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# Synthesis and SAR of calcitonin gene-related peptide (CGRP) antagonists containing substituted aryl-piperazines and piperidines

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ABSTRACT

Calcitonin gene-related peptide (CGRP) is a potent neuropeptide implicated in the pathophysiology of migraine. In the course of seeking CGRP antagonists with improved oral bioavailability, metabolic stability, and pharmacokinetic properties, lower molecular weight, structurally simpler piperidine and piperazine analogs of BMS-694153 were prepared. Several were found to have nM binding affinity in vitro. The synthesis and SAR of these substituted piperidine and piperazine CGRP antagonists are discussed.



Migraine is a debilitating primary headache disorder characterized by moderate-severe pain which is unilateral, pulsating and/or aggravated by activity which can last for days, and which is accompanied by nausea/vomiting and/or sensitivity to light and sound.[1] The current standard of care, 5-$HT_{1B/D}$ agonists (called triptans) alleviate migraines primarily through constriction of intracranial arteries and additionally possibly by inhibition of central pain transmission and peripheral neuronal inhibition.[2] Unfortunately, triptans also constrict coronary arteries resulting in a contraindication for patients with cardiovascular (CV) disease and hypertension.[3]

Calcitonin gene-related peptide (CGRP), a 37 amino acid peptide belonging to the calcitonin family of peptides, is a potent neuropeptide heavily localized in the central and peripheral terminals of nociceptive afferents.[2] Studies have shown that serum levels of CGRP are elevated during migraine, and that treatment with anti-migraine drugs normalizes CGRP levels.[4] Clinical proof of concept was first demonstrated with *iv* administration of the small molecule BIBN-4096BS/olcegepant[5] which alleviated migraine symptoms without the CV side effects associated with the use of triptans.

Previously, we reported the identification of BMS-694153, a potent CGRP receptor antagonist with rapid intranasal exposure.[6] Following this discovery, our strategy turned to the search for a compound that would have the appropriate properties to allow for oral dosing. The cyclic urea portion of the dihydroquinazolinone GPCR-privileged component in BMS-694153 was seen as detrimental for bilayer permeability. We envisioned that compounds with fewer hydrogen bond acceptors and/or donors might allow us to maintain subnanomolar potency, while simultaneously

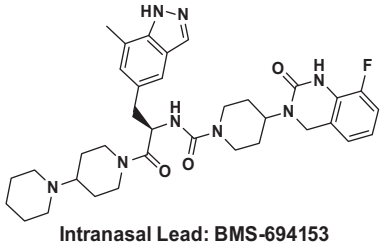


**Figure 1.** Simpler piperidine and piperazine analogs.

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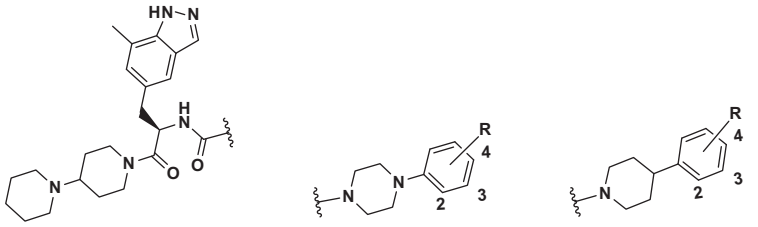
**Table 1**
CGRP receptor binding of piperazine and piperidine derivatives




| Phenyl substitution (R) | Compound | $IC_{50}$ (nM) | Compound | $IC_{50}$ (nM) |
|---|---|---|---|---|
| H | **3a** | 44 | **4a** | 460 |
| 2-Cl | **3b** | 15 | **4b** | 9.8 |
| 3-Cl | **3c** | 19 | **4c** | 150 |
| 4-Cl | **3d** | 77 | **4d** | 41 |
| 2-Br | **3e** | 12 | | |
| 3-Br | **3f** | 22 | **4f** | 130 |
| 4-Br | **3g** | 33 | **4g** | 13 |
| 2-F | **3h** | 130 | **4h** | 170 |
| 4-F | **3i** | 130 | | |
| 2-CN | **3j** | 8.9 | | |
| 4-CN | **3k** | 99 | | |
| 2-$CH_3$ | | | **4l** | 170 |
| 4-$CH_3$ | | | **4m** | 240 |
| 2-$COOCH_3$ | **3n** | 110 | **4n** | 54 |
| 4-$COOCH_2CH_3$ | **3o** | 44 | | |
| 2-Ph | **3p** | 120 | | |
| 4-Ph | **3q** | 46 | | |
| 2,3-Di-Cl | **3r** | 350 | | |
| 2,4-Di-Cl | **3s** | 4.3 | **4s** | 1.1 |
| 3,4-Di-Cl | **3t** | 12 | **4t** | 19 |
| 2-Cl-4-$CH_3$ | | | **4u** | 16 |
| 2-Cl-4-$SO_2CH_3$ | **3v** | 7.0 | | |
| 2,4-Di-F | **3w** | 140 | **4w** | 92 |
| 3,4-Di-F | **3x** | 97 | | |
| 2-F-3-$CH_3$ | | | **4y** | 120 |
| 2-F-4-$SO_2CH_3$ | **3z** | 34 | | |
| 2-$SO_2CH_3$-4-F | **3aa** | 2.9 | | |
| 2,4-Di-$CF_3$ | | | **4ab** | 24 |
| 3,5-Di-$CF_3$ | **3ac** | 190 | | |

improving passive absorption for oral or sublingual administration. We used the PAMPA and Caco-2 assays to measure permeability. To this end, we explored the SAR of the GPCR-privileged portion of the molecule using simple aryl piperidines and aryl piperazines as shown in Figure 1.

The synthesis of these compounds began with hydrolysis of **1**[7] followed by amide coupling using PyBOP to install the 1,4′-bis-piperidine moiety. Deprotection of the amine by hydrogenation gave intermediate **2**. Treatment of amine **2** with carbonyldiimidazole, followed by addition of the aryl piperazines or aryl piperidines gave the target compounds **3** and **4**, respectively. The aryl piperazine and aryl piperidine starting materials were selected from commercially available sources or were readily prepared using known literature procedures.[8,9]

Analogs with both mono- and di-substitution of the aryl ring are shown in Table 1 along with binding data for the human CGRP receptor.[6] In general, 2-substitution with simple substituents was most favorable for both piperidines and piperazines. It was tempting to visualize that the chloro (**3b** and **4b**), bromo (**3e**), and especially cyano (**3j**) groups are mimics of the quinazolinone carbonyl oxygen. In this respect, it was notable that the most strongly hydrogen bonding of these groups, cyano, showed the largest difference (10-fold) between 2- and 4-substitution (**3j** vs **3k**). An interesting exception was fluorine, where both the 2- (**3h**) and 4- (**3i**) substituted analogs showed poor activities. Larger substituents, such as esters (**3n** vs **3o**) and phenyl (**3p** vs **3q**), or simple methyl (**4l** vs **4m**) favored 4- versus 2-substitution.

The disubstituted analogs tended to show a preference for the 2,4 substitution pattern, with several examples showing single-digit nM potency (**3s**, **4s**, **3v** and **3aa**). Again the exceptions were those with fluorine at the 2-position (**3w**, **3z**, **4w** and **4y**). Compounds with 2,3- or 3,4-disubstitution (**3r**, **3t** and **3x**) showed only modest potency.

As part of this study, we also explored selected naphthyl piperidines. When comparing the 1-napthyl and 2-naphthyl piperidines, the latter showed far superior activity. Encouraged by this result and drawing from the results we obtained in the aryl derivatives, we sought to incorporate chloro (**4af**) and cyano (**4ag**) substituents into the 2-naphthyl piperidine compound to improve potency. As neither of the piperidine starting materials were commercially available, we set out to synthesize them.

As shown in Scheme 2, we began with preparation of the boronic acid **6**[10] from 2-bromo-3-chloronaphthalene **5**[11] followed by palladium catalyzed coupling with triflate **7**[12] to give compound **8** in modest yield. Selective reduction of the double bond without removal of the chloro-functionality was accomplished using platinum on sulfide carbon to give intermediate **9**. A portion of this was converted to the nitrile intermediate **10** via palladium catalyzed coupling with zinc cyanide. Deprotection of **9** and **10** with trifluoroacetic acid followed by exchange with HCl gave the desired naphthyl piperidine HCl salts **11** and **12**, respectively. These piperidines were then coupled as described above in Scheme 1 to form the urea and give compounds **4af** and **4ag**.