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SYNTHESIS, CHARACTERIZATION AND ANTIFUNGAL POTENTIAL OF SOME NEW SCHIFF AND MANNICH BASES OF 5-METHYLINDOLIN-2, 3-DIONE

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ABSTRACT

A new series of 1-substituted -3-{4'-(4''-fluorobenzyloxy)-benzoylhydrazono}-5-methylindolin-2-ones (Schiff bases) and 1-aminomethyl-3-{4'-(4''-fluorobenzyloxy)-benzoylhydrazono}-5-methylindolin-2-ones (Mannich bases) have been synthesised and screened for their antifungal potential against human pathogenic fungi (Candida albicans, Cryptococcus neoformans, Candida parapsilosis, Trichophyton mentagrophytes and *Aspergillus fumigatus). The structures of the Schiff and Mannich bases have been elucidated with the help of elemental analysis and spectral data (IR, PMR and Mass).*

Keywords: 5-Methylindolin-2,3-diones, Schiff bases, Mannich Bases, antifungal activity.

Introduction

Indolin-2,3-dione and its derivatives possess wide variety of biological activities viz., antimicrobial[1], anticancer[2], antiinflammatory[3], analgesic[4], anticonvulsant[5], antitubercular[6], antimalarial[7], antioxidant[8], antimycobacterial[9], sedative-hypnotic[10] and enzyme inhibitory[11].

Number of review[12] articles have been published on the chemistry and biological potential of indolin-2, 3-diones. In the light of biological activity profile of indolin-2, 3-diones and in continuation of our research work[12] on indolin-2, 3-dione derivatives, a new series of 1-substituted -3-{4'-(4''-fluorobenzyloxy)-benzoylhydrazono}-5-methylindolin-2-ones (Schiff bases) and 1-aminomethyl-3-{4'-(4''-fluorobenzyloxy)-benzoylhydrazono}-5-methylindolin-2-ones (Mannich bases) is being reported here.

4-(4'-Fluorobenzyloxy)-benzoylhydrazine **2** was prepared by hydrazinolysis of methyl 4-(4'-fluorobenzyloxy) benzoate **1** which in turn was prepared by O-benzylation of methyl paraben with 4-fluorobenzyl chloride. 4-(4'-Fluorobenzyloxy)-benzoylhydrazine **2** on condensation with 5-methylindolin-2,3-dione and 1-substituted-5-methylindolin-2,3-diones in equimolar proportion, gave 3-{4'-(4''-fluorobenzyloxy)-benzoylhydrazono}-5-methylindolin-2-one **3** and 1-substituted-3-{4'-(4''-fluorobenzyloxy)-benzoylhydrazono}-5-methylindolin-2-ones (Schiff bases) **4-8** respectively. Schiff base **3** on being subjected to aminomethylation with aliphatic and heterocyclic secondary amines in the presence of formaldehyde, gave 1-aminomethyl-3-{4'-(4''-fluorobenzyloxy)-benzoylhydrazono}-5-methylindolin-2-ones (Mannich bases) **9-20** (**Scheme 1**).

Antifungal Activity

All the Schiff **3-8** and Mannich **9-20** bases were screened for their *in-vitro* antifungal potential against human pathogenic fungi viz., *Candida albicans*, *Cryptococcus neoformans*, *Candida parapsilosis*, *Trichophyton mentagrophytes* and *Aspergillus fumigatus* using Tube Dilution Method[13] at a maximum concentration of 50 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^{o}C and Minimum Inhibitory Concentration (MIC) in μg/mL was recorded by visual observation after 24-72 hours 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. Antifunal activity data are presented in **Table-1**

Table-1

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

Compd	*Candida albicans*	*Cryptococcus neoformans*	*Candida parapsilosis*	*Trichophhyton mentagrophytes*	*Aspergillus fumigatus*
3	6.25	25	6.25	3.12	3.12
4	6.25	25	6.25	6.26	6.26
5	12.5	25	25	3.12	3.12
6	12.5	25	25	6.26	6.26
7	3.12	6.25	6.25	3.12	3.12
8	3.12	6.25	6.25	3.12	3.12
9	3.12	25	12.5	3.12	3.12
10	3.12	25	12.5	3.12	3.12
11	3.12	25	12.5	12.5	12.5
12	3.12	25	12.5	12.5	12.5
13	6.25	25	25	3.12	3.12
14	6.25	25	25	3.12	3.12
15	12.5	25	25	12.5	12.5
16	12.5	25	25	12.5	12.5
17	3.12	25	25	3.12	3.12
18	3.12	25	25	3.12	3.12
19	6.25	25	25	6.25	6.25
20	6.25	25	25	3.12	3.12
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). Mass spectra were recorded on Jeol-JMS-300 spectrometer.

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)-benzoylhydrazono}-5-methylindolin-2-one, 3

A mixture of 4-(4'-fluorobenzyloxy)-benzoylhydrazine **2** (0.005 mol) and 5-methylindolin-2, 3-dione (0.005 mol) in ethanol (20 mL) containing 2-3 drops of glacial acetic acid was refluxed for I hr and left overnight at room temperature. The separated solid was filtered and washed with methanol. Yield 80%, m. p. 275-276^{o}C; IR (cm^{-1}): 3456, 3172 (NH), 1688 (CO), 1245 (-CH_2O-), 1055 (C-F); MS m/z: 403 ($M^{+\bullet}$). (Found C, 68.31, H, 4.39, N, 10.38 Calcd. for $C_{23}H_{18}FN_3O_3$: C, 68.48, H, 4.50, N, 10.42 %).

Schiff bases **4-8** were synthesised similarly using 1-methyl, 1-acetyl, 1-benzoyl, 1-hydroxymethyl and 1-benzyl-5-methylindolin-2, 3-diones respectively.

1-Methyl-3-{4'-(4"-fluorobenzyloxy)-benzoylhydrazono}-5-methylindolin-2-one, 4

Yield 74 %, m. p. 220^{o}C; PMR (DMSO-d_6) δppm: 2.55 (3H, s, 5-Me), 2.62 (3H, s, NMe), 5.36 (2H, s, -CH_2O-) , 6.98-8.00 (11H, m, Ar-H), 13.88 (1H, s, CONH); MS m/z: 417 ($M^{+\bullet}$). (Found C,68.91, H, 4.78, N, 9.96 Calcd. for $C_{24}H_{20}FN_3O_3$: C, 69.05 , H, 4.83, N, 10.07 %).

1-Acetyl-3-{4'-(4"-fluorobenzyloxy)-benzoylhydrazono}-5-methylindolin-2-one, 5

Yield 70 %, m. p. 214-216^{o}C; PMR (DMSO-d_6) δppm: 2.32 (3H, s, COMe), 2.55 (3H, s, 5-Me), 5.39 (2H, s, -CH_2O-) , 6.98-8.05 (11H, m, Ar-H), 13.89 (1H, s, CONH); MS m/z: 445 ($M^{+\bullet}$). (Found C,67.30, H, 4.48, N, 9.36 Calcd. for $C_{25}H_{20}FN_3O_4$: C, 67.41 , H, 4.53, N, 9.43 %).

1-Benzoyl-3-{4'-(4"-fluorobenzyloxy)-benzoylhydrazono}-5-methylindolin-2-one, 6

Yield 70 %, m. p. 198-200^{o}C; PMR (DMSO-d_6) δppm: 2.48 (3H, s, 5-Me), 5.39 (2H, s, -CH_2O-), 6.98-8.05 (16H, m, Ar-H), 13.84 (1H, s, CONH); MS m/z: 507 ($M^{+\bullet}$). (Found C,69.92, H, 4.32, N, 8.22 Calcd. for $C_{30}H_{22}FN_3O_4$: C, 71.00 , H, 4.37, N, 8.28 %).

1-Hydroxymethyl-3-{4'-(4"-fluorobenzyloxy)-benzoylhydrazono}-5-methylindolin-2-one, 7

Yield 62 %, m. p. 248-250^{o}C; PMR (DMSO-d_6) δppm: 2.55 (3H, s, 5-Me), 4.98 (2H, s, NCH_2OH), 5.39 (2H, s, -CH_2O-), 5.42 (1H, s, NCH_2OH), 6.94-8.00 (11H, m, Ar-H), 13.80 (1H, s, CONH); MS m/z: 433 ($M^{+\bullet}$). (Found C,66.46, H, 4.58, N, 9.60 Calcd. for $C_{24}H_{20}FN_3O_4$: C, 66.51 , H, 4.65, N, 9.69 %).

1-Benzyl-3-{4'-(4"-fluorobenzyloxy)-benzoylhydrazono}-5-methylindolin-2-one, 8

Yield 66 %, m. p. 184-186^{o}C; PMR (DMSO-d_6) δppm: 2.53 (3H, s, 5-Me), 4.62 (2H, s, NCH_2Ph), 5.36 (2H, s, $-CH_2O-$) , 6.92-8.00 (16H, m, Ar-H), 13.90 (1H, s, CONH); MS m/z: 493 ($M^{+\bullet}$). (Found C,72.91, H, 4.86, N, 8.46 Calcd. for $C_{30}H_{24}FN_3O_3$: C, 3.01 , H, 4.90, N, 8.51 %).

1-Morpholinomethyl-3-{4'-(4"-fluorobenzyloxy)-benzoylhydrazono}-5-methylindolin-2-one, 9

To a suspension of **3** (0.005 mol) in DMF, formaldehyde (0.5 mL, 37 % aqueous solution) and morpholine (0.005 mol) were added with vigorous stirring and the reaction mixture was warmed on a water bath for 2-3 min and left overnight at room temperature. The solid product so obtained was filtered, washed with methanol, dried and recrystallised from chloroform: petroleum ether 60-80^{o} (1:1). Yield 73 %, m. p. 184-186^{o}C; IR (cm^{-1}): 3470 (NH), 2813 (>N-CH_2-N<), 1986 (CO), 1245 (-CH_2O-), 1060 (C-F); PMR ($CDCl_3$) δppm: 2.53 (3H, s, 5-Me), 2.60-2.63 (4H, t, -CH_2-N-CH_2-), 3.50-3.54 (4H, t, -CH_2-O-CH_2-), 4.52 (2H, s, >N-CH_2-N<), 5.40 (2H, s, -CH_2O-) , 6.82-8.10 (11H, m, Ar-H), 13.73 (1H, s, CONH), MS m/z: 502 ($M^{+\bullet}$). (Found C,66.81, H, 5.38, N, 11.06 Calcd. for $C_{28}H_{27}FN_4O_4$: C, 66.92 , H, 5.42, N, 11.15 %).

Mannich bases **10-20** were prepared using similar method by using piperidine, 2-methylpiperidine, pyrrolidine, dimethylamine, diethylamine, di-n-propylamine, diisopropylamine, N-methylpiperazine, N-ethylpiperazine, N-phenylpiperazine and N-benzylpiperazine respectively.

1-Piperidinomethyl-3-{4'-(4"-fluorobenzyloxy)-benzoylhydrazono}-5-methylindolin-2-one, 10

Yield 70 %, m. p. 166-168^{o}C; IR (cm^{-1}): 3450 (NH), 2826 (>N-CH_2-N<), 1690 (CO), 1245 (-CH_2O-), 1062 (C-F), PMR ($CDCl_3$) δppm: 1.56-1.62 (6H, m, -$CH_2CH_2CH_2$-), 2.50 (3H, s, 5-Me), 2.58-2.61 (4H, t, -CH_2-N-CH_2-), 4.52 (2H, s, >N-CH_2-N<), 5.35 (2H, s, -CH_2O-) , 7.07-8.01 (11H, m, Ar-H), 13.83 (1H, s, CONH), MS m/z: 500 ($M^{+\bullet}$). (Found C, 69.51, H, 5.75, N, 11.10 Calcd. for $C_{29}H_{29}FN_4O_3$: C, 69.58 , H, 5.84, N, 11.19 %).

1-(2-Methyl) piperidinomethyl-3-{4'-(4"-fluorobenzyloxy)-benzoylhydrazono}-5-methylindolin-2-one, 11

Yield 60 %, m. p. 132-134^{o}C; PMR ($CDCl_3$) δppm: 1.21 (3H, d, CHMe), 1.56-1.62 (6H, m, -$CH_2CH_2CH_2$-), 2.50 (3H, s, 5-Me), 2.56-2.62 (3H,m, -CH_2-N-CH-), 4.52 (2H, s, >N-CH_2-N<),

5.35 (2H, s, -CH_2O-) , 7.07-8.00 (11H, m, Ar-H), 13.79 (1H, s, CONH); MS m/z: 514 ($M^{+\bullet}$). .(Found C, 69.91, H, 6.98, N, 10.80 Calcd. for $C_{30}H_{31}FN_4O_3$: C, 70.02, H, 6.07, N, 10.89 %).

1-Pyrrolidinomethyl-3-{4'-(4"-fluorobenzyloxy)-benzoylhydrazono}-5-methylindolin-2-one, 12

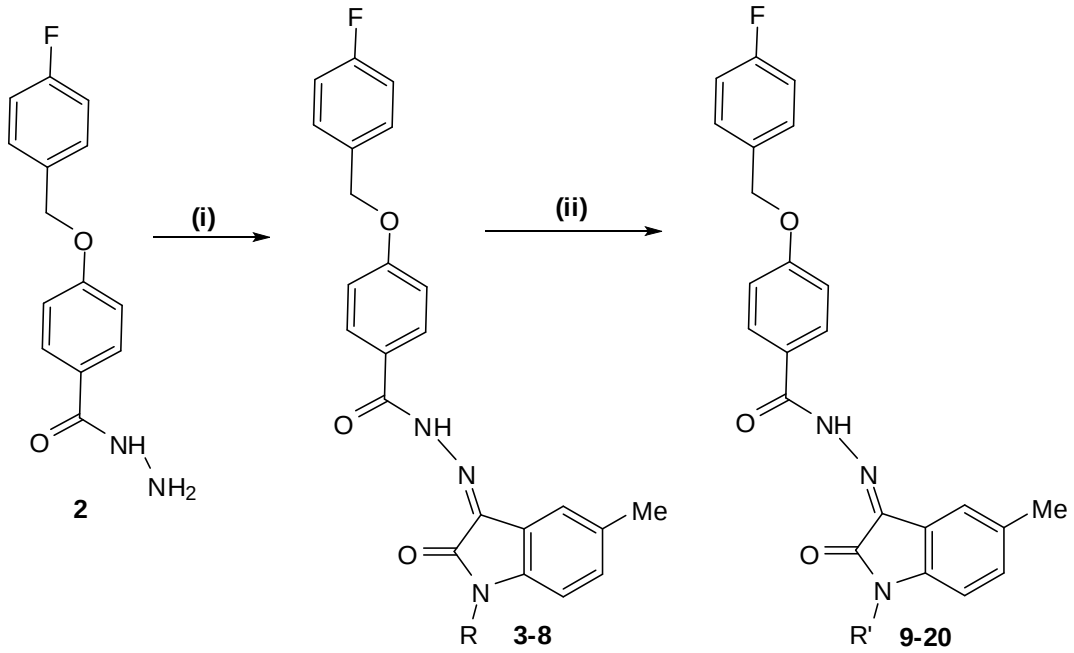
Yield 70 %, m. p. 170-172^oC; IR (cm^{-1}): 3450 (NH), 2834 (>N-CH_2-N<), 1688 (CO), 1245 (-CH_2O-), 1059 (C-F); PMR ($CDCl_3$) δppm: 1.36-1.42 (4H, m, -$CH_2CH_2CH_2$-), 2.33-2.40 (4H, t, -CH_2-N-CH_2-), 2.59 (3H, s, 5-Me), 4.54 (2H, s, >N-CH_2-N<), 5.40 (2H, s, -CH_2O-) , 7.05-8.15 (11H, m, Ar-H), 13.83 (1H, s, CONH); MS m/z: 486 ($M^{+\bullet}$). (Found C, 69.04, H, 5.50, N, 11.46 Calcd. for $C_{28}H_{27}FN_4O_3$: C, 69.12 , H, 5.59, N, 11.52 %).

1-Dimethylaminomethyl-3-{4'-(4"-fluorobenzyloxy)-benzoylhydrazono}-5-methylindolin-2-one, 13

Yield 72 %, m. p. 198-200^oC; IR (cm^{-1}): 3440 (NH), 2838 (>N-CH_2-N<), 1699 (CO), 1235 (-CH_2O-), 1052 (C-F); PMR ($CDCl_3$) δppm: 2.33 (6H, s, NMe_2), 2.63 (3H, s, 5-Me), 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), MS m/z: 460 ($M^{+\bullet}$). (Found C, 67.74, H, 5.40, N, 12.11 Calcd. for $C_{26}H_{25}FN_4O_3$: C, 67.81 , H, 5.47, N, 12.17 %).

1-Diethylaminomethyl-3-{4'-(4"-fluorobenzyloxy)-benzoylhydrazono}-5-methylindolin-2-one, 14

Yield 70 %, m. p. 188^oC; IR (cm^{-1}): 3433 (NH), 2830 (>N-CH_2-N<), 1692 (CO), 1235 (-CH_2O-), 1052 (C-F); PMR ($CDCl_3$) δppm: 1.87-2.09 (6H, t, CH_2Me), 2.19-2.22 (4H, q, CH_2Me), 2.56 (3H, s, 5-Me), 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), MS m/z: 460 ($M^{+\bullet}$). (Found C, 68.79, H, 5.93, N, 11.39 Calcd. for $C_{28}H_{29}FN_4O_3$: C, 68.84, H, 5.98, N, 11.47 %).



(i) 5-Methylindolin-2,3-diones, gl. AcOH; EtOH

(ii) Amines, CH_2O; DMF

R = H, Me, COMe, COPh, CH_2OH, Bz

R' = Morpholinomethyl, piperidinomethyl, 2-methylpiperidinomethyl, pyrrolidinomethyl, dimethylaminomethyl, diethylaminomethyl, di-n-propylaminomethyl, diisopropylaminomethyl, N-methylpiperazinomethyl, N-ethylpiperazinomethyl, N-phenylpiperazinomethyl and N-benzylpiperazinomethyl

SCHEME-1

1-Di-n-propylaminomethyl-3-{4'-(4"-fluorobenzyloxy)-benzoylhydrazono}-5-methylindolin-2-one, 15

Yield 65 %, m. p.194(d)^oC; PMR ($CDCl_3$) δppm: 1.20-1.33 (6H, t, CH_2CH_2Me), 1.56-1.60 (4H, m, CH_2CH_2Me), 2.19-2.22 (4H, t, CH_2CH_2Me), 2.46 (3H, s, 5-Me), 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), MS m/z: 516 ($M^{+\bullet}$). (Found C, 69.79, H, 6.33, N, 10.76 Calcd. for $C_{30}H_{33}FN_4O_3$: C, 69.75 , H, 6.44, N, 10.85%).

1-Diisopropylaminomethyl-3-{4'-(4"-fluorobenzyloxy)-benzoylhydrazono}-5-methylindolin-2-one, 16

Yield 60 %, m. p. 198-200^{o}C; PMR ($CDCl_3$) δppm: 1.18-1.21 (12H, d, $CH(Me)_2$), 2.16-2.22 (2H, q, $CH(Me)_2$), 2.48 (3H, s, 5-Me), 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); MS m/z: 516 ($M^{+\bullet}$). (Found C, 69.71, H, 6.38, N, 10.79 Calcd. for $C_{30}H_{33}FN_4O_3$: C, 69.75, H, 6.44, N, 10.85%).

1-N-Methylpiperazinomethyl-3-{4'-(4"-fluorobenzyloxy)-benzoylhydrazono}-5-methylindolin-2-one, 17

Yield 69 %, m. p.160-162^{o}C; PMR ($CDCl_3$) δppm: 1.87 (3H, s, N-Me), 2.33-2.39 (4H, t, -CH_2-N-CH_2-), 2.50 (3H, s, 5-Me), 2.56-2.65 (4H, t, -CH_2-N(Me)-CH_2-), 4.51 (2H, s, >N-CH_2-N<), 5.47 (2H, s, -CH_2O-), 6.88-7.88 (11H, m, Ar-H), 13.87 (1H, s, CONH); MS m/z: 515 ($M^{+\bullet}$). (Found C, 67.49, H, 5.83, N, 13.50 Calcd. for $C_{29}H_{30}FN_5O_3$: C, 67.56, H, 5.86, N, 13.58%).

1-N-Ethylpiperazinomethyl-3-{4'-(4"-fluorobenzyloxy)-benzoylhydrazono}-5-methylindolin-2-one, 18

Yield 66 %, m. p.140-142^{o}C; PMR ($CDCl_3$) δppm: 1.87-1.92 (3H, t, -CH_2Me), 2.00-2.09 (2H, q, -CH_2Me), 2.33-2.39(4H, t, -CH_2-N-CH_2-), 2.55 (3H, s, 5-Me), 2.59-2.67 (4H, t, -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); MS m/z: 529 ($M^{+\bullet}$). (Found C, 67.97, H, 6.00, N, 13.17 Calcd. for $C_{30}H_{32}FN_5O_3$: C, 68.04, H, 6.09, N, 13.22%).

1-N-Phenylpiperazinomethyl-3-{4'-(4"-fluorobenzyloxy)-benzoylhydrazono}-5-methylindolin-2-one, 19

Yield 60 %, m. p.180-182^{o}C; IR (cm^{-1}): 3450 (NH), 2839 (>N-CH_2-N<), 1680 (CO), 1235 (-CH_2O-), 1060 (C-F); PMR ($CDCl_3$) δppm: 2.33-2.41 (4H, t, -CH_2-N-CH_2-), 2.55 (3H, s, 5-Me), 2.60-2.69 (4H, t, -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); MS m/z: 577 ($M^{+\bullet}$). (Found C, 70.62, H, 5.50, N, 12.03 Calcd. for $C_{34}H_{32}FN_5O_3$: C, 70.69 , H, 5.58, N, 12.12%).

1-N-Benzylpiperazinomethyl-3-{4'-(4"-fluorobenzyloxy)-benzoylhydrazono}-5-methylindolin-2-one, 20

Yield 56 %, m. p.138-140^{o}C; PMR ($CDCl_3$) δppm: 2.31-2.41 (4H, t, -CH_2-N-CH_2-), 2.55 (3H, s, 5-Me), 2.62-2.71 (4H, t, -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); MS m/z: 591 ($M^{+\bullet}$) (Found C, 70.97, H, 5.70, N, 11.73 Calcd. for $C_{35}H_{34}FN_5O_3$: C, 71.05 , H, 5.79, N, 11.84%).

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References

1. (a) H. Ramadoss, D. Saravanan, S. P. N. Sudhan and S.S. Mansoor, *Der Pharma Chemica*, 2016, **8**, 94; (b) P. S. Bhasin, N. Sachdeva, S. N. Pandeya, G. Nath and S.K. Singh, *Acta Pharm. Turcica*, 2005, **47**, 21; (c) S. Katherashala, B. Bollam, S. Garrepalli and S. Bethi, *Asian J. Pharm. Clin. Res*., 2014,**7**, 182; (d) S.M.H. Al-Majidi and K.T.A. Al-Sultani, *Al-Mustansiriya J. Sci*., 2010, **21**, 61.
2. (a) S. S. Reddy, R. Pallela, D-M Kim, M-S Won, and Y-B Shim, *Chem. Pharm. Bull*., 2013, **61**, 1105; **(b)** A. El-Faham, M. Farooq, S. N. Khattab, N. Abutaha, M. A. Wadaan, H. A. Ghabbour and H-K Fun, *Molecules*, 2015, **20**, 14638; doi:10.3390/ molecules 200814638.
3. K. Swathi and M. Sarangapani, *World J. Pharm. Pharma. Sci.*, 2014, **3**, 49.
4. S. Suresh, K. B. Priyanka, P. Maharaj, Ch. Srikanth, K. Karthik and G. Sammaiah, *Asian J. Pharm. Clin. Res*., 2013, **1**, 65.
5. G. Saravanan, V. Alagarsamy and P. Dineshkumar, *Bulletin of Faculty of Pharmacy, Cairo University*, 2014, **52**, 115.
6. T. Aboul-Fadl and F. A. S. Bin-Jubair, *Int. J. Res. Pharm.*, 2010, **1**, 113.
7. S. C. Shingade, S. B. Bari, P. Agarwal and K. Srivastava, *Indian J. Chem.*, 2013, **52B**, 1236.
8. K. Karthik, K. B. Priyanka, S. Manjula and G. Sammaiah, *Int. J. Pharm. Pharma. Sci*., 2013, **5**, 224.
9. T. Aboul-Fadl, A. A. Radwan, H. A. Abdel-Aziz. M. Baseeruddin, M. J. Attia and A. Kadi, *Digest J. Nanomaterials Biostructures*, 2012, **7**, 329.
10. B. Minugonda, K. Swathi, K. N. Kumar and M. Sarangapani, *Int. J. Pharm. Bio. Sci.*, 2013, **3,** 335.
11. (a) S. Tiwari, *Int. J. Chem. Pharm. Sci*., 2014; **2**,1225; (b) D. K. Chaudhary, S. Ahmad, S. Maity and M. S. Alam, *Der Pharmacia Lett*., 2013; **5**, 285; (c) M. Verma, S. N. Pandeya, K. N. Singh and J. P. Stables, *Acta Pharm*., 2004; **54**, 49; (d) M. Pal, N. K.

Sharma, Priyanka and K. K. Jha, *J. Adv. Sci. Res*., 2011; **2**, 35; (e) B. Bhrigu, D. Pathak, N. Siddiqui, M. S. Alam and W. Ahsan, *Int. J. Pharm. Sci. Drug. Res*., 2010, **2**, 229; (f) N. D.Wakchaure, S.S. Shejwal, V. K. Deshmukh and S. R. Chaudhari, *Am. J. PharmTech Res*., 2012, **2**, 288; (g) T. Aboul-Fadl and F. A. S. Bin-Jubair, *Int. J. Res. Pharm. Sci.*, 2010, **1**,113; (h) C. R. Prakesh, T. Anusha, P. Ashok, K. Rajasekhar, U. Pavankumar, P. Jayaraju and B. S. Rao, *Int. J. Health Pharm. Sci.*, 2012, **1**, 5; (i) M. Asif, *Universal J. Chem.*, 2016, **1**, 29; (j) P. Phogat and P. Singh, *Central Nervous System Agents Med. Chem.*, 2015, **15**, 28; (k) R. Hajare, S. Kulkarni, M. Thakar and R. Paranjape. *World J. Pharm. Pharma. Sci*, 2016, **5**, 569; (l) S. N. Pandeya, S. Smitha, M. Jyoti and S. K. Sridhar, *Acta Pharm.*, 2005, **55**, 27; (m) A. Singh, *Int. J. Pharm. Res*., 2014, **6**, 1.

12. (a) R. K. Tiwari, N. Rastogi, R. Sethi and S. Shukla, *J. Indian Chem. Soc*., 2008, **85**, 85; (b) N. Rastogi, D. A. Harrison and A. Agarwal, *Indian J. Chem*., Sect. B, 2011, **50**, 330; (c) D. A. Harrison, N. Rastogi and M. Rahman, *Indian J. Heterocyclic Chem.*, 2013, **23**, 21; (d) D. A. Harrison, N. Rastogi and M. Rahman, *J. Indian Chem. Soc.*, 2014, **91**, 319; (e) D. A. Harrison, N. Rastogi and M. Rahman, *Indian J. Heterocyclic Chem*., 2014, **23**, 41; (f) N. Rastogi, P. Kant and D. A. Harrison, *Int. J. Res. Engineering Applied Sci*., 2016, **6**, 44.

13. (a) M. L. Dhar, M. M. Dhar, B. N. Dhawan, B. N. Mehrotra and C. Ray, *Indian J. Exp. Biol.*, 1968, 6, 232; (b) Z. K. Khan, *"In vitro and in vivo screening techniques for antibacterial and antifungal activity in Medicinal Plants, their bioactivity, screening and evaluation*", Proceedings Int. workshop UNIDO-CDRI, 1997, pp 210-211**.**