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Discovery of a series of potent, orally active α,α-disubstituted piperidine NK_1 antagonists ☆

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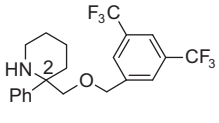
ABSTRACT

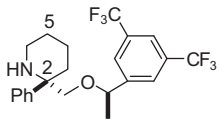
Modification of prototype NK_1 antagonist **2** resulted in the synthesis of a series of simple amides **6** and retroamides **9**. These compounds were shown to be potent and orally active NK_1 antagonists.

The neurokinin 1 (NK_1) receptor belongs to the family of G-protein coupled receptors (GPCRs). This receptor mediates the action of substance P and other tachykinins in both the central and peripheral nervous systems. Therefore, the NK_1 receptor antagonists may have therapeutic values in treating emesis, anxiety, depression, inflammation, and pain.[1–4] Recently, FDA approved Emend® for the treatment of chemotherapy-induced nausea and vomiting (CINV). This demonstrated the clinic utility of NK_1 antagonists and several other compounds have undergone clinical trials for a variety of medical indications.[5]

As part of the search for novel NK_1 antagonists, we became interested in the 2,2-disubstituted piperidine **1** (Fig. 1).[6] Our own work in this area resulted in the discovery of a novel chemistry of metallation of *N*-Boc-2-phenylpiperidine and the application of this chemistry to a target-oriented synthesis of a non-racemic NK_1 antagonist **2**.[7] Shortly after the establishment of **2** as our program lead compound for in-depth medicinal study of NK_1 antagonists, we also accomplished two complimentary-modular stereoselective asymmetric syntheses[8] of **2**. Armed with this chemistry, we undertook an SAR investigation of **2** to improve its overall biological profiles. In this Letter, we would like to disclose some amide and retroamide derivatives that demonstrated excellent in vitro and in vivo activity and pharmacokinetic profiles.



1 Ki (NK_1) = 1.0 nM



2 Ki (NK_1) = 0.3 nM

Figure 1.

When **2** was first discovered, it was shown that this compound had a poor pharmacokinetic (PK) profile and poor in vivo activity in gerbil foot thumping (GFT) model. We were inspired by the earlier work on the 4,4-substituted piperidine NK_1 antagonist[9] and decided to introduce some polar groups to the 5 position of piperidine ring. The synthesis commenced from the key intermediate **3** from our asymmetric synthesis of **2**.[8] The olefin was ozonolyzed followed by TBAI reduction to afford the corresponding aldehyde, which upon treatment of Wittig reagent methyl 2-(*tert*-butoxycarbonylamino)-2-(dimethoxyphosphoryl)acetate and DBU to afford **4**. Compound **4** was then hydrogenated and subsequently reacted with HCl to remove two nitrogen protecting groups. Further treatment with base resulted in cyclization to lactam **5**. Subsequent reduction using LAH/$AlCl_3$ produced a diamine which was selectively acylated at the primary amine to afford a series of amides. Initially, the mixture of diamines was acetylated to afford a pair of diastereomers **6a** and **6b**, which were then separated by HPLC. The relative stereochemistry of these amides was determined by NOE study (Scheme 1).

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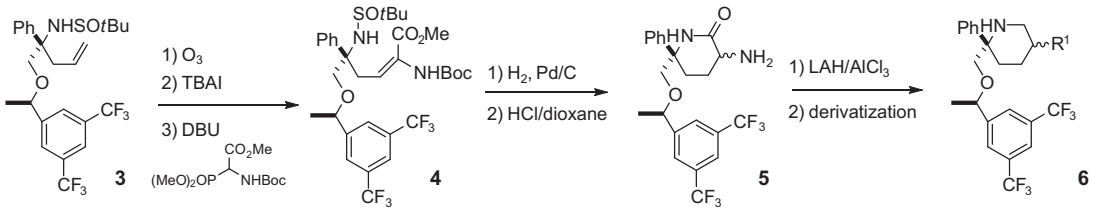
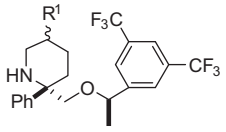
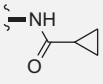
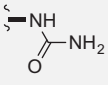
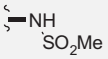


Scheme 1.

Although the in vitro NK_1 potencies[10] of the two isomers were similar, the in vivo activity showed marked difference. The (*R*) isomer **6a** was much more potent in GFT assay[11] with better rat PK profile,[12] therefore, the subsequent study was concentrated on the (*R*) derivatives. It was interesting to note that although the binding activities were similar throughout the series, the in vivo GFT activity deteriorated with the increase of molecular weight from **6a** to **6c**–**6e**. Unlike in vitro assay, the potency of GFT assay also displayed remarkable preference towards amide moiety, since the ureas **6f** and **6g** were less potent. Similarly, sulfonamide **6h** and imine mimics of carbonyl analogs **6i** and **6j** reduced GFT activity dramatically (Table 1).

Table 1

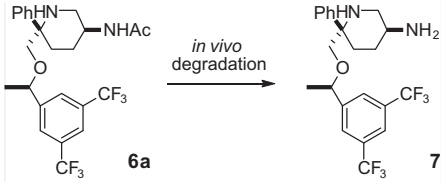


Entry	R^1	K_i (NK_1) (nM)	GFT at 4 h	Rat AUC (0–6, po) at 10 mpk ng h/ml
6a		0.15	100% at 1 mpk 99% at 0.3 mpk 83% at 0.1 mpk	10,040 $T_{1/2}$ = 3.2 h, BA = 63%
6b		0.35	76% at 1 mpk 36% at 0.3 mpk	795
6c		0.29	100% at 1 mpk 93% at 0.3 mpk 50% at 0.1 mpk	1947
6d		0.23	100% at 1 mpk 79% at 0.3 mpk	5263
6e		0.26	61% at 1 mpk	13,828
6f		0.69	96% at 1 mpk 6% at 0.3 mpk	6035
6g		0.59	86% at 1 mpk 71% at 0.3 mpk	ND
6h		1.03	90% at 1 mpk 25% at 0.3 mpk	5943
6i		0.33	5% at 1 mpk	ND
6j		0.28	37% at 1 mpk	ND

The most potent acetamide **6a** was investigated extensively. Additional PK study established its half-life as 3.2 h and bioavailability at 63% in rat. However, it was found that **6a** was metabolized in vivo to diamine **7**, which, as shown in Scheme 2, accumulated in rat brain (Fig. 2). This phenomenon has been observed for a number of dibasic amines and was believed to likely cause phospholipidosis.[13–15]

Confronted with undesirable metabolism of amide analogs, we sought to eliminate the liability by introducing retroamide analogs. If retroamides undergo similar in vivo degradation, the metabolites would be a series of aminoacids, which should be eliminated more readily. The retroamides were synthesized from the common intermediate **3** through an alkylation/olefin metathesis[16] as the key step for piperidine ring closure. Further elaboration of the intermediate **8** afforded the desired retroamides **9** (Scheme 3).

The retroamides **9** were generally potent NK_1 antagonists. Unlike the amide analogs, the two diastereomeric retroamide series did not show a profound difference in their in vivo activity. However, in the same diastereomer series, the interesting trend of decreasing in vivo activity with increase of molecular weight was observed again. The lead analog **9a**, demonstrated most potent in vitro and in vivo activity, with a good PK profile and bioavailability of 65% in rat (Table 2).



Scheme 2.

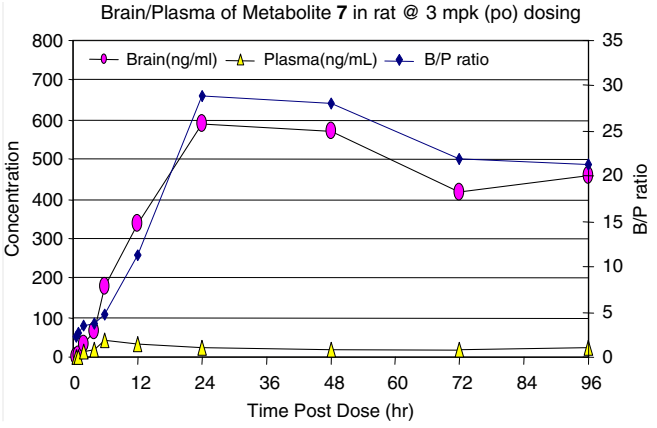
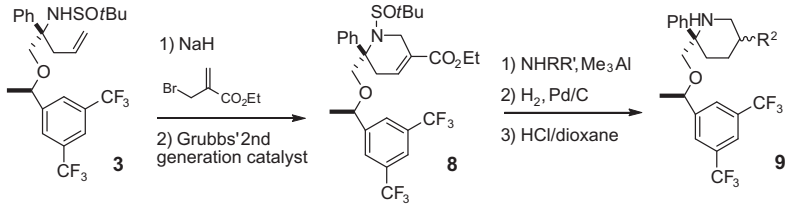
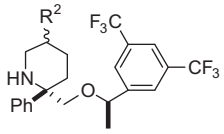


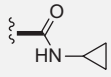
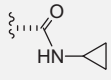
Figure 2. Brain/plasma of metabolite **7** in rat at 3 mpk (po) dosing.



Scheme 3.

Table 2



Entry	R^2	K_i (NK_1) (nM)	GFT at 4 h	Rat AUC (po) ng h/ml
9a		0.22	92% at 1 mpk 82% at 0.3 mpk	2600 at 5 mpk, 24 h $T_{1/2}$ = 3.4 h, BA = 68%
9b		0.19	90% at 1 mpk 75% at 0.3 mpk	1693 at 10 mpk, 6 h
9c		0.26	91% at 1 mpk 29% at 0.3 mpk	ND
9d		0.56	80% at 1 mpk	166 at 10 mpk, 6 h
9e		0.37	92% at 1 mpk 28% at 0.3 mpk	3676 at 10 mpk, 6 h
9f		1.13	78% at 1 mpk	ND
9g		0.34	45% at 1 mpk	1939 at 10 mpk, 6 h
9h		0.40	69% at 1 mpk	ND

In conclusion we presented two series of piperidine NK_1 antagonists, which demonstrated potent in vivo and in vitro activity. They also have distinct metabolic pathways. Further optimization of these analogs to obtain drug candidates with optimum in vitro, in vivo and pharmacokinetic properties will be reported in due course.

Acknowledgments

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References and notes

1. Jones, S.; Gibbins, J. M. *Curr. Opin. Pharmacol.* **2008**, *8*, 114.
2. Alvaro, G.; Di Fabio, R. *Curr. Opin. Drug Discovery Dev.* **2007**, *10*, 613.
3. Duffy, R. A. *Exp. Opin. Emerg. Drugs* **2004**, *9*, 9.
4. Albert, J. S. *Exp. Opin. Ther. Pat.* **2004**, *14*, 1412.
5. Dando, T. M.; Perry, C. M. *Drugs* **2004**, *64*, 777.
6. Harrson, T.; Willaims, B. J.; Swain, C. J. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2733.
7. Xiao, D.; Lavey, B. J.; Palani, A.; Wang, C.; Aslanian, R. G.; Kozlowski, J. A.; Shih, N. Y.; McPhail, A. T.; Randolph, G. P.; Lachowicz, J. E.; Duffy, R. A. *Tetrahedron Lett.* **2005**, *46*, 7653.
8. Xiao, D.; Wang, C.; Palani, A.; Reichard, G.; Aslanian, R.; Shih, N.-Y.; Buevich, A. *Tetrahedron: Asymmetry* **2006**, *17*, 2596.
9. Stevenson, G. I.; MacLeod, A. M.; Huscroft, I.; Cascieri, M. A.; Sadowski, S.; Baker, R. *J. Med. Chem.* **1995**, *38*, 1264.
10. NK_1 assay: Binding data are the average of two or three independent determinations. Receptor binding assays were performed on membrane preparations from CHO cells in which recombinant human NK_1 receptors were expressed. [^{3}H]-Sar-Met substance P was used as the ligand for the NK_1 assay, at concentrations near the experimentally derived K_d value. K_i values were obtained using the Cheng and Prusoff equation. Cascieri, M. A.; Macleod, A. M.; Underwood, D.; Shiao, L. L.; Ber, E.; Sadowski, S.; Yu, H.; Merchant, K. J.; Swain, C. J.; Strader, C. D.; Fong, T. M. *J. Biol. Chem.* **1994**, *269*, 6587.
11. For determination of Gerbil Foot Thump (GFT) activity: The NK_1 agonist GR73632 (3 pmol in 5 μl) was administered centrally to female Mongolian gerbils via icv injection. Immediately following recovery from the anesthesia, gerbils were placed into clear Plexiglas boxes for 5 min, and the duration of foot tapping was measured. Foot tapping was defined as rhythmic, repetitive tapping of the hind feet. NK_1 antagonists were administered orally in 0.4% methylcellulose in distilled water at the dose indicated at various pretreatment times prior to injection of GR73632. Data are expressed as a percent decrease (% inhibition) in the amount of time spent foot tapping compared to vehicle-treated controls. Rupniak, N. M. J.; Williams, A. R. *Eur. J. Pharmacol.* **1994**, *265*, 179.
12. The rat PK assay was run at 10 mpk (unless otherwise specified) using oral dosing with 20% HPBCD as vehicle. AUC was determined from 0 to 6 h. For reference: Cox, K. A.; Dunn-Meynell, K.; Korfmacher, W. A.; Broske, L.; Nomeir, A. A.; Lin, C. C.; Cayen, M. N.; Barr, W. H. *Drug Discovery Today* **1999**, *4*, 232.
13. Bonaventure, P.; Letavic, M.; Dugovic, C.; Wilson, S.; Aluisio, L.; Pudiak, C.; Lord, B.; Mazur, C.; Kamme, F.; Nishino, S.; Carruthers, N.; Lovenberg, T. *Biochem. Pharmacol.* **2007**, *73*, 1084.
14. Gum, R. J.; Hickman, D.; Fagerland, J. A.; Heindel, M. A.; Gagne, G. D.; Schmidt, J. M.; Michaelides, M. R.; Davidsen, S. K.; Ulrich, R. G. *Biochem. Pharmacol.* **2001**, *62*, 1661.
15. Ruben, Z.; Dodd, D. C.; Rorig, K. J.; Anderson, S. N. *Toxicol. Appl. Pharmacol.* **1989**, *97*, 57.
16. Choi, T.-L.; Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1277.