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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME NEW SCHIFF AND MANNICH BASES OF 5-BROMOINDOLIN-2, 3-DIONE

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Abstract

1-substituted/1-aminomethyl-3-[4′-(4″-nitrobenzyloxy) benzoylhydrazono]-5-bromoindolin-2-ones (Schiff bases and Mannich bases) have been synthesized and screened for their antimicrobial potential against human pathogenic fungi and bacteria. The structures of the compounds have been elucidated with the help of elemental analysis and spectral data (IR, ^{1}H NMR and Mass).

Introduction

Isatins (1*H*-indole-2, 3-diones) and their derivatives possess wide variety of biological activities viz., anthelmintic[1], antiinflammatory[2,3], analgesic[4], antimalarial[5], antioxidant[6], anti-epileptic[7], anticonvulsant[8,9], antitubercular[10], cytotoxic[11,] antimicrobial[12,13], antifertility[14], CNS depressant[15] and enzyme inhibitory[16]. In the light of biological activity profile of indole-2, 3-diones and in continuation of our work on indole-2, 3-dione derivatives[17-20] synthesis and amtimicrobial potential of some new schiff and Mannish bases of 5-bromoindolin-2,3-diones is being reported here.

4-(4′-Nitrobenzyloxy)-benzoylhydrazine[21] **2** was prepared by hydrazinolysis of methyl 4-(4′-nitrobenzyloxy)-benzoate **1** which in turn was obtained by O-benzylation of methyl 4-hydroxybenzoate with 4-nitrobenzyl bromide. Benzoylhydrazine **2** on condensation with 5-bromoindolin-2, 3-diones in equimolar proportion, gave 3-[4′-(4″-nitrobenzyloxy)-benzoylhydrazono] - 5-bromoindolin-2-ones (Schiff bases) **3-8**. Compound **3** on being subjected to aminomethylation[22] with secondary amines in the presence of formaldehyde, gave 1-aminomethyl-3-[4′-(4″-nitrobenzyloxy)-benzoylhydrazono] -5-bromoindolin-2-ones (Mannich bases) **9-17 (Scheme I)**.

Antimicrobial activity

Compounds **3-17** were screened for their *in-vitro* antimicrobial potential against human pathogenic bacteria *viz*; *Escherichia coli* (ATCC 9637) (EC), *Pseudomonas aeruginosa* (ATCCBAA 427 PA), *Staphylococcus aureus* (ATCC 25923) (SA), *Klebsiella pneumoniae* (ATCC 27736) (KP) and fungi *Candida albicans*(CA*)*, *Cryptococcus neoformans* (CN)*, Trichophyton mentagrophytes* (TM)*, Aspergillus fumigatus* (AF) using tube dilution method at maximum concentration of 50 µg/mL and minimum inhibitory concentration (MIC) values were determined in µg/mL. Gentamycin and fluconazole were taken as standard drugs for bacteria and fungi respectively. Antimicrobial activity data are presented in **Table I**.

Table I — Minimum Inhibitory Concentration, MIC (µg/mL) of compounds against bacteria and fungi

Compd	EC	PA	SA	KP	CA	CN	TM	AF
3	>50	>50	>50	>50	50	>50	50	>50
4	>50	>50	>50	>50	50	>50	25	>50
5	>50	>50	>50	>50	50	50	>50	>50
6	>50	>50	>50	3.12	50	12.5	6.25	6.25
7	50	50	>50	3.12	3.12	>50	3.12	6.25
8	50	25	50	6.25	25	>50	6.2.5	6.25
9	25	25	50	6.25	25	>50	6.25	25
10	25	>50	>50	12.5	25	>50	3.12	25
11	25	>50	>50	6.25	25	12.5	3.12.	12.5
12	50	>50	>50	25	12.5	12.5	50	25
13	50	>50	>50	25	6.25	50	>50	25
14	50	>50	>50	>50	>50	50	50	50
15	50	50	25	>50	6.25	50	50	25
16	50	50	25	6.25	6.25	12.5	3.12	25
17	50	50	25	6.25	6.25	12.5	3.12.	25
Gentamycin (Antibacterial) standard	0.18	25	6.25	0.18	-	-	-	-
Fluconazole (Antifungal) standard	-	-	-	-	0.5	1.0	1.0	2.0

EC = *Escherichia coli,* PA =*Pseudomonas aeruginosa,* SA = *Staphylococcus aureus,* KP = *Klebsiella pneumoniae.* CA=*Candida albicans*, CN=*Cryptococcus neoformans,* TM =*Trichophyton mentagrophytes,* AF=*Aspergillus fumigatus*.

Experimental Section

The melting points were obtained in open capillaries in sulfuric acid bath and are uncorrected. IR spectra were recorded in KBr on a Perkin Elmer RX1 spectrophotometer and ^{1}H NMR on Bruker Avance 400 spectrometer. $CDCl_3$/DMSO-d_6 were used as solvent and TMS as internal reference. Chemical shifts are expressed in δ (ppm). Mass spectra were recorded on Shimadzu GC-MS Q P2010 instrument. Elemental analysis data were obtained on Carlo Erba

1108 analyser. Homogeneity of the compounds were checked by TLC silica gel G plates and spots were located by exposure to iodine vapors.

3-[4′-(4″-Nitrobenzyloxy)-benzoylhydrazono]-5-bromolindolin-2-one, 3

A mixture of 4-(4-nitrobenzyloxy)-benzoylhydrazine **2** (0.01 mol) and 5-bromoindolin-2,3-dione (0.01 mol) in ethanol (50 mL) containing 2-3 drops of glacial acetic acid was refluxed for 1 hr and left overnight at RT. The separated solid was filtered and washed with methanol. Yield 70%, m.p. 278°C; IR (cm-1): 3474, 3178 (NH), 1695(CO), 1530, 1345 (NO_2), 1254 (-CH_2O-), 563 (C-Br); MS (m/z): 494 ($M^{+\cdot}$), 496 ($M^{+\cdot}$+2). (Found: C, 53.28; H, 3.00; N, 11.26.Calcd. for $C_{22}H_{15}BrN_4O_5$: C, 53.35; H, 3.05; N, 11.31%).

Compounds **4-8** were synthesised by similar methods using 1–Methyl, ethyl, propyl, benzyl and acetyl-5-bromoindolin-2, 3-diones.

1-Methyl-3-[4′-(4″-nitrobenzyloxy)-benzoylhydrazono]-5-bromoindolin-2-one, 4

Yield 79%; m.p.266 (d)°C; ^{1}H NMR (DMSO-d_6) δppm: 2.60 (3H, s, Me), 5.24 (2H, s -CH_2O-), 6.93-8.02 (11H, m, Ar-H), 13.98 (1H, s, CONH), MS m/z: 508 ($M^{+\cdot}$), 510 ($M^{+\cdot}$+2). (Found: C, 54.16; H, 3.23; N, 11.16. Calcd. for $C_{23}H_{17}BrN_4O_5$: C, 54.24; H, 3.36; N, 11.00%).

1-Ethyl-3-[4′-(4″-nitrobenzyloxy)-benzoylhydrazono]-5-bromoindolin-2-one, 5

Yield 74 %; m.p 204-06°C; ^{1}H NMR (DMSO-d_6) δppm: 1.14-1.19 (3H, t, NCH_2CH_3), 2.79-3.00 (2H, q, NCH_2CH_3), 5.25 (2H, s, -CH_2O-), 6.86-8.12 (11H, m, Ar-H), 13.98 (1H, s, CONH), MS m/z: 522 ($M^{+\cdot}$), 524 ($M^{+\cdot}$+2). (Found: C, 54.97; H, 3.57; N, 10.67. Calcd. for $C_{24}H_{19}BrN_4O_5$: C, 55.08; H, 3.66; N, 10.71%).

1-Propyl-3-[4′-(4″-nitrobenzyloxy)-benzoylhydrazono]-5-bromoindolin-2-one, 6

Yield 67 %; m.p 202-04°C; ^{1}H NMR (DMSO-d_6) δppm: 0.99-1.11 (3H, t, $NCH_2CH_2\underline{CH_3}$), 1.34-1.49 (2H, q, $NCH_2\underline{CH_2}CH_3$), 2.78-3.00 (2H, q, $N\underline{CH_2}CH_2CH_3$), 5.25 (2H, s, -$CH_2O$-), 6.86-8.12 (11H, m, Ar-H), 13.98 (1H, s, CONH), MS m/z: 522 ($M^{+\cdot}$), 524 ($M^{+\cdot}$+2). (Found: C, 54.97; H, 3.57; N, 10.67. Calcd. for $C_{24}H_{19}BrN_4O_5$: C, 55.08; H, 3.66; N, 10.71%).

1-Benzyl-3-[4′-(4″-nitrobenzyloxy)-benzoylhydrazono]-5-bromoindolin-2-one, 7

Yield 67 %; m.p 198-200°C; ^{1}H NMR (DMSO-d_6) δppm: 4.76(2H, s, CH_2), 5.25 (2H, s, -CH_2O-), 6.90-8.11 (16H, m, Ar-H), 13.96 (1H, s, CONH), MS m/z: 584 ($M^{+\cdot}$), 586 ($M^{+\cdot}$+2). (Found: C, 59.47; H, 3.60; N, 9.63. Calcd. for $C_{29}H_{21}BrN_4O_5$: C, 59.50; H, 3.62; N, 9.57%).

1-Acetyl-3-[4′-(4″-nitrobenzyloxy)-benzoylhydrazono]-5-bromoindolin-2-one, 8

Yield 66 %; m.p.230 (d); ^{1}H NMR (DMSO-d_6) δppm: 2.45 (3H, s, COMe), 5.25 (2H, s, -CH_2O-), 6.91-8.02 (10H, m, Ar-H), 13.89 (1H, s, CONH), MS m/z: 536 ($M^{+\cdot}$), 538 ($M^{+\cdot}$+2). (Found: C,

53.52; H, 3.23; N, 10.37. Calcd. for $C_{24}H_{17}BrN_4O_6$: C, 53.65; H, 3.19; N, 10.43%);

1-Morpholinomethyl-3-[4′-(4″-nitrobenzyloxy)-benzoylhydrazono]-5-bromoindolin -2-one, 9

To a suspension of **3** (0.005 mol) in DMF, formaldehyde (0.5mL, 37% aq. solution) and morpholine (0.005 mol) were added with vigorous stirring, and the reaction mixture was warmed for 2 min. on a water bath and left overnight at RT. The solid product thus obtained was filtered, washed with methanol, dried and purified by recrystallization from chloroform: pet.-ether (60-80°C) (1:1). Yield 74 %, m.p.212-14^{0}C; IR (cm-^{1}): 3475 (NH), 2824 (>N-CH_2-N<), 1683 (CO), 1529, 1349 (NO_2), 1253 (-CH_2O-) 1157 (-CH_2-O-CH_2-), 570 (C-Br);; ^{1}H NMR ($CDCl_3$) δppm: 2.60-2.67 (4H, t, -CH_2-N-CH_2-), 3.65-3.72 (4H, t, -CH_2-O-CH_2-), 4.52 (2H, s, >N-CH_2-N<), 5.25 (2H, s, -CH_2O-), 6.77-8.12 (11H, m, Ar-H), 13.77 (1H, s, CONH); MS m/z: 593 ($M^{+\cdot}$), 595 ($M^{+\cdot}$+2). (Found: C, 54.44; H, 3.94; N, 11.67. Calcd. for $C_{27}H_{24}BrN_5O_6$: C, 54.56; H, 4.07; N, 11.78 %).

Mannich bases **10-17** were synthesised by similar method and using different secondary amines.

1-Piperidinomethyl-3-[4′-(4″-nitrobenzyloxy)-benzoylhydrazono]-5-bromoindolin -2-one, 10

Yield 68 %, m.p.218^{0}C; IR (cm-^{1}): 3445 (NH), 2850 (>N-CH_2-N<), 1686 (CO), 1521, 1349 (NO_2), 1250 (-CH_2O-), 570 (C-Br); ^{1}H NMR ($CDCl_3$): 1.42-1.54 (6H, m,-$CH_2CH_2CH_2$-), 2.52-2.61 (4H, t, -CH_2-N-CH_2-), 4.57 (2H, s, >N-CH_2-N<), 5.25 (2H, s,-CH_2O-), 7.27-8.01 (11H, m, Ar-H), 13.87 (1H, s, CONH); MS m/z: 591 ($M^{+\cdot}$), 593 ($M^{+\cdot}$+2). (Found: C, 56.62; H, 4.46; N, 11.78. Calcd. for $C_{28}H_{26}BrN_5O_5$: C, 56.77; H, 4.42; N, 11.82 %).

1-Pyrrolidinomethyl-3-[4′-(4″-nitrobenzyloxy)-benzoylhydrazono]-5-bromoindolin-2-one, 11

Yield 68 %, m.p.178-80 ^{0}C; IR (cm-^{1}): 3438 (NH), 2840 (>N-CH_2-N<), 1687 (CO), 1522, 1345 (NO_2), 1251 (-CH_2O-), 569 (C-Br);^{1}H NMR ($CDCl_3$): 1.35-1.45 (4H, m, -CH_2CH_2-), 2.33-2.41 (4H, t, -CH_2-N-CH_2-), 4.54 (2H, s, >N-CH_2-N<), 5.25 (2H, s, -CH_2O-), 7.05-8.15 (11H, m, Ar-H), 13.83 (1H, s, CONH); MS m/z: 577 ($M^{+\cdot}$), 579 ($M^{+\cdot}$+2). (Found: C, 55.00; H, 4.26; N, 12.07. Calcd. for $C_{27}H_{30}BrN_5O_5$: C, 55.07; H, 4.18; N, 12.11 %).

1-N-Methylpiperazinomethyl-3-[4′-(4″-nitrobenzyloxy)-benzoylhydrazono]-5-bromoindo -

lin-2-one, 12

Yield 69 %, m.p.220 ^{0}C; ^{1}H NMR ($CDCl_3$): 2.10 (3H, s, N-Me), 2.33-2.39 (4H, t, -CH_2-N-CH_2-), 2.53-2.65 (4H, t, -CH_2-N(Me)-CH_2-), 4.59 (2H, s, >N-CH_2-N<), 5.25 (2H, s,-CH_2O-),

6.84-7.88 (11H, m, Ar-H), 14.01 (1H, s, CONH); MS m/z: 606 ($M^{+\cdot}$), 608 ($M^{+\cdot}$+2). (Found: C, 55.30; H, 4.39; N, 13.77. Calcd. for $C_{28}H_{27}BrN_6O_5$: C, 55.36; H, 4.48; N, 13.83 %).

1-N-Ethylpiperazinomethyl -3-[4′- (4″-nitrobenzyloxy)- benzoylhydrazono] -5-bromoindolin-2-one, 13

Yield 69 %, m.p.210 ^{0}C; ^{1}H NMR ($CDCl_3$): 1.87-1.92 (3H, t, Me), 2.00-2.09 (2H, q, -CH_2Me), 2.33-2.39 (4H, t, -CH_2-N-CH_2-), 2.59-2.67 (4H, t, -CH_2-N(Et)-CH_2-), 4.50 (2H, s, >N-CH_2-N<), 5.25 (2H, s, -CH_2O-), 6.68-7.99 (11H, m, Ar-H), 13.89 (1H, s, CONH); MS m/z: 620 ($M^{+\cdot}$), 622 ($M^{+\cdot}$+2). (Found: C, 55.98; H, 4.68; N, 13.47. Calcd. for $C_{29}H_{29}BrN_6O_5$: C, 56.05; H, 4.70; N, 13.52 %).

1-N-Phenylpiperazinomethyl-3-[4′-(4″-nitrobenzyloxy)-benzoylhydrazono]-5-bromoindolin

-2-one, 14

Yield 60 %, m.p.220 (d); IR (cm-^{1}): 3450 (NH), 2834 (>N-CH_2-N<), 1682 (CO), 1529, 1346 (NO_2), 1244(-CH_2O-), 569 (C-Br); ^{1}H NMR ($CDCl_3$): 2.33-2.41(4H, t, -CH_2-N-CH_2-),2.62-2.69 (4H, t, -CH_2-N(Ph)-CH_2-), 4.55 (2H, s, >N-CH_2-N<), 5.29 (2H, s, -CH_2O-), 7.34-8.28 (16H, m, Ar-H), 13.90 (1H, s, CONH); MS m/z: 668 ($M^{+\cdot}$), 670 ($M^{+\cdot}$+2). (Found: C, 59.22; H, 4.26; N, 12.47. Calcd. for $C_{33}H_{29}BrN_6O_5$: C, 59.20; H, 4.37; N, 12.55 %).

1-N-Benzylpiperazinomethyl-3-[4′-(4″-nitrobenzyloxy)-benzoylhydrazono]-5-bromopindolin-2-one, 15

Yield 55 %, m.p.162 (d) ; ^{1}H NMR ($CDCl_3$): 2.33-2.41 (4H, t, -CH_2-N-CH_2-), 2.66-2.71 (4H, t, -CH_2-N(CH_2Ph)-CH_2-), 4.46 (2H, s, CH_2Ph), 4.56 (2H, s, >N-CH_2-N<), 5.25 (2H, s, -CH_2O-), 7.14-8.26 (16H, m, Ar-H), 13.93 (1H, s, CONH); MS m/z: 682 ($M^{+\cdot}$), 684 ($M^{+\cdot}$+2). (Found: C, 59.72; H, 4.46; N, 12.13. Calcd. for $C_{34}H_{31}BrN_6O_5$: C, 59.74; H, 4.57; N, 12.29 %).

1-Dimethylaminomethyl-3-[4′-(4″-nitrobenzyloxy)-benzoylhydrazono]-5-bromoindolin-2-one, 16

Yield 48 %, m.p.228-30 ^{0}C; IR (cm-^{1}): 3427 (NH), 2831 (>N-CH_2-N<), 1703 (CO), 1523, 1348 (NO_2), 1255 (-CH_2O-), 560 (C-Br); ^{1}H NMR ($CDCl_3$): 2.30 (6H, s, Me), 4.31 (2H, s, >N-CH_2-N<), 5.26 (2H, s, -CH_2O-), 7.07-8.26 (11H, m, Ar-H), 13.98 (1H, s, CONH); MS m/z: 551 ($M^{+\cdot}$), 553 ($M^{+\cdot}$+2). (Found: C, 54.31; H, 3.94; N, 12.50. Calcd. for $C_{25}H_{22}BrN_5O_5$: C, 54.36; H, 4.01; N, 12.68 %).

1-Diethylaminomethyl-3-[4′-(4″-nitrobenzyloxy)-benzoylhydrazono]-5-bromoindolin-2-one, 17

Yield 48 %, m.p.232 ^{0}C; IR (cm-^{1}): 3413 (NH), 2835 (>N-CH_2-N<), 1697 (CO), 1523, 1345

(NO_2), 1258 (-CH_2O-), 568 (C-Br); ^{1}H NMR ($CDCl_3$): 1.81-2.09 (6H, t, Me), 2.21-2.28 (4H, q, CH_2Me), 4.45 (2H, s, >N-CH_2-N<), 5.25 (2H, s, -CH_2O-), 7.23-8.29 (10H, m, Ar-H), 13.98 (1H, s, CONH); MS m/z: 579 ($M^{+\cdot}$), 581($M^{+\cdot}$+2). (Found: C, 55.80; H, 4.46; N, 12.00. Calcd. for $C_{27}H_{26}BrN_5O_5$: C, 55.87; H, 4.52; N, 12.07 %).

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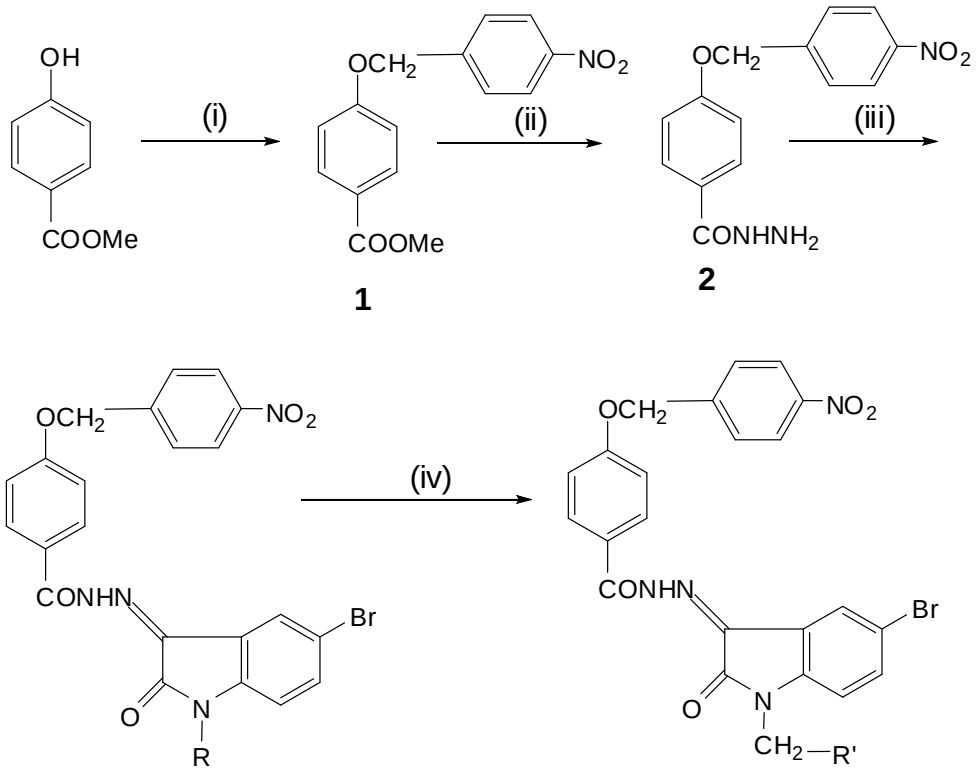

1 **2** **3-8** **9-17**

(i) 4-Nitrobenzyl bromide
K_2CO_3(anhyd); Me_2CO
(ii) $N_2H_4.H_2O$; 1-Propanol
(iii) 5-Bromoindolin-2,3-diones,
gl. AcOH; EtOH
(iv) Amines,CH_2O; DMF

R = H, Me, Et, n-Pr, Bz, $COCH_3$
R′ = morpholino, piperidino, pyrrolidino
N-methylpiperazino, N-ethylpiperazino,
N-phenylpiperazino, N-benzylpiperazino,
dimethylamino,diethylamino

Scheme I