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Cyclic urea derivatives as potent NK_1 selective antagonists

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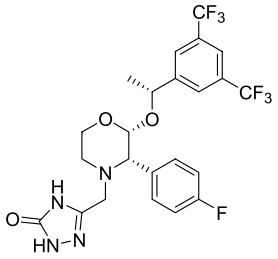
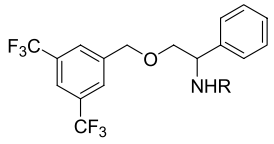
Abstract—A series of novel five- and six-membered ring urea derivatives have been described as potent and selective NK_1 receptor antagonists. Several compounds in this series exhibited good oral activity and brain penetration. Syntheses of these compounds are also described herein.

Substance P is a member of the tachykinin family of neurotransmitters that selectively binds to the NK_1 receptor. Substance P has been implicated in a number of pathological disorders in the central nervous system (CNS) and peripheral tissues,[1,2] including pain, inflammation, depression, emesis and cough.[3–6] Consequently, an antagonist of the NK_1 receptor has potential therapeutic use in the treatment of cough,[6] inflammation,[7] asthma,[8] pain,[9] chemotherapy-induced emesis,[10] migraine,[11] anxiety, and depression.[12] Recently, Emend was approved for the treatment of CINV (chemotherapy-induced nausea and vomiting), and several NK_1 antagonists are in clinical trails for anxiety and depression.[13]



Emend



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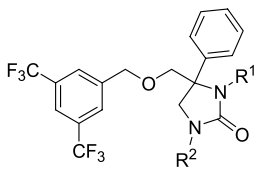

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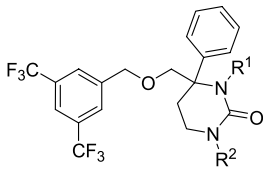

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Herein, we report the discovery of novel cyclic urea derivatives **2** and **3** as potent and selective NK_1 antagonists that are orally active and have good CNS penetration. These cyclic ureas provide structural novelty while possessing the minimal pharmacophoric elements of phenylglycinol-derived NK_1 antagonists of type **1**.[14]

The racemic 4,4-disubstituted-2-imidazolidinones (**2a**–**j**) shown in Table 1 were prepared by the synthetic route illustrated in Scheme 1.[15] Alkylation of 3,5-bis(trifluoromethyl)benzyl alcohol **4** with 2-iodo-*N*-methoxy-*N*-methylacetamide **5**, which was prepared in acetone from its chloride derivative using sodium iodide, afforded Weinreb amide **6**. The coupling of Weinreb amide **6** with phenyllithium gave the ketone **7** in excellent yield (80%). Treatment of ketone **7** with trimethylsilyl cyanide and ammonia in presence of zinc iodide afforded amine–nitrile intermediate **7a**, which was subsequently reduced without isolation to give the diamine compound **8**. The

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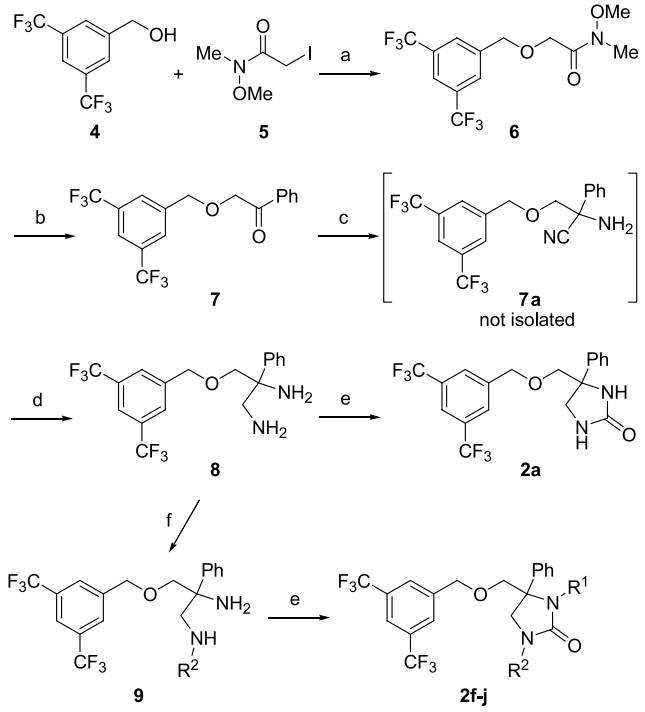
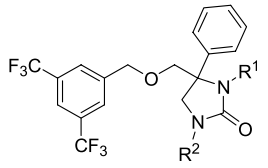
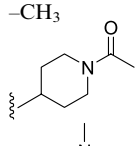
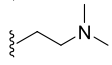
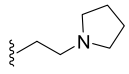
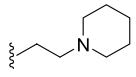
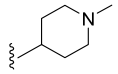


Scheme 1. Reagent and conditions: (a) $KN(TMS)_2$/THF, 0–25 °C, 18 h, 60%; (b) PhLi/THF, −78 °C, 1.5 h then rt, 80%; (c) TMSCN/ZnI_2/THF, rt, 1 h, filtered, concd then NH_3/MeOH, 45 °C, 2 h then filtered, concd; (d) $LiAlH_4$/ether, −78 °C then rt, 18 h, 25–35% from **7**; (e) CDI/THF, rt, 18 h, 97%; (f) ketone, aldehyde/$NaBH(OAc)_3$/CH_2Cl_2, rt or $NaBH_3CN$/MeOH or alkyl halide/DMF.

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



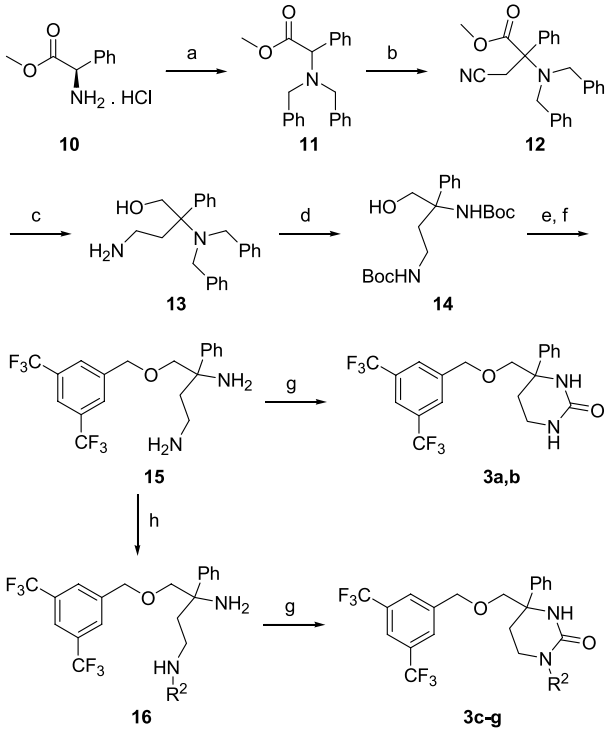
Compound[a]	R^1	R^2	NK_1[b] K_i (nM)	GFT[b] (%inh.)
2a	–H	–H	16	NT[c]
2b (*S*)	–H	–H	332	NT[c]
2c (*R*)	–H	–H	6	54
2d (*R*)	$-CH_3$	–H	94	NT[c]
2e (*R*)	–H	$-CH_3$	8	0
2f	–H		4	18
2g	–H		0.7	23
2h	–H		1	68
2i	–H		0.5	15
2j	–H		1	0

[a] Unless defined as (*R*) or (*S*), the compounds in the table are racemic.
[b] See Ref. 17–20.
[c] NT = not tested.

cyclization of diamine **8** in the presence of *N*,*N*′-carbonyldiimidazole (CDI) afforded the unsubstituted urea compound **2a**. An alternative four-step sequence to compound **2a** from compound **4** in higher overall yield has previously been reported.[16] Treatment of compound **8** with 1 equiv of ketone/aldehyde in the presence of a reducing agent, such as sodium triacetoxyborohydride, or an alkylating reagent, followed by CDI cyclization afforded the *N*-substituted cyclic ureas **2f**–**j**. In order to determine the effect of the absolute stereochemistry on binding activity, compound **2a** was resolved to the enantiomers **2b** and **2c** by chiral HPLC on a Daicel Chiralpak AD® column. The assignment of absolute configuration of enantiomer **2c** was made based on the established chiral synthesis.[16] The chiral *N*-methylated compounds (**2d** and **2e**) were prepared by alkylation of the chiral compound **2c** with methyl iodide in the presence of sodium hydride in *N*,*N*-dimethylformamide.

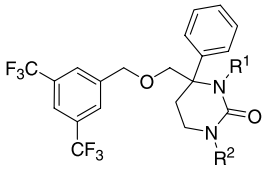
The in vitro NK_1 binding and in vivo NK_1 agonist-induced gerbil foot-tapping (GFT) inhibition data for 4,4-disubstituted-2-imidazolidinones (**2a**–**j**) are listed in Table 1. The NK_1 binding assay determines the affinity of these compounds (**2a**–**j**) toward the NK_1 receptor while the GFT inhibition measures the potency of these compounds antagonizing an NK_1 receptor-mediated CNS effect. As shown in Table 1, the unsubstituted five membered urea analogue **2a** exhibited good NK_1 binding affinity (K_i = 16 nM). It was noted that enantiomer **2c** (*R*-isomer) had higher affinity for the NK_1 receptor than the enantiomer **2b** (*S*-isomer) (6 vs 330 nM). In addition, compound **2c** was active in the GFT assay (54% inhibition of foot-tapping at 1 mg/kg po after a 2 h pretreatment time) which demonstrated CNS penetration and NK_1 antagonist activity. In order to understand the importance of the urea NH protons for affinity, the *N*-methyl derivatives of **2c** were synthesized. When the hindered NH of the urea ring was methylated (**2d**), the binding affinity was greatly reduced (K_i = 94 nM). On the other hand, when the less hindered NH was methylated (**2e**), retention of the binding affinity was observed (K_i = 8 nM). This suggested that the NH proton adjacent to the tertiary position of the cyclic urea is more important for NK_1 receptor binding. Consequently, substitutions at the less hindered NH were further explored. We found that a polar amide side chain improved potency (e.g., **2f**, K_i = 4 nM). Further increase in polarity from a neutral substitution to basic amino group containing side chains, significantly improved NK_1 affinity and in some cases (**2g** and **2i**) picomolar binding was achieved. Both the acyclic **2g** and cyclic (**2h**–**j**) amine side chains were well tolerated and the position of the basic nitrogen did not significantly affect the binding (**2g**, K_i = 0.7 nM and **2j**, K_i = 1 nM). The best representative of the amine side chain containing compounds was analogue **2h**, which bound with high affinity (K_i = 1 nM) and produced good activity (68% inhibition) in the GFT assay.

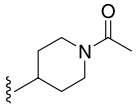
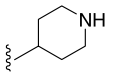
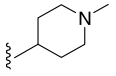
A series of racemic six-membered cyclic urea derivatives (**3a**–**g**) were prepared by the synthetic route shown in Scheme 2[15] and their biological data are listed in Table 2. The chiral compounds **3a** and **3b** were prepared by



Scheme 2. Reagent and conditions: (a) $PhCH_2Br$, Et_3N/THF/80 °C, 48 h, 46%; (b) LDA/ICH_2CN/THF, −78 °C to −20 °C, 51%; (c) LAH/THF, −78 °C to rt, 64%; (d) *t*-BOC-anhydride/20% $Pd(OH)_2$–C, H_2, 50 psi, 18 h, 85%; (e) Ag_2O/DMF, 3,5-bis(trifluoromethyl)benzyl bromide, rt, 18 h, 64%; (f) HCl/Et_2O, rt, 18 h, 99%; (g) CDI/THF, 0–25 °C, 18 h, 48–63%; (h) ketone/HOAc/$NaBH_3CN$/MeOH, or CH_3I/K_2CO_3/DMF or R^2CH_2Br/DMF.

Table 2. NK_1 receptor binding affinity and GFT inhibition for compounds **3a**–**g**



Compound[a]	R^1	R^2	NK_1[b] K_i (nM)	GFT[b] (%inh.)
3a (*S*)	–H	–H	350	NT[c]
3b (*R*)	–H	–H	9	0
3c	–H	$-CH_3$	14	18
3d	–H		9	16
3e	–H		3	47
3f	–H		2	2
3g	–H		0.5	56

[a] Unless defined as (*R*) or (*S*), the compounds in the table are racemic.
[b] See Ref. 17–20.
[c] NT = not tested.

the chiral HPLC separation of the racemic mixture **3a**,**b** on a Daicel Chiralpak AS® column.

As shown in Table 2, the six-membered ureas also exhibited good NK_1 receptor binding affinities. Similar to five-membered urea derivatives, the activity of six-membered urea derivatives also resided mostly in the *R*-isomer, for an example, compound **3b** (*R*-isomer, $K_i = 9$ nM) versus compound **3a** (*S*-isomer, $K_i = 350$ nM). However, compound **3b** was found to be inactive in GFT assay. This may be due to a poorer pharmacokinetic profile of the latter. Based on the SAR of the five-membered ureas, the substitutions at the less hindered NH were subsequently explored in the six-membered series. The *N*-methyl derivative **3c** and acetylpiperidine derivative **3d** retained the binding while the pyran analogue **3e** showed improvement in both binding ($K_i = 3$ nM), and in vivo activity (47% inhibition). As previously observed with five-membered analogues, incorporation of basic amine side chains (**3f**,**g**) improved the binding, and in the case of methyl-piperidine analogue (**3g**), sub-nanomolar NK_1 affinity ($K_i = 0.5$ nM) was achieved. The analogue **3g** showed the best GFT activity (56% inhibition) in the six-membered urea series which was comparable to the most potent five-membered series analogues **2c** and **2h**.

In conclusion, we have identified a novel series of cyclic urea derivatives of structures **2** and **3** as potent NK_1 antagonists. Several compounds in these series exhibit good NK_1 selectivity, are orally active and have good brain penetration. For example, compound **2c** (SCH 388714) showed an excellent selectivity (NK_2, $NK_3 > 1$ μM), good oral bioavailability (69% in rat) and it displayed very good brain penetration (brain/plasma ratio 4 in rat). Further details of the SAR effort to improve potency of this class of NK_1 antagonist will be reported in due course.

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17. 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.
18. 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.
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