REVIEW OF LITERATURE
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Globally more than 10-15% of the prescriptions are written for the patients suffering from mental disorders. Drugs which are used for the treatment of mental disorders are psychotropic agents.

Psychotropic agents can be placed into 4 major categories. Anti-anxiety-sedative agents particularly benzodiazepines are those used for the drug therapy of anxiety disorders. Anti-depressant (mood-elevating agents) and antimanic (mood-stabilizing drugs) particularly Lithium salts and certain anticonvulsants and are used to treat affective or mood disorders and relative conditions. Antipsychotic or neuroleptic drugs are those which are used to treat very severe psychiatric illness the psychosis and mania. They have beneficial effect on mood and thought but many standard neuroleptic agents carrying the risk of producing characteristic side effects that mimic neuroleptic diseases, whereas modern antipsychotics are associated with weight gain and adverse metabolic effects such as diabetes.

Psychotropic drugs are the heterogenous group of compounds like indoles (oxypertine, indolylethyl-pyridines), phenothiazines (chlorpromazine, fluphenazine) dibenzoazepine (lozapine succinate), dibenzothiazepine (quetiapine fumarate), benzodiazepines (olanzapine, clozapine) etc. These drugs possess diverse mechanism of actions the most widely used mechanism of action of this class of drugs is to antagonize dopamine D2 receptors (typical antipsychotic drugs) or to antagonize dopamine D1, D3, D4 and D5 receptors (atypical antipsychotic drugs)
Indole derivatives

Oxypertine

Indoleethylpyridines

Phenothiazine derivatives

Chlorpromazine

Fluphenazine

Dibenzothiazepine derivatives

Quetiapine fumarate

Dibenzoxazepine derivatives

Loxapine succinate

Dibenzodiazepine derivatives
Olanzapine  
Clozapine

In addition to these known typical and atypical antipsychotic drugs, a larger number of derivatives of different heterocyclic moieties like indole, phenothiazine, benzothiazepine, benzoxazepine, quinazolinone etc. have been synthesized and screened for their psychotropic or antipsychotic activity by different scientists, which are described as follows-
INDOLE DERIVATIVES

Indole derivatives have been found to be biologically versatile compounds which possess potent antihypertensive, anticonvulsant, anti-pyretic, anti-inflammatory, hypnotic and antipsychotic properties. In addition many indole derivatives notably molindone, oxypertin and inolylethylpyridines are well known for their neuroleptic or antipsychotic action. Moreover, several scientists have also elucidated that the modification (at position 2 or 3) in the indole nucleus by different heterocyclic moieties yields the potent antipsychotic agents which is proved by the synthesis of the following compounds by various scientists.

Some 2-indolylmethyl and 3-indolylmethylhydrazines (I) elicited potent psychotropic activity (Alemany et al., 1971).

\[
\text{R} = \text{Me}, \text{R}^1 = \text{CH}: \text{NHNH}_2
\]

(I)

Some indolyl-2-amino-2-methyl propanones (II) have reported as useful psychotropic agents (Parcel et al., 1971).

\[
\text{R} = \text{Me}, \text{R}^1 = \text{R}^2 = \text{H}
\]

(II)
Mashkovskii et al. (1973) have reported psychotropic 1,10-trimethylene-8-methyl-1,2,3,4-tetrahydropyrazine [1,2-a]indole (III).

![Diagram of molecule III](image)

Yoshina et al. (1975) have reported furo [3,2-b]indoles (IV) as a psychotropic agents.

![Diagram of molecule IV](image)

R = H, halo, alkyl etc., R' = H, alkyl

(IV)

Pyrimidinylindoles (V) have reported as psychotropic agents by Biere et al. (1976).

![Diagram of molecule V](image)

R = H, Me, (CH₂)₃ NE₂, R' = H, NH₂, Me, R³ = H₁, OH, OMe

(V)

2,3,4,4a,5,9b-Hexahydro-1H-pyrido[4,3-b]indole (VI) derivatives exhibited prominent psychotropic activity (Nagai et al., 1977).
Indolo [3,2,1-de] [1,5] naphthyridine derivatives (VII) showed psychotropic and antianoxic properties as reported by Koletar et al. (1978).

\[ R, R^1 = \text{Me, Et} \]

(VI)

\[ R = \text{H, CO}_{2}\text{Me, CONMe}, R^1 = \text{Me, Bz, NCCH}_{2}\text{CH}_2, \]
\[ R^2 = \text{H, 9-or 10-Me,F,Cl}, R^3 = \text{Me}; R^4 = \text{OH}; R^5 = \text{H} \]

(VII)

2-Substituted-2,3,4,5-tetrahydro-1H-pyrido[4,5-b]indole derivatives (VIII) exhibited psychotropic activity as reported by Nagai et al. (1980).

\[ R= \text{H, Cl, Me}, R^1 = \text{Me, CH}_2, R^2 = \text{Ph CH}_2 \]

(VIII)
Zhungietu et al. (1980) reported neurotropic activity in 2-acylindole-3-carboxylic acids (IX).

![Chemical Structure of IX](image)

\[ R^1 = \text{Ph, p- Cl C}_6\text{H}_4, \text{p- Br C}_6\text{H}_4, R^2 = \text{H, me, } R^3 = \text{H, Br, MeO, Cl} \]

(IX)

Grinev et al. (1981) reported the marked psychotropic activity in 1, 10-trimethylene-1,2,3,4-tetrahydropyrazino[1,2-a]indoles (X).

![Chemical Structure of X](image)

\[ R = \text{Me, Cl, Br, H, } R1 = \text{H, Cl, } R2 = \text{H, Cl, } R3 = \text{Me, Et, Pr} \]

(X)

Anticonvulsant spiro[indoline-3,4'-piperidine]s (XI) were reported. (Ong & profilt, 1982).

![Chemical Structure of XI](image)

\[ R = \text{H, alkyl, cyano etc, } R^1 = \text{H, alkyl, } R^2 = \text{H, halo alkyl etc, } R^3 = Q[R_4, R_5 = \text{H, halo etc}} \]

(XI)
3-Hydroxy indoles (XII) as potential anticonvulsants were reported by pojouhesh et al. (1983).

\[
\begin{align*}
R &= \text{H, alkyl, cyano etc., } R^1 = \text{H, alkyl, } R^2 = \text{H, halo alkyl etc.,} \\
R^3 &= \text{Q|R^4, R^5 = H, halo etc.}
\end{align*}
\]

(XII)

1-Phenyl-2-(1H,3H)-indolones (XIII) as psychotherapeutic agents have been reported by Howard & Sarges (1984).

\[
\begin{align*}
R &= \text{H, alkyl, } R^1, R^2, R^3 = \text{H, Me, R^4 = H, alkyl, alkoxy, Cl, F, CF}_3, \\
R^5 &= \text{H, alkyl, alkoxy.}
\end{align*}
\]

(XIII)

Synthesis and pharmacological screening of 1-(substituted aminomethyl)-2-oxo-3-amino-(4-phenyl-5-arylazothiazolyl)indoles (XIV) have been carried out by Agarwal et al. (1986).
$\text{Ph}$

$\text{N=N}$

$\text{N=N}$

$\text{N=N}$

$\text{R} = 4$-Cl, 2-NO$_2$, 4-Me, R$^1$ = Piperdinomethyl,

(XIV)

3,4,5,6-Tetrahydro-1H-azepino[5,4,3-c,d]indole derivatives (XV) as a psychotropic agents were reported by Somei et al. (1987).

$\text{Me_2C=CH}$

$\text{R}$

$\text{N}$

$\text{NH}$

$\text{R=H, AC.}$

(XV)

3-Aminomethyl derivatives of indan, indoline and [dihydrobenzo] furan and thiophene (XVI) for treatment of central nervous system disorders were reported by Boegesoe & Perreggard (1989).

$\text{X = H}_2\text{C}_1\text{O}_1\text{S}_1\text{RN, R=H, C}_1\text{-6, alkyl, R}^1\text{-h, alkenyl etc, R}^2\text{-H, C}_1\text{-6, alkyl.}$

$\text{R}^3\text{- (un)substitued OH, R}^4\text{-H, halo, CF3 etc.}$

(XVI)
1-Indolylalkyl-4-(substituted-pyridinyl)piperazines (XVII) were synthesized by Smith et al. (1990) and this compounds have shown promising antidepressant activity.

\[
\begin{align*}
R^1, R^2 &= \text{H}, \text{C}_{1-4} \text{ alkyl, } R^3, R^4, R^6, R^9 &= \text{H}, \text{C}_{1-4} \text{ alkyl etc, } R^8 &= R^9 = \text{H}. \\
R^6, R^7 &= \text{H, Me, } R^6 R^7 &= \text{CH}_2, Z = \text{C}_{5-7} \text{ alkylene, } \text{Cycloalkenylene etc.}
\end{align*}
\]

(XVII)

Synthesis and pharmacological screening of sertindole prodrugs (XVIII) have been reported (Perregaard & Perdersen, 1992). These compounds have shown antipsychotic and antidepressant activities.

\[
\begin{align*}
X &= \text{CO or CS, } R &= \text{H, alkyl, alkenyl, Ph, cycloakyl etc.}
\end{align*}
\]

(XVIII)

Indolecaboxamides (XIX) have also been prepared and used as potential psychotropic agents (Costa et al., 1993).
$R^1, R^2 = \text{H, C}_{3-12} \text{ alkyl, (alkyl) aryl, } R^1R^2 = 4-6 \text{ membered (4n) satd. ring.}$

$R^3, R^4 = \text{H, C}_{1-12} \text{ alkyl, } \text{O}_2\text{N, H}_2\text{N, N}_3, \text{cyano, halo, RO}_2\text{C, RO, RS (where in}}$

$\text{R=H, alkyl), } A = \text{C}_{1-3} \text{ alkylene, } Z = \text{O, NH, S, CH : CH, } n = 1-3$

(XIX)

Andersen & Sharsfeldt (1993) have synthesized 3-arylidindole and 3-arylidazole derivatives (XX) which are used for the treatment of psychoses.

$Ar = (\text{substituted}) \text{ phenyl, } R^1 = R^4 = \text{H, halo, loweralkyl etc.}$

$R^6 = \text{H, cycloalkyl, lower alkyl etc, } X = \text{CH}_2 (\text{when dotted line indicates no double bonds}), X = \text{N, CR}_6^6 (R^5 = \text{H, halo, CF}_3, \text{lower alkyl}) \text{where d}

\text{otted line indicates a double bond), Y =, CH (when dotted line indicate no dotted line indicate no double bound).}$

(XX)
Perregaard et al. (1995) have synthesized new series of chloro (fluorophenyl)[(dihydroimidazolonyl) ethyl] piperidinyl] indoles (XXI) which are useful in the treatment of psychosis and depression.

\[ R^1-R^4 = \text{H, halo, alkyl, aryl, OH, alkoxy arythio.} \]  

(XXI)

Antidepressant and anxiolytic activities were exhibited in substituted pyrido [3,4-b]indoles (XXII) (Commons et al., 1996).

\[ R^1 = R^5 = \text{H, F halo, loweralkyl etc, } R^6 = \text{H, alkyl} \]
\[ R^3, R^4 = \text{H, } R^6, R^7 = \text{H, (un) substituted alkyl, alkenyl, cycloalkyl etc.} \]  

(XXII)

Macor & Wythes (1997) have synthesized some indole derivatives (XXIII) as potent serotonin agonists (5-HT) (psychotherapeutics).
Several 2-aminomethyl-3,4,7,9-tetrahydro-2H-pyranopyrano [2,3-e]indol-8-ones (XXIV) were reported as dopamine autoreceptor agonists (antipsychotics) (Stack & Mewshaw, 1997).

Hasegawa et al. (1998) have synthesised several oxindole derivatives (XXV). The compounds are used as psychotropic agents.
3-(Piperidin-3-yl)-1H-indole derivatives (XXVI) elicited psychotropic activity (Hallett & Rowley, 1999).

\[ W = \text{cyclohexyl, carboxylic acid ester, (un) substituted carboxamide, (un) substituted Ph. Etc, } X, Y = \text{H, halogen CF}_3, \text{ alkyl, alkoxy, Ph.} \]

\[ Q = (\text{un}) \text{ substituted piperidin-3-yl, } R^3 = \text{H or alkyl.} \]

(XXVI)

5-Aminoethyl- and 6-aminomethyl4-oxotetrahydroindole (XXVII) was found to possess potent antipsychotic activity (Masaguer et al., 1999).

(XXVII)

3-(Piperidin-4-yl)-2-phenyl indoles (XXVIII) have been prepared compounds were found to possess antipsychotic activity (Maxey et al., 1999).

(XXVIII)

\[ A, B = \text{H, halo CN, } X, Y = \text{H, halo; alkyl etc.} \]

\[ R1 = \text{alkyl, (un) substituted aryl (C}_{1-5} \text{) alkyl group.} \]
Crawforh et al. (2000) have synthesized 3-azabicyclooctyl-2-phenylindoles (XXIX) as selective antagonist of 5-HT$_{2A}$ receptors.

![Chemical Structure](image)

A,B= H, halo, CN, NO$_2$ etc., AB = methylenedioxy

X,Y=H, halo, CF$_3$, OCF, etc., Q= CH$_2$CH$_2$, (CH$_2$)$_3$.

R$^1$=H, alkyl, (substitued) aralkyl etc., R$^2$= H, halo, alkyl OH, alkoxy.

(XXIX)

3-(4-Fluoropiperidin-3-yl)-2-phenylindoles (XXX) have been reported as h$_5$-HT$_{2A}$ receptor antagonists (Michael et al., 2001).

![Chemical Structure](image)

R=H, aryl, substituted aryl etc.

(XXX)

Synthesis of piperazinyl (or piperidinyl)-substituted indole derivatives (XXXI) have been reported by Bang et al. (2002). These compounds are useful for the treatment of CNS disorders.
R_{1-4}, R_5, R_9 = H, halo, R=H, alkyl, acyl etc.

\[ W = \text{a bond, } O, S, \text{ etc.} \]

\[ X = C, \text{ etc.} \]

\[ N, n = 0-5, m = 0-5, u + w = 1-6. \]

\[ \chi = \text{O, S, \text{ etc.}} \]

\[ \gamma = \text{O, S, } \text{ etc.} \]

\[ \beta = \text{O, S, \text{ etc.}} \]
PHENOTHIAZINE DERIVATIVES

Phenothiazines comprises an important and valuable class of psychopharmacological agents and are still used as an antipsychotics. Chlorpromazine, a phenothiazine derivative, is being successfully used for the treatment of psychiatric disorders and several other derivatives of phenothiazine are reported in the literature to have psychopharmacology applications.

10-[2-(diethylamino)propionyl]-2-trifluoromethylphenothiazine hydrochloride (I) has been reported as potent psychotropic agent (Zhuravlev et al., 1970).

(I)

A potent psychotropic activity (Blondel & Fouche, 1971) has been reported in compound (II).

(II)

10-[γ-[4-(β-hydroxyethyl)-1-piperazinyl]-propyl]-3-trifluoromethylphenothiazine (III) has been found to possess promising psychotropic activity (Marcinkiewicz, 1972).
1-Piperazinylalkyl-substituted phenothiazines (IV) have been synthesized and reported as potent psychotropic agents (Nakanishi et al., 1973).

\[ X = X, \text{CH}_2\text{CH}_2, \text{CH:CH}. \ Q = (\text{CH}_2)_3, \text{CH}_2\text{CHMe} \text{ or CH}_2\text{CHMeCH}_2 \]
\[ R = \text{H,Cl,CF}_3, \text{SMe etc. n = 0,1,2 R'} = 2-3- \text{or 4-pyridyl, 2-furfuryl, or 2-thienyl} \]

Some new derivatives of phenothiazines have been reported as potent psychotropic agents (V) (Yashitomi Pharmaceutical Ind. Ltd., 1973).

\[ R, R' = \text{Me, R}^2 = \text{H, R}^3 = \text{Cl, X = S, CH}_2\text{CH}_2, \text{CMe}_2 \]

Shavyrina et al. (1974) reported promising psychotropic activity in 2- and 3-(dimethyl sulfamoyl)phenothiazine derivatives (VI).
R=COCH₂CH₂X; X=Cl. or R=(CH₂)₃X; X=Cl.

(VI)

Nakanishi & Arimura (1975) reported promising psychotropic activity in some spirocyclic compounds (VII).

Z=S. Z¹=(CH₂)₃. R=Cl. Z₂=CHMe

(VII)

Some new phenothiazine derivatives (VIII) have been reported as potent psychotropic agents (Nakanishi & Arimura, 1975).

R=H, Me., R¹=H, Cl, CF₃, SMe, OMe, CoMe.

X=CH₂CH₂, (CH₂)₃, CH₂CHMe, CH₂. X¹=S, (CH₂)₂, Me₂C, CH : CH.

(VIII)

Singh et al. (1976) reported promising anticonvulsant activity in 10-(2-arylimino-3 acetylamino-4-thiazolidinyl)phenothiazines (IX, X).
R= aryl

(IX, X)

Preparation of psychotropic activity of 10-[3-(4-hydroxypiperidino)propyl] phenothiazine-2-carbonitrile (XI) has been reported by Kawata & Hasegawa (1977).

(XI)

10-(β-Dialkylamino)ethylaminophenothiazines (XII) have shown potent antipsychotic activity (Corral et al., 1978).

(XII)

\[R= \text{Me, Et, } NR_2 = 1\text{-pyrrolidinyl, piperidino. } R^1 = R^2 = H, Cl.\]

Jaiswal et al. (1981) have synthesized 10-[3,5-diaryl-2-pyrazoline-1-yl) acetyl] phenothiazines (XIV). These compounds are potent anticonvulsant agents.
Some phenothiazines and phenoxazines (XV) have shown CNS depressant activity (Vierfond et al., 1983).

R=H, Cl, CF₃, R¹ = R² = H, X = O, S

Nemeryuk et al. (1986) have synthesized a novel series of 4-methoxy-7,8-dihydro-1,3-diazaphenothiazine aminoderivatives (XVI). Compounds were found to possess pronounced neurotropic activity.

R=Bu, Ph, hexyl, heptyl, CH₂CH₂CO₂H,
(CH₂)₃CO₂H, Me₂CH, cyclohexyl etc.

(XVI)
Synthesis and pharmacological evaluation of some phenothiazines (XVII, XVIII) as antidepressants were reported by Singh et al. (1992).

\[ R^1 = R^2 = \text{Aryl} \]

(XVII, XVIII)

5-Arylidene-2-aryl-3-(2-chlorophenothiazinoacetamido)-4-thiazolidinones (XIX) have been synthesized and were used as anticonvulsant and antifungal agents (Srivastava et al., 2000).

\[ R = 2-, 3-, 4-	ext{Cl}; 2-, 3-, 4-	ext{NO}_2; 2-, 3-, 4-	ext{Br}. \]

(XIX)
BENZOTHIAZEPINE DERIVATIVES

1,5-Benzothiazepine derivatives have been gained much significant in the recent years, due to its wide range of pharmacological applications like anticoagulant, antidepressant, sedative, psychopharmacological and tranquilizing activities etc. Importantly research on this nucleus led to the development of many antipsychotic agents. One of the used antipsychotic drug, Quetiapine furmarate, has benzothiazepine ring condensed with various heterocyclic nucleus is of great interest. Many pharmacologically active compounds have been found to exhibit antidepressant, anticonvulsant, neuroleptic or antipsychotic activities which are as follows:

4,5-dihydrobenzo[b]thieno [3,2-f] [1,4] thiazepines (I) have been synthesized by Rajsner & Protiva (1968) and reported as potent neurotropic and psychotropic agents.

\[ \text{R=Me, Ph.} \]

Some 11-(4-piperidyl)dibenz[b,f] [1,4] oxazepines and thiazepines (II) were found to possess potent tranquilizing activity (Howell et al., 1970).
R=Me, R¹=H, R²=H, R³=2-Cl, X=O,S.

(II)

6H-Dibenzo[b, f] [1,4,5]oxathiazepine-5,5-dioxides (III) have been reported as a psychotropic agents by Umeto & Chika (1971).

R¹=Br, NO₂, Cl,H, R²=H, Me,Cl, n=2,3.

(III)

1, 5-Benzothiazepine derivative (IV) elicited psychotropic activity (Kugita et al., 1971).

R¹=H, 4-Me etc, R²=H, Me, X=H,Cl.

(IV)
Nakanishi et al. (1972) have reported psychotropic piperazinyl thienobenzothiazepine derivatives (V & VI).

\[
\begin{align*}
\text{V} & \quad \text{VI} \\
\end{align*}
\]

\[n=1,2, \text{ R}=2\text{-thienyl}, 2\text{-pyridyl}, \text{ Ph}.
\]

Nacci et al. (1973) synthesized 5-phenyppyrollo[2, 1-b] [1, 5]benzothiazepine 6, 6-dioxide and 1,2,3,3a, 4, 5-hexahydro-5-phenyppyrollo [2,1-d] [1 5]benzothiazepine-1,4-dione-6,6 dioside (VII & VIII). These compounds showed promising sedative, anticonvulsant and psychotropic activity.

\[
\begin{align*}
\text{VII} & \quad \text{VIII} \\
\end{align*}
\]

1-Substitutedpyrazolo[4,3-b] [1, 5]benzothiazepin-10-(9H)-ones (IX) have shown psychotropic activity (Maki & Suzuki, 1974).

\[
\begin{align*}
\text{IX} \\
\end{align*}
\]

\[R=\text{alkyl} \]
Synthesis and pharmacological evaluation of 11-(2'-dimethylaminoethyl)-5-methyl-5, 11-dihydro dibenz[b, e][1, 4]thiazepine and related compounds (X) have been done by Ueda & Umo (1975). The compounds showed potent neurotropic and psychotropic activity.

\[
\begin{align*}
R &= \text{CH}_2\text{CH}_2R^1, H, R1=\text{Et}_2\text{N, Me}_2\text{N etc.} \\
(X)
\end{align*}
\]

Pharmacological evaluation of dibenzothiazepine derivatives (XI) have been reported (Nakanishi et al., 1976).

\[
\begin{align*}
X &= S, \text{SO}_2, \text{NMe}, \text{NH etc.}, R1, R2=\text{H, halo, alkyl, alkylthio, haloalkyl.} \\
R &= \text{OH or active group.} \\
(XI)
\end{align*}
\]

Shete (1982) synthesized 11-oxo and 11, 11-diphenyl derivatives of dibenzo[b,f][1,4]-thiazepines and dibenzo[b,f][1,4]oxazepines (XII).

\[
\begin{align*}
X &= O, S \\
(XII)
\end{align*}
\]
Marked sedative activity has been reported in 5-phenylpyrrolo[2, 1-d] (1, 5)benzothiazepines (XIII) (Nacci et al., 1984).

\[ \text{R}=\text{Cl, NO}_2 \]

(XIII)

The following 1, 5-Benzo[b]thiazepine derivative (XIV) has been synthesized by Matsumura (1986). This compound is useful as psychotropic and vasodilator agent.

\[ \text{R}^1=\text{H}, \text{halo, CF}_3, \text{NH}_2, \text{R}^2, \text{R}^3=\text{alkyl}, \text{NR}^2\text{R}^3=\text{heterocycle}. \]

(XIV)

Aminothienobenzothiazepines (XV) have been synthesized and reported as potent antipsychotic agents (Corral et al., 1987).

(XV)
Tanabe Seiyako Co.Ltd. (1987) has reported 1, 5-benzothiazepine derivatives (XVI) and their salts as coronary vasodilators and psychoneurotropics.

\[
\begin{align*}
\text{Ar} &= \text{alkoxy-substituted Ph.}, \quad R^1 = \text{alkyl}, \quad R^1 R^2 = \text{alkyl}, \quad Y = \text{alkylene} \\
\text{(XVI)}
\end{align*}
\]

Benzothiazepinones (XVII) elicited anticonvulsant activity as reported by Buckett et al. (1993).

\[
\begin{align*}
\text{n} &= 0-2, \quad R^1 = \text{halo, } C_{1-4}\text{alkoxy, } C_{1-4}\text{ haloalkyl}, \quad O_2 N, C H, H O_2 C \text{ etc.} \\
R^2 - R^6 &= H, C_{1-4}\text{alkyl}; m = 0-4. \\
\text{(XVII)}
\end{align*}
\]

Several 1,4-benzothiazepines (XVIII) were synthesized (Housley et al., 1994). The compounds are useful as neurological agents.

\[
\begin{align*}
R^1 &= R^2 = H, \text{ Cl, Br,} \quad R^3, R^4 = H, \text{ alkyl.} \\
\text{(XVIII)}
\end{align*}
\]
Synthesis and pharmacological tests of some new substituted tetracyclic oxazepine and thiazepine derivatives (XIX) have been reported by Fernandez et al. (1996).

\[
\text{R}^1, \text{R}^2 = \text{H, C1-6 alkyl etc., } \text{R}^3 - \text{R}^{10} = \text{H, CN, OH, CF}_3 \text{ etc}
\]

\[
\text{R}^{11} = \text{H, C1-5 alkyl, CF}_3, \text{ R12} = \text{H, C1-6 alkyl, CN or CF}_3.
\]

\[
n = 0-6, \text{ X} = \text{O, S (}::\text{O) or S (}::\text{O)}_2.
\]

(XIX)

Compiani et al. (2000) have prepared pyrrolo[2,1-b] [1, 3]benzothiazepines (XX). The compounds showed pronounced antipsychotic activity.

\[
\text{R} = \text{H, C1Br etc., } \text{R}^1 = \text{dialkylamino etc., } \text{R}^2 = \text{H, alkoxy etc.}
\]

(XX)
BENZOXAZEPINE DERIVATIVES

Researches in the field of medicinal chemistry, led to the discovery of psychopharmacological applications of 1,5-Benzoazepine derivatives. Several benzoazepine congeners exhibit potent antipsychotic activity with prominent antidopaminergic activity like loxapine, clothiapine, metiapine, zotepine and other. Thus, it is worthwhile to point out the antidepressant, anticonvulsant, sedative, hypnotic and antipsychotic actions of various substituted benzoazepine derivatives like Hunziker et al. (1971) have synthesized 11-(1-piperazinyl)-dibenzo [b,f] [1, 4]-oxazepines (I). These compounds have shown promising psychotropic activity.

\[ \text{X} = \text{S, SO}_2, \text{R} = \text{H, Me Et etc.} \]

(I)

Oxazepin-4-one derivatives (II) have been synthesized by Nour et al. (1972) and reported as potent psychotropic agents.

\[ \text{R} = \text{H, Me, Et etc.} \]

(II)
Kotelko & Rokita (1973) have synthesized hexahydeo-1,4-oxazepine
derivatives (III) which showed pronounced psychotropic activity.

\[ \text{(III)} \]

\[ R = \text{Ph, p-ClC}_6\text{H}_4, \text{0-C}_1\text{C}_6\text{H}_4 \text{ etc., } n=2,3 \]

Antidepressant and tranquilizing activities were exhibited by 7-amino-2-chloro-11-(4-methyl-1-peperazinyldibenz [b, f] oxazepines (IV) (Howell & Greenblat, 1973).

\[ \text{(IV)} \]

\[ R = \text{NH}_2, \text{NO}_2, \text{OH.} \]

Vander Burg (1975) synthesized amino-substitutedpiperidine derivatives (V).

\[ \text{(V)} \]

\[ R^1 = \text{NH}_2, \text{H, } R^2 = \text{H, CH}_2\text{NH}_2 \]
Marked antidepressant activity has been reported in 7,7-diphenylhexahydro-1,4-oxazepines (VI) (Bowmen, 1976).

\[
\text{R}=\text{PhCH}_2, \text{H, Me etc.}, \text{R}^1=\text{H, F, R}^2=\text{H,MeO, Cl,F.} \\
\text{R}^3=\text{H, MeO, F,OH, R}^4=\text{H,F,MeO, R}^5=\text{H,MeO.} \\
\text{(VI)}
\]

7,7-Diphenylhexahydro-1,4-oxazepines (VII) have reported to possess promising antidepressant activity (Bowmen, 1977).

\[
\text{R}=\text{H,F, R}^1=\text{H,MeO,Cl,F, R}^2,\text{R}^4=\text{H,MeO.} \\
\text{R}^3=\text{H,F,MeO, R}^5=\text{PhCH}_2,\text{Me, allyl etc., X-H}_2. \\
\text{(VII)}
\]

Several imidazo [5,1-c](1,4)-benzoxazepines (VIII) were synthesized and evaluated for psychotropic, anticonvulsant and sedative activities (Schaub & Gerhards, 1978).
R\(^1\)=H, C\(_{1-4}\)alkyl, R\(^2\)=H, SH, alkylthio etc.

R\(^3\)=H, C\(_{1-4}\), alkyl, aminoalkyl, X-H, halo, NO\(_2\), alkyl etc.

(VIII)

Meckenzie & Brown (1981) reported pronounced antipsychotic activity in some 11-(1,2,3,6-tetrahydro-substituted-4-pyridyl)-dibenzo[b,f] [1,4] oxazepines (IX).

R, R\(^1\)=H, halo, alkyl, alkoxy etc., R\(^2\)=alkyl, hydroxyalkyl.

(IX)

Hirai et al. (1982) reported the synthesis of some [4,1]benzoazepines (X) and these compounds were screened for anticonvulsant activity.

R=H, alkyl, R\(^1\)=halo, H, Niro., R\(^2\)=halophey1, pyridyl (trihalomethyl)

phenyl, X-X\(^1\)=NH(C (:Z)), Z=O, S

(X)
7-Phenyl-7-phenoxy methylhexahydro-1,4-oxazepines (XI) have been found as potent antidepressant agents (Treiber et al., 1984).

\[
\begin{align*}
\text{Ph} &\quad \text{CH}_2\text{O} &\quad \text{Ph} \\
\text{O} &\quad \text{NR} &\quad \text{R}^1
\end{align*}
\]

\[R=\text{H,Me}, \text{R}^1=\text{H,Cl,MeO}.
\]

(XI)

Nagarajan et al. (1985) reported promising anticonvulsant and psychotropic activity in 10,11-dihydrodibenz [b,f] [1,4] oxazepines derivatives (XII & XIII).

\[
\begin{align*}
\text{R}^1 &\quad \text{C}(\text{Z})\text{R} &\quad \text{R}^2 \\
\text{Z}=\text{O,S., R}=\text{H}_2, \text{MeNH, EtNH, PrNH, cyclohexylamino, PhNH etc.} \\
\text{R}^1=\text{H,NO2,NH2, AcNH. Z'}=\text{O,H2, R}^2=\text{NH2, NO2, R}^3=\text{H,Me}
\end{align*}
\]

(XII & XIII)

Synthesis and pharmacological screening of dibenzoazepine derivatives (XIV) have been reported by Sawanishi et al. (1992).

\[
\begin{align*}
\text{N} &\quad \text{Cl} &\quad \text{N}(\text{CH}_2\text{n})\text{CO}_2\text{R} \\
\text{Cl} &\quad \text{Cl} \\
\text{O} &\quad \text{O}
\end{align*}
\]

\[n=1-5, \text{R=H,lower alkyl}.
\]

(XIV)
by Muramatsu et al. (1993).

Pharmacological evaluation of N-(alkylcyclobutyl) acid derivatives of 4-(2-}

chlorodibenz[b,d] [1,4] oxazepino-1,1'-benzoxazepines (XV) has been carried out.


Synthesis and pharmacological screening of 1,4-benzoxazepino-3,5-diones

(XVII) have been done by yourself & Said, (1997).
QUINAZOLINONES DERIVATIVES

Many scientists have pointed out the interesting pharmacological properties of Quinazolinones in recent years. Quinazolinones constitute an important class of heterocycles with a broad range of biological activities, such as antipsychotic, anticonvulsant, antidepressant, antihypertensivs, antibiotic and anti-inflammatory activities. Furthermore, Quinazolinone nucleus has gained medicinal importance as its derivatives affect various enzymetic systems of the body which are intimately concerned with the normal functioning of the central nervous system. Variation at position 2 and 3 by various heterocyclic moieties in the pharmacodynamic nucleus, yield the potent antipsycotic agents such as Kirchner & Zalay (1968) have reported substituted 3-amino-2, 3-dihydro-4 (1H) quinazolinones (I). The compounds showed promising anticonvulsant activity.

\[
\begin{align*}
R=R^5=H, & \quad R^1=R^2=Me, & \quad NR^3R^4=anilino \\
(I)
\end{align*}
\]

Some novel imidazo-and pyrimidoquinazolines (II) have shown psychoanaleptic, antidepressant adrenotymimetric and broncholytic activities (Schindler, 1968).
n = 2 or 3., R=2-furyl, 2-thienyl.

(II)

CNS depressant activity has been reported in 11H-quinazolinone-[2,3-b]quinazolin-11, 13 (5H)-diones (III) (Bell, 1970).

R¹, R²=iso-propyl, aryl

(III)

Synthesis and antidepressant activity have been reported (Bell & Wei, 1970) in 1-alkyl-5-oxo-5H-thiazolo, [3,2-a]quinazoline-2-carboxylates (IV).

(IV)

Various 4(3H) quinazolinones (V) have been found to possess hypnotic activity similar to that of methaqualone (Somashekhara et al., 1971).
Synthesis and biological evaluation of various fluoroinated quinazolinones derivatives of 2-alkyl-3-aryl-4(3H)-quinazolinones and corresponding thioquinazolinones (VI) have been reported by Joshi et al. (1973). These compounds were found to possess marked CNS depressant activity.

Kuwada et al. (1973) have reported quinazoline derivatives (VII) which were useful as sedative, antidepressant and antitrichomonas agents.
Karamchand and Premchand Pvt. Ltd. (1974) has reported 2-[2-(3-pyridyl)vinyl]-3-o-tolyl-3,4-dihydro-quinazolin-4-one (VIII) as anticonvulsant, hypnotic, tranquilizing and muscle relaxant agent.

(VIII)

3-(Substituted phenyl)-4(2H)-quinazolinones (IX) have reported as potent hypnotic and sedative agents (Hebeck et al., 1974).

(IX)

\[ R = \text{PrO, MeO, EtO etc., } R^1 = \text{H, Cl.} \]

Sen Gupta et al. (1976) have reported potent psychotropic 2-(N\(^4\)-Arylpiperazinocarbonyl-methylthio)-3-aryl-6-bromo-4(3H)-quinazolones (X).

(X)

3,4-Dihydro-4-(2-methylindolyl)-2-quinazolone solvate (XI) as psychotropic agent (Postovskii et al., 1977).
\[ R^1 = H, o-, m-p, Me, p-Cl, \quad R^2 = H, o-, m-p, Me \]

(XI)

7-Chloro-9-phenyl-3,3-diethyl-3H-pyrazolo[5,1-b]quinazolin-10-ium-2-olate (XII) has been reported as potential psychotropic agent. (Orzalesi et al., 1978).

(XII)

Some typical 4(3H)-quinazoline derivatives (XIII) have been synthesized and reported as CNS depressant, anticonvulsant, antimalarial, antibacterial and fungicidal by Bhargava & Shyam (1978).

(XIII)

\[ R = H, 4-MeO, 3-Me, 4-Cl \text{ etc.}, \quad R^1 = Ac, \text{ CH}_2\text{CH}_2\text{CO}_2\text{Et etc.} \]

(XIII)

Wolfe & Rathman (1980) have reported 2-oxoalkyl-4(H)-quinazolinones (XIV) as anticonvulsant and CNS depressant agents.
\[
\begin{align*}
\text{Z}= & C_{1-10}, \text{ alkylene}, \quad R=\text{alkyl, halo or dihalophenyl} \\
R' = & \text{alkyl, alkenyl, pyridyl, } R^2, R^3=\text{H, OH, NH}_2, \text{halo, CF, etc.}
\end{align*}
\]

(XIV)

Synthesis and biological activity of some 2-substituted 3-(4'-carboxyphenyl)-7-nitro-4(3H)-quinazolinones (XV) have reported (Verma et al., 1981).

\[
\begin{align*}
R= & \text{H, Me, Et, } R'=\text{Me}
\end{align*}
\]

(XV)

Isomers of 3-aryl-2-[1-(p-nitrophenyl)-1,3-dihydroxy 2-propylamino]methyl-4(3H)-quinazolinones (XVI) were reported as hypnotic, anticonvulsant, analgesic and antispasmodic agents by Ahmed (1983).

(XVI)
Preparation, crystal structure and biological activity of 2-methyl-3-(4-oxo-3-phenylthiazolidin-2-ylidene-amino)-4 (3H)-quinazolinone (XVII) has been done by (Bueyuektimkin et al., 1984).

(XVII)

Abdel et al. (1994) have synthesized 4(3H)-quinazolinones (XVIII). These compounds possessed promising sedative, hypnotic, anticonvulsant and anti-inflammatory activities.

(XVIII)

Some novel derivatives of 1, 3-disubstituted quinazolin-2, 4-diones (XIX) have been reported as anticonvulsant agents (El. Hakim et al., 1996).

(XIX)
Synthesis and biological evaluation of 2-(b-carboxyethyl)-4-chloroquinazolines (XX) have been reported by Amine (1998).

\[
\begin{align*}
X, X^1 &= \text{H, Br, } R=\text{COOC}_2\text{H}_5, \text{Ar}=\text{C}_6\text{H}_4\text{CH}_2-(p) \\
(XX)
\end{align*}
\]

Some novel central nervous system agents like (4, 4'-bridges bis-2,4-dimaminoquinazolines (XXI) have been synthesized by Schohe et al. (1998).

\[
(XXI)
\]

Synthesis and anticonvulsant testing of some new 3-substituted 6,8-dichloro-2-phenyl-4(3H)-quinazolinone derivatives (XXII) have been reported by Ibrahim, (2000).

\[
(XXII)
\]
of some new quinazolinones (XXIII).
THIAZOLIDINONE DERIVATIVES

Thiazolidinones constitute an important class of heterocyclic compounds with a broad range of biological activities like antibacterial, animicrobial, antimalarial, anti-inflammatory, anticonvulsant, antidepressant and antipsychotic activities. Several scientists have reported antipsychotic, antidepressant and anticonvulsant activities in the various following thiazolidinone congeners.

Arimura & Hideki (1976) have reported some newer psychotropic agents viz. 6,1'-disubstituted 5,7-dioxoimidazolido [1,5-c]-thiazolidine-3-spiro-4'-piperidine derivatives (I).

![Chemical Structure](image)

\[ R = \text{alkyl, aralkyl, cycloalkyl etc.}, \ Z = O, S. \]

\[ R' = R^2C_6H_4CO(CH_2)_{n-1}(R^2C_6H_4)-CH(CH_2)_n \]

\[ [R^2 = H, \text{halo, alkyl etc.; } n = 1-3]. \]

(I)

2, 4-Thiazolidinedione derivatives (II) have been found to possess potent-anticonvulsant and antidepressant activities. (Bigg, 1980).

![Chemical Structure](image)

\[ n = 2, 3, \ R^2 = H, \text{alkyl,Bz,Ac,PhCH}_2, \ R^3 = H, \text{alkyl.} \]

(II)
Synthesis and biological activity of some 3-(1,3,4-oxadiazol-2-yl)-2-aryl-4-thiazolidinones (III) have been reported. (Bhatt, 1984).

$$\text{III}$$

$$R = \text{Ph, anisyl, HO}C_6H_4\text{etc., } R^1 = \text{Ph, HO}C_6H_4, \text{anisyl etc., } R^2 = H, \text{Me}.$$  

Gaikawad et al., (1984) reported substituted-4-thiazolidinones (IV) as anticonvulsants.

$$\text{IV}$$

$$R = \text{secy. amines.}$$

Some novel 4-thiazolidinone derivatives (V) have been reported as potent anticonvulsant agents (Gaikwad et al., 1986).

$$\text{V}$$

$$R = H, \text{CH}_2\text{N(CH}_3\text{)}_2, \text{CH}_2\text{N(CH}_2\text{CH}_2\text{OH})_2 \text{etc.}$$

Synthesis of 4-oxo-3-(4-diphenylmethylpiperazin-1-yl-carbonylmethyl) thiazolidine-1, 1-dioxide or its salts (VI) have been reported by Takasugi & Saki (1990). These compounds showed psychotropic activity.
Z = S, SO₂, R = H, Et.

(VI)

Some novel thiazolidinone congeners (VII) have been reported (Tripathi et al., 1993). The compounds showed promising antidepressant activity.

R = H, Cl, OMe.

(VII)

3-(4-(1-Substituted-4-piperazinyl) butyl)-4-thiazolidinone derivatives (VIII) showed pronounced antipsychotic, analgesia, anticonvulsant and anxiolytic properties (Hrib & Jurcak, 1996).

n = 0, 1, 2, X = H, halo, lower alkyl, OH etc.

Z = connecting site., K = N, CH; m = 1, 2. R¹, R² = H, lower alkyl, COHMe, etc., R³, R⁴ = H, loweralkyl etc.

(VIII)
Miscellaneous

Some isoxazole derivatives (I) have been synthesized (Kano & Takahashi, 1974) and these compounds have been evaluated for their anticonvulsant, antipyretic, analgesic and antiinflammatory activities.

\[
R = \text{OH, } R^1 = \text{Pyrrolidino, piperidino, morpholino etc.}
\]

(I)

Some 1,2-benzisoxazole-3-acetamidoxime hydrochlorides (II) have also been found to possess promising psychotrophic activity (Shimizu et al., 1974).

(II)

Nishimura et al. (1975) have synthesized 1,2-Benzisoxazoles (III) as potent antidepressant and hypotensive agents.

\[
R^1 R^2 = \text{H, halogen, alkyl, OH, alkoxy, NO}_2 \text{ or NH}_2.
\]

\[
n = 0-2, \text{ } R^3 = \text{NHOH, NH}_2, \text{ alkylamino etc.}
\]

(III)
3-(1,2-Epoxythyl)- and 3-(1-hydroxy-2-aminothyl)-5-phenylisoxazoles (IV) were synthesized by Hamashima & Minami (1976). These compounds were also screened for their anticonvulsant activity.

![Chemical Structure of IV](image)

(IV)

Novel formazans and tetrazolium indoles (V) as potential CNS active agents have been reported by (Sathi et al., 1983).

![Chemical Structure of V](image)

(V)

Singh et al. (1997) have synthesized some spiroazetidinones (VI). These compounds were found to possess anticonvulsant and antiepileptic properties.

![Chemical Structure of VI](image)

R = Ph, 4-Me, 4-MeO, 4-Cl, 4-O₂NC₆H₄.

(VI)
Synthesis of aryloxyazetidines (VII) and related compounds as selective 5-HT$_2c$ agonists have been reported by Broekkamp et al. (1998).

A = (unstd) (substd.) 5-, membered (heterocyclic) ring.

$R_1, R_2, R_3 = H$, alkyl, alkoxy, halo etc., $X = O, S; n = 1, 2$.

(VII)

Some benzoisoxazoles (VIII), as selective dopamine D$_4$ antagonists, have been reported by Den Hartog et al. (1999).

$Y = CH_2, CH_2CH_2$, $R^2 = Me, Et$ etc., $A = CH_2(CHR)_{p1}$; $R = H, Me$; $p = 0, 1$.

B = (substituted)$_2$-indolyl, 3-indolyl etc.

(VIII)

3-[(aminoalkoxy)phenyl]benzo[d]-isoxazoles and analogs (IX) were synthesized as dopamine D$_4$ antagonists (Shutske et al., 2001).