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(*E*)-Alkenes as replacements of amide bonds: Development of novel and potent acyclic CGRP receptor antagonists

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ABSTRACT

A new class of CGRP receptor antagonists was identified by replacing the central amide of a previously identified anilide lead structure with ethylene, ethane, or ethyne linkers. (*E*)-Alkenes as well as alkynes were found to preserve the proper bioactive conformation of the amides, necessary for efficient receptor binding. Further exploration resulted in several potent compounds against CGRP-R with low susceptibility to P-gp mediated efflux.

The Calcitonin Gene-Related Peptide (CGRP) is a 37 amino acid neuropeptide that mediates several biological actions including vasodilation and nociception, and has been implicated in the pathology of cerebrovascular disorders such as migraine.[1,2] The CGRP receptor is a G-Protein coupled receptor (GPCR) and a heterodimeric complex, consisting of calcitonin receptor-like receptor (CLR) and receptor activity modifying protein-1 (RAMP1). The components of the receptor have been found in the smooth muscle of intracranial vessels and sensory trigeminal neurons and fibers in the periphery as well as central nervous system, and the activation of the receptors by CGRP is thought to contribute to headache pain during migraine attacks.[3] In clinical trials, elevated levels of CGRP have been found in the jugular vein during migraine attacks.[4] Antagonists of CGRP-R are thought to reduce signaling in the trigeminovascular pathway to relieve acute migraine pain. Clinical studies with olcegepant, telcagepant, MK-3207 and BI-44370 have demonstrated that the blockade of CGRP-R is effective in treating acute attacks of migraine, similar to that of the triptans, with a lower incidence of adverse effects.[5–8] A recent study with a PET tracer [^{11}C]MK-4232 revealed that telcagepant has low receptor occupancy in CNS at a clinically efficacious dose and, therefore, the efficacy of telcagepant is likely to be driven by antagonism of CGRP-R in periphery.[9,10] However, it is yet unknown if improved migraine efficacy may be achieved with centrally acting CGRP-R antagonists.

Previous publications from our laboratories disclosed a novel class of CGRP receptor antagonists, represented by compound 1.[11,12] Introduction of the potency-enhancing azaoxindole in place of the hydantoin produced compound **2** with 9-fold improvement in binding affinity, similar to the improvement observed previously in the program.[13] In addition to the improved potency, compound **2** exhibited low susceptibility to P-gp transport and good membrane permeability, which positioned it to be a good lead in developing CNS penetrant CGRP-R antagonists.[14] However, it still contained a central anilide in the molecule, and it was desirable to find a replacement of the central amide functionality. We have previously disclosed quinolines as a replacement of the central amide in this series (**3**), to constrain and rigidify the molecule.[15] This modification resulted in lower susceptibility to P-gp efflux compared to its parent compound **2** (Fig. 1).

Concurrent with this effort, alkene, alkane, and alkyne linkers were explored as amide bond isosteres. An (*E*)-olefin mimics the size, geometry, bond angle and bond length of the peptide bond.[16] Also it is a non-hydrolysable group, thus eliminating the possibility of aniline metabolite formation. Here, we report the synthesis and the evaluation of CGRP receptor antagonists containing all hydrocarbon linkers as amide replacements.

In a retrosynthetic approach, one can envision that the western and eastern fragments of the molecules such as **8a** can be coupled using Heck reaction conditions to form a double bond. Western portion **5** of compounds **8** and **9** were prepared by allylation of a primary amine followed by acylation (Scheme 1).[17] Eastern portion **6** and **7** were synthesized via nitration followed by halogenation of

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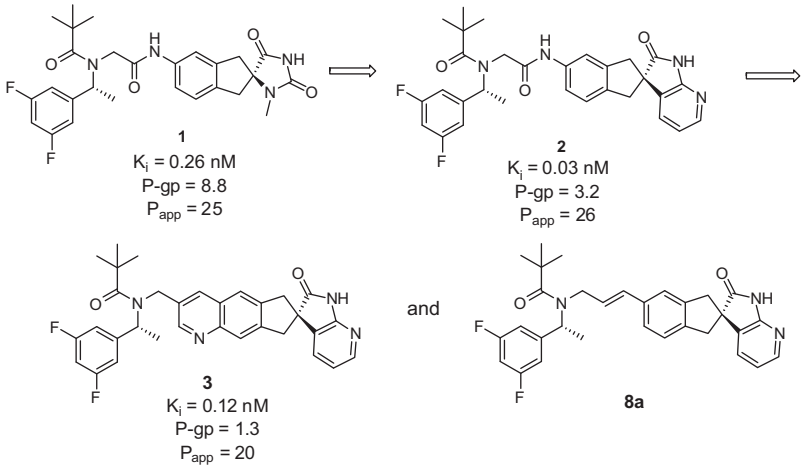
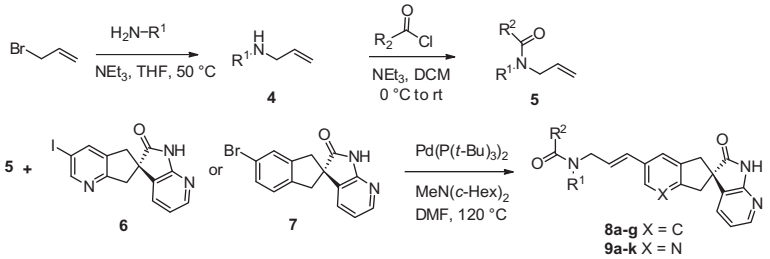


Figure 1. Previously disclosed CGRP-R antagonists.

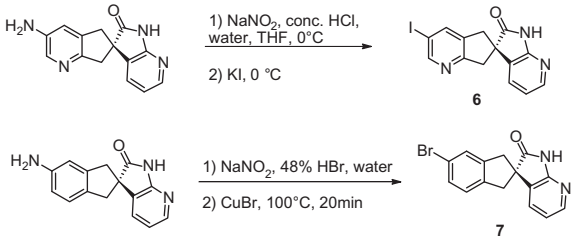


Scheme 1. Synthesis of compounds **8a**–**g** and **9a**–**k**.

the corresponding amines (Scheme 2), which were prepared according to previously described methods.[13,18] Heck coupling between **5** and aryl halides (**6** or **7**) using bis(tri-*t*-butylphosphine) palladium(0) and bis(*c*-hexyl)methylamine utilizing a microwave reactor afforded **8a**–**g** and **9a**–**k** (Table 1).

Alkyne analogs (Table 2) were prepared in similar fashion to Scheme 1, starting from propargylamine. The alkane analogs (Table 3) were obtained by hydrogenation of either alkynes or alkenes using 10% Pd/C as catalyst.

Compound **8a** showed a 5-fold loss of potency compared to amide compound **2**, but still retained subnanomolar binding affinity. The reduced binding affinities observed were possibly due to the limited ability for rotation, or a lack of hydrogen bonding ability.[19] Introduction of nitrogen into the phenyl ring was an attractive option to change the electronics of the aromatic ring and to possibly increase both solubility and free fraction. The resulting pyridyl analog **9a** was 4-fold more potent than **8a** and equipotent



Scheme 2. Synthesis of intermediates **6** and **7**.

with amide analog **2**. Additionally **9a** was not a substrate to P-gp mediated efflux.

After successfully implementing alkenes as an amide replacement, known SAR derived from the anilide series[11] and quinoline series[15] was applied to **8a** and **9a** to generate a new class of potent CGRP-R antagonists that were not P-gp substrates (Table 1). SAR trends of the new class of compounds remained similar to that of the amide and quinoline series. Pyridyl analogs **9a**–**k** were generally more potent than phenyl analogs **8a**–**g**. In the R^2 region, a variety of groups were tolerated in replacing the *t*-butyl moiety of the lead structures **8a** and **9a**. The more potent of these analogs were tetrahydropyran **8e**, 1-(trifluoromethyl)cyclopropyl **9h** and *N*-methylimidazole **9j**, though a range of heterocycles were also tolerated. In R^1 region, (*R*)-methyl substitution at the benzylic position was essential in maintaining potency, as **9d** lost 25-fold in binding affinity, compared to **9a**. Both (*R*)-1-indane and (*R*)-1-phenethyl were also well tolerated (**8b** and **8c**). One surprising departure from the amide series, however, was *N*-cycloheptyl **9e**, as it lost considerable binding affinity (20-fold as compared to **9a**), while it was equipotent to (*R*)-1-(3,5-difluorophenyl)ethyl in the amide series. *para*-Substitution on the benzyl group had little impact on potency **(9f)** while *meta*-substitution was found to be essential in maintaining good binding affinity (**9g**). Low P-gp efflux of **9a** was maintained in most analogs. Exceptions were compounds with polar moieties in the R^2 region, which elevated P-gp susceptibility (**8f**, **9j**, **9k**). Table 2 shows the pharmacokinetic profile of **9a** in rats. It had moderate clearance, long half-life and good bioavailability of 51%.

These results indicate that the *trans*-double bond maintained the proper bioactive conformation necessary for receptor binding