1. INTRODUCTION

Pharmaceutical chemistry, a discipline firmly rooted in synthetic organic chemistry, has increasingly close links to structural chemistry, computational chemistry, and molecular biology at the discovery interface, to toxicology and pharmacology at the development interface and also to medicine at clinical interface. Thus, pharmaceutical chemistry has occupied the central position and will continue to play a critical role in the new drug discovery processes.

Since, drug discovery process is an extremely complicated endeavor as it encompasses several diversified disciplines united by a common goal, namely the development of novel therapeutic agents. In the view of above considerations, it is based on tailor made approach of drug design in search of new potent bioactive drug molecules. The process of search for new potent bioactive drug can be divided functionally into two stages: discovery and development, in order to get an effective molecule with lesser toxicity by synthesizing new class of compounds as well as establishing variety of empirical and semi-empirical structure-activity relationship through the replacement and modification of functional groups.

During the later decades of 20th century traditional dividing lines between biological, chemical and physical sciences were erased and in the present millennium, new border line of investigations such as molecular biology, molecular pharmacology, biomedicine, cellular biology, genetics and other began to capture the interest of medicinal scientist. Since the ancient times, the mankind was under misery and suffering as his life was associated with many physiological and pathological disorders like cancer, AIDS, inflammation, hypertension, diabetes and analgesia, the diseases caused by several bacterial and fungal infections.

For the therapy, it was proven in the research that fluoro-benzothiazole nucleus found to play an important role as antimicrobial, anti-inflammatory, anticancer and antidiabetic agent. We report herein the new and unreported yet the synthesis of fluoro-benzothiazole derivatives and then followed by screening for antibacterial, antifungal and anti-inflammatory activity.
1.1 BENZOTHIAZOLE

Heterocycles bearing nitrogen and sulphur atom constitute the core structure of a number of biologically interesting compounds viz. thiadiazine, thiazole and benzothiazole. Among all sulphur and nitrogen containing heteronucleus, benzothiazoles found to be most interesting nucleus regarding research because it used as a starting material for the synthesis of larger, usually bioactive structures. Modifications on the benzothiazole nucleus have resulted in a large number of compounds having diverse pharmacological activities. Thus, synthesis and biological activities of benzothiazole derivatives have long been focused for interest of research in the field of medicine especially 2-substituted benzothiazole derivatives with fluoride functional group as substituents (Jian Haoa, 2007).

In 1950s, a number of 2-aminobenzothiazole derivatives were studied as central muscle relaxants but the medicinal chemists had not taken active interest in this chemical family. Since benzothiazoles have been known from ages to be biologically active (Lacova, M. et al., 1991) and as the Riluzole (6-trifluoro-2-benzothiazolamine; Bryson, M. et al., 1996) discovered, benzothiazole derivatives have been studied extensively and found to have diversified chemical reactivity as well as broad spectrum of biological activity viz antitumor (Beneteau, V. et al., 1999; Wells, G. et al., 2000; Shi, D. et al., 2001; Hutchinson, I. et al., 2003), antitubercular (Palmer, F.J. et al., 1971), antimalarial (Bujdakova, H. et al., 1994), anticonvulsant (Alam, M. 2004; Chakole, R. D. et al., 2005), anthelmintic (Jayachandran, E. et al., 2003), analgesic and anti-inflammatory (Siddiqui, N. 2004; Gurupadayya, B.M. et al., 2005) and antimicrobial (Yalcin, I. et al., 1992; Latrofa, A. et al., 2005).

1.1.1 SYNTHESIS AND CYCLISATION OF BENZOTHIAZOLE

In 1887, A. W. Hofmann first synthesized 2-substituted benzothiazole derivatives then because of its diversified activity as well as simple cyclisation mechanism, many synthetic routes had been reported. 2-substituted benzothiazoles are most commonly synthesized via one of two major routes: the most common direct
method involves the condensation of an ortho-amino thiophenol with a substituted aromatic aldehyde, carboxylic acid, acyl chloride or nitrile. This method, however, is often not appropriate for many substituted 2-arylbenzothiazoles due to the difficulties encountered in the synthesis of the readily oxidisable 2-amino thiophenols bearing substituent groups.

Another method of 2-substituted benzothiazole involves the use of potassium ferricyanide (Jacobsen cyclisation) which is based on radical cyclisation of thiobenzanilides viz. synthesis of 6-substituted benzothiazoles (Ben Alloum, et al., 1997). Roe and Tucker have also observed a similar mixture of regioisomeric products from the Jacobsen cyclisation for the synthesis of 5- and 7-fluoro-2-phenylbenzothiazoles (Roe, A. et al., 1965). A regiospecific synthesis of 2-aryl benzothiazoles unsubstituted in the phenyl ring was developed through the use of a bromo substituent ortho to the anilido nitrogen and formation of a benzyne intermediate followed by intramolecular cyclisation. A similar strategy has been developed for the synthesis of wide range of 7-substituted benzothiazoles via ortho metallation followed by benzyne formation and subsequent cyclisation (Stanetty, P. et al., 1996).

These strategies, however, were found to be incompatible with the nitro functional group on the aryl ring and do not represent a general route to functionalized 2-arylbenzothiazoles (Hutchinson, Ian 2000; Shi, D. 1996).

Recently, several new methods have been reported, some of the most common methods for the synthesis of 2-substituted benzothiazole are as follows:

1.1.1.1 Hofmann Method

A. W. Hofmann first obtained 1-Mercapto-benzothiazole in an attempt to prepare the disulphhydryl derivative of thiocarbanilide by the reaction of carbon disulfide on o-aminothiophenol. Hofmann obtained the same substance by the action of sodium hydro- sulfide on chlorophenyl mustard oil (1-chloro-benzothiazole). The product thus obtained, after recrystallization from alcohol, melted at 179\(^\circ\)C and was easily oxidized to a disulfide, melting at 180\(^\circ\)C. Hofmann also noted the formation of 2- anilino benzothiazole from the reaction of 2-aminothiophenol and phenyl isothiocyanate (Hofmann, 1887).
1.1.1.2 Jacobsen cyclisation
Jacobson and Frankenbacher synthesized 2-substituted benzothiazole by heating of azobenzene with carbon disulfide in a sealed tube at 250°C for 5 hours. The product melted at 174°C which was found identical with Hofmann's 1-mercapto-benzothiazole. The disulfide obtained by the oxidation of this product with potassium dichromate in acetic acid solution after recrystallization from benzene melted at 186°C. Jacobson and Frankenbacher further reported synthesis and cyclization of 2-substituted benzothiazole by use of potassium ferricyanide with sodium hydroxide (Jacobson, P.1886).

1.1.1.3 Modified Jacobson method
Min Wang synthesized 4-fluorinated 2-phenylbenzothiazoles that include benzylation of starting material 3-hydroxy-4-methoxybenzaldehyde was achieved by the protection of phenolic hydroxyl group with benzyl bromide to provide 3-benzyloxy-4-methoxybenzaldehyde. Oxidation of this compound using sodium chlorite produces 3-benzyloxy-4-methoxybenzoic acid which reacted with thionyl chloride to give 3-benzyloxy-4-methoxybenzoyl chloride. 2-Fluorobenzamides N-(2-fluorophenyl)-3-benzyloxy-4-methoxybenzamide and N-(2-fluorophenyl)-3,4-dimethoxybenzamide were prepared by condensation of 3-benzyloxy-4-methoxybenzoyl chloride, or commercially available starting material 3, 4-dimethoxybenzoyl chloride with 2-fluoroaniline. The benzamides were converted to their thiobenzamides N-(2-fluorophenyl)-3-benzyloxy-4-methoxythiobenzamide and N-(2-fluorophenyl)-3,4-dimethoxythiobenzamide with Lawesson’s reagent in hexamethylphosphoramide (HMPA). Cyclization of thiobenzamides by a modified method of Jacobson thioanilide radical cyclization using potassium ferricyanide and aqueous sodium hydroxide gave 4-fluorobenzothiazoles viz 4-fluoro-2-(3-benzyloxy-4-methoxyphenyl) benzothiazole (Min Wang, et al., 2006).
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1.1.1.4 Bromine as catalyst

Recently several methods have been reported which utilize bromine as catalyst. Basically cyclization with bromine achieved by oxidation of aniline, substituted aniline and aryl thiourea in acid or chloroform with alkali thiocyanate.

- Hugerschoff in early 1900s synthesized 2-amino benzothiazole and found that an aryl thiourea can be cyclized with liquid bromine in chloroform to form a 2-aminobenzothiazoles (Hugerschoff, H. 1901).

\[
\text{NH}_2 + \text{Br}_2 + \text{KSCN} \rightarrow \text{N} \begin{array}{c} \text{S} \\ \text{NH}_2 \end{array}
\]

- Johanson and Hamilton prepared 2-amino-6-substituted mercaptobenzothiazole by oxidation of 4-Methylmer captophenyl thiourea with bromine as a catalyst (Johanson, et al., 1949).

\[
\text{S} \begin{array}{c} \text{NH} \\ \text{NH}_2 \end{array} + \text{Br}_2 + \text{CHCl}_3 \rightarrow \text{S} \begin{array}{c} \text{N} \\ \text{NH}_2 \end{array}
\]

- Stuckwisch used potassium thiocyanate to cyclize p-substituted aniline into 2-amino-6-substituted benzothiazole in the presence of bromine as a catalyst (Stuckwisch, C.G., 1949).

\[
\text{O} \begin{array}{c} \text{NH}_2 \end{array} + \text{Br}_2 + \text{KSCN} \rightarrow \text{O} \begin{array}{c} \text{N} \\ \text{NH}_2 \end{array}
\]

- Alaimo and coworkers prepared 2-amino-5,6-dichloro and 2-amino-6,7-dichlorobenzothiazole by cyclization of suitable substituted aniline with the help of thiocyanogen (Alaimo, R.j. et al., 1971).
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Jeng Li et al prepared 6-substituted-2-aminobenzothiazole by cyclization of p-substituted anilines with the help of ammonium thiocyanate and bromine (Jeng Li, et al., 1981).

Naim et al. synthesized 2-aminobenzoyhiazole-6-carboxalic acid and 2-amino-6-substituted-carbonyl benzothiazoles by reaction of the corresponding 4-substituted anilines with potassium thiocyanate followed by oxidative cyclizations of the resultant thioureas with bromine (Naim, S.S., 1991).

Dogruer, D. S and coworkers prepared 2-amino-6-fluoro-7-chlorobenzothiazole by cyclization of 3-chloro-4-fluoroaniline and potassium thiocyanate in presence of catalytic bromine (Dogruer D. S. et al., 1998). It is also synthesized by using similar method and materials by Nargund et al (Nargund, L.V.G, et. al., 1999).
• Patel and coworkers were synthesized various 4(5 or 6)-substituted-2-aminobenzothiazoles through reaction of 4(5 or 6)-substituted anilines with ammonium thiocyanate and bromine (Patel, N.B. et al., 2006).

• Jimonet et. al. synthesized various substituted-2-benzothiazolamines derivatives by different methods. One-pot reaction of appropriate anilines with thiocyanogen generated from bromine and alkaline thiocyanate in acetic acid medium lead to formation of the desired product in good to moderate yields (Jimonet, P. et al., 1991).

• Matsui, et. al., prepared 6-substituted-2-aminobenzothiazoles by the reaction of 4-substituted anilines with potassium thiocyanate in presence of bromine (Matsui, M. et. al., 1998).
• Francisco Lopez Calahorra reported reaction of benzoyl chloride with ammonium thiocyanate initially gave benzoyl isothiocyanate, which underwent addition with 3-fluoroaniline to afford 3-fluorophenylthiourea. 2-amino-5-fluorobenzothiazole was then obtained from the cyclization of 3-fluorophenylthiourea with bromine (Francisco Lopez-Calahorra, et al., 2004).

1.1.1.5 Sulfuric acid as a catalyst
• Allen used sodium thiocyanate and cyclized p-substituted aniline into 2-amino-6-substituted benzothiazole in the presence of sulfuric acid as a catalyst (Allen, C.H.F., 1942).
1.1.1.6 Benzene as a catalyst
• Tweit et al reported cyclizations of isothiocyanates to 2-amino benzothiazole in presence of benzene (Tweit, R.C., 1970).

\[
\begin{array}{c}
\text{RNCS} \\
\text{RCH}
\end{array}
\begin{array}{c}
\text{SH} \\
\text{NH}_2
\end{array}
\begin{array}{c}
n \text{NH} \\
\text{R}
\end{array}
\text{S}
\]

1.1.1.7 Benzyltrimethylammonium tribromide as catalyst
• Jordan et. al. used benzyltrimethylammonium tribromide (PhCH\textsubscript{2}NMe\textsubscript{3}Br\textsubscript{3}) which is a electrophilic bromine source for the conversion of substituted arylthioureas to 2-aminobenzothiazoles under mild conditions in a variety of solvents with good yields (Jordan, A.D. et. al., 2003).

\[
\begin{array}{c}
\text{NH}_2 \\
\text{NH}
\end{array}
\begin{array}{c}
\text{SH} \\
\text{O}
\end{array}
\begin{array}{c}
\text{R}
\end{array}
\begin{array}{c}
\text{NH}_2
\end{array}
\begin{array}{c}
\text{PhCH}_2\text{NMe}_3\text{Br}_3
\end{array}
\]

1.1.1.8 Copper- and palladium-catalyzed cyclization
• Batey et. al. reported the synthesis of 2-aminobenzothiazoles through analogous C-S bond forming methodology. They formed the intramolecular C-S bond with the help of copper and palladium-catalyst. Copper and palladium-catalyzed intramolecular C-S bond formation by cross coupling between aryl halide and thioureas functionality is demonstrated for the synthesis of 2-amino benzothiazoles (Batey, R.A. et. al., 2003).

\[
\begin{array}{c}
\text{R} \\
\text{X}
\end{array}
\begin{array}{c}
\text{S}
\end{array}
\begin{array}{c}
\text{R}_1 \\
\text{R}_2
\end{array}
\begin{array}{c}
\text{R}
\end{array}
\begin{array}{c}
n \text{NH} \\
\text{R}_1
\end{array}
\begin{array}{c}
\text{S}
\end{array}
\begin{array}{c}
\text{R}_2
\end{array}
\]

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1.1.1.9 Chloroformamidinium salt

- El-Faham et al. synthesized 2-aminobenzothiazoles derivatives by using efficient reagents that is Chloroformamidinium salt which allowed to react with o-substituted aniline to afford 2-aminobenzothiazole (El-Faham, A. et al., 2006).

\[
\begin{array}{c}
\text{SH} \\
\text{NH}_2
\end{array} + \begin{array}{c}
\text{R}_1 \text{N} - \text{N} \text{PFe} \\
\text{R}_2 \text{R}_3 \text{R}_4
\end{array} \rightarrow \begin{array}{c}
\text{NH}_2 \\
\text{S} \\
\text{N} \text{N} \text{R}_1 \text{R}_2 \text{R}_3 \text{R}_4 \text{PFe}
\end{array}
\]

1.1.1.10 Appel’s salt

- Chi B. Vu synthesized benzothiazole nucleus through cyclisation which involve reaction of 2-Bromo-4-nitroaniline with 4,5-dichloro-1,2,3-dithiazol-1-ium chloride, also referred to as Appel’s salt, to form 2-bromo-N-(4-chloro-5H-1,2,3-dithiazol-5-ylidene)-4-nitroanilin. This intermediate could be cyclized to the desired benzothiazole (Chi, B. V. et al., 2009).

\[
\begin{array}{c}
\text{Br} \\
\text{O}_2\text{N} \\
\text{NH}_2
\end{array} + \begin{array}{c}
\text{S}^\text{+} \text{S} \\
\text{Cl} \text{Cl} \text{Cl} \text{Cl}
\end{array} \xrightarrow{\text{THF; RT}} \begin{array}{c}
\text{Cl} \\
\text{S} \\
\text{S} \\
\text{N} \\
\text{Br} \\
\text{O}_2\text{N}
\end{array} \xrightarrow{\text{Cul; Pyridine; 110 } ^\circ \text{C}} \begin{array}{c}
\text{Br} \\
\text{O}_2\text{N} \\
\text{CN}
\end{array}
\]
1.1.1.1 Lawesson’s reagent

Stephen O. synthesized (pyridinyl) benzoazole using palladium complexes through 4-tert-butylpicolinic acid, 4-tert-butyl aniline, DCC, 4-PP and CH₂Cl₂ to produce 2-tert-Butyl-pyridine-2-carboxylic acid (4-tert-butylphenyl)-amide which on reaction with Lawesson’s reagent produce carbothionic acid and finally cyclisized to benzothiazole by potassium ferrocyanate (Stephen, O. et al., 2007).

- Serdons. K. reported synthesis of benzothiazole in which o-anisidine was first reacted with p-nitrobenzoyl chloride to form N-2’-methoxyphenyl-4-nitrobenzamide. The amide was then converted to the thiobenzamide using Lawesson’s reagent (2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulphide) which is a useful thiation reagent to replace the carbonyl oxygen atoms of ketones, amides and esters by sulphur. In the presence of potassium ferricyanide it was than cyclized to the 2-(4’-nitrophenyl)-benzothiazole (Serdons, K. et al., 2009).
1.1.1.12 Bakers’ yeast to catalyze cyclization

Umesh R. Pratap successfully employed bakers’ yeast to catalyze the condensation of 2-aminothiophenol and aldehydes in DCM to yield 2-substituted benzothiazoles in moderate to good yields under mild reaction condition. A mixture of an aldehyde (8 mmol), 2-aminothiophenol (8 mmol), bakers’ yeast (2 g), was stirred at room temperature for 24 h in DCM. After completion of the reaction, bakers’ yeast was filtered through a bed of Celite, and the filtrate was concentrated under reduced pressure. On cooling, the solid product obtained was separated and crystallized from ethanol to afford the pure benzothiazole. Bakers’ yeast is a known source of extracellular enzymes. These enzymes might be accelerating the cyclocondensation of 2-aminothiophenol and aldehydes by forming either an initial enzyme–2-aminothiophenol non-covalent complex or an enzyme–aldehyde complex, resulting in intermediate benzothiazolines. The coenzymes, nicotinamide adenosine dinucleotide /flavin adenosinedinucleotide-dependent oxidoreductase available in bakers’ yeast, may be catalyzing the aromatization by dehydrogenation involving hydride ion transfer and the subsequent abstraction of a proton. The second step could be a rate determining step. The intermediate may have better solubility in DCM compared to other solvents, thus permitting better interaction with the cofactors resulting in high yields of the benzothiazoles (Umesh, R. Pratap, et al., 2009).

\[
\begin{align*}
\text{Baker's yeast} & \quad \text{CH}_2\text{Cl}_2, \text{RT} \\
\text{Enzyme} & \quad \text{CH}_2\text{Cl}_2, \text{rt} \\
\text{FAD} & 
\end{align*}
\]
1.1.1.13 One-pot intramolecular cyclization

Fenglian Ge synthesized benzothiazole derivative according to Uneyama’s preparation of fluorinated imidoyl chlorides to the efficient synthesis of various 2-trifluoromethyl and 2-difluoromethyl substituted benzo-1,3-diazole derivatives via a rapid and mild one-pot intramolecular cyclization process. Subsequential bromination of 2-difluoromethyl benzo-1,3-diazole products by the photolysis with NBS leads to the formation of bromodifluoromethyl benzo-1,3-diazoles (Fenglian, Ge. et al., 2007).

\[ \text{SH} \quad \text{NH}_2 \quad \text{F} \quad \xrightarrow{\text{CF}_3\text{COOH, PPh}_3} \quad \text{Et}_3\text{N (excess)} \quad \text{CCl}_4, \text{Refluxing} \]

\[ \text{F} \quad \xrightarrow{\text{NBS / CCl}_4} \quad \text{Sunlamp / Refluxing} \]

\[ \text{N} \quad \text{CF}_2\text{Br} \]

1.1.1.14 Micellaneous Methods

- Yong-Qian Wu et. al. used Di(imidazole-1-yl)methanimine for formation of nitrogen containing heterocyclic nucleus. Di(imidazole-1-yl)methanimine was synthesized by treating cyanogens bromide with imdazole. The reaction complete smoothly with 2-substituted anilines, regardless of their nucleophilicity and this may suggest that second imidazole displacement is not the rate-limiting step due to the strong tendency towards cyclizations (Yong-Qian Wu, et al., 2003).

\[ \text{SH} \quad \text{NH}_2 \quad + \quad \xrightarrow{\text{Di(imidazole-1-yl)methanimine}} \quad \text{NH}_2 \]
Alessandra Napolitano has reported cyclisation of benzothiazole by oxidation of 1, 4-benzothiazine species which then undergo nucleophilic attack of the hydroxyl anion at C-2 to afford a transient bemithioketal, involved in the alkali-induced ring contraction of 2H-1, 4- benzooxazines. Then undergo rearrangement and oxidation. Further oxidation and aromatization of intermediate eventually yield 2-carboxy-4-hydroxy-6-(2-amino-2-carboxylethyl) benzothiazole (Alessandra, N. et al., 1996).
1.1.2 Therapeutic Importance of Benzothiazoles

The 2-substituted benzothiazoles found to possess broad spectrum of pharmacological activity of clinical importance, which listed as follows.

- Anticancer agents.
- Antitubercular activity.
- Carbonic anhydrase inhibitors (Diuretic).
- Local anaesthetics.
- Hypoglycemic agents.
- Anti-inflammatory agents.
- Antimicrobial agents.
- Cardiovascular drugs.
- Enzyme inhibitors.
- Central dopaminergic agents.
- Choleretic agents.
- Miscellaneous.
1.1.2.1 Anticancer agents:

Schnus., Rodney.C. and co-workers synthesized N-(5-fluoro benzothiazol 2-yl)-2-guanidino thiazole 4-carboxamide (01, 02) as systematic antitumor agents against Lewis lung carcinoma (Schnus, et al., 1991).

\[
\begin{align*}
1 & : \text{N}^2\text{H}_2\text{N} - \text{N} - \text{S} - \text{O} - \text{N} - \text{H} - \text{N} - \text{H} - \text{O} - \text{N} - \text{S} - \text{H}_2\text{N} - \text{N} - \text{S} \ (\text{fluoro benzothiazole derivative}) \\
2 & : \text{N}^2\text{H}_2\text{N} - \text{N} - \text{S} - \text{O} - \text{N} - \text{H} - \text{N} - \text{H} - \text{O} - \text{N} - \text{S} - \text{H}_2\text{N} - \text{N} - \text{S} \ (\text{fluoro benzothiazole derivative})
\end{align*}
\]

Jagabandhu Das and coworkers synthesized 2-{{[(tert-butylamino) carbonyl] amino}}-N-(2-chloro-6-methylphenyl)-1, 3-benzothiazole-6-carboxamide (03) for anti cancer activity. (Jagabandhu, Das. et al., 2003)

\[
\begin{align*}
3 & : \text{Me} - \text{O} - \text{N} - \text{H} - \text{N} - \text{H} - \text{O} - \text{N} - \text{S} - \text{Me} - \text{Me} - \text{Cl} - \text{NH} - \text{N} - \text{H} - \text{N} - \text{H} - \text{O} - \text{N} - \text{S} \ (\text{cyano alkynyl benzothiazole derivative})
\end{align*}
\]

Hutchinson Ian, reported 3’-cyano and 3’-alkynyl-substituted 2-(4’-aminophenyl) benzothiazole (04) for anticancer activity (Hutchinson, Ian. et al., 2003).

\[
\begin{align*}
4 & : \text{H}_2\text{N} - \text{N} - \text{S} - \text{R} \ (R = \text{H}, \text{F}; R' = \text{CN})
\end{align*}
\]
Linhong Jin, reported synthesis of N-(benzothiazole-2-yl)-1-(fluorophenyl)-O-dialkyl-α-aminophosphonate (05) for anticancer activity (Linhong, Jin, et al., 2006).

\[
\begin{array}{c}
\text{N} \quad \text{S} \\
\text{P} \quad \text{O} \quad \text{R}_3 \\
\text{O} \quad \text{R}_3 \\
\text{R}_1 = 4-\text{CH}_3, 6-\text{OCH}_3 \\
\text{R}_2 = 2-\text{F}, 4-\text{F}, 4\text{CF}_3 \\
\text{R}_3 = \text{Me, Et, n-Pr, iPr, nBu}
\end{array}
\]

Stanton Hon and coworkers reported synthesis of 2-[6-(trifluoromethoxy)-1,3-benzothiazol-2-yl]-1H-isoinole-1,3(2H)-dione (06) and evaluated for anticancer activity (Stanton, Hon, et al., 2008).

Eun Young Song synthesized a series of amide and urea derivatives of benzothiazole (07, 08) and initially evaluated for their antiproliferative profile in a panel of cancer cell lines. Further potent compounds were investigated for their ability to inhibit Raf-1 activity (Eun Young Song, et al., 2008).

\[
\begin{array}{c}
\text{N} \quad \text{S} \\
\text{N} \quad \text{O} \\
\text{X} \quad \text{Y} \\
\text{Z}
\end{array}
\]
Richard B and coworkers reported synthesis of novel benzothiazole derivatives (09) for anticancer activity (Richard, B. et al., 2007).

![Chemical structure](image)

Dong-Fang Shi, synthesized 2-(4-Aminophenyl) benzothiazole Sulfamate Salt (10) for antitumor activity (Dong-Fang Shi, et al., 2001).

![Chemical structure](image)

Masao Yoshida and coworkers reported synthesis of 2-methyl-4-nitro-2H-pyrazole-3-carboxylicacid [2-(cyclohexanecarbonylamino) benzothiazol-6-1] amide (11) for anticancer activity (Yoshida Masao, et al., 2005).

![Chemical structure](image)
Cedric J. reported synthesis and pharmacological activity of 4-(5/6/7-fluoro-1,3-benzothiazol-2-yl)-4-hydroxycyclohexa-2,5-dien-1-one (12) against tumor cell lines (Cedric, J. et al., 2006).

\[ \text{NSOH} \]

\[ \text{F} \]

\[ \text{N} \]

\[ \text{N} \]

\[ \text{HO} \]

\[ \text{N} \]

\[ \text{N} \]

\[ \text{2} \]

\[ \text{3a',7a'-dihydro-2,4'-bi-1,3-benzothiazole (14) derivatives against carcinoma cells (Shu-Ting Huang, et al., 2006).} \]
Wells G. studied the oxidation reactions of 2-(4-hydroxy-3-methoxyphenyl) benzothiazole (15) against the human breast cancer cell lines. In *in vitro* growth inhibition tests against the human breast cancer cell lines MCF-7 and MDA-468 (over 7 and 10 d, respectively) determined by MTT assay, the phenolic benzothiazole gave IC\textsubscript{50} values (dose to inhibit cell growth by 50\%) of 0.62 and 0.06 µM, respectively (Wells, G. *et al.*, 2000).

![Structure of 15](image)

Bradshaw, T.D reported Quinol esters and ethers derived from the oxidation of 2-(4-hydroxyphenyl) benzothiazoles (16) and quinine monoketals (17) from the oxidation of 2-(3-hydroxyphenyl benzothiazoles, respectively, have significantly improved and extended antitumor potency *in vitro* against breast and human colon tumor cell lines (Bradshaw, T.D. *et al.*, 2000).

![Structure of 16](image)

R = Me, Et

![Structure of 17](image)

R = Me, Et, AO, Pr
Caleta and coworkers synthesized 6-Amidino-substituted -2-aminobenzothiazoles, N-methyl-2- (4-cyanostyryl) benzothiazolium, cyano-substituted-2-styryl benzothiazoles and amidino and bis-amidino-substituted 2-styryl benzothiazoles (18, 19, and 20). All new compounds were tested on cytostatic activities against malignant cell lines. The compounds exerted a different inhibitory effect, depended on concentration and type of the cells. The best inhibitory effect was achieved with compounds (3) and (4) with slight differences among them. All of them inhibited the growth of examined tumor cell lines and also normal fibroblasts. Other examined compounds exhibited a moderate inhibitory effect, depending on type of the cells. (Caleta, et al., 2004).
Hutchinson I, reported synthesis of fluorinated analogues of 2-(4-aminophenyl) benzothiazole (21) derivatives which successfully block C-oxidation. All the compounds were screened in vitro against human breast and ovarian tumor xenografts (Hutchinson, I. et al., 2001).

\[
\text{SN}_2\text{NHR} \quad R = H, \text{F} \quad R_1 = \text{F}
\]

Shi, D.F. and coworkers synthesized 2-(4-Aminophenyl) benzothiazoles (22) comprise a novel mechanistic class of antitumor agents. All the compounds screened for certain colon, lung, melanoma, renal and ovarian cell lines (Shi, D.F. et al., 1996).

\[
\text{SN} \quad \text{R} \quad R = \text{H, CH}_3, \text{Cl, I, Br}
\]

Shu-Ting Huang reported synthesis of novel benzothiazole (23, 24) derivatives and screened for anti-tumor activity (Shu-Ting Huang, et al., 2006).
Min Wang, reported preparation of 4-fluorinated 2-arylbenzothiazoles (25, 26) by a modification of Jacobson thioanilide radical cyclization and screened as new potential antitumor drugs, which show potent and selective inhibitory activity against breast, lung, and colon cancer cell lines (Min Wang, et al., 2006).

\[
\text{R} = 4\text{-F}, 5\text{-F}, 6\text{-F} \quad \text{R}_1 = \text{R}_2 = \text{R}_3 = \text{O}^{11}\text{CH}_3, \text{OCH}_3
\]

Suk-June Choi synthesized 2-(4-aminophenyl) benzothiazole (27) derivatives which display potent and selective antitumor activity against breast, ovarian, colon, and renal cell lines (Suk-June Choi, et al., 2006).

\[
\text{R}_1 = \text{SC}_2\text{H}_5, \text{HOCH}_3, \text{F}, \text{Cl}, \text{SCHF}_2
\]
\[
\text{R}_2 = \text{H}, \text{Cl}, \text{NH}_2, \text{CH}_2\text{Cl}, \text{OCF}_3, \text{OCH}_3, \text{SCHF}_2, \text{NO}_2
\]
\[
\text{R}_3 = \text{H}, \text{N(CH}_3)_2, \text{CH}_3, \text{t-Butyl}, \text{OCH}_3, \text{n-Heotyl}, \text{NO}_2, \text{Cl}, \text{NH}
\]
Beneteau, V. and coworkers synthesized series of novel 2-cyano-4,7-dimethoxybenzothiazole (28) derivatives as anticancer drugs (Beneteau, V. et al., 1999).

![Chemical structure of 28](image)

**R = H, NHAc**

### 1.1.2.2 Antimicrobial agents:

Osceigyimah Peter., synthesized (4-isothiazolin-3-one-5-thio) benzothiazole (29) as antimicrobial agents (Osceigyimah Peter, et al., 1992).

![Chemical structure of 29](image)

Trivedi P. et al synthesised 2(substituted benzal hydrazino carbomyl methyl thio) benzothiazoles (30) for antimicrobial activity (Trivedi, P. et al., 1992).

![Chemical structure of 30](image)

R= Ph, C₆H₄Cl₂, C₆H₄NO₂, C₆H₄OH

\[
\begin{align*}
N & \quad \text{SR}_1 \\
31 \\
R_1 &= H_3NO_2,
\end{align*}
\]


\[
\begin{align*}
N^+ & \quad \text{R}_1 \\
32 \\
R_1 &= \text{Me, PhCH}_2,-\text{CH}_2\text{COOH}
\end{align*}
\]

Sutoris V., synthesized 3 and 2,3 substituted benzothiazolinium salt (33) and investigated for their antimicrobial activity (Sutoris, V. et al., 1984).

\[
\begin{align*}
N^+ & \quad \text{R}_1 \\
33 \\
X &= \text{MeSO}_4, \text{Iodo, ClO}_4 \\
R &= \text{H, Me} \quad R_1 = \text{Et, Bu}
\end{align*}
\]
Sutoris. V., synthesised 3,4,6-substituted benzothiazolium salts (34) for antimicrobial activity (Sutoris, V. et al., 1984).

![Chemical Structure of 34]

\[ R_1 = \text{Me}, \text{Allyl} \quad X = \text{Br}, \text{Iodo} \]

Lipthay T, reported synthesis of arenazo (benzylthio) benzothiazoles (35) for fungicidal activity (Lipthay, T. et al., 1981).

![Chemical Structure of 35]

\[ R = \text{H}, \text{4-Cl} \quad R_1 = \text{4-OHC}_6\text{H}_4 \]

Sutoris. V, synthesized 2-alkyl and 2-alkyl-sulphonyl benzothiazoles (36) for antimicrobial property (Sutoris, V. et al., 1981).

![Chemical Structure of 36]

\[ R = \text{H}, \text{4-Cl} \quad R_1 = \text{4-OHC}_6\text{H}_4 \]
Ahmad M. Farag et al., synthesized 4-(imidazo[2,1-b]benzothiazole-3-yl)-5-methyl-1-phenyl-3-phenylcarbamoyl-1H-pyrazole (37) and evaluated for antimicrobial activity (Ahmad M. Farag et al., 2008).

Gaurav et al., reported synthesis of novel 2(4′-chlorophenyl)-1′-ethylhydrazinyl)-6-methyl benzothiazole (38) as antibacterial agents (Gaurav. et al., 2010).

Ahmad M., synthesized 4-benzothiazol-5-methyl-1-phenyl-3-phenylcarbamoyl-1H-pyrazole (39) for anti microbial activity (Ahmad, M. et al., 2008).
Ricardo A. Tapia, synthesized 6,7-Dihydrobenzothiazolo[6,5-h]pyrrolo[1,2,3-de]quinoxaline-11-one (40) for antiprotozoal activity (Ricardo, A. Tapia, et al., 2003).

Seckin Ozden, reported synthesis of series of novel benzothiazole (41) derivatives for antimicrobial activity (Seckin Ozden, et al., 2008).

Marian Zajac, reported 2-substituted benzothiazole (42, 43) derivatives as antimicrobial agent (Marian Zajac, et al., 2008).
Petra Marinko, synthesized 4-aminomethyl-4,5,6,7-tetrahydro-1,3-benzothiazole (44, 45) for antimicrobial activity (Petra Marinko, et al., 2001).

Bondock Samir and coworkers synthesized pyrazoles [3,2-a]pyrimidine, tetrazolo[1,5-a]pyrimidine, pyrido[1,2-a]pyrimidine, 1,5-benzodiazepine, benzothiazole (46) and screened for antimicrobial activity (Bondock Samir, et al., 2009).

Kazuo Yamazaki, reported synthesis of 2 and 6-substitutes benzothiazole (47) derivatives as antifungal agent (Kazuo Yamazaki, et al., 2005).
Wei Huang, synthesized 5-Chloro-2-(2-fluoro-benzylsulfanyl)-6-trifluoromethyl-benzothiazole (48) for fungicidal activity (Wei Huang, *et al.*, 2006).

![Diagram of 5-Chloro-2-(2-fluoro-benzylsulfanyl)-6-trifluoromethyl-benzothiazole (48)]

Bhusari S. R. prepared some new 2-(substituted phenylsulfonamido)-6-substituted benzothiazoles (49) and screened them for their antibacterial activity (Bhusari, S.R. *et al.*, 2001).

![Diagram of 2-(substituted phenylsulfonamido)-6-substituted benzothiazoles (49)]

R = Cl, Br, CH₃, OCH₃

R₁ = CH₃, NH₂

Sreenivasa M.V. reported synthesis of fluoro-benzothiazole (50) derivatives which found to possess good activity against *S. aureus*, *E. coli* and *C. ablicans* (Sreenivasa, M.V. *et al.*, 1998).

![Diagram of fluoro-benzothiazole (50) derivatives]
Ojha K. G. reported various benzothiazolyl carboxamido pyrazoline (51) derivatives and studied their antimicrobial activity (Ojha, K.G. et al., 2002).

\[ \text{R} = \text{Cl, CH}_3 \]
\[ \text{R}_1 = \text{C}_6\text{H}_5, \text{o-CH}_3\text{C}_6\text{H}_5, \text{p-OCH}_3\text{C}_6\text{H}_4 \]

Gopkumar P. synthesized some 6-fluoro-7-(substituted)-(2-N-p-anilinosulfonamido) benzothiazoles (52) for antimicrobial activity (Gopkumar, P. et al., 2001).

\[ \text{R} = \text{o- Nitroanilino, M-Nitroanilino, p-Nitroanilino} \]
\[ \text{o-Chloroanilino, m-Chloroanilino, p-Chloroanilino} \]
\[ \text{Morpholino, Piprazino, Dimethylaniline} \]
INTRODUCTION

Bhawsar, S.B., synthesized some 8-[(6'-substituted-1',3'-benzothiazol-2'-yl)aminomethyl] substituted hydroxy coumarins (53) were screened for antibacterial activity (Bhawsar, S.B. et al., 1996).

\[
\begin{array}{c}
\text{N} \quad \text{S} \\
\text{R} \quad \text{NH} \\
\text{O} \quad \text{HO} \\
\text{CH}_2\text{COOCH}_3
\end{array}
\]

53

\(R= \text{H, Cl, CH}_3, \text{OCH}_3, \text{NO}_2\)

Barede A.R. worked on a few 5,6-disubstituted-2-(substituted phenyl carboxamido) benzothiazoles (54) for antimicrobial activity (Barede, A.R. et al., 1998).

\[
\begin{array}{c}
\text{N} \\
\text{S} \\
\text{X} \quad \text{Y}
\end{array}
\]

54

\(X = \text{S, SO}_2 \quad Y = 4-\text{NH}_2;\)

Ghoneim K.M, synthesized 2-[(4-amino/2, 4-diaminophenyl) sulfonyl derivatives of benzothiazoles (55) and found to possess good activity against E. coli (Ghoneim, K.M. et al., 1998).
Yilidiz-Oren, synthesized a series of multisubstituted benoxazoles, benzimidazoles and benzothiazoles (56) as non-nucleoside fused isosteric heterocyclic compounds and tested for their antibacterial activities (Yilidiz-Oren, et al., 2004).

Latrofa A. prepared a series of N-cycloalkylidene-2,3-dihydro-1,3-benzothiazoles (57) as antimicrobial agent (Latrofa, A. et al., 2005).
Bhagwant University, Ajmer

1.1.2.3 Antitubercular agents:

Shieke. V.G., synthesised 2(Substituted aryl amino)-5,6-disubstituted/6-substituted (1,3) benzothiazoles (58) for anti-tubercular activity (Shieke, V.G. *et al.*, 1991).

Sidoova and his associates reported synthesis of series of novel 2-Alkylthio-6-(4-nitrobenzylidene amino) benzothiazoles (59) for antimycobacterial activity (Sidoova, E. *et al.*, 1987).
Sidoova, E., synthesized 6-acetamido-2-alkylthio benzothiazoles (60) for antimycobacterial activity (Sidoova, E. et al., 1986).

\[ \text{R = Octyl} \]

\[ \text{ACHN} \]

Panday, Anil. V., synthesised 2-substituted alkyl/aryl amino-6-methyl benzothiazoles (61) for antitubercular activity (Panday Anil, et al., 1982).

\[ \text{R = Ph, PhCH}_2 \]

\[
\begin{align*}
\text{R} &= \text{Me, Et, Pr, Bu} \\
\end{align*}
\]

1.1.2.4 Cardiovascular agents:
Mouysset Genevieve. reported various substituted 2-phenyl benzothizoles (63) as calcium channel blocker (Mouysset Genevieve, et al., 1991).

\[
\begin{align*}
\text{R} &= \text{Me, C(Me)}_3, \text{CH}_2\text{SH} \\
\end{align*}
\]

Rose Ulrich., synthesized 2-aryl substituted benzannulated ring heterocycles (64) as potential cardiovascular agents (Rose, et al., 1991).

\[
\begin{align*}
\text{R} &= \text{Substituted Ph, Pyridyl} \\
\text{X} &= \text{F, Cl} \\
\end{align*}
\]
Millard, reported synthesis of amino derivatives of 4,5,6,7-tetrahydro benzothiazoles (65) for cardiovascular activity (Millard, *et al*., 1985).

\[
\text{R} = \text{H} \\
\text{R}_1 = 4,5,6-\text{CH}_2\text{NH}_2
\]

Otsuka pharmaceutical company Ltd., reported benzothiazolinones (66) showed cardiotonic and coronary vasodialatory activity (Otsuka, 1985).

\[
\text{R} = \text{Haloalkyl, } \text{R}_1 = \text{H, Haloalkyl} \\
\text{R}_2 = \text{H, Alkenyl, Alkyl}
\]

Foscolos G., prepared new benzothiazole (67) derivatives as vasodilating agents (Foscolos, G. *et al*., 1985).

\[
\text{R} = \text{H, OMe, Me,Cl} \\
\text{NR}_1\text{R}_2 = \text{NMe}_2, \text{NEt}_2, \text{Piperazino, Morpholino} \\
\text{R}_1 = \text{R}_2 = \text{OMe, Cl, Me, OEt}
\]
1.1.2.5 Enzyme inhibitors:

Greco Micheal. N., reported benzothiazole hydroxy ureas (68) as 5-lipoxygenase enzyme inhibitors (Greco Micheal, N. et al., 1992).

![Chemical Structure](image)

68

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

\[ R_2 = \text{OH}, \text{H}, \text{OMe}, \quad R_3 = \text{Me}, \text{H}, \text{CHMe} \]

\[ n = 1-3 \]

Sutoris. V. and Co-Workers synthesized 3-(2-alkoxy carbomyl-ethyl) 2-benzothiazolinones (69) and their regulating activity on the growth of Triticum oestivum (Sutoris, V. et al., 1991).

![Chemical Structure](image)

69

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

Woltersdrof O.W., synthesized 1-o-acyl derivatives of hydroxy benzothiazole 2-Sulfonamide (70) as topically active carbonic-anhydrase enzyme inhibitors (Woltersdrof, O.W. et al., 1989).

![Chemical Structure](image)

70

\[ R = \text{OAC, (Me) 3CO}_2, \text{Ph CO}_2, \text{(Me)}_2 \text{NSO}_3 \]
Scholewald, Ronald D., reported sulfanamido benzothiazole (71) derivatives as topical carbonic anhydrase enzyme inhibitors (Scholewald Ronald, D. et al., 1984).

\[
\text{\begin{array}{c}
R \quad \text{S}\quad \text{SO}_2\text{NH}_2 \\
\end{array}}
\]

\[70\]

\[R = \text{H, OH, Et, } R_1=\text{H,Me,Ac.}\]

1.1.2.6 Local anaesthetics
Costakes, E., synthesized 2-(alkylamino acyl imino) 3-methyl benzothiazolines (71) exhibited local anaesthetic activity (Costakes, E. et al., 1979).

\[
\text{\begin{array}{c}
R \quad \text{S}\quad \text{NCO} (\text{CHR})_n \text{NR}_1 R_2 \\
\end{array}}
\]

\[71\]

\[R = \text{Me, H, n=1,2, } R_1-R_1=\text{Me,ET, } NR_1 R_2=\text{Piperdino, Marpholino : Mehra S.C., synthesized alkyl/arylamino propionyl 2-amino benzothiazole and 2-amino (substituted) benzothiazole (72) as potential local anaesthetics (Mehra, S.C. et al., 1980).}

\[
\text{\begin{array}{c}
R_2 \quad \text{S}\quad \text{NCOCH}_2\text{CH}_2\text{NNR}_1 \\
\end{array}}
\]

\[72\]

\[NRR_1=\text{AMINO, } R_2=\text{H, 4-Me, 6-Me.}\]
1.1.2.7 Hypoglycemic agents:

Chernykh, V.P., synthesised ethyl N-[6-substituted benzo-(tetrahydrobenzo) 2-thiazolyl] oxamates (73) for hypoglycemic activity (Chernykh, V.P. et al., 1983).

![Chemical structure of 73]

R=H, Me, NH₂, Br.

Hermenegilda Moreno-Díaz, synthesized N-(6-Substituted-1,3-benzothiazol-2-yl)benzenesulfonamide (74) derivatives for antidiabetic activity (Hermenegilda Moreno, et al., 2008).

![Chemical structure of 74]

R = OH, NO₂

Hiroki Fujieda, synthesized chloro benzothiazole (75) derivatives and screened for antidiabetic activity (Hiroki Fujieda, et al., 2008).
Hermenegilda synthesized N-(6-Substituted-1,3-benzothiazol-2-yl) benzenesulfonamide (76) derivatives and evaluated for their *invivo* antidiabetic activity in a non-insulin-dependent diabetes mellitus in rat models (Hermenegilda, *et al.*., 2008).

\[
\begin{align*}
\text{R}_1 &= \text{NO}_2, \text{OCH}_3, \text{OCH}_2\text{CH}_3, \text{CH}_3 \\
\text{R}_2 &= \text{OCH}_3, \text{NHCOCH}_3, \text{H}, \text{NO}_2, \text{CH}_3, \text{Cl}
\end{align*}
\]

1.1.2.8 Cholerectic agents:

Strielets. L.N. synthesised benzothiazolyl-2-mercaptoacetic acid hydrazide hydrazone (77) for choleretic activity in rats (Strielets, L.N. *et al.*, 1985).

\[
\begin{align*}
\text{R} &= \text{NHNCHR}_1, \text{R}_1 = \text{Unsubstituted Ph.}
\end{align*}
\]
1.1.2.9 Central dopaminergic agents:
Millard, synthesized amino derivatives of 4,5,6,7-tetrahydro benzothiazoles and N-Methyl amino derivatives (78) showed central dopaminergic activity (Millard, et al., 1985).

\[
\begin{array}{c}
\text{R} \\
\text{N} \\
\text{R} \\
\text{S} \\
78 \\
\text{R}=\text{H, Me, Pr, R'}=\text{H, Me, Bu}
\end{array}
\]

1.1.2.10 Anticonvulcent
Jimonet P. synthesized a lot of substituted-2-benzothiazolamines (79). All these compounds were found to possess significant anticonvulcent activity (Jimonet, P. et al., 1991).

\[
\begin{array}{c}
\text{R} \\
\text{NH}_2 \\
\text{S} \\
\text{N} \\
\text{N} \\
79 \\
\text{R} = \text{CH}_3, \text{C}_2\text{H}_5, \text{n-Prop, n-But, n-Pent, t-Pent, OCHF}_2, \text{OCH}_3, \text{CF}_3, \text{C}_2\text{H}_5, \text{OC}_2\text{H}_5, \text{CF}_3, \text{C}_2\text{H}_5 \\
\text{OC}_2\text{H}_5, 4-\text{OCF}_3, 5-\text{OCF}_3, 7-\text{OCF}_3
\end{array}
\]
Siddiqui et al reported a series of benzothiazolyl guanidines (80). The compounds with R=4-CH₃ and 4-Cl were found to be equipotent (100%) in activity to phenobarbitone in maximal electroshock seizure test and blocked subcutaneous pentylenetetrazole and strychnine induced seizures to some extent. All other compounds also had significant anticonvulsant activity (Siddiqui, et al., 1992).

\[
\text{SNH} = \text{SNHAr}
\]

\[
\text{80}
\]

\[
R = R_1 \ 2-\text{CH}_3, 3-\text{CH}_3, 4-\text{CH}_3, 2-\text{Cl}
\]

Singh synthesized some 2-(4-arylthiosemicarbazidocarbonylthio) benzothiazoles (81). The compounds were screened for their anticonvulsant activity against pentylenetetrazole induced convulsions in mice and found that all the compounds possess measurable anticonvulsant activity (Singh, et al., 1978).

\[
\text{SNCH} = \text{SNHAr}
\]

\[
\text{81}
\]

\[
\text{Ar} = \text{C}_6\text{H}_5, o-\text{CH}_3\text{C}_6\text{H}_4, p-\text{CH}_3\text{C}_6\text{H}_4, m-\text{CH}_3\text{C}_6\text{H}_4, o-\text{OCH}_3\text{C}_6\text{H}_4, p-\text{OCH}_3\text{C}_6\text{H}_4, p-\text{ClC}_6\text{H}_4, p-\text{BrC}_6\text{H}_4
\]
Huseyin U.A, reported large number of 2-(3 H)-benzothiazolone derivatives (82) and evaluated for their anticonvulsant activity in mice (Huseyn, U. et al., 1998).

\[
\begin{align*}
\text{R} & = \text{H, CH}_3, \text{Cl, F, OCH}_3, \text{NO}_2 \\
\text{R}_1 & = \text{H, CH}_3, \text{C}_2\text{H}_5, \text{i-C}_3\text{H}_7, \text{Br, CH}_2\text{COOH}
\end{align*}
\]

1.1.2.11 Antiinflammatory activity:
Oketani investigated Invitro pharmacological profiles of E3040, 6-hydroxy-5,7-dimethyl-2-(methylamino)-4-(3-pyridylmethyl) benzothiazoles (83) against the 5-lipooxygenase (Oketani, et al., 2001).

\[
\begin{align*}
\text{Sawhney et al. prepared some novel 2-(2-benzothiazolyl)-6-aryl-4,5-dihydro-3(2 H)-pyridazinone (84) and found that they possessed low to moderate anti-inflammatory activity (Sawhney, et al., 1987).}
\end{align*}
\]
Singh et al. prepared some new 2-(4'-butyl-3', 5'-dimethylpyrazol-1'-yl)-6-
substituted benzothiazole (85) and found to display significant anti-inflammatory 
activity (Singh, et al., 1986).

\[
\text{R} = \text{H, Cl, F, CH}_3, \text{OCH}_3
\]

Sangal. S. K., synthesized 2-hydrazino benzothiazoles (86) as possible anti-
inflammatory agents (Sangal, S. K. et al., 1980).

S.P. Singh reported synthesis of novel 2-(4'-butyl-3', 5'-dimethyl pyrazol-1'-yl)-
6-substituted benzothiazole (87) as antiinflammatory agents (Singh, S.P. et al., 
1986).

Paramshivappa et al prepared a series of 2-[(2-alkoxy-6-pentadecylphenyl)
 methyl] thio]-1 H - benzothiazoles (88) and investigated their ability to inhibit 
Dogruer et al synthesized sixteen (2-benzothiazolone-3-yl and 2-benzoxazolone-3yl) acetic acid derivatives (89) and tested them for antiinflammatory activity (Dogruer, et al., 1998).

\[
\begin{align*}
R_1 H, C\{R_2 = H, \text{CH}_3, \text{C}_6\text{H}_5\text{CO}, (\sigma)-\text{Cl-C}_6\text{H}_4\text{CO} \\
A = \text{l-morpholinyl, l-pyrrolidinyl diethylamino, OCH}_3, \text{OC}_2\text{H}_5, \text{OH}
\end{align*}
\]

1.1.2.12 Anti-alzheimer's activity

K. Serdons reported a 6-hydroxy-2-(40-aminophenyl)-1,3-benzothiazole (90, 91, 92, 93) performed radiolabelling with carbon-11 and investigated their \textit{invivo} and \textit{invitro} properties. Specific binding to amyloid plaques was demonstrated \textit{invitro} using post-mortem brain homogenates of AD patients; transgenic AD mice brain sections and postmortem human AD brain sections. The three structural analogues have a high potential as tracer agents for \textit{in-vivo} visualization of amyloid plaques in AD patients (Serdons, K. et al., 2009).
Yuli Xie studies the interaction of benzothiazole derivatives (94, 95) with amyloid beta peptide (Ab) and Ab-binding alcohol dehydrogenase (ABAD) and it recently implicated in the pathogenesis of Alzheimer’s disease (AD) (Yuli Xie, et al., 2006).

![Chemical Structure 94](image)

![Chemical Structure 95](image)

1.1.2.13 Antileishmanial activity

Delmas et al synthesized (1,3-benzothiazol-2-yl) amino-9- (10 H )-acridinone derivatives (96) and were assessed for their *in vitro* antileishmanial (Delmas, et al; 1992).

![Chemical Structure 96](image)
1.1.2.14 Anthelmintic activity

Nargund synthesized few novel 8-fluoro-9-substituted (1,3)benzothiazolo (5, 1-b)-1, 3, 4-triazoles (97). All these compounds were studied for their anthelmintic activity against earthworm, Perituma posthuma (Nargund, et al., 1999).

\[
\begin{align*}
R_2 &= \text{Anilino, o-Nitroanilino, m-Nitroanilino, p-Nitroanilino} \\
&\quad \text{o-Chloroanilino, o-Methylanilino guanidino} \\
&\quad \text{hydrazino, p-Methylanilino, Diphenylanilino,} \\
&\quad 2\text{-Carboxylanilino, 4-Carboxylanilino, Morpholino, Piperazino} \\
R_1 &= \text{F, Br}
\end{align*}
\]

Amit and coworkers reported some substituted imidazobenzothiazoles (98) and tested for *in vivo* anthelmintic activity against *H. nana* infection and found to show good to moderate activity (Amit, et al; 2000).

\[
\begin{align*}
R &= \text{H, 4-F, 5-F, 3-CF}_3, 4\text{-OCH}_3, 2\text{-OH, 3-NO}_2} \\
&\quad 4\text{-NO}_2, 2,4\text{-DiCl, 3,4-DiCl, 5-Chlorothienyl}
\end{align*}
\]
1.1.2.15 Miscellaneous

Caryolle R., synthesized 2-aryl benzothiazoles (99) and reported anti-parasitic properties (Caryolle, R. et al., 1990).

\[
\begin{align*}
\text{R} &= \text{C}_6\text{H}_4\text{Cl}-p, \text{C}_6\text{H}_4\text{NO}_2-p \\
\end{align*}
\]

Nagarajan Srinivasan R., Gary A. De Crescenzo synthesized and reported benzothiazole derivatives (100) as Protease inhibitors for anti HIV activity (Srinivasan R. Nagarajan, et al., 2003).

Brown et al reported a series of pyridazinylpiperidinyl (101) capsid-binding compounds with novel bicyclic substituents and screened against human rhinovirus (HRV) (Brown, et al., 2005).

\[
\begin{align*}
Y &= \text{CH}_2, \text{CH}_2\text{CH}_3, \text{SCH}_3, \text{OCH}_2\text{CH}_3, \text{SCH}_2\text{CH}_3 \\
&\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\Quad
Takeda chemical industries Ltd. reported benzothiazole derivatives (102, 103) as appetite suppressants.

![Chemical Structures](102, 103)

R= H, Halo; R$_1$ =CF$_3$  R$_3$= H, Halo

Obbe P. Zuiderveld, prepared a 1-[(2-benzothiazole)-4-n-propyl]piperazine (104) and *in vitro* tested as H3-receptor antagonists (the electrically evoked contraction of the guinea-pig jejunum) (Obbe P. Zuiderveld, *et al.*, 2005).

![Chemical Structure](104)

Diouf *et al.*, synthesized original derivatives of 2-piperazinyl benzothiazoles (105) and studied as mixed ligands for serotoninergic 5-HT$_{1A}$ and 5-HT$_3$ receptors (Diouf, *et al*; 1995).
1.2 Fluorine

The study of fluorine-containing molecules, which began as a new area of research almost half a century ago and found to play most important role in drug therapy. Since, fluorine is the most electronegative element with an atomic size close to that of hydrogen and imparts unique and often unpredictable characteristics to the molecules. Today, fluorine-containing molecules are prominent in all branches of chemistry, particularly in agro-chemicals and medicinal chemistry. It is estimated that almost 20% of all pharmaceuticals in the market contain at least one fluorine atom in their structure (Ojima, I. et al., 2009; Kenneth, L. 2006).

- **Therapeutic Importance of Fluorine**

  The rapid progress of organic fluorine chemistry since 1950 has been translated as a pathfinder to invent useful biodynamic agents in medicine. The new generation antibiotics like Norfloxacin, Ciproflaxacin, Flufloxacin, which were incorporated with fluorobenzene moiety proved their efficacy as potent bioactive molecules. Now a day’s vast number of compounds with fluorobenzene moiety featured in diverse areas like antibacterial, antifungal, anti-inflammatory and psychoactive agents (Filler, R. et al., 1986). The reasons forever increasing importance of fluorine incorporated bioactive molecules may be listed below.

- Fluorine being the second smallest substituent next to Hydrogen closely mimics hydrogen in enzyme-receptor interactions.

- The substitution of fluorine to hydrogen increases lipid solubility, which in turn increases the transport and absorption of drug *in vivo*.
➢ 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.

➢ The replacement of ‘Hydrogen’ by ‘Fluorine’ at or near reactive sites causes inhibition of metabolism due to high C-F bond energy (Conte, L. et al., 1995).