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Molecular properties prediction, synthesis, and antimicrobial activity of bis(azolyl)sulfonamidoacetamides

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Abstract

A library of bis(azolyl)sulfonamidoacetamides was prepared by the reaction of azolylsulfonylamines with azolylchloroacetamides in the presence of pyridine/4-(dimethylamino)pyridine (DMAP) under ultrasonication. The reaction proceeded well with DMAP, resulting in a higher yield of the products. The antimicrobial activity of the compounds indicated that *N*-{5-[*N*-(2-{[4-(4-chloro-1*H*-pyrrol-2-yl)-1*H*-imidazol-2-yl)amino}-2-oxoethyl)sulfamoyl]-4-phenylthiazol-2-yl}benzamide (**22a**), *N*-{5-[*N*-(2-{[4-(4-chloro-1*H*-pyrrol-2-yl)-1*H*-imidazol-2-yl]amino}-2-oxoethyl) sulfamoyl]-4-(4-chlorophenyl)thiazol-2-yl}benzamide (**22c**), and *N*-{5-[*N*-(2-{[4-(4-chloro-1*H*-pyrrol-2-yl)-1*H*-imidazol-2-yl]amino}-2-oxoethyl)sulfamoyl]-4-(4-chlorophenyl)-1*H*-imidazol-2-yl}benzamide (**24c**) exhibited a low minimal inhibitory concentration (MIC) against *Bacillus subtilis*, equal to the standard drug, chloramphenicol. Compounds **22c** and **24c** also showed low MICs against *Aspergillus niger*, equal to the standard drug, ketoconazole. The molecular properties of the synthesized molecules were studied to identify druglikeness properties of the target compounds. On the basis of molecular properties prediction, **19a**, **19b**, **20b**, **20c**, **21a–c**, **22b**, **22c**, and **23a–c** can be treated as drug candidates.

KEYWORDS

antibacterial activity, antifungal activity, bis(azolyl)sulfonamidoacetamides, molecular properties, ultrasonication

1 | INTRODUCTION

Microbial world has always had the molecular tools to drive resistance, thus stimulating the need to discover novel antimicrobial agents.[1] As classic heterocycles, azole derivatives exhibit a broad spectrum of biological activities. The oxazole nucleus is ubiquitous in natural products such as pyrronazol,[2] ulapualide,[3] diazonamide,[4] and rhizopodin.[5] Thiazole is an essential core found in thiamine (vitamin B1), thiamine pyrophosphate, and medicinally important molecules.[6,7] Imidazole derivatives are associated with antitumor,[8] antibacterial,[9] antiviral,[10] antioxidant,[11] anti-inflammatory,[12] and antifungal[13] activities. Azoles are also valuable precursors in various biochemical and synthetic transformations in addition to a part of the unit in many drugs such as oxaprozin, bengazole-A, inthomycin-C, meloxicam, tiazofurin, cimetidine, ketoconazole, omeprazole[14] (Figure 1), and so forth.

Drug absorption and drug delivery are the main factors for the development of oral drugs.[15] About 30% of oral drugs fail in usage due to poor pharmacokinetics,[16] mainly bioavailability.[17] Thus, the prediction of bioavailability and bioavailability-related properties such as solubility and lipophilicity are the main factors for the molecules to be treated as drugs.[17] An in silico model for predicting

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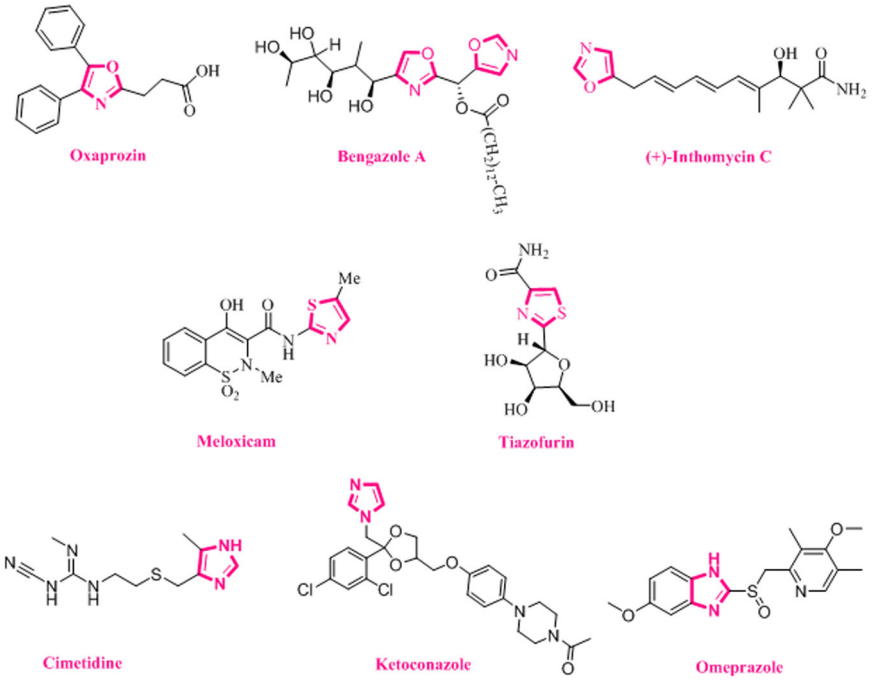


FIGURE 1 Drugs containing oxazole, thiazole, and imidazole units

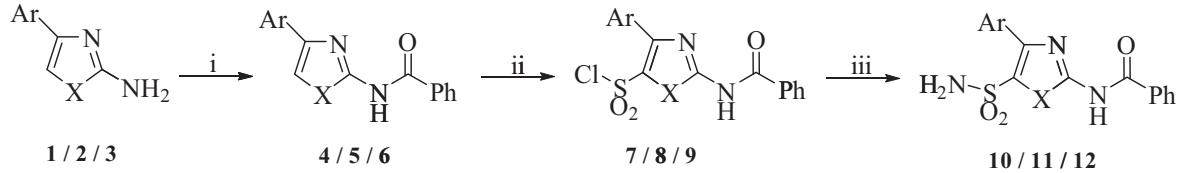
oral bioavailability is very important in the early stage of drug discovery to select the most promising compounds for further optimization and in the later stage to identify candidates for clinical development. In the present investigation, a new class of bisazoles (**19**–**24a**–**c**) linked by amido-sulfonamido group is synthesized and subjected to druglikeness by MolSoft (MolSoft 2007) software to identify the compounds as promising drug agents, and their antimicrobial activity is also studied.

2 | RESULTS AND DISCUSSION

2.1 | Chemistry

The azolyl amines 4-aryloxazolyl-2-amine (**1**) and 4-arylthiazolyl-2-amine (**2**) were synthesized by the reaction of phenacyl bromide with urea and thiourea in methanol.[18] 4-Arylimidazolyl-2-amine (**3**) was obtained by the hydrolysis of *N*-4-aryl-1*H*-imidazol-2-yl acetamide in the presence of H_2SO_4. The latter compound was prepared by the treatment of phenacyl bromide with acetyl guanidine.[19] *N*-Arylation of **1**, **2**, and **3** with benzoyl chloride furnished *N*-(4-aryloxazol-2-yl) benzamide (**4**), *N*-(4-arylthiazol-2-yl)benzamide (**5**), and *N*-(4-aryl-1*H*-imidazol-2-yl)benzamide (**6**). Chlorosulfonylation of **4**, **5**, and **6** with chlorosulfonic acid under ultrasonication at a frequency of 46 kHz resulted in trisubstituted azoles *N*-[5-(chlorosulfonyl)-4-aryloxazol-2-yl]benzamide (**7**), *N*-[5-(chlorosulfonyl)-4-arylthiazol-2-yl]benzamide (**8**), and *N*-[5-(chlorosulfonyl)-4-aryl-1*H*-imidazol-2-yl]benzamide (**9**)[20] (Scheme 1). Functionalization of sulfonyl chloride in **7**, **8**, and **9** to sulfonamide was effected by treating with 25% NH_4OH, which led to the formation of *N*-[5-(aminosulfonyl)-4-aryloxazol-2-yl] benzamide (**10**), *N*-[5-(aminosulfonyl)-4-arylthiazol-2-yl]benzamide (**11**), and *N*-[5-(aminosulfonyl)-4-aryl-1*H*-imidazol-2-yl]benzamide (**12**)[20] (Scheme 1).

However, the reaction of 2-bromo-1-(4-chloroheteroaryl)ethan-1-one with acetyl guanidine resulted in *N*-[4-(4-chlorofuran-2-yl)-1*H*-imidazol-2-yl]acetamide/*N*-[4-(4-chloro-1*H*-pyrrol-2-yl)-1*H*-imidazol-2-yl]



(i) PhCOCl / Toluene / Δ
(ii) $ClSO_3H$ / $CHCl_3$ /)))
(iii) 25 % NH_4OH / rt /)))

X= O, S, NH

Ar = a) Ph
b) 4-Me.Ph
c) 4-Cl.Ph

SCHEME 1 Synthesis of *N*-(4-aryl-5-sulfamoyloxazol/thiazol/1*H*-imidazol-2-yl)benzamide

acetamide, which on hydrolysis in the presence of sulfuric acid gave 4-(4-chlorofuran-2-yl)-1*H*-imidazol-2-amine (**15**)/4-(4-chloro-1*H*-pyrrol-2-yl)-1*H*-imidazol-2-amine (**16**) (Scheme 2). Functionalization of heteroarylamines was reported by several methods.[18,21] In fact, we have achieved *N*-sulfonylation of heteroarylamines with ethyl chloroacetate in the presence of dispersed sodium in tetrahydrofuran (THF).[22] It was observed that the reaction proceeded effectively with dispersed Na. As such, we have carried out the reaction of **15** with methyl 2-chloroacetate in the presence of dispersed sodium under ultrasonication at a frequency of 46 kHz wherein 2-chloro-*N*-[4-(4-chlorofuran-2-yl)-1*H*-imidazol-2-yl] acetamide (**17**) was obtained in an excellent yield. Adopting a similar methodology, 2-chloro-*N*-[4-(4-chloro-1*H*-pyrrol-2-yl)-1*H*-imidazol-2-yl] acetamide (**18**) was prepared by the treatment of **16** with methyl 2-chloroacetate (Scheme 2). In the presence of dispersed sodium, carbonyl free radical generated from methyl chloroacetate reacted with heteroaryl amine to obtain the corresponding amide by the expulsion of H_2 (Scheme 3).

The reaction of heteroarylamines and heteroarylmethyl chlorides was reported in the presence of diisopropyl ethylamine,[23] triethylamine,[24] potassium carbonate,[25] and sodium hydride[26] under conventional methods. However, most of the reactions required longer reaction times and maintenance of anhydrous conditions, and also in some instances, they led to lower yields. Recently, we have reported the reaction of heteroarylmethyl halides with heteroarylamines in the presence of pyridine in dichloromethane (DCM)[27] and 4-(dimethylamino)pyridine (DMAP) in DCM under ultrasonication.[27] As such, the reaction was performed by both methods. It was observed that the reaction proceeded at a faster rate in the presence of DMAP, leading to the formation of a higher yield of the products. This may be due to the more basicity of DMAP enhanced by the presence of *N*,*N*-dimethylamino group at 4-position. Thus compounds *N*-{5-[*N*-(2-{[4-(4-chlorofuran-2-yl)-1*H*-imidazol-2-yl]amino}-2-oxoethyl)sulfamoyl]-4-aryloxazol-2-yl}benzamide (**19**), *N*-{5-[*N*-(2-{[4-(4-chloro-1*H*-pyrrol-2-yl)-1*H*-imidazol-2-yl]amino}-2-oxoethyl)sulfamoyl]-4-aryloxazol-2-yl}benzamide (**20**), *N*-{5-[*N*-(2-{[4-(4-chloro-furan-2-yl)-1*H*-imidazol-2-yl]amino}-2-oxoethyl)sulfamoyl]-4-arylthiazol-2-yl}benzamide (**21**), *N*-{5-[*N*-(2-{[4-(4-chloro-1*H*-pyrrol-2-yl)-1*H*-imidazol-2-yl)amino}-2-oxoethyl)sulfamoyl]-4-aryl-thiazol-2-yl}benzamide (**22**), *N*-{5-[*N*-(2-{[4-(4-chlorofuran-2-yl)-1*H*-imidazol-2-yl]amino}-2-oxo-ethyl)sulfamoyl]-4-aryl-1*H*-imidazol-2-yl}benzamide (**23**), and *N*-{5-[*N*-(2-{[4-(4-chloro-1*H*-pyrrol-2-yl)-1*H*-imidazol-2-yl] amino}-2-oxoethyl)sulfamoyl]-4-aryl-1*H*-imidazol-2-yl}benzamide (**24**) were prepared by the reaction of **10**/**11**/**12** with **17**/**18** in the presence of pyridine (Method A) and also DMAP (Method B) (-Scheme 4). The ^{1}H nuclear magnetic resonance (NMR) spectra of **19a**, **21a** displayed four broad singlets at 7.86, 7.90 (SO_2NH), 9.54, 9.85 (CH_2CONH), 11.69, 11.76 (CONH), 12.23, 12.41 (imidazole NH). The compounds **20a**, **22a** showed five broad singlets at 7.80, 7.92 (SO_2NH), 9.65, 9.94 (CH_2CONH), 11.34, 11.47 (pyrrole NH), 11.70, 11.68 (CONH), 12.31, 12.49 (imidazole NH), whereas **23a** and **24a** exhibited four broad singlets at 7.86, 8.10 (SO_2NH), 9.91, 9.89 (CH_2CONH), 11.68, 11.84 (CONH), 12.37, 12.48 (imidazole NH). Besides, **24a** showed another broad singlet at 11.36 due to pyrrole NH. The signals of NH disappeared on deuteration.

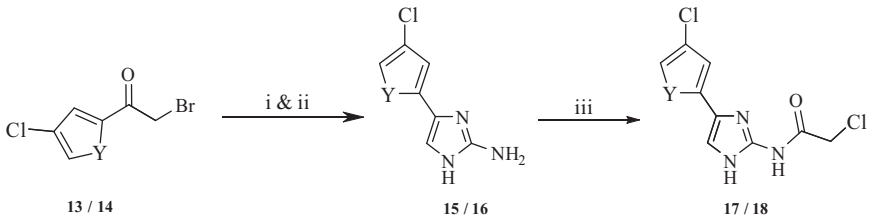
2.2 | Biology

2.2.1 | Antibacterial activity

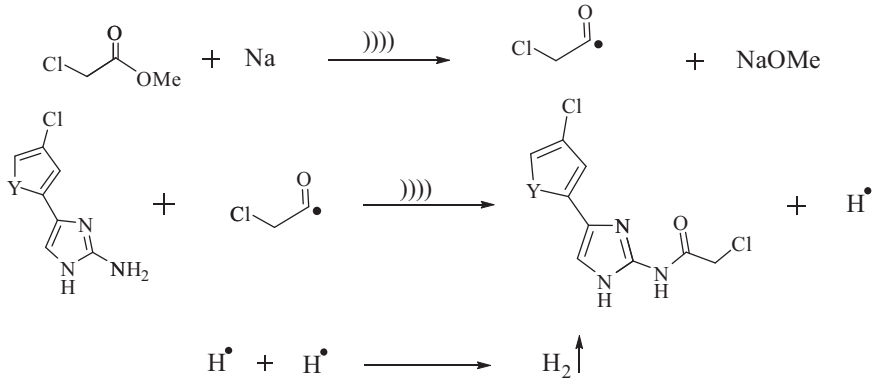
The results of antibacterial activity depicted in Table 1 and Figure 2 revealed that all the compounds except **19b** displayed more activity against Gram-positive bacteria than against Gram-negative bacteria. The imidazolylthiazole derivatives (**21**, **22**) exhibited greater activity than imidazolyloxazoles (**19**, **20**) and bis(imidazolyl) derivatives (**23**, **24**). Among the latter compounds, **23**, **24** showed more activity than **19**, **20**. It was noticed that 4-chloropyrrolyl compounds **20**, **22**, and **24** exhibited slightly higher activity than 4-chlorofuryl derivatives **19**, **21**, and **23**. The presence of an electron-withdrawing group on the aromatic ring enhanced the activity. In fact, 4-chloro-substituted compounds showed higher activity than methyl and unsubstituted ones in the respective series. Compounds **22a**, **22c**, and **24c** displayed excellent antibacterial activity against *Bacillus subtilis*, greater than the standard drug, chloramphenicol.

2.2.2 | Antifungal activity

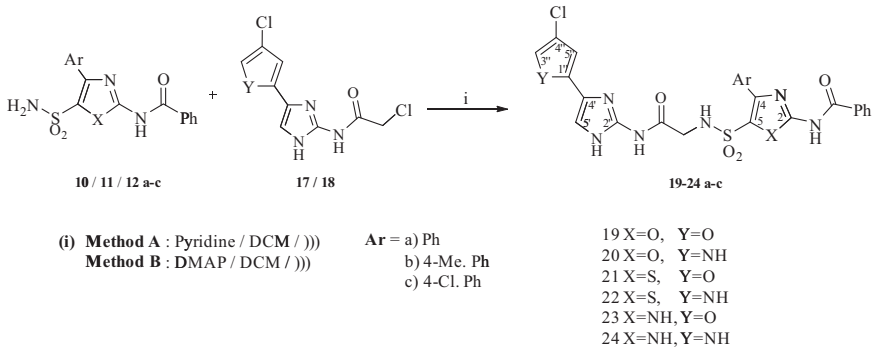
All the compounds inhibited the spore germination of tested fungi except **19a**, **19b**, **20a**, and **20b** (Table 2 and Figure 3). The tested compounds showed higher activity against *Aspergillus niger* than against *Penicillium chrysogenum*. The bis(imidazolyl) derivatives



SCHEME 2 Synthesis of 2-chloro-*N*-[4-(4-chlorofuran-2-yl/4-chloropyrrol-2-yl)-1*H*-imidazol-2-yl]acetamide. DMF, dimethylformamide



SCHEME 3 Mechanism



SCHEME 4 Synthesis of *N*-{5-[*N*-(2-{[4-(4-chlorofuran-2-yl)-pyrrol-2-yl-imidazol-2-yl]amino}-2-oxoethyl)sulfamoyl]-4-arylazol-2-yl}benzamide. DCM, dichloromethane; DMAP, 4-(dimethylamino)pyridine

(**23**, **24**) showed greater activity than imidazolyloxazoles (**19**, **20**) and imidazolylthiazoles (**21**, **22**). Compounds **21**, **22** showed higher activity than **19**, **20**. Furthermore, compounds with 4-chloropyrrole substituent showed higher activity than those with 4-chlorofuran. Among the compounds with substituents on aromatic ring, those with 4-chlorophenyl moiety displayed greater activity in the respective series due to the electron-withdrawing effect. Compounds **22c** and **24c** showed excellent antifungal activity against *A. niger* higher than the standard drug, ketoconazole.

2.2.3 | Minimal inhibitory concentration (MIC), minimum bactericidal concentration (MBC), and minimum fungicidal concentration (MFC) of compounds **22a**, **22c**, and **24c**

The MIC (the lowest concentration of an antimicrobial that inhibits the visible growth of a microorganism), MBC (the lowest concentration of antibiotic required to kill a particular bacterium), and MFC (the lowest concentration of antibiotic required to kill a particular fungus) of the compounds tested are listed in Table 3. When MIC is determined, MBC/MFC can be known by performing additional set of steps. The antimicrobials are usually regarded as bactericidal/fungicidal if the MBC/MFC is not greater than four times the MIC.[28] Compounds **22a**, **22c**, and **24c** exhibited a low MIC against *B. subtilis*, equal to standard drug chloramphenicol. The MBC was found to be 2 × MIC. Moreover, **22c** and **24c** showed a low MIC against *A. niger*, equal to standard drug ketoconazole. The MFC was found to be 2 × MIC. The structure–activity relationship of these molecules indicated that thiazolylimidazoles (**22**) and bisimidazoles (**24**) having 4-chloropyrrole substituent displayed excellent antimicrobial activity against *B. subtilis* and *A. niger*.

2.3 | Molecular properties and druglikeness

Molecular property prediction depends on various features such as hydrophobicity, molecular size, flexibility, and bioavailability that influence the behavior of molecules in living organs. Good bioavailability can be achieved with an appropriate balance between solubility and partitioning properties. A wide array of tools and approaches are available for the assessment of molecular diversity, which is an important factor to design drugs. As such, computational sensitivity analysis and structural analysis have been used to study the druglikeness of the molecules. Thus, to achieve good oral drugs, we have subjected a series of bisazoles linked by amido-sulfonamido group (**19**–**24a**–**c**) for the prediction of absorption, polar surface area (PSA), and other properties.

2.3.1 | Absorption, PSA, and other properties

High oral bioavailability is the major factor for the development of bioactive molecules as therapeutic agents. Good oral bioavailability can be predicted from good intestinal absorption, reduced molecular flexibility, low PSA, and total hydrogen bond count (sum of donors

TABLE 1 The in vitro antibacterial activity of compounds **19–24a–c**

	Zone of inhibition (mm)											
	Gram-positive bacteria						Gram-negative bacteria					
	Staphylococcus aureus			*Bacillus subtilis*			*Pseudomonas aeruginosa*			*Klebsiella pneumoniae*		
Compound no.	50 µg/well	75 µg/well	100 µg/well	50 µg/well	75 µg/well	100 µg/well	50 µg/well	75 µg/well	100 µg/well	50 µg/well	75 µg/well	100 µg/well
19a	12 ± 1.3	14 ± 1.9	16 ± 2.0	15 ± 1.9	16 ± 1.2	19 ± 1.3	10 ± 1.5	13 ± 1.9	15 ± 2.1	11 ± 2.0	13 ± 2.3	16 ± 2.5
19b	-	-	-	-	-	-	-	-	-	-	-	-
19c	13 ± 1.9	17 ± 2.0	19 ± 1.4	22 ± 2.2	25 ± 1.6	26 ± 2.1	14 ± 1.8	15 ± 2.1	17 ± 2.3	16 ± 2.2	17 ± 1.3	20 ± 1.7
20a	18 ± 1.2	21 ± 1.5	23 ± 2.3	20 ± 1.7	22 ± 2.5	25 ± 1.8	12 ± 2.3	14 ± 1.2	15 ± 2.4	15 ± 1.9	16 ± 1.2	19 ± 2.4
20b	-	11 ± 2.3	13 ± 1.6	13 ± 0.8	15 ± 1.2	17 ± 1.5	-	8 ± 1.8	10 ± 2.0	10 ± 1.3	12 ± 2.2	13 ± 2.4
20c	16 ± 1.7	20 ± 2.5	22 ± 1.5	24 ± 1.9	26 ± 2.1	28 ± 1.8	13 ± 1.7	15 ± 1.4	17 ± 2.2	17 ± 2.3	18 ± 1.5	21 ± 1.2
21a	19 ± 1.4	22 ± 1.8	25 ± 1.2	26 ± 2.0	29 ± 2.3	32 ± 1.6	16 ± 2.9	18 ± 1.9	20 ± 2.4	17 ± 1.7	20 ± 1.0	22 ± 2.3
21b	17 ± 2.2	19 ± 1.5	23 ± 2.3	24 ± 2.4	28 ± 1.5	30 ± 1.5	14 ± 1.8	15 ± 1.4	18 ± 2.1	15 ± 1.3	17 ± 1.6	20 ± 1.4
21c	21 ± 1.3	24 ± 2.8	26 ± 1.4	31 ± 1.7	33 ± 3.0	35 ± 1.7	17 ± 2.6	20 ± 2.1	22 ± 2.3	20 ± 2.2	21 ± 1.3	23 ± 1.7
22a	22 ± 1.2	25 ± 2.6	27 ± 1.3	34 ± 1.2	36 ± 2.6	39 ± 1.3	19 ± 1.8	22 ± 2.2	25 ± 2.5	24 ± 1.6	25 ± 2.4	27 ± 1.3
22b	18 ± 1.7	22 ± 2.5	26 ± 1.6	30 ± 1.7	31 ± 2.5	34 ± 1.6	16 ± 1.7	18 ± 1.4	19 ± 2.2	20 ± 2.3	22 ± 1.5	24 ± 1.2
22c	27 ± 1.1	28 ± 2.7	31 ± 1.8	39 ± 1.8	40 ± 1.4	43 ± 2.5	22 ± 2.5	24 ± 1.7	26 ± 2.9	25 ± 2.1	26 ± 2.5	29 ± 1.7
23a	16 ± 1.8	20 ± 1.4	23 ± 2.5	22 ± 2.4	26 ± 2.2	28 ± 1.3	14 ± 2.3	17 ± 1.5	19 ± 2.9	16 ± 2.1	18 ± 2.5	20 ± 1.4
23b	14 ± 1.3	18 ± 2.8	21 ± 1.4	22 ± 1.7	25 ± 3.0	27 ± 1.7	12 ± 1.8	14 ± 2.1	17 ± 2.3	12 ± 2.2	13 ± 1.3	16 ± 1.5
23c	18 ± 2.2	22 ± 2.4	25 ± 1.1	28 ± 1.5	30 ± 2.8	31 ± 2.1	17 ± 2.7	19 ± 2.2	20 ± 1.3	19 ± 1.5	21 ± 1.6	23 ± 2.2
24a	20 ± 1.1	23 ± 2.7	26 ± 1.8	31 ± 2.7	33 ± 2.3	35 ± 1.2	16 ± 1.9	18 ± 1.3	19 ± 2.6	17 ± 1.1	20 ± 2.6	22 ± 1.9
24b	17 ± 1.2	19 ± 2.6	22 ± 1.3	28 ± 2.5	30 ± 2.9	31 ± 2.4	16 ± 1.6	19 ± 2.3	22 ± 2.1	15 ± 1.4	16 ± 2.3	19 ± 1.8
24c	23 ± 1.8	25 ± 2.1	28 ± 2.8	37 ± 1.8	39 ± 2.1	40 ± 2.8	20 ± 1.9	23 ± 1.3	25 ± 2.7	23 ± 1.1	24 ± 2.6	26 ± 1.2
Chloramphenicol	30 ± 1.9	33 ± 1.8	35 ± 2.4	32 ± 2.1	34 ± 2.4	38 ± 1.6	25 ± 2.1	27 ± 1.5	30 ± 2.8	38 ± 2.0	40 ± 2.7	42 ± 2.1
Control (DMSO)	-	-	-	-	-	-	-	-	-	-	-	-

Note: Data are presented as ±*SD*.

Abbreviations: DMSO, dimethyl sulfoxide; -, no activity.

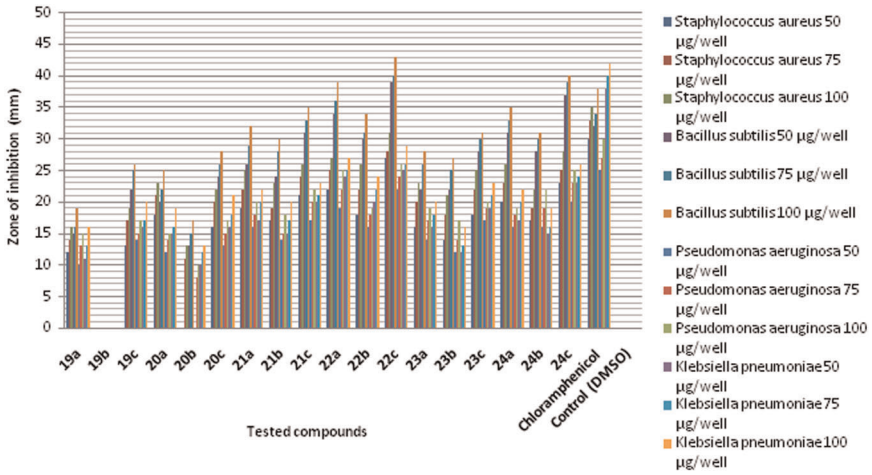


FIGURE 2 The in vitro antibacterial activity of compounds **19–24a–c**. DMSO, dimethyl sulfoxide

TABLE 2 The in vitro antifungal activity of compounds **19–24a–c**

	Zone of inhibition (mm)					
	Aspergillus niger			*Penicillium chrysogenum*		
Compound no.	50 µg/well	75 µg/well	100 µg/well	50 µg/well	75 µg/well	100 µg/well
19a	-	-	-	-	-	-
19b	-	-	-	-	-	-
19c	8 ± 1.0	10 ± 1.2	13 ± 2.2	-	8 ± 1.8	10 ± 2.3
20a	-	-	-	-	-	-
20b	-	-	-	-	-	-
20c	9 ± 1.5	12 ± 2.6	14 ± 2.8	8 ± 1.7	10 ± 2.3	13 ± 2.5
21a	18 ± 2.1	20 ± 2.0	24 ± 1.3	14 ± 2.4	16 ± 2.5	18 ± 2.8
21b	-	9 ± 1.8	11 ± 1.2	-	9 ± 1.8	12 ± 1.4
21c	21 ± 1.0	24 ± 1.4	26 ± 2.0	16 ± 2.2	17 ± 2.4	21 ± 1.3
22a	28 ± 2.5	29 ± 2.8	32 ± 2.7	24 ± 2.9	26 ± 2.6	29 ± 2.7
22b	16 ± 2.1	19 ± 1.9	23 ± 2.4	-	10 ± 1.3	14 ± 2.2
22c	33 ± 1.5	35 ± 2.3	38 ± 1.7	15 ± 1.6	21 ± 1.5	19 ± 2.4
23a	22 ± 1.3	25 ± 1.6	27 ± 2.7	17 ± 2.5	20 ± 2.1	23 ± 1.0
23b	18 ± 1.0	20 ± 2.4	24 ± 2.3	14 ± 2.1	17 ± 1.2	20 ± 1.8
23c	23 ± 1.5	25 ± 1.7	27 ± 1.5	19 ± 1.8	21 ± 2.4	25 ± 1.2
24a	29 ± 1.7	31 ± 2.5	34 ± 1.4	13 ± 2.7	16 ± 1.9	18 ± 2.3
24b	23 ± 1.8	26 ± 2.2	28 ± 1.8	10 ± 2.5	13 ± 1.4	14 ± 2.1
24c	36 ± 2.4	38 ± 2.7	41 ± 1.6	19 ± 2.3	22 ± 1.7	26 ± 2.8
Ketoconazole	31 ± 2.0	33 ± 1.6	36 ± 2.1	35 ± 1.7	36 ± 2.5	38 ± 1.4
Control (DMSO)	-	-	-	-	-	-

Note: Data are presented as ±*SD*.

Abbreviations: DMSO, dimethyl sulfoxide; -, no activity.

and acceptors).[29,30] Molecular properties, namely membrane permeability and bioavailability, are associated with basic molecular descriptors like log *P* (partition coefficient), hydrogen bond acceptors, and hydrogen bond donors in a molecule.[31]

Lipinski's rule[32] states that molecules with good membrane permeability should have log *P* ≤ 5, molecular weight ≤500, number of hydrogen bond acceptors ≤10, and number of hydrogen bond donors ≤5. This rule is used to identify drug-like properties of

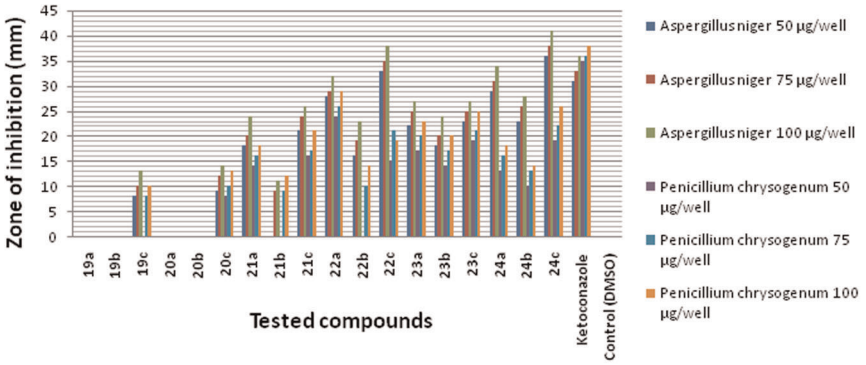


FIGURE 3 The in vitro antifungal activity of compounds **19**–**24a**–**c**

TABLE 3 MIC, MBC, and MFC of compounds **22a**, **22c**, and **24c**

	MIC (MBC/MFC) µg/well					
Compound no.	*Staphylococcus aureus*	*Bacillus subtilis*	*Pseudomonas aeruginosa*	*Klebsiella pneumoniae*	*Aspergillus niger*	*Penicillium chrysogenum*
22a	25 (100)	6.25 (12.5)	12.5 (50)	100 (>200)	12.5 (50)	100 (>200)
22c	12.5 (100)	6.25 (12.5)	12.5 (50)	100 (>200)	6.25 (12.5)	200 (-)
24c	12.5 (100)	6.25 (12.5)	12.5 (50)	100 (>200)	6.25 (12.5)	200 (-)
Chloramphenicol	6.25	6.25	6.25	12.5	-	-
Ketoconazole	-	-	-	-	6.25	12.5

Note: Data are presented as MIC (SD)

Abbreviations: MBC, minimum bactericidal concentration; MFC, minimum fungicidal concentration; MIC, minimal inhibitory concentration; -, no activity.

molecules. Although the molecular weight of the compounds is higher than 500, most of the compounds satisfied the other properties (Table 4). The magnitude of absorption is expressed by the percentage of absorption. Absorption percent was calculated using the following expression: % ABS = 109 − 0.345 PSA.[33] PSA was determined by the fragment-based method reported by Ertl and coworkers.[34,35] The presence of more than 5 H-bond donors and 10 H-bond acceptors indicates poor permeation or absorption. Hydrogen-bonding capacity has been also identified as an important parameter for describing drug permeability.[19] Molecules **19a**–**c**, **20a**–**c**, **21a**–**c**, **22a**–**c**, and **23a**–**c** except **24a**–**c** possess ≤5 hydrogen bond donors and all the compounds have ≤10 hydrogen bond acceptors (Table 4).

Molecular PSA indicates the prediction of drug transport properties of a molecule. PSA is the sum of surfaces of polar atoms (usually oxygen and nitrogen) in a molecule. PSA and volume are inversely proportional to % ABS. Compounds **21a**–**c** and **22a**–**c** have maximum absorption (64.25–64.18%), as their corresponding PSA and volume are least among the series (Table 4). The druglikeness model score (a combined effect of physicochemical properties, pharmacokinetics, and pharmacodynamics of a compound represented by a numerical value) was computed by MolSoft (MolSoft 2007) software for the molecules under study, and the values are presented in Table 4. As depicted in Figure 4, those with green color indicates non-drug-like behavior and with blue color are considered as drug-like. Compounds having zero or negative value cannot be considered as drug-like. The druglikeness score was found to be 0.08–0.71 for compounds **19a**, **19b**, **20b**, **20c**, **21a**–**c**, **22b**, **22c**, **23a**–**c**, **24b**, and **24c** under investigation. However, **24a**–**c** have hydrogen bond donors >5. Thus, based on the molecular properties prediction, **19a**, **19b**, **20b**, **20c**, **21a**–**c**, **22b**, **22c**, and **23a**–**c** can be treated as drug candidates.

3 | CONCLUSION

A new class of bis(azolyl)sulfonamidoacetamides was prepared by the reaction of azolylsulfonylamines with azolylchloroacetamides in the presence of pyridine/DMAP under ultrasonication. The reaction proceeded well with DMAP, resulting in higher yield of the products. This may be due to the presence of electron-donating *N*,*N*-dimethylamino group at 4-position, which enhances the basicity of DMAP. The antimicrobial activity of the compounds indicated that *N*-{5-[*N*-(2-{[4-(4-chloro-1*H*-pyrrol-2-yl)-1*H*-imidazol-2-yl)amino}-2-oxoethyl)sulfamoyl]-4-phenylthiazol-2-yl}benzamide (**22a**), *N*-{5-[*N*-(2-{[4-(4-chloro-1*H*-pyrrol-2-yl)-1*H*-imidazol-2-yl]amino}-2-oxoethyl) sulfamoyl]-4-(4-chloro-phenyl)thiazol-2-yl}benzamide (**22c**), and *N*-{5-[*N*-(2-{[4-(4-chloro-1*H*-pyrrol-2-yl)-1*H*-imidazol-2-yl]amino}-2-oxoethyl)sulfamoyl]-4-(4-chlorophenyl)-1*H*-imidazol-2-yl}benzamide (**24c**) exhibited a low MIC against *B. subtilis*, equal to standard drug chloramphenicol. Compounds **22c** and **24c** also showed a low MIC against *A. niger*, equal to standard drug ketoconazole. Molecular

TABLE 4 Calculated absorption, polar surface area, and druglikeness model score of compounds **19**–**24a**–**c**

Compound no.	Molecular formula	% ABS	Mol Vol (Å^3)	Mol PSA (Å^2)	Mol log *P*	No. of HBA	No. of HBD	Mol log *S* log (mol/l) 0.00 (in mg/L)	Formula weight	Druglikeness model score
19a	$C_{25}H_{19}ClN_6O_6S$	61.08	490.21	138.89	3.68	9	4	−8.37	566.08	0.09
19b	$C_{26}H_{21}ClN_6O_6S$	61.08	511.15	138.89	4.08	9	4	−8.82	580.09	0.34
19c	$C_{25}H_{18}Cl_2N_6O_6S$	61.08	507.40	138.89	4.39	9	4	−9.32	600.04	−0.66
20a	$C_{25}H_{20}ClN_7O_5S$	61.00	493.82	139.11	3.40	8	5	−8.55	565.09	−0.17
20b	$C_{26}H_{22}ClN_7O_5S$	61.00	514.76	139.11	3.80	8	5	−9.00	579.11	0.08
20c	$C_{25}H_{19}Cl_2N_7O_5S$	61.00	511.02	139.11	4.12	8	5	−9.50	599.05	0.38
21a	$C_{25}H_{19}ClN_6O_5S_2$	64.25	494.28	129.69	4.69	9	4	−8.25	582.05	0.15
21b	$C_{26}H_{21}ClN_6O_5S_2$	64.25	515.22	129.69	5.09	9	4	−8.70	596.07	0.38
21c	$C_{25}H_{18}Cl_2N_6O_5S_2$	64.25	511.47	129.69	5.40	9	4	−9.21	616.02	0.71
22a	$C_{25}H_{20}ClN_7O_4S_2$	64.18	497.89	129.91	4.41	8	5	−8.43	581.07	−0.08
22b	$C_{26}H_{22}ClN_7O_4S_2$	64.18	518.83	129.91	4.81	8	5	−8.88	595.09	0.16
22c	$C_{25}H_{19}Cl_2N_7O_4S_2$	64.18	515.09	129.91	5.13	8	5	−9.39	615.03	0.46
23a	$C_{25}H_{20}ClN_7O_5S$	60.38	488.97	140.92	3.78	8	5	−8.98	565.09	0.13
23b	$C_{26}H_{22}ClN_7O_5S$	60.38	509.91	140.92	4.18	8	5	−9.44	579.11	0.36
23c	$C_{25}H_{19}Cl_2N_7O_5S$	60.38	506.17	140.92	4.49	8	5	−9.94	599.05	0.68
24a	$C_{25}H_{21}ClN_8O_4S$	45.49	492.58	141.13	3.50	7	6	−9.16	564.11	−0.09
24b	$C_{26}H_{23}ClN_8O_4S$	45.49	513.52	141.13	3.90	7	6	−9.61	578.13	0.15
24c	$C_{25}H_{20}Cl_2N_8O_4S$	45.49	509.78	141.13	4.21	7	6	−10.12	598.07	0.44

Abbreviations: HBA, hydrogen bond acceptor; HBD, hydrogen bond donor; Mol log *P*, octanol/water partition coefficient; Mol log *S*, water solubility; Mol PSA, molecular polar surface area; Mol Vol, molecular volume % ABS, percentage of absorption.

properties of synthesized molecules were studied to identify druglikeness behavior of the molecules. Molecules **19a**–**c**, **20a**–**c**, **21a**–**c**, **22a**–**c**, and **23a**–**c** possess ≤5 hydrogen bond donors and ≤10 hydrogen bond acceptors. However, **24a**–**c** have hydrogen bond donors >5. Furthermore, PSA and volume indicated that the compounds **21a**–**c** and **22a**–**c** have maximum absorption. The druglikeness score was found to be 0.08–0.71 for compounds **19a**, **19b**, **20b**, **20c**, **21a**–**c**, **22b**, **22c**, **23a**–**c**, **24b**, and **24c**. Thus, based on molecular properties prediction, **19a**, **19b**, **20b**, **20c**, **21a**–**c**, **22b**, **22c**, and **23a**–**c** can be treated as drug candidates.

4 | EXPERIMENTAL

4.1 | Chemistry

4.1.1 | General

Melting points were determined in open capillaries on a Mel-Temp apparatus and were uncorrected. The purity of the compounds was evaluated by thin-layer chromatography (TLC) (silica gel H, BDH, ethyl acetate/hexane, 1:3). The infrared (IR) spectra were recorded on a Thermo Nicolet IR 200 FT-IR spectrometer as KBr pellets and the wavenumbers were given in cm^{-1}. The ^{1}H and ^{13}C NMR spectra (see the Supporting Information) were recorded in dimethyl sulfoxide (DMSO)-d_6 on a Bruker spectrometer operating at 400 and 100 MHz. The chemical shifts are reported in δ (ppm) using tetramethylsilane as an internal standard. The high-resolution mass spectra are recorded on micromass Q-TOF micromass spectrometer using electrospray ionization. Ultrasonication was performed in a Bandelin SONOREX RK 12 H ultrasonic bath operating at a frequency of 46 kHz. The microanalyses were performed on a PerkinElmer 240C elemental analyzer. The progress of the reaction was monitored by TLC using silica gel plates (silica gel 60 F254 0.25 mm), and components were visualized by observation under UV light (254 and 365 nm). Compounds 4-phenyloxazol-2-amine (**1**), 4-phenylthiazol-2-amine (**2**), 4-phenyl-1*H*-imidazol-2-amine (**3**), 4-(4-chlorofuran-2-yl)-1*H*-imidazol-2-amine (**15**), and 4-(4-chloro-1*H*-pyrrol-2-yl)-1*H*-imidazol-2-amine (**16**) were prepared as per the literature procedures.[14,28] Compounds 4-(4-chlorophenyl)-1*H*-pyrrol-2-amine (**7**), 2-bromo-1-(4-chlorofuran-2-yl)ethan-1-one (**13**), and 2-bromo-1-(4-chloro-1*H*-pyrrol-2-yl)ethan-1-one (**14**) were purchased from Sigma-Aldrich.

The InChI codes of the investigated compounds, together with some biological activity data, are provided as Supporting Information.

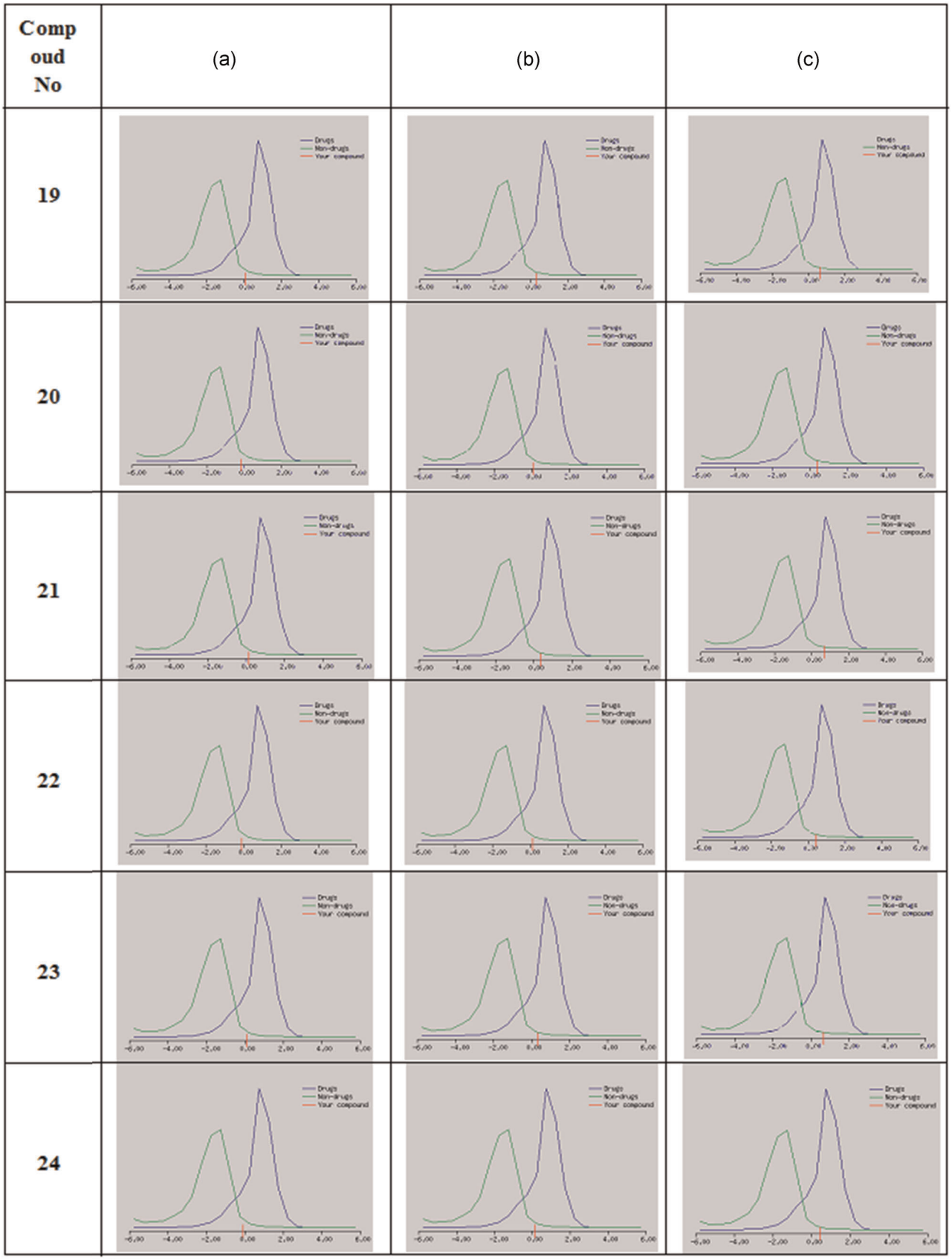


FIGURE 4 (a) phenyl, (b) 4-methyl phenyl (Toluene), (c) means- 4-chloro phenyl. Graph showing compounds **19**–**24a**–**c** of the druglikeness model score using Molsoft 2007

4.1.2 | Preparation of dispersed sodium

Clean sodium metal (10 g) was weighed under dry ether and introduced into a 500-ml round-bottomed flask containing sodium-dried xylene (100 cm^3) fitted with an air condenser carrying a calcium chloride guard tube and placed on a sand bath. The flask was covered with a dry cloth and the sand bath was heated slowly. The ring of condensed vapors of xylene was carefully observed. When the ring of condensed vapor had risen to the neck of the flask, the flame was extinguished. The condenser was replaced by the stopper and the flask was wrapped with a pre-dried cloth. The stopper was then held firmly and shaken vigorously for 2–3 min until the molten sodium was converted into a fine dispersion. Immediately the stopper was removed and the flask was placed on the cork ring. The sodium was obtained in the form of small spheres, depending upon the time and rapidity of shaking. Then the contents were cooled to room temperature, xylene was decanted, and sodium was washed with sodium-dried ether. The dispersed sodium as small spheres was preserved in absolute ether.[31]

4.1.3 | General procedure for the synthesis of 2-chloro-*N*-[4-(4-chlorofuran/1*H*-pyrrol-2-yl)-1*H*-imidazol-2-yl]acetamide (**17**/**18**)

A mixture of methyl 2-chloroacetate (0.001 mol), dispersed sodium (1.8 mg atom), and THF (3 ml) was sonicated for 15 min in a sonic bath at a frequency of 46 kHz at 35°C. To this, 4-(4-chlorofuran-2-yl)-1*H*-imidazol-2-amine (**15**)/4-(4-chloro-1*H*-pyrrol-2-yl)-1*H*-imidazol-2-amine (**16**) was added, and sonication was continued for 15–22 min. After completion of the reaction (monitored by TLC), the organic matter was filtered, washed with water, extracted with ether, and dried. Removal of the solvent under reduced pressure gave a solid that was recrystallized from ethanol.

2-Chloro-N-*[4-(4-chlorofuran-2-yl)-1*H*-imidazol-2-yl]acetamide (**17**)*

Yield 65%; mp 132–134°C. IR (KBr): 3376 (NH), 1676 (C═O), 1645 (C═C), 1583 (C═N) (cm^{-1}); ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.38 (s, 2H, CH_2), 7.09–7.41 (m, 3H, C_5''–H, C_5'–H and C_3''–H), 10.23 (br s, 1H, CONH), 12.46 (br s, 1H, imidazole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 43.4 (CH_2–C), 168.3 (C═O), 112.5, 115.9, 122.3, 137.8, 140.1, 153.7, 157.0 (aromatic carbon C_2', C_4', C_5', C_1'', C_3'', C_4'', and C_5'') ppm. HRMS (*m/z*): 283.0632 $[M+Na]^+$; anal. calcd. for $C_9H_7Cl_2N_3O_2$: C, 41.56; H, 2.71; N, 16.16; found: C, 41.64; H, 2.75; N, 16.25%.

2-Chloro-N-*[4-(4-chloro-1*H*-pyrrol-2-yl)-1*H*-imidazol-2-yl]acetamide (**18**)*

Yield 68%; mp 146–148°C. IR (KBr): 3369 (NH), 1680 (C═O), 1638 (C═C), 1575 (C═N) (cm^{-1}); ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.42 (s, 2H, CH_2), 6.57–7.43 (m, 3H, C_5''–H, C_5'–H and C_3''–H), 10.31 (br s, 1H, CONH), 11.65 (br s, 1H, pyrrole NH), 12.52 (br s, 1H, imidazole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 44.2 (CH_2–C), 167.6 (C═O), 105.4, 108.7, 117.5, 121.9, 130.4, 141.6, 149.3 (aromatic carbon C_2', C_4', C_5', C_1'', C_3'', C_4'', and C_5'') ppm. HRMS (*m/z*): 282.0804 $[M+Na]^+$; anal. calcd. for $C_9H_8Cl_2N_4O$: C, 41.72; H, 3.11; N, 21.62; found: C, 41.78; H, 3.08; N, 21.73%.

4.1.4 | General procedure for the synthesis of *N*-{5-[*N*-(2-{[4-(4-chlorofuran-2-yl)-pyrrol-2yl-imidazol-2-yl]-amino}-2-oxoethyl)sulfamoyl]-4-arylazol-2-yl}-benzamide (**19**–**24**)

Method A: *N*-(4-Phenyl-5-sulfamoyloxazol/thiazol/1*H*-imidazol-2-yl) benzamide (**10**/**11**/**12**) (1 mmol) and 2-chloro-*N*-[4-(4-chlorofuran-2-yl)-1*H*-imidazol-2-yl]acetamide (**17**)/2-chloro-*N*-[4-(4-chloro-1*H*-pyrrol-2-yl)-1*H*-imidazol-2-yl]acetamide (**18**) (1 mmol) were dissolved in DCM (20 ml), and pyridine (3 mmol) was added dropwise to this. The contents were subjected to ultrasound irradiation at a frequency of 46 kHz for 45–60 min at room temperature. After completion of the reaction (checked by TLC), the residue was poured on crushed ice and solid separated was filtered, dried, and recrystallized from ethanol.

Method B: Compounds **10**–**12** (1 mmol) and **17**, **18** (1 mmol) were dissolved in DCM (15 ml). To this, DMAP (1 mmol) and triethylamine (1 mmol) were added dropwise and sonicated at a frequency of 46 kHz at room temperature for 35–40 min. After the reaction was completed, the contents were poured on crushed ice and the solid was filtered, dried, and recrystallized from ethanol.

N-*{5-[*N*-(2-{[4-(4-Chlorofuran-2-yl)-1*H*-imidazol-2-yl]amino}-2-oxoethyl)sulfamoyl]-4-phenyloxazol-2-yl}benzamide (**19a**)*

Yield 64% (Method A), 71% (Method B); mp 142–144°C. IR (KBr): 3384 (NH), 1688 (C═O), 1639 (C═C), 1579 (C═N), 1340–1135 (SO_2) (cm^{-1}); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.42 (s, 2H, CH_2), 6.44 (s, 1H, C_5''–H), 7.46–7.72 (m, 12H, Ar–H, C_3''–H, and C_5'–H), 7.82 (br s, 1H, SO_2NH), 9.54 (br s, 1H, CH_2CON*H*), 11.69 (br s, 1H, CONH), 12.23 (br s, 1H, imidazole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 45.6 (CH_2–C), 152.3 (C-2), 153.7 (C-2′), 160.4 (C-1″), 165.1 (CONH), 169.3 (CH_2CONH), 109.3, 114.9, 119.6, 125.4, 127.1, 129.0, 132.5, 134.7, 136.3, 137.2, 138.1, 139.6, 141.3, 142.8, 144.1 (aromatic carbons, C_4, C_5, C_4', C_5', C_3'', C_4'', and C_5'') ppm. HRMS (*m/z*): 589.9621 $[M+Na]^+$; anal. calcd. for $C_{25}H_{19}ClN_6O_6S$: C, 52.96; H, 3.38; N, 14.82; found: C, 53.04; H, 3.33; N, 14.93%.

N-*{5-[*N*-(2-{[4-(4-Chlorofuran-2-yl)-1*H*-imidazol-2-yl]amino}-2-oxoethyl)sulfamoyl]-4-(*p*-tolyl)oxazol-2-yl}benzamide (**19b**)*

Yield 65% (Method A), 73% (Method B); mp 155–157°C. IR (KBr): 3374 (NH), 1678 (C═O), 1634 (C═C), 1573 (C═N), 1325–1128 (SO_2) (cm^{-1}); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.29 (s, 3H, CH_3), 3.40 (s, 2H, CH_2), 6.39 (s, 1H, C_5''–H), 7.40–7.68 (m, 11H, Ar–H, C_3''–H and C_5'–H), 7.78 (br s, 1H, SO_2NH), 9.50 (br s, 1H, CH_2CON*H*), 11.61 (br s, 1H, CONH), 12.18 (br s, 1H, imidazole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.3 (CH_3–C), 43.6 (CH_2–C), 151.9 (C-2), 152.6 (C-2′),

159.4 (C-1″), 163.2 (CONH), 167.1 (CH_2*C*ONH), 110.6, 113.4, 116.7, 119.0, 121.2, 122.8, 124.1, 128.9, 133.7, 135.0, 137.6, 138.5, 139.3, 140.5, 143.4 (aromatic carbons, C_4, C_5, C_4', C_5', C_3'', C_4'', and C_5'') ppm. HRMS (*m/z*): 603.9890 $[M+Na]^+$; anal. calcd. for $C_{26}H_{21}ClN_6O_6S$: C, 53.75; H, 3.64; N, 14.47; found: C, 53.67; H, 3.60; N, 14.38%.

N-*{5-[N-(2-{[4-(4-Chlorofuran-2-yl)-1H-imidazol-2-yl]amino}-2-oxoethyl)sulfamoyl]-4-(4-chlorophenyl)oxazol-2-yl}benzamide (**19c**)*

Yield 62% (Method A), 76% (Method B); mp 161–163°C. IR (KBr): 3386 (NH), 1683 (C═O), 1648 (C═C), 1581 (C═N), 1342–1139 (SO_2) (cm^{-1}); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.48 (s, 2H, CH_2), 6.47 (s, 1H, C_5''–H), 7.49–7.76 (m, 11H, Ar–H, C_3''–H and C_5'–H), 7.89 (br s, 1H, SO_2NH), 10.08 (br s, 1H, CH_2CON*H*), 11.93 (br s, 1H, CONH), 12.25 (br s, 1H, imidazole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 44.2 (CH_2–C), 152.4 (C-2), 153.6 (C-2′), 161.7 (C-1″), 164.0 (CONH), 168.9 (CH_2*C*ONH), 112.3, 114.7, 119.1, 120.5, 121.4, 122.8, 127.3, 130.4, 133.2, 134.7, 136.3, 138.2, 139.5, 140.7, 142.2 (aromatic carbons, C_4, C_5, C_4', C_5', C_3'', C_4'', and C_5'') ppm. HRMS (*m/z*): 624.4054 $[M+Na]^+$; anal. calcd. for $C_{25}H_{18}Cl_2N_6O_6S$: C, 49.93; H, 3.02; N, 13.97; found: C, 49.85; H, 3.08; N, 13.84%.

N-*{5-[N-(2-{[4-(4-Chloro-1H-pyrrol-2-yl)-1H-imidazol-2-yl]amino}-2-oxoethyl)sulfamoyl]-4-phenyloxazol-2-yl}benzamide (**20a**)*

Yield 60% (Method A), 75% (Method B); mp 150–152°C. IR (KBr): 3370 (NH), 1678 (C═O), 1640 (C═C), 1577 (C═N), 1334–1124 (SO_2) (cm^{-1}); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.45 (s, 2H, CH_2), 6.43 (s, 1H, C_5''–H), 6.82 (s, 1H, C_3''–H), 7.39–7.66 (m, 11H, Ar–H and C_5'–H), 7.80 (br s, 1H, SO_2NH), 9.68 (br s, 1H, CH_2CON*H*), 11.34 (br s, 1H, pyrrole NH), 11.70 (br s, 1H, CONH), 12.31 (br s, 1H, imidazole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 44.7 (CH_2–C), 149.1 (C-2), 151.6 (C-2′), 163.8 (CONH), 166.5 (CH_2*C*ONH), 106.5, 107.6, 109.4, 111.7, 115.2, 119.1, 120.4, 127.7, 129.4, 132.0, 133.8, 135.3, 136.5, 138.2, 139.6, 140.1 (aromatic carbons, C_4, C_5, C_4', C_5', C_1'', C_3'', C_4'', and C_5'') ppm. HRMS (*m/z*): 588.9783 $[M+Na]^+$; anal. calcd. for $C_{25}H_{20}ClN_7O_5S$: C, 53.05; H, 3.56; N, 17.32; found: C, 53.00; H, 3.61; N, 17.45%.

N-*{5-[N-(2-{[4-(4-Chloro-1H-pyrrol-2-yl)-1H-imidazol-2-yl]amino}-2-oxoethyl)sulfamoyl]-4-(p-tolyl)oxazol-2-yl}benzamide (**20b**)*

Yield 66% (Method A), 76% (Method B); mp 164–166°C. IR (KBr): 3357 (NH), 1674 (C═O), 1637 (C═C), 1572 (C═N), 1331–1135 (SO_2) (cm^{-1}); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.35 (s, 3H, CH_3), 3.43 (s, 2H, CH_2), 6.45 (s, 1H, C_5''–H), 6.78 (s, 1H, C_3''–H), 7.30–7.65 (m, 10H, Ar–H, and C_5'–H), 7.82 (br s, 1H, SO_2NH), 9.61 (br s, 1H, CH_2CON*H*), 11.46 (br s, 1H, pyrrole NH), 11.75 (br s, 1H, CONH), 12.28 (br s, 1H, imidazole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.1 (CH_3–C), 43.2 (CH_2–C), 148.3 (C-2), 150.8 (C-2′), 162.3 (CONH), 166.2 (CH_2*C*ONH), 106.1, 107.4, 112.5, 118.3, 119.8, 121.2, 123.1, 125.6, 127.3, 128.5, 129.0, 131.4, 134.8, 138.1, 139.9, 141.5 (aromatic carbons, C_4, C_5, C_4', C_5', C_1'', C_3'', C_4'', and C_5'') ppm. HRMS (*m/z*): 603.0064 $[M+Na]^+$; anal. calcd. for $C_{26}H_{22}ClN_7O_5S$: C, 53.84; H, 3.82; N, 16.90; found: C, 53.74; H, 3.75; N, 16.98%.

N-*{5-[N-(2-{[4-(4-Chloro-1H-pyrrol-2-yl)-1H-imidazol-2-yl]amino}-2-oxoethyl)sulfamoyl]-4-(4-chlorophenyl)oxazol-2-yl}benzamide (**20c**)*

Yield 62% (Method A), 73% (Method B); mp 185–187°C. IR (KBr): 3375 (NH), 1679 (C═O), 1645 (C═C), 1580 (C═N), 1342–1141 (SO_2) (cm^{-1}); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.51 (s, 2H, CH_2), 6.48 (s, 1H, C_5''-H), 6.95 (s, 1H, C_3''–H), 7.45–7.73 (m, 10H, Ar–H and C_5'–H), 7.88 (br s, 1H, SO_2NH), 9.72 (br s, 1H, CH_2CON*H*), 11.52 (br s, 1H, pyrrole NH), 11.83 (br s, 1H, CONH), 12.43 (br s, 1H, imidazole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 44.4 (CH_2–C), 150.0 (C-2), 152.2 (C-2′), 164.7 (CONH), 167.0 (CH_2*C*ONH), 109.8, 111.2, 115.0, 118.6, 121.7, 126.4, 127.6, 128.5, 129.8, 130.4, 132.6, 135.2, 137.7, 139.0, 140.5, 142.9 (aromatic carbons, C_4, C_5, C_4', C_5', C_1'', C_3'', C_4'', and C_5'') ppm. HRMS (*m/z*): 623.4212 $[M+Na]^+$; anal. calcd. for $C_{25}H_{19}Cl_2N_7O_5S$: C, 50.01; H,3.19; N, 16.33; found: C, 50.09; H, 3.14; N, 16.26%.

N-*{5-[N-(2-{[4-(4-Chlorofuran-2-yl)-1H-imidazol-2-yl]amino}-2-oxoethyl)sulfamoyl]-4-phenylthiazol-2-yl}benzamide (**21a**)*

Yield 59% (Method A), 71% (Method B); mp 162–164°C. IR (KBr): 3369 (NH), 1675 (C═O), 1636 (C═C), 1591 (C═N), 1330–1125 (SO_2) (cm^{-1}); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.52 (s, 2H, CH_2), 6.58 (s, 1H, C_5''–H), 7.41–7.80 (m, 12H, Ar–H, C_3''–H and C_5'–H), 7.97 (br s, 1H, SO_2NH), 9.85 (br s, 1H, CH_2CON*H*), 11.76 (br s, 1H, CONH), 12.41 (br s, 1H, imidazole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 43.9 (CH_2–C), 151.2 (C-2′), 157.6 (C-1″), 159.3 (C-2), 163.4 (CONH), 167.4 (CH_2*C*ONH), 104.8, 109.4, 112.3, 115.1, 119.5, 124.6, 128.5, 129.7, 130.0, 131.4, 136.2, 138.9, 140.4, 141.5, 143.8 (aromatic carbons, C_4, C_5, C_4', C_5', C_3'', C_4'', and C_5'') ppm. HRMS (*m/z*): 606.0238 $[M+Na]^+$; anal. calcd. for $C_{25}H_{19}ClN_6O_5S_2$: C, 51.50; H, 3.28; N, 14.41; found: C, 51.48; H, 3.31; N, 14.45%.

N-*{5-[N-(2-{[4-(4-Chlorofuran-2-yl)-1H-imidazol-2-yl]amino}-2-oxoethyl)sulfamoyl]-4-(p-tolyl)thiazol-2-yl}benzamide (**21b**)*

Yield 65% (Method A), 73% (Method B); mp 167–169°C. IR (KBr): 3365 (NH), 1672 (C═O), 1632 (C═C), 1576 (C═N), 1326–1133 (SO_2) (cm^{-1}); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.38 (s, 3H, CH_3), 3.54 (s, 2H, CH_2), 6.53 (s, 1H, C_5''–H), 7.35–7.69 (m, 11H, Ar–H, C_3''–H and C_5'–H), 7.85 (br s, 1H, SO_2NH), 9.76 (br s, 1H, CH_2CON*H*), 11.70 (br s, 1H, CONH), 12.36 (br s, 1H, imidazole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.5 (CH_3–C), 44.7 (CH_2–C), 151.0 (C-2′), 156.3 (C-1″), 158.7 (C-2), 162.9 (CONH), 166.7 (CH_2*C*ONH), 105.1, 108.3, 110.6, 114.0, 119.2, 123.5, 128.1, 129.4, 131.2, 133.4, 135.0, 137.3, 139.5, 141.2, 143.3 (aromatic carbons, C_4, C_5, C_4', C_5', C_3'', C_4'', and C_5'') ppm. HRMS (*m/z*): 620.0513 $[M+Na]^+$; anal. calcd. for $C_{26}H_{21}ClN_6O_5S_2$: C, 52.30; H, 3.55; N, 14.08; found: C, 52.38; H, 3.49; N, 14.17%.

N-*{5-[N-(2-{[4-(4-Chlorofuran-2-yl)-1H-imidazol-2-yl]amino}-2-oxoethyl)sulfamoyl]-4-(4-chlorophenyl)thiazol-2-yl}benzamide (**21c**)*

Yield 63% (Method A), 76% (Method B); mp 173–175°C. IR (KBr): 3375 (NH), 1680 (C═O), 1641 (C═C), 1593 (C═N), 1341–1140 (SO_2) (cm^{-1}); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.60 (s, 2H, CH_2), 6.61

(s, 1H, C_5''–H), 7.46–7.85 (m, 11H, Ar–H, C_3''–H, and C_5'–H), 7.94 (br s, 1H, SO_2NH), 9.90 (br s, 1H, CH_2CONH), 11.84 (br s, 1H, CONH), 12.45 (br s, 1H, imidazole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 46.3 (CH_2–C), 152.5 (C-2′), 156.8 (C-1″), 159.7 (C-2), 165.1 (CONH), 167.7 (CH_2CONH), 103.5, 109.6, 112.7, 116.3, 119.7, 123.1, 129.2, 130.8, 134.6, 135.4, 137.0, 139.3, 140.5, 142.7, 144.1 (aromatic carbons, C_4, C_5, C_4', C_5', C_3'', C_4'', and C_5'') ppm. HRMS (*m/z*): 640.4653 $[M+Na]^+$; anal. calcd. for $C_{25}H_{18}Cl_2N_6O_5S_2$: C, 48.63; H, 2.94; N, 13.61; found: C, 48.55; H, 2.98; N, 13.76%.

N-*{5-[N-(2-{[4-(4-Chloro-1H-pyrrol-2-yl)-1H-imidazol-2-yl]amino}-2-oxoethyl)sulfamoyl]-4-phenylthiazol-2-yl}benzamide (**22a**)*

Yield 66% (Method A), 74% (Method B); mp 158–160°C. IR (KBr): 3377 (NH), 1676 (C═O), 1629 (C═C), 1585 (C═N), 1337–1128 (SO_2) (cm^{-1}); ^1H NMR (400 MHz, DMSO-d_6): δ 3.56 (s, 2H, CH_2), 6.64 (s, 1H, C_5''–H), 6.88 (s, 1H, C_3''–H), 7.38–7.90 (m, 11H, Ar–H and C_5'–H), 7.92 (br s, 1H, SO_2NH), 9.94 (br s, 1H, CH_2CONH), 11.47 (br s, 1H, pyrrole NH), 11.68 (br s, 1H, CONH), 12.48 (br s, 1H, imidazole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 44.5 (CH_2–C), 152.9 (C-2′), 160.2 (C-2), 164.1 (CONH), 167.4 (CH_2CONH), 104.2, 108.7, 113.4, 116.1, 119.0, 123.9, 125.7, 127.2, 129.5, 131.3, 133.6, 135.2, 137.6, 139.5, 140.2, 143.6, (aromatic carbons, C_4, C_5, C_4', C_5', C_1'', C_3'', C_4'', and C_5'') ppm. HRMS (*m/z*): 605.0393 $[M+Na]^+$; anal. calcd. for $C_{25}H_{20}ClN_7O_4S_2$: C, 51.59; H, 3.46; N, 16.85; found: C, 51.65; H, 3.40; N, 16.79%.

N-*{5-[N-(2-{[4-(4-Chloro-1H-pyrrol-2-yl)-1H-imidazol-2-yl]amino}-2-oxoethyl)sulfamoyl]-4-(p-tolyl)thiazol-2-yl}benzamide (**22b**)*

Yield 59% (Method A), 73% (Method B); mp 149–151°C. IR (KBr): 3370 (NH), 1682 (C═O), 1635 (C═C), 1570 (C═N), 1329–1135 (SO_2) (cm^{-1}); ^1H NMR (400 MHz, DMSO-d_6): δ 2.30 (s, 3H, CH_3), 3.60 (s, 2H, CH_2), 6.58 (s, 1H, C_5''–H), 6.83 (s, 1H, C_3''–H), 7.35–7.81 (m, 10H, Ar–H and C_5'–H), 7.87 (br s, 1H, SO_2NH), 9.89 (br s, 1H, CH_2CONH), 11.38 (br s, 1H, pyrrole NH), 11.70 (br s, 1H, CONH), 12.40 (br s, 1H, imidazole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.4 (CH_3–C), 43.2 (CH_2–C), 151.4 (C-2′), 159.3 (C-2), 163.4 (CONH), 166.5 (CH_2CONH), 103.7, 107.3, 109.2, 116.0, 119.5, 122.4, 123.2, 124.7, 127.9, 129.2, 130.8, 132.4, 134.7, 137.1, 139.5, 141.2 (aromatic carbons, C_4, C_5, C_4', C_5', C_1'', C_3'', C_4'', and C_5'') ppm. HRMS (*m/z*): 619.0674 $[M+Na]^+$; anal. calcd. for $C_{26}H_{22}ClN_7O_4S_2$: C, 52.39; H, 3.72; N, 16.45; found: C, 52.46; H, 3.75; N, 16.55%.

N-*{5-[N-(2-{[4-(4-Chloro-1H-pyrrol-2-yl)-1H-imidazol-2-yl]amino}-2-oxoethyl)sulfamoyl]-4-(4-chlorophenyl)thiazol-2-yl}benzamide (**22c**)*

Yield 65% (Method A), 78% (Method B); mp 165–167°C. IR (KBr): 3383 (NH), 1677 (C═O), 1646 (C═C), 1596 (C═N), 1345–1147 (SO_2) (cm^{-1}); ^1H NMR (400 MHz, DMSO-d_6): δ 3.63 (s, 2H, CH_2), 6.67 (s, 1H, C_5''–H), 6.97 (s, 1H, C_3''–H), 7.41–7.85 (m, 10H, Ar–H and C_5'–H), 7.97 (br s, 1H, SO_2NH), 10.02 (br s, 1H, CH_2CONH), 11.55 (br s, 1H, pyrrole NH), 11.73 (br s, 1H, CONH), 12.52 (br s, 1H, imidazole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 46.9 (CH_2–C), 152.7 (C-2′), 159.0 (C-2), 165.2 (CONH), 168.3 (CH_2CONH), 106.5, 109.2, 114.7, 118.3, 120.8, 123.1, 125.0, 126.4, 128.2, 129.7, 131.6, 133.1, 135.5, 137.2, 139.8, 141.7 (aromatic carbons, C_4, C_5, C_4', C_5', C_3'', C_3'', C_4'', and C_5'') ppm. HRMS (*m/z*): 639.4823 $[M+Na]^+$; anal. calcd. for $C_{25}H_{19}Cl_2N_7O_4S_2$: C, 48.71; H, 3.11; N, 15.90; found: C, 48.80; H, 3.09; N, 15.98%.

N-*{5-[N-(2-{[4-(4-Chlorofuran-2-yl)-1H-imidazol-2-yl]amino}-2-oxoethyl)sulfamoyl]-4-phenyl-1H-imidazol-2-yl}benzamide (**23a**)*

Yield 63% (Method A), 74% (Method B); mp 166–168°C. IR (KBr): 3363 (NH), 1687 (C═O), 1650 (C═C), 1582 (C═N), 1332–1136 (SO_2) (cm^{-1}); ^1H NMR (400 MHz, DMSO-d_6): δ 3.51 (s, 2H, CH_2), 6.63 (s, 1H, C_5''–H), 7.32–7.72 (m, 12H, Ar–H, C_3''–H and C_5'–H), 7.86 (br s, 1H, SO_2NH), 9.91 (br s, 1H, CH_2CONH), 11.72 (br s, 1H, CONH), 12.37 (br s, 2H, imidazole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 44.1 (CH_2–C), 150.1 (C-2 and C-2′), 157.3 (C-1″), 164.7 (CONH), 168.3 (CH_2CONH), 110.6, 113.4, 118.1, 120.5, 122.7, 126.2, 127.7, 129.5, 130.8, 132.5, 135.0, 137.6, 139.4, 141.3, 143.7 (aromatic carbons, C_4, C_5, C_4', C_5', C_3'', C_4'', and C_5'') ppm. HRMS (*m/z*): 588.9783 $[M+Na]^+$; anal. calcd. for $C_{25}H_{20}ClN_7O_5S$: C, 53.05; H, 3.56; N, 17.32; found: C, 53.14; H, 3.49; N, 17.24%.

N-*{5-[N-(2-{[4-(4-Chlorofuran-2-yl)-1H-imidazol-2-yl]amino}-2-oxoethyl)sulfamoyl]-4-(p-tolyl)-1H-imidazol-2-yl}benzamide (**23b**)*

Yield 61% (Method A), 75% (Method B); mp 155–157°C. IR (KBr): 3356 (NH), 1676 (C═O), 1633 (C═C), 1578 (C═N), 1328–1129 (SO_2) (cm^{-1}); ^1H NMR (400 MHz, DMSO-d_6): δ 2.41 (s, 3H, CH_3), 3.52 (s, 2H, CH_2), 6.47 (s, 1H, C_5''–H), 7.27–7.68 (m, 11H, Ar–H, C_3''–H and C_5'–H), 7.84 (br s, 1H, SO_2NH), 10.05 (br s, 1H, CH_2CONH), 11.87 (br s, 1H, CONH), 12.45 (br s, 2H, imidazole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.8 (CH_3–C), 42.8 (CH_2–C), 149.6 (C-2 and C-2′), 157.1 (C-1″), 163.7 (CONH), 166.3 (CH_2CONH), 109.0, 112.7, 115.5, 120.8, 125.2, 126.3, 128.6, 129.5, 131.0, 133.9, 135.1, 136.3, 138.6, 139.4, 143.6 (aromatic carbons, C_4, C_5, C_4', C_5', C_3'', C_4'', and C_5'') ppm. HRMS (*m/z*): 603.0062 $[M+Na]^+$; anal. calcd. for $C_{26}H_{22}ClN_7O_5S$: C, 53.84; H, 3.82; N, 16.90; found: C, 53.76; H, 3.87; N, 16.78%.

N-*{5-[N-(2-{[4-(4-Chlorofuran-2-yl)-1H-imidazol-2-yl]amino}-2-oxoethyl)sulfamoyl]-4-(4-chlorophenyl)-1H-imidazol-2-yl}benzamide (**23c**)*

Yield 60% (Method A), 73% (Method B); mp 181–183°C. IR (KBr): 3364 (NH), 1681 (C═O), 1641 (C═C), 1587 (C═N), 1348–1142 (SO_2) (cm^{-1}); ^1H NMR (400 MHz, DMSO-d_6): δ 3.65 (s, 2H, CH_2), 6.62 (s, 1H, C_5''–H), 7.45–7.90 (m, 11H, Ar–H, C_3''–H and C_5'–H), 8.13 (br s, 1H, SO_2NH), 9.87 (br s, 1H, CH_2CONH), 11.79 (br s, 1H, CONH), 12.50 (br s, 2H, imidazole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 45.6 (CH_2–C), 151.5 (C-2 and C-2′), 158.6 (C-1″), 165.0 (CONH), 169.4 (CH_2CONH), 112.3, 115.2, 118.6, 125.5, 127.3, 129.1, 132.3, 134.8, 137.1, 139.7, 140.5, 142.3, 143.7, 145.0, 146.1 (aromatic carbons, C_4, C_5, C_4', C_5', C_3'', C_4'', and C_5'') ppm. HRMS (*m/z*): 623.4205 $[M+Na]^+$; anal. calcd. for $C_{25}H_{19}Cl_2N_7O_5S$: C, 50.01; H, 3.19; N, 16.33; found: C, 49.92; H, 3.24; N, 16.45%.

*N-{5-[N-(2-{[4-(4-Chloro-1H-pyrrol-2-yl)-1H-imidazol-2-yl]amino}-2-oxoethyl)sulfamoyl]-4-phenyl-1H-imidazol-2-yl}benzamide (**24a**)*

Yield 65% (Method A), 77% (Method B); mp 186–188°C. IR (KBr): 3373 (NH), 1674 (C=O), 1639 (C=C), 1572 (C=N), 1335–1137 (SO_2) (cm^{-1}); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.58 (s, 2H, CH_2), 6.57 (s, 1H, C_5''–H), 6.84 (s, 1H, C_3''–H), 7.43–7.84 (m, 11H, Ar–H, and C_5'–H), 8.10 (br s, 1H, SO_2NH), 9.89 (br s, 1H, CH_2CONH), 11.36 (br s, 1H, pyrrole NH), 11.84 (br s, 1H, CONH), 12.48 (br s, 2H, imidazole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 46.1 (CH_2–C), 150.7 (C-2 and C-2′), 158.0 (C-1″), 165.8 (CONH), 168.6 (CH_2CONH), 106.8, 108.2, 117.5, 120.4, 122.0, 126.3, 128.7, 129.4, 131.6, 133.2, 136.5, 138.7, 140.3, 142.8, 145.8 (aromatic carbons, C_4, C_5, C_4', C_5', C_3'', C_4'', and C_5'') ppm. HRMS (*m/z*): 587.9943 $[M+Na]^+$; anal. calcd. for $C_{25}H_{21}ClN_8O_4S$: C, 53.15; H, 3.75; N, 19.83; found: C, 53.06; H, 3.79; N, 19.97%.

*N-{5-[N-(2-{[4-(4-Chloro-1H-pyrrol-2-yl)-1H-imidazol-2-yl]amino}-2-oxoethyl)sulfamoyl]-4-(p-tolyl)-1H-imidazol-2-yl}benzamide (**24b**)*

Yield 62% (Method A), 74% (Method B); mp 175–177°C. IR (KBr): 3358 (NH), 1671 (C=O), 1628 (C=C), 1575 (C=N), 1339–1132 (SO_2) (cm^{-1}); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.46 (s, 3H, CH_3), 3.62 (s, 2H, CH_2), 6.52 (s, 1H, C_5''–H), 6.84 (s, 1H, C_3''–H), 7.37–7.90 (m, 10H, Ar–H, and C_5'–H), 8.11 (br s, 1H, SO_2NH), 9.98 (br s, 1H, CH_2CONH), 11.42 (br s, 1H, pyrrole NH), 11.76 (br s, 1H, CONH), 12.40 (br s, 2H, imidazole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 23.2 (CH_3–C), 45.4 (CH_2–C), 149.3 (C-2 and C-2′), 157.2 (C-1″), 164.2 (CONH), 167.9 (CH_2CONH), 105.3, 107.6, 118.3, 119.5, 121.2, 123.7, 125.4, 127.0, 128.7, 131.3, 134.1, 136.4, 138.9, 140.5, 143.1 (aromatic carbons and C_4, C_5, C_4', C_5', C_3'', C_4'', C_5'') ppm. HRMS (*m/z*): 602.0213 $[M+Na]^+$; anal. calcd. for $C_{26}H_{23}ClN_8O_4S$: C, 53.93; H, 4.00; N, 19.35; found: C, 54.04; H, 4.06; N, 19.46%.

*N-{5-[N-(2-{[4-(4-Chloro-1H-pyrrol-2-yl)-1H-imidazol-2-yl]amino}-2-oxoethyl)sulfamoyl]-4-(4-chlorophenyl)-1H-imidazol-2-yl}benzamide (**24c**)*

Yield 62% (Method A), 73% (Method B); mp 194–196°C. IR (KBr): 3379 (NH), 1673 (C=O), 1643 (C=C), 1594 (C=N), 1347–1145 (SO_2) (cm^{-1}); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.69 (s, 2H, CH_2), 6.65 (s, 1H, C_5''–H), 6.98 (s, 1H, C_3''–H), 7.35–8.10 (m, 10H, Ar–H and C_5'–H), 8.24 (br s, 1H, SO_2NH), 10.05 (br s, 1H, CH_2CONH), 11.50 (br s, 1H, pyrrole NH), 11.87 (br s, 1H, CONH), 12.56 (br s, 2H, imidazole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 46.5 (CH_2–C), 151.8 (C-2 and C-2′), 158.4 (C-1″), 166.5 (CONH), 169.8 (CH_2CONH), 107.2, 109.5, 119.0, 121.4, 122.6, 125.8, 127.7, 129.1, 132.3, 135.6, 137.2, 138.5, 139.1, 141.6, 144.3 (aromatic carbons, C_4, C_5, C_4', C_5', C_3'', C_4'', and C_5'') ppm. HRMS (*m/z*): 622.4374 $[M+Na]^+$; anal. calcd. for $C_{25}H_{20}Cl_2N_8O_4S$: C, 50.09; H, 3.36; N, 18.69; found: C, 50.00; H, 3.32; N, 18.79%.

4.2 | Biological assays

Compounds **19**–**24a**–**c** were evaluated for in vitro antimicrobial activity at three different concentrations (50, 75, and 100 µg/well) using chloramphenicol for antibacterial activity and ketoconazole for antifungal activity as standard drugs.[36–39]

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CONFLICTS OF INTERESTS

The authors declare that there are no conflicts of interests.

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