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RESEARCH ARTICLE

Synthesis and Biological Evaluation of Novel Schiff Bases and their Derivatives

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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 ortho nitro benzoic acid with 2- hydroxy benzaldehyde, 4- hydroxy benzaldehyde and 2 furfuraldehyde. The synthesized Schiff base derivatives (2-azetidinones) were characterized by IR, and 1H NMR spectroscopy. The Schiff base ligands and derivatives 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 antifungal activities.

KEYWORDS

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

INTRODUCTION

Schiff base are associated with antibacterial, antifungal and antitubercular activities and have diverse biological activities.[1] Literature revealed that 2-azetidinone derivatives occupy an important place in medicinal chemistry as they show a variety of microbiological activity.[2,3]

β-Lactam antibiotics are the most commonly used antibiotics. The 2-carbonyl derivative of azetidine (four-membered heterocyclic ring with nitrogen as the hereroatom) is designated as 2-azetidinone or, more commonly, β-lactam. A large number of 3-chloro monocyclic β-lactams having substitution at positions 1 and 4 possess powerful anti-bacterial, anti-microbial, sedative, anti-fungal and anti-tubercular activity.[4-14]

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In view of these facts we can clear about that Schiff base are important not only in medical chemistry, but also in organic synthetic chemistry. Schiff base perhaps are synthesized in various method.

Recently, catalytic Schiff base formation from nitroarenes and carbonyls has been reported.[15,16]

Azetidinones can be prepared from Schiff's bases, which are the condensation products of aldehydes and amino compounds. They are considered significant owing to their wide range of biological applications. They are also employed as intermediates in chemical synthesis.

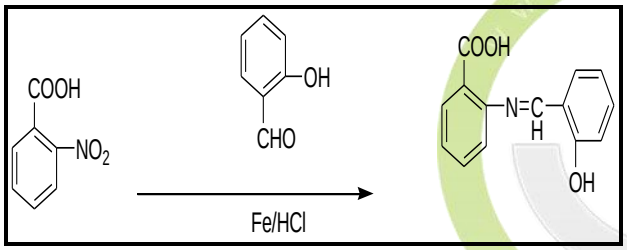
On consideration of the above factors, it was decided to synthesize some new substituted azetidinone derivatives from the 2 nitro benzoic acid moiety with 2- hydroxy benzaldehyde, 4-hydroxy benzaldehyde and 2 furfuraldehyde and

screen them for their antibacterial and antifungal activities. The structures of the synthesized compounds were assigned on the basis of their FTIR, 1H NMR and mass spectral data.

EXPERIMENTAL

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.

Synthesis of Schiff Base 2-(2-hydroxybenzylideneamino) Benzoic Acid



Hydrochloric acid (0.13 mL, 4.5 mmol) was added to a mixture of 2 nitro benzoic acid (1.20 gr, 0.72 mmol) 2 hydroxy benzaldehyde (0.87gr, 0.72 mmol), and iron powder (0.419 g, 7.32 mmol) in 24 mL of EtOH–H_2O (2:1 v/v) solution. The reaction was heated to 65°C for 3 h before being filtered while hot. The filtrate was extracted using CH_2Cl_2 (2 × 25 mL) after which the organic layers were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo to yield orange colored 2-(2-hydroxybenzylideneamino)benzoic acid 1.65g (80%). Melting point: 196-198^{O}C.

λmax: 335.00nm

IR (KBr.cm^{-1}, 3000-3100(O-Hstr), 1616(C=Nstr), 1685(C=Ostr)

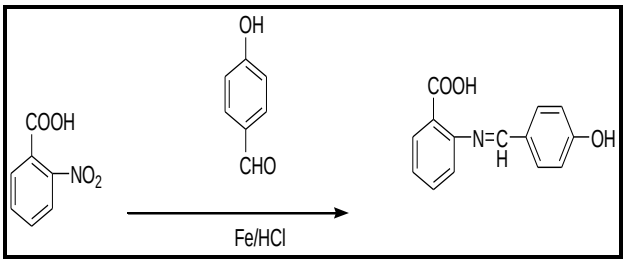
1HNMRppm:6.4-7.1Ar-H 8H), 10.1 s. N-CH, 1 H)

MS m/z: 224 (M+1)

Anal calculated. For $C_{14}H_{11}O_3N$.

C: 69.70 H: 4.56, N: 5.80% found: C: 68.90, H: 4.55 N: 5.79%

Synthesis of Schiff Base 2-(4-hydroxybenzylideneamino) Benzoic Acid



Hydrochloric acid (0.13 mL, 4.5 mmol) was added to a mixture of 2 nitro benzoic acid (1.20 gr, 0.72 mmol) 4 hydroxy benzaldehyde (0.87 gr, 0.72 mmol), and iron powder (0.419 g, 7.32 mmol) in 24 mL of EtOH–H_2O (2:1 v/v) solution. The reaction was heated to 65°C for 3 h before being filtered while hot. The filtrate was extracted using CH_2Cl_2 (2 × 25 mL) after which the organic layers were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo to yield yellow colored 2-(4-hydroxybenzylideneamino) benzoic acid 1.65g (80%). Melting point: 220-222^{O}C

λmax: 284.00nm

IR (KBr.cm^{-1}, 3330(O-Hstr), 1608(C=Nstr), 1708(C=Ostr)

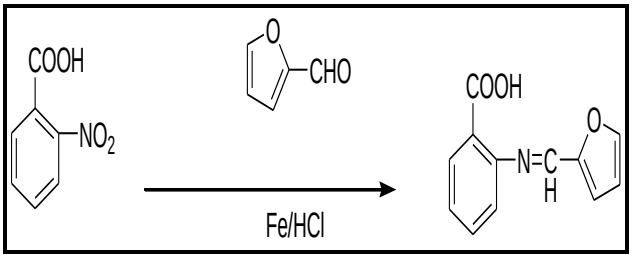
1HNMRppm:6.5-7.2 (m,Ar-H 8H), 9.7(s. N-CH, 1 H)

MS m/z: 242 (M+1)

Anal calculated. For $C_{14}H_{11}O_3N$.

C: 69.70 H: 4.56, N: 5.80% found: C: 69.90, H: 4.52 N: 5.79%

Schiff Base 2-(furan-2-ylmethyleneamino) Benzoic Acid



Hydrochloric acid (0.13 mL, 4.5 mmol) was added to a mixture of 2 nitro benzoic acid (1.20 gr, 0.72 mmol) Furan-2-carbaldehyde (0.79 gr, 0.72 mmol), and iron powder (0.419 g, 7.32 mmol) in 24 mL of EtOH–H_2O (2:1 v/v) solution. The reaction was heated to 65°C for 3 h before being filtered while hot. The filtrate was extracted using CH_2Cl_2 (2 × 50 mL) after which the organic layers were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo to yield ash colored 2-(furan-2-ylmethyleneamino)benzoic acid 1.69g (85%). Melting point: 175-177^{O}C

λmax: 340.00nm

IR (KBr.cm^{-1}), 2770-3200 (O-Hstr), 1618(C=Nstr), 1731(C=Ostr)

1HNMRppm:6.6-7.8 (m, Ar-H 8H), 8.4(s. N-CH, 1 H)

MS m/z: 216 (M+1)

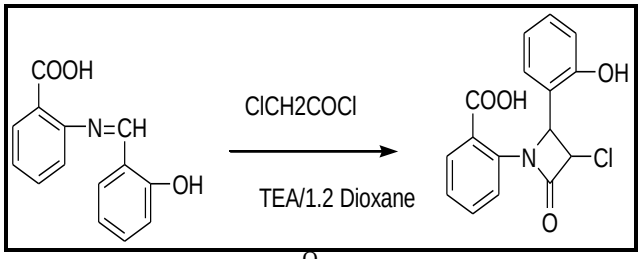
Anal calculated. For $C_{13}H_9O_3N$.

C: 72.70 H: 4.16, N: 6.51 % found: C: 72.90, H: 4.02 N: 6.60%

Synthesis of Azetidinones

To a mixture of Schiff base (0.01 mol) and triethyl amine (3.49 ml 0.025 mol) in dioxane (10 ml), chloro acetyl chloride (1.99ml, 0.025 mol) was added drop wise at 5-10^{O}C. The reaction mixture was stirred for 8 hours. The reaction was monitored by TLC using toluene:ethyl acetate:methanol as mobile phase in the ration of 3:6:1. After the completion of reaction, the reaction mixture was poured into crushed ice to get solid, which was filtered and dried.

Azetidinone 1 (3-chloro-2-(2-hydroxyphenyl)-4-oxoazetidin-1-yl) Benzoic Acid



Melting point: 180-182^{O}C

λmax: 253.00nm

IR (KBr.cm^{-1}), 3292-3500 (O-Hstr), 1631(C=OCOONstr), 16911(C=O β lactum str)

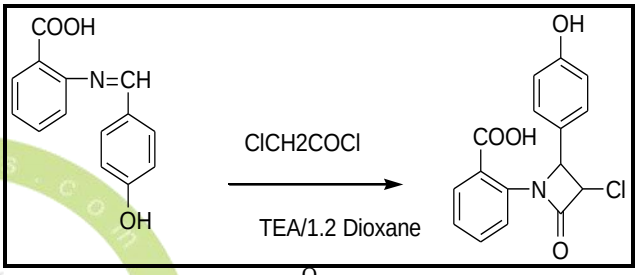
1HNMRppm:4.2 (s CH-Cl S), 7.14 (d. ArCHCHCl, 1 H), 7.5-7.8(m, Ar-H,8H).

MS m/z: 318 (M+1), 300, 271

Anal calculated. For $C_{16}H_{12}O_4NCl$.

C: 60.42.70 H: 3.78, N: 4.44 % found: C: 60.90, H: 3.79 N: 4.41%

Azetidinone 2- (3-chloro-2-(4-hydroxyphenyl)-4-oxoazetidin-1-yl) Benzoic Acid



Melting point: 184-186^{O}C

λmax: 253.00nm

IR (KBr.cm^{-1}), 2750-3100 (OHstr), 1641(C=OCOONstr), 1693(C=O β lactum str)

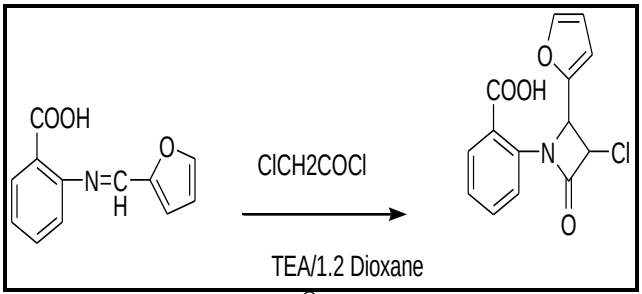
1HNMRppm:4.3 (s CH-Cl S), 7.1 (d. ArCHCHCl, 1 H), 7.6-8.2(m, Ar-H, 8H).

MS m/z: 318 (M+1), 300, 272

Anal calculated. For $C_{16}H_{12}O_4NCl$.

C: 60.48 H: 3.78, N: 4.44 % found: C: 60.49, H: 3.79 N: 4.41%

Azetidinone 3, 2-(3-chloro-2-(furan-2-yl)-4-oxoazetidin-1-yl) Benzoic Acid



Melting point: 150-152^{O}C

λmax: 254.00nm

IR (KBr.cm^{-1}), 2750-3250 (OH str), 1664(C=OCOONstr), 1681(C=O β lactum str)

1HNMRppm:3.6 (s CH-Cl 1H), 7.0 (d. ArCHCHCl, 1 H), 7.5-7.9(m, Ar-H,7H).

MS m/z: 292 (M+1), 274

Anal calculated. For $C_{14}H_{10}O_4NCl$.

C: 57.42.70 H: 3.44, N: 4.8 % found: C: 57.90, H: 3.59 N: 4.81%

Antimicrobial and Antifungal Screening

Antimicrobial activity of the synthesized compounds was screened using the disc diffusion method against selected pathogens. 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 45o C, and fungal organism in sterile sabouraud's dextrose agar medium at 45o 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 gentamycin (100 µg /disc) and fluconazole (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±1o 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.

Table 1: Antimicrobial activities of synthesized Schiff base and derivatives azetidinones

Compound	Bacteria and fungal along with zone of inhibition (mm)								
	S. Aureaus (µ/ml)			E. Coli (µ/ml)			A. Niger (µ/ml)		
	50	100	200	50	100	200	50	100	200
SB1	---	---	15	10	10	15	---	15	15
SB2	--	---	20	5	10	15	10	15	15
SB3	--	15	15	15	--	10	--	10	10
SBA1	-	10	15	20	10	15	10	15	15
SBA2	10	15	20	5	10	15	10	--	15
SBA3	--	---	--	--	10	15	--	10	15
gentamycin	20	25	25	15	20	25	---	----	----
fluconazole	--	---	---	---	---	---	10	15	15

RESULTS AND DISCUSSION

Schiff bases and their derivatives have been prepared by a simple and environmentally friendly reductive imination procedure. This methodology uses only Fe powder in acidic $EtOH/H_2O$ as a reducing agent which upon reduction spontaneously condenses with an aldehyde in situ. The structures of the synthesized compounds were supported by physical data and following spectral analysis.

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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