

EXPERT OPINION

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Corticotropin-releasing factor 1 receptor antagonists: a patent review

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Introduction: Corticotropin-releasing factor (CRF) is a 41 amino acid peptide hypothalamic factor that plays a key role in the body's response to stress. The receptors for CRF (CRF₁ and CRF₂) are members of the class B G-protein coupled receptor family and several small molecule antagonists have been evaluated clinically in stress-related disorders.

Areas covered: The present review covers the disclosures of non-peptide CRF₁ antagonists in the patent literature since 2006.

Expert opinion: Antagonists of the CRF₁ receptor have failed to demonstrate clinical utility. All of the compounds evaluated are similar structures and are allosteric inhibitors of the CRF₁ receptor. Further clinical evaluation of new compounds appears unlikely unless novel structures are identified that interact with the receptor distinct to the first-generation antagonists.

Keywords: adrenocorticotrophic hormone, corticotropin-releasing factor, CRF₁ antagonist, stress

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1. Introduction

Isolation of corticotropin-releasing factor (CRF) was a key milestone in the history of the current understanding of stress biology [1]. It was evident that the systemic response to stress was initiated in the hypothalamic region of the brain and that there were 'factors' that triggered the release of adrenocorticotrophic hormone (ACTH) from the pituitary. The 41 amino acid neuropeptide CRF proved to be that factor and its identification catalyzed a cascade of discoveries which include the identification of the CRF receptors (CRF₁ [2] and CRF₂ [3]) as well as additional CRF receptor ligands, the urocortins (1 – 3) [4-6]. CRF receptors are class B G-protein coupled receptors (GPCRs) that signal primarily through the stimulation of cyclic adenosine monophosphate (cAMP) and CRF is a high affinity CRF₁ receptor ligand with an EC₅₀ value of 4 nM. Animals display anxiety-like behaviors when CRF is administered centrally and these behaviors can be reversed by centrally administered peptide antagonists of the CRF₁ receptor. This plus a vast amount of CRF-associated research not reviewed here [7] suggested that blockade of the CRF₁ receptor may result in new therapies to treat human stress-related disorders like anxiety and depression. As a consequence, pharmaceutical companies began an aggressive hunt for central nervous system penetrating small molecule CRF₁ antagonists and this review chronicles the results of this work that have been reported in the patent literature since 2006 [8].

2. Clinical evaluation of CRF₁ antagonists

Small molecule CRF₁ antagonists were first disclosed in 1991 and have been the subject of multiple reviews [9]. A decade would pass between the first report of the 3-pyrazolone 1 (Figure 1) [10] and the evaluation of R121919 (2) in an open-label Phase IIa trial with depressed patients [11]. In that study, the Hamilton

Article highlights.

- Corticotropin-releasing factor (CRF) is a 41 amino acid peptide hypothalamic factor that plays a key role in the body's response to stress.
- Several small molecule antagonists have been evaluated clinically in stress-related disorders.
- The most prevalent subclass of CRF₁ antagonists are those with two atoms separating an aryl region moiety from the core nitrogen atom.
- A unique structural class of CRF₁ antagonists which incorporates a *trans*-4-aminomethylcyclohexylamino core with links to two aryl groups has been reported.
- Further clinical evaluation of new CRF receptor antagonists appears unlikely unless novel structures are identified that interact with the receptor distinct to the first-generation CRF₁ antagonists.

This box summarizes key points contained in the article.

depression (HAM-D) and anxiety (HAM-A) scores were reduced in the patients studied but further evaluation of compound 2 was halted due to the elevation of liver enzymes described in two healthy subjects in a volunteer trial. While this first Phase IIa trial provided hope for the field, another decade would lapse before NBI34041 (3) was administered to 24 male volunteers who were subjected to the Trier Social Stress Test [12]. This standardized public speaking exercise was used to elicit a stress hormone response and compound 3 successfully blunted the stress-induced increase in ACTH and cortisol without adversely affecting the basal levels of these hormones. Again, a tantalizing hint at efficacy in human disease but the ultimate test would be patients with depression or anxiety versus placebo.

Nearly 30 years after CRF was isolated, Pfizer reported a placebo-controlled study in patients with major depressive disorder with the CRF₁ antagonist CP-316,311 (4) [13]. Compound 4 was given to patients twice a day for 6 weeks but no improvement in the HAM-D scores was observed. This was followed by a similar result with verucerfont (5) [14] as well as a failure of pexacerfont (6) in a general anxiety trial [15]. Despite these major setbacks, there remains current interest in the development of CRF₁ antagonists. Verucerfont (5) is still being studied in post-traumatic stress disorder [16] and substance abuse [17] while pexacerfont (6) is being investigated for stress-induced relapse in craving responses to food [18], nicotine [19] and alcohol [20]. In addition, there are several new disclosures of structures in the patent literature, including a new structural class previously unseen in the CRF literature.

3. Type I CRF₁ antagonists

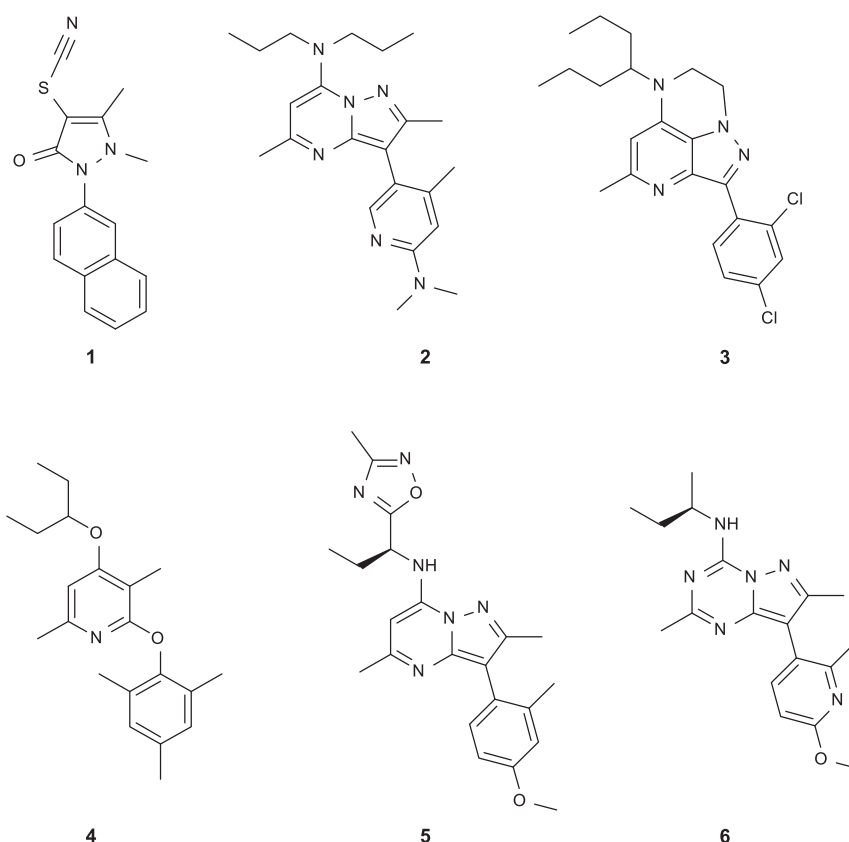
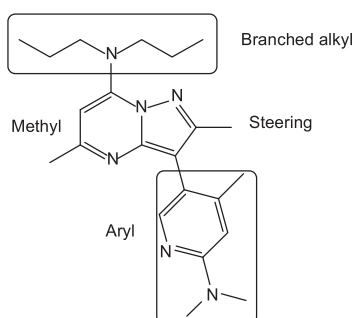
The typical CRF₁ antagonist consists of a 'core' nitrogen heterocycle with an 'aryl' substituent adjacent to the core nitrogen atom and a 'branched alkyl' group attached at the opposite end of the core [21]. The most prevalent subclass (designated Type I for the purpose of this review) of CRF₁

antagonists are those with two atoms separating the aryl region moiety from the requisite core nitrogen atom (which may play the role of a hydrogen bond acceptor when bound by the receptor). This is illustrated by compound 2 (Figure 2) with the 3-pyridyl group serving in the role as the aromatic substituent attached at the C-3 position of the pyrazolo [1,5-*a*]pyrimidine core and the dipropylamino group at C-7 represents the branched alkyl region. The methyl group at the C-4 position of the pyridyl and the methyl at C-2 of the core serve to steer the aryl group out of plane relative to the central heterocycle. Historically, CRF₁ antagonists have been associated with less than optimal physicochemical properties and it was assumed that these were a major contributor to CRF₁ antagonist struggles in the clinic.

Lead optimization efforts reported in the recent patent literature were aimed at improving the physicochemical properties of CRF₁ antagonists. One established tactic was to restrict the conformational freedom of the branched alkyl side chain, which in the case of compound 7 (Figure 3) resulted in NBI34041 (3) [22]. Restricting rotation of the lone pair of electrons in the nitrogen linking atom increased the basicity of the core pyrazolopyridine heterocycle leading to the observed decrease in the logD. Similar logic was employed in the preparation of 8 [23], a tricyclic analog of 9 [24] which was reported to have an IC₅₀ value below 50 nM in a monkey CRF binding assay using ¹²⁵I-CRF as the radiolabel. There are no additional reports of further evaluation of 8 but Emory University also disclosed a related series of tricyclic CRF₁ antagonists 10 [25]. The aim of the disclosure was to identify less lipophilic CRF₁ antagonists as potential positron emission tomography (PET) tracers. There were no biological data reported with respect to the tricyclic analogs but the bicyclic analog 11 was listed as an explicit example with CRF₁ binding data (*K_i* = 9 nM).

Compound 12 (Figure 4) is a structure that is reminiscent of the first-generation CRF₁ antagonists and, at first glance, would not appear to represent an improvement with respect to physicochemical properties [26]. It was later revealed that compound 12 has a longer 'residence time' on the receptor [27] and CRF₁ antagonists with longer residence times were more effective in reducing plasma ACTH levels in adrenalectomized rats [28]. Adrenalectomized rats are unable to regulate the ACTH levels since they lack the negative feedback of adrenal cortisol that controls ACTH release thus providing a sustained elevated level of the ACTH biomarker. The CRF₁ antagonist R121919 (2), with a preliminary hint of clinical efficacy, has a longer residence time versus CP-316,311 (4) which may prove to be an important factor in future CRF₁ antagonist development.

Another successful tactic used to increase polarity in CRF₁ antagonists is the introduction of aromatic heterocycles in the aryl region of the molecules as demonstrated in compound 2. There are two recent patent disclosures that utilize the same pyrazolo[1,5-*a*]pyrimidine core but incorporate new heterocycles in the aryl region. Eli Lilly reported 5-thiazolyl 13 [29]

Figure 1. First-generation CRF₁ antagonists.Figure 2. Regions of CRF₁ antagonist SAR.

and 2-thienyl 14 [30] substituted pyrazolopyrimidines but in contrast to 2, the branched alkyl group is attached directly to the core through a carbon atom (Figure 4). Compound 14 contains an additional heterocyclic substituent in the aryl region which is an approach also utilized in a series of pyrazolopyridines exemplified by compound 15 [31]. Transposition of the nitrogen atoms in the core heterocycle led to the related

imidazo[1,2-*b*]pyridazine CRF₁ antagonists 16 [32] and 17 [33]. These new CRF₁ antagonists are functionally active since compound 16 was reported as a high affinity ($K_i = 10$ nM), orally bioavailable antagonist which blocked stress-induced relapse in alcohol-seeking behavior by alcohol-dependent rats [34].

Reducing the number of carbon atoms in the core region is another avenue to decrease CRF₁ antagonist lipophilicity. Dupont Pharmaceuticals first reported the 5,5-bicyclic imidazo[4,5-*c*]pyrazole 18 [35] and Eisai has followed with the disclosure of 5,5-bicyclic pyrazolo[3,2-*b*][1,3]oxazoles as illustrated by compound 19 (Figure 5) [36]. Compound 19 utilizes a nitrogen atom as a linker to the branched alkyl group whereas compound 20 employs an oxygen atom [37]. Novartis reported 21, where a disubstituted 1,2,4-triazole is used as a replacement for the traditional branched alkyl group [38]. A closely related pyrazolo[3,2-*b*][1,3]thiazole 22 [39] has a methyl group adjacent to the nitrogen in the fused pyrazole ring while a less lipophilic methoxy group is present in compound 23 [40]. Additionally, compound 23 is an orally bioavailable, high-affinity antagonist ($IC_{50} = 70$ nM) that demonstrated anxiolytic activity in the light/dark test in

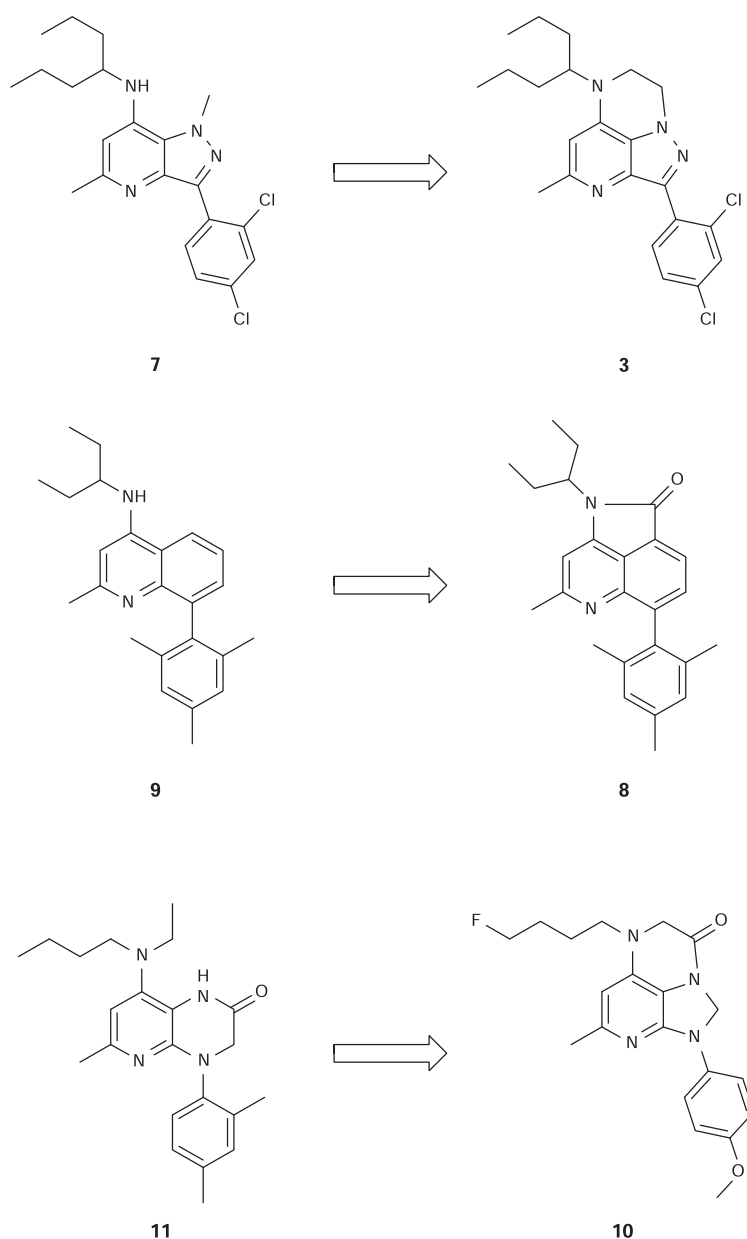


Figure 3. Tricyclic CRF₁ antagonists.

mice at 30 mg/kg [41]. Reducing the number of carbons further can be accomplished by eliminating the second ring altogether, as seen in the monocyclic pyrazinone antagonist **24** (Figure 6) [42]. The compound, apparently not exemplified in the original patent [43], has a low molecular weight branched alkyl group, a substituted pyridine in the aryl region and a core heterocycle with only one exposed carbon subunit. Of the remaining carbon atoms in the core, one is attached to the nitrogen linking atom, another is part of a carbonyl and

the remaining carbon is attached to a cyano group. Compound **24** ($\log D = 3.9$, $IC_{50} = 0.86$ nM) was active in the defensive withdrawal paradigm at an oral dose of 1.8 mg/kg which corresponded to 70% receptor occupancy [44]. Further modification of the branched alkyl region is represented by the pyrazinone **25**, where a polar carbamate moiety is utilized in place of the methoxy subunit [45].

The cyano group in pyrazinone **24** represents a new tactic in reducing the lipophilicity of CRF₁ antagonists. Early

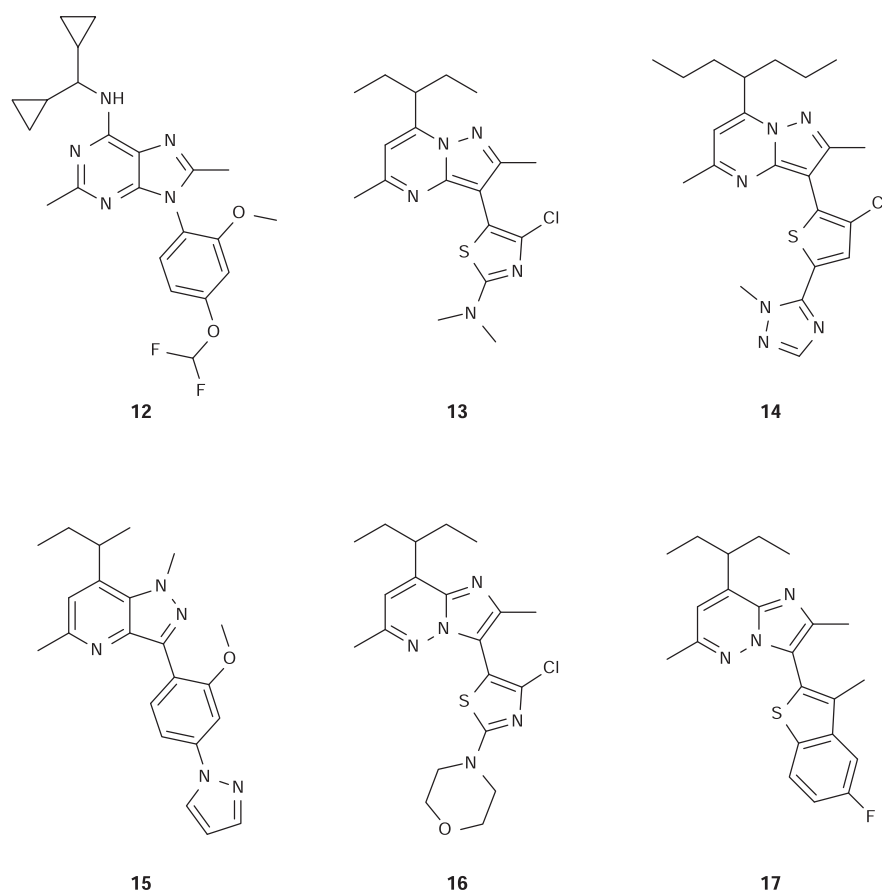


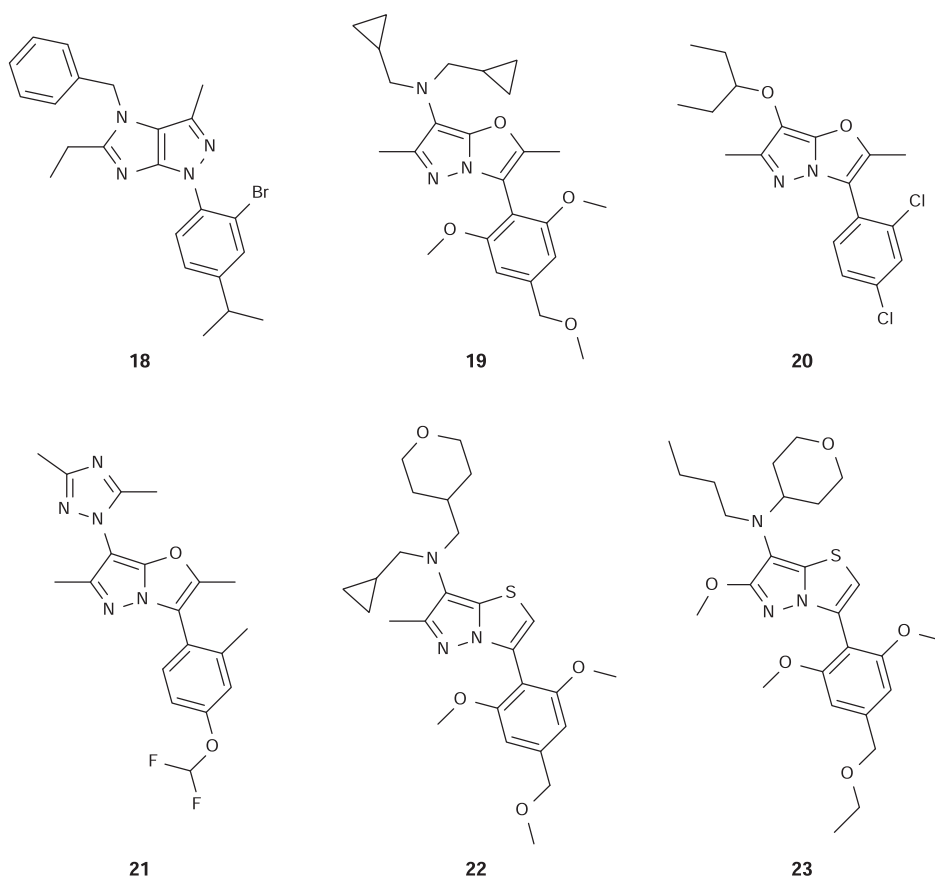
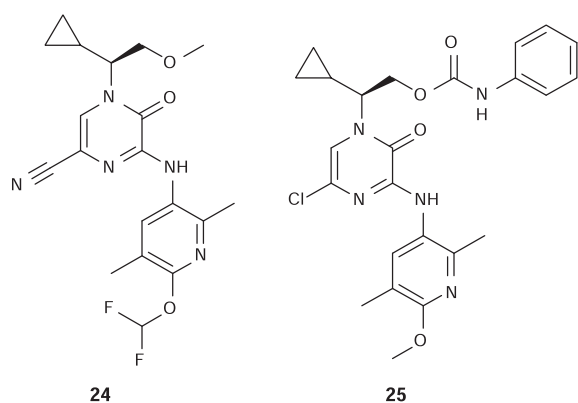
Figure 4. Type I 6,5-bicyclic CRF₁ antagonists.

structure–activity relationship (SAR) studies suggested that the ‘methyl’ region (Figure 2) adjacent to the core nitrogen only allowed for the presence of a methyl group for optimal CRF₁ binding activity [46]. A group from Ono Pharmaceuticals also challenged the accepted wisdom with the report of the tricyclic antagonist 26 (Figure 7) [47]. The addition of the third ring had no detrimental effect on the binding affinity ($K_i = 4$ nM) and 26 demonstrated anxiolytic activity in animals by increasing the time a rat spent in the open arms of an elevated plus maze following swim stress at an oral dose of 3 mg/kg. Heterocycles can be used instead of a lipophilic cyclopentyl ring as seen in the bicyclic analog 27 [48]. Tanabe reported compound 28 and in this example a second phenyl group is used in place of the typical branched alkyl moiety [49]. As seen in the earlier CRF₁ antagonist 18, 5-membered heterocycles can also be used in the core region. In the fused benzimidazole 29, the imidazolo group represents the key nitrogen heterocycle and a phenyl group in the ‘methyl’ region but, in contrast to compound 26, the phenyl now supports the branched alkyl moiety (Figure 8) [50]. There are also examples of bicyclic benzimidazoles 30 [51] as well as quinolines 31 [52]

where the aryl substituent is linked to the core through an oxygen atom. Analogous to compound 31 there is an oxygen linking the aryl side-chain in benzimidazole 32 [53] and there are also examples of carbon linkers 33 [54].

4. Type II CRF₁ antagonists

Antagonists of the CRF₁ receptor with only one atom separating the aryl group from the central nitrogen are designated as Type II and Elf Sanofi was the first to report a Type II compound 34 (Figure 9) [55]. Type II CRF₁ antagonists have many of the same features in common with the Type I antagonists but the branched alkyl region initially appeared to require more complicated side chains for biological activity. For example, the lead optimization of 34 ultimately led to SR-125543 (35) which was evaluated in major depressive disorder patients in 2011 [56]. Type II compounds with less complicated side chains were first reported by Neurogen and the pyrimidine 36 demonstrates the incorporation of a pentyl group in the branched alkyl region [57]. Restriction of the conformational freedom of the pentyl side chain resulted in the

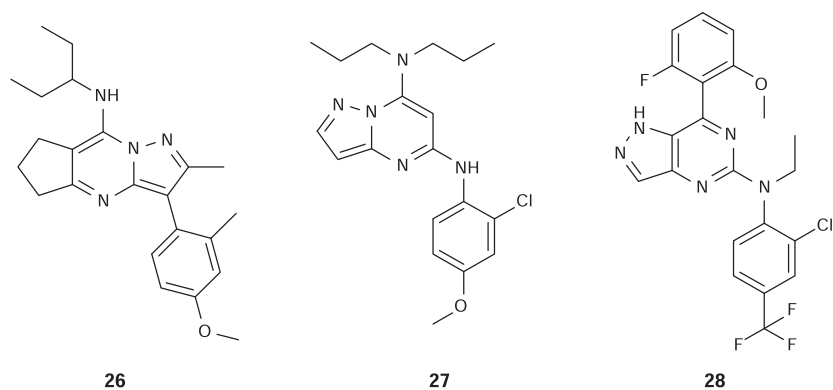
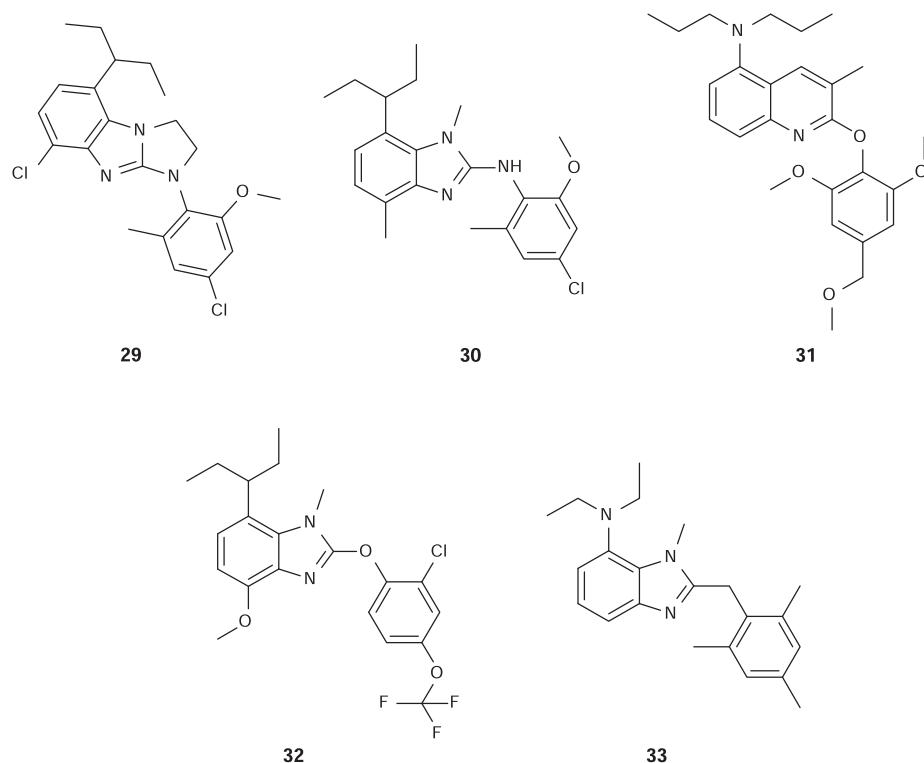
Figure 5. Type I 5,5-bicyclic CRF₁ antagonists.Figure 6. Type I monocyclic CRF₁ antagonists.

fused bicyclic benzimidazole 37 (Figure 10) [58]. This is an example of a 5,6-bicyclic ring system but there are also 6,5-systems 38 [59], 39 [60] as well as 6,6-ring systems 40 [61]. Compound 38 incorporated the same polar aryl region

substituent as R121919 (2) and the Type II analog 41 [62] incorporated the same aryl side chain as compound 16. These new bicyclic CRF₁ antagonists are functionally active (39, EC₅₀ = 3.2 nM) demonstrating anxiolytic activity in the elevated plus maze paradigm with swim stress at an oral dose of 10 mg/kg [63].

5. Cyclohexyl amide CRF₁ antagonists

Historically, there have been unique structures that do not appear to be directly related to the traditional Type I or II CRF₁ antagonists. Neurogen reported benzimidazole-containing amides 42 but similarity of the trisubstituted benzamide suggested that the amide moiety may be playing the same role as the core nitrogen in the typical CRF₁ antagonists (Figure 11) [64]. There was also a very unusual phenol 43 reported by Japan Tobacco [65] as well as two unique structures from the Combichem group, amidrazones 44 [66] and *N*-phenylphenyl glycines 45 [67]. Other than compound 43 demonstrating a reduction in plasma ACTH levels following colorectal distension [68], there has been no follow-up with

Figure 7. CRF₁ antagonists with rings adjacent to the core nitrogen heterocycle.Figure 8. CRF₁ antagonists with the branched alkyl region supported by additional ring.

respect to the biological activity of these unusual compounds and certainly no clinical evaluation reported.

Novartis revealed another unique structural class of CRF₁ antagonists that do not appear to overlap in similar chemical space with the traditional compounds. Compound 46

(IC₅₀ = 13 nM) comprises a *trans*-4-aminomethylcyclohexylamine with links to two aryl groups, one through an amide bond to a substituted phenyl and the second to a substituted pyridine via an alkylamine (Figure 12) [69]. With respect to the second aryl group, compound 47 [70] has the aryl group

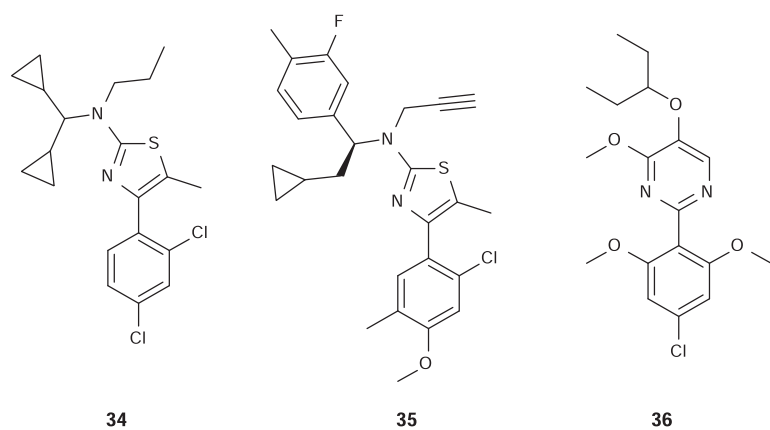


Figure 9. Monocyclic Type II CRF₁ antagonists.

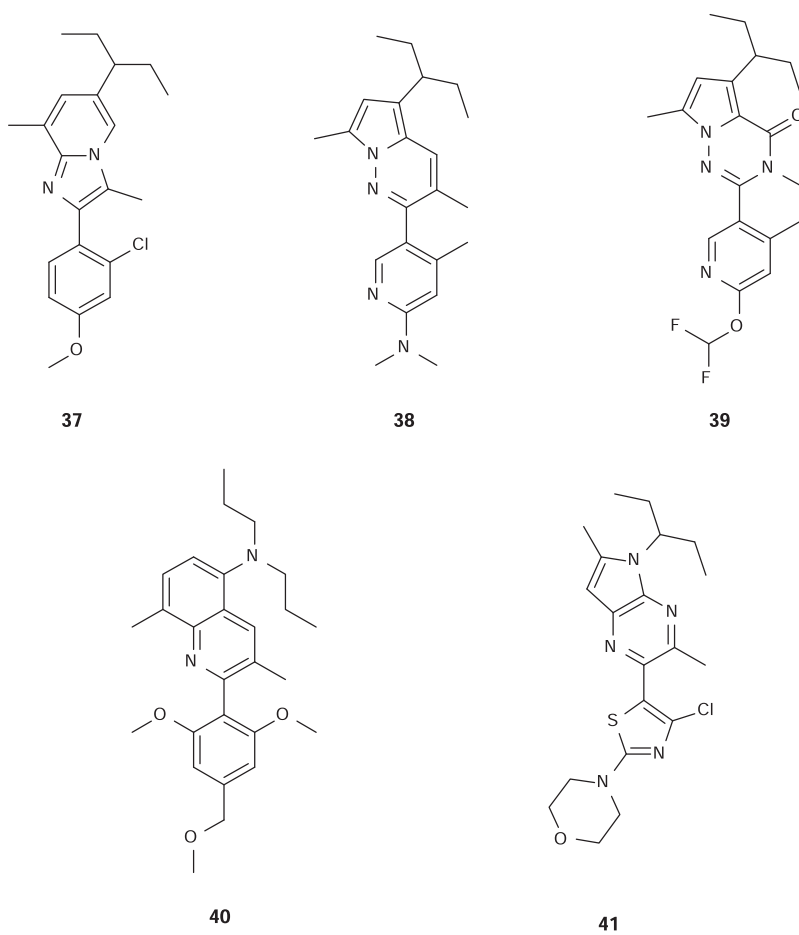


Figure 10. Bicyclic Type II CRF₁ antagonists.

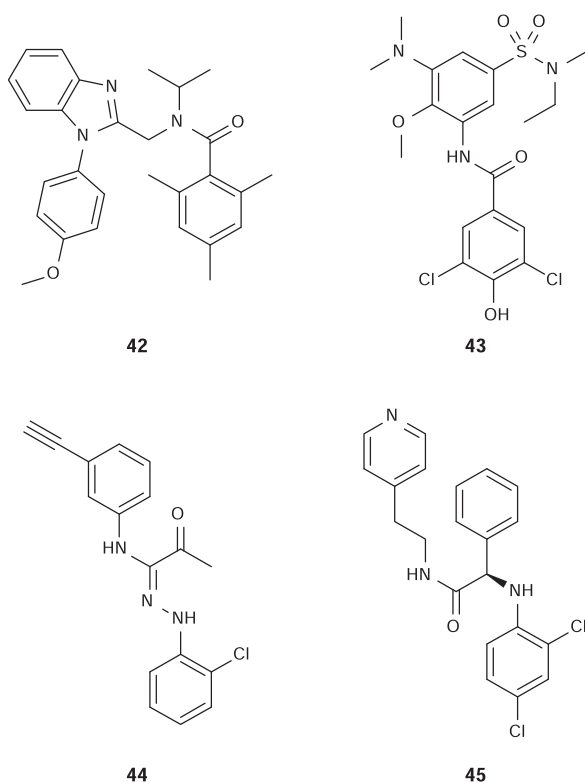


Figure 11. Atypical CRF₁ antagonists.

incorporated into an indolinone or can be part of a biaryl 3-phenylpyrazolyl group 48 [71]. Like the atypical compounds of the past, there is no additional information regarding the biological evaluation of these new series, leaving one only to speculate on future prospects.

6. Expert opinion

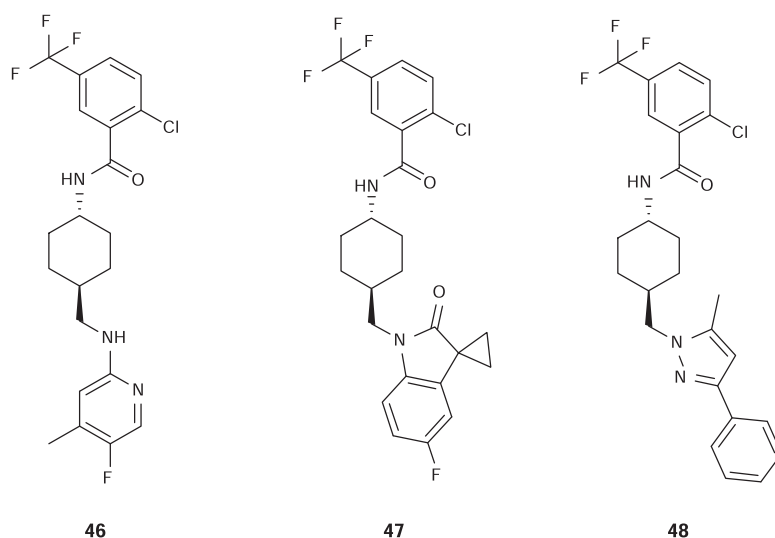
Antagonists of the CRF₁ receptor have not demonstrated clinical utility despite over 30 years of research and hundreds of patents. This is a very surprising result considering the central role that CRF plays in the human response to stress. One reason for this outcome could lie in the design of the trials or in the recruitment/screening of the patients since anxiety and depression are multifaceted complicated diseases [72]. From a pragmatic perspective, it is hard to imagine that efficacious compounds would not have been recognized in the trials. While these failures may seem daunting and cast little hope for the successful treatment of anxiety and depression with CRF₁ antagonists, perhaps the clinical application of CRF₁ antagonists needs to be re-assessed [73].

Another possibility is that there is a deficiency in the compounds evaluated to date.

It may be that small molecule (< 500 MW) CRF receptor antagonists will never effectively compete with peptide agonists that are > 10 times larger in molecular weight. The only compounds evaluated clinically have been the typical Type I or II CRF₁ antagonists and because this type of compound appeared to be the only lead available, the pharmaceutical industry focused solely on these motifs. It is possible that the way the typical antagonists block CRF binding may be inadequate and, as a result, unable to demonstrate robust functional activity in the most challenging *in vivo* paradigms (like depressed patients). There are major differences in the ability of CRF₁ antagonists to modulate plasma ACTH in adrenalectomized rats depending on receptor dissociation off rates of the antagonists from the CRF₁ receptor. The suggestion that small molecule CRF₁ antagonists have to remain engaged with the receptor for a long period implies that CRF has an inherent signaling advantage, which is not surprising considering the two-domain model of peptide agonist binding [74]. In this model, CRF binds to the extracellular domain (ECD) with moderate affinity (100 nM), effectively tethering the agonist to the juxtamembrane (J-domain) and the J-domain is the region where CRF activates the receptor with very high affinity resulting in intracellular signaling. The compounds that have been evaluated clinically are allosteric and interact with the CRF₁ receptor in the J-domain region, which blocks CRF signaling but not necessarily binding to the ECD. Would a molecule that targets the ECD region of the CRF₁ (and/or CRF₂?) receptor actually work in a clinical trial?

An encouraging development in the field of CRF receptor antagonism is a new report of an atypical series of cyclohexyl amide CRF₁ antagonists (Section 5) reported by Novartis. Unfortunately, there are no data available to establish if this new series (or any of the unusual CRF₁ antagonists) bind to the ECD region of the receptor and directly compete with CRF during the initial binding event. Compounds that bind to the ECD may also prove to be antagonists of the CRF₂ receptor and may contribute clinical activity even though the evidence supporting a role for a CRF₂ antagonist is ambiguous. CRF₂ knockout mice display an anxiogenic phenotype but this may just be a compensatory effect by the CRF₁ system [75]. Intracerebroventricular (ICV) delivery of peptide CRF₂ antagonists do not confirm these results and studies in double knockout animals suggest that there is a role for CRF₂ upstream of CRF₁ in the endocrine stress response [76].

The remaining question is why are there no ECD binding CRF receptor antagonists? There is no doubt that CRF receptors have been screened against many large pharmaceutical company small molecule libraries but there are no reports of validated ECD binding or CRF₂ antagonist leads. It is clear that targeting class B GPCRs like the CRF receptors remains a difficult challenge and will require an innovative screening approach. It seems unlikely that there will be a breakthrough in the near future as the window on CRF

Figure 12. Cyclohexyl amide CRF₁ antagonists.

antagonist research may be closing due to the inability of several innovator companies to achieve success in the clinic with a CRF₁ antagonist and since pharmaceutical companies are fleeing the area of central nervous systems disorders [77].

Declaration of interest

The author is an employee of Neurocrine Biosciences and veru-
cerfont is currently in the company's development portfolio.
The author declares no other conflict of interest.

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