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Research Article

SYNTHESIS, CHARACTERIZATION & β-LACTAMASES ACTIVITY OF 4-THIAZOLIDINE DERIVATIVES

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ABSTRACT

Some novel 4-thiazolidinone derivatives have been synthesized by the condensation of isatin/5-chloroisatin with thiosemicarbazide to yield thiosemicarbazones, which were then cyclized to form corresponding thia-3,4, 9-triaza-fluoren-2-ylamines. These were reacted with substituted aldehydes to give corresponding Schiff bases, which were cyclized using thioglycolic acid in the presence of zinc chloride to obtain the 4-thiazolidinone derivatives. All the synthesized compounds were characterized by spectral (IR, MS and NMR) and elemental analysis. The compounds were screened for their antibacterial activity against Gram-positive bacteria (B. subtilis, S. aureus, B. pumilus and M. luteus), Gram-negative bacteria (P. aeruginosa, E. coli and P. fluorescens) and for antifungal activity against A. niger and P. chrysogenum by agar-diffusion method. The minimum inhibitory concentrations of these compounds were also determined by tube dilution method. The antimicrobial effectiveness of all the compounds was found to be concentration dependent. Two compounds—2- methyl-3-(1-thia-3, 4, 9-triaza-fluoren-2-yl)-thiazolidin-4- one (7aI) and 2-naphthalen-1-yl-3-(1-thia-3, 4, 9-tri aza-fluoren-2-yl)-thiazolidin-4-one (7aII)—exhibited good antibacterial activity. The antibacterial activity of all the compounds was found to be better than the antifungal activity.

Keywords: Antimicrobial Agents, Isatin, 4-Thiazolidinone, Thiosemicarbazone, Fluorene.

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INTRODUCTION

β-Lactams have been the most effective class of antibacterial agents used in clinical practice for the past half century, owing to their high level of activity and good tolerability profiles [1-3]. However, the emergence and spread of β-lactamases have eroded their effectiveness on Gram-negative bacteria, and this antibiotic resistance currently represents a highly relevant global public health issue.

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β-Lactamases can inactivate almost all β-lactam antibiotics by hydrolyzing the amide bond in the β-lactam ring, which poses a great challenge in the treatment of bacterial infections [4-6]. Continuous evolvement of the β-lactamases broadens their substrate spectrum and makes the situation more discouraging. Based on the primary sequence homology, β-lactamases have been grouped into four classes: classes A, B, C, and D [7-8]. Class A, C and D β-lactamases are serine enzymes, which catalyze the hydrolysis of the β-lactams via a serine-bound acyl intermediate in the active site. While for class B β-lactamases (the so called metallo- β-lactamases, MβLs), one or two zinc ions in the active site are required for their activity [9-10].

MATERIALS AND METHODS

All the chemicals and solvents used in the synthesis of 4-thiazolidinone were procured from S. D. Fine Chem. Ltd., Mumbai and Sigma-Aldrich Chemical Co., Lancaster and were used directly without any further

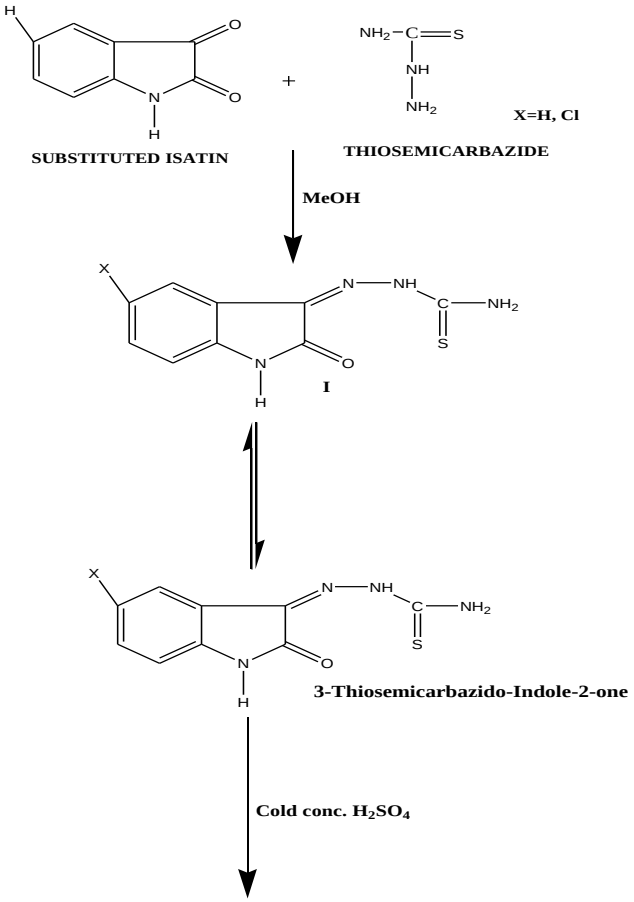
purification. Thin layer chromatography was used for monitoring the progress of reaction and product formation. The thin layer chromatography of synthesized compounds carried out on 0.25 mm pre-coated plate of silica gel $60F_{254}$, E. Merck, Darmstadt, Germany by using different solvent medium. Identification of spots was done under UV lamp and in Iodine chamber. Detection of spots under UV lamp was done at both short and long wavelength. The melting points were determined by open capillary method and are uncorrected.

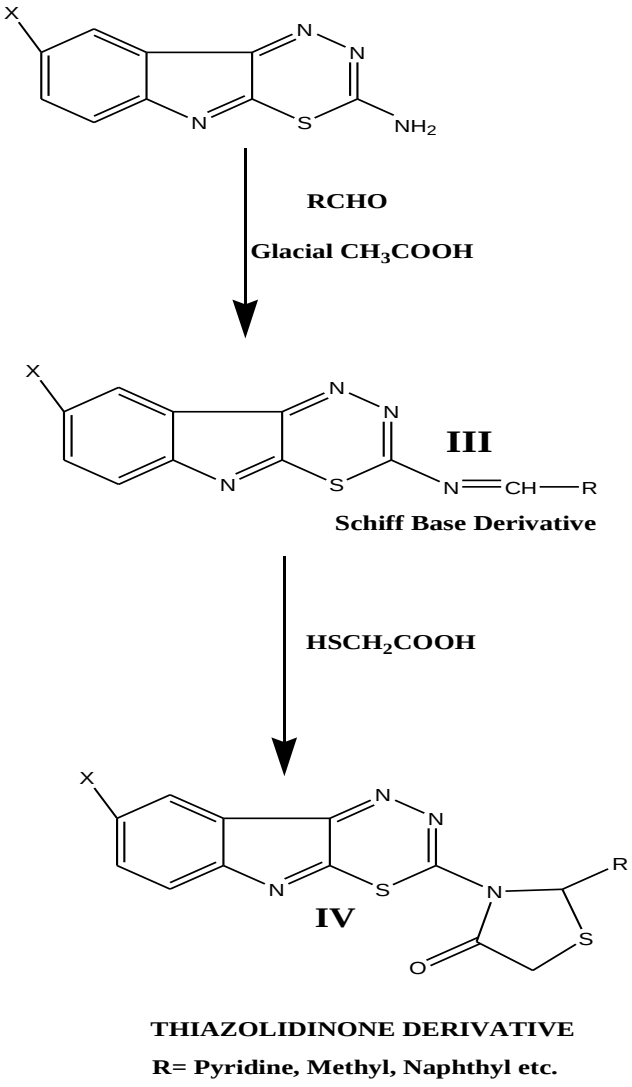
Infrared spectra (ν_{max} in cm^{-1}) of synthesized compounds were recorded on a Shimadzu FTIR-8400s, Perkin Elmer 881in the range of 400-4000 cm^{-1} in potassium bromide.

Mass spectra were recorded on JEOL SX 102/DA-600 instrument using fast atomic bombarding method, Micromass Quattro II instrument using electron spray ionization method and JEOL Accutof-DARTMS using direct analysis in real time technique.

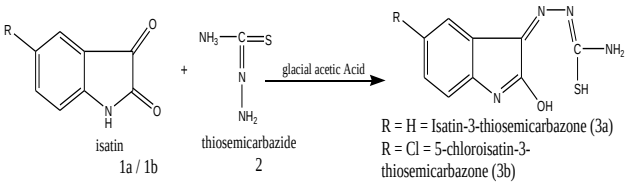
^{1}HNMR spectra (ppm, δ) were recorded on Brucker ADVANCE DRX 300 MHz/200MHz spectrometer with TMS as the internal standard.

Elemental analyses (carbon, hydrogen and nitrogen) were performed on Elementar Vario EL III.



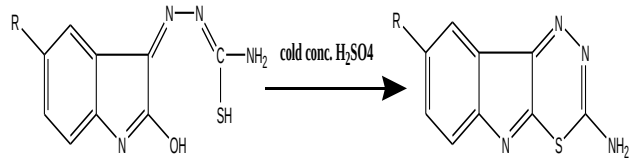


Step 1: Preparation of thiosemicarbazone derivative (3a-3b):



General Procedure: An equimolar mixture of isatin (1a) / chloroisatin (1b) and thiosemicarbazide (2) were dissolved in 90% ethanol and refluxed for 1 hr in the presence of few drops of glacial acetic acid. The completion of reaction was checked by TLC using solvent system chloroform: methanol (95:5). Excess ethanol was distilled off and residue was poured into ice water. Solid product was filtered, washed with water, dried and recrystallized using ethanol.

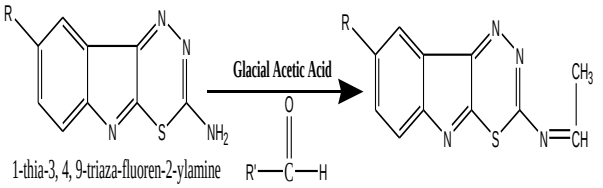
Step 2: Preparation of Thia-3, 4, 9-triaza-fluoren-2-ylamine derivatives (4a-b):



R = H = Isatin-3-thiosemicarbazone (3a) R = H = 1-thia-3, 4, 9-triaza-fluren-2-ylamine (4a)
R = Cl = 5-chloroisatin-3-thiosemicarbazone (3b).R = Cl = 6-chloro-1-thia-3, 4, 9-triaza-fluren-2- ylamine (4a)

General Procedure: An equimolar mixture of isatin-3-thiosemicarbazone (3a)/ 5-chloroisatin-3-thiosemicarbazone (3b) and 4-5 drops of cold con. H_2SO_4 were dissolved in ethanol and refluxed about 8 hrs. The completion of reaction was checked by TLC using chloroform: methanol (98:2). The reaction mixture was cooled and neutralized with liquid ammonia. The neutralized mixture was then poured into ice-water. Filtered, dried and recrystallized using rectified spirit.

Step: 3 Preparation of Imine derivatives (6aI-6bIII):

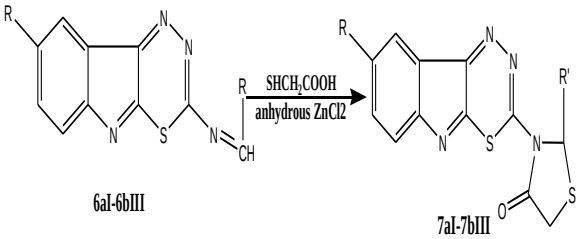


R=H= 1-thia-3, 4, 9-triaza-fluoren-2-ylamine (4a)
R' = Methyl = Acetaldehyde (5I)
R= Cl=6-chloro-1-thia-3, 4, 9-triaza-fluren-2-yl-amine (4b) R' = Napthyl = Napthyaldehyde (5II)
R' = Pyridine = Pyridine-2-aldehyde (5III)

1. **R= H and R' = Methyl: -** Ethylidene- (1-thia-3, 4, 9-triaza-fluoren-2-yl)-amine **(6aI).**
2. **R= H and R' = Napthyl: -** Naphthalen-1-ylmethylene-(1-thia-3, 4, 9-triaza-fluoren-2-yl)-amine **(6aII).**
3. **R= H and R' = Pyridine: -** Pyridin-2-ylmethylene-(1-thia-3, 4, 9-triaza-fluoren-2-yl)-amine **(6aIII).**
4. **R= Cl and R' = Methyl: - (6-chloro-** 1-thia-3, 4, 9-triaza-fluoren-2-yl)-ethylidene-amine **(6bI).**
5. **R= Cl and R' = Napthyl: - (6-chloro-**1-thia-3, 4, 9-triaza-fluoren-2-yl)-naphthalen-1-ylmethylene-amine **(6bII).**
6. **R= Cl and R' = Pyridine: -** (6-chloro-1-thia-3, 4, 9-triaza-fluoren-2-yl)-pyridine-2-ylmethylene-amine **(6bIII).**

General Procedure: Equimolar quantities of thia-3, 4, 9-triaza-fluoren-2-ylamine derivative and appropriate aldehyde were dissolved in 20 ml absolute ethanol in the presence of 5-6 drops of glacial acetic acid and reaction mixture was refluxed till completion of reaction. The completion of reaction was checked by TLC using different solvent system. After completion of reaction, the hot mixture was poured onto crushed ice. Then the crude product was purified using recrystallization using ethanol.

Step: 4: Preparation of thiazolidin-4-one derivatives (7aI-7bIII): -



1. **R= H and R' = Methyl: -** Ethylidene- (1-thia-3, 4, 9-triaza-fluoren-2-yl)-amine **(6aI).**
2. **R= H and R' = Napthyl: -** Naphthalen-1-ylmethylene-(1-thia-3, 4, 9-triaza-fluoren-2-yl)-amine **(6aII).**
3. **R= H and R' = Pyridine: -** Pyridin-2-ylmethylene-(1-thia-3, 4, 9-triaza-fluoren-2-yl)-amine **(6aIII).**
4. **R= Cl and R' = Methyl: -** (6-chloro- 1-thia-3, 4, 9-triaza-fluoren-2-yl)-ethylidene-amine **(6bI).**
5. **R= Cl and R' = Napthyl: -** (6-chloro-1-thia-3, 4, 9-triaza-fluoren-2-yl)-naphthalen-1-ylmethylene-amine **(6bII).**
6. **R= Cl and R' = Pyridine: -** (6-chloro-1-thia-3, 4, 9-triaza-fluoren-2-yl)-pyridine-2-ylmethylene-amine **(6bIII).**
7. **R= H and R' = Methyl: -** 2-methyl -3-(1-thia-3, 4, 9-tri aza-fluoren-2-yl)-thiazolidin-4-one **(7aI)**.
8. **R= H and R' = Napthyl: -** 2-naphthalen-1-yl- 3-(1-thia-3, 4, 9-tri aza-fluoren-2-yl)-thiazolidin-4-one **(7a II)**.
9. **R= H and R' = Pyridine: -** 2-pyridin-2-yl-3-(1-thia-3, 4, 9-triaza-fluoren-2-yl)-thiazolidin-4-one **(7aIII)**.
10. **R= Cl and R' = Methyl: -** 3-(6-chloro-1-thia-3, 4, 9-triaza-fluoren-2-yl) - 2-methyl -thiazolidin-4-one **(7b I)**.
11. **R= Cl and R' = Napthyl: -** 3-(6-chloro-1-thia-3, 4, 9-triaza-fluoren-2-yl) - 2-naphthalen-1-yl-thiazolidin-4-one **(7b II)**.
12. **R= Cl and R' = Pyridine: -**3-(6-chloro-1-thia-3, 4, 9-triaza-fluoren-2-yl) - 2-pyridin-2-yl-thiazolidin-4-one **(7b III)**.

General Procedure: Equimolar quantities of imine derivatives were dissolved in 50 ml of methanol. An eqimolar quantity of thioglycolic acid was added

dropwise in presence of anhydrous zinc chloride and this mixture was refluxed till completion of reaction. The completion of the reaction was checked by TLC using different solvent. Excess of ethanol was distilled off and residue was poured onto ice-water. Solid product was filtered, washed with water, dried and recrystallized using ethanol.

Experimental

Microorganisms: - The microorganisms *B. pummilus* (MTCC 1456), *P. flueresceus* (MTCC 2421), *M. luteus* (MTCC 1538), *P. aeruginosa* (MTCC 424), *P. chrysogenum* (MTCC 161), *E. coli* (MTCC 1573), *A. niger* (MTCC 2546), *B. subtilis* (MTCC 441) and *S. aureus* (MTCC 1430) were purchased from Institute of Microbial Technology, Chandigarh.

Preparation of Inoculums

A loopful of microorganism were transferred into the tubes containing 5 ml of sterile nutrient broth and then incubated for 48 hrs at their specific conditions.

Preparation of sample and standard drug

The compounds 7aI-7bIII were dissolved in 10% DMSO at the concentrations of 100, 250, 500, 750, 1000, 1250 µg/ml. Norfloxacin and Fluconazole were used as standard drugs for bacterial and fungal strains respectively. The concentrations of the standard drug used were 10 µg/ml for each strain.

Microbiological testing of synthesized compounds

Procedure: A definite volume of the microbial suspension (inoculums) was poured into the sterilized nutrient agar media (cooled at 40^{o}c) and mixed thoroughly. About 20 ml of this suspension was poured aseptically in the petri plates and kept stay up till the solidification of the media. The surface of agar plates was pierced using a sterile cork borer. The prepared wells were filled with equal volume of a solution of synthesized compounds (7aI-7bIII) and standard drugs, separately. After a period of pre-incubation diffusion, the plates were incubated face up for a definite time in specified conditions. The zone of inhibition was measured and is reported in the Tables 2.

RESULTS AND DISCUSSION

The synthesis of 4-thiazolidinone was carried out in 4-steps. In first step Isatin/ 5-chloroisatin was condensed with thiosemicarbazide in the presence of few drops of glacial acetic acid in 90% ethanol to yield different thiosemicarbazones. In the second step, thiosemicarbazones cyclized in the presence of sulfuric acid to form corresponding Thia-3, 4, 9-triaza-fluoren-2-ylamines. Then Thia-3, 4, 9-triaza-fluoren-2-ylamines react with different heterocyclic aldehydes, in absolute ethanol and glacial acetic acid, to give corresponding imines. Finally corresponding imine were cyclized by thioglycolic acid in the presence of anhydrous zinc chloride to give thiazolidine-4-ones.

All the synthesized compounds were characterized by physical, spectral and elemental analysis. The purity of the compounds was established by thin layer chromatography using precoated silica gel G plates. The spots were observed under UV lamp with both, short and long wavelength. The spots were further observed in iodine chamber. Melting range were determined by open capillary method and are uncorrected.

The IR spectrum of Isatin/ 5-chloroisatin-3-thiosemicarbazone **(3a-b)** revealed the presence of C=N at 1593-1608 cm^{-1} and N-H at 3413-3415 cm^{-1} respectively. The IR spectral data of Thia-3,4,9-triaza-fluoren-2-ylamines **(4a-b)** showed characteristic bands at 1618-1627 cm^{-1} of C=N stretch and two absorption bands at 3442, 3515 and 3415, 3484 cm^{-1} of 1^{0} N-H stretching for **4a** and **4b**, respectively. In mass spectra, $[M+1]^{+}$ peaks were observed for the various compounds synthesized. In ^{1}H-NMR spectra δ value were found in the range of 3.37-3.75 for methyl proton of and 7.26-7.68 for benzyl proton, in the various synthesized compounds. Elemental analysis was carried out for the calculated by presence of carbon, hydrogen and nitrogen. The IR, MS, NMR and elemental analysis data of all the synthesized compounds (3a-7bIII) are shown in Table 1 and Table 2.

The synthesized thiazolidinone derivatives were evaluated for antimicrobial activity against bacterial and fungal strains by cup plate method. The microorganism *B. pumilus* (MTCC1456), *P. fluorescens* (MTCC 2421), *M. luteus* (MTCC 1538), *P. aeruginosa* (MTCC 424), *P. chrysogenum* (MTCC 161), *E. coli* (MTCC 1573), *A. niger* (MTCC 2546), *B. subtilis* (MTCC 441) and *S. aureus* (MTCC 1430) were procured from Institute of Microbial Technology, Chandigarh, India. Norfloxacin and Fluconazole were used as standard drugs for antibacterial and antifungal activities respectively.

The antimicrobial effectiveness of all the compounds was found to be concentration dependent. All compounds **7aI-7bIII** were found to be more effective against Gram-negative strains than Gram-positive strains. The cell wall of Gram-negative bacteria is high lipid content and low in peptidoglycan. On the other hand, the cell wall of the Gram-positive bacteria is low in lipid content and high in peptidoglycan. Compounds which were more lipophilic may have penetration into the Gram-negative bacteria than the Gram-positive bacteria. Therefore, the compounds show better activity against Gram-negative strains than Gram-positive strains.

Table 1. Physical and Analytical data of compounds 7aI – 7bIII

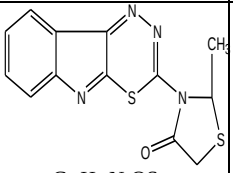
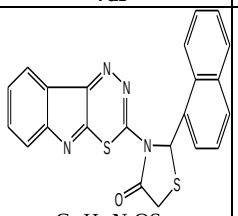
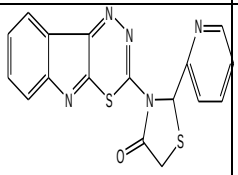
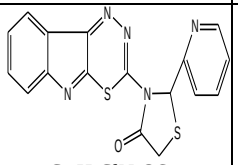
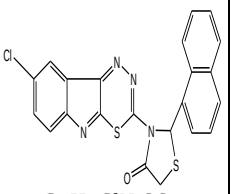
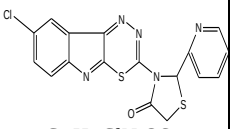
S. No.	Compound	Appearance	Reaction Time (hrs)	TLC: Solvent System	%Yield (w/w)	Melting Range (°C)	I.R. (KBr) (cm^{-1})	Mass m/z $[M+1]^+$	^1H NMR (δ ppm)	Elemental Analysis
1	 $C_{13}H_{10}N_4OS_2$ Mass: 300.85 **7aI**	Crystalline solid	16-18	n-hexane: ethyl acetate (50:50)	40. 12	230-232	1485, 1620, 1672, 3193	301	1.25 (s, 3H) 2.96-2.97 (s, 2H) 3.61-3.75 (s, 1H) 6.0-7.787 (m, 4H)	C = 51.88% H = 3.97% N = 18.86%
2	 $C_{22}H_{14}N_4OS_2$ Mass: 412.06 **7aII**	Amorphous Powder	20-22	chloroform: methanol (95:5)	45.27	250-255	1483, 1618, 1678, 3193	413	. 3.23 (s, 2H) 5.76 (s, 1H) 7.10-7.77 (m, 11H)	C = 62.93% H = 3.23% N = 13.12%
3	 $C_{17}H_{11}N_5OS_2$ Mass: 363.43 **7aIII**	Crystalline solid	14-16	chloroform: methanol (95:5)	36.87	210-211	1453, 1593, 1620, 1693	365	3.29-3.48 (s, 2H) 5.70-5.88 (s, 1H) 7.01-7.87 (m, 8H)	C = 55.15% H = 3.94% N = 19.78%
4	 $C_{13}H_9ClN_4OS_2$ Mass: 334.99 **7bI**	Crystalline solid	17-19	chloroform: methanol (98:2)	56.55	295-297	767, 1378, 1443, 1474, 1611, 1688	335	1.25 (s, 3H) 3.58 (s, 1H) 5.92 (s, 1H) 7.26-7.68 (m, 4H)	C = 46.23% H = 2.25% N = 16.38%
5	 $C_{22}H_{13}ClN_4OS_2$ Mass: 446.02 **7bII**	Crystalline solid	11-13	chloroform: methanol (95:5)	50.23	265-268	767, 1365, 1440, 1473, 1611, 1688	447	3.83 (s, 1H) 5.58 (s, 1H) 7.26-7.89 (m, 11H)	C = 58.21% H = 2.79% N = 12.98%
6	 $C_{17}H_{10}ClN_5OS_2$ Mass: 400.88 **7bIII**	Crystalline solid	8-10	chloroform: methanol (98:2)	30.23	280-284	761, 1465, 1634	401	3.19 (s, 1H) 5.57 (s, 1H) 6.89-7.68 (m, 8H)	C = 51.69% H = 2.34% N = 17.98%

Table 2. Values of the Minimum Inhibitory Concentration of the Synthesized Compounds and Reference Standards

S. No.	MIC of compounds (µg/ml)	MIC of compounds (µg/ml)							
		7aI	7aII	7aIII	7bI	7bII	7bIII	N	F
1	*Bacillus subtilis*	30	40	40	50	150	150	2.5	-
2	*Staphylococcus aureus*	250	200	200	150	150	250	5	-
3	*Bacillus pumilus*	30	20	50	40	40	50	1.25	-
4	*Escherichiia coli*	40	50	40	30	30	150	-	-
5	*Pseudomonas fluorescens*	30	40	50	150	40	50	2.5	-
6	*Micrococcus luteus*	40	250	250	150	150	250	2.5	-
7	*Pseudomonas aeruginosa*	30	40	30	50	40	30	2.5	-
8	*Aspergillus niger*	250	250	150	250	150	300	-	2.5
9	*Penicillum chrysogenum*	250	200	150	250	150	200	-	1.25

Compounds 7aI exhibited good antibacterial activity, having MIC 30 µg/mL, against *Bacillus subtilis*, *Psedomonas aeruginosa*, *Pseudomonas fluorescens* and *Bacillus pumilus*. Compounds 7aII was found to be the most effective against *Bacillus pumilus* having lowest MIC (20 µg/mL) and good activity against *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Pseudomonas fluorescens* and *Escherichia coli* having MIC 40-50 µg/mL. Two bacterial strains (*Bacillus* pumilus and Pseudomonas aeruginosa) were found to be most sensitive against all the compounds at 20-50 µg/mL. *Staphylococcus aureus* was found to be the least sensitive strain against all the synthesized compounds. The antibacterial activity of all the compounds was found to be better than antifungal activity. The antibacterial activity of the compounds was in the order of 7aI>7aII>7bII>7aIII>7bI>7bIII. The antifungal activity was in the order of 7aIII=7bII>7bIII>7aII>7aI=7bI.

CONCLUSION

Substitution at 3-position of 4-thiazolidinone nucleus can lead to a series of compounds having different biological activities. The change in indole nucleus may also lead to different compounds. The replacement of Cl in 7b series by other groups may vary the physiochemical and biological activities of the compounds.

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