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Synthesis of new bioactive venlafaxine analogs: Novel thiazolidin-4-ones as antimicrobials

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Abstract—A one-pot, three-component, microwave irradiated and conventional solution-phase synthesis of bioactive venlafaxine analogs such as 2,3-disubstituted-1,3-thiazolidin-4-ones **3a**–**j** under mild conditions and their characterization are reported. The novel thiazolidin-4-ones, 3-(2-(1-hydroxycyclohexyl)-2-(4-methoxyphenyl)ethyl)-2-phenyl-thiazolidin-4-one **3a**, 2-(2,6-difluorophenyl)-3-(2-(1-hydroxycyclohexyl)-2-(4-methoxyphenyl)ethyl)thiazolidin-4-one **3c**, and 2-(furan-2-yl)-3-(2-(1-hydroxycyclohexyl)-2-(4-methoxyphenyl)ethyl)thiazolidin-4-one **3i**, were characterized by the single crystal X-ray diffraction method. The cyclohexane ring of all the three molecules is in chair conformation. All the synthesized compounds were screened for their efficacy as antimicrobials in vitro by the disk diffusion and microdilution method against pathogenic strains such as *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas fluorescens*, *Xanthomonas campestris pvs*, *Xanthomonas oryzae*, *Aspergillus niger*, *Aspergillus flavus*, *Fusarium oxysporum*, *Trichoderma* species, and *Fusarium monaliforme* species. Among these compounds **3c**, **3j**, **3g**, **3d**, and **3e** showed potent antimicrobial activity, when compared to standard drugs.

1. Introduction

The structural and therapeutic diversity coupled with commercial viability of small molecules has fascinated organic and medicinal chemists. There has been considerable interest in the chemistry of thiazolidin-4-one ring systems, which is a core structure in various synthetic pharmaceuticals displaying a broad spectrum of biological activity[1] such as anti-mycobacterial,[2] anti-fungal,[3] anti-cancer,[4] anti-tuberculosis,[5] anti-convulsant,[6] anti-inflammatory, and analgesic[7] activities. Therefore, a general, simple, and efficient method for rapid synthesis of thiazolidine-4-ones would be greatly advantageous and warrants further investigations in drug discovery. Consequently, many different protocols have been developed that allow the synthesis of thiazolidin-4-one skeletons. Venlafaxine,[8,9] a new class of antidepressants (SNRIs), is quite different from other antidepressants having a unique structure and morphological effects. Microwave-assisted reactions have become an established tool for the high-speed synthesis of novel chemical entities.[10] Using the venlafaxine key intermediate, 1-[2-amino-1-(4-methoxy-phenyl)-ethyl]-cyclohexanol **1**, we have synthesized 2,3-disubstituted-1,3-thiazolidin-4-ones with different aromatic and heterocyclic aldehydes in one-pot, three-component solution-phase system, under conventional method using dicyclohexylcarbodiimide as cyclizing agent and also by the microwave irradiation technique. Earlier studies on the pharmacological activities of thiazolidin-4-ones showed a wide spectrum of antimicrobial activities[11] and venlafaxine key intermediate, 1-[2-amino-1-(4-methoxy-phenyl)-ethyl]-cyclohexanol **1**, used as a starting material for the synthesis of thiazolidin-4-ones shows profound bioavailability. Bearing this in mind we have synthesized a series of thiazolidin-4-ones, which have different pharmacologically active groups, which can exhibit antimicrobial activities. In connection with our efforts to synthesize thiazolidin-4-ones under the microwave irradiation technique and to screen a variety of biological targets, we herein, report the microwave-mediated solution-phase synthesis of some thiazolidin-4-one scaffolds

Keywords: Thiazolidinone; Crystal structure; Venlafaxine analogs; Antimicrobials.
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bearing venlafaxine moiety and their in vitro antimicrobial activities by the disk diffusion and microdilution method against pathogenic strains such as *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas fluorescens*, *Xanthomonas campestris pvs*, *Xanthomonas oryzae*, *Aspergillus niger*, *Aspergillus flavus*, *Fusarium oxysporum*, *Trichoderma species*, and *Fusarium monaliforme* species. The yields obtained by both microwave-mediated and conventional methods are reported and compared.

2. Chemistry

The novel synthon, 1-[2-amino-1-(4-methoxy-phenyl)-ethyl]-cyclohexanol **1**, used for the construction of various thiazolidin-4-ones **3a**–**j** is obtained by the condensation reaction of 4-methoxyphenyl acetonitrile with cyclohexanone followed by catalytic hydrogenation.[12] By using this intermediate, we have synthesized the novel thiazolidin-4-ones **3a**–**j**. The synthesis of thiazolidin-4-ones **3a**–**j** involves the one-pot, three-component condensation reactions of 1-[2-amino)-1-(4-methoxy-phenyl)-ethyl]-cyclohexanol **1**, with different aromatic and heterocyclic aldehydes **2a**–**j** and thioglycolic acid using dicyclohexylcarbodiimide as cyclizing agent. The heterocyclic aldehydes such as 2-furfuraldehyde and 2-butyl-4-chloro-imidazole-5-carbaldehyde were used to construct the new thiazolidin-4-ones. We also carried out the synthesis of thiazolidin-4-ones **3a**–**j** by the microwave irradiation technique without using cyclizing agent as shown in Scheme 1.

3. Results and discussion

3.1. Chemistry

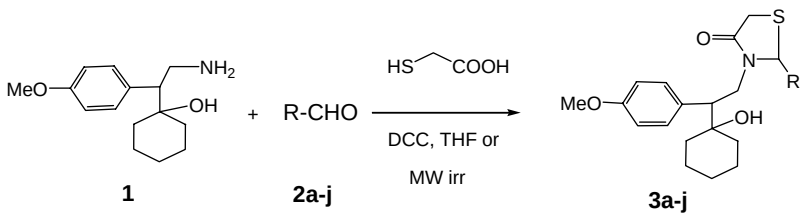
The microwave-assisted synthesis of thiazolidin-4-ones **3a**–**j** in comparison to the conventional method offers more advantages such as reduced reaction time (45–60 s), low cost, simplicity in processing, reduced pollution, and high yield. The structures of the compounds, **3a**–**j**, were deduced from their elemental analyses, their IR and ^{1}H NMR spectra. The yields were in the range of 65–70% and 80–90% for the conventional method and microwave techniques, respectively, with greater than 98% purity. The results are summarized in Table 1.

The FT-IR (KBr) spectra of all the 2,3-disubstituted-1,3-thiazolidin-4-ones show vibrational frequency for C=O in the range 1650–1691 cm^{-1}. The ^{1}H NMR spectra of all the synthesized molecules showed that the C(5)-methylenic protons appear in the region of 5.16–5.53 ppm. This proton appeared at a higher field owing to the shielding effect of the nearly coplanar sulfur orbital.[13] The protons appear as a multiplet in the region 1.1–1.7 ppm, which was assigned to the cyclohexane ring.

3.2. X-ray data collection, structure solution, and refinement

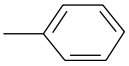
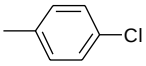
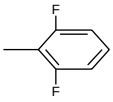
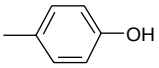
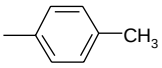
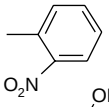
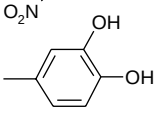
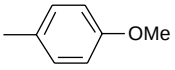
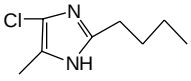
The X-ray diffraction data were collected on a DIPLabo image plate system at room temperature, in oscillation mode with a range of 5°. The data were reduced using the *DENZO*[14] and processed using *Scalepack*. No absorption corrections were applied. The structure was solved by direct methods using SHELXS-97.[15] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were fixed at chemically acceptable positions and allowed to ride on the parent atoms. Refinements were done using SHELXL-97.[16] The comparative crystallographic data of the compounds **3a**, **3c** and **3i** are given in Table 2. The ORTEP[17] of **3a** is shown in Figure 1. The cyclohexane ring is in chair conformation with a weighted average ring bond distance of 1.5253(10, 32) Å. The dihedral angle between the plane comprising of atoms N(18)–O(20)–C(21)–C(19)–S(22)–C(23) and C(24)–C(25)–C(26)–C(27)–C(28)–C(29) is 81.10 (8)° and the dihedral angle between C(24)–C(25)–C(26)–C(27)–C(28)–C(29) and O(2)–C(3)–C(4)–C(5)–C(6)–C(7)–C(8) 25.28 (8)°. Also the dihedral angle between N(18)–O(20)–C(21)–C(19)–S(22)–C(23) and O(2)–C(3)–C(4)–C(5)–C(6)–C(7)–C(8) is 55.90 (7)°. The torsion angle of S(22)–C(23)–C(24)–C(29) is −96.2 (2)° and that of N(18)–C(23)–C(24)–C(29) 145.5 (1)°. The molecule exhibits intermolecular hydrogen bonds of types O–H···O and C–H···O. The packing of molecule **3a** down *b* shown in Figure 2 indicates the linear network of hydrogen bonds.

The ORTEP of **3c** is shown in Figure 3. The cyclohexane ring is in chair conformation with a weighted average ring bond distance of 1.5250(13, 22) Å. The dihedral angle between the plane comprising of atoms N(18)–O(20)–C(21)–C(19)–S(22)–C(23) and C(24)–C(25)–F(26)–C(27)–C(28)–C(29)–C(30)–F(31) is 88.7 (1)° and the dihedral angle between C(24)–C(25)–F(26)–C(27)–C(28)–C(29)–C(30)–F(31) and O(2)–C(3)–C(4)–C(5)–C(6)–C(7)–C(8) 29.41 (8)°. Also the dihedral angle between N(18)–O(20)–C(21)–C(19)–S(22)–C(23) and O(2)–C(3)–C(4)–C(5)–C(6)–C(7)–C(8) is 59.7 (1)°. The atoms F(26) and F(31) have a deviation of 0.048(2) Å and −0.038(1) Å with respect to the phenyl ring comprising of atoms C(24)–C(25)–C(27)–C(28)–C(29)–



Scheme 1. R = phenyl, **3a**; R = 4-chloro phenyl, **3b**; R = 2,6-difluorophenyl, **3c**; R = 4-hydroxyphenyl, **3d**; R = 4-methylphenyl, **3e**; R = 2-nitrophenyl, **3f**; R = 3,4-dihydroxyphenyl, **3g**; R = 4-methoxyphenyl, **3h**; R = furfuryl, **3i**; R = 2-butyl-4-chloro-imidazole-5-yl, **3j**.

Table 1. Reaction condition and physical data of bioactive venlafaxine derivatives

Compound	R	R_f value	Reaction time		Yield (%)		Mp (°C)
			Conventional (h)	MW irr (S)	DCC	MW irr	
3a		0.82	3	50	70	90	133
3b		0.62	3	60	65	88	141
3c		0.75	2	45	70	89	178
3d		0.78	3	55	67	87	118
3e		0.82	3	45	70	90	130
3f		0.75	4	60	65	83	121
3g		0.64	3	55	65	80	189
3h		0.72	2	60	66	81	174
3i		0.67	3	45	69	88	145
3j		0.76	4	60	67	81	118

C(30), indicating that the deviations are in opposite directions with respect to the phenyl plane. The torsion angle of S(22)–C(23)–C(24)–C(30) is 110.1(2)° and that of N(18)–C(23)–C(24)–C(30) −130.3(2)°. The molecule exhibits intermolecular hydrogen bonds of types O–H···O and C–H···F and C–H···O. The packing of the molecule **3c** down *b* in Figure 4 shows a network of hydrogen bonds.

The ORTEP of **3i** is shown in Figure 5. The cyclohexane ring is in chair conformation with a weighted average ring bond distance of 11.5234(13, 28) Å. The dihedral angle between the plane comprising of atoms N(18)–O(20)–C(21)–C(19)–S(22)–C(23) and C(24)–O(25)–C(26)–C(27)–C(28) is 87.12(2)° and the dihedral angle between C(24)–O(25)–C(26)–C(27)–C(28) and O(2)–C(3)–C(4)–C(5)–C(6)–C(7)–C(8) is 25.3 (2)°. Also the dihedral angle between N(18)–O(20)–C(21)–C(19)–S(22)–C(23) and O(2)–C(3)–C(4)–C(5)–C(6)–C(7)–C(8) is 62.1(1)°. The torsion angle of S(22)–C(23)–C(24)–C(28) is −106.7(3)° and that of N(18)–C(23)–C(24)–C(28) 134.4(3)°. The molecule exhibits intermolecular hydrogen bonds of types O–H···O and C–H···O. The packing of molecule **3i** down *b* as shown in Figure 6 indicates a network of hydrogen bonds.

3.3. Biology

3.3.1. In vitro evaluation of antimicrobial activity. With a view to synthesizing new antimicrobial compounds, we have synthesized venlafaxine analogs with a thiazolidin-4-one ring. Their efficacy as antimicrobials was evaluated in vitro by disk diffusion, microdilution, and turbidometric methods against different strains. Nystatin was used as positive control against fungi and streptomycin and tetracycline against bacteria. The tests were repeated thrice and the results are reported as means of at least three determinations. Antibacterial activity of the compounds tested is shown in Tables 3 and 4. Compounds **3c**, **3j**, **3g**, **3d**, and **3e** exhibited potent inhibitory activity compared to standard drugs at the tested concentrations. From the results obtained, it reveals that the presence of two fluorine atoms at 2nd and 6th positions in **3c** and the presence of 2-butyl-4-chloro imidazole in **3j** might be the reason for the significant inhibitory activity. This result confirms our previous reports,[18,19] where the presence of fluorine atom and the substituted imidazole groups possesses significant antimicrobial activity. Also, the presence of hydroxyl groups in the molecules would enhance the inhibitory activity stoichiometrically as shown by **3g** and **3d**. But the com-

Table 2. Comparative crystallographic data

Compound	**3a**	**3c**	**3i**
CCDC No.	281243	281244	281245
Empirical formula	$C_{24}H_{29}NO_3S$	$C_{24}H_{27}F_2NO_3S$	$C_{22}H_{27}NO_4S$
Formula weight	411.54	447.53	401.51
Temperature (K)	293(2)	293(2)	293(2)
Wavelength (Å)	0.71073	0.71073	0.71073
Crystal system	*Monoclinic*	*Monoclinic*	*Monoclinic*
Space group	$P2_1/c$	$P2_1/n$	$P2_1/c$
Cell dimensions			
a (Å)	10.595(6)	10.419(9)	10.038(7)
b (Å)	14.111(8)	14.534(1)	14.455(1)
c (Å)	14.995(8)	15.523(9)	15.077(8)
α (°)	90	90	90
β (°)	100.886(2)	107.792(6)	107.579(3)
γ (°)	90	90	90
Volume (Å^3)	2201.5(2)	2238.2(3)	2085.5(2)
Z	4	4	4
Density (calculated) (mg/m^3)	1.242	1.328	1.279
F_{000}	880	944	856
Θ range for data collection (°)	2.43–32.46	2.09–32.45	2.13–32.47
Reflections collected	14640	12292	13008
Independent reflections	7778 [R_{int} = 0.0310]	6604 [R_{int} = 0.0314]	6794 [R_{int} = 0.0387]
Data/restraints/parameters	7778/0/263	6604/0/281	6794/0/255
Goodness of fit on F^2	1.02	1.06	1.06
Final R indices [$I > 2\sigma(I)$]	$R1$ = 0.0513, $wR2$ = 0.1431	$R1$ = 0.0559, $wR2$ = 0.1463	$R1$ = 0.0724, $wR2$ = 0.1947
R indices (all data)	$R1$ = 0.0905, $wR2$ = 0.1709	$R1$ = 0.0944, $wR2$ = 0.1784	$R1$ = 0.1240, $wR2$ = 0.2410
Largest diff. peak and hole (e Å^{-3})	0.317 and −0.434	0.250 and −0.551	0.604 and −0.456

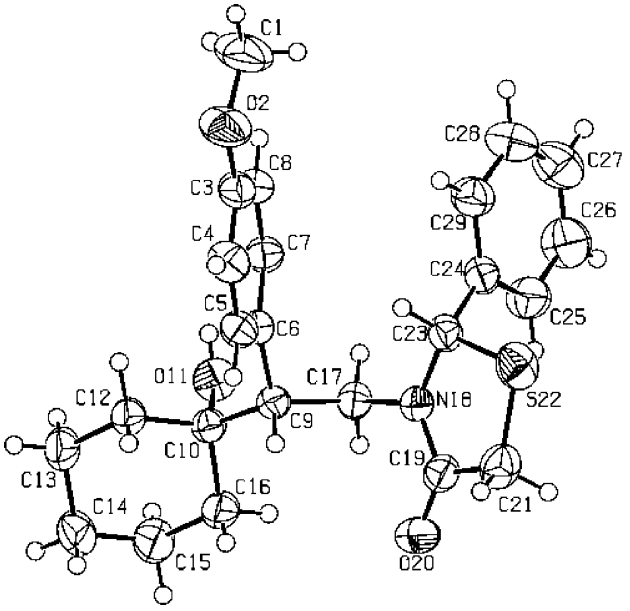


Figure 1. Ortep of **3a** at 50% probability.

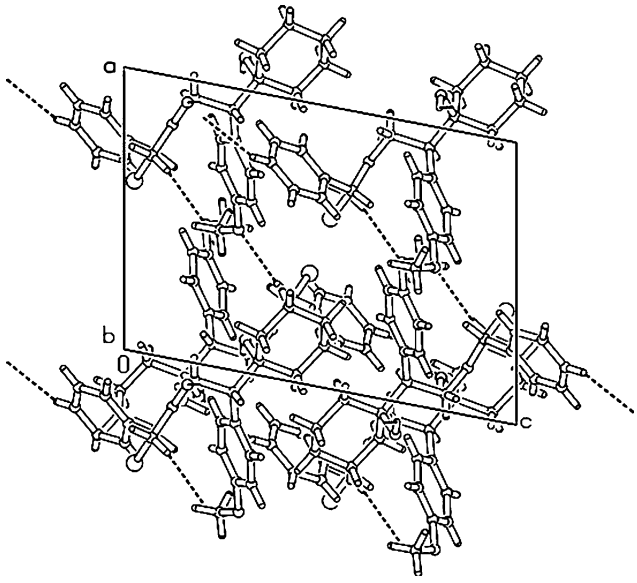


Figure 2. Packing of molecule **3a** down b axis.

pound **3a** (without the hydroxyl group) did not show any inhibitory activity. Presence of chlorine atom at 4th position in **3b** also did not show any inhibition. But in **3e**, presence of the methyl group showed considerable inhibitory activity. Therefore, this significant inhibitory activity might be attributed the presence of electron-releasing groups at 4th position. Compounds **3a**, **3b**, **3f**, **3h** and **3i** did not exhibit any inhibitory activity against any of the bacterial strains tested. Antifungal activity was evaluated by the disk diffusion and turbidometric methods. The results are depicted in Tables 5 and 6. Compounds **3c**, **3j**, **3g**, **3d**, and **3e** showed good inhibitory activity compared to nystatin. Compounds **3f**, **3a**, and **3h** bearing 2-nitro, phenyl, and 4-methoxy groups, respectively, showed moderate inhibitory activity compared to standard drugs at tested concentrations.

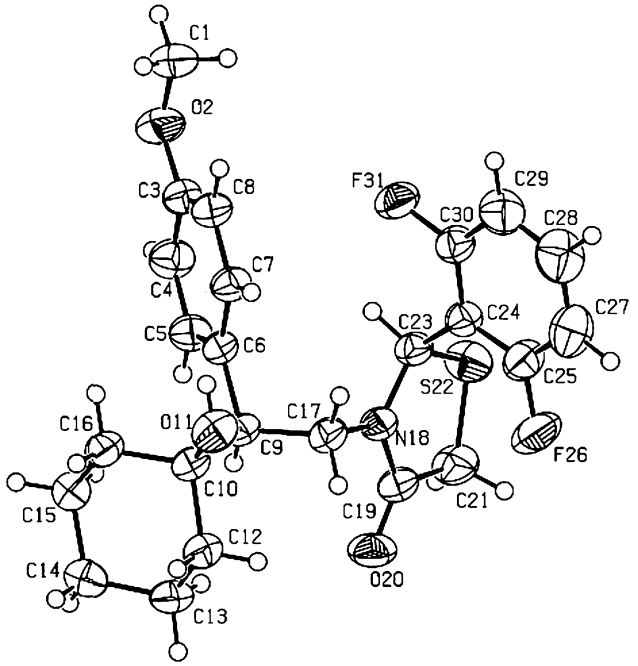


Figure 3. Ortep of **3c** at 50% probability.

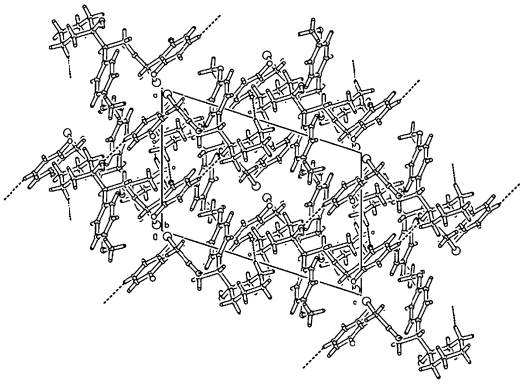


Figure 4. Packing of molecule **3c** down *b* axis.

4. Conclusion

In summary, we have synthesized novel 2,3-disubstituted-1,3-thiazolidin-4-one derivatives (**3a**–**j**) which are venlafaxine analogs under both conventional and microwave irradiation techniques (solution phase). It is thus concluded that under microwave heating, the products **3a**–**j** were conveniently and efficiently prepared in synthetically chemical yields, typically in the range of 80–90%. The simplicity of the experimental procedures, reduction of time, and high yield render this approach particularly attractive. From antimicrobial activity data, it is revealed that, the compounds **3c**, **3j**, **3g**, **3d**, and **3e** may serve as a new class of antimicrobials and the modifications in 4-thiazolidinones bearing a venlafaxine moiety deserve further investigation to develop more potent antimicrobial agents for therapeutic use (Fig. 7). The anti-depressant activities of these classes of compounds are underway.

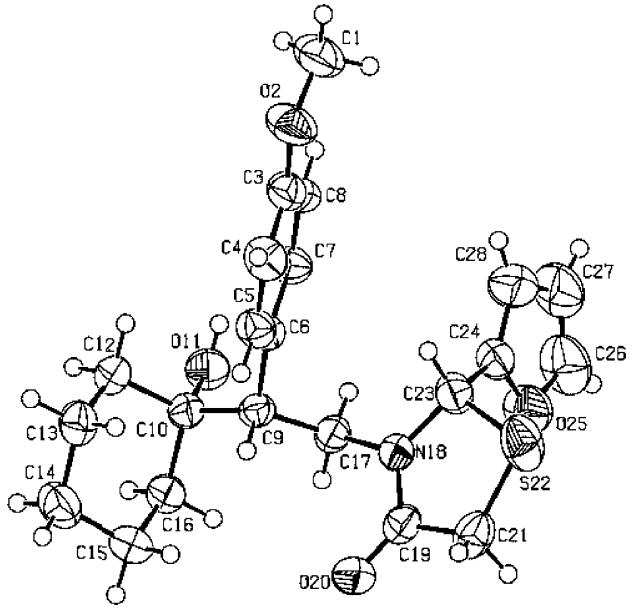


Figure 5. Ortep of **3i** at 50% probability.

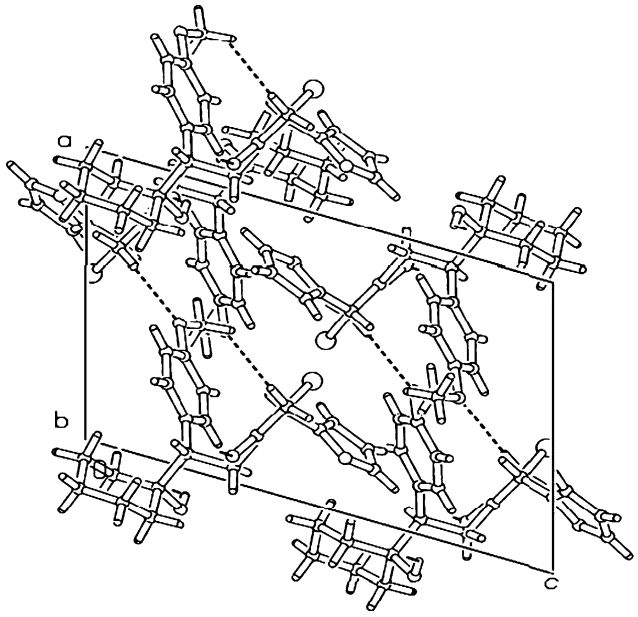


Figure 6. Packing of molecule **3i** down *b* axis.

5. Experimental

The melting points were determined on a SELACO-650 hot stage apparatus and are uncorrected. IR (KBr) spectra were recorded on a Jasco FT/IR-4100 Fourier transform infrared spectrometer, ^{1}H NMR were recorded on a Shimadzu AMX 400 spectrometer by using $CDCl_3$ as solvent and TMS as an internal standard (Chemical shift in ppm). Elemental analyses were obtained on a vario-EL instrument. Thin layer chromatography (TLC) was conducted on 0.25 mm silica gel plates ($60F_{254}$, Merck). Visualization was made with ultraviolet light. All extracted solvents were dried over anhydrous Na_2SO_4 and evaporated with a BUCHI rotary evaporator. Reagents were obtained commercially and used as received.

Table 3. Minimal inhibitory concentration (MIC) in μg/ml of compounds against tested bacterial strains by microdilution method

Compound	Minimal inhibitory concentration (MIC) (μg/ml)[a]				
	Bacillus subtilis	*Escherichia coli*	*Pseudomonas fluorescens*	*Xanthomonas campestris pvs*	*Xanthomonas oryzae*
3a	27 ± 1.2	22 ± 0.9	20 ± 0.9	16 ± 0.56	23 ± 1.1
3b	34 ± 1.3	29 ± 1.1	28 ± 1.2	18 ± 0.78	28 ± 1.2
3c	10 ± 0.4	9 ± 0.4	6 ± 0.24	5 ± 0.21	7 ± 0.3
3d	15 ± 0.6	14 ± 0.62	12 ± 0.51	11 ± 0.48	13 ± 0.5
3e	20 ± 0.9	18 ± 0.8	16 ± 0.7	14 ± 0.6	15 ± 0.7
3f	30 ± 1.2	25 ± 1.1	26 ± 1.1	17 ± 0.5	24 ± 1
3g	12 ± 0.5	11 ± 0.52	9 ± 0.41	8 ± 0.35	9 ± 0.41
3h	30 ± 1.1	26 ± 1	24 ± 0.9	20 ± 0.9	25 ± 1.1
3i	32 ± 1	28 ± 1.2	26 ± 1.1	23 ± 1	24 ± 1
3j	11 ± 0.5	10 ± 0.4	8 ± 0.35	7 ± 0.31	8 ± 0.32
Streptomycin	25 ± 1.2	19 ± 0.78	17 ± 0.7	—	—
Tetracycline	—	—	—	13 ± 0.5	19 ± 0.8

[a] Values are means of three determinations, the ranges of which are less than 5% of the mean in all cases.

Table 4. Inhibitory zone (diameter) mm of compounds against tested bacterial strains by the disk diffusion method

Compound	Inhibitory zone (diameter) (mm)[a]				
	Bacillus subtilis	*Escherichia coli*	*Pseudomonas fluorescens*	*Xanthomonas campestris pvs*	*Xanthomonas oryzae*
3a	12 ± 0.5	14 ± 0.6	16 ± 0.7	11 ± 0.42	10 ± 0.38
3b	5 ± 0.21	4 ± 0.12	6 ± 0.22	1 ± 0.0.02	3 ± 0.12
3c	27 ± 1.1	29 ± 1.2	30 ± 1.1	28 ± 1.2	32 ± 1.2
3d	20 ± 0.85	21 ± 1	23 ± 1	20 ± 0.8	24 ± 1
3e	19 ± 0.6	18 ± 0.8	20 ± 0.8	18 ± 0.7	19 ± 0.78
3f	6 ± 0.22	7 ± 0.28	9 ± 0.4	3 ± 0.12	5 ± 0.2
3g	23 ± 1	25 ± 1.1	27 ± 1.2	24 ± 1	28 ± 1.2
3h	8 ± 0.35	7 ± 0.3	9 ± 0.32	6 ± 0.25	5 ± 0.2
3i	4 ± 0.12	6 ± 0.21	7 ± 0.3	3 ± 0.12	6 ± 0.22
3j	25 ± 1.1	27 ± 1.1	29 ± 1.2	26 ± 1.1	30 ± 1.2
Streptomycin	15 ± 0.6	19 ± 0.7	22 ± 1	—	—
Tetracycline	—	—	—	16 ± 0.65	15 ± 0.65

Streptomycin sulfate (10 μg/disk), Tetracycline (10 μg/disk) were used as positive reference and compounds (25 μg/disk).
[a] Values are means of three determinations, the ranges of which are less than 5% of the mean in all cases.

Table 5. Minimal inhibitory concentration (MIC) in μM of compounds against tested fungal strains by turbidometric method

Compound	Minimal inhibitory concentration (MIC) (μM)[a]				
	Aspergillus niger	*Aspergillus flavus*	*Fusarium oxysporum*	*Trichoderma species*	*Fusarium monaliforme*
3a	28 ± 1.2	34 ± 1.5	37 ± 1.67	29 ± 1.4	32 ± 1.2
3b	44 ± 2	49 ± 1.5	55 ± 2	59 ± 2.5	64 ± 2.8
3c	15 ± 0.7	14 ± 0.6	16 ± 0.7	12 ± 0.5	15 ± 0.68
3d	22 ± 1	20 ± 0.8	24 ± 1	22 ± 0.9	23 ± 1
3e	23 ± 0.9	21 ± 1	26 ± 1.1	24 ± 0.9	25 ± 1.1
3f	29 ± 1.3	33 ± 1.4	35 ± 1.5	30 ± 1.1	31 ± 1.4
3g	19 ± 0.8	18 ± 0.8	21 ± 1	17 ± 0.7	20 ± 0.8
3h	30 ± 1.1	35 ± 1.5	36 ± 1.4	31 ± 1.1	33 ± 1.2
3i	39 ± 1.8	40 ± 1.8	48 ± 2.1	43 ± 1.8	52 ± 2.4
3j	17 ± 0.6	16 ± 0.7	19 ± 0.8	15 ± 0.65	18 ± 0.8
Nystatin	29 ± 1.2	34 ± 1.5	36 ± 1.6	30 ± 1.2	32 ± 1.2

[a] Values are means of three determinations, the ranges of which are less than 5% of the mean in all cases.

5.1. General procedures for the synthesis of 2,3-disubstituted-1,3-thiazolidin-4-ones (3a–j)

5.1.1. Conventional method. A mixture of 1-[2-amino-1-(4-methoxy-phenyl)-ethyl]-cyclohexanol **1** (1 equiv) and aldehyde **2a–j** (1.2 equiv) in dry tetrahydrofuran was stirred with ice cooling for 5 min, followed by the addition of thioglycolic acid (1.5 equiv). After 5 min, dicyclohexylcarbodiimide (1.5 equiv) was added to the reaction mixture at 0 °C and the reaction mixture was stirred for about 2–4 h at room temperature to complete the reaction. The precipitated dicyclohexylurea was filtered off, the filtrate was concentrated to dryness under reduced pressure. Deionized water was added to the residue and extracted with dichloromethane. The organic layer was washed with 5% $NaHCO_3$ solution/citric acid solution and dried over anhydrous Na_2SO_4. The crude solid obtained on evaporation of the solvent under reduced pressure was recrystallized from methanol to furnish a crystalline solid (**3a–j**).

Table 6. Inhibitory zone (diameter) mm of compounds against tested fungal strains by the disk diffusion method

Compound	Inhibitory zone (diameter) (mm)[a]				
	Aspergillus niger	*Aspergillus flavus*	*Fusarium oxysporum*	*Trichoderma species*	*Fusarium monaliforme*
3a	12 ± 0.5	13 ± 0.5	18 ± 0.8	19 ± 0.8	16 ± 0.8
3b	9 ± 0.4	7 ± 0.28	8 ± 0.32	10 ± 0.4	8 ± 0.35
3c	22 ± 1	24 ± 1	30 ± 1.2	26 ± 1.2	28 ± 1.2
3d	17 ± 0.8	19 ± 0.8	26 ± 1.1	22 ± 1	24 ± 1
3e	16 ± 0.72	17 ± 0.7	24 ± 1.1	21 ± 0.9	20 ± 0.8
3f	13 ± 0.51	14 ± 0.6	19 ± 0.8	20 ± 0.8	16 ± 0.6
3g	19 ± 0.8	21 ± 1	28 ± 1.2	24 ± 1.1	26 ± 1.1
3h	11 ± 0.45	12 ± 0.5	17 ± 0.7	18 ± 0.8	15 ± 0.7
3i	6 ± 0.24	5 ± 0.2	4 ± 0.12	3 ± 0.1	2 ± 0.09
3j	20 ± 0.9	23 ± 1	28 ± 1.1	24 ± 1.1	26 ± 1.1
Nystatin	12 ± 0.5	14 ± 0.6	18 ± 0.7	20 ± 0.9	16 ± 0.67

Nystatin (10 μg/disk) was used as positive reference and compounds (25 μg/disk).
[a] Values are means of three determinations, the ranges of which are less than 5% of the mean in all cases.

5.1.2. Microwave irradiation method. A 25 ml conical flask, charged with amine **1** (1 g, 4.02 mol), different aldehydes **2a–j** (1.2 equiv), thioglycolic acid (0.555 g, 6.03 mmol), and DMF (5 ml), was irradiated in the microwave oven at 20% power level (60 W) for 45–60 s. After completion of the reaction (TLC), 10 equivalent of water was added to the cooled (rt) contents of the flask. Using the above workup procedure, we isolated the pure products. An analytically pure sample was obtained by recrystallization from methanol.

5.1.3. 3-(2-(1-Hydroxycyclohexyl)-2-(4-methoxyphenyl)-ethyl)-2-phenylthiazolidin-4-one (3a). It was obtained from amine **1** (1 g, 4.02 mmol), benzaldehyde **2a** (0.512 g, 4.82 mmol), thioglycolic acid (0.555 g, 6.03 mmol), and dicyclohexylcarbodiimide (1.244 g, 6.03 mmol).

IR ν_{max} (KBr): 3324.6, 2928.4, 2851.2, 1508, 1686.4, 803 cm^{-1}.

^1H NMR ($CDCl_3$) δ: 1.12–1.78 (m, 10H, cycl-H), 4.67 (s, C(5)-H), 6.82–6.95 (dt, 2H, Ar-H), 6.97–7.02 (dd, 2H, J = 4 Hz, Ar-H), 7.26–7.35 (q, 3H, Ar-H), 6.86–6.9 (d, 2H, J = 8 Hz, Ar-H), 3.82–3.87 (s, 3H, –O–CH_3), 3.54–3.6 (d, 1H, J = 15 Hz), 3.0–3.06 (t, 1H, –CH–C_6H_5), 3.66–3.72 (dd, 2H, J = 2 Hz, C(2)-H), 4.11–4.18 (s, 1H, –OH).

Anal. Calcd for $C_{24}H_{29}NO_3S$: C, 70.04; H, 7.10;N, 3.40; S, 7.79. Found: C, 69.75; H, 7.105; N, 3.407; S, 7.801.

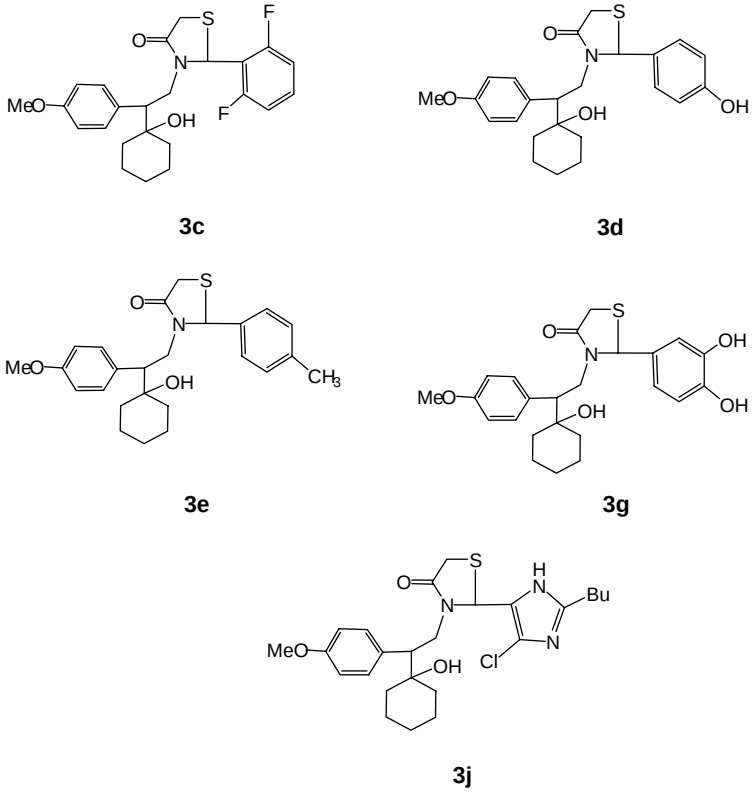


Figure 7. Structures of the potent anti-microbials of the novel thiazolidin-4-one series.

5.1.4. 2-(4-Chlorophenyl)-3-(2-(1-hydroxycyclohexyl)-2-(4-methoxyphenyl)ethyl)thiazolidin-4-one (3b). It was obtained from amine **1** (1 g, 4.02 mmol), *p*-chlorobenzaldehyde **2b** (0.678 g, 4.82 mmol), thioglycolic acid (0.555 g, 6.03 mmol), and dicyclohexylcarbodiimide (1.244 g, 6.03 mmol).

IR ν_{max} (KBr): 3328.4, 2929.1, 2858.3, 1512, 1688.4, 810 cm^{-1}.

^1H NMR ($CDCl_3$) δ: 1.1–1.6 (m, 10H, cycl-H), 5.29 (s, C(5)-H), 5.26 (s, 1H, –OH), 6.82–6.95 (dt, 2H, Ar-H), 7.1–7.18 (t, 2H, Ar-H), 7.21–7.31 (q, 2H, Ar-H), 7.33–7.38 (d, 2H, J = 7 Hz, Ar-H), 3.8–3.88 (s, 3H, –O–CH_3), 3.64–3.7 (dd, 2H, J = 2 Hz, C(2)-H), 4.36–4.46 (t, 1H, –CH–C_6H_5), 3.28–3.33 (d, 2H, J = 8 Hz).

Anal. Calcd for $C_{24}H_{28}ClNO_3S$: C, 64.63; H, 6.33; N, 3.14; S, 7.19. Found: C, 64.54; H, 6.38; N, 3.10; S, 7.14.

5.1.5. 2-(2,6-Difluorophenyl)-3-(2-(1-hydroxycyclohexyl)-2-(4-methoxyphenyl)ethyl)thiazolidin-4-one (3c). It was obtained from amine **1** (1 g, 4.02 mmol), difluoro benzaldehyde **2c** (0.686 g, 4.82 mmol), thioglycolic acid (0.555 g, 6.03 mmol), and dicyclohexylcarbodiimide (1.244 g, 6.03 mmol).

IR ν_{max} (KBr): 3331.6, 2931.7, 2868.1, 1510, 1689.4, 811 cm^{-1}.

^1H NMR ($CDCl_3$) δ: 1.14–1.69 (m, 10H, cycl-H), 5.5 (s, C(5)-H), 6.8–6.86 (d, 2H, Ar-H), 6.87–6.92 (dd, 2H, J = 6 Hz, Ar-H), 7.2–7.32 (t, 1H, Ar-H), 7.06–7.14 (d, 2H, J = 8 Hz, Ar-H), 3.72 (s, 3H, –O–CH_3), 3.64–3.7 (d, 1H, J = 12 Hz), 3.2–3.27 (t, 1H, –CH–C_6H_5), 3.46–3.52 (dd, 2H, J = 2 Hz, C(2)-H), 4.6–4.72 (s, 1H, –OH).

Anal. Calcd for $C_{24}H_{27}F_2NO_3S$: C, 64.42; H, 6.08; N, 3.13; S, 7.17. Found: C, 64.42; H, 6.07; N, 3.13; S, 7.16.

5.1.6. 3-(2-(1-Hydroxycyclohexyl)-2-(4-methoxyphenyl)-ethyl)-2-(4-hydroxyphenyl)thiazolidin-4-one (3d). It was obtained from amine **1** (1 g, 4.02 mmol), 4-hydroxybenzaldehyde **2d** (0.589 g, 4.82 mmol), thioglycolic acid (0.555 g, 6.03 mmol) and dicyclohexylcarbodiimide (1.244 g, 6.03 mmol).

IR ν_{max} (KBr): 3321.3, 2924.2, 2849.2, 1502, 1678.4, 798 cm^{-1}.

^1H NMR ($CDCl_3$) δ: 1.14–1.69 (m, 10H, cycl-H), 5.25 (s, 2H, C(5)-H), 6.82–6.92 (d, 2H, J = 2 Hz, Ar-H), 6.95–6.98 (d, 2H, J = 9 Hz, Ar-H), 7.1–7.23 (q, 2H, Ar-H), 7.23–7.28 (q, 2H, Ar-H), 3.41–3.51 (s, 3H, –O–CH_3), 3.73–3.84 (dd, 1H, J = 4 Hz, C(2)-H), 4.32–4.43 (t, 1H, –CH–C_6H_5), 2.95–3.34 (dd, 2H, J = 2 Hz, –CH–), 4.02–4.14 (s, 1H, –OH).

Anal. Calcd for $C_{24}H_{29}NO_4S$: C, 67.42; H, 6.84; N, 3.27; S, 7.499. Found: C, 67.41; H, 6.84; N, 3.28; S, 7.51.

5.1.7. 3-(2-(1-Hydroxycyclohexyl)-2-(4-metoxyphenyl)-ethyl)-2-*p*-tolylthiazolidin-4-one (3e). It was obtained from amine **1** (1 g, 4.02 mmol), tolualdehyde **2e** (0.580 g, 4.82 mmol), thioglycolic acid (0.555 g, 6.03 mmol), and dicyclohexylcarbodiimide (1.244 g, 6.03 mmol).

IR ν_{max} (KBr): 3321.6, 2926.4, 2850.2, 1506, 1684.4, 801 cm^{-1}.

^1H NMR ($CDCl_3$) δ: 1.1–1.77 (m, 10H, cycl-H), 4.64 (s, 1H, C(5)-H), 6.81–6.92 (t, 4H, Ar-H), 6.95–7.06–7.2 (q, 4H, Ar-H), 3.8–3.9 (s, 3H, –O–CH_3), 3.51–3.7 (dd, 2H, J = 16 Hz, C(2)-H), 2.3–3.38 (d, 2H, J = 14 Hz, –C_6H_5–CH_3), 4.1–4.2 (q, 1H, –OH), 3.0 (t, 1H, –CH–).

Anal. Calcd for $C_{25}H_{31}NO_3S$: C, 70.55; H, 7.34; N, 3.29; S, 7.53. Found: C, 70.558; H, 7.342; N, 3.30; S, 7.538.

5.1.8. 3-(2-(1-Hydroxycyclohexyl)-2-(4-methoxyphenyl)-ethyl)-2-(2-nitrophenyl)-thiazolidin-4-one (3f). It was obtained from amine **1** (1 g, 4.02 mmol), *o*-nitrobenzaldehyde **2f** (0.729 g, 4.82 mmol), thioglycolic acid (0.555 g, 6.03 mmol), and dicyclohexylcarbodiimide (1.244 g, 6.03 mmol).

IR: ν_{max} (KBr): 3329.6, 2930.4, 2859.2, 1512, 1691.4, 812 cm^{-1}.

^1H NMR ($CDCl_3$) δ: 1.1–1.7 (m, 10H, cycl-H), 4.43–4.54 (q, 1H, C(5)-H), 6.75–6.8 (d, 2H, J = 8 Hz, Ar-H), 7.01–7.14 (d, 2H, J = 9 Hz, Ar-H), 7.18–7.25 (t, 1H, Ar-H), 7.44–7.47 (t, 1H, Ar-H), 7.62–7.65 (t, 1H, Ar-H), 7.97–7.99 (d, 1H, J = 8 Hz, Ar-H), 3.85 (s, 3H, –O–CH_3), 3.5–3.64 (dd, 2H, J = 16 Hz, C(2)-H), 2.3–3.38 (d, 2H, J = 14 Hz, –C_6H_5–CH_3), 5.13 (q, 1H, –OH), 2.88–2.97 (t, 1H, –CH–C_6H_5), 1.74–1.83 (d, 2H, –CH_2).

Anal. Calcd for $C_{24}H_{28}N_2O_5S$: C, 63.14; H, 6.18; N, 6.14; S, 7.02. Found: C, 63.136; H, 6.179; N, 6.127; S, 7.07.

5.1.9. 3-(2-(1-Hydroxycyclohexyl)-2-(4-methoxyphenyl)ethyl)-2-(3,4-dihydroxyphenyl)thiaz olidin-4-one (3g). It was obtained from amine **1** (1 g, 4.02 mmol), 3,4-dihydroxybenzaldehyde **2g** (0.666 g, 4.82 mmol), thioglycolic acid (0.555 g, 6.03 mmol), and dicyclohexylcarbodiimide (1.244 g, 6.03 mmol).

IR ν_{max} (KBr): 3319.4, 2921.2, 2846.2, 1501, 1678.4, 794 cm^{-1}.

^1H NMR ($CDCl_3$) δ: 1.16–1.7 (m, 10H, cycl-H), 5.42 (s, 1H, C(5)-H), 4.4 (s, 1H, –OH), 6.8–6.88 (dd, 2H, Ar-H), 7.1–7.16 (s, 1H, Ar-H), 7.3–7.46 (dd, 1H, J = 8 Hz, Ar-H), 7.5–7.7.63 (d, 1H, Ar-H), 3.7–3.74 (s, 3H, –O–CH_3), 3.4–3.68 (dd, 2H, J = 8 Hz, C(2)-H), 3.0–3.12 (t, 1H, –CH–), 3.8–3.9 (d, 2H, –CH_2–), 4.8–4.9 (s, 1H, –OH).

Anal. Calcd for $C_{24}H_{29}NO_5S$: C, 64.99; H, 6.59; N, 3.16; S, 7.23. Found: C, 64.989; H, 6.52; N, 3.11; S, 7.215.

5.1.10. 3-(2-(1-Hydroxycyclohexyl)-2-(4-methoxyphenyl)ethyl)-2-(4-methoxyphenyl)thiazoli din-4-one (3h). It was obtained from amine **1** (1 g, 4.02 mmol), 4-methoxybenzaldehyde **2h** (0.656 g, 4.82 mmol), thioglycolic

acid (0.555 g, 6.03 mmol), and dicyclohexylcarbodiimide (1.244 g, 6.03 mmol).

IR: ν_{max} (KBr): 3328.6, 2926.4, 2849.2, 1505, 1681.4, 799 cm^{-1}.

^1H NMR ($CDCl_3$) δ: 1.14–1.68 (m, 10H, cycl-H), 5.95 (s, 2H, C(5)-H), 5.32 (s, 1H, –OH), 6.8–6.92 (dt, 2H, Ar-H), 7.1–7.15 (t, 2H, Ar-H), 7.2–7.35 (q, 2H, Ar-H), 7.35–7.42 (d, 2H, $J = 6$ Hz, Ar-H), 3.75–3.9 (s, 6H, –O–CH_3), 3.55–3.68 (dd, 1H, $J = 2$ Hz, C(2)-H), 4.3–4.44 (t, 1H, –CH–C_6H_5), 3.1–3.22 (d, 2H, $J = 6$ Hz).

Anal. Calcd for $C_{25}H_{31}NO_4S$: C, 67.99; H, 7.08; N, 3.17; S, 7.26. Found: C, 67.89; H, 7.08; N, 3.14; S, 7.276.

5.1.11. 2-(Furan-2-yl)-3-(2-(1-hydroxycyclohexyl)-2-(4-methoxyphenyl) ethyl) thiazolidin-4-one (3i). It was obtained from amine **1** (1 g, 4.02 mmol), 2-furfuraldehyde **2i** (0.463 g, 4.82 mmol), thioglycolic acid (0.555 g, 6.03 mmol), and dicyclohexylcarbodiimide (1.244 g, 6.03 mmol).

IR: ν_{max} (KBr): 3336.6, 2934.4, 2853.2, 1510, 1689.4, 809 cm^{-1}.

^1H NMR ($CDCl_3$) δ: 1.2–1.74 (m, 10H, cycl-H), 5.91 (s, 2H, C(5)-H), 5.32 (s, 1H, –OH), 6.8–6.92 (dt, 2H, Ar-H), 7.12–7.2 (t, 1H, Ar-H), 7.24–7.36 (dd, 2H, Ar-H), 7.45–7.6 (d, 2H, $J = 6$ Hz, Ar-H), 3.8–3.86 (s, 3H, –O–CH_3), 3.52–3.6 (dd, 1H, $J = 2$ Hz, C(2)-H), 4.2–4.34 (t, 1H, –CH–C_6H_5), 3.2–3.32 (d, 2H, $J = 8$ Hz).

Anal. Calcd for $C_{22}H_{27}NO_4S$: C, 65.81; H, 6.78; N, 3.49; S, 7.99. Found: C, 65.817; H, 6.77; N, 3.499; S, 8.005.

5.1.12. 2-(2-Butyl-4-chloro-1*H*-imidazol-5-yl)-3-(2-(1-hydroxycyclohexyl)-2-(4-methoxyphenyl) ethyl) thiazolidin-4-one (3j). It was obtained from amine **1** (1 g, 4.02 mmol), 2-butyl-4-chloro imidazolyl aldehyde **2j** (0.897 g, 4.82 mmol), thioglycolic acid (0.555 g, 6.03 mmol), and dicyclohexylcarbodiimide (1.244 g, 6.03 mmol).

IR: ν_{max} (KBr): 3326.6, 3424, 2931.4, 2864.2, 1516, 1691.4, 810 cm^{-1}.

^1H NMR ($CDCl_3$) δ: 0.87 (q, 3H CH_3), 1.05 (m, 2H CH_2), 1.15–1.7 (m, 10H, cycl-H), 2.2 (q, 2H CH_2), 2.4 (t, 2H CH_2), 5.91 (s, 2H, C(5)-H), 5.32 (s, 1H, –OH), 6.68 (s, 1H, NH), 6.8–6.92 (dt, 2H, Ar-H), 7.12–7.2 (t, 1H, Ar-H), 7.24–7.36 (dd, 2H, Ar-H), 7.45–7.6 (d, 2H, $J = 6$ Hz, Ar-H), 3.85 (s, 3H, –O–CH_3), 3.4–3.52 (dd, 1H, $J = 2$ Hz, C(2)-H), 4.12–4.26 (t, 1H, –CH–C_6H_5), 3.25–3.4 (d, 2H, $J = 7$ Hz).

Anal. Calcd for $C_{25}H_{34}ClN_3O_3S$: C, 61.02; H, 6.96; N, 8.54; S, 6.52. Found: C, 61.029; H, 6.989; N, 8.578; S, 6.61.

5.2. Biology

5.2.1. Materials and methods. Bacteria and fungal species used were obtained from Department of Studies in Microbiology, University of Mysore, India, namely, *B. subtilis*, *E. coli*, *P. fluorescens*, *X. campestris pvs*, *X. oryzae*, *A. niger*, *A. flavus*, *F. oxysporum*, *T. species*, and *F. monaliforme*. The bacterial strains were maintained on LB agar medium and the filamentous fungi were maintained on potato dextrose agar (PDA) medium at 28 °C. The disk diffusion method[20] was used to determine antibacterial and antifungal activities of synthesized compounds. Paper disks with DMSO were used as negative controls. The bacteria were grown in LB broth, centrifuged at 10,000 rpm for 5 min, pellet was dissolved in double distilled water and used to inoculate the plates. For the filamentous fungi, the inoculum was prepared with the spores derived from 5 to 15 days culture on PDA medium. The mycelia were covered with 10 ml distilled water and the conidia were scraped using a sterile pipette. The spores were recovered after filtration on sterile absorbent cotton and resuspended in sterile distilled water. The cell density of each inoculum was adjusted with hemocytometer in order to obtain a final concentration of approximately 10^4 CFU/ml and 10^6 spores/ml for the bacteria and filamentous fungi, respectively. Nystatin (Himedia) was used as a positive control against fungi, and streptomycin and tetracycline against bacteria. Each disk contained 10 μg standard drugs and 25 μg synthesized compounds. Plates were first kept at 4 °C for at least 2 h to allow the diffusion of chemicals and then incubated at 28 °C. Inhibition zones were measured after 24 h of incubation for bacteria and after 48 h of incubation for fungi. The microdilution method[21] was followed to determine the minimum inhibitory concentration (MIC) of all the compounds against bacterial strains. The nutrient liquid medium was used as test media. Tests were performed in 96-well round-bottomed sterile culture plates. The wells of the microdilution plate were inoculated with 180 ml of the culture medium containing a final inoculum of $0.5 \times 2.5 \times 10^3$ CFU/ml. All the compounds previously solubilized in DMSO were serially diluted to 2-fold in the liquid medium and had concentration between 640 and 0.1 μg/ml. Twenty microliters of each concentration was added to each well containing the culture suspension except the growth control well. The final concentration ranged from 64 to 0.01 μg/ml. Plates were incubated at 35 °C for 48 h. Growth was assessed at 494 nm by measuring the optical density in each well using an enzyme immunoassay multiwell reader (Sigma Diagnostic). Turbidometric method[22,23] was used to check antifungal activity of the compounds at different concentrations using nystatin as the positive control and DMSO as the negative control. To the culture tubes containing 1.9 ml sterile media, 0.1 ml of the test compound was added at sterile conditions. Fresh inoculum was added to all the tubes including standard and controls with a spore concentration adjusted to 1×10^6 spores/ml. After incubating all tubes at 37 °C for 48 h, absorbance was recorded at 610 nm. Percentage of inhibition was calculated according to the formula.

$$\% \text{ Inhibition} = 100(P - Q)/P,$$

where P = absorbance without test sample and Q = absorbance with test sample. Then the MIC was recorded in μM. All determinant tests were performed

in duplicate and the results were reported as means of these values.

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References and notes

1. Cantello, B. C. C.; Cawthorne, M. A.; Cottam, G. P.; Duff, P. T.; Haigh, D.; Kindley, R. M.; Lister, C. A.; Smith, S. A.; Thurlby, P. L. *J. Med. Chem.* **1994**, *37*, 3977–3985.
2. Kucukguzel, S. G.; Oruc, E. E.; Rollas, S.; Sahin, F.; Ozbek, A. *Eur. J. Med. Chem.* **2002**, *37*, 197–206.
3. Capan, G.; Ulusoy, N.; Ergenc, N.; Kiraz, M. *Monatshefte fur Chemie* **1999**, *130*, 1399–1407.
4. Bhatt, J. J.; Shah, B. R.; Shah, H. P.; Trivedi, P. B.; Undavia, N. K.; Desai, N. C. *Indian J. Chem* **1994**, *33B*, 189–192.
5. Bhat, A. R.; Shetty, S. *J. Indian. Pharm. Sci.* **1987**, 194–197.
6. Ragab, F. A.; Eid, N. M.; El-Tawab, H. A. *Pharmazie* **1997**, *52*, 926–929.
7. Vigorita, M. G.; Ottana, R.; Monforte, F.; Maccari, R.; Trovato, A.; Monforte, M. T.; Taviano, M. F. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2791–2794.
8. Carmen, A. A.; Bosch, J.; Camps, G. P.; Maria del Carmen, O. M.; Nuria, S. M. WO2001007397; *Chem. Abstr.* **2001**, *134*, 147402.
9. Jinpei, Z.; Huibin, Z.; Xuezhen, H.; Wenlong, H. *J. Chim. Pharm. Univ.* **1999**, *30*, 249–250.
10. Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717–727.
11. Geies, A. A.; Bakhite, E. A.; El-kashef, H. S. *Pharmazie* **1998**, *53*, 686–690.
12. Basappa; Kavitha, C. V.; Rangappa, K. S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3279–3281.
13. Allingham, Y.; Cookson, R. C.; Crabb, T. A. *Tetrahedron* **1968**, *24*, 1989.
14. Otwinowski, Z.; Minor, W. In *Macromolecular Crystallography*; Carter, C. M., Sweet, R. M., Eds.; Academic Press: New York, 1997; pp 307–326.
15. Sheldrick, G. M. SHELXS—97, University of Göttingen, Germany, 1997.
16. Sheldrick, G. M. SHELXL—97, University of Göttingen, Germany, 1997.
17. Spek, A. L. *Acta Crystallogr.* **1998**, *A46*, c-34, and PLATON, University of Utrecht, The Netherlands, c-34, and PLATON, University of Utrecht, The Netherlands..
18. Priya, B. S.; Basappa; Nanjunda Swamy, S.; Rangappa, K. S. *Bioorg. Med. Chem.* **2005**, *13*, 2623–2628.
19. Basappa; Sadashiva, M. P.; Mantelingu, K.; Nanjunda Swamy, S.; Rangappa, K. S. *Bioorg. Med. Chem.* **2003**, *11*, 4539–4544.
20. Lemriss, S.; Marquet, B.; Ginestet, H.; Lefeuvre, L.; Fassouane, A.; Boiron, P. *J. Mycol. Med.* **2003**, *13*, 189–192.
21. Zgoda, J. R.; Porter, J. R. *Pharm. Biol.* **2001**, *39*, 221–225.
22. Barbaro, G.; Battaglia, A.; Dondoni, A. *J. Chem. Soc.* **1970**, *B*, 588.
23. Mullen, B. G.; Decory, R. T.; Mitchell, T. J.; Allen, D. S.; Kinsolving, C. R.; Georgiev, V. S. *J. Med. Chem.* **1988**, *31*, 2008.