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Modified synthesis of NOP receptor antagonist SB612111

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Abstract

SB612111 ((5*S*,7*S*)-7-{[4-(2,6-dichlorophenyl)piperidin-1-yl]methyl}-1-methyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-ol) is a potent and selective antagonist of the nociception/orphanin FQ peptide (NOP) receptor. In the process of synthesizing *cis*-SB612111 to support ongoing animal studies, several key steps of the published syntheses in the patent literature proceeded in low yields in our hands, particularly with the route to the key intermediate piperidine **3**, the reduction of amide **14**, lactone **17** formation and the final reductive amination between **18** and **3** in the diastereoselective synthesis. We have thus explored various reaction conditions and successfully improved the yields for the necessary synthetic steps. We herein report our modified synthesis of SB612111 as the *cis*-diastereomers.

Graphical Abstract

Keywords

NOP; antagonist; modified synthesis; SB612111

The nociception/orphanin FQ peptide (NOP) receptor, previously called the opioid receptor-like receptor (ORL1, XOR1 and LC132) was discovered in 1994.^{1–5} The NOP receptor has been recognized by the International Union of Pharmacology as the fourth member of the opioid receptor family,^{3,6} although many classical opioid receptor ligands do not bind with

Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

high affinity to the NOP receptor.^{7–9} The NOP receptor is widely distributed in the central (CNS) and peripheral nervous system, specifically in regions associated with mood disorders and obesity, as well as other areas such as the cardiovascular and immune systems.^{10,11} NOP has been linked to a broad range of physiological and behavioral functions, such as pain, anxiety, depression, anorexia, obesity, and drug abuse.^{10–12}

A number of agonists and antagonists selective for the NOP receptor have been developed in order to study the biological role of this receptor system (Figure 1).^{13–17} Among these, SB612111 ((5*S*,7*S*)-7-([4-(2,6-dichlorophenyl)piperidin-1-yl]methyl)-1-methyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-ol, **1**, Figure 1) developed by GlaxoSmithKline (GSK), is one of the most potent and selective non-peptide NOP antagonists discovered to date.¹⁸ SB612111 was once proposed for Phase I clinical trials in the treatment of Parkinson's disease, but was not further developed.¹⁹

In an effort to investigate the potential role of the NOP receptor in drug addiction, particularly in mediating relapse of drugs such as nicotine,^{20,21} access to grams of SB612111 was required. We initially aimed to prepare the more accessible *cis*-diastereomeric mixture of **1** following procedures described in a patent by GSK (Figure 2).²² According to the patent, enantiomerically pure SB612111 (**1**) was attained by amide coupling of benzocycloheptanoic acid (**2**) with 4-(2,6-dichlorophenyl)-piperidine (**3**), followed by reduction of both the ketone and amide and then separation of the resulting diastereomers by chiral separation (Figure 2). In our attempt to follow these procedures, the synthesis proceeded well in general, with yields in most of the steps comparable to the original patent. However, several key steps afforded rather low yields in our hands that prevented a practical preparation of gram quantities of *cis*-**1**. We have thus explored alternate reaction conditions in these steps and successfully improved the yields. Hereby we present these findings and our solutions to the encountered issues.

The synthesis of acid **2** proceeded as expected in similar yields following the patent procedure (Scheme 1), starting from commercially available 2-(2-methylphenyl)-ethanol (**4**).²² Mesylation of the alcohol and displacement of the resulting mesylate **5** with malonate provided intermediate **6**, alkylation of which with *t*-butyl bromoacetate gave the triester **7** in high yield (81% over 3 steps, vs. 65% reported). After removal of the *t*-butyl group of **7** with TFA and conversion to the acid chloride, Friedel-Crafts acylation provided the benzoheptanone **9**, which underwent decarboxylation to give acid **2**. This 3-step sequence proceeded in 27% in the original report. While the *t*-butyl ester hydrolysis and decarboxylation steps proceeded in high yields in our hands, the yield of cyclization appeared variable, ranging from 12–38%. We found that purification of the acid **8** prior to the cyclization resulted in a cleaner Friedel-Crafts reaction and improved yields (51% for the cyclization step and 39% over 3 steps).

The synthesis of piperidine **3**,^{22,23} however, had immediate problems in the first step. Condensation between benzaldehyde **10** and two equivalents of ethyl acetoacetate in absolute ethanol, only afforded the desired cyclohexanone **11** in 23% yield after chromatography (Scheme 2). This was in contrast to the patent report where the reaction gave high yield by simple precipitation of the product with diethyl ether after removal of

reaction solvents. Replacing absolute ethanol with 96% ethanol, as per the original procedure did not alter the results. Purification of ethyl acetoacetate and piperidine by distillation did not afford any improvement, nor did extended reaction times.

The 2,6-dichlorobenzaldehyde was newly purchased and used as received. While the NMR spectrum of this aldehyde did not show any impurities, we suspected that a trace amount of the corresponding carboxylic acid from oxidation of the aldehyde could be present, possibly generated during the reaction via oxidation by the oxygen present in the nitrogen gas used as the inert gas. Since the piperidine was catalytic and only 0.2 equivalents were used as suggested by the original report, the benzoic acid could react with piperidine, rendering it unavailable as the catalyst. Therefore, we investigated the stoichiometry of the piperidine added to the reaction. We found that the subsequent addition of another 0.2 equivalents of piperidine improved the yield from 23% to 68% without chromatography purification. Further increasing the amount of piperidine did not result in improvement, consistent with the fact that only trace amount of benzoic acid was present.

Hydrolysis of the diester (**11**) to the diacid (**12**) with sodium hydroxide proceeded in quantitative yield. Condensation of **12** with ammonium hydroxide at 190°C gave the imide **13** in 34% without chromatography required. Finally, reduction of **13** to the piperidine **3** with borane dimethylsulfide proceeded in 85% with the piperidine isolated as the hydrochloride salt. This 3-step sequence proceeded with similar yields as reported.²²

With both components **2** and **3** in hand, amide coupling via the acid chloride (Scheme 3) gave the penultimate product **14** in 45% yield. Lithium aluminum hydride reduction in the presence of aluminum chloride, however, gave rather poor yields (5–14%) of the desired cis-diastereomers of **1** after chromatographic separation from the trans-diastereomers. This yield was even lower than the literature yield (25%). Modifications to the work-up procedure to increase recovery of product from the aluminates did not improve the yield. Such a poor yield at the final step precluded production of enough material for the animal studies, thus an alternate approach was sought.

The same GSK group later reported a modified diastereoselective synthesis in another patent.²⁴ Instead of a diastereomeric separation of the final product, the new diastereoselective synthesis converted acid **2** into a lactone (**17**, Scheme 4). Since only the cis diastereomer could cyclize, this conversion allows for the facile separation from the trans analogs, which would remain as the hydroxy ester. Thus, acid **2** was converted to the methyl ester **15** and the ketone was reduced to alcohol **16**. The literature method utilized sodium hydride activation to afford the next cyclization step to form the lactone **17**; however, no conversion was observed in our hands under these conditions with only starting material recovered. We instead found that catalytic p-toluene sulfonic acid²⁵ gave excellent conversion to **17** (84% conversion, 42% yield from the mixture of diastereomers), which was readily separated from the uncyclized material. It should be noted the unreacted trans-**16** could be converted to the cis isomer via hydroxyl inversion (e.g. via Mitsunobu reaction) and then to cis-**17** to improve material conversion. Diisobutylaluminum hydride reduction gave the lactol **18** in 75% yield.

For the final reductive amination step, the literature procedure²⁴ preformed the imine in methanol at 50°C for 2 hours followed by reduction with sodium borohydride at 0°C. Surprisingly, under these conditions, the desired *cis*-**1** was obtained in only 5% yield. Instead, diol **19** was isolated as the main product (entry 1, Table 1) after chromatographic separation, with piperidine **3** recovered. Although diol **19** could potentially be converted into **1** (e.g. via selective tosylation of the primary alcohol and displacement with the piperidine), effort was focused on improving the conversion of **18** to **1**. Suspecting the imine did not form appropriately under the reported conditions, we then examined another solvent, 2,2,2-trifluoroethanol, which has been reported to favor imine formation.²⁶ Under these conditions, **18** and **3** were mixed and stirred at 40°C for 5 min to preform the imine before addition of sodium borohydride. But again, diol **19** was obtained as the major product (entry 2). We next investigated sodium cyanoborohydride as the reducing agent in 2,2,2-trifluoroethanol; however, only trace amount of the desired *cis*-**1** was isolated (entry 3).

Given the unsatisfactory results with the preformation of the imine, we next examined in situ formation of imine in methanol in the presence of acetic acid with increased amount of reducing agent (entry 4). The reaction was carefully monitored by TLC and mass spectrometry. When partial conversion was observed with piperidine **3** still present after 16 hours, an additional 0.5 equivalent of lactol **18** was added. Encouragingly, significantly enhanced conversion was observed under the new conditions (40%, entry 4). When the reaction was started with 1.5 equivalents of lactol **18**, it gave a lower yield (28%, entry 5). This is possibly the result of competition between reduction of the lactol and reductive amination under the reaction conditions, where the excess of the lactol was reduced more rapidly.

Finally, sodium triacetoxyborohydride was explored as the reducing agent, with 1,2-dichloroethane as the solvent. Encouragingly, 2 equivalents of triacetoxyborohydride afforded the product in 40% yield (entry 6), similar to the best results with cyanoborohydride. Increasing the reducing agent to 4 equivalents further improved the yield to 52% (entry 7). Finally, the work-up procedure was altered from a simple aqueous work up to a bicarbonate quench and this modification further improved yield to 67% (entry 8).

In summary, modifications and improvements have been made to the previously reported synthesis of the NOP receptor antagonist SB612111 in order to support ongoing behavioral studies. While in general the reported synthesis proceeded as expected, several key steps only gave modest to very low yields under the reported conditions, including synthesis of piperidine **3**, an acid-catalyzed lactone formation (**17**) and the final reductive amination between **18** and **3**. Possible explanation of the differences include different batches of reagents used and scales of the reactions. We have thus explored various reaction conditions that resulted in significantly improved yields in these key steps. The modified reactions are amenable to scale up for gram quantity preparation of SB612111.

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General.

All solvents and chemicals were reagent grade. Unless otherwise mentioned, all were purchased from commercial vendors and used as received. Flash column chromatography was done on a Teledyne ISCO CombiFlash Rf system using prepacked columns. Solvents used were hexane, ethyl acetate (EtOAc) and dichloromethane (DCM). Purity and characterization of compounds was established by a combination of thin layer chromatography (TLC), mass spectrometry (MS) and nuclear magnetic resonance (NMR) analysis. ^1H NMR spectra were recorded on a Bruker Avance DPX-300 (300 MHz) spectrometer and were determined in chloroform-d with tetramethylsilane (TMS) (0.00 ppm) or solvent peaks as the internal reference. Chemical shifts are reported in ppm relative to the reference signal, and coupling constant (J) values are reported in Hz. TLC was done on EMD precoated silica gel 60 F254 plates, and spots were visualized with UV light or iodine staining. Low resolution mass spectra were obtained using a Waters Alliance HT/Micromass ZQ system (ESI).

Procedures

2-(2-Methylphenyl)ethyl methanesulfonate (5).

To a solution of 2-[2-methylphenyl]ethanol (**4**) (5.0 g, 36.71 mmol) in anhydrous DCM (100 mL) cooled in ice under N_2 was added triethylamine (5.94 g, 8.2 mL, 58.74 mmol) then a solution of methanesulfonyl chloride (6.73 g, 4.5 mL, 58.74 mmol) in DCM (50 mL) was added slowly via addition funnel. This resulting solution was allowed to warm to RT overnight. Water was added and the layers separated. The organic fraction was concentrated in vacuo then redissolved in diether ether. The solution was washed with 2N HCl solution and NaHCO_3 solution, dried over MgSO_4 and then the solvent removed under reduced pressure to give the desired sulfonate (7.87 g, 100%) as a clear liquid.

^1H NMR (CHLOROFORM-d, 300MHz): δ (ppm) 7.13 – 7.20 (m, 4H), 4.39 (t, $J=7.3$ Hz, 2H), 3.08 (t, $J=7.3$ Hz, 2H), 2.85 (s, 3H), 2.35 (s, 3H).

1,3-Diethyl 2-[2-(2-methylphenyl)ethyl]propanedioate (6).

Sodium metal (1.55 g, 67.58 mmol) was dissolved in absolute ethanol (50 mL) then diethyl malonate (16.24 g, 15.4 mL, 101.36 mmol) was added slowly to the solution at RT under N_2 . The resulting mixture was stirred at RT for 30 min. A solution of the methanesulfonate **5** (7.24 g, 33.79 mmol) in ethanol (25 mL) was added dropwise via addition funnel. Upon complete addition, the reaction was heated at reflux for 3 hr. The reaction was cooled and the solvent removed under reduced pressure. The crude was diluted with water and extracted 3 times with diethyl ether. The combined extracts were washed with 2N HCl and brine, dried over MgSO_4 and the solvent was removed under reduced pressure. Excess diethyl malonate was removed via nitrogen blowdown to give the diester (9.13 g, 97%).

^1H NMR (CHLOROFORM-d, 300MHz): δ (ppm) 7.08 – 7.19 (m, 4H), 4.21 (q, $J=7.2$ Hz, 4H), 3.34 – 3.44 (m, 1H), 2.60 – 2.69 (m, 2H), 2.31 (s, 3H), 2.10 – 2.21 (m, 2H), 1.28 (t, $J=7.2$ Hz, 6H).

2-tert-Butyl 1,1-diethyl 1-[2-(2-methylphenyl)ethyl]ethane-1,1,2-tricarboxylate (7).

To a solution of sodium hydride (as a 60% dispersion in mineral oil, 3.45 g, 86.22 mmol) in anhydrous THF (140 mL) was slowly added a solution of diester **6** (8.0 g, 28.74 mmol) in THF (60 mL). The mixture was stirred at RT under N₂ for 30 min then t-butyl bromoacetate (7.01 g, 5.3 mL, 35.93 mmol) was added dropwise and the resulting cloudy solution was stirred at RT under N₂ overnight. The reaction was cooled in ice and quenched with water, then extracted twice with diethyl ether. The combined extracts were dried over MgSO₄ and the solvent was removed under reduced pressure. Purification by chromatography on silica (DCM) gave the tri-ester **5** (9.42 g, 84%) as a clear liquid.

¹H NMR (CHLOROFORM-d, 300MHz): δ (ppm) 7.07 – 7.15 (m, 4H), 4.23 (q, *J*=7.2 Hz, 4H), 3.00 (s, 2H), 2.51 – 2.59 (m, 2H), 2.29 (s, 3H), 2.16 – 2.24 (m, 2H), 1.43 (s, 9H), 1.28 (t, *J*=7.2 Hz, 6H).

3,3-Bis(ethoxycarbonyl)-5-(2-methylphenyl)pentanoic acid (8).

Trifluoroacetic acid (20 mL) was added to triester **7** (12.85 g, 32.80 mmol) and the reaction stirred at RT for 90 min. Solvent was removed under reduced pressure and the crude diluted with water. It was extracted 3 times with diethyl ether, then the combined extracts were dried over MgSO₄ and the solvents removed under reduced pressure. The crude material was purified by chromatography on silica (0–10% methanol/DCM) to give the acid **6** as a yellow oil (6.80 g, 62%).

¹H NMR (CHLOROFORM-d, 300MHz): δ (ppm) 7.06 – 7.16 (m, 4H), 4.24 (q, *J*=7.1 Hz, 4H), 3.13 (s, 2H), 2.51 – 2.62 (m, 2H), 2.28 (s, 3H), 2.20 – 2.30 (m, 2H), 1.28 (t, *J*=7.2 Hz, 6H).

7,7-Diethyl 1-methyl-5-oxo-6,7,8,9-tetrahydro-5H-benzo[7]annulene-7,7-dicarboxylate (9).

To acid **8** (6.80 g, 20.22 mmol) in DCM (100 mL) cooled in ice under N₂ was added a drop of DMF then oxalyl chloride (7.70 g, 5.1 mL, 60.65 mmol) was added slowly and the reaction stirred at RT for 3 hr. All solvents were removed under reduced pressure and the crude redissolved in DCM (30 mL). This solution was added slowly via addition funnel to a solution of aluminum chloride (10.78 g, 80.86 mmol) in DCM (70 mL) cooled in ice under N₂ and the resulting mixture was allowed to warm to RT overnight. The reaction was quenched cautiously with water then made acidic with 2N HCl. The layers were separated and the aqueous portion extracted once more with DCM. The combined organics were dried over MgSO₄ and the solvent was removed under reduced pressure. The crude was purified by chromatography on silica (0–30% EtOAc/hexane) to give the desired (3.30 g, 51%) as a clear oil.

¹H NMR (CHLOROFORM-d, 300MHz): δ (ppm) 7.46 (d, *J*=7.7 Hz, 1H), 7.25 – 7.31 (m, 1H), 7.12 – 7.19 (m, 1H), 4.05 (q, *J*=7.2 Hz, 2H), 4.04 (q, *J*=7.1 Hz, 2H), 3.31 (s, 2H), 2.92 – 3.00 (m, 2H), 2.52 – 2.59 (m, 2H), 2.36 (s, 3H), 1.18 (t, *J*=7.2 Hz, 6H).

1-Methyl-5-oxo-6,7,8,9-tetrahydro-5H-benzo[7]annulene-7-carboxylic acid (2).

6N Hydrochloric acid (95 mL) was added to a solution of diester **9** (3.30 g, 10.37 mmol) in 1,4-dioxane (30 mL) and the reaction was heated at reflux overnight. It was cooled and diluted with water, then extracted 3 times with diethyl ether. The combined extracts were dried over MgSO₄ and the solvent was removed under reduced pressure to give the acid **2** (2.26 g, 100%) as an off-white solid.

¹H NMR (CHLOROFORM-d, 300MHz): δ (ppm) 7.45 (d, $J=7.5$ Hz, 1H), 7.31 (d, $J=7.3$ Hz, 1H), 7.15 – 7.23 (m, 1H), 2.95 – 3.11 (m, 3H), 2.76 – 2.92 (m, 2H), 2.37 (s, 3H), 2.06 – 2.28 (m, 2H).

¹³C NMR (CHLOROFORM-d, 75MHz): δ (ppm) 203.8, 178.8, 139.3, 138.0, 135.9, 134.1, 126.7, 126.3, 42.4, 38.1, 27.5, 25.9, 19.6.

Diethyl 2-(2,6-dichlorophenyl)-4-hydroxy-4-methyl-6-oxocyclohexane-1,3-dicarboxylate (11).

2,6-Dichlorobenzaldehyde (**10**) (5.0 g, 28.57 mmol) and ethyl acetoacetate (7.44 g, 7.2 mL, 57.14 mmol) were combined in absolute ethanol (20 mL), then piperidine (0.49 g, 0.6 mL, 5.71 mmol) was added dropwise. The reaction was stirred under N₂ overnight, then an additional aliquot of piperidine (0.6 mL) was added. After stirring for a further 24 hr, the solvent was removed under reduced pressure and the viscous oil allowed to stand until the whole oil solidified (approximately 24–48 hr). The solid was rinsed with diethyl ether and collected by filtration to give the desired product (8.10 g, 68%). ¹H NMR matches literature values.²¹

¹H NMR (CHLOROFORM-d, 300MHz): δ (ppm) 12.51 (br. s., 1H), 7.19 – 7.30 (m, 2H), 7.03 – 7.12 (m, 1H), 5.03 (d, $J=11.1$ Hz, 1H), 3.82 – 4.14 (m, 5H), 3.12 (d, $J=11.1$ Hz, 1H), 2.50 (s, 2H), 1.34 (s, 3H), 1.00 (t, $J=7.1$ Hz, 3H), 0.87 (t, $J=7.2$ Hz, 3H).

3-(2,6-Dichlorophenyl)pentanedioic acid (12).

A solution of sodium hydroxide (8.09 g, 202 mmol) in water (30 mL) was added to diester **11** (4.22 g, 10.11 mmol) in ethanol (30 mL) and the mixture heated at reflux for 3 hr. The reaction was cooled, the ethanol removed under reduced pressure and the aqueous solution acidified with 6N HCl. The solution was extracted 3 times with EtOAc, the combined extracts were dried over MgSO₄ and the solvent was removed under reduced pressure to give the di-acid (2.80 g, 100%) as a brown solid. ¹H NMR matches literature values.²¹

¹H NMR (CHLOROFORM-d, 300MHz): δ (ppm) 9.77 (br. s, 2H), 7.36 (d, $J=8.1$ Hz, 1H), 7.21 – 7.32 (m, 1H), 7.07 – 7.18 (m, 1H), 4.81 (tt, $J=10.6, 3.7$ Hz, 1H), 3.33 (dd, $J=15.3, 10.7$ Hz, 2H), 2.67 (dd, $J=15.3, 3.8$ Hz, 2H).

4-(2,6-Dichlorophenyl)piperidine-2,6-dione (13).

Di-acid **12** (3.58 g, 12.92 mmol) was suspended in concentrated ammonium hydroxide solution (28–30%, 80 mL), dissolved as far as possible via sonication and mixing. The mixture was stirred for 45 min then heated to boil away the liquid. The remaining dry residue was heated at 190°C for 3 days. The reaction was cooled and the residue dissolved in

DCM. The solution was washed with 0.1N NaOH solution, dried over MgSO₄ and the solvent was removed under reduced pressure to give the desired product (1.12 g, 34%) as a brown solid. ¹H NMR match literature values.²¹

¹H NMR (CHLOROFORM-d, 300MHz): δ (ppm) 8.25 (br. s., 1H), 7.29 – 7.45 (m, 2H), 7.16 – 7.23 (m, 1H), 4.39 (tt, *J*=13.7, 4.4 Hz, 1H), 3.62 (dd, *J*=17.7, 13.8 Hz, 2H), 2.71 (dd, *J*=17.5, 4.3 Hz, 2H).

4-(2,6-Dichlorophenyl)piperidine (**3**).

To a solution of imide **13** (1.12 g, 4.34 mmol) in anhydrous THF (50 mL) cooled in ice under N₂ was added dropwise borane-dimethylsulfide complex (as a 2M solution in THF, 21.7 mL, 43.4 mmol). Upon completion of addition, the reaction was warmed to RT then heated at reflux for 3 hr. The reaction was then cooled in ice and carefully quenched with 2N HCl, then heated at reflux again for 3 hr. The reaction was cooled and the volatile solvents were removed under reduced pressure. The reaction was diluted with water, the pH adjusted to above 7 with 2N NaOH solution then extracted 3 times with EtOAc. The combined extracts were dried over MgSO₄ and the solvent was removed under reduced pressure. The crude was taken up in DCM and 2N HCl in diethyl ether was added until acidic, then all the solvents were removed under reduced pressure. The residue was triturated with diethyl ether and the solid formed was collected by filtration as the desired piperidine **3** (1.01 g, 87%). ¹H and ¹³C NMR match literature values.²¹

¹H NMR (CHLOROFORM-d, 300MHz): δ (ppm) 9.53 – 10.01 (m, 2H), 7.22 – 7.37 (m, 2H), 7.11 (t, *J*=8 Hz, 1H), 3.71 – 3.84 (m, 1H), 3.57 – 3.71 (m, 2H), 2.91 – 3.19 (m, 4H), 1.82 (m, 2H).

¹³C NMR (CHLOROFORM-d, 75MHz): δ (ppm) 137.0, 135.3, 130.3, 128.6, 44.8, 38.3, 24.8.

7-[4-(2,6-Dichlorophenyl)piperidine-1-carbonyl]-1-methyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (**14**).

To acid **2** (0.15 g, 0.687 mmol) in DCM (10 mL) cooled in ice under N₂ was added oxalyl chloride (0.262 g, 0.17 mL, 2.062 mmol). The reaction was allowed to warm slowly to RT overnight then all solvents were removed under reduced pressure. The residue was redissolved in DCM (5 mL) then added slowly to a solution of piperidine **3** (0.183 g, 0.687 mmol) and diisopropylethylamine (0.266 g, 0.36 mL, 2.062 mmol) in DCM (5 mL) cooled in ice under N₂. The reaction was allowed to warm to RT slowly overnight. Water was added and the layers separated. The organic phase was washed with 1N HCl solution, dried over MgSO₄ and then the solvent removed under reduced pressure. The crude was then purified by chromatography on silica (0–50% EtOAc/hexane) to give the amide as a tan solid (0.133 g, 45%).

¹H NMR (CHLOROFORM-d, 300MHz): δ (ppm) 7.56 (d, *J*=5.5 Hz, 1H), 7.28 – 7.37 (m, 2H), 7.16 – 7.25 (m, 2H), 7.03 – 7.12 (m, 1H), 4.81 (d, *J*=12.4 Hz, 1H), 3.90 (d, *J*=12.6 Hz, 1H), 3.70 – 3.83 (m, 1H), 3.20 – 3.35 (m, 1H), 2.94 – 3.19 (m, 4H), 2.72 – 2.84 (m, 1H),

2.59 – 2.71 (m, 1H), 2.50 (qd, $J=12.7$, 4.0 Hz, 2H), 2.38 (d, $J=4.0$ Hz, 3H), 2.12 – 2.32 (m, 1H), 1.86 – 2.02 (m, 1H), 1.64 (d, $J=13.0$ Hz, 2H).

^{13}C NMR (CHLOROFORM- d , 75MHz): δ (ppm) 204.2, 172.5, 139.3, 138.3, 136.0, 133.9, 130.5, 128.7, 128.1, 126.5, 126.4, 46.5, 43.8, 43.1, 40.4, 35.1, 26.1, 20.0.

Methyl 1-methyl-5-oxo-6,7,8,9-tetrahydro-5H-benzo[7]annulene-7-carboxylate (15).

To a solution of acid **2** (2.26 g, 10.36 mmol) in DCM (50 mL) cooled in ice under N_2 was added oxalyl chloride (3.94 g, 2.6 mL, 31.07 mmol) and after initial reaction had subsided, the solution was stirred at RT overnight. Solvents were removed under reduced pressure, the residue was redissolved in DCM (50 mL) and cooled in ice. Methanol (20 mL) was added and the mixture stirred at RT for 1.5 hr. The reaction was diluted with water and the layers separated. The aqueous portion was extracted with DCM then the combined organic portions were dried over MgSO_4 and the solvent removed under reduced pressure to give the methyl ester (2.41 g, quant.). ^1H NMR matches literature values.²²

^1H NMR (CHLOROFORM- d , 300MHz): δ (ppm) 7.44 (d, $J=7.5$ Hz, 1H), 7.30 (d, $J=7.2$ Hz, 1H), 7.15 – 7.22 (m, 1H), 3.62 (s, 3H), 2.95 – 3.07 (m, 3H), 2.77 – 2.89 (m, 2H), 2.37 (s, 3H), 2.02 – 2.30 (m, 2H).

Methyl 5-hydroxy-1-methyl-6,7,8,9-tetrahydro-5H-benzo[7]annulene-7-carboxylate (16).

To a solution of ketone **15** (2.41 g, 10.36 mmol) in THF (50 mL) cooled in ice under N_2 was added slowly borane dimethylsulfide (2M in THF, 5.2 mL, 10.36 mmol). Reaction was stirred at RT overnight. The reaction was quenched carefully with methanol then all solvents were removed under reduced pressure. The crude was redissolved in methanol and concentrated again, then this was repeated once more. The crude was purified by chromatography on silica (0–40% EtOAc/hexane) to give the desired as a clear oil (1.90 g, 70%). ^1H NMR matches literature values.²²

^1H NMR (CHLOROFORM- d , 300MHz): δ (ppm) 7.02 – 7.42 (m, 3H), 4.97 – 5.09 (m, 1H), 3.64 – 3.70 (m, 2H), 2.99 – 3.23 (m, 1H), 2.86 (ddd, $J=15.3$, 8.0, 3.1 Hz, 1H), 2.50 (dd, $J=14.7$, 11.7 Hz, 1H), 2.32 (s, 3H), 2.10 – 2.31 (m, 2H), 1.97 – 2.10 (m, 2H), 1.84 – 1.92 (m, 1H), 1.67 – 1.81 (m, 1H).

($\pm$)-6-Methyl-12-oxa-tricyclo[8.2.1.0]trideca-2,4,6-trien-11-one (17).

To a solution of hydroxyl ester **16** (0.75 g, 3.20 mmol) (as a mixture of diastereomers) in DCM (10 mL) was added p-toluene sulfonic acid monohydrate (1.02 g, 5.12 mmol) and the solution stirred at RT for 6 hr. Water was added, the layers separated and the aqueous layer extracted with DCM. The combined organic fractions were washed with brine, dried over MgSO_4 and the solvent was removed under reduced pressure. Purification by chromatography on silica (0–2% EtOAc/DCM). Desired lactone isolated as a white solid (0.27 g, 42%). ^1H NMR matches literature values.²²

^1H NMR (CHLOROFORM- d , 300MHz): δ (ppm) 7.10 – 7.18 (m, 1H), 7.06 (t, $J=7.5$ Hz, 1H), 6.96 – 7.02 (m, 1H), 5.44 (d, $J=8.5$ Hz, 1H), 3.15 (dt, $J=16.4$, 3.9 Hz, 1H), 2.96 – 3.03

(m, 1H), 2.72 – 2.91 (m, 2H), 2.36 – 2.47 (m, 1H), 2.35 (s, 3H), 1.96 (d, $J=12.4$ Hz, 1H), 1.87 (tdd, $J=13.8, 3.1, 1.6$ Hz, 1H).

^{13}C NMR (CHLOROFORM- d , 75MHz): δ (ppm) 179.7, 139.4, 137.5, 137.4, 131.2, 126.6, 126.1, 84.7, 40.9, 37.3, 31.9, 26.3, 21.2.

($\pm$)-6-Methyl-12-oxatricyclo[8.2.1.0]trideca-2,4,6-trien-11-ol (18**).**

To a solution of lactone **17** (1.32 g, 6.53 mmol) in toluene (40 mL) cooled to -60°C was added diisobutylaluminum hydride (1M in toluene, 6.5 mL, 6.53 mmol). The reaction was stirred at -60°C for 1 hr, then methanol (50 mL) was added at -50°C , followed by a saturated solution of potassium sodium tartrate (100 mL) and the mixture allowed to warm to RT. The layers were separated, the aqueous portion was extracted 3 times with EtOAc, then the combined organics were dried over MgSO_4 and the solvent was removed under reduced pressure to give the lactol as a white solid (1.00 g, 75%). ^1H NMR matches literature values.²²

^1H NMR (CHLOROFORM- d , 300MHz): δ (ppm) 6.96 – 7.07 (m, 2H), 6.90 – 6.95 (m, 1H), 5.57 (d, $J=3.0$ Hz, 1H), 5.20 (d, $J=8.9$ Hz, 1H), 2.78 – 3.03 (m, 3H), 2.68 (dddd, $J=11.9, 8.7, 6.7, 1.7$ Hz, 1H), 2.50 – 2.58 (m, 1H), 2.31 (s, 3H), 2.04 – 2.16 (m, 1H), 1.53 – 1.68 (m, 1H).

^{13}C NMR (CHLOROFORM- d , 75MHz): δ (ppm) 142.9, 138.1, 136.8, 129.8, 125.5, 125.4, 102.0, 84.5, 43.8, 37.4, 30.2, 25.4, 21.0.

($\pm$)-*cis*-1-Methyl-7{[4-(2,6-dichlorophenyl)piperidin-1-yl]methyl}-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol (1**).**

Method 1 (from amide **14**): A solution of aluminum chloride (0.173 g, 1.298 mmol) in diethyl ether (8 mL) was added dropwise via addition funnel to a solution of lithium aluminum hydride (0.047 g, 1.236 mmol) in ether (8 mL) cooled in ice under N_2 . The resulting mixture was stirred for 10 min then a solution of amide **14** (0.133 g, 0.309 mmol) in ether (8 mL) was added dropwise. The mixture was warmed to RT and stirred for 4 hr. The reaction was cooled again in ice and quenched by addition of water, 2N NaOH solution and water. Layers were separated and the aqueous portion was extracted with ether. Combined organic fractions were dried over MgSO_4 and the solvent was removed under reduced pressure. The crude was purified by chromatography on silica (0–40% EtOAc/hexane) to obtain the desired *cis*-isomer (0.018 g, 14%).

Method 2 (from lactol **18**, Table 1, entry 1): A solution of piperidine **3** (free-base) (0.25 g, 1.10 mmol) in anhydrous methanol (3 mL) was added to a solution of lactol **18** (0.15 g, 0.73 mmol) in methanol (7 mL) and the mixture was heated to 50°C for 2 hr. The reaction was cooled in ice and sodium borohydride (28 mg, 0.73 mmol) was added portionwise, and then the reaction allowed to stir at RT overnight. The reaction was cooled again in ice and quenched with water and then the methanol was removed under reduced pressure. The solution was extracted 3 times with EtOAc and the combined extracts were dried over MgSO_4 and the solvent removed under reduced pressure. Purification by chromatography on

silica (0–40% MMA-80 (80:18:2 DCM/MeOH/NH₄OH) in DCM) gave the desired product **1** (15 mg, 5%) as well as diol **19** (100 mg, 66%).

Method 3 (from lactol **18**, Table 1, entry 8): Lactol **18** (0.24 g, 1.16 mmol) and piperidine hydrochloride **3** (0.31 g, 1.16 g) were combined in 1,2-dichloroethane (15 mL) and sodium triacetoxyborohydride (0.99 g, 4.65 mmol) was added portionwise. The reaction was stirred under N₂ at RT overnight then quenched by the addition of aqueous NaHCO₃ solution. The solution was extracted 3 times with DCM, then the combined extracts were dried over MgSO₄ and the solvent was removed under reduced pressure. Purification by chromatography on silica (0–40% EtOAc/hexane) gave the desired as a white solid (0.33 g, 67%). ¹H NMR matches literature report.^{20,22}

¹H NMR (CHLOROFORM-d, 300MHz): δ (ppm) 7.43 (d, *J*=7.3 Hz, 1H), 7.19 – 7.34 (m, 2H), 7.10 – 7.18 (m, 1H), 7.00 – 7.10 (m, 2H), 5.04 (d, *J*=10.2 Hz, 1H), 3.48 (tt, *J*=12.5, 3.7 Hz, 1H), 3.14 (dd, *J*=14.8, 7.4 Hz, 1H), 2.92 – 3.04 (m, 2H), 2.56 – 2.72 (m, 2H), 2.46 (dd, *J*=14.5, 11.9 Hz, 1H), 2.33 (s, 3H), 2.25 (d, *J*=13.2 Hz, 1H), 1.97 – 2.18 (m, 6H), 1.53 (d, *J*=12.4 Hz, 2H), 1.29 – 1.40 (m, 1H), 0.78 – 0.93 (m, 1H).

¹³C NMR (CHLOROFORM-d, 75MHz): δ (ppm) 145.1, 139.8, 138.2, 134.8, 130.2, 128.6, 127.5, 125.8, 120.6, 71.7, 65.6, 55.2, 55.2, 42.7, 40.8, 38.4, 31.0, 27.9, 27.3, 20.3.

MS (ESI) *m/z* 418 (M+H).

(±)-*cis*-7-(Hydroxymethyl)-1-methyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-ol (**19**).

¹H NMR (CHLOROFORM-d, 300MHz): δ (ppm) 7.42 (d, *J*=7.5 Hz, 1H), 7.10 – 7.18 (m, 1H), 7.03 – 7.10 (m, 1H), 5.04 (d, *J*=10.4 Hz, 1H), 3.41 – 3.52 (m, 2H), 3.15 (dd, *J*=14.6, 7.8 Hz, 1H), 2.48 (dd, *J*=14.7, 11.9 Hz, 1H), 2.33 (s, 3H), 1.97 – 2.22 (m, 4H), 1.32 – 1.47 (m, 1H), 0.86 – 1.03 (m, 1H).

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References

- (1). Bunzow JR; Saez C; Mortrud M; Bouvier C; Williams JT; Low M; Grandy DK FEBS Lett 1994, 347, 284. [PubMed: 8034019]
- (2). Fukuda K; Kato S; Mori K; Nishi M; Takeshima H; Iwabe N; Miyata T; Houtani T; Sugimoto T FEBS Lett 1994, 343, 42. [PubMed: 8163014]
- (3). Mollereau C; Parmentier M; Mailleux P; Butour JL; Moisand C; Chalon P; Caput D; Vassart G; Meunier JC FEBS Lett 1994, 341, 33. [PubMed: 8137918]
- (4). Pan YX; Cheng J; Xu J; Rossi G; Jacobson E; Ryan-Moro J; Brooks AI; Dean GE; Standifer KM; Pasternak GW Mol Pharmacol 1995, 47, 1180. [PubMed: 7603458]
- (5). Wang JB; Johnson PS; Imai Y; Persico AM; Ozenberger BA; Eppler CM; Uhl GR FEBS Lett 1994, 348, 75. [PubMed: 8026588]
- (6). Foord SM; Bonner TI; Neubig RR; Rosser EM; Pin JP; Davenport AP; Spedding M; Harmar AJ Pharmacol Rev 2005, 57, 279. [PubMed: 15914470]

- (7). Henderson G; McKnight AT Trends in pharmacological sciences 1997, 18, 293. [PubMed: 9277133]
- (8). Calo G; Guerrini R; Rizzi A; Salvadori S; Regoli D Br J Pharmacol 2000, 129, 1261. [PubMed: 10742280]
- (9). Civelli O; Nothacker HP; Reinscheid R Critical reviews in neurobiology 1998, 12, 163. [PubMed: 9847053]
- (10). Mogil JS; Pasternak GW Pharmacol Rev 2001, 53, 381. [PubMed: 11546835]
- (11). Lambert DG Nat Rev Drug Discov 2008, 7, 694. [PubMed: 18670432]
- (12). Largent-Milnes TM; Vanderah TW Expert opinion on therapeutic patents 2010, 20, 291. [PubMed: 20180617]
- (13). Toledo MA; Pedregal C; Lafuente C; Diaz N; Martinez-Grau MA; Jimenez A; Benito A; Torrado A; Mateos C; Joshi EM; Kahl SD; Rash KS; Mudra DR; Barth VN; Shaw DB; McKinzie D; Witkin JM; Statnick MA J Med Chem 2014, 57, 3418. [PubMed: 24678969]
- (14). Kawamoto H; Ozaki S; Itoh Y; Miyaji M; Arai S; Nakashima H; Kato T; Ohta H; Iwasawa Y J Med Chem 1999, 42, 5061. [PubMed: 10602690]
- (15). Yamada H; Nakamoto H; Suzuki Y; Ito T; Aisaka K Br J Pharmacol 2002, 135, 323. [PubMed: 11815367]
- (16). Spagnolo B; Carra G; Fantin M; Fischetti C; Hebbes C; McDonald J; Barnes TA; Rizzi A; Trapella C; Fanton G; Morari M; Lambert DG; Regoli D; Calo G The Journal of pharmacology and experimental therapeutics 2007, 321, 961. [PubMed: 17329552]
- (17). Rizzi A; Gavioli EC; Marzola G; Spagnolo B; Zucchini S; Ciccocioppo R; Trapella C; Regoli D; Calo G The Journal of pharmacology and experimental therapeutics 2007, 321, 968. [PubMed: 17329551]
- (18). Zaratin PF; Petrone G; Sbacchi M; Garnier M; Fossati C; Petrillo P; Ronzoni S; Giardina GA; Scheideler MA The Journal of pharmacology and experimental therapeutics 2004, 308, 454. [PubMed: 14593080]
- (19). Zaveri NT J Med Chem 2016, 59, 7011. [PubMed: 26878436]
- (20). Kiguchi N; Ding H; Ko MC Adv Pharmacol 2016, 75, 217. [PubMed: 26920014]
- (21). Toll L; Bruchas MR; Calo G; Cox BM; Zaveri NT Pharmacol Rev 2016, 68, 419. [PubMed: 26956246]
- (22). Barlocco D; Cignarella G; Giardina G; Grugni M; Ronzoni S In PCT Int. Appl; C07D211-14 ed.; Organization, W. I. P., Ed.; Smithkline Beecham S.p.A., Italy: 2001, p 47.
- (23). Trapella C; Fischetti C; Pela M; Lazzari I; Guerrini R; Calo G; Rizzi A; Camarda V; Lambert DG; McDonald J; Regoli D; Salvadori S Bioorganic & medicinal chemistry 2009, 17, 5080. [PubMed: 19527931]
- (24). Palombi G; Ronzoni S In PCT Int. Appl; C07D 211/22 ed.; Organization, W. I. P., Ed.; GlaxoSmithKline S.P.A.: 2003.
- (25). Rana S; Natarajan A Organic & biomolecular chemistry 2013, 11, 244. [PubMed: 23160888]
- (26). Tajbakhsh M; Hosseinzadeh R; Alinezhad H; Ghahari S; Heydari A; Khaksar S Synthesis-Stuttgart 2011, 490.

Figure 1.
Representative NOP antagonists

Figure 2.
Synthetic approach to SB612111

Scheme 1.
Synthesis of benzoheptanone acid **2**

Scheme 2.
Synthesis of 4-aryl piperidine **3**

Scheme 3.
SB612111 synthesis via amide

Scheme 4.
Diastereoselective synthesis of SB612111 via lactone

Table 1.Comparison of reductive amination conditions to form *cis*-(**1**).

Entry	Ratio of 18:3	Conditions	Reducing Agent	Solvent	Isolated Yield
1	2:3	Preformed imine (2 hr at 50°C); NaBH ₄ added at 0°C; RT 16 hr.	1 eq. NaBH ₄	MeOH	5%
2	1:1	Preformed imine (5 min at 40°C); NaBH ₄ added then RT 16 hr.	2 eq. NaBH ₄	CF ₃ CH ₂ OH	< 5%
3	1:1	Preformed imine (5 min at 40°C); NaBH ₃ CN added then RT 16 hr.	2 eq. NaBH ₃ CN	CF ₃ CH ₂ OH	< 5%
4	3:2	All reagents mixed with 1:1 ratio 18:3 ; additional 0.5 eq. 18 added after 16 hr; stirred additional 24 hr.	4 eq. NaBH ₃ CN	AcOH (2 eq), MeOH	40%
5	3:2	All reagents mixed; RT for 16 hr.	4 eq. NaBH ₃ CN	AcOH (2 eq), MeOH	28%
6	1:1	All reagents mixed; RT for 16 hr.	2 eq. NaBH(OAc) ₃	1,2-DCE	40%
7	1:1	All reagents mixed; RT for 16 hr.	4 eq. NaBH(OAc) ₃	1,2-DCE	52%
8	1:1	All reagents mixed; RT 16 hr; aq. NaHCO ₃ quench.	4 eq. NaBH(OAc) ₃	1,2-DCE	67%