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Exploring Heterocyclic Diversity: A Comprehensive Review on Antidepressant Drug Development

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Abstract

Depression, a common mental disorder, requires new therapeutic approaches continuously. In this review, the potential of various heterocyclic moieties found in marketed antidepressant drugs will be explored. It will highlight the synthesis techniques, derivatization strategies, and pharmacological importance of nitrogen-containing heterocyclics such as indole, piperidine, pyridine, pyrimidine, piperazine, and triazole. Furthermore, it brings to light the significance of oxygen and sulfur-based heterocycles including multi-heteroatom rings in antidepressant drug development. It has also highlighted that these compounds have great diversity in terms of their pharmacology due to their ability to regulate some key neurotransmitter systems involved in depression. Additionally, this review underpins derivatives that can change the chemical structure that affects drug delivery across BBB among many others. We also shed light on the synthesis of various heterocyclic moieties as well as their pharmacological relevance with a view to providing information for finding novel and efficient therapies against depressive illness specifically antidepressants used in practice today. Understanding the potential of heterocyclic compounds in developing antidepressant drugs holds promise for improving therapeutic efficacy and enhancing the management of depression, making it a crucial focus for psychiatry.

Keywords: heterocyclic compounds, depression, causes, indole, piperidine, pyridine.

Introduction

Depression is a complex and multidimensional psychiatric disorder that affects individuals in various ways and with varying degrees of severity. (Zimmerman, 2018; Cuijpers, 2023; Al-Abri, 2023)It often described as a silent epidemic of the modern era, transcends cultural, geographical, and socioeconomic boundaries, affecting individuals of all ages and walks of life. (Konstantinou, 2023)According to the World Health Organization, depression affects approximately 3.8 percent of the global population, with 5.7 percent of individuals over sixty and 5 percent of adults (4 percent men and 6 percent women) falling into this category. Globally, an estimated 280 million people are affected by depression.Research shows that the prevalence of depression is over 50% higher in women compared to men. Additionally, approximately 10% of new mothers and pregnant women worldwide experience depression. Tragically, suicide claims the lives of over 700,000 people each year, making it the fourth leading cause of death among individuals aged 15 to 29. (WHO site, 2024)By 2030, depression is predicted to be the most common illness globally. (Woody, 2017)Even with the availability of multiple treatment alternatives, such as pharmacotherapy and psychotherapy, a significant percentage of people with depression do not experience complete remission.(Oliveira-Maia, 2024) Consequently, there is a continuous quest for novel therapeutic agents with improved efficacy, tolerability, and safety profiles. (Voineskos, 2020)

In recent years, researchers and pharmaceutical companies have turned their attention to the exploration of heterocyclic moieties as potential components of antidepressant drugs.(Singh, 2021; Choudhary, 2024; Shah, 2021) Heterocyclic compounds are organic molecules containing at least one ring structure composed of atoms

from at least two different elements, commonly carbon and nitrogen, but may also including oxygen, sulfur and other elements.(Arora, 2012; Makhova, 2020) These diverse chemical structures offer a rich source of pharmacological diversity and have been the basis for the development of numerous drugs across various therapeutic areas.(Jampilek, 2010)

The investigation of heterocyclic moieties in the context of depression therapy holds promise due to their ability to modulate key neurotransmitter systems implicated in the pathophysiology of depression. (Siddiqui, 2011)These systems include the monoaminergic pathways involving serotonin, norepinephrine and dopamine as well as other neurotransmitter systems such as glutamate and gamma-aminobutyric acid (GABA). By targeting these neurochemical pathways, heterocyclic compounds have the potential to restore neurotransmitter balance, alleviate depressive symptoms and improve overall mood and functioning.(Siddiqui, 2011)

In this article we will explore the effects of various heterocyclic moieties present in marketed drugs on depression. We present descriptions and discussions on the most relevant synthesis methods. We aim to contribution to the ongoing efforts to improve outcomes for individuals living with depression and advancing the field of psychopharmacology.

Causes of Depression

Depression has several potential causes, such as hormone imbalances, traumatic life experiences, genetics, chronic stress, certain drugs, and underlying medical conditions including diabetes mellitus. The risk of development can also be raised by social and environmental variables such living in a stressful or unstable environment, having little social support, and having financial issues. Moreover, a higher vulnerability to depression is linked to specific psychological variables and personality features, such as poor self-esteem, negative thought patterns, and a history of abuse or trauma throughout infancy.

According to certain study, depression may result from an imbalance of various chemicals in the brain, such as dopamine and serotonin. (Neitzke, 2016; Lauber,2003)

Heterocyclic based antidepressants

Nitrogen-Based Heterocyclic Moieties-

Within the practical areas of organic chemistry, nitrogen-based heterocyclic chemistry is a distinct and significant class in which a lot of study is directed toward the synthesis of novel compounds and composites. Over the past two decades, there has been a surge in curiosity about these molecules. (Jaziri, 2023) They are widely used in the chemical sciences and have contributed to the development of several protocols for organic synthesis. Nature contains many widely dispersed N-heterocyclic compounds with physiological and pharmacological properties. Additionally, they serve as the building blocks for a wide range of molecules that are important to biology, including vitamins, drugs, antibiotics, dyes, nucleic acids and agrochemicals. (Sahu, 2023; Karaytuğ, 2023)
N-heterocyclic compounds, such as pyrimidines and purines, are integral to the pharmacological activity of many drugs. These compounds are also the building blocks of the base pairs found in DNA and RNA, including guanine, cytosine, adenine, and thymine.(da Silva Moreira, 2023)The unique properties and applications of nitrogen-containing heterocyclic compounds are gaining increasing recognition in rapidly advancing fields such as organic and medicinal chemistry, as well as the pharmaceutical industry.(SERİN, 2024)

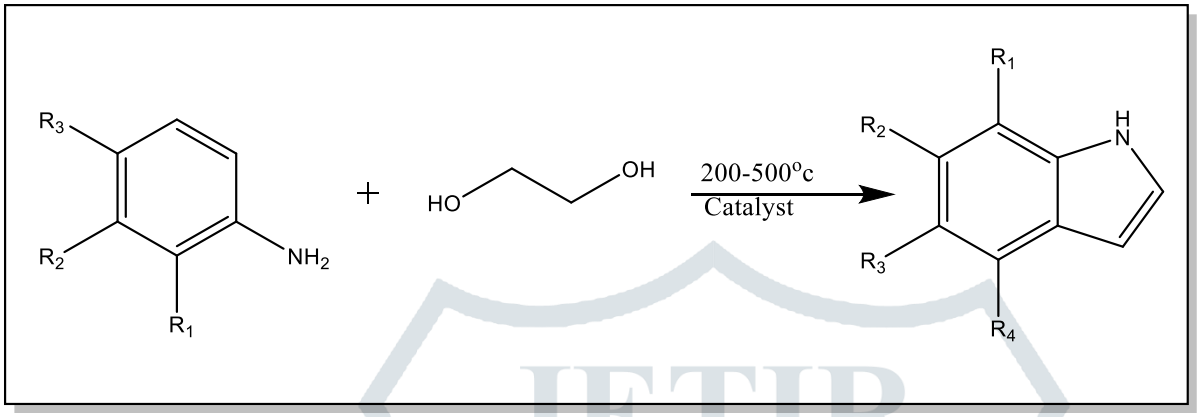
The abundantly electron-rich nitrogen heterocycle can readily take up or release a proton and generate a variety of weak interactions. The rising importance of these compounds in medicinal chemistry can be attributed to various intermolecular forces, such as the formation of hydrogen bonds, dipole interactions, hydrophobic effects, van der Waals forces, and stacking interactions among nitrogen compounds. (Verma, 2023)Additionally, these forces speed up the chemicals' ability to attach to the enzymes and receptors of different biological targets. Since their derivatives have a wide spectrum of bioactivities, their structural features are advantageous. (Sorensen, 1990)

1. INDOLE

A bicyclic molecule is formed when a six-membered benzene ring and a five-membered pyrrole ring blend together. The presence of a nitrogen atom in the pyrrole ring is the primary characteristic of indoles that gives them their pharmacological activity. (Jaziri, 2023)

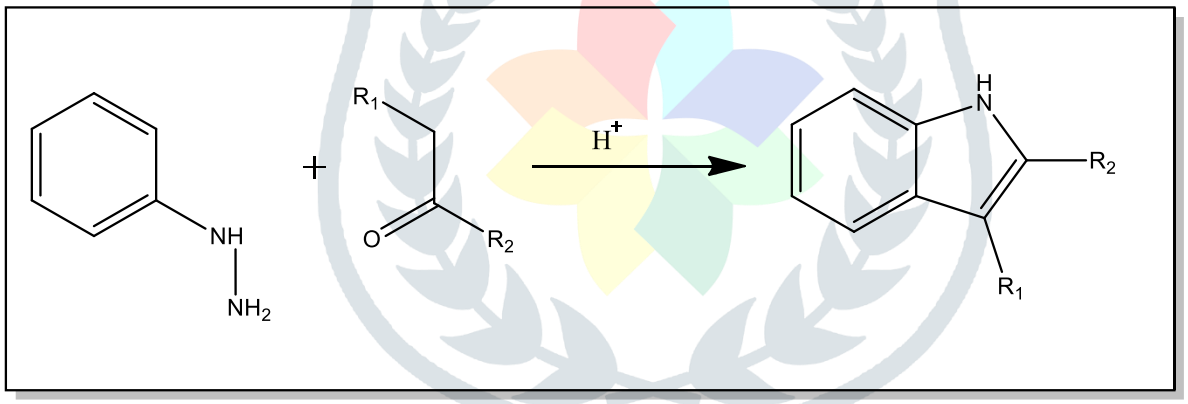
Main method of synthesis contains indole moiety

- Mainly indole moiety is synthesized by reacting aniline in a vapour phase with ethylene glycol in between 200 to 500 temperatures and in the presence of catalysis. [scheme 1] Through this process it yields about 60% of indole derivative. (Cacchi, 2005; Collin, 2000; Humphrey, 2006)



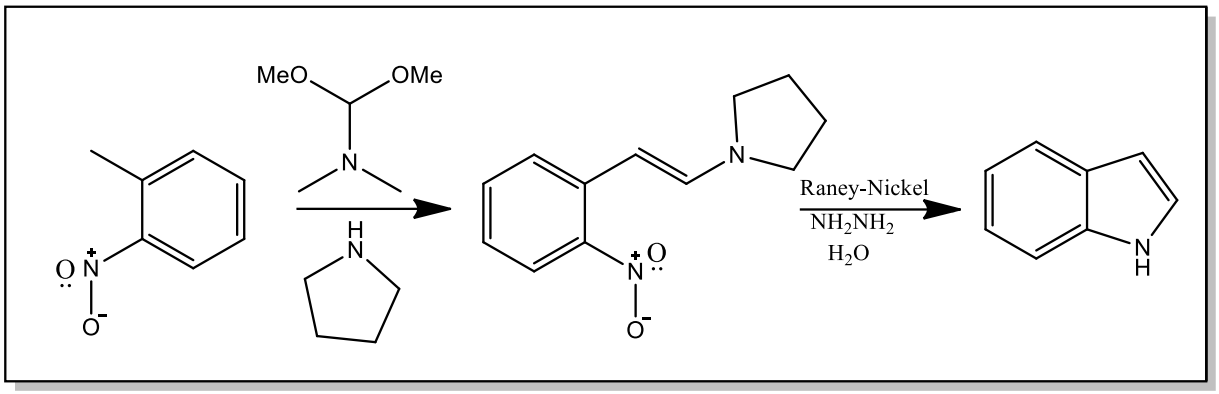
Scheme 1: Reacting aniline with ethylene glycol in the presence of catalyst.

The Fischer indole synthesis, created in 1883 by Emil Fischer, can be used to create indole. The process involves pyruvic acid and phenylhydrazine reaction, followed by decarboxylation resulting in the formation of indole-2-carboxylic acid. Described in scheme 2(Bratulescu, 2008)



Scheme 2: Reacting phenyl hydrazine with substituted ketone in acidic condition.

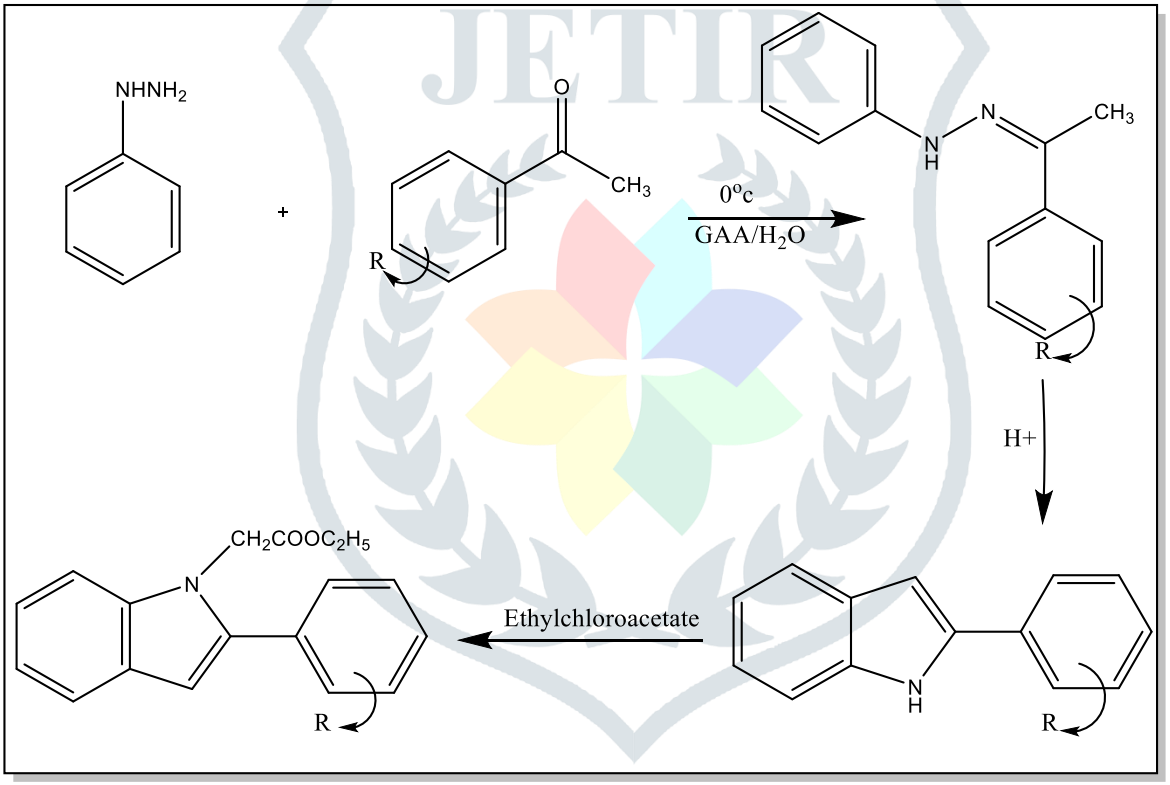
In pharmaceutical industry leimgruber-Batcho indole synthesis method are more commonly were used. The process initiates with the formation of an enamine, where dimethylamine is displaced by pyrrolidine from the dimethylformamide dimethylacetal, resulting in a higher reactive reagent. Under basic conditions, Deprotonation of the methyl group's slightly acidic hydrogens in nitrotoluene can result in the creation of the enamine shown, along with the loss of methanol. Alternatively, the N,N-dimethyl enamine can be used to continue the process in the absence of pyrrolidine, albeit in some circumstances this may need longer reaction durations. Subsequently, a Raney nickel catalyst and hydrogen are used to reduce the -NO_2 group to -NH_2 followed by the removal of the pyrrolidine and cyclization.Hydrogen is typically produced in situ when hydrazine hydrates spontaneously breaks down to H2 and N2 in the presence of nickel. [Scheme 3](Marx, 2024)



Scheme 3: Formation of indole from Nitrobenzene through hydrazine

Synthesis of indole derivative as antidepressant

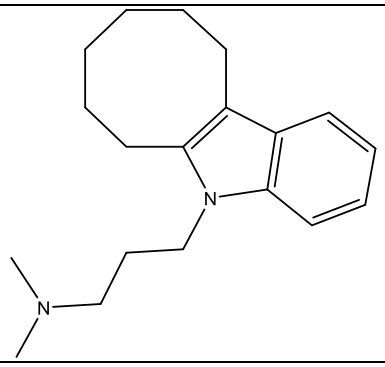
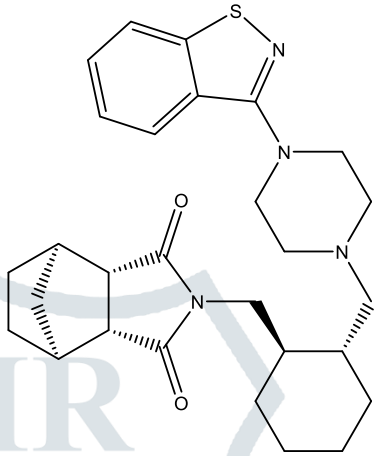
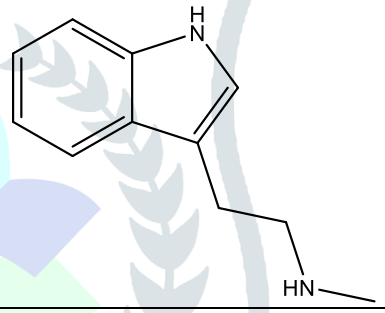
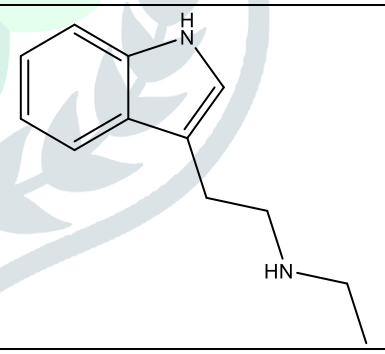
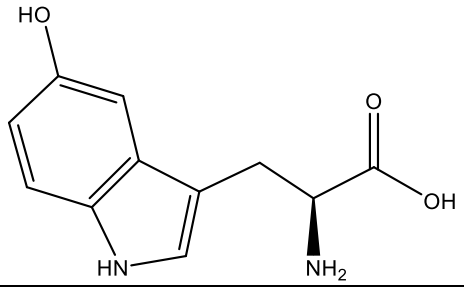
- Shahu RP et al. described a process for creating substituted phenyl indole, which involves reacting substituted phenyl hydrazone with phosphorous acid heated at 100 to 120 degrees Celsius and then refluxing with rectified spirit. They reported that 2-phenyl indole derivatives possessing antidepressant potential.(Sahu, 2023)

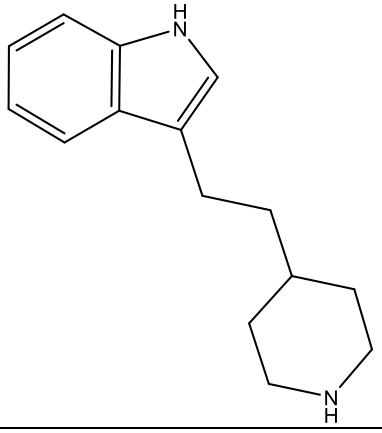
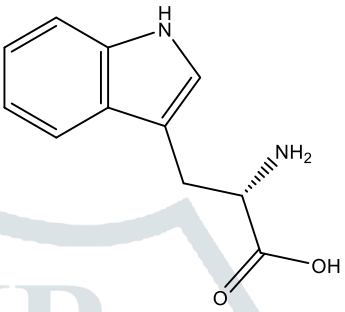


Scheme 4: Synthesis of substituted phenyl indole by the reaction of substituted phenyl hydrazone.

Table No.1: Anti Depressents In Market That Contain Indole Ring[4,8]

DRUG NAME	MECHANISM OF ACTION	STRUCTURE

Iprindole	Acts as inhibitor of the reuptake of serotonin and norepinephrine	
Lurasidone	Acts as an antagonist of the dopamine D2 and D3, serotonin 5-HT2A and 5-HT7 receptors, α2C-adrenergic receptor, and as a partial agonist of the serotonin 5-HT1A receptor	
α-Methyltryptamine	Acts as reversible inhibitor of the enzyme monoamine oxidase (MAO)	
Ethyltryptamine	Acts as non-selective serotonin receptor agonist	
Oxitriptan	Acts as precursor in serotonin biosynthesis	

Indalpine	selective serotonin reuptake inhibitor (SSRI)	
Tryptophan	Acts as precursor in serotonin and Melatonin biosynthesis	

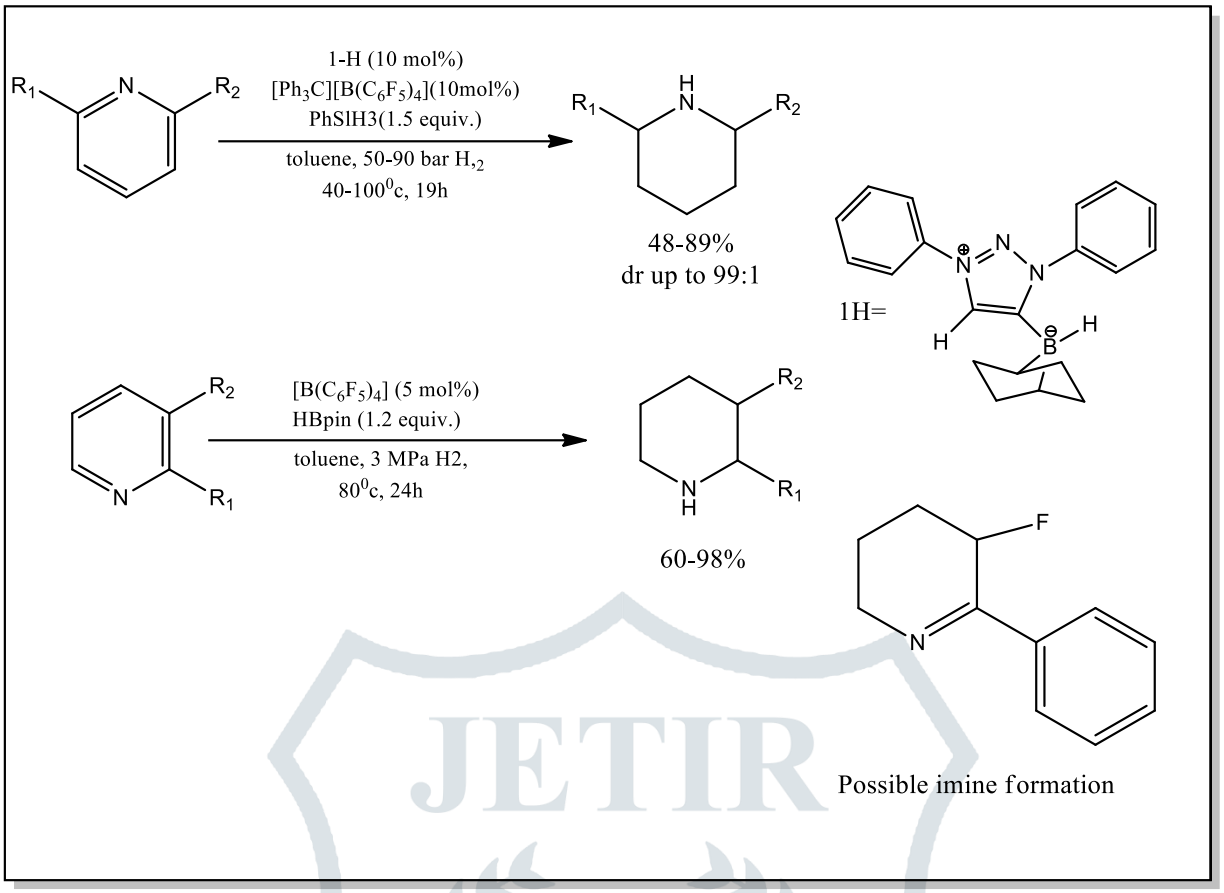
2. PIPEREDINE

One significant pharmacophore group utilized in drug development research is the piperidine ring. It has been demonstrated that a variety of compounds possessing this ring system in their chemical structure display a variety of pharmacological actions in vivo and in vitro. [20]Piperidine compounds These compounds have demonstrated notably significant effects on the Central Nervous System (CNS), including depressive, anxiolytic, anticonvulsant, antinociceptive, and antipsychotic properties. (SERİN, 2023; Song, 2023)

However, the structures of a few clinically used psychotropic medications; including paroxetine, haloperidol, risperidone, methylphenidate, and donepezil, also contain the piperidine ring system. It can also be found in a number of commercially available antidepressants. (Kane, 1988)

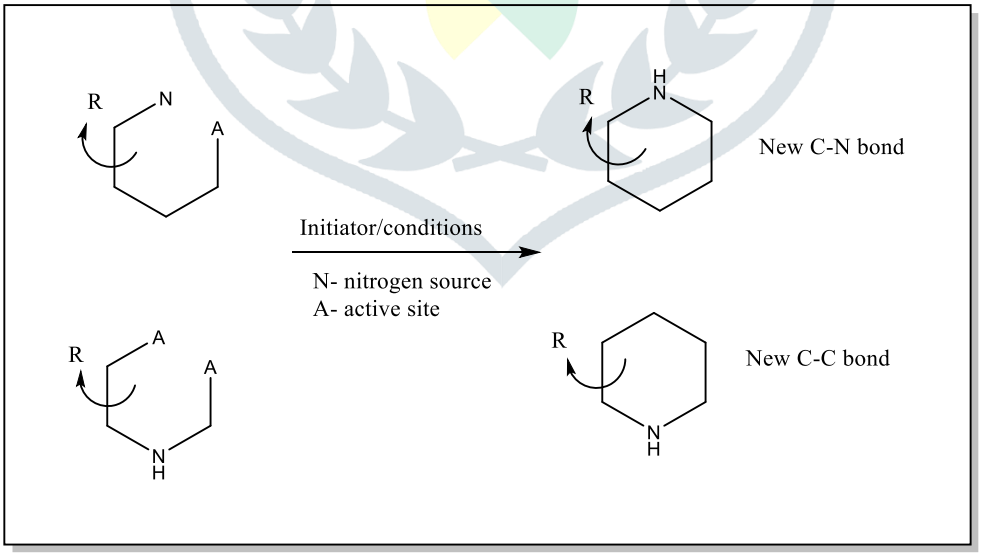
Synthesis of piperdine derivative

- In the presence of hydrosilanes, substituted pyridines are diastereoselectively reduced to piperidines by boron ions, as found by Crudden et al. Hydrogenation of bis-substituted pyridines occurred in mild circumstances, whereas pressure and temperature were more than quadrupled for ortho-derivatives. Silanes are required to stop the formation of the product-catalyst adduct. Another technique for the pyridine hydroboration/hydrogenation cascade has been devised by Wang et al. The method was *cis*-selective and especially effective for 2,3-disubstituted pyridines.(Frolov, 2023, Clarke, 2021; Yang,2021)



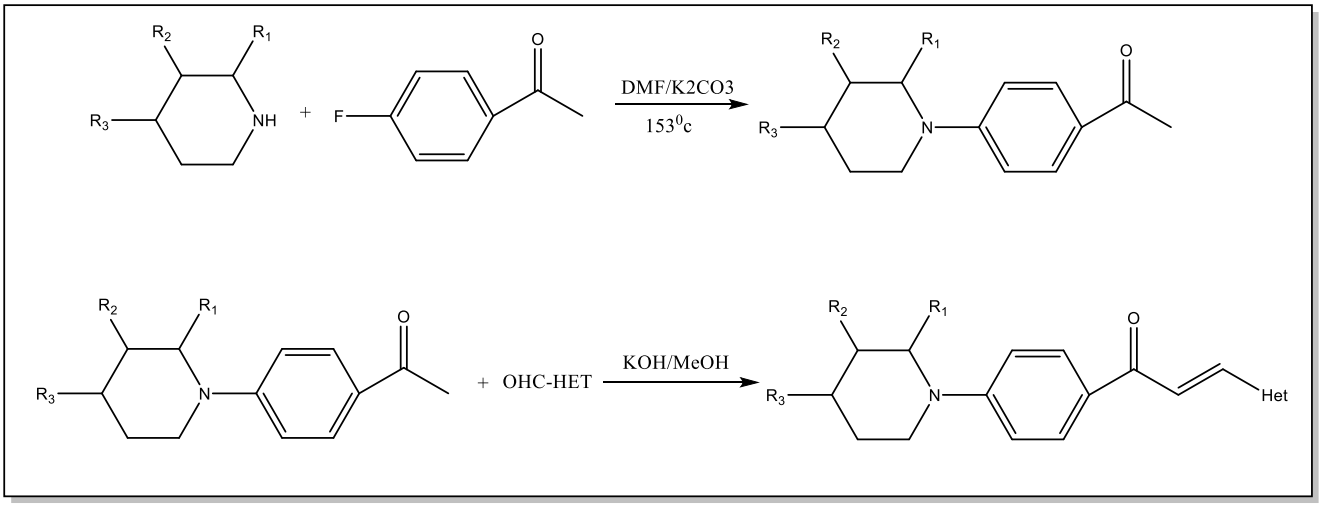
Scheme 5: Synthesis of di-substituted piperidine from bis-substituted pyridines

- In the process of intramolecular cyclization to form piperidine, the substrate commonly includes an amino group serving as a nitrogen source, along with one or more active sites directly engaged in the cyclization process. Intriguingly, the nitrogen atom's direct involvement in cyclization leads to the formation of a new C-N bond, with the possibility of a new C-C bond formation under certain conditions. Baldwin's norms, which were updated by Alabugin and Gilmore in 2016 and first proposed by Jack Baldwin in 1976, are often followed when cyclizations take place.(Baldwin, 1976; Gilmore, 2016)



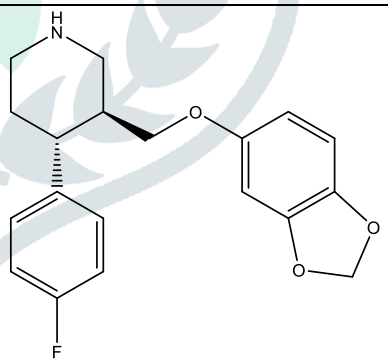
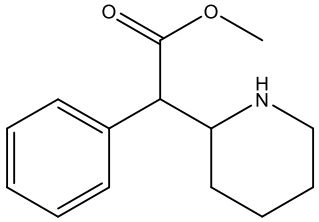
Scheme 6: Derivatization of piperidine as antidepressant

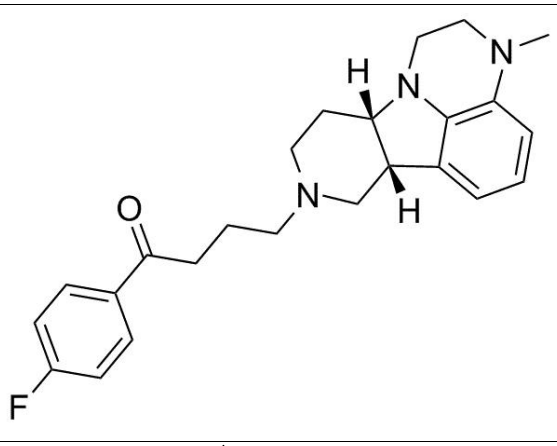
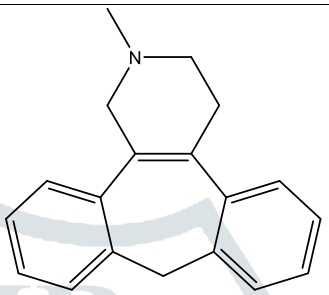
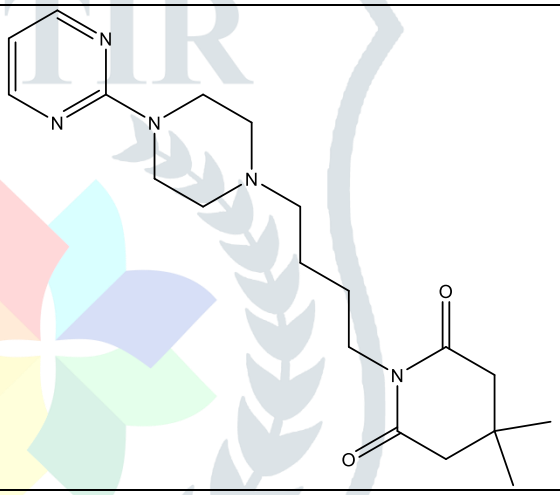
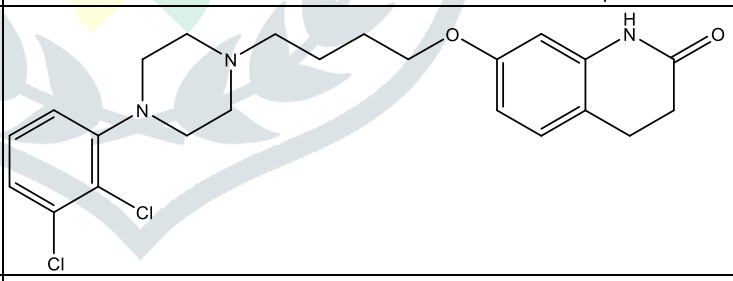
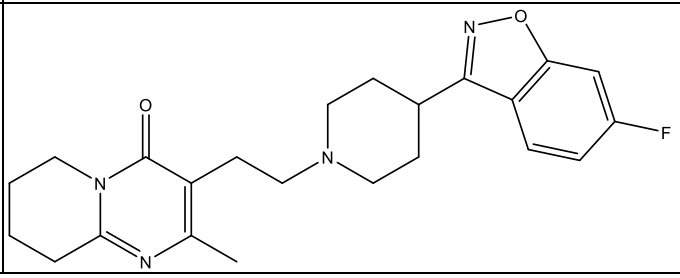
- Kaya et al. synthesized the derivative of piperidine and determine its antidepressant activity. They synthesized the derivatives by reacting 4-fluoroacetophenone with secondary amine and forming ketone derivative. The final derivative of piperidine was then obtained by a Claisen-Schmidt reaction between indole-3-carbaldehyde/pyridine-4-carbaldehyde and a previously produced ketone derivative. (Kaya, 2022)



Scheme 7: Reaction of 4-fluoroacetophenone with secondary amine leads to formation of ketone derivative

Table No.2: Anti Depressents In Market That Contain Piperidine Ring[5,10,12]

DRUG NAME	MECHANISM OF ACTION	STUCTURE
Paroxetine	Acts as Serotonin reuptake inhibitor (SSRIs)	
Methylphenidate	Acts as norepinephrine–dopamine reuptake inhibitor	

Lumateperone	Acts as a receptor antagonist of 5-HT_{2A} receptor	
Setiptiline	Acts as norepinephrine reuptake inhibitor, α_2-adrenergic and serotonin receptor antagonist	
Gepirone	Acts as selective partial agonist of the 5-HT_{1A} receptor	
Aripiprazole	Acts as partial agonist of the serotonin 5-HT_{1A} receptor	
Risperidone	Acts as antagonist of the Dopamine1 as well as the Dopamine2 family	

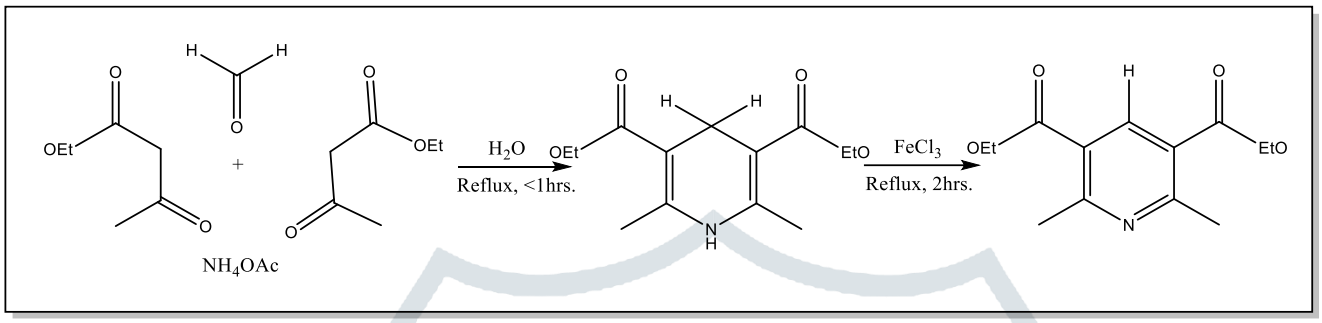
3. **PYRIDINE-**

The nitrogen atom in pyridine has replaced one of the carbons in the benzene ring, making it a heterocyclic complex consisting of six members. The pure form's colorlessness becomes yellow in the presence of impurities.(Moreira, 2021; Kumar, 2013) The chemical structure of a number ofuseful organic compounds contains the pyridine ring. Pyridine is present in numerous chemical medications, vitamins, and agrochemicals. Unlike benzene, pyridine is a polar heterocyclic molecule with a dipole moment magnitude of 2.2

Debye.[44]Compared to benzene, pyridine has one more unshared electron pair of nitrogen. Thus, pyridine and its derivatives should be more efficient corrosion inhibitors than their equivalents, benzene and its derivatives. Pyrimidines and their derivatives have received substantial attention due to their good pharmacokinetic properties and large spectrum of major pharmacological actions. (Sorensen, 1990; Koenig, 1967)

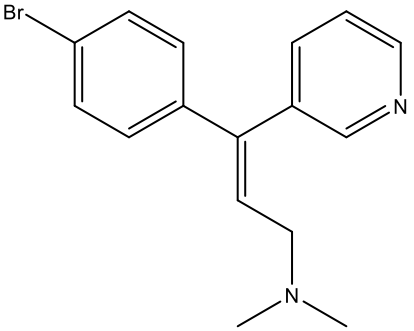
Main method of synthesis contains pyridine moiety

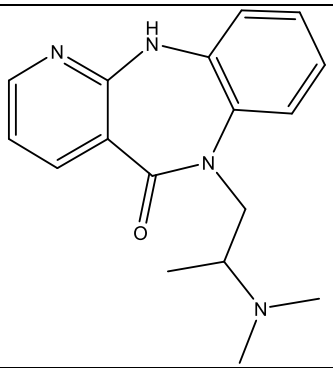
- Pyridine can be synthesized through Hantzsch pyridine synthesis in which aldehyde is reacted with 2 equivalent beta keto ester and a nitrogen doner and form the product dihydropyridine which is oxidized and form pyridine. This reaction is reported by the Arthor Rudolf in 1881. (Kolvari, 2011; Li, 2010)



Scheme 8: Synthesis of pyridine through Hantzsch pyridine synthesis.

Table No.3: Anti Depressents In Market That Contain Pyridine Ring[23,24]

DRUG NAME	MECHANISM OF ACTION	STRUCTURE
Zimelidine	Acts as strong reuptake inhibition of serotonin from the synaptic cleft	

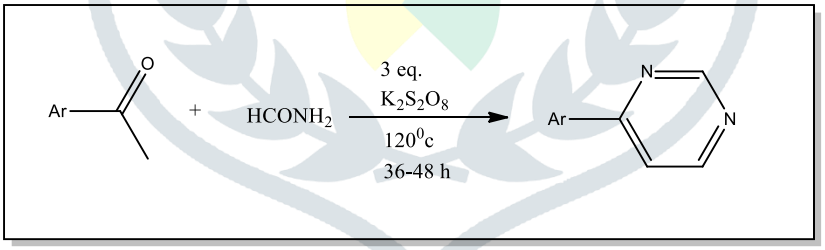
Propizepine	selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs) and norepinephrine reuptake inhibitors	

4. PYRIMIDINE-

Similar to pyridine, Pyrimidine is an aromatic heterocyclic organic compound. The nucleotides, thiamine (vitamin B1), and alloxan are among the many compounds and derivatives of the pyrimidine ring system that is widely found in nature as substituted and ringfusedstructures. (Jain, 2023; Sindhu, 2013)It can also be present in several of synthetic substances, Including barbiturates and zidovudine, an HIV medication. Even so, uric acid and alloxan are examples of pyrimidine derivatives that were known in the early 1800s. The pyrimidine nucleus demonstrated noteworthy pharmacological properties. (Sorensen, 1990; Kumar, 2021) Pyrimidine derivatives have a wide range of biological and therapeutical activities and are present in many effective medications. Heterocyclic rings containing nitrogen, like pyrimidines, present a promising structural option for drug development. (Kharb, 2011; Coppen, 1977) The antimicrobial, analgesic, anti-inflammatory, antiviral, antitubercular, anti-tumor, anti-HIV, anti-neoplastic, anti- malarial, diuretic, and cardiovascular properties of condensed pyrimidine derivatives have been documented. Pyrimidine compounds also have application in the nervous system as hypnotic medicines. (Moreira, 2021; Kase, 1969)

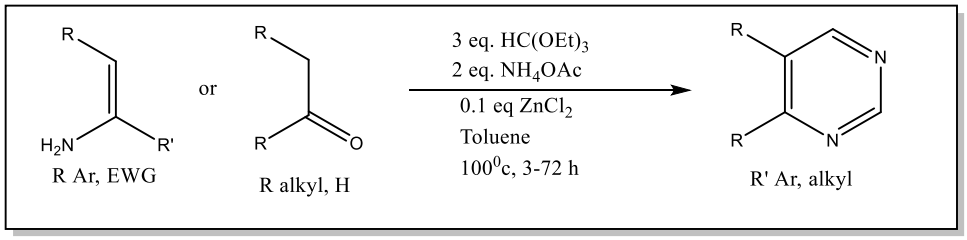
Main method of synthesis contains pyridine moiety

- Anilines, aryl ketones, and DMSO are involved in an oxidative annulation that yields 4-arylquinolines, which are methine (=CH−) equivalents stabilized by K2S2O8. On the other hand, 4-arylpyrimidines are produced by activating acetophenone-formamide conjugates. (Jadhav, 2017)



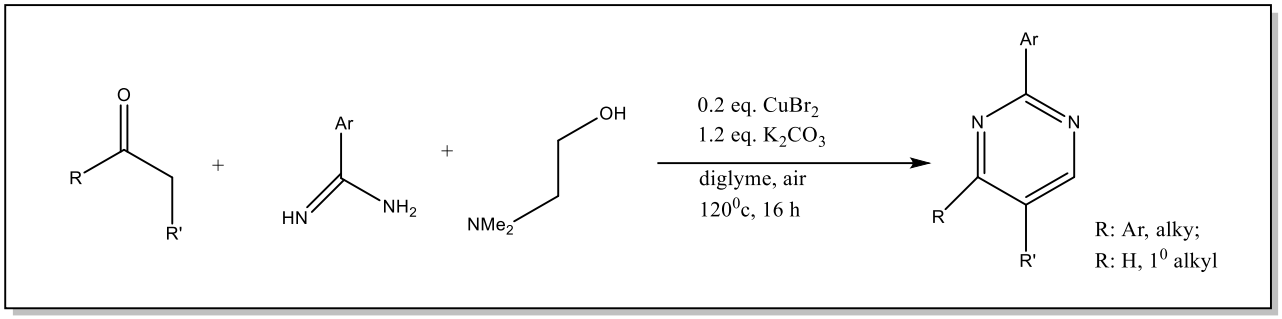
Scheme 9: Synthesis of arylpyrimidine by the reaction of aetophenone with formamide.

- Using a $ZnCl_2$-catalyzed three-component coupling procedure, various 4,5-disubstituted pyrimidine derivatives can be synthesized in a single step from functionalized enamines, triethyl orthoformate, and ammonium acetate.By substituting methyl ketone derivatives or enamines, the process may be effectively used to synthesize mono- and disubstituted pyrimidine derivatives with efficiency.(Sasada, 2009)



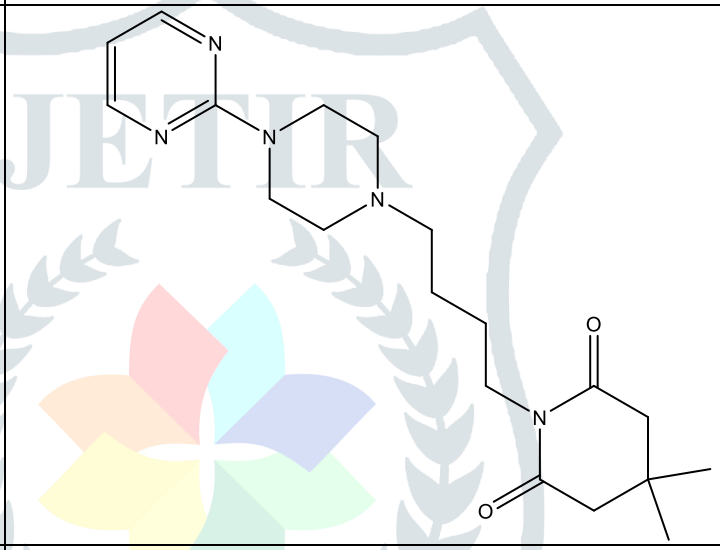
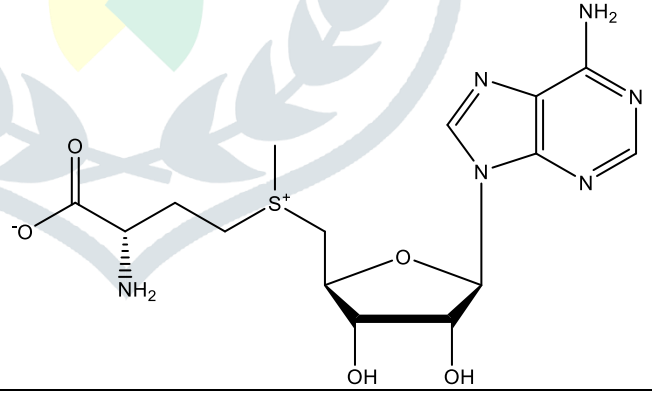
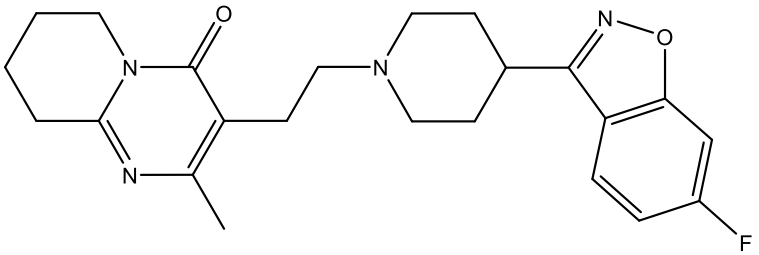
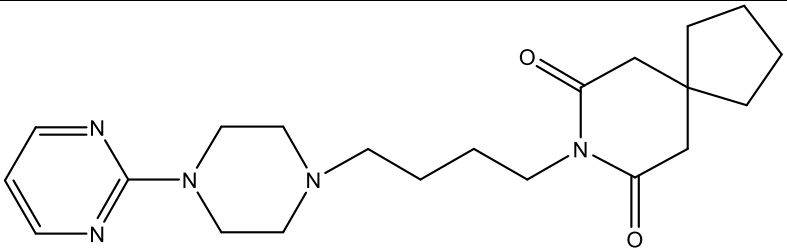
Scheme 9: Synthesis of disubstituted pyrimidine from methyl ketone derivatives or enamines

- For the simple, rapid, and ecologically safe synthesis of pyrimidine derivatives, amidines, ketones, and N, N-dimethyl amino ethanol are annulated using an oxidative [3 + 2 + 1] three-component process as the single carbon source. It can withstand a large number of significant functional groupings. (Qin, 2021)



Scheme 10: Annulation of amidines, ketones, and N, N-dimethyl amino ethanol leads to synthesis of pyrimidine derivative.

Table No.4: Anti Depressents In Market That Contain Pyrimidine Ring[20,23]

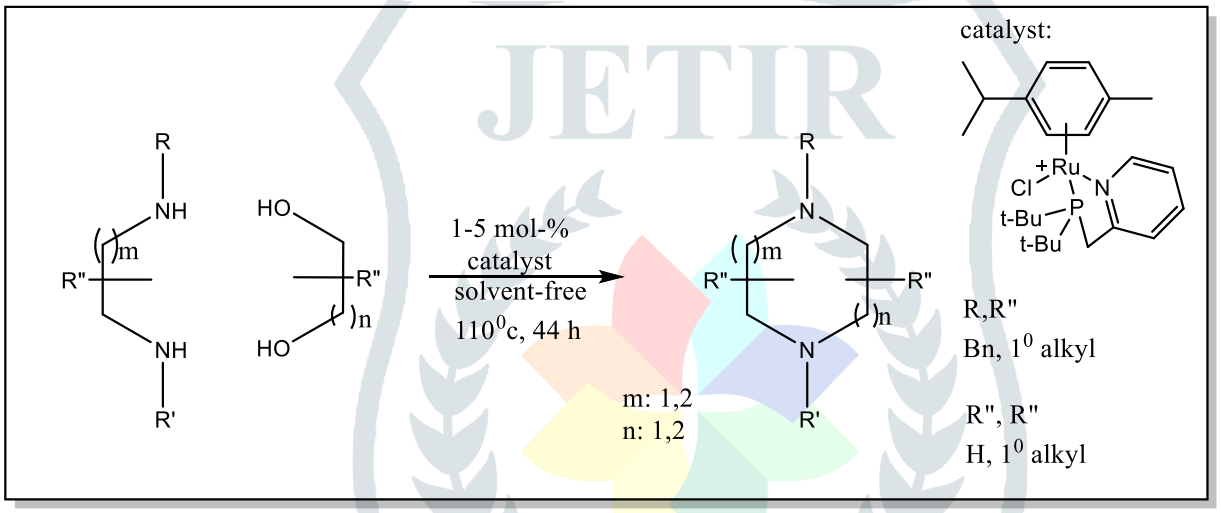
DRUG NAME	MECHANISM OF ACTION	STRUCTURE
Gepirone	Acts as selective partial agonist of the 5-HT_{1A} receptor	
S-Adenosyl methionine	Acts as cofactor in monoamine neurotransmitter biosynthesis	
Risperidone	Acts as antagonist of the Dopamine1 as well as the Dopamine2 family	
Buspirone	Acts as an agonist of the serotonin 5-HT1A receptor with high affinity	

5. PIPERAZINE-

A heterocyclic ring with six members and two opposing nitrogen atoms is called a piperazine.Strong antidepressant effects are exhibited by the piperazine nucleus. popular piperazine derivativeswith potent serotonin antagonist/reuptake inhibitor qualities are nevazodone and aripiprazole. 1-(2-Pyrimidinyl)-piperazine is one of the primary active metabolites of buspirone, ipsapirone, gepirone, and tandospirone. (Kase, 1969; WARDAKHAN, 2008) As 5-HT1A agonists, these substances also have anxiolytic and antidepressant qualities. This nucleus is important to the pharmaceutical industry because it is found in many currently marketed drugs. (Kumar, 2017)Among the antidepressants with a piperazine nucleus are amoxapine, befuraline, binospirone, alnespirone, buspirone, flesinoxan, gepirone, ipsapirone, nevazodone, piberaline, and tandospironeA blueprint for the synthesis of CNS-active drugs is provided by the arylpiperazine molecule.This is the primary serotonergic, adrenergic, and dopaminergic pharmacophoric fragment.(Kase, 1969; WARDAKHAN, 2008; Song, 2019)

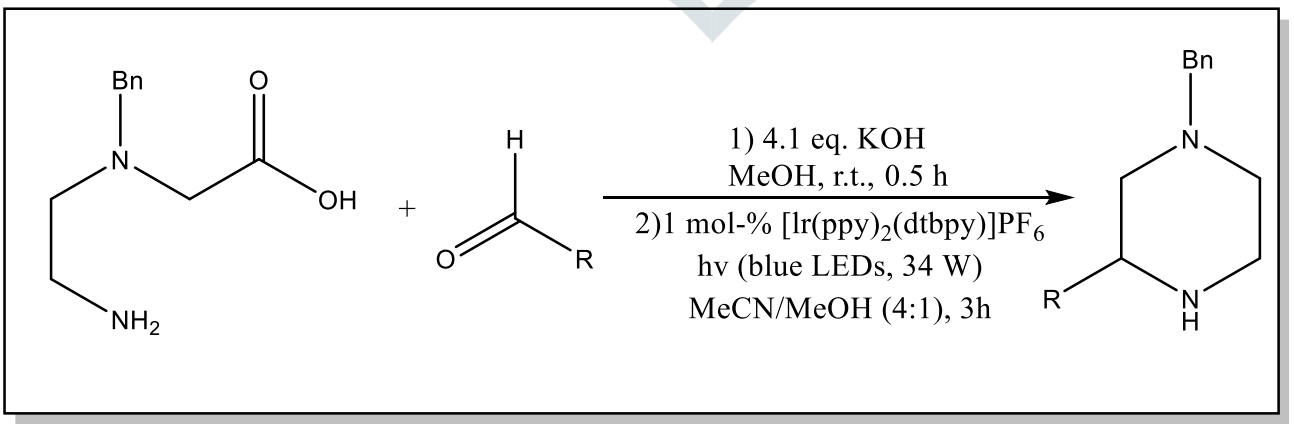
Main method of synthesis contains piperazine moiety

- A. Nalikezhathu et al. synthesized the piperazine through reacting pyridyl, phosphine-ligated ruthenium (II) catalyzes and diol-diamine. (Nalikezhathu, 2023)



Scheme 11: Synthesis of piperazine through -ligated ruthenium (II) catalyst

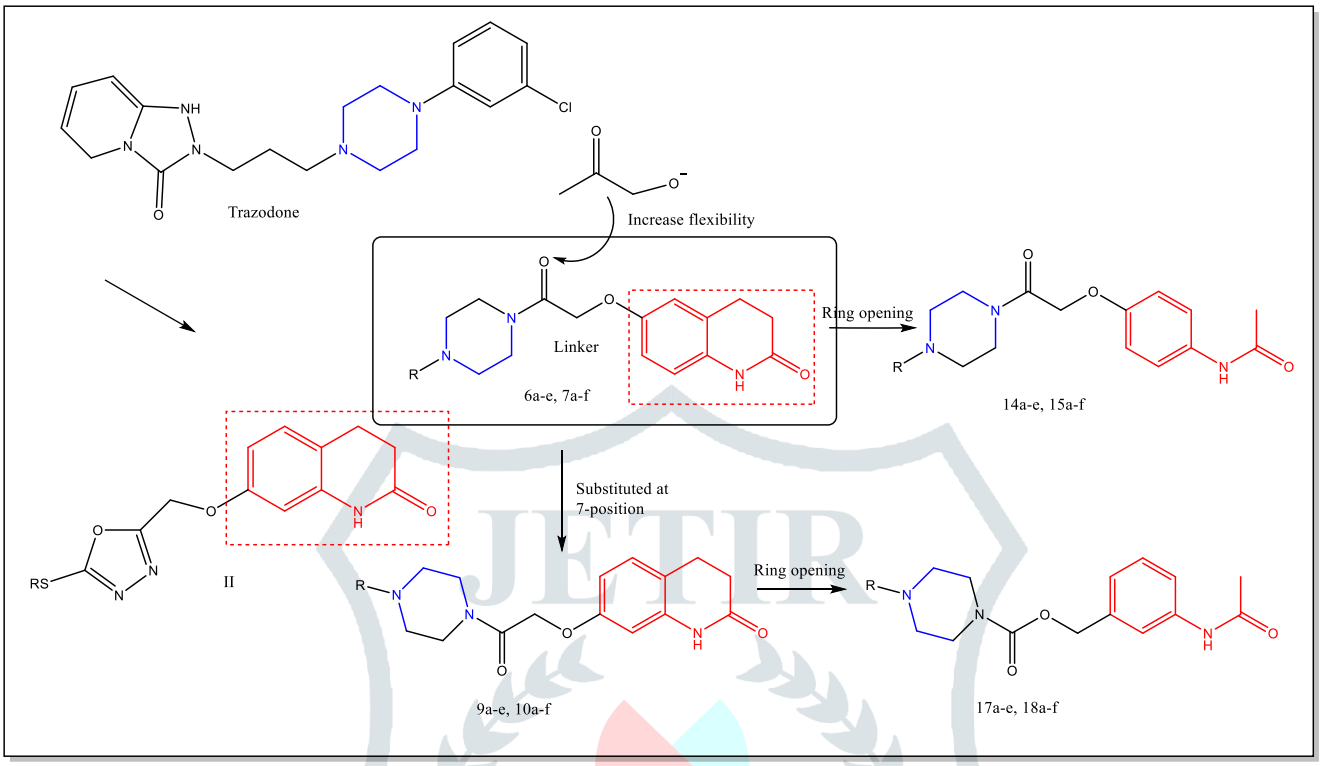
- R. Gueret al. achieved the synthesis of 2-aryl, 2-heteroaryl, and 2-alkyl piperazines under mild conditions through a visible light-induced decarboxylative annulation reaction between an aldehyde and a glycine-based diamine.Carbazolyl dicyanobenzene and the iridium-based complex PF6 efficiently catalyze this reaction in batch or continuous mode. (Gueret, 2020)



Scheme 12: Derivatization of a piperazine

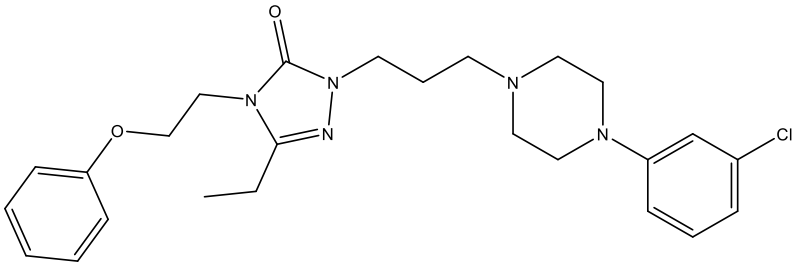
- To create Intermediate 2, 1- boc-piperazine and chloroacetyl chloride interacted in a cold bath.To prevent an increase in byproduct generation during this phase, the reaction temperature was controlled. In a high yield, Intermediate 4 was created by an alkaline reaction between Intermediate 2 and 3,4-dihydro-6-hydroxy-2(1H)-

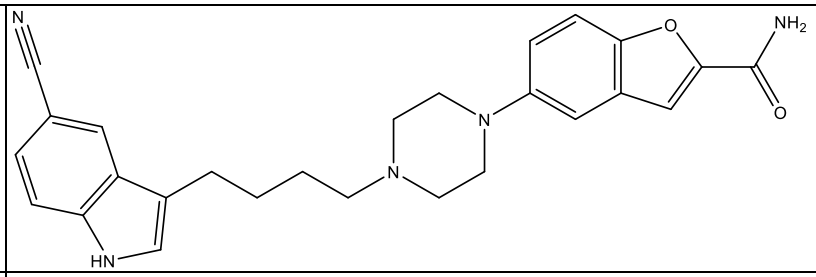
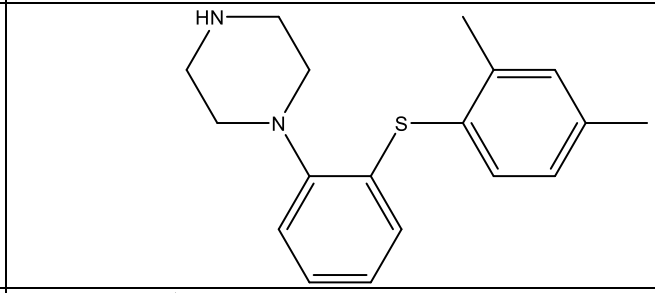
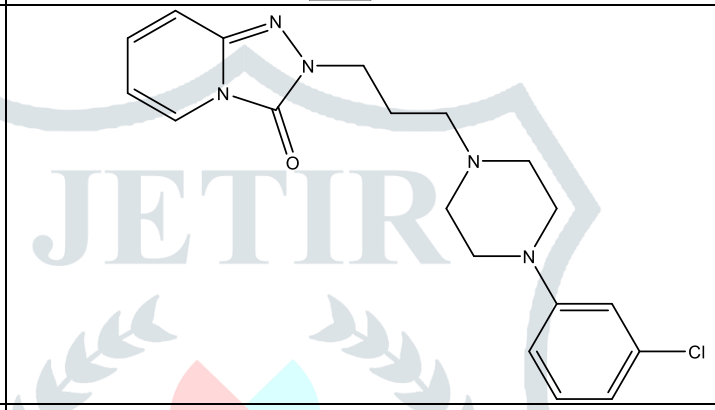
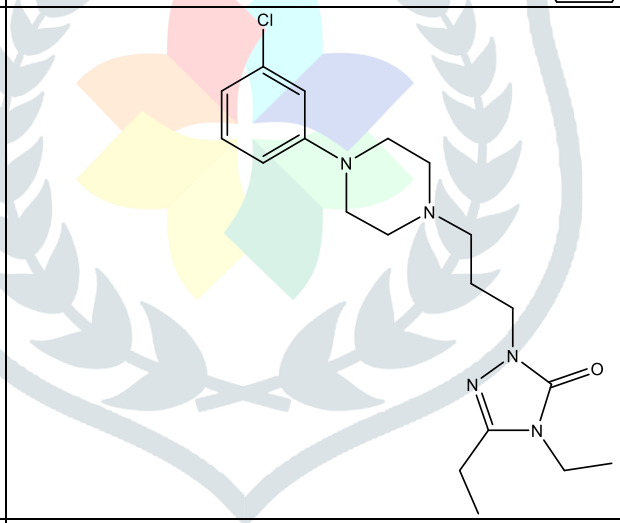
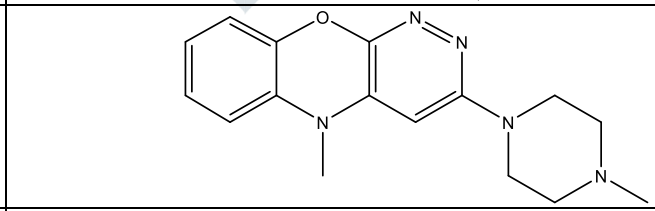
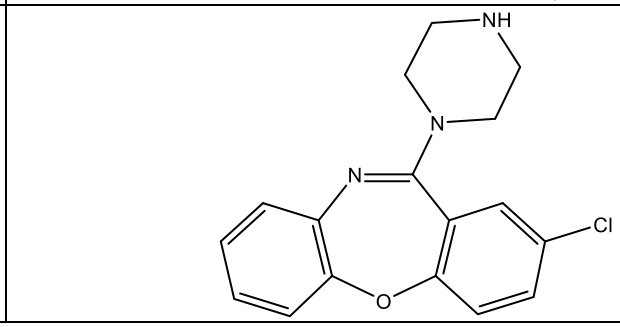
quinolinone. The synthesis of intermediate 5, an oily liquid following treatment, was carried out using tri fluoroacetic acid. This reaction is gentle and has a good yield. The goal was to remove the Boc group. In an alkaline environment, Intermediate 5 interacted with various substituted benzyl bromides and brominated alkanes to yield the target compounds 6a–e and 7a–f. The chemical 6a has been reported to have the highest level of antidepressant activity. (Zhou, 2024)

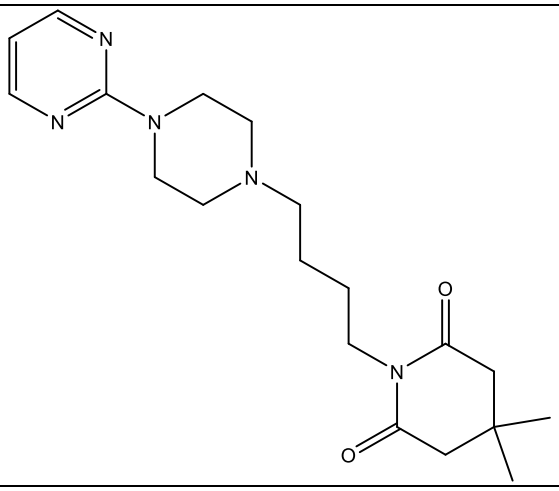
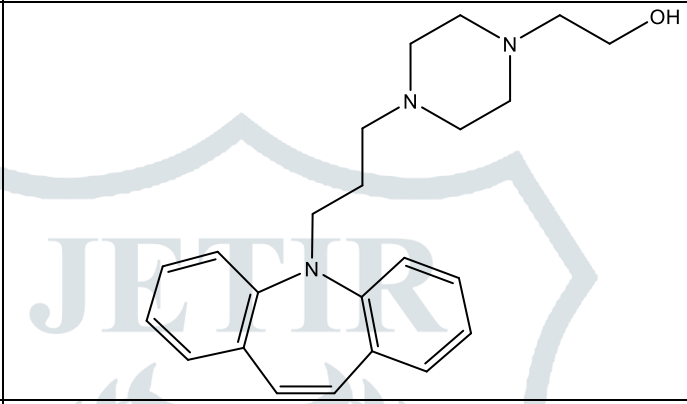
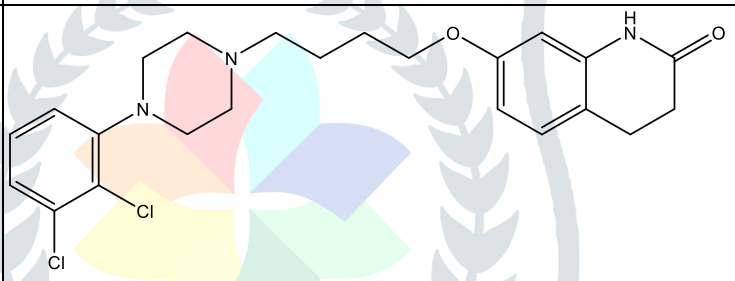
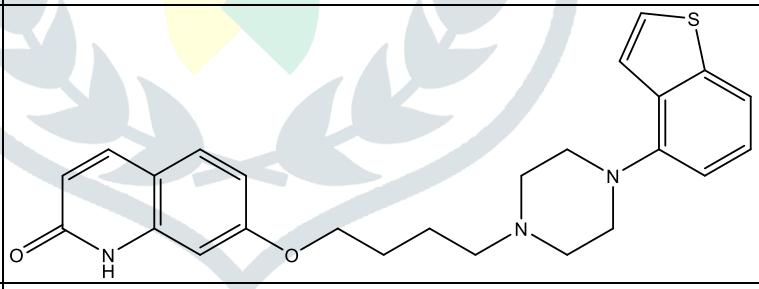
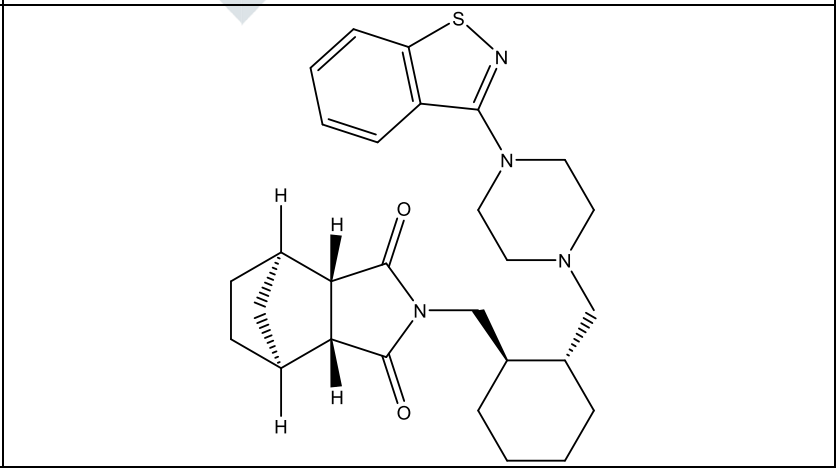


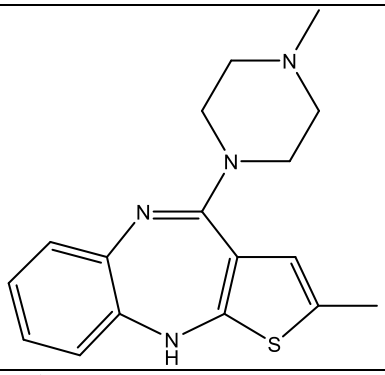
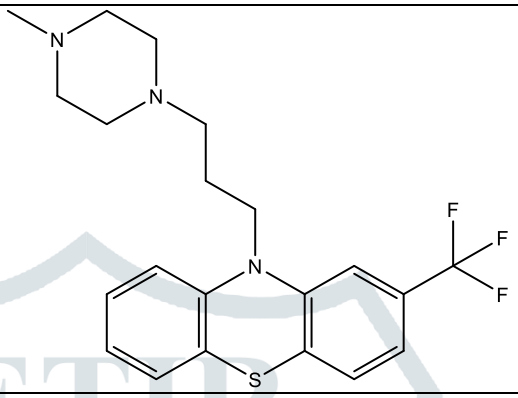
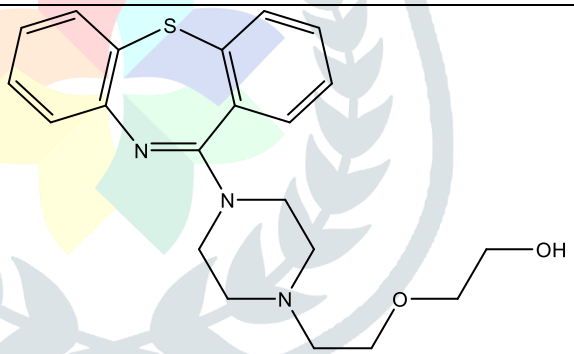
Scheme 13: Synthesis of antidepressant piperazine derivatives

Table No.5: Anti Depressents In Market That Contain Piperazine Ring[17,23,38]

DRUG NAME	MECHANISM OF ACTION	STRUCTURE
Nefazodone	Acts primarily as a potent antagonist of the serotonin 5-HT_{2A} receptor and to a lesser extent of the serotonin 5-HT_{2C} receptor	

Vilazodone	Acts as a serotonin reuptake inhibitor and 5-HT_{1A} receptor partial agonist	
Vortioxetine	Acts as a serotonin reuptake inhibitor	
Trazodone	Acts as antagonist of adrenergic receptors, weak histamine H1 receptor antagonist, and weak serotonin reuptake inhibitor.	
Etoperidone	Acts as serotonin antagonist and reuptake inhibitor	
Pipofezine	Act as a potent inhibitor of the reuptake of serotonin	
Amoxapine	Acts as moderate and strong reuptake inhibitor of serotonin and norepinephrine	

Gepirone	Acts as 5-HT1A receptor partial agonist and α2-adrenergic receptor antagonist	
Opipramol	Acts as a high affinity sigma receptor agonist	
Aripiprazole	partial agonist at dopamine D2 receptors, partial agonist at 5-HT1A receptors and an antagonist at 5-HT2A, receptors	
Brexpiprazole	Acts as a partial agonist of the serotonin 5-HT1A receptor and the dopamine D2 and D3 receptors	
Lurasidone	Acts as an antagonist of the dopamine D2 and D3 receptors, serotonin 5-HT_{2A} and 5-HT_7 receptors, and the α_2C-adrenergic receptor	

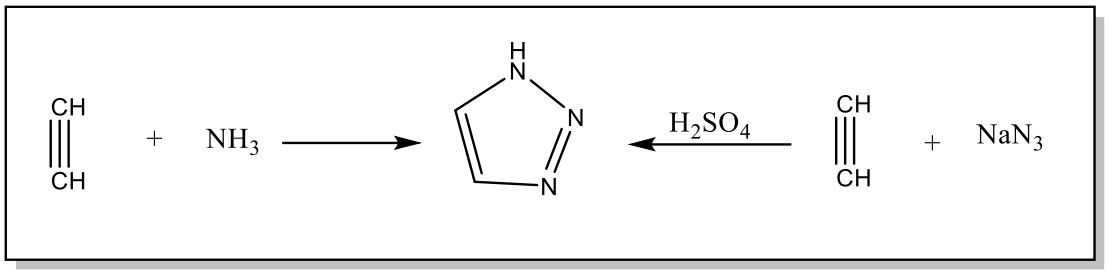
Olanzapine	Acts as an antagonist of the dopamine D2 and serotonin 5-HT_{2A} receptor	
Trifluoperazine	work by blockading dopamine D1 and D2 receptors in the mesocortical and mesolimbic pathways	
Buspirone	Acts as agonist of the serotonin 5-HT1A receptor with high affinity	
Quetiapine	Acts as dopamine, serotonin, and adrenergic antagonist, and a potent antihistamine with some anticholinergic properties	

6. TRIAZOLE

Triazoles are a class of heterocyclic compounds that have three nitrogen atoms and two carbon atoms organized in an aromatic five-membered ring. (Coppen, 1977; Santana, 2022) Triazoles are present in many strong, physiologically active compounds and have a broad spectrum of biological functions, such as hexaconazole (an antifungal medication), rizatriptan (an antimigrane medication), alprazolam (a hyptonic, sedative, and tranquilizer drug), and trazodone (an antidepressant medication). (Kumar, 2021; Santana, 2022) Thus far, studies have demonstrated that triazole ring modifications are highly effective due to their increased potency and decreased toxicity. (Koenig, 1967)

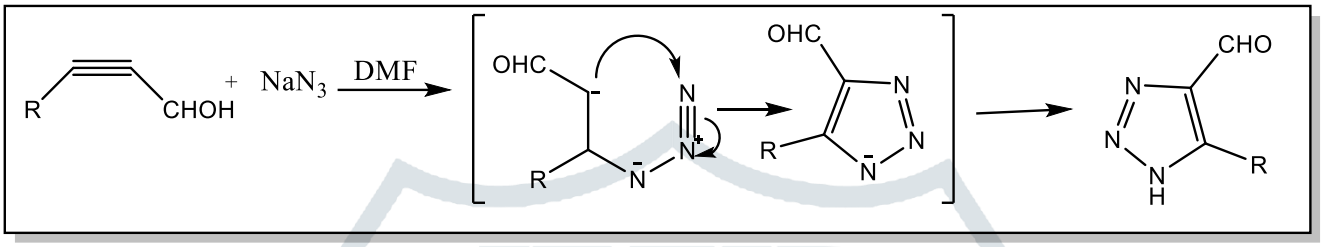
Main method of synthesis contains triazole moiety

- Dimroth and Fester initially subjected an alcoholic solution of hydrazoic acid to heating at 100°C for 70 hours, in conjunction with an acetone solution of acetylene, resulting in the production of 1H-1,2,3-triazole. Thesame chemical was also produced in an acid solution by reacting NaN3 with acetylene.



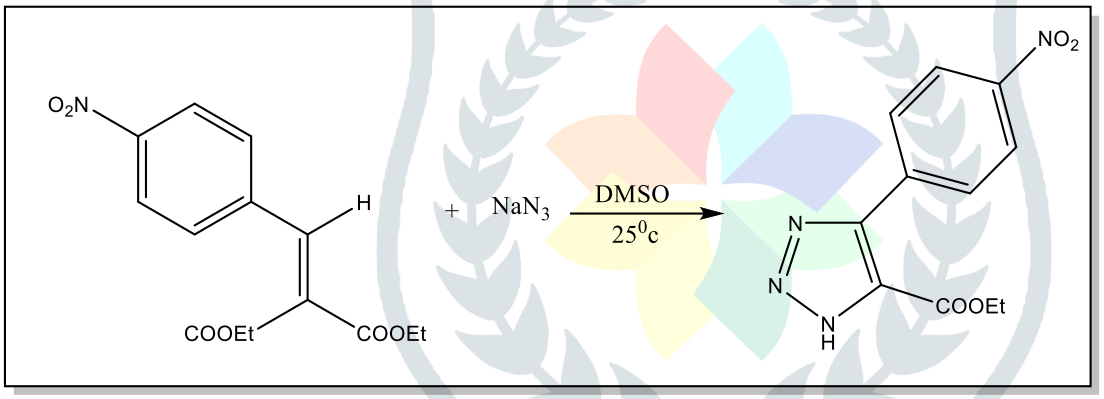
Scheme 14: Synthesis of 1H-1,2,3-triazole

- Cycloaddition of azide ions with alkynes results in moderate to high yields of 1,2,3-triazoles. Triazole yields can be quantified by alkynes with a substituent that withdraws electrons. 5-substituted 1H-1, 2, 3-triazol-4-carbaldehyde was produced by reacting sodium azide with 2-alkynals in DMSO or DMF. (Ram, 2019)



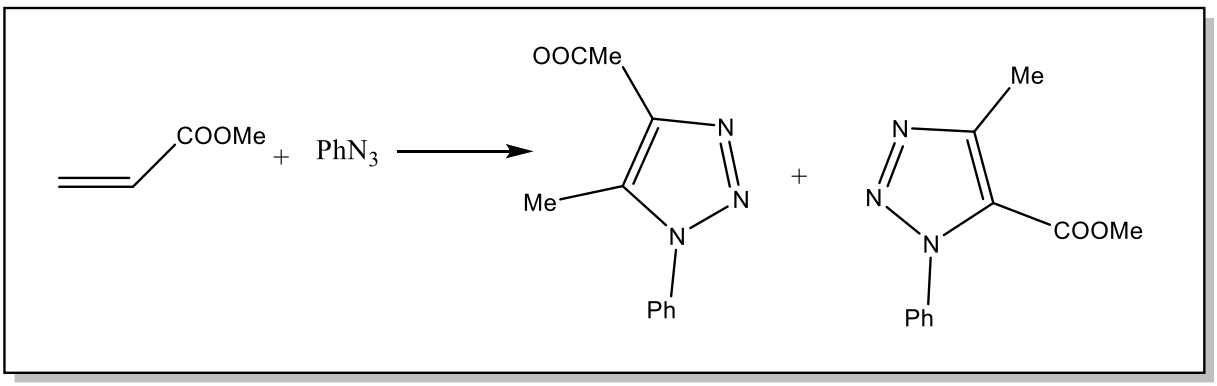
Scheme 15: Synthesis of 1,2,3-triazoles by cycloaddition of azide ions with alkynes

- Ethyl 3-(nitrophenyl)acrylate and sodium azide reacted in DMF or DMSO at 25°C for two hours, yielding 41% of ethyl 4-(p-nitrophenyl)-1H-1,2,3-triazol-5-carboxylate.



Scheme 16: Synthesis of ethyl 4-(p-nitrophenyl)-1H-1,2,3-triazol-5-carboxylate by reaction of Ethyl 3-(nitrophenyl)acrylate and sodium azide in presence of DMF

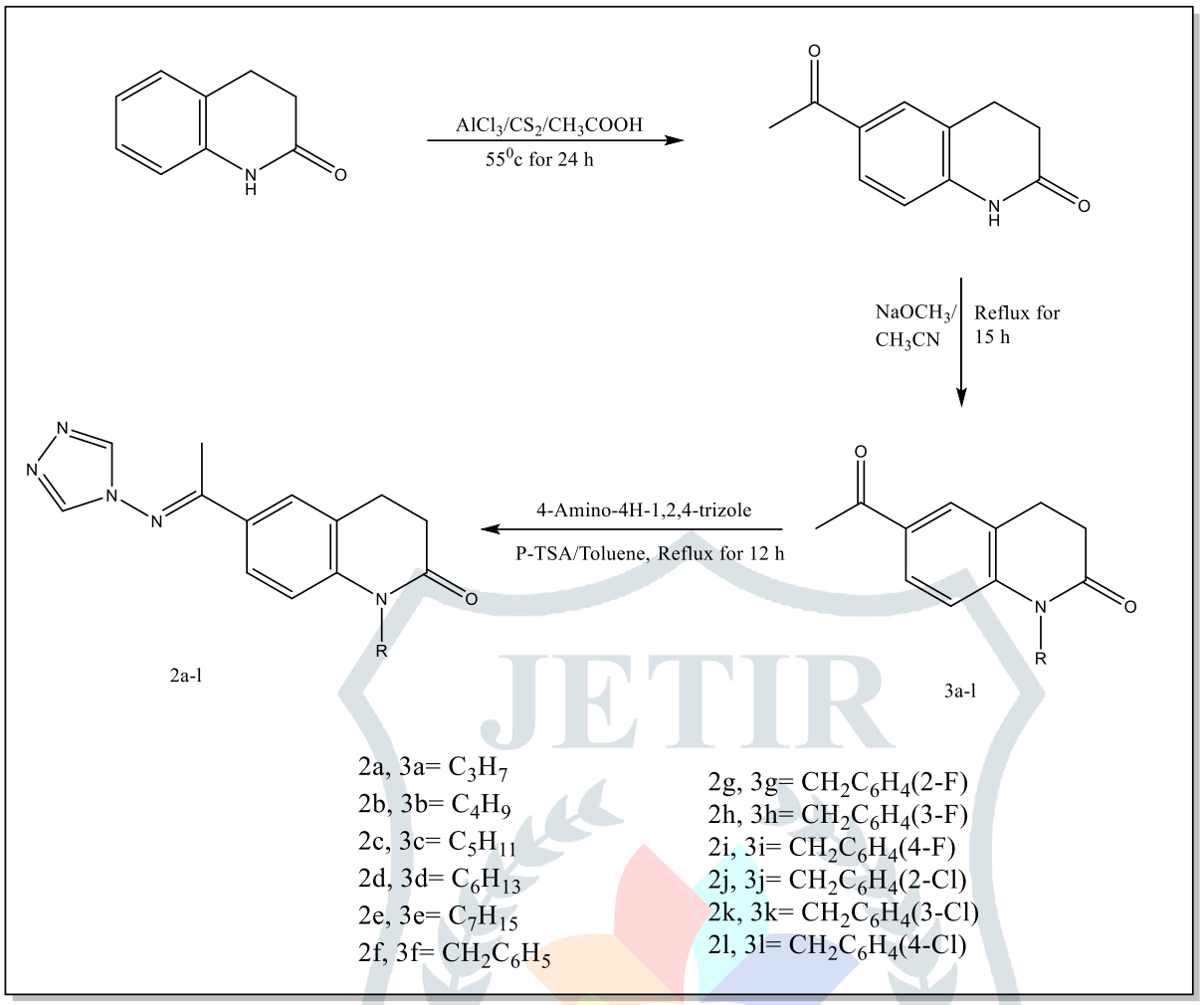
- Cyclo addition is used to combine phenyl azides with methyl but-2,3-dienoate to create a mixture of Methyl and 1-phenyl-5-methyl-4-carboxylate in a 9:1 ratio of 1-phenyl-4-methyl-5-carboxylate. (Ram, 2019)



Scheme 17: Derivatization of a triazole antidepressant

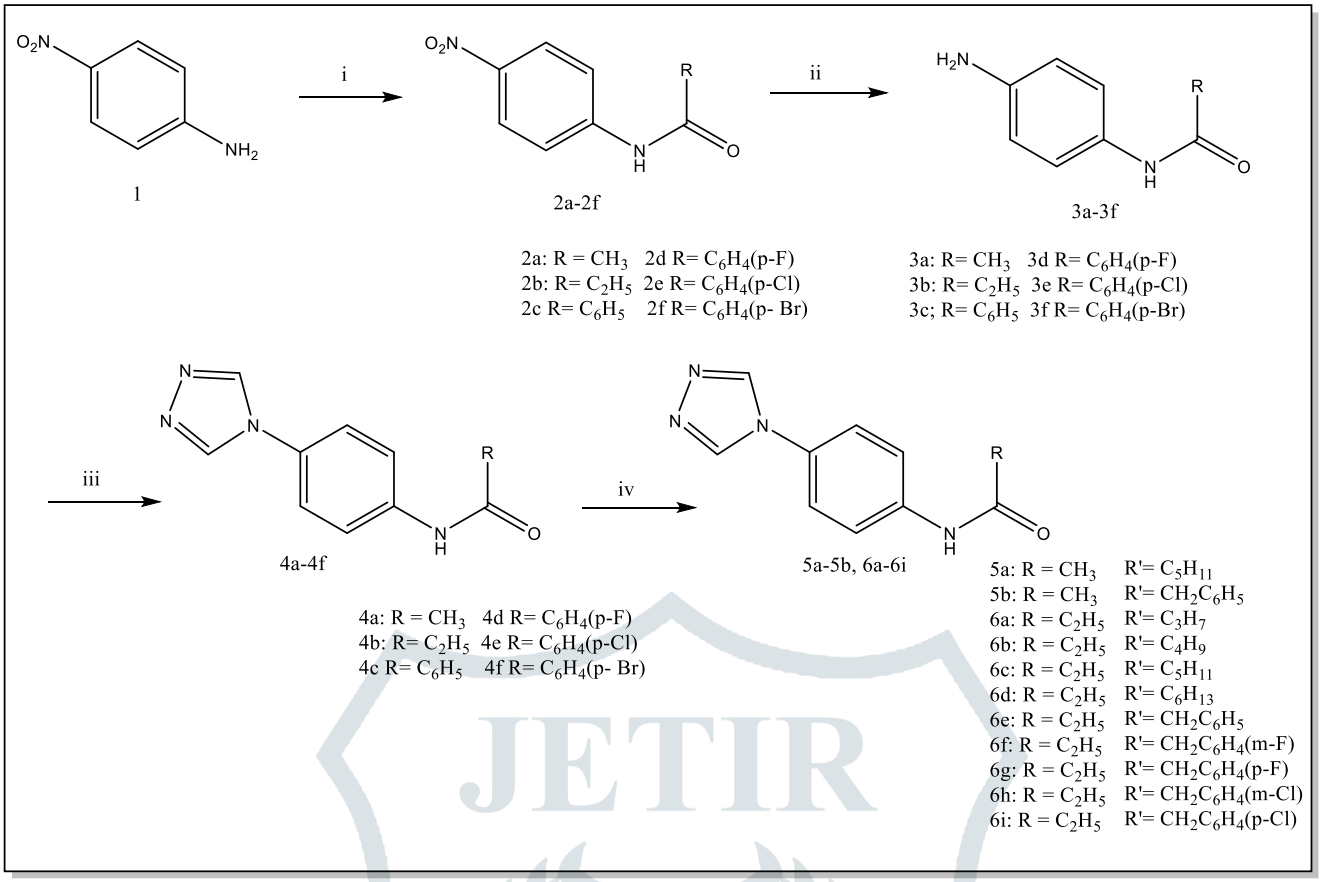
- 3,4-dihydro-2(1H)-quinolinone was first acetylated in CS2 using acetyl chloride to yield 6-acetyl-3,4-dihydroquinolin-2(1H)-one, utilizing AlCl3 as a Lewis acid. Haloalkanes alkylated the intermediate 1 in the presence of NaOCH3 to produce the intermediates 2a–l. Ultimately, compounds 2a–l was converted into compounds 3a–l by condensation with 4H-1,2,4-triazol-4-amine while PTSA was used as a catalytic condition

in refluxed toluene.(Zhao, 2023; Martinez, 1992; Deng, 2014)



Scheme 18: Derivatization of a triazole antidepressant by acetylation of 3,4-dihydro-2(1H)-quinolinone

- Scheme 1 was followed in the synthesis of the target compounds, which began with 4-nitroaniline as the raw material.Then, the compounds 2a and 2b were produced by treating acetic anhydride and propionic anhydride in the refluxed acetic acid. Compound 1 and aroyl chlorides were condensed in acetonitrile with potassium carbonate present to create compounds 2c–2f. Compounds 2a-2f was reduced using hydrazine hydrate and Pd/C as nitro-reducing conditions to get compounds 3a-3f. Triethyl ortho formate and formyl hydrazine in acetonitrile were then added to compounds 3a–3f to create compounds 4a–4f. Ultimately, compounds 5a–5b and 6a–6i were produced by alkylating compounds 4a or 4b with various alkylating agents. During the process of preparing compound 5b, compound 7 by mistake was produced. Alkaline circumstances could eliminate the acetyl group from molecules 4a or 5b. (Song, 2021; Chen, 2013; Baisch, 2013)

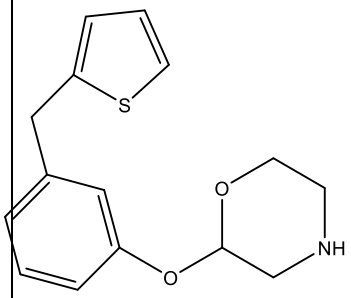


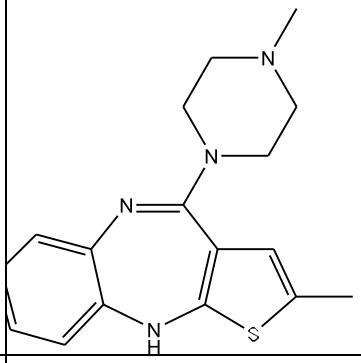
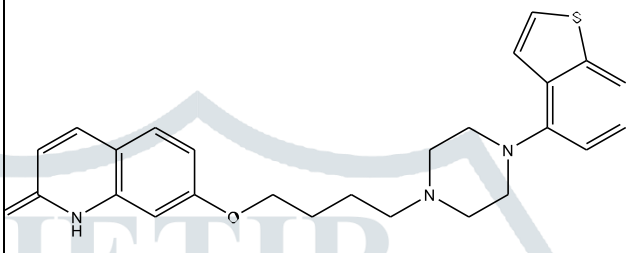
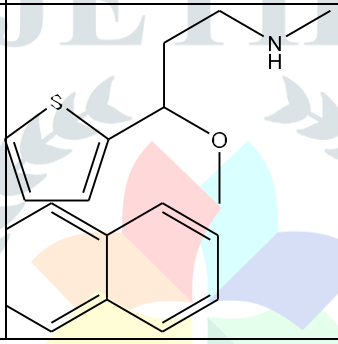
Scheme 19: Derivatization of a triazole antidepressant with 4-nitroaniline as starting material

A. Sulphur-based heterocyclic moiety-

Sulfur is present at position one in the five-membered heteroaromatic compound thiophene. A significant class of heterocyclic compounds with intriguing uses in medicinal chemistry is thiophene and its substituted derivatives. Numerous therapeutic properties, including anti-inflammatory, anti-psychotic, anti-arrhythmic, anti-anxiety, anti-fungal, antioxidant, estrogen receptor modulating, anti-mitotic, anti- microbial, kinases inhibiting, and anti-cancer effects, have been reported, with a wide range of applications in medicinal chemistry. Marketed drugs that contain thiophene are mentioned below. (Song, 2021; Coppen, 1977)

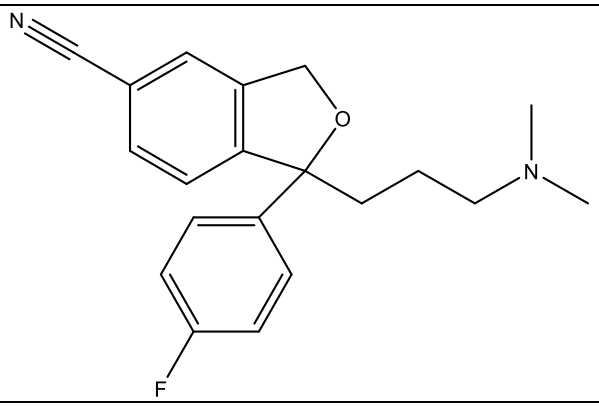
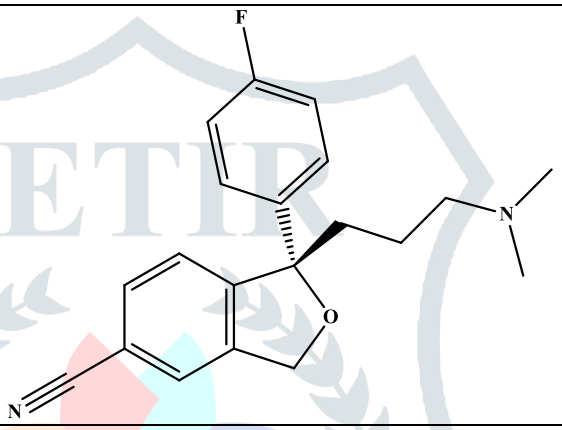
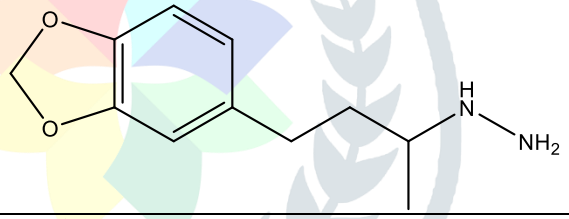
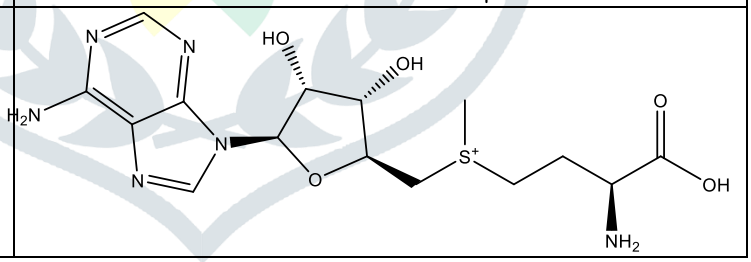
TableNo.7: Anti-Depressants in Market That Contain Thiophene moiety (Sindhu, 2013; Khan, 2016**)**

DRUG NAME	MECHANIS M OF ACTION	STRUCTURE
Teniloxazine	t acts as an ntagonist of the 5-HT2A receptor and xhibits strong nhibition of nor-pinephrine euptake, emonstrating noderate selectivity ver serotonin and lopamine ransporters.	

Olanzapine	t serves as an ntagonist of the lopamine D2 and erotonin 5-HT2A eceptors.	
Brexpiprazole	t acts as a partial gonist of the lopamine D2 and D3 receptors, along vith the serotonin -HT1A receptor.	
Duloxetine	Serotonin-Nor-pinephrine euptake inhibitor	

B. Oxygen-based heterocyclic moiety

In organic chemistry, heterocyclic with oxygen are a significant class of molecules. Tetra hydrofuran, one of these compounds, is used as a solvent, flavoring, and fragrance. The electron density will change as the aromatic ring fuses with the oxygen-heterocyclic, changing the resulting physical, chemical, and biological properties. (Sindhu, 2013) Most of marketed anti-depressant drugs contains oxygen based hetero cyclic moiety like furan, dioxole etc.

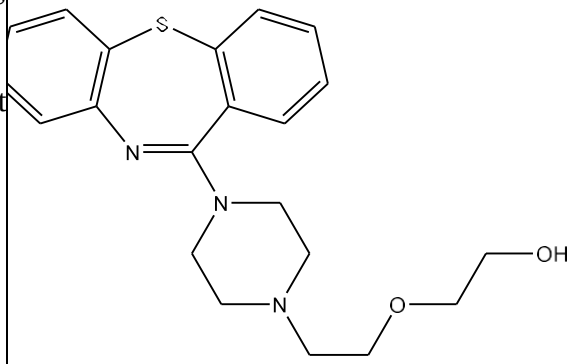
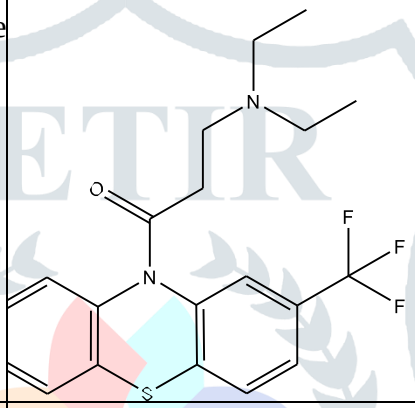
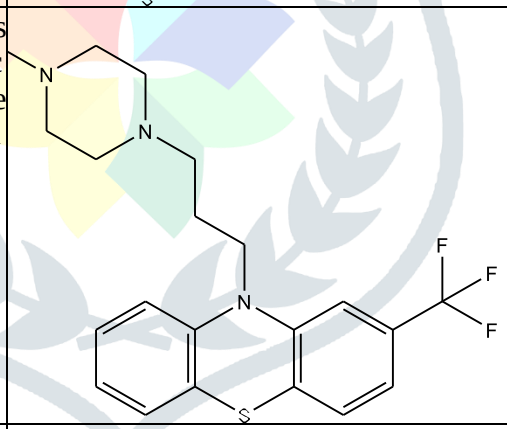
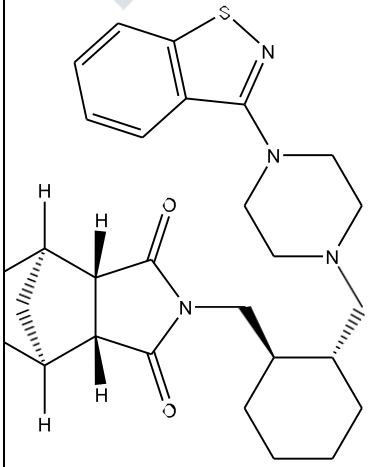
DRUG	MECHANISM OF ACTION	STRUCTURE
Citalopram	An inhibitor of elective serotonin euptake.	
Escitalopram	Selective inhibitor of erotonin reuptake.	
Safrazine	An irreversible nhibitor of monoamine oxidase.	
S-Adenosyl methionine	Cofactor for the roduction of nonoamine eurotransmitters.	

TableNo.8: Anti-Depressants in Market that Contain Furan and Dioxole Ring (Moreira, 2023; Song, 2017)

C. MULTIPLEHETEROATOMCONTAININGHETEROCYCLIC MOIETIES

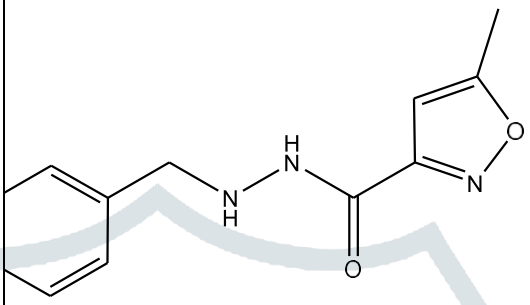
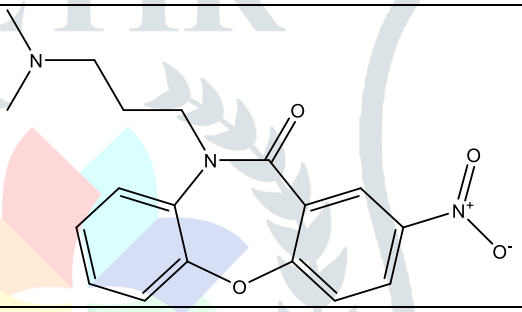
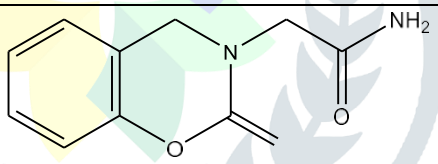
- **Nitrogen-Sulphur Containing Heterocyclic Rings-**

TableNo.9:Anti-depressants in MarketwithNitrogen-SulphurContaining Heterocyclic Rings (Sorensen, 1990; Veselý, 1967**)**

DRUG NAME	MECHANISM OF ACTION	STRUCTURE
Quetiapine	Act as dopamine, erotonin, and drenergic ntagonist,anda potent ntihistamine vithsomeanti- holinergic properties.	
luacizine	Act as a nor- pinephrine reuptake nhibitor.	
rifluoperazine	Act as lopamineD1andD2Rec ptors blocker inthe nesocorticalandmesoli nbic pathways.	
urasidone	t acts as an antagonist f the dopamine D2 nd D3 receptors, erotonin 5-HT2A and -HT7 receptors, and 2C-adrenergic eceptor, while also unctioning as a partial gonist of the erotonin 5-HT1A eceptor.	

- **Nitrogen-Oxygen ContainingHeterocyclicRings**

TableNo.10:Anti-DepressantsinMarketwith Nitrogen-Oxygen Containing Heterocyclic Rings(Halder, 2023; Bailly, 2023**)**

DRUG NAME	MECHANISM OF ACTION	STRUCTURE
socarboxazid	ncrease the levels f the monoamine eurotransmitterers erotonin, dopamine, orepinephrine, pinephrine, nelatonin, henethylamine in he brain.	
Nitroxazepine	Acts as a erotonin, nor- pinephrine reuptake nhibitor.	
Caroxazone	Reversible nonoamine oxidase nhibitor RIMA)ofbothMAO-A and MAO-B	

- **MORPHOLINE**

To enhance permeability across the blood-brain barrier (BBB) and develop medications for the central nervous system (CNS), precise chemical modifications are necessary. This involves achieving a delicate balance between size and lipophilicity. Given their physicochemical and structural properties, morpholine and its analogues are particularly valuable heterocycles in this regard. (Kumar, 2023)Indeed, the presence of weak basic nitrogen at the oxygen atom's opposite position gives the ring a unique pKa value and flexible conformation, enabling it to participate in multiple lipophilic-hydrophilic interactions and enhancing the structure's overall blood solubility and brain permeability. (Kourounakis, 2020)They structurally resemble endogenous neurotransmitters (such aryl-morpholines) and studies have demonstrated their critical role in improving blood-brain barrier bridging. For several decades, the market has already been home to a wide variety of morpholine derivatives. (Kaya, 2022)

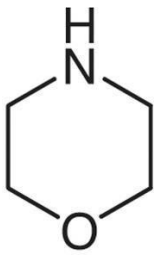
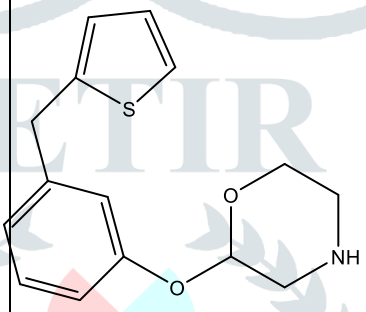
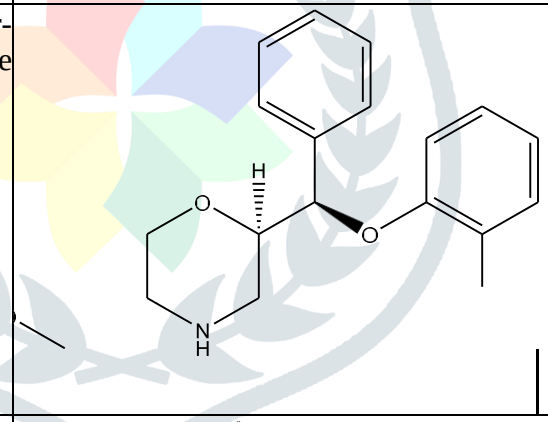
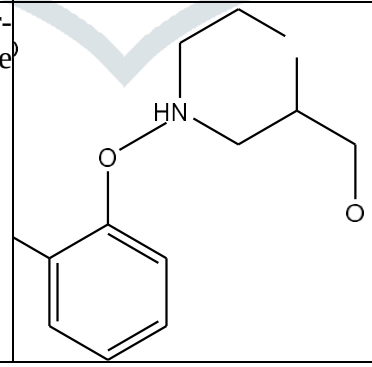
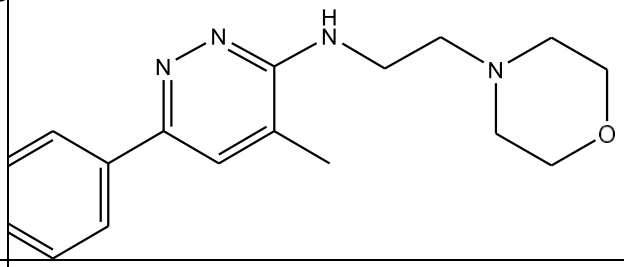
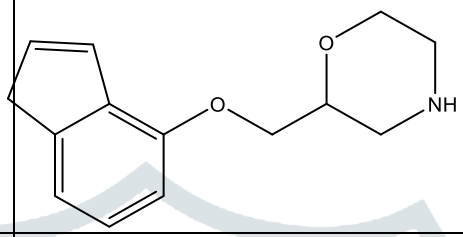
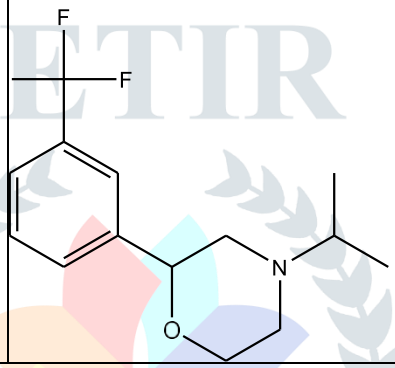


Fig 8:Morpholine

TableNo.11: Antidepressants in Market That Contain Morpholine Ring (Kumar, 2017; Zheng-Song, 2019**)**

DRUGNAME	MECHANISMOF ACTION	STRUCTURE
Teniloxazine	Functions as an ntagonist of the 5-HT2A receptor and a trong nor-epinephrine euptake inhibitor with noderate selectivity ver the serotonin and lopamine transporters.	
Reboxetine	Selective nor-pinephrine reuptake nhibitor.	
Viloxazine	Selective nor-pinephrine reuptake nhibitor.	

Minaprine	Acts as a reversible inhibitor of MAO-A.	
Indeloxazine	Selective inhibitor of nor-epinephrine reuptake.	
Oxaflozane	Function as a serotonin-5 HT1A receptor antagonist.	

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