CHAPTER 1

GENERAL INTRODUCTION AND NATURE OF THE COMPOUNDS SYNTHESISED
Heterocyclic compounds are widely distributed in nature and are essential to life. They play a vital role in the metabolism of all living systems. These compounds have a cyclic structure with two or more different kinds of hetero atoms in the ring. As the number and variety of hetero atoms increases in the ring, there is a steady transition to the expanding domain of inorganic heterocyclic system. Since the variation in the size of heterocyclic ring and variations from a large number of commonly known hetero atoms, the large number of heterocyclic compounds are known and this number is increasing very rapidly. It ranges from the pyrimidine and purine bases of genetic material like DNA, the essential amino acid, vitamins and co-enzymes precursors, the photosynthesising pigment, the oxygen transporting pigments and the haemoglobin together with most of the sugars.

There are a vast number of pharmacologically active heterocyclic compounds, many of which are in regular clinical use. Some of these are natural products, for example: Antibiotics—penicillin and cephalosporin; Alkaloids—vinblastin, ellipticine, morphine and reserpine and cardiac glycoside—digitalis. However, the large majority are synthetic heterocycles which have found widespread use, for examples as anticancer agents, analeptics, analgesics, hypnotics and vasopressor modifiers and also as pesticides, insecticides, weed killers and rodenticides etc.
There are also a large number of synthetic heterocyclic compounds with other important practical applications such as dyestuffs, co-polymers, solvents, photographic sensitizers and developers, antioxidants and vulcanization accelerators in the rubber industry and many are valuable intermediates and recently used in confectionaries. Enormous research work is going on in various laboratories at national and international levels in the fields of pharmaceuticals, drugs, pesticides, herbicides, plastics and in many other purposes and still there is a large space for new ideas in this field.

The successful applications of the heterocyclic compounds and many others in more fundamental and theoretical studies, stems from their very complexity; this ensures a virtually limitless series of structurally novel compounds with a wide range of physical, chemical and biological properties, spanning a broad spectrum of reactivity and stability. Another consequence of their varied chemical reactivity including the possible distribution of the heterocyclic ring is their increasing use in the synthesis of specifically functionalised non-heterocyclic structure.

The wide spread occurrence of heterocyclic compounds in nature, their vital role in metabolism in the living cells and their economic value as dyes and pharmaceuticals are some of the factors which have directed the attention of organic chemists in this field. Almost 80% of the drugs in clinical use are depended on heterocyclic constitution.
Drugs are substances intended for use, diagnosis, cure mitigation or prevention of disease in man or in other animals. History of medicinal chemistry shows that more effective analogous are obtained by molecular manipulation, by disjunction or through quantitative structure action relationship studies or group substitution. Earlier almost all drugs are obtained from natural sources. The isolation, characterisation and studies of various physico-chemical parameters of the active compounds of various groups such as hormones, glycosides, alkaloids etc. have provided many important drugs. All natural drugs are not commonly obtained in all parts of world because of diverse climatic conditions. So, Scientists have to pay their attention towards synthetic alternatives.

The approach employed by the modern synthetic chemists in search of better drugs start with the Search of leads. The biological activities of natural products provide a useful lead for synthesis of newer drugs. It was observed that a cattle fed with improperly stored sweet clover hay suffered from profuse bleeding. The chemical investigation of improperly stored hay leads to the isolation of anticoagulant compound, bis-hydroxy coumarin. A comparative study of biochemical process involving bacteria, men and animals have also provided leads for the synthesis of newer drugs. Once a suitable leads has been discovered next step involves molecular manipulation. The potency, specificity and various factors affecting physiological activity of drugs may be governed by its physicochemical aspects as molecular shape and size, ionisation, charge distribution and solubility, lipid-water partition co-efficient,
geometry, distribution of charges and so drugs receptor sites. The molecular orbital calculation introduced recently may indicate which atom or group are the active sites. The isomeric molecules having approximately same size and shape, are not likely to exhibit similar biological actions. The isoelectric molecules having similar electron density, resonance energy and dipole moment are also likely to behave analogously. These properties are also important in the modification of the parent compounds.

Few biologically important compounds possessing characteristic heterocyclic moiety are described herein:

1. BENZODIAZEPINES

The benzodiazepines consist of a benzene ring fused to one or more heterocyclic moieties, and play four major pharmacologic effects:

(i) An antianxiety effect can be observed at first. The antianxiety effects also include calming, muscle relaxation, protection against electrically and chemically induced convulsions, and a decrease of fear in avoidance behaviour.

(ii) Sedation can be observed through potentiation of hypnotics and improvement in sleep.

(iii) A psychostimulant effect can be observed by improved performance of animals in behavioral test. This closely parallels the observed psychostimulant effect of
benzodiazepines in patients whose behaviour changes from an anxious depressed state to a more outgoing, socially active state.

(iv) The potent anticonvulsant properties of benzodiazepines in experiment animals have been confirmed in human being.

Quite a large number of benzodiazepines\textsuperscript{1-5} are now in clinical practice, for example chlorodiazepoxide, flurazepam, lorazepam, nitrazepam, oxazepam, estazolam, triazolam, quazepam and temazepam.

2. ANTIHISTAMINS

Histamine, an imidazole compound, widely distributed in plants and animal tissues, and is also present in the venom of bees and wasps. In the mammals, it is formed by decarboxylation of the amino acid, histidine. This reaction is catalysed by an enzyme, histidine decarboxylase. Histamine is also synthesised by the microflora in gastrointestinal tract from dietary histidine. However, most of the histamine that is absorbed from the gut is destroyed during passage through the liver. Histamine [4(5)-imidazolyethylamine, tissue amine], was first potent biogenic amine, was synthesised by Windaus and Vogt (1907) because of its chemical resemblance to the naturally occurring alkaloid, pilocarpine and to the amino acid, histidine. Histamine was found to be a constituent of many tissues and came to be regarded as a substance liberated in response to injured stimuli. Also it has been shown that histamine stimulates secretion of gastric fluids. Therefore, first antihistamine
drug arose out of the search for substance to counteract the toxic manifestation of histamine release\textsuperscript{6,7}. These drugs were introduced for clinical use in allergy to provide relief from allergic seasonal shinitis (i.e. hay fever) and acute urticaria but are less effective in the treatment of chronic perennial rhinitis. Antihistamines are of some value in controlling allergic dermatoses, serum sickness, blood transfusions, reactions of nonhaemolytic, nonpyrogenic type, and drug reactions attributable to an allergic phenomenon. Burimamide\textsuperscript{8,9} was shown to be first and highly specific antagonist of histamine. Molecular manipulations have led to two other important antihistamine drugs—metiamide and cimetidine.

3. PURINE AND URACILS

The purine ring system is undoubtedly among the most ubiquitous of all the heterocyclic compounds\textsuperscript{10,11}. This arises not only from the universal occurrence of adenine and guanine in DNA or RNA, but also from subsidiary uses of the ring system in many biochemical systems. In addition to the bases of nucleic acid, the methylated purines such as caffeine, and its modified structures both of synthetic and natural origin have been a rich source of a wide variety of biologically active compounds. The 6-mercaptopyrurine derivatives are found to be used in the treatment of leukaemia, especially for children. The 9-(β-arabinofuranosyl)-adenine which is a powerful antiviral and antitumour agent, is used clinically for these purpose.

The recent epidemic of acquired immunodeficiency syndrom
(AIDS) has prompted a broadly based effort to find out a mean of preventing and cures of AIDS. A number of agents from uracil nucleus have been found to inhibit the replication of human immunodeficiency virus (HIV) in vitro. One of the compound, 3-azido-2, 3-di-deoxythymidine (syn. azidothymidine or zidovudine) has been shown to induce clinical improvement and prolong survival in patients with fulminant AIDS. This was the first demonstration that an established infection with pathogenic human ritrovirus was amenable to antiviral therapy.

Acyclovir (ACV), a purine based acyclic nucleoside continues to be the only drug for treatment of genital herpes infection. Recent data suggests that oral ACV is safe and effective when taken continuously for upto a year. Buciclovir also exhibit antiherper simplex activity.

INDOLES

A large family of hallucinogens is known that contains the parent indole ring and carries various substitution on aromatic ring or on amine nitrogen for example : bofotenin, diethyltryptamine etc. The simplest compound and one known for the longest time is N,N-dimethyl tryptamine (DMT) which is a major component of various new world snuffes and psychotropic drug decoctions. It is of relatively low potency and in man is biologically active only by parenteral administration. The N,N-diethyl and N,N-di-isopropyl homologues of DMT are little more potent.

A large number of heterocyclic compounds are known today.
The description of all the heterocycles is not possible and is beyond the scope of this thesis. However, a brief description of the selected heterocycles—carbazole, pyrrole, indole and their related derivatives has given here as the author has been engaged mainly in the synthesis of new organic compounds belonging to these heterocycles.

A large number of carbazole derivatives have been synthesised and screened for their biological activities by many workers as given in the literature. Carbazole itself showed carcinogenic effect\textsuperscript{12,13} in the liver of mice. Some new amino acyl carbazole derivatives (1) have been synthesised and were found to show antibacterial activity\textsuperscript{14} against Bacillus subtilis.

\[ R_1 \text{carbazole}\]

(1)

\[ R = phtalayl; R_1 = H, NO_2; X = glycine, \beta\text{-alanine} \]

Carbazole-N-carboxylic acid exhibited local anaesthetics activity\textsuperscript{15} of urethane types. Cis-9-acetyl hexahydro-carbazole showed hypnotic effect\textsuperscript{16}. Various N-alkyl amino carbazoles have been synthesised. Among them 9-(dimethylaminopropyl)-2-methoxy-
carbazole (2) and 2-chloro-9-(dimethylaminopropyl)-7-methoxy-carbazole (3) were found to be anticonvulsant and diuretic activities\textsuperscript{17}.

\[
\begin{align*}
&\text{(2)} \\
&\text{(3)}
\end{align*}
\]

Various 1,2,3,4-tetrahydro-carbazole (4) were synthesised and tested for their in-vitro trypanocidal activity against\textsuperscript{18} Trypanosoma cruzi in human blood which showed good activity. The compound related to structure (4) i.e. 6-bromo-9-[2-(dimethylamino) ethyl]-1,2,3,4-tetrahydrocarbazole ; 9-(2-amino ethyl)-3-tert-butyl-1,2,3,4-tetrahydro-carbazole and 9-(p-acetamidobenzylidene amine)-carbazole displayed protozoacidal\textsuperscript{18}, antisecretor\textsuperscript{19}, tuberculo-ostatic actions\textsuperscript{20} respectively.

\[
\begin{align*}
&\text{(4)} \\
&R = H/F/Cl/Br/I/CH\textsubscript{3}/OCH\textsubscript{3} ; R_1 = H/F/Cl/Br/I/CH\textsubscript{3}/OCH\textsubscript{3}
\end{align*}
\]
9-ethyl carbazole (5) the firstazo dye\textsuperscript{21} containing the carbazole nucleus was reported. A large number of dyes and pigments incorporating the carbazolyl azo group have been prepared by the dyestuff industry. The incentive for the preparation of 9-ethyl carbazole dyes was the report on the use of boron containing compound in brain tumor therapy\textsuperscript{21}.

\begin{center}
\includegraphics[width=0.2\textwidth]{carbazole}
\end{center}

(5)

Methyl substituted 3,4-benzo-carbazoles are potential anticarcinogenic agent\textsuperscript{22}. 9-substituted-6-H-pyrido-carbazole derivatives (6) are useful as schistosomicides and antitumor agents\textsuperscript{23}.

\begin{center}
\includegraphics[width=0.3\textwidth]{carbazole2}
\end{center}

(6)

\text{R = H, alkoxy, OH, aryloxy; } R_1 = H, alkyl; R_2 = alkyl, aryl

Various substituted 2,3,4,9-tetrahydro-1-H-carbazole-1-acetic acid derivatives (7) and (8) were synthesised and are useful as lipo-oxygenase inhibitors for the treatment of pain and inflammation\textsuperscript{24}.  

\begin{center}
\includegraphics[width=0.3\textwidth]{carbazole3}
\end{center}

(7)

(8)
R = alkyl; $R_1 - R_3$, $R_8$, $R_9 = H$, alkyl
$R_2, R_3, R_8, R_9 = -HC = CH - CH = CH_2$
$R_4 - R_7 = H$, alkyl, halo, haloalkyl.

Cyclization reaction of hydrazine with carbazole-2,3-methyl dicarboxylates yielded 1,4-dioxo-1,2,3,4-tetrahydropyridazino-carbazoles. Chloro dehydroxylation afforded 1,4-dichloro-pyridazino-carbazoles and nucleophilic substitution gave 1,4-dialkoxy-pyridazino-carbazole. These compounds were found to possess cytotoxic activity.\(^\text{25}\)

Cis and trans 2-[(\(\gamma\)-(p-fluorobenzoyl) propyl]-octahydro-6H-pyrido-carbazole derivative were found to possess neuroleptic and anti-inflammatory activities.\(^\text{26}\) In general oxypropanolamino side chain in any aromatic structure imparts \(\beta\)-blocking activity to a compound and such compounds are known to have antihypertensive agents. Carbazolyl-4-oxypropanol amines were found to have vasodilating and hypertensive properties. By adopting the above ideas, a number of compounds of the derivatives carbazolyl-1-
oxypropanolamine derivatives have been synthesised and exhibited β-blocking activity and antihypertensive property\textsuperscript{27}.

A new synthetic compound, 2,3-dichloro-4-nitro-pyrrole (9) has been found to exhibit antibacterial activity against few selected organisms\textsuperscript{28}.

![Chemical Structure of Compound 9]

(9)

The pyrrole alkanonic acid (10) showed analgesic activity\textsuperscript{29} while benzopyrroles have been found to exhibit antipyretic\textsuperscript{30} and local anaesthetic actions\textsuperscript{31}.

![Chemical Structure of Compound 10]

(10) \( R=H, CH_3; \ R_1=C_6H_5, \text{substituted} \ C_6H_5, 2\text{-thienyl,} 1\text{-methyl-2-pyrrolyl}; n=0,1. \)

Various pyrrolyl ketones have been found to exhibit anti-inflammatory, analgesic and antipyretic properties\textsuperscript{32}. The general action of \( \alpha\)-pyrryl-isobutyl ketone in the frog consists of a progressive abolition of spontaneous and reflux movements. The same compound was also found to produce depression on the central nervous system in rats. The narcotic action of isovaleryl-pyrrole in the mouse appears more pronounced than isobutylketone\textsuperscript{33}. N-methyl-5-(p-toluoyl) pyrrole-2-acetic acid (11) has been exhibited analgesic
and anti-inflammatory activity\textsuperscript{35,36}. 2,3-diaryl-5-[2,2,2-trifluoro-1-(trifluoromethyl) ethyl] 1H-pyrrole derivatives (12) showed anti-inflammatory activity\textsuperscript{37}.

\[
\begin{align*}
\text{(11)} & & \text{(12)} \\
\text{H}_3\text{C} & \text{CO} & \text{CH}_2\text{COOH} & \text{R}_1 & \text{R}_2 & \text{CF}_3 \\
& & \text{CH}_3 & \text{R} & \text{H} & \\
& & & \text{CF}_3 & & \\
\end{align*}
\]

\( \text{R} = \text{R}_1 = \text{3-pyridyl, C}_6\text{H}_5, \text{substituted C}_6\text{H}_5 \)

\( \text{R}_2 = \text{H, alkyl} \).

Pyrrole-2-acetic acid (13) has been synthesised and found to exhibit effective analgesic activity\textsuperscript{38} than aspirin and acetaminophen. 5-(p-chlorobenzoyl)-1,4-dimethyl-pyrrole-2-acetic acid (14) was found to show analgesic and anti-inflammatory agents\textsuperscript{39}.

\[
\begin{align*}
\text{(13)} & & \text{(14)} \\
& \text{CH}_2\text{COOH} & \text{Cl} & \text{CO} & \text{CH}_3 & \text{CH}_2\text{COOH} & \text{CH}_3 \\
& & & & & & \\
\end{align*}
\]

Pyrrolnitrin, an antifungal compound\textsuperscript{40} showed very similar biological activities to those of imidazole antimycotics on isolated mitochondria. The swelling induced by pyrrolnitrin was characterised by biphasic swelling process, a very fast initial swelling and thereafter a very slow speed secondary swelling. The increase of
pyrrolnitrin concentration exponentially enhanced the latent ATPase activity of mitochondria at the similar range of concentration to those needed for the induction of the swelling. 2-methyl-4-(2-nitro-3-chlorophenyl) pyrrole was also as effective as pyrrolnitrin. On the other hand, 3-chloro-4-(3-halophenyl)pyrrole derivatives (15) showed stronger antimicrobial activity. 1-H-pyrrrole-2-acetic or propionic acid have analgesic and anti-inflammatory effects.

\[
\begin{align*}
R & = \text{Cl, Br, CF}_3 \\
\text{Cl} & \\
\text{R} & = \text{Cl, Br, CF}_3 \\
\text{H} & \\
\text{N} & \\
(15) & 
\end{align*}
\]

Pyrrole-2,5-dihydro-1-nitroso (N-nitrosamine) exhibited mutagenic and carcinogenic properties against Salmonella typhimurium and Escherichia coli. 2,3-bis (4-methoxyphenyl) pyrroles (16) have been synthesised and found to show anti-inflammatory activity.

\[
\begin{align*}
\text{H}_3\text{CO} & \\
\text{R} & = \text{H, F} \\
\text{H}_3\text{CO} & \\
\text{S} & \\
(16) & 
\end{align*}
\]
Phenyl pyrrole derivatives have fungicidal activity\textsuperscript{45} while benzoyl pyrrole derivatives have anti-inflammatory, analgesic\textsuperscript{46} and local anaesthetic activities\textsuperscript{47}. Iodine containing pyrrole derivatives showed cardio-inhibitor on the muscular fibers\textsuperscript{48} but the iron containing pyrrole derivative exhibited to plant growth activity\textsuperscript{49}. Pure pyrrole have the property to increase pigmentation of the hair and skin\textsuperscript{50} around the site of injection especially when exposed to direct light in albino rabbits, mice and in man.

1,2,5-trisubstituted pyrrole derivatives have been synthesised which showed antispasmodic activity\textsuperscript{51}. 2-amino methyl pyrrole (17) showed antimalarial activity\textsuperscript{52-54} while 2-(2-aminoethyl) pyrrole (18) exhibited antihistaminic properties\textsuperscript{53-55}.

\[
\text{H} \quad \text{CH}_2\text{-NH}_2 \\
\text{(17)} \\
\text{H} \quad \text{CH}_2\text{-CH}_2\text{-NH}_2 \\
\text{(18)}
\]

1-phenyl-2,5-dimethyl and 1,2-diphenyl-5-methyl (19) pyrroles showed promising antispasmodic and sedative\textsuperscript{56} actions.

\[
\text{H}_3\text{C} \quad \text{N} \quad \text{R} \\
\text{C}_6\text{H}_5 \\
\text{(19)}
\]

\(\text{R}=\text{CH}_3, \text{C}_6\text{H}_5\)
Acyl and carboxaldehyde pyrroles were prepared and showed potential anticancer activity\textsuperscript{57}. Ester derivatives of substituted 3-pyrrolidinols have been exhibited anticholinergic activity\textsuperscript{58}.

The synthetic compound, 1-[2-(3-dimethyl-aminopropoxy)-ethyl] -2-methyl-5-phenyl pyrrole exhibited antihistamine effect in vitro in the guinea pig without having any cardiovascular or central nervous system effects\textsuperscript{59}. Few new pyrroolidyl alkanal esters have been prepared and tested as local anaesthetics\textsuperscript{60} which have been shown to be almost identical with that of cocaine by the intracutaneous route, though it has no action on the cornea.

1-(3'-pentadecylaryloxy acetamido) 2,5-dimethyl pyrrole derivatives (20) showed anti-inflammatory, hypotensive and motor activities\textsuperscript{61}.

\[
\begin{align*}
R &= R_2 = R_3 = H, \text{ Cl; } R_1 = C_{15}H_{31} \\
3\text{-cyano-4-phenyl pyrrole (21) has been synthesised and exhibited pesticidal activity}\textsuperscript{62,63}.
\end{align*}
\]

\[
\begin{align*}
(20) \\
(21)
\end{align*}
\]
A series of N-substituted 3,4-di-phenyl-1H pyrrole-2,5-diones (diphenylmaleimides) were synthesised and tested for their cytostatic activity. The introduction of a nitro group in the benzene ring decreased the cytostatic activity\textsuperscript{64}.

The importance of indole nucleus is well established in the pharmaceutical chemistry for example antipyretic, anticonvulsant, analgesic, antidepressant activities etc. The substitution of an oxygen atom of position-4 of the indole ring leads to compound of increased potency which are all orally active. The simplest of these is 4-hydroxy-N,N-dimethyl tryptamine (psilocin) which is naturally occurring hallucinogenic component alongwith its phosphate ester, psilocybin of the many magic mushrooms of western hemisphere.

The other indoles based heterocyclic drugs also include reserpine and related compounds which are largely responsible for the neuroleptic and hypotensive properties. The mitomycins which contain an indole ring are now becoming important drugs for cancer treatment.

N-propylamino-2,5-dimethyl-3-phenylindole (22) has been synthesised and was found to hypotensive, anthelmintic, antibacterial and antiparkinsonian activities\textsuperscript{65}. The substitution at 3-position in indole nucleus markedly affects hypotensive activity.
The some indole derivatives have been synthesised and found to exhibit anti-inflammatory, analgesic, antihistaminic and coronary vasodilatory properties. 3,3-dialkyl and 3,3-alkylene-indoline derivatives have been showed the analgesic activity. 1-benzoyl-2-methylindole-3-acetic acid (23) and β-(3-indolylmethyl) butyric acid lactone (24) derivatives have been synthesised and found to useful as anti-inflammatory, antipyretic, analgesic and cardiovascular agents respectively.

The amoebicidal and cysticidal activity of the compounds having aminoacid ester linked to the carboxylic group of substituted indole 3-acetic acid via amidic linkage have been observed. The various substituted p-aminobenzoate and salicylates linked to the
The carbonyl group of indole-3-acetic acid and propionic acid were synthesised and found to exhibit amoebicidal activity against Enatamoeda histolytica. 3-indole fatty acid (25) produced anti-inflammatory, analgesic and antipyretic activities.

In general, compounds with 1H-indole-3-acetic acid (26) possess plant harmones, ant gonadotropic, anti-ar thritic, anticomplementatory, antimicrobial, anti-inflammatory, antihypertensive, antithrombiotic and diuretic activities. 5-methoxy-3-aryl-azoindoles (27) have been synthesised and found to have antituberculosis activity. 3-[2-(3-alkyl and alkenyl-4-piperidyl) ethyl] indoles (28) have been prepared and found to exhibit antidepressant activity.

R=H, NO₂
R₁=Cl, Br, iodo, H

(27)
The pseudoindoles (29) have been synthesised and exhibited analgesic, sedative, muscle relaxant and neuroleptic properties\(^84\). 3-indoly methyl guanidine and N-acyl indole were prepared and screened for their hypotensive\(^85\), anti-inflammatory and analgesic\(^86\) activities respectively which showed positive effects.

3-[2-(4-tetra and hexahydropyridyl)-ethyl] indoles (30) and (31) were prepared which showed antidepressant activity\(^87\).

\[ R = H, \text{halo}; \ R_1 = H, \text{CH}_3, \text{C}_2\text{H}_5 \]
The various synthetic compounds derived from 3-(p-fluro) benzoyl hydrazono-5-substituted-2-indolinones have been found to exhibit antibacterial and CNS depressant activities.\textsuperscript{88}

3-indole acetic acid and its propionic acids derivatives have been found to be effective as plant growth and homolytic activities.\textsuperscript{90-92}

3-indole carboxy-aldehyde-thio-semicolonbazones have been synthesised and found to exhibit antituberculous and sensitivity activity\textsuperscript{93,94} in vitro and in vivo against tubercle bacilli. 5-methoxy (32) and 5,6,7-trimethoxy indoles (33) were prepared and showed psychotomimetic drug activity.\textsuperscript{95}

\[
\begin{align*}
\text{(32)} & \quad \begin{array}{c}
\text{H}_3\text{CO} \\
\text{N} \\
\text{H}
\end{array} \\
\text{(33)} & \quad \begin{array}{c}
\text{H}_3\text{CO} \\
\text{N} \\
\text{OCH}_3 \\
\text{H}
\end{array}
\end{align*}
\]

Indomethacin (34) and indomethacin phenyl ester (35) derivatives were found to exhibit antiulcer, analgesic, antipyretic and anti-inflammatory activities.\textsuperscript{96,97}

\[
\begin{align*}
\text{(34)} & \quad \begin{array}{c}
\text{H}_3\text{CO} \\
\text{N} \\
\text{CH}_2\text{-COOH} \\
\text{CH}_3
\end{array} & & \begin{array}{c}
\text{Cl} \\
\text{H}_3\text{CO} \\
\text{N} \\
\text{CH}_2\text{-COO} \\
\text{COOCH}_3
\end{array} \\
\text{(35)} & \quad \begin{array}{c}
\text{Cl} \\
\text{N} \\
\text{CH}_3 \\
\text{CO}
\end{array} & & \begin{array}{c}
\text{Cl} \\
\text{N} \\
\text{CH}_3 \\
\text{CO}
\end{array}
\end{align*}
\]
Two synthetic indole alkylating agents, 5-bis(2-chloroethyl) amino-indole-3-acetic acid and 5-bis(2-chloroethyl) amino-indole-3-propionic acid have been exhibited anticancer activity. Iprindole-amphetamine has been found to show psychomotor stimulation activity.

1-substituted-2-oxo-3-chloro/3-(2-chlorophenoxy)-4-(2-arylindole-3-yl)-azetidines (36) have been synthesised and were found to be CNS active and anti-inflammatory agents.

![Chemical Structure](image)

\(X = 4\text{-morpholinophenyl or } 4\text{-N,N-diphenylbenzamido}
\)

\(R = H, CH_3, Cl, OCH_3\)

The studies on dl-4(2-hydroxy-3-isoproyl amino-propoxy)-indole (37) exhibited beta-adrenergic blocking effect, antiarrhythmic and local anaesthetic properties.

![Chemical Structure](image)
Various 1-acyl-3-indole alkanoic acid derivatives have been synthesised. Among them, the compound (38) showed anti-inflammatory and antipyretic activities\textsuperscript{102}.

![Chemical structure of (38)](image)

Several halogenated 3-phenyl azoindoles were prepared by reacting indole with diazotized haloanilines and were tested for tuberculostatic activity\textsuperscript{103}. Di- and tri-halogen substituted phenyl azoindoles were less active than the monosubstituted derivatives but were generally more active than 3-phenyl azoindole.

3-aminoethyl indole was less spasmogenic on smooth muscles than tryptamine but increasing the number of side chain especially methylene group of tryptamine decreased the spasmogenic effect and increased the antiserotonin activity\textsuperscript{104}. The same occurred when methyl groups were substituted for amino group hydrogen atoms. N,N-dimethyl-γ-(3-indoly)propylamine showed a strong hyperthermic action on rabbit but further lengthening the side chain weakened the hyperthermic action\textsuperscript{104}.

3-[2-(methyl prooxy) pyrrolidinopropyl phenyl] indoline (39) was found to be cardiovascular agent\textsuperscript{105}.
4-(2-hydroxy-3-isopropyl-amino-propoxy) indole has been synthesised which showed \( \beta \)-adrenoceptor blocking activity\(^{106}\).

Some 1-(3-aminopropyl) indole, wherein the basic side chain is located on the indole nitrogen instead of the conventional 3-position of the indole nucleus, were found to be highly active antiserotonin and antihistaminic agents\(^{107}\). Several tetrahydro-\( \gamma \)-carbalines, tetrahydropyrimido indoles, and the piperizinino indoles were also found to exhibit anti-serotonin, antihistamine, CNS depressent and muscle relaxant activities. Various 1-(2-amino ethyl)-indole-2-carboxylates and 1,2,3,4-tetrahydro pyrazino indole were synthesised and found to be antiserotonin and antihistaminic activities. 1-alkyl-4-chloro-2(2,6-dichloro-4-hydroxy phenyl)-6-hydroxy indoles \(^{40}\) showed uterotrophic activity and cytostatic\(^{108}\) effects against hormone independent cells, a dual molecule of action has to be considered for the tumor inhibition.
A large number of diazepino indolo derivatives have been synthesised which acquire a unique place in neuropharmacology\textsuperscript{109,110} antihypertensive, antidepressant and sedative properties\textsuperscript{111}. \checkmark