CHAPTER 1

INTRODUCTION

1.1 MEDICINAL CHEMISTRY

Medicinal chemistry is a science whose roots lie in all branches of chemistry and biology. It involves the isolation, characterization and synthesis of new compounds that can be used as medicine for the prevention, treatment, and cure of disease. Medicinal chemistry thus provides the chemical basis for the interdisciplinary field of therapeutics. By contributing therapeutic agents, chemists have proudest innumerable achievements for the cause of medicine.

A very broad definition of a drug would include "all chemicals other than food that affect living processes." If the effect helps the body, the drug is a medicine. However, if a drug causes a harmful effect on the body, the drug is a poison. The same chemical can be a medicine and a poison depending on conditions of use and the person using it. Another definition for drug would be "medicinal agents used for diagnosis, prevention, treatment of symptoms and cure of diseases."

A disease is a condition of impaired health resulting from a disturbance in the structure or function of the body. Diseases may be classified into the following major categories:

1) Infections caused by viruses, rickettsia, bacteria, fungi, protozoa and worms.
2) Allergic diseases caused by antigens and foreign substances.

3) Metabolic disorders caused by defects in the body's ability to carry out normal reactions - these may be due to hereditary, deficiency and congenital defects.

4) Cancer.

5) Toxic diseases caused by poisons.

6) Psychosomatic and mental diseases.

Chemists in the pharmaceutical industry synthesise new compounds. In most cases, the chemist has a specific reason for synthesizing a particular compound, usually based on theoretical considerations, medicinal value, biological mechanism, or a combination of all the three. One of the major factors leading to more rational approach to new drugs has been the knowledge of biological mechanisms. In the past three decades the biological sources have undergone a major redirection towards molecular understanding of biological systems. It is important to understand the broad implications of this trend in research in the modern pharmaceutical industry.

The pharmacological activity of a compound is an involved function of the structure, and even a small change may profoundly modify the pharmacological effects. These structural modifications may involve replacing one group with another at a specific point in the molecule, shifting the same group from place to place in the parent molecule and saturating valence bonds or modifying acidity or basicity. Slight changes may, sometimes, completely change the action of the compound. Many of the currently used antispasmodics, anticonvulsants, local anesthetics, non-narcotic analgesics, chemotherapeutic agents and hypnotics have been products of this approach.
The determination of the structure of a biologically active molecule provides a two fold benefit to pharmacy and medicine. It makes possible research leading to synthesis and modification of the structure. Modifications of the structure are usually accompanied with changes in the biological activity and occasionally vast improvement is accomplished as in the case of corticosteroids from the extract of adrenal cortex and 7-chlortetracycline from streptomyces aureofaciens (Larry and Murray 1984). Studies on the structure and synthesis of penicillin led to the development of semi-synthetic penicillin and later to cephalosporins (Miller 2008). Some of the new compounds have made possible major improvements in antibiotic therapy. Total synthesis is made possible by the knowledge of chemical structure and in some instance, it is economically important in reducing the cost of drug (Larry and Murray 1984).

Pharmacological research plays two important roles in its contribution to pharmacy and medicine. The pharmacologist designs and operates model systems for detecting and evaluating the activity of compounds for control of diseases such as those of the central nervous system, the gastro-intestinal tract, the cardiovascular system and the endocrine organs.

It is rare to find a new potent drug which does not have side effects in individuals. The pharmacologist must predict an effective human dose which hopefully will produce minimum side effects. An important part of pharmacology is the study of drug absorption, distribution, metabolism and excretion. Rational drug therapy requires a thorough knowledge of the kinetics of these processes after parenteral and/or oral administration of the drug. Initial studies in animals are often performed with radio active forms of the drug to determine the dose of the drug and its metabolites which appear in blood, urine and tissues. Determination of the concentration of drugs in
biological fluids or tissues requires precise instrumental measurements. Accurate quantification of the drug and its metabolites often requires the use of modern chromatographic techniques coupled with mass spectrographic analysis. In order to be certain that a new drug is safe, detailed studies are to be made for their effect, varying dose and of prolonged administration of that drug. The toxicologist must define the acute toxicity measurement in laboratory animals.

1.2 ROLE OF HETEROCYCLIC COMPOUNDS

Heterocyclic compounds occur widely in nature and in a variety of non-naturally occurring compounds. A large number of heterocyclic compounds are essential to life. Various compounds such as alkaloids, antibiotics, essential amino acids, vitamins, hemoglobin, hormones, synthetic drug & dyes, contain heterocyclic ring systems. Knowledge of heterocyclic chemistry is useful in bio-synthesis and in drug metabolism.

A variety of atoms, such as N, O, S, Se, P, Si, B and As can be incorporated into ring structures. Heterocycles make up an exceedingly important class of compounds more than half of all known organic compounds are heterocycles.

A drug is a compound that interacts with a biological molecule, triggering a physiological effect. Organo selenium compounds have been attracting the attention of organic chemists due to their biological importance.

Benzimidazoles possess antibacterial and antifungal activities, further, the benzimidazole derivatives constitute an important class of compounds possessing several pharmacological activities including antiviral, anti-inflammatory and analgesic activity (El-Masry et al 2000).
The piperidine ring is a ubiquitous structural feature of many alkaloid natural products and drug candidates. Watson et al (2001) asserted that during the last 10-year period there were thousands of piperidine compounds mentioned in clinical and preclinical studies. Piperidones are less prominent, but often they serve a role as advanced intermediates prior to their conversion to piperidines. Reviews updating progress in the stereoselective synthesis of substituted piperidines have appeared recently (El-Subbagh et al 2000). The purpose of these reviews is to compile stereo controlled approaches to piperidone and piperidine heterocycles, focusing on the published literature. These reviews are organized highlighting the bond formation or process leading to the heterocyclic ring. Synthesis of piperidone derivatives are reviewed and are categorized by the position of the carbonyl group. It is followed by methodologies to convert piperidones to piperidines. The large volume of published literature over the past three years precludes a comprehensive review. Methodologies were selected on the basis of diversity and stereo control, with the intent of providing the reader with a variety of options for the synthesis of these useful heterocycles.

1.3 SYNTHESIS OF 4-PIPERIDONES

1.3.1 Intermolecular processes

1.3.1.1 From 1-acylpyridinium salts

2,3-Dihydro-4-pyridones are utilized in the synthesis of numerous alkaloids due to the variety of stereo controlled functionalizations that are possible (Comins et al 1997) (Scheme 1.1).

2-Substituted-N-acyl-2,3-dihydro-4-pyridones were prepared enantiomerically by the stereoselective addition of organometallic reagents and metallo-enolates to chiral 1-acylpyridinium salts (Comins et al 2001 a).
Also, a resin activation/capture approach was used for the synthesis and elaboration of 2,3-dihydro-4-pyridones on solid support (Chen and Munoz 1999).

Scheme 1.1 2,3-Dihydro-4-pyridone

According to Chen et al (1998), Watson et al (2000), Mitchenson and Nadin (2000) a strain causes the C-2 substituent to occupy an axial position thereby influencing the stereo chemical outcome of subsequent transformations. Iodocyclocarbamation of N-acyl-2-alkenyl-4-piperidones produces bicyclic carbamates in a highly stereoselective manner. Comins et al (2001 b) reported that enolate alkylations can be used to functionalize C-3 acetoxyxylations and these reactions afforded trans-2,3-disubstituted products. Organocerium reagents is added to C-4 from the face opposite the axial C-2 substituent, while reduction with sodium borohydride/cerium chloride provided C-4 equatorial alcohols. Substitution at C-5 was achieved via the corresponding vinyl iodide (prepared using iodine monochloride) (Comins et al 2000). Functionalizations at C-6 were achieved by copper catalyzed Grignard conjugate additions (Kuethe and Comins 2000), intermolecular Heck reaction (Comins and Ollinger 2001) and conjugate reduction (Brooks et al 2001). The intramolecular [2+2] photocycloaddition of a nitrogen tethered terminal olefin was a key reaction in the total synthesis of plumerinine (Comins et al 2002).
1.3.1.2 Imino Diels–Alder reactions

The hetero Diels-Alder (HDA) reaction of imines with Danishefsky’s diene (1-methoxy-3-trimethylsiloxy-1,3-butadiene) is an efficient method for construction of functionalized 2,3-dihydro-4-piperidones with control of regio-, diastereo- and enantioselectivity (Jorgensen 2000). Recently, Nafion-H (Kumareswaran et al 2001), bismuth (III) chloride and triflate (Robert et al 2000), and samarium diiodide (Collin et al 2001), were used as achiral catalysts in these reactions.

Kobayashi et al (1999) reported a switch of enantiofacial selectivity when using either 6,6’-dibromo-1,10-binaphthol or 6,6’-dibromo-3,3’diphenyl-1,10-binaphthol as the ligand in chiral zirconium catalyst systems. Initial studies from the Kobayashi laboratories reported the use of catalyst system in the enantioselective HDA reaction of Danishefsky’s diene with ortho-hydroxyphenyl imine that produced 2,3-dihydro-4-pyridone (S) (Kobayashi et al 1998). Use of a similar chiral catalyst with substituents on the 3,3’-positions, caused a reversal in the absolute configuration of the product yielding product with R configuration (Comins et al 2001 c).

Kobayashi et al (2000) also used polymer-supported (R)-1, 10-naphthols as chiral catalysts in aza Diels–Alder reactions of aldimines with Danishefsky’s diene. High yields, high enantioselectivities and low catalyst loadings were achieved. The HDA reaction of Danishefsky’s diene with the benzylimine derived from Garner’s aldehyde was used as the key step in an efficient approach to the asymmetric synthesis of carbacephem (Avenoza et al 2002) (Scheme 1.2).
Scheme 1.2  HDA reaction of Danishefsky’s diene (a) Danishefsky’s diene, Et$_2$AlCl, CH$_2$Cl$_2$, (b) 1N HCl, then chromatography

Imino derivatives of dihydro-4-pyridone was prepared under non-epimerizable conditions (Palomo et al 1992), and HDA reaction with Danishefsky’s diene catalyzed by diethylaluminum chloride gave the best diastereoselectivity for dihydro-4-pyridone (Liu and Sibi 2002). Use of Danishefsky’s diene in the HDA reaction was central in the asymmetric synthesis of functionalized indolizidines (Benito et al 2001), indolo [2, 3-a] quinolizidine (Kuethe et al 2002), tetracyclic alkaloid phyllanthine (Han et al 2000) and enantiopure pipecolic acids (Badorrey et al 2000).

Similarly, the HDA reaction of E-1-dimethylamino-3-tertiary butyldimethylsiloxoy-1,3-butadiene (Kozmin et al 2002), with activated imines at room temperature in the absence of Lewis acid catalysts provides a simple, one-pot synthesis of dihydro-4-piperidone derivatives (Huang and Rawal 2000). A convenient, large-scale synthesis of chiral 4-oxopipecolates was achieved by HDA reaction of 2-trimethylsilyloxy-1,3-butadiene with activated imines derived from condensation of ethyl glyoxalate with (R)-or (S)-methylbenzylamine (Lau et al 2002). DiastereomERICALLY pure 4-oxopiperidine-2-carboxylates were obtained by crystallization and were converted to a variety of protected 2-substituted 4-oxo-piperidine derivatives.

A one-pot, three-component synthesis of 2-substituted 2,3-dihydro-4-pyridones was accomplished by a highly efficient Aza Diels–Alder reaction.
(Yuan et al 2002). The reaction was carried out in methanol in the absence of acid and proceeded through a Mannich-type pathway. The solid-phase reaction of 2-amino-1, 3-butadienes with nitrogen-bound imines and carbon-bound imines furnished 4-piperidones with 4 points of diversity (Barluenga et al 2002).

1.3.2 Intramolecular processes

1.3.2.1 Mannich reactions

According to Davis et al (2001) the intramolecular Mannich reaction is a powerful tool for the rapid, efficient and highly stereoselective assembly of polysubstituted piperidones. Sulfinyl amines served as asymmetric precursors to δ-amino-β-ketoesters (Scheme 1.3). Treatment with excess trifluoroacetic acid removes the sulphonyl group and the chiral amine salt released reacts with an aldehyde or ketone giving polysubstituted piperidone. The major isomer was shown to have the C-2 and C-6 substituents in a cis-orientation with the C-2-and C-3substituents. For aldehydes, the nearly exclusive formation of the 2,6-cis-disubstituted piperidone was consistent with transition state. Decarboxylation was best effected with 48% HBr in methanol. Some erosion of chirality was noted and was attributed to a retro-Mannich reaction. The authors demonstrate a base-induced retro-Mannich reaction giving 6-phenylpiperidine-2,4 dione. 2,6-Disubstituted-4-piperidones serve as important building blocks for piperidine alkaloid synthesis.

Another approach to 4-piperidones using an intramolecular Mannich-type reaction was described by Carbonnel and Troin (2002), in a series of papers utilizing chiral β-amino ketals as starting materials. Enantiopure amine was condensed with decylaldehyde to form imine. Subsequent treatment with p-toluenesulfonic acid afforded a
Scheme 1.3 Intramolecular Mannich reaction (a) TFA, MeOH
(b) RCHO, CH₂Cl₂, room temperature, then aq. NaHCO₃
(c) 48% HBr
diastereoselectivity of 95%. Removal of the ketal protecting group afforded piperidone (Ciblat et al 2000). Using this intramolecular Mannich-type reaction, Ciblat et al (2001) rapidly assembled 2,2’-spiro-4-piperidone skeletons that are present in a variety of natural products.

1.3.2.2 Cycloadditions

A short, practical, milligram synthesis of both isomers of ethyl 4-oxopiperidone derivatives were achieved utilizing a 1,3-dipolar cycloaddition as the key step (Machetti et al 2001). Reaction of nitrone with 3-butena gave isoxazoline as an equimolar mixture of four diastereomers. Reaction of the mixture with mesyl chloride and treatment of the resulting mesylates with MeCN in refluxing acetonitrile gave a 1:1 mixture of epimeric at C-2. Deprotection of the separated epimers led to (R)-and (S)-4-oxopiperidonic acid derivatives.

1.3.2.3 From β-amino carboxylates

Enantiopure β-amino esters which are readily available (Machetti et al 2001) served as starting points for a simple, efficient synthesis of enantiopure 4-oxo-and 4-hydroxy-2,6-disubstituted-piperidines (Davies et al 1994). N-Deprotection of the intermediate gave a β-amino ester that is
transformed to 2,3-dihydropyridone (Machetti et al 2001). The secondary alcohol is oxidized, after the conversion of diol followed by selective protection of the amine and primary alcohol with benzyl chloroformate. Removal of the protecting groups from the resulting ketone gives hydroxyl derivative of β-amino ester which could be converted to nitro derivative of β-amino ester by a known procedure (Markus et al 1997). 3-Trifluoroacetylamino-3-arylpropionyl chloride is prepared in two steps from the corresponding β-aryl-β-amino acid and condensed with Meldrum’s acid to afford the chain homologated intermediate (Scheme 1.4). Ring opening hydrolysis of homologated intermediate with refluxing tert-butanol gave the δ-aryl-δ-trifluoroacetylamino-β-ketoester that was cyclized with aqueous NaOH in tetrahydrofuran. This represents an easy and versatile preparation of 6-aryl-piperidine-2, 4-diones (Leflemme et al 2002) (Scheme 1.5).

Scheme 1.4 Synthesis of 4-oxo and 4-hydroxy-2,6-disubstituted-piperidine (a) H₂, Pd/C (b) AcOH, then PrCOCH₂-CO₂Et (c) Na, EtOH (d) aq NaOH, EtOH (e) H₂, Pd/C (f) Cbz-Cl (g) Dess–Martin oxidation (h) H₂, Pd/C
Piperidone is a well known and widely used analgesic. Due to its high potency and generally favorable pharmacological profile, numerous analogues have been synthesised in the past three decades, which have been used clinically as narcotic analgesics. Other structurally related compounds exhibit different pharmacological activities, e.g., antihistaminic and antiarrhythmic. Analgesic activity of the anilidopiperidines is greatly enhanced by the presence of a substituent in the position 4 of the piperidine ring (Casy 1989). The chemical nature of the substituent apparently has little influence on the activity, since groups as diverse as carbomethoxy, methoxymethyl, hydroxymethyl, methylketone and aryl (Kudzma et al 1989), produce significant increase (2 to 30 times) in the potency compared to piperidone. Rather it seems that the activity depends primarily on the voluminosity of the substituent. This hypothesis can be readily proven by the synthesis of 4-alkyl piperidone analogues, where the analgesic potency would depend entirely on the steric factor. In addition, this novel series would provide better SAR for piperidone analogues in general and possibly, some new, promising opioid analgesics. Literature scanning vividly shows that 4-piperidone derivatives possess a large number of biological and pharmacological activities. Hence the present study is aimed at the synthesis of compounds containing these moieties.
1.4 REVIEW OF LITERATURE

A wide variety of 2,6-diphenyl-piperidon-4-one derivatives have been described due to their chemotherapeutic importance. Oxadiazole compounds have shown biological activity against parasites (Rizk 1993) and bacteria (Kassem et al 1995). Also, the presence of basic Mannich side chains in a drug may overcome the water insolubility problem through the formation of hydrochlorides. Some heterocyclic moieties such as triazole nucleus are known to possess antibacterial and fungicidal properties. Furthermore, Schiff’s bases possess anticancer (Popp 1961 and 1964) activities in animal screening, and pyrazoles, pyrazolones and alkylpyrazoles have shown wide ranging pharmacological applications (Clinton et al 1959).

Aridoss et al (2007) synthesised N-morpholinoacetyl-2,6-diarylpiperidin-4-ones from N-chloroacetylation followed by base catalyzed condensation with morpholine. N-morpholinoacetyl-2,6-diarylpiperidin-4-ones exerted better activity against all the tested bacterial and fungal strains.

Maihub et al (2007) prepared the Schiff base by condensing 4-[N,N-dimethylamino]benzaldehyde with o-aminophenol in ethanolic media, forming two new metal complexes of the formulae [NiL(OH)(H2O)].5H2O and [ML(OH)2(H2O)2].4H2O with Cr(III) and Fe(III) ion. These complexes were characterized by elemental analysis, molar conductance measurements, infrared and electronic spectra.

Perumal et al (2004) prepared the epimerization of r(2),c(6)-diaryl-t(3)-chloropiperidin-4-ones by treating diaryl-chloropiperidin-4-ones with ammonia in DMF. NMR spectroscopic parameters of the epimeric pair of chloropiperidones have been compared and the differences rationalized in terms of stereochemical features. Holla et al (2004) synthesised a number of new compounds containing 2-chloropyridin-5-yl-methyl substituted 1,3,4-
thiadiazole and 1,3,4-oxadiazoles with a view to study their insecticidal properties.


A number of 3,5-diarylidene-4-piperidones and some related quaternary ammonium salts were prepared principally by Dimmock et al (2001) as candidate cytotoxic agents. Selective toxicity was demonstrated by these compounds, especially toward leukemia. In general, the compounds were less cytotoxic than the reference drug melphalan in both screens. It was noted that smaller interplanar angle made by one of the arylidene groups with the central piperidine ring in the 4-pyridylmethylene moieties may contribute to the variation in cytotoxicity. From this study, various conclusions pertaining to future molecular modifications with a view of increasing cytotoxic potency were made.

Dimmock et al (2002) synthesised a number of 1,3-arylidene-2-tetralones and demonstrated their cytotoxic activity. In this screen, most of the enones were found to be more cytotoxic than the established anticancer agent memphian and some of them showed selective toxicity towards leukemic and colon cancer cells. The modes of action of representative compounds include interference with the biosyntheses of nucleic acids and proteins as well as altering redox potentials. The compounds were well tolerated when administered to mice. Thus these novel enones are promising prototypic
molecules due to their potent cytotoxic properties and lack of significant murine toxicity.

Kaya et al (1996) isolated nostocyclin, a novel 3-amino-6-hydroxy-2-piperidone-containing cyclic peptide from a hepatotoxic strain of cyanobacterium Nostoc species. Nostocyclin was non-toxic in acute in vivo bioassays, but inhibited protein phosphatase-1 activity at high concentration in vitro. Abbas et al (2002) synthesised 1-methyl-3-(3-hydroxy-3-phenylpropyl)-4-phenyl-4-piperidinol and 1-methyl-3-(3-hydroxy-3-phenylpropyl)-4-phenyl-4-propanoyloxypiperidine and tested for their pharmacological activity. These compounds were found to be potent analgesics in the writhing test.

Ozturk et al (2000) synthesised a series of 1,2,5-trisubstituted 4(1H)-pyridinone derivatives by using 4-pyrone derivatives with primary amines in ethanol. Analgesic and anti-inflammatory activities of the synthesised compounds were investigated by acetic acid-induced writhing syndrome and Carrageenan rat paw oedema tests. All the tested compounds exhibited higher analgesic activities than acetyl salicylic acid and showed higher anti-inflammatory activities than indomethacin. The anti-inflammatory activities and gastric ulceration potential of the compounds were tested using indomethacin as the reference drug. Parthiban et al (2005) evaluated the antibacterial activity of 1-methyl-2,6-diarylpyperidin-4-one o-benzylxoximes. Parthiban et al (2005) synthesised and reported NMR spectral studies of some 2,6-diarylpyperidin-4-one o-benzylxoximes.

Aridoss et al (2006) reported an efficient route to synthesise a series of novel 1-[2-(imidazo(4,5-b)pyridin-2-yl)ethoxy]-2,6-diarylpyperidin-4-ones from 2,6-diarylpyperidin-4-ones upon strategical N-hydroxylation, cyanoethylation followed by acid assisted cyclocondensation with 2,3-diaminopyridine. The synthesised compounds were evaluated for their
antibacterial and antifungal activity. The tested compounds displayed promising antifungal activity and strong *in vitro* antibacterial activity against microorganisms.

Kus et al (2001) synthesised and evaluated the antimicrobial and antifungal activities of 5-fluoro-6-substituted-1*H*-benzimidazole-2-carbamates, 5-fluoro-6-substituted-1*H*-benzimidazole-2-acetate and 2-acetamide derivatives, 2-acetamido-5-fluoro-6-(morpholin-4-yl)-1-propyl-1*H*-benzimidazole, and 1-cyclopropyl-2-ethyl-5-fluoro-6-(4-methylpiperazin-1-yl)-1*H*-benzimidazole and they showed good antimicrobial activity against.

Czarny et al (2002) investigated the disinfection of medical equipments using piperidine chloride derivatives containing hydrophobic chains of varying length, which are well recognized as membrane-disruptive, antibacterial and antifungal agents. The bacterial and *Candida* strains used in this study were clinical isolates obtained from patients. The results indicate that the newly synthesised piperidine chloride derivatives have antimicrobial activity. They found that the differences in activity depend on the structure of the lipophilic moiety. Rameshkumar et al (2003) synthesised a new series of 2,6-diaryl-3-methyl-4-piperidones by Mannich reaction (condensation) of ethyl-methyl ketone, substituted aromatic aldehydes and ammonium acetate. Oximes and thiosemicarbazone derivatives of 2,6-diaryl-3-methyl-4-piperidones were synthesised by reaction with hydroxylamine hydrochloride and thiosemicarbazide, respectively. The compounds were screened for acute toxicity, analgesic, local anaesthetic and antifungal activities. 2-(4-Methylphenyl)-3-methyl-6-(4-chlorophenyl)-piperidin-4-one exhibited the highest analgesic and local anaesthetic activities. The oximes and thiosemicarbazones were completely devoid of analgesic and local anaesthetic activities. 2-(4-Methylphenyl)-3-methyl-6-(4-hydroxyphenyl)-
piperidin-4-oxime and 2-(4-methoxyphenyl)-3-methyl-6-(4-chlorophenyl)-piperidin-4-oxime exhibited potent antifungal activity.

Tyunosin and Kiichi (1953), reported two synthetic routes for the preparation of 2-phenylcarbamoyl-5,5-dimethyl-6-(1-piperidyl)-1,3-cyclohexanedione. This compound was obtained by amination of 2-phenyl carbamoyl-5,5-dimethyl-6-bromo-1,3-cyclohexanedione with piperidine. This compound exhibited antibacterial properties.

Arimoto et al (1986) synthesised a 7β-[2-(2-aminothiazol14-yl)-2-(substituted arbamoylmethoxyimino)acetamidol with cephalosporins group at the C-7 position and with various hetero aromatics at the C-3 position. The effects of substituents on the carbamoyl group in the 7-side chain were investigated in order to improve antibacterial activity. Some of these compounds exhibited high antibacterial activity against gram-positive and gram-negative bacteria, including \textit{Pseudomonas aeruginosa}, as well as good resistance to \textit{β-lactamase}. Gupta and Narayana (1997) prepared a few Mannich bases of 1-cyclohexylidene - N(1,2-dihydro-2-oxo-3H-indol-3-ylidene and thiosemi carbazole derivatives by employing formaldehyde and morpholine and piperidine as secondary amines. These Mannich bases were characterised on the basis of different physicochemical evidences. Antibacterial activity of the synthesised Mannich bases has been studied by employing nine bacterial strains. They reported that the chloro group at position 5 broadened the spectrum of activity and the compounds with piperidine showed better activity than the compounds with morpholine, against almost all the organisms used. Zhou et al (2007) reported a series of novel 3,5-diamino-piperidine derivatives, which are antibacterial compounds that target RNA and blocks bacterial translation and growth.

Gottasova et al (1998) synthesised 2,6-disubstituted 4-anilinoquinazolines derivatives which exerted a significant effect on the
Bacillus subtilis and Staphylococcus aureus. They reported that the derivatives having the aromatic ring non-substituted or substituted by bromine, the pyrimidine ring by phenyl, morpholine or piperidine and the aniline skeleton non-substituted or substituted by methyl or amino group exerted a considerable antibacterial activity.

Sridhar and Ramesh (2001) prepared Schiff bases and phenyl hydrazone of isatins by reacting isatin and the appropriate aromatic primary amine/hydrazines. A new series of the corresponding N-Mannich bases were synthesised by reacting them with formaldehyde and diphenylamine. The compounds were screened for analgesic, anti-inflammatory and antipyretic activity. 1-Diphenylaminomethyl-3-(1-naphthylimino)-1,3-dihydroindol-3-one, 3-(1-naphthylimino)-5-bromo-1,3-dihydroindol-2-one and 1-diphenylamino methyl-3-(4-methylphenylimino)-1,3-dihydroindol-3-one were found to exhibit the highest analgesic, anti-inflammatory and antipyretic activities, respectively. 1-Diphenylaminomethyl-3-(4-methylphenylimino)-1,3-dihydroindol-3-one was found to be the most active compound in the series. Randall and Lehmann (1948) studied a series of 50 derivatives of piperidine for analgesic action and other pharmacological properties. Maximal analgesic potency was attained by the introduction of an alkyl group into the 3-position of these 1-, 5-, 4-substituted piperidines. They reported that the steric configuration determined the degree of analgesic potency. The compounds with alkyl group in the 3-position of 5-, 4-substituted piperidines were found to be four to eight times as potent as morphine and qualitatively those compounds resembled morphine in pharmacological action.

Turktekin et al (2004) synthesised 1-(2-piperidinoethyl)-1H-benzimidazole C\textsubscript{14}H\textsubscript{19}N\textsubscript{3}, from benzimidazole and N-(2-chloroethyl) piperidine hydrochloride in KOH/EtOH solution. The benzimidazole ring is connected to the piperidine ring by an ethylene group. They reported that the
piperidine ring displays a chair conformation and it was the main cause for the pharmacological activity of the benzimidazole compounds.

Makin et al (1989) reported a new path of synthesis of 1,2,5-trimethyl-4-piperidone and evaluated their anti-cancer activity. The compound with benzimidazole ring was found to exhibit potent anti-cancer activity. Sorrentino and Capasso (1971) evaluated the anti-inflammatory activity of 3-(N-piperidine)-1,1-diphenyl-1-propanol methansulfonate. Bovy et al (2006) synthesised hydroxy-3-[3-H-(4-chlorophenyl)-2-piperidone as a potential anti-inflammatory agent, which was labelled with tritium on the benzene ring in a position neighbouring a chlorine atom. They also prepared an iodinated precursor by an original six-step synthesis and this selective catalytic iodine-tritium replacement was achieved under mild reaction conditions.

Singh and Paul (2006) investigated nine derivatives of 1,3-dialkylated-pyrimidin-2,4-dione and found that these compounds were active against all 59 human tumor cell lines. The structure–activity relationship studies indicated the presence of piperidine/pyrrolidine at the end of C-6 chain, benzoyl group at C-5, and benzyl groups at N-1, N-3 of the pyrimidine ring increasing the anti-cancer activities of these molecules. Dogan et al (2005) synthesised the compound 1H-4,5-dihydro-3-(3-hydroxy-2-naphthyl)-4-substituted-1,2,4-triazoline-5-thiones from 3-hydroxy-2-naphthoic acid hydrazide in two steps. These compounds were tested in vitro for their ability to inhibit growth of 60 different human cancer cell lines by the National Cancer Institute and notable cytotoxic effect on some cancer cell lines was observed.

Adams et al (2004) synthesised a series of novel piperidone derivatives of curcumin analogs and screened them for their anti-cancer and anti-angiogenesis activities. The majority of the analogs demonstrated a
moderate degree of anti-cancer activity. In addition, they also revealed that these compounds can inhibit tumor cell growth with a higher potency than the commonly used chemotherapeutic drug, cisplatin. Analogs that were effective in the anti-cancer screens were also effective in \textit{in vitro} anti-angiogenesis assays. These compounds were found to reduce effectively the size of human breast tumors grown in female athymic nude mice. As a follow-up, they also studied a 3D quantitative structure relationship. Singer (1984) studied the effect of 3-methyl substitution on the carcinogenicity of nitroso-4-piperidone. These compounds were found to reduce the size of human tumors grown in mice and showed little toxicity.

Khairia \textit{et al} (1989) synthesised four new \textit{N}-methylpiperidone curcurmin analogs which showed high activity against cancer cells. The \textit{in vitro} anti-tumor screening revealed that the results go hand in hand with the \textit{in vitro} free radical scavenging effects. They reported that the antioxidant effect of these compounds depends mainly on the stabilization of the phenoxy free radical formed for which the \textit{p}-hydroxy phenyl moiety is essential. \textit{o-Substitution} by electron-donating groups like the \textit{o}-methoxy group increased the stability of phenoxy free radical, hence increasing both free scavenging and anti-tumor effects. Increasing the alkyl group chain on nitrogen in the series of substituted \textit{N}-alkyl piperidones as well as the extension of conjugation, increased the stabilization of phenoxy free radical and thereby the activity towards both free radical scavenging and anti-tumor effects. This was attributed to an increased positive inductive effect and/or increased lipophilicity of the new compounds.

Bekircan and Gumrukcuoglu (2005) synthesised a series of 4-arylidenamino-\textit{4H}-1,2,4-triazoles and 4-(1-aryl)ethylidenamino-\textit{4H}-1,2,4-triazoles by the treatment of 4-amino-\textit{4H}-1,2,4-triazole with certain aldehydes and ketones. These compounds were screened on three human tumor cell
lines, breast cancer, lung cancer and CNS cancer. They found that the compound exhibits antiproliferative activity in the anticancer tests. Mohd Amir et al (2004) synthesised and evaluated anti-inflammatory and antibacterial activities of a number of 2,5-substituted 1,2,4-triazole,1,3,4-thiadiazole/oxadiazole and 2,3-substituted-4-thiazolidinone derivatives. The anti-inflammatory studies were carried with 2-amino/mercapto oxadiazole and 2-substituted aryl 1,3,4-oxadiazoles. Those compounds showed anti-inflammatory activity from 22.34 to 72.36% whereas reference drug ibuprofen showed 80.85% inhibition at 100 mg/kg oral dose in this test. The antibacterial activity had been carried out on triazole, thia diazole,4-thiazolidinone and few oxadiazole derivatives. All these compounds showed significant antibacterial activity when compared with standard drug ofloxacin.

Zhao et al (2006) reported acid-catalyzed rearrangement of 1-benzyl-2-methyl-3-piperidone to 1-benzyl-2-acetylpyrrolidine. Amat et al (2006) synthesised enantiopure 5,6-disubstituted 2-piperidones by stereoselective α-amidoalkylation of phenylglycinol-derived lactams. Bylikin et al (2006) reported a general scheme of reactions between chloro (chloromethyl) dimethylstannane, N-trimethylsilylamides and lactams and established their structure by NMR and IR techniques. X-ray diffraction study of the (O–Sn)-chelate 1-(chlorodimethylstannylmethyl)-2-piperidone has been reported. They have discussed the structural parameters obtained from the X-ray study and quantum-chemical calculations.


We report here the synthesis of some derivatives of the title structure type containing the above mentioned moieties for evaluation of their pharmacological activity.

1.5 SCOPE AND OBJECTIVE OF THE PRESENT WORK

Heterocyclic compounds, particularly five and six membered ring compounds, have occupied a prominent place among various classes of
organic compounds for their diverse biological activities. Piperidones are known to possess various biological activities viz, antibacterial, antifungicidal, anti-tubercular, hypoglycemic and diuretic properties. Furthermore, the Schiff’s bases found to possess anti-cancer activity in animal screening. In view of this and our continued interest in the synthesis of biologically active heterocyclic compounds, it was thought of interest to synthesise some new piperidone derivatives. Among a wide variety of heterocycles, triazole and oxadiazole derivatives of piperidones have played an important role in medicinal chemistry that have been explored for developing pharmaceutically important molecules. Some of them have received considerable attention as potential antimicrobial agents. Moreover, triazole ring systems have acquired a special place in the heterocyclic field because they are frequently encountered structural motifs in many pharmacologically relevant heterocyclic compounds.

The present research work deals with the synthesis, characterization and pharmacological study of new 2, 6 diphenyl piperidin-4-one derivatives having benzimidazole, oxadiazole, triazole, pyrazol, selenadiazole or hydrazole derivatives.

The objectives of the present work may be summarized as follows

1) To synthesise 5-(2,6-diphenyl-4-hydrazono-piperidin-1-ylmethyl)-3H-[1,3,4]oxadiazole-2-thione [2,6-MOT], 5-(2,6-diphenyl-3-methyl-4-hydrazono-piperidin-1-ylmethyl)-3H-[1,3,4]oxadiazole-2-thione [3-MMOT], 4-amino-5-(2,6-diphenyl-4-hydrazono-piperidin-1-ylmethyl)-4H-[1,2,4]triazole-3-thiol [2,6-ATT] and 4-amino-5-(2,6-diphenyl-3-methyl-4-hydrazono-piperidin-1-ylmethyl)-4H-[1,2,4]triazole-3-thiol, [3-MATT].
2) To prepare 5-(2,6-diphenyl-4-hydrazono-piperidin-1-ylmethyl)-3-morpholin-4-ylmethyl-3H-[1,3,4]oxadiazole-2-thione [2,6-MMT], 5-(2,6-diphenyl-3-methyl-4-hydrazono-piperidin-1-ylmethyl)-3-morpholin-4-ylmethyl-3H-[1,3,4]oxadiazole-2-thione [3-MMMT], 4-(benzylidene-amino)-5-(2,6-diphenyl-4-hydrazono-piperidin-1-ylmethyl)-4H-[1,2,4]triazole-3-thiol [2,6-BTT] and 4-(benzylidene-amino)-5-(2,6-diphenyl-3-methyl-4-hydrazono-piperidin-1-ylmethyl)-4H-[1,2,4]triazole-3-thiol [3-MBTT].

3) To synthesise -[2-(3-Methyl-5-oxo-4,5-dihydro-pyrazol-1-yl)-2-oxo-ethyl]-2,6-diphenyl-piperidin-4-one [2,6-MPO], 1-[2-(3-Methyl-5-oxo-4,5-dihydro-pyrazol-1-yl)-2-oxo-ethyl]-2,6-diphenyl-3-methyl-piperidin-4-one [3-MMPO], 1-[2-(3,5-Dimethyl-pyrazol-1-yl)-2-oxo-ethyl]-2,6-diphenyl-piperidin-4-one [2,6-EDP] and 1-[2-(3,5-Dimethyl-pyrazol-1-yl)-2-oxo-ethyl]-2,6-diphenyl-3-methyl-piperidin-4-one [3-MEDP].

4) To prepare 4,6-diphenyl-4,5,6,7-tetrahydro-3-selena-1,2,5-triazo-indene [STII], 4,6-diphenyl-7-methyl-4,5,6,7-tetrahydro-3-selena-1,2,5-triazo-indene [MSTII], 1-(1H-benzoimidazol-2-ylmethyl)-2,6-diphenyl-piperidin-4-hydrazine [BDH] and 1-(1H-benzoimidazol-2-ylmethyl)-2,6-diphenyl-3-methyl-piperidin-4-hydrazine [MBDH].

5) To characterize the synthesised benzimidazole, oxadiazole, triazole, pyrazol, selenadiazole or hydrazole derivatives of 2, 6 diphenyl piperidin-4-one by various physico-chemical techniques like elemental analysis, melting point, UV, FT-IR, $^{1}$H-NMR, $^{13}$C-NMR and Mass spectra.
6) To determine the antibacterial activity of the synthesised compounds by Well diffusion method.

7) To determine the antifungal study of the synthesised compounds by Poison plate method.

8) To determine the local anaesthetic activity of the synthesised compounds by Nerve block anaesthesia method.

9) To perform the anti-inflammatory study of the synthesised compounds by Carrageenin induced hind paw Oedema in mice method.

10) To study the analgesic activity of the synthesised compounds by Tail clip method.

11) To determine the anti-cancer activity of the synthesised compounds by Fibrosarcoma-20 method.