

Electronic Supplementary Information

A new route to indoles *via in situ* desilylation-Sonogashira strategy: Identification of novel small molecules as potential anti tuberculosis agents

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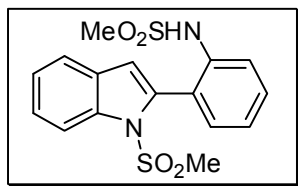
Experimental

Chemistry

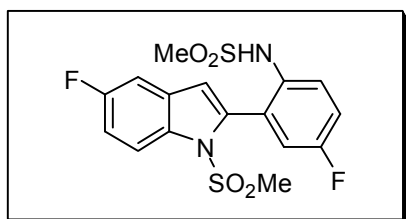
General methods: Unless stated otherwise, reactions were performed under nitrogen atmosphere using oven dried glassware. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualizing with ultraviolet light or iodine spray. Flash chromatography was performed on silica gel (230-400 mesh) using distilled hexane, ethyl acetate, dichloromethane. ^1H NMR and ^{13}C NMR spectra were recorded in CDCl_3 or $\text{DMSO-}d_6$ solution by using 400 or 200 and 100 MHz spectrometers, respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, $\delta = 0.00$) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet) as well as b (broad). Coupling constants (J) are given in hertz. Infrared spectra were recorded on a FT-IR spectrometer. Melting points were determined using melting point apparatus and are uncorrected. MS spectra were obtained on a Agilent 6430 series Triple Quad LC-MS / MS spectrometer. High-resolution mass spectra (HRMS) were recorded using a Waters LCT Premier XE instrument. Melting points (mp) were by using Buchi B-540 melting point apparatus.

General method for the preparation of indole 2

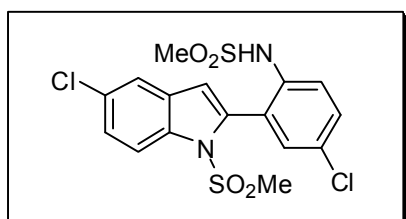
To a stirred solution of *o*-iodoanilide **1** (1.6835 mmol) in methanol (5 mL), 10% Pd/C (0.002 g, 0.0168 mmol), PPh_3 (0.018 g, 0.0673 mmol), CuI (0.032 g, 0.1685 mmol), and Et_3N (0.406 g, 4.0287 mmol) were added under a nitrogen atmosphere. The reaction mixture was allowed to stir at room temperature for 15 min, and then the reaction temperature was increased slowly to 40 °C. To this was added trimethylsilyl acetylene (0.662 g, 6.734 mmol) slowly and portion wise maintaining the reaction mixture at 40 °C. Then the reaction mixture was stirred at 60 °C according to the time indicated in Table 1. The Progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was diluted with saturated NH_4Cl solution (15 mL) and the product was extracted with ethyl acetate (3 x 15 mL). The organic layers were collected, combined, dried over anhydrous Na_2SO_4 , filtered and concentrated under a reduced pressure. The residue was purified by column chromatography over silica gel using ethylacetate - hexane.



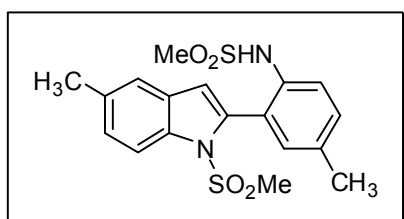
***N*-(2-(1-(methylsulfonyl)-1H-indol-2-yl)phenyl)methanesulfonamide (2a):** Yield: 67% (0.41 g), white solid; HPLC purity 99.5%; mp: 180-181 °C; R_f = 0.26 (20 % EtOAc-*n*-Hexane); IR (KBr, cm^{-1}): 3374, 2983, 1576, 1084; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ/ppm : 8.10 (d, J = 8.3 Hz, 1H), 7.73 (d, J = 8.3 Hz, 1H), 7.64 (d, J = 8.3 Hz, 1H), 7.52 – 7.31 (m, 4H), 7.23 (dd, J = 13.3 and 5.60 Hz, 1H), 6.75 (s, 1H), 6.58 (s, 1H), 2.99 (s, 3H), 2.88 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ/ppm : 137.3, 137.0, 135.5, 131.1, 131.0, 129.7, 125.9, 124.7, 124.2, 123.4, 121.4, 129.6, 115.3, 114.4, 40.6, 40.0; MS (ES mass): m/z 362.8 (M-1); HRMS: calcd, for $\text{C}_{16}\text{H}_{17}\text{N}_2\text{O}_4\text{S}_2$ (M+H): 365.0630, found: 365.0638.



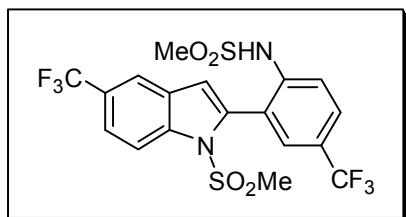
***N*-(4-fluoro-2-(5-fluoro-1-(methylsulfonyl)-1H-indol-2-yl)phenyl)methanesulfonamide (2b):** Yield: 65% (0.44 g) white solid; HPLC purity 99.8%; mp: 220-222 °C; R_f = 0.35 (20 % EtOAc-*n*-Hexane); IR (KBr, cm^{-1}): 3250, 2929, 1370, 1159; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ/ppm : 8.05 (dd, J = 9.1 and 4.3 Hz, 1H), 7.67 (dd, J = 8.9 and 5.0 Hz, 1H), 7.30 (dd, J = 8.1 and 1.9 Hz, 1H), 7.24-7.15 (m, 2H), 7.08 (dd, J = 8.1 and 2.6 Hz, 1H), 6.74 (s, 1H), 6.53 (s, 1H), 2.89 (s, 6H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ/ppm : 159.1, 158.1, 136.4, 132.7, 130.5, 123.9, 123.8, 117.8, 117.6, 116.6, 116.5, 114.4, 114.3, 107.2, 40.5, 40.2; MS (ES mass): m/z 398.8 (M-1); HRMS: calcd for $\text{C}_{16}\text{H}_{14}\text{F}_2\text{N}_2\text{O}_4\text{S}_2$: 399.1021, found: 399.1043.



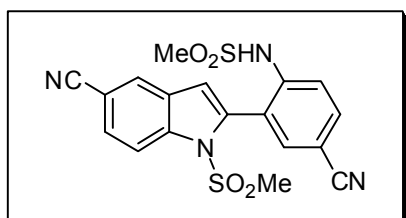
***N*-(4-chloro-2-(5-chloro-1(methylsulfonyl)-1*H*-indol-2-yl)phenyl)methanesulfonamide (2c):** Yield: 62% (0.45 g) yellow solid; HPLC purity 97.8%; mp: 142-146 °C; $R_f = 0.30$ (20 % EtOAc-*n*-Hexane); IR (KBr, cm^{-1}): 3252, 2298, 1582, 1333; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ/ppm : 8.05-7.96 (d, $J = 8.5$ Hz, 1H), 7.69-7.59 (m, 2H), 7.49-7.36 (m, 2H), 7.28 (s, 1H), 6.75 (s, 1H), 6.66 (s, 1H), 2.98 (s, 3H), 2.95 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ/ppm : 135.6, 131.0, 130.8, 130.7 (2C), 130.5, 129.7, 126.4, 124.9, 121.5 (2C), 121.1, 116.3, 113.9, 40.8, 40.2; MS (ES mass): m/z 432.8 (M+1) ; HRMS: calcd for $\text{C}_{16}\text{H}_{14}\text{Cl}_2\text{N}_2\text{O}_4\text{S}_2$ M^+ : 432.9650, found 432.9649.



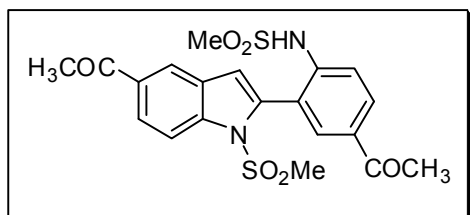
***N*-(4-methyl-2-(5-methyl-1(methylsulfonyl)-1*H*-indol-2-yl)phenyl)methanesulfonamide (2d):** Yield: 63% (0.41 g) white solid; HPLC purity 95.3%; mp: 134-136 °C; $R_f = 0.35$ (25 % EtOAc-*n*-Hexane); IR (cm^{-1}): 3280, 2930, 1365, 1169; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ/ppm : 7.96 (d, $J = 8.5$ Hz, 1H), 7.58 (d, $J = 8.5$ Hz, 1H), 7.40 (s, 1H), 7.27 -7.23 (m, 2H), 7.15 (s, 1H), 6.66 (s, 1H), 6.56 (s, 1H), 2.89 (s, 3H), 2.82 (s, 3H), 2.48 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ/ppm : 136.3, 135.6, 134.5, 134.0 (2C), 131.4, 131.3, 130.0, 127.2, 124.5, 121.3, 121.1, 115.1, 114.4, 40.0, 39.9, 21.2, 20.7; MS (ES mass): m/z 393.1 (M+1) ; HRMS: calcd, for $\text{C}_{18}\text{H}_{19}\text{N}_2\text{O}_4\text{S}_2$ (M-H): 391.0786, found: 391.0796.



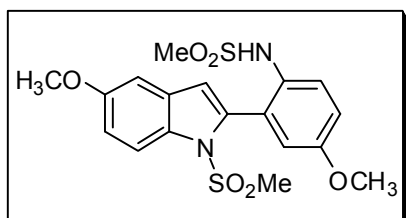
***N*-(2-(1-(methanesulfonyl)-5-(trifluoromethyl)-1*H*-indol-2-yl)-4-(trifluoromethyl)phenyl) methane sulfonamide (2e):** Yield: HPLC purity 98.6%; 60% (0.5 g) brown solid; mp: 158-160 °C; R_f = 0.20 (30 % EtOAc-*n*-Hexane); IR (KBr, cm^{-1}): 3260, 2934, 1332, 1158; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ/ppm : 8.20 (d, J = 8.8 Hz, 1H), 7.96 (s, 1H), 7.84 (d, J = 8.8 Hz, 1H), 7.73 (d, J = 8.83 Hz, 1H), 7.71 (d, J = 8.8 Hz, 1H), 7.56 (s, 1H), 6.89 (s, 1H), 6.75 (s, 1H), 3.07 (s, 3H), 2.89 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ/ppm : 140.5, 138.7, 135.2, 129.1, 128.5, 128.4, 127.9, 127.5, 123.0, 122.9, 121.9, 119.2, 119.1, 117.8, 115.5, 114.5, 41.6, 40.2; MS (ES mass): m/z 498.8 (M-1); HRMS: calcd, for $\text{C}_{18}\text{H}_{13}\text{N}_2\text{O}_4\text{F}_6\text{S}_2$ (M-H): 499.0221, found: 499.0256.



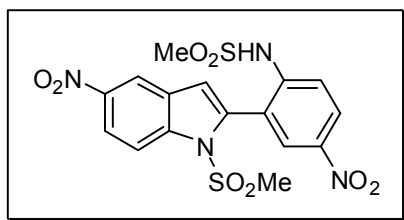
***N*-(4-cyano-2-(5-cyano-1(methanesulfonyl)-1*H*-indol-2-yl)phenyl)methanesulfonamide (2f):** Yield: 64% (0.44 g); white solid: HPLC purity 97.6%; mp: 175-177 °C; R_f = 0.25 (30 % EtOAc-*n*-Hexane); IR (KBr, cm^{-1}): 3267, 3127, 2923, 2232, 1341. $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ/ppm : 9.79 (s, 1H), 8.24 (s, 1H), 8.07 (d, J = 8.6 Hz, 1H), 7.93 (s, 1H), 7.90-7.77 (m, 2H), 7.69 (d, J = 8.6 Hz, 1H), 6.95 (s, 1H), 3.37 (s, 3H), 3.07 (s, 3H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ/ppm : 138.5, 137.7, 136.0, 134.4, 131.0, 129.7, 128.6, 127.7, 127.0, 126.5, 123.6, 119.6, 119.5, 119.3, 115.4, 105.8, 42.2, 40.6. MS (ES mass): m/z 412.8 (M-1); $^1\text{HRMS}$ (EI): calcd for $\text{C}_{18}\text{H}_{14}\text{N}_4\text{O}_4\text{S}_2$ 413.0050, found: 413.0066.



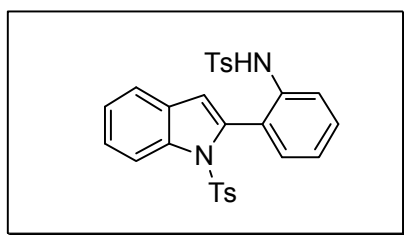
***N*-(4-acetyl-2-(5-acetyl-1(methylsulfonyl)-1*H*-indol-2-yl)phenyl)methanesulfonamide (2g):** Yield: 65% (0.49 g) white solid; HPLC purity 96.9%; mp: 234- 236 °C; R_f =0.10 (25 % EtOAc-*n*-Hexane); IR (KBr, cm^{-1}): 3156, 2930, 1669, 1338; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ /ppm: 8.40 (s, 1H), 8.26 (s, 1H), 8.04-7.90 (m, 3H), 7.69 (d, J = 8.5 Hz, 1H), 7.52 (d, J = 3.6 Hz, 1H), 6.81 (s, 1H), 3.09 (s, 3H), 2.65 (s, 3H), 2.55 (s, 3H), 2.49 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, $\text{DMSO-}d_6$) δ /ppm: 197.9, 197.0, 142.3, 139.5, 136.9, 132.9, 132.8, 131.8, 130.6, 129.8, 124.7, 123.7, 122.9, 119.5, 114.5, 113.5, 42.4, 40.9, 27.2 27.0. MS (ES mass): m/z 448.9 ($\text{M}+1$)⁺; HRMS (EI): Calcd for M^+ $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_6\text{S}_2$ 447.2016, found 447.2019.



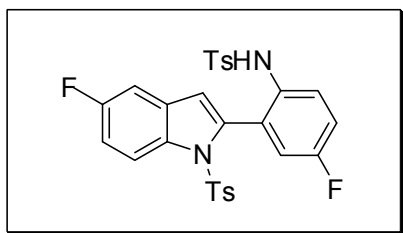
***N*-(4-methoxy-2-(5-methoxy-1(methylsulfonyl)-1*H*-indol-2-yl)phenyl)methanesulfonamide (2h):** Yield: 64% (0.45 g) brown solid; HPLC purity 96.3%; mp 171-173 °C; R_f =0.30 (30 % EtOAc-*n*-Hexane); IR (KBr, cm^{-1}): 3312, 2932, 1365, 1159; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ /ppm: 7.64 (s, 1H), 7.49 – 7.46 (m, 2H), 7.31 (s, 1H), 7.22 (d, J = 8.4 Hz, 1H), 7.0 (d, J = 8.4 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 6.58 (s, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 3.02 (s, 3H), 2.85 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ /ppm: 158.7, 140.8, 137.8, 129.0, 128.4, 123.4, 121.7, 117.4, 115.4, 114.2, 113.9, 113.2, 109.7, 99.6, 55.7, 55.7, 40.3, 39.8. MS (ES mass): m/z 425.1 ($\text{M}+1$); HRMS : Calcd for $\text{C}_{18}\text{H}_{19}\text{N}_2\text{O}_6\text{S}_2$ (M-H):423.0685, found:423.0692.



***N*-(2-(1-(methylsulfonyl)-5-nitro-1*H*-indol-2-yl)-4-nitrophenyl)methanesulfonamide (2i)**: Yield: 58% (0.44 g); yellow solid; HPLC purity 97.3%; mp: 230-232 °C; R_f = 0.10 (30 % EtOAc-*n*-Hexane); IR (KBr, cm^{-1}): 3362, 2926, 1513, 1343; $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ /ppm: 9.99 (s, 1H), 8.68 (s, 1H), 8.32-8.28 (m, 2H), 7.81 (s, 1H), 7.14 (s, 1H), 6.78-6.82 (m, 2H), 3.37 (s, 3H), 3.14 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, DMSO- d_6) δ /ppm: 143.4, 141.6, 139.6, 136.3, 129.3, 127.4, 125.6, 123.2, 122.2, 119.4, 118.2, 117.3, 114.5, 113.3, 42.3, 40.4; MS (ES mass): m/z 452.7 (M-1); HRMS Calcd, for $\text{C}_{16}\text{H}_{13}\text{N}_4\text{O}_8\text{S}_2$ (M-H): 453.0175, found 453.0194.

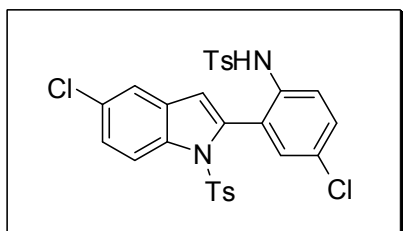


4-methyl-*N*-(2-(1-tosyl-1*H*-indol-2-yl)phenyl)benzenesulfonamide (2j): Yield: 64% (0.43 g) white solid; HPLC purity 98.1%; mp: 210-212 °C; R_f = 0.35 (% EtOAc-*n*-Hexane); IR (KBr, cm^{-1}): 3381, 3067, 1596, 1090; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 8.31 (d, J = 8.4 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.46-7.40 (m, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 4 Hz, 2H), 7.20-7.13 (m, 3H), 7.04 (d, J = 8.4 Hz, 2H) 6.94-6.86 (m, 4H), 5.71 (s, 1H), 2.30 (s, 3H), 2.29 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ : 145.2, 143.1, 137.7, 136.8, 136.2, 135.7, 134.2, 131.2, 130.1 (2C), 129.4 (2C), 129.2 (2C), 126.7 (2C), 126.7 (2C), 126.4, 125.4, 125.1, 124.7, 124.3, 120.6, 116.2, 114.7, 21.5, 21.4; MS (ES mass): m/z 515 (M-1, 100%); HRMS: calcd for: $\text{C}_{28}\text{H}_{25}\text{N}_2\text{O}_4\text{S}_2$ (M+H) 517.1256, found: 517.1249.



N-(4-fluoro-2-(5-fluoro-1-tosyl-1H-indol-2-yl)phenyl)-4-methylbenzenesulfonamide(2k):

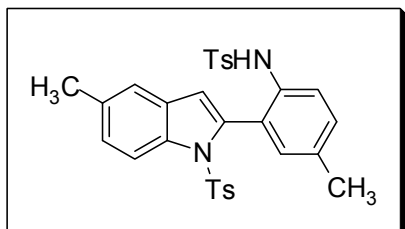
Yield: 58% (0.41 g), brown solid; HPLC purity 98.4%; R_f =0.30 (20 % EtOAc-*n*-Hexane); mp: 207-209 °C; IR (KBr, cm^{-1}): 3389, 3076, 1463,1089. ^1H NMR (400 MHz, CDCl_3) δ : 8.38 (d, J = 9.2 Hz, 1H), 7.80 (d, J = 8.8 Hz 1H), 7.39-7.30 (m, 5H), 7.21 (d, J =8.0 Hz, 2H), 7.08 (m, 2H), 7.03 (d, J =9.6 Hz, 1H), 6.98 (d, J = 8.0 Hz, 2H), 6.66 (d, J = 10.8 Hz, 1H), 5.74 (s, 1H) 2.44 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 161.2, 158.8, 145.7, 143.1, 137.0, 136.7, 133.6, 129.6 (2C), 129.1 (2C), 128.9 (2C), 126.6 (2C), 117.7, 117.5, 117.4, 117.2, 117.0, 114.9, 114.8, 113.7, 113.4, 106.3, 106.1, 21.5, 21.3. MS (ES mass): m/z 551.1 (M-1, 100%) HRMS: calcd, for $\text{C}_{28}\text{H}_{23}\text{N}_2\text{O}_4\text{S}_2\text{F}_2$ (M+H): 553.1067 found: 553.1076.



N-(4-chloro-2-(5-chloro-1-tosyl-1H-indol-2-yl)phenyl)-4-methylbenzenesulfonamide(2l):

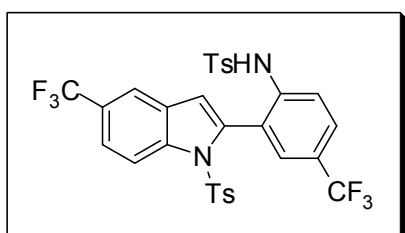
Yield: 60% (0.45 g), white solid; HPLC purity 96.9%; R_f =0.25 (20 % EtOAc-*n*-Hexane); mp: 212-214 °C; IR (KBr, cm^{-1}): 3262, 3070, 1482, 1074; ^1H NMR (400 MHz, CDCl_3) δ : 8.26 (d, J = 9.0 Hz, 1H), 7.63 (d, J = 8.2 Hz, 1H), 7.45-7.39 (m, 2H), 7.34 (d, J = 7.74 Hz, 2H), 7.14 (m, 5H), 6.95 (d, J = 7.4 Hz, 2H), 6.86 (s, 1H), 6.71 (s, 1H), 5.68 (s, 1H), 2.34 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ : 145.9, 143.5, 136.7, 136.1, 136.0, 134.4, 133.9, 131.0, 130.9, 130.8, 130.4, 130.2 (2C), 129.7 (2C), 129.3 (2C), 127.1, 126.8 (2C), 126.7 (2C), 125.9, 120.3, 117.2, 113.9,

21.6, 21.4; MS (ES mass): m/z 582.8 (M-1): HRMS: calcd, for $C_{28}H_{22}Cl_2N_2O_4S_2$: 584.1257
found: 584.1267.



4-methyl-N-(4-methyl-2-(5-methyl-1-tosyl-1H-indol-2-yl)phenyl)benzenesulfonamide(2m):

Yield: 63% (0.44 g), white solid; HPLC purity 95.9 %; R_f = 0.3 (10 % EtOAc-*n*-Hexane); mp: 204-206 °C; IR (KBr, cm^{-1}): 3300, 2921, 1456, 1039; 1H NMR (400 MHz, $CDCl_3$) δ : 8.14 (d, J = 8.8 Hz, 1H), 7.52 (d, J = 8.8 Hz, 2H), 7.32 (s, 1H), 7.29 (d, J = 8.8 Hz, 2H), 7.22 (d, J = 7.8 Hz, 2H), 7.15 (d, J = 8.4, 2H) Hz, 7.05-7.03 (m, 3H), 6.86 (d, J = 8.0, 2H), 6.57 (s, 1H), 2.46 (s, 3H), 2.30 (s, 3H), 2.29 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ : 145.0, 142.8, 137.0, 136.6, 135.9, 135.1, 134.3, 133.9, 133.0, 131.8, 130.8, 130.5, 129.2 (2C), 129.1 (2C), 126.9, 126.8 (2C), 126.7 (2C), 126.6, 125.7, 120.4, 115.9, 114.4, 21.5, 21.4, 21.2, 20.7; MS (ES mass): m/z 542.9 (M-1, 100%): HRMS: calcd, for $C_{30}H_{29}N_2O_4S_2(M+H)$: 545.1569 found: 545.1567.



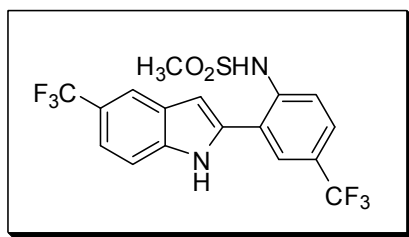
4-methyl-N-(2-(1-tosyl-5-(trifluoromethyl)-1H-indol-2-yl)-4-(trifluoromethyl)phenyl)

benzenesulfonamide (2n): Yield: 62% (0.52 g) yellow solid; HPLC purity: 97.5%; R_f = 0.30 (20 % EtOAc-*n*-Hexane); mp: 224-228 °C; IR (KBr, cm^{-1}): 3256, 2925, 1596, 1079; 1H NMR (400 MHz, $CDCl_3$) δ : 8.47 (d, J = 8.8 Hz, 1H), 7.75-7.68 (m, 4H), 7.52 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 8.4 Hz, 4H), 6.95 (s, 1H), 6.92 (s, 1H), 6.05 (s, 1H), 2.37 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ : 146.3, 144.1, 139.6, 139.1, 136.4, 135.6, 134.2,

129.9, 129.8 (2C), 129.7 (2C), 129.6, 129.2, 128.6, 127.0 (2C), 126.6 (2C), 124.4, 122.6, 122.5, 122.4, 118.5, 118.4, 118.3, 116.2, 114.2, 21.5, 21.4; MS (ES mass): m/z 650.9 (M-1, 100%)
HRMS: calcd, for $C_{30}H_{22}F_6N_2O_4S_2$: 652.0927, found: 652.0918.

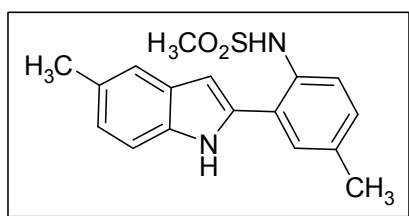
Preparation of indole 3a and 3b

A mixture of compound **2d** or **2e** (0.4008 mmol) and K_2CO_3 (0.083 g, 0.6012 mmol) in MeOH (5 mL) was refluxed for 3 h. After completion, the reaction mixture was filtered and the residue was washed with MeOH (5 mL). The filtrates were collected, combined and concentrated under reduced pressure. The residue was purified by column chromatography using 0-20% EtOAc - hexane to give the desired product.



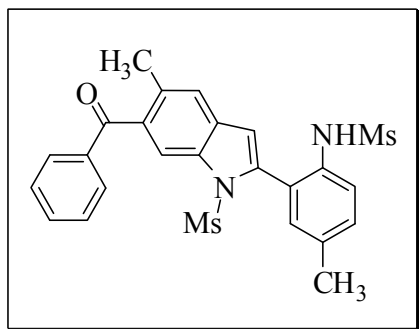
N-(4-trifluoromethyl)-2-(5-(trifluoromethyl)-1*H*-indol-2-yl)phenyl)methanesulfonamide

(3a): Yield: 86% (0.14 g); R_f = 0.50 (25 % EtOAc-*n*-Hexane); mp: 204-206 °C; IR (KBr, cm^{-1}): 2934, 1332, 1158; 1H -NMR (400 MHz, $CDCl_3$) δ /ppm: 8.78 (s, 1H), 7.97 (s, 1H), 7.84 (s, 1H), 7.75 (d, J = 8.2 Hz, 2H), 7.67 (d, J = 8.2 Hz, 2H), 7.51 (s, 1H), 6.82 (s, 1H), 3.11 (s, 3H); ^{13}C NMR (200 MHz, $CDCl_3$) δ /ppm: 139.5, 139.6, 135.2, 128.1, 128.5, 128.4, 126.8, 127.5, 122.9, 122.9, 121.9, 119.2, 119.1, 117.8, 115.5, 114.5, 40.2; MS (ES mass): m/z 420.8 (M-1); HRMS: calcd for $C_{17}H_{13}N_2F_6O_2S$ (M+H): 423.0602, found: 423.0600.



***N*-(4-methyl-2-(5-methyl-1*H*-indol-2-yl)methanesulfonamide (3b):** Yield: 92% (0.15 g); mp: 212-213 °C; $R_f = 0.50$ (30 % EtOAc-*n*-Hexane); IR (KBr, cm^{-1}): 3246, 2956, 1660, 1157; ^1H NMR (400 MHz, CDCl_3) δ : 8.38 (s, 1H), 7.50 (d, $J = 8.4$ Hz, 1H), 7.43 (s, 1H), 7.30 (d, $J = 8.4$ Hz, 2H), 7.19 (d, $J = 8.4$ Hz, 1H), 7.06 (d, $J = 8.4$ Hz, 1H), 6.96 (s, 1H), 6.56 (s, 1H), 2.94 (s, 3H), 2.46 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 135.7, 135.1, 133.7, 131.4, 130.6, 130.1, 130.1, 129.0, 125.8, 124.6, 122.1, 120.4, 110.9, 102.4, 39.8, 21.4, 20.8; MS (ES mass): m/z 312.9 ($\text{M}-1$) $^+$; HRMS: calcd for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_2\text{S}$ is 314.1086 found 314.1074.

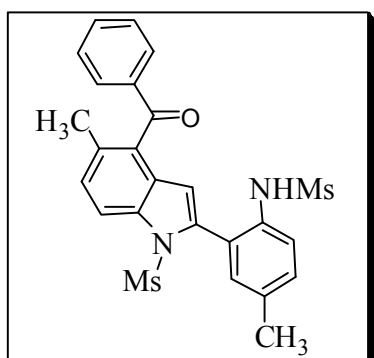
Preparation of *N*-(2-(6-benzoyl-5-methyl-1-(methylsulfonyl)-1*H*-indol-2-yl)-4-methylphenyl) methane sulfonamide (4):



A mixture of TFAA (0.85 g, 4.085 mmol) and benzoic acid (0.052 g, 0.46 mmol) was stirred at 0 °C for 20 min till all the solids are dissolved. To this was added indole **2d** (0.2 g, 0.51 mmol) with stirring followed by 85 % H_3PO_4 (0.008 g, 0.08 mmol). Then the reaction was allowed to stir at 0 °C for 20 min and at 50 °C for 4 h. The progress of the reaction was monitored by TLC. After completion of the reaction the TFA/TFAA mixture was distilled off at atmospheric pressure. The remaining liquid was partitioned between CHCl_3 and water. The organic layer was separated and washed with 5% NaOH and then brine. The mixture was dried over anhydrous Na_2SO_4 , filtered and concentrated. The crude product was purified by column chromatography on silica gel using EtOAc-hexane to give the title compound; Yield: 60% (0.15 g) white solid; $R_f = 0.40$ (30 % EtOAc-*n*-Hexane); mp: 198-200 °C; IR (KBr, cm^{-1}): 3284, 2925, 1662, 1656, 1158; ^1H NMR (400 MHz, CDCl_3) δ : 8.05 (s, 1H), 7.88 (d, $J = 1.4$ Hz, 2H), 7.60 (d, $J = 6.3$ Hz, 2H), 7.52-7.49 (m, 3H), 7.32 (d, $J = 6.8$ Hz, 1H), 7.15 (s, 1H), 6.71 (s, 1H), 6.53 (s, 1H, D_2O

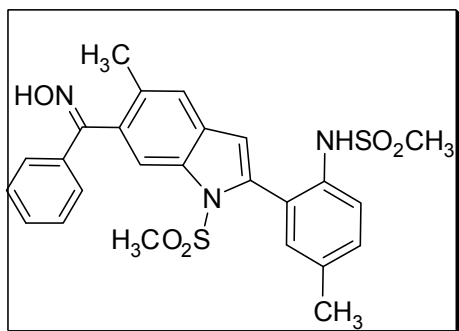
Exchange), 2.96 (s, 3H), 2.86 (s, 3H), 2.43 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 19.4, 20.6, 39.8, 40.6, 112.9, 116.4, 121.2, 123.9, 128.1, 128.4, 128.8, 129.7 (2C), 131.3 (2C), 131.6, 132.0, 133.9, 134.0, 134.1, 134.5, 135.6, 137.0, 137.1, 197.4.; MS (ES mass): m/z 497.1 ($\text{M}+1$) $^+$; HRMS: calcd for $\text{C}_{25}\text{H}_{24}\text{N}_2\text{O}_5\text{S}_2$ is 497.1210 found 497.1205.

A side product was isolated during the purification of compound **4** by using column chromatography that was identified as other regioisomer as shown below



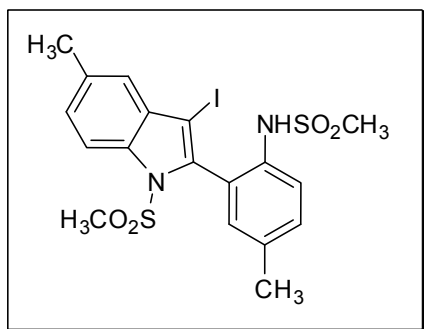
***N*-(2-(4-benzoyl-5-methylsulfonyl)-1*H*-indol-2-yl)-4-methylphenylmethanesulfonamide (4a)** :
Yield: 20% (0.05 g) white solid; R_f = 0.35 (30 % EtOAc-*n*-Hexane); mp: 190-192 °C; IR (KBr, cm^{-1}): 3281, 2928, 1662, 1367, 1163; ^1H NMR (400 MHz, CDCl_3) δ : 8.09 (d, J = 8.4 Hz, 1H), 7.80 (d, J = 7.2 Hz, 2H), 7.53 -7.51 (m, 2H), 7.45 (t, J = 7.9 Hz, 2H), 7.33 (d, J = 8.4 Hz, 1H), 7.24 (s, 1H), 7.07 (s, 1H), 6.5 (s, 1H), 6.37 (s, 1H), 2.86 (s, 3H), 2.84 (s, 3H), 2.33 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 197.5, 137.2, 137.1, 135.6, 134.6, 134.1, 134.0, 113.1, 132.1, 131.7, 131.4, 129.8 (2C), 128.9 (2C), 128.5, 128.2, 124.0, 121.2, 116.5, 113.1, 40.6, 39.9, 20.6, 19.4. MS (ES mass): m/z 496.9 ($\text{M}+1$) $^+$: HRMS: calcd for $\text{C}_{25}\text{H}_{24}\text{N}_2\text{O}_5\text{S}_2$ is 497.1208 found 497.1213.

Preparation of (*E*)-*N*-(2-(4-((hydroxyimino)(phenyl)methyl)-5-methyl-1-(methanesulfonyl)-1*H*-indol-2-yl)-4-methylphenyl)methanesulfonamide (5) :



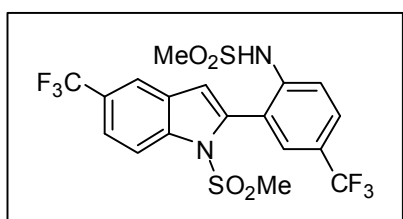
To the stirred solution of pyridine (0.35 g, 4.4 mmol) and hydroxylamine hydrochloride (0.05 g, 0.88 mmol), was added the ketone **4** (0.2 g, 0.44 mmol) and the mixture was stirred at room temperature for 12 h. Upon completion of the reaction, the mixture was diluted with cold water (15 mL) and extracted with ethyl acetate (3 x 10 mL). The organic layers were collected, combined, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography over alumina using 2: 8 ethylacetate hexane to give the desired product; Yield: 85% (0.19 g), white solid; R_f = 0.25 (30 % EtOAc-*n*-Hexane); mp: 122-124 °C; IR (KBr, cm⁻¹): 3425, 3275, 2943, 1710, 1152; ¹H NMR (400 MHz, CDCl₃) δ: 7.88 (bs, 1H D₂O Eexchangeable), 7.87 (s, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.52-7.57 (m, 3H), 7.35-7.38 (m, 3H) 7.29 (d, *J* = 8.4 Hz, 1H), 7.1 (s, 1H), 6.7 (s, 1H), 6.5 (s, 1H, D₂O Exchangeable), 3.00 (s, 3H), 2.96 (s, 3H), 2.38 (s, 3H), 2.31 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ: 136.7, 135.5, 134.4, 134.2, 132.7, 131.7, 131.5, 131.3, 130.2, 130.0, 129.7, 128.6 (2C), 127.0(2C), 123.7, 122.3, 120.5, 120.4, 114.5, 113.7, 40.8, 39.9, 20.7, 19.5; MS (ES mass): *m/z* 511.9 (M+1)⁺; HRMS: calcd for C₂₅H₂₆N₃O₅S₂ (M+H): 512.1314, found:512.1314.

Preparation of *N*-(2-(3-iodo-5-methyl-1-(methanesulfonyl)-1*H*-indol-2-yl)-4-methylphenyl)methanesulfonamide (6**):**



To the solution of indole **2d** (0.2 g, 0.51 mmol) in DMF (5 mL) was added, KOH (0.12 g, 2.04 mmol) and iodine (0.26 g, 1.01 mmol) at room temperature. The mixture was allowed stir for 12 h, at room temperature. After completion of the reaction solvent was removed under vacuum. The residue was treated with ethylacetate (15 mL), washed with 0.1% sodium bisulfate solution (10 mL), water (10 mL) and brine (10 mL). The organic layer was collected, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography over alumina using 1: 9 ethylacetate-hexane to give the desired product; Yield: 85% (0.1 g); R_f = 0.5 (25 % EtOAc-*n*-Hexane); IR (KBr, cm⁻¹) : 3269, 1665, 1225, 1150; ¹H NMR (400 MHz, CDCl₃) δ: 7.93 (d, *J* = 8 Hz, 1H), 7.65 (d, *J* = 8 Hz, 1H), 7.30 -7.35 (m, 3H), 7.1 (s, 1H), 6.32 (s, 1H), 2.94 (s, 3H), 2.93 (s, 3H), 2.53 (s, 3H), 2.4 (s, 3H); ¹³C NMR (100 M Hz, CDCl₃) δ: 134.7, 134.5, 132.6, 130.0, 129.8, 129.5, 128.1, 127.8, 124.7, 122.8, 121.5, 119.5, 108.3, 101.9, 39.5, 39.2, 20.9, 20.4; MS (ES mass): *m/z* 518.5 (M+1)⁺; HRMS: calcd for C₁₈H₁₉IN₂O₄S₂ is 517.9827 found 517.9835.

Single crystal X-ray data for compound **2e**:



Single crystals suitable for X-ray diffraction of **2e** were grown from dichloromethane. Single crystals were carefully chosen using a stereo zoom microscope supported by a rotatable polarizing stage. The data was collected at room temperature on Bruker's KAPPA APEX II CCD

Duo with graphite monochromated Mo $K\alpha$ radiation (0.71073 Å). The crystals were glued to a thin glass fibre using FOMBLIN immersion oil and mounted on the diffractometer. The intensity data were processed using Broker's suite of data processing programs (SAINT), and absorption corrections were applied using SADABS.¹ The structure was solved by direct methods and all the non-hydrogen atoms were refined anisotropically while the hydrogen atoms, except hydrogens on N which were refined by picking electron density peaks, fixed in the predetermined positions by Shelxs-97² and Shelxl-97 packages respectively.

Crystal data of **2e**: Molecular formula = C₁₈H₁₄F₆N₂O₄S₂, Formula weight = 500.45, Crystal system = Monoclinic, Space group = *Pn*, *a* = 9.922 (5) Å, *b* = 14.243 (7) Å, *c* = 14.847 (7) Å, *V* = 2092.7 (18) Å³, *T* = 296 K, *Z* = 4, *D_c* = 1.550 Mg m⁻³, μ(Mo-Kα) = 0.71073 mm⁻¹, 10680 reflections measured, 5285 independent reflections, 3766 observed reflections [*I* > 2.0 σ(*I*)], *R*_{1_}obs = 0.072, Goodness of fit = 1.357. Crystallographic data (excluding structure factors) for **2e** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 818602.

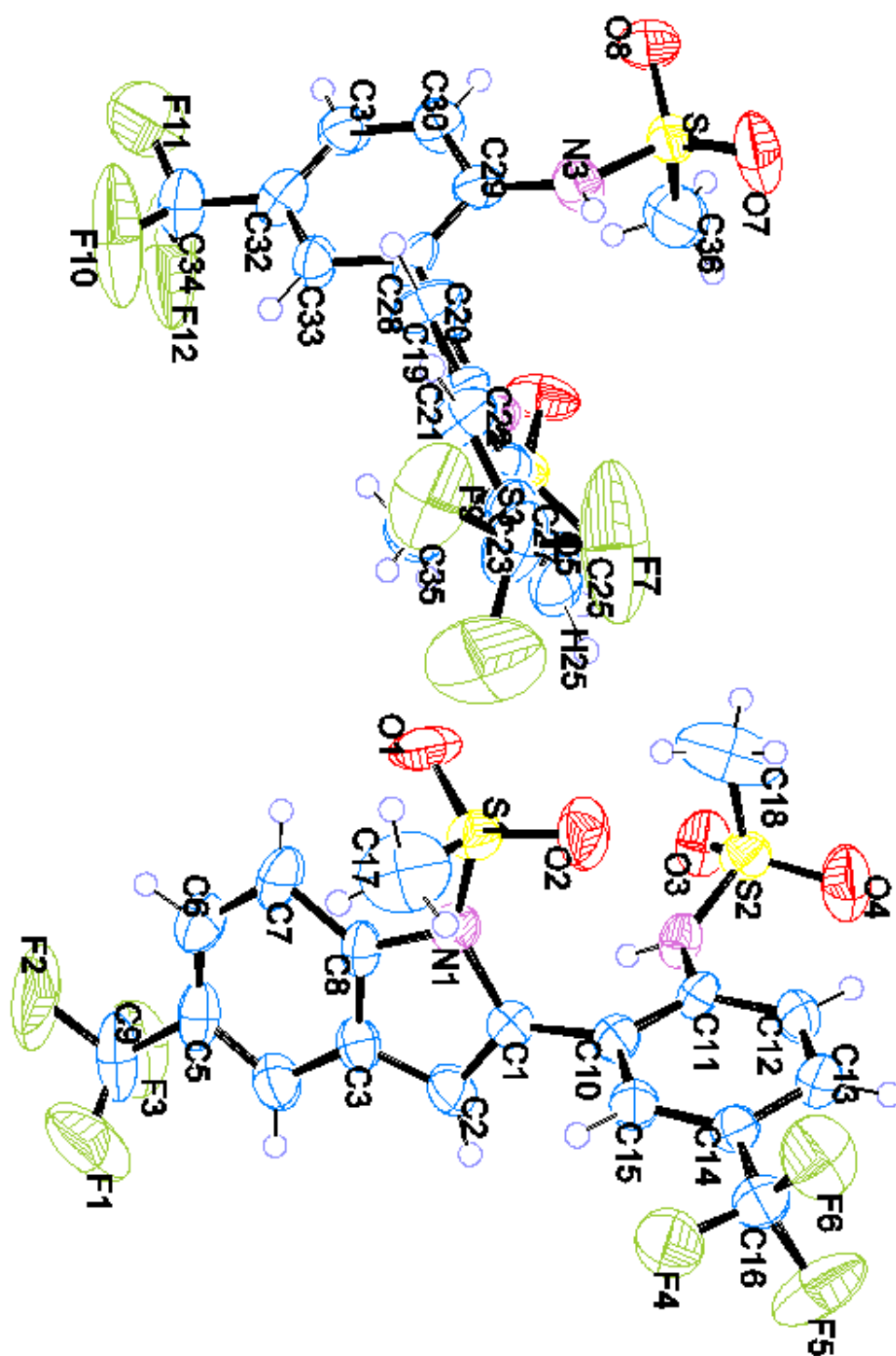
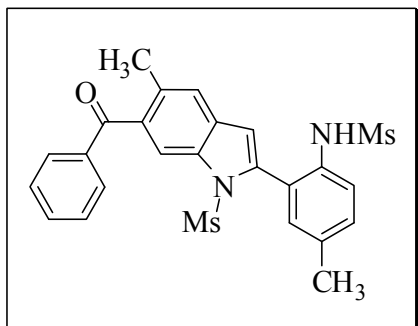


Figure 1. ORTEP representation of the compound 2e (Thermal ellipsoids are drawn at 50% probability level).

Single crystal X-ray data for compound 4



Single crystals suitable for X-ray diffraction of compound **4** were grown from dichloromethane. Single crystals were carefully chosen using a stereo zoom microscope supported by a rotatable polarizing stage. The data was collected at room temperature on Oxford XCalibur, Gemini diffractometer equipped with EOS CCD detector at 298 K. Monochromatic Mo K α radiation (0.71073 Å) was used for the measurements. Absorption corrections using multi ψ -scans were applied. Structure was solved using SHELXS-97, and refined by full-matrix least squares against F^2 using SHELXL-97 software.¹ All non-hydrogen atoms were refined anisotropically. Hydrogen atoms on the C atoms of compound **4** were introduced on calculated positions and were included in the refinement riding on their respective parent atoms. Hydrogen atom on the N was identified by the Fourier electron density and refined freely.

Crystal data of **4**: Molecular formula = C₂₅H₂₄N₂O₅S₂, Formula weight = 496.58, Triclinic, Space group = *P*-1, $a = 8.271$ (4) Å, $b = 12.010$ (6) Å, $c = 13.310$ (6) Å, $V = 1237.00$ (10) Å³, $T = 298$ K, $Z = 2$, $D_c = 1.333$ Mg m⁻³, $\mu(\text{Mo-K}\alpha) = 0.71073$ mm⁻¹, 8168 reflections were measured with 4219 unique reflections ($R_{\text{int}} = 0.0199$), of which 4219 ($I > 2\sigma(I)$) were used for the structure solution. Final R_1 ($w R_2$) = 0.0429 (0.1053), 311 parameters. The final Fourier difference synthesis showed minimum and maximum peaks of -0.273 and +0.246 e.Å⁻³ respectively. Goodness of fit = 1.061. Crystallographic data (excluding structure factors) for **4** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 818615.

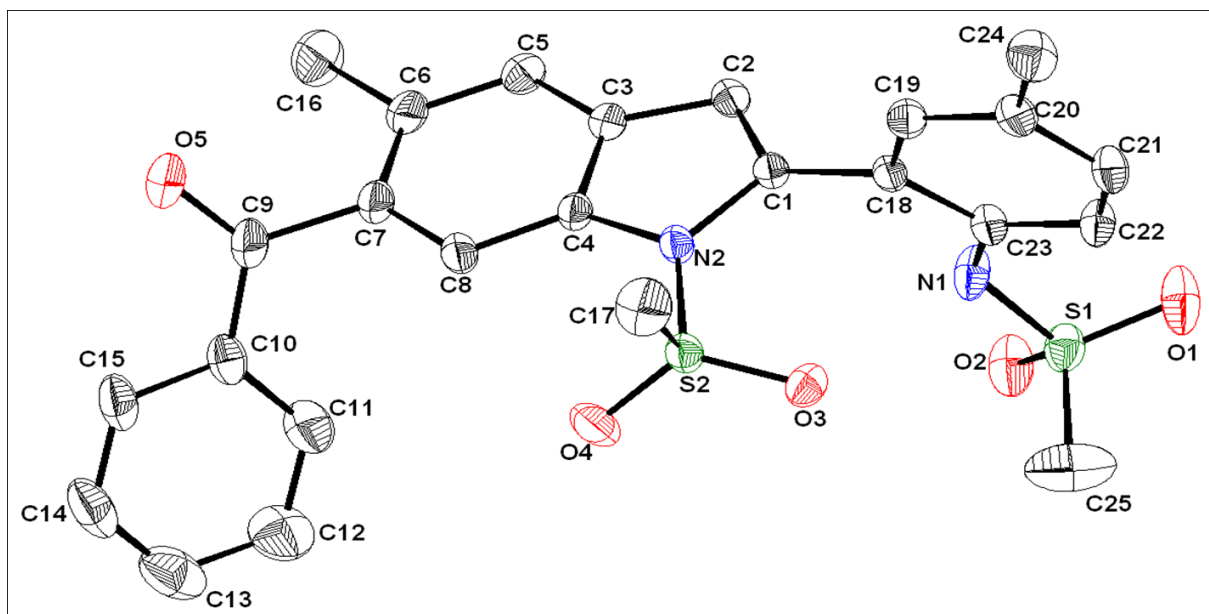


Figure 2. ORTEP representation of the compound **4** (Thermal ellipsoids are drawn at 50% probability level).

References:

1. Bruker SADABS V2008-1, Bruker AXS.: Madison, WI, USA (2008).
2. G. M. Sheldrick, SHELX93, Program for Crystal Structure Determination, University of Göttingen (1997).

Docking studies

The docking study was carried out using XP Glide application of Schrödinger software with MASTERO interface 9.1. The indole derivative **2b** was docked in CHORISMATE MUTASE protein of *Mycobacterium tuberculosis*.

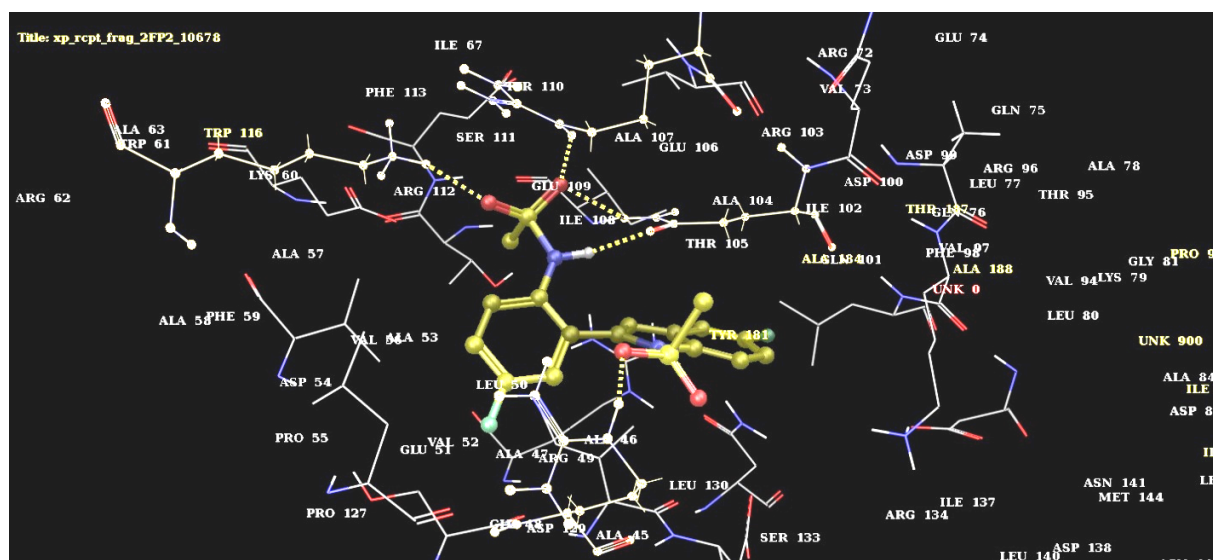
Docking procedure: In the present molecular docking studies we have performed the energy minimization and conformational search with the MACROMODEL application using the Schrodinger package. The compound **2b** is energy minimized for flexibility of the molecule and then it is followed by the conformational search. We used OPLS_2005 force field and water as implicit solvent. We have followed the PRCG (Polak-Ribier conjugate gradient) method of minimization with 500 iterations with a threshold gradient on 0.05kJ/mol. The conformational

search was based on Montecarlo multiple minimum torsional sampling. The ligands were then finally prepared with LIGPREP application.

The protein chorismate mutase (PDB ID –2FP2) crystal structure was retrieved from the protein data bank and it is refined with the PROTEIN PREPERATION WIZARD application in which the hydrogens were added and missing side chains and loops were filled with PRIME application. Water molecules were observed within the distance of 5Å and those beyond 5Å from het(hetroatom) groups were deleted. Finally the protein was then optimized and minimized with impref using OPLS_2005 force filed. GRID based docking were done in the present study. The following Glide score was obtained for the compound **2b** after docking with chorismate mutase.

GLIDE SCORE = -6.23 K.cal/mol

Fig. 1. Interaction of compound **2b** with chorismate mutase protein.



Hydrogen bonding interaction of **2b** was observed with the LYS60, ARG134, GLN76, ARG72 residues of the chorismate mutase protein.

The S=O group of **2b** is interacted with the –NH group of the LYS60, ARG134, GLN76 and ARG72 residues of chorismate mutase. The –NH group of **2b** also interacted with the –C=O group of the GLN76 residue of chorismate mutase protein.

Pharmacological studies

Chorismate Mutase activity assay: *Mycobacterium tuberculosis* chorismate mutase (MtCM) gene was PCR amplified and cloned into expression vector pET22b. MtCM was purified from over expressed culture of BL21 (DE3) harboring pET22b/ MtCM by Ni-NTA affinity chromatography.

Activity of chorismate mutase enzyme is based on the direct observation of conversion of chorismate to prephenate Spectrophotometrically at OD₂₇₄. The reaction volume of 100 µl contained 50 mM Tris-HCl (pH 7.5), 0.5 mM EDTA, 0.1 mg/ml bovine serum albumin, and 10 mM β-Mercaptoethanol, and chorismic acid 4 mM. The reaction was started by adding 180 pmol of purified protein to the pre-warmed chorismic acid solution. Inhibitory screening of the test compounds against chorismate mutase activity was measured at 50µM concentration of the effectors. The reaction was allowed to proceed at 37 °C and was terminated after 5 min with 100 µl of 1 N HCl. A blank with no enzyme for every reaction was kept as a control to account for the non enzymatic conversion of chorismate to prephenate.

The percentage of enzyme inhibition caused by the test compound is calculated by the following formula

% inhibition = 100 – residual activity of CM

$$\left[\text{Residual activity of CM} = \frac{(S + E + C) - (S + C)}{(S + E) - (S)} \times 100 \right]$$

S = Substrate absorbance at 274 nm

E = Enzyme absorbance at 274 nm

C = Compound absorbance at 274 nm

Dose Response Study for compound 2b: Dose Response study of the compound **2b** against Chorismate Mutase activity was carried out using the concentration from 1µM to 100 µM and the IC₅₀ value was found to be 17.02 µM.

References

- 1 S.-K. Kim, S. K. Reddy, B. C. Nelson, G. B. Vasquez, A. Davis, A. J. Howard, S. Patterson, G. L. Gilliland, J. E. Ladner, P T. Reddy. Biochemical and Structural Characterization of the Secreted Chorismate Mutase (Rv1885c) from *Mycobacterium tuberculosis* H37Rv: an *AroQ Enzyme Not Regulated by the Aromatic Amino Acids. *Journal of Bacteriology* 188 (2006) 8638–8648
- 2 S. Sasso, C. Ramakrishnan, M. Gamper, D. Hilvert and P. Kast, Characterization of the secreted chorismate mutase from the pathogen *Mycobacterium tuberculosis*. *FEBS Journal* 272 (2005) 375–389.
- 3 H Agrawal, A Kumar, N. C. Bal, M. I. Siddiqi and A. Arora, Ligand based virtual screening and biological evaluation of inhibitors of chorismate mutase (Rv1885c) from *Mycobacterium tuberculosis* H37Rv. *Bioorg. Med. Chem. Lett.* 17 (2007) 3053–3058.