Bioorganic & Medicinal Chemistry Letters 19 (2009) 6368–6372

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Optimization of azepanone calcitonin gene-related peptide (CGRP) receptor antagonists: Development of novel spiropiperidines

Christopher S. Burgey [a,*], Craig M. Potteiger [a], James Z. Deng [a], Scott D. Mosser [b], Christopher A. Salvatore [b], Sean Yu [c], Shane Roller [c], Stefanie A. Kane [b], Joseph P. Vacca [a], Theresa M. Williams [a]

[a] Department of Medicinal Chemistry, Merck Research Laboratories, West Point, PA 19486, USA
[b] Department of Pain and Migraine Research, Merck Research Laboratories, West Point, PA 19486, USA
[c] Department of Drug Metabolism, Merck Research Laboratories, West Point, PA 19486, USA

ARTICLE INFO

Article history:
Received 20 August 2009
Revised 16 September 2009
Accepted 17 September 2009
Available online 22 September 2009

Keywords:
CGRP
CGRP receptor antagonists
Migraine
Calcitonin gene-related peptide

ABSTRACT

Several novel spiropiperidine-based CGRP receptor antagonists have been developed that maintain good potency and have reduced potential for metabolism.

Within the field of antimigraine therapy, the development of novel drugs with enhanced safety profiles and/or improved efficacy is a current major focus. The triptan class of 5-$HT_{1B/1D}$ receptor agonists represents the current standard of treatment for a migraine attack; however, these compounds are contraindicated in patients with cardiovascular disease.[1] Calcitonin gene-related peptide (CGRP) has been proposed to be a key neuropeptide in the pathogenesis of migraine headache, engendering hope for the development of receptor antagonists as therapeutics devoid of the cardiovascular effects associated with current migraine treatments.[2]

We have undertaken a research program aimed at identifying small-molecule CGRP receptor antagonists suitable for oral administration during a migraine attack.[3] A recent report from these laboratories detailed the identification of a series of potent, orally bioavailable, small-molecule, azepanone-based CGRP receptor antagonists.[4] A development candidate was selected from this series (Fig. 1, telcagepant, MK-0974) and this compound has recently demonstrated efficacy similar to a triptan in a phase 3 migraine clinical trial; importantly, overall adverse event rates were comparable to placebo and lower than the triptan positive comparator.[5]

Research efforts have continued within the azepanone series, focusing on the identification of compounds with improved profiles. One area targeted for optimization was the elimination/modification of areas of the lead molecule known to be susceptible to oxidative metabolism (i.e., metabolic soft-spots). The primary site of metabolism is the piperidine-based 'privileged structure'. For example, telcagepant undergoes N-oxidation to afford **1** and N-dealkylation to produce hydroxypiperidine **2**. These pathways are manifested in the low oral bioavailability in rhesus, primarily due to intestinal first-pass metabolism (Fig. 1).[6]

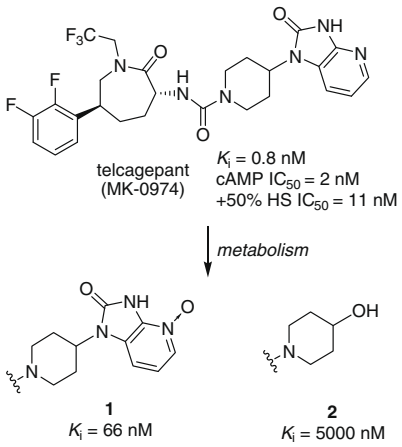


Figure 1.

* Corresponding author.
E-mail address: christopher_burgey@merck.com (C.S. Burgey).

0960-894X/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2009.09.066

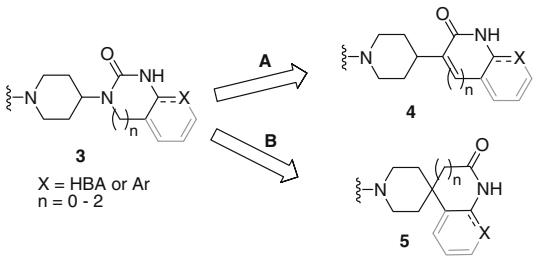


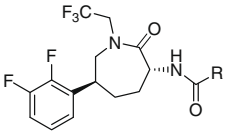
Chart 1.

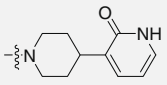
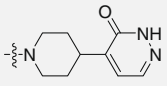
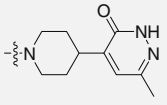
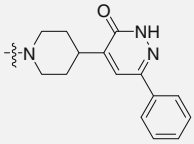
Guided by this data, in combination with the proposed pharmacophore **3**,[7] two general strategies for attenuation of metabolism were outlined. In the first (Chart 1, **A**), elimination of the N-dealkylation pathway could be achieved by replacement of the $C4_{pip}$–N_{het} bond with an $C4_{pip}$–C_{het} (sp^2) bond; alternatively, a similar result could also be achieved by spirocyclization of the two ring systems (Chart 1, **B**). In the design of specific analogs we were cognizant that an H-bond acceptor would likely be required to confer good potency (X = HBA) and if it were to be a nitrogen (X = N) then the N-oxidation pathway would not be circumvented.

All compounds prepared were tested in the CGRP receptor competitive [^{125}I]-CGRP radioligand binding assay (K_i). Selected compounds were subsequently tested for their functional ability to inhibit CGRP-stimulated cAMP production in whole cells (cAMP IC_{50}); this assay could also be conducted in 50% human serum (+HS) to estimate the impact of plasma protein binding on in vitro efficacy.[8]

According to strategy **A** (Chart 1) the piperidine-based privileged structure was pared back to the basic pharmacophore required to maintain CGRP potency, namely a cyclic amide such as pyridinone **6** (Table 1: K_i = 100 nM). Preparation of the analogous pyridazinone led to a 10-fold improvement in potency (**7**: K_i = 10 nM). In an attempt to further improve potency, lipophilic groups were installed at the 6-position of the pyridazinone. A small methyl group enhances potency modestly, while the larger phenyl group reduces binding affinity. These results suggest that the key HBA (X = N) that occupies the 'aza binding' site of the CGRP receptor can be incorporated into the same ring system as the key cyclic amide.[7] Of additional note is the relatively modest in vitro efficacy shift (~2-fold) of these pyridazinones in the presence of 50% HS.

Table 1
4-Substituted piperidine SAR



Compds	R	K_i[a] (nM)	cAMP IC_{50}[b] (nM)	+HS IC_{50}[c] (nM)
6		100	—	—
7		10	44	112
8		6.6	13	21
9		240	—	—

[a] Values are means of two experiments; inhibition of [^{125}I]-CGRP binding against the CGRP receptor (recombinant human CLR/RAMP1).
[b] Inhibition of CGRP-stimulated cAMP production in cells.
[c] Inhibition of CGRP-stimulated cAMP production in the presence of 50% human serum.

While these compounds were designed to circumvent the N-dealkylation process observed with the parent piperidine-azabenzimidazolone, the PK was not improved. For example, analog **8** exhibits low to moderate plasma clearance and bioavailability in rats (Cl = 9.8 mL/min/kg; F = 15%).

Modification of the piperidine-based privileged structure according to pathway **B** (Chart 1) offered an alternative strategy designed to overcome the metabolic susceptibility via formation of spirocycles. Previous work from our group has shown that a hydantoin can be incorporated at the piperidine C4-position to deliver potent CGRP receptor antagonists[7] and spirocyclization of this heterocycle similarly afforded potent compounds (Table 2, example **10**). Both N-methylation to **11** and preparation of the oxazolidinedione **12** led to significant losses of CGRP affinity. The spirosuccinimide **13** retains the good potency of the hydantoin, with both of these analogs exhibiting nominal shift in the presence of human serum. Deletion of the distal carbonyl group to give spiropyrrolidinone **14** illustrates the minimal structural motif to retain good potency. The two glutarimide isomers, **15** and **16**, demonstrate that a 5-member ring is optimal.

As Chart 1 illustrates, the potency of the amide pharmacophore can also be improved by strategic introduction of an aryl group (X = Ar). Examples **17** and **18** demonstrate that a pendant aryl group, preferring a trajectory from a sp^2 carbon, can access this type of interaction within the spiropiperidine motif (Table 2). Fusion of the aryl group into a bicyclic system represented by quinolone **19** leads to a significant loss in affinity. Moving the spirocyclic ring junction β to the carbonyl, as in benzoxazinone **20**, confers a substantial potency gain. Notably, significant in vitro cAMP efficacy shifts are observed in the presence of human serum.

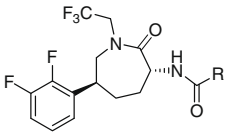
Within the 4-substituted piperidines it has been shown that proper placement of a single nitrogen within the bicyclic ring system can produce an 100-fold improvement in CGRP binding affinity ('aza binding site').[7] Furthermore, the resultant azacycles attenuate plasma protein binding and, accordingly, demonstrate minimal in vitro efficacy shift in the presence of human serum. Production of the azabenzoxazinone **21** demonstrates that this binding motif is also accessible within the spirocyclic piperidines (Table 2). The naphthyridinone **22** is slightly less potent, while the azaoxindole **23** is equipotent. Notably, these compounds do not shift to an appreciable extent in the cAMP assay with added serum.

These spiropiperidine-based CGRP receptor antagonists retain the favorable rat PK properties inherent in the azabenzimidazoles (**21** F = 37%; **22** F = 26%; **23** F = 35%); furthermore, they show reduced propensity for metabolism on the terminal ring of the spirocyclic system. For example **21** shows no evidence of oxidation on the azabenzoxazinone ring in the presence of human, rat, and rhesus liver microsomes.

The chemistry to access these piperidines, which were converted to the final ureas using previously disclosed methods,[9] is highlighted below (Schemes 1–4).[10]

The general route to the pyridazinones is delineated in Scheme 1: piperidinyl-4-acetate **24** is alkylated with allylic bromides to deliver **25** and serves to install the C6 lipophilic group. Oxidative

Table 2
Spiropiperidine SAR



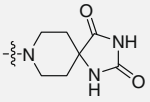
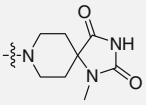
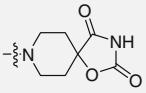
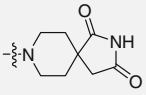
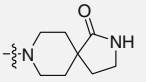
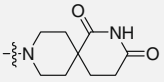
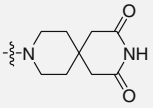
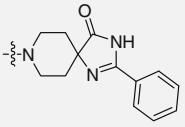
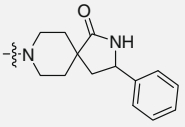
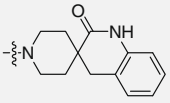
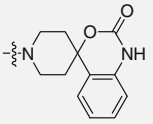
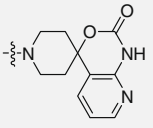
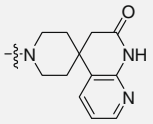
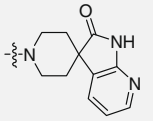
Compds	R	K_i[a] (nM)	cAMP IC_{50}[b] (nM)	+HS IC_{50}[c] (nM)
10		46	94	122
11		510	—	—
12		8900	—	—
13		41	55	95
14		140	—	—
15		340	—	—
16		390	—	—
17		30	23	871
18		380	120	692
19		1249	—	—
20		46	60	792
21		1.1	2.7	13

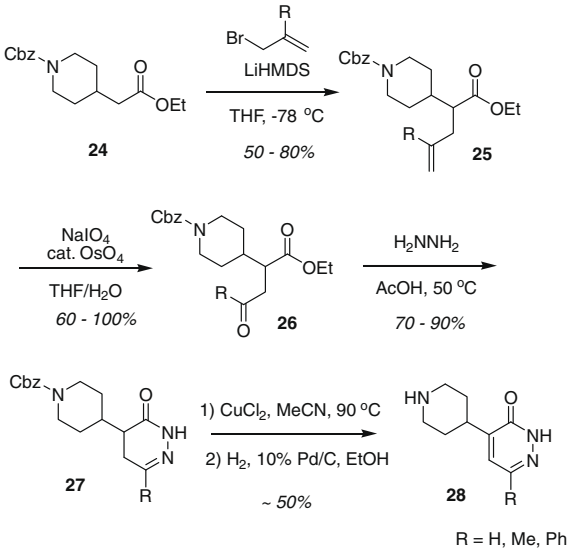
Table 2 (*continued*)

Compds	R	K_i[a] (nM)	cAMP IC_{50}[b] (nM)	+HS IC_{50}[c] (nM)
22		3.5	11	11
23		1.7	3.3	11

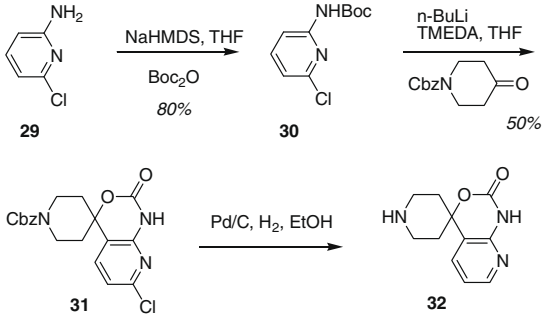
[a] Values are means of two experiments; inhibition of [^{125}I]-CGRP binding against the CGRP receptor (recombinant human CLR/RAMP1).
[b] Inhibition of CGRP-stimulated cAMP production in cells.
[c] Inhibition of CGRP-stimulated cAMP production in the presence of 50% human serum.

cleavage to ketone **26** is followed by ring closure with hydrazine to deliver **27**. Formal dehydrogenation to the pyridazinone is followed by deprotection to give piperidine **28**.

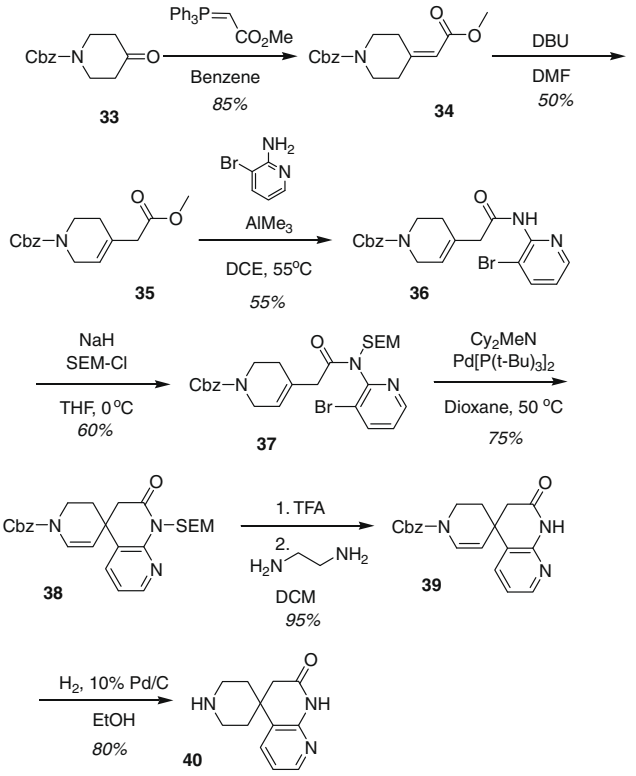
The synthesis of the spiroazabenzoxazinone can be accomplished according to Scheme 2. Ortho metalation[11] of Boc protected 2-amino-6-chloropyridine[12] **30** and addition of the resultant anion



Scheme 1.



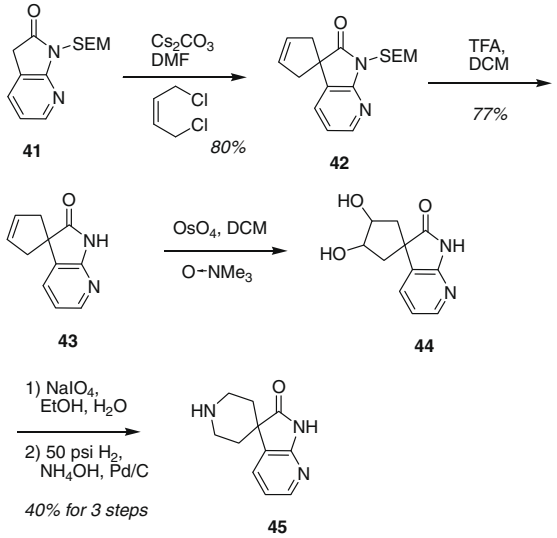
Scheme 2.



Scheme 3.

to N-benxyloxycarbonyl-4-piperidinone, gives, after in situ cylization, product **31**.[13] Final deprotection and dechlorination under standard hydrogenolysis conditions gives the piperidine **32**.

The synthesis of spironaphthyridinone **40** is summarized in Scheme 3. Olefination of the 4-ketopiperidine **33** gives the α,β-unsaturated ester **34**, which can be isomerized to the β,γ-unsaturated ester **35** under basic conditions (Scheme 3).[14] Trimethylaluminum mediated amidation with 2-amino-3-bromopyridine followed by amide alkylation gives the SEM protected product **37**.[15] The key palladium-mediated spirocyclization can be effected through the Fu modification of the Heck reaction.[16] A two-stage deprotection with concomitant double bond reduction gives the desired spironaphthyridinone **40**.



Scheme 4.

The synthesis of the spiroazaoxindole is shown in Scheme 4. Alkylation of the SEM-protected 7-azaindole **41** with cis-1,4-dichloro-2-butene affords the spirocyclopentene **42**. Removal of the SEM protecting group followed by osmium tetroxide catalyzed dihydroxylation provides the diol intermediate **44**. Periodate oxidative cleavage of the diol, followed by a double reductive amination affords the spiropiperidine **45**.[17]

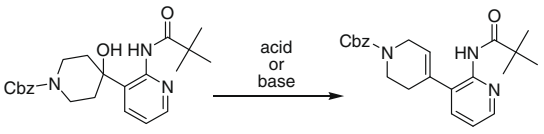
In summary, utilizing the previously proposed pharmacophore, two general strategies were outlined for attenuation of metabolism of the piperidine-based privileged structure within the azepanone series of CGRP receptor antagonists. Several novel piperidine-based privileged structures have been developed that maintain comparable potency to the phase 3 clinical compound telcagepant and have the potential for reduced metabolism. The incorporation of these novel spirocyclic privileged structures into newer non-azepanone templates to deliver second-generation CGRP receptor antagonists with differentiated profiles will be reported in the future.

Acknowledgments

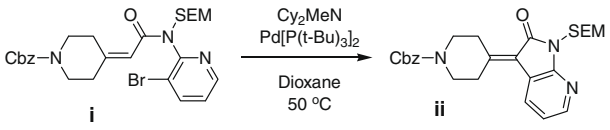
We thank the mass spectroscopy, and NMR analysis groups for their valuable assistance.

References and notes

1. Wackenfors, A.; Jarvius, M.; Ingemansson, R.; Edvinsson, L.; Malmsjo, M. *J. Cardiovasc. Pharmacol.* **2004**, *45*, 476.
2. Durham, P. L.; Russo, A. F. *Pharmacol. Ther.* **2002**, *94*, 77; Edvinsson, L. *Exp. Opin. Ther. Targets* **2003**, *7*, 377; Durham, P. L. *N. Engl. J. Med.* **2004**, *350*, 1073; Olesen, J.; Diener, H.-C.; Husstedt, I. W.; Goadsby, P. J.; Hall, D.; Meier, U.; Pollentier, S.; Lesko, L. *N. Engl. J. Med.* **2004**, *350*, 1104; Petersen, K. A.; Birk, S.; Lassen, L. H.; Krusse, C.; Jonassen, O.; Lesko, L.; Olesen, J. *Cephalalgia* **2004**, *25*, 139.
3. Williams, T. M.; Burgey, C. S.; Salvatore, C. A. *Prog. Med. Chem.* **2009**, *47*, 1.
4. Paone, D. V.; Shaw, A. W.; Nguyen, D. N.; Burgey, C. S.; Deng, Z. J.; Kane, S. A.; Koblan, K. S.; Salvatore, C. A.; Hershey, J. C.; Wong, B.; Roller, S. G.; Miller-Stein, C.; Graham, S. L.; Vacca, J. P.; Williams, T. M. *J. Med. Chem.* **2007**, *50*, 5564; Salvatore, C. A.; Hershey, J. C.; Corcoran, H. A.; Fay, J. F.; Johnston, V. K.; Moore, E. L.; Mosser, S. D.; Burgey, C. S.; Paone, D. V.; Shaw, A. W.; Graham, S. L.; Vacca, J. P.; Williams, T. M.; Koblan, K. S.; Kane, S. A. *JPET* **2008**, *324*, 416; Burgey, C. S.; Paone, D. V.; Shaw, A. W.; Deng, J. Z.; Nguyen, D. N.; Potteiger, C. M.; Graham, S. L.; Vacca, J. P.; Williams, T. M. *Org. Lett.* **2008**, *10*, 3235.
5. Ho, T. W.; Mannix, L.; Fan, X.; Assaid, C.; Furtek, C.; Jones, C.; Lines, C.; Rapoport, A. *Neurology* **2008**, *70*, 1305; Ho, T. W.; Ferrari, M. D.; Dodick, D. W., et al *Lancet* **2008**, *372*, 2115.
6. Roller, S.; Cui, D.; Laspina, C.; Miller-Stein, C.; Rowe, J.; Wong, B.; Prueksaritanont, T. *Xenobiotica* **2009**, *39*, 33.
7. Burgey, C. S.; Stump, C. A.; Nguyen, D. N.; Deng, J. Z.; Quigley, A. G.; Norton, B. R.; Bell, I. M.; Mosser, S. D.; Salvatore, C. A.; Rutledge, R. Z.; Kane, S. A.; Koblan, K. S.; Vacca, J. P.; Graham, S. L.; Williams, T. M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5052.
8. For the details of these assays, see: Bell, I. M.; Graham, S. L.; Williams, T. M.; Stump, C. A. WO 2004/087649.
9. Williams, T. M.; Stump, C. A.; Nguyen, D. N.; Quigley, A. G.; Bell, I. M.; Gallichio, S. N.; Zartman, C. B.; Wan, B.-L.; Kunapuli, P.; Kane, S. A.; Koblan, K. S.; Mallee, J. J.; Mosser, S. D.; Rutledge, R. Z.; Salvatore, C.; Graham, S. L.; Vacca, J. P. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2595.
10. For the details of the chemistry, see: Burgey, C. S.; Deng, Z. J.; Potteiger, C.; Williams, T. M. WO 2006/041830 A2.; Burgey, C. S.; Paone, D. V.; Shaw, A. W.; Nguyen, D. N.; Deng, Z. J.; Vacca, J. P.; Selnick, H. G.; Williams, T. M.; Potteiger, C. WO 2006/044504 A2.
11. Davies, A. J.; Brands, K. M. J.; Cowden, C. J.; Dolling, U.-H.; Lieberman, D. R. *Tetrahedron Lett.* **2004**, *45*, 1721.
12. Ortho metalation/cyclization attempts without the chlorine group were unsuccessful.
13. In situ cyclization via the use of a carbamate protecting group were essential, as attempted deprotection of amides led to dehydration: for example,



14. Wu, J.; Wu, H.; Wei, S.; Dai, W.-M. *Tetrahedron Lett.* **2004**, *45*, 4401. Produced a 4: 1 mixture of product: SM.
15. Attempts to affect the desired cyclization from **i** instead produced 5-exo-trig product **ii**.



16. Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989.

17. Coe, J. W. *Org. Lett.* **2000**, *26*, 4205; attempts to make this target by a Heck spirocyclization led instead to the 6-endo-trig byproduct **v**.