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Identification of potent CNS-penetrant thiazolidinones as novel CGRP receptor antagonists

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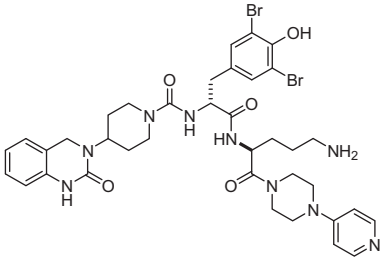
ABSTRACT

Calcitonin gene-related peptide (CGRP) has been implicated in acute migraine pathogenesis. In an effort to identify novel CGRP receptor antagonists for the treatment of migraine, we have discovered thiazolidinone **49**, a potent (K_i = 30 pM, IC_{50} = 1 nM), orally bioavailable, CNS-penetrant CGRP antagonist with good pharmacokinetic properties.

CGRP is a 37-amino acid neuropeptide that is expressed and released by the trigeminal ganglia nerve fibers, and plays a critical role in migraine.[1a] CGRP signals through a heteromeric receptor composed of a G protein-coupled receptor called calcitonin receptor-like receptor (CRLR) and a receptor activity modifying protein (RAMP1). CGRP is one of the most potent endogenous vasodilators known.[1b] Increased levels of CGRP are observed during migraine attacks and intravenous administration of CGRP can induce migraines.[1c]

An early clinical proof of concept study showed that intravenous dosing of BIBN4096 (olcegepant), a potent CGRP receptor antagonist, was efficacious in alleviating pain during migraine headaches.[1a] Olcegepant showed comparable efficacy to triptans, and showed no serious cardiovascular effects.[2] Olcegepant has poor oral bioavailability (% F < 1), and limited CNS exposure; therefore its development was discontinued due to the rapid clearance and poor physical properties of this high molecular weight (MW 855) peptidic molecule.[1a] We initiated a program to identify a potent, orally bioavailable, CNS-penetrant CGRP-receptor antagonist with good physicochemical properties. More recently, Merck[3–5] has reported positive Phase III clinical trial data for telcagepant



BIBN4096BS (Olcegepant) MW 855

Figure 1. Structure of olcegepant (BIBN4096).

Table 1

Compound	IC_{50}[a] (μM)	K_i[b] (μM)
Olcegepant	0.004 ± 0.063	0.00001 ± 0.00002
1	0.74 ± 0.29	0.282
2	0.37 ± 0.16	0.032 ± 0.026

[a] IC_{50} β-lactamse assay[7] ($n \geqslant 3$) with cells treated with CGRP, compound and cAMP antibody and represents cellular inhibition of cAMP production.
[b] K_i Binding assay ($n \geqslant 3$) SK-N-MC membrane treated with ^{125}I-CGRP, compound and $K_i = IC_{50}/(1 + [\text{radioligand}]/K_d)$ was calculated.[6]

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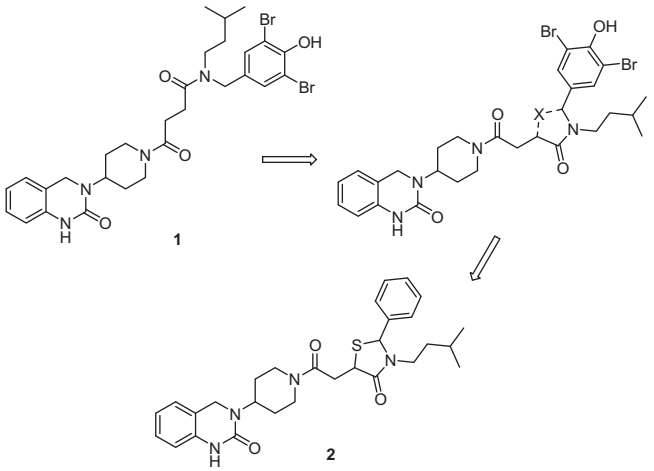


Figure 2. Conformational constraint provided potent thiazolidinone **2**.

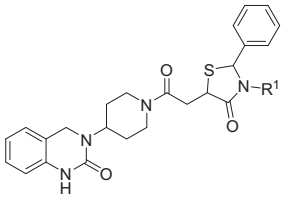
(MK-0974), a CGRP receptor antagonist with improved oral bioavailability but limited CNS exposure (Fig. 1).

Examining the structure of olcegepant, we hypothesized that reduction of its peptidic nature and lowering the molecular weight and PSA could improve oral bioavailability and provide an antagonist with better physicochemical properties. Our initial approach involved screening of smaller fragments of olcegepant to assess their CGRP receptor binding. This effort led to the identification of **1** (Table 1) which showed modest competitive binding in a [^{125}I]CGRP receptor radioligand binding assay and had significantly reduced molecular weight (MW 664).[6] Compound **1** was further tested for its functional ability to inhibit CGRP-stimulated cellular cAMP production using a reporter assay[7] and was found to be moderately potent.

We subsequently hypothesized that applying a degree of conformational constraint to **1** could potentially improve the potency of this molecule. Several cyclic cores incorporating these features were tested (data not shown) and thiazolidinone **2**, which showed a three-fold gain in CGRP receptor binding compared to **1**, was selected for further SAR exploration (Fig. 2).

The thiazolidinone scaffold was especially well suited for parallel synthesis using mercaptosuccinic acid (MSA) and a large pool of aldehydes and amines as reagents. This three-component synthesis involved formation of the imine and treatment of the reaction mixture with MSA in one pot to give the racemic thiazolidinone acetic acid.[8] Thus compound **2** was prepared (Scheme 1) from the reaction of MSA and the imine generated from benzaldehyde and isopentyl amine, and subsequent coupling of the resulting thiazolidinone acetic acid with dihydroquinazolinone using amide bond coupling conditions (HATU and DIEA in DMF at ambient temperature).

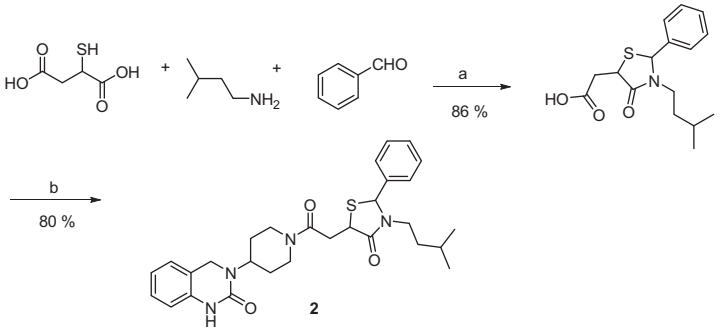
Table 2
Effect of substitution (R^1), on the amine of thiazolidinone ring



Compound	R^1	IC_{50}[a] (μM)	K_i[b] (μM)
3	Methyl	4.47 ± 3.23	0.203
4	iso-Propyl	1.5 ± 1.15	0.115 ± 0.011
5	Cyclopropyl	5.15	0.865 ± 0.416
6	Methylcyclopropyl	0.84 ± 0.08	0.045
7	Butyl	0.32 ± 0.033	0.064
8	iso-Butyl	0.37+0.16	0.032 ± 0.026
9	tert-Butyl	7.6	1.88
10	2,2,2-Trifluoroethyl	4.54 ± 1.19	0.763
11	Methoxy ethyl	1.22 ± 0.54	0.124
12	2-Diethylaminoethyl	4.88	0.303
13	1-Phenethyl	0.94 ± 0.32	0.297
14	Cyclohexyl	0.71 ± 0.31	0.088
15	3-((Tetrahydrofuran-2-yl)methyl)	0.52 ± 0.13	0.068
16	neo-Pentyl	0.25 ± 0.18	0.009 ± 0.006
17	Phenyl	2.94	0.806
18	4-Fluorobenzyl	0.75 ± 0.1	0.056
19	Methyl-3-pyridyl	0.80 ± 0.39	0.26
20	Ethyl-2-pyridyl	1.37	0.202

[a] IC_{50} β-lactamse assay ($n \geqslant 3$) with cells treated with CGRP, compound and cAMP antibody and represents cellular inhibition of cAMP production.
[b] K_i Binding assay ($n \geqslant 3$) SK-N-MC membrane treated with ^{125}I-CGRP, compound and $K_i = IC_{50}/(1+[\text{radioligand}]/K_d)$ was calculated.

The encouraging data for compound **2** prompted our initial SAR exploration of the thiazolidinone ring focusing on the amide nitrogen and phenyl ring substituents, in an effort to improve CGRP receptor binding and functional cAMP activity. Several thiazolidinones with *N*-alkyl and aromatic moieties were prepared. SAR of this series showed that aliphatic hydrophobic groups on the thiazolidinone core improved CGRP binding. Long chain and branched alkyl groups such as **8** improved binding while *N*-aryl substituted thiazolidinones such as **17** showed a loss in CGRP receptor binding compared to **2**. Compound **16**, with a *neo*-pentyl side-chain showed a seven-fold gain in binding along-with a two-fold gain in functional cAMP inhibition. We speculate that this side-chain of **16** may be accessing the same hydrophobic pocket where the side-chain of the lysine residue of olcegepant resides in the CGRP



Scheme 1. Synthesis of thiazolidinones from MSA, benzaldehyde and isopentylamine. (a) DMF, 80 °C; (b) 3-(piperidin-4-yl)-3,4-dihydroquinazolin-2(1*H*)-one, HATU, DIEA, DMF, RT.