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REVIEW ARTICLE

Medicinal significance of benzothiazole scaffold: an insight view

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Abstract

Heterocycles bearing nitrogen, sulphur and thiazole moieties constitute the core structure of a number of biologically interesting compounds. Benzothiazole, a group of xenobiotic compounds containing a benzene ring fused with a thiazole ring, are used worldwide for a variety of therapeutic applications. Benzothiazole and their heterocyclic derivatives represent an important class of compounds possessing a wide spectrum of biological activities. The myriad spectrum of medicinal properties associated with benzothiazole related drugs has encouraged the medicinal chemists to synthesize a large number of novel therapeutic agents. Several analogues containing benzothiazole ring system exhibit significant antitumour, antimicrobial, antidiabetic, anti-inflammatory, anticonvulsant, antiviral, antioxidant, antitubercular, antimalarial, antiasthmatic, anthelmintic, photosensitizing, diuretic, analgesic and other activities. This article is an attempt to present the research work reported in recent scientific literature on different pharmacological activities of benzothiazole compounds.

Keywords: Benzothiazole, riluzole, pharmacological activities, heterocycles, anticancer activity, anti-infective activity

Introduction

Chemistry of heterocycles lies at the heart of drug dis covery[1]. Investigation of fortunate organic compounds for drug discovery has been a rapidly emerging theme in medicinal chemistry. Benzothiazole (BT) and its derivatives belong to an enormously important family of synthetic compounds of heterocyclic systems[2]. Benz-fused azoles are among the most imperative classes of molecules having a common heterocyclic scaffold in several biologically active and medicinally significant compounds. The attention of biologists was drawn to this series when the pharmacological profile of riluzole, 6-trifluoromethoxy-2-benzothiazolamine, (Figure 1: compound **3**) a blocker of excitatory amino acid mediated neurotransmission, was discovered[3–6]. Since then, BT derivatives have been studied extensively and found to possess diverse chemical reactivity profile along with broad spectrum of biological actions[7]. These agents act as important pharmacophores exhibiting outstanding biological activities and hence play a vital role in field of medicinal chemistry[8]. BT s are a family of heterocyclic compounds whose chemical skeleton is constituted from a benzene **(1)** ring fused with a thiazole **(2)** ring (Figure 1: compound **4**)[9].

Pharmacological activities

BT core is highly important scaffold for drug development, because it has demonstrated a wide spectrum of pharmacological activities. Important medicinal activities associated with this class of compounds as reported in current scientific literature are antitumour,

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Abbreviations

11β-HSD1, 11β-hydroxysteroid dehydrogenase type 1;
AD, Alzheimer's disease;
AEDs, antiepileptic drugs;
AIDS, acquired immune deficiency syndrome;
AMBAN, 2-acetyl- 3-(6-methoxybenzothiazo)-2-yl-amino-acrylonitrile;
APB, 6-amino-2-n-pentylthiobenzothiazole;
BCC, basal cell carcinoma;
BHR, bronchial hyper responsiveness;
BT, benzothiazole;
CAs, carbonic anhydrases;
CAIs, carbonic anhydrases inhibitors ;
CYP, cytochrome P450;
CC50, 50% cytotoxic concentration;
CNS, central nervous system; COX, cyclooxygenase;
CVS, cardiovascular system;
EC_{50}, 50% effective concentration;
EFA, efavirenz;
EZA, ethoxzolamide;
FDA, Food and Drug Administration;
GABA, gamma amino butyric acid;
GI, gastro intestinal;
GP, guinea pig;
Hsp90, heat shock protein 90;
HIV, human immune deficiency virus;
HsNMT, homo sapiens N-myristoyltransferase;
IC_{50}, 50% inhibitory concentration;
INH, isoniazid;
ITC, isothermal titration calorimetry;
JNK, c-jun N-terminal kinase;
LO, 5-lipooxygenase;
LTD4, leukoetriene D4;
MAPK, mitogenactivated protein kinase;
MIC, minimum inhibitory concentration;
MTP, microsomal triglyceride transfer protein;
NASIDS, non steroidal anti-inflammatory;
NCEs, new chemical entities;
NCI, National Cancer Institute;
NMSC, nonmelanoma skin cancer;
NNRTIs, non-nucleoside reverse transcriptase inhibitors.; OA, ovalbumin;
PCA, passive cutaneous anaphylaxis;
PDT, photodynamic therapy;
PET, positron emission tomography;
PfNMT, N-myristoyltransferase of *Plasmodium falciparum*;
PZA, pyridazinamide;
RIA, radio immuno assay;
RIF, rifampicin;
ROS, reactive oxygen species;
RT, reverse transcriptase;
SCE, sister chromatid exchange;
ScMET, subcutaneous metrazole;
TB, tuberculosis; TSA, thermal shift assay;
WHO, World Health Organisation

LTD4 receptor antagonists, amyloid imaging agent in Alzheimer's disease (AD)[10], antimicrobial, antidiabetic, muscarinic receptor agonist[11], antiparasitic[12] anti-inflammatory, anticonvulsant, immunomodulatory and neuroprotective, antiglutamate/antiparkinsonian[13] antitubercular and antiallergic activities[14]. BT derivatives have been shown to be useful for treatment of various diseases including neurodegenerative disorders, local brain ischemia, Huntington's disease and cancer[15]. Important findings from literature on diverse biological activity profile of BTs are presented in the following sections.

Anticancer activity

Cancer is one of the most formidable afflictions in the world[16]. Despite immense advances in the field of basic and clinical research, cancer is currently the second leading cause of death after cardiovascular disorders claiming more than half a million deaths in USA alone in 2009. The major proportion of cancer caused deaths are those related to lung (30%), prostate (9%) and colorectum (9%) in men, and lung (26%), breast (15%), colorectum (9%) and ovarian (5%) cancers in women. Deaths from cancer worldwide are projected to continue rising with an estimated 12 million deaths in the year 2030[17]. A major challenge to medicinal chemistry researchers is identification of novel structures that can be potentially useful in designing new, potent selective and less-toxic anticancer agents[18]. Despite of the fact that several important advances have been achieved over recent decades in the research and development of various anticancer drugs, current antitumor chemotherapy still suffers from two major limitations. First is the lack of selectivity of conventional chemotherapeutic agents for cancer tissues, bringing about unwanted side effects. Second is the acquisition of multiple-drug resistance by cancer cells[19]. Current scenario highlights the need for the discovery and development of new lead compounds of simple structure, exhibiting optimal *in vivo* antitumor potency and new mechanisms of action. The BT moiety with various substitutions shows antitumor activity. A series of potent and selective antitumour agents were developed. Substituted 2-(4-aminophenyl) BTs represent a potent, highly selective and novel mechanistic class of antitumor agents examined, *in vitro*, shows antitumor activity in ovarian, breast, lung, renal and colon carcinoma human cell lines[20–26]. BT analogs exert their anticancer activities by acting on diverse molecular targets. Some important examples of such biotargets on which these derivatives interact are discussed in the following text.

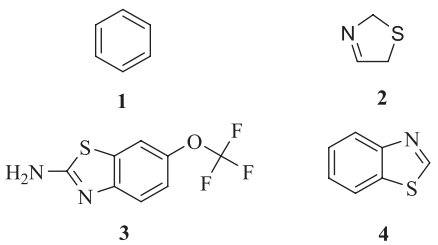


Figure 1. Chemical structures of riluzole (3) and 1,3-benzothiazole (4).

Replication and mitosis inhibitors

Drugs of this category are mitotic inhibitors and bind to tubulin, a microtubular protein and prevent polymerization and assembly of microtubules. It causes disruption of mitotic spindles and interference in cytoskeletal functions. The chromosomes fail to move apart during mitosis leading to metaphase arrest. Tuylu et al. developed derivatives of 2-aryl-substituted (*o*-hydroxy-, *m*-bromo-, *o*-methoxy-, *o*-nitro-phenyl or 4-pyridyl)benzothiazoles (Figure 2: compounds **5**–**9**) and tested their mutagenicity using *in vitro* assays: in the Ames test with *Salmonella typhimurium* TA98 and TA100 strains and (ii) in the sister chromatid exchange in cultured human lymphocytes. Compounds **5**, **7**, **8** and **9** were found to cause significant increase in revertant colonies when compared with the solvent control whereas compound **8** showed most potent mutagenic activity against TA98 and less mutagenic activity for TA100[27].

Topoisomerase II inhibitor

Suk-June et al. introduced combinatorial method for synthesis of 2-(substituted-phenyl)benzothiazoles (Figure 3: compounds **10**–**12**) and reported their antitumour activity. The structure activity relationship studies indicated that the BT nucleus was essential for potent cytotoxicity, and the substitution at 3-position of the phenyl ring with alkyl or halogen groups increased the cytotoxicity of antitumour BTs. Among these analogs, compounds **10** and **11** were observed to possess the strongest inhibitory activity against topoisomerase II with the IC_{50} of 71.7 and 70.5 μM, respectively when compared with the antitumor agent etoposide with IC_{50} of 78.4 μM. Compounds **10** and **12** possessing amino substitution showed high topo II activity[28].

Tyrosine kinase inhibitors

Protein kinases have fundamental role in signal transduction pathways. Moreover, aberrant kinase activity has also been observed in many diseases. In recent years, kinase inhibition has become a major area for therapeutic interventions and a variety of kinase inhibitor pharmacophores have been described in current literature.

A series of novel 2-phenyl-1,3-benzothiazoles (Figure 4: compounds **13**–**24**) were synthesized and evaluated for their anticancer activity against MCF-7 breast cancer cell line with the MTT assay by Bhuva and Kini. The compounds have been found to mimic the ATP-competitive binding of genistein and quercetin to tyrosine kinase. Moderate to good antibreast cancer activity was recorded against most of the compounds[29].

Inhibitors of thioredoxin signaling system

Thioredoxin/thioredoxin reductase system has the potential to act as target for anticancer drug and a small molecule inhibitor of this system is in clinical development. Lion et al. evaluated *in vitro* antitumour properties of a new series of fluorinated benzothiazole-substituted-4-hydroxycyclohexa-2,5-dienones (Figure 5: compounds **25**–**27**). The new compounds were found to be of comparable activity as compared with the non-fluorinated precursors, in terms of antiproliferative activity in sensitive human cancer cell lines and inhibitory activity against the thioredoxin signaling system. Most potent antiproliferative activity was shown by the 5-fluoro analogue (**25**)[30].

Cytochrome P450 (CYP) inhibitors

Cytochrome P450 has a crucial role in mechanism of action of some antitumour agents. Hutchinson et al. observed that fluorinated 2-(4-aminophenyl) benzothiazoles were potently cytotoxic (GI_{50} < 1 nM) *in vitro* in sensitive human breast MCF-7 (ER+) and MDA-468 (ER-) cell lines but inactive (GI_{50} > 10 IM) against PC 3 prostate, non-malignant HBL 100 breast, and HCT 116 colon cells. Most potent derivative was 2-(4-amino-3-methylphenyl)-5-fluorobenzothiazole **28**, which produced no exportable metabolites in the presence of sensitive MCF-7 cells[31]. Induction of cytochrome P450 CYP1A1, a crucial event in determining the antitumor specificity of this series of BTs, was not compromised. In the preceding year they reported synthesis of a series of water-soluble L-lysine- and L-alanyl-amide prodrugs of the lipophilic antitumour 2-(4-aminophenyl)

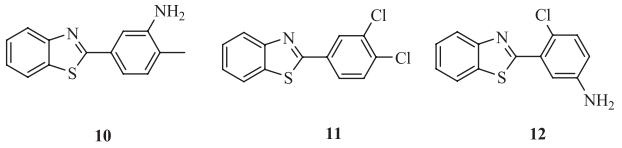


Figure 3. Chemical structure of 2-(substituted-phenyl)benzothiazole derivatives.

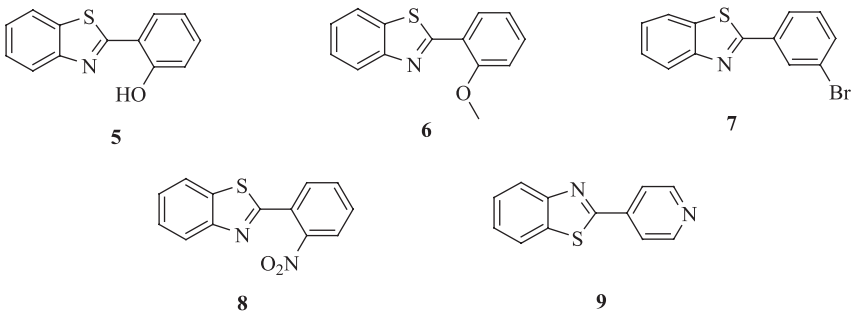
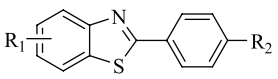
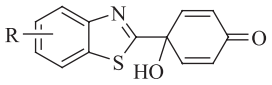


Figure 2. Chemical structure of 2-aryl-substituted (o-hydroxy (5), o-methoxy (6), m-bromo (7), o-nitro (8) and 4-pyridyl (9)) benzothiazole.



13: R_1 = 6-F; R_2 = Me
14: R_1 = 5,6-diMe; R_2 = Me
15: R_1 = 6-Br; R_2 = OMe
16: R_1 = 6-F; R_2 = OMe
17: R_1 = 6-Br; R_2 = Me
18: R_1 = 5-Br; R_2 = OMe
19: R_1 = 7-Br; R_2 = OMe
20: R_1 = 5-Cl; R_2 = OMe
21: R_1 = 7-Cl; R_2 = OMe
22: R_1 = 4-F; R_2 = OMe
23: R_1 = 5,6-diF; R_2 = OMe
24: R_1 = 4-F; R_2 = Me

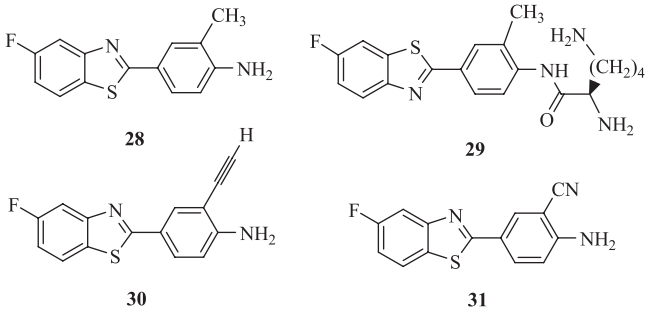
Figure 4. Chemical structure of 2-phenyl-1,3-benzothiazole derivatives.



25: R = 5-F
26: R = 6-F
27: R = 4-F

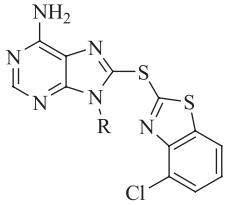
Figure 5. Chemical structure of fluorinated benzothiazole-substituted-4-hydroxycyclohexa-2,5-dienones.

benzothiazoles. The prodrugs exhibited the required pharmaceutical properties of good water solubility (in weak acid) and stability at ambient temperature and degradation to free base *in vivo*. The lysyl-amide of 2-(4-amino-3-methylphenyl)-5-fluorobenzothiazole (NSC 710305) **29** has been selected for Phase 1 clinical evaluation[32]. Furthermore, they described the synthesis of a new series of antitumour 2-(4-aminophenyl) benzothiazole analogues substituted with cyano and alkynyl group at 3′ position (Figure 6: compounds **30** and **31**). Compound **30** was active against MCF-7 and MDA-468 with GI_{50} value 0.0057 and 0.0078 μM, respectively, and compound **31** depicted GI_{50} values 0.011 and 0.0088 μM against MCF-7 and MDA-468, respectively[33].



28 **29** **30** **31**

Figure 6. Chemical structure of antitumour benzothiazole derivatives.



32: R = $CH_2CH_2PO(OCH_2CH_3)_2$
33: R = $CH_2CH_2NHCH_2C(CH_3)_3$
34: R = CH_2CH_2NH-cyclopropane

Figure 7. Chemical structure of benzothiazole derivatives.

Heat shock protein 90 (Hsp90) inhibitors

Zhang et al. synthesized a series of benzo- and pyridino-thiazolothiopurines as potent heat shock protein 90 inhibitors. Structure activity relationship showed that in case of BT series, the best analogues contained a two-carbon linker substituted with the diethyl phosphate moiety. Compounds **32**–**34** (Figure 7) were most potent inhibitors of tumour growth[34].

Other anticancer BTs

Novel series of substituted 2-phenyl-benzothiazole and substituted 1,3-benzothiazole-2-yl-4-carbothiaote derivatives (Figure 8: compounds **35**–**38**) were synthesized by Devmurari et al. Reduction in tumour volume, packed cell volume, viable cell count and non-viable cell count by administration of BT derivatives was noticed when compared with EAC control mice. Compounds **35**–**38** showed very good anticancer activity; however, compound **38** demonstrated significant toxicity[35].

A series of BTs bearing piperazino-arylsulfonamides, arylthiol and sulphonamide moieties have been synthesized and evaluated, *in vitro*, for their antiproliferative activity against a large panel of human tumour derived cell lines by Al-Soud et al. Compounds **39**–**44** (Figure 9) were the most potent analogues in this series, showing activity against both the cell lines derived from haematological and solid tumours (CC_{50} range = 8–24 μM). Compound **40** was found to be selective and non cytotoxic to normal cells[36].

Amnerkar and Bhusari reported some new prop-2-eneamido, 1-acetyl-pyrazoline and thiazolyl substituted 2-aminobenzothiazoles (Figure 10: compounds **45**–**49**) for *in vitro* human tumour cell lines screening. On the basis of structure activity relationship, compound **45** was found to be active against renal cancer cell lines especially on RXF 393 with a growth percentage of 71.40[37].

Schnur et al. studied the antitumour property of *N*-(5-fluorobenzothiaol-2-yl)-2-guanidinothiazole-4-carboxamide in micro metastatic 3LL Lewis lung carcinoma in mice. Compound **50** (Figure 11) showed excellent therapeutic index relative to the cytotoxic anticancer drug adriamycin[38].

Leong et al. presented 2-(4-aminophenyl)benzothiazoles as potent and highly selective class of antitumour agents representing a mechanistic class distinct from clinically used chemotherapeutic agents. The result demonstrated that the generation of covalent adducts in sensitive cells between electrophilic reactive intermediates of 2-(4-amino-3-methylphenyl)-5-fluorobenzothiazole (5F 203) (Figure 12: compound **51**) and DNA exacts lethal damage that precedes the exquisitely selective cell death[39].

In vitro cytotoxic activity against HL-60 and U-937 cell lines and antimicrobial activity against bacterial and fungal strains of a series of BT derivatives (Figure 13: compounds **52**–**59**) were identified by Gupta et al. From the study, it was concluded that compounds **52**, **53** and **55** exhibit

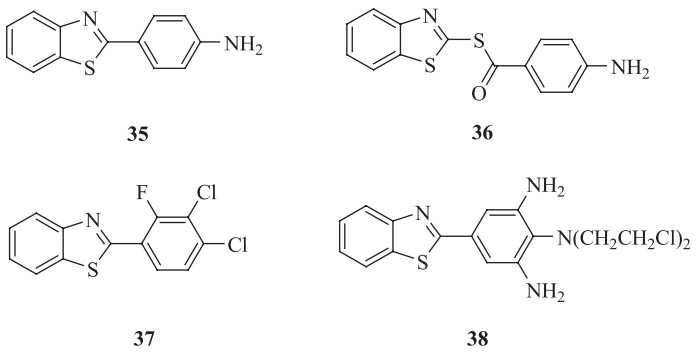


Figure 8. Chemical structure of substituted 2-phenyl-benzothiazoles.

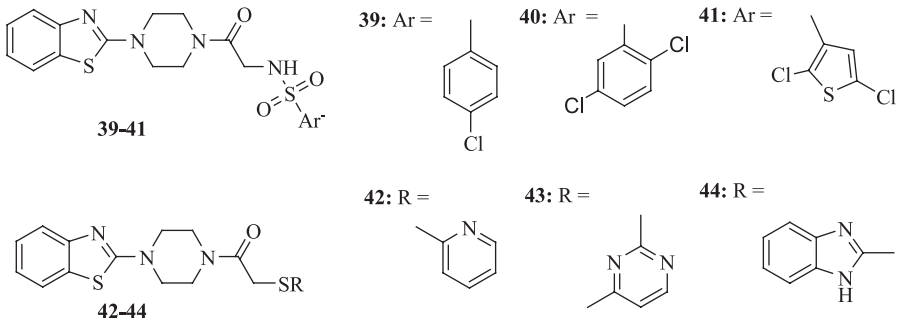


Figure 9. Chemical structure of benzothiazole derivatives containing piperazino-arylsulfonamides, arylthiol and sulphonamides moieties.

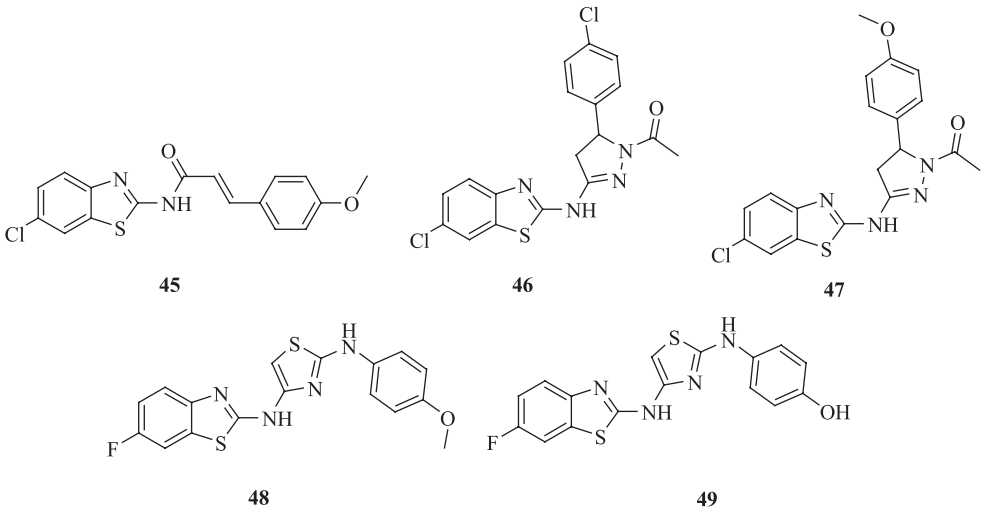


Figure 10. Chemical structure of prop-2-eneamido, 1-acetyl-pyrazoline and thiazolyl substituted 2-aminobenzothiazoles.

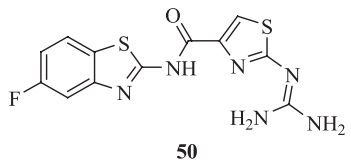


Figure 11. Chemical structure of *N*-(5-fluorobenzothiaol-2-yl)-2-guanidinothiazole-4-carboxamide.

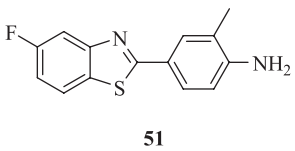


Figure 12. Chemical structure of 2-(4-amino-3-methylphenyl)-5-fluorobenzothiazole.

significant activities against all bacterial and fungal strains. Compound **53** has better activity against *Staphylococcus aureus*, *Proteus vulgaris*, *Staphylococcus epidermidis*, *Klebsiella pneumoniae* and *Candida albicans*. Compound **56** has considerable activity against *Bacillus subtilis* and *Escherichia coli*. Except monomer **54** and **55** (methoxy and unsubstituted), all other compounds have significant activity against U-937 lymphoma cell lines and compound **58**

(methylene) exhibits better activity (1.8 μM) than the reference compound cisplatin (3.2 μM)[40].

Mortimer et al. evaluated a series of new 2-phenylbenzothiazoles for *in vitro* antitumor properties against human lung, breast and colon cancer cell lines. Among the synthesized compounds, 2-(3,4-dimethoxyphenyl)-5-fluorobenzothiazole (Figure 14: compound **60**) was found to possess exquisitely potent antiproliferative activity with GI_{50} <0.1 nM for MCF-7 and MDA-468[41].

Repicky et al. examined the antiproliferative- and apoptosis-inducing activities of 2-acetyl-3-(6-methoxybenzothiazo)-2-yl-amino-acrylonitrile (AMBAN) (Figure 15: compound **61**) towards human leukaemia HL60 and U937 cells. Results demonstrated that AMBAN inhibited the growth of HL60 and U937 cells with the IC_{50} of 30.37 μM (for 24 h), 19.39 μM (for 48 h and 72 h) and 11.31 μM (for 24 h), 3.55 μM (for 48 h), 2.52 μM (for 72 h), respectively[42].

A series of new amidino-nitro and amidino-amino substituted BTs (Figure 16: compounds **62**–**63**) was efficiently prepared by Racané et al. Diamidino substituted 2-phenylbenzothiazole **62** shows exceptionally prominent tumour cell-growth inhibitory activity and cytotoxicity whereas compound amino-amidine-2-phenylbenzothiazole **63** depicts inhibitory activity towards MCF-7 and H 460 cells[43].

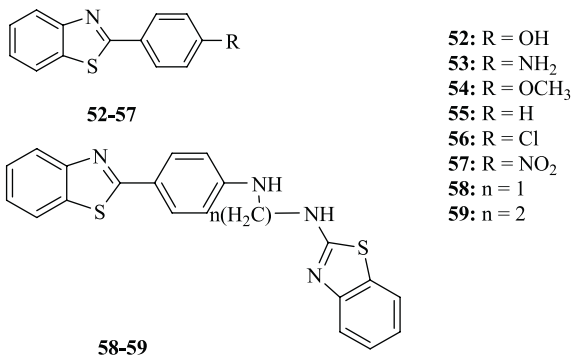


Figure 13. Chemical structure of 2-(amino-phenyl)benzothiazole.

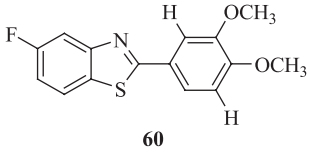


Figure 14. Chemical structure of antiproliferative 2-(3,4-dimethoxyphenyl)-5-fluorobenzothiazoles.

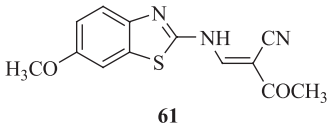


Figure 15. Chemical structure of 2-acetyl-3-(6-methoxybenzothiazo)-2-yl-amino-acrylonitrile.

Some novel imidazobenzothiazole, imidazobenzoxazole, and imidazobenzoimidazole derivatives were investigated by Trapani *et al*. and their cytotoxic activity were determined at the National Cancer Institute in Derbyshire (UK) by testing against a panel of tumour cell lines. *In vitro* cytotoxic activity was reported by compounds **64**–**67** (Figure 17). Compound **65** showed a score greater than the minimum values for xenograft testing together with a net cell kill in the hollow fiber assay[44].

A new series of 2-(4-aminophenyl)benzothiazoles (Figure 18: compounds **68**–**72**) was screened for antitumour activity by Dong-Fang et al. The molecules showed potent inhibitory activity *in vitro* in the nanomolar range against a panel of human breast cancer cell lines, but were found inactive (IC_{50} > 30 μM) against other cell types[44,45]. They also synthesized and evaluated a series of potent and selective sulfamate salt derivatives of 2-(4-aminophenyl)benzothiazoles (Figure 18: compounds **73**–**76**) as potential prodrugs for parenteral administration. It was found that sulfamate salts were less active than their parent amines[46].

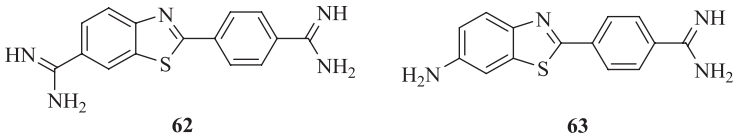
Wells et al. synthesized a series of new antitumor agents, the BT-substituted quinol, ethers and esters (Figure 19: compounds **77**–**85**). The results showed that compound **77** possesses potent antitumour activity with IC_{50} of 0.24 μM against colon cell lines[47].

Vicini et al. evaluated three new series of benzo[*d*]isothiazole, BT and thiazole, Schiff's bases against emergent and reemergent human and cattle infection diseases (AIDS, hepatitis B and C, TB, bovine viral diarrhoea) or against drug resistant cancers (leukemia, carcinoma, melanoma, multiple-drug resistant (MDR) tumours). All the benzo(d)isothiazole (Figure 20: compounds **86**–**91**) derivatives inhibited the growth of leukaemia cell lines. Benzo[d]isothiazole compounds showed a marked cytotoxicity against $CD4^+$ lymphocytes (MT-4) with CC_{50} value between 4–9 μM that were used to support HIV-1 growth[48].

Yoshida et al. synthesized 2,6-dichloro-*N*-[2-(cyclopropanecarbonylamino)benzothiazole-6-yl]benzamides and tested for antitumour activity. Excellent *in vivo* inhibitory activity on tumour growth and excellent plasma concentration ($t_{1/2}$ = 3.29 h) was shown by (Figure 21: compound **92**)[49].

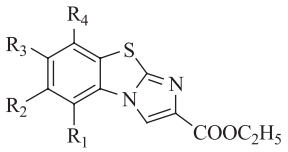
Four classes of UK-1 analogues (Figure 22: compound **93**) were synthesized and their cytotoxicity testing against human A-549, BFTC-905, RD, MES-SA and HeLa carcinoma cell lines was determined by Shu-Ting et al.[50]

Wan-Ping et al. provided evidence indicating that most of the 2-(4-aminophenyl)benzothiazoles (Figure 23: compounds **94**–**103**), under UVA light exposure, induced basal cell carcinoma (BCC) cell apoptosis. Due to these compounds having chromophoric structure and light absorption in the UVA range (320–400 nm), this *in vitro* study analyses the photosensitive effect of UVA-activated compounds in BCC cells. When cells were pre-treated with 2-(4-aminophenyl)benzothiazoles, UVA induces a markedly increased accumulation of sub-G1 phase and



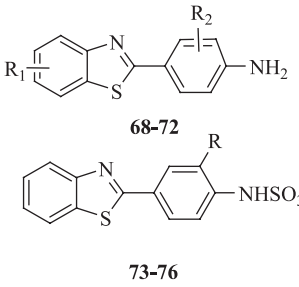
62 63

Figure 16. Chemical structure of amidino-nitro and amidino-amino substituted benzothiazoles.



64: R_1 = H; R_2 = H; R_3 = Cl; R_4 = H
65: R_1 = H; R_2 = H; R_3 = OCH_3; R_4 = H
66: R_1 = H; R_2 = H; R_3 = CH_3; R_4 = H
67: R_1 = H; R_2 = H; R_3 = Cl; R_4 = Cl

Figure 17. Chemical structure of various substituted imidazobenzothiazole.



68-72

73-76

68: R_1 = H; R_2 = H
69: R_1 = H; R_2 = 3-Me
70: R_1 = H; R_2 = 3-Br
71: R_1 = H; R_2 = 3-Cl
72: R_1 = H; R_2 = I
73: R = H; Y = Na or NH_4
74: R = Me; Y = Na
75: R = Cl; Y = Na
76: R = I; Y = Na

Figure 18. Chemical structure of 2-(4-aminophenyl)benzothiazole derivatives.

triggers apoptosis as revealed by the increased annexin V-FITC cells and the caspase-3 activation. Compounds treated with UVA induced a decrease in mitochondrial membrane potential ($\Delta\psi$mt) and ATP via enhanced reactive oxygen species generation and promoted phosphorylation of extracellular signal-regulated kinase (ERK) and p38 MAPK expression. These results suggested that compounds treated with UVA elicit photosensitive effects in mitochondria processes, which involve ERK and p38 activation, and ultimately lead to BCC cell apoptosis[51].

Aiello et al. studied the antitumour properties of new fluorinated 2-aryl benzothiazoles, -benzoxazoles and -chromen-4-ones (Figure 24: compounds **104**–**105**) and compared with potent antitumour 2-(3,4-dimethoxyphenyl)-5-fluorobenzothiazole. None of the compounds was able to recapitulate the antitumour potency of 2-(3,4-dimethoxyphenyl)-5-fluorobenzothiazole. However, compounds **104** and **105** showed potent antitumour activity against MCF-7 and MDA-468 breast cancer cell lines with submicromolar GI_{50} value 0.57, 0.20 and 0.40, 0.21 μM, respectively[52].

Anti-infective activity profile

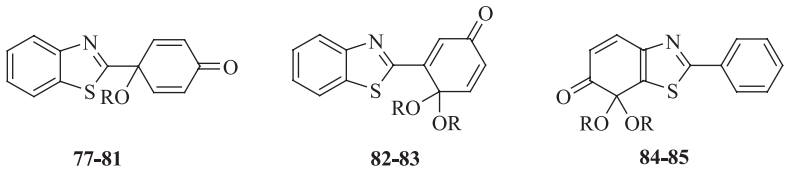
Historically, the use of anti-infective agents can be credited with saving more human lives than other area of medicinal therapy discovered to date[53]. Emergence of infectious diseases and multidrug resistance are the combined factors that remain important and challenging problems for the treatment of infectious diseases[54]. In addition, the treatment of infectious diseases is more complicated in immune-suppressed patients, such as those infected with the HIV, undergoing anticancer therapy or transplants[55].

Antimicrobial activities

Microbes are causative agents for various types of diseases such as pneumonia, ameobiasis, typhoid, malaria, common cough and cold and also some severe diseases such as tuberculosis (TB), influenza, syphilis and AIDS[56]. Infectious diseases caused by bacteria affect millions of people and are leading causes of death worldwide[57]. During the past three decades, antimicrobial agents have been introduced at a rate exceeding our ability to integrate them into clinical practice[58]. Despite several advancements in the development of antimycotic agents, antifungal chemotherapy remains problematic in many cases and search for new antifungal agents continues to be an inevitable task[59]. Despite of numerous attempts to develop new antimicrobial agents, many problems remain to be solved for currently available antimicrobial drugs[60]. BT still remains one of the most versatile classes of compounds against microbes, and therefore, are useful substructures for further molecular exploration.

Mistry and Desai synthesized heterocyclic 4-thiazolidinone benzothiazoles derivatives. The synthesized compounds were tested for their antibacterial activity against *S. aureus* and *E. coli* by measuring the inhibition area on agar plates (diffusimetric methods). Good activity against *S. aureus* and *E. coli* was shown by compounds **106**, **110**, **111** and **107**, **112**, **113**, respectively. Compounds **108**, **112**, **113** and **109**, **114**, **115** depicted low activity against *S. aureus* and *E. coli*, respectively (Figure 25: compounds **106**–**115**)[61].

Rajeeva et al. evaluated some new 2-(5-substituted-1,3,4-oxadiazole-2-yl)-1,3- BT derivatives for *in vitro* antibacterial activity at a concentration of 100 μg/mL using DMSO as a control and ciprofloxacin as standard drug against Gram positive and Gram negative bacterial strain such as *B. subtilis*, *Bacillus pummels*, *E. coli* and *Pseudomonas aeruginosa* by disc diffusion method. The analogues (Figure 26: compounds **116**–**119**) were found to possess broad spectrum of antibacterial activity[62].

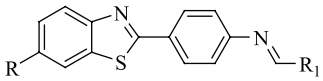


77-81 **82-83** **84-85**

77: R = Ac
78: R = Me
79: R = Et
80: R = Pr
81: R = $CH_2CH{=}CH_2$

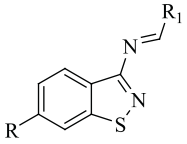
82: R = Me
83: R = Et
84: R = Me
85: R = Et

Figure 19. Chemical structure of hydroxylated 2-phenylbenzothiazoles.



86-88

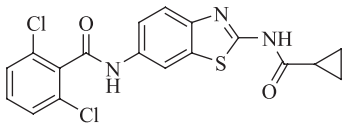
86: R = H; $R_1 = C_6H_5$
87: R = H; R_1 = 2-ClC_6H_4
88: R = F; R_1 = 3-ClC_6H_4



89-91

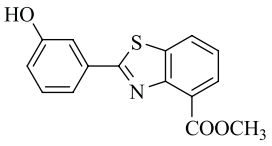
89: R = H; R_1 = 3-ClC_6H_4
90: R = H; R_1 = 4-$OCH_3C_6H_4$
91: R = H; R_1 = 5-NO_2-2-Furanyl

Figure 20. Chemical Structures of benzo[d]isothiazole, benzothiazole and thiazole Schiff's bases.



92

Figure 21. Chemical structure of 2,6-dichloro-*N*-[2-(cyclopropanecarbonylamino) benzothiazole-6-yl]benzamides.



93

Figure 22. Chemical structure of Benzothiazole derivatives.

A series of 2-(benzo[d]thiazol-2-ylthio)-*N*-(2-oxoindolin-3-ylidene)acetohydrazide, 2-(benzo [d]thiazol-2-ylthio)-*N*-(2,4′-dioxospiro[indolin-3,2′-thiazolidin]-3′-yl)acetamide and 2′-((benzo[d]thiazol-2-ylthio) methyl)spiro[indoline-3,5′-thiazol1,3,4oxadiazol]-2-one compounds were developed and screened for their antibacterial activities by Kaur et al. Most potent antibacterial against *K. pneumoniae*, *S. aureus* and *E. coli* (zone of inhibition: 22, 22 and 20 mm, respectively) and anti-inflammatory compound of this series (Figure 27: compounds **120**–**121**) was compound **120** and most potent analgesic compound was **121**[63].

A novel series of benzothiazolium derivatives (Figure 28: compounds **122**–**123**) substituted at position 5- and/or 6- on heterocyclic ring has been prepared and tested against Gram positive bacteria and yeast microorganisms by Sigmundova et al. Compounds **122** and **123** showed potent activity against *B. subtilis* and also **123** was active against *Micrococcus luteus*[64].

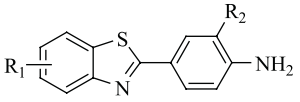
Gajdos et al. synthesized a series of new 2-styrylbenzothiazole-*N*-oxides (Figure 29: compounds **124**–**127**) and tested for their antimicrobial activities against Gram positive (*S. aureus* and *B. subtilis*) and Gram negative bacteria (*E. coli* and *Pseudomonas aeruginosa*) as well as a yeast *(C. albicans)* and a mould (*Microsporum gypseum*). However, weak activity was recorded when compared with previously prepared analogous benzothiazolium salts[65].

2,4,6-substituted-1,3,5-tris(benzothiazolyl) hexahydro-1,3,5-triazine derivatives (Figure 30: compounds **128**–**129**) were synthesized by Pareek et al. All compounds were evaluated for antibacterial, antifungal, acaricidal and antifeedant activities. Biological screening identified that very low activity was recorded against all bacterial strains with comparably higher antifungal activity. Results of acaricidal and antifeedent activities showed that compounds **128** and **129** possess good acaricidal and antifeedent activites, respectively[66].

Barot et al. screened a series of substituted fluoro BT derivatives (Figure 31: compounds **130**–**131**) for their antibacterial, antioxidant activities and for inhibition of denaturation of protein. Excellent activity against *S. aureus*, *B. subtilis* was shown by compounds **130** and **131**; moreover, compound **130** also demonstrated good antioxidant activity[11].

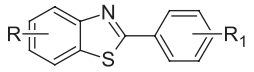
Novel BT-substituted thiazolidinone derivatives (Figure 32: compounds **132**–**139**) were evaluated for their inhibitory ability against *Proteus mirabilis*, *S. aureus*, *Salmonella typhi* and *K. pnuemoniae* by Nagarajan et al. Compounds **133**, **134**, **135** and **137** showed effective inhibition towards above mentioned four human pathogens as compared to **132**, **136**, **137** and **138**[67].

Antimicrobial activity of new 2-alkenyl-6-aminobenzothiazoles (Figure 33: compounds **140**–**141**) was screened by Sidoova et al. Results demonstrated that compounds **140** and **141** exhibit better activity as compared with standard drug 6-amino-2-*n*-pentylthiobenzothiazole (APB)[68].



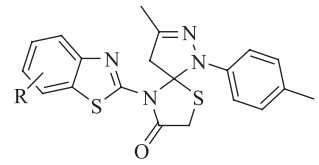
94: R_1 = H; R_2 = H
95: R_1 = 6-Et; R_2 = H
96: R_1 = 6-OCH_3; R_2 = H
97: R_1 = H; R_2 = CH_3
98: R_1 = 6-OCH_3; R_2 = CH_3
99: R_1 = 6-CH_3; R_2 = H
100: R_1 = 7-OCH_3; R_2 = H
101: R_1 = 6-CF_3; R_2 = H
102: R_1 = 6-Et; R_2 = CH_3
103: R_1 = 6-CF_3; R_2 = CH_3

Figure 23. Chemical structure of 2-(4-aminophenyl)benzothiazole derivatives.

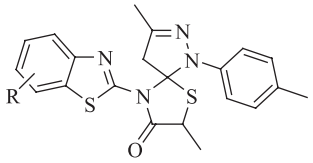


104: R = 5-F; R_1 = 3-OH
105: R = 5-F; R_1 = 4-OH

Figure 24. Chemical structure of fluorinated benzothiazole derivatives.



106-109



110-115

106: R = 6-NO_2
107: R = 6-$NHCOCH_3$
108: R = 4-NO_2
109: R = 6-Cl
110: R = 6-NO_2
111: R = 6-OCH_3
112: R = 6-OH
113: R = 4-NO_2
114: R = 6-CH_3
115: R = 6-Cl

Figure 25. Chemical structure of 4-thiazolidinone benzothiazole derivatives.

Malik et al. identified some new 2-amino-substituted-benzothiazole derivatives (Figure 34: compounds **142**–**148**) as antifungal agents. All the compounds exhibited moderate antifungal activity with minimum inhibitory concentration (MIC) range 0.63–0.31 μg/mL[69].

A novel series of Schiff bases of BT derivatives (Figure 35: compounds **149**–**155**) were screened for their antibacterial activity by Soni et al. The biological screening identified that antibacterial activity decreases with substitution at ortho and it increases with substitution at para position. Compounds **149**, **154** and **155** showed maximum antibacterial activities and compounds **149**, **150**, **153** and **155** showed antifungal activities against both the *C. albicans* and *Aspergillus niger* organisms[70].

Latrofa et al. evaluated a series of *N*-cycloalkenyl-2-acylalkylidene-2,3-dihydro-1,3-benzothiazoles, *N*-cycloalkyl-2-acylalkylidene-2,3-dihydro-1,3-benzothiazoles and *N*-alkyl-2-acylalkylidene-2,3-dihydro-1,3-benzothiazoles for antifungal and antibacterial activity. Results revealed that *N*-cycloalkenyl compounds (Figure 36: compounds **156**–**170**) did not exhibit any significant antifungal activity, but antibacterial activity was found to increase with increase in the value of acyl chain (R_1). Compounds **165** and **166** showed moderate antibacterial activities against Gram negative organisms[71].

Some new 1-aroyl-3-(substituted-2-benzothiazolyl) thioureas were evaluated for their antimicrobial activity by Saeed et al. All the compounds (Figure 37: compounds **171**–**181**) exhibited moderate antimicrobial activity[72].

Thiourea derivatives bearing BT moiety (Figure 38: compounds **182**–**186**) were reported with good antimicrobial activity by Saeed et al. Significant antimicrobial activity was showed by all the compounds[73].

Bhusari et al. synthesized a series of sulphonamide derivatives having benzothiazole moiety (Figure 39: compounds **187**–**189**). All the test compounds have been assayed *in vitro* for antibacterial activity against *B. subtilis* and *E. coli*, and for antifungal activity against *C. albicans*. Antimycobacterial activity was tested against H37Rv strain of *Mycobacterium tuberculosis*. Moderate to good potency against different bacterial strains was observed by all the newly synthesized compounds. Among synthesized derivatives, compounds **187**, **188** and **189** showed prominent antibacterial, antifungal and anti mycobacterium activity, respectively[74].

Franchini et al. synthesized 2-mercapto-1,3-benzothiazole (Figure 40: compounds **190**–**199**) derivatives with potent antimicrobial activity. The biological screening identified compound **194** as the most active one showing an interesting antibacterial activity with MIC values of 3.12 μg/mL against *S. aureus* and also compound **195** demonstrated wide antimicrobial activity against *S. aureus* and *E. coli* with MIC 1.25 and 25 μg/mL, respectively[75].

Bondock et al. described the synthesis of polyfunctionally substituted heterocycles (e.g. pyrazoles, isoxazole, pyrimidines, thiazolo[3,2-a]pyrimidine, tetrazolo[1,5-a] pyrimidine, pyrido[1,2-a]pyrimidine, 1,5-benzodiazepine, and pyrazolo[1,5-a]pyrimidine incorporating benzothiazole moiety by using enaminonitrile moiety and screened for their antimicrobial activity. Synthesized compounds (Figure 41: compounds **200**–**204**) showed moderate activity against the screened Gram positive bacteria[76].

New and simple synthetic methods for the synthesis of ethyl-8-chloro-4-(4-substituted phenyl)-2[(*N*-ethoxyphthalimido)amino]-4*H*-pyrimidino[2,1-b1,3] benzothiazole-3-carboxylates **205**–**212** and 6-chloro-*N*-[3-{2-(4-substitutedphenyl)ethenyl}-1-*N*-ethoxyphthalimidoquinoxaline-2(1*H*)-ylidene]-1,3-benzothiazole-2-amines **208**–**211** was described by Sain et al. All the compounds (Figure 42: compounds **205**–**212**) exhibited good to moderate antimicrobial activity[77].

Baheti et al. synthesized and screened 15-iminobenzothiazolo[2,3-b]pyrimido[5,6-c] pyrimido[2,3-b]benzothiazole-14(*H*)-one derivatives (Figure 43: compounds **213**–**222**) for their antimicrobial

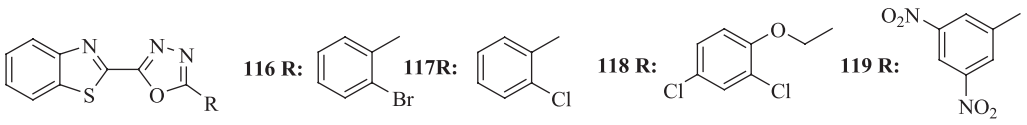
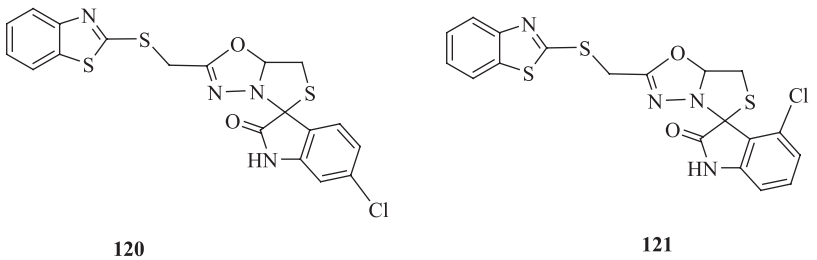
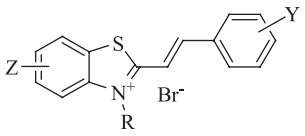


Figure 26. Chemical structure of 2-(5-substituted-1,3,4-oxadiazole-2-yl)-1,3-benzothiazole derivatives.



120 **121**

Figure 27. Chemical structure of benzothiazole derivatives.



122: Z = 5-NH-Ac, R = Allyl, Y = $N(CH_3)_2$
123: Z = 5-NH-Ac, R = Propargyl, Y = N-Piperidinyl

Figure 28. Chemical structure of substituted benzothiazolium derivatives.

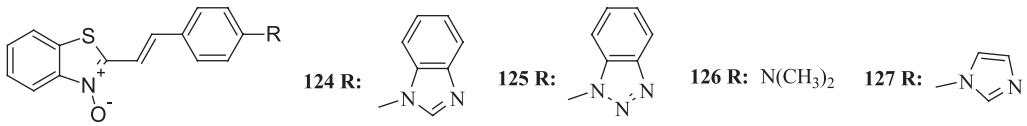
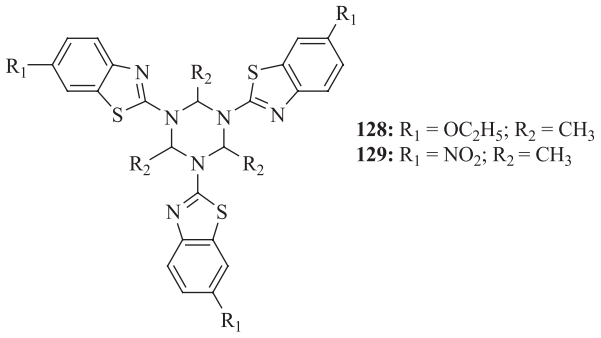
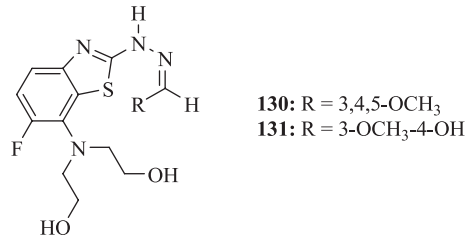


Figure 29. Chemical structure of 2-styrylbenzothiazole-N-oxides.



128: $R_1 = OC_2H_5$; $R_2 = CH_3$
129: $R_1 = NO_2$; $R_2 = CH_3$

Figure 30. Chemical structure of 2,4,6-substituted-1,3,5-tris(benzothiazolyl)hexahydro-1,3,5-triazine.



130: R = 3,4,5-OCH_3
131: R = 3-OCH_3-4-OH

Figure 31. Chemical structure of substituted fluoro-benzothiazole.

activity and it was found that compound **220** showed 10, 10, 13, 10 mm zone of inhibition and similarly **221** demonstrated 10, 9, 10, 12 mm inhibition zone against *S. aureus*, *B. substilis*, *E. coli* and *S. typhi*, respectively[78].

Substituted pyrimido[2,1-b]benzothiazoles (Figure 44: compounds **223**–**230**) were evaluated against *E. coli*, *S. aureus*, *Enterobacter* for antibacterial activity and against *C. albicans* for antifungal activity at conc of 100 µg/disc by Gupta et al. Compounds **223**, **227** and **226**, **228** showed significant activity against *E. coli*, *Enterobacter* and *S. aureus*, respectively; moreover, potent antifungal activity against *C. albicans* was shown by compounds **224**, **227**, **228** and **230**[79].

Vedavathi et al. evaluated fluorobenzothiazole incorporated with 1,3,4-thiadiazole derivatives for antimicrobial activities. Significant antibacterial and antifungal activity was demonstrated by all the compounds (Figure 45: compounds **231**–**240**)[80].

Kuchta et al. presented 6-amino-2-*n*-pentylthiobenzothiazole (APB) (Figure 46: compound **241**) as a promising new antifungal agent active against various *Candida* species *in vitro*, to inhibit the yeast mycelium conversion in *C. albicans*, and to be active *in vivo*, curing systemic candidosis in mice. Results showed that APB is an antifungal agent inhibiting ergosterol biosynthesis at the level of 4-demethylation[81].

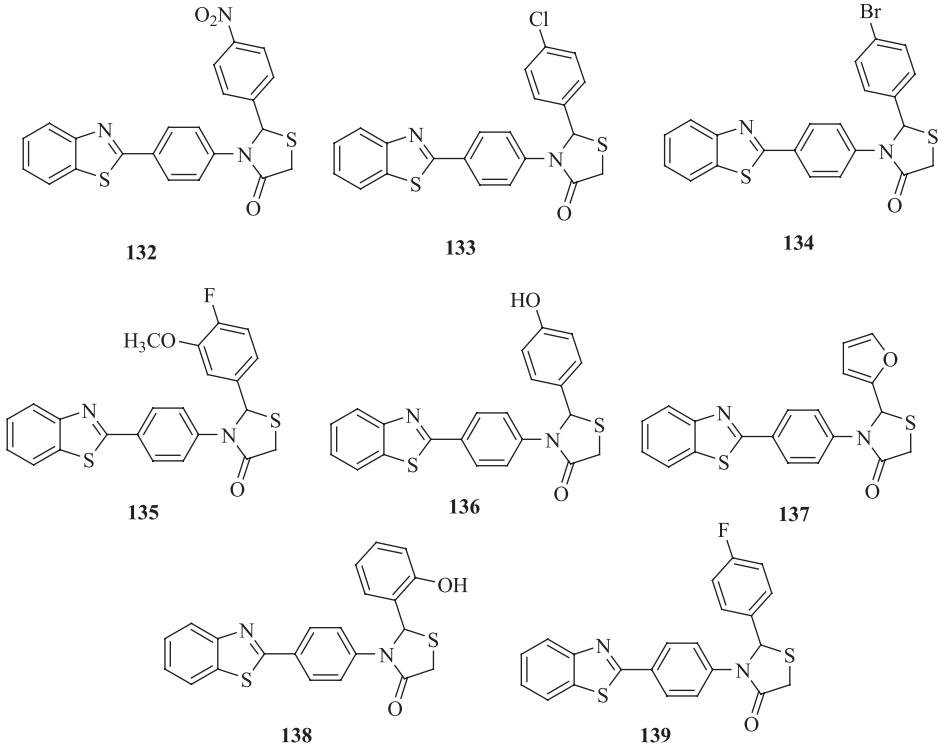
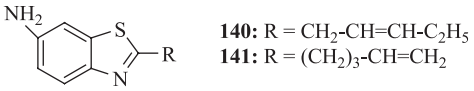


Figure 32. Chemical structure of benzothiazole substituted thiazolidinone.



140: R = CH_2-CH=CH-C_2H_5
141: R = $(CH_2)_3$-CH=CH_2

Figure 33. Chemical structure of substituted 2-alkenyl-6-aminobenzothiazoles.

New 2-methyl-3-[(substituted)-benzothiazole-2′-yl]4(3*H*)-quinazolinones (Figure 47: compounds **242**–**244**) have been synthesized and evaluated by Lakhan and Ral for antifungal activity. Compound **242** was relatively more active at the given dilutions against the fungi chosen in comparison with the commercial fungicide[82].

Polyfluorinated 2-benzylthiobenzothiazoles (Figure 48: compounds **245**–**252**) were evaluated for their fungicidal activity against *Rhizoctonia solani*, *Botrytis cinereapers* and *Dothiorella gregaria* at a dosage of 50 µg/mL by Huang and Guang-Fu. The outcomings of the study showed that compound **245** exhibited very significant activities against *R. solani*, *B. cinereapers* and *D. gregaria*[83].

A series of *N*-(6-methylbenzothiazolyl)-2,3,5,6-tetrasubstituted-4-(aryl)-1,4-dihydropyridines were evaluated for antibacterial and antifungal activities by Mithlesh et al. Maximum antimicrobial activity was depicted by the compounds **253**–**255** (Figure 49)[84].

The antimicrobial activity of 3,5-diaryl-1-benzothiazolopyrazoline derivatives has been studied against various microbes by Sharma and Sharma. The screening data revealed that compounds (Figure 50: compounds **256**–**263**) possess moderate activity against *C. albicans*, but compounds **256**, **259**, **261** and **262** show higher activity against *Cladosporium cladosporoides* and *Curvularia lunata*[85].

Argyropoulou et al. evaluated several thiazoles and BTs carrying a benzenesulfonamide moiety at position 2 of the heterocyclic nucleus as antimicrobial agents. All the derivatives (Figure 51: compounds **264**–**268**) demonstrated effective antibacterial properties against Gram positive bacteria[86].

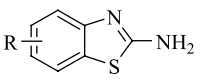
Alang et al. screened seven new derivatives of BTs (Figure 52: compounds **269**–**280**) for antibacterial activity. Compounds **271** and **275** were found to possess moderate activity against *S.aureus* and *P. aeruginosa*, while compounds **269** and **272** demonstrated similar sort of activity against *E. coli*. Compound **273** depicted excellent activity against *P. aeruginosa*, while compound **274** possessed prominent activity against *S. epidermidis* when tested at 1 mg/mL concentration taking ampicillin as a standard drug[87]. They also evaluated a series of BTs for antifungal activity against *C. albicans (MTCC 183)*, *A. niger (MTCC 228)*, *Candida tropicalis (MTCC 6192)* and *Fusarium oxysporium (MTCC 3656)*. Results showed that compound **276** possesses significant activity against *C. albicans (MTCC 183)*, *A. niger (MTCC 228)* and *F. oxysporium (MTCC 3656)* while **278** shows comparable activity against *C. albicans (MTCC 183)*, *A. niger (MTCC 228)* when tested at 1 mg/mL concentration taking clotrimazole as the standard drug[88].

Chaitanya et al. evaluated a series of BT derivatives (Figure 53: compounds **281**–**296**) for antimicrobial and anti-inflammatory activity. Compounds **281** and **291** depicted excellent antibacterial activity against *E. coli* and compounds **282**–**289** possess antifungal activity against *A. niger*. Moreover, compounds **289**, **290**,

292–**296**, possess potent antifungal activity against *Aspergillus flavus* and also compound **296** possesses good anti-inflammatory activity in carrageenan induced rat paw edema to the extent of 95.73% in comparison with the standard drug (82.56%).[89]

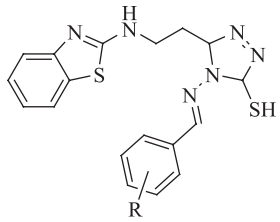
Antiviral activity

In the 19th century, humans lost their fear of God and acquired a fear of microbes, whereas in the 20th century, the anonymously acclaimed fear of microbes has been superceded by the fear of human immunodeficiency virus (HIV)[90]. HIV-I has been identified as the causative agent in the transmission and development of AIDS[91]. AIDS is now a pandemic. In 2007, it was estimated by World Health Organisation (WHO) that 33.2 million people lived with the disease worldwide, and that AIDS killed an estimated 2.1 million people, including 330,000 children[92]. In the past two and half decades, various compounds have been developed as medicinal candidates for the treatment of HIV infections aiming at one or several steps of the HIV-1 life cycle such as absorption, entry, fusion, un-coating, reverse transcription, integration, transcription and maturation[93]. Reverse transcriptase (RT) is a key enzyme, which plays an important role in the replication of virus. Three non-nucleoside reverse transcriptase inhibitors namely nevirepine, delaviridine and efavirenz (EFV) have been approved by FDA[94]. However, prolonged treatment with antiretroviral drugs results in disease progression. These concerns have drawn a strong focus on research into new drugs targeting other aspects of HIV life cycle, including viral entry and integration into the host genome (integrase inhibitors)[95].



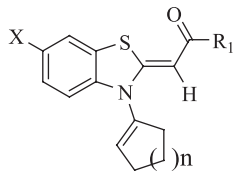
142: R = 6-COOH
143: R = 6-nitro
144: R = 7-nitro
145: R = 4-nitro
146: R = 6-bromo
147: R = 6-chloro
148: R = 4,6-di-nitro

Figure 34. Chemical structure of antifungal 2-amino-substituted-benzothiazoles.

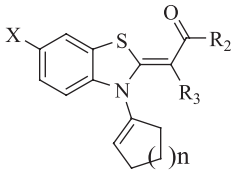


149: R = H
150: R = 4-OH
151: R = 2-NO_2
152: R = 3-NO_2
153: R = 2-Cl
154: R = 4-$N(CH_3)_2$
155: R = 3,4-OCH_3

Figure 35. Chemical structure of Schiff bases of benzothiazole derivatives.



156-165



166-170

156: X = H; n = 8; $R_1 = CH_3$
157: X = H; n = 8; $R_1 = C_2H_5$
158: X = H; n = 8; $R_1 = C_3H_7$
159: X = H; n = 8; R_1 = i-C_3H_7
160: X = H; n = 3; $R_1 = C_6H_{13}$
161: X = F; n = 3; $R_1 = C_3H_7$
162: X = OCH_3; n = 3; $R_1 = C_3H_7$
163: X = OCH_3; n = 3; R_1 = i-C_3H_7
164: X = CH_3; n = 3; R_1 = i-C_3H_7
165: X = CH_3; n = 3; $R_1 = C_4H_9$
166: X = H; n = 4; $R_2 = C_2H_5$; R_3 = H
167: X = H; n = 3; $R_2 = C_2H_5$; R_3 = H
168: X = H; n = 3; $R_2 = CH_3$; R_3 = H
169: X = H; n = 3; R_2; $R_3 = (CH_2)_3$
170: X = H; n = 3; $R_2 = C_6H_5$; R_3 = H

Figure 36. Chemical structure of antimicrobial substituted-benzothiazoles.

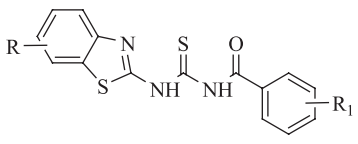
Akhtar et al. investigated a series of new BT derivatives (Figure 54: compounds **297**–**298**) for their antiviral activity. Results showed that none of the *in vitro* tested compounds was found to inhibit HIV-replication, at EC_{50} lower than the CC_{50}, compared with the antiviral agent EFV, whereas biological screening for cytotoxicity observed that compounds **297** and **298** showed strong effect on leukaemia cell lines[96].

A series of 2,5,6-substituted benzoxazole, benzimidazole, BT and oxazole(4,5-b) pyridine derivatives were evaluated for antiviral activity against HIV-I reverse transcriptase enzyme by Akbay et al. Results demonstrated that compound **299** (Figure 55) posseses good antiviral activity (IC_{50} value 0.34 μmol/L)[97].

Nagarajan et al. synthesized inhibitors of HIV-1 protease with improved potency and antiviral activities by replacement of the urea moiety by benzothiazolesulfonamide moiety. Compounds **300**–**302** (Figure 56) were observed to be potent inhibitors of HIV-1 protease and also possess good oral bioavailability[98].

Antimalarial activity

Malaria is one of the most serious global health problems in subtropical and tropical zones of the world and travellers to these endemic areas. Global estimates of malaria show that at least 300 million people are afflicted, and



171-181

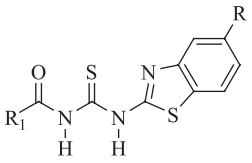
171: R = R_1 = H
172: R = H; R_1 = 2-OMe
173: R = H; R_1 = 4-Me
174: R = 6-Br; R_1 = 3-Cl
175: R = 6-Br; R_1 = 2-F
176: R = 6-Me; R_1 = 3-Cl
177: R = 6-Me; R_1 = 2-Br
178: R = 6-OMe; R_1 = H
179: R = 6-OMe; R_1 = 2,4-di-Cl
180: R = 5,6-di-Cl; R_1 = 2,4-di-Cl
181: R = 5,6-di-Cl; R_1 = H

Figure 37. Chemical structure of benzothiazole derivatives.

1–3 million people die annually from this disease. The disease is caused by four species of the malaria parasite of which *Plasmodium falciparum* is the most virulent and potentially deadly. Most serious issue is that malaria parasites develop resistance to clinically used chemotherapeutic agents such as chloroquine, mefloquine and pyrimethamine. Therefore, there is still a need for highly potent and low-priced antimalarials[99,100].

5-*n*-Undecyl and 5-*n*-pentadecyl-6-hydroxy-4,7-dioxobenzothiazole were tested for prophylactic antimalarial activity against *Plasmodium gallinaceum* in chicks by Friedman et al. and (Figure 57: compound **303**) was found to show prophylactic activity at 120 mg/kg in this sporozoite-induced malaria[101].

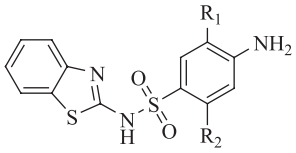
Burger and Sawhney evaluated a series of BT amino alcohols for antimalarial activity (Figure 58: compounds **304**–**306**). Results showed that several compounds possess weak activity against *Plasmodium berghei*[102].



182-186

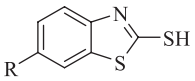
182: R_1 = 2-thiophene; R = NO_2
183: R_1 = 4-morpholine; R = NO_2
184: R_1 = 4-nitrophenyl; R = NO_2
185: R_1 = phenyl; R = NO_2
186: R_1 = n-butyl; R = NO_2

Figure 38. Chemical structure of thiourea derivatives bearing benzothiazole moiety.



187: R_1 = CH_3; R_2 = Cl
188: R_1 = COOH; R_2 = Cl
189: R_1 = OCH_3; R_2 = Cl

Figure 39. Chemical structure of 4-amino-*N*-(1,3-benzothiazol-2-yl)benzenesulphonamide.



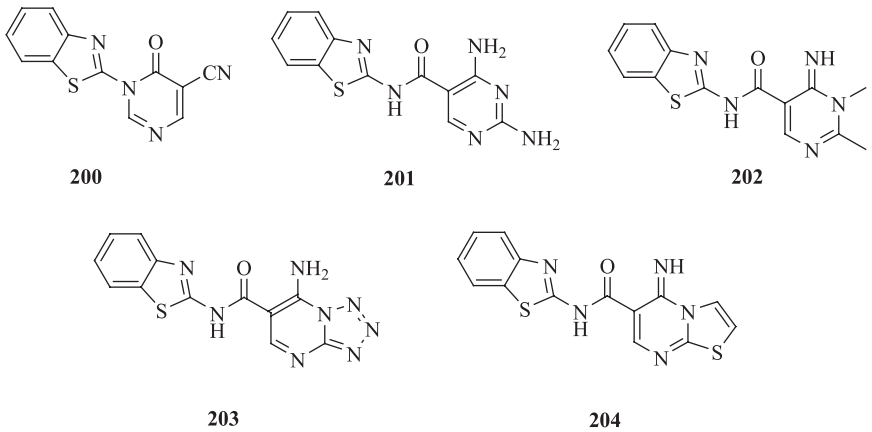
190: R = OCH_3
191: R = F
192: R = H
193: R = NH_2
194: R = NO_2
195: R = CF_3
196: R = OCH_2CH_3
197: R = $CH(CH_3)_2$
198: R = Cl
199: R = CH_3

Figure 40. Chemical structure of 2-mercapto-1,3-benzothiazole derivatives.

Bowyer et al. demonstrated the use of scintillation proximity assay for the identification of inhibitors showing activity against both recombinant N-myristoyltransferase of *Plasmodium falciparum* (PfNMT) and the cultured asexual stages of *P. falciparum*. Seven compounds showed >25% inhibitory activity against recombinant PfNMT. Data showed that three BT -containing compounds (**307**, **310** and **313**) have IC_{50} values <50 μM for PfNMT. All the compounds showed some selectivity for PfNMT, with the exception of compound **308** (Figure 59) that depicted more inhibitory action to HsNMT as compared with PfNMT. Effect of these compounds on total parasitaemia, compared with controls containing 1% (v/v) DMSO only, shows that there was a significant reduction in parasitaemia at 100 μM to a level similar to the starting parasitaemia (approximately 1%). In the case of compounds **307** and **309** at 10 μM, there was an approximately 80% reduction in parasitaemia compared with the control[103].

Antitubercular activity

TB is a contagious disease with high mortality worldwide and is currently the leading killer of the youth, women and AIDS patients worldwide[104]. The statistics indicate that 3 million people worldwide die annually from complications of TB, and there are estimated 8 million new cases each year, 95% of which occur in developing countries[105,106]. The actual development and clinical use of new therapeutics for TB have remained stagnant for years because of the complexity of the disease process, the treatment of which at present requires the administration of drug combinations over a period of 6 months and more importantly because of the alarming rise of drug-resistance. Treatment of mycobacterial infections, especially TB, has become an important problem due to the emergence of monodrug and multidrug-resistant strains of *M. tuberculosis*. It can be emphasized that there exists continuous demand for drugs of new structural classes with novel mechanisms

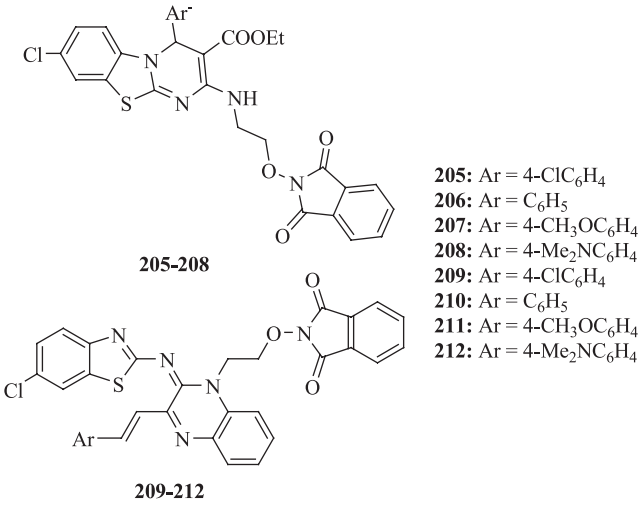


200 **201** **202**

203 **204**

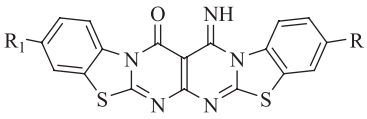
Figure 41. Chemical structure of antibacterial benzothiazole derivatives.

of action other than isoniazid, rifampicin and pyridazinamide. Hence, discovery and development of novel, more active and less-toxic anti-TB agents is an imperative task for medicinal researchers[107].



205: Ar = 4-ClC_6H_4
206: Ar = C_6H_5
207: Ar = 4-$CH_3OC_6H_4$
208: Ar = 4-$Me_2NC_6H_4$
209: Ar = 4-ClC_6H_4
210: Ar = C_6H_5
211: Ar = 4-$CH_3OC_6H_4$
212: Ar = 4-$Me_2NC_6H_4$

Figure 42. Chemical structure benzothiazole derivatives.



213: R = H; R_1 = NO_2
214: R = H; R_1 = Cl
215: R = H; R_1 = OCH_3
216: R = CH_3; R_1 = H
217: R = CH_3; R_1 = NO_2
218: R = CH_3; R_1 = Cl
219: R = OCH_3; R_1 = H
220: R = OCH_3; R_1 = NO_2
221: R = OCH_3; R_1 = Cl
222: R = OCH_3; R_1 = OCH_3

Figure 43. Chemical structure of 15-iminobenzothiazolo[2,3-b]pyrimido[5,6-c]pyrimido[2,3-b]benzothiazole-14(*H*)-one derivatives.

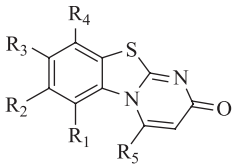
Novel 3-nitro-2-(sub)-5,12-dihydro-5-oxobenzothiazolo[3,2-a]-1,8-naphthyridine-6-carboxylic acids were synthesized and evaluated for their antitubercular activities *in vitro* and *in vivo* against *M. tuberculosis* H37 Rv (MTB) and multidrug resistant *M. tuberculosis* (MDR-TB) by Dinakaran et al. Among the synthesized compounds, 2-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)-3-nitro-5,12-dihydro-5-oxobenzothiazolo[3,2-a]-1,8-naphthyridine-6-carboxylic acid (Figure 60: compound **314**) was found to be the most active compound *in vitro* with MIC of 0.19 and 0.04 μM against MTB and MTR-TB, respectively[108].

A new class of 2-methylbenzothiazole analogues (Figure 61: **315**–**316**) depicting appreciable anti-TB properties was identified by Huang et al. These agents were found to be active against replicating *M. tuberculosis* H37Rv. From the overall results, it was predicted that the most potent compounds **315** and **316** exhibited MICs of 1.4 and 1.9 μM, respectively[109].

Palmer et al. evaluated a series of benzothiazoline derivatives for antimicrobial activity against Gram positive and Gram negative bacteria, dermatophytes, *Entamoeba histolytica* and for *in vitro* and *in vivo* activity against *M. tuberculosis*. Results demonstrated that compound **317** (Figure 62) possesses the greatest activity against *M. tuberculosis*[110].

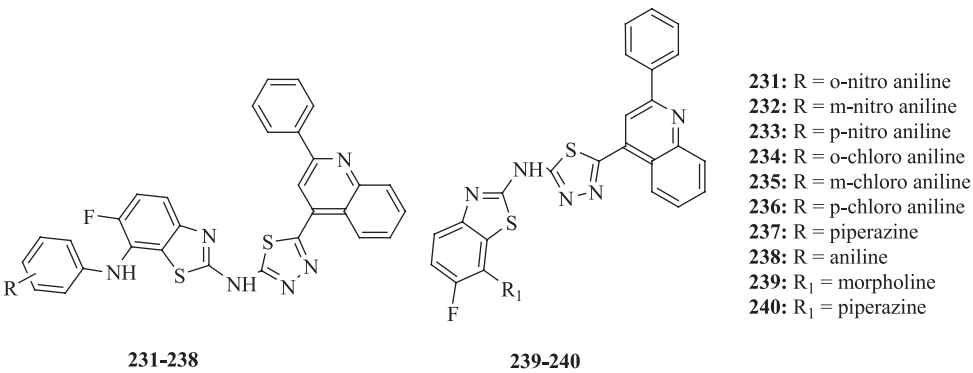
Anthelmintic activity

Helminth parasitism remains an underappreciated scourge of humans in most of the developing world. As many as 2 billion individuals harbour these parasites, with millions typically simultaneously infected with filariae, hookworms, whipworm, large roundworms and/or schistosomes, all of which often result in chronic, debilitating



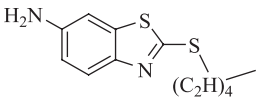
223: R_1 = H; R_2 = Cl; R_3 = H; R_4 = H; R_5 = Ph
224: R_1 = H; R_2 = cyclic C_4H_4 bonded at C_6 and C_7; R_4 = H; R_5 = Ph
225: R_1 = Me; R_2 = Me; R_3 = H; R_4 = H; R_5 = Ph
226: R_1 = H; R_2 = Me; R_3 = H; R_4 = Me; R_5 = Ph
227: R_1 = H; R_2 = Cl; R_3 = H; R_4 = H; R_5 = 1-Pentyl
228: R_1 = H; R_2 = cyclic C_4H_4 bonded at C_6 and C_7; R_4 = H; R_5 = 1-Pentyl
229: R_1 = Me; R_2 = Me; R_3 = H; R_4 = H; R_5 = 1-Pentyl
230: R_1 = H; R_2 = Me; R_3 = H; R_4 = Me; R_5 = 1-Pentyl

Figure 44. Chemical structure of substituted pyrimido[2,1-b]benzothiazoles.



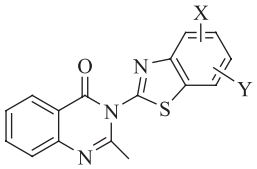
231: R = o-nitro aniline
232: R = m-nitro aniline
233: R = p-nitro aniline
234: R = o-chloro aniline
235: R = m-chloro aniline
236: R = p-chloro aniline
237: R = piperazine
238: R = aniline
239: R_1 = morpholine
240: R_1 = piperazine

Figure 45. Chemical structure of antibacterial flurobenzothiazole derivatives.



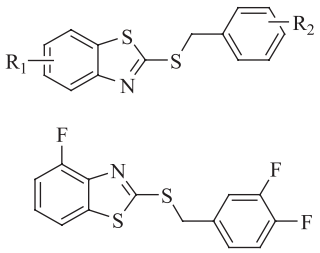
241

Figure 46. Chemical structure of 6-amino-2-n-pentylthiobenzothiazole (APB).



242: X = 5-NO_2; Y = H
243: X = 6-NO_2; Y = H
244: X = 4-Cl; Y = 6-NO_2

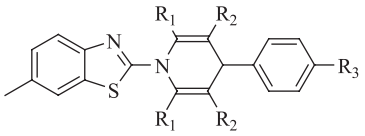
Figure 47. Chemical structure of 2-methyl-3-[(substituted) benzothiazole-2′-yl]4(3*H*)-quinazolinones.



245: R_1= 4-F; R_2= 2-F
246: R_1= 4-F; R_2= 2,6-F
247: R1= 4-F; R_2= 3,4 -F
248: R_1= 5- F; R_2= 2-f
249: R_1= 5- F; R_2= 2,6-F
250: R_1= 5-F; R_2= 3,4-F
251: R_1= 6,7-F; R_2= 2-F

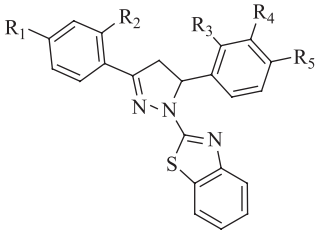
252

Figure 48. Chemical structure of polyfluorinated 2-benzylthiobenzothiazoles.



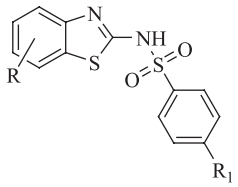
253: R_1 = Me; R_2 = COOEt; R_3 = m-NO_2
254: R_1 = OEt; R_2 = COOEt; R_3 = m-NO_2
255: R_1 = Me; R_2 = COMe; R_3 = m-NO_2

Figure 49. Chemical structure of *N*-(6-methylbenzothiazolyl)-2,3,5,6-tetrasubstituted-4-(aryl)-1,4-dihydropyridines.



256: R_2 = OH; R_1 = R_3 = R_4 = R_5 = H
257: R_3 = OH; R_2 = R_3 = R_4 = R_5 = H
258: R_1 = CH_3; R_2 = R_4 = R_5 = H; R_3 = OH
259: R_1 = OCH_3; R_2 = R_4 = R_5 = H; R_3 = OH
260: R_1 = R_3 = R_4 = H, R_2= OH; R_5 = OCH_3
261: R_1 = R_3 = R_4 = H; R_2 = OH; R_5 = Cl
262: R_1 = CH_3; R_2 = R_3= R_4 = R_5 = H
263: R_1 = CH_3; R_2 = R_3 = R_4 = H, R_5 = OCH_3

Figure 50. Chemical structure of 3,5-diaryl-1-benzothiazolopyrazoline derivatives.



264: R= 4-CH_3; R_1= NH_2
265: R= 6-Cl; R_1= NH_2
266: R= 6-OC_2H_5; R_1= NH_2
267: R= H; R_1= NO_2
268: R= 4-CH_3; R_1= NO_2

Figure 51. Chemical structure of antiparasitic substituted-benzothiazoles.

morbidity[111]. Despite remarkable advances made in the chemotherapy of parasitic diseases, even today, successful treatment and eventual eradication of filariasis remains as one of the major public health problems of the tropics. Attempts to innovate new "structural leads" in the chemotherapy of helminthiasis have led to the discovery of a series of benzothizoles anthelmintics possessing potent activity against different helminth parasites[112].

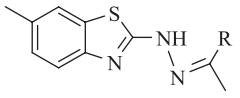
Anthelmentic activity of fluorobenzothiazole comprising sulfonamido pyrazole derivatives against earthworms, *Perituma posthuma* were demonstrated by Sreenivasa et al. Compounds **318**–**325** (Figure 63) showed significant activity as compared with the standard drug albendazole[113].

Nadkarni et al. synthesized substituted phenyl imidazo-[2,1-b]benzothiazoles (Figure 64: compounds **326**–**328**) and tested their anthelmintic activity. Results showed that all the compounds exhibited potent anthelmintic activity[114].

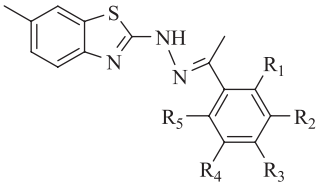
Anti-inflammatory activity

Inflammatory diseases are widely prevalent throughout the world and inflammation remains a common as well as often poorly controlled disease, which can be life threatening in extreme form of allergy, autoimmune diseases and rejection of transplanted organs; and similarly, chronic inflammation has been found to mediate a wide variety of diseases including cardiovascular diseases, cancer, diabetes, arthritis, AD, pulmonary diseases and autoimmune diseases. Non steroidal anti-inflammatory drugs (NSAIDs) have been used for the treatment of ailments such as pain, fever and inflammation and also in chronic conditions such as arthritis, psoriasis and asthma[115–120]. NSAIDs principally act by two different mechanisms: a direct contact mechanism on the gastro intestinal (GI) mucosa through oral dose and a generalized systemic action appearing after intravenous dosing[121,122]. Their use is mainly restricted by their well known and serious adverse GI side effects such as gastroduodenal erosions, ulcerations and renal toxicities and therefore the discovery of new safer anti-inflammatory drugs represents a challenging goal for researchers[123,124].

Paramashivappa et al. evaluated a series of 2-[[2-alkoxy-6-pentadecylphenyl)methyl]thio]-1*H* benzimidazoles/benzothiazoles and benzoxazoles from anacardic acid for cyclooxygenase-1 (COX-1) inhibition. Results depicted that compound **329** (Figure 65) was 470-fold selective towards COX-2 compared with COX-1[125].



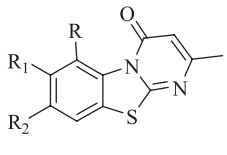
269-275



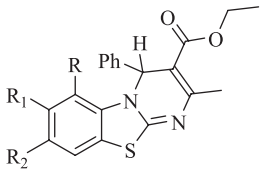
276-280

269: R = 2'-fluoroacetophenone
270: R = 4'-fluoroacetophenone
271: R = 2'-Chloroacetophenone
272: R = 4'-Chloroacetophenone
273: R = p-Hydroxyacetophenone
274: R = 2'-Hydroxyacetophenone
275: R = 2, 5-Dihydroxyacetophenone
276: R_1 = F; R_2 = NO_2; R_3 = OCH_3; R_4 = H; R_5 = CH_3
277: R_1 = OCH_3; R_2 = H; R_3 = Br; R_4 = H; R_5 = OC_2H_5
278: R_1 = OC_2H_5; R_2 = Cl; R_3 = OCH_3; R_4 = H; R_5 = OC_2H_5
279: R_1 = Cl; R_2 = OC_2H_5; R_3 = Cl; R_4 = CH_3; R_5 = OC_2H_5
280: R_1 = OCH_3; R_2 = H; R_3 = OCH_3; R_4 = OC_2H_5; R_5 = H

Figure 52. Chemical structure of benzothiazole derivatives.



281-288

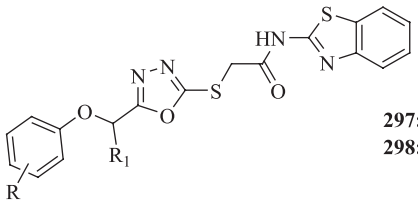


289-296

281: R = H; R_1 = Cl; R_2 = F
282: R = CH_3; R_1 = H; R_2 = H
283: R = H; R_1 = CH_3; R_2 = H
284: R = H; R_1 = H; R_2 = CH_3
285: R = H; R_1 = H; R_2 = Cl
286: R = H; R_1 = H; R_2 = NO_2
287: R = H; R_1 = H; R_2 = OH
288: R = H; R_1 = H; R_2 = COOH

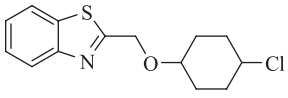
289: R = H; R_1 = Cl; R_2 = F
290: R = CH_3; R_1 = H; R_2 = H
291: R = H; R_1 = CH_3; R_2 = H
292: R = H; R_1 = H; R_2 = CH_3
293: R = H; R_1 = H; R_2 = Cl
294: R = H; R_1 = H; R_2 = NO_2
295: R = H; R_1 = H; R_2 = OH
296: R = H; R_1 = H; R_2 = COOH

Figure 53. Chemical structure of antimicrobial benzothiazole derivatives.



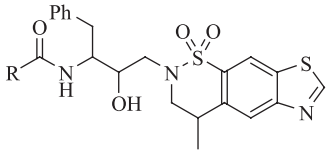
297: R = Cl; R_1 = Et
298: R = 3,4-Cl_2; R_1 = Me

Figure 54. Chemical structure of benzothiazole derivatives.



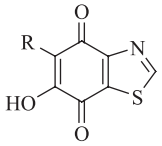
299

Figure 55. Chemical structure of 2-(p-chlorophenoxymethyl) benzothiazole.



300: R = 3-pyridylmethyloxy
301: R = 5-thiazolylmethyloxy
302: R = 3-tetrahydrofuranyloxy

Figure 56. Chemical structure of benzothiazole derivatives.



303: R = -*n*-Undecyl

Figure 57. Chemical structure of 5-n-undecyl-6-hydroxy-4,7-dioxobenzothiazole.

Singh et al. synthesized a series of 2-substituted-9-chloro-8-fluoropyrimido [2,1-b]benzothiazole-3-cyano-4(*H*)-ones (Figure 66: compounds **330**–**336**) and screened their anti-inflammatory and analgesic activity by acetic acid induced writhing method in albino mice. Results showed that none of them could inhibit albumin denaturation significantly in comparison with standard drug diclofinac sodium, which exhibited 81% inhibition of albumin denaturation[126].

Anti-inflammatory activity of 2-amino benzothiazole derivatives were reported by Venkatesh and Pandeya. Compounds **337**–**339** (Figure 67) were the most active compounds in comparison with standard drug diclofenac sodium[127].

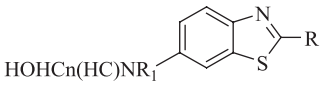
Wada et al. evaluated 2,5,6-trisubstituted benzothiazole compounds (Figure 68: compounds **340**–**347**) for their anti-inflammatory activity. It was found that presence of an acetic acid function was important for anti-inflammatory activity and also that 2-substituted 5-benzothiazoleacetic acid was better than 2-substituted 6-benzothiazoleacetic acid in anti-inflammatory activity[128].

Novel benzoheterocyclic[(methoxyphenyl)amino] oxoalkanoic acid esters have been screened as inhibitors of rat polymorphonuclear leukocytes 5-lipooxygenase (LO) *in vitro* and as inhibitors of leukoetriene D4 (LTD4) and ovalbumin induced bronchospasm in the guinea pig (GP) *in vivo* by Musser et al. Results revealed that compound **348** (Figure 69) was the most potent compound with IC_{50} of 0.36 μM[129].

Miscellaneous activities

Recent progress as anticonvulsant agents

Epilepsy is a syndrome of different cerebral disorders of the central nervous system (CNS) and is characterized



304: R = H
305: R = C_6H_5
306: R = CF_3

n = 1-3
R_1N = dialkylamino, piperidino

Figure 58. Chemical structure of benzothiazole amino alcohols.

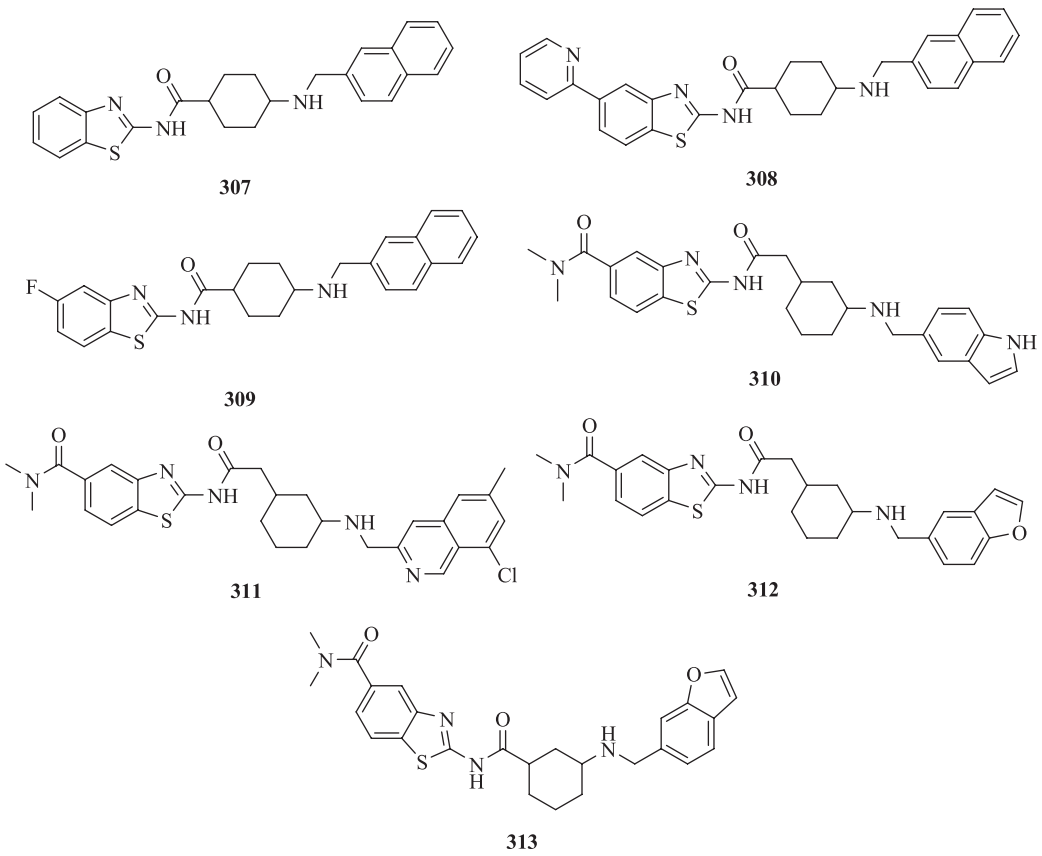


Figure 59. Chemical structure of benzothiazole derivatives.

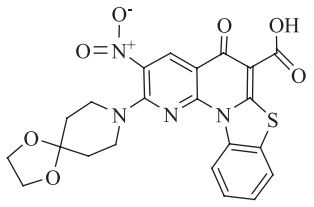


Figure 60. Chemical structure of 2-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)-3-nitro-5,12-dihydro-5-oxobenzothiazolo[3,2-a]-1,8-naphthyridine-6-carboxylic acid.

by paroxysmal, excessive and hyper synchronous discharges of large number of neurons. The overall prevalence of the disease is 0.5–1.0% of the population and up to 50 million people are affected worldwide. Data show that only 28–30% of patients are poorly treated with currently available antiepileptic drugs and these drugs may also cause serious side effects including ataxia, nausea, mental dulling and hepatotoxicity[130–132].

Sharma et al. synthesized and evaluated a series of isatin schiff's bases (Figure 70: compounds **349**–**357**) for their anticonvulsant activity; moreover, their toxicity screening was also carried out. Among the synthesized compounds, **350**–**352** showed potent anticonvulsant activity and compound **350** showed 100% protection at 300-mg dose in MES test and 60% promising protection in subcutaneous metrazole test upto 0.5 h; however, this compound has also shown 87.5% nontoxic effect[133].

In order to develop suitable anticonvulsant agents, Rana et al. synthesized a series of 1,3-benzothiazol-2-yl-benzamides. Among the hits discovered, compounds **358**–**360** (Figure 71) emerged as anticonvulsants with no neurotoxicity[134].

Anticonvulsant property of 1,3-benzothiazol-2-yl-semicarbazones were evaluated by Siddiqui et al. Results showed that compounds **361**–**364** (Figure 72) possessed 100% protection at both 0.5 h- and 4 h-time intervals except compound **361** whose percentage protection decreased to 83.3% at the 4 h indicating rapid onset but shorter duration of action against maximal electroshock (MES) test[135].

Recent advances in antidiabetic activity

Diabetes mellitus is one of the major crippling diseases in the world, leading to huge economic loses. This

metabolic disorder is a heterogeneous group of diseases characterized by derangement in carbohydrate, protein and/ or fat metabolism caused by defective production of insulin. Current estimates show that at least 150 million people worldwide have diabetes, of which two-thirds are residing in developing countries. The total number of people with diabetes is predicted to rise to about 300 million by the year 2025, with one-third of affected individuals living in India and China alone[136–138].

Pattan et al. synthesized a new series of 2-amino-[5′-(4-sulphonylbenzylidine)2,4-thiazolidinedione]-7-chloro-6-fluorobenzothiazoles and screened for their antidiabetic activity on albino mice. All the compounds **365**–**370** (Figure 73) showed significant antidiabetic activity, but compounds **365**–**367** showed maximum antidiabetic activity[139].

A new series of 2-thioether-benzothiazoles (Figure 74: compounds **371**–**375**) has been synthesized and evaluated for c-jun N-terminal kinase inhibition by De et al. Results depicted that compounds **371** and **375** show similar activity, whereas compounds **373**–**374** were inactive due to stearic hindrance[140].

Zandt et al. discovered 3-[(4,5,7-trifluorobenzothiazol-2-yl)methyl]indole-*N*-acetic acid (Lidorestat) (Figure 75: compound **376**) as highly potent and selective inhibitors of aldose reductase with an IC_{50} of 5 nM for treatment of chronic diabetic complications[141].

Su et al. evaluated BT derivatives as selective inhibitors of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) possessing a considerable potential in treatments for metabolic diseases, such as diabetes mellitus type 2 or obesity. Results demonstrated that compounds **377** and **378** (Figure 76) show inhibition for 11β-HSD1 greater than 80% at 10 μM[142].

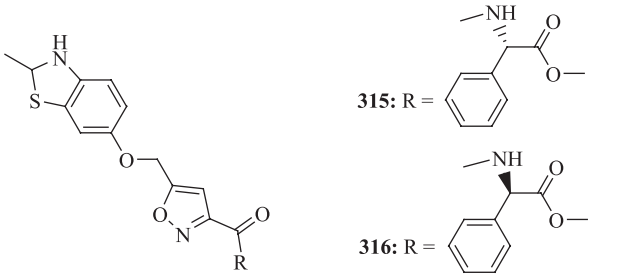
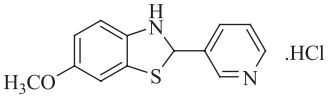
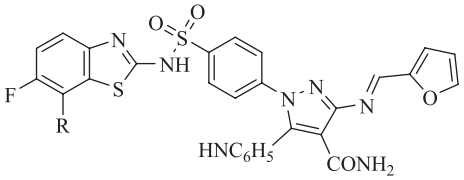


Figure 61. Chemical structure of 2-methylbenzothiazole derivatives.



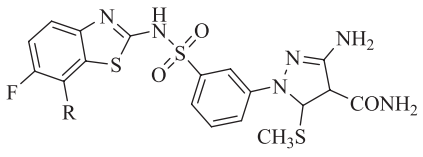
317

Figure 62. Chemical structure of benzothiazoline derivatives.



318-324

318: R = p-nitro aniline
319: R = aniline
320: R = PABA
321: R = morpholine
322: R = piperazine
323: R = dimethylanine
324: R = diphenylamine



325

325: R = PABA

Figure 63. Chemical structure of flurobenzothiazole derivatives.

Diuretic activity

N-{(substituted)-1,3-benzothiazol-2-yl}-1,1-biphenyl-4-carboxamide derivatives (Figure 77: compound **379**) were screened by Shaharyar and Ansari for their *in vivo* diuretic activity. Urinary output of this synthesized compound was highly significant 16.08 ± 0.650 ($p < 0.01$), i.e. increased by >300% with respect to control urinary output[143].

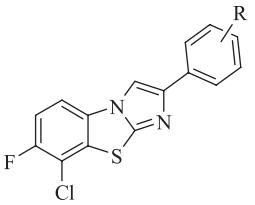
Developments in cardiovascular activity profile

Yoshino et al. evaluated a series of 4-(benzothiazol-2-yl) benzylphosphonic acid dialkyl ester derivatives (Figure 78: compounds **380**–**385**) for coronary vasodilatory activity by Langendorff's method in the isolated guinea pig heart. Results revealed that the potency of diethyl derivative **380** was superior to that of reference compounds papaverine hydrochloride or diltiazem hydrochloride[144].

Vu et al. evaluated a series of triamide derivatives bearing a BT core as potent microsomal triglyceride transfer protein inhibitors (Figure 79: compound **386**). Results demonstrated that compound **386** lowered the plasma triglycerides, glucose and insulin levels at doses as low as 3 mg/kg and also had a low systemic exposure[145].

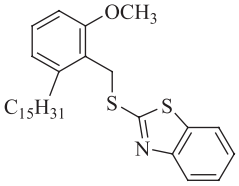
Antioxidant agent

Cressier et al. reported the synthesis and antioxidant property of new compounds derived from benzothiazoles and thiadiazoles. It was noticed that only thiols, thiosulfonic acids and phosphorothioates exhibit evident antioxidant activity and 2-mercapto-6-methylbenzothiazole (Figure 80: compound **387**) show an efficient radioprotective effect at $LD_{99.9/30Days\text{-}IRR}$[146].



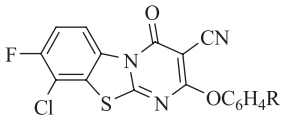
326: R = 2-F
327: R = 3-F
328: R = 3-CF_3

Figure 64. Chemical structure of phenyl imidazo-[2,1-b]benzothiazole derivatives.

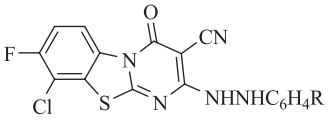


329

Figure 65. Chemical structure of 2-[[2-alkoxy-6-pentadecylphenyl)methyl]thio]-1*H*-benzothiazole.



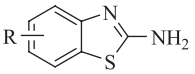
330-333



334-336

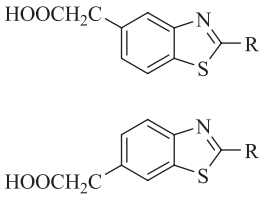
330: R = 2-Me
331: R = 3-Me
332: R = 4-NO_2
333: R = 2-Cl
334: R = Ar(H)
335: R = Ar(2,4-NO_2)
336: R = H

Figure 66. Chemical structure of 2-substituted-9-chloro-8-fluoropyrimido [2,1-b]benzothiazole-3-cyano-4(*H*)-ones.



337: R = 5-Cl
338: R = 6-methoxy
339: R = 4-methoxy

Figure 67. Chemical structure of anti-inflammatory 2-amino benzothiazole derivatives.



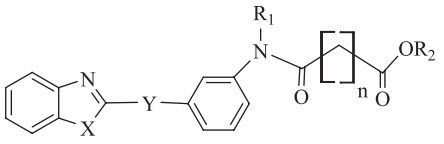
340: R = C_6H_5
341: R = 2-HOC_6H_4
342: R = 4-$CH_3C_6H_4$
343: R = 2-OH-$_3$-$CH_3C_6H_4$
344: R = C_6H_4
345: R = 2-HOC_6H_4
346: R = 3,4-$(CH_3O)_2C_6H_3$
347: R = 4-$(CH_3)_2NC_6H_4$

Figure 68. Chemical structure of 2-substituted-5-benzothiazoleacetic acid and 6-benzothiazoleacetic-2-substituted acid.

Karali et al. evaluated antioxidant property of 3*H*-spiro[1,3-benzothiazole-2,30-indol]-20(10*H*)-ones derivatives (Figure 81: compounds **388**–**395**). Compounds **388**, **389** and **391** were observed to be the most active antioxidant agents[147].

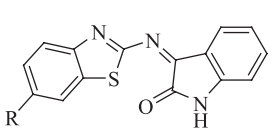
Antiasthmatic activity

Benothiazole ketone as a potent, reversible, low molecular weight tryptase inhibitors were studied by Costanzo



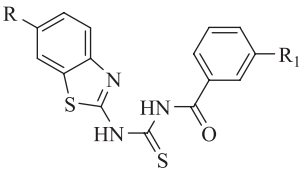
348: X = S, Y= CH_2O, R_1 = OH, R_2 = CH_3, n = 2

Figure 69. Chemical structure of benzothiazole derivatives.



349: R = H
350: R = $N(CH)_2$
351: R = OCH_3
352: R = Cl
353: R = F
354: R = Br
355: R = CH_3
356: R = C_2H_5
357: R = NO_2

Figure 70. Chemical structure of anticonvulsant benzothiazoles.



358: R = F; R_1 = H
359: R = CH_3; R_1 = 2-Cl
360: R = Br; R_1 = CH_3O

Figure 71. Chemical structure of 1,3-benzothiazol-2-yl benzamides.

et al. Results showed that transition-state mimetics possessing a heterocyclic activated ketone group possess potent tryptase inhibitory activity with a *K*i value of 10 nM (Figure 82: compound **396**)[148].

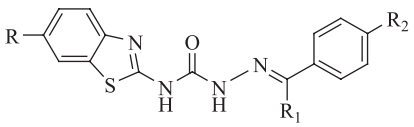
Laddha et al. evaluated the phosphodiesterase inhibitory properties of two series of 6,8-disubstituted-2-phenyl-3-(substituted benzothiazole-2-yl)-4[3*H*]-quinazolinone. Compounds 6,8-dibromo-2-phenyl-3-(5-chloro benzothiazole-2-yl)-4[3*H*]-quinazolinone (Figure 83: compound **397**) with IC_{50} of 1438 ± 85 μM and 6,8-dibromo-2-phenyl-3-(6-nitro benzothiazole-2-yl)-4[3*H*]-quinazolinone **398** with IC_{50} of 1520 ± 48 μM were found to be more potent than standard drug theophylline[149].

Antiallergic activity

Wade et al. synthesized 2- or 3-carboxy-4*H*-pyrimido [2,1-b]-benzazol-4-ones (Figure 84: compounds **399**–**401**). These acidic compounds were tested in the rat passive cutaneous anaphylaxis assay as potential antiallergic agents. Incorporation of an acidic functionality [carboxylic acid, *N*-(1*H*-tetrazole-5-yl)carboxamide, or tetrazole] at either the 2- or 3- position of the 4*H*-pyrimado[2,1-b] benzazole-4-one ring system gives good antiallergenic property[150].

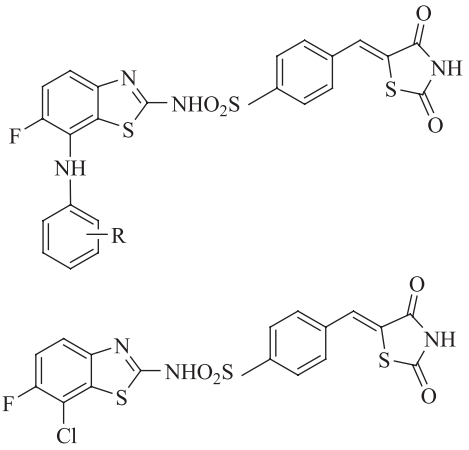
Role in AD

Alzheimer's disease is a group of progressive neurodegenerative disorder pathologically characterized by the deposition of β-amyloid (Aβ) peptide into amyloid plaques in the extracellular brain parenchyma and by intraneuronal neurofibrillary tangles caused by the abnormal phosphorylation of the tau protein[151].

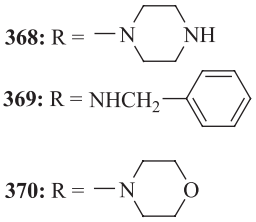


361: R = Cl; $R_1 = CH_3$; $R_2 = H$
362: R = CH_3; $R_1 = CH_3$; $R_2 = NO_2$
363: R = OCH_3; $R_1 = CH_3$; $R_2 = NO_2$
364: R = OCH_3; $R_1 = C_6H_5$; $R_2 = H$

Figure 72. Chemical structure of 1,3-benzothiazol-2-yl-semicarbazones.

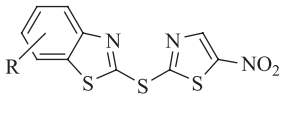


365: R = H
366: R = m-nitro
367: R = p-COOH



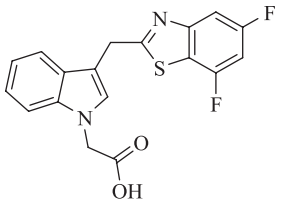
368: R =
369: R = $NHCH_2$
370: R =

Figure 73. Chemical structure of series of 2-amino[5'-(4-sulphonylbenzylidine)2,4-thiazolidinedione]-7-chloro-6-fluorobenzothiazoles.



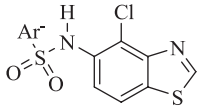
371: R = H
372: R = 5-OCH_3
373: R = 6-OC_2H_5
374: R = 5-Cl
375: R = 6-Cl

Figure 74. Chemical structure of 2-thioether-benzothiazoles.



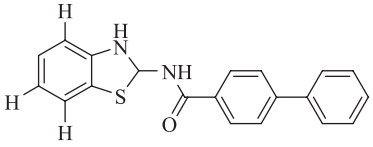
376

Figure 75. Chemical structure of benzothiazole derivatives.



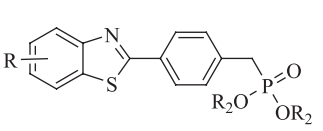
377: Ar = 2,5-dichloro phenyl
378: Ar = 4-*n*-propyl phenyl

Figure 76. Chemical structure of benzothiazole derivatives.



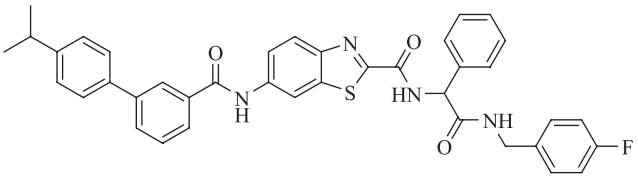
379

Figure 77. Chemical structure of *N*-(1,3-benzothiazol-2-yl)-1,1-biphenyl-4-carboxamide.



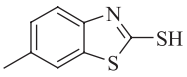
380: R = H; R_2 = Et
381: R = H; R_2 = n-Pr
382: R = H; R_2 = i-Pr
383: R = 6-Me; R_2 = Et
384: R = 6-Cl; R_2 = Et
385: R = 6-NHAc; R_2 = Et

Figure 78. Chemical structure of coronary vasodilatory active benzothiazole derivatives.



386

Figure 79. Chemical structure of triamide derivatives bearing a benzothiazole.



387

Figure 80. Chemical structure of antioxidant 2-mercapto-6-methylbenzothiazole.

A novel and convergent palladium catalyzed 2-arylbenzothiazoles was synthesized (Figure 85: compound **402**) by Majo et al. The key step in the synthesis was a Suzuki biaryl coupling of 2-bromobenzothiazole with aryl boronic acids to provide a variety of 2-arylbenzothiazole derivatives in good yield. The synthetic utility of this methodology was demonstrated by the synthesis of 2-(4-aminophenyl)-6-methoxybenzothiazole, a positron

emission tomography proves precursor for the *in vivo* imaging of AD[152].

Byeon et al. evaluated some new ferulic acid and BT dimers for their specific binding affinities to Aβ fibrils. Compound **403** (Figure 86) has shown excellent binding affinity to Aβ fibrils[153].

Anticarbonic anhydrase activity

In humans, 16 different isozymes have been described, several of these isozymes are considered as drug targets. They constitute interesting targets for the design of pharmacological agents useful in the treatment or prevention of a variety of disorders such as glaucoma, acid-base disequilibria, epilepsy and various other neuromuscular diseases such as altitude sickness, edema and obesity[154]. Carbonic anhydrases (CAs) are zinc-containing metalloenzymes and plays crucial role in various physiological processes including carbon dioxide and hydrocarbon transport, acid homeostasis, biosynthetic reactions and various pathological processes, especially tumor progression. Therefore, CAs are interesting targets for pharmaceutical research[155]. Carbonic anhydrase inhibitors (CAIs) were used as diuretics and antiglaucoma drugs and also have the potential to be used as novel antiobesity, anticancer and anti-infective drugs[156–166]. Ethoxzolamide (EZA), carbonic anhydrase inhibitor, was the first approved drug with BT scaffold. Baranauskiene and Matulis described the intrinsic binding parameters (Gibbs free energy, enthalpy, entropy and heat capacity) for several inhibitors, including EZA, trifluoromethanesulfonamide and acetazolamide, binding to recombinant human CA XIII isozyme by using isothermal titration calorimetry and thermal shift assay (TSA) methods. Intrinsic enthalpy of EZA binding is –42.1 kJ/mol, intrinsic Gibbs free energy –52.8 and the intrinsic entropy of binding is 35.9 J/(mol × K)[167].

EZA, an almost forgotten inhibitor of the metalloenzyme carbonic anhydrase, was already the lead molecule to obtain the second generation inhibitors, dorzolamide and brinzolamide, clinically used antiglaucoma agents with topical action, as well as various other investigational agents. Di Fiore et al. discussed the inhibition data of EZA with the 12 catalytically active mammalian isozymes (CA I-CA XIV) and the X-ray crystal structure with the cytosolic, ubiquitous isoform CA II. The structural analysis suggested that the introduction of bulky substituents on the bicyclic ring system of CAIs may represent a powerful strategy to obtain compounds with diverse inhibition profiles and selectivity

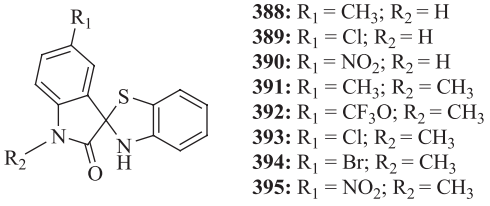
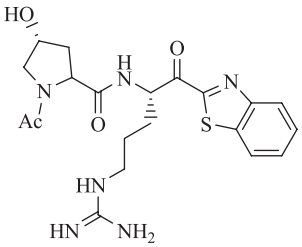
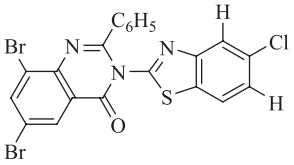


Figure 81. Chemical structure of 3*H*-spiro[1,3-benzothiazole-2,30-indol]-20(10*H*)-ones derivatives.

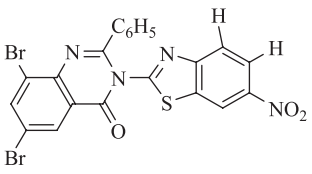


396

Figure 82. Chemical structure of substituted benzothiazole ketone.



397



398

Figure 83. Chemical structure of phosphodiesterase inhibitor benzothiazole derivatives.

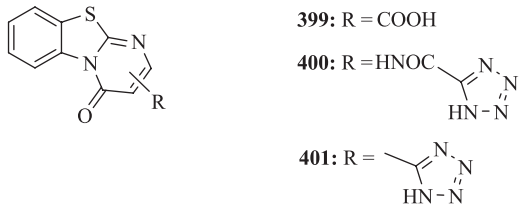
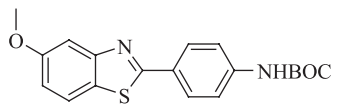
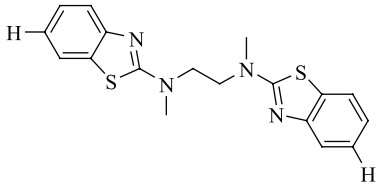


Figure 84. Chemical structure of benzothiazole derivatives.



402

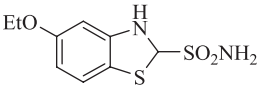
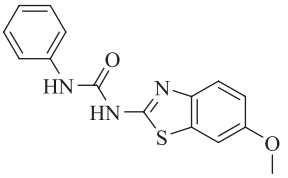
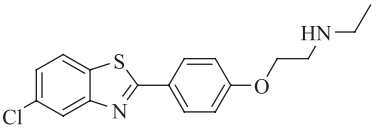
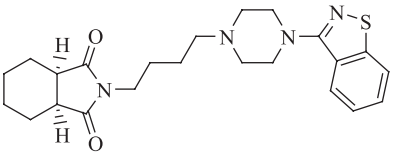
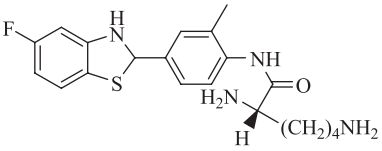
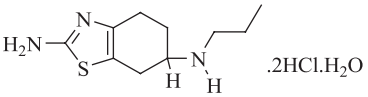
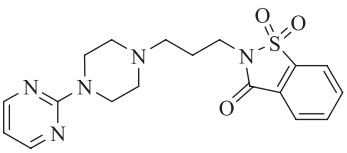
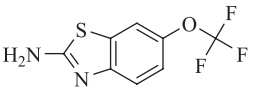
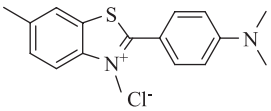
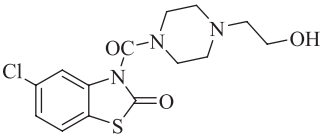
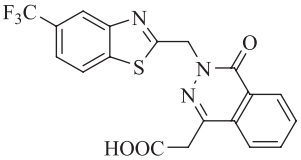
Figure 85. Chemical structure of 2-arylbenzothiazole derivatives.



403

Figure 86. Chemical structure of benzothiazole derivatives having A β-fibril binding affinity.

Table 1. Some successful benzothiazole based clinically available drugs.

Name of drug	Category	Structure	Ref. No.
Ethoxzolamide	Diuretic agent		154
Frentizole	Antiviral agent and Immunosuppressive Agent		169
Halethazole	Antiseptic agent		170
Perospirone	Antipsychotic agent		171
Phortress	Antitumour agent [under phase I in clinical trials]		172
Pramipexole	Antiparkinson's agent		173
Revospirone	Anxiolytic agent		174
Riluzole	Glutamate antagonist agent		175
Thioflavin-T	Amyloid Imaging Agent		176
Tiaramide	Anti-inflammatory agent		177
Zopolrestat	Antidiabetic agent		178

for the various mammalian CAs. These data are presumably useful for the design of novel CA inhibitors incorporating such bicyclic rings, targeting various CA isozymes[168].

Marketed drugs

Some important and clinically used drugs having BT ring in their structures are presented in the Table 1.

Conclusion

The aforementioned literature reveals that BT is a versatile heterocyclic scaffold having high potential for the development of new chemical entities for treatment of infectious diseases, cancer, CNS and cardiovascular system disorders. The broad spectrum antibacterial and antifungal activity of BT derivatives could lead to a new

series of antimicrobials. The BT derivatives have demonstrated promising anticancer and anti-inflammatory activities. Potent antitumour activity demonstrated by 2-(4-aminophenyl)benzothiazole derivatives have reinforced their perspective role in these therapies. Thus, BT scaffold is not only synthetically important but also possesses a diverse range of promising pharmacological activities. The biological profiles of these new BT derivatives would represent a fruitful matrix for further development of better medicinal agents.

Declaration of interest

The authors report no conflicts of interest.

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