RESEARCH PAPER

SYNTHESIZED 1,5- BENZODIAZEPINE TARGET COMPOUNDS FOR MOST PREVALENT EPILEPSY -A REVIEW

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ABSTRACT: Among the many prominent heterocyclic scaffold molecules found in chemistry, the benzodiazepine nucleus is essential to the development of studies on disorders of the central nervous system. Azepines are rings with seven members that contain a nitrogen atom. Diazepines are compounds with two nitrogen atoms in a seven-membered ring. Benzodiazepines are identified by the fusion of the diazepine and benzene rings. They are once more divided into 1,4-BZDs and 1,5-BZDs according to the location of the N atoms in the seven-membered ring. Diverse pharmacological and biological activities have been exhibited by these substances. Among the various structural isomers of BZDs that are available, 1,5-Benzodiazepines have a special function in pharmacological activities. Lead compounds can be created using a variety of synthetic techniques, including one-pot synthesis, two-step synthesis, two-, three-, and catalytic processes, as well as microwave synthesis and green synthesis. Therefore, during the period of 2015-2026 till date,for a decade. we have reviewed the literature on a variety of synthesized compounds produced using distinct synthetic avenues. Insightful ideas regarding the topic of in-depth research on specific substances synthesized over the period of 10 years are put forward in this review material.

KEYWORDS:1,5-BZDs, CNS ,Epilepsy, Synthetic Insightful ideas, Targeted compounds.

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INTRODUCTION:

One of the most prevalent neurological conditions, epilepsy affects 1% to 2% of people worldwide and is typified by frequent, spontaneous convulsions [1]. Epilepsy is defined as transient symptoms and indicators attributed to extreme or simultaneous neuronal activity of a population of neuronal cells in the brain[2].According to a recent study, approximately 70 million people worldwide suffer from epilepsy, the majority of whom reside in developing nations [3]. Epilepsy is a serious health issue, with 10% of affected patients being children [4]. Prior to the 19th century, "spiritual and supernatural beliefs" were the primary foundation for epileptic treatment . It has been called "Sacred disease". The first successful antiepileptic drug was potassium bromide [5].

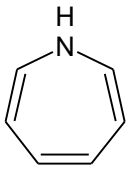
PATHOPHYSIOLOGY OF EPILEPSY:

Epilepsy is a severe neurological disorder involving spontaneous and recurrent seizures, affecting a large number of people worldwide [6]. Seizures affect the lives of 10% of the global population and result in epilepsy in 1 to 2% of people around the world [7] .The mechanism for the development and progression of epilepsy is diverse and is based on the type of epilepsy and risk factors associated with it [8].Its very crucial to understand the etiological, biochemical, structural, physiological, molecular changes and pathological conditions for the arise of epileptic brain.

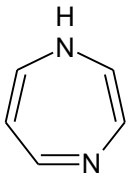
Neuroinflammation is inherently accompanied by Epilepsy, which can be targeted through disease modifying medications .There is a possibility of inflammation in the brain by pro-inflammatory molecules, cytokines such as IL-1Beta and HMGB1, which have proconvulsant activity in experimental seizure models [9] .Epilepsy occurring after a brain trauma is classified as post-traumatic epilepsy (PTE)and accounts for about 20% of total acquired epilepsy cases. Iron- induced epilepsy in rats is a widely used model for studying the pathophysiological conditions of PTE [10]. The mechanism of epilepsy appears to be connected with alterations in synapses, neurotransmitters, receptors ,oxidative stress, mitochondria, cytokines and apoptosis .Individuals suffering from medically refractory epilepsy may experience reduced quality of life, cognitive impairments and depressive symptoms. Status epilepticus (SE) is a medical emergency characterized by seizures that are prolonged or happen quickly ,one after the other ,with no recovery time[11].The most common type of self limited focal epilepsy is called self limited focal epilepsy with centrotemporal spikes. It is responsible for 6-7% of childhood epilepsy cases and affects children who had normal brain MRI before onset of seizures[12].Transition readiness refers to the degree to which patients and members of their support system like parents, health care providers etc can successfully

transition from child centred to adult oriented health care [13] .The development and progression of seizures involve multiple brain regions; thus epilepsy can be considered as a network disease[14].A better understanding of epilepsy networks can help clinicians how to disrupt these networks and enhance surgical results. The removal of nodal networks implicated in epilepsy lowers the risk of seizure recurrence.Interictal spikes are inherently associated with behavioural and cognitive deficits in epilepsy as well as other psychiatric diseases[15].

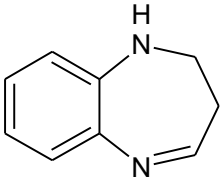
For epilepsy, anticonvulsant medication monotherapy is the primary line of treatment and has been shown to be safer and less costly than polytherapy .Depending on the type of seizure, epilepsy necessitates the long-term or perhaps lifetime use of antiepileptic medications [16]. Both the position of the nitrogen atom in relation to the second nitrogen atom and the type of substituent groups on ring determine the name of the heterocyclic compounds known as diazepines, which have a seven-ring and two nitrogen atoms. In the treatment of the central nervous system, it is essential [17].Many psychotic disorders are treated with medications based on benzodiazepines.A small number of benzodiazepine derivatives, like acrylic fiber and photographic dyes, are employed in the chemical industry due to their numerous uses and high level of interest. The seven-membered ring of benzodiazepines is extremely unsaturated due to the presence of three double bonds . In its most basic form, 1,5-BZD is known by the IUPAC name (2,3-dihydro-1H-1,5-Benzodiazepine).Positions 2 and 4 are crucial for substitutes since different substitutions at these locations result in altered actions.



Azepine

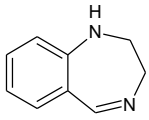


Diazepine

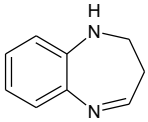


1,5-Benzodiazepines

The first benzodiazepine, chlordiazepoxide (Librium), was discovered by accident by Leo Sternbach in 1955. Hoffmann-LaRoche made it available in 1960, and since 1963, it has also been marketed as diazepam (Valium)[18]. Benzodiazepines are classified as short, intermediate, or long acting. Longer acting benzodiazepines are advised for treating anxiety [19], while 1,4- and 1,5-benzodiazepines are frequently used as anxiolytic and anticonvulsant medications . These effects are primarily mediated via the benzodiazepine receptors in the central nervous system [20].



1,4-Benzodiazepines



1,5-Benzodiazepines

A significant class of pharmaceutical compounds, benzodiazepine derivatives have a variety of biological actions, including sedative, antimicrobial, hypnotic, anticonvulsant, analgesic, anti-inflammatory, anti-cancer, lipid peroxide inhibitory activity, anti-tubercular, anti oxidant, anti-fungal, carbonic anhydrase inhibitor, anti-bacterial agent and neuroleptic properties [21-25]. Additionally, they are demonstrating activity with fused ring compounds, including pyrimidines, imidazole, thiazole, triazolo,and oxazole

The potential structural variety of 1,5-benzodiazepines as a preferred scaffold has drawn a lot more attention to this particular class of benzodiazepines [26] . Of the many medications used to treat CNS diseases, benzodiazepines are significant; yet, they have a number of negative effects, such as ataxia, confusion, sleepiness, and amnesia .All these side effects have reduced their clinical effectiveness.The pharmacological profile of benzodiazepines is altered by the introduction of modifications to their basic nucleus structure.

CURRENTLY AVAILABLE BZD DRUGS

Since 1,5-BZDs is a powerful moiety, a number of medications are on the market. In 1966, clobazam was originally created as a benzodiazepine medication . The aforementioned medication was approved by the USFDA in 2011 for use as an adjuvant therapy under various brand names. The market offers a variety of benzodiazepines, including pirenzepine, telenzepine,triflubazam,lofendazam , arfendazam , nevirapine , C1414S , cystathionine and tibo , as distinct pharmacologically active substances. HIV-I infection can be treated with nevirapine, the first non-nucleoside reverse transcriptase inhibitor [27].

HETEROCYCLIC FUSED BENZODIAZEPINES:

The benzodiazepine ring is integrated with other heterocyclic moieties, including imidazole, oxazole, thiazole, pyrimidine, and triazole rings, to create heterocyclic fused benzodiazepines[28].The resultant molecules' physicochemical characteristics, receptor affinity, and general

biological profile are all altered by this fusion. To build these fused systems with greater efficiency and yield, a variety of synthetic methods have been applied, such as multicomponent processes, microwave assisted synthesis, and green chemistry techniques[29] .

The research conducted between heterocyclic moieties fused with 1,5-BZDs has not been adequately summarized and integrated in the numerous reviews that have been published on the synthesis of BZDs. From 2013 to 2018, Singh et al. introduced synthetic methods for the synthesis of 1,5-BZDs .From 2018 to 2022, Shikha Agarwal et al. created synthetic versions of 1,4-BZDs and 1,5-BZDs [30].Khatik et al., published article on synthetic applications of 1,5-Benzodiazepines in 2023 [31].

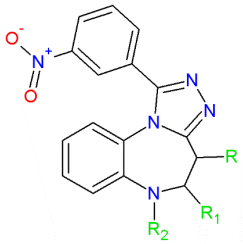
HETEROCYCLIC COMPOUNDS FUSED BENZODIAZEPINES AS TARGET COMPOUNDS:

For the synthesis of N-containing heterocycles, orthophenylene diamine (OPD) is utilized as a beginning raw material that readily condenses with different carbonyl compounds and participates in the greatest number of multicomponent green reactions [32] .BZDs are created when OPD condenses with different substrates, including β-haloketones, α, β-unsaturated carbonyl compounds, or β-dicarbonyl compounds . Examining target compounds created by different synthetic methods and designing heterocyclic fused 1,5-Benzodiazepines over the past decade are the goals of this review.

RECENT ADVANCES:

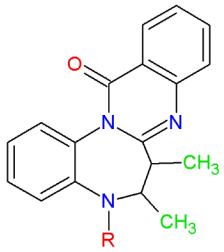
Research on improving the pharmacokinetics and selectivity of fused benzodiazepine derivatives has accelerated within the last ten years. Highly functionalized structures are now more easily accessible thanks to new synthetic pathways. Additionally, the discovery of powerful lead compounds has been sped up by computational methods like QSAR modeling and molecular docking.

Lidija Kosychava et al., [33] created a synthesis method for 1,5-BZDs using N^1-(2,3-dihydro-1H-1,5-benzodiazepin-4-yl)-3-nitrobenzohydrazides and thermal cyclisation.As 1-butanol generates the highest yields of novel tricyclic fused 1-(3-nitrophenyl)-5,6-dihydro-4H-[1,2,4] triazolo[4,3-a] [1,5] benzodiazepines, it is the ideal solvent to employ for the synthesis.Conceptual density functional theory has been used to address the reactivity of specific substances (DFT theory).



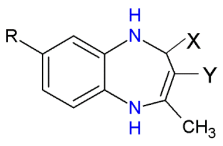
R=CH_3,H
R_1=H,CH_3
R_2=$CH_2C_6H_5$,$COCH_3$,CO-NH-C_6H_5

Gema Mikulskiene et al., [34] synthetic 6,7-dihydroquinazolino that is 5-substituted [3,2-a] Reductive N-heterocyclization is performed after 5-acyl-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one and 2-nitro benzoyl chlorides are used in a straightforward one-step sequential acylation-cyclization synthesis to produce (1,5) benzodiazepine-13(5H)-one derivatives. They computed and assessed the compounds' quantum chemical reactivity descriptors.



R=$COCH_3$,CHO,COC_6H_5,
$COOC_2H_5$,CH_3,$CH_2C_6H_5$

Lan-zhi wang et al., [35] has synthesised, computationally developed, and assessed the biological activity of derivatives of 1,5-benzodiazepines. Targeted compounds are created by combining 1,5-benzodiazepines with thiophene or thiazole and ester groups. The invitro antimicrobial activity of each synthesised derivative was assessed against different strains of S. aureus, E. coli, and candida species. Specifically, 1v and 1w show outstanding antifungal activity. When compared to conventional drugs, they demonstrated equipotent action. This study clarifies SAR aspects and found that the anti-microbial activity was significantly impacted by substituents on the thiophene and phenyl rings. Antimicrobial action depends on the size and length of the ester group (Y) at position C3, the kind of five-membered ring at position C2 (X), and the electronic substituent (R) at position C8.



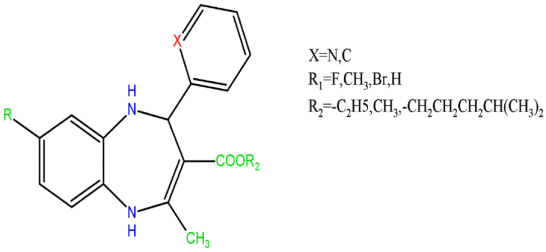
R=H,CH_3,Br,F

X=Thiopene,Thiazole

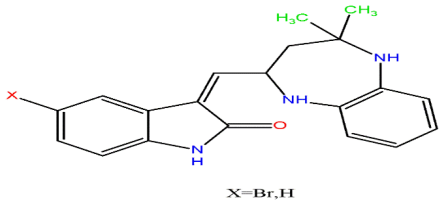
Y=COOR,$COOCH_3$,$COOC_2H_5$,
$COOC_3H_7$

Lan-Zhi Wang et al., [36] reliably synthesised a number of new 1,5-benzodiazepine compounds by combining N-O-aryl amino-β-enamino esters with dry ethanol, PMA, and substituted pyridine aldehyde. Every synthetic compound's

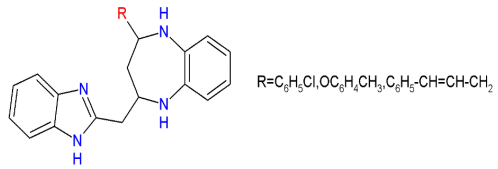
antibacterial efficacy against distinct gram-positive and gram-negative bacteria was assessed. Only a small number of synthetic chemicals repelled the examined bacteria. Every active ingredient shown superior antifungal activity over antibacterial activity. Cytotoxicity tests were performed on compounds 2a and 2b to learn more about them. The C-2, C-3, and C-8 locations of 1,5-BZDs were part of preliminary SAR analyses.



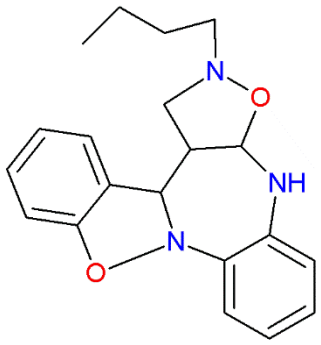
K.V. Maslov et al., [37] Isatin, OPD, and acetone in formic acid are used to create bridging 2,3,4,5-tetrahydro-1,4-methano-1H-1,5-benzodiazepine derivatives, which provide 3-[(2,3-dihydro-Ih-1,5-BZD-4yl) methylidene indolin-2-one. After these derivatives are reduced with sodium cyanoborohydride, intramolecular cyclisation occurs, resulting in the creation of a bridged target molecule. The condensation reaction consists of three components.



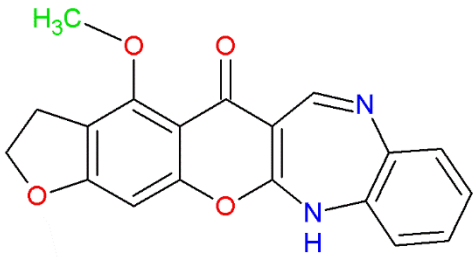
Kaur et al.,[38] have created 1,5-Benzodiazepine group of compounds and explored their antidepressant properties. A heterocyclic moiety, like benzimidazole, is synthesised by fusing the 1,5-benzodiazepine nucleus with a R group that has varied substituents.



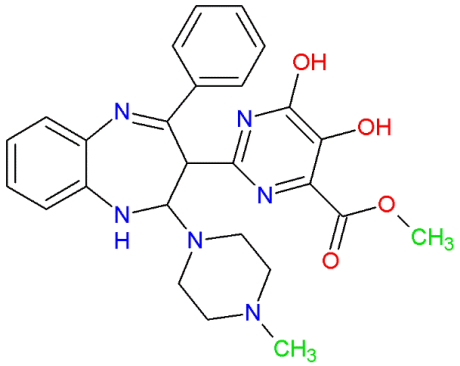
Marc Lecouvey et al., [39] created a number of new (3-Z) Alkyl/aryl amino methylene -3[4-(2-hydroxy phenyl)-1,3-dihydroxyPrimary amines are added to the benzopyrano to produce -2H-1,5-Benzodiazepin-2-ones (4,3-C).1,5-benzodiazepines-2-one (-1H-1.5). Excellent dia stereoselectivity was achieved along with high yields. X-ray diffraction analysis was used to confirm the 1D and 2D NMR characterisation. The antibacterial activity of all produced compounds was assessed in vitro, and encouraging findings were observed.



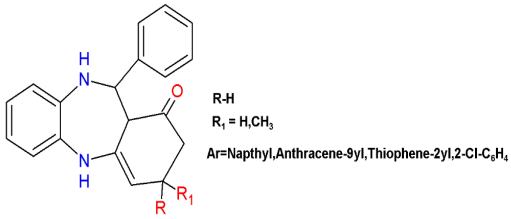
Ibrahim and co-workers., [40] constructed 1,5-BZDs by condensing 6-formyl visnagin (carbox aldehydes) with OPD in ethanol reaction medium. A catalyst-free approach is then used to produce new 4-methoxyfuro [3',2':6,7] chromeno[2,3-e]. diazepin-5(12H)-one (MFCBD) and benzo[b] [1,4]. Using polar and non-polar solvents, Density Functional Theory has conducted a hypothetical analysis of the harmony geometries of the synthesised MFCBD. The findings of this study lend credence to its applicability in the realm of photodiode application.



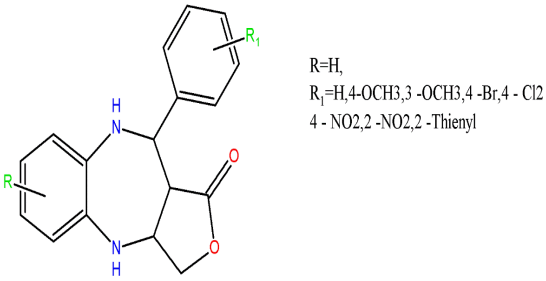
Veera sadhu and Jaya Dwivedi et al., [41] produced the desired compounds utilising four distinct schemes, one pot domino method that uses ethylcyano acetate, OPD, CS2, Base, CH3I, N-methylpiperazine, NH2OH, KOH, DMAD, and DABCO by refluxing in separate steps, and ultimately yields [b] 5,6-Dihydroxy-2-[2-(4-methyl-piperazin-1-yl)-4-phenyl-IH-benzo[15,2-diazepin-3-yl]4-carboxylic acid methyl ester of pyrimidine. Using the half maximum inhibitory concentration (IC_{50}) and the broth microdilution technique, antimicrobial activity was verified. Compound 23 was the most effective against the selected bacterial species. It changed the shape of the bacterial cells and generated the most nucleotide leakage.



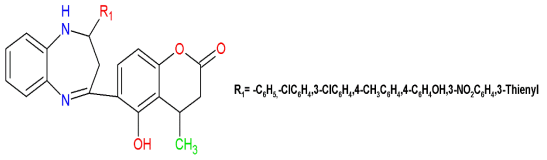
Nasr-Esfahani et al., [42] Nicotine-based organo catalyst supported by silica nanoparticles (Fe (III)-NicTC@nSiO2) replaced 1,3-cyclohexanedione and aldehyde utilising OPD. This method's characteristics include mild conditions, quick reaction times, excellent yields and selectivity, and the use of reusable catalysts.



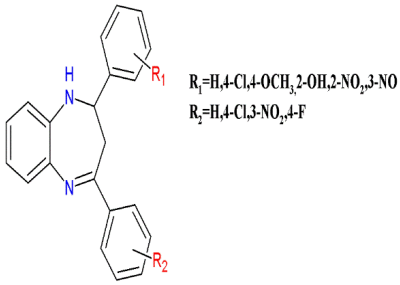
Nejadshafiee et al..,[43] created a process that uses molecular ionic liquid supported on Fe-MCM-41 nanocomposites (Fe-MCM-41-1L) to synthesise BZDs efficiently. Benefits of this ultrasound-based approach were quick, clean conversion and ease of experimental setup, which resulted in benzodiazepine production quickly in mild conditions.



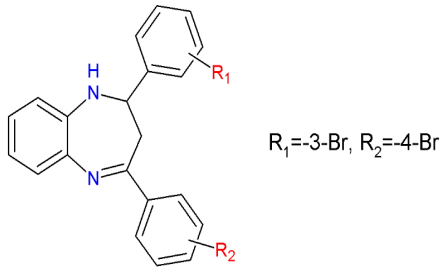
Toan et al.,[44] 2,3-dihydro-1H-1,5-benzodiazepines were created by reacting with o-phenylene diamine and enones in pure ethanol while glacial acetic acid was present as a catalyst. For the aforementioned synthesis, 6-acetyl-5-hydroxy-4-methylcoumarin's α,β-unsaturated ketones are regarded as precursors. They were assessed for biological activity using the disc diffusion method. Antibacterial and antifungal properties were demonstrated by several synthesised compounds against Candida albicans, Staphylococcus epidermidis, and E. Coli.



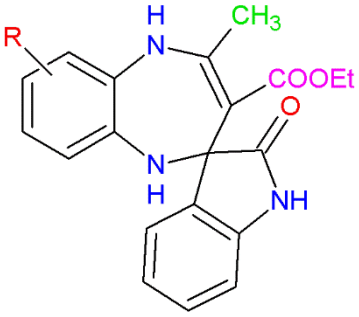
M.T. Jaffuri-Chermahini et al., [45] created a new, simple, and effective process for the synthesis of 1,5-BZDs by the interaction of chalcone with 1,2-phenylene diamine, mediated by a powerful carbocatalyst. To examine the characteristics of the graphene-doped catalyst, FE-SEM, TGA, XPS, and Raman tests were employed.



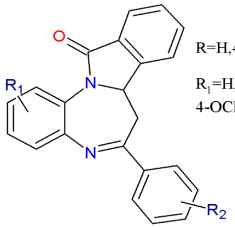
Pathade and Jagdale et al., [46] created a substantial, simple approach for the synthesis of 2,3-dihydro-IH-1,5-BZDs employing piperidine as a catalyst and OPD and chalcone in ethanol as reaction medium. 2-(3-bromo phenyl)-4-(4-bromo phenyl)-2,3-dihydro-1H-1,5-benzodiazepines are the end product. Density Functional Theory was used to calculate the different molecular characteristics of the synthesised molecules (DFT).



Zhang et al.,[47] highlighted four new methods for creating 1,5-dihydrospiro [benzo[b] [1,5] diazepine-2,3-indole] compounds using various three- and four-component reactions using Fe3O4-SiO2-PTSA as a magnetic nano catalyst in C2H5OH. In all reactions, OPD and Isatin were the two common components; however, ethyl acetoacetate, also known as 3-butyne-2-one or benzoyl acetone, was the third component. An example of a green reaction process is this study.



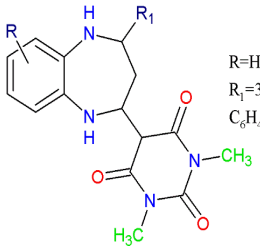
Yuan et al.,[48] created a unique process for benzodiazepine-fused iso indolinones that uses OPD, 2-formyl benzoic acid, and acetophenone with MSNPs (mesoporous silica nanoparticles) to produce tetracycline benzodiazepine-fused iso indolinone counterfeit natural products.



R=H,4,5-F_2,4,5-Cl_2

R_1=H,2-F,3-F,4-F,4-Cl,3-Br,4-CF_3,4-Me,3-OCH_3,4-OCH_3,2,4-$(OCH_3)_2$,3,5-$(OCH_3)_2$,4-Ph

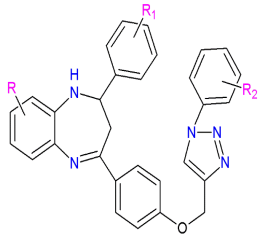
Siddiqui et al., [49] synthesised BZDs by an environmentally friendly and extremely efficient method. In order to design the target compounds, 5-acetyl-1,3-dimethyl barbituric acid, substituted benzaldehyde, and OPD are used, together with PVP (polyvinyl pyrrolidine)-CeO2/Rgo (reduced graphene oxide) as a catalyst and H2O as a solvent. In aqueous media, this high potential catalyst displays multicomponent reactions.



R=H,4-CH_3

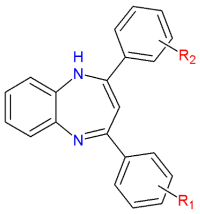
R_1=3-$NO_2C_6H_4$,2-$NO_2C_6H_4$,4-ClC_6H_4,4-$OCH_3C_6H_4$

Gupta et al., [50] CuFe2O4@MIL-10(Cr), a magnetically separable nano-catalyst, was created to synthesise benzodiazepine triazole derivatives in two hours under reflux conditions using OPD, chalcone, and azides in H2O.This protocol's benefits include gram-scale synthesis, excellent yields, and catalyst reusability.



R=H,R_1=H,3-OCH_3,R_2=H,4-Cl,4-Br,4-NO_2,4-CH_3,3-Cl,3-NO_2,2-Cl,2-Br,2-OCH_3,3,5-Br,3,5-OCH_3

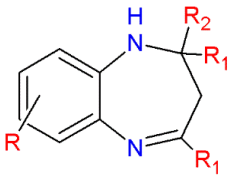
Tayde et al., [51] utilising OPD and chalcone, a mesoporous binary mixed metal oxide catalyst (SiO2-Al2O3; silica-alumina) and ethanol as a solvent, a useful and environmentally friendly synthesis of 1,5-benzodiazepines was created at a 93% yield at 800 in 60 minutes .It's a green synthesis technique.



R_1=C_6H_5,4-$OCH_3C_6H_4$,4-OHC_6H_4,4-FC_6H_4

R_2=C_6H_5,-C_6H_4,4-ClC_6H_4,2-C_6H_4

Caiana and co-authors [52] developed a novel hydroxylated analogue of 1,5-benzodiazepines with antifungal and antioxidant biological potential. Using trifluoroacetic acid as a catalyst and OPD and other acetophenones as starting materials, 1,5-BZDs are synthesised. According to the results of the biological assay, the sporothrix genus is susceptible to the high antifungal activity of the novel 2,7-dimethyl-2,4-bis(4-hydroxyphenyl)-2,3-dihydro-1H-1,5-benzodiazepine.This research endeavour has included insilico experiments.

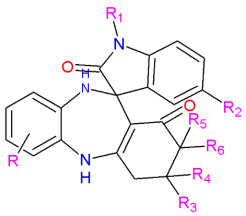


R=H,4,5-$(CH_3)_2$,4-Cl,4-CH_3

R_1=C_6H_5,4-$CH_3C_6H_4$,4-$OCH_3C_6H_4$,4-BrC_6H_4,3-BrC_6H_4

R_2=CH_3

Maury et al., [53] developed a green method for synthesising BZD by ultrasonically combining OPD, Isatin, and 1,3-diketone with water as a solvent. Using ultrasound irradiation for the first time, this study presents a simple and effective multicomponent synthesis of a benzodiazepine ring in water. When using the usual approach, the synthesised compounds provide good yields of 95%.



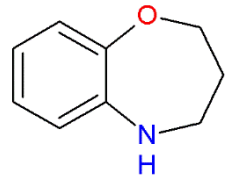
R=H,CH_3

R_1=H,C_2H_5

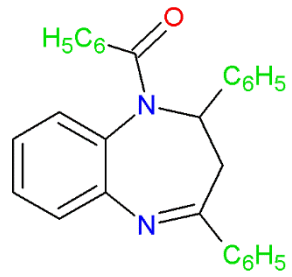
R_2=H,4-Cl,4-Br,4-NO_2

R_3,R_4,R_5,R_6=H,CH_3

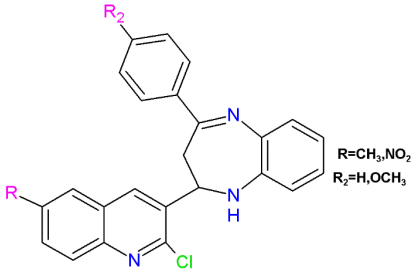
Monika Stefaniak et al., [54] examined 1,5-benzodiazepines as a powerful and distinctive scaffold for a range of functions. In 1,5-benzodiazepines, there is a bioisosteric substitution of oxygen for the first position "N."



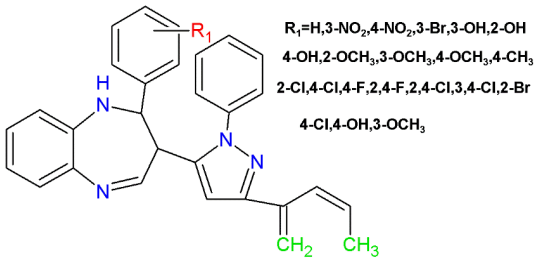
Elena A. Nikiforova et al., [55] Zinc and methyl 1-bromocycloalkanecarboxylates were used to synthesise the title-targeted compounds utilising 1-benzoyl-2,4-diphenyl-2,3-dihydro-IH-1,5-benzodiazepines. Hydrolysis of the compounds produced spiro-δ-lactams with a 2(N-benzoyl amino) phenyl substituent at the nitrogen atom.



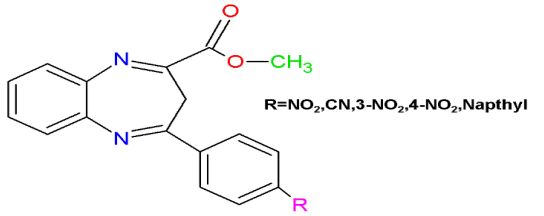
Basem Mansour et al., [56] employed acidic catalysts to create novel derivatives of 2,4-disubstituted IH-benzo[b]1,5-benzodiazepines utilising OPD with ketones, α,β-unsaturated carbonyl compounds, or β-halo ketones. Benzodiazepines are produced using piperidine-catalyzed OPDs or glacial CH3COOH, with DMF serving as a solvent. The Maximum Electroshock method and the subcutaneous pentylene tetrazole seizure test were used in the study to assess docking studies and the anticonvulsant activity of the synthesised compounds.



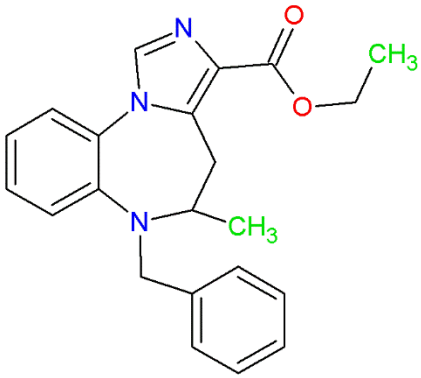
Desai et al.,[57] Utilising OPD and 3-(1,3-diphenyl-1H-pyrazol-4-yl)-1-phenylprop-2-en-1-ones with piperidine and CH3COOH as a catalyst, an effective 1,5-benzodiazepine was created. In 8–10 hours, pyrazole-bearing benzodiazepines were produced utilising a DMF solvent in reflux settings. The synthetic compounds' antibacterial properties were investigated. Compounds 2b and 2e demonstrated outstanding antibacterial activity, whereas compounds 2i and 2k demonstrated possible antifungal activity.



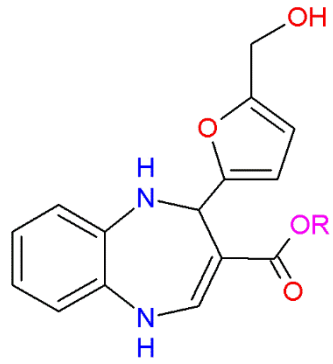
Ekaterina E. Khramtsova and Andrey N. Maslivets et al.,[58] 4-(het) aryl-3H-1,5-benzodiazepine-2-carboxylates were synthesised using (het)aroyl pyruvate esters and O-phenylene diamine. Dihydro quinoxalinones are also synthesised. The product ratio is determined by electronic effects caused by substituents as well as reaction circumstances.



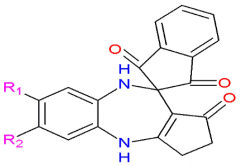
Mantas Jonusis et al.,[59] newly created imidazo derivatives [1,5-α] [1,5] Unexpectedly changed new oxazole derivatives are produced via the reaction of the amide group of the heterocycle, imino phosphate, and its cyclo condensation with ethyl isocyano acetate to yield BZD-3-carboxylic acid esters. Techniques from computational molecular modelling were used to rationalise the reaction process.



Jingjing Jiang et al.,[60] produced 1,5-benzodiazepines using a synthetic multicomponent reaction with alkyl propionate, 5-hydroxymethyl furfural (HMF), and OPD as substrates, while NH4OAc and ethyl alcohol were present. Furan molecules produced from biomass, specifically 5-HMF, are utilised to construct nitrogen heterocycles. Cycloaddition is the type of multicomponent reaction that is the 1,5-BZDs synthesised compounds are accessible in the ICBMS chemical library for upcoming biological and biochemical reactions.



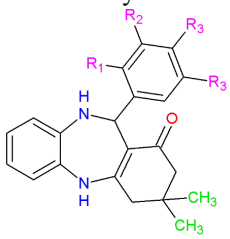
Lanzhi wang et al., [61] made up to create polycyclic fused 1,5-BZDs with quaternary carbon centres or quinoxaline rings in a single pot, the synergistic effect of Bronsted and Lewis acid (AMPA and CeCl3) (AMPA-Aminomethyl Phosphate) of the magnetic nano catalyst Fe3O4@SiO2 was investigated to activate carbonyl, imine, or enamine bonds. It is possible to reuse the catalyst seven times.



R_1=H,CH_3,Cl,Br

R_2=H,CH_3

Dnyaneshwar D subhedar et al., [62] produ benzodiazepine derivatives in a single pot solvent-free catalyst and (DBUH)(HS catalyst mentioned above is used to cr substituted -1,5-benzodiazepine derivative OPD, aromatic aldehydes, and dimedone tested for cytotoxicity against cell lin aforementioned 1,5-BZDs, 4c, 4i, and 4l good anti-tubercular activity. The compoun examined by in-silico docking studies.

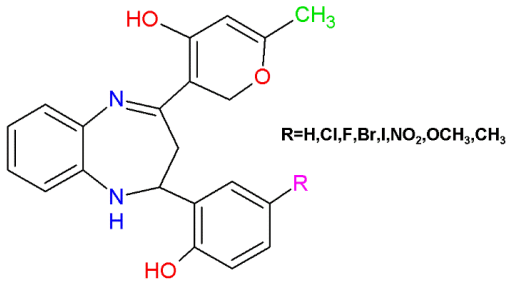


R_1=H,Br,OH

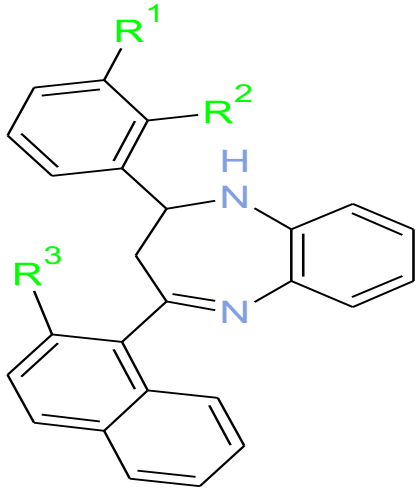
R_2= H,Cl,NO_2

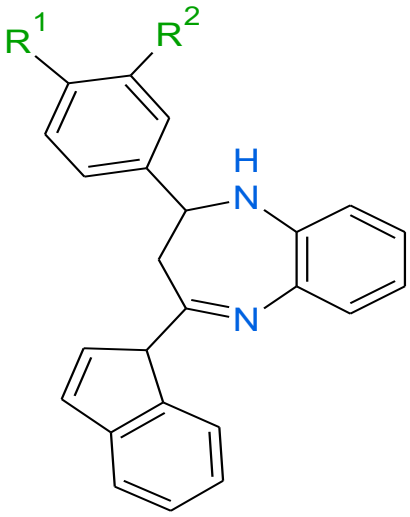
R_3=OCH_3,H,CH_3,Cl,F,Br,NO_2,OH

Elizabeth Gomez et al.,[63] constructed and investigated utilising molecular docking experiments, which use diazepam as a positive reference. These investigations use unsymmetrical Schiff bases as effective ligands to create complexes and 1,5-BZDs with anxiolytic effects. Without influencing motor response, benzodiazepines 3g and 3h had an anxiolytic effect. The GABA-A receptor binding site is impacted by 1,5-benzodiazepines, according to docking studies.



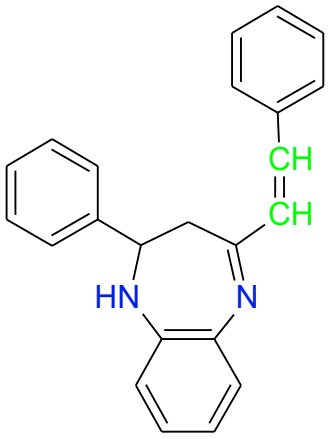
K. Varalakshmi Devi et al..,[64]This study designed 13 novel 1,5-benzodiazepine derivatives and used molecular docking to identify four with the strongest predicted antimicrobial activity. The compounds were synthesized by combining various substituted chalcones with o-phenylenediamines and characterized using IR, NMR, and mass spectrometry. In vitro testing against Gram-positive (S. aureus, B. subtilis) and Gram-negative (E. coli, S. typhi) bacteria, as well as four fungal species, used ciprofloxacin and fluconazole as references. Compound 4a showed exceptional antibacterial activity (MIC = 6.25 µg/mL) while 4c displayed notable antifungal activity at the same MIC, confirming that 1,5-benzodiazepines are promising candidates against infectious diseases and antimicrobial resistance.



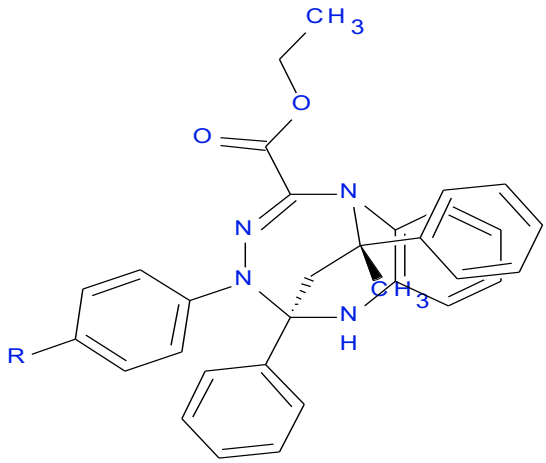


R^1 = OCH_3,CH_3,OH,NO_2 ,Cl
R^2=OCH_3,H ,Cl R^3=OH,H

Loubna Khalki et al..,[65] Benzodiazepines cause side effects like amnesia and dependence, prompting a search for safer alternatives. A novel 1,5-benzodiazepine (MAL) was assessed for GABA-A binding and toxicity. In silico, it bound the GABA-A receptor at −8.9 kcal/mol (α1, β2, γ2: −7.6, −7.5, −7.6). Acute (2 g/kg) and 28-day repeated doses (5–100 mg/kg) caused no adverse effects in mice. No changes in body/organ weight, histology, or biochemistry—no hepatotoxicity or nephrotoxicity. ProTox predicted an oral LD50 of 3 g/kg (GHS Category V), supporting MAL's safety.

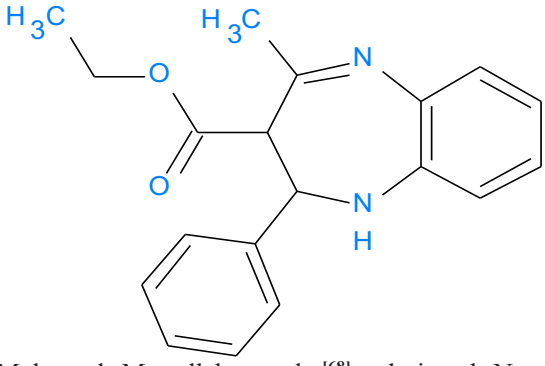


Loubna Khalki et al.., [66] A novel 1,5-benzodiazepine (MAL) was tested in mice and by docking for anti-inflammatory and analgesic effects. At the optimal 25 mg/kg, it beat diclofenac in paw edema (peak 78.54% vs 70.14%) and cut vascular permeability and neutrophil infiltration. Analgesic activity matched standards, indicating central and peripheral mechanisms. Docking showed strong binding to α1A-adrenergic (8THL) and COX-2 (3LN1) receptors (−8.9, −8.5 kcal/mol).MAL is a promising anti-inflammatory/analgesic candidate suppressing neutrophil-mediated inflammation.

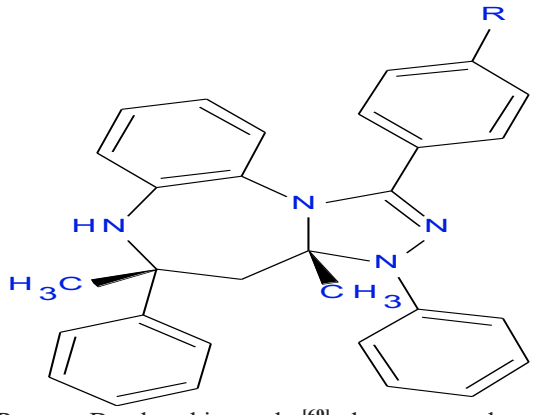


R=CH_3,Cl,OCH_3,NO_2

Joshua V et al..,[67]A green, one-pot three-component synthesis of ethyl 4-methyl-2-phenyl-substituted 1,5-benzodiazepine-3-carboxylates used recyclable phosphomolybdic acid (PMA) as catalyst, giving excellent yields (97–98%) in 30–50 min under mild conditions (confirmed by FT-IR, ^{1}H NMR). Antibacterial screening of 1a–1c showed promising activity—especially the 2-phenyl derivative (1a), approaching ciprofloxacin against Gram-positive and Gram-negative strains—highlighting a sustainable route to benzodiazepines as antimicrobial leads.

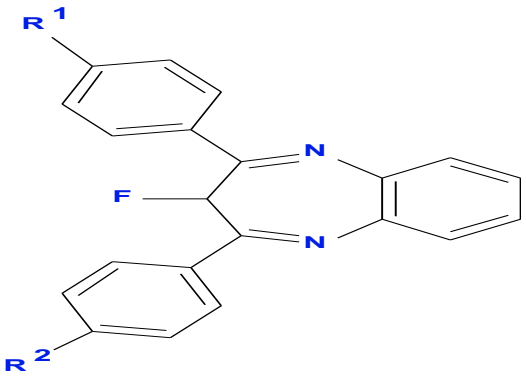


Mohamed Maatallah et al..,[68] designed New triazole–benzodiazepine diastereoisomers 4(a–b) and 5(a–b) were synthesized via [3+2] cycloaddition of BZD 1 with nitrilimines 3(a–b), and confirmed by NMR, HRMS, and X-ray (4a). DFT studies revealed an inverse electron-demand mechanism with the C=N bond as the most reactive site, supported by Fukui functions and MEP maps. Hirshfeld and NCI-RDG analyses detailed structural and non-covalent features, highlighting 5(a–b) for biological potential and 4b/5b for electronic stability. Docking and ADMET results indicate promising Bcl-2 inhibition with favourable drug-likeness.



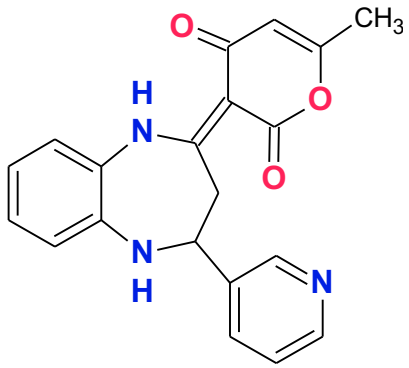
Roman Dembenski et al..,[69] done research on Cascade reactions of 2-fluoroalk-3-yn-1-ones with o-phenylenediamines give 3-fluoro-3H-benzo[b][1,5]diazepines (52–81%) via a noncatalytic, atom-economical

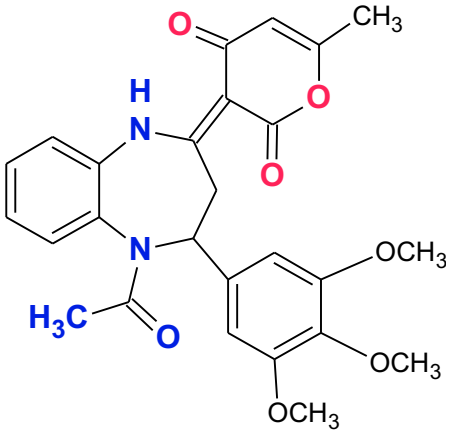
hydroamination/imination sequence forming two C–N and two C–H bonds. DFT favours initial cyclization of the nonconjugated enaminone; the conjugated isomer was detected by ^{1}H NMR. Ring conformation was confirmed by VT $^{1}H/^{19}F$ NMR and X-ray analysis.



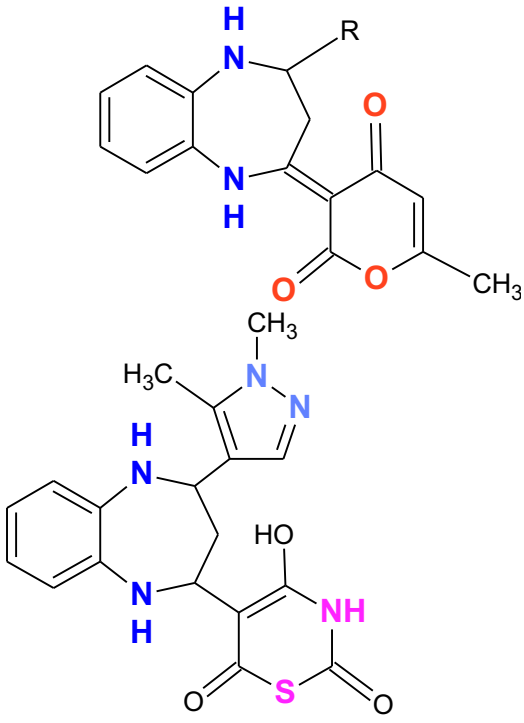
R^1 =Br,Cl, R^2 = H,CH_3,OCH_3,$C(CH_3)_3$,$C(CH_3)_2$

Nada Kheira Sebbar et al..,[70] Two new 2(E)-pyranylidene-1,5-benzodiazepines (3 and6) were synthesized and characterized by NMR and single-crystal X-ray diffraction. Hirshfeld analysis showed dominant H···H, plus C–H···O and π···π contacts. Docking studies against the GABAA receptor (6HUO) indicated favourable benzodiazepine-site binding, and both met Lipinski/Veber rules with good oral absorption. Compound 3 showed better permeability and safety; compound 6 offered higher solubility and longer exposure but possible hepatotoxicity—supporting this scaffold for GABAA receptor modulator design.



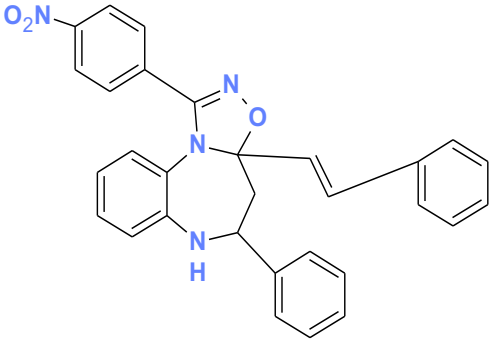


V.V.Lipson et al.., [71] Synthesized A series of 1,5-benzodiazepines was developed as SIRT1 activators. Screening identified 2,4-disubstituted 2,3-dihydro-1H-1,5-benzodiazepines as potent activators, binding an allosteric pocket (H-bond to Asn226, π-alkyl with Ile227). Lead compound pyrabentin (100 mg/kg, 8 weeks) matched metformin in improving glucose tolerance, insulin resistance, and obesity in a metabolic memory model—supporting these scaffolds as promising anti-diabetic candidates.

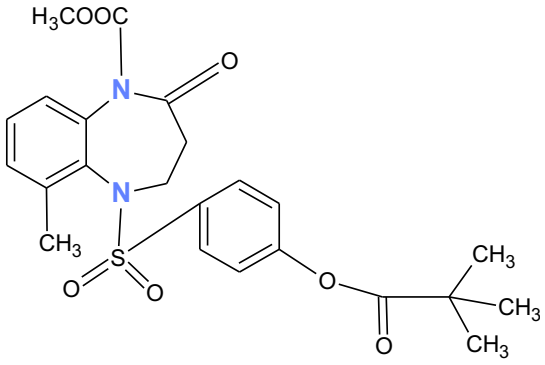


R=CH=CHC$_6$H$_5$, 2-HOC$_6$H$_4$,4-F$_2$CHOC$_6$H$_4$

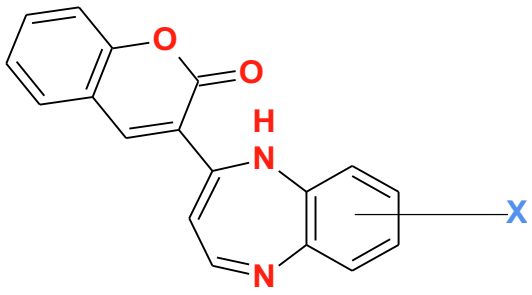
Mohamed Adardour et al..,[72] synthesized oxadiazolo-benzodiazepine diastereoisomers were prepared by selective 1,3-dipolar cycloaddition. Compound 3 showed stronger α-amylase inhibition than acarbose (IC50: 22.78 vs 123 µM), while both compounds outperformed ascorbic acid in DPPH scavenging. Computational studies DFT, docking, and ADME studies supported their potential as antidiabetic and antioxidant candidates, warranting further pharmacological evaluation.



Hidetsugu Tabata et al..,[73] designed novel 5N-sulfonyl-1,5-benzodiazepin-2-one derivatives (2b, d) showed potent neutrophil elastase inhibition. Stable atropisomers of 2d, arising from two interlocking Ar–N rotational axes, were separated by chiral HPLC. (+)-2d was identified as the more active atropisomer (eutomer), with its (aR, aR) configuration confirmed by X-ray analysis. It exhibited approximately 10-fold greater inhibitory activity than sivelestat, and docking studies supported its high activity. These findings highlight (+)-2d as a promising candidate for further investigation in acute lung injury, although therapeutic efficacy remains to be established.

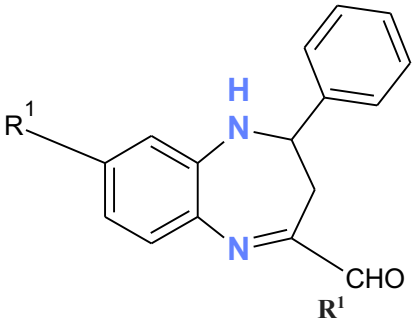


Missaoui Berini El Hadad et al.., [74]A novel series of 1,5-benzodiazepine–coumarin hybrids 3(a–d) was efficiently synthesized via a three-step molecular hybridization route.3-acetylcoumarin formation, DMF-DMA enamination, and NEt$_3$-mediated cyclo condensation with o-phenylenediamines, giving 72–78% yields. Antibacterial screening identified 3d (X = NO$_2$) as the most potent (inhibition zones 18.49–25.41 mm; MIC 12.5–25 µg/mL). SAR confirmed electron-withdrawing groups (-NO$_2$ > -Cl) boost activity over -CH$_3$ or -H, highlighting these hybrids as promising antibacterial leads.



3a:X=H,3b:X=CH$_3$,3c:X=Cl,3d:X=NO$_2$

Jun-Long Zhan et al..,[75] presents a metal-free, switchable strategy for the divergent synthesis of 1,5-benzodiazepines and quinoxaline-2-carbaldehydes from cyclopropanols and 1,2-diaminoarenes. The reaction selectivity is governed by the solvent. HFIP drives [4+3] cyclization to 1,5-benzodiazepines, while DMSO promotes [4+2] cyclization, oxidation, and isomerization to quinoxaline-2-carbaldehydes. By exploiting distinct cyclopropanol ring-opening pathways, the method enables controllable access to two valuable nitrogen heterocycles from identical substrates. This sustainable, operationally simple approach offers a versatile tool for constructing structurally diverse heterocycles, highlighting the effectiveness of solvent-controlled divergence in expanding synthetic possibilities for pharmaceutically relevant scaffolds while avoiding costly or toxic metal catalysts under mild reaction conditions.

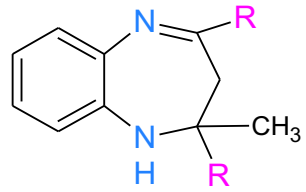


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H,Cl,Br,CN,CH$_3$

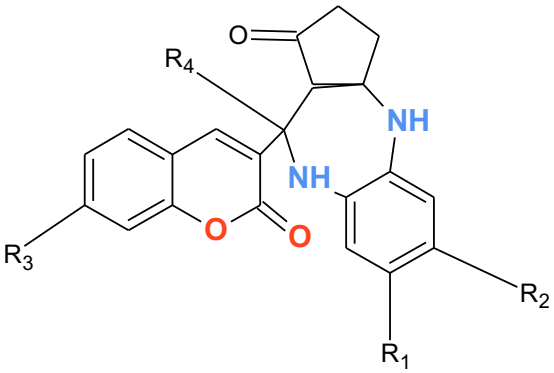
Nellya G.Grigor'Eva et al..,[76] demonstrates that the synthetic method of hierarchical H-ZSM-5 zeolites critically governs their catalytic performance in the condensation of o-phenylenediamine with ketones. The directly synthesized granular zeolite (H-ZSM-5h) outperformed the post-treated variants (H-ZSM-5a and H-ZSM-5aa), achieving 94% conversion, 83% selectivity, and 87% target-product yield with acetone. This superior activity stems from its extensive meso/macroporosity, high total acidity

(740 µmol/g), and optimal proportion of strong acid sites (43%), which together promote rapid diffusion and suppress intermediate accumulation. Mechanistic analysis confirmed that the reaction proceeds via an imine route rather than an aldol pathway, highlighting rational catalyst design for selective heterocycle synthesis.



R= -CH_3, C_2H_5, C_6H_5

Lanzhi Wang et al..,[77] done research on A cerium-rich magnetic nanocatalyst, $CoFe_2O_4$@SiO_2@CPTES@ALN-Ce(III), was developed for the one-pot synthesis of coumarin-containing 1,5-benzodiazepines and 1,5-benzoxazepines. Its dual Brønsted and Lewis acid sites enabled efficient domino reactions, producing 43 compounds with yields Rrecoverable and reusable for seven cycles with minimal activity loss. DFT-supported mechanistic studies confirmed synergistic substrate activation and demonstrated the catalyst's potential for green pharmaceutical synthesis.



R_1,R_2,R_3,R_4 = Cl,CH_3,Br,OH,NO_2,CN,F,C_2H_5,H,COOR,CF_3

RESEARCH GAPS AND FUTURE PROSPECTS:

There are still issues, such as toxicity, resistance development, and metabolic instability, despite the encouraging bioactivity profiles. Designing compounds with improved metabolic profiles, decreased side effects, and increased selectivity should be the main goal of future research. Methodologies for drug design are anticipated to be crucial.

CONCLUSION:

The creation of next-generation treatments depends on ongoing research and development in this area. A broad class of pharmacologically active substances with prospective uses in a number of therapeutic domains are heterocyclic fused benzodiazepine derivatives area. For the creation of next-generation treatments, this sector must continue to be explored and innovated.

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