**A Mini-Review on pharmacological importance of benzothiazole scaffold**

**Mohammad Asif1\* and Mohd. Imran2**

*1Department of Pharmacy, Himalayan Institute of Pharmacy and Research, Dehradun, (Uttarakhand), 248007, India*

*2Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Northern Border University, Rafha 91911, PO Box 840, Saudi Arabia*

https://orcid.org/0000-0002-6064-1040 (Mohd. Imran)

https://orcid.org/0000-0002-9352-3462 (Mohammad Asif)

imran\_inderlok@yahoo.co.in

aasif321@gmail.com

**Running Title:** Biological activities of benzothiazoles



**Graphical abstract**

**Abstract**

Heterocyclic compounds are important because they have almost all types of pharmacological properties. Due to these properties of heterocyclic compounds, they attracted the researchers for the development of more effective newer drug molecules. In this review, we are studied on benzothiazole and its derivatives, which are used for the synthesis of various biologically active molecules. Benzothiazole derivatives have been possessed the various type of pharmacological activities like antimicrobial, anti-inflammatory, analgesic, anticonvulsant, antiviral, anthelmintic, antioxidant, anticancer, and other anticipated activities. Hence, structural alterations have resulted in different benzothiazole derivatives that illustrated a wide variety of pharmacological activities.

**Keywords**: Benzothiazole, biological activities, anti-inflammatory, analgesic, antimicrobial, anticancer.

**Introduction**

Various heterocyclic compounds are having containing nitrogen (N) and sulfur (S) hetero atom and provide a distinctive and versatile scaffold for the design and development of new drug molecules.Benzothiazole is a bicyclic ring system, it contained a benzene ring fused with 4,5 positions of thiazole ring. Thiazole (**1a**) is a five‐membered heterocyclic compound containing sulfur (S) and nitrogen (N) hetero atom at 1 and 3 positions in the ring system. Benzothiazole (**1b**) is an important heterocyclic compound having wide varieties of pharmacological activities, application in drug design and discovery and still has immense scientific attention nowadays [1].  Sulfur (S) and nitrogen (N) hetero atoms constitute the core structure of thiazole and it is structurally related to pyridine and thiophene, but in most of its properties are resembles pyridine. Thiazole derivatives like benzothiazole play a vital role as an outline in the progress of remarkable compounds that have diverse pharmacological activities and valuable in the treatment of different types of diseases and infections [2]. The pharmacological activities of benzothiazole derivatives are due to the existence of sulfur (S) and nitrogen (N) heteroatoms present in the ring structure [3]. Various natural compounds, which have useful pharmacological activities due to the presence of the benzothiazole ring [4]. Benzothiazole derivatives are used in the chemical industry and research purposes and very valuable for the development of various useful compounds [5].

 

**1a 1b**

**Figure 1.** Structure of thiazole and benzothiazole.

Benzothiazole derivatives are widely used in bioorganic and medicinal chemistry due to their significant biological activities [6]. Benzothiazole derivatives have possessed numerous biological activities like antimicrobial [7-11] anticancer [12-15] anthelmintic [16], antioxidants, anti-diabetic [17], and other activities [18]. They are also used as vulcanization accelerators. Various benzothiazole derivatives like 2- arylbenzothiazoles are used as a radioactive amyloid imagining agent [19] and anticancer agents [20]. In this review, we have discussed common synthetic methods of benzothiazole derivatives and their diverse pharmacological activities.

**Biological activities of benzothiazole Derivatives**

Benzothiazole analogs are possessing diverse types of biological activities such as anti-inflammatory, analgesic, antitumor, anticonvulsant, antioxidant, antimicrobial, antimutagenic, antidiabetic, anti-hyperplasia, etc [3-5]. Benzothiazole scaffold is a flexible and multifunctional molecule, various benzothiazole derivatives are used as clinically used drugs such as neuroprotective drug (**Riluzole**), antiparkinson drug (**Pramipexole**), anti-Alzheimer's disease drug (**Thioflavine**), and diuretic drug (**Ethoxolamide**) [18-21].

 

**Riluzole Pramipexole**

 

**Thioflavine Ethoxolamide**

**Figure 2.** Structure of some clinically used benzothiazole drugs.

**Antimicrobial activity**

Some benzothiazole derivatives, (E)-5-( 1 -(benzo[d]thiazol-2-ylimino)ethyl)-4-(furan-2-yl)-6-methyl-3,4- dihydropyrimidine-2(1H)-thiones (**2a-2j**) were exhibited good antibacterial activity against gram-positive and gram-negative bacteria [22].

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **2a** | H  | **2f** | 4,6,7- Tri Cl  |
| **2b** | 6OC2H5  | **2g** | 5- CH3  |
| **2c** | 5-NO2  | **2h** | 4- NO2  |
| **2d** | 6-CH3  | **2i** | 6- NO2  |
| **2e** | 4-Cl  | **2j** | 5,6-di- CH3  |

**Figure 3.** Structure of antimicrobial compounds (**2a-2j**).

Some benzothiazole pyrimidine analogs, (E)-5-amino-6-(benzo[d]thiazol-2-yl)-2-(2- benzylidenehydrazinyl)-7-(4-chlorophenyl)pyrido[2,3-d]pyrimidin-4(3H)-one (**3**) were exhibited excellent antibacterial activity against *Staphylococcus aureus, Streptococcus pyogenes, Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumonia,* and antifungal activity against *Aspergillus fumigatus, Aspergillus flavus, Candida albicans,*  *Penicillium marneffei* [23]. Several benzothiazole analogs (**4**) were exhibited antimicrobial activity against both bacterial and fungal strains such as *S. aureus, S. pyrogens, E. coli, P. mirabilis, C. albicans,* and *A. fumigatus* and compared with Ciprofloxacin and Amphotericin B. Compound 1-[2-(6- methoxybenzothiazole -2- yldiazenyl ])naphthalene-2-ol was possessed excellent antimicrobial activity [24].

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | **R**  |   **4** |
| **3a** | 4CH3O  |
| **3b** | 4-F  |
| **3c** | 5-NO2  |
| **3d** | 2,4-(CH3)2  |
| **3e** | 4-C2H5  |

**Figure 4.** Structure of antimicrobial compounds (**3a-3e** and **4**).

Some 2-substituted benzothiazole derivatives, 2-(1,3-benzothiazole-2-yl)5-(N,N-diethylamino) phenol were exhibited antibacterial activity against *S. aureus,* and *E. coli* and antifungal activity against *A. niger* and *C. albicans*. Compound, 2-(1,3-Benzothiazole-2-yl)-5-(N,N-diethylamino)phenol (**5**) possessed good antifungal property[25]. A series of Schiff bases of benzothiazole derivatives, (E)-N-(2-(4-(benzylideneamino)-4H-1,2,4-triazol- 3- yl)ethyl) benzo[d] thiazol-2-amine (6a and 6b) were exhibited in-vitro antimicrobial activity against bacterial strains *B. subtilis*, *E. coli, S. griseus,* *C. albicans,* and *A. niger*. Compound **6a** and **6b** having fungal strains substitution were possessed the highest activity against both the *C. albicans* and *A. niger* [26].

 

**5 6a**R= 4-N(CH3); **6b** R= 3,4-OCH3

**Figure 5.** Structure of antimicrobial compounds (**5, 6a,** and **6b**).

A series of N-(benzo[d]thiazol-2-yl)-4-nitrobenzene sulfonamides were exhibited antimicrobial activity against some selected gram-positive and gram-negative bacteria and fungi. The compound, N-(benzo[d]thiazol-2-yl)-4-nitro benzenesulfonamide (**7**) was exhibited maximum activity against Gram-positive and Gram-negative bacteria [27]. Compound N-(6-fluoro-7-(piperazine-2-yl)benzo[d]thiazol-2-yl)-4-(2-(3- nitro-phenyl )-4-oxothiazolidin-3-yl)benzene sulfonamide (**8**) was exhibited anti-microbial activity [28].



**7 8**

**Figure 6.** Structure of antimicrobial compounds (**7** and **8**).

Some benzothiazole derivative containing 1,3,4-thiadiazole and imidazoline ring, N-(5-phenyl- 1,3,4-thiadiazol-2-yl) benzo [d] thiazol-2-amine (**9**) were exhibited antibacterial activity against *E. coli, S. aureus,* and antifungal activity against *A. flavus* and *C. albicans* and compare with reference drug Ofloxacin (50μg /ml) and Ketoconazole (50μg /ml) for antibacterial and antifungal activity respectively [29]. Some 2-mercapto-benzothiazoles exhibited varying antimicrobial potency by different substitutions on the benzene ring of the benzothiazole. Compounds, 4,5,6-trimethylbenzo[d]thiazole-2-thiol (**10**) was found most active antimicrobial agents against *E. coli, S. aureus*, and antifungal agent against A. flavus and C. albicans [30].



**9 10**

**Figure 7.** Structure of antimicrobial compounds (**9** and **10**).

Some 2-substituted benzothiazoles, (Z)-2-(2-(1-(2-fluoro-4-methoxy-6-methyl-3- nitrophenyl) ethylidene)hydrazinyl)-6-methylbenzo[d]thiazole (**11**) was exhibited antimicrobial activity against *E. coli* and *S. aureus* and antifungal activity against *C. albicans* and *A. niger* [31].



**11**

**Figure 8.** Structure of antimicrobial compound (**11**).

**Anticancer Activity**

Some benzothiazole acylhydrazone derivatives were exhibited anticancer activity, compound 2-((5-Chlorobenzothiazol-2-yl)thio)-N-(4-(3-methyl piperidine-1-yl)benzylidene) aceto-hydrazide was exhibited highest anticancer activity [32]. In other study, 2-amino-benzothiazole derivatives were exhibited anticancer activity and compound (E)-N-(6-chloro-1,3- benzothiazole-2-yl)-1-(2, 5-dimethoxyphenyl) methanimine (**12**) was exhibited excellent activity [33]. Some 2-substituted benzothiazole derivatives, 2-((1S,2S)2-((E)-4-nitrostyryl)cyclopent-3-en-1-yl)benzo[d]thiazole (**13a**) and 2-((1S,2S)2-((E)-4-florostyryl)cyclopent-3-en-1-yl)benzo[d] thiazole (**13b**) were exhibited good anticancer activity against pancreatic cancer cells [34].



**12 13a 13b**

**Figure 9.** Structure of anticancer compounds (**12, 13a,** and **13b**).

Different (E)-2-benzothiazole-hydrazone derivatives were exhibited anticancer activity, compound (E)-2-((2-(benzo[d]thiazol-2-yl)hydrazono)methyl)benzene-1,4-diol (**14**) was exhibited good anticancer activity [35]. Some other series of benzothiazole-thiourea derivatives were also exhibited anticancer activity, compound, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (**15**) was exhibited cytotoxic effects, and compounds **16a**, **16b**, and **16c** were found most potent anticancer agent [36].



**14 15**

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | **R** | **R1** |
| **16a** | Br | 2-thiophene |
| **16b** | NH2 | 4-morpholine |
| **16c** | Br | 4-morpholine |

**Figure 10.** Structure of anticancer compounds (**14, 15,** and **16a-16c**).

A series of 2-(3-(4-oxo-2-substituted phenyl thiazolidine -3-yl)phenyl)benzo[d]thiazole -6-carboxylic acid derivatives (**17a-d**), compound **17a** has exhibited the most considerable activity as compared with compounds **17b**, **17c**, and **17d** [37]. A series of benzothiazole containing a-Aminophosphonates and fluoro group, compound N-(dihydro phosphoryl (phenyl) methyl)-substituted benzothiazolyl-2-amine derivative (**18**) was exhibited anticancer activities against A375, A431, Bcap37, and PC3 cells in-vitro by the MTT method. The compound, 18 was very effective against PC3 cells and modest to A431 cells [38].

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | **R1** |  **18** R1=CH3; R2=2-F; R3=n-Bu |
| **17a** | p-Cl |
| **17b** | p-OCH3  |
| **17c** | p-CH3  |
| **17d** | p-OH  |

**Figure 11.** Structure of anticancer compounds (**17a-17d** and **18**).

The aryl substituted benzothiazole derivatives, compound 2-(benzo[d]thiazol-2-yl)-N,N-bis(2-chloroethyl)-5-fluoroaniline (**19**) was exhibited anticancer activity against Human Cervical Cancer cell lines [13]. A series of 2-phenyl benzothiazole derivatives (**20a** and **20b**) and 1,3-benzothiazole-2-yl-4-carbothioate derivatives were also exhibited anticancer activity. Compounds, S-benzo[d]thiazol-2-yl4-aminobenzothioate (**20a**) and S- (benzo[d]thiazol-2-yl)-N2,N2-bis(2-chloroethyl)benzene-1,2,3-triamine (**20b**) were showed very good anticancer activity [39].

  

**19 20a 20b**

**Figure 12.** Structure of anticancer compounds (**19, 20a,** and **29b**).

**Anti-Inflammatory activity**

Some benzothiazole derivatives (21a-21e) were exhibited anti-inflammatory activity, compound N-(6-{[(4-cyclohexylphenyl)sulfonyl]amino}-1,3- benzothiazol -2-yl)acetamide (21a) was shown excellent anti-inflammatory activity. While compounds N-(2-acetamido-1,3-benzothiazole-6-yl)-2-(1H-indol-3-yl) acetamide (21b), N-(2-acetamido-1,3-benzothiazol-6-yl)-2-(3-fluorophenyl)acetamide (21c), (2E)-N-(2-acetamido-1,3-benzothiazol-6-yl)-3-(2-furyl) acrylamide (21d) and N-(6-{[(3-methoxyphenyl)carbamoyl]amino}-1,3- benzothiazol-2- yl) acetamide (21e) were also shown optimal anti-inflammatory activity [40].

 

 **21a 21b**



**21c 21d 21e**

**Figure 13.** Structure of anti-inflammatory compounds (**21a-21e**).

Some pyrimido[2,1-b][1,3]benzothiazole derivatives (**22a-22c**) were exhibited their anti-inflammatory activity, compound (4R)2-amino-7-methoxy-4-(3,4,5-trimethoxyphenyl)-4Hpyrimido[2,1-b][1,3]Benzothiazole-3-carbonitrile (**22a**), (4R)2-amino-7-chloro-4-(4-chloro-phenyl)-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carbonitrile (**22b**), and (4R)2-amino-6-chloro-4-(4-chlorophenyl)- 4Hpyrimido [2,1-b][1,3]benzothiazole-3-Carbonitrile (**22c**) were exhibited excellent anti-inflammatory activity [41].



 **22a 22b 22c**

**Figure 14.** Structure of anti-inflammatory compounds (**22a-22c**).

A series of 2-mercaptobenzothiazole derivatives containing 1,2,3-triazole ring, compound 2-(((sustituted1-phenyl-1H-1,2,3-triazol-4-yl)methyl)thio)benzo[d]thiazole (**23a-23d**) were exhibited anti-inflammatory activity by using carrageenan-induced hind paw edema and cyclooxygenase (COX) activity assays. Compound **23b** was exhibited a potent, selective COX-2 inhibitory activity with a COX-2/COX-1 ratio of 0.44. Compounds **23a**, **23b**, **23c**, and **23d** were exhibited considerable anti-inflammatory activity as compared to the reference drug Ibuprofen [42]. A series of 1,3-benzothiazole-2-amine derivatives (**24a-24c**), compounds 5-chloro-1,3-benzothiazole-2-amine (**24a**), 6-methoxy-1,3-benzothiazole-2-amine (**24b**), and 4 -methoxy-1,3-benzothiazole-2-amine (**24c**) were exhibited the significant anti-inflammatory activity [43].

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | **R**  |  |  | R  |
| **23a**  | o-Cl  | **24a**  | 5-Cl  |
| **23b**  | p-F  | **24b**  | 6-methoxy  |
| **23c**  | p-Br  | **24c**  | 4- methoxy  |
| **23d** | p-NO2  |  |  |

**Figure 15.** Structure of anti-inflammatory compounds (**23a-23d** and **24a-24c**).

The benzothiazole containing azatidin-2-ones and thiazoline-4-ones moiety compounds 1-(7-chloro-6-fluorobenzo[d]thiazol-2-yl) azetidin-2-one (**25**) was exhibited good anti-inflammatory activity and compared with Diclofenac sodium as referenced drug [44]. A series of 2-[(2-alkoxy-6-pentadecylphenyl) methyl] thio-1-Hbenzothiazole (**26**) were exhibited the human COX enzyme-230 inhibitor activity [6]. Various 2-amino benzothiazole derivatives were exhibited significant anti-inflammatory activity, compound 2-amino benzothiazole (**27**) substituted at 4 or 5 positions with electron-withdrawing groups like Cl, NO2, OCH3 increase the anti-inflammatory activity [45].



**25 26**  **27** **R**=H,Cl

**Figure 16.** Structure of anti-inflammatory compounds (**25, 26,** and **27**).

**Anticonvulsant Activity**

The 2-[(6-substitutedbenzo[d]thiazol-2-ylcarbamoyl)methyl]-1-(4-substitutedphenyl)-isothiourea were exhibited good anticonvulsant activity [46]. In other study, some benzothiazole derivative, 2-benzylidene[1,3]thiazole-1,3-benzothiazole-3-ones (**28a** and **28b**) and N-(6-chloro-benzothiazol-2-yl)-4-(aryl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (**29a** and **28b**) were exhibited excellent activity anticonvulsant activity [47].

 

**28 29**

|  |  |  |  |
| --- | --- | --- | --- |
| **28a** | R= m-NO2C6H4 | **29a** | R= p-OH C6H4 |
| **28b** | R= p-OCH3C6H4 | **29b** | R= p-N(CH3)2 C6H4 |

**Figure 17.** Structure of anticonvulsant compounds (**28a-28b** and **29a-29b**).

Some benzothiazole analogs were exhibited anticonvulsant activity, compounds 2-((1H-1,2,4-triazol-3-yl)thio)-N-(6-((3-fluorobenzyl)oxy)benzo[d]thiazol-2-yl)acetamide (**30**), and 2-((1H-1,2,4-triazol-3-yl)thio)-N-(6-((4-fluorobenzyl)oxy) benzo[d]thiazol-2-yl)acetmide (**31**) were exhibited excellent anticonvulsant activity [48].



**30 31**

**Figure 18.** Structure of anticonvulsant compounds (**30** and **31**).

A series of N-(6-substituted-1,3-benzothiazole-2-yl)-4-{[(substituted-amino) carbonothioyl]amino}benzenesulfonamides, and amino-benzothiazole containing 1-acetyl-pyrazoline derivatives (**32**) were exhibited excellent anticonvulsant activity against maximal electroshock (MES) and pentylenetetrazole (scPTZ) induced seizures methods [49,50]. Compound 2‐(‐4‐aryl-thiosemicarbazido-carbonylthio)benzothiazole (**33**) was exhibited anticonvulsant activity against PTZ induced convulsions [51].

|  |  |
| --- | --- |
| **32** R= Br, Cl, F, NO2, CH3, OCH3 R1= H, 2-Cl, 4-Cl, 4-OCH3 | **33** |

**Figure 19.** Structure of anticonvulsant compounds (**32** and **33**).

**Antioxidant activity**

The 2-aryl substituted benzothiazole derivatives were exhibited antioxidant activity, compound 4-[4-(1,3-benzothiazole-2-yl) phenoxy]benzoic acid (**34**), 4-(benzothiazole-2-yl)-2-methoxy-6-nitrophenol (**35**), 2-[ 2-(4-chlorobenzoyl)phenyl]-1,3-benzothiazole (**36**) and 4-(1,3-benzothiazole-2-yl)-2-ethoxyphenol (**37**) were exhibited good antioxidant activity [52].



**34 35**



**36 37**

**Figure 20.** Structure of antioxidant compounds (**34-37**).

Amidino substituted benzothiazole derivatives were exhibited antioxidant activity, compound 6-Amidinium-2-(2,3,4-trihydroxyphenyl)benzothiazole chloride, and 6-(4,5-Dihydro-1H-imidazole-3-ium-2-yl)-2-(2,3,4-trihydroxyphenyl)benzothiazole chloride (**38**) were exhibited excellent antioxidant effect [53]. Some benzothiazole derivatives were also exhibited antioxidant activity, compound (E)-5-((benzo[d]thiazol-2-ylimino)(methyl)methylamino)-2-hydroxybenzoic acid (**39**) was exhibited good antioxidant activity [54]. The 3H-Spiro[1,3-benzothiazole-2,30-indol]-20(10H)-one derivatives were exhibited antioxidant activities by the Trolox equivalent antioxidant capacity (TEAC), Fe3+ascorbate system-induced inhibition of lipid peroxidation (LP) in liposomes, and scavenging effect on diphenyl picryl hydrazine (DPPH). These compounds were exhibited potent scavenging activities against DPPH and 2,20-azino-bis(3-ethylbenzthiazoline-6-sulphonic acid) (ABTS+) radicals, and strong inhibitory capacity on lipid peroxidation [55]. A series benzothiazole derivative (**40a-c**) was exhibited for good antioxidant activity by the DPPH or ABTS free radical scavenging using simple UV spectroscopic methods. Among these compound, 1,5-dimethyl-3H-spiro[benzo[d]thiazole-2,3-indolin]-2-one (**41**) was shown a strong antioxidant activity [56]. The 1’,5’-dimethyl-3H-spiro[benzo[d]thiazole-2,3’-indolin]-2’- ones was exhibited antioxidant activities and compound (**42**) was found to be the most potent antioxidant activity [57].



**38 39**



**40a-c** R1**=**H, CH3, OC2H5  **41 42**

**Figure 21.** Structure of antioxidant compounds (**38,39, 40a-40c, 41, 42**).

**Anti-diabetic activity**

Some 2-((benzothiazole-2-ylthio)methyl)-5-phenyl-1,3,4-oxadiazole derivatives were exhibited anti-diabetic activity, compounds 2-(((6-nitrobenzo[d]thiazol-2-yl)thio)methyl)-5-(4-nitrophenyl)-1,3,4-oxadiazole (**43**) was shown excellent anti-diabetic activity [58].



**43**

**Figure 22.** Structure of antidiabetic compounds (**43**).

Some benzothiazole derivatives were exhibited antidiabetic activity, compound 2-(benzo[d]thiazol-2- ylmethylthio )-6-ethoxybenzo[d]thiazole (**44**) was shown excellent antidiabetic activity [59]. Some other benzothiazole derivatives were also shown antidiabetic activity, compound N-(6-chlorobenzoate[d]thiazol-2-yl)-2-morpholinoacetamide (**45**) was shown excellent antidiabetic activity and found the most potent compound [57].



**44 45**

**Figure 23.** Structure of antidiabetic compounds (**44, 45**).

The 2-amino[5`(4-sulphonyl benzylidine)-2,4-thiazolidnedione]-7-chloro-6-flurobenzothiazoles (**46**) were shown antidiabetic activity [17]. Compound (3R)-3-amino-4-(2,4,5-trifluorophenyl)-N-{4-[6-(2-methoxyethoxy)-benzothiazole-2-yl]tetrahydropyran-4-yl}butanamide (**47)** was exhibited significant antidiabetic activity [60, 61].



**46 47**

**Figure 24.** Structure of antidiabetic compounds (**46, 47**).

The 2-aryl sulfonylamino-benzothiazole derivatives acted as protein tyrosine phosphatase 1B inhibitor. Compounds N-(5- methylbenzo [d]thiazol-2-yl)-4-nitro-benzenesulfonamide (**48a**) and N-(5- ethoxylbenzo [d]thiazol-2-yl)-4-nitrobenzene sulfonamide (**48b**) were exhibited most active antidiabetic agents and rapidly reversible inhibitors of PTP-1B and significantly lowered plasma glucose concentration [62].



**48a 48b**

**Figure 25.** Structure of antidiabetic compounds (**48a, 48b**).

**Anthelmintic activity**

Some 4-(6-substituted-1,3-benzothiazole-2-yl)amino-1,3-thiazole-2-amine derivatives were exhibited anthelmintic activity, compound 4-(6-Ethoxy-1,3-benzothiazole-2-yl)amino-2-(2-chlorophenyl-methylidene) amino-1,3-thiazole (**49**) was exhibited excellent anthelmintic activity [50]. The fluoro-benzothiazole derivatives were also exhibited significant anthelmintic activity [63]. A series of 6-substituted-2-hydrazino-1,3-benzothiazole derivatives (**50a-e**) were shown anthelmintic activity against *Eudrilus eugenie* A species and *Megascoplex konkanensis* [64, 65].



 **49 50 a-e R=**H, CH3, OCH3, F, Cl

**Figure 26.** Structure of anthelmintic compounds (**49, 50a-50e**).

A series of 3-(2-hydrazino benzothiazoles)-substituted Indole-2-ones, (Z)-3-(2- (benzo[d]thiazol-2-yl)hydrazono) indolin-2-one (51a-f) and (Z)-N'-(2-oxoindolin-3-ylidene) benzo[d]thiazole-2-carbohydrazide (**52a-f**) were exhibited anthelmintic activity against  earthworms *Pheretima posthuma*. Most compounds were shown good paralytic time, compared to reference albendazole drug [66]. The fluoro-benzothiazole comprising sulfonamide pyrazole derivatives, 4-(4-carbamoyl-3-(furan-2-ylamino)-5-(phenylamino)cyclopent-2-en-1-yl)-N-(6-fluoro-benzo[d]thiazol-2-yl)benzamide (**53**) was shown anthelmintic activity against *Peritum posthuma a*nd Albendazole was used as reference drug [67]. The 8‐fluoro‐9‐substituted benzothiazole(5,1‐b)‐1,3,4‐triazole derivatives (**54**) were exhibited anthelmintic activity against *Pheretima posthuma* and compound with R=o-nitro, aniline substituent was found excellent anthelmintic agents than the other compounds [68].



**51a-f 52a-f**

**R=51**aH, **51b** 5-COOH, **51c** 5-CH3, **51d**, 5-Cl, **51e** 5-NO2, **51f** 5-Br



**53 54**

**Figure 27.** Structure of anthelmintic compounds (**51a-51f, 52a-52f, 53, 54**).

Flurobenzothiazole containing sulfonamide and pyrazole derivatives (**55**) were exhibited anthelmintic activity against *Perituma posthum* and Albendazole was used as a reference drug [69].



**55**

**Figure 28.** Structure of anthelmintic compound (**55**).

**Antiviral activity**

Benzothiazole sulfonamides derivatives were exhibited HIV-1 protease inhibition, compounds N-(2-hydroxy-3-(N-isobutylbenzo[d]thiazole-5-sulfonamido)-1-(phenylamino) propyl)alkylamide (**56a**) and N-(3-(2-amino-N-isobutylbenzo[d]thiazole-5-sulfonamido)-2-hydroxy-1-(phenylamino)propyl)alkylamide (**56b**) with an IC50 value in the 2-3nM range. These carbamate compounds were exhibited better antiviral and inhibitors of HIV-1 Protease activity [70].



**56a 56b**

**Figure 29.** Structure of antiviral compounds (**56a-56b**).

**Microsomal triglyceride transfer protein (MTP) Inhibition activity**

Benzothiazole-triamide derivatives, 5-alkylamido -N-(2-((4- fluorobenzyl)amino )-2-oxo-1-phenylethyl)benzo[d]thiazole-2-carboxamide (**57**) were exhibited excellent enterocyte-specific microsomal triglyceride transfer protein (MTP) inhibitor activity. Therefore lead to a reduction in plasma triglyceride and cholesterol level [70].



**57**

**Figure 30.** Structure of MTP-inhibitor compound (**57**).

**Antimalarial activity**

Some benzothiazole analogs were exhibited antimalarial activity, compound (E)-4-((2-(benzo[d]thiazol-2-yl)hydrazono)methyl)benzene-1,2-diol (58) was shown most potent antimalarial activity [71].



**58**

**Figure 31.** Structure of antimalarial compound (**58**).

Some benzothiazole derivatives were inhibited the N-myristoyl transferase of *Plasmodium falciparum*. Compounds, N-(4-(benzo[d]thiazol-2-ylamino)-3-methoxyphenyl)-methanesulfonamide (**59a**), N-(3-methoxy-4-((6-nitro-benzo[d]thiazol-2-yl)amino)phenyl)-methanesulfonamide (**59b**) and 2-((2-((3-(diethylamino)-propyl)amino) benzo[d]thiazol -6-yl)amino)benzoic acid (**59c**) were shown good antimalarial activity [72]. Other 2-substituted-6-nitro and 6-amino benzothiazole and their anthranilic acid derivatives were shown antimalarial activity against W2 and 3D7 strains of *P. falciparum* [73].

 

**59a 59b**



**59c**

**Figure 32.** Structure of antimalarial compound (**59a-59c**).

**Antitubercular activity**

Some 4-Amino-N-(1,3-benzothiazol-2-yl)benzenesulphonamide derivatives (60) were exhibited good in-vitro antitubercular activity against *the Mycobacterium tuberculosis* H37Rv strain [74].



**60**

**Figure 33.** Structure of antitubercular compound (**60**).

**General synthetic methods of Benzothiazole derivatives** [9]

**Condensation of ortho-aminophenol with carboxylic acids**

The reaction of 2- amino thiophenol and aromatic acids in presence of Polyphosphoric acid give 2-substituted benzothiazole derivatives with good yield.



**Synthesis of benzothiazole derivatives by using various types of catalysts** [9]

**(a) Bromine**

Various methods are reported which used bromine as a catalyst. Benzothazoles are formed by cyclization of substituted anilines with thiocyanate in presence of bromine, acid, or chloroform.



The arylthiourea can be cyclized with liquid bromine in chloroform to form a 2-aminobenzothiaozles. 2-amino-5,6-dichloro and 2-amino-6,7-dichloro-benzothiazole by cyclization of substituted aniline with help of thiocyanogen.



**(b) Sulphuric acid**

Sodium thiocyanate and cyclize p-substituted aniline reacted to form 2-amino-6-substituted benzothiazole in the presence of sulphuric acid.



**(c) Benzene**

2-aminobenzothiazoles are synthesized by cyclizations 2-aminobenzenetiol with isothiocyanates in the presence of benzene.



**Discussion**

Heterocyclic chemistry plays a vital role in medicinal organic chemistry. Most of the drug molecules are having therapeutic action due to the heterocyclic scaffold. A slight alteration in heterocyclic moiety can cause a major change in the therapeutic action of the drug molecule. Benzothiazole is a unique and versatile moiety for the design and development of drug molecules. Benzothiazole derivatives have wide applications in the area of medicinal chemistry due to its important pharmacological activities [5-10]. Benzothiazole is a bicycle and both rings are accountable for its therapeutic activities. Approaches to design new drug molecules, which have effective and potent pharmacological profiles are developed by a combination of benzothiazoles with another heterocyclic moiety [70-75]. Various research reports suggested that different benzothiazole derivatives were used in the treatment of various types of diseases which concluded that the benzothiazole is one of the most significant scaffolds of medicinal chemistry for the development of the better drug molecules.

**Conclusion**

The benzothiazole derivatives have possessed various types of pharmacological activities. A further alteration in its nucleus provides more efficient compounds with a more potent and efficacious therapeutic agent. This review also illustrated some common protocols for the synthesis of benzothiazole derivatives.

**Acknowledgment**

We are thankful to the Department of Pharmaceutical Chemistry, Himalayan Institute of Pharmacy and Research, Dehradun, Uttarakhand, India, andDepartment of Pharmaceutical Chemistry, Faculty of Pharmacy, Northern Border University, Rafha, Saudi Arabia for providing necessary facilities.

**Conflict of interest**

The author declares no conflict of interest.

**References**

1. Achson, A. *An introduction to the chemistry of heterocyclic compounds*. 3rd ed.; Willy-Intersciences, India, **2009**.
2. Ul-Firdaus, J.; Siddiqui, N.; Sahu, M.; and Alam, O. A comprehensive review: benzothiazoles as emerging nucleus of biological activities. *Eur. J. Biomed. & Pharm. Sci.,* **2018**, *5*(2), 216-229.
3. Shaista, A.; and Parle, A. Benzothiazole-a magic molecule. *Inter. J. Pharm. Sci. & Res.,* **2017**, *8*(12), 4909- 4929.
4. Chaudhary, P.; Sharma, P.K.; Sharma, A.; and Varshney, J. Recent advances in pharmacological activity of benzothiazole derivatives. *Inter. J. Curr. Pharm. Res.,* **2010**, *2*(4), 5-11.
5. Hutchinson, I.; Chua, M.S.; Browne, H.L.; Trapani, V.; Bradshaw, T.D.; and Westwell, A.D. Synthesis and pharmaceutical properties of antitumor 2-(4-aminophenyl) benzothiazole amino acid prodrugs. *J. Med. Chem.,* **2001**,*44*, 1446-1449.
6. Paramashivappa, R.; Phanikumar, P.; Subbarao, P.; and Srinivasarao, A. Design synthesis and biological evaluation of benzimidazole/benzothiazole and benzoxazole derivatives as cyclooxygenase inhibitors. *Bioorg. Med. Chem. Lett.,* **2003**, *13*, 657-660.
7. Gupta, A.; and Rawat, S. Synthesis and cyclization of benzothiazole: Review. *J. Curr. Pharm. Res.,* **2010**, *3*(1), pp. 13-23.
8. Gupta, S.; Ajmera, N.; Gautam, N.; Sharma, R.; and Gauatam, D. Novel synthesis and biological activity study of pyrimido [2,1-b] benzothiazoles. *Ind. J. Chem.,* **2009**, *13*(48B), 853-858.
9. Kumbhare, R.M.; and Ingle, V.N. Synthesis of novel benzothiozole and benzisoxazole functionalized unsymmetrical alkanes and study of their antimicrobial activity. *Ind. J. Chem.,* **2009**,*48*B, 996-1000.
10. Maharan, M.; William, S.; Ramzy, F.; and Sembel, A. Synthesis and *in-vitro* evaluation of new benzothiazole derivaties as schistosomicidal agents. *Molecules*, **2007**, *12*, 622-633.
11. Sharma P.N.K.; and Jha, K.K. Benzothiazole: The molecule of diverse biological activities. *Int. J. Curr. Pharm. Res.,* **2010**, *2*, 1–6.
12. Rajeeva, B.; Srinivasulu, N.; and Shantakumar, S. Synthesis and antimicrobial activity of some new 2-substituted benzothiazole derivatives. *E-J. Chem.,* **2009**, 6(3), 775-779.
13. Kini, S.; Swain, S.; and Gandhi, A. Synthesis and evaluation of novel benzothiazole derivates against human cervical cancer cell lines. *Ind. J. Pharm. Sci.,* **2007**, *69*(1), 46-50.
14. Stanton, H.L.K.; Gambari, R.; Chung, H.C.; Johny, C.O.T.; Filly, C.; and Albert, S.C.C. Synthesis and anti-cancer activity of benzothiazole containing phthalimide on human carcinoma cell lines. *Bioorg. Med. Chem.,* **2008**, *16*, 3626-3631.
15. Wang, M.; Gao, M.; Mock, B.; Miller, K.; Sledge, G.; Hutchins, G.; and Zheng, Q. Synthesis of C-11 labeled fluorinated 2-aryl benzothiazoles as novel potential PET cancer imaging agent. *Bioorg. Med. Chem.,* **2006**,*14*, 8599-8607.
16. Sathe, B.S.; Jayachandran, E.; Jagtap, V.A.; and Sreenivasa, G.M. Anthelmintic activity of newly synthesized moieties of fluoro benzothiazole Schiff’s bases. *Res. J. Pharm. Biol. & Chem. Sci.,* **2011**, *2*(1), 510-515.
17. Kumar, S.; Rathore, D.S.; Garg, G.; Khatri, K.; Saxena, R.; and Sahu.S.K. Synthesis and evaluation of some benzothiazole derivatives as antidiabetic agents”. *Inter. J. Pharm. & Pharm. Sci.*, **2017**, *9*(2), 2017, 60-68.
18. Sulthana, S.; and Pandian, P. A review on Indole and Benzothiazole derivatives its importance. *J. Drug Delivery & Therap.,* **2019**, *9*(1-s), 505-509
19. Reddy, P.; Lin, Y.; and Chang, H. Synthesis of novel benzothiazole compounds with an extended conjugated system. *Arcivoc*, **2007**, *16*, 113-122.
20. Heo, Y.; Song, Y.; Kim, B.; and Heo, J. A highly regioselective synthesis of 2-aryl-6-chlorobenzothiazoles employing microwave-promoted Suzuki-Miyaura coupling reaction. *Tetrahed. Lett*., **2006**,*47*, 3091-3094.
21. Srivastava, A.; Mishra, A.P.; Chandra, S.; Bajpai, A. Benzothiazole derivative: a review on its pharmacological importance towards synthesis of lead. *Inter. J. Pharm. Sci. & Res.,* **2019**, *10*(4), 1553-1566.
22. Shinde, P.K.; and Waghamode, K.T. Synthesis, characterization and antibacterial activity of substituted benzothiazole derivatives. *Inter. J. Sci. & Res. Pub.,* **2017**, *7*(8), 365-370.
23. Maddila, S.; Gorle, S.; Seshadri, N.; Lavanya, P.; and Jonnalagadda, S.B. Synthesis, antibacterial and antifungal activity of novel benzothiazole pyrimidine derivatives. *Arab. J. Chem.,* **2016**,*9*(5), 681-687.
24. Bele, D.S.; Kothari, H.; and Singhvi, I. Synthesis and antimicrobial activity of some benzothiazole derivatives. *Inter. J. Pharm. & Chem. Sci.,* **2012**, *1*(4), 1238-1242.
25. Padalkar, V.S.; Borse, B.N.; Gupta, V.D.; Phatangare, K.R.; Patil, V.S.; Umape, P.G.; and Sekar, N. Synthesis and antimicrobial activity of novel 2-substituted benzimidazole, benzoxazole and benzothiazole derivatives. *Arab. J. Chem.,* **2016**, *9*(2), S1125-S1130.
26. Soni, B.; Ranawat, M.S.; Sharma, R.; Bhandari, A.; and Sharma, S. Synthesis and evaluation of some new benzothiazole derivatives as potential antimicrobial agents. *Eur. J. Med. Chem.,* **2010**, *45*, 2938-2942.
27. Geronikaki, A.; Argyropoulou, I.; Vicini, P.; and Zani, F. Synthesis and biological evaluation of sulfonamide thiazole and benzothiazole derivatives as antimicrobial agents. *Arkivoc*, **2009**, *6*, 89-102.
28. Jagtap, V.A.; Jaychandran, E.; Sreenivasa, G.M.; and Sathe, B.S. Synthesis of some fluoro substituted sulphonamide benzothiazole comprising thiazole for anti-microbial screening. *Inter. J. Pharma & Bio-Sci.,* **2010**,*1*(4), 484-490.
29. Amir, M.; Kumar, A.; Ali, I.; and Khan, S. Synthesis of pharmaceutical important 1, 3, 4-thiadiazole and imidazolinone derivatives as antimicrobials. *Ind. J. Chem.,* **2009**,*48*B, 1288-1293.
30. Murthi, Y.; and Pathak, D. Synthesis and Antimicrobial screening of Substituted 2-Mercaptobenzothiazoles. *J. Pharm. Res.,* **2008**,*7*(3), 153-155.
31. Pattan, S.; Suresh, C.; Pujar, V.; Reddy, V.; Rasal, V.; and Koti, B. Synthesis and antidiabetic activity of 2-amino[5”(4-sulphonylbenzylidine)-2,4-thiazolidinenone]-7-chloro-6-flurobenzo-thiazole. *Ind. J. Chem.,* **2005**, *44*B, 2404-2408.
32. Osmaniye, D.; Levent, S.; Karaduman, A.B.; Ilgın, S.; Ozkay, Y.; and Kaplancıkl, Z.A. Synthesis of new benzothiazole acylhydrazones as anticancer agents. *Molecules*, **2018**, *23*, 1054-1068.
33. Saipriya, D.; Prakash, A.; Kini, S.G.; Bhatt, G.V.; Pai, K.S.R.; Biswas, S.; and Shameer, K.M.Design, synthesis, the antioxidant and anticancer activity of novel Schiff's bases of 2-amino benzothiazole. *Ind. J. Pharm. Edu. & Res.,* **2018**, *52*(4s), S333-S342.
34. Uremis, N.; Uremis, M.M.; Tolun, F.I.; Ceylan, M.; Doganer, A.; and Kurt, A.H. Synthesis of 2-substituted benzothiazole derivatives and their *in-vitro* anticancer effects and antioxidant activities against pancreatic cancer cells. *Anticancer Res.,* **2017**, *37*, 6381-6389.
35. Lindgren, E.B.; De Brito, M.A.; Thatyana, R.A.; Vasconcelos.; de Moraes, M.O.; Montenegro, R.C.; Yoneda. J.D.; and Leal, K.A.Z. Synthesis and anticancer activity of (E)-2-benzothiazole hydrazones”. *Eur. J. Med. Chem.,* **2016**, *86*, 12-16.
36. Saeed, S.; Rashid, N.; Jones, P.G.; Ali, M.; and Hussain, R. Synthesis, characterization and biological evaluation of some thiourea derivatives bearing benzothiazole moiety as potential antimicrobial and anticancer agents. *Eur. J. Med. Chem.,* **2010**, *45*, 1323-1331.
37. Prabhu, P.P.; Panneerselvam, T.; Shastry, C.S.; Sivakumar, A.; and Pande, S.S. Synthesis and anticancer evaluation of 2-phenyl thiaolidinone substituted 2-phenyl benzothiazole-6-carboxylic acid derivatives. *J. Saudi Chem. Soc.,* **2012**, *19*(2), 181-185.
38. Song, B.; Jin, L.; Zhang. G.; Xu, R.; Zhang, S.; Gao, X.; Hu, D.; and Yang, S. Synthesis, X-ray crystallographic analysis, and antitumor activity of N-(benzothiazole-2-yl)-1-(fluoro phenyl)-O,O-dialkyl-alpha-aminophosphonates. *Bioorg. Med. Chem. Lett.,* **2006**, *16*, 1537-1543.
39. Devmurari, V.P.; Pandey, S.; Goyani, M.B.; Nandanwar, R.R.; Jivani, N.P.; and Perumal, P. Synthesis and anticancer activity of some novel 2-substituted benzothiazole derivatives”. *Inter. J. Chem. Tech. Res.,* **2010**, *2*, 681-689.
40. Sadhasivam, G.; and Kulanthai, K. Synthesis, charac-terization, and evaluation of anti-inflammatory and anti-diabetic activity of new benzothiazole derivatives. *J. Chem. & Pharm. Res.,* **2015**,*7*(8), 425-431.
41. Verma, A.K.; Martin, A.; and Singh, A.K. Synthesis, Characterization and evaluation of Anti-inflammatory and Analgesic activity of Benzothiazole derivatives. *Ind. J. Pharm. & Biol. Res.,* **2014**, *2*(3), 84-89.
42. Mir, F.; Shafi, S.; Zaman, M.S.; Kalia, N.P.; Rajput, V.S.; Mulakayala, C.; Mulakayala, N.; Khan, I.A.; and Alam, M.S. Sulfur rich 2-mercaptobenzothiazole and 1,2,3-triazole conjugates as novel antitubercular agents. *Eur. J. Med. Chem.,* **2014**, *76*, 274-243.
43. Venkatesh, P.; and Pandeya, S.N. Synthesis, characterization and anti-inflammatory activity of some 2-amino benzothiazole derivatives. *Inter. J. Chem. Tech. Res.,* **2009**,*1*(4), 1355-158.
44. Gurupadyya, B.; Gopal, M.; Padmashali, B.; and Manohara, Y. Synthesis and pharmacological evaluation of azatidin-2-ones and thiazolidine-4-ones encompassing benzothiazole. *Ind. J. Pharm. Sci.,* **2008**, *70*(5), 572-577.
45. Srivastava, N.; Salahuddin, M.; ShantaKumar, S. Synthesis and anti-inflammatory activity of some novel 3-(6-substituted-1,3-benzothiazole-2-yl)-2-[((4-substituted phenyl)amino) methyl]quinazolinone-4-(3*H*)-ones. *E-J. Chem.,* **2009**, *6*, 1055–62.
46. Siddiqui, N.; Alam, S.M.; Sahu, M.; Naim, M.J.; Shaharyar, M.; and Alam, O. Design, synthesis, anticonvulsant evaluation and docking study of 2-[(6-substituted benzo[d]thiazol-2-ylcarbamoyl) methyl]-1 -(4-substituted phenyl) isothio-ureas. *Bioorg. Chem.,* **2017**, *4*, 1-31.
47. Raju, G.N.; and Nadendla, R.R. Synthesis and anticonvulsant activity of newer benzothiazole derivatives. *World J. Pharm & Pharm. Sci.,* **2017**, *6*(4), 1701-1713.
48. Liu, D.; Zhang, H.; Jin, C.; and Quan, Z. Synthesis and biological evaluation of novel benzothiazole derivatives as potential anticonvulsant agents. *Molecule*, **2016**, *21*(3), 164. doi: 10.3390/molecules21030164.
49. Rana, D.; Siddiqui, N.; Khan, S.A.; Haque, S.E.; and Bhat, M.A. N-{[(6-substituted-1, 3-benzothiazole-2-yl) amino] carbonothioyl}-2/4-substituted benzamides: synthesis and pharmacological evaluation. *Eur. J. Med. Chem.,* **2008**, 43, 1114-1122.
50. Amnerkar, N.D.; Bhongade, B.A.; and Bhusari, K.P. Synthesis and biological evaluation of some 4-(6-substituted-1,3-benzothiazol-2-yl)amino-1, 3-thiazole-2-amines and their Schiff bases. *Arab. J. Chem.,* **2015**,*8*(4), 545-552.
51. Jimonet, P.; Francois, A.; Barreau, M.; Blanchard, J.C.; and Boirean, A. Riluzole Series. Synthesis and *in-vivo* “antiglutamate” activity of 6-Substituted-2-benzothiazole amines and 3-Substituted-2-imino-benzothiazolines. *Ind. J. Med. Chem.,* **1999**, *42*(15), 2828-2843.
52. Amin, S.; and Parle, A. Synthesis, characterization and antioxidant activity of 2-aryl benzothiazole derivatives. *Inter. J. Curr. Pharm. Res.,* **2018**, *10*(5), 3-8.
53. Racane, L.; Cindric, M.; Perin, N.; Roskaric, P.; Starcevic, K.; Masek, T.; Mauric, M.; Dogan, J.; and Karminski-Zamola, G. Synthesis and antioxidative potency of novel amidino substituted benzimidazole and benzothiazole derivatives. *Crotica Chemica Acta*., **2017**, *90*(2), 187-195.
54. Cabrera-Perez, L.C.; Padilla-Martınez, I.I.; Cruz. A.; Mendieta-Wejebe, J.E.; Tamay-Cach, F.; and Rosales-Hernandez, M.C. Evaluation of a new benzothiazole derivativewith antioxidant activity in the initial phase of acetaminophen toxicity. *Arab. J. Chem.,* **2016**, *12*(8), 1-12.
55. Guzel, O.; Karali, N.; Ozsoy, N.; Ozbey, S.; and Slman, A. Synthesis of new spiroindolinones incorporating a benzothiazole moiety as antioxidant agents. *Eur. J. Med. Chem.,* **2010**, 45, 1068-1077.
56. Cressier, D.; Prouillac, C.; Hernandez, P.; Amourette, C.; Diserbo, M.; Lion, C.; and Rima, G. Synthesis, antioxidant properties and radioprotective effects of new benzothiazoles and thiadiazoles. *Bioorg. & Med. Chem.,* **2009**, *17*, 5275-5284.
57. Kumar, S.; Rathore, D.S.; Garg, G.; Khatri, K.; Saxena, R.; and Sahu, S.K. Synthesis and evaluation of some 2-((benzo thiazol-2-ylthio) methyl)-5-phenyl-1,3,4-oxadiazole derivatives as antidiabetic agents. *Asian Pacific J. Health Sci.,* **2016**,*3*(4), 65-74.
58. Meltzer-Mats, E.; Babai-Shani, G.; Pasternak, L.; Uritsky, N.; Getter, T.; Viskind, O.; Eckel, J, Cerasi, E.; Senderowitz, H.; Sasson, S.; and Gruzman, A. Synthesis and mechanism of hypoglycemic activity of benzothiazole derivatives. *J. Med. Chem.,* **2013**, *56*(13), 5335-5350.
59. Mariappan, G.; Prabhat, P.; Sutharson, L.; Banerjee, J.; Patangia, U.; and Nath, S. Synthesis and antidiabetic evaluation of benzothiazole derivatives. *J. The Korean Chem. Soc.,* **2012**, *56*(2), 251-256.
60. Khokra, S.L.; Arora, K.; Mehta, H.; Aggarwal, A.; and Yadav, M. Common methods to synthesize benzothiazole derivatives and their medicinal significance: a review. *Inter. J. Pharm. Sci. & Res.,* **2011**, *2*(6), 1356-1377.
61. Nitta, A.; Fujii, H.; Sakami, S.; Nishimura, Y.; Ohyama, T.; Satoh, M.; Nakaki, J.; Satoh, S.; Inada, C.; Kozono, H.; Kumagai, H.; Shimamura, M.; Fukazawa, T.; and Kawai, H. (3R)-3-Amino-4-(2,4,5-triluorophenyl)-N-{4-[6-(2-methoxy) benzothiazol-2-yl] tetrahydro pyran-4-yl}butanamide as a potent dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes. *Bioorg. & Med. Chem. Lett.;* **2008**, *18*, 5435-5438.
62. Paoli, P.; Vazquez, G.N.; Rivera, I.L.; Molina, R.V.; Franco, J.; Andrade, R.O.; Estrada-Soto, S.; Camici, G.; Coutino, D.; Ortiz, I.; Mayorga, K.; and Diaz, H. Synthesis, in vitro and computational studies of protein tyrosine phosphatase 1B inhibition of a small library of 2-arylsulfonylamino benzothiazoles with antihyperglycemic activity. *Bioorg. & Med. Chem*., **2009**, *17*, 3332-3341.
63. Chi, B.; Jill, C.; David, P.; Song, J.; Choy, W.; Lambert, P.; and Gagne. D. Discovery of benzothiazole derivatives as efficacious and enterocyte-specific MTP inhibitors. *Bioorg. Med. Chem. Lett.,* **2009**, *19*, 1416-20.
64. Omar, A.M.M.E.; Aboulwafa, O.M.; Issa, D.A.E.; El-Shokrofy, M.M.S.; Amr, M.E.; and El-Ashmawy. I.M. Design, facile synthesis and anthelmintic activity of new O-substituted 6-methoxybenzothiazole-2- carbamates. *Med. Chem. Comm.,* **2017**, *8*(7), 1440-1451.
65. Munirajasekhar, D.; Himaja, M.; Mali, S.V.; Karigar, A.; and Sikarwar, M. Synthesis and Anthelmintic activity of 6-Substituted 2-Hydrazino-1, 3-Benzothiazoles. *J. Pharm. Res.,* **2011**,*4*(7), 2186-2187.
66. Suresh, C.H.; Rao, J.V.; and Jayaveera, K.N. Anti-inflammatory activity of 3-(2-hydrazino benzothiazoles)-substituted indole-2-one. *Inter. J.,* **2011**,*1*, 30-34.
67. Sreenivasa, G.M.; Jayachandran, E.; Kumar, R.; Jaya.; and Vijay, M.M.J. Synthesis of Bioactive molecule fluorobenzothiazole comprising potent heterocyclic moieties for Anthelmentic activity. *Arch. Pharm. Res.;* **2009**, *1*, 150-157.
68. Ghoneim, K.M.; Essawi, M.Y.H.; Mohamed, M.S.; and Kamal, A.M. Synthesis of 2-[(4-amino or 2,4-diaminophenyl) sulfonyl] derivatives of benzimidazole, benzothiazole and 6-methyluracil as potential antimicrobial agents. *Ind. J. Chem.,* **1998**, *37*B, 904-910.
69. Sreenivasa, M.; Jaychand, E.; Shivakumar, B.; Jayrajkumar, K.; and Vijaykumar, J. Synthesis of bioactive molecule flurobenzothiazole comprising potent heterocylic moieties for anthelmintic activity. *Arch. Pharm. Sci. & Res.,* **2009**, *1*(2), 150-157.
70. Nagarajan, S.; Crescenzo, G.; Getman, D.; Lu, H.; Sikorski, J.; Walker, J.; McDonald, J.; Houseman, K.; Kocan, G.; Kishore, N.; Mehta, P.; Shippy, C.; and Blystone, L. Discovery of Novel Benzothiazolesulfonamides as potent inhibitors of HIV-1 Protease. *Bioorg. & Med. Chem.,* **2003**, *11*, 4769-4777.
71. Sarkar, S.; Asim, A.; Siddiqui, A.A.; Saha, S.J.; De, R.; Mazumder, S.; Banerjee, C.; Iqbal, M.S.; Nag, S.; Adhikari, S.; and Bandyopadhyaya, U. Antimalarial activity of small-molecule benzothiazole hydrazones. *Antimicrob. Agents & Chemother.,* **2016**, *60*(7), 4217-4228.
72. Bowyer, P.W.; Gunaratne, R.S.; Grainger, M.; Withers-martinez, C.; Wickramsinghe, S.; Tate. E.W.; Leatherbarrow, R.J.; Brown, K.A.; Holder, A.A.; and Smith, D.F. Molecules incorporating a benzothiazole core scaffold inhibit the N-myristoyltransferase of *Plasmodium falciparum*. *Biochem. J.,* **2007**, *408*, 173-180.
73. Hout, S.; Azas, N.; Darque, A.; Robin, M.; Giorgio, C.; Gasquet, M.; Galy, J.; and David, P. Activity of benzothiazoles and chemical derivatives on *Plasmodium falciparum”*. *Parasitol.,* **2004,** *129*, 525-542.
74. Bhusari, K.P.; Amnerkar, N.D.; Khedekar, P.B.; Kale, M.K.; and Bhole, R.P. Synthesis and in vitro antimicrobial activity of some new 4-amino-N-(1,3-Benzothiazol-2-yl) benzenesulphonamide derivatives. *Asian J. Res. Chem.,* **2008**, *1*(2), 53-58.
75. Alang, G.; Kaur, R.; Singh, A.; Budhlakoti, P.; Singh, A.; and Sanwal, R. Synthesis, Characterization and antifungal activity of certain (E)-1-(1-(substituted phenyl)ethylidene)-2-(6-methylbenzo[d]thiazol-2-yl)hydrazine analogues. *Inter. J. Pharm. & Biol. Arch.,* **2010**,*1*(1), 56-61.