INTRODUCTION

Compounds containing heterocyclic ring systems are widely distributed in nature in animal and more particularly in plant kingdom. A few heterocycles like pyridine, pyrimidine, purine, indole etc., are known to play important role in life process in the form of vitamins, hormones, nucleic acids, proteins enzymes and so on. The use of natural and synthetic heterocyclic compounds in many basic and commercially important spheres such as dyes, drugs, polymers, food flavours etc., is enormous. A book devoted entirely "Heterocycles in Life and Society" has covered to some extent, the important uses of heterocycles.

Alkaloids which have been used in the form of crude extracts in earlier systems of medicine arc nitrogen heterocycles Plant preparations used since ancient times for the treatment of several diseases are known to contain oxygen heterocyclic ring systems such as flavones, cumarins, chromones, benzofurans etc Such natural products containing heterocyclic moieties have served as lead compounds.

This has been the basis for modern drug discovery. Most or the drugs in clinical use at present belong to one or the other following types. That are Natural products isolated from plant or animal sources, Degradation products of natural compounds, Microbiologically transformed products, Biosynthetic or semisynthetic products, Chemical modification of natural products and Synthetic compounds by random synthesis or based on rational drug design.

The last approach based on structural analogy with the existing drugs is a most common approach The structural modification which includes the synthesis of prodrugs has often yielded fruitful results The existing drugs or biologically potent heterocyclic systems, if coupled properly with another heterocycle possessing well
established biological active would be of much interest to investigate their medicinal properties.

Drug and chemicals that prevent disease or assist in restoring health to disease individual. As such they play an indispensable role in modern medicine. Medicinal chemistry is that branch of science that provides thus drug either through discovery or through design.

Medicinal chemistry has undergone many changes science ancient herbalist days, but none seems to be as significant and fruitful as the rapid elucidation of molecular biochemical mechanisms of drug action achieve in the past twenty five years. Medicinal chemistry is also treated under the term pharmaceutical chemistry, molecular pharmacology, bio-organic chemistry and selective toxicity. In many countries the term medicinal chemistry and pharmaceutical chemistry are used interchangeably. In the restricted sense pharmaceutical chemistry oriented phases of drug action or availability such as the pharmacokinetics, the thermodynamics and the assay of drug in drug system.

Medicinal chemistry, according to Burger “tries to be based on the ever increasing hope that biochemical rationales for drug discovery may be found”. The chief role of the medicinal chemistry is to design and synthesize the target structures required. Medicinal chemistry is the design and synthesized the novel drug, based on an understanding of how they work at the molecular level. The advance in molecular biology and computer science are now having revolutionary influence on drug design and production. Recombinant DNA technology and new cloning methods are making great impact. Human insulin, tissue plasminogen activator and growth hormone are example of drugs manufactured by these processes. Recombinant DNA techniques are also playing important roles in studies related to receptor.
To established the structure of the drug molecules the new invention in the physiochemical direction such as X-ray crystallography different type of chromatography, in spectroscopic studies like NMR, IR, MASS, UV immensely helpful for medicinal chemist.

Pharmaceutical chemistry is a science that makes use of the general laws of chemistry to study drugs, i.e. their proportion, chemical nature, composition, influence on an organism and studies of the physical and chemical proportion of drugs, the methods of quality control and the conditions of their storage. The primary function of pharmaceutical and medicinal chemistry is still to discover new drugs, with knowledge of principles of biochemical action of design of new drug molecule.

Medicinal chemistry are practiced uncompress both definition, but finding the biochemical path way through which drug exert their beneficial effect has become a dominating activities of the medicinal chemistry. Medicinal chemistry is the application of chemical research techniques to the synthesis of pharmaceuticals. During the early stages of medicinal chemistry development scientist were primarily concerned with the isolation of medicinal agents found in plants. Today, scientist in this field are also equally concerned with the creation of new synthetic drug compounds. Medicinal chemistry is almost always geared toward drug discovery and development.

**Medicinal chemistry** is a branch of chemistry that involves aspects of biological, medical and pharmaceutical sciences. Medicinal Chemistry is concerned with the invention, discovery, design, identification and preparation of biologically active compounds, the study of their metabolism, the interpretation of their mode of action at the molecular level and the construction of structure-activity relationships.
Medicinal chemistry involves the identification, synthesis and development of new chemical entities suitable for therapeutic use. It also includes the study of existing drugs, their biological properties, and their quantitative structure-activity relationships (QSAR). Pharmaceutical chemistry is focused on quality aspects of medicines and aims to assure fitness for the purpose of medicinal products.

Pharmaceutical Chemistry is the study of the molecular and mechanistic aspects of pharmaceuticals. The discipline emphasizes the chemistry of drug design and development, drug action, drug transport, drug delivery, and targeting. The development of new pharmaceuticals is critically dependent on a molecular-level understanding of biological processes and mechanisms of drug action. Progress in the field now depends on the design and synthesis of new molecules using tools such as structure activity relationships, combinatorial chemistry, and computer-aided drug design. In recent years rational design of drugs tuned to specific target sites is becoming a reality due to concurrent advances in chemistry and biology, including elucidation of the human genome. Chemists continue to be at the forefront of drug design, synthesis, testing, and development.

The very breadth of knowledge required by a medicinal chemist is both a challenge and a reward. Mastering and understanding of such a breadth of subject areas is no straightforward task, but by the same token there is ample intellectual stimulation in understanding the battle against disease at the molecular level and in designing molecular ‘soldiers’ to win the battle.

The first successful attempts at actually designing a drug to work at a particular target happened nearly in the 1970’s with the discovery of cimetidine, a selective H2-antagonist and captopril an angiotensin converting enzyme inhibitor. Since then the art of rational drug design has undergone an explosive evolution,
making use of sophisticated computational and structural methodology to help in the effort.

A knowledge of the biological disciplines is needed to understand the complex physiological processes based on chemical and its physical reaction that occur in an organism. This makes it possible to use drugs more rationally, observe their actions on an organism, and control the molecular structure of the drugs being developed to obtain the desired pharmacological effect. The results of pharmacological tests of drugs determine the possibility of using them in medical practice.

Pharmaceutical chemistry beginned in 16\textsuperscript{th} century and gave way to iatrochemistry (Medical Chemistry) in the second half of the 17\textsuperscript{th} century, pharmacists played a major role in the birth and development of pharmaceutical chemistry. Medicinal chemistry, according to Burger, “tries to be based on the ever increasing hope that biochemical rationales for drug discovery may be found.

The first use of synthetic organic molecules for interference with the life process was probably when chloroform and ether were introduced for anesthesia in the first half of 19\textsuperscript{th} century. Phenacetin probably was the first drug to be designed as a result of knowledge of biochemical transformations. Paul Ehrlich proposed that receptors exist in mammalian cells and that both antigen and chemotherapeutic agents (a term he coined) possess heptaphoric (anchorer) and toxophoric (poisoner) group. Chemotherapeutic agent he considered, combine with receptors areas of the cell by ordinary chemical reactions, although modified to include more types of bond formation. Ehrlich concluded that drug resistance developed, when the drug was no longer absorbed by the parasite. His ideas were thus supported by experimental facts.

To establish the structure of the drug molecules the new invention in the physico-chemical directions such as X-ray crystallography different types of
chromatography, spectroscopic studies like NMR, IR, Mass, UV-Visible immensely helpful for medicinal chemist.

The approach to practice medicinal chemistry has developed from an empirical one involving organic synthesis of new compounds, based largely on modification of structures of known activity. According to Manfred Wolf present development of medicinal chemistry has renaissance, stating that: “underlying the new age is a foundation that includes explosive development of molecular biology since 1960, the advances in physical chemistry and physical organic chemistry made possible by high speed computers, and new powerful analytical methods……”. The rapid progress of organic Fluorine chemistry since 1950 has been translated as a pathfinder to invent useful biodynamic agents in Medicinal and Biochemistry. The new generation antibiotics like Norfloxacin, Ciprofloxacin, Flufoxacin were incorporated with Fluorobenzene moiety proved their efficacy as potent bioactive molecules.

Nowadays, Fluorobenzene moiety feature in diverse areas like antibacterial, anti-fungal, anti-inflammatory, psychoactive agents, pesticides, herbicides, Anticancer, NSAID, cardiovascular agents also as central muscle relaxants. The substitution of Fluorine increases lipid solubility, which is responsible to increase the transport and absorption of drug in vivo. Fluorine at or near reactive sites causes inhibition of metabolism due to high C-F bond energy.

The 2- benzothiazoles substituted found to posses broad spectrum of pharmacological activity of clinical importance in the areas of anticancer, anti-tubercular, carbonic anhydrase inhibitors, local anaesthetics, hypoglycemic agents, anti-inflammatory, anti-microbial, cardiovascular drugs, central dopaminergic agents and choleretic agents,
**Pyrazoles** are well known to have number of biological and anti-microbial activities. This include anti-inflammatory, anti-bacterial, anti-neoplastic and anti-allergic activity. Therefore in present work we have prepared pyrazoles incorporated with substituted Benzothiazole moiety.

**Thiadiazole** drugs were the first effective chemotherapeutic agents to be employed systematically for the prevention and cure of bacterial infection in human beings (eg. Sulphamethazole). They are also choice for the drug as diuretic (eg. Acetazolamide). Benzothiazole with Thiadiazole group etc. were reported to possess various pharmacological activity of clinical importance. Thiadiazole derivatives are well known to have number of biological and antimicrobial activities, this also having anti-inflammatory, and anticonvulsant activities.

In view of the above considerations the present work has been selected with tailor made approach of drug design in search of new potent bioactive drug molecules. Based on the above, the fluoro benzothiazole incorporated with **Pyrazole, Thiadiazole, Quinazolinones, Pyrazolothiazolidinones and Pyrazoloazitidinones** starting from fluorochloroaniline, in hope of getting pharmacological agents with broad spectrum of clinical importance.

We report herein the new and unreported yet the synthesis of fluoro benzothiazoles comprising thiadiazole derivatives. The chemistry and pharmacology of thiadiazoles have been of great interest because of its various biological activities, so that the biological and pharmacological activity of thiadiazole with fluoro benzothiazoles may be taken into account for synergism.
It is well known that the introduction of fluorine atom into an organic molecule causes dramatic changes in its biological profile, mainly due to high electronegativity of fluorine, the strong carbon-fluorine bond and increased solubility in lipids. Therefore it was thought worthwhile to synthesize better kinds of drugs by incorporating thiadiazole and fluorine atom in benzothiazole moiety.

In search for new bioactive potent molecule, it was thought worthwhile to incorporate some additional heterocyclic moieties in the thiadiazole nucleus and study their biological and pharmacological activity, the review of literature prompted us to synthesize substituted Fluoro benzothiazolyl thiadiazole compounds and those will be screened for antimicrobial, anti-inflammatory and anthelmintic activity to get potent bioactive molecule.
REVIEW OF LITERATURE

Introduction to Fluor benzenes

The rapid progress of organic Fluorine chemistry since 1950 has been translated as a pathfinder to invent useful biodynamic agents in Medicinal and Biochemistry.

The new generation antibiotics like Norfloxacin, Ciprofloxacin, Flufloxacin which were incorporated with Fluorobenzene moiety proved their efficacy as potent bio-active molecules.

Now a days vast number of compounds with Fluorobenzene moiety features in diverse areas like antibacterial, antifungal, anti-inflammatory, psychoactive agents, pesticides, herbicides etc.

Based on the above observations we have synthesized some Fluoro-benzothiazolo thiadiazole derivatives starting with fluorochloroaniline in hope of getting pharmacological agents with broad spectrum of clinical activity.

* R.Filler
J.Fluorine. Chem.
33, 361-375 (1986)
FLUORO BENZENE DERIVATIVES OF PHARMACOLOGICAL INTEREST*

The reasons for the increasing importance of fluorine incorporated bioactive molecules may be listed below.

a) Fluorine being the second smallest substituent next to hydrogen closely mimics hydrogen in Enzyme-receptor interactions.
b) The substitution of fluorine by hydrogen increases lipid solubility which in turn increases the transport and absorption of drug in-vivo.
c) The strong electron withdrawing, inductive effect (-I effect) of fluorine influences stability and reactivity of functional groups which may in turn influence the reactivity of neighboring reaction centers.
d) The replacement of ‘Hydrogen’ by ‘Fluorine’ at or near reactive sites causes inhibition of metabolism due to high C-F bond energy.

Some of the pharmacologically active Fluorobenzene derivatives are listed below.

1. Psychoactive properties
2. Anticonvulsant activity
3. Antibacterial and Antifungal activity
4. Dyslipidemia statins.
5. Antidepressant activity
6. Cardiovascular action.
7. Central muscle relaxant activity.
8. Anticancer activity.
9. Non Steroidal anti-inflammatory activity

* L conte., et al.,^2
J.Fluorine, chem.
70, 175-179 (1995)
1. Psychoactive agents

Fluorobenzoyl buterophenone derivatives have shown potential psychoactive properties.

![Haloperidol](image)

2. Anti-convulsants

Fluorophenyl moiety containing drugs like PROGABIDE have anti convulsant property.

![Progabide](image)

3. Anti-bacterial and anti-fungal agents.

Compounds with Fluorobenzene moiety are used as anti-bacterial and anti fungal drugs. Some of them are used as intermediates for anti-bacterial.

a) Fluorobenzoic acid derivatives were used as intermediates for anti-bacterial agent synthesis.
b) 5-Fluoro benzoic acid derivatives were used as intermediates for anti-bacterial agents.

\[
\begin{align*}
\text{F} & \quad \text{COOH} \\
\text{Cl} & \quad \text{Cl} \\
\text{2,4-dichloro-5-Fluoro benzoic acid.}
\end{align*}
\]

4. **Dyslipidemia – Statins**

The statins are the most effective and best-tolerated agents for treating dyslipidemia.

\[
\begin{align*}
\text{F} & \quad \text{OH} \quad \text{OH} \\
\text{Cerivastatin} & \quad \text{CO}_2\text{Na}
\end{align*}
\]

\[
\begin{align*}
\text{F} & \quad \text{HO} \quad \text{CO}_2\text{Na} \\
\text{Fluvastatin}
\end{align*}
\]

5. **Antidepressants – Selective Serotonin - Reuptake Inhibitors**

Citalopram acts as a Selective Serotonin - Reuptake Inhibitor

\[
\begin{align*}
\text{N≡C} & \quad \text{F} \\
(\text{CH}_2)_3\text{N(CH}_3)_2
\end{align*}
\]

(±) Citalopram

6. **Cardiovascular agents**

Phenyl cyanoguanidine derivatives shown to possess hypotensive property.

\[
\begin{align*}
\text{F} & \quad \text{NH}\text{C}≡\text{N}\text{NH}\text{C}_2\text{H}_5 \\
\text{CN} & \quad \text{CH}_3 \\
\text{Phenyl cyanoguanidine derivative}
\end{align*}
\]
7. Central Muscle relaxants

Flurorocinnamides shown central muscle relaxant activity.

![Chemical structure of 2-(3-Fluorophenyl)-N-Cyanoprop-2-yl-butyramide]

8. Anti-cancer agents

A novel 4-quinoline carboxylic derivative Dup-785 developed by Du-part company as an anticancer agent.

![Chemical structure of Dup-785]

9. Non Steroidal anti-inflammatory drugs (NSAID)

Aralkanoic acid derivatives with Fluorobenzene moiety have shown very good analgesic and anti-inflammatory activity.

![Chemical structure of FLURBIPROFEN]
2-SUBSTITUTED BENZOTHIAZOLES FOR PHARMACOLOGICAL INTEREST

The 2-Substituted Benzothiazoles found to possess broad spectrum of pharmacological activity of clinical importance.

1. Local anesthetic activity.
2. Hypoglycemic activity.
3. Carbonic anhydrase inhibitor activity.
5. Anti-cancer activity.
6. Cardiovascular action.
7. Anti-microbial activity.
8. Enzyme inhibitor activity.
10. Central dopaminergic activity.
11. Miscellaneous.
1. Local anesthetics

a) Costakes. E, Tsatsas. G\(^3\), have synthesised 2-(alkylamino acyl imino) 3-methyl benzothiazolines exhibited local anesthetic activity.

\[
\begin{align*}
  &\text{R=Me, H, } n=1,2, \text{ NR}_1\text{R}_2=\text{Piperdino, Marpholino}
\end{align*}
\]

b) Mehra S.C. Zaman. S\(^4\), synthesised alkyl/arylamino propionyl 2-amino benzothiazole and 2-amino (substituted) benzothiazole as potential local anesthetics.

\[
\begin{align*}
  &\text{NRR}_1=\text{amino, } R_2=\text{H, 4-Me, 6-Me.}
\end{align*}
\]

2. Hypoglycemic agents

a) Chernykh. V. P, Sidorenko.O.F\(^5\), have synthesised ethyl N-[6-substituted benzo-(tetrahydrobenzo) 2-thiazolyl] oxamates for hypoglycemic activity.

\[
\begin{align*}
  &\text{R=H, Me, NH, Br.}
\end{align*}
\]

3. Carbonic anhydrase inhibitors

a) Woltersdrof O.W.Jr, Schwam\(^6\), have synthesised 1-o-acyl derivatives of hydroxy benzothiazol 2-Sulfonamide as topically active carbonic-anhydrase inhibitors.

\[
\begin{align*}
  &\text{R=OH, (Me)\(_3\)CO, Ph CO\(_2\), (Me)\(_2\) NSO\(_3\).}
\end{align*}
\]
b) Scholewald, Ronald D,\textsuperscript{7} have reported sulfonamido benzothiazole derivatives as topical carbonic anhydrase inhibitors.

\[
\begin{align*}
\text{R=H, OH, Et., R}_1&=\text{H,Me,Ac.}
\end{align*}
\]

4. Antitubercular agents

a) Shieke. V.G, Bobade. A. S\textsuperscript{8}, have synthesised 2-(Substituted aryl amino)-5,6-disubstituted/6-substituted (1,3) benzothiazoles for anti-tubercular activity.

\[
\begin{align*}
\text{R }&= \text{Ph CH}_2; \text{Substituted Ph} \\
\text{R }&= \text{F} \quad \text{R}_2=\text{Cl} \\
\text{R}_1&=\text{R}_2=\text{F} \\
\text{(6-aryl substitution)}
\end{align*}
\]

b) 2-Alkylthio-6-(4-nitrobenzylidene amino) benzothiazoles were synthesised by Sidoova. E\textsuperscript{9}, and his associates for antimycobacterial activity.

\[
\begin{align*}
\text{O}_2\text{N} &- \text{C} = \text{N} \\
\text{R}&=\text{octyl}
\end{align*}
\]

c) Sidoova E\textsuperscript{10}, has synthesised 6-acetamido-2-alkylthio benzothiazoles for antimycobacterial activity.

\[
\begin{align*}
\text{ACHN} & \quad \text{SR} \\
\text{R}&=\text{alkyl, allyl}
\end{align*}
\]
d) Panday, Anil. V, Lokhande. S.R, have synthesised 2-substituted alkyl/-aryl amino-6-methyl benzothiazoles for antitubercular activity.

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{NHR} \\
\text{R} = \text{Ph, PhCH}_2
\end{align*}
\]

e) Synthesis and Tuberculostatic activity of derivatives of 2-benzothiazolo-dithiocarbamic acid by Gogh.

\[
\begin{align*}
\text{N} & \quad \text{S} \\
\text{H} & \quad \text{3C NHR} \\
\text{PhCH}_2 & \quad \text{R} = \text{Me, Et, Pr, Bu}
\end{align*}
\]

5. Anticancer agents

a) Schnus, Rodney C and co-workers, have synthesised N-(5-fluoro benzothiazol 2-yl)-2-guanidino thiazole 4-carboxamide as synthetic anti-tumor agents against Lewis lung carcinoma.

\[
\begin{align*}
\text{F} & \quad \text{NHCO} \\
\text{N} & \quad \text{N} = \text{C} \\
\text{NH}_2 & \quad \text{NH}_2
\end{align*}
\]

b) Schnus, Rodney C, Gallaschun, Randall, have reported QSAR of anti tumor guanidino thiazole carboxamides with survival enhancement for therapy in 3LL Lewis lung carcinoma model.

\[
\begin{align*}
\text{R} = \text{H, 4-Cl, 4-Me, 4-Ome.}
\end{align*}
\]
6. Cardiovascular agents

a) Mouysset Genevieve, Desaqui, Sannes, Gilbert, Yonus, Saloma\textsuperscript{14}, have reported various substituted 2-phenyl benzothiazoles for calcium channel blocking activity.

\[
\begin{array}{c}
\text{N} \\
\text{R}
\end{array}
\]

\[R = \text{Me, C(Me)}_3, \text{CH}_2\text{SH} \ldots \text{etc}\]

b) Rose, Ulrich\textsuperscript{15}, have synthesised 2-aryl substituted benzannulated ring heterocycles as potential cardiovascular agents.

\[
\begin{array}{c}
\text{X} \\
\text{N} \\
\text{R}
\end{array}
\]

\[R = \text{Substituted Ph, Pyridyl, } X=\text{S, O}\]

c) Millard, Jacques\textsuperscript{16}, have reported synthesis of amino derivatives of 4,5,6,7-tetrahydro benzothiazoles for cardiovascular activity.

\[
\begin{array}{c}
\text{R}_1
\end{array}
\]

\[R=\text{H, } R_1=4,5,6 \text{ CH}_2\text{NH}_2\]

d) Otsuka pharmaceutical company Ltd\textsuperscript{17}, reported benzothiazolinones showed cardiotonic and coronary vasodilatory activity.

\[
\begin{array}{c}
\text{R}
\end{array}
\]

\[R = \text{haloalkyl}, R_1=\text{H, haloalkyl, } R_2 = \text{H, alkenyl, alkyl}\]

e) Foscolos G, Tsabsas G\textsuperscript{18}, prepared new benzothiazole derivatives as vasodilating agents.

\[
\begin{array}{c}
\text{R}_2
\end{array}
\]

\[R=\text{H, OMe, Me, Cl, } NR_1R_2=\text{NMe}_2, \text{NEt}_2 \text{ piperzino, morpholino, } R_3 = \text{OMe, Cl, Me, OEt}\]
7. Antimicrobial agents

a) Osceigyimah Peter, Sheshba, Samuel E\textsuperscript{19}, have synthesised (4-isothiazolin-3-one-5-thio) benzothiazole as microbicides.

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

b) Trivedi, Bhavani, Sha.V.H\textsuperscript{20}, have synthesised 2(substituted benzal hydrazino carbomyl methyl thio) benzothiazoles for antimicrobial activity.

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

R=Ph, C\textsubscript{6}H\textsubscript{4}Cl\textsubscript{2}, C\textsubscript{6}H\textsubscript{4}NO\textsubscript{2}-2, C\textsubscript{6}H\textsubscript{4}OH-2

c) Mohrram H. H\textsuperscript{21}, synthesised some benzothiazole derivatives with potential antibacterial activity.

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

R = H\textsubscript{1}NO\textsubscript{2}. R\textsubscript{2} = CMe\textsubscript{2}(OH)

d) Charlecek P\textsuperscript{22}, has synthesised 2-styryl benzothiazolinium salts for antibacterial and fungicidal activity.

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

R\textsubscript{1}=Me, PhCH\textsubscript{2}, -CH\textsubscript{2}COOH., X=MeSO\textsubscript{4}, Iodo, ClO\textsubscript{4}. 
e) 2-R-3 (2-mercapto ethyl) benzothiazolines synthesised by Charlecek S\textsuperscript{22}, showed antifungal activity.
\[
\begin{align*}
\text{NCH}_2\text{CH}_2\text{SSR}_1 \\
\text{Z=NOH, NNHCONH}_2, \quad \text{R= -COOEt.}
\end{align*}
\]

f) Halgas J, Sutoris V\textsuperscript{23}, have synthesised 3,4,6-substituted benzothiazolium salts for antimicrobial activity.
\[
\begin{align*}
\text{N}^+ \text{R}_1 \\
\text{X}^- \\
\text{R=4-Me, 4-Cl., R1=Me, allyl., X=Br, Iodo.}
\end{align*}
\]

g) Sutoris V, Halgas J\textsuperscript{24}, have synthesised 3 and 2,3 substituted benzothiazolinium salts and investigated antimicrobial activity.
\[
\begin{align*}
\text{N} \text{R}_1 \\
\text{X}^- \\
\text{R=H, Me, Pr., R}_1=\text{Et, Pr, Bu.}
\end{align*}
\]

h) Synthesis of arenazo (benzylthio) benzothiazoles for fungicidal activity by Lipthay, Foltinova. P\textsuperscript{25}.
\[
\begin{align*}
\text{R}_1\text{N=N} \\
\text{S-CH}_2 \text{R} \\
\text{R=H, 4-Cl., R}_1=\text{-4-OHC}_6\text{H}_4
\end{align*}
\]
i) Sutoris V, Foltinova P\textsuperscript{26}, have synthesised 2-alkyl and 2-alkyl sulphonyl benzothiazoles for antimicrobial property.

\[
\begin{align*}
&\text{R}_1=\text{H, 4-Cl, } \text{R}_1=\text{4-OHC}_6\text{H}_4.
\end{align*}
\]

j) Sangal S. K, \textit{et al.}\textsuperscript{27} have synthesised 2-hydrazino benzothiazoles as possible anti-inflammatory agents.

\[
\begin{align*}
&\text{X}_2=\text{H}
\end{align*}
\]

k) 2-(4'-butyl-3', 5'-dimethyl pyrazol-1'-yl)-6-substituted benzothiazoles by S.P. Singh and R.K. Vaid\textsuperscript{28}, as for inflammatory agents.
8. Enzyme inhibitors

a) Greco Micheal N, Hangman William E\textsuperscript{29}, have reported benzothiazole hydroxy urea as inhibitors of 5-lipoxygenase enzyme.

\[ R_1 = \text{H, 6-Oet, 5-Cl, 5-CF}_3, 7-\text{Cl} \]

\[ R_2 = \text{OH, H, Ome., } R_3 = \text{Me, H, CH Me., n-1-3} \]

b) Sutoris V, and Co-Workers\textsuperscript{30} have synthesised 3-(2-alkoxy carbomyl-ethyl) 2-benzothiazolinones and their regulating activity on the growth of \textit{Triticum} Oestivum.

\[ R = \text{Me, Et.} \]

9. Cholerectic agents

a) Strielets L.L, \textit{et al}\textsuperscript{31}, have synthesised benzothiazolyl-2-mercaptopoacetic acid hydrazide hydrazone for cholerectic activity in rats.

\[ R = \text{NHN CHR}^1, R^1 = \text{Unsubstituted Ph.} \]
10. Central dopaminergic agents

a) Millard, Jacques\textsuperscript{32}, have synthesised amino derivatives of 4,5,6,7-tetrahydro benzothiazoles and N-Methyl amino derivatives showed central dopaminergic activity.

\[ R=\text{H, Me, Pr, R'=H, Me, Bu} \]

11. Miscellaneous

a) Caryolle R, Loiseace P\textsuperscript{33}, have synthesised 2-aryl benzothiazoles and reported anti-parasitic properties.

\[ R=C_6H_4Cl-p, C_6H_4NO_2-p. \]

b) Takeda chemical industries Ltd.\textsuperscript{34} reported benzothiazole derivatives as appetite suppressants.

\[ R=\text{H, halo., } R_1\text{CF}_3, C_6H_4, R_2=\text{H} \quad R_1=\text{H, } R_2=\text{Cl}. \]
SYNTHESIS OF FLUOROBENZENES

Organic fluorine derivatives can be synthesised by two different routes as mentioned below.

a) Construction of fluorobenzenes from less complex fluorinated precursors available commercially can be called as Tailor made approach. The precursors usually synthesised by halogen exchange reactions.

b) Synthesis of C-F bond.

a) Tailor Made Approach:

Preparation of 4-Fluorophenol and 4-Fluorobenzoic acid by Bayer willigar oxidation reaction.

In this
i) Friedal crafts acylation reaction with benzoyl or acetyl chloride on fluorobenzene to give unsymmetrical bis aryl ketone.

ii) Peracid oxidation of ketone to give an intermediate from which the ester forms via carbon to oxygen intramolecular migration.

iii) Base hydrolysis of the ester to give corresponding phenol and carboxylic acid.

b) Synthesis of C-F Bond:

The Fluorinating agents for C-F bonds can be classified as.

a) Mild Fluorinating agents.

b) Vigorous Fluorinating agents.

a) Mild Fluorinating agents: These brings about partial fluorination

Ex :- HF, KF, SbF$_3$, SF$_4$.
b) Vigorous Fluorinating agents: These comprises elemental fluorine and compounds like halogen fluorides.

Ex: - CIF₃, BrF₃, Metal fluorides such as CoF₃, AgF₂.

DESBOIS MICHEL* has prepared 4-Fluoro-3-chloroaniline from 4-halo nitrobenzene.

Procedure: A mixture of hydrogen fluoride, 2,4-dichloronitrobenzene and palladium/carbon was heated to 80°C, and at 20 bar hydrogen to get fluorochloro aniline.

*Desbios Michel³⁵.

Eur. Pat. Appl EP. 248746 (IPC CO 7C 085 / 00)

The reaction pathway is shown below:

$$\text{C}_6\text{H}_5\text{Cl} + \text{C}_6\text{H}_5\text{Cl} \xrightarrow{\text{COCl}} \xrightarrow{\text{Friedal Craft Acylation}} \text{C}_6\text{H}_5\text{C}=\text{C}_6\text{H}_5\text{OF} \xrightarrow{\text{Peracid oxidation}} \left[\text{C}_6\text{H}_5\text{C(OH)}\text{OCOCO-R}\right] \xrightarrow{1,2\text{ migration}} \text{C}_6\text{H}_5\text{COO}\text{C}_6\text{H}_5\text{F} \xrightarrow{\text{Base hydrolysis}} \text{C}_6\text{H}_5\text{COOH} \text{ and } \text{C}_6\text{H}_5\text{OH}$$

$$\text{C}_6\text{H}_5\text{COO}\text{C}_6\text{H}_5\text{F} \xrightarrow{\text{Base hydrolysis}} \text{C}_6\text{H}_5\text{COOH} \text{ and } \text{C}_6\text{H}_5\text{OH}$$

$Z=$ may be $\text{NO}_2, \text{Cl}, \text{CH}_3$ etc.
SYNTHESES OF 2-SUBSTITUTED BENZOTHIAZoles

1) Sengoden Muthusamy et al., have reported photochemical synthesis of 2-substituted Benzothiazoles.

\[ \text{N}^1(2\text{-Chlorophenyl})\text{-N, N-diphenylthiourea. Prepared from o-chlorophenyl isothiocyanate and diphenylamine was irradiated at 254nm in methylalcohol for 21 hrs.} \]

2) Ares Jeffrey J., et al., have synthesised 2-substituted benzothiazoles from 2-fluoro phenyl isothiocyanate.

\[ \text{R=Me, Bu, Ph} \]
3) V.G. Shrike., A.S. Bobade., et al.\textsuperscript{38} synthesised 2-substituted arylamino-5,6-di substituted arylamino-5,6-di substituted/6-substituted benzothiazole by 2-amino-5-fluorothiophenol with p-chlorophenyliso-thionate in presence of dry o-xylene.

![Chemical structure](image)

R=Methoxyphenyl, Ethoxyphenyl, Chlorophenyl, etc

4) Lebedenko N.Y.,\textsuperscript{39} reported the cyclization of 1-arylthio semicarbazides in presence of acid agents. Heating \( \text{P-C}_{6}\text{H}_{5}\text{NHNCSNH}_{2} \) with alkyl or arylhalides in presence of polyphosphoric acid yielded 2-amino benzothiazoles.

![Chemical structure](image)

5) Gourely R.N.,\textsuperscript{40} Synthesised 2-amino-5-fluoro-benzothiazole (III) by treating ammonium thiocyanate with benzoylchloride (I) formed suspension containing benzoyl isothiocyanate (II) which was refluxed with 3-fluoro aniline.

![Chemical structure](image)
THIADIAZOLE COMPOUNDS AND THEIR PHARMACOLOGICAL INTEREST

The thiadiazole drugs were the first effective chemotherapeutic agents to be employed systematically for the prevention and cure of bacterial infection in human beings (eg: Sulphamethizole). They are also choice for the drug as diuretic (eg: Acetazolamide). Benzothiazole with thiadiazole group etc. were reported to possess various pharmacological activity of clinical importance.

Thiadiazole derivatives are well known to have number of biological and antimicrobial activities. They are also having anti-inflammatory and anti-convulsant activities.

1) Pattan S.R, Kekare P, Dighe N.S, Nirmal S.A, Musmade D.S, Parjane S.K, Daithankar A.V have reported Synthesis and biological evaluation of some 1, 3, 4-thiadiazoles as possible antimicrobial; anti-inflammatory; antidiabetic agents.

![Chemical structure](image)

2) Vedavathi M, Somashekar B, Sreenivasa G. M, Jayachandran E have reported Synthesis, Characterization and Anti-microbial activity of Fluoro benzothiazole incorporated with 1,3,4-Thiadiazole.
R = o, m, p – methoxy

3) Mohamed Al-Omar, Omar A. Al-Deeb, Hamad A. Al-Khamees and Ali A. El-Emam\textsuperscript{43} have reported 1,3,4-thiadiazoles. Regioselective o-demethylation on dehydrative cyclisation of 1-(3,4,5- tri methoxybenzoyl)- 4- substituted thiosemicarbazides with sulphuric acid.

![Chemical structure](image)

4) Dhanya Sunil, Arun M Isloor and Prakash Shetty\textsuperscript{44} have reported Synthesis, characterization and anticancer activity of 1,2,4-Triazolo [3,4-b]-1,3,4-thiadiazoles on Hep G2 cell lines.

![Chemical structure](image)

R = Phenoxy methyl, R\textsubscript{1} = p-chloro phenyl

5) S.K. Srivastava, Smita Verma and S.D.Srivastava\textsuperscript{45} have reported Synthesis characterization and biological activity of 1, 3-thiazolidin-4- one derivatives of 2-mercapto-5-methyl-1,3,4-thiadiazole.
6) Mohd Amir, Arun Kumar, Israr Ali & S. A. Khan\textsuperscript{46} have reported Synthesis of pharmaceutically important 1,3,4-thiadiazole and imidazolinone derivatives as antimicrobials.

\[
\begin{align*}
\text{R} &= \text{Phenyl, 4-chloro phenyl, 4-nitro phenyl}
\end{align*}
\]

7) Mohammad Asif, Chhavi Asthana\textsuperscript{47} have reported 2, 4- Di substituted-5-Imino-1, 3, 4- Thiadiazole Derivatives: Synthesis and Biological Evaluation of Antiinflammatory activities.

\[
R_1, R_2, R_3, R_4 = \text{H}
\]

8) S.L. Vasoya, D.J. Paghdar, P.T. Chovatia, and H.S. Joshi\textsuperscript{48} have reported Synthesis of some New Thiosemicarbazide and 1,3,4- Thiadiazole Heterocycles Bearing Benzo[b]Thiophene Nucleus as a Potent Antitubercular and Antimicrobial Agents.
9) Rajesh Sharma, Jitendra Sainy and Subhash Chandra Chaturvedi\textsuperscript{49} have reported Synthesis of 2-Amino-5-sulfanyl-1,3,4-thiadiazoles: A new series of selective cyclooxygenase-2 inhibitors.

![Chemical structure of 2-Amino-5-sulfanyl-1,3,4-thiadiazoles]

R = Aryl

10) Jumat Salimon, Nadia Salih, Emad Yousif, Ayad Hameed and Hiba Ibraheem\textsuperscript{50} have reported Synthesis, Characterization and Biological Activity of Schiff Bases of 2, 5-Dimercapto-1,3,4-thiadiazole.

![Chemical structure of Schiff Bases of 2, 5-Dimercapto-1,3,4-thiadiazole]

R = SO$_2$NH$_2$  R$_1$ = Cl

11) Kumar Sanjeev, S. Lamani and Oblennavar Kotresh\textsuperscript{51} have reported Synthesis and Biological Activity of Some Novel 4-(5-Mercapto-1,3,4-thiadiazol-2-yl)-2-phenyl-5-[2-phenylvinyl]-2,4-dihydro-3H-1,2,4-triazol-3-one.
12) Cherkupally Sanjeeva Reddy, Lade Sanjeeva Rao and Adki Nagaraj\textsuperscript{52} have reported Synthesis and Evaluation of Novel Bis[1,2,4]triazolo[3,4-\( b \)][1,3,4]thiadiazoles as Potent Antimicrobial Agents.

\[ R = \text{COOH}, \quad \text{Ar} = \text{C}_6\text{H}_5 \]

13) Suparna Ghosh, Suman Malik, Bharti Jain and N. Ganesh\textsuperscript{53} have reported Synthesis, Characterization and Biological Studies of Zn(II) Complex of Schiff Base Derived from 5-Acetazolamido-1,3,4 - Thiadiazole-2- Sulphonamide, A Diuretic Drug.

14) Rajiv Dua and S.K. Srivastava\textsuperscript{54} have reported Synthesis, characterization and antimicrobial activity of 2-(2'-substituted - benzylidene -hydrazino -acetyl) – mercapto -5-methyl - 1, 3, 4- thiadiazoles and 2 -[2'- {4 - substituted -aryl} - 3 -

\[
\begin{array}{c}
\text{H}_3\text{C} \quad \text{SOCH}_2\text{NHN} \equiv \text{CHAr}
\end{array}
\]

Ar = Substituted aryl groups

15) Bahar Ahmed and Md.Yusuf\textsuperscript{55} have reported Synthesis of aromatic aldehyde imine derivatives of 2-thiobenzyl-1,3,4-thiadiazole and evaluation of their anticonvulsant activity.

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

R = 2-Cl, 4- Cl, 2-NO\textsubscript{2}, 4-NO\textsubscript{2}

16) Han Song Chen, Zheng Ming Li, Yu Feng Han, Zhong Wen Wang\textsuperscript{56} have reported New Fungicidally Active Pyrazolyl-Substituted 1,3,4-Thiadiazole Compounds and Their Preparation.

\[
\begin{array}{c}
\text{H}_5\text{C}_2 \quad \text{Cl} \quad \text{N} \quad \text{N} \quad \text{Cl} \quad \text{S} \quad \text{S} \quad \text{Cl} \quad \text{C}_2\text{H}_5
\end{array}
\]

17) Sabir Hussain, Jyoti Sharma and Mohd.Amir\textsuperscript{57} have reported Synthesis and Antimicrobial Activities of 1,2,4-Triazole and 1,3,4-Thiadiazole Derivatives of 5-Amino-2- Hydroxybenzoic Acid
18) Jumat Salimon, Nadia Salih, Ayad Hameed, Hiba Ibraheem, Emad Yousif have reported Synthesis and Antibacterial Activity of Some New 1,3,4-Oxadiazole and 1,3,4-Thiadiazole Derivatives.

19) A. A. Aly and R. El-Sayed have reported Synthesis and Biological Activity of New 1,3,4-Thiadiazole Derivatives.

20) M. Imtiaz Husain and Vinay Kumar have reported synthesis of 3-[2-benzothiazolyl/benzimidazolyl methyl-1,2,4-triazolo[3,4,b][1,3,4]thiadiazole-6-yl-subsituted as possible anthelmintics.
21) Q.Bano, N.Tiwari and Nizamudin\textsuperscript{61} have reported synthesis and fungicidal activity of 1,3,4-thiadiazole.

![Chemical structure](image1)

22) M.Srinivasa and G.V.S. Rama Sharma\textsuperscript{62} have reported synthesis and antinflammatory activity of 1,3,4-thiadiazole.

![Chemical structure](image2)

\[ X_1, X_2 = \text{Br, H} \]
\[ R = \text{CH}_3, \text{C}_6\text{H}_5 \]
\[ R_1 = 2'-\text{NH}_2\text{C}_6\text{H}_5 \]

23) G.V.S. Rama Sharma, Jhon Thomas, V.Murugan and K.Elango\textsuperscript{63} have reported synthesis of nicotinyl incorporated quinazolinonyl thiaidazole as possible NSAID.

![Chemical structure](image3)

\[ X_1, X_2 = \text{Br, H} \]
\[ R = \text{CH}_3, \text{C}_6\text{H}_5 \]
\[ R_1 = \text{C}_6\text{H}_5, \text{C}_3\text{H}_4\text{N} \]

24) Jag Mohan and Anupama\textsuperscript{64} have reported synthesis and antimicrobial activity of s-triazolo[3,4-b][1,3,4]thiadiazole.

![Chemical structure](image4)
25) Manjunath Ghate and D.Srinivasan have reported the synthesis and antimicrobial, anti-inflammatory activities of 1,3,4-thiadiazole derivatives.

\[
\text{Ar} = \text{C}_6\text{H}_5\text{OCH}_3, \text{CH}_2\text{OC}_6\text{H}_5\text{Cl}
\]

26) Smita Nair, S.P.Garg and Parmila Sah have reported the synthesis and antimicrobial activity of pyrazole, pyrazolones and oxadiazole bearing 2-arylamino-5-mercapto-1,3,4-thiadiazoles.

27) R.H.Udupi, S.Ramachandra Setty, N.Srinivasulu, Nandkishore Agarwal and C.V.Suresh have reported synthesis and antimicrobial, antinflammatory activities of 3,5disubstituted-s-triazolo (3,4-b)-1,3,4-thiadiazole.

28) Jag Mohan and Ashok Kumar have reported synthesis and antimicrobial activity of imidazolo[2,1-b]-1,3,4-thiadiazole.
29) V.K. Pandey and H.S. Negi\textsuperscript{69} have reported synthesis and antiviral, antifungal activities of 1-(2′diazo-5′arylalkyl-1′3′4′-thiadiazolyl)-6-methoxy benzophenothiazines.

\[ \text{H}_3\text{CO} \]

\[ \text{H} \]

\[ \text{N} \]

\[ \text{S} \]

\[ \text{R} \]

30) Jag Mohan\textsuperscript{70} has reported the synthesis and antimicrobial, diuretic activities of 3-(2-thienyl)-s-triazolo[3,4-b][1,3,4]thiadiazole.

\[ \text{S} \]

\[ \text{S} \]

\[ \text{N} \]

\[ \text{H} \]

\[ \text{N} \]

31) Venkataswarlu Pesapati and Srikat Chitty\textsuperscript{71} have reported the synthesis and antibacterial activity of 2,5-disubstituted 1,3,4-thiadiazole derivatives.

\[ \text{S} \]

\[ \text{N} \]

\[ \text{N} \]

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

\[ \text{R} = \text{R}' = \text{CH}_3 \]

32) Ishawar Singh, S. Rathod and D. Patel\textsuperscript{72} have reported the synthesis of N-(1,3,4-thiadiazole-2-yl)5-substituted-2-amino-4,5-disubstituted-thiophen-3-carboxalic acid as analgesic and anti inflammatory agent.
33) M.R. Chajed, P.B. Khendekar and A.S. Mund have reported the synthesis and free radical scavenging activity of some 1,3,4-thiadiazole derivative.

34) N.C. Desai, P.N. Shihora and D.L. Moradia have reported the synthesis and evaluation of antibacterial, antifungal activities of aryl-N-(5-{4-[2-chlorophenyl]-4-oxo(3-hydroquinazoline)}-phenyl)(1,3,4 thiaziazol-2-yl)amides.

35) Alok Kumar Srivastava, R.R. Khare and H. Singh have reported the synthesis and fungicidal activity of some 3-(5-aryl-1,3,4-thiadiazole-2-yl)-1-(β-D-glucopyra-nosyl)-5-alkyl-2-thio-4-imidazolidinones.
RESEARCH ENVISAGED AND PLAN OF WORK

Objective Of The Present Work

The literature survey reveals that 2-amino benzothiazole were reported to possess various pharmacological activities including anticancer, anti-inflammatory, antitubercular, antioxidant, antimicrobial, anticonvul sant, and analgesic activities. Benzothiazole with substitution at 7\textsuperscript{th} position has been reported to be associated with anti-inflammatory, antioxidant and antimicrobial activity.

In continuation of this work on benzothiazole, above observations promoted us to synthesize the title compounds with presumption that incorporation of amino moiety would produce new compounds with potent biological activities.
Steps involved in plan of work

- Synthesis of 2-amino benzothiazoles
- Synthesis of 2-thiosemicarbazide-6-fluoro-7-chloro(1,3) benzothiazole
- Synthesis of N-[5-(1-amino-2-phenylethyl)-1,3,4-thiadiazole-2-yl]-7-chloro-6-fluoro-1,3-benzothiazol-2-amine
- Synthesis of title compounds
- Identification and characterization
- Melting point, \( R_f \) values, Solubility
- Spectral studies

The present work was characterized by IR, NMR and Mass spectral analysis data.

Pharmacological Evaluation

- Evaluation of Anti-oxidant activity
- Anti-bacterial activity
- Anti-fungal activity
R = p-methyl, amino, 4-hydroxy, 4-carboxy

$R^1$=Tyrosine, piperazine, dietyl amine, diphenyl amine, dimethyl amine, pyrrolidine,

$\beta$-phenyl ethyl amine, napthyl amine.
EXPERIMENTAL WORK

Materials and Methods

The following experimental methods were used for the characterization of the synthetised compounds.

- Melting points of the synthesized compounds were determined in open capillary tubes and are uncorrected.
- IR spectra were recorded on ABB BOMEM FTIR spectrometer using potassium bromide pellets.
- $^1$H-NMR spectra of the compounds in deuterated dimethyl sulfoxide was recorded on BRUKER Av 400 spectrometer.
- Mass spectra were recorded on GCMS QP 5000 Shimadzu.
- Thin layer chromatography was performed using pre-coated aluminium plates, coated with silica gel GF$_{254}$ [E.Merck]. $n$-butanol : chloroform : benzene in the ratio of 1:4:1 was used as the eluent. The spots were visualized in the iodine chamber.

Methods of Synthesis

Step 1: Synthesis of 2-amino-6-fluoro-7-chloro (1,3) benzothiazole.

To glacial acetic acid (20ml) cooled below room temperature were added 8gm (0.08mol) of potassium thiocyanate and 1.45g (0.01 mol) of fluoro chloro aniline. The mixture was placed in a water bath and stirred with magnetic stirrer while 1.6ml of bromine in 6ml of glacial acetic acid was added from a dropping funnel at such a rate that the temperature never rises beyond room temperature. After all the bromine was added (105min), the solution was stirred for 2 hours below room temperature and at room temperature for 10 hours, it was then allowed to stand overnight, during which period an orange precipitate settle at the bottom, water (6ml) was added quickly and
slurry was heated at 85°C and filtered hot. The orange residue was placed in a reaction flask and treated with 10ml of glacial acetic acid heated again to 85°C and filtered hot. The combined filtrate was cooled and neutralised with ammonia solution to the pH range 6.0 A dark yellow precipitate was collected. Recrystallised from benzene, ethanol of (1:1) after treatment with animal charcoal gave yellow crystals of 2-amino-6-fluoro-7-chloro-(1,3)-benzothiazole.

---

**Step 2 : Synthesis of 2-thiosemicarbazide-6-fluoro-7-chloro (1,3) benzothiazole**

2- amino benzothiazole on reaction with carbon disulphide, ammonia with ethanol (95%) followed by addition of hydrazine hydrate yield; 2-thiosemicarbazide-6-fluoro-7-chloro (1,3) benzothiazole.

---

**Step 3 : Synthesis of N-[5-(1-amino-2-phenylethyl)- 1,3,4-thiadiazole-2-yl]-7-chloro-6-fluoro-1,3-benzoiazole-2-amine.**

2-thiosemicarbazide-6-fluoro-7-chloro (1,3) benzothiazole treated with phenyl alanine in the presence of pyridine after the cyclization it gives N-[5-(1-amino-2-phenylethyl)-1,3,4-thiadiazol-2-yl]-7-chloro-6-fluoro-1,3-benzoiazol-2-amine.
Step 4 : Synthesis of \( N-[5-(1\text{-}amino\text{-}2\text{-}phenylethyl})\text{-}1,3,4\text{-}thiadiazol\text{-}2\text{-}yl]\text{-} 6\text{-}fluoro\text{-}7\text{-}substituted\text{-}1,3\text{-}benzothiazol\text{-}2\text{-}amine \) derivatives.

\( N-[5-(1\text{-}amino\text{-}2\text{-}phenylethyl})\text{-}1,3,4\text{-}thiadiazol\text{-}2\text{-}yl]\text{-}7\text{-}chloro\text{-}6\text{-}fluoro\text{-}1,3\text{-}benzothiazol\text{-}2\text{-}amine \) was treated with various aromatic amines in the presence of N, N-dimethyl formamide (DMF) yield various \( N-[5-(1\text{-}amino\text{-}2\text{-}phenylethyl})\text{-}1,3,4\text{-}thiadiazol\text{-}2\text{-}yl]\text{-}6\text{-}fluoro\text{-}7\text{-}substituted\text{-}1,3\text{-}benzothiazol\text{-}2\text{-}amines.

\( R = p\text{-}methyl, \text{ amino, 4-} \text{hydroxy, 4-carboxy} \\
R' = \text{tyrosine, piperazine, diethyl amine, diphenyl amine, dimethyl amine, pyrrolidine, phenyl ethyl amine, naphthyl amine} \)
### LIST OF SYNTHESIZED COMPOUNDS

<table>
<thead>
<tr>
<th>S.NO</th>
<th>Compound Code</th>
<th>Structure and Chemical Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>BTD-1</td>
<td><img src="image1" alt="Structure of BTD-1" /> 2-(2-(5-(1-amino-2-phenylethyl)-2,5-dihydro-1,3,4-thiadiazol-2-ylamino)-5-fluorobenzo[d]thiazol-4-ylamino)-3-(4-hydroxyphenyl)propanoic acid</td>
</tr>
<tr>
<td>2.</td>
<td>BTD-2</td>
<td><img src="image2" alt="Structure of BTD-2" /> (N^2-(5-(1\text{-amino-2-phenylethyl})-2,5\text{-dihydro-1,3,4-thiadiazol-2-yl})-N^4-(2\text{-aminophenyl})-5\text{-fluorobenzo[d]thiazole-2,4-diamine})</td>
</tr>
<tr>
<td>3.</td>
<td>BTD-3</td>
<td><img src="image3" alt="Structure of BTD-3" /> (N^2-(5-(1\text{-amino-2-phenylethyl})-2,5\text{-dihydro-1,3,4-thiadiazol-2-yl})-5\text{-fluoro-}\text{N}^4-p\text{-tolylbenzo[d]thiazole-2,4-diamine})</td>
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<tr>
<td></td>
<td><strong>BTD-4</strong></td>
<td><img src="image" alt="Structure of BTD-4" /></td>
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<tr>
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<td>4-(2-(5-(1-amino-2-phenylethyl)-2,5-dihydro-1,3,4-thiadiazol-2-ylamino)-5-fluorobenzol[d]thiazol-4-ylamino)benzoic acid</td>
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<td>N’-(5-(1-amino-2-phenylethyl)-2,5-dihydro-1,3,4-thiadiazol-2-yl)-5-fluoro-4-(piperazin-1-yl)benzo[d]thiazol-2-amine</td>
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<td></td>
<td><strong>BTD-6</strong></td>
<td><img src="image" alt="Structure of BTD-6" /></td>
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<td>N^2,N^4-(5-(1-amino-2-phenylethyl)-2,5-dihydro-1,3,4-thiadiazol-2-yl)-N^4,N^4-diethyl-5-fluorobenzol[d]thiazole-2,4-diamine</td>
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<td>BTD-7</td>
<td><img src="image1" alt="Chemical Structure" /></td>
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<td>(N^2-(5-(1\text{-amino-2-phenylethyl})-2,5\text{-dihydro-1,3,4-thiadiazol-2-yl})-5\text{-fluoro-N}^4,N^4\text{-diphenylbenzo[d]thiazole-2,4-diamine} )</td>
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<th>BTD-8</th>
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<td>(N^2-(5-(1\text{-amino-2-phenylethyl})-2,5\text{-dihydro-1,3,4-thiadiazol-2-yl})-5\text{-fluoro-N}^4\text{-phenethylbenzo[d]thiazole-2,4-diamine} )</td>
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<th>BTD-9</th>
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<td>(4-(2-(5-(1\text{-amino-2-phenylethyl})-2,5\text{-dihydro-1,3,4-thiadiazol-2-ylamino})-5\text{-fluorobenzo[d]thiazol-4-ylamino})phenol )</td>
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<td><strong>BTD-10</strong></td>
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<td><img src="image" alt="BTD-10" /></td>
<td>[N^2-(5-(1-amino-2-phenylethyl)-2,5-dihydro-1,3,4-thiadiazol-2-yl)-5-fluoro-N^4-(naphthalen-1-yl)benzo[d]thiazole-2,4-diamine]</td>
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<td><img src="image" alt="BTD-11" /></td>
<td>[N-(5-(1-amino-2-phenylethyl)-2,5-dihydro-1,3,4-thiadiazol-2-yl)-5-fluoro-4-(pyrrolidin-1-yl)benzo[d]thiazol-2-amine]</td>
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<td><img src="image" alt="BTD-12" /></td>
<td>[N^2-(5-(1-amino-2-phenylethyl)-2,5-dihydro-1,3,4-thiadiazol-2-yl)-5-fluoro-N^4,N^4\text{-dimethyl}benzo[d]thiazole-2,4-diamine]</td>
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## VARIOUS AMINES USED

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<th>COMPOUND CODE</th>
<th>AMINES USED</th>
<th>QUANTITY TAKEN</th>
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<tbody>
<tr>
<td>BTD-1</td>
<td>Tyrosine</td>
<td>0.7gm</td>
</tr>
<tr>
<td>BTD-2</td>
<td>o-Phenylene diamine</td>
<td>0.9gm</td>
</tr>
<tr>
<td>BTD-3</td>
<td>Toluidine</td>
<td>0.7ml</td>
</tr>
<tr>
<td>BTD-4</td>
<td>p-amino benzoic acid</td>
<td>1.3gm</td>
</tr>
<tr>
<td>BTD-5</td>
<td>Piperazine</td>
<td>0.6gm</td>
</tr>
<tr>
<td>BTD-6</td>
<td>Diethyl amine</td>
<td>1.03ml</td>
</tr>
<tr>
<td>BTD-7</td>
<td>Diphenyl amine</td>
<td>1.29ml</td>
</tr>
<tr>
<td>BTD-8</td>
<td>β-Phenyl ethyl amine</td>
<td>0.62ml</td>
</tr>
<tr>
<td>BTD-9</td>
<td>4-amino phenol</td>
<td>1.2gm</td>
</tr>
<tr>
<td>BTD-10</td>
<td>Naphthyl amine</td>
<td>1.3gm</td>
</tr>
<tr>
<td>BTD-11</td>
<td>Pyrrolidine</td>
<td>0.71ml</td>
</tr>
<tr>
<td>BTD-12</td>
<td>Dimethyl amine</td>
<td>0.5ml</td>
</tr>
</tbody>
</table>
IDENTIFICATION AND CHARACTERIZATION

Introduction

The identification and characterization of the prepared compounds were carried out by the following procedure to ascertain that all the prepared compounds have different chemical nature than the respective parent compounds.

1. Melting Point,
2. Solubility,
3. Thin layer chromatography,
4. Ultra violet -visible spectroscopy [U.V-Vis],
5. Infrared spectroscopy [I.R],
6. Nuclear Magnetic resonance spectroscopy [N.M.R.] and

1. Melting Point Determination

The melting points of the organic compounds were determined by open capillary tube method.

Melting point is a valuable criterion of purity for an organic compound as a pure crystal is having definite and sharp melting point\textsuperscript{29-35}. The synthesized compounds showed a minute change in melting point after re-crystallization.

2. Solubility

The solubility of synthesized compounds were tested in arious solvents . The solubility characters were listed
3. **Thin Layer Chromatography**

Chromatography is an important technique to identify the formation of new compounds and also to determine the purity of the compound. The Rf value is characteristic for each of the compound.

**a. Preparation of Chromatoplate:**

Cleaned and dried glass plates were taken. Uniform slurry of silica Gel-G in alcohol was prepared. The slurry was then poured into the chamber of the TLC applicator, which was fixed and the thickness was set to 0.5mm. Glass plates were moved under the applicator smoothly to get a uniform coating of slurry on the plates.

The plates were dried first at room temperature and then kept in an oven for activation at 110°C for 1 hour.

**b. Preparation of solvent system and saturation of chamber:**

The solvent system used for the development of chromatogram was prepared carefully by mixing n-Butanol: Ethyl acetate: Benzene [1:4:1]

**c. Application of sample:**

The solution of the parent compounds and its target molecule were taken in small bored capillary tube and spotted at 2 cm from the base end of the plate. After spotting the plate were allowed to dry at room temperature and plates were transferred to chromatographic chamber containing solvent system for development.

**d. Development of Chromatogram:**

Plates were developed by ascending technique when solvent front had reached a distance of 10-12cm, they were taken out and dried at room temperature.

**e. Detection of spots:**

The developed spots were detected by exposing them to iodine vapours.
f. Calculation of $R_f$ Values:

The $R_f$ values of compounds were calculated using the formula.

\[
R_f = \frac{\text{Distance travelled by the sample}}{\text{Distance travelled by the solvent front}}
\]

In all the cases the distance travelled by the sample was found to be different from that of the parent compound spotted along with it. Thus it confirms the fact that the compounds formed were entirely different from that of the parent compound. Since, the sample gave a single spot; the compounds were taken to be free from impurities. The $R_f$ value of compounds were reported.
<table>
<thead>
<tr>
<th>S. No</th>
<th>Compound Code</th>
<th>MOL. FORMULA</th>
<th>MOL Wt.</th>
<th>M.P/ B.P °C</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BTD-1</td>
<td>C_{26}H_{25}FN_{6}O_{3}S_{2}</td>
<td>552.64</td>
<td>246°C</td>
<td>62.2%</td>
</tr>
<tr>
<td>2</td>
<td>BTD-2</td>
<td>C_{23}H_{22}FN_{7}S_{2}</td>
<td>479.6</td>
<td>283°C</td>
<td>61.7%</td>
</tr>
<tr>
<td>3</td>
<td>BTD-3</td>
<td>C_{24}H_{23}FN_{6}S_{2}</td>
<td>478.61</td>
<td>278°C</td>
<td>17.0%</td>
</tr>
<tr>
<td>4</td>
<td>BTD-4</td>
<td>C_{24}H_{21}FN_{6}O_{2}S_{2}</td>
<td>508.9</td>
<td>306°C</td>
<td>12.0%</td>
</tr>
<tr>
<td>5</td>
<td>BTD-5</td>
<td>C_{21}H_{24}FN_{7}S_{2}</td>
<td>457.9</td>
<td>274°C</td>
<td>28.8%</td>
</tr>
<tr>
<td>6</td>
<td>BTD-6</td>
<td>C_{21}H_{23}FN_{6}S_{2}</td>
<td>444.5</td>
<td>256°C</td>
<td>45.4%</td>
</tr>
<tr>
<td>7</td>
<td>BTD-7</td>
<td>C_{29}H_{25}FN_{6}S_{2}</td>
<td>540.68</td>
<td>289°C</td>
<td>35.8%</td>
</tr>
<tr>
<td>8</td>
<td>BTD-8</td>
<td>C_{25}H_{25}FN_{6}S_{2}</td>
<td>492.63</td>
<td>257°C</td>
<td>40.8%</td>
</tr>
<tr>
<td>9</td>
<td>BTD-9</td>
<td>C_{23}H_{21}FN_{6}OS_{2}</td>
<td>480.58</td>
<td>246°C</td>
<td>42.5%</td>
</tr>
<tr>
<td>10</td>
<td>BTD-10</td>
<td>C_{27}H_{25}FN_{6}S_{2}</td>
<td>514.64</td>
<td>213°C</td>
<td>49%</td>
</tr>
<tr>
<td>11</td>
<td>BTD-11</td>
<td>C_{21}H_{23}FN_{6}S_{2}</td>
<td>442.58</td>
<td>208°C</td>
<td>40.9%</td>
</tr>
<tr>
<td>12</td>
<td>BTD-12</td>
<td>C_{19}H_{21}FN_{6}S_{2}</td>
<td>416.5</td>
<td>274°C</td>
<td>51.2%</td>
</tr>
</tbody>
</table>
# Table No.1.2: SOLUBILITY DATA OF THE SYNTHESIZED COMPOUNDS

<table>
<thead>
<tr>
<th>Comp. Code</th>
<th>Water</th>
<th>Acetone</th>
<th>DMF</th>
<th>DMSO</th>
<th>Ethanol</th>
<th>Methanol</th>
<th>Chloroform</th>
<th>Ether</th>
<th>Ethyl acetate</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTD-1</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>BTD-2</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>BTD-3</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>BTD-4</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>BTD-5</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>BTD-6</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>BTD-7</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>BTD-8</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>BTD-9</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>BTD-10</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>BTD-11</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>BTD-12</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

‘+++’ : Freely soluble; ‘+’ Sparingly soluble; ‘-’ Insoluble
### Table No.1.3: TLC DATA OF THE SYNTHESIZED COMPOUNDS

<table>
<thead>
<tr>
<th>S. No</th>
<th>Compound Code</th>
<th>Solvent system for developing</th>
<th>Proportion of Components</th>
<th>$R_f$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BTD-1</td>
<td>n-Butanol: Ethyl acetate: Benzene</td>
<td>1:4:1</td>
<td>0.68</td>
</tr>
<tr>
<td>2</td>
<td>BTD-2</td>
<td>n-Butanol: Ethyl acetate: Benzene</td>
<td>1:4:1</td>
<td>0.72</td>
</tr>
<tr>
<td>3</td>
<td>BTD-3</td>
<td>n-Butanol: Ethyl acetate: Benzene</td>
<td>1:4:1</td>
<td>0.76</td>
</tr>
<tr>
<td>4</td>
<td>BTD-4</td>
<td>n-Butanol: Ethyl acetate: Benzene</td>
<td>1:4:1</td>
<td>0.83</td>
</tr>
<tr>
<td>5</td>
<td>BTD-5</td>
<td>n-Butanol: Ethyl acetate: Benzene</td>
<td>1:4:1</td>
<td>0.69</td>
</tr>
<tr>
<td>6</td>
<td>BTD-6</td>
<td>n-Butanol: Ethyl acetate: Benzene</td>
<td>1:4:1</td>
<td>0.78</td>
</tr>
<tr>
<td>7</td>
<td>BTD-7</td>
<td>n-Butanol: Ethyl acetate: Benzene</td>
<td>1:4:1</td>
<td>0.59</td>
</tr>
<tr>
<td>8</td>
<td>BTD-8</td>
<td>n-Butanol: Ethyl acetate: Benzene</td>
<td>1:4:1</td>
<td>0.69</td>
</tr>
<tr>
<td>9</td>
<td>BTD-9</td>
<td>n-Butanol: Ethyl acetate: Benzene</td>
<td>1:4:1</td>
<td>0.75</td>
</tr>
<tr>
<td>10</td>
<td>BTD-10</td>
<td>n-Butanol: Ethyl acetate: Benzene</td>
<td>1:4:1</td>
<td>0.71</td>
</tr>
<tr>
<td>11</td>
<td>BTD-11</td>
<td>n-Butanol: Ethyl acetate: Benzene</td>
<td>1:4:1</td>
<td>0.81</td>
</tr>
<tr>
<td>12</td>
<td>BTD-12</td>
<td>n-Butanol: Ethyl acetate: Benzene</td>
<td>1:4:1</td>
<td>0.76</td>
</tr>
</tbody>
</table>
SPECTRAL STUDIES

Ultra Violet Spectra\textsuperscript{76-80}: 

Molecular absorption in the UV-vis region of spectrum is characteristic of structures of the molecules. The UV-vis scanning of the compounds was carried and 3-chloro-4-fluoroaniline exhibited $\lambda_{\text{max}}$ at 265nm. The UV-vis spectra of 2-amino-6-fluoro-7-chloro benzothiazole exhibited $\lambda_{\text{max}}$ 303 and 288nm. This clearly indicates that the bathochromic shift of the compounds.

IR Spectra: The IR spectrum peaks gives an idea about the probable structure of the compound IR region ranges between 4000-666 cm\textsuperscript{-1}. Quanta radiation from this spectrum region corresponds to energy differences between different vibrational levels of molecules.

The compounds were recorded on SHIMADZU FTIR 8400S spectrophotometer shows different vibration levels of molecules by using KBr pellet technique.
Table No.1.4: IR SPECTRAL DATA

<table>
<thead>
<tr>
<th>Compound</th>
<th>Ar-NH ((\text{in cm}^{-1}))</th>
<th>C=N Stretching ((\text{in cm}^{-1}))</th>
<th>C=C Stretching ((\text{in cm}^{-1}))</th>
<th>C-F ((\text{in cm}^{-1}))</th>
<th>N==N</th>
<th>C-S</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTD-1</td>
<td>1323</td>
<td>1665</td>
<td>1581</td>
<td>1038</td>
<td>1581</td>
<td>1157</td>
</tr>
<tr>
<td>BTD -2</td>
<td>1313</td>
<td>1678</td>
<td>1543</td>
<td>1071</td>
<td>1632</td>
<td>1117</td>
</tr>
<tr>
<td>BTD -3</td>
<td>1330</td>
<td>1659</td>
<td>1496</td>
<td>1021</td>
<td>1609</td>
<td>1091</td>
</tr>
<tr>
<td>BTD -4</td>
<td>1298</td>
<td>1643</td>
<td>1593</td>
<td>1048</td>
<td>1593</td>
<td>1172</td>
</tr>
<tr>
<td>BTD -5</td>
<td>1335</td>
<td>1661</td>
<td>1497</td>
<td>1090</td>
<td>1609</td>
<td>1201</td>
</tr>
<tr>
<td>BTD -6</td>
<td>1336</td>
<td>1643</td>
<td>1542</td>
<td>1067</td>
<td>1602</td>
<td>1192</td>
</tr>
<tr>
<td>BTD -7</td>
<td>1306</td>
<td>1646</td>
<td>1542</td>
<td>1067</td>
<td>1590</td>
<td>1190</td>
</tr>
<tr>
<td>BTD -8</td>
<td>1332</td>
<td>1653</td>
<td>1545</td>
<td>1089</td>
<td>1614</td>
<td>1197</td>
</tr>
<tr>
<td>BTD -9</td>
<td>1342</td>
<td>1663</td>
<td>1542</td>
<td>1071</td>
<td>1603</td>
<td>1197</td>
</tr>
<tr>
<td>BTD -10</td>
<td>1310</td>
<td>1667</td>
<td>1540</td>
<td>1069</td>
<td>1608</td>
<td>1192</td>
</tr>
<tr>
<td>BTD -11</td>
<td>1332</td>
<td>1661</td>
<td>1494</td>
<td>1091</td>
<td>1621</td>
<td>1202</td>
</tr>
<tr>
<td>BTD -12</td>
<td>1334</td>
<td>1659</td>
<td>1495</td>
<td>1088</td>
<td>1629</td>
<td>1188</td>
</tr>
</tbody>
</table>
$^{1}\text{H-}\text{NMR SPECTRA}$

NMR spectroscopy enables us to record differences in magnetic properties of the various magnetic nuclei present, and to deduce in the large measure about the position of these nuclei are within the molecule. We can deduce how many different kinds of environment are there in the molecules and also which atoms are present in neighboring groups.

The proton NMR spectra enable us to know different chemical and magnetic environments corresponding to protons in molecules.

The samples are analyzed on BRUKER 300 MHz spectrometer.
TABLE NO.1.5: $^1$H-NMR SPECTRAL DATA OF SYNTHESIZED COMPOUNDS

<table>
<thead>
<tr>
<th>S. No</th>
<th>Compound code</th>
<th>No of protons</th>
<th>Hydrogens</th>
<th>∆ (ppm)</th>
<th>Multiplity</th>
<th>Solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BTD-1</td>
<td>25</td>
<td>-H-Ar-H</td>
<td>6.68 -7.42</td>
<td>Multiplet</td>
<td>DMSO</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-H-CH$_2$</td>
<td>2.88</td>
<td>Doublet</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-1H-1OH</td>
<td>5.10</td>
<td>Singlet</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-1H-NH</td>
<td>4.05</td>
<td>Singlet</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-COOH</td>
<td>10.89</td>
<td>Singlet</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>BTD-4</td>
<td>21</td>
<td>-H-Ar-H</td>
<td>6.67 -7.46</td>
<td>Multiplet</td>
<td>DMSO</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>-1H-NH</td>
<td>4.05</td>
<td>Singlet</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-H-NH$_2$</td>
<td>2.05</td>
<td>Singlet</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-COOH</td>
<td>10.80</td>
<td>Singlet</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>BTD-6</td>
<td>25</td>
<td>-H-Ar-H</td>
<td>7.08 -7.44</td>
<td>Multiplet</td>
<td>DMSO</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-H-CH$_2$</td>
<td>3.39</td>
<td>Doublet</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-1H-NH</td>
<td>4.05</td>
<td>Singlet</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>BTD-12</td>
<td>21</td>
<td>-H-Ar-H</td>
<td>7.08-7.44</td>
<td>Multiplet</td>
<td>DMSO</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-N-CH$_3$</td>
<td>2.85</td>
<td>Doublet</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-1H-NH</td>
<td>4.01</td>
<td>Singlet</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-H-CH</td>
<td>2.8-3.3</td>
<td>Doublet</td>
<td></td>
</tr>
</tbody>
</table>
MASS SPECTROSCOPY

Mass spectroscopy enables us to know;

a) Relative molecular masses (molecular weights) with very high accuracy, from this exact molecular formula can be deduced.

b) To detect within the molecule the places at which it prefers fragmentation, from this we can deduce the presence of recognizable groups within the molecule.

c) As a method of identifying analytes by comparison of their mass spectra with libraries of digitalised mass spectra of known compounds.

Spectral data:

Compound code: BTD-10

Molecular Formula: C_{27}H_{23}FN_{6}S_{2}

Calculated Molecular Weight: 514.6

Observed Molecular Weight: 514.0

M^{+} ion peak= M/Z peak = 514.0
PHARMACOLOGICAL EVALUATION

EVALUATION OF ANTI OXIDANT ACTIVITY

MATERIALS AND METHODS

The materials used were ferric chloride, EDTA, ascorbic acid, hydrogen peroxide and p-nitroso dimethyl aniline. The solvents and the other chemicals were of analytical grade.

**Instruments**

Absorbance was measured in systronic UV- Visible spectrophotometer. Centrifugation was done using REMI centrifuge machine, pH of buffer was measured in pH meter.

**Interaction with Stable Free-Radical DPPH**

Interest in the involvement of reactive oxygen species (ROS) in various disorders has been increasing. In particular, they are thought to play an important role in the development of inflammatory disorders (Halliwell and Gutteridge, 1990; Taylor and Townsley, 1986 and Flohe et al., 1985). A radical scavenging antioxidant reacts rapidly with the $p$- nitroso dimethyl aniline ($p$- NDA). Hence the ability of the test compounds to scavenge the stable free radical has been determined.

Antioxidants react with $p$-NDA and convert it to 1,1-diphenyl-2-picryl hydrazine. The change in the absorbance produced in this reaction has been used to measure the antioxidant properties. The solutions of various concentrations of drugs were added to $p$-NDA (100 µM) in DMSO and the tubes were kept at ambient temperature for 20min and the absorbance was measured at 440 nm (Kato et al.,...
The difference in absorbance between the test and the control was taken and expressed as the percent scavenging of the DPPH radical.

**Experimental Protocol**

**Antioxidant Activity by p-NDA (p-Nitroso Dimethyl Aniline) Radical Scavenging Method**

To a solution containing ferric chloride (0.1mM, 0.5ml), EDTA(0.1mM, 0.5ml), ascorbic acid (0.1mM, 0.5ml), hydrogen peroxide (2mM, 0.5ml) and p-nitroso dimethyl aniline (0.01mM, 0.5ml) in phosphate buffer (pH 7.4, 20Mm) were added various concentrations of the test compounds in distilled DMSO or dissolving solvent or alcohol to produce final volume of 3ml. Absorbance was measured at 440nm (Elizabeth and Rao, 1990).

\[
p-\text{NDA radical Scavenging activity (\%)} = \frac{[\text{Abs (sample)} - \text{Abs (standard)}]}{[\text{Abs (sample)}]} \times 100
\]
<table>
<thead>
<tr>
<th>Compound</th>
<th>% Radical scavenging method</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Concentrations mg/ml</td>
</tr>
<tr>
<td></td>
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<td>Ascorbic acid</td>
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ANTIMICROBIAL ACTIVITY

Introduction

The chemical substances which act against the microorganism are known as “antimicrobial agents”, whereas the substances which act against bacteria are called anti-bacterial agents and those which act against fungi are called anti-fungal agents. Antimicrobial agents can be obtained from both natural and synthetic methods. The production of these synthetic agents is a lengthy and expensive process.

The modern era of antimicrobial chemotherapy began in 1929 with Fleming’s discovery of powerful bactericidal substance penicillin, and Domagk’s discovery of synthetic sulfonamides with broad antimicrobial activity in 1935.

Antimicrobial agents produced by microorganisms that kill or inhibit the microorganism are known as antibiotics. A more broadened definition included any chemical of natural origin (from any type of cell) which has the effect on the growth of other type cells. Since most clinically-useful antibiotics are produced by microorganisms and are used to kill or inhibit infections of bacteria.

The increasing incidence of systematic fungal infections in hospitalized patients, coupled with the shortage of effective and safe antifungal agents have stimulated renewed research interest in search for broad spectrum antifungal agents.

Currently, soil microbes remain as the richest source of new antibiotic agents. In 1990, the world consumed literally tons of antibiotics valued in excess of 7 billion dollars more than half of these antibiotics were of the beta lactam type.
Antibacterial activity

The following conditions must be accomplished for the determination of proper antibacterial activity.

- There should be intimate contact between the test organism and substance to be evaluated.
- Microorganism should be provided with the required condition for growth.
- Measurement of activity should be done correctly.
- Aseptic environment should be maintained.
- Condition should be maintained unchanged throughout the study.

Various methods with their own advantages and limitations have been used from time to time to evaluate the antimicrobial activity of the drug. The antimicrobial activity can be evaluated by the following techniques.

- Agar streak dilution method
- Serial dilution method
- Agar diffusion method
  - Cup plate method
  - Cylinder method
  - Paper disc method
- Turbidimetric method

In the present study, the well diffusion method was used to evaluate the antimicrobial activities of the synthesized compounds in vitro. The well diffusion method is one the methods that may be used for determining the relative effectiveness of the antibacterial activity. The results obtained by this method depend not only on
the toxicity of the antimicrobial agent but also on its liability to diffuse through the medium.

The standard antibiotics used in the present study were ciprofloxacin.

**Sensitive microorganisms are**

- Gram –ve: *E.coli* and various species of *Salmonella, Shigella, Enterobacter, Campylobacter* and *Neisseria*. Ciprofloxacin is more effective than norfloxacin against *Pseudo aeroginosa*, values of MIC range from 0.5 to 6µg/ml.
- Gram +ve (less sensitive): *Streptococci, Staphylococci* and *Histeria* species.

In the present study the following bacteria were used

- *Bacillus subtilis* (ATCC 6051)
- *Staphylococcus aureus* (ATCC 12600)
- *Klebsiella pneumonia* (ATCC 13883)
- *Escherichia coli* (ATCC 11775)

The antibacterial activity of compounds (ATZ 1-12) was studied by well diffusion method. Compounds were used in the concentration of 25µg/ml, 50µg/ml, 75µg/ml and 100µg/ml using a solvent DMSO. Ciprofloxacin 50µg/ml was used as standards.

**Media used**

Nutrient Agar was used as the media for the study.

Nutrient Agar: (Composition)

<table>
<thead>
<tr>
<th>Sl. No</th>
<th>INGREDIENTS</th>
<th>QUANTITY</th>
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<tbody>
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<td>1.</td>
<td>Beef Extract</td>
<td>3 g</td>
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<tr>
<td>2.</td>
<td>Peptone</td>
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<td>3.</td>
<td>Sodium Chloride</td>
<td>5 g</td>
</tr>
<tr>
<td>4.</td>
<td>Agar</td>
<td>15 g</td>
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<td>5.</td>
<td>Distilled Water</td>
<td>Up to 1000mL</td>
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</table>
The zone of inhibition of various concentrations of the synthesized compounds against gram positive and gram negative bacteria was measured and were tabulated.

**Materials and Methods**

**Media used** - Nutrient Agar 1.5%

**Media Sterilization**

All the culture media were sterilized by autoclaving at 15 lbs/inch² corresponding to 20 min.

**Method**

Agar streak dilution method

**Preparation of agar plates with different concentrations of test compounds**

5µg/ml stock solution of the test compound were made using DMSO as the solvent. From these stock solutions, required quantities of drug solutions were mixed with the known quantities of molten sterile agar media aseptically to provide the following concentrations 25, 50 and 100µg/ml.

About 20ml of the media containing the drug was dispensed into each sterile petri-dish (diameter about 10cm). Then the media were allowed to get solidified.

**Streaking of microorganisms**

Microorganisms were then streaked one by one on the agar plates aseptically. After streaking, all the plates were incubated in the incubator, set at 37± 1°C for 24 hrs. Then the plates were observed for the growth of the microorganisms.

**Preliminary Screening**

All the compounds possess potent to moderately potent activity against gram-positive and Gram-negative bacteria.
The antibacterial activities are performed by disc plate method (disc diffusion technique). The fresh culture of bacteria are obtained by inoculating bacteria nutrient broth media and incubated at 37 ± 2°C for 18 – 24 hours. This culture mixed with nutrient agar media and poured into petri-dishes by following aseptic techniques. After solidification of the media, the plates were placed in a refrigerator for 2 hours. After two hours of cold incubation, four discs are made at equal distance by using sterile wattman paper (5 mm diameter).

Dip these discs in to different concentrations. Dimethyl sulphoxide was used as a control. After introduction of standard drugs and synthesized compounds, the plates were placed in a refrigerator for 2hrs for proper dipping of drug into the media. After 2hrs the plate were placed in an incubator and maintained at 37°C ±2°C for 18-24 hours. After the incubation period, over mean the petri-plates were observed for zone of inhibition by using vernier scale. The results evaluated by comparing the zone of inhibition shown by the synthesized compounds with standard drug.
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ANTI-FUNGAL ACTIVITY

Introduction

The antifungal activity of the synthesized compounds was studied by disc diffusion method.

The standard drug selected for antifungal activity was Fluconazole. It is orally active broad spectrum antifungal agent.

The antifungal activity of the synthesized compounds was studied against the following organisms.

1. *Aspergillus niger* (ATCC 9029)
2. *Aspergillus flavus* (ATCC 46645)

Compounds were used in the concentrations 150 and 200µg/ml and using a solvent system consisting of DMSO. The standard used was Fluconazole 150 and 200µg/ml against both the organisms.

The disc diffusion method was employed for the screening of antifungal activity.

Materials and Methods

Media used: Potato Dextrose Agar Medium

<table>
<thead>
<tr>
<th>Sl. No</th>
<th>INGREDIENTS</th>
<th>QUANTITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Beef Extract</td>
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<td>3.</td>
<td>Sodium Chloride</td>
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<td>4.</td>
<td>Agar</td>
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<td>5.</td>
<td>Potato</td>
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<td>6.</td>
<td>Distilled Water</td>
<td>Up to 1000mL</td>
</tr>
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</table>
Microorganisms used

1. *Aspergillus niger* (ATCC 9029)
2. *Aspergillus flavus* (ATCC 46645)

Media Sterilization

All the culture media were sterilized by autoclaving at 15 lbs/inch² corresponding to 20 min.

Method

Agar streak dilution method.

Preparation of agar plates with different concentrations of test compounds

5mg/ml stock solution of the test compounds were made using DMSO as the solvent. From this stock solution, required quantities of drug solutions were mixed with the known quantities of molten sterile agar media aseptically to provide the following concentrations 150 and 200µg/ml.

About 20ml of the media containing the drug was dispensed into each sterile petri-dishes (diameter about 10cm). Then the media were allowed to get solidified.

Streaking of microorganisms

Microorganisms were then streaked one by one on the agar plates aseptically. After streaking, all the plates were incubated in the incubator, set at 37± 1°C for 48 hrs. Then the plates were observed for the growth of the microorganisms.

Preliminary Screening

Disc diffusion method

The synthesized compounds are screened against two selected fungal strains *Aspergillus niger* and *Aspergillus flavus* by using diffusion method. The 48 hours old
fungal culture inoculated into nutrient broth by following aseptic techniques and incubated for 48 hours at 37\(^0\) \(\pm\) 2\(^0\)C in an incubator. This culture mixed with well sterilized and cooled media like Potato-dextrose agar media and poured into petriplates. After solidification five discs are made at equal distance by using sterile swattmann filter paper (5 mm in diameter). Into these place different concentrations of standard drug and synthesized compounds along with control (N, N’- Dimethyl Sulphoxide) are introduced.

After introduction of standard drug and compounds, these plates are placed in a refrigerator at 8\(^0\) – 5\(^0\)C for 2hrs for proper diffusion after 2hr the petri plates are transferred to incubator and maintained at 37\(^0\) \(\pm\) 2\(^0\)C for 24-36 hours. After the incubation period, the plates were observed for zone of inhibition by using vernier scale. Results are evaluated by comparing the zone of inhibition shown by the synthesized compounds with standard drug.
<table>
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RESULTS AND DISCUSSION

1. Anti-Oxidant Activity

Compounds synthesized are screened for anti-oxidant activity. These compounds are screened for the activity at 1, 2, 3, 4 and 5 mg/ml using Ascorbic acid as standard. The % inhibition of the compounds at various concentrations is calculated from their absorbance values. Among the screened compounds, BTD-8, BTD-4, BTD-5, BTD-10 had shown the better activity against the standard.

2. Anti-Bacterial Activity

Compounds synthesized are screened for anti-bacterial activity using disc plate method at concentrations 50 and 100µg/ml using gram +ve and gram –ve strains. Such as Bacillus subtilis, Staphylococcus aureus, Klebsiella pneumonia, Escheria coli.

Among the synthesized screened compounds, BTD-12, BTD-2, BTD-1, BTD-3, and BTD-9 had shown promising anti bacterial activity against the standard.

3. Anti-Fungal Activity

Compounds synthesized are screened for anti-bacterial activity using disc plate method at concentrations 100 and 150µg/ml and the strains used for the screening are Aspergillus flavus, Aspergillus niger.

Among the synthesized screened compounds, BTD-3, BTD-7 BTD-2, BTD-1, BTD-9 had shown the better activity against the standard.
SUMMARY & CONCLUSION

In present work, fluorochloroaniline was treated with KSCN in presence of bromine in glacial acetic acid and ammonia to get 2-amino-6-fluoro-7-chloro (1,3)-benzothiazole, dissolved in ethanol and ammonia which was treated with hydrazine hydrate, carbon disulphide and sodium chloroacetate to get 6-Fluoro-7-Chloro-(1,3)-Benzothiazole-2-Thiosemicarbazide and then treated with pyridine in oil bath for 4 hours. To the above product different aromatic amines, as well as various primary and secondary amines in presence of DMF were treated to get newly targeted compounds by replacing chlorine at 7th position.

The synthesized compounds were characterized by solubility, TLC, analytical data, IR, $^1$HNMR and Mass spectral studies.

All synthesized compounds were screened for antioxidant, antibacterial and anti fungal activities.

Among the synthesized compounds BTD-8, BTD-4, BTD-5, BTD-10 had shown the better antioxidant activity against the standard.

Compounds BTD-12, BTD-2, BTD-1, BTD-3 and BTD-9 had shown promising anti bacterial activity against the standard

Compounds BTD-3, BTD-7 BTD-2, BTD-1, BTD-9 had shown the better activity against the standard

From this study, it may be concluded that benzothiazole substituted with tyrosine, p-amino benzoicacid, dimethyl amine on seventh position enhances the anti-microbial, anti-oxidant activities and hence the study would deserve for future investigation and derivatisation
REFERENCES

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