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A Review on Synthesis and Pharmacological Activity of Benzazepine

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ABSTRACT

A class of heterocyclic chemicals known as benzazepine derivatives has a variety of pharmacological properties, including as antidepressant, antipsychotic, anxiolytic, and cardiovascular actions. The several synthetic pathways, structure-activity connections, and biological activities of benzazepine derivatives are highlighted in this review, which offers a thorough overview of their synthesis and pharmacological activity. We go over the numerous synthetic techniques utilized to build the azepine ring and add different substituents, such as cyclization processes, electrophilic aromatic substitution, and metal-catalyzed cross-coupling events. We also look at the pharmacological characteristics of derivatives of benzazepine, including their in vivo and in vitro activity, receptor binding affinities, and modes of action. In addition to highlighting the derivatives' potential as therapeutic agents and outlining upcoming investigations objectives, In-depth knowledge of the synthesis and pharmacological effects of benzazepine derivatives is the aim of this investigation

Keywords: *Benzazepine, Heterocyclic compounds, Synthesis, Pharmacological activity, Derivatives of Benzazepine, Structures*

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1. OVERVIEW

Numerous naturally occurring substances, physiologically active compounds, and drugs all possess the piro-indane-1,3-dione moiety. In pharmaceutical chemistry, it is also a useful building block that can be used to create a wide range of disparate classes of pharmacophores [1]. Azepine and benzene rings are fused to give benzazepines, which are heterocyclic compounds. The biological activity of benzazepines, aza-heterocyclic fused aromatic rings, renders them interesting compounds to handle as synthons in drug discovery and natural product synthesis. The compounds are anticancer in nature due to the presence of a Spiro indane-1,3-dione unit [2]. MBH carbonates are flexible synthons that can be utilized to construct a range of cyclic molecules [6]. Despite significant advances, most published studies have primarily focused on the use of Morita Baylis Hillman (MBH) carbonates as substrates, which are derived from satins or aldehydes. In the matter of synthesis and availability of several functional ring compounds with a spiro-indane-1,3-dione unit as a potential skeleton, similar ninhydrin-derived Baylis Hillman carbonates remain vital and indispensible in comparison to standard Morita Baylis Hillman carbonates based on isatins or CHO-compounds.

In addition, the domino and one-pot reactions in an ionic liquid as a green medium at 80°C include isatoic anhydride, N-methylimidazole, alkyl bromides, activated ethanol compounds, and hydrazine, which yield high yields of pyridazino benzazepine compounds. GlaxoSmithKline has considered using pyridazines in its medicine design as they are one of the most favorable heterocyclic rings. As pyridazine analogs have already shown to be effective full ligands for a number of targets, they have been proposed as privileged scaffolds for lead optimization research [4]. With a green method, specific pyridazino benzazepine derivatives have been efficiently synthesized by a four-component reaction in an ionic liquid at 80°C with isatoic anhydride, N-methylimidazole, activated acetylenic compounds, alkyl bromides, and hydrazine.

We then describe a skeletal editing method that allows for the direct insertion of nitrogen atoms into arenols via aryl compound migration and dearomatizative azidation reactions. The Ciamician-Dennstedt rearrangement, the Beckmann rearrangement, and the Schmidt rearrangement are the oldest examples of this type of reaction. We suggest using arenols as substrates to lead in the introduction of a nitrogen atom into arenes, where it would dearomatize the aromatic ring and destabilize it. Arenols can also act as guide collectives in nitrogen addition that is site-specific. Site-selective addition of a nitrogen atom is enabled by this approach and is easier for cleaving C–C bonds compared to the usual method of introducing nitrene to benzene rings (32–35). Benzazepines are often encountered as structural motifs in biologically active compounds.

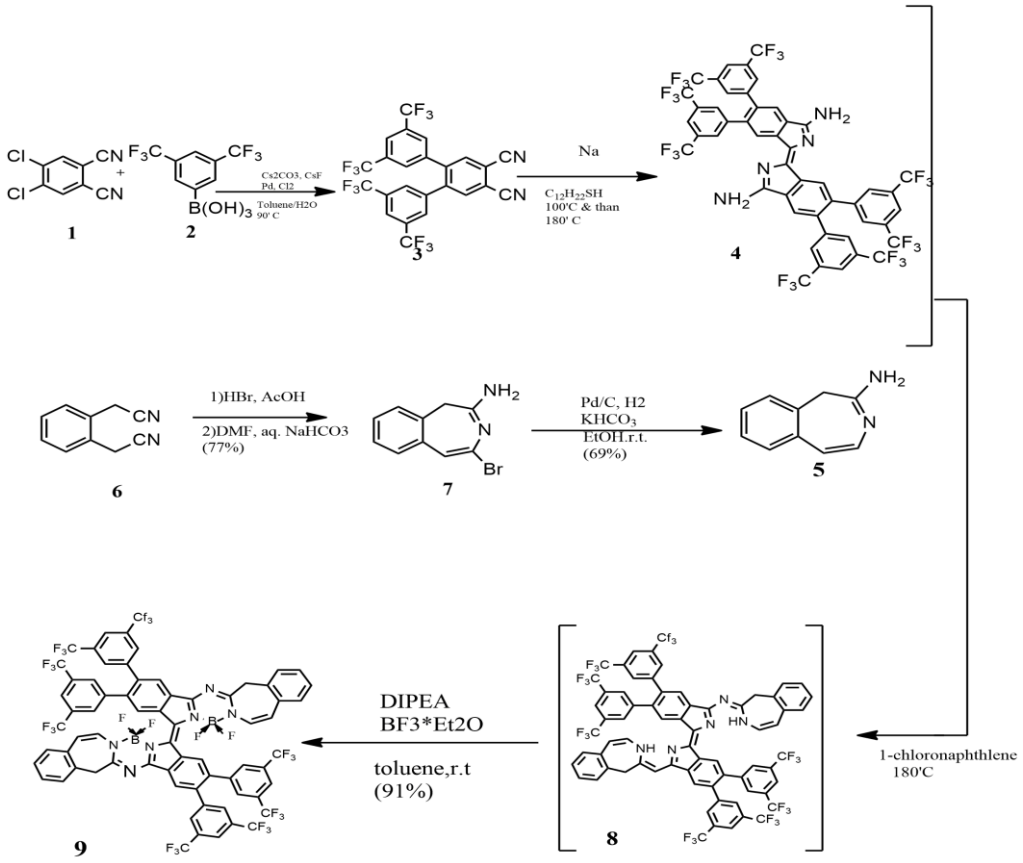
2. CHEMISTRY

2.1.Creation of a 1H-3-benzazepine related to β-isoindigo

The 4,5-dichlorophthalonitrile (1) and the 3,5-bis-trifluoromethylphenylboronic acid (2) were Suzuki-coupled by a combination of toluene oxides and water, -isoindigo skeletons, with the presence of 1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium (II) [Pd(dppf)Cl2], Cs2CO3, and CsF. The mixture yields a substituted product of 3 in 77 percent of the mixture (Scheme 1). By inhibiting molecular stacking, the inclusion of Double massive 3,5-bis-trifluoromethyl-phenyl batch enhanced the solubility of the formed dimer in standard organic solvents. With its large hydrophobic core, the dimer was anticipated to have high aggregation, which would lower solubility.

According to the method of Kobayashi et al. (2014), isoindigos are synthesized by treating 3 in 1-dodecanethiol to give an unreported isoindigo 4, which was then purified into bright orange microcrystals by silica-gel column chromatography and isolated from a solution of tetrahydrofuran (THF) and hexane. Independently, the seven-membered ring of Benzazepines 1H-3-benzazepines (5) was built in two steps already outlined, 22 Hi. Schematically, o-phenyleneediacetonitrile (6) was subjected to hydrogen bromide in acetic acid and alkaline treatment to yield Benzazepines 7. Through hydrogenation, the bromide group was removed, and five bromide groups were formed.

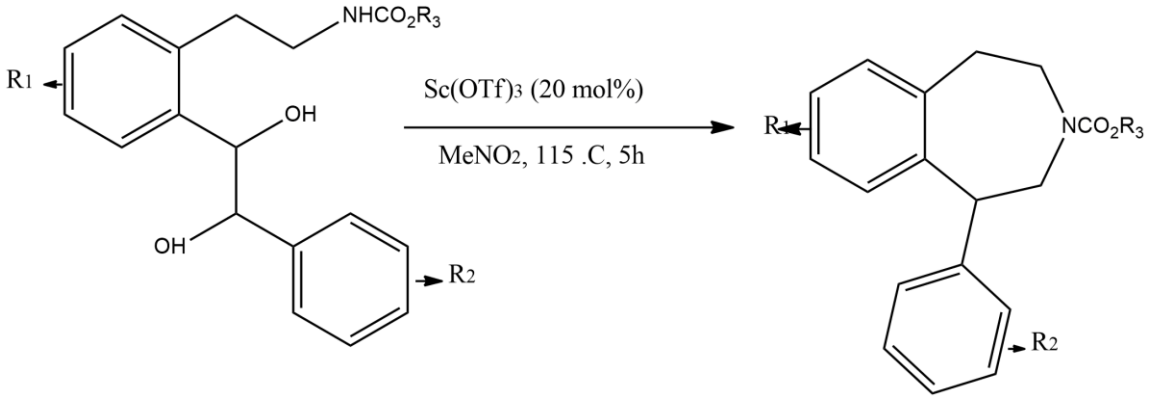
The compound was also condensed into 1-chloronaphthalene with isoindigo 4 at 180 °C, giving the proposed intermediate 8. After the in-situ addition of BF3•Et2O and N,N-diisopropylethylamine (DIPEA) without purification or characterization, dimeric product 9 was formed with an overall yield of 91%. Column chromatography was a straightforward means of separating this material, and the product was a dark blue solid.



Scheme 1. Synthesis of the dimeric aza-BODIPY analogue 9 modified with 1H-3-benzazepine.

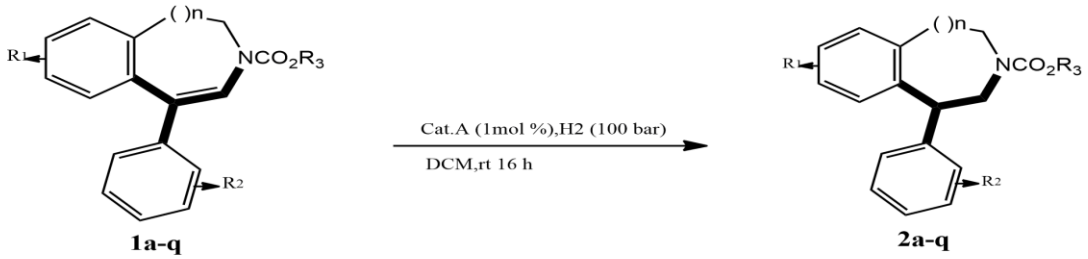
2.2.Method of Manufacturing Chiral Tetrahydro-3-benzazepine

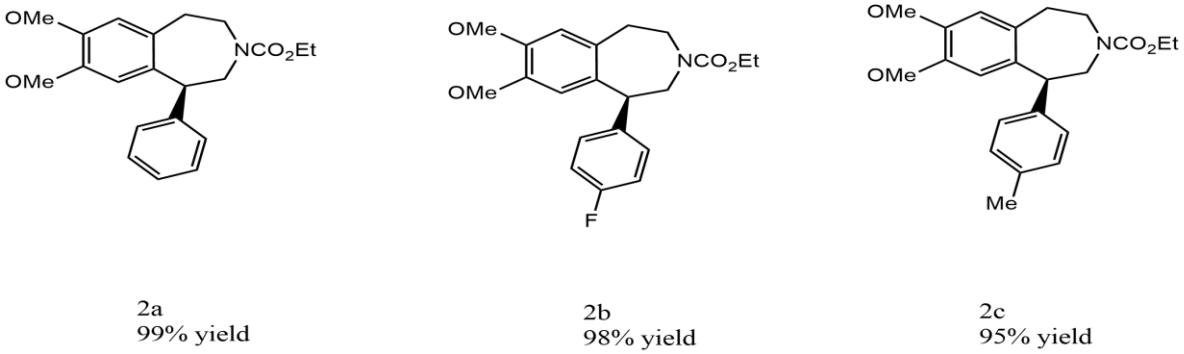
The main methods for creating substituted tetrahydro-3-benzazepines include arylation, ring expansion, reductive cyclization, and intramolecular Friedel-Crafts type alkylation.Utilizing hydrogen gas for 8 asymmetric hydrogenationis a highly reactive, enantioselective, and atom-efficient method of introducing chirality that has shown to be one of the most effective.One process for producing cyclic enecarbamate precursors is the hydrogenation of pinacolone to pinacol.



Scheme 2: Ene-cyclic Carbomer Synthesis

We began investigating the potential applications of iridium in this asymmetric ene-carbamate hydrogenation process (Scheme 3). Beginning with a crystal-rich benzene-substituted benzazepine, the model substrate 1a and the additional monobenzene-carbamate (1b1d) were hydrogenated with superior enantioselectivity (96-99%) and high isolation yields (>95%).





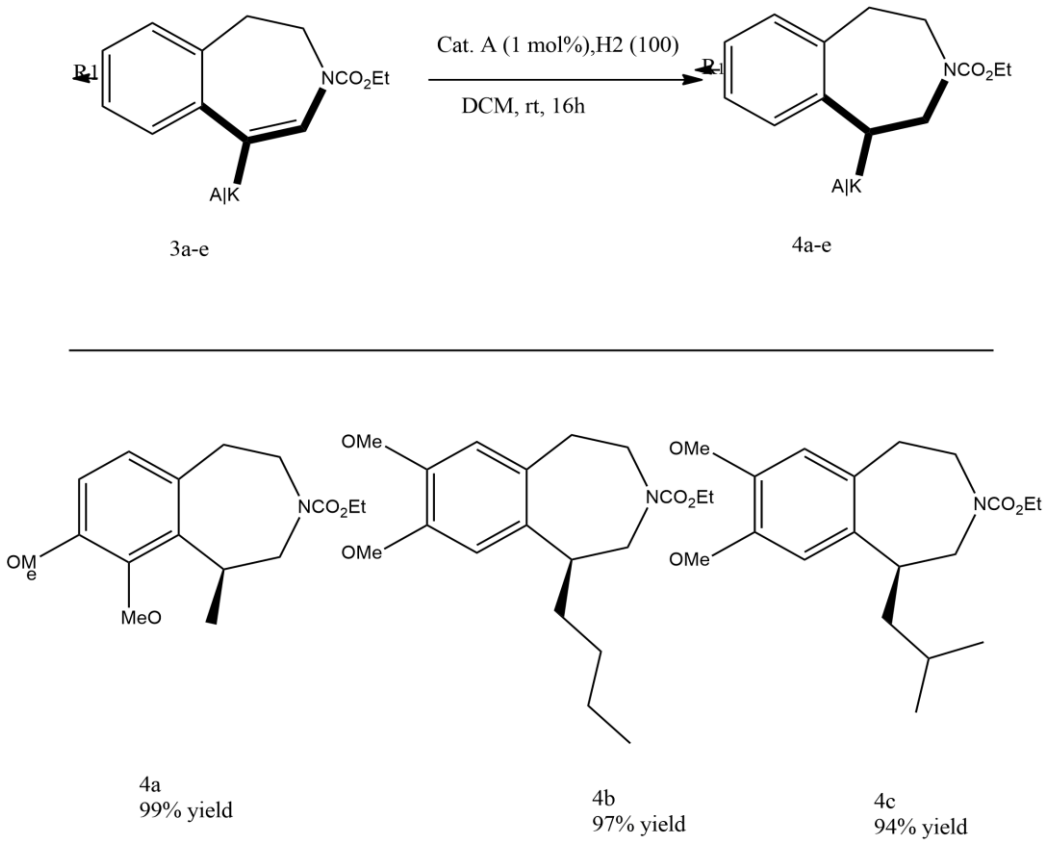
2a
99% yield

2b
98% yield

2c
95% yield

Scheme 3: Aryl Substitution

Substrates with Alkylation in ene-carbamate were subsequently investigated in order to build scaffolds of 1-alkyl tetrahydrobenzazepine (Scheme 4).16. Unless otherwise noted, the following are the reaction conditions: 16 hours, 1 mol% A, 0.05 millimol substance, 1 milliliter Dichloromethane, 100 bar H2, and rt. Assuming a hydrogenation process akin to 1a following 2a's reduction with LiAlH4 allowed for the estimation of the stereochemistry. We were able to ascertain the absolute configurationthrough contrasting the sign of the optical rotation with the value documented in the literature.Chiral stationary phases and Supercritical Fluid Chromatography analysis were used to identify the enantiomeric excess.



Scheme 4. Alkyl Substitutes

2.3. Production of functionalized scaffolds of spiro-indanone-benzazepine through the (4 + 3) annulation reaction

In order to create structurally diverse containing nitrogen heterocycles, Mesthides of aza-o-quinone, which function as aza dienes, are combined with a various of dienophiles using cycloaddition processes. Concerning the spiro indane-1, 3 dione derivatives that still hold our interest [13].

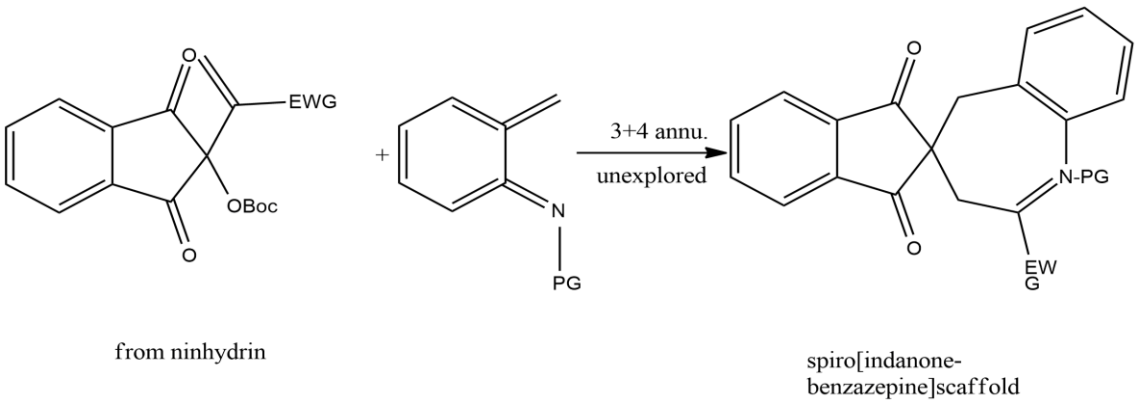


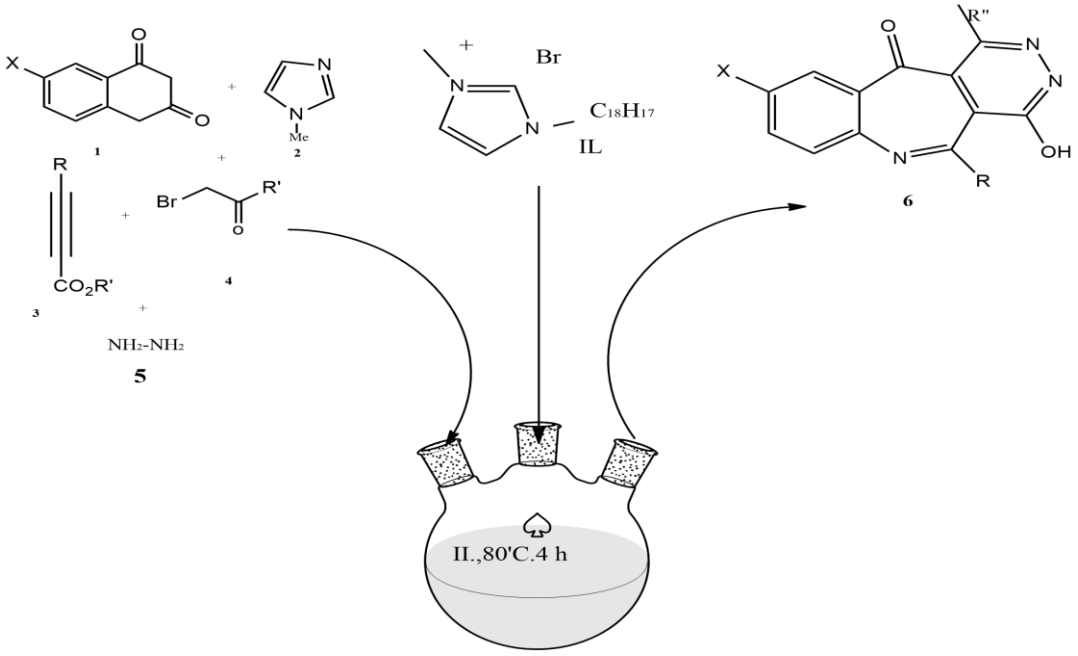
Figure 2:spiro-indanone-benzazepine

2.4.Sustainable production of novel pyridazino benzazepine derivatives:

Numerous derivatives of pyridazino benzazepine 6 were produced in an environmentally friendly manner and with good yields by a simple and easy in an ionic liquid at 80 °C, a multi-steps reaction involving isatoic anhydride 1, N-methylimidazole 2, activated acetylenic compounds 3, alkyl bromides 4, and hydrazine 5 occurs.

Table ; 1

6	R	R’	R”	X	Yield(%) of 6
A	CO_2Me	CH_3	4-OCH_3-C_6H_4	Hydrogen	95
B	CO_2Et	Et	4-OCH_3-C_6H_4	Hydrogen	93
C	H	CH_3	4-CH_3-C_6H_4	Hydrogen	90
D	H	Me	4-MeO-C_6H_4	Me	92
E	CO_2Me	Me	4-MeO-C_6H_4	Me	95
F	CO_2Me	Me	4-Me-C_6H_4	H	94
G	CO_2Me	Me	4-Me-C_6H_4	NO_2	87
H	CO_2Me	Me	4-NO_2-C_6H_4	Me	87
I	H	Et	4-Me-C_6H_4	Cl	85
J	CO_2Me	Me	CO_2Et	Me	97
K	CO_2Me	Me	CO_2Et	NO_2	87
L	H	Me	CO_2Et	Me	85
M	CO_2Et	Et	4-Br-C_6H_4	Me	90
N	CO_2Me	Me	4-Cl-C_6H_4	CH_3	91



Scheme 6. Synthesis of pyridazino benzazepine derivatives by using ionic liquid as green media

Two methods for synthesizing pyridazino benzazepine are studied. The first step involved separating the benzazepine derivatives 11 from the reaction mixture and reacting it along hydrazine 5 in an Ionic liquid at 80 ^{0}C. And the 2nd step, product 11 react with hydrazine in a similar manner without separation (Scheme 3).

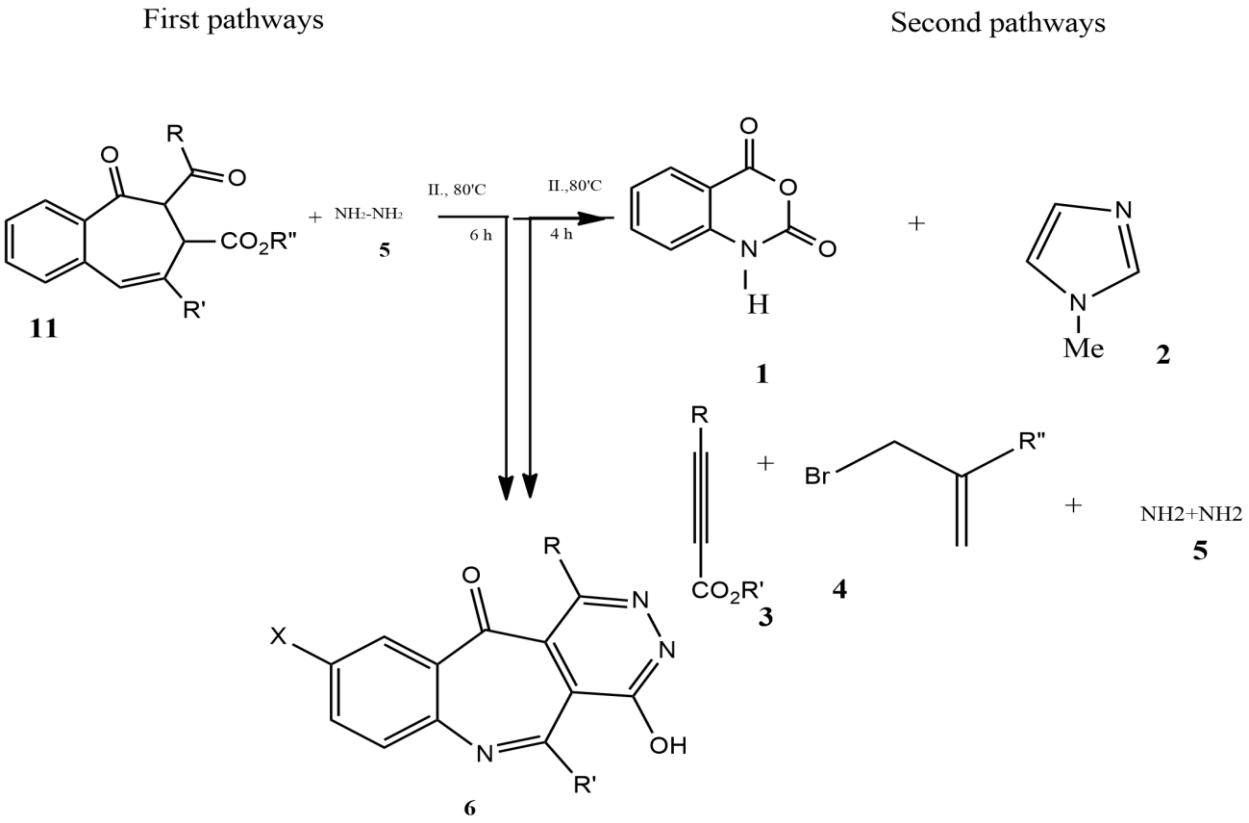


Table: 2

6	R	R’	R”	X	Yield(%) of 6	
					First Procedure	Second Procedure
1	4-OCH_3-C_6H_4	CO_2CH_3	CH_3	Hydrogen	80	94
2	4-OCH_3-C_6H_4	CO_2Et	C_2H_5	Hydrogen	75	93

Scheme 7. Two techniques for the synthesis of pyridazino benzazepine 6.

3. PHARMACOLOGICAL ACTIVITY

3.1 Antioxidant activity

Using BHT and TBHQ as benchmarks and produced antioxidants at varying doses, the antioxidant capacity of pyridazino benzazepine 6a–6d was assessed in this study. All concentrations of the newly synthesized pyridazino benzazepine exhibit good activity in comparison to BHT and TBHQ. When compound 6c was produced, it exhibited very good radical trapping activity in comparison to typical antioxidants BHT and TBHQ.

3.2Antideprsent Activity

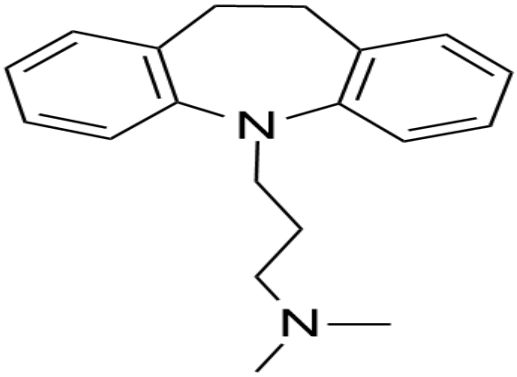


Figure 3:Imipramine

Figure 3ImipramineA 3-(dimethylamino)propyl group is added to the nitrogen atom of imipramine, a dibenzazepine, which is derived from 5H-dibenzo[b,f]azepine. It functions as an adrenergic uptake inhibitor, an antidepressant, and an inhibitor of EC 3.4.21.26 (prolyl oligopeptidase). It originates from a 5H-dibenza[b,f]zepine hydride. The suppression of serotonin and norepinephrine reuptake is the pharmacological action. Because of its tricyclic nature, imipramine can attach to serotonin and norepinephrine transporters, raising their levels in the synaptic cleft and reducing depression symptoms.

Carbamazepine (Antidepressant)

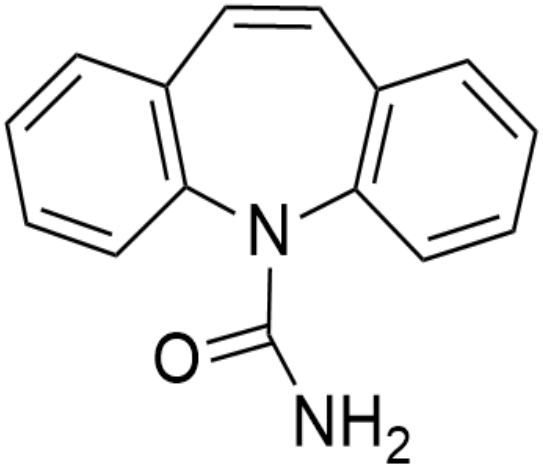


Figure 4: Carbamazepine

Figure 4Carbamazepine is a dibenzazepine that is 5H-dibenza[b,f]zepine has a carbamoyl group attached to the nitrogen of the azepine. As an anticonvulsant, it is employed. 5-H-dibenz[b,f]Tetrahepine-5-carboxamide is the chemical structure. GABA receptor modulation and sodium channel blockage are examples of pharmacological action. Justification By inhibiting sodium channels, the dibenzazepine core of carbamazepine stabilizes neuronal membranes and lowers excitability and seizure activity. Moreover, it increases GABAergic activity, which fosters inhibitory

Clotiazepam (Anxiolytic)

The action of pharmacological, regulation of serotonin receptors, agonism of GABA receptors. The benzodiazepine structure of clotiazepam makes it easier for it to bind to GABA receptors, which improves inhibitory neurotransmission and encourages anxiolytic effects. Its nitro group might possibly have a role in modulating serotonin receptors.

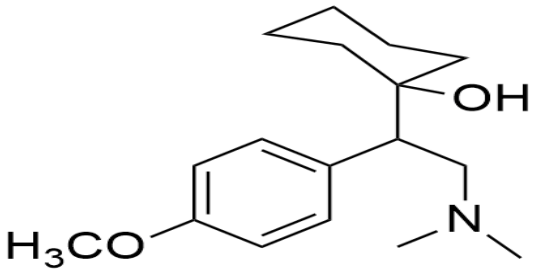
Diltiazem (Cardiovascular)

2-(2-dimethylaminoethyl)-5-(4-methoxyphenyl)-1,5-dihydro-4H-1,4-benzothiazepin-4-one is its chemical structure. Vasodilation and L-type calcium channel blockage are examples of pharmacological action. Justification Because of its benzothiazepine nature, diltiazem can attach to L-type calcium channels, which lowers calcium inflow and increases vasodilation. As a result, blood pressure drops and cardiovascular health improves.

Prazosin (Antihypertensive)

The chemical structure is 1-(4-furanylcarbonyl)-4-(2-amino-6,7-dimethoxy-2-quinazolinyl) piperazine. Vasodilation and antagonistic effects on the alpha-1 adrenergic receptor are the pharmacological actions. Justification: The quinazoline structure of prazosin makes it easier for it to bind to alpha-1 adrenergic receptors, which prevents sympathetic vasoconstriction and encourages vasodilation. As a result, blood pressure drops and heart health improves.

3.7Biological Activity



Venlafaxin

Figure 5: venlafaxine

The cyclic analogues of venlafaxine that were produced were converted to their hydrophilic salt hydrochloride in order to assess their clinical applicability. In order to assess these salts' antidepressant-like properties, they were then put through the mouse Forced Swim Test (PFST) [17,18]. The test involved forcing each mouse [19,20] to swim inside a rectangular glass jar measuring 25 × 12 × 25 cm3, which contained 15 cm of water that was maintained at 23–25°C. The animals showed periods of immobility by floating with little movement after the first two to three minutes of very active activity. When animal stays erect and slightly slumped in the water, its nose above the water's surface, passively floating it is thought to be immovable. A 6-minute total immobility period was timed with a stopwatch, and the percentage reduction in immobility period relative to the vehicle control group was computed [22]. Additionally, immobility was decreased by molecules with antidepressant-like effects at doses that either did not alter or even decreased motor behavior in the open field.

4. CONCLUSION

Such a broad scope of exploration for the synthesis and pharmacological properties of benzazepine analogs has illustrated a complicated relation between their chemistry and biological response. The advances in numerous syntheses have been instrumental in helping to identify major structural features liable for their pharmaceutical activity. In particular, the presence of particular substituents, i.e., halogens or alkyl groups, in particular positions of the azepine ring has been demonstrated to have a substantial impact on biological activity. These structural variations may increase receptor binding affinity, metabolic stability, and general therapeutic efficacy. Derivatives of benzazepine display a wide range of pharmacological activity, ranging from cardiovascular to neuropsychiatric to analgesic effects.

Some of these compounds are dopamine receptor modulators, which are valuable in the treatment of schizophrenia and Parkinson's disease. Others bind to serotonin and GABA receptors, showing promise as antidepressant, anxiolytic, and antipsychotic drugs. Benzazepine-based drugs have also been studied for their antihypertensive and anti-inflammatory effects, showing the drugs' therapeutic diversity. The fact that these compounds are potent at multiple receptor systems highlights their relevance to medicinal chemistry and drug design. Although they hold great pharmacological promise, the synthesis of benzazepine derivatives is challenging. The formation of the seven-membered azepine ring is challenging synthetically because of ring strain and possible side reactions. Regio- and stereoselective functionalization is also important to maximize their bioactivity. Improvements in synthetic methodology, such as catalytic processes, enantioselective synthesis, and green chemistry methods, have helped overcome these challenges and broaden the scope of benzazepine derivatives. In the future, more studies are needed to extensively investigate the therapeutic potential of benzazepine compounds.

Moreover, the combination of computational modeling and high-throughput screening may facilitate the discovery of new benzazepine-based drugs. By overcoming the current synthetic limitations and optimizing their pharmacological properties, benzazepine derivatives can remain an important scaffold for the design of novel therapeutic drugs in the years to come.

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