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Synthesis and Evaluation of Antimicrobial Activity of Isoflavone Analouges

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ABSTRACT: A new series of 6-fluoro-3-(2-morpholino-6-aryl-4-pyrimidinyl)-4H-4-chromenone **4(a-i)** were synthesized by the reaction of 6-fluoro-3-[(E)-3-oxo-3-aryl-1-propenyl]-4H-4-chromenone **3(a-i)** with 4-morpholinecarboximidamide. The compounds **4(a-i)** were evaluated for their antibacterial activity against Gram-positive bacteria viz. B. subtilis, B. sphaericus and S. aureus and Gram-negative bacteria viz. P. aeruginosa, K. aerogenes and C. violaceum and also screened for their antifungal activity against four fungal organisms viz. C. Albicans, A. Fumigatus, T. rubrum and T. Mentagrophytes. Compounds **4b**, **4f** and **4h** showed higher activity towards the Gram-positive bacterial strains. Compounds **4d and 4g** showed good inhibition towards B. subtilis and S. aureus. The compounds **4e, 4h** and **4i** showed highest activity against all the fungal strains used.

KEYWORDS: Isoflavone, pyrimidine, Morpholine, Antibacterial Activity, Antifungal Activity.

I. INTRODUCTION

Isoflavones and its derivatives showed diverse biological activities particularly associated with anticancer activity[1] due to binding with oestrogen receptors which is related to the inhibition of cell cycle. The other activities include antifungal[2], antioxidant[3], neuroprotective[4], HIV-inhibitory[5] and antibacterial[6]. Isoflavone derivatives are also active at benzodiazepine receptors and on lipoxygenases and cyclooxygenases[7].

Pyrimidine ring is a core nucleus in naturally occurring compounds[8] including the nucleotides, thiamine and alloxan and also in many synthetic compounds such as barbiturates and the HIV drug, zidovudine. Pyrimidine ring also present in a number of useful drugs which are associated with many biological activities[9]. The derivatives of pyrimidine have been reported as antimicrobial[10], analgesic, antiviral, antiinflammatory[11], anti-HIV[12], antitubercular[13], antitumour[14], antineoplastic[15], antimalarial[16], diuretic[17], cardiovascular[18] agents. Similarly, incorporating the morpholine ring exhibited remarkable activities such as antibacterial, anticancer, antimalarial, anticonvulsant and analgesic[19]. In general, the compounds bearing morpholine moiety, exhibited better antibacterial and antifungal activities.

In view of these reports and in continuation of our ongoing research on the synthesis of new heterocyclic derivatives, it was thought of interest to accommodate isoflavone, pyrimidine and morpholine moieties in a single molecular frame work and to obtain new heterocyclic compounds with potential biological activity. We report herein the synthesis of new series of 6-fluoro-3-(2-morpholino-6-aryl-4-pyrimidinyl)-4H-4-chromenone **4(a-i)** by the reaction of 6-fluoro-3-[(E)-3-oxo-3-aryl-1-propenyl]-4H-4-chromenone **3(a-i)** with 4-morpholinecarboximidamide and evaluation of their antimicrobial activities.

II. EXPERIMENTATION (MATARIALS AND METHODS)

All reagents are commercial grade and were used as supplied. Reactions were monitored by thin-layer chromatography (TLC) on pre-coated silica gel F254 plates from Merck, and compounds visualized by exposure to UV light. Chromatographic columns 70–230 mesh silica gel for separations were used. IR spectra were recorded using KBr disk on a Perkin–Elmer FTIR spectrometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini spectrometer (300 MHz for ^{1}H and 75 MHz for ^{13}C). Chemical shifts are reported in δ ppm units with respect to TMS as internal standard and coupling constants (J) are reported in Hz units. Mass spectra were recorded on a VG micro mass 7070H spectrometer.

Synthesis of 6-fluoro-4-oxo-4H-3-chromenecarbaldehyde (2): A solution of 5-fluoro-2-hydroxyacetophenones **1** (0.01 mol) in DMF (6 mL) was cooled to 0 ^{o}C, then $POCl_3$ (0.04

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mol) was added gradually with constant stirring. The reaction mixture was then stirred at room temperature for 12 h, after completion of the reaction it was quenched with ice water (50 mL). The solid formed was filtered, dried and purified by recrystallization from ethanol to get pure compound **2** in 58% of yield; m.p. 156-158 ^{o}C. IR (KBr) ν_{max}: 3093 (CH-Ar), 1711 (HC=O), 1689 (C=O), 1262 (C-O-C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55-7.60 (m, 3H, ArH), 8.64 (s, 1H, 2-CH), 10.17 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$): δ 113.5, 116.7, 120.4, 122.6, 124.9, 155.3, 163.2, 169.1, 171.3, 186.1; MS: m/z 192 (M^+).

General procedure for the synthesis of 6-fluoro-3-[(E)-3-oxo-3-aryl-1-propenyl]-4H-4-chromenone 3(a-i): A solution of compound **2** (0.01 mol) and the corresponding arylmethylketone (0.01 mol) in ethanol (50 mL) was treated with pyridine (1 mL). The reaction mixture was refluxed for 8 h. After completion of the reaction it was cooled to room temperature, filtered the solid thus separated and washed with water and alcohol o afford corresponding pure compounds **3(a-i)** in 56-71% of yields.

6-fluoro-3-[(E)-3-oxo-3-phenyl-1-propenyl]-4H-4-chromenone (3a): Yield 61%, m.p. 279-281 ^{o}C; IR (KBr) ν_{max}: 3047, 1691, 1682, 1605, 1257 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 6.90 (m, 2H, ArH), 7.09 (d, J = 16.2 Hz, H, α-H), 7.40-7.50 (m, 6H, ArH), 7.74 (d, J = 16.2 Hz, 1H, β-H), 7.92 (s, 1H, C_2-H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 113.0, 114.7, 117.9, 121.0, 122.9, 125.9, 127.9, 129.0, 133.1, 135.3, 151.4, 152.2, 153.5, 162.1, 176.3, 188.0; MS: m/z 295 (M^+ +1).

6-fluoro-3-[(E)-3-(4-methoxyphenyl)-3-oxo-1-propenyl]-4H-4-chromenone (3b): Yield 59%, m.p. 267-269 ^{o}C; IR (KBr) ν_{max}: 3032, 1689, 1678, 1603, 1251, 1078 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.84 (s, 3H, OCH_3), 6.71 (d, 2H, J = 8.3 Hz, 2H, ArH), 7.05 (d, J = 16.2 Hz, H, α-H), 7.40-7.50 (m, 2H, ArH), 7.72 (d, J = 16.2 Hz, 1H, β-H), 7.91 (s, 1H, C_2-H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 56.6, 111.7, 113.2, 114.5, 117.2, 121.5, 122.8, 125.7, 129.6, 130.5, 151.1, 152.9, 153.6, 162.4, 163.8, 176.1, 187.8; MS: m/z 324 (M^+).

3-[(E)-3-(4-chlorophenyl)-3-oxo-1-propenyl]-6-fluoro-4H-4-chromenone (3c): Yield 66%, m.p. 282-284 ^{o}C; IR (KBr) ν_{max}: 3032, 1692, 1681, 1609, 1254, 658 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.04 (d, J = 16.2 Hz, H, α-H), 7.35-7.45 (m, 7H, ArH), 7.71 (d, J = 16.2 Hz, 1H, β-H), 7.93 (s, 1H, C_2-H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 113.3, 114.1, 117.3, 121.5, 122.2, 125.7, 127.0, 131.1, 134.9, 137.8, 151.4, 152.5, 153.9, 162.4, 176.1, 188.2; MS: m/z 328 (M^+).

3-[(E)-3-(2-chlorophenyl)-3-oxo-1-propenyl]-6-fluoro-4H-4-chromenone (3d): Yield 71%, m.p. 267-269 ^{o}C; IR (KBr) ν_{max}: 3039, 1688, 1672, 1609, 1252, 681 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.00-7.10 (m, 3H, α-H & ArH), 7.40-7.50 (m, 5H, ArH), 7.72 (d, J = 16.2 Hz, 1H, β-H), 7.94 (s, 1H, C_2-H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 112.9, 114.6, 117.2, 121.1, 122.8, 125.7, 126.7, 127.3, 128.9, 131.0, 134.0, 138.1, 151.1, 152.3, 153.0, 162.2, 176.1, 187.2; MS: m/z 328 (M^+ +1).

6-fluoro-3-[(E)-3-(4-nitrophenyl)-3-oxo-1-propenyl]-4H-4-chromenone (3e): Yield 61%, m.p. 291-292 ^{o}C; IR (KBr) ν_{max}: 3029, 1689, 1672, 1606, 1563, 1379, 1253 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.07 (d, J = 16.2 Hz, H, α-H), 7.40-7.50 (m, 5H, ArH), 7.70-7.75 (m, 3H, β-H & ArH), 7.90 (s, 1H, C_2-H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 112.8, 114.5, 117.1, 121.3, 122.6, 123.8, 125.8, 129.6, 142.0, 150.7, 151.4, 152.4, 153.7, 162.2, 175.4, 187.3; MS: m/z 340 (M^+ +1).

6-fluoro-3-[(E)-3-(3-nitrophenyl)-3-oxo-1-propenyl]-4H-4-chromenone (3f): Yield 59%, m.p. 269-271 ^{o}C; IR (KBr) ν_{max}: 3048, 1694, 1681, 1611, 1561, 1366, 1259 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.08 (d, J = 16.2 Hz, H, α-H), 7.40-7.50 (m, 4H, ArH), 7.75 (d, J = 16.2 Hz, 1H, β-H), 7.90-7.95 (m, 2H, C_2-H & ArH), 8.40-8.45 (m, 2H, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 113.8, 114.3, 117.5, 121.2, 122.6, 123.9, 125.7, 129.1, 133.4, 135.6, 136.9, 148.5, 151.3, 152.5, 153.7, 162.4, 175.7, 186.1; MS: m/z 339 (M^+).

3-[(E)-3-(4-bromophenyl)-3-oxo-1-propenyl]-6-fluoro-4H-4-chromenone (3g): Yield 60%, m.p. 291-293 ^{o}C; IR (KBr) ν_{max}: 3061, 1694, 1680, 1607, 1252 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.05 (d, J = 16.2 Hz, H, α-H), 7.40-7.50 (m, 7H, ArH), 7.71 (d, J = 16.2 Hz, 1H, β-H), 7.96 (s, 1H, C_2-H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 113.6, 114.2, 117.8, 121.2, 122.7, 125.7, 128.8, 130.2, 132.4, 138.1, 151.0, 152.6, 153.4, 162.4, 175.0, 187.3; MS: m/z 373 (M^+).

6-fluoro-3-[(E)-3-oxo-3-(2-pyridyl)-1-propenyl]-4H-4-chromenone (3h): Yield 62%, m.p. 251-253 ^{o}C; IR (KBr) ν_{max}: 3067, 1689, 1678, 1608, 1251

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cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 7.11 (d, J = 16.2 Hz, H, α-H), 7.40-7.50 (m, 4H, ArH), 7.70-7.75 (m, 3H, β-H & ArH), 7.89 (s, 1H, C_2-H), 8.41 (m, 1H, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 112.8, 113.5, 116.2, 121.7, 122.4, 125.6, 126.3, 131.5, 139.0, 148.7, 149.7, 151.3, 152.0, 154.6, 161.6, 175.0, 185.1; MS: m/z 296 (M^+ +1).

6-fluoro-3-[(E)-3-(2-furyl)-3-oxo-1-propenyl]-4H-4-chromenone (3i): Yield 56%, m.p. 267-269 ^oC; IR (KBr) ν_{max}: 3031, 1692, 1684, 1608, 1255, 1071 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 6.62 (m, 1H, ArH), 7.02 (d, J = 16.2 Hz, H, α-H), 7.40-7.50 (m, 5H, ArH), 7.69 (d, J = 16.2 Hz, 1H, β-H), 7.91 (s, 1H, C_2-H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 110.5, 111.4, 114.0, 124.8, 125.1, 125.8, 126.2, 129.0, 145.8, 146.1, 148.5, 151.0, 152.9, 163.0, 176.1, 178.9; MS: m/z 284 (M^+ +1).

General Procedure for the synthesis of 6-fluoro-3-(2-morpholino-6-aryl-4-pyrimidinyl)-4H-4-chromenone 4(a-i): A solution of corresponding compound **3(a-j)** (0.01 mol) and 4-morpholinecarboximidamide (0.01 mol) in ethanol (25 mL) was treated with 5 mL of aqueous NaOH (0.01 mol). The reaction mixture was refluxed. TLC (EtOAc: Petroleum-ether, 2:1) showed that the reaction was complete in 8 h. The reaction mixture was poured in 50 mL of 10% cold HCl solution and the precipitate was filtered, washed with water, until free from acid and on recrystallization from benzene-ethanol gave corresponding compounds **4(a-j)** in 47-63% of yields.

6-fluoro-3-(2-morpholino-6-phenyl-4-pyrimidinyl)-4H-4-chromenone (4a): Yield 49%, m.p. 242-244 ^oC; IR (KBr) ν_{max}: 3047, 1689, 1602, 1478, 1242 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 3.50-3.55 (m, 4H, morpholine-CH_2), 3.85-3.90 (m, 4H, morpholine-CH_2), 7.40-7.45 (m, 4H, ArH), 7.6-7.70 (m, 3H, ArH), 7.94 (s, 1H, C_2-H), 8.31 (d, J = 8.1 Hz, 2H, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 47.3, 66.9, 112.8, 114.7, 116.8, 123.1, 124.2, 125.0, 128.0, 130.6, 131.2, 136.1, 153.2, 155.0, 160.8, 161.8, 162.1, 173.6, 175.1; MS: m/z 404 (M^+ +1).

6-fluoro-3-[6-(4-methoxyphenyl)-2-morpholino-4-pyrimidinyl]-4H-4-chromenone (4b): Yield 51%, m.p. 246-248 ^oC; IR (KBr) ν_{max}: 3056, 1688, 1603, 1472, 1241, 1074 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 3.50-3.55 (m, 4H, morpholine-CH_2), 3.80-3.90 (m, 7H, morpholine-CH_2 & OCH_3), 7.19 (d, J = 8.4 Hz, 2H, ArH), 7.40-7.45 (m, 4H, ArH), 7.92 (s, 1H, C_2-H), 8.38 (d, J = 8.4 Hz, 2H, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 47.5, 56.7, 66.7, 112.6, 114.9, 115.6, 116.6, 123.2, 124.4, 125.0, 130.2, 139.8, 153.2, 155.0, 159.3, 161.8, 161.2, 162.1, 173.2, 175.0; MS: m/z 433 (M^+).

3-[6-(4-chlorophenyl)-2-morpholino-4-pyrimidinyl]-6-fluoro-4H-4-chromenone (4c): Yield 63%, m.p. 239-241 ^oC; IR (KBr) ν_{max}: 3072, 1688, 1603, 1473, 1240, 688 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 3.50-3.55 (m, 4H, morpholine-CH_2), 3.85-3.90 (m, 4H, morpholine-CH_2), 7.40-7.45 (m, 6H, ArH), 7.91 (s, 1H, C_2-H), 8.32 (d, J = 8.2 Hz, 2H, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 47.4, 65.7, 112.1, 114.3, 116.5, 123.4, 124.8, 125.1, 128.6, 132.0, 134.5, 138.1, 153.4, 155.1, 160.7, 161.6, 162.1, 172.8, 174.9; MS: m/z 437 (M^+).

3-[6-(2-chlorophenyl)-2-morpholino-4-pyrimidinyl]-6-fluoro-4H-4-chromenone (4d): Yield 52%, m.p. 252-254 ^oC; IR (KBr) ν_{max}: 3056, 1687, 1605, 1479, 1241, 689 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 3.50-3.55 (m, 4H, morpholine-CH_2), 3.85-3.90 (m, 4H, morpholine-CH_2), 7.21 (m, 1H, ArH), 7.40-7.45 (m, 5H, ArH), 7.85-7.90 (m, 2H, C_2-H & ArH), 8.18 (m, 1H, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 47.5, 66.6, 112.4, 114.6, 116.8, 123.2, 124.4, 125.9, 126.6, 130.3, 132.2, 133.2, 136.7, 140.9, 152.9, 155.3, 159.2, 161.1, 162.6, 173.3, 175.2; MS: m/z 438 (M^+ +1).

6-fluoro-3-[2-morpholino-6-(4-nitrophenyl)-4-pyrimidinyl]-4H-4-chromenone (4e): Yield 47%, m.p. 263-265 ^oC; IR (KBr) ν_{max}: 3039, 1687, 1607, 1562, 1479, 1346, 1240 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 3.50-3.55 (m, 4H, morpholine-CH_2), 3.85-3.90 (m, 4H, morpholine-CH_2), 7.40-7.45 (m, 4H, ArH), 7.90 (s, 1H, C_2-H), 3.32 (d, J = 8.7 Hz, 2H, ArH), 8.72 (d, J = 8.7 Hz, 2H, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 46.2, 66.4, 112.5, 114.2, 116.3, 123.4, 124.0, 124.7, 125.3, 132.3, 140.6, 149.1, 153.1, 155.5, 160.4, 161.3, 162.5, 172.8, 174.6; MS: m/z 448 (M^+).

6-fluoro-3-[2-morpholino-6-(3-nitrophenyl)-4-pyrimidinyl]-4H-4-chromenone (4f): Yield 58%, m.p. 255-257 ^oC; IR (KBr) ν_{max}: 3051, 1686, 1606, 1566, 1475, 1362, 1243 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 3.50-3.55 (m, 4H, morpholine-CH_2), 3.85-3.90 (m, 4H, morpholine-CH_2), 7.40-7.45 (m, 4H, ArH), 7.90-7.95 (m, 3H, C_2-H & ArH), 8.56 (d,

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J = 8.3 Hz, 1H, ArH), 8.72 (s, 1H, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 47.4, 66.6, 112.4, 114.8, 116.7, 119.0, 123.3, 124.4, 125.7, 126.0, 131.5, 132.4, 138.0, 147.9, 153.1, 155.4, 160.9, 161.6, 162.7, 173.0, 175.4; MS: m/z 448 (M^+).

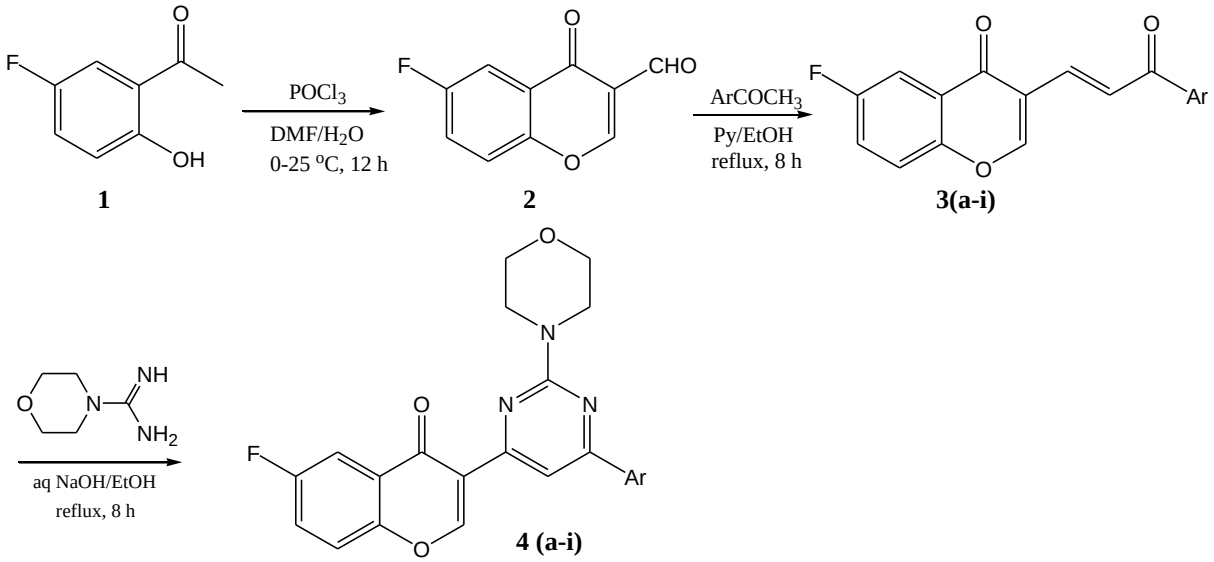
3-[6-(4-bromophenyl)-2-morpholino-4-pyrimidinyl]-6-fluoro-4H-4-chromenone (4g): Yield 55%, m.p. 282-284 ^{o}C; IR (KBr) ν_{max}: 3061, 1688, 1603, 1481, 1239, 593 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.50-3.55 (m, 4H, morpholine-CH_2), 3.85-3.90 (m, 4H, morpholine-CH_2), 7.40-7.45 (m, 4H, ArH), 7.85-7.90 (m, 3H, C_2-H & ArH), 8.17 (d, J = 8.0 Hz, 2H, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 47.0, 66.4, 112.2, 114.5, 116.6, 123.4, 124.3, 125.7, 131.3, 134.0, 136.2, 142.1, 152.8, 155.6, 159.4, 161.1, 162.4, 172.9, 175.7; MS: m/z 482 (M^+).

6-fluoro-3-[2-morpholino-6-(2-pyridyl)-4-pyrimidinyl]-4H-4-chromenone (4h): Yield 53%, m.p. 238-240 ^{o}C; IR (KBr) ν_{max}: 3046, 1691, 1611, 1468, 1241 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.50-3.60 (m, 4H, morpholine-CH_2), 3.85-3.90 (m, 4H, morpholine-CH_2), 7.10 (m, 1H, ArH), 7.40-7.45 (m, 4H, ArH), 7,89 (m, 1H, ArH), 8.85-8.90 (m, 2H, C_2-H & ArH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 47.7, 66.4, 112.5, 114.6, 116.1, 120.9, 123.0, 124.4, 124.9, 125.3, 135.8, 148.7, 153.0, 155.5, 158.1, 160.2, 161.3, 162.4, 173.0, 175.3; MS: m/z 404 (M^+ +1).

6-fluoro-3-[6-(2-furyl)-2-morpholino-4-pyrimidinyl]-4H-4-chromenone (4i): Yield 57%, m.p. 229-231 ^{o}C; IR (KBr) ν_{max}: 3059, 1687, 1607, 1472, 1244, 1061 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.50-3.55 (m, 4H, morpholine-CH_2), 3.85-3.90 (m, 4H, morpholine-CH_2), 6.20 (m, 1H, ArH), 7.00-7.10 (m, 2H, ArH), 7.40-7.45 (m, 4H, ArH), 7.97 (s, 1H, C_2-H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 48.7, 69.1, 107.7, 113.1, 116.5, 118.3, 122.9, 123.7, 124.1, 125.3, 147.7, 152.9, 153.1, 155.1, 160.2, 161.4, 164.3, 165.2, 171.1; MS: m/z 393 (M^+).

III. RESULTS AND DISCUSSION

The 6-fluoro-4-oxo-4H-3-chromenecarbaldehyde **2** was prepared according to the procedure reported in the literature[20] by cyclo-condensation of 5-fluoro-2-hydroxyaceto-phenone **1** with DMF in the presence of phosphorous oxychloride under stirring at room temperature for 12 h, gave compound **2** in 58% of yield, which was further reacted with corresponding arylmethylketone in the presence of pyridine in ethanol under reflux for 8 h to afford corresponding 6-fluoro-3-[(E)-3-oxo-3-aryl-1-propenyl]-4H-4-chromenone **3(a-i)** in 56-71% of yields[21]. Compounds **3(a-i)** on cyclo-condensation with 4-morpholinecarboximid- amide in ethanol in the presence of sodium hydroxide to afford the corresponding compounds 6-fluoro-3-(2-morpholino-6-aryl-4-pyrimidinyl)-4H-4-chromenone **4(a-i)** in 47-63% of yields (**Scheme 1**). The structures of all the newly synthesized compounds were confirmed by their EI mass, IR, ^{1}H NMR and ^{13}C NMR spectral data.



3/4: Ar = a) phenyl; b) 4-methoxyphenyl; c) 4-chlorophenyl; d) 2-chlorophenyl; e) 4-nitrophenyl;

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f) 3-nitrophenyl; g) 4-bromophenyl; h) 2-pyridyl; i) 2-furyl

Scheme 1

The IR spectrum of compound **2**, the formyl (C=O) appeared at 1711 and (C=O) of chromone ring, the skeletal stretching of (C-O-C) observed at 1689 and 1262 cm^{-1}. Its proton NMR spectrum, the formyl proton and proton of C-2 of chromone ring appeared at δ 10.17 as singlet and 8.64 ppm as singlet for C-2 proton, the aryl proton signals appeared as multiplet at δ 7.55-7.60 ppm. Its ^{13}C NMR spectrum, the signals of carbons of chromone ring appeared at δ 171.3 (C2), 116.7 (C3), 171.3 (C4), 122.6 (C5a) and 155.3 (C5b) and formyl carbon of appeared at δ 186.1 ppm.

The IR spectrum of **3a** displayed stretching bands for carbonyl (C=O) group of chromone at 1691, α,β-unsaturated carbonyl (C=O) group at 1682 and unsaturated alkene (C=C) group at 1605 cm^{-1}. Its ^{1}H NMR spectrum, displayed two doublets at δ 7.09 for α-proton and 7.74 ppm for β-proton with the coupling constant J = 16.2 Hz. The proton of C-2 appeared at δ 7.92 ppm as singlet and the other aromatic protons appeared at δ 6.90, 7.40-7.50 ppm as multiplets. Its ^{13}C NMR spectrum, showed signals at δ 153.5 (C2), 114.7 (C3), 176.3 (C4), 125.9 (C5a) and 152.2 (C5b) carbons of chromone ring. The other α-carbon, β-carbon and α,β-unsaturated carbonyl carbon signals appeared at δ 151.4, 117.9 and 188.0 ppm respectively. Its mass spectrum displayed a molecular ion peak at m/z: 295 which confirmed its molecular weight.

The IR spectrum of **4a** displayed stretching bands for carbonyl (C=O) group of chromone at 1689, and unsaturated alkene (C=C) group at 1602 cm^{-1}. Its ^{1}H NMR spectrum, displayed two multiplets at δ 3.50-3.55 and 3.85-3.90 ppm for morpholine ring protons. The proton of C-2 appeared at δ 7.94 ppm as singlet and the other aromatic protons appeared at δ 7.40-7.45 and 7.60-7.70 ppm as multiplets. Its ^{13}C NMR spectrum, showed signals at δ 160.8 (C2), 116.8 (C3), 173.6 (C4), 125.0 (C5a) and 153.2 (C5b) carbons of flavone ring. The pyrimidine carbon signals appeared at δ 155.0 (C2), 175.1 (C4), 114.7 (C5) and 161.8 (C5) ppm. Its mass spectrum displayed a molecular ion peak at m/z: 403 which confirmed its molecular weight.

ANTIBACTERIAL ACTIVITY

All the newly synthesized compounds **4(a-i)** were screened for their antibacterial activity against Gram-positive bacteria viz. Bacillus subtilis, Bacillus sphaericus and Staphylococcus aureus and Gram-negative bacteria viz. Pseudomonas aeruginosa, Klobsinella aerogenes and Chromobacterium violaceum by disc diffusion method[22]. The inhibition zones were measured at 100 µg/mL and compared with the standard drug streptomycin (**Table 1**).

The antibacterial screening indicated that all the synthesized compounds **4(a-i)** showed moderate to good inhibition towards all the tested organisms. Compounds which contain 4-methoxyphenyl (**4b**), 3-nitrophenyl (**4f**) and 2-pyridine (**4h**) substituent on pyrimidine ring showed higher activity towards the Gram-positive bacterial strains. Compounds containing 2-chlorophenyl (**4d**) and 4-bromophenyl (**4g**) substituent showed good inhibition towards B. subtilis and S. aureus. Compounds containing 4-chlorophenyl (**4c**) substituent showed considerable activity against P. aerugnosa and K. aerognosa where as compound **4f** showed good activity against C. violacium.

Table 1: Antibacterial activity of compounds **4(a-i)**

Compound	Zone of inhibition (mm) at 100 µg/mL					
	B. subtilis	**B. sphaericus**	**S. aureus**	**P. aeruginosa**	**K. aerogenes**	**C. violaceum**
4a	10	11	9	8	10	13
4b	23	22	24	10	14	11
4c	13	14	13	18	16	15
4d	19	12	14	11	8	7
4e	11	10	15	12	10	8
4f	21	20	22	13	11	21
4g	9	8	20	9	8	8

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4h	23	19	21	10	10	8
4i	15	12	13	14	8	10
Streptomycin	25	30	30	30	25	30

ANTIFUNGAL ACTIVITY

The prepared compounds **4(a-i)** were also evaluated in vitro antifungal activity against four fungi viz. Candida albicans, Aspergillus fumigatus, Trichophyton rubrum and Trichophyton mentagrophytes by agar diffusion method.[22] The inhibition zones were determined at 100 µg/mL and compared with the standards drug Amphotericin B (**Table 2**). The antifungal activity of compounds **4(a-i)** showed that most of the compounds were showed moderate to good activity. The compounds with 4-nitrophenyl (**4e),** 2-pyridine (**4h**) and 2-furyl (**4i**) substituents, showed highest activity against all the fungal strains used.

Table 2. Antifungal activity of compounds **4(a-i)**

Compound	Zone of inhibition (mm) at 100 µg/mL			
	C. albicans	A. fumigatus	T. rubrum	T.
4a	14	12	9	12
4b	16	10	9	10
4c	9	9	10	7
4d	11	13	8	10
4e	22	18	20	16
4f	13	12	11	11
4g	8	14	11	12
4h	23	21	19	19
4i	20	18	19	18
Amphotericin B	30	30	25	25

IV. CONCLUSION

A new series of 6-fluoro-3-(2-morpholino-6-aryl-4-pyrimidinyl)-4H-4-chromenone **4(a-i)** were synthesized by the reaction of 6-fluoro-3-[(E)-3-oxo-3-aryl-1-propenyl]-4H-4-chromenone **3(a-i)** with 4-morpholinecarboximidamide. The compounds **4(a-i)** were evaluated for their antibacterial activity against Gram-positive bacteria viz. B. subtilis, B. sphaericus and S. aureus and Gram-negative bacteria viz. P. aeruginosa, K. aerogenes and C. violaceum and also screened for their antifungal activity against four fungal organisms viz. C. Albicans, A. Fumigatus, T. rubrum and T. Mentagrophytes. Compounds **4b**, **4f** and **4h** showed higher activity towards the Gram-positive bacterial strains. Compounds **4d and 4g** showed good inhibition towards B. subtilis and S. aureus. The compounds **4e, 4h** and **4i** showed highest activity against all the fungal strains used.

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REFERENCES

[1]. Valenti, P., Bisi, A., Rampa, A., Belluti, F., Gobbi, S., Zampiron, A., & Carrara, M. 2000, "Synthesis and biological activity of some rigid analogues of flavone-8-acetic acid" Bioorg. Med. Chem. 8, 239-246.

[2]. Prakash, O., Kumar, R., & Prakash V. 2008, "Synthesis and antifungal activity of some new 3-hydroxy-2-(1-phenyl-3-aryl-4-pyrazolyl)chromones" Eur. J. Med. Chem. 43, 435-440.

[3]. Kuroda, M., Uchida, S., Watanabe, K., & Mimaki Y. 2009, "Chromones from the

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 909-915 www.ijprajournal.com ISSN: 2249-7781

tubers of Eranthis cilicica and their antioxidant activity" Phytochemistry, 70, 288-293.

[4]. Larget, R., Lockhart, B., Renard, P., & Largeron, M. 2000, "A convenient extension of the Wessely-Moser rearrangement for the synthesis of substituted alkyl amino flavones as neuroprotective agents in vitro" Bioorg. Med. Chem. Lett. 10(8), 835-838.

[5]. Yu, D., Chen, C. H., Brossi, A., & Lee, K. H. 2004, "Anti-AIDS agents 60. Substituted 30R,40R-Di-O-(-)-camphanoyl-20,20-dimethyldihydropyrano[2,3-f]chromone (DCP) analogues as potent anti-HIV agents" J. Med. Chem. 47, 4072-4082.

[6]. Deng, Y., Lee, J.P., Ramamonjy, M.T., Snyder, J. K., Etages, S. A., Kanada, D., Snyder, M. P. & Turner C. J. 2000, "New antimicrobial flavanones from Physena madagascariensis" J. Nat. Prod. 63, 1082-1089.

[7]. Horton, D. A., Bourne, G. T., & Smythe, M. L. 2003, "The combinatorial synthesis of bicyclic privileged structures or privileged substructures" Chem. Rev. 103, 893-930.

[8]. Lagoja, I. M.. 2007, "Pyrimidine as constituent of natural biologically active compounds". Chem. Biodiver. 2(1), 1-50.

[9]. Patil, S. B. 208, "Biological and medicinal significance of pyrimidines: A review" Int. J. Pharm. Sci. Res. 9(1), 44-52.

[10]. Mangalagiu, I., Ungureanu, M., Mangalagiu, G., Grosu, G., & Petrovanu, M. 1998, "Antimicrobial activity of some derivatives of pyrimidine" Ann. Pharm. Fr. 56(4), 181-183.

[11]. Amir, M., Javed, S. A., & Harish Kumar, 2007, "Pyrimidine as anti-inflammatory agent: A review" Indian J. Pharm. Sci. 69(3), 337-343.

[12]. Fujiwara, N., Nakajima, T., Ueda, Y., Fujita, H., & Kawakami, H. 2008, "Novel piperidinylpyrimidine derivatives as inhibitors of HIV-1 LTR activation" Bioorg. Med. Chem. 16, 9804-9816.

[13]. Ballell, L., Field, R.A., Chung, G.A.C., & Young, R.J. 2007, "New thiopyrazolo[3,4-d]pyrimidine derivatives as anti-mycobacterial agents" Bioorg. Med. Chem. Lett. 17, 1736-1740.

[14]. Wagner, E., Al-Kadasi, K., Zimecki, M., & Sawka-Dobrowolska, W. 2008, "Synthesis and pharmacological screening of derivatives of isoxazolo[4,5-d]pyrimidine" Eur. J. Med. Chem. 43, 2498-2504.

[15]. Cordeu, L., Cubedo, E., Bandres, E., Rebollo, A., Saenz, X., Chozas, H., Victoria Domínguez, M., Echeverria, M., Mendivil, B., & Sanmartin, C. 2007, "Biological profile of new apoptotic agents based on 2,4-pyrido[2,3-d]pyrimidine derivatives" Bioorg. Med. Chem. 15, 1659-1669.

[16]. Gorlitzer, K., Herbig, S., & Walter, R. D. 1997, "Indenopyrimidin-4-yl-amines" Pharmazie, 52, 670-672.

[17]. Ukrainets, I. V., Tugaibei, I. A., Bereznykova, N. L., Karvechenko, V. N., & Turov, A.V. 2008, "4-Hydroxy-2-quinolones 144*. alkyl-, arylalkyl-, and arylamides of 2-hydroxy-4-oxo4H-pyrido[1,2-a]pyrimidine3-carboxylic acid and their diuretic properties" Chem. Heterocycl. Comp. 5, 565-575.

[18]. Rusinov, V. L., Pilicheva, T. L., Chupakhin, O. N., Kovalev, G. V., & Komina, E. R. 1986 "Cardiovascular activity of nitro derivatives of azolo[1,5-a]pyrimidine" Pharm. Chem. J. 20, 550-554

[19]. Priya, G. R., Pannerselvam, Karikaln, 2011, "Synthesis, characterisation and antibacterial, antifungal activities of Schiff bases of 4-(2-aminphenyl)morpholines" Int. J. Pharm. Bio. Sci. 2(1), 267-272.

[20]. Allen, T., Gordon, Isaiah, D. I., Ramaite, & Simon. S. Mnyakeni, M. 2020, "Synthesis and biological evaluation of chromone-3-carboxamides" Arkivoc, part v, 148-160.

[21]. Musthafa, T. N. M., Siddiqui, Z. N., Husain, F. M., Ahmad, I. 2011, "Microwave-assisted solvent-free synthesis of biologically active novel heterocycles from 3-formylchromones" Med. Chem. Res. 20, 1473-1481.

[22]. H. W. Seely, D. P. J. Van, Microbes in action: A laboratory manual of microbiology, D. B. Taraporevala Sons & Co Pvt. Ltd. Bombay, 1975, pp. 55.