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Novel CGRP receptor antagonists through a design strategy of target simplification with addition of molecular flexibility

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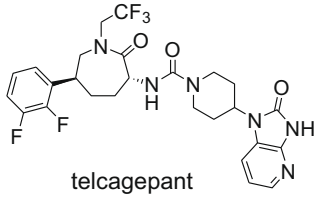
ABSTRACT

A novel class of CGRP receptor antagonists was rationally designed by modifying a highly potent, but structurally complex, CGRP receptor antagonist. Initial modifications focused on simplified structures, with increased flexibility. Subsequent to the preparation of a less-potent but more flexible lead, classic medicinal chemistry methods were applied to restore high affinity (compound **22**, CGRP K_i = 0.035 nM) while maintaining structural diversity relative to the lead. Good selectivity against the closely related adrenomedullin-2 receptor was also achieved.

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, telcagepant seems well positioned to become the first commercially available, oral CGRP receptor antagonist. Successful phase II studies with telcagepant provided continued support for the role of CGRP antagonists in migraine treatment.[6] Furthermore, Phase III clinical studies with telcagepant have shown it to be efficacious and well-tolerated, while demonstrating a lower incidence of adverse affects than zolmitriptan.[7]

Concurrent with the efforts that produced telcagepant, alternative structural series related to compound **1** were also pursued.[8,9] Although analogs of **1** displayed both high potency and good pharmacokinetics, the tragic ease with which advanced compounds can



telcagepant

fail during development necessitated the constant search for structural diversity. Since lengthy syntheses of compounds analogous to **1** would hamper the rapid exploration of structural diversity, an effort was made to simplify future targets while retaining key pharmacophores. Some of these simplifications could be described as reversing optimization based upon known SAR, causing predictable negative consequences such as reduced potency. Other simplifications were introduced on an at-risk basis. The quinoline of **1** had been previously introduced as a replacement for an amide similar to the central amide displayed in the hypothetical compound **2** (Scheme 1).[9] The re-introduction of the amide, though a seemingly backward step, was anticipated to result in little change to binding affinity, while allowing a more rapid attachment of Eastern and Western fragments via straightforward amide coupling reactions. The exchange of the Eastern azaoxindole in **1** for the hydantoin in **2** was predicted to decrease binding affinity by approximately 10-fold, based on previous studies,[10] but allowed the use of more readily available starting materials. Deletion of the Western 6-membered lactam present in **1**, an at-risk modification, simplified

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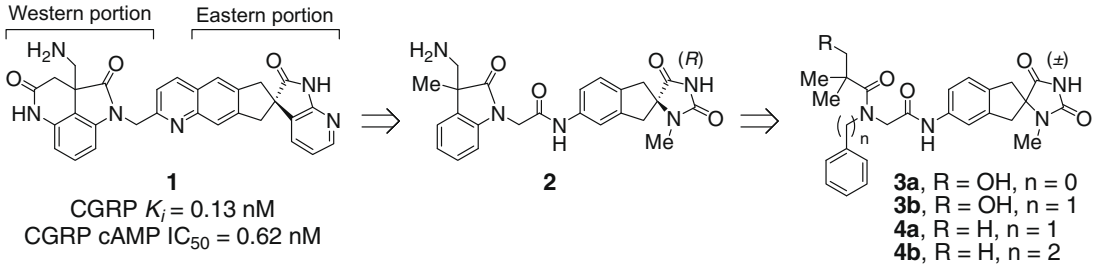


Scheme 1. Deconstruction and simplification of lead 1.

the tricycle portion to just a bicycle. Further scission of the remaining Western lactam gave target compound **3a**, which facilitated additional modifications. Most importantly, structural flexibility could now be introduced by placing a linker between the phenyl ring and the terminal amide (n = 0, 1, 2, etc.). The primary amine was replaced with a primary hydroxyl to maintain the potential for a hydrogen bond donor/acceptor interaction with the CGRP receptor, and by necessity an additional methyl group was added to prevent elimination of water. Finally, a conscious decision was made to screen these novel analogs as racemates so as not to miss the possibility of a change in preferred chirality for binding at the CGRP receptor.

Once compounds **3a** and **3b** were prepared, employing previously described methods,[11] we were pleased to find a binding affinity (K_i) for **3a** of 140 nM, only an 1100-fold reduction relative to compound **1**. But even more gratifying was the payoff received for engineering in the flexible linker (n = 1) of **3b** which displayed a K_i of 10 nM. With an eye toward further simplification, the assumption that the primary hydroxyl was still a beneficial pharmacophore was quickly challenged. Compound **4a** containing the benzyl group of **3b**, and now adorned with just a pivaloyl group, provided a further improvement in binding affinity to a value of 3.0 nM. By further lengthening the alkyl linker to the phenethyl group in **4b** (K_i = 40 nM) it appeared that the n = 1 compounds were optimal (**3b** and **4a**).

With a low-nanomolar, racemic compound such as **4a** in hand it was now time to address the question of preferred chirality. Towards this end, the individual enantiomers **5** and **6** were prepared from their corresponding single enantiomer anilines. Based on previous work with the tricycles such as **1**, it might have been predicted based upon the hypothetical compound **2** that the preferred chirality at the Eastern spirocenter would be (*R*). However, this was not the case. Compound **5**, with the (*R*) chirality, displayed a K_i = 800 nM, while compound **6**, with the opposite (*S*) chirality, demonstrated a K_i = 1.9 nM.[12] This change in preferred chirality clearly demonstrated the importance of testing novel structures as racemates whenever possible, especially in the case of structures with such subtle chirality as that found in **5** and **6**. To appreciate this interesting reversal of chirality preference, it is instructive to closely examine the Eastern spirohydantoin portions of **5** and **6**, which have been drawn in an identical orientation, but are still of opposite chirality (Fig. 1). The chirality differentiating moiety is the aniline nitrogen which is located 4 carbon atoms away from the spirocenter. In essence, this change in preferred chirality can be viewed as resulting from a shift in the attachment point of the central amide, causing the Western portion of these newer antagonists to bind in an unique manner, or location, within the CGRP receptor as compared to the lead structure **1**, thereby preferring the novel structures of this Letter.

To summarize the progress so far, we compared single enantiomer **6** to **1**, to find that these modifications had managed to drastically simplify the overall structure while only suffering a 15-fold decrease in binding affinity. Additionally, we had identified a new series of CGRP receptor antagonists where the preferred chirality at the privileged structure (Eastern portion) was now of the opposite sense.

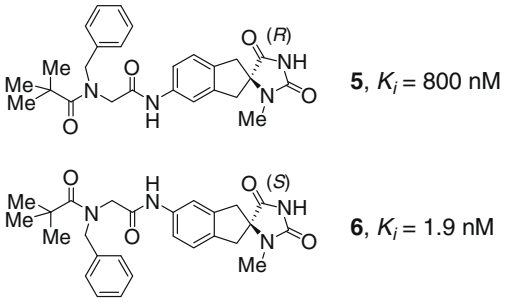
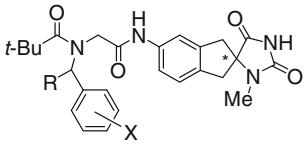


Figure 1. Enantiomers 5 and 6 demonstrate that the position of the anilide determines chirality at the spirocenter.

Moving forward, compound **6** served as an ideal starting point from which to apply classical medicinal chemistry methods to maximize potency while reducing off-target binding to the closely related adrenomedullin-2 receptor.[13] The CGRP receptor is a family B subgroup of G-protein coupled receptors (GPCR) whose transmembrane domain is constructed from the association of two separate proteins: the calcitonin receptor-like receptor (CLR) which comprises the usual 7-transmembrane portion, and a receptor activity modifying protein-1 (RAMP1), a smaller protein which transverses the cell membrane only once. There are presently two other closely related GPCRs which are constructed from CLR plus RAMP2 (the adrenomedullin-1 receptor, AM1) and CLR plus RAMP3 (the adrenomedullin-2 receptor, AM2). For the compounds presented here, selectivity against the AM1 receptor was always greater than 10,000-fold. However, as can be seen in Table 1, compound **6** displayed sub-micromolar affinity for the AM2 receptor, giving a selectivity ratio of just 370. We desired to increase this ratio through a decrease in AM2 binding, an increase in CGRP receptor affinity or, ideally, both.

An effort to improve CGRP receptor binding affinity and selectivity through substitution on the benzyl group of **6** was both facile and productive. The three mono-substituted benzyl analogs, as illustrated with a fluorine in racemic compounds **7–9**, demonstrated that substitution at the *meta* position improved CGRP receptor binding by approximately twofold, but basically left the affinity for the AM2 receptor unchanged. It is important to point out that compounds **7–14** are racemic, with the vast majority of affinity for both the CGRP and the AM2 receptors residing in just one spirohydantoin enantiomer (*S*). Alternatively, fluorine at the *para* position resulted in little change to the CGRP receptor binding affinity, but did decrease AM2 binding about threefold. Numerous other functional groups were placed at the *meta* position (**10–14**), but only the chloride of **10** produced a similar effect as the mono-

Table 1
CGRP and AM2 receptor binding affinities for the spirohydantoins **6**–**20**



Compd[a]	R	X	CGRP K_i[b,d] (nM)	AM2 K_i[b,e] (nM)	AM2: CGRP ratio
(*S*)-**6**	H	H	1.9	710	370
(±)-**7**	H	2-F	14[c]	—	—
(±)-**8**	H	3-F	1.6	1400[c]	880
(±)-**9**	H	4-F	3.7	3700[c]	1000
(±)-**10**	H	3-Cl	1.8	1400[c]	780
(±)-**11**	H	3-Me	7.9[c]	1800[c]	230
(±)-**12**	H	3-OMe	45[c]	9700[c]	220
(±)-**13**	H	3-CN	23[c]	13000[c]	570
(±)-**14**	H	3-CF_3	25[c]	6200	250
(*S*)-**15**	H	3,5-di-F	0.55	2400	4400
(*S*)-**16**	H	3-Cl, 5-F	1.2	1800	1500
(*S*)-**17**	H	3,5-di-Cl	4.4	2100	480
(*S*)-**18**	(*S*)-Me	H	56	16,000	290
(*S*)-**19**	(*R*)-Me	H	0.83	670	810
(*S*)-**20**	(*R*)-Me	3,5-di-F	0.26	1400	5400

[a] Chirality at spirohydantoin (*) in parentheses.
[b] Values represent the numerical average of at least two experiments (except where noted). Inter assay variability was ±10% for the binding assays.
[c] Values represent a single experiment.
[d] K_i values for competition with ^{125}I-hCGRP determined using membranes from HEK293 cells stably expressing cloned human CLR/RAMP1.
[e] K_i values for competition with ^{125}I-rat Adrenomedullin determined using membranes from B6 cells stably expressing cloned human CLR/RAMP3.

fluoride **8**. Among a variety of di-substitution patterns explored (not shown), only the 3,5-configuration imparted substantial benefits. The 3,5-difluorophenyl of **15** both increased CGRP receptor binding affinity threefold to a K_i of 0.55 nM, while decreasing AM2 binding threefold to a K_i of 2.4 μM, for a selectivity ratio of 4400. As the fluorines of **15** were sequentially replaced with chlorines (**16** and **17**), the selectivity ratio was eroded as a result of falling CGRP binding affinity. Even without adding functionality to the phenyl ring, binding and selectivity could be improved by placing a methyl group at the benzylic position of **6** to produce diastereomers **18** and **19**. The (*R*) configuration for the methyl group of **19** improves CGRP binding twofold, while leaving the AM2 binding relatively unchanged, for a net improvement in selectivity. Combining the enhancements of **15** and **19** into a single compound (**20**) produced an additive benefit of increased CGRP binding affinity to 0.26 nM, while improving the AM2:CGRP ratio to greater than 5000.

Returning to the improved CGRP receptor binding seen for compound **19**, relative to **6**, the most likely explanation would be that the benzylic methyl group served to conformationally bias the position of the phenyl group for improved receptor binding. An alternative method to reduce molecular flexibility is through the introduction of macrocycles or small rings. Redrawing compound **20** in Figure 2 depicts a preferred conformation for its Western portion. As shown, this confirmation minimized steric interactions between the *tert*-butyl group and the benzylic portion by placing the benzylic hydrogen in close proximity to the *tert*-butyl moiety. To the extent that this low energy conformation predicts/approximates the binding confirmation of **20**, an obvious lactam to construct would be the one that connects one of the methyl groups from the pivaloyl *tert*-butyl group to the benzylic position of the difluoro-benzyl group, but not directly to the benzylic methyl group itself as this would impart the wrong sense of chirality. With the lactam now enforcing the desired binding conformation, the benzylic methyl depicted in **20** could be removed. Additionally, to maintain a similar spatial relationship between the geminal dimethyls and the phenyl group, the 6-membered lactam should be preferred over the 5- or 7-membered lactam.[14] Straightforward application of Ellman sulfinimide methodologies as previously described[15] produced lactam **21a** (K_i = 0.23 nM), which had essentially the same CGRP receptor binding affinity as compound **20** but an improved AM2:CGRP selectivity of 10,000-fold. These results not only supported the conformation depicted for **20**, but also that the benzylic methyl of **20** might not be deleterious. This was confirmed with compound **21b**, also prepared using alternative Ellman procedures.[15] While this methyl group was not beneficial with respect to binding affinity (K_i = 0.48 nM) or AM2:CGRP ratio (6900), it was tolerated and further supports the confirmation shown for the Western region of compound **20**.

Comparing the CGRP receptor affinity between tricycle **1** (K_i = 0.13 nM) and the lactam **21a** (K_i = 0.23 nM), it was evident that this new series had already regained almost all of the receptor

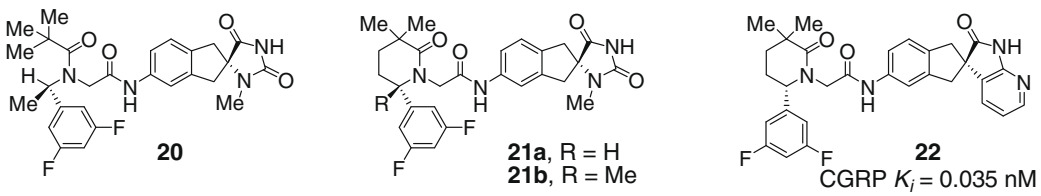


Figure 2. Conformationally constrained, CGRP receptor antagonists.

affinity given up during the initial deconstruction of **1**. What remained to be reintroduced was the potency enhancing azaoxindole Eastern portion found in **1**. Although compound **22** did not enjoy the full 10-fold boost in potency seen in previous work,[10] we were pleased to arrive at a compound with a CGRP K_i of 0.035 nM, a functional activity IC_{50} of 0.12 nM,[16] and an AM2:CGRP selectivity of 4600-fold.

In summary, through a rational design strategy of target simplification concomitant with the addition of structural flexibility, a very advanced lead was deconstructed and then re-optimized in a new direction to provide a novel structural series which now prefers the opposite chirality at the privileged structure, is easier to prepare, and even possesses improved potency. The surprising SAR arising from the re-introduction of the central quinoline constraint, SAR associated with the N-terminal acyl group in analogs of **6** and further elaboration of the lactam **22** will be the subjects of future communications.

Acknowledgments

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