

## Nonpeptide antagonists of neuropeptide receptors: Tools for research and therapy

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### Summary

The recent development of selective and highly potent nonpeptide antagonists for peptide receptors has constituted a major breakthrough in the field of neuropeptide research. Following the discovery of the first nonpeptide antagonists for peptide receptors ten years ago, numerous other antagonists have been developed for most neuropeptide families. These new, metabolically stable compounds, orally active and capable of crossing the blood brain barrier, offer clear advantages over the previously available peptide antagonists. Nonpeptide antagonists have provided valuable tools to investigate peptide receptors at the molecular, pharmacological and anatomical levels, and have considerably advanced our understanding of the pathophysiological roles of peptides in the CNS and periphery. Evidence from animal and clinical studies suggests that nonpeptide antagonists binding to peptide receptors could be useful for the treatment of disease states associated with high levels of neuropeptides.

OVER THE PAST TWO DECADES, a large number of novel peptides have been identified in the CNS, many of which fulfill the criteria to be considered potential neurotransmitters. In addition, numerous receptors and receptor subtypes that recognize peptide ligands have been described, based on pharmacological studies. The recent molecular cloning and sequencing of many neuropeptide receptor genes in various species has confirmed and extended the existing classifications. All neuropeptide receptors described so far belong to the G-protein-coupled receptor superfamily, characterized by seven transmembrane spanning regions. Despite the great amount of works dedicated to neuropeptides in the past

years, our understanding of their role in physiology and disease has been limited by the lack of suitable potent and selective receptor antagonists. Indeed, knowledge about the functional role of classical neurotransmitters has been mostly based on pharmacological studies using specific high-affinity receptor antagonists; until recently, such drugs were not available for neuropeptides, with the exception of opioid receptor antagonists such as naloxone.

Drugs with antagonistic actions for neuropeptide receptors can be classified as either peptides or nonpeptides. Antagonists of a peptide nature are available for several neuropeptides and have been widely used experimentally. However, these antagonists have several drawbacks, including high biodegradability, which precludes oral administration and implies a relatively short duration of action; high molecular weight and thus expensive synthesis; and in general, failure to cross the blood-brain barrier. Other limitations frequently encountered when using peptide antagonists include lack of selectivity for specific receptor subtypes and intrinsic agonistic properties, which contribute to their limited therapeutic and research potential. One of the most exciting advancements in the field of peptide research has been the development of nonpeptide compounds that act as selective antagonists of neuropeptide receptors. Following the discovery of the first nonpeptide antagonist of cholecystokinin (CCK) receptors in 1986<sup>1,2</sup> (Box 1), many other such compounds have been developed, including nonpeptide antagonists specific for tachykinins (substance P and related neurokinins A and B), angiotensin II, neurotensin, vasopressin, oxytocin, endothelin, neuropeptide Y (NPY), bradykinin and corticotropin releasing factor (CRF). In this article we will address the recent developments in nonpeptide antagonists for neuropeptide receptors, with a particular focus on their CNS actions.

### **Discovery of nonpeptide antagonists**

Two different strategies have been used in the discovery of nonpeptide antagonists of peptide receptors: 1) random screening of large compound libraries, using different biological assays, most frequently radioligand binding; and 2) rational drug-design strategies, *i.e.*, development of a lead compound on the basis of a known peptide ligand. Although several nonpeptide antagonists have been obtained using the rational design approach, including ligands for CCK<sup>3</sup> and NPY<sup>4</sup>, the file screening approach, based initially on natural compounds or, most recently, on synthetic chemicals, has proved most effective. For instance, SR48692, the first potent and selective nonpeptide antagonist of neurotensin receptors, was obtained by optimization of a lead compound discovered by random screening of several thousand chemicals<sup>5</sup>. Moreover, the majority of the nonpeptide tachykinin NK<sub>1</sub> and NK<sub>2</sub> receptor antagonists available today arose from targeted screening of large compound libraries using a radioligand binding assay as the primary screen<sup>6</sup>, whereas rational drug-design strategies have proved useful for the synthesis of nonpeptide tachykinin antagonists only in limited cases (Box 2). Increasing knowledge concerning

ligand-receptor interactions will likely facilitate the rational design of novel nonpeptide antagonists with high affinity for peptide receptors.

### **Molecular interaction of nonpeptide antagonists with their target receptors**

Nonpeptide receptor antagonists are chemically unrelated to the corresponding endogenous agonists, and their mechanism of action is not clear. Within the past few years, however, the molecular interaction of nonpeptide antagonists with their receptors has started to be characterized using applied molecular biology approaches, including receptor expression and site-directed mutagenesis. As most nonpeptide antagonists act as classical competitive ligands, it was initially expected that nonpeptide antagonists would share at least a major part of their binding site with the corresponding peptide agonist. However, it has become increasingly clear that this is seldom the case. The use of antagonist-derived radioligands as well as mutational analysis of receptors has suggested the existence of distinct agonist and antagonist binding domains on receptors for tachykinins<sup>7-10</sup>, CCK<sup>11,12</sup>, angiotensin<sup>13,14</sup>, opioids<sup>15</sup>, neurotensin<sup>16</sup> and vasopressin<sup>17</sup>.

The use of receptor mutagenesis to map binding sites has revealed that most peptide agonists interact primarily with residues located in the exterior part of the receptor, and contact points are frequently found in the N-terminal region (Fig. 1). In contrast, nonpeptide antagonists interact with residues located more deeply in the main ligand binding pocket, between the seven transmembrane segments<sup>18</sup>. Consequently, it has proven extremely difficult to identify point mutations which alter both peptide agonist and nonpeptide antagonist binding. In order to explain these observations, Schwartz and co-workers<sup>18</sup> have proposed an allosteric receptor model in which the ligands exert their effect by selecting and stabilizing preformed receptor conformations and thus shifting the equilibrium towards either an active or an inactive state. Hence, nonpeptide antagonists bind to the inactive form of the receptor and shift the equilibrium away from the conformation required for agonist binding and receptor activation. The binding sites for agonists and antagonists can be different or overlap, depending on the peptide receptor system. In this receptor model, there is no requirement for an overlap in binding sites between competitive ligands, as the peptide agonist and nonpeptide antagonist act as allosteric competitive ligands by binding in a mutually exclusive fashion to sites occurring in different conformations of the receptor.

### **Use of nonpeptide antagonists to define receptor subtypes**

Nonpeptide antagonists are currently being developed not only as potential drugs but also as pharmacological and physiological tools. Indeed, the existence of receptor subtypes for several neuropeptides has been established on pharmacological grounds using selective nonpeptide antagonists. For example, the discovery of nonpeptide antagonists which were highly selective for either peripheral or brain CCK receptors provided support for the existence of two subtypes of CCK receptors (Box 1). CCK<sub>A</sub> receptors are characterized by

high affinity for the antagonist L364718 (Ref. 2), whereas CCK<sub>B</sub> receptors show high affinity for the antagonist L365260 (Ref. 19). Similarly, the development of nonpeptide angiotensin II receptor antagonists led to the discovery of two pharmacologically and functionally distinct angiotensin receptors (for review, see Ref. 20). The AT<sub>1</sub> receptor binds the nonpeptide antagonist losartan (DuP753) with high affinity, whereas the AT<sub>2</sub> receptor is insensitive to losartan but shows high affinity for the antagonist PD123319.

Autoradiography with nonpeptide antagonist as radioligands or to displace agonist labeling has proved particularly useful in studying the distribution of peptide receptors in the CNS and the periphery and to discriminate between different receptor subtypes. For instance, binding of radiolabeled angiotensin II in the presence of selective nonpeptide antagonists revealed the presence of both AT<sub>1</sub> and AT<sub>2</sub> receptors in the brain<sup>21</sup>. The central distribution of AT<sub>1</sub> receptors is in agreement with their role in mediating all the major physiological actions of angiotensin II, including regulation of blood pressure and water balance<sup>20</sup>. AT<sub>2</sub> receptors are abundant during fetal life and in discrete brain regions but their function remains unclear<sup>22</sup>.

Selective nonpeptide antagonist were also used to study the brain distribution of CCK<sub>A</sub> receptors<sup>23</sup>, which had been previously identified only in the gastrointestinal tract. In autoradiographic experiments, CCK<sub>A</sub> receptors were identified by displacing <sup>125</sup>I-CCK-8 binding with the CCK<sub>A</sub> antagonist L365031, and by direct labeling with the antagonist ligand <sup>3</sup>H-L364718. CCK<sub>A</sub> receptors were observed in discrete areas of the rat CNS, including the area postrema and nucleus tractus solitarius, two regions receiving rich vagal input. This localization is in agreement with the role of CCK<sub>A</sub> receptors in the regulation of satiety, through the processing of afferent vagal information from the periphery<sup>24</sup>.

### **Nonpeptide antagonists reveal different affinity states of neuropeptide receptors**

Radiolabeled ligands derived from nonpeptide antagonists represent useful tools to characterize the different affinity states of neuropeptide receptors. By comparing results obtained from binding of agonist and antagonist radioligands, pancreatic CCK<sub>A</sub> receptors were shown to exist in three different affinity states for the agonist CCK-8; the agonist ligand (<sup>125</sup>I-CCK-8) identified the high- and the low-affinity states, while the antagonist ligand (<sup>3</sup>H-L364718) bound to the low-affinity state and to a previously unidentified very-low-affinity state which represents 80% of the receptors<sup>25</sup>. The CCK<sub>B</sub>/gastrin receptor also exists in a very low affinity state, detected by the nonpeptide antagonist <sup>3</sup>H-L365260, which recognized a significantly higher number of receptors in the brain and gastric cells than the agonist <sup>125</sup>I-CCK-8 (Ref. 26). The ability of radiolabeled nonpeptide antagonists to recognize a larger number of receptors, characterized by low affinity for the agonist, than agonist-derived radioligands, appears to be a common phenomenon. In the guinea-pig brain, the number of binding sites labeled by the nonpeptide neurotensin antagonist radioligand, <sup>3</sup>H-SR48692, exceeded by 20-fold the number of receptors labeled with the agonist <sup>125</sup>I-neurotensin (Ref.

27). The binding sites detected by  $^3\text{H}$ -SR48692 were characterized by a low affinity for neurotensin and were insensitive to guanyl nucleotides. These data indicate that the majority (96%) of neurotensin receptors in the guinea-pig brain exists in a low affinity state for the peptide, representing the G-protein uncoupled form of the receptor, whereas only a small proportion (4%) binds neurotensin with a high affinity. These data, together with current hypotheses on the molecular interactions of ligands with their receptors, suggest that radiolabeled agonists and antagonists bind to two complementary populations of receptor conformations<sup>18</sup>. Antagonists bind with high affinity to the G-protein-uncoupled receptors, whereas agonists bind with high affinity to the G-protein-coupled form, but they also bind with low affinity to the G-protein uncoupled form labeled by antagonists.

### **Species-dependent variations in the binding of nonpeptide antagonists**

In contrast to the endogenous peptide ligands, nonpeptide antagonists often show substantial differences in affinity among species, suggesting that during evolution, peptide receptors have undergone mutations that do not affect the binding of the natural peptide, but frequently modify the nonpeptide antagonist binding sites. The species-related differences in antagonist binding affinity often reflect differences in the primary structure of the receptors. Do these differences represent distinct receptor subtypes or species variants of the same receptor? This question is important not only to clarify the definition of receptor subtypes, but becomes particularly relevant when selecting animal models to test drugs with therapeutic potential.

This concept can be illustrated with the example of tachykinin NK<sub>1</sub> receptors, which exhibit profound pharmacological differences among species in their recognition of nonpeptide antagonists. CP96345 has a much lower affinity for rat and mouse NK<sub>1</sub> receptors than for NK<sub>1</sub> receptors of most species studied, including human, guinea pig and rabbit. The reverse selectivity has been reported for RP67580, which has higher affinity for rat and mouse NK<sub>1</sub> receptors. Amino acid sequence comparison of the human and rat NK<sub>1</sub> receptor reveals only 22 divergent residues among 407. Analysis of mutant receptors in which divergent residues in the human NK<sub>1</sub> receptor were substituted by the rat homologues revealed that substitution of two rat residues at positions 116 and 290 within the transmembrane domain into the human NK<sub>1</sub> receptor are sufficient to reproduce the antagonist affinities of the rat receptor<sup>9,28</sup>. Further studies have shown that the species selectivity of several other chemically distinct tachykinin nonpeptide antagonists also depends on the same amino acid residues<sup>29</sup>. Interestingly, guinea pig and mouse NK<sub>1</sub> receptors have the same residues at positions 116 and 290 as the human and rat NK<sub>1</sub> receptors, respectively, extending to other species the importance of these residues as determinants of the differential affinities of antagonist binding. Thus, the species selectivity of nonpeptide antagonists result from the existence of species variants of the NK<sub>1</sub> receptor,

rather than from different receptor subtypes. Similar inter-species differences in the affinity of nonpeptide antagonists also exist for NK<sub>2</sub> and NK<sub>3</sub> receptors<sup>30,31</sup>.

The discovery of nonpeptide antagonists for CCK<sub>B</sub> receptors has also led to the observation of differences in antagonist binding affinity between species. Although canine and human CCK<sub>B</sub> receptors share ~90% amino acid identity and have similar agonist binding affinity, they exhibit opposite rank orders of affinity for two nonpeptide CCK antagonists: L365260 shows selectivity for the human receptor, whereas L364718 displays a higher affinity for the dog CCK receptor. Mutational analysis of the CCK<sub>B</sub> receptor demonstrated that antagonist affinities can be altered dramatically by a single amino acid substitution, which in turn explain species-related differences<sup>11</sup>. The replacement of valine 319 in the sixth transmembrane region of the human receptor with the corresponding amino acid in the canine receptor, leucine, decreases the affinity of L365260 and increases the affinity of L364718 to the values seen in the canine receptor. Conversely, substitution of Leu355 to valine in the canine receptor results in antagonist affinities that resemble those observed in the human receptor. It is interesting to note that these mutations do not alter the affinity of the endogenous peptide ligand, CCK. These results support the concept that differences in amino acid sequence between these species are simply due to a species-specific polymorphism of the same receptor subtype and do not represent novel CCK receptor subtypes.

These studies emphasize the need for species-appropriate models for the screening of antagonists in drug development. Animals used in the screening of nonpeptide antagonists for potential clinical use in humans should have receptors with pharmacological profiles similar to the human homologues. For instance, screening the nonpeptide antagonists CP96345 and RP67580 on rat and mouse NK<sub>1</sub> receptors (which have marked affinity differences for these antagonist compared to the human NK<sub>1</sub> receptor) would poorly predict pharmacological action in man, whereas guinea pig or rabbit NK<sub>1</sub> receptors would be suitable models<sup>30</sup>. This is of particular importance when studying the antinociceptive effects of NK<sub>1</sub> antagonists, since most of the animal models of pain classically used employ mice or rats.

### **Use of nonpeptide antagonists to investigate the role of endogenous peptides**

In order to help in defining receptor function, antagonists must have high specificity *in vitro* and *in vivo* and should be devoid of intrinsic or partial agonist activity. As mentioned previously, most peptide antagonists do not meet these requirements, explaining why the advent of nonpeptide receptor antagonists represented a significant progress in the study of the physiological role of neuropeptides.

Recent studies with nonpeptide antagonists of CCK receptors suggest that endogenous CCK plays a role in anxiety, satiety, pain perception, and certain dopamine-mediated behaviors (for review, see Ref. 24). In particular, endogenous CCK modulates dopaminergic transmission in the nucleus accumbens, which is considered the major neural substrate for

the reinforcing properties of drugs of abuse. Converging evidence suggests that endogenous activation of CCK<sub>B</sub> receptors exerts an inhibitory influence on drug reward and locomotor activation, whereas CCK<sub>A</sub> receptors facilitate these behaviors<sup>32</sup>. Selective CCK<sub>B</sub> antagonists such as L365260 and CI988 (formerly PD134308) potentiated the rewarding effects of amphetamine and morphine in the conditioned place preference paradigm in rats<sup>33,34</sup>. Conversely, pretreatment with the CCK<sub>A</sub> antagonist devazepide blocked morphine-induced place preference. The effects of endogenous CCK are more readily observed when the dopaminergic systems have been previously stimulated, whereas the role of the peptide under basal activity is more difficult to establish. Several studies have failed to find significant effects on dopamine-related behaviors after administration of CCK<sub>A</sub> or CCK<sub>B</sub> antagonists alone<sup>24,34</sup>. It is probable that special behavioral paradigms may be needed to detect changes due to CCK antagonists, which specifically enhance the activity of dopaminergic neurons to a level likely to induce release of endogenous CCK.

Studies with nonpeptide CCK<sub>B</sub> receptor antagonists have also indicated that endogenous CCK acts as an anxiogenic molecule, since its blockade by the CCK<sub>B</sub> antagonists PD134308 and PD135158 induced potent anxiolytic effects in various animal models<sup>3</sup>. In contrast to benzodiazepines, CCK<sub>B</sub> antagonists did not induce sedation and when administered on a chronic basis, did not induce tolerance nor withdrawal symptoms. Furthermore, CCK<sub>B</sub> antagonists counteracted withdrawal anxiety induced by diazepam. Several other CCK<sub>B</sub> antagonists (L365260, LY262691, LY262684, LY247348, and LY288513), have also demonstrated anxiolytic activity in animal studies. These results strongly support the therapeutic potential of CCK<sub>B</sub> nonpeptide antagonists as anxiolytic agents and suggest that such compounds could be more selective and free of side effects when compared to benzodiazepines.

Exogenous CCK induces satiety and decreases food intake in both animals and humans; before selective antagonists for CCK<sub>A</sub> and CCK<sub>B</sub> receptors became available, it was not known which receptor subtype mediated this response. Numerous studies have now established that the CCK-induced reduction in food intake is blocked by CCK<sub>A</sub>, but not CCK<sub>B</sub>, receptor antagonists<sup>24</sup>. Studies with the CCK<sub>A</sub> antagonist devazepide, have also provided strong evidence for the role of endogenous CCK in the regulation of feeding. Systemic administration of devazepide increased food intake in rats and mice<sup>24</sup>, and clinical data suggest that CCK could also act as a satiety signal in humans<sup>35</sup>. The CCK<sub>B</sub> antagonist L365260 has also been reported to increase food intake and to postpone the onset of satiety in rats<sup>36</sup>, suggesting that in some situations, endogenous CCK may act on CCK<sub>B</sub> receptors to induce postprandial satiety. In addition, recent findings with selective CCK<sub>B</sub> receptor antagonists have revealed that endogenous CCK is implicated in the perception of pain (for review, see Ref. 37). Specifically, CCK<sub>B</sub> receptor antagonists such as L365260 and CI988 strongly enhanced morphine analgesia and prevented the development of tolerance to the

analgesic effect of morphine in rats<sup>38-40</sup>. These data raise the possibility that CCK<sub>B</sub> antagonists, alone or in combination with opiates, may be useful in the management of chronic pain.

Thanks to the development of nonpeptide antagonists highly selective for angiotensin receptor subtypes, it was possible to describe novel physiological actions for central AT<sub>1</sub> receptors, particularly concerning their involvement in the modulation of neurotransmitter systems. In the human brain, AT<sub>1</sub> receptors are associated with dopaminergic neurons in the substantia nigra and their terminals in the striatum. Accordingly, angiotensin II increased dopamine turnover in the striatum, an effect which was completely blocked by the AT<sub>1</sub>-selective antagonist, losartan<sup>41</sup>. Administration of losartan alone led to significant depression of DOPAC levels, suggesting that dopamine release is under the tonic facilitatory influence of endogenous angiotensin II. Using similar physiological approaches, AT<sub>1</sub> receptors have also been implicated in the central regulation of blood pressure and vasopressin release, through modulation of adrenaline and noradrenaline transmission, respectively.

Much of the current interest in the new nonpeptide neurotensin antagonist SR48692 has been focused on investigating the role of endogenous neurotensin in the modulation of dopaminergic systems. Data obtained with this antagonist indicate that endogenous neurotensin can exert both inhibitory and excitatory effects on dopaminergic activity, confirming the dual action of exogenous neurotensin observed in previous studies following central administration of the peptide. Thus, administration of SR48692 together with a subeffective dose of methamphetamine resulted in a significant increase in locomotion and rearing as well as in the release of dopamine in the nucleus accumbens<sup>42</sup>. SR48692 also potentiated dopamine efflux in the nucleus accumbens evoked by the concomitant administration of haloperidol and electrical stimulation of the medial forebrain bundle; when administered alone, SR48692 did not affect spontaneous dopamine release<sup>43</sup>. By contrast, SR48692 reduced yawning and turning behavior induced by dopaminergic agonists<sup>44</sup>, indicating that neurotensin facilitates the expression of certain behaviors associated with dopamine receptor stimulation. These findings also suggest that the modulatory role of endogenous neurotensin may require previous stimulation of dopaminergic neurons.

The availability of SR48692 has also allowed examination of the effects of endogenous neurotensin in the modulation of the hypothalamic-pituitary-adrenocortical (HPA) axis. Chronic administration of SR48692 at the level of the paraventricular nucleus of the hypothalamus antagonized stress-induced release of ACTH and corticosterone and reduced CRF mRNA levels in the paraventricular nucleus, suggesting that endogenous neurotensin plays a tonic stimulatory role on HPA axis activity<sup>45</sup>. In view of increasing evidence supporting a link between hyperactivity of the HPA axis and depressive disorders<sup>46</sup>, these findings raise the interesting possibility that neurotensin antagonists might be useful in the treatment of affective disorders.

In agreement with the role of tachykinins in pain transmission and neurogenic inflammation, NK<sub>1</sub> receptor antagonists, such as CP96345 (Ref. 47) and RP67580 (Ref. 48), have been shown to possess antinociceptive activity in classical analgesic tests in mice and rats. These findings suggest the utility of tachykinin antagonists as a novel class of analgesic and anti-inflammatory agents. Moreover, a role for tachykinins in the pathogenesis of asthma has been postulated, indicating that tachykinin antagonists could be useful in the treatment of this disease.

### **Therapeutic potential**

Several nonpeptide antagonists of peptide receptors offer hope as novel therapeutic agents, particularly in the context of clinical findings suggesting that neuropeptides may be hypersecreted in certain pathological states. Following are some examples illustrating the potential use of nonpeptide antagonists in therapy.

#### ***Depression, anxiety and stress-related disorders***

Corticotropin releasing factor (CRF) plays a key role in the coordination of the endocrine and behavioral responses to stress and may be involved in the pathophysiology of affective disorders<sup>46,49</sup>. Depressive patients have elevated concentrations of CRF in cerebrospinal fluid, which are normalized after administration of clinically effective antidepressants<sup>46</sup>. These findings suggest the potential utility of CRF receptor antagonists as novel antidepressants. Hypersecretion of endogenous CRF could also be implicated in anxiety-related disorders, since central administration of CRF exerts potent anxiogenic effects in experimental animals. In addition, CRF, as well as urocortin, a recently identified neuropeptide of the CRF family present in the mammalian brain, induce strong appetite-suppressing effects in rats<sup>50</sup>, suggesting a role for these peptides in eating disorders in humans, notably in anorexia nervosa. In agreement with these proposed actions of CRF, peptide CRF antagonists ( $\alpha$ -helical CRF<sub>9-41</sub> and D-Phe CRF<sub>12-41</sub>) have been shown to exert anxiolytic effects in several rodent models and inhibit stress-induced decreases in appetitive behavior<sup>49</sup>. However, peptide CRF antagonists have limited utility due to poor solubility and difficulty in penetrating the blood-brain-barrier, as well as weak potency in antagonizing CRF-induced ACTH release. Very recently, several classes of nonpeptide CRF receptor antagonists have been identified<sup>51</sup>. CP154526, the first nonpeptide CRF antagonist described, is highly selective for the CRF<sub>1</sub> receptor subtype<sup>52</sup>. Antalarmin is also a nonpeptide CRF<sub>1</sub> receptor antagonist<sup>53</sup>. Parenterally administered CP154526 and antalarmin antagonized the stimulatory effects of exogenous CRF on plasma ACTH levels, indicating that these compounds enter the CNS after peripheral administration<sup>52,53</sup>. CP154526 was also effective in decreasing the anxiogenic effects of CRF in rats<sup>52</sup>. Future studies will establish whether the pharmacological properties of these novel nonpeptide CRF antagonists make them good tools for the treatment of disease states associated with high levels of CRF.

CCK has also been implicated in mediating anxiety and panic attacks. The therapeutic potential of CCK<sub>B</sub> antagonists as anxiolytic agents appears quite promising, as animal studies have indicated that these compounds exert potent anxiolytic effects<sup>3</sup>. Clinical studies have shown that the CCK<sub>B</sub> receptor agonist CCK-4 elicits panic attacks in patients with panic disorders and in healthy volunteers; these effects are antagonized by the nonpeptide CCK<sub>B</sub> antagonist L365260<sup>54</sup>. However, L365260 was not able to block the endogenous panic attacks not stimulated by CCK-4 in humans<sup>55</sup>. Furthermore, clinical tests performed with the CCK<sub>B</sub> receptor antagonist CI988 revealed that this compound was ineffective in patients with generalized anxiety disorder<sup>56</sup> and also failed to reduce CCK-4 induced symptoms in panic disorder patients<sup>57</sup>. It is possible that this lack of effect is related to the limited solubility and brain penetrability of these first generation CCK<sub>B</sub> antagonists (Box 1).

### ***Neuropsychiatric disorders linked to dopaminergic dysfunction***

Numerous studies indicate that endogenous CCK could be involved in dopamine-related disorders such as schizophrenia, Parkinson's disease and drug addiction<sup>24</sup>. Electrophysiological studies have demonstrated that selective nonpeptide CCK<sub>B</sub> antagonists such as LY262691 and L365260, but not CCK<sub>A</sub> antagonists, decreased the number of spontaneously active neurons within the A10 and A9 nuclei, similarly to what is seen after classic antipsychotic agents<sup>58</sup>. It is interesting to note that dopamine receptor antagonists require chronic administration for 2-3 weeks to be effective, whereas CCK<sub>B</sub> antagonists were effective on acute administration. These findings have led to speculation that pharmacological disruption of CCK transmission could be beneficial in the treatment of schizophrenia. However, preliminary clinical trials with the weakly potent and nonselective CCK antagonist proglumide had no apparent effect when administered to patients with schizophrenia or Parkinson's disease. The CCK<sub>A</sub> antagonist loxiglumide was also without effect in a trial with Parkinson's disease. Further clinical trials using the newer, selective nonpeptide CCK receptor antagonists, superior in aqueous solubility, potency and brain penetrability, will be required in order to determine the clinical utility of these compounds in neuropsychiatric disorders.

### ***Hypertension***

Nonpeptide antagonists for the angiotensin II AT<sub>1</sub> receptor have been introduced recently for clinical use in the treatment of hypertension and have proved extremely successful<sup>59</sup>. The most prominent example is losartan, an orally active, selective and potent AT<sub>1</sub> receptor antagonist, that has been found to be an excellent anti-hypertensive drug, safe and without any of the traditional side effects. Other peptides have also been implicated in the pathogenesis of cardiovascular diseases. Vasopressin and endothelin-1 antagonists have potential therapeutic value in the treatment of hypertension, congestive heart failure and ischemic heart disease. The recent synthesis of nonpeptide, orally active, selective antagonists for V<sub>1A</sub> receptors<sup>60,61</sup> (responsible for the vasopressor actions of the peptide)

and for endothelin receptors<sup>62</sup> (Table 1) is likely to result in the rapid introduction of these antagonists into clinical medicine.

### ***Side-effects?***

Although nonpeptide antagonists for neuropeptide receptors have been evaluated for treatment of a wide range of conditions, most studies have used animal models, and to date, there is little or no experience with human beings concerning the effects of most of the nonpeptide antagonists developed. Drugs that block peptide receptors may be expected to have few if any side-effects. However, the wide variety of actions exerted by most peptides might give rise to potential side-effects. Highly selective antagonists interfere with the actions of the peptide on a given receptor subtype but may result in unwanted side-effects by activating other receptor subtypes. For instance, the current angiotensin receptor antagonists interfere only with the actions of angiotensin II mediated by AT<sub>1</sub> receptors. This might result in disinhibition of renin release and increased formation of angiotensin peptides, which could have unexpected effects by activating AT<sub>2</sub> receptors. Currently there is a search for mixed AT<sub>1</sub>/AT<sub>2</sub> receptor antagonists that can completely block the effects of angiotensin II.

### **Concluding remarks**

In the ten years since the report of the discovery of the first nonpeptide antagonist of a non-opioid peptide receptor, more than 100 potent and selective nonpeptide antagonists for several peptides have been developed. The entire neuropeptide field has seen a remarkable advancement, largely fuelled by the availability of effective antagonists with which to study the physiological functions of peptides. This review has highlighted some of the common concepts on nonpeptide antagonists that have emerged during the past few years.

One of the most important contributions coming from the discovery of nonpeptide antagonists has been the characterization of the molecular interactions of nonpeptide ligands with peptide receptors. Pharmacological studies using nonpeptide receptor antagonist-derived ligands coupled with molecular biology techniques have considerably increased our knowledge on ligand-receptor interactions. Understanding the molecular interactions responsible for nonpeptide antagonist binding should provide a rational basis for the future development of more potent and selective antagonists for peptide receptors and for related G-protein-coupled receptors.

The use of nonpeptide antagonists to probe the physiological and pathophysiological actions of peptide receptors and their possible therapeutic relevance has proved particularly rewarding. Increasing evidence points out to the role of endogenous neuropeptides as modulators of brain neurotransmitter systems, suggesting the potential therapeutic application of these antagonists in neuropsychiatric disorders associated with altered neurotransmitter activity.

In spite of the great number of potent and selective neuropeptide antagonists available, it still remains difficult to attribute specific functions to endogenous peptides under basal activity. This might be due to the fact that peptides are usually not released under basal conditions, but are called into play upon activation of the system, when neuronal activity is increased. As reported for co-existing peptides and catecholamines in the CNS and the periphery, the classical neurotransmitter is released at low frequencies of electrical or chemical stimulation, whereas at higher frequencies or during bursting firing the peptide is released together with the classical neurotransmitter<sup>63,64</sup>. Accordingly, neuropeptides may play a role in pathological states, when the system is up-regulated, such as during severe stress or injury, rather than under basal conditions<sup>65</sup>. Therefore, antagonists acting on neuropeptide receptors may become important therapeutic agents, since they may act preferentially on pathologically activated systems. Although the first results obtained in humans have yet to confirm the therapeutic potential of most nonpeptide antagonists of peptide receptors, present available evidence based on animal studies indicates that these agents should be considered as highly promising for the development of new drugs.

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### Box 1. Nonpeptide antagonists for cholecystokinin receptors

Cholecystokinin (CCK) is one of the most abundant neuropeptides in the mammalian CNS, where it has been implicated in the regulation of anxiety and panic disorder, dopamine-mediated behaviors, satiety and analgesia. CCK receptors exist in two forms: the CCK<sub>A</sub> receptor is found mainly in the gastrointestinal tract, but occurs also in discrete areas in the brain, while the CCK<sub>B</sub> receptor is widely distributed throughout the brain, but is indistinguishable from the gastrin receptor in the periphery. Both subtypes of CCK receptors have recently been cloned and sequenced (for review, see Ref. 1).

The first nonpeptide CCK antagonists were derived from a naturally occurring benzodiazepine, asperlicin, isolated from the fungus *Aspergillus alliaceus*. This molecule was found by random screening to have selective CCK antagonistic activity, based on radioligand binding to rat pancreas and guinea-pig brain CCK receptors<sup>2</sup>. This work led to the subsequent development of a competitive nonpeptide antagonist, L364718 (also known as devazepide or MK329), with high potency and selectivity for CCK<sub>A</sub> receptors<sup>3</sup>, as well as a selective CCK<sub>B</sub> antagonist, L365260<sup>4</sup>. More recently, other nonpeptide CCK<sub>B</sub> receptor antagonists have been developed. PD134308 (also called CI988) and PD135158 are two potent and highly selective CCK<sub>B</sub> receptor antagonists, derived by rational design from the CCK tetrapeptide<sup>5</sup>. LY262691, obtained from a screening lead, is a CCK<sub>B</sub> antagonist with a brain affinity in the nanomolar range<sup>6</sup>. Another CCK<sub>B</sub> receptor antagonist, YM022, is closely related to L365260, and exhibits high potency and selectivity both *in vivo* and *in vitro*<sup>7</sup>. These first generation compounds have provided valuable information concerning the role of CCK in the CNS and the periphery. However, they present some limitations for their use as therapeutic agents, such as poor aqueous solubility, relatively poor oral bioavailability and brain penetration, as well as partial agonistic activity in some tests *in vivo*.

The second generation of nonpeptide CCK<sub>B</sub> receptor antagonists is characterized by high affinity and selectivity for CCK receptors and increased aqueous solubility. Because the brain penetration of L365260 and related compounds was relatively low, a new series of benzodiazepine derivatives containing a cationic solubilizing group was designed. These antagonists, which include L368935 and L740093, are much more soluble than L365260, with 50-100 times higher affinities for the CCK<sub>B</sub> receptor and with excellent CNS penetration<sup>8</sup>. Another novel family of CCK<sub>B</sub> receptor antagonists includes RP69758, RP71483 and RP72540, which are potent and selective but show very low penetration into the brain<sup>9</sup>. Numerous other subtype-specific CCK receptor antagonists have been since described and further developments in this field can be anticipated, considering the therapeutic potential of these compounds.

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**Table. Nonpeptide antagonists for cholecystokinin and gastrin receptors**

Receptor subtypes	CCK <sub>A</sub>	CCK <sub>B</sub>
Endogenous ligands	CCK-8 >> gastrin = CCK-4	CCK-8 ≥ gastrin = CCK-4
Selective antagonists	devazepide (L364718, MK329), L365031, lorglumide (CR1409), SR27897, FK480, KSG504, PD140548, L743345, T0632	L365260, PD134308 (CI988), PD135158, LY262684, YM022, L368935, L740093, RP69758, RP71483, RP72540, RP73870, LY262691, LY191009, LY242040, LY202769, LY247348, LY288513, GV150013, YF476
Mixed CCK <sub>A</sub> /CCK <sub>B</sub> antagonists		PD142898, FR193108

## Box 2. Nonpeptide antagonists for tachykinin receptors

The tachykinins constitute a family of neuropeptides comprising substance P, neurokinin A and neurokinin B, which share a common C-terminal sequence. Tachykinins interact with at least three receptor subtypes, termed NK<sub>1</sub>, NK<sub>2</sub> and NK<sub>3</sub>. Substance P binds preferentially to the NK<sub>1</sub> receptor, whereas neurokinin A and neurokinin B are the preferred endogenous ligands of the NK<sub>2</sub> and NK<sub>3</sub> receptors, respectively. Substance P and related peptides are involved in a variety of biological actions, including pain transmission, vasodilatation, smooth muscle contraction and neurogenic inflammation. In the past few years, several potent and selective nonpeptide antagonists have been discovered, greatly stimulating tachykinin research (for review, see Ref. 1).

The first selective, high affinity, nonpeptide antagonist of the tachykinin NK<sub>1</sub> receptor was CP96345, discovered using a <sup>3</sup>H-substance P binding assay and random screening of file compounds<sup>2</sup>. This antagonist induced analgesic effects in various rodent models of pain and inflammation. Subsequent studies indicated that CP96345 also interacts with L-type Ca<sup>2+</sup> channels, suggesting that the *in vivo* effects of this compound should not be interpreted only in terms of its action on NK<sub>1</sub> receptors. Pfizer's follow-up compound, CP99994, has a high affinity and selectivity for NK<sub>1</sub> sites and is essentially devoid of affinity at L-type Ca<sup>2+</sup> channels<sup>3</sup>. The second nonpeptide NK<sub>1</sub> antagonist, RP67580, discovered using a chemical-file screening approach, was shown to possess antinociceptive activity and was as potent as morphine in various analgesic tests<sup>4</sup>. However, at high concentrations, RP67580 also exerts nonspecific effects on Ca<sup>2+</sup> channels. These antagonists show conspicuous differences in their affinities for NK<sub>1</sub> receptors from diverse species, due to a few differing amino acids in the receptor sequences. CP96345 has a higher affinity for the human and guinea pig NK<sub>1</sub> receptor than for the rat and mouse NK<sub>1</sub> receptor, whereas RP67580 shows the reverse species selectivity. PD154075 and CGP49823 are two nonpeptide NK<sub>1</sub> antagonists synthesized using rational design strategies, by contrast to the other tachykinin antagonists mentioned above. NK<sub>1</sub> receptor antagonists have confirmed the role of endogenous substance P in nociception, in addition to having therapeutic potential in the treatment of pain, inflammation and asthma. More recently, several NK<sub>1</sub> receptor antagonists (including CP99994, GR203040, GR205171 and CP122721) have been shown to possess potent anti-emetic activity, offering the prospect of a novel approach for the control of emesis associated with, for instance, cancer chemotherapy or radiation therapy.

Discovery of the first nonpeptide NK<sub>2</sub> receptor antagonists soon followed. SR48968 is a competitive, high affinity antagonist of NK<sub>2</sub> receptors; it is orally active, crosses the blood-brain barrier and has long-lasting effects<sup>5</sup>. Although no NK<sub>2</sub> binding sites have been visualized in the rat brain, several studies have demonstrated central effects after administration of NK<sub>2</sub> receptor agonists that are blocked by NK<sub>2</sub> antagonists. For example, SR48968 was reported to block the turning behavior and the firing of thalamic neurons induced by neurokinin A in the rat. SR48968 also inhibited NK<sub>2</sub> receptor mediated dopamine release from rat striatum<sup>6</sup>. Both SR48968 and another NK<sub>2</sub> antagonist, GR159897, have been reported to exert potent anxiolytic actions in rodent and primate models, suggesting an involvement of tachykinin NK<sub>2</sub> receptors in anxiety-related behaviors<sup>7</sup>. These findings support the existence of NK<sub>2</sub> receptors in the CNS. The lack of NK<sub>2</sub> receptors in the brain in spite of central NK<sub>2</sub> receptor mediated responses could suggest that central NK<sub>2</sub> receptors differ in their pharmacological properties from peripheral NK<sub>2</sub> receptors. Further studies with selective high-affinity NK<sub>2</sub> receptor radioligands will be required to clarify this issue.

The first nonpeptide antagonists selective for tachykinin NK<sub>3</sub> receptors have recently become available. They include SR142801 (Ref. 8), PD157672 (Ref. 9), and SB223412 (Ref. 10), which will certainly lead to additional understanding of the role of NK<sub>3</sub> receptors in brain processes.

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**Table. Nonpeptide antagonists for tachykinin receptors**

Receptor subtypes	NK <sub>1</sub>	NK <sub>2</sub>	NK <sub>3</sub>
Endogenous ligands	SP > NKA > NKB	NKA > NKB >> SP	NKB > NKA > SP
Selective antagonists	CP96345, RP67580, SR140333, CP99994, WIN51708, WIN62577, CGP49823, PD154075, LY303870, LY306740, L161664, L733060, L742694, RPR100893, CP122721, CAM4515, CAM4750, GR203040, GR205171, MEN10930	SR48968, GR159897,	SR142801, PD161182, SB223412
Mixed NK <sub>1</sub> /NK <sub>2</sub> antagonist	MDL105212A		

NKA, neurokinin A; NKB, neurokinin B; SP, substance P.

### Box 3. Nonpeptide neurotensin receptor antagonists

Neurotensin is a tridecapeptide widely distributed in the brain and periphery of several mammalian species. Neurotensin is involved in the modulation of dopamine transmission, nociception, hypothermia, and control of anterior pituitary hormone secretion. Until recently, it was believed that neurotensin acted through a single class of G-protein-coupled receptors, cloned in the rat and human. However, in the adult rat and mouse brain, neurotensin can bind to two different binding sites, which can be distinguished by their affinity for NT as well as by their sensitivity to levocabastine, a histamine H<sub>1</sub> receptor antagonist. The high affinity site is insensitive to levocabastine and corresponds to the originally cloned receptor in the rat (NT<sub>1</sub>). It was assumed that the low affinity, levocabastine-sensitive binding sites lacked signalling activity and were thus considered as acceptor sites, devoid of function. Very recently, however, a novel neurotensin receptor (called NT<sub>2</sub>) sensitive to levocabastine has been cloned in the rat hypothalamus<sup>1</sup> and mouse brain<sup>2</sup>. The biological function of NT<sub>2</sub> receptors remains to be determined.

A major advancement in the field of neurotensin research was provided by the discovery of the first highly potent and selective nonpeptide neurotensin receptor antagonist, SR48692 (Ref. 3). SR48692 is orally active, crosses the blood-brain barrier and has a long-lasting action; it shows higher affinity for NT<sub>1</sub> than for NT<sub>2</sub> receptors. This antagonist can counteract the effects of neurotensin in many *in vitro* and *in vivo* assays. Given intraperitoneally or orally, SR48692 suppressed the turning behavior<sup>3,4</sup> and locomotor activity<sup>5</sup> induced by injection of neurotensin in the striatum or ventral tegmental area, respectively. Central administration of SR48450, an analog of SR48692, antagonized the stimulatory effect of neurotensin on ACTH and corticosterone secretion<sup>6</sup>. However, SR48692 was not able to inhibit neurotensin-induced hypothermia and analgesia in rats and mice<sup>7</sup>. This compound also failed to reverse dopamine release in the nucleus accumbens evoked by neurotensin injection in the ventral tegmental area<sup>5</sup>, as well as the hypolocomotion induced by intracerebroventricular administration of neurotensin<sup>8</sup>. These findings suggest that these effects could be mediated through a neurotensin receptor subtype which is insensitive to SR48692. It would be interesting to assess the potential implication of the recently identified NT<sub>2</sub> receptor in mediating the effects of neurotensin not blocked by SR48692.

Although SR48692 has proved an important pharmacological tool for the study of neurotensin receptors and in exploring the existence of possible neurotensin receptor subtypes<sup>9</sup>, it has certain properties that could limit its usefulness. SR48692 has a very low aqueous solubility, which requires administration in nonaqueous vehicles for *in vivo* studies. More recently, Sanofi has developed a novel nonpeptide antagonist of neurotensin receptors, SR142948A, with better solubility and increased affinity in the rat and human brain<sup>10</sup>. SR 142948A recognizes with equally high affinity both NT<sub>1</sub> and NT<sub>2</sub> receptors. Interestingly, in contrast to SR48692, SR142948A blocked the hypothermia and analgesia induced by central injection of neurotensin, revealing a wider spectrum of action, probably through inhibition of different neurotensin receptor subtypes.

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**Table. Nonpeptide antagonists for neurotensin receptors**

Receptor subtypes	NT <sub>1</sub>	NT <sub>2</sub>
Endogenous ligands	NT > NN	NT = NN
Selective antagonists	SR48692	-
Mixed NT <sub>1</sub> /NT <sub>2</sub> antagonist	SR142948A	

NN, neuromedin N; NT, neurotensin.

### Box 4. Neuropeptide Y receptor antagonists

Neuropeptide Y (NPY) is a 36 amino acid peptide which shares considerable sequence homology with peptide YY (PYY) and pancreatic polypeptide (PP) and is therefore considered a member of the PP family. NPY is one of the most abundant peptides found in the mammalian brain, where it stimulates food intake and modulates the release of a variety of hormones; there is also evidence for an involvement of NPY in the pathophysiology of anxiety (for review, see Ref. 1). In the periphery, NPY is a co-transmitter of the sympathetic nervous system, and participates in cardiovascular control. The effects of NPY and related peptides are mediated through at least six distinct receptor subtypes ( $Y_1$ - $Y_6$ ), all of which have been cloned, except for  $Y_3$ . The  $Y_1$  and  $Y_2$  receptors bind NPY and PYY, whereas the  $Y_3$  receptor binds only NPY. The  $Y_4$  receptor, also referred to as  $PP_1$ , has high affinity for PP but substantially lower affinities for NPY and PYY. The  $Y_5$  receptor shows equal affinity for NPY and PYY; it is highly expressed in the rat hypothalamus and its pharmacological profile suggests that it might correspond to the so-called feeding receptor<sup>2</sup>. The most recently cloned receptor,  $Y_6$ , is functional in mice, but the human homologue is mutated, representing a non-functional pseudogene<sup>3</sup>. Despite the widespread interest in NPY, the physiological functions of this peptide have been difficult to establish due to the lack of selective antagonists. The therapeutic potential of NPY receptor antagonists in the treatment of cardiovascular diseases and obesity has stimulated intense research efforts from the pharmaceutical industry. The first attempts to synthesize NPY antagonists have yielded a series of peptidergic  $Y_1$  receptor antagonists (e.g., 1229U91)<sup>4</sup>, as well as several high affinity, selective, nonpeptide  $Y_1$  receptor antagonists<sup>5</sup>.

The first generation of nonpeptide  $Y_1$  receptor antagonists was designed to resemble the C-terminal region of NPY, considered an important site for the interaction with the  $Y_1$  receptor; it includes BIBP3226 (Ref. 6), SR120107A and SR120819A (Refs. 7, 8). These ligands have nanomolar affinity for  $Y_1$  receptors in several species and exhibit potent antagonism on  $Y_1$  receptors *in vivo* and *in vitro*. Both SR120107A and SR120819A are orally active and have a long duration of action; in contrast, BIBP3226 lacks oral bioavailability and its antagonistic effect *in vivo* is relatively short-lasting. Other limitations of this first generation of nonpeptide antagonists include nonspecific  $Y_1$  unrelated effects and inability to cross the blood-brain barrier. Most of the studies performed to date with these compounds have investigated the role of NPY in vascular control. Interestingly, BIBP3226 did not affect basal blood pressure but attenuated stress-induced hypertension, supporting the hypothesis that NPY is mainly released during stress involving intense activation of the sympathetic nervous system<sup>9</sup>. Although it was initially reported that BIBP3226 (10 nmol i.c.v.) was unable to inhibit NPY-induced feeding behavior in rats<sup>2</sup>, a recent study showed that pretreatment with a higher dose of the antagonist (60 nmol) significantly reduced NPY-induced feeding<sup>10</sup>. Since BIBP3226 does not bind to the rat  $Y_5$  receptor<sup>2</sup>, these results are against the implication of this receptor subtype in NPY-induced food intake. Future search for more effective nonpeptide  $Y_1$  receptor antagonists as well as selective antagonists for the other subtypes of NPY receptors will help in the study of the role of endogenous NPY in the regulation of brain functions and will hopefully provide new drugs for the treatment of NPY-related disorders.

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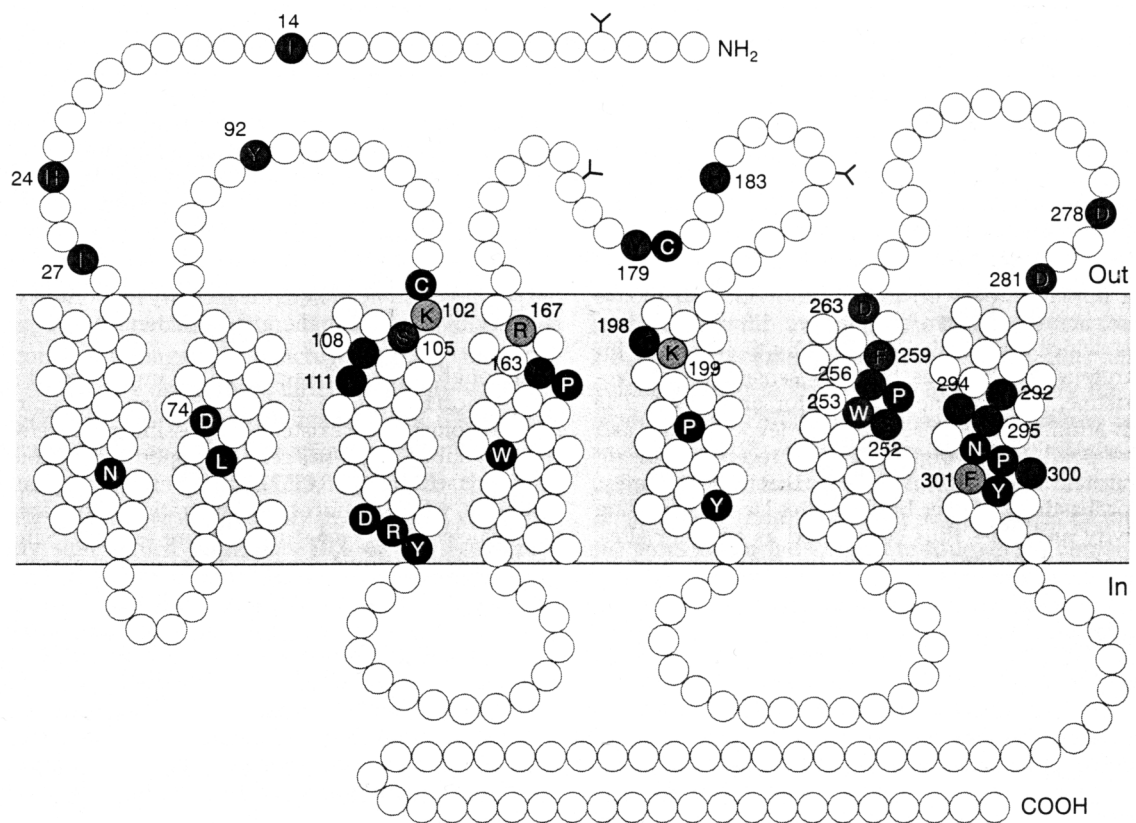
**Table. Nonpeptide antagonists for neuropeptide Y receptors**

Receptor subtypes	$Y_1$	$Y_2$	$Y_3$	$Y_4$	$Y_5$	$Y_6$
Endogenous ligands	PYY $\geq$ NPY $\gg$ PP	PYY $\geq$ NPY $\gg$ PP	NPY $\gg$ PYY	PP $\gg$ NPY=PYY	NPY=PYY $\geq$ PP	NPY=PYY $\gg$ PP
Selective antagonists	BIBP3226* SR120819A+ SR120107A+	-	-	-	-	-

NPY, neuropeptide Y; PP, pancreatic polypeptide; PYY, peptide YY.

\* selective relative to  $Y_2$ ,  $Y_3$ ,  $Y_4$ , and  $Y_5$  receptors<sup>2</sup>

+ selective relative to  $Y_2$  receptors<sup>7,8</sup>



**Figure 1.** Schematic structure of the angiotensin AT<sub>1</sub> receptor showing agonist and antagonist binding sites identified by mutational analysis. Amino acids involved in nonpeptide antagonist binding are shown as pink circles, while those implicated in angiotensin II binding are shown as blue circles. Yellow circles indicate residues implicated in both agonist and antagonist binding. The highly conserved fingerprint residues are shown as white letters on black or coloured background. Potential glycosylation sites are also indicated. (Modified from Ref. 14.)

**Table 1. Nonpeptide antagonists for peptide receptors**

<b>Angiotensin receptors</b>				
Receptor subtypes	<b>AT<sub>1</sub></b>		<b>AT<sub>2</sub></b>	
Endogenous ligands	Ang II > Ang III		Ang II = Ang III	
Selective antagonists	losartan (DuP753, MK954), DuP532, MK966 (L159282), irbesartan (SR47436, BMS186295), telmisartan (BIBR277), SKF108566, candesartan (TCV116, CV11974), valsartan (CGP48933), L158809, SC51316, SC51895, SC52458, ICID6888, ICID8731, A81282, A81988, GR117289, BMS180560, EXP3174, EXP3892, EXP3312, UP269-6, LR-B/081, UR7198, UR7280, E4177, CS866, DMP811 (L708404)		PD123177, PD123319 L161638	
Mixed AT <sub>1</sub> /AT <sub>2</sub> antagonist	BIBS39, BIBS222, L163017, XR510			
<b>Bombesin receptors</b>				
Receptor subtypes	<b>BB1</b>	<b>BB2</b>	<b>BB3</b>	
Endogenous ligands	NMB ≥ BB > GRP	GRP ≥ BB >> NMB	BB >> GRP = NMB	
Selective antagonists	PD165929	kuwanon H	-	
<b>Bradykinin receptors</b>				
Receptor subtypes	<b>B<sub>1</sub></b>		<b>B<sub>2</sub></b>	
Endogenous ligands	kallidin > BK		kallidin ≥ BK	
Selective antagonists	-		WIN 64338 FR173657	
<b>Corticotropin-releasing factor receptors</b>				
Receptor subtypes	<b>CRF<sub>1</sub></b>	<b>CRF<sub>2α</sub></b>	<b>CRF<sub>2β</sub></b>	
Endogenous ligands	urocortin > CRF	urocortin >> CRF	urocortin >> CRF	
Selective antagonist	CP154526 NB127914 antalarmin	-	-	
<b>Endothelin receptors</b>				
Receptor subtypes	<b>ET<sub>A</sub></b>		<b>ET<sub>B</sub></b>	
Endogenous ligands	ET-1 = ET-2 > ET-3		ET-1 = ET-2 = ET-3	
Selective antagonists	BMS182874, PD155080, PD156707, PD159110, PD159433, TBC11251, A127722, 97-139		Ro468443	
Mixed ET <sub>A</sub> /ET <sub>B</sub> antagonists	bosentan (Ro470203), Ro462005, SB209670, SB209598, SB217242, L749329, L754142, L751281, PD154804, PD159020			
<b>Opioid receptors</b>				
Receptor subtypes	<b>μ</b>	<b>δ</b>	<b>κ</b>	
Endogenous ligands	β-end > dynA > met > leu	β-end = leu = met > dynA	dynA >> β-end > leu = met	
Selective antagonists	-	naltrindole BNTX NTB	nor-binaltorphimine (nor-BNI)	
Nonselective antagonists	naloxone, naltrexone*			
<b>Vasopressin and oxytocin receptors</b>				
Receptor subtypes	<b>V<sub>1A</sub></b>	<b>V<sub>1B</sub></b>	<b>V<sub>2</sub></b>	<b>OT</b>
Endogenous ligands	VP > OT	VP > OT	VP > OT	OT ≥ VP
Selective antagonists	SR49059, OPC21268	-	OPC31260	L367773, L368899 L371257
Mixed V <sub>1A</sub> /V <sub>2</sub> antagonist	YM087			

\*naloxone and naltrexone are weakly selective for μ-opioid receptors.

Abbreviations: Ang II, angiotensin II; Ang III, angiotensin III; β-end, β-endorphin; BB, bombesin; BK, bradykinin; CRF, corticotropin-releasing factor; dynA, dynorphin; ET-1, endothelin 1; ET-2, endothelin 2; ET-3, endothelin 3; GRP, gastrin-releasing peptide; kallidin, lysyl-bradykinin; leu, [Leu]enkephalin; met, [Met]enkephalin; NMB, neuromedin B; OT, oxytocin; VP, vasopressin.

### Chemical names

- 97-139:** 27-O-3-(2-[3-carboxyacryloylamino]-5-hydroxyphenyl)-acryloyloxymyricerone
- A127722:** *trans-trans*-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-([*N,N*-dibutylamino]carbonylmethyl)pyrrolidine-3-carboxylate
- A81282:** 4-(*N*-butyl-*N*-[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl)amino)pyrimidine-5-carboxylic acid
- A81988:** 2-(*N*-n-propyl-*N*-[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl)amino)pyridine-3-carboxylic acid
- antalarmin:** *N*-butyl-*N*-ethyl-(2,5,6-trimethyl)-7-[2,4,6-trimethylphenyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amine
- BIBP3226:** *R-N*<sup>2</sup>-(diphenylacetyl)-*N*-(4-hydroxyphenyl)methyl-argininamide
- BIBS222:** 2-*n*-butyl-1-(4-[6-carboxy-2,5-di-chlorbenzoylamino]-benzyl)-6-*N*-(methylaminocarbonyl)-*n*-pentylamino-benzimidazole
- BIBS39:** 4'-([2-*n*-butyl-6-cyclohexylaminocarbonylamino-benzimidazole-1-yl]-methyl)biphenyl-carboxylic acid
- BMS180560:** 2-butyl-1-chloro-1-([1-{2-(2*H*-tetrazol-5-yl)phenyl}-1*H*-indol-4-yl]methyl)-1*H*-imidazole-5-carboxylic acid
- BMS182874:** 5-(dimethylamino)-*N*-(3,4-dimethyl-5-isoxazolyl)-1-naphthalenesulphonamide
- BNTX:** (5 $\alpha$ )-17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-7-(phenylmethylene)-morphinan-6-one hydrochloride
- CAM4515:** (S)-[1-(1*H*-indol-3-ylmethyl)-2-[methyl(phenylmethyl)amino]-2-oxoethyl]-2-benzofuranylmethyl ester, carbamic acid
- CAM4750:** [S-(*R*\*,*S*\*)]-[1-(1*H*-indol-3-ylmethyl)-1-methyl-2-[methyl[1-(4-pyridinyl)ethyl]amino]-2-oxoethyl]-2-benzofuranylmethyl ester monohydrochloride, carbamic acid
- CGP49823:** [(2*R*,4*S*)-2-benzyl-1-(3,5-dimethylbenzoyl)-*N*-[(4-quinolinyl)methyl]-4-piperineamine] dihydrochloride
- CP122721:** (+)-(2*S*,3*S*)-3-(2-methoxy-5-trifluoromethoxybenzyl)amino-2-phenylpiperidine
- CP154526:** butyl-ethyl-(2,5-dimethyl-7-[2,4,6-trimethylphenyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amine
- CP96345:** [(2*S*,3*S*)-*cis*-2-(diphenylmethyl)-*N*-(2-iodophenyl)-methyl]-1-azabicyclo-[2.2.2]octan-3-amine
- CP99994:** (+)-(2*S*,3*S*)-3-(2-methoxybenzylamino)-2-phenylpiperidine
- CS866:** (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxy-4-(1-hydroxy-1-methylethyl)-2-propyl-1-(4-[2-(tetrazol-5-yl)-phenyl]phenyl)methylimidazol-5-carboxylate
- DMP811 (L708404):** 4-ethyl-2-*n*-propyl-1-([2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl)imidazole-5-carboxylic acid
- DuP532:** 2-propyl-4-pentafluorethyl-1-(2'-[2*H*-tetrazol-5-yl]-1,1'-biphenyl-4-yl-methyl)1*H*-imidazole-5-carboxylic acid
- E4177:** 4'-(2-cyclopropyl-7-methyl-3*H*-imidazo[5,4-*b*]pyridine-3-yl)methyl-2-biphenylcarboxylic acid
- EXP3174:** *n*-butyl-4-chloro-1-([2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl)imidazole-5-carboxylate
- EXP3312:** 2-*n*-propyl-4-chloro-1-([2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl)imidazole-5-carboxylaldehyde
- EXP3892:** 2-*n*-propyl-4-trifluoromethyl-1-[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]imidazole-5-carboxylic acid
- FK480:** (S)-*N*-[1-(2-fluorophenyl)-3,4,6,7-tetrahydro-4-oxopyrrolo[3,2,1-*jk*][1,4]-benzodiazepine-3-yl]-1*H*-indole-2-carboxamide
- FR173657:** (E)-3-(6-acetamido-3-pyridyl)-*N*-(*N*-[2,4-dichloro-3-(2-methyl-8-quinolinyl)oxymethyl]phenyl)-*N*-methylaminocarbonyl-methyl)acrylamide
- FR193108:** (+)-3-[[5-(2-fluorophenyl)-9-methyl-2-oxo-3-[[[3-(1*H*-tetrazol-5-yl)phenyl]amino]carbonyl]amino]-2,3-dihydro-1*H*-1,4--benzodiazepin-1-yl]acetyl]-3-azabicyclo[3.2.2]nonane
- GR117289:** 1-([3-bromo-2-[2-(1*H*-tetrazol-5-yl)phenyl]-5-benzofuranyl]methyl)-2-butyl-4-chloro-1*H*-imidazole-5-carboxylic acid

- GR159897:** 5-fluoryl-3-ylethyl(4-[phenylsulphinylmethyl])piperidine
- GR203040:** (+)-(2S,3S and 2R,2R)-2-methoxy-5-tetrazol-1-yl-benzyl-(2-phenyl-piperidin-3-yl)amine
- GR205171:** (2S-cis)-*N*-[[2-methoxy-5-[5-(trifluoromethyl)-1*H*-tetrazol-1-yl]phenyl]methyl]-2-phenyl-3-piperidinamine
- GV150013:** (+)-*N*-(1-[1-adamantane-1-methyl]-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl)-*N*-phenylurea
- ICID6888:** 2-ethyl-5,6,7,8-tetrahydro-4-([2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methoxy)quinoline
- ICID8731:** 2-ethyl-4-([2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methoxy)quinoline
- KSG504:** (S)-arginium(R)-4-[*N*-(3-methoxypropyl)-*N*-pentylcarbamoil]-5-(2-naphthylsulfonyl)pentanoate monohydrate
- kuwanon H:** [1S-(1a,5a,6b)]-8-[6-[2,4-dihydroxy-3-(3-methylbut-2-enyl)benzoyl]-5-(2,4-dihydroxyphenyl)-3-methylcyclohex-2-en-1-yl]-2-(2,4-dihydroxyphenyl)-5,7-dihydroxy-3-(3-methylbut-2-enyl)-4*H*-1-benzopyran-4-one
- L158809:** 5,7-dimethyl-2-ethyl-3-(2-[1*H*-tetrazol-5-yl]biphenyl-4-yl)imidazol[4,5-*b*]pyridine
- L161638:** *N*-[2-ethyl-3-,4-dihydro-4-oxo-3-[[2'-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-6-quinazoliny]-*N*-(phenylmethyl)-2-thiophenecarboxamide
- L161664:** 1-(*N,N*-diphenylaminocarbonyl)-4-(*N,N*-di-*n*-pentylaminocarbonyl)piperazine-2-diethylaminopropylcarboxamide
- L163017:** 6-(benzoylamino)-7-methyl-2-propyl-3-([2'-(*N*-(3-methyl-1-butoxy)carbonylamino)sulfonyl)(1,1')-biphenyl-4-yl)methyl]-3*H*-imidazo(4,5-*b*)pyridine
- L365031:** 1-methyl-3-(4-bromobenzoyl)amino-5-phenyl-3*H*-1,4-benzodiazepin-2-one
- L365260:** 3R(+)-*N*-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl)-*N*-(3-methylphenyl)urea
- L367773:** (1S,2S)-2,3-dihydro-1'-(((7,7-dimethyl-2-((4-imidazolylacetyl)amino)bicyclo[2.2.1]hept-1-yl)methyl)sulfonyl)spiro(1*H*-indene-1,4'-piperidine), hydrochloride
- L368899:** 1-([2-(2-amino-4-(methylsulphonyl)butyramido)-7,7-dimethylbicyclo[2.2.1]-heptan-1-yl]methylsulphonyl)-4-(2-methylphenyl)piperazine
- L368935:** *N*-(1,3-dihydro-1-(2-methyl)-propyl-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl)-*N*-([3-(1*H*-tetrazol-5-yl)phenyl]urea)
- L371257:** 1-(1-[4-((*N*-acetyl-4-piperidinyl)oxy)-2-methoxybenzoyl]piperidin-4-yl)-4*H*-3,1-benzoxazin-2-1*H*-one
- L733060:** (2S,3S)-3-([3,5-bis(trifluoromethyl)phenyl]methoxy)-2-phenyl piperidine
- L740093:** *N*-([3R]-5-[3-azabicyclo[3.2.2]nonan-3-yl]-2,3-dihydro-1-methyl-2-oxo-1*H*-1,4-benzodiazepin-3-yl)-*N*-(3-methylphenyl)urea
- L742694:** 2-(S)-([3,5-bis(trifluoromethyl)benzyl]oxy)-3-(S)-phenyl-4-(5-{3-oxo-1,2,4-triazolo}methylmorpholine
- L743345:** 3S-*N*-(3-azabicyclo[3.2.2.]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1*H*-1,4-benzodiazepin-3-yl)-1*H*-indole-2-carboxamide
- L749329:** *N*-(2-[4-carboxy-2-propylphenoxy]-2-[dioxolo(e)phenyl]-acetyl)-(4-[1-methyl-ethyl]phenyl)sulfonylamide
- L751281:** dipotassium 4-(2-[1,3-benzodioxol-5-yl]-3-[4-isopropylphenylsulphonamido]-3-oxo-prop-1-yl)-3-propylbenzoate
- L754142:** dipotassium (-)-4-(1-[1,3-benzodioxol-5-yl]-2-[4-isopropylphenylsulphonamido]-2-oxoethoxy)-3-propylbenzoate
- LR-B/081:** methyl-2-([4-butyl-2-methyl-6-oxo-5-([2'-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl)-1(6*H*)-pyrimidinyl]methyl)-3-thiophenecarboxylate
- LY191009:** *trans*-5-(2-chlorophenyl)-3-oxo-4-phenyl-*N*-(4-[trifluoromethyl]phenyl)pyrazolidine-1-carboxamide
- LY202769:** 2-[2-(5-chloro-1*H*-indol-3-yl)ethyl]-3-[3-(1-methylethoxy)phenyl]-4(3*H*)-quinazolinone
- LY242040:** *trans*-3-oxo-4,5-diphenyl-*N*-(4-[trifluoromethyl]phenyl)pyrazolidine-1-carboxamide

- LY247348:** 2-[2-(1*H*-indol-3-yl)ethyl]-3-[3-(1-methylethoxy)phenyl]-4(3*H*)-quinazolinone
- LY262684:** *trans-N*-(4-bromophenyl)-4,5-bis(2-chlorophenyl)-3-oxopyrazolidine-1-carboxamide
- LY262691:** *trans-N*-(4-bromophenyl)-3-oxo-4,5-diphenyl-1-pyrazolidinecarboxamide
- LY288513:** (4*S*,5*R*)-*N*-(4-bromophenyl)-3-oxo-4,5-diphenyl-1-pyrazolidinecarboxamide
- LY303870:** (R)-1-(*N*-[2-methoxybenzyl]acetylamino)-3-(1*H*-indol-3-yl)-2-(*N*-[2-{4-(piperidin-1-yl)piperidin-1-yl}acetyl]amino)propane
- LY306740:** (R)-1-(*N*-[2-methoxybenzyl]acetylamino)-3-(1*H*-indol-3-yl)-2-(*N*-[2-{4-cyclohexylpiperazin-1-yl}acetyl]amino)propane
- MDL105212A:** [(R)-1-(2-[3-{3,4-dichlorophenyl}-1-{3,4,5-trimethoxybenzoyl}-pyrrolidin-3-yl]-ethyl)-4-phenylpiperidine-4-carboxamide, hydrochloride
- MEN10930:** (S)-*N*-[1-[[[2-[methyl(phenylmethyl)amino]-1-(2-naphthalenylmethyl)-2-oxoethyl]amino]carbonyl]cyclohexyl]-1*H*-indole-3-carboxamide
- MK966 (L159282):** *N*-(4'-[[5,7-dimethyl-2-ethyl-3*H*-imidazo(4,5-*b*)pyridin-3-yl]methyl][1,1'-biphenyl]-2-yl)sulfonylbenzamide
- NB127914:** 2-methyl-4-(*N*-propyl-*N*-cyclopropanemethylamino)-5-chloro-6-(2,4,6-trichloroanilino)pyrimidine
- NTB:** naltriben methasulfonate
- OPC21268:** 1-(1-[4-{3-acetylamino-propoxy}benzoyl]-4-piperidil)-3,4-dihydro-2-1*H*-quinolinone
- OPC31260:** 5-dimethylamino-1-(4-[2-methylbenzoylamino]benzoyl)-2,3,4,5-tetrahydro-1*H*-benzazepine
- PD123177:** 1-(4-amino-3-methylphenyl)methyl-3-(diphenylacetyl)-4,5,6,7-tetrahydro-1*H*-imidazol[4,5-*c*]pyridine-6-carboxylate
- PD123319:** (S)-1-(4-[dymethylamino]-3-methylphenyl)methyl-5-(diphenylacetyl)-4,5,6,7-tetrahydro-1*H*-imidazol[4,5-*c*]pyridine-6-carboxylate
- PD134308 (CI988):** 4-([2-({3-[1*H*-indol-3-yl]-2-methyl-1-oxo-2-[[tricyclo[3.3.1.1<sup>3,7</sup>]dec-2-yl]oxy)carbonyl]amino]propyl)amino)-1-phenylethyl]amino)-4-oxo-(R-[R\*,R\*])-butanoate-*N*-methyl-D-glucamine
- PD135158:** 4-([2-({3-[1*H*-indol-3-yl]-2-methyl-1-oxo-2-[(1.7.7-trimethyl-(bicyclo[2.2.1]hept-2-yl)oxy)carbonyl]amino]propyl)amino)-1-phenylethyl]amino)-4-oxo-[1*S*-1 $\alpha$ .2 $\beta$ [S\*(S\*)4 $\alpha$ ])-butanoate-*N*-methyl-D-glucamine (bicyclo system 1*S*-endo)
- PD140548:** *N*-( $\alpha$ -methyl-*N*-[[tricyclo(3.3.1.1<sup>3,7</sup>)dec-2-yl]oxy]carbonyl]-L-tryptophyl)-D-3-(phenylmethyl)- $\beta$ -alanine
- PD142898:** benzenebutanic acid,  $\beta$ -([3-{1*H*-indol-3-yl}-2-methyl-2-[[2-methylcyclohexyl]oxy]carbonyl]amino)-1-oxopropyl]amino)-(1*S*-[1 $\alpha$ {S\*(R\*)}-2 $\beta$ ])
- PD154075:** [R-(R\*,S\*)]-[1-(1*H*-indol-3-ylmethyl)-1-methyl-2-oxo-2-[(1-phenylethyl)amino]ethyl]-2-benzofuranyl methyl ester, carbamic acid
- PD154804:** 3-(1,3-benzodioxol-5-yl)-4-cyclohexylmethyl-5-hydroxy-5-(4-methoxyphenyl)-2,5-dihydrofuran-2-one
- PD155080:** 2-benzo(1,3)dioxol-5-yl-3-benzyl-4-(4-methoxyphenyl)-4-oxobut-2-enoate
- PD156707:** 2-benzo(1,3)dioxol-5-yl-4-(4-methoxyphenyl)-4-oxo-3-(3,4,5-trimethoxybenzyl)-but-2-enoate
- PD159020:** 3-(1,3-benzodioxol-5-yl)-1-(1,3-benzodioxol-5-ylmethyl)-5-methoxy-6-(phenylmethoxy)-1*H*-indole-2-carboxylic acid
- PD159110:** 3-(1,3-benzodioxol-5-yl)-1-(1,3-benzodioxol-5-ylmethyl)-6-propoxy-1*H*-indole-2-carboxylic acid
- PD159433:** 1-(1,3-benzodioxol-5-ylmethyl)-5,6-dimethoxy-3-[(3,4,5-trimethoxyphenyl)thio]-1*H*-indole-2-carboxylic acid
- PD161182:** [S-(R\*,S\*)]-[2-(2,3-difluorophenyl)-1-methyl-1-(7-ureidoheptyl)carbamoylethyl]carbamic acid-2-methyl-1-phenylpropyl ester
- PD165929:** (S)- $\alpha$ -[[[2,6-bis(1-methylethyl)phenyl]amino]carbonyl]amino]- $\alpha$ -methyl-*N*-[[1-(2-

- pyridinyl)cyclohexyl)methyl]-1*H*-indole-3-propanamide
- Ro462005:** 4-*tert*-butyl-*N*-(6-[2-hydroxyetoxy]-5-[3-methoxyphenoxy]-4-pyrimidinyl)-benzenesulphonamide
- Ro468443:** (R)-4-*tert*-butyl-*N*-(6-[2,3-dihydroxypropoxy]-5-[2-methoxyphenoxy]-2-[4-methoxyphenyl]-pyrimidin-4-yl)-benzenesulphonamide
- RP67580:** (1-imino-2-[2-methoxyphenyl]ethyl)-7,7-diphenyl-4-perhydroisoindolone (3 $\alpha$ R,7 $\alpha$ R)
- RP69758:** 3-(3-[*N*-(*N*-methyl-*N*-phenyl-carbamoylmethyl)-*N*-phenyl-carbamoylmethyl]ureido)phenylacetic acid
- RP71483:** (*E*)-2-(3-[3-hydroxyiminomethyl-phenyl]ureido)-*N*-(8-quinolyl)-*N*-([1,2,3,4-tetrahydro-1-quinolyl]carbonylmethyl)acetamide
- RP72540:** (*RS*)-2-(3-[3-{*N*-(3-methoxyphenyl)-*N*-(*N*-methyl-*N*-phenyl-carbamoylmethyl)carbamoylmethyl]ureido]phenyl)propionic acid
- RP73870:** (*RS*)-([*N*-(3-methoxyphenyl)-*N*-(*N*-methyl-*N*-phenyl-carbamoylmethyl)carbamoylmethyl]-3-ureido]-3-phenyl)-2-ethylsulfonate, potassium salt
- RPR100893:** (3*nS*,4*S*,7*aS*)-7,7-diphenyl-4-(2-methoxyphenyl)-2-[(*S*)-2-(2-methoxyphenyl)propionyl]perhydroisoindol-4-ol
- SB209598:** 3-(2-carboxymethoxy-4-methoxyphenyl)-1-(6-chloro-1,3-benzodioxol-5-ylmethyl)-indole-2-carboxylic acid
- SB209670:** (+)-1*S*,2*R*,*S*-3-(2-carboxymethoxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-prop-1-yloxyindane-2-carboxylic acid
- SB217242:** 1*S*,2*R*,3*S*-3-(2-hydroxyethoxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-propoxyindane-2-carboxylic acid
- SB223412:** (*S*)-(-)-*N*-( $\alpha$ -ethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide
- SC51316:** 5-([3,5-dibutyl-1*H*-1,2,4-triazol-1-yl)methyl)-2-(2-[1*H*-tetrazol-5-ylphenyl])pyridine
- SC51895:** 1,4-dibutyl-1,3-dihydro-3-([2'-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]-4-yl)methyl)-2*H*-imidazol-2-one
- SC52458:** 2,5-dibutyl-2,4-dihydro-4-([2-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]-4'-yl)methyl)-3*H*-1,2,4-triazol-3-one
- SKF108566:** (*E*)- $\alpha$ -([2-butyl-1-{(4-carboxyphenyl)methyl}-1*H*-imidazol-5-yl]methylene)-2-thiophenepropanoate
- SR 48692:** 2-([1-{7-chloro-4-quinoliny}]5-{2,6-dimethoxyphenyl})-1*H*-pyrazol-3-carbonyl]amino)adamantane-2-carboxylic acid
- SR120107A:** (R,R)-1-(2-[2-{2-naphtylsulphamoyl}-3-phenyl-propionamido]-3-[4-{*N*-(4-dimethylaminomethyl)-*cis*-cyclohexylmethyl)amidino}phenyl]propionyl)-pyrrolidine
- SR120819A:** (R,R)-1-(2-[2-{2-naphtylsulphamoyl}-3-phenyl-propionamido]-3-[4-{*N*-(4-dimethylaminomethyl)-*trans*-cyclohexylmethyl)amidino}phenyl]propionyl)-pyrrolidine
- SR140333:** (*S*)-1-(2-[3-{3,4-dichlorophenyl}-1-{3-isopropoxyphenylacetyl}piperidin-3-yl]ethyl)-4-phenyl-1-azoniabicyclo(2.2.2)octane chloride
- SR142801:** (*S*)-(*M*)-(1-[3-{1-benzoyl-3-(3,4-dichlorophenyl)piperidin-3-yl}propyl]-4-phenylpiperidin-4-yl)-*N*-methylacetamide
- SR142948A:** 2-([5-{2,6-dimethoxyphenyl}-1-{4-(*N*-[3-dimethylaminopropyl]-*N*-methylcarbamoyl)-2-isopropylphenyl}-1*H*-pyrazol-3-carbonyl]amino)adamantane-2-carboxylic acid, hydrochloride
- SR27897:** 1-([2-{4-(2-chlorophenyl)thiazole-2-yl}aminocarbonyl]indolyl)acetic acid
- SR48968:** (*S*)-*N*-methyl-*N*-(4-acetylamino-4-phenylpiperidino)-2-(3,4-dichlorophenyl)butylbenzamide
- SR49059:** (2*S*)-1-([2*R*,3*S*]-[5-chloro-3-{chlorophenyl}-1-{3,4-dimethoxysulphonyl}-3-hydroxy-2,3-dihydro-1*H*-indole-2-carbonyl]-pyrrolidine-2-carboxamide)
- T0632:** sodium (*S*)-3-(1-[2-fluorophenyl]-2,3-dihydro-3-[(3-isoquinoliny)]-carbonyl]amino-6-methoxy-2-oxo-1*H*-indole)propanoate
- TBC11251:** *N*-(4-chloro-3-methyl-5-isoxazolyl)-2-[2-(6-methyl-1,3-benzodioxol-5-yl)-1-oxoethyl]-thiopentene-3-sulphonamide
- UP269-6:** 5-methyl-7-propyl-8(-)[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl)methyl]-1,2,4-triazolo[1,5-

- c]pyrimidin-2(3*H*)-one
- UR7198:** *rel*-(1*R*\*,2*R*\*)-3-[[4-(2-carboxy-1-phenylpropyl)phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazol[4,5-*b*]pyridine
- UR7280:** 3-*tert*-butyl-1-propyl-5-([2'-{1*H*-tetrazol-5-yl}-1,1'-biphenyl-4-yl]methyl)-1*H*-pyrazole-4-carboxylic acid
- WIN 64338:** ([4-{(2-[[bis(cyclohexylamino)methylene]amino)-3-[2-naphthyl]-1-oxopropyl)amino}phenyl]methyl)tributylphosphonium chloride monohydrochloride
- WIN51708:** 17β-hydroxy-17α-ethynyl-5α-androstanol[3,2-*b*]pyrimido[1,2-*a*]benzimidazole
- WIN62577:** [1*R*-(1α,3αβ,3bα,15α,15bβ,17α)]-1-ethynyl-2,3,3a,3b,4,5,15,15a,15b,16,17,17a-dodecahydro-15a,17a-dimethyl-1*H*-benzimidazo[2,1-*b*]cyclopenta[5,6]naphtho[1,2-*g*]quinazolin-1-ol
- XR510:** 1-([2'-{[(isopentoxycarbonyl)amino]sulfonyl}-3-fluoro(1,1'-biphenyl)-4-yl]methyl)-5-(3-[*N*-pyridin-3-ylbutanamido]propanoyl)-4-ethyl-2-propyl-1*H*-imidazole, potassium salt
- YF476:** (3*R*)-*N*-(1-[*tert*-butylcarbonylmethyl]-2,3-dihydro-2-oxo-5-[2-pyridil]-1*H*-1,4-benzodiazepin-3-yl)-*N*-(3-[methylamino]phenyl)urea
- YM022:** (R)-1-(2,3-dihydro-1-[2'-methylphenacyl]-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl)-3-(3-methylphenyl)urea
- YM087:** 4'-(2-methyl-1,4,5,6-tetrahydroimidazo{4,5-*d*}{1}benzazepin-6-yl)carbonyl)-2-phenylbenzanilide monohydrochloride