Iğdır Üniversitesi Fen Bilimleri Enstitüsü Dergisi, 12(2): 899-907, 2022
Journal of the Institute of Science and Technology, 12(2): 899-907, 2022

ISSN: 2146-0574, eISSN: 2536-4618

Chemistry **DOI: 10.21597/jist.1039476**

Research Article

Received: 21.12.2021 **Accepted: 11.02.2022**

To Cite: Kalay E, 2022. Synthesis and Characterization of Novel Hybrid Sulfonamide Molecules with Benzothiazole Scaffold. Journal of the Institute of Science and Technology, 12(2): 899-907.

Synthesis and Characterization of Novel Hybrid Sulfonamide Molecules with Benzothiazole Scaffold

Erbay KALAY[1*]

ABSTRACT: Benzothiazole-based compounds have a wide spectrum of pharmacological activities such as anticancer, anti-diabetic, anticonvulsant, antiviral, antituberculous, antimalarial, analgesic, anti-inflammatory, antimicrobial, and fungicidal. On the other hand, compounds bearing a sulfonamide group are used to inhibit some enzymes such as carbonic anhydrase, HIV protease, cysteine protease and cyclooxygenase (COX-II) apart from their commercial applications as antibacterial/antibiotics. Due to the wide variety of biological activities of benzothiazole and sulfonamide scaffolds, the presence of such pharmacophores in synthetic organic compounds has aroused great interest in medicinal chemists. Recently, molecular hybrids have been envisaged by combining at least two pharmacophore-specific moieties to modulate multiple disease targets simultaneously. Molecular hybridization design appears to be a novel approach to develop multifunctional hybrid molecules that involve combining at least two pharmacophores in a scaffold. In this study, benzothiazole-based bissulfonamide **8a-b** and sulfonamide-amide **7a-c** hybrid compounds, which have the potential to be used in many different therapeutic applications, were synthesized effectively after a series of reactions starting from the 2-amino benzothiazole compound. The structures of the synthesized novel hybrid molecules **7a-c**, **8a-b** were elucidated by ^{1}H, ^{13}C NMR, FTIR and HRMS spectroscopy techniques.

Keywords: benzothiazole, sulfonamide, hybrid compound

[1]Erbay KALAY (**Orcid ID:** 0000-0002-4656-8254), Kafkas University, Kars Vocational School, Department of Material and Material Processing Technologies, Kars, 36100, Turkey

***Corresponding Author**: Erbay KALAY, e-mail: ekalay@kafkas.edu.tr

INTRODUCTION

Heterocyclics are a versatile class of compounds found in materials science, supramolecular and polymer chemistry, almost all-natural products, most vitamins, a dominant part of drugs, and synthetic organic compounds with pharmacological activity (Rouf and Tanyeli, 2015). Among the heterocyclics, the benzothiazoles occupy a significant position. Benzothiazole-based compounds have a wide spectrum of pharmacological activities such as anticancer, anti-diabetic, anticonvulsant, antiviral, antituberculous, antimalarial, analgesic, anti-inflammatory, antimicrobial, and fungicidal (Keri et al., 2015). Thus, the wide variety of biological effects associated with this scaffold has led to the benzothiazole ring to be viewed as a privileged structure.

On the other hand, compounds bearing a sulfonamide group are used to inhibit some enzymes such as carbonic anhydrase, HIV protease, cysteine protease and cyclooxygenase (COX-II), apart from their commercial applications as antibacterial/antibiotics. In addition, it has found application areas in the treatment of many diseases (Supuran and Scozzafava, 2000; Supuran and Scozzafava, 2001; Supuran and Scozzafava, 2007). In Figure 1, the structures of sulfonamide compounds sold in the market as drugs are shown. Amprenavir is a protease inhibitor used to treat HIV infection (Adkins and Fauld, 1998). Sultiam is a drug used as a carbonic anhydrase enzyme inhibitor and an anticonvulsant (Aggarwal et al., 2013). Sildenafil compound, which is used in many treatments such as the anti-impotence agent Viagra and sold by Pfizer, is among the examples that can be given to sulfonamide drugs (Gulçin and Taslimi, 2018). Cyclooxygenase (COX-2) specific inhibitors Celecoxib (Celebrex) and Valdecoxib are nonsteroidal anti-inflammatory drugs (Wong et al., 2005). Among the drugs that inhibit the carbonic anhydrase enzyme; Topiramate (trade name Topamax) is used to treat epilepsy in children and adults (Lyseng-Williamson KA, Yang, 2008), Zonisamide is used to treat epilepsy and Parkinson's disease (Lyseng-Williamson KA, Yang, 2008), and Acetazolamide (trade name Diamox) is used to treat epilepsy and glaucoma (Nishimoria et al., 2005). Ethoxzolamide is another sulfonamide drug that acts as a carbonic anhydrase inhibitor. It is used in the clinic for the treatment of glaucoma and duodenal ulcers and as a diuretic. Etoxzolamide binds carbonic anhydrase I and inhibits its activity in the proximal renal tubules to reduce reabsorption of water, sodium, potassium and bicarbonate (Carta and Supuran, 2013) (Figure 1).

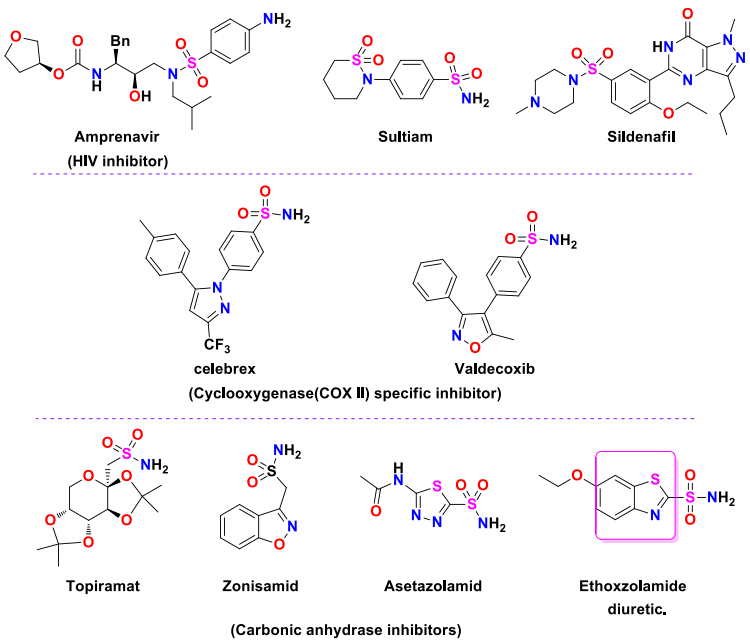

Figure 1. Commercially available sulfonamide drugs with different effects

Sulfonamides are of interest to synthetic organic chemists because of their pharmacological importance. Recently, the synthesis of molecules with this functional group and enzyme inhibition studies have been an important research topic. Supuran et al. (1996) obtained a series of Schiff bases from the condensation of the sulfonamide compound with substituted benzene and heterocyclic aldehyde. It has been found that these analogues act as inhibitors to CAI, CAII and CAIV isoenzymes and show equally high affinity. Lin et al. (2008) synthesized two series of benzenesulfonamide analogues containing 4-benzylidene amino- and 4-phenyliminomethyl- moieties and reported that these analogues selectively inhibit the cyclooxygenase-2 (COX-2) enzyme. Naaz et al. (2018) synthesized benzimidazole, indazole, benzothiazole and thiazole sulfonamide derivatives, and the antibacterial and cytotoxic activities of these molecules were evaluated. Azzam et al. (2020) synthesized new benzothiazole hybrid compounds bearing the N-sulfonamide 2-pyridone pharmacophore group. The antiviral activities of these hybrid compounds against various viruses (HSV-1, HCVcc genotype 4, CBV4 and HAdV7) were evaluated in vitro. Some derivatives have been reported to show inhibitory activity against the USP7 enzyme. Luci et al. (2014) synthesized benzoxazole and benzooxazole based sulfonamide derivatives and investigated their inhibition effects on platelet type 12-LOX enzyme. It has been reported that these compounds provide excellent selectivity towards 12-LOX and show nanomolar (nM) potential.

Recently, molecular hybrids have been envisaged by combining at least two pharmacophore-specific moieties to modulate multiple disease targets simultaneously. (Ivasiv et al., 2019). The molecular hybridization design is appearing as a new approach to develop multifunctional hybrid molecules, involving the assembly of two or more pharmacophores in a scaffold (Abbot et al., 2017). The inclusion of at least two pharmacophores in a molecule will be the combined force in providing pharmacological activity and also increase its capacity to interact with multiple biological targets (Sandhu et al., 2014; Kerru et al., 2017). Therefore, the synthesis of such compounds has been of great interest to medicinal chemists. Inspired by this, in this study, we aimed to synthesize and characterize new hybrid molecules containing pharmacophore fragments such as benzothiazole, furan, thiophene and sulfonamide (Figure 2).

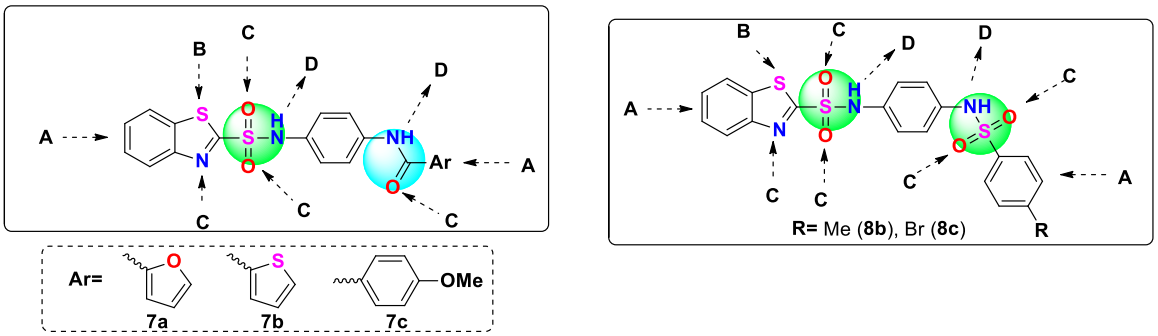

Figure 2. General chemical structure of title compounds **7a-c**, **8a-b** (A: hydrophobic aryl ring, B: Electron donor atom, C: Hydrogen bond acceptor; D: Hydrogen bond donor)

MATERIALS AND METHODS

All materials were purchased from commercial sources and used as received unless stated otherwise. Melting points of target compound **7a-c, 8a-b** were determined in open glass capillaries on a WRS-2A Microprocessor melting-point devices. The IR spectra of **7a-c, 8a-b** were recorded using an Alpha-P Bruker FTIR spectrophotometer. ^{1}H-NMR and ^{13}C NMR spectra of **7a-c, 8a-b** were recorded on a Bruker (400 MHz) spectrometers using deuterated dimethyl sulfoxide (DMSO-d_6) solution. NMR

spectra were processed with MestReNova program. HRMS spectra were recorded on an Agilent 6530 Accurate-Mass Q-TOF LC/MS system (Santa Clara, CA, USA).

Synthesis of N-(4-(N-(benzo[d]thiazol-2-yl)sulfamoyl)phenyl)acetamide 5

4-Acetamidobenzene-1-sulfonyl chloride (6.66 mmol, 1.55 g) dissolved in 6 mL of pyridine. Benzo[d]thiazol-2-amine (6.66 mmol, 1 g) was then added to reaction mixture. The solution was heated to reflux for 2 h. The progress of the reaction was followed by TLC. After the starting compound was finished in the reaction medium, the crude product in pyridine was poured into acidified ice. The precipitate formed was filtered after maturation. It was then washed with water and dried in vacuo.

Synthesis of 4-amino-N-(benzo[d]thiazol-2-yl)benzenesulfonamide 6

N-(4-(N-(benzo[d]thiazol-2-yl)sulfamoyl)phenyl)acetamide (4.89 mmol, 1.7 g) was stirred in 1 M NaOH solution (12.5 mL). The resulting mixture was heated to reflux for 2 h. Reaction was cooled down to room temperature and the crude mixture was treated with concentrated HCl solution to pH 6. The precipitate formed was filtered after maturation. It was then washed with water and dried in vacuo.

Synthesis of target compound 7

N-(4-(N-(benzo[d]thiazol-2-yl)sulfamoyl)phenyl)acetamide (0.5 mmol, 152.7 mg) dissolved in 4 mL of pyridine and acyl chloride (0.5 mmol) was added to the resulting solution. The solution was stirred at room temperature for 4 h. After the starting compound was finished in the reaction medium, the crude product in pyridine was poured into acidified ice. The precipitate formed was filtered after maturation. It was then washed with water and dried in vacuo.

N-(4-(N-(benzo[d]thiazol-2-yl)sulfamoyl)phenyl)furan-2-carboxamide 7a

White solid; yield: 81%; mp: 252-254 ºC; ^{1}H NMR (400 MHz, d_6-DMSO) δ 10.52 (s, 1H), 7.95 (d, *J* = 6.7 Hz, 2H), 7.89-7.69 (m, 4H), 7.40-7.36 (m, 2H), 7.30 (d, *J* = 7.9 Hz, 1H), 7.27-7.21 (m, 1H), 6.75 – 6.70 (m, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 166.8, 156.4, 147.0, 146.1, 142.1, 136.4, 127.1, 127.0, 126.8, 124.8, 123.5, 122.6, 119.9, 115.5, 112.8, 112.3; FTIR (neat, cm^{-1}) 3345, 3102, 1665, 1593, 1526, 1398, 1143, 829, 749. HRMS (Q-TOF) m/z: $(M + H)^+$ calcd for $C_{18}H_{13}N_3O_4S_2$, 400.0426; found 400.0420 (Figure 3).

N-(4-(N-(benzo[d]thiazol-2-yl)sulfamoyl)phenyl)thiophene-2-carboxamide 7b

White solid; yield: 79%; mp: 283-285 ºC; ^{1}H NMR (400 MHz, d_6-DMSO) δ 10.58 (s, 1H), 8.09 (d, *J* = 3.4 Hz, 1H), 7.97-7.94 (m, 2H), 7.89-7.86 (m, 3H), 7.79 (d, *J* = 7.8 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.31 (d, *J* = 7.9 Hz, 1H), 7.25 – 7.20 (m, 2H); ^{13}C NMR (100 MHz d_6-DMSO) δ 166.7, 160.2, 142.4, 139.4, 136.3, 136.2, 132.5, 129.8, 128.1, 127.2, 126.9, 124.7, 123.6, 122.7, 119.8, 112.7.; FTIR (neat, cm^{-1}) 3340, 3099, 1656, 1590, 1530, 1396, 1140, 830, 744. HRMS (Q-TOF) m/z: $(M + H)^+$ calcd for $C_{18}H_{13}N_3O_3S_3$, 416.0197; found 416.0191 (Figure 4).

N-(4-(N-(benzo[d]thiazol-2-yl)sulfamoyl)phenyl)-4-methoxybenzamide 7c

White solid; yield: 76%; mp: 294-296 ºC; ^{1}H NMR (400 MHz, d_6-DMSO) δ 13.19 (bs, 1H), 10.45 (s, 1H), 8.02 – 7.95 (m, 4H), 7.86 (d, *J* = 8.8 Hz, 2H), 7.79 (d, *J* = 7.7 Hz, 1H), 7.38 (t, *J* = 7.4 Hz, 1H), 7.31 (d, *J* = 7.8 Hz, 1H), 7.24 (t, *J* = 7.6 Hz, 1H), 7.06 (d, *J* = 8.8 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 166.7, 165.3, 162.2, 143.0, 136.2, 136.0, 129.8, 127.2, 126.8, 126.4, 124.7, 123.5, 122.7, 119.8, 113.6, 112.7, 55.4.; FTIR (neat, cm^{-1}) 3354, 3101, 2905, 1673, 1591, 1539, 1395, 1141, 827, 742. HRMS (Q-TOF) m/z: $(M + H)^+$ calcd for $C_{18}H_{13}N_3O_4S_2$, 440.0739; found 440.0734 (Figure 5).

Synthesis of target compound 8

N-(4-(N-(benzo[d]thiazol-2-yl)sulfamoyl)phenyl)acetamide (0.5 mmol, 152.7 mg) dissolved in 4 mL of pyridine and arylsulfonyl chloride (0.5 mmol) was added to the resulting solution. The reaction was stirred at room temperature for 4 h. The progress of the reaction was followed by TLC. After the starting compound was finished in the reaction medium, the crude product in pyridine was poured into acidified ice. The precipitate formed was filtered after maturation. It was then washed with water and dried in vacuo.

N-(benzo[d]thiazol-2-yl)-4-(4-methylphenylsulfonamido)benzenesulfonamide 8a

White solid; yield: 82%; mp: 254-256 ºC; ^{1}H NMR (400 MHz, d_6-DMSO) δ 13.16 (bs, 1H), 10.84 (s, 1H), 7.81-7.67 (m, 6H), 7.39-7.23 (m, 8H), 2.29 (s, 3H); ^{13}C NMR (101 MHz, DMSO) δ 166.7, 143.7, 141.5, 136.4, 136.2, 136.1, 129.8, 127.4, 127.2, 126.7, 124.7, 123.6, 122.6, 118.4, 112.7, 20.9.; FTIR (neat, cm^{-1}) 3193, 3064, 2918, 1536, 1395, 1134, 833. HRMS (Q-TOF) m/z: $(M + H)^+$ calcd for $C_{20}H_{17}N_3O_4S_3$, 460.0459; found 460.0453 (Figure 6).

N-(benzo[d]thiazol-2-yl)-4-(4-bromophenylsulfonamido)benzenesulfonamide 8b

White solid; yield: 86%; mp: 288-290 ºC; ^{1}H NMR (400 MHz, d_6-DMSO) δ 13.16 (bs, 1H), 10.98 (s, 1H), 7.84-7.67 (m, 7H), 7.37 (t, J = 7.6 Hz, 1H), 7.32-7.18 (m, 4H); ^{13}C NMR (100 MHz, DMSO) δ 166.7, 141.1, 138.4, 136.8, 136.1, 132.5, 128.6, 127.5, 127.2, 127.2, 124.7, 123.6, 122.6, 118.8, 112.7.; FTIR (neat, cm^{-1}) 3200, 3059, 1593, 1536, 1392, 1134, 829, 740, 589. HRMS (Q-TOF) m/z: $(M + H)^+$ calcd for $C_{19}H_{14}BrN_3O_4S_3$, 523.9408; found 523.9403 (Figure 7).

RESULTS AND DISCUSSION

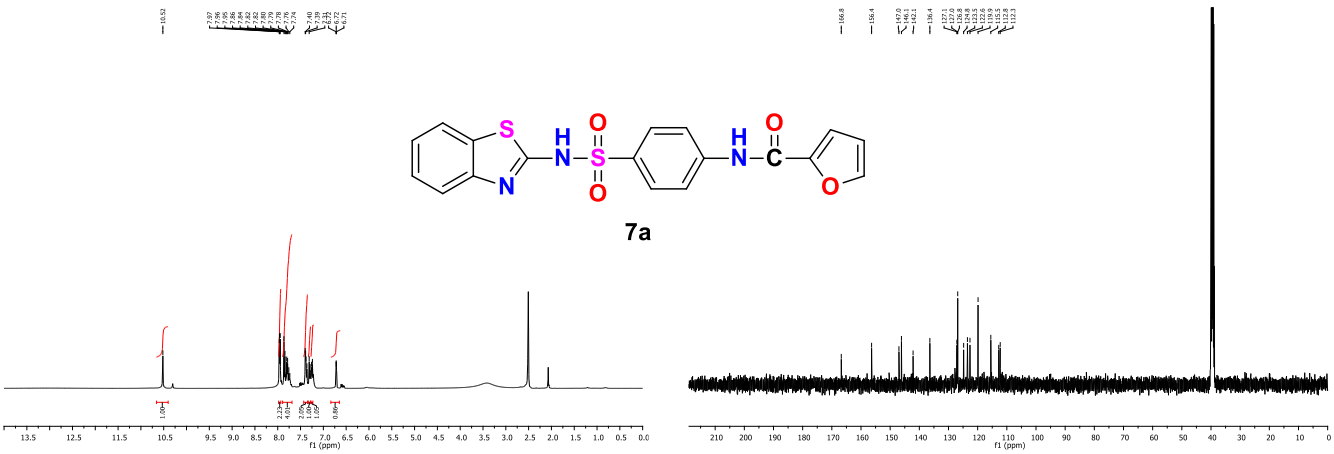

Figure 3. ^{1}H-NMR and ^{13}C-NMR spectrums of compound **7a**

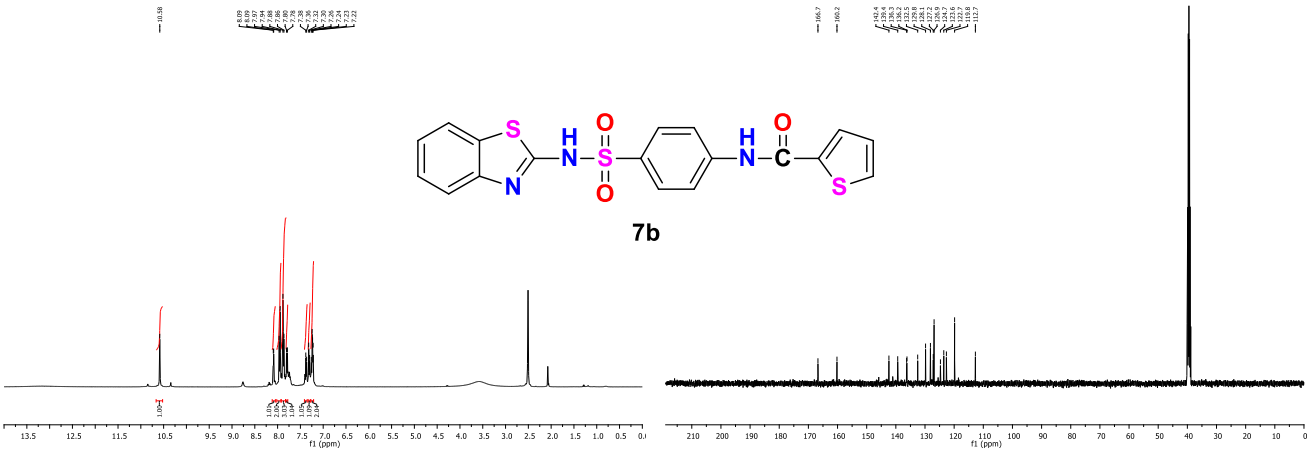

Figure 4. ^{1}H-NMR and ^{13}C-NMR spectrums of compound **7b**

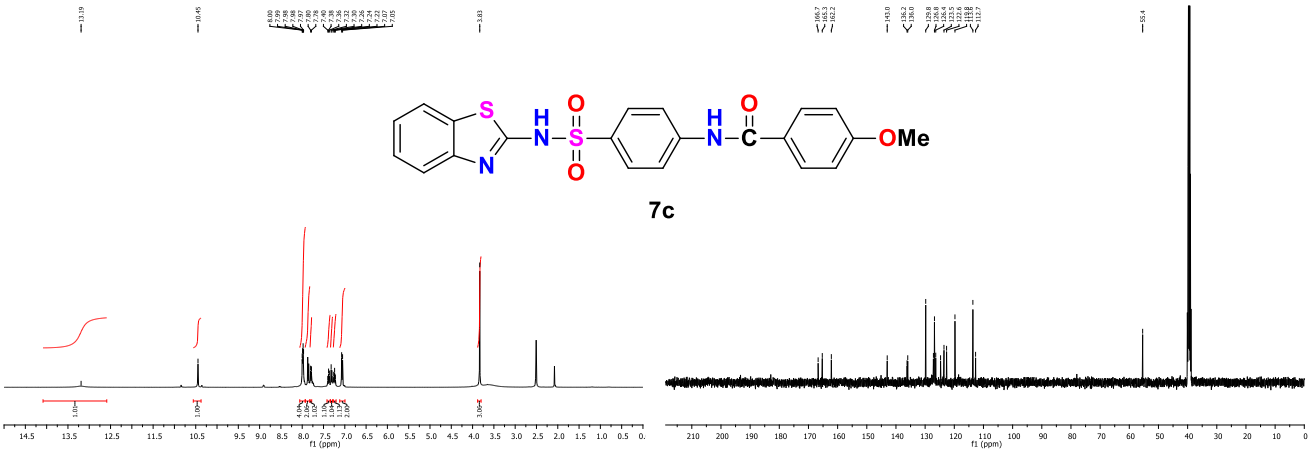

Figure 5. ^{1}H-NMR and ^{13}C-NMR spectrums of compound **7c**

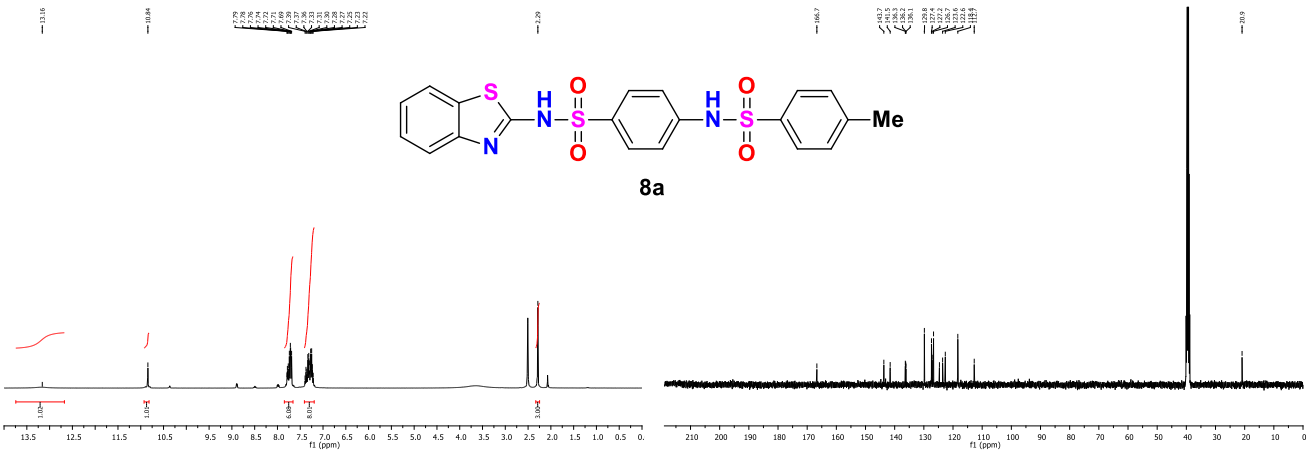

Figure 6. ^{1}H-NMR and ^{13}C-NMR spectrums of compound **8a**

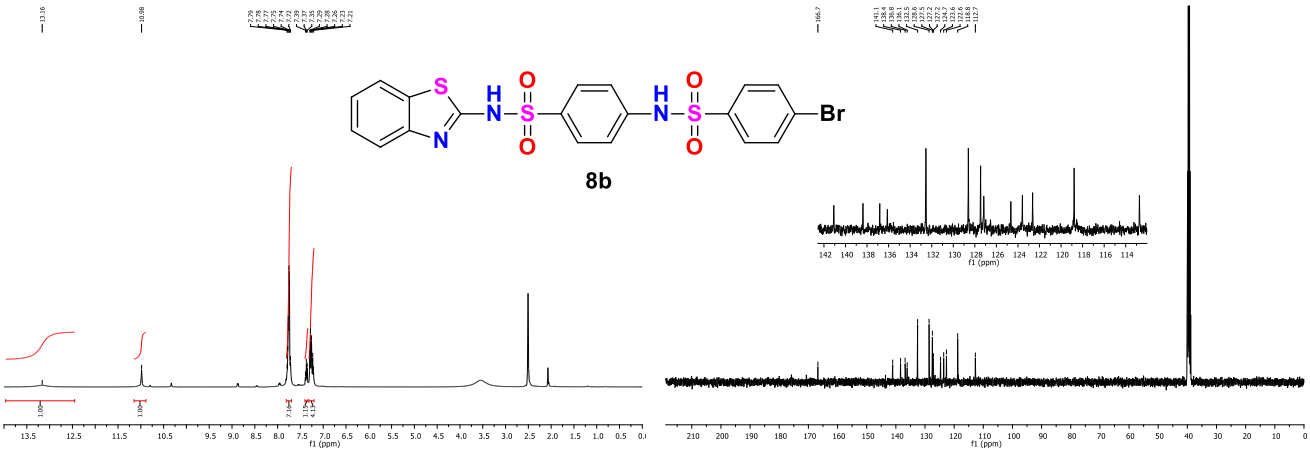

Figure 7. ^{1}H-NMR and ^{13}C-NMR spectrums of compound **8b**

İnitially, 4-amino-N-(benzo[d]thiazol-2-yl)benzenesulfonamide **6** was synthesized in two steps in high yield. According to this synthesis protocol, treating the benzo[d]thiazol-2-amine **4** with *p*-acetamidobenzene-1-sulfonyl chloride in pyridine, the desired product **5** was smoothly obtained in 74% yield. The obtained compound **5** was hydrolyzed in a basic medium. The reaction mixture was neutralized using 2 M HCl solution and the resulting solid was filtered off. The obtained solid can be passed to the next step without further purification. The corresponding aromatic amine derivative **6** was prepared in an 82% yield. Since aromatic amines are very weak bases, they can easily attack partial electropositive centres nucleophilically. From this point of view, in this study, we investigated the nucleophilic addition of amines to both aryl acyl chlorides and benzene sulfonyl chlorides having pharmacological groups. First, we performed the reaction of **6** with furan-2-carbonyl chloride. Since compound **6** is very polar, it is insoluble in polar aprotic solvents such as DCM and THF. Although it dissolves in polar protic solvents such as DMF and DMSO, it was not preferred due to the loss of yield that we may encounter in removing these solvents after the reaction. During this reaction, hydrogen chloride gas is released. When pyridine is used as a solvent, it will not only trap this gas but also accelerate nucleophilic addition. In this context, we performed the model reaction in pyridine at room temperature. The final product **7a** was obtained with 81% yield under optimized conditions. Then, when the same reaction was repeated with thiophene-2-carbonyl chloride and 4-methoxybenzoyl chloride, the resulting products **7b** and **7c** were achieved in 81% and 76% yield, respectively.

Secondly, it was started to synthesize bissulfonamide derivatives from the reaction of **6** with aryl sulfonyl chlorides. As in the above reaction, pyridine was used as both the base and the solvent in the sulfonation reactions. The reaction of **6** (1 equivalent) with tosyl chloride (1 equivalent) was carried out in pyridine at room temperature. Depletion of the starting compound was checked using TLC. After the starting compound was finished, the crude mixture was poured onto acidified ice. In this way, pyridine was converted to its salt form and dissolved in water. The organic precipitate formed was filtered and washed, and the product was purified from the reaction medium. Target compound **8a** was successfully obtained in 82% yield. Then, the same reaction conditions were repeated with 4-bromobenzenesulfonyl chloride compounds. As a result, two different bissulfonamide derivatives, unknown in the literature, were obtained with yields between 82% and 86%. Structure characterization of title compounds **7a-c**, **8a-b** were performed by taking ^{1}H-NMR, ^{13}C-NMR, FT-IR and mass spectra (Figure 8).

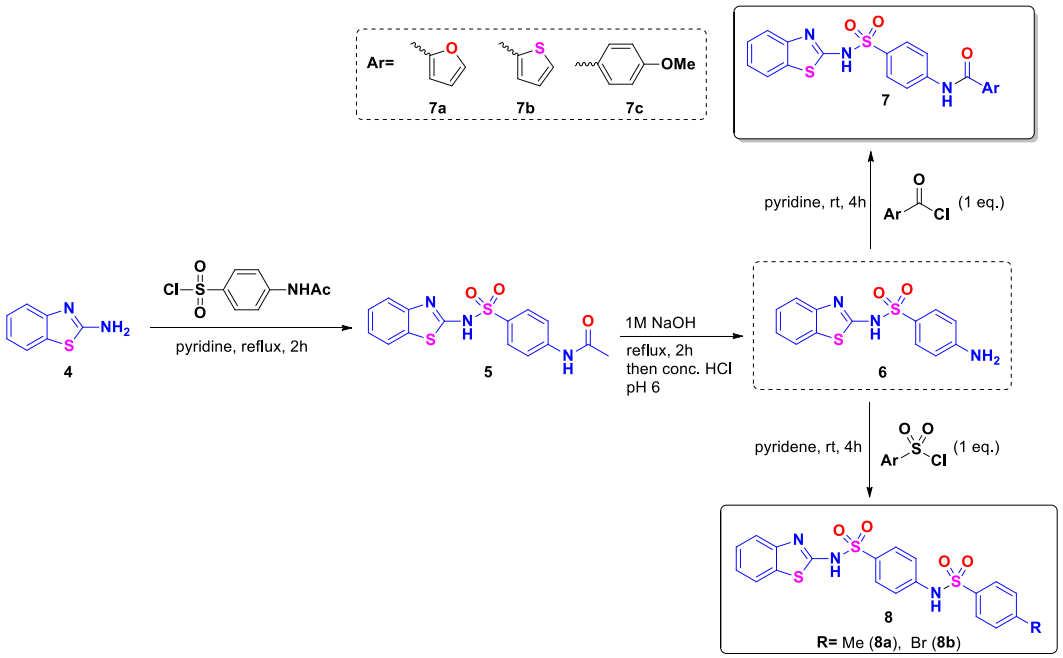

Figure 8. Synthesis design of new benzothiazole-based sulfonamide hybrid compounds **7a-c**, **8a-b**

CONCLUSION

As a result, new benzothiazole-based **7a-c** and **8a-b** hybrid analogues containing groups showing significant pharmacophore properties in a single molecule were synthesized in yields ranging from 76% to 86%. The structures of the title compounds were elucidated by spectroscopic techniques. In the outcome of ongoing synthesis studies, it is planned to synthesize new hybrid analogues and investigate the pharmacokinetics, pharmacological and chemotherapeutic effects of these structures.

Conflict of Interest

The author declares no competing financial interest.

Author's Contributions

The authors declare that they have contributed equally to the article.

REFERENCES

Abbot V, Sharma, P, Dhiman S, Noolvi MN, Patel HM, Bhardwaj V, 2017. Small hybrid heteroaromatics: resourceful biological tools in cancer research. RSC Advances, 7: 28313–28349.

Adkins JC, Faulds D, 1998. Amprenavir. Drugs, 55(6): 837-842.

Aggarwal M, Kondeti B, McKenna R, 2013. Anticonvulsant/antiepileptic carbonic anhydrase inhibitors: a patent review. Expert Opinion on Therapeutic Patents, 23: 717-724.

Azzam RA, Elboshi, HA, Elgemeie GH, 2020. Novel Synthesis and Antiviral Evaluation of New Benzothiazole Bearing N-Sulfonamide 2-Pyridone Derivatives as USP7 Enzyme Inhibitors. ACS Omega, 5: 30023−30036.

Carta F, Supuran CT, 2013. Diuretics with carbonic anhydrase inhibitory action: a patent and literature review (2005-2013). Expert Opinion on Therapeutic Patents, 23: 681-691.

Gulçin İ, Taslimi P, 2018. Sulfonamide inhibitors: a patent review 2013-present. Expert Opinion on Therapeutic Patents, 28: 541-549.

Ivasiv V, Albertini C, Gonçalves AE, Rossi M, Bolognesi ML, 2019. Molecular hybridization as a tool for designing multitarget drug candidates for complex diseases. Current Topics in Medicinal Chemistry, 19: 1694-1711.

Keri RS, Patil MR, Patil SA, Budagumpi S, 2015. A comprehensive review in current developments of benzothiazole-based molecules in medicinal chemistry, European Journal of Medicinal Chemistry, 89, 207-251.

Kerru N, Singh P, Koorbanally N, Raj R, Kumar V, 2017. Recent advances (2015–2016) in anticancer hybrids. European Journal of Medicinal Chemistry, 142: 179–212.

Lin SJ, Tsai WJ, Chiou WF, Yang TH, Yang LM, 2008. Selective COX-2 inhibitors. Part 2: Synthesis and biological evaluation of 4-benzylideneamino-and 4-phenyliminomethyl-benzenesulfonamides. Bioorganic & Medicinal Chemistry, 16: 2697–2706.

Luci DK, Jameson JB, Yasgar A, Diaz G, Joshi N, Kantz A, Markham K, Perry S, Kuhn N, Yeung J, Kerns EH, Schultz L, Holinstat M, Nadler JL, Taylor-Fishwick DA, Jadhav A, Simeonov A, Holman TR, Maloney DJ, 2014. Synthesis and Structure-Activity Relationship Studies of 4-((2- Hydroxy-3-methoxybenzyl)amino) benzenesulfonamide Derivatives as Potent and Selective Inhibitors of 12-Lipoxygenase. Journal of Medicinal Chemistry, 57: 495−506.

Lyseng-Williamson KA, Yang LPH, 2008. Spotlight on Topiramate in Epilepsy. CNS Drugs, 22: 171-174.

Murata M, Horiuchi E, Kanazawa I, 2001. Zonisamide has beneficial effects on Parkinson's disease patients. Neuroscience Research, 41: 397-399.

Naaz F, Srivastava R, Singh A, Singh N, Verma, R, Singh, VK, Singh RK, 2018. Molecular modeling, synthesis, antibacterial and cytotoxicity evaluation of sulfonamide derivatives of benzimidazole, indazole, benzothiazole andthiazole. Bioorganic & Medicinal Chemistry, 26: 3414–3428.

Nishimoria I, Vullo D, Innocenti A, Scozzafava A, Mastrolorenzo A, Supuran CT, 2005. Carbonic anhydrase inhibitors: Inhibition of the transmembrane isozyme XIV with sulfonamides. Bioorganic & Medicinal Chemistry Letters, 15: 3828-3833.

Rouf A, Tanyeli C, 2015. Bioactive thiazole and benzothiazole derivatives. European Journal of Medicinal Chemistry, 97, 911-927.

Sandhu S, Bansal Y, Silakari O, Bansal G, 2014. Coumarin hybrids as novel therapeutic agents. Bioorganic & Medicinal Chemistry, 22: 3806–3814.

Supuran CT, Nicolae A, Popescu A, 1996. Carbonic anhydrase inhibitors. Part 35. Synthesis of Schiff bases derived from sulfanilamide and aromatic aldehydes: the first inhibitors with equally high affinity towards cytosolic and membrane-bound isozymes. European Journal of Medicinal Chemistry, 31: 431-438.

Supuran CT, Scozzafava A, 2000. Carbonic anhydrase inhibitors and their therapeutic potential. Expert Opinion on Therapeutic Patents, 10: 575–600.

Supuran CT, Scozzafava A, 2000. Carbonic anhydrase inhibitors-Part 94. 1,3,4-Thiadiazole-2-sulfonamide derivatives as antitumor agents? European Journal of Medicinal Chemistry, 35: 867-874.

Supuran CT, Scozzafava A, 2001. Carbonic Anhydrase Inhibitors. Current Medicinal Chemistry, 363: 61-97.

Supuran CT, Scozzafava A, 2007. Carbonic anhydrases as targets for medicinal chemistry. Bioorganic & Medicinal Chemistry. 15: 4336–4350.

Wong D, Wang M, Cheng Y, Gerald GAF, 2005. Cardiovascular hazard and non-steroidal anti-inflammatory drugs. Current Opinion in Pharmacology, 5: 2014-210.