

Design, Synthesis, and Optimization of Balanced Dual NK₁/NK₃ Receptor Antagonists

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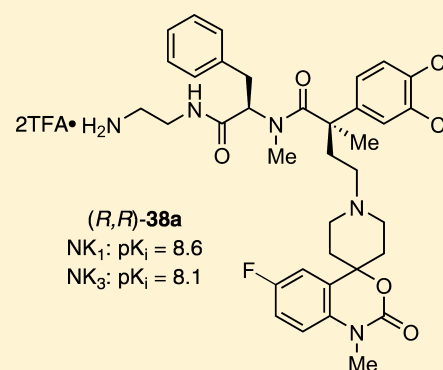
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S Supporting Information

ABSTRACT: In connection with a program directed at potent and balanced dual NK₁/NK₃ receptor ligands, a focused exploration of an original class of peptidomimetic derivatives was performed. The rational design and molecular hybridization of a novel phenylalanine core series was achieved to maximize the in vitro affinity and antagonism at both human NK₁ and NK₃ receptors. This study led to the identification of a new potent dual NK₁/NK₃ antagonist with pK_i values of 8.6 and 8.1, respectively.



KEYWORDS: Schizophrenia, peptidomimetic, dual NK₁/NK₃ receptor antagonists, molecular hybridization

Both neurokinin 1 (NK₁) and neurokinin 3 (NK₃) receptors are localized in the corticolimbic structures of the brain.¹ They modulate dopaminergic transmission, play a role in the control of mood, and are involved in the response to stress, exposure to psychostimulants, and risk factors for the induction of psychoses. Behavioral studies of neurokinin 3 antagonists in rodents suggest potential utility in the treatment of schizophrenia.^{2–5} In a recent report, we described a novel series of small molecules derived from a phenylglycine core and intended as dual human NK₁/NK₃ receptor antagonists for the potential treatment of schizophrenia.⁶ These compounds exhibited in vitro preferential NK₁ antagonist activity for the NK₁ receptor ($K_i = 7.8$) for the most active analogue, but insufficient NK₃ receptor antagonism (pK_i = 6.0 or less). In an effort to identify modifications that enhance NK₃ receptor antagonism yet preserve or augment already established NK₁ receptor affinity, we explored structure–activity relationships (SAR) focusing on modifications of the *N*- and *C*-terminal regions of the original motif.

In line with these objectives, we first examined the aminoethyl appendage in order to modulate the *C*-terminal side-chain in which the original phenylglycine central core was replaced by a *D*- or *L*-phenylalanine residue. Given the superior NK₁ receptor potency observed for the conformationally restricted *N*-methylated ligand, we started with a first generation series containing a central *N*-methyl phenylalanine core.⁷

Molecular hybridization is a well-recognized strategy of rational design of new ligands based on the recognition of pharmacophoric subunits in the molecular structure of two or more known bioactive derivatives.^{8–10} The appropriate fusion of these subunits can lead to the design of new hybrid architectures with the prospects of combining preselected characteristics of the original template.

In this context, we turned our attention to the known α -aryl acetamide derivatives **3** and **4** as potent and selective NK₁ receptor antagonists.^{11–17} Both series are structurally related with a common 3,4-dichlorophenyl acetic acid unit, either mono- or disubstituted at the benzylic position, linked via an alkyl spacer to a piperidiny or spiro-piperidiny motif. We hypothesized that the combination of this moiety with our previously identified⁶ *N*-(2-aminoethyl)phenylalanine pharmacophore, tethered by a 3,4-dichlorophenyl acetyl unit, could produce a new hybrid compound **2** with potentially improved and balanced affinity for the NK₁ and NK₃ receptors (Figure 1). Although difficult to predict, it was hoped that reduced backbone flexibility¹⁸ would lead to favorable pharmacokinetics, ultimately resulting in enhanced potency and selectivity.

The synthetic strategy developed for the preparation of the *N*-methyl compounds **11–14** is outlined in Scheme 1. It started from chiral acid (*R*)-**5**, or its enantiomer (*S*)-**6**, efficiently

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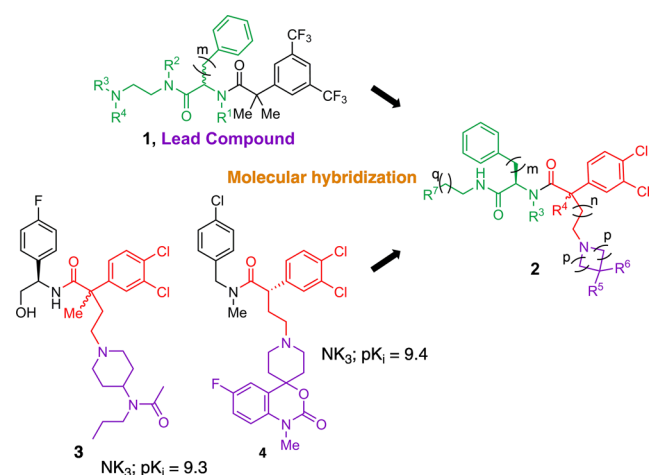
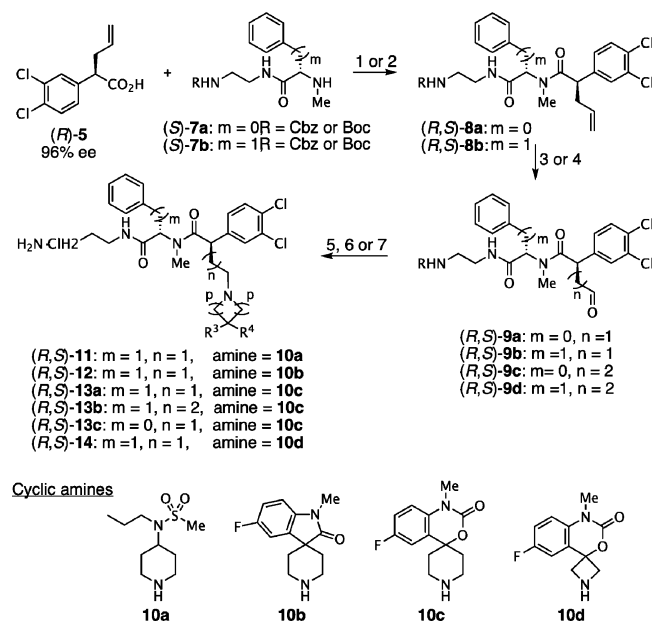


Figure 1. Rational design of dual NK₁/NK₃ receptor antagonists (generic structure **2**) by applying the molecular hybridization approach to our hit structure **1**⁶ and potent NK₃R antagonists **3** and **4** (Hoffmann–La Roche).^{11,14}

Scheme 1. Synthesis of the *N*-Methylated Analogues **11–14**^a



^aReagents and conditions: (1) BOP, Hünig's base, THF, r.t., 12 h, 99% 9:1 dr; (2) DEPBT, Hünig's base, THF, 0 °C to r.t., 8 h, 94%, 4:1 dr; (3) (i) NMO (50 wt % in H₂O), OsO₄ (4 wt % in H₂O), H₂O–THF (1:3, v/v), r.t.; (ii) NaIO₄, r.t., 87%; (4) (i) catecholborane, RhCl(PPh₃)₃ (3 mol %), THF, 0 °C to r.t. then H₂O₂ (30% w/w), EtOH, phosphate buffer pH 7.0, 0 °C to r.t.; (ii) DMP, CH₂Cl₂, r.t., 8 h, 55 to 95% (2-steps); (5) **10a–d**, DCE or CH₂Cl₂, 3 Å MS, r.t. then NaBH(OAc)₃, r.t., 42 to 90%; (6) R = Cbz, (i) H₂ (1 atm), Pd/C (10 wt %), EtOH, 4 M HCl in dioxane, r.t.; (ii) RP-HPLC-prep, 32 to 60%; (7) R = Boc, (i) HCl_(g), EtOAc, 0 °C to r.t.; (ii) RP-HPLC-prep, 40 to 57%.

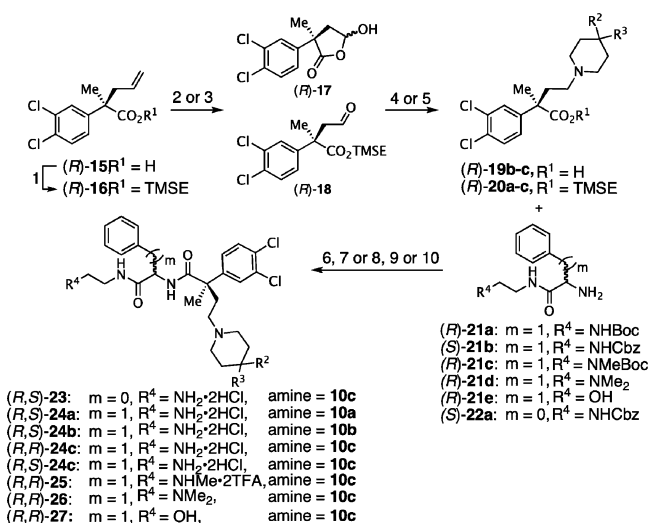
obtained by monoallylation of commercially available 3,4-dichlorophenylacetic acid followed by resolution as diastereomeric salts with (+)- and (–)- α -methylbenzylamine, respectively,^{19–23} with high enantioselectivity ($\geq 96\%$ ee).^{24–29} Phenylglycine and phenylalanine building blocks (*S*)-**7a,b** were concisely obtained by acylation of monoprotected α,ω -alkanediamines^{7,30,31} with *N*-methylated aminoacids.^{7,32,33}

With the C2 stereochemistry set, conversion to amides (*R,S*)-**8a,b** was done via standard solution-phase peptide synthesis with *N*-Boc or *N*-Cbz protected *N*-methyl amines (*S*)-**7** using DEPBT³⁴ or BOD³⁵ and Hünig's base. We explored a variety of coupling protocols to form the *N*-methyl amide linkage. Not unexpectedly, partial epimerization of the allylic α -center was observed {9:1 dr for (*R,S*)-**8a** and 4:1 dr for (*R,S*)-**8b**}. However, simple separation of diastereomers by silica gel flash chromatography easily afforded enantiopure (*R,S*)-**8a,b** in good yields. The one-pot, two-step oxidation of the allyl side chain with osmium tetroxide and *N*-methylmorpholine *N*-oxide (NMO) followed by sodium periodate cleavage afforded aldehydes (*R,S*)-**9a,b** in good yields. Alternatively, amides (*R,S*)-**8a,b** were converted to the corresponding primary alcohols via a regioselective hydroboration with catecholborane in the presence of Wilkinson's catalyst and subsequent oxidative workup using aqueous H₂O₂ under neutral conditions.^{36,37} Oxidation of these alcohols with Dess–Martin periodinane (DMP)^{38,39} in CH₂Cl₂ afforded aldehyde (*R,S*)-**9c** and (*R,S*)-**9d** in 95% overall yield. Reductive amination with 4-substituted piperidine **10a**,^{13,40,41} spirocyclic oxindole **10b**,^{42–46} spiro-piperidine **10c**,^{14,47,48} and spiroazetidine **10d**^{49,50} with aldehydes **9a** to **9d** using sodium triacetoxyborohydride in 1,2-dichloroethane^{51,52} (DCE) afforded the corresponding tertiary amines in moderate to excellent yields. The synthesis was completed by deprotection of the *N*-Cbz- or *N*-Boc carbamate groups by hydrogenation or acidolysis, respectively, followed by final purification using preparative RP-HPLC to afford compounds (*R,S*)-**11** to **14**. The corresponding diastereoisomers (*S,S*)-**11**, (*S,S*)-**12**, and (*S,S*)-**13a,b** were prepared using similar strategies starting from (*S*)-**6**.^{7,32,33}

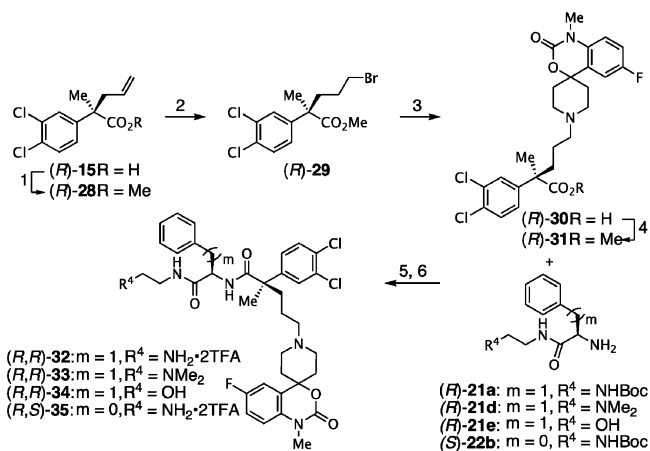
We next investigated the effect of a methyl substituent on the benzylic carbon adjacent to the 3,4-dichlorophenyl ring rather than linked to the nitrogen as exemplified by the *second* generation analogues (*R,S*)-**23** to **27** as shown in Scheme 2. Optically pure acid (*R*)-**15** with the all-carbon quaternary stereogenic center was obtained by an efficient resolution ($\geq 96\%$ ee) by fractional crystallization of diastereomeric salts.^{20,53–55} TMSE ester (*R*)-**16** was subjected to dihydroxylation and subsequent one-pot oxidative cleavage using NaIO₄ to give aldehyde (*R*)-**18**.

Alternatively, direct OsO₄-catalyzed oxidative cleavage of acid (*R*)-**15** afforded hemiacetal (*R*)-**17** as a diastereomeric mixture. Piperidine **10a** or spiro-piperidine **10b,c** motifs were efficiently introduced by reductive amination using sodium triacetoxyborohydride in DCE^{51,52} or sodium cyanoborohydride in methanol,⁵⁶ respectively. Acids (*R*)-**19b** to (*R*)-**19c** or TMSE esters (*R*)-**20a–c**, pretreated with TBAF in THF, were coupled with primary amines^{7,57} (*S*)-**21b**, (*R*)-**21a,c–e**, and (*S*)-**22** using standard peptide coupling conditions (HBTU⁵⁸ or PyBOP⁵⁹). Finally, the amino protecting groups were removed by acidolysis or hydrogenolysis to yield the desired products (*R,S*)-**23** and (*R,S*)-**24a–c** that were further purified by RP-HPLC affording the corresponding dihydrochloride salts after lyophilization. Compounds (*S,S*)-**23**, (*S,S*)-**24a–c**, and (*S,R*)-**24b** were prepared from enantioenriched acid (*S*)-**22** using a similar route.⁷

In order to explore the effect of linker length between the 3,4-dichlorophenyl acetamide core and the piperidine pharmacophore, compounds **32–35** bearing a *C*-methyl substituent on the benzylic carbon and a three-carbon spacer were prepared as described in Scheme 3. Since the synthetic routes previously described could not be applied to access these compounds, we

Scheme 2. Synthesis of the C-Methylated α,α -Disubstituted Analogues 23–27^a

^aReagents and conditions: (1) $\text{HO}(\text{CH}_2)_2\text{Si}(\text{CH}_3)_3$, EDC, Pyr, THF, r.t., 12 h, 61%; (2) NaIO_4 , OsO_4 (4 wt % in $\text{H}_2\text{O}/\text{THF}$ (1:3, v/v), r.t.); (3) (i) NMO (50 wt % in H_2O), OsO_4 (4 wt % in H_2O), $\text{H}_2\text{O}-\text{THF}$ (1:3, v/v), r.t.; (ii) NaIO_4 , r.t.; (4) **10a–c**, DCE or CH_2Cl_2 , 3 Å MS, r.t. then $\text{NaBH}(\text{OAc})_3$, r.t., 43 to 73% (2-steps); (5) TBAF, THF, r.t., 1 h; (6) HBTU, Hünig's base, THF, r.t., 12 h, 65 to 85% (2-steps); (7) PyBOP, DMAP, Hünig's base, THF, CH_2Cl_2 , r.t.; (8) $R^4 = \text{NH}(\text{Boc})$, (i) $\text{HCl}_{(\text{g})}$, EtOAc, 0 °C to r.t.; (ii) RP-HPLC-prep, 40–63%; (9) $R^4 = \text{NH}(\text{Cbz})$, (i) H_2 (1 atm), Pd/C (10 wt %), EtOH, 4 M HCl in dioxane, r.t.; (ii) RP-HPLC-prep, 35 to 59%; (10) $R^4 = \text{NMe}(\text{Boc})$, (i) TFA, CH_2Cl_2 , r.t., 2 h 76%; (ii) lyophilization.

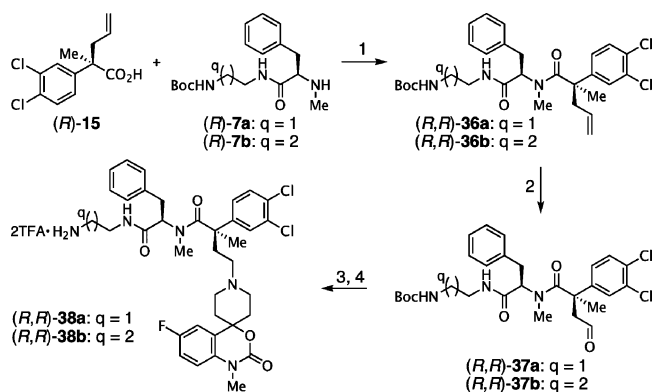
Scheme 3. Synthesis of the C-Methylated α,α -Disubstituted Analogues 32–35 with a 3-Carbon Spacer^a

^aReagents and conditions: (1) SOCl_2 , MeOH, 0 °C to r.t., 12 h, 99%; (2) $\text{HBr}_{(\text{g})}$, cat. *m*CPBA, PhMe, 0 °C, 2 h; (3) **10c**, Cs_2CO_3 , DMF, r.t., 4 h; (4) aq. LiOH, THF, reflux, 12 h, 52% (3-steps); (5) HBTU, Hünig's base, THF, r.t., 65 to 85%; (6) TFA, CH_2Cl_2 (1:1, v/v), 0 °C to r.t., 65 to 75%.

decided to introduce the spiro piperidine moiety prior to the peptide coupling. Accordingly, methyl ester (*R*)-28 was treated with hydrogen bromide in toluene under free-radical conditions to provide bromide (*R*)-29 in 80% yield. Nucleophilic displacement with spiro piperidine **10c**, followed by saponification of the methyl ester gave the key spiro piperidine acid (*R*)-31 in 62% yield over two steps.⁷ HBTU-Mediated amide

formation with the appropriate aromatic residue followed by acidolysis, if applicable, completed the synthesis of these second-generation analogues.

Finally, we focused on the synthesis of third-generation *N,C*-bismethylated α,α -disubstituted backbone peptidomimetic analogues.^{60–62} The challenging synthesis of these sterically congested derivatives could not be achieved using the peptide coupling conditions we previously developed. However, acylation with amines (*R*)-7b,c with enantioenriched acid chloride of (*R*)-15 in the presence of pyridine, afforded the desired amides (*R,R*)-36a,b (Scheme 4). Subjection of the allyl

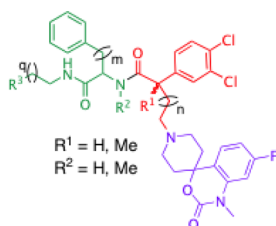
Scheme 4. Synthesis of the *N,C*-Bismethylated α,α -Disubstituted Analogues 38a–b^a

^aReagents and conditions (1) (i) SOCl_2 , PhH, reflux, 12 h; (ii) Pyr, THF, r.t., 35–70% (2-steps); (2) (i) NMO (50 wt % in H_2O), OsO_4 (4 wt % in H_2O), $\text{H}_2\text{O}-\text{THF}$ (1:3, v/v), r.t.; (ii) NaIO_4 , r.t.; (3) **10b**, NaBH_3CN , MeOH, r.t., 50–65% (2-steps); (4) TFA, CH_2Cl_2 (1:1, v/v), 75%.

side-chain to Lemieux–Johnson conditions provided aldehydes (*R,R*)-37a,b, which were then reacted with spiro piperidine **10b** using sodium cyanoborohydride in methanol.⁵⁶ Finally, upon exposure to TFA in dichloromethane, *N*-Boc deprotection yielded the desired peptidomimetics (*R,R*)-38a,b as their TFA salts in good overall yield.

The binding affinity of these hybrid compounds for human NK_1 and NK_3 receptors was determined using radioligand binding assays on membranes prepared from U-373MG cells endogenously expressing NK_1 receptors and recombinant CHO cells stably expressing NK_3 receptors.⁷ The results for selected compounds are presented in Table 1. Well balanced antagonism was observed especially with compounds bearing a benzylic quaternary C-methyl group (Table 1, entries 6, 9, 13, 14, 16). Whereas the *N*-methylated analogues (entries 1–5) showed good NK_1 receptor activity, only moderate NK_3 receptor antagonism was exhibited. Furthermore, the (*R,R*) configuration seems to be optimal for activity against NK_1/NK_3 receptor ligands. Extension of the methylene spacer arm (connecting the 3,4-dichlorophenyl acetamide and the spiro piperidine pharmacophore) had only a moderate effect on NK_1 R affinity but induced a 20–50-fold reduction in NK_3 receptor antagonism (Table 1, entries 3, 4, 12). Interestingly, the replacement of the (*R*)-phenylalanine central core by a (*R*)-phenylglycine residue (entries 1 vs 5, 6 vs 11, and 10 vs 12) did not significantly affect the dual antagonism, although the values remained modest. Concerning the influence of the C-terminal polar arm, the successive methylation of the primary amine group had a minor effect, but its replacement by an alcohol led

Table 1. pK_i Values of Hybrid Peptidomimetics 13, 23–27, 32–35, and 38 at Both Human NK₁ and NK₃ Receptors Determined by Competitive Binding Assays^a



entry	compd	R ³	n	m	q	pK _i	
						hNK ₁	hNK ₃
1	(R,S)-13a ^d	NH ₂	1	1	1	6.9	5.8
2	(S,S)-13a ^d	NH ₂	1	1	1	6.7	5.9
3	(R,S)-13b ^c	NH ₂	2	1	1	7.3	5.4
4	(S,S)-13b ^c	NH ₂	2	1	1	6.4	5.2
5	(R,S)-13c ^c	NH ₂	1	0	1	6.2	5.6
6	(R,S)-24c ^e	NH ₂	1	1	1	6.9	7.2
7	(S,S)-24c ^c	NH ₂	1	1	1	6.4	5.0
8	(S,R)-24c ^d	NH ₂	1	1	1	6.2	5.7
9	(R,R)-24c ^e	NH ₂	1	1	1	7.7	7.3
10	(R,R)-32	NH ₂	2	1	1	7.2	5.8
11	(R,S)-23 ^c	NH ₂	1	0	1	6.6	7.4
12	(R,S)-35	NH ₂	2	0	1	6.5	6.1
13	(R,R)-25	NHMe	1	1	1	7.8	7.7
14	(R,R)-26	NMe ₂	1	1	1	7.4	7.5
15	(R,R)-33	NMe ₂	2	1	1	7.7	6.0
16	(R,R)-27	OH	1	1	1	7.5	8.6
17	(R,R)-34	OH	2	1	1	7.8	6.9
18	(R,R)-38a	NH ₂	1	1	1	8.6	8.1
19	(R,R)-38b	NH ₂	1	1	2	8.4	7.6

^aEvaluation of the binding affinity (pK_i) of compounds at both (a) human NK₁ receptor and (b) human NK₃ receptor was done using [¹²⁵I]-Bolton Hunter-Substance P and [³H]-SR142801 as radioligands, respectively. Data represent n = 2 independent determinations performed in duplicate; SD < 0.2 pK_i.⁶ The selective NK₁ antagonist, vestipitant, displayed high affinity at NK₁ receptors (pK_i = 9.5), yet negligible affinity for NK₃ receptors (pK_i = 5.5 or less), while the selective NK₃ antagonist, talnetant, displayed high affinity for NK₃ receptors (pK_i = 8.5) and negligible affinity for NK₁ receptors.^{11,14}

to 12–20-fold improvement of the NK₃ receptor affinity (Table 1, entry 16).

Although promising NK₁R and NK₃R antagonist activity was seen with some third generation analogues, we were curious to see the effect of modifying the backbone conformation in N,C-bismethylated analogues. To our delight, the (R,R)-N,C-bismethylated analogue, 38a emerged as the most potent and well balanced dual antagonist (Table 1, entry 18).

In conclusion, we have prepared a series of hybrid analogues inspired from our previously reported lead compounds (generic structure 1) and the Hoffmann–La Roche NK₃ receptor antagonists 3 and 4 using phenylalanine as a central motif. In the course of this study, three generations of peptidomimetic hybrids were concisely synthesized from three sets of versatile building blocks. As a result of our lead optimization, we have found compounds with very promising in vitro antagonist activity against hNK₁ and hNK₃ receptors. Among these, analogue (R,R)-38a has particularly high and balanced affinities displaying pK_i values that compare favorably to the known

compounds 3 and 4 (Figure 1). Further optimizations in this series are in progress and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Synthetic procedures, analytical data, and assay descriptions. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

NK₁, neurokinin 1; NK₃, neurokinin 3

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