

A NEW SERIES OF 1,3,4-THIADIAZOLE SUBSTITUTED AZETIDINONE AND THIAZOLIDINONE DERIVATIVES AND THEIR ANTIMICROBIAL ACTIVITY

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ABSTRACT

The new series of 2-([5-(3-chloro-2-oxo-4-substituted-phenyl)azetidin-1-yl]-1,3,4-thiadiazol-2-yl)methyl}amino)benzoic acid (13-20) and 2-([5-(4-oxo-2-substituted-phenyl)-1,3-thiazolidin-3-yl]-1,3,4-thiadiazol-2-yl)methyl}amino)benzoic acid (21-28) have been synthesized from 2-([5-[(benzylideneamino)-1,3,4-thiadiazol-2-yl]methyl}amino)-benzoic acid (5-12). All these synthesized compounds were tested for their antimicrobial activity and established by spectroscopic data, and elemental analyses.

Keywords: 1,3,4-thiadiazole, Azetidinone, Thiazolidinone, Benzoic Acid Derivatives, Antimicrobial Activity.

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INTRODUCTION

The 1,3,4-thiadiazoles moiety are essential compounds in medicinal chemistry. 1,3,4-Thiadiazoles display a wide range of biological activities anticancer¹⁻³, antitumor⁴⁻⁵, antimicrobial⁶⁻⁹, anti-inflammatory.¹⁰ There are many commercially available drugs such as Acetazolamide, Methazolamide, Cefazedone, and Cefazolin (Fig.-1) which contain the 1,3,4-thiadiazole moiety. Furthermore, it has also been found that the azetidinone¹¹⁻¹³ and thiazolidinone¹⁴⁻¹⁵ bearing compounds show varied biological properties. Moreover, certain azetidinone and thiazolidinone congeners have also shown good antimicrobial¹⁶⁻²⁰ activity. The above-said activities in different heterocyclic nuclei having azetidinone and thiazolidinone rings prompted us to synthesize azetidinythiadiazoles and thiazolidinythiadiazoles and screened them for antimicrobial activity.

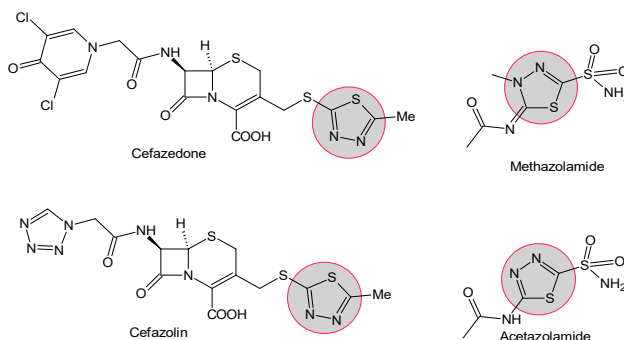


Fig.-1: 1,3,4-Thiadiazole Moiety Containing Commercially Available Drugs

EXPERIMENTAL

Material and Methods

All chemicals and reagents were purchased from Spectrochem and Sigma Aldrich, and used as such. Melting points of synthesized compounds were taken in open capillaries on a thermionic melting point apparatus. Thin layer chromatography (TLC, silica gel-G.) was used for reaction progress. IR was recorded on FTIR Paragon 500, Perkin-Elmer ((KBr) max in cm⁻¹, ¹H-NMR (in DMSO-*d*₆ on Bruker-300 FT instrument, in ppm).

General Procedure

2-[(2-Ethoxy-2-oxoethyl)amino]benzoic Acid (2)

In acetone (80 mL) one equivalent of anthranilic acid and ethyl chloroacetate was added. To this mixture, 2.5 equivalent of potassium carbonate was added and refluxed for about 18 h. The reaction mixture was cooled to RT, concentrated and it was poured into ice water. The solid filtered and recrystallized from ethanol–water to give compound 2, Compound 2: m.p. 126-116-118 °C, yield 62%, IR (cm⁻¹): 3495; 3152; 3038; 2924; 1718; 1595; ¹HNMR (DMSO-*d*₆) δ: 12.51 (s, 1H, COOH), 7.52–7.30 (m, 4H, Ar-H), 5.80 (s, 1H, NH), 4.55 (s, 2H, NCH₂), 4.22 (q, 2H, *J*=7.2 Hz, CH₂), 1.25 (t, 3H, *J*=7.2 Hz, CH₃). C₁₁H₁₃NO₄: Calc. C (59.19%), H (5.87%), N (6.27%); Found C (59.24%), H (5.85%), N (6.30%).

2-[[2-(2-carbamothioylhydrazinyl)-2-oxoethyl]amino]benzoic Acid (3)

To a solution of compound (2) (0.04 mol) and thiosemicarbazide.HCl (0.04 mol) in MeOH (100 mL) was added to anhydrous sodium hydroxide (0.1 mol) and was heated at 90°C for 18 h. The reaction mixture was concentrated and recrystallized from ethanol water to give compound 3. Compound 3: m.p. 128-130 °C. yield 76%, IR (cm⁻¹): 3470; 3130; 3050; 2930; 1710; 1565. ¹HNMR (DMSO-*d*₆) δ: 12.40 (s, 1H, COOH), 8.42 (m, 4H, NHNHCONH₂), 7.62–7.42 (m, 4H, Ar-H), 5.74 (s, 1H, NH), 4.75 (s, 2H, NCH₂). C₁₀H₁₂N₄O₃S: Calc. C (44.77%), H (4.51%), N (20.88%); Found C (44.84%), H (4.55%), N (20.93%).

2-[[5-(5-Amino-1,3,4-thiadiazol-2-yl)methyl]amino]benzoic Acid (4)

Conc. Sulphuric acid was added to compound 3 (0.05 mol) and the Reaction mixture was stirred at room temperature for overnight. The reaction mass was poured into ice-cold water and neutralized with ammonia solution. The solid was filtered and recrystallized from methanol water. Compound 4: m.p. 135-137°C, yield, 60%, IR (cm⁻¹): 3478, 3355, 3160, 3050, 2930, 1720, 1580, 1605, 1210, 752; ¹HNMR (DMSO-*d*₆) δ: 12.30 (s, 1H, COOH), 7.60-7.40 (m, 4H, Ar-H), 6.22 (bs, 2H, NH₂), 5.91 (s, 1H, NH), 4.76 (s, 2H, NCH₂). C₁₀H₁₀N₄O₂S: Calc. C (47.99%), H (4.03%), N (22.39%); Found C (48.19%), H (4.09%), N (22.49%).

2-[(5-[(Substituted-benzylideneamino)-1,3,4-thiadiazol-2-yl]methyl)amino]-benzoic Acid (5-12)

A solution of compound 4 (0.02 mol) in absolute ethanol (100 mL) was added to substituted aromatic aldehydes (0.02 mol) in the presence of acetic acid and refluxed for 18 h. The progress reaction was monitored by TLC. The reaction mixture was distilled off. The solid thus obtained was recrystallised from the appropriate solvent as given in Table-1. By this procedure, compounds (5-12) were obtained starting from benzaldehyde, 4-methyl-benzaldehyde 4-methoxy-benzaldehyde, 4-chloro-benzaldehyde, 4-bromo-benzaldehyde, 4-dimethylamino-benzaldehyde, 4-nitro-benzaldehyde and 2-chloro-benzaldehyde, respectively. Their data are given in Table-1.

2-[(5-[(4-methoxyphenyl)methylidene]amino)-1,3,4-thiadiazol-2-yl]methyl]amino]benzoic Acid (7): m.p. 188-190 °C, yield 61%, IR (cm⁻¹): 3482; 3165; 3008; 2930, 1710; 1590, 1610, 1215, 750. ¹HNMR (DMSO-*d*₆) δ: 12.43 (s, 1H, COOH), 8.21 (s, 1H, N=CH), 7.66–6.80 (m, 8H, Ar-H), 5.67 (s, 1H, NH), 4.52 (s, 2H, NCH₂), 3.75 (s, 3H, Ar-OCH₃). C₁₈H₁₆N₄O₃S: Calc. C (58.68%), H (4.38%), N (15.21%); Found C (58.88%), H (4.46%), N (15.29%).

2-[(5-[(3-Chloro-2-oxo-4-substituted-phenylazetidin-1-yl)-1,3,4-thiadiazol-2-yl]methyl]amino]benzoic Acid (13-20)

A solution of compound 7 (0.01 mol) and triethylamine (0.015 mol) in 1,4-dioxane (80 mL) was added to chloroacetyl chloride (0.012 mol) at 0 °C dropwise. The reaction mixture was refluxed for 5h. The reaction mixture was filtered and the filtrate was concentrated, the solid was recrystallized from ethanol-water to give compound 15. By this procedure compounds (13-20) were obtained starting from (5-12), respectively. The data of compounds (13-20) are given in Table-1.

2-[(5-[(3-chloro-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl)-1,3,4-thiadiazol-2-yl]methyl]amino]benzoic acid (15): m.p. 198-199 °C, yield 57%, IR (cm⁻¹): 3480; 3160; 3065; 2930, 1715; 1585, 1610, 1210, 755. ¹HNMR (DMSO-*d*₆) δ: 12.43 (s, 1H, COOH), 7.80-6.90 (m, 7H, Ar-H), 5.64 (s, 1H, NH), 5.44 (d, *J*=7.2 Hz, 1H, CHCl) 4.87 (d, *J*=7.2 Hz, 1H, N-CH), 4.56 (s, 2H, NCH₂), 3.75 (s, 3H, Ar-OCH₃). C₂₀H₁₇ClN₄O₄S: Calc. C (53.99%), H (3.85%), N (12.59%); Found: C (54.11%), H (3.89%), N (12.69%).

2-([5-(4-Oxo-2-substituted-phenyl-1,3-thiazolidin-3-yl)-1,3,4-thiadiazole-2-yl]methyl)amino) benzoic Acid (21-28)

To a solution of compound 7 (0.01 mol) in benzene was added mercaptoacetic acid (0.01 mol) and anhydrous ZnCl_2 (cat. amount). The reaction mass was refluxed using a Dean–Stark for 15 h. The reaction mixture was cooled to RT and filtered. The filtrate was concentrated under a vacuum. To the resulting residue, saturated NaHCO_3 solution was added up to pH 8. The solid was filtered, washed with water, dried under vacuum, and recrystallized from ethanol–water to obtain compound 23. Compounds (21-28) were synthesized by the same procedure. The data of compounds (21-28) are given in Table-1.

2-([5-[2-(4-methoxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-1,3,4-thiadiazol-2-yl]methyl)amino]benzoic Acid (23): m.p. 210-212 °C, yield 48%, IR (cm^{-1}): 3482; 3165; 3065; 2925, 1715; 1585, 1610, 1210, 754. ^1H NMR ($\text{DMSO}-d_6$) δ : 12.45 (s, 1H, COOH), 7.86–6.85 (m, 8H, Ar-H), 5.90 (s, 1H, N-CH-S), 5.65 (s, 1H, NH), 4.55 (s, 2H, NCH_2), 3.88-3.94 (m, 2H, -S- CH_2 -), 3.78 (s, 3H, Ar- OCH_3). $\text{C}_{20}\text{H}_{18}\text{N}_4\text{O}_4\text{S}_2$; Calc. C (54.28%) H (4.10%) N (12.66%); Found C (54.38%) H (4.12%) N (12.70%).

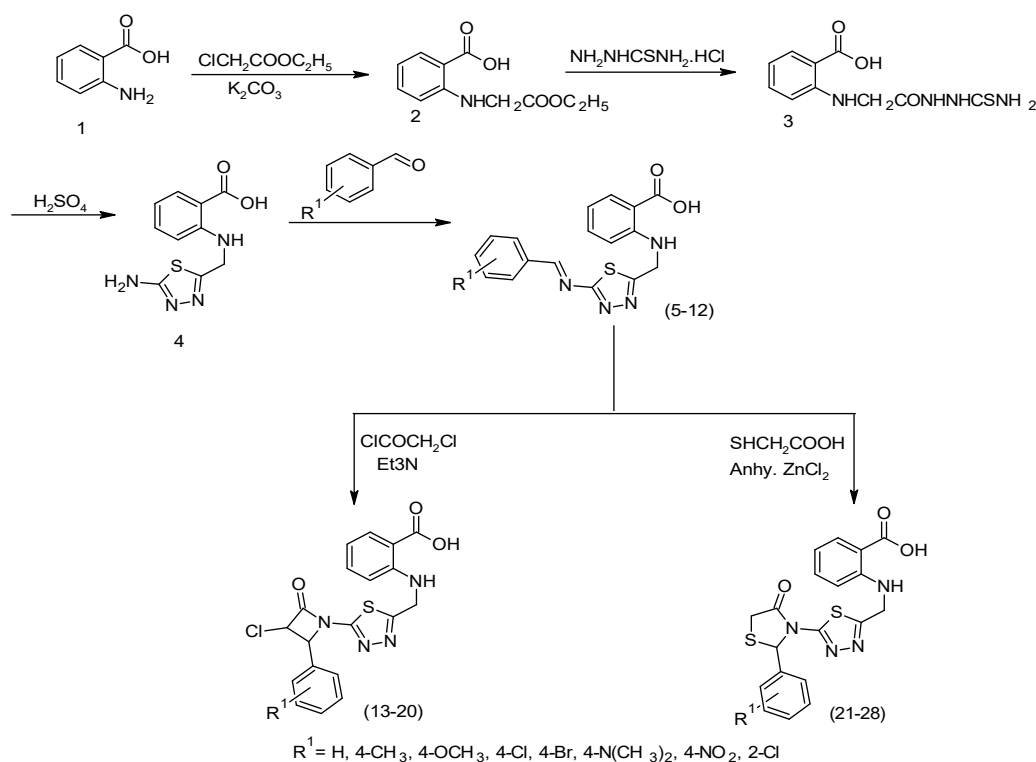
Table-1: Physical and elemental analysis of compounds (5-28)

Compd No.	R^1	M.P. (°C)	Yield (%)	Recrystallization solvent	Mol. Formula	Elemental analysis %					
						C		H		N	
						Calc.	Found	Calc.	Found	Calc.	Found
5	H	155-156	64	Ethanol-Water	$\text{C}_{17}\text{H}_{14}\text{N}_4\text{O}_2\text{S}$	60.34	60.42	4.17	4.21	16.56	16.64
6	4- CH_3	166-167	66	Ethanol-Water	$\text{C}_{18}\text{H}_{16}\text{N}_4\text{O}_2\text{S}$	61.35	61.44	4.58	4.63	15.90	15.99
7	4- OCH_3	188-190	61	Methanol-Water	$\text{C}_{18}\text{H}_{16}\text{N}_4\text{O}_3\text{S}$	58.68	58.88	4.38	4.46	15.21	15.29
8	4-Cl	187-189	65	Ethanol-Water	$\text{C}_{17}\text{H}_{13}\text{ClN}_4\text{O}_2\text{S}$	54.77	54.89	3.51	3.55	15.03	15.11
9	4-Br	155-156	72	Methanol-Water	$\text{C}_{17}\text{H}_{13}\text{BrN}_4\text{O}_2\text{S}$	48.93	49.01	3.14	3.20	13.43	13.55
10	4- $\text{N}(\text{CH}_3)_2$	154-156	66	Methanol-Water	$\text{C}_{19}\text{H}_{17}\text{N}_5\text{O}_2\text{S}$	59.82	59.94	5.02	5.10	18.36	18.44
11	4- NO_2	185-188	62	Ethanol-Water	$\text{C}_{17}\text{H}_{13}\text{N}_5\text{O}_4\text{S}$	53.26	53.34	3.42	3.48	18.27	18.35
12	2-Cl	190-191	55	Ethanol-Water	$\text{C}_{17}\text{H}_{13}\text{ClN}_4\text{O}_2\text{S}$	54.77	54.91	3.51	3.55	15.03	15.13
13	H	184-186	59	Ethanol-Water	$\text{C}_{19}\text{H}_{15}\text{ClN}_4\text{O}_3\text{S}$	55.01	55.13	3.64	3.70	13.50	13.62
14	4- CH_3	192-194	65	Methanol-Water	$\text{C}_{20}\text{H}_{17}\text{ClN}_4\text{O}_3\text{S}$	56.01	56.13	4.00	4.08	13.06	13.14
15	4- OCH_3	198-199	57	Ethanol-Water	$\text{C}_{20}\text{H}_{17}\text{ClN}_4\text{O}_4\text{S}$	53.99	54.11	3.85	3.89	12.59	12.69
16	4-Cl	176-178	60	Methanol-Water	$\text{C}_{19}\text{H}_{14}\text{Cl}_2\text{N}_4\text{O}_3\text{S}$	50.79	50.83	3.14	3.18	12.47	12.53
17	4-Br	180-182	64	Methanol-Water	$\text{C}_{19}\text{H}_{14}\text{BrClN}_4\text{O}_3\text{S}$	46.22	46.28	2.86	2.88	11.35	11.39
18	4- $\text{N}(\text{CH}_3)_2$	193-195	55	Methanol-Water	$\text{C}_{21}\text{H}_{20}\text{ClN}_5\text{O}_3\text{S}$	55.08	55.12	4.40	4.42	15.29	15.33
19	4- NO_2	201-203	65	Methanol-Water	$\text{C}_{19}\text{H}_{14}\text{ClN}_5\text{O}_5\text{S}$	49.62	49.68	3.07	3.09	15.23	15.31
20	2-Cl	212-213	59	Ethanol-Water	$\text{C}_{19}\text{H}_{14}\text{Cl}_2\text{N}_4\text{O}_3\text{S}$	50.79	50.82	3.14	3.18	12.47	12.55
21	H	197-199	65	Methanol-Water	$\text{C}_{19}\text{H}_{16}\text{N}_4\text{O}_3\text{S}_2$	55.32	55.44	3.91	3.93	13.58	13.62

22	4-CH ₃	215-217	58	Methanol-Water	C ₂₀ H ₁₈ N ₄ O ₃ S ₂	56.32	56.38	4.25	4.27	13.14	13.18
23	4-OCH ₃	210-212	48	Ethanol-Water	C ₂₀ H ₁₈ N ₄ O ₄ S ₂	54.28	54.38	4.10	4.12	12.66	12.70
24	4-Cl	195-197	58	Ethanol-Water	C ₁₉ H ₁₅ ClN ₄ O ₃ S ₂	51.06	51.10	3.38	3.42	12.54	12.58
25	4-Br	219-221	60	Methanol-Water	C ₁₉ H ₁₅ BrN ₄ O ₃ S ₂	46.44	46.46	3.08	3.10	11.40	11.44
26	4-N(CH ₃) ₂	205-207	55	Ethanol-Water	C ₂₁ H ₂₁ N ₅ O ₃ S ₂	55.37	55.45	4.65	4.69	15.37	15.41
27	4-NO ₂	219-221	51	Methanol-Water	C ₁₉ H ₁₅ N ₅ O ₃ S ₂	49.88	49.92	3.30	3.32	15.31	15.37
28	2-Cl	224-226	51	Ethanol-Water	C ₁₉ H ₁₅ ClN ₄ O ₃ S ₂	51.06	51.10	3.38	3.40	12.54	12.58

RESULTS AND DISCUSSION

The synthetic routes of compounds are outlined in Scheme-1. Anthranilic acid was converted to 2-[(2-ethoxy-2-oxoethyl)amino]benzoic acid (2), which was reacted with thiosemicarbazide.HCl to give benzoic acid derivative (3). The compound (3) on dehydration afforded 2-[(5-amino-1,3,4-thiadiazole -2-yl)methyl]amino}-benzoic acid (4) in the presence conc. sulphuric acid. This compound further reacted with substituted benzaldehyde to give compounds (5-12), which on cyclization give azetidinone 1,3,4-derivatives (13-20) and thiazolidinones (21-28) respectively. Twenty-four new compounds (5-12, 13-20, and 21-28) were tested for their pharmacological activity i.e. antifungal and antibacterial the results are given in Table-I. The characteristic feature is that anthranilic acid was substituted at the N-position with a five-member ring structure thiadiazole.



Scheme-1

Antibacterial Activity

The antibacterial activity of test compounds and standard chloramphenicol was done by filter paper disc method (Gould and Bowie, 1952)²¹ against *Staphylococcus aureus* 209 p and *Escherichia coli* ESS 2231, at a concentration of 250 mg/mL. Media with 10% DMSO in methanol was set up as control. The compounds

5-28 and the standard drug Chloramphenicol were evaluated for antibacterial activity against the bacteria *Staphylococcus aureus* 209p and *Eschericia coli* ESS 2231 at a concentration of 250 g/mL. The filter paper disc method was used to evaluate the antibacterial activity of the synthesized compounds. The results are given in Table-II. It has been found that compounds 5-12 showed moderate activity. The zones of inhibition (ZOI) result shows that compounds 5, 6, and 7 are inactive against both bacteria, while compounds 8, 9 10 11, and 12 have moderate activity. Cyclization of arylidene derivatives (5-12) into their corresponding azetidinone (13-20) and thiazolidinones (21-28) have increased the antibacterial activity. However, compounds 15, 16, and 26 are associated with good antibacterial activity. In addition to this, the screening data of antibacterial activities indicated that some compounds exhibited antibacterial activity against one or more bacteria tested. Compounds 16 and 26 exhibited excellent activity against *Eschericia coli* ESS 2231. Compounds 22 and 26 showed good activity against *Staphylococcus aureus* 209p. Furthermore, it has been found that compound 23 showed better antibacterial activities than standard Chloramphenicol against *Eschericia coli* ESS 2231 and *Staphylococcus Aureus* 209p.

Antifungal Activity

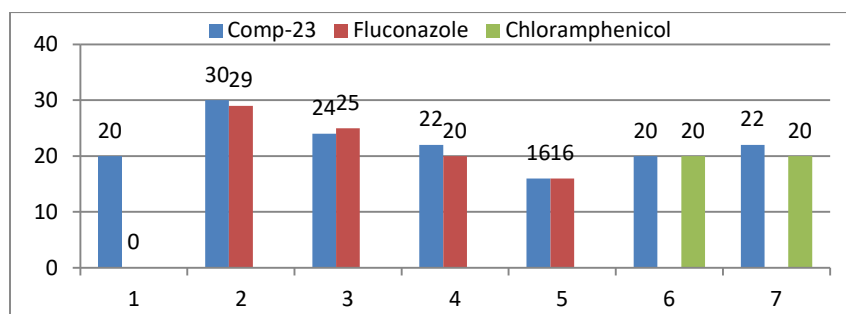
The standard agar disc diffusion method (Pai and Platt, 1995)²² was performed to evaluate the antifungal properties of test compounds and standard fluconazole. *Aspergillus fumigatus*, *Candida albicans* ATCC 2091, *Candida albicans* ATCC 10231, *Candida Krusei* GO3 and *Candida glabrata* HO5 were used in this study. All cultures were routinely maintained on SDA (A 2) and incubated at 30 °C. The compounds 5-28 were tested for antifungal profile at a concentration of 250 g/mL, and the results are shown in Table-2. It was observed that compounds 5-12 have shown antifungal activity against some strains of fungi. Compounds 10 and 11 had good antifungal activity than the rest of the compounds 5, 6, 7, 8, 9, and 12. Furthermore, compounds 13-20 enhance the activity due to the introduction of azetidinone. It has been observed that compound 20 has almost the same antifungal activity as fluconazole. It is significant to mention that compound 15 having an OCH₃ group at the IVth position, seems to be more effective than 13, 14, 16, 17, 18, 19, and 20. Cyclization of arylidene derivatives (5-12) into their corresponding thiazolidinones (21-28), these compounds exhibited moderate to good activity against one or more fungi tested. It is also observed that compound 23 having a methoxy group at the p-position shows better antifungal activity than fluconazole. The most active compound 23 and reference drug activity is shown in Fig.-2.

Table-2: Antifungal and Antibacterial Activities of Compounds 5-28 at the Concentration of 250 mg/mL (Control - 10 % DMSO)

Compounds	Antifungal activity [Diameter of the inhibition zone (mm)]					Antibacterial activity [Diameter of the inhibition zone (mm)]	
	<i>Aspergillus fumigatus</i>	<i>Candida albicans</i> ATCC 2091	<i>Candida albicans</i> ATCC 0231	<i>Candida krusei</i> G03	<i>Candida glabrata</i> H05	<i>Staphylococcus aureus</i> 209p	<i>Eschericia coli</i> ESS 2231
Control	0	0	0	0	0	0	0
Fluconazole	0	29	25	20	16	-	-
Chloramphenicol	-	-	-	-	-	20	20
5	12	14	10	08	0	0	0
6	10	08	07	06	0	0	0
7	12	11	06	09	0	0	0
8	0	10	08	08	0	10	08
9	0	12	10	10	0	12	09
10	0	08	12	12	0	13	12
11	10	12	12	12	0	10	10
12	8	10	10	11	10	11	13
13	10	12	14	12	08	11	12
14	11	14	16	14	10	14	14
15	13	16	18	12	12	16	17
16	10	18	16	15	10	16	18

17	12	10	14	12	10	14	14
18	14	11	16	11	08	14	12
19	0	09	10	12	09	15	11
20	16	12	14	10	16	14	10
21	14	18	16	14	12	16	14
22	12	16	18	12	10	17	12
23	20	30	24	22	16	20	22
24	14	20	21	16	12	14	12
25	16	22	20	12	10	16	14
26	12	21	20	16	14	17	18
27	10	25	21	15	10	11	12
28	16	24	18	14	12	10	14

—: No inhibition zone.



1. *Aspergillus fumigatus*, 2. *Candida albicans* ATCC 2091, 3. *Candida albicans* ATCC 0231, 4. *Candida krusei* G03, 5. *Candida glabrata* H05, 6. *Staphylococcus aureus* 209p, 7. *Escherichia coli* ESS 2231

Fig.-2: Antifungal and Antibacterial Activity of Most Potent Compound 23 and Reference Drug

CONCLUSION

All the newly synthesized compounds were tested for their activity. From the above results and discussion, the following conclusions can be drawn –

- Substituted benzylidene derivatives (5-12) exhibited moderate antimicrobial activities.
- The presence of azetidinone and thiazolidinone moiety in compounds has increased the antibacterial and antifungal activity.
- Appearance of the OCH_3 group, at the IInd- or IVth-position of the phenyl ring, may play a significant role in the modulation of antibacterial activity.
- The highest antifungal activity and antibacterial activity was evoked by substitution with a phenyl group.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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