Synthesis of thiophenylazolyl pyrrolylsulfamoyl acetamides as potential antimicrobial agents

Tankam Rajeswari
Sri Venkateswara University
Panga Siva Sankar
Sri Venkateswara University
Kayathi Narendra Babu
Sri Venkateswara University
Adivireddy Padmaja
Sri Venkateswara University
Venkatapuram Padmavathi (vkpuram2001@yahoo.com)
Sri Venkateswara University https://orcid.org/0000-0003-3448-1423

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Abstract

A variety of thiophenylazolyl pyrrolylsulfamoyl acetamides were prepared by the reaction of azolylsulfamoyl acetate with pyrrolylamine in the presence of sodium methoxide in methanol under ultrasonication. Chloro, nitro and dinitro substituted thiophenylthiazolyl pyrrolylsulfamoyl acetamides (**9d, 9e, 9f**) and dinitro substituted thiophenylimidazolyl pyrrolylsulfamoyl acetamide (**10f**) exhibited potential antibacterial activity against *B. subtilis.* The compound **9f** also displayed prominent antibacterial activity against *S. aureus.* The compounds **9f**, chloro and nitro substituted thiophenylimidazolyl pyrrolylsulfamoyl acetamide (**10d, 10e**) and **10f** exhibited prominent antifungal activity against *A.niger.*

Introduction

Azoles are the most prevalent heteroaromatic molecules and display a pivotal role in drug discovery. Oxazole containing molecules viz., Inthomycin C (antineoplastic) [Ibrahim et al. 2017; K. J. Hale et al. 2014], Oxaprozin (anti-inflammatory) [Mark et al. 2011], Pemoline (nervous system stimulant) [Erhorn et al. 2007, Kulikowska et al. 2002] and Bengazole A (antibiotic) [Chandrasekhar et al. 2010] are used as drugs. Thiazole derivatives are common entities in pharmaceutical arena due to their broad applications in drug development [Valentin et al. 2010; Ahmed et al. 2007; Wilson et al. 2001; Ritesh et al. 2009]. Thiazole nucleus is also an integral part of penicillins, which have revolutionized the therapy of bacterial diseases [Samir et al. 2013]. Sulfathiazole (antimicrobial), Bleomycin and Tiazofurin (antineoplastic) are some of the drugs having thiazole moiety. Imidazoles form the main structure of some well-known biomolecules of human organisms such as Histidine, Vit B12, Histamine and Biotin [Leyla et al. 2013]. Pyrrole is another important scaffold found in complex macromolecules- porphyrins of heme, chlorins, bacteriochlorins, chlorophyll and porphyrinogens [Ramandeep et al. 2018; Andrea et al. 2002; Huihua et al. 2018; Honey et al. 2012]. Various pyrrole derivatives find application as antibacterial, [Roland et al. 2004] antiviral, [Kristina et al. 2007] anti-inflammatory [Harrak et al. 2007], antifungal [Ming et al. 2011], antioxidant [Jacques et al. 1999] and anticancer agents [Debasish et al. 2012]. Besides thiophene containing molecules are known to exhibit antimicrobial [Samir et al. 2010], anti-inflammatory [Przybilla et al. 1987], platelet inhibitory [John et al. 2012], antitumor [Ronald et al. 2002] and antiviral activities [Hudson et al. 1986]. The structure-activity relationship of the molecules revealed that change of substituents resulted in varied biopotency. Our continued interest towards the development of potential heteroaromatics [Siva Sankar et al. 2019; Sowmya et al. 2018; Rekha et al. 2017], we herein report the design and synthesis of thiophenylazolyl pyrrolylsulfamoyl acetamides as potential antimicrobial agents.

Results And Discussion

Chemistry

The azolyl amines- 4-thiophenyloxazolyl-2-amine (**1**) and 4-thiophenylthiazolyl-2-amine (**2**) were prepared by the cyclocondensation of 2-bromo-1-(thiophen-2-yl)ethan-1-one with urea and thiourea in methanol [Taterao et al. 2008]. 4-Thiophenylimidazolyl-2-amine (**3**) was prepared by the hydrolysis of *N*-4-thiophenyl-1*H*-imidazol-2-ylacetamide in the presence of H_2SO_4. The latter compound was obtained by the treatment of 2-bromo-1-(thiophen-2-yl)ethan-1-one with acetylguanidine [Thomas et al. 1994]. Sulfonylation of heteroarylamines was reported by several methods [Divya et al. 2015; Pasha et al. 2014]. In fact, we have carried out *N*-sulfonylation of heteroarylamines with ethyl chlorosulfonylacetate in the presence of DMAP / Et_3N [Premakumari et al. 2014] and

also in the presence of dispersed sodium in THF [Divya et al. 2015]. It was observed that the reaction proceeded at a faster rate with dispersed Na. Based on these results, we have carried out the reaction of (**1**) with methyl 2-(chlorosulfonyl) acetate in the presence of dispersed sodium under ultrasonication at a frequency of 35 KHz where in the product methyl 2-(*N*-(4-(4-thiophen-2-yl)oxazol-2-yl)sulfamoyl)acetate (**4**) was obtained in excellent yield. Adopting similar methodology, methyl 2-(*N*-(4-(4-thiophen-2-yl)thiazol-2-yl)sulfamoyl)acetate (**5**) and methyl 2-(*N*-(4-(4-thiophen-2-yl)-1*H*-imidazol-2-yl)sulfamoyl)acetate (**6**) were prepared by the treatment of **2** and **3** with methyl 2-(chlorosulfonyl)acetate (**Scheme I**). In the presence of dispersed sodium, methyl 2-sulfonylacetate free radical was generated from methyl 2-chlorosulfonylacetate which reacted with heteroarylamines to get corresponding sulfonamides by the expulsion of H_2 (**Scheme I & Mechanism**).

Mechanism

Amidation of esters with amines was reported in the presence of different catalysts *viz*, DBU [Marcocci et al. 1994] triazabicyclo[4.4.0]dec-5-ene [Ahmad et al. 2011] and 1,2,4-triazole-DBU [Zia-ur-Rehman et al. 2009]. Inorganic catalysts like $Sb(OEt)_3$ [Kristin et al. 2009] and $Zr(OtBu)_4$-HoAt [Sabot et al. 2007] have also been used for direct amidation. Apart from these Takastri *et al* reported sodium methoxide catalyzed amidation of alkyl and aryl esters and proved sodium / potassium alkoxides possess high catalytic activity for direct amidation reactions [Xing et al. 2009]. As such we have carried out amidation of methyl 2-(*N*-(4-(4-chlorothiophen-2-yl)oxazol-2-yl)sulfamoyl)acetate (**4a**) with 4-phenyl-1*H*-pyrrol-2-amine (**7a**) in the presence of two molar equivalents of sodium methoxide in THF under ultrasonication at a frequency 35 KHz. The product *N*-(4-(4-chlorothiophen-2-yl)oxazol-2-yl)-2-(*N*-(4-phenyl-1*H*-pyrrol-2-yl)sulfamoyl)acetamide (**8a**) was obtained in low yield (38%). However when the reaction was repeated with three molar equivalents, the yield of **8a** was raised to 48%. In order to increase the yield, the reaction between **4a** and **7a** was carried out with different molar concentration of sodium methoxide. The reaction took place well in the presence of 5.0 mol% sodium methoxide leading to the formation of product **8a** in excellent yield (**Table 1**).

Then the reaction of **4, 5** and **6** was carried out with 4-aryl-1*H*-pyrrol-2-amine (**7**) in the presence of 5.0 mol% sodium methoxide to get *N*-(4-(4-chlorothiophen-2-yl)oxazol-2-yl)-2-(*N*-(4-phenyl-1*H*-pyrrol-2-yl)sulfamoyl)acetamide (**8**) / *N*-(4-(4-chlorothiophen-2-yl)thiazol-2-yl)-2-(*N*-(4-phenyl-1*H*-pyrrol-2-yl)sulfamoyl)acetamide (**9**) / *N*-(4-(4-chlorothiophen-2-yl)-1*H*-imidazol-2-yl)-2-(*N*-(4-phenyl-1*H*-pyrrol-2-yl)sulfamoyl)acetamide (**10**) (**Scheme-II**).

Biological evaluation

Antibacterial activity

All the compounds are tested for antibacterial activity at four different concentrations 12.5, 25, 50, and 100 µg/well. All the compounds displayed higher activity on Gram-positive bacteria than on Gram-negative bacteria (**Table 1**). Thiophenylthiazolyl pyrrolylsulfamoyl acetamides (**9**) showed higher activity than thiophenyloxazolyl pyrrolylsulfamoyl acetamides (**8**) and thiophenylimidazolyl pyrrolylsulfamoyl acetamides (**10**). Amongst the latter compounds **10** exhibited greater activity than **8**. It was also observed that the presence of electron withdrawing substituents enhanced the activity and the activity increased with increasing electronegativity. The compounds having nitro substituents displayed higher activity than those with chloro substituents. In fact, dinitro substituted compounds **8f, 9f** and **10f** displayed higher activity in the respective series. It was also observed that those having chloro and nitro substituents **8d**, **9d**, **10d** and **8e**, **9e**, **10e** showed slightly higher activity when compared with the

compounds having two chloro substituents **8c**, **9c** and **10c**. Further it was noticed that there was not much difference in activity amongst the compounds **8d, 9d, 10d** and **8e, 9e, 10e** which showed that the presence of more electron withdrawing nitro substituent either at 4 position of thiophene or at 4 position of aromatic ring has similar effect. Amongst all the tested compounds **9d**, **9e**, **9f** and **10f** displayed higher activity on *B. subtilis* greater than the standard drug Chloramphenicol at all tested concentrations. Further the compound **9f** displayed equal activity to the standard drug on *S. aureus* at 50 and 100 µg/well.

Antifungal activity

All the compounds effectively inhibited the spore germination of tested fungi (**Table 2**). It was noticed that compounds having imidazole unit (**10**) displayed grater activity than those with oxazole (**8**) and thiazole (**9**) moieties. Further the activity increased with increasing electronegativity of the substituents. The compounds **9f**, **10d**, **10e** and **10f** showed higher activity on *A. niger* greater than the standard drug, Ketoconazole at all tested concentrations.

The compounds which showed greater antibacterial and antifungal activities are further assayed for minimum inhibitory concentration (MIC), minimum bactericidal concentration (MBC) and minimum fungicidal concentration (MFC) and the values are listed in Table 3. MIC is the lowest concentration of an antimicrobial that will inhibit the visible growth of a microorganism. (But it is not sure that the microorganisms are completely killed). The MBC/MFC is the lowest concentration of antibiotic required to kill a particular bacterium/fungi. The MBC/MFC involves an additional set of steps performed once the MIC is determined. The antimicrobials are usually regarded as bactericidal/fungicidal if MBC/MFC is not greater than four times MIC. The compounds **9d, 9e, 9f** and **10f** displayed low MIC against *B. Subtilis*. The MIC of these compounds is equal to standard drug chloramphenicol and MBC is 2 x MIC. Further **9f** showed low MIC on *S. aureus* and MBC is found to be 2 x MIC. Moreover the compounds **9f, 10d, 10e** and **10f** exhibited low MIC against *A. niger* and MFC is 2 x MIC.

Conclusion

A variety of thiophenylazolyl pyrrolylsulfamoyl acetamides were prepared by the reaction of azolylsulfamoyl acetate with pyrrolylamine in the presence of sodium methoxide in methanol under ultrasonication. The presence of electron withdrawing substituents increased antimicrobial activity. Chloro, nitro and dinitro substituted thiophenylthiazolyl pyrrolylsulfamoyl acetamides (**9d, 9e, 9f**) and dinitro substituted thiophenylimidazolyl pyrrolylsulfamoyl acetamide (**10f**) exhibited potential antibacterial activity against *B. subtilis.* These compounds exhibited low MIC against *B. Subtilis* equal to standard drug chloramphenicol and MBC is 2 x MIC. Further **9f** showed low MIC on *S. aureus* and MBC is 2 x MIC. The compounds **9f, 10d, 10e** and **10f** displayed prominent antifungal activity against *A. niger* and MFC is 2 x MIC.

Experimental Section

Apparatus and analysis

Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected. The purity of the compounds was evaluated 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 were given in cm^{-1}. The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 on a Bruker spectrometer operating at 400 and 100 MHz. The

chemical shifts are reported in δ (ppm) using TMS 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 Bandelinsonorex RK 12 H ultrasonic bath operating at a frequency of 35 KHz. 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 compounds 4-thiophenyloxazolyl-2-amine (**1**) and 4-thiophenylthiazolyl-2-amine (**2**) 4-thiophenylimidazolyl-2-amine (**3**) were prepared as per the literature procedures [Taterao et al. 2008]. The compound 4-(4-chlorophenyl)-1*H*-pyrrol-2-amine (**7**) was purchased from Aldrich.

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 enveloped with a dry cloth and the sand bath was heated cautiously. The ring of condensed vapour 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 the sodium was washed with sodium-dried ether. The dispersed sodium as small spheres was preserved in absolute ether.

General procedure for the synthesis of methyl 4-thiophenylazolylsulfamoyl acetate **(4/5/6)**

A mixture of methyl 2-chlorosulfonylacetate (0.001 mol), dispersed sodium (0.0414 g, 1.8 mg atom) and tetrahydrofuran (3 ml) was sonicated for 8 min in a sonic bath at a frequency of 35 KHz at 25^0C. To this azolyl-2-amine (**1/2/3**) was added and continued sonication for 12–16 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 which was recrystallized from ethanol.

Methyl 2-(N-(4-(4-chlorothiophen-2-yl)oxazol-2-yl)sulfamoyl)acetate **(4a).** Yield 75%; m.p.: 122-124°C; IR (KBr): 1129, 1327 (SO_2), 1579 (C = N), 1632 (C = C), 1680 (C = O), 3356 (NH) (cm^{-1}); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.68 (s, 3H, O-CH_3), 4.36 (s, 2H, CH_2), 7.07 (s, 1H, C_5-H), 7.35 (s, 1H, C_3-H), 7.58 (s, 1H, C_5-H), 10.46 (bs, 1H, SO_2NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 49.1 (O-CH_3), 70.4 (CH_2), 121.9, 123.7, 125.4, 127.2, 141.5, 145.1, 146.6 (Aromatic carbons C-2, C-4, C-5, C-2', C-3', C-4' & C-5'), 163.0 (C = O) ppm; HRMS (*m/z*): 359.7513 [M + Na]; Anal. Calcd. for $C_{10}H_9ClN_2O_5S_2$: C, 35.67; H, 2.69; N, 8.32; Found: C, 35.74; H, 2.63; N, 8.41%.

Methyl 2-(N-(4-(4-nitrothiophen-2-yl)oxazol-2-yl)sulfamoyl)acetate **(4b).** Yield 72%; m.p.: 145-147°C; IR (KBr): 1135, 1321 (SO_2), 1587 (C = N), 1650 (C = C), 1676 (C = O), 3367 (NH) (cm^{-1}); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.64 (s, 3H, O-CH_3), 4.34 (s, 2H, CH_2), 7.61 (s, 1H, C_5-H), 8.39 (s, 1H, C_5-H), 8.66 (s, 1H, C_3-H), 10.48 (bs, 1H, SO_2NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 51.9 (O-CH_3), 65.6 (CH_2), 117.3, 127.1, 132.6, 138.0, 146.5, 149.4, 153.2 (Aromatic carbons C-2, C-4, C-5, C-2', C-3', C-4' & C-5'), 162.8 (C = O) ppm; HRMS (*m/z*): 370.3051 [M + Na]; Anal. Calcd. for $C_{10}H_9N_3O_7S_2$: C, 34.58; H, 2.61; N, 12.10; Found: C, 34.50; H, 2.66; N, 12.26%.

Methyl 2-(N-(4-(4-chlorothiophen-2-yl)thiazol-2-yl)sulfamoyl)acetate **(5a)**. Yield 76%; m.p.: 138-140°C; IR (KBr): 1143, 1335 (SO_2), 1583 (C = N), 1643 (C = C), 1688 (C = O), 3365 (NH) (cm^{-1}); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.70 (s, 3H, O-CH_3), 4.32 (s, 2H, CH_2), 7.02 (s, 1H, C_5-H), 7.10 (s, 1H, $C_{5'}$-H), 7.41 (s, 1H, $C_{3'}$-H), 10.44 (bs, 1H, SO_2NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 49.7 (O-CH_3), 63.2 (CH_2), 105.2 (C-5), 124.3, 127.0, 131.5, 140.3, 145.1 (Aromatic carbons C-4, C-2', C-3', C-4' & C-5'), 162.6 (C = O), 165.4 (C-2) ppm; HRMS (*m/z*): 375.8122 [M + Na]; Anal. Calcd. for $C_{10}H_9ClN_2O_4S_3$: C, 34.04; H, 2.57; N, 7.94; Found: C, 33.98; H, 2.62; N, 7.99%.

Methyl 2-(N-(4-(4-nitrothiophen-2-yl)thiazol-2-yl)sulfamoyl)acetate **(5b)**. Yield 74%; m.p.: 163-165°C; IR (KBr): 1124, 1341 (SO_2), 1578 (C = N), 1652 (C = C), 1674 (C = O), 3371 (NH) (cm^{-1}); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.74 (s, 3H, O-CH_3), 4.36 (s, 2H, CH_2), 7.05 (s, 1H, C_5-H), 8.35 (s, 1H, $C_{5'}$-H), 8.69 (s, 1H, $C_{3'}$-H), 10.42 (bs, 1H, SO_2NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 50.2 (O-CH_3), 64.5 (CH_2), 106.7 (C-5), 117.2 (C-3'), 128.7, 144.5, 146.4, 152.3 (Aromatic carbons C-4, C-2', C-4' & C-5'), 162.1 (C = O), 169.6 (C-2) ppm; HRMS (*m/z*): 386.3673 [M + Na]; Anal. Calcd. for $C_{10}H_9N_3O_6S_3$: C, 33.05; H, 2.50; N, 11.56; Found: C, 33.12; H, 2.54; N, 11.65%.

*Methyl 2-(N-(4-(4-chlorothiophen-2-yl)-1*H*-imidazol-2-yl)sulfamoyl)acetate* **(6a)**. Yield 77%; m.p.: 149-151°C; IR (KBr): 1148, 1330 (SO_2), 1585 (C = N), 1645 (C = C), 1687 (C = O), 3377 (NH) (cm^{-1}); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.69 (s, 3H, O-CH_3), 4.31 (s, 2H, CH_2), 7.06 (s, 1H, $C_{5'}$-H), 7.37 (s, 1H, $C_{3'}$-H), 7.40 (s, 1H, C_5-H), 10.38 (bs, 1H, SO_2NH), 12.88 (bs, 1H, Imidazole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 51.8 (O-CH_3), 61.0 (CH_2), 121.3, 123.1, 125.1, 128.6, 139.4, 143.2, 154.5 (Aromatic carbons C-2, C-4, C-5, C-2', C-3', C-4' & C-5'), 163.7 (C = O) ppm; HRMS (*m/z*): 358.7672 [M + Na]; Anal. Calcd. for $C_{10}H_{10}ClN_3O_4S_2$: C, 35.77; H, 3.00; N, 12.51; Found: C, 35.84; H, 3.04; N, 12.44%.

*Methyl 2-(N-(4-(4-nitrothiophen-2-yl)-1*H*-imidazol-2-yl)sulfamoyl)acetate* **(6b)**. Yield 75%; m.p.: 178-180°C; IR (KBr): 1136, 1322 (SO_2), 1588 (C = N), 1633 (C = C), 1675 (C = O), 3380 (NH) (cm^{-1}); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.73 (s, 3H, O-CH_3), 4.38 (s, 2H, CH_2), 7.42 (s, 1H, C_5-H), 8.38 (s, 1H, $C_{5'}$-H), 8.65 (s, 1H, $C_{3'}$-H), 10.40 (bs, 1H, SO_2NH), 12.90 (bs, 1H, Imidazole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 52.3 (O-CH_3), 62.1 (CH_2), 122.9, 124.8, 133.4, 139.0, 146.8, 152.9, 154.1 (Aromatic carbons C-2, C-4, C-5, C-2', C-3', C-4' & C-5'), 165.4 (C = O) ppm; HRMS (*m/z*): 369.3224 [M + Na]; Anal. Calcd. for $C_{10}H_{10}N_4O_6S_2$: C, 34.68; H, 2.91; N, 16.18; Found: C, 34.62; H, 2.62; N, 16.15%

*General procedure for the synthesis of N-(4-(4-chlorothiophen-2-yl)oxazol / thiazol / imidazol-2-yl)-2-(N-(4-phenyl-1*H*-pyrrol-2-yl)sulfamoyl) acetamide* (**8/9/10**)

A mixture of sodium methoxide (0.0011 mol), 4-phenyl-1*H*-pyrrol-2-amine (**7**) and methanol (5 ml) was sonicated at a frequency of 35 KHz at room temperature for 5 min. To this thiophenyl azolyl sulfamoyl acetate (**4/5/6**) (0.001 mol) was added and continued sonication for 22–30 min. The solvent was evaporated under reduced pressure. The gummy substance was recrystallized from ethanol.

*N-(4-(4-Chlorothiophen-2-yl)oxazol-2-yl)-2-(N-(4-phenyl-1*H*-pyrrol-2-yl)sulfamoyl)acetamide* (**8a**) yield 64% ; m.p.: 149-151^{o}C; IR (KBr): 3375 (CONH), 1712 (C = O), 1678 (C = C), 1579 (C = N), 1326 – 1132 (SO_2) (cm^{-1}); ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.28 (s, 2H, CH_2), 6.60 (s, 1H, $C_{3''}$-H), 7.05 (s, 1H, $C_{5''}$-H), 7.14 (s, 1H, $C_{5'}$-H), 7.40–7.66 (m, 7H, Ar-H, $C_{3''}$-H & C_5-H), 9.92 (bs, 1H, $CONH_2$), 10.32 (bs, 1H, NH), 11.45 (bs, 1H, Pyrrole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 64.2 (H_2C-CO), 104.1 (C-3''), 116.3 (C-5''), 118.8 (C-5'), 144.0 (C-2'), 151.4 (C-2), 169.8 (C = O), 121.3, 122.1, 123.5, 125.9, 126.7, 127.8, 133.3, 136.1, 138.5, 139.7 (Aromatic carbons & C-4, C-5, C-3', C-4', C-2'', C-4'') ppm.

HRMS (*m/z*): 485.9126 $[M + Na]^+$; Anal. Calcd. for $C_{19}H_{15}ClN_4O_4S_2$: C, 49.30; H, 3.27; N, 12.10; Found: C, 49.39; H, 3.35; N, 12.18%.

*N-(4-(4-Nitrothiophen-2-yl)oxazol-2-yl)-2-(N-(4-phenyl-1*H*-pyrrol-2-yl)sulfamoyl)acetamide* (**8b**) yield 68% ; m.p.: 153-155^oC; IR (KBr): 3381 (CONH), 1688 (C = O), 1679 (C = C), 1577 (C = N), 1332 – 1140 (SO_2) (cm^{-1}); ^1H NMR (400 MHz, DMSO-d_6): δ 4.29 (s, 2H, CH_2), 6.58 (s, 1H, $C_{3'}$-H), 7.08 (s, 1H, $C_{5'}$-H), 7.42–7.72 (m, 6H, Ar-H & C_5-H), 8.42 (s, 1H, $C_{5'}$-H), 8.79 (s, 1H, $C_{3'}$-H), 9.95 (bs, 1H, $CONH_2$), 10.49 (bs, 1H, NH), 11.66 (bs, 1H, Pyrrole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 65.1 (H_2C-CO), 106.6 (C-3"), 116.7 (C-5"), 118.5 (C-3'), 124.1 (C-4), 144.3 (C-2'), 149.1 (C-4'), 152.6 (C-2), 170.4 (C = O), 125.8, 128.5, 130.7, 132.4, 134.9, 135.6, 136.8, 137.6 (Aromatic carbons & C-5, C-5', C-2", C-4") ppm. HRMS (*m/z*): 496.4676 $[M + Na]^+$; Anal. Calcd. for $C_{19}H_{15}N_5O_6S_2$: C, 48.20; H, 3.19; N, 14.79; Found: C, 48.27; H, 3.14; N, 14.68%.

*2-(N-(4-(4-Chlorophenyl)-1*H*-pyrrol-2-yl)sulfamoyl)-N-(4-(4-chlorothiophen-2-yl)oxazol-2-yl) acetamide* (**8c**) yield 67% ; m.p.: 159-161^oC; IR (KBr): 3377 (CONH), 1722 (C = O), 1680 (C = C), 1582 (C = N), 1335 – 1132 (SO_2) (cm^{-1}); ^1H NMR (400 MHz, DMSO-d_6): δ 4.27 (s, 2H, CH_2), 6.56 (s, 1H, $C_{3'}$-H), 7.04 (s, 1H, $C_{5'}$-H), 7.15 (s, 1H, $C_{5'}$-H), 7.58–7.84 (m, 6H, Ar-H C_5-H & $C_{3'}$-H), 10.26 (bs, 1H, $CONH_2$), 10.41 (bs, 1H, NH), 11.81 (bs, 1H, Pyrrole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 65.2 (H_2C-CO), 106.3 (C-3"), 117.9 (C-5"), 119.2 (C-3'), 121.2 (C-5'), 140.7 (C-5), 145.6 (C-2'), 154.3 (C-2), 170.3 (C = O), 125.1, 126.3, 127.2, 130.5, 132.2, 135.4, 136.5, 137.3 (Aromatic carbons & C-4, C-4', C-2", C-4") ppm; HRMS (*m/z*): 520.3850 $[M + Na]^+$; Anal. Calcd. for $C_{19}H_{14}Cl_2N_4O_4S_2$: C, 45.88; H, 2.84; N, 11.26; Found: C, 45.80; H, 2.80; N, 11.18 %.

*2-(N-(4-(4-Chlorophenyl)-1*H*-pyrrol-2-yl)sulfamoyl)-N-(4-(4-nitrothiophen-2-yl)oxazol-2-yl) acetamide* (**8d**) yield 70%; m.p.: 165-167^oC; IR (KBr): 3372 (CONH), 1702 (C = O), 1684 (C = C), 1568 (C = N), 1335 – 1128 (SO_2) (cm^{-1}); ^1H NMR (400 MHz, DMSO-d_6): δ 4.26 (s, 2H, CH_2), 6.61 (s, 1H, $C_{3'}$-H), 7.12 (s, 1H, $C_{5'}$-H), 7.64–7.83 (m, 5H, Ar-H & C_5-H), 8.44 (s, 1H, $C_{5'}$-H), 8.75 (s, 1H, $C_{3'}$-H), 10.20 (bs, 1H, $CONH_2$), 10.48 (bs, 1H, NH), 11.93 (bs, 1H, Pyrrole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 64.5 (H_2C-CO), 107.2 (C-3"), 114.5 (C-3'), 117.3 (C-5"), 142.8 (C-2'), 154.1 (C-2), 172.1 (C = O), 149.8 (C-4'), 123.1, 125.2, 127.4, 128.8, 129.5, 132.6, 134.1, 137.9, 139.2 (Aromatic carbons, C-4, C-5, C-5', C-2" & C-4") ppm. HRMS (*m/z*): 530.9095 $[M + Na]^+$; Anal. Calcd. for $C_{19}H_{14}ClN_5O_6S_2$: C, 44.93; H, 2.78; N, 13.79; Found: C, 45.00; H, 2.74; N, 13.85 %.

*N-(4-(4-Chlorothiophen-2-yl)oxazol-2-yl)-2-(N-(4-(4-nitrophenyl)-1*H*-pyrrol-2-yl)sulfamoyl) acetamide* (**8e**) yield 66%; m.p.: 160-162^oC; IR (KBr): 3380 (CONH), 1721 (C = O), 1676 (C = C), 1575 (C = N), 1339 – 1141 (SO_2) (cm^{-1}); ^1H NMR (400 MHz, DMSO-d_6): δ 4.20 (s, 2H, CH_2), 6.74 (s, 1H, $C_{3'}$-H), 7.13 (s, 1H, $C_{5'}$-H), 7.19 (s, 1H, $C_{5'}$-H), 7.59–7.75 (m, 6H, Ar-H, $C_{3'}$-H & C_5-H), 10.15 (bs, 1H, $CONH_2$), 10.65 (bs, 1H, NH), 12.04 (bs, 1H, Pyrrole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 65.8 (H_2C-CO), 107.4 (C-3"), 118.3 (C-5"), 144.3 (C-2'), 152.5 (C-2), 172.5 (C = O), 124.2, 126.8, 128.5, 129.4, 130.5, 132.3, 134.1, 135.8, 137.6, 138.5, 139.3 (Aromatic carbons, C-4, C-5, C-3', C-4', C-5', C-2" & C-4") ppm. HRMS (*m/z*): 530.9103 $[M + Na]^+$; Anal. Calcd. for $C_{19}H_{14}ClN_5O_6S_2$: C, 44.93; H, 2.78; N, 13.79; Found: C, 44.85; H, 2.83; N, 13.87 %.

*2-(N-(4-(4-Nitrophenyl)-1*H*-pyrrol-2-yl)sulfamoyl)-N-(4-(4-nitrothiophen-2-yl)oxazol-2-yl) acetamide* (**8f**) yield 68% ; m.p.: 174-176^oC; IR (KBr): 3385 (CONH), 1736 (C = O), 1687 (C = C), 1584 (C = N), 1343 – 1148 (SO_2) (cm^{-1}); ^1H NMR (400 MHz, DMSO-d_6): δ 4.26 (s, 2H, CH_2), 6.70 (s, 1H, $C_{3'}$-H), 7.14 (s, 1H, $C_{5'}$-H), 7.60–7.83 (m, 5H, Ar-H & C_5-

H), 8.32 (s, 1H, $C_{5'}$-H), 8.65 (s, 1H, $C_{3'}$-H), 10.61 (bs, 1H, $CONH_2$), 10.72 (bs,1H, NH), 12.09 (bs,1H, Pyrrole NH) ppm; ^{13}C NMR (100 MHz, DMSO-*d_6*): *δ* 66.4 (H_2C-CO), 107.8 (C-3"), 117.3 (C-5"), 118.6 (C-3'), 128.4 (C-4), 144.3 (C-2'), 150.6 (C-4'), 153.9 (C-2), 172.6 (C = O), 127.7, 128.3, 129.2, 130.4, 133.7, 135.9, 139.8, 140.6 (C-5, C-5', C-2", C-4" & Aromatic carbons) ppm. HRMS (*m/z*): 541.4654 $[M + Na]^+$; Anal. Calcd. for $C_{19}H_{14}N_6O_8S_2$: C, 44.02; H, 2.72; N, 16.21; Found: C, 44.10; H, 2.76; N, 16.34 %.

*N-(4-(4-Chlorothiophen-2-yl)thiazol-2-yl)-2-(N-(4-phenyl-1*H*-pyrrol-2-yl)sulfamoyl)acetamide* (**9a**) yield 72% ; m.p.: 135-137^{o}C; IR (KBr): 3373 (CONH), 1689 (C = O), 1670 (C = C), 1568 (C = N), 1335 – 1130 (SO_2) (cm^{-1}); ^{1}H NMR (400 MHz, DMSO-*d_6*): *δ* 4.31 (s, 2H, CH_2), 6.61 (s, 1H, $C_{3'}$-H), 7.07 (s, 1H, $C_{5'}$-H), 7.20–7.68 (m, 7H, Ar-H, $C_{3'}$-H & $C_{5'}$-H), 7.86 (s, 1H, C_5-H), 10.14 (bs, 1H, CONH), 10.46 (bs, 1H, SO_2, NH), 11.52 (bs, 1H, Pyrrole NH) ppm; ^{13}C NMR (100 MHz, DMSO-*d_6*): *δ* 64.7 (H_2C-CO), 104.2 (C-3"), 105.9 (C-5), 116.5 (C-5"), 119.8 (C-5'), 145.5 (C-2'), 146.3 (C-4), 164.7 (C-2), 170.4 (C = O), 124.3, 125.2, 127.3, 128.9, 130.5, 133.6, 136.4, 139.2 (Aromatic carbons, C-3', C-4', C-2" & C-4") ppm. HRMS (*m/z*): 501.9743 $[M + Na]^+$; Anal. Calcd. for $C_{19}H_{15}ClN_4O_3S_3$: C, 47.64; H, 3.16; N, 11.70; Found: C, 47.70; H, 3.20; N, 11.78 %.

*N-(4-(4-Nitrothiophen-2-yl)thiazol-2-yl)-2-(N-(4-phenyl-1*H*-pyrrol-2-yl)sulfamoyl)acetamide* (**9b**) yield 65% ; m.p.: 148-150^{o}C; IR (KBr): 3379 (CONH), 1718 (C = O), 1671 (C = C), 1573 (C = N), 1323 – 1134 (SO_2) (cm^{-1}); ^{1}H NMR (400 MHz, DMSO-*d_6*): *δ* 4.30 (s, 2H, CH_2), 6.63 (s, 1H, $C_{3'}$-H), 7.12 (s, 1H, $C_{5'}$-H), 7.47–7.73 (m, 5H, Ar-H), 7.80 (s, 1H, C_5-H), 8.46 (s, 1H, $C_{5'}$-H), 8.84 (s, 1H, $C_{3'}$-H), 10.28 (bs, 1H, $CONH_2$), 10.52 (bs, 1H, NH), 11.59 (bs, 1H, Pyrrole NH) ppm; ^{13}C NMR (100 MHz, DMSO-*d_6*): *δ* 66.2 (H_2C-CO), 105.8 (C-3"), 106.5 (C-5), 119.2 (C-3'), 117.6 (C-5"), 144.3 (C-2'), 147.5 (C-4), 149.1 (C-4'), 163.8 (C-2), 171.3 (C = O), 126.5, 128.2, 129.1, 131.4, 135.2, 136.6, 138.1 (Aromatic carbons, C-2", C-4" & C-5') ppm. HRMS (*m/z*): 512.5285 $[M + Na]^+$; Anal. Calcd. for $C_{19}H_{15}N_5O_5S_3$: C, 46.62; H, 3.09; N, 14.31; Found: C, 46.53; H, 3.05; N, 14.39 %.

*2-(N-(4-(4-Chlorophenyl)-1*H*-pyrrol-2-yl)sulfamoyl)-N-(4-(4-chlorothiophen-2-yl)thiazol-2-yl) acetamide* (**9c**) yield 65% ; m.p.: 154-156^{o}C; IR (KBr): 3366 (CONH), 1715 (C = O), 1672 (C = C), 1578 (C = N), 1342 – 1146 (SO_2) (cm^{-1}); ^{1}H NMR (400 MHz, DMSO-*d_6*): *δ* 4.32 (s, 2H, CH_2), 6.62 (s, 1H, $C_{3'}$-H), 7.01 (s, 1H, $C_{5'}$-H), 7.17 (s, 1H, $C_{5'}$-H), 7.44 (s, 1H, $C_{3'}$-H), 7.62–7.87 (m, 5H, Ar-H & C_5-H), 10.41 (bs, 1H, $CONH_2$), 10.63 (bs,1H, NH), 11.78 (bs,1H, Pyrrole NH) ppm; ^{13}C NMR (100 MHz, DMSO-*d_6*): *δ* 66.1 (H_2C-CO), 105.9 (C-5), 106.6 (C-3"), 117.1 (C-5"), 145.8 (C-4), 146.1 (C-2'), 163.6 (C-2), 171.1 (C = O), 121.9, 123.5, 125.3, 126.2, 127.6, 131.3, 134.2, 138.6, 139.4 (Aromatic carbons, C-3', C-4', C-5', C-2" & C-4") ppm. HRMS (*m/z*): 536.4152 $[M + Na]^+$; Anal. Calcd. for $C_{19}H_{14}Cl_2N_4O_3S_3$: C, 44.45; H, 2.75; N, 10.91; Found: C, 44.35; H, 2.72; N, 10.80 %.

*2-(N-(4-(4-Chlorophenyl)-1*H*-pyrrol-2-yl)sulfamoyl)-N-(4-(4-nitrothiophen-2-yl)thiazol-2-yl) acetamide* (**9d**) yield 68% ; m.p.: 162-164^{o}C; IR (KBr): 3368 (CONH), 1689 (C = O), 1677 (C = C), 1572 (C = N), 1344 – 1136 (SO_2) (cm^{-1}); ^{1}H NMR (400 MHz, DMSO-*d_6*): *δ* 4.33 (s, 2H, CH_2), 6.65 (s, 1H, $C_{3'}$-H), 7.15 (s, 1H, $C_{5'}$-H), 7.56–7.85 (m, 5H, Ar-H & C_5-H), 8.49 (s, 1H, $C_{5'}$-H), 8.82 (s, 1H, $C_{3'}$-H), 10.31 (bs, 1H, $CONH_2$), 10.60 (bs, 1H, NH), 11.98 (bs, 1H, Pyrrole NH) ppm; ^{13}C NMR (100 MHz, DMSO-*d_6*): *δ* 65.6 (H_2C-CO), 106.8 (C-5), 107.9 (C-3"), 116.3 (C-5"), 118.7 (C-3'), 142.3 (C-4), 143.5 (C-2'), 150.1 (C-4'), 164.3 (C-2), 172.8 (C = O), 124.2, 124.5, 126.3, 129.1, 133.4, 135.6, 137.9 (Aromatic carbons, C-5', C-2" & C-4") ppm. HRMS (*m/z*): 546.9713 $[M + Na]^+$; Anal. Calcd. for $C_{19}H_{14}ClN_5O_5S_3$:C, 43.55; H, 2.69; N, 13.37; Found: C, 43.48; H, 2.75; N, 13.45%.

*N-(4-(4-Chlorothiophen-2-yl)thiazol-2-yl)-2-(N-(4-(4-nitrophenyl)-1*H*-pyrrol-2-yl)sulfamoyl) acetamide* (**9e**) yield 68% ; m.p.: 155-157^{o}C; IR (KBr): 3376 (CONH), 1728 (C = O), 1675 (C = C), 1579 (C = N), 1338 – 1145 (SO_2) (cm^{-1}); ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.38 (s, 2H, CH_2), 6.63 (s, 1H, $C_{3''}$-H), 7.10 (s, 1H, $C_{5''}$-H), 7.21 (s, 1H, $C_{5'}$-H), 7.68–7.84 (m, 6H, Ar-H, $C_{3'}$-H & C_5-H), 10.72 (bs,1H, NH), 11.08 (bs, 1H, $CONH_2$), 12.06 (bs,1H, Pyrrole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 66.3 (H_2C-CO), 105.8 (C-5), 107.7 (C-3"), 118.9 (C-5"), 121.8 (C-5'), 123.5 (C-3'), 146.1 (C-4), 150.4 (C-2'), 164.8 (C-2), 171.7 (C = O), 126.8, 128.4, 130.6, 133.0, 135.3, 136.5, 138.7 (Aromatic carbons, C-4', C-2" & C-4") ppm. HRMS (*m/z*): 546.9704 $[M + Na]^+$; Anal. Calcd. for $C_{19}H_{14}ClN_5O_5S_3$: C, 43.55; H, 2.69; N, 13.37; Found: C, 43.62; H, 2.64; N, 13.30 %.

*2-(N-(4-(4-Nitrophenyl)-1*H*-pyrrol-2-yl)sulfamoyl)-N-(4-(4-nitrothiophen-2-yl)thiazol-2-yl) acetamide* (**9f**) yield 70% ; m.p.: 170-172^{o}C; IR (KBr): 3374 (CONH), 1714 (C = O), 1679 (C = C), 1571 (C = N), 1335 – 1139 (SO_2) (cm^{-1}); ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.33 (s, 2H,CH_2), 6.78 (s, 1H, $C_{3''}$-H), 7.23 (s, 1H, $C_{5''}$-H), 7.72–7.84 (m, 5H, Ar-H & C_5-H), 8.45 (s, 1H, $C_{5''}$-H), 8.67 (s, 1H, $C_{3''}$-H), 10.83 (bs,1H, NH), 11.21 (bs, 1H, $CONH_2$), 12.15 (bs,1H, Pyrrole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 67.6 (H_2C-CO), 107.2 (C-5), 108.3 (C-3"), 116.2 (C-5"), 119.2 (C-3'), 151.3 (C-4'), 165.3 (C-2), 172.9 (C = O), 128.1, 130.4, 132.8, 134.3, 135.4, 136.6, 138.0, 141.2, 142.7 (Aromatic carbons, C-4, C-2', C-5', C-2" & C-4") ppm. HRMS (*m/z*): 557.5261 $[M + Na]^+$; Anal. Calcd. for $C_{19}H_{14}N_6O_7S_3$: C, 42.69; H, 2.64; N, 15.72; Found: C, 42.61; H, 2.60; N, 15.64 %.

*N-(4-(4-Chlorothiophen-2-yl)-1*H*-imidazol-2-yl)-2-(N-(4-phenyl-1*H*-pyrrol-2-yl)sulfamoyl) acetamide* (**10a**) yield 69% ; m.p.: 159-161^{o}C; IR (KBr): 3364 (CONH), 1668 (C = O), 1653 (C = C), 1565 (C = N), 1321 – 1134 (SO_2) (cm^{-1}); ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.26 (s, 2H, CH_2), 6.57 (s, 1H, $C_{3''}$-H), 7.02 (s, 1H, $C_{5''}$-H), 7.25–7.60 (m, 7H, Ar-H, $C_{3'}$-H & $C_{5''}$-H), 7.75 (s, 1H, C_5-H), 9.82 (bs, 1H, $CONH_2$), 10.27 (bs, 1H, SO_2NH), 11.40 (bs, 1H, Pyrrole NH), 12.45 (bs, 1H, Imidazole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 66.1 (H_2C-CO), 105.2 (C-3"), 117.5 (C-5"), 119.1 (C-5), 144.2 (C-2'), 153.2 (C-2), 169.6 (C = O), 122.8, 125.3, 126.7, 127.4, 128.6, 130.2, 132.1, 134.7, 136.8, 139.3 (Aromatic carbons, C-4, C-3', C-4', C-5', C-2" & C-4") ppm. HRMS (*m/z*): 484.9291 $[M + Na]^+$; Anal. Calcd. for $C_{19}H_{16}ClN_5O_3S_2$: C, 49.40; H, 3.49; N, 15.16; Found: C, 49.34; H, 3.55; N, 15.24 %.

*N-(4-(4-Nitrothiophen-2-yl)-1*H*-imidazol-2-yl)-2-(N-(4-phenyl-1*H*-pyrrol-2-yl)sulfamoyl) acetamide* (**10b**) yield 70% ; m.p.: 174-176^{o}C; IR (KBr): 3365 (CONH), 1698 (C = O), 1642 (C = C), 1568 (C = N), 1328 – 1136 (SO_2) (cm^{-1}); ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.25 (s, 2H, CH_2), 6.55 (s, 1H, $C_{3''}$-H), 7.06 (s, 1H, $C_{5''}$-H), 7.35–7.67 (m, 5H, Ar-H), 7.83 (s, 1H, C_5-H), 8.41 (s, 1H, $C_{5''}$-H), 8.80 (s, 1H, $C_{3''}$-H), 10.28 (bs, 1H, $CONH_2$), 10.60 (bs, 1H, NH), 11.46 (bs, 1H, Pyrrole NH), 12.53 (bs, 1H, Imidazole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 64.9 (H_2C-CO), 104.2 (C-3"), 116.4 (C-5"), 118.3 (C-3'), 120.2 (C-5), 144.1 (C-2'), 146.7 (C-4'), 153.5 (C-2), 171.9 (C = O), 125.6, 126.9, 129.3, 131.6, 133.2, 136.5, 138.3, 139.1 (C-4, C-5', C-2", C-4" & Aromatic carbons) ppm. HRMS (*m/z*): 495.4843 $[M + Na]^+$; Anal. Calcd. for $C_{19}H_{16}N_6O_5S_2$: 48.30; H, 3.41; N, 17.79; Found: C, C, 48.36; H, 3.47; N, 17.89 %.

*2-(N-(4-(4-Chlorophenyl)-1*H*-pyrrol-2-yl)sulfamoyl)-N-(4-(4-chlorothiophen-2-yl)-1*H*-imidazol-2-yl)acetamide* (**10c**) yield 69% ; m.p.: 185-187^{o}C; IR (KBr): 3362 (CONH), 1676 (C = O), 1668 (C = C), 1571 (C = N), 1329 – 1125 (SO_2) (cm^{-1}); ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.28 (s, 2H, CH_2), 6.54 (s, 1H, $C_{3''}$-H), 7.05 (s, 1H, $C_{5''}$-H), 7.18 (s, 1H, $C_{5'}$-H), 7.55–7.80 (m, 6H, Ar-H, $C_{3'}$-H & C_5-H), 10.17 (bs, 1H, $CONH_2$), 10.28 (bs, 1H, NH), 11.89 (bs, 1H, Pyrrole NH) 12.60 (bs,1H, Imidazole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 64.8 (H_2C-CO), 106.1 (C-3"), 117.5 (C-5"), 119.2 (C-5), 144.1 (C-2'), 153.8 (C-2), 170.1 (C = O), 122.2, 124.6, 126.7, 128.5, 130.5, 133.6, 135.4, 136.3, 137.1, 138.7 (Aromatic

carbons, C-4, C-3', C-4', C-5', C-2" & C-4") ppm. HRMS (*m/z*): 519.3705 $[M + Na]^+$; Anal. Calcd. for $C_{19}H_{15}Cl_2N_5O_3S_2$:C, 45.97; H, 3.05; N, 14.11; Found: C, 45.90; H, 3.00; N, 14.23%.

*2-(N-(4-(4-Chlorophenyl)-1*H*-pyrrol-2-yl)sulfamoyl)-N-(4-(4-nitrothiophen-2-yl)-1*H*-imidazol-2-yl)acetamide* (**10d**) yield 69% ; m.p.: 194-196^oC; IR (KBr): 3361 (CONH), 1695 (C = O), 1637 (C = C), 1570 (C = N), 1331 – 1136 (SO_2) (cm^{-1}); ^1H NMR (400 MHz, DMSO-d_6): δ 4.27 (s, 2H, CH_2), 6.58 (s, 1H, $C_{3''}$-H), 7.09 (s, 1H, $C_{5''}$-H), 7.70–7.88 (m, 5H, Ar-H & C_5-H), 8.41 (s, 1H, $C_{5'}$-H), 8.78 (s, 1H, $C_{3'}$-H), 10.38 (bs, 1H, $CONH_2$), 10.56 (bs, 1H, NH), 11.86 (bs, 1H, Pyrrole NH), 12.59 (bs, 1H, Imidazole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 64.2 (H_2C-CO), 106.8 (C-3"), 116.2 (C-5"), 117.9 (C-3'), 119.5 (C-5), 144.6 (C-2'), 149.5 (C-4'), 153.6 (C-2), 170.2 (C = O), 123.7, 126.1, 128.9, 130.3, 134.2, 136.2, 137.1, 139.3 (Aromatic carbons, C-4, C-5', C-2" & C-4") ppm. HRMS (*m/z*): 529.9264 $[M + Na]^+$; Anal. Calcd. for $C_{19}H_{15}ClN_6O_5S_2$: C, 45.02; H, 2.98; N, 16.58; Found: C, 44.96; H, 2.91; N, 16.65 %.

*N-(4-(4-Chlorothiophen-2-yl)-1*H*-imidazol-2-yl)-2-(N-(4-(4-nitrophenyl)-1*H*-pyrrol-2-yl) sulfamoyl)acetamide* (**10e**) yield 72% ; m.p.: 183-185^oC; IR (KBr): 3369 (CONH), 1718 (C = O), 1643 (C = C), 1580 (C = N), 1341 – 1138 (SO_2) (cm^{-1}); ^1H NMR (400 MHz, DMSO-d_6): δ 4.35 (s, 2H, CH_2), 6.68 (s, 1H, $C_{3''}$-H), 7.07 (s, 1H, $C_{5''}$-H), 7.16 (s, 1H, $C_{5'}$-H), 7.42 (s, 1H, $C_{3'}$-H), 7.56–7.78 (m, 5H, Ar-H & C_5-H), 10.49 (bs, 1H, $CONH_2$), 10.67 (bs, 1H, NH), 11.96 (bs, 1H, Pyrrole NH), 12.65 (bs, 1H, Imidazole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 65.5 (H_2C-CO), 106.6 (C-3"), 117.8 (C-5"), 145.8 (C-2'), 151.9 (C-2), 171.6 (C = O), 121.3, 124.6, 126.4, 127.1, 129.5, 131.1, 132.4, 133.6, 134.5, 135.9, 137.8 (Aromatic carbons, C-4, C-5, C-3', C-4', C-5', C-2" & C-4") ppm. HRMS (*m/z*): 529.9255 $[M + Na]^+$; Anal. Calcd. for $C_{19}H_{15}ClN_6O_5S_2$: C, 45.02; H, 2.98; N, 16.58; Found: C, 44.95; H, 3.03; N, 16.67%.

*2-(N-(4-(4-Nitrophenyl)-1*H*-pyrrol-2-yl)sulfamoyl)-N-(4-(4-nitrothiophen-2-yl)-1*H*-imidazol-2-yl) acetamide* (**10f**) yield 73% ; m.p.: 210-212^oC; IR (KBr): 3378 (CONH), 1728 (C = O), 1667 (C = C), 1565 (C = N), 1329 – 1141 (SO_2) (cm^{-1}); ^1H NMR (400 MHz, DMSO-d_6): δ 4.21 (s, 2H, CH_2), 6.57 (s, 1H, $C_{3''}$-H), 7.10 (s, 1H, $C_{5''}$-H), 7.58–7.72 (m, 5H, Ar-H & C_5-H), 8.28 (s, 1H, $C_{5'}$-H), 8.73 (s, 1H, $C_{3'}$-H), 10.43 (bs, 1H, $CONH_2$), 10.60 (bs,1H, NH), 11.48 (bs,1H, Pyrrole NH), 12.54 (bs,1H, Imidazole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 66.2 (H_2C-CO), 107.5 (C-3"), 116.2 (C-5"), 118.3 (C-3'), 121.5 (C-5), 149.8 (C-4'), 152.7 (C-2), 171.9 (C = O), 126.9, 128.4, 130.7, 133.7, 135.4, 137.8, 140.4, 142.6, 145.0 (Aromatic carbons, C-4, C-2', C-5', C-2" & C-4") ppm. HRMS (*m/z*): 540.4803 $[M + Na]^+$; Anal. Calcd. for $C_{19}H_{15}N_7O_7S_2$: C, 44.10; H, 2.92; N, 18.95; Found: C, 44.03; H, 2.97; N, 18.83 %.

Biological Activity Assays

The *in vitro* antimicrobial studies were determined by agar well diffusion method against test organisms [Mounyr et al. 2016]. Nutrient broth (NB) plates were swabbed with 24 h old broth culture (100 µL) of test bacteria. Wells (6 mm) were made into each petriplate using the sterile cork borer. The compounds were dissolved in DMSO (5 mg/mL) and from this 2.5, 5, 10, and 20 µL (12.5, 25, 50, 100 µg/well) were added into the wells by using sterile pipettes. The standard antibiotics (positive control), chloramphenicol for antibacterial activity and ketoconazole for antifungal activity were tested against the pathogens simultaneously. The samples were dissolved in DMSO which showed no zone of inhibition acts as negative control. The plates were incubated at 37 ^oC for 24 h for bacteria and at 28 ^oC for 48 h for fungi. The diameter of zone of inhibition of each well was measured after appropriate incubation. Duplicates were done and the average values were calculated for eventual antibacterial activity. Broth dilution test was used to determine minimum inhibitory concentration (MIC) of the above samples

[Bishnu et al. 2009]. Freshly prepared nutrient broth was used as diluents. The 24 h 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 10 mL NB). The stock solution of the compounds was prepared in DMSO by dissolving 5 mg of the compound in 1 mL of DMSO. Increasing concentrations of the test samples (2.5, 5, 10, 20 µL of stock solution contains 12.5, 25, 50, 100 µg of the compounds) were added to the test tubes containing the bacterial and fungal cultures. All the tubes were incubated at 37 ^{o}C for 24 h for bacteria and at 28 ^{o}C for 48 h for fungi. The tubes were examined for visible turbidity and using NB as control. Simultaneously control without test samples and with solvent was assayed. The MIC was recorded as the lowest concentration that inhibited visible growth of the tested organisms. To determine the minimum bactericidal concentration (MBC) [Pennsylvania et al. 2006] and minimum fungicidal concentration (MFC) [Pennsylvania et al. 2002] 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. These inoculated plates were incubated at 37 ^{o}C for 24 h (bacteria) and at 28 ^{o}C for 48 h (fungi). After incubation, the lowest concentration was noted as MBC or MFC at which no visible growth was observed.

Declarations

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Tables

Table 1: Reaction of **4a** with **7a** in the presence of different molar concentrations of NaOMe

S. No	mol % of NaOMe	Yield
1	2.0 mol %	38
2	3.0 mol %	48
3	4.0 mol %	54
4	5.0 mol %	78
5	6.0 mol %	62

Table 3. The *in vitro* antifungal activity of compounds **8-10**

(–) No activity. (±) Standard deviation

Table 4. MIC, MBC and MFC of compounds **9d, 9e, 9f, 10d, 10e** and **10f**

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

Due to technical limitations, Table 2 is only available as a download in the Supplemental Files section.

Figures

Compound No.	Zone of Inhibition (mm)							
	A. niger				*P. chrysogenum*			
	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
8a	8±1.6	-	10±1.2	12±2.1	-	-	9±1.1	11±2.2
8b	-	9±1.7	11±1.5	14±1.9	-	-	11±2.0	13±1.4
8c	10±1.1	12±2.5	13±2.0	15±1.3	-	9±1.2	12±1.5	15±2.0
8d	12±2.0	13±2.1	17±2.4	21±2.2	10±1.4	12±1.6	13±1.7	15±1.9
8e	13±1.7	15±2.0	18±2.2	20±1.9	11±1.2	13±1.8	14±2.0	16±2.6
8f	19±2.3	22±2.4	25±2.6	28±2.8	15±2.0	18±1.9	20±2.3	22±2.5
9a	12±2.6	14±2.7	16±2.0	17±1.3	9±2.2	11±2.4	14±2.5	16±2.8
9b	23±2.2	25±2.3	28±1.8	31±1.2	15±1.7	17±1.3	19±1.8	22±1.4
9c	21±1.8	25±1.2	27±1.4	29±2.0	17±1.5	18±2.2	21±2.4	24±1.3
9d	27±2.1	29±2.5	31±2.8	33±2.7	19±2.5	22±2.9	25±2.6	27±2.7
9e	26±2.3	29±2.2	30±1.9	32±2.4	21±2.8	23±2.6	26±1.3	28±2.2
9f	31±2.7	33±1.5	34±2.3	37±1.7	25±2.6	27±2.8	29±1.5	31±2.4
10a	20±1.6	23±1.3	25±1.6	26±2.7	13±2.4	15±2.5	17±2.1	20±1.0
10b	26±2.4	27±2.6	29±2.1	32±1.2	18±1.8	20±2.8	23±1.5	25±2.7
10c	27±2.1	29±2.3	30±1.7	33±1.5	21±1.6	24±1.5	26±1.6	28±1.2
10d	31±2.3	34±1.7	35±2.5	38±1.4	22±2.8	24±2.7	27±1.9	30±2.3
10e	30±2.1	32±1.8	35±2.2	38±1.8	23±2.3	25±2.5	28±1.4	30±2.1
10f	34±2.5	36±2.4	39±2.7	41±1.6	26±2.9	27±2.3	30±1.7	32±2.8
Ketoconazole	29±1.4	31±2.2	33±1.6	36±2.1	33±3.2	35±1.7	36±2.5	38±1.4
Control (DMSO)	-	-	-	-	-	-	-	-

Compound	Minimum inhibitory concentration MIC (MBC/MFC) *m*g/well					
	S. aureus	*B. subtilis*	*P. aeruginosa*	*K.pneumoniae*	*A. niger*	*P.chrysogenum*
9d	12.5(50)	6.25(12.5)	12.5(50)	100(>200)	12.5(50)	200(-)
9e	12.5(50)	6.25(12.5)	12.5(50)	100(>200)	12.5(50)	200(-)
9f	6.25(12.5)	6.25(12.5)	12.5(50)	50(200)	6.25(12.5)	100(>200)
10d	50(200)	12.5(100)	50(200)	200(-)	6.25(12.5)	100(>200)
10e	50(200)	12.5(100)	50(200)	200(-)	6.25(12.5)	100(>200)
10f	25(100)	6.25(12.5)	50(200)	200(-)	.2 6.25(12.5)	100(>200)
C Chloramphenicol	6.25	6.25	6.25	12.5	—	—
Ketoconazole	—	—	—	—	6.25	12.5

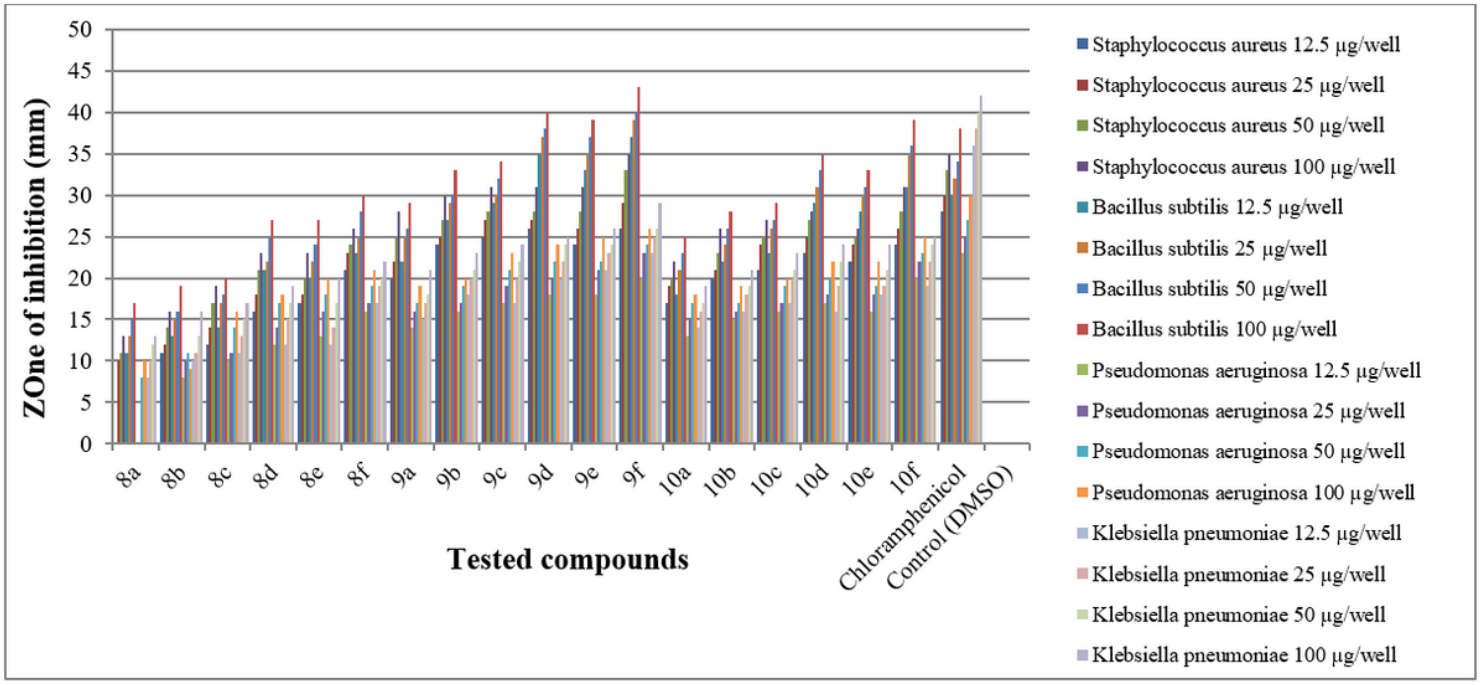

Figure 1

The invitro antibacterial activity of compounds 8-10

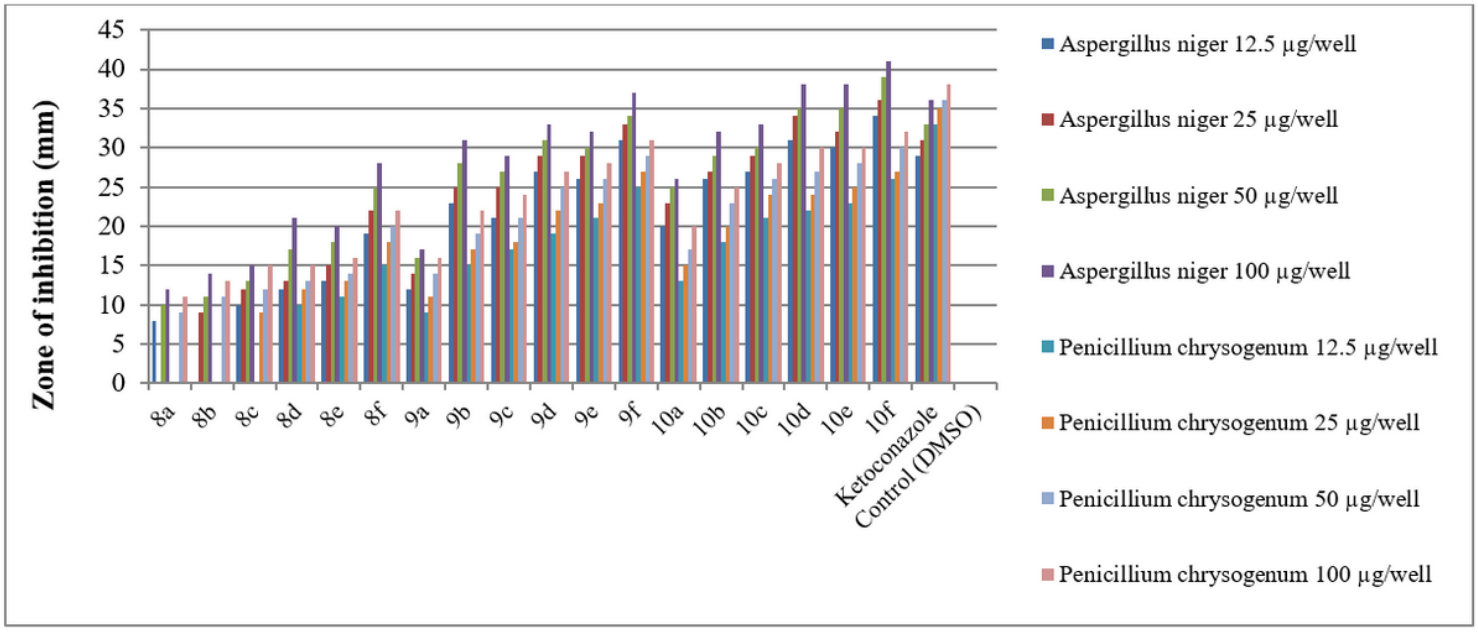

Figure 2

The in vitro antifungal activity of compounds 8-10

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

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