Indian Journal of Chemistry
Vol. 55B, November 2016, pp. 1376-1383

Synthesis and antimicrobial activity of bisazolylsulfonyl amines

Butta Ragavendra, Kuppireddy Gari Divya, Adivireddy Padmaja & Venkatapuram Padmavathi*

Department of Chemistry, Sri Venkateswara University, Tirupati 517 502, India
E-mail: vkpuram2001@yahoo.com

Received 13 August 2015; accepted (revised) 20 July 2016

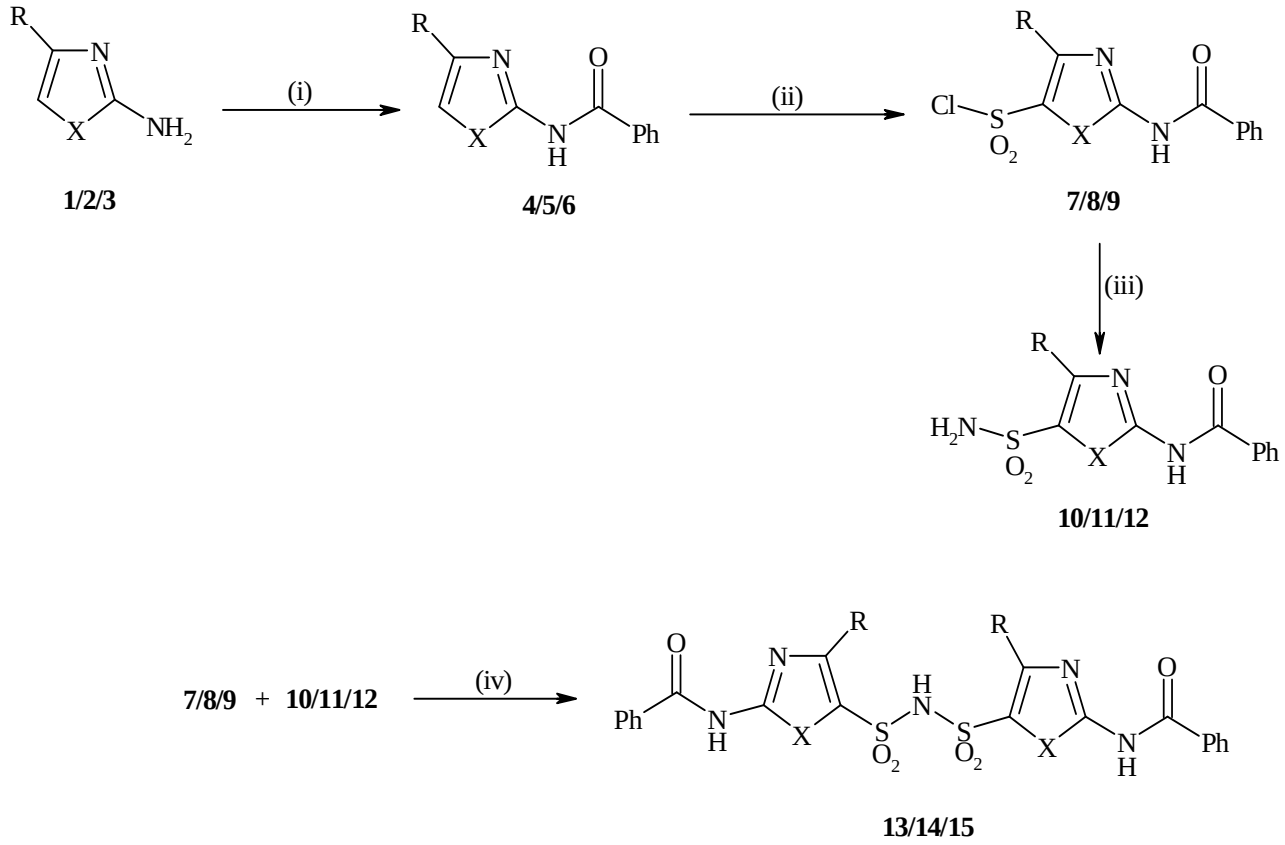
A variety of bisazolylsulfonyl amines have been prepared from azolylsulfonyl chlorides and azolylsulfonamides and their antimicrobial activity studied. The chloro substituted bisthiazolylsulfonyl amines exhibit pronounced antibacterial activity against *B. subtilis*. The unsubstituted and chloro substituted bisimidazolylsulfonyl amines show promising antifungal activity against *A. niger*.

Keywords: Oxazole, thiazole, imidazole, antimicrobial activity

In the field of medicinal chemistry, azoles which ubiquitously exists in pharmaceutical agents, have attracted a great deal of interest. 2-Alkyl oxazoles have been found in many natural products including phenoxan[1], noricumazoles[2], hennoxazoles[3], and leiodolides A & B[4]. Thiazole and its derivatives are accompanied by biological and pharmacological activities like antibacterial, antiprotozoal, antimalarial, anticancer[5], anti-allergic[6], anti-inflammatory[7] and anti-HIV infections[8]. Imidazoles are common scaffolds in highly significant biomolecules *viz*., biotin, the essential amino acid histidine, histamine and the pilocarpine alkaloids[9]. Some derivatives of imidazoles such as cimetidine, etomidate and ketoconazole have found application in drug therapy[10,11]. Thus the extensive applications and high therapeutic properties of azoles and their derivatives have encouraged an ever increasing number of synthetic chemists to enter into this field. In fact, for the last couple of years we have been involved in the synthesis of a variety of azoles linked by different pharmacophoric units and studied their biopotency[12,13]. The present work has been taken up keeping in view the encouraging results and our continued interest in the development of novel heterocycles.

Result and Discussion

The synthetic pathway approached to synthesize bisazolylsulfonyl amines is depicted in Scheme I. The *N*- aroylation of 4-aryloxazol-2-amine **1**, 4-arylthiazol-2-amine **2** and 4-aryl-1*H*-imidazol-2-amine **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 in chloroform led to 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**. The ^{1}H NMR spectra of **7a**, **8a** and **9a** displayed a broad singlet at δ 8.36, 8.27 and 8.38 due to NH besides the signals of aromatic protons. The compound **9a** showed another broad singlet at δ 11.62 due to NH of imidazole. The signals of NH disappeared on deuteration. Functionalization of sulfonyl chloride to sulfonamide in **7**, **8** and **9** 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**. The ^{1}H NMR spectra of **10a**, **11a** and **12a** exhibited two broad singlets at δ 8.41, 8.45, 8.13 and δ 6.71, 6.80, 6.54 due to NH and NH_2. Besides, compound **12a** showed another broad singlet at δ 11.58 due to NH of imidazole. The signals of highly acidic protons disappeared on deuteration. The coupling reaction between **7** and **10** in the presence of 4-dimethylaminopyridine (DMAP) and Et_3N in dichloromethane resulted in bissulfonyl amino linked bis heterocycles- bis(2-benzamido-4-aryloxazol-5-ylsulfonyl)amine **13**. Similarly bis(2-benzamido-4-arylthiazol-5-ylsulfonyl)amine **14** was prepared by the reaction of **8** with **11**. Likewise, the reaction of **9** with **12** produced bis(2-benzamido-4-aryl-1*H*-imidazol-5-



Scheme I — Synthesis of bisazolylsulfonyl amines

ylsulfonyl)amine **15**. The ^{1}H NMR spectra of **13a**, **14a** and **15a** displayed two broad singlets at δ 8.50, 8.46, 8.43 and δ 8.03, 7.95, 7.91 due to NH of amido and sulfonamido groups in addition to the signals of aromatic protons. The structures of all the compounds were further ascertained by IR, ^{13}C NMR, HRMS and elemental analyses.

Antimicrobial activity

The *in vitro* antimicrobial studies were carried out by agar well diffusion method against test organisms[14,15]. Nutrient broth (NB) plates were swabbed with 24 h old broth culture (100 µL) of test bacteria. Using the sterile cork borer, wells (6 mm) were made into each petriplate. The compounds were dissolved in DMSO (5 mg/mL) and from this, 10 and 20 µL (50 and 100 µg/well) were added into the wells by using sterile pipettes. Simultaneously, the standard antibiotics, chloramphenicol for antibacterial activity and ketocon-azole for antifungal activity (as positive control) were tested against the pathogens. The samples were dissolved in DMSO which showed no zone of inhibition and acts as negative control. The plates were incubated at 37°C for 24 h for bacteria and at 28°C for 48 h for fungi. After appropriate incubation, the diameter of zone of inhibition of each well was measured. Triplicates were maintained and the average values were calculated for eventual antimicrobial activity.

The compounds **13-15** were screened for antibacterial activity at two different concentrations, 50 and 100 µg/well and the results are presented in

Table I and Figure 1. The data revealed that Gram-positive bacteria were more susceptible towards the tested compounds than Gram-negative ones. The compounds showed slightly higher activity against *B. subtilis* than against *S. aureus*. Amongst all the compounds bisthiazolylsulfonyl amines **14** displayed higher activity than bisoxazolylsulfonyl amines **13** and bisimidazolylsulfonyl amines **15**. Amongst the latter compounds, **15** showed higher activity than **13**. In fact, the compound **13b** exhibited no activity against both Gram-positive and Gram-negative bacteria. It was also observed that the presence of electron withdrawing chloro substituent on the aromatic ring increases the activity. The compound **14c** displayed higher activity than the standard drug chloramphenicol against *B. subtilis* at both concentrations.

The compounds **13-15** were also tested for antifungal activity against *A. niger* and *P. chrysogenum* at 50 and 100 µg/well and the results are depicted in Table II and

Table II — The *in vitro* antifungal activity of compounds **13-15**

Compd	Zone of Inhibition (mm)			
	A. niger		*P. chrysogenum*	
	50 µg/well	100 µg/well	50 µg/well	100 µg/well
13a	–	10±1	–	9±2
13b	–	–	–	–
13c	17±1	20±2	12±3	15±2
14a	26±3	29±1	18±2	20±3
14b	19±2	22±3	13±1	17±2
14c	28±1	30±2	19±1	24±3
15a	31±2	36±1	23±3	26±1
15b	22±1	25±3	15±1	19±2
15c	34±3	38±2	27±1	30±3
Ketoconazole	33±1	36±2	36±3	38±1
Control (DMSO)	–	–	–	–

(–) No activity

Table I — The *in vitro* antibacterial activity of compounds **13-15**

Compd	Zone of Inhibition (mm)							
	Gram-positive bacteria				Gram-negative bacteria			
	S. aureus		*B. subtilis*		*P. aeruginosa*		*K. pneumoniae*	
	50 µg/well	100 µg/well	50 µg/well	100 µg/well	50 µg/well	100 µg/well	50 µg/well	100 µg/well
13a	–	10±2	10±3	12±2	–	8±2	–	10±1
13b	–	–	–	–	–	–	–	–
13c	13±2	15±3	16±1	20±2	11±1	14±2	15±1	17±3
14a	26±1	29±2	33±1	37±3	22±2	24±3	30±2	34±1
14b	18±3	20±1	21±2	25±1	15±3	19±2	22±1	26±3
14c	30±1	32±3	36±1	40±2	23±1	27±3	32±2	37±1
15a	20±2	22±1	27±3	29±1	18±2	21±1	24±3	28±2
15b	16±1	18±2	19±1	22±2	14±3	17±2	18±1	20±3
15c	24±3	26±1	28±2	32±3	20±1	23±3	27±2	31±1
Chloramphenicol	33±1	35±3	34±2	38±1	27±2	30±1	40±3	42±2
Control (DMSO)	–	–	–	–	–	–	–	–

(–) No activity

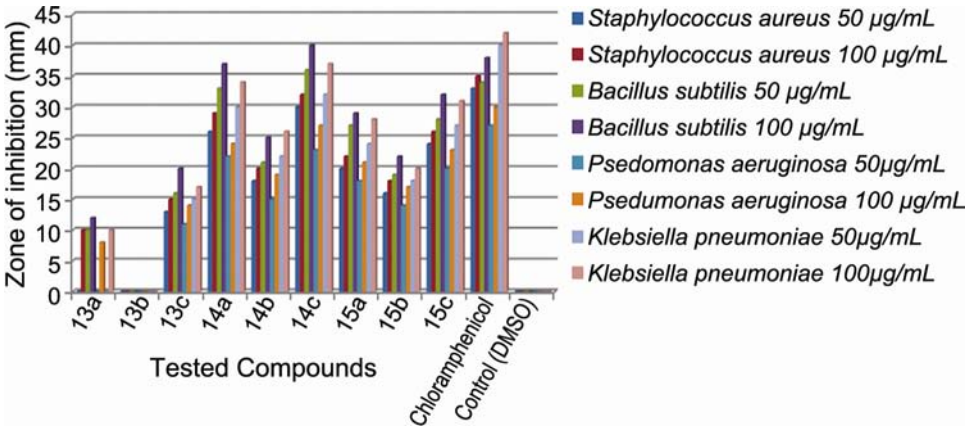


Figure 1 — The *in vitro* antibacterial activity of compounds **13-15**

Figure 2. The bisimidazolylsulfonyl amines **15** displayed promising activity against *A. niger* than against *P. chrysogenum*. The compound **15c** exhibited greater activity than the standard drug ketoconazole at all tested concentrations. The compound **15a** showed equal activity to the standard drug at 100 µg/well. The bisthiazolylsulfonyl amines **14** showed moderate to good activity whereas bisoxazolylsulfonyl amines **13** exhibited the least activity. The presence of electron withdrawing chloro substituent on the aromatic ring increases the activity.

Experimental Section

Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected. The homogeneity of the compounds was checked by TLC (silica gel H, BDH, ethyl acetate / hexane, 1:3). The IR spectra were recorded on a Thermo Nicolet IR 200 FT-IR spectrometer as KBr pellets and the wave numbers are given in cm^{-1}. The ^1H NMR spectra were recorded in DMSO-d_6 on a Bruker-400 spectrometer operating at 400 MHz. The ^{13}C NMR spectra were recorded in DMSO-d_6 on a Bruker spectrometer operating at 100 MHz. All chemical shifts are reported in (ppm) using TMS as an internal standard. The high-resolution mass spectra were recorded on micromass Q-TOF micromass spectrometer using electrospray ionization. The microanalyses were performed on a Perkin-Elmer 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). The starting compounds 4-aryloxazol-2-amine **1**, 4-arylthiazol-2-amine **2** and 4-aryl-1*H*-imidazol-2-amine **3** were prepared as per the literature precedents[16-18].

General procedure for the synthesis of N-(5-(chlorosulfonyl)-4-aryloxazol/thiazol/imidazol-2-yl) benzamide, 7/8/9

Chlorosulfonic acid (8.0 mmol) was added drop-wise to a cooled and stirred solution of *N*-(4-aryloxazol/thiazol/imidazol-2-yl)benzamide **4/5/6** (1.0 mmol) in chloroform (5 mL) and stirring was continued for 4-6 h at RT. The contents were poured into ice-cold water. The organic layer was separated and the aqueous layer was extracted with chloroform. The combined organic extract was dried over anhydrous magnesium sulfate and the solvent was removed under vacuum. The resultant solid was purified by recrystallization from 2-propanol.

N-(5-(Chlorosulfonyl)-4-phenyloxazol-2-yl)benzamide, 7a: Yield 65%. m.p.102-104°C. IR (KBr): 3355, 1664, 1562, 1326 and 1125 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H 7.31-7.92 (m, 10H, Ar-H), 8.36 (bs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 125.2, 127.5, 127.8, 128.2, 128.9, 129.3, 129.7, 130.5, 131.2 137.6, 151.9, 166.7; HRMS: *m/z* 385.7779 [M+Na]. Anal. Calcd for $C_{16}H_{11}ClN_2O_4S$: C, 52.97; H, 3.06; N, 7.72. Found: C, 53.92; H, 3.04; N, 7.83%.

N-(5-(Chlorosulfonyl)-4-*p*-tolyloxazol-2-yl)benzamide, 7b: Yield 67%. m.p.95-97°C. IR (KBr): 3352, 1667, 1569, 1324 and 1128 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H 2.36 (s, 3H, Ar-CH_3), 7.26-7.78 (m, 9H, Ar-H), 8.39 (bs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 24.7, 126.0, 126.2, 126.5, 127.2, 127.7, 128.0, 128.5, 129.1, 129.4, 136.3, 151.2, 167.4; HRMS: *m/z* 399.8042 [M+Na]. Anal. Calcd for $C_{17}H_{13}ClN_2O_4S$: C, 54.19; H, 3.48; N, 7.43. Found: C, 54.27; H, 3.52; N, 7.60%.

N-(4-(*p*-Chlorophenyl)-5-(chlorosulfonyl)oxazol-2-yl)benzamide, 7c: Yield 68%. m.p.113-15°C. IR (KBr): 3364, 1672, 1576, 1331 and 1140 cm^{-1}; ^1H NMR (400

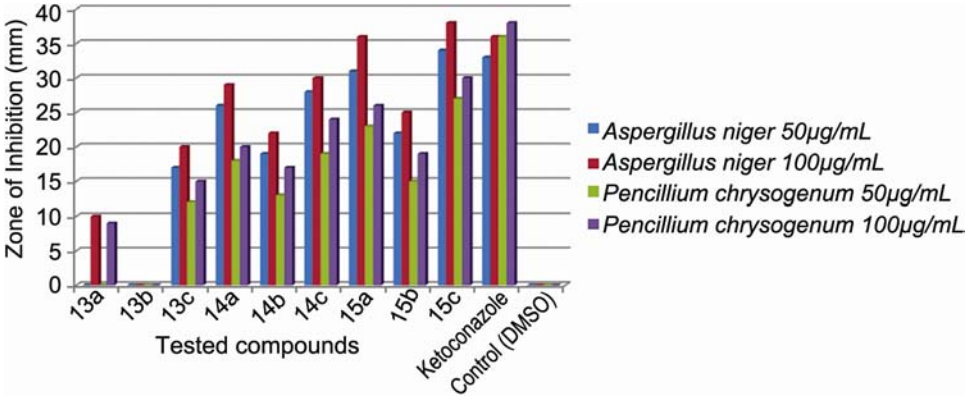


Figure 2 — The *in vitro* antifungal activity of compounds **13-15**

MHz, DMSO-d_6): δ_H 7.37-7.98 (m, 9H, Ar-H), 8.42 (bs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 126.8, 128.3, 128.6, 129.0, 129.8, 130.2, 130.5, 131.3, 131.6, 137.2, 152.4, 167.9; HRMS: *m/z* 420.2229 [M+Na]. Anal. Calcd for $C_{16}H_{10}Cl_2N_2O_4S$: C, 48.38; H, 2.54; N, 7.04. Found: C, 48.50; H, 2.55; N, 7.24%.

N-(5-(Chlorosulfonyl)-4-phenylthiazol-2-yl) benzamide, 8a: Yield 63%. m.p.107-109°C. IR (KBr): 3369, 1675, 1582, 1334 and 1131 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 7.20-7.83 (m, 10H, Ar-H), 8.27 (bs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 114.5, 128.5, 128.8, 129.6, 130.1, 130.7, 130.9, 131.6, 131.8, 151.3, 164.7, 169.4; HRMS: *m/z* 401.8425 [M+Na]. Anal. Calcd for $C_{16}H_{11}ClN_2O_3S_2$: C, 50.72; H, 2.93; N, 7.39. Found: C, 50.79; H, 2.96; N, 7.52%.

N-(5-(Chlorosulfonyl)-4-*p*-tolylthiazol-2-yl) benzamide, 8b: Yield 62%. m.p.103-105°C. IR (KBr): 3374, 1670, 1577, 1330 and 1127 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 2.42 (s, 3H, Ar-CH_3), 7.12-7.75 (m, 9H, Ar-H), 8.32 (bs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 25.3, 114.1, 126.4, 126.9, 127.2, 127.6, 128.0, 128.3, 129.5, 130.3, 150.1, 164.4, 167.1; HRMS: *m/z* 415.8690 [M+Na]. Anal. Calcd for $C_{17}H_{13}ClN_2O_3S_2$: C, 51.97; H, 3.34; N, 7.13. Found: C, 51.92; H, 3.32; N, 7.25%.

N-(4-(*p*-Chlorophenyl)-5-(chlorosulfonyl)thiazol-2-yl)benzamide, 8c: Yield 69%. m.p.117-19°C. IR (KBr): 3365, 1684, 1589, 1343 and 1145 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 7.34-7.91 (m, 9H, Ar-H), 8.45 (bs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 115.6, 127.1, 127.8, 128.4, 128.7, 129.2, 129.8, 130.1, 130.6, 150.8, 165.3, 169.0; HRMS: *m/z* 436.2872 [M+Na]. Anal. Calcd for $C_{16}H_{10}Cl_2N_2O_3S_2$: C, 46.50; H, 2.44; N, 6.78. Found: C, 46.64; H, 2.46; N, 7.04%.

N-(5-(Chlorosulfonyl)-4-phenyl-1*H*-imidazol-2-yl) benzamide, 9a: Yield 67%. m.p.122-25°C. IR (KBr): 3368, 1669, 1572, 1329 and 1142 cm^{-1}; ^{1}H NMR 400 MHz, DMSO-d_6): δ_H 7.12-7.72 (m, 10H, Ar-H), 8.38 (bs, 1H, NH), 11.62 (bs, 1H, Imidazole-NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 121.5, 126.2, 126.7, 127.0, 127.4, 127.9, 128.2, 128.6, 128.9, 129.3, 140.9, 166.2; HRMS: *m/z* 384.7930 [M+Na]. Anal. Calcd for $C_{16}H_{12}ClN_3O_3S$: C, 53.12; H, 3.34; N, 11.61. Found: C, 53.20; H, 3.38; N, 11.75%.

N-(5-(Chlorosulfonyl)-4-*p*-tolyl-1*H*-imidazol-2-yl) benzamide, 9b: Yield 66%. m.p.116-18°C. IR (KBr): 3367, 1674, 1567, 1336 and 1133 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 2.31 (s, 3H, Ar-CH_3), 7.03-7.63 (m, 9H, Ar-H), 8.32 (bs, 1H, NH), 12.34 (bs, 1H, Imidazole-NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 24.5, 121.7, 126.8, 127.3, 127.7, 128.1, 128.4, 128.9, 129.0, 130.2, 130.4 140.5, 166.9; HRMS: *m/z* 398.8199 [M+Na]. Anal. Calcd for $C_{17}H_{14}ClN_3O_3S$: C, 54.33; H, 3.75; N, 11.18. Found: C, 54.44; H, 3.76; N, 11.35%.

N-(4-(*p*-Chlorophenyl)-5-(chlorosulfonyl)-1*H*-imidazol-2-yl)benzamide, 9c: Yield 68%. m.p.131-33°C. IR (KBr): 3372, 1681, 1578, 1340 and 1137 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 7.38-7.95 (m, 9H, Ar-H), 8.29 (bs, 1H, NH), 12.40 (bs, 1H, Imidazole-NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 120.2, 127.0, 127.3, 128.1, 129.2, 129.6, 129.8, 130.5, 130.9, 131.6, 141.0, 167.5; HRMS: *m/z* 419.2368 [M+Na]. Anal. Calcd for $C_{16}H_{11}Cl_2N_3O_3S$: C, 48.50; H, 2.80; N, 10.60. Found: C, 48.56; H, 2.82; N, 10.75%.

General procedure for the synthesis of N-(5-(aminosulfonyl)-4-aryloxazol/thiazol/imidazol-2-yl) benzamide, 10/11/12

The *N*-(5-(chlorosulfonyl)-4-aryloxazol/thiazol/imidazol-2-yl)benzamide **7/8/9** (1.0 mmol) was suspended in 25% ammonium hydroxide (7.25 mL) and stirred at RT for 3-5 h. It was diluted with water. The compound separated was filtered, washed with water, dried and purified by recrystallization from 2-propanol.

N-(5-(Aminosulfonyl)-4-phenyloxazol-2-yl)benzamide, 10a: Yield 73%. m.p.145-47°C. IR (KBr): 3445 and 3328, 3363, 1668, 1568, 1322 and 1134 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 6.71 (bs, 2H, NH_2), 7.12-7.84 (m, 10H, Ar-H), 8.41 (bs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 125.4, 127.2, 127.8, 128.3, 128.5, 129.0, 129.4, 129.6, 130.2, 137.5, 151.8, 167.2; HRMS: *m/z* 366.0531 [M+Na]. Anal. Calcd for $C_{16}H_{13}N_3O_4S$: C, 55.97; H, 3.82; N, 12.24. Found: C, 56.06; H, 3.85; N, 12.41%.

N-(5-(Aminosulfonyl)-4-*p*-tolyloxazol-2-yl)benzamide, 10b: Yield 72%. m.p.139-41°C. IR (KBr): 3439 and 3319, 3350, 1665, 1565, 1320 and 1129 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 2.34 (s, 3H, Ar-CH_3), 6.74 (bs, 2H, NH_2), 7.25-7.76 (m, 9H, Ar-H), 8.43 (bs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 24.7, 125.1, 126.7, 126.9, 127.5, 128.1, 128.6, 128.9, 129.5, 129.8, 137.9, 151.6, 167.6; HRMS: *m/z* 380.3726 [M+Na]. Anal. Calcd for $C_{17}H_{15}N_3O_4S$: C, 57.13; H, 4.23; N, 11.76. Found: C, 57.26; H, 4.24; N, 11.97%.

N-(4-(*p*-Chlorophenyl)-5-(aminosulfonyl)oxazol-2-yl)benzamide, 10c: Yield 75%. m.p.166-68°C. IR

(KBr): 3452 and 3335, 3357, 1671, 1570, 1329 and 1142 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H 6.82 (bs, 2H, NH_2), 7.35-7.91 (m, 9H, Ar-H), 8.38 (bs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 126.7, 127.3, 128.4, 129.1, 130.4, 130.7, 131.3, 131.7, 132.4, 137.0, 152.3, 167.9; Ar-H), 8.43 (bs, 1H, NH); HRMS: *m/z* 400.7925 [M+Na]. Anal. Calcd for $C_{16}H_{12}ClN_3O_4S$: C, 50.87; H, 3.20; N, 11.12. Found: C, 50.98; H, 3.16; N, 11.31%.

N-(5-(Aminosulfonyl)-4-phenylthiazol-2-yl)benzamide, 11a: Yield 76%. m.p.141-43°C. IR (KBr): 3455 and 3345, 3360, 1666, 1578, 1336 and 1129 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H 6.80 (bs, 2H, NH_2), 7.22-7.87 (m, 10H, Ar-H), 8.45 (bs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 115.8, 126.8, 127.1, 127.6, 127.9, 128.1, 128.7, 129.3, 129.7, 151.5, 165.6, 166.5; Ar-H), 8.43 (bs, 1H, NH); HRMS: *m/z* 382.4132 [M+Na]. Anal. Calcd for $C_{16}H_{13}N_3O_3S_2$: C, 53.47; H, 3.64; N, 11.69. Found: C, 53.54; H, 3.66; N, 11.84%.

N-(5-(Aminosulfonyl)-4-*p*-tolylthiazol-2-yl)benzamide, 11b: Yield 75%. m.p.149-51°C. IR (KBr): 3432 and 3352, 3364, 1673, 1573, 1328 and 1142 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H 2.31 (s, 3H, Ar-CH_3), 6.67 (bs, 2H, NH_2), 7.17-7.79 (m, 9H, Ar-H), 8.49 (bs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 24.2, 114.2, 126.5, 127.4, 127.8, 128.0, 128.5, 129.2, 130.6, 130.9, 150.4, 166.7, 168.2; Ar-H), 8.43 (bs, 1H, NH); HRMS: *m/z* 396.4386 [M+Na]. Anal. Calcd for $C_{17}H_{15}N_3O_3S_2$: C, 54.67; H, 4.05; N, 11.25. Found: C, 54.62; H, 4.06; N, 11.37%.

N-(4-(*p*-Chlorophenyl)-5-(aminosulfonyl)thiazol-2-yl)benzamide, 11c: Yield 72%. m.p.172-74°C. IR (KBr): 3461 and 3356, 3371, 1679, 1584, 1332 and 1147 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H 7.12 (bs, 2H, NH_2), 7.25-7.83 (m, 9H, Ar-H), 8.51 (bs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 116.7, 127.7, 128.1, 129.0, 129.3, 129.7, 130.1, 130.5, 130.8, 151.2, 164.4, 166.8; Ar-H), 8.43 (bs, 1H, NH); HRMS: *m/z* 416.8581 [M+Na]. Anal. Calcd for $C_{16}H_{12}ClN_3O_3S_2$: C, 48.79; H, 3.07; N, 10.67. Found: C, 48.91; H, 3.04; N, 10.88%.

N-(5-(Aminosulfonyl)-4-phenyl-1*H*-imidazol-2-yl)benzamide, 12a: Yield 77%. m.p.161-63°C. IR (KBr): 3457 and 3349, 3367, 1675, 1574, 1327 and 1136 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H 6.54 (bs, 2H, NH_2), 7.06-7.75 (m, 10H, Ar-H), 8.13 (bs, 1H, NH), 11.58 (bs, 1H, Imidazole-NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 120.5, 126.2, 126.9, 127.2, 127.4, 128.3, 128.9, 129.2, 129.4, 130.6, 141.8, 166.2; Ar-H), 8.43 (bs, 1H, NH); HRMS: *m/z* 365.3628 [M+Na]. Anal. Calcd for $C_{16}H_{14}N_4O_3S$: C, 56.13; H, 4.12; N, 16.36. Found: C, 56.27; H, 4.10; N, 16.63%.

N-(5-(Aminosulfonyl)-4-*p*-tolyl-1*H*-imidazol-2-yl)benzamide, 12b: Yield 74%. m.p.156-58°C. IR (KBr): 3448 and 3337, 3372, 1669, 1563, 1321 and 1130 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H 2.28 (s, 3H, Ar-CH_3), 6.28 (bs, 2H, NH_2), 7.19-7.68 (m, 9H, Ar-H), 8.29 (bs, 1H, NH), 12.30 (bs, 1H, Imidazole -NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 24.5, 120.3, 126.3, 126.6, 127.5, 127.9, 128.2, 128.6, 128.8, 129.3, 130.2, 140.1, 168.5; Ar-H), 8.43 (bs, 1H, NH); HRMS: *m/z* 379.3893 [M+Na]. Anal. Calcd for $C_{17}H_{16}N_4O_3S$: C, 57.29; H, 4.52; N, 15.72. Found: C, 57.37; H, 4.56; N, 15.88%.

N-(4-(*p*-Chlorophenyl)-5-(aminosulfonyl)-1*H*-imidazol-2-yl)benzamide, 12c: Yield 73%. m.p.179-81°C. IR (KBr): 3465 and 3361, 3380, 1683, 1579, 1334 and 1145 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H 6.73 (bs, 2H, NH_2), 7.26-7.89 (m, 9H, Ar-H), 8.44 (bs, 1H, NH), 11.54 (bs, 1H, Imidazole-NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 121.9, 127.5, 128.0, 128.2, 128.7, 129.5, 129.8, 130.4, 130.8, 131.2, 141.5, 168.2; Ar-H), 8.43 (bs, 1H, NH); HRMS: *m/z* 399.8077 [M+Na]. Anal. Calcd for $C_{16}H_{13}ClN_4O_3S$: C, 51.00; H, 3.48; N, 14.87. Found: C, 51.13; H, 3.49; N, 15.12%.

General procedure for the synthesis of bis (2-benzamido-4-aryloxazol/thiazol/imidazol-5-ylsulfonyl)-amine, 13/14/15

To a solution of *N*-(5-(aminosulfonyl)-4-aryloxazol/thiazol/imidazol-2-yl)benzamide **10/11/12** (3.0 mmol) in dichloromethane (10 mL), triethylamine (3.1 mmol) and 4-dimethylaminopyridine (DMAP, 0.1 mmol) were added and stirred at RT for 15 min. Thereafter, a solution of *N*-(5-(chlorosulfonyl)-4-aryloxazol/thiazol/imidazol-2-yl)benzamide **7/8/9** (3.3 mmol) in dichloromethane (5 mL) was added drop-wise and the reaction mixture was stirred at 40°C under nitrogen atmosphere for 7-10 h. After completion of reaction the solvent was removed *in vacuo*. The resultant residue was neutralized with saturated $NaHCO_3$ solution. The aqueous layer was extracted with ethyl acetate, washed with water and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the solid obtained was purified by column chromatography (silica gel, 60-120 mesh) using hexane:ethyl acetate (3:1) as eluent.

Bis(2-Benzamido-4-phenyloxazol-5-ylsulfonyl) amine, 13a: Yield 69%. m.p.161-63°C. IR (KBr): 3376, 1690, 1576, 1318 and 1133 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H 7.20-7.95 (m, 20H, Ar-H), 8.03 (bs, 1H, NH-SO_2), 8.50 (bs, 2H, NH-CO); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 126.9, 127.1, 127.6, 128.8, 129.2, 129.9, 130.1, 130.5, 131.6, 138.2, 152.6, 168.1; HRMS: *m/z* 692.6741 [M+Na]. Anal. Calcd for $C_{32}H_{23}N_5O_8S_2$: C, 57.39; H, 3.46; N, 10.46. Found: C, 57.48; H, 3.48; N, 10.63%.

Bis(2-Benzamido-4-*p*-tolyloxazol-5-ylsulfonyl) amine, 13b: Yield 66%. m.p.155-57°C. IR (KBr): 3369, 1672, 1560, 1324 and 1131 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H 2.40 (s, 6H, Ar-CH_3), 7.08-7.84 (m, 18H, Ar-H), 8.07 (bs, 1H, NH-SO_2), 8.48 (bs, 2H, NH-CO); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 24.9, 125.3, 126.8, 127.4, 127.9, 128.2, 128.5, 129.6, 130.3, 131.4, 138.7, 152.5, 165.8; HRMS: *m/z* 720.1191 [M+Na]. Anal. Calcd for $C_{34}H_{27}N_5O_8S_2$: C, 58.53; H, 3.90; N, 10.04. Found: C, 58.47; H, 3.93; N, 10.18%.

Bis(2-Benzamido-4-(*p*-chlorophenyl)oxazol-5-ylsulfonyl)amine, 13c: Yield 72%. m.p.169-71°C. IR (KBr): 3388, 1686, 1585, 1329 and 1141 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H 7.31-7.92 (m, 18H, Ar-H), 7.98 (bs, 1H, NH-SO_2), 8.52 (bs, 2H, NH-CO); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 126.5, 127.6, 128.1, 128.9, 129.1, 129.5, 129.8, 130.6, 131.9, 137.2, 151.8, 168.3; HRMS: *m/z* 761.5642 [M+Na]. Anal. Calcd for $C_{32}H_{21}Cl_2N_5O_8S_2$: C, 52.04; H, 2.87; N, 9.48. Found: C, 52.14; H, 2.86; N, 9.67%.

Bis(2-Benzamido-4-phenylthiazol-5-ylsulfonyl) amine, 14a: Yield 71%. m.p.176-78°C. IR (KBr): 3362, 1674, 1573, 1335 and 1135 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H 7.95 (bs, 1H, NH-SO_2), 7.24-7.98 (m, 20H, Ar-H), 8.46 (bs, 2H, NH-CO); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 115.9, 127.2, 127.8, 128.3, 128.6, 129.4, 129.8, 130.2, 130.8, 151.6, 165.4, 168.4; HRMS: *m/z* 724.8053 [M+Na]. Anal. Calcd for $C_{32}H_{23}N_5O_6S_4$: C, 54.76; H, 3.30; N, 9.98. Found: C, 54.84; H, 3.34; N, 10.15%.

Bis(2-Benzamido-4-*p*-tolylthiazol-5-ylsulfonyl) amine, 14b: Yield 70%. m.p.163-65°C. IR (KBr): 3370, 1666, 1562, 1323 and 1140 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H 2.36 (s, 6H, Ar-CH_3), 7.19-7.83 (m, 18H, Ar-H), 8.12 (bs, 1H, NH-SO_2), 8.37 (bs, 2H, NH-CO); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 23.6, 116.6, 126.2, 126.9, 127.1, 127.5, 128.2, 129.5, 129.9, 130.5, 150.3, 165.8, 166.2; HRMS: *m/z* 752.8568 [M+Na]. Anal. Calcd for $C_{34}H_{27}N_5O_6S_4$: C, 55.95; H, 3.73; N, 9.60. Found: C, 55.90; H, 3.75; N, 9.73%.

Bis(2-Benzamido-4-(*p*-chlorophenyl)thiazol-5-ylsulfonyl)amine, 14c: Yield 73%. m.p.184-86°C. IR (KBr): 3377, 1682, 1590, 1342 and 1144 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H 7.11-7.87 (m, 18H, Ar-H), 8.05 (bs, 1H, NH-SO_2), 8.57 (bs, 2H, NH-CO); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 116.9, 126.0, 126.6, 127.3, 127.6, 128.7, 129.3, 130.0, 130.6, 151.4, 165.2, 168.7; HRMS: *m/z* 793.6957 [M+Na]. Anal. Calcd for $C_{32}H_{21}Cl_2N_5O_6S_4$: C, 49.87; H, 2.75; N, 9.08. Found: C, 50.00; H, 2.78; N, 9.32%.

Bis(2-Benzamido-4-phenyl-1*H*-imidazol-5-ylsulfonyl) amine, 15a: Yield 72%. m.p.190-92°C. IR (KBr): 3372, 1670, 1561, 1330 and 1147 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H 7.02-7.81 (m, 20H, Ar-H), 7.91 (bs, 1H, NH-SO_2), 8.43 (bs, 2H, NH-CO), 11.63 (bs, 2H, Imidazole-NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 121.8, 127.0, 127.8, 128.4, 128.8, 129.2, 129.6, 130.2, 130.5, 131.2, 141.9, 167.9; HRMS: *m/z* 690.7090 [M+Na]. Anal. Calcd for $C_{32}H_{25}N_7O_6S_2$: C, 57.56; H, 3.77; N, 14.68. Found: C, 57.65; H, 3.76; N, 14.87%.

Bis(2-Benzamido-4-*p*-tolyl-1*H*-imidazol-5-ylsulfonyl)amine, 15b: Yield 73%. m.p.195-97°C. IR (KBr): 3368, 1676, 1569, 1325 and 1136 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H 2.31 (s, 6H, Ar-CH_3), 7.86 (bs, 1H, NH-SO_2), 7.13-7.92 (m, 18H, Ar-H), 8.39 (bs, 2H, NH-CO), 11.60 (bs, 2H, Imidazole-NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 24.1, 120.4, 126.4, 126.7, 127.5, 128.0, 128.2, 128.6, 129.2, 130.1, 130.8, 142.3, 167.3; HRMS: *m/z* 718.7566 [M+Na]. Anal. Calcd for $C_{34}H_{29}N_7O_6S_2$: C, 58.69; H, 4.20; N, 14.09. Found: C, 58.76; H, 4.24; N, 14.25%.

Bis(2-Benzamido-4-(*p*-chlorophenyl)-1*H*-imidazol-5-ylsulfonyl)amine, 15c: Yield 76%. m.p.206-208°C. IR (KBr): 3361, 1685, 1575, 1337 and 1151 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H 7.29-7.96 (m, 18H, Ar-H), 8.12 (bs, 1H, NH-SO_2), 8.55 (bs, 2H, NH-CO), 12.29 (bs, 2H, Imidazole-NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 121.7, 127.3, 128.3, 128.7, 129.4, 129.7, 130.2, 130.4, 131.5, 131.9, 142.1, 168.5; HRMS: *m/z* 759.5949 [M+Na]. Anal. Calcd for $C_{32}H_{23}Cl_2N_7O_6S_2$: C, 52.18; H, 3.15; N, 13.31. Found: C, 52.32; H, 3.18; N, 13.57%.

Conclusion

A variety of bisazolylsulfonyl amines were prepared from azolylsulfonyl chlorides and azolylsulfonamides and their antimicrobial activity studied. The chloro substituted bisthiazolylsulfonyl amine exhibited pronounced antibacterial activity against ***B. subtilis***.

The unsubstituted and chloro substituted bisimidazolylsulfonyl amines showed promising antifungal activity against *A. niger*.

Acknowledgements

The authors are grateful to Board of Research in Nuclear Sciences (BRNS), Mumbai for financial assistance under major research project. One of the authors K. Divya is thankful to University Grants Commission (UGC), New Delhi for the sanction of UGC-BSR fellowship.

References

1 Jansen R, Kunze B, Wray V, Reichenbach H, Jurkiewicz E, Hunsmann G & Höfle G, *Liebigs Ann Chem*, 7 (1991) 707.

2 Barbier J, Jansen R, Irschik H, Benson S, Gerth K, Böhlendorf B, Höfle G, Reichenbach H, Wegner J, Zeilinger C, Kirschning A & Müller R, *Angew Chem Int Ed*, 51 (2012) 1256.

3 Ichiba T, Yoshida W Y, Scheuer P J, Higa T & Gravalos D G, *J Am Chem Soc*, 113 (1991) 3173.

4 Sandler J S, Colin P L, Kelly M & Fenical W, *J Org Chem*, 71 (2006) 7245.

5 Hutchinson I, Jennings S A, Vishnuvajjala B R, Westwell A D & Stevens M F G, *J Med Chem*, 45 (2002) 744.

6 (a) Hargrave K D, Hess F K & Oliver J T, *J Med Chem*, 26 (1983) 1158; (b) Gronowitz S, in *The Chemistry of Heterocyclic Compounds: Thiophene and its Derivatives*, Vol. 44, Part 3, (Chapter 2) edited by Gronowitz S (Wiley, New York, NY, USA) (1991).

7 Sharma R N, Xavier F P, Vasu K K, Chaturvedi S C & Pancholi S S, *J Enzyme Inhib Med Chem*, 24 (2009) 890.

8 Kempf D J, Sham H L, Marsh K C, Flentge C A, Betebenner D, Green B E, McDonald E, Vasavanonda S, Saldivar A, Wideburg N E, Kati W M, Ruiz L, Zhao C, Fino L M, Patterson J, Molla A, Plattner J J & Norbeck D W, *J Med Chem*, 41 (1998) 602.

9 Grimmett M R, in *Comprehensive Heterocyclic Chemistry II*, Vol. 3, edited by Katritsky A R and Scriven E F V (Pergamon, Oxford), pp.77-220 (1996).

10 (a) *Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry*, 10th edn, edited by Delgado J N and Remers W A (Lippincott-Raven, Philadelphia, PA), p.4614 (1998); (b) Bellina F, Cauteruccio S & Rossi R, *Tetrahedron*, 63 (2007) 4571.

11 Coura J R & de Castro S L, *Mem Inst Oswaldo Cruz*, 97 (2002) 3.

12 Reddy P R, Seenaiah D, Padmaja A, Padmavathi V & Krishna N S, *Med Chem Res*, 24 (2015) 86.

13 Premakumari C, Muralikrishna A, Padmaja A, Padmavathi V, Park S J, Kim T J & Reddy G D, *Arabian J Chem*, 7 (2014) 385.

14 Azoro C, *World J Biotechnol*, 3 (2002) 347.

15 Chung K T, Thomasson W R & Wu-Yuan C D, *J Appl Bacteriol*, 69 (1990) 498.

16 Pattanayak B K, Rout D N & Mahapatra G N, *Indian J Chem*, 16B (1978) 1030.

17 Kidwai M, Dave B & Bhushan K R, *Chem Papers*, 54 (2000) 231.

18 Little T L & Webber S E, *J Org Chem*, 59 (1994) 7299.