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Carbamates as potent calcitonin gene-related peptide antagonists with improved solution stability

Andrew P. Degnan [a,*], Charles M. Conway [b], Richard A. Dalterio [c], Robert Macci [c], Stephen E. Mercer [a], Richard Schartman [c], Cen Xu [b], Gene M. Dubowchik [a], John E. Macor [a]

[a] Neuroscience Discovery Chemistry, Bristol-Myers Squibb Research and Development, 5 Research Parkway, Wallingford, CT 06492-7660, USA
[b] Neuroscience Discovery Biology, Bristol-Myers Squibb Research and Development, 5 Research Parkway, Wallingford, CT 06492-7660, USA
[c] Pharmaceutical Candidate Optimization, Bristol-Myers Squibb Research and Development, 5 Research Parkway, Wallingford, CT 06492-7660, USA

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ABSTRACT

The calcitonin gene-related peptide (CGRP) receptor has been implicated in the pathogenesis of migraine. A class of urethanamide derivatives has been identified as potent inhibitors of the CGRP receptor. Compound **20** was found to be among the most potent (IC_{50} = 17 pM). It was shown to retain excellent aqueous solubility (>50 mg/mL, pH 7) while dramatically improving solution stability as compared to our previously disclosed development candidate, BMS-694153 (1).

Migraines are episodic headaches which typically last 4–72 h and may be quite severe.[1] The pain is often unilateral, throbbing, and accompanied by symptoms such as nausea and heightened sensitivity to light, sound, or odors. Migraine is the most common cause of recurrent moderate to severe headache. Nationally, migraines have a 1-year prevalence of 18% for women and 6% for men. The current standard of care, the triptans, are believed to act, in part, by the active, nonselective vasoconstriction of cranial vessels.[2] However, because they are nonselective vasoconstrictors, they are associated with a number of unpleasant cardiovascular side effects and are contraindicated in patients with hypertension or ischemic heart disease.[3]

Calcitonin gene-related peptide (CGRP), has been implicated in the pathogenesis of migraine.[4] Studies have shown that plasma levels of CGRP, a 37 amino-acid peptide, are elevated during migraine attacks.[5] Moreover, it has been shown that intravenous (iv) administration of CGRP causes migraine-like headaches in migraneurs.[6] It has also been demonstrated that iv administration of the potent CGRP receptor antagonist BIBN4096BS in migraneurs was accompanied by the alleviation of pain without the cardiovascular side effects associated with the use of triptans.[7] Although BIBN4096BS effectively demonstrated the first clinical proof of concept, evidence of significant further development of the molecule has been lacking. In this context, we undertook a medicinal chemistry effort to identify a potent CGRP antagonist that could be administered by a more convenient route.[8]

In an earlier Letter, we disclosed our intranasal (IN) development candidate BMS-694153 (**1**).[9] Compound **1** had a number of desirable properties to support its selection. It was found to be a potent competitive antagonist (IC_{50} = 26 pM). Additionally, it had a favorable preclinical toxicology profile and outstanding aqueous solubility (>500 mg/mL @ pH 7). Since we were pursuing an IN formulation, solution stability had to be sufficient to support an acceptable shelf life. Solution stability studies over time found that three significant degradants were generated upon standing as an aqueous solution (0.05 M, pH 5, 40 °C, 12 weeks) (Fig. 1). The impurity formed to the greatest extent was that arising from oxidation of the fluorodihydroquinazolinone (2%) to give hydroxylated derivative **2**. Additionally, hydrolysis of the amide to give acid **3** was also observed. Acid **3** underwent further hydrolysis to compound **4** (presumably catalyzed by the newly formed adjacent carboxylic acid), bringing the total hydrolytic degradation to 0.6%. Although this stability profile met our development criteria, we targeted improved solution stability for future development candidates.

It was thought that some pendant functionality may be assisting in the unanticipated hydrolysis. For example, intramolecular protonation of the amide by the adjacent urea as depicted in Scheme 1 (path A) might activate the amide toward nucleophilic attack by water to give the corresponding acid. Alternately, cleavage of the amide bond might be assisted by internal nucleophilic

* Corresponding author. Tel.: +1 203 677 5750; fax: +1 203 677 7884.
E-mail address: andrew.degnan@bms.com (A.P. Degnan).

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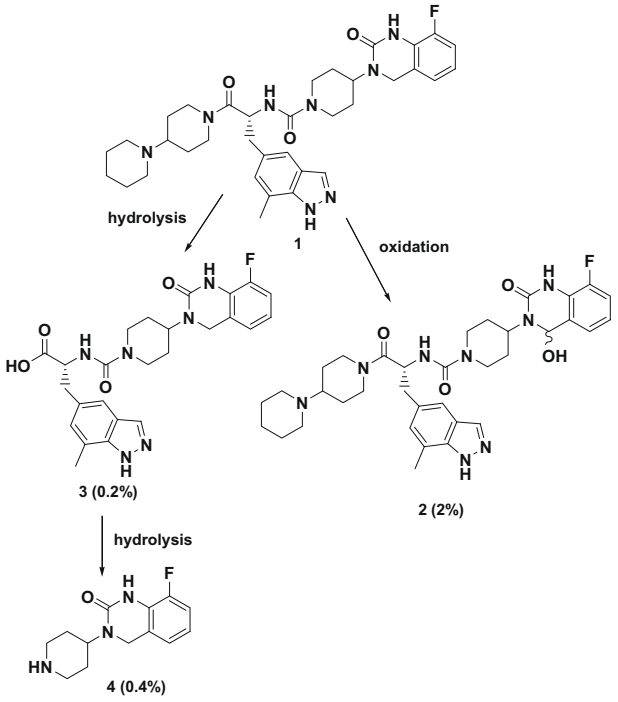
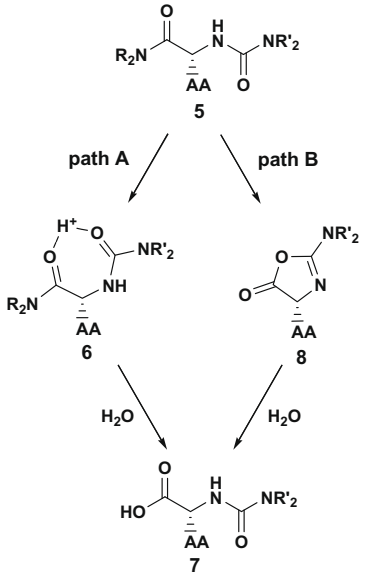


Figure 1. Compound **1** and aqueous degradation products.



Scheme 1. Possible degradation pathways.

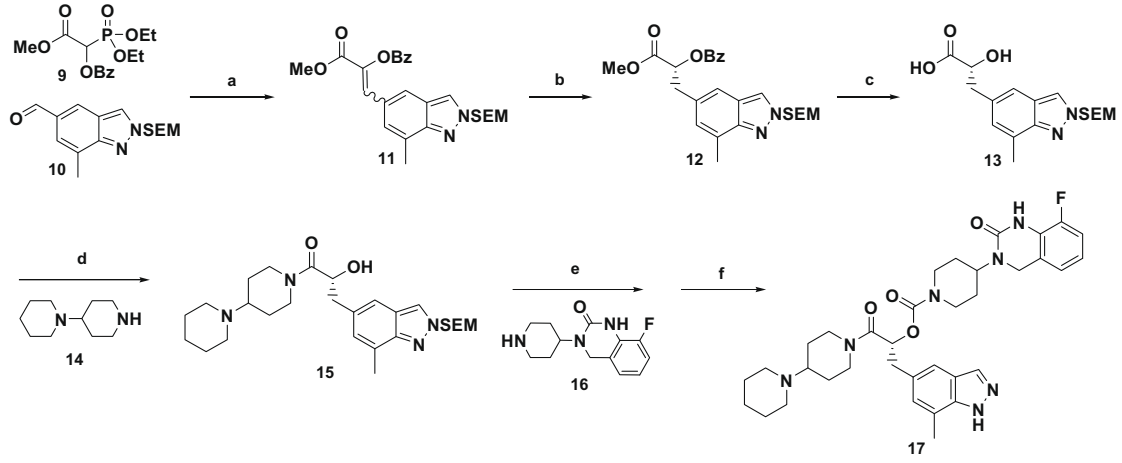
attack of the urea to give oxazolone **8** which can undergo hydrolysis to give an identical carboxylic acid (path B).

In either event, we sought to reduce this undesirable hydrolysis by converting the urea to a less basic and/or less nucleophilic functionality such as a carbamate. This perturbation would decrease both the nucleophilicity and Brønsted basicity of the compounds while maintaining the Lewis basic site (assumed to be a hydrogen bond acceptor) that was thought to be critical for maximum potency.

The synthesis of the carbamate analogue of **1** began with a Horner–Wadsworth–Emmons olefination of aldehyde **10**[10] with phosphonate **9**[11] (Scheme 2). The reaction gave olefin **11** as a 2:1 mixture of *E*- and *Z*-isomers which were used without separation. This mixture was inconsequential as both isomers were reduced with high levels of enantioselectivity to afford the same protected α-hydroxy ester (**12**) in 96% ee. Cleavage of both esters was achieved in one chemical step by the action of lithium hydroxide to give α-hydroxy acid **13**. The amide was formed by the action of PyBOP to give **15**. The carbamate was then prepared by conversion of the alcohol to a *p*-nitrophenylcarbonate, followed by treatment with piperidine **16** to furnish the carbamate in 60% yield. Finally, removal of the SEM protecting group was cleanly accomplished by the action of trifluoroacetic acid in dichloromethane to give analogue **17**.

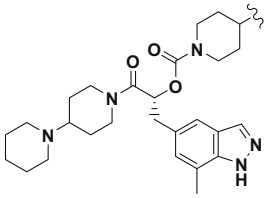
Our efforts were rewarded when it was found that **17** had outstanding in vitro potency at the CGRP receptor (IC_{50} = 11 pM). Structure–activity relationships in this new chemotype were defined by generating two small libraries—first optimizing the right hand heterocycle and subsequently varying the amide portion of the molecule. Since oxidation of the quinazolinone was the major degradant observed in solution stability studies, we focused most of our efforts in the first library on the incorporation of electron deficient heterocycles in an effort to reduce hydroxylation (Table 1). A number of different heterocycles were found to maintain outstanding potency at the receptor.

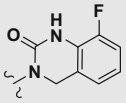
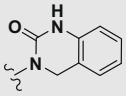
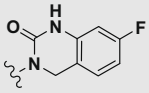
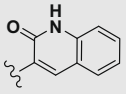
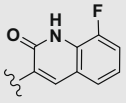
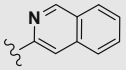
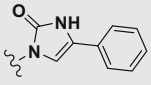
Among the most potent analogues was quinolinone **20** (IC_{50} = 17 pM). In addition to its remarkable potency, this compound



Scheme 2. Reagents and conditions: (a) LiCl/TMG/THF (94%); (b) [(2*R*,5*R*)-Et-DuPhosRh]BF_4/H_2 (60 psi)/DCM/MeOH (98%); (c) LiOH/THF/MeOH/H_2O (100%); (d) PyBOP/DIEA/DMF/DCM (91%); (e) *p*-nitrophenylchloroformate/DIEA/DMAP/DCM then **16**/DIEA/DMF (60%); (f) TFA/DCM (67%).

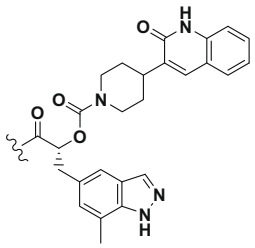
Table 1
Effect of the right-hand heterocycle on human CGRP receptor binding potency

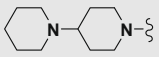
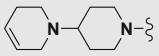
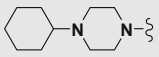
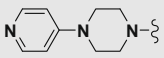
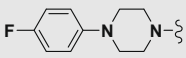


Compound	Heterocycle	CGRP IC_{50} (nM)
17		0.011
18		0.010
19		0.022
20		0.017
21		0.057
22		0.18
23		0.068

had excellent aqueous solubility (>50 mg/mL, pH 7, amorphous material) and no oxidizable benzylic methylene. As such, the quinolinone was incorporated into the subsequent amide library.

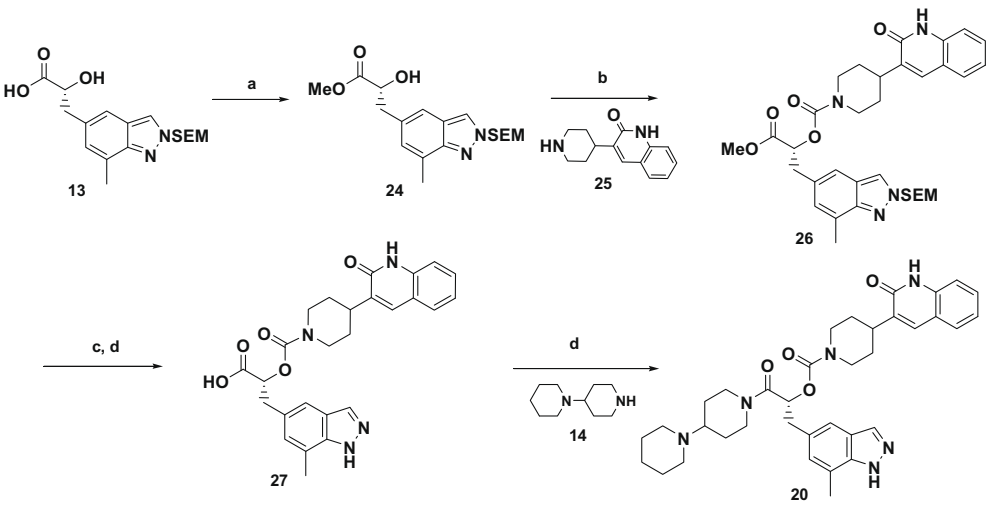
Table 2
Effect of the left-hand amide on receptor potency



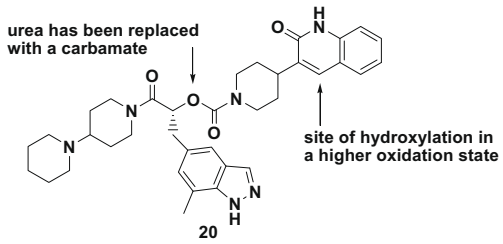
Compound	Amine	CGRP IC_{50} (nM)
20		0.017
28		1.8
29		0.053
30		0.044
31		0.020
32		0.063
33		0.13

The route developed to allow the incorporation of a variety of amides at a later stage of the synthetic sequence is shown in Scheme 3. Acid **13** was first selectively protected as its methyl ester by treatment with diazomethane. The alcohol was converted to the *p*-nitrophenylcarbonate and treated with piperidine **25** to afford the corresponding carbamate (**26**). Removal of the indazole protecting group and hydrolysis of the ester gave acid **27**. Finally, amines were efficiently coupled by the action of PyBOP to afford analogues in a single chemical step.

A number of amides were identified that maintained picomolar potencies (Table 2). However, none were found to be more potent than the original 4-piperidinyl-piperidine. Additionally, compounds



Scheme 3. Reagents and conditions: (a) CH_2N_2/Et_2O (95%); (b) *p*-nitrophenylchloroformate/DIEA/DMAP/DCM then **25**/DIEA/DMF (86%); (c) TFA/DCM (99%); (d) LiOH/THF/MeOH/H_2O (89%); (d) PyBOP/DIEA/DMF/DCM (88%).



Compound	1	20
Hydrolytic Stability[a] (% remaining)	56%	99%
Oxidative Stability[b] (% remaining)	72%	97%

Figure 2. Comparison of the solution stability of compounds **1** and **20**. (a) 0.15 mg/mL in water, pH 4, 60 °C, 4 weeks. (b) 0.15 mg/mL in water, free-radical generator added (AAPH, 5 equiv), pH 4, 40 °C, 48 h.

that incorporated this fragment were routinely found to have improved aqueous solubility and microsomal stability over other amides in the library (data not shown).

With optimized lead **20** in hand, we sought to compare its solution stability to that of our earlier clinical candidate. Conditions were used which accelerated the degradation of **1** so that the compounds could be more readily differentiated. Further, these conditions allowed us to independently look at the hydrolytic degradation of the amide apart from the oxidative degradation of the dihydroquinazolinone. The results of these studies are shown in Figure 2. By exchange of the urea for a carbamate, hydrolytic stability was found be greatly improved in **20** as compared to compound **1** under the conditions examined. By exchange of the quinazolinone of **1** for the quinolinone of **20**, thereby removing the benzylic methylene at which oxidation had occurred, the oxidative stability of the analogue was also greatly improved (97% remaining vs 72% remaining).

In conclusion, we have demonstrated that the exchange of the backbone urea of **1** (IC_{50} = 26 pM) for a carbamate in **17** was well tolerated, giving compounds with modestly improved potency (IC_{50} = 11 pM). Similar potency (IC_{50} = 17 pM) was observed upon exchange of the fluorodihydroquinazolinone for a quinolinone to give compound **20**. Compound **20** showed greatly improved solution stability, generating significantly reduced amounts of degradants in solution. In addition to its outstanding potency and improved solution stability, **20** had excellent solubility (>50 mg/mL, pH 7, amorphous material). Further characterization of this compound and additional SAR will be reported in due course.

References and notes

1. Beers, M. H., Porter, R. S., Jones, T. V., Kaplan, J. L., Berkwitz, M.; Eds.; "*Migraine*" *in Merck Manual*, 18th ed.; Merck Research Laboratories: Whitehouse Station, NJ, 2006; pp 1847.
2. Edvinsson, L.; Uddman, E.; Wackenfors, A.; Davenport, A.; Longmore, J.; Malmsjö, M. *Clin. Sci.* **2005**, *109*, 335.
3. Goadsby, P. J.; Lipton, R. B.; Ferrari, M. D. *N. Eng. J. Med.* **2002**, *346*, 257.
4. (a) Goadsby, P. J. *Drugs* **2005**, *65*, 2557; (b) Edvinsson, L. *Cephalalgia* **2004**, *24*, 611; (c) Williamson, D. J.; Hargreaves, R. *J. Microsc. Res. Tech.* **2001**, *53*, 167.
5. (a) Goadsby, P. J.; Edvinsson, L.; Ekman, R. *Ann. Neurol.* **1990**, *28*, 183; (b) Goadsby, P. J.; Edvinsson, L. *Ann. Neurol.* **1993**, *33*, 48.
6. Lassen, L. H.; Haderslev, P. A.; Jacobsen, V. B.; Iversen, H. K.; Sperling, B.; Olesen, J. *Cephalalgia* **2002**, *22*, 54.
7. Olesen, J.; Diener, H. C.; Husstedt, I. W.; Goadsby, P. J.; Hall, D.; Meier, U.; Pollentier, S.; Lesko, L. M. *N. Eng. J. Med.* **2004**, *350*, 1104.
8. Oral CGRP anatagonist medicinal chemistry efforts have been described in: (a) Bell, I. M.; Bednar, R. A.; Fay, J. F.; Gallicchio, S. N.; Hochman, J. H.; McMasters, D. R.; Miller-Stein, C.; Moore, E. L.; Mosser, S. D.; Pudvah, N. T.; Quigley, A. G.; Salvatore, C. A.; Stump, C. A.; Theberge, C. R.; Wong, B. K.; Zartman, C. B.; Zhang, X.-F.; Kane, S. A.; Graham, S. L.; Vacca, J. P.; Williams, T. M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 6165; (b) 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. Degnan, A. P.; Chaturvedula, P. V.; Conway, C. M.; Cook, D. A.; Davis, C. D.; Denton, R.; Han, X.; Macci, R.; Mathias, N. R.; Moench, P.; Pin, S. S.; Ren, S. X.; Schartman, R.; Signor, L. J.; Thalody, G.; Widmann, K. A.; Xu, C.; Macor, J. E.; Dubowchik, G. M. *J. Med. Chem.* **2008**, *51*, 4858.
10. Luo, G.; Chen, L.; Dubowchik, G. *J. Org. Chem.* **2006**, *71*, 5392.
11. Burk, M. J.; Kalberg, C. S.; Pizzano, A. *J. Am. Chem. Soc.* **1998**, *120*, 4345.