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Bioorganic & Medicinal Chemistry Letters 16 (2006) 2929–2932
Bioorganic & Medicinal Chemistry Letters

NK_1 antagonists based on seven membered lactam scaffolds

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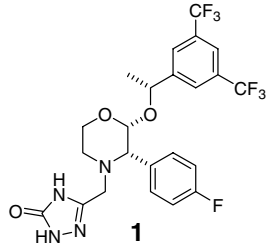
Received 2 February 2006; revised 28 February 2006; accepted 28 February 2006
Available online 29 March 2006

Abstract—A new class of high affinity hNK_1R antagonists based on seven-membered ring cores has been identified. This series, with relatively simple, compact structures, includes compounds with high affinity, good selectivity, and promising in vivo properties.

The utility of neurokinin-1 receptor (NK_1R) antagonists for the treatment of post-operative and chemotherapy-induced emesis has now been established. Aprepitant (Emend®) **1** is currently the only commercially available drug in this class.[1,2] There have been many reports of NK_1R antagonists in which the elements necessary for binding are constructed around five- or six-membered cyclic cores.[3] However, extension to larger ring sizes is rare. We have now found that the use of core scaffolds based on seven-membered rings leads to novel NK_1R antagonists with high in vitro affinity and promising in vivo properties.



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Racemic cyclohexanone **2** was prepared via palladium catalyzed α-arylation of 1,4-dioxaspiro[4.5]decan-8-one.[4] Reduction with (*R*)-2-methyl-CBS-oxaborolidine gave a 1:1 mixture of diastereomeric alcohols from which *trans*-**3** was isolated with modest ee (54%) (Scheme 1). This was improved to 100% ee in the next step, O-alkylation with the 2,2,2-trichloroacetimidate prepared from enantiomerically pure (*S*)-1-[3,5-bis(trifluoromethyl)phenyl]ethanol.[5] Deprotection and a two-step Beckmann rearrangement gave the two isomeric lactams **6a** and **6b**. The intermediate *p*-toluenesulfonyloximes **5a** and **5b** were stable at room temperature and could be easily separated by chromatography. Regioselective rearrangement occurred on heating to 100 °C in a microwave synthesizer to give **6a** and **6b**, respectively. Alternatively, a one-step modified Schmidt reaction (NaN_3, $TiCl_4$, MeCN, reflux) of **4** gave the mixed lactams directly. N-Methylation of the lactams occurred smoothly on treatment with sodium hydride and methyl iodide.

α-Methylation of the cyclohexanone **4** via the corresponding β-ketoesters gave **8a** and **8b** (Scheme 2). As expected, these were formed exclusively as the thermodynamically more stable equatorial isomers. Modified Schmidt rearrangement of **8a** gave **9a** as the major product, the result of migration of the secondary alkyl group. Migration of the primary group to give **9b** was also seen, but as a minor component. Under the same conditions, **8b** gave exclusive migration of the secondary alkyl group to give **9c**. The isomer was not detected.

Keywords: NK_1; Emesis; Lactam.
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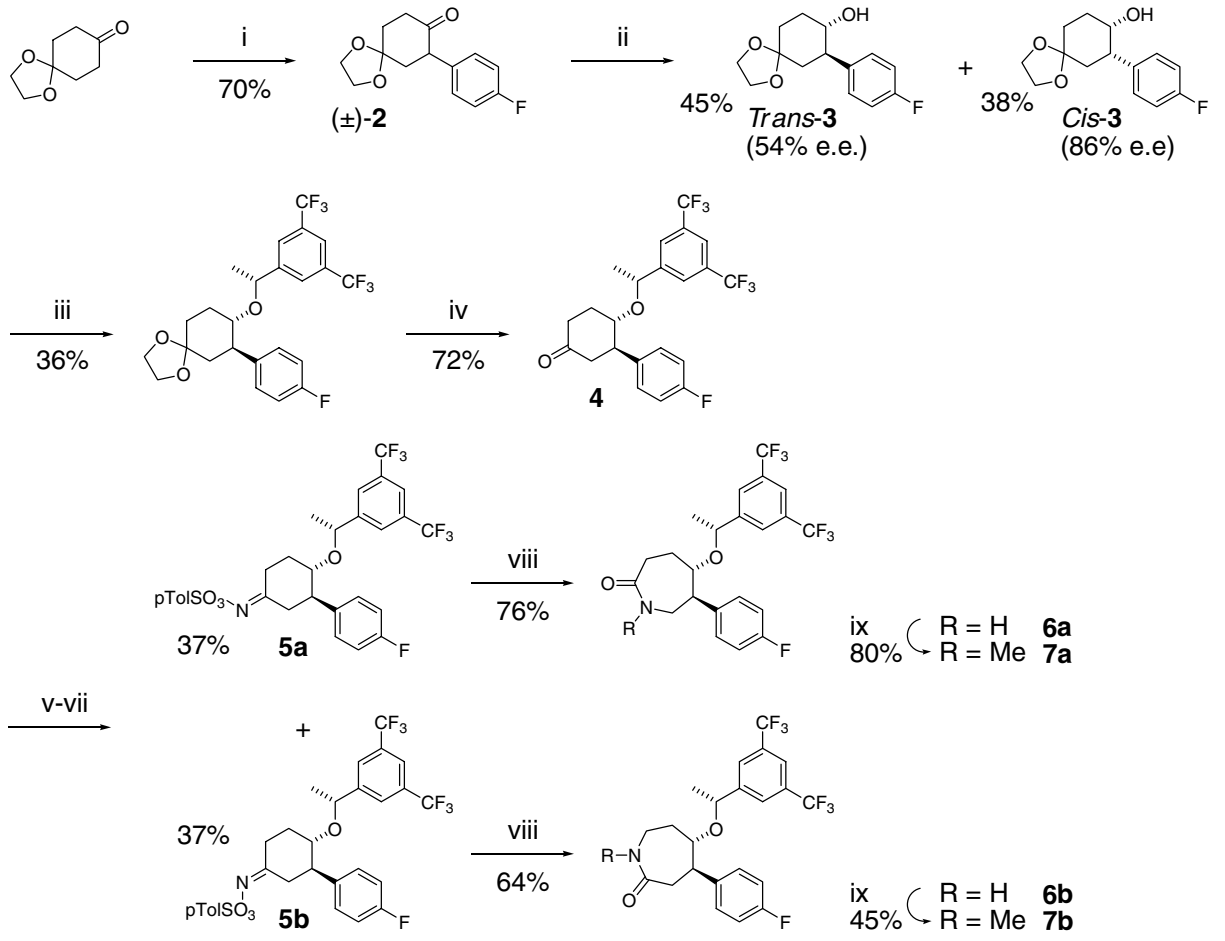
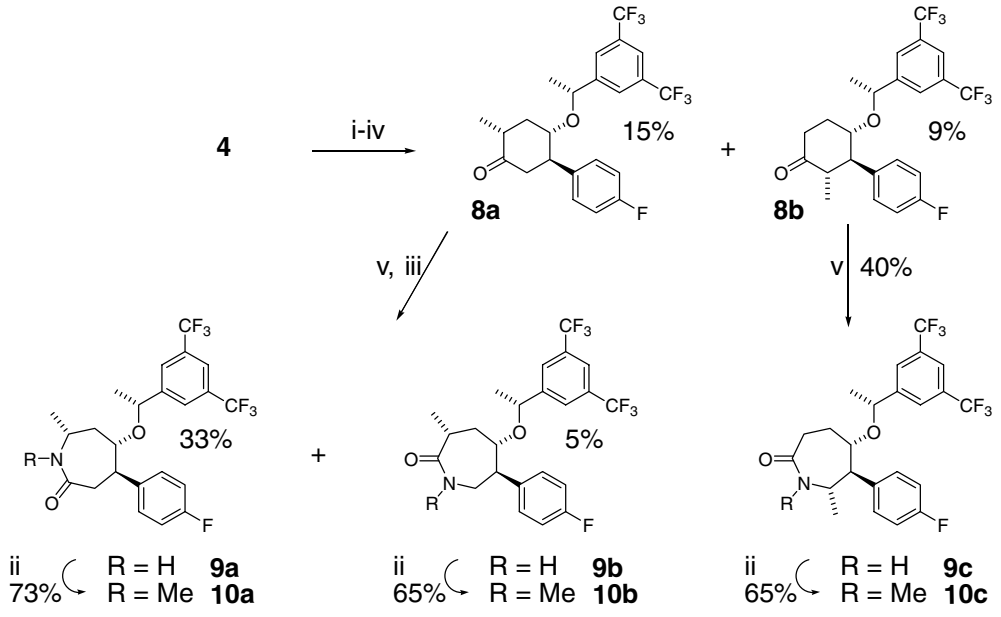
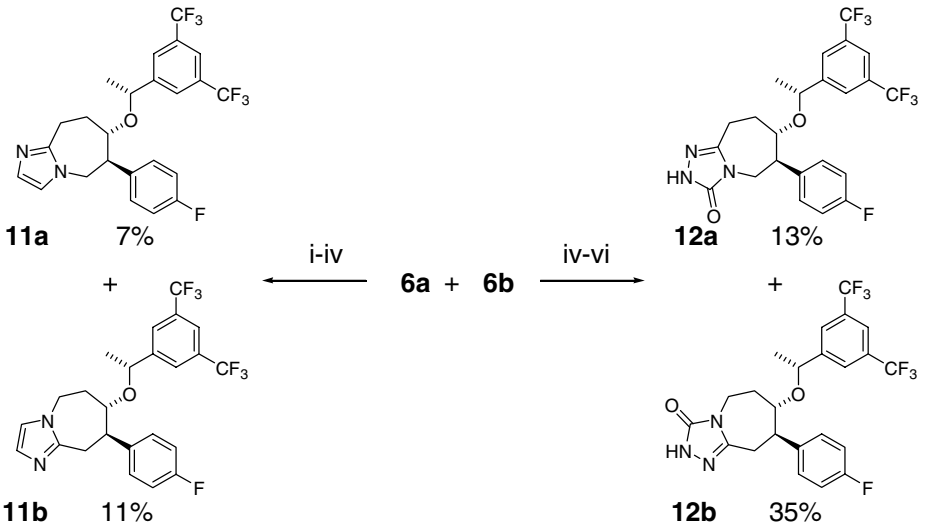
doi:10.1016/j.bmcl.2006.02.080



Scheme 1. Reagents and conditions: (i) 1-bromo-4-fluorobenzene, tris(dibenzylideneacetone)dipalladium(0), xantphos, NaO-*t*-Bu, THF, 80 °C; (ii) BH_3·DMS, (*R*)-2-methyl-CBS-oxaborolidine, $PhCH_3$, −20 °C; (iii) (*S*)-1-(3,5-bistrifluoromethylphenyl)ethyl-2,2,2-trichloroacetimidate, HBF_4, 1,2-DCE, hexanes, −16 °C; (iv) TFA, CH_2Cl_2, H_2O; (v) NH_2OH·HCl, NaOH, EtOH–H_2O, reflux; (vi) *p*-$TolSO_2Cl$, DMAP, CH_2Cl_2; (vii) separate isomers; (viii) 100 °C (microwave heating), THF–H_2O; (ix) NaH, MeI, DMF.



Scheme 2. Reagents and conditions: (i) NaH, dimethylcarbonate, THF, reflux; (ii) NaH, MeI, DMF; (iii) separate isomers; (iv) NaCl, H_2O, DMSO, 150 °C; (v) NaN_3, $TiCl_4$, MeCN, reflux.



Scheme 3. Reagents and conditions: (i) Lawesson's reagent, $PhCH_3$; (ii) $H_2NCH_2CH(OMe)_2$, $Hg(OAc)_2$, THF; (iii) *p*-TsOH, $PhCH_3$, 70 °C; (iv) separate isomers; (v) Me_3OBF_4, CH_2Cl_2; (vi) EtO_2CNHNH_2, EtOH, 150 °C.

The fused imidazoles (**11a** and **11b**) and triazolones (**12a** and **12b**) were prepared by activation of the lactams **6a** and **6b** as shown (Scheme 3).

The regiochemistry of the isomeric product pairs **6a/6b**, **11a/11b**, and **12a/12b** was determined through correlation spectroscopy (COSY) assignment of all the ^{1}H NMR signals due to protons on the seven-membered ring. The signals due to the methylene protons either side of the amide link or fused heterocycle showed characteristic chemical shifts.[6] In the case of **6a/6b**, further evidence came from coupling of the exchangeable lactam NH to the adjacent methylene. However, this was not the case for the methylated lactams **9a–c**. Correlation spectroscopy yielded the ^3J proton coupling around the ring, but the signals due to the methylene and methine protons either side of the amide link varied considerably between isomers and were therefore not characteristic. Where coupling of the exchangeable lactam NH to either an adjacent methylene or methine group was seen, an assignment of structure could be made. Further confirmation could be obtained from the ^{13}C chemical shifts for the methylene and methine carbons either side of the amide link. Unlike the proton chemical shifts, these were consistent and characteristic for all isomers. These were determined via multiplicity edited heteronuclear single quantum correlation experiments (HSQC-DEPT), which provide a reading for the carbon chemical shift to which a proton is directly connected. In this series, the signal due to the carbon adjacent to the lactam nitrogen had a characteristic chemical shift of ca. 50 ppm, whereas the signal due to the carbon adjacent to the lactam carbonyl had a characteristic chemical shift of 35–42 ppm. Assignment of this carbon through the phase of the cross peak indicated whether the carbon was part of a methylene or a methine group.

Table 1. hNK_1R affinity, hI_{Kr} affinity, and in vivo activity

Compound	hNK_1R IC_{50}[a] (nM)	hI_{Kr} K_i[b] (μM)	t = 1 h Gerbil FT[c]	
			ID_{50} (mg/kg po)	Plasma IC_{50}[d] (nM)
6a	0.14 ± 0.05	>9	1.06	57
6b	0.64 ± 0.4	>9	0% at 3	
7a	0.12 ± 0.03	>9	0.64	73
7b	0.53 ± 0.13	>9	Not tested	
9a	0.41 ± 0.11	8.5	64% at 3	
9b	0.23 ± 0.04	2.4	Not tested	
9c	0.09 ± 0.03	>9	0.09	14
10a	0.49 ± 0.15	>9	8% at 3	
10b	0.44 ± 0.10	5.4	5% at 3	
10c	0.33 ± 0.10	6.7	0.24	
11a	0.28 ± 0.03	1.8	4% at 3	
11b	0.43 ± 0.08	1.4	0% at 3	
12a	0.19 ± 0.04	>9	0.97	
12b	0.22 ± 0.08	>9	0.8	83

[a] Displacement of [^{125}I] labeled substance P from the cloned hNK_1 receptor expressed in CHO cells. Data are means ± SD (n = 3).[7]
[b] Displacement of labeled MK-499 from cloned channel expressed in HEK cells.[8]
[c] Inhibition of GR73632-induced foottapping in gerbils.[9] Where an ID_{50} value was not determined, % inhibition at 3 mg/kg po is quoted.
[d] Plasma drug levels determined by LC–MS/MS following protein precipitation.

The biological results for compounds based on both lactam and fused heterocyclic cores are shown in Table 1.

High NK_1R binding affinity was observed across the whole series. Introduction of methyl substituents, either on the ring nitrogen or α- to the lactam was well tolerated. In particular, **9c** had very high hNK_1R affinity. Good selectivity over affinity for the hERG ion channel (hI_{Kr}) was seen.

In order to assess their ability to occupy central hNK_1 receptors in vivo, selected compounds were profiled for their ability to inhibit foot tapping in gerbils induced by central infusion of the NK_1R agonist GR73632. This behavioral response is specific to gerbils, which show receptor pharmacology similar to the human receptor. The response is centrally mediated so inhibition demonstrates that a compound blocks central receptors.[9] In order to assess oral bioavailability, compounds were dosed po 1 h before the agonist challenge (Table 1). Gratifyingly, we were able to identify compounds from this series which were active at low dose and plasma drug exposure, indicating both oral bioavailability and brain penetration. Interestingly, compounds based on the 5,6-azepin-2-one core (**6a**, **7a**, **9c**, and **10c**) showed greater potency than the analogs based on the 4,5-azepin-2-one (**6b**, **9a**, and **10a**). The reasons for such differences between compounds with similar in vitro affinities are not clear. Compound **9c** was the most potent compound in this series, one of the most potent compounds from any series tested to date in this assay.

Pendant heterocycles, such as triazolone, are frequently beneficial in hNK_1R antagonists. The presence of lactams in **6a** and **6b** gave an opportunity to introduce heterocycles, but fused to the core rather than pendant. Both imidazole and triazolone were well tolerated by the receptor. The imidazoles (**11a** and **11b**) were inactive in vivo and showed increased hI_{Kr} liability. However, introduction of the triazolone gave compounds with good in vivo activity and low hI_{Kr} affinity (**12a** and **12b**).

Pharmacokinetic properties were determined for the lactam lead **6a** in rat. These indicated that the compound had moderate clearance (33 mL/min/kg) and good half-life (5.6 h).

In summary, a new class of high affinity hNK_1R antagonists based on seven-membered ring cores has been identified. This series, with relatively simple, compact structures, includes compounds with promising in vivo properties.

References and notes

1. Dando, T. M.; Perry, C. M. *Drugs* **2004**, *64*, 777.
2. Diemunsch, P.; Schoeffler, P.; Bryssine, B.; Cheli-Muller, L. E.; Lees, J.; McQuade, B. A.; Spraggs, C. F. *Br. J. Anaesth.* **1999**, *82*, 274.
3. Albert, J. S. *Expert Opin. Ther. Patents* **2004**, *14*, 1421; Gerspacher, M. *Prog. Med. Chem.* **2005**, *43*, 49.
4. Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. *J. Am. Chem. Soc.* **2000**, *122*, 1360.
5. Finke, P. E.; Maccoss, M.; Meurer, L. C.; Mills, S. G.; Caldwell, C. G.; Chen, P.; Durette, P. L.; Hale, J.; Holson, E.; Kopka, I.; Robichaud, A. WO9714671, **1997**; *Chem. Abstr.*, *127*, 17433.
6. Selected spectroscopic data. Compound (**6a**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (1H, s), 7.24 (2H, s), 6.92 (2H, m), 6.83 (2H, m), 5.92 (1H, br m), 4.42 (1H, q, J = 6.5 Hz), 3.43 (1H, m), 3.37 (1H, m), 3.15 (1H, m), 2.76 (1H, t, J = 9.6 Hz), 2.62 (1H, dd, J = 13.7, 8.6 Hz), 2.49 (1H, t, J = 13.7 Hz), 2.35 (1H, m), 1.81 (1H, m), and 1.34 (3H, d, J = 6.5 Hz).
Compound (**6b**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (1H, s), 7.23 (2H, s), 6.95 (2H, m), 6.82 (2H, m), 6.08 (1H, br m), 4.34 (1H, q, J = 6.4 Hz), 3.43 (1H, m), 3.40 (1H, m), 3.29 (1H, m), 2.88 (1H, t, J = 10.8 Hz), 2.74 (1H, dd, J = 14.0, 10.8 Hz), 2.53 (1H, d, J = 14.0 Hz), 2.33 (1H, m), 1.77 (1H, m), and 1.31 (3H, d, J = 6.4 Hz).
Compound (**11a**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (1H, s), 7.393 (2H, s), 6.88–6.71 (6H, m), 4.52 (1H, q, J = 6.4 Hz), 4.18 (1H, d, J = 14.4 Hz), 3.97 (1H, dd, J = 14.4, 8.7 Hz), 3.56 (1H, m), 3.48 (1H, dd, J = 14.5, 7.0 Hz), 2.91 (1H, t, J = 8.7 Hz), 2.84 (1H, dd, J = 14.5, 10.2 Hz), 2.26 (1H, m), 1.84 (1H, m), and 1.39 (3H, d, J = 6.4 Hz).
Compound (**11b**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (1H, s), 7.33 (2H, s), 6.88–6.79 (6H, m), 4.42 (1H, q, J = 6.4 Hz), 4.25 (1H, dd, J = 14.3, 7.7 Hz), 3.92 (1H, dd, J = 14.3, 9.6 Hz), 3.60 (1H, m), 3.23 (1H, d, J = 15.2 Hz), 2.97 (1H, dd, J = 15.2, 10.0 Hz), 2.88 (1H, t, J = 10.0 Hz), 2.33 (1H, m), 1.92 (1H, m), and 1.36 (3H, d, J = 6.4 Hz).
Compound (**12a**): ^{1}H NMR (400 MHz, CD_3OD) δ 7.75 (1H, s), 7.44 (2H, s), 7.04 (2H, m), 6.81 (2H, m), 4.635 (1H, q, J = 6.4 Hz), 3.91–3.68 (3H, m), 2.95 (1H, m), 2.78 (2H, m), 2.51 (1H, m), 1.73 (1H, m), and 1.33 (3H, d, J = 6.4 Hz).
Compound (**12b**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.95 (1H, s), 7.73 (1H, s), 7.34 (2H, s), 6.93–6.81 (4H, m), 4.44 (1H, q, J = 6.4 Hz), 4.17 (1H, dd, J = 13.8, 7.4 Hz), 3.59 (2H, m), 3.00 (1H, d, J = 15.0 Hz), 2.91 (1H, m), 2.80 (1H, dd, J = 15.0, 10.2 Hz), 2.30 (1H, m), 1.88 (1H, m), and 1.37 (3H, d, J = 6.4 Hz).
7. Cascieri, M. A.; Ber, E.; Fong, T. M.; Sadowski, S.; Bansal, A.; Swain, C. J.; Seward, E. M.; Frances, B.; Burns, D.; Strader, C. D. *Mol. Pharmacol.* **1992**, *42*, 458.
8. Cooper, L. C.; Carlson, E. J.; Castro, J. L.; Chicchi, G. G.; Dinnell, K.; Di Salvo, J.; Elliott, J.; Hollingworth, G. J.; Kurtz, M. M.; Ridgill, M. P.; Rycroft, W.; Tsao, K. L.; Swain, C. J. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1759.
9. Rupniak, N. M. J.; Tattersall, F. D.; Williams, A. R.; Rycroft, W.; Carlson, E.; Cascieri, M. A.; Sadowski, S.; Ber, E.; Hale, J. J.; Mills, S. G.; MacCoss, M.; Seward, E.; Huscroft, I.; Owen, S.; Swain, C. J.; Hill, R. G.; Hargreaves, R. J. *Eur. J. Pharmacol.* **1997**, *326*, 201.