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Cyclobutane derivatives as potent NK_1 selective antagonists

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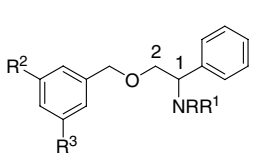
Abstract—A series of novel cyclobutane derivatives as potent and selective NK_1 receptor antagonists is described. Several compounds in this series exhibited high in vitro binding affinity ($K_i \leqslant 1$ nM), and potent inhibition of central NK_1 receptor following oral administration. Syntheses of these compounds are also described herein.

Substance P (SP) belongs to the tachykinin family of neurotransmitters that selectively binds to the NK_1 receptor. SP has been implicated in numerous pathological conditions in the central nervous system (CNS) and peripheral tissues including pain, inflammation, depression, anxiety, and emesis.[1] Hence, a NK_1 antagonist has potential therapeutic use in the treatment of wide range of central and peripheral diseases.

The phenyl glycine-based structure **1** represents a prime pharmacophore among the diverse chemotypes reported to date as NK_1 receptor antagonists. Structure **1** has spawned several acyclic[2,3] and cyclic NK_1 antagonists[4] where the nitrogen is tied together with the C1 or C2 carbon atom. Initially it appeared that the position of the nitrogen relative to the diaryl ether portion of the pharmacophore structure **1** is important but later it was shown that the nitrogen position can be varied while retaining good binding affinity (e.g., **2**, IC_{50} = 0.95 nM).[5]

High affinity of structural type **2** prompted us to explore other molecular scaffolds in place of piperidine. Herein, we report the discovery of a novel class of 3,3-disubstituted cyclobutane derivatives **3** as potent and selective NK_1 antagonists that have good CNS penetration and are orally active in vivo. The cyclobutane ring provides the structural novelty as well as the rigid conformation support to the diaryl ether pharmacophore. Compounds **3** contain a methyl group at the benzylic position since it has been reported in literature that such substitution improves binding affinity and duration of in vivo activity in the diaryl ether containing NK_1 antagonists by decreasing the benzylic site metabolism.[6]



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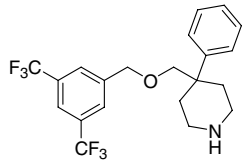

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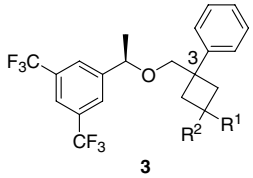

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Initially, we explored a series of 1-monosubstituted cyclobutane analogues listed in Table 1. The synthetic route for the preparation of the cyclobutanone compound **3a** and 1-monosubstituted cyclobutane derivatives **3b**–**h** is illustrated in Scheme 1.[7] Alkylation of (*R*)-α-methyl

Keywords: Cyclobutane; NK_1 antagonist; Substance P; CNS penetration; Oral in vivo activity.
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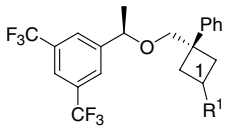
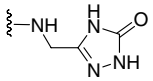
Table 1. NK_1 receptor binding affinity and GFT inhibition for compounds **3a**–**h**



3a-h

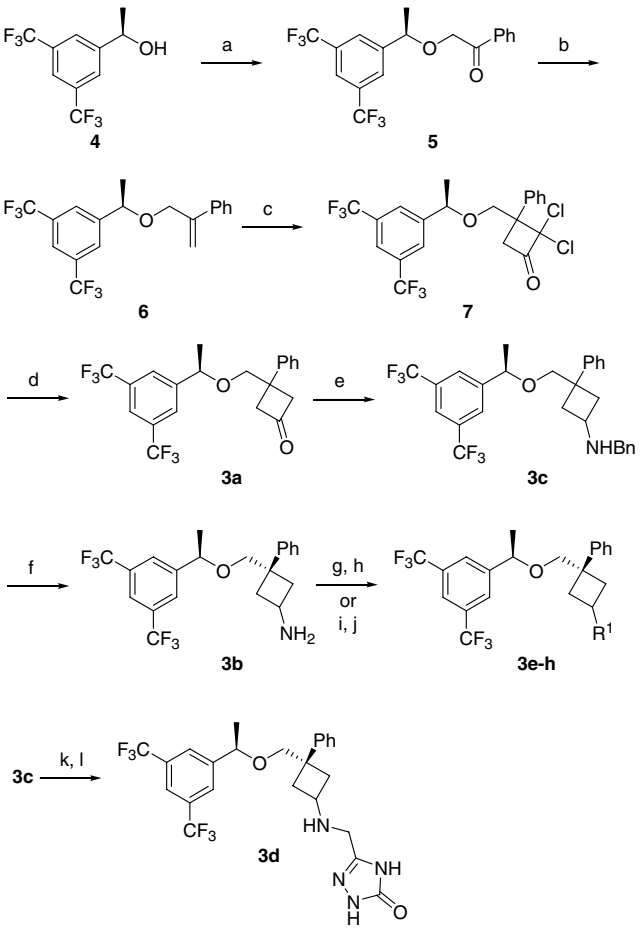
Compound	R^1	NK_1[a] K_i (nM)	GFT[b] (% inh) $t = 4$ h
3a	=O	2.4	11
3b[c]	$-NH_2$	0.02	21
3c[c]	–NHBn	0.3	25
3d[c]		0.5	22
3e (*trans*)		0.1	23
3f (*cis*)		0.4	25
3g (*trans*)		0.4	41
3h (*cis*)		0.3	3

[a] See Ref. 11.
[b] See Ref. 13.
[c] 1:1 mixture of *cis*/*trans* isomers.

3,5-bis(trifluoromethyl)benzylalcohol[8] **4** with the triflate of the 2-hydroxyacetophenone in the presence of 2,6-di-*tert*-butyl-4-methyl pyridine afforded the ketone **5**. Wittig olefination of ketone **5** provided alkene **6**.[9] Subjection of the olefine **6** to a [2+2] cycloaddition with dichloroketene afforded isomeric dichlorocyclobutanone **7**. Reduction of **7** with zinc in acetic acid gave the cyclobutanone **3a**. Reductive amination of **3a** with benzylamine afforded a *cis*/*trans* mixture of **3c**. Hydrogenation of the benzyl derivative **3c** provided a *cis*/*trans* mixture of amine **3b**. Acetylation of amine **3b** followed by separation of the isomers by HPLC provided the compounds **3e** and **3f**. Acylation of amine **3b** with 4-chlorobutyryl chloride followed by cyclization and separation of the isomers by HPLC afforded the lactam analogues **3g** and **3h**.

The *cis* and *trans* configurations of compounds **3e**–**h** were assigned based on the NOE experiments. The triazolinone compound **3d** was prepared by alkylation of **3c** with chlorotriazolinone[10] followed by deprotection of the benzyl group by hydrogenation.

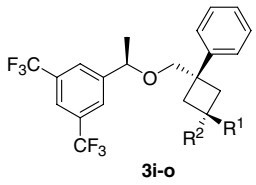
The in vitro NK_1 binding and in vivo NK_1 agonist-induced gerbil foot-tapping (GFT) inhibition data for cyclobutane derivatives (**3a**–**h**) are listed in Table 1. The NK_1 binding assay determines the affinity of these compounds (**3a**–**h**) toward the NK_1 receptor. The GFT inhibition measures the potency of these compounds to antagonize an NK_1 receptor-mediated CNS effect following oral administration. As shown in Table 1, even the simple cyclobutanone compound **3a** exhibited



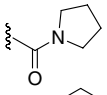
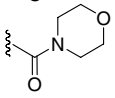
Scheme 1. Reagents and conditions: (a) 2-hydroxyacetophenone, 2,6-di-*tert*-butyl-4-methyl-pyridine, Tf_2O, $ClCH_2CH_2Cl$, rt, 3 h, then **4**, 80 °C, 4 h, 70%; (b) $NaNH_2/CH_3PPh_3Br$, THF, rt, 24 h, 92%; (c) Zn–Cu couple, Et_2O/DME, trichloroacetylchloride, reflux, 5 days, 86%; (d) Zn dust, AcOH, rt, 48 h, 82%; (e) $BnNH_2$, $NaBH(OAc)_3$, rt, 24 h, 94%; (f) H_2, 10% Pd/C, 1 atm, rt, 24 h, 81%; (g) $ClCH_2CH_2Cl$, Et_3N, $CH_3C(O)Cl$, 0 °C, 2 h, 93%; (h) separation of isomers by HPLC on a Chiralcel OD® column eluting with hexane/IPA (9:1); (i) i—$ClCH_2CH_2Cl$, Et_3N, $ClCH_2CH_2CH_2C(O)Cl$, 0 °C, 3 h; ii—THF, NaH, 0 °C, 15 min, then rt, 14 h, 80% over two-steps; (j) separation of isomers by HPLC on a Chiralpak AD® column eluting with hexane/IPA (9:1); (k) DMF, K_2CO_3, chlorotriazolinone, 0 °C, 9 h, 77%; (l) MeOH, ammonium formate, 10% Pd/C, reflux, 1 h, 92%.

good NK_1 binding affinity ($K_i = 2.4$ nM). The change of ketone to primary amine (**3b**) and secondary benzylamine (**3c**) derivatives resulted in a significant improvement in binding affinity with the unsubstituted primary amine (**3b**, $K_i = 0.02$ nM) as one of the most potent NK_1 antagonist reported to date. However, both amines **3b** and **3c** displayed poor GFT activity (21% and 25% inhibition of foot-tapping, respectively, at 1 mg/kg po after a 4 h pretreatment time). The substitution on the primary amine **3b** with a triazolinone moiety which had previously provided significant enhancement in potency in the Merck piperidine series,[15] did not lead to activity improvement (**3d**, $K_i = 0.5$ nM, 22% GFT inhibition) in the present cyclobutane series. We next evaluated the effect of modification of amine to neutral amide groups. Both *trans*- and *cis*-isomers (**3e** and **3f**, respectively) of the neutral *N*-acetyl amide retained

Table 2. NK_1 receptor binding affinity and GFT inhibition for compounds **3i–o**



3i-o

Compounds	R^1	R^2	NK_1[a] K_i (nM)	GFT[b] (% inh.) $t = 4$ h
3i	$-NH_2$	$-C(O)NH_2$	1	81
3j	$-C(O)NH_2$	$-NH_2$	0.43	30
3k	$-NH_2$	$-C(O)NHCH_3$	1	98
3l	$-C(O)NHCH_3$	$-NH_2$	0.5	58
3m	$-NH_2$	$-C(O)N(CH_3)_2$	3.3	79
3n	$-NH_2$		1.3	13
3o	$-NH_2$		1.3	15

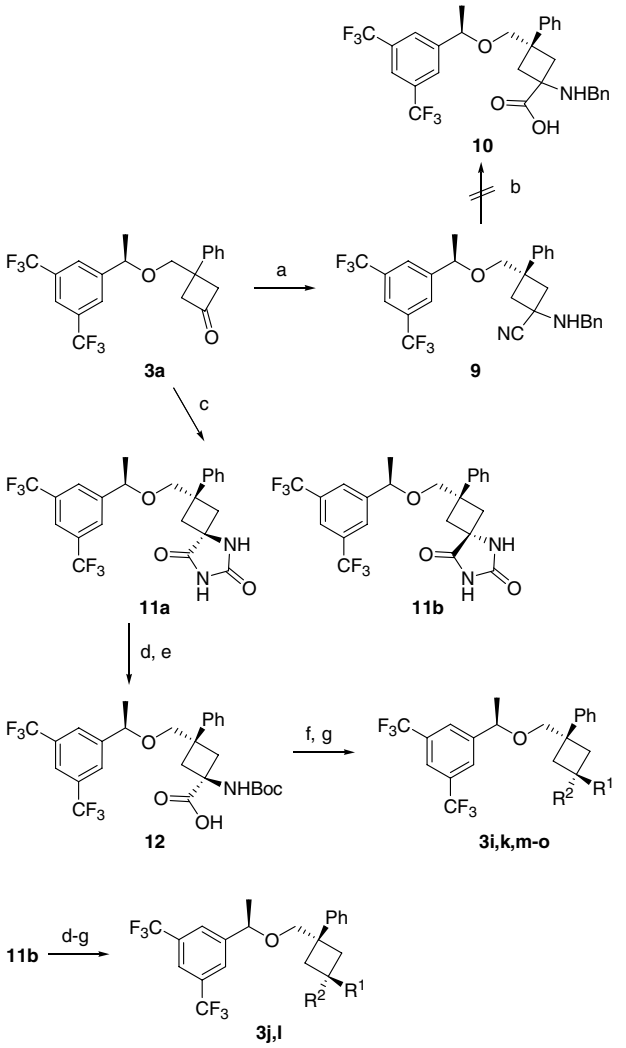
[a] See Ref. 11.
[b] See Ref. 13.

excellent NK_1binding activity suggesting that in addition to a basic amino group, the neutral polar groups are also well tolerated. However, these compounds did not provide improvement in the GFT activity. To increase metabolic stability, we prepared cyclic amides (lactams) **3g** and **3h**. The *trans* lactam analogue **3g** which maintained subnanomolar binding affinity ($K_i = 0.4$ nM) displayed modest increase in GFT activity (41% inhibition) compared to **3e** (23% inhibition). The corresponding *cis* isomer **3h** also exhibited good in vitro activity ($K_i = 0.3$ nM) but provided considerably lower GFT activity (3% inhibition). The lower GFT activity of the **3h** compared to the corresponding *trans* isomer **3g** may be due to poorer pharmacokinetic profile of the former. Overall, the lactam analogue **3g** provided the best combination of high NK_1 binding affinity and good oral in vivo activity in the 1-monosubstituted cyclobutane series.

We next evaluated 1,1-disubstituted cyclobutane analogues where an amide group (compounds **3i–o**, Table 2) was substituted at the carbon attached to the amine.

The 1,1-disubstituted cyclobutane derivatives (**3i–o**) were prepared by the synthetic route illustrated in Scheme 2. Initially, we attempted to prepare amino-amides **3i–o** from the amino-acid **10** which could be obtained from ketone **3a** via Strecker reaction followed by hydrolysis. Although amino-nitrile **9** was readily obtained from **3a** via Strecker reaction, hydrolysis of the nitrile **9** to amino-acid **10** under either acidic or basic conditions was unsuccessful. Consequently, an alternate route that employs a hydantoin, which is a suitable intermediate in the synthesis of amino-acids, was explored.[16] Heating a mixture of ketone **3a** and standard hydantoin formation reagents in a steel bomb, followed by separation of isomers, afforded the hydantoin derivatives **11a** and **11b**.[17,18] The di-protection of hydantoin **11a** with Boc-anhydride followed by hydrolysis under basic conditions provided a 7:1 mixture of amino-acid to Boc-protected amino-acid. The crude mixture was treated with Boc-anhydride to afford Boc-protected amino-acid **12**. Coupling of **12** with amines in the presence of PyBOP followed by removal of the Boc-moiety with trifluoroacetic acid afforded the desired *trans* amino-amides **3i**, **3k**, and **3m–o**. Similarly the hydantoin derivative **11b** was converted to the *cis* amino-amides **3j** and **3l**.

The biological data for the 1,1-disubstituted cyclobutane analogues (**3i–o**) are shown in Table 2. The *trans* analogue **3i** led to significant loss of in vitro activity compared to the monosubstituted lead amine compound **3b** (**3i**, $K_i = 1$ nM vs **3b**, $K_i = 0.02$ nM) but considerable improvement in the oral in vivo activity was observed for **3i** (**3i**, 81% inhibition vs **3b**, 21% inhibition). Interestingly, the in vivo activity showed conformational bias toward the *trans* isomer in the disubstituted series, for example, the *cis* isomer **3j** displayed inferior GFT activity (30% inhibition) compared to the *trans* isomer (**3i**, 81% inhibition) despite exhibiting 2-fold better binding affinity. To see an effect of increasing lipophilicity, N-alkylated amides (**3k–m**) were explored. The *trans* N-methylated amide compound **3k** retained good binding activity ($K_i = 1$ nM) and demonstrated further improvement in the in vivo activity (98% inhibition). The *cis* N-methylated compound **3l** also exhibited better GFT activity (58% inhibition) compared to the unsubstituted analogue **3j**. Additional methyl substitution on the amide NH was found to decrease the binding affinity (**3m**, $K_i = 3.3$ nM) as well as the in vivo activity (79% inhibition). Further increase in size to cyclic amides



Scheme 2. Reagents and conditions: (a) NaCN, $BnNH_2$, AcOH, MeOH, reflux, 19 h, 98%; (b) acidic or basic hydrolysis; (c) i—KCN, $(NH_4)_2CO_3$, EtOH/H_2O (1:1), steel bomb, 90 °C, 36 h; ii—separation of isomers, **11a** (46%) and **11b** (43%); (d) $(Boc)_2O$, DMAP, THF, rt, 3 h, then 1 M aq LiOH, THF, rt, 24 h; (e) $(Boc)_2O$, satd aq $NaHCO_3$, THF, rt, 24 h, (88%) over two-steps; (f) PyBOP, *i*-Pr_2EtN, CH_2Cl_2, 0 °C, 30 min then rt, 1 h, then appropriate amine, rt, 24 h; (g) TFA, CH_2Cl_2, rt, 24 h, 60–80% over two-steps.

(**3n**,**o**) was found to decrease GFT activity. Overall, the 1,1-disubstituted acyclic amide cyclobutane analogues (e.g., **3i**,**k**,**m**) displayed superior oral in vivo activity than the 1-monosubstituted compounds despite the reduced binding affinity.[19]

In conclusion, we have identified a novel series of cyclobutane derivatives as potent and selective NK_1 antagonists.[20] The initial lead (compound **3b**, $K_i = 0.02$ nM) was optimized to afford compounds with good CNS penetration and oral in vivo activity. The 1,1-disubstituted amine-amide analogues **3i** and **3k** provided the best combination of high NK_1 affinity ($K_i = 1$ nM) and excellent in vivo GFT activity (>80% inhibition at 1 mg/kg after a 4 h pretreatment). Further details of the SAR effort to improve potency in this class of NK_1 antagonists will be reported in due course.

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11. 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.[12]
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13. 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 in foot-tapping compared to vehicle-treated controls.[14]
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16. Conditions for hydantoin hydrolysis, see: Kubik, S.; Meissner, R. S.; Rebek, J., Jr. *Tetrahedron. Lett.* **1994**, *35*, 6635, and references cited therein.
17. Refluxing the reaction mixture at atmospheric pressure led to incomplete reaction. Heating in a steel bomb was required to drive the reaction to completion.
18. The absolute configurations of compounds **11a** and **11b** were assigned based on the absolute configurations of the corresponding reduced cyclic urea products, which were determined by NOE.
19. The improved in vivo activity of the 1,1-disubstituted compounds could be due to their better CNS penetration. For example, the 1-monosubstituted compound **3b** and 1,1-disubstituted compound **3i** have similar plasma levels.
20. The compounds in the cyclobutane series exhibited good selectivity over other neurokinin receptors. For example, **3b**: NK_2 = 25% inhibition at 3 μM; NK_3 K_i = 4051 nM. **3e**: NK_2 = 26% inhibition at 3 μM; NK_3 K_i = 631 nM. **3f**: NK_2 = 23% inhibition at 3 μM; NK_3 K_i = 2131 nM. **3k**: NK_2 = 1.2% inhibition at 0.3 μM; NK_3 K_i = 1999 nM.[21]
21. 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.