SUPPORTING INFORMATION

**Discovery of the First Non-Peptide Agonist of the
GPR14/Urotensin-II Receptor: 3-(4-Chlorophenyl)-3-(2-dimethylaminoethyl)-
isochroman-1-one (AC-7954)**

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Running title: Discovery of the first non-peptide urotensin-II receptor agonist

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Supplemental Text

Synthesis of 3-(4-chlorophenyl)-3-(2-dimethylaminoethyl)isochroman-1-one(1).

To synthesize **1**, a solution of *n*-butyllithium (39 mL, 62 mmol, 1.6 M in hexanes) was added dropwise over 1 h to *N*-methyl-*O*-toluamide (4.0 g, 28 mmol) in THF (25 mL) at 0°C under argon. The resulting red dilithio salt was stirred at 0-5°C for 1 h. The reaction was then cooled to -60°C and a solution of 4-chloro-3-(*N*, *N*-dimethylamino) propiophenone (3g, 14 mmol) in THF (15 mL) was added dropwise over 45 min. The resulting mixture was stirred for 1 h, allowed to warm to room temperature over 5 h and then treated with saturated NH₄Cl (20 mL). The product was extracted with EtOAc (3x20 mL) and the organic phase washed with water (2x20 mL), dried over MgSO₄, filtered and then concentrated *in vacuo*. The residue was dissolved in 1,2-dichlorobenzene (25 mL), the solution was heated to reflux for 18 h and then cooled to ambient temperature before being loaded onto a silica column. Purification by column chromatography (MeOH-CH₂Cl₂ 1:9 as eluent) afforded a yellow oil. The residue was dissolved up in pure ether (20 mL), filtered and the solution was concentrated. The oil was dissolved in CH₂Cl₂ (10 mL), HCl in dioxane (0.5 mL, 4M) was added and the mixture was stirred at ambient temp for 2h. The mixture was concentrated *in vacuo*, then recrystallized from CH₂Cl₂/ether to give 1.2 g (26%) of the title compound: mp 241-243°C; ¹H-NMR (CDCl₃, 400 MHz) δ 2.66 (m, 1H), 2.70 (s, 3H), 2.76 (s, 1H), 2.65-2.85 (m, 3H), 2.80 (s, 1H), 3.21 (m, 1H), 3.46 (d, *J*=28.92 Hz, 1H), 3.49 (d, *J*= 28.92 Hz, 1H), 7.17 (d, *J*=7.4 Hz, 1H), 7.31 (m, 5H), 7.49 (dt, *J*= 7.43 Hz, *J*= 1.37 Hz, 1H) 8.01 (dd, *J*= 7.63 Hz, *J*= 0.98 Hz, 1H), 12.6 (bs, 1H); ¹³C NMR (CDCl₃, 100.7 MHz) δ 36.65,

39.47, 42.91, 44.36, 53.67, 83.90, 124.55, 126.65, 128.20, 128.36, 129.65, 130.35,
134.69, 134.92, 136.57, 138.70, 164.30; MS m/e (FAB) 330 (MH⁺).