2. LITERATURE REVIEW

2.1. Benzimidazoles

2.1.1. Chemistry

Benzimidazole is a heterocyclic aromatic organic compound. This bicyclic compound consists of the fusion of benzene and imidazole. The most prominent benzimidazole compound in nature is N-ribosyl-dimethylbenzimidazole, which serves as an axial ligand for cobalt in vitamin B$_{12}$.\(^1\)

Benzimidazole, in an extension of the well-elaborated imidazole system, has been used as carbon skeletons for N-heterocyclic carbenes. The NHCs are usually used as ligands for transition metal complexes. They are often prepared by deprotonating an $N, N'$-disubstituted benzimidazolium salt at the 2-position with a base.\(^2,3\)

Benzimidazole is a white to slightly beige solid; melting at 172 °C, boils at 360 °C, slightly soluble in water, soluble in ethanol. It is a dicyclic compound having imidazole ring (containing two nitrogen atoms at nonadjacent positions) fused to benzene. Benzimidazole and its derivatives are used in organic synthesis and vermicides or fungicides as they inhibit the action of certain microorganisms. Examples of benzimidazole class fungicides include benomyl, carbendazim, chlorfenazole, cypendazole, debacarb, fuberidazole, furophanate, mecarbinzid, rabenzazole, thiabendazole, thiophanate. Benzimidazole structure is the nucleus in some drugs such as proton pump inhibitors and anthelmintic agents.

Benzimidazole, $pKa = 5.68$, is less basic than imidazole, but with $pKa = 12.75$ is more strongly NH-acidic.\(^4\) Like imidazoles, benzimidazoles display annular tautomerism in solution, e.g.:

Nucleophiles react faster with benzimidazoles than with imidazoles, the attack occurring at the 2-position. For instance, on treatment with sodium amide in xylene, 1-alkylbenzimidazoles give the corresponding 2-amino compounds.
The halogen in 2-halobenzimidazoles can be substituted by nucleophiles, e.g. alkoxides, thiolates or amines. However, the reactions proceed more slowly than with 2-halobenzoxazoles and 2-halobenzothiazoles. The standard synthesis for benzimidazoles is the cyclocondensation of o-phenylenediamine or substituted o-phenylenediamines with carboxylic acids or their derivatives.

\[
\text{R}^2 \text{NH}_2 + \text{HO-C-R}^1 \rightarrow \text{R}^2 \text{N-R}^1
\]

o-Phenylenediamine reacts with formic acid at 100°C to give benzimidazole in a yield of over 80%. N-monosubstituted o-phenylenediamines react with other carboxylic acids more slowly, necessitating the addition of hydrochloric or phosphoric acid. A mixture of trifluoromethanesulfonic acid anhydride and triphenylphosphane oxide in dichloromethane is a very efficient dehydrating agent \(^5\).

In light of the affinity they display towards a variety of enzymes and protein receptors, medicinal chemists would certainly classify them as privileged ‘substructures’ for drug dosing. The incorporation of the nucleus is an important synthetic strategy in studies of antimicrobial drug discovery. In the past few decades, benzimidazole and its derivatives have received much attention due to their chemotherapeutic values.

### 2.1.2. Biological Profile

#### 2.1.2.1. Anti-inflammatory

Synthesis and anti-inflammatory activity of phenyl benzimidazole (1) was reported by Leonardo et al \(^6\). Compounds 1a, 1b, 1c and 1d were screened for anti-inflammatory activity and they showed percent inhibition (22.1%, 52.2%, 54.6% and 49.6%) at 50 mg/kg each doses. By these values the compound 1c showed maximum (54.6%) inhibition of edema at doses of 50 mg/kg.
Chapter 2

2.1.2.2. Diuretic

Synthesis of 3-(2-methyl-1,2-dihydropyrimido (1,2-c)benzimidazole-1-thionyl)-6,8-dibromo-2-substituted-3H-quinazolin-4-one (2) was reported by Srinivasan et al. Compound 2a and 2b showed moderate diuretic activity.

2.1.2.3. Antimicrobial

Synthesis of benzimidazole as 1-(substituted-methyl)-2-(substituted-phenyl) benzimidazole (3) was reported by Leonardo et al. Compounds 3a, 3b and 3c were screened for their antibacterial activity against S. aureus, B. pumillus and P. Aeurugenosa. Compound 3a showed MIC (6.25) at 100 µM/mL and exhibited good antibacterial activity.

Synthesis of 2,3,4-trisubstituted-1,2-dihydropyrimido[1,2-a]benzimidazole derivatives (4) were reported by Deshmukh et al. The compounds were tested for their fungicidal activities against Aspergillus niger MTCC-2255 and Penicillium chrysogenum-NCIM-723 using Greiseofulvin as control.
The efficient synthesis of novel 3-chloro-1-5-(2-methyl-1H-bezimidazol-2-yl)-4-(substituted) phenylazetidin-2-one (5) was reported by Ansari et al. Compounds were screened for antimicrobial activity against *B. subtilis* and *E. coli* and compound 5a, 5b and 5c shown MIC at 100 µg/mL, 100 µg/mL and 200 µg/mL doses.

![Chemical structure of compound 5](image)

Ar = 2-C₆H₅Cl, 2-C₆H₅OH

### 2.1.2.4. Antiviral

Synthesis of 2-(benzylthio)-5, 6-dichloro-1-(β-D-ribofuranosyl)benzimidazoles (6) was reported by Devivar et al. Compounds 6a, 6b and 6c performed antiviral activity against HSV-1 and HCMV and compound 6c shown maximum activity at 90% inhibitory concentration (µM).

![Chemical structure of compound 6](image)

R = SCH₃, SO₂CH₃, SO₂C₆H₅

### 2.1.2.5. Antitumor

Some new benzimidazole-4,7-diones substituted at 2-position (7) were synthesized and reported by Gellis et al. Among compounds 7a, 7b and 7c (10µM, 8µM and 3µM), 7c performed excellent cytotoxic activity against colon (HT29), breast (T47D) and lung (A549) cancer cell lines and shown lowest IC₅₀ values in µM i.e., (3µM).

![Chemical structure of compound 7](image)

R₁ = -CH=CH₂(CH₃)₂, -CH₂·CH(CH₃)₂NO₂
2.1.2.6.  **Antiprotozoal**

Synthesis and anti-protozoal activity of 2-(trifluoromethyl)-1H-benzimidazole (8) were reported by Vazquez et al.\(^{12}\). A series of 2-(trifluoromethyl)-1H-benzimidazole derivatives with 5 and 6 position bio isosteric substituent (–Cl, –F, –CF\(_3\), –CN) were prepared by using short synthetic route. Analogues were tested *in vitro* against the protozoa *Giardia intestinals* and *Trichomonas vaginalis* compared with Albendazole and Metronidazole, have IC\(_{50}\) < 1 µM and compound (8), was more active than Albendazole against *T. vulgaris* and also showed moderate antimalarial activity against W2 and D6 strains of *Plasmodium falciparum*.

![2-(trifluoromethyl)-1H-benzimidazole](image)

**2.1.2.7. Antiulcer**

Series of novel pyrimidyl-thio-methyl- benzimidazole (9) pyrimidyl-sulfinyl-methylbenzimidazole (10) were synthesized and reported by Bariwal et al.\(^{13}\). Compounds evaluated for the antiulcer activity. Compound 9 and 10 at 10 and 30 mg/kg doses reduced the ulcer formation significantly comparable to standard (Omeprazole) and 10 (sulfinyl derivative) compound was more effective than 9 (thio derivative).

![Pyrimidyl-thio-methyl-benzimidazole](image)

![Pyrimidyl-sulfinyl-methylbenzimidazole](image)

**2.1.2.8.  Protein Kinase Ck2 Inhibitors**

QSAR studies were carried out on 4,5,6,7 tetra-bromo benzimidazole (11) derivatives by Tripathi *et al.*\(^{14}\) and having the inhibitory activity data (IC\(_{50}\)) and the values converted in to –log IC\(_{50}\) (µM), compound 11a (0.797), 11b (0.177), 11c (0.607), by these values compound 11b shown effective inhibitory concentration.
2.1.2.9. Antioxidant

Synthesis of some 6-flouro-5-substituted benzimidazole (12) were reported by Alagoz et al. \(^{15}\) in which indole and 1,4,4,4-tetramethyl-1,2,3,4-tetrahydro naphthalene groups were attached to the 2-position ring and tested for antioxidant activity. Compound 12e showed strong super scavenging effect on superoxide anion at \(10^{-3}\) M concentration.

![Diagram of compound 12e]

\[
R = \text{NH}_2, \text{Br}, \text{NHCH}_3
\]

\[(11)\]

2.1.2.10. Anti-Asthmatic

Syntheses of novel and functionalized benzimidazole derivatives (13) were reported by Kumar et al \(^{16}\). Compounds were tested against PDE-1V for potential anti-asthmatic effect, compound 13a, 13b and 13c shown inhibitory activity (3.40%, 13.52% and 8.91%) at 1µm dose. The 13b compound showed potential anti-asthmatic activity.

![Diagram of compound 13b]

\[
R = \text{H}, \text{C}_2\text{H}_5, \text{CH}_2\text{CH}_2\text{CH}_3
\]

\[(13)\]
2.1.2.11. Anti-Diabetic

A synthesis of a series of novel and functionalized benzimidazole derivatives (14) was reported by Kumar et al.\(^{16}\). Compounds shown anti-diabetic activity against DPP-IV and PTP-IB. compound 14a and 14b shown inhibitory activity against PTP-IB (1.64%, 2.42%) at 30µM doses and 14c shown inhibitory activity against DPP-IV (3%) at 0.3 µM doses.

\[
\text{R} = \text{H, CH}_2\text{CH}_2\text{CH}_2\text{CH}_3
\]

(14)

2.1.2.12. Cysticidal Activity

Synthesis of novel benzimidazole derivatives (15) were reported by Alonso et al.\(^{17}\). Compounds 15a, 15b and 15c had shown their \textit{in vitro} activity against \textit{Taenia crassiceps} of WFU strain (22.6%, 9.3% and 5.0%) cysts’s mortality percentage. Among three of them compound, 15c having good mortality rate.

\[
\begin{align*}
\text{R}_1 &= 4-\text{nitrobenzyl formate, 4-piperidine-carbaldehyde, -Cl} \\
\text{R}_2 &= \text{R}_3 = \text{H}, \text{R}_4 = \text{NHCOOCH}_3
\end{align*}
\]

(15)

2.1.2.13. 5-HT\textsubscript{3} Receptor Antagonist

Synthesis of novel benzimidazole-2-carboxylic acid amides and esters (16) were reported by Orjales \textit{et al.}\(^{18}\) with a quinolidine or a tropane moiety. It was evaluated for \textit{in vitro} affinity for the 5-HT\textsubscript{3} receptor. Synthesized compounds 16a, 16b, 16c having 5-HT\textsubscript{3} receptor antagonist activity (12.7, 18.4, 24.4) with ED\textsubscript{50} values of (10.6-19.1) mg/kg i.v. among these compound 16a having higher affinity for 5-HT\textsubscript{3} receptor.
2.1.2.14. Analgesic

Syntheses of a series of \(N\)-(acridin-9-yl)-4-(benzo[d]imidazol/oxazol-2-yl) benzamides (17) have been reported by Sondhi et al.\(^\text{19}\). Compound containing \(R_1 = \text{NO}_2\), \(R_3 = \text{H}, R_3 = \text{H}, X = \text{NH}\) showed significant \textit{in vitro} activity against CDK-5 (IC\(_{50} = \text{4.6 mM}\)) and CDK-1 (IC\(_{50} = \text{7.4 mM}\)) and compound having \(R_1 = \text{Cl}, R_2 = \text{H}, R_3 = \text{H}, X = \text{NH}\) showed moderate CDK-5 inhibitory activity (IC\(_{50} = \text{7.5 mM}\)). The other compounds showed moderate anti-inflammatory and analgesic activities.

\[
\begin{align*}
R_1 = & \text{Cl,NO}_2,\text{CH}_3,\text{H}; \\
R_2 = & \text{H,CH}_3; \\
R_3 = & \text{H,OCH}_3; \\
X = & \text{NH,O}
\end{align*}
\]

(17)

2.1.2.15. Spasmolytic

Syntheses of \(2\)-(aryloxyaryl)-1\(H\)-benzimidazole derivatives (18) were reported by Vazquez et al.\(^\text{12}\). Compounds 18a, 18b and 18c showed significant antispasmodic effect in a concentration dependent manner, IC\(_{50} \) 1.94 µM, 1.19 µM and 1.8 µM, compound 18c shown potent relaxant smooth muscle activity.

\[
\begin{align*}
\text{Ar} = & \text{C}_6\text{H}_5\text{COC}_2\text{H}_5, \\
& \text{4-OH-3-OCH}_3\text{C}_6\text{H}_5, \\
& \text{2,3,4 -trimethoxybenzene}
\end{align*}
\]

(18)
2.1.2.16. Hypotensive
Synthesis of 9-dialkyaminomethyl-2-oxy(dioxy)phenylimidazo[1,2-a] benzimidazole (19) was reported by Anisimova et al.\(^{20}\). Compounds 19a, 19b and 19c possessed hypotensive activity (ED\(_{50}\): 2.8 mg/kg, 0.8 mg/kg, 0.13 mg/kg), (LD\(_{50}\): 121.0 mg/kg, 182 mg/kg, 143 mg/kg) and (LD\(_{50}/\text{ED}_{50}\): 43.2, 227.5, 1100), the most active compound out of these was 19c exceeded the reference drugs (Dibazole and Apressin) (ED\(_{50}\): 22.1, 4.0) with respect to both the degree of the hypotensive action (ED\(_{50}\)) and the conditional therapeutic index (LD\(_{50}/\text{ED}_{50}\)).

\[
\begin{align*}
\text{R} &= \text{1-4 dihydroxymethylbenzene,} \\
&\text{1-3 dihydroxymethylbenzene.}
\end{align*}
\]

2.1.2.17. Antimycobacterial
Synthesis of substituted 2-polyfluroalkyl and 2-nitrobenzyl sulfanyl benzimiazole (20) were reported by Kazimierczuk et al.\(^{21}\). Compounds were evaluated for their activity against mycobacterium strains and compounds which showed appreciable antimycobacterial activity compound 20a, 20b and 20c shown their MIC values 2 µmol L\(^{-1}\), 2 µmol L\(^{-1}\) and 4 µmol L\(^{-1}\).

\[
\begin{align*}
\text{R}_1 &= \text{Cl, Br} \\
\text{R}_2 &= \text{methyl nitrobenzene, C}_4\text{F}_9
\end{align*}
\]

Camacho et al.\(^{22}\) synthesised a series of N\(^\prime\)-substituted-2-(5-nitrofuran or 5-nitrothiophene-2-yl)-3H-benzo[d]-imidazole-5-carbohydrazide derivatives (21) and investigated for their abilities to inhibit β-hematin formation, hemoglobin hydrolysis and in vivo for their antimalarial efficacy in rodent Plasmodium berghei. Selected analogues were screened for their antitubercular activity against sensitive MTB H\(_{37}\)Rv.
and multidrug-resistant MDR-MTB strains, and cytotoxic activity against a panel of human tumor cell lines and two nontumorogenic cell lines.

\[
\text{(21)}
\]

\[ R_1 = \text{H, Ar}; \, X = \text{O, S} \]

### 2.1.2.18. Anthelmintic

Synthesis of 2-benzimidazole carbamic acid methyl ester derivatives (22) were reported by Solominova et al. Compounds 22a and 22b shown anthelmintic activity against *Nippostrongilus*, *Ankilostoma* and *Haemonchus* larvae that exceeded 65% upon per oral administration in animals (rats, sheep, dogs) at a dose of 2.5-50 mg/kg. In another group of animal inhibition action is below 40% upon per oral administration in a dose of 50-100 mg/kg.

\[
\text{(22)}
\]

### 2.1.2.19. Histamine H4-Receptor Antagonist

Synthesis of 2-arylbenzimidazole derivatives (23) were reported by Dutra et al. and found to bind with high affinity to the human histamine H4 receptor. Compounds 23a, 23b and 23c shown their antihistaminic activity, among three of them 23a showed moderate affinity for H4 receptor (\(K_i = 124\) nM) and others (\(K_i = 65, 95\)).

\[
\text{(23)}
\]

\[ R = \text{methylpiperazine, dimethylpyrrolidin-3-amine, 1-5diazocanemethylamine}; \, R_1 = \text{Cl} \]
2.1.2.20. Prostaglandin Analogs

Syntheses of 2-(1-2-methylene-3-methylene-3-hydroxyoctyl)-N-(6-methoxy carbonylhexyl) benzimidazole (24) derivatives were reported by Bespalov et al \(^{25}\). Synthesized compounds 24a and 24b shown comparable results with F\(_2\)\(\alpha\) prostaglandin preparation Enzaprost and spasmogenic action of these compounds significantly lower (4-6 times) than Enzaprost.

\[
\begin{align*}
\text{R} &= \text{cyclopropylheptan-1-ol}, \\
\text{R} &= \text{cyclopropylheptan-1-one} \\
(24)
\end{align*}
\]

2.1.2.21. Anti-Amoebic

Synthesis of pyrimido [1,6-a]benzimidazole derivatives (25) were reported by Sondhi et al \(^{26}\). Compounds 25a and 25b were carried out \textit{in-vitro} against \textit{E. histolytica} and IC\(_{50}\) values obtained (1.82 \(\mu\)M, 2.62 \(\mu\)M) compared with the reference drug Metronidazole had 50% inhibitory concentration (IC\(_{50}\)) of 1.22 \(\mu\)M and the best IC\(_{50}\) value shown by 25a compound.

\[
\begin{align*}
\text{R} &= \text{CH}_3, \text{COOH}, \\
\text{R} &= \text{CH}_3, \text{H} \\
(25)
\end{align*}
\]

2.1.2.22. Antiarrhythmic

Syntheses of 9-dialkylaminoethyl-2-oxy (dioxy) phenylimidazo [1,2-a]benzimidazole derivatives (26) were reported by Anisimova \textit{et al} \(^{20}\). Compounds exhibited the antiarrhythmic activity. Compound 26a, 26b and 26c were evaluated the activity in minimum effective concentration (MIC mole/L) 2.9\(\times\)10\(^{-4}\) m/L, 2.3\(\times\)10\(^{-4}\) m/L, 2.1\(\times\)10\(^{-4}\) m/L with reference to Quinidine (3.1\(\times\)10\(^{-4}\) m/L). Hence the 26a MIC value was close to the reference drug. Concentrations but the values showed no significant result.

\[
\begin{align*}
\text{R} &= \text{diethylamine, ethoxyethylethananime} \\
\text{R} &= \text{OH}, \text{R}_2 = \text{H} \\
(26)
\end{align*}
\]
2.1.2.23. Anticonvulsant

In this synthesis of novel 1H-pyrrolo (1,2-a)benzimidazole-1-one derivative (27) were reported by Chimrri et al. 27 Compounds 27a, 27b and 27c showed (84 %, 67% and 69 %) by maximal electroshock method, at dose level 25 mg/kg orally. The compound 27a showed maximum anticonvulsant activity.

\[
\text{R}_1 = \text{Cl, F, H; } \text{R}_2 = \text{C}_6\text{H}_5,\text{CH}_3, \text{R}_3 = \text{H}
\]

(27)

Shukla et al. 28 synthesized a series of 1-heterocyclic amino/iminomethyl-2-substituted benzimidazoles (28) and were screened for their neuropharmacological and monoamine-oxidase inhibitory properties. A number of such compounds showed CNS stimulant, anticonvulsant and mono amine oxidase inhibitory activities.

\[
\text{R} = \text{H,Cl,F; } \text{R}_1 = \text{H,CH}_3,\text{C}_2\text{H}_5;
\text{R}_2 = \text{H, C}_6\text{H}_5
\]

(28)

Siddiqui et al. 29 synthesized a number of new 1-[(1-(2-substituted benzyl)-1H-benzo[d]imidazol-2-yl) methyl]-3-arylthioureas compounds (29). All the newly synthesized compounds were screened for their anticonvulsant activity in ip MES and sc PTZ model and were compared with the standard drug phenytoin. Majority of the compounds exhibited significant activity against both the animal models however compounds 29g, 29l and 29o displayed promising activity.

\[
\text{R} = \text{H, Cl ; } \text{R}_1 = \text{C}_6\text{H}_5, 2\text{-CH}_3\text{C}_6\text{H}_5, 3\text{-CH}_3\text{C}_6\text{H}_5, 4\text{-CH}_3\text{C}_6\text{H}_5, 2\text{-OCH}_3\text{C}_6\text{H}_5, 3\text{-OCH}_3\text{C}_6\text{H}_5, 4\text{-OCH}_3\text{C}_6\text{H}_5
\]

(29)
In seeking broad spectrum pharmacological activities of benzimidazole derivatives, a group of 4-thiazolidinones (30) and 1,3,4-oxadiazoles (31) containing 2-mercapto benzimidazole moiety were synthesized by Shingalapur et al.\textsuperscript{30} and screened for \textit{in vivo} anticonvulsant activity by Maximal Electroshock (MES) model and antidiabetic activity using Oral Glucose Tolerance Test (OGTT). Compounds 30c, 30d, 30g and 30i exhibited potent anticonvulsant results and 31c, 31d, 31h and 31i showed excellent antidiabetic activities and also pharmacophore derived from active molecules suggested that presence of –OH group was a common feature in all active compounds. In DNA cleavage studies, compound 31d cleaved DNA completely as no trace of DNA was found. On the other hand, a sharp streak was found for compounds 30c, 31a and 31d.

\begin{align*}
\text{(30)} & \\
\text{(31)} & \\
R = & \text{C}_6\text{H}_5, 4-\text{C}_6\text{H}_5\text{Cl}, 2-\text{C}_6\text{H}_5\text{OH}, 4-\text{C}_6\text{H}_5\text{OH}, 4-\text{C}_6\text{H}_5\text{CH}_3, 4-\text{C}_6\text{H}_5\text{OCH}_3; \\
R^1 = & \text{C}_6\text{H}_5, 4-\text{C}_6\text{H}_5\text{Cl}, 2-\text{C}_6\text{H}_5\text{OH}, 4-\text{C}_6\text{H}_5\text{OH}, 3-\text{C}_6\text{H}_5\text{OH}, 4-\text{C}_6\text{H}_5\text{CH}_3, 4-\text{C}_6\text{H}_5\text{OCH}_3
\end{align*}
2.1.3. References


2. R Jackstell; A Frisch; M Beller; D Rottger; M Malaun; B Bildstein. "Efficient telomerization of 1,3-butadiene with alcohols in the presence of in situ generated palladium(0)carbene complexes", J Molec. Cat. A: Chemica., 2002, 185(1-2), 105–112.


8. MB Deshmukh; AW Suryavanshi; SA Deshmukh; SS Jagtap. ‘Microwave assisted synthesis of 2,3,4-trisubstituted 1,2-dihydropyrimido-[1,2-a]benzimidazole ‘, Ind. J. Chem., 2009, 86B, 302-305.


27. A Chimrri; AD Sarro GD Sarro; G Giho; M Zappala. ‘Synthesis and anticonvulsant properties of 2, 3, 3a-4-tetrahydro-1-H pyrrolo (1,2-a) benzimidazol-1-one derivatives’, *Farmaco*, **2001**, 56, 821-826.


2.2. Benzothiazoles

2.2.1. Chemistry

Benzothiazole is an organosulfur compound. It is colorless, slightly viscous liquid that is used in industry and research. A derivative of benzothiazole is the light-emitting component of luciferin, found in fireflies. Some dyes, such as thioflavin, and pharmaceutical drugs, such as riluzole, have benzothiazoles as a structural motif.

Chemically benzothiazole is benzofused five membered heterocyclic system containing S and N heteroatoms. It is colorless, slightly viscous liquid with a melting point of 2 °C, and a boiling point of 227-228 °C. The density of benzothiazole is 1.238 g/ml (25 °C). It is a heterocyclic organic compound. Benzothiazole has no household use. It is used in industry and research.

By analogy to the synthesis of benzoxazoles, benzothiazoles are obtained by cyclocondensation of o-aminothiophenols or their salts with carboxylic acids, their derivatives or with aldehydes\(^1\):

![Chemical structure of benzothiazole]

This reaction proceeds by way of the isolable o-(acylamino) thiophenols as intermediates. N-Arylthioamides can be cyclized oxidatively to give benzothiazoles:

Benzothiazole \((pK_a = 1.2)\) is a weaker base than thiazole \((pK_a = 2.52)\). Butyllithium metallates in the 2-position and haloalkanes produce the quaternary 3 alkyl benzothiazolium salts. Electrophilic substitutions occur only on the benzene ring. For instance, nitration with nitrating acid at room temperature yields a mixture of 4-, 5-, 6-, and 7-nitrobenzothiazole.
2-Alkylbenzothiazoles, like 2-alkythiazoles, are CH-acidic. They are deprotonated by \( \text{butyllithium} \) in THF at \(-78^\circ\text{C}\). The lithium compounds react with aldehydes or ketones giving alcohols, e.g.:

Luciferin, which occurs in fireflies and glowworms, upon enzymatic oxidation causes bioluminescence in these insects. The herbicide Benazoline serves as an example of a synthetic benzothiazole derivative with biological activity. Polymethine dyes derived from benzothiazoles are employed for the spectral sensitization of photographic emulsions.

2.2.2. Biological Profile
2.2.2.1. Anticonvulsant
Amnerkar et al. synthesized a series of 6-substituted-2-[(1-acetyl-5-substituted)-2-pyrazolin-3-yl] aminobenzothiazole (I) using appropriate synthetic route and evaluated experimentally against maximal electroshock test. Selected compounds were evaluated for neurotoxicity, hepatotoxicity and behavioral study. The most active compound, 6-methyl-2-[(1-acetyl-5-(4-chlorophenyl))-2-pyrazolin-3-yl]aminobenzothiazole exhibited an ED\(_{50}\) of 25.49 mmol/kg, TD\(_{50}\) of 123.87 mmol/kg and high protective index (PI) of 4.86 compared to standard drug phenytoin.
New (2/4-substituted) benzaldehyde (2-oxobenzothiazolin-3-yl) acetohydrazones (2) were prepared and their anticonvulsant activities were tested by Cakir et al. \(^5\) using pentylentetrazole induced seizure test. Some compounds were found to be the most promising among the others.

\[
\begin{align*}
\text{R} &= \text{H, 2-Cl, 4-Cl, 2-CH}_3, \text{4-CH}_3, \text{2-OCH}_3, \text{4-OCH}_3, \text{2-OH} \\
&\quad \text{4-OH, 2-F, 4-F, 4-OCH}_3, \text{4-Br, 4-NO}_2, \text{4-N(CH}_3)_2
\end{align*}
\]

A series of \(N\)-(6-substituted-1, 3-benzothiazol-2-yl)-4[([substituted amino) carbonothionyl] amino] benzenesulfonamides (3) and \(N\)-(4-substituted phenyl)-4-\{[substituted aminocarbonothionyl] amino\} benzenesulfonamides was synthesized by Siddiqui et al. \(^6\) in good yield and evaluated for their possible anticonvulsant activity and neurotoxic study. Majority of the compounds were active in MES and scPTZ tests. All the compounds were less toxic than the standard drug phenytoin.

\[
\begin{align*}
\text{R} &= \text{Cl, Br, NO}_2; \text{R}_1 = \text{alkyl, aryl}
\end{align*}
\]

Siddiqui et al. \(^7\) prepared a series of 1, 3-benzothiazol-2-yl semicarbazones (4) and evaluated for their anticonvulsant, neurotoxicity and other toxicity studies. Majority of the compounds were active in MES screen. Selected compounds were checked for their lipophilic character.

\[
\begin{align*}
\text{R} &= \text{H, Cl, Br, NO}_2 \\
\text{R}_1 = \text{H, CH}_3, \text{R}_2 = \text{H, CH}_3, \text{Cl, Br}
\end{align*}
\]
Rana et al.\(^8\) reported a series of 1,3-benzothiazol-2-yl benzamides (5) that were prepared and evaluated for their anticonvulsant, neurotoxicity, CNS depressant study and other toxicity studies. Majority of the compounds were active in MES and scPTZ screen and showed the decrease in the immobility time. None of the compounds had shown neurotoxicity or liver toxicity.

![Chemical structure](image1)

\[ R = \text{Br, Cl, F, NO}_2, \text{CH}_3, \text{OCH}_3 \]
\[ R_1 = \text{H, 2-Cl, 4-Cl, 4-OCH}_3 \]

Yoggeswari et al.\(^9\) synthesized various 6-substituted benzothiazolyl-2-thiosemicarbazones (6, 7) for anticonvulsant activity screening in maximal electroshock induced seizure (MES) and subcutaneous pentylenetetrazole (scPTZ) induced seizure models in mice. 6-methyl benzothiazolyl-2-thiosemicarbazone showed anticonvulsant activity in both mice i.p. and rat oral MES screen. 6-nitro benzothiazolyl thiosemicarbazone derivative emerged as the most promising one with anti-MES activity in mice i.p., rat i.p. and rat p.o. evaluations. All the compounds exhibited lesser or no neurotoxicity compared to phenytoin. The isatinimino derivatives had shown better activity when compared to the benzylidene or acetophenone derivatives.

![Chemical structure](image2)

\[ R = \text{NO}_2, \text{CH}_3, \text{OCH}_3 \]
\[ R_1 = \text{H, CH}_3, \text{C}_6\text{H}_5 \]
\[ R_2 = \text{2-Cl, 4-N(CH}_3)_2, \text{2-OH, 4-NO}_2 \]
\[ 4-\text{NH}_2, 4-\text{OH, 4-Br} \]

A number of benzothiazole derivatives were evaluated for anticonvulsant activity and found to possess significant activity against various types of seizures. In the search of new anticonvulsant agents having benzothiazole nucleus, Jimonet et al.\(^10\) synthesised
a lot of substituted 2-benzothiazolamines (8). All these compounds were found to possess significant activity.

\[
\text{R} = \text{CH}_3, \text{C}_2\text{H}_5, \text{n-prop, i-prop, n-but, n-pent, t-pent, OCH}_2\text{, OCH}_3, \text{CF}_3, \text{C}_2\text{H}_5
\]

2.2.2. Analgesic

A series of substituted analogues based on the novel 4H-thieno[2′,3′:4,5]pyrimido[2,1-b]benzothiazole(9) and 4H-thieno[2′,3′:4,5]pyrimido[2,1-b]benzoxazole(10) ring systems was synthesized by Russo et al 11. The compounds were obtained by reaction of 2-amino-3-carbethoxy-4,5-disubstituted thiophenes with 2-chlorobenzothiazole and 2-chlorobenzoxazole, respectively. Starting from 2 carbomethoxy-3-aminothiophene, 11H-thieno[3′,2′:4,5] pyrimido[2,1-b]-benzothiazol-11-one and 11H-thieno[3′,2′:4,5] pyrimido[2,1-b] benzoxazol-11-one were prepared in the same way. Synthesized compounds were evaluated for their potential analgesic activity in phenylquinone-induced writhing test in mice and for their potential antiinflammatory activity in carrageenan-induced rat-paw oedema test, in acetic-acid peritonitis assay and in croton oil-induced mouse-ear oedema test. 9,10,11,12-Tetrahydro-12H-benzothieno[2′,3′:4,5]pyrimido[2,1-b]benzoxazol-12-one was the most active derivative in the series in all performed tests. It showed remarkable analgesic and antiinflammatory activities associated with an excellent gastric tolerance.

\[
\text{R} = \text{H, CH}_3, -(\text{CH}_2)_4; \text{R}_1 = \text{H, CH}_3, -(\text{CH}_2)_4; \text{C}_6\text{H}_5, \text{COOC}_2\text{H}_5
\]

A benzothiazole-derived compound (11a) designed to mimic the Ca–Cb bond vectors and terminal functionalities of Lys2, Tyr13 and Arg17 in x-conotoxin GVIA was synthesized by Baell et al. 12, together with analogues (11b–d), which had each side-
chain mimic systematically truncated or eliminated. The affinity of these compounds for rat brain N-type and P/Q-type voltage gated calcium channels (VGCCs) was determined. In terms of N-type channel affinity and selectivity, two of these compounds (11a and 11d) were found to be highly promising, first generation mimetics of x-conotoxin. The fully functionalised mimetic (11a) showed low Lm binding affinity to N-type VGCCs (IC50 ¼1.9 lM) and greater than 20-fold selectivity for this channel sub-type over P/Q-type VGCCs, whereas the mimetic in which the guanidine-type side chain was truncated back to an amine (4d, IC50 ¼ 4.1 lM) showed a greater than 25-fold selectivity for the N-type channel.

\[
\begin{align*}
\text{a} & = R_1 = \text{OH}; \quad R_2 = (\text{CH}_2)_3 \text{NH}_2; \quad R_3 = N=C(\text{NH}_2)_2 \\
\text{b} & = R_1 = \text{H}; \quad R_2 = (\text{CH}_2)_3 \text{NH}_2; \quad R_3 = N=C(\text{NH}_2)_2 \\
\text{c} & = R_1 = \text{OH}; \quad R_2 = \text{CH}_3; \quad R_3 = N=C(\text{NH}_2)_2 \\
\text{d} & = R_1 = \text{OH}; \quad R_2 = (\text{CH}_2)_3 \text{NH}_2; \quad R_3 = \text{NH}_2
\end{align*}
\]

2.2.2.3. Anticancer

A series of benzothiazole and benoxazole linked pyrrolobenzodiazepine conjugates (12) attached through different alkane or alkylamide spacer was prepared by Kamal et al. 13 Their anticancer activity, DNA thermal denaturation studies, restriction endonuclease digestion assay and flow cytometric analysis in human melanoma cell line (A375) were investigated. One of the compounds of the series 12d showed significant anticancer activity with promising DNA-binding ability and apoptosis caused G0/G1 phase arrest at sub-micromolar concentrations. To ascertain the binding mode and understand the structural requirement of DNA binding interaction, molecular docking studies using GOLD program and more rigorous 2 ns molecular dynamic simulations using Molecular Mechanics-Poisson–Boltzman Surface Area (MM-PBSA) approach including the explicit solvent were carried out. Further, the compound 12d was evaluated for in vivo efficacy studies in human colon cancer HT29 xenograft mice.
Havrylyuk et al.\textsuperscript{14} performed antitumor screening of several novel 4-thiazolidinones with benzothiazole moiety. Reactions of (benzothiazole-2-yl) hydrazine with trithiocarbonyl diglycolic acid or 6-methyl-2-aminobenzothiazole with 2-carbethoxymethylthio-2-thiazoline-4-one have yielded starting 3- or 2-substituted 4-thiazolidinones which have been subsequently utilized in a Knoevenagel condensation for obtaining a series of 5-arylidene derivatives. The structures of compounds have been determined by $^1$H, $^{13}$C NMR, IR and X-ray analysis. \textit{In vitro} anticancer activity of the synthesized compounds was tested by the National Cancer Institute and two of them have revealed the anticancer activity on leukemia, melanoma, lung, colon, CNS, ovarian, renal, prostate and breast cancers cell lines. Among tested compounds, 2-\{2-\[3-(benzothiazol-2-ylamino)-4-oxo-2-thioxothiazolidin-5-ylidenemethyl]-4-chlorophenoxy\}-N-(4-methoxyphenyl)-acetamide (13) was found to be the most active candidate with average logGI$_{50}$ and logTGI values $-5.38$ and $-4.45$ respectively.

Wang et al.\textsuperscript{15} synthesised a series of novel benzothiazole-2-thiol derivatives (14) for their anti proliferative activities on HepG2 and MCF-7 cells. Most compounds had inhibitory effects on cell growth, and some of them were more effective than cisplatin. Compounds 14m and 14t displayed good inhibitory activities against a panel of different types of human cancer cell lines, with IC$_{50}$ values in the low micromolar
range. Further biological evaluation indicated that 6m induced apoptosis in HepG2 cancer cells. Structure–activity relationships were also proposed.

\[
\begin{align*}
\text{R}^1 & = \text{H, Phenyl, 4-Chlorophenyl, 4-Methoxyphenyl;} \\
\text{R}^2 & = \text{Phenyl, 4-Chlorophenyl, 4-Methoxyphenyl, Methyl, Chloromethyl}
\end{align*}
\]

Saeed et al.\textsuperscript{16} synthesized five series of thiourea derivatives bearing benzothiazole moiety (15) using tetrabutyl ammonium bromide (TBAB) as phase transfer catalyst and evaluated for anticancer activity. In preliminary MTT cytotoxicity studies, the thiourea derivatives were found to be most potent. In MCF-7 and HeLa cells, the IC\textsubscript{50} values were observed in the range of 18–26 μM and 38–46 μM, respectively.

\[
\begin{align*}
\text{R} & = \text{H, NO}_2, \text{NH}_2, \text{Br} \\
\text{R}_1 & = \text{4-NO}_2\text{C}_6\text{H}_4, 2\text{-thiophene, phenyl, n-butyl}
\end{align*}
\]

2.2.2.4. Antiviral

The identification of a novel hit compound (16) as integrase binding inhibitor has been accomplished by means of virtual screening techniques by Mugnaini et al.\textsuperscript{17} A small family of structurally related molecules has been synthesized and biologically evaluated with one of the compounds showing an IC\textsubscript{50} = 12 nM.
The replacement of \( t \)-butylurea moiety by benzothiazole sulfonamide was showed by Nagarajan et al.\(^\text{18}\) provided protease inhibitors with improved potency and antiviral activity since the inhibitors incorporated a variety of isosteres including the hydroxyethylurea (17) at the protease cleavage site. Some of the compounds had shown good oral bioavailability and half-life in rats. The synthesis of benzothiazole derivatives led them to explore other heterocycles. During the course of their studies, they also developed an efficient synthesis of benzothiazole-6-sulfonic acid via a two-step procedure starting from sulfanilamide.

![Chemical structure of compound 17](image)

Vicini et al.\(^\text{19}\) synthesized a series of benzothiazole (18) and tested \textit{in vitro} with the aim of identifying novel lead compounds active against emergent and re-emergent human and cattle infectious diseases (AIDS, hepatitis B and C, tuberculosis, bovine viral diarrhoea). In particular, these compounds were evaluated \textit{in vitro} against representatives of different virus classes, such as a HIV-1 (Retrovirus), a HBV (Hepadnavirus) and the single-stranded RNA+ viruses Yellow fever virus (YFV) and Bovine viral diarrhoea virus (BVDV), both belonging to Flaviviridae. Title compounds were also tested against representatives of Gram-positive and Gram-negative bacteria (Staphylococcus aureus, Salmonella spp.), various atypic mycobacterial strains (Mycobacterium fortuitum and Mycobacterium smegmatis), yeast (Candida albicans) and mould (Aspergillus fumigatus). The benzothiazole compounds showed a marked cytotoxicity (CC50=4–9 mM) against the human CD4+ lymphocytes (MT-4) that were used to support HIV-1 growth. For this reason, the most cytotoxic compounds of this series were evaluated for their antiproliferative activity against a panel of human cell lines derived from haematological and solid tumors.
2.2.2.5. Antimicrobial

As benzothiazole has proven to be a good antimicrobial agent, a novel series of Schiff bases of benzothiazole derivatives were synthesized by Soni et al.\textsuperscript{20} Thus condensation of 5-[2-(1,3-benzothiazol-2-yl-amino)ethyl]-4-amino-3-mercapto-(4\textit{H})-1,2,4-triazole 5 with appropriate aromatic aldehydes afforded 5-[2-(1,3- benzothiazol-2-yl-amino)ethyl]-4-(arylideneamino)-3-mercapto-(4\textit{H})-1,2,4-triazoles (19). Structures of the synthesized compounds were elucidated on the basis of elemental analyses and spectral data. All the synthesized compounds were screened for their antimicrobial activity.

Bondock et al.\textsuperscript{21} used enamino nitrite as a key intermediate for the synthesis of polyfunctionally substituted heterocycles (e.g. pyrazoles, isoxazole, pyrimidines, thiazolo[3,2-\textit{a}]pyrimidine, tetrazolo[1,5-\textit{a}]pyrimidine, pyrido[1,2-\textit{a}]pyrimidine, 1,5-benzodiazepine, and pyrazolo[1,5-\textit{a}]pyrimidine) incorporating benzothiazole moiety (20) via its reactions with some \textit{N}-nucleophiles. The newly synthesized compounds were characterized by IR, \textsuperscript{1}H NMR and mass spectral studies. Representative compounds of the synthesized products were tested and evaluated as antimicrobial agents.
Patel et al. 22 prepared a novel series of Schiff bases (21) and 4-thiazolidinones (22) from the building blocks 2-chloro pyridine-3-carboxylic acid and 2-amino-6-methoxy-benzothiazole. All of the synthesized compounds have been confirmed by elemental analyses, IR, 1H NMR and 13C NMR spectral data. These newly synthesized compounds were screened for their antimicrobial activity. Variable and modest activity was observed against the investigated strains of bacteria and fungi, however, compound 22h revealed significant antibacterial activity against Escherichia coli. Compounds 21c, 21g and 21h, on the other hand, revealed potent antifungal activity against Candida albicans compared to the reference drug greseofulvin.

\[
\text{R} = \text{H, 4-OH, 2-Cl, 2-NO}_2, 4-\text{OCH}_3, 4-\text{Cl, 3-OCH}_3-4-\text{OH}, 3-\text{OCH}_3-4-\text{OH-5-NO}_2, 4-\text{NO}_2\text{C}_4\text{H}_3\text{O (Furyl)}}
\]

Desroy et al. 23 synthesized some newer benzothiazole incorporated oxazolyl pyrazole derivatives (23) as inhibitors of bacterial heptose synthesis. HldE being a bifunctional enzyme involved in the synthesis of bacterial heptoses was inhibited by the synthesized compounds. They developed a biochemical assay suitable for high-throughput screening that allowed the discovery of inhibitors of HldE kinase. Study of the structure–activity relationship of this series of inhibitors led to highly potent compounds.
Oren et al. \(^{24}\) synthesised a series of multisubstituted benzoxazoles, benzimidazoles, and benzothiazoles \((24)\) as non-nucleoside fused isosteric heterocyclic compounds was synthesized and tested for their antibacterial activities against various Gram-positive and Gram-negative bacteria and antifungal activity against the fungus *Candida albicans*. Microbiological results indicated that the synthesized compounds possessed a broad spectrum of activity against the tested microorganisms at MIC values between 100 and 3.12 \(\mu g/ml\). Structure–activity relationships (SAR) studies revealed that benzothiazole ring system enhanced the antimicrobial activity against *Staphylococcus aureus*. In these sets of non-nucleoside fused heterocyclic compounds electron withdrawing groups at position 5 of the benzazoles increased the activity against *C. albicans*.

![Chemical structure](image)

Novel FabK inhibitors with antibacterial activity against *Streptococcus pneumoniae* were synthesized and evaluated by Kitagawa et al. \(^{25}\). Through SAR studies of our initial hit compound \(2-(1H\text{-}benz[d]imidazol-2-ylthio})-N-(6-methoxycarbonylbenzo[d]thiazol-2-yl)acetamide\), a series of novel phenylimidazole \((25)\) derivatives were discovered as potent FabK inhibitors.

![Chemical structure](image)

Zitouni et al. \(^{26}\) synthesised some \(2-[(\text{benzazole-2-yl}) \text{thioacetylamino}] \text{thiazole derivatives (26)}\) by reacting 4-methyl-2-(chloroacetylamino) thiazole derivatives with benzazol-2-thiole in acetone in the presence of \(K_2CO_3\). The chemical structures of the compounds were elucidated by \(^1H\) NMR and FAB+-MS spectral data. The prepared compounds were tested for antimicrobial activity and toxicity.
2.2.2.6. Antimycobacterial

Patel et al. 27 condensed 2-(3-pyridyl)-5-(4-methylphenyl)-1, 3, 4-oxadiazole with various substituted 2-hydrazino benzothiazole results in 3-(3-pyridyl)-5-(4-methylphenyl)-4-(N-substituted-1,3-benzothiazol-2-amino)-4H-1,2,4-triazole (27) analogs. All the compounds have been characterized by elemental analysis, IR, \(^1\)H NMR, \(^13\)C NMR and mass spectral data. In vitro antitubercular activity was carried out against Mycobacterium tuberculosis H37Rv strain using Lowenstein-Jensen medium and antimicrobial activity against various bacteria and fungi using broth microdilution method. Compounds with substituents 6-F, 6-Br, 6-NO\(_2\), 6-CH\(_3\), 4-CH\(_3\), 4-NO\(_2\), 5-Cl, and 6-Cl emerged as promising antimicrobials. It was also observed that the promising antimicrobials have proved to be better antituberculars. Compound with substituent 4-Cl showed better antitubercular activity compared to rifampicin.

Novel 3-nitro-2-(sub)-5,12-dihydro-5-oxobenzothiazolo[3,2-\(\alpha\)]-1,8-naphthyridine-6-carboxylic acids (28) have been reported by Dinakaran et al. 28 from 2,6-dimethoxynicotinic acid and 2-aminothiophenol and evaluated for their antitubercular activity in vitro and in vivo against Mycobacterium tuberculosis H\(_{37}\)Rv (MTB) and multi-drug resistant M. tuberculosis (MDR-TB). Among the synthesized compounds, 2-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-nitro-5,12-dihydro-5-oxobenzothiazolo[3,2-\(\alpha\)]-1,8-naphthyridine-6-carboxylic acid was found to be the most active compound in vitro with MIC of 0.19 and 0.04 \(\mu\)M against MTB and MTR-TB, respectively. One of
the compounds showed promising activity against MDR-TB and was 208 and 1137 times more potent than gatifloxacin and isoniazid, respectively. In the in vivo animal model it decreased the mycobacterial load in lung and spleen tissues with 2.81 and 4.94-log₁₀ protections, respectively, at a dose of 50 mg/kg body weight.
2.2.3. References:


19. P Vicini; A Geronikaki; M Incerti; B Busonera; G Poni; CA Cabrasc; PL Collac. ‘Synthesis and Biological Evaluation of Benzo[d]isothiazole,


27. NB Patel; IH Khan; D Smita; Rajani. ‘Pharmacological evaluation and characterizations of newly synthesized 1,2,4-triazoles’, *Eur. J. Med. Chem.*, **2010**, 45, 4293-4299.

2.3. Isatins

2.3.1. Chemistry

Isatin or 1H-indole-2,3-dione is an indole derivative. The compound was first obtained by Erdman and Laurent in 1841 as a product from the oxidation of indigo dye by nitric acid and chromic acids. The compound is found in many plants. Schiff bases of isatin are investigated for their pharmaceutical properties. It was observed that isatin forms a blue dye if it is mixed with sulfuric acid and crude benzene. The formation of the blue indophenin was long believed to be a reaction with benzene. Victor Meyer was able to isolate the substance responsible for this reaction from benzene. This new heterocyclic compound was thiophene.

Isatin, an indole derivative, is a yellow to red needle crystalline solid; soluble in hot water; melting point 198-204 °C. It is a hetero bicyclic aromatic compound with diketone at 2 and 3 positions. Isatin class compounds are mainly used as raw material in dye manufacturing (artificial indigo, disperse dye yellows). It has lactam (a cyclic amide) structure which is an important part of antibiotics, such as penicillin. Cyclic ester structures are active nucleuses in pharmacological activity and flavorings. They are used as intermediates for the synthesis of pharmaceuticals, herbicides, and other chemical compounds.

Isatin is commercially available. It may be prepared from cyclicizing the condensation product of chloral hydrate, aniline and hydroxylamine in sulfuric acid. This reaction is called the Sandmeyer isonitrosoacetanilide Isatin Synthesis and discovered by Traugott Sandmeyer in 1919.
2.3.2. Biological Profile

2.3.2.1. Antimicrobial

Synthesis of 2-[1-(5,8-dihydro qinoxalino[2,3-b] indolo acetyl)-3(1-benzofuran-2-yl)-4,5-dihydro-1H-pyrazol-5-yl]phenyl derivatives (1) were reported by Manna et al.\(^1\) The synthesized compounds 1a, 1b, 1c showed good antimicrobial activity and MIC were found below 10 µg/mL against *E. coli* (10.0, 5.0, and 8.0), *P. aereuginosa* (5.0, 10.0, and 9.5) and *S. aureus* (7.5, 8.5 and 2.5).

![Structure 1](image1)

Synthesis of some new triazine derivatives (2) were reported by Pandeya et al\(^2\). All the synthesized compounds 2a-f were tested for their antimicrobial activity against 20 strains of gram negative and gram positive bacteria. Among the compounds tested, the compound 2d and 2e showed good antimicrobial activity in comparison to the standard Suphamethoxazole. Compound 2e was found to be most active in series against *H. Pyloria* with MIC 25 µg/mL.

![Structure 2](image2)

Synthesis of several new spiro indoline–based heterocycles (3) was reported by Abdelrahman et al\(^3\). The synthesized compounds 3a, 3b, 3c, 3d showed comparable activity in which 3b, 3c revealed very high activity against *S. subtilis* (65.0, 75.0, 66.0, 42), *E. coli* (54.0, 59.0), and *A. niger* (85.0, 70.0, 63.0, 58.0) with respect to the used references Ampicillin and chloramphenicol.
Synthesis of new 1-alkyl/cyclohexyl-3, 3-diaryl-1’-methyl-spiro [azetidine-2, 3’-indoline]–2’, 4-diones (4) were reported by Singh et al. The synthesized compounds 4a, 4b, 4c showed the activity against the bacterial strains in which 4b with two 4-methyl phenyl group showed activity against bacterial strains, \textit{B. subtilis}, \textit{P. aeruginosa}, and \textit{S. aureus}.

Synthesis of some new isatin derivatives (5) were reported by Patel et al. The synthesized compounds 5(i-v) showed antimicrobial activities which were done by disc diffusion technique which is shown in Fig.2. Among the compounds tested, the compound with 5-Br substitution showed the most favorable antimicrobial activity against \textit{A. niger}, \textit{C. albicans}.
Synthesis of 3, 4'-dihydro-3-[2'-mercaptothiazolidine] indol-2-ones derivatives (6) were reported by Pardasani et al.\(^6\). Synthesized compounds 6a, 6b, 6c showed moderate activity against *E. coli, S. facralus, R. solani* and *F. solani*.

The synthesis and antibacterial activity of two spiro [indole] thiadiazole derivatives (7) were reported by Olomola et al.\(^7\). The compound was tested for antibacterial activity against gram positive and gram negative bacterial strains. Compound showed activity against 4-gram positive and 3-gram negative bacterial strains (better activity than streptomycin, the reference standard).

Synthesis of Mannich bases of norfloxacin with formaldehyde and several isatin derivatives (8) were reported by Pandeya et al.\(^8\). The synthesized compounds 8(i-v) were evaluated for their *in vitro* antibacterial activity against many pathogenic bacterial strains (*S. typhimurium, V. paraahaemolyticus, V. cholerae*0139 etc.). The
compound 8-iii (3.7 times) and 8-iv (4.8 times) were more active (0.018-0.61µg/mL) to that of norfloxacin (1.22 µg/mL) against *B. subtilis*.

\[ \text{R}= \text{H, Cl, Br, H, Cl} \]

\[ \text{R}= \text{H, Cl, Br, H, Cl} \]

\[ \text{R}= \text{H, Cl, Br, H, Cl} \]

\[ \text{R}= \text{H, Cl, Br, H, Cl} \]

2.3.2.2. **Anticancer**

Synthesis of substituted 1*H*-indole-2,3 diones (isatin) (9) were reported by Vine *et al*. The synthesized compounds 9a, 9b, 9c showed the greater selectivity towards leukemia and lymphoma cells over breast, prostate and colorectal carcinoma cell lines. The most active compound 5, 6, 7 tribromo-isatin (9c) shown antiproliferative at low micromolar concentration and also activated the effector capsases in a dose dependant manner.

\[ \text{R}_1= \text{O}; \text{R}_2= \text{H}; \text{R}_3= \text{Br}; \text{R}_4= \text{H, Br}; \text{R}_5= \text{Br, NO}_2; \text{R}_6= \text{H} \]

Synthesis of isatin-benzothiazole analogs (10) were reported by Solomon *et al*. The synthesized compound 4-bromo-1-diethylaminomethyl 1*H* indol-2, 3-dion emerged as most active compounds. The cytotoxic effect was 10-15 folds higher on cancer than non-cancer cells.
Synthesis of a series of functionalized isoindigos structurally related to meisoindigo (1-methylisoindigo) (11) were reported by Wee et al. 11 The synthesized compounds 11a and 11b [1-phenpropylioindigo and 1-(p-methoxy-phenethyl)-isoindigo] evaluated for antiproliferative activities on a panel of human cancer cells. These compounds were more potent than meisoindigo and comparable to 6-bromoindirubin-3’oxime on leukemic K562 and liver HuH7 cell were identified.

Synthesis of 3,5-dialkylamino substituted 8H,10H,15H, 15b(S)-2,3,6,7-tetrahydro-1,5,3-dioxazepino[3,2-c]pteridine-7-one derivatives (12) were reported by Ge et al. 12 The synthesized compounds 12a and 12b showed potential anticancer agent. Preliminary results showed that they were active as inhibitors of the growth of murine leukemia L1210 cells in vitro with IC50 values of 4-20 µM, comparable to Ellipticine (reference drug).
2.3.2.3. Antiviral

Synthesis of some new 6-(2-aminoethyl)-6-H-indolo [2, 3-b] quinoxalines (13) were reported by Shibinskya et al.\textsuperscript{13} The synthesized compounds 13(a-f) were screened for the antiviral activity. The selective index (SI) value as the integral parameter of the antiviral effectiveness was determined as the ratio of the CC\textsubscript{50} to the IC\textsubscript{50} (SI = CC\textsubscript{50}).

Synthesis of N-substituted isatin derivatives (14) were reported by Chen et al.\textsuperscript{14} The synthesized compounds 14a, 14b, 14c and d shown as potent and selective inhibitors against SARS Coronaviral 3CL Protease with IC\textsubscript{50} values ranging from 0.95 to 17.50 µM and isatin 14a exhibited more potent inhibition for SARS Coronavirus Protease.
Synthesis of $6H$-indolo [2, 3-b] quinoxaline derivatives (15) were reported by Andrieu et al\textsuperscript{15}. The synthesized compounds 15a, 15b, 15c as antiviral agents and have shown to interact with the minor groove of DNA.

\textbf{(15)}
\[ R= CH_3, CH_2CH_2NH(CH_3)_2, H \]

Synthesis of a series of benzimidazole-isatin oximes (16) were reported by Sin et al\textsuperscript{16}. The synthesized compounds 16a, 16b and 16c showed the antiviral activity and as inhibitors of respiratory syncytial virus (RSV) replication in cell culture with EC\textsubscript{50} ranging from 18 to 50 µM, with excellent HLM stability.

\textbf{(16)}
\[ R = CH_2CH_2F, CH_3CF_3, CH_2CH_3F \]
\[ R = (CH_2)_4 OH, (CH_2)_4 OH, (CH_2)_3 SO_2 CH_3 \]

The synthesis of a novel series of lamivudine prodrugs involving $N^4$-substitution with isatin derivatives (17) were reported by Sriram et al\textsuperscript{17}. The synthesized compounds 17a and 17b showed \textit{in vitro} antiretroviral activities and compound 17b was found to be equipotent to lamivudine with EC\textsubscript{50} of 0.0742 ± 0.04 µM.

\textbf{(17)}
\[ R = H, F \]
Synthesis of a series of novel substituted isatin ribonucleosides (18) were reported by Oliveira et al. Synthesized compounds showed antiviral activity on HSV-1 infected cells. Compounds 18a and 18c showed inhibitory activity and ribonucleoside 18c showed 66% inhibitory activity on HIV-1 reverse transcriptase.

\[
\begin{align*}
R_1 = \text{H, Br; } R_2 = \text{H, CH}_3, \text{ OBZ=O-benzoyl-D-ribofuranose;} \\
R_3 = \text{H, Br}
\end{align*}
\]

### 2.3.2.4. Anticonvulsant

Synthesis of a series of 2-aryl-2, 5 dihydropyridazino [4,3-b]indol-3(3H)ones (19) were reported by Palluotto et al. The synthesized compounds 19a, 19b, 19c and 19d showed anticonvulsant activity. The onsets of clonic and tonic seizures were significantly reduced 45 min. after ip. (intraperitoneal) administration of derivatives 19(a-d) and comparable with standard drug (Flumazenil).

\[
\begin{align*}
R_1 = \text{H, Br, } \text{R}_2 = \text{H, CH}_3, \text{ OBZ=O-benzoyl-D-ribofuranose;} \\
R_3 = \text{H, Br}
\end{align*}
\]

Synthesis of a series of 2-aryl -2, 5-dihydropyridazino [4, 3-b] indol-3(3H) ones (20) were reported by Campagna et al. Synthesized compounds 20a, 20b and 20c were evaluated for their good ability to prevent pentylenetetrazole (PTZ) induced seizures in mice.
Synthesis of \( N \)-aryl/alkylidene-4-(1, 3-dioxo-1, 3-dihydro-2\( H \)-isoindol-2-yl) butanoyl hydrazides/butanamides (21) were reported by Rajavendran et al\(^\text{21}\). Anticonvulsant activity was determined using four animal models of seizures which included MES, subcutaneous (sc PTZ) intraperitoneal Picritoxin (ip PIC) induced seizures threshold test. Compounds were ineffective in MES test upto 300 mg/kg and showed protection in sc PTZ screen included 21i, 21ii, and 21iii. These compounds were found to be more potent when compared to standard drug phenytoin and ethosuximide, and were effective at dose 30 mg/kg.

\[
\begin{align*}
X &= \text{H, Cl, Br} \\
\text{N} &\text{N} \\
\text{O} &\text{O}
\end{align*}
\]

\[
\text{Synthesis of} \ 3-(4\text{-chloro phenylimino})-5\text{-methyl-1, 3-dihydro-indole-2-one} \ (22) \text{ was reported by Sridhar et al} \ ^{22}. \text{ The synthesized compounds 22a, 22b, 22c were active in MES test and compound 22b was found to be most active compound and showed 87\% protection at 100 mg/kg dose level with an ED}_{50} \text{ value of 53.61 mg/kg.}
\]

\[
\begin{align*}
\text{R}_1 &= \text{2-CH}_3, \ 3\text{-Cl, R}_2 = \text{4-CH}_3, \ 2\text{-CH}_3 \\
\text{R}_3 &= \text{CH}_3, \ R_4 = \text{4-CH}_3\text{C}_6\text{H}_4
\end{align*}
\]
Synthesis of 3-cycloalkanone-3,4-hydroxy-2-oxindoles derivatives (23) were reported by Raj et al.\textsuperscript{23} Synthesized compound 23a and 23b showed the MES test and PTZ test. Compound 23a was active in PTZ seizure threshold test (PTZ), thus act as a potential anticonvulsant.

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

2.3.2.5. Antiinflammatory and Analgesic

Synthesis of a novel Schiff bases (24) were reported by Panneerselvam et al.\textsuperscript{24} The synthesized compounds were investigated for analgesic (Tail-immersion method) and anti-inflammatory (Carragenan induced paw oedema method). Among the synthesized compounds 24a-d, the compound 24b, 24c and 24d exhibited remarkable analgesic and anti-inflammatory activity when compared with standard drug (Pentazocin, 10 mg/kg, i.p. and Indomethacin 20 mg/kg).

\[
\begin{align*}
R & = \text{H, F, Cl, OCH}_3 \\
R_1 & = \text{Cl, OCH}_3, \text{NO}_2, \text{OH}
\end{align*}
\]

Synthesis of isatin derivatives (25) were reported by Mathues et al.\textsuperscript{25} The synthesized compounds 25a-f inhibited the cyclooxygenase (COX-2) enzymes in RAW 264.7 activated cells. The effect of isatin derivatives on COX-2 protein expression when compared with vehicle treated groups. The incubation of cells with isatin derivatives reduced COX-2 protein expression.

\[
\begin{align*}
R & = \text{H, 5-F, 6-Cl, 7-Cl, 4-Br, 5-I, 5-CH}_3
\end{align*}
\]
2.3.2.6. Antiplasmodial

Synthesis of a new class of 4-aminoquinoline derivatives (26) based on the natural product isatin scaffold were reported by Chiyanzu et al. The synthesized compounds were screened for biological evaluation against three strains of the malaria parasite *plasmodium falciparum*. These derivatives showed antiplasmodial IC$_{50}$ values in the ranges of 1.3 - 0.079 and 2.0 – 0.050 µM against a chloroquine – sensitive (D$_{10}$) and two resistant (K$_{1}$ and W$_{2}$) strains of *P. falciparum*. Quinoline thiosemicarbazone derivatives (26a, 26b) showed better inhibition of falcipain-2 compared to the corresponding ketones.

Kumar *et al.* designed and synthesised 3-methylene-substituted indolinones (27) as falcipain inhibitors and antiplasmodial agents are described. These compounds react readily with thiols via an addition-elimination mechanism, indicating their potential as cysteine protease inhibitors. Several indolinones containing a Leu-i-amyl recognition moiety were found to be moderate inhibitors of the *Plasmodium falciparum* cysteine protease falcipain-2, but not of the related protease falcipain-3, and displayed antiplasmodial activity against the chloroquine-resistant *P. falciparum* W2 strain in the low micromolar range. Coupling a 7-chloroquinoline moiety to the 3-methylene-substituted indolinone scaffold led to a significant improvement in antiplasmodial activity.
2.3.2.7. Antitubercular

Synthesis of various substituted ciprofloxacin derivatives (28) were reported by Sriram et al.\textsuperscript{28} The synthesized compounds 28a, 28b, 28c and 28d shown better \textit{in-vivo} antitubercular activity against \textit{M. tuberculosis} than ciprofloxacin in which compound ‘28c’ decreased the bacterial load in spleen tissue with 0.76- log10 protection and was considered to be moderately active in reducing bacterial count in spleen and compound ‘28d’ was found to be more active compound with MIC of 1.21 µM and was five times more potent than ciprofloxacin in-vitro (6.04 µM).

\[
\hat{\text{R}} = \text{H, Cl, CH}_3, \text{Br}
\]
\[
\hat{\text{R}}_1 = \text{NNHCONH}_2
\]

Aboul-Fadl \textit{et al.}\textsuperscript{29} designed and synthesised schiff bases of nalidixic acid carbohydrazide and isatin derivatives (29). Structures of the synthesized derivatives were confirmed on the bases of spectral methods of analyses. Anti-TB activity of the synthesized derivatives was investigated against four Mycobacterium strains: Mycobacterium intercellulari, Mycobacterium xenopi, Mycobacterium cheleneo and Mycobacterium smegmatis. Modest anti-TB activity was observed within the investigated compounds, however, compound 29f revealed potent anti-TB activity with MIC 0.625 mg/ml, which is 20 times greater than the reference drug isoniazid, INH, (MIC \(\frac{1}{4}\) 12.5 mg/ml). A hypothetical pharmacophore model was built using Molecular Operating Environment (MOE) program and 10 compounds structurally related to the synthesized ones with reported anti-TB activity.
Kumar et al. \(^{30}\) performed one-pot three-component domino reactions of cyclic mono ketones, isatin and sarcosine/phenylglycine furnishing highly functionalised dispiropyrrolidines in moderate yields. The reaction when performed with cyclic amino acid, proline resulted in the dimerization of azomethine ylides. These compounds have been screened for their \textit{in vitro} activity against Mycobacterium tuberculosis H37Rv (MTB) using agar dilution method. Among thirty eight compounds screened, 1-methylpyrrolo(spiro[2.30]-5-bromooxindole)spiro[3.200]-100-nitrosotetrahydro-400(1H)-pyridinone (30) was found to be the most active with MIC of 1.98 mM against MTB and was 3.86 and 25.64 times more potent than the standard first line TB drugs, ethambutol and pyrazinamide respectively.

\[
\text{R = CH}_3, \text{CH}_3, 1-\text{Chloro-4-ethylbenzene} \\
\text{R}_1 = \text{OH} \\
\text{R}_2 = \text{CH}_3, \text{H, CH}_3
\]

\[X,Y = -\text{CH}_2-\text{CH}_2-, -\text{CH}_2-\text{CH}_2-\text{CH}_2-,
-\text{CH}_2-\text{N}(\text{Me})-\text{CH}_2, -\text{CH}_2-\text{N}(\text{CH}_2\text{Ph})-\text{CH}_2; \\
\text{R} = \text{H, CH}_3, \text{Cl, Br; R}^1 = \text{H, CH(C}_3)_2
\]

2.3.2.8. \textbf{Antioxidant}

Synthesis of 3, 3-bis (4-amino-2, 5-dimethoxyphenyl)-1, 3-dihydroindol-3-one derivatives (31) were reported by Andreani et al \(^{31}\). The synthesized compounds 31a-c were evaluated with 2-methods-the Briggs-Rauscher (BR) oscillating reaction method that works in acidic conditions and the Trolox equivalent antioxidant activity (TEAC) assay working at pH=7.4 and compounds 31a-c showed good chemical antioxidant activity according to the design of these molecules that included a phenolic OH or OCH\(_3\) groups in their structure.
2.3.2.9. **Anti-HIV**

Synthesis of a series of isatin β-thiosemicarbazone derivatives (32) were reported by Bal et al.\(^{32}\). The synthesized compounds 32iii, 32iv, 32vi showed significant anti-HIV activity in HTLV-III\(_B\) strain in the CEM line where upon compound 32vi was found to be the most active compound with an EC\(_{50}\) value of 2.62 µM and selectivity index of 17.41.

![Chemical Structure of Isatin β-thiosemicarbazone Derivatives](image)

\(R = N\text{-}\text{benzyl}-N\text{-}methyl (\text{phenyl})\text{methanamine, dimethylamine, 4-methylpiperazine, 4-ethyl-7-fluoro-1,4-dihydro-6-(4-methylpiperazin-1-yl) -1-oxonaphthalene-2-carboxylic acid, 4-(4-nitrophenyl)piperazine, 1:3-(trifluoromethyl)phenyl)piperazine}

Novel oxindole derivatives bearing substituted cyclopropane ring (33) have been designed by Kumari et al.\(^{33}\) on the basis of docking studies with HIV-1 RT using the software DS 2.5 and synthesized as probable NNRTIs against HIV-1 using rhodium(II) acetate-catalyzed stereoselective cyclopropanation reaction. The cyclopropane isomer, having trans relationship with respect to carbonyl of lactam moiety and functional group on the cyclopropane ring, was the major product in all cases along with a small amount of cis and methylene products. The trans isomers interacted well with HIV-1 RT through H-bonding with amino acids, like Lys101, Lys103, His235, Tyr318, constituting the non-nucleoside inhibitor binding pocket (NNIBP) during docking experiments. However, the compounds showed very little activity when subjected to *in vitro* anti-HIV-1 screening using β-galactosidase assay (TZM-bl cells) and GFP quantification (CEM-GFP cells). The very low level of *in vitro* HIV inhibition, in comparison to predicted EC\(_{50}\) values on the basis of computational studies, during CEM-GFP screening using AZT as positive control indicated that probably the HIV RT is not the viral target and the molecules work through some different mechanism.
A series of novel 5-substituted-1-(arylmethyl/alkylmethyl)-1H-indole-2,3-dione-3-(N-hydroxy/methoxy thiosemicarbazone) analogues (34, 35) were synthesized and evaluated by Banerjee et al. 34 for their anti-HIV activity and anti-tubercular activity in both log phase and starved cultures. The compound 2-(1-{(4-(4-chlorophenyl)tetrahydropyrazin-1(2H)-yl)methyl}-5-methyl-2-oxo-1,2-dihydro-3H-indol-3-yliden)-N-(methyloxy)hydrazine -1-carbothioamide displayed promising activity against the replication of HIV-1 cells (EC50 1.69 mM). In anti-mycobacterial screening it proved effective in inhibiting the growth of both log phase (MIC 3.30 mM) and starved (MIC 12.11 mM) MTB cultures. Isocitrate lyase enzyme having momentous implication in persistent TB was shown to be inhibited by 1-cyclopropyl-6-fluoro-7-[4-{{5-methyl-3-([Z]-2-{{(methyloxy)amino}carbothioyl}hydrazono)-2-oxo-1H-indol-1(2H)-yl}methyl}tetrahydropyrazin-1(2H)-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid with 63.44% inhibition at 10 mM.
2.3.3. References


13. Shibinskya MO, Lyakhov SA, Mazepa AV, Andronati SA. Synthesis, Cytotoxicity, Antiviral activity and interferon inducing ability of 6-(2-


