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Original article

Synthesis, characterization, antimicrobial and single crystal X-ray crystallographic studies of some new sulfonyl, 4-chloro phenoxy benzene and dibenzoazepine substituted benzamides

B.S. Priya [a], S. Nanjunda Swamy [a], M.V. Tejesvi [b], Basappa [a], G. Sarala [c], S.L. Gaonkar [a], S. Naveen [c], J. Shashidhara Prasad [c], K.S. Rangappa [a,*]

[a] *Department of Studies in Chemistry, University of Mysore, Manasagangotri, Mysore-570 006, Karnataka, India*
[b] *Department of Studies in Biotechnology, University of Mysore, Manasagangotri, Mysore-570 006, Karnataka, India*
[c] *Department of Studies in Physics, University of Mysore, Manasagangotri, Mysore-570 006, Karnataka, India*

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Abstract

A new class of benzamide derivatives **3a(I–VI)** and **3b(I–VI)**, bearing different bioactive moieties were synthesized and evaluated for their efficacy as antimicrobials *in vitro*. Compounds **3bVI, 3aII, 3aV, 3bIII, 3aVI, 3bII** showed significant antibacterial activity and **3bIII, 3bII, 3aIV, 3bV, 3bVI, 3aI** exhibit significant antifungal activity. The title compounds are characterized by spectral and elemental analysis. Compounds 2-methoxy-*N*-[4-(thiazol-2-yl-sulfamoyl)-phenyl]-benzamide **3aII** and 2-(2-(2-ethoxybenzoylamino) phenethyl)-*N*-(2-ethoxybenzoyl) benzenamine **3bV** are characterized by the single crystal X-ray studies. Compound **3aII** crystallizes in monoclinic space group $P2_1$ and **3bV** in triclinic space group ***P*-1**. Compounds **3aII** and **3bV** exhibit both inter and intra molecular hydrogen bonding.

Keywords: Benzamide; Antibacterial; Antifungal; Monoclinic; Triclinic

1. Introduction

The need for new antimicrobial agents is greater than ever because of the emergence of multidrug resistance in common pathogens, the rapid emergence of new infections, and the potential for use of multidrug-resistant agents in bioweapons. Solutions encouraging and facilitating the development of new antimicrobial agents are needed [1]. Compound comprising of an amide bond backbone have a wide range of biological activities. Thus among the natural and synthetic substituted amide derivatives, there are compounds possessing anti-proliferative [2], antiviral, antimalarial, general anesthetics [3], anti-inflammatory [4], antimicrobials [5] and in treatment of Alzheimer's diseases [6]. From the standpoint of elaborated complex natural product and process chemistry, we have targeted in synthesizing novel amide derivatives, which plays an extremely important role in therapeutic as well as in medicinal field. One of the important categories of medicine is antibiotic, where sulfonamides are used for the treatment of bacterial infections [7], in which the amide moiety may exert their effects by modifying the metabolic activity of the invaded pathogenic microorganisms. These categories of medicines on absorption into the system interfere with microbe's growth or kill them. Penicillin, erythromycin, tetracycline, norfloxacin, etc. come under this category for the treatment of antimicrobials. Our previous studies on the synthesis of heterocycles like isoxazolines, novel isoxazolidines, 1,2-benzisoxazole substituted amides and chroman-2-carboxamides showed a wide spectrum of antimicrobial activities [8–12]. In connection with our efforts, in synthesizing and identifying the various biological targets, herein we

* Corresponding author.
E-mail addresses: rangappaks@chemistry.uni-mysore.ac.in, rangappaks@yahoo.com (K.S. Rangappa).

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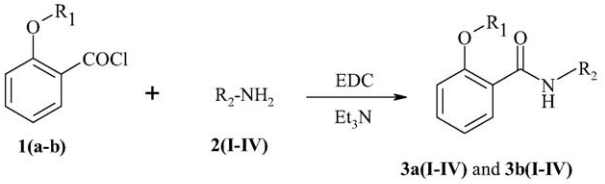
report the synthesis of new class of substituted benzamides and their antimicrobial activity *in vitro* against different strains.

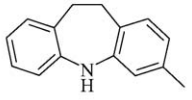
2. Chemistry

Amide moiety is versatile in organic compounds since all the three atoms in the O–C–N chain are potentially reactive. Several efficient methods have been exploited for the amidation using specific dehydrating reagents under mild liquid-phase condition. The synthesis of substituted amides began with the synthesis of various acid chlorides, where the acid chloride undergoes condensation reaction with different amines in presence of triethylamine as acid scavenger in dichloroethane as solvent. The physical data of newly synthesized molecules is shown in Table 1 and the synthetic scheme shown in Schemes 1, 2 and 3.



where R_1= a) $-CH_3$
b) $-C_2H_5$

R_2 =



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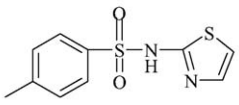

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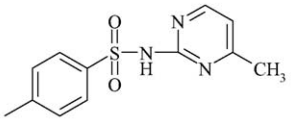
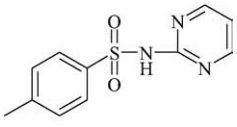
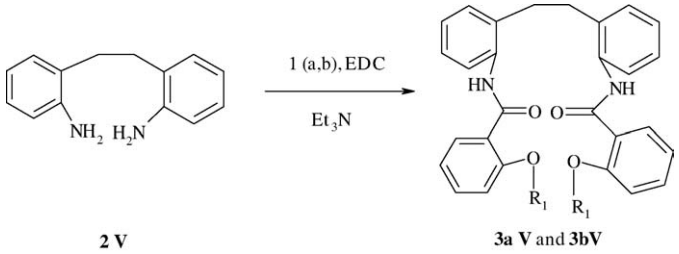


III



IV

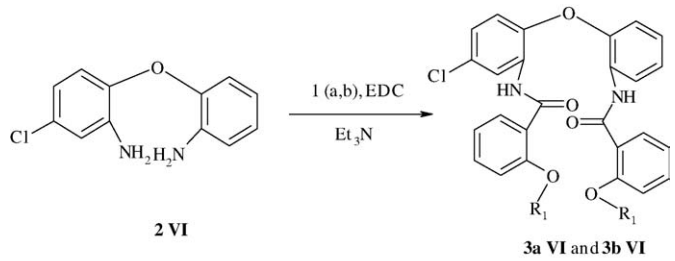
Scheme 1.



2 V

3a V and 3bV

Scheme 2.



2 VI

EDC = ethylene dichloride

3a VI and 3b VI

Scheme 3.

3. Results and discussion

3.1. Chemistry

Series of benzamides using different acid chlorides and amines were obtained in very good yield in the ratio of 70–85% with a purity of 90–95%. IR spectrum of the synthesized compounds showed N-H bond stretching in the region of 3300–3400 cm^{-1} and the C=O bond stretching in the region of 1600–1700 cm^{-1}. Synthesized compounds were characterized by spectral, elemental analysis and finally by single crystal X-ray studies for the compounds **3aII** and **3bV**.

3.2. Crystal structure analysis of *3aII* and *3bV*

Figs. 1 and 2 represent the ORTEP of the molecules **3aII** and **3bV** with thermal ellipsoids at 50% probability with selected bond lengths and bond angles. Table 2 represents crystal and experimental data of the molecules **3aII** and **3bV**. Compound **3aII** exhibits both intramolecular and intermolecu-

Table 1
Reaction condition and physical data of benzamide series

Amides	Time (h)	R_f value	Eluent	Yield (%)	m.p. (°C)
3a I	4	0.72	Chloroform/methanol 9:1	75	Oily
3a II	4	0.63	Chloroform/methanol 9:1	75	179–182
3a III	5	0.54	Chloroform/methanol 9:1	80	Oily
3a IV	6	0.66	Chloroform/methanol 9:1	85	Oily
3a V	4	0.78	Chloroform/methanol 9:1	80	Oily
3a VI	4	0.64	Chloroform/methanol 9:1	70	Oily
3b I	4	0.55	Benzene/ethyl acetate 9:1	75	130–133
3b II	5	0.82	Benzene/ethyl acetate 9:1	70	205–210
3b III	6	0.64	Benzene/ethyl acetate 9:1	70	215–217
3b IV	4	0.67	Benzene/ethyl acetate 9:1	70	224–228
3b V	4	0.58	Benzene/ethyl acetate 9:1	85	117–120
3b VI	4	0.75	Chloroform/methanol 9:1	85	98–102

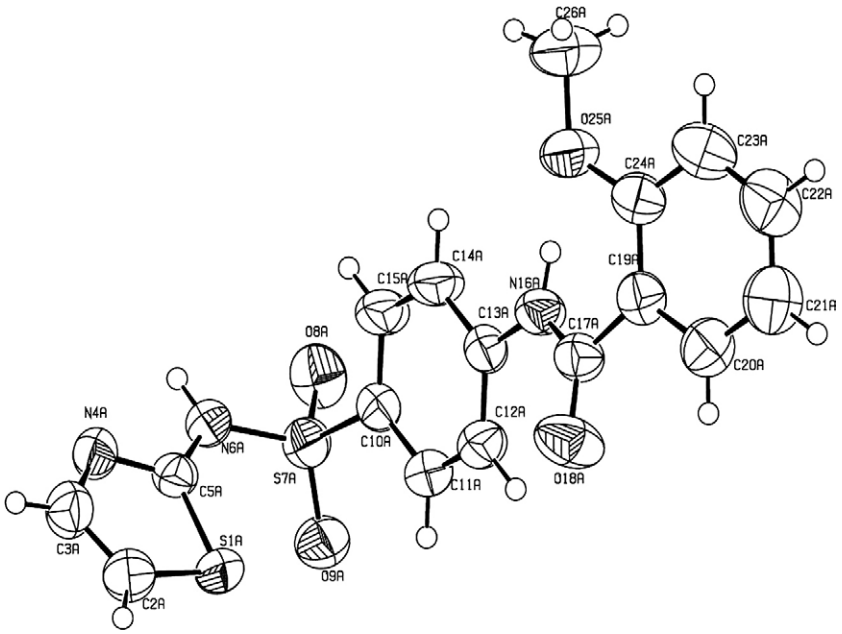


Fig. 1. ORTEP diagram of molecule **3aII** at 50% Probability.
Bond length: S1A-C2A: 1.723(4) Å, C2A-C3A: 1.329(5) Å, C3A-N4A: 1.390(4) Å, N6A-S7A: 1.602(3) Å, S7A-O9A: 1.434(2) Å, C17A-O18A: 1.210(4) Å, C19A-C24A: 1.407(5) Å, C22A-C23A: 1.390(7) Å.
Bond angles: O8A-S7A-N6A: 104.80(2)°, O9A-S7A-C10A: 107.61(2)°, N6A-S7A-C10A: 105.15(2)°, C17A-N16A-C13A: 129.0(3)°, O18A-C17A-N16A: 122.6 (3)°, O25A-C24A-C23A: 123.3(3)°, C24A-O25A-C26A: 119.5(3)°.

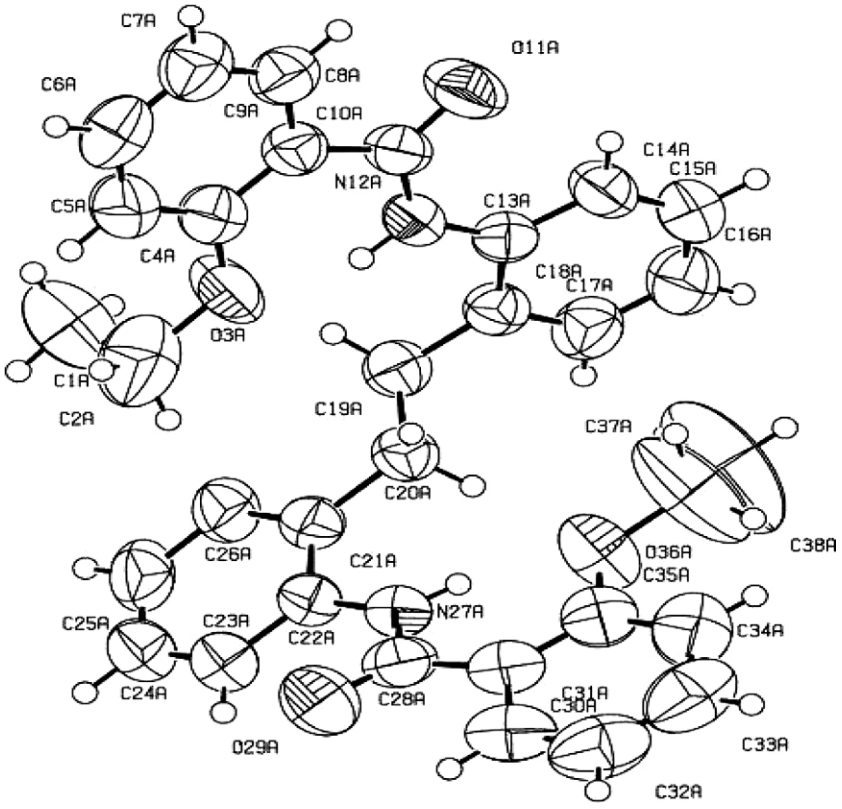


Fig. 2. ORTEP diagram of molecule **3bV** at 50% Probability.
Bond length: C1A-C2A: 1.350(8) Å, O3A-C2A: 1.504(6) Å, C19A-C20A: 1.523(5) Å, N12A-C10A: 1.351(4) Å, C10A-O11A: 1.223(4) Å, N12A-C13A: 1.406(4) Å, N27A-C28A: 1.374(5) Å, C22A-N27A: 1.409(5) Å.
Bond angles: C1A-C2A-O3A:103.5(6)°, C9A-C10A-O11A: 119.6(3)°, O11A-C10A-N12A: 122.3(3)°, N12A-C13A-C14A: 123.3(3)°, N12A-C13A-C18A: 117.8 (3)°, C18A-C19A-C20A: 111.0(3)°, N27A-C28A-O29A: 122.3(4)°, C22A-N27A-C28A: 126.9 (3)°.

Table 2
Crystal data and structure refinement for **3aII** and **3bV**

Identification code	**3aII**	**3bV**
CCDC number	293717	293718
Empirical formula	$C_{17}H_{15}N_3O_4S_2$	$C_{32}H_{32}N_2O_4$
Formula weight	389.44	508.24
Crystal size	0.3 × 0.25 × 0.25 mm	0.3 × 0.25 × 0.25 mm
Temperature	293(2) K	293(2) K
Reflections for cell determination	7270	4657
Wavelength	0.71073 Å	0.71073 Å
Crystal system	Monoclinic	Triclinic
Space group	$P2_1$	$P\,1$
Cell dimensions	a = 10.717(5) Å, b = 10.914(8) Å,	a = 11.6580(10) Å, b = 14.079(2) Å,
	c = 15.284(1) Å, α = 90°,	c = 17.447(3) Å, α = 88.402(3) Å,
	β = 90.802(4)°, γ = 90°	β = 75.728(8) Å, γ = 81.582(8) Å
Volume	1787.5(2) Å^3	2674.6(7) Å^3
Z	4	4
Density (calculated)	1.447 mg m^{-3}	1.261 mg m^{-3}
Absorption coefficient	0.326 mm^{-1}	0.083 mm^{-1}
F_{000}	808	1076
Theta range for data collection	2.29°–32.45°	2.20°–32.47°
Index ranges	$-14 \le h \le 14$	$-11 \le h \le 11$
	$-16 \le k \le 16$	$-20 \le k \le 19$
	$-23 \le l \le 23$	$-23 \le l \le 26$
Reflections collected	10874	17274
Independent reflections	10874 [R (int) = 0.0000]	11695 [R (int) = 0.0375]
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	10874/1/472	11695/0/690
Goodness-of-fit on F^2	1.092	1.332
Final R indices [$I > 2\,\sigma\,(I)$]	$R1$ = 0.0532, $\omega R2$ = 0.1360	$R1$ = 0.0962, $\omega R2$ = 0.2465
R indices (all data)	$R1$ = 0.0862, $\omega R2$ = 0.1707	$R1$ = 0.2013, $\omega R2$ = 0.2965
Extinction coefficient	0.0100(18)	0.0064(18)
Largest diff. peak and hole	0.516 eÅ^{-3} and –0.306 eÅ^{-3}	0.396 eÅ^{-3} and –0.273 eÅ^{-3}

lar hydrogen bonding. The intermolecular bonds are between N6A-H6A—N4B with bond length 2.863(4) Å, bond angle 143° and symmetry {x, –1 + y, z}, the N6B-H6B—N4A with bond length 2.926(4) Å, bond angle 144° and symmetry { x, 1 + y, z}, the C2A-H2A—O18A with bond length 3.047(5) Å, bond angle 116° and symmetry {2 – x, –1/2 + y, –z} and C15A-H15A—O9A with bond length 3.454(4) Å, bond angle 158° and symmetry {2 – x, –1/2 + y, –z}.

Compound **3bV** exhibits both intramolecular and intermolecular hydrogen bonding. The intermolecular bonds are between C2B-H2B—O11A with bond length 3.304(5) Å, bond angle 132° and symmetry {1 – x, 1 – y, 1 – z}, the C1A-H1A—O11B with bond length 3.385(6) Å, bond angle 150° and symmetry {1 – x, 1 – y, – z}, and the C37B-H37B—O29A with bond length 3.395(1) Å, bond angle 140° and symmetry {1 – X, – Y, –Z}, respectively.

Table 3
Minimal inhibitory concentration (MIC) in μg ml^{-1} of compounds against tested bacterial strains by microdilution method

Compound	Minimal inhibitory concentration (MIC) in μg ml^{-1}				
	Bacillus substilis	*Escherichia coli*	*Pseudomonas fluorescens*	*Xanthomonas campestris pvs.*	*Xanthomonas oryzae*
3a I	32 ± 1.2	28 ± 1.2	25 ± 1.1	24 ± 1	25 ± 1.1
3a II	8 ± 0.32	7 ± 0.3	6 ± 0.2	5 ± 0.2	8 ± 0.3
3a III	23 ± 1	20 ± 0.8	16 ± 0.7	12 ± 0.3	15 ± 0.6
3a IV	25 ± 0.9	17 ± 0.7	17 ± 0.72	13 ± 0.4	16 ± 0.7
3a V	9 ± 0.35	8 ± 0.3	7 ± 0.21	6 ± 0.2	9 ± 0.31
3a VI	11 ± 0.95	10 ± 0.4	12 ± 0.4	8 ± 0.3	12 ± 0.5
3b I	30 ± 1.2	29 ± 1.2	26 ± 1	23 ± 1	24 ± 1
3b II	18 ± 0.8	15 ± 0.6	13 ± 0.40	10 ± 0.36	14 ± 0.5
3b III	10 ± 0.4	9 ± 0.3	11 ± 0.4	7 ± 0.22	10 ± 0.3
3b IV	22 ± 0.9	18 ± 0.7	14 ± 0.6	13 ± 0.5	16 ± 0.6
3b V	24 ± 1	19 ± 0.75	15 ± 0.62	12 ± 0.4	15 ± 0.42
3b VI	6 ± 0.2	5 ± 0.2	4 ± 0.13	3 ± 0.1	6 ± 0.2
Streptomycin	23 ± 0.9	18 ± 0.8	15 ± 0.6	–	–
Tetracycline	–	–	–	12 ± 0.42	16 ± 0.6

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

3.3. Biology

In continuation of our efforts in synthesizing new antimicrobials, we have developed new derivatives of benzamides and tested for their efficacy as antimicrobials *in vitro* by disk diffusion, microdilution and turbidometric methods against different strains. Nystatin was used as positive control against fungi, streptomycin and tetracycline against bacteria. The tests were repeated thrice and the results are reported as mean of at least three determinations. Antibacterial activity of the compounds tested is shown in Tables 3 and 4. From our results, compounds **3bVI, 3aII, 3aV, 3bIII, 3aVI** and **3bII** showed significant inhibitory activity in the following order **3bVI > 3aII > 3aV > 3bIII > 3aVI > 3bII**. Compounds **3bVI** and **3aVI** bearing the bioactive phenoxy moiety, difference in the activity between 3bVI and 3aVI might be attributed to the presence of ethoxy and methoxy group at R_1 position, respectively. Compound **3aII** showed increased activity compared to **3bII** both bearing sulfathiazole moiety, the presence of different substituents at R_1 makes **3aII** active. Compounds **3aV** and **3b III** showed good activity bearing different moieties and substituents at R_1 and R_2 position, respectively. Compounds **3bIV** and **3aIV** bearing sulfadiazine moiety at R_2, ethoxy and methoxy at R_1, respectively, showed moderate potency. Compounds **3aI** and **3bI** were not effective against any of the strains tested. Antifungal activity of the compounds tested is shown in Tables 5 and 6. From our results, compounds **3bIII, 3bII, 3aIV, 3bV, 3bVI** and **3aI** showed significant inhibitory activity in the following order **3bIII > 3bII > 3aIV > 3bV > 3bVI > 3aI**. Interestingly, we found compounds **3aII, 3aV** and **3aVI** showed significant inhibitory activity against the fungal strains tested but they exhibited moderate potency against bacterial strains. Compound **3aI** showed good antifungal activity but was ineffective against bacteria. Compounds **3aII, 3aVI, 3bIV** and **3aIII** exhibited moderate antifungal activity. Compounds **3bI** and **3aV** were not effective against any of the fungus tested.

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

Compound	Inhibitory zone (diameter) mm				
	Bacillus substilis	*Escherichia coli*	*Pseudomonas fluorescens*	*Xanthomonas campestris pvs.*	*Xanthomonas oryzae*
3a I	6 ± 0.2	2 ± 0.06	5 ± 0.18	2 ± 0.08	3 ± 0.08
3a II	30 ± 1.1	38 ± 1.7	42 ± 1.8	28 ± 1.2	32 ± 1.2
3a III	14 ± 0.52	19 ± 0.7	23 ± 1	18 ± 0.8	16 ± 0.5
3a IV	15 ± 0.59	20 ± 0.8	22 ± 0.9	15 ± 0.65	17 ± 0.7
3a V	28 ± 1.2	36 ± 1.5	40 ± 1.6	25 ± 1.1	30 ± 1.1
3a VI	25 ± 1	30 ± 1.3	34 ± 1.5	21 ± 0.9	25 ± 0.9
3b I	4 ± 0.1	3 ± 0.09	7 ± 0.28	5 ± 0.18	4 ± 0.17
3b II	22 ± 0.9	25 ± 1.1	30 ± 1.2	19 ± 0.8	20 ± 0.8
3b III	27 ± 1.1	32 ± 1.5	36 ± 1.5	22 ± 0.9	27 ± 1
3b IV	16 ± 0.7	17 ± 0.52	20 ± 0.8	16 ± 0.6	14 ± 0.6
3b V	17 ± 0.6	18 ± 0.8	21 ± 0.82	17 ± 0.62	15 ± 0.62
3b VI	32 ± 1.2	40 ± 1.3	45 ± 2.1	30 ± 1.1	35 ± 1.23
Streptomycin	15 ± 0.5	19 ± 0.7	22 ± 0.9	–	–
Tetracycline	–	–	–	16 ± 0.61	15 ± 0.52

Streptomycin sulfate (10 μg $disc^{-1}$); Tetracycline (10 μg $disc^{-1}$); Synthesized compounds (25 μg $disc^{-1}$). [a] Values are mean 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) in μM				
	Aspergillus niger	*Aspergillus flavus*	*Fusarium oxysporum*	*Trichoderma species*	*Fusarium moniliforme*
3a I	26 ± 1.1	30 ± 1.3	32 ± 1.2	25 ± 1.05	27 ± 1.15
3a II	30 ± 1.2	34 ± 1.3	37 ± 1.4	30 ± 1.2	33 ± 1.4
3a III	31 ± 1.22	36 ± 1.4	38 ± 1.6	29 ± 1.2	35 ± 1.3
3a IV	17 ± 0.65	20 ± 0.8	19 ± 0.7	17 ± 0.7	18 ± 0.7
3a V	42 ± 1.5	47 ± 1.4	61 ± 2.5	44 ± 1.9	47 ± 1.9
3a VI	31 ± 1.1	35 ± 1.5	38 ± 1.6	29 ± 1.2	34 ± 1.4
3b I	48 ± 2	50 ± 2.1	52 ± 2.3	49 ± 1.9	51 ± 2.1
3b II	15 ± 0.6	15 ± 0.6	16 ± 0.6	13 ± 0.5	14 ± 0.5
3b III	13 ± 0.5	17 ± 0.6	18 ± 0.7	15 ± 0.55	16 ± 0.62
3b IV	29 ± 1.2	36 ± 1.4	39 ± 1.7	31 ± 1.3	35 ± 1.5
3b V	19 ± 0.67	22 ± 0.9	21 ± 0.9	20 ± 0.8	23 ± 1.1
3b VI	22 ± 1	25 ± 0.98	27 ± 1.2	22 ± 0.9	25 ± 1.5
Nystatin	30 ± 1.2	35 ± 1.4	37 ± 1.5	29 ± 0.75	33 ± 1.5

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

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

Compound	Inhibitory zone (diameter) mm				
	Aspergillus niger	*Aspergillus flavus*	*Fusarium oxysporum*	*Trichoderma species*	*Fusarium moniliforme*
3a I	16 ± 0.6	17 ± 0.71	19 ± 0.7	21 ± 1	21 ± 0.9
3a II	13 ± 0.45	14 ± 0.58	17 ± 0.65	18 ± 0.8	20 ± 0.8
3a III	11 ± 0.4	16 ± 0.7	15 ± 0.6	17 ± 0.65	17 ± 0.67
3a IV	20 ± 0.8	22 ± 0.9	24 ± 1	25 ± 1.1	28 ± 1.2
3a V	4 ± 0.14	5 ± 0.2	8 ± 0.31	2 ± 0.08	1 ± 0.02
3a VI	14 ± 0.6	15 ± 0.6	18 ± 0.78	19 ± 0.84	19 ± 0.0.8
3b I	6 ± 0.21	4 ± 0.11	2 ± 0.09	5 ± 0.19	7 ± 0.28
3b II	21 ± 0.9	24 ± 1	26 ± 1	27 ± 1.2	30 ± 1.2
3b III	24 ± 1	27 ± 1.1	29 ± 1.2	31 ± 1.3	34 ± 1.4
3b IV	12 ± 0.5	15 ± 0.59	16 ± 0.68	20 ± 0.87	18 ± 0.78
3b V	19 ± 0.8	20 ± 0.89	22 ± 0.95	23 ± 1	25 ± 1.2
3b VI	17 ± 0.7	18 ± 0.72	20 ± 0.9	21 ± 0.9	23 ± 1.1
Nystatin	13 ± 0.55	15 ± 0.62	17 ± 0.74	19 ± 0.8	18 ± 0.7

Nystatin (10 μg $disc^{-1}$); Synthesized compounds (25 μg $disc^{-1}$). [a] Values are mean of three determinations, the ranges of which are less than 5% of the mean in all cases.

4. Conclusion

In conclusion, we report the synthesis, antimicrobial studies and crystal structure analysis of newer benzamide derivatives bearing multifunctional moieties such as phenoxy, sulfathiazine, sulfamerazine, sulfadiazine, azepines, etc. Compounds **3bVI, 3aII, 3aV, 3bIII, 3aVI** and **3bII** showed significant antibacterial activity and **3bIII, 3bII, 3aIV, 3bV, 3bVI** and **3aI** exhibited antifungal activity against all the strains tested and found to be nonstrain dependent. The antimicrobial activity shown might be partly due to the delocalization of the π electrons along the O–C–N chain. This produces partial double-bond character in the C(O)–N bond. The versatility of the amide group in forming partial bonds with itself and many other functional groups is partly responsible for the structural subtleties of the biologically important proton derivatives [13,14]. The crystal data of the compounds **3aII** and **3bV** reveals that it exhibits both intra and inter molecular hydrogen bonding, which may play a pivotal role for its bioactivities. Modifications to improve the potency of this series by diversification of the position and type of amides are currently under progress in our lab.

5. Experimental

5.1. Chemistry

The melting points were determined on SELACO-650 hot stage apparatus and are uncorrected. IR (nujol) spectra were measured on Shimadzu 8300 IR spectrophotometer, ^{1}H NMR were recorded on Shimadzu AMX 400-Bruker, 400 MHz spectrometer by using $CDCl_3$ as solvent and TMS as an internal standard (chemical shift in δ ppm). Elemental analyses were obtained on a Vario-EL instrument. TLC was conducted on 0.25 mm silica gel plates ($60F_{254,}$ Merck) and Column by silica gel BDH 60–120 mesh. All extracted solvents were dried over Na_2SO_4, followed by evaporation in vacuo.

5.1.1. Substituted amides were synthesized by the reported procedure [12]

5.1.2. Synthesis of N-(10,11-dihydro-5H-dibenzo[b,f]azepin-3-yl)-2-methoxy-benzamide ***3aI***

It was obtained from the reaction of 10,11-dihydro-5*H*-dibenzo[b,f]azepin-3-yl-amine **2I** (0.25 g, 1.190 mmol), 2-methoxybenzoyl chloride (0.242 g, 1.428 mmol) and triethylamine (0.722 g, 7.14 mmol). The product obtained was oily. IR (cm^{-1} nujol): 3210.8, 1675.6, 1415.1, 1512. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.72 (s, 4H, -CH_2); 3.12 (s, 3H, -O-CH_3); 3.79 (s, 1H, NH-IDB); 6.78–7.05 (m, 9H, Ar-H); 7.42 (t, 1H, Ar-H); 7.78 (d, 1H, Ar-H), 10.04 (s, 1H, -NH). Anal. Calcd CHNS: C: 76.72, H: 5.85, N: 8.13. Found: C: 76.66, H: 5.75, N: 8.10.

5.1.3. Synthesis of 2-methoxy-N-[4-(thiazol-2-yl-sulfamoyl)-phenyl]-benzamide ***3aII***

It was obtained from the reaction of 4-amino-*N*-thiazol-2-yl-benzenesulfonamide **2II** (0.25 g, 0.979 mmol), 2-methoxybenzoyl chloride (0.2 g, 1.176 mmol) and triethylamine (0.594 g, 5.87 mmol). The product obtained was pure white crystalline solid. m.p. = 179–182 °C. IR (cm^{-1} nujol): 3345, 1700, 1478.5, 1512. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.1 (s, 3H, -O-CH_3); 6.61 (d, 1H, Th-H); 6.90–7.20 (m, 4H, Ar-H); 7.42–7.79 (m, 5H, Ar-H), 10.01 (s, 1H, -CO-NH); 10.40 (s, 1H, -SO_2-NH). Anal. Calcd CHNS: C: 52.43, H: 3.88, N: 10.79, S: 16.47. Found: C: 52.36, H: 3.72, N: 10.71, S: 16.42.

5.1.4. Synthesis of 2-methoxy-N-[4-(4-methyl-pyrimidin-2-yl-sulfamoyl)-phenyl]-benzamide ***3aIII***

It was obtained from the reaction of 4-amino-*N*-(4-methyl-pyrimidin-2-yl)-benzenesulfonamide **2III** (0.25 g, 0.946 mmol), 2-methoxybenzoyl chloride (0.192 g, 1.129 mmol) and triethylamine (0.574 g, 5.672 mmol). The product obtained was oily. IR (cm^{-1} nujol): 3300.8, 1640, 1455.7, 1523. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.50 (s, 3H, Ar-CH_3); 3.21 (s, 3H, -O-CH_3); 6.76 (d, 1H, Py-H); 6.91–7.01 (m, 2H, Ar-H); 7.45–7.95 (m, 6H, Ar-H); 8.12 (d, 1H, Py-H); 10.12 (s, 2H, -

CO-NH); 10.35 (s, 2H, -SO_2-NH). Anal. Calcd CHNS: C: 57.27, H: 4.55, N: 14.06, S: 8.05. Found: C: 57.12, H: 4.25, N: 13.99, S: 7.85.

*5.1.5. Synthesis of 2-methoxy-N-[4-(pyrimidin-2-yl-sulfamoyl)-phenyl]-benzamide **3aIV***

It was obtained from the reaction of 4-amino-*N*-pyrimidin-2-yl-benzenesulfonamide **2IV** (0.25 g, 0.998 mmol), 2-methoxybenzoyl chloride (0.203 g, 1.194 mmol) and triethylamine (0.605 g, 5.988 mmol). The product obtained was oily. IR (cm^{-1} nujol): 3260, 1620, 1428, 1534.5. ^1H NMR ($CDCl_3$, 400 MHz) δ: 3.16 (s, 3H, -O-CH_3); 6.76 (d, 1H, Py-H); 6.95–7.05 (m, 2H, Ar-H); 7.45–7.95 (m, 6H, Ar-H); 8.12 (t, 2H, Py-H); 10.05 (s, 2H, -CO-NH); 10.29 (s, 2H, -SO_2-NH). Anal. Calcd CHNS: C: 56.24, H: 4.20, N: 14.57, S: 8.34. Found: C: 56.12, H: 4.17, N: 14.92, S: 8.31.

*5.1.6. Synthesis of 2-(2-(2-methoxybenzoylamino) phenethyl)-N-(2-methoxybenzoyl) benzenamine **3aV***

It was obtained from the reaction of diamino dibenzyl **2V** (0.25 g, 1.179 mmol), 2-methoxybenzoyl chloride (0.4 g, 2.353 mmol) and triethylamine (0.713 g, 7.075 mmol). The product obtained was oily. IR (cm^{-1} nujol): 3340, 1620, 1432, 1512.6. ^1H NMR ($CDCl_3$, 400 MHz) δ: 2.71 (s, 6H, -O-CH_3); 3.06 (s, 4H, -CH_2-Ar); 6.92–7.10 (m, 10H, Ar-H); 7.38 (t, 2H, Ar-H); 7.51 (d, 2H, Ar-H), 7.79 (d, 2H, Ar-H); 10.15 (s, 2H, -CO-NH). Anal. Calcd CHNS: C: 74.50, H: 5.82, N: 5.99. Found: C: 74.425, H: 5.801, N: 5.899.

*5.1.7. Synthesis of 2-(2-(2-methoxybenzoylamino)-4-chlorophenoxy)-N-(2-methoxybenzoyl)benzamine **3aVI***

It was obtained from the reaction of 2-(2-amino-4-chlorophenoxy) benzenamine **2VI** (0.25 g, 1.21 mmol), 2-methoxybenzoyl chloride (0.288 g, 1.694 mmol) and triethylamine (0.734 g, 7.26 mmol). The product obtained was oily. IR (cm^{-1} nujol): 3320, 1645, 1422, 1499.5. ^1H NMR ($CDCl_3$, 400 MHz) δ: 3.06 (s, 6H, -O-CH_3); 6.86–6.96 (m, 5H, Ar-H); 7.05–7.24 (m, 4H, Ar-H); 7.39 (t, 2H, Ar-H); 7.79–7.88 (d, 4H, Ar-H); 10.44 (s, 2H, -NH). Anal. Calcd CHNS: C: 66.87, H: 4.61, N: 5.57. Found: C: 66.77, H: 4.55, N: 5.32.

*5.1.8. Synthesis of N-(10,11-dihydro-5H-dibenzo[b,f]azepin-3-yl)-2-ethoxy-benzamide **3bI***

It was obtained from the reaction of 10, 11-dihydro-5*H*-dibenzo[b,f]azepin-3-yl-amine **2I** (0.25 g, 1.190 mmol), 2-ethoxybenzoyl chloride (0.263 g, 1.424 mmol) and triethylamine (0.722 g, 7.14 mmol). The product obtained was pale brown solid. m.p. = 130–133 °C. IR (cm^{-1} nujol): 3410, 1650.4, 1455.9, 1489.5. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.28 (t, 3H, -CH_3); 2.79 (s, 4H, -CH_2); 3.08 (q, 2H, -O-CH_2-); 3.82 (s, 1H, NH-IDB); 6.82–7.06 (m, 9H, Ar-H); 7.44 (t, 1H, Ar-H); 7.75 (d, 1H, Ar-H), 10.02 (s, 1H, -NH). Anal. Calcd CHNS: C: 77.07, H: 6.19, N: 7.82. Found: C: 76.86, H: 6.11, N: 7.71.

*5.1.9. Synthesis of 2-ethoxy-N-[4-(thiazol-2-yl-sulfamoyl)-phenyl]-benzamide **3bII***

It was obtained from the reaction of 4-amino-*N*- thiazol-2-yl-benzenesulfonamide **2II** (0.25 g, 0.979 mmol), 2-ethoxybenzoyl chloride (0.216 g, 1.176 mmol) and triethylamine (0.594 g, 5.87 mmol). The product obtained was pure white solid. m.p. = 205–210 °C. IR (cm^{-1} nujol): 3320.8, 1632.5, 1455.6, 1457.8. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.42 (t, 3H, -CH_3); 3.19 (q, 2H, -O-CH_2-); 6.66 (d, 1H, Th-H); 6.94–7.16 (m, 4H, Ar-H); 7.38–7.75 (m, 5H, Ar-H), 10.16 (s, 2H, -CO-NH); 10.53 (s, 2H, -SO_2-NH). Anal. Calcd CHNS: C: 53.58, H: 4.25, N: 10.41, S: 15.89. Found: C: 53.46, H: 4.17, N: 10.33, S: 15.72.

*5.1.10. Synthesis of 2-ethoxy-N-[4-(4-methyl-pyrimidin-2-yl-sulfamoyl)-phenyl]-benzamide **3bIII***

It was obtained from the reaction of 4-amino-*N*-(4-methyl-pyrimidin-2-yl)-benzenesulfonamide **2III** (0.25 g, 0.946 mmol), 2-ethoxybenzoyl chloride (0.209 g, 1.132 mmol) and triethylamine (0.574 g, 5.672 mmol). The product obtained was pure white solid. m.p. = 215–217 °C. IR (cm^{-1} nujol): 3365, 1620, 1425, 1523. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.39 (t, 3H, -CH_3); 2.51 (s, 3H, Ar-CH_3); 3.09 (q, 2H, -O-CH_2-); 6.69 (d, 1H, Py-H); 6.96–7.04 (m, 2H, Ar-H); 7.44–7.91 (m, 6H, Ar-H); 8.05 (d, 1H, Py-H); 10.05 (s, 1H, -CO-NH); 10.56 (s, 1H, -SO_2-NH). Anal. Calcd CHNS: C: 58.24, H: 4.89, N: 13.58, S: 7.77. Found: C: 58.14, H: 4.75, N: 13.42, S: 7.65.

*5.1.11. Synthesis of 2-ethoxy-N-[4-(pyrimidin-2-yl-sulfamoyl)-phenyl]-benzamide **3bIV***

It was obtained from the reaction of 4-amino-*N*-pyrimidin-2-yl-benzenesulfonamide **2IV** (0.25 g, 0.998 mmol), 2-ethoxybenzoyl chloride (0.221 g, 1.197 mmol) and triethylamine (0.605 g, 5.988 mmol). The product obtained was pure white crystalline solid. m.p. = 224–228 °C. IR (cm^{-1} nujol): 3300, 1640, 1456, 1546. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.39 (t, 3H, -CH_3); 2.29 (q, 2H, -O-CH_2-); 6.74 (t, 1H, Py-H), 6.98–7.10 (m, 2H, Ar-H); 7.34 (t, 1H, Ar-H); 7.88–7.94 (m, 5H, Ar-H); 8.23 (dd, 2H, Py-H), 10.16 (s, 2H, -CO-NH); 10.48 (s, 2H, -SO_2-NH). Anal. Calcd CHNS: C: 57.27, H: 4.55, N: 14.06, S: 8.05. Found: C: 57.22, H: 4.47, N: 14.00, S: 7.95.

*5.1.12. Synthesis of 2-(2-(2-ethoxybenzoylamino)phenethyl)-N-(2-ethoxybenzoyl) benzenamine **3bV***

It was obtained from the reaction of diamino dibenzyl **2V** (0.25 g, 1.179 mmol), 2-ethoxybenzoyl chloride (0.435 g, 2.358 mmol) and triethylamine (0.713 g, 7.075 mmol). The product obtained was pale brown crystalline solid. m.p. = 117–120 °C. IR (cm^{-1} nujol): 3384, 1645, 1475, 1532. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.24 (t, 6H, -CH_3); 3.15 (s, 4H, -CH_2-Ar); 3.55 (q, 4H, -O-CH_2); 6.95–7.14 (m, 10H, Ar-H); 7.42 (t, 2H, Ar-H); 7.54 (d, 2H, Ar-H), 7.76 (d, 2H, Ar-H); 10.45 (s, 2H, -CO-NH). Anal. Calcd CHNS: C: 75.57, H: 6.34, N: 5.51. Found: C: 75.54, H: 6.72, N: 5.42.

*5.1.13. Synthesis of 2-(2-(2-ethoxybenzoylamino)-4-chlorophenoxy)-N-(2-ethoxybenzoyl) benzamine **3bVI***

It was obtained from the reaction of 2-(2-amino-4-chlorophenoxy)benzenamine **2VI** (0.25 g, 1.21 mmol), 2-ethoxybenzoyl chloride (0.312 g, 1.694 mmol) and triethylamine (0.734 g, 7.26 mmol). The product obtained was pale brown crystalline solid. m.p. = 98–102 °C. IR (cm^{-1} nujol): 3360, 1660, 1480, 1210. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.54 (t, 6H, -CH_3), 4.29 (q, 4H, -O-CH_2-), 6.79–6.92 (m, 5H, Ar-H); 7.01–7.19 (m, 4H, Ar-H); 7.41 (t, 2H, Ar-H); 7.74–7.85 (d, 4H, Ar-H); 10.45 (s, 2H, -NH). Anal. Calcd CHNS: C: 66.60, H: 4.99, N: 5.55. Found: C: 66.52, H: 4.65, N: 5.42.

*5.2. Crystal structure analysis of **3aII** and **3bV***

Single crystals of **3aII** and **3bV** suitable for X-ray diffraction studies were mounted on a glass fiber. The measurements were made on a DIPLabo Imaging Plate system with graphite monochromated MoK_α radiation. Thirty-six frames of data were collected using oscillation method. Image processing and data reduction were done using Denzo [15]. The structure was solved using maXus [16]. All the non-hydrogen atoms were revealed in the first map itself [17]. Initially, the full-matrix least squares refinement for 7270 reflections for **3aII** and 4657 reflections for **3bV** with isotropic temperature factors for all the non-hydrogen atoms was carried out [18]. The $R1$ value of **3aII** is 0.0862. The $R1$ value of **3bV** is 0.0938.

5.3. Antimicrobial activity

Bacteria and fungal species used were obtained from Department of Studies in Biotechnology, University of Mysore, India, namely, *Bacillus substilis, Escherichia coli, Pseudomonas fluorescens, Xanthomonas campestris pvs, Xanthomonas oryzae, Aspergillus niger, Aspergillus flavus, Fusarium oxysporum, Trichoderma species* and *Fusarium moniliforme*. 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 [19] was used to determine antibacterial and antifungal activity of the synthesized compounds. Paper discs 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 and used to inoculate the plates. The inoculum was prepared with the spores derived from 5 to 15 days culture on PDA medium for the filamentous fungi. The mycelia were covered with 10 ml of distilled water and the conidia were scraped using a sterile pipette. The spores were recovered after filtration on sterile absorbent cotton and were 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^{-1} and 10^6 spores ml^{-1} for the bacteria and filamentous fungi, respectively. Nystatin (Himedia) was used as a positive control for fungi and streptomycin and tetracycline for bacteria. Each disk contained 10 μg of standard drugs and 25 μg synthesized compounds. Plates were first kept at 4 °C for at least 2 hours to allow the diffusion of chemicals and then incubated at 28 °C. Inhibition zones were measured after 24 hours of incubation for bacteria and after 48 hours of incubation for fungi. The microdilution method [20] 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 bottom sterile culture plates. The wells of the microdilution plate were inoculated with 180 μl of the culture medium containing a final inoculum of $0.5 \times 2.5 \times 10^3$ CFU ml^{-1} [21]. All the compounds previously solubilized in DMSO were serially diluted twofolds in the liquid medium and had concentration 640–0.1 μg ml^{-1}. Twenty microliter 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^{-1}. Plates were incubated at 35 °C for 48 hours. 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 of 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^{-1}. After incubating all tubes at 37 °C for 48 hours, absorbance was recorded at 610 nm. Percentage of inhibition was calculated according to the formula

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

where P = absorbance without test sample and Q = absorbance with test sample. Then the MIC was recorded in μM. All determinant tests were performed duplicate and the results were reported as mean of these values.

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