Non-Monoamine-Based Approach for the Treatment of Depression and Anxiety Disorders

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Abstract: Although currently prescribed antidepressants with actions mediated through alteration of monoaminergic transmission have been proven to be useful for the treatment of depressive and anxiety disorders, they are far from ideal due to their slow onset of action and low rate of responses. Although the brain monoamine systems have long been the focus of drug therapy for depression and anxiety disorders, current drug discovery has aimed at new molecular targets outside the monoamine systems to overcome these problems. Recent increase in understanding of the molecular mechanisms of depression and anxiety has provided alternative molecular targets for these disorders. In particular, receptors within the glutamate, γ-aminobutyric acid and neuropeptide systems provide a diversity of drug targets, and molecular biological and behavioral studies of these receptors have revealed the important roles they play in depression and anxiety. Here, we review recent patents and advances in research on these emerging molecular targets for the treatment of depression and anxiety, and discuss their advantages over currently used antidepressants and anxiolytics.

Keywords: Antidepressant, anxiolytic, group I mGluR antagonist, group II mGluR agonist, group II mGluR antagonist, AMPA potentiator, $GABA_B$ positive modulator, $GABA_B$ antagonist, NK_1 antagonist, NK_2 antagonist, CRF_1 antagonist, V_{1a} antagonist, V_{1b} antagonist, MCH1R antagonist, MC_4 anatgonist.

INTRODUCTION

Major depressive disorder and anxiety disorders are among the most prevalent forms of mental illness. In the United States, it is estimated that 21% of women and 13% of men will suffer major depressive disorder at some point in their lifetime, and that, together with anxiety disorders, more than 20% of the adult population will suffer from these conditions at some point in life.

All current antidepressant medications have stemmed from study of the mechanisms of serendipitously discovered agents, the tricyclic antidepressants (e.g., imipramine) and the monoamine oxidase inhibitors (e.g., iproniazid), which exhibit effects *via* modulation of monoamine neurotransmission. This study has led to the development of newer generation antidepressants, the selective serotonin reuptake inhibitors (SSRIs) and serotonin- and noradrenaline reuptake inhibitors (SNRIs), both of which are widely prescribed today. These agents have a less serious side effect profile than first-generation drugs, but are neither more efficacious nor rapidly acting than them. Although the large majority of individuals (~70%) with depression exhibit some improvement with antidepressant medication, only ~50% of all patients exhibit remission. Moreover, currently used antidepressants require 3-6 weeks for manifestation of significant therapeutic effects.

Although many patients with anxiety disorders have been successfully treated with benzodiazepines (BZDs) in short-term use, long-term use of BDZs have been shown to increase the risk of drug dependence. Moreover, the clinical effectiveness of BDZs is limited to generalized anxiety disorder and the acute phase of panic disorder, and they failed to improve symptoms in patients with obsessive-compulsive disorder [1]. It has recently been found that antidepressants such as SSRIs and SNRIs are more effective for most anxiety disorders than BDZs, and they have become first-line treatment for these disorders as well [2]. SSRIs are now widely used for panic disorder, post-traumatic stress disorder, and obsessive-compulsive disorder, and SSRIs such as paroxetine and SNRIs such as venlafaxine have been approved for the treatment of generalized anxiety disorder. However, these medications usually take several weeks to exhibit effects, as in the case of depression.

Many of the drawbacks of current medications for depression and anxiety are likely related to the mechanisms of action of these medications. To overcome these drawbacks, the focus of drug discovery research has therefore recently shifted to non-monoamine-based strategies. Apart from biogenic amine theory, alternative hypotheses regarding the origin of depression have recently provided the rationale for new strategies for the development of antidepressants and anxiolytics. Selective compounds based on new strategies are now available for testing in animal and human studies, and some encouraging results have been obtained with them.

In this review, we focus on some attractive and seemingly promising molecular targets for the treatment of depression and anxiety, and covers patents for compounds emerging from study of these targets.

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GLUTAMATE

Glutamate is the major excitatory neurotransmitter in the brain, and is involved in a wide range of physiological processes in the central nervous system (CNS) including emotion, cognition, and motor function. Dysfunction of excitatory amino acid transmission may play a role in the etiology and pathophysiology of depression [3]. Indeed, it has been reported that a single intravenous dose of ketamine (a noncompetitive NMDA receptor antagonist) had rapid and prolonged antidepressant effects in depressed patients [4]. At present, glutamate receptors are classified into two major types: ionotropic glutamate receptors (iGluRs), in which the receptors have an ion channel structure, and metabotropic glutamate receptors (mGluRs), which are coupled to G-proteins [5]. IGluRs are also classified into *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-isoxazole-4-propionate (AMPA) and kainate receptors [5]. MGluRs are classified into three groups based on their sequence homology, second messenger coupling and pharmacological characteristics [6]. Group I mGluRs include mGluR1 and mGluR5, which are coupled to phospholipase C, while both group II mGluRs (mGluR2, mGluR3) and group III mGluRs (mGluR4, mGluR6, mGluR7, mGluR8) are negatively coupled to adenyly cyclase activity. Of these, both group I and group II mGluR ligands as well as AMPA receptor potentiators have become the focus of much attention in recent years, based on findings concerning of their distribution in the brain and preclinical animal studies with selective ligands.

Group I mGluR Antagonists (mGluR1 Antagonists, mGluR5 Antagonists)

Both mGluR1 and mGluR5 are expressed in the brain regions related to emotion, whereas mGluR5 is more abundantly expressed throughout the cerebral cortex, hippocampus and limbic system [7]. The recent discovery of mGluR5 receptor selective antagonists has revealed important roles of mGluR5 in depression and anxiety. It has, for example, been reported that a selective and noncompetitive mGluR5 antagonist, MPEP (Fig. **1**), attenuated learning deficits in the passive avoidance paradigm in the rat olfactory bulbectomy model [8] and shortened immobility in the mouse tail suspension test [7,9], suggesting antidepressant-like potential. Moreover, MPEP has been demonstrated to exhibit anxiolytic effects in a variety of animal models of anxiety including tests involving the exploratory component, conflict component and stress component [7-9], and these effects were also observed with a newly synthesized mGluR5 antagonist, MTEP (Fig. **1**) [10]. The anxiolytic-like effects of mGluR5 antagonists appear to be of the same magnitude as those of the BDZs, but with improved side effect liabilities. The anxiolytic-like potential of mGluR5 antagonists is consistent with the finding for KO mice lacking mGluR5 of an anxiolytic-like phenotype in the stress-induced hyperthermia test [11].

Unlike mGluR5 antagonists, the anxiolytic-like potential of mGluR1 antagonists has not been fully examined. It has recently been reported that JNJ16259685 (Fig. **2**), a selective and noncompetitive mGluR1 antagonist, exhibits anxiolytic effects in rodents in the conflict drinking test, but that these effects are task-dependent [12]. Likewise, anxiolytic effects were observed with another mGluR1 antagonist, LY456236 (Fig. **2**), although they were not as potent as those of mGluR5 antagonists and BDZs [13]. Of note, it has been reported that mGluR1 receptor antagonists disrupted hippocampal long-term potentiation and spatial learning [14].

More than twenty patent applications presenting mGluR5 antagonists have been published from 2003 through 2005 (Fig. **1**). Many of compounds provided in the applications have two or more aromatic rings, which are connected by a heterocyclic ring or acetylene moiety.

In 2003 and 2004, a series of patent applications presenting mGluR5 antagonists were published by Merck (e.g. compounds (**1**) - (**9**)) [15- 3]. The compounds described in the applications have the same structural feature: a 5-membered heterocyclic ring (pyrrole, imidazole, pyrazole, triazole, tetrazole), substituted with other two aromatic rings at the 1 and 3 positions. One of the aromatic rings is a 2-pyridyl group, and the other is a substituted phenyl group. Merck also published mGluR5 antagonist-related applications presenting different types of compounds (e.g. compounds (**10**) and (**11**)) [24,25].

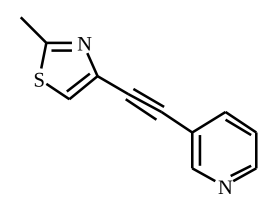
Compounds in patent applications from F. Hoffmann-La Roche AG contain an acethylene moiety functioning as a linker between two heterocyclic rings (compounds (**12**) - (**15**)) [26 - 29].

Compounds (**16**) - (**20**) [30 - 34] are examples in applications from Euro-celtique, of compounds either having or not having an acethylene linker.

Applications from AstraZeneca exemplify compounds possessing various heteroaromatic rings (e.g. compounds (**21**)-(**24**)) [35-38]. Compound (**25**) [39] and compound (**26**) [140] are examples in applications from Addex Pharmaceuticals and Novartis, respectively.

Group II mGluR Agonists and Antagonists

Group II mGluR is abundantly localized within forebrain regions, where it modulates glutamate transmission *via* presynaptic and postsynaptic mechanisms [41]. Forebrain areas that express group II mGluR include limbic structures that participate in the control of emotion. Thus, compounds acting on group II mGluRs may possibly modulate emotional states. This hypothesis is supported by the findings that oral administration of a selective group II mGluR agonist, LY354740 (Fig. **3**), showed anxiolytic-like effects in fear-potentiated startle in rats and elevated plus maze models in mice [42,43]. LY354740 also produced anxiolytic-like effects in the Vogel test in rats and a four-plate test in mice [44]. Moreover, LY354740 has been reported to prevent lactate-induced panic-like response in panic-prone rats, as did alprazolam, a clinically effective anti-panic drug [45]. Thus, group II mGluR agonists might be effective for panic disorder, a severe and often debilitating condition among anxiety disorders. Unlike BDZs, LY354740 did not exhibit undesirable CNS side effects such as sedation, deficits in neuromuscular coordination, interaction with CNS depressants, memory impairement or change in convulsive threshold at the pharmacologically effective dosage. Clinical results with LY354740 and its prodrug LY544344 have



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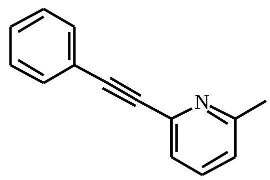
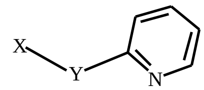


MPEP



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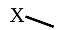
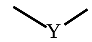
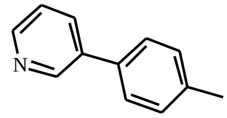
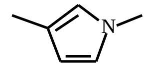
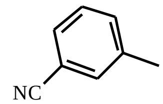
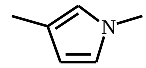
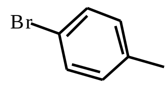
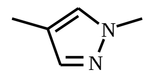
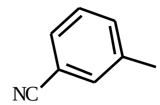
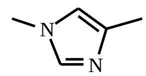
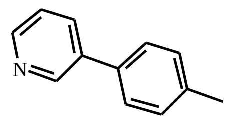
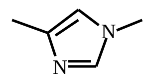
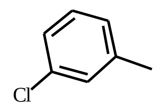
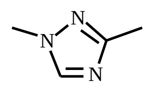
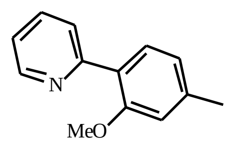
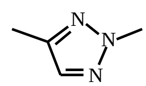
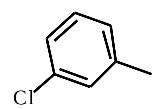
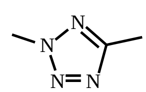
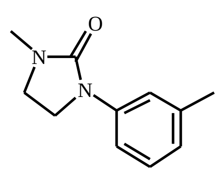
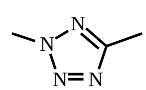
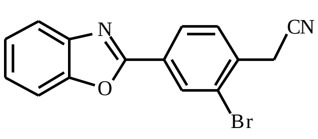
	 :	 :
1		
2		
3		
4		
5		
6		
7		
8		
9		



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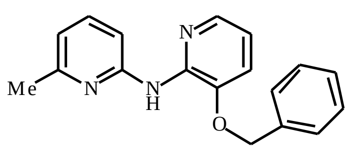

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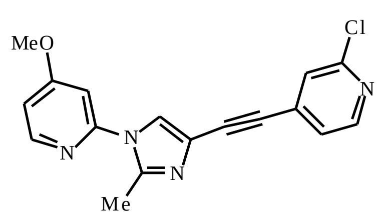

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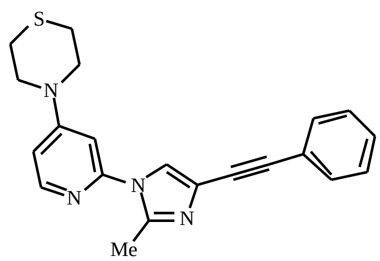

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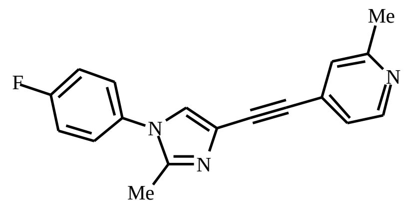

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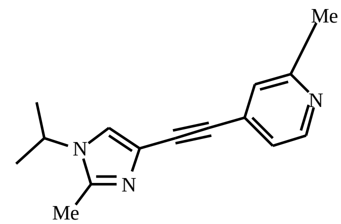

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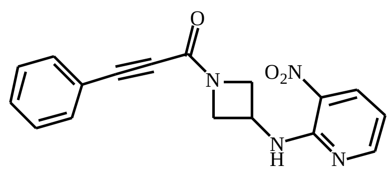

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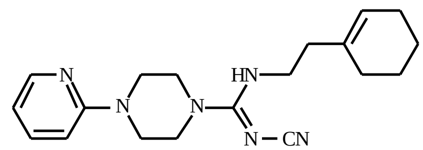

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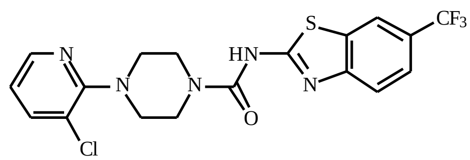

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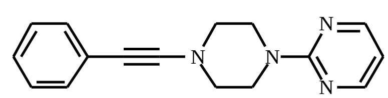

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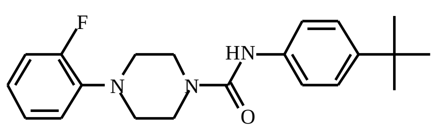

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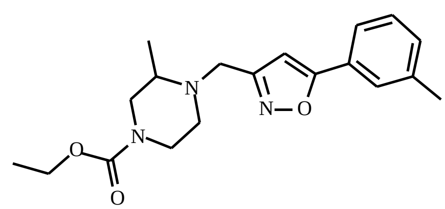

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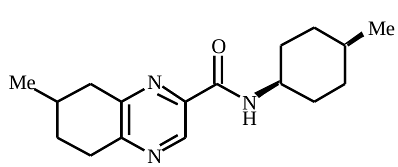

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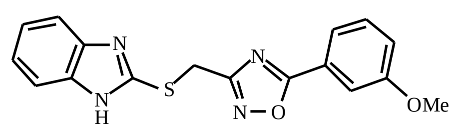

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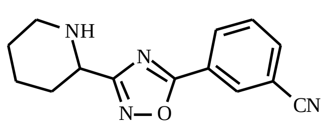

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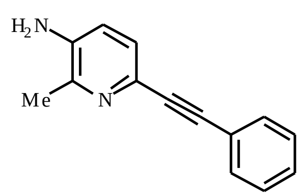

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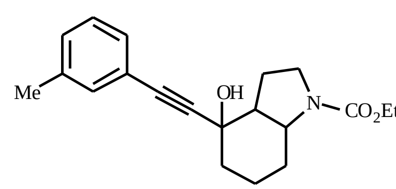

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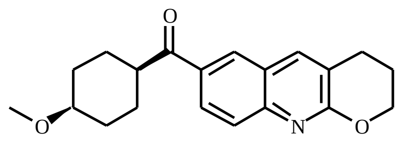
Fig. (1). mGluR5 antagonists.



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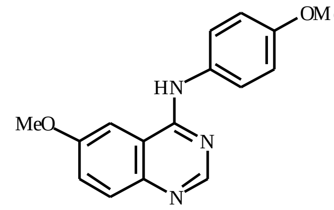

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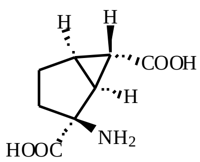
Fig. (2). mGluR1 antagonists.



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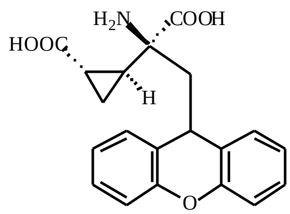

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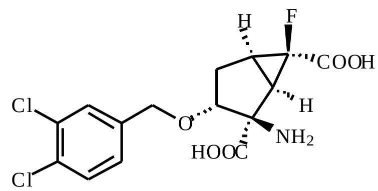

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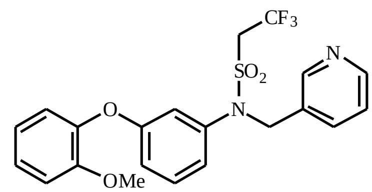

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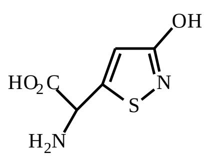

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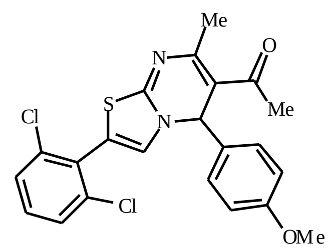

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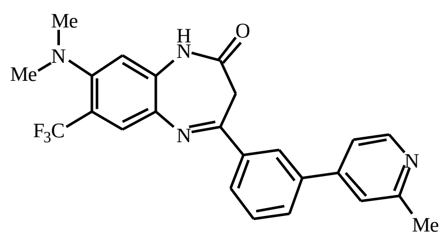

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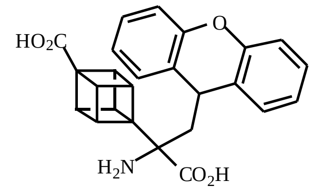

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Fig. (3). mGluR2 agonists, antagonists and allosteric potentiators.

demonstrated anxiolytic-like efficacy in a model of panic disorder (panic provocation induced by CO_2 challenge in subjects with panic disorder) [46] and in a fear-potentiated startle reflex paradigm in healthy volunteers [47], although clinical trials have been suspended because of increased probability of epileptic seizures in rodents. However, new possibilities are being pursued with recently generated mGluR2 selective allosteric potentiators [48,49]. Of note, significant *in vivo* anxiolytic and antipsychotic activities were confirmed with selective mGluR2 allosteric potentiators [48,49].

We recently found that group II mGluR antagonists exhibited antidepressant-like activity in behavioral despair models (forced swim test and tail suspension test) [50], while LY354740, a group II mGluR agonist, did not exhibit antidepressant-like effects in these models [44]. Moreover, MGS0039 (Fig. **3**), a selective group II mGluR antagonist, increased progenitor cell proliferation in the hippocampus [51] and increased serotonergic transmission [52], both of which are considered mechanisms of antidepressant-like activity. Consistent with these findings, it has been reported that LY341495 (Fig. **3**), another group II mGluR antagonist, attenuates anhedonia after nicotine withdrawal [53], providing additional evidence for its antidepressant-like potential. Given that NMDA receptor antagonists including ketamine have been shown to increase glutamate release in the nucleus accumbens [54] and that KO mice lacking mGluR7 [55], which function as autoreceptors, display an antidepressant phenotype, increase in glutamate release in certain brain regions may be a useful strategy of treatment of depression. Moreover, group II mGluR antagonists have been shown to be effective in the mouse marble burying test, an animal model predictive of obsessive-compulsive disorder [56]. In contrast, MGS0039, unlike group II mGluR agonists, exhibited no appreciable anxiolytic-like activity with acute administration in classical anxiety paradigms such as elevated plus-maze and social interaction [50].

A few patent applications presenting mGluR2 agonists (e.g. compound (**27**)) [57] and antagonists (e.g. compound (**28**) and (**29**)) [58,59] have been published in 2003-2005 (Fig. **3**). Compound (**30**) [60] has a glutamate-analogue moiety and compound (**27**) is a glutamate analogue presented as LY354740. In contrast, non-glutamate analogues were provided as mGluR2 antagonists by Hoffmann-La Roche (compound (**28**) and (**29**)) [58,59]. They have aromatic rings in the structures, and their structural features differ considerably from those of LY341495 and MGS0039, both of which include a glutamate analogue. Compound (**29**) has been reported to have an IC_{50} value of 1.2 nM for mGluR2. It is intriguing that both types of compounds, glutamate analogues and non-glutamate analogues, exhibit high affinities for mGluR2. Eli Lilly reported selective mGluR2 allosteric potentiators (e.g. 3-MPPTS) (Fig. **3**), which exhibited *in vivo* activities [48].

AMPA Receptor Potentiators

During the past several years, an emerging body of evidence has suggested that enhanced AMPA-mediated transmission may be responsible in part for the efficacy of antidepressants, and that stimulation of AMPA receptors may have antidepressant effects in preclinical animal models of depression. Chronic, but not acute, administration of antidepressants such as desipramine and paroxetine increased GluR1 and GluR2/3 levels in the membrane fractions of hippocampal extracts while not affecting levels in total extract [61], indicating increased trafficking of AMPA receptors. In addition, fluoxetine increased phosphorylation of the AMPA receptor GluR1 subunit, which in turn increases the efficacy of AMPA receptors, and this has been suggested to play an important role in mediating the antidepressant effects of fluoxetine [62]. Thus, these findings suggest that enhancement of AMPA-mediated transmission may play a role in the neuronal mechanisms responsible for the efficacy of antidepressants.

It has been reported that AMPA receptor potentiators such as LY392098 (Fig. **4**) [63], LY404187 (Fig. **4**) [64] and LY451646 (an active isomer of LY404187) [65] exhibit antidepressant-like activity in the forced swim test and tail suspension test without affecting motor activity. Moreover, it was reported that Ampakines, which are AMPA receptor potentiators, exhibited antidepressant effects during the 1^{st} week of treatment, while fluoxetine exerted effects after 2 weeks of treatment in a rat submissive behavior model [66], suggesting faster onset of action, compared to current medication.

It has been found that an AMPA potentiator increases brain-derived neurotrophic factor (BDNF) mRNA expression in the hippocampus [67] and increases adult hippocampal neurogenesis [68]. Converging lines of evidence suggest that BDNF and hippocampal neurogenesis may be a pivotal downstream mediator of antidepressant effects [69]. Chronic, but not acute, treatment with a structurally diverse group of antidepressants as well as electroconvulsive shock have been reported to elevate hippocampal levels of mRNA encoding BDNF as well as hippocampal neurogenesis [69,70], and BDNF has been found to exhibit antidepressant-like activity in animal models [71]. Interestingly, an AMPA receptor potentiator has been reported to tend to increase neurogenesis even after a single injection [68], consistent with the faster onset of action observed in the behavioral study [66].

Several patent applications providing AMPA receptor potentiators have been published by Les Laboratories Servier (Fig. **4**), e.g. compounds (**31**)-(**36**)) [72-77] and Neurosearch (compounds (**37**)) [78]. Most of the compounds have two or three ring systems that contain a sulfonyl amide moiety. Side chains attached to the ring systems are diverse and may thereforeplay key roles in determining the degree to which AMPA receptor activity is potentiated.

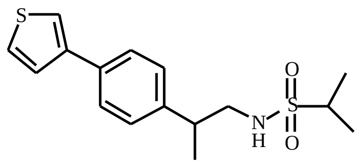
GABA

γ-Aminobutyric acid (GABA) is the most abundant inhibitory neurotransmitter in the mammalian brain, where it is widely distributed. It has recently been suggested that major depressive disorder as well as anxiety disorders are associated with dysfunction of GABAergic transmission [79]. There are two major receptor subtypes of GABA: ionotropic $GABA_A$ receptors and metabotropic $GABA_B$ receptors [80]. The involvement of $GABA_A$ receptors in anxiety disorders has been well investigated and established. However, recent studies using selective $GABA_B$ ligands (both antagonists and positive modulators) and KO mice lacking functional $GABA_B$ receptors have demonstrated important roles of the $GABA_B$ receptor subtype in depression and anxiety.

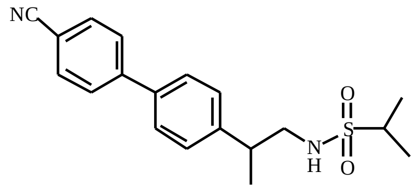
$GABA_B$ Receptor Positive Allosteric Modulators and Antagonists

$GABA_B$ receptors are abundant in the brain, particularly, in the limbic system, suggesting that they play roles in regulation of mood and affect. It has been reported that functional $GABA_B$ receptors exist as heterodimers of two subunits, $GABA_{B(1)}$ and $GABA_{B(2)}$. The findings that $GABA_B$-mediated responses are blunted in mice lacking either $GABA_{B(1)}$ or $GABA_{B(2)}$ [81] confirm that heterodimerization of $GABA_{B(1)}$ and $GABA_{B(2)}$ is necessary for receptor function. It has been found that a $GABA_B$ receptor positive modulator, GS39783, exhibits anxiolytic effects in several models such as the elevated plus-maze, elevated zero maze, light/dark box and stress-induced hyperhermia without causing the unwanted side effects observed with BDZs [82,83]. Thus, $GABA_B$ receptor positive modulators may represent a novel class of anxiolytics with a safety profile superior to that of BDZs. In accordance with these observations, $GABA_{B(1)}$-/- mice have been reported to be more anxious than wild type mice [83].

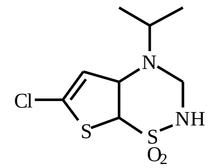
In contrast, mice with disrupted $GABA_{B(1)}$ display an antidepressant-like phenotype, with decreased immobility in the forced swim test, suggesting that blockade of $GABA_B$ receptors may serve as a novel strategy for the treatment of



LY392098



LY404187/LY451646



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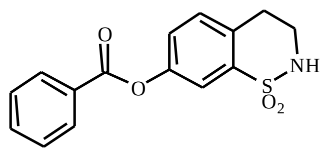

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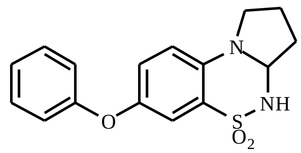

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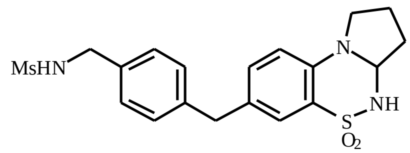

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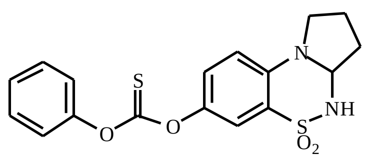

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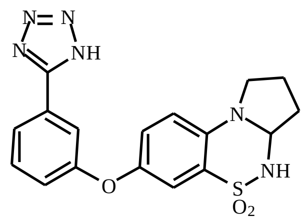

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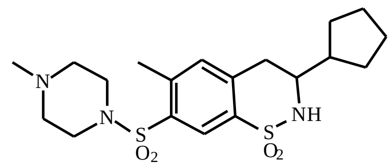

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Fig. (4). AMPA receptor potentiators.

depression [83]. In support of this, it has been reported that the $GABA_B$ receptor antagonists CGP56433A (Fig. **5**) and CGP36742 (Fig. **5**) exhibit antidepressant effects in the forced swim test and the learned helplessness test, respectively [83-85]. Moreover, it has been reported that, in the forced swim test, $GABA_B$ receptor antagonists increased swimming behavior, as observed with SSRIs, and serotonergic transmission has been suggested to play a role in mediating the antidepressant effects of $GABA_B$ receptor antagonists [85]. Given that $GABA_B$ receptors play a role in inhibiting the firing of serotonin-containing cells in the dorsal raphe nucleus [86], interaction with the serotonergic system may account for the antidepressant effects of $GABA_B$ receptor antagonists. Interestingly, it has also been reported that $GABA_B$ receptor antagonists increase BDNF mRNA in the brain, including the hippocampus [87], which may contribute to antidepressant effects [71].

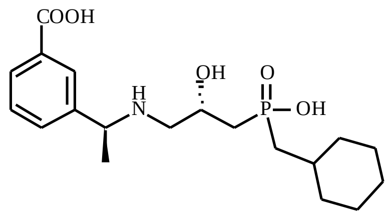
In 1989, an application for 3-aminopropyl phosphinic acids derivatives as $GABA_B$ receptor antagonists was published by Ciba-Geigy Corporation. Few applications for $GABA_B$ antagonists were published for about the next ten years. In 2001 and 2002, however, a few applications presenting new types of 3-aminoprpyl phosphinic acids for $GABA_B$ antagonists were published by AstraZeneca (Fig. **5**), compounds (**38**) – (**40**)) [88 - 90]. The claimed structures in the applications have a hydrogen, methyl, or mono-, di- or tri-fluoro methyl group on the phosphorus atom, differentiating them from those in previous patents. No biological data were provided in these applications.

NEUROPEPTIDES

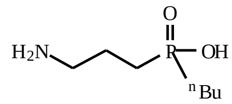
It has recently come to be recognized that stress may be the primary cause of depression and anxiety disorders. In the brain, short-chain amino acid neurotransmitters, the neuropeptides, have been suggested to play a pivotal role in stress responses. These peptides are locally produced in particular brain regions and their expression and release are altered upon exposure to stress. With recent advances in cloning of each receptor subtype gene, identification of selective nonpeptidic compounds for each receptor, as well as behavioral and neurochemical analyses using mice with targeted gene mutations, the roles of neuropeptides and their receptors in stress responses and emotional states have been delineated, and many neuropeptide systems have emerged as attractive targets in the treatment of stress-related disorders such as depression and anxiety [91]. Of these, tachykinins, corticotropin-releasing factor (CRF) and arginine vasopressin (AVP) have been well studied as regards their relationships with stress-related disorders, and clinical studies with selective antagonists for these peptide receptors are ongoing. In addition to these peptidergic systems, the list of neuropeptide systems implicated in stress responses and proposed as therapeutic targets for depression and anxiety disorders is growing.

Tachykinin Receptor Antagonists (NK_1 Receptor Antagonists, NK_2 Receptor Antagonists)

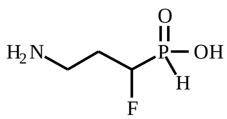
The tachykinins are a family of closely related peptides, mainly consisting of substance P, neurokinin A and



CGP56433A



CGP36742



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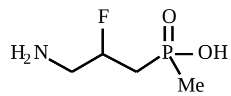

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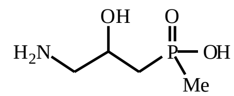

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Fig. (5). GABA$_B$ receptor antagonists.

neurokinin B. To date, three tachykinin receptor subtypes, NK$_1$, NK$_2$, NK$_3$, have been identified [92], all three of which are distributed in the CNS through with different levels of expression [92]. Of these, both NK$_1$ (the receptor for substance P) and NK$_2$ (the receptor for neurokinin A) receptors have been proposed to play important roles in depression and anxiety.

Selective nonpeptidic antagonists for each of these receptors have been developed, and their antidepressant and anxiolytic effects have been demonstrated. Although there are marked species differences in the pharmacological properties of NK$_1$ receptors, behavioral studies in species (guinea pigs, gerbils) whose pharmacological and molecular properties are closer to those in humans have provided evidence that NK$_1$ receptor antagonists exhibit antidepressant and anxiolytic-like activities in numerous animal models [93-96]. Consistent with the results obtained with NK$_1$ receptor antagonists, KO mice lacking NK$_1$ receptors exhibited reduced anxiety and depressive-like behaviors [97]. Moreover, antidepressant efficacy was demonstrated in patients with major depressive disorder in placebo-controlled trials with two highly selective NK$_1$ receptor antagonists, aprepitant (Fig. **6**) and L-759274 [93,94]. Although treatment with aprepitant in Phase II trials resulted in improvements in depression and anxiety symptoms that were quantitatively comparable to those with SSRIs and significantly greater than those with placebo, Merck recently announced discontinuation of the Phase III clinical development of aprepitant due to lack of demonstrable efficacy for depression.

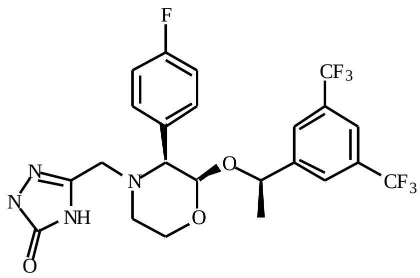
Likewise, selective NK$_2$ receptor antagonists including SR48968 (Fig. **7**) exhibit antidepressant and anxiolytic effects in several animal models [99,100] such as the force swim test, maternal separation-induced vocalization and elevated plus-maze task. Interestingly, SR48968 increased the expression of cAMP response element binding (CREB) protein mRNA in the hippocampus after repeated administration [100]. Moreover, an NK$_2$ receptor antagonist exhibited anxiolytic effects in the marmoset human intruder response test [101]. SR48968 is currently in Phase III clinical trials for depression.

In 2004 and 2005, more than ten patent applications providing NK$_1$ receptor antagonists have been published (Fig. **6**). Notably, many of the representative compounds presented in the applications have a common structural element, a 3,5-bistrifluoromethyl phenyl group, although their frameworks differ markedly one another. Six applications from Janssen Pharmaceutica provided a series of piperazines substituted with two cyclic amines, and most of the examples in the applications included the 3,5-bistrifluoromethyl phenyl group (e.g. compounds (**41**) - (**46**)) [102 - 107]. The affinities for NK$_1$ receptors were presented for the representative compounds (Table **1**). From Pfizer Products (e.g. compound (**47**)) [108], Schering Corporation (e.g. compound (**48**)) [109], Merck Sharp & Dohme (e.g. compound (**49**)) [110], Merck & Co. (e.g. compound (**50**)) [111], and Solvay Pharmaceuticals (e.g. compound (**51**)) [112], applications related to NK$_1$ antagonists have recently been published, including many representative compounds with the 3,5-bistrifluoromethyl phenyl group. However, biological data are presented for only a few of these compounds (Table **1**). Solvay Phamaceutical indicated a pKi value (9.2) for compound (**51**), and Schering Corporation indicated that the Ki value for NK$_1$ receptors of compound (**48**) was 0.3 nM. Applications from Nikem Research (e.g. compound (**52**)) [113] and AstraZeneca (e.g. compounds (**53**) and (**54**)) [114,115] provided NK$_1$ & NK$_2$ receptor antagonists and NK$_1$ receptor antagonist & serotonin reuptake inhibitors, respectively. No data on receptor selectivity were presented for these compounds.

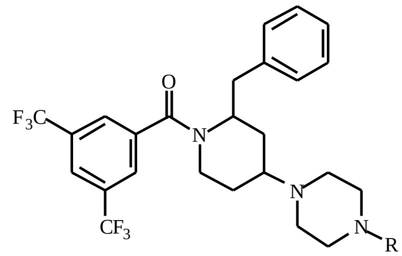
For NK$_2$ receptor antagonists, applications from SmithKline Beecham Corporation and Merck Sharp & Dohme Ltd. have recently been published (Fig. **7**). Example compounds in the applications have a quinoline ring, which is substituted with an aminocarbonyl group, a piperazinomethyl group, and an aromatic ring at the 4, 3, and 2 position, respectively (e.g. compounds (**55**) - (**58**)) [116 - 119]. They noted that the applications contained NK$_2$ and NK$_3$ receptor antagonists.

CRF$_1$ Receptor Antagonists

CRF is a 41-amino acid peptide originally purified from ovine hypothalamus [120]. It has been reported that CRF



aprepitant



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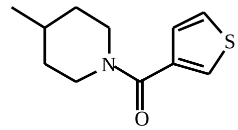

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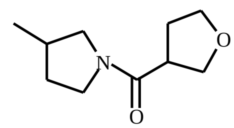

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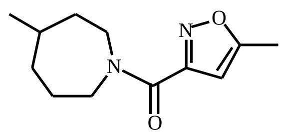

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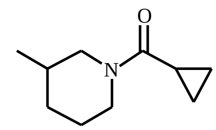

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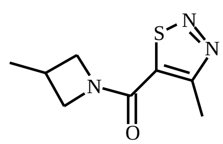

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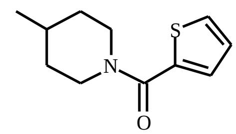

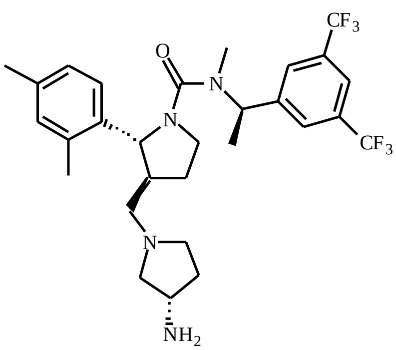

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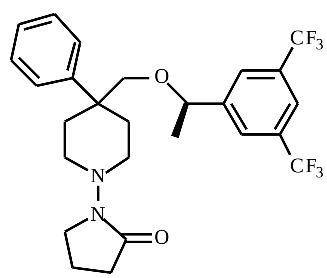

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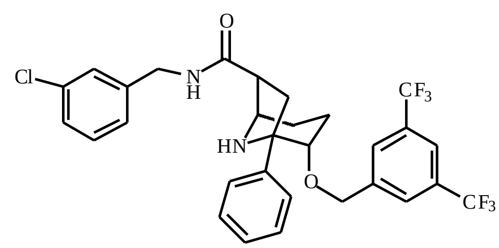

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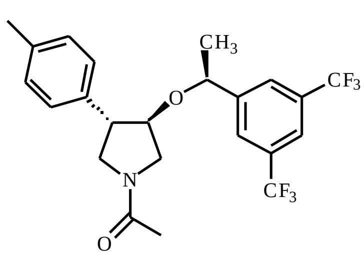

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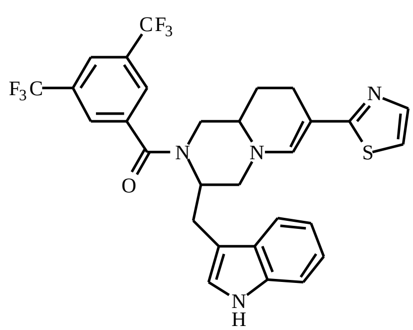

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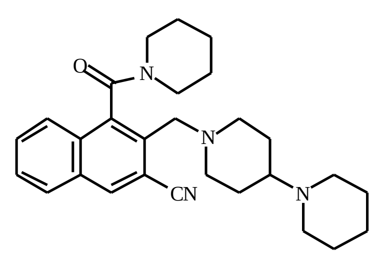

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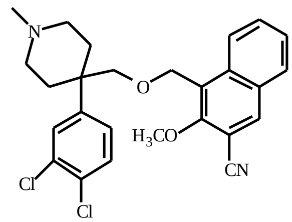

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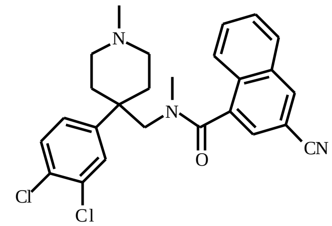

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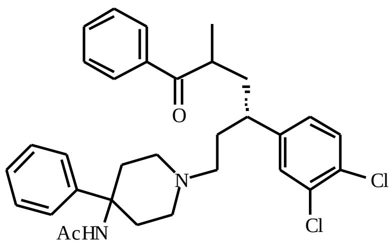
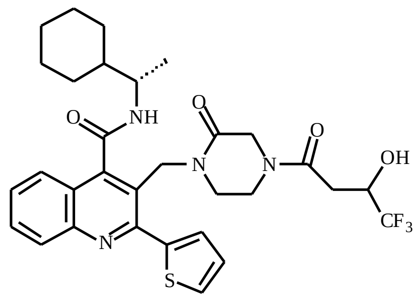
Fig. (6). NK1 receptor antagonists.



SR48968



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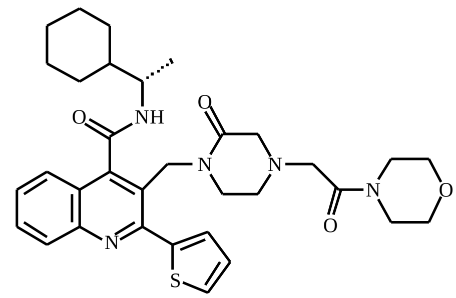

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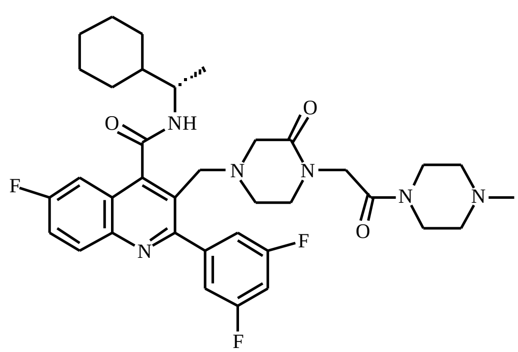

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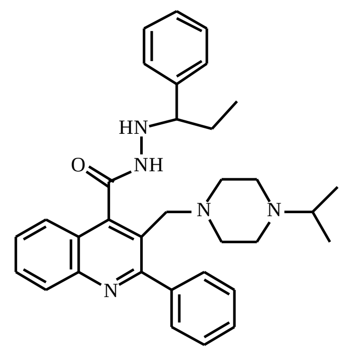

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Fig. (7). NK2 receptor antagonists.

plays a crucial role in adaptive responses to stress, as well as in the mediation of depressive and anxiety-like behavior [121]. It has been demonstrated that patients with major depressive disorder or post-traumatic stress disorder have increased cerebrospinal fluid levels of CRF [122]. Moreover, a blunted adrenocorticotropin (ACTH) response to i.v. injection of CRF has been found in patients with depression, anorexia nervosa and post-traumatic stress disorders [123,124]. CRF exerts effects through two receptor subtypes, CRF_1 and CRF_2, both of which are Gs coupled GPCRs [125], while the CRF_1 receptor has been emphasized to play a role in depressive- and anxiety-like behaviors. A number of nonpeptidic CRF_1 receptor antagonists have been introduced, and some of which, including CP-154,526 (Fig. **8**), DMP696 (Fig. **8**) and SSR125543A (Fig. **8**), have demonstrated antidepressant and anxiolytic effects in numerous rodent models, in particular those involving highly stressful conditions [126]. Moreover, we have recently reported that R278995/CRA0450 (Fig. **8**) exhibits antidepressant-like activity in the learned helplessness paradigm even with single administration, suggesting early onset of action [127]. In addition to rodent models, it has been demonstrated that antalarmin reduces anxiety-like behaviors in social stress models in a non-human primate [128]. Moreover, the results of the first open-label, dose-escalating trial with R121919 (Fig. **8**) in 20 patients with major depressive disorder revealed significant reduction in both depression and anxiety scores [129]. In a Phase II trial, R121919 was found to be safe and well-tolerated, although it produced slight elevation of liver enzyme levels [129].

Approximately twenty patent applications presenting new CRF_1 receptor antagonists have been published in 2004 and 2005 (Fig. **8**). All of the CRF_1 receptor antagonists provided in these applications have mono- or di-heterocyclic moieties in the central part of their structure. Various types of heterocyclic rings are used for this part: mono-heterocyclic rings such as pyrimidine and pyrazine, and di-heterocyclic

Table 1. Biological Data and References

compd	Biological data			reference
	target molecule	value		
1	mGluR5	IC_{50}	< 10 μM	15
2	mGluR5	IC_{50}	< 10 μM	16
3	mGluR5	IC_{50}	< 10 μM	17
4	mGluR5	IC_{50}	< 10 μM	18
5	mGluR5	IC_{50}	< 10 μM	19
6	mGluR5	IC_{50}	< 10 μM	20
7	mGluR5	IC_{50}	< 10 μM	21
8	mGluR5	IC_{50}	< 10 μM	22
9	mGluR5	IC_{50}	< 10 μM	23
10	mGluR5	IC_{50}	< 5 μM	24
11	mGluR5	IC_{50}	< 500 nM	25
12	mGluR5	Ki	12 nM	26
13	mGluR5	Ki	9 nM	27
14	mGluR5	IC_{50}	< 150 nM	28
15	mGluR5	Ki	68 nM	29
16	mGluR5	IC_{50}	110 nM	30
17	mGluR5	IC_{50}	59.4 nM	31
18	mGluR5			32
19	mGluR5	IC_{50}	555 nM	33
20	mGluR5	IC_{50}	< 10 μM	34
21	mGluR5	IC_{50}	< 10 μM	35
22	mGluR5	IC_{50}	50 nM	36
23	mGluR5	IC_{50}	< 10 μM	37
24	mGluR5	IC_{50}	50 nM	38
25	mGluR5	IC_{50}	10 μM	39
26	mGluR5			40
27	mGluR2			57
28	mGluR2	Ki	1-20 μM	58
29	mGluR2	Ki	1.2 nM	59
30	mGluR2			60
31	AMPA receptor	EC2X EC5X	4.2 +/- 0.7 μM 11 +/- 3 μM	72
32	AMPA receptor	EC2X EC5X	11.9 μM 49.3 μM	73

(Table 1) Contd….

compd	Biological data			reference
	target molecule	value		
33	AMPA receptor	EC2X EC5X	0.8 μM 3.6 μM	74
34	AMPA receptor	EC2X EC5X	0.1 μM 0.56 μM	75
35	AMPA receptor	EC2X EC5X	1.8 μM 9.6 μM	76
36	AMPA receptor	EC2X EC5X	0.2 μM 0.8 μM	77
37	AMPA receptor			78
38	$GABA_B$ receptor			88
39	$GABA_B$ receptor			89
40	$GABA_B$ receptor			90
41	NK1 receptor	pIC_{50}	10.0	102
42	NK1 receptor	pIC_{50}	7.55	103
43	NK1 receptor	pIC_{50}	8.13	104
44	NK1 receptor	pIC_{50}	8.5	105
45	NK1 receptor	pIC_{50}	8.5	106
46	NK1 receptor	pIC_{50}	10.0	107
47	NK1 receptor			108
48	NK1 receptor	Ki	0.3 nM	109
49	NK1 receptor			110
50	NK1 receptor			111
51	NK1 receptor			112
52	NK1 receptor			113
53	NK1 receptor			114
54	NK1 receptor			115
55	NK2 receptor			116
56	NK2 receptor			117
57	NK2 receptor			118
58	NK2 receptor			119
59	CRF1 receptor	IC_{50}	< 10 μM	130
60	CRF1 receptor	IC_{50}	< 10 μM	131
61	CRF1 receptor	pKi	6.91	132
62	CRF1 receptor	pKi	6.71	133
63	CRF1 receptor	pIC_{50}	7.3	134

(Table 1) Contd….

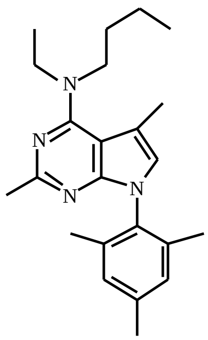
compd	Biological data			reference
	target molecule	value		
64	CRF1 receptor			135
65	CRF1 receptor			136
66	CRF1 receptor	Ki	< 5 nM	137
67	CRF1 receptor	Ki		138
68	CRF1 receptor	Ki	< 2 nM	139
69	CRF1 receptor	Ki	< 3 nM	140
70	CRF1 receptor			141
71	CRF1 receptor	Ki	< 10 μM	142
72	CRF1 receptor	Ki	< 10 μM	143
73	CRF1 receptor	Ki	< 10 μM	144
74	CRF1 receptor	Ki	< 10 μM	145
75	CRF1 receptor	Ki	< 1 μM	146
76	CRF1 receptor			147
77	CRF1 receptor	IC_{50}	1-500 nM	148
78	CRF1 receptor			149
79	V1a receptor	IC_{50}	5 nM	161
80	V1a receptor	Ki	4.5 nM	162
81	V1b receptor	IC_{50}	3.4 nM	163
82	V1b receptor			164
83	V1b receptor			165
84	MCH1R	Ki	2.4 nM	176
85	MCH1R	Ki	21 nM	177
86	MCH1R	Ki	0.4 nM	178
87	MCH1R	Ki	0.3 nM	179
88	MCH1R	IC_{50}	2.1 nM	180
89	MCH1R	IC_{50}	17 nM	181
90	MCH1R	IC_{50}	8.0 nM	182
91	MCH1R	IC_{50}	3.3 nM	183
92	MCH1R	IC_{50}	7.0 nM	184
93	MCH1R	IC_{50}	0.2 nM	185
94	MCH1R	IC_{50}	3.7 nM	186
95	MCH1R	IC_{50}	2.0 nM	187
96	MCH1R	Ki	1.7 nM	188

(Table 1) Contd….

compd	Biological data			reference
	target molecule	value		
97	MCH1R	Ki	3 nM	189
98	MCH1R	Ki	6.4 nM	190
99	MCH1R	Ki	< 30 nM	191
100	MCH1R	Ki	6-10 nM	192
101	MCH1R	IC_{50}	< 100 nM	193
102	MCH1R	IC_{50}	< 100 nM	194
103	MCH1R			195
104	MCH1R			196
105	MCH1R	IC_{50}	27 nM	197
106	MCH1R	IC_{50}	5 nM	198
107	MCH1R			199
108	MCH1R			200
109	MCH1R			201
110	MCH1R	IC_{50}	0.18 nM	202
111	MCH1R	IC_{50}	1.47 μM	203
112	MCH1R	IC_{50}	60 nM	204
113	MCH1R	IC_{50}	3 nM	205
114	MCH1R			206
115	MC4 receptor	IC_{50}	61 nM	213
116	MC4 receptor			214
117	MC4 receptor			215
118	MC4 receptor			216
119	MC4 receptor			217

ring systems such as triazolopyrazine, pyrrolopyrimidine, pyrrolopyrimidine and others. Most of the presented compounds have an aromatic ring next to the nitrogen atom in the central heterocyclic ring and a hydrophobic group on the side opposite the position where the aromatic ring is attached.

Applications from Neurogen Corporation & Aventis Pharmaceuticals Inc. include compounds with a di-heterocyclic ring system containing a pirazine ring (e.g. compounds (**59**) and (**60**)) [130,131]. Compound (**61**) [132] and its analogues exemplified in an application from F. Hoffman-La Roche have a unique spiro-ring system which could differentiate them from other CRF_1 receptor antagonists. They also made applications for compounds containing di-heterocyclic ring systems (e.g. compounds (**62**) - (**63**)) [133,134]. Compounds (**64**) and (**65**) [135,136], in applications from SB Pharmco Puerto Rico Inc. & Neurocrine Biosciences Inc., have a pyrazole ring substituted on their scaffold ring system. In 2004, nine international applications from Pharmacia & Upjohn Company were published. The compounds they published included di-heterocyclic ring systems (e.g. compounds (**66**) - (**70**)) [137 - 141] and mono-heterocyclic rings (e.g. compounds (**71**) - (**74**)) [142 - 145]. Compounds (**75**) [146] and (**76**) [147] were exemplified in the applications from Ono Pharmaceutical Co., Ltd. and Taisho Pharmaceutical Co., Ltd., respectively, and included di-heterocyclic ring systems. Compounds exemplified in an application from Novartis AG (e.g. compound (**77**)) [148], each have a bicyclic heteroaromatic ring such as a benzothiaziazole, a unique structural feature. An application from Glaxo Group Limited



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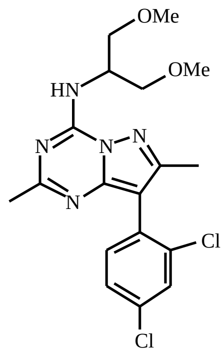

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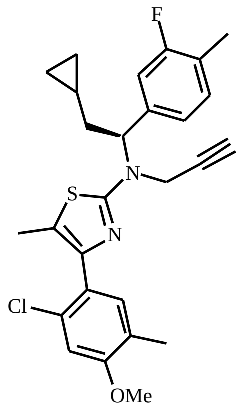

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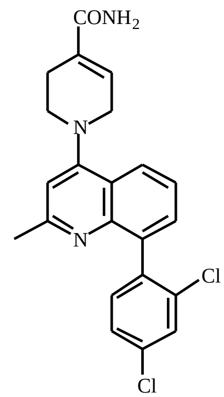

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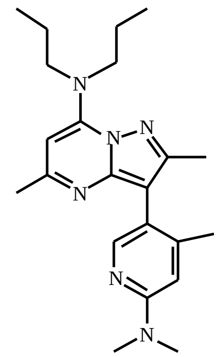

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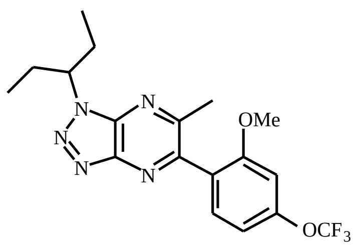

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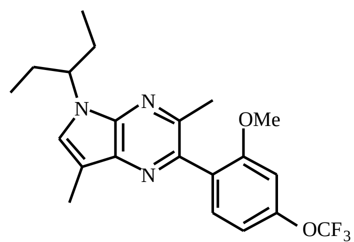

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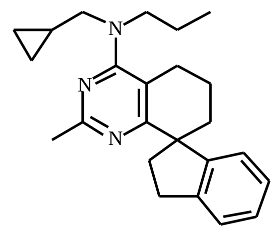

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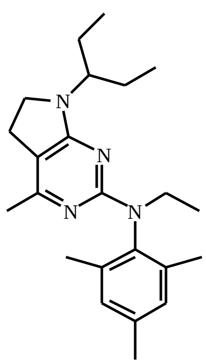

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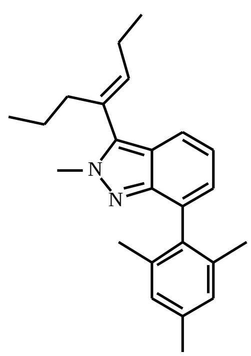

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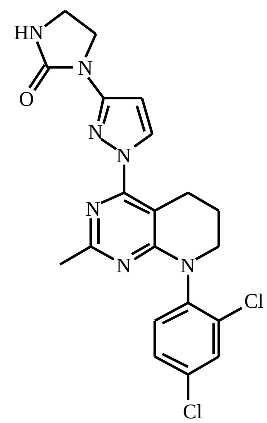

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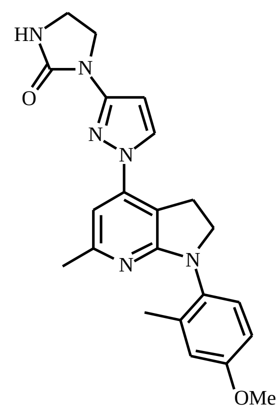

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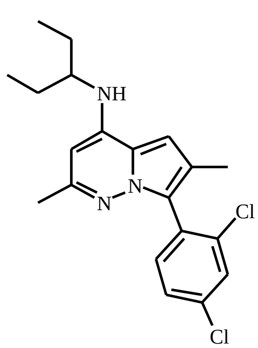

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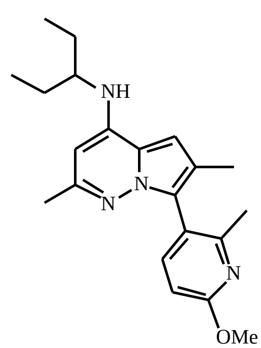

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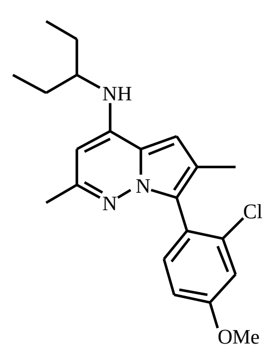

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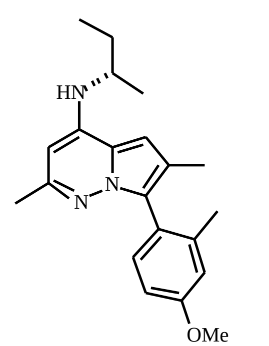

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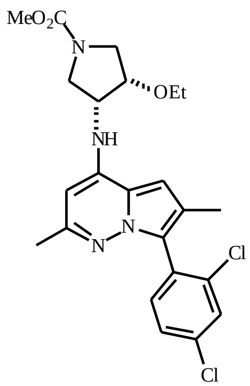

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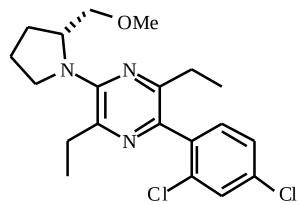

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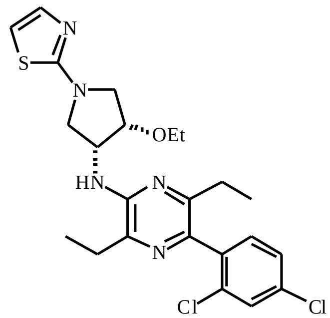

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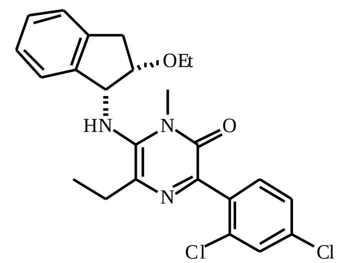

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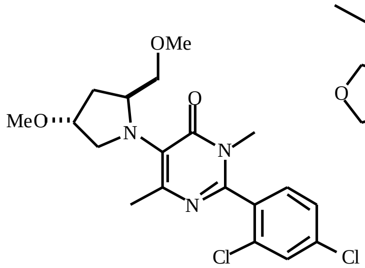

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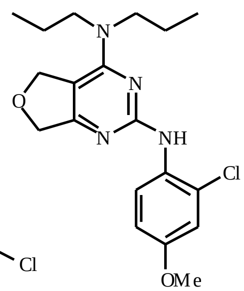

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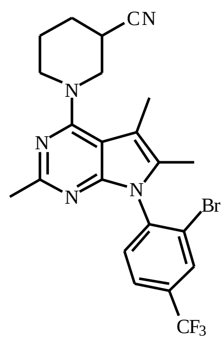

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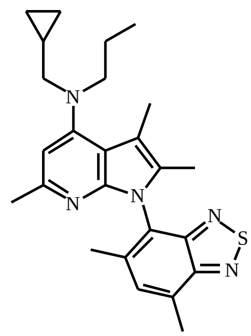

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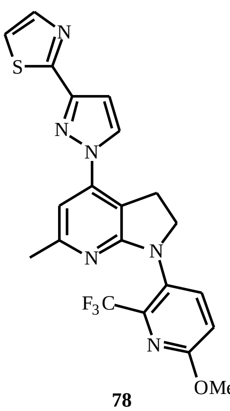

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Fig. (8). CRF1 receptor antagonists.

includes pyrazole-substituted pyrrolopyridine derivatives (e.g. compound (**78**)) [149] which are similar to CRF_1 receptor antagonists published by SB Pharmco Puerto Rico Inc. & Neurocrine Biosciences Inc. described above.

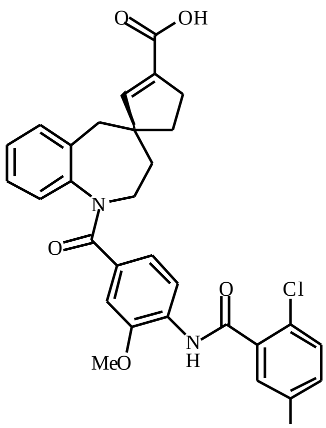
Few biological data are presented in these applications (Table **1**).

AVP Receptor Antagonists (V_{1a} Receptor Antagonists, V_{1b} Receptor Antagonists)

AVP is a cyclic nonapeptide, and has been considered the principal factor in the regulation of ACTH release from the pituitary [150]. In addition to its involvement in the regulation of hypothalamic-pituitary-adrenal (HPA) axis activity, AVP is believed to play a role in regulation of mood. Indeed, it has been reported that both plasma concentration of AVP and the number of AVP immunoreactivity in the paraventricular nucleus (PVN) are higher in depressed patients than in healthy controls [151,152]. AVP exerts effects *via* three receptor subtypes, V_{1a}, V_{1b} and V_2 receptors [153]. Of these, V_{1a} and V_{1b} receptors have been reported to be involved in emotional processes [154,155], while the V_{1b} receptor is a focus of current interest based on a series of studies using a nonpeptidic and selective V_{1b} receptor antagonist, SSR149415 (Fig. **9**). It has been reported that SSR149415 exhibits antidepressant- and anxiolytic-like activities in a variety of rodent models of depression and anxiety, with more pronounced effects in models involving stressful situations [156,157], and reverses stress-induced alterations in release of norepinephrine and ACTH [157]. It has also been reported that not only regulation of HPA axis activity but extrahypothalamic effects are involved in the antidepressant effect of the V_{1b} receptor antagonist [158]. Moreover, repeated administration of V_{1b} receptor antagonist, like CRF_1 receptor antagonist and fluoxetine, reverses stress-induced reduction of adult hippocampal neurogenesis, which has been considered one of the causes of depression [39], in a mouse chronic mild stress model, while neither a V_{1b} receptor antagonist nor a CRF_1 receptor antagonist had significant effects in non-stressed animals [159].

In addition to V_{1b} receptor antagonists, it has recently been reported that JNJ-17308616, a V_{1a} receptor antagonist, exhibits anxiolytic effects in some models of anxiety including the elevated plus-maze and separation-induced vocalization [160], raising the possibility that V_{1a} receptors could be another attractive target in the treatment of anxiety disorders.

In 2004 and 2005, several international patent applications providing V_{1a} receptor antagonists and V_{1b} receptor antagonists have been published (Fig. **9**). Compound (**79**) [161], an example in the application from Janssen Pharmaceutica, was stated to exhibit V_{1a} and V_2 receptor antagonist activity. Another application for V_{1a}



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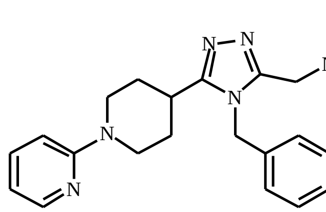

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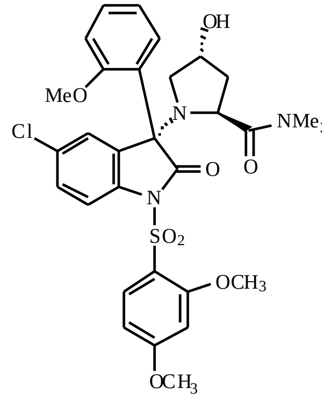

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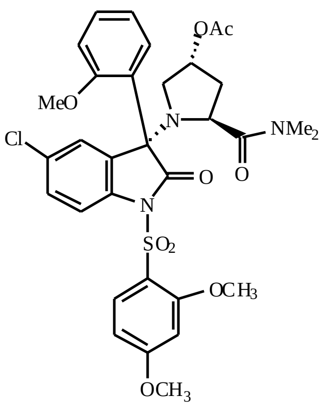

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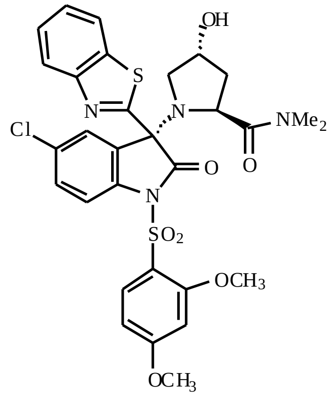

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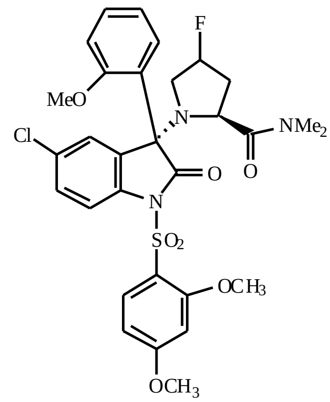

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Fig. (9). V1a & V1b receptor antagonists.

receptor antagonists from Pfizer presented triazole derivatives (e.g. compound (**80**)) [162]. Affinities for V_{1a} receptors of representative compounds among the examples in the application were presented. The Ki value of compound (**80**) was reported to be 4.5 nM. Applications for novel V_{1b} receptor antagonists have recently been published by three companies, Sanofi-Synthelabo (e.g. compound (**81**)) [163], Abbott GMBH (e.g. compound (**82**)) [164] and Taisho Pharmaceutical Co., Ltd (e.g. compound (**83**)) [165]. The claimed structures in the three applications exhibit little diversity and have a quite similar framework, 1,3-dihydroindole-2-one, which probably originated from SSR149415. Despite their similarity of structure, the compounds in each application have unique structural characteristics. Compounds published by Abbott GMBH have heterraromatic rings as substituents on the framework, these exemplified by Taisho have a fluorine atom on the proline moiety, and these from Sanofi-Synthelabo have an acyloxy moiety on the proline moiety.

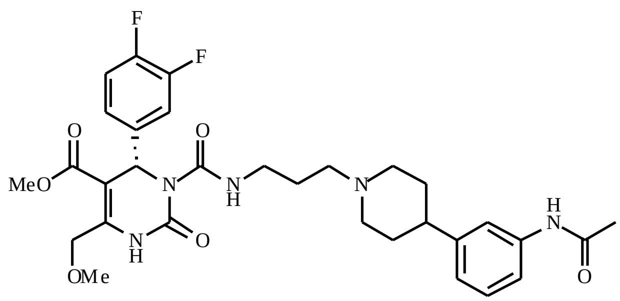
MCH1R Antagonists

Melanin-concentrating hormone (MCH) is a cyclic 19-amino acid peptide originally isolated from salmon pituitary [166]. In mammals, MCH is produced predominantly by neurons in the lateral hypothalamus and zona incerta with extensive projections throughout the brain [167], and exerts numerous physiological effects including increase in food intake and production of depressive and anxiety-like behaviors [168,169]. Two receptor subtypes have been reported, MCH1R and MCH2R, both of which belong to the GPCR superfamily [170]. Emerging lines of evidence have suggested that MCH1R mediates not only regulation of feeding behavior but also regulation of emotional states. MCH1R is densely expressed in the nucleus accumbens shell, a brain region involving motivation and reward, and it has been reported that local injection of MCH into the nucleus accumbens shell displays a depressive phenotype in the forced swim test, while local injection of an MCH1R antagonist exhibits antidepressant effects [168]. It has also been reported that MCH1R is expressed in dynorphin-positive medium spiny neurons in the nucleus accumbens shell [168] and may negatively regulate dopaminergic activity in this region [171], which may explain in part the mechanism of MCH-induced depressive behavior. In addition to regulation of dopaminergic activity in the nucleus accumbens, MCH1R has been reported to be densely distributed in the PVN of hypothalamus, where it regulates HPA axis activity through CRF secretion [172].

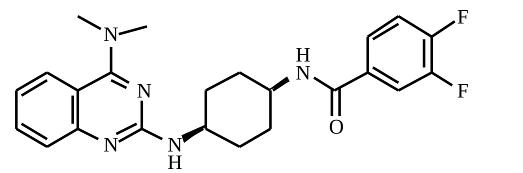
Consistent with the above findings, it has been reported that systemic administration of nonpeptidic MCH1R antagonists such as ATC0175 (Fig. **10**) and SNAP-7941 (Fig. **10**) has antidepressant and anxiolytic effects in a variety of rodent models of depression and anxiety [173,174]. These MCH1R antagonists have been reported to be devoid of sedative and motor effects [173,174]. Moreover, it was reported that another nonpeptidic MCH1R antagonist, SNAP-94847 exerted antidepressant effects in a chronic mild stress paradigm faster than citaropram, suggesting faster onset of action than SSRIs [175].

In 2004 and 2005, more than 30 patent applications presenting MCH1R antagonists have been published by over 10 pharmaceutical companies (Fig. **10**). Most compounds provided in the applications have two or more aromatic rings and some basic amines.

Recent applications published by Synaptic Pharmaceutical Co. include a variety of MCH1R antagonists, most of which have a cyclic amine and two or more aromatic rings (e.g. compounds (**84**) - (**87**)) [176 - 179]. Compounds (**88**) - (**90**) [180 - 182] are examples appeared in applications from Boehringer Ingelheim Pharma GMBH, and also have a cyclic amine and two or more aromatic rings. Applications published by Banyu Pharmaceutical Co. in 2004 and 2005 exemplify compounds having one or more



SNAP-7941



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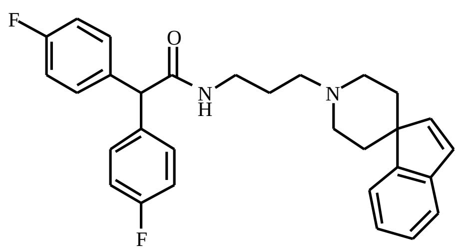

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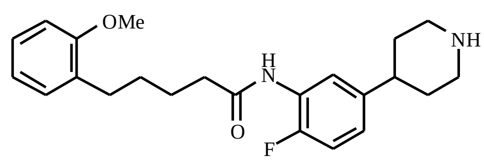

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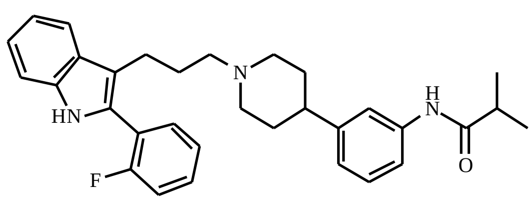

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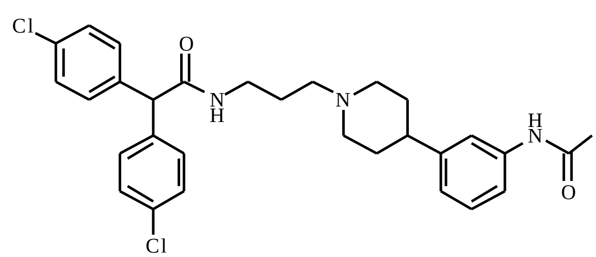

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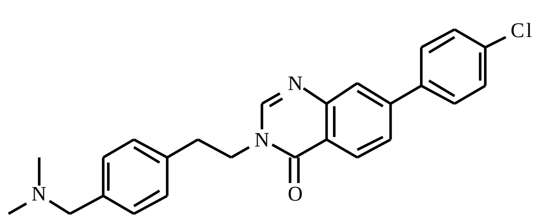

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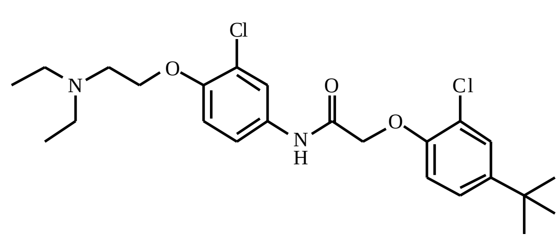

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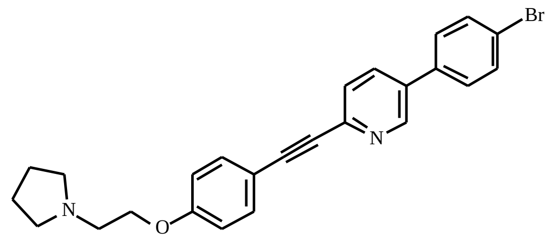

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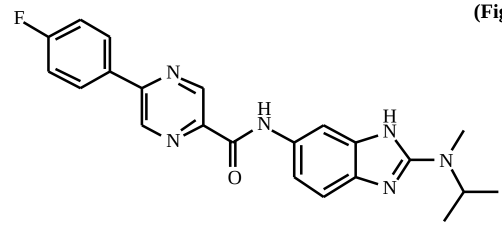

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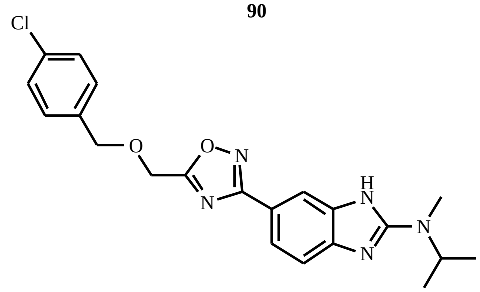

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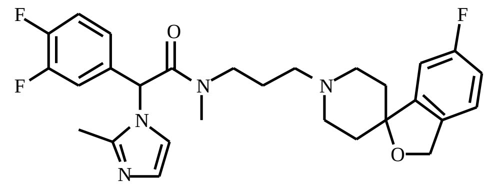

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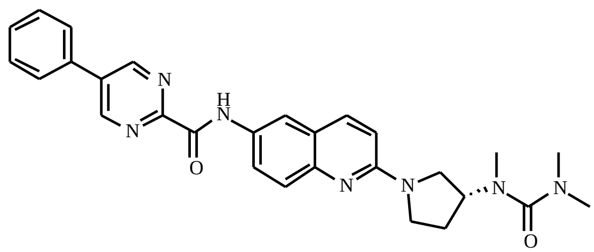

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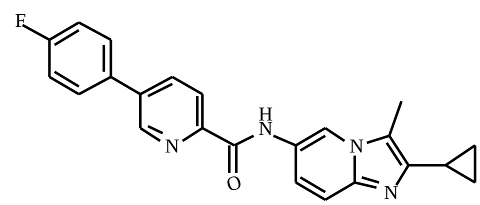

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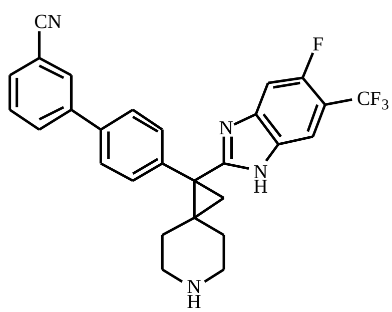

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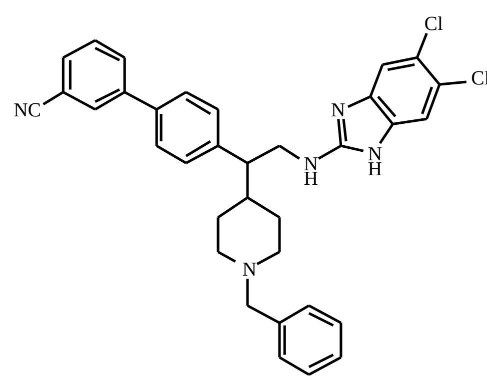

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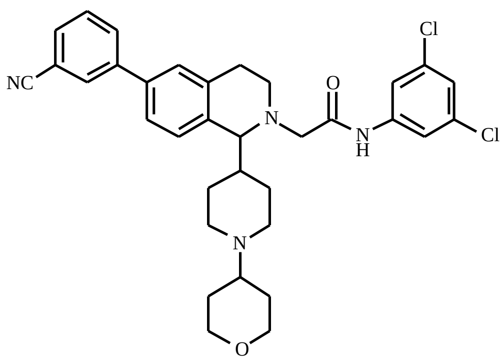

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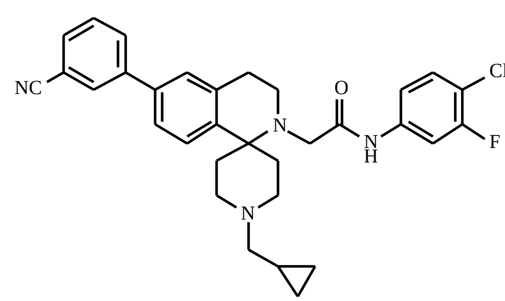

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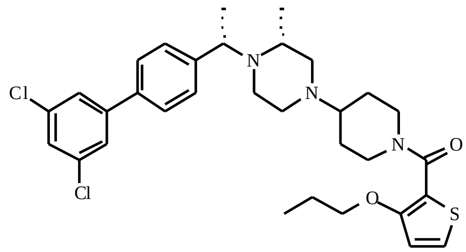
(Fig. 10) Contd….



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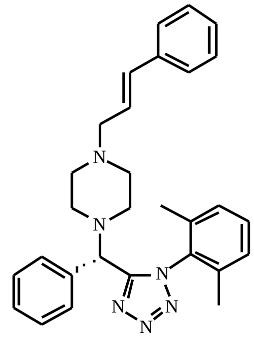

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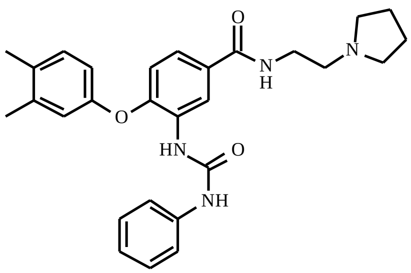

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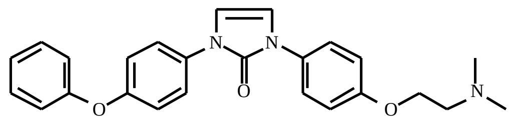

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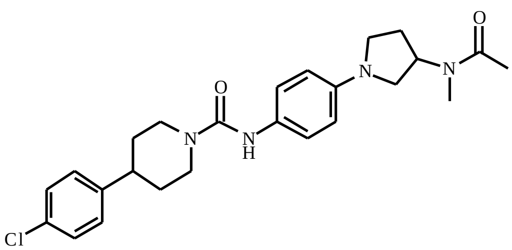

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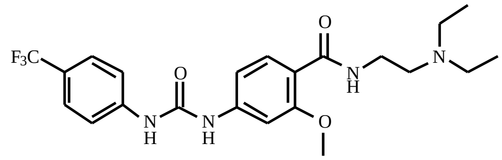

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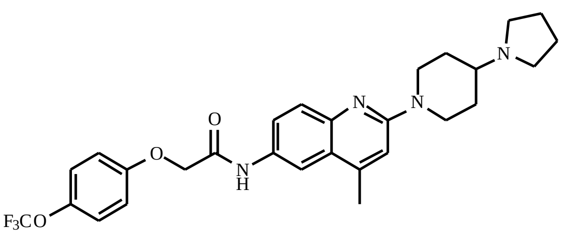

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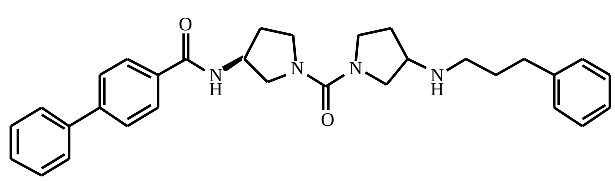

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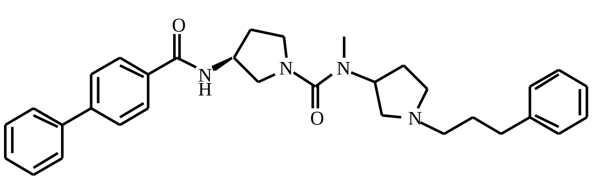

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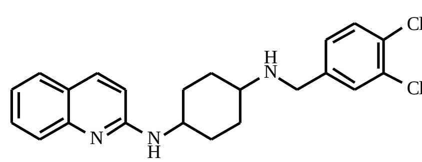

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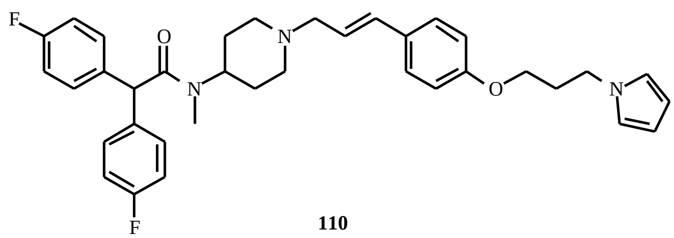

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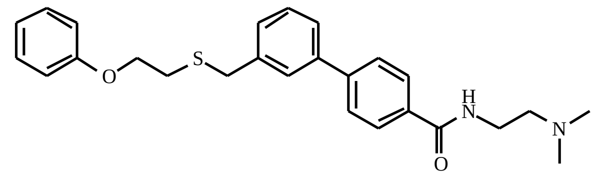

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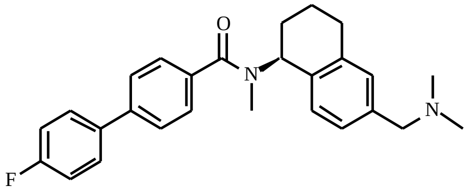

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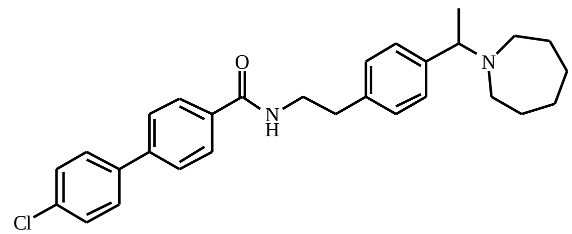

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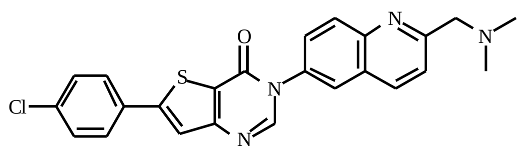

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Fig. (10). MCH1R antagonists.

heteroaromatic rings in each molecule (e.g. compounds (**91**) - (**95**)) [183 - 187]. Compounds (**96**) - (**100**) [188 - 192], which have piperidine- or piperazine-based structures, were published in applications by Schering Co. Compounds (**101**) - (**102**) [193,194], (**103**) - (**104**) [195,196], (**105**) - (**106**) [197,198] and (**107**) - (**108**) [199,200] were published by Amgen, Aventis Pharma Deutschland GMBH, 7TM Pharma A/S, and Neurocrine Biosciences, respectively. Compounds (**109**) - (**114**) [201 - 206] were published by six individual companies.

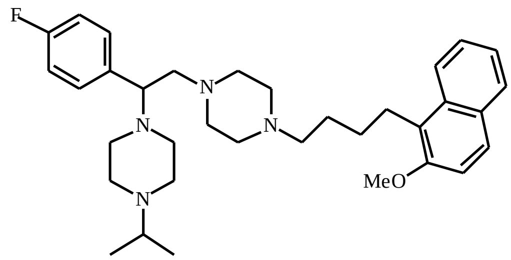
As can be seen, many applications related to MCH1R antagonists have recently been published by many pharmaceutical companies, suggesting that MCH1R is believed to have strong potential for clinical use.

Biological data for several of these compounds have been presented (Table **1**), and many of these compounds demonstrate nanomolar or subnanomolar affinities for MCH1R.

MC_4 Receptor Antagonists

Melanocortins (ACTH and α-, β- and γ-melanocyte-stimulating hormone (α-, β- and γ-MSH)) are derived from proopiomelanocortin (POMC) by enzymatic processing, and participate in a wide range of physiological functions. The melanocortins have 5 subtypes of receptors ($MC_1 – MC_5$), all of which are coupled to Gs [207]. In the brain, MC_3 and MC_4 receptors are mainly expressed, with little expression of MC_5 receptor. Of these, it has been shown that MC_4 receptor plays a role in regulation of emotion and stress responses. It has been reported that MC_4 receptor agonists induce grooming behavior in rats, and that the MC_4 receptor antagonist SHU9119 attenuates MC_4 receptor agonist-induced grooming as well as novelty-induced grooming [208]. Moreover, the MC_4 receptor has been suggested to play a role in the regulation of HPA axis activity [209], presumably through regulation of CRF secretion in the PVN of hypothalamus. In addition to the PVN, it has been reported that MC_4 in the amygdala may be involved in anxiety-like behavior [210]. An MC_4 receptor antagonist, MCL0129 (Fig. **11**), has been found to exhibit antidepressant and anxiolytic effects in several animal models [211]. MCL0129 has been demonstrated not to affect locomotor activity, rotarod performance and hexobarbital-induced anesthesia [211], suggesting that it may not have CNS side effects observed with BDZs. Anxiolytic and anti-stress effects were observed with another selective peptidomimetic MC_4 receptor antagonist, MCL0020 (Fig. **11**) [212]. Interestingly, MCL0129 exerted antidepressant effects after just a single administration in a learned helplessness paradigm [211], while fluvoxamine exhibited this effect only after subchronic administration, indicating that MCL0129 has a rapid onset of action.

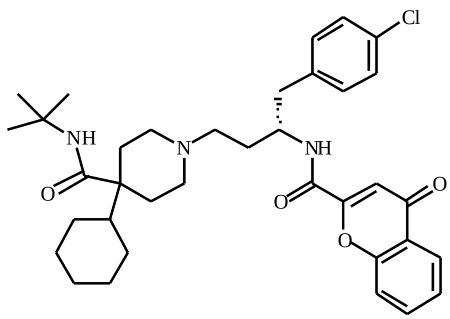
Recent applications from Myocontract (e.g. compound (**115**)) [213], The Proctor & Gamble Company (e.g. compound (**116**)) [214] and Neurocrine Bioscience (e.g. compounds (**117**) and (**118**)) [215,216] exemplify MC_4 receptor ligands that include a phenylalanine moiety (Fig. **11**). By contrast, compounds applied for by Millennium Pharmaceuticals have no amino acid moiety (compound (**119**)) [217]. Most of the applications do not indicate



MCL0129

Ac-D-2-Nal-Arg-2-Nal-NH_2

MCL0020



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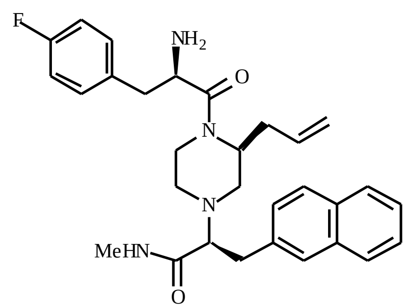

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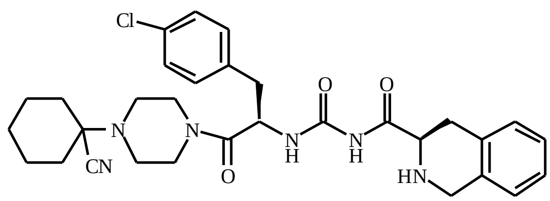

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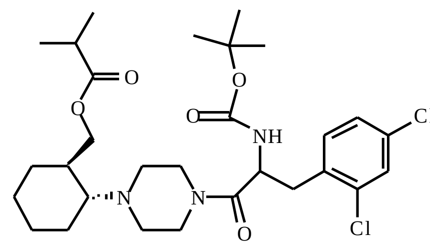

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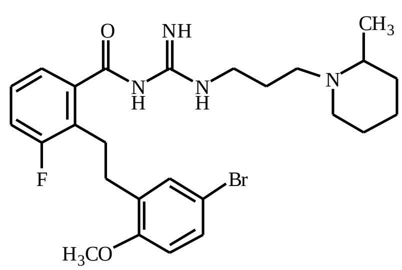

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Fig. (11). MC4 receptor antagonists.

whether their compounds have an agonist or antagonist activity. Only a few applications provided biological data for the exemplified compounds (Table **1**).

CURRENT & FUTURE DEVELOPMENTS

During the past decade, apart from biogenic amines, a variety of novel therapeutic targets have emerged for the treatment of depression and anxiety. With the development of novel pharmacological and genetic tools, the importance of these targets has been delineated. They include receptor subtypes within the glutamate, GABA and neuropeptide systems.

Based on the clinical observation that both glutamatergic and GABAergic transmission is impaired in depressed patients, and that ketamine, an NMDA receptor antagonist, exhibits antidepressant effects with acute administration, manipulation of these transmitter systems has come to be of interest. Because many compounds acting on either the glutamatergic or GABAergic system have serious side effects, attention has shifted to newer receptor subtypes (e.g. metabotropic receptors) to reduce unwanted side effects and to enhance efficacy.

Given that stress is considered a common primary cause of both depressive and anxiety disorders, stress-related neuropeptides and their receptors, in particular, those expressed in the hypothalamic nuclei, are attractive therapeutic targets for both disorders. In fact, most neuropeptide receptor ligands have been reported to be effective in animal models of both depression and anxiety, and they are more efficacious in models involving highly stressful situations, which may reflect etiology of these disorders. With recent identification of endogenous ligands for orphan GPCRs (most of which turned out to be neuropeptides) and elucidation of their physiological functions, the number of candidate neuropeptides on the list of possible therapeutic targets is increasing.

Although the outcome of a Phase III study with an NK_1 receptor antagonist (Aprepitant) was disappointing, it would be premature to judge the importance of non-monoamine-based treatment, and currently there are several compounds being tested for efficacy in clinical trials, with some encouraging results. Indeed, an NK_2 receptor antagonist is in a Phase III study for depression, and a group II mGluR agonist and a CRF_1 receptor antagonist have been found to be effective for anxiety disorder and major depressive disorder, respectively, in early proof-of-concept human studies.

Recently, it has been proposed that changes in intra-cellular events and subsequent neuronal networks are pivotal factors in the exertion of antidepressant effects. These include increases in expression of BDNF, CREB and eventually in neurogenesis in the hippocampus. The molecules controlling these events may be future targets for the treatment of depression and anxiety disorders.

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REFERENCES

[1] Borsini F, Podhorna J, Marazziti D. Do animal models of anxiety predict anxiolytic-like effects of antidepressants? Psychopharmacology (Berl) 2002; 163: 121-141.
[2] Schatzberg AF. New indications for antidepressants. J Clin Psychiatry 2000; 61 Suppl 11: 9-17.
[3] Paul IA, Skolnick P. Glutamate and depression: clinical and preclinical studies. Ann N Y Acad Sci 2003; 1003: 250-272.
[4] Berman RM, Cappiello A, Anand A, *et al.* Antidepressant effects of ketamine in depressed patients. Biol Psychiatry 2000; 47: 351-354.
[5] Nakanishi S. Molecular diversity of glutamate receptors and implications for brain function. Science 1992; 258: 597-603.
[6] Conn PJ, Pin JP. Pharmacology and functions of metabotropic glutamate receptors. Annu Rev Pharmacol Toxicol 1997; 37: 205-37.
[7] Spooren WP, Gasparini F, Salt TE, Kuhn R. Novel allosteric antagonists shed light on mglu(5) receptors and CNS disorders. Trends Pharmacol Sci 2001; 22: 331-337.
[8] Pilc A, Klodzinska A, Branski P, *et al.* Multiple MPEP administrations evoke anxiolytic- and antidepressant-like effects in rats. Neuropharmacology 2002; 43: 181-187.
[9] Tatarczynska E, Klodzinska A, Chojnacka-Wojcik E, *et al.* Potential anxiolytic- and antidepressant-like effects of MPEP, a potent, selective and systemically active mGlu5 receptor antagonist. Br J Pharmacol 2001; 132: 1423-1430.
[10] Busse CS, Brodkin J, Tattersall D, *et al.* The behavioral profile of the potent and selective mGlu5 receptor antagonist 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (MTEP) in rodent models of anxiety. Neuropsychopharmacology 2004; 29: 1971-1979.
[11] Brodkin J, Bradbury M, Busse C, Warren N, Bristow LJ, Varney MA. Reduced stress-induced hyperthermia in mGluR5 knockout mice. Eur J Neurosci 2002; 16: 2241-2244.
[12] Steckler T, Lavreysen H, Oliveira AM, *et al*. Effects of mGlu1 receptor blockade on anxiety-related behaviour in the rat lick suppression test. Psychopharmacology (Berl) 2005; 179: 198-206.
[13] Varty GB, Grilli M, Forlani A, *et al.* The antinociceptive and anxiolytic-like effects of the metabotropic glutamate receptor 5 (mGluR5) antagonists, MPEP and MTEP, and the mGluR1 antagonist, LY456236, in rodents: a comparison of efficacy and side-effect profiles. Psychopharmacology (Berl) 2005; 179: 207-217.
[14] Naie K, Manahan-Vaughan D. Pharmacological antagonism of metabotropic glutamate receptor 1 regulates long-term potentiation and spatial reference memory in the dentate gyrus of freely moving rats *via* N-methyl-D-aspartate and metabotropic glutamate receptor-dependent mechanisms. Eur J Neurosci 2005; 21: 411-421.
[15] Cosford, N.D.P., Huang, D., Roppe, J.R., Tehrani, L.R., Smith, N.D.: WO2004089308A2 and WO2004089308A3 (**2004**).
[16] Cosford, N.D.P., Smith, N.D., Huang, D.: WO2003059904 (**2003**).
[17] Cosford, N.D.P., Smith, N.D., Huang, D.: WO2003053922A2 and WO2003053922A3 (**2003**).
[18] Cosford, N.D.P., Chen, C., Eastman, B.W., *et al.*: WO2003051833A2 and WO2003051833A3 (**2003**).
[19] Cosford, N.D.P., Huang, D., Smith, N.D., Hu, E.H.: WO2004087653A2 and WO2004087653A3 (**2003**).
[20] Cosford, N.D.P., Tehrani, L.R., Roppe, J.R., Smith, N.D., Prasit, P.: WO2003051315A2 and WO2003051315A3 (**2003**).
[21] Cosford, N.D.P., Roppe, J.R., Therani, L.R., Wang, B.: WO2004089306A2 and WO2004089306A3 (**2003**).
[22] Cosford, N.D., Roppe, J., Chen, C., Smith, N., Reger, T.: WO03029210A2 and WO03029210A3 (**2003**).
[23] Poon, S. F., Chen, C., Eastman, B.W., *et al.*: WO03077918 (**2003**).
*[24] Munoz, B., Stearns, B., Vernier, J.-M., *et al.*: WO03048137 (**2003**).
[25] Kamenecka, T.M., Vernier, J.-M., Bonnefous, C., Govek, S.P., Hutchinson, J.H.: WO2005021529 (**2005**).
[26] Buettelmann, B., Ceccarelli, S.M., Jaeschke, G., Porter, R.H.P., Vieira, E.: WO2004108701 (**2004**).
[27] Buettelmann, B., Ceccarelli, S.M., Jaeschke, G., Kolczewski, S., Porter, R.H.P., Vieira, E.: WO2004111040 (**2003**).
*[28] Buettelmann, B., Ceccarelli, S.M., Jaeschke, G., Kolczewski, S., Porter, R.H.P., Vieira, E.: WO2004080998 (**2004**).
[29] Buettelmann, B., Ceccarelli, S.M., Jaeschke, G., Kolczewski, S., Porter, R.H.P., Vieira, E.: WO2005003117 (**2005**).
[30] Kyle, D.J., Sun, Q., Zhou, X.: WO2005007641 (**2005**).
[31] Kyle, D.J., Sun, Q., Tafesse, L., Zhang, C., Zhou, X.: WO2004002983A2 and WO2004002983A3 (**2005**).
[32] Sun, Q., Tafesse, L., Victory, S.: WO2004058754 (**2004**).
[33] Chen, Z., Tafesse, L.: WO2004029044 (**2004**).
[34] Kyle, D.J., Sun, Q.: WO03066595A2 and WO03066595A3 (**2003**).
[35] Mcleod, D.A., Kers, A., Malmberg, J., *et al.*: WO2004014370A2 and WO2004014370A3 (**2004**).
[36] Gyback, H., Johansson, M., Minidis, A., Nordvall, G., Raboisson, P., Wensbro, D.: WO2004069813 (**2004**).

[37] Wensbo, D., Xin, T., Stefanac, T., *et al.*: WO2004014881A2 and WO2004014881A3, WO2004014881C1 and WO2004014881B1 (**2004**).

[38] Wensbo, D., Xin, T., Stefanac, T., *et al.*: WO2004014902A2, WO2004014902A3 and WO2004014902C1 (**2004**).

[39] Bolea, C., Mutel, V., Rocher, J.-P., Bessis, A.-S., Le Poul, E.: WO2004078728 (**2004**).

[40] Gasparini, F., Auberson, Y., Ofner, S.: WO03047581 (**2003**).

[41] Schoepp DD. Novel functions for subtypes of metabotropic glutamate receptors. Neurochem Int 1994; 24: 439-449.

[42] Monn JA, Valli MJ, Massey SM, *et al.* Design, synthesis, and pharmacological characterization of (+)-2-aminobicyclo[3.1.0] hexane-2,6-dicarboxylic acid (LY354740): a potent, selective, and orally active group 2 metabotropic glutamate receptor agonist possessing anticonvulsant and anxiolytic properties. J Med Chem 1997; 40: 528-537.

[43] Helton DR, Tizzano JP, Monn JA, Schoepp DD, Kallman MJ. Anxiolytic and side-effect profile of LY354740: a potent, highly selective, orally active agonist for group II metabotropic glutamate receptors. J Pharmacol Exp Ther 1998; 284: 651-660.

[44] Klodzinska A, Chojnacka-Wojcik E, Palucha A, Branski P, Popik P, Pilc A. Potential anti-anxiety, anti-addictive effects of LY 354740, a selective group II glutamate metabotropic receptors agonist in animal models. Neuropharmacology 1999; 38: 1831-1839.

[45] Shekhar A, Keim SR. LY354740, a potent group II metabotropic glutamate receptor agonist prevents lactate-induced panic-like response in panic-prone rats. Neuropharmacology 2000; 39: 1139-1146.

[46] Schoepp DD, Wright RA, Levine LR, Gaydos B, Potter WZ. LY354740, an mGlu2/3 receptor agonist as a novel approach to treat anxiety/stress. Stress 2003; 6: 189-197.

[47] Grillon C, Cordova J, Levine LR, Morgan CA 3rd. Anxiolytic effects of a novel group II metabotropic glutamate receptor agonist (LY354740) in the fear-potentiated startle paradigm in humans. Psychopharmacology (Berl) 2003; 168: 446-454.

[48] Johnson MP, Barda D, Britton TC, *et al.* Metabotropic glutamate 2 receptor potentiators: receptor modulation, frequency-dependent synaptic activity, and efficacy in preclinical anxiety and psychosis model(s). Psychopharmacology 2005; 179: 271-283.

[49] Govek SP, Bonnefous C, Hutchinson JH, *et al.* Benzazoles as allosteric potentiators of metabotropic glutamate receptor 2 (mGluR2): Efficacy in an animal model for schizophrenia. Bioorg Med Chem Lett. 2005; 15: 4068-4072.

[50] Chaki S, Yoshikawa R, Hirota S, *et al.* MGS0039: a potent and selective group II metabotropic glutamate receptor antagonist with antidepressant-like activity. Neuropharmacology 2004; 46: 457-467.

[51] Yoshimizu T, Chaki S. Increased cell proliferation in the adult mouse hippocampus following chronic administration of group II metabotropic glutamate receptor antagonist, MGS0039. Biochem Biophys Res Commun 2004; 315: 493-496.

[52] Kawashima N, Karasawa J, Shimazaki T, *et al.* Neuropharmacological profiles of antagonists of group II metabotropic glutamate receptors. Neurosci Lett 2005; 378: 131-134.

[53] Kenny PJ, Gasparini F, Markou A. Group II metabotropic and alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA)/kainate glutamate receptors regulate the deficit in brain reward function associated with nicotine withdrawal in rats. J Pharmacol Exp Ther 2003; 306: 1068-1076.

[54] Moghaddam B, Adams BW. Reversal of phencyclidine effects by a group II metabotropic glutamate receptor agonist in rats. Science 1998; 281: 1349-1352.

[55] Cryan JF, Kelly PH, Neijt HC, Sansig G, Flor PJ, van Der Putten H. Antidepressant and anxiolytic-like effects in mice lacking the group III metabotropic glutamate receptor mGluR7. Eur J Neurosci 2003; 17: 2409-2417.

[56] Shimazaki T, Iijima M, Chaki S. Anxiolytic-like activity of MGS0039, a potent group II metabotropic glutamate receptor antagonist, in a marble-burying behavior test. Eur J Pharmacol 2004; 501: 121-125.

[57] Bunch, L., Madsen, U., Brauner-Osborne, H., Krogsgaad-Larsen, P., Grube J.C.: WO03070712 (**2003**).

[58] Adam, G., Kolczewski, S., Mutel, V., Wichmann, J., Woltering, T.J.: EP0891978 (**2005**).

*[59] Adam, G., Goetschi, E., Wichmann, J., Woltering, T.J.: WO03066623 (**2003**).

[60] Curry, K.: WO2004024709A2 and WO2004024709A3 (**2004**).

[61] Martinez-Turrillas R, Frechilla D, Del Rio J. Chronic antidepressant treatment increases the membrane expression of AMPA receptors in rat hippocampus. Neuropharmacology 2002 ; 43: 1230-1237.

[62] Svenningsson P, Tzavara ET, Witkin JM, Fienberg AA, Nomikos GG, Greengard P. Involvement of striatal and extrastriatal DARPP-32 in biochemical and behavioral effects of fluoxetine (Prozac). Proc Natl Acad Sci USA 2002; 99: 3182-3187.

[63] Li X, Tizzano JP, Griffey K, Clay M, Lindstrom T, Skolnick P. Antidepressant-like actions of an AMPA receptor potentiator (LY392098). Neuropharmacology 2001; 40: 1028-1033.

[64] Quirk JC, Nisenbaum ES. LY404187: a novel positive allosteric modulator of AMPA receptors. CNS Drug Rev 2002; 8: 255-282.

[65] Bai F, Li X, Clay M, Lindstrom T, Skolnick P. Intra- and interstrain differences in models of "behavioral despair".Pharmacol Biochem Behav 2001; 70: 187-192.

[66] Knapp RJ, Goldenberg R, Shuck C, *et al.* Antidepressant activity of memory-enhancing drugs in the reduction of submissive behavior model. Eur J Pharmacol 2002; 440: 27-35.

[67] Mackowiak M, O'Neill MJ, Hicks CA, Bleakman D, Skolnick P. An AMPA receptor potentiator modulates hippocampal expression of BDNF: an *in vivo* study. Neuropharmacology 2002; 43: 1-10.

[68] Bai F, Bergeron M, Nelson DL. Chronic AMPA receptor potentiator (LY451646) treatment increases cell proliferation in adult rat hippocampus. Neuropharmacology 2003; 44: 1013-1021.

[69] Duman RS, Nakagawa S, Malberg J. Regulation of adult neurogenesis by antidepressant treatment. Neuropsychopharmacology 2001; 25: 836-844.

[70] Nibuya M, Morinobu S, Duman RS. Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. J Neurosci 1995; 15: 7539-7547.

[71] Shirayama Y, Chen AC, Nakagawa S, Russell DS, Duman RS. Brain-derived neurotrophic factor produces antidepressant effects in behavioral models of depression. J Neurosci 2002; 22: 3251-3261.

[72] Graindorge, E., Francotte, P., Boverie, S., *et al.*: WO2004099217 (**2004**).

[73] Cordi, A., Desos, P., Lestage, P.: WO03053947 (**2003**).

[74] Cordi, A., Desos, P., Lestage, P.: WO03053979 (**2003**).

[75] Desos, P., Cordi, A., Lestage, P.: EP1486503 (**2004**).

[76] Cordi, A., Desos, P., Lestage, P.: WO03053978 (**2003**).

[77] Desos, P., Cordi, A., Lestage, P.: EP1486502 (**2004**).

*[78] Gouliaev, A.H., Larsen, M., Verming, T., *et al.*: WO03031422 (**2003**).

[79] Krystal JH, Sanacora G, Blumberg H, *et al.* Glutamate and GABA systems as targets for novel antidepressant and mood-stabilizing treatments. Mol Psychiatry 2002; 7 Suppl 1: S71-S80.

[80] Cryan JF, Kaupmann K. Don't worry 'B' happy!: a role for GABA(B) receptors in anxiety and depression. Trends Pharmacol Sci 2005; 26: 36-43.

[81] Gassmann M, Shaban H, Vigot R, *et al.* in and atypical GABAB responses in GABAB(2)-deficient mice. J Neurosci 2004; 24: 6086-6097.

[82] Cryan JF, Kelly PH, Chaperon F, *et al*. Behavioral characterization of the novel GABAB receptor-positive modulator GS39783 (*N*,*N*'-dicyclopentyl-2-methylsulfanyl-5-nitro-pyrimidine-4,6-diamine): anxiolytic-like activity without side effects associated with baclofen or benzodiazepines. J Pharmacol Exp Ther 2004; 310: 952-963.

[83] Mombereau C, Kaupmann K, Froestl W, Sansig G, van der Putten H, Cryan JF. Genetic and pharmacological evidence of a role for GABA(B) receptors in the modulation of anxiety- and antidepressant-like behavior. Neuropsychopharmacology 2004; 29: 1050-1062.

[84] Nakagawa Y, Sasaki A, Takashima T. The GABA(B) receptor antagonist CGP36742 improves learned helplessness in rats. Eur J Pharmacol 1999; 381: 1-7.

[85] Slattery DA, Desrayaud S, Cryan JF. GABAB receptor antagonist-mediated antidepressant-like behavior is serotonin-dependent. J Pharmacol Exp Ther 2005; 312: 290-296.

[86] Mannoury la Cour C, Hanoun N, Melfort M, Hen R, Lesch KP, Hamon M, Lanfumey L. GABA(B) receptors in 5-HT transporter- and 5-HT1A receptor-knock-out mice: further evidence of a transduction pathway shared with 5-HT1A receptors. J Neurochem 2004; 89: 886-896.
[87] Heese K, Otten U, Mathivet P, Raiteri M, Marescaux C, Bernasconi R. GABA(B) receptor antagonists elevate both mRNA and protein levels of the neurotrophins nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) but not neurotrophin-3 (NT-3) in brain and spinal cord of rats. Neuropharmacology 2000; 39: 449-462.
[88] Amin, K., Elebring, T., Guzzo, P., Lehmann, A., Von Unge, S.: WO02100871 (**2002**).
[89] Amin, K., Elebring, T., Guzzo, P., Olsson, T., Swanson, M., Von Unge, S.: WO01041743 (**2001**).
[90] Elebring, T., Guzzo, P., Holmen, A., Olsson, T., Swansson, M., Von Unge, S.: WO0142252 (**2001**).
[91] Holmes A, Heilig M, Rupniak NM, Steckler T, Griebel G. Neuropeptide systems as novel therapeutic targets for depression and anxiety disorders. Trends Pharmacol Sci 2003; 24: 580-588.
[92] Pennefather JN, Lecci A, Candenas ML, Patak E, Pinto FM, Maggi CA. Tachykinins and tachykinin receptors: a growing family. Life Sci 2004; 74: 1445-1463.
[93] Kramer MS, Cutler N, Feighner J, *et al*. Distinct mechanism for antidepressant activity by blockade of central substance P receptors. Science 1998; 281: 1640-1645.
[94] Cheeta S, Tucci S, Sandhu J, Williams AR, Rupniak NM, File SE. Anxiolytic actions of the substance P (NK1) receptor antagonist L-760735 and the 5-HT1A agonist 8-OH-DPAT in the social interaction test in gerbils. Brain Res 2001; 915: 170-175.
[95] Varty GB, Cohen-Williams ME, Morgan CA, Pylak U, Duffy RA, Lachowicz JE, Carey GJ, Coffin VL. The gerbil elevated plus-maze II: anxiolytic-like effects of selective neurokinin NK1 receptor antagonists. Neuropsychopharmacology 2002; 27: 371-379.
[96] Rupniak NM, Webb JK, Fisher A, Smith D, Boyce S. The substance P (NK1) receptor antagonist L-760735 inhibits fear conditioning in gerbils. Neuropharmacology 2003; 44: 516-523.
[97] Rupniak NM, Carlson EJ, Webb JK, *et al.* Comparison of the phenotype of NK1R-/- mice with pharmacological blockade of the substance P (NK1) receptor in assays for antidepressant and anxiolytic drugs. Behav Pharmacol 2001; 12: 497-508.
[98] Kramer MS, Winokur A, Kelsey J, *et al.* Demonstration of the efficacy and safety of a novel substance P (NK1) receptor antagonist in major depression. Neuropsychopharmacology 2004; 29: 385-392.
[99] Griebel G, Perrault G, Soubrie P. Effects of SR48968, a selective non-peptide NK2 receptor antagonist on emotional processes in rodents. Psychopharmacology (Berl) 2001; 158: 241-251.
[100] Steinberg R, Alonso R, Griebel G, *et al.* Selective blockade of neurokinin-2 receptors produces antidepressant-like effects associated with reduced corticotropin-releasing factor function. J Pharmacol Exp Ther 2001; 299: 449-458.
[101] Walsh DM, Stratton SC, Harvey FJ, Beresford IJ, Hagan RM. The anxiolytic-like activity of GR159897, a non-peptide NK2 receptor antagonist, in rodent and primate models of anxiety. Psychopharmacology (Berl) 1995; 121: 186-191.
[102] Janssens, F.E., Sommen, F.M., De Boeck, B.C.A.G, Leenaerts, J.E., Van Roosbroeck, Y.E.M., Meert, T.F.: WO2004110415A2 and WO2004110415A3 (**2004**).
[103] Janssens, F.E., Sommen, F.M., De Boeck, B.C.A.G, Leenaerts, J.E.: WO2004056805 (**2004**).
[104] Janssens, F.E., Sommen, F.M., De Boeck, B.C.A.G, Leenaerts, J.E.: WO2004056800 (**2004**).
[105] Janssens, F.E., Sommen, F.M., De Boeck, B.C.A.G, Leenaerts, J.E.: WO2004056799A2 and WO2004056799A3 (**2004**).
[106] Janssens, F.E., Sommen, F.M., De Boeck, B.C.A.G, Leenaerts, J.E.: WO2004056364 (**2004**).
[107] Janssens, F.E., Sommen, F.M., De Boeck, B.C.A.G, Leenaerts, J.E., Van Roosbroeck, Y.E.M., Diels, G.S.M.: WO2004033428 (**2004**).
*[108] Wager, T., Welch, W.M. Jr. O'nell, B.T.: WO2004110996 (**2004**).
[109] Shih, N.-Y., Wang, S., Reichard, G.A., Xiao, D., Wang, C.: WO2004004722 (**2004**).
[110] Curtis, N.R., Huscroft, I.T., Kulagowski, J.J., Raubo, P.A.: WO2004031185 (**2004**).
*[111] Devita, R.J., Mills, S.G., Young, J.R., Lin, P.: WO2005032464A2 and WO2005032464A3 (**2005**).
[112] Iwema Bakker, W.I., Van Scharrenburg, G.J.M., Van Den Hoogenband, A., Mccreary, A.C.: WO2005030214 (**2005**).
[113] Giardina, G.A.M., Gagliardi, S.: WO2005000845 (**2005**).
[114] Bernstein, P., Cacciola, J., Dedinas, R., Shen, L., Warwick, P.: WO2004022539 (**2004**).
[115] Bernstein, P., Dantzman, C., Dedinas, R., Shen, L., Warwick, P.: WO2004020411 (**2004**).
[116] Nie, H.: WO2005000247A2 and WO2005000247A3 (**2005**).
[117] Kerns, J., Jin, Q., Wan, Z., Nie, H., Zhu, C.: WO2004066950A2 and WO2004066950A3 (**2004**).
[118] Kerns, J., Jin, Q., Yan, H., Wan, Z.: WO2004066951A2 and WO2004066951A3 (**2004**).
[119] Chambers, M.S., Jones, P., Macleod, A.M.: WO2004072045 (**2004**).
[120] Vale W, Spiess J, Rivier C, Rivier J. Characterization of a 41-residue ovine hypothalamic peptide that stimulates secretion of corticotropin and beta-endorphin. Science 1981; 213: 1394-1397.
[121] Owens MJ, Nemeroff CB. Physiology and pharmacology of corticotropin-releasing factor. Pharmacol Rev 1991; 43: 425-473.
[122] Nemeroff CB, Widerlov E, Bissette G, *et al.* Elevated concentrations of CSF corticotropin-releasing factor-like immunoreactivity in depressed patients. Science 1984: 226: 1342-1344.
[123] Holsboer F, Von Bardeleben U, Gerken A, Stalla GK, Muller OA. Blunted corticotropin and normal cortisol response to human corticotropin-releasing factor in depression. New Engl J Med 1984; 311: 1127-1133.
[124] Taylor AL, Fishman LM. Corticotropin-releasing hormone. New Engl J Med 1988; 319: 213-222.
[125] Steckler T, Holsboer F. Corticotropin-releasing hormone receptor subtypes and emotion. Biol Psychiatry 1999; 46: 1480-1508.
[126] Kehne J, De Lombaert S. Non-peptidic CRF1 receptor antagonists for the treatment of anxiety, depression and stress disorders. Curr Drug Targets CNS Neurol Disord 2002; 1: 467-493.
[127] Chaki S, Nakazato A, Kennis L, *et al.* Anxiolytic- and antidepressant-like profile of a new CRF1 receptor antagonist, R278995/CRA0450. Eur J Pharmacol 2004; 485: 145-158.
[128] Habib KE, Weld KP, Rice KC, *et al.* Oral administration of a corticotropin-releasing hormone receptor antagonist significantly attenuates behavioral, neuroendocrine, and autonomic responses to stress in primates. Proc Natl Acad Sci USA 2000; 97: 6079-6084.
[129] Zobel AW, Nickel T, Kunzel HE, *et al.* Effects of the high-affinity corticotropin-releasing hormone receptor 1 antagonist R121919 in major depression: the first 20 patients treated. J Psychiatr Res 2000; 34: 171-181.
[130] Hodgetts, K.J., John, S., Moorcroft, N., *et al.*: WO2005028480A2 and WO2005028480A3 (**2005**).
[131] Ge, P., Horvath, R.F., Zhang, L.Y., *et al.*: WO2005023806A2 and WO200503806A3 (**2005**).
*[132] Clark, R.D.: WO2005013997 (**2005**).
[133] O'Yang, C., Schoenfeld, R.C.: WO2004099209 (**2004**).
[134] Cournoyer, R.L., Lougehead, D.G., O'Yang, C.: WO2004050634 (**2004**).
[135] St-Denis, Y.: WO2004094419 (**2004**).
[136] Andreotti, D., Bernasconi, G., Castiglioni, E., *et al.*: WO2004094420 (**2004**).
[137] Fu, J.-M.: WO2004092176 (**2004**).
[138] Fu, J.-M.: WO2004087710 (**2004**).
[139] Fu, J.-M.: WO2004087709 (**2004**).
[140] Fu, J.-M.: WO2004087708 (**2004**).
[141] Fu, J.-M.: WO2004099213A2 and WO2004099213A3 (**2004**).
[142] Mickelson, J.W.: WO2004046136 (**2004**).
[143] Corbett, J.W., Ennis, M.D., Frank, K.E., Fu, J.-M., Hoffmann, R.L., Verhoest, P.R.: WO2004099201 (**2004**).
[144] Corbett, J.W., Ennis, M.D., Hoffmann, R.L., Verhoest, P.R.: WO2004099161 (**2004**).
[145] Corbett, J.W., Ennis, M.D., Fu, J.-M., Hoffmann, R.L., Mickelson, J.W., Verhoest, P.R.: WO2004094408 (**2004**).
[146] Nakai, H., Saito, T., Obitsu, T., *et al.*: WO2005026126 (**2005**).

[147] Nakazato, A., Okubo, T., Nozawa, D., *et al.*: WO2004058767 (**2004**).
[148] Schoffter, P.: WO2004069257 (**2004**).
[149] Castiglioni, E., Di Fabio, R., Feriani, A., Micheli, F., Sabbatini, F., St-Denis, Y.: WO2004062665 (**2004**).
[150] Aguilera G, Rabadan-Diehl C. Vasopressinergic regulation of the hypothalamic-pituitary-adrenal axis: implications for stress adaptation. Regul Pept 2000; 96: 23-29.
[151] Purba JS, Hoogendijk WJ, Hofman MA, Swaab DF. Increased number of vasopressin- and oxytocin-expressing neurons in the paraventricular nucleus of the hypothalamus in depression. Arch Gen Psychiatry 1996; 53: 137-143.
[152] van Londen L, Kerkhof GA, van den Berg F, *et al.* Plasma arginine vasopressin and motor activity in major depression. Biol Psychiatry 1998; 43: 196-204.
[153] Serradeil-Le Gal C, Wagnon J, Valette G, *et al.* Nonpeptide vasopressin receptor antagonists: development of selective and orally active V1a, V2 and V1b receptor ligands. Prog Brain Res 2002; 139: 197-210.
[154] Bielsky IF, Hu SB, Szegda KL, Westphal H, Young LJ. Profound impairment in social recognition and reduction in anxiety-like behavior in vasopressin V1a receptor knockout mice. Neuropsychopharmacology 2004; 29: 483-493.
[155] Wersinger SR, Ginns EI, O'Carroll AM, Lolait SJ, Young WS 3rd. Vasopressin V1b receptor knockout reduces aggressive behavior in male mice. Mol Psychiatry 2002; 7: 975-984.
[156] Griebel G, Simiand J, Serradeil-Le Gal C, *et al.* Anxiolytic- and antidepressant-like effects of the non-peptide vasopressin V1b receptor antagonist, SSR149415, suggest an innovative approach for the treatment of stress-related disorders. Proc Natl Acad Sci USA 2002; 99: 6370-6375.
[157] Serradeil-Le Gal C, Wagnon J, Simiand J, *et al.* Characterization of (2*S*,4*R*)-1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxy-phenyl)-2-oxo-2,3-dihydro-1H-indol-3-yl]-4-hydroxy-N,N-dimethyl-2-pyrrolidine carboxamide (SSR149415), a selective and orally active vasopressin V1b receptor antagonist. J Pharmacol Exp Ther 2002; 300: 1122-1130.
[158] Stemmelin J, Lukovic L, Salome N, Griebel G. Evidence that the lateral septum is involved in the antidepressant-like effects of the vasopressin V1b receptor antagonist, SSR149415. Neuropsychopharmacology 2005; 30: 35-42.
[159] Alonso R, Griebel G, Pavone G, Stemmelin J, Le Fur G, Soubrie P. Blockade of CRF(1) or V(1b) receptors reverses stress-induced suppression of neurogenesis in a mouse model of depression. Mol Psychiatry 2004; 9: 278-286.
[160] Vaidya AH, Rosenthal D, Milewski M, *et al.* JNJ-17308616: a vasopressin-1A (V1a) receptor antagonist for the treatment of anxiety. *34th SFN Meeting.* San Diego, USA (2004). #115.2.
*[161] Patel, M., Rybczynski, P.J., Xiang, M.A.: WO2005037795 (**2005**).
[162] Armour, R.D., Baxter, A.D., Bryans, J.S., *et al.*: WO2004037809 (**2004**).
[163] Aulombard, A., Garcia, G., Pradines, A., Serradeil-Le Gal, C., Wagnon, J.: WO2004009585A2 and WO2004009585A3 (**2004**).
[164] Lubisch, W., Hornberger, W., Oost, T.K., Sauer, D.R., Unger, L., Wernet, W.: WO2005030755 (**2005**).
[165] Kumagai, T., Kuwada, T., Shibata, T., Hayashi, M., Fujisawa, Y., Sekiguchi, Y.: WO2005021534 (**2005**).
[166] Kawauchi H, Kawazoe I, Tsubokawa M, Kishida M, Baker BI. Characterization of melanin-concentrating hormone in chum salmon pituitaries. Nature 1983; 305: 321-323.
[167] Bittencourt JC, Presse F, Arias C, *et al.* The melanin-concentrating hormone system of the rat brain: an immuno- and hybridization histochemical characterization. J Comp Neurol 1992; 319: 218-245.
[168] Georgescu D, Sears RM, Hommel JD, *et al.* The hypothalamic neuropeptide melanin-concentrating hormone acts in the nucleus accumbens to modulate feeding behavior and forced-swim performance. J Neurosci 2005; 25: 2933-2940.
[169] Shimada M, Tritos NA, Lowell BB, Flier JS, Maratos-Flier E. Mice lacking melanin-concentrating hormone are hypophagic and lean. Nature 1998; 396: 670-674.
[170] Xu YL, Jackson VR, Civelli O. Orphan G protein-coupled receptors and obesity. Eur J Pharmacol 2004; 500: 243-253.
[171] Smith DG, Tzavara ET, Shaw J, *et al.* Mesolimbic dopamine super-sensitivity in melanin-concentrating hormone-1 receptor-deficient mice. J Neurosci 2005; 25: 914-922.
[172] Kennedy AR, Todd JF, Dhillo WS, *et al.* Effect of direct injection of melanin-concentrating hormone into the paraventricular nucleus: further evidence for a stimulatory role in the adrenal axis *via* SLC-1. J Neuroendocrinol 2003; 15: 268-272.
[173] Borowsky B, Durkin MM, Ogozalek K, *et al.* Antidepressant, anxiolytic and anorectic effects of a melanin-concentrating hormone-1 receptor antagonist. Nat Med 2002; 8: 825-830.
[174] Chaki S, Funakoshi T, Hirota-Okuno S, *et al*. Anxiolytic- and Antidepressant-Like Profile of ATC0065 and ATC0175: Nonpeptidic and Orally Active Melanin-Concentrating Hormone Receptor 1 Antagonists. J Pharmacol Exp Ther 2005; 313: 831-839.
[175] Wolinsky TD, Craig DA, Patel J, Lichtblau H, Papp M, Gerald CP. Anxiolytic and antidepressant-like activity of SNAP 94847, a novel MCH-1 antagonist. *34th SFN Meeting*. San Diego, USA (2004). #356.14.
[176] Marzabadi, M., Jiang, A., Lu, K., Chen, C.-A, Deleon, J., Wetzel, J.: WO2004004714 (**2004**).
[177] Marzabadi, M., Jiang, A., Lu, K., Chen, C.-A., Deleon, J., Wetzel, J.: WO2004005257 (**2004**).
[178] Marzabadi, M.R., Wetzel, J., Deleon, J.E., Jiang, Y., Chen, C.-A., Lu, K.: US6727264 (**2004**).
[179] Marzabadi, M.R., Wetzel, J.M., Chen, C.-A., Jiang, Y., Lu, K.: WO2004064764A2 and WO2004064764A3 (**2004**).
[180] Lehmann-Lintz, T., Stenkamp, D., Lenter, M., *et al.*: WO2004024702 (**2004**).
[181] Stenkamp, D., Muller, S.G., Roth, G. J., *et al.*: WO2004039764 (**2004**).
[182] Muller, S.-G., Stenkamp, D., Arndt, K., *et al.*: WO2004039780A1 and WO2004039780C1 (**2004**).
[183] Moriya, M., Kanatani, A., Iwaasa, H., Ishihara, A., Fukami, T.: WO2004011440 (**2004**).
[184] Moriya, M., Sakamoto, T., Kishino, H., Kanatani, A.: WO2004031177 (**2004**).
[185] Moriya, M., Sakamoto, T., Ishikawa, M., Kanatani, A., Fukami, T.: WO2004069798 (**2004**).
[186] Moriya, M., Suzuki, T., Ishihara, A., Iwaasa, H., Kanatani, A.: WO2004103992 (**2004**).
[187] Kishino, H., Moriya, M., Sakamoto, T., *et al.*: WO2005016928 (**2005**).
[188] Wu, W.-J., Burnett, D.A., Caplen, M.A.: WO2005021528 (**2005**).
[189] Burnett, D.A., Wu, W.-L., Sasikumar, T.K., Greenlee, W.J., Caplen, M.A., Guo, T., Hunter, R.C. : US20050054628 (**2005**).
[190] Sasikumar, T.K., Wu, W.-J., Burnett, D.A., Qiang, L.: WO2004078745 (**2004**).
[191] Burnett, D.A., Wu, W.-L., Sasikumar, T.K., Domalski, M.S.: WO2004002987 (**2004**).
[192] Palani, A., Shapiro, S.A., Josien, H.B., Bara, T.A., Clader, J.W., Pushpavanam, P.B., Li, S., McBriar, M.D.: US20050004121 (**2005**).
[193] Hulme, C., Tempest, P., Ma, V., Nixey, T., Balow, G.: WO2005019167 (**2005**).
[194] Tempest, P., Hulme, C., Ma, V.: WO2005019240 (**2005**).
[195] Schwink, L., Stengelin, S., Gossel, M., Boehme, T., Hessler, G., Rosse, G., Walser, A.: WO2004011438 (**2004**).
[196] Schwink, L., Stengelin, S., Gossel, M., Boehme, T., Hessler, G., Starhl, P., Gretzke, D.: WO2004072025 (**2004**).
[197] Little, P.B., Hogberg, T., Bjurling, A.E., Receveur, J.-M., Ulven, T., Elling, C.E., Norregaard, P.K.: WO2004048319 (**2004**).
[198] Frimurer, T.M., Ulven, T., Hogberg, T., Norregaad, P.K., Little, P.B., Receveur, J.-M.: WO2004052370A2 and WO2004052370A3 (**2004**).
[199] Goodfellow, V., Rowbottom, M., Dyck, B.P., *et al.*: WO2004080411 (**2004**).
[200] Goodfellow, V., Rowbottom, M., Dyck, B.P., *et al.*: WO2004081005 (**2004**).
[201] Ray, A.K., Sigfridsson, E.M., Linusson, A.S.M., *et al.*: WO2004004726 (**2004**).
[202] Kaku, H., Kondoh, Y., Hayashibe, S., Kamikubo, T., Iwasaki, F., Matsumoto, S., Kimura, Y., Kurama, T.: WO2004046110 (**2004**).

[203] Gillig, J.R., Heinz, L.J., Kinnick, M.D., Lai, Y.-S., Morin, J.M.J., Synder, N.J.: WO2004052848 (**2004**).
[204] Hu, X.E.: US20050075324 (**2005**).
[205] Ishihara, Y., Kamata, M., Takekawa, S.: WO2004072018 (**2004**).
[206] Barvian, K.K., Carpenter, A.J., Cooper, J.P., *et al.*: WO2004092181A1 and WO2004092181C2 (**2004**).
[207] Catania A, Gatti S, Colombo G, Lipton JM. Targeting melanocortin receptors as a novel strategy to control inflammation. Pharmacol Rev 2004; 56: 1-29.
[208] Adan RA, Szklarczyk AW, Oosterom J, Brakkee JH, Nijenhuis WA, Schaaper WM, Meloen RH, Gispen WH. Characterization of melanocortin receptor ligands on cloned brain melanocortin receptors and on grooming behavior in the rat. Eur J Pharmacol 1999; 378: 249-258.
[209] Von Frijtag JC, Croiset G, Gispen WH, Adan RA and Wiegant VM. The role of central melanocortin receptors in the activation of the hypothalamus-pituitary-adrenal-axis and the induction of excessive grooming. Br J Pharmacol 1998; 123: 1503-1508.
[210] Kokare DM, Dandekar MP, Chopde CT, Subhedar N. Interaction between neuropeptide Y and alpha-melanocyte stimulating hormone in amygdala regulates anxiety in rats. Brain Res 2005; 1043: 107-114.
[211] Chaki S, Hirota S, Funakoshi T, *et al.* Anxiolytic-like and antidepressant-like activities of MCL0129 (1-[(*S*)-2-(4-fluoro-phenyl)-2-(4-isopropylpiperadin-1-yl)ethyl]-4-[4-(2-methoxynaph-thalen-1-yl)butyl]piperazine), a novel and potent nonpeptide antagonist of the melanocortin-4 receptor. J Pharmacol Exp Ther 2003; 304: 818-826.
[212] Chaki S, Ogawa S, Toda Y, Funakoshi T, Okuyama S. Involvement of the melanocortin MC4 receptor in stress-related behavior in rodents. Eur J Pharmacol 2003; 474: 95-101.
[213] Soeberdt, M., Weyermann, P., Von Sprecher, A., Hennebohle, M.: WO2004083208 (**2004**).
[214] Ebetino, F.H., Tian, X., Mazur, W.A., Colson, A.-O.: WO2004037797 (**2004**).
[215] Dyck, B.P., Goodfellow, V., Phillips, T., *et al.*: WO2004058735 (**2004**).
[216] Chen, C., Tucci, F.C., Tran, J.A., Chen, W.-C., White, N.: WO20040058735 (**2004**).
*[217] Vos, T.J., Patane, M., Solomon, M.E., Blackburn, C., Danca, M.D.: WO2004050610A2, WO2004050610A3 and WO2004050610A1 (**2004**).