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## Pharmacological potentials of various substituted benzothiazole derivatives: A mini-review

**Mohammad Asif**

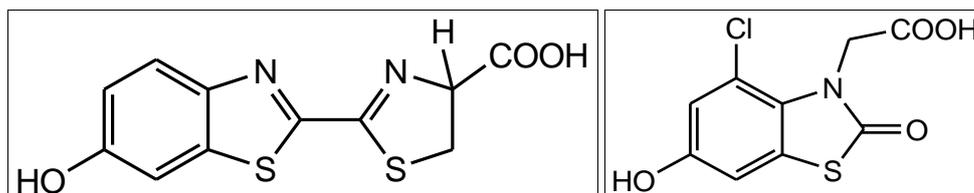
### Abstract

Benzothiazoles were found to possess a broad spectrum of pharmacological activity of clinical importance in the areas of anticancer, antitubercular, carbonic anhydrase inhibitors, local anesthetics, hypoglycemic, anti-inflammatory, analgesic, anti-microbial, cardiovascular drugs, central dopaminergic agents, and choleric agents. The substituted Benzothiazoles were found to possess a broad spectrum of pharmacological activity of clinical importance.

**Keywords:** pharmacological activities, benzothiazoles, heterocyclic compound

### Introduction

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 chosen for the drug as a diuretic (Acetazolamide). Benzothiazole with Thiadiazole group was reported to possess various pharmacological activities of clinical importance. Thiadiazole derivatives are well known to have several biological and antimicrobial activities, this also having anti-inflammatory, and anticonvulsant activities. In search of the 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 literature prompted us to substituted benzothiazole compounds with diverse biological activities [1-18]. The small and simple benzothiazole nucleus is present in compounds involved in research aimed at evaluating new products that possess interesting biological activities, such as antitumor, antimicrobial, anthelmintic, antileishmanial, anticonvulsant, and anti-inflammatory. Benzothiazole has no household use. It is used in industry and research. Luciferin, which occurs in fireflies and glowworms, upon enzymatic oxidation causes bioluminescence in these insects. The herbicide Benazoline serves as an example of a synthetic benzothiazole derivative with biological activity. Polymethine dyes derived from benzothiazoles are employed for the spectral sensitization of photographic emulsions [19-25].



Luciferin

Benazoline

### Biological Profile

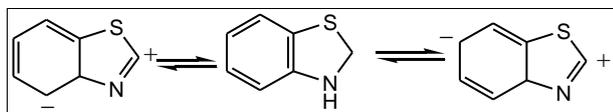
**Chemistry:** Benzothiazole is an organosulfur compound. It is a colorless, slightly viscous liquid that is used in industry and research. A derivative of benzothiazole is the light-emitting component of luciferin, found in fireflies. Some dyes, such as thioflavin, and pharmaceutical drugs, such as riluzole, have benzothiazoles as a structural motif. Chemically benzothiazole is a benzofused five-membered heterocyclic system containing S and N heteroatoms. It is a colorless, slightly viscous liquid with a melting point of 2°C, and a boiling point of 227-228 °C. The density of benzothiazole is 1.238 g/ml (25°C). It is a heterocyclic organic compound. Benzene fused heterocyclic compounds containing one

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sulfur and one nitrogen atom separated by a carbon atom are called benzothiazole. The heterocyclic system exhibits aromatic characters and shares comparable chemical, physical and biological properties of quinoline isosteres. It is sparingly soluble in water but easily soluble in CS<sub>2</sub>. Sulfur atoms exhibit characteristics of both -S-, =S=, later sulfur atom has an expanded outer shell. Resonance of this type of the benzene ring of the benzothiazole implies electrophilic substitution at positions 4 and 6 [20-30].



2-amino derivative of benzothiazole has interesting tautomerism.



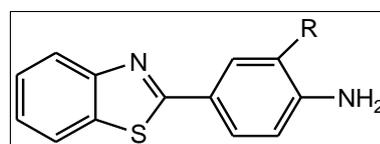
The development of new methods for the synthesis of heterocyclic compounds represents an expanding area of organic chemistry. The benzimidazole, benzoxazole, and benzothiazole structural motifs are found in numerous pharmaceutical agents with a wide range of biological properties. Although a wide range of methods is available for the synthesis of the heterocyclic compounds, a real need exists for new simple procedures that support many kinds of structural diversity and various substitution patterns in the target. Benzothiazole is a privileged bicyclic ring system due to its potent antitumor activity and other important pharmaceutical utilities, the synthesis of these compounds is of considerable interest [31-37].

**Biological Profile:** Benzothiazoles are bicyclic ring systems with multiple applications. In the 1950s, several 2-amino benzothiazoles were intensively studied as central muscle relaxants. Since then medicinal chemists have not taken an active interest in this chemical family. Biologist's attention was drawn to this series when the pharmacological profile of Riluzole [38] was discovered. Riluzole (6-trifluoromethoxy-2-benzothiazolamine, PK-26124, RP-25279, Rilutek) was found to interfere with glutamate neurotransmission in biochemical, electrophysiological, and behavioral experiments. After that benzothiazole derivatives have been studied extensively and found to have diverse chemical reactivity and a broad spectrum of biological activity.

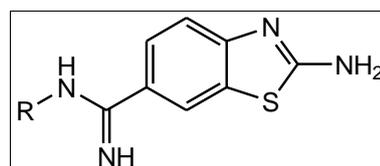
Although they have been known from long ago to be biologically active [39-41], their varied biological features are still of great scientific interest nowadays. Benzothiazoles show very intensive antitumor activity, especially the phenyl substituted benzothiazoles [42-44], whereas the condensed pyrimido benzothiazoles and benzothiazolo quinazolines exert antiviral activity [45]. Recently, Racane *et al* have [46] described the synthesis of bis-substituted amidino benzothiazoles as potential anti-HIV agents. Substituted 6-nitro- and 6-amino benzothiazoles [47] show microbiological activity. Here is a brief account of various alterations conducted on the benzothiazole ring and their associated biological activities.

**Antitumor activity:** A series of potent and selective antitumor agents mostly from substituted 2-(4-aminophenyl)

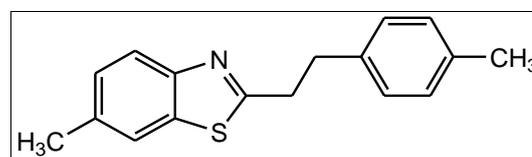
benzothiazoles were developed and examined for their *in vitro*, antitumor activity to ovarian, breast, lung, renal, and colon carcinoma human cell lines [48-58]. Pyrimido benzothiazole and benzothiazolo quinoline derivatives [59], imidazo benzothiazoles [60, 61] as well as, polymerized benzothiazoles [62] also showed antitumor activity. The 2-(4-aminophenyl) benzothiazoles [63, 64] (1) comprise a novel mechanistic class of antitumor agents. Their unusual activity was first recognized from the distinctive biphasic dose-response relationship shown in *in vitro* assays against sensitive breast tumor cell lines, e.g. MCF-7 and MDA-468. Potency against these breast lines and others was independent of the estrogen or growth factor receptor status of the cells. Introduction of methyl or halogen substituent into the 3'-position of the 2-phenyl group enhances potency and extends the spectrum of action to certain colon, lung, melanoma, renal, and ovarian cell lines. The 6-amidino-substituted-2-amino benzothiazoles (2), N-methyl-2-(4-cyano styryl) benzothiazolium, cyano-substituted-2-styryl benzothiazoles (3), and amidino and bis-amidino-substituted 2-styryl benzothiazoles (4) were prepared [65]. All compounds were tested on cytostatic activities against malignant cell lines.



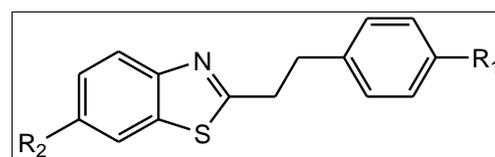
(1) R=CH<sub>3</sub>, H, Cl, Br



(2) R=CH(CH<sub>3</sub>)<sub>2</sub>, CH<sub>3</sub>CH<sub>2</sub>, 



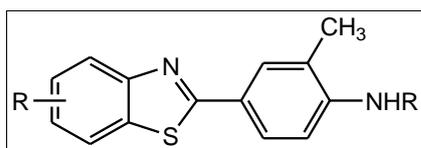
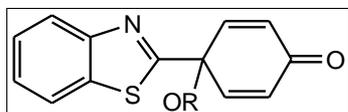
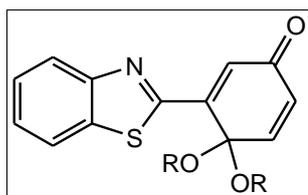
(3)



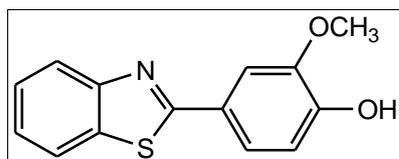
(4) R<sub>1</sub>=R<sub>2</sub>=H, CN

The synthesis of fluorinated analogs of 2-(4-aminophenyl) benzothiazoles successfully blocks C-oxidation. 2-(4-amino-3-methylphenyl)-5-fluorobenzothiazoles (5) is the favored analog for clinical consideration possessing enhanced efficacy *in vitro* and superior potencies against human breast and ovarian tumor xenografts implanted in mice [54]. Quinol esters and ethers (6) derived from the oxidation of 2-(4-hydroxyphenyl) benzothiazoles and quinone monoketals (7) from the oxidation of 2-(3-

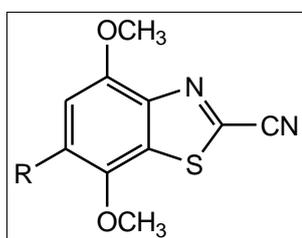
hydroxyphenyl) benzothiazoles, respectively, have significantly improved and extended antitumor potency *in vitro* against pairs of breast and colon human tumor cell lines [66].

(5) R=H, R<sub>1</sub>= 5-F(6) R=CH<sub>3</sub>CO, CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, C<sub>3</sub>H<sub>7</sub>, CH<sub>2</sub>CH=CH(7) R=CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>

The oxidation reactions of 2-(4-hydroxy-3-methoxyphenyl) benzothiazole (8) were studied. In *in vitro* growth inhibition tests against the human breast cancer cell lines MCF-7 and MDA-468 (over 7 and 10 days respectively) determined by MTT assay, the phenolic benzothiazole gave IC<sub>50</sub> values (dose to inhibit cell growth by 50%) of 0.62 and 0.06 μM, respectively [67]. The synthesis of 2-cyano-4, 7-dimethoxy benzothiazoles (9), the 2-cyano derivatives exhibit interesting *in vitro* antitumor activity [68].

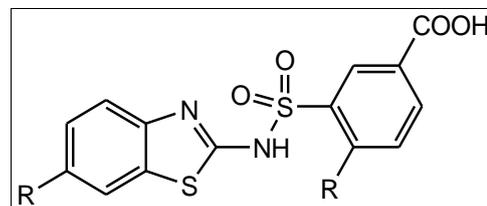
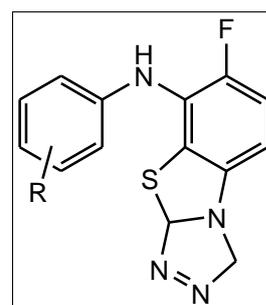
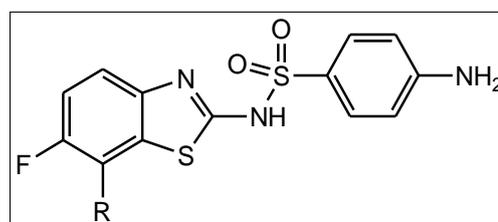


(8)

(9) R=H, NHCH<sub>3</sub>CO

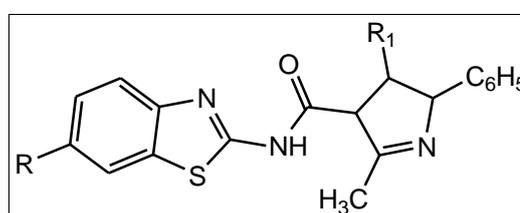
**Antimicrobial activities:** Benzothiazoles show a wide spectrum of chemotherapeutic activity and a considerable amount of work has been done on the synthesis of new potent antibacterial and antifungal benzothiazoles. Some new 2-(substituted phenyl sulfonamido)-6-substituted benzothiazoles (10) and screened them for their antibacterial activity against *B. subtilis*, *S. typhi*, and *S. dysentery*. Compounds with R = Br and R<sub>1</sub> = CH<sub>3</sub>, NH<sub>2</sub>, and I were found more active and others were less or moderately active [69]. Various benzothiazolo triazole derivatives (11) were

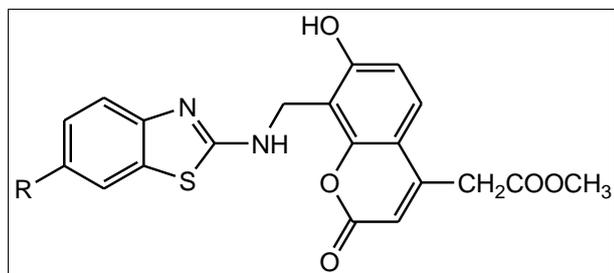
prepared and found to possess good activity against *S. aureus*, *E. coli*, and *C. albicans*. Some 6-fluoro-7-(substituted)-(2-N-p-anilinosulfonamido) benzothiazoles (12) [R=o-nitroanilino, m-nitroanilino, p-nitroanilino, o-chloroanilino, m-chloroanilino, p-chloroanilino, anilino, morpholino, piperazine, dimethylamino] were synthesized and studied for their antibacterial and antifungal activities. All compounds showed moderate activity against *S. aureus*, *S. cilbus*, and *C. ahlicans* [70, 71].

(10) R=CH<sub>3</sub>, OCH<sub>3</sub>, Cl, Br; R<sub>1</sub>=CH<sub>3</sub>, I, NH<sub>2</sub>(11) R=H, o-NO<sub>2</sub>, p-NO<sub>2</sub>, m-NO<sub>2</sub>, o-Cl, m-Cl

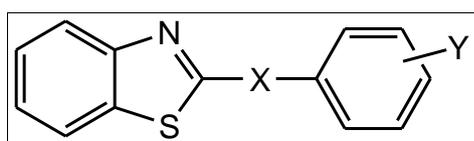
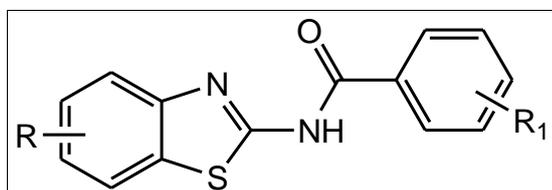
(12) R=o-nitroanilino, m-nitroanilino, p-nitroanilino, o-chloroanilino, m-chloroanilino, p-chloroanilino, morpholino, piperazino, dimethylamine

Various benzothiazolyl carboxamido pyrazoline derivatives (13) and studied their antimicrobial activity. Compounds having R=CH<sub>3</sub> and R<sub>1</sub>= o-OCH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>, showed no activity, and when R=Cl and R<sub>1</sub>= p-OCH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>, they were active against *S. aureus*. The rest of the compounds showed the activity against, *S. aureus*, *E. coli*, *P. aeruginosa*, *K. pneumoniae* and *P. mirabilis* [72]. Some 8-[(6-substituted-1,3-benzothiazol-2-yl) aminomethyl] substituted hydroxy coumarins (14) were screened for their antibacterial activity against *S. Aureus* and *E. coli*. The compounds were also screened for antifungal activity against *brassicicola* and *F. udam*. All the compounds showed moderate activity [73].

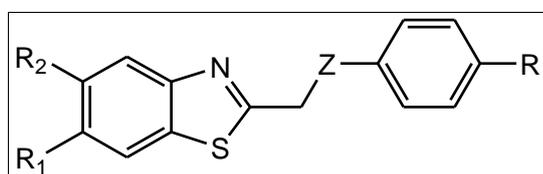
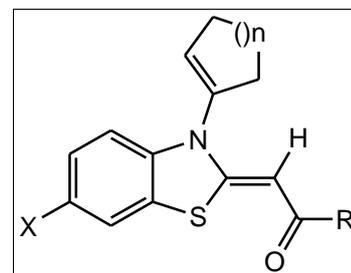
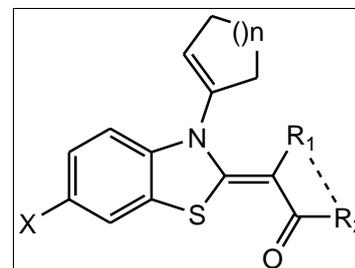
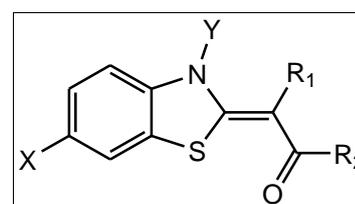
(13) R<sub>1</sub>= Cl, CH<sub>3</sub>; R<sub>2</sub>=C<sub>6</sub>H<sub>5</sub>, o-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>, p-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>

(14) R= Cl, CH<sub>3</sub>, OC<sub>2</sub>H<sub>5</sub>, H, NO<sub>2</sub>

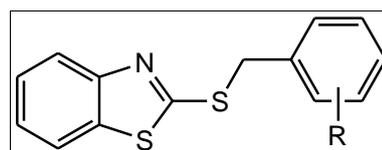
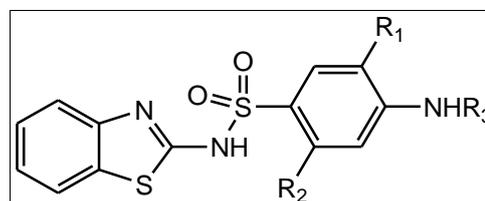
Few 5,6-disubstituted-2-(substituted phenyl carboxamido) benzothiazoles (15) and found them active against *M. tuberculosis*, *S. typhi*, *S. cinereus*, *C. albicans*, *T. rubrum*, *T. mentagrophytes* etc. The compounds were also active against some helminths like *H. iniitia*. A few 2-[(4-amino/2,4-diaminophenyl)] sulfonyl derivatives of benzothiazoles (16) were found to possess good activity against *E. coli* [74, 75].

(15) X=S, SO<sub>2</sub>; Y= 4-NH<sub>2</sub>, 2,4-diNH<sub>2</sub>, 2,4-diNHCH<sub>3</sub>COO(16) R=5-Cl, 6-F, 5,6-diCl; R<sub>1</sub>= H, 2-F, 4-F,2,6-diF, 2-CF<sub>3</sub>, 3-CF<sub>3</sub>

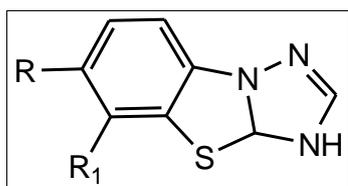
A series of multisubstituted benzoxazoles, benzimidazoles, and benzothiazoles (17) as non-nucleoside fused isosteric heterocyclic compounds and tested for their antibacterial activities against *S. aureus*, *S. faecalis*, *B. subtilis* as gram-positive and *E. coli*, *K. pneumoniae*, *F. aeruginosa* as gram-negative bacteria, and yeast *C. albicans*. The synthesized compounds possessed a broad spectrum of activity against the tested microorganisms at MIC values between 100 and 3.12 μg/ml. Benzothiazole ring system enhanced the antimicrobial activity against *S. aureus* [76]. A series of N-cycloalkylidene-2,3-dihydro-1,3-benzothiazoles (18), N-cycloalkyl-2-acylalkylidene-2,3-dihydro-1,3-benzothiazoles (19), and N-alkyl-2-acylalkylidene-2,3-dihydro-1,3-benzothiazoles (20) were tested for *in vitro* antibacterial and antifungal activities against four Gram-positive and five gram-negative bacteria. The findings obtained showed that some of the tested compounds were effective against bacterial strains, whereas only a few compounds exhibited moderate antifungal activity against the yeast strains evaluated [77].

(17) Z=O, S; R= H; R<sub>1</sub>= H, NO<sub>2</sub>, Cl; R<sub>2</sub>= H, NO<sub>2</sub>(18) X=H,F, OCH<sub>3</sub>, CH<sub>3</sub>; n=8,3 R=CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, C<sub>3</sub>H<sub>7</sub>, C<sub>4</sub>H<sub>9</sub>, C<sub>6</sub>H<sub>13</sub>(19) X=H, n=8,3 R<sub>1</sub>=CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, C<sub>6</sub>H<sub>5</sub>, -(CH<sub>2</sub>)<sub>3</sub> R<sub>2</sub>=H, (CH<sub>2</sub>)<sub>3</sub>(20) X=H, Y=C<sub>6</sub>H<sub>5</sub>; R<sub>1</sub>=C<sub>6</sub>H<sub>5</sub>, -CH<sub>2</sub>-N(CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>)-(CH<sub>2</sub>)<sub>2</sub>-; R<sub>2</sub>=H, -CH<sub>2</sub>-N(CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>)-(CH<sub>2</sub>)<sub>2</sub>-

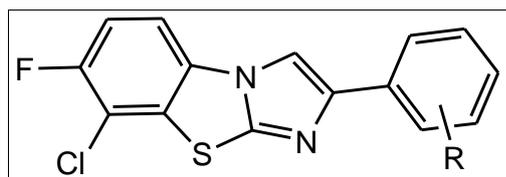
The series of 2-benzylsulfanyl derivatives of benzoxazole and benzothiazoles (21) were tested for their *in vitro* antimycobacterial activity against *M. tuberculosis* and non-tuberculous mycobacteria. The substances bearing two nitro groups or a thioamide group exhibited appreciable activity particularly against non-tuberculous strains [78]. Various substituted 2-(4-acetamidophenyl sulfonamido) benzothiazoles and 2-(4-amino phenyl sulfonamido) benzothiazoles (22) having different functional groups were tested for their *in vitro* antitubercular activity. (Compounds with R<sub>1</sub>=CH<sub>3</sub> and R<sub>2</sub>=Br, were found to be most potent. Overall the compounds having electron-withdrawing substituents (NO<sub>2</sub>, COOH, and halogens) showed better activity than unsubstituted ones [79].

(21) X=O, S; R=H, 4-NO<sub>2</sub>, 3-NO<sub>2</sub>, 2-NO<sub>2</sub>, 3,5-NO<sub>2</sub>, 2,4-NO<sub>2</sub>, 4-CN, 3-CN(22) R=H, CH<sub>3</sub>, COOH; R<sub>2</sub>=H, Cl, Br, NO<sub>2</sub>; R<sub>3</sub>= H, COCH<sub>3</sub>

**Anthelmintic activity:** Resistance to benzimidazoles has now forced the researchers to urgently develop new drugs with anthelmintic activity, to fight liehnhinthiasis, which is causing untold misery to the infected individuals. This prompted the synthesis of benzothiazole derivatives, which were sulfur isostere of benzimidazole, in the hope of achieving better anthelmintic activity. In the search of new anthelmintic agents of benzothiazole series, few 8-fluoro/bromo-9-substituted (1, 3) benzothiazolo (5, 1-b) 1, 3, 4-triazoles (23) were studied for their anthelmintic activity against earthworm, *P. posthuma*. The compound with  $R_1 = \text{fluoro}$  and  $R = \text{o-nitroanilino}$  substituent was found to possess markedly higher anthelmintic activity, than either compounds compared with standard. Whereas compounds with substituent  $R_1 = \text{bromo}$  and  $R = \text{4-carboxyanilino}$  and morpholino were found to be the most potent in the series [80, 81]. Some substituted imidazo benzothiazoles (24) were tested for *in viva* anthelmintic activity against *H. nana* infection and were found to show good to moderate activity [82].

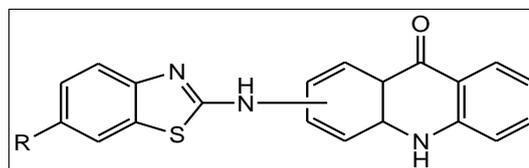


(23)  $R = \text{anilino, o-nitroanilino, m-nitroanilino, p-nitroanilino, o-chloroanilino, diphenylanilino, p-methylanilino, o-methylanilino, morpholino, piperazino, 4-carboxyanilino, 2-carboxyanilino, hydrazino, guanidino; } R_1 = \text{F, Br}$



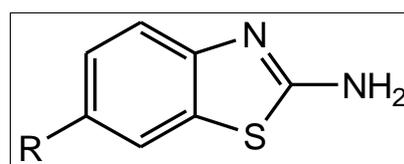
(24)  $R = \text{H, 4-F, 3-CH}_3, 4\text{-OCH}_3, 2\text{-OH, 4-OCH}_3, 3\text{-NO}_2, 4\text{-NO}_2, 2,4\text{-diCl, 3,4-Di-Cl, 5-F, 3-dilorothieryl}$

**Antileishmanial activity:** The (1, 3-benzothiazol-2-yl) amino-9-(10H)-acridinone derivatives (25) were assessed for their *in vitro* antileishmanial and anti-HIV activities. 1-(6-amino-benzothiazol-2-yl-amino)-10H-acridin-9-one, showed selective antileishmanial activity, mainly due to amastigote-specific toxicity. Addition of a benzothiazoles group on a parent amino-9-(10H)-acridinone ring could enhance antileishmanial abilities. On position 4 amino chain was essential for specific anti-amastigote properties [83]. Position 2 substitution bearing 6-nitro, 6-amino benzothiazoles, and their corresponding anthranilic acids. The *in vitro* antiparasitic activity of each derivative against the parasites of the genus *L. infantum* and *T. vaginalis* compared to their toxicity towards human monocytes was assessed. The antiprotozoal properties depended greatly on the chemical structure of the position 2-substitution-bearing group. 2-[(2-Chloro-benzothiazol-6-yl) amino] benzoic acid, demonstrated an interesting antiproliferative activity towards parasites of the species *T. vaginalis*, while compound 2-[(2-(2-hydroxyethyl) amino)-benzothiazol-6-yl] amino) benzoic acid exhibited promising activity against parasites of the species *L. infantum* in their intracellular amastigote form [84].

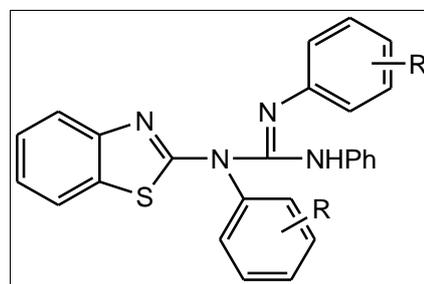


(25)  $R = \text{H, NO}_2$

**Anticonvulsant activity:** In the search of anticonvulsant agents having benzothiazole nucleus, a lot of substituted-2-benzothiazolamines (26) was found to possess significant activity [85]. A series of benzothiazolyl guanidines (27) were synthesized, compounds with  $R = \text{4-CH}_3$  and  $4\text{-Cl}$  were found to be equipotent (100%) in activity to phenobarbitone in maximal electroshock seizure (MES) test, blocked subcutaneous pentylenetetrazole (scPTZ), and strychnine seizures to some extent. All other compounds also had significant anticonvulsant activity [86].

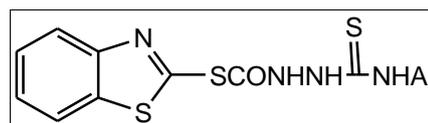


(26)  $R = \text{CH}_3, \text{OCHF}_2, \text{OCH}_3, \text{CF}_3, \text{C}_2\text{H}_5, \text{OC}_2\text{H}_5, 4\text{-OCF}_3, 5\text{-OCF}_3, 7\text{-OCF}_3, \text{n-prop, i-prop, n-but, n-pen. t-pen}$

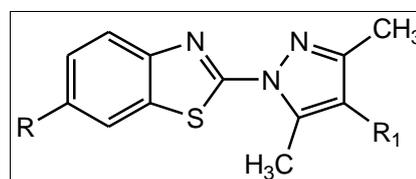


(27)  $R = \text{H, 2-CH}_3, 3\text{-CH}_3, 4\text{-CH}_3, 2\text{-Cl, 3-Cl, 4-Cl, 2-OCH}_3, 4\text{-OCH}_3, 4\text{-Br}$

Some 2-(4-arylthiosemicarbazido carbonylthio) benzothiazoles (28) were tested for their anticonvulsant activity against PTZ induced convulsions in mice and found that all the compounds possess measurable anticonvulsant activity. Various 2-(3H)-benzothiazolone derivatives (29) have been tested for their anticonvulsant activity in mice and were found to be significantly active [87, 88].

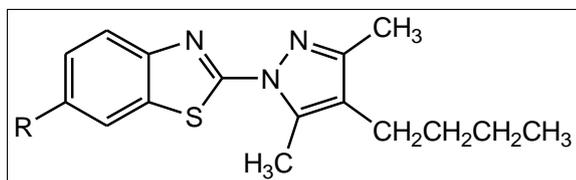
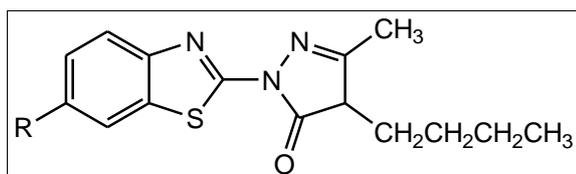
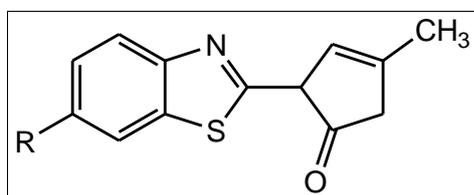


(28)  $\text{Ar} = \text{C}_6\text{H}_5, \text{o-CH}_3\text{C}_6\text{H}_4, \text{m-CH}_3\text{C}_6\text{H}_4, \text{p-CH}_3\text{C}_6\text{H}_4, \text{o-OCH}_3\text{C}_6\text{H}_4, \text{p-OCH}_3\text{C}_6\text{H}_4, \text{p-ClC}_6\text{H}_4$

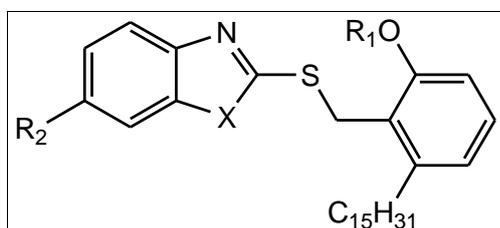
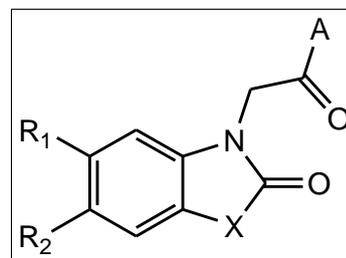


(29)  $R = \text{H, CH}_3, \text{Cl, F, OCH}_3, \text{NO}_2; R_1 = \text{H, CH}_3, \text{C}_2\text{H}_5, \text{i-C}_3\text{H}_7, \text{Br, CH}_2\text{COOH}$

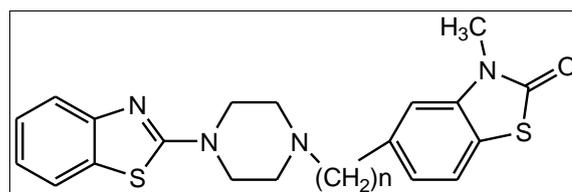
**Anti-inflammatory activity:** Pyrazolones and pyrazolinones rank among the more venerable non-steroidal anti-inflammatory agents. Various benzothiazole derivatives were found to display anti-inflammatory activity. Some 2-(2-benzothiazolyl)-6-aryl-4, 5-dihydro-3(2H)-pyridazinone (30) were found that they possessed low to moderate anti-inflammatory activity [89]. Some 2-(4-butyl-3,5-dimethylpyrazol-r-yl)-6-substituted benzothiazoles (31) and 4-butyl-1-(6-substituted-2-benzothiazolyl)-3-methylpyrazol-5-ones (32) were found to display significant anti-inflammatory activity [90].

(30) R=H, CH<sub>3</sub>, Cl, F, OCH<sub>3</sub>(31) R=H, CH<sub>3</sub>, Cl, F, OCH<sub>3</sub>(32) R= H, CH<sub>3</sub>, p-Cl-C<sub>6</sub>H<sub>5</sub>, C<sub>6</sub>H<sub>5</sub>

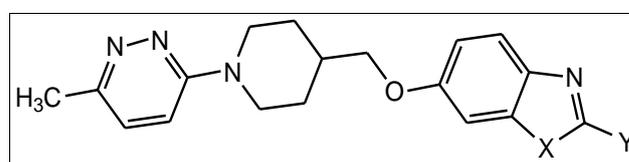
A series of 2-[(2-alkoxy-6-pentadecylphenyl) methyl] thio-1H-benzimidazoles/benzothiazoles and benzoxazoles from an anacardic acid and investigated their ability to inhibit human cyclooxygenase-2-enzyme (COX-2). The active compounds were screened for COX-1 inhibition. Compound (33a) is 384 fold and (33b) is more than 470 fold selective towards COX-2 compared to COX-I [91]. Some (2-benzothiazolone-3-yl and -2-benzoxazoione-3-yl) acetic acid derivatives (34) were tested for antinociceptive and anti-inflammatory activity. 4-[2-(6-benzoyl-2-benzoxazolone-3-yl)acetyl]morpholino, 4-[2-[6-(2-chloro-benzoyl)-2-benzoxazoione-3-yl] acetyl] morpholino, 4-[2-[6-(2-chlorobenzoyl)-2-benzoxazolone-3-yl]acetyl] morpholine, 1-[2-(5-chloro-2-benzoxazolone-3-yl)acetyl] pyrrolidine, methyl((6-methyl-2-benzoxazolone-3-yl) acetate and *N,N*-diethyl-2-(2-benzothiazolone-3'-yl) acetaniide have shown more potent antinociceptive activity than others [92].

(33a-b) aR<sub>1</sub>=H R<sub>2</sub>=OCH<sub>3</sub>, X=NH; bR<sub>1</sub>=CH<sub>3</sub>, R<sub>2</sub>=H X=S(34) X=O, S; R<sub>1</sub>=H, Cl; R<sub>2</sub>= H, CH<sub>3</sub>, C<sub>6</sub>H<sub>5</sub>CO, o-Cl-C<sub>6</sub>H<sub>4</sub>-CO A=I-morpholinyl, 1-pyrrolidinyl diethylamino, OCH<sub>3</sub>, OC<sub>2</sub>H<sub>5</sub>, OH

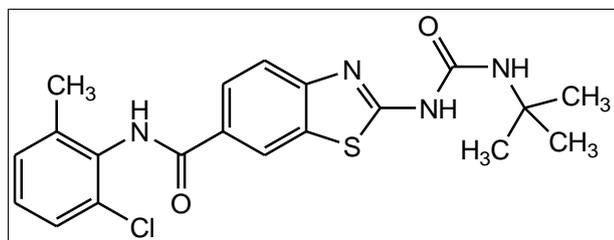
**Miscellaneous:** Derivatives of 2-piperazinyl benzothiazoles (35) were studied as mixed ligands for serotonergic 5-HT<sub>1A</sub> and 5-HT<sub>3</sub> receptors. The compounds exhibited significant affinities for these two serotonergic receptor subtypes. The pharmacological profile of these ligands was agonist for 5-HT<sub>1A</sub> receptors and antagonist for 5-HT<sub>3</sub> receptor subsites. Compounds with such a pharmacological profile are of clinical relevance in the treatment of psychotropic diseases, e.g. anxiety, depression, and schizophrenia [93]. A series of pyridazinyl piperidinyl capsid-binding compounds with bicyclic substituents and tested against human rhinovirus (HRV). HRV causes approximately one-half of all cases of respiratory tract infection (colds). Several 2-alkoxy, 2-alkylthio-benzoxazole, and benzothiazoles derivatives (36) showed excellent anti-HRV activity. When tested against a panel of 16 representatives HRV types, the 2-ethoxy-benzoxazole derivatives were found to have superior HRV activity (median EC<sub>50</sub>3.88 ng/mL) to known capsid-binders pleconaril and pirodavir [94].



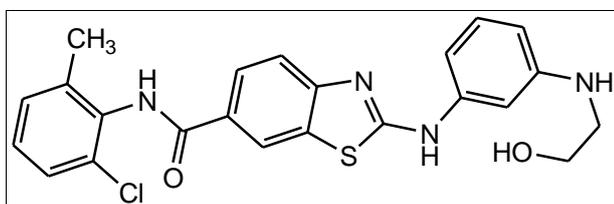
(35) n= 2,3 or 4

(36) X=O, S, NCH<sub>3</sub>; Y=CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, SCH<sub>3</sub>, OC<sub>2</sub>H<sub>5</sub>, SC<sub>2</sub>H<sub>5</sub>, OCH<sub>3</sub>, OC<sub>3</sub>H<sub>7</sub>, C<sub>3</sub>H<sub>7</sub>, (CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>

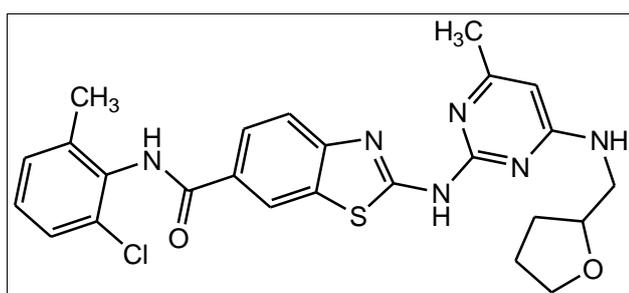
A series of structurally benzothiazoles based on small molecule inhibitors of p56<sup>lek</sup> to elucidate structure-activity relationships (SAR), respectively, and cell activity in the T-cell proliferation assay. P56<sup>lek</sup> (Lek), a member of the Src family of non-receptor protein tyrosine kinase is expressed primarily in T-lymphocytes and natural killer cells [95]. Selective inhibitors of Lek may have potential therapeutic utility in the treatment of T-cell mediated disorders such as autoimmune and inflammatory diseases and in the prevention of solid organ transplant rejection. BMS-243117 (37) is identified as a potent and selective Lck inhibitor with good cellular activity (IC<sub>50</sub>= 1.1 μM), Whereas BIVIS-350751 (38) and BMS-358233 (39) were identified as potent Lek inhibitors with excellent cellular activities against T-cell proliferation.



(37)



(38)



(39)

## Conclusion

The chemistry and pharmacology of thiazoles have been of great interest because of their various biological activities so that the biological and pharmacological activity of thiazole and benzothiazoles substituted with different groups into a new organic molecule causes dramatic changes in its biological profile. Therefore it was thought worthwhile to synthesize better kinds of drugs by incorporating thiazole and benzothiazole moiety.

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