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Der Pharmacia Lettre, 2015, 7 (5):111-130
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Synthetic advancement of 1,4 benzodiazepines as CCKA antagonists

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ABSTRACT

Cholecystokinin (CCK) is an amino acid peptide. It has been isolated from porcine duodenum. CCK is known to regulate like anxiety, schizophrenia and depression by acting on CCK_B receptor. CCK-A receptors are localized in the pancreas, gallbladder, pylorus, intestine and the vagus nerve. CCK is administered peripherally and it inhibits food consumption in humans and other many other species. CCK-A receptor antagonists suspend satiety in several species, In this review, we included the recent advancement of 1, 4 benzodiazepines as CCKA antagonist.

Key words: CCK, satiety, 1, 4 benzodiazepines.

INTRODUCTION

Cholecytokinnin (CCK) amino acid peptide hormone is isolated from porcine duodenum [1,2]. Cholecytokinnin hormone was discovered in the beginning of the 20th century and sequencing of CCK-33 was done in the 1960[3]. Gastrin has been isolated from stomach in 1964 [4].Initially, it was found that Gastrin and CCK are begin from common precursor [4]. But latter on it was discovered that both are aroused from separate prohormone[5]. CCK and gastrin has been detected in the brain of vertebrate [6]. Further another cholecytokinnin (CCK-8) was screened based on amino acid sequence, biological activity and chromatography behavior [6]. Cholecystokinin pancreozyminis synthesized from g cells from the gastric antrum and I-cells in the mucosal epithelium of the upper intestine. CCK -33 has the similar amino acid sequence as gastrin (fig. 1) [1,2]. CCK plays an important role to regulate the secretion of pancreatic enzymes, gallbladder contractions and gut motility. CCK acts as a neuropeptide in the brain [8, 9].

STRUCTURE OF CCK:-

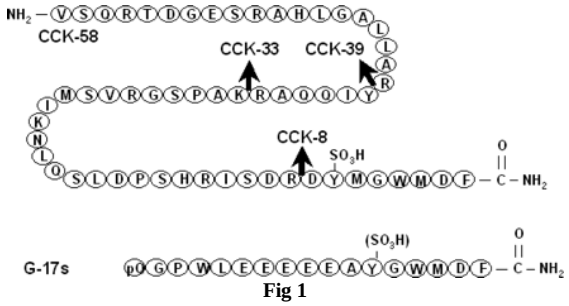


Fig 1

CCK hormone digests the fat and protein of the body [10]. In 1975 other immune reactive peptide structure like gastrin is isolated from rat brain [11]. This peptide is known as CCK-8 [12, 13, and 14] Large amount CCK is identified in peripheral nerve ending and central nervous system [15, 16, 17]. Human CCK is located on chromosome 3p22-p21. and gastric secretion is regulated by gene present on chromosome17q21 [18-22].

CHOLECYSTOKININ RECEPTORS-

There are two types of Cholecystokinin receptors (CCK receptors) i.e : CCK_A and CCK_B[24] shown in Table 1 .CCK_B has been isolated from pancreatic acini of rodents [24,25,26,27,28] and CCK-B eceptor was first found in the brain [29,30]. CCK-A has been found in the area postrema, interpeduncular nucleus, nucleus tractussolitarii, medial preoptic area, arcuate nucleus, circum ventricular regions of hypothalamus, septum, striaterminalis, habenula, substantia nigra, ventral tegmental area (VTA) and lateral geniculate nucleus of the rat brain as well as the medulla and dorsal horn of the spinal cord. Human CCK-A receptors are found much more abundant in the periphery than in the brain[31,32,33,34,35].CCK-B receptors are found in cortex, basal ganglia, stratum, pre-subiculum, amygdala, mamillary bodies, cerebellar cortex, pineal gland, striatum and nucleus accumbens [36,37] (Table 1).

Table 1: Cholecystokinin receptors (CCK_A and CCK_B

Receptor Subtype	**CCK_1 Receptors**	**CCK_2 Receptors**
Transduction Mechanism	$G_{q/11}$, G_s	G_s
Other names	CCK-A, CCK_A, Cck-ar, CCK-A receptor, CCK1-R, cholecystokinin A receptor, cholecystokinin	CCK-B, CCK-B/gastrin, CCK_B/gastrin, CCK_B, CHOLREC, Cck2r, CCK(B) receptor, CCK-B receptor, CCK-BR, CCK2receptor, CCK2-R, CholecystokininBreceptor, cholecystokinin-2receptor, gastrin/cholecystokinintypeB receptor, CCK-B/gastrin receptor
Primary Locations	Pancreas, gall bladder, intestines, vagus nerve	Brain, spinal cord, stomach
Genes	CCKAR (Hs), Cckar (Mm), Cckar (Rn)	CCKBR (Hs), Cckbr (Mm), Cckbr (Rn)
Tissue Functions	Modulates food intake, pancreatic exocrine secretion and growth, gall bladder contraction, GI motility	Modulates anxiety, nociception, neuroleptic activity, gastric acid release, gastric mucosal cell growth and histamine release
Endogenous Ligand Potency	CCK octapeptide, sulfated >> gastrin = CCK octapeptide, non-sulfated	Gastrin = CCK octapeptide, sulfated = CCK octapeptide, non-sulfated
Rank order of potency	CCK-8 >> gastrin-17, CCK-8 (desulphated) > CCK-4	CCK-8 ≥ gastrin-17, CCK-8 (desulphated), CCK-4
Selective Agonists	A-71623 (2411) JMV180 (pIC_{50} 8.3) GW-5823 (pIC_{50} 7.6)	Gastrin I (human) (3006) PBC-264 (pIC_{50} 9.1 - Rat) gastrin-17 (pIC_{50} 8.3 - Mouse)
Selective Antagonists	Devazepride (2304) SR 27897 (2190)	LY225910(1018) YM022(1408) LY288513(1524) CI988(2607) PD 135158 (2608)
Radioligands (K_d)	[^{3}H]devazepide (Antagonist) ($2x10^{-10}$ M)	[^{3}H]PD140376 (Antagonist) ($1x10^{-10}$ – $2x10^{-10}$ M - Guinea pig) [^{125}I]PD142308 (Antagonist) ($2.5x10^{-10}$ M) [^{125}I]gastrin (Agonist, Full agonist) ($1x10^{-9}$ M)

Physiological Implications of CCK Receptors

CCK receptors play an important role in maintaining the normal physiological functions. CCK act on its receptor CCK_B regulate the neurobiology of anxiety, depression, psychosis, cognition and nociception.

CCK and anxiety

Bradwejn and de Montigny (1984, 1985 a,b) et.all.,discovered pentagastrin CCK-B receptor agonist that provokes panic [38].The symptoms are similar that are produced by a standard provoking agent [39] and can be attenuated by antidepressants [40]. The Panic disordered patients were more sensitive towards CCK peptide as compared to healthy volunteers [41]. Patients with generalized anxiety disorder, premenstrual dysphoric disorder, social phobia were exhibited a augmented behavioral response to CCK-B receptor agonists. [42]. The anxiogenic effects were produced by systemically or intra cerebrally administered CCK peptide [43]. CCK agonist and antagonist effect vary due to binding and distribution characteristics of CCK receptors. The marked biological alterations, increase in heart

rate, blood pressure and minute ventilation can be seen by CCK-B receptor agonist. [44-47].. CCK-4 has a role in the anxiety exogenous CCK-4 affects nucleus tractussolitarius, medulla, and para-brachial nucleus in the brain [48]. Animal studies showed that CCK activate to brain stem and modulate respiration, heart rate and blood pressure. [49-50]. A selective CCK-B receptor antagonist (L-365, 260) is effective in the treatment of CCK-4 induced panic attacks of disorder patients [51]. Pentagastrin-induced panic symptoms in healthy volunteers [52].

CCK and Schizophrenia

The interactions of dopaminergic and CCKergic systems have been studied via electrophysiological, behavioral, and neurochemical experiment [53]. In the nucleus accumbens presence of CCK is co-localized with dopamine [54-55]. Another study showed that dopaminergic agents modulate the release of CCK and vice versa [56]. The CCK and dopamine have a complex and bidirectional interactions as CCK inhibits the action of dopamine [57]. BC 264 CCK-B receptor agonist result in dopamine release in the brain. [58]. CCK m-RNA levels are reduced in different brain areas (frontal, cerebral and entorhinal cortices, and subiculum) of schizophrenic patients [59]. The significant reductions in CCK-like immune reactivity have been studied in schizophrenic patients [60]. Also, another study showed that CCK receptor-binding site density has been reduced in schizophrenic patients [61]. The schizophrenia may be associated with the reduced CCK activity. This decreased activity of CCK is attributed to either a decreased processing of pre proreduce theeurons or some Neuro-degeneration of CCKergic neurons in schizophrenia [62].

CCK and Depression

Neuropeptide CCK has also been playing a role in modulation of dopaminergic pathway which altered during the depression. [63-64].

Peripheral Functions

CCK-A receptors are found in the periphery of gall bladder, pylorus, pancreas and vagus nerve [65]. CCK act on CCK-A receptor in the gallbladder and stimulate the contractions [66]. Commercial preparations of CCK are used to study gallbladder contraction. [67]. CCK-A receptors transmit the sensory information from the gut to the brain. Peripherally administered CCK inhibits food consumption in human and many species. [68]. CCK-A receptor antagonists postpone satiety in several species [69]. Endogenous CCK regulates the feeding behavior and intake of food act on CCK-A receptor and release of CCK. Released CCK postponed satiety by acting on CCK-A receptor on the vagus nerve. [70]. CCK-A receptor agonists can be used as anorectics [71] and CCK-A receptor antagonists for anorexia disorders [72]. In the periphery CCK-B receptors are primarily present in the stomach [73] and on the vagus nerve [74]. Gastrin acts on CCKB receptors for secretion of gastric acid [75] and CCK stimulates gastric acid secretion [76]. CCK-B receptor antagonists can block the secretion of Gastric acid [77] so these agents can be used for the treatment of gastric ulcers [78]. Activation of CCK-B receptors releases only acetylcholine but CCK-A receptor releases both substance P and acetylcholine [79].

Association CCK with diseases

Cholecystokinin releases the bile from the gallbladder and digestive enzymes from the pancreas. [80]. Recent evidence showed that hypersensitivity pain occurs during opioid withdrawal due to cholecystokinin. [81]. Cholecystokinin play a role in anxiety and panic [82, 83, & 84]. Also, Cholecystokinin involved in mental illnesses such as schizophrenia [85,86,87,88,89,90] and addictions [91,92,93,94,95,96]. The CCK concentration in cortex and limbic regions [97, 98] regulate satiety and appetite [99] thermoregulation [100.101] sexual behavior [102,103] anxiety [104,105] memory [106] response to drugs of abuse [107].

Interaction

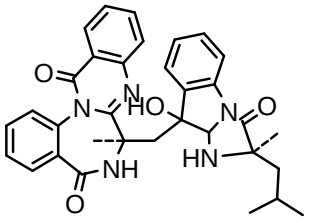
Cholecystokinin act on its receptors CCK-A & CCK-B. CCK-A is located on periphery and CCK-B on centrally [108,109,110].

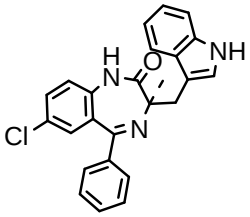
CCK Agonists:

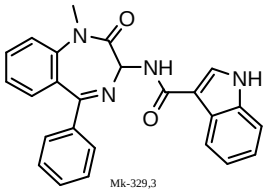
Porcine CCK-33 was isolated and used to study the biological effects of CCK. The limitation in the synthesis of CCK is, the less efficient and difficulty of the addition of the support group to the tyrosine of peptide synthesized with t-Boc (t-butyloxycarbonyl) amino acids. [111]. A recent modification in the synthesis of human and porcine CCK 33 and canine CCK 58 is done to incorporate sulfated tyrosine into the peptide backbone as an FMOC (9-fluorenyl-methoxycarbonyl) amino acid. [112].

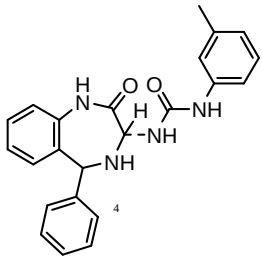
CCK Antagonists

To study the effect of CCK on peripheral part is easy as compare to study effects on the CNS [113]. Asperlicin **1** CCK antagonist is nonpeptide has potent activity in the CNS. This drug is poorly soluble in water and less bioavailable in oral route. Recent advancement in the nucleus of asperlicin **1** was done to synthesize L-364, 286 **2**, which has potency on CCK-A receptors. The modification of asperlicin **1** was carried out with 3-amide-substituted benzodiazepines. The 2-indolyl derivative L- 364, 718 results in better receptor affinity. Modification of 3-amide to a urea linkage as in compound **4** reductions in CCK-A receptor affinity. Stereochemistry at C3 discriminated between CCK-A and CCK-B receptors as (*S*) -enantiomer showing greater affinity for CCK-A receptors. The (*R*) -enantiomer has more binding to CCKB receptors decrease in gastric acid secretion [115]. The clinical trials of these drugs are not successful because poor bioavailability, but it can be promising conceptualized to find a good CCKB antagonist. [116.117] (Fig. -2)









3 **4**

Fig. -2

1, 4 Benzodiazepines as CCK Antagonists

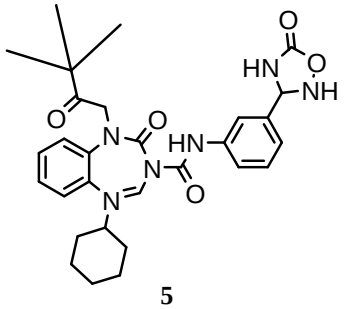
CCK Antagonists are divided in categories based upon nucleus [118]:

1. Peptide derivatives
2. Benzodiazepine derivatives
3. Non-peptide derivatives
4. Cyclic nucleotides

Peptide antagonists has poor oral bioavailability and is used to find a substitute of peptide analogues. 1, 4 benzodiazepine derivatives were examined as CCK antagonists [119-126] and designed for natural product asperlicin [127].

Recent Synthetic Advancements in 1,4 Benzodiazepines

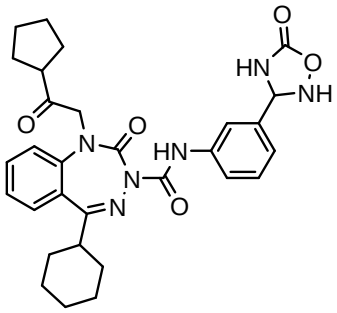
Spencer et al. 2008) synthesized Novel 1, 3, 5-benzotriazepine-2, 4-Dione derivative compound **5** (Fig 3) with CCK_2 receptor antagonist activity. These benzodiazepines has been showed high selectivity towards CCK1 receptor [128].



5

Fig. 3

McDonald et al., (2007) optimized achiral 1, 3, 4-benzodiazepine having nanomolar affinity and CCK_1 receptor selectivity towards recombinant human CCK_1 receptor (Figure4). Compound **6** has an inhibitory effect on pentagastrin stimulated acid secretion. Pentagastrin stimulated acid secretion inhibitory activity was checked by radioligand binding assay and perfused rat stomach bioassay [129].

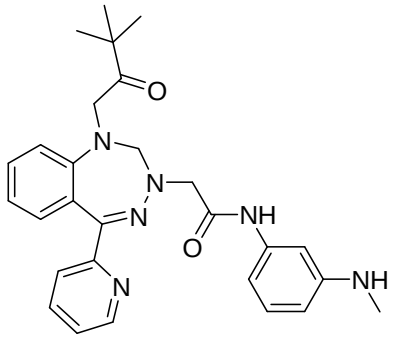


6

Inhibition of pentagastrin-stimulated gastric acid seceration ID_{50}(dose mg/kg)
compound 6 by i.v.less than 0.03

Fig. 4

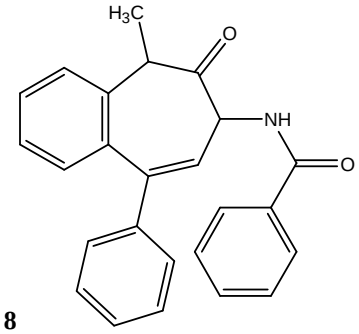
McDonald et al. (2006) designed 1, 3, 4-benzodiazepine analogues of 1,4-benzodiazepine compound **7** (Fig.5) in which urea nitrogen has been replaced with methylene group that showed moderate affinity for CCK_2 receptors. These analogues more potent at CCK_1 receptors, but its have less selectivity over CCK_2 receptors. An X-ray structure of 1, 3, 4-benzodiazepine having a lack of substitutes on N-1 and N-3 positions. In these analogues, triazepine structure was found to accept sideboard confirmation [130].



7

Fig. 5

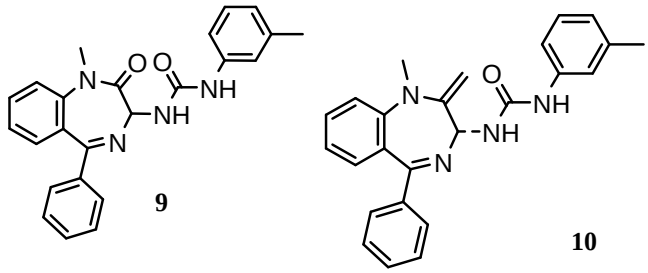
Saemian N., et al (2005) synthesized 3-substituted 1,4 benzodiazepine derivative N-(1-methyl-2-Oxo-5-phenyl-2,3-dihydro-1H-benzo [e] [1,4] diazepin-3-yl) -benzamide-[carboxyl-14C] (Fig.6) compound **8** as cck-A antagonists from benzonitrile-[cyano-14C][131].



8

Fig. 6

Akgu et. al. 2003) synthesized two novel radio iodinated [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 **9** 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 **10**[132]. They were characterized in vitro as high affinity, selective antagonists at the CCK-A and CCK-B receptors using receptor binding, Ca2+mobilization and internalization studies. Compound **9** has selective binding to CCK-A receptor in vitro as comparing to compound **10. (**Fig. 7)



9 **10**

Fig. 7

Offel et al (1998) synthesized 3-amino-[1, 4] benzodiazepines 9 and other related diverse amines from oxazepam **11** and tested for CCK receptor binding by radio label binding assay (fig. 8). The compounds **12, 13**, **14** and **15** have shown affinities at the CCK-A receptor at 11, 10, 11 and 9 NM levels, respectively. Also, these CCK-A legend was tested for antidepressant activity tail suspension and the Porsolt swimming-test. The ED_{50} values for compound **13** and **14** were 0.46 and 0.49 mg/kg respectively. The mixed antagonist **15** showed both anxiolytic and antidepressant activity [133].

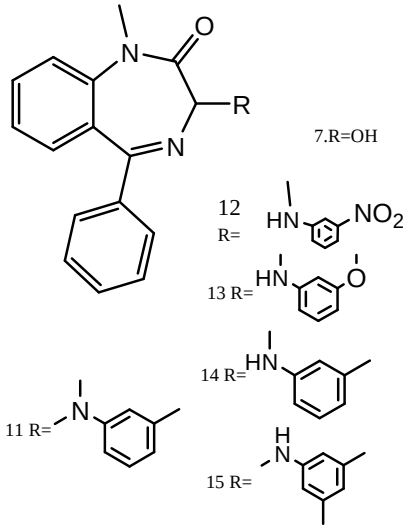
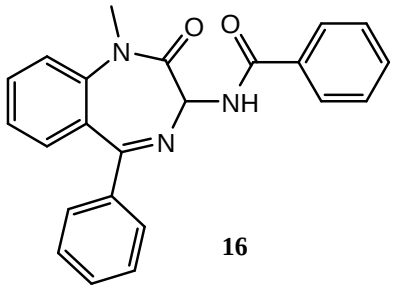


Fig. 8

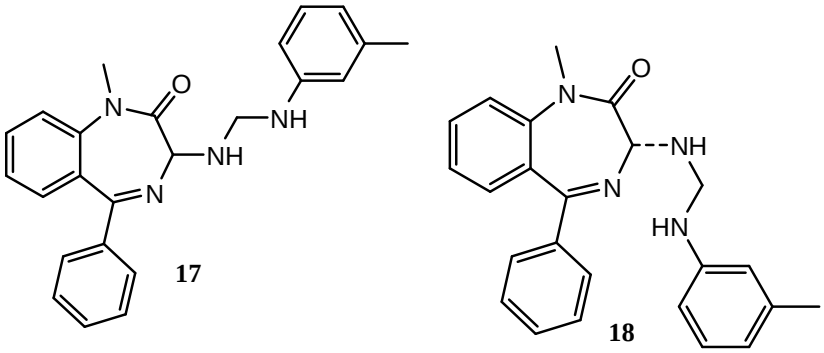
Salmon et al (1997) has reported the synthesis of carbon-14 labelled *N*-(1-methyl- 2-Oxo-5 phenyl-2, 3-dihydro-1*H*-benzo [*e*] -[1, 4] diazepin-3-yl) -benzamide-[carboxyl-14C] **16** as CCK-A receptor antagonist (fig. 9) [134].



16

Fig.9

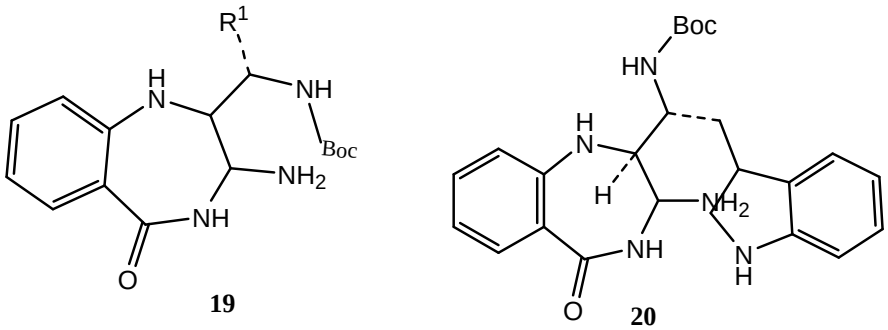
Haradahira et al (1997) has synthesized two enantiomers of 11C-labeled nonpeptide CCK receptor antagonists, [11C] L-365, 260 **17** and [11C] L-365, 346 **18** (Fig. 10). They were evaluated the imaging of CCK receptor by positron emission tomography in vivo for use. These compounds are selective for two distinct CCK receptors. [11C] L-365, 260 **17** has a low BBB permeability and compound 14 is useful for imaging peripheral CCK-A receptors with PET [135].



17 **18**

Fig. 10

Herrero et al (1997) synthesized stereo controlled synthesis of phenylalanine and tryptophan derived 5-Oxo-1, 2, 3, 4-tetrahydro-5*H*-[1, 4] -benzodiazepines **19 & 20** (Fig. 11). All the synthesized compounds were evaluated for CCK8 and CCK-A and CCK-B selective antagonist activity by their selective antagonists Tryptophan derivative [136].



19 **20**

Fig. 11

Tabuchi et al (1996) synthesized novel C9 substituted [1, 4] benzodiazepines. The novels C9 substituted [1, 4] benzodiazepines has dual activity CCK-A and Bantagonistic activities based on the dihedral angles between the N1 and C9 substituent. The compounds **21** and **22** are equally potent and the dihedral angles between these two compounds are same but compound **23** is chlorine substituted and dihedral angle is smaller as compared to

compound **21** but equally potent to compound **21** and **22.** The optimum dihedral angle (φ) between N1 and C9 substituents appears to be between 50° and60°, since the isopropyl moiety substituted compound **24**, (Fig 12) φ is >60°, was found to be dramatically diminished in potency in both receptor binding assays [137].

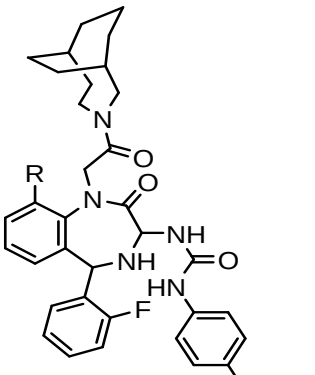


Fig. 12

Tabuchi et al (1996) synthesized 9 position methyl substituted [1, 4] benzodiazepine ring system with dual CCK-A and CCK-B antagonists. These compounds **25** are more effective for treatment of pancreatitis by antagonism of CCK-A receptor (fig. 13). Compound **(+)** -21 (FR193108) was shown high affinities for both CCK-A and CCK-B receptors. The (+) -25 was more potent as compared to (-) -25 in receptor binding assay [138].

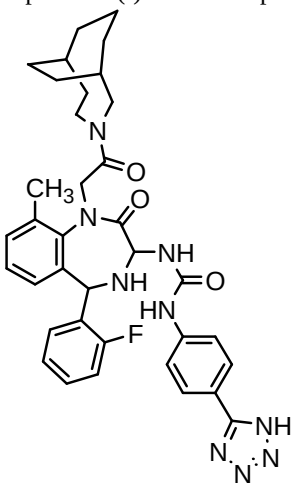
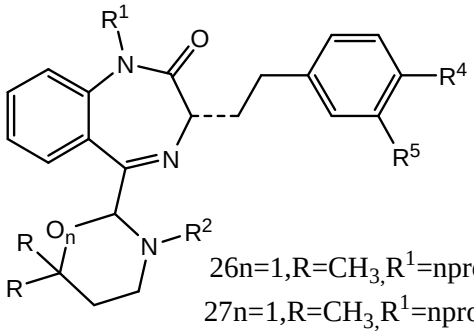


Fig. 13

Castro et al (1996) designed and synthesized apiperidin-2-yl or a homopiperidin-2-oil group substituted at C5 position [1, 4] benzodiazepine (Fig. 14). These compounds are so basic it is speculated that these compounds might be binding with the CCK - B receptor in their protonated form. Compounds **26, 27, 28** has shown good selectivity and affinity to CCK-A receptor with (IC50 < 2.5nM). [139].



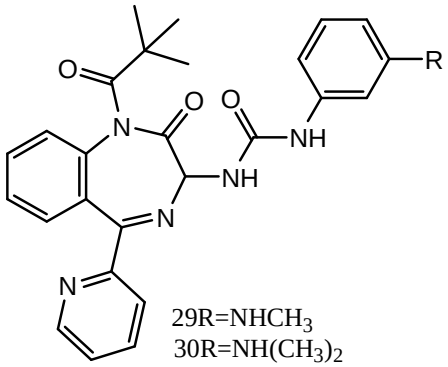
26n=1,R=CH_3,R^1=npropyl,R^2=H,R^3=CH_3,R^4=H

27n=1,R=CH_3,R^1=npropyl,R^2=H,R^3&,R^4=$CH_2CH_2CH_3$

28n=2,R=CH_3,R^1=CH_3,R^2=H,R^3&,R^4=$CH_2CH_2CH_3$

Fig. 14

Semple et al (1996) synthesized and evaluated new series of [1, 4] benzodiazepine-2-one based gastrin/CCK-B receptor antagonists. Two compounds, i.e. (3*R*) -*N*-[1-[(*tert*-butylcarbonyl) methyl] -2,3-dihydro-2-Oxo-5-(2-pyridyl) -1*H*-1,4-benzodiazepine-3-yl] -*N*-[3-(methylamino) phenyl] urea, **29** (YF476), and (3*R*) -*N*-[1-[(*tert*butylcarbonyl) methyl] -2,3-dihydro-2-Oxo-5-(2-pyridyl) -1*H*-1,4-benzodiazepine-3-yl] -*N*-[3-(dimethylamino) phenyl] ureahydrochloride26, Compound **30** (Fig.15) has more dose dependent potent effects but compound 29 has good oral bioavailability with ED_{50} 21nmol/kg P.O.in dogs [140].

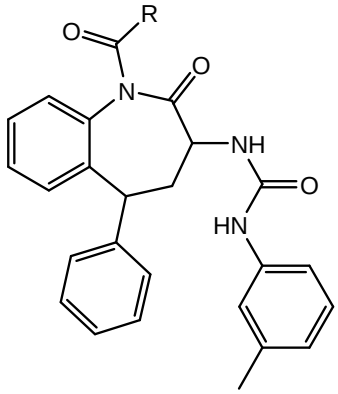


29R=$NHCH_3$

30R=$NH(CH_3)_2$

Fig. 15

Further Semple et al (1995) studied the structure-activity relationships of position 5 five and six member nitrogen containing heterocycles substituted 1,4 benzodiazepine. They were concluded that 1,4 benzodiazepines having 2 and 5 position pyridyl have better Gastrin/CCK-B receptor affinity (Fig. 16). Compound **31** has better potency and selectivity as compared to compound **32**. [141].

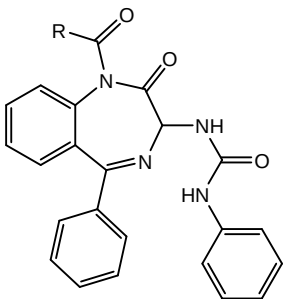


31 R=tbutyl ,Ar=2 pyridyl

32 R=tbutyl ,Ar=2 phenyl

Fig. 16

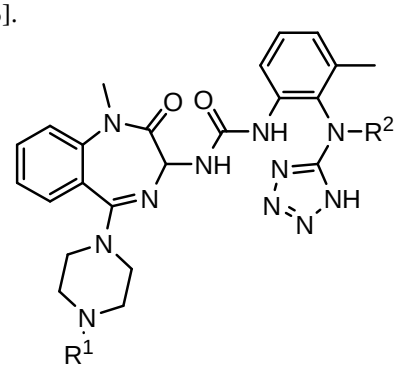
Nishida et al (1995) reported that YM022 **33** was 500 times more effective than L-365, 260.Furthur, Semple et al (1995) synthesized YM022 derivatives in which position 1 was substituted by alkyl carbonyl methyl analogues (Fig.17) with gastrin/CCK-B receptor antagonist [138]. Compound **34** showed better binding and selectivity for CCKB receptor as compared to compound YM022. The compound **35** gave improved CCKB receptor binding and showed inhibition of gastric acid secretion in rats [142-144].



33R=O tolyl
34R=Cyclohexyl
35 R=t Butyl

Fig. 17

Castro et al (1994) synthesized 1, 4 benzodiazepines series with the incorporation of 5-amine tetrazole unit. Peak of these amino tetrazoles depends on the torsion angles around bonds a and b. Among compounds **36, 37** and **38 (**fig. 18), the compound **36** was more selective (CCK-A/CCK-B, 37000) antagonists. The compound **37** showed ex-vivo binding of [140] CCK8 in BKTO mouse brain membranes (ED50, 1.7 mg/kg) and gastric acid inhibition (ID50, 0.064 mg/kg) in anesthetized rats. [145].



36 R^1=phenyl,R&R_2=CH_2CH_3
37R^1=Cyclohexyl,R=H,R_2=CH_3
38R^1=Cyclohexyl,R=CH_3,R_2=CH_3

Fig. 18

Showell et al (1994) synthesized benzodiazepine derivatives of general structure **39** on which position 5 was substituted with an *N*-methyl piperazine group (fig. 19). Compound **40** showed better CCK-B receptor antagonist activity with 51% bioavailability, high plasma level (Cmax=469 ng/ml) with the rapid rate of absorption. [146].

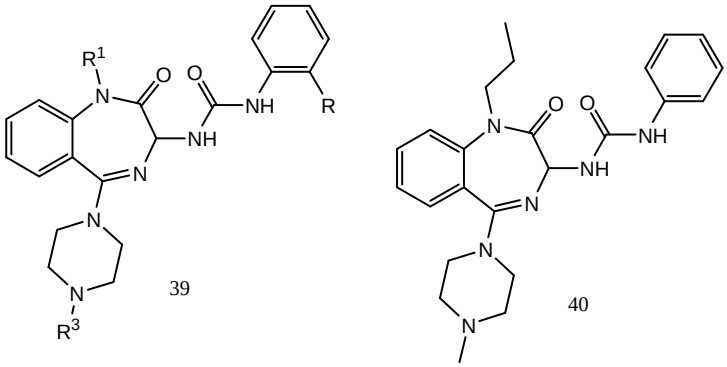
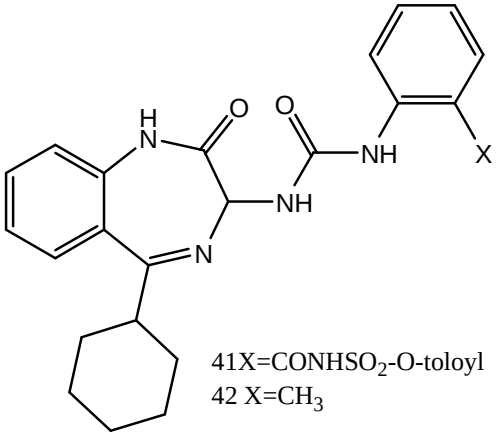


Fig. 19

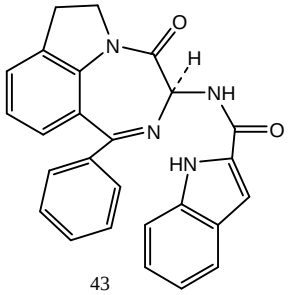
Chambers et al (1994) synthesized compound **41** and **42** 1,4 benzodiazepines (fig. 20) with alkyl sulfonamide analogues. The compound **41** ISO-toll acyl sulfonamide analogues showed better selectivity for the CCK-B receptor with better bioavailability and good aqueous solubility. [147].



41X=$CONHSO_2$-O-toloyl
42 X=CH_3

Fig. 20

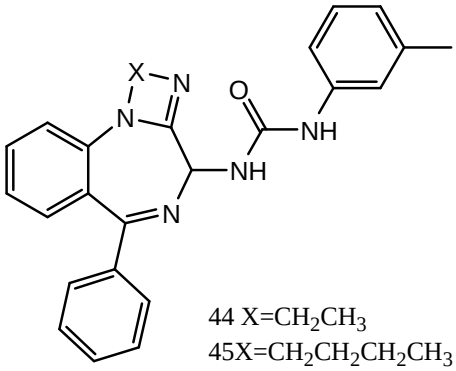
Tachibana et al (1994) synthesized compound **43** CCK antagonist (S)-*N*-[1-(2-fluorophenyl)-3,4,6,7-tetrahydro-4-oxopyrrolo-[3,2,1-*jk*][1,4]benzodiazepine-3yl]-l*H*-indole-2-carboxamide FK48038. Compound **43** (fig. 21) was showed a selective antagonist of exogenous and endogenous CCK with good oral bioavailability and a long biological half life. This compound shows an inhibitory effect on exocrine secretion of pancreas. [148].



43

Fig. 21

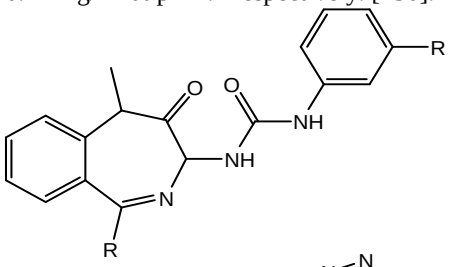
Bock et al (1993) synthesized imidazo benzodiazepine **44** (Fig.22) as CCK-B receptor antagonist. The compound **44** has equal affinity as clinical compound, L-365, 260 for CCKB receptor. They suggested that the potency and selectivity of compound **44** can be done by substituting the imidazo ring and resolving the racemic mixture to compound **45**.This compound **45** showed 800 times selectivity for CCK-B receptor antagonist. [149].



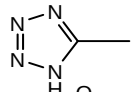
44 X=CH_2CH_3
45X=$CH_2CH_2CH_2CH_3$

Fig. 22

Bock et al (1990) synthesized compounds **46** and **47** substituted at position 3 by 3-phenyl ureido [1,4] benzodiazepine (Fig.23). Among all analogs, the compound **46** and **47** retained a high affinity towards CCK-B receptor with (42, IC50=0.27 nM;42, IC50=0.61 nM) and for the guinea pig gastric receptor gastrin: 43, IC50=0. 24nM; 42, IC50=0. 17 NM, guinea pig gastric glands). The compound **46** and **47** showed poor blood brain penetrability so can be used to antagonize peripheral CCK-B receptors. The aqueous solubility of compounds **46** and **47** were 1.4 mg/ml at pH 7and 0.41 mg/ml at pH 7.4 respectively. [150].



46 R-i Bu, R=



47 R-i Bu R=

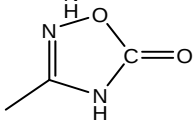
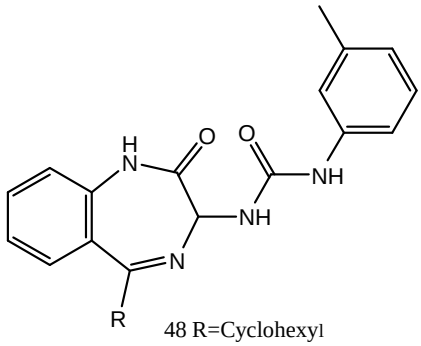


Fig. 23

Chambers et al (1989) reported the synthesis of CCKB receptor antagonist 1, 4 benzodiazepine in which 5 positions was substituted with a cyclohexyl group (Fig. 24). The benzodiazepine derivative **48** showed higher CCK-B affinity. The compound **48** showed increased affinity of the CCK-B receptor as compare to L-365, 260 [151].

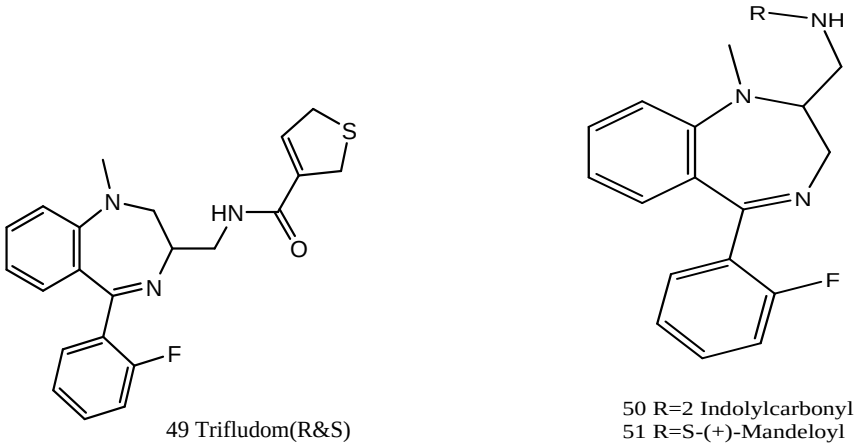


48 R=Cyclohexyl

Fig. 24

Bock et al (1989) synthesized a series of 1, 4 benzodiazepines substituted at position 2 and position 3 by aminomethyl assuming trifluadom **49** as a model (Fig.25). These compounds were tested for antagonist activity by

using radio labeled CCK to binding to rat pancreas and guinea pig receptors. The synthesized compounds **50** and **51** showed greater affinity for CCKA receptor with IC_{50} of 0.16 μM and0.6μM respectively [152].

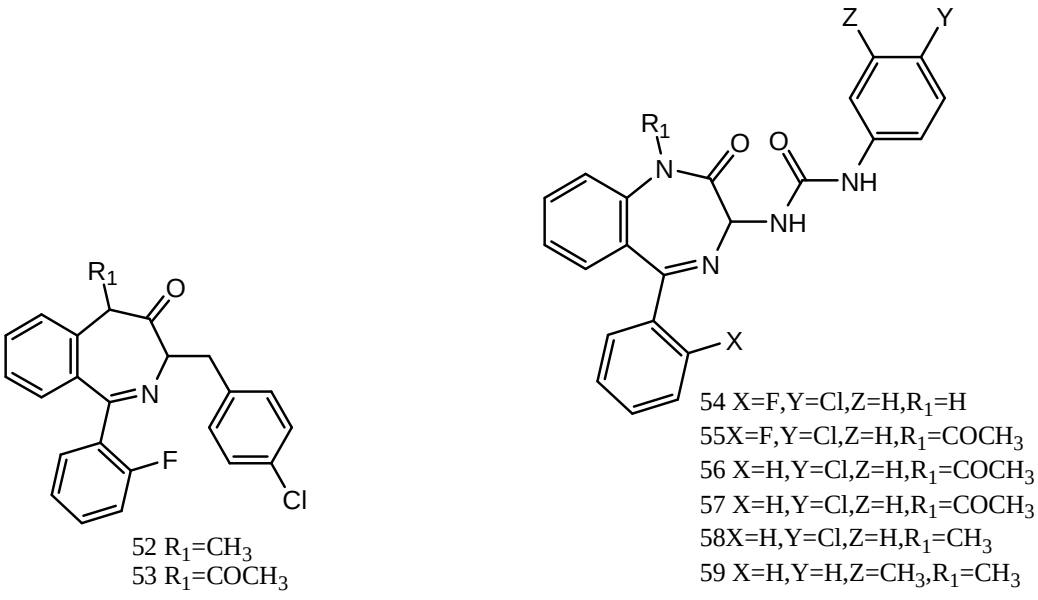


49 Trifludom(R&S)

50 R=2 Indolylcarbonyl
51 R=S-(+)-Mandeloyl

Fig. 25

Bock et al (1988) synthesized CCK (CCK-B) and gastrin receptors antagonist 1, 4 benzodiazepines (fig. 26). The compound L-365, 260 was a CCK antagonist. The N-1 of L-365, 260 was substituted with an ethyl carbonyl group as in compound **52** or the substitution of 3 amide linkage was with urea generates compound **53** with an increase in CCK-B affinity. Above both substitution in L-365, 260 generated pivotal compounds **54** and **55** with nano molar potency. These non peptide antagonists were selective for CCK-B and gastrin receptors. The optimization of the activity by the N-1 group to a pyrrolidin-amide resulted in compound **56**.The compounds **56** and **57** showed 3*S* configuration are selective for CCK-A receptor whereas as a mirror image compound **58** and **59** with 3*R* isomers were selective for CCK-B and gastrin receptors. The compound **55** was selected for CCK-B and gastrin receptor. The compound **60** was an orally effective antagonist of gastric acid secretion and interact competitively with the Lottietal [148] reported that compound **59** antagonize gastrin stimulated acid secretion in mice and guinea pig with (ED50 = 0.9 mg/kg) (ED50 =5. 1 mg/kg) respectively. In another study done by Sadzotetal et al. revealed that MK-329 was a highly selective and very high affinity antagonist at the peripheral CCK receptors [153]. The study was suggested that more than 80% specific binding was detected in the pancreas [154].

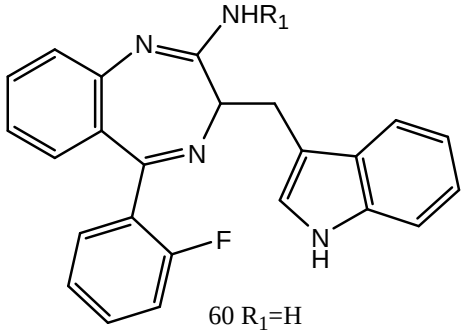


52 R_1=CH_3
53 R_1=$COCH_3$

54 X=F,Y=Cl,Z=H,R_1=H
55X=F,Y=Cl,Z=H,R_1=$COCH_3$
56 X=H,Y=Cl,Z=H,R_1=$COCH_3$
57 X=H,Y=Cl,Z=H,R_1=$COCH_3$
58X=H,Y=Cl,Z=H,R_1=CH_3
59 X=H,Y=H,Z=CH_3,R_1=CH_3

Fig. 26

Further, Bock et al (1988) synthesized position 2 substituted by amine group 1, 4 benzodiazepine analogues (Fig. 27) as CCK receptor antagonist. The unsubstituted 1, 4 benzodiazepine-2-amine **60** was more potent and selective CCK receptor antagonist as compared to compound **61,62** and **63** with small substitute. This resulted in increase aqueous solubility, compound **60** was found 1000 fold more soluble in 0.1N HCI solution than compound **63.** [155].



60 R_1=H
61 R_1=CH_3
62 R_1=$CH_2CH_2CH_3$
63 R_1=CN

Fig. 27

Bock et al (1988) synthesized a series of 4 positions substituted 1,4 benzodiazepines (Fig. 28) and tested for antagonist activity by binding of [^{125}I] CCK to rat pancreas and guinea pig brain receptor. Maximum analogues showed CCK antagonist activity in the nano molar range. The compound **64** and **65** showed a substituted 4 position with the triazolo benzodiazepine required for optimum CCK antagonist activity. [156]

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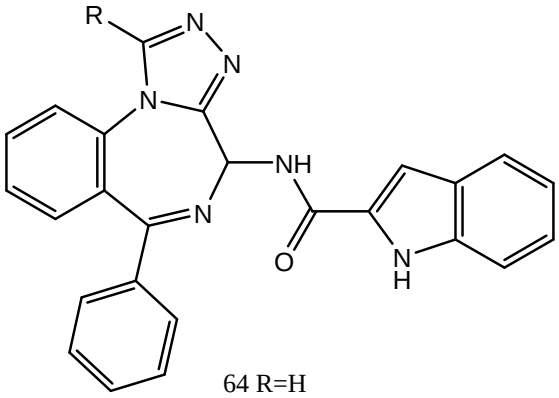
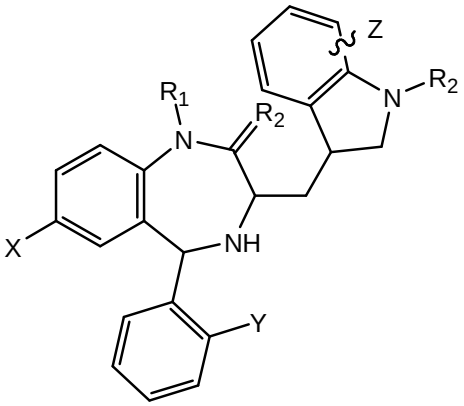


64 R=H
65 R=CH_3

Fig. 28

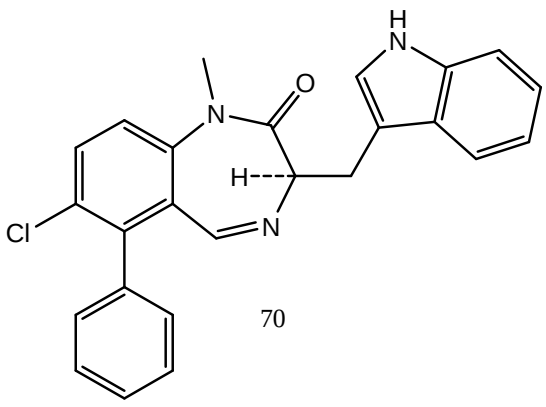
Evans et al (1987) synthesized non peptide CCK antagonists substituted at 3 positions substituted (Fig.29). The compound **66** was fluro substituted and compound **67** was triazole fusion showed better binding to the peripheral CCK receptor. The N1 position substituted with carboxy methyl resulted compound **68** with good CCK receptor affinity in the 3-substituted series. Compound **69** has >600-fold selectivity for peripheral CCK receptors as compare to central CCK [157].



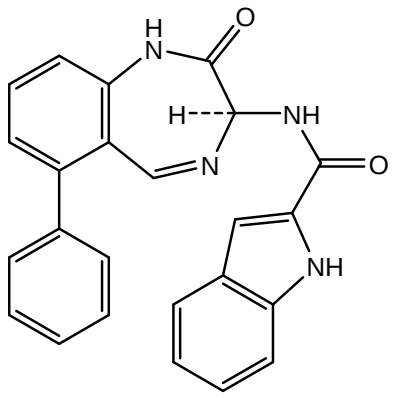
66 X=H,Y=F,Z=H,R_1=H,R_2=O,R_3=H
67X=H,Y=F,Z=H,R_1=$C(CH_3)_3$NN R_2=$C(CH_3)_3$NN,R_3=H
68 X=H,Y=F,Z=H,R_1=CH_3COOH,R_2=O,R_3=H
69 X=H,Y=H,Z=H,R_1=CH_4,R_2=O,R_3=CH_3

Fig. 29

Similarly, Kubota et al (1985) studied anti nociceptive by intra external administration of CCK8 (1.0µg/kg) that was reversed by benzodiazepines (chlordiazepoxide, diazepam, Flurazepam) dose (2- 5mg/kg), (1 mg/kg), (1 mg/kg) respectively by intra peritoneal route. Further, Kubota et al. studied the inhibition of contractility response of 1, 4 benzodiazepines on circular muscle strips from the isolated guinea-pig gallbladder to CCK8 in the presence of atropine [157]. The inhibition of contraction was assumed to be due to the Ca2+ antagonist-like action of the benzodiazepines. The maximum inhibition was depended on higher concentration of benzodiazepine and the dose response curve shifted to parallel to right by benzodiazepine by 10-6 to 10-5. Meldrum et al [158] studied the antagonist effect of benzodiazepines on the nerve mediated release of CCK and effect on pancreatic acini and smooth muscle. Chlordiazepoxide and Lorazepam showed an antagonistic effect on guinea-pig ileum, but not on the gall-bladder.Chlordiazepoxide did not show an effect on amylase release from pancreatic acini. The antagonistic effect of these Chlordiazepoxide and diazepam higher concentration inhibits contraction of gall-bladder and ileum. Evans et al [159] synthesized series of 1, 4 benzodiazepines as CCK antagonist and tested for binding specificity. These compounds showed nano molar binding affinity (Fig 30). **71** showed high oral bioavailability and high potency as comparing to compound L-364, 718 **70.** Further, Chang et al determined the binding of the selective nonpeptide CCK antagonist **70** to CCK receptor by a radio legend binding assay method [160]. The affinity of the compound **70** was showed near to similar to CCK itself.The compound **66** showed high affinity for CCKA receptor as compare to CCKB in vitro radio ligand and isolated tissue assay. In vivo the compound **70** antagonizes the contraction of guinea pig gall bladder by intravenous route. Whereas the oral dose of compound **70** (ED50, 0.04 mg/kg) was most effective for inhibition of gastric emptying in mice. [161-163].



70



71

Fig.30

Bradwejn and Montigny 1984) reported that benzodiazepines can antagonize the neuron released CCK.They studied the activity of four benzodiazepines like flurazepam**72**, diazepam **73**, lorazepam**74** and chlordiazepoxide **75** and suggested that the ability to antagonize CCK8-induced activation was a common property of all drugs in this class. The inactivity of the three anxiolytic non-benzodiazepine drug tested (haloperidol **76**, phenol barbital **77** and meprobamate**78)** constituted a preliminary indication. They were found that this property might be specific to benzodiazepines only. (Fig.31). The antagonism of CCK8-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 'neuronal' benzodiazepine antagonist, as the effect of benzodiazepines on CCK8-induced activation [164].

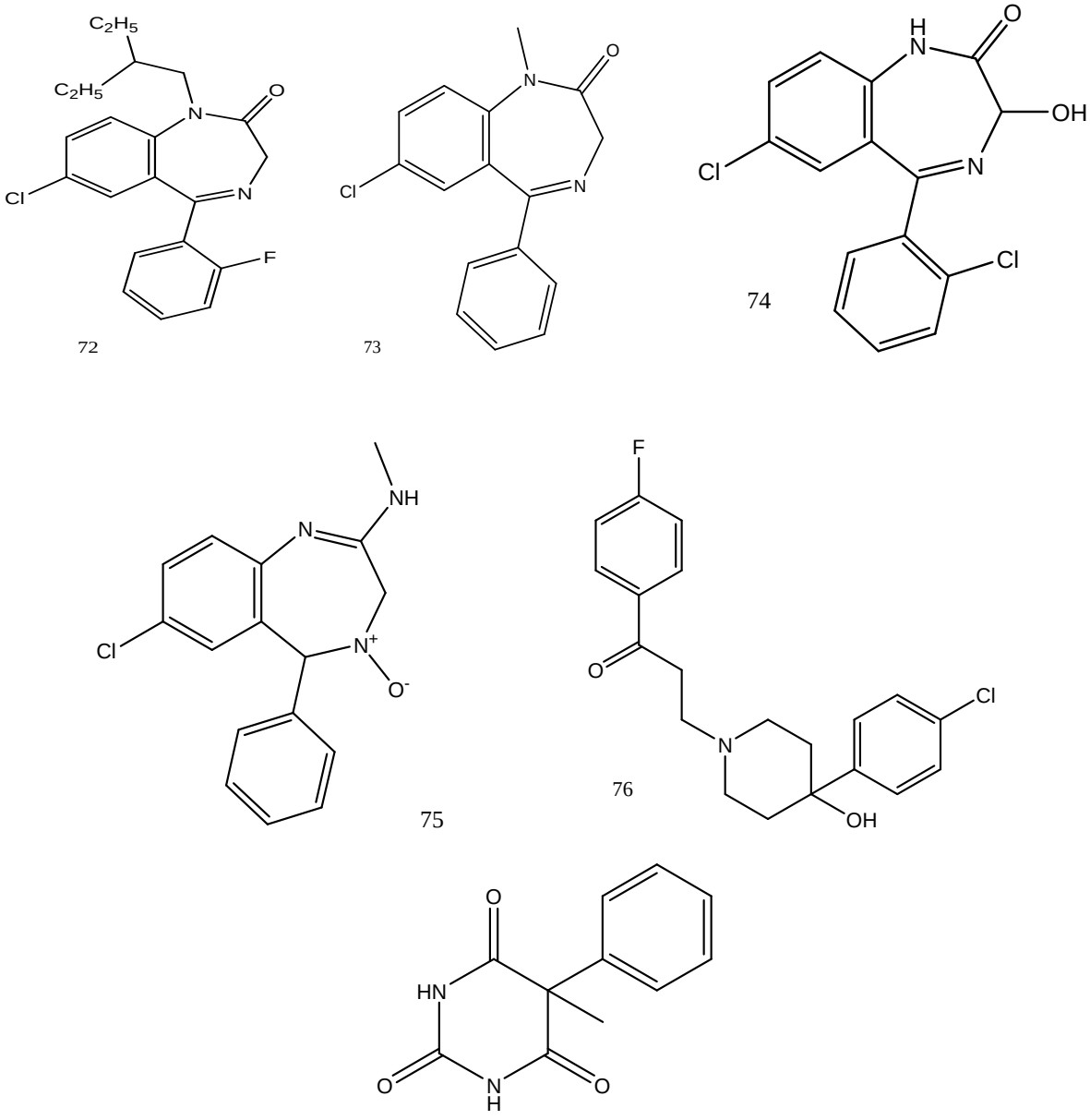


Fig. 31

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