Synthesis and Medicinal Importance of Dibenzazepine Derived Compounds: A Review

Neha Garg[1], Priyanka Jain[1], Sudesh Neyol[1], D. Kishore[1], Adarsh Sahu[2], and Dharmendra Jain[2*]
[1] Department of Chemistry, Banasthali University, Banasthali (Rajasthan), INDIA
[2] Dept. of Pharmaceutical Sciences, Dr. H. S. Gour University, Sagar (MP), India
* Corresponding Author: dharmjain@gmail.com

Abstract

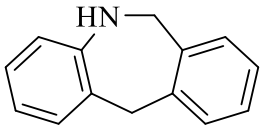
Heterocycles incorporating seven-membered rings in their molecules have found wide applications in medicinal chemistry due to their remarkable pharmaceutical effects. Among the seven membered rings, the dibenzazepine rings has been found to be associated with diverse pharmacological activities such as antiviral, anticancer, anticonvulsant, antidepressant, anti-insecticidal, vasopressin (AVP) antagonist activities. Among azepine derivatives, benzene fused azepines have been widely studied due to their various applications. In this review, we have discussed about the medicinal importance of derivatives of seven-membered rings containing nitrogen heterocyclic compounds.

KEYWORDS: ANXIOLYTIC, AZEPINE, BENZAZEPINES, 1,4- BENZODIAZEPINE, DIBENZAZEPINE.

Introduction

The derivatives of seven-membered rings containing nitrogen have continued to attract considerable attention owing to its widespread application in medicinal chemistry. Among the seven membered rings, the dibenzazepine rings has been found to be associated with diverse pharmacological activities such as antiviral, anticancer, anticonvulsant, antidepressant, anti-insecticidal, vasopressin (AVP) antagonist activities [1]. Some benzazepines and azepines form basic constituents of certain natural products [2] having biological interest and some others have emerged as important pharmacological agents [3-5]. Some hetero ring annulated azepines have found tremendous applications in the field of medicine [6].

Dibenzazepine [7] (iminostilbene) has two benzene rings fused to an azepine framework. For the synthesis of specific analgesic and antipsychotic properties, dibenzazepine has been used as an intermediate. Several anticonvulsants, tricyclic antidepressants (TCAs) including oxcarbazepine, eslicarbazepine, carbamazepine, clomipramine, doxepin, desipramine, imipramine, imipraminoxide, lofepramine, metapramine, opipramol, quinupramine and trimipramine contain saturated dibenzazepine moieties in their chemical structures [7]. We also provided a schematic description of these molecules displaying the dibenzazepine (1) moieties that has entered the market along with their pharmacological activity (Table 1). Interestingly, these molecules possess numerous pharmacological properties and systematically organising new synthetic pathways and biological properties of newly synthesized dibenzazepine could help future researchers.



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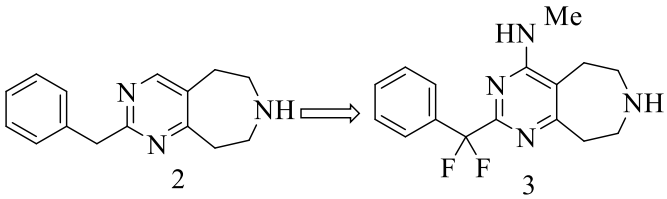
It has been observed [8] that incorporation of certain bioactive pharmacophores such as isoxazole, pyrazole, pyrimidine, benzodiazepines, benzothiazepine in the azepine moiety exerts a profound influence on the biological profiles of this molecule. A series of 4-substituted pyrimido[4,5-d]azepines have emerged as potent 5-hydroxytryptamine 2C (5-HT2C) receptor agonists with exquisite functional selectivity over 5-HT2A and 5-HT2B receptors. Its chemistry design and strategy to deliver CNS penetration coupled with SAR-based optimization of selectivity and agonist potency provided the compounds with the desired balance of preclinical properties [9]. In the first part of this review, we have discussed the various synthetic pathways developed in recent years for the synthesis of dibenzazepine containing compounds. In the second part of this review, we have reported the pharmacological properties of the synthesized dibenzazepine.



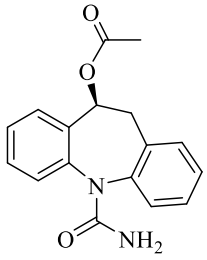
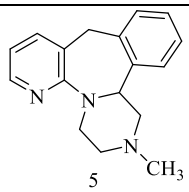
2 3

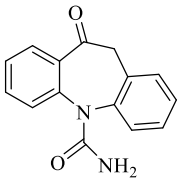
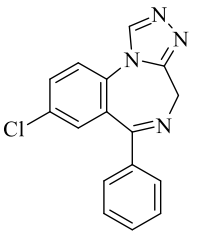
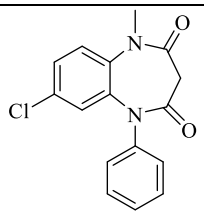
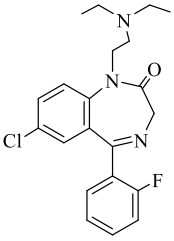
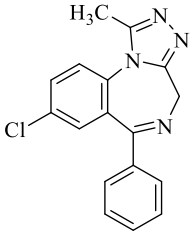
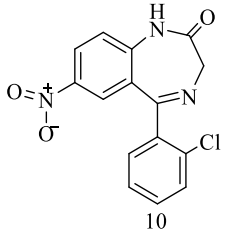
Selective 5-HT_2C agonist
CNS penetrant
Weak 5-HT_2B agonism

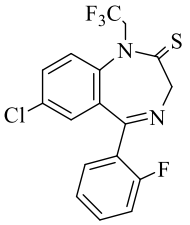
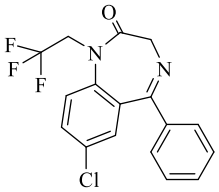
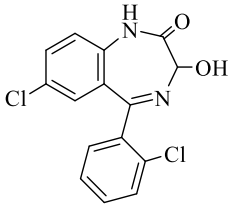
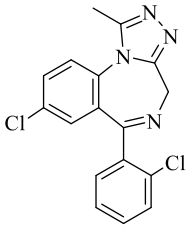
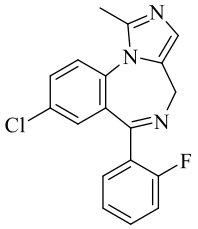
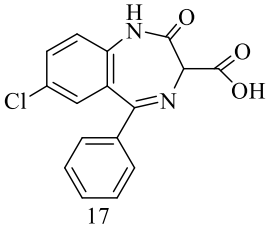
Selective 5-HT_2C agonist
CNS penetrant
No 5-HT_2B agonism

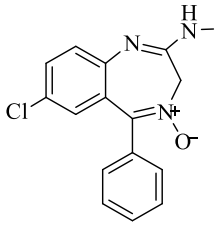
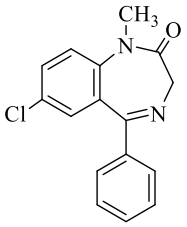
Fig.-2

Table 1: Drugs with their structure and properties

Drugs	Structure	Properties
Eslicarbazepine acetate [4] (S)-10-Acetoxy-10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide	 4	Antiepileptic
Mirtazapine [5] 1,2,3,4,10,14b-Hexahydro-2-methylpyrazino[2,1-a]pyrido[2,3-c] benzazepine	 5	Suicidality and Antidepressant

Oxcarbazepine [6] 10,11-Dihydro-10-oxo-5H-dibenz[b,f]azepine-5-carboxamide	 Fig.-5	Antiepileptic
Estazolam [7] 8-Chloro-6-phenyl-4H-1,2,4-triazolo(4,3-a)-1,4-benzodiazepine	 6	Anxiolytic, anticonvulsant, sedative and skeletal muscle relaxant
Clobazam [8] 7-Chloro-1-methyl-5-phenyl-1,5-benzodiazepine-2,4(3H)-dione	 7	Anxiolytic and anticonvulsant
Flurazepam [9] 7-chloro-1-[2-(diethylamino)ethyl]-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one	 8	Anxiolytic, anticonvulsant, sedative and skeletal muscle relaxant
Alprazolam [10] 8-Chloro-1-methyl-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine	 9	Anxiolytic, sedative, hypnotic, skeletal muscle relaxant, anticonvulsant and amnestic
Clonazepam [11] 5-(2-chlorophenyl)-7-nitro-2,3-dihydro-1,4-benzodiazepin-2-one	 10	Anxiolytic, anticonvulsant, muscle relaxant, sedative and hypnotic

Quazepam [12] 7-Chloro-5-(2-fluorophenyl)-1-(2,2,2-trifluoroethyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-thione	 11	Hypnotic and anticonvulsant
Halazepam [13] 7-Chloro-5-phenyl-1-(2,2,2-trifluoroethyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one	 13	Anxiolytic, anticonvulsant, Sedative and skeletal muscle relaxant
Lorazepam [14] (RS)-7-Chloro-5-(2-chlorophenyl)-3-hydroxy-1,3-dihydro-2H-1,4-benzodiazepin-2-one	 14	Anxiolysis, anterograde amnesia, sedation/hypnosis, anti-seizure, antiemesis and muscle relaxation.
Triazolam [15] 8-chloro-6-(2-chlorophenyl)-1-methyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine	 15	Amnesic, anxiolytic, sedative, anticonvulsant and muscle relaxant
Midazolam [16] 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine	 16	Anxiolytic, amnestic, hypnotic, anticonvulsant, skeletal muscle relaxant and sedative properties
Clorazepate [17] 7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepine-3-carboxylic acid	 17	Anxiolytic, anticonvulsant, sedative, hypnotic and skeletal muscle relaxant

Chlordiazepoxide [18] 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine-4-oxide	 18	Amnestic, anticonvulsant, anxiolytic, hypnotic and skeletal muscle relaxant
Diazepam [19] 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one	 19	Anxiolytic, anticonvulsant, hypnotic, sedative, skeletal muscle relaxant and amnestic

Synthesis of Derivatives of Seven-Membered Ring Compounds Containing Nitrogen

Benzodiazepine derivatives are considered as important chemical compounds of numerous physiological significance and pharmacological utility [4]. This section contains the various synthetic schemes developed in the recent past for the synthesis of dibenzazepine rings. We have organized these synthetic schemes in the systematic order on the basis of the starting material and the catalyst involved in the synthesis, so the future can opt the best method for synthesizing these derivatives.

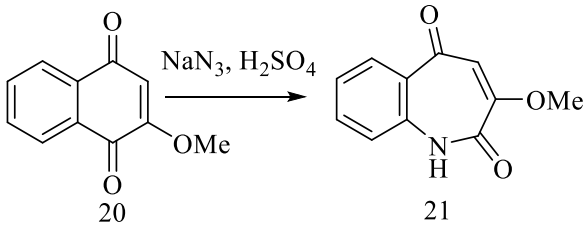
1. Reaction of 2-methoxynaphthalene-1,4-dione and sodium azide
2. Reaction of heteroring fused cyclohexanone, oxime, and DIABH
3. From chlorophenethylamine via the Heck route
4. From chlorophenethylamine via the Friedel–Crafts reaction
5. Reaction of *Z*-2-carboxymethyl-3-benzylidenephthalimidine and PPA
6. Reaction of 3,3’-(4,5-bis(decyloxy)-1,2-phenylene) bis(2-bromothiophene) and aniline
7. Reaction of carbonyl-enamine (a new mode for azepine ring closure)
8. Reaction of ethyl acetoacetate with ethyl N-phenyl-4-aminobutyrate
9. Reaction of the intramolecular Prins cyclization of an amino derivative of lapachol
10. Reaction of chloroisatoic anhydride with alanine methyl ester
11. Reaction of iminostilbene and triphosgene
12. Reaction of carbamazepine with peracids
13. Reaction of 5-aryl-3,4-diamino-1,2,4-triazole and acetophenone
14. Reaction of di-phenyl amine and furan-2,5-dione
15. Reaction of 1-(4-aminobenzoyl)-2,3,4,5-tetrahydro-1H-1-benzo-azepin-5-one with benzoyl

chloride derivatives

16. Reaction of iminostilbene with allyl bromide

Reaction of 2-methoxynaphthalene-1,4-dione and sodium azide

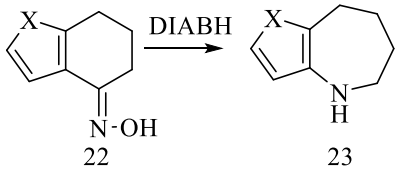
Keana and coworkers in 1996 prepared a series of aromatic ring modified derivatives of 3-hydroxy-1H-1-benzapine-2,5-dione (20). The synthesized derivatives were prepared via a Schmidt reaction of 2-methoxynaphthalene-1,4-dione **(21)** with sodium azide in the presence of sulphuric acid followed by demethylation by acid hydrolysis [10] **[Scheme-1].** The synthesized benzodiazepines were evaluated for NMDA antagonist properties.



Scheme 1. Reaction of 2-methoxynaphthalene-1,4-dione and sodium azide

Reaction of heteroring fused cyclohexanone, oxime, and Diisobutylaluminium hydride (DIABH)

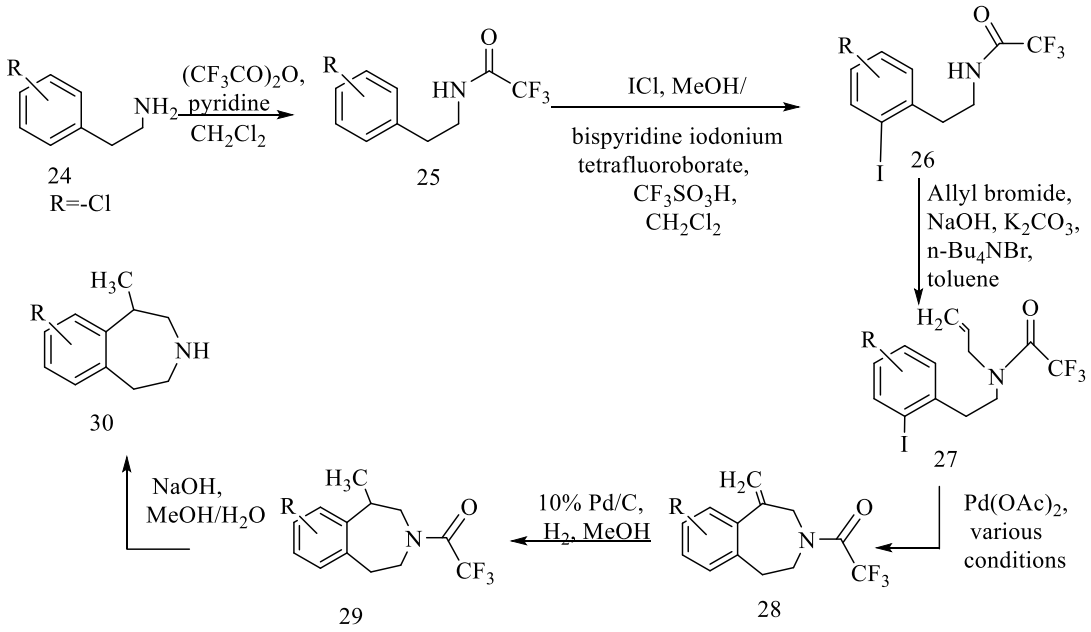
Reduction of heteroring fused cyclohexanone oxime **(22)** in presence of DIABH (diisobutylaluminum hydride) gives regioselectively heterocyclic ring fused azepine (**23)** [11] **[Scheme 2].**



Scheme 2. Reaction of heteroring fused cyclohexanone, oxime, and Diisobutylaluminium hydride

From chlorophenethylamine via the Heck route

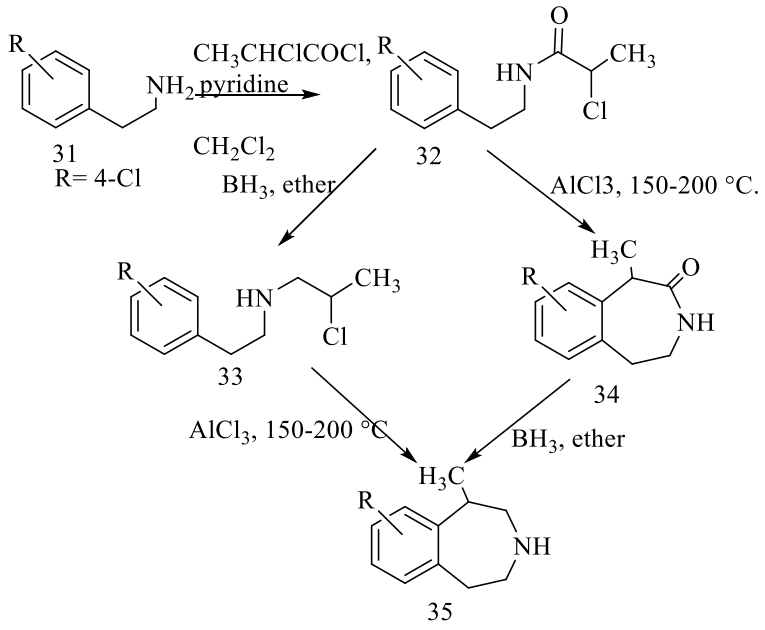
The cyclocondensation of 4-chlorophenethylamine **(24)** with trifluoroacetic acid in the presence of pyridine and DCM followed by the sequence of reaction shown in **scheme-3** gives (1R, S)-8-chloro-2,3,4,5-tetrahydro-1-methyl-1H-3-benzazepine **(25)** [12].



Scheme 3. From chlorophenethylamine via the Heck route

From chlorophenethylamine via the Friedel–Crafts reaction

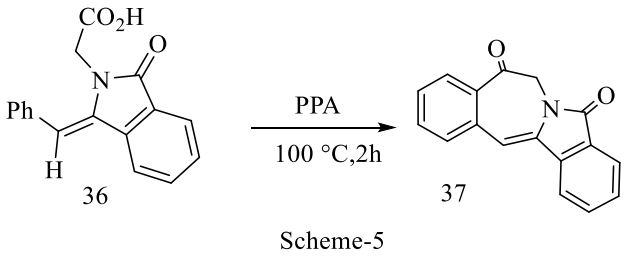
The cyclocondensation of 4-chlorophenethylamine **(31)** with $CH_3CHClCOCl$ in the presence of pyridine and DCM following the sequence of reactions shown in **scheme-4** gives (1R, S)-8-chloro-2,3,4,5-tetrahydro-1-methyl-1H-3-benzazepine **(35)** [13].



Scheme 4. From chlorophenethylamine via the Friedel–Crafts reaction

Reaction of Z-2-carboxymethyl-3-benzylidenephthalimidine and PPA

Reaction of Z-2-carboxymethyl-3-benzylidenephthalimidine **(36)** with PPA forms dihydroisoindolo[1,2-*b*]benz-3-azepine **(37)** [13] **[Scheme-5].**

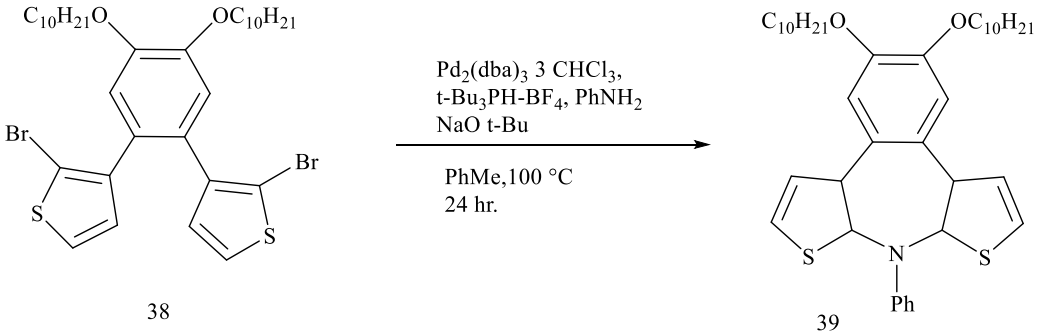


Scheme-5

Scheme 5. Reaction of *Z*-2-carboxymethyl-3-benzylidenephthalimidine and PPA

Reaction of 3,3'-(4,5-bis(decyloxy)-1,2-phenylene)bis(2-bromothiophene) and aniline

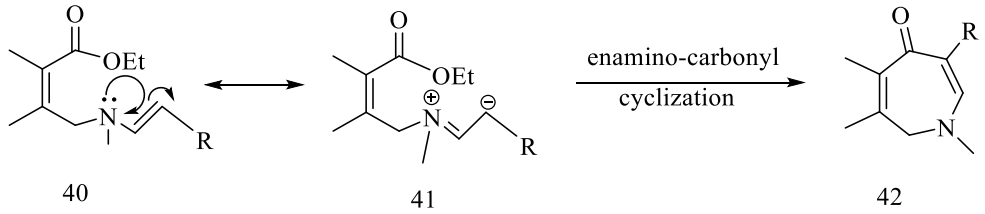
Coupling of dibromide of 3,3'-(4,5-bis(decyloxy)-1,2-phenylene)bis(2-bromothiophene) (**38)** with aniline forming 2,3-bis(decyloxy)-8-phenyl-8H-benzo[d]dithieno[2,3-b:3',2'-f]azepine **(39)** in 29% yield with the remainder of the reaction mixture containing monoaminated product has been reported [14] **[Scheme 6].**



Scheme 6. Reaction of 3,3'-(4,5-bis(decyloxy)-1,2-phenylene)bis(2-bromothiophene) and aniline

Reaction of carbonyl-enamine (a new mode for azepine ring closure)

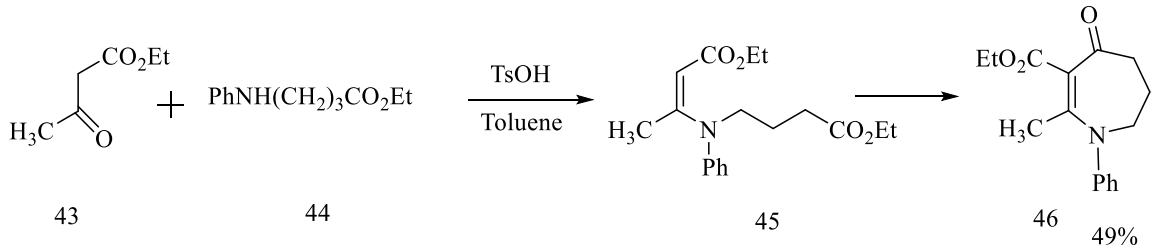
Cyclization of (Z)-ethyl-2,3-dimethyl-4-(methyl ((E)-prop-1-enyl) amino) but-2-enoate **(40)** forms the azepine derivative **42** [15] **[Scheme-7].**



Scheme 7. Reaction of carbonyl-enamine

Reaction of ethyl acetoacetate with ethyl N-phenyl-4-aminobutyrate

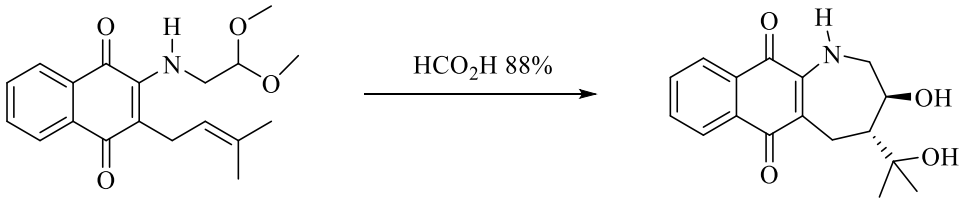
Ethyl acetoacetate **(43)** with ethyl N-phenyl-4-aminobutyrate **(44)** in toluene, in presence of p-toluenesulfonic acid forms (E)-ethyl-2-methyl-4-oxo-1-phenyl-4,5,6,7-tetrahydro-1H-azepine-3-carboxylate (**46)** [15] **[Scheme-8].**



Scheme 8. Reaction of ethyl acetoacetate with ethyl N-phenyl-4-aminobutyrate

Reaction of the intramolecular Prins cyclization of an amino derivative of lapachol

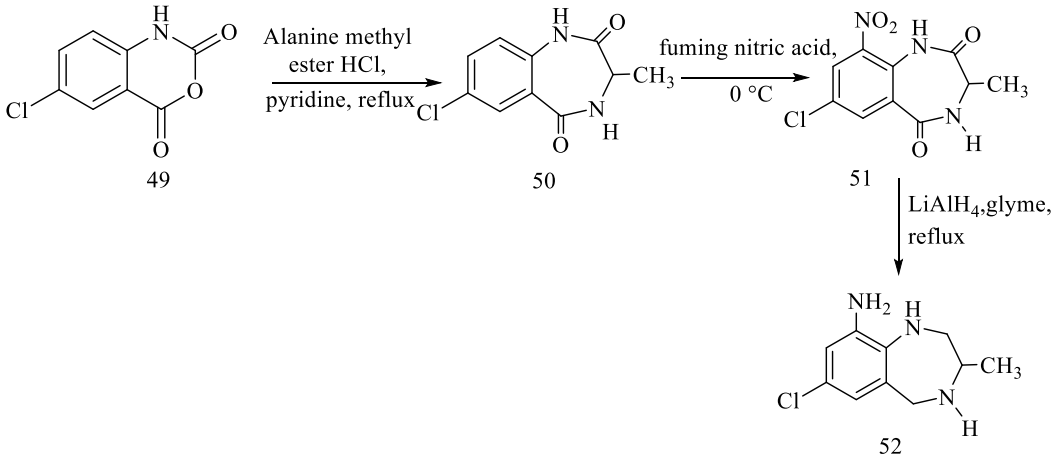
Intramolecular Prins reaction of the 2-(2,2-dimethoxyethylamino)-3-(3-methyl-2-butenyl)-1,4-dihydro-1,4-naphthalene-6,11-dione, an amino derivative of lapachol **(47)**, under hydrolytic conditions, yielded novel azepines condensed with the naphthoquinone nucleus of lapachol **(48)** [16] **[Scheme-9].**



Scheme 9. Reaction of the intramolecular Prins cyclization of an amino derivative of lapachol

Reaction of chloroisatoic anhydride with alanine methyl ester

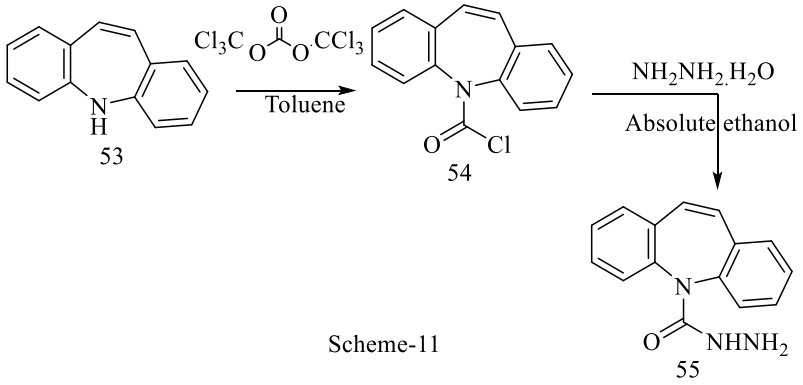
In this procedure, chloroisatoic anhydride **(49)** is treated with alanine methyl ester hydro chloride in pyridine under reflux to give (**50)** [17]. Treatment of (**31)** with cold fuming nitric acid gave a 92% yield of (**51)**. Reduction of (**51)** with lithium aluminum hydride (LAH) in refluxing glyme served to reduce both the carbonyl and nitro functionalities to yield triamine (**52)** [17] **[Scheme-10].**



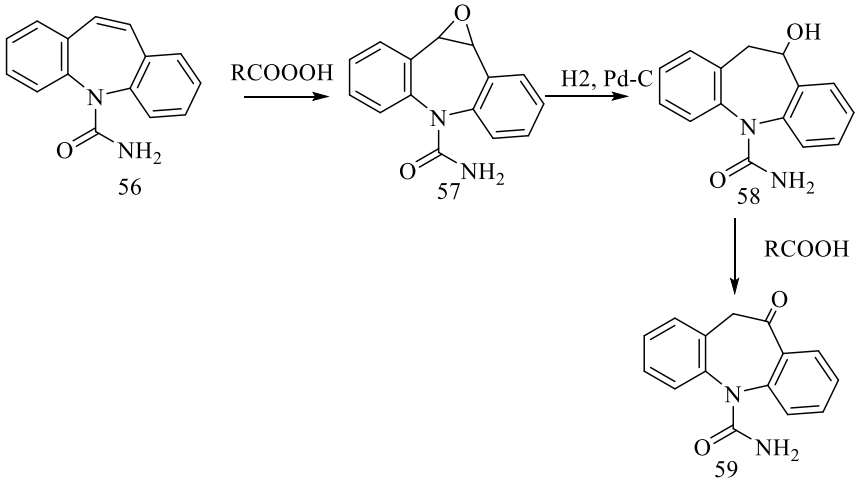
Scheme 10. Reaction of chloroisatoic anhydride with alanine methyl ester

Reaction of iminostilbene and triphosgene

Iminostilbene with triphosgene in toluene gives 5H-dibenzo(b,f)azepine-5-carbonyl chloride **(54)** which further reacts with hydrazine hydrate in absolute ethanol to give 5H-dibenzo(b,f)azepine-5-acid hydrazide **(55)** [18] **[Scheme-11].**



Scheme-11



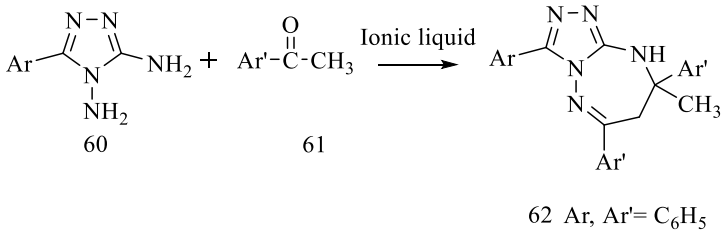
Scheme 12. Reaction of carbamazepine with peracids

Reaction of carbamazepine with peracids

Carbamazepine with peracids undergoes epoxidation to give product **57** which in the presence of H_2, Pd-C gives **58** which reacts again with peracid to give oxcarbazepine (**59)** [19] **[Scheme-12].**

Reaction of 5-aryl-3,4-diamino-1,2,4-triazole and acetophenone

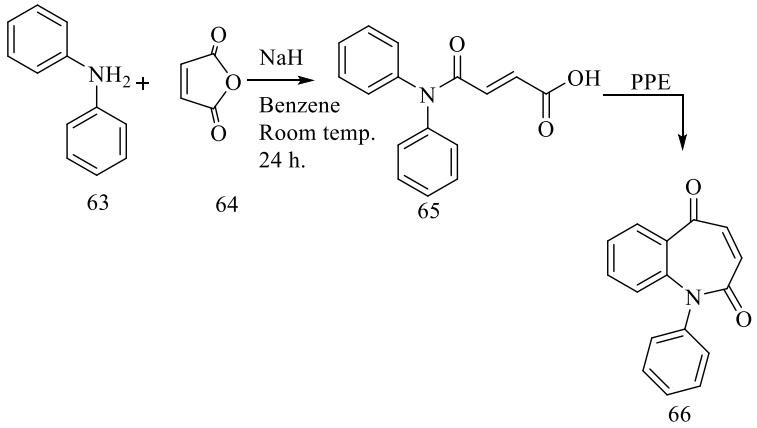
One-pot synthesis of antifungal active 8-methyl-3,6,8-trisubstituted-7H,9H-[1,2,4] triazolo[4,3- b][1,2,4] triazepines (**62)** has been reported via condensation of 5-aryl-3,4-diamino-1,2,4-triazole **(60)** and acetophenone (**61)** using ionic liquid [20]. The use of ionic liquids provided an alternative addition to "Green Chemistry." **[Scheme-13]**



Scheme 13. Reaction of 5-aryl-3,4-diamino-1,2,4-triazole and acetophenone

Reaction of di-phenyl amine and furan-2,5-dione

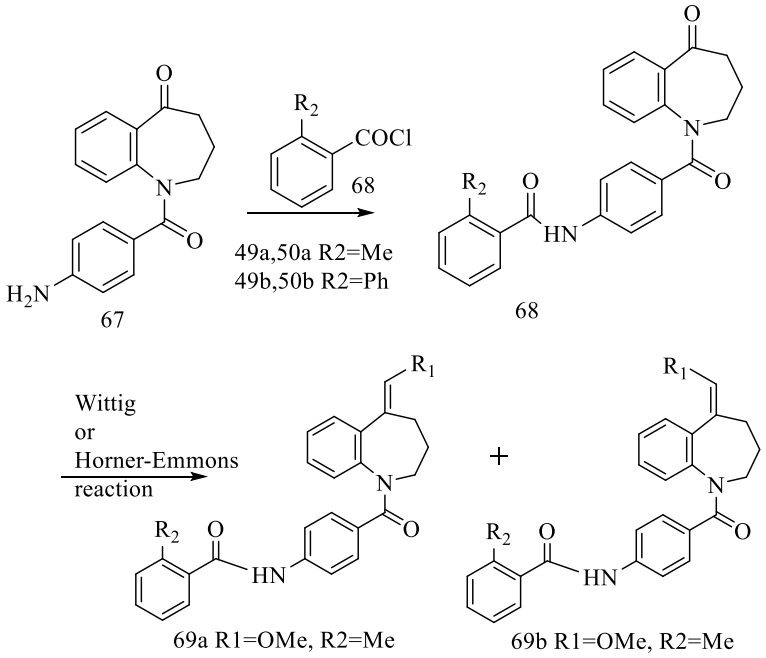
A facile synthesis of 1-phenyl-1H-benzo[b] azepine-2,3-dione **(66)**, from diphenylamine-4-oxo-2-butenoic acid **(65)** using PPE has been described. It was tested for antimicrobial activity against pathogens [21] **[Scheme-14].**



Scheme 14. Reaction of di-phenyl amine and furan-2,5-dione

Reaction of 1-(4-aminobenzoyl)-2,3,4,5-tetrahydro-1H-1-benzo-azepin-5-one with benzoyl chloride derivatives

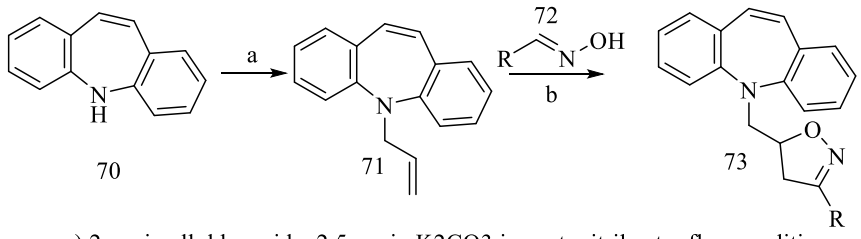
Benzoazepin-5-one derivatives (**69)** were obtained by condensation of 1-(4-aminobenzoyl)-2,3,4,5-tetrahydro-1H-1-benzo-azepin-5-one **(67)** with benzoyl chloride derivatives (**68)**. Author's described the C=C bond formation using the Wittig or Horner-Emmons reaction. Condensation of (**69a)** and (methoxy-methyl)triphenylphosphonium chloride gave two methoxy- substituted exo-olefin isomers (**69a** and **69b**) [22-23] **[Scheme-15].**



Scheme 15. Reaction of 1-(4-aminobenzoyl)-2,3,4,5-tetrahydro-1H-1-benzo-azepin-5-one with benzoyl chloride derivatives

Reaction of iminostilbene with allyl bromide

The dipolarophile (**71)** was prepared by the reaction of commercially available iminostilbene (**70)** with allyl bromide [23]. The N-allyl pendant arrangement of the intermediate (**71)** showed a major role in the formation of products. Product (**73)** was reported to be formed on the basis of either an allyl pendant bent towards the tricyclic ring or disposed outside the ring. With two scaffolds in hand, the dibenzoazepine derivatives were synthesized in a single-step operation via a successive 1,3-dipolar cycloaddition reactions. A solution of oxime (**72)** in dichloromethane was added to a mixture of N-allyl tricyclic amine (**71)**, sodium hypochlorite and Et_3N to give (**55)** [24] **[Scheme-16].**



a) 2 equiv allyl bromide, 2.5 equiv K2CO3 in acetonitrile at reflux condition
b) 5 equiv oxime, 5 equiv 4% NaOCl, 1 equiv Et_3N in MDC

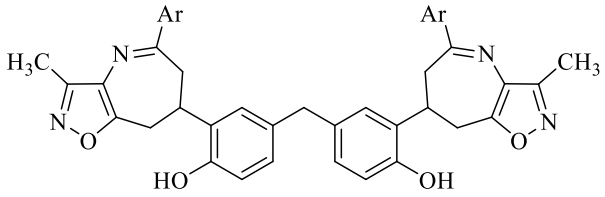
Scheme 16. Reaction of iminostilbene with allyl bromide

Biological Activities

There are many activities shown by derivatives of seven-membered ring compounds containing nitrogen, some of them are summarized here.

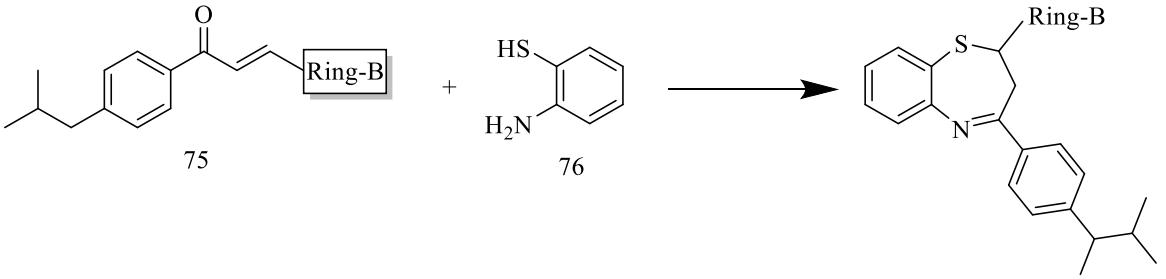
Antimicrobial and anticancer activities

Methylene-bis-isoxazolo[4,5-*b*]azepines compounds have been evaluated for antimicrobial and anticancer activities [41]. Novel methylene bis-isoxazolo[4,5-*b*]azepines (74) have been synthesized by reaction of 3,5-dimethyl-4-nitroisoxazole with an appropriate methylene bis-chalcone to obtain various Michael adducts, which on treatment with $SnCl_2$-MeOH underwent reductive cyclization. [25-41]



74

Further continuation of the research in this area, Shaik and colleagues synthesized some 1,5-benzothiazepine derivatives (77) by the reaction of isobutylchalcones (75) with 2-aminothiophenol (76) and evaluated its microbial potency. The synthesized 1,5-benzothiazepines were characterized using spectral (IR, ^{1}H-NMR, ^{13}C-NMR) as well as physicochemical methods. The compounds containing halogen atoms in the nucleus showed promising antimicrobial potency. The most potent compounds (Bt5) of the series contain a fluorine atoms in the nucleus with MIC 0.5µg/mL against E. coli [42].

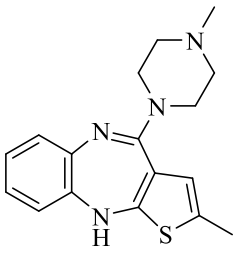


75 76

77, BT5: 4-fluorophenyl

Antipsychotic activity

Olanzapine (78) is an atypical antipsychotic [43]. Olanzapine is structurally similar to clozapine and quetiapine, but is classified as a thienobenzodiazepine. Olanzapine has been investigated for use as an antiemetic, particularly for the control of chemotherapy-induced nausea and vomiting (CINV).

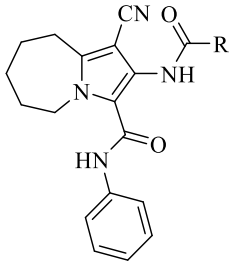


78

Anticancer activity

Pyrrolo[1,2-a]azepine (79) represents a core of over 80 alkaloids known as Stemona alkaloids separated from Stemonaceae family plants. Herbal extracts of these plants have been used for thousands of years in

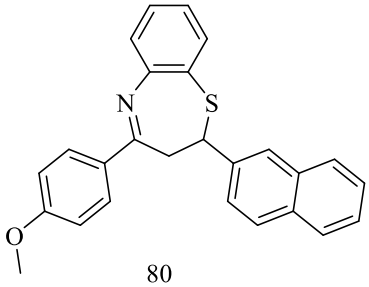
folk medicine in East Asia as cough suppressant, antibacterial, antifungal, antitubercular, and antiparasitic agents [44-46].



79

Pyrrolo[1,2-a]-azepine is the main scaffold of some antitumor active agents. The most important examples of compounds bearing the pyrrolo[1,2-a]azepine skeleton are esters of cephalotaxine, which showed significant activity as anti-leukemic agents [47]. Pyrroloazepines proved to be a promising scaffold for designing new anticancer active agents. Pyrroloazepines showed a potent inhibitory activity against liver (HepG2), breast (MCF7), and colon (HCT116) cancer cell lines [48].

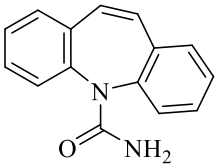
A series of twelve 1,5-benzothiazepine chalcone compounds were selected for in silico studies on the protein tyrosine kinase. The motive of the study was to estimate the biological activity of chalcone-based 1,5-benzothiazepine as potent inhibitors of breast cancer. From the results of insilico studies, some potent compounds were selected and MTT were performed for the most potent and least active analogues. The result of the MTT against MCF cell line revealed the most potent compounds of the series (80), which was found to be matching with the results of insilico studies [49].



80

Anti-convulsant activity

5H-Dibenzo[b,f]azepine-5-carboxamide(carbamazepine) is one of the synthesized effective anti-convulsant drugs, which is the most frequently prescribed first-line drug for the treatment of epilepsy [50].



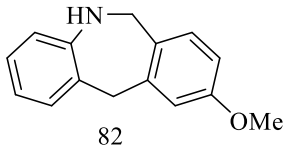
81

Antianxiety activity

Anxiety ailments are a type of psychiatric condition concerning an extreme behavioral response to strain [51]. Benzoazepine nucleus has been shown to be present in several mood disorder drugs such as diazepam, imipramine, and lorazepam. Several others molecules have been developed in recent past for

the anxiolytic activity [52, 53].

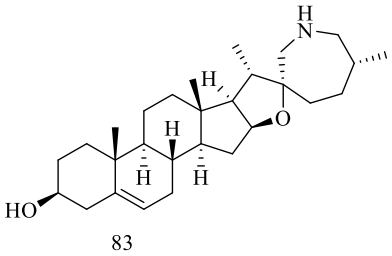
Reamtong and colleagues synthesized a series of benzodiazepine compounds and evaluated for their cytotoxicity against normal kidney cell lines. The synthesized fourteen compounds were well characterized using nuclear magnetic resonance and mass spectroscopy. Among the tested compounds, one compound showed the lowest cytotoxcicity which are comparable to the potent standard drug diazepam. From the results of the cytotoxicity studies, five benzodiazepine compounds were selected for antianxiety activity against stressed rats. From the results, it was ample clear that compound (82) showed better anxiolytic activity than diazepam without a sedative effect by showing superior hyper-locomotor activity. [54]



82

Cholinesterase inhibitory activity

Cholinesterases are a group of enzymes containing hydrolytic enzymes. The important members were acetylcholinesterase and butyrylcholinesterase. Cholinesterase is mainly involved in the pathology of Alzheimer's disease (AD), Myasthenia gravis, and glaucoma. Currently used drugs for AD were donepezil, galantamine, and rivastigmine [55]. Urszula and coworkers in 2020 reported solasodine derivative comprising a seven-membered F ring with a nitrogen atom placed at 22a. The derivatives were synthesized from diosgenin or tigogenin in a four-step synthesis comprising of the simultaneous opening of the F-ring and introduction of cyanide in position 22α activation of the 26-hydroxyl moiety after mesylation followed by cyanide displacement in position 22α, and N-cyclization. The synthesized analogues (22a(N)-homo analogues and 26a-homosolasdine) were tested as potential inhibitors of acetyl and butyryl cholinesterase and exhibited inhibition at micromolar concentrations. The most potent analogues (8) act as noncompetitive inhibitors and exerted IC50 of 8.51 µM and 7.05 µM for acetyl and butyryl cholinesterase respectively. The results of their experiments suggested that solasodine analogues inhibit and bind to acetyl and butyryl cholinesterase and are devoid of neurotoxicity [56].



83

3.

Conclusion

Seven membered moieties containing nitrogen atom can be explored to synthesize many of its analogous

which can be effectively and successfully exploited to the new molecule which shows better biological response. Various synthetic protocols have been developed in recent years, which could help researchers in synthesizing novel molecules of biological importance. Literature reports suggest that seven-membered nitrogen containing rings are important and it throws attention to the set the mind of researchers to carry out the work for developing its various analogous which can ultimately beneficial for humans beings.

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