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Syntheses of Biologically Active 1-(Substituted aminomethyl)-3-(2'-naphthoxyacetylhydrazono)indolin-2-ones

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2-Naphthoxyacetic acid hydrazide (**1**) was condensed with indole-2,3-dione in ethanol to yield 3-(2'-naphthoxyacetylhydrazono)indolin-2-one (**2**) which on aminomethylation with formaldehyde and different amines furnished 1-(substituted aminomethyl)-3-(2'-naphthoxyacetyl hydrazono)indolin-2-ones. 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, Indolin-2-ones, Antibacterial and Antifungal activity.

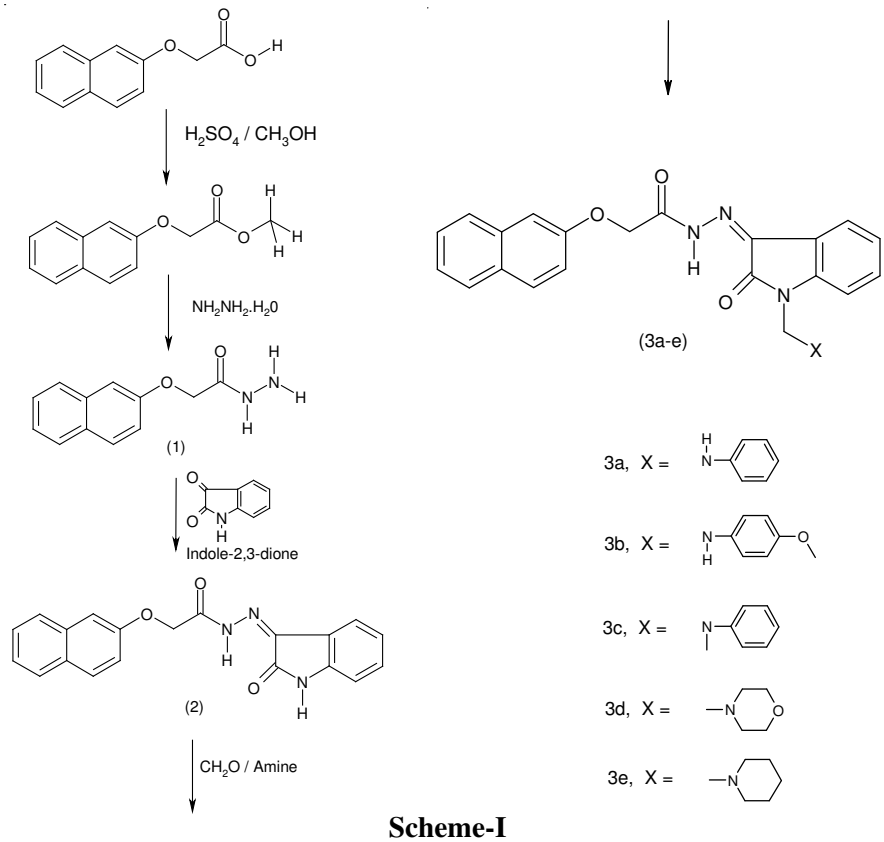
INTRODUCTION

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] and cysticidal[4] and CNS depressant[5] 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 activity.

The compound 2-naphthoxyacetic acid hydrazide[6] (**1**) was synthesized from methyl ester of 2-naphthoxyacetic acid and subsequent hydrazinolysis. The hydrazide (**1**) on condensation with indole-2,3-dione in ethanol containing catalytic amount of glacial acetic acid gave 3-(2'-naphthoxyacetylhydrazono)indolin-2-one (**2**). The compound **2** was reacted with formaldehyde and different amines to afford 1-(substituted aminomethyl)-3-(2'-naphthoxyacetyl hydrazono)indolin-2-ones (**3a-e**) (**Scheme-I**).

EXPERIMENTAL

All the melting points were taken in open capillaries and are uncorrected. IR spectra (KBr, 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.



Scheme-I

3-(2'-Naphthoxyacetyl hydrazono)indolin-2-one (2): To a solution of 2-naphthoxyacetic acid hydrazide **1** (2.16 g, 0.01 mol) in 50 mL:ethanol, indole-2,3-dione (1.47 g, 0.01 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 recrystallized from N,N-dimethyl formamide, m.p. > 300 °C, yield 75 % [found (%): C, 69.58; H, 4.39; N, 12.19. $C_{20}H_{15}N_3O_3$ requires (%) C, 69.57; H, 4.35; N, 12.17]; IR (KBr, ν_{max}, cm^{-1}): 3257 (N-H *str.*), 3056 (C-H, aromatic), 2885 (C-H *str.*), 1716 (C=O *str.*), 1683 (C=N *str.*), 1600, 1570, 1508, 1464, 1430, 1389 (C=C, aromatic), 1180 (C-O-C *str.*), 1120-830 (C-C *str.*), 1040 (C-N *str.*). ^{1}H NMR (DMSO-d_6) δ: 4.15 (s, 2H, -OCH_2), 5.5 (s, 1H, -NH), 7.90-8.04 (m, 11H, ArH), 10.8 (s, 1H, -NH-N).

1-(Substituted aminomethyl)-3-(2'-naphthoxyacetyl hydrazono)indolin-2-ones (3a-e): 3-(2'-Naphthoxyacetyl hydrazono)indolin-2-one 2 (1.50 g, 0.004 mol) was dissolved in 10 mL of N,N-dimethyl formamide. A slight excess of formaldehyde (0.125 cm^3, 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). The characterization and spectral data of compounds **3a-e** have been given in Table-1.

TABLE-1
CHARACTERIZATION DATA OF 1-(SUBSTITUTED AMINOMETHYL)-3-(2'-NAPHTHOXY ACETYL HYDRAZONO)INDOLIN-2-ONES (**3a-e**)

Compd.	X (m.f.)	m.p., ºC (Yield, %)	N (%) Req. (Found)	IR (cm^{-1})	^1H NMR
3a	Anilino ($C_{27}H_{22}N_4O_3$)	210 (72)	12.44 (12.48)	3325 (N-H *str.*), 1710 (C=O *str.*), 1675 (C=N *str.*), 1173 (C-O-C *str.*), 1051 (C-N *str.*).	4.4 (s, 2H, O·CH_2·C), 5.1 (s, 2H, N·CH_2·N), 7.2-8.3 (m, 16H, ArH), 11.0 (s, 1H, -CO·NH·N)
3b	4-Methoxyanilino ($C_{28}H_{24}N_4O_4$)	190 (70)	11.66 (11.68)	3345 (N-H *str.*), 1715 (C=O *str.*), 1675 (C=N *str.*), 1176 (C-O-C *str.*), 1052 (C-N *str.*).	3.8 (s, 3H, O-CH_3) 4.5 (s, 2H, O·CH_2·C), 5.2 (s, 2H, N·CH_2·N), 7.2-8.3 (m, 15H, ArH), 10.9 (s, 1H, -CO·NH·N)
3c	N-Methylanilino ($C_{28}H_{24}N_4O_3$)	230 (75)	12.06 (12.09)	3350 (N-H *str.*), 1720 (C=O *str.*), 1680 (C=N *str.*), 1184 (C-O-C *str.*), 1045 (C-N *str.*).	2.45 (s, 3H N-CH_3), 4.5 (s, 2H, O·CH_2·C), 5.1 (s, 2H, N·CH_2·N), 7.2-8.3 (m, 16 H, ArH), 11.0 (s, 1H, -CO·NH·N)
3d	Morpholino ($C_{25}H_{24}N_4O_4$)	165 (75)	12.60 (12.64)	3315 (N-H *str.*), 1717 (C=O *str.*), 1684 (C=N *str.*), 1179 (C-O-C *str.*), 1055 (C-N *str.*).	2.7 (t, 4H, CH_2·N·CH_2), 3.65 (t, 4H, CH_2·O·CH_2), 4.5 (s, 2H, O·CH_2·C), - 5.1 (s, 2H, N·CH_2·N), 7.2-8.1 (m, 11H, ArH), 11.2 (s, 1H, -CO·NH·N)
3e	Piperidino ($C_{26}H_{26}N_4O_3$)	180 (68)	12.66 (12.69)	3320 (N-H *str.*), 1705 (C=O *str.*), 1674 (C=N *str.*), 1180 (C-O-C *str.*), 1050 (C-N *str.*).	1.4-1.6 (m, 6H, -CH_2· CH_2·CH_2 of piperidine), 2.8 (t, 4H, -CH_2·N-CH_2), 4.5 (s, 2H, O·CH_2·C), - 5.2 (s, 2H, N·CH_2·N), 7.1-8.0 (m, 11H, ArH), 11.1 (s, 1H, -CO·NH·N)

Biological activity

Antibacterial activity: All the newly synthesized quinazolin-4-ones (**3a-e**) were screened *in vitro* for their antibacterial activity against *Staphylococcus aureus, Escherichia coli, Bacillus subtilis* and *Salmonella typhosa* by the ditch-plate technique[7] using concentrations of 2 and 5 mg/mL. Nutrient agar was employed as culture media and DMF was used as solvent control for antibacterial activity.

The compound **3a** and **3d** showed moderate activity against *E. coli* and *S. aureus*. The compound **3b** exhibited high activity against *E. coli* and moderate activity against *S. aureus*. The compounds **3c** and **3e** possess weak activity against both *E. coli* and *S. aureus*.

Antifungal acitivity: The compounds **3a-e** synthesized were screened for their antifungal activity against *Aspergillus niger, Candida albicans, Cryptococcus neoformans* and *Thielaviopsis paradoxa* by paper-disc diffusion method[8] at concentrations of 2 and 5 mg/mL. Nutrient agar was employed as culture media and DMF was used as solvent control for antifungal activity.

The compounds **3a**, **3d** and **3e** showed marked activity against *Aspergillus niger, Candida albicans* and *Cryptococcus neoformans*. The compound **3b** and **3c** showed moderate activity against *Aspergillus niger, Cryptococcus neoformans* and weak activity against *Candida albicans* and *Thielaviopsis* p.

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