Bioorganic & Medicinal Chemistry Letters 21 (2011) 2683–2686

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Orally bioavailable imidazoazepanes as calcitonin gene-related peptide (CGRP) receptor antagonists: Discovery of MK-2918

Daniel V. Paone [a,*], Diem N. Nguyen [a], Anthony W. Shaw [a], 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], Harold G. Selnick [a], 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 19 November 2010
Revised 8 December 2010
Accepted 13 December 2010
Available online 30 December 2010

Keywords:
CGRP
Migraine
Calcitonin gene-related peptide
Telcagepant
MK-2918

ABSTRACT

In our ongoing efforts to develop CGRP receptor antagonists for the treatment of migraine, we aimed to improve upon telecagepant by targeting a compound with a lower projected clinical dose. Imidazoazepanes were identified as potent caprolactam replacements and SAR of the imidazole yielded the tertiary methyl ether as an optimal substituent for potency and hERG selectivity. Combination with the azabenzoxazinone spiropiperidine ultimately led to preclinical candidate **30** (MK-2918).

Migraine is a debilitating disorder characterized by severe, episodic headaches which can lead to significant loss of productivity.[1] The current standard of care, 5-$HT_{1B/1D}$ agonists known as triptans, is contraindicated for patients with cardiovascular disease due to inherent vasoconstrictive activity.[2] Thus a novel migraine therapy with an improved cardiovascular safety profile constitutes an unmet medical need. Calcitonin gene-related peptide (CGRP) is a 37 amino acid neuropeptide present in both the central and peripheral nervous systems, with a variety of physiological functions that include nociception, vasodilation, and neurogenic inflammation.[3] Growing evidence suggests that CGRP plays a key role during migraine attacks,[4] and indeed clinical proof of concept has been established with two small-molecule CGRP receptor antagonists. The first was the intravenously-administered olcegepant,[5] which displayed triptan-like efficacy in a phase II migraine clinical trial with no reported cardiovascular effects.[6] More recently the orally-administered telcagepant demonstated comparable efficacy to a triptan positive control in a phase III clinical trial with lower overall adverse event rates.[7]

A series of reports from these laboratories detailed the evolution of a benzodiazepinone lead[8] to an azepanone scaffold[9] which ultimately led to the discovery of telcagepant (MK-0974).[10] Within the context of improving upon this development candidate, we sought to design a compound that would result in a lower anticipated clinical dose. To this end, targeted areas for improvement were potency (in vitro and in vivo) and pharmacokinetic profile (aqueous solubility, metabolism). We reasoned that incorporation of heterocyclic rings to the caprolactam core of telcagepant would improve solubility and reduce plasma protein binding, resulting in lower serum shifts. Initially surveyed was fused triazole derivative **1** (Fig. 1), and we were gratified to see comparable potencies in the CGRP binding assay[11] (K_i = 1 nM) and the cell-based functional assays (cAMP IC_{50} = 1.6 nM, cAMP + 50% human serum IC_{50} = 2.4 nM). Additionally, **1** shows improved aqueous solubility over telcagepant (fivefold).[12] However this does not translate to improved pharmacokinetics (rat F = 2%), as low permeability may be limiting oral absorption ($P_{app} = 4 \times 10^{-6}$ cm/s). Substitution to a fused imidazole substructure gives **2**, which maintains good potency and shows greatly increased permeability ($P_{app} = 24 \times 10^{-6}$ cm/s), perhaps aiding in the improved oral bioavailability observed in rats (F = 35%).[13]

Given the promising attributes of **2**, extensive SAR was conducted at both C5 and C4 of the imidazole ring (designated R^1 and R^2, respectively, in Table 1). Derivatives bearing substituents at R^2 (**4**–**6**) were routinely less potent than those with comparable substitution at R^1 (**2**, **7** and **8**) as well as the unsubstituted analog **3**. Analogs with hydrogen bond donor/acceptor (**8**–**10**) or aryl/heteroaryl (**11 and 12**) substituents all proved less potent than trifluoroethyl analog **2**. Only branched alkyl (**13**) or ether

* Corresponding author. Tel.: +1 215 993 2269; fax: +1 215 652 7310.
E-mail address: daniel_paone@merck.com (D.V. Paone).

0960-894X/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2010.12.054

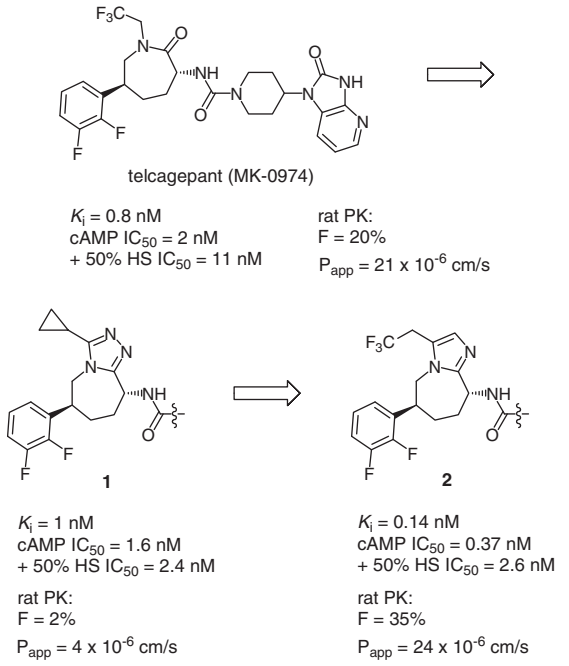


Figure 1. Fused heterocyclic analogs of telcagepant.

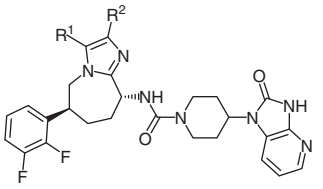
substitution (**14 and 15**) afforded compounds with comparable or improved potencies to **2**. However, these analogs typically displayed poor rat oral bioavailability (F = 4% for **15**).

We previously outlined a synthetic approach to polysubstituted imidazoles developed for acyclic systems.[14] Application of this methodology with slight modifications allowed access to the desired fused imidazoazepanes (Scheme 1). Caprolactam **16** was available in large quantities as a common intermediate in our various telcagepant syntheses.[15] Treatment with Lawesson's reagent[16] gave the corresponding thioamide **17** in high yield. Mercury-mediated addition of amino alcohol **18** provided amidine **19**, which after subsequent oxidation with pyridinium dichromate underwent spontaneous cyclization to imidazole **20**.[17] Deprotection and urea coupling of the resulting amine with substituted piperidines gave the final targets **21**.[18]

Poor rhesus PK continued to plague most of the compounds in this series, including **2**, with oral bioavailabilities in the range of telcagepant (F <2%). Concurrent efforts toward reducing metabolism of the azabenzimidazolone substructure yielded two promising spiropiperidine alternatives,[20] azaoxindole **A** and azabenzoxazinone **B** (Table 2). These novel CGRP privileged structures were coupled with several of the more potent fused imidazoazepane scaffolds with the aim of improving PK profiles while maintaining potency. Azaoxindole analogs **22**–**25** showed decreased potencies versus the corresponding azabenzimidazolones and a range of rat oral bioavailabilities depending on the nature of the R^1 substituent. The azabenzoxazinone derivatives were consistently more potent than the azaoxindoles and generally showed improved PK profiles versus the corresponding azabenzimidazolones. Trifluoroethyl analog **26** maintained good potency and was orally bioavailable in three species, including rat (F = 33%), dog (F = 28%) and rhesus (F = 17%). However more thorough characterization of **26** revealed lower than expected efficacy in our primary in vivo model, the rhesus capsaicin induced dermal vasodilation (CIDV) assay[21] (EC_{90} = 1000 nM). Additionally, undesirable levels of hERG activity were observed (IC_{50} = 3.3 μM).

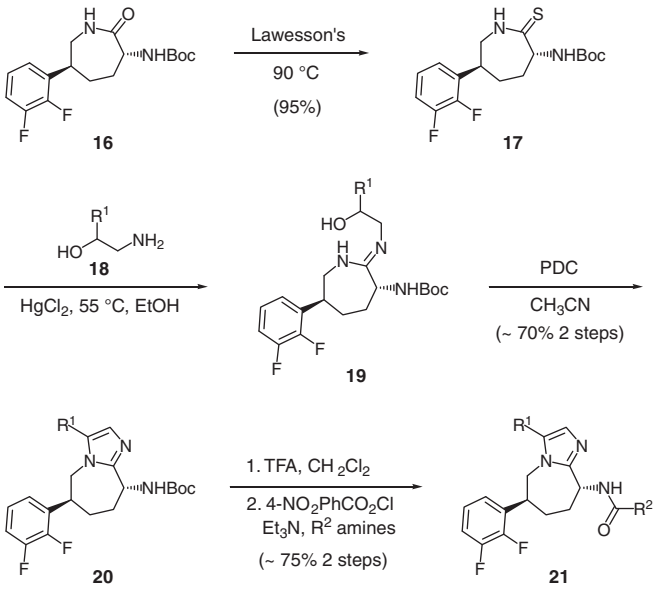
In an attempt to increase hERG selectivity fused triazoles were revisited (**27** and **28**), as these heterocycles had previously shown

Table 1
Imidazole and triazole SAR



Compd	R^1	R^2	K_i[a] (nM)	cAMP IC_{50}[b] (nM)	+HS IC_{50}[c] (nM)
2	F_3C	H	0.14	0.37	2.6
3	H	H	3.1	6.7	19
4	H	F_3C	3.9	7.2	33
5	H	HO	3.2	12	26
6	H	Me	4	8.7	28
7	Me	H	2.2	4.1	12
8	HO	H	2.5	7.9	12
9	HN	H	5.7	12	15
10	O N	H	2.8	4.1	7.4
11		H	1.1	2.6	34
12	N S	H	1.1	3.6	64
13		H	0.69	0.62	3.2
14	O	H	0.38	0.63	1.9
15	O	H	0.04	0.31	0.61

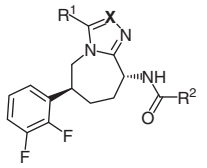
[a] Values are a means of at least two experiments; inhibition of [^{125}I]-CGRP binding to the CGRP receptor (recombinant human CLR/RAMP1).
[b] Inhibition of CGRP-stimulated cAMP production in cells.
[c] Inhibition of CGRP-stimulated cAMP production in the presence of 50% human serum.



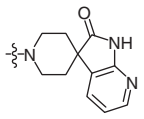
Scheme 1. Synthesis of imidazoazepanes.

to decrease hERG affinity. Though selectivities were indeed improved, the spiropiperidines were unable to rescue the poor PK imparted by the triazole scaffolds. We then focused on attenu-

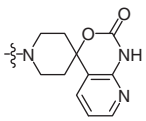
Table 2
Imidazole and triazole spiropiperidine SAR



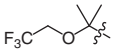
R_2 =



A



B

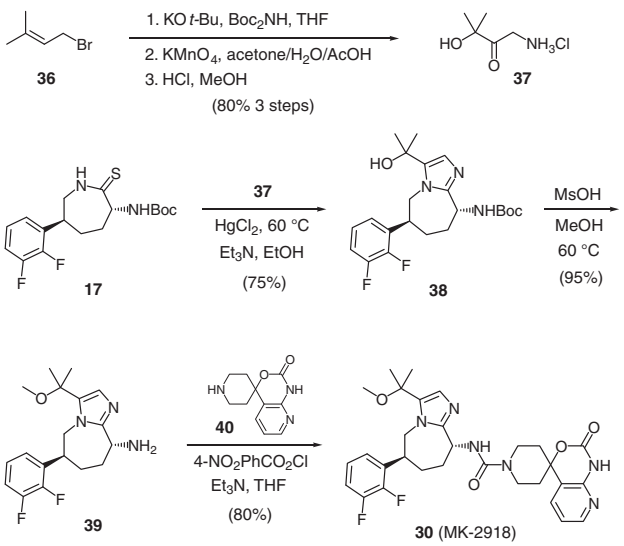
Compd	R^1	X	R^2	K_i[a] (nM)	cAMP IC_{50}[b] (nM)	+HS IC_{50}[c] (nM)	Rat %F[d]	hERG IC_{50}/cAMP IC_{50}[f]
22		CH	A	0.61	0.94	4	47	9300
23		CH	A	0.63	1.4	8.6		880
24		CH	A	0.62	1.7	4.3	21[e]	9500
25		CH	A	0.4	0.82	1.4	5[e]	9700
26		CH	B	0.07	0.41	2	33	8700
27		N	A	0.48	2.3	2.7	6[e]	>13,000
28		N	B	0.19	0.83	1.3	<1	>36,000
29		CH	B	0.14	0.61	1.7	15	8900
30		CH	B	0.05	0.24	0.63	16	32,000
31		CH	B	0.29	0.86	1.5	3	23,000
32		CH	B	0.05	0.32	2.9		23,000
33		CH	B	0.16	0.65	13		6100
34		CH	B	0.039	0.25	0.42		3200
35		CH	B	0.036	0.21	0.76	8	17,000

[a] Values are a means of at least two experiments; inhibition of [^{125}I]-CGRP binding to 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.
[d] 10 mpk po dosed as a suspension in 1% aqueous methylcellulose.
[e] 10 mpk po dosed as a solution in 1:1 imwitor:tween.
[f] Ratio of inhibition of [^{35}S]-MK-499 binding[19] to the hERG channel/cAMP IC_{50}.

ation of hERG selectivity of the fused imidazoles by variation of R^1, specifically targeting oxygenated substituents. A wide array of ethers was prepared and most were well tolerated. Tertiary methyl ether **30** showed exceptional in vitro potency (cAMP + 50% HS IC_{50} = 0.63 nM) and favorable hERG selectivity (32,000-fold). Subtle modifications to this particular motif resulted in either potency loss (alkyl chain extension analogs **32** and **33**), decrease in hERG selectivity (diethyl analog **34**), or decrease in oral bioavailability (THF analog **35**).

Further evaluation of **30** in our in vivo model indicated improved efficacy (rhesus CIDV EC_{90} = 300 nM). Though permeability ($P_{app} = 24 \times 10^{-6}$ cm/s) and aqueous solubility (sol pH 3.0 = 1.1 mg/mL) are respectable, oral bioavailability is only moderate in rat (F = 16%), and low in dog (F = 10%) and rhesus (F = 5%). However, **30** shows increased microsomal stability in human liver microsomes vs. preclinical species. The major metabolite is tertiary hydroxyl derivative **31**, which is itself a highly potent antagonist (cAMP + 50% HS IC_{50} = 1.5 nM) with similar hERG selectivity (23,000-fold) and in vivo efficacy (rhesus CIDV EC_{90} = 330 nM) but is not orally bioavailable. Because substantial levels of alcohol **31** are observed upon dosing of ether **30** (rat F_{-OH} = 26%, dog F_{-OH} = 14%, rhesus F_{-OH} = 29%),[22] **31** would be expected to contribute significantly to clinical efficacy. Taken together **30** has a lower anticipated clinical dose than telcagepant. In addition, **30** shows >6000-fold selectivity in a panel of assays representing over 160 receptors, transporters, and enzymes, and was selected as a preclinical candidate (MK-2918).

During larger scale (>10 g) campaigns toward **30**, the workup of the PDC reaction became cumbersome. Therefore an alternate sequence was developed in which the oxidation step could be circumvented by use of amino ketone **37** (Scheme 2). This synthon is



Scheme 2. Synthesis of MK-2918.

readily accessed in 3 steps from bromide **36** after alkylation with Boc-protected ammonia, oxidation with $KMnO_4$ and acidic deprotection. Steric hindrance of the adjacent quaternary center undoubtedly aids in minimizing self condensation of **37** during the addition to thioamide **17**, allowing for clean amidine formation. Continued heating then provides imidazole **38** directly.[23] Solvolysis under strongly acidic conditions in methanol yields deprotected methyl ether **39**. Finally urea coupling with azabenzoxazinone spiropiperidine **40** affords MK-2918.

In summary, fused heterocyclic derivatives of telcagepant were explored with the overall goal of achieving a lower projected clinical dose. The imidazoazepane scaffold was identified as a potent replacement for the caprolactam, with permeabilities sufficient for enabling good oral exposures. Utilization of the azabenzoxazinone spiropiperidine decreased metabolism and resulted in improved rhesus PK profiles, and the tertiary methyl ether was discovered as a potency-enhancing substituent which mitigated hERG activity. These investigations culminated in the selection of **30** (MK-2918) as a preclinical candidate for the treatment of acute migraine.

Acknowledgments

We thank the NMR, MS, PK support and analytical groups for their valuable assistance. We also thank Jim Hershey's group for performing the rhesus CIDV studies.

References and notes

1. Goadsby, P. J.; Lipton, R. B.; Ferrari, M. D. *N. Engl. J. Med.* **2002**, *346*, 257.
2. (a) Wackenfors, A.; Jarvius, M.; Ingemansson, R.; Edvinsson, L.; Malmsjo, M. *J. Cardiovasc. Pharmacol.* **2004**, *45*, 476; (b) Dodick, D.; Lipton, R. B.; Martin, V.; Papademetriou, V.; Rosamond, W.; VanDenBrink, A. M.; Loutfi, H.; Welch, K. M.; Goadsby, P. J.; Hahn, S.; Hutchinson, S.; Matchar, D.; Silberstein, S.; Smith, T. R.; Purdy, R. A.; Saiers, J. *Headache* **2004**, *44*, 414.
3. (a) van Rossum, D.; Hanisch, U.-K.; Quirion, R. *Neurosci. Biobehav. Rev.* **1997**, *21*, 649; (b) Poyner, D. R. *Pharmacol. Ther.* **1992**, *56*, 23.
4. (a) Durham, P. L. *Headache* **2008**, *48*, 1269; (b) Edvinsson, L. *Expert Opin. Ther. Targets* **2003**, *7*, 377; (c) Lassen, L. H.; Haderslev, P. A.; Jacobsen, V. B.; Iversen, H. K.; Sperling, B.; Olesen, J. *Cephalalgia* **2002**, *22*, 54.
5. Rudolf, K.; Eberlein, W.; Wolfhard, E.; Pieper, H.; Entzeroth, M.; Hallermayer, G.; Doods, H. *J. Med. Chem.* **2005**, *48*, 5921.
6. (a) 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; (b) Doods, H.; Hallermayer, G.; Wu, D.; Entzeroth, M.; Rudolf, K.; Engel, W.; Eberlein, W. *Br. J. Pharm.* **2000**, *129*, 420.
7. (a) Ho, T. W.; Ferrari, M. D.; Dodick, D. W.; Galet, V.; Kost, J.; Fan, X.; Leibensperger, H.; Froman, S.; Assaid, C.; Lines, C.; Koppen, H.; Winner, P. K. *Lancet* **2008**, *372*, 2115; (b) Ho, T. W.; Mannix, L.; Fan, X.; Assaid, C.; Furtek, C.; Jones, C.; Lines, C.; Rapoport, A. *Neurology* **2008**, *70*, 1305.
8. Williams, T. M.; Stump, C. A.; Nguyen, D. N.; Quigley, A. G.; Bell, I. M.; Gallicchio, S. N.; Zartman, C. B.; Wan, B.-L.; Della Penna, K.; Kunapuli, P.; Kane, S. A.; Koblan, K. S.; Mosser, S. D.; Rutledge, R. Z.; Salvatore, C.; Fay, J. F.; Vacca, J. P.; Graham, S. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2595.
9. Shaw, A. W.; Paone, D. V.; Nguyen, D. N.; Stump, C. A.; Burgey, C. S.; Mosser, S. D.; Salvatore, C. A.; Rutledge, R. Z.; Kane, S. A.; Koblan, K. S.; Graham, S. L.; Vacca, J. V.; Williams, T. M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4795.
10. (a) 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; (b) 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.
11. For the details of these assays see: Bell, I. M.; Graham, S. L.; Williams, T. M.; Stump, C. A. WO 2004/087649.
12. Aqueous solubilities at pH 7.4: telcagepant = 30 μg/mL; triazole **1** = 158 μg/mL.
13. As a general trend, fused heterocycles in this series with low permeability resulted in low oral exposures.
14. Paone, D. V.; Shaw, A. W. *Tetrahedron Lett.* **2008**, *49*, 6155.
15. 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.
16. Scheibye, S.; Pederson, B. S.; Lawesson, S. O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 229.
17. For additional synthetic details, see: 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.
18. All final compounds were characterized by ^{1}H NMR, HRMS, and HPLC.
19. Raab, C. E.; Butcher, J. W.; Connolly, T. M.; Karczewski, J.; Yu, N. X.; Staskiewicz, S. J.; Liverton, N.; Dean, D. C.; Melillo, D. G. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1692.
20. Burgey, C. S.; Potteiger, C. M.; Deng, J. Z.; Mosser, S. D.; Salvatore, C. A.; Yu, S.; Roller, S.; Kane, S. A.; Vacca, J. P.; Williams, T. M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6368.
21. Hershey, J. C.; Corcoran, H. A.; Baskin, E. P.; Salvatore, C. A.; Mosser, S.; Williams, T. M.; Koblan, K. S.; Hargreaves, R.; Kane, S. A. *Regul. Pept.* **2005**, *127*, 71.
22. Estimation of the oral bioavailability of alcohol metabolite **31** upon dosing of ether **30** is calculated as follows: F_{-OH} = (po normalized AUC **31** upon dosing of **30**)/ (iv normalized AUC **31** upon dosing of **31**).
23. Additions of both amino alcohols and amino ketones to thioamides were rapid, typically complete in <10 min. Cyclization of the intermediate amidine to **38** required and additional 18 h.