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Synthesis of some novel 1-aminomethyl-3-benzoylhydrazono-2-indolinones as potential antiinflammatory agents†

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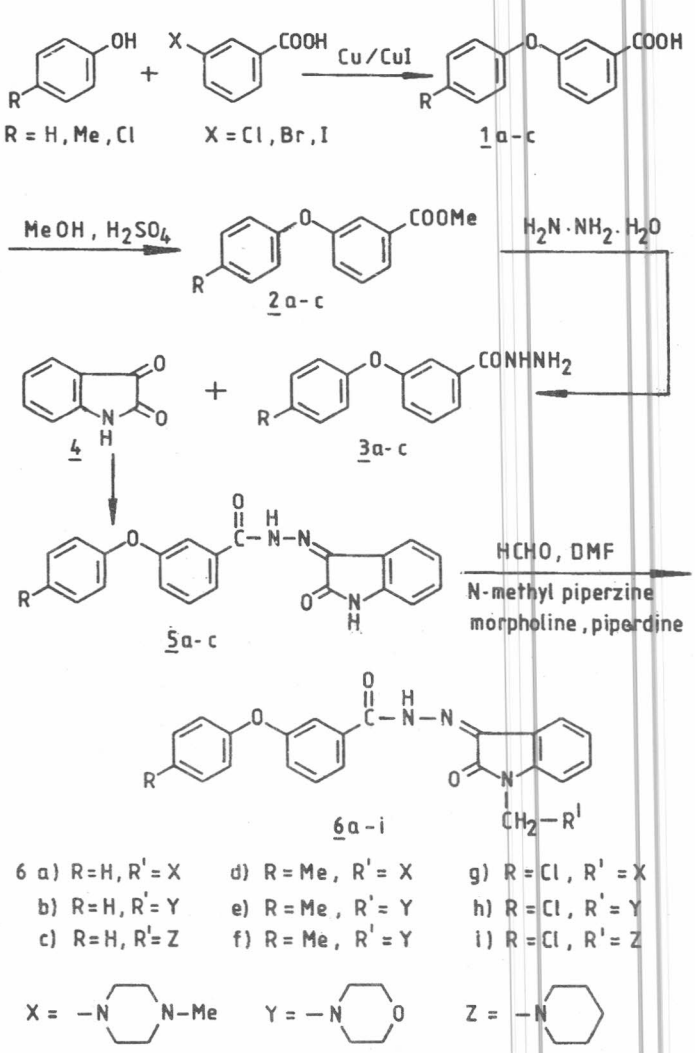
Acid-catalysed condensation of hydrazides **3**, obtained from substituted phenoxybenzoic acids **1** with indolin-2,3-dione **4**, results into hydrazono-2-indolinones **5**. Compounds **5** when subjected to Mannich reaction with different cyclic secondary amines yield 1-aminomethyl-3-benzoylhydrazono-2-indolinones **6** (Mannich bases). All these compounds (**6a-i**) exhibit significant antiinflammatory activity.

Various isatin derivatives have been reported to possess promising biological activities[1]. Moreover, some substituted diphenyl ethers[2,3] and Mannich bases of isatins are well known antiinflammatory agents[4]. In view of the above observatons a number of Mannich bases, incorporating substituted *m*-phenoxybenzoic acid residue, have been synthesized and their analgesic and anti-inflammatory activities studied in the present investigation.

We are reporting here for the first time the synthesis of 1-piperazino/morpholino/piperidino-methyl-3-(3′-phenoxybenzoylhydrazono)- 2-indolinones **6a-i** and their biological activity. The required carboxy substituted diphenyl ethers **1a-c** were prepared by the condensation of *m*-halobenzoic acid derivatives with substituted phenols by a known dry Ullmann-Goldberg method[5]. Esterification followed by hydrozinolysis of **1a-c** have resulted into the methyl esters **2a-c** and hydrazides **3a-c** respectively in good yields. Acid catalysed condensation of **3a-c** with isatin[6] **4** gave the compounds **5a-c**. The aminomethylation[7] of **5a-c** with cyclic secondary amines such as N-methylpiperazine, morpholine and piperidine led to the target Mannich bases **6a-i**. Their structures were established by their IR, ^{1}H NMR, and mass spectral data and elemental analysis. These compounds (**6a-i**) were tested for their analgesic and antiinflammatory activities.



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Analgesic and antiinflammatory activities. Analgesic and antiinflammatory activities of the compounds **6a-i** were determined by Turner[8] writhing test[9] and rat-paw edema test[10]. The inhibition of edema was recorded on a plethysmometer (UGO BASILE make) and expressed as % inhibition. The results are given in **Table I**. Compounds **6a-i** showed 31-33% inhibition in rats while aspirin and phenylbutazone at the same dose (100 mg/kg, P.O.) produced 17% and 39% inhibition of 1% carrageenan-induced inflammation, respectively. The per cent protection for each compound was calculated using the following formula:

$$\% \text{ Protection} = 100 - \frac{\text{No.of writhes in test}}{\text{No. of writhes in control}} \times 100$$

All the new compounds (**6a-i**) exhibited significant antiinflammatory activity comparable with that of phenylbutazone. However, they were found to possess weak analgesic action with reference to aspirin.

Table I—Evaluation of analgesic and antiinflammatory activities of compounds **6a-i**

Compd	Analgesic action (% protection of pain)		Antiinflammatory action (% inhibition)
	Tail clip	Writhing	(Rat paw edema)
6a	15	12	32
6b	13	11	32
6c	13	12	31
6d	14	12	32
6e	15	11	31
6f	15	12	33
6g	19	16	31
6h	16	13	33
6i	16	12	31
Aspirin (100 mg/kg)	55	46	17
Phenylbutazone (100 mg/kg)	30	26	39

The results were mean of two observations. Values of 20% inhibition or greater were significant ($P > 0.01$).

Experimental Section

General. Melting points were determined in open glas capillaries on a Metler FP5 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian (80 MHz) and Gemini (200 MHz) spectrometers (chemical shifts are recorded in δ, ppm); internal standard was TMS. Mass spectra were taken on a VG micromass 7070H or a Finnigan Met 1020B mass spectrometer.

3-Carboxydiphenyl ethers 1a-c. A mixture of 3-chlorobenzoic acid (4 mmoles), phenol (8 mmoles), K_2CO_3 anhydrous (8 mmoles), pyridine (2 mmoles), Cu powder (0.2 g) and cuprous iodide (0.2 g) in 25 mL water was kept at reflux for 2 hr. The mixture was then basified with Na_2CO_3 solution and extracted with Et_2O. The aqueous solution was acidified with HCl, and the precipitated solid filtered off, dissolved in NaOH, the basic solution filtered and acidified with acetic acid.

1a: Yield 55%, mp 145.8°C (lit.[11,12] mp 145°C); ^{1}H NMR ($CDCl_3$: δ 6.75-7.95 (m, 9H, Ar–H).

1b: Yield 52%, mp 152.6°C; ^{1}H NMR ($CDCl_3$: δ 6.68-7.80 (m, 8H, Ar–H) and 2.31 (s, 3H, $-CH_3$); MS: m/z 228 [M^+]. Anal. Calcd for $C_{14}H_{12}O_3$: C, 73.68; H, 5.26. Found: C, 73.66; H, 5.20%.

1c: Yield 58%, mp 131°C; ^{1}H NMR ($CDCl_3$): δ 6.76-7.91 (m, 8H, Ar–H). MS: m/z 248 [M^+]. Anal. Calcd for $C_{13}H_9O_3Cl$: C, 62.90; H, 3.62. Found: C, 62.87; H, 3.60%.

3-(3′-Phenoxybenzoylhydrazono)-2-indolinones 5a-c. 3-Phenoxybenzoylhydrazine (5 mmoles) and isatin (5 mmoles) in 15 mL of ethanol containing 10 drops of gl. acetic acid was heated for 3 hr and left overnight at room temperature. The solid product thus obtained was washed repeatedly with methanol.

5a: Yield 78%, mp 280.8°C (dec.); MS: m/z 357 [M^+]. Anal. Calcd for $C_{21}H_{15}N_3O_3$: C, 71.98; H, 4.20; N, 11.76. Found: C, 71.98; H, 4.20; N, 11.76%.

5b: Yield 80%, mp 277°C; MS: m/z 371 [M^+]. Anal. Calcd for $C_{22}H_{17}N_3O_3$: C, 71.15; H, 4.58; N, 11.32. Found: C, 71.11; H, 4.55; N, 11.30%.

5c: Yield 85%, mp 265.2°C; MS: m/z 396 [M^+]. Anal. Calcd for $C_{21}H_{14}ClN_3O_3$: C, 64.89; H, 3.53; N, 10.60. Found: C, 64.85; H, 3.54; N, 10.55%.

1-Morpholinomethyl-(3′-phenoxybenzoylhydrazono)-2-indolinone 6a-i. 3-(3′-Phenoxybenzoylhydrazono)-2-indinone **5** (5 mmoles) was suspended in dimethylformamide (10 mL). To that solution slightly more than 5 mmoles of aq. formaldehyde and morpholine (5 mmole) were added with vigorous stirring. The reaction mixture was heated on a water-bath for 30 min and left

overnight at room temperature. The product thus obtained was recrystallized from chloroform-hexane.

6a: Yield 86%, mp 183.2°C; IR (KBr): 3440, 2850, 1680 cm^{-1}; -^{1}H NMR (DMSO-d_6): δ 3.80 (s, 3H, N–CH_3), 2.55 (t, 4H, –CH_2–N–CH_2), 2.60 (t, 4H, –CH_2–N–CH_2), 4.45 (s, 2H, N–CH_2–N), 6,70-7.81 (m, 13H, Ar–H) and 13.68 (s, 1H, –NHCO, D_2O exchangeable); MS: m/z 469 [M^+]. Anal. Calcd for $C_{27}H_{27}N_5O_3$: C, 69.08; H, 5.75; N, 14.92. Found: C, 69.00; H, 5.71; N, 14.90%.

6b: Yield 71.5%, mp 163.8°C; IR (KBr): 3435, 2850, 1675 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.72 (t, 4H, –CH_2–O–CH_2), 2.60 (t, 4H, –CH_2–N–CH_2), 4.70 (s, 2H, N–CH_2–N), 6.68-7.82 (m, 13H, Ar–H) and 13.74 (s, 1H, –NHCO, D_2O exchangeable); MS: m/z 456 [M^+]. Anal. Calcd for $C_{26}H_{24}N_4O_4$: C, 68.42; H, 5.26; N, 12.28. Found: C, 68.40; H, 5.26; N, 12.25%.

6c: Yield 88%, mp 139.9°C; IR (KBr): 3260, 2940, 1680 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.45 [m, 6H, $(CH_2)_3$], 2.55 (m, 4H, –CH_2–N–CH_2), 4.42 (s, 2H, –N–CH_2–N), 6.66-7.80 (m, 13H, Ar–H) and 13.90 (s, 1H, –NHCO, D_2O exchangeable_; MS: m/z 454 [M^+]. Anal. Calcd for $C_{27}H_{26}N_4O_3$: C, 71.36; H, 5.72; N, 12.33. Found: C, 71.33; H, 5.70; N, 12.00%.

6d: Yield 78%, mp 252.9°C; IR (KBr): 3410, 2840, 1675 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.78 (s, 3H, N–CH_3), 2.56 (t, 4H, –CH_2–N–CH_2), 2.61 (t, 4H, –CH_2–N–CH_2), 4.45 (s, 2H, N–CH_2–N), 2.32 (s, 3H, Ar–CH_3), 6.66-7.80 (m, 12H, Ar–H) and 13.90 (s, 1H, –NHCO, D_2O exchangeable); MS: m/z 483 [M^+]. Anal. Calcd for $C_{28}H_{29}N_5O_3$: C, 69.56; H, 6.00; N, 14.49. Found: C, 69.50; H, 6.01; N, 14.41%.

6e: Yield 76.9%, mp 170°C; IR (KBr): 2850, 1665 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.70 (t, 3H, –CH_2–O–CH_2), 2.62 (t, 4H, –CH_2–N–CH_2), 4.75 (s, 2H, N–CH_2–N), 2.35 (s, 3H, Ar–CH_3), 6.70-7.81 (m, 12H, Ar–H) and 13.95 (s, 1H, –NHCO, D_2O exchangeable); MS: m/z 470 [M^+]. Anal. Calcd for $C_{27}H_{26}N_4O_4$: C, 68.93; H, 5.53; N, 11.91. Found: C, 68.90; H, 5.51; N, 11.80%.

6f: Yield 85%, mp 148°C; IR (KBr): 3265, 2950, 1680 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.47 [s,6H, $(CH_2)_3$], 2.60 (t, 4H, –CH_2–N–CH_2), 4.45 (s, 2H, –N–CH_2–N), 2.32 (s, 3H, Ar–CH_3), 6.50-7.66 (m, 12H, Ar–H) and 13.90 (s, 1H, –NHCO, D_2O exchangeable; MS: m/z 468 [M^+]. Anal. Calcd for $C_{28}H_{28}N_4O_3$: C, 71.79; H, 5.98; N, 11.96. Found: C, 71.72; H, 5.95; N, 11.98%.

6g: Yield 85%, mp 166°C; IR (KBr): 3230, 2930, 1670 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.91 (s, 3H, N–CH_3), 2.81 (m, 4H, –CH_2–N–CH_2), 2.66 (t, 4H, –CH_2–N–CH_2), 4.45 (s, 2H, –N–CH_2–N), 2.32 (s, 3H, Ar–CH_3), 6.85-8.00 (m, 12H, Ar–H) and 14.01 (s, 1H, –NHCO, D_2O exchangeable); MS: m/z 503 [M^+]. Anal. Calcd for $C_{27}H_{26}ClN_5O_3$: C, 64.41; H, 5.16; N, 13.91. Found: C, 64.40; H, 5.13; N, 13.85%.

6h: Yield 77.6%, mp 186.2°C; IR (KBr): 3410, 2830, 1660 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.72 (t, 4H, –CH_2–O–CH_2), 2.61 (t, 4H, –CH_2–N–CH_2), 4.70 (s, 2H, –N–CH_2–N), 2.40 (s, 3H, Ar–CH_3), 6.72-7.83 (m, 12H, Ar–H) and 13.77 (s, 1H, –NHCO, D_2O exchangeable); MS: m/z 490 [M^+]. Anal. Calcd for $C_{26}H_{23}ClN_4O_4$: C, 63.67; H, 4.69; N, 11.42. Found: C, 63.65; H, 4.66; N, 11.42%.

6i: Yield 86.2%, mp 131.8°C; IR (KBr): 3260, 2950, 1675 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.45 [m, 6H, $(CH_2)_3$], 2.55 (t, 4H, –CH_2-N–CH_2, 4.45 (s, 2H, –N–CH_2–N), 6.69-7.63 (m, 12H, Ar–H) and 13.89 (s, 1H, –NHCO, D_2O exchangeable); MS: m/z 488 [M^+]. Anal. Calcd for $C_{27}H_{25}ClN_4O_3$: C, 66.39; H, 5.12; N, 11.47. Found: C, 66.35; H, 5.10; N, 11.41%.

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