Bioorganic & Medicinal Chemistry Letters 20 (2010) 5405–5410

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

SAR development of a series of 8-azabicyclo[3.2.1]octan-3-yloxy-benzamides as kappa opioid receptor antagonists. Part 2

Todd A. Brugel *, Reed W. Smith, Michael Balestra, Christopher Becker, Thalia Daniels, Gerard M. Koether, Scott R. Throner, Laura M. Panko, Dean G. Brown, Ruifeng Liu, John Gordon, Matthew F. Peters

CNS Discovery Research, AstraZeneca Pharmaceuticals, 1800 Concord Pike, Wilmington, DE 19850, USA

ARTICLE INFO

Article history:
Received 18 June 2010
Revised 21 July 2010
Accepted 26 July 2010
Available online 3 August 2010

Keywords:
Kappa opioid antagonist
Depression

ABSTRACT

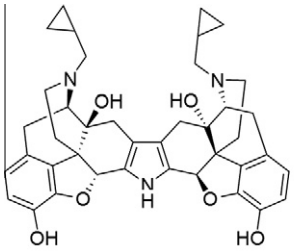
Further structure activity relationship studies on a previously reported 8-azabicyclo[3.2.1]octan-3-yloxy-benzamide series of potent and selective kappa opioid receptor antagonists is discussed. Modification of the pendant N-substitution to include a cyclohexylurea moiety produced analogs with greater in vitro opioid and hERG selectivity such as **12** (κ IC_{50} = 172 nM, μ:κ ratio = 93, δ:κ ratio = >174, hERG IC_{50} = >33 μM). Changes to the linker conformation and identity as well as to the benzamide ring moiety were also investigated.

The opioid family of G-protein coupled receptors (GPCRs) is comprised of kappa (κ), mu (μ), delta (δ), and opioid-like receptor (ORL-1). The chemistry and biology of the natural and synthetic ligands of these receptors have been extensively studied by the scientific and medical community.[1] In particular, the role of κ opioid receptor ligands in the modulation of mood has attracted great interest in recent years.[2] Originally developed as 'molecular probes' to study the behavioral effects of κ agonism, selective κ antagonists such as nor-BNI (**1**, Fig. 1) have been shown to possess potential anti-depressant activity in preclinical animal studies.[3]

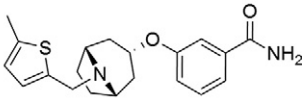
Our interest in developing potential new treatments for major depressive disorder (MDD) led to the recent identification of a series of potent and selective κ antagonists based on an 8-azabicyclo[3.2.1]octan-3-yloxy-benzamide chemotype.[4] The low molecular weight, highly CNS penetrant thiophene analog **2** (Figure 1) showed potent in vitro κ antagonism ([^{35}S]GTPγS IC_{50} = 20 nM) as well as in vivo activity through reversal of κ agonist induced rat diuresis. In this Letter, we wish to report on additional structure–activity relationship studies of this series of κ antagonists.

An issue that was recognized early on with analog **2** and other related derivatives was their potent in vitro inhibition of the hERG ion channel.[5] Methylthiophene **2** was found to inhibit hERG with an IC_{50} of 260 nM (Table 1). Non-aromatic cyclohexylmethyl analog **3** showed reduced hERG activity (IC_{50} = 2.0 μM), but with a similar loss in κ antagonism. We were aware from another internal project that urea substitution of cyclohexyl moieties was a plausible way to improve hERG selectivity while maintaining target potency. Starting with 8-azabicyclo[3.2.1]octan-3-yloxy-benzonitrile **4**,[7] hydration of the nitrile to the primary amide was followed by reductive amination with either *trans*-Boc-4-aminocyclohexanecarbaldehyde **5** or *trans*-Boc-2-(4-aminocyclohexyl)acetaldehyde **6** to provide the corresponding *trans*-Boc-4-aminocyclohexyl analogs **7** and **8** (Scheme 1). Deprotection of the carbamate group with saturated ethanolic hydrogen chloride followed by reaction of the primary amines with dimethylcarbamoyl chloride gave the desired *trans*-ureas **9** and **10**.[8]

Final compounds were tested for their ability to inhibit agonist-stimulated activation of G-proteins using a [^{35}S]GTPγS binding assay in HEK membranes containing each of the cloned human opioid receptor subtypes.[4] No measureable levels of agonism were observed at either κ or μ for analogs described below.



nor-BNI **1**
κ GTPγS IC_{50} = 2.1 ± 0.1 nM
μ GTPγS IC_{50} = 212 ± 27 nM
δ GTPγS IC_{50} = 24 ± 4 nM

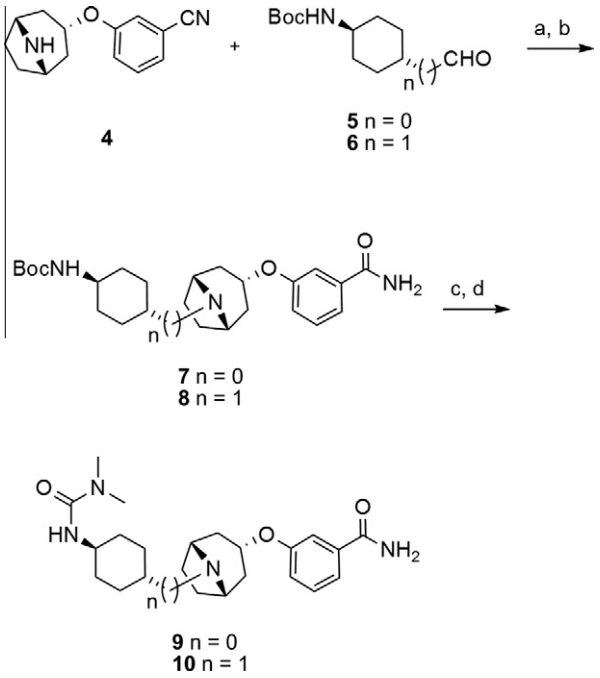


2
κ GTPγS IC_{50} = 20 ± 3 nM
μ GTPγS IC_{50} = 722 ± 47 nM
δ GTPγS IC_{50} = 8306 ± 1,635 nM

Figure 1. Selective kappa opioid antagonists nor-BNI **1** and 8-azabicyclo[3.2.1]octan-3-yloxy-benzamide **2** (in-house data).

* Corresponding author. Tel.: +1 302 885 5759; fax: +1 302 885 1806.
E-mail address: todd.brugel@astrazeneca.com (T.A. Brugel).

0960-894X/$ - see front matter © 2010 Published by Elsevier Ltd.
doi:10.1016/j.bmcl.2010.07.112



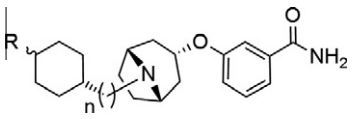
Scheme 1. Reagents and conditions: (a) **4**, KOH, *t*-BuOH, 85 °C; (b) **5** or **6**, macroporous polystyrene bound triacetoxyborohydride (MP-BH(OAc)$_3$), DCM; (c) HCl/EtOH (satd), rt; (d) dimethylcarbamoyl chloride, Et$_3$N, DCM.

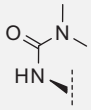
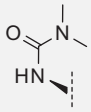
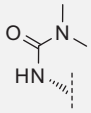
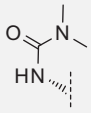
As summarized in Table 1, the methylene linked *trans*-cyclohexylurea **9** showed a ~6-fold loss in κ antagonism relative to **3**, while the ethylene linked *trans*-cyclohexylurea **10** was more similar in potency to **3** (451 nM and 204 nM, respectively). Both urea derivatives were inactive at hERG and showed high μ and δ selectivity. The corresponding *cis*-4-cyclohexylurea analogs **11** and **12** were synthesized according to the procedure outlined in Scheme 1. Once again, the methylene-linked derivative **11** showed reduced κ antagonism (20-fold relative to **3**). Conversely, ethylene linked *cis*-4-cyclohexylurea analog **12** maintained the same level of potency as **3**, but with improved κ selectivity relative to μ (93-fold) and hERG (IC_{50} >33 μM). Unfortunately, this also resulted in reduced in vitro permeability (vide infra). The improved opioid selectivity observed with this extended N-substitution could be attributed to a better fit into the 'message' and 'address' sites of the κ binding pocket.[9]

We next sought to understand the effects of modification to the linker atom between the benzamide ring and azabicyclooctane core. Initially, we investigated a change in the linker stereochemistry at C(3) of the azabicyclooctane core from *endo* to *exo*. Compared to the parent *endo* analog **13**, the *exo* derivative **14** (Table 2) showed a 34-fold decrease in κ antagonism, suggesting that this conformation change impaired the ability of *exo*-**14** to properly associate with the receptor.[10]

In addition to differences brought about by *endo* and *exo* stereochemistry changes at the C(3) position, we were also interested in modifying the linker group itself. The initial linker modification explored was a methylene replacement. Synthesis of the *endo* and *exo* isomers of the methylene linked azabicyclooctane is described in

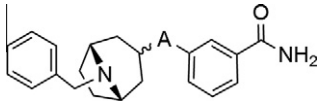
Table 1
SAR comparison of unsubstituted analogs **2**–**3** with *trans* and *cis*-4-cyclohexylurea derivatives **9**–**12**[a]



Compd	R	*n*	[^{35}S]GTPγS IC_{50} (nM)			hERG IC_{50}[d] (μM)
			κ[a]	μ[b]	δ[c]	
2	—	—	20 ± 3	721 ± 47	8306 ± 1635	0.26
3		1	204 ± 70	1826 ± 877	>30,000	2.0
trans-**9**		1	1301 ± 394	>30,000	>30,000	>33
trans-**10**		2	451 ± 39	18,862 ± 1840	>30,000	>33
cis-**11**		1	4197 ± 382	18,513 ± 4610	>30,000	>33
cis-**12**		2	172 ± 10	16,334 ± 1060	>30,000	>33

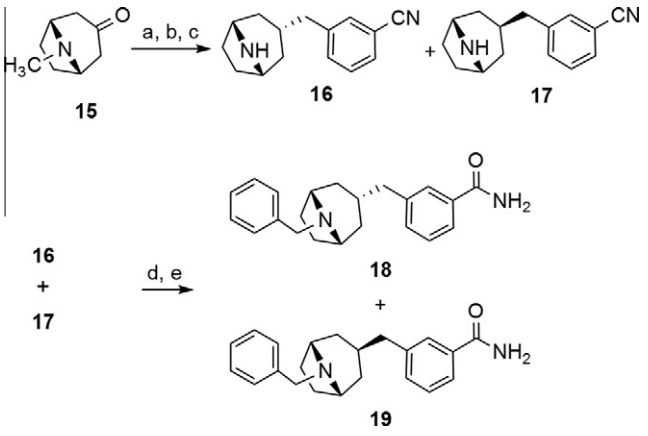
[a] Kappa (κ) antagonism was determined in a human [^{35}S]GTPγS assay using Dynorphin A(1-13) as the agonist stimulus. IC_{50}'s are reported as the mean ± SEM ($n \geqslant 2$) and without SEM where $n = 1$.
[b] Mu (μ) antagonism was determined in a human [^{35}S]GTPγS assay using DAMGO as the agonist stimulus. IC_{50}'s are reported as the mean ± SEM ($n \geqslant 2$) and without SEM where $n = 1$.
[c] Delta (δ) antagonism was determined in a human [^{35}S]GTPγS assay using SNC-80 as the agonist stimulus. IC_{50}'s are reported as the mean ± SEM ($n \geqslant 2$) and without SEM where $n = 1$.
[d] Inhibition of the human ether-a-go-go (hERG) voltage-gated ion-channel was determined using an IonWorks™ electrophysiology assay.[9] IC_{50}'s are reported as the mean of $n \geqslant 2$ experiments.

Table 2
Comparison of 3-*endo* and 3-*exo* linked 3-oxo-*meta*-benzamide-8-azabicyclo-[3.2.1]-octane analogs **13**–**14**, **18**–**19**, and **23**–**25**



Compd	A	[^{35}S]GTPγS IC$_{50}$ (nM)			hERG IC$_{50}$[a] (μM)
		κ[a]	μ[a]	δ[a]	
endo-**13**		286 ± 20	10,682 ± 1425	27,442 ± 255	0.61
exo-**14**		9680 ± 960	ND[b]	>30,000	3.0
endo-**18**		596 ± 26	3941 ± 13	>30,000	1.5
exo-**19**		2143 ± 172	11,910 ± 1310	24,290 ± 700	0.25
endo-**23**		338 ± 11	3077 ± 407	>30,000	1.1
endo-**24**		8242 ± 1966	ND[a]	>30,000	20
endo-**25**		1489 ± 78	17,039 ± 3440	14,697 ± 1250	1.1

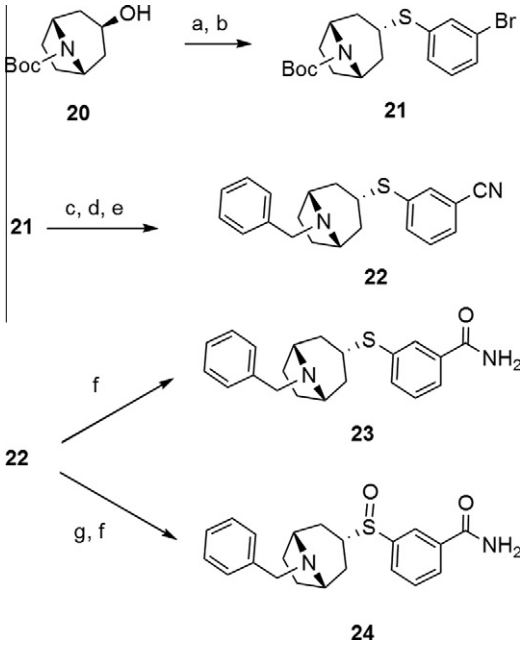
[a] See footnotes in Table 1.
[b] ND = not determined



Scheme 2. Reagents and conditions: (a) diethyl 3-cyanobenzylphosphonate, NaH, THF, 91%; (b) 10% Pd/C, H_2 (1 atm), MeOH, 50%; (c) (i) ACE-Cl, DCM, reflux, (ii) MeOH, reflux, (6:1, **16**:**17**); (d) PhCHO; DCM, $NaBH(OAc)_3$, rt; (e) [$PtH(PMe_2OH)(PMe_2O)_2H$], $EtOH/H_2O$ (6:1), 80 °C.

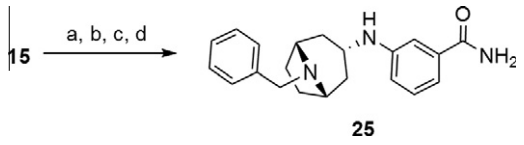
Scheme 2. Tropanone **15** underwent Horner–Wadsworth–Emmons reaction with diethyl 3-cyanobenzylphosphonate to provide the corresponding exocyclic C(3) alkene. Reduction of the olefin followed by demethylation with 1-chloroethylchloroformate (ACE-Cl) provided a 6:1 mixture of *endo*:*exo* carbon-linked products **16** and **17**. The sterically favored addition of hydrogen across the olefin from the face opposite the ethylene bridge of the azabicyclooctane core influences the level of selectivity observed for this reaction. Isomers **16** and **17** could be separated via chiral supercritical fluid chromatography (SFC) prior to reductive amination and nitrile hydration[11] to provide **18** and **19**.

It was observed that *endo*-**18** produced only a slight reduction (two-fold) in κ antagonism relative to its oxygen counterpart *endo*-**13** (Table 2). As was seen with **13**, *exo*-**19** was less potent than *endo*-**18**, but only by 3.5-fold. Although the *endo* isomer remained preferred for the methylene linked analog, the difference was markedly less. Additionally, the μ/κ selectivity for *endo*-**18** was determined to be reduced versus the oxygen linked analog (seven-fold vs 37-fold, respectively).



Scheme 3. Reagents and conditions: (a) MsCl, Et_3N, DCM; (b) 3-bromothiophenol, NaH, THF, reflux; (c) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF, 100 °C; (d) 4 M HCl/dioxane, DCM; (e) PhCHO, MP-$BH(OAc)_3$, DCM; (f) [$PtH(PMe_2OH)(PMe_2O)_2H$], $EtOH/H_2O$ (6:1), 80 °C; (g) $NaIO_4$, $MeOH/H_2O$.

We decided to explore additional linker-atom changes in the *endo* configuration. Hence, synthesis of the sulfur-linked derivatives was undertaken beginning with Boc-pseudotropine **20** (Scheme 3). Mesylation of the C(3) hydroxyl followed by nucleophilic displacement with 3-bromothiophenol produced exclusively the *endo* sulfur-linked intermediate **21**.[12] To incorporate the primary amide functionality, **21** was subjected to palladium catalyzed



Scheme 4. Reagents and conditions: (a) 3-aminobenzonitrile, $Na(OAc)_3BH$, DCE; (b) (i) ACE-Cl, DCM, reflux; (ii) MeOH, reflux; (c) PhCHO, MP-$BH(OAc)_3$, DCM; (d) $[PtH(PMe_2OH)(PMe_2O)_2H]$, $EtOH/H_2O$ (6:1), 80 °C.

cyanation[13] to afford the corresponding *meta*-benzonitrile product. Boc deprotection followed by reductive amination gave **22**. Hydration of the nitrile produced *endo*-**23**. Additionally, selective oxidation of **22** to the corresponding sulfoxide followed by nitrile hydration gave *endo*-**24**. As seen in Table 5, the thio linker proved to be an adequate replacement for oxygen as *endo*-**23** showed near equal potency to *endo*-**10**, although with somewhat reduced μ/κ selectivity. However, conversion to the sulfoxide *endo*-**24** was not well tolerated leading to reduced κ antagonism.

Finally, synthesis of the NH-linked analog *endo*-**25** commenced with reductive amination between tropanone **15** and 3-aminobenzonitrile to give exclusively the *endo* intermediate (Scheme 4). Standard manipulations as described previously produced *endo*-**25**. Subsequent testing in the κ functional assay showed that the NH-linker was the least tolerated modification, producing a five-fold decrease in antagonism.

With N-substitution and linker modifications adequately scoped, we turned our attention to the benzamide region of this series of κ antagonists. Our initial desire was to incorporate heteroatoms into the benzamide ring to lower the lipophilicity of this region in anticipation that this structural change would assist in limiting hERG activity. All four pyridyl analogs of the 3-substituted benzamide **13** were synthesized (**26**–**29**, Table 3).[14] A minimum of a 30-fold loss in κ antagonism was observed with these changes. Additionally, pyridazine analog **30** was also inactive at both κ and μ suggesting a strict criteria for a lipophilic aromatic group at this position in the receptor binding site. Furthermore, none of these modifications had a positive impact on reducing hERG inhibition.

Addition of small substitutions on the benzamide ring was explored and good tolerance for a 5-fluoro-substituent with *meta*-amide analog **31** (κ IC_{50} = 222 nM) was observed. Replacement of the fluoro for a methyl at the 5-position in **32** resulted in some reduction in κ potency. Repositioning this methyl to either the 6- (**33**) or 2-position (**34**) led to even further loss of potency.

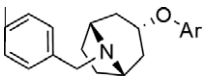
We also explored repositioning of the primary amide functionality on the aromatic ring. The *ortho* (**35**) and *para* (**36**) isomers of **13** were not well tolerated in the κ antagonist assay (Table 4). However, upon addition of a 2-methyl group to *para*-benzamide **36**, we observed a recovery of κ potency (**37**, κ IC_{50} = 462 nM) albeit with complete loss of μ/κ selectivity. We then looked to place other substituents at the 2-position including fluoro (**38**) and nitrogen (**39**), as well as nitrogen at the 3-position (**40**). Unfortunately, these modifications only resulted in a loss of activity.

In order to better understand the role of the primary amide in this series of antagonists, we explored several derivatives of this group. As seen in Table 4, neither *N*-methyl nor *N,N*-dimethyl substitution to give secondary amide **41** or tertiary amide **42**, respectively, were tolerated. This underscores the specific requirement for a primary amide to obtain any level of opioid antagonist activity. Several research groups have observed that the primary carboxamide moiety serves as an effective isostere for the phenolic group in many known peptidic and non-peptidic opioid ligands.[15] We therefore synthesized phenol analog **43** which did show equivalent κ antagonism, and slightly improved μ/κ selectivity, relative to the parent benzamide **13**.

In Table 5, the in vitro ADME profile for a pair of our novel κ antagonists is summarized. Overall, these analogs possessed low metabolism by human liver microsomes with a moderate increase observed when tested in rat microsomes. However, these results represent an attenuation of rat metabolism relative to what was observed in compounds described in our previous communication.[4] Permeability (MDCK-MDR1 P_{app} A > B) was seen as very good for carbon-linked analog **18**, while the more extended analog **12** showed limited permeability. In both cases, P-gp efflux ratios were moderate. These analogs also showed high unbound levels of compound as measures in rat plasma protein binding (PPB).

We next undertook an in vivo rat pharmacokinetic study to further understand how the in vitro properties of these analogs would translate. As summarized in Table 6, analog **18** showed high levels of plasma clearance (CL) and a moderate volume of distribution

Table 3
SAR of 3-oxo-*meta*-benzamide-8-azabicyclo-[3.2.1]-octane analogs **26**–**34** containing a modified *meta*-benzamide group



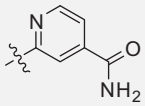
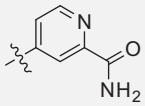
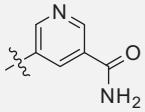
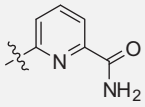
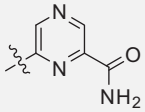
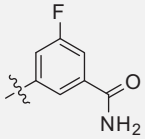
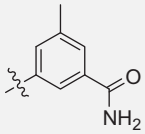
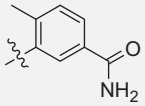
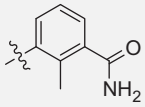
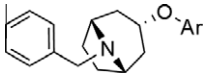
Compd	R	[^{35}S]GTPγS IC_{50} (nM)		hERG IC_{50} (μM)
		κ	μ	
26		8624 ± 705	>30,000	1.0
27		14,161 ± 385	ND	1.6
28		17,802 ± 1600	ND	1.5
29		>30,000	ND	1.0
30		>30,000	ND	15
31		222 ± 2	8084	0.68
32		1733 ± 51	17,429 ± 2495	0.66
33		3500 ± 120	>23,040	ND
34		4176 ± 790	>26,704	1.1

Table 4
SAR of 3-oxo-benzamide-8-azabicyclo-[3.2.1]-octane analogs **35**–**43** containing *ortho* and *para*-benzamides as well as amide isosteres



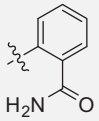
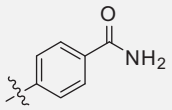
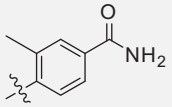
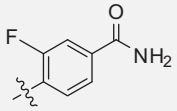
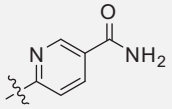
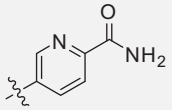
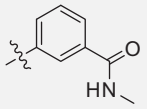
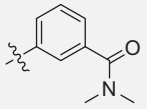
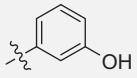
Compd	R	[^{35}S]GTPγS IC$_{50}$ (nM)		hERG IC$_{50}$ (μM)
		κ	μ	
35		>30,000	ND	0.34
36		10,729 ± 515	ND	0.68
37		462 ± 29	419 ± 28	1.0
38		2698 ± 117	8188 ± 188	1.4
39		19,287 ± 1670	ND	1.3
40		>30,000	ND	ND
41		>30,000	ND	ND
42		>30,000	ND	ND
43		347 ± 75	22,230 ± 4235	1.6

Table 5
In vitro DMPK properties for azabicyclo[3.2.1]octane derivatives **12** and **18**

Compd	κ IC$_{50}$ (nM)	hCL$_{int}$[a]	rCL$_{int}$[a]	P_{app}[b] A > B	Efflux ratio[c]	Rat PPB[d] (%free)
12	172	<4	30	19	2.9	92
18	596	<4	65	140	3.1	81

[a] Human and rat liver microsomal intrinsic clearance (hCL$_{int}$) was measured as μl/min/mg protein according to the standard human liver microsomal stability assay protocol.
[b] P_{app} A > B is the rate (nm/s) of transport in the apical to basolateral (A > B) direction as measured with MDR1 transfected MDCK1 canine kidney cells.
[c] Efflux is measured as a ratio of transport from apical to basolateral (A > B) versus basolateral to apical (B > A) directions using MDR1 P-glycoprotein (P-gp) expressed MDCK cells.
[d] Rat plasma protein binding (PPB) was determined as percent free (%free) compound available after incubation in male Sprague–Dawley rat plasma.

(VD$_{ss}$) when dosed intravenously (iv). This combination contributed to the short iv half-life ($t_{1/2}$ = 1.3 h) and low bioavailability (%F = 5%) observed for **18**. A good brain/plasma ratio of 1.9 suggested sufficient levels of CNS exposure for this compound and could be predicted from the favorable in vitro permeability data. Conversely, cyclohexylmethyl urea analog **12** possessed poor brain exposure (total brain/plasma ratio = 0.22, predicted unbound brain/plasma ratio <0.2), a result consistent with the moderate P-gp efflux liability and poor permeability identified in vitro.

In conclusion, we have followed our initial disclosure of potent and selective κ antagonists based on an 8-azabicyclo[3.2.1]octan-3-yloxy-benzamide structure with additional SAR analysis at three key regions. High tolerance for extended substitutions of the basic nitrogen was observed leading to analogs showing improved hERG

Table 6
In vivo rat pharmacokinetic profile for azabicyclo[3.2.1]octane derivatives **12** and **18**

Compd	CL[a] (ml/min/kg)	$t_{1/2}$[a] (h)	VD_{ss}[a] (L/kg)	[Br]/[Pl][a]	%*F*[b]
12	ND[c]	ND	ND	0.22	ND
18	124	1.3	6.6	1.9	5

[a] Plasma clearances (CL), half-lives ($t_{1/2}$), volume of distributions (VD_{ss}) and brain:plasma concentration ratios ([Br]/[Pl]) were measured after a 5 μmol/kg (**12**) or 2 μmol/kg (**18**) intravenous (iv) infusion dose in Sprague–Dawley rats.

[b] Percent bioavailability (%*F*) was measured using the above iv data along with data from a 2 μmol/kg (**18**) oral (po) dose in Sprague–Dawley rats.

[c] ND = not determined; these parameters were not calculated from the iv infusion data.

and opioid selectivity. Modifications to the 3-substituent of the azabicyclic core revealed a preference for the *endo* over *exo* conformation and moderate tolerance for methylene and sulfur linkers. Finally, changes to the benzamide region of this series, including increasing hydrophilicity and repositioning the primary amide, generally resulted in loss of κ antagonism and/or opioid selectivity. This knowledge has provided greater scope about this new chemotype that can be further utilized to optimize the properties of these novel κ antagonists.

Acknowledgments

We thank Jennifer Van Anda, David Coomber, Frances McLaren, and Xiaomei Ye for purification support; James Hall for NMR support; Timothy Blake for assistance with LC–MS analysis; and Norman Ledonne and Patricia Schroeder for in vitro and in vivo ADME support.

References and notes

1. For a review see: Aldrich, J. V.; Vigil-Cruz, S. C. *Burger's Medicinal Chemistry and Drug Discovery*, 6th ed.; John Wiley & Sons: New York, 2003. pp 329–481.
2. Carlezon, W. A.; Béguin, C.; Knoll, A. T.; Cohen, B. M. *Pharm. Therap.* **2009**, *123*, 334.
3. (a) Portoghese, P. S.; Lipkowski, A. W.; Takemore, S. E. *Life Sci.* **1987**, *40*, 1287; (b) McLaughlin, J. P.; Maron-Popovici, M.; Chavkin, C. *J. Neurosci.* **2003**, *23*, 5674.
4. Brugel, T. A.; Smith, R. W.; Balestra, M.; Becker, C.; Daniels, T.; Hoerter, T. N.; Koether, G. M.; Throner, S. R.; Panko, L. M.; Folmer, J. J.; Cacciola, J.; Hunter, A. m.; Liu, R.; Edwards, P. D.; Brown, D. G.; Gordon, J.; Ledonne, N. C.; Pietras, M.; Schroeder, P.; Sygowski, L. A.; Hirata, L. T.; Zacco, A.; Peters, M. F. *Bioorg. Med. Chem. Lett.* **2010**. doi:10.1016/j.bmcl.2010.07.113.
5. Inhibition of the human ether-a-go-go (hERG) voltage-gated ion-channel was determined using an IonWorks™ electrophysiology assay.[6] IC_{50}'s are reported as the mean of $n \geqslant 2$ experiments.
6. Schroeder, K.; Neagle, B.; Trezise, D. J.; Worley, J. *J. Biomol. Screening* **2003**, *8*, 50.
7. See Ref. 4 above for details on the preparation of **4**.
8. All new analogs were synthesized in >95% purity as determined by ^{1}H NMR and LC–MS analysis.
9. (a) Schwyzer, R.; Eberle, A. *Front. Horm. Res.* **1977**, *4*, 18; (b) Metzger, T. G.; Paterlini, G.; Portoghese, P. S.; Ferguson, D. M. *Neurochem. Res.* **1996**, *21*, 1287.
10. *Endo* versus *exo* stereochemistry of the linker substitution was determined using 1D-NOESY NMR experiments.
11. Gaffar, T.; Parkins, A. W. *Tetrahedron Lett.* **1995**, *36*, 8657.
12. Nagase, T.; Takahashi, T.; Sasaki, T.; Nagumo, A.; Shimamura, K.; Miyamoto, Y.; Kitazawa, H.; Kanesaka, M.; Yoshimoto, R.; Aragane, K.; Tokita, S.; Sato, N. *J. Med. Chem.* **2009**, *52*, 4111.
13. Tschaen, D. M.; Desmond, R.; King, A. O.; Fortin, M. C.; Pipik, B.; King, S.; Verhoeven, T. R. *Synth. Commun.* **1994**, *24*, 887.
14. Analogs from Tables 3 and 4 were synthesized according to the general procedure described in Ref. 4.
15. (a) Dolle, R. E.; Machaut, M.; Martinez-Teipel, B.; Belanger, S.; Cassel, J. A.; Stabley, G. J.; Gracyzk, T. M.; De Haven, R. N. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3545; (b) Wentland, M. P.; Lou, R.; Denhardt, C.; Duan, W.; Cohen, D. J.; Bidlack, J. M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1717; (c) Wentland, M. P.; Lou, R.; Ye, Y.; Cohen, D. J.; Richardson, G. P.; Bidlack, J. M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 623.