Potent, Orally Bioavailable Calcitonin Gene-Related Peptide Receptor Antagonists for the Treatment of Migraine: Discovery of *N*-[(3*R*,6*S*)-6-(2,3-Difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)azepan-3-yl]-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamide (MK-0974)

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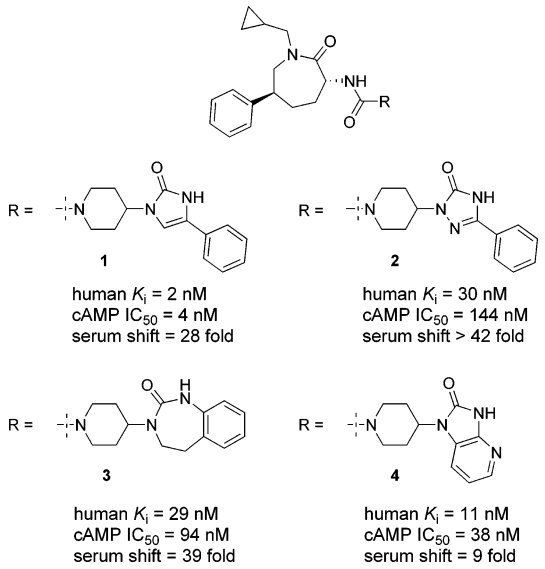
Abstract: Calcitonin gene-related peptide (CGRP) has been implicated in the pathogenesis of migraine. Herein we describe optimization of CGRP receptor antagonists based on an earlier lead structure containing a (3*R*)-amino-(6*S*)-phenylcaprolactam core. Replacement of the phenylimidazolinone with an azabenzimidazolone gave stable derivatives with lowered serum shifts. Extensive SAR studies of the C-6 aryl moiety revealed the potency-enhancing effect of the 2,3-difluorophenyl group, and trifluoroethylation of the N-1 amide position resulted in improved oral bioavailabilities, ultimately leading to clinical candidate **38** (MK-0974).

Migraines are episodic headaches lasting 4−72 h and characterized by severe pain, often accompanied by nausea and heightened sensitivity to light and sound.[1] It is estimated that 13% of the general population suffers from this disabling condition. Generally perceived as the most effective symptomatic treatment of acute migraine are members of the triptan class of compounds. However, the vasoconstrictive effect of these 5-$HT_{1B/1D}$ agonists renders these compounds contraindicated for use in patients with cardiovascular disease, and this concern poses limitations on their use.[2]

Calcitonin gene-related peptide (CGRP) is a 37 amino acid neuropeptide found in the CNS and periphery,[3] with physiological functions that include nociception, neurogenic inflammation, and vasodilation.[4] The CGRP receptor is heterodimeric, composed of the G-protein-coupled calcitonin-like receptor (CL receptor) and the receptor activity modifying protein 1 (RAMP1).[5] Activation of the CGRP receptor results in stimulation of cAMP production.

CGRP has been implicated in the pathophysiology of migraine,[6] as elevated CGRP levels are present during a migraine attack and iv infusion of CGRP can induce migraine-like headache in migraineurs.[7] Because CGRP receptor antagonists lack a direct vasoconstrictive mechanism, this class of compounds could prove effective in the relief of migraine without adverse cardiovascular effects.[8] Supporting data come from clinical trials of the CGRP receptor antagonist, olcegepant, where after iv infusion similar efficacy to the triptans was observed but with no cardiovascular side effects.[9] Our program targeted potent CGRP receptor antagonists with favorable pharmacokinetic profiles that would result in the first oral drug in this class.

Chart 1. Effect of Privileged Structure on Serum Shift



Previously we reported the discovery of a novel series of small-molecule, non-peptide CGRP receptor antagonists centered around an aminocaprolactam template.[10] This work led to **1**, a (3*R*)-amino-(6*S*)-phenylcaprolactam urea-linked to a GPCR privileged structure[11] containing a piperidinylphenylimidazolinone (Chart 1). This compound showed good potency in the CGRP binding assay[12] (K_i = 2 nM), but oral bioavailability in dogs was low (F = 6%), though more reasonable levels were attained in rats (F = 27%). Further evaluation revealed chemical instability associated with the privileged structure, specifically air oxidation of the imidazolinone ring. In addition, though **1** had good potency in a cell-based assay measuring inhibition of CGRP-stimulated cAMP production (IC_{50} = 4 nM), this value shifted 28-fold (IC_{50} = 114 nM) when run in the presence of 50% human serum, suggesting a significant degree of plasma protein binding.

Various alternatives to the phenylimidazolinone were explored with the goals of lowering serum shifts and improving chemical stabilities of the final compounds (Chart 1). Though many of the new derivatives, such as triazolinone **2** and benzodiazepinone **3**, were stable, most had equally high serum shift values to **1**. An exception was the azabenzimidazolone[13] derivative **4**, possessing only a 9-fold serum shift. This compound had good oral bioavailability in dogs (F = 41%) and was chemically stable, though potency in the presence of human serum was modest (IC_{50} = 339 nM).[14] Having identified an improved privileged structure, our attention turned to SAR of both the C-6 aryl substituent and the N-1 amide side chain moiety to derive more potency while maintaining good oral bioavailabilities.

The original synthetic route toward **1** required installation of the phenyl and amide side chain groups early in the sequence.[15] Additionally, chiral chromatography was necessary to obtain

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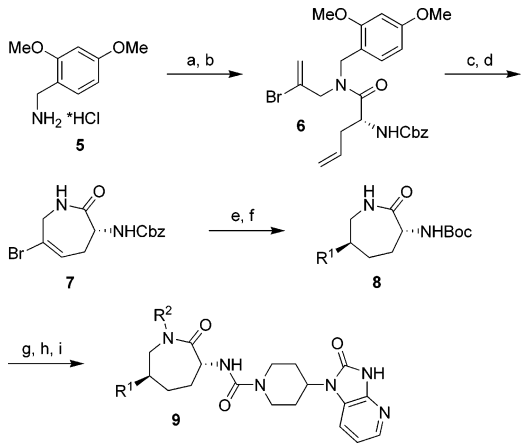
Scheme 1. Synthesis of Caprolactam Derivatives via Olefin Metathesis Route[a]



[a] Conditions: (a) 2,3-dibromopropene, Et_3N, CH_2Cl_2; (b) Cbz-D-allyl-Gly, EDC, CH_2Cl_2; (c) Grubbs second generation Ru cat., CH_2Cl_2, 40 °C; (d) TFA, CH_2Cl_2; (e) $R^1B(OH)_2$, $PdCl_2$(dppf), Na_2CO_3, DMF/H_2O, 75 °C; (f) H_2, 10% Pd/C, Boc_2O, EtOAc; (g) NaH, R^2X, DMF, 0 °C → room temp; (h) TFA, CH_2Cl_2; (i) 4-nitrophenyl chloroformate, Et_3N, THF, 0 °C, then azabenzimidazolone piperidine, room temp.

the desired pure enantiomer. Therefore, a new synthesis was developed relying on olefin metathesis chemistry (Scheme 1) that allowed for facile and independent variation at both the R^1 and R^2 positions of final targets **9**. Alkylation of amine **5** with 2,3-dibromopropene and EDC coupling with Cbz-protected D-allylglycine[16] gave diene **6** in good yield. The key cyclization was accomplished with the Grubbs second-generation ruthenium catalyst.[17] The unprecedented vinyl bromide ring-closing metathesis[18] (RCM) was low-yielding (15%)[19] and required high catalyst loading (20−30%), but after deprotection, sufficient quantities of key intermediate **7** could be obtained in only four steps.[20] Suzuki couplings with various boronic acids proceeded cleanly, and hydrogenation of the styrene products with in situ Boc reprotection resulted in readily separable cis/trans mixtures. The desired trans isomers underwent smooth amide alkylation with various electrophiles, and deprotection followed by urea coupling with the azabenzimidazolone piperidine provided the final targets **9**.

Initial investigations at the aryl position were accomplished by isolating and testing final compounds as 1:1 cis/trans mixtures, devoid of amide substitution, to allow for increased SAR efficiency (Table 1).[21] In the effort to reduce serum shifts and improve solubilities, hydroxyl and heteroaryl analogs such as **11**−**13** were among the first explored, but these compounds suffered large losses in potency compared to phenyl analog **10**. Derivatives containing alkyl-linked substituents such as isopropyl (**17**) and benzyl (**18**) were also less potent. Ultimately many derivatives were prepared, including 2, 3, and 4-substituted hydroxy, methoxy, methyl, pyridyl, chloro, and fluoro compounds. All substitutions resulted in decreased potencies save for the halogenated analogs, including the 2-fluorophenyl (**19**, K_i = 37 nM) and 3-fluorophenyl (**20**, K_i = 93 nM) derivatives. These analogs were next prepared as their single enantiomers, **21** and **22**, and potency increased to 22 and 51 nM, respectively. Combination of these elements gave the 2,3-difluorophenyl analog **23**, which resulted in a better than expected 20-fold increase in affinity (K_i = 3.6 nM) vs the parent phenyl compound **10**. Potency in the shift assay was also greatly improved (IC_{50} = 22 nM). Oral bioavailability in rats was low (5%), but overall the 2,3-difluorophenyl group provided large potency enhancements with only modest increases in molecular weight and lipophilicity.

Next, extensive variation of the amide substituent was undertaken to improve PK and further increase potency. In an attempt to maintain low serum shifts, we focused on compounds with side chains containing polar groups. Several hydroxy and alkoxy derivatives indeed showed decreases in serum shifts and corresponding potency increases in the shift assay. Methoxyethyl derivative **24** was highly potent (K_i = 0.3 nM) with only a 1.5-fold serum shift, but oral bioavailability was poor in rats and dogs. This was due in part to metabolic cleavage of the methyl ether in vivo (rat Cl = 32 mL min^{-1} kg^{-1}) giving hydroxyl metabolite **25**, which was 14-fold less active. Amino analogs generally exhibited negligible serum shifts, as morpholine **28** was highly potent in the shift assay (IC_{50} = 3 nM). However, oral bioavailability was very low, as most of the amino side chain derivatives suffered from facile N-dealkylation and extremely high clearance values.

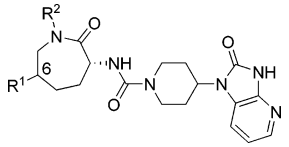
Heteroaryl amide substituents were utilized as a means of more subtly introducing polarity. Though potent compounds could be obtained, pyridinylmethyl analogs such as **29** showed only moderate to low oral bioavailabilities. The major metabolite was identified as the pyridine *N*-oxide, which when independently prepared and tested was equipotent (shift IC_{50} = 11 nM) but was not orally bioavailable in rats or dogs. Similarly, thioethers such as sulfide **30** underwent oxidative metabolism, with low levels of both the corresponding sulfoxide **31** and sulfone **32** detected in vivo. While these metabolites were actually more potent than the parent sulfide (sulfone shift IC_{50} = 2 nM), oral bioavailability was negligible.

In general, amide side chains composed of small alkyl groups provided compounds with the best pharmacokinetic profiles in this series. Though serum shifts were more pronounced for these analogs than their heteroatom counterparts, Caco-2 permeabilities were high (Papp = (22−35) × 10^{-6} cm/s) and potencies were largely maintained. Methyl and ethyl analogs **34** and **35** had particularly good dog PK profiles, with low clearances (4−8 mL min^{-1} kg^{-1}) and high oral bioavailabilities of 60% and 61%, respectively. Fluoroalkyl derivatives were more potent by 2- to 3-fold,[22] exemplified by trifluoroethyl derivative **38** with a shift IC_{50} of 11 nM. This compound also displayed good levels of oral bioavailability in rats (20%) and dogs (35%). In rats, clearance was low (9.4 mL min^{-1} kg^{-1}) with a moderate iv half-life (1.6 h) and a short po T_{max} (0.67 h). In dogs, clearance was moderate at 17 mL min^{-1} kg^{-1}.

To more clearly differentiate lead compounds **34**, **35**, and **38**, they were chosen for evaluation in our in vivo pharmacodynamic model (Table 2). This assay involves topical application of capsaicin to the forearm of a rhesus monkey, causing CGRP release and increased localized dermal blood flow.[23] Upon iv antagonist administration, inhibition of the capsaicin-induced increase in dermal blood flow can be quantified by laser Doppler imaging. Plasma levels are determined at different doses, generating a dose-response curve from which effective concentrations are calculated. While all three analogs were shown to be efficacious in this model, **38** (EC_{50} = 120 nM, EC_{90} = 1000 nM) was the most potent by >3.5-fold. This derivative also had low clearance (7.0 mL min^{-1} kg^{-1}) and a good iv half-life (2.8 h) in rhesus monkeys. Additionally, **38** showed >10000-fold selectivity in a panel of assays representing over 160 receptors, transporters, and enzymes and was selected as a clinical candidate.

In conclusion, synthetic advancements over our previous routes made possible the efficient optimization of lead capro-

Table 1. Potencies and Oral Bioavailabilities of Caprolactam CGRP Receptor Antagonists



compd	stereo[a]	R^1	R^2	K_i [b] (nM)	cAMP IC_{50} [c] (nM)	cAMP + 50% human serum IC_{50} (nM)	shift (fold)[d]	rat F [e] (%)	dog F [f] (%)
4	*S*	phenyl	cyclopropylmethyl	11 ± 2.9	38	340	9	7	41
10	*S*	phenyl	H	83	520	700	1.3		
11	*R,S*	4-hydroxyphenyl	H	770	1000				
12	*R,S*	2-pyridinyl	H	4400					
13	*R,S*	3-pyridinyl	H	9900					
14	*R,S*	3-thiophene	H	470	750	1800	2.4		
15	*R,S*	2-methoxyphenyl	H	1700					
16	*R,S*	4-methylphenyl	H	1100					
17	*R,S*	isopropyl	H	470	380	620	1.6		
18	*R,S*	benzyl	H	610	920				
19	*R,S*	2-fluorophenyl	H	37 ± 7.0	150	250	1.7		
20	*R,S*	3-fluorophenyl	H	93	340				
21	*S*	2-fluorophenyl	H	22	65	120	1.8		
22	*S*	3-fluorophenyl	H	51	220	250	1.1		
23	*S*	2,3-difluorophenyl	H	3.6	14	22	1.6	5	30
24	*S*	2,3-difluorophenyl	2-methoxyethyl	0.3	2	3	1.5	6	6
25	*S*	2,3-difluorophenyl	2-hydroxyethyl	4.2	15	23	1.5	<1	
26	*S*	2,3-difluorophenyl	2-trifluoromethoxyethyl	0.19 ± 0.03	1	6	6	3	7
27	*S*	2,3-difluorophenyl	2-dimethylaminoethyl	4.9	16	8	1	2	
28	*S*	2,3-difluorophenyl	2-morpholinylethyl	0.5	4	3	1	2	1
29	*S*	2,3-difluorophenyl	(2-pyridinyl)methyl	0.9	2	10	5	12	12
30	*S*	2,3-difluorophenyl	2-methylthioethyl	0.7	2	8	4	1	
31	*S*	2,3-difluorophenyl	2-(methylsulfinyl)ethyl	1.7	8	5	1		
32	*S*	2,3-difluorophenyl	2-(methylsulfonyl)ethyl	0.5	3	2	1		
33	*S*	2,3-difluorophenyl	cyclopropylmethyl	1.4	2	21	11	8	17
34	*S*	2,3-difluorophenyl	methyl	2.7 ± 0.4	8	22	2.8	12	60
35	*S*	2,3-difluorophenyl	ethyl	2.4 ± 0.9	6	30	5	30	61
36	*S*	2,3-difluorophenyl	2-fluoroethyl	1.4	5	10	2	17	14
37	*S*	2,3-difluorophenyl	2,2-difluoroethyl	0.9	5	15	3	25	11
38	*S*	2,3-difluorophenyl	2,2,2-trifluoroethyl	0.77 ± 0.07	2.2 ± 0.3	11 ± 2.1	5	20	35

[a] Stereochemistry at aryl position (C-6) of caprolactam ring. *R,S* refers to approximately 1:1 diastereomeric mixtures. [b] Values without SEM indicate less than three determinations; the coefficient of variation of the binding and cell-based assays is <0.3. Inhibition of [^{125}I]CGRP binding to recombinant human CL-receptor/RAMP1 membranes. [c] Inhibition of CGRP-stimulated cAMP production in E10 cells. [d] Ratio of cAMP + 50% human serum IC_{50}/cAMP IC_{50}. [e] 10 mg/kg dosed as a suspension in 1% aqueous methylcellulose. [f] 1 mg/kg dosed as a suspension in 1% aqueous methylcellulose.

Table 2. Activity in Rhesus Pharmacodynamic Assay

compd	cAMP + 50% human serum IC_{50} [a] (nM)	rhesus PD EC_{90} (nM)	rhesus Cl [b] (mL min^{-1} kg^{-1})	rhesus $t_{1/2}$ [b] (h)
34	22	4000	7.1	1.9
35	30	3600 ± 1700	8.7	2.3
38	11 ± 2.1	1000 ± 480	7.0	2.8

[a] Values without SEM indicate less than three determinations. Inhibition of CGRP-stimulated cAMP production in E10 cells. [b] 0.5 mg/kg dosed iv as a 100% DMSO solution.

lactam **1**. Phenylimidazolone replacement with the azabenzimidazolone substructure resulted in reduced serum shifts, and the 2,3-difluorophenyl ring was discovered as a key potency-enhancing group that allowed greater flexibility in the N-1 amide substituent with respect to oral bioavailability. Several analogs with promising PK profiles for oral drug development were identified. Together, these improvements led to a series of potent, orally bioavailable CGRP receptor antagonists, culminating in the discovery of **38** (MK-0974), which has recently demonstrated efficacy in a Phase II clinical trial for the treatment of acute migraine.[24]

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Supporting Information Available: Representative experimental procedures, ^{1}H NMR, HRMS, and HPLC data for all target compounds, and protocols for the CGRP binding, cAMP, and rhesus pharmacodynamic assays. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) We had previously shown that in this series the trans isomers were uniformly more potent than the cis, often by >20-fold (see ref 10). Relative stereochemistry was determined by proton NMR analysis, and absolute stereochemistry was assigned on the basis of the known chirality of commercially available, enantiomerically pure starting materials.
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