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The discovery of highly potent CGRP receptor antagonists

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ABSTRACT

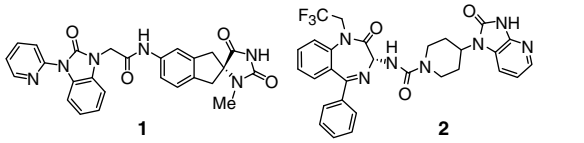
Rational modification of a previously identified spirohydantoin lead structure has identified a series of potent spiroazaoxindole CGRP receptor antagonists. The azaoxindole was found to be a general replacement for the hydantoin that consistently improved in vitro potency. The combination of the indanylspiroazaoxindole and optimized benzimidazolinones led to highly potent antagonists (e.g., **25**, CGRP K_i = 40 pM). The closely related compound **27** demonstrated good oral bioavailability in dog and rhesus.

Migraine is a disabling neurovascular disorder that affects >10% of the general population.[1] A migraine attack is characterized by unilateral head pain and is often accompanied by phonophobia, photophobia, and nausea. The current preferred method of treatment involves the use of triptans, which activate 5-$HT_{1B/1D}$ receptors. Although triptans are generally effective in the treatment of migraines, they are contraindicated in patients with cardiovascular disease due to their direct vasoconstrictive mode of action.[2] Calcitonin gene-related peptide (CGRP), a 37 amino acid neuropeptide, has been implicated in the pathogenesis of migraine.[3] Clinical studies have demonstrated the effectiveness of CGRP receptor antagonists for the acute treatment of migraine with the intravenously-administered olcegepant[4] and, more recently, with the orally-administered telcagepant.[5] Our research program continues to focus on developing non-peptidic, orally bioavailable CGRP receptor antagonists as novel therapeutics.

Previous communications from these laboratories described the independent evolution of a high throughput screening lead into two classes of potent CGRP receptor antagonists, represented by **1** and **2** (Fig. 1).[6,7] Each compound exhibited good potency in both the radioligand binding assay and the cell-based functional assay, however they both suffered from a significant loss of potency in the cell-based assay in the presence of 50% human serum.

Despite the substantial structural diversity between these two series, both contain a heterocyclic NH that is important for CGRP receptor binding. A substantial boost in potency was achieved in the benzodiazepinone series by incorporation of a hydrogen bond acceptor adjacent to this NH (Scheme 1, **3** → **4** → **2**).[7] We postulated that if the spirohydantoin and azabenzimidazolinone are binding at a similar site on the receptor, an analogous potency enhancing interaction might be achieved in the spirohydantoin series with a similarly placed pyridine nitrogen (**1** → **12** → **13**).

Initially, a series of modifications to the hydantoin was explored in order to evaluate the requirements for binding to the receptor (Table 1). The compounds in the table were tested as racemic mixtures. Spirolactam **6** indicates that only the α-carbonyl amide is needed for CGRP receptor binding, as it maintained the potency of the parent hydantoin **5**. Addition of a second carbonyl to the lactam provided imide **7**, which offered a small potency enhancement. Ring expansion to the valerolactam **8** led to a considerable loss in potency, presumably by changing the trajectory of the crit-



1
K_i = 20 nM
cAMP IC_{50} = 78 nM
cAMP IC_{50} + 50% HS = 530 nM

2
K_i = 22 nM
cAMP IC_{50} = 49 nM
cAMP IC_{50} + 50% HS = 730 nM

Figure 1. Previously disclosed CGRP receptor antagonists.

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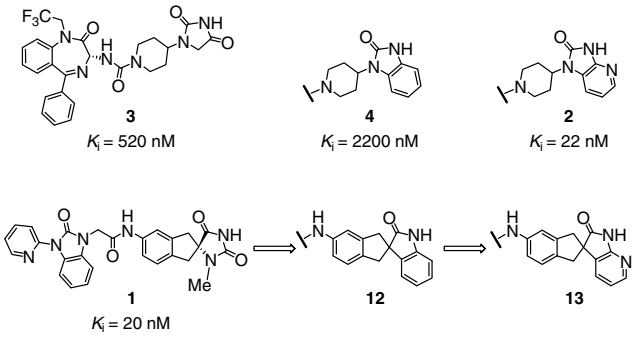


Scheme 1. SAR trends in two series of CGRP receptor anatagonists.

ical amide binding motif. The dihydroimidazolinone **9**, which has a pendant phenyl substituent next to the amide, had improved potency (K_i = 34 nM). Replacement of the 2-phenyl substituent with either a pyridine or cyclopropyl group resulted in a loss of activity (**10** and **11**). Fusion of the aromatic ring to produce oxindole **12** also led to a loss in potency (K_i = 520 nM), closely following the SAR trend of the benzodiazepinone series (Scheme 1). Gratifyingly, addition of the nitrogen to produce the spiroazaoxindole **13** resulted in a substantial improvement in potency (K_i = 3.7 nM).

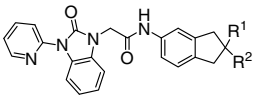
The *(S)*-enantiomer (K_i = 2.3 nM) of the spiroazaoxindole **13** was much more potent than the *(R)*-enantiomer (K_i = 140 nM), consistent with previous results in the hydantoin series.[6,8] Only the *(S)*-enantiomers of the spiroazaoxindole will be discussed in Table 2. The significant improvement in binding potency achieved with the azaoxindole over the hydantoin was maintained in the context of a variety of *N*-heteroaryl benzimidazolinones, a sampling of which is shown in Table 2 [**(*S*)-13 and 15 vs 1 and 14**]. However, while this potency advantage was maintained in the cell-based assay, much of it was lost with the addition of human serum. A likely explanation is the higher affinity for plasma protein of the more lipophilic azaoxindoles.

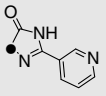
Potent CGRP receptor antagonists could also be prepared with saturated heterocycles, either as an *N*-substituent on the benzimidazolinone (**17** and **19**) or as a spiroheterocycle substituent on an oxindole (**21**). These analogs exhibited a less pronounced serum shift in the functional assay, leading to a significant improvement in potency over **13**. Modifications on the benzimidazolinone that improved intrinsic and functional potency were identified in the related hydantoin series, providing compounds **22** and **24**.[9] The incorporation of an optimized benzimidazolinone in the spiroazaoxindole series led to the very potent **23**, which had subnanomolar potency in both the binding and functional assays, as well as nanomolar potency in the presence of 50% human serum (IC_{50} = 4.1 nM). Further optimization through constraint of the glycine side chain produced an even more potent antagonist **25**, which was the first program analog with subnanomolar potency in the serum-shifted functional assay (IC_{50} = 0.62 nM). Methylation of the constrained glycine amide also produced a potent compound **27** (K_i = 0.23 nM), albeit with reduced potency in the cell-based assay with human serum (IC_{50} = 13 nM).

Calculated polar surface area (PSA) has been shown to correlate with intestinal permeability.[10] In a related series of spirohydantoin compounds, an inverse relationship between PSA and bioavailability has been observed.[6] Consistent with this, the very potent analog **25**, which has a high PSA (149 Å^2), showed no oral bioavailability in the dog. Moreover, the *N*-methyl analog **27**, which has a reduced PSA (134 Å^2), displayed good oral bioavailability and low clearance in the dog and rhesus (Table 3). However, **27** showed poor bioavailability and increased clearance in the rat (F < 1%).

The synthesis of a representative compound (**27**) is outlined in Scheme 2.[11] 1,2-*Bis*(bromomethyl)-4-nitrobenzene was synthesized in two steps from commercially available 4-nitrophthalic acid following standard procedures. The SEM-protected azaoxindole, which was prepared from commercially available 4-azaindole using the methodology of Marfat,[12] was *bis*-alkylated with the dibromide to provide the racemic indanylspiroazaoxindole. Reduction of the nitro group and chiral resolution on a Chiralcel OD column was followed by a two step SEM-deprotection to provide the desired (*S*)-aniline. The synthesis of the carboxylic acid intermediates have been reported elsewhere.[11] The final amide coupling

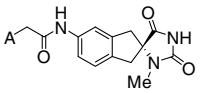
Table 1
CGRP receptor affinity of spirohydantoin and related analogs.

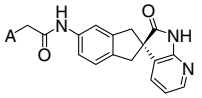


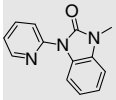
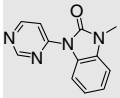
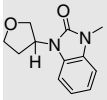
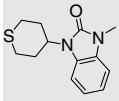
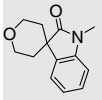
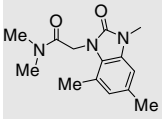
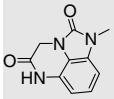
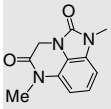
Compound	R^1, R^2	CGRP K_i[a,b] (nM)
5		230 ± 28 (4)
6		270 ± 180 (8)
7		96 ± 45 (3)
8		2700 ± 890 (4)
9		34 (2)
10		130 ± 55 (3)
11		2600 ± 680 (4)
12		520 ± 280 (4)
13		3.7 ± 0.61 (3)

[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 stably expressing human CLR/RAMP1.[5]

Table 2
Comparison of CGRP receptor antagonist activity of spriroazaoxindoles and spirohydantoins.





A	Compound	CGRP K_i [a,b] (nM)	cAMP IC_{50} [a,c] (nM)	cAMP IC_{50} + HS [a,d] (nM)	Compound	CGRP K_i [a,b] (nM)	cAMP IC_{50} [a,c] (nM)	cAMP IC_{50} + HS [a,d] (nM)
	**1**	20 ± 8 (7)	78 ± 23 (3)	530 ± (1)	**(*S*)-13**	2.3 ± 0.58 (3)	8.6 ± 2.4 (4)	420 ± 180 (3)
	**14**	16 ± 10 (5)	10 (1)	74 (1)	**15**	0.61 ± 0.26 (6)	1.6 (2)	35 (2)
	**16**	20 ± 3.6 (5)	61 ± 3.5 (3)	170 ± 97 (3)	**17**	1.2 (1)	5.2 (2)	27 (2)
	**18**	13 ± 6.2 (3)	27 (1)	220 (1)	**19**	0.87 ± 0.33 (4)	2.5 (2)	24 (1)
	**20**	35 ± 6.4 (3)	57 (1)	160 (1)	**21**	1.7 ± 0.88 (6)	5.7 (2)	39 (2)
	**22**	1.7 (2)	12 ± 7.1 (4)	23 (2)	**23**	0.21 ± 0.07 (6)	0.87 ± 0.42 (3)	4.1 ± 0.22 (3)
	**24**	0.51 (1)	2.4 (2)	5.4 (2)	**25**	0.04 ± 0.008 (8)	0.28 (2)	0.62 (2)
	**26**	7.1 (2)	31 (1)	220 (1)	**27**	0.23 ± 0.078(8)	0.88 ± 0.20 (5)	13 ± 8.4 (5)

[a] Mean value ± standard deviation, where appropriate; number of replicates in parentheses.
[b] K_i values for inhibition of ^{125}I-hCGRP binding determined using membranes from HEK293 cells stably expressing human CLR/RAMP1.[5]
[c] Inhibition of CGRP-induced cAMP production in HEK293 cells stably expressing human CLR/RAMP1.[5]
[d] Inhibition of CGRP-induced cAMP production in HEK293 cells stably expressing human CLR/RAMP1in the presence of 50% human serum.[5]

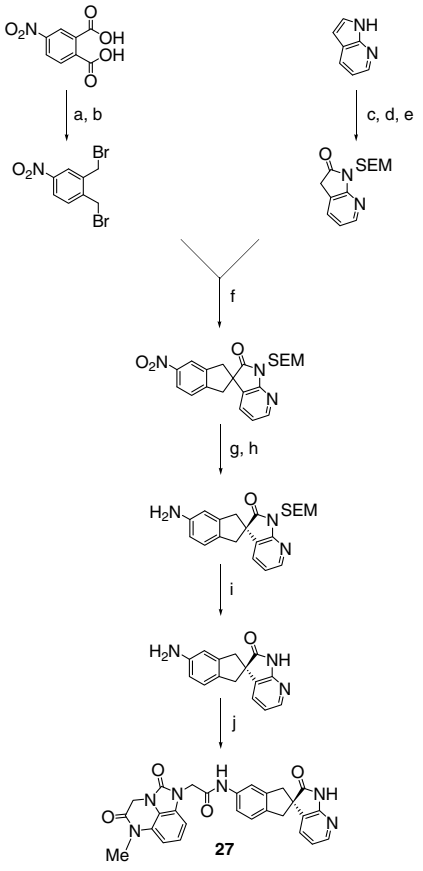
Table 3
Pharmacokinetics of compound **27**.

Species	po dose[a] (mpk)	iv dose[b] (mpk)	*F* (%)	iv $t_{1/2}$ (h)	Cl (mL/min/kg)
Rat	50	2	<1	0.99	30
Dog	1	0.5	58	2.6	3.8
Rhesus	2	0.5	35	1.8	7.5

[a] Compound dosed in 90% PEG 400:10% water.
[b] Compound dosed in DMSO.

reaction was performed using EDC and HOBT to provide the target compounds.

In conclusion, rational design led to the development of a novel series of potent indanylspiroazaoxindole CGRP receptor antagonists. The azaoxindole was found to be a general replacement for the hydantoin that improved potency by an order of magnitude in both the radioligand binding assay and the cell-based functional assay. These studies led to the first program analog that was subn-



Scheme 2. Synthesis of compound **27**. Reagents and conditions: (a) BH_3-THF, THF, 0 °C, 95%; (b) PBr_3, Et_2O, 99%; (c) NaH, SEMCl, DMF, 0 °C, 97%; (d) pyridine hydrobromide perbromide, dioxane, 80%; (e) Zn, THF, sat. NH_4Cl, 75%; (f) Cs_2CO_3, DMF, 70%; (g) H_2, Pd/C, EtOH, 95%; (h) Chiralcel OD, MeOH, first major peak is (*S*)-enantiomer; (i) HCl, MeOH, then NaOH, $NH_2CH_2CH_2NH_2$, MeOH, 79%; (j) RCO_2H, EDC, HOBT, DIEA, DMF, 76%.

anomolar in the serum-shifted functional assay, representing a 1000-fold improvement over the lead compounds **1** and **2**. One of the more potent antagonists (**27**) displayed good bioavailability in the dog and rhesus.

Acknowledgments

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