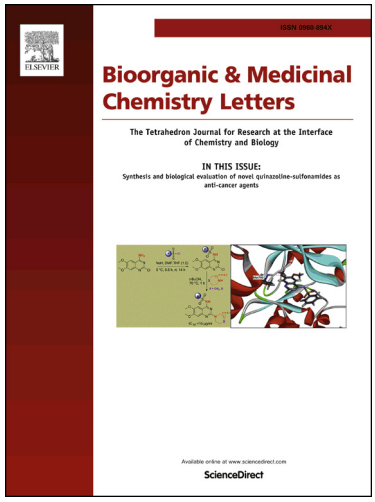


Discovery of *N*-substituted-*endo*-3-(8-aza-bicyclo[3.2.1]oct-3-yl)-phenol and -phenyl carboxamide series of μ-Opioid Receptor Antagonists

Lan Jiang, David T. Beattie, John R. Jacobsen, Samuel Kintz, Glenmar P. Obedencio, Daisuke Saito, Ioanna Stergiades, Ross G. Vickery, Daniel D. Long

PII: S0960-894X(17)30481-X
DOI: http://dx.doi.org/10.1016/j.bmcl.2017.04.092
Reference: BMCL 24945

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 23 March 2017
Revised Date: 29 April 2017
Accepted Date: 30 April 2017

Please cite this article as: Jiang, L., Beattie, D.T., Jacobsen, J.R., Kintz, S., Obedencio, G.P., Saito, D., Stergiades, I., Vickery, R.G., Long, D.D., Discovery of *N*-substituted-*endo*-3-(8-aza-bicyclo[3.2.1]oct-3-yl)-phenol and -phenyl carboxamide series of μ-Opioid Receptor Antagonists, *Bioorganic & Medicinal Chemistry Letters* (2017), doi: http://dx.doi.org/10.1016/j.bmcl.2017.04.092

Bioorganic & Medicinal Chemistry Letters
journal homepage: www.elsevier.com

Discovery of *N*-substituted-*endo*-3-(8-aza-bicyclo[3.2.1]oct-3-yl)-phenol and -phenyl carboxamide series of μ-Opioid Receptor Antagonists

Lan Jiang, David T. Beattie, John R. Jacobsen, Samuel Kintz, Glenmar P. Obedencio, Daisuke Saito, Ioanna Stergiades, Ross G. Vickery, Daniel D. Long*

Theravance Biopharma US, Inc., 901 Gateway Blvd, South San Francisco, CA 94080

ARTICLE INFO

Article history:
Received
Revised
Accepted
Available online

Keywords:
μ-Opioid receptor antagonist;
Multivalent approach;
Peripherally-restricted;
Opioid-induced constipation.

ABSTRACT

Gastrointestinal dysfunction as a consequence of the use of opioid analgesics is of significant clinical concern. First generation drugs to treat these opioid-induced side-effects were limited by their negative impact on opioid receptor agonist-induced analgesia. Second generation therapies target a localized, peripherally-restricted, non-CNS penetrant drug distribution of opioid receptor antagonists. Herein we describe the discovery of the novel *N*-substituted-*endo*-3-(8-aza-bicyclo[3.2.1]oct-3-yl)-phenol and -phenyl carboxamide series of μ-opioid receptor antagonists. This report highlights the discovery of the key μ-opioid receptor antagonist pharmacophore and the optimization of *in vitro* metabolic stability through the application of a phenol bioisostere. The compounds **27a** and **31a**, with the most attractive *in vitro* profile formed the basis for the application of Theravance Biopharma's multivalent approach to drug discovery to afford the clinical compound axelopran (TD-1211), targeted for the treatment of opioid-induced constipation.

The family of G-protein-coupled opioid receptors, μ, δ and κ mediate a range of behavioral and homeostatic functions throughout the human body. Small molecule opioid receptor modulators have thus received considerable attention as potential therapeutics to treat disorders of nociception, food intake, respiration, reward, and gastrointestinal (GI) motility.[1] In particular, μ-opioid receptor agonists such as morphine continue to play a critical role in the treatment of chronic malignant and non-malignant pain principally as a result of their activity within the central nervous system (CNS).[2] However, despite their effectiveness, opioid receptor agonists are associated with a number of undesirable, predominantly centrally-mediated side effects, including the development of analgesic tolerance and physical dependence, sedation, and respiratory depression.[3] Significant GI dysfunction due to opioids is largely peripherally mediated and is categorized as opioid bowel dysfunction (OBD).[4] The most recognized feature of OBD is opioid-induced constipation (OIC) which is a result of opioid receptor agonist mediated inhibition of rhythmic contractions associated with both GI transit and secretion. OIC is not prone to tolerance and often leads to a range of debilitating symptoms (reported to impact up to 60% of chronic opioid users) which can be so severe as to compromise compliance in maintaining therapeutic pain control.[5] Until recently, OIC patients were inadequately treated with a combination of laxatives and dietary changes. The strategy of blocking peripheral enteric opioid receptors with first generation antagonists such as naloxone (**1**) and naltrexone (**2**), Figure 1, has demonstrated clinical effects on OIC. However, these readily CNS penetrant compounds attenuate opioid-induced analgesia and provoke opioid behavioral withdrawal syndrome.[6]

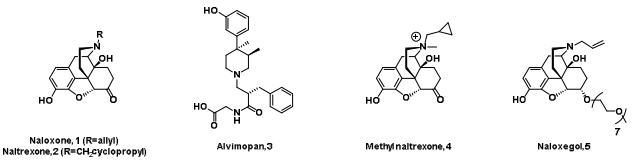


Figure 1. Opioid receptor antagonists: **1-2** CNS penetrant; **3-5** peripherally restricted.

Second generation approaches have therefore focused on a localized drug distribution targeting non-CNS penetrant, peripherally-restricted opioid receptor antagonists which have no impact on beneficial agonist analgesia, but which selectively alleviate the GI dysfunction.[7] Three peripherally-selective opioid receptor antagonists have been approved by the FDA for the treatment of opioid-related bowel dysfunction, Figure 1. Alvimopan (Entereg®) (**3**) was approved in the US in 2008 as an oral treatment to accelerate upper and lower gastrointestinal recovery following partial large or small bowel resection surgery with primary anastomosis in a hospital setting.[8] Methyl

* Corresponding author.
E-mail address: dlong@theravance.com (D.D. Long).

naltrexone (Relistor®) (**4**), approved for subcutaneous dosing (2008)[9] and as an oral formulation (2016),[10] and naloxegol (Movantik®) (**5**),[11] approved in 2014 as an oral formulation, are both indicated for the treatment of OIC for adult patients with chronic non-cancer pain. In addition, the non-opioid ligand, Amitiza® (lubiprostone), a Cl-channel activator, was approved in 2013 for the treatment of constipation caused by opioids in patients with chronic, non-cancer pain.[12]

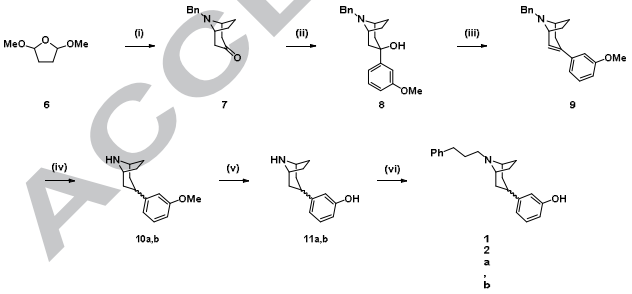
Our own approach to identify second generation, peripherally-restricted opioid receptor antagonists began with our initial discovery of novel *N*-substituted-*endo*-3-(8-aza-bicyclo[3.2.1]oct-3-yl)-phenol and -phenyl carboxamide series of μ-opioid receptor antagonists which are described herein. Alvimopan (**3**) is derived from the *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine class of opioid receptor antagonists in which the described pharmacophore is proposed to be due to the lowest energy phenyl-equatorial conformation of the core structure (**A**), Figure 2; the R-group *N*-substituent is reported to principally affect the magnitude of receptor binding of the ligand.[13] Our design considered novel *exo*-3-(8-aza-bicyclo[3.2.1]oct-3-yl)-phenol core (**B**) as an overlapping opioid receptor antagonist pharmacophore.

trans-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine, A

exo-3-(8-Aza-bicyclo[3.2.1]oct-3-yl)-phenol, B

Figure 2. Opioid receptor antagonist pharmacophore.

Scheme 1 details the first synthesis towards the desired core and a representative *N*-substituted compound.[14] Interestingly, reduction of styrene **9** resulted in a 4:1 mixture of isomers **10a,b** which upon *O*-demethylation and subsequent alkylation of the crude material **11a,b** afforded the isomeric 4:1 mixture **12a,b**, which excitingly, exhibited high binding affinity ($pK_i = 9.8$) and weak intrinsic activity (IA) consistent with an antagonist effect (IA = 22% of the maximum response achieved by DAMGO in a GTP binding assay) at the human recombinant μ-opioid receptor, Table 1.[15]



Scheme 1. Reagents and conditions: (i) aq. HCl, $BnNH_2$, 1,3-acetonedicarboxylic acid, Na_2HPO_4, 47%; (ii) $CeCl_3$, 3-methoxyphenyl magnesium bromide, THF, 0°C, 93%; (iii) 6N aq. HCl, 70°C, 91%; (iv) H_2, $Pd(OH)_2$, EtOH, 66%, ≤ 4:1 mixture by ^1H NMR; (v) BBr_3, DCM, -78°C to 0°C, 69%; (vi) 1-bromo-3-phenylpropane, DIPEA, EtOH, 60°C, 29%.

It was assumed that the favorable activity was due to the major component of the mixture, which was thus expected to be the *exo* isomer **12b**, consistent with the opioid antagonist pharmacophore (**B**) as highlighted. However, when the predominant isomer of core mixture **11a,b** was separated by crystallization, subsequent single crystal x-ray diffraction analysis[16] revealed it to be the phenyl-endocyclic compound **11a**, Figure 3.[17]

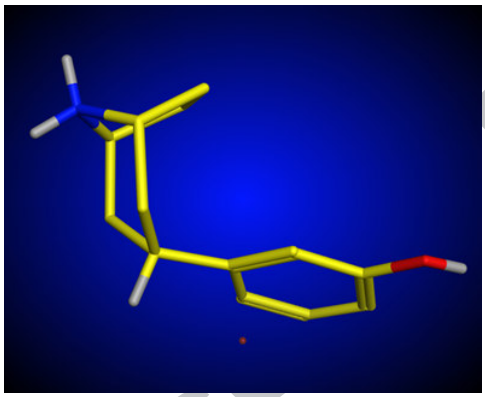
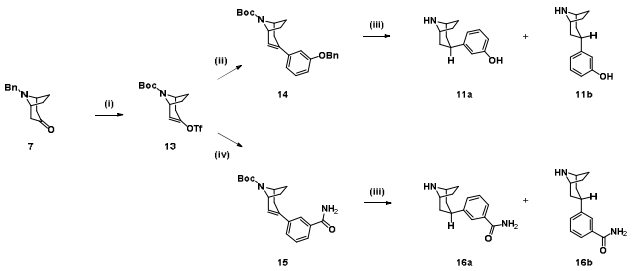
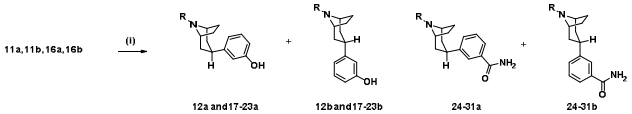


Figure 3. X-ray crystal structure of the hydrobromide salt of compound **11a**.

To further explore this structural insight as well as expand upon the discovery of the potent opioid antagonist profile, a series of both *endo*- and *exo*-*N*-substituted-3-(8-aza-bicyclo[3.2.1]oct-3-yl)-phenol compounds were prepared according to an alternative synthetic route as detailed in Schemes 2 and 3, Table 1. The separation of the isomers of core **11a,b** was achieved by reverse phase preparative HPLC and reaction with a set of alkyl bromides afforded pure *endo* isomers **12a**, **17-23a** as well as pure *exo* isomers **12b**, **17-23b**.



Scheme 2. Reagents and conditions: (i) (a) H_2, Pd/C, Boc_2O, EtOAc, 99%, (b) NaHMDS, $PhN(OTf)_2$, THF, -78°C, 82%; (ii) 3-benzyloxyphenyl-boronic acid, $PdCl_2(PPh_3)_2$, 2M aq. Na_2CO_3, THF, 80°C, 85%; (iii) (a) H_2, $Pd(OH)_2$, EtOH, (b) TFA, DCM, (c) separation by RP-HPLC; (iv) 3-carbamoylphenyl-boronic acid, $PdCl_2(PPh_3)_2$, 2M aq. Na_2CO_3, THF, 80°C, 55%.



Scheme 3. Reagents and conditions: (i) RBr, DIPEA, EtOH, 65°C.

In addition to binding affinity and functional IA at the μ-opioid receptor the binding profile at both the human δ- and guinea pig κ-opioid receptors was also determined along with an *in vitro* measure of metabolic stability upon incubation with rat, dog and human liver microsomes (RLM, DLM and HLM). The high binding affinity and weak IA profile at the μ-opioid receptor was confirmed for the single *N*-$(CH_2)_3$Ph *endo* isomer **12a** ($pK_i =$

10.0, IA = 22%); interestingly, the corresponding *exo* isomer **12b** displayed a significantly lower affinity and higher IA consistent with a partial agonist profile (pK_i = 8.3, IA = 60%). In addition, it was determined that the *endo* compound **12a** had approximately equal μ-opioid receptor affinity as for the κ-receptor (pK_i = 10.0) and approximately 10x greater affinity compared with the δ-receptor (pK_i = 9.1). For all the examples highlighted, the general trend was that the *endo* isomers **12a**, **17-23a** displayed a 1.3-1.9 log higher binding affinity for the μ-, δ- and κ-opioid receptors (with a similar μ-, δ- and κ-selectivity as described for **12a**) relative to the corresponding *exo* isomers **12b**, **17-23b**. In addition, the IA was consistently higher for the *exo* isomers. For the matched pairs **19a**, **19b** (*N*-$(CH_2)_3$OPh) and **23a**, **23b** (*N*-$(CH_2CH(OH)CH_2Ph)$, the *endo* isomers **19a** and **23a** were close to pure neutral antagonists (IA = 9% and 1%, respectively) whilst the *exo* isomers **19b** and **23b** were characterized as almost a full agonist and partial agonist (IA = 85% and 36%, respectively). The exception to this IA trend were the *endo*, *exo* isomers **20a** and **20b** with the *N*-4-*tert*-butyl-benzyl substituent which were both full agonists (IA = 100% and 97%, respectively), in contrast with the closely related *N*-2,6-difluoro-benzyl isomers **18a** and **18b** (IA = 36% and 48%, respectively). With regards to metabolic stability, all of the phenol compounds **12a**, **17-23a** and **12b**, **17-23b** had a short half-life ($t_{1/2} \leq 20$ min) in both RLM and DLM. This general instability was also evident in HLM with the exception of the *exo* isomers **18b**, **20b** and **23b** which exhibited acceptable half-lives ($t_{1/2}$ = 75, 67 and 90 min, respectively). The poor metabolic stability of the μ-opioid receptor antagonist *endo* phenol isomers precluded their further development. At this time, a patent application from Pfizer indicated a similar liability with the related *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine class of compounds, and it was ascribed to CYP2D6 metabolism of the electron-rich phenol core.[18] With this in mind, we explored phenyl primary carboxamides as phenol isosteres.[19] The synthesis of the equivalent *endo* and *exo* *N*-substituted 3-(8-aza-bicyclo[3.2.1]oct-3-yl)-carboxamide compounds is described in Schemes 2 and 3. The metabolic stability across all species was, in general, significantly improved for both the *endo* and *exo* carboxamide isomers relative to their equivalent phenol compounds. For the *endo* isomers **24a-31a**, which were of most interest, the $t_{1/2}$ in HLM was >90 min in all examples with the exception of **25a** ($t_{1/2}$ = 40 min). Additionally, there was minimal change in either the binding affinities at μ-, δ- and κ-opioid receptors, or the IA at the μ-opioid receptor comparing the carboxamide to phenol *endo* isomers, **12a** *versus* **24a**, and **17-23a** *versus* **25-31a**, thus confirming the success of the bioisosteric replacement of phenol to phenyl-carboxamide for this class of opioid-receptor antagonist.[20] The most interesting compounds were those with the *N*-$(CH_2)_3$OPh and (*N*-$(CH_2CH(OH)CH_2Ph)$ substituent, **27a** and **31a**, respectively, which were both high affinity μ-opioid receptor antagonists with a close to neutral IA and acceptable HLM stability (pK_i = 9.7 and 9.6, IA = 0 and 3%, HLM $t_{1/2}$ >90 and >90 min, respectively). These compounds and the core *endo* phenyl-carboxamide scaffold **16a** from which they are derived formed the basis for the application of Theravance Biopharma's multivalent approach to drug discovery[21] to afford the peripherally-restricted μ-opioid receptor antagonist, axelopran (TD-1211) **32**,[22] Figure 3, which will be described in detail in a future publication. Axelopran has successfully completed three Phase 2, proof-of-concept clinical trials in patients with OIC and is currently classified as Phase 3 ready. It was generally well tolerated and demonstrated a clinically meaningful response to therapy.[23]

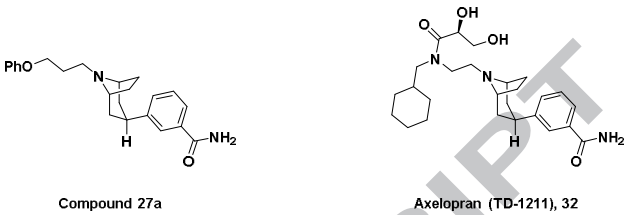


Figure 4. Compound **27a** and Axelopran (TD-1211) **32**.

In summary, a *de novo* design of a μ-opioid receptor antagonist scaffold based on the reported *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine phenyl equatorial pharmacophore of alvimopan **3**, afforded the novel *N*-substituted-*endo*-3-(8-aza-bicyclo[3.2.1]oct-3-yl)-phenol series of compounds **12a** and **17-23a** which as exemplified by the defining crystal structure of the core **11a**, adopt a phenyl axial conformation. This *endo* series in general, displayed a high affinity for the μ-, δ- and κ-opioid receptors and a functional activity at the μ-opioid receptor consistent with an antagonist profile, in contrast to the related series of novel *exo* isomers **12b** and **17-23b** which are less potent and have a higher IA. Whilst all of the *endo* phenol compounds have poor overall metabolic stability across RLM, DLM and HLM, bioisosteric replacement to the novel *N*-substituted-*endo*-3-(8-aza-bicyclo[3.2.1]oct-3-yl)-phenyl carboxamide series of compounds **24-31a** afforded comparable binding affinities and functional activity coupled with improved metabolic stability, particularly in HLM. Compounds **27a** and **31a** are key highlights as high affinity μ-opioid receptor antagonists exhibiting a close to neutral IA and acceptable HLM stability. This novel series of *N*-substituted-*endo*-3-(8-aza-bicyclo[3.2.1]oct-3-yl)-phenyl carboxamide μ-opioid receptor antagonists formed the basis for the subsequent discovery of the clinical compound axelopran, targeted for the treatment of OIC.

Acknowledgments

The authors would like to thank Dr. Adam Hughes and Dr. Tom Lam from Theravance Biopharma US, Inc. for their assistance in reviewing this article; and Dr. Sean Dalziel and Dr. Venkat Thalladi for work related to crystal structure determination.

Compound	Series	Stereo-chemistry	R	μ pK_i [a]	δ pK_i [a]	κ pK_i [a]	μ IA[b]	RLM $t_{1/2}$ (min)	DLM $t_{1/2}$ (min)	HLM $t_{1/2}$ (min)
Alvimopan	-	-	-	9.5	8.3	8.3	-6	>90	>90	>90
Methyl naltrexone	-	-	-	8.1	6.3	7.7	24	>90	>90	>90
12a,b[c]	phenol	-	$(CH_2)_3Ph$	9.8	8.9	-	22	-	-	-
12a	phenol	*endo*	$(CH_2)_3Ph$	10	9.1	10	22	2	2	15
12b	phenol	*exo*	$(CH_2)_3Ph$	8.3	7.2	8.1	64	2	2	27
24a	phenyl-carboxamide	*endo*	$(CH_2)_3Ph$	9.9	8.9	9.8	24	>90	>90	>90
24b	phenyl-carboxamide	*exo*	$(CH_2)_3Ph$	7.8	6.7	-	48	11	18	>90
17a	phenol	*endo*	$(CH_2)_6CH_3$	9.6	8.6	9.6	26	3	2	10
17b	phenol	*exo*	$(CH_2)_6CH_3$	7.7	6.6	7.6	62	2	9	2
25a	phenyl-carboxamide	*endo*	$(CH_2)_6CH_3$	9.4	8.5	9.4	28	>90	20	40
25b	phenyl-carboxamide	*exo*	$(CH_2)_6CH_3$	7.5	6.3		38	7	2	10
18a	phenol	*endo*	(CH_2)-2,6-diF-Ph	7.8	6.8	8.3	36	2	20	29
18b	phenol	*exo*	(CH_2)-2,6-diF-Ph	6.2	5.6	6.9	48	2	13	75
26a	phenyl-carboxamide	*endo*	(CH_2)-2,6-diF-Ph	7.5	6.5	7.8	26	26	>90	>90
26b	phenyl-carboxamide	*exo*	(CH_2)-2,6-diF-Ph	5.9	5.3	6.4	19	74	>90	>90
19a	phenol	*endo*	$(CH_2)_3OPh$	10	8.8	9.6	9	2	9	25
19b	phenol	*exo*	$(CH_2)_3OPh$	8.5	7.2	7.7	85	2	2	20
27a	phenyl-carboxamide	*endo*	$(CH_2)_3OPh$	9.7	8.4	9.1	0	2	7	>90
27b	phenyl-carboxamide	*exo*	$(CH_2)_3OPh$	8.2	7	7.5	95	2	6	>90
20a	phenol	*endo*	(CH_2)-4-^{t}Bu-Ph	10	9.3	10	100	2	5	16
20b	phenol	*exo*	(CH_2)-4-^{t}Bu-Ph	8.7	7.5	8.5	97	2	7	67
28a	phenyl-carboxamide	*endo*	(CH_2)-4-^{t}Bu-Ph	10	8.8	10	92	>90	>90	>90
28b	phenyl-carboxamide	*exo*	(CH_2)-4-^{t}Bu-Ph	8	6.7	7.5	73	>90	>90	>90
21a	phenol	*endo*	$(CH_2)_4$-*N*-phthalimide	9.1	7.6	9.1	26	18	11	33
21b	phenol	*exo*	$(CH_2)_4$-*N*-phthalimide	7.4	6.1	7.1	97	21	12	38
29a	phenyl-carboxamide	*endo*	$(CH_2)_4$-*N*-phthalimide	8.8	7.1	8.5	0	>90	18	>90
29b	phenyl-carboxamide	*exo*	$(CH_2)_4$-*N*-phthalimide	7.5	6.7	-	75	>90	11	>90
22a	phenol	*endo*	CH_2(CO)cyclohexyl	10	9.3	11	33	2	2	12
22b	phenol	*exo*	CH_2(CO)cyclohexyl	8.7	7.7	9.1	57	2	2	13
30a	phenyl-carboxamide	*endo*	CH_2(CO)cyclohexyl	9.8	8.7	10	41	70	21	>90
30b	phenyl-carboxamide	*exo*	CH_2(CO)cyclohexyl	7.8	6.4	7.7	93	81	9	>90
23a	phenol	*endo*	$CH_2C(OH)CH_2Ph$	9.6	8.2	-	1	2	2	32
23b	phenol	*exo*	$CH_2C(OH)CH_2Ph$	8	6.6	7.7	36	2	2	>90
31a	phenyl-carboxamide	*endo*	$CH_2C(OH)CH_2Ph$	9.6	8.4	9.5	3	31	>90	>90
31b	phenyl-carboxamide	*exo*	$CH_2C(OH)CH_2Ph$	7.5	6.3	7.1	39	14	59	>90

Table 1. [a]μ-, δ- and κ-opioid receptor binding pK_i values were determined using a [^{3}H]-DPN radioligand binding assay with membranes prepared from CHO-K1 cells stably-transfected with human recombinant μ- and δ-opioid receptor and guinea pig κ-opioid receptor; [b]functional activities were determined using GTP binding assays with [^{35}S]-GTPγS in membranes prepared from CHO-K1 cells stably-transfected with the human recombinant μ-opioid receptor: the maximum compound-evoked response (minus basal) is expressed as a percentage of the maximum response evoked by DAMGO; [c]**12a,b** is an approximate 4:1 mixture of *endo:exo* isomers **12a** and **12b**, respectively.

References and notes

[1] Stein, C. *Ann. Rev. Med.* **2016**, *67*, 433.

[2] (a) Walsh, T. D. *Seminars in Oncology* **2000**, *27*, 45; (b) Chou, R.; Fanciullo; G. J.; Fine, P. G.; Adler, J. A.; Ballantyne, J. C.; Davies, P.; Donovan, M. I.; Fishbain, D.A.; Foley, K.M.; Fudin, J.; Gilson, A. M.; Kelter, A.; Mauskop, A.; O'Connor, P. G.; Passik, S. D.; Pasternak, G. W.; Portenoy, R. K.; Rich, B. A.; Roberts, R. G.; Todd, K. H.; Miaskowski, C. *J. Pain* **2009**, *10*, 113.

[3] (a) Walsh, T. D. *J. Pain. Symptom Manag.* **1990**, *5*, 362; (b) Vanegas, G.; Ripamonti, C.; Sbanotto, A.; De Conno, F. *Cancer Nursing* **1998**, *21*, 289.

[4] Brock, C.; Olesen, S. S.; Olesen, A. E.; Frokjaer, J. B.; Andresen, T.; Drewes, A. M. *Drugs* **2012**, *72*, 1847.

[5] Walters, J. B.; Montagnini, M. *J. Opioid Management* **2010**, *66*, 435.

[6] (a) Culpepper-Morgan, J. A.; Inurrisi, C. E.; Portenoy, R. K.; Foley, K.; Houde, R. W.; Marsh, F.; Kreek, M. *J. Clin. Pharmacol. Therap.* **1992**, *52*, 90; (b) Pappagallo, M. *Am. J. Surgery* **2001**, *182*, 11S.

[7] Diego, L.; Atayee, R.; Helmons, P.; Hsiao, G.; von Gunten, C. F. *Expert Opin. Investig. Drugs* **2011**, *20*, 1047.
[8] Beattie, D. T. *Clin. Med.: Ther.* **2009**, *1*, 199.
[9] Rauck, R. L. *Drugs* **2013**, *73*, 1297.
[10] https://shared.salix.com/shared/pi/relistor-pi.pdf
[11] Garnock-Jones, K. P. *Drugs* **2015**, *75*, 419.
[12] Jamal, M. M.; Adams, A. B.; Jansen, J.-P.; Webster, L. R. *Am. J. Gastroenterol.* **2015**, *110*, 725.
[13] (a) Le Bourdonnec, B.; Goodman, A. J.; Michaut, M.; Ye, H.-F.; Graczyk, T. M.; Belanger, S.; Herbertz, T.; Yap, G. P. A.; DeHaven, R. N.; Dolle, R. E. *J. Med. Chem.* **2006**, *49*, 7278; (b) Carroll, F. I.; Dolle, R. E. *Chem. Med. Chem.* **2014**, *9*, 1638.
[14] Long, D. D.; Jacobsen, J. R.; Jiang, L.; Saito, D. R.; Stergiades, I. US **2015** 9,206,172 B2.
[15] Compounds are classified: -5<IA<25 as antagonists, 25<IA<80 as partial agonists, 80<IA<120 as full agonists
[16] CCDC 1546551 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures
[17] The *N*-Boc derivative of mixture **11a,b** was also selectively crystallized and x-ray crystal structure analysis confirmed the major isomer to be the Ph-endocyclic compound.
[18] McHardy, S.; Liras, S.; Guediche, S.; Coe, J. W. US **2004**/0204453 A1.
[19] Wentland, M. P.; Lou, R.; Ye, Y.; Cohen, D. J.; Richardson, G. P.; Bidlack, J. M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 623. Whilst an effective isostere for cyclazocine, the primary carboxamide was at the time not deemed generally applicable as it was ineffective when applied to morphine - Wentland, M. P.; Lou, R.; Denhardt, C. M.; Duan, W.; Cohen, D. J.; Bidlack, J. M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1717. However subsequent examples of the successful use of this isostere have been reported - Le Bourdonnec, B.; Belanger, S.; Cassel, J. A.; Stabley, G.; DeHaven, R. N.; Dolle, R. E. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4459.
[20] The binding affinity for the phenyl carboxamide *exo* isomers is approximately 0.5 log lower as compared to the phenol *exo* isomers.
[21] (a) Long, D. D.; Aggen, J. B.; Christensen, B. G.; Judice, J. K.; Hegde, S. S.; Kaniga, K.; Krause, K. M.; Linsell, M. S.; Moran, E. J.; Pace, J. L. *J. Antibiot.* **2008**, *61*, 595; (b) Choi, S.-K.; Green, D.; Ho, A.; Klein, U.; Marquess, D.; Taylor, R.; Turner, S. D. *J. Med. Chem.* **2008**, *51*, 3609; (c) McKinnell, R. M.; Armstrong, S. R.; Beattie, D. T.; Choi S.-K.; Fatheree, P. R.; Gendron, R. A. L.; Goldblum, A.; Humphrey, P. P.; Long, D. D.; Marquess, D. G.; Shaw, J. P.; Smith, J. A. M.; Turner, S. D.; Vickery, R. G. *J. Med. Chem.* **2009**, *52,* 5330; (d) Hughes, A. D.; Chin, K. H.; Dunham, S. L.; Jasper, J. R.; King, K. E.; Lee, T. -W.; Mammen, M.; Martin, J.; Steinfeld, T. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1354; (e) Jacobsen, J. R.; Choi, S.-K.; Combs, J.; Fournier, E. J. L.; Klein, U.; Pfeiffer, J. W.; Thomas, G. R.; Yu, C.; Moran, E. J. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 1213; (f) Long, D. D.; Armstrong, S. R.; Beattie, D. T.; Choi S.-K.; Fatheree, P. R.; Gendron, R. A. L.; Goldblum, A. A.; Humphrey, P. P..; Marquess, D. G.; Shaw, J. P.; Smith, J. A. M.; Turner, S. D.; Vickery, R. G. *Bioorg. Med. Chem. Lett.* **2012**, *22,* 4849; (g) Long, D. D.; Armstrong, S. R.; Beattie, D. T.; Choi, S.-K.; Fatheree, P. R.; Gendron, R. A. L.; Genov, D.; Goldblum, A. A.; Humphrey, P. P.; Jiang, L.; Marquess, D. G.; Shaw, J. P.; Smith, J. A. M.; Turner, S. D.; Vickery, R. G. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 6048; (h) Long, D. D.; Frieman, B.; Hegde, S. S.; Hill, C. M.; Jiang, L.; Kintz, S,; Marquess, D. G.; Purkey, H.; Shaw, J. P.; Steinfeld, T.; Wilson, M. S.; Wrench, K. *Bioorg. Med. Chem. Lett.* **2013**, *23,* 939; (i) McKinnell, R. M.; Armstrong, S. R.; Beattie, D. T.; Fatheree, P. R.; Long, D. D.; Marquess, D. G.; Shaw, J. P.; Vickery, R. G. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 4210; (j) Jacobsen, J. R.; Aggen, J. B.; Church, T. J.; Klein, U.; Pfeiffer, J. W.; Pulido-Rios, T. M.; Thomas, G. R.; Yu, C.; Moran, E. J. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 2625; (k) McKinnell, R. M.; Klein, U.; Linsell, M. S.; Moran, E. J.; Nodwell, M. B.; Pfeiffer, J. W.; Thomas, G. R.; Yu, C.; Jacobsen, J. R. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 2871; (l) Hughes, A. D.; Chen, Y.; Hegde, S. S.; Jasper, J. R.; Jaw-Tsai, S.; Lee, T.-W.; McNamara, A.; Pulido-Rios, M. T.; Steinfeld, T.; Mammen, M. *J. Med. Chem.* **2015**, *58*, 2609.
[22] (a) Armstrong, S. R.; Campbell, C. B.; Richardson, C. L.; Vickery, R. G.; Tsuruda, P. R.; Long, D. D.; Hegde, S. S.; Beattie, D. T. *Naun. Schmi. Arch. Pharmacol.* **2013**, *386*, 471; (b) Tsuruda, P. R.; Vickery, R. G.; Long, D. D.; Armstrong, Beattie, D. T. *Naun. Schmi. Arch. Pharmacol.* **2013**, *386*, 479.
[23] (a) Vickery, R.; Schwertschlag, U.; Singla, N.; Webster, L.; Canafax, D. *J. Pain* **2013**, *14*, S78; (b) Holder, R. M.; Rhee, D. *Pharmacother.* **2016**, *36*, 287.

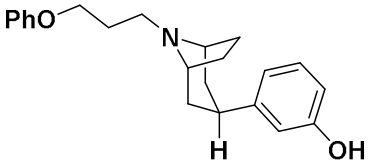
Graphical Abstract

*To create your abstract, type over the instructions in the template box below.
Fonts or

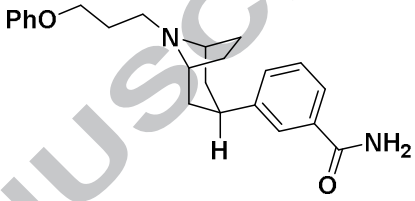
Discovery of *N*-substituted-*endo*-3-(8-aza-bicyclo[3.2.1]oct-3-yl)-phenol and -phenyl carboxamide series of μ-Opioid Receptor Antagonists

Leave this area blank for abstract info.

Lan Jiang, David T. Beattie, John R. Jacobsen, Samuel Kintz, Glenmar Obedencio, Daisuke Saito, Ioanna Stergiades, Ross G. Vickery, Daniel D. Long*



Compound 19a
endo phenol
μ pK_i = 10.0
μ IA = 9%
HLM $t_{1/2}$ = 25 min



Compound 27a
endo phenyl carboxamide
μ pK_i = 9.7
μ IA = 0%
HLM $t_{1/2}$ = 90 min