RESEARCH PAPER

Design, synthesis, and structure-activity relationship study of thiadiazole-linked phenylquinazolinone-β-lactam hybrids as potent antimicrobial agents.

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Abstract
The antimicrobial effect of a novel series of thiadiazole-linked phenylquinazolinone derivatives that incorporate Schiff base and β-lactam pharmacophores (8–17) was rationally designed, synthesized, and assessed. The quinazolinone scaffold was hybridized with azetidinone and thiadiazole motifs as part of the molecular design strategy to increase biological potency through synergistic structural features. Mass spectrometry, elemental analysis, ^{1}H NMR, and infrared spectroscopy were used to fully characterize all produced compounds. Gram +ve (*B. subtilis, S.aureus*), Gram -ve(*E. coli*), and fungal strains (*C. albicans, A. niger, C. krusei)* were used to evaluate the antimicrobial potential in vitro. With clear structure–activity relationships, a number of derivatives showed strong antibacterial and antifungal activity. Specifically, β-lactam analogues with electron-donating aromatic substituents. With low minimum inhibitory concentration of 1.56–6.25 µg/mL across several microbial strains, compound 16 was found to be the most active derivative. Its activity was comparable to that of conventional reference medications. Analysis of the structure–activity relationship showed that steric factors, hydrogen-bonding capacity, and electronic effects are important in regulating the effectiveness of antibiotics. These results show that thiadiazole–quinazolinone–β-lactam hybrids are promising lead structures for the creation of novel antimicrobial drugs.

Keywords : phenylquinazolinone, azetidinone, thiadiazole, antibacterial activity, antifungal activity.
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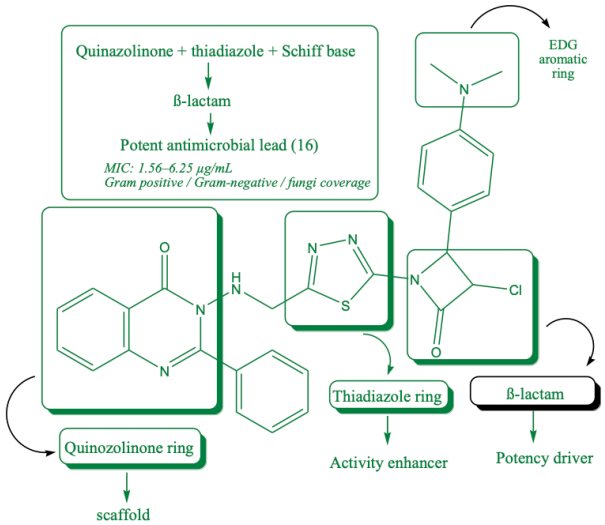
Graphical Abstract



Introduction

The urgent need for new chemotherapeutic scaffolds with enhanced efficacy and novel mechanisms of action is highlighted by the rapid emergence of microbial resistance to current antimicrobial agents [1-3], which poses a serious threat to global health. Because of their structural diversity and capacity to interact selectively with biological targets, heterocyclic compounds

continue to be important in pharmaceutical chemistry [4-6]. Due of its extensive variety of pharmacological activities, which include antimicrobial, anticancer, anti-inflammatory, and antiviral qualities, quinazolinone derivatives have garnered ongoing attention [7-10].

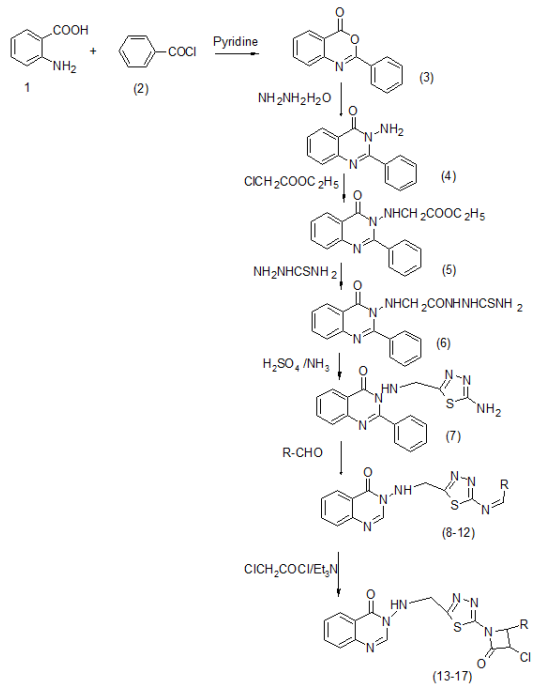
A class of nitrogen-containing bicyclic heterocycles related to the indole and isoindoline systems, quinazolinones, are particularly sensitive to molecular functionalization and substitution patterns, and many phenyl-substituted quinazolinones have been reported to exhibit antifungal and antibacterial activity against Gram +ve and Gram -ve pathogens[11-12]. Mechanistically, several quinazolinone-based compounds are known to interfere with essential microbial processes, including inhibition of enzymes involved in protein synthesis, nucleic acid replication, and cell wall biosynthesis. Additionally, they are interesting scaffolds for antimicrobial drug discovery as they can retain activity against resistant microbial strains.

Concurrently, the 1,3,4-thiadiazole moiety is acknowledged in pharmaceutical chemistry as a privileged pharmacophore, offering advantageous physicochemical characteristics like improved lipophilicity, metabolic stability, and hydrogen-bonding capacity [13-15]. Strong antibacterial and antifungal activity has been reported for compounds containing thiadiazole [16-18], frequently by disrupting microbial enzyme systems and membrane integrity. Similar to this, β-lactam (azetidinone) derivatives continue to be among the most effective classes of antimicrobial agents, mainly because of their capacity to prevent the synthesis of bacterial cell walls and inhibit penicillin-binding proteins[19-20].

A successful method for overcoming antimicrobial resistance and boosting biological activity is molecular hybridization, which entails the deliberate fusion of two or more bioactive pharmacophores into a single molecular framework. Quinazolinones, thiadiazoles, and β-lactams have been the subject of numerous individual studies, but systematic integration of these three pharmacologically significant motifs into a single molecular architecture is still largely unexplored. Our hypothesis was that by synthesis and design of a novel class of thiadiazole-linked phenylquinazolinone derivatives with Schiff base and β-lactam functionalities. The produced substances in vitro antibacterial and antifungal properties against clinically significant microbial strains were assessed. To further clarify the impact of molecular size, hydrogen-bonding ability, and electronic substituents on antimicrobial efficacy, a thorough structure–activity relationship (SAR) analysis was carried out. The findings confirm the potential of quinazolinone-based hybrids as next-generation antimicrobial agents and identify promising lead compounds for additional optimization.

Chemistry

The synthetic route commenced with the acylation of anthranilic acid (**2**) using benzoyl chloride (**1**) in pyridine, leading to intramolecular cyclodehydration and formation of 2-phenyl-4H-3,1-benzoxazin-4-one (**3**) [21]. Subsequent nucleophilic ring opening of compound 3 by hydrazine hydrate afforded 3-amino-2-phenylquinazolin-4(3H)-one (**4**). Alkylation of the exocyclic amino group in compound 4 with chloroethyl acetate produced ethyl [(4-oxo-2-phenylquinazolin-3(4H)-yl)amino]acetate (**5**). Reaction of ester 5 with thiosemicarbazide proceeded via nucleophilic substitution to yield the corresponding thiosemicarbazide derivative (**6**). Cyclodehydration of compound 6 under acidic conditions (conc. H_2SO_4), followed by neutralization with liquid ammonia, promoted intramolecular ring closure to furnish the 1,3,4-thiadiazole-containing quinazolinone derivative (**7**). Condensation of compound 7 with substituted benzaldehydes yielded the corresponding Schiff base derivatives (**8–12**). These imines subsequently underwent [2+2] cycloaddition with chloroacetyl chloride in the presence of triethylamine to afford the azetidinone derivatives (**13–17**), incorporating a β-lactam moiety. All newly synthesized phenylquinazolinone derivatives were verified by elemental analysis & spectral techniques (IR, ^{1}H NMR, and MS), as depicted in Scheme **1**.



R= -C_6H_5, -$C_6H_4OCH_3$, -C_6H_3 (OH)(OCH_3), -$C_6H_4N(CH_3)_2$, -C_6H_4OH

Scheme 1: Synthetic route for preparation of substituted phenylquinazolinone moieties Materials required and methodology

Reagents were obtained from CDH and Merck India Pvt. Ltd. Authors determined melting points using a thermoelectric melting point apparatus in an open capillary tube, without calibration. Thin-layer chromatography (TLC) on silica gel G-coated plates using various solvent systems assessed the purity of the recently synthesized compounds. Researchers measured wave numbers (v) in cm^{-1} for infrared (IR) spectra using a KBr pellet on a Perkin Elmer FTIR spectrometer; analysts measured chemical shifts (δ) in ppm for 1H-NMR spectra on a Bruker avance spectrometer in CDCl3 or DMSO-d6. Researchers used tetramethylsilane (TMS) as an internal standard. They recorded mass spectra using a Spec Finnigan Mat 8230 MS (Thermo Electron Corporation). Analysts performed carbon, hydrogen, and nitrogen elemental analyses using a Thermo Fisher Scientific with results deviating from theoretical values within ±0.4%.

Chemistry

Synthesis of 2-phenyl-4H-3,1-benzoxazin-4-one (3)

Anthranilic acid (2) was acylated with benzoyl chloride (1) in pyridine at ambient temperature, resulting in intramolecular cyclodehydration and formation of 2-phenyl-4H-3,1-benzoxazin-4-one (3). After completion, the mixture was neutralized with aqueous $NaHCO_3$. Now the precipitated product was extracted and filter, and it is purified by recrystallization from ethanol to afford compound 3 as colorless crystals[21].

Synthesis of 3-amino-2-phenylquinazolin-4(3H)-one (4)

Compound 3 underwent nucleophilic ring opening with hydrazine hydrate in refluxing ethanol, followed by cyclocondensation to generate the quinazolinone framework. Upon cooling and quenching in ice water, the solid product was filtered and dried to yield 3-amino-2-phenylquinazolin-4(3H)-one (4).

Synthesis of ethyl [(4-oxo-2-phenylquinazolin-3(4H)-yl)amino]acetate (5)

N-Alkylation of the exocyclic amino group of compound 4 was achieved by refluxing with chloroethyl acetate in anhydrous dioxane, affording ethyl [(4-oxo-2-phenylquinazolin-3(4H)-yl)amino]acetate (5). The product was isolated by precipitation in water and purified by recrystallization from ethanol.

Synthesis of 2-{[(4-oxo-2-phenylquinazolin-3(4H)-yl)amino]acetyl}hydrazine-1-carbothioamide (6)

Reaction of ester 5 with thiosemicarbazide in refluxing methanol led to nucleophilic substitution of the ester group, yielding the corresponding thiosemicarbazide derivative (6). The product was isolated by precipitation upon aqueous workup and purified by recrystallization from methanol.

Synthesis of 3-{[(5-amino-1,3,4-thiadiazol-2-yl)methyl]amino}-2-phenylquinazolin-4(3H)-one (7)

Cyclodehydration of compound 6 in concentrated sulfuric acid, followed by neutralization with aqueous ammonia, promoted intramolecular ring closure to form the 1,3,4-thiadiazole moiety. The product (7) was isolated by filtration, and purified by recrystallization from aqueous ethanol.

Synthesis of Schiff base derivatives (8–12)

Condensation of compound 7 with the appropriate substituted aromatic aldehydes in methanol, catalyzed by glacial acetic acid, yielded the corresponding Schiff base compounds (8–12). The products were isolated by precipitation and purified by recrystallization from suitable solvents.

Synthesis of azetidinone derivatives (13–17)

The Schiff base derivatives (8–12) underwent cycloaddition with chloroacetyl chloride in the presence of triethylamine to yield the β-lactam (azetidinone) derivatives (13–17). Mechanistically, this transformation proceeds via nucleophilic attack of the imine nitrogen on the activated chloroacetyl chloride, followed by intramolecular cyclization to form the four-membered β-lactam ring. The products were isolated by aqueous workup and purified by recrystallization.

The physical properties, analytical data, and spectroscopic characterization of compounds 8–17 are summarized in Tables 1 and 2.

Results and Discussion

Antimicrobial Activity

The antibacterial and antifungal activity of the newly prepared quinazolinone compounds was evaluated against a panel of representative microbial pathogens (Gram -vebacterium E. coli, Gram +ve bacteria B. subtilis and S. aureus, and the fungal strains C. albicans, A. niger, and C. krusei) using agar diffusion (zone of inhibition) [22-23] and broth microdilution (Minimum Inhibitory Concentration, MIC) [24] assays (Table 3), showing a pharmacology and structural biology.

Screening for antibacterial activity showed that compound 15 was the. most potent analogue in the series (zones of inhibition: 30, 26, and 28 mm against E. coli, B. subtilis, and S. aureus, respectively, MICs: 6.25, 3.125, and 6.25 μg/mL, respectively), and had potency similar to that of the standard drug chloramphenicol. A number of other β-lactam-containing compounds, especially 13, 14, 16, and 17, also exhibited significant antibacterial activity (MICs 6.25 to 12.5 μg/mL) against the Gram +ve strains.

We also observed a similar trend for antifungal activity, with compound 15 being the best antifungal derivative, with MICs against C. albicans, A. niger, and C. krusei of 3.125 to 12.5 μg/mL, which were comparable to fluconazole, while compounds 16 and 17 also exhibited good antifungal activity but with a reduced spectrum. In contrast, the unsubstituted phenyl Schiff base derivative 8 was inactive against all the fungal strains and had only weak antibacterial effects, suggesting that aromatic ring substitution was crucial for bioactivity

Structure-Activity Relationship (SAR) Analysis

The presence of the β-lactam ring, the electronic nature and lipophilicity of the aromatic substituents, and general molecular features were the main factors influencing the distinct and comprehensible structure-activity relationships (SAR) that were revealed by a systematic analysis of the biological data.

- The significant increase in antimicrobial activity upon cyclization of the Schiff base compounds (8–12) to their corresponding azetidinone analogues (13–17) was a key finding. For every microbial strain, this transformation consistently led to a 2-4 fold decrease in MIC values. It indicates the crucial role of the strained β-lactam ring, most likely by interfering with cell wall biosynthesis.
- The antimicrobial profiles of derivatives with electron-donating groups like $–OCH_3$, –OH, and $–N(CH_3)_2$ (13–17) were better than those of their unsubstituted or electron-neutral counterparts.

  Stronger interactions, like charge-transfer or dipole-dipole interactions, with important microbial enzymes or membrane components are thought to be made possible by the increased electron density that these EDGs provide.
- Moderate lipophilicity, which is attributed to groups like $–OCH_3$ and $–N(CH_3)_2$ was found antimicrobial efficacy against Gram +ve bacteria. More intracellular accumulation is probably made possible by increased membrane permeability. Antifungal activity was greatly increased by the presence of –OH group, as in compound 14 and 15, especially against Candida species, which indicates that these groups might participate in important hydrogen-bonding interactions inside the active sites of targets that are more specific to fungi.
- Bulky substituents were mostly advantageous. It suggests that greater molecular bulk promotes interactions within hydrophobic pockets of target proteins or biomembranes. Higher susceptibility is generally seen in Gram +ve bacteria (B. subtilis and S. aureus) in contrast to the Gram -ve (E. Coli) outer membrane corresponds with

the latter's known decreased permeability barri er.

Explicit Ranking and Lead Identification

Based on a comprehensive analysis of the MIC data (Table 3), the overall antimicrobial activity of the synthesized compounds can be ranked as follows:

16 >15 > 17 > 13 ≈ 14 > 11 > 10 > 12 > 9 > 8

- Compound 16 has a $–N(CH_3)_2$ group and it was found to be the most potent derivative in this series, with the lowest MIC values (1.56–6.25 µg/mL) for both bacterial and fungal strains.
- Compounds 15 (–OH) and 17 ($–OCH_3$) showed potent both antimicrobial activity, making them extremely promising moi ety.
- Schiff base derivatives 8–12 were consistently less active. It means that quinazolinone-Schiff base have some intrinsic activity.

Conclusion

In this study, a series of novel substituted phenylquinazolinone derivatives (8-17), bearing the thiadiazole, Schiff base, and azitidinone moieties, were successfully synthesized and their structures characterized using a combination of spectroscopic and analytical techniques. Antibacterial activity assays revealed that some of the compounds showed moderate to strong inhibitory activity against a panel of Gram +ve and Gram -vebacteria, as well as the fungal pathogen Candida albicans. Structure-activity relationship (SAR) analysis revealed that electron-donating and hydrogen-bonding substituents on the aromatic ring increased the antibacterial efficacy, with the dimethylamino and hydroxyl/methoxy derivatives showing the largest zones of inhibition and lowest MIC values, while the unsubstituted phenyl analogs showed relatively lower activity. In general, these compounds were more active against Gram +ve bacteria than against Gram –ve bacteria, which could be due to differences in cell wall permeability. The findings support the rational design strategy used in this study and suggest that the phenylquinazolinone scaffold is a potential template for antibacterial drug discovery, which would require further optimization, mechanistic studies, and in vivo experiments to realize the full therapeutic potential.

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Table 1. Physical and analytical data of synthesized compounds (3–17)

Compd	Molecular Formula	M.p. (°C)	Yield (%)	Recrystallization Solvent	Elemental Analysis (%)
					C (Calcd. / Found)
					H (Calcd. / Found)
					N (Calcd. / Found)
3	$C_{14}H_9NO_2$	123	76	EtOH	75.33 /75.37
					4.06 / 4.08
					6.27 / 6.24
4	$C_{14}H_{11}N_3O$	169	71	MeOH	70.87 / 71.24
					4.67 / 4.68
					17.71 / 17.76
5	$C_{18}H_{17}N_3O_3$:	173	68	EtOH	66.79 / 66.60
					5.30 / 5.20
					12.99 / 12.95
6	$C_{17}H_{16}N_6O_2S$	210	72	MeOH	55.42 / 55.48
					4.38 / 4.28
					22.81 / 22.41
7	$C_{17}H_{16}N_6OS$	231	69	EtOH	58.27 / 57.78
					4.08 / 4.18
					23.98 / 23.81
8	$C_{24}H_{18}N_6OS$	186	65	MeOH	65.74 / 65.72
					4.14 / 4.11
					19.17 / 19.21
9	$C_{25}H_{20}N_6O_2S$	195	70	EtOH	64.09 / 63.96
					4.30 / 4.29
					17.94 / 17.83
10	$C_{25}H_{20}N_6O_3S$	215	66	EtOH	61.97 / 62.15
					4.16 / 4.12
					17.34 / 17.21
11	$C_{26}H_{23}N_7OS$	191	55	Acetone	64.85 / 65.11
					4.81 / 4.91
					20.36 / 20.55
12	$C_{24}H_{18}N_6O_2S$	226	60	MeOH	63.42 / 63.35
					3.99 / 4.10
					18.49 / 18.28
13	$C_{26}H_{19}ClN_6O_2S$	219	58	EtOH	60.64 / 60.69
					3.72 / 3.81
					16.32 / 16.27
14	$C_{27}H_{21}ClN_6O_3S$	235	62	EtOH	59.50 / 60.01
					3.88 / 3.85
					15.42 / 15.61
15	$C_{27}H_{21}ClN_6O_4S$	254	55	DMF	57.80 / 58.01
					3.77 / 3.72
					14.98 / 15.02
16	$C_{28}H_{24}ClN_7O_2S$	223	53	Benzene/Pet. ether	60.26 / 60.05

					4.33 / 4.31
					17.57 / 17.61
17	$C_{26}H_{19}ClN_6O_3S$	243	67	EtOH	58.81 / 59.02
					3.61 / 3.71
					15.83 / 15.91

Table: 2 Spectral Data of Compound (3-17)

Compd	IR ν_max (cm^{-1})	^1H NMR δ (ppm)	MS (m/z)
3	1765–1780 (C=O), 1600–1620 (Ar C=C), 1490–1520 (C_6H_5), 1250–1280 (C–O–C), 1180–1210 (C–N), 1020–1080 (C–O), 750–780 (Ar–H)	7.43–7.75 (m, 6H, Ar–H), 7.50–8.48 (m, remaining Ar–H)	223 $[M]^+$
4	1680–1710 (C=O), 3300–3450 (NH), ~3100 (Ar–CH), 1600 (Ar C=C), 1250–1350 (C–N), 700–750 (Ar–H)	7.16–7.78 (m, Ar–H), 5.82 (br s, 2H, NH_2)	237 $[M]^+$
5	1720–1740 (COOEt), 1665–1690 (C=O), 3300–3450 (NH), 1580–1600 (Ar C=C), 1250–1350 (C–N)	7.20–7.82 (m, Ar–H), 4.45 (s, 2H, NCH_2), 4.18 (q, 2H, OCH_2), 1.25 (t, 3H, CH_3)	323 $[M]^+$
6	3210–3320 (NH/NH_2), 1650–1690 (CONH), 1600–1620 (C=O, C=N), 1020–1060 (C=S)	12.35 (s, NH–C=S), 10.60 (s, CONH), 9.20 (br, NH), 7.38–8.18 (m, Ar–H), 4.38 (s, 2H, CH_2), 7.70–7.90 (br, 2H, NH_2)	368 $[M]^+$
7	3310–3445 (NH), 1688 (C=O), 1618, 1584 (C=N, Ar C=C), 1042–1115 (C–S)	10.65 (s, NH), 7.28–8.20 (m, Ar–H), 4.25 (s, 2H, CH_2), 6.10 (br s, 2H, NH_2)	350 $[M]^+$
8	3440–3320 (NH), 1688 (C=O), 1620–1590 (C=N), 1110–1045 (C–S)	10.65 (s, NH), 8.75 (s, CH=N), 7.26–8.20 (m, Ar–H), 4.25 (s, 2H, CH_2)	438 $[M]^+$
9	3440–3320 (NH), 1688 (C=O), 1620–1590 (C=N), 1245 (Ar–O), 1110–1045 (C–S)	10.65 (s, NH), 8.72 (s, CH=N), 6.92–8.20 (m, Ar–H), 4.25 (s, 2H), 3.80 (s, 3H, OCH_3)	468 $[M]^+$
10	3435–3315 (NH, OH), 1685 (C=O), 1620–1580 (C=N), 1245 (Ar–O)	10.65 (s, NH), 9.12 (br s, OH), 8.72 (s, CH=N), 6.88–8.20 (m, Ar–H), 4.25 (s, 2H), 3.80 (s, 3H)	484 $[M]^+$
11	3440–3320 (NH), 1685 (C=O), 1620–1580 (C=N)	10.65 (s, NH), 8.70 (s, CH=N), 6.85–8.20 (m, Ar–H), 4.25 (s, 2H), 3.05 (s, 6H, $N(CH_3)_2$	477 $[M]^+$
12	3435–3315 (NH, OH), 1685 (C=O), 1620–1580 (C=N)	10.65 (s, NH), 9.05 (br s, OH), 8.70 (s, CH=N), 6.85–8.20 (m, Ar–H), 4.25 (s, 2H)	454 $[M]^+$
13	3430–3320 (NH), 1735 (β-lactam C=O), 1686 (C=O), 1620–1585	10.62 (s, NH), 7.10–8.18 (m, Ar–H), 4.85 (dd, β-lactam CH), 4.32 (s, 2H), 3.62–3.95 (dd, CH_2)	514 $[M]^+$
14	3320–3250 (NH), 1745–1730 (β-lactam C=O), 1685–1670 (C=O)	10.78 (s, NH), 6.90–8.22 (m, Ar–H), 4.55 (s, 2H), 4.25, 3.90 (d, β-lactam CH), 3.78 (s, OCH_3)	545 $[M]^+$
15	3440–3300 (NH, OH), 1745–1730 (β-lactam C=O), 1685–1670	10.80 (s, NH), 9.45 (br s, OH), 6.72–8.22 (m, Ar–H), 4.55 (s, 2H), 4.28, 3.92 (d), 3.78 (s, OCH_3)	561 $[M]^+$
16	3310–3240 (NH), 1745–1735 (β-lactam	10.72 (s, NH), 6.72–8.21 (m, Ar–H), 4.55 (s,	558 $[M]^+$

	C=O), 1685–1670	2H), 4.30, 3.95 (d), 3.02 (s, $N(CH_3)_2$)	
17	3390–3220 (NH, OH), 1750–1735 (β-lactam C=O), 1690–1675 (C=O)	10.80 (s, NH), 9.85 (br s, OH), 6.85–8.20 (m, Ar–H), 4.55 (s, 2H), 4.20, 3.85 (d)	531 $[M]^+$

Table 3 – Antimicrobial data of synthesized compounds **8-17** against tested microbial strains.

Compd no.	Antibacterial activity[#]			Antifungal activity[#]		
	E. coli	*B. subtilis*	*S. aureus*	*C. albicans*	*A. niger*	*C. krusei*
8	16 (**100**)	9 (**100**)	14 (**>125**)	-	-	-
9	13 (**>125**)	11 (**50**)	10 (**>125**)	-	-	-
10	20 (**50**)	16 (**25**)	19 (**50**)	13 (**100**)	8 (**>125**)	11 (**100**)
11	21 (**50**)	16 (**25**)	18 (**50**)	18 (**50**)	11 (**100**)	12 (**100**)
12	12 (**>125**)	15 (**25**)	17 (>**125**)	20 (**25**)	12 (**100**)	11 (**100**)
13	23 (**25**)	19 (**12.5**)	18 (**50**)	-	-	-
14	21 (**50**)	18 (**12.5**)	14 (>**125**)	-	-	-
15	27 (**12.5**)	23 (**6.25**)	22 (**12.5**)	20 (**25**)	10 (>**125**)	14 (**12.5**)
16	30 (**6.25**)	26 (**3.125**)	28 (**6.25**)	28 (**3.125**)	23 (**12.5**)	21 (**1.592**)
17	25 (12.5)	23 (6.25)	23 (**12.5**)	26 (**6.25**)	16 (**50**)	17 (**6.25**)
[a] Control	0	0	0	0	0	0
Chloroamphenicol	25 (**12.5**)	24 (**6.25**)	21 (**12.5**)			
Fluconazole				29 (**6.25**)	22 (**12.5**)	19 (**3.125**)

[#]Conc[n] was 250 µg/mL.

[a]DMSO served as control.

'-' indicate no inhibition zone.

MIC values in '( )'.