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EMERGING PHAACEUTICAL APPLICATIONS OF PIPERIDINE, PYRROLIDINE AND IT S DERIVATIES

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ABSTRACT

Heterocyclic compounds form largest classical division of organic chemistry by gaining enormous importance in industry and biology. . The mainstream of pharmaceuticals is heterocyclic. Numerous modifiers and stabilizers used in different industrial applications such as cosmetics, information storage, plastics, optics, electronics and reprography along with biologically active agrochemicals are heterocyclic in nature. Pyrrolidine and piperidine both secondary amines are members of saturated heterocyclic compounds demands main cause of interest for chemists, biologist and pharmacist due to their significant and diverse range of promising biological activities like analgesic, anti-inflammatory, CNS, antioxidant, antihistaminic, cytotoxic, antimicrobial and others from last few decades. In the present review we attempts to give information about the synthesis and biological activities of various kinds of Pyrrolidine and piperidine derivatives which might be helpful for both pharmaceutical and chemist in further research.

1. INTRODUCTION

Pyrrolidine (tetrahydropyrrole) is a cyclic secondary amine belongs to saturated heterocycles. This structure is present in various alkaloids and several important pharmaceutical drugs. Nicotine is an alkaloid present in nicotine tobacum, which contain N-methyl pyrrolidine linked to pyridine nucleus. Piperidine (Azinane) is also classify as secondary amine and present in numerous alkaloids. Morphine is an alkaloid containing piperidine nucleus. Due to the importance of pyrrolidine and piperidine nucleus in various therapeutic compounds researchers decided to synthesize different derivatives of 4-(1-pyrrolidinyl) piperidine. The

derivatives were prepared by quaternization reaction of 4-(1-pyrrolidinyl) piperidine with different substitution. The structure of the compounds was confirmed by Infra Red (IR), Ultraviolet (UV), Nuclear Magnetic Resonance (NMR) and Mass spectrometry.

The biological activities of these compounds were determined by standard methods. Analgesic activity is carried out by Tail flick method. Most of the analogues showed significant activity. Antioxidant activity is determined by DPPH and Superoxide scavenging assay technique. All compounds with parent were tested for antibacterial and antifungal activity. Most of the analogues showed better result as compared to parents against bacteria and fungi. Enzyme inhibition activity was also conducted to estimate the extent of inhibition of β-glucuronidase and urease enzyme. Most of the compounds exhibited good activity against β- glucuronidase while the parent was found inactive for this activity. Cytotoxic activity was carried out by using 3T3 and PC-3 cell line. All analogues along with parents showed no activities against PC-3 cell line while two derivatives were found cytotoxic against 3T3- cell line. Compounds were also tested for lethal activity using Brine shrimp. Results of all activity are encouraging to explore the molecules using new techniques and evaluating the compounds at the receptor level.

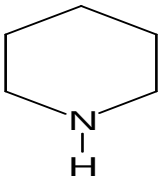
1.1 MEDICINAL CHEMISTRY

It is a multidisciplinary, chemistry-based discipline that involves aspects of biological, medical, and pharmaceutical sciences. It is concerned with the invention, discovery, design, identification, and preparation of biologically active compounds, the study of their metabolism, the interpretation of their mode of action at the molecular level, and the construction of structure-activity relationships. Medicinal chemistry has evolved rapidly into a highly inter-disciplinary field. Scientists were primarily concerned with the isolation of medicinal compounds found in plants. But nowadays, scientists in this field are also deeply concerned with the creation of new synthetic drug compound. A complete new era in medicine began in mid nineteen century with the discovery of number of therapeutically active heterocyclic compound. These heterocyclic compounds played increasingly expanded role in the drug designing.

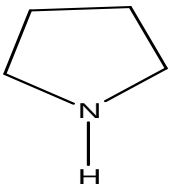
1.2 PIPERIDINE AND PYRROLIDINE

In the last few decades there have been extensive researches on piperidine and pyrrolidine ring containing compounds to evaluate their potential as pharmacologically and biologically active agents. Piperidine and pyrrolidine is a widely used building block and chemical

reagent in the synthesis of organic compounds, including pharmaceuticals. Piperidine nucleus is the part of naturally occurring alkaloids.[1] Pyrrolidine (tetrahydropyrrole) is a cyclic secondary amine belongs to saturated heterocycles. This structure is present in various alkaloids and several important pharmaceutical drugs. Nicotine is an alkaloid present in nicotine tobacum, which contain N-methyl pyrrolidine linked to pyridine nucleus. Piperidine (Azinane) is also classify as secondary amine and present in numerous alkaloids. Morphine is an alkaloid containing piperidine nucleus. Due to the importance of pyrrolidine and piperidine nucleus in various therapeutic compounds scientist started to synthesize different derivatives of 4-(1-pyrrolidinyl) piperidine. The derivatives are prepared by quaternization reaction of 4-(1-pyrrolidinyl) piperidine with different substitution.



Piperidine



Pyrrolidine

1.3 OCCURANCES AND BIOLOGICAL IMPORTANCE

Piperidine is present as the amide of piperic acid in the alkaloid piperine from commercial pepper. The Piperidine nucleus also occurs throughout the areca, hemlock, lobelia and pomegranate alkaloids. In addition it is present in a fused state in many other alkaloids such as coca, lupine, solanaceae and even in morphine groups from *cassia leptophylla*.[2] From *cyclamen coum*, structure of novel Piperidine type alkaloids was established.[3] From the seeds of African legume *angylocalyx pynaer* a polyhydroxy alkaloid has been isolated and identified as a 2-hydroxymethyl-3-4-dihydroxy-5-methylpyrrolidine.[4] Two Piperidine alkaloids hydroalkaloides were isolated from the leaves of *syphocamphylus verticellatus* one of them exhibiting antinoceceptive activity.[5]A thorough examination of the extract of bark of *Angylovsluc pynaaeratic* resulted in the discovery of fifteen polyhydroxylated alkaloids, some of them having moiety. These sugar mimic alkaloids showed the potent inhibitory activity towards bovine epididymis alpha-l-fucoside.[6] From the root bark of *Schumaniphyton magnificum* extract isolated having piperidine ring and unsubstituted hydroxyl groups on the molecule which was suggested to favor the anti-HIV activity.[7]

Analysis of stem extracts of *Piper guineesnse* resulted in the detection and identification of thirty nine isobutyl, pyrrolidyl and piperidyl amide alkaloid.[8] From aqueous ethanolic

extracts of the immature fruits and stalks of bluebell different pyrrolidine alkaloids were obtained. Certain Piperidine amides extracted *from Piper longum L*. showed activity against mosquito larvae[9]. The primary target for medicinal chemist is to get new chemical entities having better and new therapeutic effect by the modification in the structure of different chemical compounds.

Due to significant and diverse biological actions of piperidine and pyrrolidine and their derivatives, piperidine has tremendous importance from the synthetic point of view. Lots of research is going on to manipulate the piperidine and pyrrolidine structure and to establish the biological activity of the various analogues.

1.4 ANALGESIC AND ANTI-INFLAMATORY ACTIVITY

A series of spirocyclic piperidine amide derivatives as tryptase inhibitors were synthesized and Fig -1 was identified as a potent, selective tryptase inhibitor with oral efficacy in two animal models of airway inflammation (sheep and guinea pig asthma models). An X-ray co-crystal structure of it revealed a hydrophobic pocket in the enzyme's active site, which is induced by the phenylethynyl group and is comprised of amino acid residues from two different monomers of the tetrameric protein.[10] Inhibitors of tryptase have therapeutic potential for treating allergic or inflammatory disorders such as asthma.[11] and inflammatory bowel disease.[12]

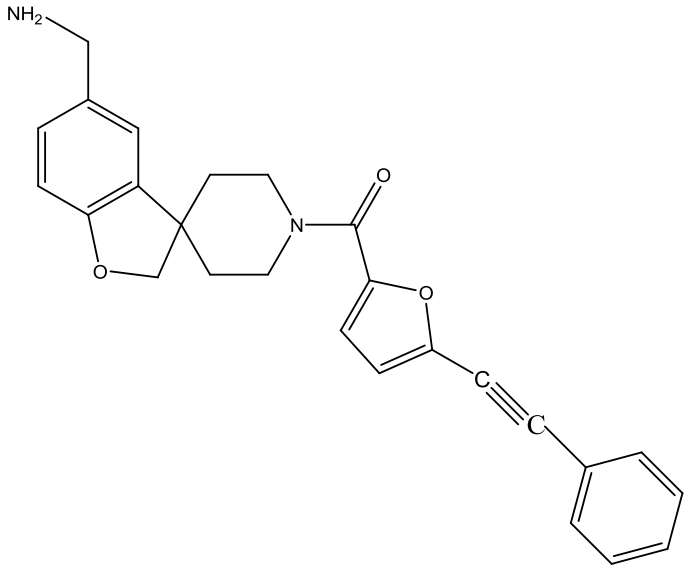


Fig-1

Selective delta opioid receptor agonists are promising potential therapeutic agents for the treatment of various types of pain conditions. A spirocyclic derivative was identified as a

promising hit through screening. Subsequent lead optimization identified compound N, N-diethyl-4-(5-hydroxyspiro [chromene-2, 4'-piperidine]-4-yl) benzamide as a potent, selective, and orally bioavailable delta agonist. This was selected as a clinical candidate for the treatment of pain.[13]

Phencyclidine 1-(1-phenylcyclohexyl) piperidine, has shown analgesic effects. It is predicted that the title compound 2-hydroxy-1-(1-phenyltetralyl) piperidine exerts a potent analgesic effect on acute and phasic pain. Some of its derivatives were synthesized and their biological properties were studied. In order to show desirable biological activity, the aromatic and piperidine rings are necessary for this compounds.[14] The N-3 position of a series of 3-phenoxypropyl piperidine benzimidazol-2-one analogues was optimised using the predictive power of a CoMFA model. The model was used to prioritize compounds for synthesis culminating in the triazole (+)-24. (+)-24 was found to be a high affinity, potent NOP agonist and demonstrated both antinociceptive and antiallodynic effects when administered to rodents.[15]

In 1939 Eisleb and Schuamann investigated the molecular structure of large number of piperidine[16] which revealed that they constituted a fragment of morphine molecule (Fig- 2) namely 4-phenyl piperidine moiety. Pethidine, (Fig-3) was the most important compound in synthetic analgesics. When Phenolic analogues of reversed esters of pethidine were prepared and characterized it was clear that the 4-phenylpiperidine and morphine differ in their mode of interaction with opiate receptors [17]

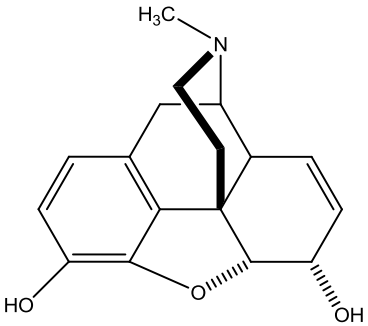


Fig- 2: Morphine

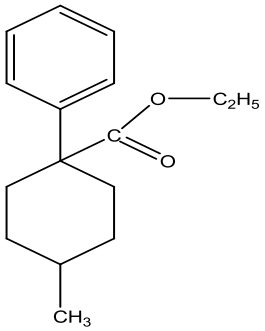


Fig- 3: Pethidine

The newly synthesized fentanyl analogue 3-carbomethoxy fentanyl (iso-carfentanil) was compared to fentanyl for its antinociceptive activity (tail-immersion test) in rats. It was revealed that the introduction of a 3-carbomethoxy group in the piperidine ring of fentanyl skeleton reduced the potency and shortened the duration of action of the parent compound,

i.e., fentanyl.[18]. Some 3- phenyl piperidine derivatives with significant analgesic activities have been reported [19-20]. The most active members have N-phenacyl or phenethyl substituents and their action is antagonized by N-allyl congeners, the latter also antagonize morphine.

The morphine-like (+)-phenylmorphan, and some analogues have been tested in receptor binding assays selective for opioid mu 1, mu 2, delta, kappa 1, and kappa 3 receptors. The selective receptor binding assays provide evidence that opioids in which the phenyl ring is constrained to be equatorial on the piperidine ring can have considerable affinity for mu receptors.[21] A series of piperinylthioindole derivatives were prepared which are used therapeutically as drugs with analgesic property.[22] 3, 4, 4-trisubstituted piperinyl N-alkylcarboxyl derivatives antagonized the peripheral opioid effect and their central activity.[23] Since a methoxy group has been added to the position 2 of the cyclohexane ring of Phencyclidine (1-(1-phenylcyclohexyl) piperidine (PCP), the resulting compound is more polar than PCP. This compound was synthesized using an improved method with a higher yield. Its analgesic effect was studied using the tail-flick test on rats and was compared with that of ketamine. The results showed that 2-methoxyphencyclidine increased tall-flick latencies as compared to the control group. The maximum analgesic effect of the compound occurred 5-10 min after its injection, while the effect of examine was observed 10-25 min after injection.[24]

Structure-activity relationships (SAR) of kappa opioid binding affinities, and antagonistic properties of a series of novel highly selective kappa opioid (3R)-7-Hydroxy-N-((1S)-1-[[(3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl]-2-methylpropyl)-1,2,3,4-tetrahydro-3-isoquinolinecarboxamide (JDTic) containing piperidine ring was reported.[25] N-{(2′S)-[3-(4-hydroxyphenyl) propanamidol]-3′-methylbutyl}-3R, 4R)-dimethyl-4-(3-hydroxyphenyl) piperidine was discovered as a novel κ opioid receptor selective ligand.[26]A study of the binding site requirements associated with N-substituent of (+)-(3R, 4R)-dimethyl-4-(3-hydroxyphenyl)-piperidine derivatives was undertaken using a set of rigid Vs flexible N-substituents. Trans-cinnamyl analogues of (+)-(3R, 4R) dimethyl-4- (3-hydroxyphenyl) piperidine retain opioid pure antagonist activity and possess picomolar antagonist potency at the μ receptor. [27]

Structure-activity relationships (SAR) are studied in the series of 4, 4-disubstituted piperidine morphinomimetics (42 compounds) by means of the Electronic-Topological Method (ETM).

This technique provides a basis of a system used to predict analgesic activity. The results of this study could be used for computer screening and design of novel compounds with analgesics properties as new potential drugs.[28] A study of the effect of transposition of the internal nitrogen atom for the adjacent benzylic carbon atom in delta-selective agonists such as BW373U86 (1) and SNC-80 (2) has been undertaken .It was shown that high-affinity, fully efficacious, and delta opioid receptor-selective compounds can be obtained from this transposition. [29]

Neuroprotective effect of sigma (1)-receptor ligand 4-phenyl-1-(4-phenylbutyl) piperidine (PPBP) is linked to reduced neuronal nitric oxide production.[30]. Derivatives of anpirtoline and deazaanpirtoline modified in the side chain have been synthesized and compared with anpirtoline. Their receptor binding profiles (5-HT1A, 5-HT1B) and analgesic activity (hot plate, acetic acid induced writhing) has been studied.[31]

A group of scientist ascertain roles of the two basic nitrogen atoms in 1-substituted 4-[2,(3-hydroxyphenyl)-1-phenylethyl]-piperazine derivatives .A methane group was added at N-1 position to obtain 4- substituted 1-[2-(3-hydroxyphenyl)-1-phenylethyl]piperidine derivatives It was concluded that the substitution at N -I contributes to the expression of narcotic antagonist activity, whereas the nitrogen atom at the 4-position corresponds for the expression of mu-opioid agonist activity.[32] N-aryl/arylalkyl 3-(1-pyrolidinyl/piperidinyl) butyramides were synthesized and tested as analgesics using hot plate method showed that analgesia produced was less potent than morphine and of shorter duration of action.[33] The analgesic studies of N-(2-octahydrobenzofurylmethyl)-n-methyl piperidine iodide were carried out and the compound showed remarkable activity. [34] Number of Piperidine derivatives showing significant analgesic activity were synthesized by different workers [35-37] one of which was proved to be a novel κ-opioid receptor selective ligand.[38] Kawamoto *et al*. in 2000 [39] synthesized 2-oxoimidazole derivatives as antagonist of nociception. These compounds were claimed to be effective as analgesic agents, narcotic antagonists, antidepressant and antiobesity agents. One of the compounds and its salt showed IC_{50} of 5.2 nM for inhibiting the binding of [^{125}I] Tyr^{14}-nociceptin to recombinant nociceptin receptor. Several novel compounds having piperidine moiety, as nociceptin/orphanin FQ receptor agonists were reported by Sabine *et al* [40] Some new compounds were designed and synthesized by optimizing the 4-amino-piperidine template. One of these compounds was demonstrated to block N-type Ca^{2+} channels with higher selectivity. The results suggested

that compound was a high selective blocker targeting N-type Ca2+ channels, and may have a potential to be developed as a novel analgesic agent.[41]

Number of peptide substituted and unsubstituted alkyl, cycloalkyl, aryl, aryloxy, benzo-fused pyrrolidinyl, piperidinyl, morpholinyl, carbamoyl-acyl derivatives have been prepared for the treatment of inflammatory diseases.[42-43] Nitrogen containing aromatic heterocyclic compounds and their salts were reported by Sasaki *et al* [44] for the treatment of pollalkiuria, urinary incontinence and inflammation. These compounds showed in vitro a maximum 66% inhibition of rhythmic contraction of mouse bladder. Many of the piperidine derivatives synthesized as metalloprotease inhibitors (Fig-4) were found effective against a wide variety of conditions notably as anti-inflammatory, antiangiogenesis and antitumor agents.[45] These compounds were also useful for the treatment of arthritis of different origin, asthma, chronic obstructive pulmonary disease, osteoporosis, migraine, peripheral neuropathy etc. and showed IC_{50} > 10,000 μM against MMP enzymes**.**

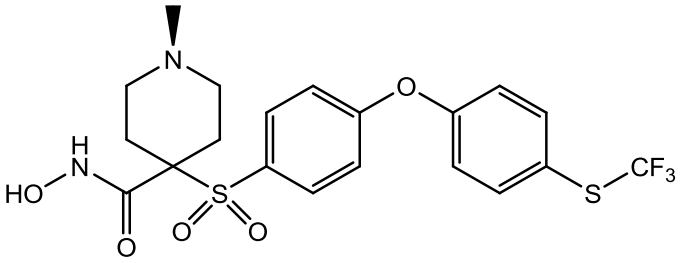


Fig-4

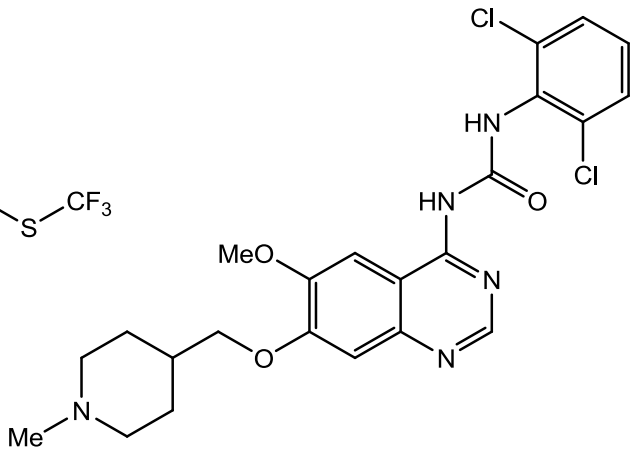


Fig-5

Some quinazolinyl ureas, thioureas and guaindine derivatives of piperidine (Fig- 5), have been reported for use to cure and or prevent T-cell mediated diseases or medical conditions such as transplant rejection or rheumatoid arthritis. These compounds exhibited IC_{50} of 0.001-10 μM in vitro T cell proliferation assay.[46] Sham *et al*., reported several heterocyclic compounds such as pyrimidine, imidazole, benzimidazole, thiazole, thiazolidine, alkanoic acid derivatives and other related heterocyclic piperidine like compounds have shown promising anti-inflammatory activity [47] Further research on this parameter may lead to more efficacious and safer anti-inflammatory drugs.

Janssen and Jageneau [48] investigated basic amides related to methadone, highest activity being found among N-pyrrolidino and dimethyl amino-amides. Dextromoramide (Fig-6) was found the most active member of series.[49-54]

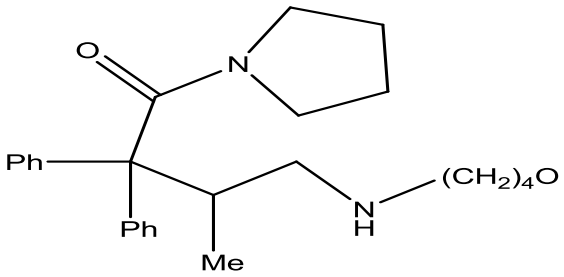
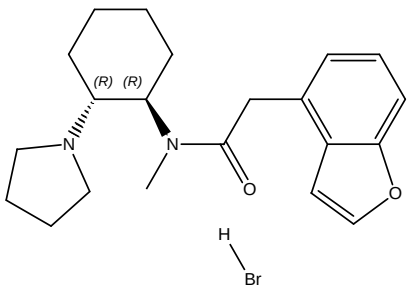


Fig-6

New analgesic compounds, which are prepared by the hydrolysis of N-acylated 4-hydroxyphenylamine derivatives, their synthesis and pharmaceutical compositions containing them are disclosed. These compounds surprisingly possess high analgesic activity with little hepatotoxic effect, making them more useful than conventional non-steroidal anti-inflammatory drugs (NSAIDs) in the treatment of chronic pain. [55]

Crooks designed number of pyrrolidine derivatives as confirmationaly restricted analogues of profadol including N-Methylspiro [5-hydroxytetralin-1, 3'-pyrrolidine] and N-methylspiro [7-hydroxytetralin-1, 3'-pyrrolidine] Spiro [tetralin-2, 2'-pyrrolidine] and spiro [6-methoxytetralin-2, 2'-pyrrolidine] for analgesic activity. Some derivatives showed good analgesic activity. [56-58]

Synthesis, structure-activity relationships (SAR) of mu and kappa opioid binding affinities, and analgesic properties of a series of novel highly selective kappa opioid N-[(2-minocyclohexyl) aryl] acetamide and N-[(2-aminocyclohexyl) aryloxy] acetamide derivatives containing pyrrolidine ring was reported. Ten compounds showed a marked kappa selectivity of greater than 100:1 over mu binding, with high affinity for the kappa opioid



(S,S-trans)-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-4-benzo[b] furanacetamide hydrobromide

Fig-7

receptor. Compound, (S, S-trans)-N-methyl-N-[2-(1-pyrrolidinyl) cyclohexyl]-4-benzo[b] furanacetamide hydro- bromide, (Fig-7) has the highest mu/kappa selectivity. [59]

Conjugate addition of pyrrolidine or piperidine to methyl crotonate, and hydrolysis of the resulting methyl butyrates gave the (+/-)-3-pyrrolidino or piperidinobutyric which were tested as analgesics using the hot-plate method. (+/-)-N-(2-Phenethyl)-3-(1-pyrrolidinyl) butyramide showed naloxone-attenuated analgesia but was considerably less potent than morphine and of shorter duration of action. In all cases, analgesia was accompanied by an inhibition of spontaneous motor activity and sedation.[60] A series of thirty 2-(3-pyridylaminomethyl) azetidine, pyrrolidine and piperidine analogues as nicotinic acetylcholine receptor (nAChR) ligands was explored. In general, pyrrolidinyl and many azetidinyl compounds were found to bind with enhanced affinity relative to the piperidines. These were about as analgesic as nicotine in a tail-flick assay in mice after subcutaneous injections.[61]

A series of glycolamide esters of niflumic acid (some containing pyrrolidine ring) have been prepared. Selected compounds were evaluated for anti-inflammatory activity in carrageenan induced paw oedema in rats at the doses of 45, 90 and 150 mg/kg. Pyrrolidine derivatives were among the compounds showed highest activity.[62]

1.5 CNS ACTIVITY

In the last few decades numbers of Piperidine and pyrrolidine compounds have been synthesized because of their significant CNS activity. Several novel derivatives of piperidine (Fig-8abc, 9) had been synthesized for their CNS potentials and proved to be effective in the treatment of psychiatric illness and other CNS disorders.[63-69]

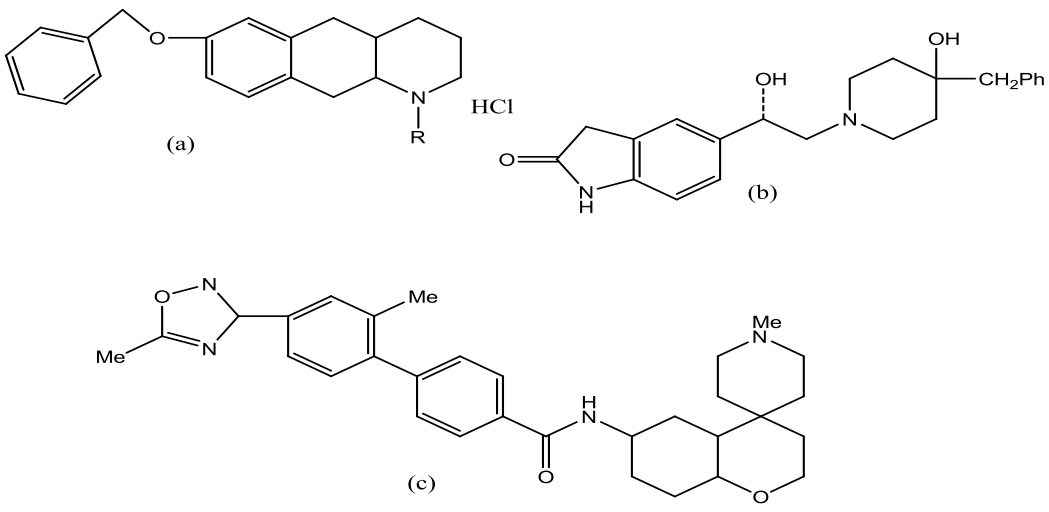


Fig-8

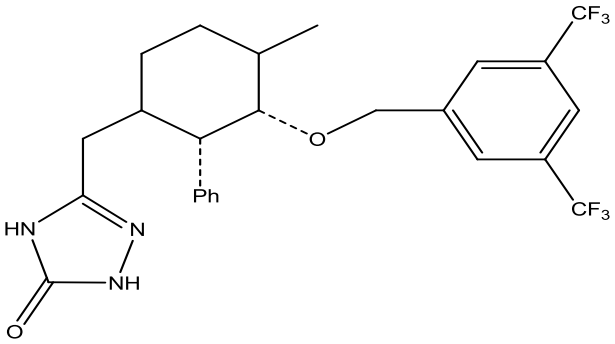


Fig-9

For having high affinity ligands for monoamine transport different derivatization have been done**.** Fourphit (4-isothiocynato-1-[1-phenylcyclohexyl] piperidine), (20mg/kg, i.v) was tested in rats for its ability to block the increased locomotor activity caused by cocaine (15or40mg/kg (-)cocaine×HCl(i.p)24 h later.[70]

Azabicycloderivatives(C-3 substituted tropane) bind with high affinity to the dopamine transporter to inhibit dopamine reuptake these compounds have much lower affinity for muscarinic-1-site at least 100 folds than benzotropine.[71] synthesis. Structure activity relationship of 4-[2-(diphenylmethoxy) ethyl]-1-benzylpiperidine analogues were studied by altering substitution in the benzyl moiety and assessed for both invivo transporter assay and *in vivo* behavioral activity measurements**.**[72]A great number of researchers prepared piperidine derivatives and explored them as monoamine oxidize (MAO), substance P, neuropeptide Y receptor and Y-5 receptor antagonists[73-76] **(**Fig. 10-13).

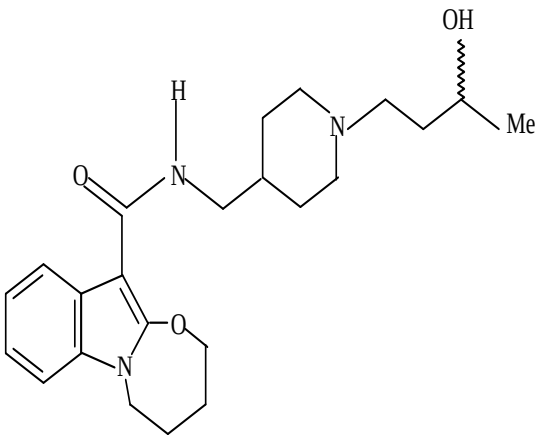
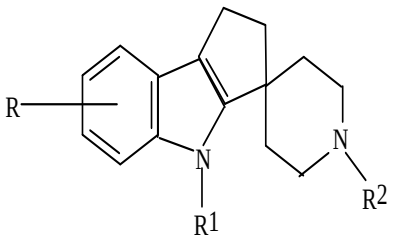


Figure: 10



R = H or 1 or 2 of holo, alkyl, aloxy et
R^1 = H or alkyl
R^2 = H, CH_2R^3, COR^3, CH_2OR^3 etc
R_3 = (Un) substituted Ph

Figure: 11

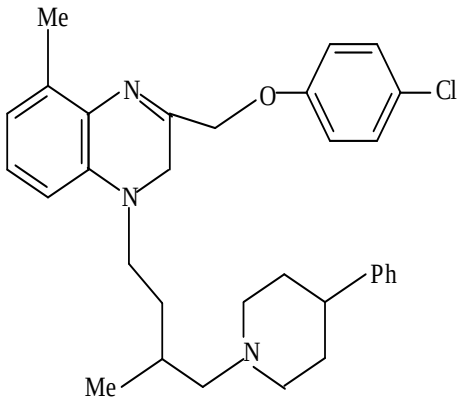


Figure: 12

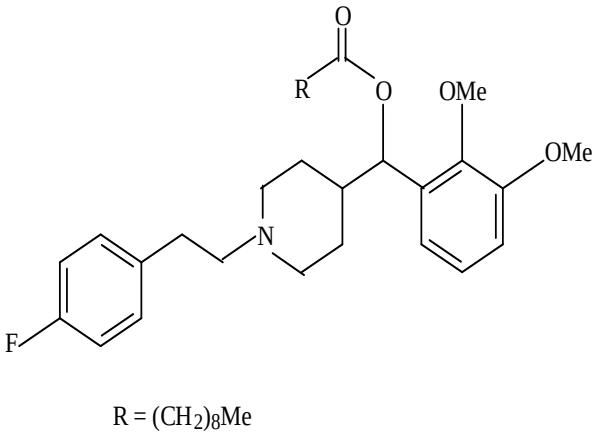


Figure: 13

Derivatizing the exocyclic N atom at the 3 position of the cis 3, 6 –di substituted piperidine derivatives to obtain substituted phenyl and heterocyclic derivatives[77-78] having the affinity for serotonin transporter (SERT), dopamine transporter (DAT), nor epinephrine transporter (NET). 3, 6 –di substituted piperidine converted to pyran derivatives that exhibited greater activity for the dopamine transporter compared to transisomer.[79]

A series of 3-carboxamide, indazole-3-carboxamides and benzimidazolene-3-carboxamides was synthesized and evaluated for antagonist affinity at the 5-HT4 receptor in the rat esophagus and observed that by the N-alkylation of the aromatic heterocycle further increases the 5HT4 receptor antagonistic activity.[80] 4-(Phenylsulfonyl) piperidine; a series of acyclic sulfones have been identified as high-affinity, selective 5-HT (2A) receptor antagonists.[81] Scientists have discovered that introduction of two methyl groups on the piperidine ring brought about a dramatic change in the pharmacological profile of 2-[(cis- and trans-3, 5-dimethyl)-piperidinyl) ethyl]-4-amino-5-chloro-2-methoxybenzoate (Fig.14, inhibiting the relaxant action of 5-HT on rat esophagus muscles.[82]

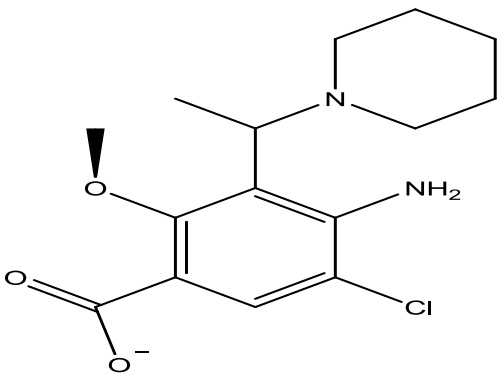


Figure: 14

4-(6-Fluorobenzioxozol-3-yl) piperidine was reported having 5HT-antagonist activity.[83] Piperidinylethylamide derivatives (figure-14) were observed having $5HT_{1A}$ antagonists or partial agents with additional antihistaminic activity and are useful as anxiolytic agents.[84]

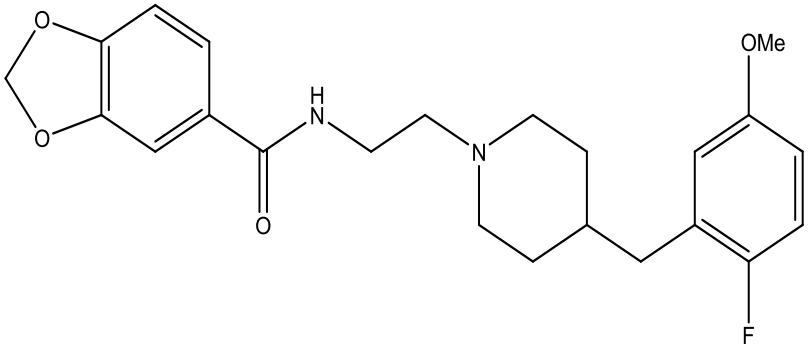
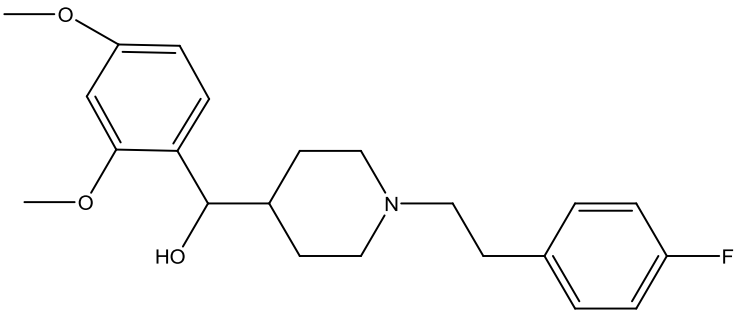


Fig: 15

Recently, a new class of 5-heteroaryl-substituted 1-(4-flourophenyl)-1H-indole as highly selective and potential CNS active α1 adrenoceptor agonist was described by Thomas *et al*.[85] In the rat microdialysis assay, a number of highly potent M2 receptor antagonists with >100-fold selectivity against the M1 and M3 receptor subtypes is design and synthesize which showed pronounced enhancement of brain acetylcholine release after oral administration.[86] Diphenylsulfone muscarinic antagonists with high selectivity and improved potency for the M2 receptor have been identified. Compounds of this class may be useful for the treatment of cognitive disorders such as Alzheimer's disease (AD).[87]

A series of benzo[h] [1, 6] naphthyridine and azepino [3, 2-c] quinoline derivatives were prepared by substituting the chlorine atom of benzonaphthyridines and azepinoquinolines with various N-alkyl-4-piperidinylmethanolates as selective antagonist of 5-HT4 receptors.[88] A great number of researchers prepared piperidine derivatives **(**Fig-16) as neuroactive agents and found to be potent 5-HT2A receptor antagonists.[89-90] They have explored effectiveness of these derivatives in treating various conditions such as psychoses and schizophrenia.[91]



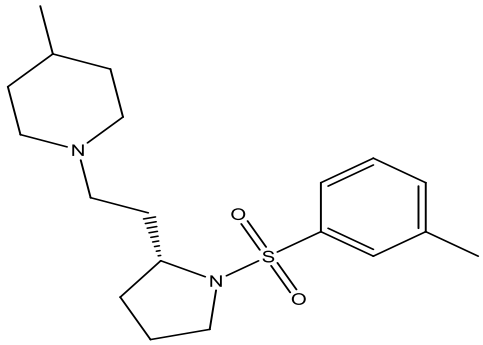
R-(+)-α-(2, 3-dimethoxy-phenyl)-1-[2-(4-flouro phenyl)] – 4 piperidine methanol

Fig: 16

Piperidine carboxylic acid derivatives have been evaluated as potential anticonvulsants.[92] The inhibitory potency of 1, 2, 3-trimethyl-3-(3-hydroxyphenyl)-piperidine on electric eel and rat brain acetylcholinesterase (AChE) and horse serum butyrylcholinesterase (BuChE) was investigated.[93]

In search of potential therapeutic compounds for different CNS disorders pyrrolidine nucleus has been received a great interest because of the encouraging results they showed when evaluated for different CNS studies.[94-101]

6-((R)-2-[2-[4-(4-Chloro-phenoxy)-piperidin-1-yl]-ethyl]-pyrrolidine-1-sulpho-nyl)-1H-indole hydrochloride) is a novel 5-hydroxytryptamine (5-HT (7) receptor antagonist. The compound displayed at least 30-fold selectivity for the human 5-HT (7a) receptor versus other human cloned 5-HT receptors apart from the 5-HT (1D) receptor.[102] In a study, a systematic modification of the substituents on the aminopyrrolidine ring was performed, to afford several compounds with high affinity and selectivity for the H (3) receptor.[103]

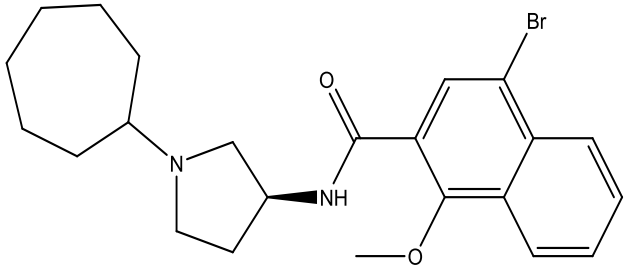


R-(+)-1-(toluene-3-sulfonyl)-2-[2-(4-methylpiperidin-1-yl)ethyl]-pyrrolidine

Fig-17

A series of 5-HT7 receptor antagonists have been developed. Among them R-(+)-1-(toluene-3-sulfonyl)-2-[2-(4-methylpiperidin-1-yl)ethyl]-pyrrolidine, (Fig-17) was one of the most potent and specific compounds.[104]

A series of naphthamides having pyrrolidine and piperidine ring were synthesized, and the affinities of these compounds were determined for dopamine D2 and D3 receptors using radio ligand binding techniques. The most potent analogue in this series was (S)-N-(1-cycloheptylpyrrolidin-3-yl)-4-bromo-1-methoxy-2-naphtha-mide (Fig-17) while the most selective analogue was (R)-N-(1-cycloheptyl-2-pyrrolidinylmethyl)-4-bromo-1-methoxy-2-naphthamide (fig- 18).[105]



(S)-N-(1-cycloheptylpyrrolidin-3-yl)-4-bromo-1-methoxy-2-naphthamide

Fig-18

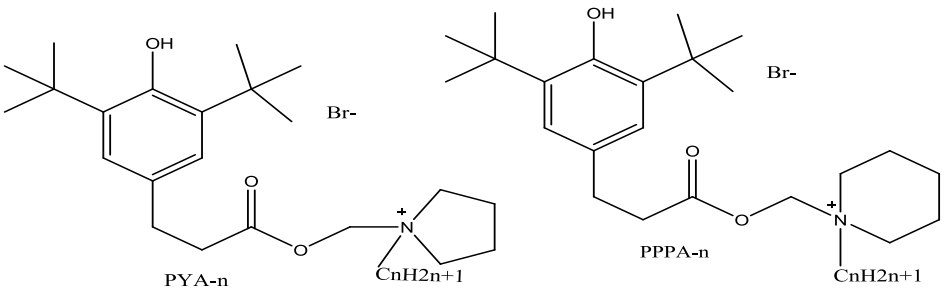
1.5 Antioxidant Activity

Piperidine and pyrrolidine analogue were studied for antioxidant activity and majority of the compounds in different studies showed good results.[106-107]

Nerve growth factor (NGF) differentiated pheochromocytoma PC12 cells exposed to 1-methyl-4-phenylpyridinium (MPP+) toxin were used as an *in vitro* pharmacological model of Parkinson's disease to examine the neuroprotective effects of 4-hydroxy-2,2,6,6-tetramethyl piperidine-n-oxyl (Tempol), a free radical scavenger and a superoxide dismutase-mimetic compound. The result obtained supports the neuroprotective effect of Tempol in the MPP+-induced PC12 cell death model and its use as a potential drug for treatment of Parkinson's disease.[108]

Piperidine nitroxide TEMPOL, which has an antioxidant activity, was combined with UV absorber, 2-ethyl hexyl – 4- methoxy cinnamate (OMC). The spectral properties of the new nitroxide-based sunscreen (MC-NO) as well as its efficacy to prevent photo-oxidative damage to lipids induced by UVA, natural sunlight and 4-tert-butyl-4-methoxydibenzoylmethane (BMDBM), a photo-unstable sunscreen which generates free radicals upon UV radiation, was studied. The results obtained demonstrate that MC-NO: (a) absorbs in the UVB region even after UVA irradiation; (b) acts as free radical scavenger as demonstrated by EPR experiments; (c) strongly reduces both UVA-, sunlight- and BMDBM-induced lipid peroxidation in liposomes, measured as reduced TBARS levels; and (d) has comparable antioxidant activity to that of commonly used vitamin E and BHT in skin care formulations.[109] Piperidine and pyrrolidine derivatives comprising a nitric oxide (NO) donor and a super oxide ion (O_2^-) scavenger are used in the treatment of conditions associated with oxidative stress or endothelial dysfunction.[110]

High-level ab initio calculations have been used to determine the oxidation and reduction potentials of a large number of nitroxides including derivatives of piperidine, pyrrolidine, substituted with COOH, NH_2, NH_3^+, OCH_3, OH, and NO_2 groups. Piperidine and pyrrolidine derivatives have intermediate oxidation potentials but on average pyrrolidine derivatives display more negative reduction potentials. Within a ring, the substituents have a relatively small effect with electron donating groups such as amino and hydroxyl groups stabilizing the oxidized species and electron withdrawing groups such as carboxyl groups stabilizing the reduced species, as expected.[111] Two series of pyrrolidinium (PYA-*n*) and piperidinium (PPPA-*n*) bromides (Fig-19) with incorporated antioxidant function were synthesized. Both have hydrocarbon chains with odd number of the carbon atoms (*n*) ranging between 7 and 15. Two series of pyrrolidinium and piperidinium bromides with incorporated antioxidant function were synthesized. Both have hydrocarbon chains with odd number of the carbon atoms (n) ranging between 7 and 15. Erythrocytes (RBC) were used to study antioxidant activity of these compounds. The measurements showed that pyrrolidinium bromides were slightly more effective in a protection of erythrocytes than the corresponding piperidinium ones. The possible reason of such behaviour may be the difference in lipophilicity between piperidine and pyrrolidine rings.[112]



n=7,9,11,13,15

Fig-19

The measurements showed that pyrrolidinium bromides were slightly more effective in a protection of erythrocytes than the corresponding piperidinium ones. The possible reason of such behaviour may be the difference in lipophilicity between piperidine and pyrrolidine rings.[113] Previous studies on Adriamycin (ADR) cardiotoxicity have reported that the formation of free reactive oxygen radicals might be involved in ADR cardiotoxicity. Pyrrolidine dithiocarbamate (PDTC) is a potent antioxidant *in vivo* and *in vitro*. This study was undertaken to examine the effects of PDTC on antioxidant enzymes in cardiomyopathy induced by ADR in rats. PDTC prevented ADR cardiomyopathy in rats by upregulating

Glutathione peroxidase (GSH-Px) and superoxide dismutase activation, which is associated with changes in the expression of GSH-Px and Mn-SOD transcript and protein levels. [114]

1.6 Antihistaminic Activity

A series of indolylpiperidinyl derivatives (Fig-20) were synthesized and evaluated for their activity as histamine H_1 antagonist activity. Substitution of fluorine in position 6 on the indolyl ring led to higher *in vivo* activity in the inhibition of histamine-induced cutaneous vascular permeability assay but lower selectivity toward $5HT_2$ receptor. Extensive optimization was carried out within this series and a number of histamine H_1 antagonists showing potency and long duration of action *in vivo* and low brain penetration or cardiotoxic potential were identified.[115]

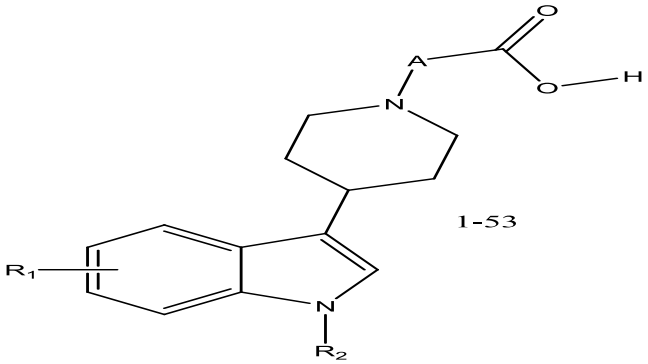


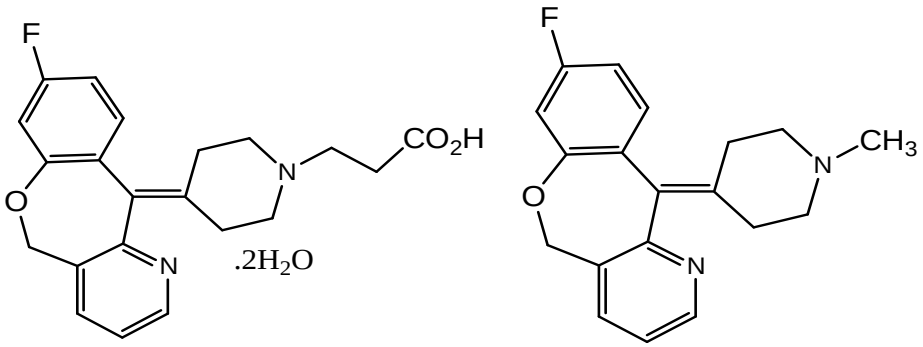
Fig-20

R_1: H, halogen, OMe, Me,

R_2: alkyl, alkoxyalkyl, heteroarylalkyl

A: alkoxyaryl, alkylaryl, alkylaryl, alkylheteroaryl

The pharmacological characteristics of HSR-609 (3-[4-(8-fluoro-5,11-dihydrobenz[b]oxepino[4,3-b]pyridin-11-ylidene)-piperidino]propionic acid dihydrate), a novel amphoteric antiallergic agent, on the central nervous system (CNS) was studied and Its selectivity for the histamine H1-receptor and its ability to penetrate into the CNS were compared with nonamphoteric basic compound PY-608(8-fluoro-5,11-dihydro-l l-(1-methyl-4-piperidylidene)benz[b]oxepino[4,3-b]pyridine), which has a chemical structure similar to that of HSR-609 (Fig-21). It was found that HSR-609 has high selectivity for the H1-receptor and poor ability to penetrate into the CNS in mice and guinea pigs due to its amphoteric chemical structure.[116]



HSR-609 **PY-608**

Fig-21

1.7 Cytotoxic Activity

Piperidine and pyrrolidine derivatives have also been found possessing cytotoxic activity and anti-HIV activity. In 1-(1-methyl-4-piperidinyl)-1H-indole cyclocondensed with iso-pr-1-methyl-3-indolylacetimidate (Fig-22) had IC_{50} of 0.02 and 0.01μM against β_1 and β_2 isoenzyme of protien kinase C, respectively.[117]Gariboldi reported the study of Tempol (4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl; TPL), a stable nitroxide free radical, inhibits the growth of C6 glioma cells both *in vitro* and *in vivo*[118] treatment with TPL induced a significant dose-dependent decrease in tumour growth, without signs of general or organ toxicity.

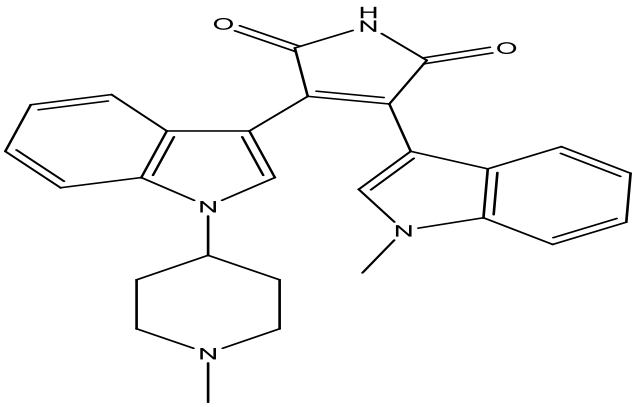


Fig-22

A series of platinum (II) complexes of the type [Pt (II) (mmap) X] (where mmap, 1-methyl-4-(methylamino) piperidine and X, 1, 1-cyclobutanedicarboxylato (CBDCA), oxalato, malonato, methylmalonato, dimethylmalonato, ethylmalonato, diethylmalonato or 2, 3-naphthalene dicarboxylato (NDCA)) have been synthesized. The complexes were evaluated for their cytotoxic potential against the sensitive A2780 tumor model and cisplatin-resistant clone derived *in vitro* from potential cells.[119]

Chemotherapeutic compounds for the treatment of cancer containing substituted piperidine and pyrrolidine analogues have been reported some of them having farnesyl protien transferase inhibiting activity.[120-123] Fujawara and coworkers[124] described the formation of more than 300 compounds prepared by condensation of acetophenone with Ethyl 1-benzoyl isonipecotate using NaH and THF. Their pharmaceutically acceptable salts were effective for inhibiting the secretion of tumor necrosis factor (TNF). Another group reported the preparation of 5-aminoindenol [1,2-c]-cyclopyrazol-4-ones as anticancer and antiproliferative agent.[125]

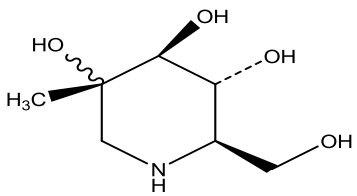
A novel class of protein tyrosine kinase, kinase C and cyclin kinase inhibitors have been synthesized from Piperidine.[126-128] Kinase inhibitors are useful for the treatment of proliferative diseases. In another study Hauer and his fellows[129] have synthesized and studied the arylcarbonyl, alkylcarbonyl, alkoxyalkyl, pyrrolidinyl, morpholinyl and piperidinyl derivatives showing 31-100 % α_1 antagonism at 100 nM and at 100 μM inhibited proliferation of NIH-3T3 mouse fibroblast by 33-100%. The activation of nuclear factor-kappa B (NF-kappa B) has been implicated in the development, progression and metastasis of renal cell carcinoma (RCC).The effect of pyrrolidine dithiocarbamate (PDTC), a NF-kappa B inhibitor, on two metastatic human RCC cell lines, ACHN and SN12K1 was investigated. Invesatigation suggested that PDTC has the potential to be an anticancer agent in some forms of RCC.[130] Search for more potent and effective compounds in this direction is going on.

1.8 Antimicrobial Activity

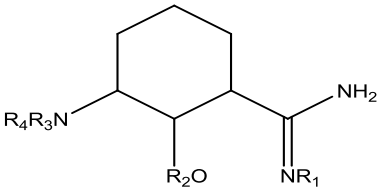
The synthesis of a new series of 1ββ-methylcarbapenems having a 5-(1,2-disubstituted ethyl) pyrrolidine moiety is described. Their *in vitro* antibacterial activities against both Gram-positive and Gram-negative bacteria were tested and the effect of the substituent on the pyrrolidine ring was investigated. A particular compound IIIf having a 1-methoxyimino-2-carbamoylethyl substituted moiety showed the most potent antibacterial activity.[131]

Pyrrolidine dithiocarbamate (PDTC) has been studied for antimicrobial activity against various bacteria. The antibacterial activity of PDTC was evaluated *in vitro* by the broth microdilution method against *Porphyromonas gingivalis*, *Actinobacillus actinomycetemcomitans*, *Staphylococcus aureus*, and *Escherichia coli*. Bacterial growth was inhibited by PDTC, where a wide range of sensitivity was demonstrated among the tested bacteria. The antibacterial activity of PDTC was reduced by the addition of copper chloride;

in contrast, it was enhanced considerably by zinc chloride. These results demonstrated for the first time that PDTC possesses an antibacterial activity, for which zinc is required, and suggest that PDTC, possessing a dual anti-inflammatory and antibacterial activity, may be considered for topical use for inflammatory diseases of bacterial origin.[132] Antimicrobial, anti-fungal and antiviral activity of numbers of piperidine and pyrrolidine derivatives was evaluated. Another group of workers synthesized an imidazole derivative of piperidine (Fig-23a, b) and investigated it as a member of novel class of antitumour agents, exhibited direct macrophage-induced cytotoxicity against a variety of marine tumor cell lines.[133] Scientists reported useful inhibitors of both farensyl protein transferase and geramyl protein tranferase in the treatment of cell proliferative diseases.[134] Similarly 1-amidino-3-amino-2-hydroxy piperidine derivatives and 1,5-dideoxy-1,5-(alkylimino-2-C-methyl-D-glucitols[135-136] possess-ed antiviral activity. Some other compounds also reported having anti fungal and antiviral activity.[137]



(a)

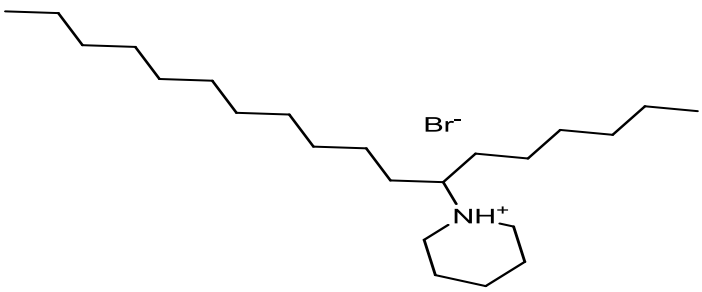


(b)

R1= Guanidinoprotecting group
R2|= alkyl, aryl, acyl,
R3 = R4 = H, alkyl,aryl,acyl

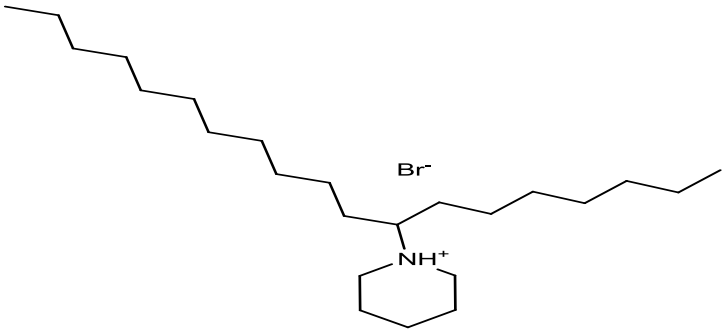
Fig-23a, b

Antimicrobial activity of N-alkyl-N-dodecylpiperidinium bromides and N-ethyl-N-dodecylheterocycloalkyl ammonium bromides (pyrrolidine, morpholine, perhydroazepine) determined on Gram-positive and Gram-negative bacteria, yeasts and moulds. The most active compounds were N-heptyl-and N-hexyl-N-dodecylpiperidinium bromides (Fig-24, 25).[138]



N-hexyl-N-dodecyl piperidinium bromide

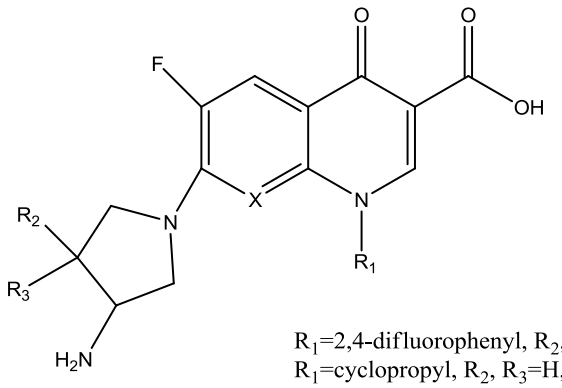
Fig-24



N-heptyl-N-dodecyl piperidinium bromide

Fig-25

Novel quinolone antibacterials, which bear an alkyloxime substituent in the 4-position and an amino methyl substituent in the 3-position of the pyrrolidine ring, have been designed and synthesized (Fig-21). These fluoroquinolones were found to possess extremely potent antimicrobial activity against Gram-positive organisms including resistant strains such as methicillin-resistant *Staphylococcus aureus* (MRSA).[139-140]



R_1=2,4-difluorophenyl, R_2, R_3=H, X=N
R_1=cyclopropyl, R_2, R_3=H, X=CCl
R_1=-2-fluorocyclopropyl, R_2,R_3=CH_2CH_2, X=CCL

Fig: 26

Several amides, mainly those bearing isobutyl, pyrrolidine, dihydropyridone and piperidine moieties were isolated. Bioactivity-guided fractionation of extracts from leaves of Piper arboreum yielded two new amides, N-[10-(13,14-methylenedioxyphenyl)-7(E),9(Z)-pentadienoyl]-pyrrolidine, arboreumine together with the known compounds N-[10-(13,14-methylenedioxyphenyl) -7 (E)-pentaenoyl]- pyrrolidine and N-[10-(13,14-methylenedioxyphenyl) -7(E),9(E)-pentadienoyl]-pyrrolidine. Catalytic hydrogenation of 3 yielded the amide N-[10-(13,14-methylenedioxyphenyl)-pentanoyl]-pyrrolidine. All Compounds showed antifungal activity as determined by direct bio autography against *Cladosporium sphaerospermum* while compounds N-[10-(13, 14methylenedioxyphenyl)-

7(E)-pentaenoyl]-pyrrolidine and N-[10-(13,14-methylenedioxyphenyl)-7(E),9(E)-pentadienoyl]-pyrrolidine showed antifungal activity against C. cladosporioides15.[141]

1.9 Other Activities

A variety of piperidines (2–12, 14–26) with variable substituents at N -atoms have been synthesized and evaluated as urease inhibitors. The synthesized compounds showed varying degree of urease inhibitory activity ranging from 31.97 to 254Mm.[142] Piperidine alkaloid, piperine, isolated from the ethanol extract from the fruits of *Piper longum* was synthesized and show monoamine oxidase (MAO) inhibitor activity.[143]

Fused piperidine substituted aryl sulfonamides are &#x0b32$_3$ adrenergic receptor agonists with very little &#x0b32$_1$ and &#x0b32$_2$ adrenergic receptor activity and as such the compounds are capable of increasing lipolysis and energy expenditure in cells. The compounds thus have potent activity in the treatment of Type II diabetes and obesity. The compounds can also be used to lower triglyceride levels and cholesterol levels or raise high density lipoprotein levels or to decrease gut motility. In addition, the compounds can be used to reduced neurogenic inflammation or as antidepressant agents.[144]

The *N*-methylpyrrolidine (Fig- 27) has been isolated[145] from tubers of *Arisarum vulgare Targ.*(Araceae). This compound was active in the brine shrimp assay showing an LC50 of 1.5 μg ml^{-1}

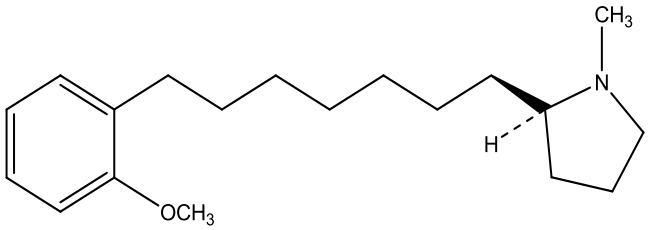


Fig- 27

A whole series of broussonetines A–L and broussonetinines A and B have been isolated by extraction from branches of *Broussonetia kazinoki* (Oriental tree, termed ‘himekouzo’ in Japan). These compounds have a common functionalized pyrrolidine ring system: broussonetinines A–F **28-35** [146-148] differ only in stereochemistry at C-3 and in the functionalisation along the long hydrocarbon chain at the 5-alkyl position of the pyrrolidine ring. All of these compounds are strong inhibitors of α- and β-glucosidase, β-galactosidase and α and β-mannosidase enzymes and they display different selectivities for the different enzymes.

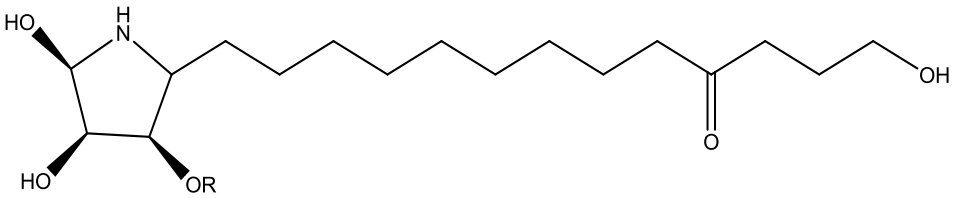


Fig- 28 R= β- D- glucopyranosyl brousonetine A

Fig- 29 R= H broussonetinine A

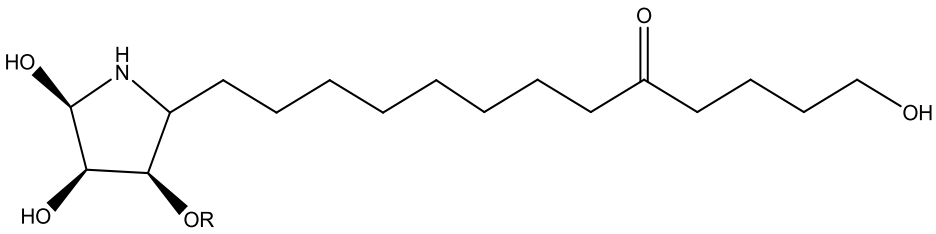


Fig – 30 R= β- D- glucopyranosyl brousonetine B

Fig – 31 R= H broussonetinine B

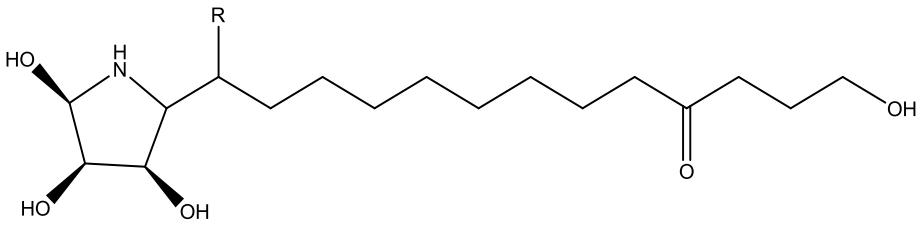


Fig – 32 R= H broussonetinine C

Fig – 33 R= H broussonetinine E

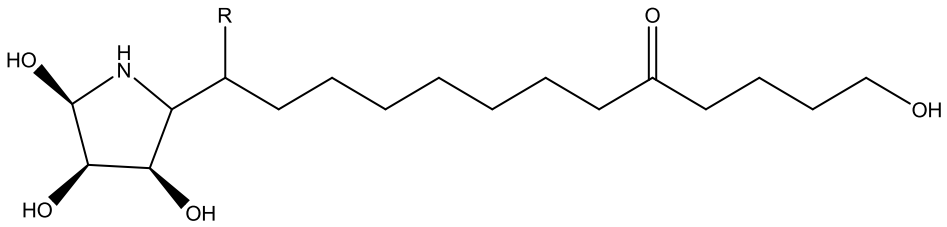


Fig – 34 R= H broussonetinine D

Fig – 35 R= H broussonetinine F

Adenine, guanine, thymine and cytosine monomers of oxy-peptide nucleic acid that contain a pyrrolidine ring in the main chain have been synthesized for use in the synthesis of novel peptide nucleic acid.[149]Piperidine containing moieties were also evaluated for number of other activities and the results obtained displayed good results.[150-152] Taking into account the potential pharmacological activities, it is significant to prepare some new derivatives of 4-(1-pyrrolidinyl) piperidine moiety and explore the potential of these compounds for different activities.

Table of summarized activity profile

ACTIVITY		COMPOUND NO.					
		1	**2**	**3**	**4**	**5**	**6**
Analgesic activity		-	+ + + +	+ + + +	+ + + +	+ + + +	-
Antioxidant activity	DPPH Radical Scavenging Assay	-	-	-	-	-	-
	Superoxide Scavenging Assay	-	-	-	-	-	+
Antibacterial activity	Gram positive	-	-	+	+ + +	-	+ + + +
	Gram negative	+ +	+	-	+ +	-	+ + + +
Antifungal activity		+ + +	-	-	+ +	-	+ + + +
Enzyme Inhibition	β-glucoronidase inhibition activity	-	+ + +	+ +	+ +	-	+
	Urease inhibition activity	-	-	+ +	-	-	-
Brine shrimp activity		-	+ +	-	-	-	-
Cytotoxic Activity	Using 3T3 Cell		-	+ + +	-	-	+ + + +
	Using PC-3 Cell	-	-	-	-	-	-

- = no activity

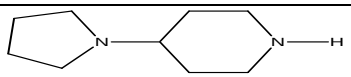
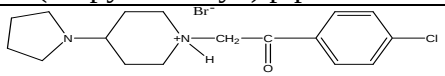
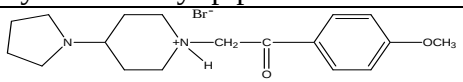
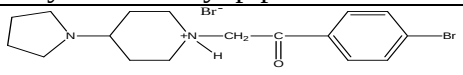
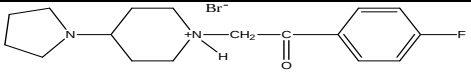
+ = very weak activity

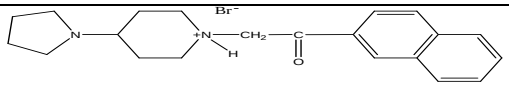
+ + = weak activity

+ + + = good activity

+ + + + = very good activity

List of compound

Compound no.	Structures with IUPAC name
1	 4- (1- pyrrolidinyl) piperidine
2	 1-[2-(4″-chloro-phenyl)-2-oxo-ethyl]- 4-Pyrrolidin-1′-yl-piperidi-nium bromide
3	 1-[2-(4″-methoxy-phenyl)-2-oxo-ethyl]-4-Pyrrolidin-1′-yl piperidi-nium bromide
4	 1-[2-(4″-bromo-phenyl)-2-oxo-ethyl] 4-Pyrrolidin-1´-yl-piperidi-nium bromide
5	 1-[2-(4″-floro-phenyl)-2-oxo-ethyl]- 4-Pyrrolidin-1′-yl piperidi-nium bromide

6	 4-Pyrrolidin-1´-yl-1-[2-naphthalen-2-yl-2-oxo-ethyl]-piperidinium bromide

CONCLUSION

Heterocyclic play an important role in biochemical processes. Heterocyclic compounds have upheld the interest of researchers through decades because of their biological activities and unique structures that led to several applications in diverse areas of agrochemical research, pharmaceutical and material sciences. Pyrrolidine and piperidine are the most important and well known heterocyclic compounds which are common and integral feature of a variety of natural products and medicinal mediator. Pyrrolidine and piperidine nucleus are present as a core structural component in various drugs, and become the main cause of interest for pharmacists due the vast and significance range of promising biological activities since last few decades. Thus the pyrrolidine and piperidine nucleus could be considered as the magic potion for the management of various diseases. The present review is an attempt to appraise the different biological activities reported for pyrrolidine and piperidine heterocyclic in the existing literature with an update of recent research findings on these nuclei.

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Kindly check the reference no mention in literature as well as in references

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