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Review Paper

1,4-Benzodiazepine as Cholecystokinin receptor antagonist: A Review

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Abstract: 1,4-Benzodiazepines have been used since long for their interesting biological properties such as anxiolytic, sedatives, anticancer, antidiuretics, antimicrobial, antifungal, antiviral and many others. 1,4-Benzodiazepines as cholecystokinin antagonist has been of great interest for many research groups in the world. In this review, we have highlighted the biological profile of cholecystokinin with its structure, function and its antagonists. We have tried to cover utmost references from the literature elucidating the evolution of cholecystokinin receptor antagonists during the last few decades.

1. Introduction

Cholecystokinin (CCK) is derived from Greek word chole, "bile"; cysto, "sac"; kinin, "move"; hence, it means move the bile-sac (gallbladder), it is a peptide hormone in the gastrointestinal system responsible for stimulating the digestion of fat and proteins. Previously, it was called pancreozymin, synthesized by I-cells in the mucosal epithelium of the small intestine. It is secreted in the duodenum which causes the release of digestive enzymes and bile from the pancreas and gallbladder, respectively. It also acts as a hunger suppressant and plays a major role in drug tolerance to opioids like morphine and heroin. It is partly implicated in experiences of pain hypersensitivity during opioids withdrawal. [1,2]

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2. Structure of CCK

The peptide CCK was originally discovered in the gastrointestinal tract [3] which has been shown to mediate pancreatic secretion and contraction of gallbladder. The CCK was described in the mammalian central nervous system (CNS) as a gastrin-like immunoreactive material [4]. It is now generally believed to be the most widespread and abundant neuropeptide in the CNS. This peptide, initially characterized as a 33-amino-acid sequence is present in a variety of biologically active molecular forms derived from a 115-amino-acid precursor molecule prepro-CCK; [5] such as CCK-58, CCK-39, CCK-33, CCK-22, sulfated CCK-8 [Asp-Tyr(SO_3H)-Met-

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Gly-Trp-Met-Asp-Phe-NH_2] and CCK-7, unsulfated CCK-8 and CCK-7, CCK-5, and CCK-4 (Trp-Met-Asp-Phe NH_2); (Figure-1)[6]. The presence of CCK in the gut and the brain raises the intriguing issue of the evolutionary significance of separate pools of a peptide in two systems originating from different embryonic zones.

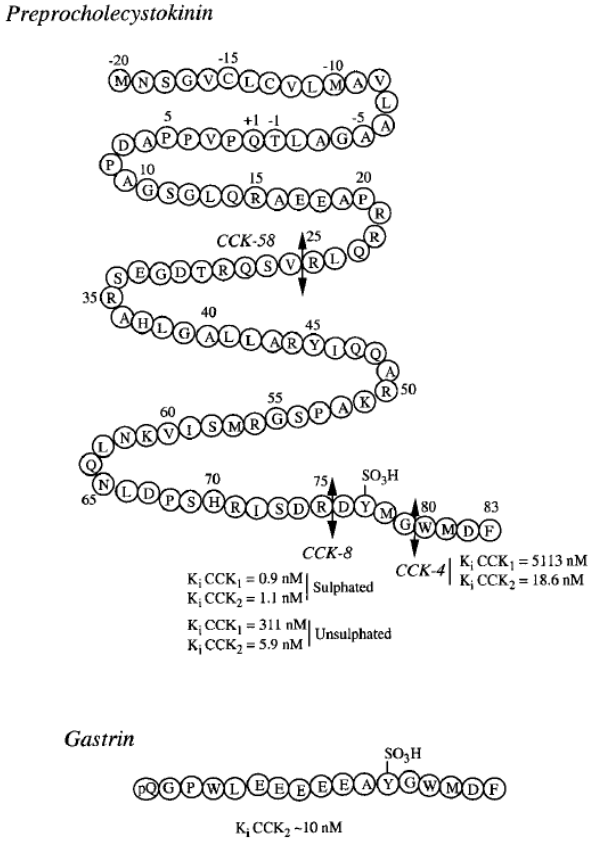

Figure-1: Predicted structure of human preprocholecystokinin. The signal peptide consists of residues 220 to 21. The amino terminal flanking peptide consists of residues 1 to 25. The largest characterized form from brain and intestine, CCK-58, consists of residues 26 to 83. Other active molecular forms are derived from this precursor, such as CCK-39, CCK- 33, CCK-22, CCK-7, and CCK-5.

3. CCK Receptors

CCK exerts its biological effects by binding to specific receptors on its target tissues. CCK receptors are a group of G-protein coupled receptors. Originally these receptors were characterized on pancreatic acinar cells, islets, gallbladder and brain by radio-ligand binding and autoradiography [7]. In the pancreas and gallbladder, CCK bound with an affinity that was ~1,000-fold greater than that of either unsulfated CCK or gastrin. These receptors were termed CCK-A. In the brain, however, CCK and gastrin bound with similar affinities. These receptors are known as CCK-B. (B for brain origin) Along with these two types of CCK receptors, a third related type, “gastrin receptor,” which exhibited binding properties similar to those of the brain CCK receptor, was believed to transmit the biological actions of gastrin in the stomach. However, with recent cloning and expression of the CCK receptor cDNAs, it has become clear that there are only two type of CCK receptors, CCK-A and CCK-B, and the gastrin receptor is identical to the CCK-B receptors. The CCK-A receptor complementary DNA was cloned following purification of the receptor protein from rat pancreatic acinar cells. [8] The cDNA encodes a seven transmembrane protein typical of G protein-coupled receptors. It consists of 444 amino acids, which when expressed in transfected cells, demonstrates high affinity for sulfated CCK and much lower affinity for unsulfated CCK or gastrin. The CCK-B receptor cDNA was identified by expression cloning from canine gastric parietal cells. [9] Tissue distribution, their ligands and functions of CCK receptors has been tabulated in Table-1. [10][11]

4. Physiological Implications of CCK Receptors

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CCK receptors play very important role in maintaining the normal physiological functions which may be divided into following sub-headings:

4.1. Peripheral Functions

CCK-A receptors in the periphery are primarily localized in the pancreas, gallbladder, pylorus, intestine and vagus nerve [12]. In the pancreas, CCK acts at CCK-A receptors on acinar cells to stimulate the secretion of the digestive enzyme pancreatic amylase. [13] In the gallbladder, CCK acts at CCK-A receptors to stimulate gallbladder contraction. [14] Commercial preparations of CCK are used clinically to evaluate gallbladder contraction in human gallbladder disease. [15] CCK-A receptors appear to mediate the transmission of sensory information from the gut to the brain. Peripherally administered CCK inhibits food consumption, even after fasting, in many species, including humans. [16] CCK-A receptor antagonists increase food consumption and postpone satiety in several species, supporting the idea that endogenous CCK participates in the physiological regulation of feeding behavior. [17] The entry of food into the intestine triggers the release of endogenous CCK by the intestinal mucosa, thereby activating CCK-A receptors in the periphery. In particular, CCK-A receptors on the vagus nerve appear to be critical for the satiety-inducing action of CCK [18]. CCK-A receptor agonists have been proposed as anorectics for the treatment of obesity. [19] Conversely, CCK-A receptor antagonists have also been proposed for the treatment of anorexia disorders. [20] CCK-B receptors in the periphery are primarily localized in the stomach [21] and on the vagus nerve in some species [22]. It has been demonstrated that gastrin acts at CCK-B receptors to stimulate gastric acid secretion[23]. Similarly, CCK stimulates gastric acid secretion [24], and this effect can be blocked by CCK-B receptor antagonists [25]. CCK-B receptor antagonists have been proposed for the treatment of gastric ulcers. [26] It has been shown that activation of CCK-B receptors released only acetylcholine, whereas activation of CCK-A receptor is responsible for the release of both substance P and acetylcholine. [27]

4.2. Central Functions

With wide distribution in the brain, CCK is involved in the modulation/control of multiple central functions. Numerous experimental and clinical studies have clearly shown that CCK participates in the neurobiology of anxiety, depression, psychosis, cognition, and nociception through its action at CCK-A and CCK-B receptors.

4.2.1. CCK in panic attacks and anxiety.

The initial suggestion that the CCK system might be involved in anxiety came from the observation of Bradwejn and de Montigny (1984, 1985a,b) that showed that benzodiazepine receptor agonists could attenuate CCK-induced excitation of rat hippocampal neurons which subsequently demonstrated that CCK-B receptor agonist pentagastrin provoke panic attacks in patients with panic disorders [28] The induced symptoms are comparable to those produced by a standard panic-provoking agent [29] and can be attenuated by antipanic pharmacological agents such as antidepressants [30]. Sensitivity to the peptide is enhanced in panic disorder patients relative to healthy volunteers [31] suggesting that endogenous CCK system may be altered in panic disorder and contributes to pathological anxiety. Recent

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investigations have revealed that the panicogenic effects of CCK-B receptor agonists are not limited to panic disorder, because individuals with social phobia, generalized anxiety disorder, obsessive compulsive disorder, and premenstrual dysphoric disorder also exhibit an augmented behavioural response to these ligands [32]. A number of investigators have reported that the CCK peptides (Boc-CCK-4, BC 197) administered systemically or intracerebrally produce anxiogenic-like effects in different animal species, including mouse, rat, guinea pig, cat and monkey [33] The effects of CCK compounds could vary considerably because of existing differences in the distribution and binding characteristics of CCK receptor types and/or affinity states among species. The behavioral effects of CCK-B receptor agonists in humans are accompanied by marked biological alterations, including robust increases in heart rate, blood pressure, and minute ventilation [34], increased hypothalamic-pituitary-adrenal axis activity [35], and elevated blood levels of dopamine, epinephrine, norepinephrine, and neuropeptide Y [36]. In a study with healthy volunteers shows that CCK-4-induced anxiety is associated with the cerebral blood flow activation in the anterior cingulate gyrus, the claustrum-insular-amygdala region, and the cerebellar vermis [37]. Although these studies indicate that the brain mechanisms are activated after CCK-4 administration, they do not elucidate the precise neuronal circuitry subserving CCK-4-induced panic. It has been proposed that brainstem nuclei, including nucleus tractus solitarius, medulla, and parabrachial nucleus, are important sites of action of exogenous CCK-4 [38]. These structures contribute to the regulation of respiration and cardiopulmonary function and have close anatomical and functional links with the locus ceruleus, a brain region involved in the expression of fear and anxiety. Studies in animals have shown that CCK interacts with brainstem structures to modulate respiration, heart rate, and blood pressure [39], and it is likely that the prominent cardiorespiratory symptoms elicited by exogenous CCK-4 in humans result from direct or indirect stimulation of CCK receptors in brainstem nuclei. The emotional symptoms evoked by CCK-4 may rise from an action of this peptide on brainstem structures and a subsequent activation or inhibition of higher CNS regions mediated through neuronal projections. The anxious behavior induced by various CCK fragments is associated with selective CCK-B receptor stimulation [40]. Thus, acute treatment with the selective CCK-B receptor antagonist L-365,260 was reported to block CCK-4-induced panic attacks in panic disorder patients [41] and pentagastrin-induced panic symptoms in healthy volunteers [42]. Studies have demonstrated that serotonin, norepinephrine, dopamine, opioids, corticotropin-releasing factor, and the benzodiazepine/γ-aminobutyric acid complex play salient roles in the induction of anxiety with CCK [43].

4.2.2. CCK and Schizophrenia.

The existence of interactions between dopaminergic and CCKergic systems has been demonstrated by a large body of electrophysiological, behavioral, and neurochemical data [44]. Moreover, dopamine has been shown to be co-localized with CCK in the posterior part of the nucleus accumbens [45]. This observation can have clinical relevance because the A-10 dopaminergic neurons that project to the nucleus accumbens, much more than the other dopaminergic systems, are probably concerned by the pathophysiological mechanisms of schizophrenia [46]. Numerous experiments have shown that

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CCK modulates the release of dopamine and that dopaminergic agents modulate the release of CCK [46]. The interactions between CCK and dopamine are complex and often bidirectional as CCK inhibits the action of dopamine which depends on the brain region. Thus, local administration of the CCK-B receptor agonists BC 264 or CCK-8 reduced dopamine release in the nucleus accumbens of microdialysed rats, whereas via the i.p. route, the former agonist produced a large increase in dopamine release in the same area [47]. One hypothesis to account for the i.p. effects of BC 264 could be that this agonist, acting on the CCK-B receptors located in the dorsal subiculum/CA1 of the hippocampus, stimulates the glutamatergic projections to the anterior nucleus accumbens, resulting in dopamine release [48]. The precise role of CCK in schizophrenia remains incompletely understood. The most prominent finding relevant to this disorder is a reduction in post-mortem CCK mRNA levels in different brain areas (frontal, cerebral and entorhinal cortices, and subiculum) of schizophrenic patients [49]. In addition, significant reductions in CCK-like immunoreactivity have been reported in several brain regions of schizophrenic patients [50], especially those with predominantly negative symptoms. On the other hand, a lower density of CCK receptor-binding sites has been found in the hippocampus and frontal cortex of schizophrenic patients compared with controls [51]. However, it should be noted that not all studies confirmed the decrease in CCK mRNA levels in schizophrenia. It suggests that elevated CCK synthesis in regions rich in dopaminergic neurons may be associated with schizophrenia. The available data suggest that schizophrenia may be associated with reduced CCK activity. This reduction may be attributed to either a decreased processing of preproCCK in neurons or a reduction in synaptic levels of CCK due to activations in catabolic or putative reuptake processes [52] or some neurodegeneration of CCKergic neurons in schizophrenia.

4.2.3. CCK and Depression.

One of the physiological actions of the neuropeptide CCK seems to involve modulation of the nigrostriatal and mesolimbic dopaminergic pathways. Taking into consideration that the mesolimbic dopaminergic pathways play a crucial role in motivation and rewarding processes, which are likely to be altered in depression [53], a role of CCK in mood disorders cannot be excluded. Several studies have shown that selective CCK-B receptor agonists, such as BC 264 and BC 197, potentiate the decrease in motor activity in mice that have been subjected to electric footshocks the day before, whereas CCK-B receptor antagonists, on their own, exert an opposite effect [54]. These results suggest that CCK-B receptor antagonists have antidepressant-like properties in mice. The involvement of CCK in behavioral responses associated with anticipatory stress has already been demonstrated and the importance of external stimuli, such as a novel environment, in revealing the behavioral effects of CCK receptor agonists or antagonists has been emphasized in several studies [55].

5. Interactions with other receptors

CCK has also been shown to interact with calcineurin in the pancreas. Calcineurin will go on to activate the transcription factors NFAT, which will stimulate hypertrophy and growth of the pancreas. CCK can be stimulated by a diet high in protein, or by protease inhibitors [56]. CCK has been shown to interact with orexin neurons which control appetite and wakefulness (sleep) [57]. CCK seems to have other indirect

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effects on sleep regulation [58]. CCK cannot cross the blood brain barrier, but certain parts of the hypothalamus and brainstem are easily reached by CCK.

6. CCK Antagonists

The effects of CCK on intestinal smooth muscle and pancreas are easy to demonstrate pharmacologically, unlike the role in the CNS, which is a matter for conjecture. It was assumed that the CNS activity must be significant, given the abundance of the peptide in the brain, and that the discovery of antagonists might lead to new drug treatments.

Asperlicin **1** is moderately potent, poorly soluble in water, and not bioavailable by the oral route. This is one of the very few non-peptides with affinity for a peptide receptor and interesting target for synthetic modification, particularly viewed as a benzodiazepine derivative with potential CNS activity. Based on the benzodiazepine nucleus, and an overt mimic of diazepam, one of the first successful synthetic analogues was L-364, 286 **2**, which had potency on CCK-A receptors similar to that of asperlicin **1**. Better receptor affinity was achieved with 3-amide-substituted benzodiazepines: the 2-indolyl derivative L-364, 718, also known as MK-329 **3**, is five orders of magnitude more potent than asperlicin **1** at CCK-A receptors. Modification of the 3-amide to give a urea linkage as in compound **4** led to a reduction in CCK-A receptor affinity. Importantly, discrimination between CCK-A and CCK-B receptors by compound **4** is governed by the stereochemistry at C3, the (*S*)-enantiomer showing greater affinity for CCK-A receptors. The (*R*)-enantiomer, prefers CCK-B receptors, antagonizes gastrin stimulated acid secretion in animal models, among other CNS effects, induces analgesia in primates and displays anxiolytic properties. Clinical trials of compounds in this series have been disappointing because of poor bioavailability, but the general concept of finding a therapeutic agent through antagonism of CCK-B receptors is still viable and it is reported that the number of patents in this area has increased in the last 5 years. (Figure-1) [59].

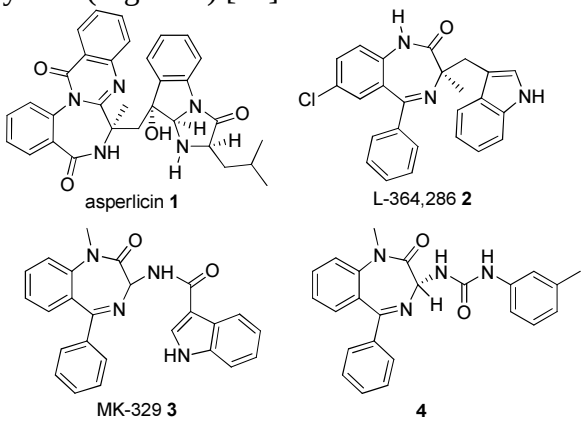

Figure-1

7. Recent advancements in 1,4-benzodiazepines

Bradwejn and Montigny [60] have reported first time that the benzodiazepines (at very low doses) can antagonize selectively the sulphated octapeptide (CCK_8)-induced activation of rat hippocampal pyramidal neurons. They studied the activity of four benzodiazepines in this study (flurazepam **5**, diazepam **6**, lorazepam **7** and chlordiazepoxide **8**) and suggested that the ability to antagonize CCK_8-induced activation is a common property of all drugs in this class. The inactivity of the three anxiolytic non-benzodiazepine drugs tested (haloperidol **9**, phenobarbital **10** and meprobamate **11**) constituted a preliminary indication that this property might be specific to benzodiazepines only. (Figure-2) This antagonism of CCK_8-induced activation might be a property common to and specific for benzodiazepines. It was fully consistent with the prevention and the reversal by Ro 15-1788, a specific

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'neuronal' benzodiazepine antagonist, as the effect of benzodiazepines on CCK_8-induced activation.

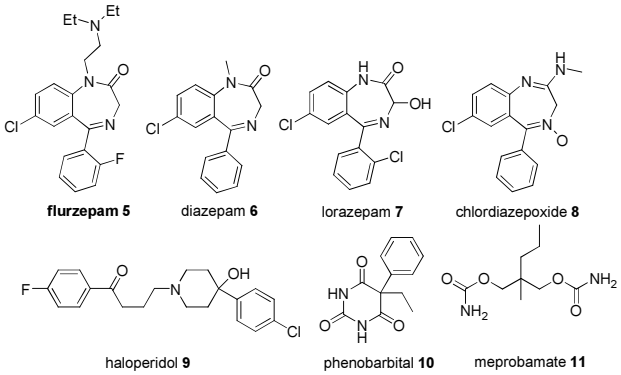

Figure-2

Similarly, Kubota et al [61] have observed the reversal of antinociceptive effect by intraperitoneally administered benzodiazepines, (chlordiazepoxide (2-5mg/kg), diazepam (1 mg/kg), flurazepam (1 mg/kg) and a benzodiazepine antagonist, Ro 15-1788 (0.5 mg/kg)) in mice which was induced by intracisternal administration of CCK_8 (1.0µg/kg).

Furthur, Kubota et al [62] reported CCK antagonism by benzodiazepines in the contractile response of the isolated guinea-pig gallbladder. They observed that benzodiazepines inhibit the contractile response of circular muscle strips from the isolated guinea-pig gallbladder to CCK_8 in the presence of atropine. The dose-response curves for CCK_8 were shifted in parallel to the right by 10^{-6} to 10^{-5} M of the three benzodiazepines, although the maximum response to CCK_8 was depressed by higher concentrations. The non-specific inhibitory action of the benzodiazepines was presumed to be due to the Ca^{2+} antagonist-like action of the benzodiazepines. The antagonism between CCK_8 and the benzodiazepines in the gallbladder was unaffected by GABA.

Meldrum et al [63] has investigated the antagonistic effect of CCK on the nerve-mediated and direct excitatory effects on smooth muscle and pancreatic acini. Results showed that the lorazepam and chlordiazepoxide selectively inhibit the nerve-mediated response of ileal longitudinal muscle to CCK, but have no effect on the direct stimulation of gall-bladder muscle or pancreatic acini by this peptide. Lorazepam and chlordiazepoxide inhibited responses of guinea-pig ileum, but not gall-bladder to CCK. Responses of both tissues to acetylcholine were unaffected and lorazepam did not inhibit ideal responses to neurotensin, 5-hydroxytryptamine and substance P which act entirely or in part by stimulating myenteric nerves. Chlordiazepoxide did not inhibit CCK-stimulated amylase release from dispersed rat pancreatic acini. Higher concentration of the same drugs and diazepam, (which has high affinity for benzodiazepine receptors on gastrointestinal muscle) inhibited responses of ileum and gall-bladder to both CCK and acetylcholine.

Evans et al [64] reported the design and synthesis of nonpeptidal antagonists of CCK. Several of these compounds have high specificity and nanomolar binding affinity and were active after oral administration. Compound **12** was the first specific nonpeptidal antagonist of CCK with highest potency and good oral bioavailability followed by compound L-364,718 **13**. Furthur, Chang et al [65] reported the biochemical and pharmacological characterization of an extremely potent and selective nonpeptide CCK antagonist **13**. The affinity of L-364,718 for both pancreatic (IC_{50}, 81 pM) and gallbladder (IC_{50}, 45 pM) CCK receptors in radioligand binding assays greatly exceeded that of other reported nonpeptide CCK antagonists and was similar to that of CCK itself. In vitro functional studies utilizing CCK-induced contractions of the isolated guinea pig ileum

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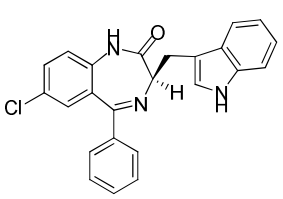
and colon further demonstrated that L-364,718 acts as a competitive CCK antagonist, which lacks agonist activity and has a similar high affinity in these tissues. The L-364,718 exhibited a very high selectivity for peripheral CCK receptors relative to brain CCK, gastrin, and various other peptide and nonpeptide receptors in both in vitro radioligand and isolated tissue assays. In vivo, low intravenous doses of L-364,718 (0.1 mg/kg) markedly antagonized the contractions of the guinea pig gallbladder produced by intravenous administration of CCK for at least 2 hr; whereas oral administered L-364,718 (ED_{50}, 0.04 mg/kg) was highly effective as an antagonist of CCK-induced inhibition of gastric emptying in mice. Further, Zelles et al [66] have studied the antagonistic effect of L-364,718 on nerve-mediated responses to CCK, i.e. on neuronal receptors of CCK located on cholinergic neurons of Auerbach's plexus in the guinea-pig ileum. The release of [^{3}H] acetylcholine ([^{3}H]ACh) from Auerbach's plexus and the contraction of longitudinal muscle strips in response to the administration of CCK were measured and recorded simultaneously. The peripheral CCK receptor antagonist, L-364,718, antagonized the AcH releasing effect of CCK in a dose-dependent manner. The IC_{50} value and the dissociation constant (K_D) were 41.0±2.0 pM and 0.06±0.01 nM, respectively.

Melville et al [67] have also reported that L-364, 718 (devazepide) is a potent and selective CCK-A antagonist and can reverse the inhibitory effect of exogenously administered CCK_8 on food intake.



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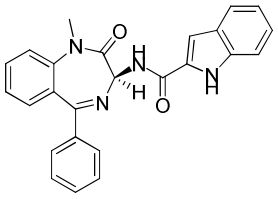
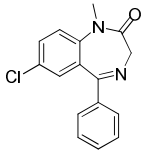


13; L-364,718

Evans et al [68] have reported the synthesis of a new series of 3-substituted 5-phenyl-[l,4]-benzodiazepines as a nonpeptidal antagonists of the peptide hormone CCK. The activity results of the newly synthesized compounds showed that 2'-fluoro substituent **14** and triazole fusion **15** enhance binding to peripheral CCK receptors. These modifications have been reported to enhance antianxiety activity in structure **16** in similar fashion. On the other hand, N1-(carboxymethyl) modification as in **17**, gave compound with good CCK receptor affinity in the 3-substituted series and compound **18** has 100 nM affinity and >600-fold selectivity for peripheral CCK receptors to central CCK or gastrin receptors.



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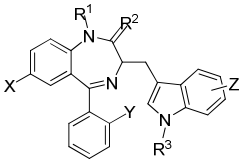

14; X=H, Y=F, Z=H, R^1=H, R^2=O, R^3=H, 3-stereo=R
15; X=H, Y=F, Z=H, R^1-R^2=C(CH_3)=NN, R^3=H, 3-stereo=R
17; X=H, Y=F, Z=H, R^1=CH_2COOH, R^2=O, R^3=H, 3-stereo=R
18; X=H, Y=H, Z=H, R^1=CH_3, R^2=O, R^3=CH_3, 3-stereo=R

Bock et al [69] have prepared a new series of 4-substituted 4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepines by standard methodology. These compounds were tested in radio ligand binding assay as antagonists for the binding of [^{125}I] CCK to rat pancreas and guinea pig brain receptors and binding of [^{125}I] gastrin to guinea pig gastric glands. All compounds were proved to have greater affinity for the peripheral CCK receptor with some analogues having activity in the

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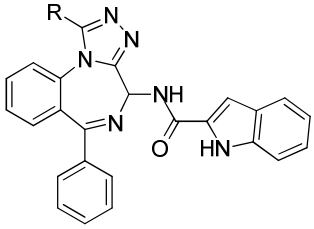
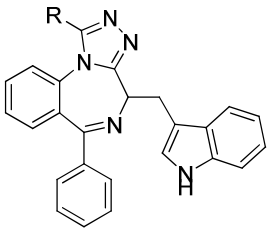
subnanomolar range. The most potent and selective CCK antagonists are compound **19** and **20**. The substituent attached to the 4-position of the triazolobenzodiazepine ring, which is optimum for CCK antagonist potency, was again found to be the indole moiety. Similar to previous findings, an aminocarbonyl linkage from the benzodiazepine ring to the 2-position of indole is preferred to a methylene bridge to the 3-position of the indole nucleus (cf. **21** and **19**, **22** and **20**).

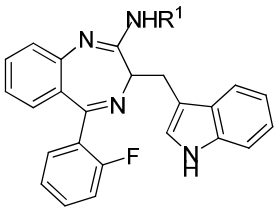


19; R=H
20; R=CH_3

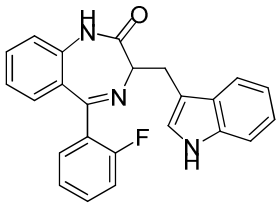


21; R=H
22; R=CH_3

Further, Bock et al [69] have synthesized and evaluated eight novel 3-substituted-[1,4]benzodiazepin-2-amines as CCK receptor antagonist. The most potent and selective compounds among the benzodiazepin-2-amines proved to be the unsubstituted 2-amino derivative **23**, and those bearing small substituents, e.g., **24**, **25**, and **26**. This study concludes that the more potent benzodiazepin-2-amines displayed a marked improvement in aqueous solubility compared to their benzodiazepin-2-one counterparts. For example, compound **22** was found to be 1000-fold more soluble in 0.1N HCI solution than compound **27**, whereas the two compounds were almost equipotent (1.7 µM vs 0.5 µM, respectively). In addition, the 3-substituted [1,4]benzodiazepin-2-amines display a marked enhancement in aqueous solubility over their 3-substituted 1,4-benzodiazepin-2-one counterparts.



23; R^1=H, **24**; R_1=CH_3,
25; R^1=$CH_2CH_2CH_3$,
26; R^1=CN,



27

Bock et al [70] have reported new series of benzodiazepines which bind selectively to brain CCK (CCK-B) and gastrin receptors. It was previously reported that 4-chlorobenzoyl CCK antagonists such as **28** rival MK-329 (L-365,260) in potency and selectivity. [2] When either the N-1-methyl substituent of **28** is substituted with an ethoxycarbonyl group as in compound **29** or the 3-amide linkage is replaced with a urea as in compound **30**, the CCK-A affinity decreases substantially and the CCK-B affinity increases modestly. Combination of these two features yielded the pivotal compounds **31** and **32**, the first nanomolar potency, nonpeptide ligands selective for the CCK-B and gastrin receptors. The potency and selectivity exhibited by **32** were further enhanced by transforming the N-1 group to a pyrrolidinamide. The resultant compound **33** was a nonpeptide with receptor affinity comparable to that of the native peptide ligands. The enantiomers of 3*S* configuration, compound **34** and **35** shows selectivity for the CCK-A receptor, whereas the mirror image 3*R* isomers, compound **36** and **37** are selective for the CCK-B and gastrin receptors. The compound of principal interest developed in these studies is compound **37** (L-365,260), a potent and selective CCK-B and gastrin receptor ligand. In a separate report, compound **37** was shown to interact competitively with these receptors and to be orally effective as an antagonist of gastrin-stimulated acid secretion in various animal models. Lotti et

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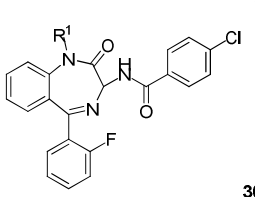
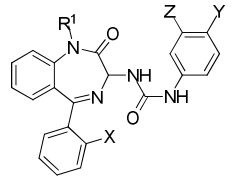
al [71] have studied and reported that compound **37** interacted in a stereoselective and competitive manner with guinea pig stomach gastrin and CCK-B receptors. The affinity of L-365,260 for both gastrin (K_i = 1.9 nM) and brain CCK-B (K_i = 2.0 nM) receptors was > 2 orders of magnitude higher than its affinity for peripheral pancreatic CCK-A receptors or various other receptors. In vivo, oral administration of L-365, 260 antagonized gastrin-stimulated acid secretion in mice (ED_{50} = 0.03 mg/kg), rats (ED_{50} = 0.9 mg/kg) and guinea pigs (ED_{50} = 5.1 mg/kg). [3] In another study by Sadzot et al [72], reviles that MK-329 is a highly selective and very high affinity antagonist at the peripheral CCK receptors. This study reviles that more than 80% specific binding was detected in the pancreas.



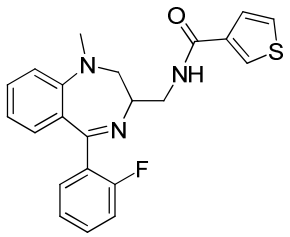
28; R^1=CH_3, stereo-*S*
29; R^1=CH_2CO_2Et, stereo-*RS*



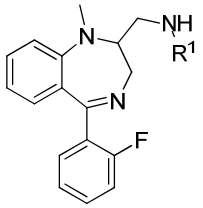
30; X=F, R^1=H, stereo-*RS*, Y=Cl, Z=H
31; X=F, R^1=CH_2CO_2Et, stereo-*RS*, Y=Cl, Z=H
32; X=H, R^1=CH_2CO_2Et, stereo-*RS*, Y=Cl, Z=H
33; X=H, R^1= CH_2CON stereo-*RS*, Y=Cl, Z=H

34; X=H, R^1=CH_3, stereo-*S*, Y=Cl, Z=H
35; X=H, R^1=CH_3, stereo-*S*, Y=H, Z=CH_3
36; X=H, R^1=CH_3, stereo-*R*, Y=Cl, Z=H
37; X=H, R^1=CH_3, stereo-*R*, Y=H, Z=CH_3

Bock et al [73] utilized tifluadom **38**, a κ-opioid agonist and CCK-A receptor antagonist, as a model to prepare a series of 2-(aminomethyl)- and 3-(aminomethyl)[1,4]benzodiazepines. These compounds were tested in vitro as inhibitors of the binding of [^{125}I] CCK to rat pancreas and guinea pig brain receptors. All compounds with IC_{50} less than 100 µM proved to have greater affinity for the CCK-A receptor, the most potent analogues, **39** and **40**, having an IC_{50} of 0.16 µM and 0.6µM respectively.

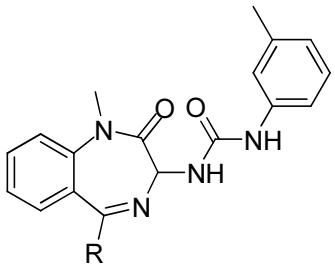


38; (*R,S*)-tifluadom



39; R^1=2-indolylcarbonyl
40; R^1=(*S*)-(+)-mandeloyl

Chambers et al [74] have reported the synthesis of C5-cyclohexyl analogue of the CCKB receptor antagonist L-365,260. The derivative, L-708,474 **41** has significantly higher CCK-B affinity and markedly improved CCK-B/CCK-A receptor selectivity (6,500 v. 87-fold) than the parent compound and about thirty-fold higher in affinity than L-365,260 at the CCK-B receptor.



L-365,260; R = Ph
41; L-708,474; R = cyclohexyl

Showell et al [75] have reported a series of water-soluble 5-amino[1,4]benzodiazepines CCK-B/gastrin receptor antagonists containing a cationic solubilizing group. The CCK receptor affinities of all the ligands were evaluted in vitro using radioligand binding techniques on rat pancreatic membranes (for CCK-A) and guinea pig cortical membranes (for CCK-B). Compound **42** showed highest CCK-B receptor affinity (IC_{50}, 0.10 nM) while also displaying excellent receptor subtype selectivity (CCK-A/CCK-B = 16 000). The aqueous solubility of the crystalline

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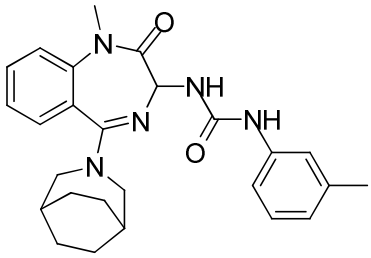
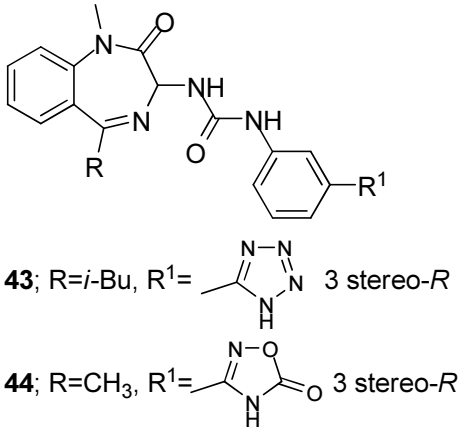
hydrochloride salt of **42** was measured as 0.15 mg/mL, log P (octanol/pH 7.4 aqueous buffer) 4.7, and the pK_a was 7.1.



42

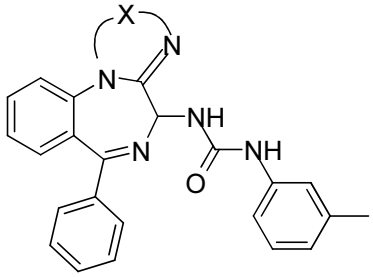
Bock et al [76] have explored the CCK-B receptor binding affinities and solubility properties of 3-phenylureido[1,4]benzodiazepines. Among all analogs, compound **43** and **44** retain high affinity for the human CCK-B receptor from human cerebral cortex (**43**, IC_{50}=0.27 nM; **44**, IC_{50}=0.61 nM) and for the guinea pig gastrin receptor ([^{125}I] gastrin: **43**, IC_{50}=0.24nM; **7**, IC_{50}=0.17 nM, guinea pig gastric glands). The aqueous solubility of compound **43** and **44** are 1.4 mg/ml at pH 7 and 0.41 mg/ml at pH 7.4 respectively. As CCK-4 interacts selectively with CCK-B receptors and is unlikely to cross the blood-brain barrier, the relatively poor brain penetrability displayed by **43** and **44** could be advantageous in elucidating certain effects attributed to CCK-B receptors that may be peripherally mediated.



43; R=*i*-Bu, R^1= 3 stereo-*R*

44; R=CH_3, R^1= 3 stereo-*R*

Bock et al [77] have presented the synthesis and biological properties of imadazobenzodiazepines as CCK-B receptor antagonists. The parent imidazobenzodiazepine, **45**, displays CCK-B receptor affinity equivalent to the clinical compound, L-365,260. Optimization of the potency and selectivity of **45** by substituting the imidazo ring and by resolving stereomeric mixtures led to the identification of *N*[(2*S*,4*R*)-methyl-6-phenyl-2,4-dihydro-1*H*-imidazo[1,2-*a*][l,4]benzodiazepin-4-y1]-*N*'-[3-methylphenyl]-urea **46** as a high affinity CCK-B receptor antagonist with greater than 800-fold selectivity versus the CCK-A receptor.



45; X=CH_2CH_2

46; X= 

Tachibana et al [78] have synthesized new benzodiazepine derivative (S)-*N*-[1-(2-fluorophenyl)-3,4,6,7-tetrahydro-4-oxo-pyrrolo-[3,2,1-*jk*][1,4]benzodiazepine-3yl]-l*H*-indole-2-carboxamide FK480 **47**, a CCK-A receptor antagonist and examined its inhibitory effects on pancreatic exocrine secretion in vivo in anesthetized rats. In vivo study has demonstrated that FK480 is a selective and highly potent antagonist of the action of endogenously released as well as exogenously administered CCK, having a relatively high oral bioavailability and a long biological half-life.

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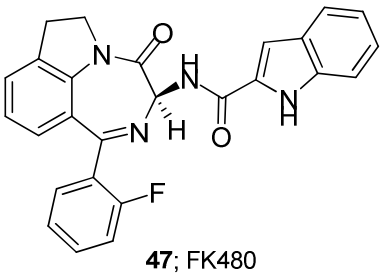
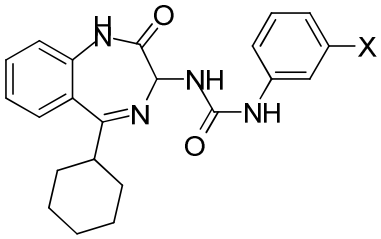


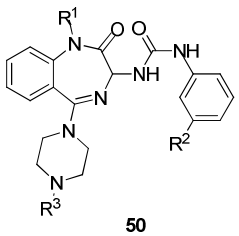
47; FK480

Chambers et al [79] have reported the synthesis and evaluation of acylsulphonamide analogues **48** of the meta-tolylurea **49** (L-708,474) as CCK-B receptor antagonists. Such derivatives retain very high affinity and subtype selectivity for the CCK-B receptor and have good aqueous solubility. The *o*-tolyl acylsulphonamide **48** (L-736,309) is orally bioavailable and can penetrant in the brain of rats.

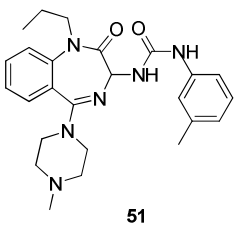


48; X= $CONHSO_2$-*o*-tolyl
49; X= CH_3

Showell et al [80] have synthesized a novel series of potent and water-soluble benzodiazepines of general structure **50** as CCK-B/gastrin antagonists which incorporate an *N*-methylpiperazine group at the C5 position of the benzodiazepine ring system. Compound **51** has a bioavailability of 51%, and is rapidly absorbed (t_{max}=5 min) with high plasma levels (C_{max}=469 ng/mL) and with plasma half-life of 55 min with a high affinity and selectivity. Compound **51** has potent CCK-B receptor antagonist activity in vitro, with good bioavailability and excellent oral absorption providing high plasma levels in vivo.

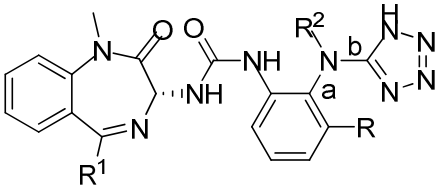


50



51

Castro et al [81] have reported the design, synthesis, and biological activity of a series of CCK-B receptor antagonists that incorporate a 5-aminotetrazole unit. Interestingly, the pKa of these compounds could be gradually modified by rationally controlling the torsion angles around bonds a and b using simple conformational constraints. X-ray crystallographic evidence was obtained to support the conformational dependence of the pKa of the aminotetrazoles. Compound **52**, **53** and **54** bears the highest affinity. The compound **52**, is the most selective (CCK-A/CCK-B, 37 000) antagonists so far reported for this receptor. The C5-cyclohexyl compound **53** (L-736,380) dose dependently inhibited gastric acid secretion in anesthetized rats (ID_{50}, 0.064 mg/kg) and ex vivo binding of [^{125}I]CCK_8 in BKTO mice brain membranes (ED_{50}, 1.7 mg/kg) and is one of the most potent acidic CCK-B receptor antagonists yet described.



52: R^1= phenyl, R and R^2= -CH_2-CH_2-
53: R^1= cyclohexyl, R= H, R^2= methyl
54: R^1= cyclohexyl, R= methyl, R^2= methyl

Nishida et al [82] have reported that YM022 **55** is ≈500 times more effective than L-365,260 as an inhibitor of pentagastrin induced gastric acid secretion in rats. Furthur, Semple et al [83] have prepared a novel series of 1-alkylcarbonylmethyl

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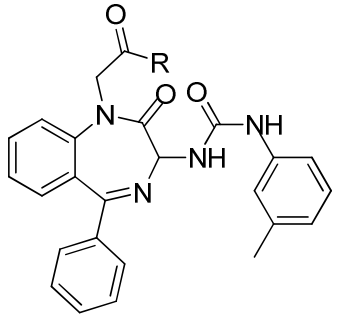
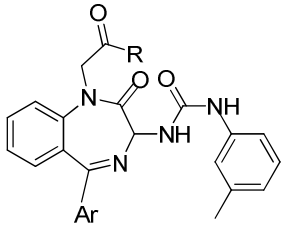
analogues of the potent gastrin/CCK-B receptor antagonist YM022 in which the arylcarbonylmethyl group is replaced by a range of cyclic and branched alkylcarbonylmethyl groups. Compound **56** showed improved binding and enhanced selectivity for this receptor over CCK-A receptors. A second compound **57** gave improved in vivo inhibition of gastric acid secretion in rats. Both analogues were shown to have significantly better activity in the same model following i.d. dosing than either YM022 or L-365,260.



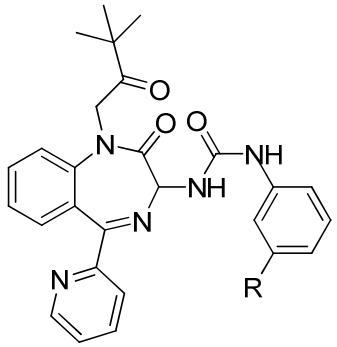
55; YM022; R= *o*-tolyl
56; R= cyclopentyl
57; R=*t*-butyl

Further, Semple et al [84] reported the structure-activity relationships of a series of derivatives of YM022 in which five and six-membered aromatic nitrogen containing heterocycles have been incorporated at 5-position of the parent benzodiazepine. It was noticed from this study that the insertion of a 2-pyridyl substituent at the 5-position gave a compound with better affinity for the gastrin/CCK-B receptor comparable to that of the 5-phenyl analogue. Compound **58** was shown improved both potency and selectivity as compared to **59**.



58; R=*t*-butyl, Ar= 2-pyridyl
59; R= *t*-butyl, Ar= phenyl

Semple et al [85] synthesized and evaluated new series of [1,4]benzodiazepin-2-one-based gastrin/CCK-B receptor antagonists which were closely related to compound YM022. Two compounds, i.e. (3*R*)-*N*-[1-[(*tert*-butylcarbonyl)methyl]-2,3-dihydro-2-oxo-5-(2-pyridyl)-1*H*-1,4-benzodiazepin-3-yl]-*N*-[3-(methylamino)phenyl]urea, **59** (YF476), and (3*R*)-*N*-[1-[(*tert*-butylcarbonyl)methyl]-2,3-dihydro-2-oxo-5-(2-pyridyl)-1*H*-1,4-benzodiazepin-3-yl]-*N*-[3-(dimethylamino)phenyl]urea hydrochloride, **60**, showed potent dose dependent effects with the former showing excellent oral bioavailability and an ED_{50} of 21nmol/kg p.o. in dogs.



59; R= $NHCH_3$
60; R= $N(CH_3)_2$

Castro et al [86] have designed and synthesized a novel series of [1,4]benzodiazepine as high-affinity, ligands for the CCK-B receptor which incorporate a piperidin-2-yl or a homopiperidin-2-yl group attached to C5 of a benzodiazepine core structure. In view of their basicity, it would be tempting to speculate that the present series of compounds might be binding to the CCK-B receptor in their protonated form. Compounds such as **61**, **62** and **63** showed high affinity for this receptor (IC50 < 2.5 nM) and very good selectivity over CCK-A (CCK-A/CCK-B > 2000), even as the racemates.

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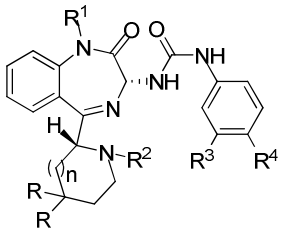
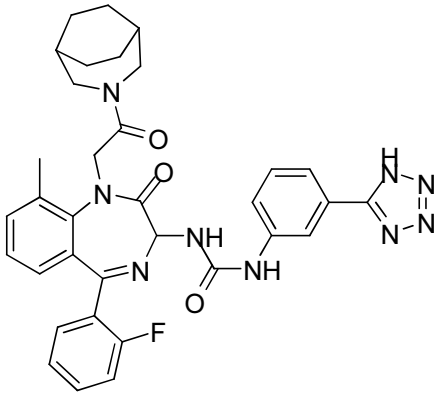


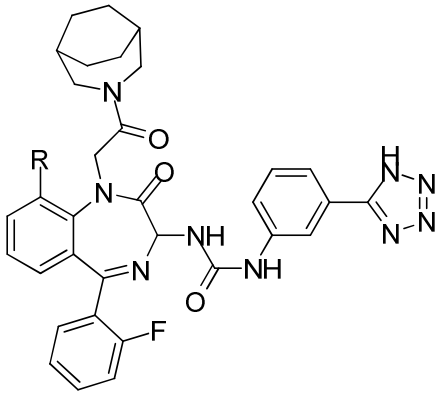
61; n=1, R=CH_3,R^1=*n*-propyl, R^2=H,R^3=CH_3,R^4=H
62; n=1, R=CH_3,R^1=*n*-propyl, R^2=H,R^3 and R^4= -$CH_2CH_2CH_2$-
63; n=2, R=CH_3,R^1=CH_3, R^2=H, R^3 and R^4= -$CH_2CH_2CH_2$-

Tabuchi et al [87] have synthesized a novel series of potent CCK-A and CCK-B dual antagonists which incorporate a methyl substituent at the 9 position of the [1,4]benzodiazepine ring system. They are expected to be more efficacious for the treatment of pancreatitis than selective CCK-A receptor antagonists, because gastric acid secretion is suppressed by their CCK-B receptor antagonistic activity concurrently with the decrease of pancreatic exocrine secretion by their CCK-A receptor antagonistic activity. Compound **(+)-64** (FR193108) was shown very high and well-balanced affinities for both CCK-A and CCK-B receptors that inhibits pancreatic exocrine secretion. The (+)-**64** was found to be more potent in receptor binding assay than the (-)-**64**.



(+)-**64** (FR193108)

Tabuchi et al [88] have described the preparation of novel C9 substituted [1,4]benzodiazepines and the relationship of the dihedral angles between the N1 and C9 substituents and their dual CCK-A and -B antagonistic activities. The dihedral angles (Φ) of the compounds substituted at the C9 position with methyl and ethyl groups (**65** and **66**) were found to be almost equal, but the chlorine-substituted compound **67** was smaller than that of **65**, contrary to expectation based on steric size. However, they were found to be almost equally potent in their biological evaluations. The optimum dihedral angle (Φ) between N1 and C9 substituents appears to be between 50° and 60°, since the isopropyl moiety substituted compound **68**, Φ is >60°, was found to be dramatically diminished in potency in both receptor binding assays.



65; R=CH_3, **66**; R=C_2H_5
67; R=Cl**68**, R=i-C_3H_7

Herrero et al [89] have described the stereo controlled synthesis of phenylalanine and tryptophan derived 5-oxo-1, 2, 3, 4-tetrahydro-5*H*-[1,4]-benzodiazepines **69**. All the synthesized molecules were evaluated as CCK-A and CCK-B receptor ligands, by measuring the inhibition of the specific [3*H*]propionyl-CCK_8 binding to rat pancreas and cerebral cortex homogenates, using CCK_8 and the CCK-A and CCK-B selective antagonists. Only tryptophan derivative (2*R*)-**70** showed the selective affinity for CCK-A receptors, with an IC_{50} of 156.53±3.2 nM.

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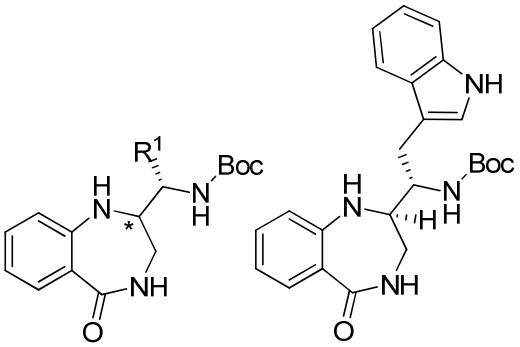
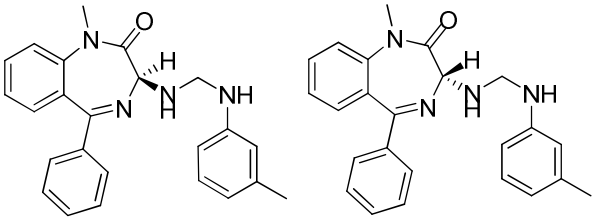


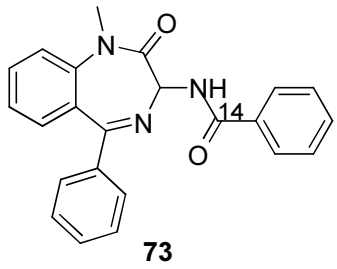
69 (2R)-**70**

Haradahira et al [90] have reported the synthesis of two enantiomers of ^{11}C-labeled nonpeptide CCK receptor antagonists, [^{11}C]L-365,260 **71** and [^{11}C]L-365,346 **72** and evaluated in vivo for use in CCK receptor imaging with positron emission tomography (PET). These radioligands showed high in vivo selectivity to the two distinct CCK receptors. [^{11}C]L-365,260 **71**, however, had no potential as a PET tracer for imaging brain CCK-B receptors because of its very low BBB permeability. [^{11}C]L-365,346 **72**, on the other hand, may be useful for imaging peripheral CCK-A receptors with PET.



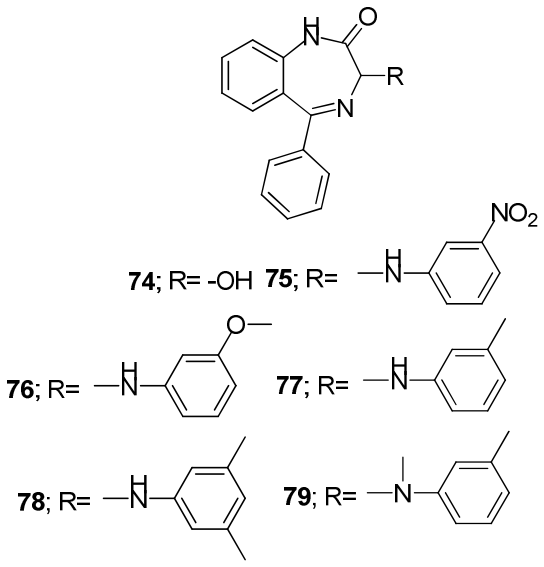
[^{11}C]L-365,260 **71** [^{11}C]L-365,346 **72**

Saemian et al [91] have reported the synthesis of carbon-14 labelled *N*-(1-methyl-2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*]-[1,4]diazepin-3-yl)-benzamide-[carboxyl-^{14}C] **73** as CCK-A receptor antagonist for pharmacokinetic and drug metabolism studies of the compounds.



73

Offel et al [92] prepared 3-amino-[1,4]benzodiazepines as well as chemically related diverse amines from oxazepam **74** and subsequently screened on the CCK receptor in a radiolabel binding assay. The substituted 3-anilino-[1,4]benzodiazepine structure was identified as lead structure in a diverse series of 3-amino-[1,4]benzodiazepines. The compounds **75**, **76**, **77** and **78** have shown affinities at the CCK-A receptor at 11, 10, 11 and 9 nM level, respectively. These equipotent CCK-A ligands were fully evaluated in behavior pharmacological essays. An antidepressant effect was identified in the tail suspension and the Porsolt swimming-test. The ED_{50} values for **76** and **77** were determined in these assays as 0.46 and 0.49 mg/kg. The mixed antagonist **79** also showed anxiolytic properties in addition to the antidepressant effects.



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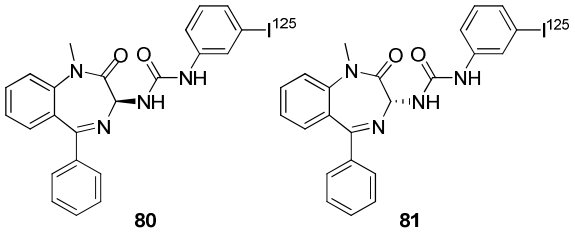
Akgu et al [93] have developed two novel radioiodinated [1,4]benzodiazepines, (*S*)-1-(3-iodophenyl)-3-(1-methyl-2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)urea **80** and (*R*)-1-(3-iodophenyl)-3-(1-methyl-2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)-urea **81**. They were characterized in vitro as high affinity selective antagonists at CCK-A and CCK-B receptors using receptor binding, Ca^{2+} mobilization and internalization studies. Compound **80** is an excellent radioiodinated nonpeptidic antagonist ligand for direct and selective labeling of CCK-A receptors in vitro.



80 81

8. Conclusion

The 1,4-benzodiazepine nucleus is a useful tool for the development of CCK inhibitors. From last three decades, many of the research groups around the globe are continuously making their efforts in finding potent and selective CCK inhibitors for the clinical use. With these efforts, we have many benzodiazepines, which at very low doses, antagonizes the CCK induced activation with selectivity. The efforts of scientist have also focused for the development of more hydrophobic inhibitors to improve bioavailability and selectivity. This is interesting to note that modification of C-3 position of 1,4-benzodiazepines selectively shifts the activity as CCK inhibitors, as observed in most of the discussed examples in this review. From this point we may conclude that benzodiazepine being one of the "Privileged" structure, will serve the mankind with clinically used candidates in future. Efforts of medicinal chemist and pharmacologist will dedicate large number of reports to this wonderful pharmacophore that are yet to come!

Table-1: Tissue distribution, their ligands and functions of CCK receptors

Protein	Gene	Tissue distribution	Preferred ligand	Function
CCK-A(CCK1)	CCKAR	Primarily GIT, lesser amounts in the CNS	Sulfated CCK >> nonsulfated CCK ≈ nonsulfated CCK	Stimulation of bicarb secretion, gall bladder emptying and inhibiting gut motility
CCK-B(CCK2)	CCKBR	Primarily CNS, lesser amounts in the gastrointestinal tract	Gastrin ≈ CCK (receptor does not descriminate between sulfated and nonsulfated peptides)	Regulation of nociception, anxiety, memory and hunger

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