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NOTE

Synthesis and Characterization of Biologically Active 1-(substituted aminomethyl)-3-(3′-bromo-4′-methoxy-benzoylhydrazono)indolin-2-ones

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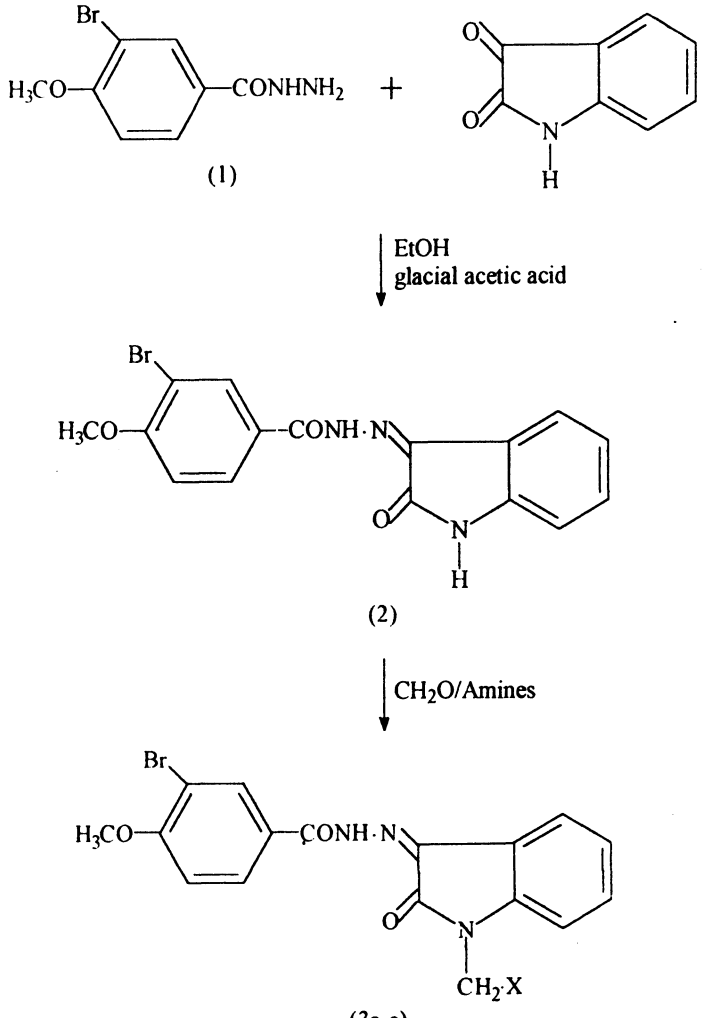
3-Bromo-4-methoxybenzoyl hydrazine (**1**) was condensed with indole-2,3-dione in ethanol to yield 3-(3′-bromo-4′-methoxybenzoylhydrazono) indolin-2-one (**2**) which on aminomethylation with formaldehyde and different amines furnished 1-(substituted aminomethyl)-3-(3′-bromo-4′-methoxybenzoylhydrazono) indolin-2-ones (**3a–e**). The structures of the newly synthesized compounds have been established by analytical and spectral methods. These compounds have shown promising biological activity.

Key Words: Synthesis, 1-(substituted aminomethyl)-3-(3′-bromo-4′-methoxybenzoylhydrazono)indolin-2-ones, Biological activity.

Mannich bases[1] having indolin-2-one moiety are found to be good antifungal agents. Isatin and its derivatives are a class of biologically active compounds which have been associated with antibacterial[2], amoebicidal[3], cysticidal[4] and CNS depressant activity. In view of these observations it was contemplated to synthesize Mannich bases containing indolin-2-one nucleus with the objective of screening them for their antibacterial and antifungal activity.

The compound 3-bromo-4-methoxybenzoyl hydrazine (**1**) required for the preparation of the target compounds, was synthesized from methyl ester of 4-methoxybenzoic acid by bromination and subsequent hydrazinolysis. The hydrazide (**1**) on condensation with indole-2,3-dione in ethanol containing catalytic amount of glacial acetic acid gave 3-(3′-bromo-4′-methoxybenzoyl-hydrazono)indolin-2-one (**2**). The compound (**2**) was reacted with formaldehyde and different amines to afford 1-(substituted aminomethyl)-3-(3′-bromo-4′-methoxybenzoylhydrazono) indolin-2-ones (**3a–e**) (**Scheme-1**).

Screening for biological activity: The compounds (**3a–e**) synthesized were screened *in vitro* for their antibacterial activity against *Staphylococcus aureus, Escherichia coli, Bacillus subtilis* and *Salmonella typhosa* by the ditch-plate technique[7] and for antifungal activity against *Aspergillus niger, Candida albicans, Cryptococcus neoformans* and *Thielaviopsis paradoxa* by paper disc diffusion method using concentrations of 2 and 5 mg/mL. Nutrient agar was employed as culture media and DMF was used as solvent control for both antibacterial and antifungal activity. The results of such studies are given in Table-2.



Scheme-1

TABLE-1
CHARACTERIZATION DATA OF 1-(SUBSTITUTED AMINOMETHYL-3-(3′-BROMO-4′-METHOXYBENZOYLHYDRAZONO)INDOLIN-2-ONES (**3a–e**)

Compd.	X	m.p. (°C)	Yield (%)	m.f.	Analysis (%) N	
					Required	Found
3a	Anilino	210	72	$C_{23}H_{19}N_4O_3Br$	11.69	11.75
3b	4-Methoxyanilino	190	70	$C_{24}H_{21}N_4O_4Br$	11.00	11.04
3c	N-Methylanilino	280	75	$C_{24}H_{21}N_4O_3Br$	11.36	11.40
3d	Morpholino	275	75	$C_{21}H_{21}N_4O_4Br$	11.84	11.87
3e	Piperidino	180	68	$C_{22}H_{23}N_4O_3Br$	11.89	11.90

TABLE-2
BIOLOGICAL ACTIVITY DATA OF COMPOUNDS

		Compounds				
		3a	**3b**	**3c**	**3d**	**3e**
Antibacterial activity						
S. aureus	2 mg/mL	–	–	–	+	+
	5 mg/mL	+	+	–	++	++
E. coli	2 mg/mL	–	+	–	–	–
	5 mg/mL	+	+	+	+	+
B. subtilis	2 mg/mL	+	–	–	–	+
	5 mg/mL	++	–	–	+	+
S. typhosa	2 mg/mL	–	–	+	–	–
	5 mg/mL	–	–	+	+	+
Inhibition zone diameter in mm:		(–) < 11 mm		(+) 11-14 mm	(++)	15-18 mm
Antiftuigal activity						
A. niger	2 mg/mL	–	–	+	–	+
	5 mg/mL	+	+	+	+	+
C. albicans	2 mg/mL	–	–	–	+	+
	5 mg/mL	+	–	–	+	++
C. neoformans	2 mg/mL	–	–	–	–	+
	5 mg/mL	+	–	+	+	+
T. paradoxa	2 mg/mL	–	–	+	–	+
	5 mg/mL	+	+	+	+	+

EXPERIMENTAL

All the melting points were taken in open capillaries and are uncorrected. IR spectra (KBr in cm^{-1}) were recorded on Shimadzu 8201 PC FTIR spectrophotometer. ^1H NMR spectra were recorded on a Varian 300 MHz NMR spectrophotometer using DMSO-d_6 as solvent and TMS as internal standard (chemical shifts in δ ppm). The purity of the compounds was monitored by thin layer chromatography.

3-(3′-Bromo-4′-methoxybenzoylhydrazono) indolin-2-one (2)

To a solution of 3-bromo-4-methoxybenzoyl hydrazine **1** (3.67 g, 0.015 mole) in 50 mL ethanol, indole-2,3-dione (2.21 g, 0.015 mol) was added. A catalytic amount of glacial acetic acid was added and the mixture was refluxed for 0.5 h. The reaction mixture was then allowed to cool to room temperature. The separated yellow-coloured solid was filtered, washed with methanol and crystallized from N,N-dimethylformamide (3.74 g, 70%), m.p. 291°C. (Found: C, 51.42; H, 3.26; N, 11.27. $C_6H_{12}N_3O_3Br$ requires: C, 51.34; H, 3.21; N, 11.23%); IR (cm^{-1}) (KBr): 3160 ν(N—H), 3000 ν(C—H, aromatic), 2800 ν(C—H), 1680 ν(C=O), 1620 ν(C=N), 1600, 1540, 1500, 1470 ν(C=C, aromatic), 1270 ν(C—O), 1150–810 ν(C—C), 1010 ν(C—N), 570 ν(C—Br).

1-(Substituted aminomethyl)-3-(3′-bromo-4′-methoxybenzoyl-hydrazono)indolin-2-ones (3a–e)

3-(3′-Bromo-4′-methoxybenzoylhydrazono)indolin-2-one **2** (1.50 g, 0.004 mole) was dissolved in 10 mL N,N-dimethylformamide. A slight excess of formaldehyde (0.125 cm, 0.0045 mol) and appropriate amine (0.004 mol) was added with vigorous stirring. The reaction mixture was refluxed for 0.5 h and allowed to cool to room temperature. The crystalline product obtained was filtered, washed with water and recrystallized from petroleum ether (60–80°C). **3e:** IR (cm^{-1}) (KBr) 3468 ν(N—H), 3161 ν(C—H, aromatic), 2939 ν(C—H), 1681 ν(C=O), 1619 ν(C=N), 1597, 1535, 1493, 1466 ν(C=C, aromatic), 1270 ν(C—O), 1156–817 ν(C—C), 1011 ν(C—N), 569 ν(C—Br1); NMR (DMSO-d_6) δ 1.4–1.6 (m, 6H, —CH_2·CH_2·CH_2 of piperidine), 2.8 (t, 4H, —CH_2·N—CH_2), 3.4 (s, 2H, —N—CH_2·N), 3.9 (s, 3H, —OCH_3), 7.0–8.0 (m, 7H, ArH), 13.9 (s, 1H, —CO—NH·N).

The characterization data of compounds **(3a–e)** have been given in Table-1.

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