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RESEARCH ARTICLE

Novel Synthesis, Characterization and Antimicrobial Evaluation 2-Azetidinone and 4-Thiazolidinone Derived from 4 Nitro Benzoic Acid Schiff Bases

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ABSTRACT

In the present study an intermolecular reductive Schiff base formation from nitro derivative and benzaldehydes is carried out in the presence of iron powder and dilute acid. Schiff base synthesis is usually acid-catalyzed and usually require refluxing the mixture of aldehydes (or ketone) and amine in polar organic medium. In the present study new Schiff base compounds derived from para nitro benzoic acid with 4 hydroxy benzaldehyde and 4 dimethylamino benzaldehyde. The synthesized Schiff base derivates 2-azetidinone and 4-thiazolidinone were characterized by IR, and 1H NMR spectroscopy. The Schiff base ligands have also been tested in vitro for their antibacterial and anti fungal activity. The experimental results suggest that Schiff base derivatives are more potent in anti bacterial and anti fungal activities.

KEYWORDS

Schiff bases, 4 nitro benzoic acid, 4 hydroxy benzaldehyde and 4 dimethyl amino benzaldehyde, Antibacterial activity; Antifungal activity

INTRODUCTION

One of the main objectives of organic and medicinal chemistry is the design, synthesis and production of molecules having value as human therapeutic agents. Nitrogen containing compounds are very widely distributed in nature and are essential to life; they play a vital role in the metabolism of all living cells.

In the last couple of years, antibiotic resistance, especially multiple drug resistance, has appeared as one of the most significant challenges in the management of infectious diseases. The wider use of antibiotics in humans and animals and in areas other than the treatment and prophylaxis of disease have resulted in a serious problem of drug resistance. Various strategies have been worked out and tried to cope with the resistance problem and enhance the activity, or broaden the spectrum of drugs.[1-4]

2-Azetidinones 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.

Azetidinones and their derivatives are an important group of heterocyclic compounds which have also been recognized as TACE inhibitors[5], and biological activities such as anti

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cancer[6], anticonvulsant[7], anticoccidal[8], cardiovascular[9], antiviral[10], mutagenic property[11] and anti-inflammatory.[12]

4-Thiazolidinones are the derivatives of thiazolidines with carbonyl group at the 4th-position and the compounds exhibited various biological activities such as antibacterial[13], antifungal[14], antioxidant[15], cytotoxic[16], analgesic, antiinflammatory[18], anticonvulsant[19], anticancer[20], anti-HIV[21], antitubercular[22] and anthelmintic activities[23].

In the present study, a series of 2-azetidinone and 4-thiazolidinone were synthesized from 4-nitro benzoic acid. The intermolecular reductive Schiff base formation of appropriate aldehydes with p-nitro benzoic acid (SB1-SB2) which undergoes reaction with chloroacetyl chloride in presence of tri ethylamine results in the formation of corresponding 2-azetidinone derivatives (SSA1-SSA2) by Staudinger reaction. Similarly, the Schiff bases (SB1-SB2) reacted with mercaptoacetic acid to give 4-thiazolidinone derivatives (SST1-SST2).

The structures of the synthesized compounds were confirmed by IR, 1H-NMR, Mass spectral analysis and the compounds were screened for antimicrobial activity.

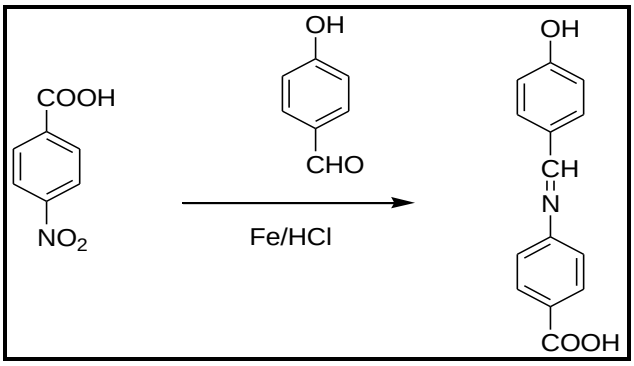
The present aim of the work is to synthesize Schiff base derivatives from 4-nitro benzoic acid with different aldehydes and to characterize them and study their antibacterial activities.

MATERIALS AND METHOD

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. 1H-NMR spectra were recorded on JEOL JNM-α 400 spectrometer using DMSO-d6 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.

Synthesis of Schiff bases (SB1-SB2)

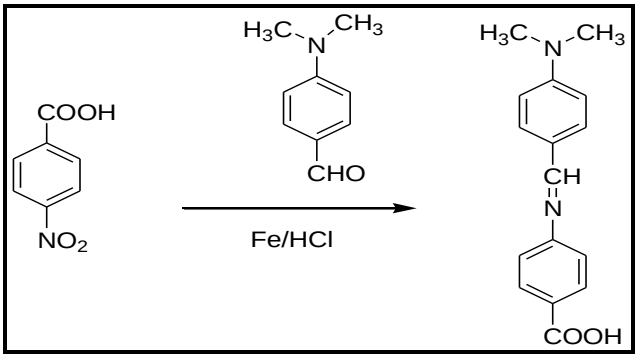
SB1-4-(4-hydroxybenzylideneamino) benzoic acid



Hydrochloric Acid (0.13 mL, 4.5 mmol) was added to a mixture of 4 nitro benzoic acid (1.20 gr, 0.72 mmol) 4 hydroxy benzaldehyde (0.88gr, 0.72 mmol), and iron powder (0.409 g, 7.32 mmol) in 24 mL of EtOH–H_2O (2:1 v/v) solution. The reaction was heated to 65°C for 1.5 h before being filtered while hot. The filtrate was extracted using CH_2Cl_2 (2 × 20 mL) after which the organic layers were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo to yield 1.764g (85%).

IR (KBr) ν cm^{-1}: 2885 (Ar-H), 1685 (C=N), 1421 (C-O-H), 1285 (C=O), 3240 (Ar-OH); 1H-NMR (DMSO-d6) 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).

(SB2) 4-(4-(dimethylamino)-benzylideneamino)benzoic acid



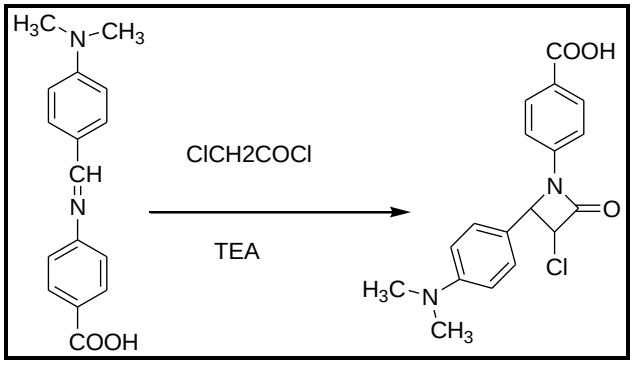
Hydrochloric Acid (0.13 mL, 4.5 mmol) was added to a mixture of 4 nitro benzoic acid (1.20 gr, 0.72 mmol) 4 dimethyl amino benzaldehyde (1.08 gr, 0.72 mmol), and iron powder (0.409 g, 7.32 mmol) in 24 mL of EtOH–H_2O (2:1 v/v) solution. The reaction was heated to 65°C for 1.5 h before being filtered while hot. The filtrate was extracted using CH_2Cl_2 (2 × 20 mL) after which the organic layers were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo to yield 1.82g (80%).

IR (KBr) ν cm^{-1}: 2917 (Ar-H), 1679 (C=N), 1417 (C-O-H), 1286 (C=O), 1434 (N-CH_3); 1H-NMR (DMSO-d6) 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).

General method of synthesis of 2-azetidinone (SSA1-SSA2)

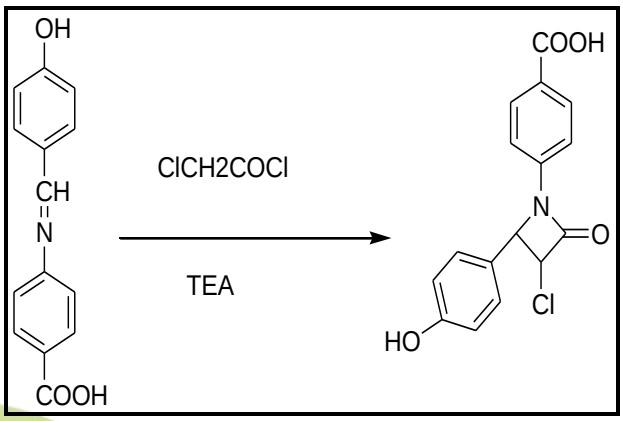
A mixture of Schiff base (0.01 mol) and triethyl amine (0.02 mol) was dissolved in 1, 4-Dioxane (15 ml). To this, a solution of chloroacetyl chloride (0.02 mol) was added in portion wise with vigorous shaking at room temperature for 20 min. The reaction mixture was heated under reflux for 3 h and the 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[24].

(SSA1) 4-[3-chloro-2-[4-dimethylaminophenyl]-4-oxoazetidin-1-yl] benzoic acid



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); 1H-NMR (DMSO-d6) 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).

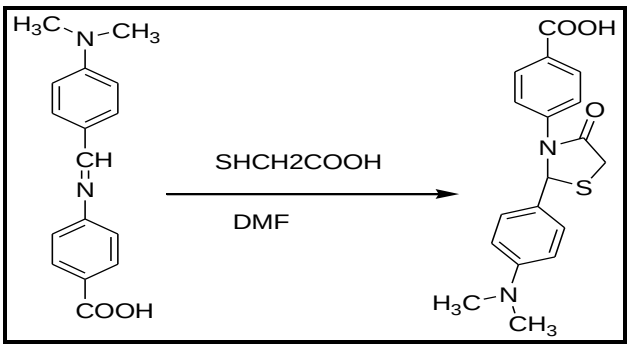
(SSA2) 4-[3-chloro-2-(4-hydroxyphenyl)-4-oxoazetidin-1-yl] benzoic acid



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); 1H-NMR (DMSO-d6) 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 $C_{16}H_12O_4NCl$: 317).

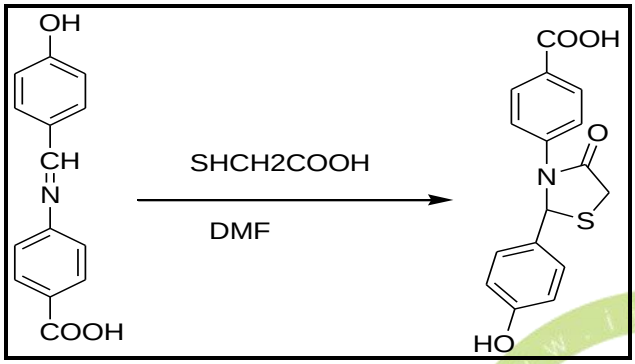
General method of synthesis of 4-thiazolidinone (SST1-SST2) A mixture of schiff base (0.01 mol) and mercapto acetic acid (0.012 mol) in DMF (25 ml) containing a pinch of anhydrous zinc chloride was refluxed for 8 h. The reaction mixture was then cooled and poured into ice-cold water. The resulting solid was filtered, washed several times with water and then recrystallized from ethanol[25].

(SST1) 4-[2-[4-dimethylaminophenyl]-4-oxo-1,3-thiazolidin-3-yl]benzoic acid



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); 1H-NMR (DMSO-d6) 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).

(SST2) 4-{2-[4-hydroxyphenyl]-4-oxo-1,3-thiazolidin-3-yl}benzoic acid



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); 1H-NMR (DMSO-d6) δ: 10.22 (1H, s, Ar-COOH), 9.78 (1H, s, Ar-OH), 7.22 (1H, s, S-CH-N), 4.76 (2H, s, CH2-S), 7.1-8.0 (8H, m, Ar-H); EI-MS m/z (M+): 315 (calcd for $C_{16}H_{13}O_4NS$: 315).

Antimicrobial screening

Antimicrobial activity of the synthesized compounds was screened using the disc diffusion method[26] 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 (antibacterial activity) and sabouraud dextrose agar medium (antifungal activity) was prepared and sterilized by an autoclave (121ºC 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 45ºC, and fungal organism in sterile sabouraud's dextrose agar medium at 45ºC in aseptic condition. Sterile whatman 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 ± 1ºC for antibacterial activity and 48 h at 37±1ºC 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 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 1H NMR spectra of the compounds (SSA1-SSA2), confirmed the formation of 3-chloro-2-azetidinone nucleus. The C=O band (1658-1686cm^{-1}) and C-S-C band (691-698cm^{-1}) in IR spectra and N-CH proton signal (δ 4.52-4.76) and CH_2-S (δ 7.22-7.36) in 1H NMR spectra of the compounds (SST1-SST2) confirmed the formation of 4-thiazolidinone nucleus.

This type reaction is economically attractive method for synthesis of Schiff base compounds and their derivatives such as 2-azetidinone and 4-thiazolidinone. Schiff base have been prepared by a simple and environmentally friendly reductive imination procedure. This process tolerates various functional groups and often proceeds quantitatively with no need for purification. This methodology uses only Fe powder in acidic EtOH/H_2O as a reducing agent for nitro derivatives which upon reduction spontaneously condense with an aldehyde in situ. Above Schiff base compounds shows inherent new generation of series of pharmaceutically important compounds such as 2-azetidinone and 4-thiazolidinone (Table-2). The structures of the synthesized compounds were supported by physical data (Table-1) and following spectral analysis.

Table 1: Physical and analytical data of the synthesized compounds

compound	R	Mol formula	Mol wt	Melting point	yield	UV (max)
SB1	$N(CH_3)_2$	$C_{16}H_{16}N_2O_2$	268.31	201	80%	349, 269
SB2	OH	$C_{14}H_{11}NO_3$	241.24	215	85%	284.5, 220
SSA1	$N(CH_3)_2$	$C_{18}H_{17}O_3N_2Cl$	344.79	182	65.37	339.5, 285.5
SSA2	OH	$C_{16}H_{12}O_4NCl$	317.72	197	70.11	282.0
SST1	$N(CH_3)_2$	$C_{18}H_{18}N_2O_3S$	342.41	172	69.60	340.0, 270.5
SST2	OH	$C_{16}H_{13}O_4NS$	314.34	248	63.21	264.5

Table 2: MIC studies of schiff bases and their derivatives

S No	Compound	Diameter of zone of inhibition (in mm)								
		Staphylococcus aureus			Escherichia coli			Candida albicans		
		25mg	100mg	Std*	25mg	100mg	Std*	25mg	100mg	Std**
1	SB1	15	24	30	22	24	25	20	24	28
2	SB2	17	23	30	20	23	25	20	23	28
3	SSA1	20	29	30	20	22	25	22	29	28
4	SSA2	15	23	30	22	20	25	20	23	28
5	SST1	29	28	30	19	23	25	23	28	28
6	SST2	14	32	30	18	22	25	22	32	28

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

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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