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α-Hydroxy amides as a novel class of bradykinin B_1 selective antagonists

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Abstract—Antagonism of the bradykinin B_1 receptor represents a potential treatment for chronic pain and inflammation. Novel antagonists incorporating α-hydroxy amides were designed that display low-nanomolar affinity for the human bradykinin B_1 receptor and good bioavailability in the rat and dog. In addition, these functionally active compounds show high passive permeability and low susceptibility to phosphoglycoprotein mediated efflux, predictive of good CNS exposure.

Bradykinin (BK) B_1 and B_2 receptors are G-protein coupled receptors that function in pain and inflammation pathways.[1] The peptides, bradykinin and kallidin, act as the physiological agonists for the constitutively expressed BK B_2 receptor to evoke acute pain immediately after tissue injury.[2] Bradykinin and kallidin are metabolized to [des-Arg^9]BK (DABK) and [des-Arg^{10}]kallidin which serve as the natural agonists for the bradykinin B_1 receptor.[3] While this receptor is not widely expressed peripherally in non-diseased states, it is induced upon injury and is believed to play a role in persistent pain and inflammation. Studies suggest that the BK B_1 receptor is constitutively expressed in the central nervous system (CNS) of mice,[4] rats,[5] and primates,[6] implicating a central role for these receptors in addition to the accepted peripheral mode of action. The therapeutic potential for a selective BK B_1 antagonist has been supported by recent studies of B_1 knockout mice.[7] Additionally, peptidic antagonists,[8] and more recently non-peptidic antagonists,[9,10] have shown promising results in inflammatory pain animal models across a variety of species.

Concurrent with our work on cyclopropylamino acid amide[11,12] BK B_1 antagonists (representative structure **1**), we initially sought to simplify the overall structure by modifying the *N*-terminus. Herein, we disclose that remarkably simple α-hydroxy amides can serve as viable replacements for the cyclopropylamino acid amides in this novel class of BK B_1 receptor antagonists. The compounds appearing in Tables 1 and 2 were prepared employing standard amide bond forming procedures beginning with the known biaryl benzylic amines previously disclosed.[12,13] K_i values (nM) were determined radiometrically using the appropriate radioligand and Chinese hamster ovary (CHO) cells stably expressing the human, monkey, rabbit, dog or rat BK B_1 receptor.[14] In vitro functional activity was assessed in standard fluorescence imaging plate reader (FLIPR) experiments (IC_{50}, nM). Full details for the above experiments[9] and the protocol for determining rat and dog

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Table 1. Bradykinin B_1 receptor binding affinities for the lead α-hydroxy amide analogs of **2** (Scheme 1)

Compound	R^1	R^2	Human K_i[a] (nM)
2	–CH_2–	–CH_2–	59.1
3	H	H	516
4	Me	Me	125
5	Et	Et	1090
6	CF_3	CF_3	95.0
(*S*)-**7**	Me	H	660
(*R*)-**8**	H	Me	1050
(*R*)-**9**	CF_3	H	109
(*S*)-**10**	H	CF_3	479
(*S*)-**11**	*i*-Pr	H	71.5
(*S*)-**12**	*t*-Bu	H	88.5
(*S*)-**13**	*i*-Pr	Me	83.5
(*R*)-**14**	CF_3	Me	24.5
(*S*)-**15**	Me	CF_3	579

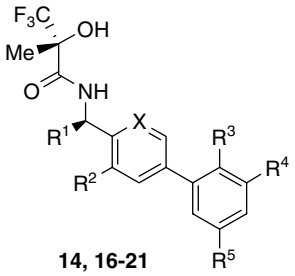
[a] Values represent the numerical average of at least two experiments. Interassay variability was ±10% for the binding assay.

pharmacokinetic (PK) properties were previously described.[9,15] Phosphoglycoprotein (Pgp) efflux ratios for compounds in Table 2 (the ratio of a compound's rate of basolateral to apical movement over its rate of apical to basolateral movement across a monolayer of MDR1 transfected LLC-PK1 cells) and the corresponding apparent permeabilities (P_{app}, 10^{-6} cm/s) were determined in the standard fashion.[12] This assay served as an in vitro model of the blood–brain barrier, such that compounds with higher Pgp ratios were more likely to be actively transported out of the CNS than those with Pgp ratios approaching unity.

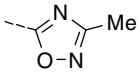
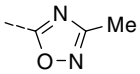
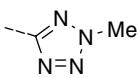
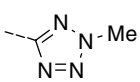
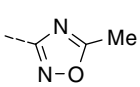
The design strategy which led to the discovery of the α-hydroxy amide class was supported by the substantial body of structure–activity relationship (SAR) data developed for the diaminopyridine[16] and cyclopropylamino acid amide series.[11,12] These studies indicated that it was necessary to retain both hydrogen bond donors in **1** to maintain efficient binding but suggested that replacing one amidic N–H hydrogen bond donor with a hydroxyl group might afford similar receptor binding, concomitant with a significant decrease in both molecular complexity and molecular weight. According to this reasoning, compound **2** (Table 1), with a 1-hydroxycyclopropyl amide moiety, was chosen as the initial replacement for the *N*-acylcyclopropyl amide portion of compound **1**.

Since compound **2** displayed only a 40-fold reduction in binding affinity at the BK B_1 receptor relative to **1**, this dramatic structural change warranted further investigation. The hydroxyl group in **2** was shown to be critical for binding by comparison to the *des*-hydroxy com-

Table 2. BK B_1 binding affinities, FLIPR values, Pgp ratios, and permeability data for the α-hydroxy amides



14, 16-21

Compound	R^1	R^2	X	R^3	R^4	R^5	h K_i[a] (nM)	h FLIPR IC_{50}[b] (nM)	Pgp ratio	P_{app}[b] (10^{-6} cm/s)
14	H	F	CH	CO_2Me	F	H	24.5	43.6	1.6	32
16	Me	F	N	CO_2Me	Cl	Cl	0.35	3.93	1.6	23
17	Me	F	N		Cl	Cl	0.79	6.65	1.3	33
18	Me	F	N		F	Cl	0.66	6.65	1.7	35
19	Me	F	N		F	Cl	0.59	4.90	2.8	36
20	Me	Cl	N		F	Cl	0.43	—	1.8	26
21	Me	F	N		F	Cl	0.66	4.47	1.6	27

[a] Values represent the numerical average of at least two experiments. Interassay variability was ±10% for the binding assay and ±25% for the FLIPR experiments.

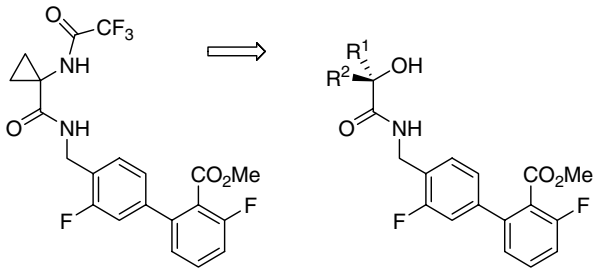
[b] Values represent the numerical average of at least three experiments. Interassay variability was ±20%.

pound (not shown) which had a $K_i = 3.0\ \mu M$. Subsequently, through the application of SAR developed for the diaminopyridine[16] and cyclopropyl-amino amide[12] series of BK B_1 antagonists, biaryl-modified analogs of **2** were quickly optimized to promising drug-like structures displaying subnanomolar binding affinities and appropriate PK properties (data not shown). Unfortunately, detailed metabolic investigation of these cyclopropylhydroxyl-containing compounds revealed a limitation toward further development. Consistent with literature precedent of related structures,[17] we confirmed that the cyclopropylhydroxyl moiety was prone to single electron oxidation of the hydroxyl followed by ring opening of the strained cyclopropyl ring to form undesired, reactive metabolites.

Returning to the optimization of the α-hydroxy amide, the glycolamide (**3**) suffered an unacceptable decrease in binding affinity of almost an order of magnitude. Simply breaking open the cyclopropyl ring to arrive at the gem-dimethyl analog (**4**) was less detrimental. Such a small decrease in binding affinity (2-fold) upon scission of the cyclopropyl ring implied that the hyper-conjugative overlap between the cyclopropyl bonds and the π-bond of the amide carbonyl, required to properly constrain the amide-containing compounds similar to **1**,[11] was no longer necessary in the α-hydroxy series. Instead, lipophilic interactions with the receptor by this portion of the molecule were now more important (vide infra). An initial probe of these lipophilic interactions with the receptor binding site was examined using the gem-diethyl version of **4** (compound **5**). A loss of nearly 9-fold in binding affinity relative to **4** showed that negative steric interactions with the receptor could also occur. The gem-trifluoromethyl compound **6** provided the first indication that electronic tuning of the hydroxyl could be beneficial and might even override the negative steric interactions likely to be present in this similarly bulky molecule.

Comparison of the natural (**7**) and unnatural (**8**) lactic amide derivatives indicated a slight preference of the BK B_1 active site for the (*S*)-enantiomer. The related comparison between trifluoro-lactic amides **9** and **10** showed a larger preference for the (*R*)-enantiomer, the enantiomer which placed the CF_3 group in the same chiral space as the CH_3 of (*S*)-lactic acid (note change in chirality prioritization). In all cases large groups were most beneficial for binding when they appeared on the α-face of the generic structure appearing in Scheme 1, as drawn (R^1). Introduction of the *iso*-propyl group at R^1 in **11** afforded increased affinity. However, there was a limit to the benefit gained from increasingly large groups at this position, as the *tert*-butyl analog **12** showed a decrease in binding affinity relative to the smaller *iso*-propyl analog **11**.

While the secondary alcohols **7**–**12** were instrumental in determining the importance of chirality for efficient binding, the significance of tertiary alcohols was not overlooked (compare **7** and **8** with **4**). The incorporation of an α-methyl group into **11** forming **13** was theorized to improve binding. This compound's binding affinity



1, human bradykinin B_1 K_i = 1.5 nM
Pgp ratio = 4.1, P_{app} = 23 (*10^{-6} cm/s)

2 - 15

Scheme 1.

did not increase as expected.[18] However, when the trifluoro-lactic amide analog **9** was substituted with an additional α-methyl group, the expected increase in binding affinity was observed for **14**. These results show the importance of balancing both steric and electronic effects for obtaining improved binding affinity. This compound displayed a K_i of 24.5 nM, a 2-fold improvement over the initial α-hydroxy amide **2**. Compound **15** showed a 24-fold decrease in binding affinity relative to its enantiomer **14**. This trifluoromethyl lactic moiety has previously found utility in dissimilar structures targeting a range of indications.[19]

Compound **14** served as an excellent platform upon which to explore variations in the biaryl motif. In general the SAR developed in our related series of BK B_1 antagonists[12,16] was conserved in this new series, with a few notable exceptions. Perhaps the most significant deviation can be seen by comparing Pgp ratios. Compound **1**, with a Pgp ratio greater than 2, would be considered a moderate Pgp efflux substrate. By contrast, the analogous compound containing the trifluoromethyl lactic amide (**14**, redrawn in Table 2) is not an efficient Pgp substrate as demonstrated by its Pgp ratio of less than ~2. In the case of analogs similar to **1**, it was essential that our BK B_1 antagonists contained a benzylic methyl group and to a lesser extent a pyridyl biaryl (X = N, Table 2) to lower Pgp ratios. Although introduction of these elements had little effect on Pgp ratios in the new series, they did result in a 70-fold boost in potency (**16**). In the presence of a methyl ester on the terminal ring ($R^3 = CO_2Me$), the optimal substitution pattern was found to be the 3,5-dichloro arrangement in **16**. This compound showed a subnanomolar binding affinity, low nanomolar functional activity in vitro, and a Pgp ratio predictive of good CNS exposure.

The 3-methyl oxadiazole served as a viable surrogate for the methyl ester providing compound **17**. In the case of this heterocycle and subsequent heterocycles (data not shown), the 3,5-dichloro substitution was not optimal. Illustrating another point of divergence from previously developed SAR, the optimal halogenation pattern on the terminal phenyl ring was found to be that of compound **18**. Applying this knowledge to the 2-methyl tetrazole analog **19** provided a potent compound that unfortunately displayed susceptibility toward Pgp-mediated efflux with a Pgp ratio of 2.8. This efflux ratio

could be reduced to an acceptable value (ratio < 2) simply by changing the halogen on the pyridine ring to a chlorine (**20**, Pgp ratio = 1.8).

Ultimately a superior balance among the myriad of pharmacologic properties was achieved by employing the 5-methyl oxadiazole as an ester surrogate (compound **21**, vide infra). While the SAR data for the 5-methyl oxadiazoles were similar to those of the esters and 3-methyl oxadiazoles, they routinely showed reduced Pgp efflux ratios relative to their 2-methyl tetrazole analogs (full data not shown, but compare **21** to **19**). Furthermore, when tested against a panel of 159 enzymes, receptors, and transporters, **21** showed greater than 4000-fold selectivity for the human BK B_1 receptor.

Dog and rat PK parameters for the compounds in Table 2 are shown in Table 3. Dog PK was regularly determined through IV (only) cassette dosing as previously reported. Compounds warranting further investigation were then evaluated in Sprague–Dawley rats. The trifluoromethyl lactic amide **14** showed a relatively short half-life and moderate clearance in the dog. As expected, introduction of a central pyridine ring and chlorine substitution at the 5-position of the phenyl ring, as in **16**, improved PK parameters significantly. This substitution in the context of the 3-methyl oxadiazoles (**17**, **18**) continued to instill acceptable PK in both species. A tremendous boost in PK was seen for compound **19**. Inhibition of CYP3A4, 2C9, and 2D6 was evaluated as a possible explanation for the astonishing PK results. However, this was not the case; IC_{50} inhibition values for each of the P450 isoforms were greater than 10 μM. Despite the excellent PK determined for **19**, its susceptibility to active transport across the blood–brain barrier (Pgp ratio = 2.8, Table 2) suggested it would not afford high levels of CNS exposure. The minor change in the halogenation of the pyridine in compound **20** resulted in a significant decrease in PK values. Returning to a fluoropyridine, the 5-methyl oxadiazole **21** displayed the good PK parameters shown in Table 3. Further PK experiments with **21** (single dosing) in dog (n = 2, IV dose = 1 mg/kg, oral dose = 3 mg/kg) and rhesus monkey (n = 2, IV dose = 1 mg/kg, oral dose = 1 mg/kg) gave similarly good results. Dog PK was in good agreement with the cassette dosing: F% = 84%, $t_{1/2}$ = 11 h, and CL = 0.45 mL/min/kg. Rhesus PK values were as follows: F% = 52%, $t_{1/2}$ = 1.3 h, and CL = 7.1 mL/min/kg.

Table 3. Pharmacokinetic parameters for selected compounds (Table 2)

Compound	Rat PK[a] F%, $t_{1/2}$, CL, Vd	IV dog PK[b] $t_{1/2}$, CL, Vd
14	—	1.4, 16, 1.2
16	47, 5.6, 7.8, 1.2	3.6, 3.2, 0.73
17	21, 3.9, 20, 1.0	9.5, 0.91, 0.66
18	32, 1.2, 22, 1.3	15, 1.0, 1.2
19	53, 27, 1.0, 0.54	38, 0.22, 0.47
20	71, 4.9, 2.4, 0.86	9.8, 1.3, 0.74
21	34, 2.0, 4.9, 0.52	17, 0.42, 0.51

[a] F% oral bioavailability, half-life in hours, CL in mL/min/kg, Vd in L/kg. Sprague–Dawley rats (n = 3). Oral dose = 10 mg/kg, IV dose = 2 mg/kg. Interanimal variability was less than 20%.

[b] Beagle dogs (n = 2). IV dose 0.25 mg/kg as a cocktail of 3–6 compounds (plus reference standard) in DMSO. Interanimal variability was less than 20% for all values.

Similar to other bradykinin B_1 antagonists[12,16] compound **21** showed a high selectivity for primate BK B_1 receptors over the non-primate species (BK B_1 K_i = 1.85 nM (monkey), 13.0 nM (rabbit), 205 nM (dog), and 2.18 μM (rat)), attributable to the limited receptor homology for the BK B_1 receptor across species.[3] Consequently, it would be difficult or unethical to test this compound in classic models of pain. Alternatively, an in vivo pharmacodynamic readout for **21** could be obtained using a recently described Rhesus blood pressure model.[12,20] For this experiment, functional BK B_1 receptors were induced in the vasculature by IV administration of bacterial lipopolysaccharide, as evidenced by a depressor blood pressure response to the BK B_1 agonist DABK. Antagonists are then evaluated based on their ability to reverse this depressor effect, in a dose dependent fashion, resulting in the generation of AD_{90} values which represent the required dose necessary to block 90% of agonist's effect. Compound **21** compared favorably to previously published results displaying an AD_{90} = 17 μg/kg (IV).[12,21]

With regard to CNS receptor occupancy, we employed a previously described transgenic rat model to determine the concentration required to occupy 90% of the human B_1 receptors expressed in the rat CNS.[12] An Occ_{90} = 140 nM was determined for compound **21**, representing one of the lowest values determined to date.[21] This demonstration of improved receptor occupancy in the humanized rat model and improved in vivo efficacy in the Rhesus model supported the selection of compound **21** as our next clinical candidate for the treatment of inflammatory pain.

In conclusion, novel bradykinin B_1 receptor antagonists have been developed, with the most potent members demonstrating subnanomolar binding affinity and low-nanomolar functional activity. This α-hydroxy amide class of compounds was optimized for pharmacokinetic properties and a low susceptibility to Pgp-mediated efflux, predictive of good CNS exposure. An optimized compound displayed improved in vivo efficacy through antagonist activity at the monkey bradykinin B_1 receptor and improved receptor occupancy relative to our first clinical candidate.

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18. The enantiomer of **13** displayed lower affinity (h BK B_1 $K_i = 3.57$ μM).
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21. For easy comparison, the AD_{90} for our first clinical candidate in the Rhesus LPS assay was 47 μg/kg and the Occ_{90} in the transgenic rat was 520 nM.