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AN INSIGHT INTO MEDICINAL AND BIOLOGICAL SIGNIFICANCE OF PRIVILEGED SCAFFOLD: 1,4-BENZODIAZEPINE

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ABSTRACT

This article outlines the medicinal and biological significance of privileged scaffold, the 1,4-benzodiazepine. 1,4-benzodiazepine derivatives are showing very promising and excellent therapeutic effectiveness either as single heterocyclic derivatives or in fusion with the other cycles. An attempt is made in this article to highlight the medicinally active compounds which were reported to posses various biological activities.

KEYWORDS: 1,4-Benzodiazepine, Privileged Scaffold, Medicinal significance, Biological significance.

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INTRODUCTION

Now a days research is concentrated towards the introduction of new and safe therapeutic agents of clinical importance. The heterocycles are enjoying their importance as being the center of activity. The nitrogen containing heterocycles are found in abundance in most of the medicinal compounds. A seven-member ring of carbon atoms with one nitrogen is called an *azepine* ring while with two nitrogen atoms, it is called a *diazepine* ring, where the topmost nitrogen is designated position one. So, using a standard numbering the complete name of this molecule is 1,4-diazepine. A benzene ring fused on the 10 and 11- positions of the 1,4-diazepine ring forms 1,4-benzodiazepine. Depending upon the substituents over 50 derivatives have been identified by the period. This ring system has demonstrated considerable utility in drug design, with derivatives demonstrating a wide range of biological activities. The series of compounds containing the 1,4-benzodiazepine scaffold are an important class of prototypical ‘‘privileged’’ structures associated with various biological activities and therapeutic uses. The 1,4-benzodiazepines form the most extensively explored group in the benzodiazepine series, largely owing to the discovery of a number of interesting biological properties of these molecules. An idea about the clinical use of benzodiazepines may be obtained from the recent report of Palfai and Jankiewiz. According to this report roughly 8000 tons of benzodiazepines are consumed every year, with 53 million prescriptions for Valium only. Chemically, Valium (diazepam) is 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepine-2-one. [1] Ubiquitous presence of 1,4-benzodiazepines in chemical literature is undoubtedly a consequence of the multifarious biological response which they elicit in combating a variety of body ailments. The impressive biological response of 1,4-benzodiazepines has stimulated intense research efforts to be directed toward the synthesis of their structural analogues on the premise that different constitution and biological activities in the new materials could allow them to be used as novel chemotherapeutic agents. [2]On account of the wide range of biological properties displayed by benzodiazepine derived compounds, benzodiazepine scaffolds have been considered among the most important privileged structures for drug discovery. Particularly, 5-aryl-1,4-benzodiazepine templates are recurrent structures in anxiolytic, hypnotics, anticonvulsant, anti-HIV activity and anti arrhythmics. Furthermore, diverse 1,4-benzodiazepine derivatives have also been used as constrained dipeptide mimics or non-peptide scaffolds in search of peptidomimetics either as enzyme inhibitors or as ligands of diverse G-protein coupled receptors such as cholecystokinin, fibrinogen, integrin, vasopressin, oxytocin, bradykinin or k-opioid receptors.

Biological activities associated with 1,4-benzodiazepine derivatives

Analgesic activity: Pyrrolobenzodiazepines (Fig.-1) have been reported to exert potent and efficacious analgesic activity without displaying the serious undesirable side effects associated with morphine and its relative compounds. [3]

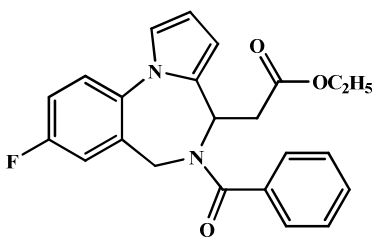


Figure-1

Anorexigenic effect

K. S. Andronati et al. has prepared 3-Amino-1,2-dihydro-3H-1,4-benzodiazepin-2-one (Fig.-2) derivatives *via* interaction with 3-chlorobenzodiazepines, diethylamine, 1,6-diaminohexane or *p*-nitroaniline, which exhibit a pronounced anticonvulsant activity and produce significant anorexigenic effect. [4]

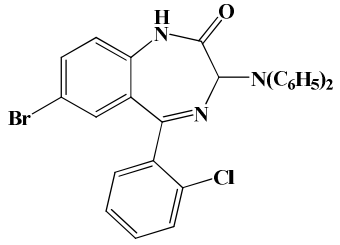


Figure-2

Antagonists for the Bradykinin

Antagonists for the Bradykinin receptor is given below in Fig.-3: [5]

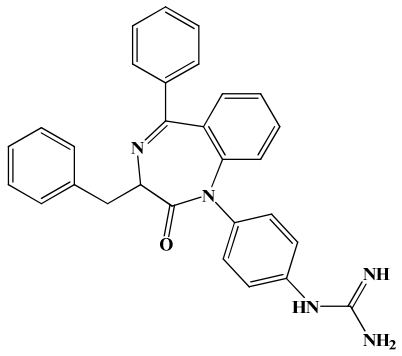
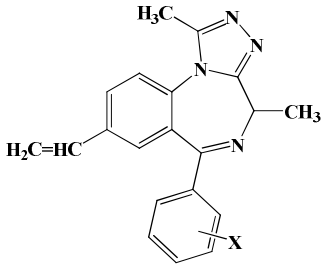


Figure-3

Antagonists of platelet activating factor

Walser A. et al. have prepared [1,2,4]triazolo[4,3-*a*][1,4]benzodiazepines (Fig.-4) bearing an ethynyl functionality at the 8-position and the isostericthieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepines *(Fig.-5)* and evaluated them as antagonists of platelet activating factor. [6]



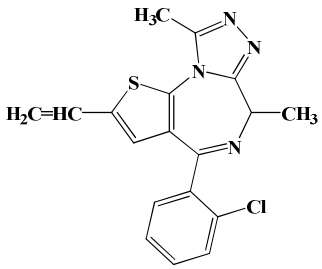


Figure4 **Figure5**

Anti-allergic

Buckle et al. has prepared 1*H*-benzo-1,5-diazepine-2,4-(3H,5H)-diones (Fig.-6) which is anti-allergic substance useful in the treatment of rhinitis, hay fever and certain type of asthma. [7]

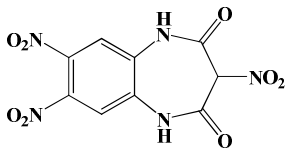


Figure-6

Anti-anaesthetic

Numerous different BZDs have been synthesized, but only a few are used in everyday clinical anesthesia like midazolam, (Fig.-7) diazepam, lorazepam and temazepam and the antagonist flumazenil. [8]

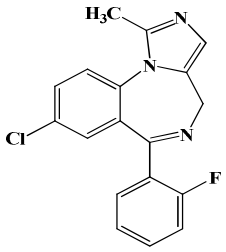


Figure-7
Midazolam

Anti-arrhythmicagents

1,4-benzodiazepine (Fig.-8) act as an anti-arrhythmic agents. [9]

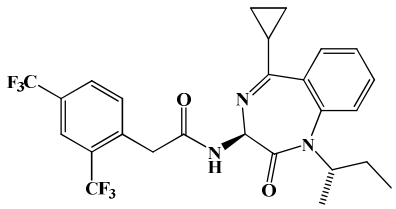


Figure-8

Anti-bacterial

Pyrrolo-1,4-benzodiazepine analogs had been reported for their anti-bacterial activity against a range of Gram positive and Gram negative bacteria *i.e. Enterococcus* species, *Enterobacter cloacae*, *Listeria monocytogenes*, *Streptococcus agalactiae* and *Salmonella* species. [10]

***Anti-cancer*:**

Recently, a number of structurally modified PBDs have been synthesized and examined for their biological properties, particularly their anticancer potential including the novel dimers of PBD (Fig.-9) given below. [11]

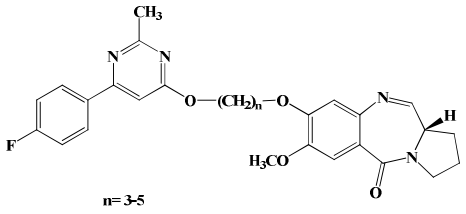


Figure-9

1,4-benzodiazepines are used as starting materials for the synthesis of anthramycin-inspired anti-cancer agents like (Fig.-10-13)

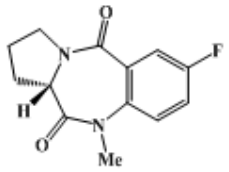


Figure10

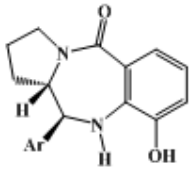


Figure11

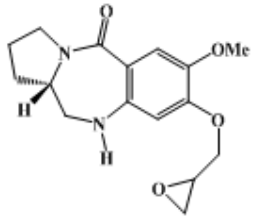


Figure12

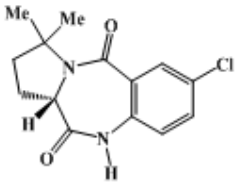


Figure13

Anti-convulsants

The benzodiazepines substituted analogues (Fig.-14) may be useful to segregate the proconvulsant, anti-convulsant and antagonist actions. [12]

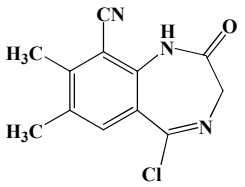


Figure-14

Anti-depressant

The 1,4-benzodiazepine analogue 7-fluoro-5-(2-fluorophenyl)-l,3-dihydro-l-(Cpiperidinyl)-W-l,4-benzodiazepin-2-one (loa) (Fig.-15) has the potential to become a useful anti-depressant drug. [13]

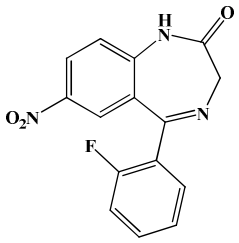


Figure-15

Anti-epileptic

Clonazepam (Fig.-16) is used in anti-epileptic treatments. [14]

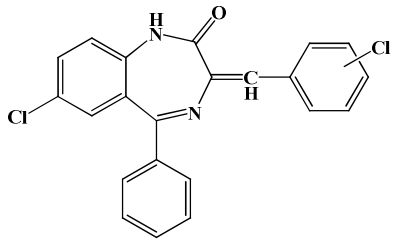


Figure-16

Antifungal

1,4-benzodiazepine (Fig.-17) synthesized compounds has been screened for the anti-fungal activity in vitro. [15]

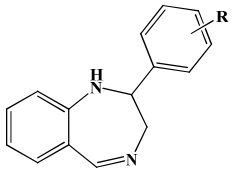


Figure-17

Anti-hepatitis B virus

A series of 4-aryl-6-chloro-quinolin-2-ones and 5-aryl-7-chloro-1,4-benzodiazepine **(Fig.-18)** were synthesized. Some of the tested compounds were active against hepatitis B virus. [16]

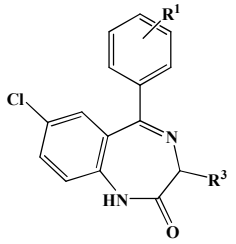
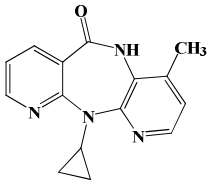


Figure-18

Anti-HIV

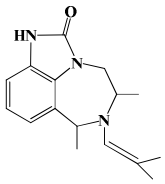
More recent analogues of the benzodiazepines (Fig.-19) have attracted interest as anti-HIV compounds such as the clinically used nevirapine. [17]



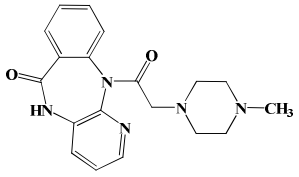
Nevirapine

Figure-19

These compounds can serve as potential agents for the control and treatment of AIDS has stimulated further interest in these compounds from yet another perspective such as TIBO (Fig.-20) and Pirenzepine (Fig.-21).



TIBO



Pirenzepine

Figure-20 **Figure-21**

Anti-inflammatory

A series of 2,3-dihydro-1,4-benzodiazepines (Fig.-22) were synthesized and evaluated for anti-inflammatory effects in microglia cells. [18]

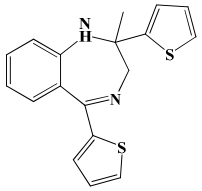
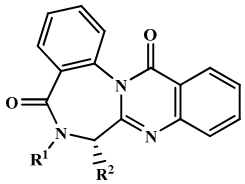


Figure-22

Anti-insectant

Sclerotigenin, isolated in 1999 from Penicllium sclerotigenum Yamamoto was shown to display potent anti-insectant activity against *Helicoverpa,* is a 1,4-benzodiazepine derivative (Fig.-23). [19]

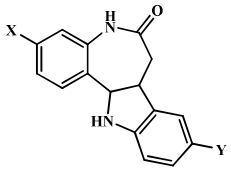


Sclerotigenin; $R^1 = R^2 = H$
Benzomalvin; $R^1 = H$, $R^2 = CH_2Ph$
Cirumdatin; $R^1 = H$, $R^2 = CH_3$

Figure-23

Anti-leishmanial

The parallel synthesis of a series of 1,4-benzodiazepin-2,5-diones, (Fig.-24-25) structurally related to the paullone nucleus, was recently reported as presenting anti-leishmanial activities. [20]



Paullone

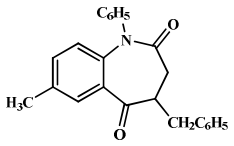


Figure-24 **Figure-25**

Anti-malarial

Twelve α-substituted norstatines (Fig.-26) were designed, synthesized and evaluated for their inhibitory potencies against plasmepsin II and the plasmepsin IV orthologues present in the digestive vacuoles of all four Plasmodium species causing malaria in man. [21]

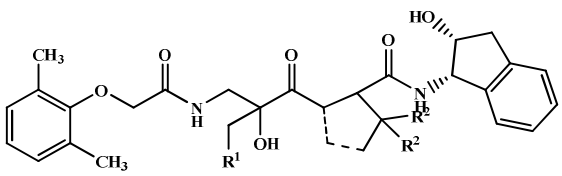


Figure-26

Anti-microbial

1,4-benzodiazepines derivative 4-(2-oxo-2*H*-chromen-3-yl)-1,5-dihydrospiro-[benzo[*b*][1,4]diazepine-2,3'-indolin]-2'-one (Fig.-27) have been screened for their anti-microbial activity. [22]

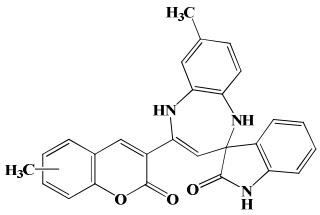


Figure-27

Anti-nociception

Tifluadom is a 2-[(acylamino)-methyl]-1,4-benzodiazepine (Fig.-28) shows high affinity for the opioid receptor and causes anti-nociception in several animal models. [23]

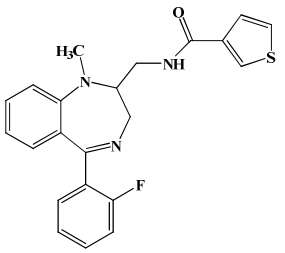


Figure-28

Anti-oxidant

Oxazepam and its derivative (7-chloro-5-phenyl-1*H*-1,4-benzodiazepine-2,3-dione) (Fig.-29) belong to the tranquillizers of 1,4-benzodiazepines group showed anti-oxidant properties. [24]

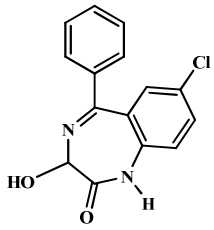


Figure-29

Anti-proliferative

A few years ago, some of these benzodiazepines (Fig.-30) compounds showed anti-proliferative properties against some tumor cell lines. [25]

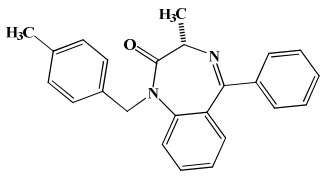


Figure-30

Anti-psychotic

The synthesis of a new class of annulated 1,4-benzodiazepines with anti-psychotic activity was exemplified by preparation of 10-fluoro-3-methy1-7-(2-thieny1)-1,2,3,4,4a,5-hexahydropyrazino[1,2-*a*][1,4]benzodiazepine (Fig.-31). [26]

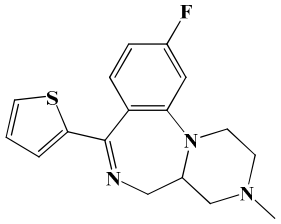


Figure-31

Anti-trypanosomiasis

A library of 1,4-benzodiazepines (Fig.-32) has been synthesized and evaluated against trypanosoma brucei, a causative parasite of Human African Trypanosomiasis. [27]

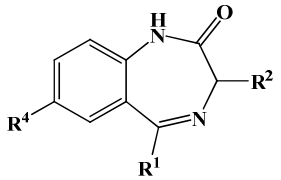


Figure-32

Anti-tumor agent

Pyrrolo[2,1-c][1,4]benzodiazepines usually interact covalently with DNA in a sequence-selective manner and have generated as potential anti-cancer and alkylation agents. The PBDs (Fig.-33) and its derivatives may combine with base pair guanine of DNA to inhibit the DNA of the cancer cell transcription. [28]

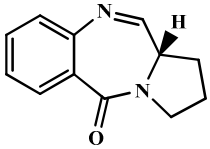


Figure-33

Anxiolytic

Alprazolam (Fig.-34) is for management of anxiety disorders and for short term symptomatic relief of excessive anxiety. [29]

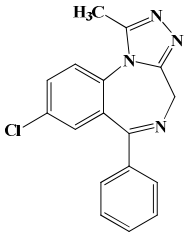


Figure-34

Central nervous system

Sternbach had made some easily modified compounds called benzoheptoxdiazines (Fig.-35) during his postdoctoral work at the University of Cracow, Poland, in the early 1930's had showed central nervous system effect. [30]

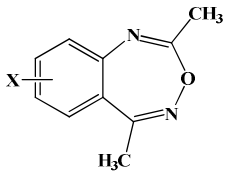


Figure-35

Cholecystokinin Receptor Agonists

1,4-benzodiazepin-2-ones (Fig.-36-37) have also been shown to be antagonists of the peptide hormone cholecystokinin A in the gastrointestinal system and CCK-B in the central nervous system. [31]

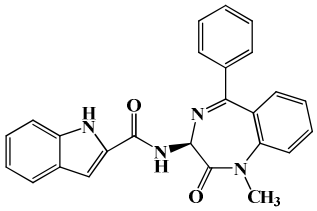


Figure-36

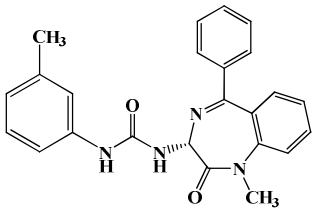


Figure-37

Cytotoxicity

The 1,4-benzodiazepines such as pyrrolo-[1,4]-benzodiazepine (Fig.-38) and dibenzo[*b*,*e*][1,4]diazepin-11-one (Fig.-1) have been reported to display cytotoxic activity. [32]

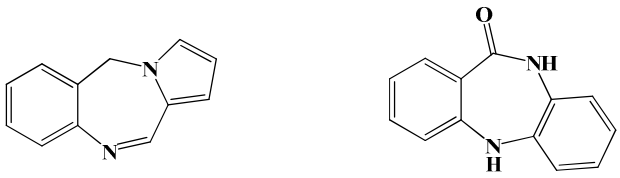


Figure-38

Endocrine disorders

Compounds containing the 1,4-benzodiazepin-2,5-dione (Fig.-39) skeleton have received attention as potential therapeutics for endocrine disorders. [33]

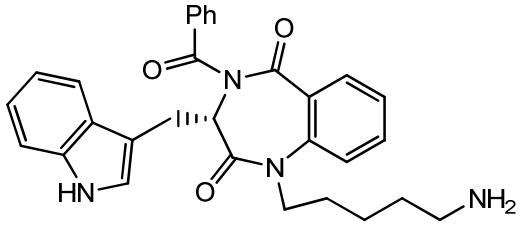


Figure-39

Endothelin receptors

In the process of searching for the nonpeptide endothelin antagonists, we speculated that 1,4-benzodiazepine-2,5-dione (Fig.-40) derivatives bearing appropriate substituents might serve for this purpose. [34]

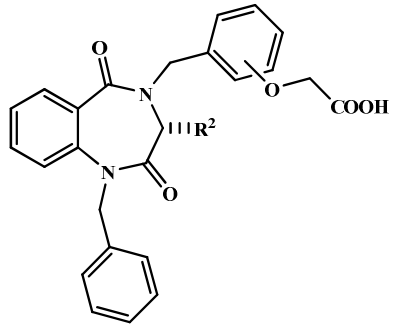


Figure-40

Farnesyl-protein transferase inhibitors

1,3-substituted 1,4-benzodiazepine (Fig.-41) templates were developed into farnesyl-protein transferase inhibitors. [35

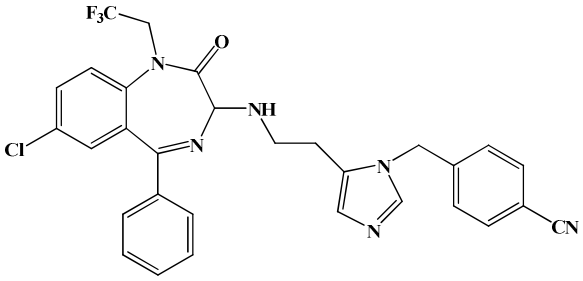


Figure-41

GABAA receptors

Since the discovery of benzodiazepines (Fig.-42) as anxiolytics in the 1960's, the classical structures of this class of compounds have been widely varied, resulting in benzodiazepine ligands that bind to specific subtypes of the GABAA receptors. [36]

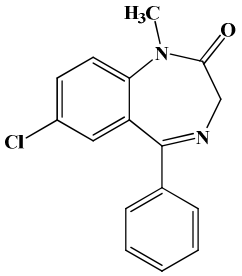


Figure-42

HDM2-p53 protein antagonists

1,4-benzodiazepine-2,5-dione (Fig.-43) scaffold serve to mimic the side-chains presented by the hydrophobic face of two turns of an a-helix derived from the tumor suppressor protein p53 and thus antagonize the HDM2-p53 protein-protein binding interaction. [37]

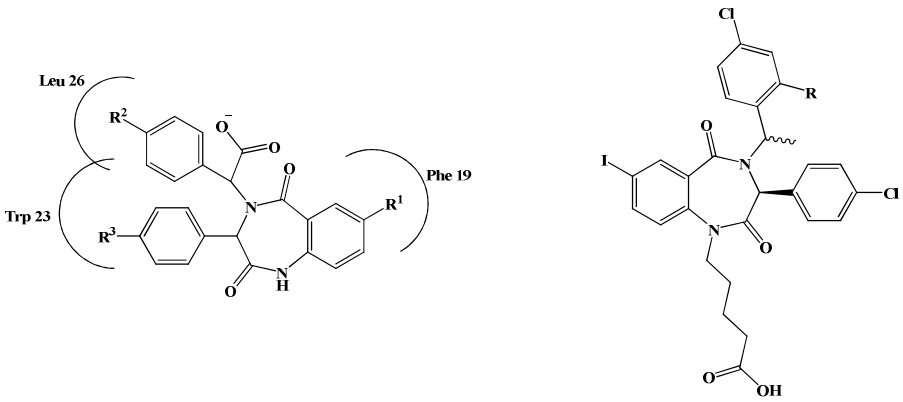


Figure-43

Herbicides

1,4-benzodiazepines (Fig.-44) have shown promised activity as herbicides. [38]

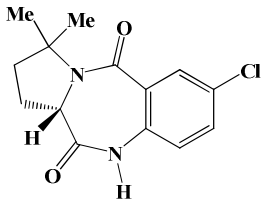


Figure-44

Hypnotic

Flurazepam (Dalmane) (Fig.-45) is a hypnotic. [30]

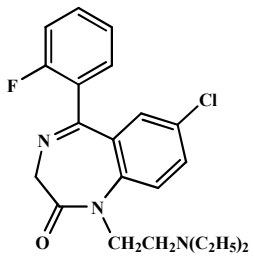


Figure-45

Infantile spasma

Nitrazepam (Fig.-46) also used for infantile spasma. [29]

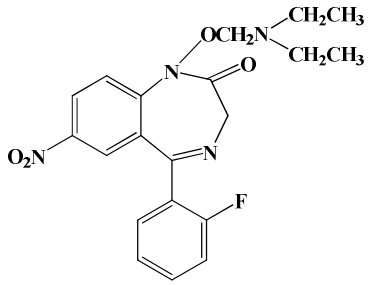
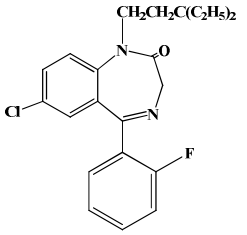


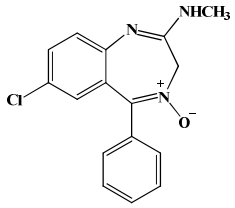
Figure-46

Insomnia

Chlorodiazepoxide (Librium) (Fig.-47-48) BZD's are often prescribed for treating insomnia. [39]



Chlorodiazepoxide



Flurazepam

Figure-47 **Figure-48**

Muscle relaxant

Bromazepam (Lexotan) (Fig.-49) is used for muscle relaxant and agitation in the patient. [30]

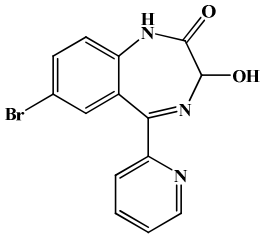


Figure-49

Neurokinin receptor

4-substituted ureidobenzodiazepines (Fig.-50) have been modified into neurokinin receptor antagonists. [40]

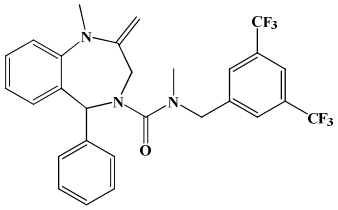


Figure-50

Neuroleptic

Lorazepam (Ativam) (Fig.-51) is used for the relief of neural problems. [41]

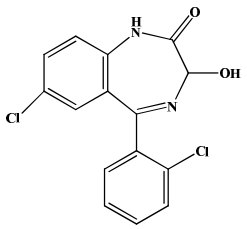


Figure-51

Neurotoxicity

Aniline derivatives of 7-chloro-5-phenyl-1,3-dihydro-1H,3H-1,4-benzodiazepine-2-one (Fig.-52) compounds exhibited significant neurotoxicity activity. [42]

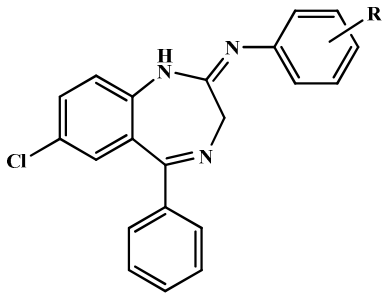


Figure-52

Opiate receptor

Tifluadom, (Fig.-53) is a 2-substituted 1,4-benzodiazepine, binding to the opiate receptor and represents a well known μ receptor antagonist. [43]

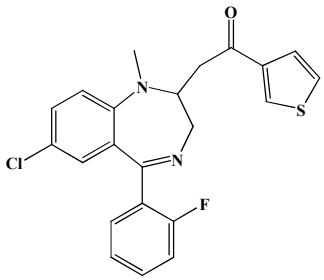


Figure-53

Oxytocin receptor

1,4-benzodiazepine derivative (Fig.-54) represents the first disclosed, non-peptide, low molecular weight agonists of the hormone oxytocin. [44]

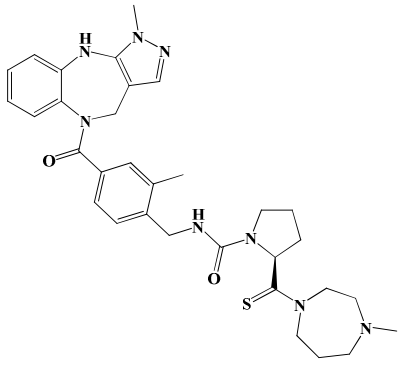


Figure-54

Peptidomimetic building

The tryptophan-derived 2-substituted-5-oxo-1,2,3,4-tetrahydro-5H-1,4-benzodiazepines (Fig.-55) functionalized at position 4 by alkylation or acylation reactions showed significant selective binding affinity for peptidomimetic building. [45]

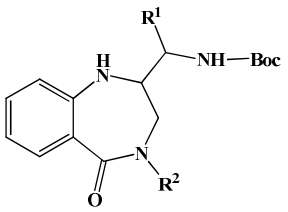


Figure-55

Pharmacological mimics

1,4-benzodiazepin-2,5-diones (Fig.-56) have been reported to be valuable pharmacological mimics of the tripeptide RGD (Arg-Gly-Asp). [46]

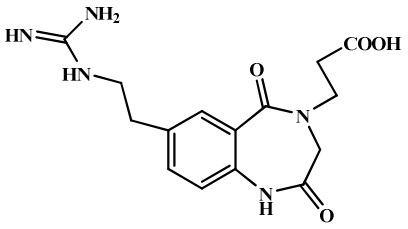
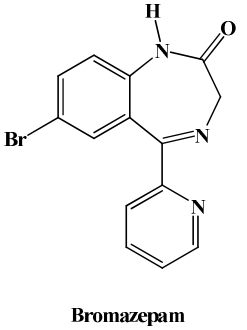


Figure-56

Psychotropic

Bromazepam (7-bromo-1,3-dihydro-5-(2'-pyridyl-2H-1,4-benzodiazepin-2-one) (Fig.-57) belongs to the group of 1,4-benzodiazepines, compounds which are widely used as psychotropic drugs. [47]



Bromazepam

Figure-57

Ras farnesyltransferase inhibitors

1,4-benzodiazepine (Fig.-58) shows ras farnesyltransferase inhibitors in cancer cells. [48]

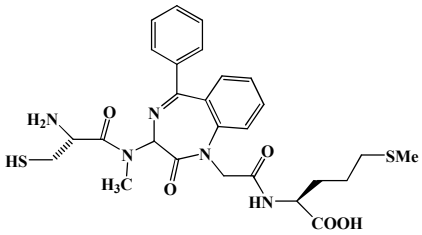


Figure-58

Respiratory syncytial virus

Malcolm et al. have been synthesized acetamido-1,4-benzodiazepine (Fig.-59) analogs which worked as inhibitor of respiratory syncytial virus. [49]

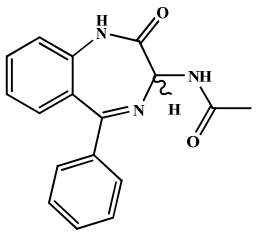


Figure-59

Schizophrenia

Benzodiazepines (Fig.-60) are important class of compounds used as a drugs having effect on central nervous system, for example, clozapine, olanzapine, and quetiapine are used in the clinic for treating schizophrenia. [50]

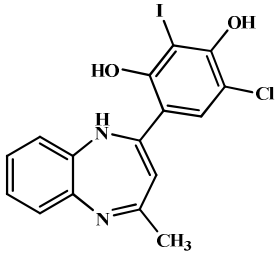


Figure-60

Sedative

The sedative activity of these compounds is such that their use in therapeutics is widespread. [51]

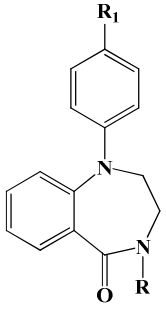


Figure-61

Seizures

The compounds provided significant protection against maximal electroshock induced seizures (MES) and seizures indicated by pentetrazole administration. [52]

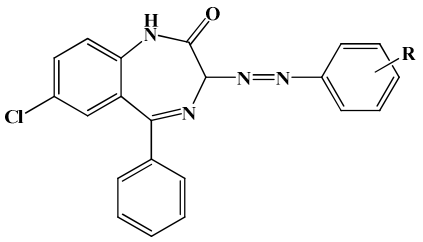


Figure-62

Somnolytic

Inverse agonists related to Ro 15-4513 exhibit anxiogenic and somnolytic activity. [53]

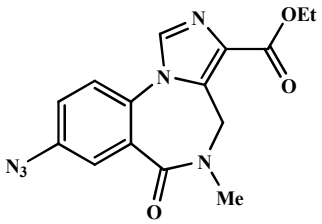


Figure-63

Tranquilizers

Nakanishi et al. have reported the pharmacological activity of tetrazolo, oxadiazolo and imidazothienodiazepines derivatives (Fig.-64-66) and found as minor tranquilizers. [54]

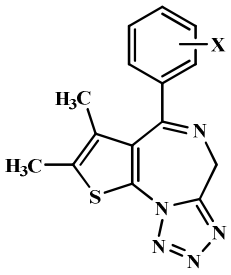


Figure-64

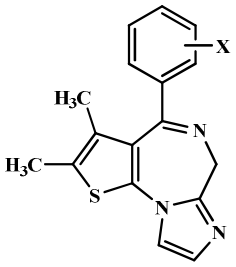


Figure-65

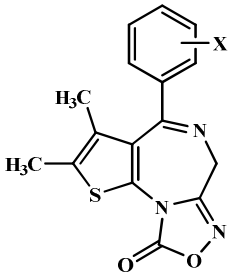


Figure-66

CONCLUSION

1,4-Benzodiazepines occupy distinct and unique place in the medical field. Benzodiazepines have attracted attention as an important class of heterocyclic compounds in the field of drugs and pharmaceuticals. Research on this scaffold for various diseases has increased significantly. Research has of course continued in the effort to develop this scaffold which would be more specific for various ailments with lesser sedative effects or liability for abuse.

REFERENCES

1. N. G. R. Rao, S. M. Ghurghure, M. Munde, A. Hadi, Design and characterization of gas powered system of zidovudine using synthetic polymers, Int. J. Pharma and Bio. Sci., 2, 269 (2011).
2. Y. Paul, S. Tyagi, B. Singh, Formulation and evaluation of taste masked dispersible tablets of zidovudine, Int. J. Pharma and Bio. Sci., 2, 20 (2011).
3. A.Mai, R. D. Santo, S. Massa et al., Pyrrolobenzodiazepines with antinociceptive activity, Eur. J. Med. Chem. 30, 593 (1995).
4. K. S. Andronati, E. K. Kostenko, T. L. Karaseva et al., Synthesis and Pharmacological Properties of 3-Amino-1,2-dihydro-3H-1,4-benzodiazepin-2-one Derivatives, Pharmaceutical Chemistry Journal., 7, 356 (2002).
5. M. R. Wood, C. F. Homnick, K. L. Murphy et al., Benzodiazepines as potent and selective bradykinin B1 antagonists, J. Med. Chem., 46, 1803 (2002).
6. A.Walser, T. Flynn, C. Mason et al., Triazolobenzo- and triazolothienodiazepines as potent antagonists of platelet activating factor, J. Med. Chem., 34, 1209 (1991).
7. D. R. Buckel, B. V. Cantello, N. Morgan, British Patent, 1460938; Chem. Abstr., 1977, 87, 68438.
8. S. L. Raymond, Chang, J. V. Lotti, Biochemical and pharmacological characterization of an extremely potent and selective nonpeptide cholecystokinin antagonist, Medical Sciences, Proc. Natl. Acad. Sci. USA, 83, 4923 (1986).
9. J. W. Butcher, N. J. Liverton, D. A. Claremon et al., Novel 5-cyclopropyl-1,4-benzodiazepin-2-ones as potent and selective IKs-blocking class III antiarrhythmic agents, Bioorg. Med. Chem. Lett., 13, 1165 (2003).
10. H. Benzeid, K. Khedid, S. Hassani et al., Antibacterial activity of ethylpyrrolobenzodiazepines, Int. J. Agri. Biol., 10, 541 (2005).
11. A.Kamal, K. L. Reddy, V. Devaiah et al., Synthesis and biological activity of c-8 fluoroaryl substituted pyrimidine linked-pyrrolobenzodiazepine conjugates, Letters in Drug Design & Discovery, 2, 55 (2005).
12. A.A.Fatmi, N. A. Vaidya, W. B. Iturrian et al., Synthesis of previously inaccessible quinazolines and 1,4-benzodiazepines as potential anticonvulsants, J. Med. Chem. 27, 772 (1984).
13. T. Sugasawa, M. Adachi, K. Sasakura et al., 1-Azacycloalkyl-1,4-benzodiazepin-2-ones with antianxiety-antidepressant actions, J. Med. Chem., 28, 699 (1985).
14. N. Fukumitsu, S. Ogi, M. Uchiyama et al., Effects of diazepam on 125 I-iomazenil-benzodiazepine receptor binding and epileptic seizures in the El mouse, Annals of Nuclear Medicine, 20, 541 (2006).
15. J. L. Silen, A. T. Lu, D. W. Solas et al., Anti-inflammatory action of an s-triazine derivative in rats, Arzneimittelforschung, 25, 230 (1975).
16. P. Cheng, Q. Zhang, Y. B. Maa et al., Synthesis and in vitro anti-hepatitis B virus activities of 4-aryl-6-chloroquinolin-2-one and 5-aryl-7-chloro-1,4-benzodiazepine derivatives, Bioorg. Med. Chem. Lett. 18, 3787 (2008).
17. K. Hemming, B. Anwar, P. Grimsey et al., A thiazine-S-oxide, Staudinger:aza-Wittig based synthesis of benzodiazepines and benzothiadiazepines, Tetrahedron Lett., 41, 10107 (2007).
18. S. K. Ha, D. Shobha, E. Moon et al., Anti-neuroinflammatory activity of 1,5-benzodiazepine derivatives, Bioorg. Med. Chem. Lett., 20, 3969 (2010).
19. H. Naim, A. Said, Z. N. Ishtaiwi, Synthesis of N-Substituted Quinazolino[1,4]benzodiazepine: A Facial Route to N-Benzylsclerotigenin, Acta Chim. Slov, 52, 328 (2005).
20. R. L. Clark, K. C. Carter, A. B. Mullen et al., Identification of the benzodiazepines as a new class of antileishmanial agent, Bioorg. Med. Chem. Lett., 17, 624 (2007).
21. K. M. Orrling, M. R. Marzahn, G. Teran et al., Alpha-substituted norstatines as the

transition-state mimic in inhibitors of multiple digestive vacuole malaria aspartic proteases, Bioorg. Med. Chem., 17, 5933 (2009).
22. R. A. Kusanur, M. Ghate, M. V. Kulkarni, Synthesis of spiro [indolo-1,5-benzodiazepines] from 3-acetyl coumarins for use as possible antianxiety agents, J. Chem. Sci., 116, 265 (2004).
23. A.Cappelli, M. Anzini, S. Vomero et al., Synthesis, biological evaluation and quantitative receptor docking simulations of 2-[(acylamino)ethyl]-1,4-benzodiazepines as novel tifluadom-like ligands with high affinity and selectivity for opioid receptors, J. Med. Chem., 39, 860 (1996).
24. E. I. Korotkova, Y. A. Karbainov, O. A. Avramchik, Investigation of antioxidant properties of pharmaceuticals by voltammetry, J. Anal. Bioanal. Chem., 375, 465 (2003).
25. J. Dourlat, W. Q. Liu, N. Gresh et al., Novel 1,4-benzodiazepine derivatives with antiproliferative properties on tumor cell lines, Bioorg. Med. Chem. Lett., 17, 2527 (2007).
26. W. Heitmann, H. Liepmann, U. Matzel et al., 1,4-Benzodiazepines and 1,5-benzodiazocines XI. Synthesis and biological activity, Eur. J. Med. Chem., 23, 249 (1988).
27. J. Spencer, R. P. Rathnam, A. L. Harvey et al., Synthesis and biological evaluation of 1,4-benzodiazepin-2-ones with antitrypanosomal activity, Bioorg. Med. Chem., 19, 1802 (2011).
28. Y. Y. Huang, C. F. Lin, S. Y. Wang et al., Pharmacophore/receptor models for GABAA/BzR subtypes via a comprehensive ligand-mapping approach, Anti-Canc. Agents Med. Chem., 9, 1 (2009).
29. S. M. Murphy, P. Tyrer, A double-blind comparison of the effects of gradual withdrawal of lorazepam, diazepam and bromazepam in benzodiazepine dependence, Br. J. Psyc., 158, 511 (1991).
30. L. H. Sternbach, The benzodiazepine story, J. Med. Chem., 22, 1 (1979).
31. R. G. Sherrill, J. M. Berman, L. Birkemo et al., 1,4-Benzodiazepine peripheral cholecystokinin (CCK-A) receptor agonists, Bioorg. Med. Chem. Lett., 11, 1145 (2001).
32. D. P. Mahana, C. E. Bustos, J. M. Raipan et al., Microwave-assisted synthesis and regioisomeric structural elucidation of novel benzimidazo[1,2d][1,4]benzodiazepinone derivatives, ARKIVOC, XIII, 131 (2009).
33. M. Ishikura, M. Mori, M. B. Terashima, A new synthesis of anthramycin via palladium-catalyzed carbonylation, J. Chem. Soc. Chem. Commun., 741 (1982).
34. M. F. Cheng, J. M. Fang, Liquid-phase combinatorial synthesis of 1,4-benzodiazepine-2,5-diones as the candidates of endothelin receptor antagonism, J. Comb. Chem., 6, 99 (2004).
35. R. Roskoski, P. A. Ritchie, Time-dependent inhibition of protein farnesyltransferase by a benzodiazepine peptide mimetic, Biochemistry, 40, 9329 (2001).
36. E. Lattmann, D. C. Billington, D. R. Poyner, Synthesis and evaluation of Asperlicin analogues as non-peptidal Cholecystokinin-antagonists, Drug Des Discov., 17, 219 (2001).
37. M. D. Cummings, C. Schubert, D. J. Parks et al., Substituted 1,4-benzodiazepine-2,5-diones as alpha-helix mimetic antagonists of the HDM2-p53 protein-protein interaction, Biol. Drug Des., 67, 201 (2006).
38. G. M. Karp, M. C. Manfredi, M. A. Guaciaro et al., Synthesis and herbicidal activity of 1,H-1,4-benzodiazepine-2,5-diones, J. Agric. Food. Chem., 45, 493 (1997).
39. P. Jain, Ph.D. Thesis, Application of η^6-Arenetricarbonylchromium complexes in the synthesis of 1,4-benzodiazepines, Banasthali Vidyapith, Banasthali, 2002.
40. G. B. P. Varty, C. Ursula, J. Galen, The gerbil elevated plus-maze II: anxiolytic-like effects of selective neurokinin NK1 receptor antagonists,

Neuropsychopharmacology, 27, 371 (2002).
41. W. Nawrocka, B. Sztuba, A. Opolski et al., Synthesis and antiproliferative activity in vitro of novel 1,5-benzodiazepines, Arch. Pharm. Med. Chem., 334, 3 (2001).
42. M. Rashid, B. Ahmad, R. Mishra, Synthesis and psychotropic activity of some substituted aniline derivatives of 7-chloro-5-phenyl-1, 3-dihydro-1h, 3h-1, 4-benzodiazepine-2-one, Int. J. Pharma. Sci., 2, 617 (2010).
43. M. Sansone, C. Castellano, F. Pavone, Opioid benzodizapine tifluadom and drug-induced hyperactivity in mice-lack of benzodiazepine-like effects, Pol. J. Pharmacol. Pharm., 37, 585 (1985).
44. G. R. W. Pitt, A. R. Batt, R. M. Haigh et al., Non-peptide oxytocin agonists, Bioorg. Med. Chem. Lett., 14, 4585 (2004).
45. S. Herrero, M. T. Garc-Lopez, E. Cenarruzabeitia et al., Versatile synthesis of chiral 2-substituted-5-oxo-1,2,3,4-tetrahydro-5H-1,4-benzodiazepines as novel scaffolds for peptidomimetic building, Tetrahedron, 59, 4491 (2003).
46. E. Addicks, R. Mazitschek, A. Giannis, Synthesis and biological investigation of novel tricyclic bezodiazepinedione-based RGD analogues, Chem. Bio. Chem., 3, 1078 (2002).
47. L. B. Pfendt, G. V. Popovi, T. Damjanovi et al., Protolytic equilibria of bromazepam, J. Serb. Chem. Soc., 67, 187 (2002).
48. G. L. James, J. L. Goldstein, M. S. Brown et al., Benzodiazepine peptidomimetics: potent inhibitors of Ras farnesylation in animal cells, Science (Washington, DC, U. S.), 260, 1937 (1993).
49. M. C. Carter, D. G. Alber, R. C. Baxter et al., 1,4-Benzodiazepine analogues as inhibitors of respiratory syncytial virus, J. Med. Chem., 49, 2311 (2006).
50. A.Y. Vibhute, S. B. Zangade, V. M. Gurav et al., Synthesis of series of 2-methyl-4-(substituted phenyl)-1,5-benzodiazepines and evaluation of antibacterial activity, J. Chem. Pharm. Res., 3, 438 (2011).
51. C.Bagolini, P. Witt, L. Pacifici et al., Synthesis and pharmacological activity of some derivatives of 1-phenyl-1,2,3,4-tetrahydro-5H-1,4-benzodiazepin-5-one, J. Med. Chem. 21, 477 (1978).
52. M. Rashid, R. Mishra, A. Husain et al., Synthesis of some new 4-Thiazolidinone derivatives as anticonvulsant agents, Chemical Sciences Journal, 5 (2000).
53. Q. Haung, X. He, C. Ma et al., Pharmacophore/receptor models for GABA(A)/BzR subtypes (alpha1beta3gamma2, alpha5beta3gamma2, and alpha6beta3gamma2) via a comprehensive ligand-mapping approach, J. Med. Chem., 43, 71 (2000).
54. M. Namanishi, T. Tahara, K. Araki et al., US Patent, 3920679, 1975.