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Caprolactams as potent CGRP receptor antagonists for the treatment of migraine

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Abstract—Calcitonin gene-related peptide (CGRP) has been implicated in the pathogenesis of migraine. Replacements for the benzodiazepine core of an earlier lead structure **1** including 5-, 6-, and 7-membered lactams were explored. Within the 7-membered ring scaffold, phenyl substitution at various positions afforded the potent (3*R*)-amino-(6*S*)-phenyl caprolactam template. The phenylimidazolinone privileged structure gave additional potency enhancements, as **24** showed good potency in both CGRP binding ($K_i = 2$ nM) and cAMP ($IC_{50} = 4$ nM) assays and was orally bioavailable in rats (27%).

Migraines are episodic headache attacks usually lasting 4–72 h which can be accompanied by nausea and sensitivity to light and sound.[1] It is estimated that 13% of the general population suffer from this condition.[2] The current gold standard for the treatment of migraine is the class of $5\text{-HT}_{1B/1D}$ agonists known as triptans. However, these compounds are contraindicated in patients with cardiovascular disease due to their direct vasoconstrictive effect.[3] Development of a migraine drug that does not cause direct vasoconstriction would have significant therapeutic value.

Calcitonin gene-related peptide (CGRP) is a 37 amino acid neuropeptide present in the CNS and periphery,[4] with physiological functions that include nociception, vasodilation, and neurogenic inflammation.[5] Increased levels of CGRP are observed during a migraine attack and IV administration of CGRP can induce migraine in migraineurs.[6] In a clinical trial, infusion of a selective, small molecule CGRP receptor antagonist demonstrated relief of migraine headache pain similar to that of the triptan class of compounds without any cardiovascular side effects.[7] Based on these studies our program sought to identify potent, orally bioavailable, non-peptide small molecule CGRP receptor antagonists for the treatment of migraine.

Previously we have reported the identification and SAR of a novel series of benzodiazepines as non-peptide CGRP receptor antagonists.[8] These compounds consisted of an *N*-alkyl 3-aminobenzodiazepine linked through a urea bond to a variety of GPCR privileged structures. While compound **1** (Fig. 1) had good activity in the CGRP binding assay ($K_i = 55$ nM), it suffered from poor oral bioavailability (4% in rats). In general, these benzodiazepine derivatives displayed poor pharmacokinetic profiles. Thus we sought to replace the benzodiazepine core with alternate scaffolds to improve physicochemical properties and oral bioavailability.

One strategy pursued was to successively remove the two aryl groups in **1** to arrive at the 7-membered ring core. To investigate the effect of the pendant phenyl ring, fused caprolactam **2** was prepared. This compound exhibited a substantial loss in potency[9] compared to benzodiazepine **1** in both the CGRP binding assay and the cAMP cell-based functional assay.[10] Further simplification by removal of the fused phenyl ring gave

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Keywords: CGRP; CGRP receptor antagonist; Migraine; Caprolactam.

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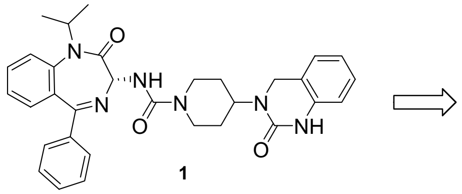
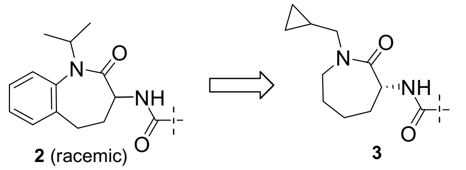


1
human K_i = 55 nM
cAMP IC_{50} = 65 nM



2 (racemic)
human K_i = 3.7 μM
cAMP IC_{50} = 3.1 μM

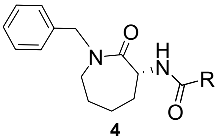
3
human K_i = 7.8 μM
cAMP IC_{50} = 2.4 μM

Figure 1. Effect of phenyl group removal.

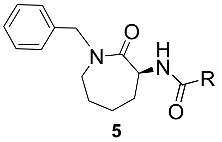
caprolactam **3**, prepared from Boc-D-Lys.[11] Although another potency loss was observed, we were encouraged that such a simplified structure as **3** retained activity in both assays.

With the dramatic change to the 7-membered ring core, we next explored different lactam ring sizes. The 5-, 6-, and 7-membered analogs (**4**–**7**, Fig. 2) were prepared and tested as individual enantiomers.[11,12] The (*R*) enantiomer **4** was found to be approximately 6-fold more active than the (*S*) enantiomer **5**. Additionally the (*R*) enantiomer analogs of the 5-membered lactam **6** and 6-membered lactam **7** lost considerable potency relative to the corresponding 7-membered compounds. We therefore focused our subsequent efforts on the (3*R*)-amino caprolactam template, attempting to build back potency by reincorporating phenyl substitution around the caprolactam ring.

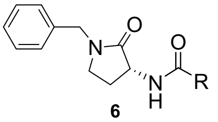
Preparation of the various 7-phenyl caprolactam stereoisomers revealed that the trans enantiomers **12** were 9-fold less active then the cis enantiomers **13** in the CGRP binding assay (Table 1). Separation of the racemic cis mixture **13** showed that all the activity was associated with just one of the enantiomers (**14** and **15**).[13] Replacement of the *N*-*t*-butyl acetate group with the cyclopropylmethyl group in **16** resulted in a small improvement in potency and was utilized for all subsequent SAR studies. Within the 6-phenyl substituted analogs the racemic trans mixture **18** was 22-fold more active than the racemic cis mixture **17** in the CGRP binding assay. Interestingly, this represents a reversal in the more active configuration between the 6 and 7-substituted phenyl caprolactams, possibly due to the phenyl ring occupying a pseudo-equitorial site on the caprolactam ring for optimal potency. After separation of the trans diastereomers (**19** and **20**), it was again found most of the CGRP binding affinity resided in one trans enantiomer (3*R*,6*S*) **20** with a K_i = 25 nM.[13]



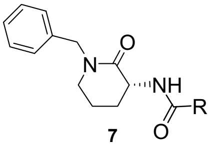
4
human K_i = 1.8 μM



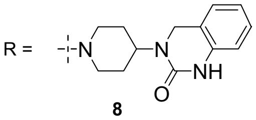
5
human K_i = 11.1 μM



6
human K_i = 63% @ 100 μM



7
human K_i = 46%@ 100 μM



8

Figure 2. Effect of ring size and stereochemistry.

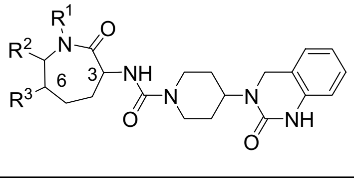
The synthesis of both the 6- and 7-substituted phenyl caprolactams was carried out using a modification of the procedure described by Yanagisawa.[14] A representative synthesis of a 6-phenyl caprolactam is shown in Scheme 1. Treatment of lactam **9** with sodium hydride and cyclopropylmethyl bromide gave the *N*-alkylated caprolactam selectively. Bromination with phosphorus pentachloride and bromine was followed by displacement with sodium azide to give **10** as a 3:1 trans/cis mixture. The azide was hydrogenated with 10% palladium on carbon to the primary amine which underwent smooth urea formation with *p*-nitrophenyl chloroformate and the dihydroquinazolinone privileged structure (**8**)[15] to yield **11** as a mixture of four compounds which were separated by chromatography.[16]

The 5-phenyl substituted caprolactams required a slightly different synthetic route (Scheme 2). Using the Aube variation of the Schmidt rearrangement,[17] 4-phenyl cyclohexanone **21** was treated with cyclopropylmethyl azide and $TiCl_4$ to give **22**. Bromination followed by displacement with azide and hydrogenation gave **23** as a 1:1 mixture of cis and trans diastereomers.

Due to sensitivity toward oxidative decomposition of the benzylic methylene on the dihydroquinazolinone,[18] alternate privileged structures[19] were examined to improve chemical stability. The most potent (3*R*,6*S*) phenyl caprolactam was chosen as a screening template and it was found that coupling with benzodiazepinone **A** and triazolinone **B** gave compounds (**25** and **26**) that were equipotent to the dihydroquinazolinone **20** (Table 2). Importantly, the derivatives were more stable relative to compound **20**. Utilization of phenylimidazolinone **C** gave **24**, which resulted in a 10-fold potency increase in both CGRP binding (K_i = 2 nM) and cAMP (IC_{50} = 4 nM) assays.

Having established a correlation with the newer privileged structures, the racemic 5-phenyl caprolactams were coupled with triazolinone **B** (**27** and **28**) and found to be substantially less active than the corresponding 6-phenyl caprolactams (Table 2). Interestingly, the

Table 1. Potencies of 6- and 7-substituted phenyl caprolactams



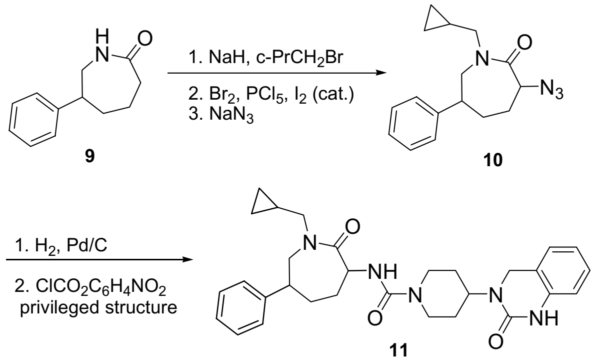
Compound	R^1	R^2	R^3	Stereo[a]	K_i[b,c] (nM)	cAMP IC_{50}[d] (nM)
12	*t*-Butyl acetate	Phenyl	H	trans racemic	16950	—
13	*t*-Butyl acetate	Phenyl	H	cis racemic	1993	2118
14	*t*-Butyl acetate	Phenyl	H	cis (3*S*,7*S*)	>10,000	471
15	*t*-Butyl acetate	Phenyl	H	cis (3*R*,7*R*)	934	—
16	Cyclopropylmethyl	Phenyl	H	cis (3*R*,7*R*)	689	408
17	Cyclopropylmethyl	H	Phenyl	cis racemic	695	778
18	Cyclopropylmethyl	H	Phenyl	trans racemic	31	54
19	Cyclopropylmethyl	H	Phenyl	trans (3*S*,6*R*)	5828	6626
20	Cyclopropylmethyl	H	Phenyl	trans (3*R*,6*S*)	25	36

[a] Stereochemistry at aryl substituted position of caprolactam ring.

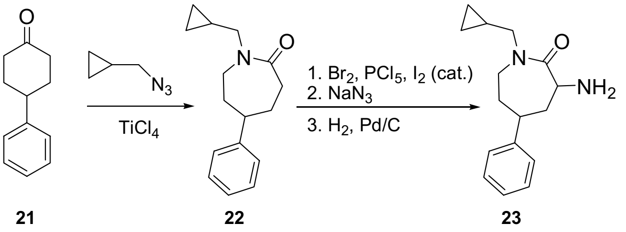
[b] Values are means of at least two determinations.

[c] Inhibition of [^{125}I]-CGRP binding to native human CL–receptor/RAMP1 membranes.

[d] Inhibition of CGRP-stimulated cAMP production in native human E10 cells.



Scheme 1. 6-Phenyl caprolactam synthesis.



Scheme 2. 5-Phenyl caprolactam synthesis.

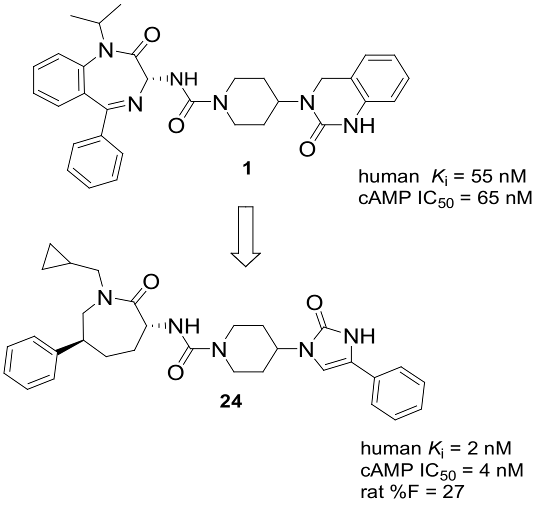
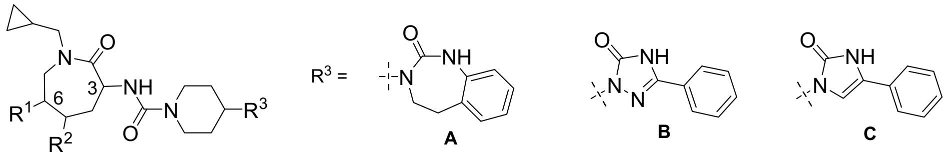


Figure 3. Evolution of caprolactam.

potency difference between the trans and cis diastereomers was less dramatic at only 2-fold. Once again use of the phenylimidazolinone privileged structure increased potency 10-fold (**29** and **30**). Though potent (K_i = 17 nM), the racemic trans diastereomers **30** are still 9-fold less potent than **24**. An even larger discrepancy is seen in the cAMP assay, where **30** is approximately 35-fold less potent. Therefore, of the phenyl caprolactams examined, we concluded that the 6-phenyl caprolactam was the most favorable replacement for the benzodiazepine core of **1** (Fig. 3). Compound **24** was further characterized and found to have good oral bioavailability in rats (F = 27%) with moderate clearance (36 mL/min/kg).[20]

In conclusion, the 5-, 6-, and 7-substituted phenyl caprolactams were synthesized and examined as benzodiazepine replacements, with the trans (3*R*)-amino-(6*S*)-phenyl caprolactam scaffold consistently providing the most activity in both the CGRP binding and cAMP assays. Replacement of the dihydroquinazolinone privileged structure with the phenylimidazolinone provided an additional 10-fold potency increase, resulting in **24** with K_i = 2 nM. A reduction in molecular weight was achieved by removal of the fused phenyl group of the benzodiazepine which may have contributed to an increase in oral bioavailability (27%).[21] With these changes we have identified a new series of caprolactams derived from benzodiazepine lead **1**, which have paved the way for a new series of orally bioavailable CGRP receptor antagonists.

Table 2. Potencies of 5- and 6-substituted caprolactams with different GPCR privileged structures



Compound	R^1	R^2	R^3	Stereo[a]	K_i[b,c] (nM)	cAMP IC_{50}[d] (nM)
25	Phenyl	H	A	trans (3*R*,6*S*)	29	32
26	Phenyl	H	B	trans (3*R*,6*S*)	29	45
24	Phenyl	H	C	trans (3*R*,6*S*)	2	4
27	H	Phenyl	B	cis racemic	544	3821
28	H	Phenyl	B	trans racemic	266	488
29	H	Phenyl	C	cis racemic	35	133
30	H	Phenyl	C	trans racemic	17	141

[a] Stereochemistry at aryl substituted position of caprolactam ring.

[b] Values are means of at least two determinations.

[c] Inhibition of [^{125}I]-CGRP binding to native human CL–receptor/RAMP1 membranes.

[d] Inhibition of CGRP-stimulated cAMP production in native human E10 cells.

Acknowledgments

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