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Benzodiazepine calcitonin gene-related peptide (CGRP) receptor antagonists: Optimization of the 4-substituted piperidine

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Abstract—In our continuing effort to identify CGRP receptor antagonists for the acute treatment of migraine, we have undertaken a study to evaluate alternative 4-substituted piperidines to the lead dihydroquinazolinone **1**. In this regard, we have identified the piperidinyl-azabenzimidazolone and phenylimidazolinone structures which, when incorporated into the benzodiazepine core, afford potent CGRP receptor antagonists (e.g., **18** and **29**). These studies produced a potent analog (**18**) which overcomes the instability issues associated with the lead structure **1**. A general pharmacophore for the 4-substituted piperidine component of these CGRP receptor antagonists is also presented.
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The triptan class of 5-$HT_{1B/1D}$ receptor agonists represents the current standard of treatment for a migraine attack; presumably due to 5-HT_{1B} mediated nonselective vasoconstriction,[1] however, these compounds are contraindicated in patients with cardiovascular disease. Thus, development of a therapy devoid of these cardiovascular liabilities would represent a considerable therapeutic advance. Calcitonin gene-related peptide (CGRP) has been implicated in the pathogenesis of migraine headache[2] and clinical proof of concept has recently been demonstrated with the intravenous administration of the potent receptor antagonist BIBN 4096 (olcegepant).[3] Importantly, this efficacy was achieved without an effect on cerebral or systemic hemodynamics.[4]

In this context, we have undertaken a research program aimed at identifying small-molecule CGRP receptor antagonists suitable for oral administration during a migraine attack. A recent report from these laboratories detailed the identification and initial SAR of a benzodiazepine high-throughput screening lead.[5] Replacement of the tetralone-derived spirohydantoin with a traditional GPCR privileged structure,[6] namely the piperidinyldihydroquinazolinone, afforded a series of potent CGRP antagonists (e.g., **1**: K_i = 48 nM, cAMP IC_{50} = 34 nM). A liability associated with this series of compounds was that the dihydroquinazolinone suffered benzylic oxidation under ambient laboratory conditions. Herein, we report the development of a series of potent CGRP antagonists containing alternative 4-substituted piperidines which demonstrate improved stability profiles.

All compounds prepared were tested in the CGRP receptor (recombinant human CLR/RAMP1) competitive [^{125}I]CGRP radioligand binding assay (K_i). Selected compounds were subsequently tested for their functional ability to inhibit CGRP-stimulated cAMP production in whole cells (cAMP IC_{50}).[7]

Initial focus was placed on the ring contracted benzimidazolones (Fig. 1, **2**), which would eliminate the oxidation-prone benzylic position. As the unsubstituted analog was previously shown to have weak affinity for the CGRP receptor (Table 1, **4**: K_i = 2250 nM),[5] a series of substituted benzimidazolones (**5**–**17**) were prepared in an effort to improve potency. This study revealed that

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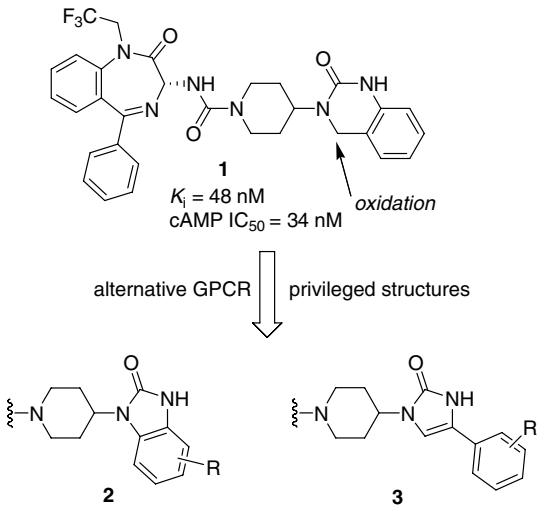
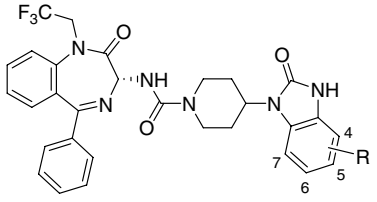


Figure 1.

Table 1. Benzimidazolone SAR



Compound	R	K_i[a] (nM)	cAMP IC_{50} (nM)
4	H	2250	1583
5	4-Me	6900	
6	4-F	375	373
7	4-Cl	143	446
8	5-Me	6100	
9	5-CF_3	3800	
10	5-F	2800	
11	5-Cl	>10,000	
12	5-CO_2H	810	715
13	5-$CONH_2$	1055	
14	5-SO_2Me	260	220
15	6-F	983	1396
16	7-Me	20,000	
17	7-Cl	6400	
18	4-Aza	23	49
19	5-Aza	685	1381
20	6-Aza	853	1398
21	7-Aza	427	1135
22	4-Aza oxide	1000	
23	4,6-Diaza	51	430
24	4,7-Diaza	156	286

[a] Values are means of 2 experiments.

the majority of these analogs did not lead to a significant improvement in binding affinity (Table 1). Notable exceptions included the 5-substituted methylsulfone (**14**) and the 4-fluoro and chloro analogs (**6** and **7**), which were substantially more potent in both the intrinsic CGRP binding and cAMP functional assays. Importantly, no decomposition of the benzimidazolones was observed upon prolonged storage.

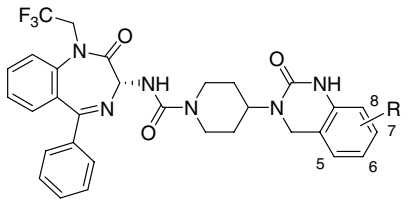
In an extension of this study, introduction of a nitrogen atom into the benzimidazolone aryl ring (to form each of the four possible pyridine isomers) revealed a profound effect on potency: installation of the nitrogen at the 4-position afforded a 100- and 30-fold improvement in binding and functional potency, respectively (Table 1, **18**). N-Oxidation of this derivative to give **22** led to a 40-fold loss in potency. Incorporation of the 4,6- and 4,7-diaza modifications gave **23** and **24**, analogs which retained good potency in the CGRP binding assay.

Having established the considerable potency improvement upon incorporation of a nitrogen atom into the benzimidazolone nucleus, we sought to exploit this feature within other piperidine-derived privileged structures. Unfortunately, a corresponding 'aza binding site' does not appear to be operative in the context of the dihydroquinazolinones, as preparation of all four of the fused pyridine isomers led to decreased affinity for the CGRP receptor (Table 2).

The phenylimidazolinone[3] (**3**, Fig. 1) is an alternative heterocycle which maintains both the cyclic urea and aryl substituent of the parent dihydroquinazolinone but removes the benzylic site of oxidation. Preparation of the phenylimidazolinone derivative **29** afforded a potent CGRP receptor antagonist (Table 3, K_i = 11 nM, cAMP IC_{50} = 14 nM). A limited scan of phenyl ring substituents (**30**–**36**) revealed that the addition of a 3-methoxy group produced a 10-fold improvement in potency (**31**: K_i = 1.1 nM, cAMP IC_{50} = 5.1 nM). Replacement of the phenyl with a 2-pyridyl ring, in an effort to access the 'aza binding site,' did not lead to an improvement in binding affinity (**37**: K_i = 27 nM).

Although incorporation of the piperidinyl-phenylimidazolinone into the benzodiazepine-based template affords very potent CGRP antagonists, this heterocycle also experiences degradation under ambient laboratory conditions. Decomposition products were observed that are consistent with oxidation occurring at the electron-rich double bond of the imidazolinone ring;[8] consequently, a range of non-aryl imidazolinone substituents were explored in an attempt to stabilize this ring system (Table 3, **38**–**44**). Although these analogs

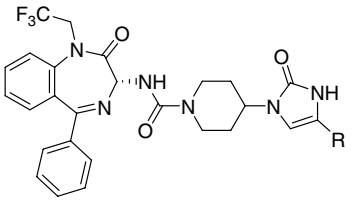
Table 2. Aza-dihydroquinazolinone SAR



Compound	R	K_i[a] (nM)	cAMP IC_{50} (nM)
1	H	48	34
25	8-Aza	295	616
26	7-Aza	350	224
27	6-Aza	320	627
28	5-Aza	965	1837

[a] Values are means of 2 experiments.

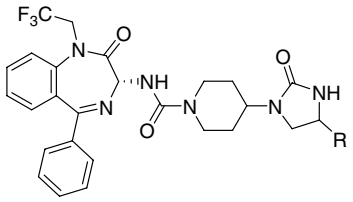
Table 3. Imidazolinone SAR



Compound	R	K_i[a] (nM)	cAMP IC_{50} (nM)
29	Ph	11	14
30	3-FPh	11	46
31	3-MeOPh	1.1	5.1
32	4-FPh	11	107
33	4-MePh	6.3	85
34	4-MeOPh	205	193
35	4-CF_3OPh	104	431
36	4-CHF_2OPh	19	74
37	2-Pyr	27	37
38	CH_2Ph	1125	450
39	CO_2Me	110	156
40	CO_2H	2900	
41	CH_2OH	20,000	
42	CN	575	990
43	H	583	672
44	iPr	5337	

[a] Values are means of 2 experiments.

Table 4. Imidazolidinone SAR



Compound	R	K_i[a] (nM)	cAMP IC_{50} (nM)
49[b]	H	855	3100
50[b]	Ph	339	790
51[b]	2-Pyr	2000	
52[b]	3-Pyr	1050	
53[b]	4-Pyr	720	804

[a] Values are means of 2 experiments.
[b] Mixture of imidazolidinone diastereomers.

were qualitatively more stable than their aryl congeners, they experienced a significant loss of potency (>10-fold). In contrast, the corresponding phenyltriazolinone **45** (Chart 1) is a stable ring system[9] that only forfeits 2-fold in CGRP receptor affinity. Additionally, a range of reduced imidazolinones (i.e., imidazolidinones) were prepared (Table 4, **49**–**53**): these stable analogs were significantly less potent than their dehydro analogs.

Based on the SAR generated herein a general pharmacophore for the 4-substituted piperidine privileged structures can be proposed (Fig. 2). A 5- or 6-membered cyclic urea, with the terminal nitrogen unalkylated,[5] appears to represent the basic criterion for CGRP receptor affinity (e.g., **43** and **49**). To increase potency, this core ring can be substituted with an aryl moiety, the orientation of which is crucial. When $n = 0$ (5-membered ring), a pendant aryl group (X = Ar) is required: fusion of a benzene ring onto **43** to give **4** leads to a loss in potency, while appendage of the phenyl group (as in **29**) improves potency by 50-fold.[10] As evidenced by the moderate potency of **50**, the 5-membered ring must also maintain a planar orientation to obtain full benefit of the aryl substituent. The inactivity of **47** serves to demonstrate that when $n = 1$ (6-membered ring) the aryl group should be fused distally to the piperidine ring, as in **1**.

Alternatively, substitution of the principal cyclic urea core with a hydrogen bond acceptor (Fig. 2, X = HBA) can deliver a large improvement in CGRP receptor affinity. This strategy is demonstrated by the comparison of **4** and **18** in which introduction of the HBA ring nitrogen serves to improve potency by 100-fold. Furthermore, the comparison of **49** to **48** reinforces the concept that an aryl group is not required to deliver potent CGRP antagonists, but can be attained with a simple hydrogen bond acceptor.

Attempts to combine both an aryl group and a hydrogen bond acceptor, as in **25** and **37**, reveal that these potency enhancing modifications appear to be mutually exclusive.

The benzimidazolone SAR could be rapidly evaluated using a modification of the literature conditions

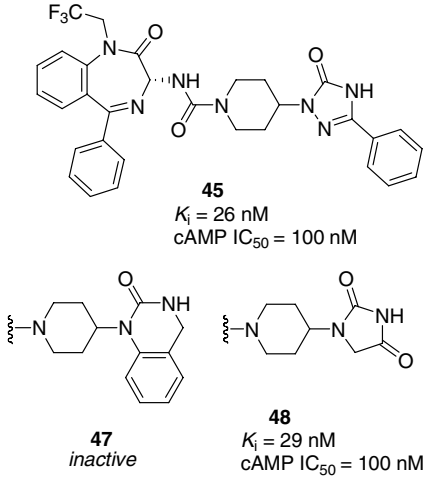


Chart 1.

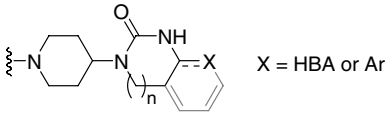
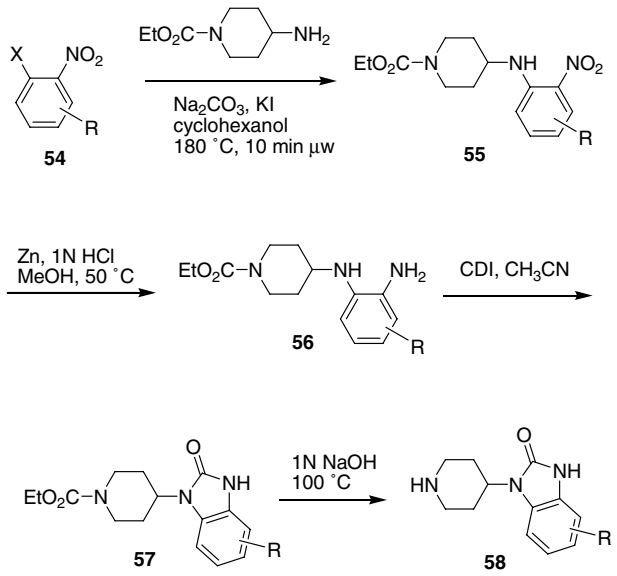
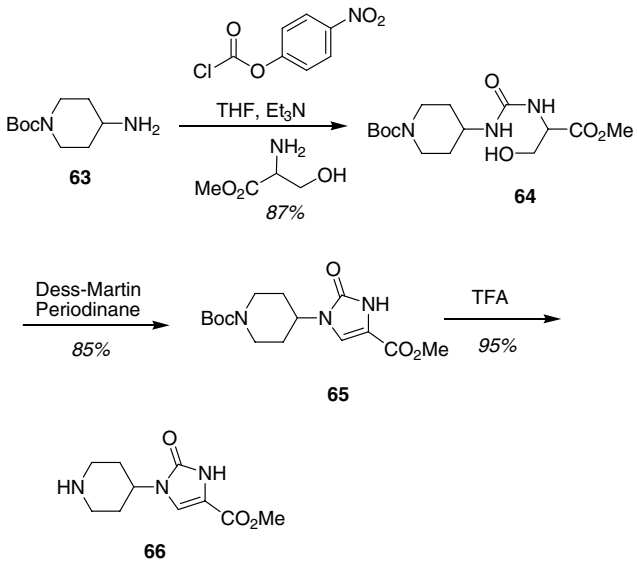


Figure 2.



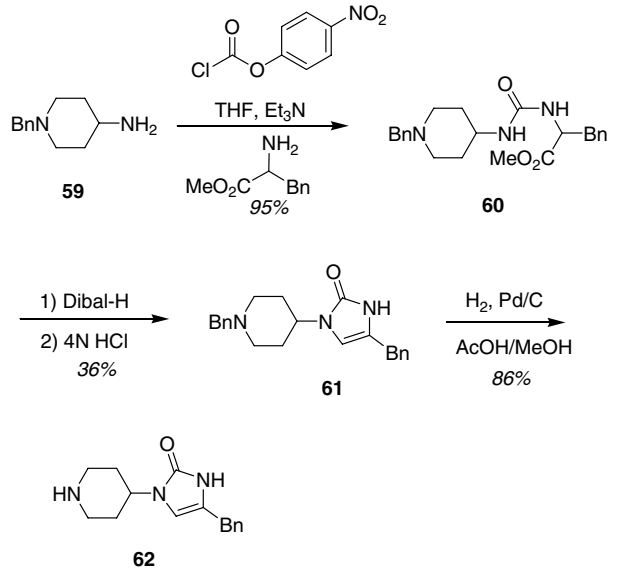
Scheme 1.



Scheme 3.

(Scheme 1).[11] Ethyl 4-amino-1-piperidinecarboxylate could be added to a range of substituted *o*-halonitroaromatics **54**, followed by nitro group reduction of the product **55** with Zn metal in acidic methanol to deliver the *o*-amino anilines **56**. Ring closure with carbonyldiimidazole, followed by ethyl carbamate deprotection, afforded the substituted benzimidazolones **58**.[12]

Reductive cyclization methodology was implemented to prepare the imidazolinones (Scheme 2).[13] For example, urea formation between the 4-aminopiperidine **59** and phenylalanine methyl ester was accomplished using 4-nitrophenyl chloroformate. Half-reduction of ester **60** was followed by acid-catalyzed cyclodehydration to form the imidazolinone **61**. Deprotection then afforded the desired piperidine **62**.



Scheme 2.

Alternatively, substrates which contain functional groups that are acid labile, or susceptible to Dibal-H reduction, can be prepared via an oxidative variant of the preceding route (Scheme 3). Amino alcohols, such as serine methyl ester, are coupled to the 4-aminopiperidine **63** to afford the urea **64**. Treatment with Dess–Martin periodinane produces the imidazolinone **65** directly and does not necessitate a separate dehydration step.

The piperidines prepared through the preceding routes (Schemes 1–3) were converted to the final ureas using the previously disclosed method.[5]

In conclusion, we have identified the piperidinyl-azabenzimidazolone and phenylimidazolinone as alternative privileged structures which when incorporated into the benzodiazepine core afford potent CGRP receptor antagonists (e.g., **18** and **29**). The former analog (**18**) overcomes the instability issues associated with the lead structure **1**. A general pharmacophore for the 4-substituted piperidine component of these CGRP receptor antagonists was also proposed. The optimization of this series is currently being pursued and the results will be disclosed in due course.

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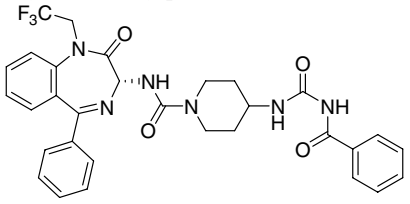
7. For the details of these assays, see: Bell, I. M.; Graham, S. L.; Williams, T. M.; Stump, C. A. WO 2004/087649.
8. A major degradation by-product formed was:



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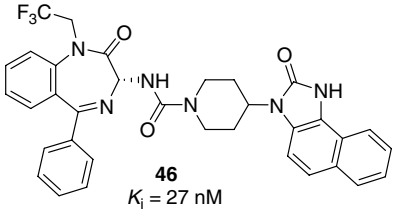
10. Interestingly, the hybrid molecule **46** is nearly equipotent to **29**:



46
K_i = 27 nM
cAMP IC_{50} = 369 nM

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