Review

Maged Henary*, Shirish Paranjpe and Eric A. Owens

Substituted benzothiazoles: synthesis and medicinal characteristics

Abstract: The attractiveness of heterocyclic compounds in medicinal chemistry has increased significantly in the past few decades as they have been proven to be highly active for a number of purposes. More specifically, the benzothiazole-containing heterocyclic compounds have shown great promise in the pharmaceutical industry. As continuation of our first review article of the synthesis and specific applications of various benzothiazole cyanine dyes (Henary, M.; Paranjpe, S.; Owens, E. A. Synthesis and application of benzothiazole containing cyanine dyes. Heterocycl. Commun. 2013, 19, 1–11), we will focus in this review on the synthesis and medical applications of alternate compounds that utilize the benzothiazole scaffold as a part of their molecular structure. Benzothiazole derivatives encompass an attractive heterocyclic class that exhibits exciting medicinal properties. The applicability of these heterocyclic structures includes positron emission tomography probes for monitoring Alzheimer's disease progression; furthermore, these compounds exhibit antimicrobial, anti-inflammatory, anticancer, antidiabetic and anti-HIV activity. Benzothiazole-containing heterocyclic structures are prominent throughout the literature and it is very important to acknowledge their efficacy and applicability. Herein, we review the recent developments covering the past few years concerning the advancements in synthetic methodology for the preparation of medicinally relevant benzothiazole-containing heterocyclic structures.

Keywords: benzothiazole; heterocyclic compounds; PET probes; review; synthesis.

***Corresponding author: Maged Henary,** Department of Chemistry, Georgia State University, Atlanta, 30303 GA, USA, e-mail: mhenary1@gsu.edu
Shirish Paranjpe and Eric A. Owens: Department of Chemistry, Georgia State University, Atlanta, 30303 GA, USA

Introduction

In the past few years, there has been an increasing interest in the chemistry of benzothiazole related compounds. These types of compounds have shown significant biological activities with a wide range of practical applications in the medical field. The following is a brief review of heterocyclic compounds containing the benzothiazole moiety and the corresponding advancements in the medical field utilizing this heterocyclic scaffold. Benzothiazole-containing heterocycles are becoming ever more prevalent within pharmacological research due to their amenability for diverse modifications with the potential for structurally tailoring the heterocycle towards exciting medical purposes. The broad spectrum of medical applications includes uses as anti-inflammatory agents and therapeutic compounds for combating cancer at very effective nanomolar concentrations; to begin, we introduce thioflavin-T and the synthesis of corresponding analogs for radiolabeled imaging of β-amyloid plaques in Alzheimer's disease patients for determining the presence, progression and prognosis of the disease.

Positron emission tomography (PET) probes

Benzothiazole derivatives are recognized as a promising class of compounds for the imaging of β-amyloid (Aβ) plaques. Thioflavin-T is a benzothiazole-containing imaging agent which shows fluorescence enhancement upon binding to aggregates of protein amyloids [1, 2].

Patients with Alzheimer's disease (AD) show the accumulation of β-amyloid fibrils in the brain [3, 4] and these fragments are then converted into hard plaques which directly contribute to the progression of AD. In recent studies, it has been suggested that by imaging these plaques, the severity and prognosis of AD can be estimated [5]. Among the existing molecular imaging technologies, PET possesses several advantages such as high intrinsic sensitivity, increased penetration depth and excellent spatial resolution while being fully quantitative [5]. PET is a widely recognized nuclear imaging technique employed to determine the severity of AD which makes use of nuclear probes containing positron emitters;

specifically, radiolabeled benzothiazole derivatives are finding great applicability as potential PET probes. Several synthetic approaches have been explored for synthesizing various derivatives of thioflavin-T (Figure 1), including uncharged derivatives [6]. The synthesis of an uncharged derivative, compound **1**, is shown in Equation 1. Commercially available substrate 6-Me-BTA-0 is allowed to react with methyl iodide in the presence of potassium carbonate to furnish compound **1** in 18% yield (the acronym BTA refers to benzothiazole-aniline backbone).

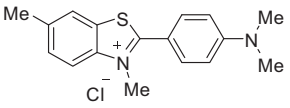


Figure 1 Structure of thioflavin-T.

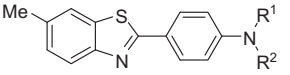
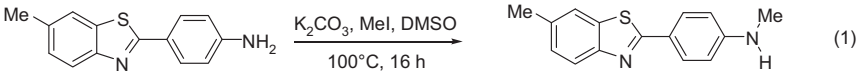


Figure 2 6-Me-BTA compounds.



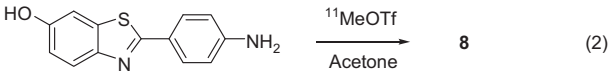
1 (1)

The neutral derivatives of thioflavin-T exhibit higher affinity towards Aβ than the cationic thioflavin-T as evident by the affinity for the inhibitor (K_i) values (Table 1). The 6-Me-BTA-1 was further radiolabeled with ^{11}C at the aniline nitrogen atom to form *N*-methyl-^{11}C analog of 6-Me-BTA-2 which demonstrated high uptake and improved clearance from the rodent brain during animal experimentation (Figure 2).

Klunk et al. at the University of Pittsburgh developed another benzothiazole-based compound, *N*-methyl-[^{11}C]2-[4′-(methylamino)phenyl]-6-hydroxybenzothiazole (compound **8** in Scheme 1), more popularly known as Pittsburgh compound B (PIB) that exhibits high binding affinity towards Aβ plaques [5]. Commercially available 4-methoxyaniline (**2**) was treated with *p*-nitrobenzoyl chloride in the presensce of pyridine to give compound **3** that was subsequently reacted with Lawesson's reagent. The resulting compound **4** was cyclized to the benzothiazole derivative **5** through the Jacobsen synthesis using potassium ferricyanide and aqueous sodium hydroxide. The methoxy group of compound **5** was demethylated in the subsequent step and the resultant hydroxy group was then protected by using the labile methoxymethyl group (product **6**), which on reduction with sodium borohydride in the presence of cupric acetate yielded compound **7**. The radiolabeling was then achieved by treatment with sodium hydride in *N,N*-dimethylformamide (DMF), then with ^{11}MeI followed by hydrolysis of the methoxymethyl group to furnish final compound **8** in approximately 15% radiochemical yield.

PIB retention in the brain of AD patients was found to be selectively higher than in non-AD patients. PIB is considered as a popular choice as radiotracer for PET imaging of Aβ plaques in AD patients [7].

A new and improved route for the synthesis of [^{11}C] PIB is shown in Equation 2 [8]. The reaction was carried out using [^{11}C] methyl triflate in the absence of base in acetone on the unprotected hydroxybenzothiazole base. This reaction resulted in increasing radiochemical yield for the compound to approximately 60% at the end of the synthesis; this important report is significant when designing compounds for clinical use to maximize the radiolabeled output for imaging.

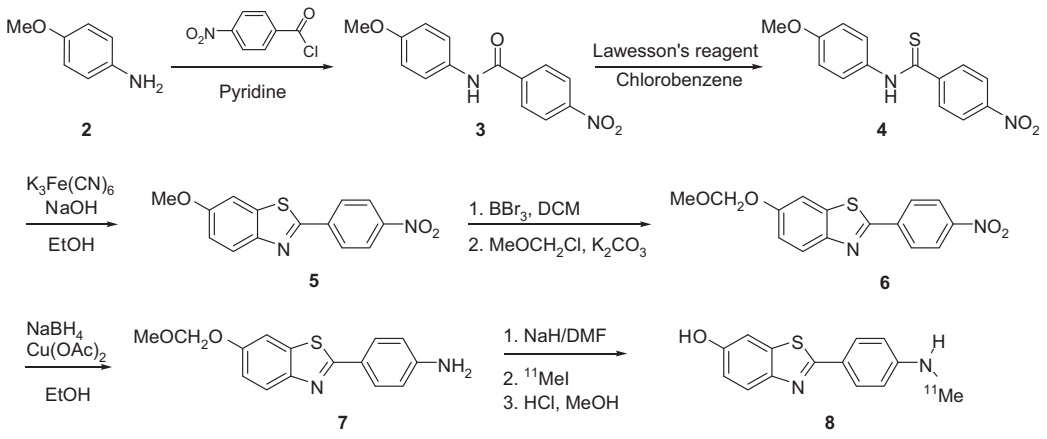


8 (2)

Table 1 K_i values of various benzothiazole derivatives.

Compound	K_i (nM)
Thioflavin-T	820±92
6-Me-BTA-2 ($R^1 = R^2 = Me$)	143±19
6-Me-BTA-1 ($R^1 = H$; $R^2 = Me$) (**1**)	20.3±3.0
6-Me-BTA-0 ($R^1 = R^2 = H$)	30.3±5.9

As shown above, several PET probes containing the benzothiazole core structure have been developed in the past few years. These probes have been modified based on the thioflavin-T structure and these derivatives were successfully demonstrated to bind Aβ plaques in the brain [9, 10].



Scheme 1

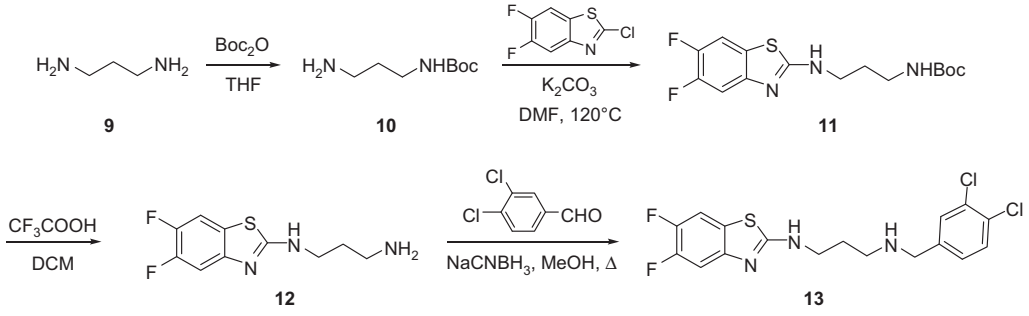
Pharmacological activities of benzothiazole compounds

The general benzothiazole structure is an important scaffold for drug development, and the corresponding derivatives have been extensively studied for their pharmacological applications. This idea of incorporating benzothiazole in designing medicinal compounds will be further expanded in the following sections, especially nuanced towards the ability to combat dangerous microbes, reduce inflammation, fight diabetes and improve the prognosis of patients diagnosed with HIV [11].

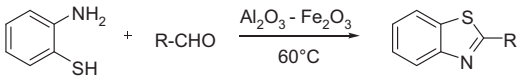
Antimicrobial activity

Ouyang et al. (Scheme 2) reported the synthesis of various benzothiazole derivatives bearing secondary amine functionalities as potential antimicrobial agents [12]. The synthesized compounds were evaluated for their antibacterial activity against American Type Culture Collection (ATCC) strains of *Staphylococcus aureus, Enterococcus faecalis* and *Escherichia coli* using the standard broth dilution method. Compound **13** demonstrated exciting inhibition properties towards Gram-positive bacteria as well as displayed promising behavior against drug-resistant bacteria such as methicillin-resistant *S. aureus* and vancomycin-resistant *E. faecalis*. Active compound **13** was synthesized as shown in Scheme 2. Commercially available propanediamine (**9**) was treated with Boc anhydride in tetrahydrofuran (THF), and the resulting mono-Boc protected compound **10** was then allowed to react with 2-chloro-5,6-difluorobenzothiazole in the presence of potassium carbonate to afford compound **11**. Compound **11** in the next step was hydrolyzed with trifluoroacetic acid to the corresponding primary amine **12** which, using the coupling strategy shown, was transformed into compound **13**.

Bandyopadhyay et al. synthesized a series of 2-substituted benzothiazoles using an Al_2O_3-Fe_2O_3 nanocatalyst as shown in Equation 3 [13]. The antibacterial activity of the synthesized compounds was evaluated using the Kirby-Bauer disc diffusion method. Compound **14** exhibited enhanced inhibitory activity against *Vibrio cholerae, Bacillus cereus* and *Shigella dysenteriae* compared with the well-known antibacterial drug ciprofloxacin. Compound **15** showed complete bactericidal activity within 24 h compared with 48 h for ciprofloxacin.



Scheme 2



(3)

14: R = 2-EtPh
15: R = 4-HOPh

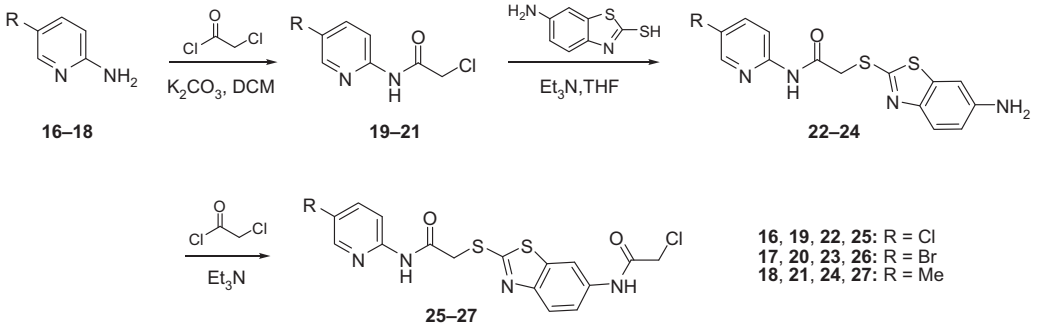
Anticancer properties

Shi et al. reported the synthesis of benzothiazole-2-thiol derivatives as potential anticancer agents. These compounds were evaluated against various cancer cell lines [14]. Synthesis was carried out as shown in Scheme 3. Commercially available amines **16–18** were reacted with 2-chloroacetyl chloride in the presence of potassium carbonate, and the resulting compounds **19–21** were reacted with 6-aminobenzothiazole-2-thiol to afford compounds **22–24**. In the last step of the synthetic scheme, compounds **22–24** were treated with 2-chloroacetyl chloride in the presence of triethylamine to furnish final compounds **25–27** in 70–90% yield. Compound **26** demonstrated promising activity against SKRB-3 human breast cancer cells (IC_{50} = 1.2 nM), SW620 colon cancer cells (IC_{50} = 4.3 nM), A549 (IC_{50} = 44 nM) and HepG2 hepatic carcinoma cells (IC_{50} = 48 nM) as well as induced apoptosis in HepG2 cancer cells.

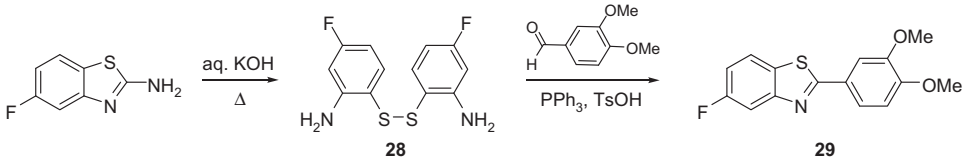
A series of 2-phenylbenzothiazoles was synthesized by Mortimer et al. and evaluated *in vitro* against breast and colon cancer cell lines [15]. The synthesis of the most efficient compound 2-(3,4-dimethoxyphenyl)-5-fluorobenzothiazole (**29**) was performed as shown in Scheme 4; the 2-amino-5-fluoro-benzothiazole was converted to compound **28** by treatment with an aqueous potassium hydroxide solution followed by acidification and air oxidation. The disulfide **28** was then treated with 3,4-dimethoxybenzaldehyde in the presence of triphenylphosphine and a catalytic amount of *p*-toluenesulfonic acid in refluxing toluene to yield final compound **29** in 88% yield. Compound **29** possesses antiproliferative activity against a breast cancer cell line (GI_{50} < 0.1 nM) and a colon cancer cell line (GI_{50} < 0.25 nM).

Activation of phosphoinositide 3-kinase (PI3K) is assumed to be one of the major causes for tumor growth in humans. PI3K signaling leads to activation of the mammalian target of rapamycin (mTOR) which in turn promotes uncontrollable cell growth. D'Angelo et al. reported the synthesis of aminobenzothiazole derivatives that have dual PI3K and mTOR inhibitory properties [16]. The synthesis of the most promising compound **32** is shown in Scheme 5. The starting compound, 2-amino-6-bromobenzothiazole, was first acylated using acetic anhydride in the presence of 4-dimethylaminopyridine (DMAP) and then the product was converted to boronate **30**. Commercially available 5-bromo-2-chloropyridin-3-amine was reacted with compound **30** utilizing Suzuki coupling to furnish compound **31**. Compound **31** in the last step was reacted with 4-fluorosulfonyl chloride in the presence of pyridine and 4-dimethylaminopyridine to prepare the final compound **32**.

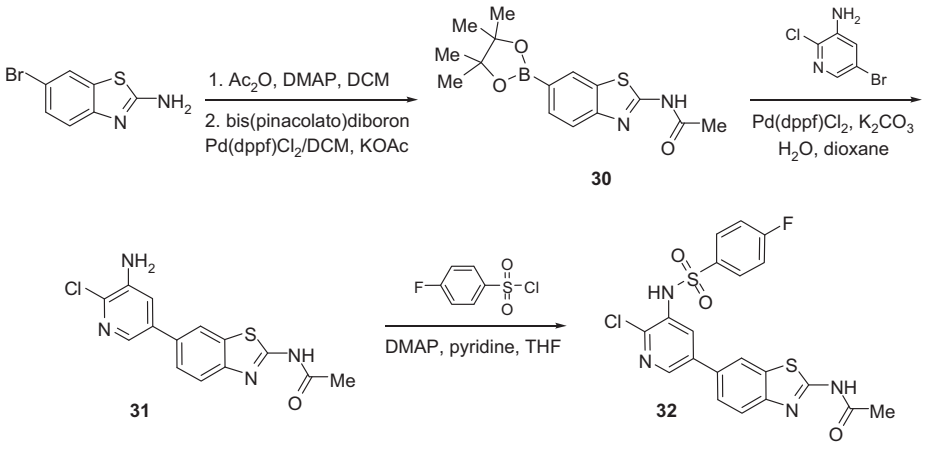
Compound **32** not only displays potent inhibitory activity against PI3Kα (K_i = 1.2±0.9) mTOR (K_i = 2.0±4.8) but also inhibits tumor growth in mouse xenograft models (tumor type: glioblastoma, lung adenocarcinoma and colorectal).



Scheme 3



Scheme 4



Scheme 5

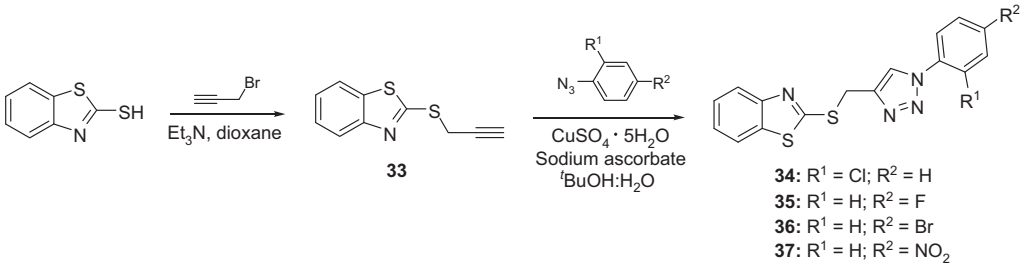
Anti-inflammatory activity

In addition to antimicrobial and chemotherapeutic properties, benzothiazole-based compounds have shown promising activity towards the development of anti-inflammatory agents. Specifically, Shafi et al. reported the synthesis of 2-mercaptobenzothiazole and 1,2,3-triazole based bis-heterocyclic compounds as potential anti-inflammatory agents [17]. The synthetic scheme for the synthesis of bis-heterocyclic compounds is shown in Scheme 6. Commercially available benzothiazole-2-thiol was reacted with propargyl bromide in dioxane in the presence of triethylamine to obtain compound **33** which was then treated with aromatic azides using click chemistry to afford final compounds **34–37**.

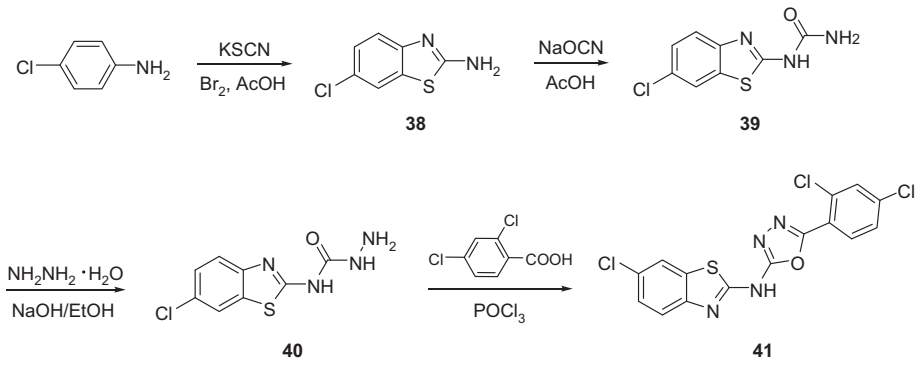
Compounds **34–37** were tested for anti-inflammatory activity via biochemical cyclooxygenase (COX) activity assays and carrageenan-induced hind paw edema. Compound **35** exhibited selective COX-2 inhibition with an IC_{50} ratio of 0.44 of COX-2/COX-1 and displayed a better *in vivo* anti-inflammatory activity profile when compared with the industry standard, ibuprofen. Compound **35** showed increased analgesic activity compared with ibuprofen when tested using the Writhing method. Importantly, the synthesized compounds **34–37** displayed no gastric ulceration which has been a major downside to the clinical use of ibuprofen.

Gilani et al. synthesized a series of *N*-(6-chlorobenzo[*d*]thiazol-2-yl)hydrazine carboxamide benzothiazole derivatives and evaluated these compounds for corresponding anti-inflammatory activity [18]. The synthetic scheme for the compound **41** with best activity is shown in Scheme 7 beginning with the treatment of 4-chloroaniline with potassium thiocyanate in glacial acetic acid followed by the addition of a bromine solution to furnish compound **38**. Compound **39** was furnished by heating precursor **38** with a solution of sodium cyanate in glacial acetic acid. Reaction of compound **39** with a hydrazine hydrate solution in the presence of concentrated sodium hydroxide solution afforded compound **40**. In the final step, compound **40** was heated under reflux with 2,4-dichlorobenzoic acid in phosphorus oxychloride to furnish product **41** in 67% yield.

The tumor necrosis factor-α (TNF-α) is associated with several inflammatory diseases, and designing small molecule inhibitors of TNF-α activity is considered a potential target for developing anti-inflammatory therapeutics [19]. The mitogen-activated protein kinase activated protein kinase 2 (MAPKAP-K2) gene is associated



Scheme 6



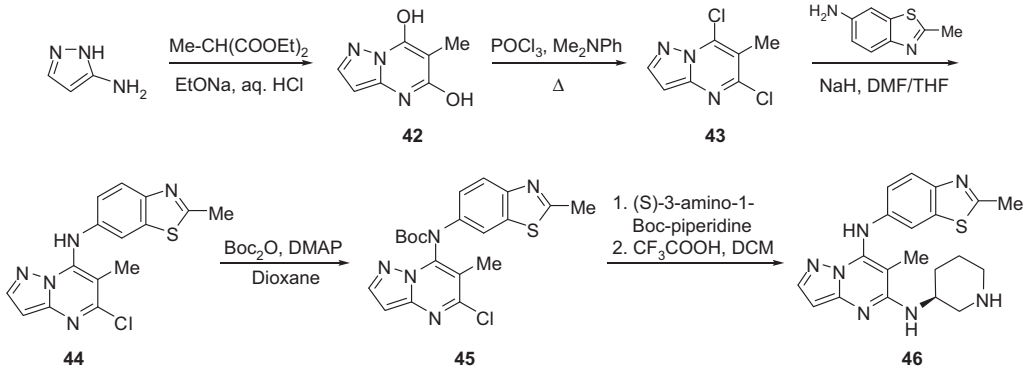
Scheme 7

with inflammatory response as it regulates the TNF-α. A series of pyrazolo[1,5-*a*]pyrimidine based compounds was synthesized and evaluated as MAPKAP-K2 inhibitors [19]. The most potent inhibitor **46** was synthesized as depicted in Scheme 8. Commercially available 3-aminopyrazole was treated with diethyl methylmalonate in a solution of sodium ethoxide in ethanol to yield compound **42**. Compound **43** was obtained by refluxing a solution of **42** with *N,N*-dimethylaniline and phosphorus oxychloride. Compound **43** in the next step was treated with 6-amino-2-methylbenzothiazole in tetrahydrofuran in the presence of sodium hydride in DMF to afford compound **44**. The amino group of **44** was protected using Boc anhydride, and the resultant derivative **45** was coupled with (*S*)-3-amino-1-Boc-piperidine. Removal of the Boc groups using trifluoroacetic acid furnished the final product **46**.

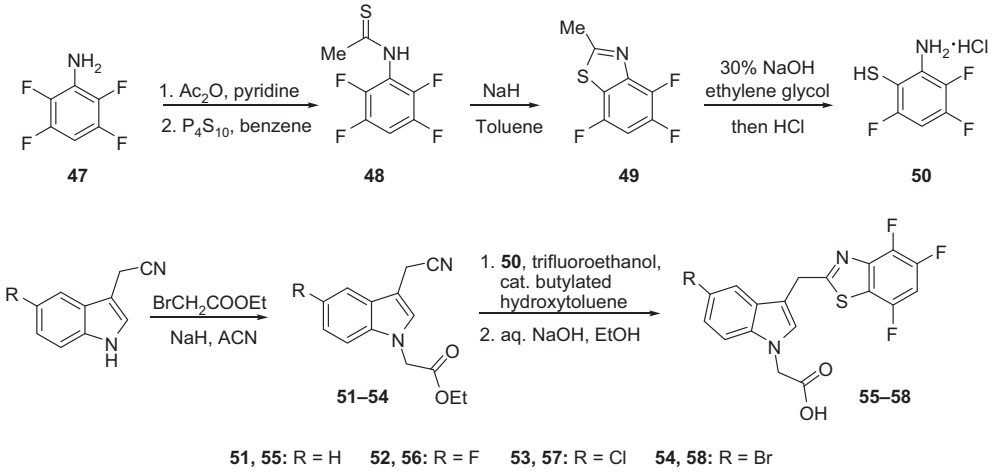
Antidiabetic activity

Estimates predict that over 150 million people suffer from diabetes, and through synthetic efforts, medicinally relevant heterocyclic compounds containing the benzothiazole moiety show promising activity towards combating diabetes. Van Zandt et al. synthesized a series of conjugated indole-*N*-acetic acid with benzothiazoles and evaluated these compounds for antidiabetic activity [20]. The synthetic scheme for various benzothiazole derivatives is shown in Scheme 9. The starting material, 2,3,5,6-tetrafluoroaniline, was first acylated with acetic anhydride in pyridine and then the product was treated with phosphorus pentasulfide in benzene to yield thioamide compound **48**. Thioamide was then cyclized in the presence of sodium hydride in toluene. The resulting compound **49** was hydrolyzed using a sodium hydroxide solution followed by treatment with hydrochloric acid to afford 2-aminothiophenol hydrochloride **50**. Indole-3-acetonitrile and its 5-substituted analogs were alkylated with ethyl bromoacetate in the presence of sodium hydride to furnish compounds **51**–**54**. Compound **50**, in the final step, was condensed with individual compounds **51–54** in the presence of trifluoroethanol followed by treatment with aqueous sodium hydroxide to furnish final products **55–58**.

Compounds **55–58** inhibited aldose reductase with IC_{50} values in the range of 5–13 nM. Compound **55** was the most potent aldose reductase inhibitor with IC_{50} of 5 nM and displayed promising features such as the



Scheme 8



Scheme 9

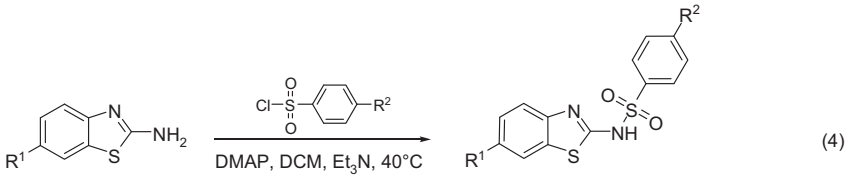
normalization of nerve sugars and prevention of diabetic cataracts in STZ-induced diabetic rat models.

The enzyme 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) is responsible for glucocorticoid activity at the tissue level primarily in adipose and liver tissues [21]. Glucocorticoids are insulin action antagonists and are the possible cause for the commonly elevated blood sugar concentration in diabetes patients. Moreno-Díaz et al. reported a series of benzothiazole benzenesulfonamides as shown in Equation 4 as potential 11β-HSD1 inhibitors for the treatment of noninsulin-dependent diabetes mellitus [21]. Starting material 2-amino-6-methoxybenzothiazole was condensed in dichloromethane with arylsulfonyl chlorides in the presence of triethylamine and a catalytic amount of DMAP to furnish compounds **59**–**62**. Compounds **59** and **60** displayed effective inhibition activity of 11β-HSD1 in an *in vitro* cell-based assay with 38% and 53% inhibition, respectively.

Anti-HIV activity

Towards the goal of designing novel anti-HIV agents, Massari et al. synthesized 1,8-naphthyridone benzothiazole derivative **67** as a potential inhibitor of the HIV-1 Tat-mediated transcription and antiviral activity in HIV-infected cells (Scheme 10) [22]. Acrylamide **63** was treated with methylamine in a diethyl ether/ethanol mixture to yield compound **64**. Compound **65** was obtained by cyclization of the precursor **64** in the presence of potassium carbonate in DMF. The intermediate product **65** was then condensed with 1-(benzothiazol-2-yl)piperazine in DMF to furnish compound **66** which was then hydrolyzed to afford the final product **67**. Compound **67** displayed EC_{50} = 0.03 μg/mL and 0.02 μg/mL with HIV-1 and HIV-2 metallothionein 4 (MT-4) cells.

Jonckers et al. synthesized benzothiazole amides **74** and **75** as shown in Scheme 11 [23]. Commercially available

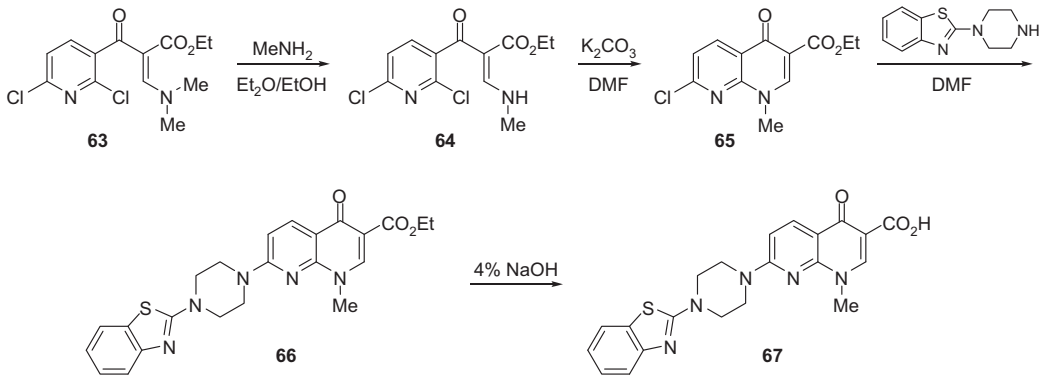


(4)

59: R^1 = OMe; R^2 = H
60: R^1 = OMe; R^2 = NO_2
61: R^1 = Me; R^2 = Cl
62: R^1 = Me; R^2 = NO_2

As shown above, benzothiazole-based heterocyclic compounds are becoming prevalent when discussing active drugs that combat various diseased states; however, discovering antiviral agents, specifically anti-HIV agents, remains of paramount importance in pharmaceutical research.

epoxide **68** was treated with an excess of isobutylamine in isopropanol to yield compound **69**. Compound **69** was coupled with a benzothiazole-6-carboxylic acid using *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU) as an activating agent in the



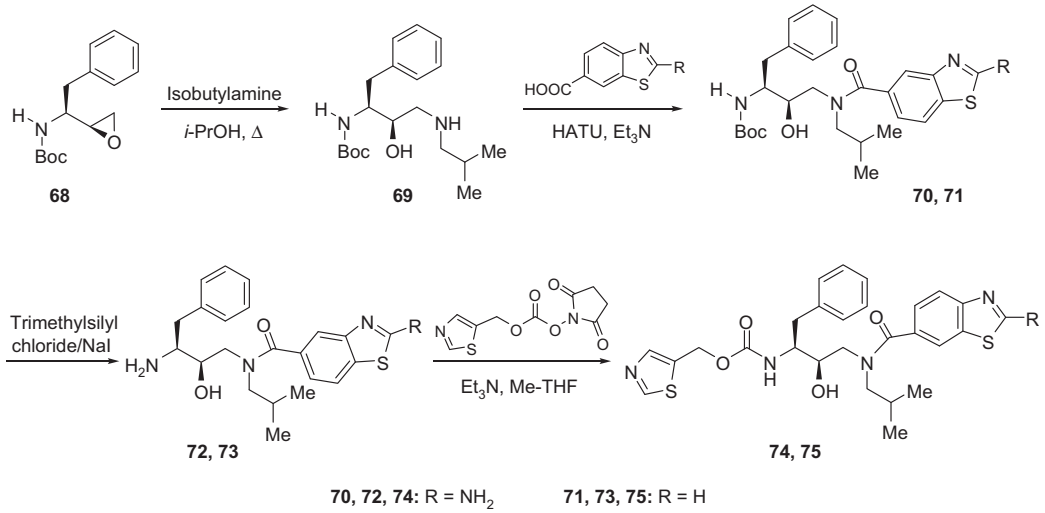
Scheme 10

presence of triethylamine to afford compounds **70** and **71**, the subsequent treatment of which with trimethylsilyl chloride and sodium iodide furnished derivatives **72** and **73**. In the final step, a triethylamine-mediated coupling of compounds **72** and **73** with 2,5-dioxopyrrolidin-1-yl thiazol-5-ylmethyl carbonate furnished final products **74** and **75** in approximately 85% yield. Compounds **74** and **75** were evaluated as pharmacokinetic enhancers of HIV protease inhibitors.

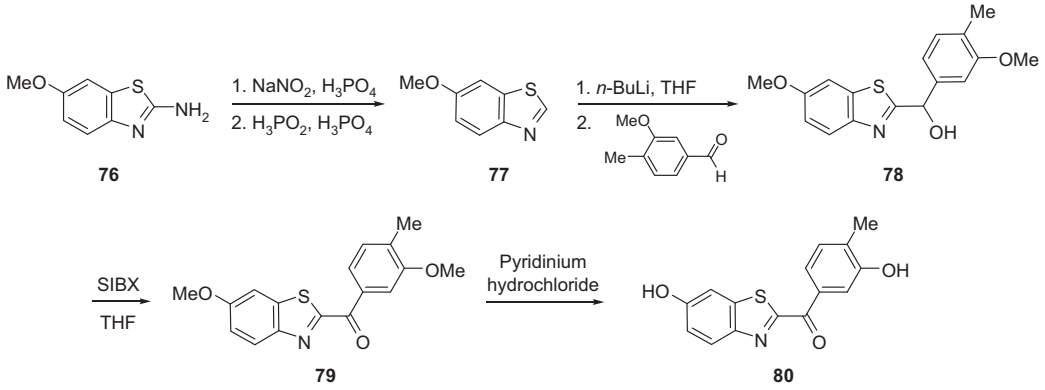
Miscellaneous activities

Spadaro et al. described a synthesis of various hydroxybenzothiazole compounds and evaluated them as potential agents for the treatment of estrogen-related diseases [24]. The synthesis of the most potent compound **80** is depicted in Scheme 12. 2-Amino-6-methoxybenzothiazole (**76**) was deaminated in two steps to afford compound **77**. Compound **77** was treated with *n*-butyllithium and the resulting *in situ* formyl anion was then allowed to react with 4-methyl-3-methoxybenzaldehyde to yield compound **78**. Compound **79** was obtained by treatment of **78** with iodoxybenzoic acid in anhydrous THF. Demethylation of **79** to the final product **80** in the next step was accomplished by heating with pyridinium hydrochloride. Compound **80** inhibits 17β-hydroxysteroid dehydrogenase 1 (17β-HSD1) with IC_{50} = 27 nM and shows selectivity towards 17β-HSD2.

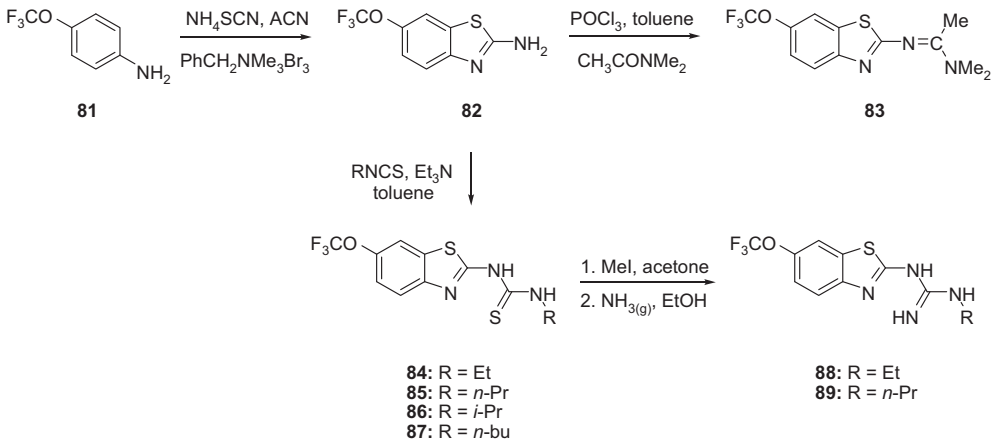
Anzini et al. developed various amidine, guanidine and thiourea derivatives of 2-amino-(6-trifluoromethoxy) benzothiazole **83–89** that were structurally related to riluzole, a neuroprotective drug, as illustrated in Scheme 13 [25]. These compounds were evaluated as neuroprotective agents via an *in vitro* procedure of ischemia/reperfusion injury. Condensation of 4-(trifluoromethoxy)aniline (**81**) with ammonium thiocyanate and benzyltrimethylammonium tribromide in acetonitrile yielded 2-amino-6-(trifluoromethoxy)benzothiazole (**82**). Treatment of **82** with *N,N*-dimethylacetamide and phosphorus oxychloride in toluene furnished amidine **83**. The reaction of **82** with various isothiocyanates in the presence of triethylamine



Scheme 11



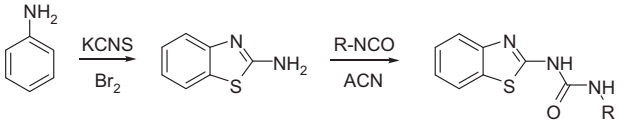
Scheme 12



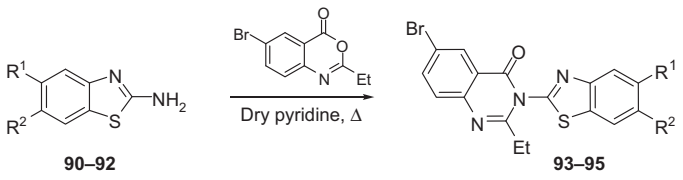
Scheme 13

yielded various thiourea derivatives **84–87**. Compounds **84** and **85** were further treated with methyl iodide in acetone followed by the reaction with gaseous ammonia to afford guanidine derivatives **88** and **89**. Compounds **83–87** displayed a significant reduction in neuronal injury.

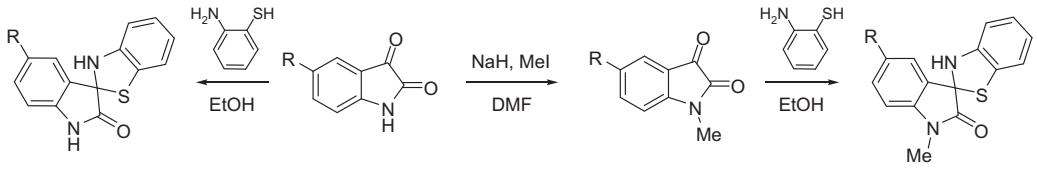
Ugale et al. reported the synthesis of quinazoline-substituted benzothiazoles **93–95** as shown in Equation 5. These compounds were evaluated as anticonvulsant agents by maximal electroshock and PTZ-induced seizure methods [26]. In the preparation of **93–95**, substrates **90–92** and 6-bromo-2-ethyl-4*H*-benzo[*d*][1,3]oxazin-4-one in dry pyridine were heated under reflux. Compound **93** showed remarkable activity against tonic seizure, whereas compound **95** showed promising results against clonic seizure. Significantly, none of the compounds exhibited neurotoxicity or hepatotoxicity.



Scheme 14



(5)



104: R = Me
105: R = Cl
106: R = NO_2

102

103

107: R = Me
108: R = CF_3O
109: R = Cl
110: R = Br
111: R = NO_2

Scheme 15

Azam et al. synthesized a series of benzothiazole-urea derivatives as potential agents to combat Parkinson's disease. The synthesis is shown in Scheme 14 [27]. The reaction of aniline with potassium thiocyanate and bromine afforded 2-aminobenzothiazole (**96**), the treatment of which with appropriate isocyanate furnished compounds **97–101**. Compounds **97–101** exhibited reduction in catalepsy by more than 70% in a standard bar test.

Karalı et al. synthesized benzothiazole containing spiroindolinones and screened these compounds for antioxidant activity [28]. The synthetic scheme is shown in Scheme 15. 1*H*-Indole-2,3-dione (**102**) was alkylated with methyl iodide to furnish compound **103**. Compounds **102** and **103** were then allowed to react with 2-aminothiophenol in ethanol to afford final compounds **104–111**. The methyl analog **107** was found to be the most potent antioxidant in the whole set of compounds compared with α-tocopherol and ascorbic acid.

As discussed above and in our other recent review [1], benzothiazole-based compounds have widespread medicinal applicability when conjugated with various heterocyclic and cyanine moieties. The extensive literature presentations in the preceding sections show that the benzothiazole heterocyclic structure is effective in the preparation of novel heterocyclic compounds and functions as the basic scaffold for determining the prognosis of patients suffering from AD through PET scans and generating anti-HIV medication. We have previously shown that benzothiazole-containing cyanine dyes have extensive medicinal applications and as synthetic and medicinal chemists further develop these compounds, it is likely that the benzothiazole system will remain an integral portion of the design of compounds in the future.

Received February 7, 2013; accepted February 23, 2013; previously published online March 25, 2013

References

[1] Henary, M.; Paranjpe, S.; Owens, E. A. Synthesis and application of benzothiazole containing cyanine dyes. *Heterocycl. Commun.* **2013**, *19*, 1–11.

[2] Robbins, K.; Liu, G.; Lin, G.; Lazo, N. Detection of strongly bound thioflavin T species in amyloid fibrils by ligand-detected ^{1}H NMR. *J. Phys. Chem. Lett.* **2011**, *2*, 735–740.

[3] Sisodia, S.; Price, D. Role of the β-amyloid protein in Alzheimer's disease. *FASEB J.* **1995**, *9*, 366–370.

[4] Yan, P.; Bero, A.; Cirrito, J.; Xiao, Q.; Hu, X.; Wang, Y.; Gonzales, E.; Holtzman, D.; Lee, J. -M. Characterizing the appearance and growth of amyloid plaques in APP/PS1 mice. *J. Neurosci.* **2009**, *29*, 10706–10714.

[5] Klunk, W.; Engler, H.; Nordberg, A.; Wang, Y.; Blomqvist, G.; Holt, D.; Bergström, M.; Savitcheva, I.; Huang, G.-F.; Estrada, S.; et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh compound-B. *Ann. Neurol.* **2004**, *55*, 306–319.

[6] Klunk, W.; Wang, Y.; Huang, G.-F.; Debnath, M.; Holt, D.; Mathis, C. Uncharged thioflavin-T derivatives bind to amyloid-β protein with high affinity and readily enter the brain. *Life Sciences* **2001**, *69*, 1471–1484.

[7] Landau, S.; Breault, C.; Joshi, A.; Pontecorvo, M.; Mathis, C.; Jagust, W.; Mintun, M. For the Alzheimer's Disease Neuroimaging Initiative. Amyloid-β imaging with Pittsburgh compound B and florbetapir: comparing radiotracers and quantification methods. *J. Nucl. Med.* **2013**, *54,* 476–490.

[8] Wilson, A.; Garcia, A.; Chestakova, A.; Kung, H.; Houle, S. A rapid one-step radiosynthesis of the β-amyloid imaging radiotracer *N*-methyl-[^{11}C]2-(4′-methylaminophenyl)-6-hydroxybenzothiazole ([^{11}C]-6-OH-BTA-1). *J. Label. Compd. Rad.* **2004**, *47*, 679–682.

[9] Yousefi, B.; Manook, A.; Drzezga, A.; Reutern, B.; Schwaiger, M.; Wester, H.-J.; Henriksen, G. Synthesis and evaluation of ^{11}C-labeled imidazo[2,1-*b*]benzothiazoles (ibts) as PET tracers for imaging β-amyloid plaques in Alzheimer's disease. *J. Med. Chem.* **2011**, *54*, 949–956.

[10] Ribeiro Morais, G.; Paulo, A.; Santos, I. A synthetic overview of radiolabeled compounds for β-amyloid targeting. *Eur. J. Org. Chem.* **2012**, *7*, 1279–1293.

[11] Yadav, P.; Devprakash; Senthilkumar, G. Benzothiazole: different methods of synthesis and diverse biological activities. *Int. J. Pharm. Sci. Drug Res.* **2011**, *3*, 1–7.
[12] Ouyang, L.; Huang, Y.; Zhao, Y.; He, G.; Xie, Y.; Liu, J.; He, J.; Liu, B.; Wei, Y. Preparation, antibacterial evaluation and preliminary structure-activity relationship (SAR) study of benzothiazol- and benzoxazol-2-amine derivatives. *Bioorg. Med. Chem.* **2012**, *22*, 3044–3049.
[13] Bandyopadhyay, P.; Sathe, M.; Ponmariappan, S.; Sharma, A.; Sharma, P.; Srivastava, A.; Kaushik, M. Exploration of in vitro time point quantitative evaluation of newly synthesized benzimidazole and benzothiazole derivatives as potential antibacterial agents. *Bioorg. Med. Chem.* **2011**, *21*, 7306–7309.
[14] Shi, X.-H.; Wang, Z.; Xia, Y.; Ye, T.-H.; Deng, M.; Xu, Y.-Z.; Wei, Y.-Q.; Yu, L.-T. Synthesis and biological evaluation of novel benzothiazole-2-thiol derivatives as potential anticancer agents. *Molecules* **2012**, *17*, 3933–3944.
[15] Mortimer, C.; Wells, G.; Crochard, J.-P.; Stone, E.; Bradshaw, T.; Stevens, M.; Westwell, A. Antitumor benzothiazoles. 26.[1] 2-(3,4-dimethoxyphenyl)-5-fluorobenzothiazole (GW 610, NSC 721648), a simple fluorinated 2-arylbenzothiazole, shows potent and selective inhibitory activity against lung, colon, and breast cancer cell lines. *J. Med. Chem.* **2006**, *49*, 179–185.
[16] D'Angelo, N.; Kim, T.-S.; Andrews, K.; Booker, S.; Caenepeel, S.; Chen, K.; D'Amico, D.; Freeman, D.; Jiang, J.; Liu, L.; et al. Discovery and optimization of a series of benzothiazole phosphoinositide 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) dual inhibitors. *J. Med. Chem.* **2011**, *54*, 1789–1811.
[17] Shafi, S.; Mahboob Alam, M.; Mulakayala, N.; Mulakayala, C.; Vanaja, G.; Kalle, A.; Pallu, R.; Alam, M. Synthesis of novel 2-mercapto benzothiazole and 1,2,3-triazole based bis-heterocycles: their anti-inflammatory and anti-nociceptive activities. *Eur. J. Med. Chem.* **2012**, *49*, 324–333.
[18] Gilani, S.; Khan, S. Synthesis and pharmacological evaluation of *N*-(6-chlorobenzo[*d*]-thiazol-2-yl)hydrazine carboxamide derivatives of benzothiazole. *Med. Chem. Res.* **2012**, *19*, 1–13.
[19] Kosugi, T.; Mitchell, D.; Fujino, A.; Imai, M.; Kambe, M.; Kobayashi, S.; Makino, H.; Matsueda, Y.; Oue, Y.; Komatsu, K.; et al. Mitogen-activated protein kinase-activated protein kinase 2 (MAPKAP-K2) as an antiinflammatory target: discovery and in vivo activity of selective pyrazolo[1,5-a]-pyrimidine inhibitors using a focused library and structure-based optimization approach. *J. Med. Chem.* **2012**, *55*, 6700–6715.
[20] Van Zandt, M.; Jones, M.; Gunn, D.; Geraci, L.; Jones, J.; Sawicki, D.; Sredy, J.; Jacot, J.; DiCioccio, A.; Petrova, T.; et al. Discovery of 3-[(4,5,7-trifluorobenzo-thiazol-2-yl)methyl] indole-*N*-acetic acid (Lidorestat) and congeners as highly potent and selective inhibitors of aldose reductase for treatment of chronic diabetic complications. *J. Med. Chem.* **2005**, *48*, 3141–3152.
[21] Moreno-Díaz, H.; Villalobos-Molina, R.; Ortiz-Andrade, R.; Díaz-Coutiño, D.; Medina-Franco, J.; Webster, S.; Binnie, M.; Estrada-Soto, S.; Ibarra-Barajas, M.; León-Rivera, I.; et al. Antidiabetic activity of *N*-(6-substituted-1,3-benzothiazol-2-yl)benzen-esulfonamides. *Bioorg. Med. Chem.* **2008**, *18*, 2871–2877.
[22] Massari, S.; Daelemans, D.; Barreca, M.; Knezevich, A.; Sabatini, S.; Cecchetti, V.; Marcello, A.; Pannecouque, C.; Tabarrini, O. A 1,8-naphthyridone derivative targets the HIV-1 Tat-mediated transcription and potently inhibits the HIV-1 replication. *J. Med. Chem.* **2010**, *53*, 641–648.
[23] Jonckers, T.; Rouan, M.-C.; Haché, G.; Schepens, W.; Hallenberger, S.; Baumeister, J.; Sasaki, J. Benzoxazole and benzothiazole amides as novel pharmacokinetic enhancers of HIV protease inhibitors. *Bioorg. Med. Chem.* **2012**, *22*, 4998–5002.
[24] Spadaro, A.; Frotscher, M.; Hartmann, R. Optimization of hydroxybenzothiazoles as novel potent and selective inhibitors of 17β-HSD1. *J. Med. Chem.* **2012**, *55*, 2469–2473.
[25] Anzini, M.; Chelini, A.; Mancini, A.; Cappelli, A.; Frosini, M.; Ricci, L.; Valoti, M.; Magistretti, J.; Castelli, L.; Giordani, A.; et al. Synthesis and biological evaluation of amidine, guanidine, and thiourea derivatives of 2-amino(6-trifluoromethoxy)-benzothiazole as neuroprotective agents potentially useful in brain diseases. *J. Med. Chem.* **2010**, *53*, 734–744.
[26] Ugale, V.; Patel, H.; Wadodkar, S.; Bari, S.; Shirkhedkar, A.; Surana, S. Quinazolino-benzothiazoles: fused pharmacophores as anticonvulsant agents. *Eur. J. Med. Chem.* **2012**, *53*, 107–113.
[27] Azam, F.; Prasad, M.; Thangavel, N. Structure-based design, synthesis, and molecular modeling studies of 1-(benzo[*d*] thiazol-2-yl)-3-(substituted aryl)urea derivatives as novel anti-Parkinsonian agents. *Med. Chem. Res.* **2012**, *21*, 2630–2643.
[28] Karalı, N.; Güzel, Ö.; Özsoy, N.; Özbey, S.; Salman, A. Synthesis of new spiroindolinones incorporating a benzothiazole moiety as antioxidant agents. *Eur. J. Med. Chem.* **2010**, *45*, 1068–1077.