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Novel CGRP receptor antagonists from central amide replacements causing a reversal of preferred chirality

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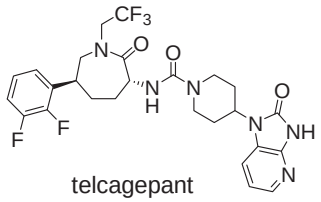
ABSTRACT

A previously utilized quinoline-for-*N*-phenylamide replacement strategy was employed against a central amide in a novel class of CGRP receptor antagonists. A unique and unexpected substitution pattern was ultimately required to maintain reasonable affinity for the CGRP receptor, while at the same time predicting acceptable heterocycle positioning for related analogs. Subsequently, specific quinoline and naphthyridine compounds were prepared which supported these structural predictions by displaying CGRP binding affinities in the 0.037–0.15 nM range.

The calcitonin gene-related peptide (CGRP) is a 37 amino acid neuropeptide which exhibits very potent vasodilation activity and is strongly implicated in the pathogenesis of migraine.[1] In particular, IV administration of CGRP to established migraineurs induces migraine-like headaches.[2] Conversely, treatment of migraines with sumatriptan results in a normalization of circulating CGRP levels concomitant with pain relief.[3] More compelling, however, is the clinically demonstrated success of the two small molecule CGRP receptor antagonists, olcegepant and telcagepant.[4] Proof of concept was first achieved with an IV formulation of olcegepant in a phase II clinical trial, which demonstrated efficacy similar to that of the triptans.[5] Although the development of olcegepant appears on hold, the oral CGRP receptor antagonist telcagepant has progressed to phase III clinical studies. In those studies, telcagepant has been shown to be efficacious and well-tolerated, while demonstrating a lower incidence of adverse effects than zolmitriptan.[6,7]



telcagepant

A recent publication from these laboratories disclosed a novel class of CGRP receptor antagonists that were developed via a rational design strategy initiated by the simplification of target structures followed by a re-optimization along a different path.[8] Part of this structural simplification exercise entailed the replacement of a central quinoline with an *N*-phenylamide in order to facilitate the more rapid production of analogs. Naturally, it would make sense to eventually explore what benefits could be obtained by once again reinstating the quinoline in any subsequent series of new lead.

One of the earliest leads containing a central amide, compound **1**, shown in Figure 1 as the preferred (*S*) enantiomer has a K_i = 1.9 nM against a human recombinant CGRP receptor. The straightforward production of a quinoline core analog whereby the position of the amidic nitrogen becomes the position for the quinoline nitrogen, according to known chemistry,[9] provided racemic compound **2**. Contrary to analogous substitutions on earlier lead series, which had minimal effect on CGRP receptor binding affinity, the introduction of this quinoline core resulted in a nearly 3 log unit decrease in K_i to a value of 2.2 μM. Examining the two individual enantiomers of **2**, neither of which would be expected to have a CGRP receptor affinity of less than ~1 μM, we realized that (***S***)-**2** displayed a spatially similar connectivity to that of compound **1** with respect to the *N*-acyl-benzyl amine terminus (drawn suggestively for easy mental overlays). While compound (***R***)-**2** displayed the positioning of the quinoline nitrogen similar to known and potent quinoline CGRP receptor antagonists.[8,9] Realization of these two critical pieces of SAR prompted the preparation of racemic compound **3** which displayed more

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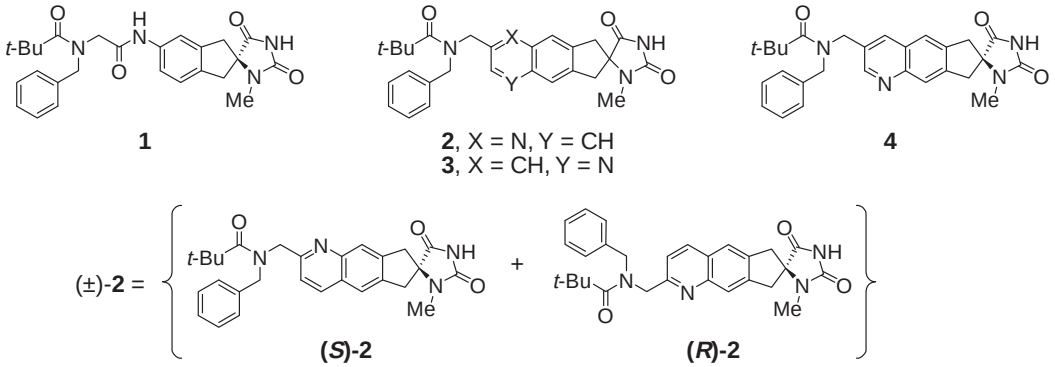


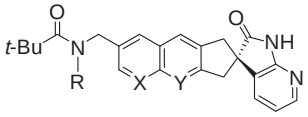
Figure 1. Introduction of quinoline cores to the lead structure **1**.

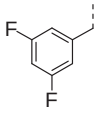
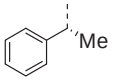
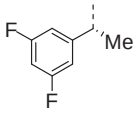
reasonable CGRP K_i = 35 nM. Ultimately the single (*R*) enantiomer **4**, predicted by the above analysis of (***S***)-**S** and (***R***)-**2**, suffered a much smaller decrease in binding affinity relative to the starting amide analog **1** by displaying a K_i of 12 nM. The interesting change in preferred spirohydantoin chirality between **1** and **4** results from the change in location of their amidic and quinolinic nitrogens, respectively, but does not reflect a shift in positioning of their *N*-acyl-benzyl amine termini. This would suggest that basic nitrogens or heteroatoms might be best tolerated on one side of these quinolines, and related, structures (vide infra).

The preparation of **4** is depicted in Scheme 1 starting from the known hydantoin **5**[10] and the 'vinamidinium' bis-tetrafluoroborate salt **6**[11] to give quinoline aldehyde **7**. The aldehyde is then reductively aminated and acylated under standard conditions to provide **4**.

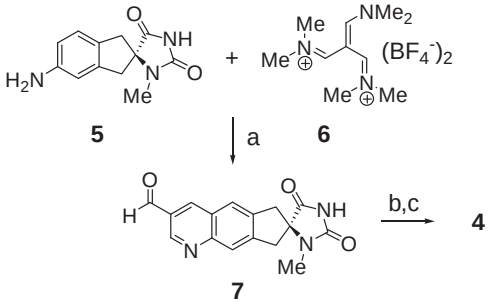
Although the binding affinity for **4** was encouraging we knew from prior experience[12] that there was the potential for an up to 10-fold improvement in K_i upon replacement of the hydantoin with an azaoxindole to provide **8**, shown in Table 1.[13] Indeed, an approximate ninefold improvement in binding affinity was achieved to arrive at a K_i of 1.3 nM for compound **8**. Applying known SAR derived from the anilide series analogous to **1**[8] we were surprised to find some interesting departures. While introduction of two fluorines to give **9** still improved K_i by roughly fourfold this effect was about half of that previously observed. However, the benefit to CGRP receptor binding affinity resulting from the presence of a benzylic methyl in compound **10** encompassed an order of magnitude improvement rather than a simple doubling of affinity as previously observed. Furthermore, the combination of both fluorination and methylation was not additive in this instance, but instead caused a decrease in CGRP receptor binding affinity for compound **11**, relative to the non-fluorinated analog **10**. Although the presence of two fluorines did not appear to be generally beneficial an attempt was already underway to produce

Table 1
CGRP receptor binding affinities for the azaoxindoles **8**–**11** and **18**–**20**



Compd[a]	R	X	Y	CGRP K_i[a,b] (nM)
8		N	CH	1.3
9		N	CH	0.69
10		N	CH	0.10
11		N	CH	0.12
18		N	CH	0.037
19		CH	N	0.11
20		N	N	0.15

[a] Values represent the numerical average of at least two experiments. Interassay variability was ± 10% for the binding assays.
[b] K_i values for competition with ^{125}I-hCGRP determined using membranes from HEK293 cells stably expressing cloned human CLR/RAMP1.



Scheme 1. Synthesis of compound **4**. Reagents and conditions: (a) HOAc, KOAc, 90 °C, 40–60%; (b) benzylamine, $NaHB(OAc)_3$, $CHCl_3$, 70–90%; (c) pivaloyl chloride, *N*-methyl morpholine, 0 °C, 85–95%.

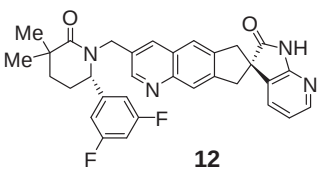


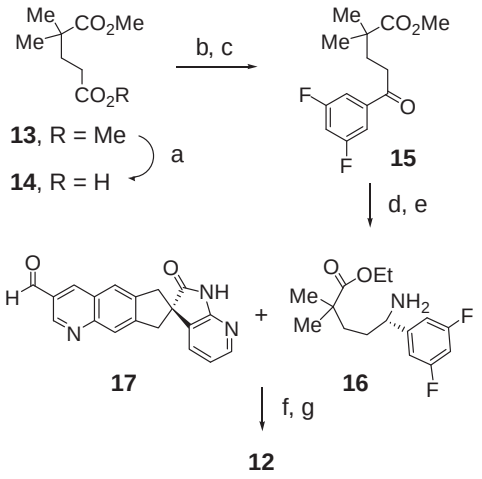
Figure 2. Lactam constraint applied to compound **11** to arrive at compound **12**.

a lactam-constrained version of **11**. As shown in Figure 2, compound **12** actually lost CGRP receptor affinity providing a K_i of 0.30 nM, and further demonstrated that although the exchange of

a central amide for a central quinoline was tolerated at the CGRP receptor, this modification had significantly altered preferred structures in this new series.

Preparation of **12** initiated with the diester **13** shown in Scheme 2. Carefully controlled hydrolysis of the less hindered ester produced **14**. Weinreb amide formation followed by aryl Grignard addition yielded the ketone **15**. The use of Ellman sulfinimide methodologies[14] allowed the introduction of the primary amine in **16**, concomitantly the methyl ester was transformed to an ethyl ester resulting from the use of titanium tetraethoxide. Reductive alkylation of **16** with aldehyde **17** and subsequent lactamization at elevated temperatures provided **12**.

Moving forward, cognizant that present SAR suggested that difluorination and lactam constraints were no longer preferred characteristics in this quinoline series of CGRP receptor antagonists, attempts were made to bias the position of the pendent aryl ring in alternative fashions. The (*R*)-1-aminoindanyl constraint shown for compound **18** (Table 1) provided a nearly threefold improvement in K_i relative to the less conformationally biased compound **10**. This sub-nanomolar affinity for the CGRP receptor puts compound **18** in a similar potency range as some of our best antagonists published to date.[8]

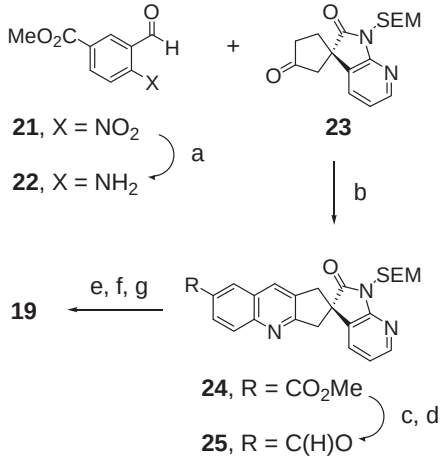


Scheme 2. Synthesis of compound **12**. Reagents and conditions: (a) K_2CO_3, THF/MeOH/H_2O (2:3:2), rt, 54%; (b) oxalyl chloride, NEt_3, DCM, MeHNOMe, 0 °C, 79%; (c) 3,5-difluorophenyl magnesium bromide, THF, 0 °C, 85%; (d) (i) (*S*)-*tert*-butyl sulfinimide, $Ti(OEt)_4$, THF, 60 °C; (ii) $NaHB(OAc)_3$, 0 °C, 72%; (e) (i) $HCl_{(g)}$, MeOH, 0 °C, 30 min; (ii) aqueous $NaHCO_3$, 99%; (f) $NaHB(OAc)_3$, HOAc, $CHCl_3$, rt, 95%; (g) xylenes/HOAc (9:1), 140 °C, 48%.

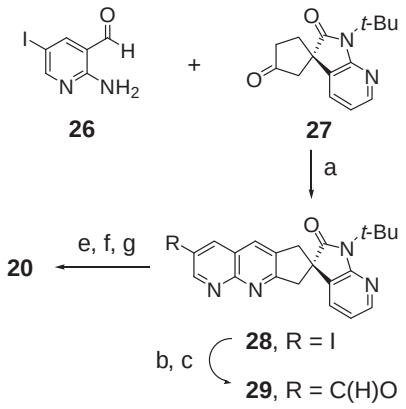
Returning to the idea that nitrogen atoms might only be tolerated on the side opposite to that of the terminal alkyl attachment (see compounds **2** and **3**), an alternative quinoline was prepared wherein the nitrogen is now at the Y position in the Table 1 parent structure. This modification present in compound **19** was tolerated, but caused a minor decrease in the CGRP receptor binding affinity. Further demonstrating that nitrogen atoms were tolerated at both X and Y positions simultaneously naphthyridine **20** displayed a CGRP K_i similar to **19**. Neither analog displayed a K_i superior to quinoline **18**.

Preparation of **19**, according to Scheme 3, began with the reduction of nitro-aldehyde **21**. Condensation of aniline **22** with ketone **23**[15] gave ester **24**. Direct reduction of this ester with hydride sources proved problematic, so a two step procedure of hydrazide formation, followed by reduction with potassium ferrocyanide delivered aldehyde **25**. The SEM protecting group on **25** was then removed, followed by reductive amination of the aldehyde with (*R*)-1-aminoindane and subsequent acylation to produce **19**. In a similar manner compound **20** was prepared according to Scheme 4 starting from the commercially available iodide **26**. Condensation of **26** with ketone **27**[15] gave naphthyridine **28**. Installation of the required aldehyde **29** occurred through initial vinylation, followed by osmium tetroxide catalyzed oxidation. Reductive amination of naphthyridine aldehyde **29** with (*R*)-1-aminoindane, was followed by *tert*-butyl protecting group removal, and ultimately by carefully controlled acylation with pivaloyl chloride to give **20**. This alternative order of chemical transformations, relative to Scheme 3, was necessitated due to the chemical instability of aldehyde-naphthyridine to the strongly acidic conditions used to cleave the *tert*-butyl protecting group.

In summary, a modified quinoline for *N*-phenyl amide core replacement strategy was successfully employed to arrive at a novel series of CGRP receptor antagonists which displayed unique SAR relative to their amide progenitors. Additionally, predictions based on the tolerability of central nitrogen atoms allowed for the preparation of similarly novel quinoline and naphthyridine analogs which displayed sub-nanomolar affinity for the CGRP receptor.



Scheme 3. Synthesis of compound **19**. Reagents and conditions: (a) Pd/C, H_2 (1 atm.), MeOH, 45%; (b) MeOH, piperidine, 75 °C, boil dry (2×), 50%; (c) EtOH, hydrazine, 70 °C, quant.; (d) $K_4Fe(CN)_6$, concd NH_4OH, DCM, H_2O, rt, 38%; (e) (i) $HCl_{(g)}$, MeOH, rt, 18 h; (ii) concentrate in vacuo; (iii) MeOH, concd NH_4OH, 94%; (f) (*R*)-1-aminoindane, $NaHB(OAc)_3$, HOAc, $CHCl_3$, 95%; (g) pivaloyl chloride, NEt_3, DCM, 0 °C, 63%.



Scheme 4. Synthesis of compound **20**. Reagents and conditions: (a) EtOH, piperidine, boil dry (3×), 65%; (b) bis(triphenylphosphine) palladium(II) chloride, tributyl(vinyl)stannane, dioxane, 85 °C, 18 h, 62%; (c) OsO_4(cat.), $NaIO_4$, THF, H_2O, rt, 2 h, 35%; (d) (*R*)-1-aminoindane, $NaHB(OAc)_3$, HOAc, $CHCl_3$, 29%; (e) $MeSO_3H$ (neat), 55 °C, 2 h, quant.; (f) pivaloyl chloride, NEt_3, DCM, 0 °C, 50%.

Acknowledgments

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