



## The Importance of Six Membered Saturated Nitrogen Containing Ring in Psychological disorders

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### ABSTRACT

CNS disorders have been estimated approximately up to 20% of the nationwide cost of healthcare in the developed countries, Because of various socioeconomic problem in developed as well as developing country the number of patient related to psychological disorder are increasing day by day. Various survey projections indicate that sales of drugs to treat neurological diseases and other CNS drugs will approach more that \$70 billion and that expected to approach up to \$ 225 billion in next five years reflecting an absence of effective treatments for another years. The current review is focused on the account of six membered saturated ring containing nitrogen heteroatom. Of which many of the successful drugs are having piperazine and piperidine ring as pharmacophore.

**Key words:** psychological disorders, neurological disorders, piperazine, piperidine.

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### INTRODUCTION

A Psychological disorder or mental illness is a psychological or behavioral pattern that occurs in an individual and is thought to cause distress or disability that is not expected as part of normal development or culture. The recognition and understanding of mental disorders has changed over time and across cultures. Definitions, assessments, and classifications of mental disorders can vary, but guideline criteria listed in the ICD, DSM and other manuals are widely accepted by mental health professionals. Categories of diagnoses in these schemes may include dissociative disorders, mood disorders, anxiety disorders, psychotic disorders, eating disorders, developmental disorders, personality disorders, ambulatory disorders and many other categories. In many cases there is no single accepted or consistent cause of mental disorders, although they are often explained in terms of a diathesis-stress model. Mental disorders have been found to be common, with over a third of people in most countries reporting sufficient criteria at some point in their life. Services for mental disorders may be based in hospitals or in the community. Mental health professionals diagnose individuals using different methodologies, often relying on case history and interview. Psychotherapy and psychiatric medication are two major treatment options, as well as supportive interventions and self-help. Treatment may be involuntary where legislation allows. Several movements campaign for changes to services and attitudes. [1]

#### Various Psychological disorders include:

- Schizophrenia.
- Depression.
- Anxiety & Panic Disorders.
- Hallucination.
- Illusion.
- Insomnia.
- Body Dysmorphic Disorder.
- Signs of Mental illness.

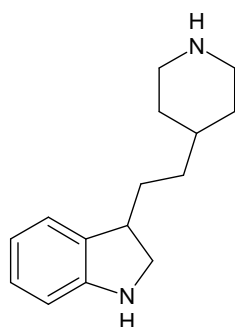
- Suicide
- False Memory

### Drug designing for CNS drugs

The CNS is functionality far more complex than any other system in the body so the drugs that act at CNS level it is difficult to understand its mechanism clearly. Nearly all the substances entering the brain have to pass through the endothelial cell membranes, that is, through the blood–brain barrier. This makes it more difficult for polar substances to enter the brain unless they are actively transported. Consequently, this factor must be taken into account when designing drugs to target the brain. In general as a result, the lipid solubility increases the drug easily diffuses through blood–brain barrier and gives its effect. Another factor is the fact that the blood–brain barrier also contains enzymes that protect the brain. Consequently, this factor must be taken into account when designing drugs to target the brain. [2] A heterocyclic compound is a cyclic compound which has atoms of at least two different elements as members of its ring(s).[3] The counterparts of heterocyclic compounds are homocyclic compounds, the rings of which are comprised of a single element. Although heterocyclic compounds may be inorganic, most contain at least one carbon atom, and one or more atoms of elements other than carbon within the *ring structure*, such as sulfur, oxygen or nitrogen.[4] Since in organic chemistry non-carbons usually are considered to replace carbon atoms, they are called heteroatoms, meaning different from carbon and hydrogen (rings comprised of heteroatoms of the same element are homocyclic). Heterocyclic rings systems that are formally derived by fusion with other rings, either carbocyclic or heterocyclic, have a variety of common and systematic names. For example, with the benzo fused unsaturated nitrogen heterocyclic, pyrrole provides indole or isoindole depending on the orientation. The pyridine analog is quinoline or isoquinoline. For azepine, benzazepine is the preferred name. Similarly, the compounds with two benzene rings fused to the central heterocyclic are carbazole, acridine, and dibenzoazepine.

**Piperazine:** Piperazine was originally named because of their chemical similarity with piperidine, a constituent of piperine in the black pepper plant (*Piper nigrum*). It is important to note, however, that Piperazine is not derived from plants in the *Piper* genus. [5] Piperazine is freely soluble in water and ethylene glycol, but insoluble in diethyl ether. It is a weak base with a  $pK_b$  of 4.19; the pH of a 10% aqueous solution is 10.8-11.8. Piperazine readily absorbs water and carbon dioxide from the air. Although many Piperazine derivatives occur naturally, Piperazine itself can be synthesized by reacting alcoholic ammonia with 1,2-dichloroethane, by the action of sodium and ethylene glycol on ethylene diamine hydrochloride, or by reduction of pyrazine with sodium in ethanol. Six membered ring containing two opposing nitrogen atoms. Piperazine exists as small alkaline deliquescent crystals with a saline taste. The Piperazine is a broad class of chemical compounds, many with important pharmacological properties, which contain a core Piperazine functional group. Piperazine is also a fluid used for CO<sub>2</sub> and H<sub>2</sub>S scrubbing in association with methyl diethanolamine. Most of these agents can be classified as either phenyl piperazines, benzyl piperazines, diphenylmethyl piperazines (benzhydrylpiperazines), pyridinylpiperazines, pyrimidinyl piperazines, or tricyclics (with the piperazine ring attached to the heterocyclic moiety via a side chain).[6]

### Indalpine:



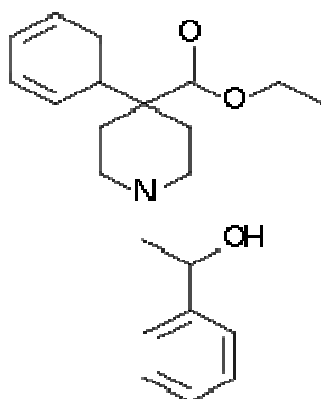
**Fig: (01) 03-[2-(piperidin-4-yl) ethyl]-2, 3-dihydro-1H-indole**

**Piperidine:** Piperidine other names hexahydropyridine azacyclohexane pentamethyleneamine azinane. Piperidine (azinane after the hantzsch Weidman nomenclature) is an organic compound with the molecular formula (CH<sub>2</sub>)<sub>5</sub>NH. This heterocyclic amine consists of a six-membered ring containing five methylene units and one nitrogen atom. It is a colorless fuming liquid with an odor described as ammoniacal, pepper-like;[7] the name comes from the genus name *Piper*, which is the Latin word for pepper.[8] piperidine is a widely used building block and chemical reagent in the synthesis of organic compounds, including pharmaceuticals. A significant industrial application of piperidine is for the production of dipiperidinyl dithiuram tetrasulfide, which is used as a rubber vulcanization accelerator.[9][10] Otherwise piperidine and its derivatives are ubiquitous building blocks in the synthesis of

pharmaceuticals and fine chemicals. The piperidine structure is e.g. found in the pharmaceuticals paroxetine, risperidone, methylphenidate, raloxifene, minoxidil, thioridazine, haloperidol, droperidol, mesoridazine, meperidine, melperone the psychochemical agents Ditrans-B (JB-329), N-methyl-3-piperidyl benzilate (JB-336) and in many others. Piperidine is also commonly used in chemical degradation reactions, such as the sequencing of DNA in the cleavage of particular modified nucleotides. Piperidine is also commonly used as a base for the deprotection of amino acids used in solid-phase peptide synthesis.[11]

Indalpine (Upstene, LM-5008) is a 4-alkyl-piperidine derivative that was developed in 1977 as a serotonergic antidepressant drug by a small Paris based pharmaceutical firm Pharmuka, a subsidiary of Fournier Freres, one of the oldest and most respected pharmaceutical houses in France. Citalopram (Lundbeck) and Zimelidine (Astra Pharmaceuticals) were developed in the early 70's, but Indalpine was the first to achieve marketing approval and commercial availability in or about 1982. A selective serotonin reuptake inhibitor (SSRI), Indalpine was one of three different serotonergic molecules (along with viqueline and pipequeline) developed by the pharmacologists Le Fur and Uzdán at Pharmuka based on the findings by shopsin *et al.*[12]

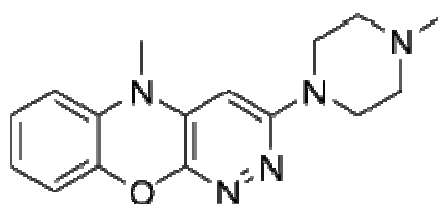
#### Oxpheneridine:



**Fig:(02) Ethyl-1-(2-hydroxy-2-phenylethyl)-4-phenylpiperidine-4-carboxylate**

Oxpheneridine Carbamethidine is a 4-phenylpiperidine derivative that is related to the opioid analgesic drug pethidine (meperidine). In Canada, Oxpheneridine is specifically excluded from the illegal drugs list on the Controlled Drugs and Substances Act schedules, presumably on the basis of the lack of addictive potential found by the UNODC. Canada also lists "Carbamethidine" as another excluded drug on its schedule, but this appears to be a double entry as the chemical name listed for carbamethidine is actually the chemical name of oxpheneridine, and the chemical name given for oxpheneridine on the Canadian drug schedules is chemically incorrect and does not correspond to a compound that could exist.[13][14]

#### Pipofezine:



**Fig: (03) 5-methyl-3-(4-methylPiperazine-1-yl) pyridazino [3, 4-b][1,4] benzoxazine**

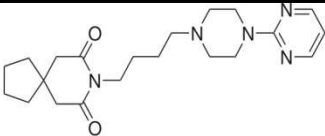
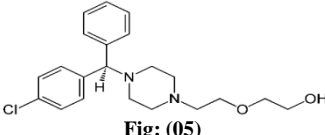
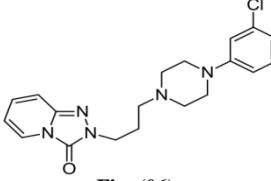
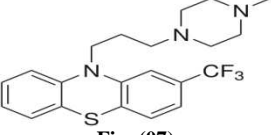
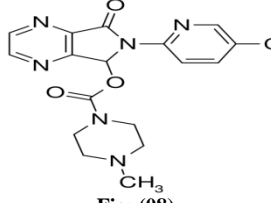
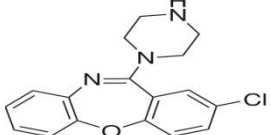
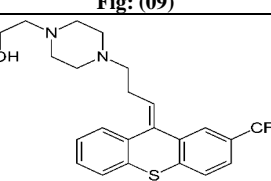
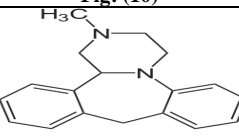
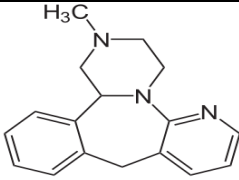
Pipofezine (Azafen or Azaphen) is a tricyclic antidepressant (TCA) approved in Russia for the treatment of depression. [15][16][17][18]

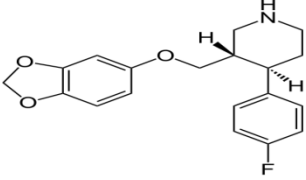
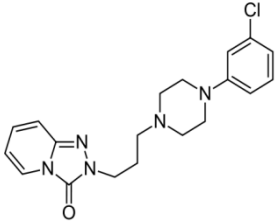
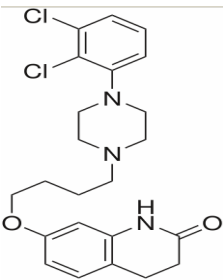
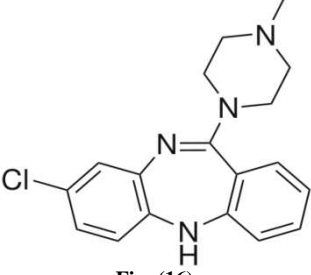
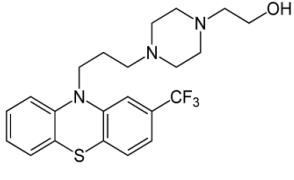
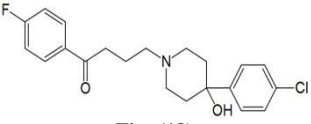
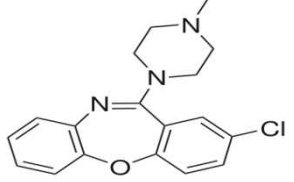
It was introduced in the late 1960s and is still used today. [19][20]

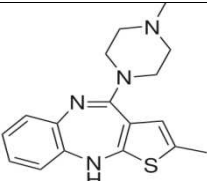
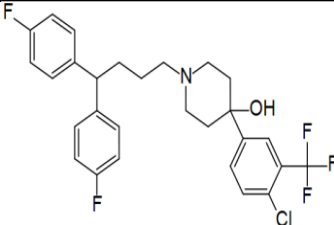
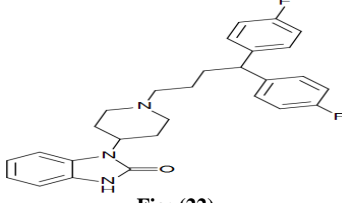
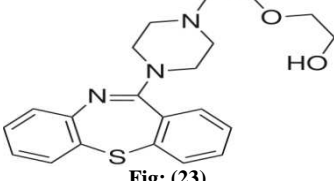
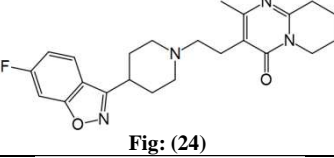
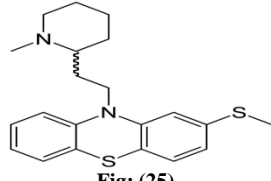
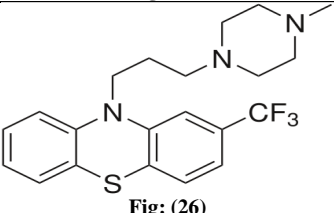
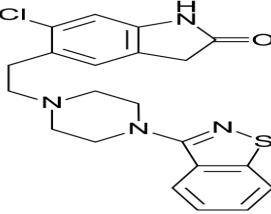
Pipofezine has been shown to act as a potent inhibitor of the reuptake of serotonin. [21][22][23]

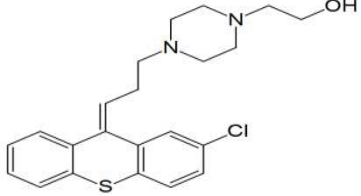
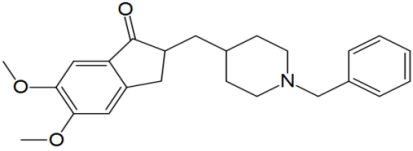
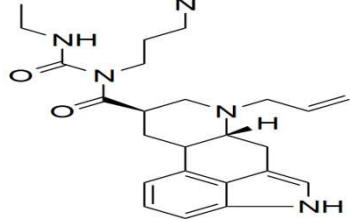
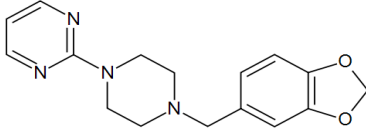
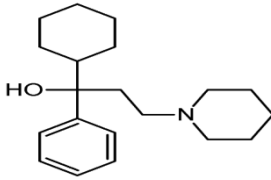
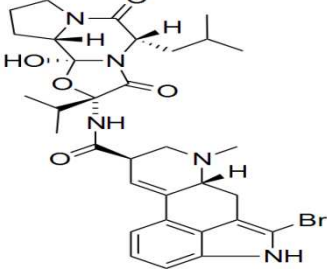
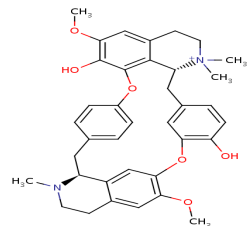
In addition to its antidepressant action, pipofezine has sedative effects as well, indicating antihistamine activity.

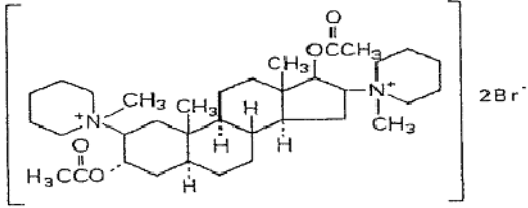
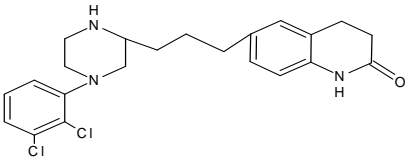
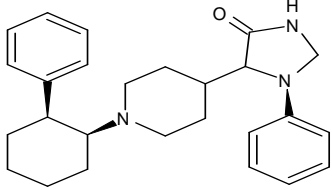
**Table: I. Six membered saturated nitrogen containing ring in successful drugs of psychological disorders. [24-51]**

Name/Category	Structure	Chemical Name
Bupirone (Anxiolytics)	 <b>Fig: (04)</b>	8-[4-(4-pyrimidin-2-yl Piperazine-1-yl)butyl]-8-azaspiro [4.5] decane-7,9- dione
Hydroxyzine (Anxiolytics, Antihistamines & Antiallergics)	 <b>Fig: (05)</b>	(±)-2-(2-{4-[(4-chlorophenyl)-phenylmethyl] Piperazine-1-yl} ethoxy) ethanol
Trazodone HCl (Anxiolytics, Antidepressants)	 <b>Fig: (06)</b>	2-(3-[4-(3-chlorophenyl)Piperazine-1-yl]propyl)-[1, 2, 4] triazolo [4, 3-a] pyridin-3(2H)-one
Trifluoperazine (Anxiolytics / Antipsychotics / Antiemetic)	 <b>Fig: (07)</b>	10-[3-(4-methylPiperazine-1-yl)propyl]-2-(trifluoromethyl)-10H-phenothiazine
Zopiclone (Hypnotics & Sedatives)	 <b>Fig: (08)</b>	(RS)-[8-(5-chloropyridin-2-yl)-7-oxo-2,5,8-triazabicyclo[4.3.0]nona-1,3,5-trien-9-yl]4-methylPiperazine-1-carboxylate
Amoxapine (Antidepressants)	 <b>Fig: (09)</b>	2-Chloro-11-(Piperazine-1-yl)dibenzo[b, f] [1, 4] oxazepine
Flupentixol (Antidepressants)	 <b>Fig: (10)</b>	<i>EZ</i> -2-[4-[3-[2-(trifluoromethyl) thioxanthene-9-ylidene] propyl]Piperazine-1-yl]ethanol
Mianserin (Antidepressants)	 <b>Fig: (11)</b>	(±)-2-methyl-1, 2, 3, 4, 10, 14b-hexahydrodibenzo[c,f] pyrazino[1,2-a]azepine
Mirtazapine (Antidepressants)	 <b>Fig: (12)</b>	(±)-1,2,3,4,10,14b-hexahydro-2-[11C]methylpyrazino(2,1-a)pyrido(2,3-c)(2)benzazepine

<p>Paroxetine (Antidepressants, OCD, Panic disorder)</p>	 <p><b>Fig: (13)</b></p>	<p>(3<i>S</i>,4<i>R</i>)-3-[(2<i>H</i>-1,3-benzodioxol-5-yl)oxy]methyl]-4-(4-fluorophenyl)piperidine</p>
<p>Trazodone (Anxiolytics, Antidepressants)</p>	 <p><b>Fig: (14)</b></p>	<p>2-(3-[4-(3-chlorophenyl) Piperazine-1-yl] propyl)-[1, 2, 4]triazolo[4,3-<i>a</i>]pyridin-3(2<i>H</i>)-one</p>
<p>Aripiprazole (Antipsychotics)</p>	 <p><b>Fig: (15)</b></p>	<p>7-[4-[4-(2,3-dichlorophenyl) Piperazine-1-yl] butoxy]-3,4-dihydroquinolin-2(1<i>H</i>)-one</p>
<p>Clozapine (Antipsychotics)</p>	 <p><b>Fig: (16)</b></p>	<p>8-chloro-11-(4-methylPiperazine-1-yl)-5<i>H</i>-dibenzo[<i>b,e</i>][1,4]diazepine</p>
<p>Fluphenazine (Antipsychotics)</p>	 <p><b>Fig: (17)</b></p>	<p>2-[4-[3-[2-(trifluoromethyl)-10<i>H</i>-phenothiazin-10-yl]propyl]Piperazine-1-yl]ethanol</p>
<p>Haloperidol (Antipsychotics)</p>	 <p><b>Fig: (18)</b></p>	<p>4-[4-(4-chlorophenyl)-4-hydroxy-1-piperidyl]-1-(4-fluorophenyl)-butan-1-one</p>
<p>Loxapine (Antipsychotics)</p>	 <p><b>Fig: (19)</b></p>	<p>2-Chloro-11-(4-methylPiperazine-1-yl) dibenzo [b,f][1,4] oxazepine</p>

Olanzapine (Antipsychotics)	 <b>Fig: (20)</b>	2-methyl-4-(4-methyl-1-Piperazineyl)-10H-thieno [2, 3- <i>b</i> ] [1, 5]benzodiazepine
Penfluridol (Antipsychotics)	 <b>Fig: (21)</b>	1-[4,4-bis(4-fluorophenyl)butyl]-4-[4-chloro-3-(trifluoromethyl)phenyl] piperidin-4-ol
Pimozide (Antipsychotics)	 <b>Fig: (22)</b>	1-[1-[4,4-bis(4-fluorophenyl)butyl]-4-piperidinyl]-1,3-dihydro-2H-benzimidazole-2-one
Quetiapine (Antipsychotics)	 <b>Fig: (23)</b>	2-(2-(4-dibenzo [ <i>b,f</i> ][1,4]thiazepine- 11-yl)-1-Piperazineyl)ethoxyethanol
Risperidone (Antipsychotics)	 <b>Fig: (24)</b>	4-[2-[4-(6-fluorobenzo[ <i>d</i> ]isoxazol-3-yl)-1-piperidyl]ethyl]-3-methyl-2,6-diazabicyclo[4.4.0]deca-1,3-dien-5-one
Thioridazine (Antipsychotics)	 <b>Fig: (25)</b>	10-{2-[( <i>RS</i> )-1-Methylpiperidin-2-yl]ethyl}-2-methylsulfanylphenothiazine
Trifluoperazine (Antipsychotics)	 <b>Fig: (26)</b>	10-[3-(4-methylPiperazine-1-yl)propyl]-2-(trifluoromethyl)-10H-phenothiazine
Ziprasidone (Antipsychotics)	 <b>Fig: (27)</b>	5-[2-[4-(1,2-benzisothiazol-3-yl)-1-Piperazineyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one

Zuclopenthixol (Antipsychotics)	 <p style="text-align: center;"><b>Fig: (28)</b></p>	<i>cis</i> -(Z)-4-[3-(2-chlorothioxanthen-9-ylidene)propyl]-1-Piperazineethanol
Donepezil (Neurodegenerative Disease Drugs)	 <p style="text-align: center;"><b>Fig: (29)</b></p>	(R <i>S</i> )-2-[(1-benzyl-4-piperidyl) methyl] - 5, 6-dimethoxy-2, 3-dihydroinden-1-one
Cabergoline (Antiparkinsonian Drugs)	 <p style="text-align: center;"><b>Fig: (30)</b></p>	N-[3-(Dimethylamino)propyl]-N-[(ethylamino)carbonyl]-6-(2-propenyl)-8-ergoline-8-carboxamide
Piribedil (Antiparkinsonian Drugs)	 <p style="text-align: center;"><b>Fig: (31)</b></p>	2-[4-(benzo[1,3]dioxol-5-ylmethyl) Piperazine-1-yl] pyrimidine
Trihexyphenidyl (Antiparkinsonian Drugs)	 <p style="text-align: center;"><b>Fig: (32)</b></p>	1-cyclohexyl-1-phenyl-3-(1-piperidyl) propan-1-ol
Bromocriptine (Antiparkinsonian Drugs)	 <p style="text-align: center;"><b>Fig: (33)</b></p>	Ergotaman-3',6',18-trione, 2-bromo-12'-hydroxy-2'-(1-methylethyl)-5'alpha-(2-methylpropyl)-
Tubocurarine: (Neuromuscular Blocking Agents)	 <p style="text-align: center;"><b>Fig: (34)</b></p>	7, 12 -dihydroxy-6,6-dimethoxy- 2,2 2 - trimethyltubocuraranium chloride hydrochloride pentahydrate.

Pancuronium (Neuromuscular Blocking Agents)	 <p style="text-align: center;"><b>Fig: (35)</b></p>	Plant steroidal compound with piperidine derivatives.
Compound Q (Antipsychotic)	 <p style="text-align: center;"><b>Fig: (36)</b></p>	1-(3-chlorophenyl)-piperazine hydrochloride
Spiropiperidines. (Gly T1 inhibitors)	 <p style="text-align: center;"><b>Fig: (37)</b></p>	N-(2-aryl-cyclohexyl) substituted spiropiperidines

## DISCUSSION AND CONCLUSION

These six membered saturated moiety containing nitrogen atoms can be explore to synthesize many of its analogous which can be effectively and successfully exploit to obtained the new molecule which shows better biological response as to treat psychological and neurological disorders. Since the prevalence of mental health problems, particularly psychosis, schizophrenia, depression and anxiety, in the general population is around one in six people, and around 40% of people with mental health problems will have symptoms of both anxiety and depression. Drug acting on the central nervous system (CNS) include the centrally acting (mainly opoid) analgesics, anti-epileptics and anti-Parkinson agents, as well as those for psychiatric disorders.

Based on the literature it may be conclude that six membered saturated nitrogen containing rings are important and it throws attention to set the mind of researchers to carry out the work for developing its various analogous used in neurological & Psychological disorders which can ultimately beneficial for humans beings.

Data will give the idea to further explore with the six membered saturated ring containing other heteroatoms like oxygen, sulphur etc.

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