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Synthesis, characterization and antimicrobial evaluation of 2-azetidinone and 4-thiazolidinone derivatives

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ABSTRACT

In the present study, a new series of 2-azetidinone and 4-thiazolidinone derivatives were synthesized from 4-aminobenzoic acid. The structures of the synthesized compounds were confirmed by IR, ^{1}H-NMR and Mass spectral studies. The compounds were screened for their antimicrobial activity against Staphylococcus aureus (ATCC 25923), Esherichia coli (ATCC 25922) and Candida albicans (ATCC 2091) and the zone of inhibition was determined by disc diffusion technique. All the synthesized compounds exhibited promising antimicrobial activity against the studied set of microorganisms. However, the activity was less than that of standard drugs used in this study.

Keywords: Schiff base, 2-azetidinone, 4-thiazolidinone, antimicrobial activity.

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INTRODUCTION

2-Azetidinones and 4-thiazolidinones are the most common and important groups among the small ring heterocyclic compounds. 2-Azetidinones, commonly known as β-lactams, are the derivatives of azetidines with carbonyl group at 2nd-position. The activity of the famous antibiotics such as penicillins, cephalosporins and carbapenems are attributed to the presence of 2-azetidinone ring in them. A large number of 3-chloromonocyclic β-lactam possess powerful antibacterial [1], antifungal [2], anti-inflammatory [3], antitubercular [4], anticonvulsant [5], analgesic [6] and cholesterol inhibitory activities [7]. 4-Thiazolidinones are the derivatives of thiazolidines with carbonyl group at the 4th-position and the compounds exhibited various biological activities such as antibacterial [8], antifungal [9], antioxidant [10], cytotoxic [11], analgesic, antiinflammatory [12], anticonvulsant [13], anticancer [14], anti-HIV [15], antitubercular [16] and anthelmintic activities [17].

In the present study, a series of 2-azetidinone and 4-thiazolidinone were synthesized from 4-amino benzoic acid. The condensation of appropriate aldehydes with p-amino benzoic acid resulted in formation of corresponding Schiff bases **(SB_1-SB_3)** which undergoes reaction with chloroacetyl chloride in presence of tri ethylamine results in the formation of corresponding 2-azetidinone derivatives **(SS_1-SS_3)** by Staudinger reaction. Similarly, the Schiff bases **(SB_1-SB_3)** reacted with mercaptoacetic acid to give 4-thiazolidinone derivatives **(SS_4-SS_6)**. The structures of the synthesized compounds were confirmed by IR, ^{1}H-NMR, Mass spectral analysis and the compounds were screened for antimicrobial activity.

MATERIALS AND METHODS

All the chemicals used were of synthetic grade procured from various chemical units like Merck, Qualigens, S.D.Fine, Mumbai. Melting points of all the synthesized compounds were determined in open capillary tubes and the values were uncorrected. The UV spectra were recorded by using Double beam SHIMADZU 1700 UV spectrometer. The IR spectra were recorded on FT-IR 8101 (Shimadzu) spectrometer by KBr pellets technique. ^{1}H-NMR spectra were recorded on JEOL JNM-α 400 spectrometer using DMSO-d_6 as solvent and TMS as internal standard. Mass spectra were recorded on JEOL GC mate mass spectrometer. The purity of the compounds was checked by TLC on pre-coated silica gel G plates by using benzene: acetone (9:1) as a mobile phase and visualized in iodine vapour. The organisms were obtained from Kings Institute of Preventive Medicine, Guindy, Chennai. The agar medium and the standard drugs were purchased from HI media Laboratories Ltd., Mumbai, India.

General method of synthesis of Schiff bases (SB_1-SB_3)

Equimolar quantity of p-amino benzoic acid (0.01 mol) and substituted aromatic aldehydes (0.01 mol) were dissolved in 30 ml ethanol containing few drops of glacial acetic acid. The reaction mixture was refluxed for 3 to 5 h, cooled and then poured into crushed ice .The solid obtained was filtered, washed with water and recrystallized from ethanol [18].

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General method of synthesis of 2-azetidinone (SS_1-SS_3)

A mixture of Schiff base (0.01 mol) and triethyl amine (0.02 mol) was dissolved in 1, 4-Dioxane (15 m1). To this, a solution of chloroacetyl chloride (0.02 mol) was added in portion wise with vigorous shaking at room temperature for 20 min. The reaction mixture was heated under reflux for 3 h and the content was kept at room temperature for 48 h and poured into ice-cold water. The resulting solid was filtered, washed several times with water and then recrystallized from ethanol [19].

General method of synthesis of 4-thiazolidinone (SS_4-SS_6)

A mixture of schiff base (0.01 mol) and mercapto acetic acid (0.012 mol) in DMF (25 ml) containing a pinch of anhydrous zinc chloride was refluxed for 8 h. The reaction mixture was then cooled and poured into ice-cold water. The resulting solid was filtered, washed several times with water and then recrystallized from ethanol [20].

Antimicrobial screening

Antimicrobial activity of the synthesized compounds was screened using the disc diffusion method [21] against selected pathogens such as Escherichia coli, Staphylococcus aureus and Candida albicans. The compounds were dissolved in DMSO and sterilized by filtering through 0.45 µm millipore filter. Nutrient agar (anti bacterial activity) and sabouraud dextrose agar medium (antifungal activity) was prepared and sterilized by an autoclave (121º C and 15 Ibs for 20 min) and transferred to previously sterilized petridishes (9 cm in diameter). After solidification, petriplates were inoculated with bacterial organisms in sterile nutrient agar medium at 45^{o} C, and fungal organism in sterile sabouraud's dextrose agar medium at 45^{o} C in aseptic condition. Sterile whatmann filter paper discs (previously sterilized in U.V. lamp) were impregnated with synthesized compounds at a concentration of 25,100 mg/disc was placed in the organism-impregnated petri plates under sterile condition. The plates were left for 30 min to allow the diffusion of compounds at room temperature. Antibiotic discs of ciprofloxacin (100 µg /disc) and ketaconazole (100 µg /disc) were used as positive control, while DMSO used as negative control. Then the plates were incubated for 24 h at 37 ± 1^{o} C for antibacterial activity and 48 h at 37±1^{o} C for antifungal activity. The zone of inhibition was calculated by measuring the minimum dimension of the zone of no microbial growth around the each disc.

RESULTS AND DISCUSSION

The synthesis of 2-azetidinones and 4-thiazolidinones has been described in Scheme-1. The structures of the synthesized compounds were supported by physical data (Table-1) and following spectral analysis.

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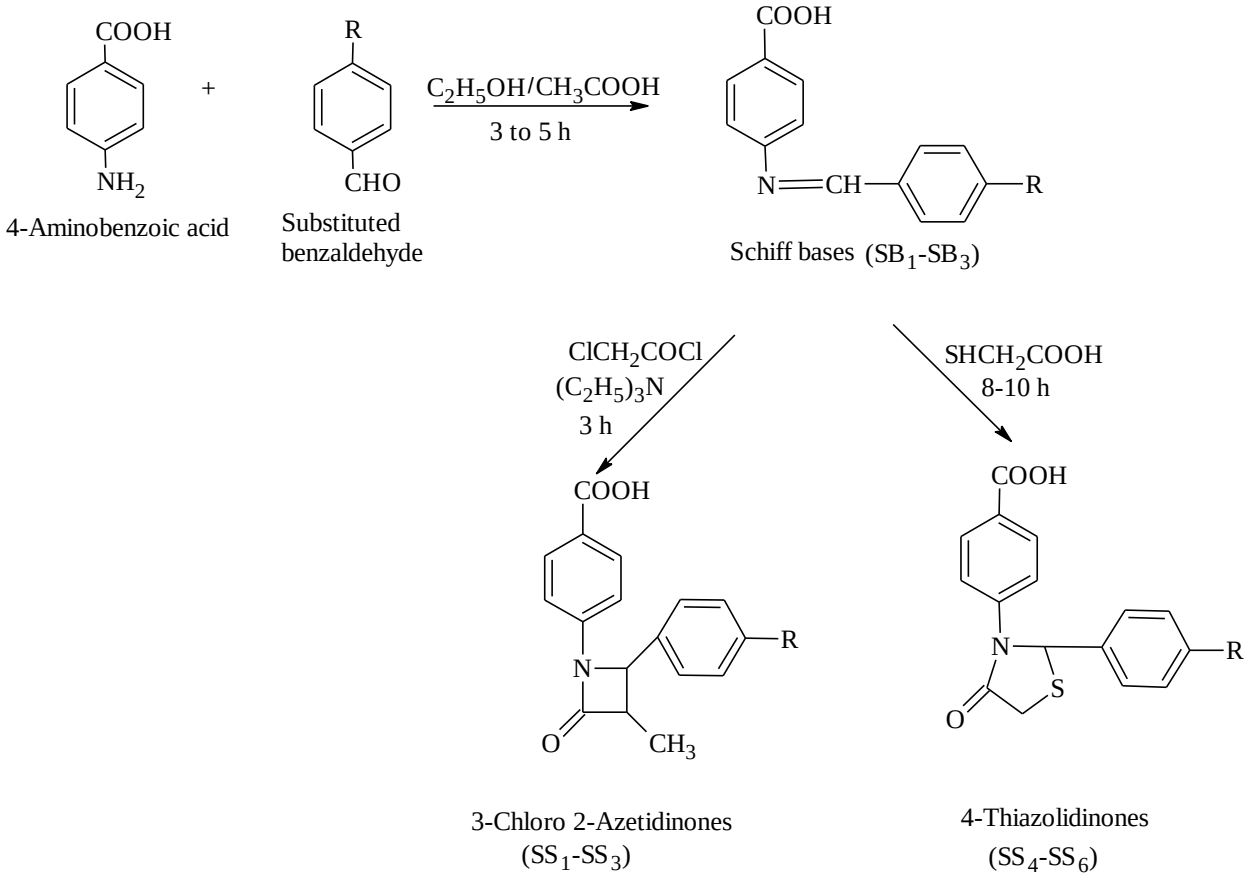

Scheme-1: Synthetic scheme of 2-azetidinone and 4-thiazolidinone derivatives

Table-1 Physical and analytical data of the synthesized compounds

compound	R	mol. formula	mol.wt	m.p° C	% yield	R_f value	UV (λmax)
SB_1	$N(CH_3)_2$	$C_{16}H_{16}N_2O_2$	268.31	201	80.37	0.71	341.0, 267.0
SB_2	NO_2	$C_{14}H_{10}N_2O_4$	270.24	262	75.24	0.67	275.0
SB_3	OH	$C_{14}H_{11}NO_3$	241.24	215	73.72	0.45	284.5, 220
SS_1	$N(CH_3)_2$	$C_{18}H_{17}O_3N_2Cl$	344.79	182	65.37	0.71	339.5, 285.5
SS_2	NO_2	$C_{16}H_{11}O_5N_2Cl$	346.72	227	72.34	0.51	175.5
SS_3	OH	$C_{16}H_{12}O_4NCl$	317.72	197	70.11	0.66	282.0
SS_4	$N(CH_3)_2$	$C_{18}H_{18}N_2O_3S$	342.41	172	69.60	0.47	340.0, 270.5
SS_5	NO_2	$C_{16}H_{12}N_2O_5S$	344.34	298	75.98	0.62	290.0
SS_6	OH	$C_{16}H_{13}O_4NS$	314.34	248	63.21	0.53	264.5

Spectral data of the synthesized compounds

4-[4-(dimethylaminobenzylidene) amino] benzoic acid (SB_1)

IR (KBr) ν cm^{-1}: 2917 (Ar-H), 1679 (C=N), 1417 (C-O-H), 1286 (C=O), 1434 (N-CH_3); ^{1}H-NMR (DMSO-d_6) δ: 10.17 (1H, s, Ar-COOH), 8.60 (1H, s, CH=N), 6.8-8.1 (8H, m, Ar-H), 3.02 (6H, s, N $(CH_3)_2$): EI-MS m/z (M+): 268 (calcd for $C_{16}H_{16}N_2O_2$: 268).

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4-[4-(nitrobenzylidene) amino] benzoic acid (SB_2)

IR (KBr) ν cm^{-1}: 3074 (Ar-H), 1681 (C=N), 1427 (C-O-H), 1295 (C=O), 1516, 1343 (Ar-NO2); ^{1}H-NMR (DMSO-d_6) δ: 10.17 (1H, s, Ar-COOH), 8.60 (1H, s, CH=N), 7.4-8.1 (8H, m, Ar-H); EI-MS m/z (M+): 270 (calcd for $C_{14}H_{10}N_2O_4$: 270).

4-[4-(hydroxybenzylidene) amino] benzoic acid (SB_3)

IR (KBr) ν cm^{-1}: 2885 (Ar-H), 1685 (C=N), 1421 (C-O-H), 1285 (C=O), 3240 (Ar-OH); ^{1}H-NMR (DMSO-d_6) δ: 10.17 (1H, s, Ar-COOH), 8.52 (1H, s, CH=N), 6.8-8.1 (8H, m, Ar-H): EI-MS m/z (M+): 241 (calcd for $C_{14}H_{11}NO_3$: 241).

4-[3-chloro-2-[4-dimethylaminophenyl]-4-oxoazetidin-1-yl] benzoic acid (SS_1)

IR (KBr) ν cm^{-1}: 2916 (Ar-H), 1366 (C-N), 1659 (β-lactam C=O), 1436 (C-O-H), 1285 (C=O), 1436 (N-CH_3); ^{1}H-NMR (DMSO-d_6) δ: 10.17 (1H, s, Ar-COOH), 4.65 (1H, d, CH-N), 5.50 (1H, d, CH-Cl), 6.6-8.0 (8H, m, Ar-H), 2.91 (6H, s, $N(CH_3)_2$); EI-MS m/z (M+): 344 (calcd for $C_{18}H_{17}O_3N_2Cl$: 344).

4-[3-chloro-2-(4-nitrophenyl)-4-oxoazetidin-1-yl] benzoic acid (SS_2)

IR (KBr) ν cm^{-1}: 3074 (Ar-H), 1317 (C-N), 1682 (β-lactam C=O), 1426 (C-O-H), 1294 (C=O), 1517, 1344 (Ar-NO_2); ^{1}H-NMR (DMSO-d_6) δ: 10.17 (1H, s, Ar-COOH), 4.76 (1H, d, CH-N), 5.03 (1H, d, CH-Cl), 7.3-8.0 (8H, m, Ar-H); EI-MS m/z (M+): 346 (calcd for $C_{16}H_{11}O_5N_2Cl$: 346).

4-[3-chloro-2-(4-hydroxyphenyl)-4-oxoazetidin-1-yl] benzoic acid (SS_3)

IR (KBr) ν cm^{-1}: 2966 (Ar-H), 1313 (C-N), 1685 (β-lactam C=O), 1421 (C-O-H), 1285 (C=O), 3247 (Ar-OH); ^{1}H-NMR (DMSO-d_6) δ: 10.22 (1H, s, Ar-COOH), 4.58 (1H, d, CH-N), 5.43 (1H, d, CH-Cl), 6.6-8.0 (8H, m, Ar-H), 9.57 (1H, s, Ar-OH); EI-MS m/z (M+): 317 (calcd for $C_{16}H_{12}O_4NCl$: 317).

4-[2-[4-dimethylaminophenyl]-4-oxo-1,3-thiazolidin-3-yl]benzoic acid (SS_4)

IR (KBr) ν cm^{-1}: 2923 (Ar-H), 1362 (C-N), 1658 (thiazolidinone C=O), 1437 (C-O-H), 1252 (C=O), 691 (C-S), 1456 (N-CH_3); ^{1}H-NMR (DMSO-d_6) δ: 10.17 (1H, s, Ar-COOH), 7.30 (1H, s, S-CH-N), 4.76 (2H, s, CH_2-S), 6.6-7.9 (8H, m, Ar-H), 2.91 (6H, s, $N(CH_3)_2$); EI-MS m/z (M+): 342 (calcd for $C_{18}H_{18}N_2O_3S$: 342).

4-{2-[4-nitrophenyl]-4-oxo-1,3-thiazolidin-3-yl} benzoic acid (SS_5)

IR (KBr) ν cm^{-1}: 3106 (Ar-H), 1347 (C-N), 1679 (thiazolidinone C=O), 1408 (C-O-H), 1247 (C=O), 698 (C-S), 1517, 1316 (Ar-NO2); ^{1}H-NMR (DMSO-d_6) δ: 10.22 (1H, s, Ar-COOH), 7.37 (1H, s,

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S-CH-N), 4.52 (2H, s, CH_2-S), 7.6-8.1 (8H, m, Ar-H); EI-MS m/z (M+): 344 (calcd for $C_{16}H_{12}N_2O_5S$: 344).

4-{2-[4-hydroxyphenyl]-4-oxo-1,3-thiazolidin-3-yl}benzoic acid (SS_6)

IR (KBr) ν cm^{-1}: 2922 (Ar-H), 1315 (C-N), 1686 (thiazolidinone C=O), 1421 (C-O-H), 1254 (C=O), 691 (C-S), 3309 (Ar-OH); ^{1}H-NMR (DMSO-d_6) δ: 10.22 (1H, s, Ar-COOH), 9.78 (1H, s, Ar-OH), 7.22 (1H, s, S-CH-N), 4.76 (2H, s, CH_2-S), 7.1-8.0 (8H, m, Ar-H); EI-MS m/z (M+): 315 (calcd for $C_{16}H_{13}O_4NS$: 315).

The C=O band (1659-1685 cm^{-1}), CH-Cl band (773-775 cm^{-1}) in IR spectra and the N-CH proton signal (δ 4.58-4.76) and CH-Cl (δ 5.03-5.50) in ^{1}H NMR spectra of the compounds (SS_1-SS_3), confirmed the formation of 3-chloro-2-azetidinone nucleus. The C=O band (1658-1686 cm^{-1}) and C-S-C band (691-698 cm^{-1}) in IR spectra and N-CH proton signal (δ 4.52- 4.76) and CH_2-S (δ 7.22-7.36) in ^{1}H NMR spectra of the compounds (SS_4-SS_6) confirmed the formation of 4-thiazolidinone nucleus.

Table-2 In vitro anti microbial activity of synthesized compounds by disc diffusion method

S.No	Compound	Diameter of zone of inhibition (in mm)								
		Staphylococcus aureus			Escherichia coli			Candida albicans		
		25 mg	100 mg	Std*	25 mg	100 mg	Std*	25 mg	100 mg	Std**
1.	SS_1	18	29.5	32	14	18	29	11	17	30
2.	SS_2	17	28	32	11	13.5	29	14	18	30
3.	SS_3	12	18.6	32	22	27	29	19	22	30
4.	SS_4	10	14	32	11	14.5	29	21	25.4	30
5.	SS_5	11	17	32	12	17	29	23	27	30
6.	SS_6	14	19	32	15	21	29	16	24.3	30

Std* - Ciprofloxacin (100 µg /disc) Std** - Ketaconazole (100 µg /disc)

All the compounds showed promising antimicrobial activity even at the tested concentration and the observed zone of inhibition was presented in Table-2. The SS_1, 4-[3-chloro-2-[4-dimethylaminophenyl]-4-oxoazetidin-1-yl] benzoic acid was found to be more active against Staphylococcus aureus (gram +ve bacteria). The SS_3, 4-[3-chloro-2-(4-hydroxyphenyl)-4-oxoazetidin-1-yl] benzoic acid was found to be more potent active against Escherichia coli (gram –ve bacteria). The SS5, 4-{2-[4-nitrophenyl]-4-oxo-1, 3-thiazolidin-3-yl} benzoic acid was found to be active against Candida albicans. However, the antimicrobial activity of the synthesized compounds against the tested organisms was found to be less than that of the standard drugs used in this study.

CONCLUSION

The present study described the synthesis and antimicrobial activity of a series of 2-azetidinone and 4-thiazolidinone derivatives. From the data obtained from antimicrobial

studies, it was evident that the 2-azetidinones was more active against the bacterial strains and 4-thiazolidinones were more active against the fungal strains. Since only few strains had been tested in this study, further testing with other strains will be quite desirable. The synthesized compounds therefore, present a new scaffold that can be used to yield potent antimicrobial compounds. It can be concluded that these compounds certainly holds great promise towards good active leads in medicinal chemistry

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