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Synthesis and characterization of some novel chromones and chromanones derivatives and its biological screening

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ABSTRACT

Novel (3E)-3-[[4-(Aryl or Alkyl sulfonyl, Aryl carbonyl and Heteroaryl) piperazin-1-yl] methylene] chroman-4-one and N-[1-(Aryl or Alkyl sulfonyl, Aryl carbonyl and Heteroaryl) -4-piperidyl]-6-methyl-4-oxo-chromene-3-carboxamide were synthesized and identified by spectroscopic techniques like NMR, IR, MS and elemental analysis. Antibacterial study of the same derivatives were done using bacterial model like E. coli, P.aeruginosa, S. aureus, and S.Pyogenus and antifungal study of the same were carried out using Candida albicans, A. Niger and A.Clavatus. Results show that the compound having 3-chloropropane sulfonyl type linkage has shown good activity against the bacterial strains, while some of the derivatives have shown moderate improvement in activity against pathogenic strains.

Keywords: Chromones, Chromanones, Biological activity, BOC-anhydride, EDC, HOBT.

INTRODUCTION

Chromones and other related ring systems, have several interesting biological activities. According to the literature survey, chromone compounds are associated with various physiological and biological properties and thus, find important use in medicine.

A series of sulfonamide derived chromones, previously reported as inhibitors of carbonic anhydrase, have been reported to show in vitro antibacterial and antifungal activity[1]. 4-chromanone derivative have been reported to show Antibacterial activity[2-3]. Substituted 4-chromanone and chroman-2-carboxamide derivative possess antioxidant activity[4]. Soraphane and moiramide B are known ACC inhibitors, exhibit an antibacterial effect and an antifungal effect via growth inhibition [5-7]. Chromones having heterocyclic substituent's at 2- position have been reported to possess anti-bacterial and antifungal activities and also found to exhibit good

phosphodiesterase-IV inhibition activity and some chromones have potential HIV-integrase inhibition activity[8] as well as Spiro amine derivatives having antiarrythmic activity [9-12].

MATERIALS AND METHODS

Experimental

Melting points are uncorrected. IR Spectra were recorded on a Perkin-Elmer spectrum RXI (4000-450 cm^{-1}) FTIR Spectrometer.1H NMR were obtained on Bruker DRX-400(400 MHz FT NMR) NMR spectrometer for sample in DMSO-d6 with TMS as an internal reference. The mass spectra were recorded on water-2996 LCMS instruments. The solvent were purchased from commercial grade and reagents were purchased from Sigma-Aldrich, Lancastor and Alfa-Aesar.
In present work, Oxidation of chroman-3-carboaldehyde was carried out by careful addition of sodium chlorite solution in water into the mixture of aldehyde **1** and sulfamic acid in methylene chloride at 0°C. Amide formation of acid **2** and N-BOC-4-aminopiperidine was successfully done in THF using EDC and HOBT. BOC protection of compound **3** was removed in methylene chloride using TFA at RT. Condensation of Aryl sulfonyl chloride, Aryl carbonyl chloride and Heteroaryl chloride with compound **4** was carried out using various bases like TEA(for Aryl sulfonyl chloride), K_2CO_3 (for Aryl carbonyl chloride), and DIEA(Heteroaryl chloride) respectively produce compound **5a-j** [**Scheme-1**].

[**Scheme-1**]

Compound **7** was synthesized by DMFDMA condensation reaction reported in literature[13-14]. Compound **7** was heated with BOC-piperazine without any base gives directly substituted product **8**. BOC deprotection was carried out using trifluoroacetic acid in methylene chloride produce TFA salt of amine **9**. Coupling reaction of amine **9** was done using various basic conditions like, sulfonyl chloride condensation was performed in THF using TEA as base, carbonyl chloride condensation was done in THF using K_2CO_3 as base, Heteroaryl condensation was carried out in THF using DIEA as base[**Scheme-2**].

[**Scheme-2**]

The structures of the compound **5** and **10** are confirmed by spectral techniques (MS, IR and ^1H NMR). In ^1H NMR of compound **5** all aromatic protons resonate between 8.5 δ to 6.85 δ in addition -O-C**H**- & three -C**H**- of chromene ring resonate near 8.4 δ, 7.7 δ, 7.4 δ and 7.1 δ, methylene proton of –N (CH_2)$_2$- resonate near 3.8 δ & 2.6 δ as a multiplates, –N (CH_2-CH_2-)$_2$- resonate near 2.1 δ &1.9 δ as a multiplates, –C**H**- of piperidine ring resonates near 3.4 δ as a multiplates, aromatic –CH_3 resonate near 2.4 δ as a singlet and IR stretching band of Ar-**CO**- absorption observe near 1693 cm^{-1}. -N–**SO**$_2$- absorption observes near 1334 cm^{-1} and 1159 cm^{-1}. Ether linkage of chromone ring resonates near 1251 cm^{-1} and 1152 cm^{-1}. In ^1H NMR of compound **10** all aromatic protons resonate between 8.5 to 6.85 δ in addition four aromatic -C**H**- of chromone ring resonate between 7.35-7.7 δ in the form of two triplets and two doublets, –C**H**- of exocyclic double bond resonate near 8.0 δ as a doublet, piperazine proton resonate as triplets near 3.6 δ & 2.6 δ with each signal having 4H, methylene proton of chromanone ring resonate near 3.5 δ as a singlet and IR stretching band of Ar-**CO**- and -**CO**NH-absorption observe near 1710 cm^{-1} and 1677 cm^{-1} respectively. -N–**SO**$_2$- absorption observes near 1339 cm^{-1} and 1168 cm^{-1}. Ether linkage of chromone ring resonates near 1279 cm^{-1} and 1155 cm^{-1}.

General procedure

6-methyl-4-oxo-4*H*-chromene-3-carboxylic acid (2).

A mixture 6-methyl- 4-oxo-chromene-3-carboxaldehyde (5 gm, 1.0 M) and sulfamic acid (10.21 gm, 4.0 M) in MDC (25 ml) was cool to 0 – 5 ^{o} C. A solution of Sodium Chlorite (8.33 gm, 3.5 M) in 15 ml water was added drop wise between 0 – 5^{o} C. Reaction mass was stirred for 3 hr at room temperature. Progress of reaction was monitored by TLC. Water (100 ml) was added after completion of reaction and product was extracted with methylene chloride (200 ml). Organic layer was dried over Na_2SO_4 and solvent was removed under reduce pressure gave 4.6 gm 4-oxo-4*H*-chromene-3-carboxylic acid as off white solid.

Tert-butyl 4-[(6-methyl-4-oxochromene-3-carbonyl) amino] piperidine-1-carboxylate (3).

A mixture of 4-oxo-4*H*-chromene-3-carboxylic acid (3.8gm, 0.018M) and N-Boc-4-aminopiperidine (3.91gm, 0.019M) in methylene chloride (50 ml) was stirred at room temperature. 4-dimethylaminopyridine (454.0mg), triethylamine (2.16ml, 0.022M) and N-ethyl-N'- dimethylaminopropylcarbodiimide (4.6gm, 0.024) was added sequentially. Progress of reaction was monitored by TLC. Water (100 ml) was added after completion of reaction and product was extracted using methylene chloride. Methylene chloride was dried over Na_2SO_4 and solvent was removed under reduced pressure gave 6.9 gm tert-butyl 4-[(4-oxochromene-3-carbonyl) amino] piperidine-1-carboxylate as a semisolid mass.

6-methyl-4-oxo-N-(4-piperidyl) chromene-3-carboxamide TFA Salt (4).

A solution of *tert*-butyl 4-[(E)-(4-oxochroman-3-ylidene) methyl] piperazine-1-carboxylate (6.9 gm) in MDC (25ml) was added drop wise into dried and cooled solution of trifluoroacetic acid (14 ml) in MDC (25 ml). Mixture was stirred for 12 hr at room temperature. Trifluoroacetic acid was removed under reduced pressure. Residual mass was further diluted with THF (100 ml) and concentrated to dryness. Residue was stirred with Diethyl ether (25 ml) and separated solid was filtered off, washed with diethyl ether (10 ml) and dried under reduced pressure to obtain 5.4 gm white solid.

General procedure for synthesis of N-[1-(Aryl or Alkyl sulfonyl, Aryl carbonyl and Heteroaryl)-4-piperidyl]-6-methyl-4-oxo-chromene-3-carboxamide (5a-j).

6-methyl-4-oxo-N-(4-piperidyl) chromene-3-carboxamide TFA salt (0.75M) was charged in 20 ml dichloromethane. Base (1.88 M) and aryl sulfonyl chloride or Aryl carbonyl chloride or heteroaryl chloride (0.9M) was added sequentially at room temperature. Progress of reaction was monitored by TLC. After completion of reaction, solvent was evaporated and residual mass was stirred with saturated solution of $NaHCO_3$ (20ml) and stirred for 2 hr. Solid was filtered off and washed with water (10 ml). Solid was dried under vacuum to obtain crude product as an off white solid. The crude product was purified on a silica gel column, packed in hexane. Column was eluted using Hexane: Ethyl acetate (80: 20 v/v) gave the pure compound **5a-j** as white solid.

Spectroscopic and analytical data

N-[1-[4-(difluoromethyl)phenyl]sulfonyl-4-piperidyl]-6-methyl-4-oxo-chromene-3-carboxamide (5a).

Yield: 74 %; m.p.: 245-247 °C; IR (KBr, cm^{-1}): 3310, 1710, 1677, 1339, 1279, 1168, 1155 cm^{-1}. 1H-NMR (400 MHz, DMSO-d6, δ / ppm): 11.99(1H, *s*, -CO-N**H**-) 8.38 (1H, *d*, Chr.), 7.86-7.76 (3H, m, -C**H**- of Chr. & 2-C**H**- Ar), 7.38-7.36 (1H, *dd*, Chr.), 7.30 (2H, *d*, Ar), 7.14-7.11(1H, m, Chr.), 6.63(1H, *s*, -C**H**F_2), 3.80-3.77(2H, m, -NC**H**$_2$- pipe.), 3.47-3.41(1H, m, -C**H**- of pipe.),

2.63-2.57(2H, *t*, -NC**H**$_2$-), 2.39(3H, s, Ar-C**H**$_3$), 2.15-2.12(2H, m, -C**H**$_2$- pipe.), 1.94-1.86(2H, m, -C**H**$_2$- pipe.); MS (m/z): 475(M-1); Anal. Calcd. for $C_{23}H_{22}F_2N_2O_5S$: C, 57.97; H, 4.65;N; 5.88 %. Found: C, 58.08; H, 4.71; N, 5.96 %.

N-[1-(2-chloro-4-fluoro-phenyl)sulfonyl-4-piperidyl]-6-methyl-4-oxo-chromene-3-carboxamide (5b).
Yield: 68 %; m.p.: 187-189 °C; IR (KBr, cm^{-1}): 3315, 1709, 1678, 1337, 1279, 1166, 1157 cm^{-1}. 1H-NMR (400 MHz, DMSO-d6, δ / ppm): 11.66(1H, s, -CO-N**H**-), 8.46 (1H, *d*, Chr.), 8.08-8.05 (1H, m, Ar), 7.81-7.78 (1H, *m*, Chr.), 7.72(1H, *d*, Ar), 7.47-7.46 (2H, *d*, -CH- of Ar & -CH- of Chr.), 7.22-7.17(1H, m, Chr.), 3.80-3.71(2H, *m*, -NC**H**$_2$-), 3.49-3.43(1H, m, -C**H**- of pipe.) 2.89-2.2.73(2H, *m*, -NC**H**$_2$-), 2.36(3H, *s*, Ar-C**H**$_3$), 2.03-1.96 (2H, m, -C**H**$_2$- pipe.), 1.90-1.79(2H, m, -C**H**$_2$- pipe.); MS (m/z): 478.7(M+1); Anal. Calcd. for $C_{22}H_{20}ClFN_2O_5S$: C, 55.17; H, 4.21; N; 5.85 %. Found: C, 55.09; H, 4.29; N, 5.79 %.

N-[1-(3-cyano-4-fluoro-phenyl)sulfonyl-4-piperidyl]-6-methyl-4-oxo-chromene-3-carboxamide (5c).
Yield: 62 %; m.p.: 160-162 °C; IR (KBr, cm^{-1}): 3308, 2235, 1708, 1676, 1337, 1277, 1169, 1157 cm^{-1}. 1H-NMR (400 MHz, DMSO-d6, δ / ppm): 12.03(1H, *s*, -CO-N**H**-)), 8.39 (1H, *d*, Chr.), 7.86 (1H, *s*, Ar), 7.78 (1H, *s*, Chr.),7.58 (1H, *d*, Ar), 7.38-7.35 (1H, *dd*, Chr.), 7.31 (1H, *d*, Ar), 7.17-7.12(1H, *m*, Chr.), 3.79-3.76(2H, *m*, -NC**H**$_2$- pipe.), 3.49-3.43(1H, *m*, -C**H**- of pipe.), 2.63-2.57(2H, *t*, -NC**H**$_2$-), 2.38(3H, *s*, Ar-C**H**$_3$), 2.16-2.14(2H, *m*, -C**H**$_2$- pipe.), 1.96-1.88(2H, *m*, -C**H**$_2$- pipe.); MS (m/z): 467.9 (M-1); Anal. Calcd. for $C_{23}H_{20}FN_3O_5S$: C, 58.84; H, 4.29;N; 8.95 %. Found: C, 58.79; H, 4.13; N, 8.77 %.

N-[1-[(5-bromo-6-chloro-3-pyridyl)sulfonyl]-4-piperidyl]-6-methyl-4-oxo-chromene-3-carboxamide (5d).
Yield: 69 %; m.p.: 260-262 °C; IR (KBr, cm^{-1}): 3310, 1710, 1679, 1340, 1277, 1168, 1156 cm^{-1}. 1H-NMR (400 MHz, DMSO-d6, δ / ppm): 12.03(1H, *s*, -CO-N**H**-), 8.70-8.69(1H, m, -CH- of py.), 8.39 (1H, *d*, Chr.), 8.28-8.27 (1H, m, -C**H**- py.), 7.79-7.75 (1H, *t*, Chr.), 7.40-7.35 (1H, *d*, Chr.), 7.14-7.11(1H, *t*, Chr.), 3.90-3.84(2H, m, -NC**H**$_2$- pipe.), 3.51-3.45(1H, m, -C**H**- of pipe.), 2.77-2.70(2H, *t*, -NC**H**$_2$-), 2.40(3H, s, Ar-C**H**$_3$), 2.21-2.16(2H, m, -C**H**$_2$- pipe.), 1.98-1.88(2H, m, -C**H**$_2$- pipe.); MS (m/z): 539.9(M-1); Anal. Calcd. for $C_{21}H_{19}BrClN_3O_5S$: C, 46.64; H, 3.54;N; 7.77 %. Found: C, 46.43; H, 3.48; N, 7.61 %.

N-[1-[(6-chloro-3-pyridyl)sulfonyl]-4-piperidyl]-6-methyl-4-oxo-chromene-3-carboxamide (5e).
Yield: 72 %; m.p.: 279-281 °C; IR (KBr, cm^{-1}): 3307, 1708, 1678, 1336, 1276, 1165, 1159 cm^{-1}. 1H-NMR (400 MHz, DMSO-d6, δ / ppm): 12.03(1H, *s*, -CO-N**H**-), 8.73-8.71(1H, *m*, -CH- of py.), 8.37 (1H, *d*, Chr.), 8.28-8.27(1H, *dd*, -C**H**- py.), 7.78-7.71(2H, *m*, -C**H**- py. & -CH- of Chr.), 7.38-7.34(1H, *m*, Chr.), 7.17-7.13(1H, *m*, Chr.), 3.87-3.82(2H, *m*, -NC**H**$_2$- pipe.), 3.46-3.40(1H, *m*, -C**H**- of pipe.), 2.79-2.71(2H, *t*, -NC**H**$_2$-), 2.39(3H, *s*, Ar-C**H**$_3$), 2.20-2.15(2H, *m*, -C**H**$_2$- pipe.), 1.97-1.88(2H, *m*, -C**H**$_2$- pipe.);MS (m/z): 460.0(M-1); Anal. Calcd. for $C_{21}H_{20}ClN_3O_5S$: C, 54.60; H, 4.36; N, 9.10 %. Found: C, 54.69; H, 4.34; N, 9.06 %.

N-[1-[(6-chloro-4-methyl-3-pyridyl)sulfonyl]-4-piperidyl]-6-methyl-4-oxo-chromene-3-carboxamide (5f).
Yield: 67 %; m.p.: 206-208 °C; IR (KBr, cm^{-1}): 3312, 1710, 1679, 1339, 1278, 1170, 1158 cm^{-1}. 1H-NMR (400 MHz, DMSO-d6, δ / ppm): 11.63(1H, *s*, -CO-N**H**-), 8.73 (1H, *s*, py.), 8.45 (1H, *d*, Chr.), 7.77 (1H, *s*, py.), 7.73-7.69 (1H, *m*, Chr.), 7.48-7.46 (1H, *m*, Chr.), 7.22-7.17(1H, *m*, Chr.), 3.80-3.69(3H, *m*, -C**H**- of pipe.& -NC**H**$_2$-), 2.82-2.73(2H, *m*, -NC**H**$_2$-), 2.60(3H, *s*, Py-

C**H**$_3$), 2.36(3H, *s*, Ar-C**H**$_3$), 2.02-1.96 (2H, m, -C**H**$_2$- pipe.), 1.89-1.83(2H, m, -C**H**$_2$- pipe.); MS (m/z): 473.9(M-2), 476(M-); Anal. Calcd. for $C_{22}H_{22}ClN_3O_5S$: C, 55.52; H, 4.66; N; 8.83 %. Found: C, 55.73; H, 4.72; N, 8.99 %.

N-[1-(3-bromo-4-methoxy-benzoyl)-4-piperidyl]-6-methyl-4-oxo-chromene-3-carboxamide (5g).
Yield: 78 %; m.p.: 179-181 °C; IR (KBr, cm^{-}): 3310, 1708, 1678, 1337, 1278, 1167, 1157 cm^{-1}. 1H-NMR (400 MHz, DMSO-d6, δ / ppm): 12.05(1H, s, -CO-N**H**-), 8.38 (1H, *d*, Chr.), 8.33-8.29 (1H, s, Ar), 7.78-7.76 (1H, *m*, Chr.), 7.69(1H, *d*, Ar), 7.47-7.46 (1H, *d*, Chr.), 7.26-7.24(1H, d, Ar), 7.22-7.17(1H, m, Chr.), 3.89(3H, s, -OC**H**$_3$), 3.81-3.72(2H, *m*, -NC**H**$_2$-),3.46-3.40(1H, *m*, -C**H**- of pipe.), 2.89-2.74(2H, *m*, -NC**H**$_2$-), 2.38(3H, *s*, Ar-C**H**$_3$), 2.01-1.94 (2H, m, -C**H**$_2$- pipe.), 1.89-1.78(2H, m, -C**H**$_2$- pipe.); MS (m/z): 498.8(M+), 500.7(M+2); Anal. Calcd. for $C_{24}H_{23}BrN_2O_5$: C, 57.73; H, 4.64; N; 5.61 %. Found: C, 57.59; H, 4.56; N, 5.51 %.

N-[1-(6-chloropyridine-3-carbonyl)-4-piperidyl]-6-methyl-4-oxo-chromene-3-carboxamide (5h).
Yield:86 %; m.p.: 147-149 °C; IR (KBr, cm^{-1}): 3308, 1709, 1679, 1338, 1276, 1171, 1160 cm^{-1}. 1H-NMR (400 MHz, DMSO-d6, δ / ppm): 12.01(1H, *s*, -CO-N**H**-), 8.89-8.86(1H, *m*, -CH- of py.), 8.37 (1H, *d*, Chr.), 8.56-8.52(1H, *dd*, -C**H**- py.), 7.78-7.71(2H, *m*, -C**H**- py. & -C**H**- of Chr.), 7.38-7.35(1H, *m*, Chr.), 7.18-7.14(1H, *m*, Chr.), 3.88-3.83(2H, *m*, -NC**H**$_2$- pipe.), 3.47-3.41(1H, *m*, -C**H**- of pipe.), 2.81-2.78(2H, *t*, -NC**H**$_2$-), 2.41(3H, *s*, Ar-C**H**$_3$), 2.19-2.14(2H, *m*, -C**H**$_2$- pipe.), 1.98-1.89(2H, *m*, -C**H**$_2$- pipe.); MS (m/z): 425.7(M+1); Anal. Calcd. for $C_{22}H_{20}ClN_3O_4$: C, 62.05; H, 4.73; N, 9.87 %. Found: C, 61.88; H, 4.54; N, 9.77 %.

N-[1-(1, 3-benzoxazol-2-yl)-4-piperidyl]-6-methyl-4-oxo-chromene-3-carboxamide (5i).
Yield: 78 %; m.p.: 212-214 °C; IR (KBr, cm^{-1}): 3309, 1712, 1680, 1342, 1281, 1172, 1161 cm^{-1}. 1H-NMR (400 MHz, DMSO-d6, δ / ppm): 12.01(1H, *s*, -CO-N**H**-), 8.39 (1H, *d*, Chr.), 7.76-7.73(1H, *sd*, Chr.), 7.59-7.48(2H, *m*, benzox.), 7.37-7.33(1H, *m*, Chr.), 7.26-7.22(2H, *m*, benzox.), 7.18-7.15(1H, *m*, Chr.), 3.88-3.83(2H, *m*, -NC**H**$_2$- pipe.), 3.49-3.44(1H, *m*, -C**H**- of pipe.), 2.78-2.76(2H, *t*, -NC**H**$_2$-), 2.40(3H, *s*, Ar-C**H**$_3$), 2.17-2.14(2H, *m*, -C**H**$_2$- pipe.), 1.96-1.89(2H, *m*, -C**H**$_2$- pipe.);MS (m/z): 403.9(M+1); Anal. Calcd. for $C_{23}H_{21}N_3O_4$: C, 68.47; H, 5.25; N, 10.42 %. Found: C, 68.64; H, 5.38; N, 10.53 %.

N-[1-(1,3-benzothiazol-2-yl)-4-piperidyl]-6-methyl-4-oxo-chromene-3-carboxamide (5j).
Yield: 59 %; m.p.: 137-139°C; IR (KBr, cm^{-1}): 3307, 1713, 1679, 1338, 1281, 1171, 1159 cm^{-1}. 1H-NMR (400 MHz, DMSO-d6, δ / ppm): 12.01(1H, *s*, -CO-N**H**-), 8.37 (1H, *d*, Chr.), 7.76-7.73(1H, *sd*, Chr.), 7.56-7.47(2H, *m*, benzoth.), 7.38-7.35(1H, *m*, Chr.), 7.28-7.23(2H, *m*, benzoth.), 7.18-7.14(1H, *m*, Chr.), 3.87-3.82(2H, *m*, -NC**H**$_2$- pipe.), 3.48-3.43(1H, *m*, -C**H**- of pipe.), 2. 76-2.74(2H, *t*, -NC**H**$_2$-), 2.40(3H, *s*, Ar-C**H**$_3$), 2.18-2.14(2H, *m*, -C**H**$_2$- pipe.), 1.99-1.90(2H, *m*, -C**H**$_2$- pipe.); MS (m/z): 418.0(M-1); Anal. Calcd. for $C_{23}H_{21}N_3O_3S$: C, 65.85; H, 5.05; N, 10.02 %. Found: C, 65.74; H, 4.96; N, 10.08 %.

General procedure

(3E)-3-(dimethylamino methylene) chroman-4-one (7).
A mixture 4-chromanone (5 gm, 0.033M) and N, N-dimethyl formamide dimethylacetal (5.5 ml) was heated to 80°C. Progress of reaction was monitored by TLC. After completion of reaction, heating was removed and unreacted dimethylformamide dimethylacetal was removed under reduced pressure. Residue was stirred with 50 ml water for 1hr. Isolated solid was filtered off

and washed with water (10 ml). Solid was dried under reduced pressure to obtain 6.1 gm of yellow solid

Tert-butyl 4-[(E)-(4-oxochroman-3-ylidene) methyl] piperazine-1-carboxylate (8).
A mixture (3E)-3-(dimethylamino methylene) Chroman-4-one (6.1 gm, 0.030M) and N–BOC piperazine (6.7gm, 0.036M) was heated to 120^{o}C for 15hr. Progress of reaction was monitored by TLC. After completion of reaction, residual mass was stirred with hexane (100 ml) at 20°C for 30 minute. Isolated solid was filtered off and washed with water (50 ml). Solid was dried under reduced pressure to obtain 7.34 gm of yellow solid

(3E)-3-(piperazin-1-ylmethylene) chroman-4-one .TFA salt (9).
Tert-butyl 4-[(E)-(4-oxochroman-3-ylidene) methyl] piperazine-1-carboxylate (7.34 gm, 0.021M) was added portion wise into the cold solution of trifluoroacetic acid (14 ml) in MDC (100 ml). Progress of reaction was monitored by TLC. After completion of reaction, trifluoroacetic acid was removed under reduced pressure. Residual mass was further diluted with THF (100 ml) and concentrated to dryness. Residue was stirred with diethyl ether (25 ml) and separated solid was filtered off, washed with diethyl ether (10 ml) and dried under reduced pressure to obtain 6.3 gm white solid.

General procedure: (3E)-3-[[4-(Aryl or Alkyl sulfonyl, Aryl carbonyl and Heteroaryl) piperazin-1-yl] methylene] chroman-4-one (10a-j).
(3E)-3-(piperazin-1-ylmethylene) chroman-4-one TFA salt (0.84M) was charged in 20 ml dichloromethane at room temperature. Base (2.1M) and Aryl sulfonyl chloride or Aryl carbonyl chloride or heteroaryl chloride (1.0M) was added sequentially at room temperature. Progress of reaction was monitored by TLC. After completion of reaction, solvent was evaporated and residual mass was stirred with saturated solution of $NaHCO_3$ (20ml) and stirred for 2 hr. solid was filtered off and washed with water (10 ml). Solid was dried under reduced pressure to obtain crude **(**3E)-3-[[4-(Arylsulfonyl) piperazin-1-yl] methylene] chroman-4-one as off white solid. The solid was purified by silica gel column chromatography (20 % ethyl acetate in hexane) to obtain pure compound **10a-j** as white solid.

Spectroscopic and analytical data
(3E)-3-[[4-[(6-chloro-3-pyridyl) sulfonyl] piperazin-1-yl] methylene] chroman-4-one (10a).
Yield: 68 %; m.p.: 184-186 °C; IR(KBr, cm^{-1}):1693, 1334, 1251, 1159, 1152 cm^{-1}. 1H-NMR (400 MHz, DMSO-d^{6}, δ / ppm): 8.65(1H, *sd*, -CH- of py.), 8.22 (1H, *d*, -CH- of py.), 8.20 (1H, *dd*, Chr.), 7.98(1H, *s*, -CH- of exocyclic double bond), 7.87 (1H, *d*, -CH- of py.), 7.69-7.65 (1H, *t*, Chr.), 7.45-7.43 (1H, *d*, Chr.), 7.43-7.39 (1H, *t*, Chr.), 3.48 (2H, *s*, -O-CH2- of Chr.), 3.13-3.11 (4H, *t*, pip.), 2.67-2.65 (4H, *t*, pip.); MS (m/z): 419.8(M+1); Anal. Calcd. for $C_{19}H_{18}ClN_3O_4S$: C, 54.35; H, 4.32; N; 10.01 %. Found: C, 54.21; H, 4.19; N, 9.88 %.

(3E)-3-[[4-[(5-bromo-6-chloro-3-pyridyl) sulfonyl] piperazin-1-yl] methylene] chroman-4-one (10b).
Yield: 72 %; m.p.: 178-180 °C; IR (KBr, cm^{-}):1693, 1336, 1252, 1160, 1154 cm^{-1}. 1H-NMR (400 MHz, DMSO-d^{6}, δ / ppm): 8.74(1H, *sd*, -CH- of py.), 8.20 (1H, *dd*, Chr.), 8.01(1H, *s*, -CH- of exocyclic double bond), 7.71-7.67 (1H, *t*, Chr.), 7.51-7.41 (3H, *m*, -CH- of py. & -C**H**- of Chr.), 3.48 (2H, *s*, -O-CH2- of Chr.), 3.18-3.15 (4H, *t*, pip.), 2.77-2.72 (4H, *t*, pip.); MS (m/z): 497.7(M+), 499.7(M+2); Anal. Calcd. for $C_{19}H_{17}BrClN_3O_4S$: C, 45.75; H, 3.44; N; 8.42%. Found: C, 45.82; H, 3.51; N, 8.53 %.

(3E)-3-[[4-[4-(trifluoromethoxy) phenyl] sulfonylpiperazin-1-yl] methylene] chroman-4-one (10c).
Yield: 63 %; m.p.: 192-194 °C; IR (KBr, cm^{-1}): 1692, 1337, 1255, 1163, 1151 cm^{-1}. 1H-NMR (400 MHz, DMSO-d^6, δ / ppm): 8.21-8.19(2H, d, Ar), 8.04(1H, s, -CH- of exocyclic double bond), 7.79-7.76 (1H, *t*, Chr.), 7.58-7.56(2H, d, Ar), 7.51 (1H, *d*, Chr.), 7.45-7.41 (1H, *t*, Chr.), 7.39 (1H, *d*, Chr.), 3.61 (2H, *s*, -O-C**H**$_2$- of Chr.), 3.25-3.23(4H, *t*, pip.), 2.76-2.72 (4H, *t*, pip.); MS (m/z): 468.7(M+1); Anal. Calcd. for $C_{21}H_9F_3N_2O_5S$: C, 53.84; H, 4.09; N; 5.98 %. Found: C, 53.72; H, 3.98; N, 5.89 %.

(3E)-3-[[4-(8-quinolylsulfonyl) piperazin-1-yl] methylene] chroman-4-one (10d).
Yield: 66 %; m.p.: 110-112°C; IR (KBr, cm^{-1}): 1693, 1333, 1255, 1158, 1153 cm^{-1}. 1H-NMR (400 MHz, DMSO-d^6, δ / ppm): 8.26 (1H, *d*, Ar), 8.18 (1H, *dd*, Chr.), 8.01(1H, *s*, -CH- of exocyclic double bond), 7.92(1H, *d*, Ar), 7.69-7.65 (1H, t, Chr.), 7.53-7.51(1H, *m*, Ar), 7.51-7.43 (2H, *m*, Chr. &Ar), 7.39-7.37 (1H, *t*, Chr.), 7.38-7.33(2H, *m*, Ar), 3.43 (2H, *s*, -O-CH2- of Chr.), 3.23-3.21 (4H, *t*, pip.), 2.70-2.67 (4H, *t*, pip.); MS (m/z): 435.9(M+1) Anal. Calcd. for $C_{23}H_{21}N_3O_4S$: C, 63.43; H, 4.86; N; 9.65 %. Found: C, 63.28; H, 4.76; N, 9.57 %.

(3E)-3-[[4-(o-tolylsulfonyl) piperazin-1-yl] methylene] chroman-4-one (10e).
Yield: 59 %; m.p.: 124-126 °C; IR (KBr, cm^{-1}): 1692, 1333, 1250, 1160, 1151 cm^{-1}. 1H-NMR (400 MHz, DMSO-d^6, δ / ppm): 8.20 (1H, *dd*, Chr.), 7.98(1H, *s*, -CH- of exocyclic double bond),7.94(1H, *d*, Ar), 7.69-7.65 (1H, t, Chr.), 7.53-7.47(2H, *m*, Ar), 7.45-7.43 (1H, *d*, Chr.), 7.43-7.39 (1H, *t*, Chr.), 7.33-7.30(1H, *t*, Ar), 3.45 (2H, *s*, -O-CH2- of Chr.), 3.21-3.18 (4H, *t*, pip.), 2.71-2.69 (4H, *t*, pip.), 2.37(3H, s, Ar-C**H**$_3$); MS (m/z): 398.9(M+1); Anal. Calcd. for $C_{21}H_{22}N_2O_4S$: C, 63.30; H, 5.56; N; 7.03 %. Found: C, 63.06; H, 5.41; N, 6.92 %.

(3E)-3-[[4-(1, 3-benzoxazol-2-yl) piperazin-1-yl] methylene] chroman-4-one (10f).
Yield: 82 %; m.p.: 136-138 °C; IR (KBr, cm^{-1}): 1693, 1332, 1256, 1161, 1152 cm^{-1}. 1H-NMR (400 MHz, DMSO-d^6, δ / ppm): 8.24(1H, *d*, benzoxazole), 8.20 (1H, *dd*, Chr.), 8.01(1H, *s*, -CH- of exocyclic double bond), 7.70-7.66 (1H, *t*, Chr.), 7.47 (1H, *d*, Chr.), 7.44-7.40 (1H, *t*, Chr.), 7.24 (1H, *d*, benzox.), 7.18-7.14 (1H, *t*, benzox.), 7.04-7.00 (1H, *t*, benzox.), 3.76-3.74(4H, *t*, pip.), 3.59 (2H, *s*, -O-CH2- of Chr.), 2.73-2.70 (4H, *t*, pip.); MS (m/z): 362(M+1); Anal. Calcd. for $C_{21}H_{19}N_3O_3$: C, 69.79; H, 5.30; N; 11.63 %; Found: C, 69.57; H, 5.13; N, 11.39 %.

(3E)-3-[[4-(3-chloropropylsulfonyl) piperazin-1-yl] methylene] chroman-4-one (10g).
Yield: 62 %; m.p.: 98-100 °C; IR (KBr, cm^{-1}): 1694, 1335, 1254, 1159, 1151 cm^{-1}. 1H-NMR (400 MHz, DMSO-d^6, δ / ppm): 8.32(1H, *s*, -CH- of exocyclic double bond), 8.07(1H, *d*, Chr.), 7.83-7.79(1H, *t*, Chr.), 7.67-7.65(1H, *d*, Chr.), 7.52-7.48(1H, *t*, Chr.), 3.75-3.72 (2H, *s*, -O-CH2- of Chr.), 3.35 (4H, *t*, pip.), 3.21-3.14 (8H, *m*, -N(C**H**$_2$)$_2$- of pip. , -SO_2C**H**$_2$- & -C**H**$_2$-Cl), 2.12-2.09(2H, m, -SO_2CH_2C**H**$_2$-); MS (m/z): 384.8(M+1); Anal. Calcd. for $C_{17}H_{21}ClN_2O_4S$: C, 53.05; H, 5.50; N, 7.28%; Found: C, 52.91; H, 4.41; N, 7.18 %.

(3E)-3-[[4-[5-(trifluoromethyl)-2-pyridyl] piperazin-1-yl] methylene] chroman-4-one (10h).
Yield: 55 %; m.p.: 138-140 °C; IR (KBr, cm^{-1}):1693, 1334, 1252, 1158, 1153 cm^{-1}. 1H-NMR (400 MHz, DMSO-d^6, δ / ppm): 8.44(1H, *sd*, -CH- of py.), 8.17-8.15 (1H, *dd*, Chr.), 8.09(1H, *s*, -CH- of exocyclic double bond), 7.87-7.85(1H, *dd*, -CH- of py.), 7.80-7.76 (1H, *t*, Chr.), 7.60-7.58(1H, *d*, Chr.), 7.54(1H, *d*, -CH- of py.), 7.50-7.46 (1H, *t*, Chr.), 3.79-3.76 (4H, *t*, pip.), 3.47 (2H, *s*, -O-CH2- of Chr.), 2.66-2.62 (4H, *t*, pip.); MS (m/z): 390.4(M+1); Anal. Calcd. for $C_{20}H_{18}F_3N_3O_2$: C, 61.69; H, 4.66; N, 10.79%; Found: C, 61.56; H, 4.58; N, 10.62 %.

(3E)-3-[[4-(6-chloropyridine-3-carbonyl) piperazin-1-yl] methylene] chroman-4-one (10i).
Yield: 75 %; m.p.: 116-118 °C; IR (KBr, cm^{-1}): 1694, 1332, 1249, 1157, 1150 cm^{-1}. 1H-NMR (400 MHz, DMSO-d^6, δ / ppm): 8.36(1H, *s*, -CH- of pyridine), 8.23-8.21 (1H, *d*, Chr.), 8.05(1H, *s*, -CH- of exocyclic double bond), 7.71-7.67 (1H, *t*, Chr.), 7.63-7.60(1H, *dd*, Chr.),7.49(1H, *d*, -CH- of py.), 7.44-7.40 (1H, *t*, Chr.), 6.65(1H, *d*, -CH- of py.), 3.68-3.66 (4H, *t*, pip.), 3.54 (2H, *s*, -O-CH2- of Chr.), 2.66-2.62 (4H, *t*, pip.); MS (m/z): 384.3(M+1); Anal. Calcd. for $C_{20}H_{18}ClN_3O_3$: C, 62.58; H, 4.73;N; 10.95%. Found: C, 62.70; H, 4.82; N, 11.07 %.

(3E)-3-[[4-(2-methoxycarbonylthiophene)-3-sulfonyl) piperazin-1-yl] methylene] chroman-4-one (10j).
Yield: 57 %; m.p.: 139-141 °C; IR (KBr, cm^{-1}): 1693, 1334, 1252, 1160, 1152 cm^{-1}. 1H-NMR (400 MHz, DMSO-d^6, δ / ppm): 8.22-8.20 (1H, *d*, Chr.), 7.91(1H, *s*, -CH- of exocyclic double bond), 7.69-7.65 (1H, *t*, Chr.), 7.48-7.38 (4H, *m*, 2-CH- of thioph. & 2-CH- of Chr.), 3.9(3H, *s*, -$COOCH_3$), 3.50 (2H, *s*, -O-CH2- of Chr.), 3.37-3.34 (4H, *t*, pip.), 2.62-2.59 (4H, *t*, pip.); MS (m/z): 449.3(M+1); Anal. Calcd. for $C_{20}H_{20}N_2O_6S_2$: C, 53.56; H, 4.49; N; 6.25%. Found: C, 53.33; H, 4.32; N, 6.07 %.

Antimicrobial activity – The invitro antimicrobial activity of test compounds were assessed against 24 hr cultures of several selected bacteria and fungi. The bacteria used were *E. coli, S. aureus, P. aeruginosa*, and *S. pyogenus*; the fungi used were *C. albicans, A. niger, and A. clavatus.*

The antimicrobial activity was performed by agar diffusion method at 1 mg/ml concentration in DMSO. Nutrient agar and potato dextrose agar were used to culture the bacteria and fungi respectively. Ampicilin and Greseofulvin were used as standard for the evaluation of antibacterial and antifungal activities respectively. The activity was reported by zone of inhibition in mm. The results are summarized in **Table-I**.

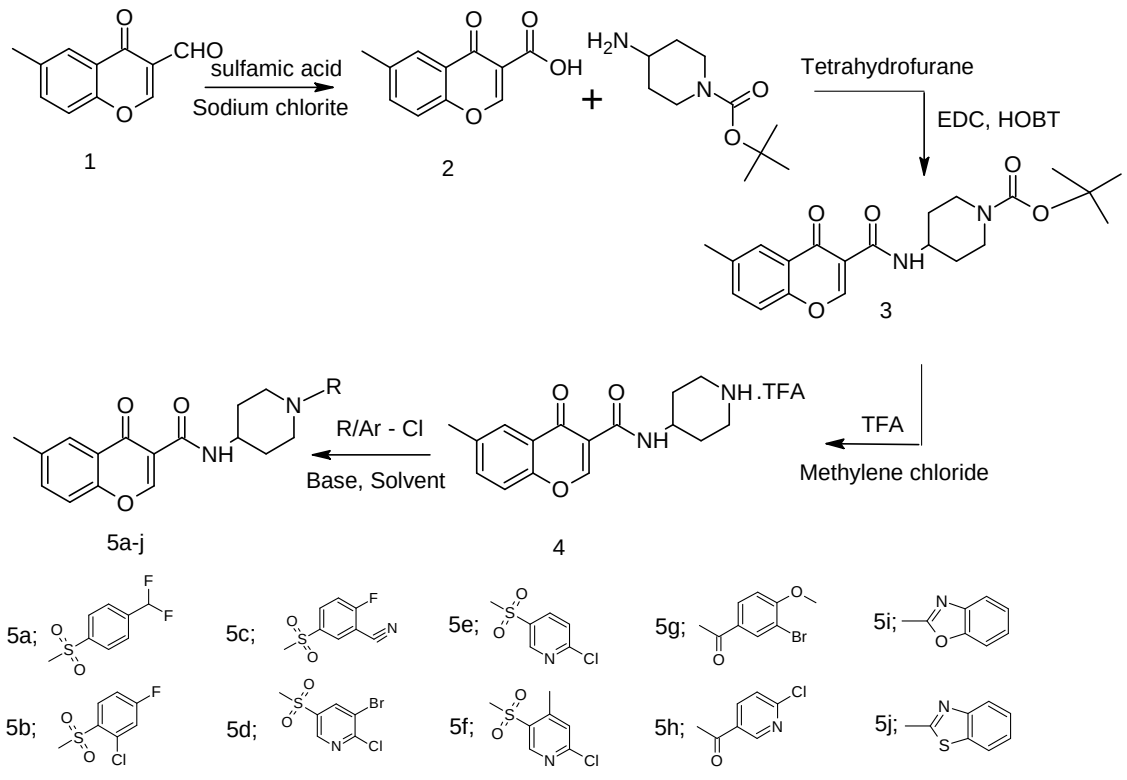
Biological screening result of 6-methyl-4-oxo-*N*-(piperidin-4-yl)-4*H*-chromene-3-carboxamide based derivatives shows that 2-methyl substituted phenyl sulfonamide compound (**5f**) have shown good activity against some of the pathogenic strain like *E. coli, S. aureus, P. aeruginosa*. Compounds with substitution 4-difluoromethyl phenyl sulfonyl (**5a**), benzoxazole (**5i**) and benzothiazole (**5j**), have shown moderate improvement in antifungal activity against *C. albicans*, while rest of all derivatives does not shown improvement on activity against any pathogenic strains.

Amongst synthesized compounds based on (3*E*)-3-(piperazin-1-ylmethylidene)-2, 3-dihydro-4*H*-chromen-4-one (**10**), 3-chloropropane sulfonyl (**10g)** linked compound have shown good activity against all bacterial strains, while chromanone derivatives like 6-chloro-4-methylpyridine-3-sulfonyl (**10e**) and benzoxazole (**10f**) have shown good activity against *E. coli, S. aureus, P. aeruginosa*. Benzoxazole (**10f**) and 5-trifluoromethylpyridine-2-yl (**10h**) substitutions have shown moderate antifungal activity against *C. albicans*, while rest of all derivatives does not shown improvement on activity against any biological strains.

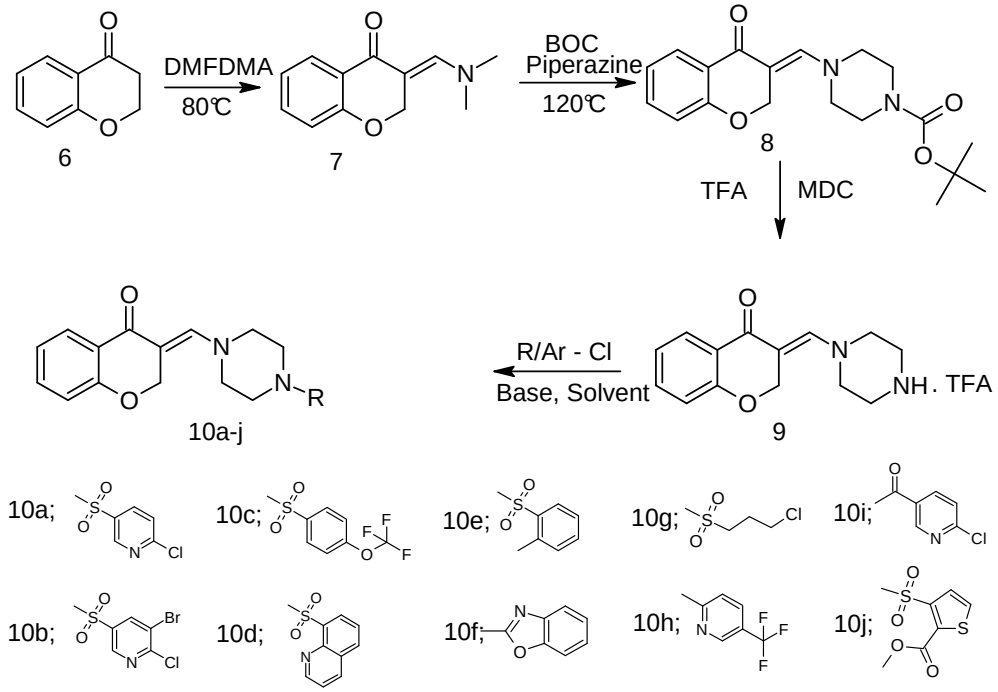
Table I: Biological screening test result of compounds 5a-j and 10a-j

Sr.No.	Entry	Bacterial model(MIC, µg/ml)				Fungi model(MIC, µg/ml)		
		E.coli MTCC 443	*P.aeru. MTCC 1688*	*S.aur. MTCC 96*	*S. Pyog. MTCC 442*	*C. Alb. MTCC 228*	*A.Niger MTCC 282*	*A.Clav. MTCC 1323*
1	5a	100	200	200	200	250	500	500
2	5b	100	250	250	500	500	1000	1000
3	5c	250	250	500	500	500	1000	1000
4	5d	500	500	100	62.5	1000	200	500
5	5e	250	200	200	200	1000	>1000	>1000
6	5f	62.5	100	250	200	1000	500	1000
7	5g	*200*	100	250	250	*500*	1000	1000
8	5h	250	200	125	500	>1000	>1000	>1000
9	5i	250	500	500	500	250	>1000	>1000
10	5j	500	200	250	125	250	1000	1000
11	10a	250	250	250	250	100	1000	1000
12	10b	100	200	100	100	200	500	500
13	10c	200	250	200	200	1000	250	250
14	10d	200	200	200	200	1000	250	250
15	10e	50	100	250	250	500	1000	1000
16	10f	100	125	250	250	250	>1000	>1000
17	10g	25	50	200	100	500	>1000	>1000
18	10h	500	500	500	500	200	500	500
19	10i	100	100	500	500	>1000	500	>1000
20	10j	200	200	125	200	500	500	>1000
Control	*Ampicillin*	100	100	250	100	-	-	-
Control	*Greseofulvin*	-	-	-	-	500	100	100

Scheme-1



Scheme-2



CONCLUSION

In summary, we have described the synthesis and antimicrobial activity of novel (3E)-3-[[4-(Aryl or Alkyl sulfonyl, Aryl carbonyl and Heteroaryl) piperazin-1-yl] methylene] Chroman-4-one and N-[1-(Aryl or Alkyl sulfonyl, Aryl carbonyl and Heteroaryl)-4-piperidyl]-6-methyl-4-oxo-chromene-3-carboxamide derivatives. MIC values revealed that amongst newly synthesized compound having 3-chloropropane sulfonyl type linkage has shown good activity against the bacterial strains. Rest of all compounds exhibit moderate improvement in activity against some of the pathogenic strains.

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