CHAPTER - 1

BIOLOGICALLY SIGNIFICANT
INDOLE DERIVATIVES

INTRODUCTION
Search of human being for new substances with the help of which he can lead comfortable and joyful life is everlasting. In order to overcome pain and sufferings he discovered medicine. He had entered into systematic and modern methods of chemotherapy which are based on rational thoughts and applications. The major stream of investigations that encompass biologically active compounds have led to the discovery and synthesis of potential therapeutic agents. The success of man lies in the fact that many of the deadly diseases which threatened the very existence of human race have been nearly brought under control and some of them have been completely eradicated.

The approach involves synthesis of new compounds based largely on modifications of structures of known activity. Minor group modification may bring about changes in biological effect. With the development of the receptor concept of drug action, there is an increased emphasis on the importance of the physical and chemical properties of the drug and the relation of such properties to biological action. In the search for safer and more potent therapeutic agents, a popular approach is to synthesize and evaluate biologically active compounds with chemical structures analogous to those having the desired biological activity. The drugs that are being currently used for curing human ailments mainly comprise of several natural products having complex structures. These are derived from terrestrial micro-organisms, plants and animals. The synthetic analogues of the above or other synthetic compounds that are totally non-natural also serve as drugs. A survey of literature reveals that “HETEROCYCLES” have been increasingly important not only in the field of medicinal world but also in the agriculture. As far as chemotherapy is concerned, they have unequivocally qualified as life saving drugs.

Nitrogen heterocyclic compounds play a vital role in the metabolism of all living cells, which are widely distributed in nature and are essential to life. The essential amino acids, pyrimidine and purine bases of the genetic materials, DNA, proline oxygen transporting pigment haemoglobin are some of the important biomolecules which incorporate nitrogen heterocyclic systems in
their structures. A large number of synthetic nitrogen heterocyclic compounds find diverse applications such as dye-stuff, plant growth regulators, agrochemicals, herbicides, reductives, antibacterials and antitumour agents. Because of their multiplicity of type, their unique and manifold reactions, nitrogen heterocyclic compounds offer an interesting and challenging field for the chemists to explore.

**Indole**

Indole and its derivatives have occupied the unique place in the chemistry of nitrogen heterocycles because of their varied biodynamic properties. The derivatives of indole were also known for their dying properties. Many compounds having structural resemblance to ancient dye indigo are known. Indole or benzo[b]pyrrole 1 is a planar molecule in which benzene ring is fused to the 2- and 3- positions of the pyrrole ring.

\[ \text{\includegraphics{molecule.png}} \]

Indole exhibits aromaticity with ten $\pi$-electrons and two of these originate from nitrogen atom. The delocalisation of electron density from nitrogen atom to the ring $\pi$ system diminishes the electron density at the nitrogen atom and hence, indole is a very weak base. Indole is highly reactive towards electrophilic substitution reactions, position 3 being the most preferred site for such substitution. The high reactivity of position-3 is due to $\pi$-electron density on indole moiety 2 (Frontier electron density information obtained from the molecular orbital calculations).
Indole is widely distributed in natural products of animal and plant origin. Indole itself is found in coal-tar. Indole constitutes about 2.5% of jasmine oil and 0.1% orange blossom oil. In both cases it contributes to their fragrances. It is commercially important as a component of perfumes. In the animal body it is found along with pus, liver, pancreas, the brain and bile. Indole and its methyl analogue i.e. Skatole are produced during pancreatic digestion or putrefactive decomposition of proteins and hence both are found in intestines and faeces. Of several natural products containing indole nucleus, mention may be made of the essential amino acid L-tryptophan, the plant growth hormone indole-3-acetic acid, the vasoconstrictor serotonin, a large number of alkaloids like abrine, reserpine, bufotenin, brucine, yohimbine, strychnine and lysergic acid derivatives and also the medicinally important antibiotics like mitomycin, indolomycin, gliotoxin and aparanotin.

Indole and its derivatives have been synthesised by various procedures and one of the prominent being the Nenitzescu indole synthesis.

**Biologically active indoles**

The synthesis and isolation of compounds having structural resemblance to the important derivatives of indole which are known for their varied properties, are the main objects of research in this field. The research work centers mainly around few indole derivatives namely serotonin, tryptophan, heteroauxin, tryptamine, isogramine, indole alkaloids, indole derived antibiotics, indole fused to other heterocyclic systems, also bisheterocycles containing indole nucleus.
Serotonin

Rapport and coworkers isolated serotonin for the first time from the blood serum. Earlier, Erspamer had found that there was a substance responsible for the characteristic staining reaction of argantaffin cells of the gastrointestinal mucosa. He had shown that cells containing the above substance is responsible for contractions of smooth muscles. Later, the above substance isolated by Erspamer was identified as serotonin i.e. 5-hydroxytryptamine, it is also known as eteramine.

Serotonin is uniformly distributed in various parts of the mammalian brain. Its highest concentration was found to be in basal ganglia and pineal glands. Carcinoid tissue has been shown to synthesise serotonin. A method for the prompt detection of serotonin was reported by Curzon and Green. Basal ganglia are thought to be the area of brain concerned with emotions. These observations suggested that any change in concentration of serotonin in the brain either by drugs or by mental disorder would result in psychosis.

Serotonin elevates mood and produces sense of well being. Lack of serotonin or abnormalities in serotonin metabolism is associated with neurogenic conditions including Parkinson's disease, tardive, dyskinesia, Akathisia, distonia, Huntington's disease, familial tremor, restless leg syndrome, myoclonus, tourette syndrome, multiple sclerosis, sleep disorders and dermentia. Psychiatric disorder including depression, anxiety, agression, compulsive behaviour, seasonal effective disorder, childhood hyperactivity, mania, hypersexuality, schizophrenia and behavioural disorder in gastric patients have been associated with impaired central serotonin function. There
are number of ways to increase serotonin level including antidepressant drugs and increased consumption of carbohydrates and fats. Safest and efficient way is to provide body with natural precursors are of fewer negative side effects.

Tryptophan was found to be the source for the formation of serotonin in the body. When 5-hydroxytryptophan\textsuperscript{22,23}, was injected in the animal body, marked increase in the serotonin level was noticed. 5-Hydroxytryptophan is available from food sources. However, it has been found in high concentration in seeds of African legume, \textit{Griffonia simplicifolia}\textsuperscript{24}. 5-HTP prevents migraines in some patients. In an Italian study of 40 migraine patients, about half of those given 5-HTP supplement (400 mg / day for 2 months) reported at least a 50\% improvement with fewer less severe migraine of shorter duration\textsuperscript{25}.

Fibromyalgia patients often have low serotonin levels. In a group of 50 patients given 5-HTP 100 mg (3 times daily), about ½ improved in pain, fatigue, anxiety and sleep quality.

Tryptophan 4 is believed to undergo hydroxylation at position-5 in the presence of enzyme hydroxylase to give 5-hydroxytryptophan 5, which upon decarboxylation by an enzyme 5-hydroxytryptophan decarboxylase\textsuperscript{26} gives 5-hydroxytryptamine 3. Himwich\textsuperscript{27} had shown that the enzyme 5-hydroxytryptophan decarboxylase and monoamine oxidase are not uniformly distributed throughout the brain but are present in high concentration in the area of brain where serotonin is prevalent.
Serotonin was first synthesised by Hamlin and Fischer\textsuperscript{28}. Because of psychopharmacological properties of serotonin, several compounds containing serotonin moiety have been synthesised with a hope to get compounds possessing either serotonin like or antagonistic properties. Reserpine has been shown to be active in reducing the concentration of serotonin in central tissues\textsuperscript{29}.

Hence, the synthesis of compounds possessing similar structure as that of serotonin or containing tryptamine residue or having aminoindole moiety has attracted much attention in recent years. A vast number of investigations\textsuperscript{30,31} on neurotransmitter serotonin have indicated that its imbalanced metabolism in brain leads to certain mental disorders. It has been shown\textsuperscript{32} that the serotonin level in brain is elevated by the administration of various CNS depressants to the rats. Grinev and coworkers\textsuperscript{33} have reported that the dimekarbene (1,2-dimethyl-3-carbethoxy-5-hydroxyindole) and its analogues possess strong serotonin antagonistic activity and dimekarbene is used along with another drug for the treatment of hypertension.

Carruba \textit{et. al}\textsuperscript{34} and Glennon have reported that the neurotransmitter serotonin appears to play a role in modulating mood, social behaviour, appetite, sexual behaviour and pain. Currently, serotonin has received renewed interest
and widespread attention due to the recent identification of 5-HT binding receptor sites.

Indoles containing free NH₂ group in the 3-position such as serotonin were found to be most potent in inhibiting mixed function oxidase activity. This was followed by the experiments³⁵ with liver microsomes from phenobarbital treated rabbits using various compounds containing indole. The general survey made by Rollag³⁶ on 5-hydroxytryptamine derivatives for antigonadal capability indicated that only 5-methoxytryptamine derivatives and acetyl derivative (melatonin) were active. The antigonadotropic activity of the former was 10% of that of the latter. Mate and coworkers³⁷ studied the regulation of gastric acid secretion by serotonin and secretin separately and also in combination. The intravenous administration of serotonin or secretin alone in dogs inhibited pentagastrin induced gastric acid secretion. The combined administration of serotonin and secretin inhibited pentagastrin induced gastric secretion to a greater extent than either secretagogue alone. A correlation study³⁸ of therapeutic actions of O-alkylated serotonins with their pharmacological and radioprotective effects suggested that increase in the alkyl chain length increased the toxicity and decreased radioprotective (against γ rays) and vasoconstrictor effects.

A facile 5-substituted N,N-dimethyl tryptamine of the type 6 has been reported³⁹ as a potent 5-HT₁D receptor agonist.

![Chemical Structure](image)

Recently, Perez et al⁴⁰ have prepared 5-piperazinylcarbonylmethoxy derivative of serotonin of the type 7 as a new class of potent selective 5-HT₁D receptor agonists.
They have demonstrated that such tryptamine derivatives 7 are high affinity ligands to both receptor subtypes and inhibition of forskoline mediated cydase studies with human 5-HT\textsubscript{1D\alpha} and 5-HT\textsubscript{1α} receptors and showed that they are very efficient and selective 5-HT\textsubscript{1D\alpha} agonists.

A facile indole-2-ones of the type 8 have been reported\textsuperscript{41} as 5-HT\textsubscript{1D\alpha} and 5-HT\textsubscript{2A} ligands.

\[
\begin{align*}
R_1, R_2 & = \text{H, C}_1\text{,}_4\text{alkyl, C}_1\text{,}_4\text{alkoxy}, & R_3, R_4 & = \text{H, halo, NO}_2 \\
R_6, R_7 & = \text{H, C}_1\text{,}_4\text{alkyl}; n = 1-6 & X & = O, S
\end{align*}
\]

Recently, Gaster L. M.\textsuperscript{42} has synthesised the 1-biphenylcarbonyl-1H-indole derivative 9 as 5-HT\textsubscript{1D} antagonist.
Research group\textsuperscript{43-45} of Merck Sharp and Dohme Ltd., U.K. has synthesised 3-alkylpiperazine-5-triazolylindoles 10 as 5-HT\textsubscript{1Da} receptor agonists selectively.

\begin{center}
\begin{tikzpicture}
\node[draw,rectangle,inner sep=0pt] (m) at (0,0) {10};
\end{tikzpicture}
\end{center}

\begin{align*}
10a & \quad R = -\text{CH}_2\text{CH}_2\text{-C}_6\text{H}_4\text{F}-m \\
10b & \quad R = -\text{CH}_2\text{CH}\text{-C}_6\text{H}_4\text{-CH}_2\text{-OH} \\
10c & \quad R = -\text{CO}\text{-CF}_2\text{Ph}
\end{align*}

Recently, Meng et. al\textsuperscript{46} have prepared 5-substituted tryptamine analogues 11 and 12 for use as 5-HT\textsubscript{1D} receptor agonists and consequently, these have shown potency in the alleviation of symptoms of migraine. Compound 12 showed 84\% and 14\% inhibition of binding when tested for affinity for the 5-HT\textsubscript{1D8} and 5-HT\textsubscript{1Da} receptors respectively.

\begin{center}
\begin{tikzpicture}
\node[draw,rectangle,inner sep=0pt] (m) at (0,0) {11};
\end{tikzpicture}
\end{center}

\begin{center}
\begin{tikzpicture}
\node[draw,rectangle,inner sep=0pt] (m) at (0,0) {12};
\end{tikzpicture}
\end{center}

\begin{itemize}
\item \textbf{Y} = bond connecting alkyl group
\item \textbf{T} = furanyl, thieryl
\item \textbf{Z} = amino, N-containing heterocycles such as pyrrolidinyl, pyrrolinyl, azetidinyl, piperidinyl.
\end{itemize}
Recently, Ogilvie and coworkers\textsuperscript{47} reported a new process for the preparation of anti-migraine drug eletriptan 13.

![Chemical structure of eletriptan](image)

Simeone \textit{et. al}\textsuperscript{48} synthesised chiral β-methyl tryptamine derived GnRH antagonists 14 and 15.

![Chemical structures of 14 and 15](image)

**Tryptophan**

Tryptophan 4 has occupied the most vital position among the naturally occurring indole derivatives because of its presence in plant and animal proteins. It is one of the naturally occurring essential amino acids and is protein structural unit.
Tryptophan is not synthesised in animal body and hence must be supplied through diet. Deficiency of tryptophan causes characteristic syndrome in animals. It is having vital role in biosynthesis of cellular proteins and porphyrins in animals. The metabolic pathway of tryptophan indicates that it can be a substitute for nicotinic acid in higher animals\(^4\).

A large number of methyl substituted tryptophans have been synthesised and screened for their biological activities. Anderson\(^5\) has synthesised and demonstrated that 5-methyltryptophan inhibits the growth of *Escherichia coli*. Fildes and Rydon\(^5\) have synthesised several derivatives of 2-methyltryptophan which had little inhibition against growth of *B. typhosum*. Freter\(^5\) studied monoamine oxidase inhibition activity of 2-phenyltryptophan and 2,5-dihydroxytryptophan. Several Bz-substituted-2-phenyltryptophans\(^5\) were synthesised and screened for their activity against *Escherichia coli*. Synthesis of Bz-methyl and methoxynitrotryptophans were reported by Hiremath and Siddappa\(^5\). Ambekar and Siddappa\(^5\) synthesised some Bz-haloalkyl substituted tryptophans for the assessment of their biological activity. Recently, a new class of phosphonic analogue of tryptophan has been reported by Subtowski *et al*\(^6\).

**Heteroauxin**

Heteroauxin 16 which is also known as indole-3-acetic acid is a naturally occurring plant growth hormone. Higher plants degrade tryptophan to heteroauxin. Different routes for the synthesis of the analogues of this hormone have been reviewed by Sundburg\(^4\).

\[^4\]Tryptophan, 2-amino-4,5-dihydro-1H-pyrrolo[3,2-b]pyridine-3-carboxylic acid.

\[^5\]Refer to Table 2.
Various structural analogues of this hormone, such as indole-3-propionic acid, indole-3-butyric acid and indole-3-pyruvic acid have been synthesised and tested for their photohormonal activity. 4-Chloroindole-3-acetic acid\(^57\) was found to possess a considerable activity against *A. Coleoptile*.

![Image of indole-3-propionic acid analogues](16)

Some Bz-nitrosubstituted indole-3-acetic acids were prepared by Hiremath and Siddappa\(^58\). Amongst them, 7-nitroindole-3-acetic acid was reported to be mutagenic and its activity\(^59\) was found to be more than heteroauxin itself. The preparations of some Bz-halomethyl\(^58\) substituted and linear benzindole\(^55\) analogues of heteroauxin and various derivatives\(^60\) of indole-3-propionic acid and indole-1-propionic acid were reported.

Shen and Sarett\(^61\) have shown that indole-3-acetic acid and propionic acids possess antipyretic or antiinflammatory activity. Indole-1, 2-diacetic acid derivatives\(^62\) were found to be useful in the treatment of arthritic and dermatological disorders.

The discovery of indomethacin \(^17\)\(^53\), a very important nonsteroidal antiinflammatory and antipyretic agent gave an impetus to synthesise large number of its structural analogues.

![Image of indomethacin analogues](17)

The combination of indomethacin with an anticoagulant viz., 4-hydroxy-2-oxo-3-(1-phenylpropyl)-2H-chromene produced slow acting rodenticides\(^64\)
which were lethal after a single injection and were relatively nontoxic for human and domestic animals. The action of indomethacin in tumor growth inhibition and potentiation of immunotherapy is also well known. Indomethacin relieves pain, tenderness, inflammation and stiffness caused by gout and arthritis. Fluorobenzoyl and fluoroalkylbenzoyl indole acetic acids were found to be good antiinflammatory agents which exhibited an oral ED\textsubscript{50} of 2.2 mg/kg against carrageenan induced inflammations in rats \textit{viz.}, an oral ED\textsubscript{50} 4.2 mg/kg for indomethacin.

Recently, Shoko and Kunio\textsuperscript{67} have shown that a cellular support layer, a fabric or nonwoven fabric layer and an adhesive layer containing isoprenestyrene block copolymer 100, cyclic saturated hydrocarbon resins 85-160, liquid paraffin 180-270, Fe\textsubscript{2}O\textsubscript{3} 0.01-0.6, dibutyl hydroxytoluene 2-7, crotamiton 6-12, red pepper extracts tapes in the treatment of muscle ache or back ache. The above preparations showed good bioavailability and also generated heat.

Martin \textit{et. al.}\textsuperscript{68} synthesised N-benzylindole-3-acetic acid derivatives of the type 18 as potentiators for the use in the treatment of multi-drug resistance cancer and leishmaniasis.

\[
\begin{align*}
R & = \text{Me, Et; } R = (\text{un})\text{substituted C}_{1-6}\text{ alkyl; } y = \text{OH or NH}_2 \\
X & = \text{H, Cl, Br, F}
\end{align*}
\]

Recently Wardman \textit{et. al.}\textsuperscript{69} reported the synthesis of indole-3-acetic acid derivatives of the type 19 and tested them for activity against a number of
human cancer cell lines such as breast carcinoma MCF7 and colon adenocarcinoma LS174T.

\[ \text{R}^1, \text{R}^2, \text{R}^3, \text{R}^3' = \text{H, alkyl}; \text{R}^4, \text{R}^5, \text{R}^6, \text{R}^7 = \text{H, alkyl, alkoxy, aryl, aryloxy, halo} \]

**Gramines and Isogramines**

Gramines serve as nerve tonic and sedative. They are useful for epilepsy, depression and nicotine withdrawal. Gramines modulate blood pressure, lowers brain blood serum cholinesterase activity by 61%. Also, they have application in alleviating early symptoms of Alzheimer's disease.

Several synthetic gramine 20 have been screened to evaluate their serotonin antagonistic activity. Bhat synthesized some Bz-substituted-2-isogramines and screened them to evaluate their serotonin antagonistic activity on isolated rat uterus. Some of them were found to be more potent than BAS.

\[ \text{R} = \text{H, CH}_2 - \text{C}_6\text{H}_5, \quad \text{R}_1 = \text{H, CH}_3 \]

\[ \text{R}_2 = \text{H, OH, O-CH}_2-\text{C}_6\text{H}_5, \text{CH}_3, \text{Br, Cl, NH}_2, \]

\[ \text{R}_3 = \text{H, OCH}_2-\text{C}_6\text{H}_5. \]
Grinev and coworkers\textsuperscript{33,73} have synthesised some 4-isogranines of 5-hydroxyindole 21 which were evaluated for their antiserotonin and antihistamine activities.

\[ \text{CH}_2\text{N(CH}_3)_2 \]

\[ \text{COOC}_2\text{H}_5 \]

\[ \text{R = o-tolyl, p-tolyl, p-chlorophenyl} \]

Gadaginamath and associates\textsuperscript{74} have synthesised various 4-isogranines of 2-phenyl-5-hydroxyindoles which displayed interesting antibacterial and antiserotonin activities. Panisheva and coworkers\textsuperscript{75} have reported the synthesis and evaluation of antiviral and antiarrythmic activities of 4-isogranines. The uses of 4-isogranines as diuretics, cardiovascular agents\textsuperscript{76} and also for the treatment of circulatory disorders\textsuperscript{77} have been reported.

Trofimov and associates\textsuperscript{78} have reported the synthesis of 4-isogranines of 5-hydroxyindoles of the type 22 as potential antiviral drug known as arbidol.

\[ \text{(H}_3\text{C)}_2\text{N} \]

\[ \text{CH}_2 \]

\[ \text{COOC}_2\text{H}_5 \]

\[ \text{CH}_2\text{S--Ph} \]

\[ \text{CH}_3 \]

Gadaginamath and coworkers\textsuperscript{79} have synthesised several 4-isogranines which displayed interesting antimicrobial activities.
Indole alkaloids

A few indole alkaloids have acquired significant clinical importance. Reserpine was shown to exhibit tranquillising and hypotensive activities. Yohimbine, aspidospermine and strychnine are among the other alkaloids which have found occasional medicinal use.

Reserpine

Extracts of plants like *Rauwolfia serpentina* were used in primitive Hindu medicines for a variety of diseases, including snake bite, hypertension, insomnia and insanity. Therapeutic applications of the extract of root of *Rauwolfia serpentina* have been described in Indian medicinal journal in 1931 by Sen and Bose. In 1954, Kline reported the use of Rauwolfia or reserpine in the treatment of psychotic patients.

Reserpine is widely used as an antihypertensive agent. The antihypertensive effect of chronic administration of reserpine is reported to be associated with reduced cardiac output in man. Reserpine is said to act centrally to produce characteristic sedation and a state of indifference to environmental stimuli, which is said to be presumably due to the depletion of stores pertaining to catecholamines and 5-HT in the brain. It produces tranquilization, increase in parasympathetic activity and depression of responses to peripheral adrenergic nerve activity, causes slowly developing fall in blood pressure associated with bradycardia. Patients with chronic mental
illness treated with reserpine become relaxed, sociable and co-operative. Reserpine finds application in treatment of hypertension, mild anxiety status and chronic psychosis.

The oral antihypertensive doses of reserpine ranges from 0.1 to 1.0 mg daily for three weeks for full antihypertensive effects. Reserpine (Sandrill, Serpasil) is available in tablets or capsules that contain 0.1 to 1.0 mg. Reserpine is reported to commonly increase gastrointestinal tone and motility, with abdominal cramps and diarrhoea.

**Bromocriptine**

Several ergot derivatives like bromocriptine lisuride, pergolide and mesulergine demonstrated dopaminergic activity in animal models of parkinsonism and mimic the neuroendocrinological effects of dopamine on the secretion. Bromocriptine 24 is a derivative of lysergic acid.

It is used in the treatment of patients with Parkinson disease who experience excessive "on-off" phenomenon. Bromocriptine is rapidly, but only partially (about 30%) absorbed by the gastrointestinal tract. Initial side effects like nausea, vomiting and postural hypotension are reported. Bromocriptine mesylate (parlodel) is available in 2.5 mg tablets and 5 mg capsules. It is in therapy of hyperprolactinemia including lactation and infertility. Bromocriptine is also used as an adjunctive agent in the treatment of pituitary tumors associated with hyperprolactinemia.

![](image)

\[ R = CH(CH_3)_2 \quad R_1 = CH_2CH(CH_3)_2 \]
Lysergic acid and its derivatives

Among the various derivatives of alkaloids of therapeutic interest are amide derivatives of D-Lysergic acid. Because of the intense hallucinogenic activity, D-Lysergic acid N-N-diethylamide (LSD) occupies the vital position among the known psychotomimetic drugs.

It displayed strong antiserotonin activity on isolated rat uterus and it has been adopted as the reference standard compound for evaluating the relative activity of various antiserotonin drugs. The action of the LSD is selective. It also prevents the antidiuretic action of serotonin.

Vincristine and Vinblastine

Perennial herb periwinkle plant (Vinca rosea Linn.) known for pink or white flowers contains indole alkaloids, vincristine, vinblastine, vinleurosine and vinrosidine. Two of these, vincristine and vinblastine are important clinical agents.

The most important use of vinblastine is with bleomycin and cisplatin in the therapy of metastatic testicular tumors. Its usage is also reported in the treatment of Hodgkin’s disease. It is said to be active in kaposis sarcoma, neoblastoma as well as in carcinoma of breast and choriocarcinoma in women. The toxic effects of vinblastine include neurological manifestations, gastrointestinal disturbances including nausea, vomiting, diarrhea, hair loss, low blood cell counts, headache, stomach pain, constipation and mouth sores.
Vinblastine sulphate (velban) is supplied in vials containing 10 mg of dry powder for preparation of solutions (10 ml). The drug is given intravenously.

Another drug of choice is vincristine. Vincristine sulphate (Oncovin) is available as solution of vials containing either 1, 2 or 5 mg of drug. Vincristine is used presently against childhood leukaemia. Adult patients with carcinoma of lymphomas responded to weekly intravenous doses of 0.02 to 0.05 mg/kg. Vincristine is used as present drug of choice against the neoplastic diseases like acute lymphocytic leukaemia, neuroblastoma Wilm’s tumor, Hodgkin’s disease and rhabdomyosarcoma in children and other patients.

The clinical toxicity of vincristine is said to be most neurological. Severe constipation may be prevented by using laxatives and hydrophilic agents. Anaemia, polyurea, disurea, fever and gastrointestinal symptoms have also been reported.

![Chemical Structures]

Vincristine  Vinblastine  Vindesine

<table>
<thead>
<tr>
<th>R₁</th>
<th>CHO</th>
<th>CH₃</th>
<th>CH₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>R₂</td>
<td>OCH₃</td>
<td>OCH₃</td>
<td>NH₂</td>
</tr>
<tr>
<td>R₃</td>
<td>COCH₃</td>
<td>COCH₃</td>
<td>H</td>
</tr>
</tbody>
</table>
Recently, a semisynthetic derivative of vindesine is available as vindesine sulphate in 5 mg vials. The drug is given intravenously for the treatment of chronic granulocytic leukemia and systematic mastocytosis. Mild neurotoxicity is the usual toxic manifestation. Another semisynthetic derivative of vinblastine is vinorelbine which is currently in phase II clinical trials as a treatment for ovarian cancer.

**Hemacanthin B**

This 27 was isolated from deep water marine sponge *Hamacantha sp.* and has been reported to show significant antimicrobial activities against *Candida albicans* and *Cryptococcus neoformans*.

![Hemacanthin B](image)

Biao Jiag\textsuperscript{86} reported the total synthesis of Hamacanthin B.

**Indole Derived Antibiotics**

**Mitomycin**

The mitomycin family of antibiotics is represented by structural formula 28. These compounds which are isolated\textsuperscript{87} from *streptomyces* cultures are indoline quinones and the members of this family have been found to be active against bacteria and also useful in cancer chemotherapy. Several derivatives of mitomycin have been synthesised for their pharmacological evaluation.
Mitomycin-C is useful for the treatment of gastric adenocarcinoma and also carcinomas of colon, rectum, pancreas, breast, bladder, head, neck and lung. It has also shown activity against lymphomas and leukaemia. Mitomycin-C (Mutamycin), a current drug, is available as deep blue violet crystals in vials containing 5 mg or 20 mg and is administered intravenously.

Usubuchi et al. have screened many mitomycin-C derivatives against Hirosaki ascites sarcoma in rats and claimed that the anticancer activity of mitomycin-C depends not only on the bifunctional alkylating actions caused by the protonations of the carbamoyloxymethyl and aziridine groups but also on the aminoquinone moiety. Mitomycin-C derivatives are unique antitumor agents. Oboshi et al. have reported that the removal of aziridine and carbamoyloxymethyl groups resulted in the loss of antitumor effect. Weiss and coworkers have synthesised various indoloquinones which showed high in vitro antibacterial activity against Gram-positive microorganisms.
Yamada et al. have synthesised 2-methylpiperazino[1,2-α]indole-6,9-dione 30, mitomycin analogue and reported that it was effective in vitro against *Staphylococcus aureous*.

Roquefortine

Roquefortine C 31 was isolated by independent groups from *Penicillium roqueforti* Thom stain along with several other indole compounds (roquefortines A and B)\(^{92-95}\). Since its initial discovery, roquefortine C has been found in number of other *Penicillium roqueforti* cultures\(^{96, 97}\) as well as in *Penicillium* strains isolated from a variety of food cultures\(^{98-101}\). Iso-roquefortine C 32 has not been isolated from nature but it is the 3,12-double bond isomer of 31. This has been obtained with complete conversion from the natural product under photochemical conditions\(^{102}\). 31 is found in the blue vein of roqueforti and other blue cheeses and also has been detected in other sources such as feed grain. Neurotoxic properties were reported by Wagner et al.\(^{100}\) (paralytic activity) and Scott et al.\(^{102}\). Clinical symptoms observed in cows included extensive paralysis which did not respond to calcium treatment. The disease symptoms disappeared as soon as the cows were no longer fed moldy grain.
The same symptoms were observed in human study and were linked to the presence of 31 in a contaminated commercial beer\textsuperscript{103}.

Recently, Bruno \textit{et al.}\textsuperscript{104} reported the total synthesis of isoroquefortine C.

![Chemical structure of 31 and 32](image)

\textbf{Gliotoxin}

Johnson and coworkers\textsuperscript{105} isolated another antibiotic, gliotoxin 33 containing indole moiety. It is an antibiotic of fungal origin with a tetrahydroindole ring and bicyclic bisulphide unit.

![Chemical structure of 33](image)

\textbf{Pentagastrin}

The potent physiological gastric secretagogue, gastrin is released in response to feeding. Gastrin\textsuperscript{80d} is a heptadecapeptide having the indole moiety. A synthetic pentapeptide derivative, pentagastrin 34 is reported to be still more active. Pentagastrin is N-t-butyloxycarbonyl-\textbeta-alanyl-L-tryptophanyl-L-methionyl-L-aspartyl-L-phenylalanine amide.
The prominent action of pentagastrin is to stimulate the secretion of gastric acid pepsin, which stimulates pancreatic secretion, contracts the smooth muscle of the lower esophageal sphincter and stomach and increases blood flow in the gastric mucosa.

\[
\text{HN} \text{--CO--(CH}_2\text{)}_2 \text{--NH--COOC(CH}_3\text{)}_3
\]

\[
\text{CH}_2 \text{--CH} \mid \text{CONH--CH--CONH--CH--CONH--CH--CONH}_2 \\
(\text{CH}_2\text{)}_2 \mid \text{CH}_2 \mid \text{CH}_2 \\
\text{SCH}_3 \mid \text{COOH} \mid \text{C}_6\text{H}_5
\]

Pentagastrin is reported to elicit reproducible gastric secretory responses comparable to those induced by histamine or betazole. The side effects are usually minor and transient, viz., nausea, faintness and dizziness. Pentagastrin (peptarlon) is marketed in ampules containing 0.25 mg/mL, the diagnostic dose being 6 mg / kg administered by subcutaneous injection.

3-Acyllindoles

Many simple indole derivatives showed interesting biological actions. Keasling et. al\textsuperscript{106} have reported that a considerable number of 3-acyllindoles possessed anticonvulsant action that can be compared to the activity of phenobarbital. Various 3-carboxamido-1-phenyllindoles \textsuperscript{35} synthesised by Claude et. al\textsuperscript{107} have exhibited analgesic, antiinflammatory, hypotensive, vasodilator, anticonvulsant, sedative, muscle relaxant and parasympatholytic activities.
Zorin and coworkers\textsuperscript{108} have synthesised various substituted 3-acetyl-indoles 36 and reported their antineoplastic and cytotoxic activities.

Bourdais and Allain\textsuperscript{109} have synthesised several 3-acyl-2-aminoindoles 37 which displayed sedative and antidepressant activities.

Allais et al\textsuperscript{110} have reported the synthesis, analgesic and antiinflammatory activities of 1-carboxyalkyl-3-acylindoles. Compound 38 (R = 4-ClC\textsubscript{6}H\textsubscript{4}, R\textsubscript{1} = 6-OCH\textsubscript{3}) had an analgesic ED\textsubscript{50} of 5 mg / kg orally in mice and antiinflammatory ED\textsubscript{40} of 35 mg / kg orally in rats.
R = phenyl, substituted phenyl, methyl, cyclohexyl, CH = CHC₆H₅, 2-furyl, 3-pyridyl
R₁ = 6-NO₂, 6-NH₂, H, 5-alkoxy, 6-alkoxy, 6-halo, 5-halo, 6-SO₂CH₃,

5,6-Dihydroxyindoles

The role of 5,6-dihydroxyindole as additives for hair dying is very interesting in the field of cosmetics. Dye solutions based on 5,6-dihydroxyindoles 39 are described as additives for hair colouring preparations, which produce a light chestnut brown colour when applied to hair for 20 minutes.

Another German patent reported that a sequential procedure for colouring hair by formation of melanin involves treatment with alkali metal salt solution, an alkaline 5,6-dihydroxyindole solution and then with H₂O₂ to adjust the colour to the desired shade formed. 5,6-Dihydroxyindole acts as an intermediate in the conversion of tyrosine to melanin.

Fused heterocycles containing indole nucleus

A large number of alkaloids are known to possess indole nucleus. Some antibiotics derived from microbial sources are also known to contain indole nucleus to obtain a compound which can exhibit either like or antagonistic
property. With respect to alkaloids or antibiotics, a large number of their structural analogues have been synthesised and screened to know their biological properties. Hiremath and Purohit\textsuperscript{113} have synthesised various heterocycles containing indole nucleus. Hiremath and Kaddargi\textsuperscript{114,115} have reported the synthesis of 3,4-dihydropyrimido(3,4-a)indoles. These compounds were also screened for antiserotonin and antihistamic activities. Gadaginamath \textit{et. al}\textsuperscript{116} have reported the synthesis and biological activities of various substituted 3,4-dihydropyrimido(3,4-a)indoles.

Basanagoudar \textit{et. al}\textsuperscript{60c} have synthesised some 1,2,3,4-tetrahydro-pyrazino[1,2-a]indoles 40 and their ability to exhibit interesting antiserotonin and antihistamine activities.

![Diagram](image_url)

$R_1 = \text{C}_6\text{H}_5, \text{CH}_3 \quad R_2 = \text{CH}_3, \text{OCH}_3, \text{OC}_2\text{H}_5$

Furo[3,2-b]indol-2-carboxamides 41 have been prepared by Yataka and coworkers\textsuperscript{117} to study structure-activity relationship. These furindoles 41 were found to exhibit platelet aggregation inhibitory effect\textsuperscript{118}, analgesic and antiinflammatory activities.

![Diagram](image_url)

$R = \text{H}, \text{CH}_3, \text{Cl}, \text{F}, \text{O-CH}_3, \text{CF}_3; R_1 = \text{H}, \text{CH}_3, \text{C}_2\text{H}_5, \text{COOC}_2\text{H}_5, \text{COOCH}_3 \quad R_2 = \text{N}((\text{CH}_2\text{CH}_2\text{OH})_2, \text{piperidiny}, \text{propylamino, morpholino}$
Recently, Gadaginamath and associates\textsuperscript{119} have synthesised fused heterocycles and reported their antibacterial and antifungal activities.

\begin{center}
\centerline{\includegraphics[width=0.5\textwidth]{image1.png}}
\end{center}

\[ X = H, \text{Br} \]

Gadaginamath and Kavali\textsuperscript{120} have also synthesised novel linearly fused pyranoindoles 44 and 45 and reported their antimicrobial activities.

\begin{center}
\centerline{\includegraphics[width=0.5\textwidth]{image2.png}}
\end{center}

\[ R = C_6H_5, C_6H_4-Cl-p, C_6H_4-CH_3-p \]
Nakkadi et al.\textsuperscript{121} synthesised the linearly fused 2H-thiopyrano indoles 47 as antiinflammatory agents.

Mitsunobu et al.\textsuperscript{122} have reported the synthesis of linearly fused quinoxanylindoles 48 with potent antitumor activity.

Sarapani et al.\textsuperscript{123} reported the synthesis of the compounds of the type 49.
Indolin-2-ones

Indolin-2-one have acquired importance because of their use in the treatment of autism, depression and schizophrenia. Garcia and Foulon\textsuperscript{124} synthesised indolin-2-one derivatives 50 as oxytocin ligands.

Terence and Jiang\textsuperscript{125} have synthesised novel indolones 51 which are used as antiinflammatory agents.
Indolylquinones

Inspired by mitomycin group of antibiotics, attempts are made to synthesise indoles possessing quinone group which showed various interesting biological activities. Harris et. al\textsuperscript{126} synthesised 6-(2-phenylindol-3-yl-)-2,3,5-tribromo-1,4-quinone 52 as antitumor agent.

![52](image)

Pelaez et. al\textsuperscript{127} have synthesised indolylquinones 53 which possessed antidiabetic property.

![53](image)

Tang et. al\textsuperscript{128} synthesised bisindolylquinones 54 as GRD-2 adaptor protein inhibitors and treatment of cell proliferative disorders and insulin related disorders.
Bystroem et al. have synthesised benzoindolediones 55 as antidiabetics.

R<sup>1</sup> = H, alkoxy, phenylalkoxy; R<sup>2</sup> = OH, alkoxy, ocoalkyl;
R<sup>3</sup>, R<sup>4</sup> = alkyl or cyclohexane

**Bisheterocycles containing indole nucleus**

The literature survey reveals that there are number of heterocyclic compounds in which indole is substituted with another heterocyclic system. Such type of substitution may enhance the biological property of parent nucleus. Hiremath and coworkers have synthesised 3-oxadiazolyl, 3-thiadiazolyl and 3-triazolylaminoindoles 56.

R = H, Cl; R<sub>1</sub> = SH, C<sub>6</sub>H<sub>5</sub>, NHCH<sub>3</sub>, NHC<sub>6</sub>H<sub>5</sub>; X = O, S, NCH<sub>3</sub>, NC<sub>6</sub>H<sub>5</sub>
Some of these compounds were screened for their antimicrobial activity and some were also screened for their antihistaminic activity.

Unangst *et. al*\(^{131}\) synthesised a series of indole carboxamidotetrazoles 57 as potential antiallergic agents. Many of these compounds demonstrated potent inhibition of histamine release. The compounds with best inhibitory potential contained 3-alkoxy, 5-alkoxy and 1-phenyl substituents on the indole core structure.

\[ R_1 = 5-\text{OCH}_3, 5-\text{C}_6\text{H}_5-\text{CH}_2\text{O}, 5-\text{CH}_3, 5-\text{Br}, 5-\text{Cl}, 5,6-\text{Cl}, \text{H} \\
R_2 = \text{C}_6\text{H}_5, 4-\text{CH}_3\text{O}-\text{C}_6\text{H}_4, \text{H}, \text{CH}_3, \text{CH}_2\text{C}_6\text{H}_5 \\
R_3 = \text{OH}, \text{OCH}_3, \text{OC}_2\text{H}_5, \text{OCH}(\text{CH}_3)_2, \text{OC}_6\text{H}_{19}, \text{OCH}_2\text{C}_6\text{H}_5, \text{H}, \text{CH}(\text{CH}_3)_2, \text{O}(4-\text{NO}_2-\text{C}_6\text{H}_4), \text{SCH}_3, \text{SO}_2\text{CH}_3, \text{SC}_6\text{H}_5, \text{SCH}(\text{CH}_3)_2. \]

Recently, Purohit and coworkers\(^{132}\) have reported synthesis and antiserotonin activities of indole containing piperazine ring systems 58 and 59.

\[ R_1 = \text{H}, \text{Bz} ; R_2 = \text{H}, \text{CH}_3, \text{Bz} \]
Gadaginamath et al. have synthesised several bisheterocycles containing indole and other heterocyclic ring systems 60-67 and also reported their antimicrobial activities.
R = n- butyl, benzyl, p – chlorophenyl, m – chlorophenyl; X = H, Br

R = CH₃, C₂H₅; Ar = C₆H₅; C₆H₄ - Cl (p), C₆H₄ - OCH₃ (p)
Triazinoindoles\textsuperscript{134} exhibiting interesting antiinflammatory activity, thiazolylindoles\textsuperscript{135} with CNS depressant activity and coumarinyl indoles\textsuperscript{136} displaying antimicrobial activities are also reported in the literature.

Filla and Krushinki\textsuperscript{137} synthesised octahydroindolizinyldole 68 which showed 5HT1F agonist antimigraine activity.

\[
\text{H}_2\text{N} \quad \begin{array}{c} \text{N} \\ \text{H} \\
\end{array} \quad \begin{array}{c} \text{N} \\ \text{H} \\
\end{array} \quad \begin{array}{c} \text{N} \\ \text{H} \\
\end{array}
\]

\textbf{68}

Asakai and Sodeoka\textsuperscript{138} have reported the synthesis of pyrrolylindoles 69 which possessed cell death inhibitor property.

\[
\begin{array}{c} \text{N} \\
\end{array} \quad \begin{array}{c} \text{H} \\
\end{array} \quad \begin{array}{c} \text{H} \\
\end{array}
\]

\textbf{69}

Peglion \textit{et. al}\textsuperscript{139} have synthesised cyclobutaindolecarboxamide 70 as CNS agent.

\[
\begin{array}{c} \text{N} \\
\end{array} \quad \begin{array}{c} \text{N} \\
\end{array} \quad \begin{array}{c} \text{O} \\
\end{array} \quad \begin{array}{c} \text{H} \\
\end{array} \quad \begin{array}{c} \text{H} \\
\end{array}
\]

\textbf{70}
Ruzinsky and Dzurilla\textsuperscript{140} have prepared 2-(3-indolyl)benzothiazole 71 and its thiazole analogue of camalexin 72 which displayed good antifungal activity.

Douglas \textit{et. al}\textsuperscript{141} have reported the synthesis and immunosuppressant activity of 1-(quinolin-2-yl)indole 73.

Rowley \textit{et. al}\textsuperscript{142} have reported the synthesis of 3-(piperidin-3-yl)-1H-indole 74 as 5H R\textsubscript{2A} receptor antagonists for the treatment of psychotic disorders such as schizophrenia.
Wilfried et. al\textsuperscript{143} have prepared an efficient antidepressant, 4-(5-fluoro-1H-indol-3-yl)piperidine-1-carboxylic acid [4-methoxy-3-(4-methylpiperazin-1-yl)-phenyl]amide 75.

Donald et. al\textsuperscript{144} have reported the synthesis of quinolinyindole 76 as antimicrobial agent.

Xie Roger et. al\textsuperscript{145} have synthesised 2-(3-indolyl)quinoline 77 as antibacterial agent.
Gilbert and coworkers\textsuperscript{146} have reported the synthesis of arylpiperazinyl-cyclohexylinolde 78 which was used for the treatment of depression.

![78](attachment:image)

Pflieger \textit{et. al}\textsuperscript{147} have reported the synthesis of diaminopyrimidinyl-methylindoles 79 as potent antibacterial agents.

![79](attachment:image)

R\textsubscript{1} = Alkyl, alkenyl, alkynyl, cycloalkyl,
R\textsubscript{2} = H, halo, alkyl, R\textsubscript{3} = H, alkyl, R\textsubscript{4} = alkyl, alkenyl, alkynyl, cycloalkyl.

Chakravarthy and coworkers\textsuperscript{148} have prepared 5-[4-benzylpiperidinyl]indole carboxamide 80 as the inhibitor of p38 kinase.

![80](attachment:image)

Albert \textit{et. al}\textsuperscript{149} have prepared indolylmaleimide 81 and 82 derivatives as protein kinase c inhibitors.
Andreani et al.\textsuperscript{150} have synthesised the compounds of the type 83 which displayed antitumour activity.

Heller and coworkers\textsuperscript{151} synthesised 5-(2-pyridyl)indole 84.

\textbf{Indole derivatives from marine sources}

The number of active products being discovered from the terrestrial biosystem is declining. This has prompted the scientists to look for marine
natural products and results in the discovery of amazing array of compounds with good pharmaceutical potential from the sea. Compounds from marine sources differ structurally from those obtained from terrestrial sources. These compounds generally incorporate usual heterocyclic ring systems.

Rinehart and coworkers\textsuperscript{152} obtained a series of brominated indoles from the red alga \textit{laurencia brongiartii}. Only one, the 2,3,5,6-tetrabromo indole \textit{85} was reported to be cytotoxic towards L1210 cell line (ED\textsubscript{50} 3.6 µg/mL) and also to be antimicrobial.

\begin{center}
\includegraphics[width=0.3\textwidth]{85.png}
\end{center}

Dendrodoine \textit{86} obtained from the tunicate \textit{Dendrooa grossularia}\textsuperscript{153} provided an indole with a rare 1,2,4-thiazole ring incorporated to the side chain. This compound was reported to have cytotoxic activity towards the L1210 cell line. Hogan and Sainsbury\textsuperscript{154} have reported a one pot synthesis of Dendrodoine \textit{86}.

\begin{center}
\includegraphics[width=0.3\textwidth]{86.png}
\end{center}

A cytotoxic compound citorellamine \textit{87} was isolated from the tunicate \textit{Polycitorella mariae}. This showed activity towards the L1210 cell lines (ED\textsubscript{50} 3.7 µg / mL) and was strongly antibacterial\textsuperscript{155}.
From sponge of the genus *Jaspis* from Fiji and Palau, Jaspamide (Jasplakinolide) 88 was isolated. This is the first bioactive marine natural peptoid to be isolated. Jaspamide was reported to have insecticidal activity against *Heliothis virescens* with an LC$_{50}$ of 4 ppm and showed *in vivo* topical activity against *Candida* infections in mice. It was cytotoxic against a larynx epithelial carcinoma cell line and a human embryonic lung cell line.

\[
\text{OH} \\
89 \quad \text{P-Q--} = \text{--C--CH--} \\
\text{ch}_2 \\
89a \quad \text{P-Q--} = \text{--C--CH--} \\
\text{ch}_2
\]
Along with Jaspamide 88, two new Jaspamide derivatives Jaspamide B 89 and Jaspamide C 89a were isolated from Jaspis splendans, a marine sponge collected from Vanuatu157. Compounds 89 and 89a were reported to have the in vitro growth inhibition against NSCLC-N8 human tumour cell lines.

A pyrroloiminoquinone alkaloid, wakayin 90, isolated from Fijian ascidian Clavelina sp.158 exhibited in vitro cytotoxicity against the human colon tumour cell line HCT-116 with an IC50 of 0.5 µg/mL. This compound also inhibited topoisomerase II at 250 µm. Its toxicity has been suggested to result from interference with or damage of DNA.

![Diagram of wakayin 90]

An unexpectedly potent antifungal agent 2,3-indolinedione also known as Isatin159 91 was found to be formed during the fermentation of the isolated bacterium Altermonas sp.

![Diagram of 2,3-indolinedione 91]

From the philippine, ascidian Polyandrocarpa sp., four new indole containing metabolites, polyandrocarpamides A 92, B 93, C 94, D 95 were isolated. These compounds contain derivatives of 4-hydroxyphenethylamine linked to an indole ring through α-dicarbonyl subunit160.
Hollenbeak and Schmitz isolated Aplysinospin 96, from the sponges *Aplysinopsis* sp and *Smenospongia echina* (reported as *Verongina spongellii*)\(^{161-163}\). Aplysinospin has also been isolated from other sponges of the family *Thorectidae*\(^{161}\) and also from *Dercitus* sp.\(^{164}\).

From the extract of British columbian barrowing sponge, *Cliona celata*\(^{165-166}\). Clionamide 97, was isolated. This compound was mildly antibiotic against *S. aureus*.
Celenamides\textsuperscript{167} obtained from the East Pacific sponge, \textit{Cliona celata} were closely related to integerrin, a peptide alkaloid from the Rhamnaceae plant \textit{Ceanothus integerrimia}\textsuperscript{168}. It was also reported that the Celenamides A 98, B 99, C 100 are similar to tunichromes, the blood pigments of Vanadium concentrating tunicates\textsuperscript{169}.

\begin{equation}
R_1 = \text{CH}_2\text{CH} (\text{CH}_3)_2, \ R_2 = \text{OH}
\end{equation}

\begin{equation}
R_1 = \text{CH}(\text{CH}_3)_2, \ R_2 = \text{OH}
\end{equation}

\begin{equation}
R_1 = \text{CH}_2\text{CH} (\text{CH}_3)_2, \ R_2 = \text{H}
\end{equation}

The solitary \textit{ascidian} \textit{Halocyanthia} roretzi\textsuperscript{170, 171} was the source of two novel linear tetrapeptides, Halocyamines A 101 and B 102. The compounds were isolated from the blood of the ascidian.
The halocyanamines showed antiviral activity against fish RNA viruses in RTG-2 cells and antimicrobial activity towards several gram positive bacteria and yeasts. These compounds are also cytotoxic to some cultured mammalian cells.