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Discovery of a novel, potent and orally active series of γ-lactams as selective NK_1 antagonists

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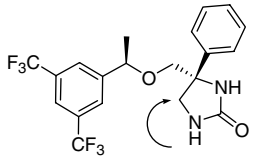
ABSTRACT

Strategic replacement of the nitrogen of the lead compound **1** in the original cyclic urea series with a carbon resulted in the discovery of a novel, potent and orally more efficacious γ-lactam series of selective NK_1 antagonists. Optimization of the lactam series culminated in the identification of compounds with high binding affinity and excellent oral CNS activity.

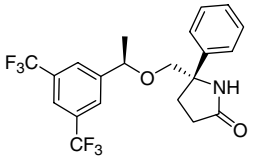
The mammalian tachykinin Substance P (SP) has been implicated in a number of pathological conditions in the central nervous system (CNS) and peripheral tissues including pain, inflammation, depression, anxiety, emesis and nausea.[1] SP preferentially binds to the NK_1 receptor. Therefore, an antagonist of the NK_1 receptor has potential therapeutic use in the treatment of a variety of central and peripheral diseases.

Recently, we reported a novel series of cyclic urea derivatives as potent and selective NK_1 receptor antagonists that are orally active and have good CNS penetration.[2] SAR evaluation in this series led to the identification of a five-membered unsubstituted urea analogue **1** as the lead compound.[2b] Compound **1** exhibited sub-nanomolar binding affinity for the NK_1 receptor (K_i = 0.6 nM) and moderate oral CNS activity (57% inhibition of foot tapping at 1 mg/kg po following a 4 h pretreatment time) in the in vivo gerbil foot tapping (GFT) inhibition assay.[3]

Metabolism studies of **1** indicated hydroxylation at the carbon next to urea nitrogen as the major route of metabolism. In an effort to alter the metabolic processing of the urea ring, while improving the biology of the compound, we sought to replace the urea nitrogen adjacent to the site of oxidative metabolism of **1** with a carbon. The resulting γ-lactam compound **2** was prepared and evaluated for biological response.[5]



1



2

The synthesis of the unsubstituted γ-lactam **2** is outlined in Scheme 1. Hydrolysis of chiral amino amide **3**[6] to amino acid by heating with barium hydroxide, followed by treatment with Boc-anhydride provided Boc-protected amino acid **4**.[7] Reaction of **4** with triphosgene afforded useful Boc–NCA intermediate **5**.[8] Subsequent reduction of **5** with lithium borohydride followed by oxidation with sodium hypochlorite provided aldehyde **6**. Horner-Emmons olefination of **6** with methyl diethylphosphonoacetate followed by hydrogenation gave the compound **7**. Cyclization of **7** in presence of trimethylaluminum and subsequent deprotection provided the desired γ-lactam **2**.[9]

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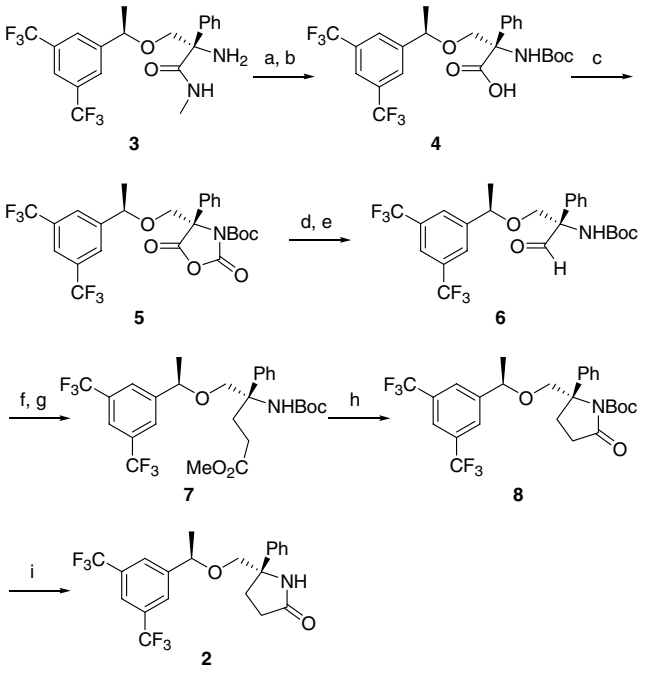
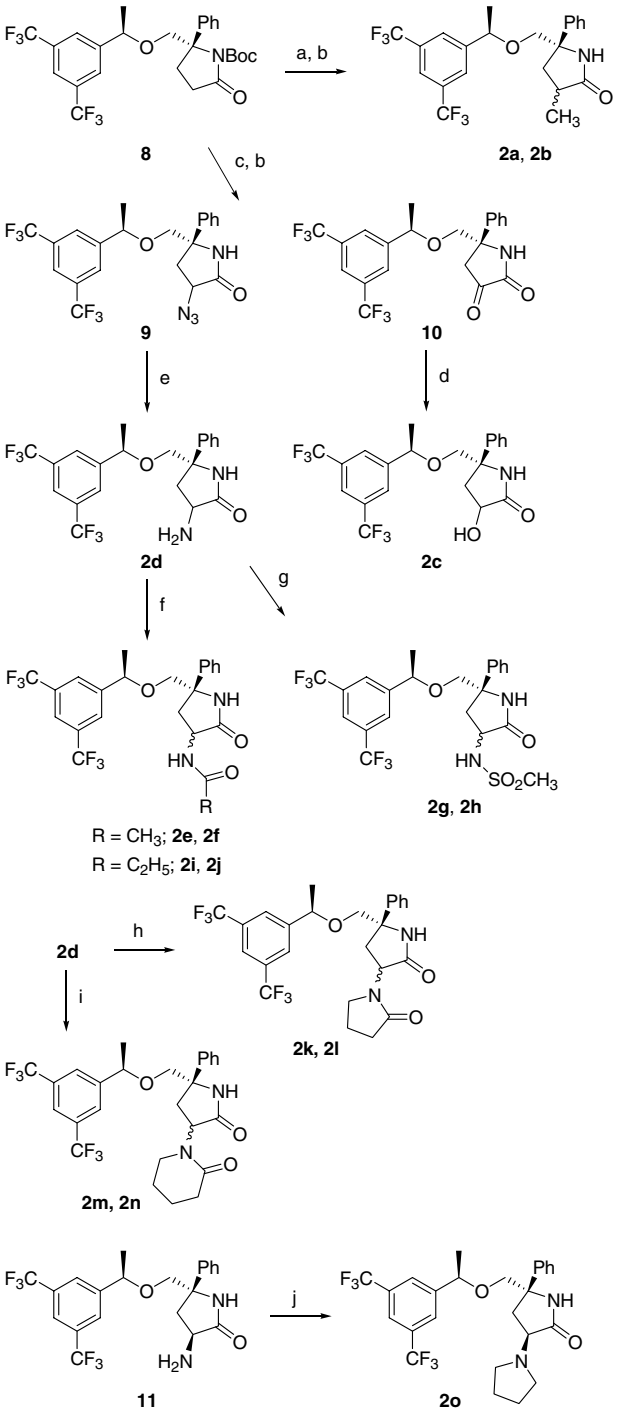


Scheme 1. Reagents and conditions: (a) $Ba(OH)_2$, H_2O, 156 °C, 72 h; (b) $(Boc)_2O$, THF, rt, 18 h, 65% over two steps; (c) $(CCl_3O)_2CO$, *i*-Pr_2EtN, CH_2Cl_2, 0 °C, 15 min, then rt, 18 h; (d) $LiBH_4$, THF, 0 °C, 15 min, then rt, 18 h; (e) TEMPO, NaOCl, NaBr, satd aq $NaHCO_3$, EtOAc, 0 °C, 1.5 h, 92% over three steps; (f) $(C_2H_5O)_2P(O)CH_2CO_2CH_3$, NaH, THF, 0 °C, 15 min, then rt, 2.5 h, 92%; (g) H_2, 10% Pd/C, 1 atm, rt, 18 h, 91%; (h) $(CH_3)_3Al$, toluene, 0 °C, 15 min, then rt, 30 min, 84%; (i) TFA, CH_2Cl_2, rt, 2.5 h, 84%.

γ-Lactam **2** retained high NK_1 binding affinity (K_i = 1 nM) and maintained good selectivity over NK_2 and NK_3 receptors.[10] Moreover, lactam **2** demonstrated superior oral activity compared to **1** (GFT inhibition at 1 mg/kg: **2** = 92, 78, 47%; **1** = 35, 57, 48% following 2, 4, 6 h pretreatment times, respectively).

We next investigated substitutions effect at the carbon alpha to the carbonyl of the γ-lactam **2**. The syntheses of the α-substituted γ-lactam analogues **2a**–**o** are shown in Scheme 2. Alkylation of Boc-protected lactam **8** with methyl iodide using LDA followed by separation of isomers by column chromatography and subsequent deprotection with trifluoroacetic acid afforded α-methyl substituted lactams **2a** and **2b**. Treatment of the anion derived from **8** with trisyl azide and subsequent deprotection provided the desired azide substituted compound **9** and a side product **10**. Reduction of **10** with lithium borohydride yielded a diastereomeric mixture of hydoxy-lactam **2c**. Hydrogenation of azide-lactam **9** afforded amino-lactam **2d** as a mixture of diastereomers. Acylation of **2d** with acetyl chloride and propionyl chloride followed by separation of isomers provided compounds **2e**, **2f** and **2i**, **2j**, respectively. Similarly, treatment of amine **2d** with methanesulfonyl chloride and separation of isomers afforded compounds **2g** and **2h**. Alkylation and subsequent cyclization of amine **2d** with ethyl 4-bromobutyrate in presence of trimethylaluminum followed by separation of isomers by HPLC on a Chiracel OD® column afforded five-membered cyclic amide substituted analogues **2k** and **2l**. Acylation of amine **2d** with 5-chlorovaleryl chloride followed by subsequent cyclization upon heating with sodium hydride in THF at 60 °C provided six-membered cyclic amide substituted analogues **2m** and **2n**. Cyclization of amine **11** with 1,4-dibromobutane afforded cyclic amine compound **2o**.

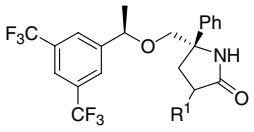
The in vitro NK_1 receptor binding and in vivo GFT inhibition data for α-substituted γ-lactams **2a–o** are listed in Table 1. All the compounds except two (**2c** and **2d**) were tested as single isomer.[12] It can be seen that high affinity is generally achieved, most

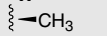
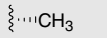
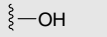
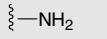
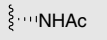
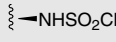
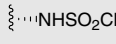
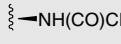
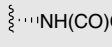
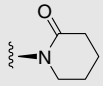
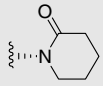


Scheme 2. Reagents and conditions: (a) i—0.5 M LDA, THF, −78 °C, 1 h, then CH_3I, ii—separation of isomers; (b) 4 M HCl/dioxane, CH_2Cl_2, 0 °C, 3 h, **2a** (17%) and **2b** (36%) over two steps; (c) 0.5 M KHMDS, THF, −78 °C, 30 min, trisyl azide, −78 °C, 4 h, AcOH, separate desired two compounds, then step b, **9** (30%) and **10** (22%) over two steps; (d) $LiBH_4$, THF, rt, 6 h, 83%; (e) H_2, 10% Pd/C, 1 atm, rt, 24 h, 68%; (f) i—RCOCl, *i*-Pr_2EtN, CH_2Cl_2, 0 °C, 15 min, then rt, 18 h, ii—separation of isomers; (g) CH_3SO_2Cl, *i*-Pr_2EtN, CH_2Cl_2, 0 °C, 15 min, then rt, 2 h, **2g** (39%) and **2h** (28%); (h) i—2 M $AlMe_3$, toluene, 0 °C to rt, 15 min, ethyl 4-bromobutyrate, 100 °C, 18 h; ii—separation of isomers by HPLC on a Chiralcel OD® column eluting with 10% hexane/90% IPA, **2k** (35%) and **2l** (18%); (i) i—5-chlorovaleryl chloride, Et_3N, CH_2Cl_2, 0 °C, 5 min, then rt, 18 h, ii—NaH, THF, 0 °C, 5 min, then 60 °C, 5 h; iii—separation of isomers by HPLC on a Chiralcel OD® column eluting with 10% hexane/90% IPA, **2m** (42%) and **2n** (19%); (j) 1,4-dibromobutane, toluene, 110 °C, 48 h, 36%.

compounds having a K_i below 1 nM. α-Substitution by a methyl group provided diastereomers **2a** and **2b**. Diastereomer **2a** having

Table 1
NK_1 receptor binding affinity and GFT inhibition for compounds **2a–o**



Compound[a]	R^1	NK_1[b] K_i (nM)	GFT[c] (% inh.)		
			t = 2 h	t = 4 h	t = 6 h
2	–H	0.6	92	78	47
2a		0.7	77	85	44
2b		2.0	11	2	36
2c		0.5	27	35	1
2d		0.4	5	13	11
2e		0.3	94	94	91
2f		0.9	80	97	71
2g		0.6	10	58	43
2h		2.6	0	15	0
2i		0.3	84	97	90
2j		0.3	83	16	19
2k		0.2	100	100	98
2l		0.5	49	46	39
2m		0.2	74	37	63
2n		0.2	20	26	56
2o		0.4	78	60	45

[a] Compounds **2c** and **2d** are mixture of diasteromers; all other analogues are single isomer.
[b] See Ref. 13.
[c] See Ref. 3.

a *cis* configuration of methyl group relative to the phenyl group exhibited better binding and GFT inhibition activity than the diastereomer **2b**. Though methyl substituted lactam **2a** possessed good potency and oral efficacy, it did not display any advantage over the unsubstituted lactam lead compound **2**.

We next evaluated the effect of α-substitution by polar groups. Introduction of a hydroxyl group (**2c**) and an amino group (**2d**) at the α-position slightly improved the NK_1 affinity compared to the lead compound **2** but resulted in significantly reduced GFT inhibition activity. The acetylation of the amino group of compound **2d** provided compounds **2e** and **2f** with high NK_1 affinity (**2e**, K_i = 0.3 nM and **2f**, K_i = 0.9 nM) and excellent GFT profile (**2e**, >90% inhibition and **2f**, >70% inhibition following 2–6 h pretreatment). Surprisingly, methyl sulfonamides **2g** and **2h** did not show good in vivo activity. Extension of methyl to ethyl amides **2i** and **2j** retained excellent in vitro activity (K_i = 0.3 nM for both). Interestingly, these diastereomers showed different GFT profile despite the same binding affinity. Diastereomer **2i** having ethyl amide group *cis* to the phenyl group exhibited superior GFT inhibition activity than the other diastereomer **2j**.

In addition to the acyclic, the cyclic amides such as lactams **2k–n** were also found to be well tolerated. Compared to six-membered cyclic amides **2m** and **2n**, corresponding five-membered cyclic amides **2k** and **2l**, respectively, demonstrated better GFT inhibition profile. As previously seen with acyclic analogues, the cyclic amides **2k** and **2m** having the cyclic amide groups *cis* relative to the phenyl displayed greater GFT inhibition activity than the corresponding *trans* isomers **2l** and **2n**, respectively. The reason for generally superior GFT profile seen with isomer having a *cis* configuration than *trans* between the R^1 group and phenyl is not clear. Among all the cyclic amides tested, five-membered amide **2k** exhibited the best combination of high NK_1 affinity (K_i = 0.2 nM) and excellent oral activity (>98% GFT inhibition following 2–6 h pretreatment). Removal of the carbonyl group of **2k** provided compound **2o** which maintained good NK_1 activity (K_i = 0.4 nM) but displayed decreased GFT inhibition activity.

Similar to the unsubstituted γ-lactam **2** the α-substituted lactams retained good selectivity over other neurokinin receptors. For example, **2e**: NK_2 = 1.4% inhibition at 3 μM, NK_3 = 43% inhibition at 10 μM; **2k**: NK_2 = 28% inhibition at 3 μM, NK_3 K_i = 1254 nM.

In conclusion, changing urea to γ-lactam core structure resulted in the discovery of a novel and potent series of selective NK_1 antagonists with significantly improved in vivo activity. Optimization of the γ-lactam lead compound **2** by α-substitution provided compounds **2e** and **2k** which display high NK_1 affinity ($K_i \leqslant 0.3$ nM) and excellent oral activity (>90% GFT inhibition following 2–6 h pretreatment).

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3. Gerbil foot tapping (GFT) inhibition assay measures the potency of compounds to antagonize an NK_1-receptor mediated CNS effect (GFT) induced by an NK_1 agonist administered centrally. Gerbil foot tapping inhibition assay: 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 a dose of 1 mg/kg (unless otherwise stated) 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.[4]
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7. Attempt to directly hydrolyze amino amide **1** to corresponding amino acid under acidic condition by heating with concentrated hydrochloric acid was unsuccessful. This result is consistent with Seebach's observation with similar substrates (see Studer, A.; Seebach, D. *Liebigs Ann. Chem.* **1995**, *2*, 217). Seebach's solution to this problem was a four steps procedure utilizing an intermediate benzamide for anchimeric assistance. Herein, we report that hindered α,α-disubstituted amino amide can be cleaved to respective amino acids in one step by heating amino amide with barium hydroxide at 156 °C.
8. Urethane-protected *N*-carboxy anhydrides (UNCA) have been reported as useful intermediates for peptide synthesis (see Fuller, W. D.; Chen, M. P.; Shabankareh, M.; Blair, R. K. *J. Am. Chem. Soc.* **1990**, *112*, 7414). The reports of UNCA to date have been restricted to α-amino acids and the standard procedure for their synthesis is acylation of the corresponding NCA. We found that α,α-disubstituted UNCA derivative (Boc–NCA) can be prepared from corresponding amino acid by first treatment of the amino acid with Boc anhydride and then reaction with triphosgene.
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10. NK_2 = 0.1% inhibition at 3 μM; K_i (NK_3) = 3815 nM.[11]
11. NK_2 and NK_3 binding assays: 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_2 and NK_3 receptors were expressed. [^{3}H]-Neurokinin A and [^{125}I]-neurokinin B were used as the ligands for the $NK_2$and NK_3 receptor assays, at concentrations near their experimentally derived K_d value. K_i values were obtained using the Cheng and Prusoff equation.
12. Configuration of R^1 group was assigned based on the NOE experiments. In *cis*-isomers, NOEs are seen from the CH hydrogen of the CH(R^1) group to one of the methylene (CH_2) hydrogen of the ether side chain, indicating R^1 group is *cis* to phenyl. In *trans*-isomers, NOEs are observed from the CH hydrogen of the CH(R^1) group to the *o*-hydrogens of the phenyl group, suggesting R^1 group is *trans* to phenyl.
13. NK_1 binding assay: Binding data are the average of two or three independent determinations. Receptor binding assay was performed on membrane preparations from CHO cells in which recombinant human NK_1 receptor was 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.[14]
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