Discovery of CP-866087; a Mu Opioid Receptor Antagonist for the Treatment of Alcohol abuse and Dependence

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Supplementary material

Experimental procedures and spectral data for compounds 6, 7, 8, 10, 14, 15 and key intermediates.

Please note**,** spectral data for all final compounds in the document (e.g. **12**, **13**, **14**, **15**) can be found in reference 12 in the document. Also, for full experimental procedures for all final compounds, intermediates described in the paper and related analogs, please see: S. F. McHardy, S. Liras, S. D. Heck, *WO 2003035622*.

Also, Animals were handled and cared for in accordance with the guide for the care and use of laboratory animals (National Research Council 1996) and all procedures were performed with the approval of the Pfizer Animal Care committee.

Compound 6

To a stirring solution of 1-(3-Bromo-phenyl)-propylidene-hydrazine (29. 40 mmol) in 60. 0mL of dioxane at room temperature was added MnO_2. The mixture stirred for 45 min. at which point the black suspension that had formed was filtered off over a pad of celite, which was then washed with 20.0 mL of dioxane. The resulting deep red solution was then treated with 1-Benzyl-pyrrole-2, 5-dione (1. 1 equiv.) in portions over a 20 min. period. The mixture stirred at room temperature for 1.75 h. It was then heated to100 ^{o}C for 21h. , cooled to room temperature, and was concentrated under reduced pressure. The light yellow oil was then treated with warm CHSOH and a white solid was filtered off. The solid was recrystallized from CH_3OH to yield the desired product (64%) as a white solid.

400 MHz ^{1}H NMR ($CDCI_3$) δ 7.36-7.43 (m, 4H), 7.15-7.30 (m, 5H), 4.58 (s, 2H), 2.70 (s, 2H), 1.40 (q, J=7.47 Hz, 2H), 0.66 (t, J=7.47 Hz, 3H).

Compound 7

In flame-dried glassware under N_2, compound **6** (8. 64 mmol) and sodium borohydride (689 mg, 18. 15 mmol) were combined in 100 mL of anhydrous THF. The mixture was cooled to – 5 ^{o}C and borontritluoride diethylethrate (24. 19 mmol) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 2 h. It was then heated to reflux for 3h. The mixture was then cooled to 0 ^{o}C and piperazine (51. 85 mmol) was carefully added dropwise in 30 mL of H_2O. The reaction was then heated to reflux for 18 h. The mixture was then allowed to cool to room temperature, upon which it was diluted with H_2O and extracted twice with ethyl acetate. The combined extracts were washed twice with H_20, washed once with a saturated solution of

NaCI, and dried over $MgSO_4$. The liquid was then concentrated under reduced pressure to yield the desired product as a clear, colorless oil.
400 MHz ^{1}H NMR ($CDCI_3$) δ 7.39-7.40 (m, 1H), 7.21-7.34 (m, 6H), 7.09-7.18 (m, 2H), 3.66 (s, 2H), 3.05 (d, J=9.64 Hz, 2H), 2.77-2.81 (m, 2H), 2.04-2.10 (m, 2H), 1.73-1.78 (m, 2H), 0.85 (t, J=7.47, 3H).

Experimental procedure for the preparation of amides

To a stirring solution of **7** (14. 0 mmol) in 75 mL anhydrous DMF at room temperature was added zinc cyanide (2. 5 g, 21. 0 mmol) and tetrakis triphenylphosphine palladium (8. 1 g, 7. 0 mmol). The mixture was cooled to -78 ^{o}C and de-oxygenated with vacuum/N_2 purge. The mixture was warmed to room temperature and then heated at 85 ^{o}C for 3 hours. The mixture was cooled to room temperature and diluted with ethyl acetate and water. The layers were separated, the aqueous layer extracted with ethyl acetate, the combined organic layers were dried over MgSO4 and filtered through a small silica gel plug. The solution was concentrated to yield the crude nitrile which was used without purification. To a stirring solution of the nitrile prepared above (11. 2 mmol) in 90 mL DMSO at room temperature was added 30% H_2O_2 (5. 7 mL, 56 mmol) and potassium carbonate (216 mg, 1. 57 mmol). After stirring for 3.5 hours, the mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated to yield 3.17 gm of product.

400 MHz ^{1}H NMR ($CDCI_3$) δ 7.30-7.39 (m, 5H), 7.09 (t, 1H), 6.70-6.71 (m, 1H), 6.61-6.63 (m, 1H), 6.49-6.51 (m, 1H), 3.70 (s, 2H), 3.56 (br s, 2H), 3.04-3.10 (m, 2H), 2.82-2.87 (m, 2H), 2.04-2.10 (m, 2H), 1.77-1.79 (m, 2H), o.85-0.89 (m, 3H).

Experimental procedure for the preparation of sulfonamides

To a stirring solution of compound **7** (8.98 mmol) in 25 mL anhydrous toluene at room temperature was added benzophenone imine (1.81 mL, 10.8 mmol), BINAP (8 mg, 0.013 mmol), palladium (II) acetate (2.0 mg, 0.009 mmol) and sodium tert-butoxide (1.2 g, 12.57 mmol). The mixture was cooled to -78 ^{o}C and de-oxygenated with vacuum/nitrogen purge. The mixture was heated at mild reflux for 16 hours and cooled to room temperature. The mixture was then treated with 7 mL of concentrated HCI and 30 mL of water and was heated at reflux for 4 hours. The mixture was cooled to 0 ^{o}C and the pH was adjusted to 12 with 1N NaOH. The- layers were separated, the aqueous layer was extracted with CH_2CI_2 (3 x 30 mL) and the combined organic layers were dried and concentrated to yield an intermediate aniline. The crude aniline was used in the next step without purification.
To a stirring solution of the aniline (1.0 g, 3. 42 mmol) prepared above in 10 mL anhydrous pyridine at 0 ^{o}C was added methylsulfonyl chloride (5.13 mmol). The reaction was warmed to room temperature and stirred for 3 hours. Cold saturated $NaHCO_3$ was added and the mixture was diluted with ethyl acetate. The layers were separated, the aqueous layer extracted with ethyl acetate and the combined organic layers were dried over $MgSO_4$ and concentrated. The crude material was purified by flash chromatography with 70% ethyl acetate/hexanes to yield pure methysulfonamide.

400 MH_Z ^{1}HNMR (CD_3OD) δ 7.28-7.33 (m, 4H), 7.19-7.23 (m, 2H), 7.15 (s, 1H), 7.05-7.11 (m, 2H), 3.64 (s, 2H), 2.91-2.97 (m, 2H) 2.90 (s, 3H), 2.82-2.88 (m, 2H), 1.96-2.05 (m, 2H), 1.79-1.82 (m, 2H), 0.83 (t, 3H).

General procedure for the reductive debenzylation to furnish compounds 8 and 10 and similar analogs.

(a) To a stirring solution of N-benzyl amine (1.47 mmol) and amonium formate (277 mg, 4. 395 mmol) in 14. 0 mL of CH_3OH was added palladium on carbon (10% Pd, 184 mg). The mixture was then heated to reflux for 4 h., cooled to room temperature and filtered through a pad of celite, washing with CH_3OH. The filtrate was then concentrated under reduced pressure to yield oily white solids. The solids were then dissolved in CH_2CI_2 , basified with 1M NaOH (aq), and neutralized with HCI (aq) and $NaHCO_3$ (aq). The aqueous layer was then extracted three times with CH_2CI_2. The combined extracts were dried over MgS04 and concentrated under reduced pressure to yield the desired product as clear, colorless oil (30-80%).

(b) N-Benzyl amine (4.14 mmol) was dissolved in 60 mL methanol at room temperature in a 500 mL Parr bottle. To this solution was added 350 mg of 10% Pd(C). The mixture was hydrogenated under 50 psi H_2 at 60 ^oC for 18 hours. The mixture was cooled to room temperature and filtered through a plug of celite and the pad was washed several times with methanol. The resulting solution was concentrated under reduced pressure to yield the desired product as oil (60-90%).

Compound 8. 400 MHz ^1H NMR (CD_3OD) δ 7.61-7.80 (m, 2H), 7.26-7.41 (m, 2H), 3.21-3.33 (m, 2H), 3.12-3.20 (m, 2H), 1.88-1.97 (m, 2H), 1.77-1.83 (m, 2H), 0.79 (t, 3H). MS (M+1) 231.3.

Compound 10. 400 MHz ^1H NMR (CD_3OD) δ 7.29 (t, 1H), 7.19-7.22 (m, 1H), 7.09 7.12 (m, 1H), 3.71-3.78 (m, 2H), 3.28-3.31 (m, 2H), 2.95 (s, 3H), 2.30-2.38 (m, 2H), 1.59-1.64 (m, 2H), 0.86 (t, 3H).

General procedure for the preparation of compounds 14 and 15.

To a stirring solution of a compound **8** or **10** in ethanol (0.1 M) at room temperature was added triethyl amine (3 equiv.) and the appropriate epoxide (1. 2 equiv.). The resulting mixture was heated to 80 ^oC for 1-5 hours and then cooled to room temperature. The mixture was then concentrated under reduced pressure and the resulting crude material was purified by flash chromatography to yield the desired tertiary amines in 60-80% yield.

(**14**) 400 MH_Z ^{1}HNMR (CD_3OD) δ 7.76 (s, 1H), 7.63-7.65 (m, 1H), 7.41-7.44 (m, 1H), 7.31-7.35 (m, 1H), 7.12-7.14 (m, 2H), 7.01-7.09 (m, 2H), 3.18-3.28 (m, 2H), 3.05-3.10 (m, 2H), 2.98-3.01 (M, 2H), 2.86-2.89 (m, 2H), 2.73 (s, 2H), 1.94-1.99 (m, 2H), 1.81-1.84 (m, 2H), 0.79 (t, J=7.4 Hz, 3H); MS (M+1) 377.2.
(**15**) 400 MH_Z ^{1}HNMR ($CDCl_3$) δ□ 7.10-7.25 (m, 7H), 6.99-7.05 (m, 1H), 3.19-3.22 (m, 2H), 3.06-3.09 (m, 2H), 2.96-2.99 (m, 7H), 2.81 (s, 2H), 1.83-1.90 (m, 4H), 0.83 (t, J=7.4 Hz, 3H); MS (M+1) 427.1.