REVIEW
OF
LITERATURE
In this modern world a number of patients suffering from mental diseases, are markedly increasing. The main cause is that the modern society has developed an atmosphere of glamour and violent distraction, which is far away from mental peace. Further the increasing population, competition for professional opportunities and various other complexities have raised the incidence of psychosomatic and mental disorders. The main endeavour of life science has been to improve the quality of human life in this planet. Modification of behaviour, mood and emotion by drug has always been a favourable indulgence of mankind. The substances like caffeine, nicotine, opium, cocaine, hashish etc. are known since ancient times. These have been employed even today in many segments of society to make life more bearable but rarely with the aim of curing the disease. These substances are psycho-pharmacological or psychiatric agents. The traditional psycho-active agents like wine and opium, principally used to produce abnormal mental states in normal people, whereas the modern psycho-active drugs are primarily used to treat mentally disturbed patients with the view of influencing their abnormal behaviour and restoring their mental balance. Numerous synthetic and naturally occurring compounds have been used to overcome the diseases concerning central nervous system. Off and on new compound is introduced which has better therapeutic value and lesser toxicity. These agents are called as psychotropic drugs. This development of clinically effective psychotropic agent has created a profound interest in various
psychopharmacological studies. These studies have established
the psychopharmacology as a separate discipline of pharmacology,
which is concerned primarily with the synthesis of new psycho-
pharmacodynamically important drugs and studies of their pharma-
cological effects.

Norosta jatamansi, commonly known as balchar, was used for
a variety of mental disorders such as epilepsy, hysteria, corea
and other nervous disorders. By the middle of nineteenth
century the use of pure alkaloid, rather than crude opium pre-
paration, began to spread throughout the medical world. The
morphine produces drowsiness, analgesia, change in mood and
mental clouding in man. In the therapeutic doses of morphine
the painful stimulus may be recognized, but it may not be
percieved as painful and patients report that though pain is
still present, but they feel more comfort. Morphine relieves
pain by action on different parts of central nervous system from
spinal cord upto cortex. However, the precise mechanism by which
the opioid exert their effect remain uncertain. Evidences show
that opioid interact with neurotransmitter either directly or
indirectly. Acetyl choline catecholamine and 5-hydroxytrypta-
mine may be in their analgesic effect.

In 1931 Sen Gupta and Bose described the therapeutic use
of Rauwolfia serpentina for the control of hypertension and
inscanity. In small dose reserpine, isolated from the root of
rauwolfia serpentina showed to relieve mental tension without
causing sedation, but in high doses sedation produced without inhibiting sensorism. In 1937 Insullin shock pentylene-tetrazole induced convulsion and electroconvulsive therapy became available for both depression and Schizophrenia.

Several synthetic drugs have been then introduced as psychoactive agents. The first synthetic drug is Amphetamine. In 1955 chlorpromazine was synthesized in France. Ladoit studied the unique effect of chlorpromazine, whereas Delay and Deniker used it clinically on several psychiatric patients.

In 1954 Berger marked the beginning of the investigation of antianxiety drug. In 1957 chlordiazepoxide (librium) and diazepam (valium, calmose) were introduced. In the following year Janssen discovered the antipsychotic properties of haloperidol and butyrophenone. In 1958, Kuhn reported that imipramine has anti-depressant effect, iproniazid though introduced as anti-tubercular drug but was also found to possess antidepressant and monoamine oxidase inhibitory property.

In 1960 there was a rapid expansion of psychopharmacological research and many new theories of psychoactive drug effects were introduced. The barbiturates have been used for many years to calm both agitated neurotics and psychotics for the relief of anxiety, sedation and induction of sleep. Phenobarbitone is commonly used for treatment of epilepsy. The use of other drugs of this group became widespread to treat psychiatric disorders. Recent investigations are commonly concerned with the biochemical
aetiology of mental illness and mode of action of these drugs.

In search of new and better psychotropic agents for therapeutic uses, large number of the chemical substances have been synthesized and isolated from the natural products. Some of the synthetic chemical substances acting on CNS have been reviewed here.

1. **Quinazolones**

Due to the presence of quinazolone nucleus in many ancient herbal drugs interest aroused in quinazolone chemistry. Fefribugine, an antimalarial herbal, is a derivative of 4-quinazolone.¹

The 4-quinazolones have been investigated for a variety of physiological effects, such as hypnotic,² analgesic,³ anti-spasmodic,⁴ anticholinergic⁶ muscle relaxant⁵ and anti-inflammatory⁷ properties. Gujral et al.⁸ observed that 2-methyl-3-(0-tolyl)-4-(3H)-quinazolone (I) (METHAQUALONE) as potent CNS depressant. Further work of Kacker and Zaheer⁹ gave a new guideline in the development of chemistry of 4-(3H)-quinazolone. They introduced 2-methyl-3-(0-tolyl)-4-(3H)quinazolone into therapy of nonbarbiturate hypnotic. A series of the compounds have been synthesized and screened for the hypnotic activity.¹⁰,¹¹ The most active member of the series was 2-methyl-3-(0-tolyl)-4-(3H)-quinazolone (I), which was described as being more potent than phenobarbital. Clinical efficacy of 2-methyl-3-
(0-tolyl)-4-(3H)-quinazolone (I) has been reported by Duchastel who carried out a study of 100 patients.

Swift et al.\textsuperscript{12} reported potent anticonvulsant and muscle relaxant property with the same compounds. Methaquolone has also been reported to exhibit anticonvulsant activity in rat and mice.\textsuperscript{13}

Structure variation with an aryl group at position 3 such as 2-methyl-3-(4-bromophenyl)-4-(3H)-quinazolone (II) showed effective anticonvulsant activity against electroshock induced convulsions in mice and 2-methyl-3-(2-chlorophenyl)-4-(9H)-quinazolone (III) as hypnotic.\textsuperscript{14,15}

Zaheer et al.\textsuperscript{16} reported 2-alkyl-3-aralkyl-4-(3H)-quinazolone (IV, V) as CNS depressant. At comparable dose of LD\textsubscript{50} of these compounds produced more sedation and tranquilization without loss of muscle tone as compared to methaquolone:
Parmar et al.\textsuperscript{17} and Rastogi et al.\textsuperscript{18} have synthesized a large number of substituted quinazolone hydrazides and investigated them for their effect on the activity of the rat brain mitochondria. All of these quinazolone hydrazides were found to inhibit rat liver monoamine oxidase (MAO). Substitution at positions 6, 7 and 8 of the quinazolone nucleus effect the potency of quinazolone. It was found that substitution of halogen increased the potency to inhibit MAO activity. A number of synthesized quinazolones were tested for pyruvate oxidase inhibitory activity and it was found that all of them inhibit pyruvate oxidase.\textsuperscript{19-22}

Misra et al.\textsuperscript{23} synthesized several styryl quinazolone and tested for MAO inhibitory property by the deamination of benzylamine. They found that these quinazolones inhibit rat brain monoamine oxidase.

Among the several styryl quinazolone, the 2-(3-methyl-4-(hydroxystyryl)-3-(4-benzylhydrazide)-4-quinazolone (VI) showed maximum inhibition. All these styrylquinazolone possess anticonvulsant activity against pentylenetetrazole induced seizure...
Husain et al. synthesized some new 2-aryloxymethyl-3-substituted carboxymethyl-6,8-substituted-4-quinazolones and found them to possess 20-60% anticonvulsant properties against pentylenetetrazole induced seizure. The monoamine oxidase inhibitory activity of (VII) were also reported.

A series of 2-substituted 1-aryl-4-quinazolones were synthesized and tested for different biological activities. These compounds were found to possess anti-inflammatory, CNS depressant and analgesic activity.
Several 1-heterocyclic, alkyl-1,2,3,4-tetrahydroquinazolones (IX) were also synthesized and these compounds possess narcotic antagonist, local anesthetic, tranquillizing, anti-convulsant properties and were useful for gastro-intestinal utility.\textsuperscript{29}

![Image of compound IX]

Chaurasia et al.\textsuperscript{30} synthesized some new 4-(3H)-quinazolinone (X) by condensing the appropriate N-acetyl-anthranilic acid with aminobenzothiazole in the presence of PCl\textsubscript{3} followed by reaction with benzaldehyde and tested them for CNS depressant activity in mice and found to be active.

![Image of compound X]

Substitution in quinazolone nucleus at various position have profound influence on pharmacological activity of quinazolone has been reported that 3-phenyl-4-quinazolone moiety (XI) is essential for the CNS depressant properties.\textsuperscript{31}
The extensive chemical variation of the quinazolone nucleus and their biological investigations offered the opportunity of establishing a certain pattern of structure activity relationship.

**SUBSTITUTION AT POSITION 2**

It was found by various workers that the methyl group at position 2 of the quinazolone nucleus is essential for establishing the hypnotic and anticonvulsant properties. 2-Methyl-3-(Q-tolyl)-4-quinazolone (I) is a potent anticonvulsant being superior than phenobarbitone. When methyl group at the position -2 of the quinazolone nucleus was replaced by certain larger group e.g., styryl (XII) or β-pyridyl ethenyl (XIII), hypnotic activity was found to decrease with simultaneous increase in anticonvulsant properties.
When the methyl group of the quinazolone nucleus was replaced by ethyl or higher alkyl group, the hypnotic activity was markedly decreased. The 2-methyl group when replaced by aryloxy methyl group as in 2-aryloxymethyl-3-αC-substituted carboxymethyl-6,8-substituted-4-quinazolone (XIV), compound showed 20-60% anticonvulsant property. The compound also showed monoamine oxidase inhibition.

But when the methyl group of the 3-phenyl ring of the methaquo- lone was replaced by the chlorine the above effect, i.e., hypnotic and anticonvulsant was maintained as such. All the other substitution at the 3-phenyl ring causes decrease in anticonvulsant properties.

**SUBSTITUTION AT N³-POSITION**

The CNS depressant activity seems to be incipient in 3-phenyl-4-quinazolone moiety, was found to attain substantial level in the 2-methyl (XV) and 2-ethyl (XVI) analogs. These investigations show that a resonance nucleus at the N³ position with small alkyl group at C² in the 4-quinazolone moiety seems to be very essential feature for electron availability. Due to
the presence of this feature, these molecules showed a favourable action. However, the condensed nuclei at the N\textsuperscript{3} led to the inactivity of the compound:

![Chemical Structures](image)

Sareen et al.\textsuperscript{34} have reported that the presence of phenyl group at the position 3 of the quinazolone is essential for the hypnotic and anticonvulsant activities of the quinazolone. These workers have also reported that, when methyl group of the 3-phenyl ring replaced by other substituent, hypnotic and anticonvulsant activities enhanced. Compounds, having fluorine, chlorine, bromine, iodine and cyano substituted at the 2 position of phenyl ring in 3-phenyl-4-quinazolone, were found to exhibit hypnotic effect comparable on even more marked than those observed in the 2-methyl-3-(2-methylphenyl)-4-quinazolone (methaqualone)\textsuperscript{35} (I). The quinazolones, having chlorine or bromine at the ortho- and para-position of the phenyl ring in 3-phenyl-4-quinazolone, showed good anticonvulsant and hypnotic activities. 2-Methyl-3-(p-bromophenyl)-4-(3H)quinazolone (XVII) has been shown effective anticonvulsant\textsuperscript{36} and 2-methyl-3-(o-chlorophenyl)-4-(3H)-quinazolone (XVIII) was claimed as hypnotic.\textsuperscript{37}
3-(o-Trifluoromethylphenyl)-4-quinazolone (XIX) was also observed to possess CNS depressant, muscle relaxant, anticonvulsant and tranquillizing effects.

Recently, it was observed by various workers that when phenyl group was replaced by any other group, the quinazolone showed good anticonvulsant and hypnotic effect. Misra et al. have synthesized some 2-phenyl-3-(4-substituted-1,3-thiazol)-2-yl-4-quinazolones (XX) and reported that when these compounds were tested on albino mice, an increase in spontaneous motor activity (SMA) and in writhing was observed.
Zaheer et al.\textsuperscript{16} replaced an aralkyl group at the 3 position of the quinazolone nucleus. Compared to the methaquolone the LD\textsubscript{50} of compound 2-methyl-3-(2-chlorophenylethyl)-4-(3H)-quinazolone (XXI) and 2-methyl-3-(3,4-dichlorophenylethyl-4-(3H)-quinazolone (XXII) was found nearly 100\% higher. The hypnotic property of compound (XXI) and (XXII) was much less compared to methaquolone. At comparable dose of the LD\textsubscript{50} of these compounds produced more sedation and tranquillization without loss of muscle tone in compared to methaquolone

\begin{align*}
\text{XXI} & \quad \text{XXII} \\
\text{XXX} & \quad \text{XXIV}
\end{align*}

**SUBSTITUTION AT POSITION-4**

The carbonyl group has been showed to be essential for the various activities e.g., anticonvulsant, bronchiodilater and spasmolytic activity. When the C=O group was replaced by C=S group, it was observed that the thiosubstituted quinazolone was less active than parent compound:
SUBSTITUTION AT C-6 AND C-8

Substitution of various groups at positions 6, 7 and 8 of the quinazolone nucleus resulted in different important derivatives. Substitution of a benzene ring at the 6, 7 positions in 4-quinazolone molecule resulted in synthesis of 6,7-benz-4-quinazolone. This compound was found to be strong bronchoditator as compared to parent compound. Chaturvedi et al. synthesized some useful 2-methyl-3,6,8-trisubstituted-4-quinazolones. It was found that amongst the various quinazolone the 2-methyl-6-chloro-3-(2-furylmethyl)-4-quinazolone produced maximum protection of 80% against convulsion produced by pentylenetetrazole.

Substitution of Cl, Br and I at position 6 of the quinazolone nucleus was found to cause slight increase in the inhibitory activity of these quinazolones while di-substitution of both positions 6 and 8 resulted in decrease in their inhibitory ability to inhibit pyruvic acid oxidation as compared with monosubstituted quinazolone.

Parmar and Arora synthesized various quinazolone hydrazides having substitution at position 6 or positions 6 and 8 of the quinazolone nucleus. It was found that monosubstituted quinazolone hydrazides exhibited maximum MAO inhibition while di-substituted quinazolone resulted in a decrease in their ability to inhibit enzyme MAO. Several substituted quinazolone hydrazides and 2,3,6,8-tetrasubstituted quinazolone hydrazides have
been synthesized and tested for MAO inhibitory activity.\textsuperscript{42-43}

Substitution of less electronegative atom imparted more MAO inhibitory activity. Disubstituted quinazolones have been found to possess better inhibitory activity than the mono-substituted, it shows that increase of halogen substitution at position 6 or 8 increases inhibition of MAO.\textsuperscript{44}

2. Barbiturates

Barbiturates comprise an important and valuable class of CNS depressant, and are frequently prescribed by physicians. Barbiturates produce all degree of depression of CNS ranging from mild sedation to coma. From the very early times psychiatrist used barbiturates to induce sleep in the patients complaining insomnia. As sedative, they are used in anxiety states, psychoneurosis hypertension, hyperthyroidism, prior to surgery and many other diseases.

Barbiturates are derivatives of barbituric acid. It has a pyrimidine nucleus, obtained condensation of malonic acid and urea.\textsuperscript{45} So it may be regarded as a derivative of malonic acid and urea, it is, therefore, sometimes also called malonyl-urea.

\[
\begin{align*}
\text{CH}_2\text{COOH} & \quad \text{NH}_2\text{C}=\text{O} \\
\text{COOH} & \quad \text{NH}_2
\end{align*}
\]
The barbituric acid, synthesized as such is found to be devoid of hypnotic activity. The diethyl derivative, Barbital, introduced in 1903, was the first hypnotic. Hence, it was concluded that the barbituric acid is not itself a hypnotic but substitution of various organic radicals, like alkyl or aryl for hydrogen atom on C-5, give compounds with hypnotic action.\textsuperscript{46,47} It has been observed by various workers, that, an increase in the length of one or both alkyl groups present at the side chain at position 5, resulted in enhanced potency and diminished duration of depression, but if the side chains are too longer (i.e., over five to six carbon atoms), the hypnotic activity decreased and convulsant property may be found. It is not necessary that the two side chains should be identical; many compounds, with different side chains, were found to be of clinical importance e.g., Amobarbital (XXVI), Butabarbital (XXVII) and Secobarbital (XXVIII).
Anticonvulsant properties appear in barbiturates, when a phenyl group is present on C-5 and are more marked in straight chain alkyl derivatives than in those with branched chains.

When an alkyl group is attached to one of the nitrogen atoms of barbiturates, the potency is found to increase but the duration of action is reduced. When the alkyl groups is attached to both the nitrogen atoms it tends to yield convulsant compounds.

The barbiturates, commonly used for clinical practice, are phenobarbital (XXIX), mephobarbital (XXX) and methabarbital. Phenobarbital is the most active for this purpose. Methabarbital possess some anti-convulsant activity but its tropism is less strict than that of its phenylated derivative. The phenobarbital has been reported to be disadvantageously associated with hypnotic properties. Phenobarbital is the oldest anticonvulsant drug.

\[
\text{XXX}
\]
Swissman\textsuperscript{52} prepared a series of acyloxybarbiturate, which on preliminary testing, indicated that compound retain CNS activity, but do not exhibit abnormally long action.

Duckert et al.\textsuperscript{53} have reported that 5-ethyl-5-(3-hydroxy-1-methylbutyl)barbituric acid has a very weak anticonvulsant activity.

The N-substituted and N,N-disubstituted allyl derivatives of the barbital phenobarbital, hexobarbital and diallylbarbital have been synthesized and tested for CNS activities, but none of the above compounds approached phenobarbital in term of pharmacological potency.\textsuperscript{54}

Amongst other newly synthesized salts and bis-derivatives of phenobarbital 1,3-bis(N-phenyl-2-isothioureidomethyl)phenobarbital dihydrobromide (XXXII) exhibited a definite weak anticonvulsant activity and has low LD\textsubscript{50} value.\textsuperscript{55}

Various 5-(2,4-diarylamino-5-triazin-6-yl)-thiobarbituric acid (XXXIII) potentiated pentobarbitones induced sleep in mice at 100 mg/kg.\textsuperscript{56}
Replacement of oxygen atom on C-2 by a sulphur atom gives thiobarbituric acid, the basis of thiobarbiturates. Thiobarbiturate undergo desulphuration to give barbiturate with activity similar to that of parent compound.

Large number of thio-analogs of barbituric acid have been synthesized but only few thiobarbiturates with high molecular weight, have a satisfactory margin of safety for clinical use. Thiopental (XXXIV), commonly called as pentothal, is the thio-analog of pentabarbitorne. It is a very short acting derivative.

The amylobarb比特one, (Amytal) (XXXV), is a short acting barbitone, used clinically as sedative and hypnotic. It is the thioanalog of secobarbital.
Pandey et al.\(^5\) synthesized various 1-aryl-3-cyclohexyl-thiobarbiturates (XXXVI) and found that these compounds possess anticonvulsant and SDH inhibitory properties.

![XXXVI Diagram]

Recently, Anjali et al.\(^6\) have reported the syntheses of some 1-aryl-3-(2-pyridyl)-thiobarbiturates and found that these compounds possessed anticonvulsant and succinate dehydrogenase (SDH) inhibitory properties. These compounds have been reported to have low toxicity.

![XXXVII Diagram]

The classical barbitones were broken down by oxidation of their alkyl side chain and produce hypnotically inactive compound. The N-methyl derivatives were demethylated to give hypnotically active barbiturates and these quickly appeared in urine.

It is, thus, evident that slight changes in chemical structure of substituted groups in the barbituric acid nucleus, affects significantly the action/fate and excretion of the resulting compounds.
3. Thiosemicarbazides and Triazoles

The biological activities of the thiosemicarbazides have been reported to be broad spectrum. Various thiosemicarbazides and thiocarbamides have been found useful as spasmyltic, 3-imidazolyl (XXXVIII) and 2-pyramidyl, thiocarbamide (XXXIX) and thiosemicarbazide have been used as hypertensive and analgesic agents.

Bream et al. synthesized various thiosemicarbazides and screened them for anticonvulsant properties. Among these compounds 1-[\(\text{F}-(2,6\)-dichlorophenyl)ethyl]semicarbazide (XXXX) have been shown to possess strong anticonvulsant, muscle relaxant and antiepileptic properties.

A large number of the thiosemicarbazides have been reported to possess spasmyltic activity e.g., cinnamic acid derivatives
possess these activities. 2-\((p\)-Acetamidobenzamido\)-cinnamic acid hydrazide and aryl isothiocyanate on refluxing, gave thiosemicarbazide which exhibited spasmolytic activity with low toxicity.

\[
\begin{align*}
&\text{XXXI} \\
&\text{NHCOCH}_3
\end{align*}
\]

Various thiocarbamide benzimidazole derivatives were found to possess most potent anticonvulsant properties, such as compound (XXXII).

\[
\begin{align*}
&\text{XXXII} \\
\end{align*}
\]

Different semicarbazone and thiosemicarbazone derivatives of barbituric acid were found to possess spasmolytic activities at a dose of 70 mg/kg.

Some \(N'\)-(N-morpholinoacetyl)-1-aryl-3-thiosemicarbazides (XXXIII) were synthesized and it was found that these thiosemicarbazides and their cyclized product exhibited anticonvulsant activity against pentylenetetrazole induced seizure.
Jaiswal et al. synthesized some 10-(1-acetyl-4-substituted)-semicarbazide phenothiazine and reported that these compounds possessed both anticonvulsant and MAO inhibitory properties.

Various 4-aryl-1-(2,3,4-trihydroxyacetophenone)-3-thiosemicarbazide (XXXIV) were synthesized and reported to possess 10-60% protection against pentylenetetrazole-induced seizure and 10-40% protection against MES.

In order to establish the structure activity relationship of the thiosemicarbazides, various tricyclic amines were obtained and it was observed that these compounds, having O-bridge (XXXV), are most active anticonvulsants.
These thiosemicarbazides can be cyclized into their corresponding triazoles. Like the parent compounds, triazoles too possess broad spectrum of the pharmacologic activities, e.g. 4-phenyl-1,2,4(\(H\))triazole has been found to produce convulsion and 1-phenyl-1,2,4(\(H\))triazole possesses anticonvulsant activities. Various other triazoles were found to possess different pharmacological properties. The various biological activities, they possess, are the CNS depressant, analgesic, antitubercular, diuretic and anti-inflammatory etc.

3-Amino-1,2,4-triazole, commonly known as amizole, is a commercial herbicide. Several other triazoles and other triazole derivatives have been found to possess bactericidal, fungicidal, pesticidal and insecticidal properties.

Pellizzari et al. have reported CNS affecting properties of the different triazoles. They investigated 4-phenyl-1,2,4(\(H\))-triazole to produce convulsions.

Later Gibson, Swanson and Meyer reported the pharmacological properties and structure of isomeric compounds 1-phenyl-1,2,4-triazole and 4-phenyl-1,2,4-triazole. Their results sustained the earlier report of Pellizzari, which stated that 4-phenyl-1,2,4-triazole was a convulsant. In contrast they found 1-phenyl-1,,2,4-triazole to be an anticonvulsant.

Anisworth et al. studied the convulsant and anticonvulsant activities of 1 and 4-substituted triazoles. They
showed that, depending upon the dose and route of administration, the triazoles were able to behave both as convulsant as well as anticonvulsant. 1-Aryl-4-(3- and 4-substituted phenyl)-1,2,4-triazoles are anticonvulsant, whereas 4-(2-chlorophenyl)-1,2,4-triazole and 4-(2-tolyl)-1,2,4-triazole are convulsant. 4-(2-Methoxyphenyl)-1,2,4-triazole was reported as an anticonvulsant, when given orally, but behaved as a convulsant when administered by intraperitoneal injection. Thus, the anticonvulsant and convulsant properties of triazoles depend on the dose and the way of administration of the drug.

Some triazole-pyridines have also been shown to exhibit CNS stimulant activity. Hester et al. reported the sedative and anticonvulsant activities. Pharmacological investigations of these compounds showed that they possess high CNS activity with low toxicity.

Parmar et al. synthesized some 5-(2-benzimazolyl)ethyl-4-substituted-3-hydrazine carbonyl methylthio-1,2,4(4H)-triazoles. These compounds have been reported to be CNS depressants. Martin et al. synthesized some 5-(aminomethyl)-4-(2-benzyl/benzoyl-4-chlorophenyl)-3-methyl-4(H)-1,2,4-triazoles and studied the sedative, tranquilizing and nicotine antagonist effect in mice by these compounds.

Joshi et al. synthesized some 1-fluoroalkyl-4-alkyl/aryl-thiosemicarbazide and their corresponding triazoles, 2-fluorinated aroyl-4-alkyl/aryl-5-mercapto-1,2,4-triazole. Some compounds
of this series were alkylated at position 5, e.g., 1-alkyl-3,5-disubstituted 1,2,4-triazole was recently patented for tranquillizing properties.\textsuperscript{85}

4. Thiazoles

From the pharmacological point of view thiazole derivatives are of considerable importance. These derivatives possess a wide variety of biological properties. The presence of a thiazole nucleus in the thiamin (vitamin B\textsubscript{1}) has further enhanced its clinical importance.

Thiazole and their derivatives have drawn attention of chemists due to their prodigious range of activity. They are chiefly used as anesthetic, antihypertensive, spasmolytic, vascoditating, tranquillizer, hypnotic and antiepileptic.\textsuperscript{86-89} Chloromethiazole is found to possess sedative and anticonvulsant activities. It assured temporary protection against metrozol seizure. It is specially used in the treatment of alcohol intoxication or withdrawal syndrome. Although it is a safe drug but its use is still warranted.\textsuperscript{90}

Several 4-methyl-5-(\textit{\textit{\chi}}-chloroalkyl)thiazoles-1,2-ethane-disulfonate synthesized by some workers\textsuperscript{91} and they reported them as CNS active agents. They studied the effect of the length of side chain of thiazole on the CNS activity and found that 4-methyl-5-(\textit{\textit{\chi}}-chloromethyl)thiazole-1,2-ethane disulfonate is CNS stimulant while ethyl, propyl and butyl-derivatives are
CNS depressant. The hypnotic and anticonvulsant effects are maximum in methyl derivative and decreases as the number of alkyl group increases.

The triaryl thiazole derivative (XXXVI) have been reported as analgesic and anticonvulsant compound.\(^{92}\)

![Chemical Structure XXXVI](image)

Compounds, having thiazole ring attached to quinazolinone, have been reported to possess CNS stimulant properties.\(^{38}\) But when a benzothiazole moiety attached to a quinazolone ring compound showed CNS depressant effect.\(^{93}\)

![Chemical Structure XXXVII](image)

Whremeister et al.\(^{94}\) synthesized a series of thiazolines and found that these compounds possess CNS depressant and tranquilizing activities in mice and rats.

![Chemical Structures XXXVIII and XXXIX](image)
Various other thiazolines are reported as analgesic, nematodes bactericides, fungicides.\textsuperscript{95,96}

The thiazolidines are the most important, tetrahydroderivative of thiazoles. Various \(3-[3-(4\text{-chloro-3-sulfamoylbenzoylthio})\text{propionyl}]-2-(\text{o-hydroxyphenyl})-4R\)-thiazolidine carboxylic acid and its salts are found as potent antihypertensive (L) and \(N\)-(mercaptoacyl)thiazolidine carboxylic acid (LI and LII) also reported as anti-hypertensive.\textsuperscript{97}

Various thiazolidinones are also known to possess diverse biological properties, such as hypnotic,\textsuperscript{98} local anesthetic\textsuperscript{99} and anticonvulsant.\textsuperscript{100,101} These compounds have also been found to possess CNS active\textsuperscript{102} and antibacterial properties.\textsuperscript{103} Some
2-arylimino-3-(2-benzimidazoyl alkyl)thiazolidinones (LIII) have been reported to display good anticonvulsant activity.\textsuperscript{104}

\[ \text{LIII} \]

Gupta et al.\textsuperscript{105} synthesized some substituted thiazolidinones and evaluated for amoebicidal, fungical and anti-convulsant activities. The compound 2-(p-ethoxyphenyl)-3-(2'-pyridyl)-4-thiazolidinone (LIV) is found to possess maximum anticonvulsant activity:

\[ \text{LIV} \]

Recently, 3-(2'-aryl-4'-oxothiazolidin-3-yl)-2-phenylquinazolin-4-(3H)-ones (LV) have been reported as antibacterial and CNS active agents.\textsuperscript{106}
Some N-substituted derivatives of thiazolidinones, when screened for the anticonvulsant activity against maximal electroshock seizure test, showed promising activities, but when screened by metrazol seizure the compounds showed no protection. Various other thiazolidinones have been found to be antibacterial, antiviral and other properties.108-112

5. Indoles

Reserpine, a clinically important Rauwolfia alkaloid, has the indole nucleus. The presence of indole nucleus in reserpine molecule aroused interest in the study of indole derivatives. Large number of indole derivatives, having substitution at 1,2,3-positions, are found to be antidepressant, anticonvulsant and analgesic.113-116 Further studies of 5-hydroxytryptamine (5HT) and other tryptamines on biological systems showed that deficiency of 5-hydroxytryptamine content led to some mental disorders.117-120 These amines and various synthetic indole derivatives, reported as potential psychotropic agents,121-123 generated interest in the syntheses of indole derivatives to step ahead in treatment of mental disorders.

Protiva et al.124 synthesized several tryptamine derivatives containing 3,4,5-trimethoxy benzoyl radical. Numerous synthetic and naturally occurring 5-HT (LVI) derivatives have been shown to possess varying degree of pharmacological activities.
The tryptamine derivatives, having psychotomimetic and psychedelic activities, are of three types: (i) N,N-dimethyl derivatives, e.g., bufotenines, N,N-dimethyl-5-hydroxytryptamine (LVI), (ii) the tryptamine derivatives in which ethylamine chain appear as a part of a carboline system, i.e., harmine, harmaline (LVIII), (iii) the tryptamine derivatives in which the ethylamine chain become part of the two rings of a partly saturated quinoline system condensed with the 3,4-positions of indoles, i.e., lysergic acid (LIX) derivatives. The Psilocine is 4-hydroxy-N,N-dimethyltryptamine and its ester psilocylic is 4-phosphosyloxy, N,N-dimethyltryptamine lysergic acid diethylamine (LSD) also contain a 4-substituted tryptamine.\textsuperscript{125,126}
Several 3-acetyl indoles were synthesized and the effect of the length of side chain on pharmacological activities were studies. It was observed that 3-isobutyryl-1-methylindole possess anticonvulsant activity approximately one third as phenobarbital in rats and approximately one forth in mice and other corresponding compounds, in which the carbon chain was less than three carbon atoms, was found to be less active. In an unbranched 3-(α-carbonyl) side chain 3-carbon is optimal, but, if the side chain was branched by additional carbons the activity enhanced. The CNS depressant effect was observed in indole-glycoxamides. Further studies showed that the presence of an alkyl group at the 2 position has been shown to enhance the CNS activity.\textsuperscript{127}

Alemany et al.\textsuperscript{128} reported the syntheses of several indolyl-carbohydrazides and stated that 1-(indole-2-carbonyl)-2-alkylhydrazine (LIX), 1-(indole-3-carbonyl)-2-alkylhydrazine (LX), and 1-(indole-3-acetyl)-2-alkylhydrazines (LXI) are psychotropic agent.
They also studied the MAO inhibitory properties of these compounds and observed that six of these compounds were found to inhibit monoamine oxidase activity of calf liver mitochondria, \textit{in vitro}.

Substituted indole alkylamine and indole benzyl hydrazide (LXIII) have also been reported as effective anticonvulsant.

Recently, Agarwal et al.\textsuperscript{129} synthesized various substituted indole benzyl hydrazines (LXIV). These compounds showed 10-15\% protection against pentylenetetrazole induced convulsion. Maximum protection was observed when $R_1 = \text{CH}_3$, $R_2 = \text{OCH}_3$, $R_3 = \text{OCH}_3$ and $R_4 = \text{OCH}_3$ and compound shows corresponding low mortality.
Rastogi et al.\textsuperscript{130} reported some 2,3-disubstituted indoles (LXV) as MAO inhibitors.

Several indole derivatives, containing piperazine moiety, were reported to possess CNS depressant activities, e.g., 5,6-dimethoxy-2-methyl-3-[2-(4-phenyl-1-piperazinylethyl]-indole (LXVI) was reported as CNS depressant: \textsuperscript{131}

Various other workers synthesized substituted piperazino indoles and evaluated for hypotensive activity. Only one compound, (LXVII), exhibited promising hypotensive activity:
various indolyl ethyl-pyridines have been reported to produce neutroleptic action in animals, e.g., bis-1-N-piperadinyl-methylindolyl methane, \( \text{LXXIII} \), has been reported as CNS depressants.\(^{132}\)

\[ \text{LXVII} \]

Archibald et al.\(^{133}\) synthesized a series of benzamides-piperidyl ethylindoles and evaluated them for the hypotensive activities. Only 3,2-(4-benzamido-piperidyl)-ethylindole was found to be most potent compound. The sustained hypotensive action of this compound was believed to be due to combination of local anesthetic and \( \alpha \)-receptor blocking properties:

\[ \text{LXIX} \]

Several 2,3,4,4a,5a,b-hexahydro-1H-pyrido-1,3b-indoles were synthesized and reported as CNS active.\(^{134}\)
Among the series of 1,2,3,4,5,6-hexahydrozeopine(4,5b)-indoles evaluated for their effect on CNS. 10-Methoxy-1,2,3,4,5,6-hexahydrozeopine(4,5b) indole (LXXI) has found to possess potency similar to that of chlorpromazine.\textsuperscript{135}

Several-3-indolylacetohydroxamine add LXXI were found to possess analgesic, antipyritic and anti-inflammatory activity.\textsuperscript{136}
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