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Synthesis and Antimicrobial Activity of Azetidinone and Thiazolidinone Derivatives from Azolylindolyl Schiff's Bases

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Abstract

A new class of azolyl indolyl thiazolidinones and azetidinones were prepared from azolyl indolyl Schiff's bases on reaction with thioglycolic acid and chloroacetyl chloride, respectively under ultrasonication at a frequency of 46 KHz. The chloro substituted thiazolyl indolyl azetidinone (**12c**) and imidazolyl indolyl azetidinone (**13c**) are prominent antibacterial agents against *B. subtilis* whereas **13c** is the prominent antifungal agent against *A. niger*.

Keywords: Antimicrobial activity; Thiazolidinone derivatives; Schiff's bases

Introduction

Molecules with azomethine group (Schiff's base) gained importance in medicinal and pharmaceutical arena due to potential biological activities *viz.*, anti-inflammatory [1,2], analgesic [3,4], antimicrobial [5,6], antioxidant [7] and anthelmintic [8] they possess. Besides, they are also used as synthons in the synthesis of a number of biologically active molecules. 4-Thiazolidine and their derivatives find applications as anticonvulsant [9], anticancer [10], antifungal [11], anti-inflammatory [12] and analgesic [13]. They also inhibit bacterial enzyme Mur B, a key enzyme responsible for the synthesis of peptidoglycan [14]. The synthesis of 1,3-thiazolidin-4-ones was reported by the reaction of a carbonyl compound, an amine and mercaptoacetic acid either in a one-step or in a two–step manner [15]. Ultrasound sonochemistry was also exploited for the preparation of these compounds from piperonilamine [16]. The 2-azetidinone ring system is commonly found in a number of β-lactam antibiotics such as penicillins, cephalosporins, carbapenems, nocardicins and monobactams which are used to treat bacterial infections. The most common method for the synthesis of azetidinones was [2+2] Staudinger's ketene-imine cycloaddition. In addition, the reaction of an acid chloride and an imine in the presence of a base or a diazoketone as ketene precursor [17] or by enolate-imine condensation [18] also afforded azetidinones. In fact, we have reported some N-isoxazolyl-2-heteroarylthiazolidinones and N-isoxazolyl-2-heteroarylazetidinones from Schiff's base [19]. Thus, the biopotency of these heterocycles impelled to continue our research on the synthesis and bioassay of azetidinone and thiazolidinone derivatives from azolylindolyl Schiff's bases.

Chemistry

The synthetic pathway to achieve azolylindolylthiazolidinones and azolylindolylazetidinones is depicted in Scheme 1. The cyclocondensation of phenacyl bromide with urea and thiourea resulted in 2-amino-4-aryloxazoles (**1**) and 2-amino-4-arylthiazoles (**2**), respectively [20]. 2-Amino-4-arylimidazoles (**3**) were prepared by the reaction of phenacyl bromide with acetylguanidine followed by hydrolysis in the presence of sulfuric acid [20]. The Schiff's bases-*E*-1-(1*H*-indol-2-yl)-*N*-(4-aryloxazol-2-yl)methanimine (**5**), *E*-1-(1*H*-indol-2-yl)-*N*-(4-arylthiazol-2-yl)methanimine (**6**) and *E*-1-(1*H*-indol-2-yl)-*N*-(4-aryl-1*H*-imidazol-2-yl)methanimine (**7**) were prepared by the reaction of **1**/**2**/**3** with indolylaldehyde (**4**) (Aldrich) in the presence of acetic acid in methanol under ultrasonication at a frequency of 46 KHz. The ^{1}H NMR spectra of **5a**, **6a** and **7a** showed two singlets at δ 8.73, 8.76, 8.80 and 6.94, 7.02, 6.90 due to CH of imine and C_3-H of indole. Besides a broad singlet was observed at δ 9.72, 9.74 and 9.79 ppm for indole NH which disappeared on deuteration. The singlet due to C_5-H of azole appeared at downfield region and merged with aromatic protons.

The imine functionality present in **5**/**6**/**7** was used to develop heteroarylthiazolidinones. The reaction of **5**/**6**/**7** with mercaptoacetic acid under ultrasonication at a frequency of 46 KHz gave 2-(1*H*-indol-2-yl)-3-(4-aryloxazol-2-yl)thiazolidin-4-one (**8**), 2-(1*H*-indol-2-yl)-3-(4-arylthiazol-2-yl)thiazolidin-4-one (**9**), 2-(1*H*-indol-2-yl)-3-(4-aryl-1*H*-imidazol-2-yl)thiazolidin-4-one (**10**). The ^{1}H NMR spectra of **8a**, **9a** and **10a** exhibited two doublets at δ 3.59, 3.72; 3.52, 3.74 and 3.58, 3.76 due to methylene protons flanked between sulfanyl and carbonyl groups, and a singlet at δ 4.56, 4.54, 4.59 due to C_2'-H of thiazolidin-4-one. In addition to these a broad singlet was observed at δ 9.72, 9.70, 9.69 ppm due to indole-NH which disappeared on deuteration. The Schiff's bases **5**/**6**/**7** were also used to develop heteroarylazetidinones-3-chloro-4-(1*H*-indol-2-yl)-1-(4-aryloxazol-2-yl)azetidin-2-one (**11**), 3-chloro-4-(1*H*-indol-2-yl)-1-(4-arylthiazol-2-yl)azetidin-2-one (**12**), 3-chloro-4-(1*H*-indol-2-yl)-1-(4-aryl-1*H*-imidazol-2-yl)azetidin-2-one (**13**) by the reaction of **5**/**6**/**7** with chloroacetyl chloride in the presence of triethylamine under ultrasonication at a frequency of 46 KHz. The ^{1}H NMR spectra of **11a**, **12a** and **13a** showed two doublets at δ 4.62, 4.69, 4.67 and 5.65, 5.62, 5.66 due to C_3'-H and C_4'-H of azetidinone. Besides a broad singlet was appeared at 9.71, 9.70 and 9.80 ppm due to indole NH which disappeared on deuteration. The structures of all the compounds were further confirmed by IR, ^{13}C NMR, mass spectral data and elemental analyses.

Biology

Biological activity

The compounds **5**-**13** were dissolved in DMSO at the concentrations of 12.5, 25, 50 and 100 μg/well. Bacterial strains *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and fungi *Aspergillus niger*, *Penicillium chrysogenum* were obtained from

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Antimicrobial activity

The compounds **5-13** were assayed for antimicrobial activity at four concentrations 12.5, 25, 50 and 100 µg/ml. Most of the compounds displayed higher antibacterial activity towards Gram-positive bacteria than on Gram-negative bacteria. The compounds showed slightly higher activity on *B. subtilis* than on *S. aureus* amongst Gram-positive bacteria and also on *K. pneumoniae* than on *P. aeruginosa* amongst Gram-negative bacteria. However, the compounds **5b**, **6b**, **7b**, **8a**, **8b**, **9a**, **9b** and **10a**, **10b** were inactive. Further it was observed that those with azetidinone unit **11**, **12** and **13** exhibited greater activity than Schiff's bases **5**, **6** and **7**. On the other hand, compounds with thiazolidinone ring **8**, **9** and **10** showed least activity. It was also noticed that the compounds with imidazole showed more activity than those having oxazole and thiazole units in the respective series. Amongst the latter, thiazole containing compounds showed more activity. Further the presence of electron withdrawing chloro substituent on the aromatic ring increased the activity. In fact, compounds **12c** and **13c** displayed potential antibacterial activity against *B. subtilis* greater than the standard drug Chloramphenicol at all tested concentrations. The compound **7c** exhibited equal antibacterial activity at 50 and 100 µg/ml (Table 1).

Some of the compounds **5b**, **6b**, **7b**, **8a**, **8b**, **9a**, **9b**, **10b**, **11b** and **12b** displayed no activity against the tested fungi whereas the remaining compounds effectively inhibited the spore germination of the tested fungi. The compounds showed slightly higher activity towards *A. niger* than on *P. chrysogenum*. In addition those with azetidinone moiety (**11-13**) exhibited higher activity than thiazolidinone (**8-10**) and azomethine (**5-7**) containing compounds in the respective series. Further imidazole containing compounds showed more activity than those with oxazole and thiazole units. The presence of electron withdrawing chloro substituent on the aromatic ring increased the activity. This was evidenced that the compound **13c** exhibited greater activity than the standard drug Ketoconazole at all tested concentrations (Table 2).

MIC, MBC and MFC of compounds 7c, 12c and 13c

The minimum inhibitory concentration (MIC), minimum bactericidal concentration (MBC) and minimum fungicidal concentration (MFC) of the compounds tested 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 when once the minimum inhibitory concentration (MIC) is determined. The antimicrobials are considered as bactericidal / fungicidal if the MBC / MFC is not greater than four times the MIC. The compounds **12c** and **13c** exhibited low MIC when compared with **7c** and the MBC was 2 × MIC in case of *B. subtilis*. The compound **13c** also showed low MIC on *A. niger* when compared with **7c** and **12c** and MFC was 2 × MIC. The structure-activity relationship of the compounds revealed that those with azetidinone in combination with thiazole (**12**) and imidazole (**13**) are prominent antimicrobial agents than the compounds having thiazolidinone moiety. The Schiff's bases (**5**,**6**,**7**) showed good activity than thiazolidinone containing azoles (**8**, **9**, **10**).

Experimental Section

Chemistry

Melting points were recorded 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 ^1H NMR spectra were recorded in DMSO-d_6 on a Bruker-400 spectrometer (400 MHz). The ^{13}C NMR spectra were recorded in DMSO-d_6 on a Bruker spectrometer operating at 100 MHz. The chemical shifts are reported in δ (ppm) using TMS as an internal standard. The mass spectra were recorded on Jeol JMS-D 300 and Finnigan Mat 1210 B at 70 Ev with an emission current of 100 µA. Ultrasonication was performed in a Bandelin sonorex RK 102 H ultrasonic bath operating at a frequency of 46 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).

Biological activity assays

The *in vitro* antimicrobial studies were determined by agar well diffusion method against test organisms [21]. 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 of 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°C for 24 h for bacteria and at 28°C for 48 h for fungi. The diameter of zone of inhibition of each well was measured after appropriate incubation (Figures 1 and 2). 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 [22]. 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 (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 24 h for bacteria and at 28°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) [23] and minimum fungicidal concentration (MFC) [24] 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°C for 24 h (bacteria) and at 28°C for 48 h (fungi). After incubation, the lowest concentration was noted as MBC or MFC at which no visible growth was observed.

Synthesis and spectra data

General procedure for the synthesis of Schiff's bases (5/6/7): The indolylaldehyde (4, 1 mmol), 4-aryloxazole-2-amine/ 4arylthiazole-2-amine/ 4aryl- imidazole-2-amine (**1/2/3**, 1 mmol), acetic acid (2 drops) and methanol (10 mL) were sonicated at 30°C for 10-14 min

Compound	Zone of inhibition (mm)															
	Gram-positive bacteria								Gram-negative bacteria							
	Staphylococcus aureus				*Bacillus subtilis*				*Pseudomonas aeruginosa*				*Klebsiella pneumoniae*			
	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	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	-	-	-	-	-	-	9 ± 2.7	12 ± 1.9		-	-	-	-	-	8 ± 2.8	11 ± 1.8
5b	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5c	-	-	-	10 ± 1.2	-	10 ± 1.8	13 ± 1.3	15 ± 2.4	-	-	-	-	-	-	12 ± 1.1	15 ± 2.1
6a	-	-	9 ± 2.9	12 ± 1.8	10 ± 0.9	13 ± 1.1	14 ± 2.3	16 ± 0.5	-	-	-	-	9 ± 2.8	11 ± 1.9	14 ± 0.8	16 ± 1.2
6b	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6c	14 ± 1.8	15 ± 1.6	17 ± 0.5	19 ± 2.1	25 ± 1.1	28 ± 1.9	30 ± 1.2	33 ± 2.1	11 ± 1.3	14 ± 2.2	16 ± 0.6	19 ± 1.8	21 ± 1.1	24 ± 1.5	26 ± 1.6	29 ± 1.2
7a	-	10 ± 1.1	12 ± 2.1	15 ± 2.2	14 ± 1.2	15 ± 1.7	18 ± 0.8	20 ± 1.6	-	-	-	11 ± 2.2	12 ± 0.5	14 ± 2.1	17 ± 1.1	19 ± 1.9
7b	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
7c	19 ± 1.2	21 ± 2.2	23 ± 1.2	24 ± 2.1	29 ± 1.3	31 ± 1.8	34 ± 2.1	38 ± 1.1	15 ± 2.2	18 ± 0.5	20 ± 1.8	23 ± 1.1	24 ± 1.8	27 ± 2.2	29 ± 1.3	32 ± 1.5
8a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
8b	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
8c	-	-	-	-	-	-	11 ± 0.6	13 ± 2.1	-	-	-	-	-	-	10 ± 1.8	13 ± 1.1
9a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
9b	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
9c	-	9 ± 2.9	10 ± 2.1	13 ± 2.1	12 ± 1.1	14 ± 2.2	17 ± 1.6	19 ± 1.1	-	-	-	9 ± 2.8	11 ± 0.6	13 ± 2.3	15 ± 1.1	18 ± 1.7
10a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
10b	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
10c	11 ± 1.2	14 ± 2.2	16 ± 1.3	18 ± 1.9	21 ± 0.5	23 ± 2.1	26 ± 1.4	29 ± 1.7	9 ± 2.6	11 ± 2.1	14 ± 1.2	16 ± 2.2	18 ± 1.1	20 ± 1.8	23 ± 0.6	25 ± 2.2
11a	10 ± 2.1	12 ± 2.1	15 ± 2.2	19 ± 1.2	18 ± 2.1	20 ± 0.5	23 ± 2.1	25 ± 0.9	-	-	10 ± 0.5	13 ± 1.8	14 ± 0.5	17 ± 1.9	19 ± 1.2	22 ± 2.1
11b	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
11c	14 ± 0.9	16 ± 1.3	19 ± 2.4	20 ± 1.3	24 ± 2.1	27 ± 1.6	28 ± 1.8	34 ± 1.2	13 ± 1.7	16 ± 1.2	18 ± 1.3	21 ± 1.1	23 ± 1.8	25 ± 1.3	28 ± 1.7	31 ± 1.3
12a	12 ± 1.1	15 ± 1.9	17 ± 0.6	21 ± 1.8	19 ± 0.5	22 ± 2.1	24 ± 1.2	27 ± 1.9	-	9 ± 1.1	12 ± 1.9	14 ± 1.3	16 ± 2.1	19 ± 1.1	21 ± 2.2	25 ± 0.5
12b	-	-	-	-	-	-	9 ± 2.9	10 ± 2.6	-	-	-	-	-	-	-	10 ± 0.6
12c	20 ± 0.5	22 ± 2.3	23 ± 1.3	25 ± 1.4	32 ± 1.1	34 ± 2.3	36 ± 0.5	39 ± 1.5	16 ± 0.9	19 ± 0.7	21 ± 1.1	24 ± 1.2	26 ± 0.6	29 ± 0.5	33 ± 1.9	35 ± 1.2
13a	16 ± 1.2	18 ± 1.6	20 ± 1.1	24 ± 2.4	23 ± 1.2	25 ± 1.3	28 ± 1.8	30 ± 1.3	10 ± 1.9	13 ± 1.1	15 ± 1.8	17 ± 1.3	20 ± 1.8	23 ± 0.7	25 ± 1.1	27 ± 1.9
13b	9 ± 2.1	11 ± 2.1	13 ± 0.5	17 ± 1.9	16 ± 0.6	17 ± 1.2	20 ± 1.8	22 ± 1.2	-	-	9 ± 1.6	12 ± 1.1	13 ± 1.8	15 ± 1.3	18 ± 1.2	21 ± 2.2
13c	22 ± 1.1	24 ± 1.8	25 ± 1.1	28 ± 2.1	33 ± 1.1	35 ± 0.9	38 ± 1.2	41 ± 1.5	18 ± 1.1	21 ± 1.5	23 ± 1.2	26 ± 2.2	28 ± 1.1	31 ± 0.5	34 ± 2.2	36 ± 1.1
Chloram-phenicol	28 ± 1.8	30 ± 2.7	33 ± 2.1	35 ± 1.8	30 ± 1.9	32 ± 1.6	34 ± 2.4	38 ± 1.9	23 ± 1.4	25 ± 2.8	27 ± 1.1	30 ± 2.8	36 ± 0.5	38 ± 2.1	40 ± 1.2	42 ± 1.8
Control (DMSO)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

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

Table 1: The *in vitro* antibacterial activity of compounds **5-13.**

Compound	Zone of inhibition (mm)							
	Aspergillus niger				*Penicillium 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
5a	-	9 ± 1.1	11 ± 2.2	14 ± 0.9	-	-	-	-
5b	-	-	-	-	-	-	-	-
5c	-	-	10 ± 1.9	12 ± 1.2	-	-	-	-
6a	-	10 ± 1.3	13 ± 2.1	15 ± 1.2	-	-	-	10 ± 1.3
6b	-	-	-	-	-	-	-	-
6c	20 ± 1.1	22 ± 1.8	25 ± 2.1	29 ± 1.2	14 ± 1.9	17 ± 1.3	20 ± 2.1	22 ± 1.9
7a	11 ± 0.9	12 ± 1.2	15 ± 1.9	19 ± 1.1	-	-	10 ± 2.3	13 ± 1.2
7b	-	-	-	-	-	-	-	-
7c	24 ± 1.1	27 ± 2.2	29 ± 0.5	33 ± 1.9	18 ± 0.8	20 ± 2.1	23 ± 1.3	26 ± 1.7
8a	-	-	-	-	-	-	-	-
8b	-	-	-	-	-	-	-	-
8c	-	-	10 ± 1.6	12 ± 0.5	-	-	-	-
9a	-	-	-	-	-	-	-	-
9b	-	-	-	-	-	-	-	-
9c	10 ± 0.6	11 ± 1.8	14 ± 0.8	17 ± 1.4	-	-	-	11 ± 0.7
10a	-	-	9 ± 1.1	10 ± 2.2	-	-	-	-
10b	-	-	-	-	-	-	-	-
10c	17 ± 1.2	19 ± 2.1	22 ± 0.8	25 ± 1.6	11 ± 0.6	13 ± 1.5	17 ± 1.1	19 ± 1.7

11a	14 ± 1.1	17 ± 1.6	19 ± 0.9	22 ± 1.5	-	11 ± 1.2	13 ± 1.6	16 ± 1.1
11b	-	-	-	-	-	-	-	-
11c	22 ± 0.6	25 ± 1.5	27 ± 1.1	31 ± 1.8	16 ± 0.7	18 ± 1.7	21 ± 1.3	24 ± 1.1
12a	15 ± 0.8	18 ± 1.9	20 ± 1.1	24 ± 2.1	9 ± 0.6	12 ± 1.8	14 ± 1.1	18 ± 2.1
12b	-	-	-	-	-	-	-	-
12c	27 ± 0.5	29 ± 1.3	32 ± 1.1	34 ± 2.2	20 ± 1.1	22 ± 1.1	25 ± 2.3	27 ± 1.1
13a	19 ± 1.1	21 ± 2.1	24 ± 1.2	28 ± 1.8	13 ± 0.8	15 ± 1.5	18 ± 0.6	20 ± 2.2
13b	12 ± 0.9	14 ± 1.6	17 ± 0.8	20 ± 2.2	-	9 ± 1.8	12 ± 1.2	14 ± 1.3
13c	32 ± 1.3	34 ± 2.1	37 ± 0.9	40 ± 2.3	23 ± 1.1	25 ± 1.9	26 ± 1.3	28 ± 2.2
Ketoconazole	29 ± 0.9	31 ± 2.5	33 ± 2.1	36 ± 2.4	33 ± 2.8	35 ± 1.1	36 ± 1.4	38 ± 2.4
Control (DMSO)	-	-	-	-	-	-	-	-

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

Table 2: The *in vitro* antifungal activity of compounds **5-13.**

Compound	Minimum inhibitory concentration MIC (MBC/MFC) µg/well					
	S. aureus	***B. subtilis***	***P. aeruginosa***	***K. pneumoniae***	***A. niger***	***P. chrysogenum***
7c	100 (>200)	6.25 (50)	50 (200)	100 (>200)	12.5 (50)	100 (>200)
12c	50 (>200)	6.25 (12.5)	50 (200)	50 (200)	12.5 (50)	100 (>200)
13c	50 (200)	6.25 (12.5)	25 (100)	50 (200)	6.25 (12.5)	100 (>200)
Chloramphenicol	6.5	6.25	6.25	12.5	-	-
Ketoconazole	-	-	-	-	6.25	12.5

(-) No activity; (±) Standard deviation

Table 3: MIC, MBC and MFC of compounds **7c**, **12c** and **13c.**

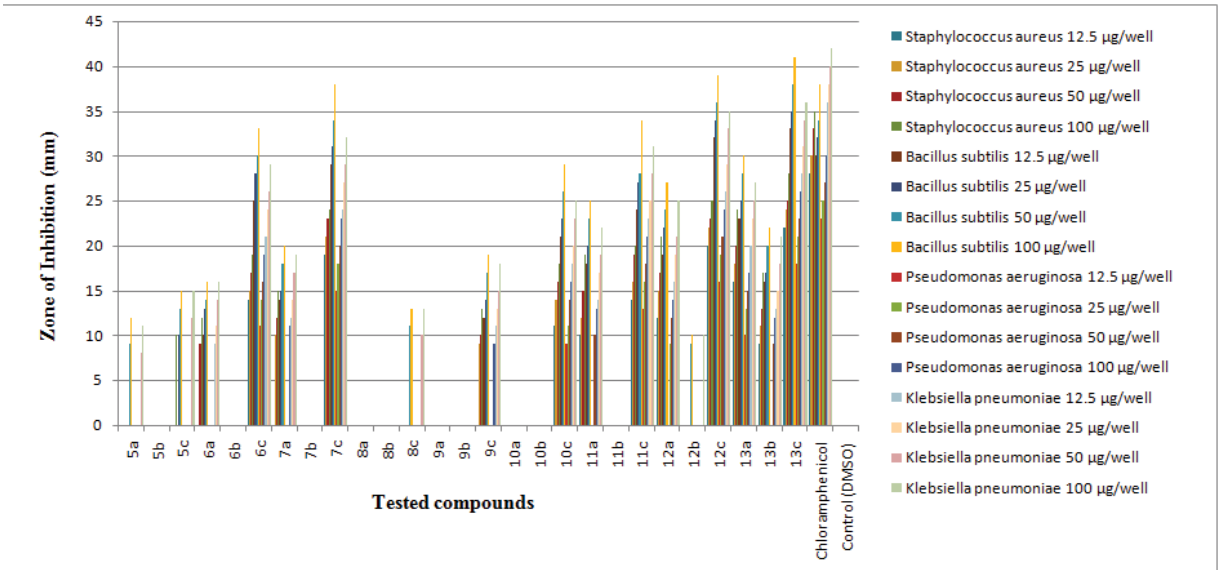

Figure 1: The *in vitro* antibacterial activity of compounds **5-13**.

at a frequency of 46 KHz. The progress of the reaction was monitored by TLC. After completion of the reaction the solvent was evaporated under reduced pressure. The resultant residue was recrystallized from dimethylformamide.

E-1-(1H-Indol-2-yl)-N-(4-phenyloxazol-2-yl)methanimine (5a): White solid (0.198 g, 69%); mp 133-135°C. IR (KBr): 3,332 (NH), 1,625 (C=C), 1564 (C=N) (cm^{-1}); ^{1}H NMR (400 MHz, DMSO-d_6) : δ 6.94 (s, 1H, In-H), 7.32-7.84 (m, 10H, Ar-H, In-H and C_5-H), 8.73 (s, 1H, CH=N), 9.72 (bs, 1H, Indole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 138.2 (C-5), 142.4 (C-4), 155.7 (C-2), 160.8 (C=N), 101.8, 111.2, 118.7, 120.2, 121.8, 122.0, 124.2, 128.4, 128.8, 129.2, 130.5, 131.2 ppm (aromatic and indole carbons). HRMS (*m/z*): 310.0960 $[M+Na]^+$; Anal. Calcd. for $C_{18}H_{13}N_3O$: C, 75.25; H, 4.56; N, 14.63; Found: C, 75.36; H, 4.58; N, 14.53%.

E-1-(1H-Indol-2-yl)-N-(4-(p-tolyl)oxazol-2-yl)methanimine (5b): White solid (0.201 g, 67%); mp 127-129°C. IR (KBr) 3,337 (NH), 1,622 (C=C), 1560 (C=N) (cm^{-1}); ^{1}H NMR (400 MHz, DMSO-d_6) : δ 2.32 (s, 3H, Ar-CH_3), 7.01 (s, 1H, In-H), 7.25-7.79 (m, 9H, Ar-H, In-H and C_5-H), 8.78 (s, 1H, CH=N), 9.70 (bs, 1H, Indole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.2 (Ar-CH_3), 138.6 (C-5), 141.9 (C-4), 155.2 (C-2), 160.3 (C=N), 101.3, 111.4, 118.2, 120.6, 121.2, 122.4, 124.6, 128.2, 128.6, 129.1, 130.3, 131.4 ppm (aromatic and indole carbons).

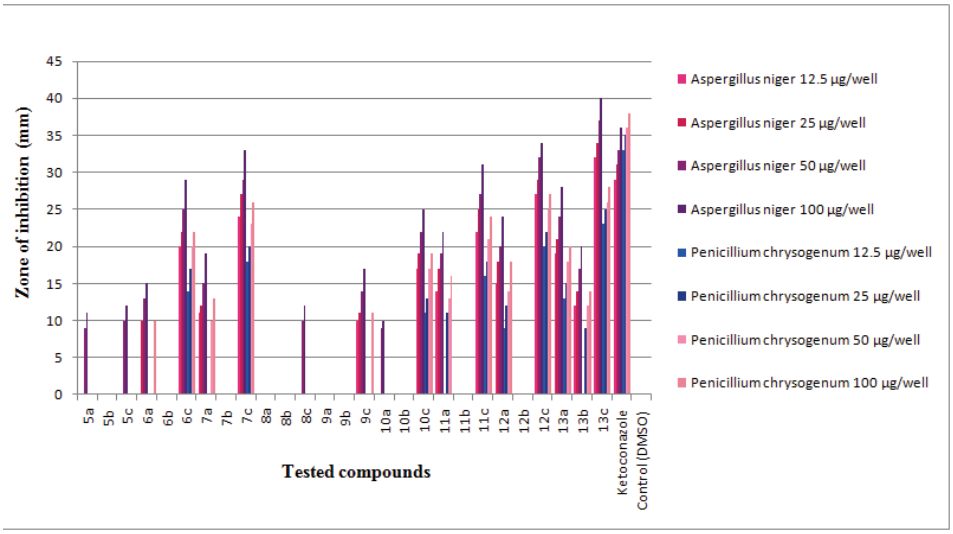

Figure 2: The *in vitro* antifungal activity of compounds **5-13**.

HRMS (*m/z*): 324.1120 $[M+Na]^+$; Anal. Calcd. for $C_{19}H_{15}N_3O$: C, 75.73; H, 5.02; N, 13.94. Found: C, 75.64; H, 5.06; N, 14.07%.

***E-N-(4-(4-Chlorophenyl)oxazol-2-yl)-1-(1H-indol-2-yl) methanimine* (5c):** White solid (0.209 g, 65%); mp 144-146°C. IR (KBr): 3,330 (NH), 1,629 (C=C), 1567 (C=N) (cm^{-1}); ^1H NMR (400 MHz, DMSO-d_6) : δ 7.03 (s, 1H, In-H), 7.34-7.96 (m, 9H, Ar-H In-H and C_5-H), 8.69 (s, 1H, CH=N), 9.77 (bs, 1H, In-NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 138.1 (C-5), 142.8 (C-4), 155.8 (C-2), 160.5 (C=N), 101.6, 111.9, 118.5, 120.3, 121.7, 122.9, 124.2, 129.0, 129.6, 130.1, 130.8, 131.6 ppm (aromatic and indole carbons). HRMS (*m/z*): 344.0572 $[M+Na]^+$; Anal. Calcd. for $C_{18}H_{12}ClN_3O$: C, 67.19; H, 3.76; N, 13.06. Found: C, 67.07; H, 3.79; N, 13.22%.

***E-1-(1H-Indol-2-yl)-N-(4-phenylthiazol-2-yl)methanimine* (6a):** White solid (0.215 g, 71%); mp 140-148°C. IR (KBr) 3,341 (NH), 1,624 (C=C), 1570 (C=N) (cm^{-1}); ^1H NMR (400 MHz, DMSO-d_6) : δ 7.02 (s, 1H, In-H), 7.39-7.76 (m, 10H, Ar-H, In-H and C_5-H), 8.76 (s, 1H, CH=N), 9.74 (bs, 1H, Indole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 110.3 (C-5), 152.6 (C-4), 160.1 (C=N), 175.2 (C-2), 102.3, 112.1, 117.9, 120.8, 121.0, 123.1, 124.7, 128.3, 128.7, 129.4, 130.7, 131.0 ppm (aromatic and indole carbons). HRMS (*m/z*): 326.0722 $[M+Na]^+$; Anal. Calcd. for $C_{18}H_{13}N_3S$: C, 71.26; H, 4.32; N, 13.85. Found: C, 71.34; H, 4.37; N, 13.97%.

***E-1-(1H-Indol-2-yl)-N-(4-(p-tolyl)thiazol-2-yl)methanimine* (6b):** White solid (0.216 g, 68%); mp 146-148°C. IR (KBr): 3,339 (NH), 1,627 (C=C), 1568 (C=N) (cm^{-1}); ^1H NMR (400 MHz, DMSO-d_6) : δ 2.35 (s, 3H, Ar-CH_3), 7.04 (s, 1H, In-H), 7.42-7.80 (m, 9H, Ar-H, In-H and C_5-H), 8.86 (s, 1H, CH=N), 9.81, (bs, 1H, Indole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.5 (CH_3), 110.5 (C-5), 152.9 (C-4), 160.7 (C=N), 175.0 (C-2), 101.9, 111.9, 118.2, 120.1, 121.3, 123.6, 124.1, 128.4, 129.7, 129.2, 130.4, 131.5 ppm (aromatic and indole carbons). HRMS (*m/z*): 340.0891 $[M+Na]^+$; Anal. Calcd. for $C_{19}H_{15}N_3S$: C, 71.90; H, 4.76; N, 13.24. Found: C, 72.00; H, 4.80; N, 13.41%.

***E-N-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(1H-indol-2-yl) methanimine* (6c):** White solid (0.235 g, 70%); mp 153-155°C. IR (KBr) (cm^{-1}): 3,342 (NH), 1,631 (C=C), 1562 (C=N) (cm^{-1}); ^1H NMR (400 MHz, DMSO-d_6) : δ 6.93 (s, 1H, In-H), 7.45-7.84 (m, 9H, Ar-H In-H and C_5-H), 8.82 (s, 1H, CH=N), 9.85 (bs, 1H, Indole -NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 110.9 (C-5), 153.1 (C-4), 161.2 (C=N), 175.6 (C-2), 102.4, 112.6, 119.6, 120.4, 121.5, 124.3, 124.9, 128.1, 129.9, 130.1, 130.6, 131.8 ppm (aromatic and indole carbons). HRMS (*m/z*): 360.0343 $[M+Na]^+$; Anal. Calcd. for $C_{18}H_{12}C_lN_3S$: C, 64.00; H, 3.58; N, 12.44. Found: C, 63.92; H, 3.61; N, 12.55%.

E-1-(1H-Indol-2-yl)-N-(4-phenyl-1H-imidazol-2-yl) methanimine (7a): White solid (0.205 g, 72%); mp 137-139°C. IR (KBr): 3,331 (NH), 1,620 (C=C), 1572 (C=N) (cm^{-1}); 1H NMR (400 MHz, DMSO-d6) : δ 6.90 (s, 1H, In-H), 7.31-7.75 (m, 10H, Ar-H, In-H and C5-H), 8.80 (s, 1H, CH=N), 9.79 (bs, 1H, In-NH), 11.42 (bs, 1H, Imidazole-NH) ppm; 13C NMR (100 MHz, DMSO-d6): δ 118.2 (C-5), 140.3 (C-4), 144.7 (C-4), 161.4 (C=N), 102.7, 111.7, 117.3, 120.8, 121.4, 122.7, 124.0, 128.2, 129.3, 129.7, 130.2, 131.5 ppm (aromatic and indole carbons). HRMS (*m/z*): 309.1121 $[M+Na]^+$; Anal. Calcd. for $C_{18}H_{14}N_4$: C, 75.50; H, 4.93; N, 19.57. Found: C, 75.59; H, 4.91; N, 19.71%.

E-1-(1H-Indol-2-yl)-N-(4-(p-tolyl)-1H-imidazol-2-yl) methanimine (7b): White solid (0.222 g, 74%); mp 143-145°C. IR (KBr): 3,337 (NH), 1,628 (C=C), 1578 (C=N) (cm^{-1}); 1H NMR (400 MHz, DMSO-d6) : δ 6.94 (s, 1H, In-H), 7.39-7.76 (m, 10H, Ar-H, In-H and C5-H), 8.82 (s, 1H, CH=N), 9.81 (bs, 1H, Imidazole-NH) ppm; 13C NMR (100 MHz, DMSO-d6): δ 119.3 (C-5), 141.2 (C-4), 145.1 (C-2), 161.3 (C=N), 102.1, 111.4, 118.4, 120.5, 121.7, 124.5, 124.7, 128.0, 129.2, 129.6, 130.1, 131.2 ppm (aromatic and indole carbons). HRMS (*m/z*): 323.1269 $[M+Na]^+$; Anal. Calcd. for $C_{19}H_{16}N_4$: C, 75.98; H, 5.37; N, 18.65. Found: C, 76.05; H, 5.42; N, 18.50%.

E-N-(4-(4-Chlorophenyl)-1H-imidazol-2-yl)-1-(1H-indol-2-yl)methanimine (7c): White solid (0.224 g, 70%); mp 157-159°C. IR (KBr): 3,340 (NH), 1,632 (C=C), 1572 (C=N) (cm^{-1}). 1H NMR (400 MHz, DMSO-d6) : δ 6.94 (s, 1H, In-H), 7.39-7.76 (m, 10H, Ar-H, In-H and C5-H), 8.82 (s, 1H, CH=N), 9.81 (bs, 1H, Imidazole-NH) ppm.13C NMR (100 MHz, DMSO-d6): δ 119.3 (C-5), 141.2 (C-4), 145.1 (C-2), 161.3 (C=N), 102.1, 111.4, 118.4, 120.5, 121.7, 124.5, 124.7, 128.0, 129.2, 129.6, 130.1, 131.2 ppm (aromatic and indole carbons). HRMS (*m/z*): 343.0722 $[M+Na]^+$; Anal. Calcd. for $C_{18}H_{13}C_lN_4$: C, 67.40; H, 4.09; N, 17.47. Found: C, 67.51; H, 4.11; N, 17.35%.

General procedure for the synthesis of 2-(1H-indol-2-yl)-3-(4-aryloxazol/thiazol/imidazol-2-yl)thiazolidin-4-one (8/9/10): A

solution of Schiff's base (5/6/7, 1 mmol) and mercaptoacetic acid (1 mmol) in toluene (20 mL) was sonicated at 40°C for 13-18 min at a frequency of 46 KHz. The reaction mixture was washed with saturated $NaHCO_3$ solution, dried (an. $MgSO_4$) and the solvent was removed. The resultant solid was purified by recrystallization from 2-ethanol.

2-(1H-Indol-2-yl)-3-(4-phenyloxazol-2-yl)thiazolidin-4-one (8a): White solid (0.238 g, 66%); mp 160-162°C. IR (KBr): 3,336 (NH), 1,771 (CO), 1,626 (C=C), 1,563 (C=N) (cm^{-1}). 1H NMR (400 MHz, DMSO-d6) : δ 3.59 (d, 1H, C5'-Hb, J =14.9 Hz), 3.72 (d, 1H, C5'-Ha, J =15.3 Hz), 4.56 (s, 1H, C2'-H), 6.97 (s, 1H, In-H), 7.44-7.82 (m, 10H, Ar-H, In-H and C5-H), 9.72 (bs, 1H, Indole -NH) ppm.13C NMR (100 MHz, DMSO-d6): δ 33.7 (C-5'), 64.3 (C-2'), 138.5 (C-5), 141.2 (C-4), 150.6 (C-2), 171.6 (C-4') 101.6, 111.2, 119.5, 120.2, 121.4, 128.3, 128.8, 129.4, 129.9, 134.2, 136.1 136.8 ppm (aromatic and indole carbons). HRMS (*m/z*): 384.0787 $[M+Na]^+$; Anal. Calcd. for $C_{20}H_{15}N_3O_2S$: C, 66.47; H, 4.18; N, 11.63. Found: C, 66.57; H, 4.21; N, 11.77%.

(1H-Indol-2-yl)-3-(4-(p-tolyl)oxazol-2-yl)thiazolidin-4-one (8b): White solid (0.258 g, 69%); mp 153-155°C. IR (KBr): 3,338 (NH), 1,769 (CO), 1,630 (C=C), 1560 (C=N) (cm^{-1}). 1H NMR (400 MHz, DMSO-d6) : δ 2.31 (s, 3H, Ar-CH3), 3.57 (d, 1H, C5'-Hb, J=15.1 Hz), 3.70 (d, 1H, C5'-Ha, J=15.2 Hz), 4.58 (s, 1H, C2'-H), 6.92 (s, 1H, In-H), 7.41-7.76 (m, 9H, Ar-H, In-H, and C5-H), 9.75 (bs, 1H, Indole -NH) ppm. 13C NMR (100 MHz, DMSO-d6): δ 21.3 (CH3), 33.9 (C-5'), 64.1 (C-2'), 138.9 (C-5), 141.6 (C-4), 150.3 (C-2), 171.8 (C-4'), 101.2, 111.6, 120.0, 120.7, 121.2, 128.5, 128.9, 129.2, 129.6, 134.0, 136.3, 136.7 ppm (aromatic and indole carbons). HRMS (*m/z*): 398.0935 $[M+Na]^+$; Anal. Calcd. for $C_{21}H_{17}N_3O_2S$: C, 67.18; H, 4.56; N, 11.19. Found: C, 67.30; H, 4.52; N, 11.30%.

3-(4-(4-Chlorophenyl)oxazol-2-yl)-2-(1H-indol-2-yl)thiazolidin-4-one (8c): White solid (0.268 g, 68%); mp 174-176°C. IR (KBr): 3,346 (NH), 1,774 (CO), 1,637 (C=C), 1,569 (C=N) (cm^{-1}). 1H NMR (400 MHz, DMSO-d6): δ 3.61 (d, 1H, C5'-Hb, J =15.0 Hz), 3.79 (d, 1H, C5'-Ha, J =15.4 Hz), 4.61 (s, 1H, C2'-H), 6.95 (s, 1H, In-H), 7.47-7.86 (m, 9H, Ar-H, In-H and C5-H), 9.70 (bs, 1H, Indole-NH) ppm. 13C NMR (100 MHz, DMSO-d6): δ 34.1 (C-5'), 64.8 (C-2'), 138.7 (C-5), 141.0 (C-4), 151.2 (C-2), 171.2 (C-4'), 102.4, 111.8, 119.2, 120.6, 121.6, 128.5, 128.7, 129.1, 129.5, 134.3, 135.8, 136.2 ppm (aromatic and indole carbons). HRMS (*m/z*): 418.0398 $[M+Na]^+$; Anal. Calcd. for $C_{20}H_{14}C_lN_3O_2S$: C, 60.68; H, 3.56; N, 10.62. Found: C, 60.59; H, 3.51; N, 10.78%.

2-(1H-Indol-2-yl)-3-(4-phenylthiazol-2-yl)thiazolidin-4-one (9a): White solid (0.263 g, 70%); mp 163-165°C. IR (KBr): 3,343 (NH), 1,772 (CO), 1,633 (C=C), 1574 (C=N) (cm^{-1}). 1H NMR (400 MHz, DMSO-d6) : δ 3.52 (d, 1H, C5'-Hb, J =14.8 Hz), 3.74 (d, 1H, C5'-Ha, J =15.2 Hz), 4.54 (s, 1H, C2'-H), 7.01 (s, 1H, In-H), 7.23-7.62 (m, 10H, Ar-H, Indole -H and C5-H), 9.70 (bs, 1H, Indole-NH) ppm. 13C NMR (100 MHz, DMSO-d6): δ 35.2 (C-5'), 66.2 (C-2'), 105.8 (C-5), 151.6 (C-4), 161.3 (C-2), 171.2 (C-4'), 101.4, 112.6, 120.4, 120.8, 121.5, 128.1, 128.4, 129.6, 129.9, 134.1, 135.2, 136.6 ppm (aromatic and indole carbons). HRMS (*m/z*): 400.0559 $[M+Na]^+$; Anal. Calcd. for $C_{20}H_{15}N_3OS_2$: C, 63.64; H, 4.01; N, 11.13. Found: C, 63.71; H, 4.03; N, 11.00%.

2-(1H-Indol-2-yl)-3-(4-(p-tolyl)thiazol-2-yl)thiazolidin-4-one (9b): White solid (0.258 g, 66%); mp 158-160°C. IR (KBr): 3,341 (NH), 1,768 (CO), 1,640 (C=C), 1573 (C=N) (cm-1). 1H NMR (400 MHz, DMSO-d6) : δ 2.34 (s, 3H, Ar-CH3), 3.55 (d, 1H, C5'-Hb, J =15.1 Hz), 3.71 (d, 1H, C5'-Ha, J =15.3 Hz), 4.52 (s, 1H, C2'-H), 6.99 (s, 1H, In-H), 7.32-7.71 (m, 9H, Ar-H, In-H, and C5-H), 9.73 (bs, 1H, Indole -NH) ppm. 13C NMR (100 MHz, DMSO-d6): δ 21.5 (CH3), 35.6 (C-5'), 66.8 (C-2'), 105.4 (C-5), 151.2 (C-4), 161.8 (C-2), 171.7 (C-4'), 101.6, 112.0, 119.2, 120.5, 121.2, 128.4, 128.8, 129.0, 130.2, 134.8, 135.3, 136.2 ppm (aromatic and indole carbons). HRMS (*m/z*): 414.0716 $[M+Na]^+$; Anal. Calcd. for $C_{20}H_{15}N_3OS_2$: C, 64.43; H, 4.38; N, 10.73. Found: C, 64.54; H, 4.42; N, 10.88%.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-2-(1H-indol-2-yl) thiazolidin-4-one (9c): White solid (0.279 g, 68%); mp 178-180°C. IR (KBr): 3,350 (NH), 1,770 (CO), 1,620 (C=C), 1,567 (C=N) (cm-1). 1H NMR (400 MHz, DMSO-d6): δ 3.58 (d, 1H, C5'-Hb, J =15.0 Hz), 3.76 (d, 1H, C5'-Ha, J =15.4 Hz), 4.61 (s, 1H, C2'-H), 7.05 (s, 1H, In-H), 7.41-7.83 (m, 9H, Ar-H, In-H and C5-H), 9.79 (bs, 1H, Indole-NH) ppm. 13C NMR (100 MHz, DMSO-d6): δ 35.0 (C-5'), 67.1 (C-2'), 105.1 (C-5), 151.5 (C-4), 161.5 (C-2), 171.8 (C-4'), 101.9, 112.9, 119.0, 120.8, 121.2, 128.6, 129.2, 129.5, 130.1, 134.2, 135.7, 136.4 ppm (aromatic and indole carbons). HRMS (*m/z*): 434.0159 $[M+Na]^+$; Anal. Calcd. for $C_{20}H_{14}C_lN_3OS_2$: C, 58.32; H, 3.43; N, 10.20. Found: C, 58.41; H, 3.46; N, 10.32%.

2-(1H-Indol-2-yl)-3-(4-phenyl-1H-imidazol-2-yl)thiazolidin-4-one (10a): White solid (0.248 g, 69%); mp 145-147°C. IR (KBr): 3,339 (NH), 1,765 (CO), 1,639 (C=C), 1,575 (C=N) (cm-1). 1H NMR (400 MHz, DMSO-d6): δ 3.58 (d, 1H, C5'-Hb, J =15.0 Hz), 3.76 (d, 1H, C5'-Ha J =15.3 Hz), 4.59 (s, 1H, C2'-H), 7.36-7.72 (m, 10H, Ar-H, In-H and C5-H), 9.69 (bs, 1H, In-NH), 11.44 (bs, 1H, Imidazole-NH) ppm. 13C NMR (100 MHz, DMSO-d6): δ 32.9 (C-5'), 63.8 (C-2'), 118.6 (C-5), 140.3 (C-4), 151.4 (C-2), 169.7 (C-4'), 102.3, 111.5, 120.6, 120.9, 121.6, 128.2, 128.5, 129.0, 130.6, 134.8, 136.1, 136.7 ppm (aromatic and indole carbons). HRMS (*m/z*): 383.0947 $[M+Na]^+$; Anal. Calcd. for $C_{20}H_{16}N_4OS$: C, 66.65; H, 4.47; N, 15.54. Found: C, 66.77; H, 4.45; N, 15.68%.

2-(1H-Indol-2-yl)-3-(4-(p-tolyl)-1H-imidazol-2-yl)thiazolidin-4-one (10b): White solid (0.261 g, 70%); mp 146-148°C. IR (KBr): 3,344 (NH), 1,776 (CO), 1,634 (C=C), 1,572 (C=N) (cm-1). 1H NMR (400 MHz, DMSO-d6): δ 2.37 (s, 3H, Ar-CH3), 3.53 (d, 1H, C5'-Hb, J =15.2 Hz), 3.71 (d, 1H, C5'-Ha, J =15.4 Hz), 4.50 (s, 1H, C2'-H), 6.94 (s, 1H, In-H), 7.45-7.68 (m, 9H, Ar-H, In-H, and C5-H), 9.72 (bs, 1H, In-NH), 11.38 (bs, 1H, Imidazole-NH) ppm. 13C NMR (100 MHz, DMSO-d6): δ 32.7 (C-5'), 63.5 (C-2'), 118.2 (C-5), 140.8 (C-4), 151.7 (C-2), 169.2 (C-4'), 101.5, 112.2, 120.1, 121.4, 121.9, 128.6, 128.8, 129.0, 129.7, 134.2, 136.5, 136.8 ppm (aromatic and indole carbons). HRMS (*m/z*): 397.1093 $[M+Na]^+$; Anal. Calcd. for $C_{21}H_{18}N_4OS$: C, 67.36; H, 4.85; N, 14.96. Found: C, 67.46; H, 4.90; N, 14.85%.

3-(4-(4-Chlorophenyl)-1H-imidazol-2-yl)-2-(1H-indol-2-yl) thiazolidin-4-one (10c): White solid (0.256 g, 65%); mp 173-175°C. IR (KBr): 3,349 (NH), 1,780 (CO), 1,631 (C=C), 1,581 (C=N) (cm-1). 1H NMR (400 MHz, DMSO-d6): δ 3.59 (d, 1H, C5'-Hb, J =14.9 Hz), 3.78 (d, 1H, C5'-Ha, J =15.3 Hz), 4.59 (s, 1H, C2'-H), 7.09 (s, 1H, In-H), 7.48-7.81 (m, 9H, Ar-H, In-H and C5-H), 9.78 (bs, 1H, Indole-NH), 11.47 (bs, 1H, Imidazole-NH) ppm. 13C NMR (100 MHz, DMSO-d6): δ 32.1 (C-5'), 63.7 (C-2'), 118.9 (C-5), 140.1 (C-4), 151.2 (C-2), 169.5 (C-4'), 102.6, 112.0, 120.4, 121.5, 121.7, 128.1, 128.6, 129.2, 129.8, 134.6, 135.3, 136.2 ppm (aromatic and indole carbons). HRMS (*m/z*): 417.0558 $[M+Na]^+$; Anal. Calcd. for $C_{20}H_{15}C_lN_4OS$: C, 60.83; H, 3.83; N, 14.19. Found: C, 59.75; H, 3.86; N, 14.36%.

General procedure for the synthesis of 3-chloro-4-(1H-indol-2-yl)-1-(4-aryoxazol/thiazol/imidazol-2-yl)azetidin-2-one (11/12/13): To a solution of 5/6/7 (1 mmol) and triethylamine (5-6 drops) in methanol (20 mL), chloroacetyl chloride (1 mmol) was added and sonicated at 40°C for 15-23 min at a frequency of 46 KHz. The contents were filtered and the filtrate was poured onto crushed ice with constant stirring. The solid separated was recrystallized from 2-ethanol.

3-Chloro-4-(1H-indol-2-yl)-1-(4-phenyloxazol-2-yl)azetidin-2-

one (11a): White solid (0.238 g, 66%); mp 152-154°C. IR (KBr): 3,332 (NH), 1,775 (CO), 1,638 (C=C), 1,565 (C=N) (cm-1). 1H NMR (400 MHz, DMSO-d6): δ 4.62 (d, 1H, C3'-H), 5.65 (d, 1H, C4'-H), 7.30-7.69 (m, 10H, Ar-H, In-H and C5-H), 9.71 (bs, 1H, Indole-NH) ppm. 13C NMR (100 MHz, DMSO-d6): δ 63.7 (C-3'), 66.2 (C-4'), 139.8 (C-5), 141.6 (C-4), 151.3 (C-2), 162.5 (C-2'), 101.7, 111.2, 119.1, 121.3, 128.2, 128.5, 129.7, 129.9, 131.2, 134.0, 136.2, 136.7 ppm (aromatic and indole carbons). HRMS (*m/z*): 386.0676 $[M+Na]^+$; Anal. Calcd. for $C_{20}H_{14}C_lN_3O_2$: C, 66.03; H, 3.88; N, 11.55. Found: C, 66.12; H, 3.93; N, 11.41%.

3-Chloro-4-(1H-indol-2-yl)-1-(4-(p-tolyl)oxazol-2-yl)azetidin-2-one (11b): White solid (0.244 g, 65%); mp 146-148°C. IR (KBr): 3,330 (NH), 1,762 (CO), 1,637 (C=C), 1,571 (C=N) (cm-1). 1H NMR (400 MHz, DMSO-d6): δ 2.32 (s, 3H, Ar-CH3), 4.60 (d, 1H, C3'-H), 5.68 (d, 1H, C4'-H), 6.92 (s, 1H, In-H), 7.37-7.72 (m, 9H, Ar-H, In-H, and C5-H), 9.74 (bs, 1H, Indole -NH) ppm. 13C NMR (100 MHz, DMSO-d6): δ 21.5 (CH3), 63.4 (C-3'), 66.0 (C-4'), 139.4 (C-5), 141.2 (C-4), 151.5 (C-2), 162.8 (C-2'), 101.2, 111.4, 119.3, 121.5, 128.4, 128.8, 129.2, 129.5, 131.4, 134.2, 136.1, 136.5 ppm (aromatic and indole carbons). HRMS (*m/z*): 400.0834 $[M+Na]^+$; Anal. Calcd. for $C_{21}H_{16}C_lN_3O_2$: C, 66.76; H, 4.27; N, 11.12. Found: C, 66.88; H, 4.25; N, 11.23%.

3-Chloro-1-(4-(4-chlorophenyl)oxazol-2-yl)-4-(1H-indol-2-yl) azetidin-2-one (11c): White solid (0.269 g, 68%); mp 163-165°C. IR (KBr): 3,335 (NH), 1,773 (CO), 1,640 (C=C), 1,575 (C=N) (cm-1). 1H NMR (400 MHz, DMSO-d6): δ 4.67 (d, 1H, C3'-H), 5.61 (d, 1H, C4'-H), 6.98 (s, 1H, In-H), 7.44-7.87 (m, 9H, Ar-H, In-H and C5-H), 9.78 (bs, 1H, Indole-NH) ppm. 13C NMR (100 MHz, DMSO-d6): δ 63.1 (C-3'), 66.7 (C-4'), 139.2 (C-5), 141.8 (C-4), 151.1 (C-2), 162.7 (C-2'), 101.1, 112.0, 120.2, 121.7, 128.2, 128.9, 129.1, 129.5, 130.7, 134.5, 136.0, 136.3 ppm (aromatic and indole carbons). HRMS (*m/z*): 420.0283 $[M+Na]^+$; Anal. Calcd. for $C_{20}H_{13}C_{l2}N_3O_2$: C, 60.32; H, 3.29; N, 10.55. Found: C, 60.22; H, 3.33; N, 10.70%.

3-Chloro-4-(1H-indol-2-yl)-1-(4-phenylthiazol-2-yl)azetidin-2-one (12a): White solid (0.260 g, 69%); mp 157-159°C. IR (KBr): 3,333 (NH), 1,767 (CO), 1,632 (C=C), 1,563 (C=N) (cm-1). 1H NMR (400 MHz, DMSO-d6): δ 4.69 (d, 1H, C3'-H), 5.62 (d, 1H, C4'-H), 6.91 (s, 1H, In-H), 7.40-7.85 (m, 10H, Ar-H, In-H and C5-H), 9.70 (bs, 1H, Indole-NH) ppm. 13C NMR (100 MHz, DMSO-d6): δ 63.4 (C-3'), 66.9 (C-4'), 105.7 (C-5), 151.4 (C-4), 161.5 (C-2), 163.2 (C-2'), 102.7, 112.3, 119.0, 121.3, 128.2, 129.6, 129.8, 130.4, 131.2, 134.7, 135.8, 136.1 ppm (aromatic and indole carbons). HRMS (*m/z*): 402.0449 $[M+Na]^+$; Anal. Calcd. for $C_{20}H_{14}C_lN_3OS$: C, 63.24; H, 3.72; N, 11.06. Found: C, 63.36; H, 3.75; N, 10.96%.

3-Chloro-4-(1H-indol-2-yl)-1-(4-(p-tolyl)thiazol-2-yl)azetidin-2-one (12b): White solid (0.266 g, 68%); mp 146-148°C. IR (KBr): 3,341 (NH), 1,777 (CO), 1,635 (C=C), 1,576 (C=N) (cm-1). 1H NMR (400 MHz, DMSO-d6): δ 2.36 (s, 3H, Ar-CH3), 4.64 (d, 1H, C3'-H), 5.60 (d, 1H, C4'-H), 7.03 (s, 1H, In-H), 7.36-7.74 (m, 9H, Ar-H, In-H, and C5-H), 9.76 (bs, 1H, Indole -NH) ppm. 13C NMR (100 MHz, DMSO-d6): δ 21.3 (CH3), 63.8 (C-3'), 66.2 (C-4'), 105.1 (C-5), 151.7 (C-4), 161.9 (C-2), 163.8 (C-2), 102.0, 111.5, 119.4, 121.7, 128.0, 128.7, 129.5, 129.7, 131.4, 134.2, 135.4, 136.7 ppm (aromatic and indole carbons). HRMS (*m/z*): 416.10 $[M+Na]^+$; Anal. Calcd. for $C_{21}H_{16}C_lN_3OS$: C, 64.04; H, 4.09; N, 10.67. Found: C, 63.95; H, 4.11; N, 10.80%.

3-Chloro-1-(4-(4-chlorophenyl)thiazol-2-yl)-4-(1H-indol-2-yl) azetidin-2-one (12c): White solid (0.272 g, 66%); mp 162-164°C. IR (KBr): 3,337 (NH), 1,780 (CO), 1,627 (C=C), 1,581 (C=N) (cm-1). 1H NMR (400 MHz, DMSO-d6): δ 4.60 (d, 1H, C3'-H), 5.64 (d, 1H, C4'-H), 7.01 (s, 1H, In-H), 7.41-7.89 (m, 9H, Ar-H, In-H and C5-H), 9.72 (bs, 1H, Indole-NH) ppm. 13C NMR (100 MHz, DMSO-d6): δ 63.7 (C-3'), 66.5 (C-4'), 105.6 (C-5), 151.2 (C-4), 161.7 (C-2), 163.5 (C-2') 101.8, 111.2, 119.3, 121.4, 128.2, 128.5, 129.1, 129.8, 131.2, 134.1, 135.6, 136.7 ppm (aromatic and indole carbons). HRMS (*m/z*): 436.0059 $[M+Na]^+$; Anal. Calcd. for $C_{20}H_{13}C_{l2}N_3OS$: C, 57.98; H, 3.16; N, 10.14. Found: C, 58.06; H, 3.11; N, 10.26%.

3-Chloro-4-(1H-indol-2-yl)-1-(4-phenyl-1H-imidazol-2-yl) azetidin-2-one (13a): White solid (0.252 g, 70%); mp 139-141°C. IR (KBr): 3,342 (NH), 1,776 (CO), 1,641 (C=C), 1,579 (C=N) (cm-1). 1H NMR (400 MHz, DMSO-d6): δ 4.67 (d, 1H, C3'-H), 5.66 (d, 1H, C4'-H), 6.98 (s, 1H, In-H), 7.33-7.73 (m, 10H, Ar-H, C5-H), 9.80 (bs, 1H, Indole-NH) ppm. 13C NMR (100 MHz, DMSO-d6): δ 62.4 (C-3'), 65.8 (C-4'), 119.7 (C-5), 141.2 (C-4), 151.6 (C-2), 161.5 (C-2') 101.0, 111.8, 118.2, 121.4, 128.1, 128.9, 129.0, 129.7, 130.4, 134.1, 135.2, 136.6 ppm (aromatic and indole carbons). HRMS (*m/z*): 385.0825 $[M+Na]^+$; Anal. Calcd. for $C_{20}H_{15}C_lN_4O$: C, 66.21; H, 4.17; N, 15.44. Found: C, 66.31; H, 4.14; N, 15.60%.

3-Chloro-4-(1H-indol-2-yl)-1-(4-(p-tolyl)-1H-imidazol-2-yl) azetidin-2-one (13b): White solid (0.258 g, 69%); mp 146-148°C. IR (KBr): 3,347 (NH), 1,761 (CO), 1,629 (C=C), 1,575 (C=N) (cm-1). 1H NMR (400 MHz, DMSO-d6): δ 2.31 (s, 3H, Ar-CH3), 4.62 (d, 1H, C3'-H), 5.62 (d, 1H, C4'-H), 6.95 (s, 1H, In-H), 7.38-7.69 (m, 9H, Ar-H, In-H, and C5-H), 9.84 (bs, 1H, In-NH), 11.40 (bs, 1H, Imidazole-NH) ppm. 13C NMR (100 MHz, DMSO-d6): δ 21.6 (CH3), 62.7 (C-3'), 65.1 (C-4'), 119.5 (C-5), 140.9 (C-4), 151.9 (C-2), 161.8 (C-2') 101.7, 111.5, 118.9, 120.2, 128.7, 129.4, 129.7, 130.1, 130.7, 134.8, 135.2, 136.3 ppm (aromatic and indole carbons). HRMS (*m/z*): 399.0993 $[M+Na]^+$; Anal. Calcd. for $C_{21}H_{17}C_lN_4O$: C, 66.93; H, 4.55; N, 14.87. Found: C, 66.82; H, 4.57; N, 15.00%.

3-Chloro-1-(4-(4-chlorophenyl)-1H-imidazol-2-yl)-4-(1H-indol-2-yl)azetidin-2-one (13c): White solid (0.285 g, 72%); mp 166-168°C. IR (KBr): 3,349 (NH), 1,766 (CO), 1,630 (C=C), 1,583 (C=N) (cm-1). 1H NMR (400 MHz, DMSO-d6): δ 4.66 (d, 1H, C3'-H), 5.69 (d, 1H, C4'-H), 6.92 (s, 1H, In-H), 7.42-7.87 (m, 9H, Ar-H, In-H and C5-H), 9.79 (bs, 1H, Indole-NH), 11.44 (bs, 1H, Imidazole-NH) ppm. 13C NMR (100 MHz, DMSO-d6): δ 62.9 (C-3'), 65.8 (C-4'), 119.2 (C-5), 141.7 (C-4), 151.5 (C-2), 161.4 (C-2'), 101.9, 112.7, 118.3, 120.7, 128.1, 128.3, 129.2, 129.9, 130.2, 134.6, 136.1, 136.8 ppm (aromatic and indole carbons). HRMS (*m/z*): 419.04438 $[M+Na]^+$; Anal. Calcd. for $C_{20}H_{14}C_{l2}N_4O$: C, 60.47; H, 3.55; N, 14.87. Found: C, 66.82; H, 4.57; N, 13.94%.

Conclusion

Schiff's bases were used as synthons to develop indolylazolylthiazolidinones and azetidinones on reaction with thioglycolic acid and chloroacetyl chloride, respectively under ultrasonication at a frequency of 46 KHz. The azetidinone in combination with thiazole (**12c**) and imidazole (**13c**) exhibited prominent antibacterial activity against *B. sublitis* whereas **13c** also showed prominent antifungal activity against *A. niger*. The Schiff's bases displayed good activity than thiazolidinone derivatives.

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