

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

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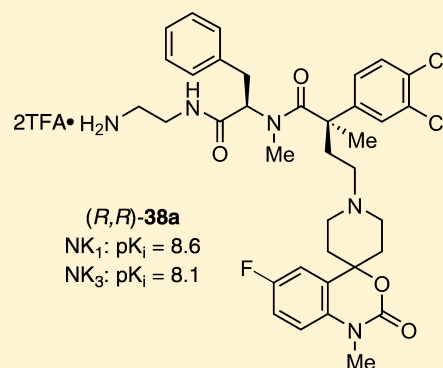
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S Supporting Information

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.

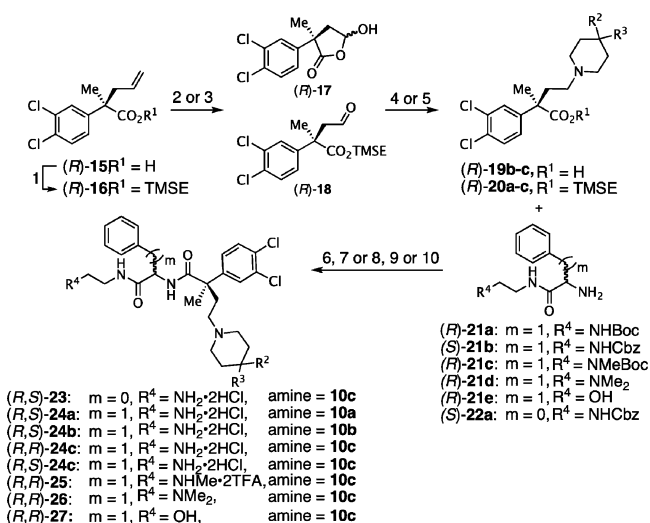
The synthetic strategy developed for the preparation of the *N*-methyl compounds **11–14** is outlined in Scheme 1. It started from chiral acid (*R*)-**5**, or its enantiomer (*S*)-**6**, efficiently

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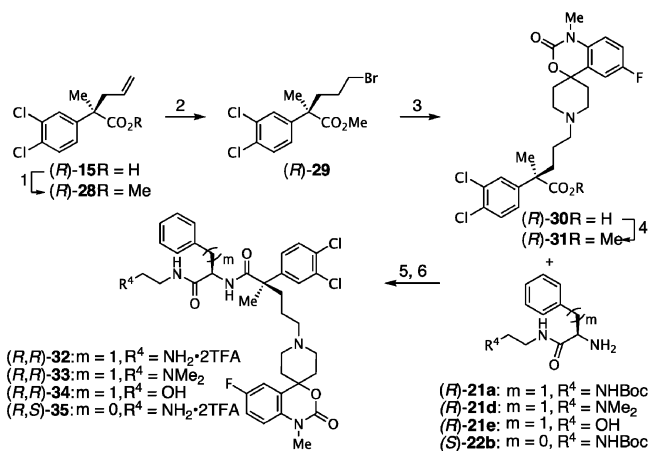
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Scheme 2. Synthesis of the C-Methylated α,α -Disubstituted Analogues 23–27^a

^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.

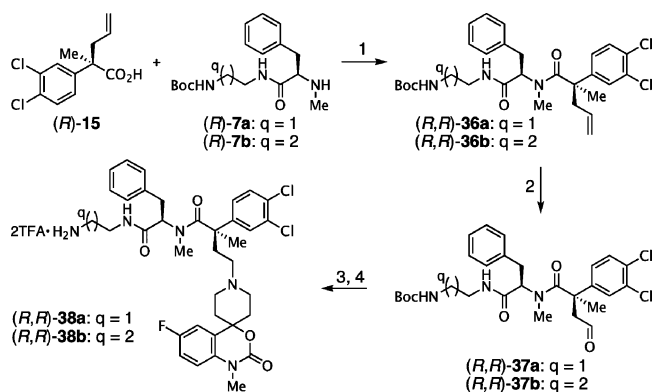
Scheme 3. Synthesis of the C-Methylated α,α -Disubstituted Analogues 32–35 with a 3-Carbon Spacer^a

^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 receptor 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

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