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Structure–activity relationship studies of carboxamido-biaryl ethers as opioid receptor antagonists (OpRAs). Part 1

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Abstract—A structurally unique and new class of opioid receptor antagonists (OpRAs) that bear no structural resemblance with morphine or endogenous opioid peptides has been discovered. A series of carboxamido-biaryl ethers were identified as potent receptor antagonists against mu, kappa and delta opioid receptors. The structure–activity relationship indicated *para*-substituted aryloxy-aryl primary carboxamide bearing an amine tether on the distal phenyl ring was optimal for potent in vitro functional antagonism against three opioid receptor subtypes.

In recent years obesity among the general public is increasing at an alarming rate and in an epidemic proportion especially among children and teenagers.[1] The frequent association of serious clinical conditions such as diabetes and cardiovascular diseases with obesity has become a serious concern in the medical community, and therefore a pharmacological intervention for reducing weight in obese subjects is warranted. Opioid receptor (mu, kappa, and delta) agonists are known to stimulate, while antagonists against opioid receptors inhibit, food consumption in preclinical obesity models.[2] Obesity and fasting elevates endogenous opioid peptides in animal models and man.[3] Reduced consummatory behaviors appear to be most pronounced when animals are obese or fed a palatable cafeteria diet containing large amounts of a preferred macronutrient.[4] A current hypothesis is that opioid receptor antagonists produce their effects on food intake by preventing central reward mechanisms that occur when overeating a preferred or palatable diet and/or by preventing the craving associated with dieting/abstinence. In this manner, opioidergic control of appetite for palatable energy-dense foods may share common neural substrates responsible for the development of nicotine, alcohol, and narcotic dependence and addiction. Human clinical studies with naltrexone, an opioid receptor antagonist, demonstrated short-term effects on food intake, albeit at doses that were higher than needed to precipitate opiate withdrawal.[5] Hepatotoxicity limited the dose of naltrexone utilized in chronic studies and failed to demonstrate consistent long-term effects on body weight. Therefore, the clinical hypothesis evaluating the efficacy of an opioid receptor antagonist (OpRA) as a treatment for obesity has yet to be fully investigated.

Previous efforts at Lilly have demonstrated that LY255582 is a nonselective OpRA that is very potent and efficacious in rat obesity models.[6] This effect appears to be mediated via antagonizing all three mu, kappa, and delta receptor subtypes. LY255582 was found to have substantially better anti-obesity activity in rats than the clinically approved OpRAs such as naloxone or naltrexone. Unfortunately, the poor oral bioavailability and unacceptable margin of safety resulting from irritation at the site of drug administration of LY255582 via various routes precluded its clinical development. In the course of our efforts to find a new class of OpRAs, we discovered carboxamido-biaryl ethers that were structurally unrelated to the opiate morphine (Fig. 1). We then launched structure–activity relationship (SAR) studies to develop an orally efficacious OpRA with activity comparable to that of LY255582 with fewer side effects for the treatment of obesity. In this paper

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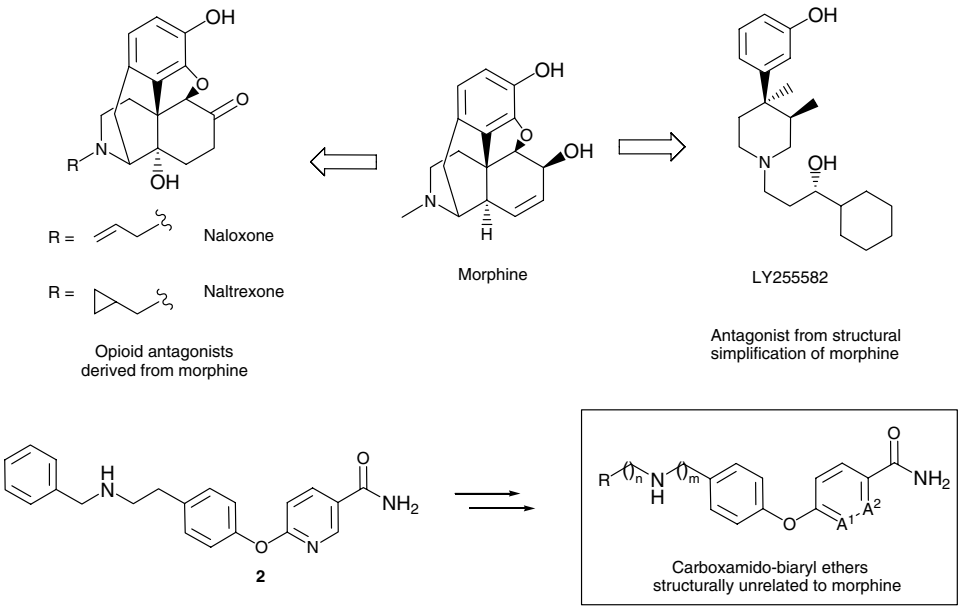
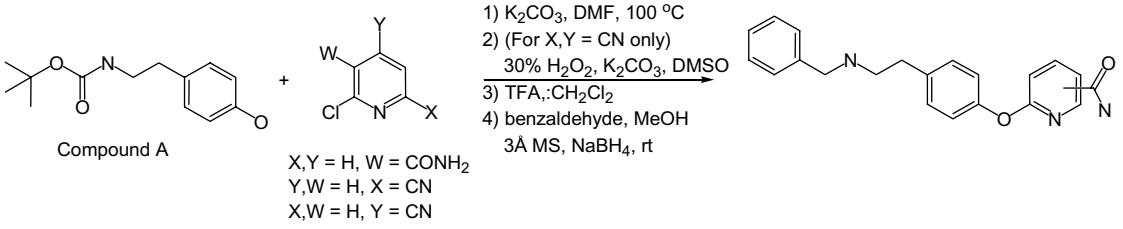


Figure 1. Opioid receptor antagonists.

we report initial findings of our SAR study efforts on the series of novel carboxamido-biaryl ether opioid receptor antagonists.

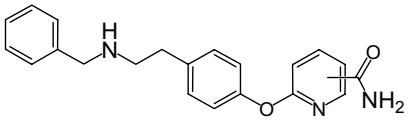
In our early SAR study, we identified 6-(4-(2-benzylaminoethyl)phenoxy)nicotinamide (**2**) as an initial lead having good binding affinities at mu, kappa, and delta opioid receptors (Table 2). We then explored the SAR surrounding the lead structure **2**. We first examined the regiochemical effect of the carboxamide functionality. The compounds were readily prepared by methods as shown in Scheme 1. The results in Table 1 show that *para*-orientation between the aryloxy group and the carboxamide on the pyridine ring (**2**) was required for the opioid receptor antagonism at the three receptor subtypes.

We then sought a replacement of the carboxamide by converting the 6-aryloxynicotinonitrile intermediate to various functionalities **R** (Scheme 2 and Table 2). The results in Table 2 indicate that a primary amide (**2** and **9**) is optimal for antagonizing the three opioid receptors. The substituents on the amide nitrogen were not well tolerated especially at kappa and delta receptors (**12**–

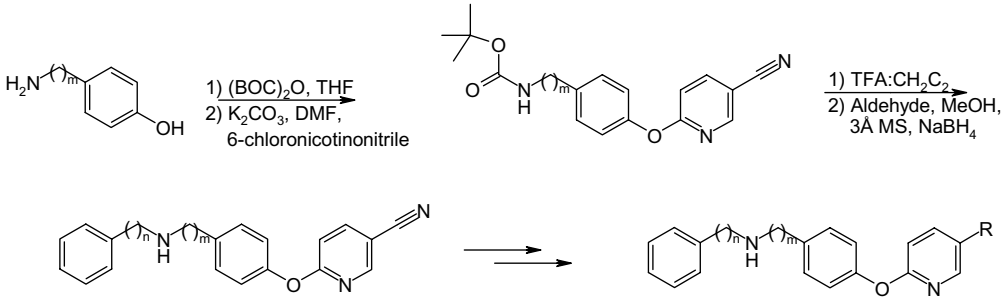


Scheme 1.

Table 1. Effects of carboxamide regiochemistry on the opioid receptor binding affinities

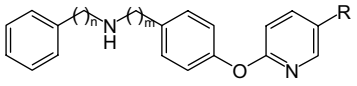


Compound	Amide position	Receptor binding affinity at high Na, K_i (nM)[7]		
		Mu	Kappa	Delta
1	2	643.47 ± 45.10	>5000	>5000
2	3	7.44 ± 2.94	136.26 ± 59.55	70.21
3	4	>2500	>5000	>5000
4	5	>2500	>5000	>5000



Scheme 2.

Table 2. Effects of bioisosteric replacement of the carboxamide on the opioid receptor binding affinities



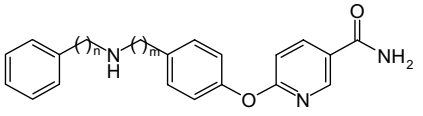
Compound	*m*	*n*	R	Receptor binding affinity at high Na, K_i (nM)[7]		
				Mu	Kappa	Delta
2	2	1	$CONH_2$	7.44 ± 2.94	136.26 ± 59.55	70.21
5	2	1	CN	1076.86 ± 179.58	>5000	>5000
6	2	1	CH_2NH_2	>2500	>5000	>5000
7	2	1	CO_2H	>2500	>5000	>5000
8	2	1	SO_2NH_2[a]	>2500	>5000	>5000
9	1	2	$CONH_2$	0.17 ± 0.02	8.38 ± 2.30	1.16 ± 0.23
10	1	2	$C(NH)NH_2$	20.55 ± 1.93	1147.5 ± 145.98	214.73 ± 6.35
11	1	2	C(NH)NHMe	234.53 ± 15.41	>5000	3458.36 ± 244.32
12	1	2	CONHMe	52.29 ± 2.20	>5000	718.45 ± 33.98
13	1	2	CONHEt	57.15 ± 1.07	2808.74	673.58 ± 27.70
14	1	2	CONH*i*-Pr	52.27 ± 13.74	>5000	2414.41 ± 38.48
15	1	2	COPip[b]	389.49 ± 61.60	>5000	>5000

[a] Benzenesulfonamide was prepared from 4-fluorobenzenesulfonyl chloride and [2-(4-hydroxyphenyl)ethyl]carbamic acid *tert*-butyl ester as starting materials.
[b] Pip = 1-piperidine.

15). Particularly detrimental seems to be a tertiary or a cyclic amide (**15**). Replacement of the amide with amidine (**10** and **11**) also suffered significant loss in binding affinities at kappa and delta receptors.

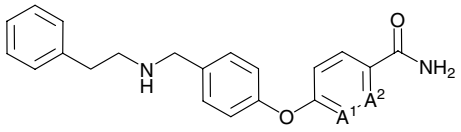
Along with this SAR we also examined the positioning of secondary amine nitrogen of the amine tether by interchanging the carbon chain length (C_m and C_n) between the terminal and middle phenyl rings. Interestingly, the phenethylaminomethyl compound **9** (where $m = 1$ and $n = 2$) exhibited an order of magnitude greater affinities at all three receptors than the benzylaminoethyl compound **2** (where $m = 2$ and $n = 1$). This prompted us to examine further the optimal position of the secondary amine nitrogen in the in vitro functional antagonism (Table 3). By fixating the linker

Table 3. Effects of the position of amine tether of the 6-phenoxynicotinamide on the in vitro functional antagonism at the opioid receptors



Compound	*m*	*n*	GTPγS functional antagonism, K_b (nM)[8]		
			Mu	Kappa	Delta
2	2	1	2.25 ± 0.47	18.41 ± 7.99	23.14 ± 6.88
9	1	2	0.07 ± 0.02	1.15 ± 0.24	0.97 ± 0.14
16	2	2	16.56 ± 2.49	23.34 ± 1.93	128.07 ± 52.19
17	2	3	18.47 ± 3.34	24.15 ± 1.87	211.63 ± 83.06
18	3	1	22.26 ± 0.33	45.83 ± 1.83	495.99 ± 12.24
19	3	0	>1000	>1000	>1000
20	0	3	>1000	>1000	>1000
21	1	1	4.09 ± 1.1.44	2.47 ± 0.36	54.15 ± 16.31

Table 4. Effects of the replacement of pyridyl ring with other aryl rings[9] on the opioid receptor antagonism



Compound	A^1	A^2	Receptor binding affinity at high Na, K_i (nM)[7]			GTPγS functional antagonism, K_b (nM)[8]		
			Mu	Kappa	Delta	Mu	Kappa	Delta
9	N	C	0.17 ± 0.02	8.38 ± 2.30	1.16 ± 0.23	0.07 ± 0.02	1.15 ± 0.24	0.97 ± 0.14
22	C	C	0.29	15.04	1.88 ± 0.17	0.15 ± 0.01	1.22 ± 0.33	0.92 ± 0.11
23	C	N	1.77 ± 0.16	69.27 ± 22.70	8.54 ± 1.40	0.44 ± 0.12	9.60 ± 1.14	2.86 ± 0.30
LY255582			0.15 ± 0.01	4.68 ± 0.83	4.82 ± 0.49	0.043 ± 0.008	0.32 ± 0.03	1.19 ± 0.21
Naltrexone			0.87 ± 0.02	5.28 ± 0.12	16.31 ± 0.28	0.59 ± 0.02	2.99 ± 0.10	11.06 ± 0.32

atom numbers to four in the chain, the nitrogen was moved along the chains from $m = 0$–3 (**2**, **9**, **19**, and **20**). The position of nitrogen benzylic from the middle phenyl ring (**9** where $m = 1$ and $n = 2$) was confirmed optimal for the in vitro antagonism, as the same trend seen with the binding affinities. The loss of antagonizing activity with an aniline link either at the terminal phenyl (**19**) or the middle phenyl (**20**) ring indicates that a basic nitrogen is required for the receptor antagonism. We also changed the number of carbon linkers $n = 1$–3 while maintaining $m = 2$ (**2**, **16**, and **17**). As the chain length increased, functional antagonism decreased especially at the delta receptor. These results suggest that the four-atom linker between the two phenyl rings may be optimal for the in vitro antagonism (also seen with **2** vs. **18**). This was also confirmed by the shorter linker compound **21** (where $m = n = 1$) which was less potent than **9** at all three receptors, particularly at delta.

With these findings, we then explored other aryl amides as a potential replacement for the nicotinamide (Table 4). Benzamido- (**22**) and 2-pyridinecarboxamido- (**23**) biaryl ethers exhibited comparable binding affinities at the three opioid receptors as the nicotinamide **9**, albeit the 2-pyridinecarboxamide **23** was much less potent at the kappa receptor. However, all the carboxamido-biaryl ethers possessed excellent in vitro functional antagonist activities at all three receptors, which were several fold more potent than the binding affinities.

In conclusion, we have discovered potent opioid receptor antagonists in vitro, which are structurally unrelated to the typical opiate morphine. Further SAR exploration of each series of carboxamido-biaryl ethers shown above will be reported separately in due course.

Acknowledgment

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