2-Phenyl indole & Arylsulphonamide: novel scaffolds bactericidal against *Mycobacterium tuberculosis*

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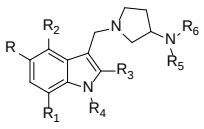
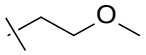
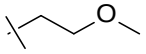
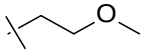
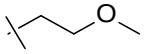
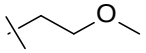
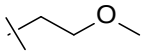
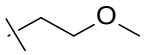
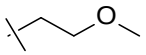
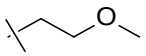
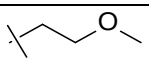
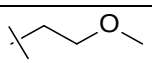
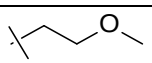
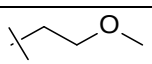
Chemical synthesis

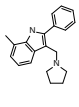
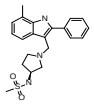
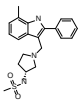
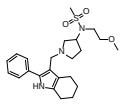
All anhydrous solvents, reagent grade solvents for chromatography and starting materials were purchased from either Sigma Aldrich Chemical Co. or Fisher Scientific. Water was distilled and purified through a Milli-Q water system (Millipore Corp., Bedford, MA). General methods of purification of compounds involved the use of silica cartridges purchased from Grace and Combiflash Purification systems. The reactions were monitored by TLC on pre-coated Merck 60 F254 silica gel plates and visualized using UV light (254 nm). All compounds were analyzed for purity by HPLC and characterized by ^{1}H NMR using Bruker 300 MHz NMR and/or Bruker400 MHz NMR spectrometers. Chemical shifts are reported in ppm (δ) relative to the residual solvent peak in the corresponding spectra; chloroform δ 7.26, methanol δ 3.31, DMSO δ 2.5, and coupling constants (J) are reported in hertz (Hz) (where s = singlet, bs = broad singlet, d = doublet, dd =double doublet, bd = broad doublet, ddd = double doublet of doublet,t = triplet, tt = triple triplet, q = quartet, m = multiplet) and analyzed using ACD NMR data processing software. Mass spectra values are reported as m/z. All reactions were conducted under nitrogen unless otherwise noted. Solvents were removed in vacuo on a rotary evaporator. All final compounds for biological testing were purified by reverse phase HPLC with >95% purity (Shimadzu HPLC instrument with a Hamilton reversed phase column (HxSil, C18, 3 µm, 2.1 mm × 50 mm (H2)). Eluent A, 5% CH_3CN in H_2O; eluent B, 90% CH_3CN in H_2O. A flow rate of 0.2 mL/min was used with UV detection at 254 nm and 214 nm. Abbreviations: NMP = N-methyl pyrrolidine, HCl = hydrochloric acid DMF = N, N-dimethylformamide,NaH = sodium hydride. EI =electrospray ionization, HRMS = high resolution mass spectrometry

Abbreviations: NMP= N-methyl Pyrrolidine; HCl = hydrochloric acid; DMF = dimethylformamide; DCM = dichloromethane; NaH= sodium hydride.

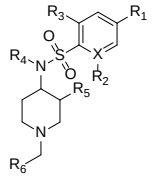


Supporting Table 1: SAR modifications of 2-Phenyl indoles

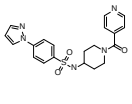
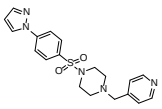
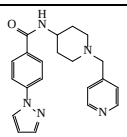
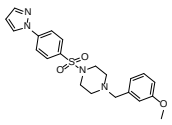
Compound	R	R_1	R_2	R_3	R_4	R_5	R_6	MIC(µM)
1	H	CH_3	H	Phenyl	H	methanesulphonyl		1.10
2	H	CH_3	H	Phenyl	H	methanesulphonyl	H	1.50
3	H	CH_3	H	Phenyl	CH_3	methanesulphonyl		1.50
4	H	CH_3	H	Phenyl	H	Isopropylsulphonyl	H	3.12
5	H	CH_3	H	Phenyl	H	H		3.12
6	H	CH_3	H	Phenyl	H	H	H	3.12
7	H	CH_3	H	4-Fluoro Phenyl	H	methanesulphonyl		6.25
8	H	OCH_3	H	Phenyl	H	methanesulphonyl		6.25
9	H	H	H	Phenyl	H	methanesulphonyl		6.25
10	H	CH_3	H	4-Methyl Phenyl	H	methanesulphonyl		25
11	H	CH_3	H	H	Benzyl	methanesulphonyl		25
12	CH_3	CH_3	H	Phenyl	H	methanesulphonyl		100
13	H	CH_3	H	H	H	methanesulphonyl		100
14	H	CH_3	H	4-Pyridine	H	methanesulphonyl		200
15	H	Isopropyl	H	Phenyl	H	methanesulphonyl		12.5
16	H	CH_3	F	Phenyl	H	methanesulphonyl		25

 **17** MIC 12.5 µM	 **18** MIC 3.1 µM	 **19** MIC 3.1 µM	 **20** MIC 3.1 µM

Supporting Table 2: SAR modifications of Arylsulphonamides

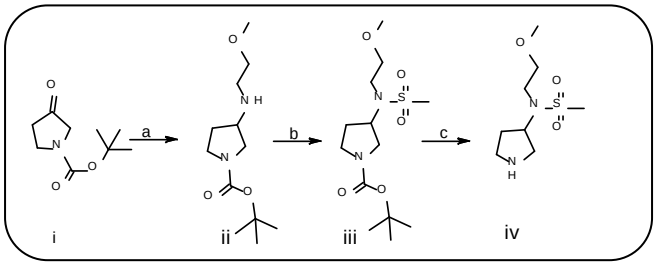


Compound	R_1	R_2	R_3	R_4	R_5	R_6	X	MIC (µM)
21	Pyrazole	H	H	H	H	4-pyridinemethyl	C	1.10
22	Pyrazole	H	CH_3	H	H	4-pyridinemethyl	C	0.39
23	Pyrazole	-	H	H	H	4-pyridinemethyl	N	1.50
24	Oxazole	H	H	H	H	4-pyridinemethyl	C	6.25
25	Pyrazole	H	H	CH_3	H	4-pyridinemethyl	C	12.5
26	Pyrazole	H	H	H	OCH_3	4-pyridinemethyl	C	25
27	Pyrazole	H	H	H	H	3-pyridinemethyl	C	100
28	Pyrazole	-	CH_3	H	H	4-pyridinemethyl	N	6.25
29	Phenyl	H	H	H	H	4-pyridinemethyl	C	6.25

 **30** MIC 6.3 µM	 **31** MIC 12.5 µM	 **32** MIC >200	 **33** MIC >200

Phenyl indoles: Preparation of key Intermediates and final compounds

Scheme 1: Synthesis of N-(2-methoxyethyl)-N-(pyrrolidin-3-yl) methane sulfonamide



Reagents and conditions: (a) 2-methoxyethanamine, sodium cyanoborohydride, DCM, 5h, 51% (b) methanesulphonylchloride, triethylamine, dichloromethane, RT, 1h, 41 % (c) dichloromethane, TFA RT, 1h, 78%

(1)Synthesis of tert-butyl 3-((2-methoxyethyl) amino) pyrrolidine-1-carboxylate(ii). Yield: 51 %.

To a stirred solution of tert-butyl 3-oxopyrrolidine-1-carboxylate **(i)** (1.5 g, 8.11 mmol) in DCM (15 mL) were added 2-methoxyethan-1-amine (0.66 g, 8.918 mmol) and AcOH (0.1 mL) at RT. Subsequently to this sodium cyano borohydride(0.76 g. 12.162 mmol) was added in portion wise at 0 °C and stirred for 5 h at RT. The progress of the reaction was monitored by TLC. After completion of starting material, the reaction mixture was poured into water and extracted with DCM (2 X50 mL). The combined organic extracts were washed with H_2O, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography eluting with 2-3 % MeOH in DCM to afford tert-butyl 3-((2-methoxyethyl) amino) pyrrolidine-1-carboxylate **3** as a pale yellow liquid. Yield: 1 g, 51 %.
MS (ES+): m/z =245.19 (m+1)

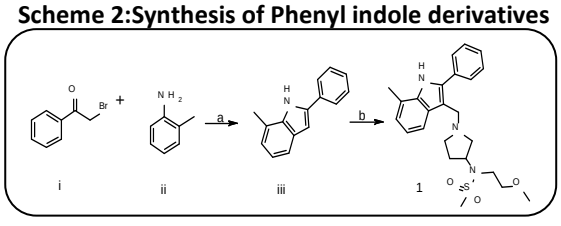
(2)Synthesis of tert-butyl 3-(N-(2-methoxyethyl) methylsulfonamido) pyrrolidine-1-carboxylate (iii). Yield: 35%

To a stirred solution of tert-butyl 3-((2-methoxyethyl) amino) pyrrolidine-1-carboxylate **(ii)** (1 g, 4.098 mmol) in DCM (10 mL) were added triethylamine (0.85 mL, 6.14 mmol) followed by methane sulfonyl chloride (0.56 g, 4.91 mmol) at 0°C. The resulting mixture was stirred at RT for 1 h. After the completion of the reaction, the reaction mixture was poured into water and extracted with DCM (2 X50 mL). The combined organic extracts were washed with H_2O, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography eluting with 0-1% MeOH in DCM to afford tert-butyl 3-(N-(2-methoxyethyl)methylsulfonamido)pyrrolidine-1-carboxylate **(iii)** as a pale yellow liquid. Yield: (0.46 g, 35%).
MS (ES+): m/z =323.42 (m+1)

(3)Synthesis of N-(2-methoxyethyl)-N-(pyrrolidin-3-yl) methane sulfonamide (iv). Yield: 78%

To a stirred solution of tert-butyl 3-(N-(2-methoxyethyl) methylsulfonamido) pyrrolidine-1-carboxylate **(iii)** (0.28 g, 0.86 mmol) in DCM (5 mL) was added TFA (0.6 mL) at 0°C and stirred at RT for 2 h. Then the reaction mixture was concentrated under vacuum. The residue was dissolved in 10% MeOH in DCM and basified with solid $NaHCO_3$. The solid remained was filtered. The filtrate was concentrated under vacuum to afford N-(2-methoxyethyl)-N-(pyrrolidin-3-yl) methane sulfonamide **(iv)** as a pale yellow liquid. Yield: 150 mg, 78 %.
MS (ES+): m/z =223.30(m+1)

Scheme 2:Synthesis of Phenyl indole derivatives

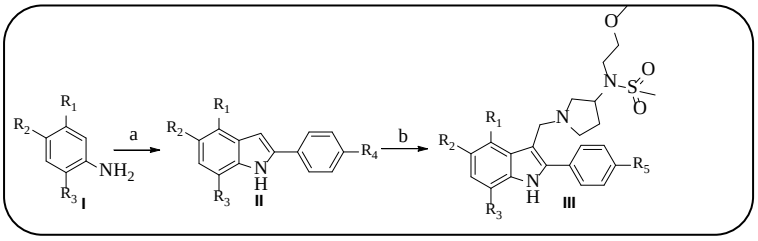


Reagents and conditions: (a) dimethyl aniline, xylene, overnight, 100^{o}C, 48% (b)N-(2-methoxyethyl)-N-(pyrrolidin-3-yl)methane sulphonamide, 40% formalin,dioxane, 22%

(4) Synthesis of 7-Methyl-2-phenyl-1H-indole (iii). Yield : 48%

To a stirred solution of *o*-toluidine**(ii)** (3.22 g, 30 mmol) in dimethylaniline (4 mL) was added a solution of 2-bromo-1-phenylethan-1-one **(i)** (2 g, 10 mmol) in xylene (10 mL) drop wise at 100 ^{0}C. Then the reaction mixture was heated at 150 ^{0}C (overnight) and the progress of the reaction was monitored by LCMS. After completion of the reaction, dilute HCl (10 mL, 1.5 N) was added to the reaction mixture, stirred for 10 minutes and was extracted with EtOAc (2 X50 mL). The combined organic extracts were washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified over by column chromatography eluting with 1% EtOAc in Hexane to afford 7-methyl-2-phenyl-1H-indole **(iii)** as a white solid. Yield: 1g, 48%. MS (ES+): m/z =208.27(m+1)

Scheme 3: Synthesis of phenyl indole derivatives



R_1=H, F; R_2=H, CH_3; R_3=CH_3, F, CF_3

Reagents and conditions: (a) acetophenone, N,N-dimethylaniline, MW, 140^{0}C (b) amine, $ZnCl_2$, Formaldehyde, Ethanol, 2h, RT

(5)N-(2-Methoxyethyl)-N-(1-((7-methyl-2-phenyl-1H-indol-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide (1). Yield: 22%

To a cold solution of glacial acetic acid (3 mL), N-(2-methoxyethyl)-N-(pyrrolidin-3-yl) methane sulfonamide **(intermediate iv in Schem-1)** (1.07 g, 4.83 mmol) and 40% formalin (5 mL), was added in drop wise a solution of 7-methyl-2-phenyl-1H-indole (0.5 g, 2.415 mmol) in dioxane (5 mL). Then the reaction mixture was allowed to stirred at 25°C for 12 h. Saturate $NaHCO_3$ solution was added to the reaction mixture and extracted with DCM (2x50 mL). The combined organic layer was washed with water, brine solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude material was purified over PREP TLC eluting with 5% MeOH in DCM to afford the N-(2-Methoxyethyl)-N-(1-((7-methyl-2-phenyl-1H-indol-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide(1), (230 mg, 22 %) as a white solid.

^{1}H NMR (400MHz,DMSO-d_6) δ ppm 2.09-2.23 (m, 2H), 2.25 (s, 3H), 2.60 - 2.53 (m, 2H), 2.79 (d, *J* = 7.1 Hz, 2H), 2.87 (s, 3H), 3.14 (s, 3H), 3.45 - 3.35 (m, 4H), 3.76 - 3.59 (m, 2H), 4.35- 4 .25 (m, 1H), 6.98 - 6.87 (m, 2H), 7.44 - 7.35 (m, 1H), 7.55 - 7.48 (m, 3H), 7.88 (d, *J* = 7.6 Hz, 2H), 11.05 (s, 1H); HRMS: m/z(ES+) 442.21606 (MH+) for $C_{24}H_{31}N_3O_3S$

(6)N-(1-((7-methyl-2-phenyl-1H-indol-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide(2). Yield: 62.8%

To a solution of 1-((7-methyl-2-phenyl-1H-indol-3-yl)methyl)pyrrolidin-3-amine (109 mg, 0.36 mmol) in DCM (5 mL) was added N,N'-Diisopropylethylamine (1 mL, 0.36 mmol) and stirred for 20 minutes. Methanesulfonyl chloride (0.028mL, 0.36 mmol) was added and stirred the reaction mixture for 2h at RT. After the completion of the reaction, the reaction mixture was diluted with dichloromethane and washed with water, brine solution. The organic layer was dried over sodium sulphate, and concentrated under reduced pressure to get the crude compound which was purified by chromatography using silica gel and methanol/dichloromethane as eluent to getN-(1-((7-methyl-2-phenyl-1H-indol-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide (86 mg, 62.8 %).

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.55-1.69 (m, 2H), 2.00-2.23 (m, 2H), 2.25-2.42 (m, 2H), 2.53-2.61 (m, 1H), 2.84 (s, 3H), 3. 14-3.22 (m, 1H), 3.63-3.83 (m, 4H), 6.85-6.99 (m, 2H), 7.33-7.44 (m, 1H), 7.46-7.57 (m, 3H), 7.81-7.91 (m, 2H), 10.52(s, 1H), 11.03 (s, 1H); HRMS: *m/z* (ES+) = 384.17405 (MH^+) for $C_{21}H_{25}N_3O_2S$.

(7)N-(1-((1,7-dimethyl-2-phenyl-1H-indol-3-yl)methyl)pyrrolidin-3-yl)-N-(2-methoxyethyl)methanesulfonamide(3). Yield: 33%

To a solution of N-(2-methoxyethyl)-N-(pyrrolidin-3-yl)methanesulfon amide (219 mg, 0.99 mmol) in ethanol (10 mL) was added zinc chloride (46.2 mg, 0.99 mmol), formaldehyde solution (0.027mL, 0.99 mmol) and1,7-dimethyl-2-phenyl-1H-indole (109mg, 0.49 mmol).The reaction mixture was stirred for a period of 2 h at rt. After the completion of the reaction, the reaction mixture was diluted with water and basified with aqueous sodium hydroxide solution. The aqueous was extracted with ethylacetate. The organic layer was washed with water, brine solution and dried over anhydrous sodium sulphate. The organic layer was evaporated under reduced pressure to get the crude compound which was purified by chromatography using silica gel and methanol/dichloromethane as eluent to get N-(1-((1,7-dimethyl-2-phenyl-1H-indol-3-yl)methyl)pyrrolidin-3-yl)-N-(2-methoxyethyl)methanesulfonamide(74.0 mg, 33.0 %).

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.72-1.87 (m, 1H), 2.01 (s, 1H), 2.06-2.28 (m, 2H), 2.49 (dd, *J* = 10.36, 8.29 Hz, 1H), 2.73 (dd, *J* = 10.46, 4.05 Hz, 1H), 2.79-2.88 (m, 4H), 2.89-3.02 (m, 3H), 3.27 (s, 3H), 3.37-3.47 (m, 3H), 3.70 (s, 2H), 3.80-3.89 (m, 3H), 4.34 (dd, *J* = 8.10, 3.96 Hz, 1H), 6.95-7.08 (m, 2H), 7.39-7.55 (m, 5H), 7.61 (d, *J* = 7.72 Hz, 1H); HRMS: *m/z* (ES+) = 456.23150 (MH^+) for $C_{25}H_{33}N_3O_3S$.

(8) N-(1-((7-methyl-2-phenyl-1H-indol-3-yl)methyl)pyrrolidin-3-yl)propane-2-sulfonamide(4). Yield: 26%
The compound was synthesised according to the procedure mentioned for compound(3)

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.05 - 1.22 (m, 6H), 1.58 - 1.71 (m, 2H), 2.04 - 2.20 (m, 1H), 2.25 - 2.40 (m, 1H), 2.53 - 2.60 (m, 1H), 2.67 - 2.91 (m, 1H), 2.98 - 3.16 (m, 1H), 3.32 (s, 3H), 3.70 (s, 2H), 3.75 - 3.87 (m, 1H), 6.80 - 7.01 (m, 2H), 7.09 - 7.26 (m, 1H), 7.31 - 7.43 (m, 1H), 7.48- 7.53 (m, 3H), 7.78 - 7.97 (m, 2H), 11.02 (s, 1H) HRMS: *m/z* (ES+) = 412.20521 (MH^+) for $C_{23}H_{29}N_3O_2S$.

(9) N-(2-methoxyethyl)-1-((7-methyl-2-phenyl-1H-indol-3-yl)methyl)pyrrolidin-3-amine(5). Yield: 9.60%

1-((7-methyl-2-phenyl-1H-indol-3-yl)methyl)pyrrolidin-3-amine (140 mg, 0.46 mmol) was taken in acetonitrile (4 mL). DIPEA (0.160 mL, 0.92 mmol) was added and allowed to stir at RT for 10 min. 1-bromo-2-methoxyethane (96 mg, 0.69 mmol) was added and stirred at 65°C for 4hrs. After the completion of the reaction, evaporated the volatiles, the residue was partitioned between dichloromethane and water. The dichloromethane layer was washed with water and brine solution. The organic layer was dried over sodium sulphate, evaporated to get the crude compound by chromatography using silica gel and methanol/dichloromethane as eluent to get N-(2-methoxyethyl)-1-((7-methyl-2-phenyl-1H-indol-3-yl)methyl)pyrrolidin-3-amine(5). (16.00 mg, 9.60 %)

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.31 - 1.53 (m, 1 H), 1.72 - 2.02 (m, 4 H), 2.16 - 2.35 (m, 1 H), 2.51 - 2.53 (m, 3 H), 2.53 - 2.63 (m, 2 H), 2.66 - 2.79 (m, 1 H), 3.20 (s, 3 H), 3.29 - 3.36 (m, 2 H), 3.63 - 3.71 (m, 2 H), 6.74 - 7.04 (m, 2 H), 7.29 - 7.43 (m, 1 H), 7.43 - 7.63 (m, 3 H), 7.79 - 7.98 (m, 2 H), 10.87 (s, 1H), 11.09 (s, 1H) HRMS: *m/z* (ES+) = 469.2918 (MH^+) for $C_{23}H_{29}N_3O$.

(10)1-((7-methyl-2-phenyl-1H-indol-3-yl)methyl)pyrrolidin-3-amine(6). Yield: 30.6%

(a) **Synthesis of tert-butyl (1-((7-methyl-2-phenyl-1H-indol-3-yl)methyl)pyrrolidin-3-yl)carbamate. Yield: 44.3 %**

tert-butyl pyrrolidin-3-ylcarbamate(202 mg, 1.09mmol) was taken in ethanol(5mL). Added zinc chloride (197 mg, 1.45 mmol) followed by the addition of formaldehyde solution (0.134 mL, 1.45 mmol). To this stirred reaction mixture was added 7-methyl-2-phenyl-1H-indole (150 mg,0.72 mmol). The reaction mixture was allowed to stir at RT for 1hr. After the completion of the reaction, the volatiles were removed, the residue was partitioned between ethylacetate and aqueous sodium bicarbonate solution. The organic layer was separated, washed with water and brine solution. The organic layer was dried over sodium sulphate, evaporated under vacuum to give crude compound which was purified by column chromatography to give tert-butyl (1-((7-methyl-2-phenyl-1H-indol-3-yl)methyl)pyrrolidin-3-yl)carbamate (130 mg, 44.3 %)
m/z (ES+) = 406(M+1)

(b) **1-((7-methyl-2-phenyl-1H-indol-3-yl)methyl)pyrrolidin-3-amine. Yield: 30.6%**

tert-butyl (1-((7-methyl-2-phenyl-1H-indol-3-yl)methyl)pyrrolidin-3-yl)carbamate (130 mg, 0.32 mmol) was taken in 1,4-dioxane (2 mL).4N HCl in Dioxane (2 mL, 0.32 mmol) was added and allowed to stir at RT for 1hr. After the completion of the reaction the volatiles were removed by evaporation under high vacuum, the residue was purified by reverse phase column chromatography to give pure 1-((7-methyl-2-phenyl-1H-indol-3-yl)methyl)pyrrolidin-3-amine (30.0 mg, 30.6 %)

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.24 - 1.43 (m, 1H), 1.76 - 1.91 (m, 1H), 1.93 - 2.06 (m, 1H), 2.11 - 2.25 (m, 1H), 2.39 - 2.48 (m, 1H), 2.51 - 2.53 (m, 3H), 2.54 - 2.63 (m, 1H), 2.64 - 2.77 (m, 1H), 3.67 (s, 2H), 5.02(br. s,2H), 6.81 - 6.98 (m, 2H), 7.31 - 7.42 (m, 1H), 7.50 (s, 3H), 7.78 - 7.99 (m, 2H), 10.79 - 11.12 (m, 1H)
HRMS: *m/z* (ES+) = 306.1959 (MH^+) for $C_{20}H_{23}N_3$

(11) N-(1-{[2-(4-fluorophenyl)-7-methyl-1H-indol-3-yl]methyl}pyrrolidin-3-yl)-N-(2-methoxyethyl)methanesulfonamide(7). Yield: 14.5%

To a solution of N-(2-methoxyethyl)-N-(pyrrolidin-3-yl)methanesulfonamide (0.98 g, 4.43 mmol), acetic acid (0.5 mL) and 37% formalin (0.164 g, 4.439mmol) in 1,4-dioxane (10 mL) was added in drop wise a solution of 2-(4-fluorophenyl)-7-methyl-1H-indole(0.5 g, 2.219mmol) in dioxane (2 mL) at 0 °C. The reaction mixture was stirred for 12 h at room temperature. After the completion of the reaction, the volatiles were evaporated and the residue was partitioned between saturated $NaHCO_3$ and dichloromethane. The organic layer was washed with water, brine solution and dried over anhydrous Na_2SO_4.The organic layer was concentrated under reduced pressure. The obtained crude compound was purified by column chromatography using 2% DCM in methanol as eluent to afford N-(1-((2-(4-fluorophenyl)-7-methyl-1H-indol-3-yl)methyl)pyrrolidin-3-yl)-N-(2-methoxyethyl)methanesulfonamideas a gummy solid. Yield: (0.160 g, 14.5%).

^{1}H NMR (400MHz, DMSO-d_6) δ ppm 1.66-1.88 (m, 1H), 2.08 - 2.28 (m, 2H), 2.52 (s, 3H), 2.77 (d, *J* = 7.2 Hz, 2H), 2.86 (s, 3H), 3.14 (s, 3H), 3.35 (br s,2H), 3.36 - 3.45 (m, 3H), 3.54 - 3.73 (m, 2H), 4.29 (d, *J* = 8.2 Hz, 1H), 6.86 - 6.99 (m, 2H), 7.34 (t, *J* = 8.8 Hz, 2H), 7.48 (d, *J* = 7.4 Hz, 1H), 7.92 (dd, *J* = 8.4, 5.6 Hz, 2H), 11.05 (s, 1H)
HRMS: *m/z* (ES+) = 460.20593 (MH^+) for $C_{24}H_{30}FN_3O_3S$

(12) N-(1-((7-methoxy-2-phenyl-1H-indol-3-yl)methyl)pyrrolidin-3-yl)-N-(2-methoxyethyl)methanesulfonamide(8). Yield: 33%
The compound was synthesised according to the procedure mentioned for compound(3)

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.07 - 2.29 (m, 2H), 2.45-2.56 (m, 2H), 2.71 - 2.83 (m, 2H), 2.86 (s, 3H), 3.13 (s, 3H), 3.33 - 3.48 (m, 4H), 3.56 - 3.73 (m, 2H), 3.93 (s, 3H), 4.21 - 4.39 (m, 1H), 6.60 - 6.77 (m, 1H), 6.86 - 7.08 (m, 1H), 7.22 - 7.30 (m, 1H), 7.31 - 7.40 (m, 1H), 7.41 - 7.53 (m, 2H), 7.78 - 7.92 (m, 2H), 11.24 (br.s , 1H)
HRMS: *m/z* (ES+) = 458.21094 (MH^+) for $C_{24}H_{31}FN_3O_4S$

(13)N-(2-methoxyethyl)-N-(1-((2-phenyl-1H-indol-3-yl) methyl) pyrrolidin-3-yl) methanesulfonamide (9). Yield:33.9 %.
The compound was made according to the procedure mentioned for compound(3)

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.65-1.82 (m, 1H), 2.10-2.30 (m, 2H), 2.53-2.63 (m, 1H), 2.81 (dd, *J* = 9.80, 3.58 Hz, 2H), 2.86-2.90 (m, 3H), 3.12 (s, 3H), 3.34 (s, 2H), 3.36-3.43 (m, 2H), 3.69 (q,*J* = 12.81 Hz, 2H), 4.30 (d, *J* = 8.48 Hz, 1H), 6.98-7.06 (m, 1H), 7.07-7.15 (m, 1H), 7.34-7.42 (m, 2H), 7.46-7.55 (m, 2H), 7.67 (d, *J* = 7.72 Hz, 1H), 7.86 (d, *J* = 7.16 Hz, 2H), 11.38 (s, 1H)
HRMS: *m/z* (ES+) = 428.20025 (MH^+) for $C_{23}H_{29}N_3O_3S$.

(14)N-(2-methoxyethyl)-N-(1-((7-methyl-2-(p-tolyl)-1H-indol-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide(10). Yield: 17.8%

To a solution of N-(2-methoxyethyl)-N-(pyrrolidin-3-yl)methanesulfonamide (1.07 g, 4.85 mmol), acetic acid (0.5 mL) and 37% formalin (0.178 g, 4.854 mmol) in 1,4-dioxane (10 mL) was added in drop wise a solution of 7-methyl-2-(p-tolyl)-1H-indole (0.2 g, 0.966 mmol) in dioxane (2 mL) at 0 °C. The reaction mixture was stirred for 12 h at room temperature. To the reaction mixture was added saturated $NaHCO_3$ and extracted with DCM. The combine organic layer was washed water, brine and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The obtained crude was purified by column chromatography using 6% DCM in methanol as

eluent to afford N-(2-methoxyethyl)-N-(1-((7-methyl-2-(p-tolyl)-1H-indol-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamideas a white solid. Yield: 17.8%.

^{1}H NMR (400MHz ,DMSO-d_6) δ ppm 1.79 - 1.70 (m, 1H), 2.25 - 2.14 (m, 2H), 2.38 (s, 3H), 2.50 (b s, 2H), 2.78 (d, *J* = 7.6 Hz, 2H), 2.87 (s, 4H), 3.15 (s, 4H), 3.44 - 3.35 (m, 4H), 3.73 - 3.54 (m, 2H), 4.30 (br s, 1H), 6.96 - 6.85 (m, 2H), 7.32 (d, *J* = 7.8 Hz, 2H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.77 (d, *J* = 7.8 Hz, 2H), 10.98 (s, 1H)
HRMS: *m/z* (ES+) = 456.23124 (MH^+) for $C_{25}H_{33}N_3O_3S$

(15) N-(1-((1-benzyl-7-methyl-1H-indol-3-yl)methyl)pyrrolidin-3-yl)-N-(2-methoxyethyl)methanesulfonamide(11). Yield: 36%.
N-(2-methoxyethyl)-N-(1-((7-methyl-1H-indol-3-yl)methyl)pyrrolidin-3 yl)methanesulfonamide (100 mg, 0.27 mmol) was taken in dry N,N-dimethylformamide (3 mL). Sodium hydride (21.89 mg, 0.55 mmol) was added slowly and allowed to stir at RT for 10 minutes. Bromomethylbenzene(0.039 mL, 0.33 mmol) was added and allowed to stir at RT for 1hr. After the completion of the reaction,poured the reaction mixture into water and extracted with ethyl acetate. The organic portion was washed with water, brine solution and dried with anhydrous sodium sulfate and evaporated to get the crude compound which was purified by chromatography using silica gel and methanol/dichloromethane as eluent give N-(1-((1-benzyl-7-methyl-1H-indol-3-yl)methyl)pyrrolidin-3-yl)-N-(2-methoxyethyl)methanesulfonamide (45.0 mg, 36 %)

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.65 - 1.85 (m, 1H), 2.07 - 2.24 (m, 2H), 2.41 (s, 3H), 2.68 - 2.84 (m, 2H), 2.87 (s, 3H), 3.13 (s, 3H), 3.21-3.45(m, 5H), 3.69 (s, 2H), 4.26 - 4.29 (m, 1H), 5.60 (s, 2H), 6.72 - 6.81 (m, 1H), 6.81 - 6.95 (m, 3H), 7.30 (s, 4H), 7.44 - 7.54 (m, 1H)
HRMS:*m/z* (ES+) = 456.23319 (MH^+) for $C_{25}H_{33}N_3O_3S$

(16)N-(1-((5,7-dimethyl-2-phenyl-1H-indol-3-yl)methyl)pyrrolidin-3-yl)-N-(2-methoxyethyl)methanesulfonamide(12). Yield: 20.72%.
The compound was made according to the procedure mentioned for compound(3)

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.12-2.22 (m, 2H), 2.35 (s, 3H), 2.47 (s, 3H), 2.52-2.57 (m, 2H), 2.78 (d, *J* = 6.59 Hz, 2H), 2.87 (s, 3H), 3.14 (s, 3H), 3.32 (s, 1H), 3.35-3.42 (m, 3H), 3.55-3.72 (m, 2H), 4.29 (d, *J* = 7.54 Hz, 1H), 6.73 (s, 1H), 7.27 (s, 1H), 7.33-7.42 (m, 1H), 7.45-7.54 (m, 2H), 7.85 (d, *J* = 7.54 Hz, 2H), 10.90 (s, 1H)
HRMS: *m/z* (ES+) = 456.23106 (MH^+) for $C_{25}H_{33}N_3O_3S$.

(17)N-(2-methoxyethyl)-N-(1-((7-methyl-1H-indol-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide(13).

Yield: 53%

7-methyl-1H-indole-3-carbaldehyde (65 mg,0.41 mmol) and N-(2-methoxyethyl)-N-(pyrrolidin-3-yl)methanesulfonamide (91 mg, 0.41 mmol) was taken in DCE (3 mL). Few drops of acetic acid was added and allowed to heat at 60 °C for 1hr. The reaction mixture was allowed to cool and sodium triacetoxyborohydride (113 mg, 0.53 mmol) was added and the resulting reaction mass was allowed to stiratroom temperature for overnight. After the completion of the reaction, the volatiles were removed and the residue was partitioned between saturated sodium bicarbonate solution and ethyl acetate. The organic portion was washed with water and brine solution, dried over sodium sulphate and evaporated under vacuum to give crude compound which was purified by reverse phase purification system to give N-(2-methoxyethyl)-N-(1-((7-methyl-1H-indol-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide (80 mg, 53 %).

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.05 - 2.23 (m, 2H), 2.44 (s, 3H), 2.67 - 2.82 (m, 2H), 2.87 (s, 3H), 3.17 (s, 3H), 3.32 (br. s., 3 H), 3.36 - 3.48 (m, 3H), 3.68 (s, 2H), 4.18 - 4.36 (m, 1H), 6.80 - 6.95 (m, 2H), 7.20 (d, *J* = 2.07 Hz, 1H), 7.43 (dd, *J* = 6.40, 2.64 Hz, 1H), 10.87 (s, 1H)
HRMS: *m/z* (ES+) = 366.18455 (MH^+) for $C_{18}H_{27}N_3O_3S$.

(18) N-(2-methoxyethyl)-N-(1-{[7-methyl-2-(pyridin-4-yl)-1H-indol-3-yl]methyl}pyrrolidin-3-yl)methanesulfonamide(14). Yield: 28%
7-methyl-2-(pyridin-4-yl)-1H-indole (200 mg,0.96 mmol) was taken in absolute EtOH (10 mL). N-(2-methoxyethyl)-N-(pyrrolidin-3-yl)methanesulfonamide (427 mg, 1.92 mmol) was added followed by the addition of formaldehyde solution (144 mL, 1.92 mmol) and zinc chloride (90 mL, 1.92 mmol).

The reaction mass was stirred at RT for 24. After the completion of the reaction evaporated the volatiles, the residue was partitioned between saturated sodium bicarbonate solution and ethyl acetate. The organic layer was washed with water, brine solution. The organic layer was dried with anhydrous sodium sulphate, evaporated under high vacuum to get the crude compound which was purified by chromatography using silica gel and methanol/dichloromethane as eluent to get **)** N-(2-methoxyethyl)-N-(1-{[7-methyl-2-(pyridin-4-yl)-1H-indol-3-yl]methyl}pyrrolidin-3-yl)methanesulfonamide(48 mg, 28%)

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.64-1.78 (m, 1H), 1.89 (s, 3H), 2.03-2.32 (m, 3H), 2.52-2.63 (m, 4H), 3.12 (s, 3H), 3.27-3.45 (m, 5H), 3.64-3.83 (m, 2H), 4.30 (d, *J*=4.52 Hz, 1H), 6.90-7.04 (m, 2H), 7.48-7.62 (m, 1H), 7.92 (d,*J*=6.03 Hz, 2H), 8.67 (d, *J*=5.84 Hz, 2H), 11.23 (s, 1H)
HRMS: *m/z* (ES+) = 443.21117 (MH^+) for $C_{23}H_{30}N_4O_3S$.

(19)N-(2-methoxyethyl)-N-(1-{[2-phenyl-7-(propan-2-yl)-1H-indol-3-yl]methyl}pyrrolidin-3-yl)methanesulfonamide(15). Yield: 36.10%

The compound was made according to the procedure mentioned for compound (3)

^{1}H NMR (300 MHz, DMSO- d_6) δ ppm 1.24-1.35 (m, 6H), 1.67-1.80 (m, 1H), 2.17-2.26 (m, 1H), 2.75-2.82 (m, 2H), 2.84-2.91 (m, 3H), 3.12 (s, 3H), 3.15-3.20 (m, 1H), 3.31 (s, 2H), 3.34-3.43 (m, 3H), 3.53-3.75 (m, 3H), 4.29 (d, *J* = 4.52 Hz, 1H), 6.94-7.05 (m, 2H), 7.34-7.44 (m, 1H), 7.45-7.57 (m, 3H), 7.86 (d, *J* = 7.35 Hz, 2H), 11.00 (s, 1H)
HRMS: *m/z* (ES+) = 470.24771 (MH^+) for $C_{26}H_{35}N_3O_3S$.

(20)N-{1-[(4-fluoro-7-methyl-2-phenyl-1H-indol-3-yl)methyl]pyrrolidin-3-yl}-N-(2-methoxyethyl)methanesulfonamide(16). Yield: 12%

The compound was made according to the procedure mentioned for compound(3)
^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.25 (br. s., 1H), 1.65-1.80 (m, 1H), 2.09-2.29 (m, 2H), 2.47 (s, 2H), 2.56 (s, 1H), 2.51-2.59 (m, 1H), 2.75 (dd, *J* = 10.27, 3.67 Hz, 2H), 2.86 (s, 3H), 3.10 (s, 3H), 3.28-3.33 (m, 3H), 3.68-3.78 (m, 2H), 4.27 (d, *J* = 8.48 Hz, 1H), 6.67 (dd, *J* = 11.68, 7.91 Hz, 1H), 6.83 (dd, *J* = 7.63, 4.80 Hz, 1H), 7.37-7.46 (m, 1H), 7.47-7.59 (m, 2H), 7.89 (d, *J* = 7.35 Hz, 2H),11.33 (s, 1H);
HRMS: *m/z* (ES+) = 460.20578 (MH^+) for $C_{24}H_{30}FN_3O_3S$.

(21)N-(2-methoxyethyl)-N-(2-{methyl[(7-methyl-2-phenyl-1H-indol-3-yl)methyl]amino}ethyl)methanesulfonamide(17). Yield: 26.5%

To a cold solution of glacial acetic acid (1 mL), N-(2-methoxyethyl)-N-(2-(methylamino) ethyl) (methanesulfonamide **6** (0.38 g, 1.93 mmol) and 40% formalin (0.5 mL), was added 7-methyl-2-phenyl-1H-indole(0.2 g, 0.97 mmol) portion-wise in dioxane (5 mL). Then the reaction mixture was allowed to stir at 25°C for 5 h. Saturated sodium bicarbonate solution was added to the reaction mixture and extracted with DCM (2 x 50 mL). The combine organic layer was washed water, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The obtained crude was purified by column chromatography using 1% DCM in MeOH to afford required compound N-(2-methoxyethyl)-N-(2-(methyl ((7-methyl-2-phenyl-1H-indol-3-yl) methyl) amino) ethyl) methanesulfonamide as a colorless gummy solid. Yield: 0.11 g, 26.5%.

^{1}H NMR (400MHz, DMSO-d_6) δ ppm 2.19 (s, 3H), 2.25 (s, 3H), 2.60 (t, *J* = 6.8 Hz, 2H), 2.83 (s, 3H), 3.14 (s, 3H), 3.17 (d, *J* = 5.4 Hz, 2H), 3.31 - 3.21 (m, 4H), 3.63 (s, 2H), 6.99 - 6.85 (m, 2H), 7.44 - 7.35 (m, 1H), 7.58 - 7.47 (m, 3H), 7.90 (d, *J* = 7.6 Hz, 2H), 11.06 (s, 1H),
HRMS: *m/z* (ES+) = 430.21587 (MH^+) for $C_{23}H_{31}N_3O_3S$.

(22)N-{(3R)-1-[(7-methyl-2-phenyl-1H-indol-3-yl)methyl]pyrrolidin-3-yl}methanesulfonamide(18). Yield: 11.35%
(R)-1-((7-methyl-2-phenyl-1H-indol-3-yl)methyl)pyrrolidin-3-amine (267 mg, 0.87 mmol) was taken in DCM (5 mL). N,N'-Diisopropylethylamine (1 mL, 0.87 mmol) was added and stirred for 20 minutes. To this clear reaction mixture was added methanesulfonyl chloride (0.068 mL, 0.87 mmol) and stirred at RT for 2h.
After the completion of the reaction diluted with dichloromethane, washed the organic layer with water, brine solution. The organic layer was separated, dried over sodium sulphate, evaporated under reduced pressure to get the crude compound. The crude compound was purified by chromatography using silica gel and

methanol/dichloromethane as eluent to give (R)-N-(1-((7-methyl-2-phenyl-1H-indol-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide (38.0 mg, 11.35 %).

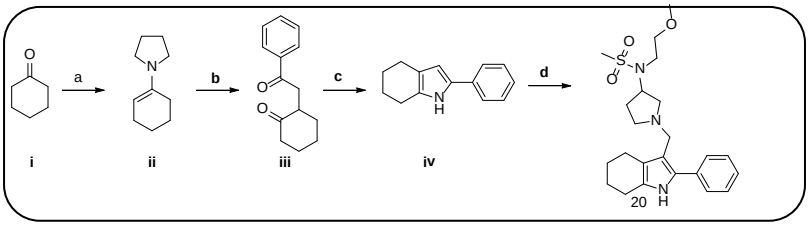
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.67-1.81 (m, 1H), 2.27 (dtd, *J* = 13.09, 8.71, 8.71, 3.96 Hz, 2H), 2.35-2.46 (m, 1H), 2.55 (s, 3H), 2.60-2.69 (m, 1H), 2.70-2.78 (m, 1H), 2.81-2.87 (m, 3H), 2.89-3.02 (m, 1H), 3.93 (d, *J* = 6.78 Hz, 2H), 4.95 (d, *J* = 12.06 Hz, 1H), 7.01-7.15 (m, 2H), 7.38-7.46 (m, 1H), 7.47-7.56 (m, 2H), 7.60 (d, *J* = 7.72 Hz, 1H), 7.69-7.77 (m, 2H), 8.25 (s, 1H), 10.95(br.s, 1H);
HRMS: *m/z* (ES+) = 384.17351 (MH^+) for $C_{21}H_{25}N_3O_2S$.

(23)N-{(3S)-1-[(7-methyl-2-phenyl-1H-indol-3-yl)methyl]pyrrolidin-3-yl}methanesulfonamide(19). Yield: 40%:

The compound was made according to the procedure mentioned for compound(18)

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.53 - 1.72 (m, 1H), 1.90 (s, 3H), 2.05 - 2.23 (m, 1H), 2.28 - 2.41 (m, 1H), 2.52 - 2.62 (m, 2H), 2.84 (s, 3H), 2.85-2.88 (m,1H), 3.70(s, 2H), 3.76 - 3.80 (m, 1H), 6.84 - 6.99 (m, 2H), 7.12 - 7.25 (m, 1H), 7.33 - 7.43 (m, 1H), 7.45 - 7.57 (m, 3H), 7.77 - 7.98 (m, 2H), 10.90 - 11.15 (m, 1H)
HRMS: *m/z* (ES+) = 384.17375 (MH^+) for $C_{21}H_{25}N_3O_2S$.

Scheme 4: Synthesis of N-(2-methoxyethyl)-N-(1-((2-phenyl-4,5,6,7-tetrahydro-1H-indol-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide(20)



Reagents and conditions: (a) pyrrolidine, toluene, 125^{o}C, 12h (b) phenacybromide, DMF, RT, 10h (c) ammonium acetate, ethanol, 82^{o}C, 2h (d) Amine, formaline solution, acetic acid, RT, 12h, 1,4-,dioxane,

(24)1-(Cyclohex-1-en-1-yl)pyrrolidine (ii). Yield: 72% To a stirred solution of cyclohexanone (4 g, 43 mmol) in toluene (20mL) was added pyrrolidine (6 mL) and refluxed the reaction mixture using Dean-Stark apparatus for 16 h. The completion of the reaction was monitored by TLC. Then the reaction mixture was distilled off under reduced pressure to give 1-(Cyclohex-1-en-1-yl) pyrrolidine **ii** as a brown liquid. The crude material was taken as such for next step. Yield: 4.2 g.

(25)2-(2-Oxo-2-phenylethyl) cyclohexan-1-one (iii). Yield: 51%: To a solution of l-cyclohex-l-en-l-ylpyrrolidine(2.4 mL) in anhydrous DMF (100 mL), was added a solution of 2-bromo-l-phenylethanone (4.12 g) in anhydrous DMF (35 mL) under nitrogen and stirred for 10 h at RT. Then to this was added water (90 mL) and continued stirring for another 11 hours under nitrogen. The solution was then extracted with ethyl acetate washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 2-(2-oxo-2-phenylethyl) cyclohexan-1-one **iii** as a pale yellow oil. Yield: 1.5 g.

(26)2-Phenyl-4,5,6,7-tetrahydro-1H-indole (iv). Yield: 85%: To a stirred solution of 2-(2-oxo-2-phenylethyl) cyclohexan-1-one (1 g, 4.6 mmol) in EtOH (15 mL) was added NH_4OAc (1.78 g, 23.1mmol) and heated the reaction mixture at 80 °C for 2 h. After the reaction mixture was concentrated and the crude residue was taken in ethylacetate and washed with water, brine, dried over sodium sulfate and concentrated under reduced pressure. The crude was purified by was purified by column chromatography using 10% ethylacetate in petether to afford 2-Phenyl-4, 5, 6, 7-tetrahydro-1H-indole **iv** as a orange solid. Yield: 0.9 g.

(27)N-(2-methoxyethyl)-N-(1-((2-phenyl-4,5,6,7-tetrahydro-1H-indol-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide(20). Yield: 10.9%

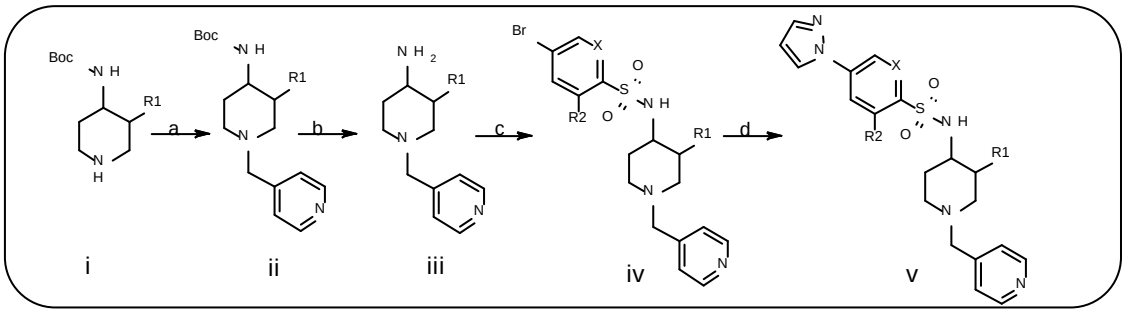
To a cold solution of glacial acetic acid (0.3 mL), N-(2-methoxyethyl)-N-(pyrrolidin-3-yl) methane sulfonamide (0.22 g, 1.01 mmol) and 40% formalin (0.2 mL), was added 2-phenyl-4,5,6,7-tetrahydro-1H-indole (0.1 g 0.506 mmol) portion-wise in dioxane (5 mL) at 0 °C. Then the reaction mixture was allowed to stir at 25°C for 12 h. To the reaction mixture was added saturated $NaHCO_3$ and extracted with DCM. The combine organic layer was washed water, brine and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude

material was purified over reverse phase PREP HPLC to afford the title compound N-(2-Methoxyethyl)-N-(1-((2-phenyl-4,5,6,7-tetrahydro-1H-indol-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamideas a brown gummy solid. Yield: 23 mg, 10.9%.

^{1}H NMR (400MHz,DMSO-d_6) δ ppm 1.79 - 1.65 (m, 4H), 2.21 - 2.07 (m, 2H), 2.47 - 2.40 (m, 3H), 2.55 (d, *J* = 5.9 Hz, 2H), 2.85 - 2.73 (m, 2H), 2.90 (s, 3H), 3.22 - 3.13 (m, 5H), 3.27 - 3.19 (m, 2H), 3.41 (d, *J* = 4.4 Hz, 2H), 4.29 (d, *J* = 7.8 Hz, 2H), 7.20 - 7.11 (m, 1H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.62 (d,*J* = 7.6 Hz, 2H), 10.55 (s, 1H),
HRMS: *m/z* (ES+) = 432.2322 (MH^+) for $C_{23}H_{33}N_3O_3S$.

Arylsulphonamides: Preparation of key Intermediates and final compounds

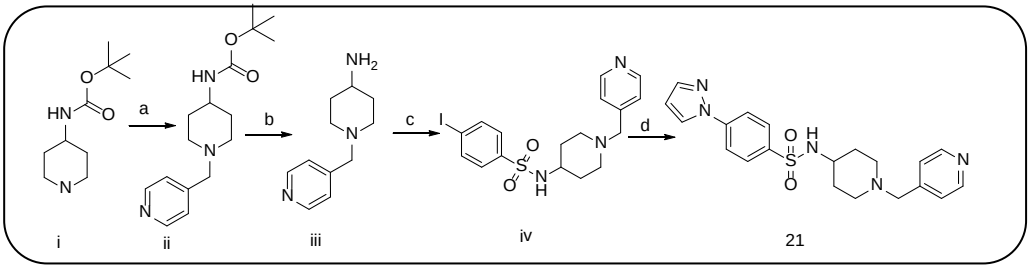
Scheme 5: General synthesis of arylsulphonamide derivatives.



R_1=H, OCH_3, R_2=H,CH_3,F,CF_3, X=C, N

Reagents and conditions: (a) 4-pyridinemethylchloride, potassium carbonate, DMF, RT, 5h, 82% (b) HCl in dioxane, RT, 100% (c) potassium carbonate, phenyl sulphonyl chloride, RT, 3h, RT (d) (1R,2R)-(-)-1,2-diaminocyclohexane, copper iodide, pyrazole, 1,4-dioxane, MW, 30 minutes

Scheme 6: 4-(1H-Pyrazol-1-yl)-N-(1-(pyridin-4-ylmethyl) piperidin-4-yl) benzenesulfonamide (21).



Reagents and conditions: (a) 4-pyridinemethylchloride, potassium carbonate, DMF, RT, 5h, 82% (b) HCl in dioxane, RT, 100% (c) potassium carbonate, phenyl sulphonyl chloride, RT, 3h, RT (d) (1R,2R)-(-)-1,2-diaminocyclohexane, copper iodide, pyrazole, 1,4-dioxane, MW, 30 minutes

(28)Tert-butyl (1-(pyridin-4-ylmethyl) piperidin-4-yl) carbamate (ii). Yield: 42 %

To a stirred solution of 4-(chloromethyl) pyridine hydrochloride (2.0 g, 12.19 mmol) in DMF was added Cs_2CO_3(9.8 g, 30.48 mmol) at 0°C and stirred for 10 min. To this tert-butyl piperidin-4-ylcarbamate **(i)** (2.42 g, 12.19 mmol) was added and continued stirring for 16 h at RT. The reaction progress was monitored by TLC. After completion of stating material the reaction mixture was poured into crushed ice water and solid precipitated was filtered under vacuum and dried to afford tert-butyl (1-(pyridin-4-ylmethyl)piperidin-4-yl)carbamate **(ii)** as a white solid. Yield: 1.5 g, 42 %.

(29)1-(Pyridin-4-ylmethyl) piperidin-4-amine (iii). Yield: 100 %

To a stirred solution of tert-butyl (1-(pyridin-4-ylmethyl) piperidin-4-yl) carbamate **(3)** (1 g, 3.43 mmol) in 1, 4-dioxane (10 mL) was added 4.5 M HCl in dioxane (5 mL) at 0°C and stirred at RT for 2 h. Then solvents were evaporated under reduced pressure and the resulting solid was washed with ether and dried to afford HCl salt of 1-(pyridin-4-ylmethyl) piperidin-4-amine **(4)** as a white solid. Yield: 0.9 g.

(30)4-Iodo-N-(1-(pyridin-4-ylmethyl) piperidin-4-yl) benzene sulfonamide (iv). Yield: 23%

To a stirred solution of HCl salt of 1-(pyridin-4-ylmethyl) piperidin-4-amine (0.65 g, 2.90 mmol) in DMF (10 mL) were added K_2CO_3 (1.0 g, 7.254 mmol) followed by the addition of 4-iodobenzenesulfonyl chloride (0.87 g, 2.90 mmol) at 0°C. Then the reaction mixture was stirred at room temperature for 30 min and poured in to crushed ice water and extracted with EtOAc (2 X50 mL). The combined organic extracts were washed with H_2O, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography eluting with 10% EtOAc in pet-ether to afford 4-iodo-N-(1-(pyridin-4-ylmethyl) piperidin-4-yl) benzene sulfonamide **6** as a white solid. Yield: 300 mg, 23 %

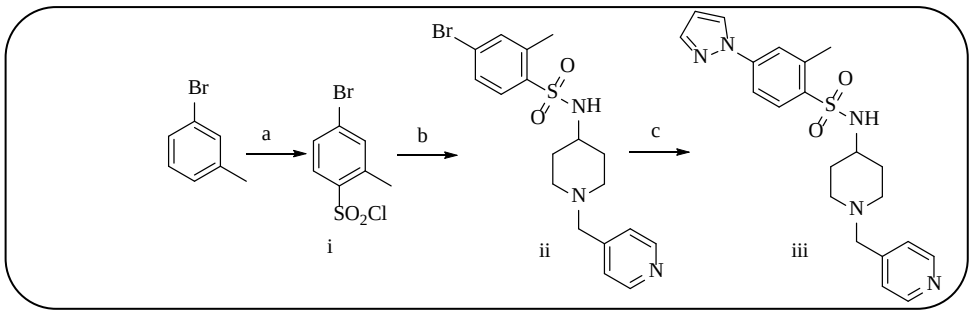
(31)4-(1H-Pyrazol-1-yl)-N-(1-(pyridin-4-ylmethyl) piperidin-4-yl) benzenesulfonamide(21). Yield: 25%

To a stirred solution of 4-iodo-N-(1-(pyridin-4-ylmethyl) piperidin-4-yl) benzene sulfonamide (0.3 g, 0.656 mmol) in 1, 4-Dioxane (10 mL) in a sealed tube were added K_2CO_3 (0.181 g, 1.313 mmol) and pyrazole (0.067 g, 0.984 mmol) at room temperature. The mixture was degassed for 10 minutes and then were added CuI (0.037 g, 0.196 mmol) and (±)-*trans*-1,2-diaminocyclohexane (0.037 g, 0.328mmol). The resulting mixture was stirred at 120 °C for 16 h. Then the reaction mixture was filtered through a celite pad and the filtrate was concentrated under reduced pressure. The crude material was purified over PREP TLC eluting (twice) with 5% MeOH in Dichloromethane to afford the title compound 4-(1H-Pyrazol-1-yl)-N-(1-(pyridin-4-ylmethyl)piperidin-4-yl)benzenesulfonamideas a white solid. Yield: 65 mg, 25%.

^{1}H NMR (400MHz ,DMSO-d_6) δ ppm 1.48 - 1.30 (m, 2H), 1.56 (d, *J* = 10.8 Hz, 2H), 1.93 (t, *J* = 10.8 Hz, 2H), 2.63 (d, *J* = 11.7 Hz, 2H), 2.98 (dd, *J* = 10.8, 4.2 Hz, 1H), 3.41 (s, 2H), 6.63 - 6.60 (m, 1H), 7.25 (d, *J* = 5.6 Hz, 2H), 7.80 (d, *J* = 7.3 Hz, 1H), 7.83 (d, *J* = 1.5 Hz, 1H), 7.92 (d, *J* = 8.8 Hz, 2H), 8.06 (d, *J* = 8.8 Hz, 2H), 8.47 (d, *J* = 5.9 Hz, 2H), 8.63 (d, *J* = 2.4 Hz, 1H)

HRMS: *m/z* (ES+) = 398.16449 (MH^+) for $C_{20}H_{23}N_5O_2S$.

Scheme 7: Synthesis of 2-methyl-4-(1H-pyrazol-1-yl)-N-(1-(pyridin-4-ylmethyl)piperidin-4-yl)benzenesulfonamide (22).



Reagents and conditions: (a) chlorosulphonic acid, chloroform, 0^{o}C, 3h, 53% (b) 1-(pyridin-4-ylmethyl)piperidin-4-amine , potassium carbonate, DMF, RT, 16h, 61% (c) (1R,2R)-(-)-1,2-diaminocyclohexane, copper iodide, pyrazole, 1,4-dioxane, MW, 30 minutes, 18%

(32)4-bromo-2-methylbenzenesulfonyl chloride (i). Yield: 53%

To a cold solution of 3-bromo toluene (1.03g,6 mmol) in dry chloroform (10 mL) was added chloro sulfonic acid (2.5 mL, 37.6 mmol) drop wise at 0 °C and the resulting solution was stirred at 0 °C for 3 h. Then the reaction mixture was poured into crushed ice and extracted with ethyl acetate. The combined organic layer was washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was taken for next step without further purification. Yield: 0.8 g (53%)

(33)4-Bromo-2-methyl-N-(1-(pyridin-4-ylmethyl)piperidin-4-yl)benzenesulfonamide (ii). Yield: 61%

To a solution of 1-(pyridin-4-ylmethyl)piperidin-4-amine (0.2 g, 1.01 mmole) in DMF (80 mL) were added K_2CO_3 (0.26 g, 1.56 mmol), 4-bromo-2-methylbenzenesulfonyl chloride (0.337 g, 1.25 mmol) and stirred at rt for 16 h under N_2. The progress of the reaction was monitored by TLC. Then the resulting mixture was evaporated

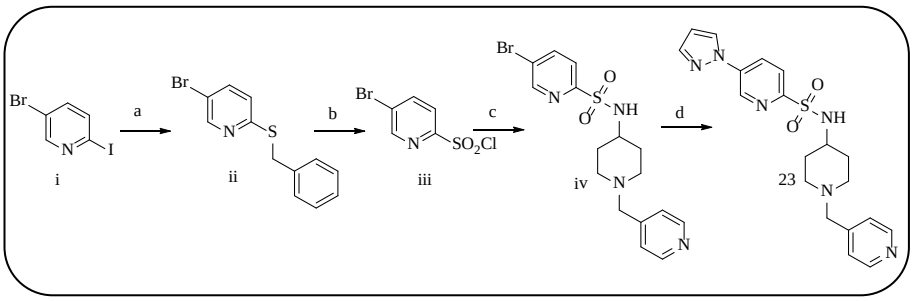
under reduced pressure and diluted with EtOAc. The organic layer was washed with H_2O, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography using 12% EtOAc in hexane as an eluent to give 4-bromo-2-methyl-N-(1-(pyridin-4-ylmethyl)piperidin-4-yl)benzenesulfonamide as a colorless liquid. Yield: 0.21 g (61%).

(34)2-Methyl-4-(1H-pyrazol-1-yl)-N-(1-(pyridin-4-ylmethyl)piperidin-4-yl)benzenesulfonamide(22). Yield: 18%

To a solution of 4-bromo-2-methyl-N-(1-(pyridin-4-ylmethyl)piperidin-4-yl)benzenesulfonamide (0.2 g, 0.47 mmol) in 1,4-dioxane (5 mL) were added pyrazole (0.038 g, 0.566 mmol), K_2CO_3 (0.129 g, 0.94 mmol) CuI (0.017g, 0.094 mmol) and the mixture was stirred at RT for 15 min under N_2. To this trans-1,2-cyclohexane diamine (0.011 g, 0.244 mmol) was added and reaction mixture was heated at 120 °C for 16 h in sealed tube. The completion of the reaction was monitored by TLC. Then the reaction mixture was evaporated completely and the residue was taken in EtOAc. Then the organic layer was washed with H_2O and concentrated under reduced pressure. The crude product was purified by PREP HPLC to afforded 2-Methyl-4-(1H-pyrazol-1-yl)-N-(1-(pyridin-4-ylmethyl)piperidin-4-yl) benzenesulfonamide Yield: 0.035 g (18%).

^{1}H NMR (400MHz ,DMSO-d_6) δ ppm 1.64-1.61 (m, 2H), 1.77 (b s, 2H), 2.63 (s, 3H), 2.96 (b s, 2H), 3.30-3.26 (m, 3H), 4.20 (b s, 2H), 6.62 (br s, 1H), 7.44 (br s, 2H), 8.06 - 7.70 (m, 4H), 8.10 (br s, 1H), 8.65 (d, *J* = 12.7 Hz, 2H), 9.72 (br s, 1H),
HRMS: *m/z* (ES+) = 412.18014 (MH^+) for $C_{20}H_{23}N_5O_2S$.

Scheme 8: 5-(1H-pyrazol-1-yl)-N-[1-(pyridin-4-ylmethyl)piperidin-4-yl]pyridine-2-sulfonamide(23).



Reagents and conditions: (a) benzyl mercaptan, NaH, THF, 0°C to 25°C, 3h, 91.2% (b) sulfuryl chloride, water, DCM, 0°C to RT, 73.3% (c)1-(pyridin-4-ylmethyl)piperidin-4-amine , potassium carbonate, DMF, RT, 16h, 64% (d) (1R,2R)-(-)-1,2-diaminocyclohexane, copper iodide, potassium carbonate, pyrazole, 1,4-dioxane, MW, 30 minutes, 37.5%

(35) 2-(Benzylthio)-5-bromopyridine (ii). Yield: 91.2%

To the solution of benzyl mercaptan (0.88 g, 7.04 mmol) in dry THF (20 ml) was added NaH 60% (0.4 g, 8.4 mmol) 0 °C and the resulting thick slurry was stirred at 0 °C for 15 min. To this was added 5-bromo-2-iodo pyridine (2 g, 7.04 mmol) and stirred at 25 °C for 3 h. Then the reaction RM was quenched with crushed ice and organic layer was separated, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product 2-(benzylthio)-5-bromopyridine was taken for next step without further purification. Yield: 1.8 g (91.2%).

(36)5-Bromopyridine-2-sulfonyl chloride (iii). Yield: 73.3%

To a solution of 2-(benzylthio)-5-bromopyridine (1.7 g, 6.06 mmol) in DCM (25 mL) were added water (5 ml) and sulfuryl chloride (5.7 g, 42.42 mmol) at 0 °C. The reaction mixture slowly warmed to RT and stirred for 30 min under N_2 atm. Then the mixture was evaporated completely and diluted with dichloromethane. The organic layer was separated, dried and concentrated under reduced pressure. The crude product 5-bromopyridine-2-sulfonyl chloride was taken for next step without further purification. Yield: 1.1 g (73.3%).

(37)5-Bromo-N-(1-(pyridin-4-ylmethyl)piperidin-4-yl)pyridine-2-sulfonamide (iv). Yield: 64%

To a solution of 1-(pyridin-4-ylmethyl)piperidin-4-amine (0.2 g, 1.01 mmol) in DMF (80 mL) were added K_2CO_3 (0.26 g, 1.56 mmol), 5-bromopyridine-2-sulfonyl chloride (0.337 g, 1.25 mmol) and stirred at RT for 16 h under N_2 atm. After completion of the reaction the mixture was evaporated completely to dryness and dissolved in EtOAc. Then EtOAc layer was concentrated and crude product was purified by column chromatography using

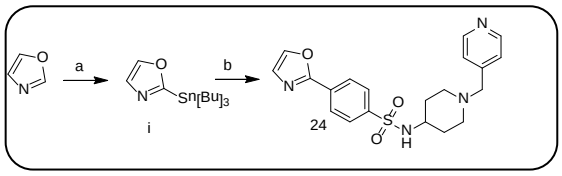
0.8 % MeOH in DCM as an eluent to give 5-bromo-N-(1-(pyridin-4-ylmethyl)piperidin-4-yl)pyridine-2-sulfonamide as light yellow solid. Yield: 0.22 g (64%).

(38)5-(1H-pyrazol-1-yl)-N-(1-(pyridin-4-ylmethyl)piperidin-4-yl)pyridine-2-sulfonamide(23). Yield: 37.5%

To a solution 4-bromo-2-methyl-N-(1-(pyridin-4-ylmethyl)piperidin-4-yl)benzenesulfonamide (0.25 g, 0.61 mmole) in 1,4-Dioxane (5 mL) were added pyrazole (0.061 g, 0.915 mmol), K_2CO_3(0.169 g, 1.2 mmol), CuI (0.022 g, 0.12 mmol) and stirred at rt for 15 min. Then trans-1,2-cyclohexane diamine (0.027 g, 0.244 mmol) was added and reaction mass was heated at 120 °C for 16 h in sealed tube. Then the reaction mixture was evaporated completely and the residue was taken in EtOAc. Then organic layer was washed with H_2O and concentrated under reduced pressure. The crude product was purified by column chromatography using 4% MeOH in DCM as an eluent to give 5-(1H-pyrazol-1-yl)-N-(1-(pyridin-4-ylmethyl)piperidin-4-yl)pyridine-2-sulfonamide as a white solid. Yield: 0.09 g (37.5%).

^{1}H NMR (400MHz ,DMSO-*d*$_6$) δ ppm 1.51 - 1.38 (m, 2 H), 1.60 (d, *J* = 10.0 Hz, 2 H), 1.93 (t, *J* = 10.9 Hz, 2 H), 2.66 (d, *J* = 12.0 Hz, 2 H), 3.16 (bs, 1H), 3.42 (s, 2 H), 7.26 (d, *J* = 4.4 Hz, 2 H), 7.91 (d,*J* = 1.7 Hz, 1 H), 8.01 (d, *J* = 6.6 Hz, 1 H), 8.06 (d,*J* = 8.6 Hz, 2 H), 8.50 - 8.44 (m, 3 H), 8.74 (d, *J* = 2.4 Hz, 1 H), 9.25 (d, *J* = 2.4 Hz, 1 H),
HRMS: *m/z* (ES+) = 399.15894(MH^+) for $C_{19}H_{22}N_6O_2S$.

Scheme 9: Synthesis of 4-(oxazol-2-yl)-N-(1-(pyridin-4-ylmethyl) piperidin-4-yl) benzenesulfonamide



Reagents and conditions: (a*) t*-butyltinchloride, *n*-butyllithium, THF, -78^{0}C to 0^{o}C, 56.2% (b) 4-bromo-N-(1-(pyridin-4-ylmethyl) piperidin-4-yl)benzenesulfonamide , Pd[PPh_3]Cl_2, THF, MW, 100^{o}C, 1h, 22%

(39) 2-(Tributylstannyl) oxazole ii. Yield: 56.2%

To a solution of oxazole (1 g, 14.4 mmol) in dry THF (20 ml) at -78°C under N_2 atm, was added *n*-BuLi (1.6 M, 10 ml, 15.9mmol) and stirred for 15 min. Then tributyl tin chloride (4.7 g, 14.4 mmol) was added slowly and the resulting reaction mixture was stirred for 1h at the same temperature. Then the reaction mixture was quenched with excess water and extracted with diethyl ether. The combined organic layer was washed with H_2O, KF solution, dried and concentrated under reduced pressure to give 2-(Tributylstannyl)oxazole (**i)**as a colour less liquid which was taken for next step without purification. Yield: 2.7 g (56.2%).

(40) 4-(oxazol-2-yl)-N-(1-(pyridin-4-ylmethyl) piperidin-4-yl) benzenesulfonamide(24). Yield: 22%

To a solution of 4-bromo-N-(1-(pyridin-4-ylmethyl) piperidin-4-yl)benzenesulfonamide **3** (0.2 g, 0.4 mmol) in dry THF (5 mL) was added 2-(tributylstannyl)oxazole **2** (0.207g, 0.59 mmol) and stirred under nitrogen for 15 min. Then Pd[PPh_3]Cl_2 (0.014 g, 0.02 mmol) was added and reaction mixture was stirred at 100°C for 16 h.. Then the reaction mixture was evaporated completely and diluted with EtOAc. The organic layer was washed with H_2O and concentrated under reduced pressure. The crude product was purified by column chromatography first by using 5% MeOH in DCM as an eluent which was subsequently purified by Prep HPLC to give title compound as colorless liquid. Yield: 0.042 g (22%).

^{1}H NMR (400MHz ,DMSO-*d*$_6$) δ ppm 1.45 - 1.32 (m, 2 H), 1.54 (d, *J* = 9.9 Hz, 2 H), 1.92 (t, *J* = 10.6 Hz, 2 H), 2.69 - 2.53 (m, 2 H), 2.98 (d, *J* = 5.1 Hz, 1 H), 3.40 (s, 2 H), 7.24 (d, *J* = 5.6 Hz, 2 H), 7.46 (s, 1 H), 7.90 (d, *J* = 6.7 Hz, 1 H), 7.94 (d, *J* = 8.6 Hz, 2 H), 8.15 (d, *J* = 8.3 Hz, 2 H), 8.31 (s, 1 H), 8.45 (d, *J* = 5.4 Hz, 2 H); HRMS: *m/z* (ES+) = 399.14838 (MH^+) for $C_{20}H_{22}N_4O_3S$.

(41) N-methyl-4-(1H-pyrazol-1-yl)-N-[1-(pyridin-4-ylmethyl)piperidin-4-yl]benzenesulfonamide(25). Yield: 51.4%

N-methyl-N-(piperidin-4-yl)-4-(1H-pyrazol-1-yl)benzenesulfonamide (250 mg, 0.78 mmol) was taken in DCE (10 mL). Isonicotinaldehyde (0.073 mL, 0.78 mmol) was added followed by few drops of acetic acid and allowed to stir at 70 °C for 1hr. Reaction mixture was cooled and Sodium triacetoxyborohydride (496 mg, 2.34 mmol) was added and allowed to stir at RT for 3h. After the completion of the reaction the volatiles were removed from

the reaction mixture at high vacuum. The residue was partitioned between saturated sodium bicarbonate solution and ethyl acetate. The ethyl acetate layer was washed with water, brine solution, dried over anhydrous sodium sulfate and evaporated under vacuum to give the crude compound which was purified by column chromatography to give N-methyl-4-(1H-pyrazol-1-yl)-N-(1-(pyridin-4-ylmethyl)piperidin-4-yl)benzenesulfonamide (165 mg, 51.4 %).

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.26 (d, *J* = 10.36 Hz, 2H), 1.55-1.72 (m, 2H), 2.01 (t, *J* = 11.02 Hz, 2H), 2.73 (s, 4H), 3.32 (s, 3H), 3.69 (t, *J* = 11.96 Hz, 1H), 6.62 (t, *J* = 2.07 Hz, 1H), 7.27 (d, *J* = 5.65 Hz, 2H), 7.83 (d, *J* = 1.70 Hz, 1H), 7.91 (d, *J* = 8.67 Hz, 2H), 8.07 (d, *J* = 8.67 Hz, 2H), 8.47 (d, *J* = 5.84 Hz, 2H), 8.65 (d, *J* = 2.45 Hz, 1H);
HRMS: *m/z* (ES+) = 412.18015 (MH^+) for $C_{21}H_{25}N_5O_2S$.

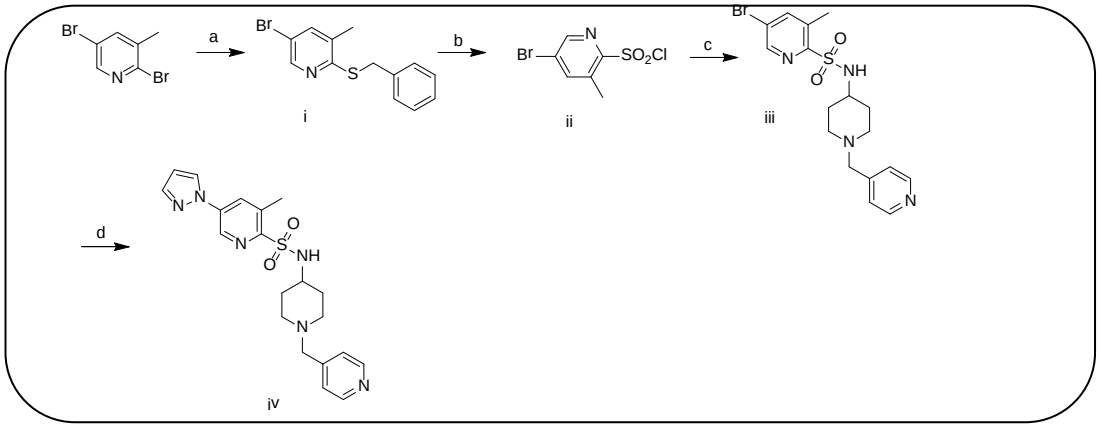
(42)Synthesis of N-methyl-N-(piperidin-4-yl)-4-(1H-pyrazol-1-yl) benzenesulfonamide. Yield: 100%
tert-butyl 4-(4-(1H-pyrazol-1-yl)phenylsulfonamido)piperidine-1-carboxylate (300 mg, 0.74 mmol) was added to the solution containing sodium hydride (89 mg, 2.21 mmol) in DMF (10 mL)at 0°C . After stirring for 10 minutes at0°C, iodomethane (0.046 mL, 0.74 mmol) was added and allowed to stir at 0°C for 30 min and then at room temperature for 1hr.
After the completion of the reaction the reaction mixture was poured into ice and the aqueous was extracted with ethyl acetate. The ethyl acetate layer was washed with water, brine solution and dried over sodium sulphate. The organic layer was then concentrated under reduced pressure to get the required compound tert-butyl 4-(N-methyl-4-(1H-pyrazol-1-yl) phenylsulfonamido) piperidine-1-carboxylate (310 mg, 100 %).

(43)N-[3-methoxy-1-(pyridin-4-ylmethyl)piperidin-4-yl]-4-(1H-pyrazol-1-yl)benzenesulfonamide(26). Yield: 83%
N-(3-methoxypiperidin-4-yl)-4-(1H-pyrazol-1-yl)benzenesulfonamide (100 mg, 0.30 mmol) was taken in dry DMF (10 mL) to get a clear solution. Potassium carbonate (82 mg,0.59 mmol) was added and stirred at RT for 5 minutes. 4-(chloromethyl)pyridine hydrochloride (48.8 mg, 0.30 mmol) was added and stirred at 80 °C for 2h.After the completion of the reaction cooled to RT and poured into water, the solid obtained is filtered and washed with water and dried. The compound was purified by chromatography using silica gel and methanol/dichloromethane as eluent to get pure N-[3-methoxy-1-(pyridin-4-ylmethyl)piperidin-4-yl]-4-(1H-pyrazol-1-yl)benzenesulfonamide(83%)

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.30 (d, *J*=10.36 Hz, 1H), 1.52-1.81 (m, 2H), 1.58-1.78 (m, 2H), 2.06 (d, *J* = 10.93 Hz, 2H), 2.72 (br. s., 1H), 3.07-3.19 (m, 1H), 3.22-3.57 (m, 3H), 3.36-3.56 (m, 2H), 6.54-6.65 (m, 1H), 7.27 (d, *J* = 5.65 Hz, 2H), 7.82 (d, *J* = 1.51 Hz, 1H), 7.88-7.99 (m, 2H), 8.00-8.11 (m, 2H), 8.47 (d, *J* = 6.03 Hz, 2H), 8.62 (d, *J* = 2.45 Hz, 1H), 9.84 (br. s, 1H)
HRMS: *m/z* (ES+) = 428.17488 (MH^+) for $C_{21}H_{25}N_5O_3S$.

(44) 4-(1H-pyrazol-1-yl)-N-[1-(pyridin-3-ylmethyl)piperidin-4-yl]benzenesulfonamide(27). Yield: 32.9%
The compound was made according to the procedure mentioned for compound(3)
^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.29-1.45 (m, 2H), 1.48-1.61 (m, 2H), 1.91 (t, *J* = 10.64 Hz, 2H), 2.63 (d, *J* = 11.68 Hz, 2H), 2.89-3.04 (m, 1H), 3.41 (s, 2H), 6.61 (t, *J* = 1.88 Hz, 1H), 7.31 (dd, *J* = 7.72, 4.71 Hz, 1H), 7.63 (d, *J* = 7.91 Hz, 1H), 7.76 (d, *J* = 7.16 Hz, 1H), 7.83 (d, *J* = 1.51 Hz, 1H), 7.91 (d, *J* = 8.67 Hz, 2H), 8.00-8.10 (m, 2H), 8.39-8.46 (m, 2H), 8.62 (d, *J* = 2.45 Hz, 1H), 9.64 (br. s, 1H)
HRMS: *m/z* (ES+) = 398.16487 (MH^+) for $C_{20}H_{23}N_5O_2S$.

Scheme 10: Synthesis of 3-methyl-5-(1H-pyrazol-1-yl)-N-[1-(pyridin-4-ylmethyl)piperidin-4-yl]pyridine-2-sulfonamide(28).



Reagents and conditions: (a) benzyl mercaptan, NaH, THF, 0°C to 25°C, 3h, 86.9% (b) sulfuryl chloride, water, DCM, 0°C to RT, 66.6% (c)1-(pyridin-4-ylmethyl)piperidin-4-amine, potassium carbonate, DMF, RT, 16h, 57.6% (d) (1R,2R)-(-)-1,2-diaminocyclohexane, copper iodide, potassium carbonate, pyrazole, 1,4-dioxane, MW, 30 minutes, 16%

(45) 2-(Benzylthio)-5-bromo-3-methylpyridine (i). Yield: 86.9%

To a solution of benzyl mercptan (1 g, 7.97 mmol) in THF (20 mL) were added NaH (0.229 g, 9.564 mmol) and 2,5-dibromo-3-methylpyridine (2 g, 7.97 mmol) at 0 °C and the resulting solution was stirred at RT for 4 h. Then the reaction mixture was diluted with H_2O and extracted with EtOAc. The combined organic layer was washed with H_2O, brine, dried over Na_2SO_4 and evaporated under reduced pressure to afford 2-(benzylthio)-5-bromo-3-methylpyridine **2** as a green color solid. Yield: 2 g, 86.9%.

(46) 5-Bromo-3-methylpyridine-2-sulfonyl chloride (ii). Yield: 66.6%

To a solution of 2-(benzylthio)-5-bromo-3-methylpyridine **2** (2g,8.4973 mmol) in DCM (50 mL) was added sulfuryl chloride drop wise at 0°C. The resulting solution was stirred at rt for 2 h. Then the reaction mixture was poured into ice cold water then extracted with dichloromethane. The combined organic layer was washed with H_2O, brine, dried over Na_2SO_4 and evaporated under reduced pressure to afford 5-bromo-3-methylpyridine-2-sulfonyl chloride **3** as a green oily liquid. The crude product was taken as such for next step without purification. Yield: 1.2 g, 66.6%.

(47) 5-Bromo-3-methyl-N-(1-(pyridin-4-ylmethyl)piperidin-4-yl)pyridine-2-sulfonamide (iii). Yield: 57.6%

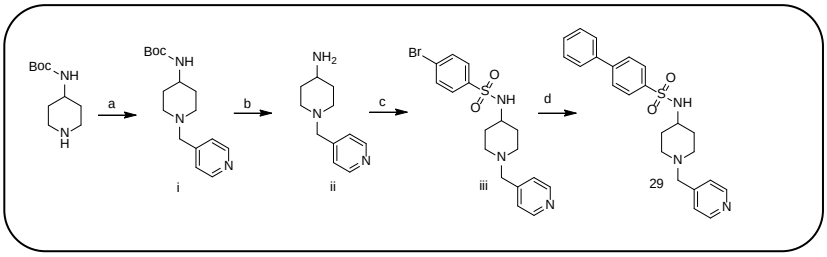
To a solution of 1-(pyridin-4-ylmethyl)piperidin-4-amine (2 g,10.45 mmole) in DMF were added K_2CO_3 (4.3 g, 31.36 mmol), 5-bromo-3-methylpyridine-2-sulfonyl chloride **3** (1. 2g, 12.54mmol) and the resulting mixture was stirred at room temperature for 2 h. Then the reaction mixture was poured into crushed ice and precipitated solid was filtered. The crude product was purified by column chromatography using 2% methanol in dichloromethane to give 5-Bromo-3-methyl-N-(1-(pyridin-4-ylmethyl)piperidin-4-yl)pyridine-2-sulfonamide **4** as a white solid. Yield: 1.5 g, 57.6%.

(48) 3-Methyl-5-(1H-pyrazol-1-yl)-N-(1-(pyridin-4-ylmethyl)piperidin-4-yl)pyridine-2-sulfonamide(28). Yield: 16%

To a solution 5-bromo-3-methyl-N-(1-(pyridin-4-ylmethyl)piperidin-4-yl)pyridine-2-sulfonamide (0.3 g, 0.71 mmol) in 1,4-Dioxane (5 mL) were added pyrazole (0.096 g, 1.42 mmol), K_2CO_3 (0.192g, 1.42 mmol), CuI (0.026 g, 0.142 mmol) and stirred at RT for 15 min with proper degassing with nitrogen. To this was added trans-1,2-cyclohexane diamine (0.040 g, 0.35 mmol) and the resulting mixture mass was heated at 120°C for 16 h in sealed tube. Then the reaction mixture was filtered through celite and filtrate was evaporated completely under reduced pressure and the residue was taken in EtOAc. The organic layer was washed with H_2O and concentrated under reduced pressure. The crude product was purified by column chromatography using 4% MeOH in dichloromethane as an eluent and the obtained compound was subsequently purified by reverse phase HPLC to give 3-methyl-5-(1H-pyrazol-1-yl)-N-(1-(pyridin-4-ylmethyl)piperidin-4-yl)pyridine-2-sulfonamide.

^{1}H NMR (400MHz ,DMSO-d_6) δ ppm 1.76-1.73 (m, 2H), 2.11-2.02 (m, 2H), 2.51 (s, 3H), 3.00 (b s, 2H), 3.36-3.33 (m, 3H), 4.26 (b s, 2H), 6.67 (dd, *J* = 2.3, 1.8 Hz, 1H), 7.49 (d, *J* = 4.6 Hz, 2H), 7.89 (d, *J* = 1.5 Hz , 1H), 8.31 (d, *J* = 6.4 Hz, 1H), 8.38 (s, 1H), 8.69 (d, *J* = 2.6 Hz, 2H), 9.00 (s, 1H), 9.64 (b s, 1H);
HRMS: *m/z* (ES+) 413.14565 (MH^+) for $C_{20}H_{24}N_6O_2S$.

Scheme 11: Synthesis of N-[1-(pyridin-4-ylmethyl)piperidin-4-yl]biphenyl-4-sulfonamide(29).



Reagents and conditions: (a) 4-pyridinemethylchloride, K_2CO_3, DMF, 12h, RT, 62.5%, (b) HCl-Dioxane, RT, 1h, 89.6% (c) *p*-bromobenzene sulphonyl chloride, K_2CO_3, DMF, RT, 57.1% (d) Phenylboronic acid, palladium tris-triphenyl phospine, Na_2CO_3, water, 110^{o}C, 16h, 41.9%

(49)Tert-butyl (1-(pyridin-4-ylmethyl)piperidin-4-yl)carbamate (i). Yield: 62.5%
To a solution of tert-butyl piperidin-4-ylcarbamate (5 g, 0.025 mol) in DMF (25 mL) were added potassium carbonate (6.9 g, 0.05 mol) and 4-(chloro methyl)pyridine (4.3 g, 0.0275 mol). The resulting mixture was stirred for 4 h at RT and poured into crushed ice. The precipitated solid was filtered and purified by column chromatography using 4% methanol in dichloromethane as a eluent to give tert-butyl (1-(pyridin-4-ylmethyl)piperidin-4-yl)carbamate as a white solid. Yield: 4.5 g, 62.5%.

(50)1-(Pyridin-4-ylmethyl)piperidin-4-amine (ii). Yield: 89.6%
: To a solution of tert-butyl (1-(pyridin-4-ylmethyl)piperidin-4-yl)carbamate **(i)** (4.5 g, 0.015 mol) in DCM (25 mL) was added 1,4 dioxane HCl (10 mL) dropwise at 0°C and the resulting solution was stirred at rt for 1h. Then the mixture was evaporated under reduced pressure and dissolved in dichloromethane basified with solid sodium bicarbonate (pH ~ 8 to 9). The organics were separated, dried over Na_2SO_4 and evaporated under reduced pressure to afford 1-(pyridin-4-ylmethyl) piperidin-4-amine as a red colour solid. Yield: 2.5g, 89.6%.

(51)4-Bromo-N-(1-(pyridin-4-ylmethyl)piperidin-4-yl)benzenesulfonamide (iii). Yield: 57.1%
To a solution of 1-(pyridin-4-ylmethyl)piperidin-4-amine (1 g, 5.23 mmol) in DMF (10ml) were added potassium carbonate (2.1g, 15.687mmol) 4-bromobenzenesulfonyl chloride (1.6g, 6.27 mmol) and the resulting mixture was stirred for 2h at RT. Then the reaction mixture was poured into crushed ice and precipitated solid was filtered and purified by column chromatography using 2% methanol in dichloromethane as eluent to give4-bromo-N-(1-(pyridin-4-ylmethyl)piperidin-4-yl)benzenesulfonamide as a white solid. Yield: 1.2 g, 57.1%.

(52)N-(1-(Pyridin-4-ylmethyl)piperidin-4-yl)-[1,1'-biphenyl]-4-sulfonamide(29). Yield: 41.9%

To a solution 4-bromo-N-(1-(pyridin-4-ylmethyl)piperidin-4-yl)benzenesulfonamide (0.3 g, 0.732 mmol) in 1,4-dioxane (5 mL) were added phenyl boronic acid (0.133 g, 1.10 mmol), Na2CO3 (0.387g, 13.66 mmol) and water (2 ml) respectively. The resulting mixture was stirred at room temperature for 15 min and to this was added palladium tris-triphenyl phospine (0.042g, 0.03657 mmol). The reaction mass was heated at 110 °C for 16 h and progress of the reaction was monitored by TLC. After the completion of the reaction, the mixture was evaporated completely under reduced pressure and the residue was taken in EtOAc. The organic layer was washed with H_2O, brine, dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography using 4% MeOH in DCM as an eluent and obtained compound was subsequently purified by PREP HPLC purification to give N-(1-(pyridin-4-ylmethyl)piperidin-4-yl)-[1,1'-biphenyl]-4-sulfonamide as a gummy liquid.Yield: 0.125 g (41.9%)

^{1}H NMR (400MHz ,DMSO-d_6) δ ppm 1.49 - 1.36 (m, 2H), 1.59 (d, *J* = 9.8 Hz, 2H), 1.95 (t, *J* = 10.9 Hz, 2H), 2.72 - 2.58 (m, 2H), 3.05 - 2.95 (m, 1H), 3.42 (s, 2H), 7.26 (d, *J* = 5.8 Hz, 2H), 7.47 - 7.41 (m, 1H), 7.55 - 7.48 (m, 2H), 7.77 - 7.72 (m, 2H), 7.81 (d, *J* = 7.3 Hz, 1H), 7.88 (s, 4H), 8.50 - 8.45 (m, 2H);
HRMS: m/z (ES+) 408.17403 (MH+) for C23H25N3O2S.

(53)4-(1H-pyrazol-1-yl)-N-[1-(pyridin-4-ylcarbonyl)piperidin-4-yl]benzenesulfonamide(30). Yield: 20.85%.
isonicotinic acid (60.3 mg, 0.49 mmol) was taken in DMF (5 mL). O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (248 mg, 0.65 mmol) was added followed by the addition of N,N'-Diisopropylethylamine (1 mL, 5.73 mmol).N-(piperidin-4-yl)-4-(1H-pyrazol-1-yl)benzenesulfonamide (100 mg, 0.33 mmol) was added and stirred at RT for 2 hours.After the completion of the reaction the volatiles were removed, and the residue was partitioned between ethyl acetate and water. The ethyl acetate layer was washed with water, brine solution. The organic layer was dried over sodium sulphate, evaporated under high vacuum to get the crude compound which was purified by chromatography using silica gel and methanol/dichloromethane as eluent.

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.21-1.46 (m, 3H), 1.55 (br. s., 1H), 1.71 (d, *J* = 11.30 Hz, 1H), 2.91-3.11 (m, 2H), 4.16 (d, *J* = 14.13 Hz, 2H), 6.59-6.64 (m, 1H), 7.49 (d, *J* = 5.65 Hz, 2H), 7.79-7.86 (m, 1H), 7.88-7.99 (m, 3H), 8.00-8.11 (m, 2H), 8.63 (d, *J* = 2.45 Hz, 1H), 8.72 (d, *J* = 6.03 Hz, 2H);
HRMS: *m/z* (ES+) = 412.14421 (MH^+) for $C_{20}H_{21}N_5O_3S$.

(54) 1-{[4-(1H-pyrazol-1-yl)phenyl]sulfonyl}-4-(pyridin-4-ylmethyl)piperazine(31). Yield: 25.4%
1-(pyridin-4-ylmethyl)piperazine (100 mg, 0.56 mmol) was taken in DMF (10 mL). Potassiumcarbonate (156 mg, 1.13 mmol) was added and stirred at RT for 20 minutes and then 4-(1H-pyrazol-1-yl)benzene-1-sulfonyl chloride (205 mg, 0.85 mmol) was added and stirred it for 2h at rt.
After completion of the reaction, poured the reaction mixture into water, and extracted the aqueous with dichloromethane. The organic layer was washed with water, brine solution. Concentrated the organic layer and purified with reverse phase chromatography to get the product1-((4-(1H-pyrazol-1-yl)phenyl)sulfonyl)-4-(pyridin-4-ylmethyl)piperazine (55.0 mg, 25.4 %).

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.39-2.48 (m, 4H), 2.95-3.08 (m, 3H), 3.17 (d, *J* = 5.27 Hz, 1H), 3.51 (s, 2H), 6.65 (dd, *J* = 2.54, 1.79 Hz, 1H), 7.25 (d, *J* = 6.03 Hz, 2H), 7.79-7.89 (m, 3H), 8.09-8.18 (m, 2H), 8.41-8.48 (m, 2H), 8.69 (d, *J* = 2.45 Hz, 1H)
HRMS: *m/z* (ES+) = 384.14936 (MH^+) for $C_{19}H_{21}N_5O_2S$.

(55) 4-(1H-pyrazol-1-yl)-N-[1-(pyridin-4-ylmethyl)piperidin-4-yl]benzamide(32). Yield: 31.2%
4-(1H-pyrazol-1-yl)benzoic acid (75 mg, 0.40 mmol) was taken in DMF (5 mL) . HATU (227 mg, 0.60 mmol) was added and stirred at RT for 5 minutes. DIPEA (0.139 mL, 0.80 mmol) was added followed by the addition of1-(pyridin-4-ylmethyl)piperidin-4-amine (114 mg, 0.60 mmol). The reaction mixture was stirred at RT for 2h. After the completion of the reaction, poured the reaction mixture into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with water, brine solution. The organic layer was dried over sodium sulphate, concentrated under high vacuum to get the crude compound which was purified by reverse phase chromatography to get the product4-(1H-pyrazol-1-yl)-N-(1-(pyridin-4-ylmethyl)piperidin-4-yl)benzamide (45.0 mg, 31.2 %).

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.29-0.66 (m, 4H), 0.86 (t, *J* = 11.30 Hz, 2H), 1.50-1.72 (m, 2H), 2.29 (s, 2H), 5.37-5.38 (m, 1H), 6.13 (d, *J* = 4.52 Hz, 2H), 6.54-6.83 (m, 5H), 7.13-7.42 (m, 4H), 10.25 (s, 1H);
HRMS: *m/z* (ES+) = 362.19786 (MH^+) for $C_{21}H_{23}N_5O$.

(56)N-(1-(3-methoxybenzyl)piperidin-4-yl)-4-(1H-pyrazol-1-yl)benzenesulfonamide(33) Yield: 28%
The compound was made according to the procedures mentioned in **Scheme 6**(3-methoxybenzylchloride was used instead of pyridine-4-methylchloride)

^{1}H NMR (400MHz ,DMSO-d_6) δ ppm 1.48 - 1.30 (m, 2H), 1.56 (d, *J* = 10.8 Hz, 2H), 1.93 (t, *J* = 10.8 Hz, 2H), 2.63 (d, *J* = 11.7 Hz, 2H), 2.98 (dd, *J* = 10.8, 4.2 Hz, 1H), 3.40(s, 3H), 3.51 (s, 2H), 6.63 - 6.60 (m, 1H), 7.25 (d, *J* = 5.6 Hz, 2H), 7.80 (d, *J* = 7.3 Hz, 1H), 7.83 (d, *J* = 1.5 Hz, 1H), 7.92-7.98 (m, 2H), 8.06 (d, *J* = 8.8 Hz, 2H), 8.47 (d, *J* = 5.9 Hz, 2H), 8.63 (d, *J* = 2.4 Hz, 1H); HRMS: *m/z* (ES+) = 427.48563 (MH^+) for $C_{21}H_{23}N_4O_2S$.

Biology assays

Microbiology assays:

Assays to determine MIC for H37Rv and clinical isolates, MBC under aerobic and hypoxic conditions, potency in intracellular THP-1 (human lung adenocarcinoma epithelial cell line) potency was carried out as described before.[1]

InhA assay:

InhA enzymatic reaction was set up in a 25 µl volume containing 30 mM PIPES pH 6.8, 50mM NaCl, 0.05% CHAPS, 2mM DTT and 0.1mM EDTA. 10µl of InhA enzyme (0.3nM final) pre-incubated with NADH (50µM final) for 15min. After 10min of incubation, reaction was started by the addition of 15 µl of dodecyl coA (100µM final) and allowed to continue for 45min at 25°C. 50µl Acetonitrile quench containing 100ng/ml Carbamazepine as internal standard was dispensed at the end of 45min to stop the reaction. Substrate ddcoA and product rddcoA were quantified by LC-MS/MS method. The area under curve (AUC) of ddcoA and rddcoA peaks calculated by Quantlynx software were considered for % product conversion calculations.

RNA Polymerase assay :

RNA Polymerase assay buffer contains 50 mM Tris-Cl pH=8.0, 12.5 mM $MgCl_2$, 0.1mM DTT, 50mM NaCl, 0.05mM EDTA, 2% Glycerol, 50 mM Potassium Glutamate and 0.002% Brij-35. 30 µl assay contains 15 µl of enzyme mix (66nM of RNA polymerase enzyme, 66nM of SigmaA, 0.01U/ml of pyrophosphatase) and 10 µg/ml of T4 phage DNA in assay buffer. The reaction was started by the addition of 15 µl of substrate mix in assay buffer containing 100 µM of each of the following nucleotide-ATP, GTP, CTP and UTP. The reaction was carried out for 2 hrs at 25 °C. At the end of the reaction, 30 µl of Baykov's reagent[25] was added and mixed well and incubated for 30 minutes at room temperature. The amount of Pi released is measured by monitoring the absorbance at 630 nm using SpectraMax (Molecular Devices).

DNA gyrase supercoiling assay:

Supercoiling reaction was carried out in 96-well plates (Bio-rad) and assay mix contained 12.5 nM Mtb DNA gyrase holoenzyme, 50 ng of relaxed pBR322 DNA, 40 mM HEPES-KOH pH 7.5, 100 mM potassium glutamate, 15 mM KCl, 1 mM spermidine, 10 mM $MgCl_2$, 4 mM DTT, 8% glycerol, 0.36 mg/mL BSA and 75 µM ATP in 30 µL volume. The assay was started with the addition of DNA and ATP mix and continued for 90 min at 37°C. The reaction was stopped by addition of 0.75 µL Proteinase K (20 mg/mL, 40 U/mg) and 3 µL of 2% SDS followed by incubation at 37 °C for 1 hour. Supercoiled and relaxed forms of DNA were separated by gel electrophoresis for 16 h at 1 V/cm, on a 0.8 % agarose in buffer containing 45 mM Tris-borate and 1 mM EDTA, ethidium bromide (0.7 µg/ml) and the bands were visualized using a gel documentation system (Phosphorimager, FUJI). The supercoiled/relaxed bands were quantified using Quantity1 software.

DNA toposisomerase (Topo) 1 relaxation assay:

Relaxation activity of Mtb topo I was tested using supercoiled DNA as substrate, in 30 µL assay volume in 96 well half area black plates. 100 µg/ml of supercoiled pJT519 was incubated with 1.35 nM of Mtu topo I in 50 mM Tris HCl, pH 8.0 containing 100 mM K-glutamate, 10 mM $MnCl_2$, 1 mM DTT and 0.005% Brij-35. 1 µL of compound, 1 µL of DMSO, or 1uL of quench buffer (0.5M NaCl/0.5M Na-acetate) was added to test, positive control and negative control wells respectively and incubated at P kept at 37 °C for 100 minutes. Reaction was stopped by addition of SDS-Proteinase K and further incubated for 1h at 37 °C. 4 µL of the assay mix was loaded onto 0.8% agarose gels and run in TBE buffer overnight at 30V. Gels are stained with ethidium bromide (0.5 µg/ml) and the bands were visualized using a gel documentation system (Phosphorimager, FUJI). The supercoiled/relaxed bands were quantified using Quantity 1 software.

NADH driven ATP synthesis inhibition:

The ATP synthesis activity was determined in isolated membrane vesicles from *Mycobacterium smegmatis* by energizing them with NADH and quantifying the amount of ATP produced using the luciferin/luciferase system. The assay was run in 384 well format with an assay volume of 30 µl. Briefly, 15 µl of enzyme mix containing 8 µg/ml *M. smegmatis* membrane vesicles and 5 mM $MgCl_2$ in HEPES-NaOH buffer, pH 7.6 was added to 384 well plates containing 1 µl of 30X compound dilutions. The reaction was initiated by adding 15 µl of substrate mix containing 0.3 mM NADH, 15 µM ADP and 0.1 mM KH_2PO_4. Plates were incubated for 60 min at room temperature. The amount of ATP synthesised is measured by adding 30 µL of luciferin/luciferase reagent and

measuring the luminescence using TECAN Infinite F500 immediately. IC_{50} values are calculated using graphpad prism software.

Precursor incorporation to assess RNA and protein synthesis:
Mycobacterium bovis(BCG) was grown in Middlebrook 7H9 broth (BD Diagnostics) containing 0.2% glycerol, and 0.05% Tween 80 at 37 °C to 0.3-0.4 OD (~107 CFU/ml). MultiscreenTM 96 well filtration plate assembly containing Glass Fiber plates (Type B filter 0.65µm hydrophilic Durapore Membrane) was used. To pre-wet filtration plates 20µl of test compound (4 fold serially diluted), 40µl of 0.3 - 0.4 OD BCG culture and 40µl radioactive precursor solution was added and plate was incubated at 37 °C. Each test and reference compound was analyzed individually for incorporation of radiolabeled Acetate, Adenine, Leucine and Uracil respectively. 0.01mCi /ml of [1-^{14}C]acetate (Perkin Elmer), 0.025mCi/ml of [8-^{3}H]adenine (GE Healthcare), 0.025mCi/ml of [4,5-^{3}H]leucine (Amersham Biosciences) and 0.01mCi /ml of [5,6-^{3}H]uracil (Amersham Bosciences) were used. Reactions were stopped using 20% ice cold trichloroacetic acid (TCA, S.D.Fine Chem.) and plates were incubated overnight at 4°C. Subsequent day plates are washed with 5% TCA three times and then with absolute alcohol. 50µl of Scintillant (Optiphase Supermix Liquid Scintillation cocktail: Wallac) was added to dried assay plates. The plates were counted next day using Liquid Scintillation and Luminiscence counter (1450 MicroBeta Trilux) from Wallac. The data was analyzed using XL-Fit (version 5.2) where IC_{50} is calculated using sigmoidal fit model (606) and formula (((A*B)+(C*(x^D)))/(B+(x^D))). Reference drugs used for the assay were cerulenin (Sigma), sparfloxacin (Dr. Reddy's), chloramphenicol (Sigma) and rifampicin (Sigma).

Reference-

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