Cyclopropylamino Acid Amide as a Pharmacophoric Replacement for 2,3-Diaminopyridine. Application to the Design of Novel Bradykinin B_1 Receptor Antagonists

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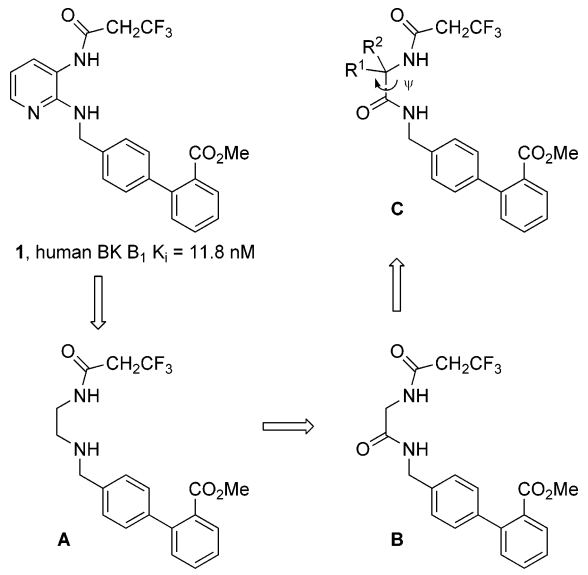
Abstract: Antagonism of the bradykinin B_1 receptor represents a potential treatment for chronic pain and inflammation. Novel antagonists were designed that display low-nanomolar affinity for the human bradykinin B_1 receptor and good bioavailability in the rat.

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 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 nondiseased 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 systems of mice,[4] rats,[5] and primates,[6] implicating a central role for these receptors and 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. These mice display a reduced sensitivity to various types of noxious, painful stimuli and inflammatory agents, such as carrageenan, while remaining otherwise normal and fertile.[7] Additionally, peptidic antagonists,[8] and more recently nonpeptidic antagonists,[9,10] have shown promising results in inflammatory pain animal models across a variety of species. While these antagonists have helped to validate BK B_1 receptors as a therapeutic target, they lack the physical properties or pharmacokinetic characteristics required of an orally active pharmaceutical.

Concurrent with our work on benzodiazepine[9] and dihydroquinoxalinone[10] BK B_1 antagonists, we explored a class of 2,3-diaminopyridines represented by **1** (Scheme 1). Although analogues of **1** were thoroughly investigated,[11] reactive metabolites associated with the diaminopyridine core could complicate further development.[12] Herein, we disclose that a

Scheme 1



cyclopropylamino acid amide can serve as a viable replacement for the problematic diaminopyridine structure in these inhibitors of the BK B_1 receptor. In addition, structural studies suggest that this substitution may have general utility.

The compounds appearing in Table 1 were prepared employing standard amide bond forming procedures beginning with the known methyl 4′-(aminomethyl)biphenyl-2-carboxylate.[13] The requisite *N*-Boc-cyclobutylamino acid for the synthesis of **8** was prepared according to a published procedure.[14]

K_i values (nM) were determined radiometrically using the appropriate radioligand and Chinese hamster ovary (CHO) cells stably expressing the human BK B_1 receptor.[15] Full details for the above experiment and the protocol for determining rat pharmacokinetic properties were previously described.[9]

The design strategy that led to the replacement of the diaminopyridine core was supported by the substantial body of SAR data developed for the biphenyl motif and the *N*-acyl region for analogues similar to **1**.[11] We inferred that it was necessary to retain both N−H bonds, the *N*-acyl group, and its spacial proximity to the biphenyl region. The most direct way to tether the two N−H groups would be to connect the *N*-acyl group and the biphenylamine with an ethylene linker to afford **A** (Scheme 1). To retain a heteroatom at the location of the pyridine nitrogen, a carbonyl group was installed to maintain any relevant lone pair interactions (see **B**). This carbonyl group also served to attenuate the basicity of the benzylic amine to more closely resemble that of its diaminopyridine analogue.[16] Since this glycine-linked analogue is unlikely to adopt a conformation similar to that of **1**, we exploited the Thorpe−Ingold effect[17] and installed a *gem*-dimethyl group at the C_α position to yield **C**. This modification was intended to ease rotation[17] about the carbonyl−C_α bond with the expectation that this would increase the population of conformations more closely resembling **1**. According to this reasoning, **2** (Table 1), with an α-aminoisobutyric acid (Aib) moiety, was chosen as the initial replacement for the 2,3-diaminopyridine core.

Compound **2** displayed measurable binding affinity at the bradykinin B_1 receptor with a K_i of 3.45 μM (290-fold less than that of compound **1**). As anticipated, the binding affinity of **3** was reduced relative to **2**. To dissect the importance of the two

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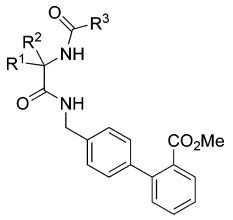
Table 1. Bradykinin B_1 Receptor Binding Affinities and Rat Pharmacokinetics for the Substituted Glycines



compd[a]	R^1, R^2	*n*	R^3	human K_i [b] (nM)	rat *F* (%), $t_{1/2}$ (h), CL (mL min^{-1} kg^{-1})
1	NA	NA	CH_2CF_3	11.8	9 (±3), 0.15 (±0.01), 35 (±3)
2	Me, Me		CH_2CF_3	3450	35 (±8), 6.6 (±2.1), 4.2 (±0.9)
3	H, H		CH_2CF_3	52000	
(*R*)-**4**	Me, H		CH_2CF_3	1580	
(*S*)-**5**	H, Me		CH_2CF_3	>50000	
6	$-(CH_2)_n-$	5	CH_2CF_3	752	25 (±13), 12 (±5), 2.6 (±1.1)
7	$-(CH_2)_n-$	4	CH_2CF_3	462	
8	$-(CH_2)_n-$	3	CH_2CF_3	119	
9	$-(CH_2)_n-$	2	CH_2CF_3	63.0	26 (±10), 9.5 (±1.6), 9.3 (±2.7)
10	$-(CH_2)_n-$	2	5-pyrimidinyl	25.5	
11	$-(CH_2)_n-$	2	5-(CF_3)-pyridin-3-yl	1.80	

[a] All compounds were >95% pure by HPLC and characterized by ^{1}H NMR and HRMS. [b] Values represent the numerical average of at least two experiments. Interassay variability was ±10% for the binding assay.

geminal methyl groups present in **2**, the enantiomeric alanine analogues **4** and **5** were prepared. Clearly, the D-alanine analogue, **4**, is preferred over its antipode and displays a 2-fold greater affinity for the BK B_1 receptor than compound **2**. Given the lack of measurable binding of the L-alanine isomer at the BK B_1, it is interesting that the binding affinity of the α-aminoisobutyric acid analogue **2** is approximately half that of the D-alanine analogue, consistent with the idea that conformationally the Aib residue can represent a consensus set between D- and L-alanine. Although the preceding observations point to the potential of the D-amino acid series, an alternative path of exploration was pursued.

Comparing the diaminopyridine **1** with the Aib analogue **2**, we proposed that additional alkyl functionality at the C_α carbon of **2** serves also to restore lipophilic interactions available to the aromatic pyridine portions of **1**. The cyclohexylamino acid analogue **6** was therefore prepared and found to have an approximately 4-fold improved binding affinity over **2**. Continued reductions in ring size afforded concomitant increases in binding affinity (cf. **6**−**8**). Ultimately, the cyclopropylcarbonyl moiety in **9** proved to be the best replacement for the diaminopyridine core, displaying a binding affinity just 5-fold lower than the 2,3-diaminopyridine-containing compound **1** (K_i = 11.8 nM).

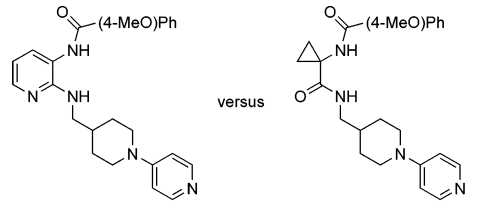
The BK B_1 receptor binding affinity of **9** could be further improved with modifications to the N-terminal acyl group. Thus, exchange of trifluoroethyl with 5-pyrimidinyl gave analogue **10** and a 2-fold improvement in potency. The 5-trifluoromethyl-3-pyridyl analogue **11** is representative of the most potent analogues in this structural class and displayed a 6-fold greater affinity for the human BK B_1 receptor when compared to the 2,3-diaminopyridine **1**.

Compounds in which the 2,3-diaminopyridine core was replaced with a substituted glycine linker showed improved pharmacokinetic properties. For example, the initial replacement with Aib to afford **2** resulted in a 4-fold improvement in oral bioavailability, a 44-fold increase in intravenous (iv) half-life, and an 8-fold decrease in clearance relative to **1**. The cyclohexyl analogue **6** and the cyclopropyl analogue **9** showed similar improvements over **1**. These more favorable pharmacokinetic profiles likely result from the stability of the unnatural α-amino acids to cleavage by peptidases[18] and from the removal of the metabolically labile diaminopyridine. Moreover, this substitution by a cyclopropylamino acid amide addressed the issue of reactive metabolites associated with the diaminopyridine core (vida supra) and provided scaffolds not prone to form active metabolites, despite the presence of small, highly strained carbocycles.

The ability of a cyclopropylamino acid amide to efficiently function as a pharmacophoric surrogate for a 2,3-diaminopyridine deserves further discussion. A detailed explanation for the preceding observations depends heavily on the peptide descriptor angle ψ. The diaminopyridine core of **1** can be viewed as a peptidomimetic with a ψ dihedral angle constrained to 0°, by virtue of the fact that the two nitrogens at the 2 and 3 positions are coplanar (the pyridine nitrogen serves as the carbonyl oxygen in this pseudo-peptide). Therefore, analogues of general structure **C** (Scheme 1) whose ψ angles most closely approach 0° should bind in fashion similar to **1**.

In support of this proposal, the glycine analogue **3**, likely with a preferred ψ angle of 180°, has low affinity for the BK B_1 receptor. By contrast, the Aib analogue **2**, with a preferred ψ angle of −30° (±20°) and +30° (±20°),[19] begins to approach the "ideal" angle of 0°. Consequently, **2** binds with improved affinity relative to **3**. Both enantiomeric alanine compounds **4** and **5** should have identical preferred ψ angles but with opposite signs. The large discrepancy in their respective binding affinities is attributable to the chiral nature of the BK B_1 receptor binding pocket which appears to strongly favor the D-amino acid.

The preferred ψ angles for **2** and **6** are likely to be similar, and for this comparison it is probably an increased lipophilic interaction of **6** with the BK B_1 receptor that increases its binding affinity relative to **2**. However, if this lipophilic interaction with the BK B_1 receptor were the dominant factor, one would expect a decrease in binding affinity as the cycloalkyl ring is contracted (cf. **7**−**9**). This is not observed. Here again, a ψ angle argument can explain the observed affinities. This is most important for the cyclobutyl and cyclopropyl analogues. These smaller rings, especially the cyclopropyl ring, contain carbon−carbon bonds with increasing p character. As a result, favorable $\pi-\pi$ hyperconjugative overlap between the carbonyl π bond and the cyclopropyl carbon−carbon bond orbitals can



12
human BK B_1 K_i >10 μM
human Factor Xa K_i = 39 nM

13
human BK B_1 K_i >10 μM
human Factor Xa K_i = 175 nM

Figure 1. Demonstration of the generality of replacing a 2,3-diaminopyridine with a cyclopropylamino acid amide as applied to a factor Xa inhibitor.

occur.[20a] This overlap is maximized at ψ angles of 0° and 180°. In effect, the cyclopropylamino acid is uniquely endowed with the ability to adopt and stabilize ψ angles close to 0°. Dihedral ψ angles in this range have been observed in crystal structures and inferred from NMR experiments.[20]

The ring strain found in the cyclopropyl ring also serves to increase the bond angle between geminal substituents, forcing them apart. This angle is now closer to 116° rather than the tetrahedral bond angle of 109° for an sp^3 carbon. Once again, this more closely approximates the sp^2 bond angles of 120° found in the diaminopyridine system. Additionally, as the size of the ring contracts, its steric bulk decreases, allowing the *N*-acyl group to adopt a conformation more similar to that found in **1**, where the steric demands of a flat aryl ring are minimal. These stereoelectronic arguments explain why the cyclopropylamino acid moiety may serve as a general replacement for similar 2,3-diaminopyridine structures.

In support of the preceding proposition, the identical substitution of a 2,3-diaminopyridine by a cyclopropylamino acid amide was performed on a compound that, although of similar structure, binds to an enzyme. Compound **12** (Figure 1) is a nanomolar (K_i = 39) factor Xa inhibitor.[21,22] By comparison, the cyclopropylamino acid amide analogue **13** yielded a K_i of 175 nM. The 5-fold loss in affinity of **12** compared to **13** matches almost identically the decrease in binding affinity when comparing **1** to its cyclopropyl analogue **9**. These two examples clearly demonstrate the potential of making similar modifications and suggest that the substitution may be of general utility. Although a decrease in binding affinity was observed in both cases, reoptimization of the *N*-acyl group might quickly restore the lost affinity to factor Xa as it did for the human BK B_1 receptor (vida supra).

In conclusion, a novel class of human BK B_1 receptor antagonists has been developed, with the most potent members demonstrating low-nanomolar binding affinity to the human BK B_1 receptor and good rodent bioavailability. The structural similarities between a cyclopropylamino acid amide and a 2,3-diaminopyridine have been rationalized on stereoelectronic grounds, and the generality of interchanging these pharmacophoric templates has been demonstrated. The ultimate optimization of these cyclopropylamino acid amides will be disclosed in due course.

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Supporting Information Available: Spectral data and HRMS data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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