Electronic Supplementary Material (ESI) for Medicinal Chemistry Communications

Structure-based design, synthesis, and profiling of a β-tryptase inhibitor with a spiro-piperidineamide scaffold, benzylamine P1 group, and a substituted indole P4 group

(Supplementary information)

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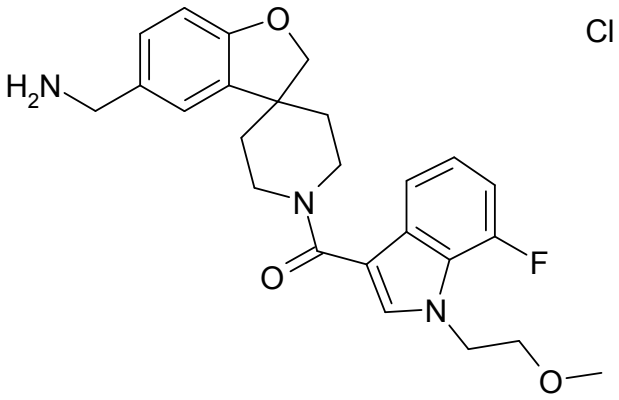
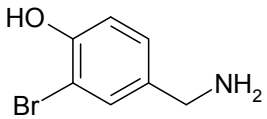
1-(7-Fluoro-1-(2-methoxy-ethyl)-indole-3-yl)-carbonyl-5'-aminomethyl-spiro[piperidine-4,3'-(2H)-benzo[b]furan] hydrochloride



A. 3-Bromo-4-hydroxybenzylamine hydrobromide



The title compound is prepared according to the procedure by Smith, L.H. *J. Med. Chem.* **1977**, *20*, 1254-1258 using 4-hydroxybenzylamine as the starting material. ^{1}H NMR

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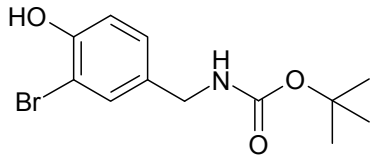
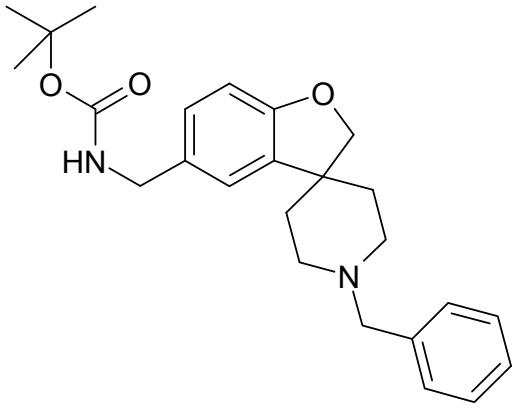
(300 MHz, DMSO-d_6) δ 8.0 (bs, 2H), 7.6 (m, 1H), 7.3 (m, 1H), 7.0 (m, 1H), 6.8 (m, 1H), 3.9 (m, 2H).

B. (3-Bromo-4-hydroxy-benzyl)-carbamic acid tert-butyl ester.



To a solution of 3-bromo-4-hydroxybenzylamine hydrobromide (18.4g, 65 mmol) in CH_2Cl_2 (600 mL) is added DIEA (32 ml, 195 mmol) and Boc-anhydride (16.6 g, 78 mmol). The reaction mixture is stirred for 4 h and diluted with CH_2Cl_2 (300 mL). The reaction mixture is washed with water, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue is purified by SiO_2 chromatography eluting with 2% MeOH/CH_2Cl_2 to yield 19 g (96%) of the titled compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4 (m, 1H), 7.15 (m, 1H), 7.0 (m, 1H), 6.8 (m, 1H), 5.5 (m, 1H), 4.2 (m, 2H), 1.5 (s, 9H).

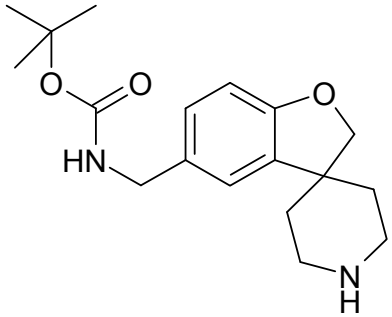
C. 1-Benzyl-5'(tert-butyloxycarbonyl-aminomethyl)-spiro[piperidine-4,3'-benzo[b]furan]



The title compound is prepared in a similar manner according to the procedure by Allerton, C. et al. PCT Int Appl., WO 2007/075775 using (1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)methanol and (3-bromo-4-hydroxy-benzyl)-carbamic acid tert-butyl ester as the starting materials. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4 (m, 5H), 7.1 (m,

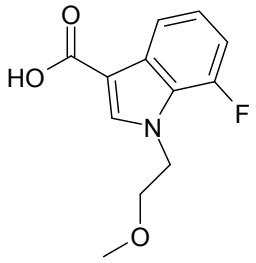
2H), 6.7 (m, 1H), 4.8 (bs, 1H), 4.4 (s, 2H), 4.2 (m, 2H), 3.5 (s, 2H), 2.9 (m, 2H), 2.0 (m, 4H), 1.7 (m, 2H), 1.4 (s, 9H). LCMS *m/z:* $[M+H]^+$=409.

D. 5'-(tert-butyloxycarbonyl-aminomethyl)-spiro[piperidine-4,3'-(2H)-benzo[b]furan]



A solution of 1-Benzyl-5'(tert-butyloxycarbonyl-aminomethyl)-spiro[piperidine-4,3'-benzo[b]furan] (6.0 g, 14.7 mmol) and 10% Pd/C (1 g) in 60 ml MeOH and acetic acid (1 ml) is subjected to H_2 at 50 psi for 5h. The reaction mixture is filtered through celite and is concentrated down *in vacuo*. The reaction mixture is taken up in EtOAc and is washed with sat $NaHCO_4$ (2X), brine, dried with Na_2SO_4, filtered and is concentrated *in vacu* to give 4.54 g (97% yield) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.1 (m, 2H), 6.8 (m, 1H), 4.8 (bs, 1H), 4.4 (s, 2H), 4.2 (m, 2H), 3.3 (s, 2H), 2.7 (m, 2H), 1.8 (m, 2H), 1.4 (s, 9H).

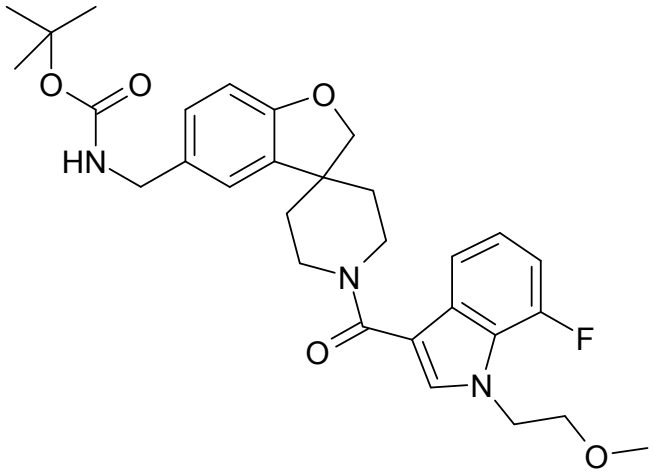
E. 7-Fluoro-1-(2-methoxy-ethyl)-1*H*-indole-3-carboxylic acid



The title compound is prepared in a similar manner according to the procedure by Choi-Sledeski, Yong Mi et al. PCT Int Appl., WO 2010/022196 using 7-fluoro-1*H*-indole) as the starting material. ^{1}H NMR (300 MHz, DMSO-d_6) δ □12.17 (s, 1H), 8.04 (s, 1H),

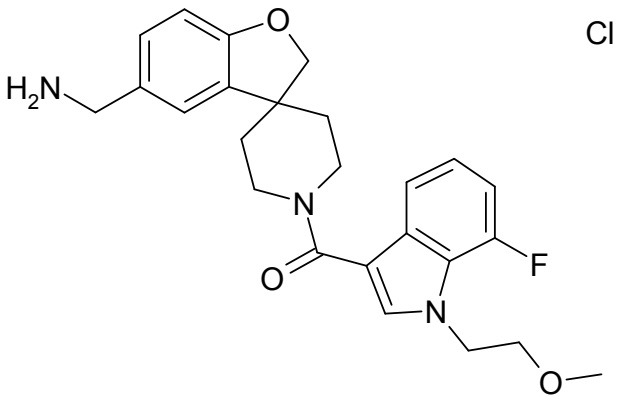
7.83 (d, J = 7.5 Hz, 1H), 7.18-7.11 (m, 1H), 7.08-7.01 (m, 1H), 4.50 (t, J = 5.1 Hz, 2H), 3.69 (t, J = 5.1 Hz, 2H), 3.22 (s, 3H); ^{19}F NMR (300 MHz, DMSO-d_6) δ -134.07 (d, 1F).

F.1-(7-Fluoro-1-(2-methoxy-ethyl)-indole-3-yl)-carbonyl-5'-(tert-butyloxycarbonyl-aminomethyl)-spiro[piperidine-4,3'-(2H)-benzo[b]furan]



To a solution of 7-fluoro-1-(2-methoxy-ethyl)-1*H*-indole-3-carboxylic acid (474 mg, 2.0 mmol), 5'-(tert-butyloxycarbonyl-aminomethyl)-spiro[piperidine-4,3'-(2H)-benzo[b]furan] (636 mg, 2.0 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (460 mg, 2.4 mmol) in CH_2Cl_2 is added triethylamine (0.56 ml, 4.0 mmol). The resulting mixture is stirred at room temperature overnight. The mixture is diluted with EtOAc and washed with water, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on SiO_2 gives the titled compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.5 (m, 2H), 7.1 (m, 3H), 6.9 (m, 1H), 6.75 (d, 1H), 4.8 (bs, 1H), 4.5 (m, 4H), 4.4 (m, 2H), 4.3 (m, 2H), 3.8 (t, 2H), 3.3 (s, 3H), 3.2 (m, 2H), 1.9 (m, 2H), 1.8 (m, 2H), 1.4 (s, 9H). LCMS *m/z:* $[M+H]^+$=538.

G. 1-(7-Fluoro-1-(2-methoxy-ethyl)-indole-3-yl)-carbonyl-5'-aminomethyl-spiro[piperidine-4,3'-(2H)-benzo[b]furan] hydrochloride



To a solution of 1-(7-fluoro-1-(2-methoxy-ethyl)-indole-3-yl)-carbonyl-5'-(tert-butyloxycarbonyl-aminomethyl)-spiro[piperidine-4,3'-(2H)-benzo[b]furan] (371 mg, 0.69 mmol) in dioxane (5 mL) is added 2M HCl in dioxane (10 mL, 20.0 mmol). The reaction mixture is stirred for 2h then concentrated *in vacuo*. The residue is triturated with ether for 2h and the resulting solid collected to give the titled compound.. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.2 (bs, 2H), 7.8 (s, 1H), 7.5 (m, 2H), 7.4 (m, 2H), 7.2 (m, 1H), 6.8 (d, 1H), 4.5 (m, 4H), 4.2 (m, 2H), 3.9 (m, 2H), 3.7 (m, 2H), 3.3 (m, 2H), 3.2 (s, 3H), 1.83 (m, 4H). LCMS *m/z:* $[M+H]^+$=438. Purity = 97.93%.