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Synthesis of 1-aminomethyl-3-[4′-(4″-fluorobenzyloxy)-benzohydrazono]-5-ethylisatins as antifungal agents

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A new series of 1-aminomethyl-3-[4′-(4″-fluorobenzyloxy)-benzohydrazono]-5-ethylisatins (Mannich bases) has been synthesized and screened for their antifungal potential against human pathogenic fungi. The structures of the compounds have been established by means of elemental analysis and spectral data (IR and ^{1}H PMR).

Keywords: 5-Ethylisatin, Schiff base, Mannich base, antifungal activity.

Introduction

Isatins[1], their Schiff and Mannich bases have been reported to possess wide variety of activities viz. anticancer[2], antitubercular[3], antileishmanial[4], antimicrobial[5], anticonvulsant[6], antiviral[7], antioxidant[8], antiinflammatory[9], analgesic[10], anthelmintic[11], antimalarial[12], antifertility[13], amoebicial[14], anti HIV[15], antidiabetic[16] and enzyme inhibitory[17] etc. Numbers of review[18] articles have been published on synthesis, chemistry and biological potential of isatin derivatives. In the light of these articles, a new series of Mannich bases of 5-ethylisatin is being reported here.

Chemistry:

4-(4′-Fluorobenzyloxy)-benzohydrazide[19] **2** was prepared by hydrazinolysis of methyl 4-(4′-fluorobenzyloxy)-benzoate **1** which in turn was obtained by *O*-benzylation of methyl-4-hydroxybenzoate with 4-fluorobenzyl chloride. Benzohydrazide **2** on condensation with 5-ethylisatin/N-substituted-5-ethylisatins in equimolar proportion, gave 3-[4′-(4″-fluorobenzyloxy)-benzohydrazono]-5-ethylisatin **3**/1-substituted-3-[4′-(4″-fluorobenzyloxy)-benzohydrazono]-5-ethylisatins **4-6** (Schiff bases). Schiff base **3** on being subjected to aminomethylation[20] with secondary amines (aliphatic and heterocyclic) in the presence of formaldehyde, gave 1-aminomethyl-3-[4′-(4″-fluorobenzyloxy)-benzohydrazono]-5-ethylisatins **7-17** (Mannich bases) (Scheme 1). 5-Ethylisatin was synthesised by the reaction of 4-ethylaniline with chloral hydrate and hydroxylamine hydrochloride to get isonitrosoacetanilide intermediate which on cyclization with concentrated sulfuric acid gave orange colored solid. N-Methyl, N-acetyl and N-benzoyl-5-ethylisatins were obtained by the reaction of 5-ethylisatin with dimethylsulphate, acetic anhydride and benzoyl chloride.

Antifungal activity:

All the compounds **3-17** were screened for their *in vitro* antifungal potential against human pathogenic fungi viz. *Candida albicans* (CA), *Cryptococcus neoformans* (CN), *Candida parapsilosis* (CP), *Trichophyton mentagrophytes* (TM) and *Aspergillus fumigatus* (AF) using Tube Dilution Method[21] at a maximum concentration of 100 μg/mL in DMSO. The spore suspension of 10^5 spores/mL was used for this purpose. The drug dilutions were made serially. The test was performed at 29°C and Minimum Inhibitory Concentration (MIC) in μg/mL was recorded by visual observation after 24–72 h incubation. Suitable controls: broath control (without infection), growth control (with infection), solvent DMSO, drug controls (all test compounds) and fluconazole (as standard drug) were set under identical conditions. The last tube with no apparent growth of organism represented the MIC of compounds. Antifungal activity data are presented in Table 1. Schiff bases were found to be inactive or showed MIC of no significance against all the tested fungi. However, on aminomethylation which resulted into

Mannich bases, compounds showed good to weak activity against fungi. Mannich bases **8, 9** and **11** with morpholinomethyl, piperidinomethyl and pyrrolidinomethyl groups showed activity against CN, TM and AF with MIC 3.12 μg/mL. Compounds **12, 13, 16** and **17** showed MIC 3.12 against TM and AF, while **18** and **19** showed MIC 3.12 against TM only. Compounds **8, 9** and **10** showed MIC 3.12 against CP. Mannich bases were found to be good to moderately active against TM and AF while most of them were found to inactive against CA and CP. The trend of antifungal activity of Mannich bases was so diverse that no structure activity relationship (SAR) could be established in terms of amines.

Table 1. Minimum Inhibitory Concentration (MIC) in μg/mL of compounds against fungi

Compd.	*Candida albicans*	*Cryptococcus neoformans*	*Candida parapsilosis*	*Trichophyton mentagrophytes*	*Aspergillus fumigatus*
3	>100	50	>100	50	50
4	>100	50	>100	50	50
5	>100	50	>100	25	25
6	>100	50	>100	25	25
7	>100	50	>100	50	50
8	25	3.12	3.12	3.12	3.12
9	25	3.12	3.12	3.12	3.12
10	50	25	3.12	6.25	12.5
11	25	3.12	25	3.12	3.12
12	50	6.25	25	3.12	3.12
13	50	6.25	25	3.12	3.12
14	50	6.25	25	6.25	12.5
15	50	12.5	25	6.25	12.5
16	50	12.5	25	3.12	3.12
17	50	12.5	50	3.12	6.25
18	50	25	50	3.12	6.25
19	50	25	50	3.12	6.25
Fluconazole (Standard drug)	0.5	1.0	2.0	1.0	2.0

Experimental

The melting points were determined in open capillary tubes in sulphuric acid bath and are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer spectrophotometer and frequencies are presented as cm^{-1}. PMR spectra were recorded on Bruker Avance 300 spectrometer using DMSO-d_6/$CDCl_3$ as solvent and TMS as internal reference. Chemical shifts values are expressed in δ (ppm). Elemental analysis data were obtained on Carlo Erba 1108 analyser. Homogeneity of the compounds was checked on TLC silica gel G plates and spots were located by exposure to iodine vapours.

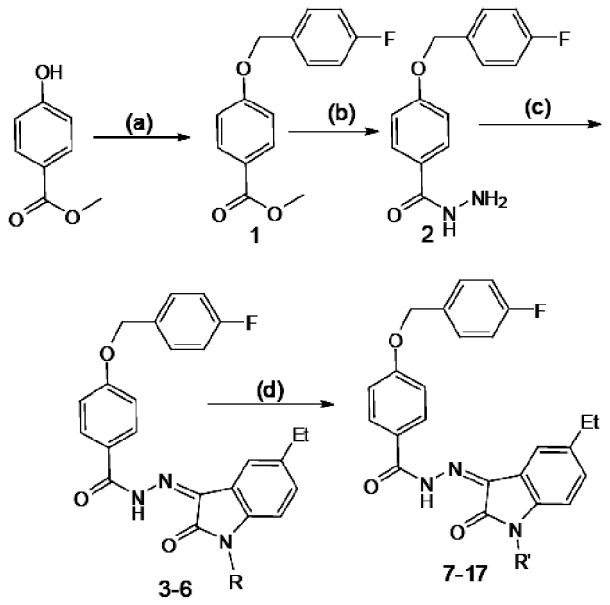
3-[4′-(4″-Fluorobenzyloxy)-benzohydrazono]-5-ethylisatin, ***3****:*

A mixture of 4-(4′-fluorobenzyloxy)-benzohydrazide **2** (0.01 mol) and 5-ethylisatin (0.01 mol) in ethanol (70 mL) containing 2–3 drops of glacial acetic acid was refluxed for 2 h and left overnight at room temperature. The separated solid was filtered and washed with methanol. m.p. 228°C, yield 70%; IR (cm^{-1}): 3440, 3179 (NH), 1688 (CO), 1250 (-CH_2O-), 1055 (C-F); Anal. Found: C, 68.97; H, 4.76; N, 9.98. $C_{24}H_{20}FN_3O_3$ requires: C, 69.05; H, 4.83; N, 10.07%.

Schiff bases **4-6** were synthesised by similar method using N-methyl, N-acetyl and N-benzoyl-5-ethylisatins.

1-Methyl-3-[4'-(4"-fluorobenzyloxy)-benzohydrazono]-5-ethylisatin, ***4****:*

m.p. 210°C, yield 66%; PMR (DMSO-d_6): δ 1.21 (3H, t, *J* 7.6 Hz, CH_2CH_3), 2.58 (2H, q, *J* 7.6 Hz, CH_2CH_3), 2.63 (3H, s, NMe), 5.36 (2H, s, -CH_2O-), 7.00–8.10 (11H, m, Ar-H), 13.80 (1H, s, CONH). Anal. Found: C, 69.50; H, 5.06; N, 9.68. $C_{25}H_{22}FN_3O_3$ requires: C, 69.59; H, 5.14; N, 9.74%.



(a) 4-Fluorobenzyl chloride, anhyd. K_2CO_3, Me_2CO

(b) $N_2H_4.H_2O$, 1-propanol

(c) 5-Ethylisatin/N-substituted-5-ethylisatins, EtOH, gl. AcOH

(d) Amines, CH_2O, DMF

R = H, Me, COMe, COPh

R′ = Morpholinomethyl, piperidinomethyl, pyrrolidinomethyl, *N*-methylpiperazinomethyl, *N*-ethylpiperazinomethyl, *N*-phenylpiperazinomethyl, *N*-benzylpiperazinomethyl, dimethylaminomethyl, diethylaminomethyl, di-*n*-propylaminomethyl, diisopropylaminomethyl

Scheme 1

1-Acetyl-3-[4′-(4″-fluorobenzyloxy)-benzohydrazono]-5-ethylisatin, ***5****:*

m.p. 202–204°C, yield 72%; PMR (DMSO-d_6): δ 1.21 (3H, t, *J* 7.6 Hz, CH_2CH_3), 2.32 (3H, s, COMe), 2.58 (2H, q, *J* 7.6 Hz, CH_2CH_3), 5.39 (2H, s, -CH_2O-), 6.98–8.05 (11H, m, Ar-H), 13.85 (1H, s, CONH). Anal. Found: C, 67.92; H, 4.76; N, 9.09. $C_{26}H_{22}FN_3O_4$ requires: C, 67.97; H, 4.83; N, 9.15%.

1-Benzoyl-3-[4'-(4"-fluorobenzyloxy)-benzohydrazono]-5-ethylisatin, ***6****:*

m.p. 180°C, yield 68%; PMR (DMSO-d_6): δ 1.21 (3H, t, *J* 7.6 Hz, CH_2CH_3), 2.57 (2H, q, *J* 7.6 Hz, CH_2CH_3), 5.39 (2H, s, -CH_2O-), 6.94–8.15 (16H, m, Ar-H), 13.84 (1H, s, CONH). Anal. Found: C, 71.32; H, 4.56; N, 8.00. $C_{31}H_{24}FN_3O_4$ requires: C, 71.39; H, 4.64; N, 8.07%.

1-Morpholinomethyl-3-[4′-(4″-fluorobenzyloxy)-benzohydrazono]-5-ethylisatin, ***7****:*

To a suspension of **3** (0.005 mol) in DMF, formaldehyde (0.5 mL, 37% aq. solution) and morpholine (0.005 mol) were added with vigorous stirring, warmed for 2 min on a water bath and left overnight at room temperature. The solid product thus obtained was filtered, washed with methanol, dried and purified by recrystallization from chloroform: pet.-ether (60–80°C) (1:1), m.p. 190–192°C, yield 70%; IR (cm^{-1}): 3478 (NH), 2816 (>N-CH_2-N<), 1966 (CO), 1248 (-CH_2O-), 1060 (C-F); PMR ($CDCl_3$) δ ppm: δ 1.21 (3H, t, *J* 7.6 Hz, CH_2CH_3), 2.37 (4H, t, *J* 7.0 Hz, -CH_2-N-CH_2-), 2.58 (2H, q, *J* 7.6 Hz, CH_2CH_3), 3.53 (4H, t, *J* 7.0 Hz, -CH_2-O-CH_2-), 4.55 (2H, s, >N-CH_2-N<), 5.38 (2H, s, -CH_2O-) , 6.92–8.10 (11H, m, Ar-H), 13.77 (1H, s, CONH). Anal. Found: C, 67.36; H, 5.59; N, 10.80. $C_{29}H_{29}FN_4O_4$ requires: C, 67.43; H, 5.66; N, 10.85%.

1-Piperidinomethyl-3-[4'-(4"-fluorobenzyloxy)-benzohydrazono]-5-ethylisatin, ***8****:*

m.p. 198°C (d), yield 73%; IR (cm^{-1}): 3458 (NH), 2826 (>N-CH_2-N<), 1694 (CO), 1245 (-CH_2O-), 1060 (C-F); PMR ($CDCl_3$) : δ 1.21 (3H, t, *J* 7.6 Hz, CH_2CH_3), 1.56–1.61 (6H, m, -$CH_2CH_2CH_2$-), 2.38 (4H, t, *J* 4.8 Hz, -CH_2-N-CH_2-), 2.57 (2H, q, *J* 7.6 Hz, CH_2CH_3), 4.50 (2H, s, >N-CH_2-N<), 5.40 (2H, s, -CH_2O-), 7.07–8.11 (11H, m, Ar-H), 13.88 (1H, s, CONH). Anal. Found: C, 69.96; H, 5.92; N, 10.80. $C_{30}H_{31}FN_4O_3$ requires: C, 70.02; H, 6.07; N, 10.89%.

1-Pyrrolidinomethyl-3-[4'-(4"-fluorobenzyloxy)-benzohydrazono] -5-ethylisatin, ***9****:*

m.p. 192°C (d), yield 68%; IR (cm^{-1}): 3455 (NH), 2839 (>N-CH_2-N<), 1688 (CO), 1240 (-CH_2O-), 1055 (C-F); PMR ($CDCl_3$) : δ 1.21 (3H, t, *J* 7.6 Hz, CH_2CH_3), 1.36–1.41 (4H, m, -CH_2CH_2-), 2.35 (4H, t, *J* 4.6 Hz, -CH_2-N-CH_2-), 2.57 (2H, q, *J* 7.6 Hz, CH_2CH_3), 4.54 (2H, s, >N-CH_2-N<), 5.44 (2H, s, -CH_2O-), 7.00–8.05 (11H, m, Ar-H), 13.78 (1H, s, CONH). Anal. Found: C, 69.50; H, 5.82; N, 11.02. $C_{29}H_{29}FN_4O_3$ requires: C, 69.58; H, 5.84; N, 11.19%.

1-N-Methylpiperazinomethyl-3-[4'-(4"-fluorobenzyloxy)-benzohydrazono]-5-ethylisatin, ***10****:*

m.p. 152–154°C, yield 66%; PMR ($CDCl_3$): δ 1.21 (3H, t, *J* 7.6 Hz, CH_2CH_3), 1.87 (3H, s, N-Me), 2.36 (4H, t, *J* 4.8 Hz, -CH_2-N-CH_2-), 2.57 (2H, q, *J* 7.6 Hz, CH_2CH_3), 2.62 (4H, t, *J* 4.8 Hz, -CH_2-N(Me)-CH_2-), 4.52 (2H, s, >N-CH_2-N<), 5.47 (2H, s, -CH_2O-), 6.98–7.88 (11H, m, Ar-H), 13.87 (1H, s,

CONH). Anal. Found: C, 67.96; H, 5.94; N, 13.13. $C_{30}H_{32}FN_5O_3$ requires: C, 68.04; H, 6.09; N, 13.22%.

1-N-Ethylpiperazinomethyl-3-[4'-(4"-fluorobenzyloxy)-benzohydrazono]-5-ethylisatin, ***11****:*

m.p. 144–146°C, yield 60%; PMR ($CDCl_3$) : δ 1.21 (3H, t, *J* 7.6 Hz, CH_2CH_3), 1.89 (3H, t, *J* 7.2 Hz, -CH_2Me), 2.04 (2H, q, *J* 7.2 Hz, -CH_2Me), 2.36 (4H, t, *J* 5.2 Hz, -CH_2-N-CH_2-), 2.58 (2H, q, *J* 7.6 Hz, CH_2CH_3), 2.63 (4H, t, *J* 5.2 Hz, -CH_2-N(Et)-CH_2-), 4.51 (2H, s, >N-CH_2-N<), 5.50 (2H, s, -CH_2O-), 6.88–7.99 (11H, m, Ar-H), 13.87 (1H, s, CONH). Anal. Found: C, 68.41; H, 6.22; N, 12.80. $C_{30}H_{31}FN_5O_3$ requires: C, 68.49; H, 6.30; N, 12.88%.

1-N-Phenylpiperazinomethyl-3-[4'-(4"-fluorobenzyloxy)-benzohydrazono]-5-ethylisatin, ***12****:*

m.p. 174°C, yield 50%; IR (cm^{-1}): 3445 (NH), 2835 (>N-CH_2-N<), 1686 (CO), 1235 (-CH_2O-), 1055 (C-F); PMR ($CDCl_3$) : δ 1.21 (3H, t, *J* 7.6 Hz, CH_2CH_3), 2.35, (4H, t, *J* 4.9 Hz, -CH_2-N-CH_2-), 2.58 (2H, q, *J* 7.6 Hz, CH_2CH_3), 2.64 (4H, t, *J* 4.9 Hz, -CH_2-N(Ph)-CH_2-), 4.55 (2H, s, >N-CH_2-N<), 5.47 (2H, s, -CH_2O-), 7.04–8.28 (16H, m, Ar-H), 13.87 (1H, s, CONH). Anal. Found: C, 70.96; H, 5.72; N, 11.80. $C_{35}H_{34}FN_5O_3$ requires: C, 71.05; H, 5.79; N, 11.84%.

1-N-Benzylpiperazinomethyl-3-[4'-(4"-fluorobenzyloxy)-benzohydrazono]-5-ethylisatin, ***13****:*

m.p. 144–146°C, yield 60%; PMR ($CDCl_3$): δ 1.21 (3H, t, *J* 7.6 Hz, CH_2CH_3), 2.36 (4H, t, *J* 4.8 Hz, -CH_2-N-CH_2-), 2.57 (2H, q, *J* 7.6 Hz, CH_2CH_3), 2.65 (4H, t, *J* 4.8 Hz, -CH_2-N(CH_2Ph)-CH_2-), 4.49 (2H, s, CH_2Ph), 4.54 (2H, s, >N-CH_2-N<), 5.47 (2H, s, -CH_2O-), 7.04–8.26 (16H, m, Ar-H), 13.80 (1H, s, CONH). Anal. Found: C, 71.6; H, 5.92; N, 11.50. $C_{36}H_{36}FN_5O_3$ requires: C, 71.39; H, 5.99; N, 11.56%.

1-Dimethylaminomethyl-3-[4'-(4"-fluorobenzyloxy)-benzohydrazono]-5-ethylisatin, ***14****:*

m.p. 200–102°C, yield 65%; IR (cm^{-1}): 3440 (NH), 2838 (>N-CH_2-N<), 1699 (CO), 1235 (-CH_2O-), 1052 (C-F); PMR ($CDCl_3$): δ 1.21 (3H, t, *J* 7.6 Hz, CH_2CH_3), 2.33 (6H, s, NMe_2), 2.58 (2H, q, *J* 7.6 Hz, CH_2CH_3), 4.34 (2H, s, >N-CH_2-N<), 5.42 (2H, s, -CH_2O-), 7.00–8.25 (11H, m, Ar-H), 13.98 (1H, s, CONH). Anal. Found: C, 68.26; H, 5.62; N, 11.78. $C_{27}H_{27}FN_4O_3$ requires: C, 68.34; H, 5.74; N, 11.81%

1-Diethylaminomethyl-3-[4'-(4"-fluorobenzyloxy)-benzohydrazono]-5-ethylisatin, ***15****:*

m.p. 172–174°C, yield 66%; IR (cm^{-1}): 3433 (NH), 2830 (>N-CH_2-N<), 1692 (CO), 1235 (-CH_2O-), 1052 (C-F); PMR ($CDCl_3$): δ 1.21 (3H, t, *J* 7.6 Hz, CH_2CH_3), 1.98 (6H, t, *J* 6.8 Hz, CH_2Me), 2.20 (4H, q, *J* 6.8 Hz, CH_2Me), 2.58 (2H, q, *J* 7.6 Hz, CH_2CH_3), 4.47 (2H, s, >N-CH_2-N<), 5.42 (2H, s, -CH_2O-), 7.00–8.29 (11H, m, Ar-H), 13.98 (1H, s, CONH). Anal. Found: C, 69.26; H, 5.14; N, 11.10. $C_{29}H_{31}FN_4O_3$ requires: C, 69.30; H, 6.22; N, 11.15%.

1-Di-n-propylaminomethyl-3-[4´-(4˝-fluorobenzyloxy)-benzohydrazono]-5-ethylisatin, ***16****:*

m.p. 170°C, yield 60%; PMR ($CDCl_3$): δ 1.21 (3H, t, *J* 7.6 Hz, CH_2CH_3), 1.31 (6H, *J* 7.5 Hz, t, CH_2CH_2Me), 1.56–1.60 (4H, m, CH_2CH_2Me), 2.20 (4H, t, *J* 7.5 Hz, CH_2CH_2Me), 2.58 (2H, q, *J* 7.6 Hz, CH_2CH_3), 4.42 (2H, s, >N-CH_2-N<), 5.51 (2H, s, -CH_2O-), 7.14–8.19 (11H, m, Ar-H), 13.88 (1H, s, CONH). Anal. Found: C, 69.96; H, 5.92; N, 10.80. $C_{30}H_{31}FN_4O_3$ requires: C, 70.02; H, 6.07; N, 10.89%.

1-Diisopropylaminomethyl-3-[4'-(4"-fluorobenzyloxy)-benzohydrazono]-5-ethylisatin, ***17****:*

m.p. 178–180°C, yield 56%; PMR ($CDCl_3$): δ 1.21 (3H, t, *J* 7.6 Hz, CH_2CH_3), 1.28 (12H, d, *J* 7.4 Hz, $CH(Me)_2$), 2.19 (2H, q, *J* 7.4 Hz, $CH(Me)_2$), 2.57 (2H, q, *J* 7.6 Hz, CH_2CH_3), 4.47 (2H, s, >N-CH_2-N<), 5.47 (2H, s, -CH_2O-), 7.14–8.19 (11H, m, Ar-H), 13.87 (1H, s, CONH). Anal. Found: C, 69.92; H, 5.95; N, 10.82. $C_{30}H_{31}FN_4O_3$ requires: C, 70.02; H, 6.07; N, 10.89%.

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