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Antimicrobial activity screening of a series of taurine derivatives

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Abstract

In this study, a series of taurinamide derivatives 1–18 were assessed for their in vitro antimicrobial activity. Enterococcus faecalis, which is the third most commonly isolated nosocomial pathogen among hospital infections, was found to be more susceptible to the tested compounds than other pathogens. Two of the tested compounds, 1 and 18, showed promising activity against E. faecalis, with minimal inhibitory concentrations (MICs) of 128 and 64 µg/mL, respectively. On the other hand, compound 3 was distinguished from other compounds by its better activity against G(−) Escherichia coli bacteria, with a MIC of 512 µg/mL. None of the compounds displayed better activity than the standard drugs Ciprofloxacin and Fluconazole.

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Taurine derivatives, Antimicrobial activity, Broth microdilution method.

1. Introduction

Taurine is the only free and non-proteogenic amino acid in mammalian species. Indeed, as an organoelement isostere of amino acids, taurine possess sulfonic acid instead of carboxylic acid, which imparts permeability, acidity, and biological activities different from those of conventional amino acids [1–4]. Besides taurine's wide range of biological activities, it also possesses antibacterial, antifungal, and antiviral effects [5,6]. The antibacterial effect of taurine is believed to depend on the formation of low cytotoxic taurinechloramine (TCA) formation during inflammation process of the body (Figure 1) [7,8]. Moreover, a stable derivative of TCA which is known as NVC-422 (*N*,*N*-dichloro-2,2-dimethyltaurine) was reported as a broad spectrum antibacterial agent that reached to phase II clinic studies however didn't approve as a drug substance (Figure 1) [9,10]. In the search for finding effective antimicrobial taurine derivatives, Winterbottom et al. functionalized taurine's sulfonic acid as a secondary or tertiary sulfonamide and connected its amino group to pantothenic acid in an amide form to obtain pantolytaurinamide derivatives (Figure 1). These derivatives were tested for their antiplasmodial and antibacterial activities and reported to have promising results [11]. In another study, the sulfonic acid moiety of taurine was converted to its primary sulfonamide analog and introduced into a meropenem structure via an amide connection (Figure 1). This final compound was reported to increase the in vivo efficacy and stability of the parent compound meronepem [1]. Those studies indicate that taurine is a promising building block that can be used in antimicrobial drug development that has reached an impasse in recent years. This problem is mostly the result of resistance mechanisms that pathogens have developed to existing chemical structures. According to the World Health Organization, bacterial resistance has become a worldwide threat that will cause 10 million deaths per year by 2050 [12]. As a result; finding new structures distinct from the known antibiotic scaffolds, would be useful for averting resistance. From this point of view; taurine serves a distinctive feature for medicinal chemists.

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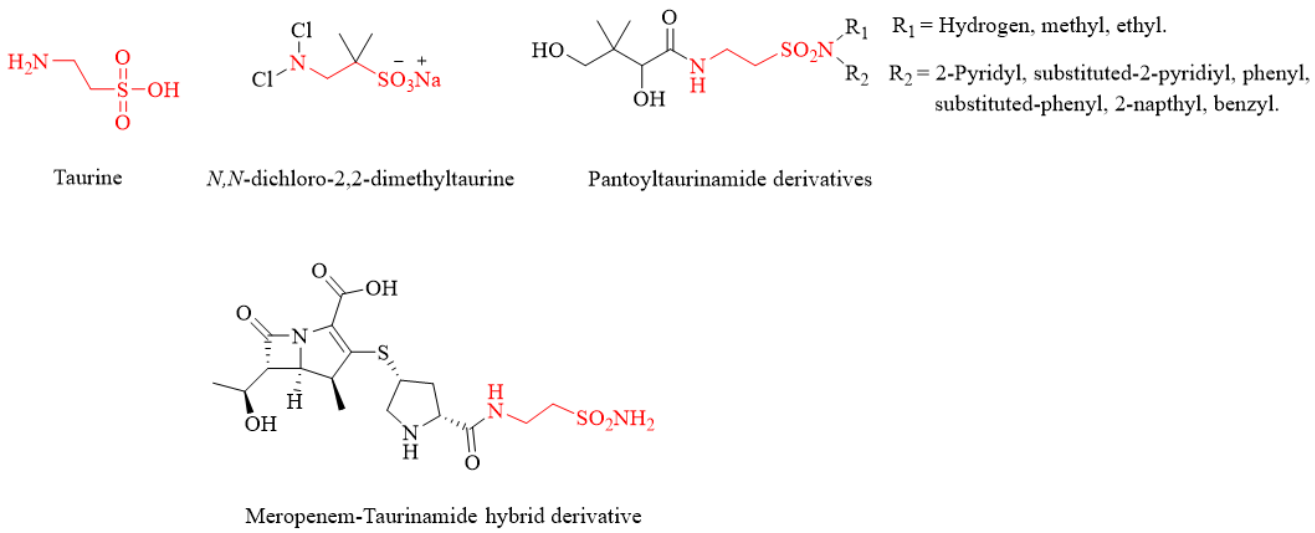


Figure 1. Taurine and its biologically active derivatives.

In our previous study, we added a phthalimido moiety to taurine via its amine while functionalizing it with either hydrogen, a substituted aniline, or morpholine from its sulfonic acid group to achieve primary, secondary, and tertiary sulfonamides, respectively (Figure 2). Synthesized molecules were evaluated for their antimicrobial and antifungal features. Interestingly, among the tested compounds, two compounds having methyl and methoxy moieties on a phenyl ring displayed fairly good activity equal to gentamicin with a minimum inhibitory concentration (MIC) of 4 µg/mL [13]. This result prompted us to continue our research on taurine derivatives to investigate the key structural requirements for obtaining effective antimicrobial agents. For improving the biological activity of a known compound, ring opening is the most well-known strategy that has been used from the beginning of drug discovery [14]. This method is believed to change the flexibility, binding energy, membrane penetration, and absorption of the previously investigated scaffold, thus providing additional contacts with the proposed biological targets. Pursuing this strategy herein, we decided to investigate the amide derivatives of taurinamide as open analogs of phthalamide. Pursuing this strategy herein, we decided to investigate the amide derivatives of taurinamide as open analogs of phthalamide (Figure 3). For this purpose, we functionalized the sulfonic acid part of taurine as primary, secondary (with aniline and 4-methoxyaniline substitution), or tertiary sulfonamides (with morpholine substitution) and coupled the amine group with substituted benzoic acids to obtain amide derivatives. Compounds **1**–**4** and **6**–**17** were evaluated for their cytotoxic activities and presented in our previous study, whereas we report **5** and **18** here for the first time. None of the compounds have been previously inspected for their antimicrobial activity [15].

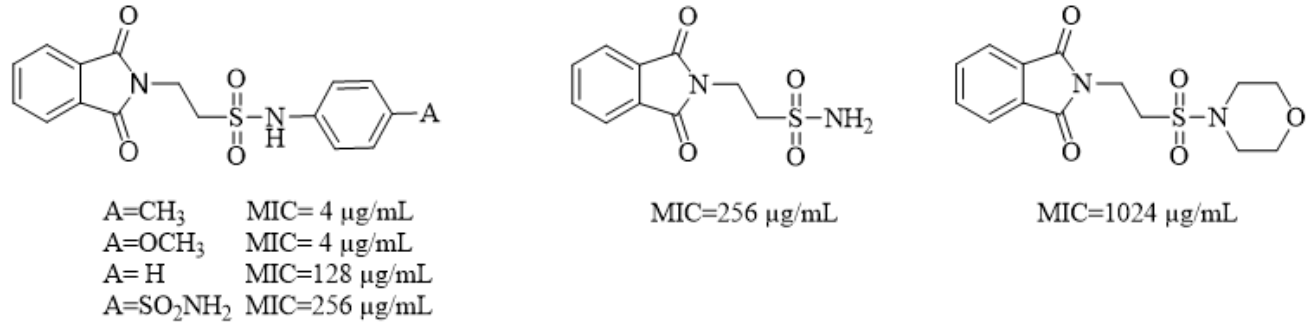


Figure 2. The general structure and antimicrobial activities of previously discovered taurine derivatives.

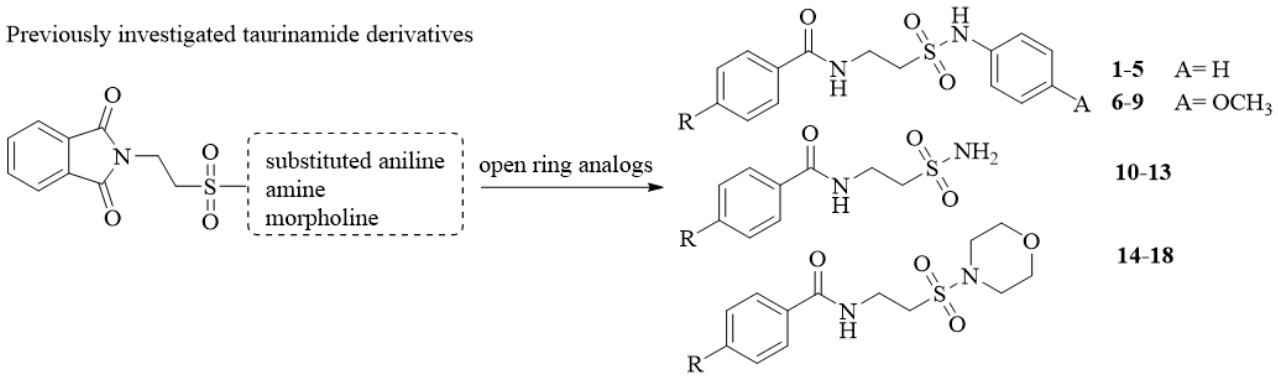
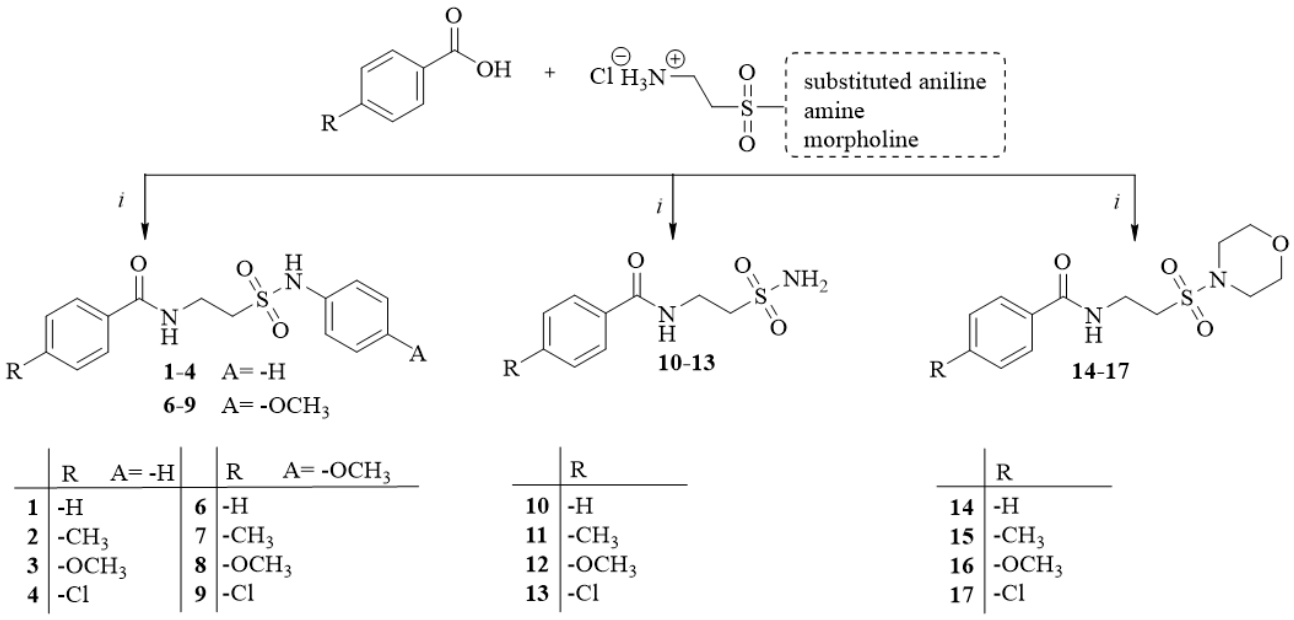


Figure 3. The drug design strategy.

2. Materials and Methods

2.1. Chemistry

Sigma-Aldrich and Interlab (Germany) were the suppliers of the anhydrous solvents and all reagents that were used in our studies. Agilent 600 MHz PremiumCOMPACT NMR spectrometer was used for examining ^{1}H and ^{13}C NMR spectra and DMSO-d_6 was used as a solvent. Parts per million (ppm) unit was used to report chemical shifts and the coupling constants (*J*) were stated in Hertz (Hz). Splitting patterns were assigned as; *s* (singlet); *d* (doublet); *t* (triplet); *m* (multiplet); *br s* (broad singlet). Merck silica gel F-254 plates were utilized for analytical thin-layer chromatography (TLC). Flash chromatography purifications were implemented by using Merck silica gel 60 (230–400 mesh ASTM) as the stationary phase. Stuart® (SMP30) melting point apparatus was used to detect melting points of the compounds in open capillary tubes whereas the values were uncorrected. Elemental analyses (C, H, N, and S) were functioned with a Leco TruSpec CHNS Micro analyzer (Leco Corporation, St. Joseph, MI, USA) and outcomes were within ± 0.4% of calculated values.



	R A= -H		R A= -OCH_3
1	-H	6	-H
2	-CH_3	7	-CH_3
3	-OCH_3	8	-OCH_3
4	-Cl	9	-Cl

	R
10	-H
11	-CH_3
12	-OCH_3
13	-Cl

	R
14	-H
15	-CH_3
16	-OCH_3
17	-Cl

Figure 4. Synthesis of compounds 1-4, 6-17 [15].

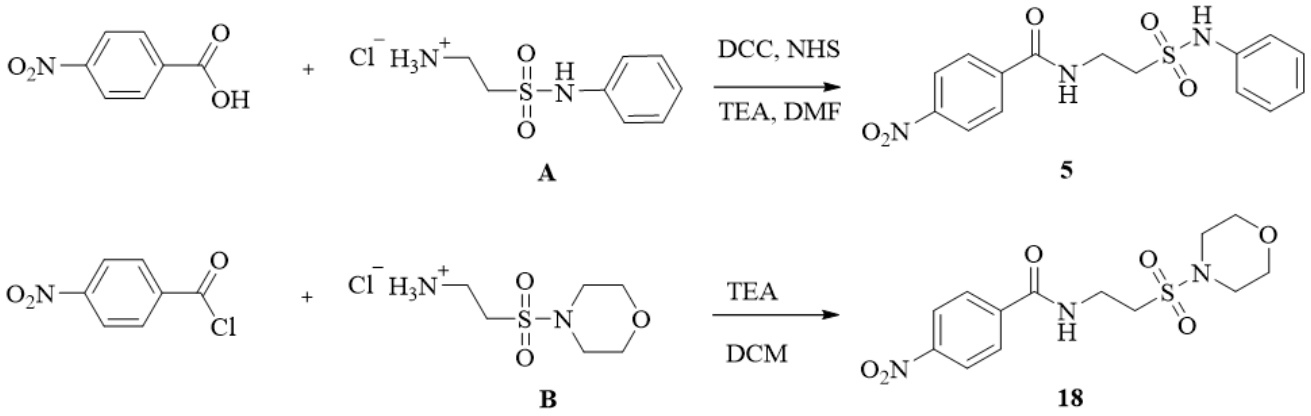


Figure 5. Synthesis of compounds **5** and **18**.

2.2. Synthesis of the Final Compounds 5 and 18

2.2.1. Synthesis of 4 – nitro – *N* - (2 - (*N* – phenylsulfamoyl) ethyl) benzamide (5).

2-(*N*-phenylsulfamoyl)ethanamine hydrochloride salt **(A)** was synthesized according to procedure that was described before [13, 15]. 4-Nitrobenzoic acid (1 mmol), *N*,*N*′-dicyclohexylcarbodiimide (DCC, 1.1 mmol) and *N*-hydroxysuccinimide (NHS, 1 mmol) were dissolved in dimethylformamide (DMF) and stirred for half an hour. 2-(*N*-phenylsulfamoyl)ethanamine hydrochloride salt (**A**, 1 mmol) and trimethylamine (NEt_3, 2 mmol) was added to this reaction mixture and stirred at room temperature. The reaction was pursued with TLC and the solvent was evaporated after the starting compounds consumed. The resulted solid was subjected to extraction by using ethyl acetate (EtOAc), dilute hydrochloric acid (dil. HCl) and dilute sodium bicarbonate (dil. $NaHCO_3$) solution. The ethyl acetate phase was evaporated, and the residue exposed to flash column chromatography (EtOAc: Hxn 2:1). The related fractions were collected and evaporated to give the final compound **5**.

Yellow solid. Yield 25%. Mp: 173.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.43-3.39 (m, 2H, CH_3), 3.73-3.68 (m, 2H, CH_2), 7.16-7.12 (m, 1H, CH_2), 7.27-7.25 (m, 2H, Ar-H), 7.37-7.33 (m, 2H, Ar-H), 8.04 (d, *J* 8.8 Hz, 2H, Ar-H), 8.34 (d, *J* 8.8 Hz, 2H, Ar-H), 8.95-8.93 (m, 1H, NH), 9.89 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 35.3 (Aliph-C), 50.3 (Aliph-C), 120.7 (2 × Ar-C), 124.4 (2 × Ar-C), 124.9 (Ar-C), 129.5 (2 × Ar-C), 130.2 (2 × Ar-C), 138.8 (Ar-C), 140.4 (Ar-C), 150.0 (Ar-C), 165.5 (C=O). IR υ_{maks} (cm^{-1}): 3381, 3108 (N-H stretching), 1654 (amide I band), 1548 (amide II band), 1326 (SO_2 asymmetric stretching), 1135 (SO_2 symmetric stretching). Elemental analysis calculated (%) for $C_{15}H_{15}N_3O_5S$: C, 51.57; H, 4.33; N, 12.03; S, 9.18. Found: C, 51.69; H, 4.31; N, 12.01; S, 9.52.

2.2.2. Synthesis of *N*-(2-(morpholinosulfonyl) ethyl)-4-nitrobenzamide (18).

2-(morpholinosulfonyl)ethanamin hydrochloride salt (B) was synthesized according to procedure that was described before [13, 15]. 4-Nitrobenzoyl chloride (1 mmol), 2-(morpholinosulfonyl)ethanamin hydrochloride salt (B, 1 mmol) was reacted with 4-nitrobenzoyl chloride by using NEt_3 (2 mmol) as a base in dichloromethane (DCM) solution at room temperature. The reaction was followed with TLC and the solvent was removed *in vacuo* after the starting compounds consumed. The mixture put through to flash column chromatography by using EtOAc: Hxn (2:1) solvent system and the pertinent fractions were collected and evaporated to obtain the final compound 18 as a yellow solid that was crystallized from isopropanol.

Yellow solid. Yield 20%. Mp: 199.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.23-3.20 (m, 4H, CH_2), 3.40-3.39 (m, 2H, CH_2), 3.74-3.67 (m, 6H, CH_2), 8.10 (d, *J* 8.6 Hz, 2H, Ar-H), 8.37 (d, *J* 8.5 Hz, 2H, Ar-H), 9.07-9.04 (m, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 34.9 (Aliph-C), 46.1 (Aliph-C), 47.4, 66.7, 124.5 (2 × Ar-C), 129.5 (2 × Ar-C), 140.5 (Ar-C), 150.0 (Ar-C), 165.61 (C=O). IR υ_{maks} (cm^{-1}): 3399, 3070 (N-H stretching), 1657 (amide I band), 1524 (amide II band), 1320 (SO_2 asymmetric stretching), 1148 (SO_2 symmetric stretching). Elemental analysis calculated (%) for $C_{13}H_{17}N_3O_6S$: C, 45.48; H, 4.99; N, 12.24; S, 9.34. Found: C, 45.51; H, 4.79; N, 12.09; S, 9.43.

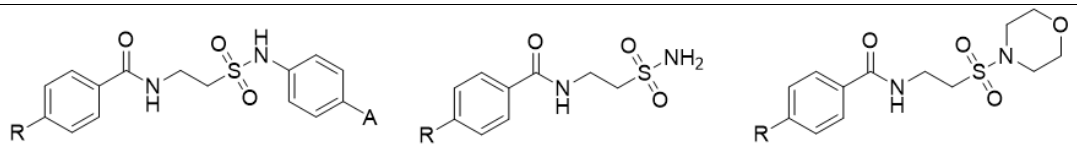
2.3. Antimicrobial activity

2.3.1. Determination of minimum inhibitory concentration (MIC)

Staphylococcus aureus (ATCC 29213), Enterococcus faecalis (ATCC 29212), Escherichia coli (ATCC 25922), Pseudomonas aeruginosa (ATCC 27853),

Candida albicans (ATCC 90028) and Candida parapsilosis (ATCC 22019) were used in this experiments. All bacteria and yeast strains were stored in Brain-Heart Infusion Broth (Merck, Germany) with 10% glycerol at -80 °C. The antibacterial and antifungal activity of taurinamide derivatives were performed for each strain using broth microdilution method according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria [16]. Bacteria and yeast strains were grown on Mueller-Hinton Agar (Merck, Germany) and Sabouraud Dextrose Agar (Oxoid, UK) at 37 °C for 24 h, respectively. Bacteria and yeast colonies were taken with sterile swabs and then, these colonies were suspended with sterile physiological saline in glass tubes. The bacterial and fungal cells density in tubes were prepared to 0.5 McFarland by densitometer (Biosan, DEN-1), and the suspensions were diluted at rate of 100-fold and 10-fold for bacteria and yeasts, respectively. Mueller-Hinton broth (Merck, Germany) (50 µl) and RPMI (Sigma, UK) with 2% of glucose (RPMI 2% G) were added into the each well of sterile 96-well microdilution plates for bacteria and yeasts, respectively. 50 µl from each of the tubes compassing the corresponding concentration of new compounds were included into first wells each column of the microdilution plate. The medium and compound in the first well of each vertical line was mixed using sterile pipette and serial dilutions were accomplished. Diluted bacterial and yeast suspensions were added each well of plate with 50 µL, and the microplates were incubated for 24 h at 37 °C. Growth control for each organisms and sterility control for medium are also tested as positive and negative controls. The final concentrations of the compounds were ranged from 2048 to 64 µg/mL. *Ciprofloxacin* (Santa Cruz, US) and *Fluconazole* (Sigma, UK) were used as reference agents for antibacterial and antifungal activities, respectively. Quality control ranges were also evaluated according to EUCAST. Microdilutions was performed with triplicates for each substances and DMSO, which is used as a solvent, was also tested separately for antibacterial and antifungal activity. After incubation period, MICs were defined the lowest concentration of synthesized compounds, which prohibits macroscopic microbial growth.

Table 1 *In vitro* MICs (µg/mL) of compounds **1–18** against selected bacterial and fungal strains.



1-5 A= H Phenyl derivatives
6-9 A= OCH_3 Methoxy derivatives
10-13 Sulfonamide derivatives
14-18 Morpholine derivatives

Compound		Bacterial strains				Fungal strains	
		Gram (+)		Gram (-)			
	R	*S. a.*	*E. f.*	*E. c.*	*P. a.*	*C. a.*	*C. p.*
1	-H	1024	128	2048	1024	1024	1024
2	$-CH_3$	2048	2048	1024	1024	2048	2048
3	$-OCH_3$	1024	2048	512	1024	>2048	>2048
4	-Cl	1024	2048	1024	1024	2048	>2048
5	$-NO_2$	2048	512	1024	1024	>2048	>2048
6	-H	2048	2048	1024	1024	1024	1024
7	$-CH_3$	2048	1024	1024	1024	1024	1024
8	$-OCH_3$	2048	2048	1024	1024	1024	1024
9	-Cl	2048	2048	1024	1024	2048	>2048
10	-H	2048	2048	1024	1024	1024	1024
11	$-CH_3$	2048	2048	1024	1024	1024	1024
12	$-OCH_3$	2048	2048	1024	1024	1024	1024
13	-Cl	2048	2048	1024	1024	1024	1024
14	-H	2048	2048	204 8	1024	1024	1024
15	$-CH_3$	2048	256	1024	1024	>2048	>2048
16	$-OCH_3$	1024	2048	>2048	>2048	>2048	>2048
17	-Cl	>2048	1024	2048	2048	>2048	>2048
18	$-NO_2$	1024	64	1024	1024	>2048	>2048
Ciprofloxacin		0.25	1	0.008	0.5	nt	nt
Fluconazole		nt	nt	nt	nt	32	2

S.a: Staphylococcus aureus ATCC 29213, *E. f.*: *Enterococcus faecalis* ATCC 29212, *E.c.: Escherichia coli* ATCC 25922, *P.a.: Pseudomonas aeruginosa* ATCC 27853, *C. a.: Candida albicans* ATCC 90028, *C. p.: Candida parapsilosis* ATCC 22019.
nt: not tested.

3. Results and Discussion

3.1. Chemistry

The final compounds 1–4 and 6–22 were obtained according to the procedure described previously (Figure 4) [13, 17, 18]. Compounds 5 and 18 reported here were synthesized by using different reaction mediums and are reported here for the first time (Figure 5). The starting compounds 2-(*N*-phenylsulfamoyl)ethanamine hydrochloride salt (A) and 2-(morpholino sulfonyl)ethanamine hydrochloride salt (B) were synthesized by following the previously described method [13]. 4-Nitro-*N*-(2-(*N*-phenylsulfamoyl)ethyl)benzamide (5) was obtained by a coupling reaction of A with 4-nitrobenzoic acid in the presence of DCC, NEt_3, and NHS in DMF solution. The treatment of 2-(morpholinosulfonyl)ethanamine hydrochloride salt (B) with 4-nitrobenzoyl chloride and NEt_3 in DCM solution yielded with *N*-(2-(morpholinosulfonyl)ethyl)-4-nitrobenzamide (18) as a raw product. This product was purified by utilizing a column chromatography method and required crystallization from an appropriate solvent. Finally, the intended molecules were achieved in 20–25% yields as yellow solids. The results of the ^{1}H and ^{13}C NMR, IR, and elemental analysis were coherent with the intended structures (*cf.* experimental section).

3.2.Antimicrobial activity

Final compounds were tested for their *in vitro* antibacterial and antifungal activities against two G(+) bacteria, *Staphylococcus aureus* and *Enterococcus faecalis;* two G(−) bacteria, *Escherichia coli* and *Pseudomonas aeruginosa*; and two fungal strains, *Candida albicans* and *C. parapsilosis* by employing broth microdilution method, with *Ciprofloxacin* and *Fluconazole* used as as reference agents for antibacterial and antifungal activities. The data in Table 1 were analyzed to evaluate the effects of substitutions on the designed skeleton.

Considering G(+) *S. aureus*; the antimicrobial activities of compounds 1, 3, and 4 bearing phenyl and 16, and 18 comprising morpholine group on the sulfonamide unit of the molecule were weak but 2-fold better than those of the other compounds.

E. faecalis was found to be susceptible to phenyl derivative 1 with a MIC of 128 μg/mL. Introduction of an electron withdrawing nitro group (compound 5) to 1 decreased the activity 4-fold (MIC=512 μg/mL), whereas other substitutions as in compounds 2, 3, and 4 diminished the activity (MIC=2048 μg/mL). The methoxy derivative 12 demonstrated a 2-fold more potent activity (MIC=1024 μg/mL) relative to that of its congeners 11, 13, and 14. Considering morpholine derivatives 14–18; the best antibacterial activity was observed with compound 18 bearing an electron-withdrawing nitro substitution with a MIC of 64 μg/mL against *E. faecalis*. Replacement of nitro in 18 with an electron-donating methyl 15 and chloro group 17 decreased the activity 2- and 4-fold (MIC=256 and 1024 μg/mL), respectively. On the other hand, compounds 14 and 16 demonstrated a weak activity against *E. faecalis* (MIC=2048 μg/mL).

Considering G(–) *E. coli* bacteria, among the phenyl derivatives, compound 3 having methoxy substitution was found to be the most potent analog, with a MIC of 512 μg/mL. Compounds 2, 4 and 5 were equipotent inhibitors with a MIC of 1024 μg/mL, whereas compound 1 displayed a poorer activity profile relative to that of the other phenyl derivatives 1–5. On the other hand 1–5 exhibited the same MICs of 1024 μg/mL against G(–) *P. aerıgonasa* bacteria. The rest of the molecules 6–13, 15, and 18 displayed equipotent activity with MICs of 1024 μg/mL against both of the G(–) bacteria.

Considering the fungal strains *C. albicans* and *C. parapsilosis*, among the phenyl derivatives (1–5), 1 was found to have the best activity, with a MIC of 1024 μg/mL. Introduction of a chloro or methoxy group to 1 decreased the activity 2-fold against *C. albicans*, whereas neither of the fungal strains susceptible to the other phenyl analogs. Among the methoxy derivatives 11–14, nonsubstituted derivative 11 and electron-donating methyl and methoxy-substituted derivatives (12 and 13, respectively) exhibited the same activity profiles, with MICs of 1024 μg/mL. The activity was found to be diminished with the introduction of a chloro group, as in 14. Interestingly, all of the primary sulfonamide derivatives 15–18 exhibited the same activity profile against fungal strains, with MICs of 1024 μg/mL. The morpholine derivative 19 exhibited antifungal activity, with a MIC of 1024 μg/mL, whereas introduction of electron-withdrawing and -donating groups to 19 diminished the activity against both of the fungal strains. It is interesting to note that fungal strains were found to gain greater susceptibility to all of the nonsubstituted final compounds 1, 6, 10, and 14 than their previously investigated phthalimide derivatives [19]. However, none of the compounds exhibited better activity than the reference drugs *Ciprofloxacin* and *Flucanozole*.

4. Conclusion

A series of taurinamide derivatives 1-18 were assessed for their *in vitro* antimicrobial activity. Interestingly, compound 3 was distinguished from other compounds due to its better activity against G(–) *E. coli* bacteria, with a MIC of 512 μg/mL. On the other hand, *E. faecalis* was found to be more susceptible than the other pathogens to the tested compounds. In recent years, *Enterococcus* has emerged as a serious nosocomial pathogen having intrinsic antibiotic resistance [20]. For this reason, *Enterococcus* has become the target of antimicrobial drug development studies. In our antimicrobial screening test, the best activity was observed for nitro-substituted morpholine derivative 18, with a MIC of 64 μg/mL against *E. faecalis*. The same bacteria were also moderately inhibited by nonsubstituted phenyl derivative 1 and methyl-substituted morpholine derivative 15, with MICs of 128 and 256 μg/mL, respectively. However, none of the compounds exhibited low MICs against the tested bacterial strains, as observed with previously investigated phthalamide derivatives [13]. On the other hand, it is interesting to note that; fungal strains were found to gain increased susceptibility to all of the nonsubstituted final compounds 1, 6, 10, and 14 compared to their phthalimide derivatives which were previously reported (Figure 2) [13]. These results seem to be uncorrelated with the lipophilicity of the drugs. As a result, expanding the substitution patterns of the derivatives or trying different functionalization strategies would provide more insights to design effective antimicrobial agents.

Acknowledgment

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Conflicts of interest

The authors have declared no conflict of interest.

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