Chemistry and Biological Activities of 1,3-Benzothiazoles

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Abstract: Benzothiazoles and its derivatives are an important group of heterocyclic compounds that exhibit a wide range of pharmacological properties such as antitumor, antimicrobial, antidiabetic, anticonvulsant and anti-inflammatory. These different biological applications for benzothiazole compounds have motivated new efforts in search for novel derivatives with improved biological activity and diverse applications in pharmaceutical industry. Owing to the importance of this system, the aim of this review is to highlight aspects reported on the chemistry and biological activity of benzothiazoles during the past few years (2000-2010).

Keywords: 1,3-Benzothiazoles, synthesis, biological activity, drugs.

INTRODUCTION

Heterocyclic compounds comprise a class of substances of great synthetic interest due to their occurrence in natural products and pharmacologically active molecules [1-3]. Several heterocyclic systems with five-membered rings fused to a benzene nucleus have been reported to possess a wide range of biological activities. Benzothiazole-based compounds are important pharmacophores with diversified pharmacological activities like antitumor, antimicrobial, antidiabetic, anticonvulsant and anti-inflammatory [4,5]. Thus, continuous efforts have been made to develop new methods for their construction.

1,3-Benzothiazoles represent an important class of heterocyclic compounds that possess an atom of sulfur at position 1 and an atom of nitrogen at position 3 (Fig. **1**). Benzothiazoles derivatives have been studied extensively for their potential broad spectrum of biological activity. Owing to the importance of this system, the aim of this review is to present the main aspects of the chemistry and biological properties of this heterocyclic core during the past few years (2000-2010).

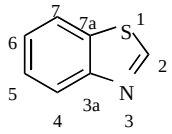
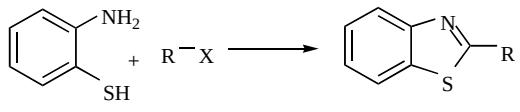


Fig. (1). General structure for benzothiazole nucleus.

Synthetic Procedures for Benzothiazoles

The most commonly used synthetic route for the synthesis of benzothiazoles involves the condensation of 2-aminothiophenols with aldehydes [6] or carboxylic acids and its derivatives (Scheme **1**) [7].

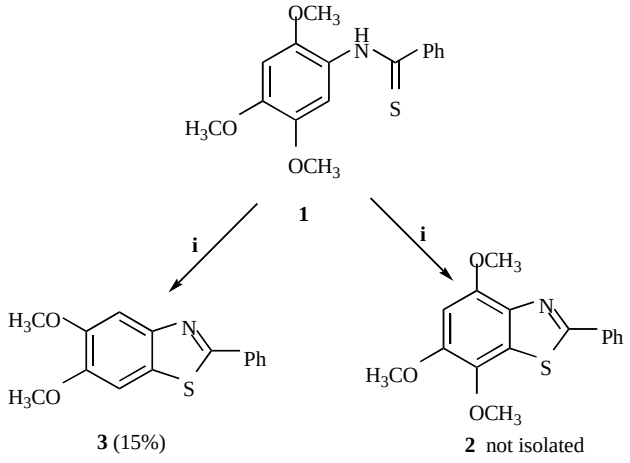


R= alquil or aryl
X= CHO, COOH, COCl,
COOR, $CONH_2$, CN

Scheme 1. Synthesis of benzothiazoles from 2-aminothiophenols.

Particularly for the condensation of 2-aminothiophenols with aldehydes numerous catalysts have been reported such as I_2, TMSCl and PCC [8]. Regarding the direct condensation of carboxylic acids with 2-aminothiophenols the use of PPA, PPE and P_2O_5/CH_3SO_3H (1/10) have been described [7]. Although it is a classic route, 2-aminothiophenols are not easily accessible and many of these methods also have limitations such as drastic reaction conditions, long times, possibility of side reactions and tedious work-up. So, many efforts have been made in order to develop new convenient methods for the synthesis of this important scaffold.

Downer and Jackson have described an efficient route to synthesize benzothiazoles from *o*-methoxythiobenzamides *via ipso* substitution of a methoxy group in an aromatic system [9]. Authors also investigated the mechanism of Jacobson synthesis of benzothiazoles reported in 1886 [10]. According to the method previously described by Jacobson, after treatment of thiobenzamide **1** with potassium ferricyanide, $K_3Fe(CN)_6$, in basic medium, it would be expected to obtain, in high yield, the benzothiazole **2**. However, the cyclization occurred from *ipso* substitution of a methoxy group, affording the unexpected benzothiazole **3** in low yield (Scheme **2**).



i: $K_3Fe(CN)_6$ 20% aq. / 1.5M NaOH, r.t., 15h

Scheme 2. Benzothiazole **3** obtained *via ipso* substitution of a methoxy group.

In order to investigate this result and considering the presence of three electron donating groups on the primary ring of **1,** the authors submitted three other similarly activated thiobenzamides (**4-6**) to the same reactions conditions (Scheme **3**). The occurrence of cyclization with substitution of the *ortho*-methoxy group was confirmed and the products **7-9** were also obtained in low yields.

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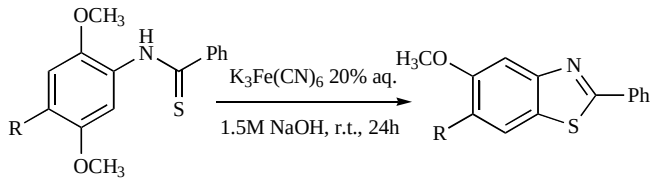
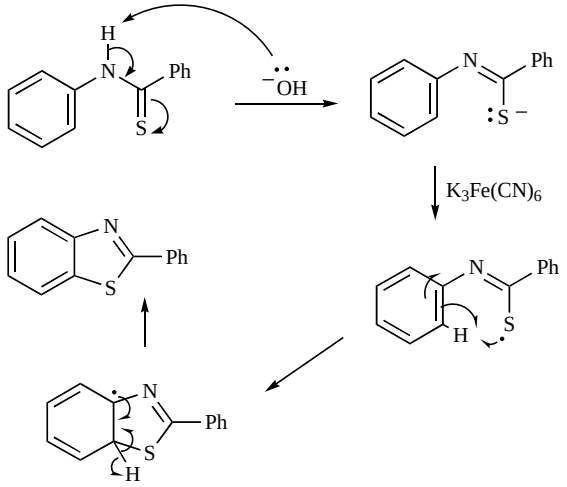


4: R= NH_2
5: R= NHTs
6: R= NHAc

7-9 (5-10%)

Scheme 3. Cyclization reactions *via ipso* substitution of methoxy group.

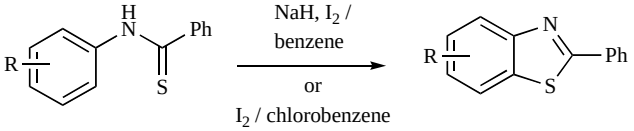
Based on the two mechanisms proposed in the literature for the Jacobson synthesis, it was considered that the one proposed by Stevens *et al*. (Scheme **4**) [11] seemed the most probable attempt to explain the cyclization through *ipso* substitution of the methoxy group, since the other proposed by Metzger and Plank [12] would require the loss of the methoxy group as a cation.



Scheme 4. Mechanism proposed by Stevens *et al.* involving the formation of a thiol radical.

Based on this proposed radical mechanism, Jackson and Downer tested these same cyclization reactions employing AIBN as radical initiator and the benzothiazoles **3**,**7-9** were obtained with better yields, 81-98%, suggesting that the Jacobson and AIBN-induced cyclizations were occurring from distinct reaction intermediates. Therefore, it was concluded that the nature of the groups and the degree of substitution on the primary ring have determined the way of the reactions. For example, the presence of one or two electron donating groups on the structure of *o*-methoxythiobenzamides directs the Jacobson cyclization with replacement of the *ortho* hydrogen. On the other hand, the presence of three electron donating groups, leads to products of cyclization from *ipso* substitution of the *ortho* methoxy group.

More recently, the same authors have studied the use of iodine in the formation of benzothiazoles from thiobenzamides without an *ortho* alkoxy or ester group (Scheme **5**). Treatment of thiobenzamides **10-12** with iodine in refluxing chlorobenzene or heating with sodium hydride and iodine in refluxing benzene for 2h led to the corresponding benzothiazoles **13-15** in yields of up to 87%. However, treatment of non-substituted thiobenzamides or bearing an electron-attractive group, such as bromine, didn't lead to the expected benzothiazoles, probably by compromising the nucleophilic attack involved in the reaction [13]. They also observed that in the same reaction conditions *ortho*-alkoxy or *ortho* ester thiobenzamides yielded the corresponding 2-phenylbenzoxazoles.



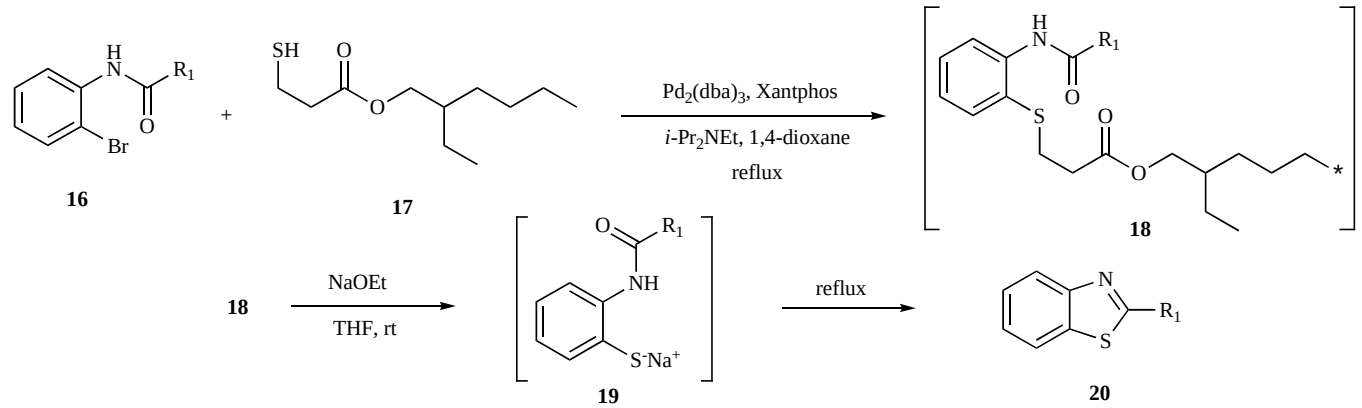
10: R= 3-OMe
11: R= 4-OMe
12: R= 3,4-OMe

13-15 (27-87%)

Scheme 5. Synthesis of benzothiazoles mediated by iodine.

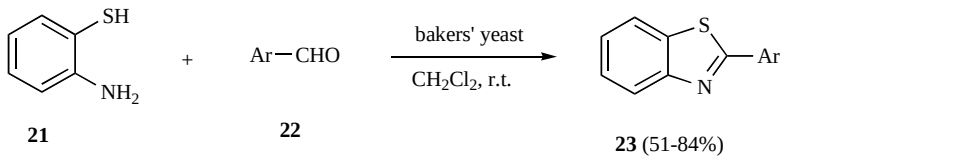
Later, Itoh and Mase have developed a new synthetic procedure for benzothiazoles from 2-bromoanilides with a thiol surrogate coupling reaction (Scheme **6**) [14]. Initially, the process involves the formation of sulfite **18** from reaction between 2-bromoanilides **16** and 2-ethylhexyl 3-mercaptopropionate **17**, as a thiol surrogate, under $Pd_2(dba)_3$/Xantphos. After that, **18** is treated with NaOEt in THF at room temperature affording the corresponding sodium thiolate **19** that suffer intramolecular cyclization under reflux leading to the desired benzothiazoles **20** in good yields.

From these studies, it was concluded that the yields and the conditions for the intramolecular condensation depend on the nature of the substrates. For example, substrates containing an electron-deficient or neutral carbonyl group of amides were prompt cyclized under basic conditions at reflux temperature. On the other hand, amides that possessed electron-rich groups underwent cyclization under basic conditions with quite low yield. The reactions were also tested under acidic conditions and it was found that in this media



R_1= Me (82%)
R_1= 3-Me-4-NO_2Ph (75%)
R_1= 4-ClPh (83%)
R_1= 4-MeOPh (low)

Scheme 6. Synthetic route from 2-bromoanilides *via* Pd-catalyzed.



21 **22** **23** (51-84%)

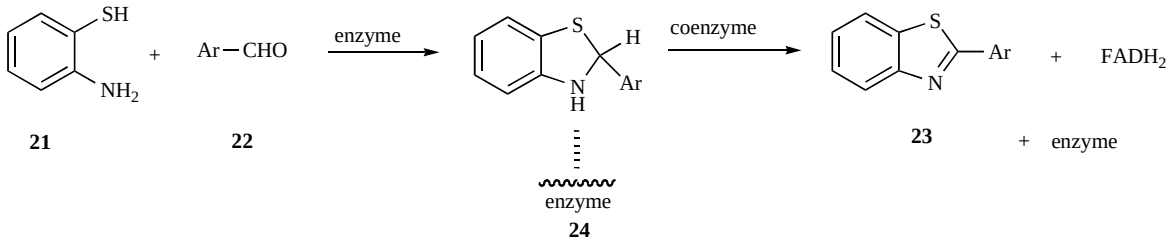
Ar= C_6H_6, 4-$CH_3OC_6H_4$, 4-$CH_3C_6H_4$, 3-$(CH_3)_2NC_6H_4$, 2-HOC_6H_4,2-ClC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-FC_6H_4, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 2-pyridyl, 2-furyl

Scheme 7. Synthesis of benzothiazoles catalyzed by baker´s yeast.

the benzothiazoles were obtained with better yields and shorter reaction time. The interesting point of this process is the possibility to obtain a variety of 2-substituted benzothiazoles from varying the amido groups of the 2-bromoanilides.

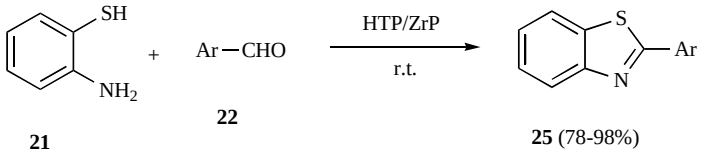
In order to improve the yields and also the laborious reactions conditions, other new synthetic methodologies to obtain benzothiazoles were developed. Pratap *et al.* have described an some heterocyclic aldehydes **22** with 2-aminothiophenol **21** (Scheme **7**). No significant substituent effect was observed on the yields of the products.

Authors have also reported that the mechanism involving this catalysis is probably related to its enzymes that accelerate the condensation by forming either an initial enzyme-2-aminothiophenol non-covalent complex or an enzyme-aldehyde



21 **22** **24** **23** + enzyme

Scheme 8. Proposed mechanism of catalysis of bakers' yeast.



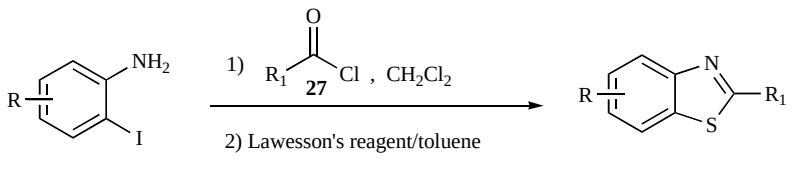
21 **22** **25** (78-98%)

Ar= Ph, 2-$CH_3OC_6H_4$, 4-$CH_3OC_6H_4$, 2-HOC_6H_4, 4-HOC_6H_4, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 2-Furyl, 2-Pyridyl, C_5H_{11}

Scheme 9. Synthesis of benzothiazoles from HTP/ZrP catalysis.

efficient and economic synthesis for 2-substitutedbenzothiazoles from 2-aminothiophenol and aldehydes in good yields mediated by the biocatalyst bakers' yeast [15]. Initially, they promoted a model reaction between *p*-anisaldehyde and 2-aminothiophenol catalyzed by bakers' yeast in different solvents in order to evaluate its effect. After selecting dichloromethane as the better solvent, they synthesized a series of 2-arylbenzothiazoles **23** in moderate to good yields from the cyclocondensation of different benzaldehydes and complex, that generate the intermediate **24** and posteriorly, coenzymes such as FAD, promote the dehydrogenation and subsequent abstraction of a proton (Scheme **8**).

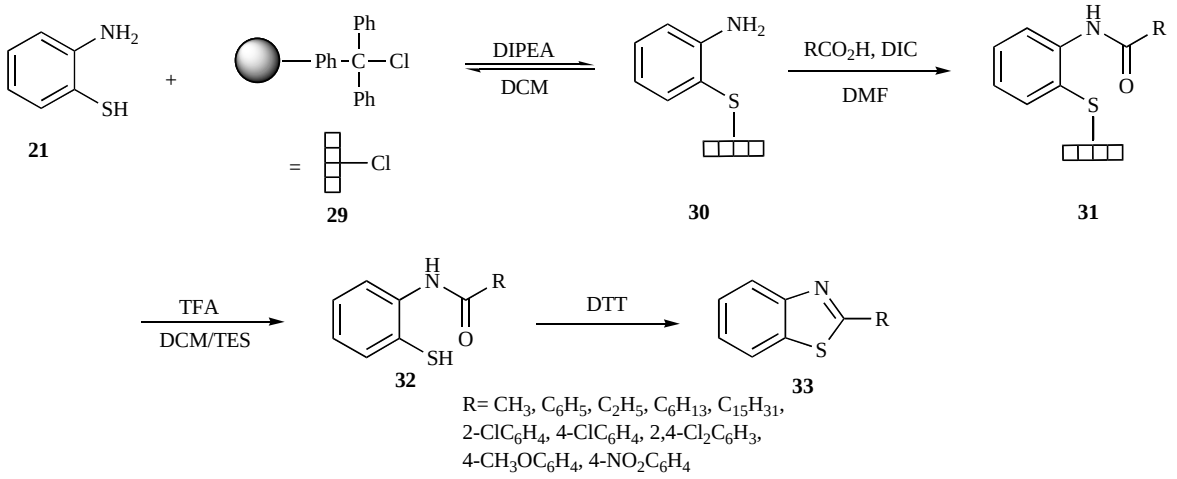
Aliyan *et al*. reported an efficient synthesis of 2-arylbenzothiazoles from reactions of 2-aminothiophenol **21** with various aldehydes using tungstophosphoric acid impregnated zirconium phosphate as catalyst in absence of solvent (Scheme **9**) [16].



26 **28** (75-95%)

R= H, 4-CH_3, 4-F, 4-CF_3
R_1= C_6H_5, 4-$CH_3OC_6H_4$, 3-$CH_3C_6H_4$, 2-$CH_3OC_6H_4$, 3,5-$(CF_3)_2C_6H_3$, CH_3, 2-furyl

Scheme 10. Synthesis of benzothiazoles using Lawesson's reagent.



Scheme 11. Synthesis of benzothiazoles in solid phase.

The best yields were achieved with a molar ratio of 2-aminothiophenol to aldehydes of 1.5:1 in the presence of 40% HTP/ZrP (5 mol%) at room temperature for 15 minutes under solvent-free conditions. They also observed the possibility of recovering the catalyst in spite of it becoming less active.

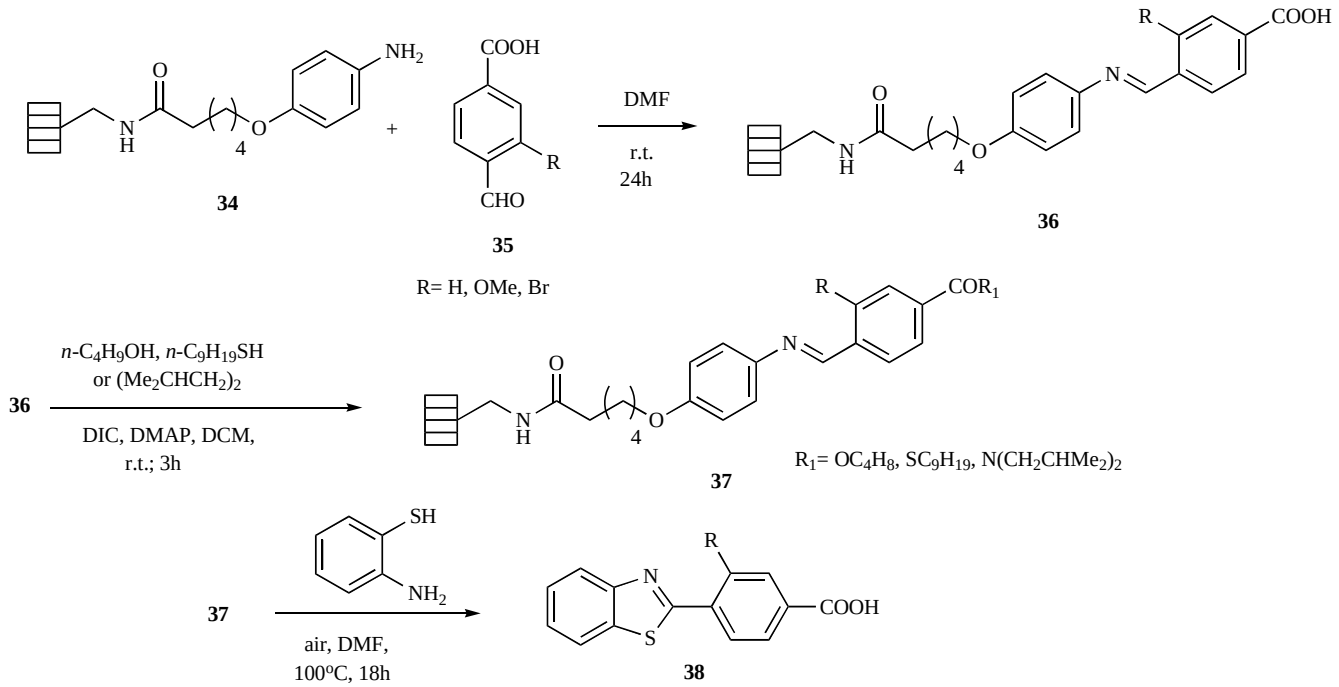
The main advantages of this methodology are the short reaction times, high yields, mild conditions and the use of an inexpensive and green catalyst.

Ding and co-workers have developed a new synthetic procedure to obtain benzothiazoles from cascade one-pot reactions of 2-iodoanilines **26** with acid chlorides **27** in the presence of Lawesson's reagent. The expected benzothiazoles **28** were obtained in good yields after the addition of DBU (Scheme **10**) [17].

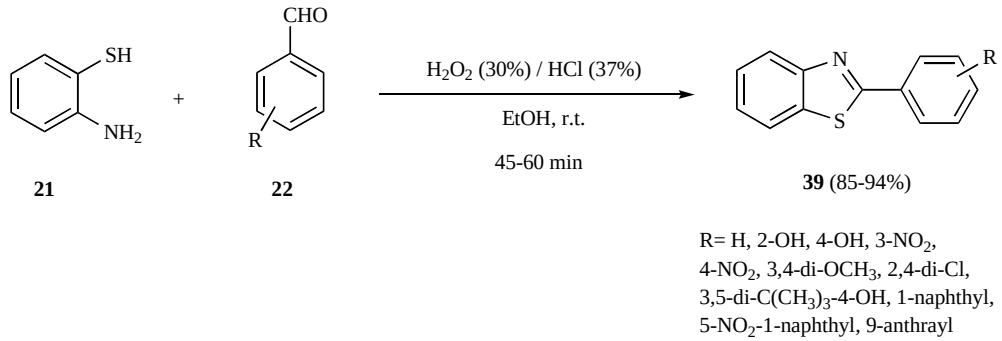
The authors also studied these reactions in the presence of CuI, 1,10-phenanthroline as ligand and a base (DABCO or DBU), a well-known procedure for the synthesis of heterocycles via copper-catalysis [18,19]. It was found that even in the absence of CuI the reactions have been occurred satisfactory.

Mourtas *et al.* have described the synthesis of 2-substituted benzothiazoles through solid phase synthesis. Treatment of 2-aminothiophenol **21** with the trityl-chloride resin **29** in diisopropylethylamine (DIPEA) and dichloromethane (DCM) led to the corresponding resins **30**. After that, these resins **30** were acylated with acyl- or aroyl chloride and acid anhydrides affording the acyl derivatives **31** that were then cleaved with trifluoroacetic acid solutions in DCM. Further treatment of the resin-released intermediate **32** with dithiothreitol (DTT) in DMF/methanol yielded the corresponding benzothiazoles in 90-95% (Scheme **11**) [20].

Hioki *et al.* have reported the combinatorial synthesis of benzothiazoles using a traceless aniline linker (Scheme **12**). According to this process, resin-bound azomethines **36** could be obtained from condensation between 4-formylbenzoic acids **35** and an aniline linker **34** on the solid support. Further reactions of **36** with alcohols, thiols and amines generate the respective azomethines **37** which are cleaved by 2-aminothiophenols under neutral conditions to afford the respective benzothiazoles **38** [21]. The interesting point of this process in comparison with others that



Scheme 12. Combinatorial synthesis of benzothiazoles using a traceless aniline linker.

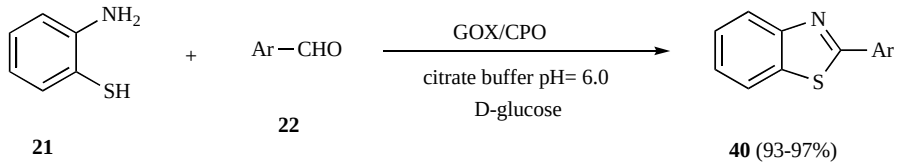


Scheme 13. Synthesis of 2-substituted benzothiazoles using H_2O_2/HCl system.

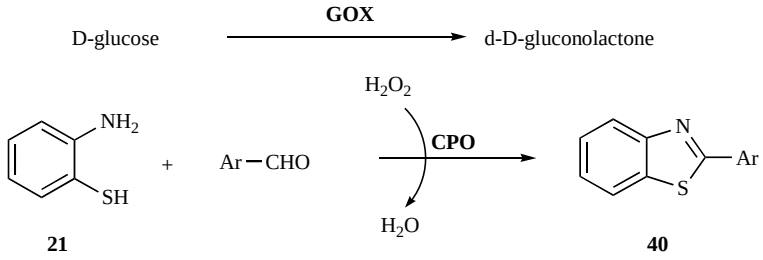
also involve solid-phase synthesis is the cleavage of the products without the use of oxidants.

A general procedure for the synthesis of benzothiazoles has been reported by Guo and co-workers from 2-aminothiophenol and arenealdehydes using H_2O_2/HCl system (Scheme **13**) [22]. The between arenealdehydes and 2-aminothiophenol using glucose oxidase (GOX)-chloroperoxidase (CPO) catalytic enzymatic system under oxygen atmosphere (Scheme **14**) [23].

The glucose oxidase catalyses the oxidation of D-glucose by oxygen to δ-D-gluconolactone and hydrogen peroxide. The



Scheme 14. Bienzymatic synthesis of benzothiazoles.

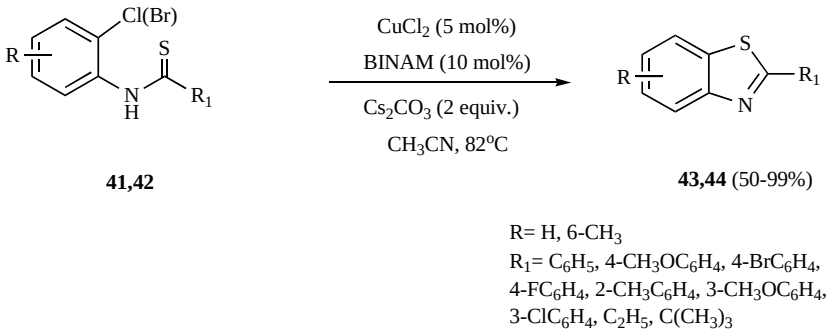


Scheme 15. Catalytic mechanism of GOX/CPO enzymatic system.

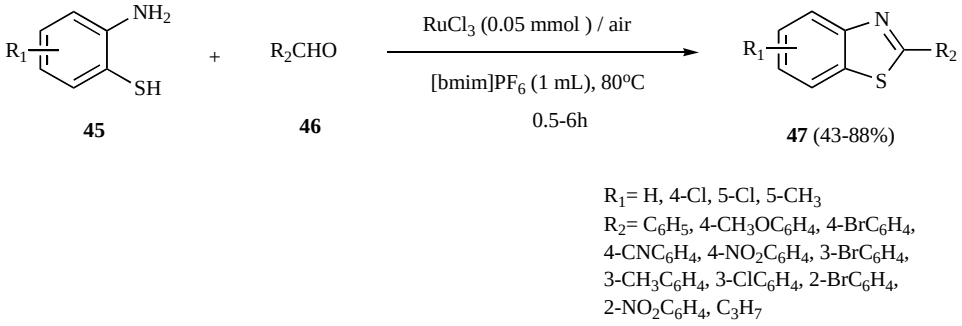
methodology described is simple, allows quick and easy isolation of the products, short reaction time and excellent yields.

Kumar and co-workers have described an efficient and environmental attractive methodology for 2-arylbenzothiazoles employing biocatalysis. The procedure involves the reaction hydrogen peroxide generated *in situ* is then reduced by the peroxidase for the synthesis of benzothiazoles (Scheme **15**).

Jaseer *et al.* have reported a synthetic method for 2-aryl and 2-alkyl benzothiazoles through intramolecular cyclization of various *N*-(2-chlorophenyl)benzothioamides **41** and *N*-(2-



Scheme 16. Synthesis of benzothiazoles using copper(II)-BINAM as catalyst.



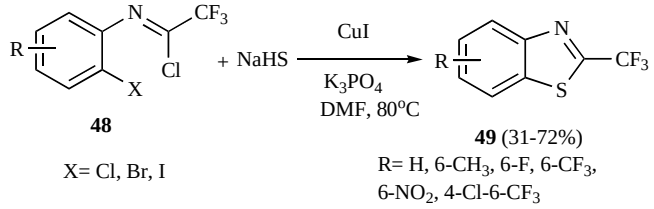
Scheme 17. Synthesis of benzothiazoles using $RuCl_3$ as catalyst.

bromophenyl)benzothioamides **42** under mild conditions using copper(II)-BINAM as catalyst [24]. In this study, they have determined the effect of different ligands and copper salts, various solvents and bases and the best results were obtained using the optimized conditions showed in Scheme **16**.

Fan and co-workers have developed a general procedure to obtain 2-substituted benzothiazoles using $RuCl_3$ as catalyst in oxidative condensations of 2-aminothiophenols with aldehydes. Authors have studied the reaction in different conditions (catalysts, solvents, temperature and reaction time) using as standard reaction the condensation between benzaldehyde and 2-aminothiophenol. From the optimized reaction conditions, they have synthesized a series of benzothiazoles in moderate to good yields (Scheme **17**) [25].

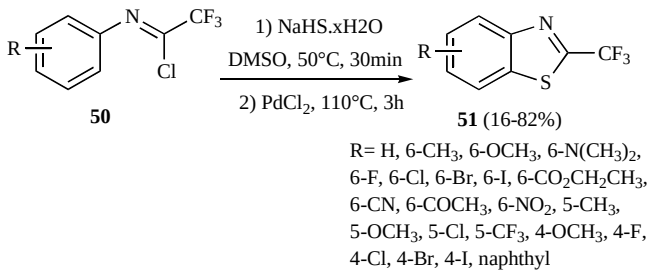
The advantages of this method include the use of a green solvent, the 1-butyl-3-methylimidazolium hexafluorophosphate - [bmim]PF_6, the use of air as oxidant and the possibility of reusing $RuCl_3$/[bmim]PF_6.

Li *et al.* have described a new one-pot methodology for 2-trifluoromethyl benzothiazoles by copper-catalyzed thiolation annulations of 1,4-dihalides with sodium hydrosulfide. According to this process, treatment of a series of 2,2,2-trifluoro-*N*-(2-haloaryl)acetimidoyl chlorides **48** with NaHS in the presence of CuI and K_3PO_4 led to the corresponding benzothiazoles **49** in moderate to good yields. The lower yields have been obtained from the less reactive (chlorophenyl) chlorides (Scheme **18**) [26].



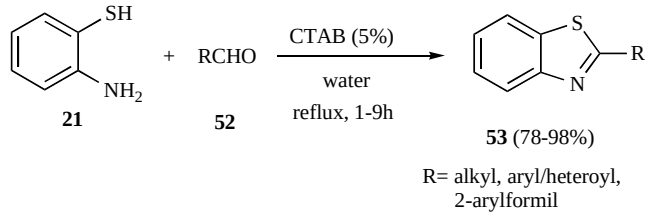
Scheme 18. Synthesis of 2-trifluoromethyl benzothiazoles.

In the same year, Zhu and co-workers reported a similar methodology for the synthesis of 2-trifluoromethylbenzothiazoles from trifluoroimidoyl chlorides **50** and sodium hydrosulfide using $PdCl_2$ in DMSO (Scheme **19**) [27]. It should be noted that the usage of this catalyst allows the reaction to occur without any other additives or oxidants.



Scheme 19. Synthesis of 2-trifluoromethyl benzothiazoles using $PdCl_2$ as catalyst.

Yang and co-workers have reported a practical and green procedure for the synthesis of 2-substituted benzothiazoles in good to excellent yields from the condensation of 2-aminothiophenol with different aldehydes using cetyltrimethyl ammonium bromide (CTAB) as catalyst in water (Scheme **20**) [28]. The main advantages of this method are the use of a cheap catalyst, water as solvent and simple work-up.



Scheme 20. Synthesis of benzothiazoles using CTAB as catalyst.

Biological Properties

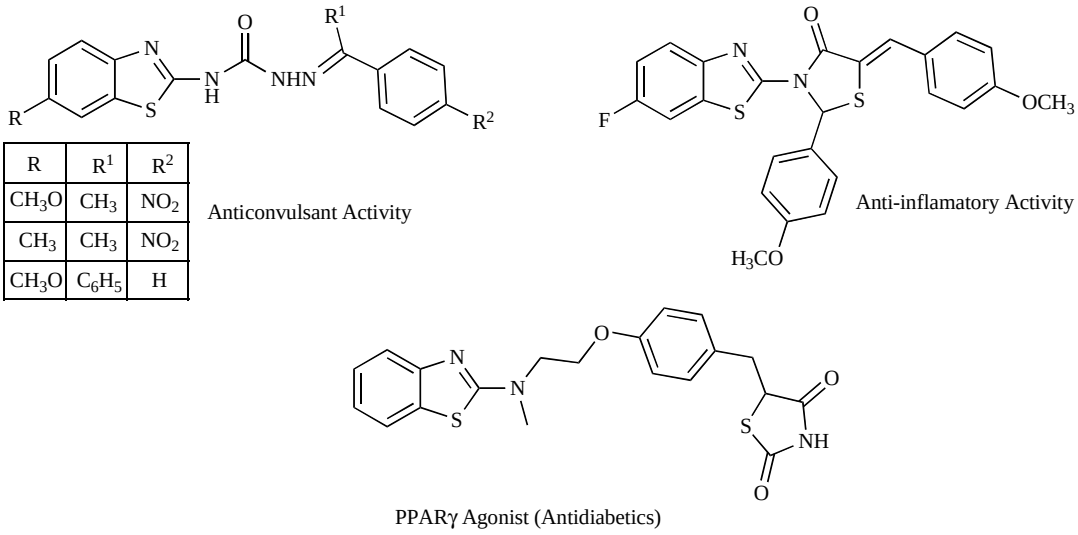
Since the discovery of Zopolrestat as a potent aldose reductase inhibitor back in 1991 [29] and its posterior approval for clinical use, diverse biological activities for the benzothiazole core have been reported by many authors. In this part we will highlight some of the efforts made towards the discovery of novel antimicrobial and anticancer leads. It should be noted, though, that some researchers are focusing their efforts on the development of new drugs containing the potentially active benzothiazole moiety for the treatment of various other diseases [30-35] (Fig. **2**).

Antimicrobial Activity

Bondock *et al.* [36] have synthesized a series of novel thiophenes, pyrazoles and thiazoles derivatives containing the benzothiazole moiety that were screened for their antibacterial activity against some bacterial and fungic strains.

It was found that compounds containing the benzothiazole moiety combined with different thiophenes and pyrazoles exhibited improved antibacterial activity when compared to the ones obtained by the combination of thiazoles with the benzothiazole moiety. Several of the substances reported by the authors (**54**-**59**) displayed promising antibacterial activity with MIC values equivalent to the reference drugs. Also, substances **60** and **61** have shown promising results as antifungal agents against *F. oxysporum* and *A. fumigatus*, respectively, with a MIC value of 6.25 µg/mL when compared to the reference drug cycloheximide (Fig. **3**).

Aggarwal *et al.* have reported in 2006 a series of 2-(pyrazo-2-yl)benzothiazoles that possess high activity against diverse bacterial strains [37]. Later, Moy *et al.* have identified, a 6-chloro-2-(pyrazo-2-yl)benzothiazole capable of curing *C. elegans* nematodes infected



R	R^1	R^2
CH_3O	CH_3	NO_2
CH_3	CH_3	NO_2
CH_3O	C_6H_5	H

Fig. (2). Some biologically active benzothiazoles.

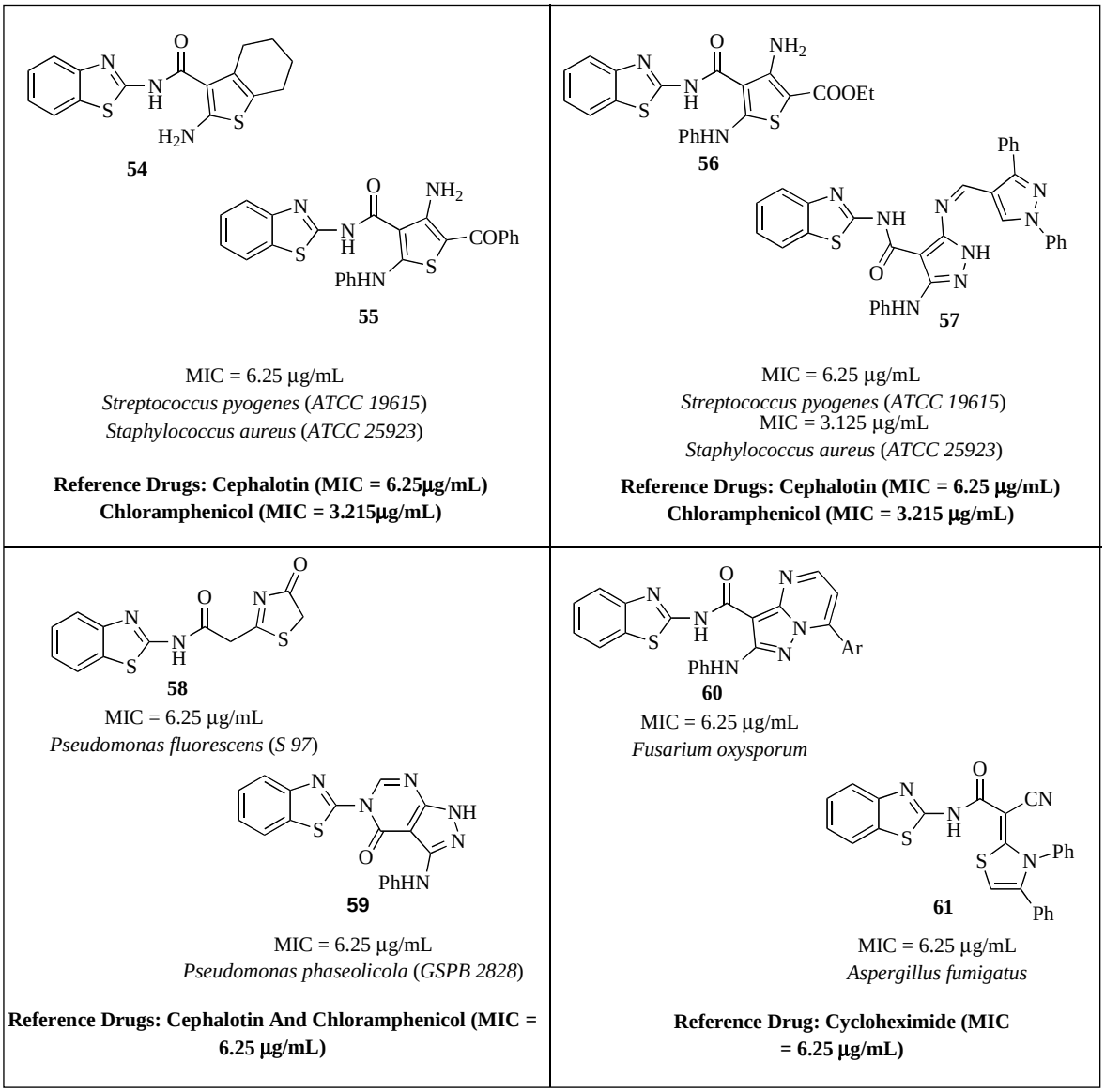
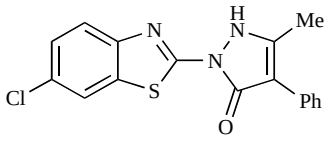
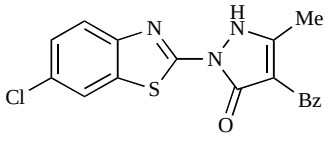


Fig. (3). Benzothiazoles with antimicrobial activity reported by Bondock *et al.*

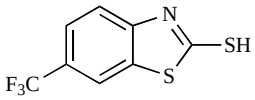


62

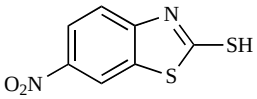


63

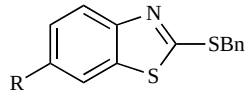
Fig. (4). Example of benzothiazoles with potent antibacterial activity.



64



65



No Antimicrobial activity observed

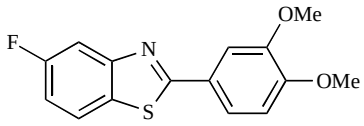
R = $CH(CH_3)_2$; Cl; CH_3; OCH_3; CF_3; F; H; NH_2; OCH_2CH_3; NO_2

Fig. (5). Benzothiazoles containing SH and SBn substituent at position 2.

with *Enterococcus fecalis* [38]. Recently, in an attempt to further understand the antibacterial activity associated with this kind of structure, Stella *et al*. conducted a systematic structure-activity relationship study [39]. The authors have found that a Cl-atom at the position 6 of the benzothiazole core and an aromatic nucleus such as phenyl or benzyl on the pyrazole moiety are essential for the biological activity. Their strategy also resulted in the screening of the potent antibacterial compounds **62** and **63** with MIC values of 3.43 and 3.30 μM, respectively, against *S. aureus* (*ATCC 65388*) and *Pseudomonas aeruginosa* (*PAO1*) (Fig. **4**).

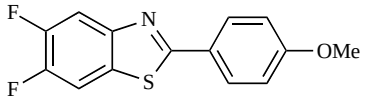
These results suggest the importance of the molecular hybridization strategy involving the benzothiazole core in the search for new antimicrobial lead compounds.

Franchini *et al.* [40] synthesized a series of compounds in order to explore the substituent effect at positions 2 and 6 of the benzothiazole core on the antibacterial activity. It was noted that small structure changes at position 6 did not alter the biological activity significantly for those screened substances, a result that differs from the ones reported by Stella *et al*. for their benzothiazole derivatives, with the exception of compounds **64** and **65** (Fig. **5**)



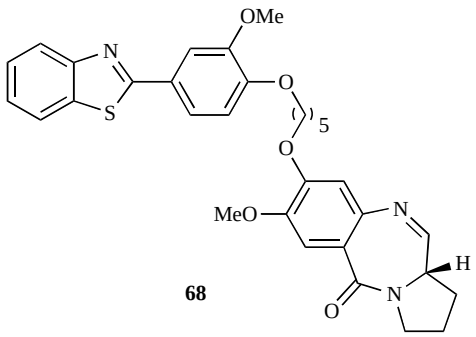
66

GI_{50} < 0.1 nM
MCF-7 and MDA 468
(Breast Cancer)



67

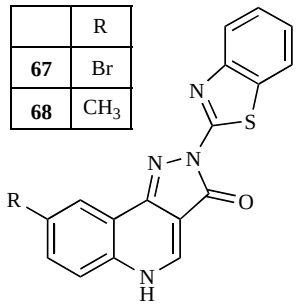
20.46% Growth Inhibition at 100mM
MCF-7 (Breast Cancer)



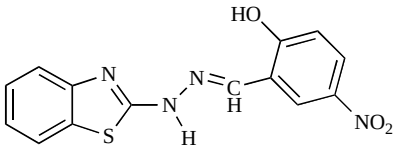
68

GI_{50} = 17.3 - 346.7 nM
Various Cancer Cell Strains

	R
67	Br
68	CH_3



69: IC_{50} = 1.6 mg/mL (MDAMB-435)
3.0 mg/mL (HL-60)
70: IC_{50} = 2.3 mg/mL (MDAMB-435)



71

IC_{50} = 0.52 mg/mL (HL-60)
4.40 mg/mL (MDAMB-435)

Fig. (6). Benzothiazoles derivatives as potential anticancer agents.

carrying a trifluoromethyl group and a nitro group at position 6, respectively. The former was described by the authors as a potent and selective inhibitor of *S. aureus* exhibiting MIC value of 3.12 μg/mL against the *ATCC 29213* strain and the latter was identified as an *Escherichia coli ATCC 8739* strain growth inhibitor with a MIC value of 25 μg/mL.

All compounds reported by Franchini *et al.* carrying an S-H moiety at the 2 position displayed at least moderate antibacterial activity against Gram Positive strains. In contrast, compounds bearing the S-Bn moiety did not show any antibacterial activity, a result that point out the importance of the substituent at position 2 for the biological activity of these structures.

Many other molecules containing the benzothiazole core have been reported as potential antimicrobial agents in the past few years [41-45].

Antitumor Activity

Cancer is, nowadays, the second main cause of death worldwide [46]. Its control depends on the development of novel and more powerful drugs since current chemotherapy lacks selectivity towards cancerous cells [47]. Researchers have been identifying many potential targets for the development of anticancer drugs, such as the proteins tyrosin kinase and toposisomerase I/II, DNA and cell structures like microtubules [48-50].

Bradshaw and co-workers have made large contributions in the field of antitumor benzothiazoles by reporting many molecules with interesting biological activity [51-54]. Among them, compound **66** was described as possessing potent and selective antiproliferative *in vitro* activity with GI_{50} lower than 0.1 nM (Fig. **6**). The mechanism of action underlying the biological properties of the reported molecule is still unknown. So far, biological assays have shown that the antitumor activity does not rely on the induction of CYP1A1 expression but is probably related to the binding of **66** to the aryl hydrocarbon receptor [52,54]. Bhuva & Kini have conducted a molecular docking study in attempt to correlate the *in vitro* cytotoxic activity of some 2-phenyl-1,3-benzothiazoles against MCF-7 human breast cancer cell line to the inhibition of the epidermal growth factor receptor (EGFR) tyrosine kinase [50]. Unfortunately, no correlation between the *in vitro* activities and the proposed docking study could be observed and, therefore, no conclusion could be drawn on the molecules mechanism of action since the highest negative dock score was obtained with structure **67** (Fig. **6**), the least active compound tested.

Kamal *et al.* have also performed molecular docking studies in attempt to correlate the anticancer *in vitro* activity of some compounds with their DNA-binding affinities. In this case, the authors could successfully observe that the compounds binding affinity had dependence on the linker length and on the sulfur atom on the benzothiazole nucleus **68** (Fig. **6**) [55].

Recently, our research group reported novel benzothiazoles derivatives as potential antitumorals. Compounds **69** and **71** exhibited moderate to good *in vitro* activity against the human cancer cell lines MDAMB-435 (breast cancer) and HL-60 (leukemia). Compound **70** exhibited good activity against MDAMB-435 (Fig. **6**) [56,57]. Further studies are underway in order to elucidate the molecular mechanism underlying the referred compounds toxicity

CONCLUSION

In this work, we reviewed the literature data of synthesis and biological activities of benzothiazoles during the past few years. Several methods have been developed for the preparation of this important scaffold in order to improve yields and reaction conditions, including the use of biocatalysts. Since the approval of Zopolrestat for clinical use as an aldose reductase inhibitor, diverse biological activity for the benzothiazole core have been reported such as antitumor, antimicrobial, antidiabetic, anticonvulsant and anti-inflammatory. Various benzothiazoles derivatives have been reported with equivalent or better activity than standard drugs and could become a new medicine on the market in the future. Therefore, benzothiazole derivatives represent promising compounds in the search of new lead molecules.

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