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Cyclic urea derivatives as potent NK_1 selective antagonists. Part II: Effects of fluoro and benzylic methyl substitutions

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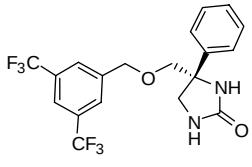
Abstract—A series of novel five-membered urea derivatives as potent NK_1 receptor antagonists is described. The effects of substitution of a 4-fluoro group at the phenyl ring and the introduction of an α-methyl group at the benzylic position to improve potency and duration of in vivo activity are discussed. Several compounds with high affinity and sustained in vivo activity were identified.

Substance P (SP) is a member of the tachykinin family of neuropeptides that acts primarily through the NK_1 receptor. SP has been associated with numerous pathological conditions in the central nervous system (CNS) and peripheral tissues including pain, inflammation, depression, anxiety, and emesis.[1] Hence, 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] Preliminary SAR evaluation in this series led to the identification of a five-membered unsubstituted urea analogue **1** (SCH 388714) as a lead compound. SCH 388714 has single digit nanomolar binding affinity for the NK_1 receptor (K_i = 6 nM), excellent brain penetration (brain/plasma ratio of 18 in gerbil and 4 in rat), and good oral in vivo activity in the gerbil foot-tapping (GFT) assay which measures the potency of compounds to antagonize an NK_1-receptor mediated CNS effect (54% inhibition of foot-tapping at 1 mg/kg po following a 2 h pretreatment time).



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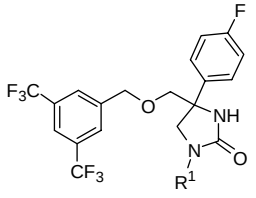

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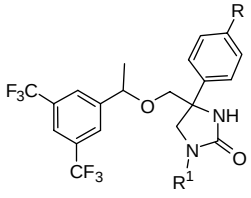

3 (R = H)
4 (R = F)

However, the duration of in vivo activity for SCH 388714 was short, giving only 12% inhibition of foot-tapping at 1 mg/kg po following a 4 h pretreatment time.

Keywords: NK_1 antagonist; Sustained in vivo activity; Improved potency.
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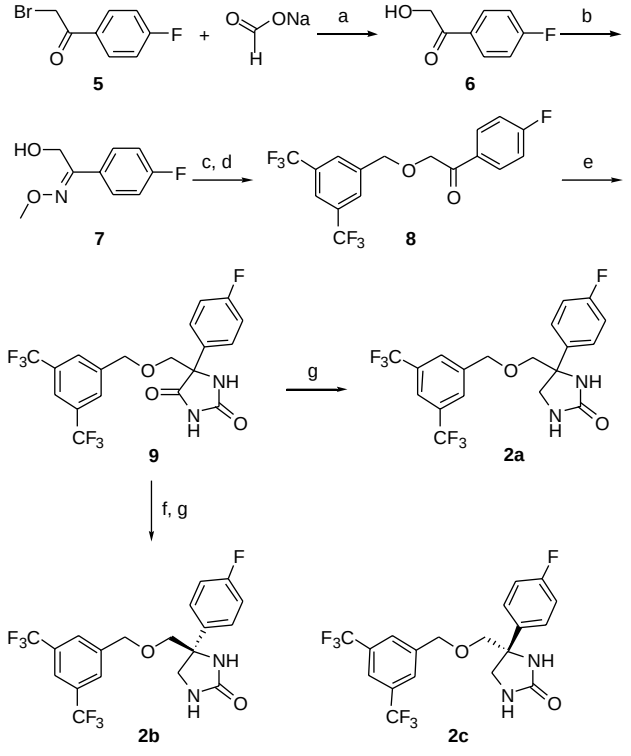
In this paper, we describe the optimization of SCH 388714 to increase the duration of in vivo activity, while further improving the NK_1 receptor binding affinity and maintaining good brain penetration.

In an effort to improve the duration of action, we sought to block the potential sites of metabolism at the phenyl ring and the benzylic position. To prevent the hydroxylation of the phenyl ring, a fluoro group was placed at the 4-position (**2**), and a methyl group was introduced at the benzylic position to block the oxidation at that site (**3**,**4**).[3]

The 4-fluorophenyl cyclic urea analogues (**2a**–**c**) of compound **1** were prepared by the synthetic route illustrated in Scheme 1.[4] Treatment of 2-bromo-4′-fluoroacetophenone **5** with sodium formate in the presence of aqueous ethanol afforded compound **6**. Direct assembly of **8** via O-alkylation of **6** with 3,5-bis(trifluoromethyl)benzyl bromide was unsuccessful and resulted in the decomposition of **6**. In order to decrease the reactivity of compound **6**, the ketone group was protected as an oxime to give compound **7**. The O-alkylation of alcohol-oxime **7** proceeded smoothly and subsequent deprotection afforded the ketone **8**. Subjection of ketone **8** to Bücherer–Bergs conditions provided the hydantoin **9**.[5]

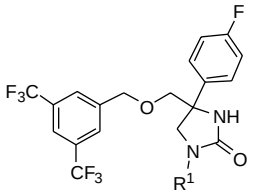


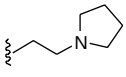
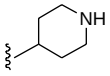
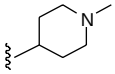
Scheme 1. Reagent and conditions: (a) 85% aq EtOH, 80 °C, 5 h, 85%; (b) methoxylamine hydrochloride, Et_3N, EtOH, 85 °C, 2.5 h, 97%; (c) NaH, THF, 3,5-bis(trifluoromethyl)benzyl bromide, rt, 1.5 h, 98%; (d) 6 N aq HCl 1,4-dioxane, 100 °C, 48 h, 56%; (e) KCN, $(NH_4)_2CO_3$, EtOH/H_2O (1:1), 60 °C, 48 h, 73%; (f) separation of isomers by HPLC on a Chiralcel OD® column eluting with CH_3CN; (g) $LiAlH_4/AlCl_3$, ether, 0 °C, 15 min then rt, 18 h, 82%.

Reduction of hydantoin **9** with lithium aluminum hydride and aluminum chloride mixture gave racemic urea compound **2a**.[6,7] Separation of hydantoin **9** by HPLC on a Chiralcel OD® column followed by reduction afforded chiral urea compounds **2b** and **2c**. The absolute configurations of **2b** and **2c** were assigned based on the established chiral synthesis.[8] The racemic *N*-substituted urea compounds **2d**–**g** were prepared from ketone **8** by methods as previously described for the corresponding non-fluoro compounds.[2]

The in vitro NK_1 binding and in vivo NK_1 agonist-induced GFT inhibition data for 4-fluorophenyl cyclic ureas (**2a**–**g**) are listed in Table 1. As shown in Table 1, the racemic five-membered fluorophenyl urea analogue **2a** exhibited good NK_1 affinity (K_i = 4.5 nM). Similar to phenyl urea series, the activity of 4-fluorophenyl urea analogues also resided mostly in the *R*-isomer, for example, compound **2c** (*R*-isomer, K_i = 2.7 nM) versus compound **2b** (*S*-isomer, K_i = 89 nM). In comparison to the lead compound **1**, the fluoro analogue **2c** showed a two-fold better binding affinity. Moreover, compound **2c** displayed an improved in vivo activity at the 4 h time point compared to **1** (55% inhibition at 1 mg/kg for **2c** vs 12% for **1**), and it also maintained good GFT activity at the 6 h time point (51% inhibi-

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



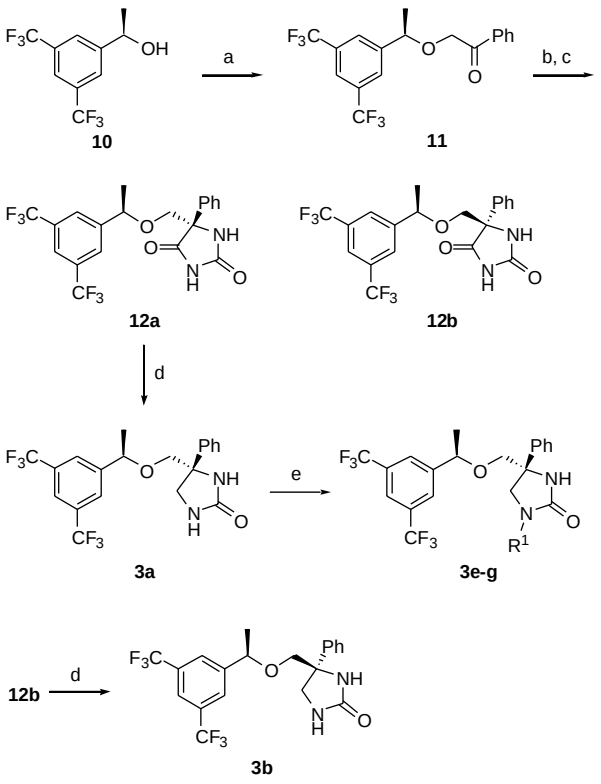
Compound[a]	R^1	NK_1[b] K_i (nM)	GFT[b] (% inh)		
			t = 2 h	t = 4 h	t = 6 h
2a	–H	4.5	NT[c]	NT[c]	NT[c]
2b (*S*)	–H	89	NT[c]	NT[c]	NT[c]
2c (*R*)	–H	2.7	22	55	51
2d		6.3	22	0	NT[c]
2e		1.6	2	0	0
2f		0.9	0	0	NT[c]
2g		0.4	3	0	NT[c]

[a] Unless defined as (*R*) or (*S*), the compounds in the table are racemic.
[b] See Refs. 9–12.
[c] NT, not tested.

tion). The lower activity of **2c** at the 2 h time point could be due to its slower absorption. Based on the SAR of phenyl urea series, the substitutions at the less hindered NH were subsequently explored in the 4-fluorophenyl series. We found that the neutral groups such as pyran (compound **2d**) retained good binding (K_i = 6 nM) but did not give sustained GFT activity (0% inhibition at 4 h). Substitutions with basic amine side chains (**2e–g**) improved in vitro activity and in some cases (**2f** and **2g**) sub-nanomolar binding affinities were observed; however, the in vivo GFT activity was significantly reduced. The latter may be due to the poor pharmacokinetic profile of the amine side chain containing compounds. Overall, the unsubstituted analogue **2c** was the best compound in this series, exhibiting good NK_1 binding affinity, excellent brain penetration (brain/plasma ratio 16 in gerbil) and bioavailability (93% in rat), and improved duration of oral GFT activity compared to compound **1**.

As previously reported that the introduction of a methyl group at the benzylic position improves binding affinity and duration of in vivo activity in the 3-benzyloxy-2-phenylpiperidine NK_1 antagonist ether series,[3] we next explored a series of benzylic methyl urea derivatives. The synthetic route of preparation of these compounds (**3a–g**) is illustrated in Scheme 2. Alkylation of (*R*)-α-methyl 3,5-bis(trifluoromethyl)benzyl alcohol[8] with the triflate of the 2-hydroxyacetophenone in the presence of 2,6-di-*tert*-butyl-4-methyl-pyridine afforded the ketone **11** with a good yield (70%). Hydantoin formation followed by subsequent separation of the mixture of isomers by HPLC on a Chiralcel OD® column provided the pure hydantoin isomers **12a** and **12b**. Reduction of **12a** with lithium aluminum hydride/aluminum trichloride produced the desired urea compound **3a**. The assignment of absolute configuration of the diastereomer **3a** was made based on the established chiral synthesis.[8] Similarly hydantoin **12b** was converted to urea compound **3b**. An attempt to prepare the alkyl-substituted urea analogues **3e–g** by alkylation of **12a** followed by treatment with lithium aluminum hydride/aluminum trichloride resulted only in partial reduction to the hydroxyl-urea compound due to steric hindrance. However, reduction of **12a** to **3a** followed by alkylation provided the compounds **3e–g**. The compounds **3c** and **3d** were prepared in a similar manner to compounds **3a** and **3b** starting from (*S*)-α-methyl 3,5-bis(trifluoromethyl)benzyl alcohol in place of (*R*)-α-methyl 3,5-bis(trifluoromethyl)benzyl alcohol. 4-fluorophenyl analogues **4a–d** were synthesized by the synthetic sequences shown in Scheme 2 for phenyl analogues.

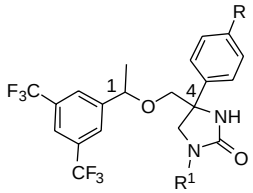
The biological data for the benzylic methyl urea analogues are shown in Table 2. Analogous to the non-benzylic methyl series the (*S*) configuration at the quaternary chiral center is less preferred to the (*R*) configuration, for example, compound **3a** (K_i = 0.6 nM) versus compound **3b** (K_i = 41 nM). At the benzylic methyl center the (*R*) absolute stereochemistry is required for high-affinity NK_1 binding (e.g., 1*R*,4*R*-isomer, **3a**, K_i = 0.6 nM vs 1*S*,4*R*-isomer, **3c**, K_i = 93 nM). The latter result is in agreement with the molecular modeling analysis which showed (Fig. 1) that the energy-minimum conformation of compound **3a** superimposed almost perfectly with that of the original lead compound **1** when aligned with the ether oxygen and the three ring centroids. The exact overlap of energy-minimized conformations of **3c** and **1** could not be achieved. Similar folding conformations between two aryl rings as observed for **3a** have been reported to be the bioactive conformations in the literature.[3,13] The significantly improved binding affinity of **3a** compared to the original lead compound **1** (0.6 vs 6 nM) may stem from the favorable conformational constraints caused by the α-methyl benzylic substitution; additionally, the benzylic methyl group could participate in a hydrophobic interaction with the receptor. A similar benzylic methyl effect was first seen in the 3-benzyloxy-2-phenylpiperidine NK_1 antagonist ether series.[3]



Scheme 2. Reagent and conditions: (a) 2-hydroxyacetophenone, 2,6-di-*tert*-butyl-4-methyl-pyridine, Tf_2O, $ClCH_2CH_2C1$, rt, 3 h, then **10**, 80 °C, 4 h, 70%; (b) KCN, $(NH_4)_2CO_3$, EtOH/H_2O (1:1), 60 °C, 48 h, 73%; (c) separation of isomers by HPLC on a Chiralcel OD® column eluting with 4% hexane/96% CH_3CN, **12a** (59%) and **12 b** (41%); (d) $LiAlH_4/AlCl_3$, ether, 0 °C, 15 min then rt, 18 h, 62%; (e) NaH, alkyl halide, DMF, 0 °C to rt, 18 h, 30–35%.

In addition to the sub-nanomolar binding affinity, compound **3a** displayed excellent oral bioavailability (100% in rat), retained good brain penetration (brain/plasma of 10 in gerbil and 4.4 in rat), and demonstrated much more sustained GFT activity (57% and 48% inhibition at 4 and 6 h, respectively) than **1**. To see an effect of increasing lipophilicity, some N-alkylated analogues

Table 2. NK_1 receptor binding affinity and GFT inhibition for compounds **3a**–**g** and **4a**–**d**



Compound	R	R^1	NK_1[a] K_i (nM)	GFT[a] (% inh)		
				t = 2 h	t = 4 h	t = 6 h
3a (1*R*, 4*R*)	–H	–H	0.6	35	57	48
3b (1*R*, 4*S*)	–H	–H	41	NT[b]	NT[b]	NT[b]
3c (1*S*, 4R)	–H	–H	93	NT[b]	NT[b]	NT[b]
3d (1*S*, 4*S*)	–H	–H	22% inh at 3 μM	NT[b]	NT[b]	NT[b]
3e (1*R*, 4*R*)	–H	$-CH_3$	0.5	86	62	31
3f (1*R*, 4*R*)	–H	$-CH_2CH_3$	1.7	45	46	NT[b]
3g (1*R*, 4*R*)	–H	$-CH(CH_3)_2$	3.1	NT[b]	NT[b]	NT[b]
4a (1*R*, 4*R*)	–F	–H	1.5	40	44	41
4b (1*R*, 4*R*)	–F	$-CH_3$	3.6	65	57	63
4c (1*R*, 4*R*)	–F	$-CH_2CH_3$	0.8	9	0	NT[b]
4d (1*R*, 4*R*)	–F	$-CH_2C(O)NH_2$	0.4	14	20	NT[b]

[a] See Refs. 9–12.
[b] NT, not tested.

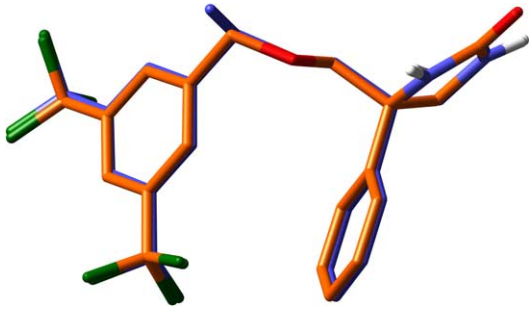


Figure 1. Overlay of the energy-minimum conformations of compound **1** and its (*R*)-α-methyl analogue **3a**.[14] Oxygen atoms are colored red; N, blue; F, green; C atoms of **1**, orange and C of **3a**, blue.

were explored. The *N*-methyl derivative **3e** maintained good binding affinity and GFT activity. The increase in size to ethyl (**3f**) and isopropyl (**3g**) groups resulted in loss of vitro activity, suggesting that the big lipophilic groups may not be tolerated at the R^1 position.

We next evaluated the effect of 4-fluoro substitution in the benzylic methyl series. Similar to the phenyl benzylic methyl compound **3a**, the corresponding 4-fluorophenyl benzylic methyl analogue **4a** also displayed good in vivo duration of activity (Table 2). The *N*-methyl derivative **4b** also retained a good GFT profile even though the binding affinity was slightly decreased. Placement of the ethyl group (**4c**) and a polar methyl amide group (**4d**) on the nitrogen improved the binding affinity in the 4-fluorophenyl series but the in vivo activity was significantly reduced. Overall, the 4-fluorophenyl analogues in the benzylic methyl series (e.g., **4a**, **4b**) demonstrated comparable in vivo activities to the phenyl benzylic methyl analogues (**3a**, **3e**) despite slightly inferior binding affinities.

In conclusion, we found that both the 4-fluoro substitution at the phenyl ring and the introduction of the α-methyl group at the benzylic position improved duration of in vivo activity. In addition, α-methyl substitution provided a significant enhancement in binding affinity. Several compounds (e.g., **3a**, **3e**, **4a**, and **4b**)[15] were identified which retained good brain penetration and demonstrated improved potency and duration of oral in vivo activity compared to the original lead compound **1**.

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7. Reduction with lithium aluminum hydride reagent only was not clean. A partial reduction of hydantoin was observed and reduction of trifluoromethyl group to difluoromethyl was noticed. On the other hand, the reduction with lithium aluminum hydride and aluminum chloride was clean, providing the desired product.

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9. 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 rear the experimentally derived K_d value. K_i values were obtained using the Cheng and Prusoff equation.
10. 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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14. The energy-minimum conformations were generated using MCMM conformational search approach in MacroModel method as implemented in Schrödinger modeling package. 5000 steps of conformational search each followed by energy minimization using MMFF94s force field parameters were carried out for every compound.
15. In contrast to most known NK_1 antagonists which carry basic center, the most efficacious urea antagonists are neutral, for example, compound **4b** ($c\log P = 5.1$; solubility in pH 7.4 buffer = 3 μM).