

Tachykinin Receptors Antagonists: From Research to Clinic

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Abstract: In this chapter it is described how, starting from different approaches and through extensive medicinal chemistry studies, several discovery compounds were optimized and reached the development stage.

The first tachykinin receptor antagonist to reach the market in 2003 for chemotherapy-induced emesis has been aprepitant. Other clinical candidates (for central nervous system disorders: osanetant, talnetant and saredutant; for irritable bowel syndrome: nepadutant and saredutant) are in advanced clinical phase.

The clinical studies reported in the literature and the destiny of the clinical candidates, where available, will be reviewed.

Key Words: Tachykinin, antagonist, clinical development, medicinal chemistry, emesis, irritable bowel syndrome, schizophrenia.

1. INTRODUCTION

There are more than 500 patents claiming tachykinins (TKs) antagonists and their different uses as drugs. Most of them have been applied starting from 1990 to date, in correspondence with the discovery of the first non peptide antagonists. The patent applications, which will be not reviewed here but are a clear sign of industrial interest, were filed mainly in the years 1994-1996. Almost 80 % of the existing patents are related to NK-1 antagonists. Patent applications describing novel structures or claiming different uses (veterinary uses included) and drugs combinations are still appearing.

Historically, substance P and NK-1 tachykinin receptors were the first to be described. For this or for the number and importance of pathologies in which NK-1 receptor could be involved, the first tachykinin antagonist to reach the market, more or less 30 years after the isolation of substance P, was an NK-1 receptor selective antagonist.

In this chapter it will be described how, starting from different approaches and through extensive medicinal chemistry studies, several discovery compounds were optimized and reached the development stage. A description of the clinical studies reported in the literature and of the destiny of the clinical candidates, where available, will be reported. Noteworthy, many companies implemented studies on this field through a period of 15 years, and the panorama of pharmaceutical companies changed dramatically during this time. Therefore, the discontinuation of the development of a drug candidate is not necessarily related to a bad performance in the preclinical or clinical phase.

2. NK-1 RECEPTOR SELECTIVE ANTAGONISTS

The first NK-1 receptor antagonists were developed in the 80s and derived from SP sequence. Although they have been quite useful as pharmacological tools, the drawbacks typical of peptide compounds as pharmaceuticals (complex structure, poor oral bioavailability, metabolic instability) let companies to decide to proceed in the search for non peptide antagonists. Therefore, no advanced development of peptide compounds was performed and the subject will be not reviewed here (see [1] and references therein).

The era of non-peptide antagonists for the tachykinin receptors began in 1991, when three distinct research groups divulged their results [1, 2]. As already mentioned since these original reports, increasing number of publications and patents describing new structures, has appeared. The field of non peptide NK-1 receptor

antagonists developed as an area of intense competition to reach its top in late 90s. As the search for non peptide NK-1 antagonists reached its goal, i.e., compounds suitable for clinical development, the competition moved to the proof of concept for the therapeutic uses claimed. Despite early experiments made by Pfizer, Merck was the first to reach the market.

Since the panorama of NK-1 receptor antagonists is quite complex and company related in particular in the final phase of development, it seemed convenient for a better comprehension to describe the field analyzing each company route, even if some of them explored and are continuing to divulgate and claim diverse structural series of compounds. Therefore, each company will be described in a separated paragraph, reporting briefly the partially overlapping structures of discovery antagonists and more in detail the compounds which reached the development phase.

Among the first series divulged, Eastman Kodak and Sterling Winthrop described two classes of steroids derived from the screening of natural products chemical collections [3-5]. The series were abandoned for their structural complexity and toxicity of compounds when administered *in vivo*.

Rhone-Poulenc

The structural motif of Rhone-Poulenc NK-1 receptor antagonists was the perhydroisoindolone ring, present in a series of compounds selected by screening of a chemical collection and divulged in 1991 [6]. The prototype of the series, RP-67580 (Fig. (1)), shows three aromatic residues, the quite rigid perhydroisoindolone bicycle and an amidine basic moiety, with strictly defined configuration at stereogenic centers for good pharmacological activity. RP-67580 shows nanomolar affinity for rat NK-1 receptor and good antagonist activity *in vitro* and *in vivo*. Several SAR studies were performed on this class of compounds (see [1] for review). The introduction of a further aromatic ring yielded RPR-100893 (Fig. (1)) [7], selective for the human NK-1 receptor (IC₅₀=13 nM on human IM9 cells). This higher affinity for human receptor was in some extent counterbalanced by the increased structural complexity. RP-100893 (dapitant) possesses good activity *in vivo* on plasma extravasation models in rats and in models of pain after oral administration. It was developed up to phase II for the treatment of migraine (1994) [8], but then discontinued, as happened to other NK-1 antagonists, which have been found not active in humans for this indication (vide infra).

Pfizer

In 1991, Pfizer group disclosed the structure of CP-96345 (Fig. (2)) [9]. The compound derived from the screening of a chemical

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collection and a first optimization of the lead [10]. The relatively simple structure of CP-96345 (a rigid quinuclidine scaffold containing a basic nitrogen atom, a benzhydryl moiety and an *o*-methoxy-benzylamine group) was the starting point for several SAR studies performed from different companies, aimed to ameliorate the pharmacological and pharmacokinetic properties and to obtain patentability (see [1] for review). Among the analogs synthesized, most aimed to mask the strongly basic quinuclidine nitrogen, which was considered responsible for the undesired activity at the Ca²⁺ channels [11, 12].

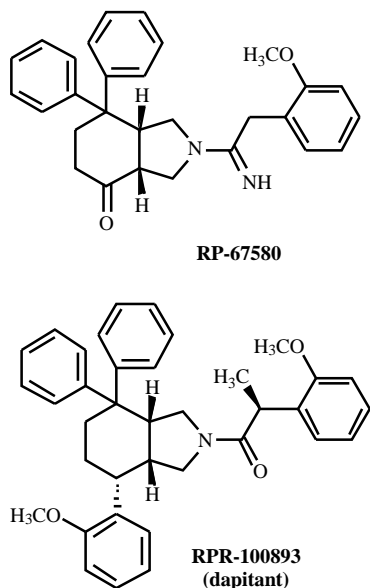


Fig. (1).

A satisfactory improvement in physico-chemical properties was achieved with CJ-11,974, a close analog of CP-96,345 bearing an isopropyl group on the methoxybenzyl ring. CJ-11,974 (ezlopitant, Fig. (2)) shows subnanomolar affinity for NK-1 human receptor and is able to block cisplatin-induced emesis in the ferret at a dose of 3 mg/kg. Its action *in vivo* seems due to the parent compound and one active metabolite [13]. Ezlopitant was developed up to phase II in US and Europe for chemotherapy-induced emesis, but although the compound resulted well tolerated and effective in controlling emesis, it was less effective in nausea and development was discontinued. A pilot study was conducted in IBS patients in 2000 to check the efficacy in the relief of symptoms [13]. Despite the encouraging results, the development for this indication was not carried further.

In order to simplify CP-96345 structure, it was settled a pharmacophoric model including the proximity and the relative orientation among the benzylamino portion, the central saturated ring and one of the phenyls in the benzhydryl moiety. Following conformational considerations, the quinuclidine ring and the benzhydryl moiety were replaced by a piperidine and a benzyl group, respectively, leading to CP-99994 (Fig. (2)) [14]. The X-ray crystal structure and the molecular modeling studies performed on CP-99994 confirmed the searched parallel orientation of the two aromatic rings. CP-99994 retains high affinity for the human NK-1 receptor (IC₅₀=0.17 nM on human IM9 cells). Many other SAR studies were performed to investigate further the structural requirements for NK-1 receptor affinity, and different kinds of constraints were introduced to look for a univocal active conformation [15-20 and 1 for review]. Despite the good results obtained in terms of affinity retention, no advantages were achieved for *in vivo* activity, and the constrained structures resulted in general more complex to synthesize. There-

fore, different studies were devoted to the search of more favorable physico-chemical or pharmacological properties which could facilitate the development phase. Parameters like undesired Na⁺ or Ca²⁺ channels blockade, blood brain barrier (BBB) penetration and oral bioavailability were considered crucial to reach good results in clinical phase [21]. But in the meantime companies like Merck, Glaxo, Novartis etc profited from the acquired knowledge on the field to build their own series of antagonists (*vide infra*).

CP-99994 was characterized in a number of pharmacological models [22 for review]. The anti emetic activity was checked in dogs and ferrets [23]. The inhibition of induced plasma extravasation, mucus secretion and bronchoconstriction proved in animal models [24] appeared not reproducible in asthmatic patients [25]. CP-99994 alleviated dental pain in humans, but with a short duration of action when administered intravenously at 0.75 mg/kg [26].

Due to the poor oral bioavailability (< 10 %) [27], the phase II clinical trials of CP-99994 in the US were discontinued.

As mentioned before, several studies were carried on at Pfizer to ameliorate the physico-chemical properties of its early antagonists. The introduction of a trifluoromethoxy group in the *o*-methoxybenzyl ring of CP-99994 gave a compound (CP-122721, Fig. (2)) [28] with comparable receptor affinity but enhanced up to 50-fold *in vivo* potency [29]. CP-122721 blocks plasma protein extravasation elicited by aerosolized capsaicin in guinea-pig lungs with an ID₅₀= 0.01 mg/Kg p.o., and antagonizes [Sar⁹, Met(O₂)¹¹]SP induced locomotor activity in guinea-pigs with an ID₅₀=0.2 mg/Kg [28].

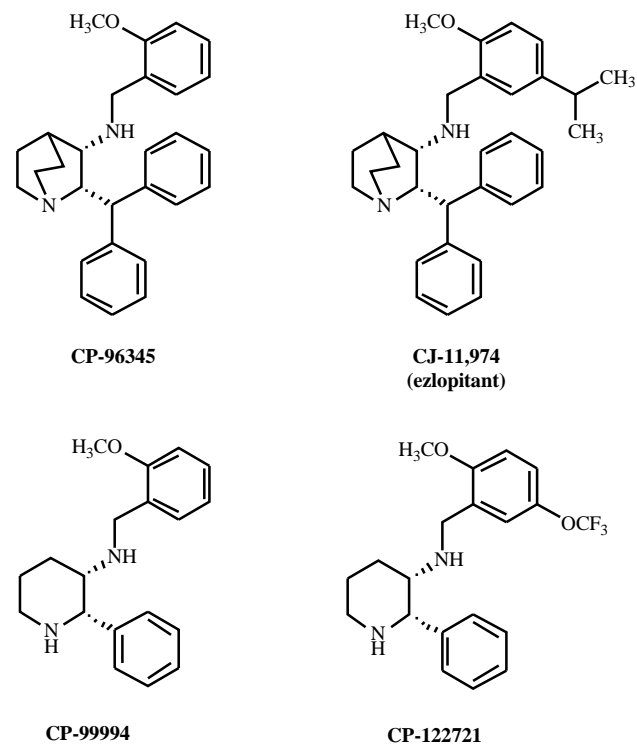


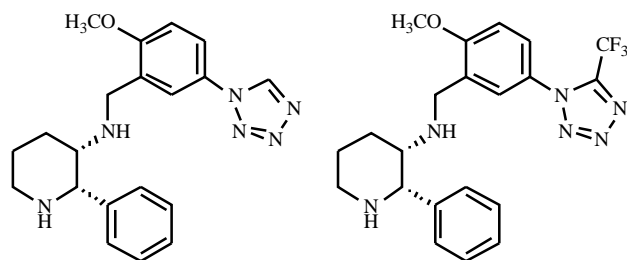
Fig. (2).

It underwent phase II clinical trials for the treatment of depression, emesis and inflammatory diseases including asthma and irritable bowel syndrome (IBS). CP-122721 (p.o.) was evaluated for the treatment of postoperative nausea and vomiting [30], in dose-ranging trials for acute and delayed emesis following treatment with cisplatin [31], and gave interesting trial results in patients with ad-

vanced solid tumors [32]. Despite the encouraging premises, no further development was reported after 2000 [33].

Glaxo

The structure of CP-99994 was the starting point for NK-1 receptor antagonists search at Glaxo. The screening to assess the pharmacological activity of the designed analogs was performed either in binding tests or in a model of radiation-induced emesis in ferrets, chosen as a likely clinical target. The preferred point of variation was position 4 of the benzyl ring of CP-99994, where heterocycles like tetrazole variously substituted were placed, like in GR-203040 [27] and GR-205171 (Fig. (3)) [34]. Both the compounds showed subnanomolar affinity for NK-1 receptor, metabolic stability and activity in the screening emesis test (100 % inhibition at 0.3 mg/Kg and 0.1 mg/kg p.o., respectively) [35]. The tetrazole ring was supposed to enhance oral bioavailability and to improve the pharmacokinetic properties. GR-205171 (vofopitant) has been evaluated in clinical phase II for postoperative nausea and vomiting [36], migraine and motion sickness, where it resulted ineffective [37]. Despite the good results in emesis, the development was discontinued in 1999.



GR-203040

GR-205171
(vofopitant)

Fig. (3).

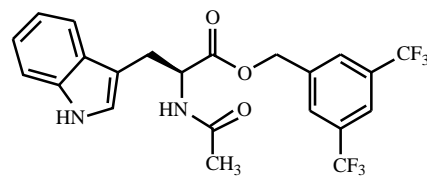
Merck

The first class of antagonists published by Merck derived from the screening of a chemical collection, from which N-ethyl-L-tryptophan benzyl ester was found to bind at micromolar concentration to the human NK-1 receptor expressed in CHO cells [38]. This simple lead was optimized to yield compound L-732,138 ($IC_{50}=1.6$ nM, Fig. (4)), which bears the acetylated amino group and the 3,5-bis(trifluoromethylated) phenyl moiety, a structural motif common to many of the non peptide NK-1 antagonists described in the literature [39]. Conformational analysis suggested a specific reciprocal orientation of the aromatic rings as a key structural motif [40], and constrained cyclic structures able to fix this feature were designed [41]. The ester bond, susceptible of rapid metabolic degradation, was then replaced with a ketone and the resulting structure was optimized to improve solubility and bioavailability, leading to L-737,488 (Fig. (4)) which bears a quinuclidine basic moiety. L-737,488 showed high *in vivo* activity ($ID_{50}=1.8$ mg/Kg p.o. in inhibiting plasma protein extravasation in guinea-pig), weak affinity for Ca^{2+} channels and good solubility in water [42]. No further development was reported for the series.

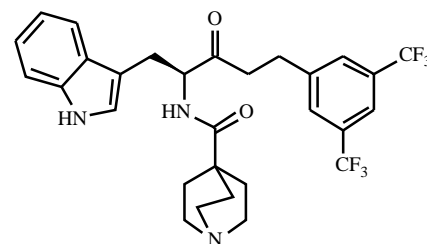
In 1993, Merck started to divulgate series of NK-1 antagonists structurally related to compounds previously known in the literature. Both quinuclidine (CP-96345) and piperidine (CP-99994) templates were chosen as starting point for SAR studies.

A series of CP 96345 analogs bearing the substitution of the amino with an ether function [43], lead to the optimization of the benzyl ether group introducing a 3,5-bis(trifluoromethyl) analog (compound L-709,210, Fig. (5)) [44]. Applying the simplification strategy at a further level ('toward the minimum pharmacophore'),

Merck scientists discovered that the quinuclidine or piperidine ring are not essential, since acyclic benzhydryl or phenyl aminoethyl ethers also preserve a good affinity for the NK-1 receptor [45]. Moreover, the basic nitrogen could be replaced by an oxygen and the insertion of an acetamido moiety allowed to obtain subnanomolar affinity and reduced Ca^{2+} channels affinity, like in compounds 1, 2 and 3 described in Fig. (5) [43, 46, 47].

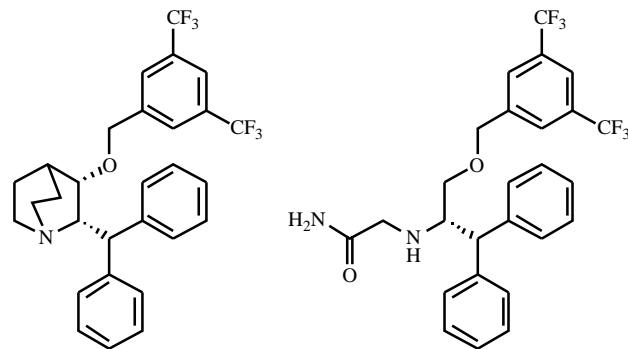


L-732,138



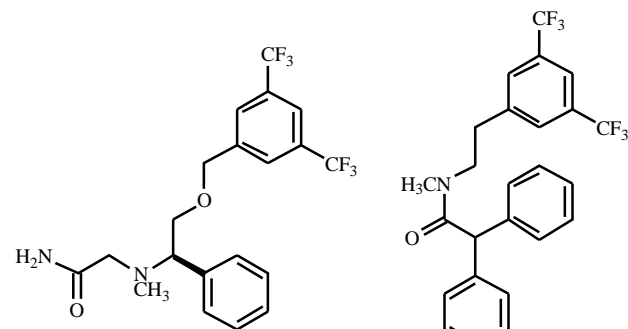
L-737,488

Fig. (4).



L-709,210

1



2

3

Fig. (5).

The SAR studies which allowed the selection of compounds for development were based on the structure of CP-99994. The compound L-733,060 (Fig. (6)) [48], shows a 3,5-bistrifluoromethyl benzylether piperidine in the place of the 2-methoxy benzylamine moiety of the parent compound. The piperidine nitrogen was then functionalized with various groups, in order to decrease its basic character [49]. The 3-oxo-1,2,4-triazol-5-yl moiety resulted the best in terms of basicity modulation and improvement in oral bioavailability, like in compounds L-741,671 and L-742,694 (Fig. (6)) [50, 51] which showed an ID_{50} of 0.037 and 0.009 mg/Kg p.o., respectively, in inhibiting SP-induced cutaneous inflammation in guinea-pig. The morpholine nucleus introduced in L-742,694 was maintained in the further refinement. To avoid possible metabolic deactivation (debenzylation, oxidation of the phenyl ring at C-3), several modifications were introduced, like methylation on the C alpha of the benzyl ring and fluorination on the phenyl ring [52]. This afforded MK-869 (Fig. (6)) and analogs, which like L-742,694 showed high affinity for the NK-1 receptor and high oral activity. MK-869 (or L-754,030 or, as it will be referred throughout the text, aprepitant) was selected for further studies in pain, migraine, emesis and psychiatric disorders because of its high potency and central activity.

While the clinical activities were carried on with aprepitant, it was found necessary to improve its pharmacokinetic characteristics. In fact, aprepitant shows low solubility in water (0.2 microg/ml) and it was almost impossible to find an intravenous formulation acceptable in early clinical phases for administration to humans. The phosphorylation of the oxotriazolyl ring in aprepitant produced a phosphorylated water soluble pro-drug (L-758,298, Fig (6), [53]). A series of experiments were performed to demonstrate that L-758,298 rapidly and univocally converted to aprepitant both *in vitro* and *in vivo* in the conditions of the pathophysiological models.

Clinical studies of phase II were performed with L-758,298 in emesis [54] and migraine [55]. The compound showed favorable tolerability profile and efficacy in the treatment of chemotherapy-induced emesis, but not in migraine. Later on, an analog of aprepitant suitable for both intravenous and oral clinical administration has been described (compound 4, Fig. (6)) [56]. In the new antagonist the 3-oxo-1,2,4-triazol-5-yl moiety present in aprepitant was substituted with a 5-aminomethyl-1,2,3-triazol-4-yl moiety, isolated as hydrochloride. The pharmacological performances were comparable to those of the parent compound in pathophysiological models, but water solubility, oral bioavailability and CNS penetration were considerably enhanced. Despite this excellent pharmacological profile, no clinical development has been reported.

But what happened to aprepitant? As described before, hopes were strong to find a new class of analgesic and antidepressant. The analgesic hope was dropped in an early stage of development, as despite the positive preclinical results in animal models of pain, the compound was found inactive in dental surgery derived pain, peripheral neuropathy, osteoarthritis and migraine [57]. This result was a matter of debate in the scientific community [58].

Another equally important target was at the horizon: depression. Aprepitant in fact had been proven effective in a number of pathophysiological models of depression and anxiety [59]. Phase II studies on major depressive disorders (MDD) strongly confirmed the expectations [60-62], although some difficulties in results interpretation came out in the early phase of development [63]. Merck phase III trial started in 2001. In November 2003, however, it was announced that no significant results were obtained with aprepitant in comparison with placebo in a total of five phase III trials. The development for this indication was discontinued [64].

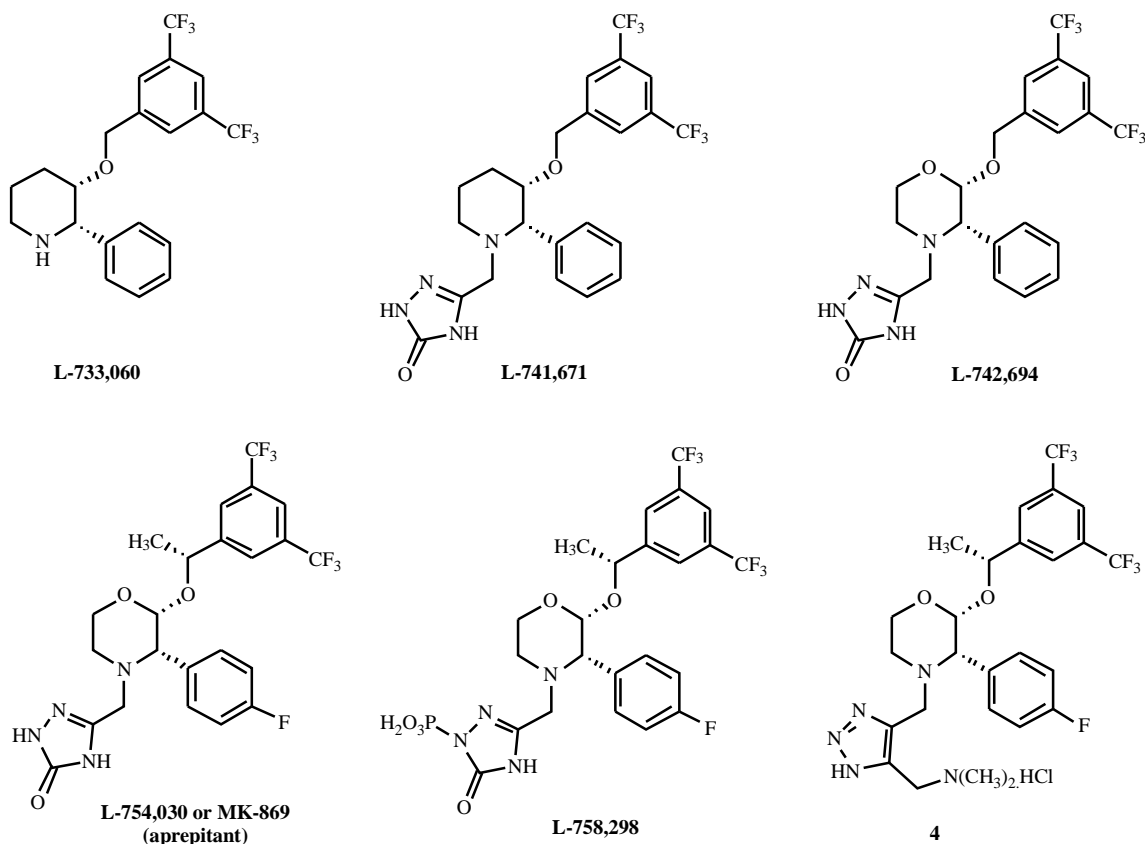


Fig. (6).

At the same time of these investigations, Merck was evaluating aprepitant in emesis. As mentioned before, vofopitant and ezlopitant have been evaluated in clinical phase for postoperative nausea, vomiting and motion sickness. The phase II studies on aprepitant started in 1998. The compound was found active in the control of chemotherapy - induced emesis, in combination with granisetron and dexamethasone [54]. Phase III was implemented in 1999, and in 2003 the results of two phase III trials with a combination of aprepitant, a 5-HT₃ antagonist and a corticosteroid were completed [65]. The compound was launched in 2003 in the US, and in 2004 in EU with the name of Emend. In November 2004, Ono Pharmaceuticals licensed the development in Japan.

Sanofi

Through the random screening of a chemical collection and subsequent optimization of the lead, Sanofi researchers discovered the highly potent NK-1 receptor antagonist SR-140333 (Fig. (7)) [66] and the potent NK-2 receptor antagonist SR-48968 (Fig. (7)) [67]. The structure of SR-140333 shows a piperidine scaffold substituted on the nitrogen with an acyl aromatic group and gem-disubstituted in position 3. Three aromatic groups seemed essential for high affinity interaction with the NK-1 receptor ($K_i=0.019$ nM on IM9 cells) and selectivity. SR-140333 shows high activity *in vivo* in antagonizing SP-induced hypotension in dogs and guinea-pigs and in blocking plasma protein extravasation in rats, also demonstrating activity at central level [68]. In 2002, Sanofi published the pharmacological characterization of a follow up of SR-140333. In the new analog, SSR-240600, the central piperidine ring was substituted with a morpholine ring and the quinuclidine moiety with a piperidine. The 3,5 bistrifluorophenyl group also appears in this compound. SSR-240600 (Fig. (7)) shows nanomolar affinity at

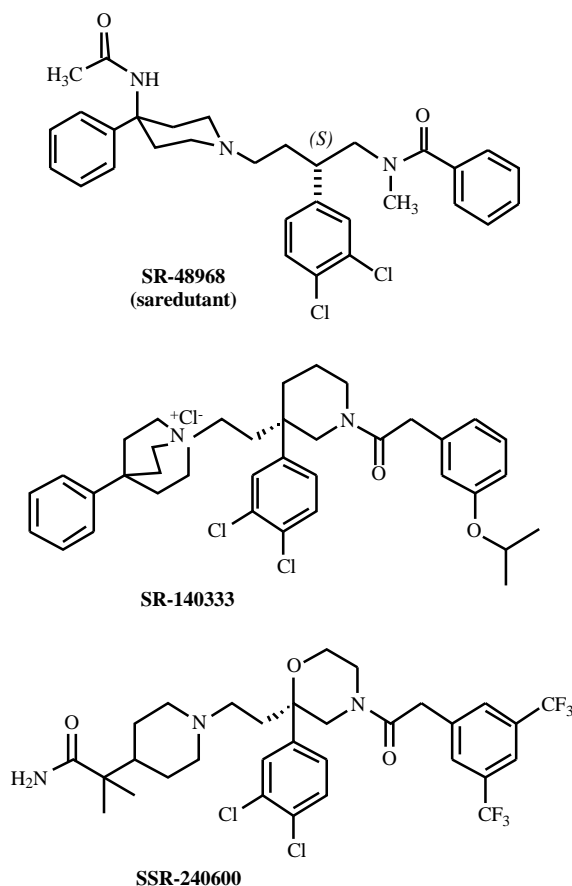


Fig. (7).

human NK-1 receptor and high selectivity [69]. It is active *in vivo* in citric acid - induced cough in guinea pigs, in reducing micturition frequency without effects on micturition pressure, urethral pressure or urethral relaxation during micturition and also acts as an antidepressant [70]. Pharmacokinetic studies in guinea pigs showed its efficient brain penetration. The compound is in development (phase I) for the potential treatment of overactive bladder.

Ciba Geigy

Ciba Geigy (Switzerland) developed a class of NK-1 selective antagonists through the modification of a lead identified by screening of a chemical collection. The 'two aromatic groups five-to-nine atoms apart', considered as the minimum requirements for affinity, was optimized to obtain CGP-47899 (Fig. (8)) [71], which shows high affinity for NK-1 receptor. Further optimization with the insertion of a quinoline group in the place of the phenyl group lead to the follower CGP-49823 (Fig. (8)), possessing an $IC_{50}=12$ nM at the human NK-1 receptor and good oral bioavailability [72]. CGP-49823 was found active in the inhibition of intracerebroventricular SP-methyl ester-induced thumping behavior in gerbils [73] and it was developed through phase I for anxiety disorders, but the development was discontinued in 1998.

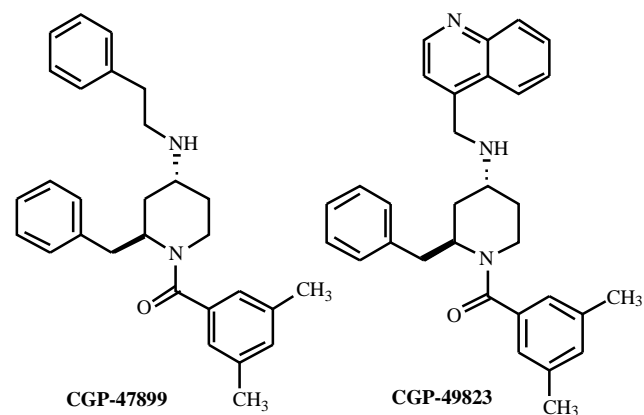


Fig. (8).

Parke-Davis

Pfizer (former Parke-Davis) discovered a series of tryptophan based compounds through the screening of a dipeptide library [74]. The dipeptide lead was optimized by methylation to introduce conformational constraints and by selection of the appropriate aromatic group to obtain high affinity. PD-154075 (or CI-1021 as it was later referred to, Fig. (9)) [75] shows an $IC_{50}=1$ nM for binding to the human NK-1 receptor and displays a good activity in *in vivo* tests, such as in a guinea-pig plasma protein extravasation model ($ID_{50}=0.02$ mg/Kg i.v.). Further SAR activities were based on the rational of an intramolecular hydrogen bond increasing the apparent lipophilicity of the compound, in order to enhance CNS penetration. In the best compound of the series the alpha methyl group was substituted with a dimethylaminomethyl group (compound 5, Fig. (9)) [76], to obtain enhanced brain penetration after oral administration in rats and efficacy at lower doses in *in vivo* tests. However, no further development was described.

Eli Lilly

By optimization of N-acetylated tryptophan amides and esters, another class of antagonists was discovered at Eli Lilly [77]. LY-303870 (lanepitant, Fig. (10)), can be considered an N-acetylated reduced amide of L-tryptophan. The two piperidine rings were chosen to enhance affinity for the NK-1 receptor and to increase basicity and water solubility. Interestingly, the tryptophan configura-

tion is opposite to that present in L-737,488. LY-303870 shows an IC_{50} =0.15 nM for the NK-1 receptor on IM9 cells, and possesses high potency on an *in vivo* neurogenic inflammation assay in guinea-pigs (ED_{50} =15 ng/Kg i.v. and 91 ng/Kg p.o.), with a duration of action longer than 8 hours.

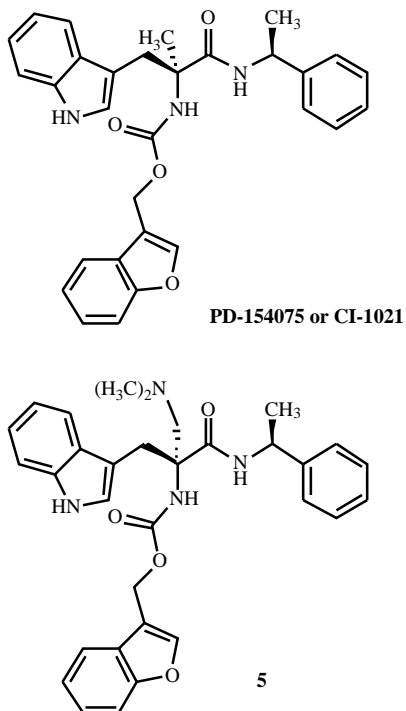


Fig. (9).

Lanepitant entered clinical trials by 2000. In a phase IIa study, it was used in the treatment of osteoarthritis pain, but no significant effect was checked in comparison with placebo or naproxen [78]. Since Lanepitant showed poor oral bioavailability and caused irritation upon iv injection, probably due to the dibasic 2-[4-(piperidin-1-yl)piperidin-1-yl]-acetyl group [79], Eli Lilly performed further SAR work on its structure. The dibasic moiety was substituted with various aryloxyacetic and acetylarlyloxy moieties, to yield a class of compounds devoid of irritant effects, showing ameliorated bioavailability and microsomal stability (compounds **6**, **7** and **8**, Fig. (10)).

Takeda

In 1995, Takeda described a series of N-benzylcarboxyamides developed through a general hypothesis on peptidergic G-protein

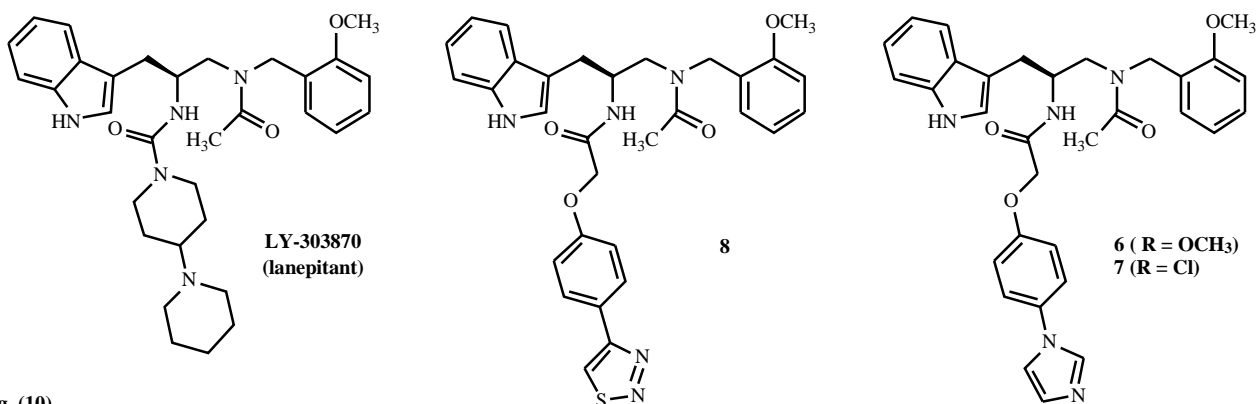


Fig. (10).

coupled receptors binding site [80]. The early antagonists (structure **9**, Fig. (11)), bearing a naphthyridine ring and the 3,5 difluoromethyl phenyl motif, were modified to avoid rotational atropisomerism in the exocyclic amide bond. In fact, the separation of the atropisomers was difficult and the use of racemate in clinical development was judged too risky [81]. The exocyclic amide bond was therefore included in a 8-member azacyclic ring, and the insertion of a methyl group in position 9 (TAK-637, Fig. (11)) effectively solved the isomerism problem [80].

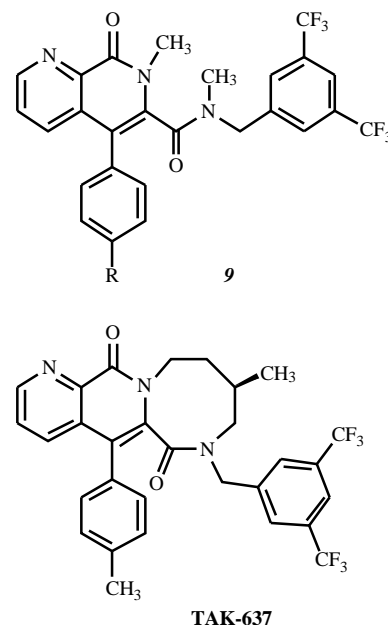


Fig. (11).

TAK-637 has an IC_{50} value of 0.45 nM at the human NK-1 receptor, and good selectivity toward human NK-2 and NK-3 receptors. In guinea pigs, ID₅₀ values for capsaicin-induced tracheal extravasation were 4.3 microg/kg for TAK-637 administered iv and 33 microg/kg for po administration [80]. In another *in vivo* study in guinea pigs, TAK-637, at the dose of 0.03 to 0.3 mg/kg iv, inhibited bladder contractions [82].

TAK-637 was found effective after oral administration in a number of different models of gastrointestinal disfunctions on lower urinary tract function in guinea pigs and cats [83]. The systemic administration of TAK-637 decreased the number but not the amplitude of distension-induced rhythmic bladder contractions in guinea pig [81].

TAK-637 was licensed to Abbott Pharmaceuticals for codevelopment. The compound entered Phase II trials in Europe, Japan and US for urinary incontinence, depression and IBS in 1999, but the clinical development was discontinued in 2003 (Company web site).

3. NK-2 RECEPTOR SELECTIVE ANTAGONISTS

Peptide or non peptide tachykinin NK-2 receptor antagonists have been described since 1992, and review articles on selected compounds [84-87], and their potential uses in therapy [88-90] have appeared during the last 10 years.

In the search for novel antagonists, we can recognize at least three different general approaches that have been followed by different research groups. The disclosure of the Sanofi non-peptide antagonist saredutant laid the basis for the first approach, with several compounds proposed by other companies and research groups, through modifications and optimization of the saredutant structure. The proposed definition of the minimal requirements for receptor affinity led Glaxo researchers to select and optimize small molecule NK-2 antagonist in an in-house collection of compounds. Finally, modeling and elaboration on the structure of the first cyclic peptide antagonists led to the identification of further peptide and non-peptide antagonists with high affinity at the human tachykinin NK-2 receptor.

Sanofi

The Sanofi non-peptide compound SR-48968 (saredutant, Fig. (7)), was described more than 10 years ago as the first highly potent, selective, tachykinin NK-2 receptor antagonist [91, 92]. *In vitro*, saredutant showed subnanomolar affinity at the human tachykinin NK-2 receptor, with high selectivity vs. the tachykinin NK-1 and NK-3 receptors. The compound was active *in vivo* in several animal models of NK-2 agonist induced effects [93], targeted at the respiratory [94], gastrointestinal [95], urinary [96] systems and also in a number of CNS preclinical studies [97-99].

On the basis of these results, saredutant was progressed to clinical studies, initially in the respiratory field. In a first study, the compound demonstrated significant activity in inhibiting bronchoconstriction induced by inhalation of neurokinin A in mild asthmatic patients [100]. In this study, saredutant was administered by the oral route, at the dose of 100 mg, and the challenge with neurokinin A was performed at 1.5 and 24 h after dosing.

Although this study constituted the first evidence of inhibition of sensory neuropeptide induced bronchoconstriction in humans by a selective tachykinin receptor antagonist, in a following study saredutant did not show significant bronchodilatory or bronchoprotective effect in allergic asthmatic patients [101]. The compound, orally administered at the dose of 100 mg (as in the previous study) for 9 days failed to improve bronchial obstruction and adenosine hyperresponsiveness in the patients. At that time, the hypothesis, also based on preclinical studies, that contemporary blocking of tachykinin NK-1 and NK-2 receptors may be necessary in the treatment of asthma, was raised. No further development of saredutant in the asthma indication has been reported.

According to Sanofi-Aventis [102], saredutant is presently in phase III clinical trials for depression. Results of a placebo and fluoxetine controlled multicenter phase IIb study in 120 patients with major depressive disorders were disclosed [103]. Compared with patients treated with fluoxetine (20 mg), a greater number of patients taking saredutant (100 mg) exhibited a sustained response. Saredutant also demonstrated an improved profile as for adverse events.

Further therapeutical indications in which saredutant is being evaluated include irritable bowel syndrome (IBS), although no data are available concerning these studies.

The structure of saredutant shares common features with the Sanofi selective tachykinin NK-1 and NK-3 receptor antagonists, SR-140333 (Fig. (7)) and osanetant (SR-142801, Fig. (20)), respectively. This general structure provided a suitable model for further elaboration, and a number of selective tachykinin NK-2 antagonists, together with double NK-1/NK-2 antagonists, have resulted from further research.

Again, Sanofi described the selective NK-2 antagonist SR-144190 (Fig. (12)). Together with other changes in the substituents, the N-methylated benzamide on the right end of the saredutant structure in Fig. (7) is "closed", in the structure of SR-144190, in a more rigid morpholine ring. Compared to saredutant, SR-144190 demonstrated an improved profile of selectivity and was found more active in several models, particularly in CNS studies, due to its improved bioavailability in the central nervous system [104]. A clinical development for SR-144190 was initiated, then discontinued in the asthma and CNS fields.

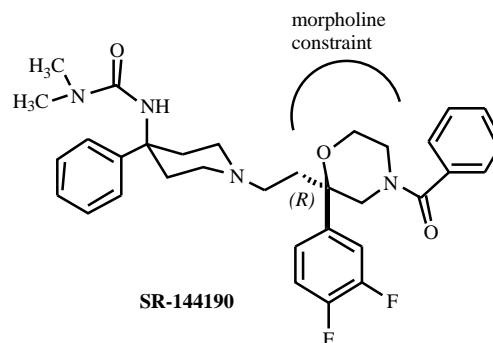


Fig. (12).

Nippon Kayaku

Another compound that appears to be derived from a constrained form of saredutant structure, although the medicinal chemistry regarding the molecule has not been published, is NK-5807 by Nippon Kayaku (Fig. (13)). The compound is reported to be active in a bronchoconstriction model in guinea pigs after intravenous and oral administration [105] and also showed activity in animal models of asthma [106]. In both studies, the effects were similar for NK-5807 and saredutant.

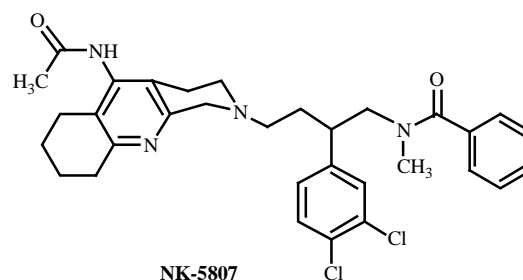


Fig. (13).

Pfizer

An extensive structure-activity relationship study was conducted by Pfizer researchers [107], using again saredutant structure as the starting point. Slight modification gave origin to the 4-hydroxy-4-phenylpiperidine lead **10** (Fig. (14)). Using parallel synthesis of a library and single compound preparation, the roles of the cyclic amine (piperidine in saredutant) and of the ring substitution in conferring potency were both explored. This strategy finally led to the selection of UK-224671 [108] (Fig. (14)), where the me-

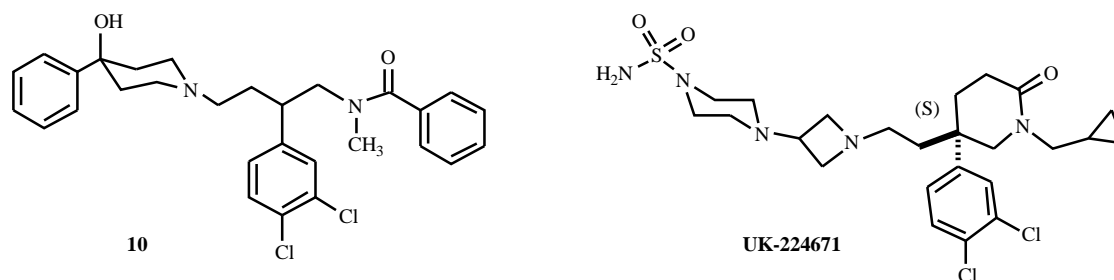


Fig. (14).

tabolically vulnerable N-methylamide function was incorporated into a more stable six-membered lactam ring, resulting in increased stability to human liver microsomes, and the cyclopropylmethyl group attenuates the lipophilicity of the former benzene ring substituent in order to decrease CYP-450 mediated oxidative metabolism.

UK-224671 was then progressed to phase I clinical studies, in view of its development for the treatment of urinary incontinence. The compound exhibited species differences in oral bioavailability [109] that was good in dogs (55%), lower in rats (7%) and in humans (7.5% in fasted volunteers and 3.6% in fed volunteers). These results finally led to termination of clinical development. Further studies indicated the compound to be a substrate for P-glycoprotein, with signs of transporter mediated efflux in the Caco2 cell model [110].

Zeneca

Zeneca (now AstraZeneca) researchers have described a number of selective tachykinin NK-2 receptor antagonists. Structure-activity relationship studies [111] on the piperidine region of saredutant led to replace the 4-phenyl-4-acetamido substitution pattern of this molecule (see Fig. (7)) with simple alkyl and acyl substituents. Appropriate placement of an alcohol functional group afforded compounds such as **11** (Fig. (15)), that were shown to be nearly as potent as saredutant both *in vitro* and, following oral administration, in a dyspnea model. A different elaboration of the terminal parts of the molecule led to ZD-7944 (Fig. (15)) [112] that also showed activity both *in vitro* and *in vivo* [113]. Both compounds of Fig. (15) maintain the (S)-configuration of saredutant at the dichlorophenyl bearing carbon atom. No further development was reported by AstraZeneca on these selective tachykinin NK-2 antagonists.

Glaxo

A completely different approach was followed by Glaxo researchers in 1994 which described the highly potent, orally active, non-peptide tachykinin NK-2 receptor antagonist GR-159897 (Fig. (16)) [114]. On the basis of their previously reported peptide an-

tagonists [115] they indicated the minimal requirements for receptor affinity in the presence of an indole ring and at least one other aromatic ring. Hence they searched their in-house compound archive for molecules bearing these two structural features, identifying low affinity leads such as structure **12** and **13** (Fig. (16)) and then combining and elaborating them to enhance potency. This led at the end to GR-159897, which showed high potency and long duration of action *in vivo* in a bronchoconstriction model in guinea pig [116] and remarkable oral bioavailability (87%) in beagle dog. It is worth noting that this was realized with a small molecule compound, featuring only two aromatic rings and a central tertiary amine as the key moieties. In addition, the sulfoxide group in GR-159897 was suggested to positively interact with the NK-2 receptor, while both sulfide and sulfone analogs showed a lower potency. This might be explained by adverse steric or electronic interactions with the receptor.

Constrained analogs of GR-159897, with the benzyl terminal moiety attached to a spiro-piperidine ring such as in structure **14** (Fig. (16)), were also synthesized and showed similar activity *in vitro* and *in vivo* [117].

Peptide Antagonists

Peptide antagonists described in the very early years of this field of research have already been the subject of review articles [87]. Linear peptides were derived from classical amino acid substitution in the sequence considered as the minimum active fragment of either NKA or SP. Lower molecular weight modified di- or tri-peptides ("peptoids") were also described. A different approach led to cyclic peptides, with the double aim of enhancing selectivity, by mimicking and blocking in a rigid structure the conformational arrangement of the ligands when interacting at the tachykinin NK-2 receptor, and of increasing the resistance of the peptide to metabolic degradation.

Merck

Head-to-tail cyclization of linear peptides with weak NK-2 antagonist properties led Merck researchers to obtain L-659,877 or cyclo(-Met1-Gln2-Trp3-Phe4-Gly5-Leu6) ([118], (Fig. (17)). The

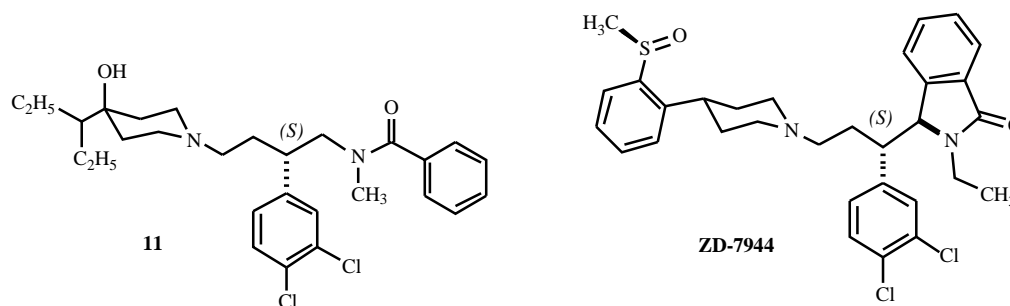


Fig. (15).

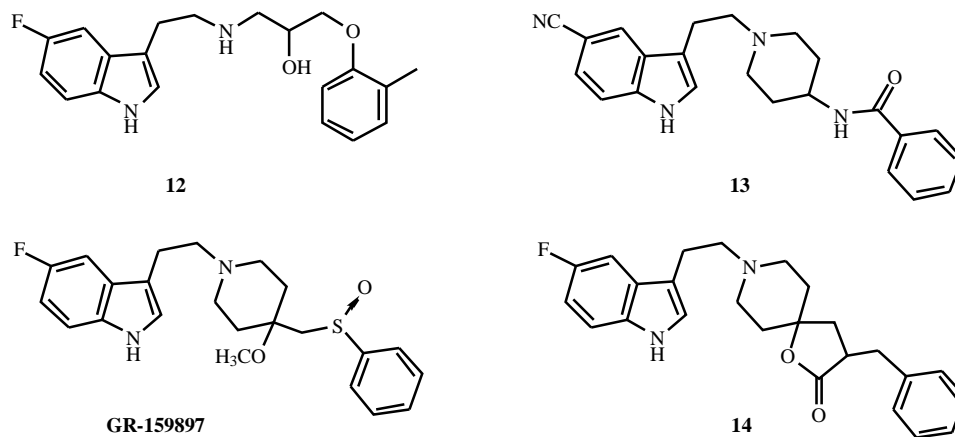


Fig. (16).

compound showed enhanced activity and selectivity at the tachykinin NK-2 receptor, thus suggesting that a favorable conformation for specific interaction with the NK-2 receptor was mimicked.

Menarini

The cyclic structure of L-659,877 was taken by Menarini researchers as a model to obtain even more potent bicyclic peptides. By relating conformational (NMR) and molecular modeling studies, the most favorable conformation of L-659,877 for interaction with the NK-2 receptor was postulated and the constrained analog MEN-10627 (cyclo(-Met1-Asp2-Trp3-Phe4-Dpr5-Leu6)-cyclo(2-5)), Fig. (17)) was designed and synthesized [119], ideally connecting the α -chain of Gln2 with the opposite β -carbon of Gly5 through a second cyclization on the same peptide skeleton. MEN-10627 displayed affinity for NK-2 receptors at least 10 times higher than its monocyclic precursor and also showed high potency in several *in vivo* models, with long duration of action, poor CNS penetration and almost complete protection from metabolic degradation [120, 121]. However, despite these favorable characteristics, further development of MEN-10627 as a drug candidate was hampered by some of its chemical-physical properties, mainly its low solubility

in water solutions. Aiming at an improvement of the hydrophilicity of MEN 10627 without altering its receptor affinity, Menarini researchers synthesized a number of sugar linked analogs. These kind of modifications, generally known to allow increases in solubility and serum half-life, were also showed to maintain antagonist activity at the tachykinin NK-2 receptor when the sugar was inserted in the N-terminal position of linear peptides [122]. When a similar approach was used for MEN-10627, the bicyclic, glycosylated hexapeptide nepadutant (MEN-11420, or cyclo{[Asn(-D-GlcNAc)-Asp-Trp-Phe-Dpr-Leu]cyclo(2-5)}), Fig. (17)) was obtained. In addition to a net increase in water solubility as compared to MEN-10627, nepadutant maintained affinity at human tachykinin NK-2 receptor at nanomolar concentrations, showed very high selectivity, with negligible binding affinity ($pIC_{50} < 6$) at 50 different receptors and ion channels, and showed a markedly improved profile of action when compared to the parent compound, with superior *in vivo* potency (about 10-fold) and longer duration of action, possibly due to a greater metabolic stability [123].

On these bases, nepadutant was progressed to clinical studies in the gastrointestinal and respiratory fields, with potential indications in IBS and asthma. In healthy volunteers, nepadutant, at the intra-

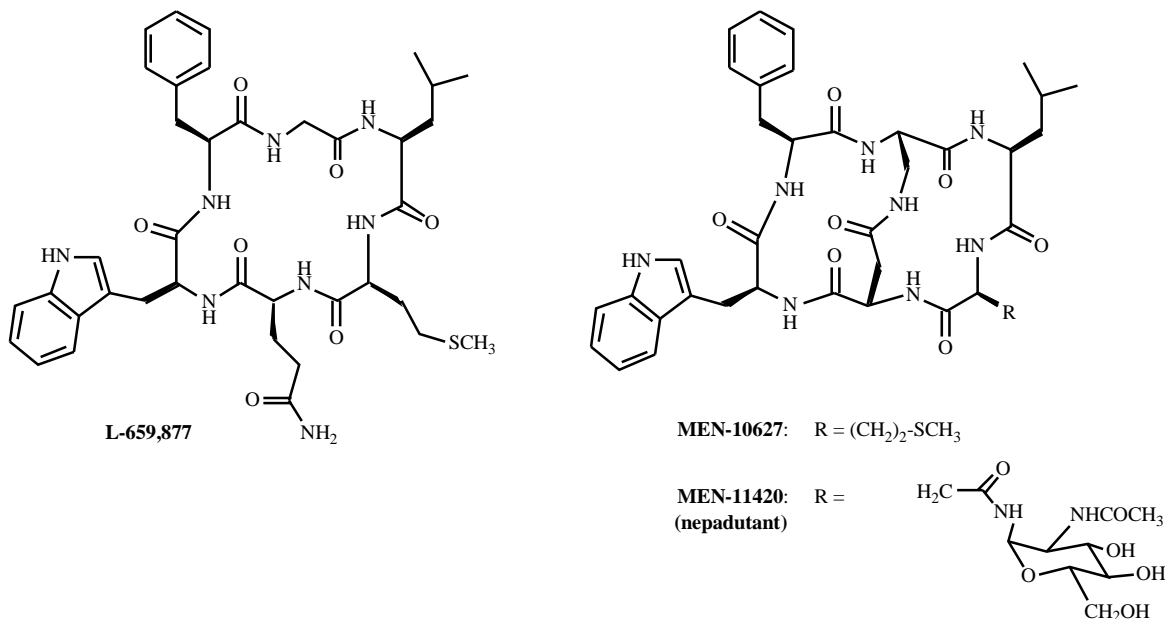


Fig. (17).

venous dose of 8 mg, was able to block the increase in gastrointestinal motility induced by infusion of neurokinin A [124]. In the same study, the cluster of "IBS-like" adverse events arising through activation of NK-2 receptors by neurokinin A were also inhibited by nepadutant administration in human volunteers. Notably, the compound did not affect unstimulated, basal intestinal motility suggesting its possible development for the treatment of IBS.

In addition, nepadutant at the doses of 2 and 8 mg i.v., was able to significantly inhibit bronchoconstriction induced by inhalation of neurokinin A in mild asthmatic patients [125].

Further investigations were carried on by Menarini researchers to simplify the nepadutant structure while maintaining antagonist affinity at the NK-2 receptor, and to derive, by conformational and structure-activity studies, suitable moieties that could be inserted on a non-peptide skeleton. Structural studies indicated the presence in MEN-10627 of two β -turns (type I and type II, respectively) with Trp-Phe and Leu-Met as corner residues [126]. Site directed mutagenesis on labeled nepadutant suggested a primary role of the Trp-Phe moiety in the binding interactions with the tachykinin NK-2 receptor [127]. This background led to obtain monocyclic pseudotetrapeptides, such as **15** (Fig. (18)) that maintained the structure of the larger bicyclic peptide with exact overlapping of the Trp-Phe motif and still showed affinity ($pK_i = 5.9$) at the human tachykinin NK-2 receptor [128]. Insertion in the part of the molecule opposite to the Trp-Phe fragment of aspartic acid moieties bearing basic substituents, such as in **16** (Fig. (18)), allowed to restore high level NK-2 receptor affinity ($pK_i = 10$) and *in vivo* activity [129]. A different elaboration of crucial features for the interaction with the receptor, such as the indole aromatic group and a basic moiety as that found in **16**, led to non-peptide diamides such as **17**, Fig. (18), still retaining good affinity ($pK_i = 8.4$) at the human tachykinin NK-2 receptor [130].

4. NK-3 RECEPTOR SELECTIVE ANTAGONISTS

A relatively low number of selective tachykinin NK-3 antagonists have been described over the years [131-133 for review]. Therapeutic targets were generally in the central nervous system (CNS) field (schizophrenia, anxiety, pain/inflammation) and in some pulmonary (chronic obstructive pulmonary disease, COPD) and gastrointestinal tract diseases.

With the exception of peptide and "peptoid" antagonists disclosed in the early part of 1990's by Parke-Davis (such as PD-161182, Fig. (19), [134,135]), two research trends are easily recognizable in the literature, leading to dichlorophenylalkylpiperidine

(Sanofi) and quinoline (SmithKline Beecham, now GSK) antagonists, respectively. Each of them gave origin to a clinical candidate, osanetant (Sanofi, SR-142801) and talnetant (GSK, SB-223412).

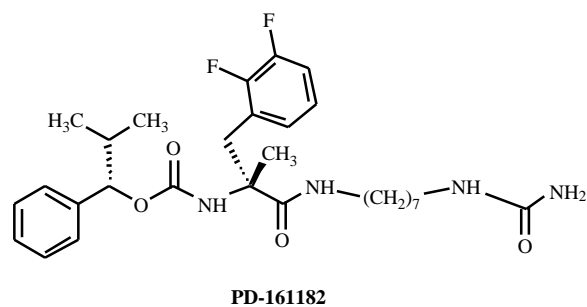


Fig. (19).

Sanofi

Osanetant was described in 1995, as the first potent and selective tachykinin NK-3 antagonist [136]. Its structure (Fig. (20)) resembles very closely that of the Sanofi selective tachykinin NK-2 antagonist saredutant (see Fig. (7)). Osanetant showed affinity at the human tachykinin NK-3 receptor at subnanomolar concentrations ($K_i = 0.40$ nM) [137] and high *in vitro* activity in binding studies both in peripheral (ileum) and central (cerebral cortex) tissues of guinea-pig [138]. In *in vivo* models, osanetant was shown to penetrate the blood-brain barrier and to exhibit a long duration of action, being active after both oral or intravenous administration [139, 140]. These properties were considered of particular interest for the possible treatment of CNS disorders such as psychosis or anxiety.

Clinical studies, up to phase IIb, were conducted on osanetant in MDD. However, in a 6-week phase IIb study at three fixed oral doses (50, 100 and 200 mg) of osanetant, *versus* paroxetine (20 mg) and placebo, non conclusive results were obtained, with no significant differences over paroxetine and placebo [141]. This led to the discontinuation of studies in this indication.

Presently osanetant is developed by Sanofi-Aventis for the potential treatment of schizophrenia. Phase IIb clinical studies for this indication were ongoing in March 2005 [102].

Sanofi has also reported SSR-146977 (Fig. (20)), a back-up compound of osanetant with slightly modified substituents at the

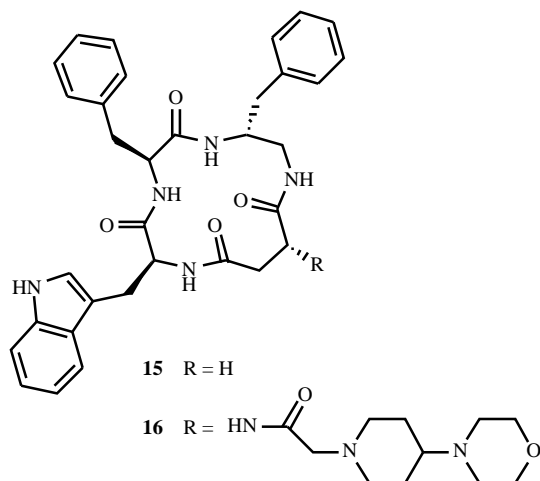
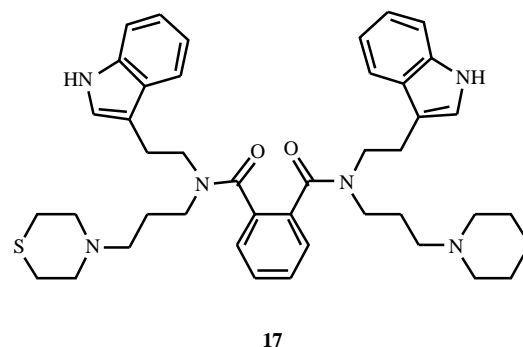


Fig. (18).



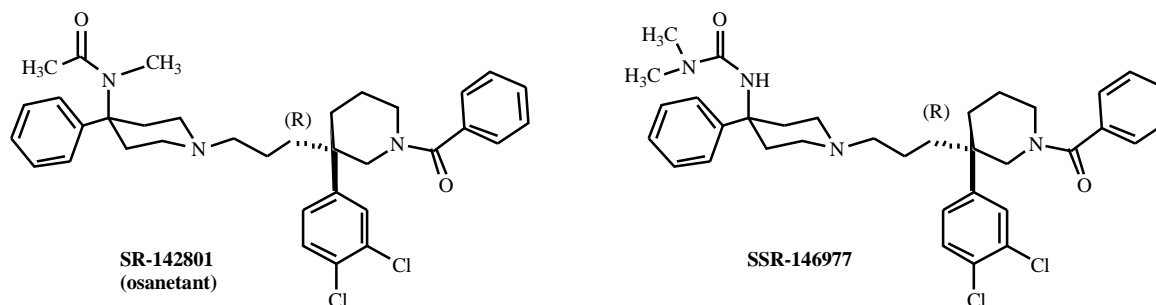


Fig. (20).

piperidine ring. In 2004, clinical phase I studies were ongoing in the CNS field (depression, schizophrenia) [142].

Merck

Using the osanetant molecule as a common structural template, researchers at Merck derived both NK-3 and NK-2 selective antagonists with high affinity at the human cloned receptors [143].

SmithKline Beecham

In 1996, researchers at SmithKline Beecham (now GSK) described a series of differently substituted 4-quinolinecarboxamides as tachykinin NK-3 receptor selective antagonists [144]. One of them, talnetant, was later selected as a clinical candidate. Initially, they synthesized compound **18** (Fig. (21)) aimed at the tachykinin NK-1 receptor. However, **18** was shown to possess no affinity for human NK-1 receptors while having moderate affinity at the human NK-3 receptor. Iterative optimization [145] of NK-3 affinity and selectivity led to talnetant (SB-223412, Fig. (21)) [146], that was shown *in vitro* to be as potent (hNK-3 binding: $K_i = 1$ nM) as osanetant but more selective than the reference compound. In mice, oral administration of talnetant produced dose-dependent inhibition of behavioral responses induced by the NK-3 receptor selective agonist, senktide, with $ED_{50} = 12.2$ mg/kg. Pharmacokinetic evaluation of talnetant in rat and dog indicated low plasma clearance, good oral bioavailability ($F = 62$ and 71% in rats and dogs, respectively) and high and sustained plasma concentrations after 4 to 8 mg/kg oral dosages [147].

Talnetant is presently in clinical development for the potential treatment of schizophrenia. In a placebo-controlled study, talnetant (200 mg) or risperidone (3 to 6 mg) were administered orally for 6 weeks to schizophrenic patients, reaching the primary endpoint [148] for 40% and 48% of patients, respectively (30% for patients who received placebo). Talnetant resulted well-tolerated, with

lower prolactin levels elevation and testosterone reduction as compared to risperidone, and no weight gain. In addition, improved cognitive effects were noticed in patients with high talnetant plasma exposure ($n = 20$, dose not disclosed) [149]. Following these results, GSK announced the development of a new formulation of talnetant, claimed to maintain safety and tolerability of the previous one, to be used for further phase II studies.

According to GSK, talnetant is also investigated in phase II studies in IBS, although no clinical data are available in this indication. This follows encouraging preclinical data of talnetant in a rat model of visceral hypersensitivity [150]. Other potential indications in which talnetant was investigated include urinary incontinence, COPD and cough. However, these studies were terminated [151].

5. MULTIPLE ACTIVE TACHYKININ RECEPTORS ANTAGONISTS

Since 1996, dual active NK-1/ NK-2 receptor antagonists were reported by different authors (see [152] and [153] for review). The even inhibition of SP and NKA effects was judged important for the therapy of pathologies involving the airways, where both the transmitters play a role. In the following years, an increasing interest in the development of multiple TKs antagonists aroused from preclinical evidences that the simultaneous blockade of NK-1 and NK-2 receptors could synergistically improve the treatment of several pathologies, like gastrointestinal diseases, CNS disorders and urinary incontinence.

From the molecular point of view, the primary sequence of TKs receptors show a certain omology [154], and many hypotheses have been made on the partially overlapping binding sites for NK-1, NK-2 and NK-3 receptors [155]. As a matter of fact, it was possible through relatively simple structural changes to switch from one TK receptor to the other (*vide infra*) and to develop ligands with high affinity for two or all of the three receptors.

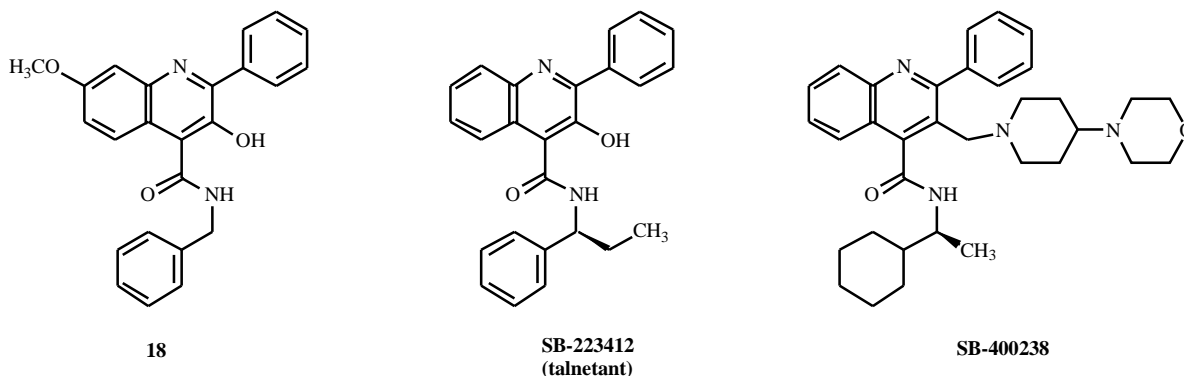


Fig. (21).

5.1. Dual NK-1/NK-2 Antagonists

Merrell-Dow

Hoechst Marion Roussel (now Sanofi Aventis) developed a series of NK-1/NK-2 dual receptor antagonists starting from the main pharmacophoric features of the NK-2 and NK-1 selective antagonists SR-48968 (Fig. (7)) and CP-96345 (Fig. (2)). The basic nitrogen and two aromatic rings of the said compounds were constrained with a pyrrolidine ring, giving MDL-105212A (Fig. (22)) [156]. MDL-105212A shows good affinity for the human NK-1 ($IC_{50}=3.11$ nM) and NK-2 ($IC_{50}=8.40$ nM) receptors and it is active on *in vivo* models of dyspnea, cough and plasma protein extravasation, even after oral administration despite the modest oral bioavailability [157].

With the aim to balance the dual activity and to ameliorate the pharmacokinetic properties, further SAR studies were performed, leading to the compound MDL-105172A (Fig. (22)), bearing a morpholine ring in the place of the primary amide. This modification was able to enhance the oral activity, as in the inhibition of capsaicin induced increase in pulmonary insufflation pressure, the ED_{50} po was 20 mg/kg for MDL-105172A and 50 mg/kg for MDL-105212A. Both the compounds show nanomolar affinity for guinea pig NK-3 receptor. MDL-105212A was found active on *in vivo* models of TK-induced dyspnea, cough and plasma protein extravasation, even after oral administration [158]. Some analogs substituted in the primary amide function with piperazines or morpholines showed higher metabolic stability and affinity *in vitro* at both receptors, but no improvements were found in *in vivo* efficacy and duration of action [159].

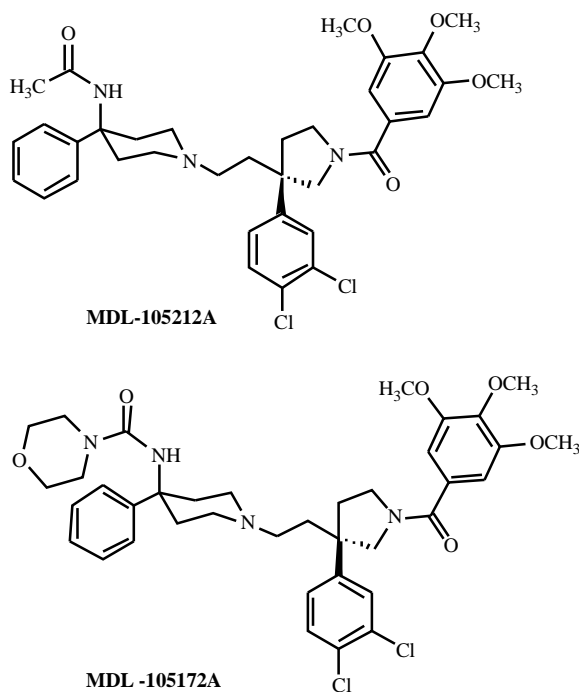


Fig. (22).

Yamanouchi

SR-48968 was the starting point also for Yamanouchi researchers. Examining the conformational features of two acetamidophenylpiperidines chosen as models, they speculated that a spiroisobenzofuranpiperidine could be the right constraint to orient the phenyl ring of SR 48968. The compound designed with this rationale, however (YM-35375, Fig. (23)), showed an affinity at the hamster NK-2 receptor 20 times lower than the precursor and submicromo-

lar affinity at the NK-1 receptor [160]. Interestingly, its antagonist activity *in vivo* in guinea-pigs was comparable to that of SR-48968. SAR studies on this lead compound were aimed at optimizing the various pharmacophoric groups for NK-2 receptor affinity [161]. The spiroisobenzofuran moiety resulted the most suitable for this purpose and compound YM-38336, bearing a spirobenzothiophene moiety, showed an affinity at hamster NK-2 receptor comparable to that of SR-48968 and good efficacy *in vivo* after iv and id administration [93]. The submicromolar affinity of YM-35375 at the NK-1 receptor was the objective of further medicinal chemistry aimed to obtain dual NK-1/NK-2 receptor antagonist activity [162]. First the phenyl ring of the benzamido moiety was substituted with electron-withdrawing groups which were known to enhance NK-1 receptor affinity. The 3,4,5-trimethoxy analog thus obtained was studied *via* NMR and in the most represented conformation the two phenyl groups resulted close to each other, a feature common to NK-1 ligands. The NK-2 receptor affinity was enhanced replacing the benzofuran moiety with a 3-isoquinolone group. The resulting compound, YM-44778 (Fig. (23)), showed high and balanced antagonist activity at NK-1 and NK-2 receptors.

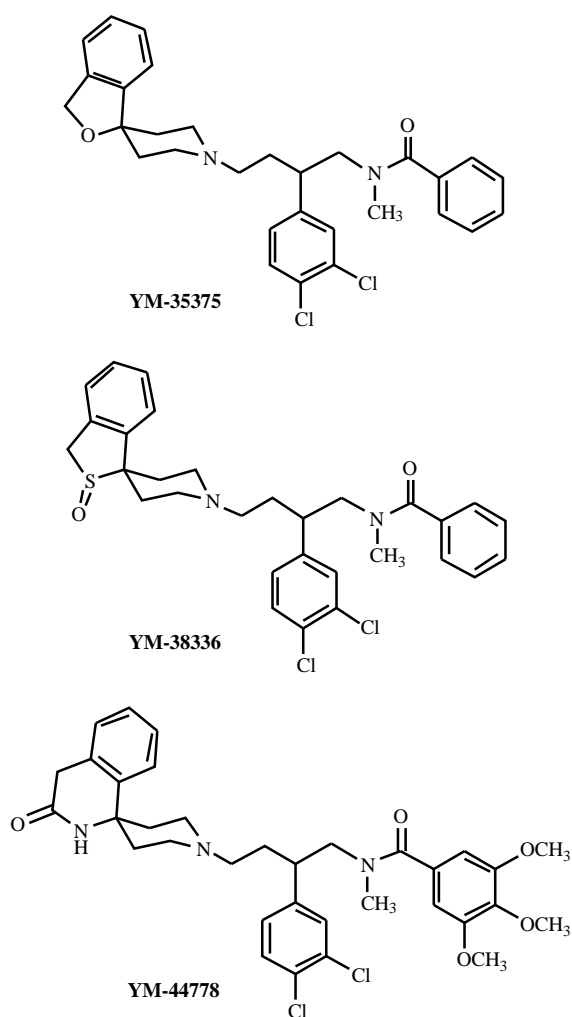


Fig. (23).

Schering

Schering-Plough researchers chose a different NK-1 receptor selective antagonist to select suitable pharmacophoric groups able to confer NK-1 receptor affinity when inserted in SR-48968 [163].

They developed two new classes of potent dual antagonists containing diamine and oxime functionalities. Interestingly, they found that modifying the backbone of SR-48968 the stereochemical preferences for high affinity can be significantly affected by functional groups adjacent to the benzylic center. In fact, the compounds most active at the NK-2 receptor (**19** and **20**, Fig. (24)) showed a stereochemistry opposite to that of SR 48968. The piperidine ring can be replaced by substituted piperazines [164], and the 4-hydroxy-4-phenyl substituent of piperidine is quite tolerant of structural modifications which could allow to further optimize the pharmacological profile of the series [165]. In fact, the exploration of the series continued with oxime analogs containing 3,5 disubstituted aryl ethers, whose nature and lipophilicity resulted able to shift the selectivity toward one or the other of NK-1 and NK-2 receptors [166]. The same effect could be obtained substituting the ether with different linkages, the best for dual high affinity being an amide. A combination of different substituents checked in an extensive SAR work [167, 168], lead to the identification of SCH-206272 (Fig. (24)), which showed high affinity for all the three TKs receptors (K_i (nM)= 1.3, 0.4, 0.3 for NK-1, NK-2, NK-3 receptors respectively) and improved oral bioavailability in the dog [153]. Since for certain therapeutic targets the NK-3 affinity was considered detrimental, SCH-206272 structure was explored in order to reduce this feature [168]. As a result, a series of benzimidazolones with micromolar affinity for NK-3 receptor was identified (compound **21**, Fig. (24)).

The *in vivo* pharmacological profile of SCH-206272 was investigated in the guinea pig and in the dog, where the compound shows excellent oral bioavailability (66%), in bronchoconstriction induced by SP and NKA [169]. Despite the excellent pharmacological and pharmacokinetic profile, no development has been reported for this compound or for its analogs.

Sankyo

The structure of MDL-105212 was chosen by Sankyo researchers as a starting point for further structure-activity studies [170]. Analogs bearing a morpholine ring in the place of the pyrrolidine and a spirobenzothiophenepiperidine were optimized. Strictly defined stereochemistry allowed to develop compounds endowed with nanomolar affinity at all the three tachykinin receptors, a right conclusion for the 'selectivity tournament' started in 1996. The efficacy of compound **22** as a racemate (Fig. (25)) to inhibit the effects of SP, NKA and NKB was confirmed *in vivo* [171]. No development has been reported for this series.

Merck

As already mentioned, an indole and a phenyl ring are good pharmacophoric groups for NK-1 and NK-2 receptors. Moreover, a number of selective NK-1 or NK-2 antagonists have been developed from a common template. Therefore researchers at Merck started from the indole-based NK-1 receptor selective antagonist L-732,138 (Fig. (4)) to develop dual active NK-1/NK-2 receptor

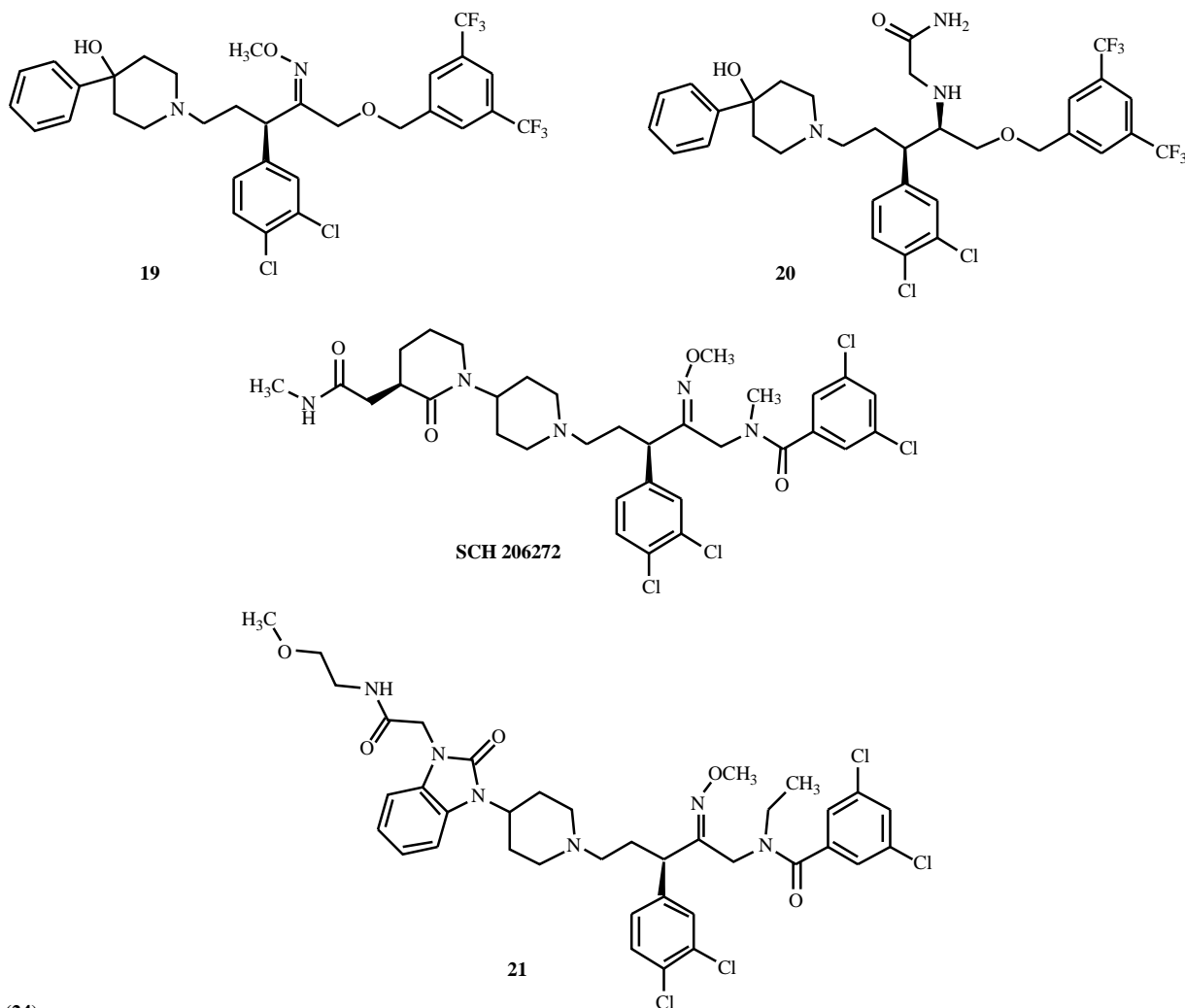


Fig. (24).

ligands [172]. They inserted the piperidine type functionality of SR-48968 at the N-terminus of Trp amides to form a urea. The best compound of the series (**23**, Fig. (25)) showed nanomolar affinity for both the receptors. The substituents on the phenyl ring were found crucial, as electron-withdrawing groups like trifluoromethyl are detrimental for NK-2 receptor affinity. The indole ring is necessary for high affinity at both the target receptors [172].

Novartis

Novartis examined the NK-1 receptor selective antagonist CGP-49823 (Fig. (8)) as starting point for dual NK-1/ NK-2 receptor antagonist activity [173]. Through a series of modifications it was optimized to compound **24** (Fig. (25)), which shows nanomolar affinity for both the receptors and is active after oral administration in $[Sar^9]SP$ and $[Ala^8]NKA$ induced bronchoconstriction in guinea-pigs ($ED_{50}=0.036$ and 0.9 mg/kg, respectively). No development has been reported.

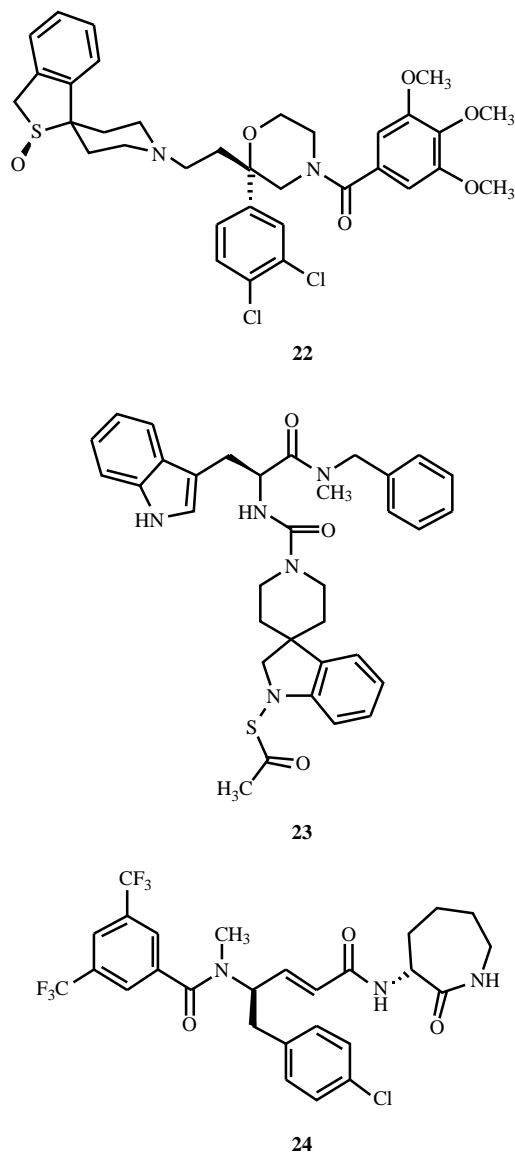


Fig. (25).

Astra Zeneca

AstraZeneca based its search for dual NK-1/NK-2 TKs antagonists on SR-48968 structure. The compound identified, ZD-6021

(Fig. (26)) [174], bearing a piperidine and a naphthamide region, shows similarities with Schering series (vide supra). ZD-6021 is a subnanomolar ligand at NK-1 and NK-2 receptors, and it shows some selectivity toward NK-3 receptor [175]. It is orally active in pathophysiological models of asthma.

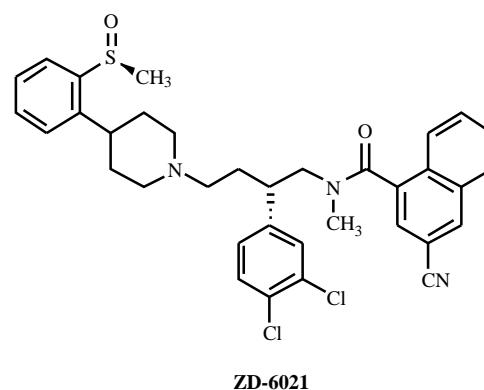


Fig. (26).

In a further SAR study, the two structural regions were variously substituted and this allowed to balance the affinities for the two receptors or to obtain a selective NK-1 ligand [176]. A recent SAR study was published which allowed to identify novel dual NK-1/NK-2 antagonists and an NK-1 preferential antagonist, ZD-4974, which shows K_i values of 0.17 and 67 nM at the NK-1 and NK-2 receptors, respectively and oral bioavailability similar to that of ZD-6021. ZD-4974 is a mixture of interconverting atropisomers and by substituting the 2-position of the naphthalene ring a slower rate of interconversion can be obtained [177]. No development has been reported for these antagonists.

5.2. Dual NK-2/NK-3 Antagonists

Two examples of dual tachykinin NK-2/NK-3 antagonists have been reported.

In the first approach, SmithKline Beecham (GSK) researchers modulated the structure of talnetant (*see above*) through stepwise chemical modification assisted by modeling studies, being able to produce potent NK-2/NK-3 combined antagonists without major changes in the chemical template. Best compound was SB-400238 (Fig. (21)), with subnanomolar affinity to both the human NK-2 and NK-3 receptors [178].

Recently (March 2005), Sanofi Aventis has announced the beginning of preclinical development for the dual NK-2/NK-3 antagonist SSR-241586 with a series of potential therapeutic indications (IBS, COPD and CNS diseases). However, no data have been published on this compound nor its structure has been disclosed [102].

6. CONCLUSIONS

In conclusion, through defeats and successes the story of TKs receptor antagonists reached its first goal with the launch of aprepitant. For CNS disorders, despite the failure of phase III trials with aprepitant, osanetant and talnetant are in phase IIb for the potential treatment of schizophrenia and saredutant entered phase III for depression. At least two compounds, nepadutant and saredutant, are in advanced development for IBS.

Since compounds with highly favorable pharmacological, pharmacokinetic and physico-chemical characteristics have been developed, TKs receptors antagonists are ready to be tested and hopefully proved efficacious in a number of other therapeutic applications.

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