Intelligent Pharmacy 1 (2023) 122–132

Contents lists available at ScienceDirect

Intelligent Pharmacy

journal homepage: www.keaipublishing.com/en/journals/intelligent-pharmacy

Synthesis and biological activities of benzothiazole derivatives: A review

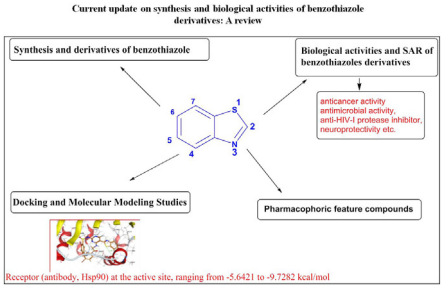
Kumari Priyanka Yadav [a], Md Azizur Rahman [a,*], Suprabha Nishad [a], Shubham Kumar Maurya [a], Mohd Anas [a], Mohd Mujahid [b]

[a] Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Integral University, Lucknow, Uttar Pradesh, 226026, India
[b] Department of Pharmacy Practice, College of Pharmacy, Hafr-Al-Batin University, Kingdom of Saudi Arabia

HIGHLIGHTS

- Benzothiazole-based compounds are effective in the treatment of diseases like cancer, and cardiovascular diseases.
- Several synthetic methods have been developed.
- Benzothiazole derivatives have exhibited several biological activities.
- Present review will serve a useful resource for researchers working in the field of synthetic chemistry and drug discovery.

GRAPHICAL ABSTRACT



ARTICLE INFO

Keywords:
Benzothiazole
Synthesis
Pharmacological activities
Heterocyclics

ABSTRACT

The research and development of benzothiazole derivatives have gained significant interest in recent years due to their diverse range of pharmacological activities. Benzothiazole-based compounds have been found to be effective in the treatment of various diseases including cancer, microbial infections and cardiovascular diseases. The synthesis of benzothiazole derivatives has been an active area of research, and several synthetic methods have been developed to access these compounds. The development of new.synthetic approaches and the modification of existing methods have allowed for the creation of novel scaffolds with improved biological properties and specificity. Benzothiazole derivatives have exhibited a wide range of biological activities including antitumor, antibiotic, antifungal, antimicrobial, HIV–I protease inhibition, and antiarteriosclerosis activities. The exploration of the pharmacological properties of benzothiazole derivatives continues to be an exciting area of research with the potential for the discovery of new drugs and therapies. Present review of benzothiazole and its derivatives provides a comprehensive overview of their synthesis and biological activities. This review will serve as a useful resource for researchers working in the field of synthetic chemistry and drug discovery, and it is expected to inspire further research and development of benzothiazole-based compounds with enhanced pharmacological properties.

* Corresponding author.
E-mail address: aziz0pharmacy@gmail.com (M.A. Rahman).

Production and Hosting by Elsevier on behalf of KeAi

https://doi.org/10.1016/j.ipha.2023.06.001
Received 5 June 2023; Received in revised form 7 June 2023; Accepted 7 June 2023
Available online 9 June 2023
2949-866X/© 2023 The Authors. Publishing services by Elsevier B.V. on behalf of KeAi Communications Co. Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Heterocyclic compounds, such as benzothiazole, are of great significance in organic chemistry and drug discovery due to their diverse range of physiological functions.[1] Benzothiazole and its derivatives have been extensively studied for their potential biological activities. In the 1950s, derivatives of benzothiazole, particularly 2-aminobenzothiazoles were investigated for their muscle relaxant properties. Since then, benzothiazole analogues have been found to exhibit a wide range of pharmacological actions including antibacterial, anti-inflammatory, analgesic, anticonvulsant, antiviral, anthelmintic, anti-oxidant and anticancer properties.[2,3]

There are several methods for synthesizing benzothiazole analogues. One common approach involves the condensation process where acyl chlorides, carboxylic acids, esters, nitriles and *o*-aminothiophenols containing substituted aldehydes are reacted to form benzothiazole derivatives. Another widely employed method is Pd/Cu/Mn/chloranil catalyzed cyclization of *o*-halothioformanilide. These synthetic methods have enabled the synthesis of numerous benzothiazole derivatives with diverse structural modifications and pharmacological effects. Ongoing research continues to explore the potential applications and properties of benzothiazole compounds and their derivatives.[4]

2. Different schemes for the synthesis of benzothiazole and its derivatives

Different schemes for the synthesis of benzothiazole and its derivatives are shown in Fig. 1, Fig. 2, Fig. 3, Figs. 4 and 5. Synthesis of benzothiazole heterocyclic via condensation of 2-aminothiophenol with aldehydes is simple and efficient method (scheme 1). The reaction is catalyzed by H_2O_2/HCl and carried out at room temperature for 1 h. The use of electron-withdrawing aldehydes and electron-donating substituents allows for the synthesis of a diverse range of benzothiazole derivatives with good yields (85–94%). One of the advantages of this method is that it is a one-pot reaction which reduces the number of steps required for the synthesis of benzothiazoles. Additionally, the products can be easily separated and the reaction time is relatively short.[5]

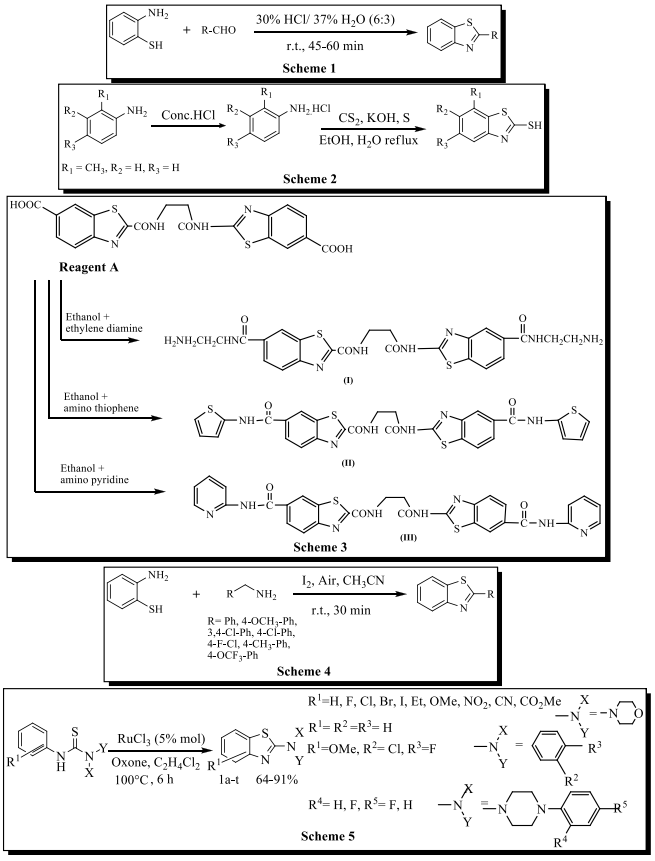


Fig. 1. Schemes 1, 2, 3, 4 and 5.

Scheme 2 is for the synthesis of substituted 2-mercaptobenzothiazoles with different substituents at positions 4, 5, and 6. This method has advantage that it does not require the use of hazardous reagents.[6]

Synthesis of benzothiazole derivatives using reagent-A is carried out by refluxing reagent-A (0.01 mol) with different amine compounds like ethylene diamine (0.02 mol) or aminothiophene (0.02 mol) or aminopyridine (0.02 mol) for 3 h (Scheme 3). The resulting reaction products are benzothiazole derivatives labelled as **I**, **II**, and **III** respectively.[7]

The reaction for the synthesis of benzothiazole proceeds by treating 2-mercaptoaniline with an amine compound in the presence of iodine under ambient conditions (Scheme 4). The use of iodine in the reaction suggests its role as an oxidizing agent or catalyst for the conversion of 2-mercaptoaniline and the amine to benzothiazoles.[8]

Substituted 2-aminobenzothiazoles were synthesized through from *N*-arylthiourea in a one-pot reaction using $RuCl_3$ as the transition metal catalyst (Scheme 5). The reaction proceeded by the deprotonation of *N*-arylthiourea with base to form an intermediate which then reacted with 2-bromoaniline to form a new intermediate. In the next step, $RuCl_3$ acted as a catalyst to facilitate the intramolecular cyclization of the intermediate leading to the formation of the final product, substituted 2-aminobenzothiazoles, in upto 91% yield. The reaction was found to be more efficient with electron rich substrates as compared to electron deficient ones.[9]

Suzuki–Miyaura coupling reaction involved the use of benzene boronic acid, $PhB(OH)_2$ as a reactant and $Pd(PPh_3)_4$ as a catalytic species and converted 2-chlorothiazole in the presence of a base, such as potassium carbonate (K_2CO_3) in the desired product by subjecting reaction mixture to microwave irradiation (Scheme 6). It exhibited outstanding regioselectivity. The high regioselectivity indicates the efficiency and reliability of the reaction.[10]

The synthesis of benzothiazoles with 2-substitution was achieved via a thorough condensation reaction using 2-aminothiophenol and olefinic compounds in a solvent-free environment with the assistance of microwave irradiation and using P_4S_{10} as the catalyst (Scheme 7). This method is highly efficient with a completion time requiring approximately 3–4 min. The use of microwave irradiation and a solvent-free environment contributed to the rapid reaction kinetics. Additionally, the reaction of the desired benzothiazole products in high yields indicated its effectiveness.[11]

General method of benzothiazole synthesis (Scheme 8) involves (i) activation of carboxylic acid by the addition of a dehydrating agent such as thionyl chloride, phosphorous oxychloride, or acetic anhydride to convert it into a more reactive intermediate which then undergo (ii) condensation with 2-aminothiophenol catalyzed by a suitable catalyst such as concentrated sulfuric acid, zinc chloride, or *p*-toluene sulfonic acid. The catalyst facilitates the condensation of the activated carboxylic acid intermediate with 2-aminothiophenol to form the desired benzothiazole derivatives.[12]

The synthesis of 2-aminobenzothiazoles from sodium dithiocarbamates and 2-iodoanilines via an Ullmann-like reaction process is a simple and efficient one-pot method (Scheme 9). The reaction is catalyzed by copper(II) in the presence of a base and a solvent, and conducted at a temperature of 120 °C. In the first step of the reaction, sodium dithiocarbamate is formed by the reaction of CS_2 with a primary amine in the presence of a base such as cesium carbonate. Next, 2-iodoaniline is added to the reaction mixture, and the Ullmann-like reaction is catalyzed by copper(II) in the presence of solvent such as dimethyl formamide. The reaction proceeds via formation of a copper thiolate intermediate which undergoes C–Ar bond formation with the 2-iodoaniline to form the desired 2-aminobenzothiazole derivative. The yield of the product is high reaching up to 97%, and unaffected by the electronic properties of substituents on the aromatic ring. Therefore, this method

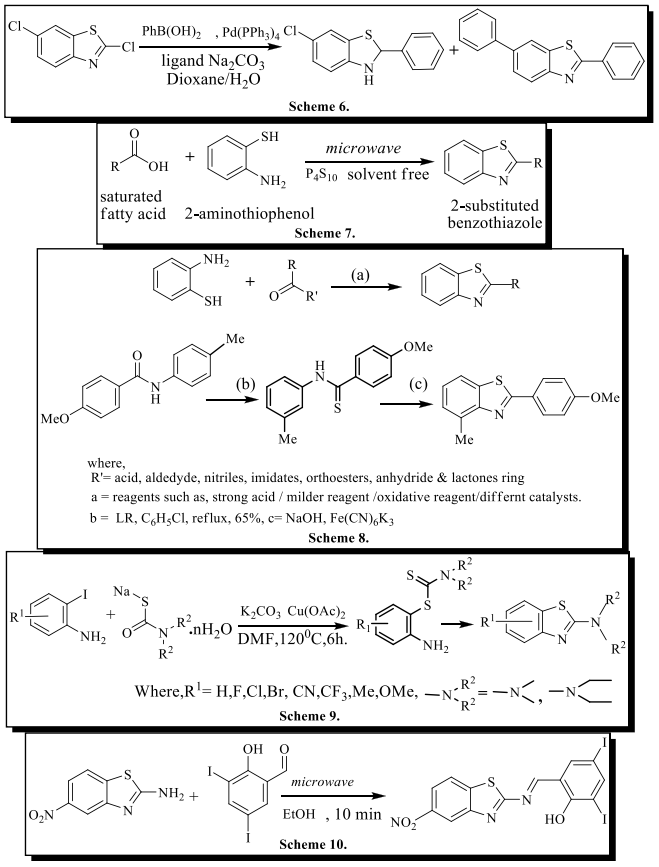


Fig. 2. Schemes 6, 7, 8, 9 and 10.

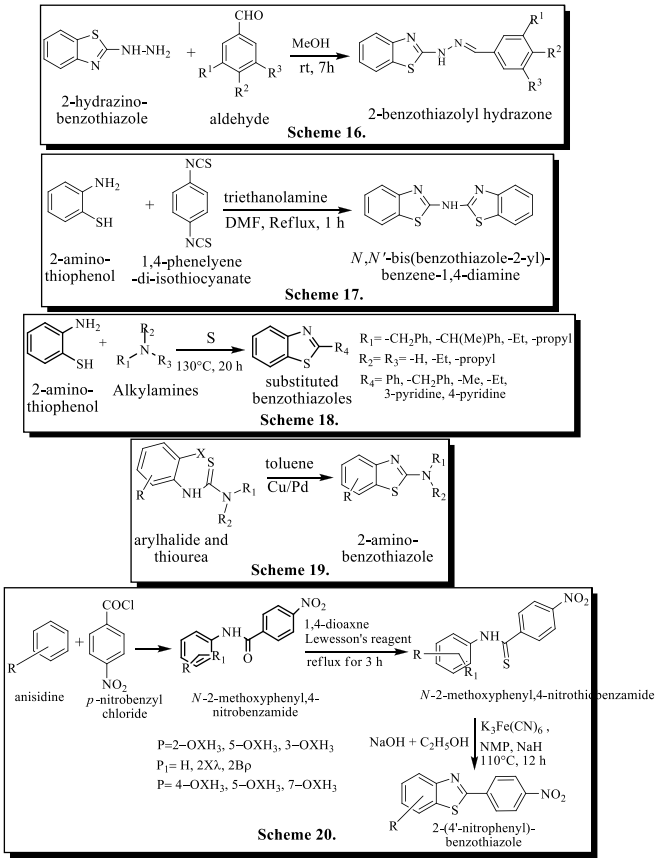


Fig. 4. Schemes 16, 17, 18, 19 and 20.

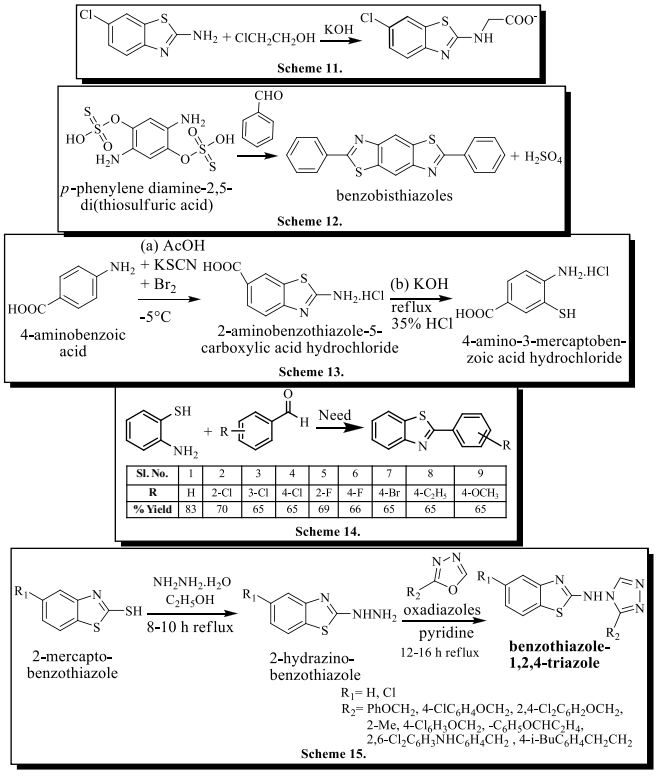


Fig. 3. Schemes 11, 12, 13, 14 and 15.

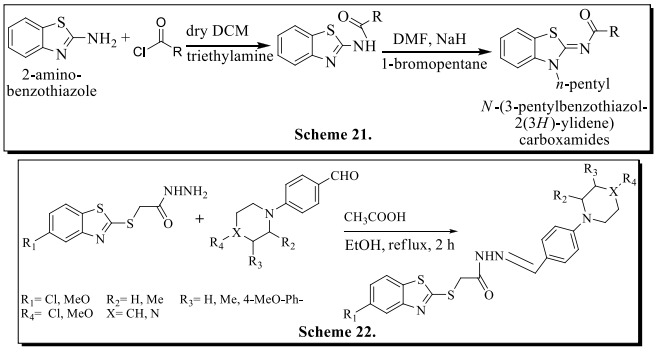


Fig. 5. Schemes 21 and 22.

provides a useful approach for the synthesis of diverse 2-aminobenzothiazole derivatives.[13]

The microwave assisted synthesis of Schiff's base derivative from 2-amino-6-nitrobenzothiazole and 3,5-diiodosalicylaldehyde was carried out in ethanol under mild reaction conditions at room temperature with 76–80% yield after 8–10 min (Scheme 10).[13]

Separate solutions of KSCN and *p*-chloroaniline in acetic acid were chilled and mixed together, and mixture of bromine in acetic acid was slowly added while shaking the mixture to keep the temperature between 10 and 100 °C. The filtered product was reacted with chloroethanol to yield 6-chloro-2-aminoacetate benzothiazole (Scheme 11).[14]

The reaction of *p*-phenylenediamine-2,5-di(thiosulfuric acid) with benzaldehydes when heated produced benzobisthiazole (Scheme 12).[15]

Potassium thiocyanate is reacted with 4-aminobenzoic acid in the presence of bromine and an acidic environment at −5 °C leads to the

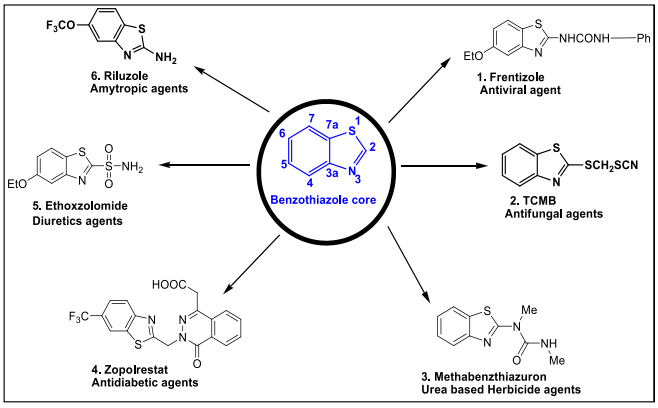


Fig. 6. Marketed drugs containing benzothiazole ring.

formation of 2-amino-benzothiazole-6-carboxylic acid which upon alkaline hydrolysis and heating results in the production of hydrochloride salt of the 4-amino-3-mercaptobenzoic acid (Scheme 13).

2-Aminothiophenol and various benzaldehydes are condensed together under ultrasonic irradiation to give benzothiazole derivatives (yield 65–83%) which proceeds without the use of a catalyst and solvent (Scheme 14).[16]

2-Hydrazinobenzothiazole was synthesized by reacting 2-mercaptobenzothiazole with hydrazine hydrate in the presence of ethanol and then, reacted with oxadiazole in the presence of dry pyridine under reflux conditions resulting in the formation of benzothiazole-1,2,4-triazole (yield 70–82%) through a ring-closure system (Scheme 15).[17]

The synthesis of antimalarial derivatives like benzothiazolyl hydrazones involves reaction of 2-hydrazino-benzothiazole with aldehydes (Scheme 16). This specific structural motif is believed to interact with the target molecules involved in the malarial infection process, potentially disrupting their function and inhibiting the growth of the parasites.

A condensation reaction between 1,4-phenylene-di-isothiocyanate and 2-aminothiophenol in the presence of triethanolamine and *N*,*N*-dimethylformamide as the reaction medium produced *N*,*N*′-bis(benzothiazole-2-yl)-benzene-1,4-diamine (Scheme 17).[18]

Chemoselective oxidative coupling of various alkylamines with 2-mercaptoaniline using elemental sulfur (S_8) as an oxidizing agent under suitable reaction conditions produces substituted benzothiazoles (Scheme 18).[19]

The synthesis of 2-aminobenzoylhydrazines utilizing a strategy involving C–S bond formation with intramolecular bond formation involves activation of thiourea moiety within the molecule leading to the formation of a cyclic intermediate (Scheme 19). Subsequently, a palladium-catalyzed aryl cross-coupling reaction occurs. This reaction involves the coupling of an aryl halide with the cyclic intermediate formed in the previous step, resulting in the formation of desired 2-aminobenzoylhydrazine product.[20]

The synthesis of 2-(4′-nitrophenyl) benzothiazole was done using Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide) as thiation reagent (Scheme 20). The reaction begins with the interaction between anisidine and *p*-nitrobenzoyl chloride resulting in the formation of *N*-2′-methoxyphenyl-4-nitrobenzamide. Lawesson's reagent is known for its ability to replace the carbonyl oxygen atoms in ketones, amides and esters with sulfur. The thiation reaction transforms the amide into thiobenzamide. Subsequently, in the presence of potassium iron cyanide, cyclization occurs leading to the formation of 2-(4′-nitrophenyl) benzothiazole.[21]

The reaction between 3-pentylbenzothiazole and various carboxylic acids produces an intermediate. The carboxylic acid reacts with the amino group of 3-pentylbenzothiazole leading to the formation of *N*-(3-pentylbenzothiazol-2(3*H*)-ylidene) carboxamides which exhibit strong anti-inflammatory properties (Scheme 21).[22]

The synthesis involves the combination of *p*-hetaryl substituted benzaldehydes with acylhydrazides derived from 2-mercaptobenzothiazoles substituted with five different groups. The reaction between the benzaldehydes and acylhydrazides leads to the formation of hydrazones of benzothiazolyl acyl compounds (Scheme 22).[23]

3. Benzothiazole and its derivatives exhibiting different pharmacological activities

Some marketed drugs containing benzothiazole are shown in Fig. 6.[24]

3.1. Anticancer activity

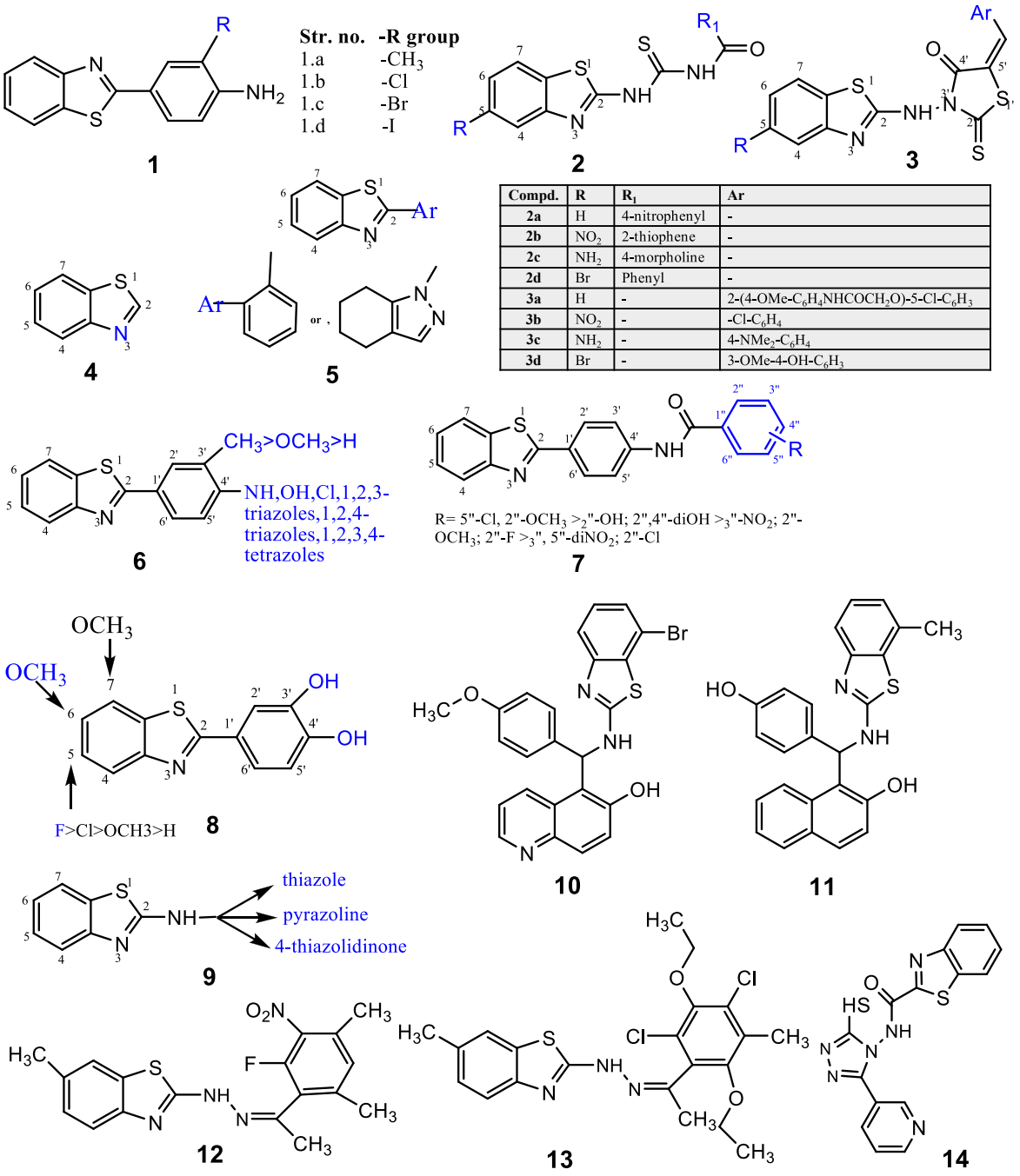
In-depth research on the systems of benzothiazole chains was performed to develop new lead compounds to treat various cancers.[3] A variety of the 2-(4-aminophenyl) benzothiazole that having it replaced with hydroxy, cyano, alkoxy and alkyl groups **(1.a-1. d)** have been demonstrated to have *in vitro* anticancer activity. Compound with $–CH_3$ sustitution (**1.a**) demonstrated by far effective development restriction (suppression) towards both ER- (MT-1 and MT-2) and ER+ (MCF-7 and BO) cancers.[25,26]

The sequence of benzothiazoles derivatives with 2-thiourea substitution were synthesized and found to possess ability to fight cancer in MCF-7 as well as HeLa cellular lines (Compound, **2**).[25,27] Based on research done by two different research groups to investigate benzothiazole's interactions and the thiourea moiety upon the topoisomerases enzyme I and II, used a hybrid approach into the best activity was demonstrated by molecules with derivatives of the thiourea-benzothiazole replaced with thiophene or morpholine, which enhanced apoptosis via activating the caspase-3 signalling.[28] The same group of researchers synthesised 4′-thiazolidinyl metabolites of the substituted 2-aminobenzothiazole (Compound, **3**) for this study based on an earlier inquiry on the moiety of 4-thiazolidinone.[29,30] A number of cancerous cellular lines are applied to analyze the antitumor efficacy for the synthesized compounds (carcinoma, central nervous system, ovaries, kidney, lungs, colonic, leukaemia and lines for chest tumor). The most noteworthy action against all the cell lines was exhibited by 4-chlorophenoxy-*N*-(4-methoxyphenyl)-acetamide.[31] The significance of hybridized design phase for a novel molecule involving benzothiazole derivatives for treatment of cancer was disclosed by this research.

3.1.1. Structure activity relationship in benzothiazole derivatives concerning anticancer activity

The core structural properties of benzothiazole have indicated the significance of a ring structure in the cancer therapies. The biological activity is especially to substituted benzothiazole molecules substituted at the 2nd position and at C-5, C-6, C-7 positions, all of which are important to the activities.

1. The *N*-atom must be free and unhindered for the rings of benzothiazole structure to have anticancer activity (Compound, **4**).
2. The structure should be planar because given significant feature for linkages between the DNA-containing benzothiazole molecules.
3. The aryl group at C-2 position in the benzothiazole's ring is vital for the anticancer activity, and it was determined by research relating between structure and activities (compound, **5**).
4. Researchers examined the results of various substitutions, including the impacts of the electrons withdrawing group (F), electron donating group (OCH_3) and H, CH_3 at C-3′ position of the benzothiazole moiety. They discovered that the methyl group in C-3′ position significantly increased the activity (compound, **6**).
5. The –NH, –OH and -Cl groups at the C-4′ positioned in phenyl ring strongly affect the anticancer properties of benzothiazole derivatives (compound, **6**). The results show that 1,2,4-triazole rings



Compd.	R	R_1	Ar
2a	H	4-nitrophenyl	-
2b	NO_2	2-thiophene	-
2c	NH_2	4-morpholine	-
2d	Br	Phenyl	-
3a	H	-	2-(4-OMe-$C_6H_4NHCOCH_2O$)-5-Cl-C_6H_3
3b	NO_2	-	-Cl-C_6H_4
3c	NH_2	-	4-NMe_2-C_6H_4
3d	Br	-	3-OMe-4-OH-C_6H_3

Fig. 7. Compounds with anticancer activity (1–9), with antibacterial activity (10,11), with antifungal activity (12–14).

are more important for activities along with the 1,2,3-triazole as well as 1,2,3,4-tetrazole moiety (compound, **6**).

6. Amide-substituted derivatives of 2-phenyl benzothiazole demonstrated effective antitumor activity against a wide range of cancers types (cervical tumors, human leukaemia cell singling). The key action of compound is determined by pattern of substitution in region within the phenyl rings replaced with amide bonds (compound, **7**).
7. The analysis of effectiveness in many substituents on the benzothiazole rings system at C-5, C-6, and C-7 regions: By adding electron-withdrawing group (notably F) at C-5 and methoxy/methyl group at C-6 position, then activity was greatly boosted. However, this chemicals' antiproliferative properties were significantly reduced by the addition of methoxy groups at the C-5 and C-7 position (i.e., rings series of tri-substituted benzothiazoles) (compound, **7**).
8. Additionally, studies have indicated the –F group substitution at benzothiazole molecule at 5th position is vital for anticancer activity. Halogen and alkyl groups must be present at the proper location because their absence caused issues with metabolism and activity (compound, **8**).
9. While the weak anticancer activity of aminobenzothiazole is caused by the synthesis of thiazole and pyrazoline substitution in the ring from C-2 location. The 4-thiazolidinone moieties existence at C-2 positions is viable technique for the analysis of anticancer medications in the future (compound, **9**).
10. The increased anticancer properties of acetamide group with the 4-chlorophenoxy-*N*-methoxyphenyl is added to 5th position in 4-

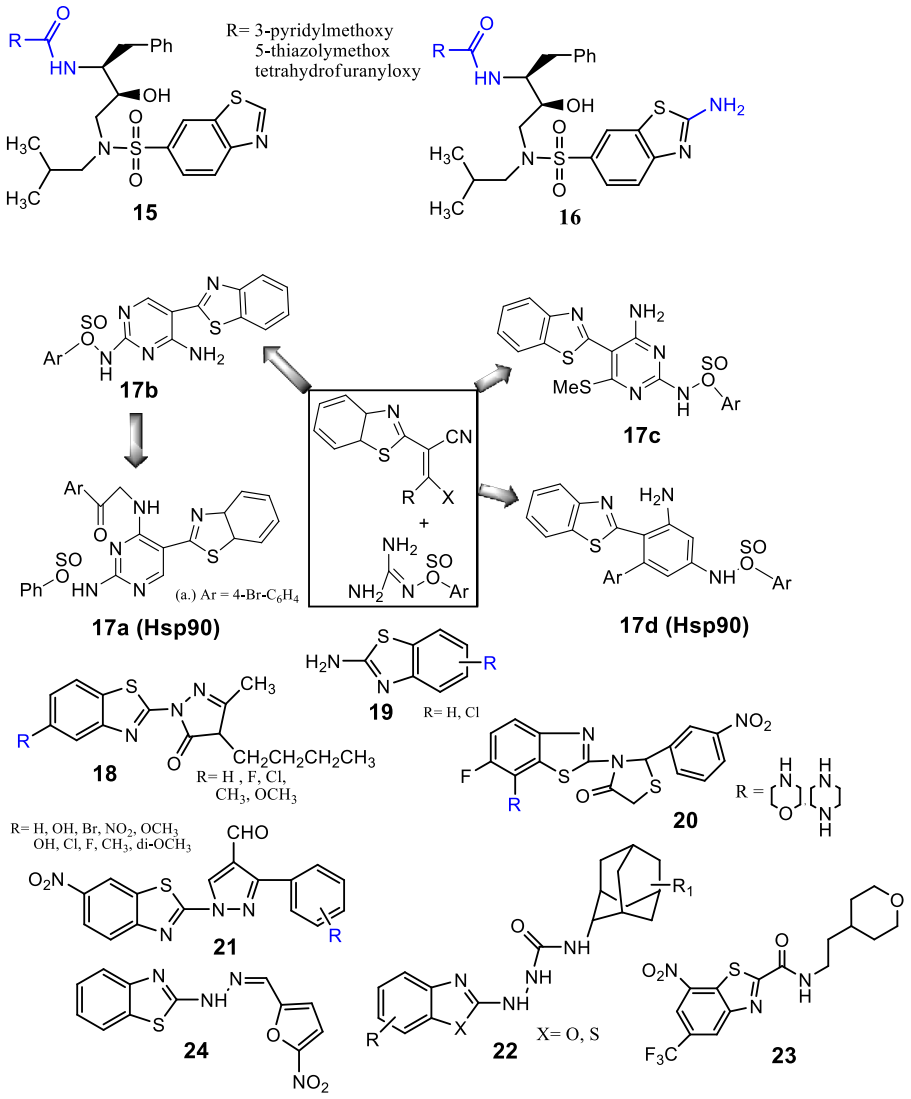


Fig. 8. Compounds with antiviral activity (**15–17**), with anti-inflammatory activity (**18,19**), with antitubercular activity (**20–24**).

thiazolidinone molecule (compound, **9**). Hydroxyl group at 4th-position of 2-aryl moiety is essential for anticancer activities, substituting a bigger group at 4th position at 2-aryl moieties may promote anticancer activity. Thus, this SAR understanding may be applied to synthesize stronger benzothiazole compounds as anti-tumor medicines.[32,33]

3.2. Antibacterial activity

Compound, **10** was synthesised and evaluated for its antibacterial activity and antifungal activity against *B. subtilis, S. aureus*, and *E. coli*.[34] It exhibited antibacterial activity and also exhibited minor antifungal activity against *C. albicans* and *A. niger*. Compound, **10** was demonstrated to have most potent antimicrobial activities and so, it followed by another compounds against every bacterial species that was examined and highly effective. To further assess the collected docking data for antibiotic properties, with *E. coli* dihydro-orotase was examined and observed antimicrobial activities. The basic ligand HDDP and HIS254, ARG20, ASN44, LEU222, ALA266 and HIS139 formed a large *H*-bonding network. The phenol grouping compound, **10** enters into the cavity holding HDDP which causes one *H*-bond to form along with LEU222's branch chains.[35] Similarly, with compound **10**, *H*-bond was formed between inside chain of ALA266 and the oxygen from methoxy group. In addition, the ring made of naphthalene also forms THR143, GLU141 and PRO105 are hydrophobic contacts near to the cavity of the catalytic *E. coli* dihydro-orotase.

Conversely, compound, **11** had a little amount of efficacy against the tested bacterial strains.[36] Few research on the antibacterial properties as the derivatives of benzothiazole against infectious of fungi and bacteria have been produced. Compound, **11** methyl-benzothiazole interacts extensively as well as braches chains that CYS221, CYS256 and ARG258. During the limited several groups that could serve as donors or receptors that may be establish hydrogen is joined to the receptor, a lower predicted docking score by the loss of *H*-bonds.[34] Furthermore, stacking of the compound, **11** with HIS254 affects the transition state of the enzyme which resulted in loss of activity.

The bactericidal substances based on benzothiazole connected to various bacterial cells and respond to the role of enzyme inhibitors for vital bacterial cell functions like cell differentiation, DNA reproduction, and production of cell wall synthesis or the biogenesis of necessary compounds were reported.[37]

Numerous articles dihydroorotase inhibition with regard to both Gram + ve as well as Gram -ve bacteria have been examined showing its usefulness for the synthesis and target for invention of the antimicrobial medications.[38,39]

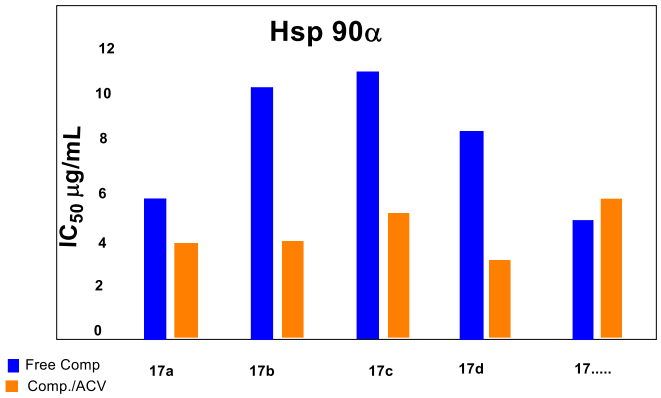


Fig. 9. Hsp90 protein's reaction to numerous medications with varying IC_{50} values and their combinations with acyclovir.

3.3. Antifungal activity

Several 2-substituted benzothiazoles (Compounds **12**, **13**) along with 4-(2′-substituted benzothiaoles 5-mercapto-3-(substituted)-1,2,4-triazole analogues (compound, **14**) were synthesized and examined for their antibacterial efficacy in *E. coli* as well as *S. aureus*, and antifungal activities towards *C. albicans* as well as *A. niger*.[40] The bulk of drugs displayed favourable findings for both activities.

Compounds with anticancer activity (**1–9**), with antibacterial activity (**10, 11**), with antifungal activity (**12–14**) are shown in Fig. 7.

3.4. Antiviral activity

Novel benzothiazole sulphonamides (compounds, **15** and **16**) were discovered to inhibit HIV-1 protease with an IC_{50} value within 2–3 nM.[41] It was shown that the carbamate equivalents are more potent antiviral agents and HIV-1 protease inhibitors. The antiviral potency of new substituted 2-pyrimidylbenzothiazoles towards either amino compound, its sulphonamide moiety, just at the pyrimidine ring's C2 was evaluated. The novel ring structure was produced by combining several ylidene benzothiazole derivatives with guanidine or *N*-arylsulfonated guanidine by the Michael addition routes.

Compounds with antiviral activity (**15–17**), with anti-inflammatory activity (**18, 19**), with antitubercular activity (**20–24**) are shown in Fig. 8.

Using the Hsp90 (C-Terminal) blocker screening assay kit, the potent HSV-1 antiviral medications **17a, 17b, 17c, 17d, and 17 ….**were investigated for their effects on Hsp90 and found potent antiviral agents. Acyclovir (ACV, the reference drug) and each powerful compound in 1:1 combination were also tested. Protein 90 Heat-Shock (Hsp90) is necessary for the folding, assembly and replication of viral proteins.[42] It was found that Hsp90 inhibitors also prevented HSV-1 infection. Fig. 9 displays the findings for IC_{50} values of each medication.[43]

3.4.1. Structure activity relationship of antiviral drugs

The development of additional amino aryl-ethanone compounds on the pyrimidine chain (17a-b) from the starting molecule enhances the antiviral effects. Furthermore, the compound 17a that contains an alteration of the *para*-position with Br at the aryl molecule showed stronger antiviral activity than compound 17b. It is protected versus CBV4, HSV-1, HAV, and HAdV7 by a Cl-substituent. But, when the aryl moiety's bromide group is exchanged to an electron-donating group, like a $–CH_3$ group, its activity was decreased. The activity of compounds containing electron withdrawing group, for example a collection of fluorides or chlorides are based on *para*-position its aryl groups (pyrimidine ring's position), 17d, as well as 17 …, was greater activity than electron donating group, such as $–CH_3$ or $–OCH_3$ groups.

3.4.2. Docking and molecular modeling studies

The compounds 17a, 17b, 17c, 17d, and 17 … had indicated good binding affinity with the receptor (antibody, Hsp90) at the active site, ranging from −5.6421 to −9.7282 kcal/mol, according to the docking analysis using reference medicine acyclovir. Only one molecule, 17a demonstrated *H*-bonding contact between sulphur atom from the benzothiazole nucleus as also the amino acid sequence Asp102 at a range of 3.84. Additionally compounds 17a and 17b functioned in polar bond interactions with Tyr 139 as well as Met 98, similarly, on amino acid residues. However, molecules 17b and 17d respectively showed only one instance of connection between Thr 184 with Asn 51 respectively. Compound, 17d has a docking value of the −8.1512 kcal/mol, and compound, 17a had a docking value of the −8.6521 kcal/mol according to docking study, and docking score of the reference drug, acyclovir had been −5.642 kcal/mol.

3.5. Anti-inflammatory activity

Several novel benzothiazoles such as 2-(4′-butyl-3′,5′-dimethylpyrazol-1′-yl) with 4-butyl-1-(6′-susbtituted-2′-benzothiazolyl) benzothiazoles with a 6-substitution were prepared in order to treat inflammation and it was shown that compound, **18** had potent anti-inflammatory effect.[44,45]

Anti-inflammatory drugs based on benzothiazoles were synthesized and novel 2-amino-benzothiazole derivative, compound **19** was tested for their ability to reduce inflammation. It was observed that the anti-inflammatory activity was increased significantly when the 2-amino benzothiazole was substituted at positions 4 or 5 including an electron-withdrawing group, such as -Cl, $–NO_2$ and $–OCH_3$.[46]

3.6. Antitubercular activity

Compound, **20** was found to possess significant *in vitro* antitubercular activity against *Mycobacterium tuberculosis*.[47]

6-Nitro-2-[4-formyl-3-(phenyl substituted) pyrazolyl] benzothiazoles were synthesized and investigated for antitubercular activity against H37RV strain of *Mycobacterium tuberculosis*. In antitubercular screens, benzothiazoles (compound, **21**) exhibited most promising activity.[48] An updated patent had shown the antimycobacterial activity for derivatives of adamantanyl benzothiazoles.[49,50] One amongst them, the compound, **22,** with a MIC_{90} of 0.03 g/ml against H37Rv was discovered to be isoniazid-equivalent.

Compound, **23** from the series has demonstrated good growth inhibition of *Mycobacterium tuberculosis* with an MIC of 224 nM. The nitrofuranyl-benzothiazole hydrazones, compound **24** had MIC>16 g/ml as an antitubercular drug.

3.7. Anti-oxidant activity

Indole-hydrazones, benzofuranhydrazones, benzimidalzolidrazones, arylbenzimidazoles including benzothiazole analogues were synthesized and evaluated for their anti-oxidant and antitumor activities.[51] These substances produced strong anti-oxidant capacities as well as favourable photo-protective or antitumor activity profiles. In particular, compound **25** displayed IC_{50} levels of 2 g/ml towards the studied dermatophytes and also an excellent *in vitro* anti-oxidant activity in DPPH and FRAP tests ultimately showing its IC_{50} equal to 9.7 µM against human melanoma cells.

3.8. Antidiabetic activity

Benzothiazole derivatives exhibit antidiabetic effects, and future use of the benzothiazole core could lead to the development of a safe antidiabetic drugs.[52] The enzyme known as adenosine-5′-monophosphate activated protein kinase (AMPK) is among the main targets of the cutting-edge antidiabetic medications. 2-Chloro-5-((*Z*)-((*E*)-((4,

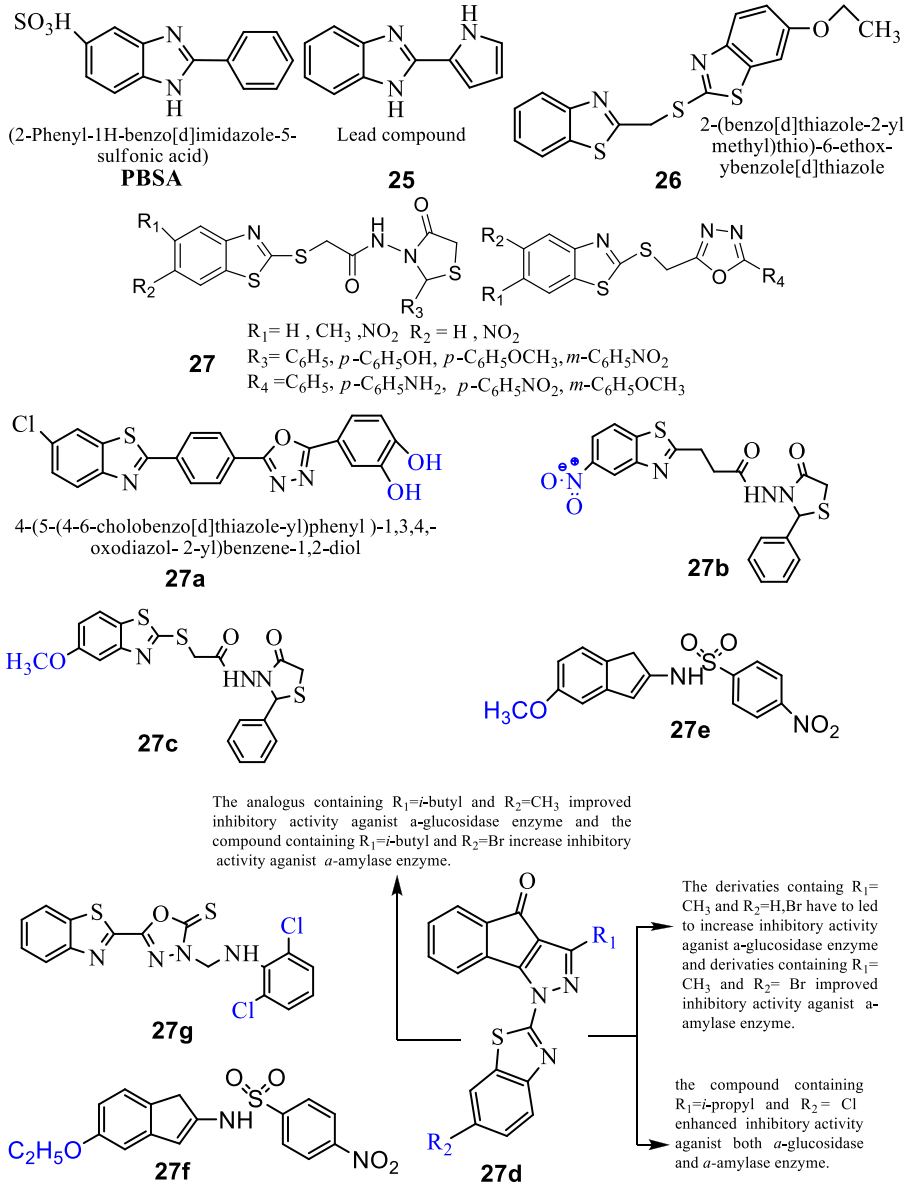


Fig. 10. Compounds with anti-oxidant activity (PBSA, 25), with antidiabetic activity (26, 27, 27a-27g).

5-dimethyl-2-nitrophenyl)furan-2-yl)methylene)-4-oxothiazolidin-2-ylidene)benzoic acid (PT-1) decreases auto-inhibition of AMPK enzymes. Several benzothiazoles with similar structures accelerated the glucose absorption in AMPK-reliant mechanism approach in L6 myocytes. 2-(Benzo[*d*]thiazol-2-ylmethylthio)-6-ethoxybenzo[*d*]thiazol, **26** had shown high glucose absorbing speed.[53]

The heterocyclic compound, benzothiazole has a broad range of biological activities and due to its fast rising scientific interest to develop potent, safe, and medically beneficial antidiabetic drugs, there was large amount synthesis of benzothiazole derivatives.[54]

3.8.1. Structure activity relationship of benzothiazole as antidiabetic agent

1. Dihydroxy analogues of benzothiazole e.g., **27a** are effective diabetes-lowering medications.
2. An antidiabetic effect is produced by the substitution of $–NO_2$ and $–OCH_3$ moiety in the benzothiazole's 6th position, **27b** and **27c.**
3. 2-Mercaptobenzimidazole compounds with sulfonamide I (R = –H, 6-OMe; R_1 = 4-OMe, 4-NO_2, 4-Br; R_2 = 2-Me, 2-Cl, 2-NO_2) were developed and evaluated in the search for effective inhibitors, **27d.**[55,56]
4. Methoxy or ethoxy group replacement at 6th position results in effective antidiabetic activity. For the SAR research, with -Cl and $–OCH_3$ substitution in the 4th, 5th and 6th-positions in phenyl ring system of benzothiazoles, **27e** and **27f** have also demonstrated improved anti-inflammatory and antidiabetic efficacy.[46]
5. Electron withdrawing group(s) has improved antidiabetic activity compared to electron-donating group. Furthermore, the inhibitory activity was reduced when these groups are moved to ortho-para position. Significantly more inhibition is produced when the electron-withdrawing class of –Cl group is added to benzothiazole rings, **27g.**[57]

Compounds with anti-oxidant activity (**PBSA, 25**) and with antidiabetic activity (**26, 27, 27a-27g**) are shown in Fig. 10.

3.9. Neuroprotective activity

Ab42 peptides were administered to Alzheimer's disease, MCI (mild

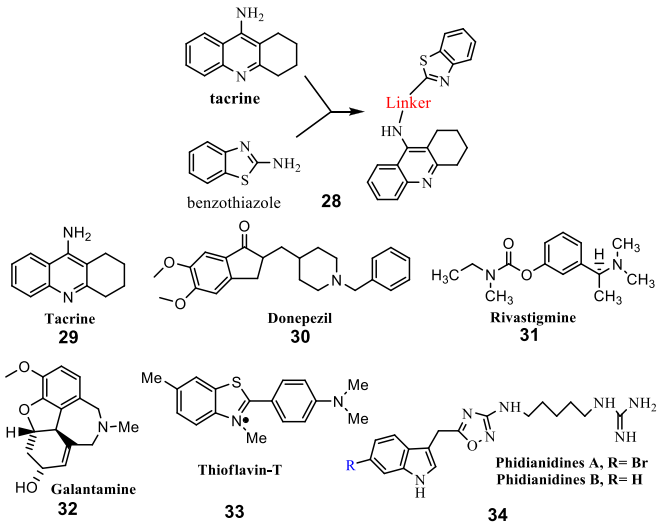


Fig. 11. Compounds with neuroprotective activity: tacrine-benzothiazole hybrids (28), USFDA approved acetylcholinesterase inhibitors (29–32), Ab-aggregation inhibitor (33) and phidianidines (34).

cognitive impairment), SHSY-5Y cells or control hybrids in order to assess combination compounds made of tacrine and benzothiazole that may have medicinal benefits.[58] Since Ab42 therapies in human cell lines mirror some features of the neurodegeneration that underlies the pathophysiology of Alzheimer's disease, they serve as a trust worthy model for testing possible neuroprotective drugs. Due to significance of multi-specific antineurodegeneration medications, the disease-modifying drugs such as tacrine-benzothiazole hybrids, **28** were synthesized which function as acetylcholinesterase (AChE) and Ab oligomerization inhibitors in preventing toxicity caused by Ab42 peptides. They demonstrated the protective characteristics of this new class of hybrid tacrine-benzothiazole compound, to prevent pathogenesis of Alzheimer's disease.[59]

The USFDA has given its approval to a number of AChE inhibitors including tacrine (**29**), donepezil (**30**), rivastigmine (**31**), galantamine (**32**), and inhibitor of Ab-aggregation (thioflavin-T) (**33**). The symptoms of cognitive, functional, and behavioural impairment are ameliorated by these inhibitors.[60,61]

Unique and convergent 2-arylbenzothiazole through the Suzuki biaryl synthesis between aryl boronic and 2-bromobenzothiazole acids produced a number of compounds of 2-arylbenzothiazoles in high yield.[62] In contrast, a group of heterocyclic molecules known as oxadiazoles has a wide range of biological functions in particularly, compounds of 1,3,4-oxadiazole showed remarkable compatibility with Ab groupings. Structural characteristics of Phidianidines A and B, **34** were analysed, and these compounds comprised three incomplete, moieties A, B, and C.[63] The moieties A, is a significant pharmacophore that is present in many different bioactive natural medications.[41] Drug development programmes have included moieties B, of the 1,2,4-oxadiazole ring, as a crucial component of the pharmacophore that contributes to ligand binding while the various replaced benzene ring that replaced the guanidine moiety are necessary for their bioactivity.[64] Compounds with neuroprotective activity: tacrine-benzothiazole hybrids (**28**), USFDA approved AChE inhibitors (**29–32**), Ab-aggregation inhibitor (**33**) and phidianidines (**34**) are shown in Fig. 11.

The moiety C has the current basic connections between structure and activity analysis which revealed to the neuroprotective action of guanidine just was not dependent on the structure target, **35** (Fig. 12).

The pharmacophore located on the benzothiazole nuclei was predicted that it is similar to GABA and capable of binding to the GABA-receptor in large numbers, and possess a beneficial combination with antidepressant impact due to enhanced lipophilicity.[65] An important

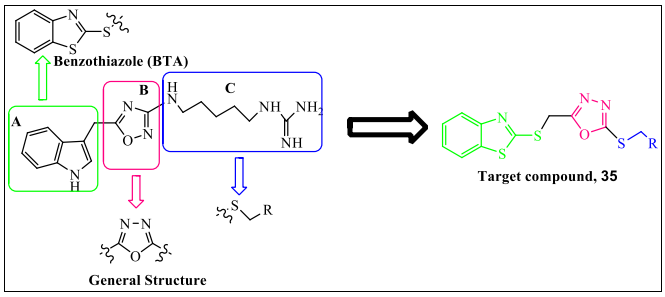


Fig. 12. Structure modification.

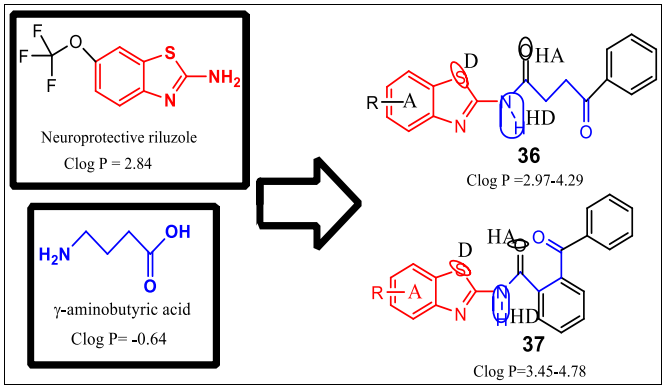


Fig. 13. Design and development of molecules as anticonvulsant-neuroprotective drugs with the necessary pharmacophoric components [HD: hydrogen donor, HA: hydrogen acceptor, D: electron donor atom, and A: aryl unit/hydrophobic domain].

antidepressant pharmacophoric feature of the above mentioned compounds is present in an amide domain of using hydrogen bonds donor.[66] The molecules (**36** and **37**) as anticonvulsant-neuroprotective drugs with the necessary pharmacophoric components are shown in Fig. 13. The features influencing the blood brain barrier antipsychotics activity are shown to investigate their potential neuroprotective and anticonvulsant properties.

These compounds' overall structural activity relationship indicated the compounds having the groups with releasing electrons were significantly more energetic compared to those of electron withdrawing group. Hydrophilic methoxy compounds were more effective than lipophilic methyl compounds as among electron donating groups. However, one of the various halogen iso-electronics, and lipid soluble -Cl groups well at 6th place of the benzothiazole ring have greater power, and little less harmful in nervous system than the presence of bromo, fluoro, and nitro compounds. It's also amazing to observe that its insertion like a hydrophilic electron-withdrawing domain, including an acetyl group to benzolthiazole ring resulted in the removal of neurotoxic effect and a significant increase in anticonvulsant effectiveness.[67]

4. Conclusion

The recent literature on benzothiazoles highlights their synthetic methods and diverse biological functions. Researchers have employed various techniques, including the use of biocatalysts to enhance yields and optimize reaction conditions during synthesis. The benzothiazole core exhibits a wide range of biological activities including anticancer, antibacterial, anti-inflammatory, antidepressant and antidiabetic properties. Benzothiazole derivatives have become an attractive area of research for identifying novel lead molecules due to their intrinsic variety of activities. The discovery of Zopolrestat, an aldose reductase inhibitor, has paved the way for exploring the medicinal potential of

benzothiazoles. Some benzothiazole derivatives have shown comparable or superior activity to existing standard medications indicating their promise as potential therapeutic agents. This suggests that there may be upcoming treatments in the market based on benzothiazole-derived products.

Author contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for.

Important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

Data availability

Open for all.

Declaration of competing interest

None.

Acknowledgements

Authors pay gratitude to Prof. SW Akhtar, honourable chancellor, Integral University, Lucknow for continuous ambition and motivations. Authors are also thankful to administration and academicians of Faculty of Pharmacy, Integral University for the research atmosphere and motivation (Manuscript communication number: IU/R&D/2023-MCN0001855).

References

1. Ingle RG, Marathe RP. Review on literature study of benzothiazole. *Int J Pharmaceut Res Allied Sci.* 2012;1(4):11–15.
2. Khare E, Sharma S, Singh Y, Keshri P. A comprehensive review on the biological aspects of emerging benzothiazole. *Pharma.* 2019;7(2):1–8.
3. Pathak N, Rathi E, Kumar N, Kini SG, Rao CM. A review on anticancer potentials of benzothiazole derivatives. *Mini-Rev Med Chem.* 2020;20(1):12–23.
4. Asif M, Imran M. A mini-review on pharmacological importance of benzothiazole scaffold. *Rev Organic Chem.* 2021;18(8):1086–1097.
5. Gao X, Liu J, Zuo X, Feng X, Gao Y. Recent advances in synthesis of benzothiazole compounds related to green chemistry. *Molecules.* 2020;25(7):1675.
6. Yadav PS, Prakash D, Senthilkumar GP. Different methods of synthesis of benzothiazole and diverse biological activities. *Int J Pharmaceut Sci Drug Res.* 2011;3(1):1–7.
7. Aljamali DNM, Chfat HG, Jawd DSM. Benzothiazol derivatives (synthesis, investigation, bio-studying). *Int J Pharmaceut Res.* 2019;11(1):1–8.
8. Lihumis HS, Alameri AA, Zaooli RH. Recent development and biological applications of benzothiazole derivatives. *Progr Chem Biochem Res.* 2022;5(2):147–164.
9. Sharma S, Pathare RS, Maurya AK, et al. Ruthenium catalyzed intramolecular C-S coupling reactions: synthetic scope and mechanistic insight. *Org Lett.* 2016;18(3):356–359.
10. Heo Y, Song Y, Kim B, Heo J. A highly regioselective synthesis of 2-aryl-6-chlorobenzothiazoles employing microwave-promoted Suzuki-Miyaura coupling reaction. *Tetrahedron Lett.* 2006;47:3091–3094.
11. Gulati S, Wakode S, Kaur A, Anand K. Synthesis, biological activity and recent advancement of benzothiazoles : a classical review. *World J Pharm Pharmaceut Sci.* 2017;6(6):1842–1869.
12. Keri RS, Patil MR, Patil SA, Budagumpi S. A comprehensive review in current developments of Benzothiazole based molecules in medicinal chemistry. *Eur J Med Chem.* 2015;89:207–251.
13. Zhilitskaya LV, Shainyan BA, Yarosh NO. Modern approaches to the synthesis and transformations of practically valuable benzothiazole derivatives. *Molecules.* 2021;26(8):2190.
14. Kumar S, Mittal A, Pathak A, Sahu Sk. Biological assessments of substituted benzothiazole derivatives in streptozocin induced diabetes rats. *Plant Archives.* 2020;20(2):3250–3253.
15. Shaista A, Amrita P. Benzothiazole - a magic molecule. *Int J Pharmaceut Sci Res.* 2017;8(12):4909–4929.
16. Tariq S, Alam O, Amir M. Synthesis p38α MAP kinase inhibition, anti-inflammatory activity, and molecular docking studies of 1,2,4-triazole-based benzothiazole-2-amines. *Arch. Pharm. Chem. Life Sci.* 2018;351(3–4), 1700304.
17. Tariq S, Kamboj P, Alam O, Amir M. 1,2, 4-Triazole-based benzothiazole/benzoxazole derivatives: design, synthesis, p38α MAP kinase inhibition, anti-inflammatory activity and molecular docking studies. *Bioorg Chem.* 2018;81(9):630–641.
18. El-Sharief S, Ammar Y, Zahran M, Sabet HK. *Phosphorus, Sulfur Silicon Related Element.* vol. 179. 2004:267–275.
19. Nguyen TB, Ermolenko L, Dean WA, Al-Mourabit A. Benzazoles from aliphatic amines and o-amino/mercaptan/hydroxyanilines - elemental sulfur as a highly efficient and traceless oxidizing agent. *Org Lett.* 2012;14:5948–5951.
20. Evindar G, Batey RA. Copper- and palladium-catalyzed intramolecular aryl guanidinylation: an efficient method for the synthesis of 2-aminobenzimidazoles. *Org Lett.* 2003;5(2):133.
21. Gupta A, Rawat S. Synthesis and cyclization of benzothiazole: review. *J Curr Pharmaceut Res.* 2010;3(1):13–23.
22. Ugwu DL, Okoro UC, Ukoha PO, Gupta A, Okafor SN. Novel anti-inflammatory and analgesic agent: synthesis, molecular docking and *in-vivo* studies. *J Enzym Inhib Med Chem.* 2018;33(1):405–415.
23. Osmaniy D, Levent S, Karaduman AB, Ilgın S, Özkay Y, Kaplancıklı ZA. Synthesis of new benzothiazole acylhydrazones as anticancer agents. *Molecules.* 2018;23(5):1054.
24. Gupta K, Sirbaiya AK, Kumar V, Rahman MA. Current perspective of synthesis of medicinally relevant benzothiazole based molecules: potential for antimicrobial and anti-inflammatory activities. *Mini Rev Med Chem.* 2022;22(14):1895–1935.
25. Hutchinson I, Chua MS, Browne HL, et al. Antitumor benzothiazoles. 14. Synthesis and *in vitro* biological properties of fluorinated 2-(4- aminophenyl) benzothiazoles. *J Med Chem.* 2001;44(9):1446–1455.
26. Bhuva HA, Kini SG. Synthesis, anticancer activity and docking of some substituted benzothiazoles as tyrosine kinase inhibitors. *J Mol Graph Model.* 2010;29(1):32–37.
27. Hutchinson I, Sahin B, Yaglioglu AS, Ceylan M. Synthesis and cytotoxic activities of novel 2-(1,5-bis (aryl) penta-1,4-dien-2-yl) benzo[d]thiazol derivatives. *Org Commun.* 2016;9(3):65.
28. Manjula SN, Noolvi NM, Parihar KV, et al. Synthesis and antitumor activity of optically active thiourea and their 2-aminobenzothiazole derivatives: a novel class of anticancer agents. *Eur J Med Chem.* 2009;44(7):2923–2929.
29. Saeed S, Rashid N, Jones PG, Ali M, 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(4):1323–1331.
30. Lesyk BR, Zimenkovsky BS. 4-Thiazolidones: centenarian history, current status and perspectives for modern organic and medicinal chemistry. *Curr Org Chem.* 2004;8(16):1547–1577.
31. Havrylyuk D, Mosula L, Zimenkovsky B, Vasylenko O, Gzella A, Lesyk R. Synthesis and anticancer activity evaluation of 4-thiazolidinones containing benzothiazole moiety. *Eur J Med Chem.* 2010;45(11):5012–5021.
32. Wang K, Guengerich FP. Bioactivation of fluorinated 2-arylbenzothiazole antitumor molecules by human cytochrome P450s 1A1 and 2W1 and deactivation by cytochrome P450 2S1. *Chem Res Toxicol.* 2012;25(8):1740–1751.
33. Bolelli K, Musdal Y, Aki-Yalcin E, Mannervik B, Yalcin I. Synthesis and activity mechanism of some novel 2-substituted benzothiazoles as hGSTP1-1 enzyme inhibitors. *SAR QSAR Environ Res.* 2017;28(11):927–940.
34. Morsy MA, Ali EM, Kandeel M, et al. Screening and molecular docking of novel benzothiazole derivatives as potential antimicrobial agents. *Antibiotics.* 2020;9(5):221.
35. Lee M, Chan CW, Graham SC, Christopherson RI, Guss JM, Maher MJ. Structures of ligand-free and inhibitor complexes of dihydroorotase from *Escherichia coli*: implications for loop movement in inhibitor design. *J Mol Biol.* 2007;370:812–825.
36. Maddili SK, Li Z, Kannekanti VK, et al. Azoalkyl ether imidazo[2,1-b]benzothiazoles as potentially antimicrobial agents with novel structural skeleton. Bioorganic Med. *Chem Lett.* 2018;28(1):2426–2431.
37. Thakkar SS, Thakor P, Ray A, Doshi H, Thakkar VR. Benzothiazole analogues: synthesis, characterization, MO calculations with PM6 and DFT, *in silico* studies and *in vitro* antimalarial as DHFR inhibitors and antimicrobial activities. *Bioorg Med Chem.* 2017;25(20):5396–5406.
38. Rice AJ, Lei H, Santarsiero BD, Lee H, Johnson ME. Ca-asp bound X-ray structure and inhibition of *Bacillus anthracis* dihydroorotase (DHOase). *Bioorg Med Chem.* 2016;24:4536–4543.
39. Truong L, Hevener KE, Rice AJ, Patel K, Johnson ME, Lee H. High-level expression, purification, and characterization of *Staphylococcus aureus* dihydroorotase (PyrC) as a cleavable His-SUMO fusion. *Protein Expr Purif.* 2013;88(1):98–106.
40. Khokra SL, Arora K, Mehta H, Aggarwal A, Yadav M. Common methods to synthesize benzothiazole derivatives and their medicinal significance: a review. *Int J Pharmaceut Sci Res.* 2011;2(6):1356–1377.
41. Nagaraj Chaluvaraju KC, Niranjan MS, Kiran S. 3,4-Oxadiazole: a potent drug candidate with various pharmacological activities. *Int J Pharm Pharmaceut Sci.* 2011;3(3):9–16.
42. Geller R, Taguwa S, Frydman J. Broad action of Hsp90 as a host chaperone required for viral replication. *Biochim Biophys Acta.* 2012;1823(3):698, 670.
43. Azzam RA, Osman RR, Elgemeie GH. Efficient synthesis and docking studies of novel benzothiazole-based pyrimidinesulfonamide scaffolds as new antiviral agents and HSP90A inhibitors. *ACS Omega.* 2020;5(3):1640–1655.
44. Kumar A, Shakya AK, Siddiqui HH. Synthesis and anti-inflammatory activity of some novel 2-aminobenzothiazole derivatives. *Indian J Heterocycl Chem.* 2016;25:243–249.

45. Kumar N, Chowdhary A, Gudaparthi O, Patel NG, Soni SK, Sharma P. A simple and highly efficient process for synthesis of Gefitinib and its intermediate. *Indian J Chem*. 2014;53B:1269–1274.
46. Venkatesh P, Pandeya SN. Synthesis, characterization and anti-inflammatory activity of some 2-amino benzothiazole derivatives. *Int J ChemTech Res*. 2009;1(4): 1354–1358.
47. Sathe BS, Jaychandran E, Jagtap VA, Sreenivasa GM. Anti-tubercular activity of fluoro benzothiazole comprising potent thaizolidinone. *Int J Pharma Bio Sci*. 2010; 1(4):495–500.
48. Wang Z, Shi XH, Wang J, et al. Synthesis, structure activity relationships and preliminary antitumor evaluation of benzothiazole-2-thiol derivatives as novel apoptosis inducers. *Bioorg Med Chem Lett*. 2011;21(4):1097–1101.
49. Guillemont JEG, Motte MMS, Koul A, Lounis N. *Antimycobactrial Compounds. WO096300*. 2014.
50. Pellet A. *Nitrobenzothiazole Derivatives, Their Preparation, and Their Use in Treating Tuberculosis*. 2012:2–3. WO069743.
51. Djuidje EN, Barbari R, Baldisserotto A, et al. Benzothiazole derivatives as multifunctional antioxidant agents for skin damage: structure-activity relationship of a scaffold bearing a five-membered ring system. *Antioxidants*. 2022;11(2):407.
52. Meltzer-Mats E, Babai-Shani G, Pasternak L, et al. Synthesis and mechanism of hypoglycemic activity of benzothiazole derivatives. *J Med Chem*. 2013;56(13): 5335–5350.
53. Bhagdev K, Sarkar S. Benzothiazole: as an antidiabetic agent. *Annals of R.S.C.B*. 2021; 25(4):20269–20285.
54. Usman B, Mahajan S, Mehta M, et al. Prediction of alpha-glucosidase inhibition activity for the management of type 2 diabetes using the prediction of activity spectra of substances software. *Asian J Pharm*. 2019;13(3):225–232.
55. Hussain S, Taha M, Rahim F, et al. Synthesis of benzimidazole derivatives as potent inhibitors for α-amylase and their molecular docking study in management of type-II diabetes. *J Mol Struct*. 2021;1232, 130029.
56. Mor S, Sindhu S. Synthesis, Type II diabetes inhibitory activity, antimicrobial evaluation and docking studies of indeno[1,2-c]pyrazol-4(1H)-ones. *Med Chem Res*. 2020;29(1):46–62.
57. Gong Z, Peng Y, Qiu J, Cao A, Wang G, Peng Z. Synthesis, *in vitro* α-glucosidase inhibitory activity and molecular docking studies of novel benzothiazole-triazole derivatives. *Molecules*. 2017;22(9):1555.
58. Keri RS, Quintanova C, Marques SM, Esteves AR, Cardoso SM, Santos MA. Design, synthesis and neuroprotective evaluation of novel tacrine-benzothiazole hybrids as multi-targeted compounds against Alzheimer's disease. *Bioorg Med Chem*. 2013; 21(15):4559–4569.
59. DeKosky ST, Marek K. Looking backward to move forward: early detection of neurodegenerative disorders. *Science*. 2003;302(5646):830–834.
60. Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. *Neurology*. 1998;50:136–145.
61. Cummings JL. Cholinesterase inhibitors: a new class of psychotropic compounds. *Am J Psychiatr*. 2000;157(1):4–15.
62. Majo VJ, Prabhakaran J, Mann JJ, Kumar JSD. An efficient palladium catalyzed synthesis of 2-arylbenzothiazoles. *Tetrahedron Lett*. 2003;44:8535–8537.
63. Kochanowska-Karamyan AJ, Hamann MT. Marine indole alkaloids: potential new drug leads for the control of depression and anxiety. *Chem Rev*. 2010;110(8): 4489–4497.
64. Fu Y, Gong J-X, Wang Z-Z, Xiao W, Zhang H-Y, Guo Y-W. Isorhapontigenin prevents β-amyloid-associated cognitive impairments through activation of the PI3K/AKT/ GSK-3β pathway. *Bioorg Med Chem Lett*. 2015;25:216.
65. Hassan MZ, Khan SA, Amir M. Design, synthesis and evaluation of *N*-(substituted benzothiazol-2-yl) amides as anticonvulsant and neuroprotective. *Eur J Med Chem*. 2012;58:206–213.
66. Unverferth K, Engel J, Höfgen N, et al. Synthesis, anticonvulsant activity, and structure-activity relationships of sodium channel blocking 3-aminopyrroles. *J Med Chem*. 1998;41(1):63–73.
67. Waterbeemed V. Quantitative approaches to structure activity relationships. In: Wermuth CG, ed. *The Practice of Medicinal Chemistry*. vol. 4. London: Academic Press; 1996:367.