Synthesis and Antimicrobial Activity of Azole Derivatives

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A new class of mono and bis heterocycles, sulfonylmethaneamido linked oxazoles, thiazoles, imidazoles, pyrrolyl oxazoles, pyrrolyl thiazoles and pyrrolyl imidazoles were prepared adopting simple and versatile synthetic methodologies. The compound chloro substituted imidazolyl styrylsulfonylacetamide is the most potent antimicrobial agent particularly against *Pseudomonas aeruginosa* and *Penicillium chrysogenum*.

Key words oxazole; thiazole; imidazole; pyrrole; antimicrobial activity

The ubiquity of azoles in a wide variety of naturally occurring and synthetic molecules and their pivotal role as synthetic intermediates has attracted the attention of both industrial and academic communities. In particular mixed *N,S*- or *N,O*-heterocycles such as thiazoles and oxazoles are thiopeptide antibiotics^{1,2} and are recognized as signature metal binding sites common to clinically important macrocyclic peptides *i.e.*, Bistratamides,³ Didmolamides,⁴ Lyngbyabellin,⁵ Calyculins^{5,6} and show cytotoxic, antimicrobial and multiple drug resistance activities. Imidazole-based drugs such as Cimetidine, Etomidate and Ketoconazole are currently in clinical use.⁷ The Hantzsch reaction of α -halocarbonyl compounds with thioureas or thioamides is the most commonly used method for the synthesis of thiazoles.^{8,9} Methods for the synthesis of substituted oxazoles include Robinson–Gabriel synthesis of cyclodehydration of α -acylaminocarbonyl compounds,^{10–15} the Cornforth and Cornforth method,¹⁶ improved by Yokoyama,^{17,18} the Hantzsch-type reaction of α -halo/acyloxy carbonyl compounds with amides,¹⁹ dehydrative cyclization of β -hydroxy amides followed by oxidative dehydrogenation^{19–26} and pyrolysis of α -acylisoxazolones.²⁷ The synthesis of imidazoles was first reported by Radziszewski reaction from glyoxal, formaldehyde and ammonia.²⁸ Apart from these, pyrroles constitute the core unit of many natural products and serve as building blocks for porphyrin synthesis.^{29,30} Members of this family have wide applications in medicinal chemistry, being used as antimalarial, antiinflammatory, antibacterial and antiviral agents.^{31–33} Many synthetic methods have been employed for the synthesis of pyrroles including Knorr,³⁴ Paal–Knorr,^{35–37} Hantzsch synthesis,³⁸ 1,3-dipolar cycloaddition reactions,³⁹ reductive coupling⁴⁰ and aza-Wittig reactions.⁴¹ Recently, we have studied the antimicrobial activity of amido linked pyrrolyl and pyrazolyl oxazoles, thiazoles and imidazoles and identified imidazolyl cinnamamide as potential antimicrobial agent.⁴² Motivated by the aforesaid findings, herein we report on the preparation and antimicrobial assay of some new sulfonylmethaneamido linked heterocycles using a simple synthetic approach from easily accessible building blocks.

Chemistry For the synthesis of bis heterocycles mentioned in the scheme, the compounds 4-aryloxazol-2-amine⁴³ (1), 4-arylthiazol-2-amine⁴³ (2), 4-aryl-1*H*-imidazol-2-amine⁴⁴ (3) and *Z*-(arylethenesulfonyl)acetic acid⁴⁵ required as the starting materials were prepared by adopting the literature

precedent. The *Z*-(arylethenesulfonyl)acetyl chloride (4) was prepared by the chlorination of *Z*-(arylethenesulfonyl)acetic acid with thionyl chloride. The heteroaryl *Z*-styrylsulfonylmethane amides, *Z*-(2-arylethenesulfonyl)-*N*-(4-aryloxazol-2-yl)acetamide (5), *Z*-(2-arylethenesulfonyl)-*N*-(4-arylthiazol-2-yl)acetamide (6), and *Z*-(2-arylethenesulfonyl)-*N*-(4-aryl-1*H*-imidazol-2-yl)acetamide (7) were obtained by the reaction of 1, 2, and 3 with 4. The ¹H-NMR spectra of 5a, 6a, and 7a showed two singlets at δ 7.30, 6.34, 7.28, and 4.25, 4.22, 4.25 ppm due to C₅-H and methylene protons flanked between CO and SO₂ groups. A broad singlet was observed at 7.95, 7.91 and 7.92 ppm due to NH. The compound 7a showed another broad singlet at 12.26 ppm due to NH of imidazole ring. The signals of NH disappeared on deuteration. In addition, two doublets were observed at δ 7.16, 7.13, 7.14, and 6.47, 6.46, 6.47 ppm which were accounted for olefin protons, H_A and H_B, respectively. The coupling constant value $J \approx 9.3$ Hz indicated that they possess *cis* geometry. The olefin moiety present in these compounds was used to develop pyrrole ring. Thus, the 1,3-dipolar cycloaddition of tosylmethyl isocyanide to 5, 6 and 7 in the presence of sodium hydride in ether and dimethyl sulfoxide (DMSO) led to bis heterocycles, *Z*-(4'-aryl-1'*H*-pyrrol-3'-ylsulfonyl)-*N*-(4-aryloxazol-2-yl)acetamide (8), *Z*-(4'-aryl-1'*H*-pyrrol-3'-ylsulfonyl)-*N*-(4-arylthiazol-2-yl)acetamide (9), and *Z*-(4'-aryl-1'*H*-pyrrol-3'-ylsulfonyl)-*N*-(4-aryl-1*H*-imidazol-2-yl)acetamide (10) (Chart 1).

The ¹H-NMR spectra of 8a, 9a and 10a displayed two singlets at δ 6.82, 6.79, 6.80 and 6.73, 6.70, 6.71 ppm due to C₂-H and C₅-H respectively, in addition to the signals of methylene protons, C₅-H and NH. The structures of all the compounds were further established by IR, ¹³C-NMR and elemental analyses.

In-Vitro Antimicrobial Study The compounds 5–10 were screened for antimicrobial activity at four different concentrations, 12.5, 25, 50, and 100 μ g/well. Investigation of antibacterial screening data depicted in Table 1 and Fig. 1 showed that Gram-negative bacteria were more susceptible towards the tested compounds than Gram-positive ones. It was observed that the compounds 7c and 10c were effective particularly against *Pseudomonas aeruginosa* at the tested concentrations when compared with the standard drug Chloramphenicol. It was also observed that mono heterocyclic compound with styryl moiety 7 exhibited slightly higher activity than the corresponding bis heterocyclic compound 10. Amongst bis heterocyclic compounds 8–10, those with pyrrole

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Chart 1

Fig. 1. The *in-Vitro* Antibacterial Activity of Compounds 5–10

in combination with imidazole (10) displayed greater activity than the compounds having pyrrole and oxazole (8) or thiazole (9). However, the compounds 6c and 9c exhibited moderate activity. On the other hand, the compounds 5 and 8 displayed least activity. The presence of chloro substituent on the aromatic ring enhances the activity.

All the tested compounds inhibited the spore germination against tested fungi except 5a, 5b, 8a, and 8b. In general, most of the compounds showed slightly higher antifungal activity towards *Penicillium chrysogenum* than *Aspergillus niger*. The compounds 7c and 10c exhibited excellent activity particularly against *Penicillium chrysogenum* almost equivalent to the standard drug Ketoconazole. However, the compounds 6c and 9c displayed moderate inhibition against the tested fungi (Table 2, Fig. 2).

The minimum inhibitory concentration (MIC), minimum bactericidal concentration (MBC) and minimum fungicidal concentration (MFC) values of the tested compounds are listed in Table 3. The compound 7c exhibited low MIC values when compared with 10c. Besides, the MBC value is 2×MIC in case of *Bacillus subtilis* and *Pseudomonas aeruginosa* and MFC value is 2×MIC in case of *Penicillium chrysogenum*. On the other hand, compound 10c displayed bactericidal and

fungicidal effects greater than 2×MIC. It was observed that mono heterocyclic compounds (5–7) are slightly more potent than bis heterocyclic systems (8–10). This may be due to the presence of styrylsulfonyl moiety in mono heterocyclic compounds. Further, imidazole analogues (7, 10) are more potent than oxazole or thiazole analogues (5, 6, 8, 9). It was also observed that 4-chlorophenyl analogues are more potent than unsubstituted phenyl or 4-methylphenyl analogues. In continuation of our earlier work,⁴²⁾ it was inferred that sulfonylmethaneamido linked heterocycles displayed greater activity than amido linked bis heterocycles. Thus the presence of sulfonylmethane moiety enhanced the activity.

Conclusion

A new class of mono and bis heterocycles, sulfonylmethaneamido linked oxazoles, thiazoles, imidazoles, pyrrolyl oxazoles, pyrrolyl thiazoles and pyrrolyl imidazoles were prepared adopting simple, and versatile synthetic methodologies. The compound imidazolyl styrylsulfonylacetamide is the most potent antimicrobial agent.

Experimental

Melting points were determined in open capillaries on a

Table 1. The *in-vitro* Antibacterial Activity of Compounds 5–10

Compound	Zone of inhibition (mm)															
	Gram-positive bacteria								Gram-negative bacteria							
	<i>Staphylococcus aureus</i>				<i>Bacillus subtilis</i>				<i>Pseudomonas aeruginosa</i>				<i>Klebsiella pneumoniae</i>			
	12.5 μ g/well	25 μ g/well	50 μ g/well	100 μ g/well	12.5 μ g/well	25 μ g/well	50 μ g/well	100 μ g/well	12.5 μ g/well	25 μ g/well	50 μ g/well	100 μ g/well	12.5 μ g/well	25 μ g/well	50 μ g/well	100 μ g/well
5a	8 $\pm$ 1	10 $\pm$ 3	12 $\pm$ 2	14 $\pm$ 4	12 $\pm$ 4	13 $\pm$ 3	15 $\pm$ 1	17 $\pm$ 5	—	—	—	—	—	—	—	—
5b	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
5c	18 $\pm$ 1	20 $\pm$ 6	23 $\pm$ 3	25 $\pm$ 4	16 $\pm$ 2	18 $\pm$ 1	21 $\pm$ 4	24 $\pm$ 3	17 $\pm$ 3	20 $\pm$ 4	21 $\pm$ 1	23 $\pm$ 2	18 $\pm$ 5	21 $\pm$ 4	23 $\pm$ 1	25 $\pm$ 2
6a	14 $\pm$ 2	17 $\pm$ 4	20 $\pm$ 3	23 $\pm$ 6	17 $\pm$ 7	20 $\pm$ 6	22 $\pm$ 4	25 $\pm$ 2	14 $\pm$ 5	15 $\pm$ 7	17 $\pm$ 3	19 $\pm$ 2	20 $\pm$ 3	23 $\pm$ 7	25 $\pm$ 4	28 $\pm$ 6
6b	13 $\pm$ 7	15 $\pm$ 2	18 $\pm$ 1	21 $\pm$ 3	15 $\pm$ 3	18 $\pm$ 1	20 $\pm$ 4	23 $\pm$ 5	10 $\pm$ 1	13 $\pm$ 4	15 $\pm$ 6	17 $\pm$ 5	16 $\pm$ 1	19 $\pm$ 2	22 $\pm$ 1	24 $\pm$ 3
6c	23 $\pm$ 5	25 $\pm$ 7	27 $\pm$ 1	30 $\pm$ 4	20 $\pm$ 3	22 $\pm$ 7	25 $\pm$ 2	27 $\pm$ 1	18 $\pm$ 4	20 $\pm$ 2	22 $\pm$ 3	25 $\pm$ 1	26 $\pm$ 4	28 $\pm$ 7	30 $\pm$ 6	34 $\pm$ 1
7a	18 $\pm$ 5	20 $\pm$ 6	22 $\pm$ 3	24 $\pm$ 2	21 $\pm$ 3	23 $\pm$ 2	25 $\pm$ 1	28 $\pm$ 1	13 $\pm$ 7	16 $\pm$ 1	19 $\pm$ 4	21 $\pm$ 3	22 $\pm$ 3	25 $\pm$ 2	27 $\pm$ 5	29 $\pm$ 1
7b	14 $\pm$ 5	17 $\pm$ 1	19 $\pm$ 2	22 $\pm$ 5	17 $\pm$ 4	19 $\pm$ 5	21 $\pm$ 3	24 $\pm$ 2	13 $\pm$ 2	15 $\pm$ 1	17 $\pm$ 4	19 $\pm$ 5	17 $\pm$ 2	20 $\pm$ 4	23 $\pm$ 2	25 $\pm$ 5
7c	27 $\pm$ 6	29 $\pm$ 3	31 $\pm$ 1	35 $\pm$ 3	28 $\pm$ 5	30 $\pm$ 4	33 $\pm$ 7	38 $\pm$ 6	26 $\pm$ 2	28 $\pm$ 1	30 $\pm$ 4	33 $\pm$ 3	34 $\pm$ 1	36 $\pm$ 3	38 $\pm$ 4	40 $\pm$ 5
8a	7 $\pm$ 4	9 $\pm$ 3	10 $\pm$ 7	13 $\pm$ 6	8 $\pm$ 2	10 $\pm$ 5	13 $\pm$ 3	15 $\pm$ 1	—	—	—	—	—	—	—	—
8b	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
8c	15 $\pm$ 2	17 $\pm$ 1	19 $\pm$ 4	23 $\pm$ 1	16 $\pm$ 4	18 $\pm$ 2	20 $\pm$ 2	23 $\pm$ 5	14 $\pm$ 2	17 $\pm$ 5	19 $\pm$ 1	22 $\pm$ 3	18 $\pm$ 4	20 $\pm$ 1	22 $\pm$ 3	24 $\pm$ 4
9a	8 $\pm$ 2	10 $\pm$ 5	12 $\pm$ 1	14 $\pm$ 7	9 $\pm$ 3	11 $\pm$ 2	13 $\pm$ 1	16 $\pm$ 4	6 $\pm$ 2	9 $\pm$ 5	11 $\pm$ 7	13 $\pm$ 4	10 $\pm$ 1	13 $\pm$ 2	16 $\pm$ 1	18 $\pm$ 4
9b	—	8 $\pm$ 6	9 $\pm$ 3	11 $\pm$ 4	6 $\pm$ 5	8 $\pm$ 3	10 $\pm$ 1	13 $\pm$ 2	—	6 $\pm$ 2	8 $\pm$ 1	11 $\pm$ 5	9 $\pm$ 2	11 $\pm$ 1	13 $\pm$ 3	15 $\pm$ 4
9c	24 $\pm$ 2	26 $\pm$ 5	28 $\pm$ 1	30 $\pm$ 4	23 $\pm$ 5	25 $\pm$ 3	27 $\pm$ 7	31 $\pm$ 4	22 $\pm$ 3	23 $\pm$ 2	25 $\pm$ 1	27 $\pm$ 4	28 $\pm$ 2	30 $\pm$ 1	32 $\pm$ 5	34 $\pm$ 7
10a	14 $\pm$ 5	16 $\pm$ 2	19 $\pm$ 3	22 $\pm$ 2	15 $\pm$ 2	18 $\pm$ 6	20 $\pm$ 7	22 $\pm$ 2	13 $\pm$ 5	16 $\pm$ 7	18 $\pm$ 6	20 $\pm$ 3	18 $\pm$ 6	20 $\pm$ 3	22 $\pm$ 4	24 $\pm$ 1
10b	11 $\pm$ 7	13 $\pm$ 6	16 $\pm$ 1	18 $\pm$ 2	12 $\pm$ 4	14 $\pm$ 1	17 $\pm$ 3	20 $\pm$ 5	10 $\pm$ 2	13 $\pm$	15 $\pm$ 3	17 $\pm$ 1	14 $\pm$ 5	17 $\pm$ 2	19 $\pm$ 3	21 $\pm$ 6
10c	28 $\pm$ 5	30 $\pm$ 4	31 $\pm$ 3	33 $\pm$ 2	29 $\pm$ 2	31 $\pm$ 7	33 $\pm$ 6	36 $\pm$ 5	25 $\pm$ 2	27 $\pm$ 4	28 $\pm$ 1	32 $\pm$ 3	32 $\pm$ 1	34 $\pm$ 7	36 $\pm$ 4	38 $\pm$ 5
Chloramphenicol	28 $\pm$ 1	30 $\pm$ 4	33 $\pm$ 1	35 $\pm$ 2	30 $\pm$ 1	32 $\pm$ 3	34 $\pm$ 4	38 $\pm$ 1	23 $\pm$ 1	25 $\pm$ 5	27 $\pm$ 6	30 $\pm$ 2	36 $\pm$ 6	38 $\pm$ 1	40 $\pm$ 2	42 $\pm$ 3
Control (DMSO)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

(—) No activity. ($\pm$) Standard deviation.

Fig. 2. The *in-Vitro* Antifungal Activity of Compounds 5–10Table 2. The *in-Vitro* Antifungal Activity of Compounds 5–10

Compound	Zone of inhibition (mm)							
	<i>Aspergillus niger</i>				<i>Penicillium chrysogenum</i>			
	12.5 µg/well	25 µg/well	50 µg/well	100 µg/well	12.5 µg/well	25 µg/well	50 µg/well	100 µg/well
5a	—	—	—	—	—	—	—	—
5b	—	—	—	—	—	—	—	—
5c	18±4	20±3	23±2	26±7	21±2	24±4	25±5	28±3
6a	18±5	20±1	21±6	23±4	19±2	21±1	24±3	26±7
6b	13±1	15±2	17±3	19±7	17±2	19±1	21±4	23±5
6c	24±5	26±2	28±4	32±3	28±2	30±1	32±4	33±5
7a	21±1	24±5	26±7	28±2	22±3	25±2	27±1	29±4
7b	17±3	19±1	20±5	24±2	19±5	21±2	23±1	25±4
7c	27±4	29±1	31±3	35±7	33±5	35±7	36±6	38±3
8a	—	—	—	—	—	—	—	—
8b	—	—	—	—	—	—	—	—
8c	17±3	18±2	20±1	23±7	19±7	20±4	22±2	24±1
9a	15±6	17±2	19±5	21±4	19±3	20±4	23±5	25±1
9b	13±2	15±3	16±6	18±1	15±3	16±4	18±2	21±1
9c	23±2	26±1	28±3	30±5	24±7	27±4	30±6	32±2
10a	19±4	22±1	24±2	26±3	21±1	23±3	25±5	28±6
10b	15±4	17±5	19±2	23±3	17±7	20±1	22±2	24±7
10c	27±1	28±4	30±2	34±5	27±4	30±2	33±1	35±6
Ketoconazole	29±1	31±6	33±4	36±3	33±3	35±1	36±2	38±3
Control (DMSO)	—	—	—	—	—	—	—	—

(—) No activity. (±) Standard deviation.

Table 3. MIC, MBC and MFC of Compounds 7c and 10c

Compound	Minimum inhibitory concentration MIC (MBC/MFC) µg					
	<i>Staphylococcus aureus</i>	<i>Bacillus subtilis</i>	<i>Pseudomonas aeruginosa</i>	<i>Klebsiella pneumoniae</i>	<i>Aspergillus niger</i>	<i>Penicillium chrysogenum</i>
7c	12.5 (50)	12.5 (25)	12.5 (25)	25 (100)	12.5 (50)	12.5 (25)
10c	25 (100)	12.5 (50)	25 (100)	50 (200)	12.5 (50)	25 (100)
Chloramphenicol	6.25	6.25	6.25	12.5	—	—
Ketoconazole	—	—	—	—	6.25	12.5

(—) No activity.

Mel-Temp apparatus and are uncorrected. The purity 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 wavenumbers were given in cm^{-1} . The ^1H -NMR spectra were recorded in $\text{DMSO}-d_6$ on a Bruker-400 spectrometer

(400 MHz). The ^{13}C -NMR spectra were recorded in $\text{DMSO}-d_6$ on a Bruker spectrometer operating at 100 MHz. All chemical shifts are reported in δ (ppm) using tetramethylsilane as an internal standard. The microanalyses were performed on a Perkin-Elmer 240C elemental analyzer. The compounds 4-aryloxazol-2-amine⁴³ (**1**), 4-arylthiazol-2-amine⁴³ (**2**), 4-aryl-1*H*-imidazol-2-amine⁴⁴ (**3**) and *Z*-(arylethenesulfonyl)acetic acid⁴⁵ required as the starting materials were prepared by adopting the literature precedent.

General Procedure for the Synthesis of *Z*-(Arylethenesulfonyl)acetyl Chloride (4a–c**)** To the compound *Z*-(arylethenesulfonyl)acetic acid⁴⁵ (3 mmol), thionyl chloride (5 mmol) was added and refluxed for 30–45 min. The excess thionyl chloride was removed by vacuum distillation and the residue was poured onto crushed ice. The separated solid was collected by filtration, washed with water, dried and recrystallized from ethanol.

***Z*-(Phenylethenesulfonyl)acetyl Chloride (**4a**):** White solid, yield 82%, mp 126–128°C; ^1H -NMR ($\text{DMSO}-d_6$) δ : 4.83 (s, 2H, $\text{SO}_2\text{-CH}_2$), 6.46 (d, 1H, H_B , $J=9.3$ Hz), 7.14–7.62 (m, 6H, H_A , Ar-H). ^{13}C -NMR ($\text{DMSO}-d_6$) δ : 56.1 ($\text{SO}_2\text{-CH}_2$), 121.5 (C- H_B), 143.8 (C- H_A), 172.1 (C=O), 125.3, 126.9, 127.7, 133.3 (aromatic carbons). IR (KBr) cm^{-1} : 1748 (C=O), 1634 (C=C), 1337, 1134 (SO_2).

***Z*-(4-Methylphenylethenesulfonyl)acetyl Chloride (**4b**):** White solid, yield 84%, mp 112–114°C; ^1H -NMR ($\text{DMSO}-d_6$) δ : 2.29 (s, 3H, Ar- CH_3), 4.78 (s, 2H, $\text{SO}_2\text{-CH}_2$), 6.45 (d, 1H, H_B , $J=9.2$ Hz), 7.06–7.60 (m, 5H, H_A , Ar-H). ^{13}C -NMR ($\text{DMSO}-d_6$) δ : 21.2 (Ar- CH_3), 55.6 ($\text{SO}_2\text{-CH}_2$), 120.3 (C- H_B), 143.6 (C- H_A), 172.0 (C=O), 125.1, 126.4, 127.3, 132.1 (aromatic carbons). IR (KBr) cm^{-1} : 1732 (C=O), 1631 (C=C), 1332, 1129 (SO_2).

***Z*-(4-Chlorophenylethenesulfonyl)acetyl Chloride (**4c**):** White solid, yield 85%, mp 133–135°C; ^1H -NMR ($\text{DMSO}-d_6$) δ : 4.85 (s, 2H, $\text{SO}_2\text{-CH}_2$), 6.47 (d, 1H, H_B , $J=9.5$ Hz), 7.12–7.72 (m, 5H, H_A , Ar-H). ^{13}C -NMR ($\text{DMSO}-d_6$) δ : 56.2 ($\text{SO}_2\text{-CH}_2$), 120.6 (C- H_B), 140.9 (C- H_A), 172.4 (C=O), 126.9, 127.8, 128.2, 134.9 (aromatic carbons). IR (KBr) cm^{-1} : 1751 (C=O), 1638 (C=C), 1341, 1137 (SO_2).

General Procedure for the Synthesis of *Z*-(2-Arylethenesulfonyl)-*N*-(4-aryloxazol-2-yl)acetamide (5a–c**), *Z*-(2-Arylethenesulfonyl)-*N*-(4-arylthiazol-2-yl)acetamide (**6a–c**) and *Z*-(2-Arylethenesulfonyl)-*N*-(4-aryl-1*H*-imidazol-2-yl)acetamide (**7a–c**)** The compound **4** (1.1 mmol), **1–3** (1 mmol) and toluene (1.5 mL) were heated to reflux for 15–18 h. The reaction mixture was cooled and was decolorized by treating it with 50:50 carbon–celite (v/v). The contents were passed through a pad of silica gel (50 mL) and eluted the product with 10% ethyl acetate–hexane. The crude product was then recrystallized from ethyl acetate–hexane.

***Z*-(2-Phenylethenesulfonyl)-*N*-(4-phenyloxazol-2-yl)acetamide (**5a**):** Yellow solid, yield 73%, mp 139–141°C; ^1H -NMR ($\text{DMSO}-d_6$) δ : 4.25 (s, 2H, $\text{SO}_2\text{-CH}_2$), 6.47 (d, 1H, H_B , $J=9.4$ Hz), 7.12–7.72 (m, 12H, H_A , Ar-H, C₅-H), 7.95 (br s, 1H, CO-NH). ^{13}C -NMR ($\text{DMSO}-d_6$) δ : 57.6 ($\text{SO}_2\text{-CH}_2$), 122.6 (C- H_B), 135.2 (C-5), 138.2 (C-4), 141.5 (C- H_A), 149.1 (C-2), 171.6 (C=O), 126.4, 127.8, 128.2, 128.6, 130.3, 132.8, 134.9 (aromatic carbons). IR (KBr) cm^{-1} : 3321 (NH), 1631 (C=O), 1628 (C=C), 1576 (C=N), 1332, 1128 (SO_2). MS m/z : 368.42 (M^+). Anal. Calcd for $\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}_4\text{S}$: C, 61.94; H, 4.37; N, 7.60. Found: C, 61.82; H, 4.29; N, 7.73.

***Z*-(2-(4-Methylphenyl)ethenesulfonyl)-*N*-(4-(4-methylphenyl)oxazol-2-yl)acetamide (**5b**):** Yellow solid, yield 70%, mp 125–127°C; ^1H -NMR ($\text{DMSO}-d_6$) δ : 2.26 and 2.29 (s, 6H, Ar- CH_3), 4.26 (s, 2H, $\text{SO}_2\text{-CH}_2$), 6.45 (d, 1H, H_B , $J=9.3$ Hz), 7.10–7.60 (m, 10H, H_A , Ar-H, C₅-H), 7.93 (br s, 1H, CO-NH). ^{13}C -NMR ($\text{DMSO}-d_6$) δ : 21.6 and 21.9 (Ar- CH_3), 57.3 ($\text{SO}_2\text{-CH}_2$), 121.4 (C- H_B), 134.9 (C-5), 138.0 (C-4), 140.9 (C- H_A), 149.8 (C-2), 169.1 (C=O), 126.2, 127.2, 128.3, 130.1, 131.9, 132.7, 133.1, 134.4 (aromatic carbons). IR (KBr) cm^{-1} : 3317 (NH), 1660 (C=O), 1621 (C=C), 1571 (C=N), 1330, 1133 (SO_2). Anal. Calcd for $\text{C}_{21}\text{H}_{20}\text{N}_2\text{O}_4\text{S}$: C, 63.61; H, 5.08; N, 7.06. Found: C, 63.70; H, 5.00; N, 7.14.

***Z*-(2-(4-Chlorophenyl)ethenesulfonyl)-*N*-(4-(4-chlorophenyl)oxazol-2-yl)acetamide (**5c**):** Yellow solid, yield 75%, mp 162–164°C; ^1H -NMR ($\text{DMSO}-d_6$) δ : 4.23 (s, 2H, $\text{SO}_2\text{-CH}_2$), 6.51 (d, 1H, H_B , $J=9.5$ Hz), 7.14–7.71 (m, 10H, H_A , Ar-H, C₅-H), 7.96 (br s, 1H, CO-NH). ^{13}C -NMR ($\text{DMSO}-d_6$) δ : 57.8 ($\text{SO}_2\text{-CH}_2$), 122.9 (C- H_B), 135.3 (C-5), 138.5 (C-4), 141.7 (C- H_A), 149.4 (C-2), 171.9 (C=O), 125.9, 128.4, 128.9, 130.0, 131.7, 132.6, 134.4, 137.3 (aromatic carbons). IR (KBr) cm^{-1} : 3328 (NH), 1632 (C=O), 1631 (C=C), 1578 (C=N), 1335, 1126 (SO_2). Anal. Calcd for $\text{C}_{21}\text{H}_{16}\text{N}_2\text{O}_4\text{S}$: C, 63.61; H, 5.08; N, 7.06. Found: C, 63.70; H, 5.00; N, 7.14.

***Z*-(2-Phenylethenesulfonyl)-*N*-(4-phenylthiazol-2-yl)acetamide (**6a**):** Yellow solid, yield 68%, mp 144–146°C; ^1H -NMR ($\text{DMSO}-d_6$) δ : 4.22 (s, 2H, $\text{SO}_2\text{-CH}_2$), 6.34 (s, 1H, C₅-H), 6.46 (d, 1H, H_B , $J=9.6$ Hz), 7.10–7.63 (m, 11H, H_A , Ar-H), 7.91 (br s, 1H, CO-NH). ^{13}C -NMR ($\text{DMSO}-d_6$) δ : 56.9 ($\text{SO}_2\text{-CH}_2$), 121.0 (C- H_B), 122.6 (C-5), 141.1 (C- H_A), 143.2 (C-4), 156.8 (C-2), 169.7 (C=O), 126.8, 128.1, 128.7, 129.1, 129.5, 133.1, 133.8, 135.2 (aromatic carbons). IR (KBr) cm^{-1} : 3326 (NH), 1648 (C=O), 1634 (C=C), 1565 (C=N), 1322, 1142 (SO_2). MS m/z : 384.48 (M^+). Anal. Calcd for $\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}_3\text{S}_2$: C, 59.35; H, 4.19; N, 7.28. Found: C, 59.47; H, 4.09; N, 7.37.

***Z*-(2-(4-Methylphenyl)ethenesulfonyl)-*N*-(4-(4-methylphenyl)thiazol-2-yl)acetamide (**6b**):** Yellow solid, yield 66%, mp 135–137°C; ^1H -NMR ($\text{DMSO}-d_6$) δ : 2.24 and 2.26 (s, 6H, Ar- CH_3), 4.20 (s, 2H, $\text{SO}_2\text{-CH}_2$), 6.33 (s, 1H, C₅-H), 6.43 (d, 1H, H_B , $J=9.4$ Hz), 7.07–7.58 (m, 9H, H_A , Ar-H), 7.88 (br s, 1H, CO-NH). ^{13}C -NMR ($\text{DMSO}-d_6$) δ : 21.3 and 21.6 (Ar- CH_3), 55.7 ($\text{SO}_2\text{-CH}_2$), 121.7 (C- H_B), 122.1 (C-5), 140.8 (C- H_A), 142.0 (C-4), 155.5 (C-2), 170.2 (C=O), 126.5, 127.8, 128.0, 128.9, 129.7, 130.1, 132.7, 133.8 (aromatic carbons). IR (KBr) cm^{-1} : 3324 (NH), 1640 (C=O), 1627 (C=C), 1581 (C=N), 1324, 1147 (SO_2). Anal. Calcd for $\text{C}_{21}\text{H}_{20}\text{N}_2\text{O}_3\text{S}_2$: C, 61.14; H, 4.88; N, 6.78. Found: C, 61.06; H, 4.96; N, 6.69.

***Z*-(2-(4-Chlorophenyl)ethenesulfonyl)-*N*-(4-(4-chlorophenyl)thiazol-2-yl)acetamide (**6c**):** Yellow solid, yield 74%, mp 188–189°C; ^1H -NMR ($\text{DMSO}-d_6$) δ : 4.24 (s, 2H, $\text{SO}_2\text{-CH}_2$), 6.36 (s, 1H, C₅-H), 6.47 (d, 1H, H_B , $J=9.5$ Hz), 7.11–7.66 (m, 9H, H_A , Ar-H), 7.92 (br s, 1H, CO-NH). ^{13}C -NMR ($\text{DMSO}-d_6$) δ : 57.1 ($\text{SO}_2\text{-CH}_2$), 121.1 (C- H_B), 122.5 (C-5), 141.3 (C- H_A), 143.6 (C-4), 156.9 (C-2), 170.6 (C=O), 127.1, 127.9, 128.5, 129.3, 130.2, 131.4, 133.8, 137.7 (aromatic carbons). IR (KBr) cm^{-1} : 3332 (NH), 1649 (C=O), 1634 (C=C), 1583 (C=N), 1327, 1126 (SO_2). Anal. Calcd for $\text{C}_{19}\text{H}_{14}\text{Cl}_2\text{N}_2\text{O}_3\text{S}_2$: C, 50.33; H, 3.11; N, 6.17. Found: C, 50.40; H, 3.18; N, 6.26.

***Z*-(2-Phenylethenesulfonyl)-*N*-(4-phenyl-1*H*-imidazol-2-yl)acetamide (**7a**):** Yellow solid, yield 72%, mp 167–169°C; ^1H -NMR ($\text{DMSO}-d_6$) δ : 4.25 (s, 2H, $\text{SO}_2\text{-CH}_2$), 6.47 (d, 1H,

H_B, $J=9.3$ Hz), 7.11–7.66 (m, 12H, H_A, Ar-H, C₅-H), 7.92 (br s, 1H, CO-NH), 12.26 (br s, 1H, C₅-NH). ¹³C-NMR (DMSO-*d*₆) δ : 55.2 (SO₂-CH₂), 122.3 (C-H_B), 134.5 (C-5), 136.8 (C-2), 140.3 (C-H_A), 142.1 (C-4), 170.1 (C=O), 126.4, 127.6, 128.4, 129.9, 131.3, 133.7, 134.8 (aromatic carbons). IR (KBr) cm⁻¹: 3336 (NH), 1633 (C=O), 1629 (C=C), 1570 (C=N), 1331, 1135 (SO₂). MS m/z : 367.43 (M⁺). *Anal.* Calcd for C₁₉H₁₇N₃O₃S: C, 62.10; H, 4.66; N, 11.43. Found: C, 62.00; H, 4.72; N, 11.36.

Z-(2-(4-Methylphenyl)ethenesulfonyl)-*N*-(4-(4-methylphenyl)-1*H*-imidazol-2-yl)acetamide (**7b**): Yellow solid, yield 65%, mp 155–157°C; ¹H-NMR (DMSO-*d*₆) δ : 2.25 and 2.28 (s, 6H, Ar-CH₃), 4.22 (s, 2H, SO₂-CH₂), 6.45 (d, 1H, H_B, $J=9.7$ Hz), 7.09–7.63 (m, 10H, H_A, Ar-H, C₅-H), 7.91 (br s, 1H, CO-NH), 12.15 (br s, 1H, C₅-NH). ¹³C-NMR (DMSO-*d*₆) δ : 21.4 and 21.6 (Ar-CH₃), 57.0 (SO₂-CH₂), 122.1 (C-H_B), 132.2 (C-5), 136.6 (C-2), 141.0 (C-H_A), 141.7 (C-4), 169.6 (C=O), 125.6, 126.8, 127.2, 127.9, 128.7, 130.4, 132.2, 133.6 (aromatic carbons). IR (KBr) cm⁻¹: 3229 (NH), 1628 (C=O), 1630 (C=C), 1586 (C=N), 1334, 1126 (SO₂). *Anal.* Calcd for C₂₁H₂₁N₃O₃S: C, 63.77; H, 5.35; N, 10.62. Found: C, 63.88; H, 5.42; N, 10.74.

Z-(2-(4-Chlorophenyl)ethenesulfonyl)-*N*-(4-(4-chlorophenyl)-1*H*-imidazol-2-yl)acetamide (**7c**): Yellow solid, yield 70%; mp 192–194°C; ¹H-NMR (DMSO-*d*₆) δ : 4.26 (s, 2H, SO₂-CH₂), 6.50 (d, 1H, H_B, $J=9.6$ Hz), 7.13–7.67 (m, 10H, H_A, Ar-H, C₅-H), 7.94 (br s, 1H, CO-NH), 12.32 (br s, 1H, C₅-NH). ¹³C-NMR (DMSO-*d*₆) δ : 57.5 (SO₂-CH₂), 122.4 (C-H_B), 134.7 (C-5), 137.1 (C-2), 140.6 (C-H_A), 142.3 (C-4), 170.7 (C=O), 126.6, 127.5, 128.6, 129.8, 130.8, 131.2, 133.6, 135.9 (aromatic carbons). IR (KBr) cm⁻¹: 3242 (NH), 1642 (C=O), 1636 (C=C), 1596 (C=N), 1332, 1124 (SO₂). *Anal.* Calcd for C₁₉H₁₅Cl₂N₃O₃S: C, 52.30; H, 3.46; N, 9.63. Found: C, 52.41; H, 3.54; N, 9.50.

General Procedure for the Synthesis of *Z*-(4'-Aryl-1'*H*-pyrrol-3'-ylsulfonyl)-*N*-(4-aryloxazol-2-yl)acetamide (8a-c**), *Z*-(4'-Aryl-1'*H*-pyrrol-3'-ylsulfonyl)-*N*-(4-arylthiazol-2-yl)acetamide (**9a-c**) and *Z*-(4'-Aryl-1'*H*-pyrrol-3'-ylsulfonyl)-*N*-(4-aryl-1*H*-imidazol-2-yl)acetamide (**10a-c**)** A mixture of tosylmethyl isocyanide (1 mmol) and **5–7** (1 mmol) in diethyl ether–DMSO (2:1) was added dropwise to a stirred mixture of sodium hydride (0.05 g) in dry diethyl ether (10 mL) at room temperature and stirring was continued for 12–14 h. Then it was diluted with water and extracted with ether. The ethereal layer was dried (an. Na₂SO₄) and the solvent was removed under reduced pressure. The resultant solid was purified by passing through a column of silica gel (ethyl acetate–hexane 1:3) as eluent.

Z-(4'-Phenyl-1'*H*-pyrrol-3'-ylsulfonyl)-*N*-(4-phenyloxazol-2-yl)acetamide (**8a**): Brown solid, yield 69%, mp 146–148°C; ¹H-NMR (DMSO-*d*₆) δ : 4.32 (s, 2H, SO₂-CH₂), 6.73 (s, 1H, C₅-H), 6.82 (s, 1H, C₂-H), 7.18–7.82 (m, 11H, Ar-H, C₅-H), 7.94 (br s, 1H, CO-NH), 9.70 (br s, 1H, C₂-NH). ¹³C-NMR (DMSO-*d*₆) δ : 57.9 (SO₂-CH₂), 113.2 (C-3'), 115.6 (C-5'), 123.2 (C-2'), 128.6 (C-4'), 136.3 (C-5), 138.8 (C-4), 149.5 (C-2), 172.2 (C=O), 127.6, 128.3, 129.2, 130.1, 132.6, 133.9, 134.8 (aromatic carbons). IR (KBr) cm⁻¹: 3228 (NH), 1683 (C=O), 1634 (C=C), 1593 (C=N), 1330, 1133 (SO₂). MS m/z : 407.45 (M⁺). *Anal.* Calcd for C₂₁H₁₇N₃O₄S: C, 61.90; H, 4.20; N, 10.31. Found: C, 62.03; H, 4.28; N, 10.44.

Z-(4'-(4-Methylphenyl)-1'*H*-pyrrol-3'-ylsulfonyl)-*N*-(4-(4-methylphenyl)oxazol-2-yl)acetamide (**8b**): Brown solid, yield

65%, mp 143–145°C; ¹H-NMR (DMSO-*d*₆) δ : 4.32 (s, 2H, SO₂-CH₂), 6.73 (s, 1H, C₅-H), 6.82 (s, 1H, C₂-H), 7.18–7.82 (m, 11H, Ar-H, C₅-H), 7.94 (br s, 1H, CO-NH), 9.70 (br s, 1H, C₂-NH). ¹³C-NMR (DMSO-*d*₆) δ : 57.9 (SO₂-CH₂), 113.2 (C-3'), 115.6 (C-5'), 123.2 (C-2'), 128.6 (C-4'), 136.3 (C-5), 138.8 (C-4), 149.5 (C-2), 172.2 (C=O), 127.6, 128.3, 129.2, 130.1, 132.6, 133.9, 134.8 (aromatic carbons). IR (KBr) cm⁻¹: 3224 (NH), 1675 (C=O), 1632 (C=C), 1576 (C=N), 1334, 1139 (SO₂). *Anal.* Calcd for C₂₃H₂₁N₃O₄S: C, 63.43; H, 4.86; N, 9.64. Found: C, 63.34; H, 4.93; N, 9.76.

Z-(4'-(4-Chlorophenyl)-1'*H*-pyrrol-3'-ylsulfonyl)-*N*-(4-(4-chlorophenyl)oxazol-2-yl)acetamide (**8c**): Brown solid, yield 66%, mp 174–176°C; ¹H-NMR (DMSO-*d*₆) δ : 4.35 (s, 2H, SO₂-CH₂), 6.75 (s, 1H, C₅-H), 6.83 (s, 1H, C₂-H), 7.32–7.88 (m, 9H, Ar-H, C₅-H), 7.95 (br s, 1H, CO-NH), 9.72 (br s, 1H, C₂-NH). ¹³C-NMR (DMSO-*d*₆) δ : 58.1 (SO₂-CH₂), 112.5 (C-3'), 115.7 (C-5'), 123.0 (C-2'), 128.9 (C-4'), 136.5 (C-5), 138.9 (C-4), 147.7 (C-2), 173.8 (C=O), 127.8, 128.4, 128.9, 129.3, 130.3, 132.2, 135.6, 136.3 (aromatic carbons). IR (KBr) cm⁻¹: 3235 (NH), 1682 (C=O), 1636 (C=C), 1563 (C=N), 1332, 1124 (SO₂). *Anal.* Calcd for C₂₁H₁₅Cl₂N₃O₄S: C, 52.95; H, 3.17; N, 8.82. Found: C, 53.04; H, 3.12; N, 8.74.

Z-(4'-Phenyl-1'*H*-pyrrol-3'-ylsulfonyl)-*N*-(4-phenylthiazol-2-yl)acetamide (**9a**): Brown solid, yield 64%, mp 149–151°C; ¹H-NMR (DMSO-*d*₆) δ : 4.28 (s, 2H, SO₂-CH₂), 6.70 (s, 1H, C₅-H), 6.79 (s, 1H, C₂-H), 7.15–7.74 (m, 11H, Ar-H, C₅-H), 7.90 (br s, 1H, CO-NH), 9.69 (br s, 1H, C₂-NH). ¹³C-NMR (DMSO-*d*₆) δ : 57.5 (SO₂-CH₂), 110.6 (C-3'), 115.1 (C-5'), 121.8 (C-5), 122.8 (C-2'), 128.2 (C-4'), 143.7 (C-4), 157.3 (C-2), 171.4 (C=O), 127.3, 128.1, 129.5, 130.6, 132.5, 133.3, 134.9 (aromatic carbons). IR (KBr) cm⁻¹: 3240 (NH), 1664 (C=O), 1631 (C=C), 1578 (C=N), 1333, 1148 (SO₂). MS m/z : 423.51 (M⁺). *Anal.* Calcd for C₂₁H₁₇N₃O₃S₂: C, 59.55; H, 4.04; N, 9.92. Found: C, 59.62; H, 4.00; N, 9.85.

Z-(4'-(4-Methylphenyl)-1'*H*-pyrrol-3'-ylsulfonyl)-*N*-(4-(4-methylphenyl)thiazol-2-yl)acetamide (**9b**): Brown solid, yield 66%, mp 140–142°C; ¹H-NMR (DMSO-*d*₆) δ : 2.23 and 2.26 (s, 6H, Ar-CH₃), 4.25 (s, 2H, SO₂-CH₂), 6.65 (s, 1H, C₅-H), 6.78 (s, 1H, C₂-H), 7.12–7.76 (m, 9H, Ar-H, C₅-H), 7.86 (br s, 1H, CO-NH), 9.70 (br s, 1H, C₂-NH). ¹³C-NMR (DMSO-*d*₆) δ : 21.4 and 21.6 (Ar-CH₃), 57.2 (SO₂-CH₂), 108.8 (C-3'), 114.5 (C-5'), 121.7 (C-5), 122.5 (C-2'), 127.5 (C-4'), 143.4 (C-4), 156.1 (C-2), 171.1 (C=O), 127.2, 127.8, 128.1, 129.1, 129.7, 130.8, 132.5, 133.6 (aromatic carbons). IR (KBr) cm⁻¹: 3227 (NH), 1656 (C=O), 1630 (C=C), 1571 (C=N), 1336, 1141 (SO₂). *Anal.* Calcd for C₂₃H₂₁N₃O₃S₂: C, 61.17; H, 4.68; N, 9.30. Found: C, 61.24; H, 4.75; N, 9.41.

Z-(4'-(4-Chlorophenyl)-1'*H*-pyrrol-3'-ylsulfonyl)-*N*-(4-(4-chlorophenyl)thiazol-2-yl)acetamide (**9c**): Brown solid, yield 71%, mp 193–195°C; ¹H-NMR (DMSO-*d*₆) δ : 4.29 (s, 2H, SO₂-CH₂), 6.63 (s, 1H, C₅-H), 6.81 (s, 1H, C₂-H), 7.21–7.78 (m, 9H, Ar-H, C₅-H), 7.92 (br s, 1H, CO-NH), 9.68 (br s, 1H, C₂-NH). ¹³C-NMR (DMSO-*d*₆) δ : 57.8 (SO₂-CH₂), 111.2 (C-3'), 115.3 (C-5'), 122.1 (C-5), 123.1 (C-2'), 128.3 (C-4'), 144.0 (C-4), 157.5 (C-2), 171.8 (C=O), 127.5, 128.6, 129.1, 129.9, 131.1, 131.8, 133.4, 137.3 (aromatic carbons). IR (KBr) cm⁻¹: 3243 (NH), 1674 (C=O), 1632 (C=C), 1568 (C=N), 1335, 1133 (SO₂). *Anal.* Calcd for C₂₁H₁₅Cl₂N₃O₃S₂: C, 51.22; H, 3.07; N, 8.53. Found: C, 51.33; H, 3.00; N, 8.62.

Z-(4'-Phenyl-1'*H*-pyrrol-3'-ylsulfonyl)-*N*-(4-phenyl-1*H*-imidazol-2-yl)acetamide (**10a**): Brown solid, yield 64%, mp

175–177°C; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ : 4.26 (s, 2H, $\text{SO}_2\text{-CH}_2$), 6.71 (s, 1H, $\text{C}_5\text{-H}$), 6.80 (s, 1H, $\text{C}_2\text{-H}$), 7.16–7.81 (m, 11H, Ar-H, $\text{C}_5\text{-H}$), 7.91 (br s, 1H, CO-NH), 9.71 (br s, 1H, $\text{C}_2\text{-NH}$), 12.46 (br s, 1H, $\text{C}_5\text{-NH}$). $^{13}\text{C-NMR}$ ($\text{DMSO-}d_6$) δ : 55.6 ($\text{SO}_2\text{-CH}_2$), 111.8 (C-3'), 115.2 (C-5'), 123.0 (C-2'), 128.3 (C-4'), 134.8 (C-5), 137.3 (C-2), 143.1 (C-4), 171.8 (C=O), 127.5, 128.2, 129.6, 130.8, 131.4, 133.9, 134.7 (aromatic carbons). IR (KBr) cm^{-1} : 3273 (NH), 1684 (C=O), 1628 (C=C), 1577 (C=N), 1332, 1152 (SO_2). MS m/z : 406.47 (M^+). Anal. Calcd for $\text{C}_{21}\text{H}_{18}\text{N}_4\text{O}_3\text{S}$: C, 62.05; H, 4.46; N, 13.78. Found: C, 62.14; H, 4.51; N, 13.64.

Z-(4'-(4-Methylphenyl)-1'-H-pyrrol-3'-ylsulfonyl)-N-(4-(4-methylphenyl)-1H-imidazol-2-yl)acetamide (**10b**): Brown solid, yield 69%, mp 182–184°C; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ : 2.24 and 2.28 (s, 6H, Ar- CH_3), 4.28 (s, 2H, $\text{SO}_2\text{-CH}_2$), 6.68 (s, 1H, $\text{C}_5\text{-H}$), 6.77 (s, 1H, $\text{C}_2\text{-H}$), 7.14–7.80 (m, 9H, Ar-H, $\text{C}_5\text{-H}$), 7.85 (br s, 1H, CO-NH), 9.65 (br s, 1H, $\text{C}_2\text{-NH}$), 12.38 (br s, 1H, $\text{C}_5\text{-NH}$). $^{13}\text{C-NMR}$ ($\text{DMSO-}d_6$) δ : 21.5 and 21.8 (Ar- CH_3), 56.4 ($\text{SO}_2\text{-CH}_2$), 111.2 (C-3'), 114.9 (C-5'), 121.8 (C-2'), 127.6 (C-4'), 134.6 (C-5), 137.8 (C-2), 142.7 (C-4), 171.9 (C=O), 127.1, 128.6, 128.9, 129.5, 130.7, 132.9, 133.4, 134.9 (aromatic carbons). IR (KBr) cm^{-1} : 3271 (NH), 1683 (C=O), 1626 (C=C), 1567 (C=N), 1337, 1157 (SO_2). Anal. Calcd for $\text{C}_{23}\text{H}_{22}\text{N}_4\text{O}_3\text{S}$: C, 63.57; H, 5.10; N, 12.89. Found: C, 63.45; H, 5.02; N, 12.99.

Z-(4'-(4-Chlorophenyl)-1'-H-pyrrol-3'-ylsulfonyl)-N-(4-(4-chlorophenyl)-1H-imidazol-2-yl)acetamide (**10c**): Brown solid, yield 72%, mp 202–201°C; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ : 4.25 (s, 2H, $\text{SO}_2\text{-CH}_2$), 6.73 (s, 1H, $\text{C}_5\text{-H}$), 6.82 (s, 1H, $\text{C}_2\text{-H}$), 7.22–7.84 (m, 9H, Ar-H, $\text{C}_5\text{-H}$), 7.94 (br s, 1H, CO-NH), 9.71 (br s, 1H, $\text{C}_2\text{-NH}$), 12.46 (br s, 1H, $\text{C}_5\text{-NH}$). $^{13}\text{C-NMR}$ ($\text{DMSO-}d_6$) δ : 57.9 ($\text{SO}_2\text{-CH}_2$), 112.3 (C-3'), 115.4 (C-5'), 123.4 (C-2'), 127.0 (C-4'), 135.0 (C-5), 137.6 (C-2), 142.4 (C-4), 172.2 (C=O), 126.6, 127.8, 128.4, 128.9, 129.3, 130.8, 134.0, 137.1 (aromatic carbons). IR (KBr) cm^{-1} : 3277 (NH), 1687 (C=O), 1629 (C=C), 1582 (C=N), 1334, 1146 (SO_2). Anal. Calcd for $\text{C}_{21}\text{H}_{16}\text{Cl}_2\text{N}_4\text{O}_3\text{S}$: C, 53.05; H, 3.39; N, 11.78. Found: C, 52.97; H, 3.32; N, 11.65.

Antimicrobial Testing The compounds **5–10** were dissolved in DMSO at different concentrations of 12.5, 25, 50 and 100 $\mu\text{g}/\text{well}$. Bacterial strains *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and fungi *Aspergillus niger*, *Penicillium chrysogenum* were obtained from Department of Microbiology, S.V. University, Tirupati.

Antibacterial and Antifungal Assays The *in-vitro* antimicrobial studies were carried out by agar well diffusion method against test organisms.^{46,47} Nutrient broth (NB) plates were swabbed with 24h old broth culture (100 μL) of test bacteria. Using the sterile cork borer, wells (6mm) were made into each petriplate. The compounds were dissolved in DMSO of 5mg/mL and from this 2.5, 5, 10, and 20 μL (12.5, 25, 50, 100 $\mu\text{g}/\text{well}$) were added into the wells by using sterile pipettes. Simultaneously the standard antibiotics, chloramphenicol for antibacterial activity and ketoconazole for antifungal activity (as positive control) were tested against the pathogens. The samples were dissolved in DMSO which showed no zone of inhibition acts as negative control. The plates were incubated at 37°C for 24h for bacteria and at 28°C for 48h for fungi. After appropriate incubation, the diameter of zone of inhibition of each well was measured. Duplicates were main-

tained and the average values were calculated for eventual antibacterial activity.

Broth dilution test was used to determine minimum inhibitory concentration (MIC) of the above mentioned samples.^{48,49} Freshly prepared nutrient broth was used as diluents. The 24h old culture of the test bacteria *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* and the test fungi *Aspergillus niger* and *Penicillium chrysogenum* were diluted 100 folds in nutrient broth (100 μL bacterial cultures in 10mL NB). The stock solution of the synthesized compounds was prepared in DMSO by dissolving 5mg of the compound in 1mL of DMSO. Increasing concentrations of the test samples (1.25, 2.5, 5, 10, 20, 40 μL of stock solution contains 6.25, 12.5, 25, 50, 100, 200 μg of the compounds) were added to the test tubes containing the bacterial and fungal cultures. All the tubes were incubated at 37°C for 24h for bacteria and at 28°C for 48h for fungi. The tubes were examined for visible turbidity and using NB as control. Control without test samples and with solvent was assayed simultaneously. The lowest concentration that inhibited visible growth of the tested organisms was recorded as MIC. To determine the minimum bactericidal concentration (MBC)⁵⁰ and minimum fungicidal concentration (MFC)⁵¹ for each set of test tubes in the MIC determination, a loopful of broth was collected from those tubes which did not show any growth and inoculated on sterile nutrient broth (for bacteria) and PDA (for fungi) by streaking. Plates inoculated with bacteria and fungi were incubated at 37°C for 24h and at 28°C for 48h, respectively. After incubation, the lowest concentration was noted as MBC (for bacteria) or MFC (for fungi) at which no visible growth was observed.

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References

- 1) Hughes R. A., Thompson S. P., Alcaraz L., Moody C. J., *J. Am. Chem. Soc.*, **127**, 15644–15651 (2005).
- 2) Glover C., Merritt E. A., Bagley M. C., *Tetrahedron Lett.*, **48**, 7027–7030 (2007).
- 3) You S.-L., Kelly J. W., *Tetrahedron*, **61**, 241–249 (2005).
- 4) You S.-L., Kelly J. W., *Tetrahedron Lett.*, **46**, 2567–2570 (2005).
- 5) Yokokawa F., Sameshima H., Shioiri T., *Tetrahedron Lett.*, **42**, 4171–4174 (2001).
- 6) Pihko P. M., Koskinen A. M. P., *J. Org. Chem.*, **63**, 92–98 (1998).
- 7) Pathan M. Y., Paik V. V., Pachmase P. R., More S. P., Ardhapure S. S., Pawar R. P., *ARKIVOC*, 205–210 (2006).
- 8) Hantzsch A., *Ber. Dtsch. Chem. Ges.*, **21**, 942–947 (1888).
- 9) Wiley R. H., England D. C., Behr L. C., "Organic Reactions," Vol. 6, John Wiley, 1951, pp. 367–409.
- 10) Robinson R., *J. Chem. Soc.*, **95**, 2167–2174 (1909).
- 11) Gabriel, *Chem. Ber.*, **43**, 1283–1287 (1910).
- 12) Gordon T. D., Singh J., Hansen P. E., Morgan B. A., *Tetrahedron Lett.*, **34**, 1901–1904 (1993).
- 13) Brain C. T., Paul J. M., *Synlett*, **1999**, 1642–1644 (1999).
- 14) Morwick T., Hrapchak M., DeTuri M., Campbell S., *Org. Lett.*, **4**, 2665–2668 (2002).
- 15) Roy S., Haque S., Gribble G. W., *Synthesis*, 3948–3954 (2006).
- 16) Cornforth J. W., Cornforth R. H., *J. Chem. Soc.*, 96–102 (1947).
- 17) Shin C.-G., Sato Y., Sugiyama H., Nanjo K., Yoshimura J., *Bull.*

- Chem. Soc. Jpn.*, **50**, 1788–1792 (1977).
- 18) Yokoyama M., Menjo Y., Watanabe M., Togo H., *Synthesis*, 1467–1470 (1994).
- 19) Review on oxazolines: Gant T. G., Meyers A. I., *Tetrahedron*, **50**, 2297–2360 (1994).
- 20) Evans D. L., Minster D. K., Jordis U., Hecht S. M., Mazzu A. L. Jr., Meyers A. I., *J. Org. Chem.*, **44**, 497–501 (1979).
- 21) Kashima C., Arao H., *Synthesis*, 873–874 (1989).
- 22) Barrish J. C., Singh J., Spergel S. H., Han W.-C., Kissick T. P., Kronenthal D. R., Mueller R. H., *J. Org. Chem.*, **58**, 4494–4496 (1993).
- 23) Wipf P., Miller C. P., *J. Org. Chem.*, **58**, 3604–3606 (1993).
- 24) Meyers A. I., Tavares F. X., *J. Org. Chem.*, **61**, 8207–8215 (1996).
- 25) Williams D. R., Lowder P. D., Gu Y.-G., Brooks D. A., *Tetrahedron Lett.*, **38**, 331–334 (1997).
- 26) Phillips A. J., Uto Y., Wipf P., Reno M. J., Williams D. R., *Org. Lett.*, **2**, 1165–1168 (2000).
- 27) Prager R. H., Smith J. A., Weber B., Williams C. M., *J. Chem. Soc., Perkin Trans. I*, 2659–2672 (1997).
- 28) Wang Z., “Comprehensive Organic Name Reactions and Reagents,” John Wiley & Sons, Inc., Hoboken, NJ, 2009, pp. 2293–2297.
- 29) Jones R. A., Bean G. P., “The Chemistry of Pyrroles,” Academic, London, 1977.
- 30) Woo J., Sigurdsson S. T., Hopkins P. B., *J. Am. Chem. Soc.*, **115**, 3407–3415 (1993).
- 31) Cooney J. V., McEwen W. E., *J. Org. Chem.*, **46**, 2570–2573 (1981).
- 32) Lee D., Swager T. M., *J. Am. Chem. Soc.*, **125**, 6870–6871 (2003).
- 33) Peschko C., Winkelhofer C., Terpin A., Steglich W., *Synthesis*, 3048–3052 (2006).
- 34) Cheng L., Lightner D. A., *Synthesis*, 46–58 (1999).
- 35) Knorr L., *Chem. Ber.*, **17**, 1635–1642 (1884).
- 36) Patterson J. M., *Synthesis*, 281–304 (1976).
- 37) Bean G. P., “The Chemistry of Heterocyclic Compounds, Pyrroles,” Vol. 48, ed. by Jones R. A., Wiley, New York, NY, 1990, p. 105.
- 38) Hantzsch A., *Ber. Dtsch. Chem. Ges.*, **23**, 1474–1483 (1890).
- 39) Plaskon A. S., Ryabukhin S. V., Volochnyuk D. M., Shivanyuk A. N., Tolmachev A. A., *Tetrahedron*, **64**, 5933–5943 (2008).
- 40) Furstner A., Weintritt H., Hupperts A., *J. Org. Chem.*, **60**, 6637–6641 (1995).
- 41) Katritzky A., Jiang J., Steel P. J., *J. Org. Chem.*, **59**, 4551–4555 (1994).
- 42) Padmavathi V., Prema Kumari C., Venkatesh B. C., Padmaja A., *Eur. J. Med. Chem.*, **46**, 5317–5326 (2011).
- 43) Little T. L., Webber S. E., *J. Org. Chem.*, **59**, 7299–7305 (1994).
- 44) Potewar T. M., Ingale S. A., Srinivasan K. V., *Tetrahedron*, **64**, 5019–5022 (2008).
- 45) Reddy M. V. R., Reddy N. S., *Synthesis*, 322–323 (1984).
- 46) Chung K. T., Thomasson W. R., Wu-Yuan C. D., *J. Appl. Bacteriol.*, **69**, 498–503 (1990).
- 47) Azoro C., *World J. Biotechnol.*, **3**, 347–357 (2002).
- 48) Janovska D., Kubikova K., Kokoska L., *J. Food Sci.*, **21**, 107–110 (2003).
- 49) Bishnu J., Sunil L., Anuja S., *J. Science. Eng. Technol.*, **5**, 143–150 (2009).
- 50) Clinical and Laboratory Standards Institute, “Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically, 7th edition; approved standard, CLSI Document M7-A7,” Ways, Pennsylvania, 2006.
- 51) Clinical and Laboratory Standards Institute, “Method for broth dilution antifungal susceptibility testing of yeasts, approved standard NCCLS Document M27-A2,” Ways, Pennsylvania, 2002.