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The synthesis and SAR of calcitonin gene-related peptide (CGRP) receptor antagonists derived from tyrosine surrogates. Part 1

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ABSTRACT

We have systematically studied the effects of varying the central unnatural amino acid moiety on CGRP receptor antagonist potency and CYP inhibition in a series of ureidoamides. In this Letter, we report the discovery of compound **23**, a potent CGRP receptor antagonist with only weak CYP3A4 inhibition. Unlike the triptans, compound **23** did not cause active constriction of ex vivo human cerebral arteries. At doses of 0.3–1 mg/kg (sc), **23** showed robust inhibition of CGRP-induced increases in marmoset facial blood flow, a validated migraine model. Ureidoamide **23** derives from a novel amino acid, 1*H*-indazol-5-yl substituted alanine as a tyrosine surrogate.

Migraines are severe episodic headaches which can last 4–72 h. The pain is often accompanied by nausea and heightened sensitivity to light, sound or odors.[1] It is estimated that 18% of women and 7% of men suffer from migraine and 23% of households have at least one migraneur. Annually, 12% of the general population suffers from this disabling condition.[2] The current standard of care for migraine are triptans (5-$HT_{1B/D}$ agonists). Because triptans are non-selective vasoconstrictitors, they are contraindicated in patients with cardiovascular disease and hypertention.[3] This limitation and the somewhat limited efficacy of triptans[4] underscores the need to develop new migraine drugs that are more effective and do not cause active vasoconstriction.

Calcitonin gene-related peptide (CGRP) is a 37-amino acid neuropeptide that is expressed in the trigeminal ganglia, and has been implicated in the pathogenesis of migraine.[5] Increased levels of CGRP are observed during a migraine attack, and intravenous administration of CGRP can induce headache in migraineurs.[6] In a Phase II clinical trial, intravenous administration of the potent CGRP receptor antagonist BIBN4096BS (olcegepant, 1) demonstrated efficacy in treating migraines that was comparable to that of the triptans, but without the cardiovascular side effects.[7] This result motivated us and others[8,9] to commence a medicinal chemistry effort to identify potent CGRP antagonists that could be administered by other routes of administration, including intranasal[10] and oral[8] administrations.

Previously we reported the identification and SAR of novel CGRP receptor antagonists derived from thiophenylalanines.[11] Compound **2** was found to be a potent CGRP antagonist, but it also was a potent inhibitor of cytochrome P450 3A4 (CYP3A4). In this Letter, we report the structure–activity relationship effort that led to the discovery of BMS-694153,[10] and optimization of compound **23** (Fig. 1), a potent CGRP antagonist with only weak CYP3A4 inhibition. We also describe its activity in a validated in vivo migraine model.[10]

Our medicinal chemistry strategy was to study the effects of varying the central unnatural amino acid moiety on CGRP receptor antagonist potency and CYP inhibition.[12] Our initial observations indicated an important influence of the unnatural D-amino acid on the extent of the CYP3A4 interaction. These results are summarized in Table 1.

From Table 1 it is clear that the human CGRP receptor shows a clear preference for hydrophobic aromatic residues that optimally contain a hydrogen-bond donating group (i.e., **23**) that can spatially mimic a D-tyrosine hydroxyl, such as the 2,6,-dibromo-D-tyrosine (**10**) found in BIBN-4096-BS (**1**). The best CGRP potency was achieved when the aromatic ring was attached to the amino acid backbone by one methylene group (**4** vs **5** and **6**, and **7** vs **8**). Comparing aniline **12** with phenol **7** suggested that a stronger hydrogen bond donor increased CGRP binding affinity. Ether 9

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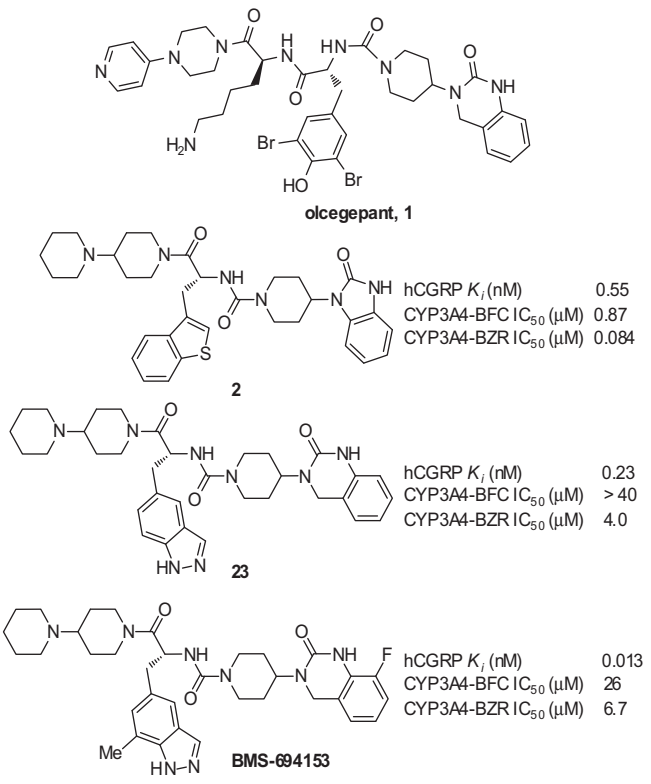


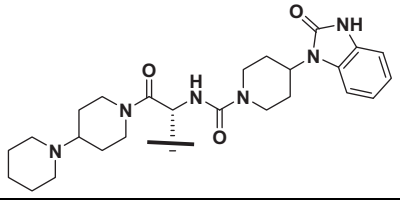
Figure 1.

and amide **13** are much less active, possibly due to a lack of tolerance for hydrogen bond acceptors in that part of the receptor binding pocket or simply from a steric effect. In the absence of a hydrogen-bonding group, fused aromatics or pendant biaryls tended to improve CGRP binding potency. In the case of the biphenyl (**16**) or naphthyl groups (**14** and **15**), 1-naphthyl substitution (**14**) was clearly superior. *N*-methyl-3-indole **18** was comparable to **14**, while the des-methyl analog, **17**, was somewhat less active. Compared to the 2-naphthyl compound (**15**), the 5-indolyl (**19**) and 5-indazolyl (**20**) derivatives were more potent, presumably due to the hydrogen bond donating N–H. In the absence of an aromatic spacer, glutamate (**21**) or glutamine (**22**) side chains offered no advantage.

Selected compounds were tested for in vitro CYP3A4 inhibition using benzyloxyresorufin (BZR) as the substrate. In general, CYP3A4 inhibition correlated with lipophilicity of the aromatic D-amino acid side chains. Both naphthyl derivatives **14** and **15** were potent inhibitors, each showing sub-micromolar potency. Addition of a polar OH (**7**) or an NH in 3-indolyl (**17**) dramatically reduced inhibition, but the 5-indolyl group (**19**) had a much smaller effect on CYP3A4 activity, suggesting specific spatial preferences. Inhibition could be exacerbated by increasing lipophilicity in **10** with the dibromo addition to **7**, and capping the NH of **17** with methyl in **18**. On the other hand, increasing polarity from indole **19** to indazole **20** significantly attenuated inhibition.

Encouraged by the CGRP potency of **19** and **20**, coupling with their diminished CYP3A4 affinities, we continued to explore heteroaromatic D-tyrosine mimetics while also replacing the piperidyl-imidazolone GPCR recognition motif with the piperidyl-quinazolinone, which generally resulted in improved CGRP binding affinities (Table 2). Indeed, sub-nanomolar affinity was achieved with all new examples save **24**, the *S*-enantiomer of indazole **23** and the 2-methylbenzimidazole **28**. The latter was interesting in that it may be another example of a limited steric tolerance for non-aromatic lipophilicity in this part of the receptor binding pock-

Table 1
CGRP receptor binding and CYP3A4 inhibition of ureidoamides **3–21**



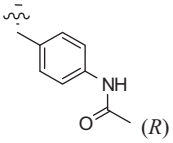
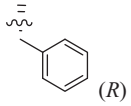
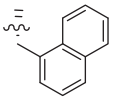
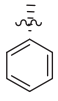
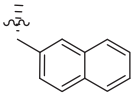
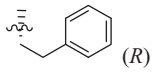
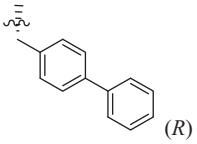
Compounds	AA Moiety (Stereochemistry)	K_i (nM)	CYP3A4 (IC_{50}BZR, μM)	Compounds	AA Moiety (Stereochemistry)	K_i (nM)	CYP3A4 (IC_{50}BZR, μM)
3	 (*R*)	2400	16	**13**	 (*R*)	1900	–
4	 (*R*)	300	–	**14**	 (*R*)	7.2	0.03
5	 (R)	>1000	–	**15**	 (*R*)	230	0.03
6	 (*R*)	>1000	–	**16**	 (*R*)	250	1.3

Table 1 (*continued*)

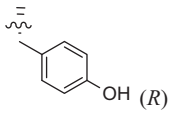
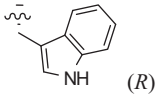
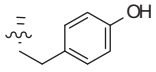
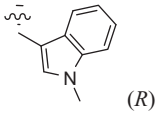
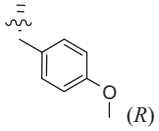
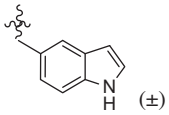
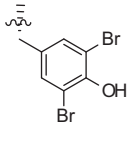
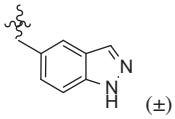
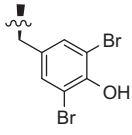
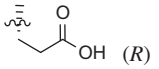
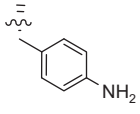
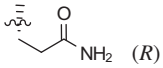
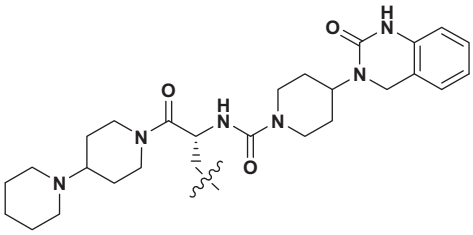
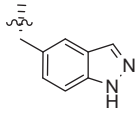
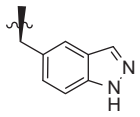
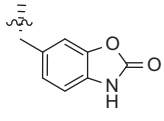
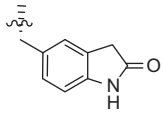
Compounds	AA Moiety (Stereochemistry)	K_i (nM)	CYP3A4 (IC_{50}BZR, μM)	Compounds	AA Moiety (Stereochemistry)	K_i (nM)	CYP3A4 (IC_{50}BZR, μM)
7	 (*R*)	2.5	>40	**17**	 (*R*)	84	>40
8	 (*R*)	2100	–	**18**	 (*R*)	16	0.10
9	 (*R*)	1400	–	**19**	 (±)	32	2.5
10	 (*R*)	0.65	2.4	**20**	 (±)	68	17
11	 (*S*)	>1000	–	**21**	 (*R*)	>1000	–
12	 (*R*)	750	–	**22**	 (*R*)	>1000	–

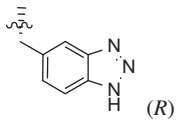
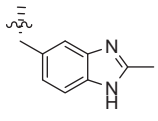
Table 2
CGRP receptor binding and CYP3A4 inhibition of ureidoamides **23**–**28**



Compounds	AA Moiety (Stereochemistry)	K_i (nM)	CYP3A$ (IC_{50}, μM) BZR
23	 (*R*)	0.23	4.0
24	 (*S*)	250	7.3
25	 (*R*)	0.27	30
26	 (*R*)	0.65	11

(*continued on next page*)

Table 2 (*continued*)

Compounds	AA Moiety (Stereochemistry)	K_i (nM)	CYP3A$ (IC_{50}, μM) BZR
27	 (*R*)	0.55	23
28	 (*R*)	28	–

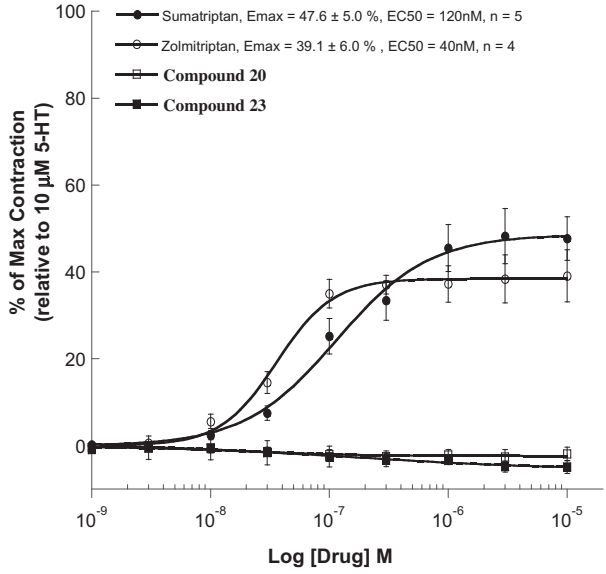


Figure 2. Effect of sumatriptan, zolmitriptan and compounds **20** and **23** on ex vivo human coronary arteries.

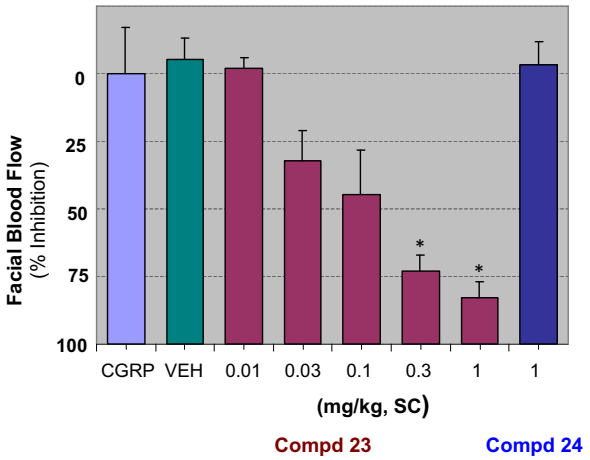


Figure 3. Effects of compounds **23** and **24** on CGRP-induced marmoset facial blood flow.

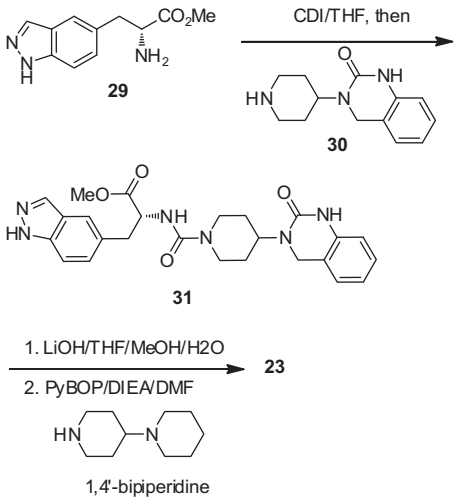
et as was previously seen with **9** and **13**. On the other hand, the fact that benzoxazolinone **25** and indolone **26** were equipotent with **23** might imply some tolerance in the hydrogen bond donor-acceptor interaction. All of these compounds maintained favorable CYP3A4 BZR inhibition profiles (Table 2).

We chose compound **23** for further ex vivo and in vivo studies. To confirm that compound 23 did not have the vasoconstriction liability of 5-$HT_{1B/1D}$ agonists (triptans), we measured basal artery tension upon cumulative addition of **23** to ex vivo human coronary arteries. As a positive control, serotonin (10 μM) was added to each tissue bath at the end of a test session to provide a control measure of maximal contractility in each vessel. Compounds 23 and **20** did not produce measurable contraction in ex vivo human arteries up to 10 μM (Fig. 2). In contrast, both sumatriptan and zolmitriptan produced concentration-dependent vessel contraction up to approximately 48% of the serotonin derived maximum (EC_{50} = 120 nM) and 39% of maximum (EC_{50} = 40 nM), respectively. The absence of active constriction using **23** indicated the different mechanism of action for CGRP receptor antagonists, which is an antidilatory effect—returning dilated vessels to normal. This adds to the body of evidence that CGRP antagonists should be free from mechanism-based cardiovascular liabilities associated with the triptans; and these results are in good agreement with Merck's work on telcagepant (MK-0974).[13].

We used a marmoset facial blood flow model to assess the in vivo efficacy of our CGRP receptor antagonists.[10] In this model, marmosets were anesthetized, and facial blood flow was increased by intravenous (iv) administration of hαCGRP (10 μg/kg) at 45 min intervals (−30, 15, 60, and 105 min). The effect of antagonist, delivered at 0 min, on CGRP-induced changes in facial blood flow were measured by laser Doppler flowmetry. In this study (Fig. 3), compound **23** (**0.3–1** mg/kg) showed a dose-dependent inhibition of CGRP-induced increase in marmoset facial blood flow upon subcutaneous (sc) dosing. In the same study, compound **24**, the *S*-enantiomer of **23** was inactive.

The synthesis of compound **23** is shown in Scheme 1. The coupling of amino ester **29** and quinazolinone **30** afforded urea **31**. Saponification of the methyl ester of **31** with LiOH gave the carboxylic acid, which was coupled with 1,4′-bipiperidine to afford compound **23**. The other compounds in this paper were prepared in the same way using amino esters that were either commercially available or whose synthesis has been reported by us previously.[14]

In summary, we have found that ureidoamides derived from novel amino acids containing hydrogen-bond donors in the alpha substituent, namely 1*H*-indazol-5-yl (**23**), 2-oxo-2,3-dihydrobenzo[*d*]oxazol-6-yl (**25**), 2-oxoindolin-5-yl (**26**), and 1*H*-benzo[*d*][1,2,3]triazol-5-yl (**27**) substituted alanines, were potent CGRP receptor antagonists with relatively weak CYP3A4 inhibition. Unlike the triptans, compound **23** did not cause active constriction of ex vivo human cerebral arteries. At doses of 0.3–1 mg/kg, (sc), 23 showed robust inhibition of CGRP-induced increases in marmoset facial blood flow, a validated migraine model.[10] Efforts to further



Scheme 1. Synthesis of compound **23**.

optimize the potency and pharmacokinetics properties of compound **23** will be reported in due course.

Acknowledgments

We thank the members of Discovery Analytic Sciences in MSCO for their help in the purification and characterization of compounds contained herein.

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9. (a) IDDB, Thomson Scientific reports that the development of BIBN4096BS has been discontinued.; (b) Merck & Co., Inc. announced discontinuation of the clinical development program for MK-3207 on Sept. 10, 2009.
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