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Preparation of imidazoles as potent calcitonin gene-related peptide (CGRP) antagonists

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ABSTRACT

Several new potent CGRP receptor antagonists have been prepared in which the amide bond of lead compound **1** has been replaced by bioisosteric imidazole moieties. Substitution at N-1 of the imidazole was optimized to afford compounds with comparable potency to that of lead **1**. Conformational restraint of the imidazole to form tetrahydroimidazo[1,5-*a*]pyrazine **43** gave substantially improved permeability.

Migraine is a common and debilitating primary headache which can cause significant pain for hours or even days.[1] Characterized by a unilateral throbbing pain, migraine is often accompanied by one or more of the following symptoms: nausea, vomiting, dizziness, tingling or numbness in the face, visual disturbance, and extreme sensitivity to light, touch and smell.[2] Approximately 13% of the US adult population (mostly women), experience migraines.[3] Whereas the direct cost of medication and absenteeism from work continue to rise,[4] the economic consequence of migraines remains largely unrecognized and underappreciated. Currently the triptans are used as the standard of care. Triptans are selective 5-$HT_{1B/1D}$ receptor agonists and are believed to act primarily by simple vasoconstriction of cranial vessels, which are dilated during a migraine attack.[5] However, because the 5-$HT_{1B/1D}$ receptor agonists are non-selective vasoconstrictors, triptans are associated with a number of cardiovascular side effects and are contraindicated in patients with hypertension or ischemic heart disease.[1]

Calcitonin gene-related peptide (CGRP) is a 37-amino acid peptide that belongs to a family of structurally related peptides including adrenomedullin and amylin and has been strongly implicated in the pathogenesis of migraine.[6] Cranial CGRP levels are elevated in patients with migraine, and in fact, infusion of CGRP has been shown to trigger migraine attacks in migraineurs.[7] Moreover, it has been shown clinically that administration of 4 structurally different CGRP receptor antagonists [BIBN4096BS (olcegepant), MK-974 (telcagepant), MK-3207 and BI-44370] have aborted acute migraine[8] with a significant effect at the 2 h endpoint. Importantly, BIBN4096BS (olcegepant) achieved efficacy without the cardiovascular side effects associated with the use of triptans.[9]

Although BIBN4096BS provided a proof of concept for the treatment of acute migraine headache with a CGRP receptor, it was administered by intravenous infusion during clinical trials. Intranasal medications for the treatment of migraine have recently received increased attention, and our earlier letter disclosed our intranasal (IN) development compound BMS-694153 (**1**),[10] which had a number of desirable properties to support its selection. However, it is important to emphasize that a preference study has shown that most migraine patients preferred oral tripan tablets to an intranasal formulation.[11] Although intranasal tryptans have a rapid onset and good tolerability profile, most patients cannot tolerate their unpleasant taste.[12] Therefore, we also sought to identify an orally active CGRP antagonist to treat acute migraine headache.[13]

Although compound **1** exhibited excellent intranasal bioavailability in rabbit (F_{IN} = 55–59%), it did not exhibit significant oral bioavailability in cynomolgus monkey or rat (Fpo ⩽0.3%). We hypothesized that the poor intrinsic permeability of **1** (PAMPA = 11 nm/s @ pH 7.4) was responsible for the poor oral exposure. In order to improve the permeability of our molecules, we targeted isosteric replacement of the amide (Fig. 1). However,

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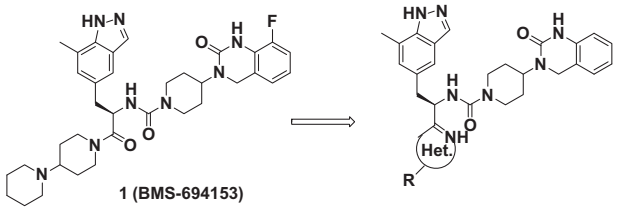


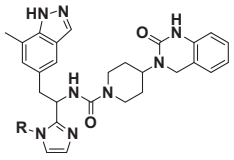
Figure 1. Bioisosteric amide replacement with heterocycle.

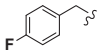
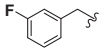
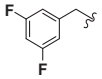
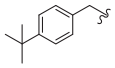
development of a hydrolytically stable amide isostere with the correct orientation proved challenging. Various heterocycles were explored including tetrazoles and oxadiazoles but the imidazole ring, which is more basic and more hydrolytically stable than most other five-membered-ring heterocycles, appeared to be the most promising candidate in this respect.[14] We sought to truncate the piperidine portion of compound **1** and replace the amide bond with an imidazole ring. We envisioned that this modification would reduce molecular weight, increase lipophilicity and ultimately improve the permeability of our molecules.

The imidazole was readily accessed via a Horner–Wadsworth–Emmons olefination of aldehyde **2**[15] with phosphonate **3** to afford olefin **4**, which was reduced with palladium on carbon under an atmosphere of hydrogen to afford ester **5** (Scheme 1). Compound **5** was quantitatively reduced to the alcohol with lithium borohydride to afford alcohol **6**. This was oxidized to aldehyde **7** with sulfur trioxide–pyridine complex, and **7** was converted to imidazole **8** by reaction with glyoxal timer and ammonium hydroxide. Alkylation of the imidazole **8** with benzyl bromide in the presence of base afforded compound **9**, which was globally deprotected and coupled to piperidine **11** in the presence of carbonyldiimidazole to install the urea and afford compound **12** as shown in Scheme 1.

All compounds were tested for binding affinity for the human CGRP receptor, which was determined by inhibition of ^{125}I-CGRP binding in SK-N-MC cell membranes.[10] Compounds of interest were further tested in a functional assay, measuring concentration-dependent inhibition of CGRP-stimulated cAMP production in SK-N-MC cells.[10] All compounds were found to be full, competitive antagonists, and imidazoles substituted with phenethyl and a small selection of benzyl groups were found to be quite potent

Table 1
Human CGRP receptor binding data for compounds **12–20**

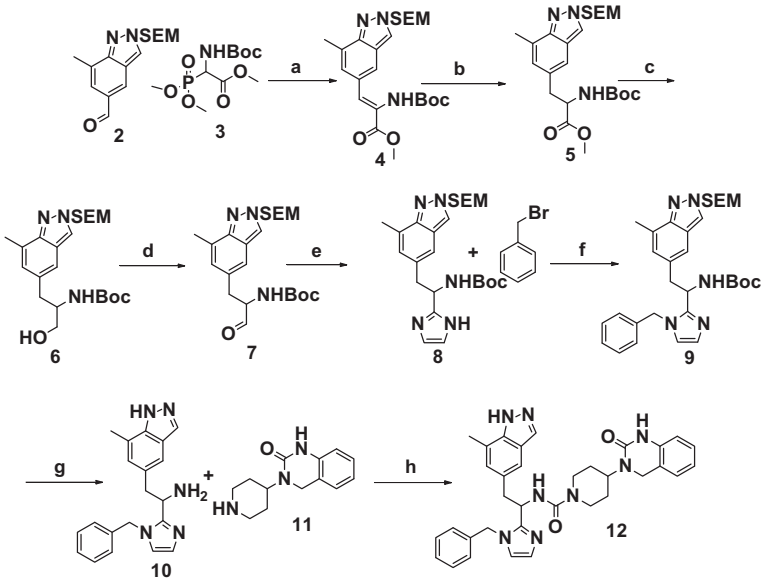


Compound[a]	R	IC_{50} (nM)
12		0.77
13	Methyl	4.8
14	H	97
15		0.88
16		1.9
17		0.98
18		0.63
19		0.39
20		0.19

[a] Compounds are racemic; nd = not determined.

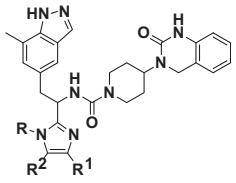
antagonists at the CGRP receptor (Table 1). Compound **19** and compound **20** were particularly interesting as they were the most potent antagonists in this series (0.39 nM and 0.19 nM, respectively).

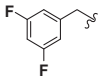
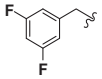
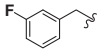
Since multiple substitutions were tolerated at N1 of the imidazole, we further sought to improve potency by substituting at the C4 and C5 positions of the imidazole ring. A series of substituted imidazoles were prepared (Scheme 2), but improvements in potency were not realized (Table 2). However, compound **24**, differing from compound **19** by only a single bromine at C5, and compound **26** differing by a single methyl at C4 from compound **19**, showed



Scheme 1. Reagents and conditions: (a) tetramethylguanidine, THF, 83%; (b) H_2/Pd–C, MeOH, 63%; (c) $LiBH_4$, THF, quant; (d) sulfur trioxide–pyridine complex, TEA, DMSO, 74%; (e) gyloxal, ammonium hydroxide, 1,4-dioxane/H_2O, 70 °C, 54%; (f) cesium carbonate, DMF, 63%; (g) HCl//1,4-dioxane; (h) CDI, THF, 47%.

Table 2
SAR of C-substituted imidazoles



Compound[a]	R	R1	R^2	IC_{50} (nM)	Met stab[16] (H, R, M)
19		H	H	0.39	84, 78, 66
24		Br	H	0.39	100, 100, 93
25	H	Me	H	120	nd
26		H	Me	0.37	100, 87, 85
27	H	H	Br	7.4	nd
28	H	Br	Br	4.8	nd

[a] Compounds are racemic; nd = not determined.

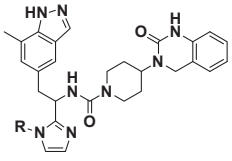
improved in vitro microsomal stability[16] across all species examined while retaining identical potency (Table 2).

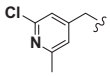
In order to improve the physical properties of our compounds, the benzyl ring was replaced with more polar pyridines. It was anticipated that this would increase solubility and improve oral bioavailability. Compounds **29–33** were synthesized and were found to retain potency at the CGRP receptor (Table 3). However all compounds in this series had very poor microsomal stability (Table 3). Compounds in this series lacking the pyridine (compounds **24** and **26**, Table 2) had excellent microsomal stability. We hypothesized that the pyridine nitrogen may be the site of oxidative metabolism via the formation of the N-oxide. Accordingly compound **33** was designed to shield the pyridine nitrogen and prevent the formation of the putative N-oxide. While **33** achieved excellent potency at the CGRP receptor (IC_{50} = 0.078 nM), which compared quite favorably with our earlier clinical candidate, **1** (IC_{50} = 0.026 nM), no improvement in microsomal stability relative to unsubstituted pyridines, **29–30** was realized.

The excellent potency observed in compound **33** coupled to a small improvement in its permeability (PAMPA = 38 nm/s @ pH 7.4) compared to our clinical candidate, **1** (PAMPA = 11 nm/s @ pH 7.4) encouraged us to evaluate its in vivo pharmacokinetic properties in rats. Upon intravenous administration of 1.0 mg/kg, compound **33** attained an AUC of 1.7 ± 0.2 μM, but was rapidly cleared, presumably due to its poor microsomal stability. We were further disappointed to find that compound **33** had negligible oral exposure (BLLQ), suggesting it was not sufficiently permeable to achieve systemic exposure.

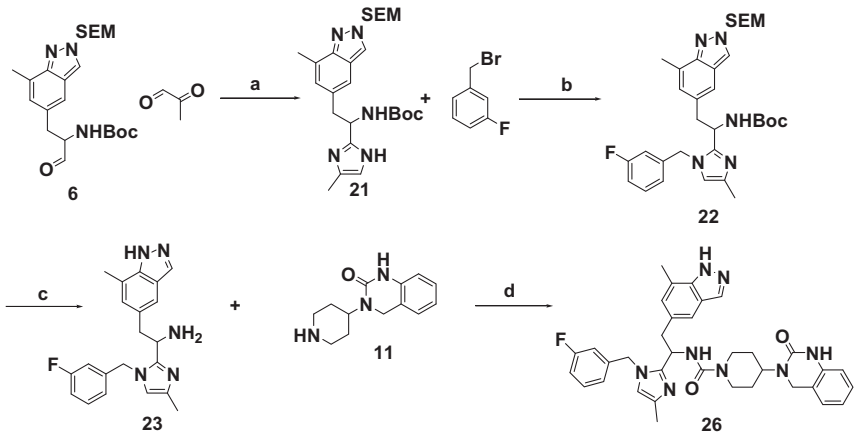
In an earlier communication,[17] we demonstrated that the backbone urea of compound **1** could be replaced with a carbamate and the fluorodihydroquinazoline replaced with a quinolone. These modifications were made in the series under study. Not only were they well tolerated, but they also greatly enhanced microsomal stability. As such, these moieties were incorporated into a final heterocyclic amide replacement. We also reasoned that removal of a hydrogen bond donor (the NH of the urea) may reduce solvation and improve permeability. We sought to maximize potency by bridging N1 and C5 of the imidazole to lock it into a conformation which modeled well with the acyclic scaffolds, restricting the imidazole into a tetrahydroimidazo[1,5-*a*]pyrazine moiety (Scheme 3).

Table 3
Effect of pyridines on CGRP receptor binding

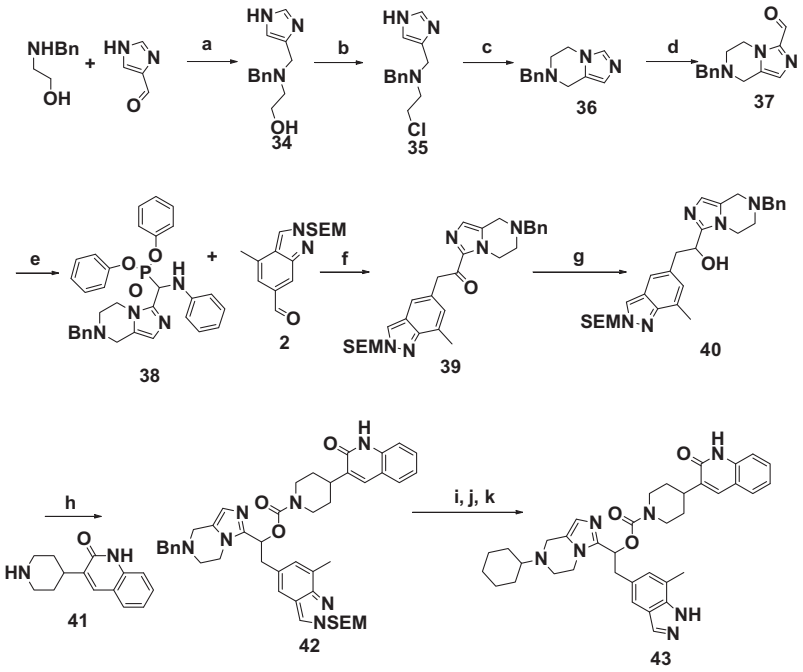


Compound[a]	R	IC_{50} (nM)	Met Stab[16] (H, R, M)
29		1.6	1, 1, 0
30		0.42	4, 20, 2
31		0.83	nd
32		0.13	1, 2, 1
33		0.078	2, 2, 0

[a] Compounds are racemic; nd = not determined.

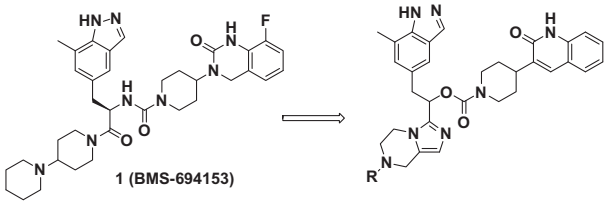


Scheme 2. Reagents and conditions: (a) NH_3 in water, pyruvic aldehyde, 1,4-dioxane/H_2O, 80 °C, 25%; (b) K_2CO_3, DMF, 74%; (c) HCl/1,4-dioxane, rt, quant.; (d) CDI, THF, 74%.



Scheme 3. Reagents and conditions: (a) $NaBH(OAc)_3$, THF, 85%; (b) $SOCl_2$, DCM, 40 °C, 100%; (c) TEA, CH_3CN, 82 °C, 31%; (d) *n*Buli, THF (−78 °C → 0 °C → −78 °C), then DMF, 80%; (e) aniline, diphenyl phosphite, IPA, 85%; (f) Cs_2CO_3, THF/IPA (4:1), 24%; (g) $NaBH_4$, EtOH, 97%; (h) *p*-nitrophenylchloroformate, TEA, DMF, then **38**, NaH, THF, 63%; (i) TFA, DCM, 40%; (j) Pd/C, H_2, 57%; (k) cyclohexanone, $NaBH_3CN$, HOAc (cat.), EtOH, 66%.

Table 4
Conformational restraint of imidazole



Compound[a]	R	IC50 (nM)	Met Stab[16] (H,R,M)	Pampa (nM/s)
43		0.22	41, 30, 21	71
44		0.26	41, 32, 9	15
45		1.7	nd	nd
46	H	2.9	nd	nd

[a] Compounds are racemic; nd = not determined.

The sequence (Scheme 3) began with a reductive amination to afford alcohol **34**, which was converted to the alkyl chloride by action of thionyl chloride to afford **35**. Compound **35** was then treated with base and spontaneously cyclized to the desired conformationally restricted tetrahydroimidazo[1,5-*a*]pyrazine backbone **36**, which was deprotonated with *n*Buli and trapped with dimethylformamide to afford aldehyde **37**. Compound **37** was treated with diphenyl phosphite in the presence of aniline to afford phosphonate **38** which was elaborated to compound **39** via Horner–Wadsworth–Emmons olefination using aldehyde **2.**[13] The ketone was then reduced with sodium borohydride to afford the alcohol, which was converted to its *p*-nitrophenylcarbamate and treated with piperidine **41** to afford carbamate **42**. Debenzylation of **42**, followed by reductive amination with cyclohexanone and SEM removal gave compound **43**.

We were pleased to find that this novel heterocyclic amide replacement was well tolerated, delivering compound **43** (IC_{50} = 0.22 nM) which was essentially equipotent to our most potent acyclic imidazole (**33**, 0.078 nM). PAMPA was significantly improved in **43** compared to amide **1** (Table 4). Unfortunately, this analog did not retain sufficient microsomal stability for advancement. Further optimization of the microsomal stability of this series will be disclosed in due course.

In summary, replacement of the amide of lead compound **1** with a series of substituted imidazoles was well-tolerated and led to the discovery of a novel series of potent CGRP receptor antagonists. Extending these findings identified a conformationally-restrained series, bridging across N1 and C5 of the imidazole and identifying a novel tetrahydroimidazo[1,5-*a*]pyrazine (i.e., compound **43**) which had comparable potency to the acyclic imidazoles.

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