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Structure activity relationship studies of carboxamido-biaryl ethers as opioid receptor antagonists (OpRAs). Part 2

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Abstract—A series of 6-bicycloaryloxynicotinamides were identified as opioid receptor antagonists at mu, kappa, and delta receptors. Compounds in the 6-(2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-7-yloxy)nicotinamide scaffold exhibited potent in vitro functional antagonism at all three receptors.

The prevalence of obesity in the industrialized world, particularly in the United States, has reached epidemic proportions.[1] Today close to 65% of the adult population in the US is overweight (BMI $\geqslant$ 25) or obese (BMI $\geqslant$ 30). More alarming trend is the increase in the number of overweight children and teenagers (10–15% of the youth population). International data indicate that the epidemic is not isolated to the US but is in fact a growing global health problem. In other words, the prevalence of obesity is not only rising in other developed and affluent countries but also is now spreading to less affluent countries. The prevention and treatment of excess weight is critical for the health of both individuals and our society not only because obesity increases the risk of a number of diseases, such as type 2 diabetes mellitus, dyslipidaemia, hypertension, and coronary heart disease, but also because it disposes an enormous economic impact on our society. Medical intervention along with lifestyle modification is now considered a necessity to prevent the growing and multilateral negative consequences of overweight and obesity.

Flurries of research activities to discover effective and safe antiobesity agents have spurred in recent years as fenfluramine and dexfenfluramine (Fen–Phen) were removed from the market, and orlistat and sibutramine, the current approved drugs, have limited clinical use due to their poor efficacy and significant side effect profiles.[2] Most recently, Rimonabant was approved for the treatment of obesity in Europe and a high hope was raised for this CB1 antagonist as a new therapeutic agent that held promise not only to treat obesity but also to alleviate other metabolic syndromes.[3] But its submission to FDA in the US was withdrawn just prior to its initially expected approval when concerns over its side effects especially on patients with history of depression were raised and its risk/benefit ratio was questioned by the FDA Advisory Board, who unanimously voted down its approval as a result. Continual research and development of an antiobesity agent with favorable side effect profiles for a long-term use is, therefore, warranted and required. We have reported that nonselective opioid receptor antagonist (OpRA) LY255582 and its analogs demonstrated potent anorectic activity, reducing body fat in obese rats by decreasing food intake and stimulating lipid utilization.[4] LY255582, however, precluded its clinical development due to its poor oral bioavailability and unacceptable margin of safety resulting from irritation at the site of drug administration via other routes. We then began to search an orally efficacious OpRA with activity comparable to LY255582 and acceptable safety profiles for the treatment of obesity and recently discovered new carboxamido-biaryl ethers that were structurally unrelated to morphine (Fig. 1). We identified and reported[5] 6-(4-(2-benzylaminoethyl)phenoxy)nicotinamide (**1**) as an initial lead having good

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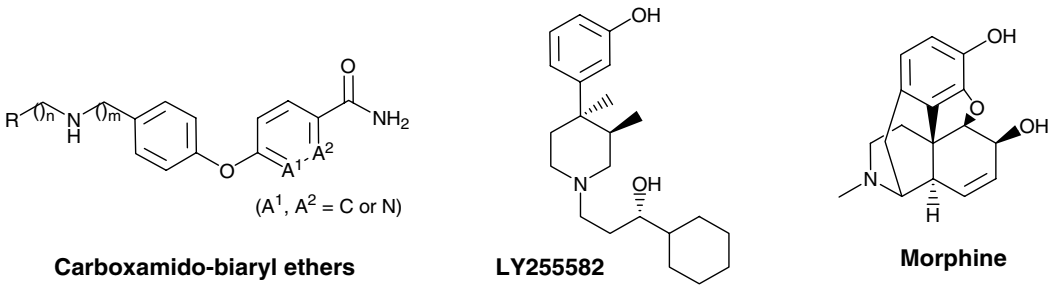
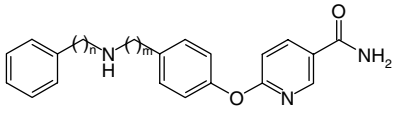


Figure 1. Carboxamido-biaryl ethers, novel opioid receptor antagonists structurally unrelated to morphine.

Table 1. Opioid receptor antagonism of carboxamido-biaryl ethers



Compound	*m*	*n*	Receptor binding affinity at high Na, K_i (nM)[6]			GTP$_\gamma$S functional antagonism, K_b (nM)[7]		
			Mu	Kappa	Delta	Mu	Kappa	Delta
1	2	1	7.44 ± 2.94	136.26 ± 59.55	70.21	2.25 ± 0.47	18.41 ± 7.99	23.14 ± 6.88
2	1	2	0.17 ± 0.02	8.38 ± 2.30	1.16 ± 0.23	0.07 ± 0.02	1.15 ± 0.24	0.97 ± 0.14
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

The data are expressed in mean ± SEM where the assay run $n \geqslant 2$ and value without SEM where $n = 1$.

binding affinities at mu, kappa, and delta opioid receptors (Table 1). We also reported how the carbon chain length and the position of the amine nitrogen between the two phenyl rings affected the receptor binding affinities and identified a more potent antagonist **2** at all three opioid receptor subtypes.

One of the concerns raised in our early SAR exploration of this series of compounds was the stability of unsubstituted benzylic carbon of the side chain. We therefore considered two aspects of further SAR exploration: (1) conformational constraint of the benzylic nitrogen atom in a ring system with one of the neighboring phenyl rings, e.g., as isoindoline, tetrahydroisoquinoline, or benzoazepine; and (2) replacement of the terminal benzylic amine tether with other amine tether. For the first modification there are two possible sites to constrain the amine nitrogen in a ring system: (a) tie the nitrogen into the middle phenyl ring; or (b) attach it to the terminal phenyl ring (Fig. 2).

Compounds with these modifications were prepared as shown in Scheme 1.[8] 3,4-Dimethylphenyl methyl ether was dibrominated with NBS in the presence of benzoyl peroxide radical initiator in CCl_4 at reflux in 32% (Route A). Treatment with benzylamine in the presence of benzyltriethylammonium chloride in 50% NaOH/toluene solution afforded *N*-benzylisoindolin-5-yl methyl ether in a 71% yield. Demethylation with 48% HBr at reflux followed by etherification with 6-chloronicotinamide and K_2CO_3 in *N*,*N*-dimethylacetamide/toluene solution at reflux produced the compound **3** in 40%. Debenzylation by hydrogenolysis followed by alkylation with 2-phenethylbromide and Et_3N in DMF at 70 °C furnished **4**. Compounds **5**–**7** were prepared from 3-methoxyphenethylamine, which was first converted to a tetrahydroisoquinoline intermediate with paraformaldehyde and CH_3COCl in 88% HCO_2H as shown in Route B. Demethylation and *N*-BOC protection set up the intermediate ready for etherification with 6-chloronicotinamide (47% for 3 steps). BOC-deprotection with TFA in

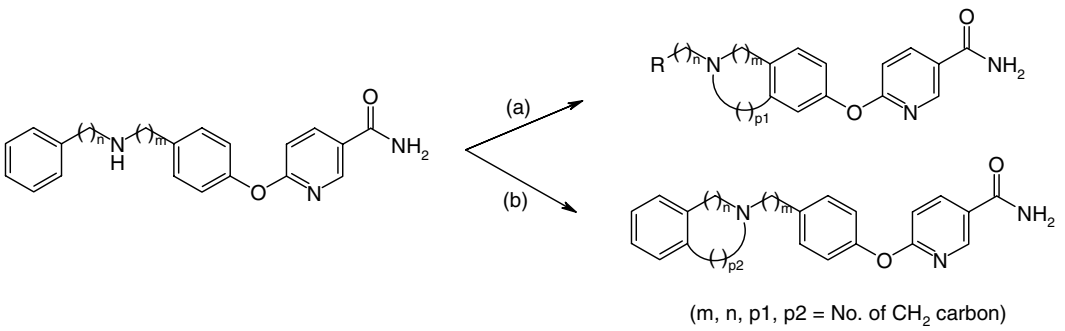
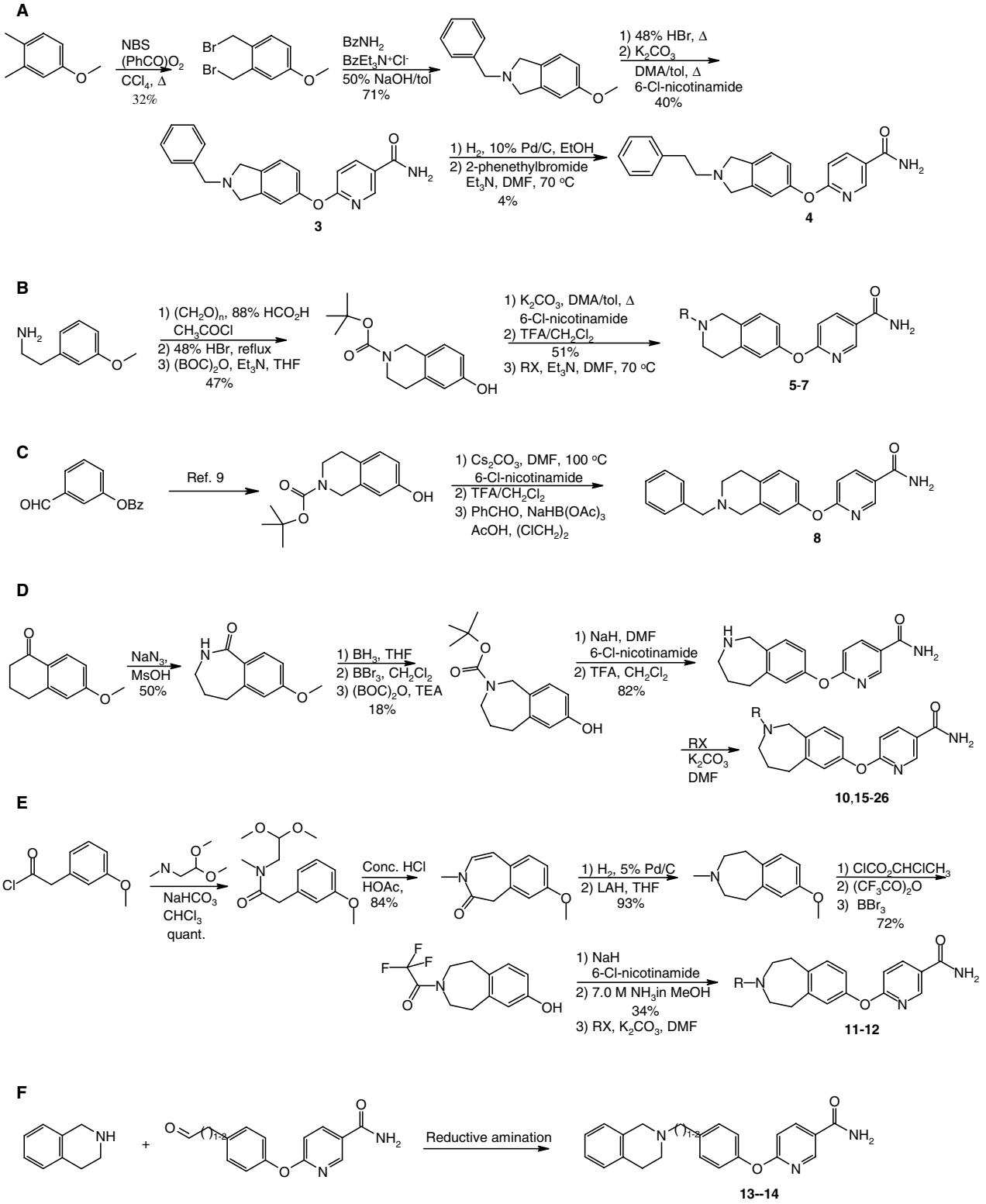


Figure 2. Modification of carboxamido-biaryl ether side chain.



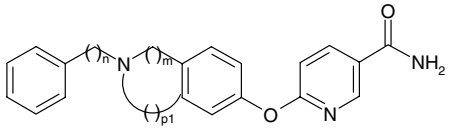
Scheme 1. Synthesis of 6-bicycloaryloxynicotinamides.[8]

CH_2Cl_2 after the 6-aryloxynicotinamide formation and alkylation with an appropriate halide (RX) as in Route A afforded the target compounds. Compounds **8** and **9** were prepared as exemplified by **8** in Route C. *N*-BOC-7-hydroxy-3,4-dihydro-1*H*-isoquinoline was prepared according to a literature procedure.[9] Etherification with 6-chloronicotinamide and Cs_2CO_3 in DMF at 100 °C, BOC-deprotection, and reductive amination of benzaldehyde with the resultant isoquinoline in the presence of $NaHB(OAc)_3$ and acetic acid in dichloroethane yielded **8**. Reductive amination of phenylacetaldehyde similarly afforded the compound **9**. The compound **10**

was prepared as shown in Route D. 6-Methoxytetralone was treated with NaN_3 in methanesulfonic acid to form 7-methoxy-2,3,4,5-tetrahydro-1H-benzo[*c*]azepin-1-one in a 50% yield.[10] Reduction of the amide to the amine with BH_3 in THF, demethylation with BBr_3 in CH_2Cl_2, and *N*-BOC protection afforded a precursor phenol for etherification with 6-chloronicotinamide. *N*-BOC deprotection after the biaryl ether formation and alkylation with phenethyl bromide and K_2CO_3 in DMF as described above provided **10**. Route E describes the synthesis of compounds **11** and **12**. An amide formation from 3-methoxyphenylacetyl chloride with methylaminoacetaldehyde dimethyl acetal and $NaHCO_3$ in $CHCl_3$ followed by acid-catalyzed cyclization afforded 8-methoxy-3-methyl-1,3-dihydro-benzo[*d*]azepin-2-one in an excellent yield. Sequential treatment of the intermediate by (1) reduction of the double bond, (2) deoxygenation of the amide oxygen with LAH, (3) *N*-demethylation with 1-chloroethyl chloroformate, (4) trifluoroacetylation of the resultant amine, and (5) *O*-demethylation with BBr_3 provided *N*-trifluoroacetyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-7-ol in good yields. Treatment of the alcohol with NaH, etherification with 6-chloronicotinamide, deacetylation with 7.0 M NH_3 in MeOH, and alkylation with an appropriate alkyl halide as before afforded the target compound **11** or **12**.

Table 2 shows the results of modification (a). Isoindoline incorporation (**3** and **4**) was most detrimental to the receptor antagonism activities. Isoquinolinyl derivatives **5**–**9** also suffered considerable loss in the binding affinity, especially at kappa and delta receptors. The trend that we saw before in the effects of terminal chain lengths[5] was translated into the ring system where **6** ($n = 2$) exhibited best overall activities among **5**–**7** ($n = 1$–3). More pronounced effect of the ring system itself was observed with the isoquinolin-7-yl analog **9** ($m = 2$, $p1 = 1$), which almost completely lost activities at all three receptors as compared to the isoquinolin-6-yl **6** ($m = 1$, $p1 = 2$). This may be explained by the fact that the terminal phenethyl chain was forced to change its location and orientation due to the ring constraint in **9**. Compounds **5** and **8**, however, showed similar activities at all three receptors. This rationale was also supported by the results of benzoazepinyl derivatives **10**–**11**. The more flexible benzo[*c*]azepinyl **10** ($m = 1$, $p1 = 3$) regained activities comparable to **1** and **6**, whereas the benzo[*d*]azepinyl **11** or **12** ($m = 2$, $p1 = 2$) lost considerable activities presumably due to the change in the orientation of their terminus. Among the constrained ring systems studied, the compound **10** showed the best overall profiles at the three receptors.

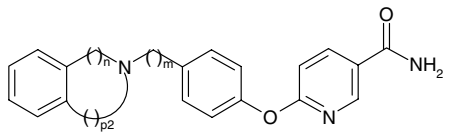
Table 2. Effects of incorporation of nitrogen atom into a bicyclic system with the middle phenyl ring



Compound	No. of CH_2 carbon			Receptor binding affinity at high Na, K_i (nM)[6]		
	m	*n*	*p*1	Mu	Kappa	Delta
3	1	1	1	1008	>5000	>5000
4	1	2	1	658.8 ± 118.5	>5000	2274 ± 315
5	1	1	2	179.0	2150	2351 ± 201
6	1	2	2	15.95	1221	179.6 ± 27.8
7	1	3	2	185.0 ± 18.9	555.9 ± 112.5	2139 ± 37
8	2	1	1	231.59	2428.17	2448.94 ± 29.29
9	2	2	1	>3333	3606	>5000
10	1	2	3	10.09 ± 1.85	360.6 ± 34.6	169.39 ± 5.80
11	2	1	2	405.8	2873	2708 ± 55
12	2	2	2	91.49	>4897	1377 ± 70

The data are expressed in mean ± SEM where the assay run $n \geqslant 2$ and value without SEM where $n = 1$.

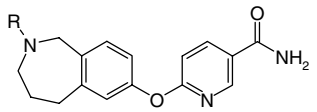
Table 3. Effects of incorporation of nitrogen atom into a bicyclic system with the terminal phenyl ring



Compound	No. of CH_2 carbon			Receptor binding affinity at high Na, K_i (nM)[6]			GTPγS functional antagonism, K_b (nM)[7]		
	m	*n*	*p*2	Mu	Kappa	Delta	Mu	Kappa	Delta
13	1	2	1	nd	nd	nd	27.42 ± 4.69	38.49 ± 7.05	146.68 ± 24.24
14	2	1	2	5.05 ± 0.92	187.97 ± 34.70	144.07 ± 4.71	0.97 ± 0.16	38.87 ± 0.10	130.99 ± 7.31
1	2	1	–	7.44 ± 2.94	136.26 ± 59.55	70.21	2.25 ± 0.47	18.41 ± 7.99	23.14 ± 6.88

The data are expressed in mean ± SEM where the assay run $n \geqslant 2$ and value without SEM where $n = 1$. nd = not determined.

Table 4. Side chain SAR of 6-(2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-7-yloxy)nicotinamide



Compound	R	Receptor binding affinity at high Na, K_i (nM)[6]			GTPγS functional antagonism, K_b (nM)[7]		
		Mu	Kappa	Delta	Mu	Kappa	Delta
15	*n*-Butyl	20.81 ± 0.09	nd	503.7 ± 29.1	4.22 ± 0.36	11.06 ± 0.33	>43
16	*n*-Pentyl	11.86 ± 1.60	105.88 ± 21.12	187.00	5.73 ± 2.99	9.99 ± 0.93	>28
17	*n*-Hexyl	12.03 ± 1.96	116.41 ± 30.74	163.22	1.94 ± 0.35	11.28 ± 0.56	5.91 ± 0.68
18	3-Methylbutyl	11.14 ± 1.49	78.09 ± 7.79	232.46 ± 27.76	2.36 ± 0.10	5.49 ± 0.13	48.24 ± 21.24
19	4-Methylpentyl	7.55 ± 1.41	105.95 ± 4.92	107.88 ± 9.38	1.39 ± 0.27	8.94 ± 2.16	15.22 ± 5.13
20	5-Methylhexyl	11.93 ± 0.52	318.95 ± 20.94	239.77	4.14 ± 2.06	>13	>28
21	3,3-Dimethylbutyl	18.33 ± 2.55	71.62 ± 20.57	409.29 ± 59.44	9.12 ± 0.18	7.58 ± 0.30	>58
22	2-Ethylbutyl	42.03 ± 0.16	61.65 ± 12.85	3888 ± 282	15.77	25.76	>58
23	4,4,4-Trifluorobutyl	24.42 ± 7.06	nd	388.15 ± 2.46	3.87 ± 0.18	>37	>43
24	3-Cyclohexylpropyl	41.67 ± 6.69	703.78 ± 11.43	466.27	5.14	186.75	>28
25	2-Morpholin-4-ylethyl	128.70 ± 3.46	359.89 ± 51.63	1909	>23	>13	>28
26	3-Morpholin-4-ylpropyl	215.87 ± 28.05	3254 ± 575	2576	>23	>13	>28

The data are expressed in mean ± SEM where the assay run $n \geqslant 2$ and value without SEM where $n = 1$. nd = not determined.

Another possible incorporation of the nitrogen atom is to incorporate it with the terminal phenyl ring (route (b), Fig. 2). Two isoquinolinyl derivatives **13** and **14** in Table 3 were prepared from tetrahydroisoquinoline and an appropriate aldehyde intermediate (prepared by slight modification of methods reported earlier[5]) via conventional reductive amination (Route F in Scheme 1). The compound **14** that mimics **1** showed comparable binding affinities with **1**, though less potent in the in vitro functional antagonism at the delta receptor. The compound **13** showed much less potent functional activities as compared to **2** presumably due to the differences in the orientation of the terminal region between the two. Though these two compounds showed respectable in vitro functional antagonism, the compounds with the nitrogen incorporated into the ring system with the middle phenyl ring, shown in Table 2, were chosen for further SAR exploration, as they provided more versatile and simple side chain modifications.

As stated earlier, one of our initial concerns was the in vivo stability of the benzylic side chains. We therefore decided to explore the feasibility of alkyl or cycloalkyl side chains in the benzo[*c*]azepinyl series based on **10** (Table 2). Alkyl (**15**–**17**) or branched alkyl chains (**18**–**22**) showed reasonable binding affinities at the three opioid receptor subtypes, although more variable and less potent at the kappa and delta receptors. Cycloalkyl termini such as cyclohexyl (**24**) and morpholinyl (**25**–**26**) groups were not favored. Most compounds in Table 4 exhibited excellent in vitro antagonism at the mu and kappa receptors. The compounds **17**–**19** showed respectable in vitro functional antagonism at all three receptors. This suggests that requirement of the amino side chain terminus of the carboxamido-biaryl ether series does not limit to the aryl group but rather seems more related to the hydrophobic or steric environment in order to antagonize the three opioid receptors.

In conclusion, we discovered several biaryl ethers having a wide range of amine tethers with excellent activity against three opioid receptor subtypes through the SAR study of carboxamido-biaryl ethers as opioid receptor antagonists. The 6-(2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-7-yloxy)nicotinamide scaffold (Table 4) holds potential for further modification and development to identify potent and metabolically stable opioid receptor antagonists.

Acknowledgments

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