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Synthesis and Antimicrobial Screening of 4-(3-Chloro-2-oxo-4-substituted phenylazetidine-1-yl)benzoic Acids

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Various 4-{[(1E)-substituted phenyl methylene]amino} benzoic acids (**IIIa-e**) have been synthesized by condensation of *p*-amino benzoic acid with different aldehydes. The cyclocondensation reaction of **IIIa-e** with chloroacetyl chloride afforded 4-(3-chloro-2-oxo-4-substituted phenyl-azetidine-1-yl)benzoic acid (**IVa-e**). The structures of the synthesized compounds have been established on the basis of their analytical and spectral data. All the compounds have been screened for their antimicrobial activities.

Key Words: Azetidinone, Antimicrobial activity.

INTRODUCTION

The β-lactam heterocycles are still the most prescribed antibiotics used in medicine. A large number of 3-chloro mono cyclic β-lactams posses powerful antimicrobial[1], antiinflammatory[2], sedative[3], anticonvulsant[4] and antitubercular[5] activities. They also function as an enzyme inhibitor and are effective on the central nervous system[6]. Herein, the synthesis of 4-(3-chloro-2-oxo-4-substituted phenylazetidine-1-yl)benzoic acids (**IVa-e**) and their antimicrobial activity have been reported.

EXPERIMENTAL

The melting points of the compounds were determined by open capillary method and are uncorrected. Purity of the compounds were checked by micro TLC using silica getl G coated glass plate using benzene-methanol (90:10) as irrigant and iodine vapour as detecting agent. The IR spectra (cm^{-1}) were recorded in KBr discs on a Perkin-Elmer IR-283 spectrometer. ^1H NMR spectra (DMSO-d_6) were recorded on Bruker DPX-200 MHz NMR spectometer using TMS as internal standard (chemical shift in δ ppm). GCMS spectra were recorded in Shimadzu QP 50000. Elemental analyses were done using Carlo Erba 1106 CHN analyzer and were within 0.4 % of the theoretical values.

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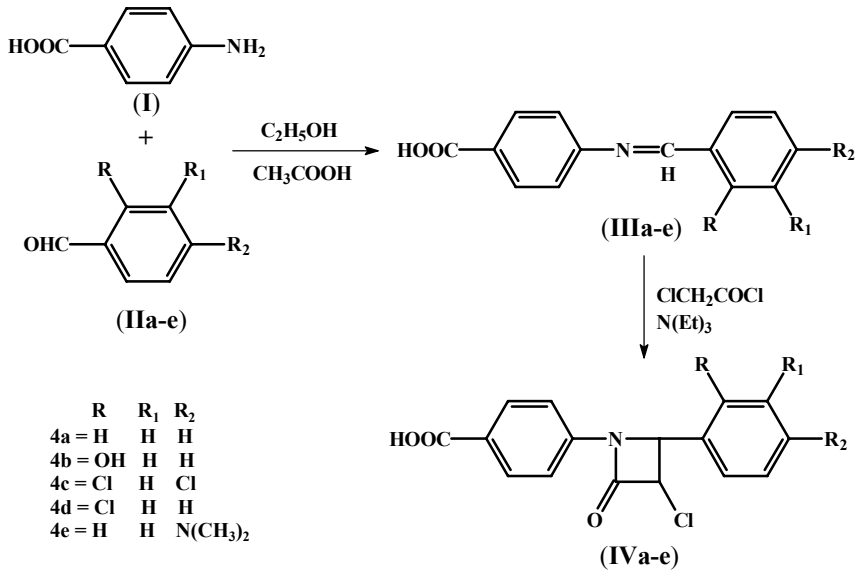
4-{[(1E)-(Substituted phenyl)methylene]amino}benzoic acid (IIIa-e): 4-Amino benzoic acid (**I**) 1.37 g, 0.01 mol) was dissolved in 30 mL of ethanol containing a few drops of glacial acetic acid (GAA). Appropriate aldehyde (**IIa-e**) (0.01 mol) was added and the reaction mixture was refluxed for 3 h cooled and then poured onto crushed ice. The solid obtained was filtered, washed with water and recrystallized from appropriate solvents (**Scheme-I**).



Scheme-I

4-(3-Chloro-2-oxo-4-substituted phenylazetidine-1-yl)benzoic acid derivatives (IVa-e): 4-{[(1E)-(Substituted phenylazetidine1-yl)benzoic acid (**IIIa-e**) was dissolved in N,N-dimethylformamide (40 mL) and triethylamine (0.02 mol) was added to it. Chloroacetyl chloride (0.02 mol) was added dropwise over a period of 0.5 h. The reaction mixture was refluxed for 5 h and filtered to separate the salt formed. The filtrate was concentrated to half its initial volume and then poured on to crushed ice. The product obtained was filtered, washed with water and recrystallized from DMF to get final compound **IVa-e**. The physical data of the compounds are given in Table-1.

IVa: Yield 62 %, m.p. 132ºC, IR (KBr, cm^{-1}): 1772 ν(C=O), 1604 ν(C=O, COOH), 1357 ν(C–N), 769 ν(C–Cl). ^{1}H NMR: δ 10.82 (1H, s, COOH), 7.35-7.52 (9H, m, Ar–H), 4.65 (1H, s, N–CH) and 3.35 (1H, s, CH–Cl). MS: m/z 301 (M^+). Found: C 63.76, H 4.24, N 4.44; $C_{16}H_{12}NO_3Cl$ Calcd.: C 63.69, H 4.04, N 4.64 %.

TABLE-1
PHYSICAL DATA OF COMPOUNDS **IVa-e**

Compd.	R	R_1	R_2	Solvent	m.p. (ºC)	Yield (%)
IVa	H	H	H	DMF	132	62
IVb	OH	H	H	DMF	206	58
IVc	Cl	H	Cl	Acetone	180	52
IVd	Cl	H	H	DMF	164	57
IVe	H	H	$N(CH_3)_2$	GAA	186	60

IVb: Yield 58 %, m.p. 206ºC, IR (KBr, cm^{-1}): 1770 ν(C=O), 1596 ν(C=O, COOH), 1355 ν(C–N), 765 ν(C–Cl). ^{1}H NMR: δ 10.82 (1H, s, COOH), 7.40-7.56 (8H, m, Ar–H), 4.62 (1H, s, N–CH) and 3.35 (1H, s, CH–Cl). MS: m/z 317 (M^+). Found: C 60.28, H 3.62, N 4.56; $C_{16}H_{12}NO_4Cl$ Calcd.: C 60.48, H 3.81, N 4.41 %.

IVc: Yield 52 %, m.p. 180ºC, IR (KBr, cm^{-1}): 1778 ν(C=O), 1596 ν(C=O, COOH), 1359 ν(C–N), 767 ν(C–Cl). ^{1}H NMR: δ 10.82 (1H, s, COOH), 7.41-7.50 (7H, m, Ar–H), 4.62 (1H, s, N–CH) and 3.35 (1H, s, CH–Cl). MS: m/z 369 (M^+). Found: C 64.08, H 5.30, N 11.62; $C_{16}H_{10}NO_3Cl_3$ Calcd.: C 64.58, H 5.42, N 11.89 %.

IVd: Yield 57 %, m.p. 164ºC, IR (KBr, cm^{-1}): 1776 ν(C=O), 1602 ν(C=O, COOH), 1357 ν(C–N), 848 ν(Ar–Cl), 767 ν(C–Cl). ^{1}H NMR: δ 10.82 (1H, s, COOH), 7.41-7.52 (8H, m, Ar–H), 4.62 (1H, s, N–CH) and 3.35 (1H, s, CH–Cl). MS: m/z 335 (M^+). Found: C 57.05, H 3.48, N 4.36; $C_{16}H_{11}NO_3Cl_2$ Calcd.: C 57.17, H 3.30, N 4.17 %.

IVe: Yield 60 %, m.p. 186ºC, IR (KBr, cm^{-1}): 1770 ν(C=O), 1600 ν(C=O, COOH), 1371 ν(C–N), 767 ν(C–Cl). ^{1}H NMR: δ 10.82 (1H, s, COOH), 7.41-7.52 (8H, m, Ar–H), 4.62 (1H, s, N–CH), 3.35 (6H, s, N–$(CH_3)_2$) and 3.35 (1H, s, CH–Cl). MS: m/z 344 (M^+). Found: C 64.28, H 5.10, N 11.62; $C_{18}H_{17}N_2O_3Cl$ Calcd.: C 64.58, H 5.42, N 11.89 %.

RESULTS AND DISCUSSION

4-{[(1E)-(Substituted phenyl methylene]amino}benzoic acids (**IIIa-e**) have been synthesized by condensation of *p*-amino benzoic acid with various aldehydes, in presence of few drops of glacial acetic acid, in dry ethanol. The resulting 4-{[(1E)-(substituted phenyl methylene]amino}-benzoic acids (**IIIa-e**) were cyclocondensed with chloroacetyl chloride in presence of triethylamine in dimethylformamide to yield 4-(3-chloro-2-oxo-4-substituted phenylazetidin-1-yl)benzoic acids (**IVa-e**).

The structure of the synthesized compounds have been established on the basis of their analytical and spectral data. All the compounds have been screened for their antimicrobial activities.

Antibacterial and antifungal activity

The synthesized compounds were screened for their antibacterial and antifungal activity (Table-2). The antibacterial activity against *Staphylococcus aureus, Proteus vulgaris, Pseudomonas aureginosa, Escherichia coli*. Serial dilution method[7] was used to determine the minimum inhibitory concentration (MIC) of the compound to inhibit the growth of the microorganism. The MIC was measured in µg/mL and the activity was compared with ampicillin (30 µg).

TABLE-2
ANTIMICROBIAL SCREENING RESULTS OF COMPOUNDS **IVa-e**
MINIMUM INHIBITOR CONCENTRATION (MIC)

Compd.	Antibacterial			Antifungal		
	S. aureus	*P. vulgaris*	*P. aureginosa*	*E. coli*	*C. albicans*	*A. niger*
IVa	125	32.5	250	62.5	250	250
IVb	250	125.0	500	125.0	125	125
IVc	250	500.0	500	125.0	250	125
IVd	250	62.5	250	62.5	125	500
IVe	250	500.0	500	250.0	500	250

All the synthesized compounds exhibited antibacterial activity but at various MIC levels. Compound **IVa** exhibited good activity against *Escherichia coli* and *Staphylococcus aureus* with MIC of 62.5 µg/mL, moderate activity against *Bacillus subtilis* with a MIC of 125 µg/mL and poor activity against *Pseudomonas aureginosa* with a MIC of 250 µg/mL. Compound **IVb** exhibited moderate activity against *Escherichia coli* and *Staphylococcus aureus* with a MIC of 125 µg/mL and poor activity against *Bacillus subtilis* and *Pseudomonas aureginosa* with a MIC of 250 and 500 µg/mL, respectively. Compound **IVc** exhibited moderate activity against *Staphylococcus aureus* with a MIC of 125 µg/mL and poor activity against *Bacillus subtilis, Escherichia coli* and *Pseudomonas aureginosa* with a MIC of 250, 500 and 500 µg/mL, respectively. Compound **IVd** exhibited good activity against *Escherichia coli* and *Staphylococcus aureus* with MIC of 62.5 µg/mL and poor activity against *Bacillus subtilis* and *Pseudomonas aureginosa* with MIC of 250 µg/mL. Compound **IVe** exhibited poor activity against *Bacillus subtilis, Escherichia coli, Pseudomonas aureginosa* and *Staphylococcus aureus*, with a MIC of 250, 500, 500 and 250 µg/mL, respectively.

The synthesized compounds were screened for their antifungal activity against *Candida albicans* and *Aspergillus niger*. Serial dilution method[7]

was used to determine the MIC of the compounds to inhibit the growth of the microorganism. The MIC was measured in µg/mL and the activity was compared with clotrimazole (10 µgm).

All the synthesized compounds exhibited antifungal activities but a various MIC levels. Compound **IVa** exhibited poor activity against *Candida albicans* and *Aspergillus niger* with a MIC of 250 µg/mL. Compound **IVb** exhibited moderate activity against *Candida albicans* and *Aspergillus niger* with a MIC of 125 µg/mL. Compound **IVc** exhibited moderate activity on *Aspergillus niger* with a MIC of 125 µg/mL and poor activity against *Candida albicans* with a MIC of 250 µg/mL. Compound **IVd** exhibited moderate activity against *Candida albicans* with a MIC of 125 µg/mL and poor activity against *Aspergillus niger* with a MIC of 500 µg/mL. Compound **IVe** showed poor activity against *Candida albicans* and *Aspergillus niger* with a MIC of 500 and 250 µg/mL, respectively.

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