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MK-8825: A potent and selective CGRP receptor antagonist with good oral activity in rats

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ABSTRACT

Rational modification of the clinically tested CGRP receptor antagonist MK-3207 (**3**) afforded an analogue with increased unbound fraction in rat plasma and enhanced aqueous solubility, 2-[(8*R*)-8-(3,5-difluorophenyl)-8-methyl-10-oxo-6,9-diazaspiro[4.5]dec-9-yl]-*N*-[(6S)-2′-oxo-1′,2′,5,7-tetrahydrospiro[cyclopenta[*b*]pyridine-6,3′-pyrrolo[2,3-b]pyridin]-3-yl]acetamide (MK-8825) (**6**). Compound **6** maintained similar affinity to **3** at the human and rat CGRP receptors but possessed significantly improved in vivo potency in a rat pharmacodynamic model. The overall profile of **6** indicates it should find utility as a rat tool to investigate effects of CGRP receptor blockade in vivo.

Migraine is a common disorder estimated to afflict 11% of the global adult population[1] with prevalence ranges of 15–17% among women and 6–9% among men.[2] The incidence of migraine is highest during peak productive years of life (30–50 years of age)[3] and this, coupled with the frequency and severity of attacks, results in migraine remaining one of the most widespread and disabling neurological disorders.

Intense research to identify novel drug targets for migraine has resulted in the identification of a key neuronal messenger: calcitonin gene-related peptide (CGRP). CGRP is a 37 amino acid neuropeptide that is widely expressed in the peripheral and central nervous system consistent with its involvement in vasodilation and nociceptive transmission.[4] Although a complete understanding of the role of CGRP in migraine remains elusive, multiple lines of evidence have clearly implicated this neuropeptide as a key element in the pathogenesis of this important disorder.[4]

The evidence of a role for CGRP in triggering migraine primarily focused drug discovery efforts on the development of small molecule CGRP receptor antagonists. Multiple clinical studies involving antagonism of the CGRP receptor have validated this approach for the acute treatment of migraine headache.[5–8] Clinical proof-of-concept in the acute treatment of migraine first was demonstrated with an intravenous formulation of the Boehringer Ingelheim CGRP receptor antagonist olcegepant (BIBN4096BS).[5] Olcegepant (**1**, Chart 1) is highly potent for the human CGRP receptor, but displayed > 100-fold lower potency for the rodent receptor.[9]

At Merck, two orally bioavailable CGRP receptor antagonists have been developed and advanced to clinical studies, telcagepant (**2**, Chart 1)[10] and MK-3207 (**3**, Chart 1).[11] Like compound **1**, **2** and **3** both displayed marked species selectivity. Compound **2** displayed a similar affinity for the human and rhesus monkey CGRP receptors but > 1,000-fold lower affinity for the rat receptor.[12] Although **3** is structurally distinct from **1** and **2** it nonetheless displays approximately 400-fold higher affinity for the human and rhesus monkey CGRP receptors compared to the rat receptor.[13]

A major consequence of the pronounced species selectivity exhibited by these small molecule CGRP receptor antagonists is the requirement to utilize a nonhuman primate model to evaluate in vivo potency. We developed a non-invasive pharmacodynamic model in rhesus monkey, based on topical capsaicin-induced dermal vasodilation (CIDV).[14] In this model, topical application of

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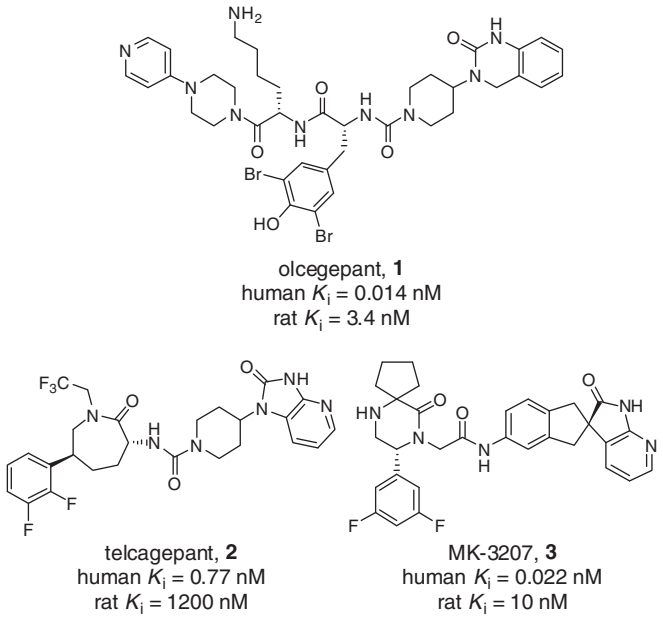


Chart 1. Selected CGRP receptor antagonists.

capsaicin to the ventral side of the rhesus forearm resulted in an increase in dermal blood flow that could be quantified using laser Doppler imaging. The CIDV assay was translated to the clinical setting and used as a pharmacokinetic/pharmacodynamic (PK/PD) model in the early clinical development of **2** to assess peripheral target engagement.[15]

Empirically, the nonhuman primate is the most similar to human, but the ability to evaluate small molecule CGRP receptor antagonists in a rodent model is highly desirable to both expand the diversity of experimental models available and to minimize the use of nonhuman primates. Although the CGRP receptor is a clinically validated target for the acute treatment of migraine, the underlying pathophysiology of CGRP and migraine has yet to be fully elucidated. Therefore a suitable rat tool compound could shed additional insight into the complex peripheral and central processes of CGRP receptor antagonism. Additionally, the availability of a highly selective CGRP receptor antagonist with pharmacological activity in rodents could open up other therapeutic avenues beyond migraine.

As discussed (vide supra), MK-3207 (**3**) exhibited significantly lower affinity for non-primate CGRP receptors. However, since it was a picomolar antagonist at the human CGRP receptor, this translated to nanomolar activity (K_i = 10 nM) at the canine and rat CGRP receptors.[13] Unfortunately, the nanomolar in vitro rat CGRP receptor affinity of **3** did not translate into good in vivo potency. In the rat pharmacodynamic CIDV model of CGRP receptor antagonism,[14] **3** was determined to block endogenous CGRP at relatively high plasma levels (EC_{50} = 58 μM; Fig. 1A). Consequently, very high oral doses would be required to evaluate the effects of this CGRP receptor antagonist in rats, making it an unattractive choice for such studies.

Reasoning that the suboptimal potency of this antagonist in rats was in part due to its low unbound fraction (rat f_u = 0.84%, see Table 1), we sought to modify the structure in order to increase the free fraction. Previous work had shown that **3** had a significantly lower unbound fraction in rat plasma compared with dog, monkey, and human (Table 2).[11] Moreover, the high rat plasma protein binding was apparently due to molecular recognition by a protein in rat plasma, and this interaction seemed to be significantly affected by changes to the piperazinone stereocenter.[11] For example, inversion of this C-6 stereocenter led to a significant (> 10-fold) increase in unbound fraction in rat plasma.[11] Addition of a methyl substituent to C-6 of the piperazinone was found to produce a similar effect on free fraction. Thus, compound **4** (Table 1) had a similar unbound fraction to **3** in human, dog, and monkey plasma but a seven-fold higher unbound fraction in rat plasma (Table 2), indicating that the in vivo potency of **4** may not be shifted as dramatically in the rat. Gratifyingly, **4** maintained similar affinity for the human and rat CGRP receptors to **3** (Table 1).

In an attempt to further reduce plasma protein binding and also improve aqueous solubility, a nitrogen atom was incorporated into the indanyl moiety of **3** to provide the azaindanyl derivative **5**. As detailed in Table 1, this structural change was tolerated in terms of human CGRP receptor affinity, although **5** did exhibit reduced

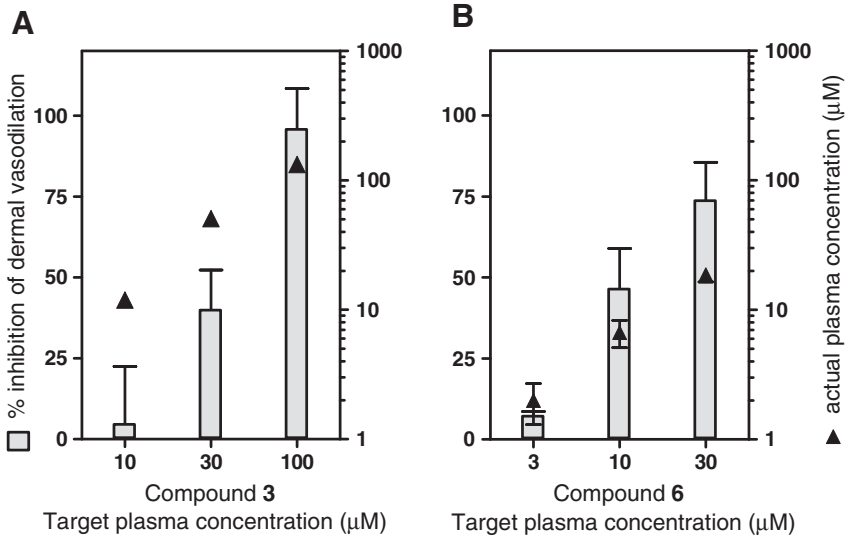
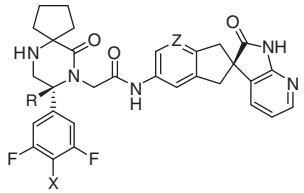


Figure 1. Effects of **3** and **6** on CIDV in rat. Compounds **3** and **6** dose-dependently inhibit CIDV in the rat abdomen. Bar graphs depict the data from several experiments (n = 5–7 per target exposure) in which various plasma concentrations were targeted, actual plasma concentrations were measured, and the percent inhibitions of CIDV were determined. (A) The calculated EC_{50} = 58 μM (95% confidence interval from 37 to 92 μM) for compound **3**. (B) The calculated EC_{50} = 7.4 μM (95% confidence interval from 4.9 to 11 μM) for compound **6**.

Table 1
Data for CGRP receptor antagonists [16]



Compound	R	X	Z	Human K_i[a,b] (pM)	Rat K_i[a,c] (nM)	Rat f_u[a,d] (%)
3	H	H	CH	22 ± 2 (14)	10 ± 1 (4)	0.84 (3)
4	Me	H	CH	40 ± 12 (8)	3.4 ± 0.4 (6)	6.1 (1)
5	H	H	N	28 ± 7 (5)	38 (1)	0.96 (1)
6	Me	H	N	47 ± 20 (13)	17 ± 6 (5)	23 (3)
7	H	Cl	N	14 (2)	18 (1)	0.57 (1)
8	Me	Cl	N	16 (2)	13 ± 3 (4)	3.4 (1)
9	Et	H	N	250 ± 61 (3)	60 ± 6 (4)	3.3 (1)

[a] Mean value ± standard deviation, where appropriate; the number of replicates is in parentheses.
[b] The K_i value for inhibition of ^{125}I-hCGRP binding was determined using membranes from HEK293 cells stably expressing human CLR/RAMP1.[12]
[c] The K_i value for inhibition of ^{125}I-hCGRP binding was determined using membranes from rat brains.[12]
[d] Unbound fraction in rat plasma.

Table 2
Unbound fraction in plasma for selected compounds

Compound	Human f_u (%)[a]	Rat f_u (%)[a]	Dog f_u (%)[a]	Monkey f_u (%)[a]
3	9.4 ± 0.3 (3)	0.84 ± 0.03 (3)	6.1 ± 0.2 (3)	9.6 ± 0.1 (3)
4	10.6 (2)	6.1 (1)	7.9 (2)	10.4 (2)
6	35 ± 3 (3)	23 ± 1 (3)	17 ± 2 (3)	37 ± 1 (3)

[a] Mean value ± standard deviation, where appropriate; the number of replicates is in parentheses.

affinity for the rat CGRP receptor compared with **3**. Moreover, the unbound fraction of **5** in rat plasma was not meaningfully improved (rat f_u = 0.96% for **5** vs 0.84% for **3**). However, application of the same modification to compound **4** led to the azaindanyl analogue **6**, which possessed a more attractive profile. Compound **6** had similar affinity for the rat CGRP receptor to compound **3** but exhibited a significant improvement in rat unbound fraction (Table 1).

Attempts to modify compounds **5** and **6** with the goal of identifying antagonists which combined improved receptor affinity with high rat free fraction were unsuccessful. For example, addition of a chloro substituent to the difluorophenyl ring afforded analogues **7** and **8** (Table 1), which exhibited modest improvements in human CGRP receptor affinity but reduced rat f_u compared with their *des*-chloro counterparts. It also appeared that the 6-methyl substituent on the piperazinone provided the optimal balance of potency and unbound fraction. Replacement of this substituent with a larger group led to marked reductions in receptor affinity and free fraction. For example, the 6-ethyl analogue **9** (Table 1) exhibited reduced affinity for both human and rat CGRP receptors and a seven-fold lower rat f_u, compared with **6**. Overall, compound **6** seemed to offer the best overall balance of receptor affinity and high rat free fraction. Indeed, **6** also exhibited a significantly improved unbound fraction in all four species compared with both **3** and **4** (Table 2).

In rat plasma, the unbound fraction of **6** was about 30-fold higher than the corresponding value for **3**. Moreover, **6** exhibited improved aqueous solubility compared with **3** (at pH 7 in phosphate buffer, solubility = 0.36 mg/mL for **6** and 0.017 mg/mL for **3**) and this suggested that **6** had greater potential for a variety of formulation options. Consistent with the weakly basic piperazinone and pyridine functionality present in **6**, its solubility was greater at acidic pH in citrate buffer (3.2 mg/mL at pH 4; 33 mg/mL at pH 2). Based on its attractive initial profile, a more detailed evaluation of **6** was conducted.

In vitro assays were conducted as described previously.[12,13] In competition binding studies with ^{125}I-hCGRP, compound **6** displayed high affinity for the native human CGRP receptor in SK-*N*-MC cells and for the recombinant human receptor, with K_i values of 0.052 ± 0.007 nM (n = 11) and 0.047 ± 0.020 (n = 13) respectively. High affinity was also observed for the rhesus monkey receptor (K_i = 0.059 ± 0.002 nM; n = 3); however, similar to previous observations with **2** and **3**, the affinity of **6** was significantly reduced for the rat (K_i = 17 ± 6 nM; n = 5), dog (K_i = 39 ± 7 nM; n = 4), rabbit (K_i = 15 ± 3 nM; n = 4) and mouse (K_i = 19 ± 1 nM; n = 4) CGRP receptors.

In a functional assay, **6** blocked hCGRP-stimulated cAMP responses in HEK293 cells stably expressing the human CGRP receptor, with an IC_{50} value of 0.23 ± 0.08 nM (n = 6). Addition of 50% human serum to this assay had little effect on the potency of **6** (IC_{50} = 0.34 ± 0.16 nM; n = 6), consistent with the high unbound fraction in human plasma (f_u = 35%). Increasing concentrations of **6** caused parallel rightward shifts in the CGRP dose-response curves in a cAMP functional assay and the dose-ratio plot displayed a straight line with a slope of 1.1 and a pA_2 of 9.84 (n = 2; K_B = 0.15 nM; Fig. 2). These data are consistent with competitive antagonism; however it is difficult to determine conclusively whether **6** is strictly a competitive antagonist rather than an allosteric antagonist. Indeed, it seems unlikely that a small molecule antagonist could directly compete with CGRP for the putative large agonist binding site on the receptor. More likely, as suggested by recent structural studies on the extracellular domain of the CGRP

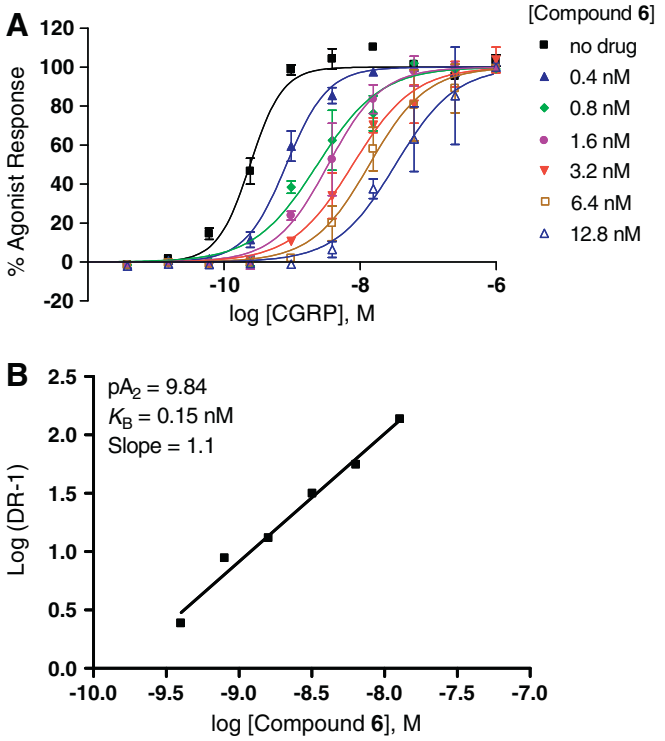


Figure 2. Concentration-response curve and Schild plot analysis of compound **6**. (A) Concentration response curves of CGRP-induced cAMP production in HEK293 cells stably expressing human CGRP receptor in the absence or presence of increasing concentrations of **6** (n = 2). (B) Schild plot showing the effect of **6** on cAMP production in HEK293 cells stably expressing human CGRP receptor.

Table 3
Preclinical pharmacokinetics of compound **6**

Species	PO dose (mpk)	F^a (%)	IV $t_{1/2}{}^b$ (h)	Cl^b (mL/min/kg)	$Vd_{ss}{}^b$ (L/kg)
Rat	5	28	0.6	31	0.81
	50	15			
Dog	2	64	1.3	7.2	0.67
Monkey	2	7	2.3	22	2.4
	20	20			
Mouse	10	1.3	1.1	26	1.7

[a] Determined after dosing in 0.5% methocel.
[b] Determined after dosing in DMSO at 2 (rat & mouse) or 0.5 mpk (dog & monkey).

receptor, small molecule antagonists like telcagepant bind to part of the peptide agonist binding site.[17]

The selectivities of compound **6** for the human CGRP receptor versus the related human adrenomedullin (AM), calcitonin (CT), and amylin (AMY) receptors were evaluated in competition binding experiments. While **6** displayed moderate selectivity against human AMY_1 receptor (K_i = 0.64 ± 0.20 nM; n = 4), it had excellent selectivity versus the other human receptors: AM_1 (K_i > 20,000 nM; n = 8); AM_2 (K_i = 590 ± 200 nM; n = 15); CT (K_i = 3,200 ± 1,300 nM; n = 3); and AMY_3 (K_i = 1,100 ± 550 nM; n = 3). Compound **6** was found to have excellent selectivity against cardiac ion channels in voltage clamp experiments, with IC_{50} > 20,000 nM for I_{Kr}, I_{Ks}, $Na_v1.5$, and $Ca_v1.2$. When **6** was screened against a diverse panel of more than 160 enzymes, receptors, channels, and transporters, no other off-target activities were identified (IC_{50} < 10,000 nM) in any assay except for the human calcitonin receptor, which was consistent with our in-house determination.

The in vivo pharmacokinetic profile of **6** was evaluated in rat, dog, monkey and mouse. As shown in Table 3, **6** exhibited moderate clearance across species with plasma half-lives of around 1–2 h. After dosing of the hydrochloride salt in 0.5% methocel vehicle, the oral bioavailability ranged from poor in the mouse (F = 1.3%) to good in the dog (F = 64%). In rhesus monkey, oral bioavailability appeared to improve as the dose was increased from 2 to 20 mpk (Table 3). Similar nonlinearity of oral pharmacokinetics was observed in monkey for both **2** and **3** and this finding is consistent with saturable first-pass metabolism which contributes to the low oral bioavailability in this species.[18]

A comparison with published data reveals that **3** and **6** have similar overall pharmacokinetic profiles.[11] The plasma clearance values of **3** in dog (Cl = 8.0 mL/min/kg) and monkey (Cl = 15 mL/min/kg) were similar to those observed for **6**, in spite of the fact that **6** has significantly higher unbound fraction in both species (Table 2). Notably, the clearance of **6** in rat was only 3-fold higher than that of **3** (Cl = 11 mL/min/kg) while the unbound fraction was almost 30-fold higher (Table 2). Taken together, these data indicate that the structural modifications found in **6** imparted significantly reduced intrinsic clearance.

The CIDV model of in vivo pharmacological blockade of the CGRP receptor has been validated in our laboratories in both non-human primate and rat.[14] The in vivo potency of **3** was less than desirable in our rat PD model of CGRP receptor antagonism as mentioned previously, with a plasma EC_{50} value of 58 μM (Fig. 1A). In contrast, when evaluated in the analogous PD model in rhesus monkey the EC_{50} value of **3** was determined to be 0.8 nM.[13] Although **3** possessed approximately 400-fold higher affinity for the rhesus monkey CGRP receptor versus the rat receptor in vitro (K_i = 0.024 nM and 10 nM, respectively),[13] this alone cannot explain the large potency difference in vivo. The low unbound fraction in rat (f_u = 0.84%; Table 2) compared to monkey (f_u = 9.6%; Table 2) most likely was a significant contributor. As **3** and **6** have similar affinities for the rat CGRP receptor (Table 1) we expected that the increased free fraction of **6** would translate into enhanced rat in vivo potency. Indeed compound **6** produced a concentration–dependent inhibition of capsaicin-induced dermal blood flow in the rodent abdomen affording an EC_{50} value of approximately 7.4 μM (Fig. 1B). This potency enhancement has provided a pharmacological exposure target which can be readily achieved via multiple routes of administration.

In conclusion, we have identified a CGRP receptor antagonist with suitable potency, selectivity and pharmacokinetics to interrogate the in vivo effects of receptor blockade in the rat. Rational modification of compound **3** led to **6**, which possessed a 30-fold higher unbound fraction in rat plasma and increased aqueous solubility while maintaining similar in vitro potency to **3**. Most importantly, **6** was determined to be significantly more potent in vivo which will allow detailed investigation of CGRP receptor antagonism in one of the most characterized species, the rat.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2012.04.105.

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