Supplementary information

Discovery of N-[4-(1H-Pyrazolo[3,4-b]pyrazin-6-yl)-phenyl]-Sulfonamides as Highly Active and Selective SGK1 Inhibitors

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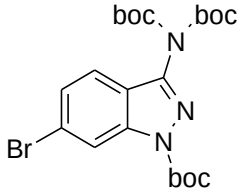
Chemistry:
All chemicals, reagents, and solvents were used without further purification as purchased from commercial sources. All ^{1}H-NMR spectra were recorded at room temperature on a 500 MHz Bruker spectrometer. Chemical shifts are reported in δ values in ppm with tetramethylsilane as the internal standard. Mass spectra were recorded by ESI-MS. Purity of all compounds tested in biological assays were determined to be >95% as determined by LC-MS.

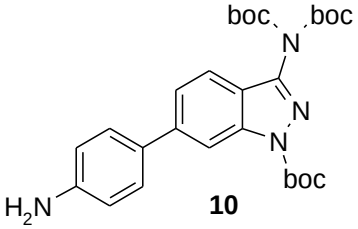
Tert-butyl 3-[bis(tert-butoxycarbonyl)amino]-6-bromo-indazole-1-carboxylate **9**



9

Commercially available 6-bromo-1H-indazol-3-amine (25.0g, 1.0 equiv) was dissolved in 400 ml acetonitrile and di-tert-butyl dicarbonate (128.0g, 5.0 equiv.) was added together with DMAP (0.72g, 0.05 equiv.) and the mixture was heated to reflux for 3 hours. The reaction mixture was cooled and evaporated to dryness, redissolved in EtOAc and washed with NH_4Cl (aq. sat.) and brine before being dried over Na_2SO_4. This afforded the tert-butyl 3-[bis(tert-butoxycarbonyl)amino]-6-bromo-indazole-1-carboxylate **9** as a brown oil in high purity and quantitative yield after evaporation. The product solidified upon cooling to ambient temperature and was used without further purification in the next step.

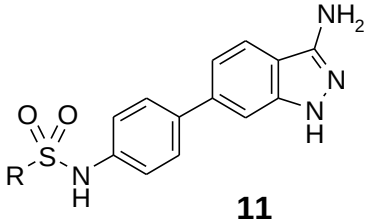
Tert-butyl 6-(4-aminophenyl)-3-[bis(tert-butoxycarbonyl)amino]indazole-1-carboxylate **10**



10

Tert-butyl 3-[bis(tert-butoxycarbonyl)amino]-6-bromo-indazole-1-carboxylate **9** (60.0g, 1.0 equiv.), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline(25.7g, 1.0 equiv.), Cesium carbonate (114.5g, 3.0 equiv) and (1,1'-bis(diphenylphosphino)ferrocene)palladium(II) chloride (6.85g, 0.08 equiv.) were added to the reaction vessel and purged with argon for 5 minutes. Then 100 ml water and 1.0 l dioxane were added and the mixture was heated to 100°C for 2 hours. The reaction mixture was cooled and quenched with $NaHCO_3$ (aq. sat.) and the phases separated. The organic phase was dried over Na_2SO_4, filtered through a celite plug and a silica plug to remove spent catalyst and then evaporated to afford the crude product as a black oil. The crude product was redissolved in EtOAc and the product precipitated by slow addition to heptane under stirring. This afforded 43.1 g (70%) tert-butyl 6-(4-aminophenyl)-3-[bis(tert-butoxycarbonyl)amino]indazole-1-carboxylate **10** as yellow solid after filtration and drying under vacuum.
^{1}H-NMR (DMSO-d_6) δ 1.41 (s, 18H), 1.67 (s, 9H), 5.40 (s, 2H), 6.69 (d, 2H, *J* = 8.6 Hz), 7.46 (d, 2H, *J* = 8.6 Hz), 7.60 (d, 1H, *J* = 8.3 Hz), 7.64 (dd, 1H, *J* = 1.4, 8.3 Hz), 8.20 (s, 1H); MS (ES+) Calcd.: [M+H] 525.3, Found: 525.2.

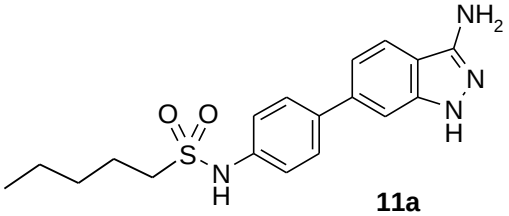
Library synthesis of 3-aminoindazoles **11** (350 compounds)



11

The sulfonyl chloride (0.165 mmol) was dissolved in 3.0 ml dry CH_2Cl_2 and tert-butyl 6-(4-aminophenyl)-3-[bis(tert-butoxycarbonyl)amino]indazole-1-carboxylate **10** (0.15 mmol) was added together with pyridine (0.5 mmol) as stock solution in dry CH_2Cl_2 and the reaction mixture was stirred overnight at ambient temperature. Then 1.5 ml TFA was added and the reaction mixture stirred for another 3h. Toluene (5 ml) was added and the reaction mixture evaporated to dryness, redissolved in DMF (2.0 ml), filtered and purified by HPLC using a water/MeCN gradient with 0.1% TFA. The product was obtained as its trifluoroacetate after freezedrying.

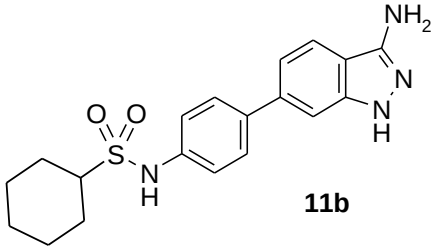
N-[4-(3-amino-1H-indazol-6-yl)phenyl]pentane-1-sulfonamide trifluoroacetate **11a**



11a

^{1}H-NMR (DMSO-d_6) δ 0.82 (t, 3H, *J* = 7.2 Hz), 1.26 (sextet, 2H, *J* = 7.2 Hz), 1.32 (quintet, 2H, *J* = 7.3 Hz), 1.68 (quintet, 2H, *J* = 7.3 Hz), 3.11 (dd, 2H, *J* = 7.2, 7.8 Hz), 7.31 (d, 2H, *J* = 8.6 Hz), 7.30-7.33 (m, 1H), 7.48 (s, 1H), 7.69 (d, 2H, *J* = 8.6 Hz), 7.84 (d, 1H, *J* = 8.5 Hz), 9.92 (s, 1H); MS (ES+) Calcd.: [M+H] 359.15, Found: 359.16.

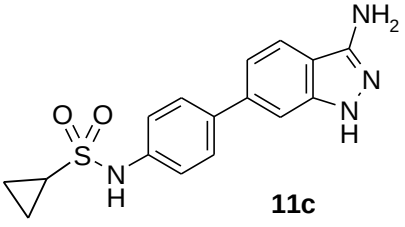
N-[4-(3-amino-1H-indazol-6-yl)phenyl]cyclohexanesulfonamide trifluoroacetate **11b**



11b

^{1}H-NMR (DMSO-d_6) δ 1.06-1.27 (m, 3H), 1.44 (dq, 2H, *J* = 2.9, 12.5 Hz), 1.59 (d, 1H, *J* = 12.4 Hz), 1.77 (d, 2H, *J* = 12.9 Hz), 2.05 (d, 2H, *J* = 11.9 Hz), 3.03 (tt, 1H, *J* = 3.2, 11.9 Hz), 7.33 (d, 2H, *J* = 8.6 Hz), 7.38 (d, 1H, *J* = 8.5 Hz), 7.52 (s, 1H), 7.69 (d, 2H, *J* = 8.6 Hz), 7.90 (d, 1H, *J* = 8.5 Hz), 9.92 (s, 1H); MS (ES+) Calcd.: [M+H] 371.15, Found: 371.20.

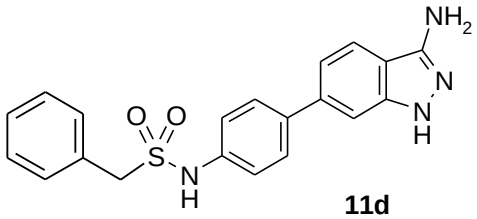
N-[4-(3-amino-1H-indazol-6-yl)phenyl]cyclopropanesulfonamide trifluoroacetate **11c**



11c

^{1}H-NMR (DMSO-d_6) δ 0.94-0.99 (m, 4H), 2.64-2.70 (m, 1H), 7.32-7.36 (m, 1H), 7.35 (d, 2H, *J* = 8.6 Hz), 7.51 (s, 1H), 7.70 (d, 2H, *J* = 8.6 Hz), 7.87 (d, 1H, *J* = 8.5 Hz), 9.88 (s, 1H); MS (ES+) Calcd.: [M+H] 329.11, Found: 329.10.

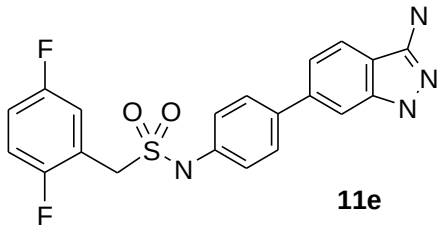
N-[4-(3-amino-1H-indazol-6-yl)phenyl]-1-phenyl-methanesulfonamide trifluoroacetate **11d**



11d

^{1}H-NMR (DMSO-d_6) δ 4.52 (s, 2H), 7.27-7.33 (m, 4H), 7.36 (d, 2H, *J* = 1.8 Hz), 7.37-7.39 (m, 2H), 7.53 (s, 1H), 7.71 (d, 2H, *J* = 8.7 Hz), 7.89 (d, 1H, *J* = 8.3 Hz), 10.01 (s, 1H); MS (ES+) Calcd.: [M+H] 379.12, Found: 379.09.

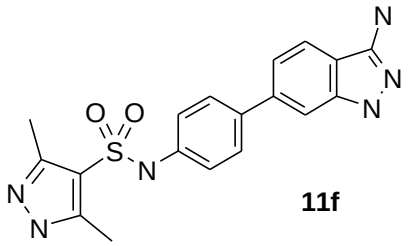
N-[4-(3-amino-1H-indazol-6-yl)phenyl]-1-(2,5-difluorophenyl)methanesulfonamide trifluoroacetate **11e**



11e

^{1}H-NMR (DMSO-d_6) δ 4.58 (s, 2H), 7.20-7.24 (m, 1H), 7.25-7.29 (m, 2H), 7.29 (d, 2H, *J* = 8.5 Hz), 7.33 (d, 1H, *J* = 8.8 Hz), 7.49 (s, 1H), 7.69 (d, 2H, *J* = 8.8 Hz), 7.85 (d, 1H, *J* = 8.4 Hz), 10.18 (s,1H); MS (ES+) Calcd.: [M+H] 415.10, Found: 415.21.

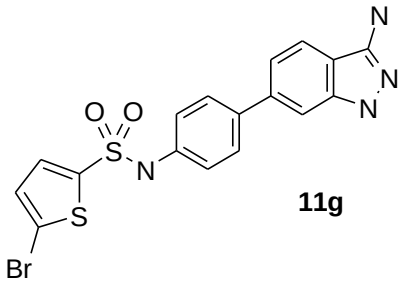
N-[4-(3-amino-1H-indazol-6-yl)phenyl]-3,5-dimethyl-1H-pyrazole-4-sulfonamide trifluoroacetate **11f**



11f

^{1}H-NMR (DMSO-d_6) δ 2.27 (s, 6H), 7.16 (d, 2H, *J* = 8.6 Hz), 7.30 (d, 1H, *J* = 8.5 Hz), 7.46 (s, 1H), 8.62 (d, 2H, *J* = 8.7 Hz), 7.84 (d, 1H, *J* = 8.4 Hz), 10.19 (s, 1H); MS (ES+) Calcd.: [M+H] 383.13, Found: 383.14.

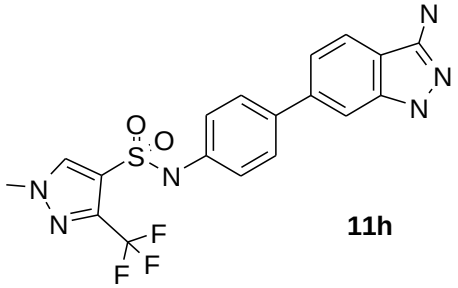
N-[4-(3-amino-1H-indazol-6-yl)phenyl]-5-bromo-thiophene-2-sulfonamide trifluoroacetate **11g**



11g

^{1}H-NMR (DMSO-d_6) δ 7.26 (d, 2H, *J* = 8.7 Hz), 7.30-7.33 (m, 1H), 7.32 (d, 1H, *J* = 4.1 Hz), 7.44 (d, 1H, *J* = 4.0 Hz), 7.49 (s, 1H), 7.68 (d, 2H, *J* = 8.7 Hz), 7.85 (d, 1H, *J* = 8.4 Hz), 10.74 (s, 1H); MS (ES+) Calcd.: [M+H] 448.97, Found: 449.07.

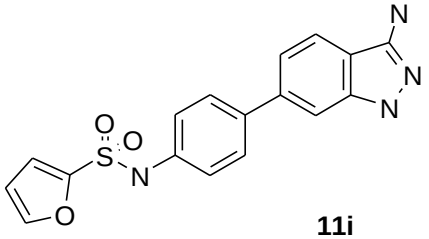
N-[4-(3-amino-1H-indazol-6-yl)phenyl]-1-methyl-3-(trifluoromethyl)pyrazole-4-sulfonamide trifluoroacetate **11h**



11h

^{1}H-NMR (DMSO-d_6) δ 3.92 (s, 3H), 7.22 (d, 2H, *J* = 8.6 Hz), 7.30 (d, 1H, *J* = 8.3 Hz), 7.46 (s, 1H), 7.64 (d, 2H, *J* = 8.6 Hz), 7.84 (d, 1H, *J* = 8.5 Hz), 8.60 (s, 1H), 10.67; MS (ES+) Calcd.: [M+H] 437.10, Found: 437.14.

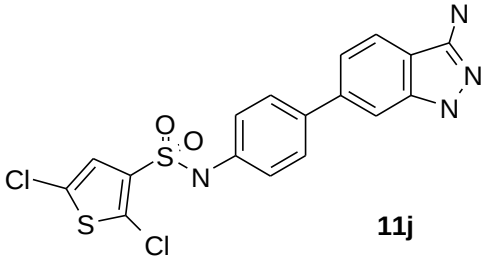
N-[4-(3-amino-1H-indazol-6-yl)phenyl]furan-2-sulfonamide trifluoroacetate **11i**



11i

^{1}H-NMR (DMSO-d_6) δ 6.65 (dd, 1H, *J* = 1.7, 3.5 Hz), 7.21 (d, 1H, *J* = 3.6 Hz), 7.24 (d, 2H, *J* = 8.5 Hz), 7.28 (d, 1H, *J* = 8.3 Hz), 7.45 (s, 1H), 7.64 (d, 2H, *J* = 8.5 Hz), 7.83 (d, 1H, *J* = 8.3 Hz), 7.98 (s, 1H), 10.81 (s, 1H);); MS (ES+) Calcd.: [M+H] 355.09, Found: 355.11.

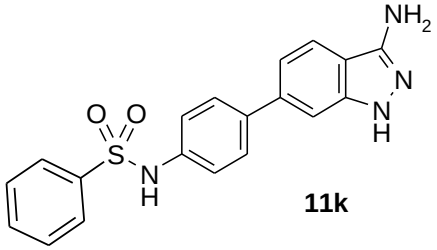
N-[4-(3-amino-1H-indazol-6-yl)phenyl]-2,5-dichloro-thiophene-3-sulfonamide trifluoroacetate **11j**



11j

^{1}H-NMR (DMSO-d_6) δ 7.25 (d, 2H, *J* = 8.6 Hz), 7.32 (d, 1H, *J* = 8.7 Hz), 7.38 (s, 1H), 7.49 (s, 1H), 7.68 (d, 2H, *J* = 8.6 Hz), 7.85 (d, 1H, *J* = 8.6 Hz), 10.87 (s, 1H); MS (ES+) Calcd.: [M+H] 438.99, Found: 439.08.

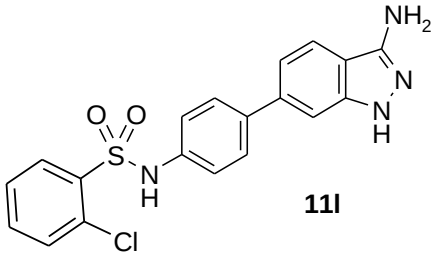
N-[4-(3-amino-1H-indazol-6-yl)phenyl]benzenesulfonamide trifluoroacetate **11k**



11k

^{1}H-NMR (DMSO-d_6) δ 7.20 (d, 2H, *J* = 8.6 Hz), 7.27 (d, 1H, *J* = 8.6 Hz), 7.44 (s, 1H), 7.55-7.64 (m, 5H), 7.80-7.84 (m, 3H), 10.46 (s, 1H); MS (ES+) Calcd.: [M+H] 365.11, Found: 365.12.

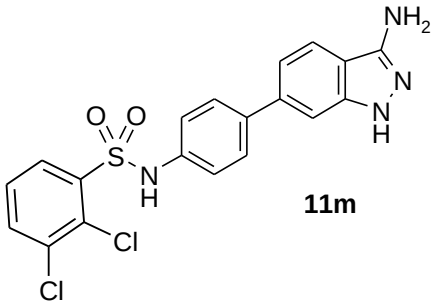
N-[4-(3-amino-1H-indazol-6-yl)phenyl]-2-chloro-benzenesulfonamide trifluoroacetate **11l**



11l

^{1}H-NMR (DMSO-d_6) δ 7.21 (dd, 2H, *J* = 2.1, 8.6 Hz), 7.26 (d, 1H, *J* = 8.6 Hz), 7.43 (s, 1H), 7.54 (ddd, 1H, *J* = 2.5, 6.3, 8.3 Hz), 7.60 (d, 2H, *J* = 8.6 Hz), 7.61-7.66 (m, 1H), 7.65 (d, 1H, *J* = 1.9 Hz), 7.82 (d, 1H, *J* = 8.6 Hz), 8.10 (d, 1H, *J* = 7.8 Hz), 10.78; MS (ES+) Calcd.: [M+H] 399.07, Found: 399.10.

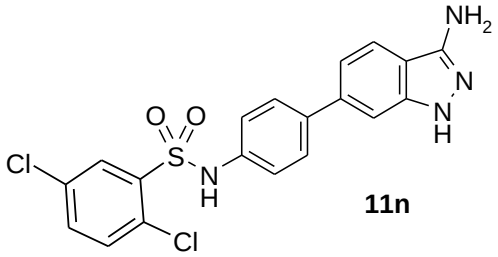
N-[4-(3-amino-1H-indazol-6-yl)phenyl]-2,3-dichloro-benzenesulfonamide trifluoroacetate **11m**



11m

^{1}H-NMR (DMSO-d_6) δ 7.21 (d, 2H, *J* = 8.7 Hz), 7.27 (d, 1H, *J* = 8.6 Hz), 7.44 (s, 1H), 7.58 (t, 1H, *J* = 8.1 Hz), 7.62 (d, 2H, *J* = 8.7 Hz), 7.83 27 (d, 1H, *J* = 8.5Hz), 7.94 (dd, 1H, *J* = 1.5, 8.1 Hz), 8.09 (dd, 1H, *J* = 1.5, 8.0 Hz), 10.96 (s, 1H); MS (ES+) Calcd.: [M+H] 433.03, Found: 433.02.

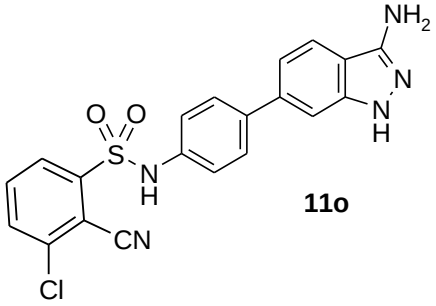
N-[4-(3-amino-1H-indazol-6-yl)phenyl]-2,5-dichloro-benzenesulfonamide trifluoroacetate **11n**



11n

^{1}H-NMR (DMSO-d_6) δ 7.22 (d, 2H, *J* = 8.7 Hz), 7.29 (d, 1H, *J* = 8.5 Hz), 7.46 (s, 1H), 7.64 (d, 2H, *J* = 8.7 Hz), 7.71 (d, 1H, *J* = 8.6 Hz), 7.75 (dd, 1H, *J* = 2.5, 8.5 Hz), 7.84 (d, 1H, *J* = 8.4 Hz), 8.04 (d, 1H, *J* = 2.5 Hz), 10.95 (s, 1H); MS (ES+) Calcd.: [M+H] 433.03, Found: 433.03.

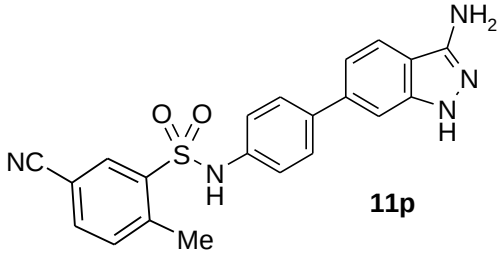
N-[4-(3-amino-1H-indazol-6-yl)phenyl]-3-chloro-2-cyano-benzenesulfonamide trifluoroacetate **11o**



11o

^{1}H-NMR (DMSO-d_6) δ 7.21 (d, 2H, *J* = 8.6 Hz), 7.28 (d, 1H, *J* = 8.5 Hz), 7.46 (s, 1H), 7.65 (d, 2H, *J* = 8.6 Hz), 7.83 (d, 1H, *J* = 8.5 Hz), 7.93 (t, 1H, *J* = 8.1 Hz), 8.05 (dd, 1H, *J* = 1.1 5.7 Hz), 8.07 (dd, 1H, *J* = 1.1 5.7 Hz), 11.14 (s, 1H); MS (ES+) Calcd.: [M+H] 424.06, Found: 424.17.

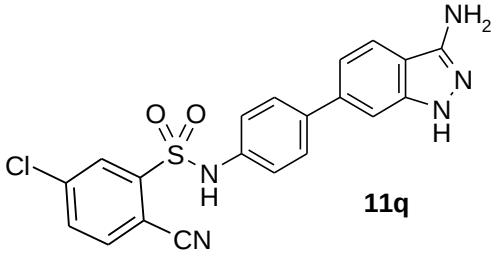
N-[4-(3-amino-1H-indazol-6-yl)phenyl]-5-cyano-2-methyl-benzenesulfonamide trifluoroacetate **11p**



11p

^{1}H-NMR (DMSO-d_6) δ 2.69 (s, 3H), 7.19 (d, 2H, *J* = 8.6 Hz), 7.28 (d, 1H, *J* = 8.4 Hz), 7.45 (s, 1H); 7.62 (d, 2H, *J* = 8.6 Hz), 7.64 (d, 1H, *J* = 7.8 Hz), 7.83 (d, 1H, *J* = 8.5 Hz), 8.01 (dd, 1H, *J* = 1.7, 7.8 Hz), 8.28 (d, 1H, *J* = 1.7 Hz), 10.83 (s, 1H); MS (ES+) Calcd.: [M+H] 404.12, Found: 404.18.

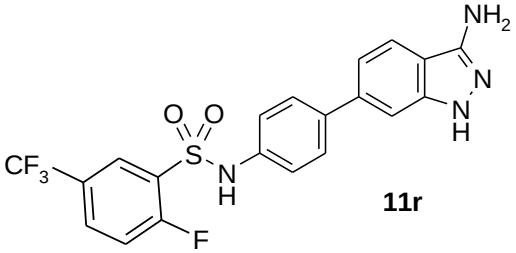
N-[4-(3-amino-1H-indazol-6-yl)phenyl]-5-chloro-2-cyano-benzenesulfonamide trifluoroacetate **11q**



11q

^{1}H-NMR (DMSO-d_6) δ 7.22 (d, 2H, *J* = 8.7 Hz), 7.30 (d, 1H, *J* = 8.4 Hz), 7.47 (s, 1H), 7.67 (d, 2H, *J* = 8.7 Hz), 7.85 (d, 1H, *J* = 8.4 Hz), 7.97 (dd, 1H, *J* = 2.1, 8.3 Hz), 8.07 (d, 1H, *J* = 2.1 Hz), 8.14 (d, 1H, *J* = 8.3 Hz), 11.06 (br s, 1H); MS (ES+) Calcd.: [M+H] 424.06, Found: 424.02.

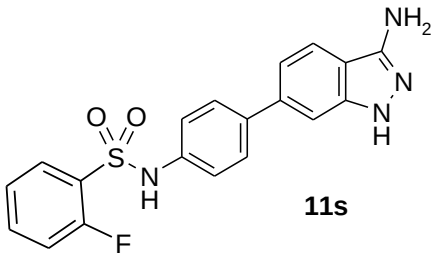
N-[4-(3-amino-1H-indazol-6-yl)phenyl]-2-fluoro-5-(trifluoromethyl)benzenesulfonamide trifluoroacetate **11r**



11r

^{1}H-NMR (DMSO-d_6) δ 7.23 (d, 2H, *J* = 8.7 Hz), 7.29 (d, 1H, *J* = 8.3 Hz), 7.46 (s, 1H), 7.65 (d, 2H, *J* = 8.7 Hz), 7.74 (t, 1H, *J* = 9.2 Hz), 7.85 (d, 1H, *J* = 8.4 Hz), 8.11 (dd, 1H, *J* = 2.2, 6.2 Hz), 8.13-8.18 (m, 1H), 11.02 (s, 1H); MS (ES+) Calcd.: [M+H] 451.09, Found: 450.93.

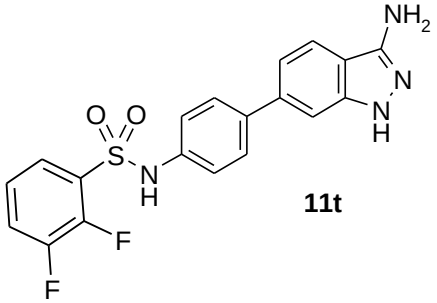
N-[4-(3-amino-1H-indazol-6-yl)phenyl]-2-fluoro-benzenesulfonamide trifluoroacetate **11s**



11s

^{1}H-NMR (DMSO-d_6) δ 7.21 (dd, 2H, *J* = 2.1, 8.8 Hz), 7.22 (m, 1H), 7.38 (t, 1H, *J* = 7.6 Hz), 7.41 (s, 1H), 7.44 (d, 1H, *J* = 9.2 Hz), 7.67-7.72 (m, 1H), 7.79 (d, 1H, *J* = 8.4 Hz), 7.88 (t, 1H, *J* = 7.6 Hz), 10.77 (s, 1H); MS (ES+) Calcd.: [M+H] 383.10, Found: 383.10.

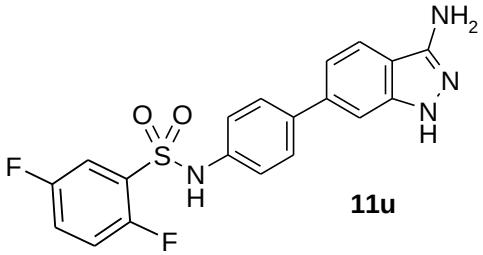
N-[4-(3-amino-1H-indazol-6-yl)phenyl]-2,3-difluoro-benzenesulfonamide trifluoroacetate **11t**



11t

^{1}H-NMR (DMSO-d_6) δ 7.22 (d, 2H, *J* = 8.6 Hz), 7.26 (d, 1H, *J* = 8.2 Hz), 7.38-7.43 (m, 1H), 7.43 (s, 1H), 7.63 (d, 2H, *J* = 8.6 Hz), 7.69 (t, 1H, *J* = 7.2 Hz), 7.73-7.78 (m, 1H), 7.81 (d, 1H, *J* = 8.4 Hz), 10.95 (s, 1H); MS (ES+) Calcd.: [M+H] 401.09, Found: 401.20.

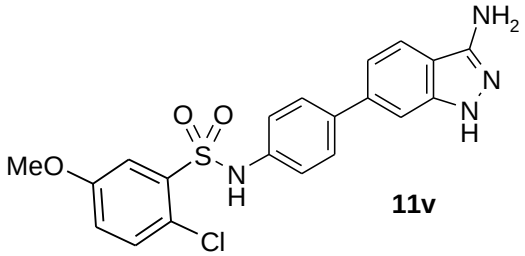
N-[4-(3-amino-1H-indazol-6-yl)phenyl]-2,5-difluoro-benzenesulfonamide trifluoroacetate **11u**



11u

^{1}H-NMR (DMSO-d_6) δ 7.23 (d, 2H, *J* = 8.6 Hz), 7.26 (d, 1H, *J* = 8.3 Hz), 7.46 (s, 1H), 7.53 (dt, 1H, *J* = 4.0, 9.3 Hz), 7.57-7.61 (m, 1H), 7.64 (d, 2H, *J* = 8.6 Hz), 7.66-7.71 (m, 1H), 7.83 (d, 1H, *J* = 8.5 Hz), 10.92 (s, 1H); MS (ES+) Calcd.: [M+H] 401.09, Found: 401.14.

N-[4-(3-amino-1H-indazol-6-yl)phenyl]-2-chloro-5-methoxy-benzenesulfonamide trifluoroacetate **11v**



11v

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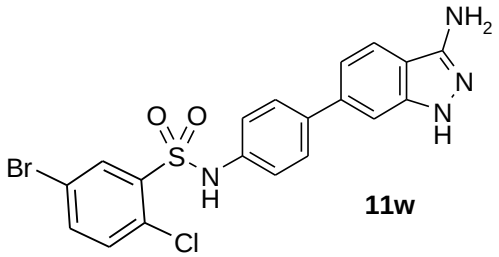
^{1}H-NMR (DMSO-d_6) δ 3.81 (s, 3H), 7.19-7.24 (m, 3H), 7.27 (d, 1H, *J* = 8.4 Hz), 7.44 (s, 1H), 7.54 (s, 1H), 7.56 (d, 1H, *J* = 4.9 Hz), 7.61 (d, 2H, *J* = 8.5 Hz), 7.82 (d, 1H, *J* = 8.4 Hz), 10.78 (s, 1H); MS (ES+) Calcd.: [M+H] 429.08, Found: 429.10.

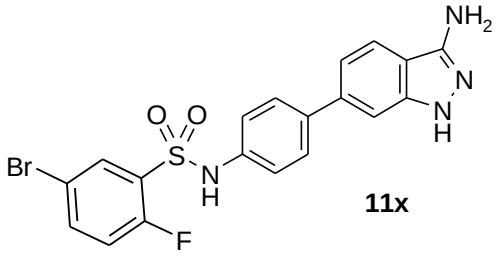
N-[4-(3-amino-1H-indazol-6-yl)phenyl]-5-bromo-2-chloro-benzenesulfonamide trifluoroacetate **11w**



11w

^{1}H-NMR (DMSO-d_6) δ 7.20-7.25 (m, 1H), 7.21 (d, 2H, *J* = 8.6 Hz), 7.41 (s, 1H), 7.61-7.64 (m, 1H), 7.63 (d, 2H, *J* = 8.5 Hz), 7.79 (d, 1H, *J* = 9.0 Hz), 7.86 (dd, 1H, *J* = 2.5, 8.6 Hz), 8.14 (d, 1H, *J* = 2.5 Hz), 10.91(s, 1H); MS (ES+) Calcd.: [M+H] 476.98, Found: 477.04.

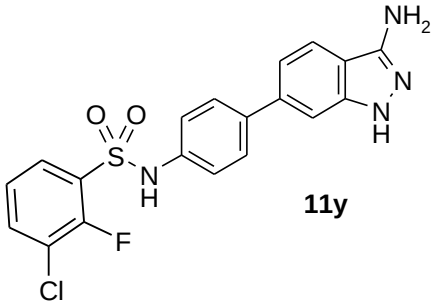
N-[4-(3-amino-1H-indazol-6-yl)phenyl]-5-bromo-2-fluoro-benzenesulfonamide trifluoroacetate **11x**



11x

^{1}H-NMR (DMSO-d_6) δ 7.23 (d, 2H, *J* = 8.6 Hz), 7.30 (d, 1H, *J* = 8.6 Hz), 7.46 (t, 1H, *J* = 9.3 Hz), 7,47 (s, 1H), 7.66 (d, 2H, *J* = 8.6 Hz), 7.85 (d, 1H, *J* = 8.5 Hz), 7.89-7.96 (m, 2H), 10.94 (s, 1H); MS (ES+) Calcd.: [M+H] 461.01, Found: 460.92.

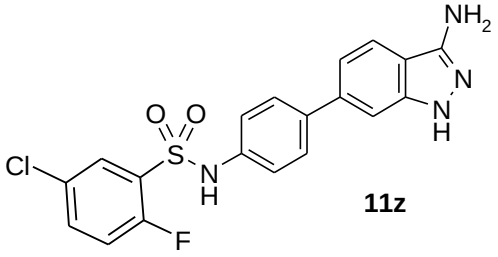
N-[4-(3-amino-1H-indazol-6-yl)phenyl]-3-chloro-2-fluoro-benzenesulfonamide trifluoroacetate **11y**



11y

^{1}H-NMR (DMSO-d_6) δ 7.22 (d, 2H, *J* = 8.7 Hz), 7.29 (dd, 1H, *J* = 1.2, 8.5 Hz), 7.42 (t, 1H, *J* = 8.1 Hz), 7.46 (s, 1H), 7.64 (d, 2H, *J* = 8.7 Hz), 7.82-7.88 (m, 1H), 7.84 (d, 1H, *J* = 8.6 Hz), 7.91 (ddd, *J* = 1.6, 6.9, 8.3 Hz), 11.00 (s, 1H); MS (ES+) Calcd.: [M+H] 417.06, Found: 417.03.

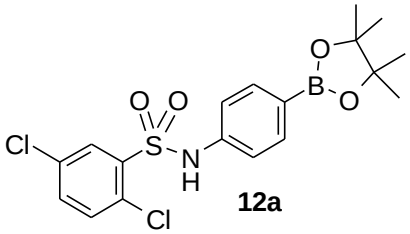
N-[4-(3-amino-1H-indazol-6-yl)phenyl]-5-chloro-2-fluoro-benzenesulfonamide trifluoroacetate **11z**



11z

^{1}H-NMR (DMSO-d_6) δ 7.23 (d, 2H, *J* = 8.5 Hz), 7.29 (d, 1H, *J* = 8.4 Hz), 7.47 (s, 1H), 7.53 (t, 1H, *J* = 9.3 Hz), 7.64 (d, 2H, *J* = 8.5 Hz), 7.80 (ddd, *J* = 3.0, 4.1, 7.8 Hz), 10.93 (s, 1H); MS (ES+) Calcd.: [M+H] 417.06, Found: 417.11.

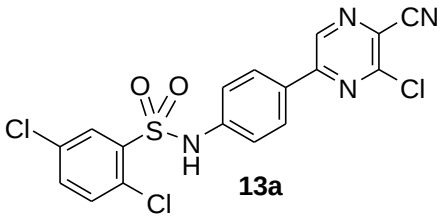
General procedure for the preparation of aryl sulfonamides **12** as exemplified by the synthesis of 2,5-dichloro-N-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]benzenesulfonamide **12a**



12a

Commercially available 2,5-dichloro-benzenesulfonyl chloride (5.0 g, 1.0 equiv.) and 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenylamine (4.51g, 1.0 equiv.) were added to a reaction vessel containing a magnetic stirring bar, followed by 100 ml dry dichloromethane and pyridine (4.9 ml, 3.0 equiv). The reaction mixture was stirred at ambient temperature for 1 hour before being evaporated to dryness. The crude reaction mixture was purified by flash chromatography on silica gel using a gradient of EtOAc and dichloromethane as the eluent to afford 2,5-dichloro-N-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]benzenesulfonamide **12a** (8.4g, 98%) as a colorless oil, that solidified upon standing, after evaporation of the solvents under reduced pressure. ^{1}H-NMR (DMSO-d_6) δ 1.24 (s, 12H), 7.12 (d, 2H, *J* = 8.5 Hz), 7.53 (d, 2H, *J* = 8.5 Hz), 7.67 (d, 1H, *J* = 8.6 Hz), 7.73 (dd, 1H, *J* = 2.5, 8.6 Hz), 11.01 (s, 1H); MS (ES-) Calcd.: [M-H] 426.05, Found: 426.13.

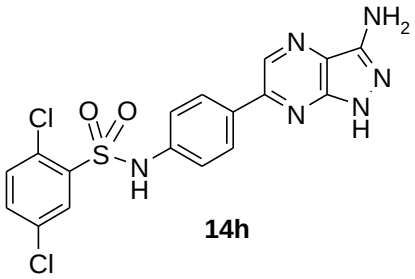
General procedure for the preparation of aryl sulfonamides **13** as exemplified by the synthesis of 2,5-dichloro-N-[4-(6-chloro-5-cyano-pyrazin-2-yl)phenyl]benzenesulfonamide **13a**



13a

To a reaction vessel containing a magnetic stirring bar 2,5-dichloro-N-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-benzenesulfonamide **12a** (2.39 g, 1.0 equiv.) was added together with 3,5-dichloro-pyrazine-2-carbonitrile (1.18 g, 1.0 equiv.), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) dichloride ($Pd(dppf)_2Cl_2$) (390 mg, 0.08 equiv.) and cesium carbonate (6.55 g, 3.0 equiv.), followed by 50 ml dioxane and 5 ml water, and the mixture heated to 100°C under stirring. After 3 h the reaction mixture was cooled to RT and quenched with a saturated aqueous sodium bicarbonate solution (50 ml) and extracted with EtOAc (3 x 100 ml). The combined aqueous phases were dried over sodium sulfate, filtered and evaporated to afford the crude product as a brown oil. Purification by flash chromatography on silica gel using a gradient of EtOAc and heptane as the eluent afforded 2,5-dichloro-N-[4-(6-chloro-5-cyano-pyrazin-2-yl)phenyl]benzenesulfonamide **13a** (1.83g, 74%) as a light brown foam after evaporation of the solvents under reduced pressure.
^{1}H-NMR (DMSO-d_6) δ 7.30 (d, 2H, *J* = 8.8 Hz), 7.69 (d, 1H, *J* = 8.6 Hz), 7.76 (dd, 1H *J* = 2.5, 8.5 Hz), 8.12 (d, 1H, *J* = 2.5 Hz), 8.14 (d, 2H, *J* = 8.8 Hz), 9.35 (s, 1H) 11.39 (s, 1H); MS (ES-) Calcd.: [M-H] 436.94, Found: 437.00.

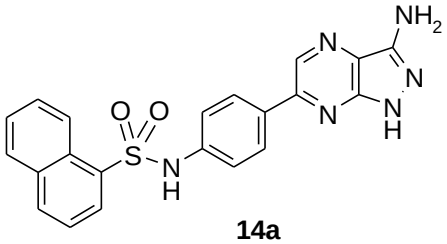
<u>General procedure for the preparation of aryl sulfonamides **14** as exemplified by the synthesis of N-[4-(3-amino-1H-pyrazolo[3,4-b]pyrazin-6-yl)phenyl]-2,5-dichloro-benzenesulfonamide hydrochloride **14h**</u>



14h

200 mg 2,5-dichloro-N-[4-(6-chloro-5-cyano-pyrazin-2-yl)phenyl]benzenesulfonamide **13a** was suspended in a mixture of 1.0 ml iPrOH and 1.0 ml 35% hydrazine in water at RT and heated to 120°C by microwave irradiation for 20 min under stirring in a sealed vessel. The reaction mixture was cooled to ambient temperature, diluted with $NaHCO_3$ (aq., sat.) and extracted with EtOAc. The organic phase was dried over Na_2SO_4 and evaporated to afford the crude product that was purified by HPLC using a water/MeCN gradient with 0.1% TFA. This afforded the N-[4-(3-amino-1H-pyrazolo[3,4-b]pyrazin-6-yl)phenyl]-2,5-dichloro-benzenesulfonamide hydrochloride **14h** (48.2 mg, 22%) after freezedrying with hydrochloric acid.
^{1}H-NMR (DMSO-d_6) δ 5.67 (br s, 2H), 7.26 (d, *J* = 8.8 Hz, 2H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.93 (dd, *J* = 1.4, 8.0 Hz, 1H), 8.06 (d, *J* = 8.8 Hz, 2H), 8.11 (dd, *J* = 1.5, 8.0 Hz, 1H), 8.86 (s, 1H), 12.30 (s,1H).; MS (ES+) Calcd.: [M+H] 435.02, Found: 434.94.

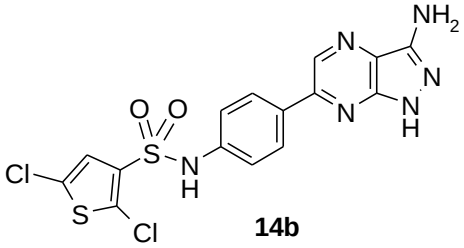
<u>N-[4-(3-amino-1H-pyrazolo[3,4-b]pyrazin-6-yl)phenyl]naphthalene-1-sulfonamide trifluoroacetate **14a**</u>



14a

^{1}H-NMR (DMSO-d_6) δ 7.20 (d, *J* = 8.8 Hz, 2H), 7.65 (t, *J* = 7.8 Hz, 1H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.77 (t, *J* = 7.8 Hz, 1H), 7.98 (d, *J* = 8.8 Hz, 2H), 8.08 (d, *J* = 8.0 Hz, 1H), 8.23 (d, *J* = 8.1 Hz, 1H), 8.30 (d, *J* = 7.5 Hz, 1H), 8.76 (d, *J* = 8.7 Hz, 1H), 8.80 (s, 1H), 11.05 (s, 1H), 12.31 (br, 1H); MS (ES+) Calcd.: [M+H] 417.11, Found: 417.21.

N-[4-(3-amino-1H-pyrazolo[3,4-b]pyrazin-6-yl)phenyl]-2,5-dichloro-thiophene-3-sulfonamide trifluoroacetate **14b**

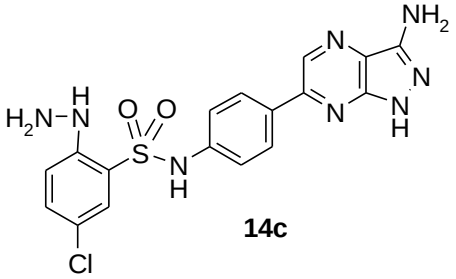


14b

^{1}H-NMR (DMSO-d_6) δ 5.73 (br), 7.30 (d, *J* = 8.5 Hz, 2H), 7.40 (s, 1H), 8.13 (d, *J* = 8.5 Hz, 2H), 8.91 (s, 1H), 11.05 (s, 1H), 12.33 (br, 1H); MS (ES+) Calcd.: [M+H] 440.98, Found: 441.11.

N-[4-(3-amino-1H-pyrazolo[3,4-b]pyrazin-6-yl)phenyl]-5-chloro-2-hydrazino-benzenesulfonamide hydrochloride **14c**

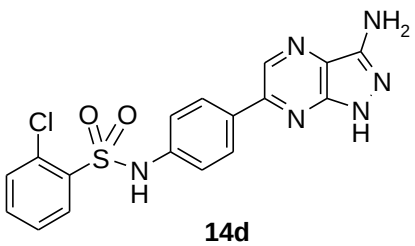
Obtained as a byproduct from the synthesis of **14h**



14c

^{1}H-NMR (DMSO-d_6) δ 7.21-7.24 (m, 1H), 7.25 (d, *J* = 8.8 Hz, 2H), 7.57 (br, 2H), 7.64 (d, *J* = 2.4 Hz, 1H), 8.09 (d, *J* = 8.8 Hz, 2H), 8.88 (s, 1H), 12.32 (br, 1H); MS (ES+) Calcd.: [M+H] 431.08, Found: 431.03.

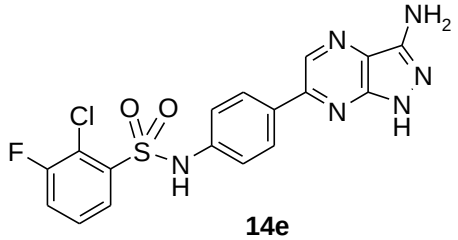
N-[4-(3-amino-1H-pyrazolo[3,4-b]pyrazin-6-yl)phenyl]-2-chloro-benzenesulfonamide trifluoroacetate **14d**



14d

^{1}H-NMR (DMSO-d_6) δ 7.26 (d, *J* = 8.8 Hz, 2H), 7.52-7.58 (m, 1H), 7.62-7.66 (m, 2H), 8.04 (d, *J* = 8.8 Hz, 2H), 8.12 (d, *J* = 7.8 Hz, 1H), 8.85 (s, 1H), 10.96 (s, 1H), 12.32 (br, 1H); MS (ES+) Calcd.: [M+H] 401.06, Found: 401.10.

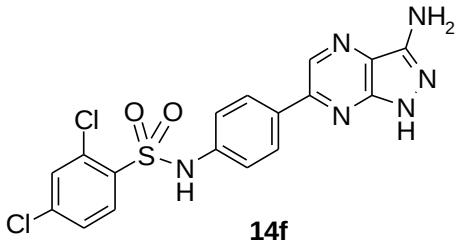
N-[4-(3-amino-1H-pyrazolo[3,4-b]pyrazin-6-yl)phenyl]-2-chloro-3-fluoro-benzenesulfonamide trifluoroacetate **14e**



14e

^{1}H-NMR (DMSO-d_6) δ 7.26 (d, *J* = 8.8 Hz, 2H), 7.61 (dt, *J* = 5.1, 8.1 Hz, 1H), 7.73 (dt, *J* = 1.2, 8.6 Hz, 1H), 7.97 (d, *J* = 7.8 Hz, 1H), 8.06 (d, *J* = 8.8 Hz, 2H), 8.86 (s, 1H), 11.12 (s, 1H), 12.33 (br, 1H), MS (ES+) Calcd.: [M+H] 419.05, Found: 419.05.

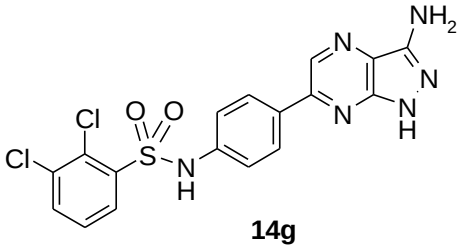
N-[4-(3-amino-1H-pyrazolo[3,4-b]pyrazin-6-yl)phenyl]-2,4-dichloro-benzenesulfonamide trifluoroacetate **14f**



14f

^{1}H-NMR (DMSO-d_6) δ 7.33 (d, *J* = 8.8 Hz, 2H), 7.65 (dd, *J* = 2.0, 8.6 Hz, 1H), 7.84 (d, *J* = 2.0 Hz, 1H), 8.13-8.18 (m, 1H), 8.15 (d, *J* = 8.8 Hz, 2H), 9.16 (s, 1H); MS (ES+) Calcd.: [M+H] 435.02, Found: 434.96.

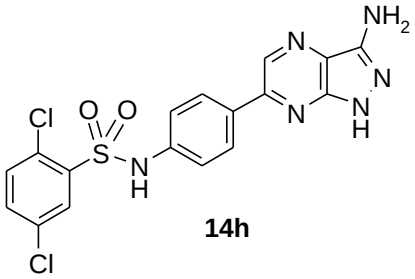
N-[4-(3-amino-1H-pyrazolo[3,4-b]pyrazin-6-yl)phenyl]-2,3-dichloro-benzenesulfonamide trifluoroacetate **14g**



14g

^{1}H-NMR (DMSO-d_6) δ 7.27 (d, *J* = 8.8 Hz, 2H), 7.58 (t, *J* = 8.1 Hz, 1H), 7.94 (dd, *J* = 1.4, 8.0 Hz, 2H), 8.07 (d, *J* = 8.8 Hz, 2H), 8.12 (dd, *J* = 1.4, 8.0 Hz, 2H), 8.89 (s,1 H), 11.15 (s, 1H); MS (ES+) Calcd.: [M+H] 435.02, Found: 435.03.
The purity of compound **14g** was determined to be >98% by LCMS and elemental analysis. The structure was confirmed by ^{1}H-NMR spectroscopy.

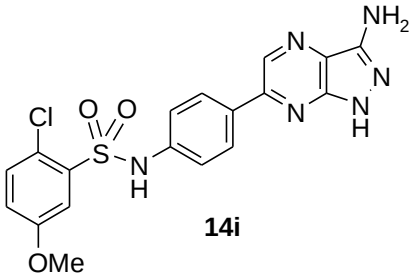
N-[4-(3-amino-1H-pyrazolo[3,4-b]pyrazin-6-yl)phenyl]-2,5-dichloro-benzenesulfonamide trifluoroacetate **14h**



14h

^{1}H-NMR (DMSO-d_6) δ 7.28 (d, *J* = 8.8 Hz, 2H), 7.70 (d, *J* = 8.5 Hz, 1H), 7.75 (dd, *J* = 2.5, 8.5 Hz, 1H), 8.07-8.09 (m, 1H), 8.09 (d, *J* = 8.8 Hz, 2H), 8.89 (s, 1H), 11.13 (s, 1H), MS (ES+) Calcd.: [M+H] 435.02, Found: 434.94.

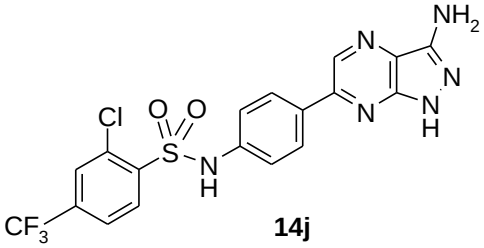
N-[4-(3-amino-1H-pyrazolo[3,4-b]pyrazin-6-yl)phenyl]-2-chloro-5-methoxy-benzenesulfonamide trifluoroacetate **14i**



14i

^{1}H-NMR (DMSO-d_6) δ 3.82 (s, 3H), 7.21 (dd, *J* = 3.0, 8.8 Hz, 1H), 7.27 (d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 8.8 Hz, 1H), 7.58 (d, *J* = 3.0 Hz, 1H), 8.07 (d, *J* = 8.8 Hz, 2H), 8.87 (s, 1H), 10.98 (s, 1H); MS (ES+) Calcd.: [M+H] 431.07, Found: 431.14.

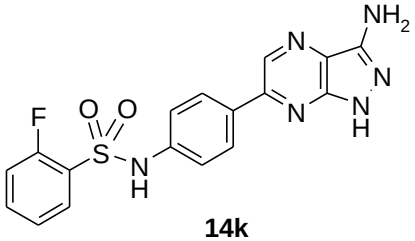
N-[4-(3-amino-1H-pyrazolo[3,4-b]pyrazin-6-yl)phenyl]-2-chloro-4-(trifluoromethyl)benzenesulfonamide trifluoroacetate **14j**



14j

^{1}H-NMR (DMSO-d_6) δ 7.27 (d, *J* = 8.8 Hz, 2H), 7.96 (d, *J* = 8.5 Hz, 1H), 8.07 (d, *J* = 8.8 Hz, 2H), 8.14 (s, 1H), 8.32 (d, *J* = 8.3 Hz, 1H), 8.87 (s, 1H), 11.24 (s, 1H), 12.34 (br, 1H); MS (ES+) Calcd.: [M+H] 469.04, Found: 469.18.

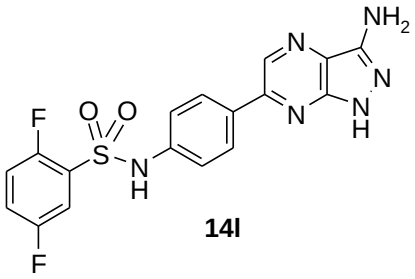
N-[4-(3-amino-1H-pyrazolo[3,4-b]pyrazin-6-yl)phenyl]-2-fluoro-benzenesulfonamide trifluoroacetate **14k**



14k

^{1}H-NMR (DMSO-d_6) δ 7.27 (d, *J* = 8.8 Hz, 2H), 7.36 -7.46 (m,1H), 7.40 (d, *J* = 7.2 Hz, 1H), 7.66-7.73 (m, 1H), 7.91 (d, *J* = 7.5 Hz, 1H), 8.06 (d, *J* = 8.8 Hz, 2H), 8.87 (s, 1H), 10.96 (s, 1H); MS (ES+) Calcd.: [M+H] 385.09, Found: 385.15.

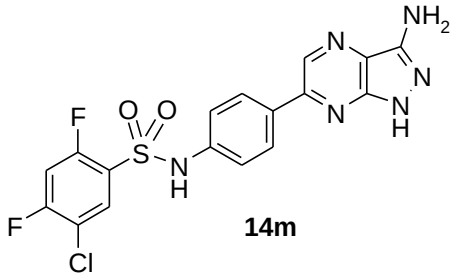
N-[4-(3-amino-1H-pyrazolo[3,4-b]pyrazin-6-yl)phenyl]-2,5-difluoro-benzenesulfonamide trifluoroacetate **14l**



14l

^{1}H-NMR (DMSO-d_6) δ 7.29 (d, *J* = 8.8 Hz, 2H), 7.52 (dt, *J* = 4.0, 9.3 Hz, 1H), 7.56-7.63 (m, 1H), 7.69-7.74 (m, 1H), 8.09 (d, *J* = 8.8 Hz, 2H), 8.88 (s, 1H), 11.09 (s, 1H); MS (ES+) Calcd.: [M+H] 403.08, Found: 403.08.

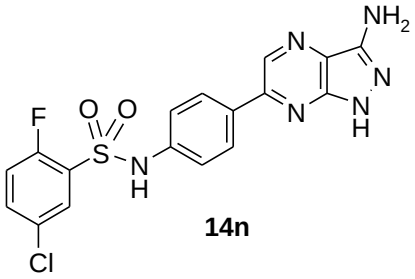
N-[4-(3-amino-1H-pyrazolo[3,4-b]pyrazin-6-yl)phenyl]-5-chloro-2,4-difluoro-benzenesulfonamide trifluoroacetate **14m**



14m

^{1}H-NMR (DMSO-d_6) δ 7.29 (d, *J* = 8.8 Hz, 2H), 7.85 (t, *J* = 9.4 Hz, 1H), 8.07-8.11 (m, 1H), 8.10 (d, *J* = 8.8 Hz, 2H), 8.89 (s, 1H), 11.14 (s, 1H), 12.37 (br, 1H); MS (ES+) Calcd.: [M+H] 437.04, Found: 437.13.

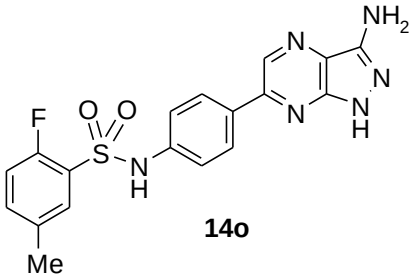
N-[4-(3-amino-1H-pyrazolo[3,4-b]pyrazin-6-yl)phenyl]-5-chloro-2-fluoro-benzenesulfonamide hydrochloride **14n**



14n

^{1}H-NMR (DMSO-d_6) δ 7.27 (d, *J* = 8.8 Hz, 2H), 7.55 (t, *J* = 8.7 Hz, 1H), 7.81 (m, 1H), 7.88 (m, 1H), 8.10 (d, *J* = 8.8 Hz, 2H), 8.91 (s, 1H), 11.10 (s, 1H). MS (ES+) Calcd.: [M+H] 419.05, Found: 418.99.

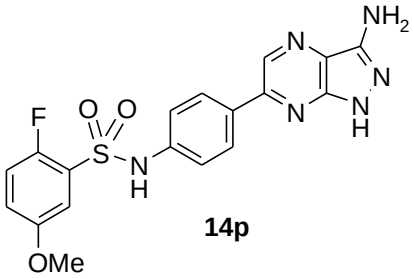
N-[4-(3-amino-1H-pyrazolo[3,4-b]pyrazin-6-yl)phenyl]-2-fluoro-5-methyl-benzenesulfonamide trifluoroacetate **14o**



14o

^{1}H-NMR (DMSO-d_6) δ 2.34 (s, 3H), 7.27 (d, *J* = 8.8 Hz, 2H), 7.28-7.33 (m, 1H), 7.46-7.51 (m, 1H), 7.72 (dd, *J* = 1.9, 6.8 Hz, 1H), 8.07 (d, *J* = 8.8 Hz, 2H), 8.88 (s, 1H), 10.92 (s, 1H); MS (ES+) Calcd.: [M+H] 399.10, Found: 399.17.

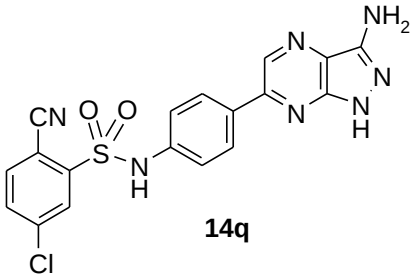
N-[4-(3-amino-1H-pyrazolo[3,4-b]pyrazin-6-yl)phenyl]-2-fluoro-5-methoxy-benzenesulfonamide trifluoroacetate **14p**



14p

^{1}H-NMR (DMSO-d_6) δ 3.79 (s, 3H), 5.69 (s, 2H), 7.23 (dt, *J* = 8.9, 3.4 Hz, 1H), 7.28 (d, *J* = 8.7 Hz, 2H), 7.33 (dt, *J* = 3.2, 5.5 Hz, 1H), 7.37 (t, *J* = 9.3 Hz, 1H), 8.08 (d, *J* = 8.7 Hz, 2H), 8.87 (s, 1H), 10.97 (s, 1H), 12.31 (s, 1H); MS (ES+) Calcd.: [M+H] 415.10, Found: 415.20.

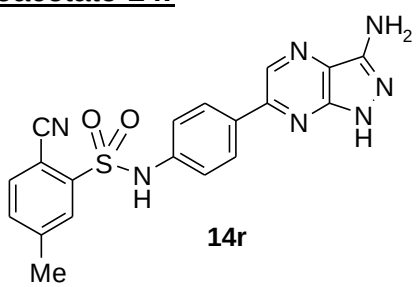
N-[4-(3-amino-1H-pyrazolo[3,4-b]pyrazin-6-yl)phenyl]-5-chloro-2-cyano-benzenesulfonamide trifluoroacetate **14q**



14q

^{1}H-NMR (DMSO-d_6) δ 7.29 (d, *J* = 8.7 Hz, 2H), 8.08-8.24 (m, 6H), 8.90 (s, 1H), 9.15 (s, 1H), 12.35 (br, 1H); MS (ES+) Calcd.: [M+H] 426.05, Found: 426.13.

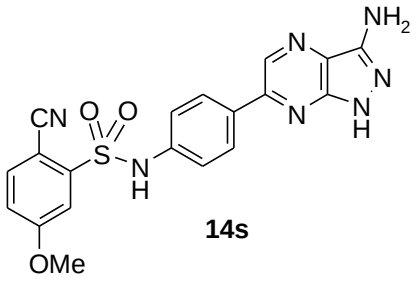
N-[4-(3-amino-1H-pyrazolo[3,4-b]pyrazin-6-yl)phenyl]-2-cyano-5-methyl-benzenesulfonamide trifluoroacetate **14r**



14r

^{1}H-NMR (DMSO-d_6) δ 7.27 (d, *J* = 8.8 Hz, 2H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.95-8.00 (m, 2H), 8.09 (d, *J* = 8.8 Hz, 2H), 8.89 (s, 1H), 11.10 (s, 1H); MS (ES+) Calcd.: [M+H] 406.19, Found: 406.18.

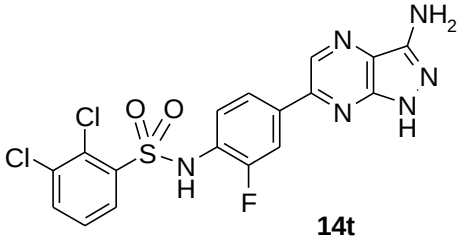
N-[4-(3-amino-1H-pyrazolo[3,4-b]pyrazin-6-yl)phenyl]-2-cyano-5-methoxy-benzenesulfonamide trifluoroacetate **14s**



14s

^{1}H-NMR (DMSO-d_6) δ 3.89 (s, 3H), 5.69 (br s, 2H), 7.29 (d, *J* = 8.7 Hz, 2H), 7.36 (dd, *J* = 2.5, 8.6 Hz, 1H), 7.54 (d, *J* = 2.5 Hz, 1H), 8.02 (d, *J* = 8.6 Hz, 1H), 8.10 (d, *J* = 8.7 Hz, 2H), 8.88 (s, 1H), 11.13 (br s, 1H), 12.32 (s, 1H); MS (ES+) Calcd.: [M+H] 422.10, Found: 422.30.

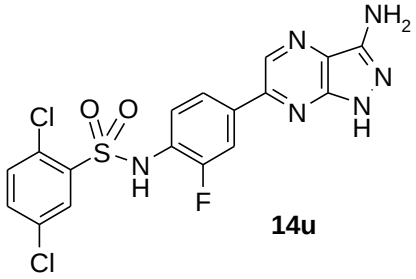
N-[4-(3-amino-1H-pyrazolo[3,4-b]pyrazin-6-yl)-2-fluoro-phenyl]-2,3-dichloro-benzenesulfonamide trifluoroacetate **14t**



14t

^{1}H-NMR (DMSO-d_6) δ 5.73 (br s, 2H), 7.44 (t, *J* = 8.3 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.93-8.01 (m, 3H), 7.97 (d, *J* = 8.4 Hz, 1H), 8.94 (s, 1H), 10.88 (br s, 1H), 12.39 (s, 1H); MS (ES+) Calcd.: [M+H] 453.01, Found: 452.93.

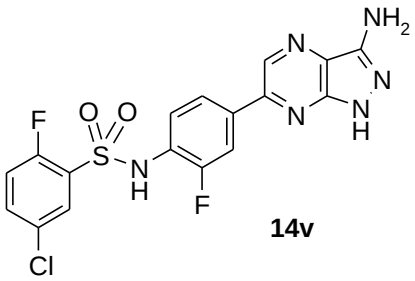
N-[4-(3-amino-1H-pyrazolo[3,4-b]pyrazin-6-yl)-2-fluoro-phenyl]-2,5-dichloro-benzenesulfonamide trifluoroacetate **14u**



14u

^{1}H-NMR (DMSO-d_6) δ 5.74 (br s, 2H), 7.45 (t, *J* = 8.0 Hz, 1H), 7.75-7.77 (m, 2H), 7.92 (dd, *J* = 0.6, 2.2 Hz, 1H), 7.97-8.03 (m, 2H), 8.96 (s, 1H), 10.89 (br s, 1H), 12.40 (s, 1H); MS (ES+) Calcd.: [M+H] 453.01, Found: 452.93.

N-[4-(3-amino-1H-pyrazolo[3,4-b]pyrazin-6-yl)-2-fluoro-phenyl]-5-chloro-2-fluoro-benzenesulfonamide trifluoroacetate **14v**

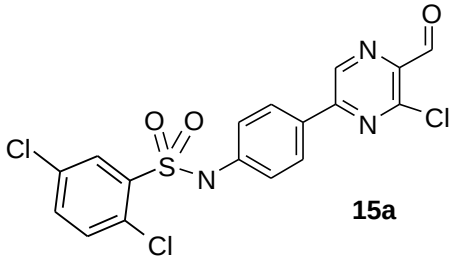


14v

^{1}H-NMR (DMSO-d_6) δ 5.75 (br s, 2H), 7.47 (t, *J* = 8.2 Hz, 1H), 7.57 (t, *J* = 9.5 Hz, 1H), 7.75 (dd, *J* = 2.7, 6.0 Hz, 1H), 7.83 (ddd, *J* = 2.7, 4.0, 7.8 Hz, 1H), 8.01 (d, *J* = 9.8 Hz, 1H), 8.97 (s, 1H), 10.92 (br s, 1H), 12.41 (s, 1H); MS (ES+) Calcd.: [M+H] 437.04, Found: 436.96.

The aryl sulfonamides **16** were prepared by route B as exemplified by the synthesis of 2,5-dichloro-N-[4-(1H-pyrazolo[3,4-b]pyrazin-6-yl)phenyl]benzenesulfonamide **16a.**

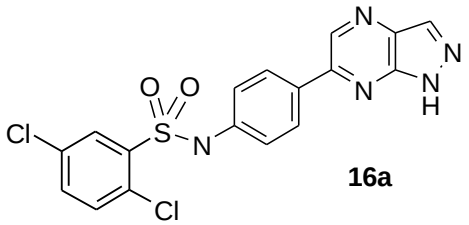
2,5-Dichloro-N-[4-(6-chloro-5-formyl-pyrazin-2-yl)phenyl]benzenesulfonamide **15a**



15a

A solution of 100 mg of 3,5-dichloro-pyrazine-2-carbaldehyde, 241 mg 2,5-dichloro-N-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-benzenesulfonamide and 552 mg of cesium carbonate in 3.4 ml of dioxane and 0.6 ml of water was purged with argon. Then, 33 mg of 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) dichloride were added and the reaction mixture was heated to 100 °C. After 40 min, the reaction mixture was cooled to RT and diluted with water. After filtration through a chem elut® cartridge by eluting with EtOAc the solvents were removed under reduced pressure and the crude product was purified by chromatography on silica gel eluting with a gradient of n-heptane/EtOAc and finally methanol. The fractions containing the product were combined and the solvent evaporated under reduced pressure to afford the 2,5-dichloro-N-[4-(6-chloro-5-formyl-pyrazin-2-yl)phenyl]benzenesulfonamide **15a** in 36% yield. The product was directly used in the next step.

2,5-Dichloro-N-[4-(1H-pyrazolo[3,4-b]pyrazin-6-yl)phenyl]benzenesulfonamide hydrochloride **16a**

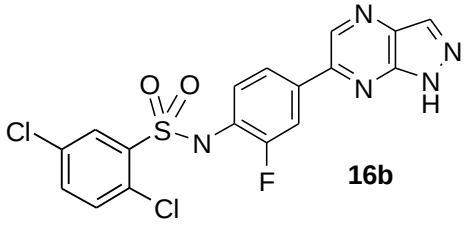


16a

To a solution of 90 mg of 2,5-dichloro-N-[4-(6-chloro-5-formyl-pyrazin-2-yl)-phenyl]-benzenesulfonamide **15a** in 0.7 ml isopropanol 0.7 ml of a hydrazine solution (35% in isopropanol) was added and the reaction mixture was heated for 20 min to 120 °C under microwave irradiation. The reaction mixture was cooled to RT and diluted with acetic acid (20%). The precipitated product was collected by filtration and purified by

HPLC using a water/MeCN gradient with 0.1% TFA. The fractions containing the product were lyophilized to yield the title compound in the form of its trifluoroacetate as a solid, which was dissolved in 1 ml of a water/acetonitrile mixture. 0.5 ml of a 1 M aqueous hydrochloric acid was added and the solution was again lyophilized afford 2,5-dichloro-N-[4-(1H-pyrazolo[3,4-b]pyrazin-6-yl)phenyl]benzenesulfonamide hydrochloride **16a** in 6% yield. MS (ES+) Calcd.: [M+H] 420.01, Found: 420.18.

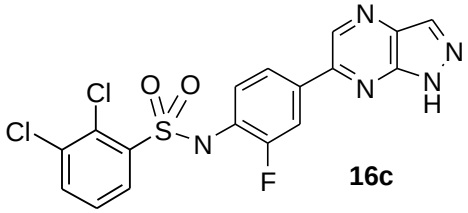
2,5-Dichloro-N-[2-fluoro-4-(1H-pyrazolo[3,4-b]pyrazin-6-yl)phenyl]benzenesulfonamide hydrochloride **16b**



16b

MS (ES+) Calcd.: [M+H] 438.00, Found: 438.16.

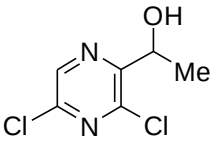
2,3-Dichloro-N-[2-fluoro-4-(1H-pyrazolo[3,4-b]pyrazin-6-yl)phenyl]benzenesulfonamide hydrochloride **16c**



16c

MS (ES+) Calcd.: [M+H] 438.00, Found: 438.09.
The methyl-1H-pyrazolo[3,4-b]pyrazines **21a-g** were prepared by route C as exemplified by the synthesis of **21f** or for **21a-c** with a sligthly modified procedure as described in WO2013041119.

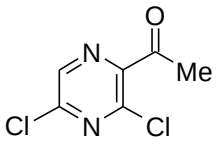
1-(3,5-Dichloro-pyrazin-2-yl)-ethanol **17**



17

5.0 g commercially available 3,5-dichloro-pyrazine-2-carbaldehyde was dissolved in 100 ml dry tetrahydrofuran in a reaction vessel equipped with a magnetic stirring bar under an argon atmosphere. The solution was cooled on an ice-bath before slow addition of 10.3 ml methylmagnesium bromide solution (3M in tetrahydrofuran), keeping the internal temperature in the reaction vessel below 5°C. After the addition the cooling bath was removed and the reaction mixture stirred for another 10 min. Then the reaction mixture was quenched with a saturated aqueous sodium bicarbonate solution (100 ml) and extracted with EtOAc (3 x 200 ml). The combined organic phases were dried over sodium sulfate, filtered and evaporated to afford 5.23g (96%) 1-(3,5-dichloro-pyrazin-2-yl)-ethanol as a dark brown oil. ^{1}H-NMR (DMSO-d_6) δ 1.42 (d, J = 6.5 Hz, 3H), 5.09 (q, J = 6.5 Hz, 1H), 8.83 (s, 1H); MS (ES+) Calcd.: [M+H] 192.99, Found: 192.90.

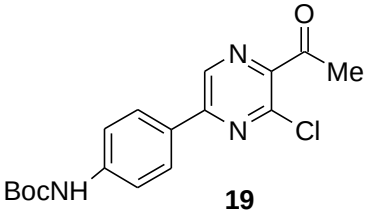
1-(3,5-Dichloro-pyrazin-2-yl)-ethanone **18**



18

5.0 g of 1-(3,5-dichloro-pyrazin-2-yl)-ethanol **17** was dissolved in 100 ml dry DCM at rt in a reaction vessel containing a magnetic stirring bar and 80.7 ml Dess-Martin periodinane (1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1H)-one) solution (15% in DCM) was slowly added. The reaction mixture was stirred for 30 min before the it was quenched with a saturated aqueous sodium bicarbonate solution (100 ml) and extracted with EtOAc (3 x 200 ml). The combined organic phases were dried over sodium sulfate, filtered and evaporated to afford the crude product as a brown oil. Purification by flash chromatography on silica gel using a gradient of EtOAc and heptane as the eluent afforded 1.90 g (38%) 1-(3,5-dichloro-pyrazin-2-yl)-ethanone **18** as a colorless oil after evaporation of the solvents under reduced pressure. ^{1}H-NMR (DMSO-d_6) δ 2.63 (s, 3H), 8.95 (s, 1H); MS (ES+) Calcd.: [M+H] 190.98, Found: 190.99.

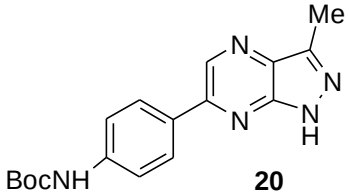
Tert-butyl N-[4-(5-acetyl-6-chloro-pyrazin-2-yl)phenyl]carbamate **19**



19

To a reaction vessel containing a magnetic stirring bar, 674 mg 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) dichloride and 11.2 g cesium carbonate was added 2.20 g 1-(3,5-dichloro-pyrazin-2-yl)-ethanone **18** and 2.70 g commercially available (4-tert-butoxycarbonyl-aminophenyl)boronic acid followed by 100 ml dioxane and 10 ml water, and the mixture heated to 100°C under stirring. After 1h the reaction mixture was cooled to RT and quenched with a saturated aqueous sodium bicarbonate solution (50 ml) and extracted with EtOAc (3 x 100 ml). The combined organic phases were dried over sodium sulfate, filtered and evaporated to afford the crude product as a dark brown oil. Purification by flash chromatography on silica gel using a gradient of EtOAc and heptane as the eluent afforded 2.44g (61%) tert-butyl N-[4-(5-acetyl-6-chloro-pyrazin-2-yl)phenyl]carbamate **19** as a colorless solid after evaporation of the solvents under reduced pressure. ^{1}H-NMR (DMSO-d_6) δ 1.50 (s, 9H), 2.65 (s, 3H), 7.47-7.57 (m, 1H), 7.67 (d, *J* = 8.8 Hz, 2H), 8.15 (d, *J* = 8.8 Hz, 2H), 9.30 (s, 1H), 9.75 (s,1H); MS (ES+) Calcd.: [M+H] 348.11, Found: 348.05.

Tert-butyl N-[4-(3-methyl-1H-pyrazolo[3,4-b]pyrazin-6-yl)phenyl]carbamate **20**

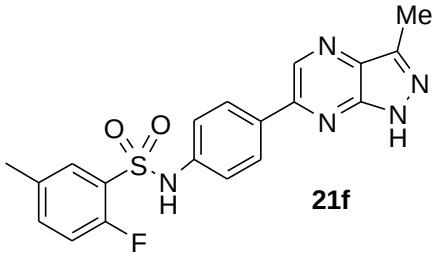


20

2.18 g tert-butyl N-[4-(5-acetyl-6-chloro-pyrazin-2-yl)phenyl]carbamate **19**

was suspended in a mixture of 21 ml iPrOH and 21 ml 35% hydrazine in water at RT and heated to 120°C by microwave irradiation for 20 min under stirring in a sealed vessel. The reaction mixture cooled to RT, quenched with a saturated aqueous sodium bicarbonate solution (10 ml) and extracted with EtOAc (3 x 30 ml). The combined organic phases were dried over sodium sulfate, filtered and evaporated to afford the crude product. Purification by trituration in boiling EtOAc and subsequent filtration afforded 1.42 g (70%) tert-butyl N-[4-(3-methyl-1H-pyrazolo[3,4-b]pyrazin-6-yl)phenyl]carbamate **20** as a yellow solid. ^{1}H-NMR (DMSO-d_6) δ 1.50 (s, 9H), 2.56 (s, 3H), 7.65 (d, *J* = 8.8 Hz, 2H), 8.14 (d, *J* = 8.8 Hz, 2H), 9.13 (s, 1H), 9.64, 13.53 br, 1H); MS (ES+) Calcd.: [M+H] 326.16, Found: 326.12.

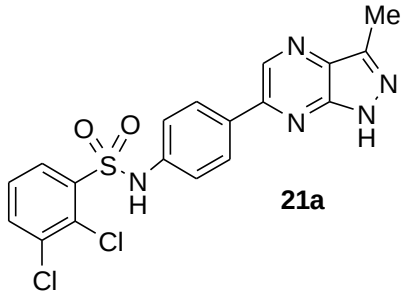
2-Fluoro-5-methyl-N-[4-(3-methyl-1H-pyrazolo[3,4-b]pyrazin-6-yl)phenyl]benzenesulfonamide **21f**



21f

To a reaction vessel containing a magnetic stirring bar and 179 mg tert-butyl N-[4-(3-methyl-1H-pyrazolo[3,4-b]pyrazin-6-yl)phenyl]carbamate **20** was added 3 ml 4N hydrogen chloride in dioxane solution, and the mixture stirred at RT. After 2 h the reaction mixture was evaporated to dryness under reduced pressure and the residue redissolved in 3 ml pyridine, and 116 mg 2-fluoro-5-methyl-benzenesulfonyl chloride was added and the mixture heated to 100°C in a sealed vessel. After 30 min the reaction mixture was cooled and evaporated to dryness, redissolved in DMF and purified by preparative HPLC (C18 reversed phase column, elution with a water/MeCN gradient with 0.1% TFA). The fractions containing the product were lyophilized to yield the title compound in the form of its trifluoroacetate in 14% yield. ^{1}H-NMR (DMSO-d_6) δ 2.34 (s, 3H), 2.55 (s, 3H), 7.31 (d, *J* = 8.6 Hz, 2H), 7.53 (dd, *J* = 8.6, 9.2 Hz, 1H), 7.80 (m, 1H), 7.89 (dd, *J* = 2.7, 6.0 Hz, 1H), 8.14 (d, *J* = 8.6 Hz, 2H), 9.09 (s, 1H), 11.15 (s, 1H), 13.58 (br, 1H); MS (ES+) Calcd.: [M+H] 398.11, Found: 398.23.

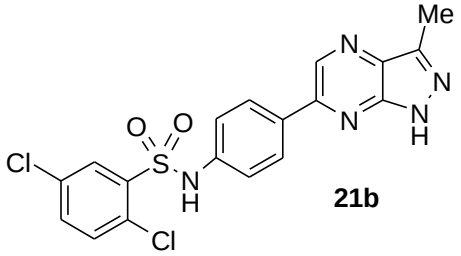
2,3-Dichloro-N-[4-(3-methyl-1H-pyrazolo[3,4-b]pyrazin-6-yl)phenyl]benzenesulfonamide **21a**



21a

^{1}H-NMR (DMSO-d_6) δ 2.54 (s, 3H), 7.28 (d, *J* = 8.8 Hz, 2H), 7.59 (t, *J* = 8.0 Hz, 1H), 7.94 (dd, *J* = 1.5, 8.1 Hz, 1H), 8.10 (d, *J* = 8.8 Hz, 2H), 8.13 (dd, *J* = 1.5, 8.0 Hz, 1H), 9.07 (s, 1H), 11.18 (s, 1H), 13.57 (s,1H); MS (ES+) Calcd.: [M+H] 434.02, Found: 434.06.

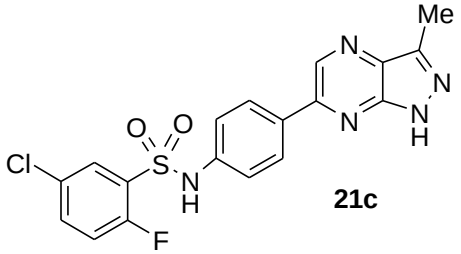
2,5-Dichloro-N-[4-(3-methyl-1H-pyrazolo[3,4-b]pyrazin-6-yl)phenyl]benzenesulfonamide **21b**



21b

^{1}H-NMR (DMSO-d_6) δ 2.55 (s, 3H), 7.29 (d, *J* = 8.8 Hz, 2H), 7.70 (d, *J* = 8.5 Hz, 1H), 7.76 (dd, *J* = 2.5, 8.5 Hz, 1H), 8.09 (d, *J* = 2.5 Hz, 1H), 8.12 (d, *J* = 8.8 Hz, 2H), 9.08 (s, 1H), 11.17 (s, 1H), 13.57 (br,1H); MS (ES+) Calcd.: [M+H] 434.02, Found: 434.05.

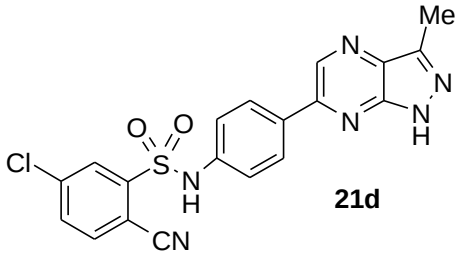
5-Chloro-2-fluoro-N-[4-(3-methyl-1H-pyrazolo[3,4-b]pyrazin-6-yl)phenyl]benzenesulfonamide **21c**



21c

^{1}H-NMR (DMSO-d_6) δ 2.55 (s, 3H), 7.31 (d, *J* = 8.6 Hz, 2H), 7.53 (dd, *J* = 8.6, 9.2 Hz, 1H), 7.80 (m, 1H), 7.89 (dd, *J* = 2.7, 6.0 Hz, 1H), 8.14 (d, *J* = 8.6 Hz, 2H), 9.09 (s, 1H), 11.15 (s, 1H), 13.58 (br, 1H); MS (ES+) Calcd.: [M+H] 418.05, Found: 418.07.

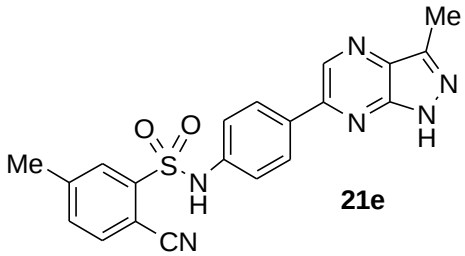
5-Chloro-2-cyano-N-[4-(3-methyl-1H-pyrazolo[3,4-b]pyrazin-6-yl)phenyl]benzenesulfonamide **21d**



21d

^{1}H-NMR (DMSO-d_6) δ 2.55 (s, 3H), 7.31 (d, *J* = 8.8 Hz, 2H), 7.97 (dd, *J* = 2.2, 8.3 Hz, 1H), 8.11 (d, *J* = 2.2 Hz, 1H), 8.14 (d, *J* = 8.3 Hz, 1H), 8.16 (d, *J* = 8.8 Hz, 2H), 9.10 (s, 1H), 11.25 (s, 1H), 13.58 (br, 1H); MS (ES+) Calcd.: [M+H] 425.06, Found: 425.17.

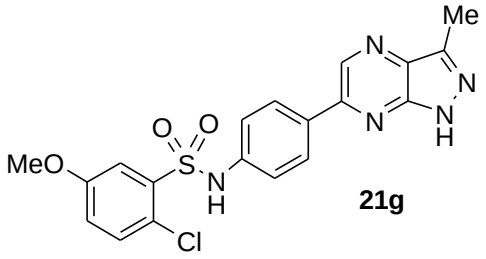
2-Cyano-5-methyl-N-[4-(3-methyl-1H-pyrazolo[3,4-b]pyrazin-6-yl)phenyl]benzenesulfonamide **21e**



21e

^{1}H-NMR (DMSO-d_6) δ 2.47 (s, 3H), 2.55 (s, 3H), 7.29 (d, *J* = 8.7 Hz, 2H), 7.32 (d, *J* = 8.6 Hz, 1H), 7.46-7.51 (m, 1H), 7.72 (dd, *J* = 2.1, 7.1 Hz, 1H), 8.10 (d, *J* = 8.7 Hz, 2H), 9.07 (s, 1H), 10.93 (s, 1H), 13.55 (br, 1H); MS (ES+) Calcd.: [M+H] 405.11, Found: 405.26.

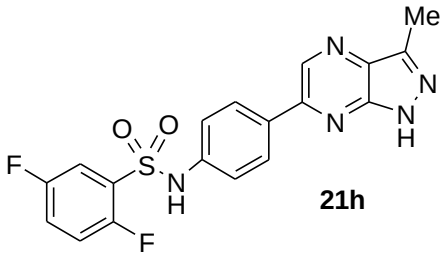
2-Chloro-5-methoxy-N-[4-(3-methyl-1H-pyrazolo[3,4-b]pyrazin-6-yl)phenyl]benzenesulfonamide **21g**



21g

^{1}H-NMR (DMSO-d_6) δ 2.54 (s, 3H), 3.82 (s, 3H), 7.21 (dd, *J* = 3.1, 8.7 Hz, 1H), 7.29 (d, *J* = 8.8 Hz, 2H), 7.54 (d, *J* = 8.7 Hz, 1H), 7.59 (d, *J* = 3.1 Hz, 1H), 8.10 (d, *J* = 8.8 Hz, 2H), 9.07 (s, 1H), 10.99 (s, 1H), 13.55 (br, 1H); MS (ES+) Calcd.: [M+H] 430.07, Found: 430.19.

2,5-Difluoro-N-[4-(3-methyl-1H-pyrazolo[3,4-b]pyrazin-6-yl)phenyl]benzenesulfonamide **21h**



21h

^{1}H-NMR (DMSO-d_6) δ 2.55 (s, 3H), 7.30 (d, *J* = 7.8 Hz, 2H), 7.52 (br, 1H), 7.59 (br, 1H), 7.72 (br, 1H), 8.12 (d, *J* = 7.8 Hz, 2H), 9.08 (s, 1H), 11.12 (s, 1H), 13.56 (br, 1H); MS (ES+) Calcd.: [M+H] 402.08, Found: 401.94.

In-silico methods:

Docking protocol

For docking, the protein structure with pdb code 2R5T was prepared using the protein preparation workflow available in the computer program MAESTRO (Schrödinger, 120 West 45th Street 17th Floor, Tower 45 New York, NY 10036-4041). Ligand structures were prepared with LigPrep. Ligand molecular docking was performed in the Glide module using single precision and standard parameter settings. Ligand interactions were analyzed using MAESTRO diagrams.

Shape-based screening

The program ROCS (version 3.1.1.) was used, which performs shape-based overlays of conformers for target molecules to the query molecule in one or multiple conformations. The ROCS algorithm maximizes the rigid overlay of atom-centered Gaussian functions and thereby maximizes the overlap between a query molecule and a single conformation of a target molecule. Multiconformer files for available molecules were generated by OMEGA, with a maximum of 100 conformers per molecule and saved in the oeb.gz format.

Assays:

Enzymatic activity assay

The compounds were tested for serum and glucocorticoid-regulated kinase 1 (SGK-1) inhibitory activity in a substrate phosphorylation assay designed to measure the ability of the isolated enzyme to catalyze the transfer of phosphate from ATP to serine/threonine residues in a fluorescein-labeled substrate peptide, using recombinant human SGK-1 enzyme produced in a baculovirus system (Biomol, Hamburg, Germany, Cat. No. 4-331). The synthetic fluorescently labeled peptide substrate contained (5(6)-Carboxyfluorescein)-RPRAATF-NH2. The phosphorylated substrate peptide and non-phosphorylated substrate peptide were separated with caliper life science's lab-chip technology based on a micro fluidics method. All fluid flow was established on the chip by applying a vacuum of a few psi to the waste well transporting fluid from various sources through interconnecting channels. Because the phosphoryl group is double negatively charged, under the pressure-driven hydrodynamic flow and the voltage-driven flow within the electric field, the fluorescently labeled peptide substrate and its phosphorylation product appear at different times in the detection window to the detection point. Substrate turnover can thus be determined as the ratio of the product peak area and the sum of substrate peak area and product peak area.

The enzyme reaction was carried out in a buffer containing 25 mM Tris-HCl (pH 7.4), 5 mM $MgCl_2$, 2 mM $MnCl_2$, 2 mM DTT, and 0.03% bovine serum albumine. The enzyme was pre-incubated with the test compound for 30 min at 24°C. The kinase reaction was initiated by addtion of the substrate mixture containing the peptide substrate (final concentration 1 µM) and ATP (final concentration 10 µM). After 60 min incubation at 37°C, the enzyme reaction was terminated by adding a buffer containing 100 mM Hepes (pH 7.4) and 35 mM EDTA.
For the determination of the compound dose response, a 10 mM DMSO stock solution was diluted and tested in a ten-point, three-fold dilution series run in duplicate beginning at 30 µM final concentration. Data were analyzed using a four-parameter curve fit with a fixed minimum and maximum experimentally defined as the average positive and negative controls on each plate.

Cellular SGK-1 dependent phosphorylation assay

Determination of the effect on SGK-1 dependent phosphorylation of GSK3beta in U2OS cells
It has been shown that glycogen synthase kinase 3beta (GSK3beta) is a phosphorylation target of SGK-1 (Sakoda,H., Gotoh,Y., Katagiri,H., Kurokawa,M., Ono,H., Onishi,Y., Anai,M., Ogihara,T., Fujishiro,M., Fukushima,Y., Abe,M., Shojima,N., Kikuchi,M., Oka,Y., Hirai,H., Asano,T.; Differing roles of Akt and serum- and glucocorticoid-regulated kinase in glucose metabolism, DNA synthesis, and oncogenic activity. J. Biol. Chem. 278 (2003), 25802–25807). The ability of the compounds of the invention to inhibit the enzymatic activity of serum and glucocorticoid-regulated Kinase 1 (SGK-1) was determined in a cellular assay which measures the SGK-1 dependent phosphorylation of GSK3beta in U2OS cells (ATCC HTB-96) overexpressing recombinant SGK-1 and GSK3beta after transfection with recombinant BacMam viruses.

U2OS cells were cultured in 1:1 Dulbecco modified Eagle medium / Ham's F12 and 10% heat inactivated fetal calf serum (FCS Gold) at 37°C, 7% CO_2 and 95% relative humidity. Cells were harvested and mixed with BacMam virus containing expression constructs for human SGK-1 (amino acids S61 - L431 with serine 422 replaced by aspartate) at an MOI (multiplicity of infection) of 50 and BacMam virus containing expression constructs for human GSK3beta at an MOI of 125. Cell suspension mixed with BacMam viruses was seeded in 96 well µCLEAR plates (Greiner) at $3x10^4$ cells per well in 250 µL medium. To reduce background phosphorylation of GSK3beta by AKT, 1 µL of a selective Akt-inhibitor was added (final concentration 2 µM). 1 µL of a solution of the test compound at 250 x final concentration was added. Cells are incubated at 37°C, 7% CO_2 and 95% relative humidity. After 6 h, medium was aspirated and 50 µl of fixation solution (3.7% paraformaldehyde in phosphate buffered saline (PBS)) was added for 10 min. After removing the fixation solution, cells were permeabilised by adding 200 µl PBT (0.2% Triton X-100 in PBS) per well for 5 min. After removing PBT, cells were blocked by adding 200 µl of blocking solution (1% bovine serum albumine in PBS) per well. Blocking solution was removed and 50 µl of primary antibody (rabbit anti-phospho-GSK-3beta (Ser9), and mouse anti-GSK-3beta) were added for 1h. After washing the cells 3 times with PBS, 50 µl of secondary antibody (Alexa Fluor 594 goat anti-rabbit IgG, and Alexa Fluor 488 goat anti-mouse IgG) were added and incubated for 1 h in the dark. After washing the cells 3 times with PBS, 200 µl of PBS were added. Fluorescence signals were measured with the ImageXpress MICRO (Molecular Devices). IC_{50} values were calculated using the ratio of phosphorylated GSK3beta to total GSK3beta to compensate for unspecific effects and are given in Table 3.

Pharmacokinetic Studies:
All experimental procedures have been conducted in accordance to German Animal Protection Law, as well as according to international animal welfare legislation and rules.

Male Sprague Dawley rats from Harlan Winkelmann, Germany were used in the described PK study (weight range 200-250 g).

Plasma and urine concentrations of **14g** were determined in a non-serial sampling study after an oral administration of 3.0 mg/kg and 30 mg/kg **14g** in a 15% glycofurol/ 5% solutol / 40% PEG400 solution to male Sprague Dawley rats (sampling time 0.12; 0.25; 0.5; 1; 2; 4; 8; 24h). Brain, liver and kidney samples were taken.

Metabolic stability on liver microsomes.

Incubation conditions with hepatic microsomal fractions and further experimental conditions used throughout were as follows: microsomal proteins concentration = 1 mg/mL, bovine serum albumin (BSA) concentration = 1 mg/mL; substrate concentration = 5 µM; incubation duration = 20 min; cytochrome P-450 monooxygenases (CYPs) and flavin-containing monooxygenases (FMOs) cofactor = 1 mM NADPH. Enzyme activity was stopped with 1 volume of acetonitrile (ACN). Hepatic microsomal fractions: from Swiss CD1 male mouse (m7), Sprague− Dawley male rat (m21), humans (pool of H-19, six donors). Inhibitor: quinidine at a final concentration of 8 µM (20-fold its Ki for CYP2D6) was used for the specific and

potent inhibition of enzyme reactions catalyzed by CYP2D6. Ketoconazole at a final concentration of 1.5 µM (100-fold its Ki for CYP3A4) was used for the specific and potentinhibition of enzyme reactions catalyzed by CYP3A4. For each test compound and for each microsomal preparation, three incubations were prepared: absolute reference in buffer (without enzyme material, i.e., microsomes); incubation without NADPH cofactor (with microsomal fractions); incubation with NADPH (with microsomal fractions). For most compounds, biotransformation, as observed in hepatic microsomal fractions in the presence of the NADPH cofactor, consists of oxidative reactions catalyzed by either CYP or FMO. In these conditions, the percentage of total metabolism, which corresponds to oxidative metabolism, was determined as follows: [% total metabolism] ≈ [% oxidative metabolism] = [1(UC peak area − NADPH UC peak area + NADPH)] × 100, where NADPH corresponds to the enzyme cofactor for oxidation reactions catalyzed by either CYP or FMO, and UC represents the unchanged compound.

IC50 determination for CYP P450 enzyme inhibition

The in vitro procedure for IC50 determination of a test compound as direct, reversible inhibitor against CYP3A4, CYP2D6 and CYP2C9 in human liver microsomes (HLM) was as follows: inhibition of the turn-over of probe substrates of CYP3A4 (Midazolam 3µM, 10 minutes and Testosterone 50µM, 30 minutes), CYP2D6 (Dextromethorphan 5µM, 30 minutes) and CYP2C9 (Diclofenac 5 µM, 10 minutes) to their specific metabolites i.e. 1´-Hydroxymidazolam, 6ß-Hydroxytestosterone, Dextrorphan and 4´-Hydroxydiclofenac by NCEs was evaluated. For scientific reasons, CYP3A4 inhibition was studied with two different probe substrates.

The specific metabolites were quantified by LC-MS/MS analysis.

CYP Inhibition conditions: 50 mM Phosphate buffer (no BSA in incubation medium), 0.5 mM EDTA, 6 mM MgCl2, 1mM NADPH, 0.1 or 0.2 mg microsomal protein/mL, maximum 0.5% DMSO with test compound(s) concentration range including 30, 10, 3, 1, 0.3 µM). • Incubations were carried out at 37°C. Incubations were terminated at the appropriate time with acetonitrile containing an appropriate internal standard.

Permeability testing using CACO-2 TC7 cells

Cellular permeability was tested using CACO-2 TC7 cells at passages 20 to 70, 21 to 28 days post seeding on filters (HTS plate membrane PET 1 µm, 3 wells). Transport medium forapical compartment : Hank's balanced salt solution; HEPES 10 mM; 0.5 % BSA; adjusted pH 6.5; for basal compartment : Hank's balanced salt solution; HEPES 10 mM; 5 % BSA; adjusted pH 7.4. Test compound concentration was 20 µM; incubation duration = 120 minutes under agitation at 37°C without CO_2.
Sampling was done at Time 0 (Apical compartment) and Time 120 (Apical and Basal compartments), Calibration curve used 3 concentration levels (at least) and transport in the "Apical-to-Basal" direction was evaluated. Following protein precipitation with acetonitrile and their removal by centrifugation, supernatant fluids were analysed by UPLC/ESI-MS-MS or equivalent assays.
Permeability values were calculated as follows:

Permeability coefficient (in nm/sec) = $\frac{\text{Amount Basal at time 120}}{\text{Time} * \text{Filter Area} * \text{Apical concentration at time 0}}$

Kinase panel

Compound **14g**, **n** were tested against the following 60 kinases at 1 µM concentration and 2Km ATP concentration.

ABL	INSR	PIM2	LCK	CamK1a
AKT1	JAK3	cRAF	LYN	LRRK2(G2019S)
VEGFR2-KDR	AMPK-alpha2/beta1/gamma1	EPHA1	MET	PEK(EIF2AK3)
AurB	BRSK2	EPHA3	MST1R (RON)	CDK5
KIT	CDK9	EPHB1	P70S6K	LRRK2(G2019S)
CAMK2 delta	MST2	EPHB4	PAK4	DDR2
MELK	CDC2/Cycline B1	Erk1	PIM1	HcK
p38a	DYRK1B	FLT1	ALK	PKCb2
CLK2	PDGFR_alpha	Flt3	BTK	DDR1
p38-gamma (MAPK12)	PKA	GSK3b	RSK1	PKCepsilon
EGFR	PKCz	GSK3-alpha	IKBKE (IKK epsilon)	TRKA(NTRK1)
FGFR1	PLK1	SRC	SYK	PKC Theta

CEREP data

Binding Assays

Assay Cerep Compound I.D.	Client Compound I.D.	Test Concentration (M)	% Inhibition of Control Specific Binding
A_1 *(h)* (antagonist radioligand)			
9770126-1	**14g**	1.0E-05	62
A_{2A} *(h)* (agonist radioligand)			
9770126-1	**14g**	1.0E-05	66
α_{1A} (antagonist radioligand)			
9770126-1	**14g**	1.0E-05	15
α_{2A} *(h)* (antagonist radioligand)			
9770126-1	**14g**	1.0E-05	5
β_1 *(h)* (agonist radioligand)			
9770126-1	**14g**	1.0E-05	10
β_2 *(h)* (agonist radioligand)			
9770126-1	**14g**	1.0E-05	-1
CB_1 *(h)* (agonist radioligand)			
9770126-1	**14g**	1.0E-05	-7
CB_2 *(h)* (agonist radioligand)			
9770126-1	**14g**	1.0E-05	4
D_1 *(h)* (antagonist radioligand)			
9770126-1	**14g**	1.0E-05	9
D_{2S} *(h)* (antagonist radioligand)			
9770126-1	**14g**	1.0E-05	7
glycine (strychnine-sensitive) (antagonist radioligand)			
9770126-1	**14g**	1.0E-05	2
H_1 *(h)* (antagonist radioligand)			
9770126-1	**14g**	1.0E-05	-6
H_2 *(h)* (antagonist radioligand)			
9770126-1	**14g**	1.0E-05	-49
M_1 *(h)* (antagonist radioligand)			
9770126-1	**14g**	1.0E-05	8
M_2 *(h)* (antagonist radioligand)			
9770126-1	**14g**	1.0E-05	7
M_3 *(h)* (antagonist radioligand)			
9770126-1	**14g**	1.0E-05	6
N neuronal $\alpha4\beta2$ *(h)* (agonist radioligand)			
9770126-1	**14g**	1.0E-05	-16
N muscle-type *(h)* (antagonist radioligand)			
9770126-1	**14g**	1.0E-05	-1
μ (MOP) *(h)* (agonist radioligand)			
9770126-1	**14g**	1.0E-05	16
PCP (antagonist radioligand)			
9770126-1	**14g**	1.0E-05	0
5-HT_{1A} *(h)* (agonist radioligand)			
9770126-1	**14g**	1.0E-05	10
5-HT_{2A} *(h)* (antagonist radioligand)			
9770126-1	**14g**	1.0E-05	14
5-HT_{2B} *(h)* (antagonist radioligand)			
9770126-1	**14g**	1.0E-05	22
Ca^{2+} channel (L, dihydropyridine site) (antagonist radioligand)			
9770126-1	**14g**	1.0E-05	24
K_V channel (antagonist radioligand)			
9770126-1	**14g**	1.0E-05	-39
SK_{Ca} channel (antagonist radioligand)			
9770126-1	**14g**	1.0E-05	-2
Cl^- channel (GABA-gated) (antagonist radioligand)			

Assay Cerep Compound I.D.	Client Compound I.D.	Test Concentration (M)	% Inhibition of Control Specific Binding
9770126-1	**14g**	1.0E-05	59
norepinephrine transporter *(h)* (antagonist radioligand)			
9770126-1	**14g**	1.0E-05	28
dopamine transporter *(h)* (antagonist radioligand)			
9770126-1	**14g**	1.0E-05	65

Enzyme Assays

Assay Cerep Compound I.D.	Client Compound I.D.	Test Concentration (M)	% Inhibition of Control Values
PDE3A *(h)*			
9770126-1	**14g**	1.0E-05	69
acetylcholinesterase *(h)*			
9770126-1	**14g**	1.0E-05	22
MAO-A *(h)*			
9770126-1	**14g**	1.0E-05	-4
ATPase (Na^+/K^+)			
9770126-1	**14g**	1.0E-05	3