acetate (PMA) was evaluated [47]. Dilazep also blocked the expression of TF antigen induced by each stimulant on the surface of HUVECs as determined by flow cytometric analysis. In addition, in HUVECs, it significantly decreased the expression of TF mRNA and the total TF antigen induced by thrombin or PMA, but not those induced by TNF, suggesting that dilazep blocks the TF expression induced by PMA or thrombin at a transcriptional level and that induced by TNF at a posttranscriptional level. Western blot analysis showed that dilazep reduces the accumulation of native TF but increases that in lower molecular weight TF derivatives. In brief, the current study showed for the first time that dilazep, a commonly used antiplatelet drug, strongly inhibits the TF expression in HUVECs and monocytes. Dilazep may have a potent therapeutic value in patients with hypercoagulable state for its inhibitory property on the procoagulant activity of endothelial cells and monocytes.
A series of $N,N'$-substituted piperazine and homopiperazine derivatives have been synthesized with the objective of producing compounds that interact with polyamine modulatory sites on $N$-methyl-D-aspartate (NMDA) receptors [48]. These novel compounds exhibited polyamine-like actions, enhancing $[^3H]$ MK-801 binding to NMDA receptors in rat forebrain membranes. The potencies of $N,N'$-bis(2-aminoacetyl)homopiperazine 25, $N,N'$-bis(N-methyl-4-aminobutyl)-piperazine 26 and $N,N'$-bis(3-aminopropyl)homopiperazine 27 (EC$_{50}$ 18.0, 21.3, and 24.4 pM, respectively) to enhance $[^3H]$MK-801 binding were comparable to that of spermine (EC$_{50}$ 5.2 pM). However, the efficacies of 25, 26 and 27 in this measure were lower (by -40%, 32%, and 24%, respectively) than spermine, which may be indicative of partial agonist actions. Like spermine, the ability of these piperazine and homopiperazine derivatives to enhance $[^3H]$MK-801 binding could be inhibited by both a competitive polyamine antagonist (arcaine) and a specific, noncompetitive polyamine antagonist (conantokin-G). However, unlike endogenous polyamines, high concentrations (up to 1mM) of these novel polyamine-like compounds did not inhibit $[^3H]$MK-801 binding. $N,N'$-Aminoalkylated, aminoacylated piperazine and homopiperazine derivatives may prove useful for studying polyamine recognition sites associated with NMDA receptors.
The effects of a newly developed vasodilator agent, HA1 077 [1-(5-isoquinolinesulfonyl)-homopiperazine hydrochloride] 28, were investigated on the proliferation of cultured bovine aortic vascular smooth muscle cells (VSMC) [49]. HA1 077 (1 0-1 00 µM) inhibited both fetal calf serum-induced proliferation and $[^3]$H thymidine incorporation into DNA of the growth-arrested VSMC in a dosedependent manner. When quiescent cells were stimulated with platelet-derived growth factor followed by insulin, HA1 077 (1-30 µM), administered together with either stimulation, showed dosedependent inhibition of $[^3]$H thymidine incorporation. Further reduction of $[^3]$H thymidine incorporation was observed when HA1077 was present at both stimulations, suggesting that HA1077 suppresses DNA synthesis acting in both competence and progression stages. HA1077 inhibited $[^3]$H thymidine incorporation when it was added either from 12 hr to 15 hr or from 21 hr to 24 hr after serum stimulation. In addition, when percent inhibition of $[^3]$H thymidine incorporation by continuous exposure to HA1 077 was examined as a function of the time it was added, reductions of the value were observed at 0 to 3 hr, 12 to 18 hr and 21 to 24 hr. Thus, we concluded that HA1 077 suppresses DNA synthesis of bovine VSMC acting at the
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G_{0}/G_{1} and the G_{1}/S phase transitions and also in the S phase of the cell cycle. It is suggested that this agent may act as a potent inhibitor of VSMC proliferation as well as a vasodilator.

It is known that those 1,4 disubstituted piperazines 29, homopiperazines 30 and piperidines 31 are highly potent ligands for various receptors that belong to the family of G protein-coupled receptors [50]. They are frequently found as a key structural element in compounds possessing broad therapeutic effects for several diseases [51].

The synthesis, anti-Pneumocystis carinii activity and DNA binding properties of eight new N,N-bis[4-(N-alklamidi-no)phenyl]homopiperazines are reported by Tien L.Hauang., et al [52]. Compounds 32 and 33 were the most potent and caused about 70% inhibition of Pneumocystis carinii growth in a cell culture model at 1 mM concentrations.
During the course of program to develop a potential T-type calcium channel blocker, Su Jin Gu, et al., [53] have found that 1,3-dioxoisooindoline derivatives showed high potency and excellent selectivity against the T-type calcium channel over the N-type calcium channel [54]. However, further studies revealed that this particular molecular scaffold did not represent an acceptable pharmacological profile.

To overcome this hurdle, Su Jin Gu, et al tried to find a new structural motif using the 3D ligand based pharmacophore model, which previously had been established by the hypothesis approach (HipHop) implemented in the CATALYST program [55]. They designed the 1, 4-diazepane derivatives 34 and 35 having two hydrophobic aromatic components on both sides of the 1, 4-diamines.

Comparing these compounds with Mibefradil, they hypothesized that the benzimidazoyl 1,4-diazepane might be acting as an inhibitory element.
Su Jin Gu, et al., have synthesized and evaluated two series of 1,4-diazepane derivatives 34/35 as potential T-type calcium channel blockers. Using the FDSS HTS system, they rapidly screened the title compounds and selected several having high potency. On comparing the biological activities of Mibebradil, Su Jin Gu, et al identified the potent and highly selective T-type calcium channel blocker 4s, which displays an excellent pharmacokinetic profile in rats. These results suggest that the 1,4-diazepane analogue 36 will be a potential therapeutic candidate for the treatment of various neurological diseases related to the T-type calcium channel without cardiovascular side effects.

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{O} \\
& \quad \text{CF}_3
\end{align*}
\]

(36)

A series of conformationally restricted congeners of pentamidine in which the flexible pentyl bridge of pentamidine was replaced by trans-1,2-bismethylenecyclopropyl, phenyl, pyridinyl, piperazinyl, homopiperazinyl and piperidinyl groups were synthesized [56]. The compounds were evaluated for trypanocidal activity in vitro and in vivo against one drug-sensitive and three drug-resistant trypanosome isolates. The DNA binding affinity of the compounds was also studied using calf thymus DNA and poly (dA-dT). The nature of the linker influenced the DNA binding affinity as well as the trypanocidal activity of the compounds. Albeit with comparable DNA binding affinity, \(N,N'-\text{Bis}(4\text{-amidinophenyl})\)homopiperazine 37 was the most potent trypanocide in vitro against all four trypanosome isolates studied.
Despite optimization efforts, using both traditional medicinal chemistry and library-based approaches to identify potent CCR2b inhibitors in this series, binding affinity remained in the micromolar range [57]. These results required us to evolve away from this homopiperazine core and to develop alternative structural series. Drug Discovery Engine was utilized to assist in this lead evolution process [58], leading to the discovery of several alternative diamine derived series with nanomolar activity in the CCR2b binding and CCR2b chemotaxis assays. Optimization of the homopiperazine series, using either traditional medicinal chemistry techniques or through library-based approaches, led to the identification of CCR2b antagonists with µM binding affinities [59]. The most potent compounds identified in series 1 and 2 were 38 with an IC₅₀ value of 0.7 µM and 39 with an IC₅₀ value of 7.4 µM, respectively. Although approximately 800 compounds were prepared in the homopiperazine series, further improvement of activity could not be established and alternative structural series were investigated using a process called the Drug Discovery Engine.
Factor Xa (fXa) is a serine protease involved in the coagulation cascade, which has received great interest as a potential target for the development of new antithrombotic drugs. Hiroyuki Koshio, et al [60] report a novel series of fXa inhibitors in which the 1,4-diazepane moiety was designed to interact with the S4 aryl-binding domain of the fXa active site. Compound 40 (YM-96765) showed potent fXa inhibitory activity ($IC_{50} = 6.8$ nM) and effective antithrombotic activity without prolonging bleeding time.

Furthermore, this compound showed effective oral antithrombotic activity in rats without prolonging bleeding time.
Paul J. Coleman, et al., [61] described the discovery of a novel series of diazepane dual orexin receptor antagonists including 2-\{4-[5-methyl-2-(2H-1,2,3-triazolyl-2-yl)benzoyl]-1,4-diazepan-1-yl\}quinazoline 41 [62]. It is a brain-penetrant, potent dual orexin receptor antagonist that has excellent OX2R/OX1R receptor affinity.

\[
\text{OX}_1\text{RK}_i = 1.2 \text{ nM} \\
\text{OX}_2\text{RK}_i = 0.6
\]

Antagonism of the orexin (or hypocretin) system has recently been identified as a novel mechanism for the treatment of insomnia [63]. In a recent Communication, Christopher D. Cox, et al., [64] described the discovery of a novel series of HTS-derived dual (OX1R/OX2R) orexin receptor antagonists based on a 1,4-diazepane core [65]. This effort culminated in the discovery of 41, a potent and brain-penetrant compound that demonstrates efficacy for silencing orexin signaling in freely locomoting rats, including the induction of REM and non-REM sleep.

The identification and evaluation of aryl-(1,4)diazepane ureas as functional antagonists of the chemokine receptor CXCR3 are described. Chemokines are a class of chemotactic cytokines, between 70 and 90 amino acids in length that play an important role in inflammatory and immune responses. They are subdivided into different classes based on the structural separation of conserved cysteine residues in the chemokine sequence.

An investigation of the secondary carboxamide substituent (R) and the benzamide substituent (Ar) was initially conducted to probe the steric and electronic requirements at these two positions for CXCR3 activity. A strong preference for
phenethyl-based functionality was observed for the secondary amide, with 2,4-dichlorosubstitution 42 being optimal based on the analogs synthesized.

![Diagram 42](image)

Phenethyl-based systems incorporating mono halo substitution 43 also maintained reasonable activity superior to the unsubstituted phen-ethyl derivative. Incorporation of the racemic trans-cyclopropylphenethyl derivative also displayed a moderate increase in potency in comparison to the parent phenethyl system. The unsubstituted benzylic analog resulted in only moderate activity. However, as observed for the phenethyl-based analogs, a ~5-fold increase in potency was realized on inclusion of a 4-chloro substituent. Small aliphatic components such as isopropyl and cyclopropylmethyl resulted in a significant reduction in activity, displaying IC$_{50}$ values in the micromolar range. Compounds involving removal of the amide carbonyl acceptor (not shown) displayed no activity versus CXCR3.

![Diagram 43](image)
Biological activities of platinum complexes with homopiperazine ligands were evaluated \textit{in vitro} [66]. Against sensitive A2780 cells, the compounds displayed cytotoxicity with IC$_{50}$ in the range 0.8 to 17.8 µM. In the Pt(II) series, complexes with hpip ligands were about 4-fold more potent (low IC$_{50}$) than those with mhpip. In this series, the bidentate CBDCA or methylmalonate group in the equatorial position had given similar cytotoxic potencies. The overall potencies of the homopiperazine Pt(IV) complexes, however, were less than those obtained for cisplatin (IC$_{50}$ 0.17 µM). These resistance factors are, nevertheless, still high and leads to the conclusion that the decrease in intrastrand adducts by homopiperazine analogs [67] does not favor a substantial decrease in the resistance factor. However, resistance is multifactorial [68] and additional studies may be necessary to define which of the mechanisms of resistance (e.g. reduced uptake, increased repair, or increased DNA damage) are being circumvented by the homopiperazine analogs.

In screening a large number of chemical compounds which are modified structurally from Kimura, et al., [69] have selected one, \textit{N-p}-chloro-benzydryl-\textit{N'}-methyl-homopiperazine dihydrochloride (homochlor-cyclizine, or SA-97), that has a spectrum of pharmacologic actions expected to offer possible clinical usefulness [70]. These properties include a high degree of antiserotonin activity, potent antihistaminic action, bronchodilator effect, mild anti-acetylcholine action, and antagonism to slow-reacting substance. In addition, the drug was shown to possess antifibrillatory and coronary dilator qualities and a certain degree of central stimulation.

\textit{N-p}-chloro-benzydryl-\textit{N'}-methyl-homopiperazine dihydrochloride is a drug possessing a wide range of clinical effect and is useful in certain types of asthma and allergic cough and resistant cases of seasonal and perennial allergic
rhinitis, urticaria, dermatitis, and some other allergic and allergic-like manifestations.

Synthesis were conducted of novel benzimidazole derivatives that suppress histamine release from mast cells, inhibit 5-lipoxygenase, and possess antioxidative action [71]. Among the compounds synthesized, 1-[2-[2-(4-hydroxy-2,3,5 trimethylphenoxy)ethoxy]ethyl]-2-(4-methyl-1-homopiperazino)benzimidazole 44 potently suppressed histamine release from rat peritoneal mast cells triggered by the antigen-antibody reaction, inhibited 5-lipoxygenase in rat basophilic leukemia-1 (RBL-1) cells, and prevented the NADPH-dependent lipid peroxidation induced by Fe$^{2+}$-ADP in rat liver microsomes, in addition to an antagonizing the contraction of guinea pig ileum caused by histamine.

\[
\begin{align*}
R_1 &= - (\text{CH}_2)_2 \text{O} \text{(CH}_2\text{)_2O} \\
R_2 &= \text{Me}
\end{align*}
\]

(44)

Emily M. Stocking, et al., [72] have designed and prepared a series of pyrrolidines that are high affinity histamine H3 receptor antagonists. Selected members efficiently penetrate the CNS and occupy the histamine H3 receptor. The compounds tested are all antagonists at the rat H3 receptor and typically were slightly less potent at the rat H3 receptor than at the human H3 receptor. Compounds 45, 46 and 47 have some affinity for the hERG channel in this assay. Following up on these initial findings, 48, 49 and 50 were screened in a hERG patch clamp assay.
45 \quad R_1 = \text{c-Bu} \quad R_2 = \text{H} \quad R_3 = 3-\text{F}

46 \quad R_1 = \text{c-Bu} \quad R_2 = \text{H} \quad R_3 = 4-\text{F}

47 \quad R_1 = \text{c-Bu} \quad R_2 = \text{H} \quad R_3 = 4-\text{Cl}

48 \quad R_1 = \text{c-Bu} \quad R_2 = \text{H} \quad R_3 = 4-\text{F}

49 \quad R_1 = \text{c-Bu} \quad R_2 = \text{H} \quad R_3 = 4-\text{CN}

50 \quad R_1 = \text{c-Bu} \quad R_2 = \text{Ac} \quad R_3 = 3-\text{F}

Compound 50 was extensively characterized and was found to occupy the rat H₃ receptor, promote wake in rat and to increase the levels of extracellular acetylcholine in rat cortex. This compound has potential as a clinical candidate based on its strong preclinical profile.

The pyrrolotriazine core is oriented in the ATP binding site such that there is a hydrogen bond between N-1 and the hinge region Met 769 NH, and the C-4 benzyl indazole group extends back into a deep hydrophobic pocket formed partially by the alpha-C-helix [73]. The C-5 substituent extends out into the ribose phosphate pocket where the protonated homopiperazine NH can hydrogen bond with the side chains of Asp831, Asn818 and/or the backbone carbonyl oxygen of Arg817. In this model, there is also an intramolecular hydrogen bond between the C-4 aniline NH and the homopiperazine tertiary nitrogen atom.
pyrrolotriazines with diamino solubilizing groups that are tethered to C-5 showed potent inhibition of both EGFR and HER2 kinases. Modeling studies suggested that the solubilizing group can extend into the ribose–phosphate binding region of the ATP binding pocket where it can participate in multiple hydrogen bonding interactions. The homopiperazine analog 52, emerged as a key lead and it exhibited potent kinase inhibition, antiproliferative activity and oral efficacy in tumor xenograft models.

Structural juxtaposition of the 3,4,5-trimethoxyphenyl group in the same molecule with a piperazine or homopiperazine ring has been realized in a series of mescaline analogues 52-55 as part of an investigation into the pharmacological properties of the seven-membered perhydro-1,4-diazepines (homopiperazines) [74]. The analogous six-membered piperazines were synthesized and tested as for the reference substances to determine whether the seven-membered ring conveyed special properties. A variety of pharmacological tests of action on the CNS showed that replacement of the amino group in mescaline by the heterocycles significantly alters the biological activity. In particular, both the piperazine and the homopiperazine derivatives displayed sedative activity to about the same extent.
The discovery of the CNS-penetrant and selective $\alpha_{2C}$ adrenergic receptor antagonist $N\{2-[4-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethyl)-[1,4]diazepan-1-yl]-ethyl\}-2-phenoxy nicotinamide 56 is described. Structure–activity studies demonstrate the structural requirements for binding affinity, functional activity and selectivity over other $\alpha_{2}$-AR subtypes [75].

A series of novel bisbenzamidines and bisbenzimidazolines with different linkers connecting the aromatic groups was tested in vitro for NMDA receptor antagonist activity [76]. IC$_{50}$ values for these compounds ranged from 1.2 to >200 $\mu$M. The bisbenzamide with a homopiperazine ring as the central linker 57 was found to be the most potent NMDA receptor antagonist with IC$_{50}$ value 45.8(38.7-54.3) $\mu$M among all the pentamidine analogues tested so far.
By pursuing a prodrug approach, Hiroyuki Koshio, et al., [77] were able to improve the oral anticoagulant activity of potent fXa inhibitors such as compounds 1 and 28. In particular, amidoxime derivatives possessing an ethyl ester moiety 58 and 59 showed quite potent activity ex vivo after oral dosing in mice and prolonged PT about 2-fold. Interestingly, the ester moiety was found to be essential for the expression of potent oral activity in this series of Prodrugs.

The isopropyl diazepanes 60 are also high affinity histamine H3 ligands and SERT inhibitors. Kiev S. Ly, et al., [78] also prepared the cyclopropyl diazepanes 61. These cyclopropyl diazepanes proved to be very high affinity histamine H3 ligands and, with the appropriate aryloxy substituent, they are also potent SERT inhibitors.
The crystal structure of Acetylcholine Binding Protein (AChBP), homolog of the ligand binding domain of nAChR, has been used as model for computational investigations on the ligand–receptor interactions of derivatives of 6-chloropyridazine substituted at C\textsubscript{3} with 3,8-diazabicyclo[3,2,1]octane, 2,5-diazabicyclo[2,2,1]heptane and with piperazine and homopiperazine, substituted or not at N\textsubscript{4} [79]. The ligand-receptor complexes have been analyzed by docking techniques using the binding site of HEPES complexed with AChBP as template.

5-chloro-7-methyl-2-(4-methyl-1-homopiperazinyl)benzoxazole 62 and 5,7-dimethyl-2-(4-methyl-1-homopiperazinyl)benzoxazole 63, exhibited a high binding affinity to 5-HT3 receptor [80-83].

Enrique Sotoca, et al., [84] reported an experimentally simple multicomponent domino sequence for the synthesis of 1,4-diazepane derivatives from easily accessible starting materials. The sequence does not require any harmful reagents, and liberate water as the only by-product.
1.2. **Scope of the present work**

Heterocyclic chemistry is a vast and expanding area of chemistry, because of the obvious applications of compounds derived from heterocyclic rings in pharmacy, medicine, agriculture and other fields. This study is of great interest both from the theoretical as well as practical standpoint. Seven-membered heterocycles with two heteroatoms in the 1,4-positions are well known because of their unique pharmacological activity towards the central nervous system. These properties strongly depend on the nature of the heterocyclic core, particularly on the relative positions of the two nitrogen atoms and the type of ring fused to the seven-membered ring. This ring system has demonstrated considerable utility in drug design, with derivatives demonstrating a wide range of biological activities. In this connection the present investigation is undertaken and is divided into three chapters. Chapter-I gives the introduction to homopiperazine derivatives. The homopiperazine derivatives are associated with diverse pharmacological significance and thus considered as Privileged scaffold. The homopiperazine scaffold displays inhibition of platelet aggregation, peptidoglycan synthesis inhibition, 5-HT antagonists, H₃ receptor antagonists, as peptidomimetic scaffolds, biological tools, protein kinase inhibitors, matrix metalloproteinase inhibitors (MMPs) and acetylcholinesterase inhibitors. Such varieties of interesting biological activity for this class of compounds prompted us to synthesize homopiperazine derivatives and investigate their biological importance. It is expected that these would result in highly potent and selective pharmaceutical agents. Chapter-II deals with the synthesis of 1-(1,4-diazepan-1-yl)-2-(4-(2,4-dimethoxybenzoyl)phenoxy)ethanone derivatives and investigates their antimicrobial and anticancer activity. Chapter-III contains evaluation of 1-benzhydryl-1,4-diazepane derivatives as antimicrobial and anticancer agents.
1.3. References


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