Drugs of the Future 2002, 27(3): 273-287

CCC: 0377-8282/2002

Review Article

Small-molecule neuropeptide Y Y_5 antagonists

Scott L. Dax

Drug Discovery, Johnson & Johnson Pharmaceutical Research and Development, Welsh and McKean Roads, Spring House, PA 19477, USA

CONTENTS

Introduction

Regulation and function of the mammalian central nervous system is governed by a series of interdependent neuronal receptors, neurotransmitters and proteins. The neurons play a vital role in this system, for when stimulated, they release neurotransmitters that bind to specific receptors and initiate a cascade of events that can lead to a physiological response. Endogenous small-molecule neurotransmitters such as acetylcholine, adrenaline, norepinephrine, dopamine, serotonin, glutamate and γ-aminobutyric acid are well known, as are the specific receptors that recognize these substances as ligands (1). For decades, organic-based small molecules have been sought to block, modulate or enhance the actions of these classical neurotransmitters. This strategy has proven to be very successful and has led to many marketed drugs that treat disorders or diseases associated with some part of the nervous system including, in some cases, neurodegenerative diseases and affective disorders such as anxiety, depression, pain and schizophrenia.

However, in addition to the endogenous small-molecule neurotransmitters, it has been demonstrated more recently that neuropeptides play an integral role in neuronal operations. Neuropeptides may be co-localized with perhaps more than half of the 100 billion neurons of the human central nervous system. The view that neuropeptides serve only supporting roles or are redundant in mammalian physiology is falling by the wayside, as more neuropeptides are being shown to play inherently vital roles. In some cases, these findings are supported by elegant studies in transgenic or knockout animals.

Neuropeptides have been discovered in a number of animal species and rather strikingly, the composition of some of these complex peptides is remarkably homogenous among species. This finding suggests that the function of these neuropeptides is vital and has been impervious to evolutionary changes. Furthermore, neuropeptides, unlike small-molecule neurotransmitters, are typically synthesized by the neuronal ribosome. In some cases, the active neuropeptides are produced as part of a larger protein that is enzymatically processed to yield the active substance. Based upon these differences compared to small-molecule neurotransmitters, neuropeptide-based strategies may offer novel therapies for CNS diseases and disorders.

Isolation and description of neuropeptide Y

First isolated from porcine brain (2), neuropeptide Y is now recognized as being a very important and abundant neurotransmitter. Neuropeptide Y (NPY) is a single-chain protein that consists of 36 amino acids containing an amidated C-terminus. In solution, NPY is structurally similar to other members of the pancreatic polypeptide (PP) family such as peptide YY, which is primarily synthesized by endocrine cells in the gut, and pancreatic polypeptide, which is synthesized by the pancreas. Like other members of the pancreatic polypeptide family, NPY has a distinctive conformation that consists of an N-terminal polyproline helical region and an amphiphilic α-helix joined by a characteristic PP fold (3). Furthermore, NPY sequences from a number of animal species have been elucidated and all show a high degree of amino acid homology to the human protein (> 94% in rat, dog, rabbit, pig, cow, sheep) (4). This high level of conservation throughout evolution may be suggestive of a vital role in homeostatis or brain function.

Pharmacology of neuropeptide Y

The physiological actions of NPY are mediated through endogenous receptor proteins that bind NPY and related peptides. Five different receptor subtypes (Y_1, Y_2, Y_4 [PP_1], Y_5 and y_6 (formerly designated as a Y_5 receptor) have been identified, cloned and expressed (5-15). To date, all known NPY receptor proteins belong to the family of G-protein-coupled receptors (GPCRs). The neuropeptide Y_5 receptor is negatively coupled to cellular cyclic adenosine monophosphate (cAMP) levels via the

action of adenylate cyclase (16). NPY inhibits forskolin-stimulated cAMP production/levels in a (neuroblastoma) cell line and a Y_5 ligand that mimics NPY in this fashion is an agonist. Conversely, a ligand that binds to the Y_5 receptor and competitively reverses the NPY inhibition of forskolin-stimulated cAMP production is an antagonist.

Neuropeptide Y itself is the archetypal substrate for the NPY receptors and its binding can elicit a variety of pharmacological and biological effects *in vitro* and *in vivo*. For this reason, many research groups have been studying the NPYergic systems and trying to develop small-molecule drugs that can modulate the downstream actions of NPY receptors. It is useful to briefly summarize here some of the actions of NPY with a focus on potential therapeutic indications, although it is important to realize that the utility of any Y_5 antagonist has yet to be established in a human patient population.

As might be expected for a neuropeptide, NPY can alter animal behavior in established models that can correlate to known human conditions and disorders. For example, when administered to the brain of live animals (intracerebroventricularly [i.c.v.] or into the amygdala), NPY produces anxiolytic effects in established animal models of anxiety such as the elevated plus-maze, Vogel punished drinking and Geller-Seifter's bar-pressing conflict paradigms (17-19). Therefore, compounds that mimic NPY have been postulated to be useful for the treatment of anxiety disorders. Neuropeptide Y also improves memory and performance scores in animal models of learning (20) and therefore may serve as a cognition enhancer for the treatment of neurodegenerative diseases such as Alzheimer's disease as well as AIDS-related and senile dementia.

Neuropeptide Y immunoreactivity is notably decreased in the cerebrospinal fluid of patients with major depression, in suicide victims (21), and rats treated with tricyclic antidepressants display significant increases of NPY relative to a control group (22). These findings suggest that an inadequate NPY response may play a role in some depressive illnesses, and that compounds that regulate the NPYergic system may be useful for the treatment of depression.

Elevated plasma levels of NPY are present in animals and humans experiencing episodes of high sympathetic nerve activity such as surgery, newborn delivery and hemorrhage (23). Thus, chemical substances that alter the NPYergic system may be useful for alleviating migraine, pain and the condition of stress.

Neuropeptide Y also mediates endocrine functions such as the release of luteinizing hormone in rodents (24). Since luteinizing hormone is vital for mammalian ovulation, a compound that mimics the action of NPY could be useful for the treatment of infertility, particularly in women with so-called luteal phase defects.

However, NPY has received its notoriety due to its ability to produce virtual feeding frenzy in animals upon direct administration into the brain. In fact, NPY is the most powerful stimulant of food intake discovered to date (25-28). Injection of 100 ng of NPY into the hypothalamic paraventricular nucleus of live rats caused satiated animals to overeat and a dose of 1 μg induced animals to consume within 4 h an amount of food approximately equivalent to the normal daily intake in an age-matched, vehicle-treated group (27, 28). In other studies, chronic i.c.v. administration of NPY produced a profound increase in daily food intake compared to a vehicle group. Furthermore, the NPY-treated animals gained body weight much more rapidly and became obese. Interestingly, when NPY treatment was discontinued, the animals resumed normal food consumption and their body weights eventually returned to nearly that of the vehicle group (29). These studies have demonstrated that NPY can play a role in feeding and may contribute to eating-related disorders such as obesity.

Neuropeptide Y Y_5 antagonists

The birth of research aimed at discovering modulators of the NPY Y5 receptor can be traced to several events. In 1996, it was disclosed that the Synaptic Pharmaceutical Corporation, led by C. Gerald, had identified a unique Y_1-like receptor (30). The group used a ^{125}I-PYY-based expression cloning technique to isolate a rat hypothalamic cDNA that encoded an "atypical Y_1" protein. The group used this information to isolate and characterize the human homolog as well. The newly discovered Y_5 receptor bound various fragments and analogs of NPY and PYY with affinities that were different from that of the other known neuropeptide receptors; however, the profile was in agreement with that described for the feeding response in rodents. Furthermore, the NPY analog [D-Trp^{32}]NPY was found to bind with high affinity to rY_5 (K_i = 53 nM) but not to Y_1 (K_i > 1000 nM). Since [D-Trp^{32}]NPY, a full agonist of the Y_5 receptor with no appreciable Y_1 activity, was shown to stimulate food intake when injected into the hypothalamus of rats, activation of the Y_5 receptor is at least partially responsible for the NPY-mediated feeding response (16). From this, the hypothesis that compounds that antagonize the Y_5 receptor should be effective in inhibiting food intake, particularly that stimulated by NPY, was born. Other studies have supported this theory. For example, the NPY fragment NPY2-36 is a potent inducer of feeding despite poor binding at the classic Y_1 receptor (31). Conversely, a potent and selective Y_1 agonist has been reported to be inactive at stimulating feeding in animals (32).

In their ensuing search for antagonists of the Y_5 receptor, the Synaptic group reported on the first small-molecule Y_5 ligand, 1-amino-2-(2-naphthylmethylamino)-3-phenylpropane (Fig. 1) and subsequent work following an insightful strategy afforded even more potent compounds. In this review, binding (^{125}I-PYY as radioligand) and functional activity is from data reported using various cell lines stably transfected with the human NPY Y_5 receptor (see individual references for details). It was recognized that the benextramine, a known albeit modest Y_1

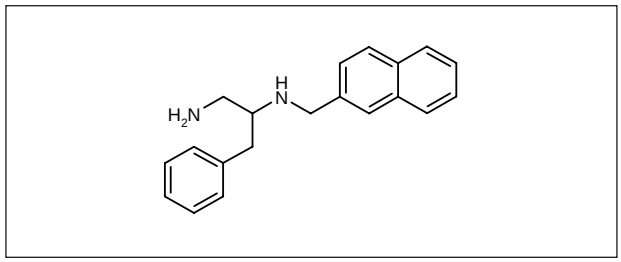


Fig. 1.

ligand (K_i = 2 μM) from which potent Y_1 antagonists were developed, possessed weak affinity for the Y_5 receptor (K_i = 5 μM). From this finding, various diamines related to benextramine were prepared and assayed for binding to Y_5. Congeners that were capped with aryl groups retained low micromolar affinity, and during these early studies it was found that the spacing between the amine centers also influences binding. However, the replacement of an amine center with a sulfonamido group enhanced binding significantly and when these two alterations were incorporated simultaneously, submicromolar affinity was observed. During the course of this work, it was also found that a C6 linear spacer between the amine and sulfonamido groups was somewhat optimal in terms of binding affinity. From this, constrained versions were then examined, thus leading to the methyl(cyclohexyl)methyl-scaffold. The combination of these preferred structural features afforded compounds with nanomolar affinity and thus the first series of potent and selective Y_5 antagonists, the arylsulfonamido-alkyl-aralkylamines, was born (Fig 2).

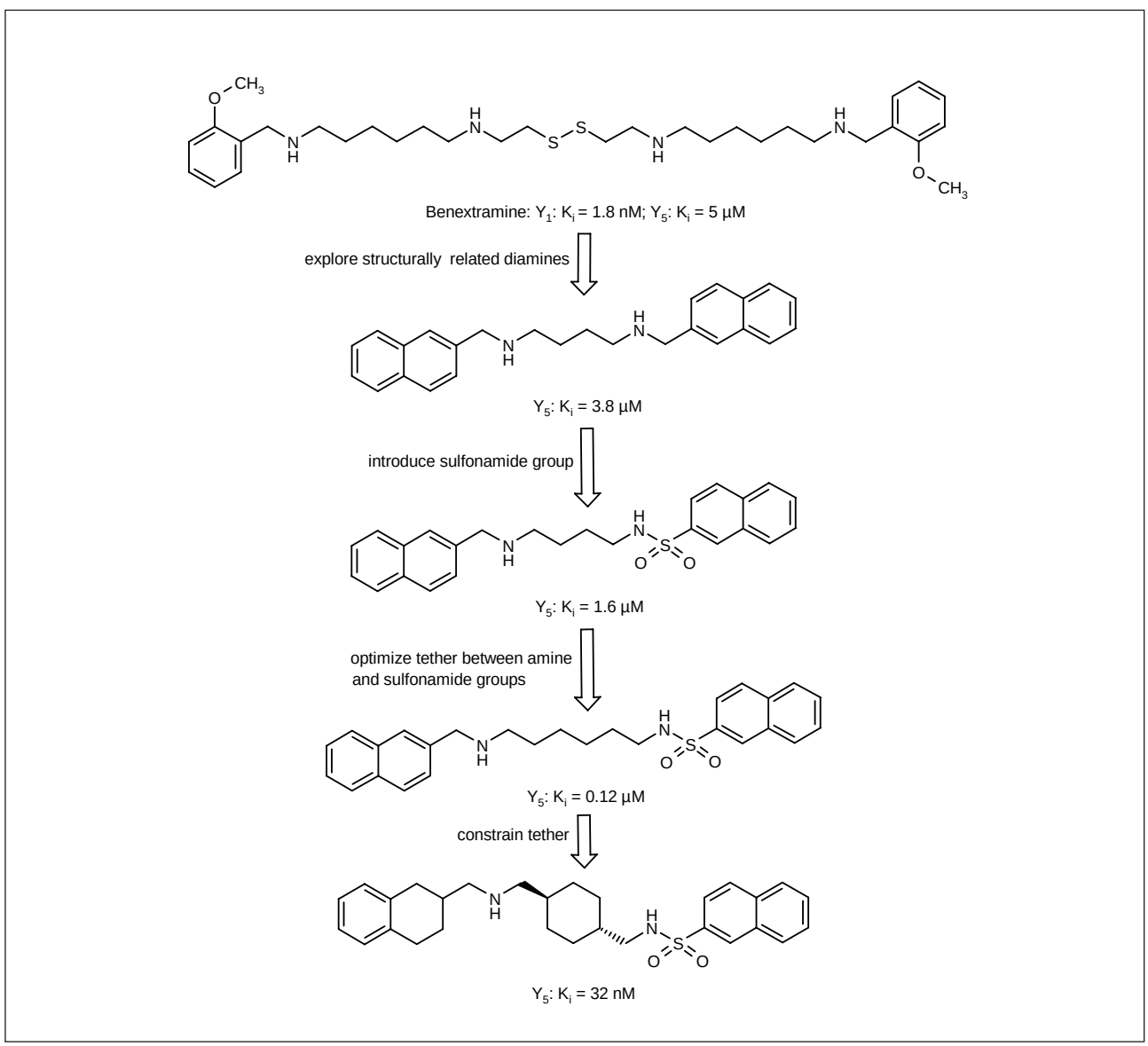


Fig. 2.

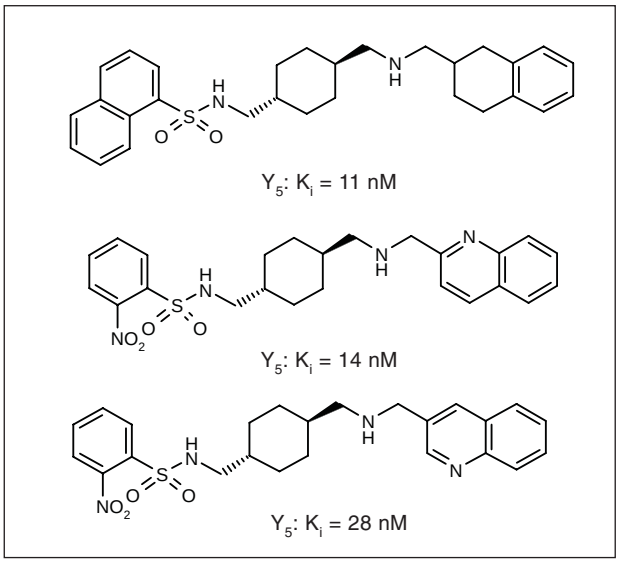


Fig. 3.

The Synaptic group went on to demonstrate that Y_5 antagonism did indeed play a role in the regulation of food consumption in several rodent models (33). When administered intraperitoneally (30 mg/kg), a proprietary naphthylsulfonamido amine markedly suppressed NPY-induced feeding (300 pmol porcine NPY administered i.c.v.). Drug-treated rats ate less chow (1.5 ± 0.6 g) over a 4-h period than the untreated NPY-stimulated group (4.9 ± 0.4 g) and less than a vehicle group (2.8 ± 0.9 g) receiving neither NPY nor Y_5 antagonist. In another model, food-deprived (24 h) rats treated i.p. with a Y_5 antagonist also ate less over a 2-h period compared to a vehicle group without causing overt adverse effects or illness. For example, the nitrobenzyl-sulfonamido quinolinylmethylamines shown below sharply reduced feeding by 73% and 84%, respectively (Fig. 3).

The Novartis group similarly went on to develop a number of interesting variations based upon this general theme (34-36). A key feature was the incorporation of aminoquinazoline ring system as the amine component along with variations of cycloalkyl scaffolds (Fig. 4). Several compounds from this series, when administered i.p. (30 mg/kg) to food-deprived rats, produced profound decreases in food consumption (60-80% or more).

More potent compounds of this general family followed (Fig. 5) and several are reported to essentially halt feeding in fasted rats (36). The series culminated in the discovery of CGP-71683A, which today is one of the most potent and extensively studied Y_5 antagonists (Fig. 6).

CGP-71683A and analogs have been shown to reduce food consumption in rodents although it is unclear if this effect is due solely to antagonism of the Y_5 recep-

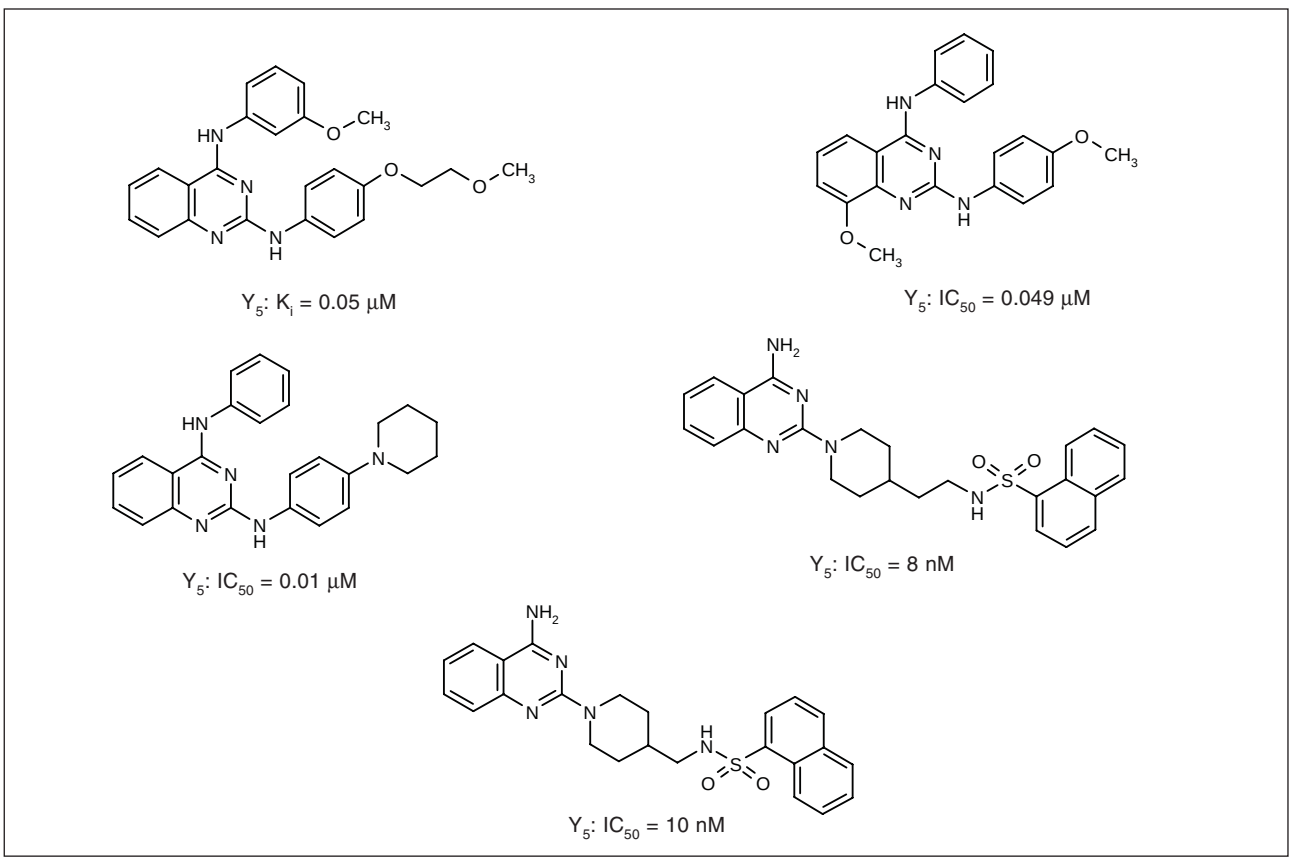


Fig. 4.

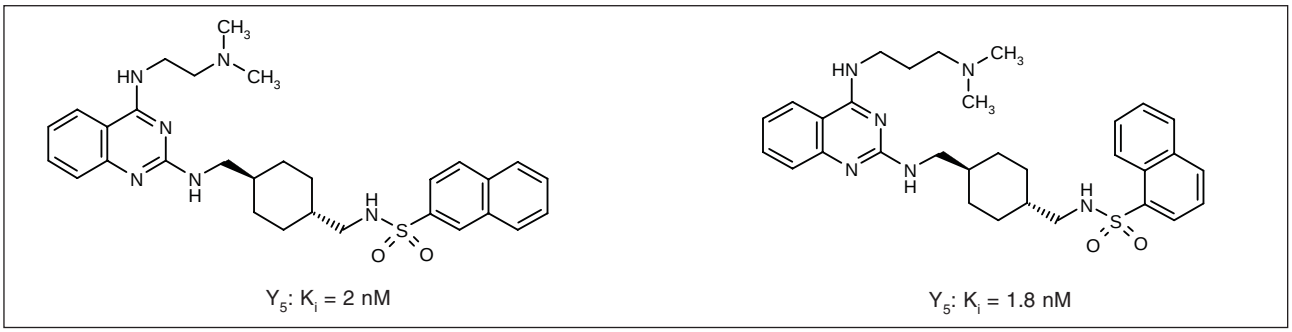


Fig. 5.

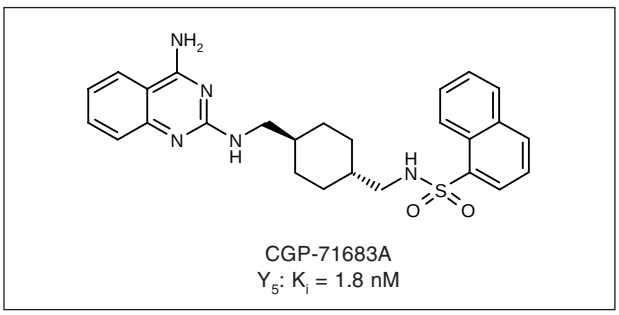


Fig. 6.

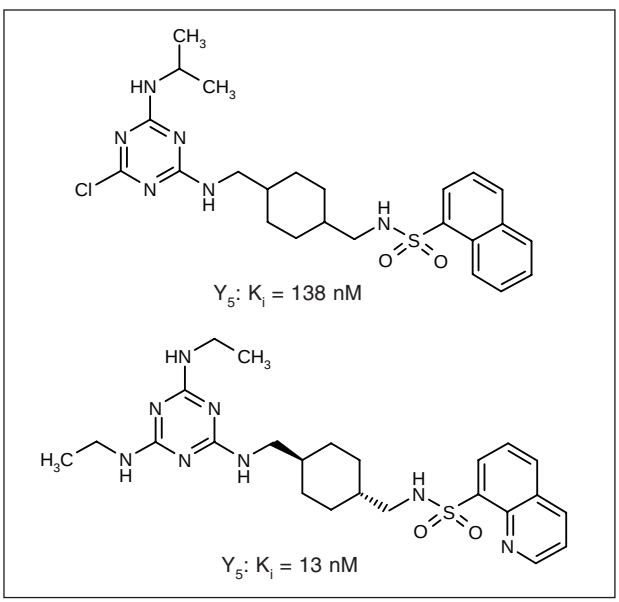


Fig. 7.

tor. CGP-71683A apparently has nanomolar affinity for muscarinic receptors and the serotonin uptake recognition site (37).

The design, synthesis and SAR of the Novartis aminoquinazoline series has been recently described (38). Using an insightful integrated approach, weak Y_5 hits were identified from a Y_1 program and from this, a Y_5 pharmacophore model was generated with the Catalyst® program. 2-Substitued-4-amino-quinazoline series were then pursued using a combinatorial strategy, which produced compounds with low micromolar affinity for the Y_5 receptor. Directed chemistry efforts, utilizing the Topliss decision tree and Hansch analysis, afforded hand-crafted optimized compounds with low nanomolar affinity, including CGP-71683A.

More recently, the Synaptic group has extended this line of research to include triazinyl congeners (Fig. 7) (39) and a vast diverse collection of other sulfonamido-(amino)heterocycles (Figs. 8, 9) (40).

Using a multiplex screening paradigm, researchers at the R.W. Johnson Pharmaceutical Research Institute identified a novel aminotetralin that exhibited low micromolar binding affinity for the cloned human Y_5 receptor (41). As with the Synaptic series, it was found that attachment of (arylsulfonamido)alkyl groups to the aminotetralin core produced antagonists that bound with nanomolar

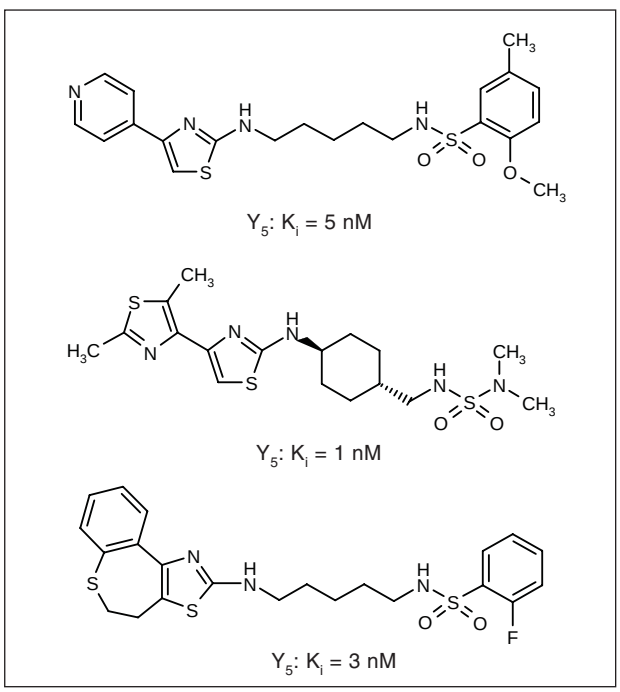


Fig. 8.

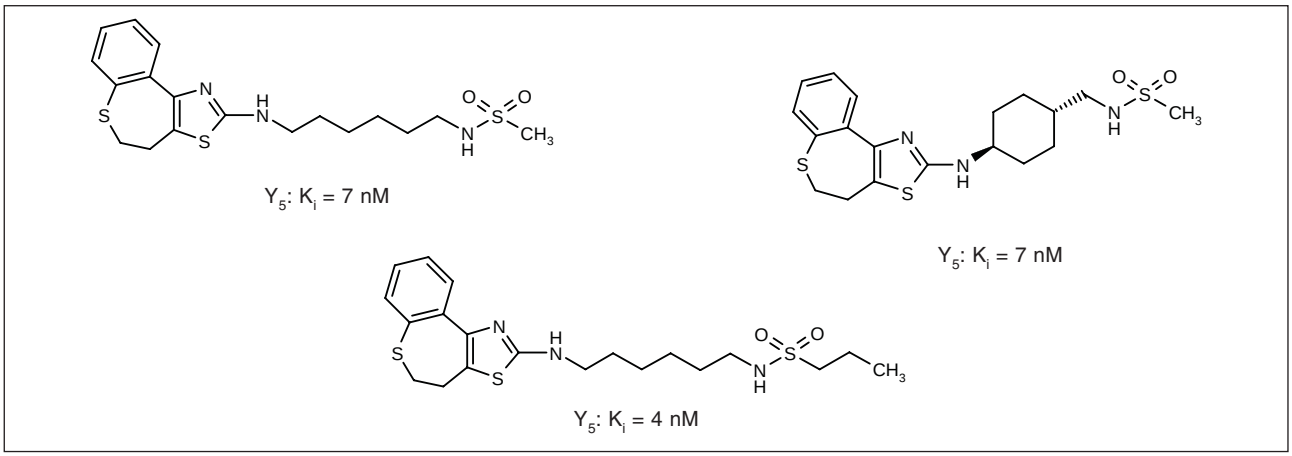

Y_5: K_i = 7 nM
Y_5: K_i = 7 nM
Y_5: K_i = 4 nM

Fig. 9.

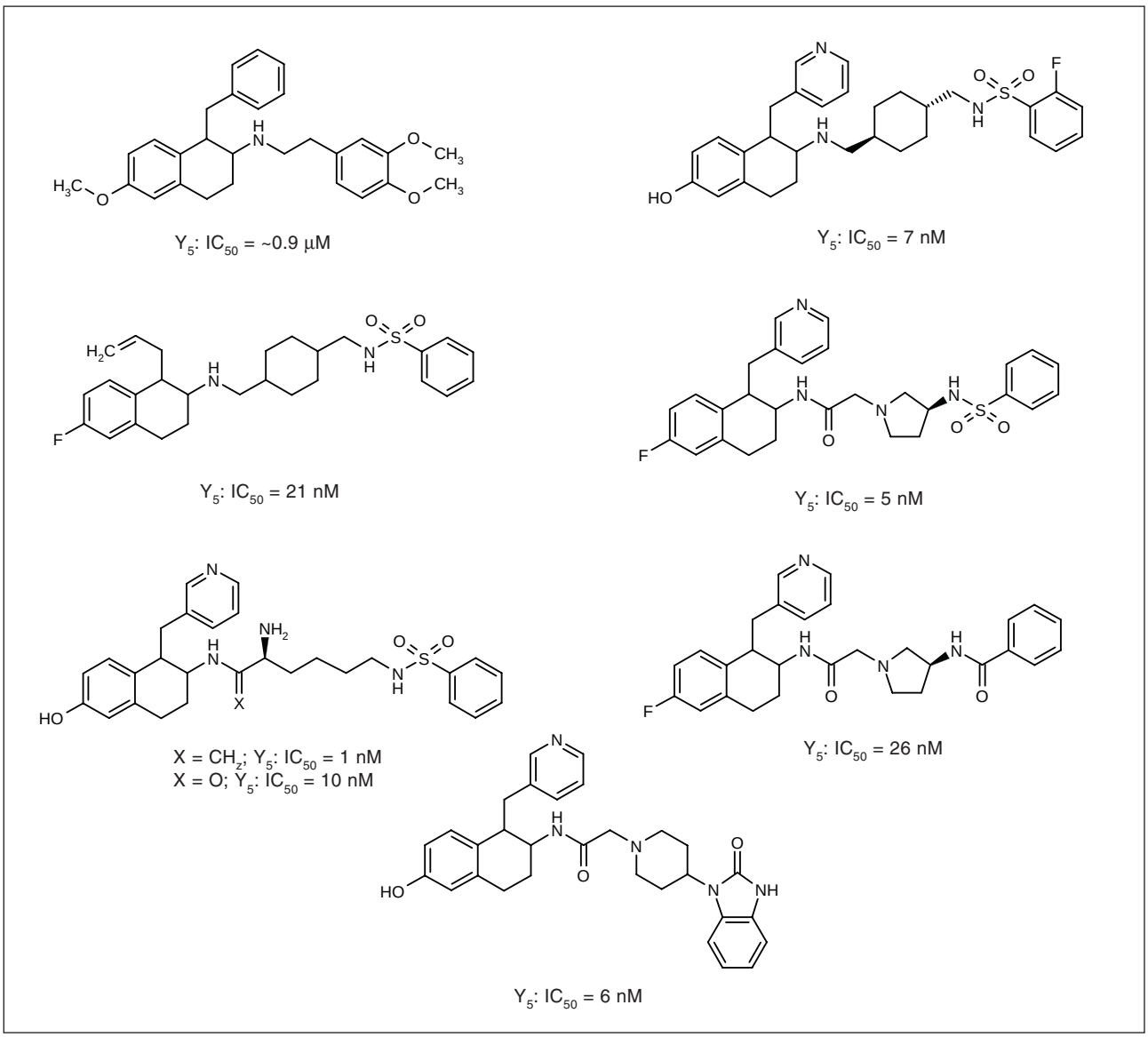
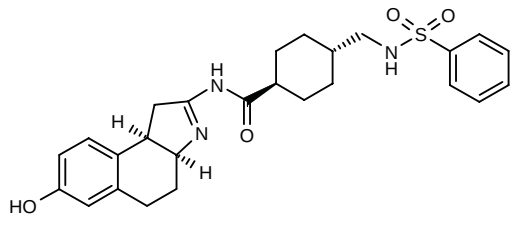
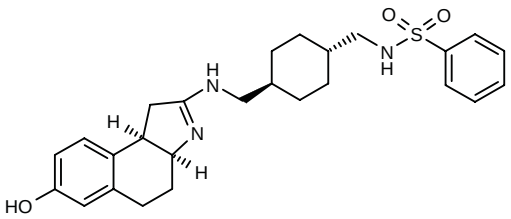

Y_5: IC_{50} = ~0.9 μM
Y_5: IC_{50} = 7 nM
Y_5: IC_{50} = 21 nM
Y_5: IC_{50} = 5 nM
X = CH_z; Y_5: IC_{50} = 1 nM
X = O; Y_5: IC_{50} = 10 nM
Y_5: IC_{50} = 26 nM
Y_5: IC_{50} = 6 nM

Fig. 10.

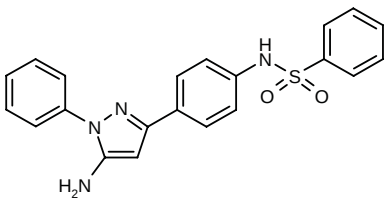


Y_5: IC_{50} = 9 nM

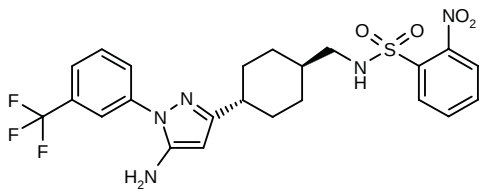


Y_5: IC_{50} = 1 nM

Fig. 11.



Y_5: IC_{50} = 38 nM



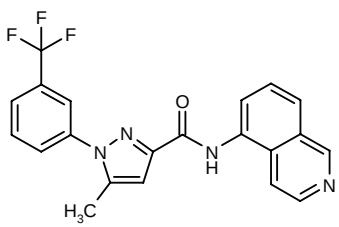
Y_5: IC_{50} = 20 nM

Fig. 12.

affinity (41-46). However, the SAR development of this series diverged from the Synaptic series and afforded various subsets of unique and potent Y_5 antagonists (Fig. 10). One salient feature was the replacement of the previously indispensable arylsulfonamido terminus with appropriate benzimidazolone, arylamido or arylcarbamoyl surrogates, a feature also disclosed by the Bayer group (see below). A second key finding was that amine-containing tethers, such as those derived from aminopyrrolidine and aminopiperidine, as well as from lysine, could be utilized to construct compounds with lower lipophilicity and enhanced water solubility while keeping nanomolar affinity for Y_5. These developments also led to the rather striking finding that the free amine center is not needed for potent binding and that the corresponding amido congeners derived from (α-pyridyl)tetralinamides can likewise exhibit robust Y_5 binding and antagonism. Collectively, these findings allowed for the synthesis of hundreds of structurally diverse Y_5 antagonists, many of which exhibited activity in a rodent model of food consumption.

During the course of this research, in attempts to prepare a key cyanomethylated aminotetralin, an interesting cyclization was realized that afforded the novel tetrahydro-1*H*-benzo[e]indol-2-ylamine ring system (47, 48). Rather surprisingly, the SAR from the aminotetralin subset carried over and thus tethering arylsulfonamido groups produced potent Y_5 antagonists (Fig. 11).

The R.W. Johnson group also developed an aminopyrazolyl benzenesulfonamide series after the Y_5 binding of a bis-sulfonamido screening hit was shown to be due to a mono-sulfonamide contaminant (Fig. 12) (49, 50). As with



Y_5: IC_{50} = 80 nM

Fig. 13.

the aminotetralin series, proper spacing of the basic amine (aminopyrazole) from a benzenesulfonamide moiety afforded compounds with nanomolar affinity.

The same group pursued a series of pyrazole carboxamides from a closely related triazolocarboxamide screening hit. Although members of this structural series possess only modest Y_5 binding affinity, an aminoisoquinolinyl pyrazolecarboxamide was reported to cause a decrease in food consumption (38% relative to a vehicle-treated group) in a rodent model of feeding (fasted) (Fig. 13) (51, 52).

A variation on this general theme has been disclosed by a French research group who has introduced a hydrazo moiety (Fig. 14) (53) in conjunction with the sulfonamido functionality.

More recent perturbations on the structural themes described above, namely arylamides tethered to arylsulfonamides, is manifested in a series of carbazolyl amides disclosed by Meiji (Fig. 15) (54).

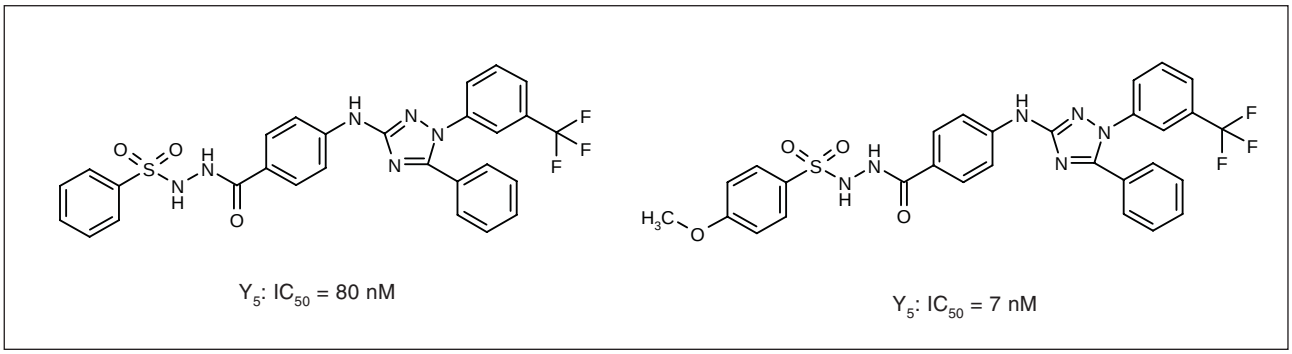


Fig. 14.

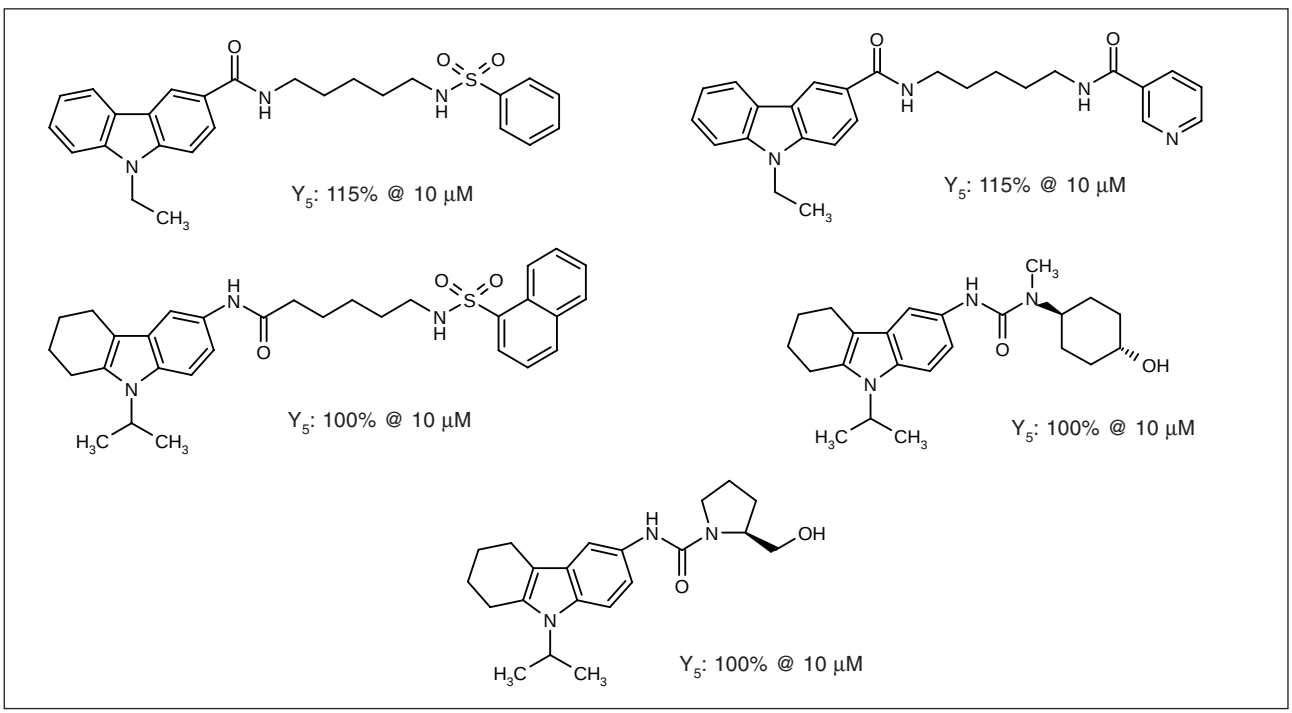


Fig. 15.

The Bayer group was the first to disclose exquisitely potent non-sulfonamido NPY Y_5 antagonists (Fig. 16) (55-57). The 4-(2-keto-1-benzimidazolinyl)piperidinyl acetamido fluorenone and 4-acetyl-4-phenylpiperinyl acetamido benzophenone are representative although much simpler variations can retain submicromolar or even nanomolar affinity. The most potent compounds contain a piperidinyl scaffold that separates a substituted phenylacetamide from a terminus that contains both an aryl moiety and hydrogen-bond acceptor functional groups. As with the non-sulfonamido aminotetralin-derived Y_5 antagonists from R.W. Johnson, the benzimidazolone group is prominent in compounds that exhibit low nanomolar affinity for the Y_5 receptor. However, many simple arylthio- and heteroarylthioethers are quite potent for structurally simple molecules (Figs. 17, 18).

A group at Schering Corporation has been working on compounds related to this general theme but the most potent congeners are urea derivatives as opposed to amides. In some cases, compounds are reported to bind to the Y_5 receptor with subnanomolar affinity (Fig. 19) (58).

Researchers at Amgen have also recently disclosed a series of small-molecule trisubstituted phenylureas that are potent antagonists of Y_5. Starting from a screening hit, binding affinity was optimized by separately modifying stereochemical centers and aryl portions to afford compounds with subnanomolar affinity. Select analogs were also shown to inhibit NPY-induced reversal of forskolin-stimulated cAMP production, thus indicating functional antagonism of the receptor (Fig. 20) (59, 60).

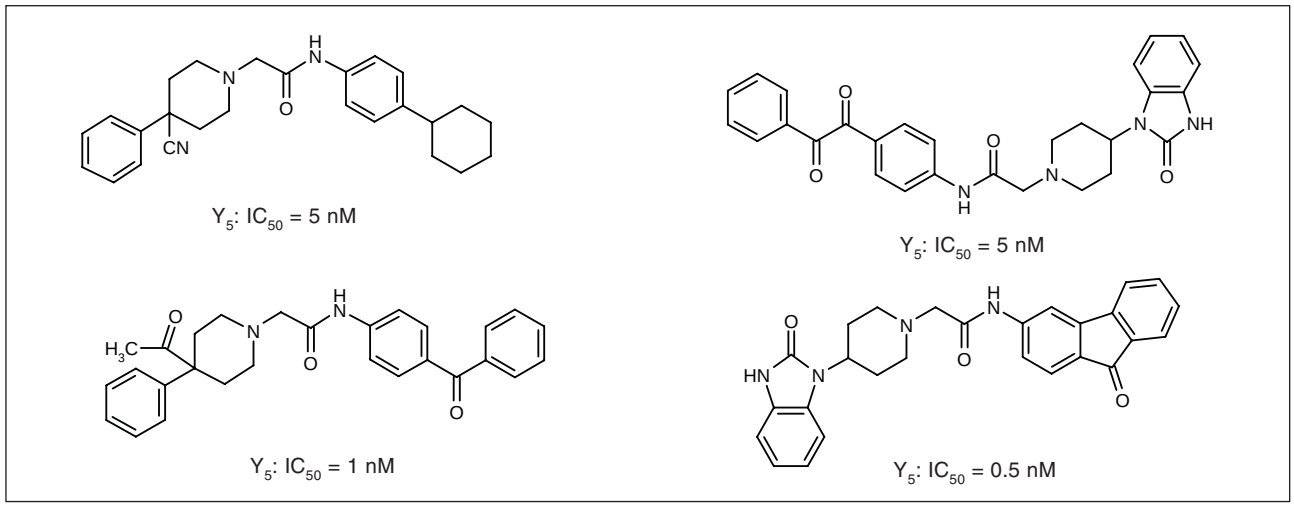


Fig. 16.

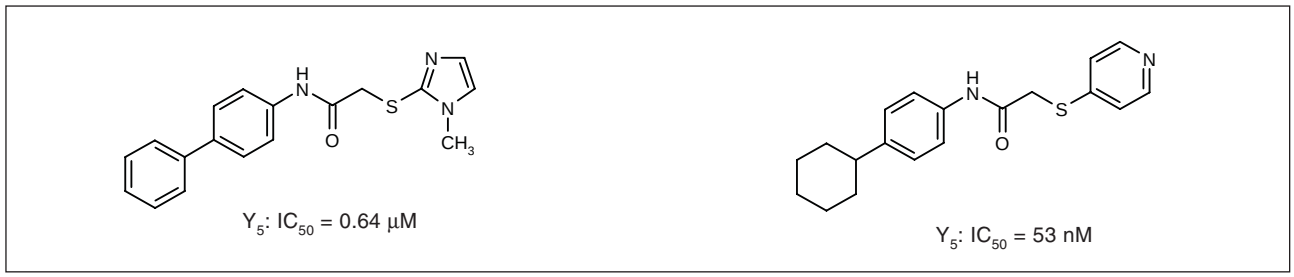


Fig. 17.

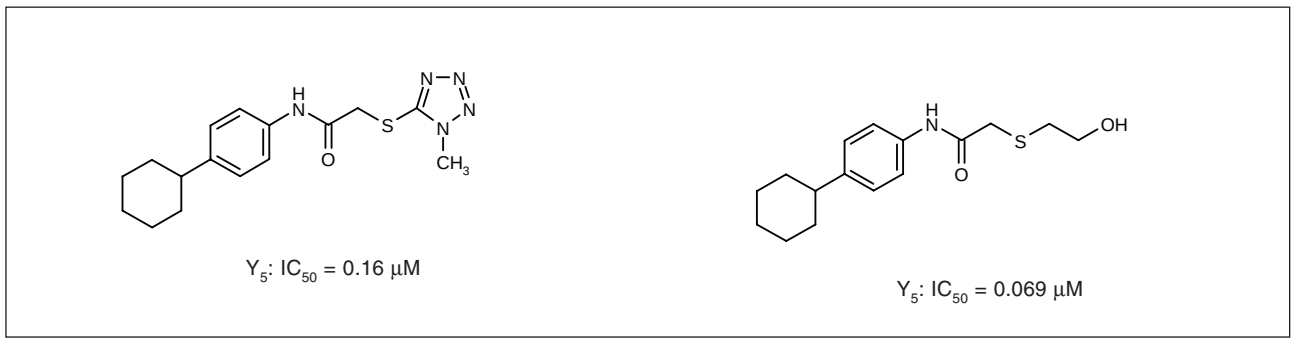


Fig. 18.

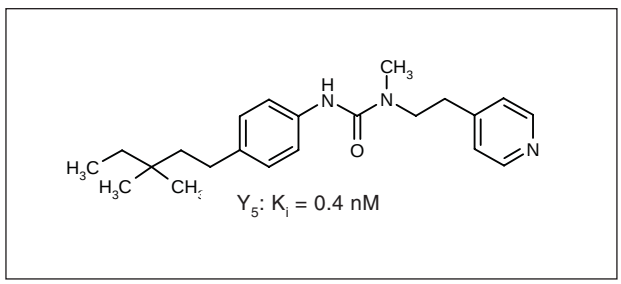
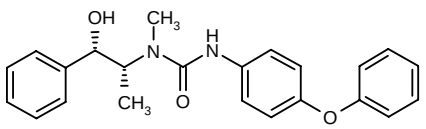


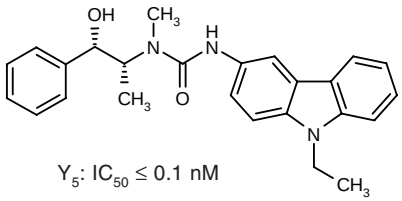
Fig. 19.

Banyu researchers have been particularly successful in discovering and developing diverse small-molecules antagonists of the neuropeptide Y_5 receptor. This includes a diverse set of aminopyrazole carboxamide ligands (Fig. 21) (61-63) that are structurally distinct and more potent than the R.W. Johnson series.

A series of amides derived from 2-aminobenzimidazole were recently reported by the GlaxoSmithKline group (Fig. 22) (64-68). The most potent compounds bind to the Y_5 receptor with nanomolar affinity, exhibit functional antagonism and inhibit food intake in fasted rats. A key

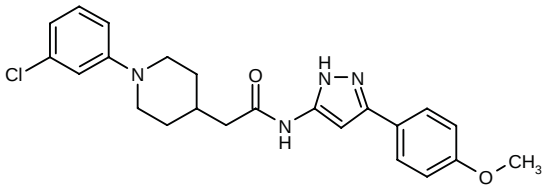


Y_5: IC_{50} = 6.5 nM

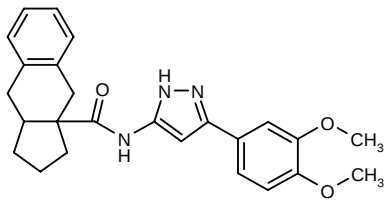


Y_5: $IC_{50} \leq 0.1$ nM

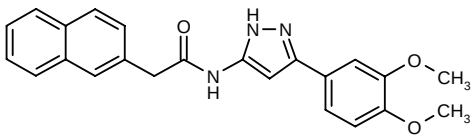
Fig. 20.



Y_5: IC_{50} = 33 nM

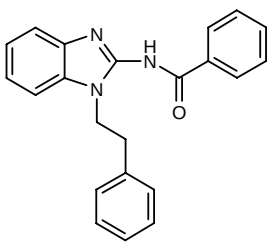


Y_5: IC_{50} = 2.5 nM

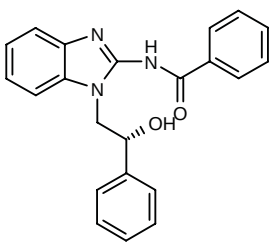


Y_5: IC_{50} = 8.3 nM

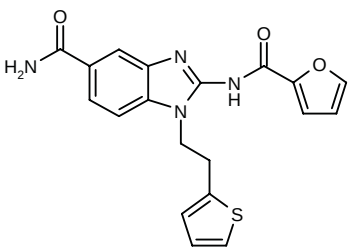
Fig. 21.



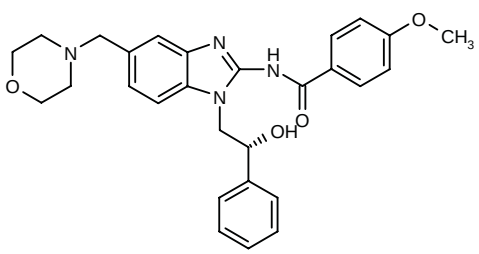
Y_5: IC_{50} = 170 nM



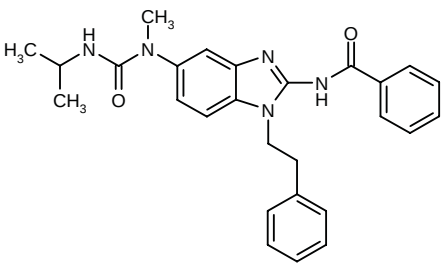
Y_5: IC_{50} = 40 nM



Y_5: pIC_{50} = 7.5 nM

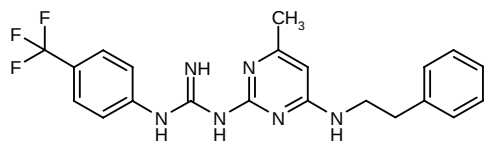


Y_5: IC_{50} = 24 nM



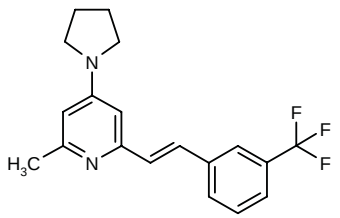
Y_5: IC_{50} = 81 nM

Fig. 22.



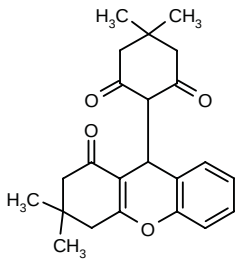
Y_5: IC_{50} = 6 nM

Fig. 23.



Y_5: IC_{50} = 4 nM

Fig. 24.



L-152804
Y_5: K_i = 26 nM
IC_{50} $[Ca^{2+}]_i$ (100 nM NPY) = 210 nM

Fig. 25.

compound was demonstrated to be metabolically robust and permeable in a kidney cell line and able to penetrate into brain of whole animals. However, a related analog was extensively degraded in rat liver. In any event, the GlaxoSmithKline series holds much promise given the simplicity of the structures, the chemistry used to construct the compounds and the rich diversity of highly active small-molecule Y_5 antagonists.

The GlaxoSmithKline group has also disclosed a bis-heteroaryl guandine that is a potent Y_5 antagonist that reduced food consumption in a dose-dependent manner in Zucker fatty rats (Fig. 23) (69).

Banyu has disclosed a series of aminopyridines that are remarkably simple but yet bind with exquisite affinity. For example, (*E*)-2-methyl-4-pyrrolidino-6-[2-(3-trifluoromethylphenyl)vinyl]pyridine was reported to have a K_i value of 4 nM (Fig. 24) (70).

Banyu has also reported on a series of (oxoxanthenyl)cyclohexane-1,3-diones as Y_5 antagonists (71). As part of a collaborative effort with Merck,

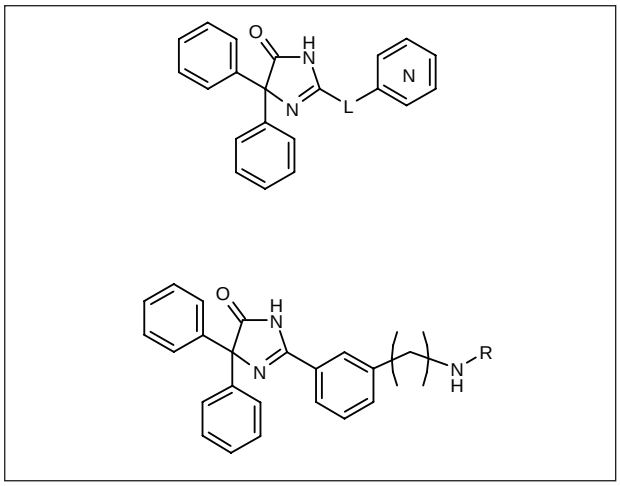


Fig. 26.

L-152804 (Fig. 25) has emerged as a leading compound of the series. L-152804 is reported to bind to both human and rat Y_5 with nanomolar affinity and to inhibit NPY-induced increases in intracellular calcium levels in cells expressing recombinant receptor (72). Furthermore, L-152804, administered i.c.v. (30 μg) or orally (10 mg/kg), inhibited food intake evoked by i.c.v.-injected bovine pancreatic polypeptide (bPP, 5 μg given i.c.v.) in satiated rats. However, it was not effective in suppressing NPY-induced feeding, thus fueling speculation that the Y_5 receptor does not elicit feeding effects of NPY (at least exogenously applied).

Bristol-Myers-Squibb has disclosed a vast series of imidazolone-derived Y_5 antagonists but pharmacological data was not included (Fig. 26) (73, 74).

Similarly, Neurogen reported on a broad series of diaryl imidazoles as Y_5 antagonists although no pharmacological data was given (Fig. 27) (75). Some of these compounds may not be novel in terms of composition of matter but are striking in terms of structural simplicity.

Pfizer claimed a somewhat related series of arylated imidazoles and a (piperazinyl)pyridine group seems to be a preferred substituent (Fig. 28) (76).

Merck-Banyu reported on a series of spiro-indolines as neuropeptide Y Y_5 antagonists (Fig. 29) (77). The work encompasses a broad variety of substituted aromatic and heterocyclic aromatic groups that are joined by way of a urea linkage to the spiro-system. One compound was highlighted as suppressing (i.c.v. administered) bPP-induced food intake in a dose-dependent manner without causing adverse side effects.

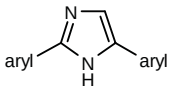


Fig. 27.

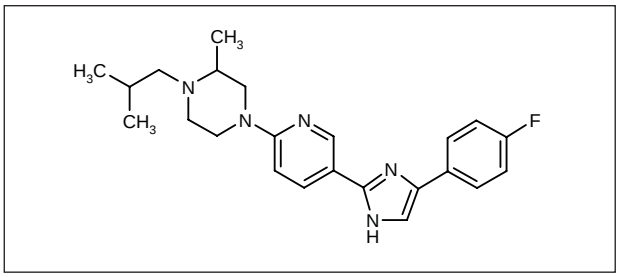


Fig. 28.

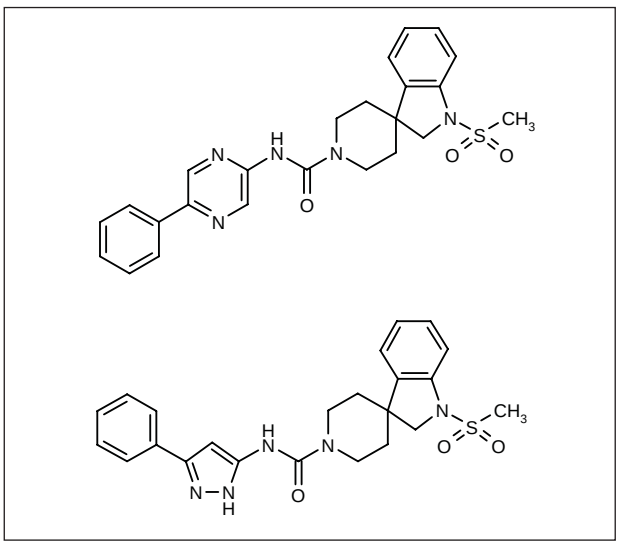


Fig. 29.

Amgen has recently reported the SAR of a series of pyrrolopyrimidine-based Y_5 antagonists (Fig. 30) (78, 79). This impressive work encompasses a number of synthetic approaches and the preparation of a host of diverse compounds, including congeners that bind with low or even subnanomolar affinity. In addition, the researchers put forth a pharmacophore model for the human NPY Y_5 receptor based upon the SAR of their series.

Novartis has pursued a series of substituted benzenesulfonamides that have potent Y_5 affinity (Fig. 31) (80) but yet are structurally distinct from the sulfonamido series including the work by the group at Synaptic.

Research at Bayer led to the discovery of a series of heterocyclic ketonic sulfones that are potent neuropeptide Y Y_5 antagonists (Fig. 32) (81). The chemistry used to make these compounds is elegant in making use of uncommon cyclobutenedione intermediates. The most potent compounds disclosed bind with submicromolar affinity to both rat and human Y_5 and are selective in having extremely poor affinity for Y_1, Y_2 and Y_4.

Conclusions

It is clear from the many series of structurally diverse small-molecule neuropeptide Y Y_5 antagonists that research continues at a rapid pace and that great advances have been made in developing Y_5 selective antagonists. However, while some studies have been encouraging in terms of reducing food consumption or body weight in controlled animal experiments, there have

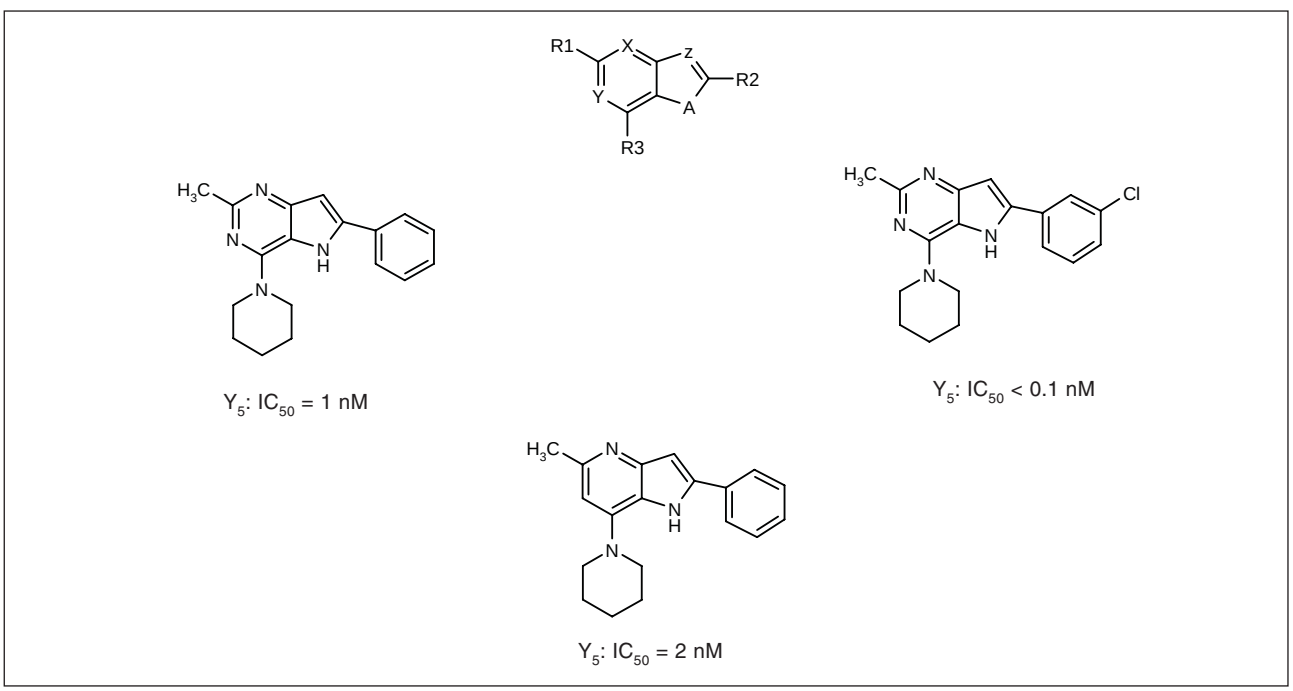


Fig. 30.

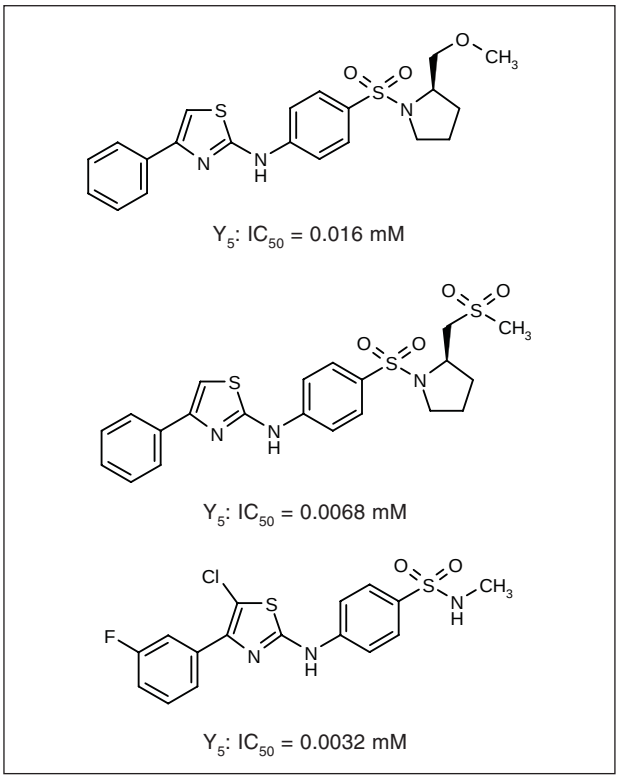


Fig. 31.

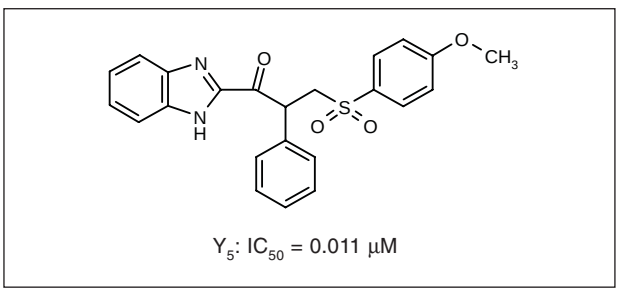


Fig. 32.

been other reports that question Y_5 antagonism as a strategy to combat obesity in humans (82). The issue remains unresolved since, to date, no Y_5 antagonist has entered human clinical trials. The enormous task of setting up suitable human trials and the complexity of targeting obesity or changes in body weight as an endpoint, are sure to be major obstacles in bringing any Y_5 compound to market. Furthermore, in retrospect, given the many biological systems and social factors that influence eating, it may be overly ambitious to rely on antagonism of a lone receptor as a means to alter such an innate behavior such as feeding. That said, NPY research, nonetheless, is entering an era in which many of these fundamental questions may now be answered, in part due to the birth of many series of potent Y_5 antagonists.

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