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The identification of potent, orally bioavailable tricyclic CGRP receptor antagonists

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ABSTRACT

A series of tricyclic CGRP receptor antagonists was optimized in order to improve oral bioavailability. Attenuation of polar surface area and incorporation of a weakly basic indoline nitrogen led to compound **5**, a potent antagonist with good oral bioavailability in three species.

Migraine is an episodic neurovascular disorder, characterized by attacks of severe head pain that is often accompanied by sensitivity to light, sound, and movement, as well as nausea. The attacks can last from several hours to several days and are typically highly disabling.[1] Triptans are generally considered to be the best acute migraine-specific drugs, although they are contraindicated for use in the presence of cardiovascular disease because they are vasoconstrictors.[2]

Calcitonin gene-related peptide (CGRP) is a 37-amino-acid neuropeptide, which has been implicated in the pathophysiology of migraine.[3] Clinical studies with two CGRP receptor antagonists, the intravenously-infused olcegepant[4] and the orally-administered telcagepant[5–7] (Fig. 1), have demonstrated that such agents have the potential to be effective in the acute treatment of migraine. In particular, telcagepant 300 mg was found to have comparable efficacy to zolmitriptan 5 mg but with fewer associated adverse events.[8]

We have previously described the discovery of novel CGRP receptor antagonists based on a spiroindane template.[9] More recently, we detailed the evolution of such compounds to give highly potent CGRP receptor antagonists, such as compound **1** (Table 1).[10] While the tricyclic compound **1** exhibited picomolar potency (CGRP K_i = 39 pM), it was not orally bioavailable (rat F < 1%; Table 2).

In a related series of CGRP receptor antagonists, we observed that oral bioavailability was inversely correlated with calculated polar surface area (PSA), suggesting that membrane permeability was a key limitation to absorption.[9] For that series of antagonists, it appeared that the probability of good oral bioavailability was much better for compounds with PSA <130 Å^2 than for those with PSA >140 Å^2, and this observation is consistent with the literature.[11]

Compound **1** had a calculated PSA of 149 Å^2 (Table 2), suggesting that poor membrane permeability likely contributed to the lack of oral bioavailability. Other factors that probably had a negative impact on the bioavailability of compound **1** included high plasma

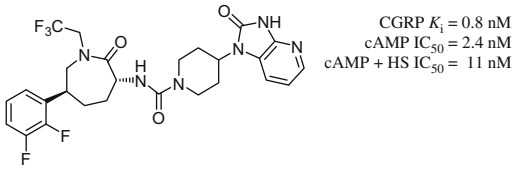

Figure 1. Structure and activity of telcagepant.

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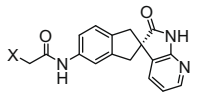
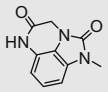
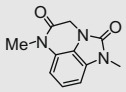
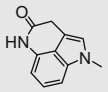
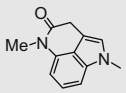
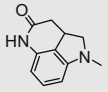
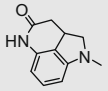
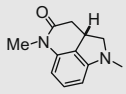
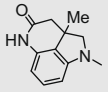
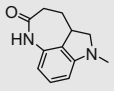
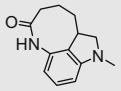
Table 1
CGRP receptor antagonist activity for compounds **1**–**10**



Compound	X	CGRP K_i[a,b] (nM)	cAMP IC_{50}[a,c] (nM)	cAMP + HS IC_{50}[a,d] (nM)
1		0.039 ± 0.011 (8)	0.28 (2)	0.62 (2)
2		0.23 ± 0.078 (8)	0.88 ± 0.20 (5)	13 ± 8.4 (5)
3		0.12 ± 0.10 (9)	0.61 ± 0.14 (6)	2.0 ± 0.52 (6)
4		1.4 ± 0.29 (3)	4.1 (2)	67 (2)
5	 Isomer A	0.35 ± 0.19 (10)	2.4 ± 1.1 (6)	8.1 ± 3.9 (6)
6	 Isomer B	1.2 ± 0.48 (3)	5.3 ± 1.4 (4)	24 ± 2.0 (4)
7[e]	 Isomers A & B	9.7 (2)	37 (1)	530 (1)
8	 Isomer A	0.28 ± 0.067 (4)	1.3 ± 0.43 (5)	6.5 ± 2.8 (5)
9	 Isomer A	1.1 (1)	3.0 ± 0.98 (4)	23 ± 9.7 (4)
10	 Isomer A	2.2 (2)	7.2 (1)	37 (1)

[a] Mean value ± standard deviation, where appropriate; number of replicates in parentheses.
[b] K_i value for inhibition of ^{125}I-hCGRP binding determined using membranes from HEK293 cells stably expressing human CLR/RAMP1.[6]
[c] Inhibition of CGRP-induced cAMP production in HEK293 cells stably expressing human CLR/RAMP1.[6]
[d] Inhibition of CGRP-induced cAMP production in HEK293 cells stably expressing human CLR/RAMP1 in the presence of 50% human serum.[6]
[e] Compound **7** is a 1:1 mixture of diastereomers.

Table 2
Pharmacokinetic data for select CGRP antagonists in rats

Compound	PSA[a] (Å^2)	Solubility[b] (μg/mL)	F[c] (%)	iv $t_{1/2}$[d] (h)	Cl (mL/min/kg)
1	149	0.24	<1	0.8	72
2	134	0.40	1	1.0	30
3	123	<0.5	6	1.5	8.8
5	125	6.1	25	1.4	26

[a] Polar surface area calculated by the method of Clark.[11]
[b] Aqueous solubility determined at pH 7.4 on amorphous material.
[c] Oral bioavailability determined in rats following dosing of the compound at 10 mpk po in 90% PEG400 vehicle.
[d] Half-life determined in rats following dosing of the compound at 2 mpk iv in DMSO.

clearance in rats (Cl = 72 mL/min/kg) and low aqueous solubility (0.24 μg/mL at pH 7.4). As previously reported, *N*-methylation of compound **1** to give **2** effected a reduction in PSA to 134 Å^2 (Table 2) but did not significantly improve aqueous solubility or oral bioavailability in rats, a key species for safety studies.[10]

One approach to reducing PSA is to remove polar functionality, as illustrated by the removal of an amido group from compound **1** to afford the indole-based tricyclic compound **3** (Table 1). This modification led to a threefold reduction in potency both intrinsically (K_i = 0.12 nM) and in the serum-shifted functional assay (IC_{50} = 2.0 nM). *N*-Methylation of **3** provided analogue **4**, which provided a further reduction in PSA to 110 Å^2, but led to a significant loss of potency in the functional assay (cAMP + HS IC_{50} = 67 nM).

Based on our previous observations, the PSA value of compound **3** (123 Å^2) was consistent with good membrane permeability, although its aqueous solubility was no better than that of compound **1** (Table 2). Compound **3** exhibited modest oral bioavailability in rats (F = 6%), suggesting that the reduced PSA was beneficial.

In an attempt to improve aqueous solubility without increasing PSA, the indole moiety in **3** was replaced with an indoline ring. This modification had little effect on PSA but it introduced a weakly basic amine (calculated pK_a = 2.87; ACD/Labs 11.0) into the tricyclic ring system. It was anticipated that this would lead to increased solubility under acidic conditions, for example in the stomach, and that this would improve oral bioavailability.

The two indoline epimers **5** and **6** were prepared and it was determined that compound **5** was the more potent isomer (Table 1), possessing similar potency in the serum-shifted functional assay to the clinical compound telcagepant.[6]

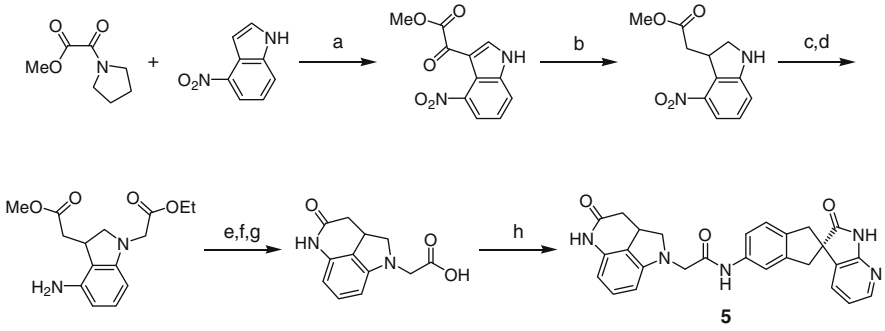
Compound **5** exhibited some improvement in solubility at neutral pH (6.1 μg/mL at pH 7.4) relative to compound **1**. Gratifyingly, the combination of reduced PSA and enhanced solubility correlated with an improvement in rat oral bioavailability (F = 25%, Table 2).

Further modification of the indoline tricyclic ring system did not lead to significantly improved potency compared with compound **5** (Table 1). In analogy with the benzimidazolone **2** and the indole **4**, *N*-methylation of the tricyclic anilide group led to a

Table 3
Pharmacokinetic data for compound **5**

Species	F (%)	iv $t_{1/2}$ (h)	Cl (mL/min/kg)	Vd_{ss} (L/kg)
Rat	25[a]	1.4[d]	26	1.6
Dog	34[b]	4.2[e]	5.5	1.8
Monkey	49[c]	2.2[e]	9.3	1.4

[a] Dosed at 10 mpk in 90% PEG400 vehicle.
[b] Dosed at 1 mpk in 1% methylcellulose.
[c] Dosed at 2 mpk in 1% methylcellulose.
[d] Dosed at 2 mpk in DMSO.
[e] Dosed at 0.5 mpk in DMSO.



Scheme 1. Synthesis of compound **5**. Reagents and conditions: (a) diphosphoryl chloride, 0 °C to rt, 97%; (b) triethylsilane, TFA, 91%; (c) ethyl bromoacetate, Na_2CO_3, KI, acetone, reflux, 57%; (d) H_2, Pd/C, EtOH, 96%; (e) *p*-TsOH·H_2O, toluene, reflux, 68%; (f) ChiralPak AS, MeOH, second major peak is isomer A; (g) LiOH, H_2O, EtOH, THF, 97%; (h) (*S*)-5-amino-1,3-dihydrospiro[indene-2,3′-pyrrolo[2,3-*b*]pyridin]-2′(1′*H*)-one,[10] EDC, HOBT, DIEA, DMF, 81%.

significant loss of potency (compound **7**, Table 1). Methylation at the indoline 3-position was well tolerated (compound **8**), but ring-expansion of the lactam ring gave the less-potent analogues **9** and **10** (Table 1). None of these analogues offered a significant advantage over compound **5**, which was selected for a more in depth pharmacokinetic evaluation (Table 3).

Compound **5** was found to have low to moderate plasma clearance in rat, dog, and monkey, with a plasma half-life ranging from 1.4 h in rats to 4.2 h in dogs (Table 3). The volume of distribution was similar in all three species. Following dosing of a suspension of the compound in 1% methylcellulose, the oral bioavailability was moderate to good in dogs ($F = 34\%$) and monkeys ($F = 49\%$), but poor in rats ($F = 7\%$). The oral bioavailability of compound **5** in rats was improved following dosing of a solution formulation in 90% PEG400 ($F = 25\%$). When the compound was dosed in dogs using the same 90% PEG400 vehicle, the oral bioavailability was also improved ($F = 75\%$). These data suggest that the solubility of compound **5** is high enough to allow moderate oral bioavailability, but is not optimal.

For the data shown in Table 3, it may be noted that the dose of compound **5** given orally to rats (10 mpk) was significantly higher than the dose given orally to dogs (1 mpk) or monkeys (2 mpk). It is possible that such differences in dosing could affect the oral bioavailability determinations if, for example, oral absorption was non-linear due to limited solubility. However, for compound **5**, oral AUC was essentially dose proportional between 10 mpk and 45 mpk in rats, and between 2 mpk and 20 mpk in monkeys (data not shown).

In order to assess the ability of compound **5** to function as a CGRP receptor antagonist in vivo, it was evaluated in the rhesus monkey capsaicin-induced dermal vasodilation pharmacodynamic (CIDV PD) assay.[12] It is known that the results obtained with telcagepant in this rhesus monkey PD assay are in good agreement with those observed in the clinic.[13] Evaluation of **5** in this rhesus monkey PD assay demonstrated that the compound effectively inhibited 90% of the capsaicin-induced vasodilation response at a plasma level of 2 μM (PD $EC_{90} = 2$ μM),[14] similar to the results obtained with telcagepant.[6]

The synthesis of compound **5**, which is representative of the methodology used to prepare the compounds described herein, is shown in Scheme 1.[15] The tricyclic indole and indoline ring systems were prepared by derivatization of 4-nitroindole using standard chemistry. In Scheme 1, Vilsmeier glyoxylation of 4-nitroindole was carried out using the procedure of Downie et al.[16] to provide the methyl glyoxylate derivative shown. Reduction of this intermediate using excess triethylsilane in trifluoroacetic acid afforded a 4-nitroindoline, which was alkylated with ethyl bromoacetate. Following reduction of the nitro moiety to an amino group, acid-catalyzed formation of the tricyclic ring system and subsequent saponification led to a key carboxylic acid intermediate. This acid was coupled to (*S*)-5-amino-1,3-dihydrospiro[indene-2,3′-pyrrolo[2,3-*b*]pyridin]-2′(1′*H*)-one[10] using EDC and HOBT, to provide the final compound.

In summary, we have identified a series of CGRP receptor antagonists containing novel tricyclic ring systems. Reduction of polar surface area and incorporation of a weakly basic indoline nitrogen afforded potent antagonists with good oral bioavailability.

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14. Compound **5** was administered intravenously using a dose-escalating protocol similar to that described for **MK-0974** (telcagepant) in Ref. 6.
15. All final compounds were characterized by ^{1}H NMR, HPLC, and HRMS. Additional synthetic details are provided in: Bell, I. M.; Gallicchio, S. N.; Stump, C. A.; Theberge, C. R.; Vacca, J. P.; Zartman, C. B.; Zhang, X.-F. WO 2006/031491.
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