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NOTE

Synthesis and antimicrobial potential of Mannich bases of 4-chloro-3-{4-(chlorobenzyloxy)-benzoylhydrazono}-indolin-2-ones

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Abstract : 4-Chloro-3-{4-(chlorobenzyloxy)-benzoylhydrazono}-indolin-2-ones (1-4) were synthesised by the condensation of 4-(chlorobenzyloxy)-benzoylhydrazines and 4-chloroisatin. On being subjected to aminomethylation in the presence of formaldehyde and heterocyclic secondary amines, indolinones 1-4, furnished aminomethylated indolinones (Mannich bases) 5-20. The structures of the compounds have been established by means of elemental analysis and spectral data (IR, PMR and Mass). The compounds have been screened for their antimicrobial potential against human pathogenic bacteria and fungi.

Keywords : Isatin, aminomethylation, Mannich bases, antimicrobial agents.

Introduction

Isatins[1] and their derivatives have been reported to possess broad spectrum of biological activities viz. antiviral[2], cytotoxic[3], antimicrobial[4], antifertility[5], amoebicidal[6], anti-HIV[7], antileukemic[8], anticonvulsant[9], CNS-depressant[10], analgesic and antiinflammatory[11]. Recently a review[12] has been published on biological potential of isatin derivatives. In the light of these observations and in continuation[13] of our work on biologically active heterocycles, synthesis of a new series of Schiff's bases [4-chloro-3-{4-(chlorobenzyloxy)-benzoylhydrazono}-indolin-2-ones] (**1-4**) and Mannich bases [1-aminomethyl-4-chloro-3-{4-(chlorobenzyloxy)-benzoylhydrazono}-indolin-2-ones] (**5-20**) is being reported in the present communication.

Results and discussion

Methylparaben was treated with chlorosubstituted benzyl chlorides to get methyl-4-(chlorobenzyloxy)-benzoates which on hydrazinolysis gave 4-(chlorobenzyloxy)-benzoylhydrazines. Acid catalysed condensation of hydrazines with 4-chloroisatin in equimolar proportion gave 4-chloro-3-{4-(chlorobenzyloxy)-benzoylhydrazono}-indolin-2-ones (**1-4**). On being subjected to aminomethylation[14] with heterocyclic secondary amines in the presence of formaldehyde (**1-4**), gave l-aminomethyl-4-chloro-3-{4-(chlorobenzyloxy)-benzoylhydrazono}-indolin-2-ones (**5-20**) (Scheme 1).

Antimicrobial activity :

Compounds **5-20** were tested for their antimicrobial potential against human pathogenic bacteria viz. *Escherichia coli* (ATCC 9637) (EC), *Pseudomonas aeruginosa* (ATCC- BAA427) (PA), *Staphylococcus aureus* (ATCC 25923) (SA), *Klebsiella pneumoniae* (ATCC 27736) (KP) and fungi viz. *Candida albicans* (CA), *Cryptococcus neoformans* (CN), *Sporothrix schenckii* (SS), *Trichophyton mentagrophytes* (TM), *Aspergillus fumigatus* (AF) and *Candida parapsilosis* (ATCC 22019) (CP) by tube dilution technique[15] recommended by NCCLS. Compounds were tested at maximum concentration 50 μg/mL and MIC value in μg/mL were determined and results are presented in Table 2. Gentamycin and fluconazole were taken as standard for bacteria and fungi respectively.

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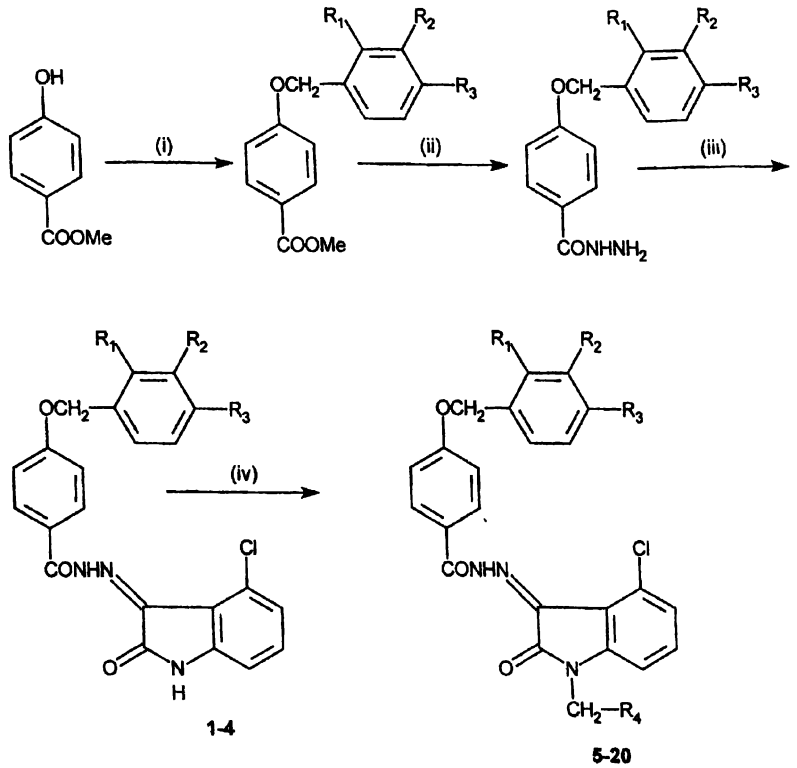

(i) Chlorobenzyl chlorides, K_2CO_3 (anhyd.)

(ii) $N_2H_4.H_2O$

(iii) 4-Chloroisatin, EtOH, AcOH

(iv) Amines, CH_2O, DMF

R_1,R_2,R_3 = H, Cl,

R_4 = —N O , —N , —N N—Me , —N

Scheme 1

Experimental

The melting points were taken in open capillaries in sulfuric acid bath and are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer RX1 spectrophotometer and PMR on Bruker Avance 400 spectrometer. $CDCl_3$ was used as solvent and TMS as internal reference. Chemical shifts are expressed in δ ppm. Mass spectra were recorded on Jeol-JMS-D-300 spectrometer at 70 eV with direct inlet system. Elemental analysis data were obtained on Carlo Erba 1108 analyser. Purity of the compounds was checked by TLC silica gel G plates and spots were located by exposure to iodine vapors. The physical data of the compounds prepared, are presented in Table 1.

Table 1. Characterization data of the compounds prepared

Compd.	R_1	R_2	R_3	R_4	M.p. (°C)	Yield (%)	Molecular formula	Elemental analysis (%) : Found (Calcd.)		
								C	H	N
1	H	H	H	-	260-262	72	$C_{22}H_{16}ClN_3O_3$	-	-	-
2	Cl	H	H	-	264-266	72	$C_{22}H_{16}Cl_2N_3O_3$	-	-	-
3	H	Cl	H	-	254-256	70	$C_{22}H_{16}Cl_2N_3O_3$	-	-	-
4	H	H	Cl	-	258-260	76	$C_{22}H_{16}Cl_2N_3O_3$	-	-	-
5	H	H	H	Morpholino	172-174	86	$C_{27}H_{25}ClN_4O_4$	59.88 (60.00)	4.58 (4.62)	10.28 (10.37)
6	H	H	H	Piperidino	198-200	75	$C_{28}H_{27}ClN_4O_3$	65.39 (62.45)	4.88 (5.01)	10.34 (10.40)
7	H	H	H	N-Me-Piperazino	180-182	72	$C_{28}H_{28}ClN_5O_3$	60.66 (60.75)	4.98 (5.06)	12.60 (12.65)
8	H	H	H	Pyrrolidino	174-176	86	$C_{27}H_{25}ClN_4O_3$	61.74 (61.83)	4.66 (4.77)	12.60 (10.68)
9	Cl	H	H	Morpholino	174-176	80	$C_{27}H_{24}Cl_2N_4O_4$	59.80 (60.00)	4.55 (4.62)	10.31 (10.37)
10	Cl	H	H	Piperidino	166-168	73	$C_{28}H_{26}Cl_2N_4O_3$	62.35 (62.45)	4.90 (5.01)	10.32 (10.40)
11	Cl	H	H	N-Me-Piperazino	162-164	68	$C_{28}H_{27}Cl_2N_5O_3$	60.62 (60.75)	5.00 (5.06)	12.59 (12.65)
12	Cl	H	H	Pyrrolidino	172-174	77	$C_{27}H_{24}Cl_2N_4O_3$	61.78 (61.83)	4.68 (4.77)	10.50 (10.60)
13	H	Cl	H	Morpholino	186-188	80	$C_{27}H_{24}Cl_2N_4O_4$	59.82 (60.00)	4.58 (4.62)	10.29 (10.37)
14	H	Cl	H	Piperidino	180-182	70	$C_{28}H_{26}Cl_2N_4O_3$	62.40 (62.45)	4.90 (5.01)	10.31 (10.40)
15	H	Cl	H	N-Me-Piperazino	158-160	70	$C_{28}H_{27}Cl_2N_5O_3$	60.66 (60.75)	4.90 (5.06)	12.55 (12.65)
16	H	Cl	H	Pyrrolidino	156-158	77	$C_{27}H_{24}Cl_2N_4O_3$	61.79 (61.83)	4.00 (4.77)	10.60 (10.68)
17	H	H	Cl	Morpholino	196-198	82	$C_{27}H_{24}Cl_2N_4O_4$	59.92 (60.00)	4.57 (4.62)	10.33 (10.37)
18	H	H	Cl	Piperidino	190-192	68	$C_{28}H_{26}Cl_2N_4O_3$	62.32 (62.45)	4.90 (5.01)	10.33 (10.40)
19	H	H	Cl	N-Me-Piperazino	174-176	68	$C_{28}H_{27}Cl_2N_5O_3$	62.66 (60.75)	4.88 (5.06)	12.57 (12.65)
20	H	H	Cl	Piperidino	172-174	72	$C_{27}H_{24}Cl_2N_4O_3$	61.70 (61.83)	4.69 (4.77)	10.60 (10.68)

Table 2. Minimum Inhibitory Concentration MIC (μg/mL) of compounds against pathogenic bacteria and fungi by tube dilution technique

Compd.	EC	PA	SA	KP	CA	CN	SS	TM	AF	CP
5	>50	>50	>50	>50	50	>50	>50	6.25	>50	>50
6	>50	>50	>50	>50	>50	>50	>50	6.25	>50	>50
7	>50	>50	12.5	>50	>50	>50	>50	12.5	>50	>50
8	>50	>50	>50	50	>50	>50	>50	25	>50	>50
9	>50	50	>50	50	>50	50	3.12	>50	>50	>50
10	>50	50	12.5	50	>50	25	>50	>50	>50	6.25
11	>50	>50	12.5	25	50	>50	>50	>50	>50	3.12
12	>50	>50	>50	25	25	>50	>50	>50	>50	50
13	>50	25	>50	25	>50	>50	3.12	>50	>50	50
14	>50	>50	>50	>50	>50	>50	50	3.12	>50	>50
15	>50	>50	>50	>50	12.5	3.12	50	>50	>50	>50
16	>50	>50	>50	>50	12.5	3.12	>50	25	>50	>50
17	>50	>50	>50	>50	50	25	>50	>50	>50	>50
18	>50	>50	>50	>50	>50	25	>50	>50	>50	>50
19	>50	>50	>50	>50	>50	50	>50	>50	>50	>50
20	>50	>50	>50	>50	>50	25	>50	>50	>50	>50
Gentamycin	0.18	25	6.25	0.18	-	-	-	-	-	-
Fluconazole	-	-	-	-	0.50	1.0	2.0	1.0	2.0	1.0

4-Chloro-3-{4-(chlorobenzyloxy)-benzoylhydrazono}-indolin-2-ones (**1-4**) : *(General method)* :

A mixture of 4-(chlorobenzyloxy)-benzoylhydrazines (0.01 mol) and 4-chloroisatin (0.01 mol) in ethanol (50 mL) containing 3–4 drops of glacial acetic acid was refluxed for one hour and left overnight at room temperature. The solid product so obtained was washed with methanol; **1** IR (cm^{-1}) : 3417.5, 3161.3 (NH), 1743.6, 1670.6 (-CO-), 1250.4 (-CH_2O-), 744.1 (C-Cl); MS (*m/z*) : 405 (M^+), 407 (M+2); **2** IR (cm^{-1}) : 3482.0, 3151.8 (NH), 1700.6, 1667.3 (-CO-), 1252.0 (-CH_2O-), 751.9 (C-Cl); MS (*m/z*) : 440 (M^+), 442 (M+2), 444 (M+4); **3** IR (cm^{-1}) : 3460.9, 3166.4 (NH), 1743.4, 1673.1 (-CO-), 1251.3 (-CH_2O-), 778.2 (C-Cl); **4** IR (cm^{-1}) : 3454.9, 3149.9 (NH), 1704.2, 1671.7 (-CO-), 1248.4 (-CH_2O-), 780.1 (C-Cl).

1-Aminomethyl-4-chloro-3-{4-(chlorobenzyloxy)-benzoylhydrazono}-indolin-2-ones (**5-20**) : *(General method)* :

To a suspension of **1-4** (0.005 mol) in DMF, formaldehyde (0.5 mL, 37%) and amines (0.005 mol) were added with vigorous stirring. The solution was warmed for 2 min on a water bath and left overnight at room temperature. The solid product thus obtained was filtered, dried and recrystallized from chloroform : pet ether (60–80 °C) (1 : 1); **5** IR (cm^{-1}) : 3450.0 (NH), 2929.9 (>N-CH_2-N<), 1684.3, 1658.4 (-CO-), 1249.2 (-CH_2O-), 1146.5 (-C-O-C-), 758.7 (C-Cl); PMR δ (ppm) : 2.61–2.64 (4H, t, -CH_2-N-CH_2-), 3.70–3.72 (4H, t, -CH_2-O-CH_2-), 4.50 (2H, s, >N-CH_2-N<), 5.25 (2H, s, -CH_2O-), 6.97–8.04 (12H, m, Ar-H), 13.86 (1H, s, CONH); MS (*m/z*) : 504 (M^+), 506 (M+2); **6** IR (cm^{-1}) : 3440.4 (NH), 2932.6 (>N-CH_2-N<), 1686.8, 1654.6 (-CO-), 1248.0 (-CH_2O-), 758.2 (C-Cl); PMR δ (ppm) : 1.42–1.59 (6H, m, -$CH_2CH_2CH_2$-), 2.52–2.58 (4H, t, -CH_2-N-CH_2-), 4.50 (2H, s, >N-CH_2-N<), 5.25 (2H, s, -CH_2O-), 7.00–8.04 (12H, m, Ar-H), 13.99 (1H, s, CONH); MS (*m/z*) : 502 (M^+), 504 (M+2); **7** PMR δ (ppm) : 1.99 (3H, s, N-Me), 2.28–2.41 (4H, t,-CH_2-N-CH_2-), 2.52–2.62 (4H, t, -CH_2-N(Me)-CH_2-), 4.50 (2H, s, >N-CH_2-N<), 5.25 (2H, s, -CH_2O-), 6.98–8.04 (12H, m, Ar-H), 13.89 (1H, s, CONH); MS (*m/z*) : 517 (M^+), 519 (M+2); **8** IR (cm^{-1}) : 3421.7 (NH), 2965.6 (>N-CH_2-N<), 1683.2, 1654.6 (-CO-), 1248.8 (-CH_2O-), 761.9 (C-Cl); PMR δ (ppm) : 1.24–1.57 (4H, m, -CH_2CH_2-), 2.27–2.67 (4H, t, -CH_2-N-CH_2-), 4.68 (2H, s, >N-CH_2-N<), 5.15 (2H, s, -CH_2O-), 7.00–8.04 (12H, m, Ar-H), 13.92 (1H, s, CONH); MS (*m/z*) : 488 (M^+), 490 (M+2); **9** IR (cm^{-1}) : 3434.3 (NH), 2927.0 (>N-CH_2-N<), 1681.1, 1650.2 (-CO-), 1247.5 (-CH_2O-), 1171.8 (-C-O-C-), 753.9 (C-Cl); PMR δ (ppm) : 2.61–2.64 (4H, t, -CH_2-N-CH_2-), 3.68–3.71 (4H, t, -CH_2-O-CH_2-), 4.50 (2H, s, >N-CH_2-N<), 5.26 (2H, s, -CH_2O-), 6.97–8.05 (11H, m, Ar-H), 14.04 (1H, s, CONH); **10** IR (cm^{-1}) : 3436.8 (NH), 2929.6 (>N-CH_2-N<), 1685.3, 1649.2 (-CO-), 1250.2 (-CH_2O-), 753.1 (C-Cl); PMR δ (ppm) : 1.44–1.59 (6H, m, -$CH_2CH_2CH_2$-), 2.55–2.58 (4H, t, -CH_2-N-CH_2-), 4.66 (2H, s, >N-CH_2-N<), 5.25 (2H, s, -CH_2O-), 7.00–8.05 (11H, m, Ar-H), 14.01 (lH, s, CONH); MS (*m/z*) : 538 (M^+), 540 (M+2); **12** IR (cm^{-1}) : 3446.3 (NH), 2933.9 (>N-CH_2-N<), 1681.6, 1652.3 (-CO-), 1252.2 (-CH_2O-), 753.1 (C-Cl); PMR δ (ppm) : 1.25–1.36 (4H, m, -CH_2CH_2-), 2.69–2.72 (4H, t, -CH_2-N-CH_2-), 4.68 (2H, s, >N-CH_2-N<), 5.25 (2H, s, -CH_2O-), 7.03–8.05 (11H, m, Ar-H), 14.04 (1H, s, CONH); **14** IR (cm^{-1}) : 3421.2 (NH), 2941.8 (>N-CH_2-N<), 1686.4, 1651.8 (-CO-), 1252.0 (-CH_2O-), 777.4 (C-Cl); PMR δ (ppm) : 1.62–1.81 (6H, m, -$CH_2CH_2CH_2$-), 2.50–2.71 (4H, t, -CH_2-N-CH_2-), 4.52 (2H, s, >N-CH_2-N<), 5.35 (2H, s, -CH_2O-), 6.97–8.04 (11H, m, Ar-H), 13.92 (1H, s, CONH); **15** IR (cm^{-1}) : 3447.7 (NH), 2938.3 (>N-CH_2-N<), 1695.3, 1661.2 (-CO-), 1251.2 (-CH_2O-), 773.0 (C-Cl); PMR δ (ppm) : 1.89 (3H, s, N-Me), 2.27–2.43 (4H, t, -CH_2-N-CH_2-), 2.49–2.67 (4H, t, -CH_2N-(Me)CH_2-), 4.52 (2H, s, >N-CH_2-N<), 5.35 (2H, s, -CH_2O-), 7.00–8.04 (11H, m, Ar-H), 13.98 (1H, s, CONH); MS (*m/z*) : 553 (M^+), 555 (M+2); **17** IR (cm^{-1}) : 3458.9 (NH), 2950.4 (>N-CH_2-N<), 1698.2, 1672.8 (-CO-), 1248.3 (-CH_2O-), 1153.6 (-C-O-C-), 775.5 (C-Cl); PMR δ (ppm) : 2.58–2.61 (4H, t, -CH_2-N-CH_2-), 3.69–3.72 (4H, t, -CH_2-O-CH_2-), 4.68 (2H, s, >N-CH_2-N<), 5.20 (2H, s, -CH_2O-), 7.00–8.04 (11H, m, Ar-H), 13.84 (1H, s, CONH); **20** IR (cm^{-1}) : 3448.1 (NH), 2925.0 (>N-CH_2-N<), 1700.1, 1676.9 (-CO-), 1250.1 (-CH_2O-), 764.4 (C-Cl); PMR δ (ppm) : 1.25–1.42 (4H, m, -CH_2CH_2-), 2.36–2.49 (4H, t, -CH_2-N-CH_2-), 4.68 (2H, s, >N-CH_2-N<), 5.20 (2H, s, -CH_2O-), 7.01–8.05 (11H, m, Ar-H), 13.97 (1H, s, CONH).

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