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Calcitonin gene-related peptide (CGRP) receptor antagonists: Investigations of a pyridinone template

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Abstract—In our effort to find potent, orally bioavailable CGRP receptor antagonists for the treatment of migraine, a novel series based on a pyridinone template was investigated. After optimizing the privileged structure and the placement of the attached phenyl ring, systematic SAR was carried out on both the *N*-alkyl and C-5 aryl substituents. Several analogs with good potency and pharmacokinetic profiles were identified.

Calcitonin gene-related peptide (CGRP) is a 37-amino acid neuropeptide that is expressed in trigeminal ganglia nerves. Activation of trigeminal sensory nerves and CGRP release play a central role in the pathophysiology of migraine.[1,2] Current standard treatment for migraine is the triptan class of 5-$HT_{1B/1D}$ receptor antagonists. Though effective, these triptans are contraindicated in patients with cardiovascular disease.[3,4] When dosed iv, the potent CGRP receptor antagonist BIBN4096BS (olcegepant) was revealed in clinical trials to have similar efficacy against migraine attacks to the triptans but without the cardiovascular or other serious ancillary effects.[5,6] In this context, our program focused on finding orally bioavailable CGRP receptor antagonists for the treatment of migraine headache.

In prior work, the discovery of the amino caprolactam template gave rise to a series of lower molecular weight, non-peptide CGRP receptor antagonists[7,8] (Fig. 1). Because the trans isomer was significantly more potent than the cis isomer, we thought that perhaps the pseudo-equatorial arrangement of the *N*-alkyl side chain, aryl group, and urea-linked substituent was a key contributing factor to the potency of the compound. When exploring alternative templates, we reasoned that use of a central pyridinone substructure would allow for a planar, spatial orientation of the appended substituents similar to the caprolactam. In addition, the achiral pyridinone core would greatly simplify synthesis, thus facilitating rapid SAR studies. The inherent rigidity and the degree of unsaturation in the pyridinone heterocycle could improve pharmacokinetic profiles versus the caprolactams due to less oxidative metabolism. Herein we describe the syntheses and the inhibitory and pharmacokinetic profiles of compounds from this novel pyridinone series.

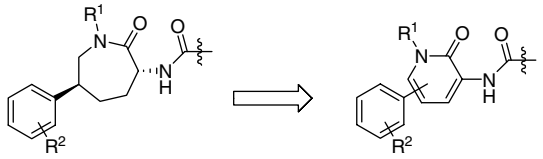

Figure 1.

We assessed the potency of these compounds using recombinant human CL-receptor/RAMP1 in a [^{125}I]-CGRP radioligand binding assay (K_i). Selected com-

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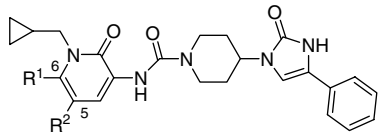
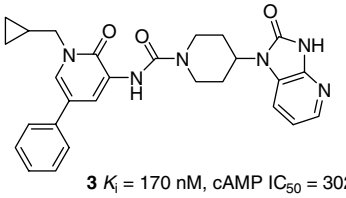
pounds were subsequently tested for their functional ability to inhibit CGRP-stimulated cAMP production in whole cells (cAMP IC_{50}). The functional assay can also be run in the presence of 50% human serum to give an indication of the extent of protein binding.

Initially we wanted to determine the optimal position of the aryl group for potency (Fig. 2). The incorporation of the phenyl ring at the C-6 position (**1**) resulted in moderate CGRP receptor affinity (K_i = 3400 nM). However, shifting the phenyl to the C-5 position (**2**) increased potency by 43-fold (K_i = 80 nM). Additionally, this analog was a potent functional antagonist (cAMP IC_{50} = 360 nM). This result correlated well with the caprolactam series where the C-6 phenyl compound was significantly more potent than the C-7 phenyl analog.[7] Although the phenylimidazolinone privileged structure[9] provided the best potency in the caprolactam series, additional studies indicated that this substructure was chemically unstable due to air oxidation of the imidazolinone ring.[8,10] As an alternative, the azabenzimidazolone was shown to be stable and therefore was used in the pyridinone series to provide compound **3** (K_i = 170 nM). Though the binding affinity of **3** was 2-fold less than **2**, its functional potency was slightly better (cAMP IC_{50} = 302 nM).

Though compound **1** was synthesized according to a literature procedure,[11] most of the pyridinone compounds described were synthesized as shown in Scheme 1. 5-Bromo-3-nitropyridin-2-ol (**4**) was first converted to pyridinone **5** by *N*-alkylation with alkylhalides using cesium carbonate as base to minimize *O*-alkylation. The nitro group was then reduced to the amine with tin(II) chloride at ambient temperature. Urea coupling between **5** and azabenzimidazolone piperidine **6** was accomplished using phosgene and afforded **7** in good yield. Bromide **7** underwent Suzuki coupling with various substituted arylboronic acids to arrive at final compounds **8**. The water-soluble ligand 3,3′,3″-phosphinidynetris(benzenesulfonic acid) trisodium salt used in the palladium-catalyzed coupling helped facilitate the isolation of the compounds, as most of the reactions were simply loaded directly onto a reverse phase purification system without filtration. For desired compounds in which the aryl

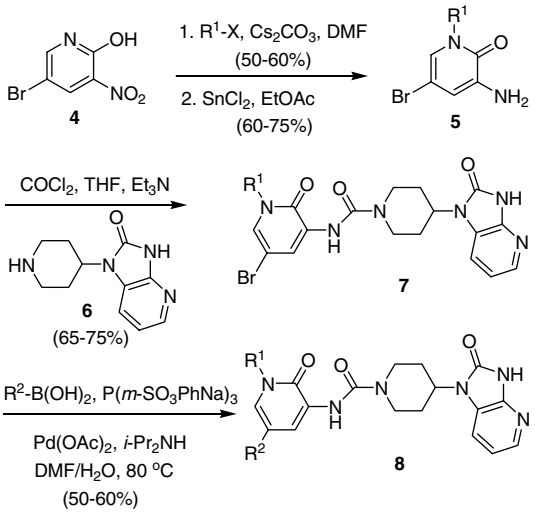


1 R^1 = Ph, R^2 = H; K_i = 3400 nM
2 R^1 = H, R^2 = Ph; K_i = 80 nM, cAMP IC_{50} = 360 nM



3 K_i = 170 nM, cAMP IC_{50} = 302 nM

Figure 2.



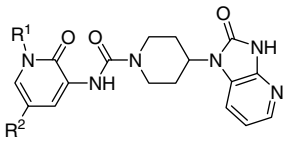
Scheme 1.

boronic acids were not commercially available, the bromide intermediate **7** could be converted to the corresponding boronic acid[12] prior to coupling with different aryl bromides.

Initial SAR studies were aimed at optimizing potency by varying aryl groups at the C-5 position while keeping a fixed *N*-methyl group (Table 1). The parent phenyl analog **9** had similar potency in both binding and functional assays (K_i = 498 nM and cAMP = 495 nM). Compounds **10**–**13** had low to moderate binding affinity at the CGRP receptor (K_i = 2 μM–9 μM). In general, 4-substituted phenyls were not well tolerated with the exception of the 4-hydroxyphenyl analog (**16**) (K_i = 43 nM, cAMP IC_{50} = 88 nM). Although 2-hydroxyphenyl analog **14** was not as active as **16**, 3-hydroxyphenyl derivative **15** had similar activity in both the intrinsic binding and cAMP assay (K_i = 42 nM, cAMP IC_{50} = 142 nM). 4-Methoxyphenyl **17**, differing only by a methyl group from **16**, suffered large losses in potency (K_i = 495 nM, cAMP IC_{50} = 1528 nM). The 3-pyridyl compound **18** was potent in the binding assay (K_i = 270 nM) but not as active in the functional assay (cAMP IC_{50} = 1066 nM). Comparing 5-membered heterocycles, the 3-pyrazole analog (**19**) was 29-fold more potent (K_i = 71 nM, cAMP IC_{50} = 184 nM) than the 4-imidazole analog (**12**), while the 3-thiophene derivative (**20**) was potent in both the binding and functional assays (K_i = 75 nM, cAMP IC_{50} = 330 nM). Unlike the caprolactam series, where the 2,3-difluorophenyl derivative was 10-fold more potent than either the 2-fluorophenyl or 3-fluorophenyl analog independently,[8] compounds **21**, **22**, and **23** had similar potencies.

In an effort to derive more potency, different *N*-alkyl substituents were explored. Two of the more potent groups based on the caprolactam series were 2-methoxyethyl and 2,2,2-trifluoroethyl. Each of the two groups was integrated with the more potent aryl groups from the SAR study noted above. With the *N*-2-methoxyethyl derivatives, the phenyl analog **24** exhibited 2-fold better binding affinity (K_i = 228 nM) compared to **9**, though it

Table 1. SAR at *N*-1 alkyl and C-5 aryl position of the pyridinones



Compound	R^1	R^2	K_i[a] (nM)	cAMP IC_{50}[b] (nM)	cAMP + 50% human serum IC_{50}[b] (nM)
9	CH_3	Phenyl	498	495	10,900
10	CH_3	4-Benzoic acid	9000	—	—
11	CH_3	2,6-Pyrimidine	1900	—	—
12	CH_3	4-Imidazole	2050	—	—
13	CH_3	4-(Methanesulfonyl)phenyl	1750	—	—
14	CH_3	2-Hydroxyphenyl	220	827	—
15	CH_3	3-Hydroxyphenyl	42	142	715
16	CH_3	4-Hydroxyphenyl	43	88	—
17	CH_3	4-Methoxyphenyl	495	1528	—
18	CH_3	3-Pyridyl	270	1066	—
19	CH_3	3-Pyrazole	71	184	872
20	CH_3	3-Thiophene	75	330	—
21	CH_3	2-Fluorophenyl	213	477	—
22	CH_3	3-Fluorophenyl	155	337	—
23	CH_3	2,3-Difluorophenyl	166	567	—
24	2-Methoxyethyl	Phenyl	228	665	—
25	2-Methoxyethyl	3-Thiophene	390	540	—
26	2-Methoxyethyl	3-Pyridyl	695	1190	—
27	2-Methoxyethyl	3-Pyrazole	140	307	394
28	2-Methoxyethyl	4-Hydroxyphenyl	74	170	280
29	2-Methoxyethyl	2,3-Difluorophenyl	41	164	1004
30	2,2,2-Trifluoroethyl	Phenyl	95	209	—
31	2,2,2-Trifluoroethyl	3-Thiophene	105	345	—
32	2,2,2-Trifluoroethyl	3-Pyridyl	635	651	—
33	2,2,2-Trifluoroethyl	3-Pyrazole	205	550	1421
34	2,2,2-Trifluoroethyl	4-Hydroxyphenyl	96	282	971
35	2,2,2-Trifluoroethyl	2-Fluorophenyl	54	186	—
36	2,2,2-Trifluoroethyl	3-Fluorophenyl	42	119	—
37	2,2,2-Trifluoroethyl	2,3-Difluorophenyl	17	18	811

[a] Values are means of at least two determinations.
[b] The coefficient of variation of the cell-based assays is <0.3.

had similar potency in the functional assay (cAMP IC_{50} = 665 nM). Other analogs in this group were either similar or slightly less potent compared to their *N*-methyl counterparts with the exception of **29** which was 4-fold more potent than **23** in the binding assay (K_i = 41 nM). In general, the SAR of the *N*-2,2,2-trifluoroethyl analogs did not correlate with those of the *N*-methyl analogs. Phenyl derivative **30** was 5-fold more potent than **9** in the binding assay. Although the 3-pyridyl derivative (**32**) was 2-fold less potent in the binding assay (K_i = 635 nM) compared to its *N*-methyl counterpart, it was 2-fold better in the functional assay (cAMP IC_{50} = 651 nM). The 3-pyrazole (**33**) and the 4-hydroxyphenyl (**34**) analogs were approximately 3-fold less potent than **19** and **16**, respectively. The 2-fluorophenyl analog (**35**) and 3-fluorophenyl analog (**36**) were both more potent than **30**. As was observed within the caprolactam series, the 2,3-difluorophenyl group added more potency than the 2-fluorophenyl or 3-fluorophenyl groups did separately.[8] Compound **37** had excellent potency in both CGRP binding and functional cAMP assays (K_i = 17 nM, cAMP IC_{50} = 18 nM). Several compounds were also tested in the cAMP assay in the presence of 50% human serum. In general, serum shifts increased with increasing lipophilicity of the C-5 aryl group (difluorophenyl **37** = 45-fold shift), whereas they decreased with increasing polarity of these aryl groups (pyrazole **27** = 1.3-fold shift, hydroxyphenyl **28** = 1.6-fold shift). When comparing amongst the *N*-alkyl groups, the *N*-methyl compounds show the greatest serum shifts while the *N*-2-methoxyethyl analogs generally show lower shifts.

Pharmacokinetic profiles of selected compounds were obtained in either rat or dog (Table 2). All the compounds tested had low to moderate clearances and reasonable iv half-lives for an acute migraine indication (1–6 h). The *N*-methyl derivatives had low oral bioavailability with the exception of the phenyl analog (**9**) (rat F = 40%) and the 3-thiophene analog (**20**) (rat F = 47%). The *N*-2-methoxyethyl derivatives generally had higher clearances which may have contributed to lower bioavailability with the exception of **24** (rat F = 37%). Several compounds of the *N*-2,2,2-trifluoroethyl group had very good oral bioavailability, including phenyl analog **30** (rat F = 31%, dog F = 58%), 3-thiophene **31** (rat F = 44%), and 3-pyridyl **32** (rat F = 56%). Compound **37** had very good oral bioavailability in both rat (F = 34%) and dog (F = 65%) with long half-lives and extremely low clearances.

Table 2. Pharmacokinetic profiles in rat[a] and dog[b]

Compound	Species	$t_{1/2}$ (h)	Cl (mL/min/kg)	C_{max} (μM)	F (%)
9	Rat	3.0	1.3	20.3	40
16	Rat	1.1	16.1	0.1	2
16	Dog	2.9	0.6	0.6	3
19	Dog	1.2	2.8	0.3	6
20	Rat	1.0	8.9	7.4	47
24	Rat	0.5	25.3	1.3	37
25	Rat	2.8	23.5	0.08	1
30	Rat	2.5	2.3	5.3	31
30	Dog	3.7	0.2	10.3	58
31	Rat	0.9	9.6	5.1	44
32	Dog	5.4	0.3	7.4	56
37	Rat	6.3	0.8	9.4	34
37	Dog	3.3	0.2	9.4	65

[a] Dosed at 2.0 mpk IV as DMSO solution and 10 mpk PO as 1% methylcellulose suspension.

[b] Dose at 0.5 mpk IV as DMSO solution and 1.0 mpk PO as 1% methylcellulose suspension.

In conclusion, we have discovered the pyridinone as an alternative template for the CGRP receptor antagonist program. These pyridinones are achiral and structurally simple, and therefore provided easy access for either *N*-alkyl or C-5 aryl substitution. SAR studies revealed many compounds with good potency in both the intrinsic binding assay and functional cAMP assay. In general, compounds containing polar groups, especially H-bond donors such as 4-hydroxyphenyl and 3-pyrazole, had poor bioavailability but exhibited small serum shifts. Analogs containing more lipophilic aryl groups had greatly improved oral bioavailability; however, these compounds displayed higher serum shifts. Most notable was **37** which possessed the best balance of potency and pharmacokinetic profiles.

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