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Synthesis, Characterization and Biological Studies of New Schiff Bases and Azetidinones Derived from Propionic Acid Derivatives

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Phenyl propionohydrazide (**2**), a hydrazinated derivative of methyl phenyl propanoate (**1**), when refluxed with aromatic aldehydes yielded Schiff bases **3A-E**, which on subsequent cyclization with triethylamine and chloroacetylchloride yielded azetidinones **4A-E**. The novel series of compounds were elucidated on the basis of spectral studies and screened for antibacterial and antifungal studies.

Key Words: Phenyl propionohydrazide, Methyl phenyl propanoate, Schiff base, Azetidinones, Antibacterial and Antifungal activity.

INTRODUCTION

It is established that several derivatives of azetidinones, Schiff bases and propionic acid possess antibacterial[1], antiinflammatory[2], CNS active[3], antimicrobial[4-6], antitubercular[7,8], anticancer[9] and anticonvulsant[10] activity. On the other hand it is known that Schiff bases and azetidinones can be synthesized from ester moieties[6,10]. As per the literature survey, an attempt is made to convert phenyl propionohydrazide (**2**), a hydrazinated derivative of methyl phenyl propanoate (**1**), into some novel N-(3-chloro-2-oxo-4-substituted phenylazetidin-1-yl)-3-phenylpropanamide (**4A-E**) *via* Schiff base **3A-E** to generate more potent antibacterial and antifungal compounds. The newly synthesized compounds were further elucidated spectrally and screened for antibacterial and antifungal activities.

EXPERIMENTAL

Melting points were determined in open capillary tubes. IR spectra were recorded (in KBr) on Bruker PCIR, ^{1}H NMR spectra on Bruker DPX 300 and mass spectra on MASPEC system (MSW/9629). Purity of synthesized compounds was checked by TLC aluminium sheets-silica gel 60 F254 (0.2 mm).

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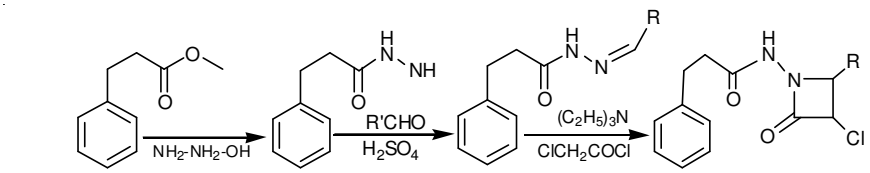
N-(Substituted benzylidene)-3-phenylpropionohydrazide (3A-E): Mixture of compound **2** (0.01 mol) derived from hydrazination of compound **1**, was refluxed with different aromatic aldehydes (0.01 mol) for 6 h containing few drops of acetic acid. The crystals formed were recrystallized from methanol to yield compounds **3A-E**.

N-{3-Chloro-2-oxo-4-(substituted phenylazetidinyl)}-3-phenylpropanamide (4A-E): Mixture of compound **3A-E** (0.01 mol), chloroacetyl chloride (0.012 mol) and triethylamine (0.02 mol) in dried dioxane (50 mL) was stirred for 18-20 h. Product formed was isolated and recrystallized from methanol to yield compounds **4A-E**.

Biological activity: The synthesized compounds **3A-E** and **4A-E** were screened for antibacterial (*S. aureus*, *E. coli* and *P. aeruginosa*) and antifungal (*C. albicans*, *A. flavus* and *A. fumigatus*) by disk diffusion method at a concentration of 2 mg/mL using DMF as solvent. The results were recorded using ampicillin 1 mg/mL and fluconazole 2.5 mg/mL as standards given in Table-4.

RESULTS AND DISCUSSION

N-(Substituted benzylidene)-3-phenylpropionohydrazides (**3A-E**) synthesized from compound **2**, when cyclized with triethyl amine and chloroacetyl chloride leads to potent antibacterial and antifungal N-{3-chloro-2-oxo-4-(substituted phenylazetidinyl)}-3-phenylpropanamide **(4A-E)** (**Scheme-I**). Physical data of compounds **3A-E** and **4A-E** are given in Table-1. The assigned structure, molecular formulae and the anomeric configuration of the novel compounds **3A-E** and **4A-E** were confirmed and elucidated by Mass, ^{1}H NMR and IR spectral data (Tables 2 and 3). All the synthesized compounds **3A-E** and **4A-E** have shown antibacterial and antifungal activity to certain extent. Among synthesized compounds **3A**, **3B**, **4A** and **4B** have shown good antibacterial and antifungal activity and some of the remaining compounds have shown moderate activity on tested organisms (Table-4).



where R = various aryl groups indicated in Table-1

Scheme-I

TABLE-1
PHYSICAL CHARACTERISTICS OF SYNTHESIZED COMPOUNDS **3A-E** AND **4A-E**

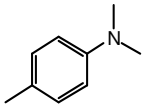
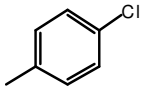
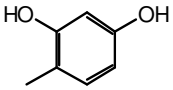
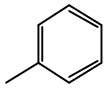
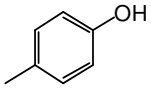
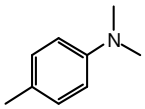
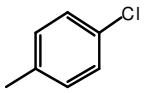
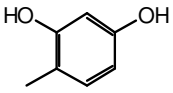
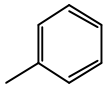
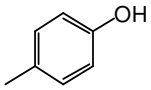
Compd. (m.f.)	R	Physical characteristics	Yield (%)	m.w. (m.p. ºC)
3A ($C_{18}H_{21}N_3O$)		White crystals	69.26	295.38 (210-211)
3B ($C_{16}H_{15}N_2OCl$)		White crystals	65.32	286.76 (198-199)
3C ($C_{16}H_{16}N_2O_3$)		White crystals	62.52	284.31 (206-207)
3D ($C_{16}H_{16}N_2O$)		White crystals	69.84	252.31 (194-195)
3E ($C_{16}H_{16}N_2O_2$)		White crystals	66.45	268.31 (202-203)
4A ($C_{20}H_{22}N_3O_2Cl$)		Light brown crystals	58.24	371.86 (223-224)
4B ($C_{18}H_{16}N_2O_2Cl_2$)		White crystals	56.86	363.24 (209-210)
4C ($C_{18}H_{17}N_2O_4Cl$)		Pale yellow crystals	51.23	360.79 (219-220)
4D ($C_{18}H_{17}N_2O_2Cl$)		White crystals	57.45	328.79 (206-207)
4E ($C_{18}H_{17}N_2O_3Cl$)		White crystals	54.22	344.79 (215-216)

TABLE-2
MASS AND ^{1}H-NMR DATA OF **3A-E** AND **4A-E**
^{1}H-NMR Spectral data of protons of phenyl group and R in compounds **3A-E** and **4A-E** are depicted as Ar-H and Ar′-H′, respectively.

Compd.	Mass (m/z)	^{1}H NMR (ppm)
3A	m/z: 295(M^+), 190(base Peak), 162, 147, 148, 120, 105, 91	2.52 δ (2H, t, 6.6 Hz, -CH_2-CO-), 2.80 δ (2H, t, 6.9 Hz, Ar-CH_2), 2.87 δ (6H, s, -N(CH_3)$_2$), 6.58 δ (2H, d, 7.5 Hz, Ar′-H3′&5′), 7.05 δ (5H, m, Ar-H), 7.44 δ (2H, d, 7.8Hz, Ar′-H2′ & 6′), 8.1 δ (1H, s, N=CH), 9.50 δ (1H, s, NH)

Compd.	Mass (m/z)	^{1}H NMR (ppm)
3B	286(M^+), 181(base Peak), 153, 148, 138, 111, 105, 91	2.55 δ (2H, t, 6.6 Hz, -CH_2-CO-), 2.80 δ (2H, t, 6.9 Hz, Ar-CH_2), 7.08 δ (5H, m, Ar-H), 7.38 δ (2H, d, 7.2 Hz, Ar′-H3′ & 5′), 7.65 δ (2H, d, 7.5Hz, Ar′-H2′&6′), 8.56 δ (1H, s, N=CH), 9.65 δ (1H, s, NH)
3C	m/z: 284(M^+), 148 (base Peak), 179, 151, 136, 109, 105, 91	2.59 δ (2H, t, 6.9 Hz, -CH_2-CO-), 2.85 δ (2H, t, 6.9 Hz, Ar-CH_2), 5.16 δ (1H, s, OH), 5.24 δ (1H, s, OH), 6.26 δ (1H, s, Ar′-H3′), 6.38 δ (1H, d, 7.2 Hz, Ar′-H5′), 7.02 δ (5H, m, Ar-H), 7.39 δ (1H, d, 7.5Hz, Ar′-H6′), 8.59 δ (1H, s, N=CH), 9.42 δ (1H, s, NH)
3D	m/z: 252(M^+), 147(base peak), 148, 119, 105, 104, 77	2.50 δ (2H, t, 6.9 Hz, -CH_2-CO-), 2.78 δ (2H, t, 6.9 Hz, Ar-CH_2), 7.06 δ (5H, m, Ar-H), 7.31 δ (2H, m, Ar′-H3′, 4′ & 5′), 7.61 δ (2H, d, 7.5Hz, Ar′-H2′&6′), 8.52 δ (1H, s, N=CH), 9.61 δ (1H, s, NH)
3E	m/z: 268 (M^+), 163(base Peak), 148, 105, 135, 120, 93, 91	2.53 δ (2H, t, 6.6 Hz, -CH_2-CO-), 2.81 δ (2H, t, 6.6 Hz, Ar-CH_2), 5.22 δ (1H, s, OH), 6.84 δ (2H, d, 7.2 Hz, Ar′-H3′ & 5′), 7.08 δ (5H, m, Ar-H), 7.45 δ (2H, d, 7.5Hz, Ar′-H2′&6′), 8.62 δ (1H, s, N=CH), 9.54 δ (1H, s, NH)
4A	m/z: 371(M^+), 223(base Peak), 266, 148, 147, 120 105, 91	2.50 δ (2H, t, 6.6 Hz, -CH_2-CO-), 2.79 δ (2H, t, 6.6 Hz, Ar-CH_2), 2.85 δ (6H, s, -$N(CH_3)_2$), 5.07 δ (1H, d, 7.2 Hz, N-CH), 5.25 δ (1H, d, 7.2 Hz, CH-Cl), 6.58 δ (2H, d, 7.5 Hz, Ar′-H3′&5′), 6.98 δ (2H, d, 7.8 Hz, Ar′-H2′ & 6′), 7.06 δ (5H, m, Ar-H), 9.40 δ (1H, s, NH)
4B	m/z: 362(M^+), 258 (base Peak), 223, 214, 148, 138, 111, 105, 91	2.52 δ (2H, t, 6.6 Hz, -CH_2-CO-), 2.80 δ (2H, t, 6.6 Hz, Ar-CH_2), 5.07 δ (1H, d, 7.2 Hz, N-CH), 5.25 δ (1H, d, 7.2 Hz, CH-Cl), 6.94 δ (2H, d, 7.5 Hz, Ar′-H2′ & 6′), 7.01 δ (5H, m, Ar-H), 7.19 δ (2H, d, 7.5Hz, Ar′-H2′&6′), 9.65 δ (1H, s, NH)
4C	m/z: 360(M^+), 255(base Peak), 223, 212, 148, 136, 109, 105, 91	2.54 δ (2H, t, 6.6 Hz, -CH_2-CO-), 2.85 δ (2H, t, 6.6 Hz, Ar-CH_2), 5.08 δ (1H, d, 7.2 Hz, N-CH), 5.12 δ (1H, s, OH), 5.20 δ (1H, s, OH), 5.25 δ (1H, d, 7.2 Hz, CH-Cl), 6.12 δ (1H, s, Ar′-H3′), 6.24 δ (1H, d, 7.2 Hz, Ar′-H5′), 6.79 δ (1H, d, 7.5Hz, Ar′-H6′), 7.06 δ (5H, m, Ar-H), 9.42 δ (1H, s, NH)
4D	m/z: 328(M^+), 223 (base Peak), 180, 148, 105, 104, 91, 77	2.50 δ (2H, t, 6.9 Hz, -CH_2-CO-), 2.78 δ (2H, t, 6.9 Hz, Ar-CH_2), 5.12 δ (1H, d, 7.2 Hz, N-CH), 5.22 δ (1H, d, 7.2 Hz, CH-Cl), 7.06 δ (10 H, m, Ar & Ar′), 9.58 δ (1H, s, NH)
4E	m/z: 344(M^+), 198(base Peak), 239, 223, 196, 148, 120, 105, 91	2.51 δ (2H, t, 6.6 Hz, -CH_2-CO-), 2.79 δ (2H, t, 6.6 Hz, Ar-CH_2), 5.08 δ (1H, s, OH), 5.15 δ (1H, d, 7.2 Hz, N-CH), 5.24 δ (1H, d, 7.2 Hz, CH-Cl), 6.62 δ (2H, d, 7.2 Hz, Ar′-H3′ & 5′), 6.94 δ (2H, d, 7.5 Hz, Ar′-H2′&6′), 7.08 δ (5H, m, Ar-H), 9.54 δ (1H, s, NH)

TABLE-3
IR DATA OF COMPOUNDS **3A-E** AND **4A-E**

Compd.	IR (cm^{-1})
3A	3252, 1632 for NH of CONH, 1643 for CO of CONH, 1585, 1469, 1292, 1191, 1162, 1125, 1083, 867, 836, 770 for C=C & C-H of aromatic ring
3B	3259, 1628 for NH of CONH, 1646 for CO of CONH, 1596, 1466, 1284, 1157, 1133, 1081, 852, 841, 761 for C=C & C-H of aromatic ring
3C	3511for OH on phenyl ring, 3310, 1628 for NH of CONH, 1642 for CO of CONH, 1590, 1441, 1282, 1190, 1171, 1153, 907, 780 for C=C & C-H of aromatic ring
3D	3250, 1630 for NH of CONH, 1644 for CO of CONH, 1589, 1469, 1293, 1198, 1155, 1084, 895, 869, 747 for C=C & C-H of aromatic ring
3E	3506 for OH on phenyl ring, 3310, 1632 for NH of CONH, 1640 for CO of CONH, 1588,1481, 1290, 1173, 1142, 941, 872, 787 for C=C & C-H of aromatic ring
4A	3253, 1634 for NH of CONH, 1758 for CO of azetidinone ring, 1641 for CO of CONH, 1595, 1471, 1290, 1197, 1160, 1119, 1084, 862, 831, 778 for C=C & C-H of aromatic ring
4B	3254, 1629 for NH of CONH, 1755 for CO of azetidinone ring, 1646 for CO of CONH, 1590, 1467, 1298, 1162, 1130, 1087, 872, 831, 769 for C=C & C-H of aromatic ring
4C	3513 for OH on phenyl ring, 3318, 1621 for NH of CONH, 1754 for CO of azetidinone ring, 1644 for CO of CONH, 1592,1447, 1297, 1191, 1175, 1156, 901, 782 for C=C & C-H of aromatic ring
4D	3250, 1622 for NH of CONH, 1740 for CO of azetidinone ring, 1643 for CO of CONH, 1591, 1464, 1294, 1192, 1158, 1086, 893, 860, 741 for C=C & C-H of aromatic ring
4E	3511 for OH on phenyl ring, 3312, 1630 for NH of CONH, 1736 for CO of azetidinone ring, 1641 for CO of CONH, 1588,1480, 1293, 1176, 1143, 949, 872, 788 for C=C & C-H of aromatic ring

TABLE-4
ANTIMICROBIAL ACTIVITY OF COMPOUNDS **3A-E** AND **4A-E**

Compd.	MIC (Diameter of zone of inhibition in mm) mg/mL					
	Antibacterial activity			Antifungal activity		
	S. aureus	*E. coli*	*P. aeruginosa*	*C. albicans*	*A. flavus*	*A. fumigatus*
3A	23	24	23	13	12	10
3B	24	22	23	12	10	11
3C	21	18	18	12	9	10
3D	23	12	17	11	10	12
3E	18	17	22	10	11	9
4A	24	23	21	15	11	11
4B	23	24	23	15	14	10
4C	16	18	14	10	11	10
4D	17	14	11	12	10	11
4E	21	19	16	11	9	10
Ampicillin	25	25	24	-	-	-
Fluconazole	-	-	-	17	16	17

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