Small Molecule Antagonists of the Tachykinin NK_2 Receptor

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Abstract: The NK_2 receptor (member of the tachykinin receptor family) is mainly located in the smooth muscle of the urinary, respiratory and gastrointestinal tracts, with limited presence in the CNS. This has raised interest in tachykinin NK_2 receptor antagonists for the treatment of urological disorders, asthma. This review outlines progress done after 1998 in the field of NK_2 small molecule antagonists, both acting on the NK_1/NK_2, NK_2/NK_3, $NK_1/NK_2/NK_3$ receptors and selective for the NK_2 one.

Keyword: NK_2 receptor antagonists.

INTRODUCTION

The family of tachykinins includes three related neuropeptides (Substance P, neurokinin A and neurokinin B) that possess the same C-terminal sequence (Phe-X-Gly-Leu-Met-NH_2). They interact to different degrees with three G-protein coupled receptors, which have all been cloned and characterized, known as NK_1, NK_2, and NK_3. Each peptide has selectivity for one of the receptors: substance P shows greatest affinity for NK_1, neurokinin A for NK_2, and neurokinin B for NK_3 receptors.

The NK_1 receptor is widely distributed in tissues throughout the periphery and the CNS [1], while the NK_2 receptor is mainly located in the smooth muscle of the urinary, respiratory and GI (gastro intestinal) tracts, with limited presence in the CNS [2]. In contrast, the NK_3 receptor is primarily expressed in the CNS, although it is also found in the GI tract [3].

They produce an array of biological responses, including smooth muscle contraction and relaxation, vasodilatation, activation of the immune system, regulation of pain transmission and neurogenic inflammation, and have been proposed to play a pathophysiological role in a range of CNS and peripheral disorders, including migraine, depression, anxiety, emesis, asthma and irritable bowel syndrome [4]. The pharmacology of tachykinin receptors has been extensively reviewed [1,5], and will not be discussed in detail in this paper.

In recent years an outstanding number of publications has appeared in describing both diverse chemical classes and specific compounds as selective NK_1, NK_2 and NK_3 receptor antagonists or combined tachykinin receptor antagonists [6].

This review focuses on recent advances in the development of selective and combined non-peptidic NK_2 receptor antagonists.

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PHARMACOLOGICAL INTEREST OF SELECTIVE AND COMBINED NK_2 ANTAGONISTS

The human tachykinin NK_2 receptor has been validated as a suitable target for the development of novel drugs to be used for the treatment of a number of diseases in the respiratory, gastrointestinal and genitourinary tract [1].

Two different potent and selective tachykinin NK_2 receptor antagonists, the non-peptide compound Saredutant (Sanofi-Synthélabo) [7] and the glycosylated bicyclic hexapeptide Nepadutant (Menarini) [8] are currently in Phase II clinical trials for treatment of depression and inflammatory bowel syndrome the former and for bronchial asthma and irritable bowel syndrome the latter. A second Sanofi-Synthélabo selective tachykinin NK_2 receptor antagonist, SR-144190, with increased bioavailability in the central nervous system compared with Saredutant [9], has been progressed to phase I studies for depression and anxiety, before being recently discontinued. Finally, a selective antagonist from Pfizer (UK-224671 [10]) is also reported to have reached Phase I clinical trials for urinary incontinence therapy.

It is interesting to note that, in spite of the reported limited presence of NK_2 receptors in the CNS [2], some of the NK_2 antagonists are in clinical trial, as stated above, for depression and anxiety. Unfortunately trial results for these indications haven't been published up to now.

During the last few years an increasing involvement in dual antagonists has been shown by several companies [11,12]. The rationale of synthesizing combined antagonists for the tachykinin receptors is mainly based on the potent synergistic effect associated with multiple receptor interactions.

Interest in dual tachykinin NK_1/NK_2 antagonists has been based in part on the expectation that a drug showing these activities would affect favourably several undesirable elements of bronchial asthma: substance P is known to be involved in the extravasation and consequent inflammation of the airways, and neurokinin A appears to be involved in bronchoconstriction and cough [13].

With regards to the NK_2 and NK_3 receptors, the potential for synergistic pharmacological effects is supported by their different locations. Pulmonary, bladder, and GI tract

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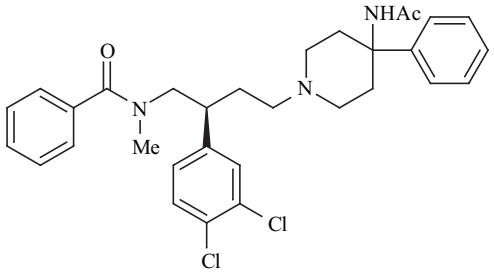
disorders are believed therefore to be the main potential therapeutic targets for combined NK_2/NK_3 receptor antagonists [14].

SELECTIVE NK_2 ANTAGONISTS

SR-48968 (Saredutant) from Sanofi-Synthélabo, was described as the first selective and highly potent non-peptide competitive tachykinin NK_2 receptor antagonist in 1992. It was developed from a lead structure identified by random screen [15]. As shown in Fig. (**1**), SR-48968 has a very high affinity for the tachykinin NK_2 receptor from various species, including humans [16], while shows low or no affinity at all for NK_1 and NK_3 tachykinin receptors. Of note that affinity for the human tachykinin NK_1 receptor was observed to be dependent of the human cell line used [15,17].



Saredutant

	Receptors	K_i (nM)[15]
Rat duodenum	NK_2	0.46
Rat urinary bladder	NK_2	0.44
Hamster urinary bladder	NK_2	2.34
Guinea pig ileum	NK_2	0.27
COS-1 (human cells)[16]	NK_2	2.7
Rat brain cortex	NK_1	3100
IM9 (human cells)	NK_1	184
U373MG (human cells)	NK_1	970
STTG1 (human cells)	NK_1	920
COS-7 (human cells)[17]	NK_1	320
Rat brain cortex	NK_3	>10000
Guinea pig brain cortex	NK_3	132
Gerbil brain cortex	NK_3	853
Human (CHO cells)	NK_3	362

Fig. (1). Inhibition constants (K_i of Saredutant (SR-48968) in tachykinin radioligand binding assays.

In many occasions Saredutant has been used as a model for the preparation both of selective and dual tachykinin NK_2 receptor antagonists.

Researchers from Yamanouchi [18] constructed a putative 3-D structure of 4-acetamido-1-methyl-4-phenylpiperidine by energy minimization, as a simplified model of SR-48968. The phenyl group was placed in an equatorial position and the acetamido group in an axial position. This conformation was found to be 1.68 kcal/mol more stable than the other one with an axial phenyl group and an equatorial acetamido group. Speculating that the phenyl group may be immobilized in the equatorial position by the axial acetamido group and that compounds with more restricted equatorial phenyl groups may show higher affinity for the NK_2 receptor, they designed 1'-methylspiro[isobenzofuran-1(3H),4'-piperidine] as a conformationally restricted 4-phenylpiperidine. Conformational analysis of this compound suggested that the phenyl group lies in an equatorial position. This conformation resulted 2.51 kcal/mol more stable than the other one with an axial phenyl group. Synthesis of the corresponding SR-48968 analogue (YM-35375), Fig. (**2**), showed that its IC_{50} (binding affinity for the hamster urinary bladder NK_2 receptor) was only 84 nM, a 20-fold decrease in potency relative to (+/-)-SR-48968. However, the decreased *in vitro* affinity of YM-35375 when compared to (+/-)-SR-48968 did not correspond to a lower activity *in vivo*. In a model of bronchoconstriction induced by the selective NK_2 agonist βAla^8-NKA(4-10) in guinea pig, YM-35375 and (+/-)-SR-48968 showed ID_{50} values of 41μg/kg (i.v.) and 68 μg/kg (i.v.), respectively. It is not clear from the available data whether this discrepancy is due to the different species used for the two tests or to a real advantage of YM-35375 over (+/-)-SR-48968 when tested *in vivo*.

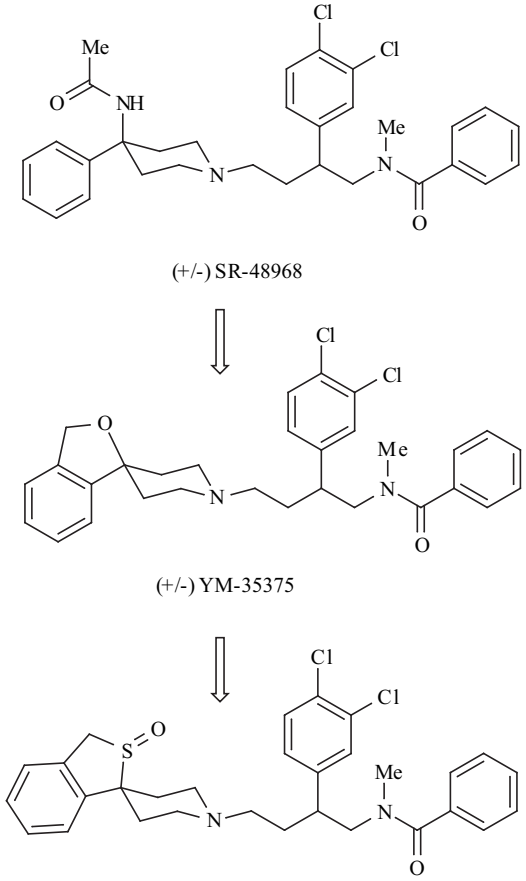


Fig. (2). YM-35375 and YM-38336.

Further elaboration of the spirocyclic structure, lead to YM-38336 [19] with an IC_{50} of 8.9 nM (binding affinity for

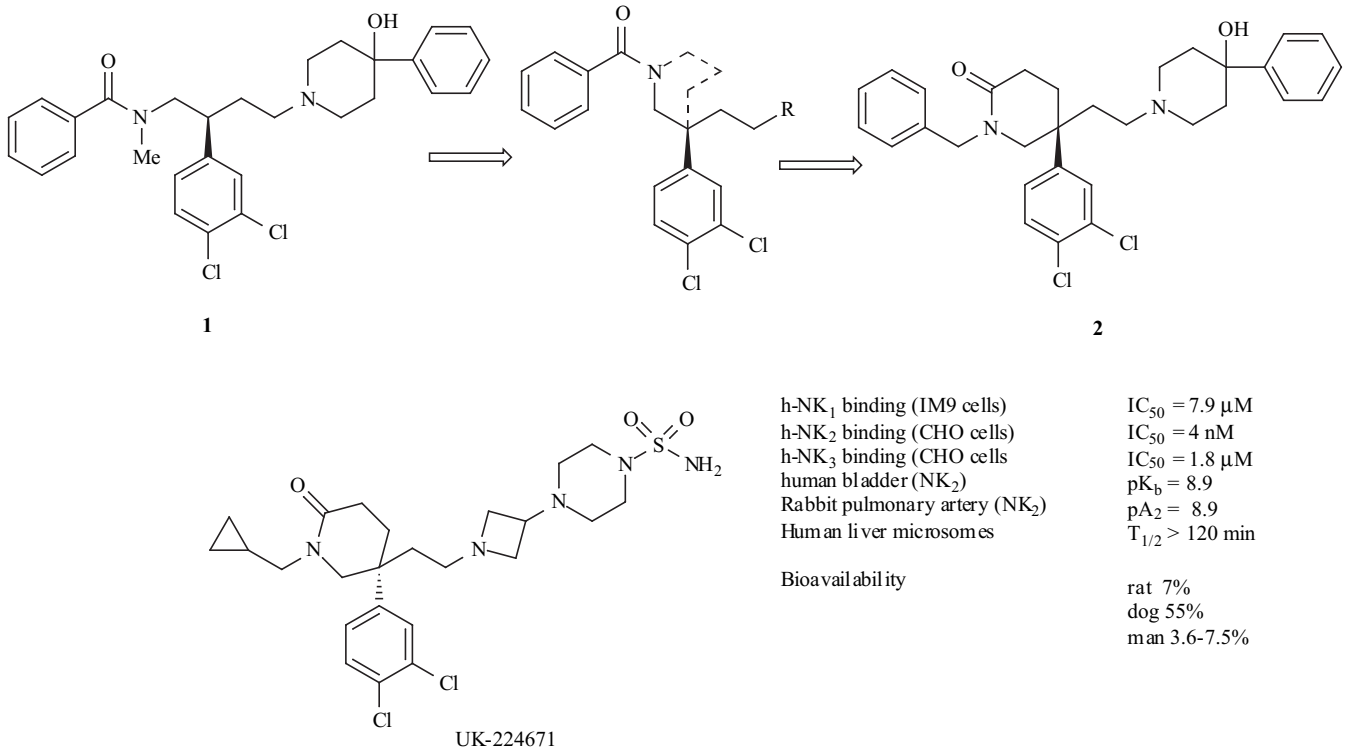


Fig. (3). Pfizer strategy leading to UK-224671.

the hamster urinary bladder NK_2 receptor) and a selectivity index versus the NK_1 receptor of 76 *vs.* a selectivity index > 240 for (+/-)-SR-48968 and one of 8.5 for YM-35375 [14]. Moreover in the same bronchoconstriction model as above, this compound showed an ID_{50} of 20 μg/kg (i.v.) and 85% inhibition of agonist induced bronchoconstriction after intraduodenal administration of a 3 mg/kg dose.

Middleton and co-workers (Pfizer), after *in vitro* evaluation of **1**, Fig. (**3**), (close analogue of SR-48968) metabolic stability, found that its $t_{1/2}$ in human liver microsomes was < 10 min. Metabolic route identification work revealed that a major pathway in this process was amide N-demethylation to give an essentially inactive secondary amide. They reasoned that incorporation of this vulnerable methyl group into a cyclic system could reduce the potential for metabolism at this site. Following this idea they prepared a series of cyclic templates among which the δ-lactam **2** showed an increased $t_{1/2}$ (30 min), while retaining potency.

Then through a process of optimization of physico-chemical and *in vitro* ADME properties of this class of compounds they produced UK-224671 [10], which is reported to have entered Phase I for treatment of urinary incontinence. UK-224671 revealed to have a low rat and men bioavailability (7 - 8 %). This was shown in the rats case, to be due to a combination of moderate intestinal permeability and extensive first-pass metabolism by the gut and not to poor gastrointestinal absorption *per se* [20, 21].

Another structure that appears to be originated from that of SR-48968, although the medicinal chemistry regarding the molecule has not been published, is the Nippon Kayaku compound NK-5807, Fig. (**4**). The compound is reported to be active in inhibiting the Nle^{10}-NKA(4-10)-induced bronchoconstriction in anhaestetized guinea pigs after intravenous and oral administration [22] and also showed activity in animal models of asthma [23]. In both studies, the effects were similar for NK-5807 and SR-48968.

The structure of ZD-7944, Fig. (**4**), from Astra-Zeneca shows, even if data concerning the rational leading to this molecule are not available, that very likely it has originated from SR-48968 [24].

ZD-7944 is a highly potent and selective, non-peptide neurokinin NK_2 receptor antagonist shown to bind with high affinity to cloned human lung NK_2 receptors (Ki = 1.1 nM) and to have over 2,500-fold less affinity for cloned human NK_1 or NK_3 receptors. In functional studies, it competitively antagonized contractile responses to NKA in human bronchus and to βAla^8-NKA(4-10) in guinea pig trachea or rabbit pulmonary artery with $-\log K_B$ values of 8.8-9.41. ZD-7944 did not antagonize histamine or muscarinic receptors in pulmonary airways or vascular tissues at concentrations of up to 30 μM. In conscious guinea pigs, it provided greater than 50% protection against aerosolized βAla^8-NKA(4-10)-induced dyspnea at an oral dose of 0.6 μmol/kg, with a pharmacological half-life of about five to six hours.

Actually Astra-Zeneca, is entering clinical trials for urinary incontinence with AZD-5106, claimed to be a selective tachykinin NK_2 receptor antagonist: unfortunately the molecular structure has not been disclosed.

A different strategy was applied by T. Harrison and collaborators, Fig. (**4**) [25] According to their report, they started from the selective NK_3 antagonist SR-142801 and explored a new series of lactam derivatives in which the amide carbonyl of SR-142801 has been transposed into the piperidine ring and which contains a range of novel cyclic

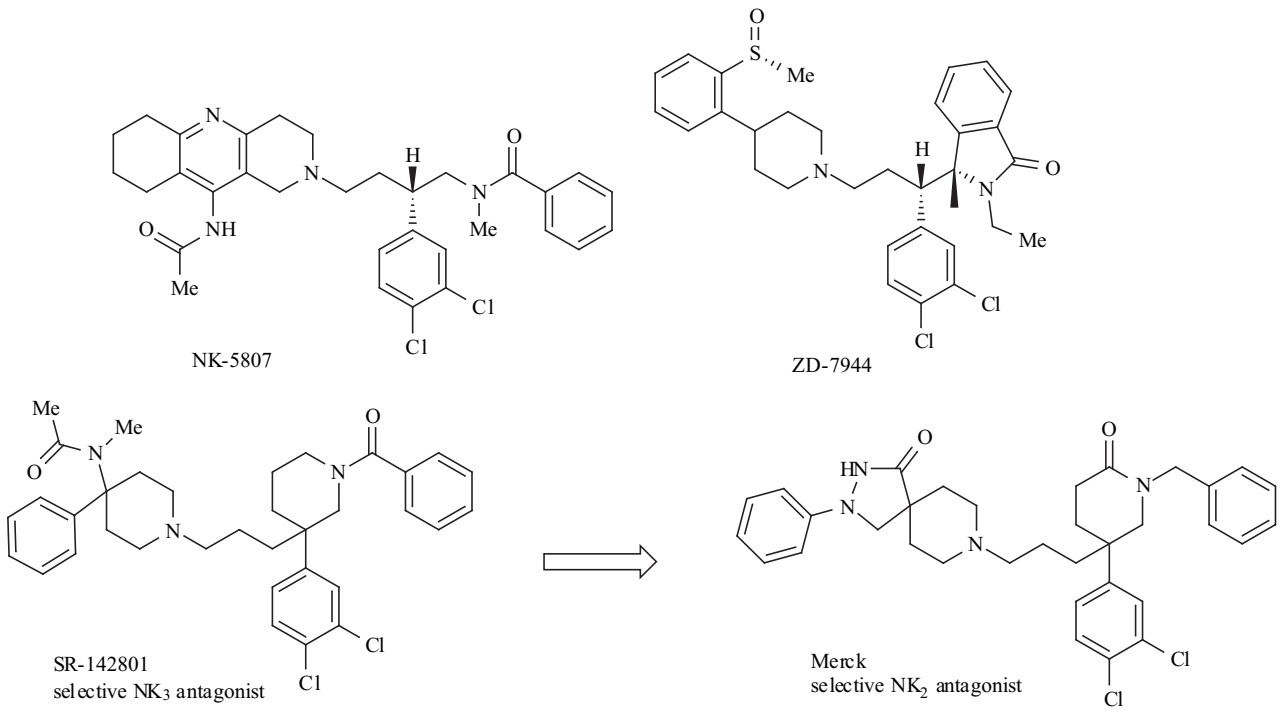


Fig. (4). Selective NK_2 antagonists.

amines replacing the phenyl acetamidopiperidine moiety. Through this transposition they succeeded in inverting selectivity from NK_3 to NK_2. It is interesting to note that following different lines of thought researchers from Pfizer and Merck obtained analogous core structures.

A successful bridging from a peptide to a non-peptide selective tachykinin NK_2 antagonist was achieved by a Menarini research group, Fig. (**5**) [26]. Starting from the bicyclic hexapeptide MEN 10627 [27], at that time one of the most potent and selective known NK_2 antagonists, and

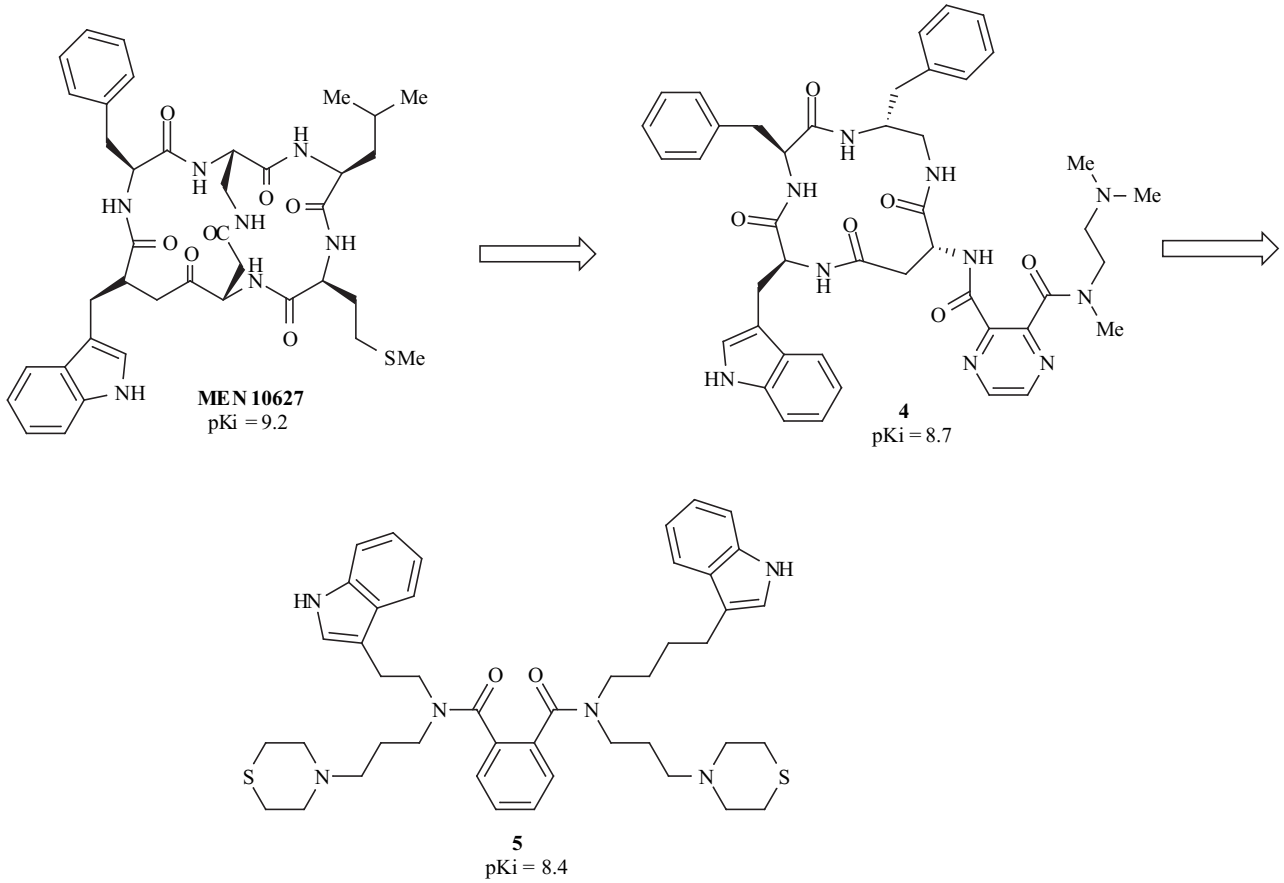


Fig. (5). Menarini work: from cyclic peptides to small molecules.

from the insight that only one of the two cycles in that compound is essential for bioactivity [28], the monocyclic pseudopeptide **4** was synthesized and found to retain the potency of the parent compound. The elaboration of the exocyclic diamide framework in **4** as a new non-peptide scaffold led to a series of *o*-phthaloyl tertiary diamides. Some of them, such as compound **5** showed nanomolar affinity at the human tachykinin NK_2 receptor.

DUAL ANTAGONISTS NK_1/NK_2

A large amount of work has been recently published concerning dual NK_1/NK_2 receptor antagonists.

A common way to achieve this result has been to consider an NK_1 selective antagonist, an NK_2 selective antagonist and build hybrid molecules containing the key features for binding to both receptors.

Already in 1996 Aventis researchers reasoned that dual activity could be built up in SR-48968 which has a low, but significant affinity for the NK_1 receptor. Comparison of the low energy conformations of SR-48968 and CP-96345 [29] (the first reported non-peptide antagonist selective for NK_1) suggested them that constraining the 3,4-dichlorophenyl-butylbenzamide side chain of SR-48968 in a pyrrolidine ring would mimic the low energy conformations and give a good overlap of the 3,4-dichlorophenyl and benzamide rings in the two compounds. MDL-103220 was synthesized and found to have good affinity for the NK_2 receptor (IC_{50} = 2.25 nM, displacement of [^{125}I]-iodohystidyl-NKA in HSKR-1 cells, *vs*. IC_{50} = 0.44 nM or SR-48968 in the same test) and slightly improved affinity for the NK_1 receptor (IC_{50} = 161 nM, displacement of [^{125}I]-labeled substance P in human IM-9 cells, *vs*. IC40 = 593 nM for SR-48968 in the same test) [30]. Further elaboration suggested by molecular modelling studies resulted in MDL-105212 with the affinities of 3.11 nM and 8.40 nM respectively for NK_1 and NK_2 receptors, Fig. (**6**). For these molecules is also evident a major modification on the piperidino ring vs. SR-48968: the inversion of the 4-amido group. In spite of the fact that, according to their studies, this ring seems to be important for NK_2, but not for NK_1 affinity; the authors afford no explanation for their choice. Data concerning *in vivo* properties are not available for this series.

Susbtitution of the pyrrolidine ring of MDL-105212 with an oxazolidine one, allowed people from Sankyo to create a novel series of dual NK_1/NK_2 antagonists [31]. Among this series the most interesting was compound **6**, Fig. (**7**), which had, for what concerns *in vitro* binding, an $IC_{50}(NK_1)$ = 6.7 nM (displacement of [^{3}H]-substance P, NK_1 receptors from guinea pig lung) and $IC_{50}(NK_2)$ = 7.5 nM (displacement of [^{3}H]-SR-48968, NK_2 receptors from guinea pig ileum) while *in vivo* showed an ID_{50} (i.v.) of 25 μg/mL for inhibitory activity against SP-induced vascular hyperpermeability in guinea pigs and an ID_{50} (i.v.) of 74 μg/mL for what concerns inhibitory activity against Nle^{10}-NKA[4-10]-induced bronchoconstriction in guinea pigs.

Kubota and coworkers [32] took advantage of the informations collected during the elaboration of the selective NK_2 antagonist YM-35375, and were able to introduce NK_1 affinity through insertion of three methoxy groups on the aromatic amide moiety and a 6-membered lactam on the spirocyclic system: YM-44778, $IC_{50}(NK_1)$ 18 nM (guinea pig urinary bladder) , $IC_{50}(NK_2)$ 16 nM (hamster urinary bladder), Fig. (**7**).

Using as starting points SR-48968 and ZD-7944, researchers from AstraZeneca were able to produce ZD-6021, Fig. (**7**), an high affinity and selective dual NK_1/NK_2 receptor antagonist [33,34]. Interestingly the first molecule of the series showing a good binding for both receptors and in the *in vivo* model was the 3-nitro substituted derivative. However because of concern over possible metabolic transformation to a β-naphthyl amine derivative, alternative 3-substituents were explored. Since substituent constants (π, MR and σ_1) for cyano (-0.57, 6.3, and 0.53) highlighted it as a replacement for nitro (-0.28, 7.36, and 0.67), and as such arylnitriles are not implicated as potential toxicophores, the 3-cyano analogue (ZD-6021) was specifically targeted. An ED_{50} of 13 mg/kg was determined for orally dosed ZD-6021 against a βA1a^8-NKA(4-10) -induced (NK_2) bronchoconstric-tion in the guinea pig model. Orally dosed ZD-6021 was also examined in an ASMPS-induced (NK_1) guinea pig model of extravasation of plasma proteins, it showed an ED_{50} = 0.5 mg/kg.

For Merck researchers the starting points were the NK_1 selective antagonist L-tryptophan benzyl ester **7** (hNK_1 IC_{50} = 1.6 nM, hNK_2 IC_{50}> 5μM) and the NK_2 receptor selective antagonist SR-48968 [35], Fig. (**8**). In comparing the two molecules it occurred to them that the 3,4-dichloro phenyl and the indolyl moieties might interact with the receptor in a similar fashion; the phenyl group of the ester in compound **7**

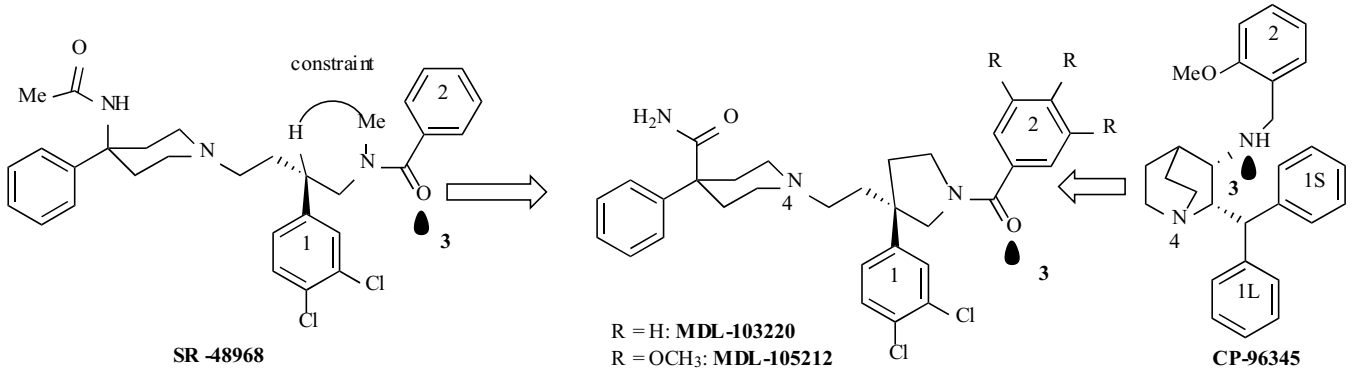


Fig. (6). From SR-489688 (selective NK_2 receptor antagonist) and CP-96345 (selective NK_1 receptor antagonist) to MDL-103220 and MDL-105212: potential common pharmacophore.

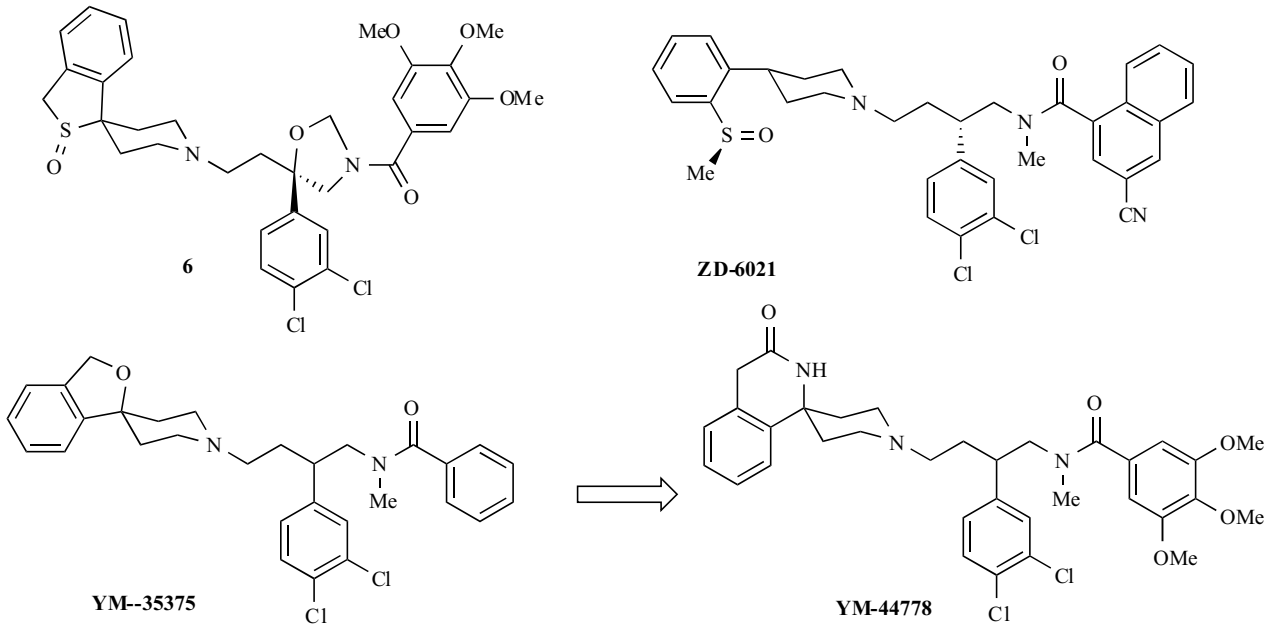


Fig. (7). Dual NK_1/NK_2 antagonists from Sankyo, Yamanouchi and AstraZeneca.

and the phenyl group of benzamide in SR-48968 are connected by four single bonds to the indolylmethyl or 3,4-dichlorophenyl. Because of the flexibility of the substituents on the nitrogen for the NK_1 activity in the triptophan ester series, they rationalized that by incorporating the piperidine type functionality of SR-48968 into the triptophan ester or amide system to form an urea might result in compounds possessing both NK_1 and NK_2 receptor affinity. On the other side, the best terminal group obtained in the triptophan series was inserted in the SR-48968. Optimization of both the piperidine and benzamide portions have led to orally active NK_1/NK_2 antagonists, as compound **8**, with sub-nanomolar potencies [36].

The selective NK_1 receptor antagonist CGP-49823 from Novartis has originated a new series of orally active

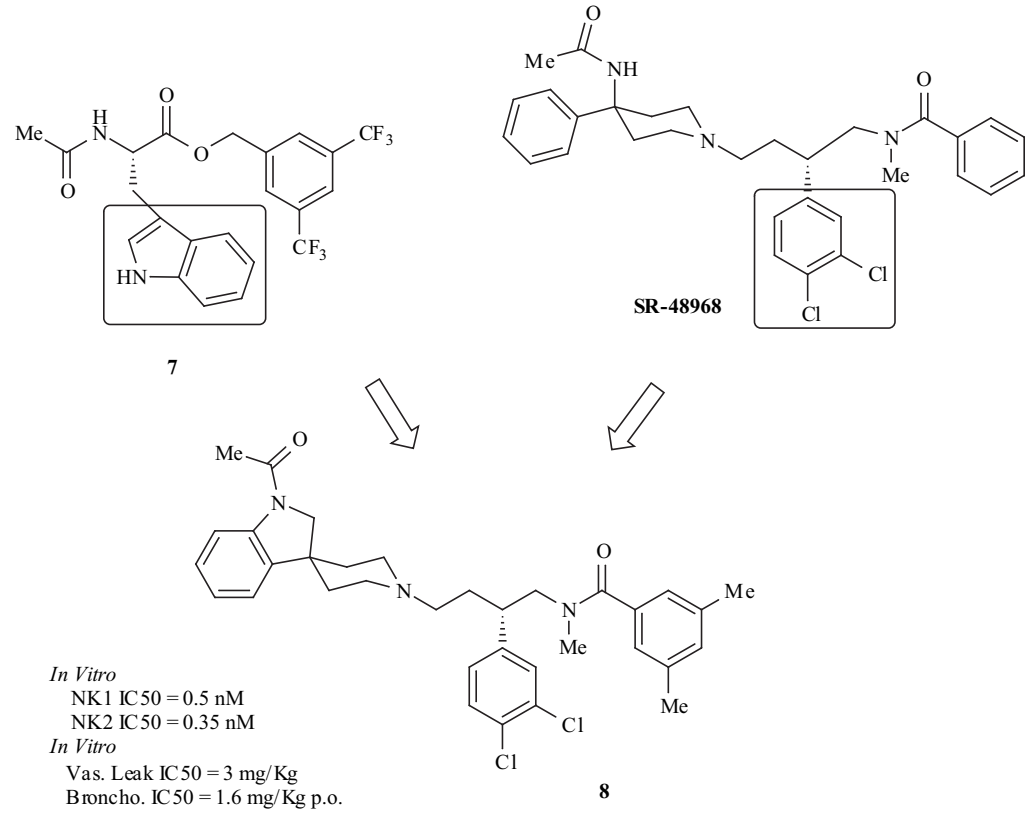
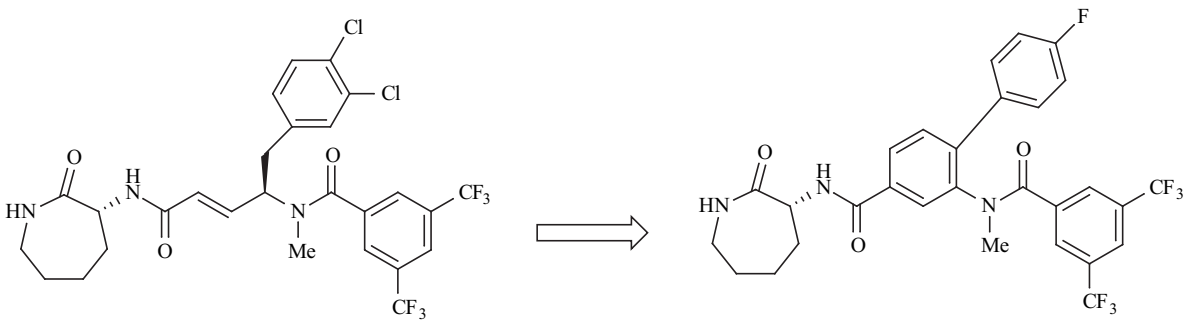


Fig. (8). From selective NK_1 and NK_2 antagonists to dual NK_1/NK_2 antagonists (Merck).



DNK-333 **9**

Fig. (9). DNK-333 and further improvements towards a non-peptidic structure.

NK_1/NK_2 dual antagonists [11a,37]. From this work emerged DNK-333, Fig. (**9**), which after having reached Phase II for COPD (chronic obstructive pulmonary disease), asthma and rhinitis, was recently discontinued.

In an effort to simplify the latter antagonist, an analysis with molecular models suggested that a suitably substituted biphenyl derivative would place the two aromatic rings in the correct orientation as required for receptor binding eliminating in addition a stereocenter. This family of molecules was rapidly synthesized and optimized resulting in several compound having IC_{50} <10 nm for the NK_1 receptor and IC_{50} < 50 nM for the NK_2 receptor. Additionally some of the compounds, like **9**, displayed potent *in vivo* po activities in guinea pigs against either NK_1 or NK_2 agonist-induced bronchoconstriction [38].

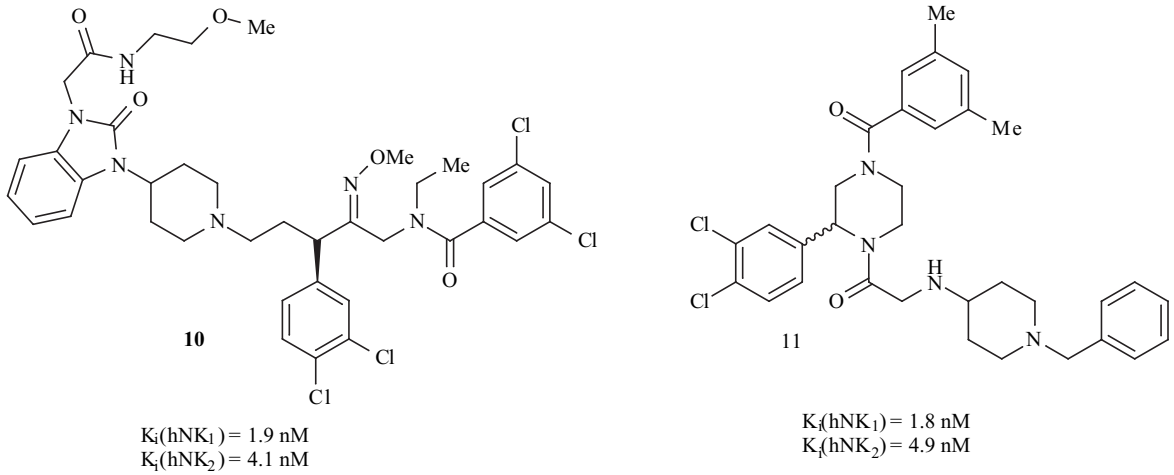
Schering-Plough researchers decided at first to understand the effects of systematically appending various functional groups to the carbon backbone of SR-48968 with the aim of probing this structure for building points that NK_2 receptor would tolerate. This functionality was then used to construct branched dual antagonists by the incorporation of an NK_1 pharmacophore into the NK_2 antagonist backbone. Acyclic NK_1 antagonists developed at Merck were considered to be model pharmacophores to incorporate into backbone substituted analogues of the NK_2 antagonists SR-48968 [39]. While trying other methods for amine production, they prepared oximes as intermediates: the oxime reduction was unsuccessful, but oximes themselves were actives.

Structural modifications of an oxime lead structure [40] resulted in the identification of **10** [11b], Fig. (**10**), as a potent dual NK_1/NK_2 antagonist showing pharmacological *in vivo* activity in both guinea pigs and dogs [41].

An additional effort, always had the 1-phenylethylene diamine fragment present in the early Pfizer lead, CP-99,994, a potent NK_1 antagonist, as a starting point, and the goal to introduce there NK_2 receptor affinity. An extensive and reiterative work produced **11**, Fig. (**10**), with an affinity of 1.8 nM for the NK_1 receptor and 4.9 nM for the NK_2 receptor[42].

DUAL ANTAGONISTS NK_2/NK_3

Only two examples of dual NK_2/NK_3 antagonists have been reported. The first derives from Talnetant, a selective tachykinin NK_3 receptor antagonists, now in Phase II. Through Talnetant stepwise chemical modification assisted by modelling and docking studies, researchers from SKB were able to produce potent NK_2/NK_3 combined antagonists without major changes in the chemical template [14]. Position 3 was identified through modeling studies, as the best point of the quinoline nucleus for chemical variation. A broad investigation of substitution at this position followed, with a particular focus to tertiary amines with the objective of improving water solubility and brain penetration. The best example obtained was SB-400238, Fig. (**11**), with $Ki(hNK_3) = 0.8$ nM and $Ki(hNK_2) = 0.8$ nM.



10 11

$K_i(hNK_1) = 1.9$ nM
$K_i(hNK_2) = 4.1$ nM

$K_i(hNK_1) = 1.8$ nM
$K_i(hNK_2) = 4.9$ nM

Fig. (10). Schering-Plough dual antagonists NK_1/NK_2 .

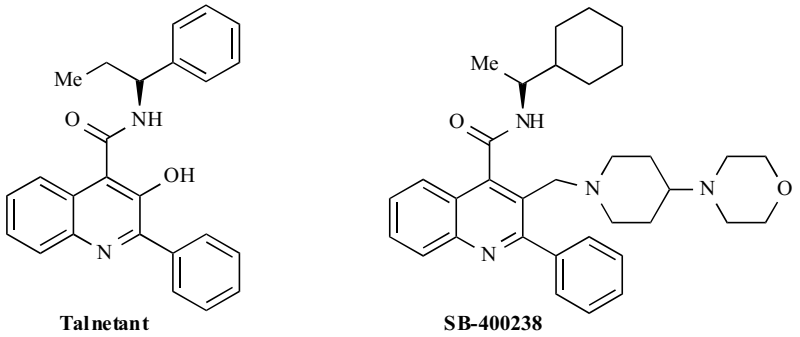


Fig. (11). From Talnetant to dual NK_2/NK_3 antagonists.

Very recently Sanofi-Synthelabo has announced the beginning of preclinical development for SSR-241586, a selective NK_2/NK_3 receptors antagonist whose structure has not been disclosed.

TRIPLE ANTAGONISTS $NK_1/NK_2/NK_3$

A class of molecules having good binding affinity for NK_1, NK_2 and NK_3 receptors [12b] was published in 2000 by Sankyo researchers. One of their compounds, R-113281, is now reported to have entered phase II for the treatment of COPD (oral administration). R-113281, Fig. (**12**), has high affinity for NK_1, NK_2 and NK_3 receptor subtypes (Ki = 3.5, 1.9 and 1 nM, respectively, in guinea pig tissues); it also binds with nanomolar affinity to human NK_1, NK_2 and NK_3 receptors expressed in CHO cells and exhibits high selectivity over a number of other receptors. In guinea pigs, this compound was shown to antagonize tracheal hyperpermeability induced by substance P, neurokinin B (NKB) and neurokinin A (NKA) at 0.1-0.33 mg/kg i.v., as well as the bronchoconstriction induced by NKA and NKB (ED_{50} = 0.040-0.063 mg/kg i.v.).

More recently, pharmacology of the Schering-Plough triple inhibitor (K_i = 1.3, 0.4, 0.3 nM respectively for human tachykinin NK_1, NK_2 and NK_3 receptors) SCH-206272, Fig. (**13**), has been published [43].

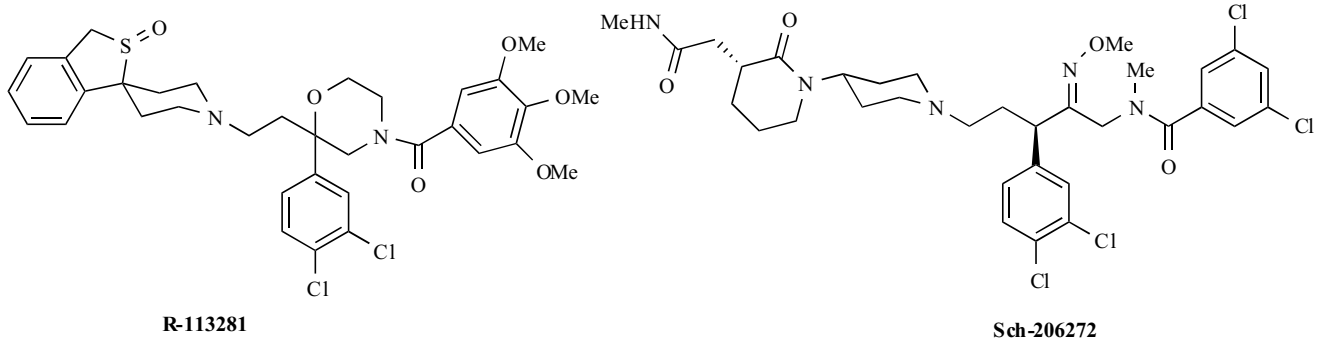


Fig. (12). Triple $NK_1/NK_2/NK_3$ antagonists.

MODELLING AND MUTATIONAL STUDIES

Tachykinin receptors belong to the heptahelical family of G-protein coupled receptors (GPCRs). As in the case for all GPCRs, except rhodopsin, NK receptors have not yet been crystallised, therefore no experimental structures are available.

A three-dimensional model of the NK_2 receptor has been reported by Donnely and collaborators [44], who studied the effects of agonist and antagonist binding, agonist-induced activation and agonist-induced desensitisation of the human tachykinin NK_2 receptor mutated at polar residues Asn-51, Asp-79, Asn-303, which are highly conserved in the transmembrane domain in the rhodopsin family of GPCRs.

A 3D model of the hNK_2 was also developed by SKB researchers [14] and used as a guide for antagonists modifications.

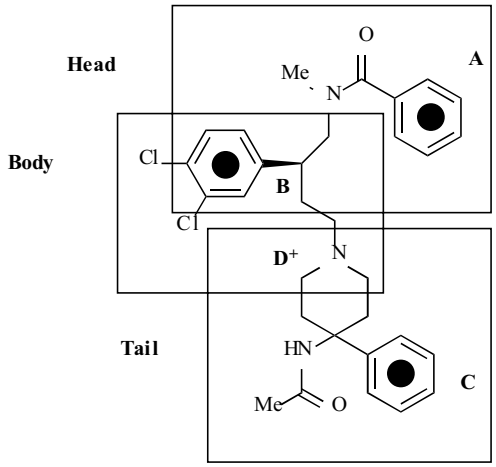


Fig. (13). Definition of fragments with Saredutant as an example. Centroids and "+" marks the selected pharmacophore elements A-D.

Mutations studies have revealed that the binding sites for peptide agonists and antagonists overlap but differ from those of non-peptide antagonists. Giolitti and collaborators [45] have reported the analysis of binding site of the peptide antagonist MEN-11420 and the non peptide SR-48968 using point mutations at residues Gln166, Ser170, Thr171, His198, Tyr206, Tyr266, His267, Phe270 and Tyr289. The overall picture resulting from this study shows a binding site for MEN-11420 including critical residues located on TM IV, V and VI, while in the case of SR-48968 the critical residues are located on TM VI and VII: the two antagonists show significantly different binding modes.

An NK_2 antagonist pharmacophore model has been developed on the basis of five non-peptide antagonists from structurally diverse classes [46], Fig. (**13**). The model consists of three hydrophobic pharmacophore elements (A, B and C) and one hydrogen bond donor acceptor interaction represented as a vector (D). The hydrophobic groups are generally aromatic rings, but this is not a requirement. The antagonists bind in an extended conformation with pharmacophore elements A and B in a parallel displaced and tilted arrangement. The model was evaluated against 20 structurally diverse, high affinity NK_2 and dual NK_1 and NK_2 antagonists. For all compounds, except two, a low energy conformation was found that fitted the model; moreover the enantioselectivity of SR-48968 and GR-159897 was successfully explained.

Concerning dual antagonists an interesting study on MDL-103392 (NK_1/NK_2 dual antagonist) appeared in 1999 [47]. Site directed mutagenesis of the NK_1 and NK_2 receptors was used to elucidate which amino acids are important for binding and functional activity of MDL-103392. The results indicate that different conformations of this compound binds to either receptor despite the high homology degree between the two receptors.

CONCLUSIONS

As summarized in this paper, the structure of the selective antagonist Saredutant remains the starting point for a number of modifications aimed at improving its properties or obtaining dual NK_1/NK_2 activity. Nevertheless, different approaches have successfully and independently furnished novel compounds, such as the GlaxoSmithKline quinolines acting as NK_2/NK_3 antagonists. In addition, recent years have seen the first validation studies of tachykinin NK_2 receptor antagonists in the clinical treatment of different diseases, such as irritable bowel syndrome [48] or asthma [49].

As for the future, valuable suggestions for the synthesis of novel compounds would likely arise from further advances in modeling and mutational studies and (hopefully) from the obtainment of the crystal structure of the NK_2 receptor.

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ABBREVIATIONS

ADME	=	Absorption, distribution, metabolism and excretion
CNS	=	Central nervous system
COPD	=	Chronic obstructive pulmonary disease
GI	=	Gastro intestinal
GPCR	=	G-protein coupled receptor
NKA	=	Neurokinin A
NKB	=	Neurokinin B
SP	=	Substance P
TM	=	Transmembrane

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