HL **ISSN: 2231 – 3087(print) / 2230 – 9632 (Online)**
http://heteroletters.org **Vol. 2: (3), 2012, 361-377**

BENZOTHIAZOLES: KEY CONSTITUENTS OF BIOLOGICALLY ACTIVE COMPOUNDS

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Thiazole is a heterocyclic compound featuring both a nitrogen atom and sulfur atom as part of the aromatic five-membered ring (Fig.1). Recently the applications of thiazoles were found in drug development for the treatment of allergies, hypertension, inflammation, schizophrenia, bacterial, HIV infections, hypnotics and more recently for the treatment of pain, as fibrinogen receptor antagonists with antithrombotic activity and as new inhibitors of bacterial DNA gyrase B.

Benzothiazoles are bicyclic ring systems having S and N at 1 and 3 positions of the ring. (Fig.2). A number of 2- aminobenzothiazoles (Fig. 3) have been studied as central muscle relaxants and are found to interfere with glutamate neurotransmission in biochemical, electrophysiological and behavioral experiments. Benzothiazole derivatives have been studied and found to have various chemical and biological activities. Benzothiazole ring is made from thiazole ring fused with benzene ring. Benzothiazole ring is found to be possessing pharmacological activities such as antiviral, antibacterial, antimicrobial and fungicidal. They are also useful as antiallergic, antidiabetic, antitumor, antiinflammatory, anthelmintic, and anti HIV agents.

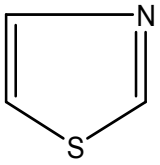


FIGURE 1

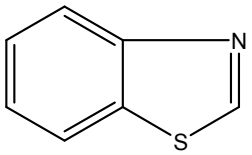


FIGURE2

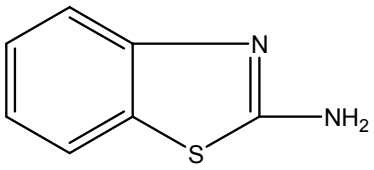


FIGURE 3

Benzothiazoles show antitumor activity, the phenyl substituted benzothiazoles with condensed pyrimido benzothiazoles and benzothiazolo quinazolines show antiviral activity and substituted 6-nitro and 6-aminobenzothiazoles show antimicrobial activity.

Given below is a brief account of various biological activities of benzothiazole ring and its derivatives.

PHARMACOLOGICAL ACTIVITIES OF BENZOTHIAZOLE AND ITS DERIVATIVES

I ANTITUMOR ACTIVITY

The benzothiazole moiety with various substitutions show antitumor activity. Its aminomethylphenyl (Fig.4) and carbonitrile (Fig.5) derivatives show selective growth inhibitory properties against human cancer cell lines[1] and proliferation of cells[2] respectively. Chlorinated and fluorinated derivatives of this moiety exhibit good antitumor activity in vitro as well as in vivo.

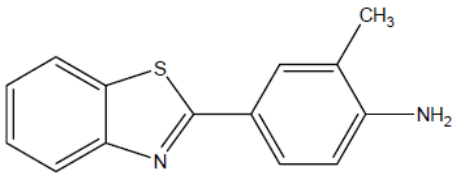


FIGURE 4

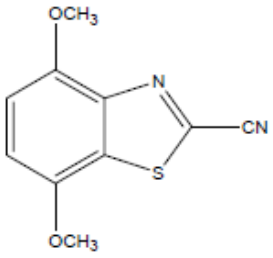


FIGURE 5

A further class of benzothiazoles have been synthesized which exhibit potent antitumor activity e.g. benzothiazole-substituted - 4-hydroxy cyclohexadienone[3] against renal, colon cancer cell lines and prodrug Phortess[4], human mammary tumor Xenografs[5].

Yoshida et al.[6] have synthesized a highly potent benzothiazole derivative bearing an amido group that displays excellent in vivo inhibitory effect on tumor growth. Yaseen Al-Soud et al.[7] synthesized series of N-[2-(4-(benzo[d] thiazol-2-yl) piperazin-1-yl-2-oxoethyl] benzene sulfonamide [Fig. 6] and tested in vitro, against a large panel of human cell lines derived from haematological [CD4+ human T-cells containing an integrated HTLV-1 genome (MT-4), CD4+ human acute T-lymphoblastic leukaemia (CCRF-CEM), human splenic β-lymphoblastoid cells (WIL-2NS), Human acute β-lymphoblastic leukemia (CCRF-5B)] and solid [skin melanoma (SK-28), breast adenocarcinoma (MCF-7), lung squamous carcinoma (SK-MES-1), hepatocellular carcinoma (HepG-2), Prostate carcinoma (DU-145) or normal tissues [lung fibroblasts (MRC-5)].

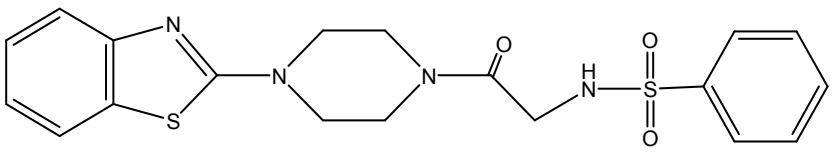
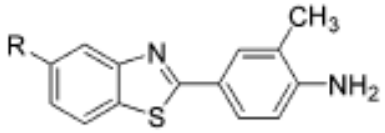


FIGURE 6

A series of new 2-phenylbenzothiazoles have been synthesized on the basis of the discovery of the potent and selective in vitro antitumor properties of 2-(3,4-dimethoxyphenyl)-5-

fluorobenzothiazole. Synthesis of analogues substituted in the benzothiazole ring was achieved via the reaction of o-aminothiophenol disulfides with substituted benzaldehydes under reducing conditions. Compounds were evaluated in vitro in four human cancer cell lines, and one of the compounds was found to possess exquisitely potent antiproliferative activity (GI50 < 0.1 nM for MCF-7 and MDA 468). Potent and selective activity was also observed in the NCI 60 human cancer cell line panel. Structure-activity relationships established that the compound stands on a pinnacle of potent activity, with most structural variations having a deactivating in vitro effect. Mechanistically, this new series of agents contrasts with the previously reported 2-(4-aminophenyl) benzothiazoles. One of the compounds is not reliant on induction of CYP1A1 expression for antitumor activity [8].



R=H FIGURE 7
R=F FIGURE 8

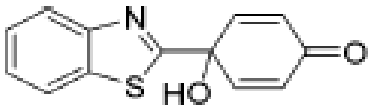


FIGURE 9

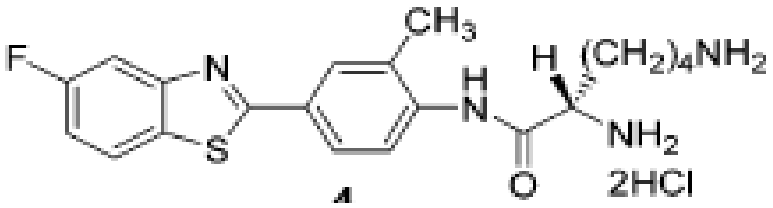


FIGURE 10
Chemical Structures of Antitumor Benzothiazoles (FIGURE 7-10)

II ANTIMICROBIAL ACTIVITY

Microbes are the causative agents for various types of diseases like pneumonia, ameobiasis, typhoid, malaria, common cough, cold and various infections and cause some severe diseases like tuberculosis, influenza, syphilis, and AIDS etc. To check the role of benzothiazole moiety as anti-microbial agent various approaches have been made. Benzothiazoles show chemotherapeutic activity and a considerable amount of work has been done on the synthesis of new potent antibacterial and antifungal benzothiazoles.

2-(Substituted phenyl sulfonamido)-6-substituted benzothiazoles[9] (Fig.11) were prepared and screened for their antibacterial activity against Bacillus subtilis, Salmonella typhii and dysentery. Several benzothiazolotriazole derivatives (Fig.12) were prepared[10] and found to possess good antibacterial activity against Staphylococcus aureus, Escherichia. coli and Candida albicans.

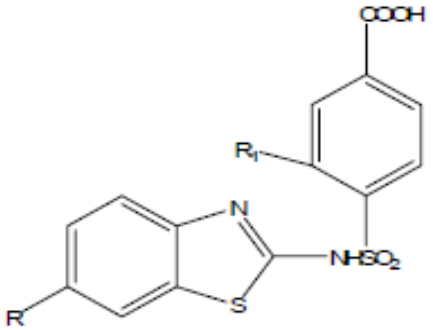


FIGURE 11

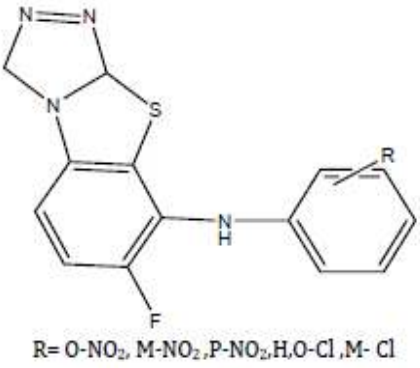
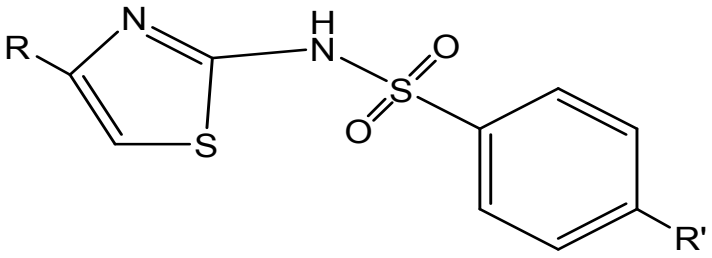


FIGURE 12

Iro Argyropoulou et al.[11], synthesized sulfonamidethiazole and benzothiazole derivatives [Fig.13] and reported their antimicrobial activity.



R = -4-CH_3, -5-CH_3 -H

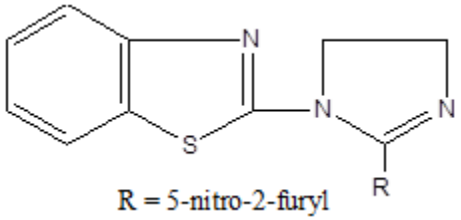
R′ = -NH_2, -NO_2, -CH_3

R = -OC_2H_5, -6-Cl, -4-CH_3

R′ = NO_2, -NH_2, -Cl

FIGURE 13

V. N. Koshelev[12] and V. I. Kelarev[13] reported the unique utility of derivatives of benzothiazoles. They produced data on the possibility of using 1-(2-benzothiazolyl)-2-R-Δ2-imidazolines as antimicrobial additive to rocket fuels. It was established that the most active in this series of compounds was 2-(5-nitro-2-furyl)-Δ2-imidazoline [Fig. 14], which fully suppresses the growth of microorganisms at concentrations of 0.005-0.01 wt. percent.



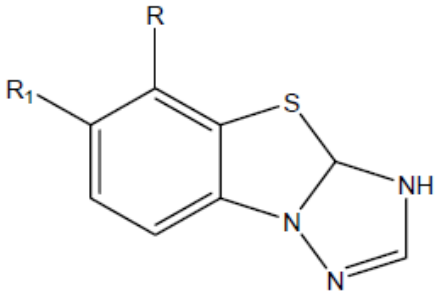
FIGURE– 14

III. ANTHELMINTIC ACTIVITY

Vijaya Javali et al.[14] synthesized, characterized and carried out the anthelmintic activity (perituma-posthuma) of fluoro substituted benzothiazole for biological and pharmacological screening. Various substituted 7-chloro-6-fluoro-N-(1,3-thiazol-2-yl)-1,3 benzothiazol-2-amine 1-(7-chloro-6-fluoro-1,3-benzothiazol-2-yl) thiourea containing different functional groups have been synthesized by condensing chloroacetyl chloride with 2-aminobenzothiazole in ammonium thiocyanate/HCl. The synthesized compounds were identified and confirmed on the basis of their spectral (UV-VIS, IR,^{1}HNMR and MASS) data. All the compounds have been screened for their antibacterial activity. M.M.J. Vijay Kumar et al.[15] carried out the synthesis and characterization of novel anthelmintic agents: N-Substituted-3-chloro-2-azetidinones. Various substituted 4-(m-hydroxy-p-methoxy phenyl)-1-[(6'-fluoro-7'-substituted (1,3)-benzothiazol-2'-yl) amido-2-phenyl]-3-chloro azetidin–2–one containing different functional groups have been synthesized by treating fluorochloroaniline with KSCN in presence of bromine in glacial acetic acid and ammonia to get 2-amino-6-fluoro-7-chloro-(1,3)-benzothiazole, which was treated with anthranillic acid in presence of dry pyridine to get 2-amino-N-(6-fluoro-7-chloro-(1,3)-benzothiazol-2-yl) benzamide. The above compound was refluxed with vanillin and alcohol in presence of conc. HCl to get 2-(3-hydroxy-4-methoxy benzylidene amino phenyl amido)-6-fluoro-7-chloro-(1, 3)- benzothiazole or Schiff's base. A solution of Schiff's base in 1, 4-dioxane was added to well-stirred mixture of chloroacetyl chloride and triethylamine to get azetidinone. To the above product different primary and secondary aromatic amines in presence of DMF were treated to get newly targeted compound by replacing chlorine at 7th position. The lead compounds were characterized by M.P., TLC, calculated elemental analysis, UV, IR, ^{1}HNMR and Mass spectral studies. The compounds were tested for anthelmintic activity against earthworms, Perituma posthuma and showed significant activity at low and high concentrations compared to standard; still further studies are requested.

Recent reports on benzimidazoles have forced the researchers to develop new drugs with anthelmintic activity, to fight against helminthiasis, which is causing untold misery to the infected individuals. Benzothiazole derivatives have been synthesised, which are sulfur isostere of benzimidazole, in the hope of achieving better anthelmintic activity. 8-Fluoro-9-substituted benzothiazolo (5, 1-b)-1, 3, 4-triazoles[16] (Fig.15), compounds were prepared and were studied for their anthelmintic activity against earthworm, Perituma posthuma. A compound with R= o -

nitro anilino substituent was found to possess excellent anthelmintic activity, than the other compounds, whereas all other compounds were found to possess low level of activity. 8-Bromo-9-substituted benzothiazolo (5, 1-b) -1, 3, 4-triazoles compounds were synthesized and examined for their anthelmintic activity against earthworm, Perituma posthuma . Some substituted imidazobenzothiazoles were examined in vivo for anthelmintic activity against H. nana infection and were found to show good to moderate activity[17]. The antiprotozal properties depended on the chemical structure of the position 2 substitution bearing group.



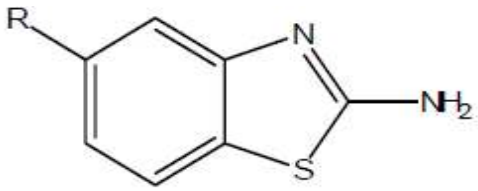
R = aniline, o-nitroanilino, m-nitroanilino, p-nitroanilino, o-methylanilino guanidine, hydrazine, p-methylanilino, diphenylamino, 2-carboxyanilino, 4-carboxyanilino, morpholino, piperzino

R1=F ,Br

FIGURE 15

IV. ANTICONVULSANT ACTIVITY

For anticonvulsant activity a large number of benzothiazole derivatives were evaluated and found to possess significant activity against various types of seizures. In the search of new anticonvulsant agents having benzothiazole nucleus, Amit B.N. et al.[18] synthesized a lot of substituted-2-benzothiazolamines (Fig.16).



R=CH_3, C_2H_5, n-prop,i-prop,n-but,n-pent, t-pent,$OCHF_2$,CF_3,OC_2H_5,CF_3,4-OCF_3, 5-OCF_3,7-OCF_3

FIGURE 16

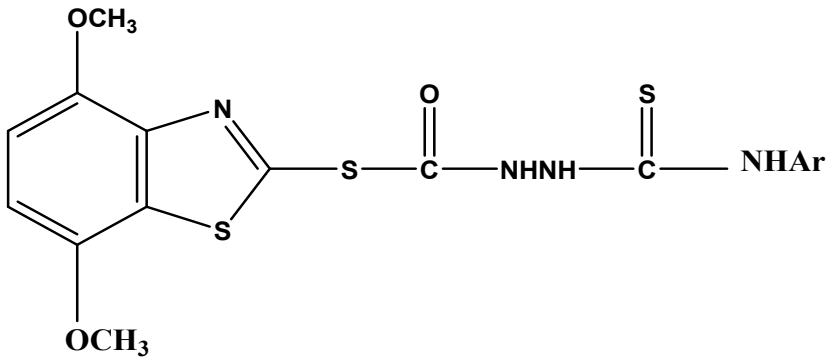


FIGURE 17

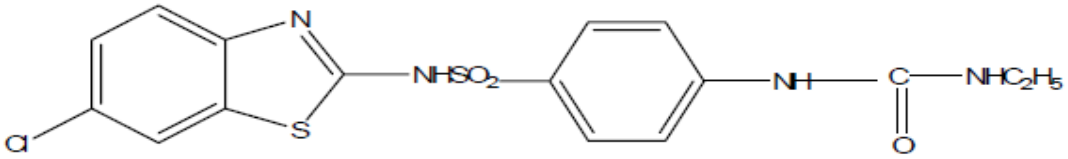


FIGURE 18

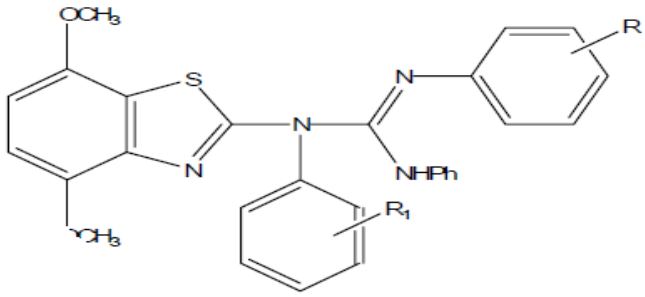


FIGURE 19

Nadeem Siddiqui et al.[19] synthesized benzothiazole semicarbazones as novel anticonvulsants. A series of 1,3-benzothiazol-2-yl semicarbazones were prepared in satisfactory yield and evaluated for their anticonvulsant, neurotoxicity and other toxicity studies. All the synthesized compounds were in good agreement with elemental and spectral data. Majority of the compounds were active in MES screen. Selected compounds were checked for their lipophilic character. Nadeem Siddiqui and Waquar Ahsan[20] synthesized and carried out anticonvulsant screening of benzothiazole incorporated barbituric acid derivatives.

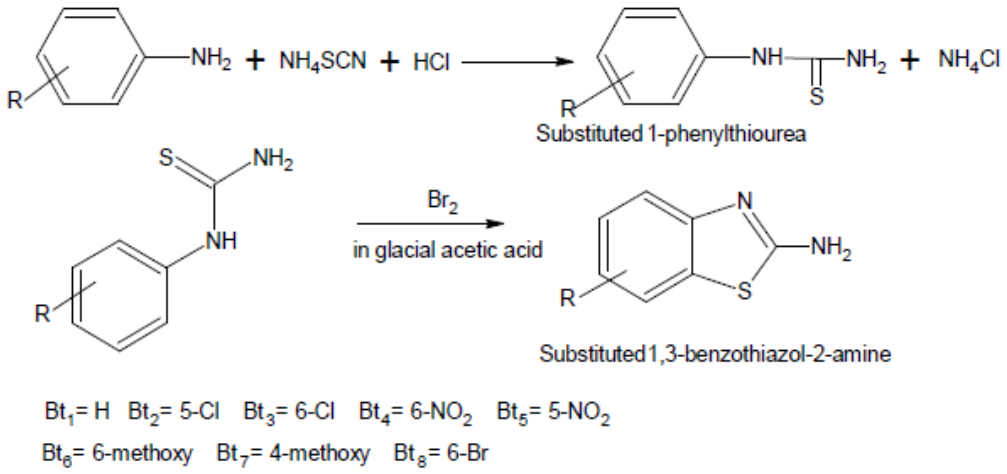
A series of 1-(6-substituted-1,3-benzothiazol-2-yl)-3-(substituted phenyl) hexahydro-2,4,6-pyrimidinetriones were synthesized starting from substituted anilines. These compounds contained two active anticonvulsant pharmacophores, benzothiazole and barbituric acid. Structures of the compounds were confirmed on the basis of different spectroscopic techniques. All the compounds were evaluated for their anticonvulsant activity. Three compounds showed promising anticonvulsant activities in Maximal Electroshock Seizure test (MES) and

subcutaneous pentylenetetrazole test (scPTZ). They also displayed a wide safety profile when tested for the minimal motor impairment test.

V. ANTI INFLAMMATORY ACTIVITY

Pyrazolones and pyrazolinones are more valuable non-steroidal anti-inflammatory agents. Phenylbutazone and its congeners incorporating a pyrazoline-3, 5-dione structure are more potent anti-inflammatory agents. In the recent years a number of benzothiazole derivatives have been synthesized and found to posses anti-inflammatory activity. A series of 2-(2-alkoxy-6-pentadecylphenyl) methyl thio-1H-benzimidazoles/ benzothiazoles and benzoxazoles were investigated for their ability to inhibit human cycloxygenase-2-enzyme (COX-2).[21]

P. Venkatesh and S.N. Pandeya[22] carried out the synthesis, characterisation and anti-inflammatory activity of some 2-amino benzothiazole derivatives. A series of some novel 2-amino benzothiazole derivatives were synthesized and evaluated for anti-inflammatory activity. The titled compounds were synthesized from the substituted aromatic amines through the intermediate substituted 1-phenylthiourea oxidation by bromine water in acidic medium. The purity of the synthesized compounds was judged by their C, H and N analysis and the structure was analyzed on the basis of IR, ^{1}HNMR and Mass spectral data. The anti-inflammatory activities of new compounds were determined by λ-Carrageenan-induced mice paw edema method using diclofenac sodium as a standard. Among the compounds tested three compounds Bt2 (5-chloro-1,3-benzothiazole-2-amine), Bt (6-methoxy-1,3-benzothiazole-2-amine) and Bt7 (6-methoxy-1,3-benzothiazole- 2-amine) were the most active compounds in these series when compared with diclofenac sodium. In the SAR study, the phenyl ring substituted with chloro at 5 position, methoxy substitution at 4 and 6-position in benzothiazole ring system showed better anti-inflammatory activity.



SYNTHESIS OF BENZOTHIAZOLES
FIGURE 20

C. Suresh et al.[23] carried out the anti-inflammatory activity of 3-(2-hydrazino benzothiazoles) -substituted indole-2-one. Benzothiazoles and Isatins have emerged as structurally novel anti inflammatory agents. Therefore various 3-(2-hydrazino benzothiazoles)-substituted indole-2-one, were synthesized by condensation of various 2-hydrazino benzothiazole, 2-hydrazino -1,4-thiazine and 2-acid hydrazide benzothiazoles with different substituted indole -2,3-diones

(Isatins). The structures of the synthesized compounds were characterized by FTIR, ^{1}HNMR and elemental analysis. All the synthesized compounds were screened for anti inflammatory activity by using carrageenan induced rat hind paw odema model. Kamlesh D. Niranjane and Mayura A. Kale [24] did the synthesis and anti-inflammatory activity of some novel derivatives of 2-amino-3-cyano-14-imino-10-methoxy-4-methylthio pyrimido [2,1-b] pyrazolo [4,5-d] pyrimido [2,1-b] benzothiazole. Novel derivatives of 2-amino-3-cyano-14-imino-10-methoxy-4-methylthio pyrimido [2,1-b] pyrazolo [4,5-d] pyrimido [2,1-b] benzothiazole were synthesized from starting material 2- amino -6-methoxy benzothiazole and evaluated for their anti-inflammatory activity. It was concluded that some of the compounds showed excellent anti-inflammatory activity as compared with others.

VI. ANTIOXIDANT ACTIVITIES

Antioxidants were important as prophylactic and therapeutic agents in many diseases. Free radicals are formed as a result of normal organ functions or excessive oxidative stress[25]. Free radicals of high levels can cause damage to biomolecules such as lipids, proteins, enzymes and DNA in cells and tissues, resulting in mutations which can lead to malignancy. DNA mutation is a critical step in carcinogenesis. Role of free radicals was discovered in cancer, diabetes, cardiovascular diseases, autoimmune diseases, neurodegenerative disorders, aging and other diseases which has led to new medical insight[26, 27]. Minimizing a oxidative damage is primary prevention or treatment of these diseases, since antioxidants may stop the free-radical formation, or interrupt an oxidizing chain reaction. The antioxidant behaviour of a series of substituted indoline-2-ones and indoline-2-thiones was investigated using an oxygen radical absorbance capacity assay. The results indicated that the examined indoline derivatives had effective activities as radical scavengers[28].

Nilgun Karal, et al. [29] carried out the synthesis of new spiroindolinones incorporating a benzothiazole moiety as antioxidant agent. 3H-Spiro[1,3-benzothiazole-2,30-indol]-20(10H)-ones were synthesized by treating the 5-substituted 1H-indole-2,3-diones with 2-aminothiophenol in ethanol. The structures were confirmed by elemental analysis, spectrometry (IR, ^{1}H NMR, ^{13}C NMR, HSQC-2D and LCMS-APCI) and single crystal X-ray analysis. The new compounds were screened for their antioxidant activities such as the Fe3þ/ascorbate system induced inhibition of lipid peroxidation (LP) in liposomes, trolox equivalent antioxidant capacity (TEAC), scavenging effect on diphenylpicryl hydrazine (DPPH_), and reducing power. These compounds showed potent scavenging activities against DPPH_ and 2,20-azino-bis(3-ethylbenzthiazoline- 6-sulphonic acid) (ABTS_þ) radicals, reducing powers, and showed strong inhibitory capacity on lipid peroxidation. Compound 4a incorporating methyl both at R1 and R2 was found to be the most potent antioxidant described in this study. Compounds 3b and 4b were selected as representative compounds by the National Cancer Institute for screening against anticancer activity and these compounds were found to be cytotoxic against CNS cancer cell line SNB-75 in the primary screen.

C. Suresh et al.[30] carried out the synthesis of 2-hydrazino benzothaizoles-2-amino-(4-substituted)-acetanilides for anti oxidant activity. Benzothiazoles and N-Substituted-α-chloro acetanilides have emerged as structurally novel anti oxidant agents. Therefore various 2-hydrazino benzothiazoles (substituted)-2-amino-(4-substituted) acetanilides, were synthesized by an aromatic amine treated with chloro acetyl chloride in presence of glacial acetic acid and

sodium acetate which gives chloro acetanilides. The condensation of various substituted chloro acetanilides with 2-hydrazino benzothiazoles, 2-hydrazino benzothiazine and 2-acid hydrazide benzothiazole in the presence of dry 1,4-dioxane and triethyl amine gave title compounds. The structures of the synthesized compounds were characterized by FT IR, ^{1}HNMR and elemental analysis. All the synthesized compounds were screened for antioxidant activity by 1,1-diphenyl-2-picryl hydrazil method. All the compounds showed very good anti-oxidant activity with IC50 values in the range 6.8 to 12.93 μM. Damien Cressier et al.[31] carried out the synthesis, antioxidant properties and radioprotective effects of new benzothiazoles and thiadiazoles. The work included the synthesis and characterization of new compounds derived from benzothiazoles and thiadiazoles. It was observed that structural modifications on these skeletons affected the antioxidant activity. Thiol and aminothiol compounds derived from thiadiazoles and benzothiazoles showed an interesting antioxidant property. The radioprotective activity has also been evaluated in mice. Some of these compounds could be good radioprotectors.

VII. MISCELLANEOUS

S. Hout *et al*.[32] synthesized 2-substituted 6-nitro benzothiazoles and 2-substituted -6-amino benzothiazoles [Fig 21] and assessed in vitro anti-proliferative activity of benzothiazole on malarial parasites and also examined their toxicity on human monocytes.

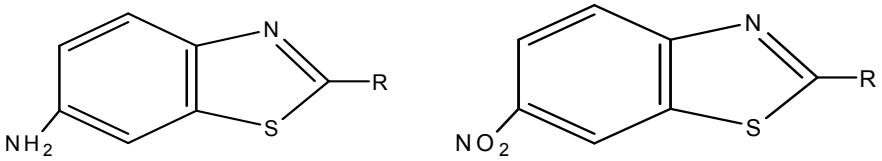
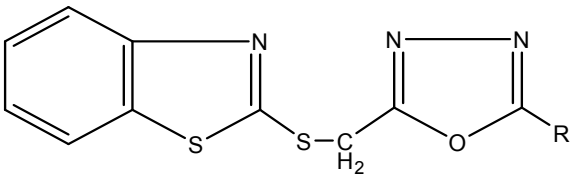


FIGURE 21

1-R-2-(2-Benzothiazolylthiomethyl)-Δ^2-imidazolines are effective antioxidant and polyfunctional additives for lubricating oils[33] where as 2-(2-benzothiazolyl-thiomethyl)-5-R-1,3,4-oxadiazoles [Fig. 22] were proposed for use as light and heat stabilizers for polymeric composites and cellulose containing textile materials[34] and are also highly effective in the inhibition of the thermal polymerization of styrene and 2-methyl-5-vinylpyridine[35].



R = 2-Benzothiazolyl thiomethyl

FIGURE 22

Diuretics are an important class of drugs used in the treatment of edema, heart failure or in hepatic, renal and pulmonary diseases. They are used, alone or in combination of antihypertensive agents in the treatment of high blood pressure. Etoxzolamide [Fig. 23] a benzothiazole derivative is clinically effective diuretic carbonic anhydrase inhibitor. It is orally active but upsets the acid-base balance and could only be given intermittently[36].

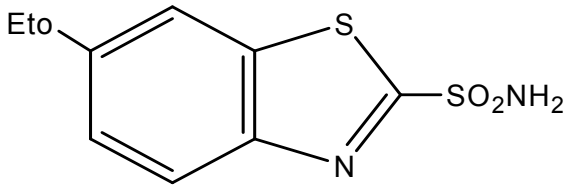


FIGURE 23

A number of benzothiazoles showed selective antiproliferative activity, especially the phenyl substituted benzothiazoles while condensed pyrimido benzothiazoles and benzothiazolo quinazolines exert antiviral activity. Substituted 2-(4-aminophenyl) benzothiazoles were developed and examined, in vitro, for their antiproliferative activity in ovarian, breast, renal and colon carcinoma human cell lines, imidazo benzothiazoles as well as polymerized benzothiazoles and other substituted benzothiazoles showed remarkable antitumor activity against malignant cell lines[37]. A series of potent and selective antitumor agents, mostly from substituted 2-(4-aminophenyl) benzothiazoles, were developed and comprised a novel class of antitumor active compounds, especially against sensitive breast tumor cell lines, e.g. MCF-7 and MDA 468 and extended to certain colon, lung, melanoma, renal and ovarian tumor cell lines.

Pyrimido benzothiazoles and benzothiazolo quinoline derivatives, imidazo benzothiazoles as well as polymerized benzothiazoles showed remarkable antitumor activity[38]**.**

Jitender K. Malik *et al.*[39] synthesized some new benzothiazole derivatives and reported their antibacterial activity against gram (+ve) and gram (–ve) bacteria: *Bacillus subtilis, Bacillus pumilus, Escherichia coli* and *Pseudomonas aureginosa.*

Thiazole derivatives are proved agents against constipation[40], as potent and selective human adenosine A_3 receptor antagonists[41-43], as inhibitors of VEGF receptors I and II[44], as vanilloid receptor I TRPVI antagonists[45], as potent and selective acetyl CoA carboxylase 2 inhibitors[46] and have potential as possible treatment of Alzheimer's[47], as disease noncovalent DNA-binding properties related to leinamycin[48].

Hutchinson *et al.*[49] synthesized fluorinated analogues of 2-(4-aminophenyl) benzothiazoles and 2-(4-nitrophenyl) benzothiazole [Fig. 26] which successfully block C-oxidation. Entry of fluorine enhances potency, broadens the antitumor spectrum and hopefully optimizes the clinical utility of this enigmatic group of compounds.

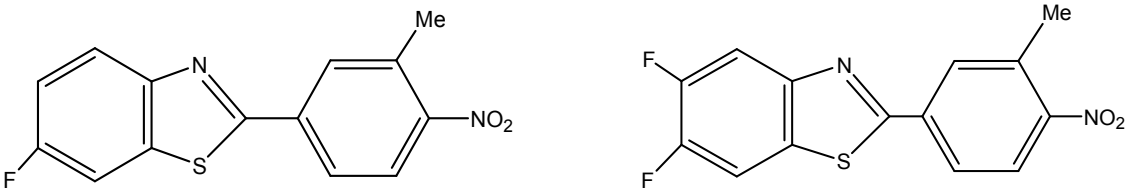


FIGURE 26

H. M. Dıaz et al.[50] carried out the antidiabetic activity of N-(6-substituted-1,3-benzothiazol-2-yl) benzenesulfonamides. N-(6-Substituted-1,3-benzothiazol-2-yl) benzenesulfonamide derivatives were synthesized and evaluated for their in vivo antidiabetic activity in a non-insulin-dependent diabetes mellitus rat model. Several compounds synthesized showed significant lowering of plasma glucose level in this model. As a possible mode of action, the compounds were in vitro evaluated as 11b-hydroxysteroid dehydrogenase type 1 (11b-HSD1) inhibitors. The most active compounds were docked into the crystal structure of 11b-HSD1. Docking results indicated potential hydrogen bond interactions with catalytic amino acid residues. Pattan S. et al.[51] synthesized2-amino[5`(4-sulphonylbenzylidine)-2,4-thiazolidnedione]-7-chloro-6-flurobenzothi-azole series and screened for their antidiabetic activity on albino rat by alloxan induced tail tipping method.

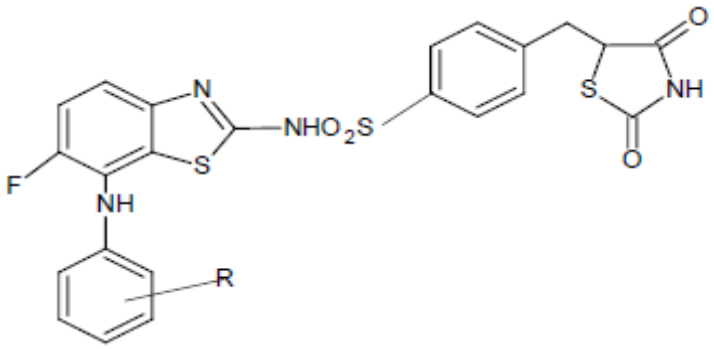


FIGURE 27

Serdons K et al.[52] synthesized F-labeled 2-(4′-fluorophenyl)-1-3-benzothiazoles. They evaluated it as amyloid imaging agent in Alzheimers disease in comparison with [11C]PIB (11C labeled 6-hydroxy-2-(4”-N- [11C] methylaminophenol)-1,3- benzothiazole and showed excellent characteristics comparable with those of [11C]PIB, namely good affinity for amyloid plaques present in human Alzheimers disease.

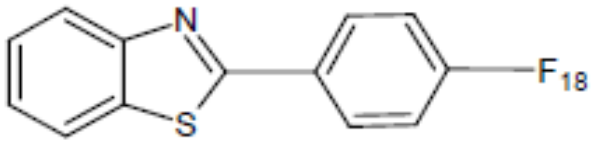
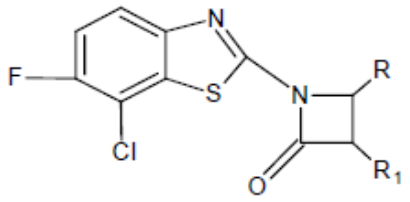


FIGURE 28

Gurupadayya B et al.[53]synthesized azatidin-2-ones and thiazoline-4-ones encompassing benzothiazole derivatives and evaluated for anti-inflammatory activity using carrageenan induced rat hind paw oedema method. Diclofenac sodium was used as standard drug.



R= H $R_1 = C_6H_5$

FIGURE 29

Chi B et al. [54] synthesized triamide derivatives based on benzothiazole templet. A series of these compounds showed potent enterocyte-specific microsomal triglyceride transfer protein (MTP) inhibitors. Inhabitation of MTP by small molecules, therefore lead to reduction in plasma triglycerides and cholesterol level. Maharan M et al. [55] synthesized series of benzothiazole-2- yl-dithiocarbamates along with copper complexes via reaction of suitable alkyl or heteroaryl halide with sodium salt of benzothiazole-2-yl-dithiocarbamic acid followed by complexation with copper sulphate and selected derivatives checked for their schistosomicidal activity against Schistosoma mansoni.

Amir M et al [56] synthesized 1, 3, 4-thiadiazole and imidazolline derivatives containing benzothiazole and screened for both antibacterial and antifungal activity using cup-plate agar diffusion method. Ofloxacine (50µg/ml) and ketokonazole (50µg/ml) were used as std. drug for antibacterial and antifungal activity respectively. Antimicrobial screening was performed against E. coli, S. aureus, C. albicans and antifungal activity against Aspergillus flavus and Candida albicans.

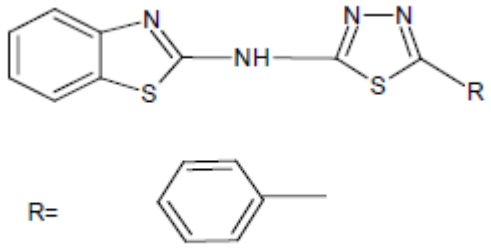


FIGURE 30

Nagarajan A et al.[57] synthesized benzothiazole substituted thiazolidinone. Compounds were tested against pathogenic bacteria P. mirabilis, S. Aureus and S. typhi by disc diffusion method. Streptomycin was used as standard drug.

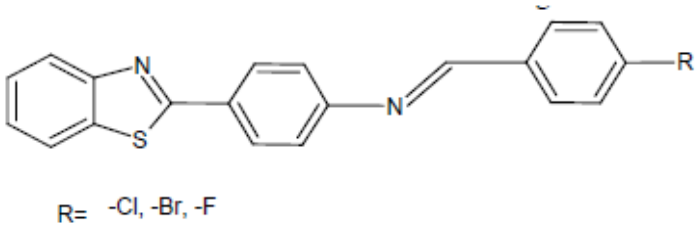


FIGURE 31

Murthi Y et al.[58] synthesized some new 2- mercaptobenzothiazoles and correlated the effect on antimicrobial potency by varying the substituents in benzene part of the benzothiazole ring system. Anti-microbial screening was performed against E. coli, S. aureus, C. albicans and antifungal activity against Aspergillus flavus and Candida albicans at conc. 100µg/ml using agar plate Kirby-Bauer disc diffusion method in DMF as solvent. Ofloxacine (100µg/ml) and griciofulvin (100µg/ml) were used as standard drugs for antibacterial and antifungal activity respectively.

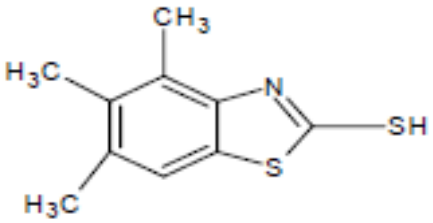


FIGURE 32

Rajeeva B, et al.[59] synthesized some new 2-substituted benzothiazole derivatives by refluxing benzothiazolylcarboxyhydrazide with different aryl acids in phosphoryl chloride and screened the derivative for antimicrobial activity against B. subtilis, E. coli and P. aeruginosa by disc diffusion method at conc. 100µg/ml. The activity was compared to antibiotic ciprofloxine.

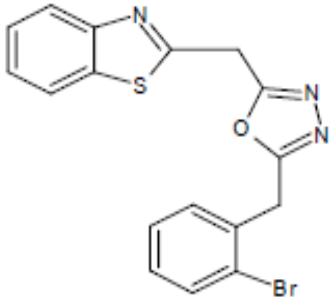


FIGURE 33

Gupta S et al.[60] reported synthesis of series of pyrimido [2, 1-b] benzothiazoles by conjugation addition to imino nitrogen of 2-aminobenzothiazoles to alkyne β-carbon atom of aceytylenic acid followed by ring closure and synthesized compounds were studied for antimicrobial activity against E. coli and Enterobacter as test organisms at conc 100µg per disc using vancomycine and meropenam as standard drugs.

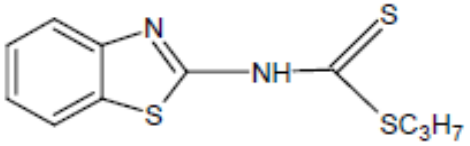


FIGURE 34

Kumbhare RM et al.[61]synthesized new benzothiozole and benzisoxazole from 2-amino 5/6-hydroxybenzothiazole, 6- hydroxy-3-methyl-1, 2-benzisoxal and different dihaloalkanes and screened for their antimicrobial activity against Staphylococcus aureus, and E. coli by disc diffusion method and anti fungal activity against Aspergillus flavus, and Candida albicans. Ciprofloxacin (10µg/ml) and fluconazole (10µg/ml) were used as standard drugs for antibacterial and antifungal activity respectively.

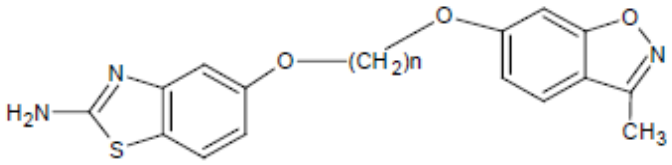


FIGURE 35

VIII. RECENT ADVANCES

Xuan-Hong Shi et al.[62] carried out the synthesis and biological evaluation of novel benzothiazole-2-thiol derivatives as potential anticancer agents. A series of novel benzothiazole-2-thiol derivatives were synthesized and their structures determined by ^{1}H-NMR, ^{13}C-NMR and HRMS (ESI). The effects of all compounds on a panel of different types of human cancer cell lines were investigated. Among them, pyridinyl-2-amine linked benzothiazole-2-thiol compounds exhibited potent and broad-spectrum inhibitory activities. One of the compounds displayed the most potent anticancer activity on SKRB-3 (IC50 = 1.2 nM), SW620 (IC50 = 4.3 nM), A549 (IC50 = 44 nM) and HepG2 (IC50 = 48 nM) and was found to induce apoptosis in HepG2 cancer cells. P. Ravi Prasad et al.[63] carried out the synthesis and biological evaluation of some fused pyrimido-benzothiazole derivatives. New series of 2-substituted aryl amine, hetero-aryl amine and active methylene group compound derivatives of 9-chloro- 3-cyano-8-fluoro-2-methylthio-4-oxo-4H-pyrimido [2, 1-b] [1, 3] benzothiazole were synthesized. The antimicrobial activity of the synthesized compounds was studied by disc diffusion method using various strains of microbes and compared with the standard drug streptomycin. The antifungal activity was also evaluated against four fungal strains and compared with Amphotericin-B as standard. The biological activity of the synthesized compounds was found to be good to moderate.

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Received on June 2, 2012.