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**Der Chemica Sinica, 2012, 3(1):80-90**

Der Chemica Sinica
Pelagia Research Library
ISSN: 0976-8505
CODEN (USA) CSHIA5

# Synthesis of spirochromanone derivatives as antimicrobial agents

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**ABSTRACT**

A series of new methyl 3-[4-(4-oxo-6-phenyl-spiro [chromane-2,4'-piperidine]-1'-yl)sulfonyl phenyl]propanoate **5a-j** and N-[5-(1'-acetyl-4-oxo-spiro[chromane-2,4'-piperidine]-6-yl)-2-methyl-phenyl]-3-alkylamide or alkyl sulfonamide **9a-i** has been synthesized and cheracterized via IR, $^{1}$H NMR, $^{13}$C NMR, MS elemental analysis. All the newly synthesized compounds were screened for their antibacterial activity against *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa*, and *Bacillus subtilis* and antifungal activity against *Candida albicans.* Some of the compounds exhibited moderate inhibition on bacterial and fungal growth as compared to standard drugs.

**Keywords**: Spirochromones, Antimicrobial acivity, Antifungal activity.

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## INTRODUCTION

Chromones and related ring systems are the promising heterocyclic compounds in the field of medicinal chemistry. They possess various physiological and biological activities and thus, find important place in medicinal chemistry.

Molecules with the chromone scaffold are privileged substructures exhibiting a range of biological activities, including antioxydent, antifungal, antiviral, antimicrobial, antiallergenic, anti-inflammatory, antiproliferative and antitumor activity [1-7] and are present in large quantities in human diets. In addition, chromones represent an attractive source of medicinally interesting compounds due to their low toxicity. In addition, many flavonoids are based on the chromone structure and have been found to possess several therapeutically interesting biological activities [8].

Spirochromanone derivatives have been also found to exhibit a broad range of biological activities Acetyl CoA carboxylase (ACC) – Inhibitor [9], antiarrythmic activity [10], Delta Opioid Receptor Agonists for the treatment of Pain [11]. ACC exist also in plant, parasites, bacteria and fungi, and participates in the growth of cells [12-16]. ACC-inhibitor also acts as an antibecteril and anti fungal agents via growth inhibition. As part of our research work, we report here efficient and convenient synthetic methods for synthesis of some new spirochromanone moities. Newly synthesized compound **5a-j** and **9a-I** were evaluated against bacterial and fungal pathogenic strains and results are summarized here as a MIC value.

## MATERIALS AND METHODS

**Experimental**

**1)General synthetic procedure for synthesis of 5a-j.**

**Methyl 3-[4-(6-bromo-4-oxo-spiro [chromane-2, 4'-piperidine]-1'-yl) sulfonylphenyl] propionate (4);** A solution of substituted methyl 3-[4-(chlorosulfonyl) phenyl] propanoate (3.53 gm, 0.0065 M) was added to a stirred and cooled solution of compound **3** (5.0 gm, 0.0122 M), catalytic Dimethylaminopyridine and triethylamine (2.0 ml, 0.007 M) in dry methylene chloride. The reaction mixture was stirred at room temperature for 10 h. Reaction mixture was evaporated to dryness under reduced pressure. The residue was dissolved in ethyl acetate and washed with 5 % aqueous hydrochloric acid (50 ml) followed by saturated sodium bicarbonate (50 ml) solution and water (50 ml). Ethyl acetate layer was dried and evaporated under reduced pressure. The residue crude product was purified over silica gel column chromatography using hexane: ethyl acetate (4:1) as an eluant, gave 4.97 gm pure compound **4** as white solid. Yield: 78 %; m.p.: 183-185 $^{\circ}$C; 1H-NMR (400 MHz, DMSO-d6, δ / ppm): 8.03 (1H, *sd*, 5-H Chr. *J* = 2.4 Hz), 7.72-7.70 (2H, *d*, Aromatic, *J* = 8 Hz), 7.68 (1H, *dd*, 7-H Chr., *J* = 2.4 Hz, *J* = 8.4 Hz), 7.41-7.39 (2H, *d*, Aromatic, *J* = 8 Hz), 6.86 (1H, *d*, 8-H Chr., *J* = 8.8 Hz), 3.72(3H, *s*, -COOC**H$_3$**), 3.64(2H, *broad-d*, -N(C**H$_2$**)-, *J* = 11.6 Hz), 3.02(2H, *t*, -C**H$_2$**-COOCH$_3$, *J* = 7.6 Hz), 2.83(2H, *t*, -N(C**H$_2$**)-, *J* = 12.4 Hz), 2.71(2H, *s*, -CO-C**H$_2$**-), 2.69(2H, *t*, Ar-C**H$_2$**-CH$_2$-, *J* = 8.0 Hz), 2.08(2H, *broad-d*, C-C**H$_2$**-CH$_2$-, *J* = 13.0 Hz), 1.8(2H, *m*, C-C**H$_2$**-CH$_2$-, *J* = 13.4 Hz); MS (m/z): 523.4(M+1).

**Methyl 3-[4-(4-oxo-6-phenyl-spiro [chromane-2, 4'-piperidine]-1'-yl) sulfonylphenyl] propionate (5);** A solution of sodium carbonate (1.4 M) in water (5 ml) was mixed with a solution of arylboronic acid (0.46 M) in ethanol (10 ml) and stirred for 15 min. A solution of compound 4 (0.38 M) in toluene (20 ml) was added under nitrogen followed by Tetrakistriphenyl phosphinopalladium (0.02 M) and heated at reflux for 15 hr. Product was extracted using ethyl acetate (50 ml) and washed it with saturated sodium bicarbonate solution (50 ml), Water (50 ml), Ethyl acetate layer was dried and evaporated under reduced pressure gave solid residue. The residue crude product was purified over silica gel column chromatography using hexane: ethyl acetate (4:1) as an eluant, gave the pure compound **5a-j** as white solid.

**2)Spectroscopic and analytical data**

**Methyl 3-[4-[6-(4-tert-butylphenyl)-4-oxo-spiro [chromane-2,4'-piperidine]-1'-yl] sulfonylphenyl] propanoate (5a).** Yield: 68 %; m.p.: 157-160 °C; Anal. Calcd for $C_{33}H_{37}NO_6S$: C, 68.85; H, 6.48; N; 2.43 %. Found: C, 68.58; H, 6.39; N, 2.41 %; IR (KBr, cm$^{-1}$): 1736, 1691, 1339, 1274, 1162, 1148 cm$^{-1}$. $^1$H-NMR (400 MHz, DMSO-d6, δ / ppm): 8.05 (1H, *sd*, 5-H Chr., *J* = 2.4 Hz), 7.71 (2H, *d*, Aromatic, *J* = 8 Hz), 7.69 (1H, *dd*, 7-H Chr., *J* = 2.4 Hz, *J* = 8.4 Hz), 7.46 (4H, *q*, Aromatic, *J* = 7.8 Hz), 7.40 (2H, *d*, Aromatic, *J* = 8 Hz), 6.85 (1H, *d*, H Chr., *J* = 8.4 Hz), 3.7(3H, *s*, -COOC**H$_3$**), 3.6(2H, *broad-d*, -N(C**H$_2$**)-, *J* = 11.6 Hz), 3.0(2H, *t*, -C**H$_2$**-COOCH$_3$, *J* = 7.6 Hz), 2.8(2H, *t*, -N(C**H$_2$**)-, *J* = 11.6 Hz), 2.7(2H, *s*, -CO-C**H$_2$**-), 2.68(2H, *t*, Ar-C**H$_2$**-CH$_2$-, *J* = 7.6 Hz), 2.1(2H, *broad-d*, C-C**H$_2$**-CH$_2$-, *J* = 13.6 Hz), 1.8(2H, *t*, C-C**H$_2$**-CH$_2$-, *J* =11.6 Hz), 1.34(9H, s, -C(C**H$_3$**)$_3$); $^{13}$C-NMR (500 MHz, DMSO-d6, δ / ppm):191.76, 172.43, 157.35, 146.17, 136.31, 135.65, 134.61, 133.19, 130.71, 129.52, 129.32, 129.27, 128.83, 127.42(2C), 126.12(2C), 123.08, 120.43, 118.72, 76.78, 51.38, 46.69, 41.47(2C), 34.31, 34.29, 32.47(2C), 31.47(3C), 29.97; MS (m/z): 576.2(M+1).

**Methyl 3-[4-[6-(3,4-difluorophenyl)-4-oxo-spiro[chromane-2,4'-piperidine]-1'-yl]sulfonyl phenyl] propanoate (5b).** Yield: 63 %; m.p.: 132-135°C; Anal. Calcd for $C_{29}H_{27}F_2NO_6S$: C, 62.69; H, 6.90; N; 2.52 %. Found: C, 68.61; H, 6.93; N, 2.45 %; IR (KBr, cm$^{-1}$): 1731, 1696, 1332, 1278, 1163, 1151 cm$^{-1}$. $^1$H-NMR (400 MHz, DMSO-d6, δ / ppm): 7.95 (1H, *sd*, 5-H Chr., *J* = 2.4 Hz), 7.71 (2H, *d*, Aromatic, *J* = 8 Hz), 7.60 (1H, *dd*, 7-H Chr., *J* = 2.4 Hz, *J* = 8.6 Hz), 7.40 (2H, *d*, Aromatic, *J* = 8 Hz), 7.36 (1H, *m*, Aromatic), 7.26 (1H, *s*, Aromatic), 6.92 (1H, *m*, Aromatic) 6.88 (1H, *d*, 8-H Chr., *J* = 8.6 Hz), 3.7(3H, *s*, -COOC**H$_3$**), 3.6(2H, *broad-d*, -N(C**H$_2$**)-, *J* = 11.6 Hz), 3.0(2H, *t*, -C**H$_2$**-COOCH$_3$, *J* = 7.6 Hz), 2.8(2H, *t*, -N(C**H$_2$**)-, *J* = 11.8 Hz), 2.7(2H, *s*, -CO-C**H$_2$**-), 2.68(2H, *t*, Ar-C**H$_2$**-CH$_2$-, *J* = 7.6 Hz), 2.1(2H, *broad-d*, C-C**H$_2$**-CH$_2$-, *J* = 12.8 Hz), 1.8(2H, *t*, C-C**H$_2$**-CH$_2$-, *J* = 13.6 Hz);$^{13}$C-NMR (500 MHz, DMSO-d6, δ / ppm):191.56, 172.37, 157.39, 146.27, 136.34, 135.74, 134.65, 133.11, 132.27, 130.71, 130.27, 129.52, 129.37, 129.30, 127.42, 126.08(2C), 123.03, 120.41, 118.66, 76.87, 51.44, 46.65, 41.48(2C), 34.26, 32.44(2C), 30.01; MS (m/z): 556.3(M+1).

**Methyl 3-[4-[4-oxo-6-(p-tolyl) spiro [chromane-2, 4'-piperidine]-1'-yl] sulfonylphenyl] propanoate (5c).** Yield: 72 %; m.p.: 179-182 °C; Anal. Calcd for $C_{30}H_{31}NO_6S$: C, 67.52; H, 5.86; N; 2.62 %. Found: C, 67.68; H, 5.90; N, 2.68 %; IR (KBr, cm$^{-1}$): 1726, 1689, 1333, 1274, 1171, 1145 cm$^{-1}$. $^1$H-NMR (400 MHz, DMSO-d6, δ / ppm): 7.89

(1H, *sd*, 5-H Chr., *J* = 2.2 Hz), 7.79 (1H, *dd*, 7-H Chr., *J* = 2.2 Hz, *J* = 8.4 Hz), 7.68 (2H, *d*, Aromatic, *J* = 8 Hz), 7.54 (2H, *d*, Aromatic, *J* = 8 Hz), 7.49 (2H, *d*, Aromatic, *J* = 8 Hz), 7.25 (2H, *d*, Aromatic, *J* = 8 Hz), 6.87 (1H, *d*, 8-H Chr., *J* = 8.4 Hz), 3.60(3H, *s*, -COOC**H**$_3$), 3.5(2H, *broad-d*, -N(C**H**$_2$)-, *J* = 11.6 Hz), 2.99(2H, *t*, -C**H**$_2$-COOCH$_3$, *J* = 7.2 Hz), 2.84(2H, *s*, -CO-C**H**$_2$-), 2.74(2H, *t*, -N(C**H**$_2$)-, *J* = 10.4 Hz), 2.58(2H, *t*, Ar-C**H**$_2$-CH$_2$-, *J* =7.6 Hz), 2.32(3H, *s*, Ar-C**H**$_3$), 2.0(2H, *broad-d*, C-C**H**$_2$-CH$_2$-, *J* = 13.6 Hz), 1.8(2H, *t*, C-C**H**$_2$-CH$_2$-, *J* = 12.4 Hz); $^{13}$C-NMR (500 MHz, DMSO-d6, δ / ppm):191.21, 172.4, 157.47, 146.37, 136.71, 135.83, 134.55, 133.27, 129.63(3C), 129.30(2C), 127.52(2C), 126.08(2C), 123.03, 120.41, 118.74, 76.97, 51.40, 46.60, 41.42(2C), 34.22, 32.54(2C), 30.04, 20.61; MS (m/z): 534.1(M+1).

**Methyl 3-[4-[6-(4-methoxyphenyl)-4-oxo-spiro [chromane-2, 4'-piperidine]-1'-yl] sulfonylphenyl] propanoate (5d):** Yield: 72 %; m.p.: 159-162 °C; Anal. Calcd for $C_{30}H_{31}NO_7S$: C, 65.56; H, 5.68; N; 2.55 %. Found: C, 67.38; H, 5.46; N, 2.43 %; IR(KBr, cm$^{-1}$): 1739, 1695, 1331, 1268, 1171, 1162 cm$^{-1}$. $^1$H-NMR (400 MHz, DMSO-d6, δ / ppm): 7.92(1H, *sd*, 5-H Chr., *J* = 2.4 Hz), 7.81(1H, *dd*, 7-H Chr., *J* = 2.4 Hz, *J* = 8.6 Hz), 7.70(2H, *d*, Aromatic, *J* = 8 Hz), 7.51(2H, *d*, Aromatic, *J* = 8.2 Hz), 7.46(2H, *d*, Aromatic, *J* = 8 Hz), 7.25(2H, *d*, Aromatic, *J* = 8.2 Hz), 6.87(1H, *d*, 8-H Chr., *J* = 8.6 Hz), 3.79(3H, *s*, -OC**H**$_3$), 3.67(3H, *s*, -COOC**H**$_3$), 3.5(2H, *broad-d*, -N(C**H**$_2$)-, *J* = 11.6 Hz), 3.00(2H, *t*, -C**H**$_2$-COOCH$_3$, *J* = 7.6 Hz), 2.84(2H, *s*, -CO-C**H**$_2$-), 2.75(2H, *t*, -N(C**H**$_2$)-, *J* = 10.8 Hz), 2.58(2H, *t*, Ar-C**H**$_2$-CH$_2$-, *J* =7.8 Hz), 2.0(2H, *broad-d*, C-C**H**$_2$-CH$_2$-, *J* =12.0 Hz), 1.8(2H, *t*, C-C**H**$_2$-CH$_2$-, *J* =12.8 Hz); $^{13}$C-NMR (500 MHz, DMSO-d6, δ / ppm):191.42, 172.37, 157.43, 146.21, 136.67, 135.73, 134.45, 133.28, 129.11, 129.67(2C), 129.35(2C), 127.62(2C), 126.12(2C), 123.07, 120.36, 118.67, 76.83, 55.14, 51.43, 46.61, 41.44(2C), 34.26, 32.55(2C), 30.05; MS (m/z): 550.1(M+1).

**Methyl 3-[4-[6-(3,5-dimethylphenyl)-4-oxo-spiro[chromane-2,4'-piperidine]-1'-yl] sulfonylphenyl] propanoate (5e).** Yield: 72 %; m.p.: 172-175 °C; Anal. Calcd for $C_{31}H_{33}NO_6S$: C, 67.99; H, 6.07; N; 2.56 %. Found: C, 67.87; H, 6.93; N, 2.58 %; IR(KBr, cm$^{-1}$): 1736, 1690, 1332, 1268, 1172, 1163 cm$^{-1}$. $^1$H-NMR (400 MHz, DMSO-d6, δ / ppm): 7.79(1H, *sd*, 5-H Chr., *J* = 2.2 Hz), 7.72(2H, *d*, Aromatic, *J* = 8 Hz), 7.42-7.37(3H, *m*, 7-H Chr. & Aromatic), 7.13(1H, *d*, Aromatic, *J* = 7.8 Hz), 7.06(1H, *d*, Aromatic, *J* = 7.8 Hz), 6.98(1H, s, aromatic), 6.82(1H, *d*, 8-H Chr., *J* = 8.8 Hz), 3.69(3H, *s*, -COOC**H**$_3$), 3.6(2H, *broad-d*, -N(C**H**$_2$)-, *J* = 12.0 Hz), 3.0(2H, *t*, -C**H**$_2$-COOCH$_3$, *J* = 7.6 Hz), 2.84(2H, *t*, -N(C**H**$_2$)-, *J* = 12.0 Hz), 2.72(2H, *s*, -CO-C**H**$_2$-), 2.70(2H, *t*, Ar-C**H**$_2$-CH$_2$-, *J* = 7.6 Hz), 2.32(6H, *s*, Ar(C**H**$_3$)$_2$), 2.1(2H, *broad-d*, C-C**H**$_2$-CH$_2$-, *J* = 13.4 Hz), 1.8(2H, *t*, C-C**H**$_2$-CH$_2$-, *J* = 12.0 Hz); $^{13}$C-NMR (500 MHz, DMSO-d6, δ / ppm): 191.27, 172.47, 157.52, 146.31, 136.69, 135.78, 134.54, 133.18, 130.61, 130.19, 129.57, 129.29(2C), 127.53(2C), 126.68, 126.12, 123.17, 120.52, 118.69, 76.92, 51.38, 46.57, 41.46(2C), 34.22, 32.58(2C), 30.03, 20.44, 19.58; MS (m/z): 548.1(M+1).

**Methyl 3-[4-[6-(2, 4-difluorophenyl)-4-oxo-spiro [chromane-2, 4'-piperidine]-1'-yl] sulfonylphenyl] propanoate (5f).** Yield: 69 %; m.p.: 139-142°C; Anal. Calcd for $C_{29}H_{27}F_2NO_6S$: C, 62.69; H, 6.90; N; 2.52 %. Found: C, 68.43; H, 6.76; N, 2.39 %; IR(KBr, cm$^{-1}$): 1730, 1691, 1341, 1261, 1156, 1147 cm$^{-1}$. $^1$H-NMR (400 MHz, DMSO-d6, δ / ppm): 7.81(1H, *sd*, 5-H Chr., *J* = 2.2 Hz), 7.73(2H, *d*, Aromatic, *J* = 8 Hz), 7.59(1H, *m*, Aromatic), 7.56(1H, *dd*, 7-H Chr., *J* = 2.2 Hz, *J* = 8.4 Hz), 7.40(2H, *d*, Aromatic, *J* = 8 Hz), 7.36(1H, *s*, Aromatic), 7.04(1H, *m*, Aromatic) 6.88(1H, *d*, 8-H Chr., *J* = 8.4 Hz), 3.69(3H, *s*, -COOC**H**$_3$), 3.6(2H, *broad-d*, -N(C**H**$_2$)-, *J* = 12.0 Hz), 3.0(2H, *t*, -C**H**$_2$-COOCH$_3$, *J* = 8.4 Hz), 2.81(2H, *t*, -N(C**H**$_2$)-, *J* = 11.8 Hz), 2.72(2H, *s*, -CO-C**H**$_2$-), 2.68(2H, *t*, Ar-C**H**$_2$-CH$_2$-, *J* = 7.4 Hz), 2.1(2H, *broad-d*, C-C**H**$_2$-CH$_2$-, *J* = 12.4 Hz), 1.8(2H, *t*, C-C**H**$_2$-CH$_2$-, *J* = 13.2 Hz); $^{13}$C-NMR (500 MHz, DMSO-d6, δ / ppm):191.89, 172.39, 157.42, 146.30, 136.37, 135.72, 134.67, 133.13, 132.26, 130.72, 130.28, 129.53, 129.33, 129.37, 127.46, 126.13(2C), 123.06, 120.45, 118.63, 76.84, 51.47, 46.64, 41.47(2C), 34.29, 32.46(2C), 30.07; MS (m/z): 556.1(M+1).

**Methyl 3-[4-[6-(1, 3-benzodioxol-5-yl)-4-oxo-spiro [chromane-2, 4'-piperidine]-1'-yl] sulfonylphenyl] propanoate (5g).** Yield: 58 %; m.p.: 145-147 °C; Anal. Calcd for $C_{30}H_{29}NO_8S$: C, 63.93; H, 5.19; N; 2.49 %. Found: C, 63.72; H, 4.98; N, 2.39 %; IR(KBr, cm$^{-1}$):1733, 1694, 1334, 1270, 1166, 1159 cm$^{-1}$. $^1$H-NMR (400 MHz, DMSO-d6, δ / ppm): 7.83 (1H, *sd*, 5-H Chr., *J* = 2.4 Hz), 7.75 (1H, *dd*, 7-H Chr., *J* = 2.4 Hz, *J* = 8.8 Hz), 7.68 (2H, *d*, Aromatic *J* = 8 Hz), 7.54 (2H, *d*, Aromatic, *J* = 8 Hz), 7.18 (1H, *sd*, Aromatic *J* = 1.6 Hz), 7.06 (1H, *dd*, Aromatic *J* = 1.6 Hz, *J* = 8 Hz), 6.96 (1H, *d*, Aromatic *J* = 8 Hz), 6.84 (1H, *d*, 8-H Chr., *J* = 8.8 Hz), 6.04(2H, *s*, -OC**H**$_2$O-), 3.60(3H, *s*, -COOC**H**$_3$), 3.55(2H, *broad-d*, -N(C**H**$_2$)-, *J* = 11.6 Hz), 3.0(2H, *s*, -CO-C**H**$_2$-), 2.8(2H, *t*, -N(C**H**$_2$)-, *J* = 10.8 Hz), 2.73(2H, *t*, -C**H**$_2$-COOCH$_3$, *J* = 7.6 Hz), 2.57(2H, *t*, Ar-C**H**$_2$-CH$_2$-, *J* = 7.6 Hz), 2.0(2H, *broad-d*, C-C**H**$_2$-CH$_2$-, *J* = 13.6 Hz), 1.79(2H, *t*, C-C**H**$_2$-CH$_2$-, *J* = 13.0 Hz); $^{13}$C-NMR (500 MHz, DMSO-d6, δ / ppm):191.78, 172.34, 157.41, 146.32, 136.29, 135.70, 134.67, 133.21, 132.31, 130.67, 130.31, 129.48, 129.27, 129.32, 127.47,

126.09(2C), 123.07, 120.45, 118.63, 95.21, 76.94, 51.47, 46.68, 41.45(2C), 34.22, 32.45(2C), 30.04; MS (m/z): 564.0(M+1).

**Methyl 3-[4-[6-(4-dimethylaminophenyl)-4-oxo-spiro [chromane-2, 4'-piperidine]-1'-yl]sulfonylphenyl] propanoate (5h):** Yield: 46 %; m.p.: 141-145 °C; Anal. Calcd. for $C_{31}H_{34}N_2O_6S$: C, 66.17; H, 6.09; N; 4.98 %. Found: C, 66.28; H, 6.18; N, 5.12 %; IR(KBr, $cm^{-1}$): 1742, 1697, 1343, 1264, 1159, 1141 $cm^{-1}$. $^1$H-NMR (400 MHz, DMSO-$d^6$, δ / ppm): 7.89(1H, *sd*, 5-H Chr., *J* = 2.4 Hz), 7.70(2H, *d*, Aromatic, *J* = 8 Hz), 7.67(1H, *dd*, 7-H Chr., *J* = 2.4 Hz, *J* = 8.8 Hz), 7.62(2H, *d*, Aromatic *J* = 7.8 Hz), 7.47(2H, *d*, Aromatic, *J* = 8 Hz), 7.42(2H, *d*, Aromatic *J* = 7.8 Hz), 6.83(1H, *d*, 8-H Chr., *J* = 8.8 Hz), 3.69(6H, s, -N(C**H**$_3$)$_2$) 3.61(3H, *s*, -COOC**H**$_3$), 3.58(2H, *broad-d*, -N(C**H**$_2$)-, *J* = 12.0 Hz), 2.99(2H, *t*, -C**H**$_2$-COOCH$_3$, *J* = 8.0 Hz), 2.8(2H, *t*, -N(C**H**$_2$)-, *J* = 11.8 Hz), 2.7(2H, *s*, -CO-C**H**$_2$-), 2.60(2H, *t*, Ar-C**H**$_2$-CH$_2$-, *J* = 7.8 Hz), 2.1(2H, *broad-d*, C-C**H**$_2$-CH$_2$-, *J* = 12.4 Hz), 1.8(2H, *t*, C-C**H**$_2$-CH$_2$-, *J* = 13.0 Hz); $^{13}$C-NMR (500 MHz, DMSO-d6, δ / ppm):191.26, 172.42, 157.44, 146.34, 136.78, 135.86, 134.56, 133.23, 130.01, 129.67(2C), 129.34(2C), 127.49(2C), 126.07(2C), 123.08, 120.39, 118.71, 76.96, 51.39, 46.63, 41.43(2C), 40.36(2C), 34.24, 32.55(2C), 30.09; MS (m/z): 563.0(M+1).

**Methyl 3-[4-[4-oxo-6-[4-(trifluoromethyl) phenyl] spiro [chromane-2, 4'-piperidine]-1'-yl] sulfonylphenyl] propanoate (5i):** Yield: 75 %; m.p.: 130-135 °C; Anal. Calcd for $C_{30}H_{28}F_3NO_6S$: C, 61.32; H, 4.80; N; 2.38 %. Found: C, 61.22; H, 4.63; N, 2.41 %; IR(KBr, $cm^{-1}$): 1727, 1694, 1339, 1268, 1171, 1152 $cm^{-1}$; $^1$H-NMR (400 MHz, DMSO-$d^6$, δ / ppm): 7.83(1H, *sd*, 5-H Chr., *J* = 2.4 Hz), 7.68(2H, *d*, Aromatic, *J* = 8 Hz), 7.70(1H, *dd*, 7-H Chr., *J* = 2.4 Hz, *J* = 8.4 Hz), 7.58(2H, *d*, Aromatic, *J* = 8 Hz), 7.45(2H, *d*, Aromatic, *J* = 8 Hz),7.39(2H, *d*, Aromatic, *J* = 8 Hz), 6.84(1H, *d*, 8-H Chr., *J* = 8.4 Hz), 3.69(3H, *s*, -COOC**H**$_3$), 3.61(2H, *broad-d*, -N(C**H**$_2$)-, *J* = 11.6 Hz), 3.0(2H, *t*, -C**H**$_2$-COOCH$_3$, *J* = 7.6 Hz), 2.79(2H, *t*, -N(C**H**$_2$)-, *J* = 12.4 Hz), 2.7(2H, *s*, -CO-C**H**$_2$-), 2.67(2H, *t*, Ar-C**H**$_2$-CH$_2$-, *J* = 7.2 Hz), 2.0(2H, *broad-d*, C-C**H**$_2$-CH$_2$-, *J* = 11.6 Hz), 1.8(2H, *t*, C-C**H**$_2$-CH$_2$-, *J* = 12.4 Hz); $^{13}$C-NMR (500 MHz, DMSO-d6, δ / ppm):191.23, 172.47, 157.47, 146.38, 136.77, 135.84, 134.59, 133.29, 130.09, 129.63(2C), 129.37(2C), 127.52(2C), 126.11(2C), 123.07, 120.37, 118.68, 83.57, 76.97, 51.38, 46.61, 41.41(2C), 34.23, 32.57(2C), 30.07; MS (m/z): 588.0(M+1).

**Methyl 3-[4-[4-oxo-6-[4-(trifluoromethoxy) phenyl] spiro [chromane-2, 4'-piperidine]-1'-yl] sulfonylphenyl] propanoate (5j):** Yield: 49 %; m.p.: 135-139 °C; Anal. Calcd for $C_{30}H_{28}F_3NO_7S$: C, 59.69; H, 4.68; N; 2.32 %. Found: C, 59.54; H, 4.52; N, 2.28 %; IR(KBr, $cm^{-1}$): 1731, 1691, 1336, 1267, 1163, 1154 $cm^{-1}$. $^1$H-NMR (400 MHz, DMSO-$d^6$, δ / ppm): 7.81(1H, *sd*, 5-H Chr., *J* = 2.2 Hz), 7.71(2H, *d*, Aromatic, *J* = 7.8 Hz), 7.68(1H, *dd*, 7-H Chr., *J* = 2.2 Hz, *J* = 8.4 Hz), 7.54(2H, *d*, Aromatic, *J* = 7.8 Hz), 7.44(2H, *d*, Aromatic, *J* = 8 Hz), 7.40(2H, *d*, Aromatic, *J* = 8 Hz), 6.85(1H, *d*, 8-H Chr., *J* = 8.4 Hz), 3.69(3H, *s*, -COOC**H**$_3$), 3.6(2H, *broad-d*, -N(C**H**$_2$)-, *J* = 11.6 Hz), 2.99(2H, *t*, -C**H**$_2$-COOCH$_3$, *J* = 8.0 Hz), 2.81(2H, *t*, -N(C**H**$_2$)-, *J* = 12.8 Hz), 2.76(2H, *s*, -CO-C**H**$_2$-), 2.64(2H, *t*, Ar-C**H**$_2$-CH$_2$-, *J* = 7.6 Hz), 2.06(2H, *broad-d*, C-C**H**$_2$-CH$_2$-, *J* = 12.8 Hz), 1.79(2H, *t*, C-C**H**$_2$-CH$_2$-, *J* = 13.4 Hz); $^{13}$C-NMR (500 MHz, DMSO-d6, δ / ppm):191.24, 172.45, 157.46, 146.40, 136.73, 135.85, 134.61, 133.31, 130.21, 129.65(2C), 129.38(2C), 127.55(2C), 126.10(2C), 123.06, 120.39, 118.65, 86.76, 76.95, 51.36, 46.63, 41.42(2C), 34.22, 32.55(2C), 30.05; MS (m/z): 604.0(M+1).

**3)General synthetic procedure for synthesis of 9a-i.**

**1'-acetyl-6-bromo-spiro [chromane-2, 4'-piperidine]-4-one (6);** A solution of acetyl chloride (1.14 gm or 1 ml, 0.0146 M) in methylene chloride was added to a stirred and cooled solution of compound **3** (5 gm, 0.012 M), catalytic dimethylaminopyridine and triethylamine (2.48 ml, 0.018 M) in dry methylene chloride. The reaction mixture was stirred at room temperature for 2-3 h. Solvent was evaporated under vacuum gave solid residue. The residue was then dissolved in ethyl acetate and washed with 5 % aqueous hydrochloric acid (50 ml) followed by saturated sodium bicarbonate solution (50 ml) and water (50 ml). Ethyl acetate layer was dried and evaporated under reduced pressure gave solid residue. The residue crude product was purified over silica gel column chromatography using hexane: ethyl acetate (4:1) as an eluant, gave the (3.7 gm) pure compound **6** as white solid. Yield: 89% ; m.p.: 130-132°C; $^1$H-NMR (400 MHz, DMSO-$d^6$, δ / ppm): 7.90(1H, *sd*, 5-H chromanone, *J* = 2 Hz), 7.88-7.86(1H, *dd*, 7-H chromanone, *J* = 2 Hz, *J* = 8 Hz), 7.20-7.18(1H, *d*, 8-H chromanone, *J* = 8 Hz), 4.12-3.63 (2H, *2d*, -N(C**H**$_2$)-, *J* = 11.6 Hz, *J* = 12.4 Hz), 3.43-2.98(2H, *2t*, -N(C**H**$_2$)-, *J* = 12.0 Hz, *J* = 12.8 Hz), 2.87(2H, *s*, -CO-C**H**$_2$-), 2.34(3H, *s*, -COC**H**$_3$), 1.99-1.90(2H, *m*, C-C**H**$_2$-CH$_2$-), 1.78-1.56(2H, *2t*, C-C**H**$_2$-CH$_2$-, *J* = 12.8 Hz, *J* = 12.4 Hz); MS (m/z): 339.2(M+1).

**1'-acetyl-6-(4-methyl-3-nitro-phenyl) spiro [chromane-2, 4'-piperidine]-4-one (7);** A solution of sodium carbonate (4.06 gm, 0.0383M) in water (25 ml) was mixed with a solution of 4-methyl-3-nitrophenylboronic acid

(2.38 gm, 0.013 M) in ethanol (50 ml) and stirred for 15 min. A solution of compound 4 (3.7 gm, 0.0109 M) in toluene (100 ml) was added under nitrogen followed by tetrakistriphenyl phosphinopalladium (632 mg, 0.00054 M) and heated at reflux for 15 hr. Product was extracted using ethyl acetate (500 ml) and washed it with saturated sodium bicarbonate solution (500 ml), Water (500 ml), Ethyl acetate layer was dried and evaporated under reduced pressure gave solid residue. The residue crude product was purified over silica gel column chromatography using hexane: ethyl acetate (4:1) as an eluant, gave (3.42 gm) pure compound **7** as white solid. Yield: 79 %; m.p.: 192-195°C; $^1$H-NMR (400 MHz, DMSO-d$^6$, δ / ppm): 8.12(1H, *s*, Aromatic), 7.90(1H, *sd*, 5-H chromanone, *J* = 2 Hz), 7.88-7.86(1H, *dd*, 7-H chromanone, *J* = 2 Hz, *J* = 8 Hz), 7.42-7.40(1H, *d*, Aromatic, *J* = 7.8 Hz), 7.32-7.30(1H, *d*, Aromatic, *J* = 7.8 Hz), 7.20-7.18(1H, *d*, 8-H chromanone, *J* = 8 Hz), 4.12-3.63 (2H, *2d*, -N(C**H**$_2$)-, *J* = 12.4 Hz, *J* = 12.0 Hz), 3.43-2.98(2H, *2t*, -N(C**H**$_2$)-, *J* = 11.6 Hz, *J* = 12.0 Hz), 2.87(2H, *s*, -CO-C**H**$_2$-), 2.34(3H, s, -COC**H**$_3$), 2.01(3H, *s*, Ar-C**H**$_3$), 1.99-1.90(2H, *m*, C-C**H**$_2$-CH$_2$-), 1.78-1.56(2H, *2t*, C-C**H**$_2$-CH$_2$-, *J* = 12.4 Hz, *J* = 12.4 Hz); MS (m/z): 395.6(M+1).

**Methyl 3-[4-[6-(3-amino-4-methyl-phenyl)-4-oxo-spiro [chromane- 2, 4' -piperidine]-1'-yl] sulfonylphenyl] propanoate (8);** Ammonium format (3.45 gm, 1 Eq. w/w) was added into the clear solution of compound 7(3.45 gm, 0.0087 M) in methanol (100 ml). 10 % palladium on carbon (345 mg) was added under nitrogen atmosphere. Heated at reflux for 24 hr and cooled to room temperature. Palladium on carbon was removed by filtration. Filtrate was concentrated to dryness. Residue was stirred with water for 30 minute and suspended solid was collected by filtration gave (2.9 gm) technically pure compound **8** as white solid. Yield: 92 %; m.p.: 172-174°C. $^1$H-NMR (400 MHz, DMSO-d$^6$, δ / ppm): 7.91(1H, *sd*, 5-H chromanone, *J* = 1.8 Hz), 7.89-7.87(1H, *dd*, 7-H chromanone, *J* = 2 Hz, *J* = 8 Hz), 7.85-7.83(1H, *d*, Aromatic, *J* = 7.8 Hz), 7.72(1H, *s*, Aromatic), 7.42-7.40(1H, *d*, Aromatic, *J* = 7.8 Hz), 7.19-7.17(1H, *d*, 8-H chromanone, *J* = 8 Hz), 4.63(2H, *broad-s*, -NH$_2$)4.11-3.62 (2H, *2d*, -N(C**H**$_2$)-, *J* = 12.0 Hz, *J* = 12.8 Hz), 3.43-2.97(2H, *2t*, -N(C**H**$_2$)-, *J* = 12.4 Hz, *J* = 12.4 Hz), 2.88(2H, *s*, -CO-C**H**$_2$-), 2.33(3H, s, -COC**H**$_3$), 2.01(3H, *s*, Ar-C**H**$_3$), 2.01-1.92(2H, *m*, C-C**H**$_2$-CH$_2$-), 1.79-1.57(2H, *2t*, C-C**H**$_2$-CH$_2$-, *J* = 12.4 Hz, *J* = 12.0 Hz); MS (m/z): 364.7(M+1).

**Methyl 3-[4-[6-[3-(Alkylsulfonamido)-4-methyl-phenyl]-4-oxo-spiro [chromane-2, 4'-piperidine]-1'-yl] sulfonylphenyl] propanoate (9a-i);** A solution of substituted benzenesulfonyl chloride (0.0065 M) was added to a stirred and cooled solution of compound **8** (0.00054 M), catalytic dimethylaminopyridine and triethylamine (0.0065 M) in dry methylene chloride. The reaction mixture was stirred at room temperature for 12 h. Reaction mixture was evaporated to dryness under reduced pressure. The residue was dissolved in ethyl acetate and washed with 5 % hydrochloric acid solution (50 ml) followed by saturated sodium bicarbonate solution (50 ml) solution and water (50 ml). Ethyl acetate layer was passed through anhydrous sodium sulphate and evaporated under reduced pressure. The residue crude product was purified over silica gel column chromatography using hexane: ethyl acetate (4:1) as an eluant, gave the pure compound **9a-i** as white solid.

**4)Spectroscopic and analytical data**

**N-[5-(1'-acetyl-4-oxo-spiro[chromane-2,4'-piperidine]-6-yl)-2-methyl-phenyl]methane sulfonamide (9a).** Yield: 68 %; m.p.: 247-250 °C; Anal. Calcd. for $C_{23}H_{26}N_2O_5S$: C, 62.42; H, 5.92;N; 6.33 %. Found: C, 62.19; H, 5.67; N, 6.18%; IR(KBr, cm$^{-1}$): 3267, 1690, 1641, 1370, 1272, 1146, 1123 cm$^{-1}$. $^1$H-NMR (400 MHz, DMSO-d$^6$, δ / ppm): 9.11(1H, *s*, -NH-SO$_2$-), 7.79(1H, *sd*, 5-H chromanone, *J* = 2 Hz), 7.86(1H, *dd*, 7-H chromanone, *J* = 2 Hz, *J* = 8.2 Hz), 7.76(1H, *s*, Aromatic), 7.32(1H, *d*, Aromatic, *J* = 8 Hz), 7.27(1H, *d*, Aromatic, *J* = 8 Hz), 7.19(1H, *d*, 8-H chromanone, *J* = 8.2 Hz), 4.12-3.63 (2H, *2d*, -N(C**H**$_2$)-, *J* = 11.6 Hz, *J* = 12.0 Hz), 3.43-2.98(2H, *2t*, -N(C**H**$_2$)-, *J* = 12.0 Hz, *J* = 12.8 Hz), 2.97(3H, *s*, -SO$_2$C**H**$_3$), 2.87(2H, *s*, -CO-C**H**$_2$-), 2.23(3H, s, -COC**H**$_3$), 2.01(3H, *s*, Ar-C**H**$_3$), 1.94(2H, *m*, C-C**H**$_2$-CH$_2$-), 1.78-1.54(2H, *2t*, C-C**H**$_2$-CH$_2$-, *J* = 12.4 Hz, *J* = 12.0 Hz); $^{13}$C-NMR (500 MHz, DMSO-d6, δ / ppm):191.52, 171.93, 157.94, 137.12, 136.57, 134.50, 132.85, 131.06, 130.08, 122.98,122.47, 122.21, 120.47, 119.17, 78.33, 46.77, 43.83, 41.33, 36.42, 33.38, 21.27, 17.55, 14.07; MS (m/z): 441.1(M-1).

**N-[5-(1'-acetyl-4-oxo-spiro[chromane-2,4'-piperidine]-6-yl)-2-methyl-phenyl]cyclopropane carboxamide (9b).** Yield: 72 %; m.p.: 173-175 °C; Anal. Calcd. for $C_{26}H_{28}N_2O_4$: C, 72.20; H, 6.53; N; 6.48 %. Found: C, 72.34; H, 6.65; N, 6.52 %; IR(KBr, cm$^{-1}$): 3264, 1689, 1639, 1373, 1275, 1148, 1127 cm$^{-1}$. $^1$H-NMR (400 MHz, DMSO-d$^6$, δ / ppm): 9.58(1H, *s*, -NH-CO-), 7.9(1H, *sd*, 5-H chromanone, *J* = 2 Hz ), 7.85(1H, *dd*, 7-H chromanone, *J* = 2 Hz, *J* = 8.4 Hz), 7.77(1H, *s*, Aromatic), 7.34(1H, *d*, Aromatic, *J* = 8 Hz), 7.28(1H, *d*, Aromatic, *J* = 7.8 Hz), 7.18(1H, *d*, 8-H chromanone, *J* = 8.4 Hz), 4.13-3.64(2H, *2d*, -N(C**H**$_2$)-, *J* = 12 Hz, *J* = 12 Hz), 3.42-2.97(2H, *2t*, -N(C**H**$_2$)-, *J* = 12 Hz, *J* = 10.8 Hz), 2.89(2H, *s*, -CO-C**H**$_2$-), 2.26(3H, s, -COC**H**$_3$), 2.01(3H, *s*, Ar-C**H**$_3$), 1.99(1H, m, -COC**H**-), 1.92(2H, *m*, C-C**H**2-CH2-), 1.79-1.56(2H, *2t*, C-C**H**2-CH2-, *J* = 12.4 Hz, *J* = 12.0 Hz), 0.82-0.79(4H, *m*, (CH$_2$)$_2$ of

cyclopropane); $^{13}$C-NMR (500 MHz, DMSO-d6, δ / ppm):191.50, 171.90, 168.26, 157.98, 137.09, 136.54, 134.51, 132.87, 131.02, 130.07, 122.97,122.45, 122.19, 120.46, 119.14, 78.32, 46.79, 41.31, 36.40, 33.37, 33.04, 21.23, 17.54, 14.08, 7.10(2C); MS (m/z): 433.0(M+1).

**N-[5-(1'-acetyl-4-oxo-spiro[chromane-2,4'-piperidine]-6-yl)-2-methyl-phenyl]-2-methyl-propanamide (9c).**Yield: 57 %; m.p.: 224-227 °C; Anal. Calcd. for $C_{26}H_{30}N_2O_4$: C, 71.87; H, 6.96; N, 6.45 %. Found: C, 71.76; H, 6.79; N, 6.32%; IR(KBr, cm$^{-1}$): 3266, 1690, 1638, 1376, 1273, 1147, 1129 cm$^{-1}$. $^1$H-NMR (400 MHz, DMSO-d$^6$, δ / ppm): 9.57(1H, *s*, -NH-CO-), 7.87 (1H, *sd*, 5-H chromanone, *J* = 2 Hz ), 7.82 (1H, *dd*, 7-H chromanone, *J* = 2 Hz, *J* = 8.2 Hz), 7.78 (1H, *s*, Aromatic), 7.31(1H, *d*, Aromatic, *J* = 8 Hz), 7.29 (1H, *d*, Aromatic, *J* = 8 Hz), 7.19(1H, *d*, 8-H chromanone, *J* = 8.2 Hz), 4.13-3.65(2H, *2d*, -N(C**H**$_2$)-, *J* = 12.0 Hz, *J* = 12.0 Hz), 3.41-2.96(2H, *2t*, -N(C**H**$_2$)-, *J* = 12.0 Hz, *J* = 12.4 Hz), 3.38(1H, *m*, -C**H** ($CH_3$)$_2$), 2.87(2H, *s*, -CO-C**H**$_2$-), 2.24(3H, s, -COC**H**$_3$), 2.01(3H, *s*, Ar-C**H**$_3$), 1.93(2H, *m*, C-C**H**$_2$-$CH_2$-), 1.78-1.54(2H, *2t*, C-C**H**$_2$-$CH_2$-, *J* = 11.6, Hz, *J* = 12.0 Hz), 1.13(6H, *d*, -CH (C**H**$_3$)$_2$ *J* = 8.4 Hz); $^{13}$C-NMR (500 MHz, DMSO-d6, δ / ppm):191.56, 171.91, 168.38, 157.97, 137.09, 136.54, 134.51, 132.82, 131.04, 130.05, 122.95, 122.49, 122.25, 120.43, 119.20, 78.31, 46.76, 41.31, 36.41, 33.39, 33.15, 21.23, 17.52, 14.08, 7.15(2C); MS (m/z): 435.2(M-1).

**N-[5-(1'-acetyl-4-oxo-spiro[chromane-2,4'-piperidine]-6-yl)-2-methyl-phenyl]-2-chloro-acetamide (9d).** Yield: 64 %; mp: 233-237 °C; Anal. Calcd. for $C_{24}H_{25}ClN_2O_4$: C, 65.38; H, 5.71; N; 6.35 %. Found: C, 65.07; H, 5.53; N, 6.29 %; IR(KBr, cm$^{-1}$): 3267, 1690, 1616, 1388, 1161, 1274, 1141 cm$^{-1}$. $^1$H-NMR (400 MHz, DMSO-d$^6$, δ / ppm): 9.73(1H, *s*, -NH-CO-), 7.91(1H, *sd*, 5-H chromanone, *J* = 2 Hz), 7.87(1H, *dd*, 7-H chromanone, *J* = 2 Hz, *J* = 8 Hz), 7.7(1H, s, Aromatic), 7.41(1H, *d*, Aromatic, *J* = 7.8 Hz), 7.31(1H, *d*, Aromatic, *J* = 8 Hz), 7.19(1H, *d*, 8-H chromanone, *J* = 8 Hz), 4.34(2H, *s*, -COC**H**$_2$Cl), 4.13-3.63(2H, *2d*, -N(C**H**$_2$)-, *J* = 12.8 Hz, *J* = 13.2 Hz), 3.42-2.93(2H, *2t*, -N(C**H**$_2$)-, *J* = 12.4 Hz, *J* = 11.6 Hz), 2.89(2H, *s*, -COC**H**$_2$-), 2.24(3H, *s*, -COC**H**$_3$), 2.01(3H, *s*, Ar-C**H**$_3$), 1.94(2H, *m*, C-C**H**2-CH2-), 1.78-1.55(2H, *2t*, C-C**H**2-CH2-, *J* = 13.4 Hz, *J* = 12.8 Hz); $^{13}$C-NMR (500 MHz, DMSO-d6, δ / ppm):191.48, 171.96, 168.33, 157.97, 137.10, 136.55, 134.53, 132.87, 131.04, 130.09, 122.96, 122.49, 122.24, 120.46, 119.15, 78.36, 68.32, 46.78, 41.32, 36.44, 33.35, 21.24, 17.57, 14.09; MS (m/z): 441.0(M+1).

**N-[5-(1'-acetyl-4-oxo-spiro[chromane-2,4'-piperidine]-6-yl)-2-methyl-phenyl]-2-methyl-propane-1-sulfonamide (9e).** Yield: 55 %; MP: 95-98 °C; Anal. Calcd. for $C_{26}H_{32}N_2O_5S$: C, 64.44; H, 6.66; N, 5.78%. Found: C, 64.23; H, 6.52; N, 5.64%; IR(KBr, cm$^{-1}$): 3267, 1687, 1635, 1376, 1278, 1149, 1128 cm$^{-1}$. $^1$H-NMR (400 MHz, DMSO-d$^6$, δ / ppm): 9.10(1H, *s* ,-NH-$SO_2$-), 7.89(1H, *sd*, 5-H chromanone, *J* = 1.8 Hz), 7.84(1H, *dd*,7-H chromanone, *J* = 2 Hz, *J* = 8.4 Hz), 7.52(1H, *s*, Aromatic), 7.4(1H, *d*, Aromatic, *J* = 8. Hz), 7.30(1H, *d*, Aromatic, *J* = 7.8 Hz), 7.19(1H, *d*, 8-H chromanone, *J* = 8.4 Hz), 4.12-3.63(2H, *2d*, -N(C**H**$_2$)-, *J* = 12.8 Hz, *J* = 13.2 Hz), 3.42-2.97(2H, *2t*, -N(C**H**$_2$)-, *J* = 12.4 Hz, *J* = 12.0 Hz), 3.32(2H, *d*, -$SO_2$-C**H**$_2$-, *J* = 8.4 Hz), 2.89(2H, *s*, -CO-C**H**$_2$-), 2.34(3H, s, -COC**H**$_3$), 2.45(1H, *m*, -SO2-$CH_2$-C**H**-), 2.01(3H, *s*, Ar-C**H**$_3$), 1.99-1.90(2H, *t*, C-C**H**$_2$-$CH_2$-, *J* = 7.6 Hz), 1.77-1.56(2H, *2t*, C-C**H**$_2$-$CH_2$-, *J* = 12.4 Hz, *J* = 13.2 Hz), 1.28(6H, *d*, -CH (C**H**$_3$)$_2$, *J* = 7.6 Hz); $^{13}$C-NMR (500 MHz, DMSO-d6, δ / ppm):191.48, 171.90, 157.99, 137.07, 136.53, 134.56, 132.86, 131.06, 130.07, 122.93, 122.48, 122.28, 120.41, 119.23, 78.28, 46.74, 41.33, 36.45, 33.41, 33.17, 21.22, 17.53, 14.09, 12.28, 7.12(2C); MS (m/z): 483.3(M-1).

**N-[5-(1'-acetyl-4-oxo-spiro [chromane-2,4'-piperidine]-6-yl)-2-methyl-phenyl] cyclopentane sulfonamide (9f).** Yield: 46 %; MP: 170-173 °C; $C_{27}H_{32}N_2O_5S$: C, 65.30; H, 6.49; N; 5.64%. Found: C, 65.13; H, 6.34; N, 5.56%; IR(KBr, cm$^{-1}$): 3262, 1692, 1641, 1375, 1271, 1153, 1132 cm$^{-1}$. $^1$H-NMR (400 MHz, DMSO-d$^6$, δ / ppm): 9.10(1H, *s*, -NH-$SO_2$-), 7.93(1H, *sd*, 5-H chromanone, *J* = 2 Hz ), 7.88(1H, *dd*, 7-H chromanone, *J* = 2 Hz, *J* = 8 Hz), 7.76(1H, *s*, Aromatic), 7.33(1H, *d*, Aromatic, *J* = 8 Hz), 7.27(1H, *d*, Aromatic, *J* = 8 Hz), 7.19(1H, *d*, 8-H chromanone, *J* = 8.2 Hz), 4.12-3.56(3H, *m*, -N(C**H**$_2$)- & -$SO_2$-C**H**-), 3.42-2.97(2H, *2t*, -N(C**H**$_2$)-, *J* = 11.6 Hz, *J* = 12.0 Hz), 2.89-(2H, *s*, -CO-C**H**$_2$-), 2.26(3H, s, -COC**H**$_3$), 2.25-1.94(7H, *m*, Ar-C**H**$_3$ & -(C**H**$_2$)$_2$- cyclopentane), 1.93-1.23(8H, *m*, C-(C**H**$_2$)$_2$- & -(C**H**$_2$)$_2$- cyclopentane); $^{13}$C-NMR (500 MHz, DMSO-d6, δ / ppm):191.51, 171.93, 157.97, 137.08, 136.51, 134.56, 132.86, 131.04, 130.09, 122.95, 122.48, 122.21, 120.47, 119.17, 78.35, 46.81, 41.30, 36.42, 33.39, 33.05, 30.52, 29.21, 21.25, 19.87, 19.78, 17.56, 14.07; MS (m/z): 495.3(M-1).

**N-[5-(1'-acetyl-4-oxo-spiro[chromane-2,4'-piperidine]-6-yl)-2-methyl-phenyl]-3-chloro-propane-1-sulfonamide (9g).** Yield: 52 %; MP: 175-178 °C; $C_{25}H_{29}ClN_2O_5S$: C, 59.46; H, 5.79; N, 5.55%. Found: C, 59.26; H, 5.56; N, 5.48%; IR(KBr, cm$^{-1}$): 3268, 1687, 1636, 1374, 1272, 1144, 1124 cm$^{-1}$. $^1$H-NMR (400 MHz, DMSO-d$^6$, δ / ppm): 9.78(1H, *s*, -NH-$SO_2$-), 7.87(1H, *sd*, 5-H chromanone, *J* = 1.8 Hz), 7.87(1H, *dd*, 7-H chromanone, *J* = 2

Hz, *J* = 8.2 Hz), 7.64(1H, s, Aromatic), 7.39(1H, *d*, Aromatic, *J* = 8 Hz), 7.32(1H, *d*, Aromatic, *J* = 8 Hz), 7.19(1H, *d*, 8-H chromanone, *J* = 8 Hz), 4.13-3.62(4H, *m*, -N(C**H**$_2$)- & -SO$_2$C**H**$_2$-), 3.42-2.93(2H, *2t*, -N(C**H**$_2$)-, *J* = 12.4 Hz, *J* = 13.2 Hz), 2.89(2H, *s*, -COC**H**$_2$-), 2.53-2.39(2H, m, -C**H**$_2$-Cl), -2.25(3H, *s*, -COC**H**$_3$), 2.06(3H, *s*, Ar-C**H**$_3$), 1.95(2H, *m*, C-C**H**$_2$-CH$_2$-), 1.79-1.56(2H, *2t*, C-C**H**$_2$-CH$_2$-, *J* = 12.0 Hz, *J* = 12.8 Hz), 1.03-0.96(2H, *q*, -C**H**$_2$CH2-Cl, *J* = 8.4 Hz,); $^{13}$C-NMR (500 MHz, DMSO-d6, δ / ppm):191.51, 171.97, 157.96, 137.12, 136.57, 134.55, 132.84, 131.07, 130.11, 122.99, 122.50, 122.26, 120.45, 119.16, 78.38, 68.34, 46.75, 43.68, 41.33, 36.45, 33.37, 32.19, 21.27, 17.59, 14.08; MS (m/z): 503.2(M-1).

**N-[5-(1'-acetyl-4-oxo-spiro[chromane-2,4'-piperidine]-6-yl)-2-methyl-phenyl]propane-2- sulfonamide (9h).** Yield: 65 %; m.p.: 165-168 °C; Anal. Calcd. for $C_{25}H_{30}N_2O_5S$: C, 63.81; H, 6.43;N; 5.95%. Found: C, 63.98; H, 6.41; N, 6.02%; IR (KBr, cm$^{-1}$): 3265, 1689, 1640, 1373, 1275, 1148, 1127 cm$^{-1}$. $^1$H-NMR (400 MHz, DMSO-d$^6$, δ / ppm): 9.57(1H, *s*, -NH-CO-), 7.87(1H, *sd*, 5-H chromanone, *J* = 2 Hz), 7.81 (1H, *dd*, 7-H chromanone, *J* = 2 Hz, *J* = 8 Hz), 7.78(1H, *s*, Aromatic), 7.32(1H, *d*, Aromatic, *J* = 7.8 Hz),7.27(1H, *d*, Aromatic, *J* = 7.8 Hz), 7.17(1H, *d*, 8-H chromanone, *J* = 8 Hz), 4.13-3.65(2H, *2d*, -N(C**H**$_2$)-, *J* = 12.4 Hz, *J* = 12.0 Hz), 3.41-2.96(2H, *2t*, -N(C**H**$_2$)-, *J* = 12.0 Hz, *J* = 13.2 Hz), 3.32(1H, *m*, -C**H** (CH$_3$)$_2$), 2.89(2H, *s*, -CO-C**H**$_2$-), 2.23(3H, *s*, -COC**H**$_3$), 2.01(3H, *s*, Ar-C**H**$_3$), 1.93(2H, *m*, C-C**H**$_2$-CH$_2$-), 1.78-1.54(2H, *2t*, C-C**H**$_2$-CH$_2$- *J* = 12.8 Hz, *J* = 13.0 Hz), 1.12(6H, *d*, -CH (C**H**$_3$)$_2$, *J* = 7.6 Hz); $^{13}$C-NMR (500 MHz, DMSO-d6, δ / ppm):191.53, 171.93, 157.96, 137.13, 136.56, 134.52, 132.85, 131.05, 130.06, 122.98, 122.47, 122.18, 120.47, 119.17, 78.36, 46.80, 41.34, 36.43, 33.36, 33.03, 21.22, 20.78, 19.95, 17.53, 14.06; MS (m/z): 469.1(M-1).

**N-[5-(1'-acetyl-4-oxo-spiro [chromane-2,4'-piperidine]-6-yl)-2-methyl-phenyl]morpholine-4-carboxamide (9i).** Yield: 57 %; m.p.: 118-121 °C; Anal. Calcd. for $C_{27}H_{31}N_3O_5$: C, 67.91; H, 6.54; N, 8.80%. Found: C, 67.78; H, 6.38; N, 8.59 %; IR (KBr, cm$^{-1}$): 3263, 1687, 1640, 1376, 1277, 1151, 1131 cm$^{-1}$. $^1$H-NMR (400 MHz, DMSO-d$^6$, δ / ppm): 9.56(1H, *s*, -NH-CO-), 8.14 (1H, *s*, Aromatic), 7.90 (1H, *s*, 5-H chromanone, *J* = 2 Hz), 7.79(1H, *dd*, 7-H chromanone, *J* = 2 Hz, *J* = 8.2 Hz), 7.74 (1H, *d*, Aromatic, *J* = 8 Hz), 7.35(1H, *d* , Aromatic, *J* = 7.8 Hz), 7.25(1H, *d* , 8-H chromanone, *J* = 8.2 Hz), 4.13-3.65(2H, *2d*, -N(C**H**$_2$)-, *J* = 12.4 Hz, *J* = 12.0 Hz), 3.67(4H, *m*, morpholine), 3.43(4H, *m*, morpholine), 3.42-2.97(2H, *2t*, -N(C**H**$_2$)-, *J* = 11.6 Hz, *J* = 12.0 Hz), 2.89(2H, *s*, -CO-C**H**$_2$-), 2.23(3H, s, -COC**H**$_3$), 2.01(3H, *s*, Ar-C**H**$_3$), 1.94(2H, *m*, C-C**H**$_2$-CH$_2$-), 1.77-1.57(2H, *2t*, C-C**H**$_2$-CH$_2$-, *J* = 13.2 Hz, *J* = 11.6 Hz); $^{13}$C-NMR (500 MHz, DMSO-d6, δ / ppm):191.52, 179.52, 171.94, 157.97, 137.08, 136.52, 134.50, 132.85, 131.03, 130.06, 122.98, 122.46, 122.18, 120.45, 119.12, 78.31, 68.89(2C), 46.77, 41.34, 36.43, 33.38, 33.27(2C), 21.22, 17.56, 14.09; MS (m/z): 478.2(M+1).

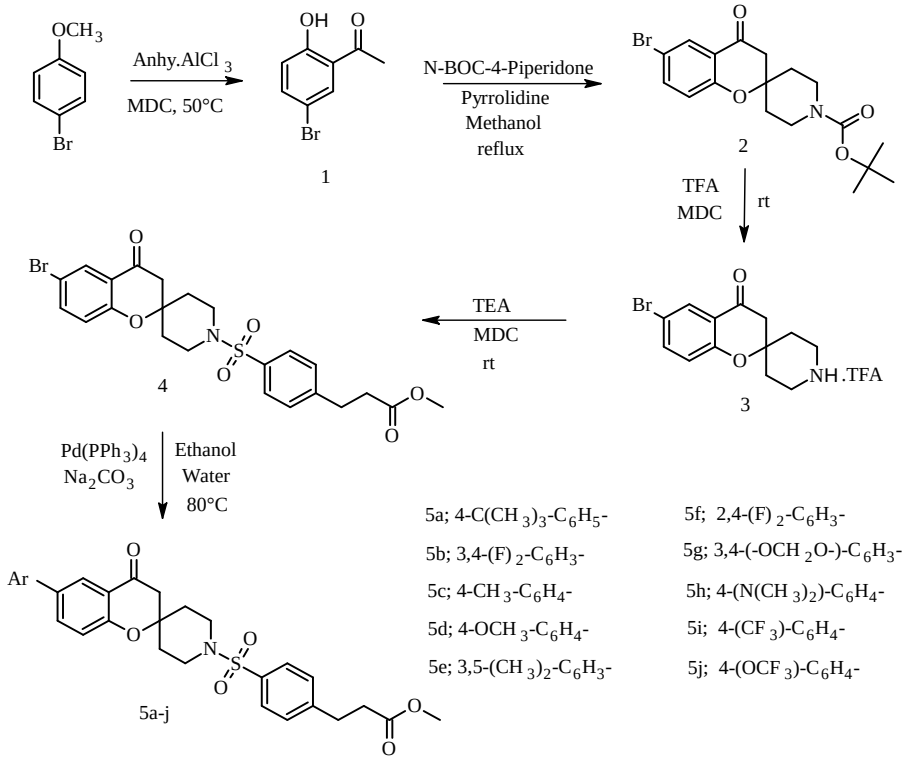
## RESULTS AND DISCUSSION

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 a Bruker DRX-400(400 MHz FT NMR) NMR spectrometer for a sample in DMSO-d6 with TMS as an internal reference. The mass spectra were recorded on a water-2996 LCMS instruments. The reagents were of LR grade and used without further purification.

In present work, compound **3** was synthesized accoarding to method reported literature [2]. Reaction between spirocyclicamine **3** and methyl (4-chlorosulfonylphenyl) propionate using triethylamine in tetrahydrofuran provided sulfonamide **4** in good yield. The isolated compound **4** was treated with different phenyl boronic acid in the presence of tetrakis triphenylphosphine palladium afforded compound **5a-j** in good yields.

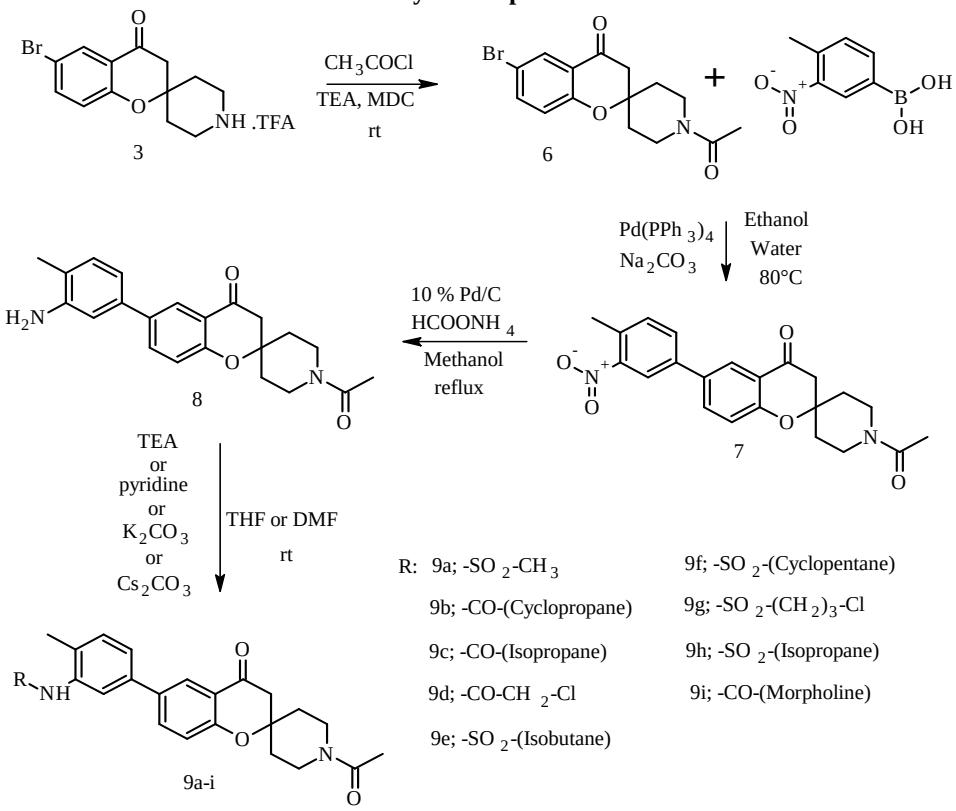
Compound **6** was synthesized by N-acetylation of the spirocyclic amine **3** with acetyl chloride at room temperature. Suzuki coupling reaction of intermediate **6** and 4-methyl -3-nitrophenyl boronic acid was done at 80°C in the presence of tetrakis triphenylphosphine palladium produced intermediate **7.** Reduction of nitro group was carried out using 10 % palladium on carbon & ammonium formate in refluxing methanol furnished amine **8**. Reaction of amine **8** with different alkyl sulfonyl chlorides or alkyl carbonyl chlorides afforded sulfonamide derivatives **9a-i**.

**Scheme-I: Synthetic protocol for 5a-j.**




5a; 4-C(CH 3)3-C6H5-
5b; 3,4-(F) 2-C6H3-
5c; 4-CH 3-C6H4-
5d; 4-OCH 3-C6H4-
5e; 3,5-(CH 3)2-C6H3-
5f; 2,4-(F) 2-C6H3-
5g; 3,4-(-OCH 2O-)-C6H3-
5h; 4-(N(CH 3)2)-C6H4-
5i; 4-(CF 3)-C6H4-
5j; 4-(OCF 3)-C6H4-

**Scheme-II: Synthetic protocol for 9a-i**




R: 9a; -SO 2-CH 3
9b; -CO-(Cyclopropane)
9c; -CO-(Isopropane)
9d; -CO-CH 2-Cl
9e; -SO 2-(Isobutane)
9f; -SO 2-(Cyclopentane)
9g; -SO 2-(CH 2)3-Cl
9h; -SO 2-(Isopropane)
9i; -CO-(Morpholine)

The structures of the compound **5** & **9** were confirmed by spectral techniques (ms, IR and $^1$H NMR). In $^1$H NMR all aromatic protons resonate between 8.05 to 6.85 δ. Compound **5** showed sharp singlet resonate near 3.7 δ due to -COOC**H**$_3$, protons of -N(C**H**$_2$)$_2$- & -C(C**H**$_2$)$_2$- of piperidine ring resonate between 3.6-3.0 δ and 2.1-1.1 δ respectively, Ar-COC**H**$_2$- resonate near 2.7 δ, -C**H**$_2$-COOCH$_3$ and Ar-C**H**$_2$- resonate near 2.8 and 2.68 δ respectively and IR stretching band of -**CO**OCH$_3$- and Ar-**CO**- absorption observes near 1733 cm$^{-1}$ and 1694 cm$^{-1}$ respectively. >N-**SO**$_2$- absorption observes near 1334 cm$^{-1}$ and 1159 cm$^{-1}$. Ether linkage of chromone ring resonates at 1270 cm$^{-1}$ and 1166 cm$^{-1}$. In case of Compound **9**, all aromatic protons and -NH- resonate between 9.6-7.1 δ. protons of -N(C**H**$_2$)$_2$- resonate between 4.13-3.64 δ & 3.42-2.97 δ and protons of -C-(C**H**$_2$)$_2$- resonate between 1.90-2.03 δ & 1.79-1.56 δ. Two methyl protons of -COC**H**$_3$ and Ar-C**H**$_3$ resonate near 2.26 δ and 2.01 δ respectively. IR stretching absorption of -**NH**SO$_2$- Ar-**CO**-, and -N-**CO**CH$_3$ absorption observe near 3264 cm$^{-1}$, 1689 cm$^{-1}$ and 1639 cm$^{-1}$ respectively. -NH-**SO**$_2$- absorption observes near 1373 cm$^{-1}$ and 1148 cm$^{-1}$. Ether linkage of chromone ring observes near 1275 cm$^{-1}$ and 1127 cm$^{-1}$.

**Antimicrobial Activity**

The MICs of synthesized compounds were carried out by broth microdilution method as described by Rattan [17]. Antibacterial activity was screened against two gram positive bacteria (*S. aureus* MTCC 96, *S. pyogenes* MTCC 442) and two gram negative bacteria (*E. coli* MTCC 443, *P. aeruginosa* MTCC 1688). Ampicillin was used as a standard antibacterial agent. Antifungal activity was screened against three fungal species *C. albicans* MTCC 227, *A. niger* MTCC 282 and *A. clavatus* MTCC 1323. Griseofulvin was used as a standard antifungal agent. All MTCC cultures were collected from Institute of Microbial Technology, Chandigarh and tested against above mentioned known drugs. Mueller hinton broth was used as nutrient medium to grow and dilute the drug suspension for the test. Inoculum size for test strain was adjusted to 108 CFU (Colony Forming Unit) per milliliter by comparing the turbidity. DMSO was used as diluents to get desired concentration of drugs to test upon standard bacterial strains. Serial dilutions were prepared in primary and secondary screening. The control tube containing no antibiotic was immediately sub cultured (before inoculation) by spreading a loopful evenly over a quarter of plate of medium suitable for the growth of the test organism and put for incubation at 37 °C overnight. The tubes were then incubated overnight. The MIC of the control organism was read to check the accuracy of the drug concentrations. The lowest concentration inhibiting growth of the organism was recorded as the MIC. All the tubes not showing visible growth (in the same manner as control tube described above) was sub cultured and incubated overnight at 37 °C. The amount of growth from the control tube before incubation (which represents the original inoculum) was compared. Subcultures might show: similar number of colonies indicating bacteriostatic; a reduced number of colonies indicating a partial or slow bactericidal activity and no growth if the whole inoculum has been killed. The test must include a second set of the same dilutions inoculated with an organism of known sensitivity. Each synthesized drug was diluted obtaining 6400 µg/ml concentration, as a stock solution. In primary screening 1280 µg/ml, 640µg/ml and 320 µg/ml concentrations of the synthesized drugs were taken. The active synthesized drugs found in this primary screening were further tested in a second set of dilution against all microorganisms. The drugs found active in primary screening were similarly diluted to obtain 160 µg/ml, 80 µg/ml, 40 µg/ml, and 20 µg/ml concentrations. The highest dilution showing at least 99 % inhibition is taken as MIC.

In case of compound **5**, from the activity data of compound showed that groups like 4-*tert*-butyl **5a**, 4-methyl **5c**, 4-methoxy **5d** and 4-trifluoromethyl **5i** at para position showed moderate activity againsts *E.coli* and *B.subtilis*, while 4-dimethylamine **5h**, 4-trifluoromethoxy **5j** at para position showed moderate activity againsts *P.aeruginosa* and *B.subtilis*. 3, 4-methylinedioxy **5g** like bicyclic system also showed equivelent activity to 4-methyl **5c**. MIC results showed that disubstituted compounds were more active then mono substituted compounds. 3, 4-difluoro **5b** and 2, 4-difluoro **5f** were more active then mono substitution, but showed different activity profile. **5b** showed moderate activity against all bacterial strain except *E.coli*, while **5f** showed moderate activity against all bacterial strain except *P.aeruginosa*. 3, 5-dimethyl **5e** showed best activity profile ever synthesized derivatives **5a-j**.

Except 4-trifluoromethy **5i,** all ather derivatives showed moderate activity against fungai *C.albicans*. 4-*tert*-butyl **5a**, 3, 5-dimethyl **5e,** 2, 4-difluoro **5f** and 4-trifluoromethoxy **5j** was less active then 4-methyl **5c,** 4-methoxy **5d** and 4-dimethylamine **5h**. 3, 4-difluoro **5b** and 3, 4-methylinedioxy **5g** showed best activity profile ever synthesized derivatives **5a-j**.

Activity data of compounds **5a-j** and **9a-i** showed that replacement of 4-(3-methoxybut-3-en-1-yl) benzene sulfonyl group by simple acetyl group showed significant improvement in activity.

In case of sulfonamide linked compounds methyl **9a** and isopropane **9h**, both showed less activity against *P.aeruginosa*. But compare to **9h**, **9a** showed litter better activity profile with other bacterial strain. Isobutane **9e** showed moderately improved activity against all becterial strain. Alicyclic ring system like cyclopentane **9f** also showed moderate activity with all becteria except *S.aureas*. 3-chloropropane **9g** showed best activity profile ever synthesized derivatives **5a-j** and **9a-i**.

**Table I: Antimicrobial screening results of compounds 5a–j and 9a–i.**

| Compound | R/Ar | MIC, µg/ml | | | | |
|---|---|---|---|---|---|---|
| | | Bacterial model | | | | Fungal model |
| | | *P.aeruginosa* | *E.coli* | *S.aureas* | *B.subtilis* | *C.albicans* |
| **5a** | 4-$C(CH_3)_3$-$C_6H_4$- | >1280 | 640 | 1280 | 320 | 640 |
| **5b** | 3,4-$(F)_2$-$C_6H_3$- | 320 | 1280 | 640 | 640 | 160 |
| **5c** | 4-$CH_3$-$C_6H_4$- | >1280 | 640 | 1280 | 160 | 320 |
| **5d** | 4-$OCH_3$-$C_6H_4$- | 1280 | 640 | 1280 | 320 | 320 |
| **5e** | 3,5-$(CH_3)_2$-$C_6H_3$- | 640 | 320 | 640 | 320 | 640 |
| **5f** | 2,4-$(F)_2$-$C_6H_3$- | 1280 | 320 | 640 | 160 | 640 |
| **5g** | 3,4-(-$OCH_2O$-)-$C_6H_3$- | 1280 | 640 | >1280 | 160 | 160 |
| **5h** | 4-(-$N(CH_3)_2)_3$-$C_6H_4$- | 640 | 1280 | >1280 | 160 | 320 |
| **5i** | 4-$(CF_3)$-$C_6H_4$- | >1280 | 640 | 1280 | 320 | 1280 |
| **5j** | 4-$(OCF_3)$-$C_6H_4$- | 320 | 1280 | >1280 | 320 | 640 |
| **9a** | $CH_3$-$SO_2$- | 1280 | 160 | 320 | 800 | 160 |
| **9b** | (Cyclopropane)-CO- | 1280 | 640 | 160 | 400 | 320 |
| **9c** | (Isopropane)-CO- | 640 | 160 | 640 | 160 | 800 |
| **9d** | Cl-$CH_2$-CO- | >1280 | 800 | 640 | 320 | 160 |
| **9e** | (Isobutane)-$SO_2$- | 640 | 320 | 320 | 800 | 800 |
| **9f** | (Cyclopentane)-$SO_2$- | 160 | 800 | 1280 | 160 | 160 |
| **9g** | Cl-$(CH_2)_3$-$SO_2$- | 640 | 160 | 160 | 160 | 800 |
| **9h** | (Isopropane)-$SO_2$- | 1280 | 800 | 160 | 400 | 320 |
| **9i** | (morpholine)-CO- | 1280 | 640 | 640 | 160 | 320 |
| - | *Ciprofloxacin* | 10 | 20 | 10 | 5 | - |
| - | *Flucanazole* | - | - | - | - | 10 |

In case of amide linkage cyclopropane **9b**, chloromethylene **9d** and morpholine urea **9i** was less active against *P.aeruginosa* but showed moderate activity trend against remaining all bacterial strains. Isopropane **9c** showed best activity trend with all becteria compare to other amide compounds.

Cyclopropane carboxamide **9b**, isopropane sulfonamide **9h** and morpholine urea **9i** showed significant activity then isopropane carboxamide **9c**, isobutene sulfonamide **9e** and 3-chloropropane sulfonamide **9g** against fungai *C.albicans*. Compounds methane sulfonamide **9a**, chloromethylene carboxamide **9d** and cyclopentane sulfonamide **9f** showed best activity amongs **9a-i** against *C.albicans***.**

## CONCLUSION

In conclusion, we have described efficient synthetic method for synthesis of spirochromanone based new chemical entiety. Synthesized compounds were evaluated against some becteria and fungai. The structure-activity relationship studies revealed that compound with ortho and meta substitutions are more activite then para substation. 4-*tert*-butyl **5a**, 4-methyl **5c**, 4-methoxy **5d**, 4-trifluoromethyl **5i**, 4-dimethylamine **5h** and 4-trifluoromethoxy **5j** all are moderately active against some bacterial strain. Disubstituted derivatives are more active then mono substituted compounds. 3, 5-dimethyl **5e** is the most active compound ever synthesized **5a-j**.

In case of sulfonamide linkage, linear aliphatic chain places more impact on activity. Compare to isopropyl **9h**, methyl **9a** shows better activity profile, isobutene **9e** shows moderate activity against all becteril strain and 3-chloropropane **9g** shows best activity profile ever synthesized derivatives **5a-j** and **9a-i**. In case of amide linkage, Isopropane **9c** shows best activity compare to cyclopropane **9b**, chloromethylene **9d** and morpholine urea **9i.**

All **5a-j** & **9a-i** are moderately activity against *C.albicans* except 4- trifluoromethyl **5i**. 3, 4-Disubstituted derivatives like 3, 4-difluoro **5b**, & 3, 4-methylenedioxy **5g** are best activite moity compare to rest all **5a-j**. In case of **9a-i**, methane sulfonamide **9a**, chloromethylene carboxamide **9d** & cyclopentane sulfonamide **9f** shows significantly improved activity against *C.albicans*.

**Acknowledgement**
The authors are thankful to the DNC Pharma Ltd. Ahmedabad, Gujarat, India for providing laboratory facilities & analytical support. The authors are also thankful to the central diagnostic laboratory, Surat, Gujarat, India for biological activity acquisition coordinating facility.

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