



1,4-BENZODIAZEPINE: AN OVERVIEW OF BIOLOGICAL PROPERTIES

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ABSTRACT

The term benzodiazepine is the chemical name for the heterocyclic ring system, which is a fusion of benzene and diazepine ring systems. 1,4-benzodiazepine is related with a huge range of biological properties. These ring systems are incorporated into drugs used for AIDS, cancer, anti-viral treatment etc. 1,4-benzodiazepine derivatives are well established in the literature as important biologically active compounds. They have a long history of application in agrochemicals and pharmaceutical industry as herbicides and active pharmaceuticals. 1,4-benzodiazepine and their numerous derivatives have continued to capture the concentration of chemists since their existence in the biologically active materials have been known to produce additive effect on the bio-efficacy of the molecules.

Key words: 1,4-benzodiazepine, anti-viral, bio-efficacy.

INTRODUCTION

History of benzodiazepines was started after the discovery of diazepam (Fig. 1) in 1955 by Leo Sternbach. From that day the research on 1,4- benzodiazepine nucleus is continue. There is a lots of drugs having 1,4-benzodiazepine nucleus. 1,4-Benzodiazepine nucleus containing drugs mostly used for the treatment of anxiety, but they also are useful in treating several other conditions in human. It is a most common prescribed drug for CNS disorders. Benzodiazepines affect a neurotransmitter chemical, gamma-aminobutyric acid (GABA), which is used by nerves to communicate with one another¹. Since scientists believe that excessive activity of nerves in the brain may be the cause of anxiety and other psychological disorders, and GABA reduces the activity of nerves in the brain, benzodiazepine increase the effects of GABA in the brain and spinal cord. Several 1,4-benzodiazepines are widely used as anti-convulsant², anti-anxiety³, sedative⁴, hypnotic⁵, neuroleptic agents⁶ and muscle-relaxants⁷. This interesting examination totally shifted the interest of medicinal chemist for [1,4]-benzodiazepine from CNS acting drugs to anti-cancer agent. Recently, they have been reported to show anti-proliferative⁸, anti-microbial⁹, antiinflammatory¹⁰, anti-HIV¹¹, anti-plateletanti-ulcer¹², cholecystokinin antagonists¹³, endothelia antagonis¹⁴ and vasopressin antagonist activity¹⁵.

Effects of Benzodiazepines on the human body

Benzodiazepines effect on the central nervous system, acting selectively on gamma-aminobutyric acid-A (GABA-A) receptors in the brain. It enhances response to the inhibitory neurotransmitter GABA, by

opening GABA-activated chloride channels and allowing chloride ions to enter the neuron, making the neuron negatively charged and resistant to excitation. Benzodiazepines are usually divided into two classes; these are determined by the duration of action of the two groupings. Short-acting compounds have a half-life of 12 hours, and long acting compounds, which have a half-life of over 24 hours¹⁶⁻¹⁷.

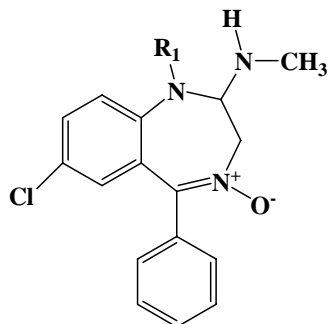


Fig. 1

Whereas short acting drugs are used for the treatment of depression, anxiety, muscle sickness and sleeping disorder and long acting drugs are using for the treatment of physical relaxation, nausea and drowsiness etc.

Mechanism of action of benzodiazepines

1,4-benzodiazepines increase the effect of the neurotransmitter gamma-aminobutyric acid, which results in sedative, hypnotic (sleep-inducing), anxiolytic (anti-anxiety), anti-convulsant, muscle relaxant. 1,4-benzodiazepines enhance the effects of GABA binding at the GABA_A, and increasing the frequency of the Cl⁻ ion channel opening in response to GABA¹⁸. This reduces the communication between neurons and, therefore, has a calming effect on many of the functions of the brain such as sedative, hypnotic, anti-anxiety and sleep inducing etc. GABA controls the excitability of neurons by binding to the GABA receptor¹⁹. A GABA receptor is actually a macromolecular complex that, in addition to containing sites for binding GABA, also contains sites for binding other molecules such as benzodiazepines that modulate GABA's activity. When benzodiazepines bind to a specific site on a GABA receptor, they do not stimulate it directly. Instead, they make it more efficient by increasing the frequency with which the chlorine channel opens when GABA bind to its own site on its receptor Fig. 2. The resulting increase in the concentration of Cl⁻ ions in the post-synaptic neuron immediately hyperpolarizes this neuron, thus making it less excitable. Barbiturates bind to other site on the GABA receptor, with similar effect. But the advantage of benzodiazepines is that, unlike barbiturates, they do not open the Cl⁻ channels directly.

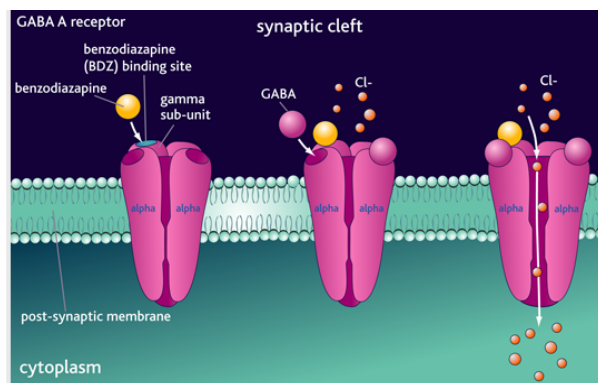


Fig. 2

1, 4-Benzodiazepin drugs

Since the introduction of Diazepam in 1960, a large number of 1,4-benzodiazepine drugs have been investigated as tranquillizers, hypnotic, sedative and anti-depressants. 1, 4-benzodiazepines fused to a five-membered heterocyclic ring are the most commonly prescribed group of drugs for the treatment of CNS disturbances. Triazolobenzodiazepines such as alprazolam or triazolam and imidazobenzodiazepines such as midazolam. The most successful have been nitrazepam, flurazepam, temazepam, and triazolam as hypnotics, and diazepam, lorazepam, and alprazolam as tranquilizers. In the last decade, the area of biological interest of 1,4-benzodiazepines has been extended to several disease such as cancer²⁰ and HIV²¹. On account of pharmacological properties, 1,5-benzodiazepine nucleus has been recognized in the literature as 'privileged medicinal scaffold' and research in this area is very active and is directed towards the synthesis of compounds with enhanced pharmacological profile.

Some benzodiazepine derivatives, shown in Fig. 3, are highly pharmacologically active molecules.

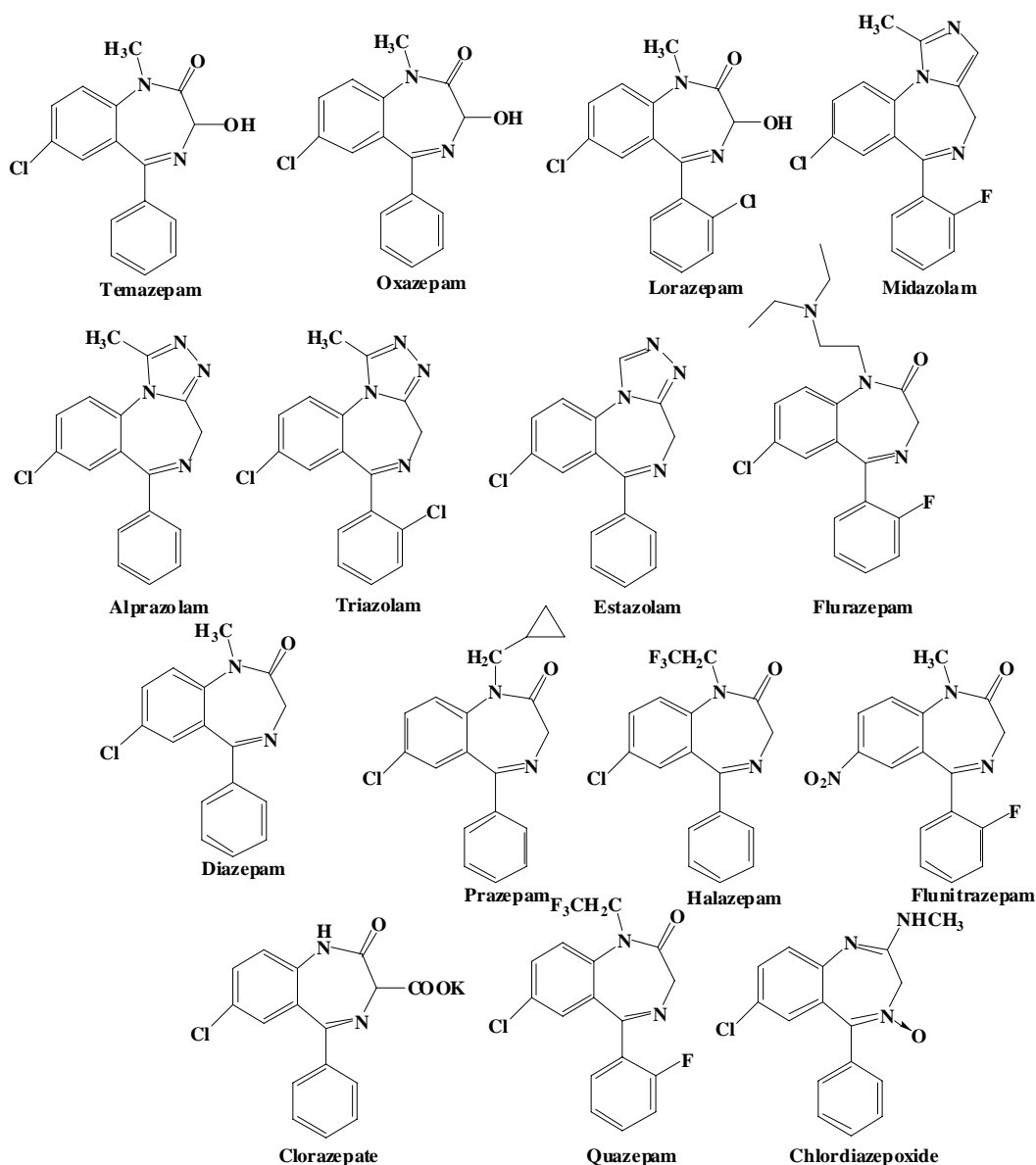


Fig. 3

Effect of substitution on the biological activity of benzodiazepines

In the basic structure of 1,4-BZ, early SAR studies indicated that the seven-membered imino ring B was essential for its affinity towards the BZ-binding site²² Further QSAR and SAR studies²³ found that the molecular lipophilicity properties of numerous BZs played a significant role in their corresponding receptor affinity. Additionally, the carbonyl group at position 2, and the 4,5 double bond within the ligand have also been shown to substantially contribute to the binding affinity of the compound. The removal of carbonyl group results in a decrease in the binding affinity of the BZ by two orders of magnitude, while saturation of the 4,5 double bond results in a complete loss of *in vitro* affinity.

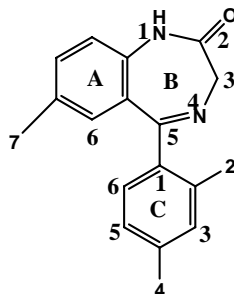


Fig. 4

Presence of seven membered imino-lactam ring (ring B) is essential for activity and substitution can advantageously done only in positions 1, 3, 7 and 2'.

Ring A Substitution

Electron withdrawing substituent (Cl, NO₂, CF₃ etc.) at position 7 increases the activity while the substitution at positions 8 and 9 and electron releasing substituent at position 7 decreases the activity.

Ring B Substitution

1. Methyl group substitution at position 1 increases the activity.
2. Introduction of carbonyl function at position 2 and or a phenyl substituent at position 5 increases the anxiolytic activity.
3. The following modifications decrease the activity:
 - a) Reduction of the carbonyl functions at position 2.
 - b) Introduction of a hydroxyl group at position 3.
 - c) Heteroaromatic or cycloalkyl substituent at position 5 (except Bromazepam).
 - d) Shift of double bond to the 3, 4 position decreases activity.

Ring C Substitution

Chlorine and fluorine at ortho position and disubstitution in both ortho positions increases the activity. Any substitution at meta or para position decreases the activity.

Ring A : (position 7) generally, increased by electron-withdrawing groups, e.g. NO and CF and decreased by electron-releasing groups such as C, H and OCH, decreased by any substituents in any positions other than 7. Ring B: increased by a methyl group at position 1; decreased by larger substituents; tert-butyl derivative is completely inactive. Ring C: increased by halogens at the 2' position (e.g. Cl and F); very strongly decreased by a substituent at the 4 position.

Pyrrolo [2, 1-c][1, 4]benzodiazepines (PBDs) as anti-cancer agents

The pyrrolo[2,1-c][1,4]benzodiazepines (PBDs) and their dimers belonging to the class of DNA-interactive anti-tumour anti-biotics have the potential as regulators of gene expression with possible therapeutic application in the treatment of genetic disorders including cancer. The first PBD anti-tumour antibiotic anthramycin has been discovered by Leimgruber et. al. in 1963²⁴, and since then a number of compounds have been developed based on PBD ring system leading to DNA binding ligands.

The PBD cytotoxins exert a powerful anti-tumoural activity by binding in the minor groove of double stranded DNA and forming a covalent bond to the exocyclic amino group of a central guanine within a three base pair recognition site. These agents bind selectively in the minor groove of DNA via a covalent amination bond between the electrophilic C11-position of the PBD and the nucleophilic C2-amino group of a guanine base, resulting in the observed biological activity²⁵. Well-known members of this group are Anthramycin, DC-81, Sibiromycin, Tomamycin, Chicamycin and Neothramycin²⁶ etc.

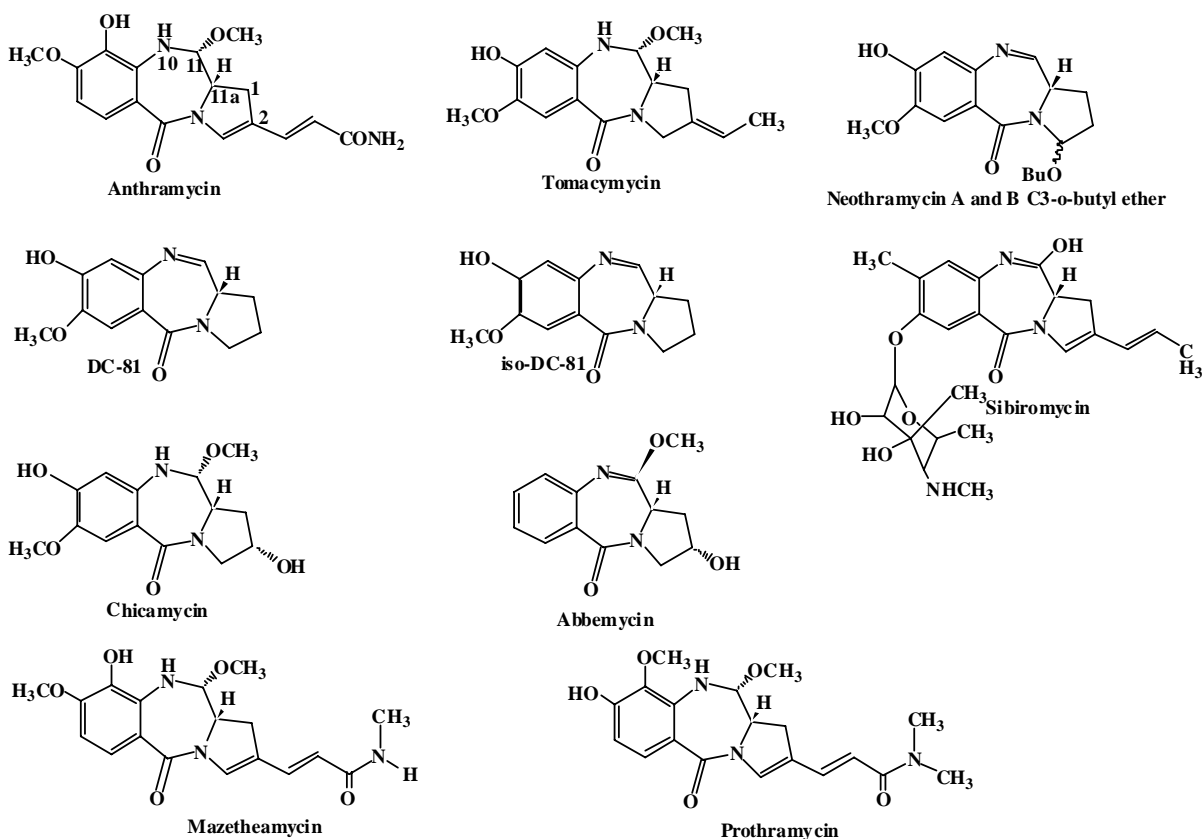


Fig. 5: Pyrrolo [2, 1-c][1, 4]benzodiazepines (PBDs)

1,4-Benzodiazepine as Cholecystinin receptor antagonist

1,4-benzodiazepine derivatives found to act as antagonists of cholecystinin or CCK, which is a specific type of receptor antagonist that blocks the receptor sites for the peptide hormone²⁷. Cholecystinin in the gastrointestinal system responsible for stimulating the digestion of fat and proteins.

There are two type of this receptor antagonists known at present, define as CCK_A and CCK_B. CCK_A is mainly expressed in the small intestine, and is involved in the regulation of enzyme secretion by the pancreas, secretion of gastric acid in the stomach, intestinal motility and signalling of satiety (fullness).

CCK_B is expressed mainly in the central nervous system, and has functions relating to anxiety and the perception of pain.

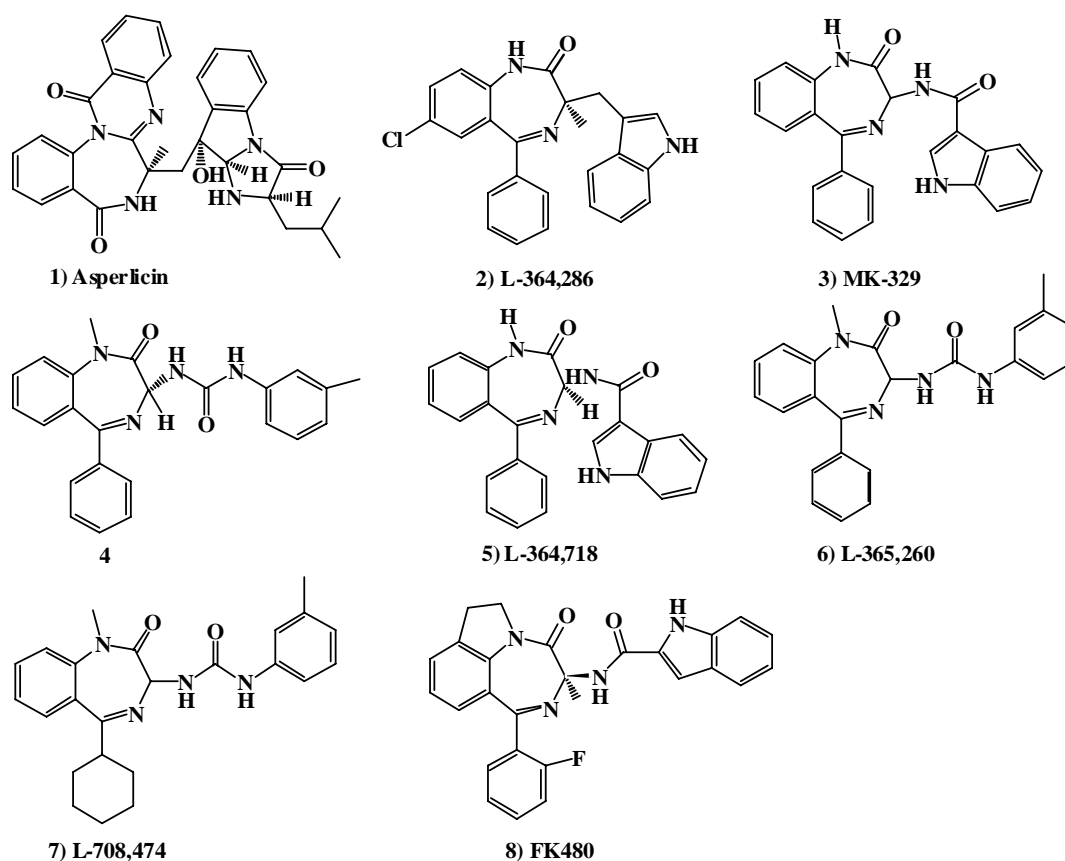


Fig. 6: CCK Receptors antagonists of benzodiazepines

Benzodiazepine as anti-HIV agent

In the search for more effective and safe chemotherapeutic agents there has been considerable interest in non-nucleoside reverse transcriptase inhibitors or NNRTI's., inhibition of HIVRT has evolved to become an important part of anti-HIV therapies²⁸. Tetrahydro-imidazo[4,5,1-jk] [1,4]-benzodiazepin-2(1H)-one and -thione (TIBO) derivatives were shown to specifically block human immunodeficiency virus type 1 (HIV-1) replication through a unique interaction with the HIV-1 reverse transcriptase.

TIBO derivatives: A series of 4, 5, 6, 7-tetrahydro-5-methylimidazo [4, 5, 1-j, k] [1,4]benzodiazepin-2(1H)-one) have been found to possess significant inhibitory activity against the human immunodeficiency virus type 1 (HIV-1)²⁹.

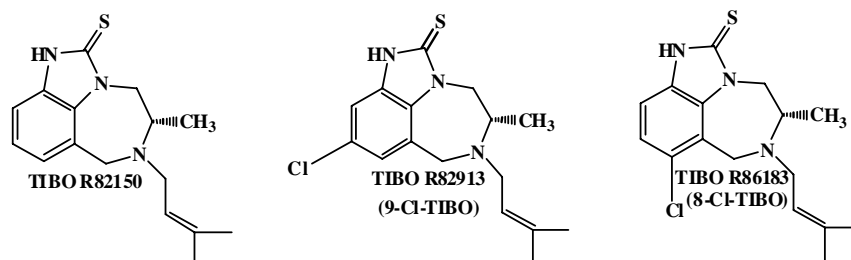


Fig. 7: Structure of some TIBO derivatives

CONCLUSION

The enormous commercial achievement of 1,4-benzodiazepines and their help to society in the modern treatment of mental illness and other broad range of disease have caused the chemistry of these systems to develop into a major part of research in the field of heterocyclic chemistry. On account of pharmacological properties, 1,4-benzodiazepine nucleus has been recognized in the literature as 'privileged medicinal scaffold' and research in this area is very active and is directed towards the synthesis of compounds with enhanced pharmacological profile.

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