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ORIGINAL ARTICLE / ÖZGÜN MAKALE

NEW SULFONAMIDO-BENZOXAZOLE DERIVATIVES AS ANTIMICROBIAL AGENTS: DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION

ANTİMİKROBİYAL AJAN OLARAK YENİ SÜLFONAMİDO-BENZOKSAZOL TÜREVLERİ: TASARIM, SENTEZ VE BİYOLOJİK DEĞERLENDİRME

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ABSTRACT

Objective: *Many investigations are conducted in the battle against infectious diseases in order to develop new drug-active ingredient candidate compounds and to identify leading compounds. The goal of this study was to synthesis a total of seven compounds, six of which are novel, with the general structure 2-(4-tert-butylphenyl)-5-(4-substitutedphenylsulfonamido)benzoxazole, to elucidate their structures, and to test their antimicrobial activities using the microdilution method.*
Material and Method: *The synthesis of the compounds was carried out in two stages. In the first stage, under PPA catalyst 2,4-diaminophenol and 4-tert-butylbenzoic acid were refluxed, and target compounds were produced in the second step by reacting 4-substitutedbenzenesulfonyl chloride with 5-Amino-2-(4-tert-butylphenyl)benzoxazole. The compounds' antimicrobial activity was determined by using Enterococcus faecalis, Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Candida albicans, and drug-resistant strains of these microorganisms in vitro antimicrobial activity studies. Furthermore, estimated ADME profiles were calculated using the SwissADME online software.*
Result and Discussion: *The structures of the synthesized compounds were elucidated using ^{1}H-NMR, ^{13}C-NMR and Mass spectroscopy, and also their melting points were determined. The antimicrobial activities of the compounds ranged from 64 µg/ml to >512 µg/ml and were weaker than the reference drugs. The best antimicrobial activity was reported against an isolate of E. faecalis, with all compounds having MIC values of 64 µg/ml. The fact that six of the seven synthesized compounds are novel and that their antimicrobial activity will be tested for the first time will make a significant contribution to studies to develop new or alternative antimicrobial agents.*
Keywords: *ADME, antimicrobial activity, benzoxazole, sulfonamide*

ÖZ

Amaç: *Bulaşıcı hastalıklarla mücadelede yeni ilaç-etkin madde aday bileşikleri geliştirmek ve öncü bileşiklere ulaşmak için birçok araştırma yapılmaktadır. Bu çalışmanın amacı, genel yapısı 2-(4-tert-bütilfenil)-5-(4-sübstitüefenilsülfonamido)benzoksazol olan altısı yeni olmak üzere toplam yedi bileşiğin yapılarını aydınlatmak ve mikrodilüsyon yöntemini kullanarak antimikrobiyal*

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aktivitelerini test etmektir.
Gereç ve Yöntem: *Bileşiklerin sentezi iki aşamada gerçekleştirilmiştir. İlk basamakta, PPA katalizörü altında 2,4-diaminofenol ve 4-tert-bütilbenzoik asit refluks edilmiş ve ikinci aşamada 4-sübstitüebenzensülfonil klorürün 5-Amino-2-(4-tert-bütilfenilbenzoksazol ile reaksiyona sokulmasıyla hedef bileşikler üretilmiştir. Bileşiklerin antimikrobiyal aktivitesi, Enterococcus faecalis, Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Candida albicans ve bu mikroorganizmaların ilaca dirençli suşları kullanılarak in vitro antimikrobiyal aktivite çalışmaları ile belirlenmiştir. Ayrıca, SwissADME çevrimiçi yazılımı kullanılarak tahmini ADME profilleri hesaplanmıştır.*
Sonuç ve Tartışma: *Sentezlenen bileşiklerin yapıları, ^{1}H-NMR, ^{13}C-NMR ve Kütle spektroskopisi kullanılarak aydınlatıldı ve ayrıca erime noktaları belirlenmiştir. Bileşiklerin antimikrobiyal aktiviteleri 64 µg/ml ila >512 µg/ml aralığındaydı ve referans ilaçlardan daha zayıftı. En iyi antimikrobiyal aktivite, tüm bileşiklerin 64 µg/ml MİK değerlerine sahip olduğu bir E. faecalis izolatına karşı rapor edilmiştir. Sentezlenen yedi bileşikten altısının yeni olması ve antibakteriyel aktivitelerinin ilk kez test edilecek olması, yeni veya alternatif antimikrobiyal ajanların geliştirilmesine yönelik çalışmalara önemli katkı sağlayacaktır.*
Anahtar Kelimeler: *ADME, antimikrobiyal aktivite, benzoksazol, sülfonamid*

INTRODUCTION

Bacterial and fungal diseases occur all over the world and cause quite large epidemics [1]. Unicellular organisms such as bacteria and fungi live in harmony in the bodies of multicellular organisms such as humans due to their natural habitats. When this balance is disturbed, opportunistic bacteria that take advantage of this situation cause infection [2,3]. Furthermore, drug-induced or microorganism-induced resistance of various phenotypes that develop in situations such as unnecessary drug use and multiple drug use, misdiagnosis, incorrect treatment methods, prescriptions written only to eliminate symptoms, and patients' abandonment of their treatment make fighting infectious diseases difficult [4-9]. Recent studies revealing mortality and morbidity rates increase the concern about infection cases, and microbial resistance developed by bacteria and fungi is added to this concern [10,11]. Because of the rapid development of antimicrobial drug resistance, researchers have been working hard to produce new and effective medications having these effects and agree that generating novel compounds with different structures than existing medications can help to prevent the development of resistance. For this reason, research is carried out on many compounds with different structures [12,13].

Today, benzoxazole derivative compounds are an important group on which antimicrobial activity studies are carried out intensively [14]. Compounds with the benzoxazole ring system are employed as active medicinal components in treatment due to their anticancer [15], anti-inflammatory [16], antioxidant [17], anti-alzheimer [18], and anticonvulsant [19]. Because of its structural resemblance to adenine and guanine bases, the benzoxazole ring is predicted to interact more easily with biopolymers in biological systems. So far, substitutions at the second position of the ring have been thoroughly studied, yielding a wealth of information on their structural properties and impacts.

In some previous studies, 5-ethylsulfonyl-2-(4-substitutedphenyl and/or substituted benzyl and/or phenylethyl)benzoxazole derivative compounds were synthesized, their antimicrobial activities were examined, and promising results were obtained [20]. In light of this information, the design and synthesis of compounds with the general formula 2-(4-tert-butylphenyl)-5-(4-substitutedphenylsulfonamido)benzoxazole were carried out within the scope of the study, and their structures were proven using ^{1}H-NMR, ^{13}C-NMR, and Mass spectroscopy analysis methods. The antimicrobial activities of the compounds were evaluated using Minimum Inhibitory Concentration (MIC). Finally, the estimated ADME parameters were calculated.

MATERIAL AND METHOD

Chemistry

All chemicals used in this research were purchased from Sigma Aldrich, Merck, Riedel de Haen,

and Fluka. Varian Mercury 400 MHz High-Performance Digital FT-NMR spectrometer (Palo Alto, CA, USA) was used to record the ^{1}H- and ^{13}C Nuclear Magnetic Resonance spectra. TMS was utilized as an internal standard in this spectrometer, while deuterated chloroform ($CDCl_3$) was used as a solvent. Melting points were determined using an electrothermal device, and the results were not corrected. On a Waters 2695 Alliance Micromass ZQ LC/MS spectrometer (Milford, MA, USA), mass analyses were done using the Electrospray Ionization (ESI) (+) method. In this investigation, 7 compounds were synthesized, 6 of which were novel.

General Synthesis of N2-N8

Firstly, 1 mmol 2,4-diaminophenol dihydrochloride and 1 mmol 4-tert-butyl benzoic acid were reacted at 160-190°C for around 3 h in the presence of polyphosphoric acid (PPA). At the end of the reaction, the product was poured into ice and stirred. After thoroughly mixing, it was neutralized with 10% NaOH and filtered. Finally, it was cleaned with activated charcoal and crystallized from ethanol-water. This compound (**N1**) obtained is not original [14]. The reaction of 5-Amino-2-(4-tert-butylphenyl)benzoxazole with 4-substitutedbenzenesulphonyl chloride in the presence of dichloromethane and pyridine yielded **N2-N8** in the second stage (Figure 1). Crystallization from ethanol-water was used to purify the desired products. **N2** is a commercially available product that is not original.

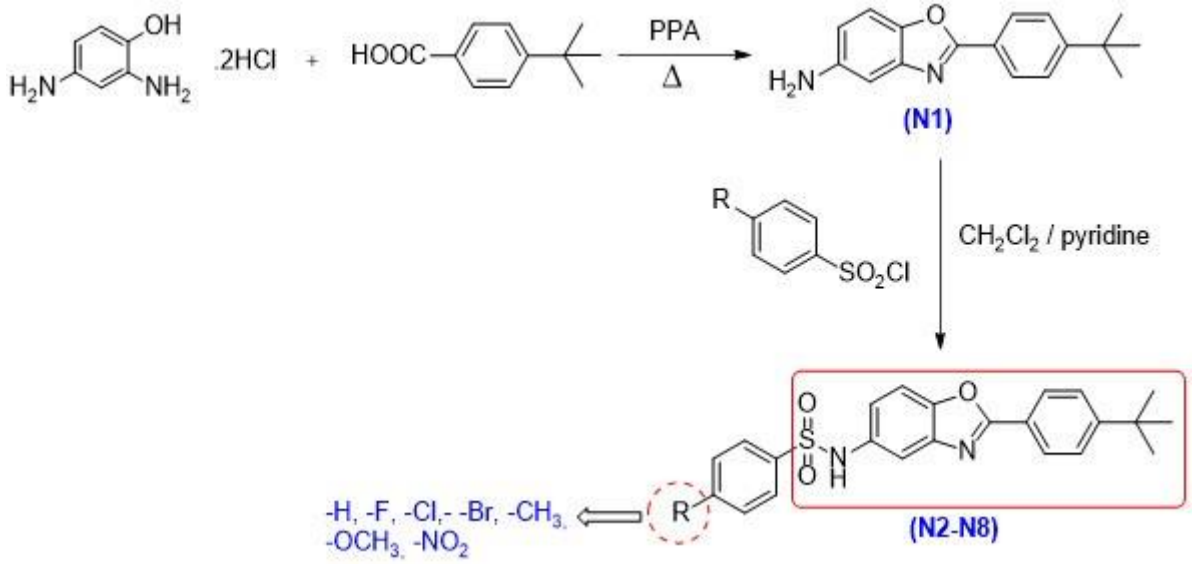

Figure 1. Synthesis of 2-(4-tert-butylphenyl)-5-(4-substitutedphenylsulfonamido)benzoxazole derivatives

Antimicrobial Activity

As in the previous investigations, the *in vitro* antimicrobial activity of compounds was appointed using the microdilution method as the minimal inhibitory concentration [14,21]. Standard strains and clinical isolates of *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, and *Candida albicans* ATCC 10231 were employed. Standard strains and clinical isolates were obtained from the Trakya University Faculty of Medicine Microbiology Laboratory.

***In Silico* ADME Prediction**

The SwissADME web server as used to calculate some critical ADME characteristics, such as the physicochemical and pharmacokinetic features of the drugs. Some parameters of the compounds such as physicochemical properties, lipophilicity, water solubility, pharmacokinetic properties, and drug similarity were estimated.

RESULT AND DISCUSSION

Chemistry

The **N2-N8** series was synthesized in our work following the procedure described in the literature, as shown in Figure 1 [22,23]. Initially, 5-Amino-2-(4-tert-butylphenyl)benzoxazole was obtained by reaction of 2,4-diaminophenol with 4-tert-butylbenzoic acid in PPA. The target compounds were then synthesized by reacting 4-substitutedbenzenesulfonyl chlorides with 5-Amino-2-(4-tert-butylphenyl)benzoxazole. After TLC and melting point were used to determine the purity of the synthesized compounds, their structures were determined using ^{1}H-NMR and ^{13}C-NMR and Mass spectroscopy. When the compounds' ^{1}H-NMR spectra were investigated, aromatic protons were observed in the range of 7.20-8.26 ppm, tert-butyl protons as a 9H singlet at 1.36-1.37 ppm, and methoxy proton as a singlet at 3.81 ppm. The ^{13}C-NMR spectra revealed aliphatic carbon in the 21.53-55.53 ppm range and aromatic carbon in the 110.44-166.54 ppm range. Electrospray ionization positive (ESI+) method was used for mass spectral analysis and their relative intensities as (M+H)+ ions were easily monitored. In all compounds, a M+H peak was identified in the mass spectrum analysis. M+H+2 and M+H+4 peaks were also found in compounds containing elements with isotope abundances that were reasonably close or equal, such as bromine and chlorine.

2-(4-Tert-butylphenyl)-5-(phenylsulfonamido)benzoxazole (N2)

Yield: 75%, mp: 225-226°C**.** ^{1}H-NMR (400 MHz, $CDCl_3$, δ): 1.36 (9H, s), 6.97 (1H, s), 7.11-7.14 (1H, dd, J_m=1.6, J_o=8.6), 7.40-7.45 (4H, m), 7.50-7.54 (3H, m), 7.78 (2H, d, J_o=7.2), 8.12 (2H, d, J_o=8.8). ^{13}C -NMR (100 MHz, $CDCl_3$, δ): 31.11, 35.10, 110.87, 114.45, 120.88, 123.88, 125.97, 127.31, 127.52, 129.08, 132.98, 133.07, 138.78, 142.78, 148.86, 155.56, 164.49. MS (ESI+) m/z: 407.2 (M+H)(100).

2-(4-Tert-butylphenyl)-5-(4-fluorophenylsulfonamido)benzoxazole (N3)

Yield: 55%, mp: 195-198°C**.** ^{1}H-NMR (400 MHz, $CDCl_3$, δ): 1.36 (9H, s), 6.99 (1H, s), 7.07-7.13 (3H, m), 7.43-7.47 (2H, m), 7.53 (2H, d, J_o=8.8), 7.77-7.80 (2H, m), 8.12 (2H, d, J_o=8.4). ^{13}C -NMR (100 MHz, $CDCl_3$, δ): 31.11, 35.11, 110.98, 114.56, 116.26, 116.49, 120.93, 123.80, 125.99, 127.55, 130.04, 130.14, 132.75, 142.83, 148.96, 155.65, 164.00, 164.61, 166.54. MS (ESI+) m/z: 425.5 (M+H)(100).

2-(4-Tert-butylphenyl)-5-(4-chlorophenylsulfonamido)benzoxazole (N4)

Yield: 60%, mp: 229-230°C**.** ^{1}H-NMR (400 MHz, $CDCl_3$, δ): 1.37 (9H, s), 6.96 (1H, s), 7.10-7.13 (1H, dd, J_m=2.4, J_o=8.8), 7.39 (2H, d, J_o=8.4), 7.43-7.47 (2H, m), 7.46 (1H, d, J_o=8.4), 7.53 (2H, d, J_o=8.4), 7.69 (2H, d, J_o=8.8), 8.13 (2H, d, J_o=8.4). ^{13}C -NMR (100 MHz, $CDCl_3$, δ): 31.11, 35.12, 111.02, 114.61, 120.95, 123.79, 126.00, 127.56, 128.76, 129.40, 132.61, 137.24, 139.68, 142.85, 149.00, 155.67, 164.64. MS (ESI+) m/z: 441.2 (M+H)(100), 443.3 (33).

2-(4-Tert-butylphenyl)-5-(4-bromophenylsulfonamido)benzoxazole (N5)

Yield: 50%, mp: 224-226°C**.** ^{1}H-NMR (400 MHz, $CDCl_3$, δ): 1.36 (9H, s), 6.99 (1H, s), 7.10-7.12 (1H, dd, J_m=2, J_o=8.8), 7.44-7.47 (2H, m), 7.52-7.56 (4H, m), 7.62 (2H, d, J_o=8.8), 8.12 (2H, d, J_o=8.4)**.** ^{13}C -NMR (100 MHz, $CDCl_3$, δ): 31.11, 35.12, 111.03, 114.59, 120.94, 123.79, 126.00, 127.56, 128.22, 128.83, 132.39, 132.59, 137.78, 142.85, 149.00, 155.66, 164.64. MS (ESI+) m/z: 485.2 (M+H)(100), 487.2 (90).

2-(4-Tert-butylphenyl)-5-(4-methylphenylsulfonamido)benzoxazole (N6)

Yield: 70%, mp: 227-229°C**.** ^{1}H-NMR (400 MHz, $CDCl_3$, δ): 1.37 (9H, s), 2.36 (3H, s), 6.92 (1H, s), 7.13-7.15 (1H, dd, J_m=2, J_o=8.4), 7.21 (2H, d, J_o=8.4), 7.41-7.45 (2H, m), 7.53 (2H, d, J_o=8.8), 7.66 (2H, d, J_o=8.4), 8.12 (2H, d, J_o=8.4).^{13}C -NMR (100 MHz, $CDCl_3$, δ): 21.53, 31.11, 35.10, 110.84, 114.26, 120.81, 123.89, 125.97, 127.35, 127.51, 129.70, 133.18, 135.81, 142.72, 143.93, 148.77, 155.53, 164.43. MS (ESI+) m/z: 421.5 (M+H)(100).

2-(4-Tert-butylphenyl)-5-(4-methoxyphenylsulfonamido)benzoxazole (N7)

Yield: 65%, mp: 206-207°C**.** ^{1}H-NMR (400 MHz, $CDCl_3$, δ): 1.37 (9H, s), 3.81 (3H, s), 6.77 (1H, s), 6.87 (2H, d, J_o=9.2), 7.12-7.14 (1H, dd, J_m=2, J_o=8.4), 7.40-7.46 (2H, m), 7.53 (2H, d, J_o=8.8), 7.70 (2H, d, J_o=9.2), 8.13 (2H, d, J_o=8.4). ^{13}C -NMR (100 MHz, $CDCl_3$, δ): 22.68, 35.10, 55.53, 110.83, 114.22, 114.32, 120.87, 123.90, 125.97, 127.51, 129.50, 130.33, 133.25, 142.75, 148.78, 155.53, 163.14, 164.44. MS (ESI+) m/z: 437.4 (M+H)(100).

2-(4-Tert-butylphenyl)-5-(4-nitrophenylsulfonamido)benzoxazole (N8)

Yield: 45%, mp: 239-240°C**.** ^{1}H-NMR (400 MHz, $CDCl_3$, δ): 1.37 (9H, s), 6.96 (1H, s), 7.10-7.13 (1H, dd, J_m=2, J_o=8.8), 7.44-7.49 (2H, m), 7.53 (2H, d, J_o=8.4), 7.93 (2H, d, J_o=8.4), 8.12 (2H, d, J_o=8.4), 8.26 (2H, d, J_o=8.8). ^{13}C -NMR (100 MHz, $CDCl_3$, δ): 31.08, 35.11, 111.19, 115.03, 121.14, 123.66, 124.28, 126.01, 127.61, 128.60, 131.90, 143.03, 144.54, 149.32, 150.31, 155.85, 164.91. MS (ESI+) m/z: 452.4 (M+H)(100).

Antimicrobial Evaluation

The MIC (μg/ml) values for the antimicrobial activity of the synthesized compounds and reference drugs were given in Table 1. When the antimicrobial activities of the synthesized compounds were evaluated as MIC values, they were found in the range of 64 ->512 μg/ml . According to the study's results, the best antimicrobial activity was observed against *E. faecalis* isolate (VREF), and all compounds showed MIC value of 64 μg/ml. The synthesized compounds have MIC of 128 μg/ml against *S. aureus* and its isolate (MRSA), *E. faecalis, E. coli* and its isolate, *P. aeruginosa* and its isolate. The antifungal activities of the compounds against *C. albicans* were >512 μg/ml, and were much less effective than amphotericin B (0.5 μg/ml). As a result, it was shown that the compounds in the study showed moderate antibacterial, and very low antifungal activity and the change of substituents had no effect on the activity. These derivatives will make an essential addition to research to develop new or alternative antibacterial agents due to the uniqueness of the compounds in our study and the first evaluation of their antimicrobial activity.

Table 1. *In vitro* antimicrobial MIC values (μg/ml) of **N2-N8** and reference drugs

Compound	S. a.	S.a.*	E.f.	E.f. *	E. c	E. c*	P. a	P. a*	C. a
N2	128	128	128	64	128	128	128	128	>512
N3	128	128	128	64	128	128	128	128	>512
N4	128	128	128	64	128	128	128	128	>512
N5	128	128	128	64	128	128	128	128	>512
N6	128	128	128	64	128	128	128	128	>512
N7	128	128	128	64	128	128	128	128	>512
N8	128	128	128	64	128	128	128	128	>512
Vancomycin	<0,0625	<0,0625	<0,0625	>8 (R)	-	-	-	-	-
Ampicillin	2	>8 (R)	2	>8 (R)	2	2	-	-	-
Meropenem	<0,0625	>8 (R)	-	-	<0.0625	<0.0625	0.5	0.5	-
Ciprofloxacin	0,5	0,5	2	2	<0.0625	<0.0625	1	2 (R)	-
Gentamicin	1	2 (R)	-	-	0.25	0.25	0.5	>8 (R)	-
Amphotericin B	-	-	-	-	-	-	-	-	0.5

S. a: *Staphylococcus aureus* ATCC 29213; S. a.*: Methicillin-Resistant *Staphylococcus aureus* (MRSA); E.f. : *Enterococcus faecalis* ATCC 29212; E.f.*: Vancomycin resistant *E. faecalis* (VREF); E. c.: *Escherichia coli* ATCC 25922; E.c.*: *E. coli* isolate; P.a.: *Pseudomonas aeruginosa* ATCC 27853; P.a.*: *P. aeruginosa* isolate; C.a.: *Candida albicans* ATCC 1023. **(R)**: Resistant (according to CLSI and EUCAST)

***In Silico* ADME Calculation**

Data on ADME properties should be supplied as early as possible in the drug research process to identify prospective candidates. Many drug candidates fail early in the drug development process due to poor ADME characteristics such as inadequate absorption and extensive first-pass metabolism. By identifying the best drug development candidates and excluding those who are unlikely to succeed, early

assessment of ADME features minimizes screening, trial time, and costs. It also offers the information required for proper dosage forms and formulation. Predicting ADME features in silico is therefore critical for drug research and development. As a result, some of the compounds' physicochemical properties were determined using the SwissADME program, and these guidelines, as well as the compliance of the synthesized compounds with these rules, are shown in Table 2. The compounds' molecular weights ranged between 406.5 and 485.39 g/mol. All compounds had poor water solubility. There was low GI absorption and BBB permeability. It obeyed all the limiting rules of Lipinski and Veber. PAINS, Brenk, and Leadlikeness values were suitable for all compounds, and synthetic accessibility was in the easy class.

Table 2. Calculated SwissADME parameters of **N2-N8**

	N2	N3	N4	N5	N6	N7	N8
Physicochemical Properties							
Molecular weight	406.50	424.49	440.94	485.39	420.52	436.52	451.49
Num. heavy atoms	29	30	30	30	30	31	32
Num. arom. heavy atoms	21	21	21	21	21	21	21
Num. rotatable bonds	5	5	5	5	5	6	6
Num. H-bond acceptors	4	5	4	4	4	5	6
Num. H-bond donors	1	1	1	1	1	1	1
Molar Refractivity	115.83	115.79	120.84	123.53	120.79	122.32	124.65
TPSA	80.58	80.58	80.58	80.58	80.58	89.81	126.40
Lipophilicity							
Log Po/w(iLOGP)	3.70	3.63	3.23	3.90	3.76	3.94	3.07
Log Po/w(XLOGP3)	5.62	5.72	6.25	6.31	5.98	5.59	5.45
Log Po/w(WLOGP)	6.48	7.04	7.14	7.25	6.79	6.49	6.39
Log Po/w(MLOGP)	3.60	3.97	4.08	4.18	3.54	3.00	2.69
Log Po/w(SILICOS-IT)	4.28	4.70	4.92	4.96	4.81	4.35	2.12
Consensus Log Po/w	4.74	5.01	5.12	5.32	4.98	4.67	3.94
Water Solubility							
Log S (ESOL)	-6.11	-6.26	-6.70	-7.01	-6.40	-6.17	-6.16
Class	Poorly	Poorly	Poorly	Poorly	Poorly	Poorly	Poorly
Log S (Ali)	-7.08	-7.18	-7.73	-7.79	-7.45	-7.24	-7.86
Class	Poorly	Poorly	Poorly	Poorly	Poorly	Poorly	Poorly
Pharmacokinetics							
GI absorption	Low	Low	Low	Low	Low	Low	Low
BBB permeant	No	No	No	No	No	No	No
CYP1A2 inhibitor	Yes	No	No	No	No	No	No
CYP2C19 inhibitor	Yes	Yes	Yes	Yes	Yes	Yes	Yes
CYP2C9 inhibitor	Yes	Yes	Yes	Yes	Yes	Yes	Yes
CYP2D6 inhibitor	Yes	Yes	Yes	Yes	No	Yes	No
CYP3A4 inhibitor	Yes	Yes	Yes	No	Yes	Yes	Yes
Log Kp	-4.79 cm/s	-4.83 cm/s	-4.55 cm/s	-4.78 cm/s	-4.62 cm/s	-4.99 cm/s	-5.18 cm/s
Druglikeness							
Lipinski	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ghose	No	No	No	No	No	No	No
Veber	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Egan	No	No	No	No	No	No	No
Muegge	No	No	No	No	No	No	No
Medicinal Chemistry							
PAINS	0 alert	0 alert	0 alert	0 alert	0 alert	0 alert	0 alert
Brenk	0 alert	0 alert	0 alert	0 alert	0 alert	0 alert	2 alerts
Leadlikeness	No	No	No	No	No	No	No
Synthetic accessibility	3.52	3.50	3.52	3.55	3.64	3.58	3.67

The study attempts to find new drug-active candidate compounds to fight infectious diseases or to reveal the investigations required to find the leading compounds. As a result, 7 sulfonamido-benzoxazole derivative compounds, 6 of which were novel, were developed, and synthesized in two steps, their structures validated by ^{1}H-NMR, ^{13}C-NMR, and Mass spectroscopy, and their antibacterial properties were tested on 9 distinct microorganisms. Standard strains of nosocomial infectious pathogens and drug-resistant isolates in people were used to create the test microorganisms. The synthesized compounds were shown to have lower antibacterial activity than the reference drugs. In

addition, some estimated ADME parameters have been calculated and are estimated to show low gastrointestinal absorption, although generally complying with the limiting rules. The compounds are essential as they are newly synthesized and tested for the first time against selected bacterial, fungal, and clinical isolates. The development of resistance against existing treatment methods will significantly contribute to the studies conducted to develop new or alternative drugs with promising antimicrobial activities.

AUTHOR CONTRIBUTIONS

Concept: M.E., C.A., Ö.T.A.; Design: M.E., C.A., Ö.T.A.; Control: M.E., C.A., G.K., A.S.S., Ö.T.A.; Sources: M.E., C.A., G.K., A.S.S., Ö.T.A.; Materials: M.E., C.A., G.K., A.S.S., Ö.T.A.; Data Collection and/or Processing: M.E., C.A., G.K., A.S.S., Ö.T.A.; Analysis and/or Interpretation: M.E., C.A., G.K., A.S.S., Ö.T.A.; Literature Review: M.E., C.A., G.K., A.S.S., Ö.T.A.; Manuscript Writing: M.E., C.A., G.K., A.S.S., Ö.T.A.; Critical Review: M.E., C.A., G.K., A.S.S., Ö.T.A.; Other: -

CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

ETHICS COMMITTEE APPROVAL

The authors declare that the ethics committee approval is not required for this study.

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