Drugs of the Future 1999, 24(8): 883-892

CCC: 0377-8282/99

Review Article

Dual neurokinin NK_1/NK_2 receptor antagonists

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Introduction

Neurokinins (NKs), also known as tachykinins (TKs), are members of a family of small peptides sharing the common C-terminal amino acid sequence Phe-X-Gly-Leu-Met-NH_2 (1-3). NKs are widely distributed throughout the central and peripheral nervous systems where they are released from neuronal sensory afferents (1). In mammals, the most prominent NKs – substance P, NKA and NKB – act as neurotransmitters and neuromodulators (1, 4). Both substance P and NKA are products of the preprotachykinin A gene which is expressed in the peripheral and central nervous systems (CNS), whereas NKB is produced by the preprotachykinin B gene selectively in the CNS (2). The effects of NKs are mediated via specific 7-transmembrane G-protein-coupled receptor subtypes which have been termed NK_1, NK_2 and NK_3 receptors. Substance P displays the highest affinity for the NK_1 receptors and NKA and NKB for the NK_2 and NK_3 receptor, respectively (5, 6).

NKs are involved in a number of pathological conditions including pain, arthritis, migraine, emesis, cancer, anxiety, depression, schizophrenia, asthma and airway diseases and NK receptor antagonists (mostly selective NK_1 antagonists) have been proposed to have potential clinical benefits (7-11).

The results obtained from animal and clinical studies in recent years provide emerging pharmacological evidence that NKs play an important role in airway disease induction and progression (7, 12-15) via the activation of NK_1 and NK_2 receptors. Furthermore, the studies suggest that NK receptor antagonists, especially dual NK_1/NK_2 antagonists, may represent a new treatment option for asthma and other airway diseases since lung tissue from asthma patients has been shown to overexpress NK_1 and NK_2 receptors (16, 17). The aim of this review is to provide an overview of the currently available dual NK_1/NK_2 antagonists as potential drug candidates for the treatment of airway diseases.

Neurokinins, NK receptors and NK antagonists in the airways

The respiratory tract is richly innervated with sensory nerves. Activation of NK-containing C-fibers by different stimuli such as capsaicin, cigarette smoke or respiratory viral infections, leads to the release of neuropeptides (notably substance P and NKA) within the lung. The release of the neuropeptides, in turn, causes an acute inflammatory response. This neurogenic inflammation is characterized by a number of NK receptor-mediated events (14, 15, 18-20) (Fig. 1).

The use of selective NK_1 antagonists such as CP-96345 (**1**) (21), CP-99994 (**2**) (22), FK-888 (**3**) (23, 24) and SR-140333 (**4**) (25), selective NK_2 antagonists such as saredutant (SR-48968; **5**) (26) and MEN-10,627 (**6**) (27) and dual NK_1/NK_2 antagonists such as FK-224 (**8**) (23, 24), MDL-105212A (**10**) (28) and S-16474 (**9**) (29), greatly facilitated the understanding of the physiological and pathological roles of NKs in airway diseases and elucidated the roles of the involved NK receptor subtypes. Microvascular leakage and vasodilation leading to protein plasma extravasation and edema, mucus hypersecretion, recruitment of inflammatory leukocytes, mast cell degranulation (histamine release), as well as the release of cytokines from the invading leukocytes are effects which are thought to be linked to the activation of NK_1 receptors, whereas bronchoconstriction, cough and, to some extent, bronchial hyperresponsiveness are triggered mainly via the NK_2 receptor (14, 15).

Indeed, SR-48968 was able to significantly inhibit NKA-induced bronchoconstriction in asthmatics for up to 24 h after a 100 mg p.o. dose (30). The potent and selective NK_1 antagonist FK-888, after an inhaled dose of 2.5 mg, shortened the recovery time of asthmatics in acute

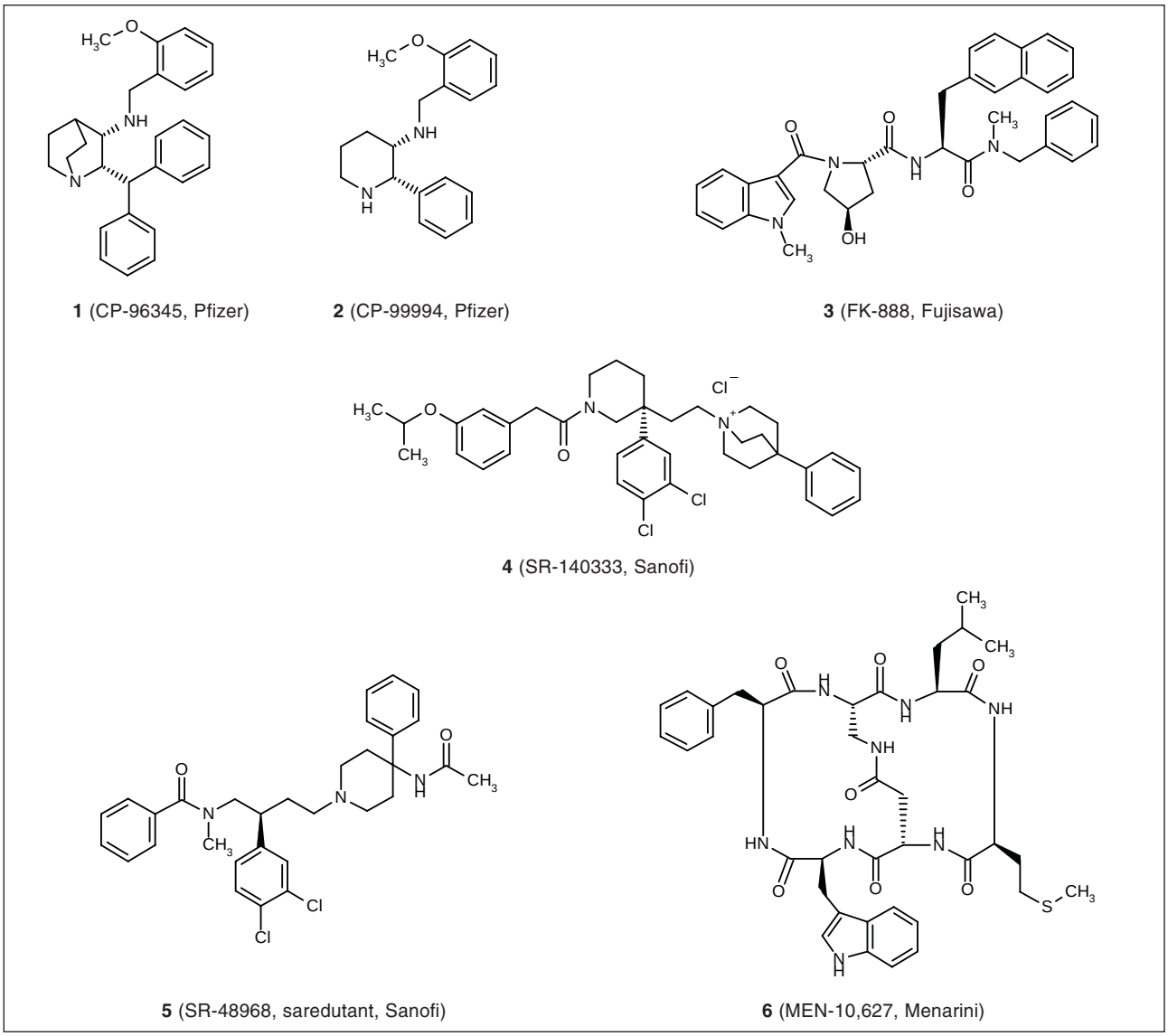


Fig. 1. Structures of selective neurokinin antagonists.

exercise-induced bronchoconstriction but did not affect the fall in specific airway conductance (9, 31). CP-96345 (a selective NK_1 antagonist) was shown to block cigarette smoke-induced airway edema (24) and NK_1 receptors were demonstrated to mediate substance P- or capsaicin-induced inflammatory cell adhesion in rat trachea (32). On the other hand, the selective NK_1 antagonist CP-99994, in a clinical trial for the treatment of asthma, had no effect on bronchoconstriction and cough induced by hypertonic saline after an i.v. dose of 0.25 mg/kg (33). This disappointing result is consistent with animal and human studies that indicated the involvement of NK_2 receptors rather than NK_1 receptors in bronchoconstriction and cough (34-36) (Fig. 2).

NK_3 receptors might also play a role in airway diseases since the selective NK_3 antagonist SR-142801 (osanetant; **7**) (37) has been shown to reduce substance P-induced bronchial hyperresponsiveness and microvascular leakage in guinea pigs (38).

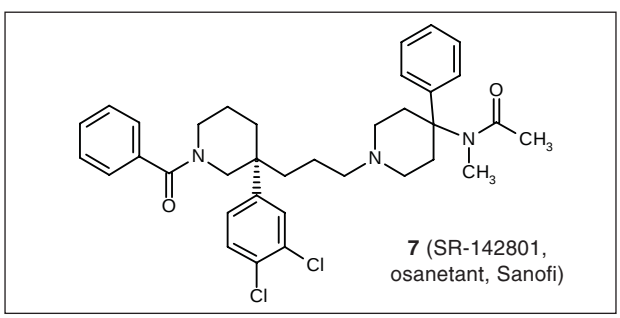


Fig. 2. Structure of SR-142801, an NK_3 antagonist.

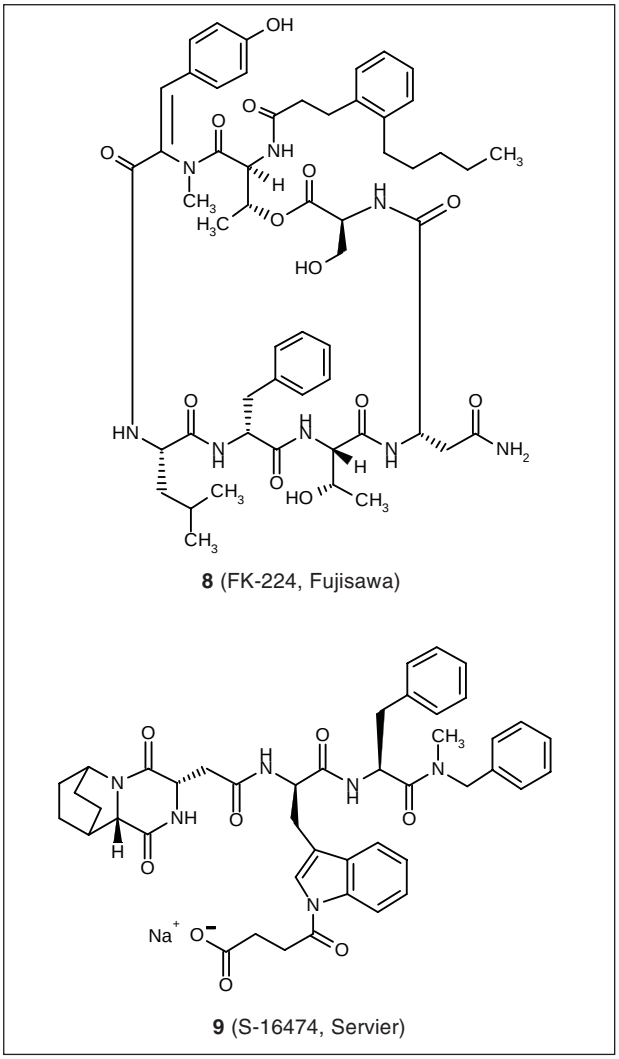
The observation that both NK_1 and NK_2 receptors are involved in the pathogenesis of airway diseases suggests

that an antagonist capable of blocking both NK_1 and NK_2 receptors (possibly with a balanced affinity for both receptors) may be the better treatment option over selective NK antagonists. In fact, some animal experiments in which NK_1 and NK_2 antagonists were coadministered suggest the existence of a synergistic effect. In a primate study, it was demonstrated that simultaneously administered NK_1 (CP-99994) and NK_2 (SR-48968) antagonists reduced eosinophil recruitment in bronchoalveolar lavage fluids induced by antigen challenge, whereas each antagonist administered alone had no such effect (25). In another study, coadministration of SR-140333 or FK-888 together with SR-48968 in cough experiments was able to potentiate the effect of SR-48968 administered alone. These findings led pharmaceutical companies to believe that the simultaneous blockade of NK_1 and NK_2 receptors offers an improved strategy for the treatment of airway diseases and to initiate drug discovery programs aimed at the identification of dual NK_1/NK_2 antagonists for the treatment of asthma and airway diseases.

Peptidic structures as dual NK_1/NK_2 antagonists

Fujisawa's FK-224 (**8**), a natural product from microbial cultures, showed moderate affinity to human NK_1 and NK_2 receptors (IC_{50} = 190 nM) (23). Despite the rather modest binding affinities, the compound proved to be active in a number of animal models. In guinea pigs, FK-224 (10 μg/kg i.v.) was able to completely inhibit substance P-induced plasma protein extravasation in the lower trachea and main bronchi (24). Activity could also be observed in cigarette smoke- or vagus nerve stimulation-induced plasma protein extravasation models in guinea pigs. The compound was also an effective inhibitor of β-Ala^8-NKA(4-10)- and [Sar]-substance P-induced bronchoconstriction. With an ED_{50} value of 10 μg/knee, antiinflammatory properties of FK-224 could also be demonstrated in carrageenin- and substance P-induced plasma protein extravasation models in rats (39). Due to its activity in guinea pig models of asthma, FK-224 was chosen for clinical evaluation. In a clinical trial, a 2 mg aerosol dose of FK-224 over several weeks had no effect on lung function (40) and in another study 4 mg of aerosolized FK-224 showed no protection against NKA-induced bronchoconstriction in mild to moderate asthmatics (17). However, a 4 mg aerosol dose of the compound had a beneficial effect on bradykinin-induced bronchoconstriction and cough in asthma patients (41). Due to this controversial and rather disappointing outcome of the clinical trial, development of FK-224 was suspended.

Another peptidic structure, Servier's S-16474 (**9**), was reported to inhibit substance P-, NKA- and capsaicin-induced bronchoconstriction in guinea pigs after i.v. application. In anesthetized guinea pigs, S-16474 (29) inhibited bronchospasms induced by substance P (ED_{50} = ~4 μmol/kg i.v.), NKA (ED_{50} = ~7 μmol/kg i.v.) and capsaicin (~30% inhibition at 20 μmol/kg i.v.) and also inhibited plasma extravasation (induced by endogenous release of TKs under vagus nerve stimulation) at a dose of 10 μmol/kg i.v. The peptidic nature of S-16474, together with the modest IC_{50} values of 85 and 129 nM for the binding affinity to human NK_1 and NK_2 receptors, respectively, probably prevents the clinical development of this compound (Fig. 3).



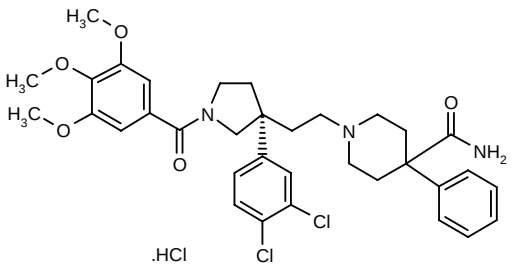
8 (FK-224, Fujisawa)

9 (S-16474, Servier)

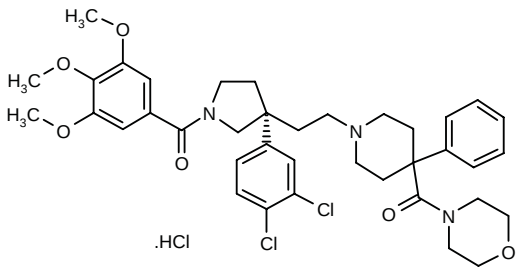
Fig. 3. Structures of FK-224 and S-16474.

Dual NK_1/NK_2 antagonists based on the structure of SR-48968

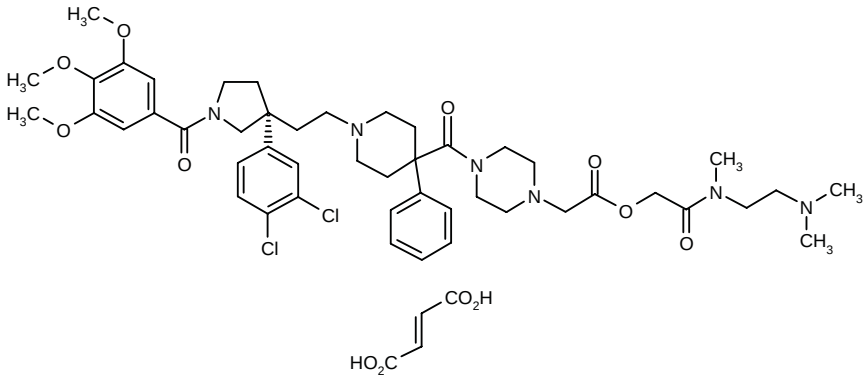
The first really potent nonpeptidic dual NK_1/NK_2 antagonist is MDL-105212A (**10**) from Hoechst Marion Roussel. This compound was structurally derived from SR-48968 using modeling comparisons with NK_1 antagonists. Subsequent side chain optimization led to compounds with nanomolar affinities to human NK_1 and NK_2 receptors. In binding studies performed with human NK



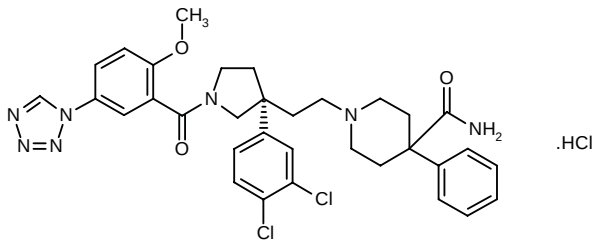
10 (MDL-105212A, Hoechst Marion Roussel)



11 (MDL-105172A, Hoechst Marion Roussel)



12 (Hoechst Marion Roussel)



13 (Hoechst Marion Roussel)

Fig. 4. Structures of MDL-105212A and related compounds.

receptors, MDL-105212A had IC_{50} values of 3.1 nM (IM-9 cells, NK_1) and 8.4 nM (HSKR-1 cells, NK_2) (42). Although oral activity (see below) was at a rather modest level, the compound clearly demonstrated beneficial effects in a variety of asthma models in guinea pigs (28, 43). MDL-105212A inhibited protein plasma extravasation in guinea pig trachea and primary bronchi (ED_{50} = 0.2 mg/kg i.v.), NKA (aerosol)-induced respiratory collapse in guinea pigs (ED_{50} = 5 mg/kg i.v.) and capsaicin-induced increases in pulmonary insufflation pressure (ED_{50} = 0.5 mg/kg i.v.). Inhibition of capsaicin-induced effects with ED_{50} values of 50 mg/kg after oral application, however, remained at a rather modest level. Interestingly, MDL-105212A also showed affinity for the guinea pig NK_3 receptor (guinea pig cerebral cortex, IC_{50} = 21 nM).

MDL-105172A (**11**) is a closely related analog with a more balanced affinity to human NK_1 and NK_2 receptors and slightly improved oral activity in guinea pigs. MDL-105172A is also characterized by a high affinity to (guinea pig) NK_3 receptors. *In vivo*, MDL-105172A showed improved activity in comparison to MDL-105212A. It inhibited NKA (aerosol)-induced respiratory collapse in guinea pigs (ED_{50} = 0.5 mg/kg i.v.) and showed slightly enhanced oral activity (ED_{50} = 20 mg/kg p.o. for the inhibition of capsaicin-induced effects) (44). In an attempt to further improve potency and balanced NK_1/NK_2 affinity of MDL-105212A, a series of compounds exemplified by **12** and **13** were prepared. In NK binding assays (guinea pig lung, NK_1; 3T3 fibroblast cells, NK_2), **12** had IC_{50} values of 2.09 and 0.9 nM, respectively, whereas **13** had IC_{50} values of 2.79 and 16.3 nM, respectively (45, 46) (Fig. 4).

Obviously, researchers from Merck also used SR-48968 and SR-140333 as lead compounds for the design of dual antagonists. Modification of the piperidine residue and the introduction of trifluoromethyl groups into

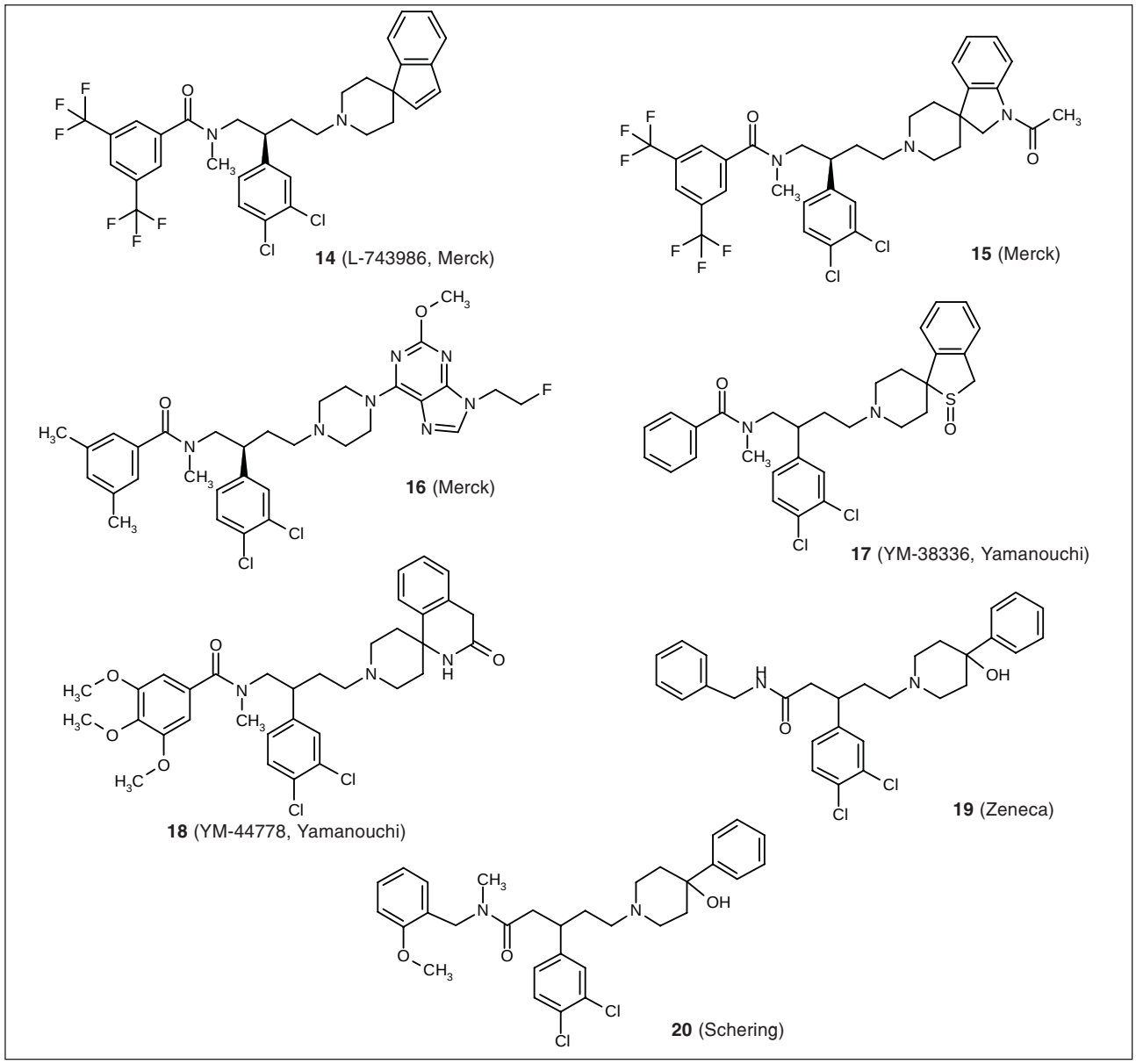


Fig. 5. Dual NK_1/NK_2 antagonists derived from SR-48968, I.

the benzoyl substituent led to L-743986 (**14**) and analogous compounds (47, 48). Compound **15** was reported to exhibit IC_{50} values of 0.2 and 1.5 nM to cloned human NK_1 and NK_2 receptors, respectively, and oral activity was demonstrated in guinea pigs (inhibition of resinaferatoxin-induced PPE, ED_{50} = 0.3 mg/kg p.o.). In a series of substituted aryl piperazines, replacement of the spiropiperidine residue of L-743986 with (2-fluoroethyl)-2-methoxypurin-yl)piperazine led to compound **16** with IC_{50} values of 0.45, 9 and 25 nM for the cloned human NK_1, NK_2 and NK_3 receptors, respectively (49). Another spiro-substituted piperidine dual NK_1/NK_2 antagonist, YM-38336 (**17**), is structurally based on SR-48968. YM-38336 was reported to exhibit binding affinities to the NK_2 and NK_1 receptors with IC_{50} values of 8.9 and 680 nM, respectively. YM-38336 inhibited contraction of hamster trachea rings induced by NKA (100 nM) with an IC_{50} of 2.6 nM and also inhibited substance P (1 nM)-induced guinea pig ileum strip contraction with an IC_{50} value of 2.3 μM. In *in vivo* studies using guinea pigs, YM-38336 was able to inhibit β-Ala^8-NKA(4-10)-induced bronchoconstriction with ED_{50} values of 20 μg/kg after i.v. application (ED_{50} of SR-48968 in this assay was 68 μg/kg) and 405 μg/kg after i.d. application (50). Modification of the spiropiperidine ring system led to YM-44778 (**18**), a compound that exhibited high and balanced affinity for NK_1 and NK_2 receptors with IC_{50} values of 18 nM in inhibiting [^{125}I]-substance P binding and 16 nM in inhibiting [^{125}I]-NKA binding in guinea pig and hamster urinary bladder, respectively (51) (Fig. 5).

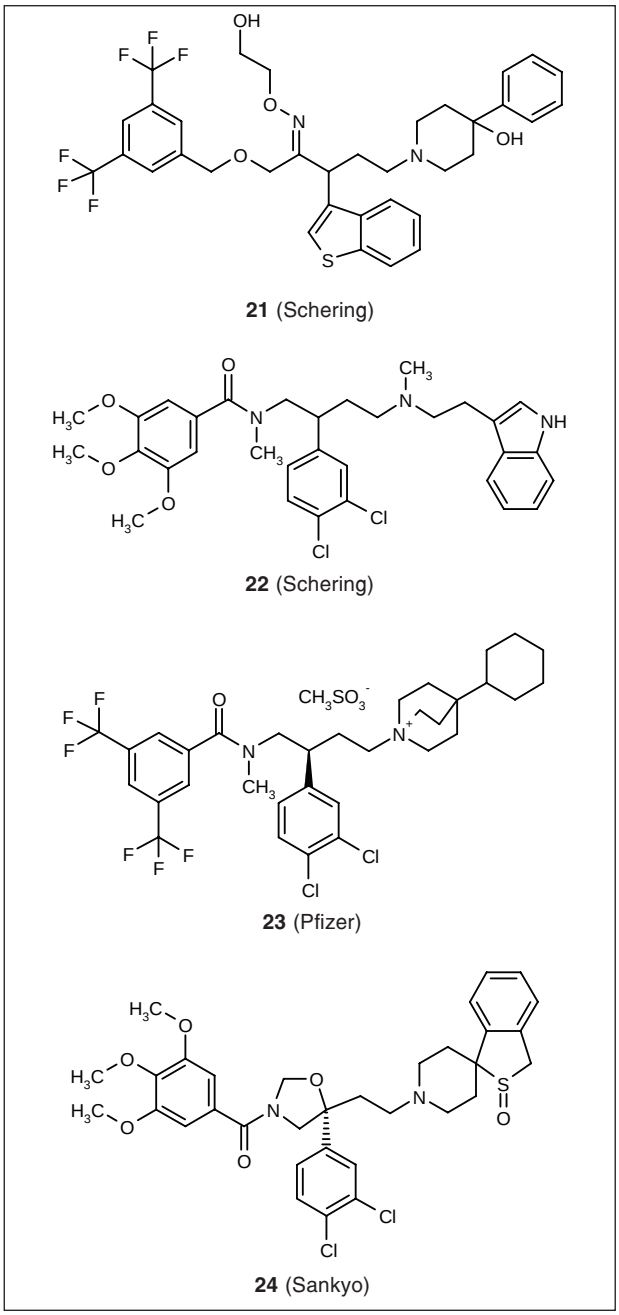


Fig. 6. Dual NK_1/NK_2 antagonists derived from SR-48968, II.

Modification of the benzoyl moiety of SR-48968 led Zeneca to the discovery of 5-(4-substituted-piperidinyl-1)-3-aryl-pentanoic acid derivatives as dual NK_1/NK_2 antagonists, exemplified by **19**, which demonstrated a K_i value of 30 nM in a substance P binding assay (NK_1) and a K_i of 15 nM in a NKA receptor binding assay (NK_2) (52). Closely related to the Zeneca compound is **20**, a piperidine derivative disclosed by Schering; **20** exhibited K_i values of 7.5 and 33 nM at NK_1 and NK_2 receptors, respectively (53).

In a series of oxime derivatives, **21** (Schering) showed K_i values of 1.8 nM in a NK_1 and 23 nM in a NK_2 binding assay (54). Another compound from Schering, **22** exhibited K_i values of 25 nM in a NK_1 binding assay and 33 nM in a NK_2 binding assay (55). In addition, **21** inhibited substance P-induced contractions in guinea pig vas deferens and NKA-induced contractions in hamster trachea by 81 and 87%, respectively.

Introduction of a quaternary ammonium residue in place of the piperidine moiety gave **23** (Pfizer), which was able to inhibit the contractile effects of substance P and β-Ala^8-NKA(4-10) in guinea pig tracheal strips with pK_b and pA_2 values of 7.3 in both tests (56) (Fig. 6).

Based on the structure of MDL-105212A and YM-38336, a series of azaheterocyclic compounds have been disclosed in a patent application by Sankyo. Compounds, exemplified by **24**, are claimed to exhibit equipotent effects in antagonizing both NK_1 and NK_2 receptors (57).

Dual NK_1/NK_2 antagonists based on selective NK_1 antagonists

Combination of a spiropiperidine moiety with a structural element found in the selective NK_1 receptor antagonist FK-888 led Merck to the discovery of tryptophan ureas exemplified by **25**. When binding affinities (CHO-cells expressing human NK_1 or NK_2 receptors) were determined, **25** exhibited balanced dual activities with IC_{50} values of 20 and 12 nM for the NK_1 and NK_2 receptors, respectively (58). Replacement of the indolyl moiety by benzyl markedly reduced binding affinity of the resulting compounds. From this series of compounds it was also possible to obtain potent and selective somatostatin sst_2 receptor antagonists (59) (Fig. 7).

Recently Novartis disclosed a series of 5-aryl-4-benzoylamino-pent-2-ene-carboxamides as dual NK_1/NK_2 antagonists derived originally from the selective NK_1 antagonist CGP-49823 (**26**) (60, 61). Formal elimination of a CH_2 group from the piperidine ring led to a new series of "open chain" NK receptor antagonists. In general, compounds from this structural class exhibited highly potent affinity to the NK_1 receptor (inhibition of

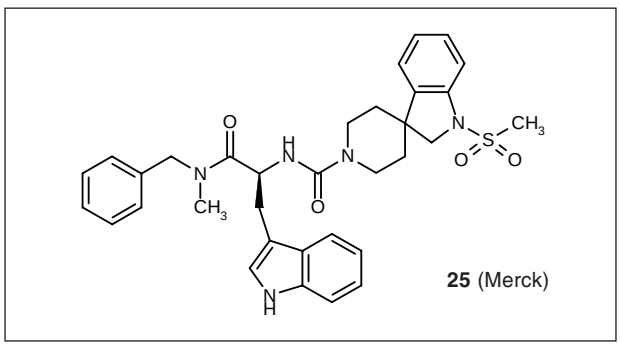


Fig. 7. Dual NK_1/NK_2 antagonist derived from FK-888.

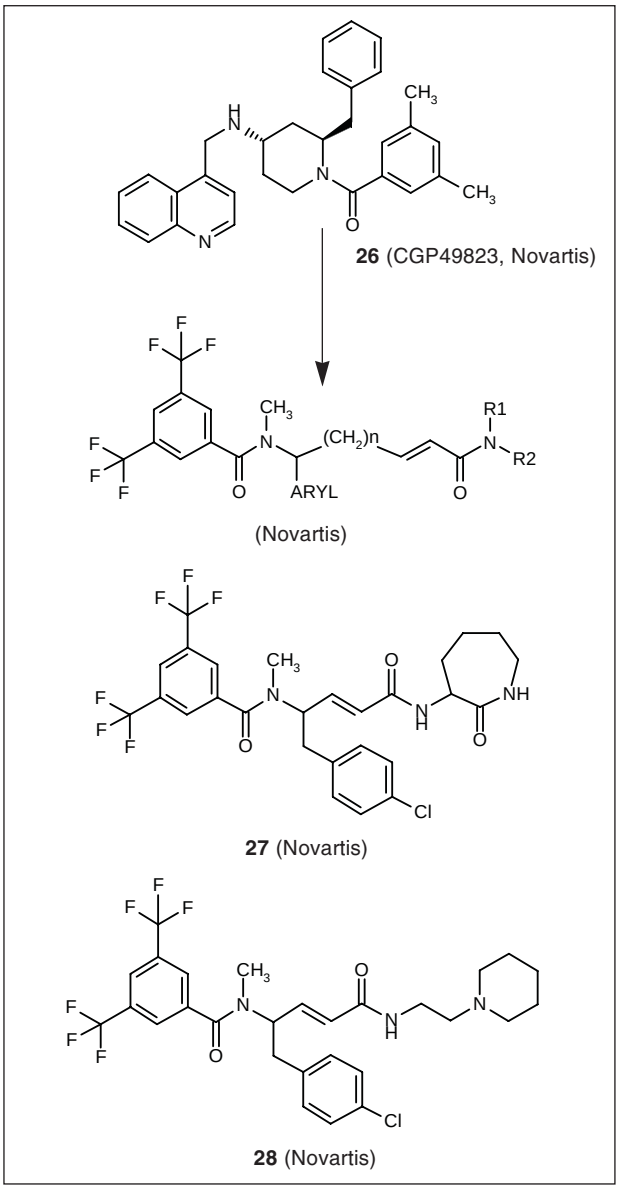


Fig. 8. Dual NK_1/NK_2 antagonists derived from the selective NK_1 antagonist CGP-49823.

[^{3}H]-Sar^9-substance P binding to bovine retinal membranes) and good affinity to the NK_2 receptor (inhibition of [^{125}I]-NKA binding to human NK_2 CHO-cells). In these binding assays, **27** and **28** exhibited IC_{50} values for NK_1 and NK_2 of 0.7 and 55 nM and 10 and 49 nM, respectively (Fig. 8).

Structural modifications on the selective NK_1 antagonist LY-303870 (lanepitant, **29**) (62) led to the discovery of moderately active dual NK_1/NK_2 antagonists, exemplified by **30**. NK_1 receptor binding was evaluated using IM-9 cells and NK_2 binding was determined in CHO cells expressing human NK_2 receptors with IC_{50} values of 41 and 82 nM obtained, respectively (63). A combination of structural features found in MDL-105212A (**10**) and

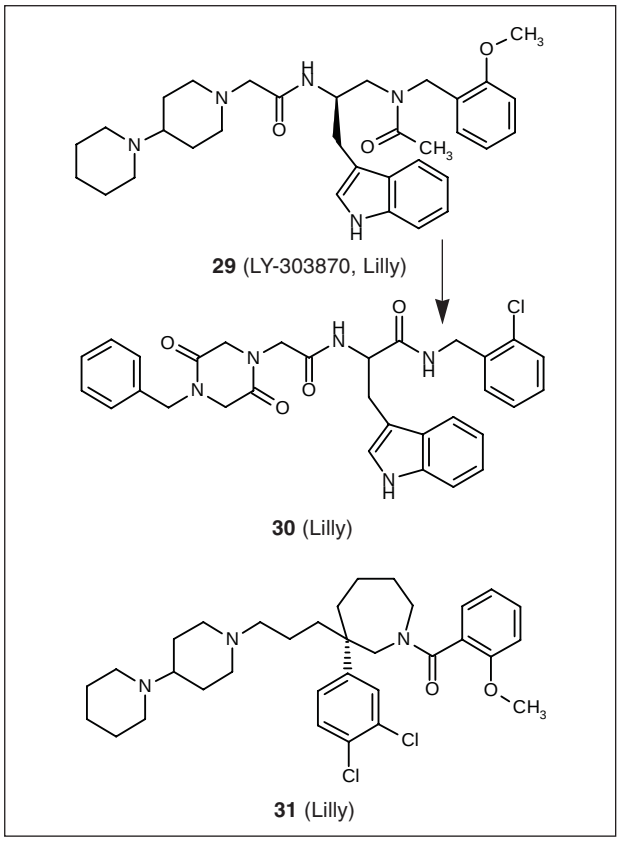


Fig. 9. Dual NK_1/NK_2 antagonists derived from the selective NK_1 antagonist LY-303870.

LY-303870 (**29**) led to the discovery of a series of compounds exemplified by **31**, which are claimed to be dual NK_1/NK_2 antagonists (64) (Fig. 9).

Takeda's efforts in the NK field led to the discovery of benzylbenzodiazepines, exemplified by **33** (65), as potent dual NK_1/NK_2 antagonists based on the structure of the selective NK_1 antagonist **32** (66). Compounds from this structural class have been shown to inhibit [^{125}I]-substance P (NK_1) binding to IM-9 cells with IC_{50} values ranging from 0.1-2 nM and inhibit [^{125}I]-NKA (NK_2) binding using transfected COS-7 cells with IC_{50} values of 6-9.5 nM. In guinea pigs, **33** was able to inhibit substance P-induced plasma extravasation with an ED_{50} value of 1.6 μg/kg after i.v. application (65) (Fig. 10).

Dual NK_1/NK_2 antagonists based on other templates

3-Indolyl-piperazinyl and dichlorophenyl-piperazinyl derivatives, exemplified by **34**, **35**, **36**, have been claimed in recent patent applications to be dual NK_1/NK_2 receptor antagonists by Hoechst Marion Roussel (67) and Schering (68). Compound **36** (Schering) showed K_i values of 3 and 25 nM on human NK_1 and NK_2 receptors, respectively, expressed in transfected mice CHO cells (Fig. 11).

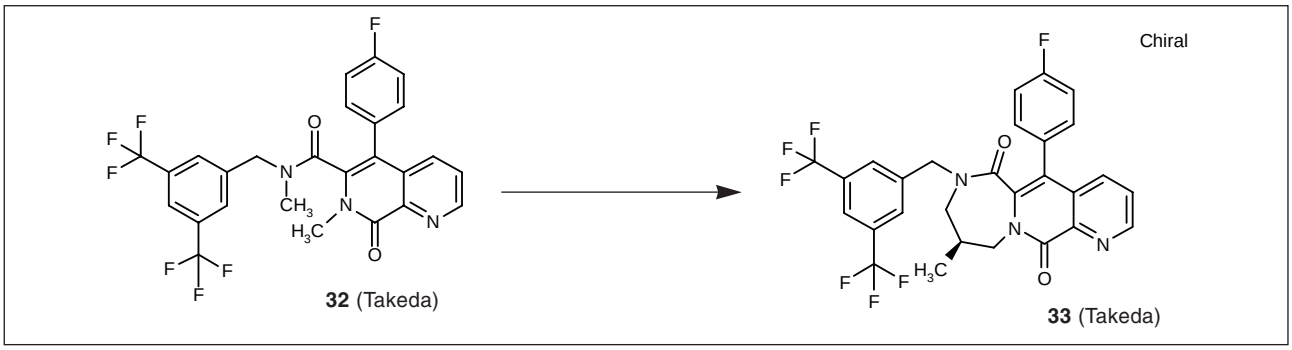


Fig. 10. A benzylbenzadiazepine as a dual NK_1/NK_2 antagonist.

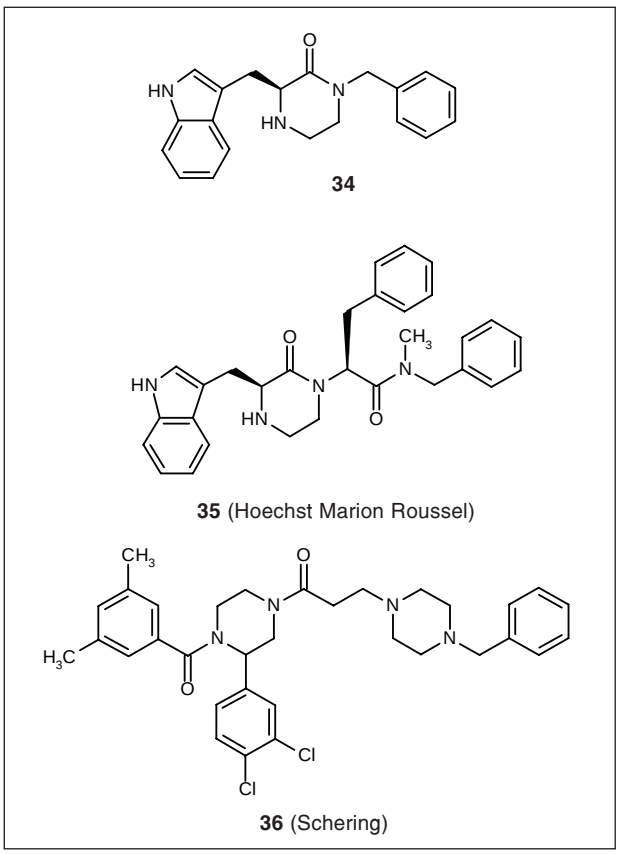


Fig. 11. 3-Indolyl-piperazinyl and dichlorophenyl-piperazinyl derivatives as dual NK_1/NK_2 antagonists.

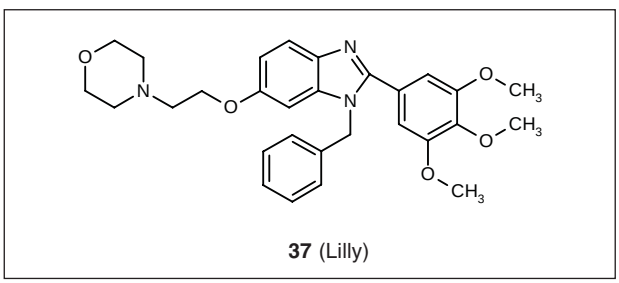


Fig. 12. A benzimidazole derivative as a dual NK_1/NK_2 antagonist.

Another structural class of compounds, benzimidazole derivatives, exemplified by **37**, have also been identified as dual NK_1/NK_2 receptor antagonists by Lilly (69) (Fig. 12).

Conclusions

There is now considerable evidence that NKs are involved in a number of diseases, especially airway diseases. Animal studies with selective NK antagonists and dual NK_1/NK_2 antagonists demonstrate that NKs are involved in cough reflex, bronchoconstriction, bronchial hyperreactivity, inflammatory responses in the lung and as mediators of neurogenic inflammation. In addition, clinical studies using NK antagonists suggest that NKs and their receptors may contribute to the pathogenesis of airway diseases. After the search for selective NK antagonists, several pharmaceutical companies shifted their effort in TK antagonist research from selective NK antagonists towards the discovery of nonpeptidic compounds exhibiting dual NK_1/NK_2 antagonist properties (and compounds with additional NK_3 antagonist activity) for the treatment of airway diseases. Many companies successfully designed dual NK_1/NK_2 antagonists based on the structures of known selective (NK_1 or NK_2) NK antagonists. Today, a variety of compounds from different structural classes exhibiting dual NK_1/NK_2 antagonism are available.

Further clinical trials in patients with NK receptor antagonists from these new and “unselective” classes of compounds are needed to provide conclusive evidence for the usefulness of such agents in the treatment of airway diseases. In addition, such clinical trials with potent dual NK_1/NK_2 antagonists will also provide information as to the extent of advantage an unselective NK antagonist has over selective NK antagonists and whether a synergistic effect in the blockade of both receptors can be demonstrated.

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