CHAPTER 2

Section 2.1: Literature survey and biological importance of 1,2,3-benzotriazole and related compounds.

Section 2.2: Literature survey and biological importance of 1H-indole and related compounds.

Section 2.3: Literature survey and biological importance of azetidinones and their derivatives.

Section 2.4: Aim and work plan of the research.
SECTION 2.1: LITERATURE SURVEY AND BIOLOGICAL IMPORTANCE OF 1,2,3-BENZOTRIAZOLE AND RELATED COMPOUNDS

The name triazole was given to a carbon-nitrogen ring system by Baldin in 1885. Pechmann discovered the first 1,2,3-triazole in 1888. 1,2,3-Benzotriazole is also named as azimidobenzene and benzisotriazole in the early literature. It exists in two forms 1-H form and 2-H form but 1-H form is dominant over another form.

1,2,3-Benzotriazole 1-H form of 1,2,3-Benzotriazole 2-H form of 1,2,3-Benzotriazole

1,2,3-Benzotriazole has been found numerous applications in organic synthesis in medicines and in the industry as biologically active systems, as dyestuffs and fluorescent compounds, as corrosion inhibitors, photostabilizers and as agrochemicals. Benzotriazole derivatives possess potent biological activity such as anthelmintic, anticonvulsant, antifungal, analgesic, antithyroid and CNS stimulant. 1-chloro, 1-bromo-and (less) 1-iodo-benzotriazole have proved to be powerful oxidants.
One of the most widely used 1,2,3-benzotriazole derivatives is the 1-hydroxy compound (76) which has proved to be a very valuable mediator substance for activating carboxyl groups for peptide synthesis\textsuperscript{97-98}. Furthermore, benzotriazolyl-N-hydroxytris (dimethylamino) phosphonium hexafluorophosphate (77) has been used for coupling reaction in peptide synthesis\textsuperscript{99-101}.

![Chemical Structures](image)

(76) \hspace{2cm} (77)

Some 1,2,3-benzotriazole derivatives have been reported to significant biological activity such as 4-alkyl-1,2,3-benzotriazoles shows the inhibition against some microorganisms. Furthermore, some benzotriazole analogues of histamine exhibit antihistaminic\textsuperscript{102} and antiacetylcholine\textsuperscript{103-105} activities, while the 1,2,3-triazole ring is antagonistic to the imidazole ring in triazole analogues of adenine and guanine. Ethanolamino derivatives of 1,2,3-benzotriazole show mydriatic action\textsuperscript{106-109}.

In a more recent work sulphonyl hydrazides and their derivatives (78) of 1,2,3-benzotriazole have been reported to inhibit the
growth of *Staphylococcus aureus*, *Escherichia coli* and *Salmonella typhi*\textsuperscript{110,111} 1,2,3-Benzotriazole-1,8-naphthyridine\textsuperscript{112,113} derivatives (79 and 80) have been synthesized and showed analgesic\textsuperscript{114}, sedative\textsuperscript{115} and fungicidal\textsuperscript{116-119} activities. Both 5- and 6-chloro-1-arylbenzotriazoles (81) and (82) revealed antiinflammatory\textsuperscript{120} activities.

![Chemical structure](image)

where $R = \text{CONHN}=\text{CH}_2$, $R^1=\text{H}$

$R = \text{CO}_2\text{H}$, $R^1=\text{SO}_2\text{NHN}=\text{CH}_2$

(78)

![Chemical structure](image)

where $R=\text{Ph/CO}_2\text{Et/AC/CH}_2\text{Ph/CONHPh}$

$R_1=\text{NH}_2/\text{Me/Ph/CH}_2\text{CO}_2\text{Et}$

(79)
Several benzo-substituted 1,2,3-benzotriazole (83) are cytostatically active against sarcomas and erythroleukomyelosis\textsuperscript{121,122}.

where $R=\text{H/NH}_2/\text{NHAc/CHNH}_2\text{CO}_2\text{H}$
5-Arylidene-2-aryl-3-benzotriazoloacetamidy1)-1,3-thiazolidin-4-ones (84) have been synthesized and found to exhibit anticonvulsant, analgesic and antimicrobial activities\textsuperscript{123}. 1,2-Dichloro-1,2-di benzotrizoly1-ethane (85) behave as an antifungal agent\textsuperscript{124}. 1-(p-Toluenesulphonyl)-benzotriazole (86) acts as CNS stimulant\textsuperscript{125}.

where \( R = R^2 = H; R^1 = R^3 = \text{Sub.aryl} \)

(84)
Numerous patents have appeared in the last few years which deal with 1,2,3-benzotriazole and other triazoles as part of optical brightening molecules. These consists in most case of stilbene moieties with suitable heterocyclic chromophores attached, and as a consequence hundreds of brighteners are available today on the world market. Special applications are whitening of fibres for example, poly(ethyleneterephthalate), cellulose acetate and poly-(acrylonitrile). Benzotriazole derivatives (87) and (88) are used in whitening of fibres, cellulose acetate and plastics\textsuperscript{127-128}.

\begin{center}
\includegraphics[width=0.8\textwidth]{image}
\end{center}

\textbf{(87)}

\begin{center}
\includegraphics[width=0.8\textwidth]{image2}
\end{center}

where \( R = R^1 = \text{Ph} / \text{Me} / \text{Et} \)

\textbf{(88)}

1,2,3-Benzotriazole and its derivatives have proved to be a powerful corrosion inhibitors for many metal alloys\textsuperscript{128-131} including copper, solder, brass, steel, cast iron and aluminium for example heat exchangers,
heating systems or automatic radiators. Associated with the above properties of corrosion inhibition, triazoles and 1,2,3-benzotriazoles to form complexes with the different metals. 1,2,3-Benzotriazole and its 5-bromoderivatives can be used in quantitative determination of silver ion in the presence of copper, nickel, bismuth, thallium, lead, cadmium, zinc, iron, cobalt and chloride ions.

The synthesis and properties of chelate resins containing 1,2,3-benzotriazole-5,6-dicarboxylic acid as an anchor group have been described\textsuperscript{132,133}. The 2-vinyltriazole (89) was copolymerized with divinylbenzene to yield cross-linked product and then saponified to give CO\textsubscript{2}H containing resins\textsuperscript{134}.

![Chemical Structure](image)

\begin{equation}
(89)
\end{equation}

1,2,3-Benzotriazoles have been successfully applied as photostabilizers for fiber, plastic or dyestuffs and for the protection of human skin from harmful UV irradiation\textsuperscript{135,136}.

The wavelengths of available sunlight which affect the chemical bonds usually found in polymer backbones are in the region of
300-400 nm. 1,2,3-Benzotriazole for example (90) is widely used absorber. Several 2-phenylated 2H-1, 2, 3-benzotriazole (91) has been reported as light stabilizer for organic material especially polymer$^{137-141}$.

(90)

(91)

1,2,3-Benzotriazoles have been found application as herbicides, fungicides and antibacterial agents in the area of agrochemicals. 1-Ethoxy-4-nitrobenzotriazole (92) and 1-methoxy-4-nitrobenzotriazole$^{142}$ (93) have been found to display strong herbicidal activity$^{143}$.
Ethyl-2-(5-phenoxy-N¹-benzotriazolyl)-propionate (94) has also exhibited herbicidal activity whereas benzotriazolyl alkanoic acids (95) are reported as plant growth promotic agents\textsuperscript{144}.

1,2,3-Benzotrizole is most useful synthetic auxiliary because it confers at least five different types of reactivity to groups to which it is attached. These different types are summarized in Scheme (A) in the following ways.
(i) 1,2,3-Benzotriazole is a good leaving group\textsuperscript{145-148}, generating a cation which can react further with for example, a Grignard reagent;

(ii) 1,2,3-Benzotriazole activates an attached $\alpha$-CH group to loss by stabilizing the resultant anion\textsuperscript{149,150}, allowing the introduction of an electrophile;

(iii) When a 1,2,3-benzotriazole residue and another leaving group are attached to some carbon, 1,2,3-benzotriazole can donate electrons to stabilize the cation formed\textsuperscript{151-153} by loss of the other leaving group.

Furthermore, the bond between 1,2,3-benzotriazole and a carbon atom can be cleaved by

(iv) Single electron transfer generating a carbon-centered radical\textsuperscript{154-156} and

(v) By the transfer of two electrons from lithium metal to generate a carbanion\textsuperscript{157,158}.

**SCHEME – A**

1,2,3-Benzotriazole as a leaving group

![Diagram of 1,2,3-Benzotriazole as a leaving group](attachment:image.png)
1,2,3-Benzotriazole as a Proton Activator

\[ \text{BuLi} \rightarrow \text{for example} \]

1,2,3-Benzotriazole as a Cation Stabilizer

\[ \text{for example} \]

1,2,3-Benzotriazole as a Radical Precursor

\[ +{e^{-}} \rightarrow \text{trapped} \]
1,2,3-Benzotriazole as a Anion Precusor

\[
\begin{align*}
\text{RCH}_2^- & \xrightarrow{\text{e.g.}} \text{RCH}_2R^1R^2 \\
\text{R} & = \text{Alkyl}, \quad R_1 = R_2 = \text{CO}_2\text{Et}, X=\text{Me}, \text{Ph}, \text{CO}_2\text{Et}
\end{align*}
\]

The uses of 1,2,3-benzotriazole in the formation of small heterocyclic ring and then go on to consider the construction of five membered, six membered, and larger heterocyclic rings.

(i) The construction of small heterocyclic rings\textsuperscript{159-165}:

Treatment of 1-(triphenylphosphoranylidene anminomethyl)-1,2,3-benzotriazole with Grignard reagent displaces the 1,2,3-benzotriazolyl moiety to give an imino phosphorane intermediate. Further creation with epoxides forms aziridines\textsuperscript{91-94} as shown in the Scheme B.

\[\text{SCHEME – B}\]

\[
\begin{align*}
\text{CH}_2\text{N} = \text{PPh}_3 & \xrightarrow{\text{RmgX}} \text{CH}_2\text{N} \xrightarrow{\text{RPh}_3} \text{CH}_2\text{N} \xrightarrow{\text{R}^1} \text{CH}_2\text{N} \\
\text{where} & \quad R = \text{Me}, \quad R^1 = \text{Ph}
\end{align*}
\]
(ii) The construction of five membered heterocyclic rings\textsuperscript{166-175}:

Pyrrolidines have been prepared by 1,3-cyclo-additions as shown in the Scheme C. Thermally induced desilylation of 1,2,3-benzotriazolylmethyl aminosilanes easily prepared from 1,2,3-benzotriazole an aldehyde, and an (aminomethyl) silane provides a novel route to azomethine ylide equivalents. In the presence of dipolarophiles, the azomethine ylide undergoes stereospecific 1,3-dipolar cycloadditions to give substituted pyrrolidines.

\textbf{SCHEME – C}

where \[ R = \text{Alkyl}, \ Y=\text{CO}_2\text{Et}, \ X = \text{Me Ph CO}_2\text{Et etc.}\]
(iii) *The construction of six-membered heterocyclic rings*\(^{176-182}\): A simple yet versatile method for preparation of 1-substituted and 1,2,6-trisubstituted-piperadines is given in Scheme D.

**SCHEME-D**

![Chemical Structure](image)

where \( R = \text{Me} / \text{Ph} / \text{CO}_2\text{Et} \)
SECTION 2.2: LITERATURE SURVEY AND BIOLOGICAL IMPORTANCE OF 1H-INFOLE AND RELATED COMPOUNDS

Indole was first prepared by Baeyer in 1986 by zinc dust distillation of oxindole. It finds an important place in Chemistry because of its relationship to the naturally occurring dye, indigo. The chemical degradation of this dye yields indoxyl, oxindole and finally indole. Indole is found in coal tar and is essential oils (Jesamine oil and Orange oil) of many plants. It also occurs in amino acid (tryptophan), as a plant growth hormone (indole 3-acetic acid), in alkaloids\(^{183}\) (brucine, psilecene) and dyestuff (indigo). The indole ring comprises of a benzene ring fused to 2- and 3-positions of a pyrrole nucleus.

The IUPAC name of indole is 1H-benzo \([b]\) pyrrole, it is being the b-face benzo fused isomer. The atoms are numbered as shown commencing from the nitrogen atom and going counter clockwise around the two condensed rings.
The bridgehead carbons are assigned position 3a and 7a. Positions-2 and-3 are also sometimes designated as α and β respectively. Many substituted indoles have acquired trivial names such as skatole, gramine, trptophan etc.

The tautomeric forms of indole are known as indolenines; 3H-indolenine and 2H-indolenine. Tautomerism in indole is similar to that in pyrrole where the two tautomers are called pyrrolenines. Structure (A) is anticipated to be stable but structure (B) corresponds to a quinonoid which would obviously be much less stable. However, the loss of aromatic resonance energy of indole to indolenine is much less than that for pyrrole to pyrrolenine. Most indoles exist predominantly in the indole form.

1-Benzoyl-2-methylindole-3-acetic acid (96) and β-(3-indolymethyl)-butyri acid lactone (97) derivatives have been synthesized and found to be useful as antiinflammatory, antipyretic, analgesic and cardiovascular agents respectively\textsuperscript{184}.
Tryptophan derived substances in the plant kingdom include indole-3-yI-acetic acid (98) a plant growth-regulating hormone, and structural variety of secondary metabolites the indole alkaloids\textsuperscript{185}.

Vincristine (99) a dimeric indole alkaloid is still extremely important in the treatment of leukaemia\textsuperscript{186}.
Brassinin (100) isolated from turnips is a phytoalexin—one of a group of compounds produced by plants as a defence mechanism against attack by microorganisms\textsuperscript{187}.

The physiological activity of lysergic acid diethylamide is notorious (101). The synthetic indole-3-yl-acetic acid derivatives indomethacin (102) is used for the treatment of rheumatoid arthritis\textsuperscript{188}. 
In animal, serotonin (5-hydroxytryptamine) (103) is a very important neurotransmitter in the central nervous system\textsuperscript{189,190} and also in the cardiovascular\textsuperscript{191} and gastrointestinal systems. The structurally similar hormone melatonin (104) is thought to control the diurnal rhythm of physiological functions.

3-Indole fatty acid (105) produced anti-inflammatory, analgesic and antipyretic activities\textsuperscript{192}. 
5-methoxy-3-aryl-azinonoles (106) have been synthesised and found to have antituberculosis activity$^{193}$. 

where $R=H/NO_2$, $R^1=Cl/Br/I/H$

(106)

Recently 1-p-nitrobenzoyl-3-(3-substituted-2-hydroxypropyloximino)-indole-2,3-diones (107) possess CNS activity$^{194}$. 

(107)
2, (3)-carboxy-(alkyl)-indole (108) derivatives were reported to be potent thromboxane synthase$^{195}$, phospholipase-A$_2$$^{196}$, cyclooxygenase-2, steroid-5$\alpha$ reductase inhibitors and glycine/NMDA antagonists$^{197}$. 

(107)
3-(substituted indole-2-(carboxamido)-2-phenylimino-4-thiazolidinones\(^{198}\) (109) possess antitubercular\(^{199}\), anaesthetic\(^{200}\), antifungal and hypnotic\(^{201}\) activities.

\[
\begin{align*}
\text{R} &= \text{Ph} / \text{Me} \\
\text{R}^1 &= 5-\text{Ome} / 5-\text{Cl} / 5-\text{OH} \\
\end{align*}
\]

\[\text{(109)}\]

Antimicrobial activity was displayed by 4-thiazolidinonylindoles\(^{202}\) (110).

\[
\begin{align*}
\text{where ,} & \quad \text{R} = \text{Me/Ph} ; \\
\text{Ar} &= \text{C}_6\text{H}_5 - \text{C}_6\text{H}_4\text{Cl} - \text{C}_6\text{H}_4\text{NO}_2
\end{align*}
\]

\[\text{(110)}\]
Molindone-(3-ethyl-1,5,6,7-tetrahydro-2 methyl-5-(4-morpholonyl methyl)-4H-indole-4-one) (111) has extensively been used as sedative and tranquillizer\textsuperscript{203-206}.

\begin{center}
\includegraphics{molindone.png}
\end{center}

(111)

3-[2-(3-Alkyl and alkenyl-4-piperidyl)-ethyl]-indoles (112) have been prepared and found to exhibit antidepressent activity\textsuperscript{207}.

\begin{center}
\includegraphics{3-alkyl_and_alkenyl.png}
\end{center}

(112)

where $R = \text{Et}$

$R' = \text{Me/Et}$

The pseudoindoles (113) have been synthesized and exhibited analgesic, sedative, muscle relaxent and neuroleptic properties\textsuperscript{208}.
1-Alkyl-4-chloro-2-(2,6-dichloro-4-hydroxyphenyl)-6-hydroxy indoles (114) showed uterotropic and cytostatic\textsuperscript{209} effect against hormone independent cells. A dual molecules of action has to be considered for tumour inhibition.

3-Amino-5H-pyrimido-[5,4-b]-indole-4-one (115) has been synthesised and reported as the inhibitor of the platelet aggregation induced by arachidonic acid\textsuperscript{210}.
3-(2'-Carboxy-5'-methoxyindolyl)-4-substituted phenyl)-aminoethyl-5-substitutedphenyl)-2-isoxazolines (116) and 3-(2'-5'-methoxyindolyl)-5-substitutedphenyl)-2-isooazolines (117) have been reported to possess potent antiinflammatory and ulcerogenic activities.
2-Arylamino-1,3,4-thiadiazino [6,5-b] indoles (118) and 2 aryl-1,3,4-oxadiazolo-[2,3-c]-1,2,4-triazino-[5,6-b]-indoles (119) showed fungicidal activity\textsuperscript{212}.

\begin{equation}
\text{where } R = \text{H/Cl/Br/F/OMe}
\end{equation}

(118)

\begin{equation}
\text{where } R = \text{H/Cl/Br/F/NO}_2/\text{OMe}
\end{equation}

(119)

5-Methoxy (120) and 5,6,7-trimethoxy indoles (121) were prepared and showed psychotomimetic drug activity\textsuperscript{213}.

(120)  (121)
3-[2-(Methyl propyloxy)-pyrrolidinopropylphenyl]-indoline (122) was found to be cardiovascular agent\(^{214}\).

![Structure of 3-[2-(Methyl propyloxy)-pyrrolidinopropylphenyl]-indoline (122)](image)

Poly (1-benzyl-5-vinylindole) (123) prepared from monomer via either radical or anionic polymerization, has been used to prepare polymeric analogues of a variety of biologically active indole derivatives\(^{215}\).

![Structure of Poly (1-benzyl-5-vinylindole) (123)](image)
Indomethacin (124) and indomethacin phenyl ester (125) derivatives were found to exhibit antiulcer, analgesic, antipyretic and antiinflammatory activities\textsuperscript{216}.

![Chemical structures](124) ![Chemical structures](125)

Various 1-acyl-3-indole alkanoic derivatives have been synthesized. Among them, the compound (126) showed fungicidal activity\textsuperscript{217}.

![Chemical structure](126)
A large number of indole alkaloids have been divided into five categories\textsuperscript{218-222} namely:

(a) The simple alkaloids;
(b) The ergot alkaloids;
(c) The yohimbine alkaloids;
(d) The harmala alkaloids and
(e) The strychnos alkaloids.

The first type of alkaloids is closely related structurally to tryptophan. Some examples are gramine (127), produced in sprouting barely, bufotenine (128) occurs in fungi (mushrooms) and has been shown to be the active principle of narcotic snuff.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{images/alkaloids.png}
\caption{(127) and (128)}
\end{figure}

The most important number of yohimbine class of alkaloids is reserpine (129). This alkaloids is used considerably in the treatment of hypertension and is a good tranquillizer.
The harmala alkaloids include harman (130) and harmine (131) and exhibited antihypertension activity.

Among the strychnos alkaloids, the most popular examples are strychnine (132) and brucine (133) which showed antiinflammatory activity.

Where

\[ (132) \: R = H \]
\[ (133) \: R = OMe \]
A new alkaloid of potential pharmacological activity is sorelline (134).
SECTION 2.3: LITERATURE SURVEY AND BIOLOGICAL IMPORTANCE OF AZETIDINONES AND THEIR DERIVATIVES

The carbonyl derivative of azetidine is designated as 2-azetidinone or more commonly known as β-lactam. This ring system has been known since 1907 but the investigation of their chemistry laid dormant till 1943. In that year it was found that the important penicillin and cephalosporin series of the antibiotics contain the β-lactam ring. Since then these compounds have been studied extensively and a variety of synthetic methods have been developed for their preparation.

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{2} \\
\text{3} \\
\text{H} \\
\end{array}
\]

A large number of antibiotics contain azetidinone moiety\textsuperscript{223,224}. The reactivity of azetidinones influences largely on substitution\textsuperscript{225,226}. 2-Azetidinones and their derivatives possess variety of therapeutic activities\textsuperscript{227,228}.

\[\text{N}^{10}\text{-Arylidenehydrazidophenothiazine}\] and thiazolinones and 2-azetidinones (135) have been synthesized and exhibited antibacterial and antifungal activities\textsuperscript{229}.
where \( R = \text{Alkyl / aryl} \)
\( X = \text{Cl/Br/NO}_2 \)

(135)

1-[2-Alkyl-4(3H)-oxoguainazoliny]-4-aryl-3-chloro-2-azetidinones have been synthesized and found to be antiparkansonian activity against hypokinesia and catatonia\(^{230}\).

1-[5'-{(substituted phenoxy)methyl}-1,3,4-thiadiazol-2'-yl]-4-substituted-2-azetidinones (136) and 1-[5'-aryl-1,3,4-thiadiazol-2'-yl] 3-chloro-4-substituted-2-azetidinones (137) were reported and showed potential antifungal agents\(^{231,232}\).
where $X = \text{Me}/\text{Me}/\text{NO}_2/\text{Cl}/\text{Br}$

(137)

1-Substituted-2-oxo-3-chloro/3-(2-chlorophenoxy)-4-(2-aryl indole-3-yl)-azetidines (138) have been synthesized and were found to be CNS active and antiinflammatory agents$^{233}$. 

where $R = \text{H} / \text{Me} / \text{OMe}$

$X = \text{Br} / \text{Cl} / \text{F}$

(138)
2-Oxo-azetidines\textsuperscript{234}(139) has showed antibacterial activity.

![Chemical structure of 2-Oxo-azetidines](image)

(139)

4-\((p\text{-substituted/unsubstituted})\)-phenyl thiazolyl-2'-\((4\text{-phenyl-3-chloro-2-oxo-azetidines})\) (140 \(a,b,c\)) are reported to possess CNS depressant activity\textsuperscript{235}.

![Chemical structure of 4-\((p\text{-substituted/unsubstituted})\)-phenyl thiazolyl-2'-(4-phenyl-3-chloro-2-oxo-azetidines)](image)

(140)

(140a) \(\text{Ar} = 2\text{-Amino-4-phenyl thiazole}\)

(140b) \(\text{Ar} = 2\text{-Amino-4-}(p\text{-chloro})\text{-phenylthiazole}\)

(140c) \(\text{Ar} = 2\text{-Amino-4-}(p\text{-fluro})\text{-phenylthiazole}\)

Clavulanic acid (141) is powerful inhibitor of \(\beta\)-lactomases and has been used clinically in admixture with amoxycillin (142). Two series of compounds without a second ring fused to the \(\beta\)-lactam have been found. The nocardicins for example nocardicin (143) has structural
features around the nitrogen atom like those in the other β-lactam antibiotics but the sulphamate compounds or monobactams for example sulphazecin (144) represent an entirely new type\textsuperscript{236}.

(141)  

(142)  

(143)  

(144)
1-[2-Alkyl-4-(3H)-oxo-3-quiazolinyl]-4-aryl-3-chloro-azetidinones (145) are found to display antipakinsonian, antitubercular and antirigidity activities\textsuperscript{237}.

\[
\text{where} \quad X = \text{H/CH}_3/\text{OMe/NO}_2/\text{Cl/OH}
\]

(145)

Substituted-2-oxo-3-chloro-3-(2-chlorophenoxy-4-aryindol-3-yl)-azetidines (146) have reported as CNS depressant and antiinflammatory agents\textsuperscript{238}.

\[
\text{where} \quad X = \text{H/Me/OMe/OH/NO}_2
\]

(146)

4-Arly-3-chloro-1-(4-phenyl-2-oxazolyl)-azetidine-2-ones (147) and 1"-[4"-aryl-(2',4'-bithiazol)-2'-yl]-4"-aryl-2"-azetidinones (148) displayed antibacterial activity\textsuperscript{239,240}. 
where \( X = \text{Me/Me/NO}_2/\text{Cl/Br} \)

(147)

where \( X = \text{Me/Ome/NO}_2/\text{Cl/Br} \)

(148)

Benzothiazolosulphonamidoazetidin-2-ones (149) are reported to exhibit antimicrobial activity against \( B. \) \( \text{susbtilis} \), \( S. \) \( \text{aureus} \), \( E. \) \( \text{coli} \) and \( P. \) \( \text{aeruginosa} \)\textsuperscript{241}.

where \( X = \text{Me/OMe/NO}_2/\text{Cl/Br} \)

(149)
3-chloro-2-oxo-4-(substituted phenyl)-azetidin-1-yl-thioureas (150) are found to exhibit antiparkinsonian activity\textsuperscript{242}.

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{C} & \quad \text{NH} & \quad \text{N} & \quad \text{Cl} \\
& & & & \\
& & & & \text{X}
\end{align*}
\]

where \( X = \text{Me/OMe/NO}_2/\text{Cl/Br} \)

(150)

1,3,7,9-Tetrabromo-10-[a-{2-(2-hydroxyphenyl)-3-chloro-4-oxo-1-azetidinylamino}-acetyl]-phenothiazines (151) have been shown tuberculstatic activity\textsuperscript{243}.

\[
\begin{align*}
\text{Br} & \quad \text{S} & \quad \text{Br} \\
\text{Br} & \quad \text{Br} & \quad \text{Br} \\
& & & & \text{X} \\
& & & & \text{COCH}_2 & \text{N} & \text{Cl} \\
& & & & & & \text{X}
\end{align*}
\]

where \( X = \text{Me/OMe/OH/NO}_2/\text{Cl} \)

(151)
4-Aryl-1-[phenothiazinoamidyl]-2-azetidinones (152) and 5-aryl-2-[spiro-(1,3-dithialone)-2,4,3'-chloro-2'-azetidinon)-1'-yl]-1,3,4-oxathiadiazoles (153) are found to exhibit antiinflammatory activity\textsuperscript{244}.

![Chemical Structure](image)

(152)

where \( \text{Ar} = \) Phenyl/sub-phenyl

(153)
SECTION 2.4: AIM AND WORK PLAN OF THE RESEARCH:

The literature survey on structure activity relationship of 1,2,3-benzotriazole, indole and their azetidinones has promoted the author to synthesize some new $N^1$-$\alpha$-arylidenehydrazino and their azetidinones derivatives and to record their biological activity to get new compounds as possible new age drugs.

WORK PLAN OF THE RESEARCH:

The work plan of the research has been divided into three parts.

Part-I: Synthesis of new heterocyclic compounds.

Part-II: Characterization of the compounds by microanalytic techniques, physical methods, chromatography and spectral data.

Part-III: Evaluation of the biological activity of the synthesized products viz.

(a) Antibacterial.

(b) Antifungal.

(c) Antiinflammatory and

(d) Anticonvulsant.

PART-I: SYNTHESIS OF NEW HETEROCYCLIC COMPOUNDS:

Four series of the compounds have been synthesised by following the Schemes-1 (general), 2 and 3 respectively.
Scheme-1

\[
\begin{align*}
\text{Het} & \text{NH} \\
\downarrow & \\
\text{CICOCH}_2\text{Cl} \\
\downarrow & \\
\text{Het} & \text{NCOCH}_2\text{Cl} \\
\downarrow & \\
\text{NH}_2\text{NH}_2 \\
\downarrow & \\
\text{Het} & \text{NCOCH}_2\text{NHNH}_2 \\
\downarrow & \\
\text{O} & \text{C} \\
\downarrow & \\
\text{Het} & \text{NCOCH}_2\text{NHN} = \text{C} \\
\downarrow & \\
\text{CICOCH}_2\text{Cl} \\
\downarrow & \\
\text{Het} & \text{NCOCH}_2\text{NH} \text{C} \text{C} \text{Cl} \\
\end{align*}
\]

where

\[
\begin{align*}
\text{Het} & \text{NH} = 1,2,3\text{-benzotriazole} / 1\text{H-indole} \\
R & = \text{H} / \text{alkyl} \\
\text{Ar} & = \text{Aryl} / \text{substituted aryl}
\end{align*}
\]
### TABLE 1: LIST OF THE COMPOUNDS SYNTHESISED UNDER SERIES-1.

<table>
<thead>
<tr>
<th>Compounds Code No.</th>
<th>Chemical Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>SG 3</td>
<td>N(^1)-[(\alpha)-(benzylidenehydrazino)-acetyl]-1,2,3-benzotriazole.</td>
</tr>
<tr>
<td>SG 4</td>
<td>N(^1)-[(\alpha)-(2-chloro benzylidenehydrazino)-acetyl]-1,2,3-benzotriazole.</td>
</tr>
<tr>
<td>SG 5</td>
<td>N(^1)-[(\alpha)-(4-chloro benzylidenehydrazino)-acetyl]-1,2,3-benzotriazole.</td>
</tr>
<tr>
<td>SG 6</td>
<td>N(^1)-[(\alpha)-(2-chloro acetophenonlidinhydrazino)-acetyl]-1,2,3-benzotriazole.</td>
</tr>
<tr>
<td>SG 7</td>
<td>N(^1)-[(\alpha)-(4-chloro acetophenonlidinhydrazino)-acetyl]-1,2,3-benzotriazole.</td>
</tr>
<tr>
<td>SG 8</td>
<td>N(^1)-[(\alpha)-(2-bromo benzylidenehydrazino)-acetyl]-1,2,3-benzotriazole.</td>
</tr>
<tr>
<td>SG 9</td>
<td>N(^1)-[(\alpha)-(2-hydroxy benzylidenehydrazino)-acetyl]-1,2,3-benzotriazole.</td>
</tr>
<tr>
<td>SG 10</td>
<td>N(^1)-[(\alpha)-(4-hydroxy benzylidenehydrazino)-acetyl]-1,2,3-benzotriazole.</td>
</tr>
<tr>
<td>SG 11</td>
<td>N(^1)-[(\alpha)-(2-hydroxy acetophenonlidinhydrazino)-acetyl]-1,2,3-benzotriazole.</td>
</tr>
<tr>
<td>SG 12</td>
<td>N(^1)-[(\alpha)-(4-hydroxy acetophenonlidinhydrazino)-acetyl]-1,2,3-benzotriazole.</td>
</tr>
</tbody>
</table>
Scheme-2
**TABLE 2: LIST OF THE COMPOUNDS SYNTHESISED UNDER SERIES-2.**

<table>
<thead>
<tr>
<th>Compounds Code No.</th>
<th>Chemical Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>SG 13</td>
<td>(N^1)-[(\alpha)-(4-phenyl-3-chloro-2-oxo-1-azetidinylamino) acetyl]-1,2,3-benzotriazole.</td>
</tr>
<tr>
<td>SG 14</td>
<td>(N^1)-[(\alpha)-{4-(2-chlorophenyl)-3-chloro-2-oxo-1-azetidinylamino} acetyl]-1,2,3-benzotriazole.</td>
</tr>
<tr>
<td>SG 15</td>
<td>(N^1)-[(\alpha)-{4-(4-chlorophenyl)-3-chloro-2-oxo-1-azetidinylamino} acetyl]-1,2,3-benzotriazole.</td>
</tr>
<tr>
<td>SG 16</td>
<td>(N^1)-[(\alpha)-{4-(2-chlorophenyl)-3-chloro-2-oxo-4-methyl-1-azetidinyl} acetyl]-1,2,3-benzotriazole.</td>
</tr>
<tr>
<td>SG 17</td>
<td>(N^1)-[(\alpha)-{4-(4-chlorophenyl)-3-chloro-4-methyl-2-oxo-1-azetidinylamino} acetyl]-1,2,3-benzotriazole.</td>
</tr>
<tr>
<td>SG 18</td>
<td>(N^1)-[(\alpha)-{4-(2-bromophenyl)-3-chloro-2-oxo-1-azetidinylamino} acetyl]-1,2,3-benzotriazole.</td>
</tr>
<tr>
<td>SG 19</td>
<td>(N^1)-[(\alpha)-{4-(2-hydroxyphenyl)-3-chloro-2-oxo-1-azetidinylamino} acetyl]-1,2,3-benzotriazole.</td>
</tr>
<tr>
<td>SG 20</td>
<td>(N^1)-[(\alpha)-{4-(4-hydroxyphenyl)-3-chloro-2-oxo-1-azetidinylamino} acetyl]-1,2,3-benzotriazole.</td>
</tr>
<tr>
<td>SG 21</td>
<td>(N^1)-[(\alpha)-{4-(2-hydroxyphenyl)-3-chloro-4-methyl-2-oxo-1-azetidinylamino} acetyl]-1,2,3-benzotriazole.</td>
</tr>
<tr>
<td>SG 22</td>
<td>(N^1)-[(\alpha)-{4-(4-hydroxyphenyl)-3-chloro-4-methyl-2-oxo-1-azetidinylamino} acetyl]-1,2,3-benzotriazole.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Compounds Code No.</th>
<th>Chemical Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>SG 25</td>
<td>N(^1)-[(\alpha)-(benzylidenehydrazino)-acetyl]-1H-indole.</td>
</tr>
<tr>
<td>SG 26</td>
<td>N(^1)-[(\alpha)-(2-chloro benzylidenehydrazino)-acetyl]-1H-indole.</td>
</tr>
<tr>
<td>SG 27</td>
<td>N(^1)-[(\alpha)-(4-chloro benzylidenehydrazino)-acetyl]-1H-indole.</td>
</tr>
<tr>
<td>SG 28</td>
<td>N(^1)-[(\alpha)-(2-chloro acetophenonlidinhydrazino)-acetyl]-1H-indole.</td>
</tr>
<tr>
<td>SG 29</td>
<td>N(^1)-[(\alpha)-(4-chloro acetophenonlidenehydrazino)-acetyl]-1H-indole.</td>
</tr>
<tr>
<td>SG 30</td>
<td>N(^1)-[(\alpha)-(2-bromoplenzylidenehydrazino)-acetyl]-1H-indole.</td>
</tr>
<tr>
<td>SG 31</td>
<td>N(^1)-[(\alpha)-(2-hydroxybenzylidenehydrazino)-acetyl]-1H-indole.</td>
</tr>
<tr>
<td>SG 32</td>
<td>N(^1)-[(\alpha)-(4-hydroxybenzylidenehydrazino)-acetyl]-1H-indole.</td>
</tr>
<tr>
<td>SG 33</td>
<td>N(^1)-[(\alpha)-(2-hydroxyacetophenolidinhydrazino)-acetyl]-1H-indole.</td>
</tr>
<tr>
<td>SG 34</td>
<td>N(^1)-[(\alpha)-(4-hydroxyacetophenolidinhydrazino)-acetyl]-1H-indole.</td>
</tr>
</tbody>
</table>
Scheme-3

\[
\begin{align*}
    &\text{N} \\
    &\text{CICOCH}_2\text{Cl} \\
    &\text{N} \\
    &\text{COCH}_2\text{Cl} \\
    &\text{SG 23} \\
    &\text{NH}_2\text{NH}_2 \\
    &\text{N} \\
    &\text{COCH}_2\text{NNNH}_2 \\
    &\text{SG 24} \\
    &\text{O} \quad \text{C} \\ &\quad \text{R} \\
    &\text{N} \\
    &\text{COCH}_2\text{NNN} \\ &\quad \text{C} \\ &\quad \text{R} \\
    &\text{SG 25-34} \\
    &\text{CICOCH}_2\text{Cl} \\
    &\text{N} \\
    &\text{COCH}_2\text{NN} \\ &\quad \text{N} \\ &\quad \text{C} \\ &\quad \text{R} \\ &\quad \text{Ar} \\
    &\text{SG 35-44} \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>Compounds Code No.</th>
<th>Chemical Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>SG 35</td>
<td>N^1-[(α-(4-phenyl-3-chloro-2-oxo-1-azetidinyl amino) acetyl]-1H-indole.</td>
</tr>
<tr>
<td>SG 36</td>
<td>N^1-[(α-(4-(2-chlorophenyl)-3-chloro-2-oxo-1-azetidinyl amino)-acetyl]-1H-indole</td>
</tr>
<tr>
<td>SG 37</td>
<td>N^1-[(α-(4-(4-chlorophenyl)-3-chloro-2-oxo-1-azetidinyl amino)-acetyl]-1H-indole</td>
</tr>
<tr>
<td>SG 38</td>
<td>N^1-[(α-(4-(2-chlorophenyl)-3-chloro-4-methyl-2-oxo-1-azetidinyl amino)-acetyl]-1H-indole</td>
</tr>
<tr>
<td>SG 39</td>
<td>N^1-[(α-(4-(4-chlorophenyl)-3-chloro-4-methyl-2-oxo-1-azetidinyl amino)-acetyl]-1H-indole</td>
</tr>
<tr>
<td>SG 40</td>
<td>N^1-[(α-(4-(2-bromophenyl)-3-chloro-2-oxo-1-azetidinyl amino)-acetyl] -1H-indole.</td>
</tr>
<tr>
<td>SG 41</td>
<td>N^1-[(α-(4-(2-hydroxyphenyl)-3-chloro-2-oxo-1-azetidinyl amino)-acetyl]-1H-indole.</td>
</tr>
<tr>
<td>SG 42</td>
<td>N^1-[(α-(4-(4-hydroxyphenyl)-3-chloro-2-oxo-1-azetidinyl)-acetyl]-1H-indole.</td>
</tr>
<tr>
<td>SG 43</td>
<td>N^1-[(α-(4-(2-hydroxyphenyl)-3-chloro-4-methyl-2-oxo-1-azetidinyl]-acetyl]-1H-indole.</td>
</tr>
<tr>
<td>SG 44</td>
<td>N^1-[(α-(4-(4-hydroxyphenyl)-3-chloro-4-methyl-2-oxo-1-azetidinyl]-acetyl]-1H-indole.</td>
</tr>
</tbody>
</table>
PART – II : CHARACTERIZATION OF THE SYNTHESIZED COMPOUNDS.

The melting points of the compounds were determined in an open capillary and were uncorrected. Rf. values were determined by TLC on silica gel coated plates using iodine as a developer. All the compounds were analysed for C, H and N percentage. The infrared spectra of the representative compounds were recorded in KBr plates on Acculab-10, spectrophotometer and $^1$H-NMR spectra of the representative compounds were recorded on Brucker DRX 300 spectrometer at 200 MHz using TMS as an internal standard.

PART – III : BIOLOGICAL ACTIVITY OF THE SYNTHESIZED COMPOUNDS.

The synthesized compounds were screened for their antibacterial, antifungal, antiinflammatory and anticonvulsant activities. Some of the compounds were found to display remarkable biological activity.