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Potent benzimidazolone-based CGRP receptor antagonists

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ABSTRACT

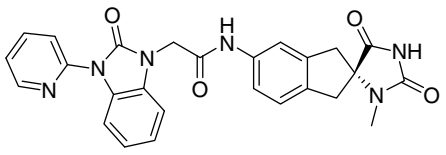
The previously disclosed spirohydantoin-based CGRP receptor antagonists were optimized for potency through modification of the benzimidazolone substituents. Compounds were identified which had minimal shift in the cAMP functional assay containing 50% human serum. Blockade of CGRP-mediated vasodilation was observed with these compounds in a rhesus pharmacodynamic assay and the in vivo potency correlated with the in vitro activity in the serum-shifted functional assay.

Migraine is an episodic disorder which affects 10% of adults and can include a number of debilitating symptoms.[1] Dilation of cranial blood vessels and subsequent activation of the trigeminovascular system is thought to cause a variety of effects, including severe unilateral headache, photophobia, phonophobia, and nausea.[2] Normal physical activity typically exacerbates these symptoms in affected individuals. The current standard of treatment for acute migraine is the triptan class of $5HT_{1B/1D}$ receptor agonists, although these compounds are contraindicated for patients with cardiovascular disease since they are vasoconstrictors.[3] Current research implicates the neuropeptide calcitonin gene-related peptide (CGRP) as playing a key role in migraine pathology.[4] A potent, orally bioavailable CGRP receptor antagonist may offer advantages over triptans in acute migraine therapy. Clinical efficacy has been demonstrated in a Phase II trial with the orally administered, selective CGRP antagonist telcagepant (MK-0974).[5]

Previously,[6] we described the identification of an (*R*)-indanylspirohydantoin compound **1**, a novel CGRP receptor antagonist (Fig. 1). While **1** possessed an attractive profile, it had suboptimal potency in the serum-shifted functional assay. Preliminary results indicated that substitutions around the benzimidazolone core were tolerated, so a systematic approach was taken to identify more potent analogs.[7]

Our first study was focused on substitution of the benzimidazolone aryl ring (Table 1). Analogs were tested in a radioligand binding assay as well as a cell-based functional assay run in the presence of 50% human serum.[8] It quickly became apparent that 4- and 6-substitution of the benzimidazolone gave respectable binding activity, both individually and in concert. The 4,6-dimethyl compound **3** was particularly potent, and exhibited the highest potency in the functional assay (cAMP IC_{50} = 23 nM).

In general, the addition of human serum to the functional assay led to a significant decrease in potency (Table 1). The most potent analog in the binding and functional assays without human serum (**3**) was selected for further optimization of N-substituents



K_i = 21 nM
cAMP IC_{50} = 78 nM
cAMP + 50% HS = 530 nM

1

Figure 1. Previously described CGRP receptor antagonist.

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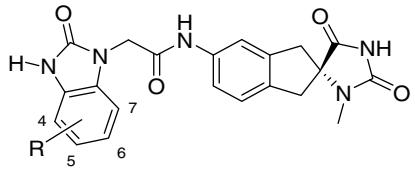
Table 1
Benzimidazolone aryl substitution



Compound	R	CGRP K_i[a,b] (nM)	cAMP IC_{50}[a,c] (nM)	cAMP IC_{50} + 50% HS[a,d] (nM)
2	H	38 ± 26 (7)	110 (2)	1200 (1)
3	4,6-Me	5.5 (2)	23 (1)	—
4	4-Me	41 (2)	59 (1)	—
5	4-Cl	13 (2)	42 (1)	2000 (1)
6	4-F	32 ± 29 (3)	76 (2)	1200 (1)
7	4-OMe	26 (2)	260 (1)	4400 (1)
8	5-Me	100 (2)	590 (1)	—
9	5-Cl	15 (2)	60 (1)	490 (1)
10	5-F	18 (2)	150 (1)	—
11	5-OMe	62 (1)	98 (1)	4500 (1)
12	6-Me	23 (2)	130 (1)	—
13	6-Cl	9.5 (2)	64 (1)	—
14	6-F	15 (2)	780 (1)	1200 (1)
15	6-OMe	120 (2)	1500 (1)	—
16	7-Cl	250 (2)	450 (1)	—

[a] Mean value ± standard deviation, where appropriate; number of replicates in parentheses.
[b] K_i values for competition with ^{125}I-hCGRP determined using membranes from HEK293 cells expressing cloned human CLR/RAMP1 (line E10).[4]
[c] Inhibition of CGRP-induced CAMP production in the E10 cell line.[4]
[d] Inhibition of CGRP-induced CAMP production in the E10 cell line in the presence of 50% human serum.[4]

(Table 2). Most retained potency in the binding assay, but only the *N*,*N*-dimethyl glycinamide **21** (cAMP IC_{50} + 50% HS = 23 nM) exhibited improved cell-based assay potency in the presence of human serum compared with lead structure **1**. Other glycine-based substituents (**18–20, 22**) and alkyl groups (**17**) offered less improvement over **21**.

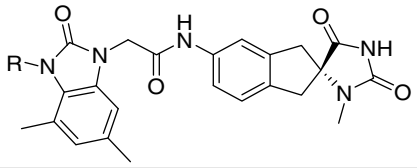
Compounds **17** and **21** became useful pharmacological tools in the validation of our rhesus monkey pharmacodynamic assay.[9] In this assay, topical administration of capsaicin to the forearm of anesthetized monkeys results in the release of CGRP, leading to local vasodilation. The concomitant increase in blood flow is visualized by Laser Doppler imaging (Fig. 2), and blockade of the effect by administration of a CGRP antagonist can be quantified. Analysis of the plasma concentrations of compound allowed an estimate of CGRP antagonist potency in vivo. In the vascular images, the effect of topical capsaicin on blood flow to the upper ring area is clearly seen, with blue representing low flow and red high flow.

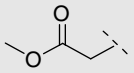
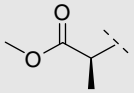
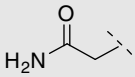
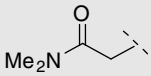
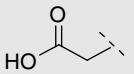
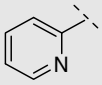
In our cell-based assay, **21** had very little serum shift, while **17** was highly shifted in the presence of human and rhesus serum. Comparing the two compounds in the rhesus pharmacodynamic assay (Fig. 3), we found that the unshifted compound **21** reached 100% inhibition of the vasodilatory response at a plasma concentration of 2 μM, whereas **17** afforded only 50% inhibition of vasodilation at a plasma concentration of 10 μM. This observation demonstrated the antagonism of CGRP-mediated vasodilation in vivo as well as the relevance of our functional assay in the presence of serum. Additionally, we were able to determine that the EC_{50} for **21** was approximately 300 nM, and that **17** had an EC_{50} of 10 μM. The difference in the EC_{50} values for these compounds is in excellent accord with their performance in the rhesus monkey serum-shifted functional assay.

Increasing the chain length of the *N*,*N*-dimethylglycinamide arm to $n = 3$ (Table 3) resulted in minor potency gains (**28 and 29**), however dramatic potency improvements were observed when we constrained the glycinamide arm against the benzimidazolone aryl ring in order to form **30–33** (Fig. 4). The rigidified tricyclic compound **33** delivered a 70-fold potency boost in the radioligand binding assay and showed significant improvement in the functional assay as well.

The synthesis of representative compound **30** is outlined in Scheme 1. Reduction of bis-alkylated 3-nitrobenzimidazolone re-

Table 2
N-Substitution of 3,5-dimethyl benzimidazoles



Compound	R	CGRP K_i[a,b] (nM)	cAMP IC_{50}[a,c] (nM)	cAMP IC_{50} + 50% HS[a,d] (nM)
3	H	5.5 (2)	23 (1)	—
17	Me	2.7 ± 1.0 (5)	10 (2)	1200 (2)
18		2.1 (2)	5.6 (1)	150 (1)
19		21 (2)	72 (1)	—
20		1.9 (2)	13 (2)	140 (1)
21		1.7 (2)	12 ± 7.1 (4)	23 (2)
22		26 (2)	44 (4)	4100 (2)
23		4.3 ± 1.6 (6)	26 (2)	426 (2)

[a] Mean value ± standard deviation, where appropriate; number of replicates in parentheses.
[b] K_i values for competition with ^{125}I-hCGRP determined using membranes from HEK293 cells expressing cloned human CLR/RAMP1 (line E10).[4]
[c] Inhibition of CGRP-induced CAMP production in the E10 cell line.[4]
[d] Inhibition of CGRP-induced CAMP production in the E10 cell line in the presence of 50% human serum.[4]

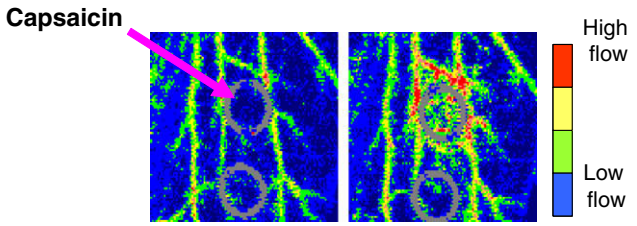
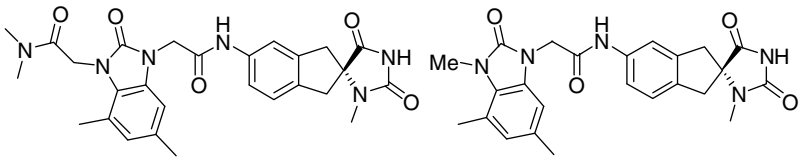


Figure 2. Laser Doppler imaging of topical capsaicin utilized in noninvasive rhesus pharmacodynamic assay. Intravenous administration of CGRP antagonists blocks vasodilatory response and allows estimate of clinically efficacious plasma levels.



21
K_i = 1.7 nM
cAMP IC_{50} = 12 nM
cAMP IC_{50} + HS = 23 nM
cAMP IC_{50} + RS = 14 nM

no shift

17
K_i = 2.7 nM
cAMP IC_{50} = 10 nM
cAMP IC_{50} + HS = 1200 nM
cAMP IC_{50} + RS = 370 nM

37-fold shift

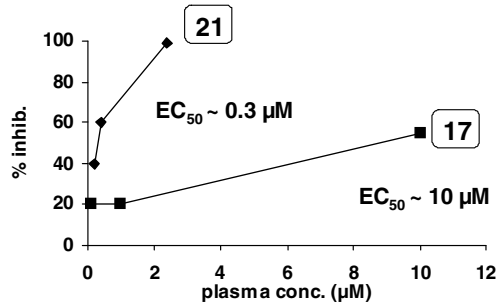
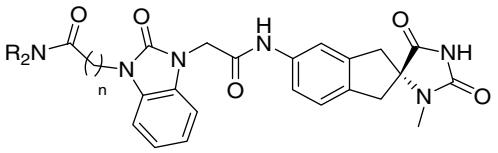
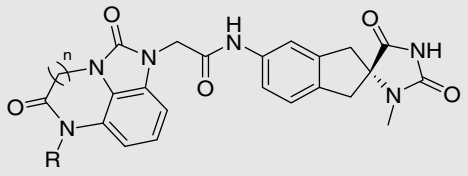


Figure 3. Demonstration of in vivo antagonism of CGRP-mediated vasodilation and validation of cell-based assay in rhesus using compounds with high (**17**) and low (**21**) serum shift.

Table 3
Arm modification and constraint



Compound	*n*	R	CGRP K_i[a,b] (nM)	cAMP IC_{50}[a,c] (nM)	cAMP IC_{50} + 50% HS[a,d] (nM)
24	1	H	37 (2)	150 (1)	130 (1)
25	1	Me	22 (2)	280 (1)	—
26	2	H	31 (2)	—	—
27	2	Me	36 (2)	120 (1)	—
28	3	H	13 (2)	43 (1)	76 (1)
29	3	Me	9.6 (2)	30 (1)	24 (1)



30	1	H	0.51 (1)	2.4 (2)	5.4 (2)
31	1	Me	7.1 (2)	31 (1)	220 (1)
32	3	H	4.7 (2)	14 (2)	21 (2)
33	3	Me	2.2 ± 0.43 (6)	12 (1)	13 (1)

[a] Mean value ± standard deviation, where appropriate; number of replicates in parentheses.
[b] K_i values for competition with ^{125}I-hCGRP determined using membranes from HEK293 cells expressing cloned human CLR/RAMP1 (line E10).[4]
[c] Inhibition of CGRP-induced CAMP production in the E10 cell line.[4]
[d] Inhibition of CGRP-induced CAMP production in the E10 cell line in the presence of 50% human serum.[4]

sults in formation of the tricyclic ester. Subsequent hydrolysis of the ester and coupling to the previously described amine[6] gives desired product **30**.

In conclusion, a series of novel, potent indanone-based spirohydantoins were synthesized. Elaboration of the benzimidazolone core associated with primary lead **1** resulted in marked improve-

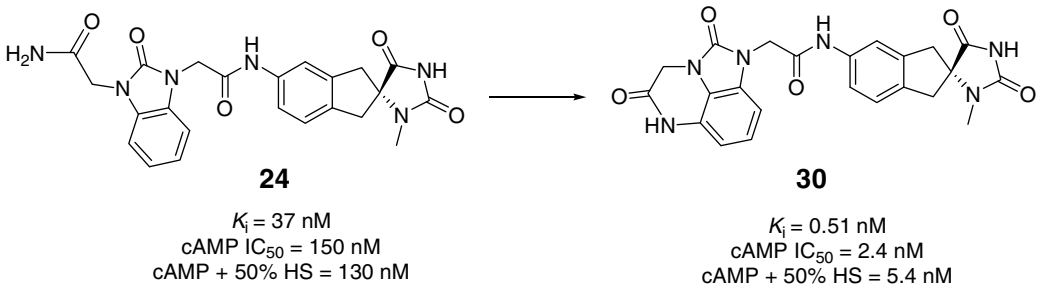
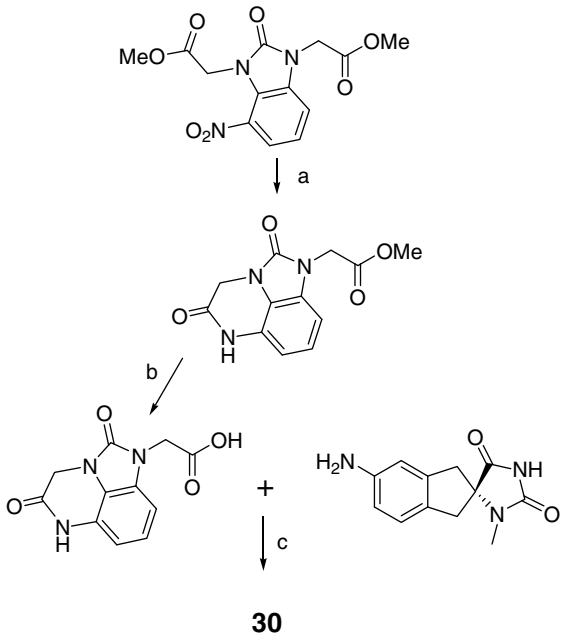


Figure 4. Potency improvement observed with constraint of glycinamide functionality.



Scheme 1. Synthesis of tricyclic compound **30**. Reagents and conditions: (a) H_2, Pd/C, EtOH, 95%; (b) LiOH, MeOH, 85%; (c) EDC, HOBT, DIEA, DMF, 76%.

ments in potency. Additionally, we identified analogs that demonstrated a good correlation between the in vitro serum-shifted functional assay and the in vivo pharmacodynamic assay.

Acknowledgments

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