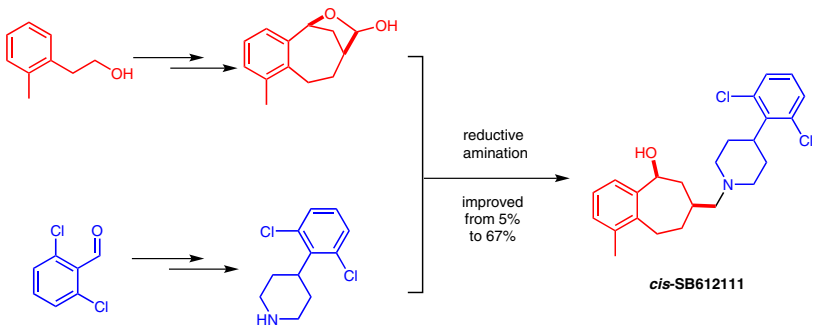
Synthesis D. A. Perrey et al. Paper

Modified Synthesis of NOP Receptor Antagonist SB612111

David A. Perrey[a]
Jun-Xu Li[b]
Yanan Zhang*[a]

[a] Research Triangle Institute, Research Triangle Park, NC 27709, USA
yzhang@rti.org
[b] Department of Pharmacology and Toxicology, University at Buffalo, Buffalo, NY 14214, USA



Received: 09.09.2016
Accepted after revision: 27.11.2016
Published online: 19.12.2016
DOI: 10.1055/s-0036-1588379; Art ID: ss-2016-m0600-op

Abstract SB612111 [(5*S*,7*S*)-7-{[4-(2,6-dichlorophenyl)piperidin-1-yl]methyl}-1-methyl-6,7,8,9-tetrahydro-5*H*-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 in the route to the key intermediate 4-(2,6-dichlorophenyl)piperidine, the reduction of 7-[4-(2,6-dichlorophenyl)piperidine-1-carbonyl]-1-methyl-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-one, the formation of (±)-6-methyl-12-oxatricyclo[8.2.1.$0^{2,7}$]trideca-2,4,6-trien-11-one, and the final reductive amination between (±)-6-methyl-12-oxatricyclo[8.2.1.$0^{2,7}$]trideca-2,4,6-trien-11-ol and 4-(2,6-dichlorophenyl)piperidine 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.

Key words 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 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-5*H*-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]

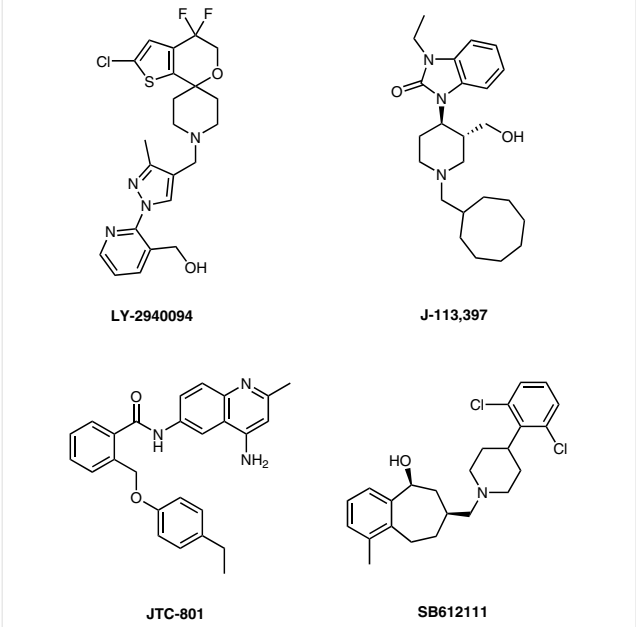
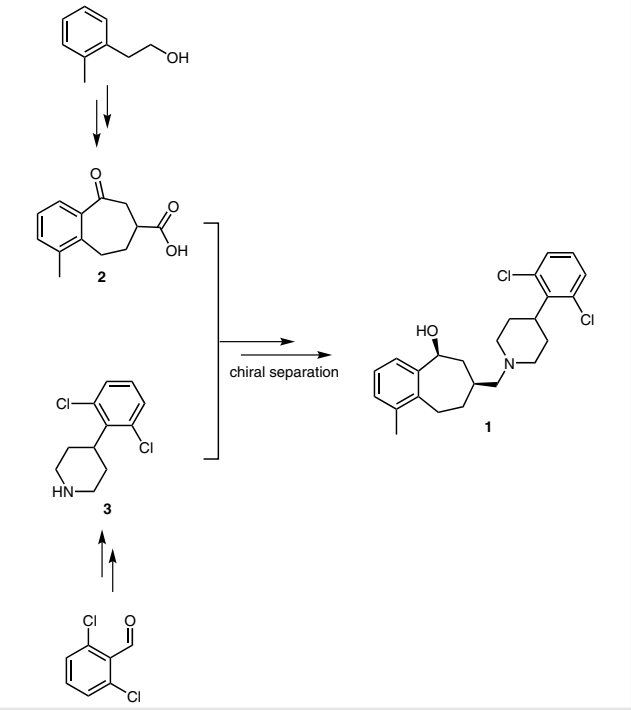


Figure 1 Representative NOP antagonists

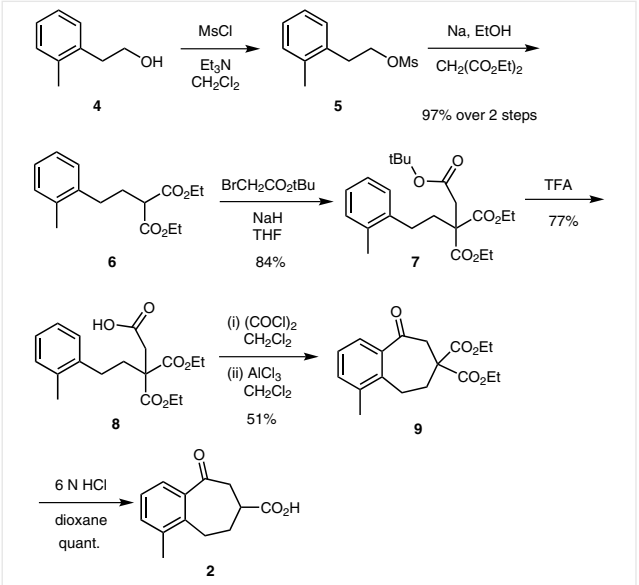
In an effort to investigate the potential role of the NOP receptor in drug addiction, particularly in mediating relapse of drugs such as nicotine,[20,21] access to grams of SB612111 was required. We initially aimed to prepare the more accessible *cis*-diastereomeric mixture of **1** following procedures described in a patent by GSK (Scheme 1).[22] Ac-

cording 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 (Scheme 1). 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.



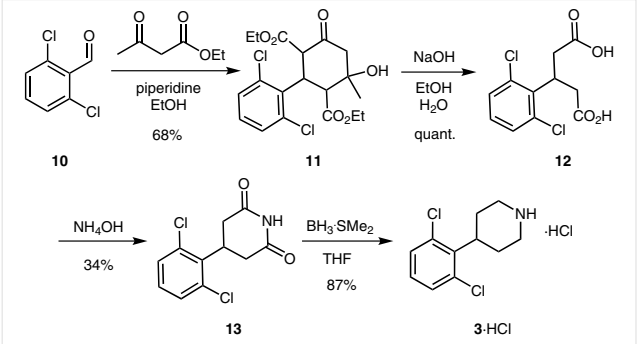
Scheme 1 Synthetic approach to SB612111

The synthesis of acid **2** proceeded as expected in similar yields following the patent procedure (Scheme 2), 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 *tert*-butyl bromoacetate gave the triester **7** in high yield (81% over 3 steps, vs. 65% reported). After removal of the *tert*-butyl group of **7** with TFA and conversion into 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 *tert*-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).



Scheme 2 Synthesis of benzoheptanone acid **2**

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 3). 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, and extended reaction times also did not afford any improvement.

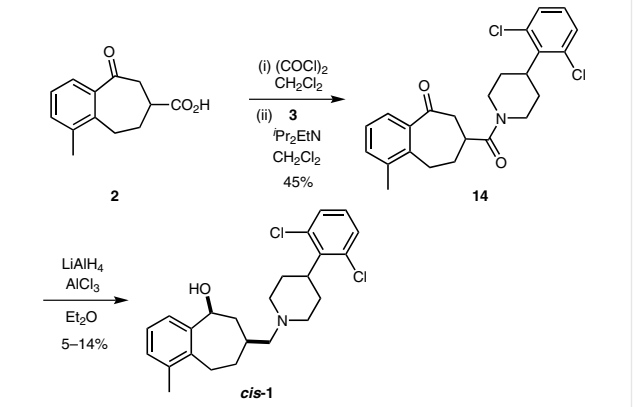


Scheme 3 Synthesis of 4-arylpiperidine **3**

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.

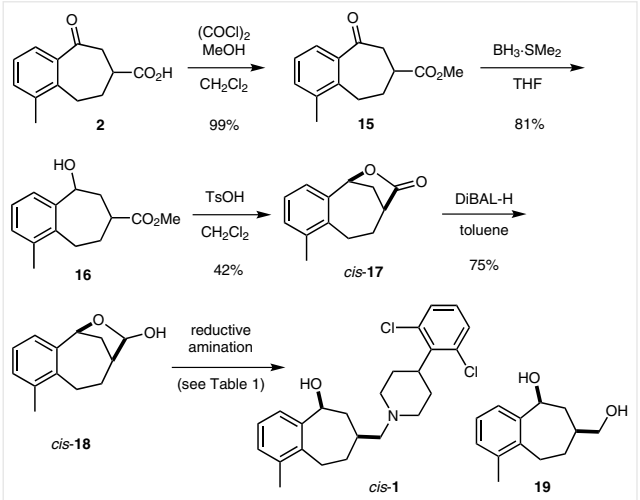
Hydrolysis of the diester **11** to the diacid **12** with sodium hydroxide proceeded in quantitative yield. Condensation of **12** with ammonium hydroxide at 190 °C gave the imide **13** in 34% without chromatography required. Finally, reduction of **13** to the piperidine **3** with borane–dimethyl sulfide proceeded in 87% yield with the piperidine isolated as the hydrochloride salt. This three-step sequence proceeded with similar yields as reported.[22]

With both components **2** and **3** in hand, amide coupling via the acid chloride (Scheme 4) gave the penultimate product **14** in 45% yield. Lithium aluminum hydride reduction in the presence of aluminum trichloride, 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.



Scheme 4 SB612111 synthesis via amide

The same GSK group later reported a modified diastereoselective synthesis in another patent.[24] Instead of diastereomeric separation of the final product, the new diastereoselective synthesis converted acid **2** into a lactone **17** (Scheme 5). Since only the *cis*-diastereomer could cyclize, this conversion allows for the facile separation from the *trans* analogues, which would remain as the hydroxy ester. Thus, acid **2** was converted into 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 4-toluenesulfonic acid[25] gave excellent conversion into **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 into 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.



Scheme 5 Diastereoselective synthesis of SB612111 via lactone

For the final reductive amination step, the literature procedure[24] 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 (Table 1, entry 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** into **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

Table 1 Comparison of Reductive Amination Conditions To Form *cis*-**1**

Entry	Ratio of **18**/**3**	Conditions	Reducing agent (equiv)	Solvent	Isolated yield (%)
1	2:3	1. preformed imine (50 °C, 2 h) 2. $NaBH_4$, 0 °C then r.t., 16 h	$NaBH_4$ (1)	MeOH	5
2	1:1	1. preformed imine (40 °C, 5 min) 2. $NaBH_4$, r.t., 16 h	$NaBH_4$ (2)	CF_3CH_2OH	<5
3	1:1	1. preformed imine (40 °C, 5 min) 2. $NaBH_3CN$, r.t., 16 h	$NaBH_3CN$ (2)	CF_3CH_2OH	<5
4	3:2	all reagents mixed (ratio **18**/**3** 1:1); at 16 h, **18** (0.5 equiv) added; then stirring 24 h	$NaBH_3CN$ (4)	AcOH (2 equiv), MeOH	40
5	3:2	all reagents mixed; r.t., 16 h	$NaBH_3CN$ (4)	AcOH (2 equiv), MeOH	28
6	1:1	all reagents mixed; r.t., 16 h	$NaBH(OAc)_3$ (2)	DCE	40
7	1:1	all reagents mixed; r.t., 16 h	$NaBH(OAc)_3$ (4)	DCE	52
8	1:1	all reagents mixed; r.t., 16 h; aq $NaHCO_3$ quench	$NaBH(OAc)_3$ (4)	DCE	67

3 were mixed and stirred at 40 °C for 5 minutes 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 the in situ formation of the 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 hydrogen carbonate 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**, the acid-catalyzed formation of lactone **17**, and the final reductive amination between **18** and **3**. Possible explanations of the differences include different batches of reagents used and scale 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.

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, EtOAc, and CH_2Cl_2. Purity and characterization of compounds was established by a combination of TLC, MS, and NMR analysis. ^1H NMR spectra were recorded on a Bruker Avance DPX-300 (300 MHz) spectrometer and were determined in $CDCl_3$ with TMS (δ = 0.00) or solvent peaks as the internal reference. TLC was done on EMD precoated silica gel 60 F254 plates, and spots were visualized with UV light or iodine staining. LR-MS were obtained using a Waters Alliance HT/Micromass ZQ system (ESI).

2-(2-Methylphenyl)ethyl Methanesulfonate (5)

To a solution of 2-(2-methylphenyl)ethanol (**4**, 5.0 g, 36.71 mmol) in anhyd CH_2Cl_2 (100 mL) cooled in ice under N_2 was added Et_3N (5.94 g, 8.2 mL, 58.74 mmol) then a solution of MsCl (6.73 g, 4.5 mL, 58.74 mmol) in CH_2Cl_2 (50 mL) was added slowly via addition funnel. This resulting solution was allowed to warm to r.t. overnight. Water was added and the layers separated. The organic fraction was concentrated in vacuo then redissolved in Et_2O. The solution was washed with 2 N HCl solution and $NaHCO_3$ solution, and dried ($MgSO_4$); the solvent removed under reduced pressure to give the desired sulfonate (7.87 g, 100%) as a clear liquid.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.13–7.20 (m, 4 H), 4.39 (t, *J* = 7.3 Hz, 2 H), 3.08 (t, *J* = 7.3 Hz, 2 H), 2.85 (s, 3 H), 2.35 (s, 3 H).

Diethyl 2-[2-(2-Methylphenyl)ethyl]propanedioate (6)

Na metal (1.55 g, 67.58 mmol) was dissolved in abs EtOH (50 mL) then diethyl malonate (16.24 g, 15.4 mL, 101.36 mmol) was added slowly to the solution at r.t. under N_2. The resulting mixture was stirred at r.t. for 30 min. A solution of the methanesulfonate **5** (7.24 g,

33.79 mmol) in EtOH (25 mL) was added dropwise via addition funnel. Upon complete addition, the mixture was heated at reflux for 3 h. The mixture was cooled and the solvent removed under reduced pressure. The crude was diluted with water and extracted Et_2O (3 ×). The combined extracts were washed with 2 N HCl and brine, and dried ($MgSO_4$); the solvent was removed under reduced pressure. Excess diethyl malonate was removed via N_2 blowdown to give the diester (9.13 g, 97%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.08–7.19 (m, 4 H), 4.21 (q, *J* = 7.2 Hz, 4 H), 3.34–3.44 (m, 1 H), 2.60–2.69 (m, 2 H), 2.31 (s, 3 H), 2.10–2.21 (m, 2 H), 1.28 (t, *J* = 7.2 Hz, 6 H).

2-*tert*-Butyl 1,1-Diethyl 1-[2-(2-Methylphenyl)ethyl]ethane-1,1,2-tricarboxylate (7)

To a solution of NaH (as a 60% dispersion in mineral oil, 3.45 g, 86.22 mmol) in anhyd 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 r.t. under N_2 for 30 min then *tert*-butyl bromoacetate (7.01 g, 5.3 mL, 35.93 mmol) was added dropwise and the resulting cloudy solution was stirred at r.t. under N_2 overnight. The mixture was cooled in ice and quenched with water, then extracted with Et_2O (2 ×). The combined extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure. Purification by chromatography (silica gel, CH_2Cl_2) gave the triester **5** (9.42 g, 84%) as a clear liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.07–7.15 (m, 4 H), 4.23 (q, *J* = 7.2 Hz, 4 H), 3.00 (s, 2 H), 2.51–2.59 (m, 2 H), 2.29 (s, 3 H), 2.16–2.24 (m, 2 H), 1.43 (s, 9 H), 1.28 (t, *J* = 7.2 Hz, 6 H).

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

TFA (20 mL) was added to triester **7** (12.85 g, 32.80 mmol) and the mixture stirred at r.t. for 90 min. Solvent was removed under reduced pressure and the crude diluted with water. It was extracted with Et_2O (3 ×), then the combined extracts were dried ($MgSO_4$) and the solvents removed under reduced pressure. The crude material was purified by chromatography (silica gel, 0–10% MeOH/CH_2Cl_2) to give the acid **6** (8.53 g, 77%) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.06–7.16 (m, 4 H), 4.24 (q, *J* = 7.1 Hz, 4 H), 3.13 (s, 2 H), 2.51–2.62 (m, 2 H), 2.28 (s, 3 H), 2.20–2.30 (m, 2 H), 1.28 (t, *J* = 7.2 Hz, 6 H).

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

To acid **8** (6.80 g, 20.22 mmol) in CH_2Cl_2 (100 mL) cooled in ice under N_2 was added a drop of DMF then oxalyl chloride (7.70 g, 5.1 mL, 60.65 mmol) was added slowly and the mixture was stirred at r.t. for 3 h. All solvents were removed under reduced pressure and the crude redissolved in CH_2Cl_2 (30 mL). This solution was added slowly via an addition funnel to a solution of $AlCl_3$ (10.78 g, 80.86 mmol) in CH_2Cl_2 (70 mL) cooled in ice under N_2, and the resulting mixture was allowed to warm up to r.t. overnight. The mixture was quenched cautiously with water then made acidic with 2 N HCl. The layers were separated and the aqueous portion extracted with CH_2Cl_2 (1 ×). The combined organics were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude was purified by chromatography (silica gel, 0–30% EtOAc/hexane) to give the product (3.30 g, 51%) as a clear oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 7.7 Hz, 1 H), 7.25–7.31 (m, 1 H), 7.12–7.19 (m, 1 H), 4.05 (q, *J* = 7.2 Hz, 2 H), 4.04 (q, *J* = 7.1 Hz, 2 H), 3.31 (s, 2 H), 2.92–3.00 (m, 2 H), 2.52–2.59 (m, 2 H), 2.36 (s, 3 H), 1.18 (t, *J* = 7.2 Hz, 6 H).

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

6 N HCl (95 mL) was added to a solution of diester **9** (3.30 g, 10.37 mmol) in 1,4-dioxane (30 mL) and the mixture was heated at reflux overnight. It was cooled and diluted with water, then extracted with Et_2O (3 ×). The combined extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure to give the acid **2** (2.26 g, 100%) as an off-white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45 (d, *J* = 7.5 Hz, 1 H), 7.31 (d, *J* = 7.3 Hz, 1 H), 7.15–7.23 (m, 1 H), 2.95–3.11 (m, 3 H), 2.76–2.92 (m, 2 H), 2.37 (s, 3 H), 2.06–2.28 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 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 abs EtOH (20 mL), then piperidine (0.49 g, 0.6 mL, 5.71 mmol) was added dropwise. The mixture was stirred under N_2 overnight, then an additional aliquot of piperidine (0.6 mL) was added. After stirring for a further 24 h, the solvent was removed under reduced pressure and the viscous oil allowed to stand until the whole oil solidified (approx. 24–48 h). The solid was rinsed with Et_2O and collected by filtration to give the product (8.10 g, 68%). ^{1}H NMR data matches that in the literature.[21]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.51 (br s, 1 H), 7.19–7.30 (m, 2 H), 7.03–7.12 (m, 1 H), 5.03 (d, *J* = 11.1 Hz, 1 H), 3.82–4.14 (m, 5 H), 3.12 (d, *J* = 11.1 Hz, 1 H), 2.50 (s, 2 H), 1.34 (s, 3 H), 1.00 (t, *J* = 7.1 Hz, 3 H), 0.87 (t, *J* = 7.2 Hz, 3 H).

3-(2,6-Dichlorophenyl)pentanedioic Acid (12)

A solution of NaOH (8.09 g, 202 mmol) in water (30 mL) was added to diester **11** (4.22 g, 10.11 mmol) in EtOH (30 mL) and the mixture heated at reflux for 3 h. The mixture was cooled, the EtOH was removed under reduced pressure, and the aqueous solution was acidified with 6 N HCl. The solution was extracted with EtOAc (3 ×), the combined extracts were dried ($MgSO_4$), and the solvent was removed under reduced pressure to give the diacid (2.80 g, 100%) as a brown solid. ^{1}H NMR data matches that in the literature.[21]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.77 (br s, 2 H), 7.36 (d, *J* = 8.1 Hz, 1 H), 7.21–7.32 (m, 1 H), 7.07–7.18 (m, 1 H), 4.81 (tt, *J* = 10.6, 3.7 Hz, 1 H), 3.33 (dd, *J* = 15.3, 10.7 Hz, 2 H), 2.67 (dd, *J* = 15.3, 3.8 Hz, 2 H).

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

Diacid **12** (3.58 g, 12.92 mmol) was suspended in concd NH_4OH 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 d. The mixture was cooled and the residue dissolved in CH_2Cl_2. The solution was washed with 0.1 N NaOH solution and dried ($MgSO_4$); the solvent was removed under reduced pressure to give the product (1.12 g, 34%) as a brown solid. ^{1}H NMR data matches that in the literature.[21]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.25 (br s, 1 H), 7.29–7.45 (m, 2 H), 7.16–7.23 (m, 1 H), 4.39 (tt, *J* = 13.7, 4.4 Hz, 1 H), 3.62 (dd, *J* = 17.7, 13.8 Hz, 2 H), 2.71 (dd, *J* = 17.5, 4.3 Hz, 2 H).

4-(2,6-Dichlorophenyl)piperidine Hydrochloride (3·HCl)

To a solution of imide **13** (1.12 g, 4.34 mmol) in anhyd THF (50 mL) cooled in ice under N_2 was added dropwise 2 M BH_3·SMe_2 in THF (21.7 mL, 43.4 mmol). Upon completion of the addition, the mixture was warmed to r.t. then heated at reflux for 3 h. The mixture was then cooled in ice and carefully quenched with 2 N HCl, then heated at reflux again for 3 h. The mixture was cooled and the volatile solvents were removed under reduced pressure. The mixture was diluted with water, the pH adjusted to >7 with 2 N NaOH solution then extracted with EtOAc (3 ×). The combined extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude was taken up in CH_2Cl_2 and 2 N HCl in Et_2O was added until acidic, then all the solvents were removed under reduced pressure. The residue was triturated (Et_2O) and the solid formed was collected by filtration as the piperidine **3** (1.01 g, 87%). ^{1}H and ^{13}C NMR data match that in the literature.[21]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.53–10.01 (m, 2 H), 7.22–7.37 (m, 2 H), 7.11 (t, *J* = 8 Hz, 1 H), 3.71–3.84 (m, 1 H), 3.57–3.71 (m, 2 H), 2.91–3.19 (m, 4 H), 1.82 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 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-5*H*-benzo[7]annulen-5-one (14)

To acid **2** (0.15 g, 0.687 mmol) in CH_2Cl_2 (10 mL) cooled in ice under N_2 was added oxalyl chloride (0.262 g, 0.17 mL, 2.062 mmol). The mixture was allowed to warm slowly to r.t. overnight then all solvents were removed under reduced pressure. The residue was redissolved in CH_2Cl_2 (5 mL) then added slowly to a solution of piperidine **3** (0.183 g, 0.687 mmol) and *i*-Pr_2EtN (0.266 g, 0.36 mL, 2.062 mmol) in CH_2Cl_2 (5 mL) cooled in ice under N_2. The mixture was allowed to warm to r.t. slowly overnight. Water was added and the layers separated. The organic phase was washed with 1 N HCl solution and dried ($MgSO_4$), and then the solvent removed under reduced pressure. The crude was then purified by chromatography (silica gel, 0–50% EtOAc/hexane) to give the amide (0.133 g, 45%) as a tan solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56 (d, *J* = 5.5 Hz, 1 H), 7.28–7.37 (m, 2 H), 7.16–7.25 (m, 2 H), 7.03–7.12 (m, 1 H), 4.81 (d, *J* = 12.4 Hz, 1 H), 3.90 (d, *J* = 12.6 Hz, 1 H), 3.70–3.83 (m, 1 H), 3.20–3.35 (m, 1 H), 2.94–3.19 (m, 4 H), 2.72–2.84 (m, 1 H), 2.59–2.71 (m, 1 H), 2.50 (qd, *J* = 12.7, 4.0 Hz, 2 H), 2.38 (d, *J* = 4.0 Hz, 3 H), 2.12–2.32 (m, 1 H), 1.86–2.02 (m, 1 H), 1.64 (d, *J* = 13.0 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 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-5*H*-benzo[7]annulene-7-carboxylate (15)

To a solution of acid **2** (2.26 g, 10.36 mmol) in CH_2Cl_2 (50 mL) cooled in ice under N_2 was added oxalyl chloride (3.94 g, 2.6 mL, 31.07 mmol) and after the initial reaction had subsided, the mixture was stirred at r.t. overnight. Solvents were removed under reduced pressure, the residue was redissolved in CH_2Cl_2 (50 mL) and cooled in ice. MeOH (20 mL) was added and the mixture stirred at r.t. for 1.5 h. The mixture was diluted with water and the layers separated. The aqueous portion was extracted with CH_2Cl_2, the combined organic portions were dried ($MgSO_4$), and the solvent was removed under reduced pressure to give the methyl ester (2.41 g, quant.). ^{1}H NMR data matches that in the literature.[22]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 7.5 Hz, 1 H), 7.30 (d, *J* = 7.2 Hz, 1 H), 7.15–7.22 (m, 1 H), 3.62 (s, 3 H), 2.95–3.07 (m, 3 H), 2.77–2.89 (m, 2 H), 2.37 (s, 3 H), 2.02–2.30 (m, 2 H).

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

To a solution of ketone **15** (0.92 g, 3.99 mmol) in THF (20 mL) cooled in ice under N_2 was added slowly BH_3·SMe_2 (2 M in THF; 2 mL, 3.99 mmol). The mixture was stirred at r.t. overnight. The reaction was quenched carefully with MeOH and then all solvents were removed under reduced pressure. The crude was redissolved in MeOH and concentrated again, then this was repeated once more. The crude was purified by chromatography (silica gel, 0–100% EtOAc/hexane) to give the product (0.75 g, 81%) as a clear oil. ^{1}H NMR data matches that in the literature.[22]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.02–7.42 (m, 3 H), 4.97–5.09 (m, 1 H), 3.64–3.70 (m, 2 H), 2.99–3.23 (m, 1 H), 2.86 (ddd, *J* = 15.3, 8.0, 3.1 Hz, 1 H), 2.50 (dd, *J* = 14.7, 11.7 Hz, 1 H), 2.32 (s, 3 H), 2.10–2.31 (m, 2 H), 1.97–2.10 (m, 2 H), 1.84–1.92 (m, 1 H), 1.67–1.81 (m, 1 H).

(±)-6-Methyl-12-oxatricyclo[8.2.1.0^{2,7}]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 CH_2Cl_2 (10 mL) was added TsOH·H_2O (1.02 g, 5.12 mmol) and the solution stirred at r.t. for 6 h. Water was added, the layers separated and the aqueous layer extracted with CH_2Cl_2. The combined organic fractions were washed with brine and dried ($MgSO_4$), and the solvent was removed under reduced pressure. Purification by chromatography (silica gel, 0–2% EtOAc/CH_2Cl_2) gave the product (0.27 g, 42%) as a white solid. ^{1}H NMR data matches that in the literature.[22]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.10–7.18 (m, 1 H), 7.06 (t, *J* = 7.5 Hz, 1 H), 6.96–7.02 (m, 1 H), 5.44 (d, *J* = 8.5 Hz, 1 H), 3.15 (dt, *J* = 16.4, 3.9 Hz, 1 H), 2.96–3.03 (m, 1 H), 2.72–2.91 (m, 2 H), 2.36–2.47 (m, 1 H), 2.35 (s, 3 H), 1.96 (d, *J* = 12.4 Hz, 1 H), 1.87 (tdd, *J* = 13.8, 3.1, 1.6 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 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.

(±)-6-Methyl-12-oxatricyclo[8.2.1.0^{2,7}]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 1 M DIBAL-H in toluene (6.5 mL, 6.53 mmol). The mixture was stirred at –60 °C for 1 h, then MeOH (50 mL) was added at –50 °C, followed by sat. potassium sodium tartrate solution (100 mL) and the mixture allowed to warm up to r.t. The layers were separated, the aqueous portion was extracted with EtOAc (3 ×), the combined organics were dried ($MgSO_4$), and the solvent was removed under reduced pressure to give the lactol (1.00 g, 75%) as a white solid. ^{1}H NMR data matches that in the literature.[22]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.96–7.07 (m, 2 H), 6.90–6.95 (m, 1 H), 5.57 (d, *J* = 3.0 Hz, 1 H), 5.20 (d, *J* = 8.9 Hz, 1 H), 2.78–3.03 (m, 3 H), 2.68 (dddd, *J* = 11.9, 8.7, 6.7, 1.7 Hz, 1 H), 2.50–2.58 (m, 1 H), 2.31 (s, 3 H), 2.04–2.16 (m, 1 H), 1.53–1.68 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 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.

(±)-*cis*-7-{[4-(2,6-Dichlorophenyl)piperidin-1-yl]methyl}-1-methyl-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-ol (1)

Method 1 (from amide **14**): A solution of $AlCl_3$ (0.173 g, 1.298 mmol) in Et_2O (8 mL) was added dropwise via addition funnel to a solution of $LiAlH_4$ (0.047 g, 1.236 mmol) in Et_2O (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 Et_2O (8 mL) was added dropwise. The mixture was warmed up to r.t. and stirred for 4 h. The mixture was cooled again in ice and quenched by the addition of water, 2 N NaOH solution, and water. The layers were separated and the aqueous portion was extracted with Et_2O. The combined organic fractions were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude was purified by chromatography (silica gel, 0–40% EtOAc/hexane) to obtain the *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 anhyd MeOH (3 mL) was added to a solution of lactol **18** (0.15 g, 0.73 mmol) in MeOH (7 mL) and the mixture was heated to 50 °C for 2 h. The mixture was cooled in ice and $NaBH_4$ (28 mg, 0.73 mmol) was added portionwise, and then the mixture was stirred at r.t. overnight. The mixture was cooled again in ice and quenched with water and then the MeOH was removed under reduced pressure. The solution was extracted with EtOAc (3 ×), the combined extracts were dried ($MgSO_4$), and the solvent removed under reduced pressure. Purification by chromatography (silica gel, 0–40% CH_2Cl_2/MeOH/NH_4OH (80:18:2)/CH_2Cl_2] gave the 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**·HCl (0.31 g, 1.16 g) were combined in DCE (15 mL) and $NaBH(OAc)_3$ (0.99 g, 4.65 mmol) was added portionwise. The mixture was stirred under N_2 at r.t. overnight then quenched by the addition of aq $NaHCO_3$ solution. The solution was extracted with CH_2Cl_2 (3 ×), then the combined extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure. Purification by chromatography (silica gel, 0–40% EtOAc/hexane) gave the product (0.33 g, 67%) as a white solid. ^{1}H NMR data matches that in the literature.[20,22]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 7.3 Hz, 1 H), 7.19–7.34 (m, 2 H), 7.10–7.18 (m, 1 H), 7.00–7.10 (m, 2 H), 5.04 (d, *J* = 10.2 Hz, 1 H), 3.48 (tt, *J* = 12.5, 3.7 Hz, 1 H), 3.14 (dd, *J* = 14.8, 7.4 Hz, 1 H), 2.92–3.04 (m, 2 H), 2.56–2.72 (m, 2 H), 2.46 (dd, *J* = 14.5, 11.9 Hz, 1 H), 2.33 (s, 3 H), 2.25 (d, *J* = 13.2 Hz, 1 H), 1.97–2.18 (m, 6 H), 1.53 (d, *J* = 12.4 Hz, 2 H), 1.29–1.40 (m, 1 H), 0.78–0.93 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 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-5*H*-benzo[7]annulen-5-ol (19)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 7.5 Hz, 1 H), 7.10–7.18 (m, 1 H), 7.03–7.10 (m, 1 H), 5.04 (d, *J* = 10.4 Hz, 1 H), 3.41–3.52 (m, 2 H), 3.15 (dd, *J* = 14.6, 7.8 Hz, 1 H), 2.48 (dd, *J* = 14.7, 11.9 Hz, 1 H), 2.33 (s, 3 H), 1.97–2.22 (m, 4 H), 1.32–1.47 (m, 1 H), 0.86–1.03 (m, 1 H).

Acknowledgment

This work was supported in part by National Institute on Drug Abuse, National Institutes of Health, USA (grants DA040693 and DA032837).

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588379.

References

(1) Bunzow, J. R.; Saez, C.; Mortrud, M.; Bouvier, C.; Williams, J. T.; Low, M.; Grandy, D. K. *FEBS Lett.* **1994**, *347*, 284.
(2) Fukuda, K.; Kato, S.; Mori, K.; Nishi, M.; Takeshima, H.; Iwabe, N.; Miyata, T.; Houtani, T.; Sugimoto, T. *FEBS Lett.* **1994**, *343*, 42.
(3) Mollereau, C.; Parmentier, M.; Mailleux, P.; Butour, J. L.; Moisand, C.; Chalon, P.; Caput, D.; Vassart, G.; Meunier, J. C. *FEBS Lett.* **1994**, *341*, 33.
(4) Pan, Y. X.; Cheng, J.; Xu, J.; Rossi, G.; Jacobson, E.; Ryan-Moro, J.; Brooks, A. I.; Dean, G. E.; Standifer, K. M.; Pasternak, G. W. *Mol. Pharmacol.* **1995**, *47*, 1180.
(5) Wang, J. B.; Johnson, P. S.; Imai, Y.; Persico, A. M.; Ozenberger, B. A.; Eppler, C. M.; Uhl, G. R. *FEBS Lett.* **1994**, *348*, 75.
(6) Foord, S. M.; Bonner, T. I.; Neubig, R. R.; Rosser, E. M.; Pin, J. P.; Davenport, A. P.; Spedding, M.; Harmar, A. J. *Pharmacol. Rev.* **2005**, *57*, 279.
(7) Henderson, G.; McKnight, A. T. *Trends Pharmacol. Sci.* **1997**, *18*, 293.
(8) Calo, G.; Guerrini, R.; Rizzi, A.; Salvadori, S.; Regoli, D. *Br. J. Pharmacol.* **2000**, *129*, 1261.
(9) Civelli, O.; Nothacker, H. P.; Reinscheid, R. *Crit. Rev. Neurobiol.* **1998**, *12*, 163.
(10) Mogil, J. S.; Pasternak, G. W. *Pharmacol. Rev.* **2001**, *53*, 381.
(11) Lambert, D. G. *Nat. Rev. Drug Discovery* **2008**, *7*, 694.
(12) Largent-Milnes, T. M.; Vanderah, T. W. *Expert Opin. Ther. Pat.* **2010**, *20*, 291.
(13) Toledo, M. A.; Pedregal, C.; Lafuente, C.; Diaz, N.; Martinez-Grau, M. A.; Jimenez, A.; Benito, A.; Torrado, A.; Mateos, C.; Joshi, E. M.; Kahl, S. D.; Rash, K. S.; Mudra, D. R.; Barth, V. N.; Shaw, D. B.; McKinzie, D.; Witkin, J. M.; Statnick, M. A. *J. Med. Chem.* **2014**, *57*, 3418.
(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.
(15) Yamada, H.; Nakamoto, H.; Suzuki, Y.; Ito, T.; Aisaka, K. *Br. J. Pharmacol.* **2002**, *135*, 323.
(16) Spagnolo, B.; Carra, G.; Fantin, M.; Fischetti, C.; Hebbes, C.; McDonald, J.; Barnes, T. A.; Rizzi, A.; Trapella, C.; Fanton, G.; Morari, M.; Lambert, D. G.; Regoli, D.; Calo, G. *J. Pharmacol. Exp. Ther.* **2007**, *321*, 961.
(17) Rizzi, A.; Gavioli, E. C.; Marzola, G.; Spagnolo, B.; Zucchini, S.; Ciccocioppo, R.; Trapella, C.; Regoli, D.; Calo, G. *J. Pharmacol. Exp. Ther.* **2007**, *321*, 968.
(18) Zaratin, P. F.; Petrone, G.; Sbacchi, M.; Garnier, M.; Fossati, C.; Petrillo, P.; Ronzoni, S.; Giardina, G. A.; Scheideler, M. A. *J. Pharmacol. Exp. Ther.* **2004**, *308*, 454.
(19) Zaveri, N. T. *J. Med. Chem.* **2016**, *59*, 7011.
(20) Kiguchi, N.; Ding, H.; Ko, M. C. *Adv. Pharmacol.* **2016**, *75*, 217.
(21) Toll, L.; Bruchas, M. R.; Calo, G.; Cox, B. M.; Zaveri, N. T. *Pharmacol. Rev.* **2016**, *68*, 419.
(22) Barlocco, D.; Cignarella, G.; Giardina, G.; Grugni, M.; Ronzoni, S. WO 2001083454, **2001**.
(23) Trapella, C.; Fischetti, C.; Pela, M.; Lazzari, I.; Guerrini, R.; Calo, G.; Rizzi, A.; Camarda, V.; Lambert, D. G.; McDonald, J.; Regoli, D.; Salvadori, S. *Bioorg. Med. Chem.* **2009**, *17*, 5080.
(24) Palombi, G.; Ronzoni, S. WO 2003040099, **2003**.
(25) Rana, S.; Natarajan, A. *Org. Biomol. Chem.* **2013**, *11*, 244.
(26) Tajbakhsh, M.; Hosseinzadeh, R.; Alinezhad, H.; Ghahari, S.; Heydari, A.; Khaksar, S. *Synthesis* **2011**, 490.