December 2008 *Volume 4 Issue 12*

Trade Science Inc.

Organic CHEMISTRY

An Indian Journal

Microreview

OCAIJ, 4(12), 2008 [486-507]

Chemistry and biological activity of benzodiazepines

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Received: 16th October, 2008 ; Accepted: 21st October, 2008

ABSTRACT

Benzodiazepines are bicyclic heterocyclic compounds possessing a benzene nucleus fused to a seven-membered ring containing two nitrogen atoms at different positions in the ring, and thus have been classified into six groups depending on the position of nitrogen atom in the seven membered ring. Many modifications and substitutions have been made in both rings by employing different methods to obtain a large number of compounds of varied types of biological activities. The information regarding their chemical, biological importance and drugs based on the skeleton of benzodiazepines is scattered in the literature, and there is no such review article available in the field. In the present article, we have reviewed the complete literature on the benzodiazepines containing seven membered diazepine ring fused with benzene ring, and have discussed various aspects including QSAR and spectral properties.

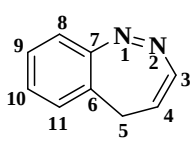
KEYWORDS

Benzodiazepines;
QSAR;
Spectral properties;
Biological properties.

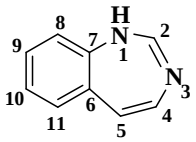
INTRODUCTION

Benzodiazepines are bicyclic heterocyclic compounds having a benzene nucleus fused to a seven-membered ring containing two nitrogen atoms. The following six formulae **(1-6)** represent the basic ring structures of benzodiazepines[1,2].

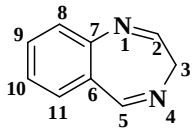
The above six classes of benzodiazepines are described together with their various substituted or reduced forms[3,4]. No attempt has been made to survey compounds having a second ring fused to the diazepine portion of the molecule e g. dibenzodiazepines **(7)** pyridobenzodiazepines **(8)** and naphthodiazepines **(9)** will not be discussed. Compounds such as the pyridodiazepine **(10)** and the quinoxalinodiazepine **(11)** will not be like-wise included. Products obtained by



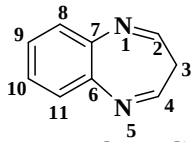
5H-1,2-benzodiazepine (1)



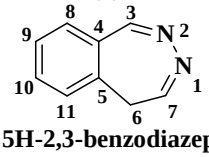
1H-1,3-benzodiazepine (2)



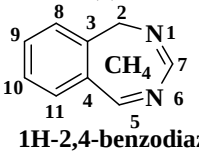
3H-1,4-benzodiazepine (3)



3H-1,5-benzodiazepine (4)

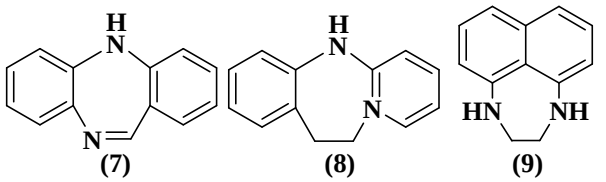


5H-2,3-benzodiazepine (5)

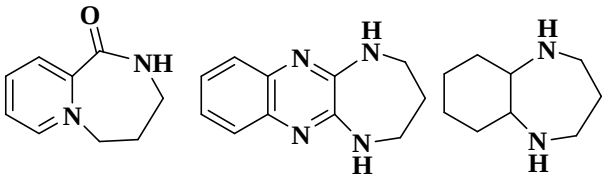


1H-2,4-benzodiazepine (6)

simple transformations, e.g. reduction as in **(12)** have



(7) **(8)** **(9)**



(10) **(11)** **(12)**

also been included.

The twelve classes of benzodiazepines constitute the most extensively explored group in this series, largely owing to the discovery of their interesting biological activity. The **(7)** and **(8)** benzodiazepines have been thoroughly studied during a period of several decades, largely because of their relatively easy synthesis from common starting materials[5]. The other four groups of benzodiazepines have so far failed to attract very much interest.

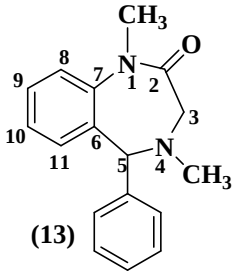
Nomenclature of benzodiazepine nucleus

Benzodiazepines are numbered starting at the position adjacent to the carbocyclic ring regardless of the positions of the nitrogen atoms[6,7]. The letters are specified by prefixed numbers as shown in **(13)** is a 1, 4-benzodiazepine whereas **(14)** is a 2, 4-benzodiazepine. The term benzodiazepine implies a maximum degree of unsaturation, i.e. a total of three double bonds in the seven-membered ring as shown in the introduction.

The position of the odd hydrogen atom (even if occupied by another mono or divalent substituent) is indicated by the term 1H, 2H, 3H. In dihydro and tetrahydro- benzodiazepines the odd hydrogen is given the lowest possible number[8,9]. This is, however, complicated by the fact that first consideration is given to the position of a functional group, which is expressed as a suffix to the name of the compound e.g.**(13)** is a 1, 3, 4, 5-tetrahydro-1H,3H-l,4-benzodiazepin-2-one and **(14)** is a 2, 3, 4, 5-tetrahydro-1H, 3H-2, 4-benzodiazepine.

Benzodiazepine story

The first compound of this type was prepared



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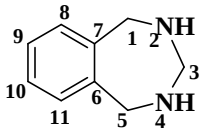

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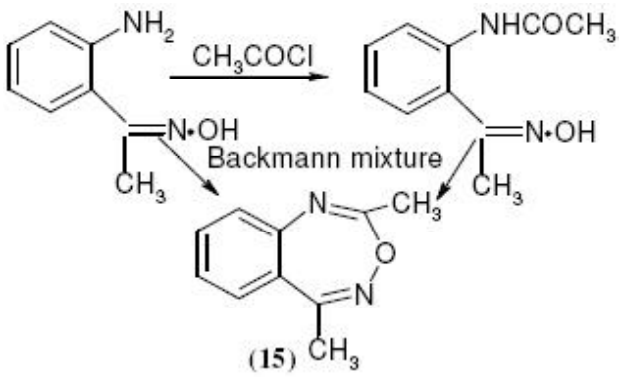
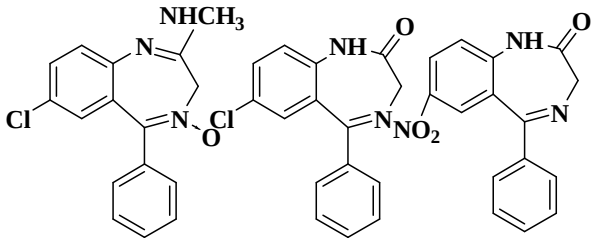


in1891 by Auwer and Von Meyenburg by the treatment of amino or acetoaminophenone oximes with a Backmann mixture[10]. The heptoxdiazine structure **(15)** was definitely established in 1924.

Drugs containing benzodiazepine nucleus

Among the large number of benzodiazepines that have been synthesized, only members of the 1, 4-benzodiazepine group **(16-30)** have shown sufficient pharmacological and clinical activity to warrant introduction as new drugs[11,12,13,14,15]. The metabolism of these compounds has been extensively studied and methods for their analytical detection and determination have been reported



Chlordiazepoxide (16) **Diazepam (17)** **Nitrazeam (18)**

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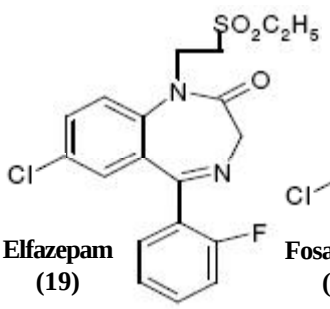
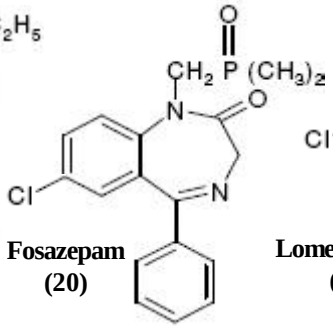
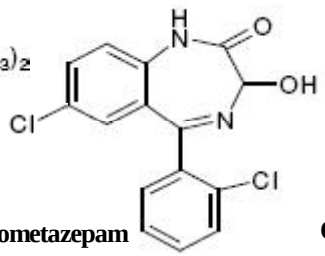


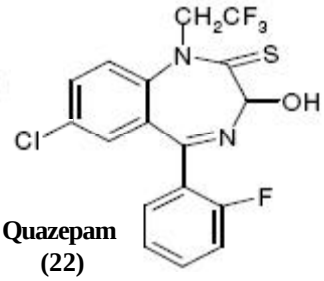
Elfazepam
(19)



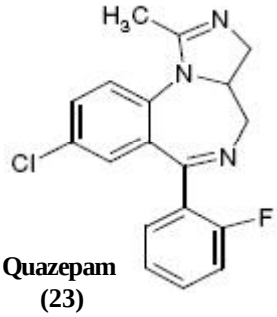
Fosazepam
(20)



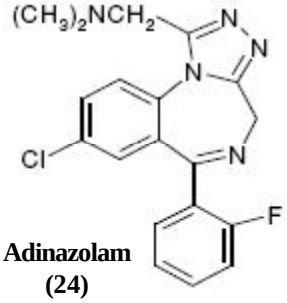
Lometazepam
(21)



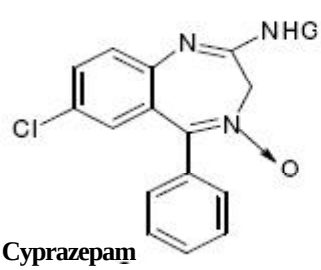
Quazepam
(22)



Quazepam
(23)



Adinazolam
(24)



Cyprazepam
(25)

Sulazepam
(26)

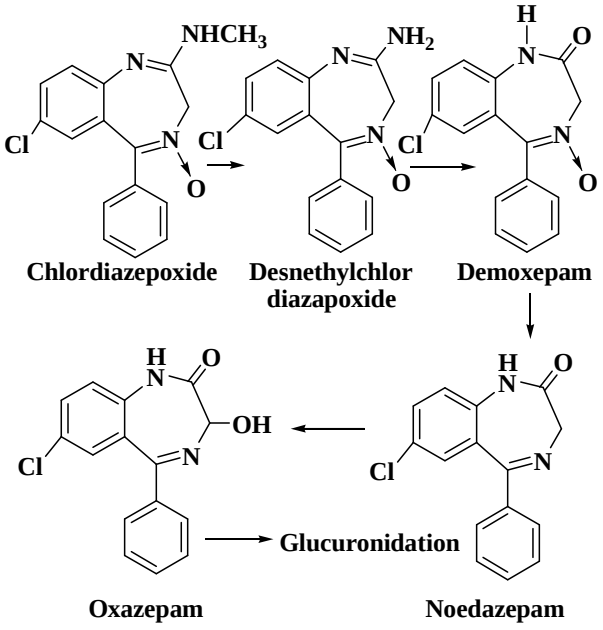
Fletazepam
(27)

Flunitrazepam
(28)

Triflubazam
(29)

Oxazepam
(30)

Metabolism of 1, 4-benzodiazepine[16]

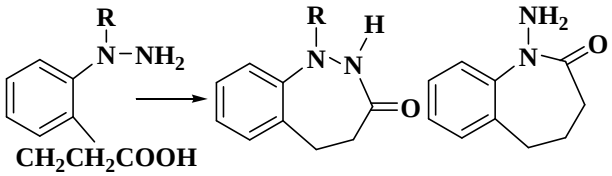


Synthetic methods of different type of benzodiazepines

The different types of benzodiazepines synthesized by the different types of method are given below.

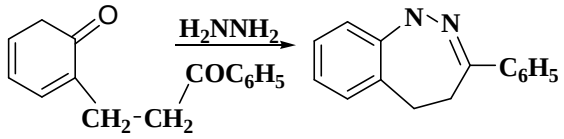
1, 2-Benzodiazepine: synthetic method

(i) Cyclization of the o-hydrazinophenylpropionic acid (31, R = ethyl) gave 1-ethyl 1, 2, 4, 5-tetra hydro-3H-1,2-benzodiazepin-3-one (32, R = ethyl) in 60-70% yield an attempt to prepare (R=H) from **(31)** (R=H) yielded only the aminoquinolone **(33)**[17].



(31) (32) (33)

(ii) Treatment of the diketone (34) with hydrazine gave the corresponding azine, 5, 5a, 6, 7, 8, 9-hexahydro-3-phenyl-4H-l, 2-benzodiazepine **(35)** in 86% yield[18].



(34) (35)

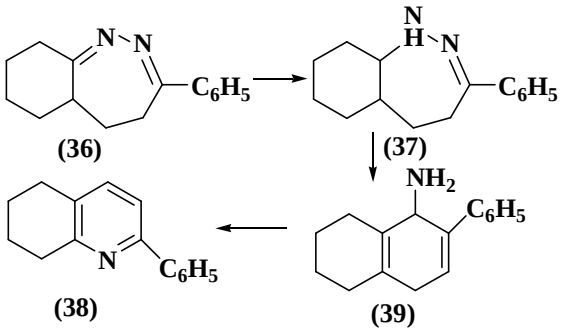
Chemical reactions

1. Hydrolysis

The benzodiazepin-3-one was stable to alkali but was readily hydrolyzed by hot hydrochloric acid to give compound **(36)**. Compound **(38)** remains unaffected under these conditions[18].

2. Ring contraction

Diazepine **(36)** was converted into 2-phenyl-5, 6, 7, 8-tetrahydroquinoline **(39)** by treatment with hydrogen chloride in the absence of solvent, or in ethanolic or aqueous solution and proceeds by isomerization of the protonated species **(37)** to the aminodihydropyridine **(38)**, which readily aromatizes, by the loss of ammonia to give compound **(39)**[19].

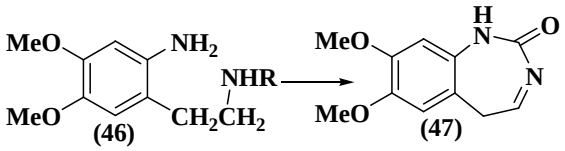


(36) (37) (38) (39)

1, 3-Benzodiazepine: Synthetic method

(i) A general synthesis for 4, 5-dihydro-3 H-l, 3- benzodiazepines **(44)** involved the condensation of o-aminophenethylamines **(40)** with imidates **(41)**, which led to mixtures containing the amidine **(42)** and the benzodiazepine. Better yields of **(44)** were obtained by the use of 2-nitrophenethylamine in the condensation reaction. Catalytic reduction of the nitro group in the intermediate **(45)** gave **(42)**, which was cyclized to **(44)** in refluxing toluene or ethanol[20].

(ii) The l, 3, 4, 5-tetrahydro-1H, 3H-1, 3-benzo diazepin -2-one **(47)** was made by treatment of o-amino phene thyl amine(R=H) with N, N'-carbonyl diimida zole.

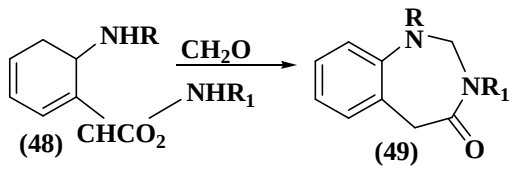


(46) (47)

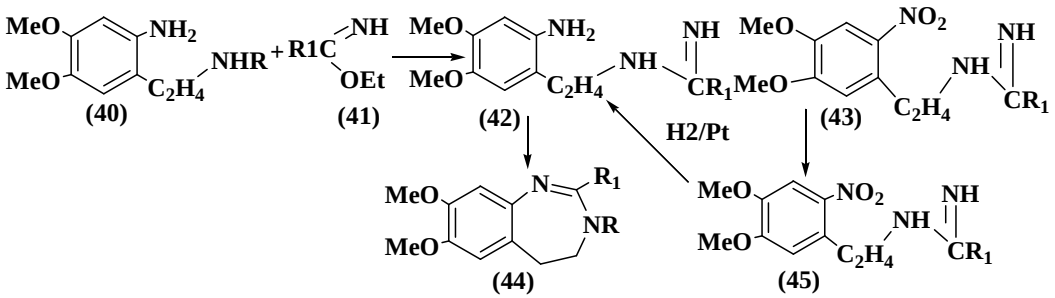
Chemical reactions

Alkylation

Compound (48, R = H or -CH_2SCH_3, R_1 = H) reacted with formaldehyde to yield 3-hydroxymethyl derivatives (49, R_1 = -CH_2OH). Methylation of **(49)** gave a monomethyl sulphate of unidentified structure it would seem probable that quaternization at position 3 had occurred. Methylation of the dihydrobenzodiazepine with n-butyllithium and methyl *p*-toluenesulphonate afforded the 3-methyl derivative and treatment with methyliodide gave1, 3-dimethylbenzodiazepinium iodide[21].



(48) (49)



(40) (41) (42) (43) (44) (45)

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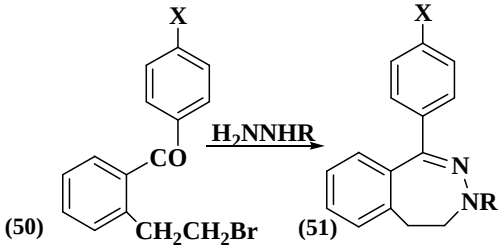
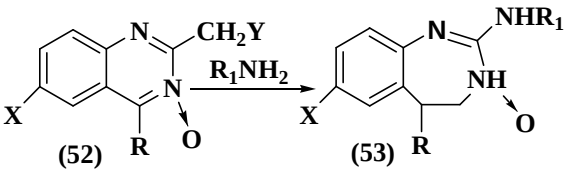
2, 3-Benzodiazepine : Synthetic method

The reaction of 2-(2-bromoethyl)-benzophenone **(50)** with hydrazine afforded 2, 3-benzodiazepine **(51)**[22].



2-Amino-1, 4-benzodiazepines: Synthetic method

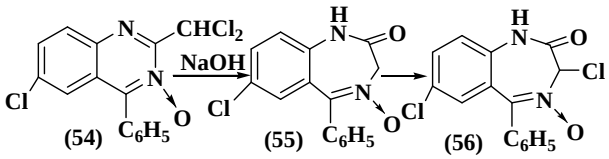
2-Amino-1, 4-benzodiazepine **(53)** is synthesized by the ring enlargement of quinazoline-3-oxides **(52)**, when treated with ammonia or primary aliphatic amines or hydrazine as described below[23].



1, 4-Benzodiazepine-2-one: Synthetic method

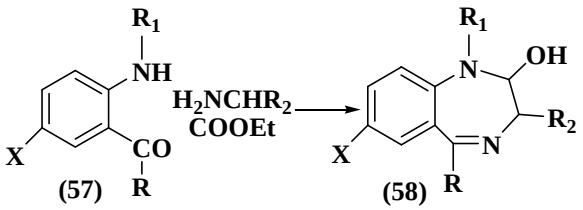
1, 4-Benzodiazepine-2-one is the most important benzodiazepines. It is synthesized by the following methods.

(i) Benzodiazepin-2-one-4-oxide have been obtained by ring enlargement of quinazoline 3-oxide on treatment with aqueous sodium hydroxide. The N-oxide oxygen could readily be removed to yield benzodiazepin-2-ones.The mechanism of the ring enlargement of 2-halomethylquinazoline-3-oxides **(54)** has been elucidated by a study of the transformation of the dichloro methyl quinazoline oxide into the benzodiazepinone-4-oxide **(55)**. Treatment with an excess of sodium hydroxide gave in almost quantitative yield. Benzodiazepin-2-one **(56)** can be readily obtained by the removal of the N-oxide oxygen from the 4-oxides[24].

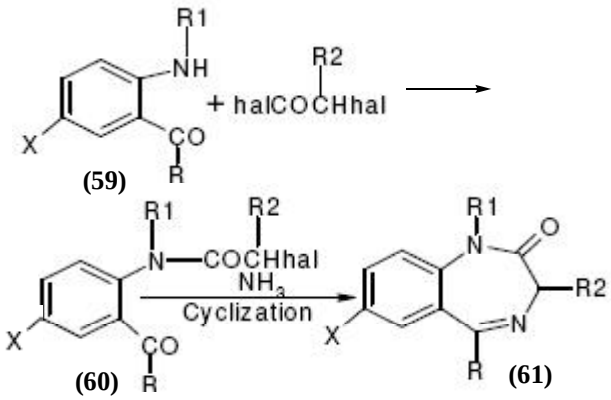


(ii) There are three principal synthetic routes, using 2-aminobenzophenones as starting materials which are given below[25].

(a) In the first method amino benzophenone **(57)** was treated with a glycine ester to give benzodiazepin-2-one **(58)**.

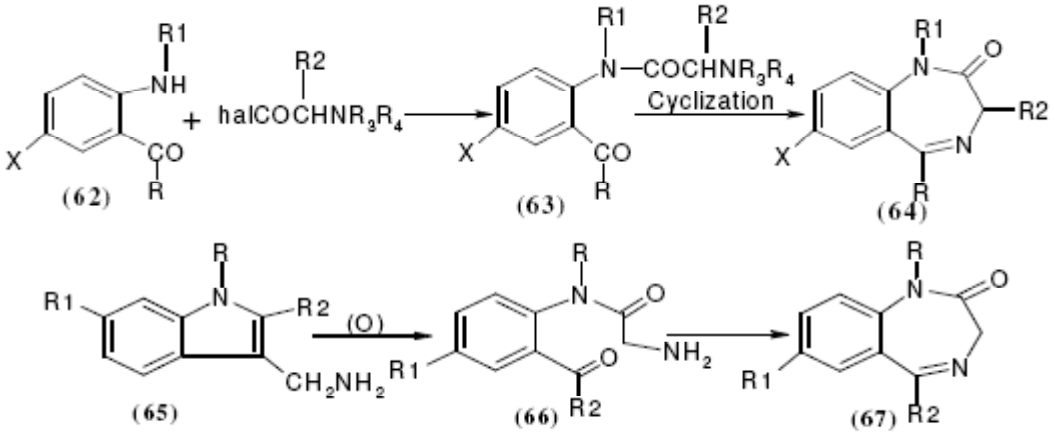


(b) The three-step of method 2 was generally more versatile and afforded higher yields; in this procedure, halo acetylation of amino benzophenone **(59)** gave the halo acetamide, which on treatment with ammonia yielded the amino acetamide **(60)**, which readily cyclized to the benzodiazepin-2-one **(61)**.

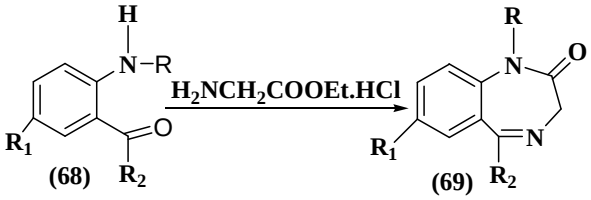


(c) In method 3a protected amino acid derivative was used to acylate the amino benzophenone **(62)**. Among the reagents that have been described for this purpose are carboben zoxygly cine, carbobenzoxyglycylchloride, carbobenzo xyglycine anhydride and phthalimido acetylchlo ride. Removal of the protecting group gave ultimately the benzodiazepin-2-one **(64)**.This synthesis has also been achieved with free amino acids and amino acid chlorides as acylating agents.

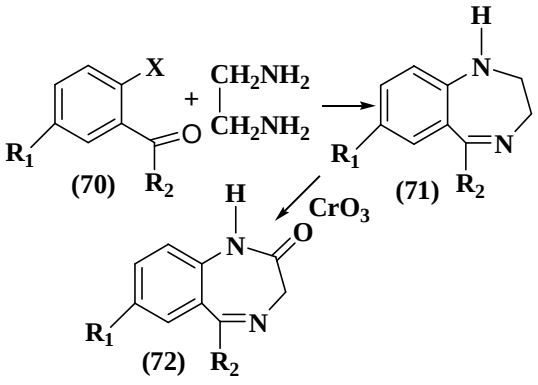
(iii) 1, 4-Benzodiazepines-2-one **(67)** have also been synthesized by the oxidation of 1-substituted indoles **(65)**[26].



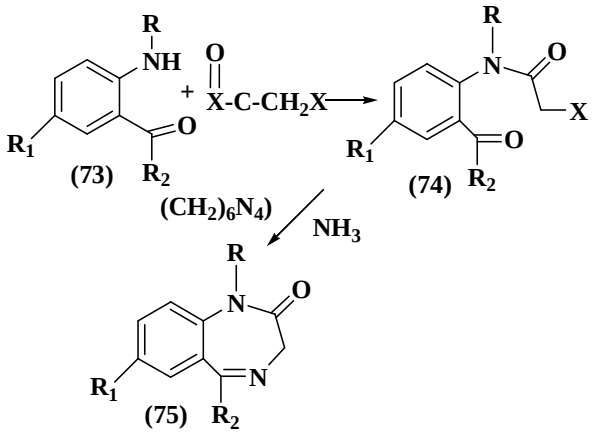
(iv) When 2-aminoaryl ketone **(68)** was condensed with a bifunctional, two carbon fragment [Glycine ethyl ester hydrochloride] to give 1, 4-benzodiazepin-2-one **(69)**[27].



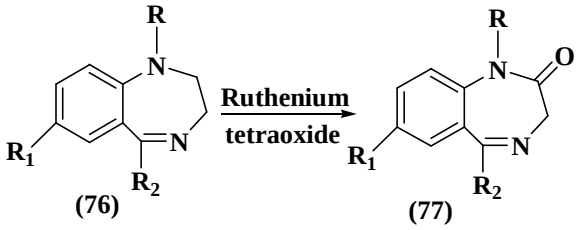
(v) 1, 4-Benzodiazepine-2-one **(72)** was synthesized from substituted dibenzophenone **(70)** which was treated with ethylene diamine to give an intermediate **(71)** that on oxidation with CrO_3 yielded **(72)**[28].



(vi) Treatment of 2-aminoaryl ketone **(73)** treated with dihaloalkyl ketone led to formation of an intermediate **(74)** which was converted into cyclized product **(75)** by the reaction with hexamethylamine in presence of ammonia[29].



(vii) When 1, 4-benzodiazepine **(76)** was oxidized with ruthenium tetra oxide. It gave formed 1, 4-benzodiazepines-2-one **(77)**[30].

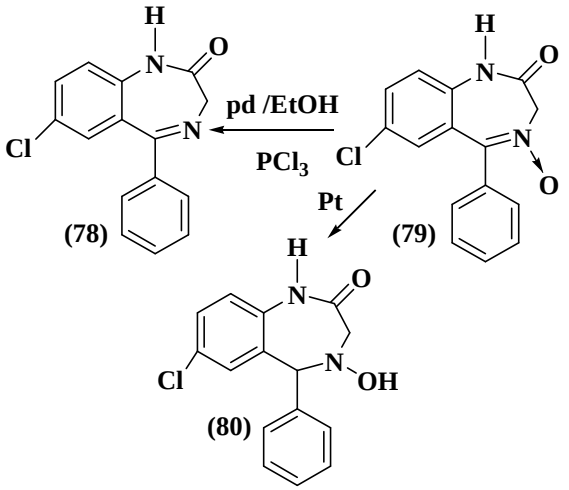


Chemical properties of benzodiazepines

The 1, 4-benzodiazepines-2-one undergoes various types of following chemical reactions.

(1) Reduction

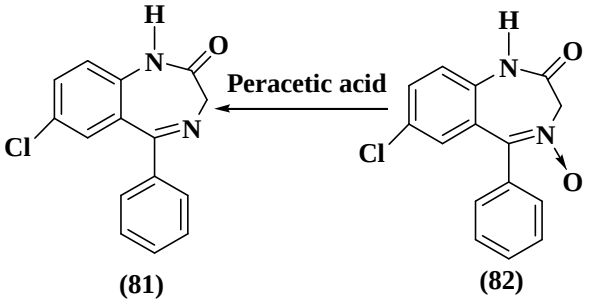
1, 4-benzodiazepines-2-one-4-oxide gave different type of product by using different type of catalytic agents. Deoxygenation of the N-oxide has been effected by catalytic hydrogenation over Raney Nickel, or by



the treatment with phosphorus trichloride, to give the following compound **(78)**. Further reduction (hydrogen over platinum) gave tetrahydrobenzodiazepinone. Catalytic reduction over platinum afforded the hydroxylamine **(80)**, whereas reduction over palladium in ethanol hydrochloric acid resulted in deoxygenation and dechlorination[31].

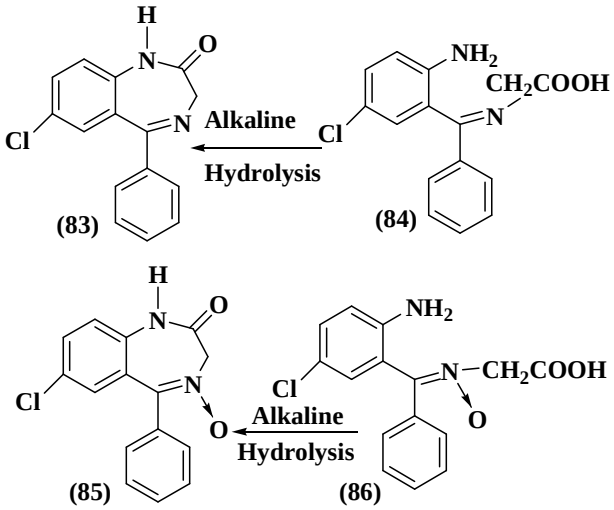
(2) Oxidation

The different type of oxidizing reagents give 1, 4-benzodiazepines-2-one **(81)** was converted into N-oxide **(82)** by oxidation with per acetic acid. Tetrahy drobenzo- diazepinones have been oxidized to the corresponding dihydro compounds using chromium trioxide, selenium dioxide, or silver oxide as oxidizing agents[32].



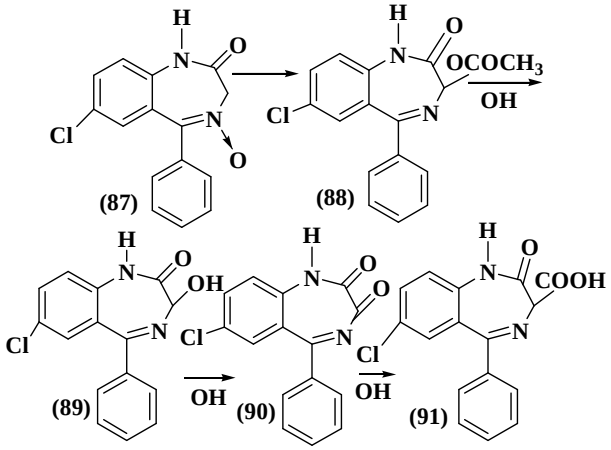
(3) Hydrolysis and aminolysis

Alkaline hydrolysis of 1, 4-benzodiazepine **(83)** and 1, 4-benzodiazepine-N-oxide **(85)** resulted in the scission of the amide linkage, giving the imines **(84)** and **(86)** respectively. Treatments of these imines with acid reconverted **(86)** into the lactum, whereas **(84)** was isolated as the sodium salt, which was hydrolyzed by acid to 2-amino-5-chlorobenzophenone and glycine [32,33].



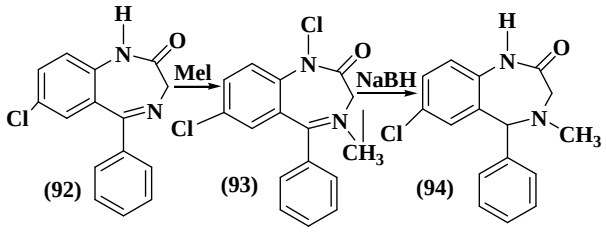
(4) Acylation

Treatment of 1, 4-benzodiazepines-2-one-N-oxide **(87)** with acetic anhydride resulted in a Polonovsky-type rearrangement to give the 3-acetoxy compound **(88)** similar rearrangement occurred with benzoyl chloride. Alkaline hydrolysis afforded initially the 3-hydroxy compound **(89)** further treatment with alkali resulted the conversion into the 2, 3-dione **(90)** and the dihydroqunoline carboxylic acid **(91)**[34].



(5) Alkylation

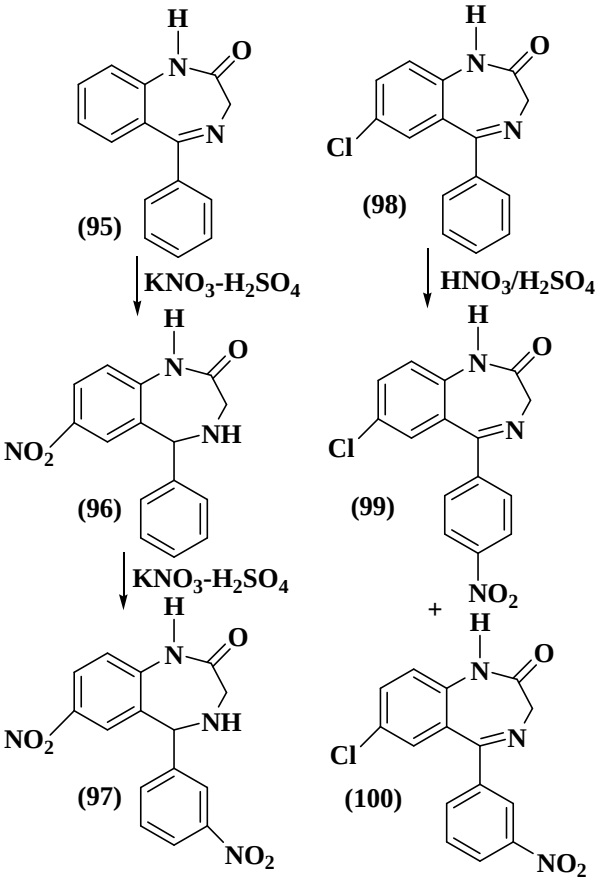
Treatment of benzodiazepin-2-ones with sodium methoxide, followed by an alkyl halide sulfate gave the



N_1-alkyl derivatives (nitrones were alkylated in the same manner). Methylation of **(92)** with methyl iodide in acetone afforded benzodiazepinium iodide **(93)**, which was reduced with sodium borohydride to methyl tetrahydrobenzodiazepin-2-one **(94)**[35].

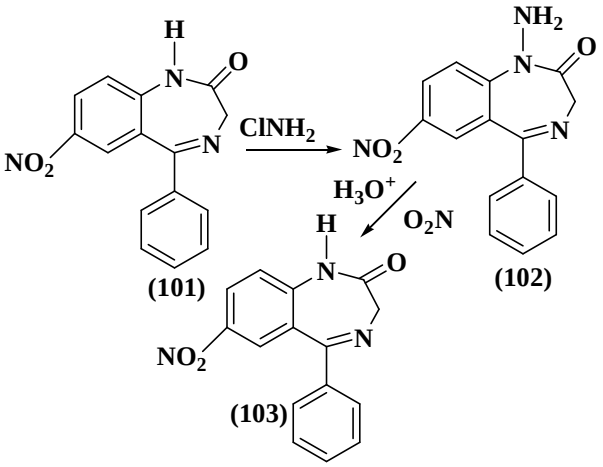
(6) Nitration

Potassium nitrate-sulfuric acid converted the 1,4-benzodiazepin-2-one **(95)** into 7-nitro-1,4-benzodiazepin-2-one derivative **(96)**. Further nitration gave the dinitro compound **(97)**. Nitration with nitrate-sulfuric acid converted 1, 4-benzodiazepin-2-one **(98)** in a mixture of 5-nitro phenyl derivatives **(99)** and **(100)** were isolated[35,36].



(7) Amination

Treatment of 1, 4-benzodiazepin-2-one **(101)** with sodium hydride and chloro amines afforded the 1-amino derivative **(102)**. Acid hydrolysis of this compound gave 7-nitro-5-phenyl-1-aminobenzodiazepin-2-one **(103)** which has been made by treatment of the corresponding 3-chloro compounds with ammonia or amines. 7-Aminobenzodiazepin-2-ones have been reduced to nitro compounds usually with hydrogen over Raney Nickel. 7-Dialkylamino compounds have obtained in one step by reductive alkylation of nitro analogs[37].



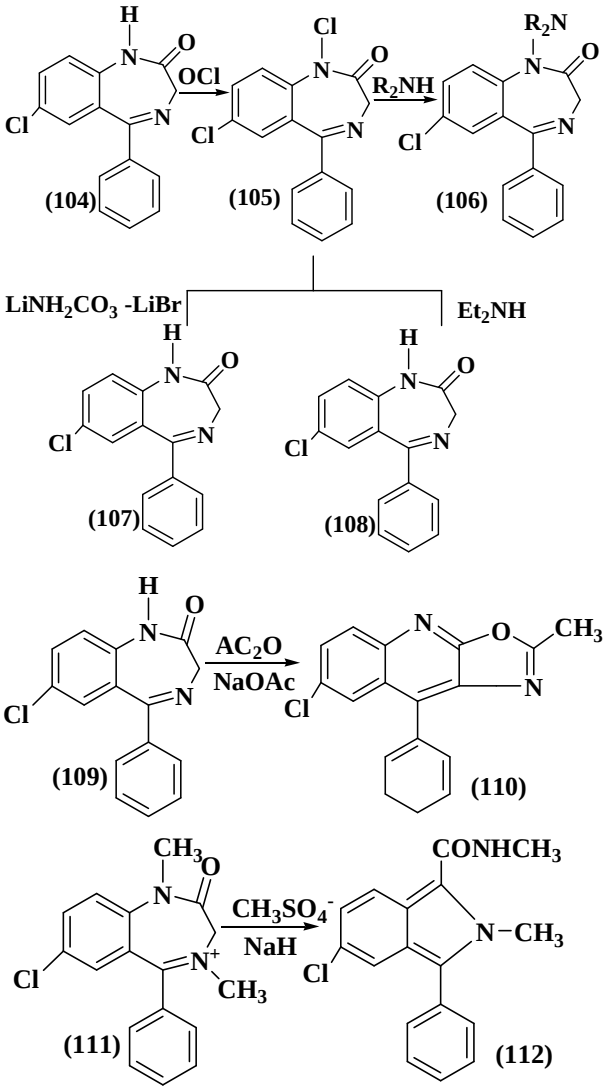
(8) Halogenation

Dihydrobenzodiazepin-2-one **(104)** on treatment with sodium hypochlorite or t-butyl hypochlorite yielded 105. This compound was oxidizing agent able to oxidize iodide to iodine. The 1-chloro derivative could readily be rearranged to give **(106)** in cases, where the R grouping has at least one hydrogen atom to position-5 of the heterocyclic ring. Dehydrohalogenation of **(105)** with a mixture of lithium carbonate and bromide, afforded the cyclohexenyl derivative **(107)** whereas use of diethyl amine gave an isomeric compound **(108)** on treatment with a number of other secondary amines[38].

(9) Skeletal rearrangements

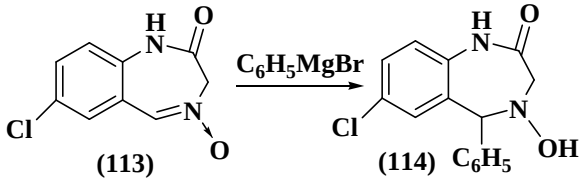
Treatment of the benzodiazepinone with acetic anhydride and sodium acetate resulted in ring contraction to the oxazoloquinoline 1-alkylsubstituted benzo diazepin-2-one **(109)** underwent a similar ring contraction to isoindolecarboxy amide **(110)**, when treated with sodium hydride in N, N-dimethyl formamide. The

benzodiazepinium methyl **(111)** sulfate likewise ring contracted under the same conditions to give the corresponding dimethylisoindole carboxamide **(112)**[39,40].



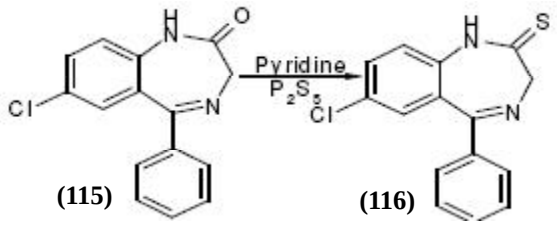
(10) Grignard reaction

Treatment of the benzodiazepinone-4-oxide **(113)** with phenylmagnesium bromide gave the 4-hydroxy-5-phenyl compound **(114)**[40].



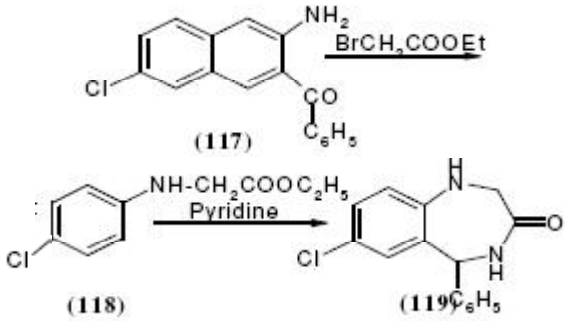
(11) Thiation

Treatment of benzodiazepin-2-one **(115)** with phosphorus pentasulfide in pyridine gave the corresponding thione **(116)**. Methylation of this thione under basic conditions afforded the S-methyl compound; S-thiobenzodiazepin-2-one was also obtained from the corresponding 3-chloro compound and thiourea[40].



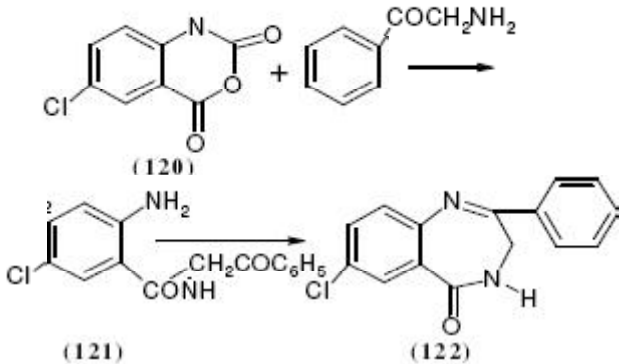
1, 4-Benzodiazepin-3-ones: Synthetic method

7-Chloro-l, 2, 4, 5-tetrahydro-5-phenyl-3H-1, 4-benzodiazepin-3-one **(119)** was synthesized from 2-amino-5-chlorobenzophenone **(117)**[41].



1, 4-Benzodiazepine-5-one: Synthetic method

Cyclization of the arylamino ketone **(121)** gave 7-chloro-3, 4-dihydro-2-phenyl 5H-1,4-benzodiazepin-5-one **(122)**. Compound arylaminoketone was prepared from 5-chloroisatoic anhydride **(120)** and aminoacetophenone[42].

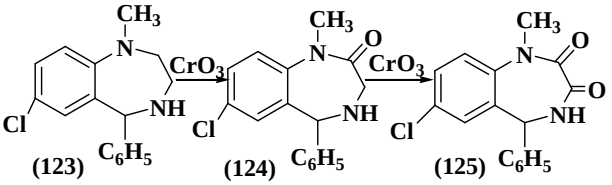


1, 4-Benzodiazepinediones: Synthetic method

Formation of a benzodiazepine-2, 3-dione **(125)**

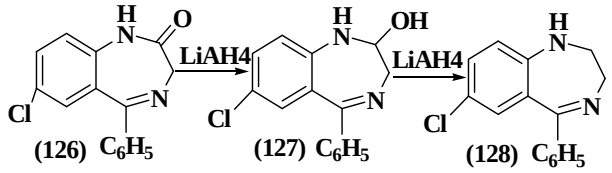
was obtained by oxidation of 7-chloro-1-methyl-5-phenyl-1, 4 benzodiazepine **(123)** with CrO_3.

The corresponding 1-methyl analog was likewise obtained by rearrangement and was also formed by oxidation of intermediate compound **(124)**[43].



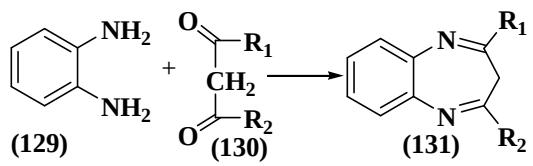
1, 4-Benzodiazepines: Synthetic method

Benzodiazepines without functional groups position-2 have mostly been made by reduction of suitable benzodiazepinones. An indirect reductive method involved conversion of benzodiazepin-2-one **(126)** into the corresponding 2-thiones, followed by Raney nickel desulphurization. In this manner the benzodiazepine-2-thione was converted in to the 2, 3-dihydrobenzodia zepine. Reduction of the benzodiazepin -2-one **(126)** with lithium aluminum hydride gave 7-chloro-2, 3-dihydro-5-phenyl-1H, 3H-l, 4-benzodiazepine **(128)** or the tetrahydroderivative depending on reaction conditions[44].



1, 5-Benzodiazepine: Synthetic method

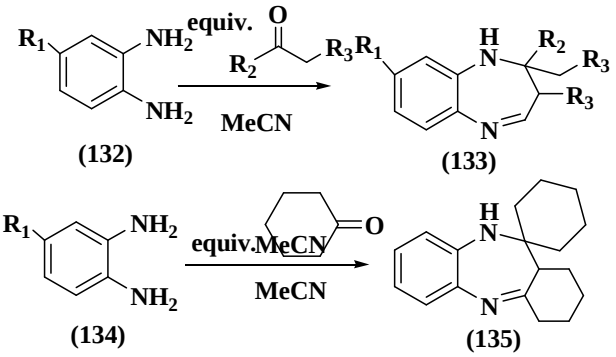
Condensation of o-phenylenediamine **(129)** with β-dicarbonyl compounds has been widely used method for the synthesis of 1, 5-benzodiazepines **(131)**[45]. The reaction has been shown to be pH dependent for the case of acetyl acetone (R_1=R_2 = CH_3), which afforded 2, 4-dimethy1-3H- l, 5-benzodiazepine (R_1 = R_2 = CH_3) in optimum yield at pH 4-6. The majority of syntheses have used acid catalysis e. g. acetic acid or dry hydrogen chloride in ethanol.



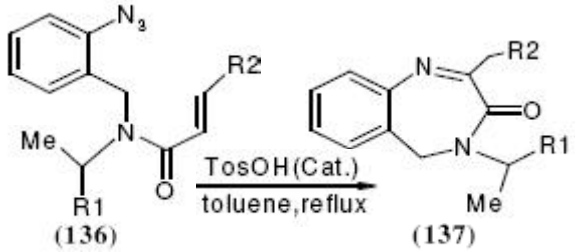
Synthesis of substituted benzodiazepine

The substituted benzodiazepines show the different types of activities. They are synthesized by the following methods.

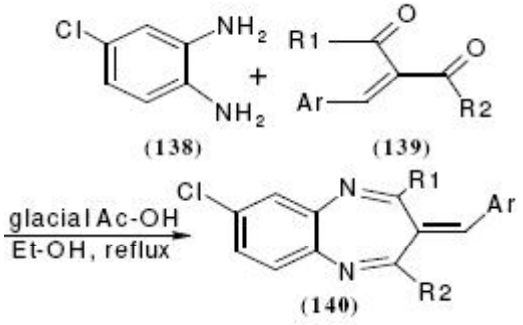
1. Synthesis of 1, 5-benzodiazepine **(133)** mediated by sulfamic acid. Condensation of o-phenylenediamine **(132)** with ketones and promoted by sulfamic acid at room temperature[46].



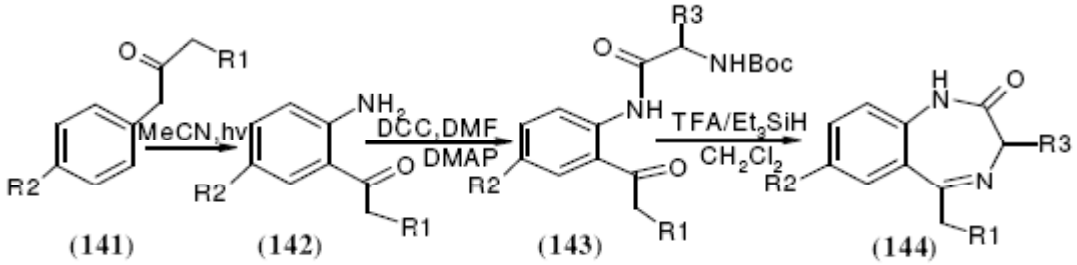
2. One step synthesis of 2-substituted 4, 5-dihydro-1, 4-benzodiazepine-3-one **(137)** by using TosOH as a catalyst and refluxing for 5-6hrs[47].



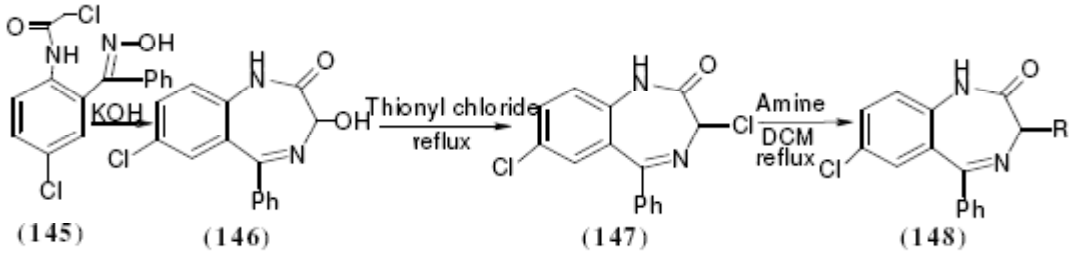
3. Synthesis of 7-chloro-2-alkyl/aryl, 4-alkyl/aryl-3-arylidene-3H-1, 5-benzodiazepine **(140)** by reacting 3-chlorodianilino **(138)** with glacial AcOH, using EtOH as a solvent and then refluxing the reaction mixture[48].



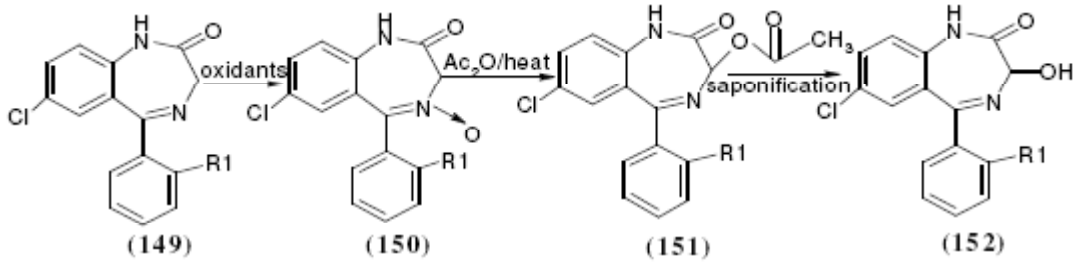
4. Synthesis of 3, 5-disubstituted 1, 4-benzodiazepines **(144)** via the photo-Fries rearrangement of anilides **(141)** initially form an intermediates **(142, 143)** and then cyclization to yield the compound **(144)**[48].



5. Synthesis of substituted 3-anilino-5-phenyl-1, 3-dihydro-1H, 3H-1,4-benzodiazepine-2-one **(148)** by using as starting material **(145)** first form oxazepam **(146)** after that refluxing with thionyl chloride to form an intermediate **(147)**[49].



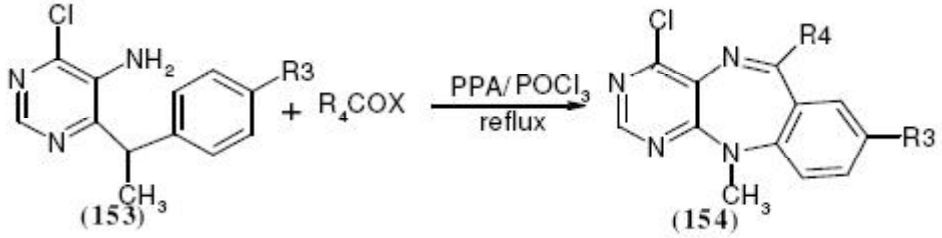
6. Synthesis of 3-hydroxy-1, 4-benzodiazepine (152, Oxazepam and Lorazepam) by acetoxylation reaction of 3-position of 1, 4-benzodiazepine-2-one **(149)**[50].

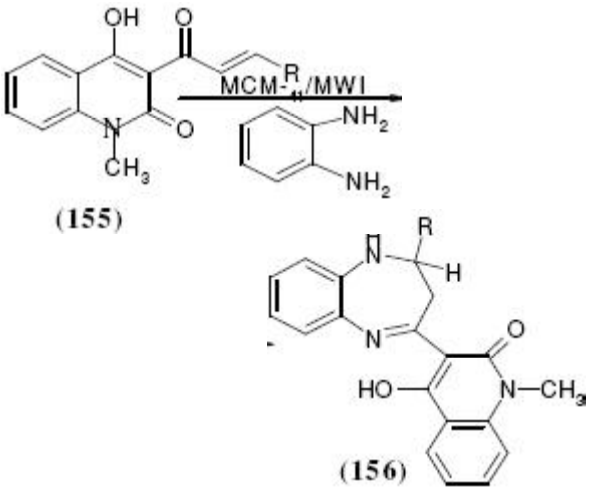


Synthesis of cyclic substituted benzodiazepines

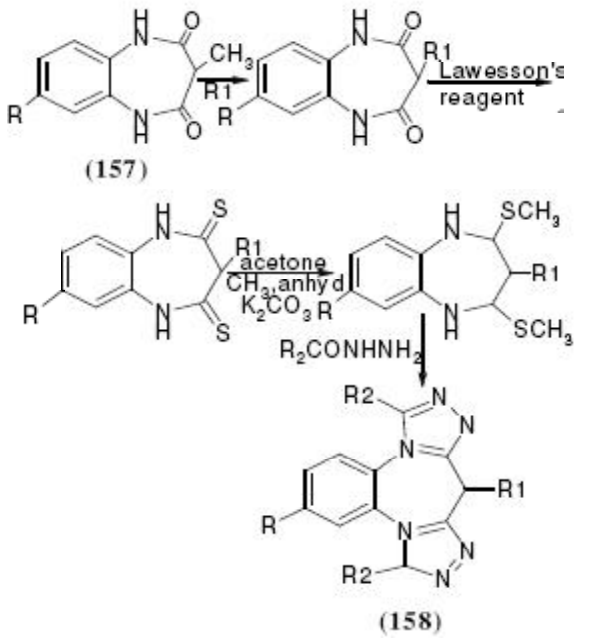
Cyclic substituted benzodiazepines also exhibit different types of activities. They are synthesized by the following methods using different types of rings.

1. Synthesis of tricyclic 4-chloro-pyrinido [4, 5-b] [1, 4] benzodiazepines **(154)** by using following type of reaction[50].
2. Microwave induced solvent-free synthesis of substituted 1, 5-benzodiazepines **(156)** by reaction of the starting material **(155)** with phenylenediamine[51].
3. Synthesis of new substituted 9H-bis-[1, 2, 4]

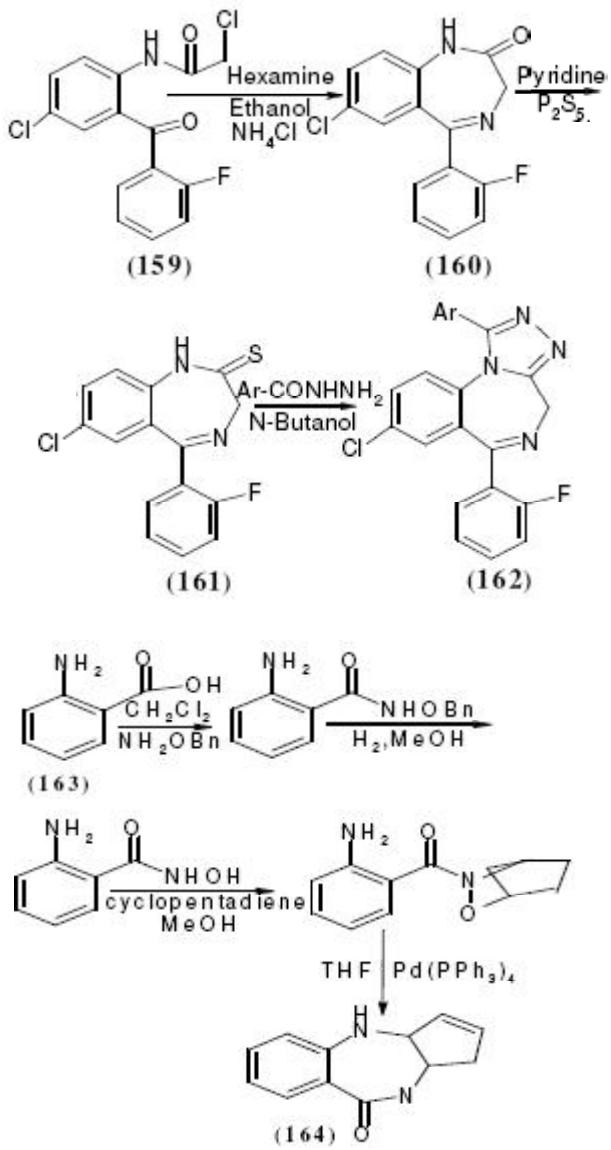




trizolo-[4,3-a:3',4'-d][1, 5]-benzodiazepines derivatives **(158)** from unsubstituted 1, 5-benzodiazepine **(157)** by converting into substituted 1, 5-benzodiazepines by using Lawesson's reagent and acetone[52].



4. Synthesis of some new substituted trizolo [4, 3-a] [1, 4]-benzodiazepines derivatives **(162)** by converting uncyclized benzophenone **(159)** to the cyclized benzodiazepine on using Hexamine and NH_4Cl then reacting with P_2S_5[53].
5. Novel 4-benzodiazepines **(164)** were synthesized from starting material acyl nitroso derivative **(163)** and by using hetero-Diel's Alder cycloadducts[54].



Solid-phase synthesis of 1, 4-benzodiazepine

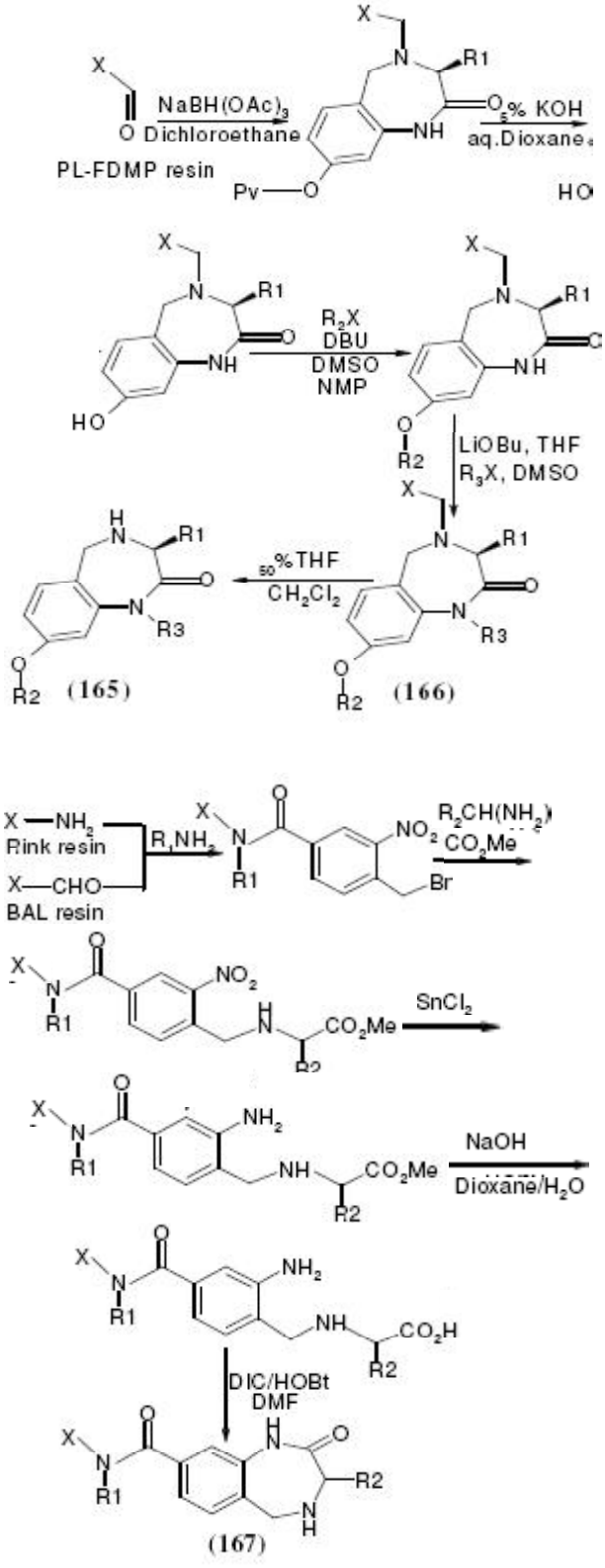
The solid-phase syntheses of benzodiazepines were done by the following methods.

1. Solid phase synthesis of tetrahydro-1, 4-benzodiazepine-2-one derivative **(165)** was carried out by using PL-FDMP resin as a starting material[55].
2. Solid-phase synthesis of tetrahydro-1, 4-benzodizepine-2-one derivative **(167)** was also done by using of different types of resins[56].

One pot synthesis of benzodiazepines

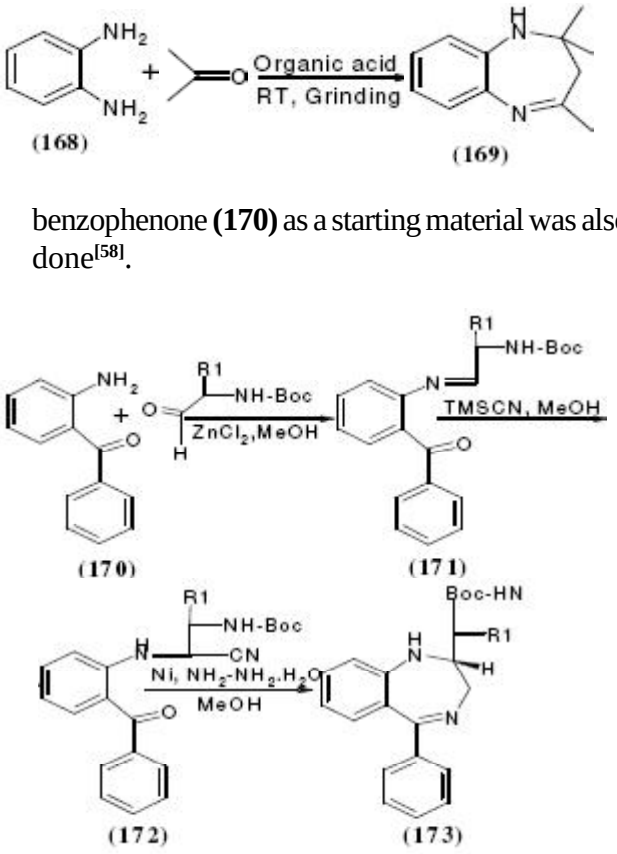
1. One-Pot synthesis and self-assembled super structure of organic salts of a 1, 5- benzodiazepine derivative was also conducted to obtain compound

Microreview



(169)[57].

2. Another one pot synthesis of novel 2-substituted-5-phenyl-1, 4-benzodiazepine **(173)** by 2-amino benzophenone **(170)** as a starting material was also done[58].



Fast atomic bombardment mass spectrometric studies

The mass fragmentation mechanisms has also been carried out under fast-atom bombardment (FAB) ionization conditions of 1,2,4-trisubstituted-3a, 4, 5, 11-tetrahydro-3H-1, 2, 4-oxadiazolo[4, 5-a][1, 5]benzodiazepines **(174)**[59, 60].

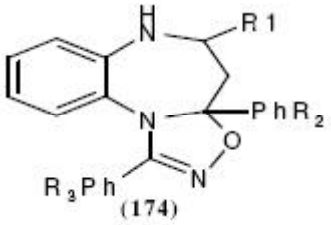


TABLE 1 : Substituted value of above benzodiazepines

Compound	R_1	R_2	R_3
1	Ph	H	H
2	Ph	p-MeO	H
3	Ph	p-Cl	H
4	p-MeOPh	H	H
5	o-BrPh	H	H
6	Ph	P-MeO	m-Br
7	p-MeOPh	H	m-Br

The FAB Mass Spectra of these compounds were obtained by using a double-focusing mass spectrometer coupled with a PDP11-250 data system, using glycerol or 1-thioglycerol as a matrix. The energy of the incident primary argon atoms was 8-kev with a gun current of 1Ma. The characteristic FAB fragment ions of these compounds have been complied in TABLE 2.

TABLE 2: FAB-MS of compounds (1-7): m/z values

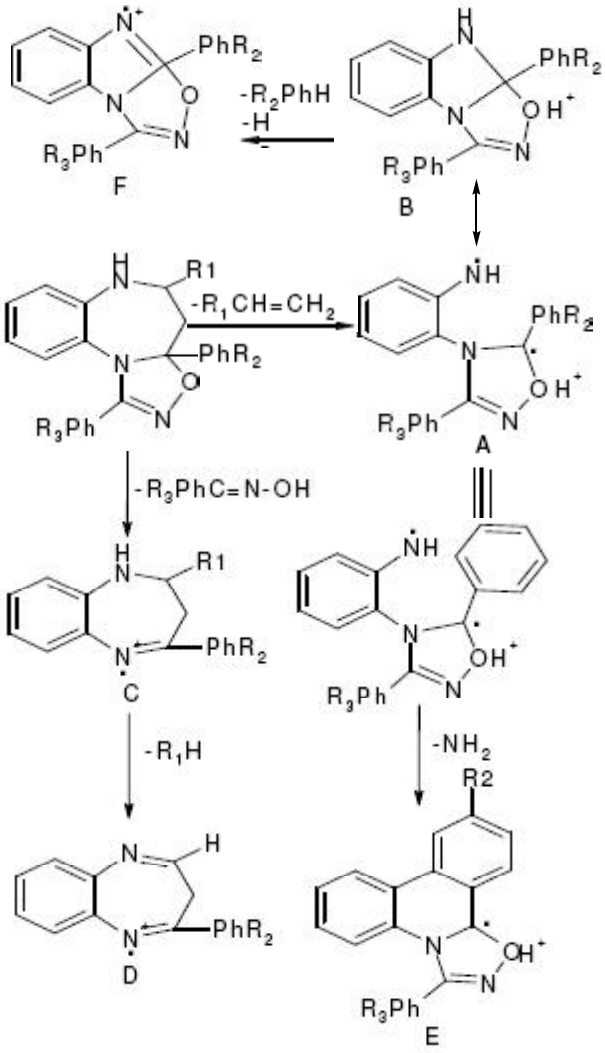
Compound	MH^+	A or b	C	D	E	F
1	418	314	298	220	298	235
2	448	344	328	250	328	235
3	452	348	332	254	332	235
4	448	314	328	220	298	235
5	496	314	376	220	298	235
6	525	422	328	250	376	343
7	526	393	328	220	406	343

Compound **174(4)** is now taken as an example to describe the fragmentation mechanism of the seven compounds. The data from the MIKE analysis of compound **174(4)** are listed in TABLE 3.

TABLE 3: MIKE spectra of compound (4)

Precursor ions (m/z)	Fragments ions (m/z)
448(MH^+)	314(A or B), 328 (C)
314 (A or B)	298(E)
298 (E)	282(G)
328(B)	220(D)

The title compounds show low intensity $[M+H]^+$ ions with 2-27% relative abundances and $[MHR_1CH = CH_2]$ ions with 2-19% relative abundances. The $[MH^+ - R_1PhCH=CH_2]$ ion further yielded benzimidazole ion and other important ions[61]. The fragmentation pathways of the title compounds may be proposed as shown in a SCHEME 1.



SCHEME 1 : Fragmentation pathways proposed for title compounds

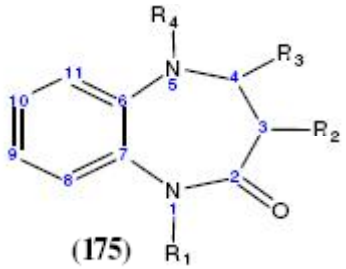
^{13}C NMR study of 1, 5- benzodiazepines-2-one

Benzodiazepines derivatives are well described heterocycles as they have found applications as an important class of therapeutic agents. The ^{13}C-NMR Spectra were obtained at 25.142 MHz on a Tesla BS 567 A spectrometer operating in the Fourier Transform mode. An ADT 1400 computer was used. Spectra were measured as 100 mg/ml solution in DMSO-d_6 with TMS as internal standard[62]. Samples were spun in 10mm o. d. tubes at 35°C.

Spectra were recorded under the following conditions.

- Spectral width 7600 Hz using 30° pulses.
- Size of data table 16K
- Pulse repetition time 3s and 3000 transients were averaged for ^{13}C-NMR spectra and 8000 for GD and off-resonance experiments.

^{13}C NMR spectral data for five tetrahydro-1, 5-benzodiazepine-2-one **(175)** are reported and chemical shift assignments are discussed[63].



(175)

TABLE 4 : Value of substitution on above benzodiazepine

No.	1	2	3	4	5	6	7	8	9
R_1	H	H	H	H	H	H	H	COMe	Ch_2Ph
R_2	H	H	H	H	Me	H	H	H	H
R_3	H	Me	H	Me	H	H	Me	H	H
R_4	H	H	COH	COH	COH	COMe	COMe	COMe	COMe

The ^{13}C-NMR spectral data of 1, 5-benzodiazepine are given in TABLES 5 and 6. The ^{13}C resonances were assigned on the basis of chemical shift theory, signal intensities and consistency arguments with respect to the spectra of the suitable model compounds. Multiplicities of the coupled carbon signals assisted in the assignment of resonances of the aromatic region. The observed splitting due to coupling with protons at N-1 and N-5 made it possible to distinguish the C-6 and C-9 resonances from those of C-7 and C-8 and C-10 from C-11. The hindered internal rotation around the hexacyclic C- N bond in 3-5 leads to E-Z isomers with an approximate intensity ratio of 11:1. The influences on ipso (C-11), *ortho* (C-6, C-10), *meta* (C-7, C-9) and *para* (C-8) carbons due to N-formulation or N-acetylation in 3, 4, 6 and 7 is similar to that in other aromatic compounds[64].

TABLE 5: ^{13}C NMR chemical shifts (ppm) of compounds (1-5)

Carbon	1	2	3	4	5
C-2	173.12	171.42	171.23	170.67	173.57
C-3	36.12	41.63	32.24, 33.59	39.56	34.07,35.59
C-4	44.24	53.04	44.93 48.13	52.47 55.91	52.41 55.71
C-6	118.23	119.25	127.15 129.01	128.68 130.69	127.25 129.38
C-7	124.42	124.28	125.32 124.45	125.18 124.84	125.42 124.84
C-8	119.23	120.13	128.64	128.88	128.45
C-9	12.06	121.23	121.98	122.04	122.44
C-10	126.23	127.83	135.53	136.76	135.66
C-11	139.23	139.17	131.44, 130.15	129.97	132.26

TABLE 6: ^{13}C NMR chemical shifts (ppm) of compounds (6-9)

Carbon	6	7	8	9
C-2	171.54	171.04	171.99	170.37
C-3	33.04	40.36	35.33	32.65
C-4	46.46	53.04	45.09	47.15
C-6	128.62	128.07	129.11	128.48
C-7	125.01	125.07	135.41	126.79
C-8	129.45	130.68	129.11	129.79
C-9	122.56	122.90	129.11	123.99
C-10	136.64	137.33	128.56	139.02
C-11	133.29	131.33	136.31	134.87

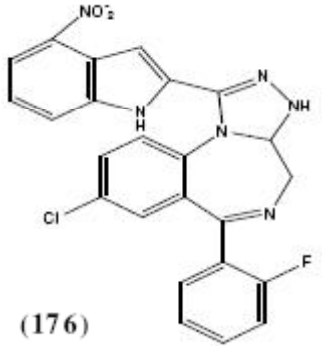
Biological evaluation

The benzodiazepines are broadly divided in to various classes according to the position of N-atom in seven membered ring discussed already in introduction. The different types of benzodiazepines have exhibited the following different type of biological activities.

Anticonvulsant agents

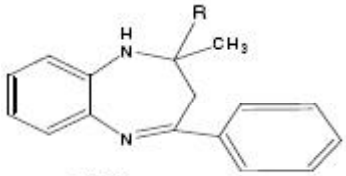
The different substituents of benzodiazepines have the anticonvulsant activity.

a. B. Narayana et al[65] has synthesized some new substituted triazolo [4, 3-a] [1, 4] benzodiazepine derivatives **(176)** as potent anticonvulsants.



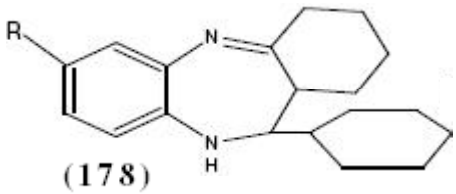
(176)

b. Adrienn Hegedus et al[66] reported anticonvulsants activity of different types of 1, 5-benzodiazepine derivatives **(177)**.



(177) R= -C6H5 ,- CH3, -C6H4Cl

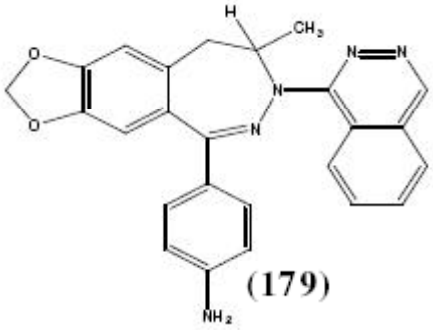
c. D. V. Jarikote et al[67] synthesized a series of 1, 5-benzodiazepine derivatives (178) under ambient condition possessing more potent anticonvulsants activity.



(178)

R= H, -CH3,-Ph,-CH(CH3)2

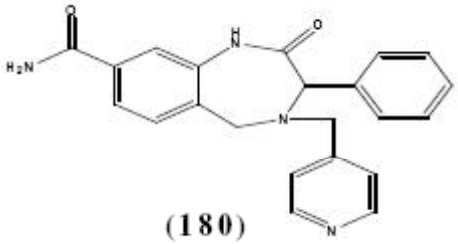
d. David Lodge et al[68] synthesized and reported anticonvulsants activity of 3-aryl -5H-2, 3-benzodiazepine **(179)** as AMPA antagonists.



(179)

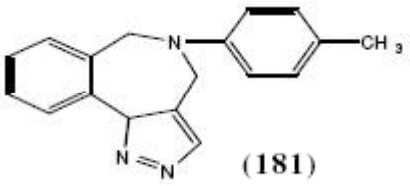
Antianxiety agents

a. Hossain Saneii et al[69] synthesized has solid-phase of tetrahydro-1, 4-benzodiazepine-2-one derivative **(180)** and reported their antianxiety activity.



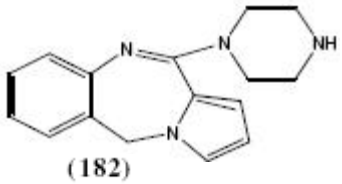
(180)

b. Aurelia Pastor et al[70] synthesized a new modular and flexible approach to [1,2,3] trizolo[1,5-a] [1,4] benzodiazepine **(181)** and evaluated their anxiolytic activity.



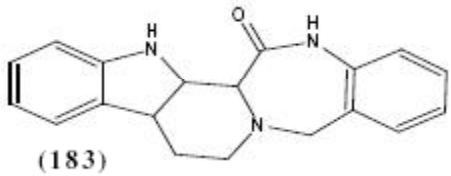
(181)

c. William B.Wright et al[71] synthesized derivatives of 1, 1- (l-piperazinyl)-5H-pyrrolo[2, 1-c][1, 4]benzodiazepine **(182)** as central nervous system agents possessing antianxiety activity.



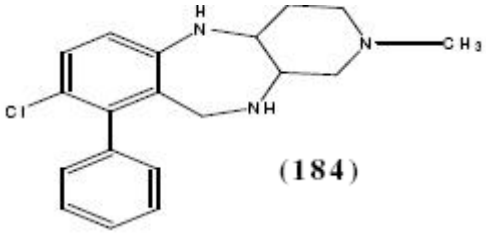
(182)

d. Jean Rossier et al[72] synthesized of β-carboline-benzodiazepine hybrid molecules (183) by using of the known structural requirements for benzodiazepine and β-carboline binding in designing a novel high-affinity ligand as required for the benzodiazepine receptor.



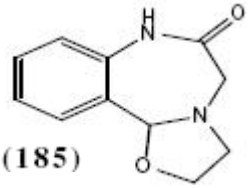
(183)

e. R. G. Smith et al[73] synthesized certain 7-substituted 1, 2, 3, 4, 4a, 5-hexahydropyrazinolo [2-a][1, 4]benzodiazepines **(184)** and reported their antianxiety activity.



(184)

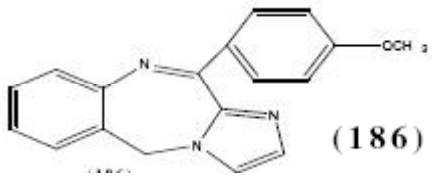
f. Tetsuaoii Yadera et al[74] synthesized and tested pharmacological activity of 1, 4-benzodiazepin-2-one [5, 4-b] oxazole **(185)** derivatives containing anxiolytic activity.



(185)

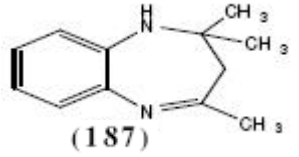
Antidepressant agents

a. Laura Zorzin et al[75] synthesized 11-aryl-5-H-imidazo [2, 1-C] [1,4] benzodiazepine **(186)** and their A-1 adenosine binding activity as antidepressants.



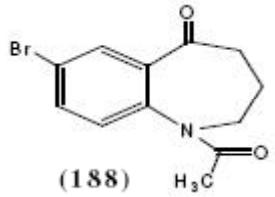
(186)

b. Gopal Das et al[76] synthesized a superstructure of organic salts of a 1, 5-benzodiazepine derivative **(187)** as antidepressants activity.



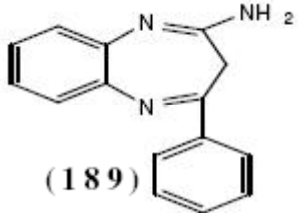
(187)

c. A.N.Osman et al[77] synthesized 1, 4-benzodea zepine derivative **(188)** and evaluated their pharmacological activity as antidepressant.



(188)

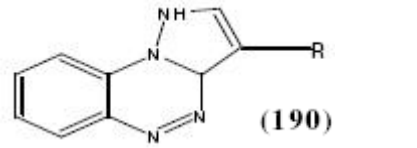
d. Arni Miller et al[78] has synthesized and evaluated for biological activity of some 2-amino-4-aryl-3H-1, 5-benzodiazepine **(189)** analogues of clozapine as antidepressant agents.



(189)

Sedative and hypnotic agents

a. Martini[79] has synthesized and evaluated pharmacological activity of 3, 7 and 8- substituted [5, 1-C] [1, 2, 4] benzotriazine derivative **(190)** as benzodiazepine receptor ligands.

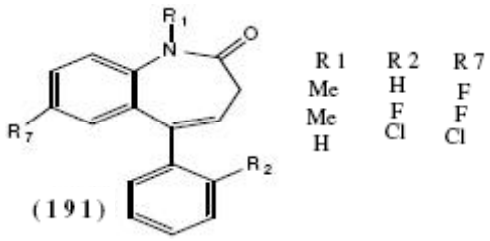


(190)

R = -Me,-Et,-C02Me, -COMe

Muscle relaxants

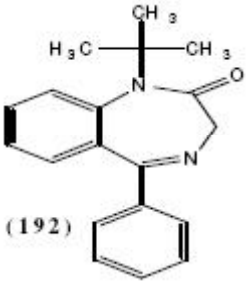
a. Mamta Thakur et al[80] studied comparative QSAR and QPAR study of benzodiazepines derivatives **(191)** as muscle relaxant activity.



R 1	R 2	R 7
Me	H	F
Me	F	F
H	Cl	Cl

(191)

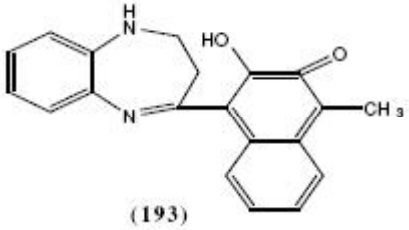
b. Perry Rosen et al[81] reported atropisomers of 1, 4-benzodiazepines and synthesized diazepam related -1, 4-benzodiazepine **(192)** as muscle relaxants.



(192)

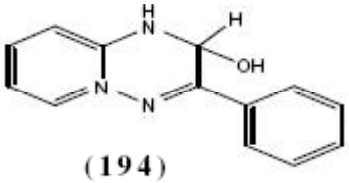
Anti-cell proliferation

a. K.Sucheta and B.Vittal Rao[82] reported 4-hydroxyqainolin-2(1H) derivative of 1, 5-benzodiazepine **(193)** as human prostrate carcinoma and tyrosine kinase inhibitor.



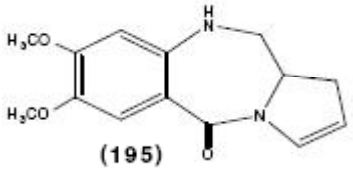
(193)

b. Julianna Kardos et al[83] reported cell proliferation activity *in vitro* of novel triazine derivatives **(194)** with benzodiazepine receptors.



(194)

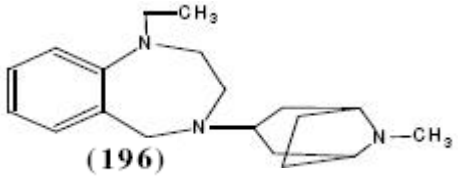
c. David E.Thurston et al[84] has synthesized a novel C-2-aryl pyrrolo [2, 1 -c]-1, 4- benzodiazepine (**(195)**, PBD) PBD dimers possessing significant *in vitro* cytotoxicity and in some cases, *in vivo* anti tumor activity.



(195)

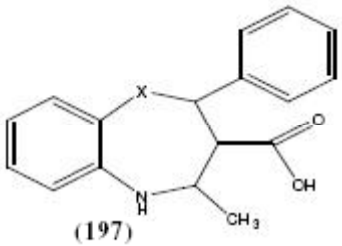
Antihypertensive agents

a. S.Arche et al[85] has synthesized-1-ethyl-4-(3-tropanyl)-tetrahydro-1H-1 and benzodiazepine **(196)** and evaluated their antihypertensive activity.



(196)

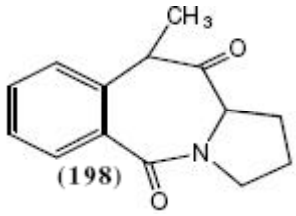
b. Suzanne M.et al[86] synthesized and reported anti-hypertensive activity of novel calcium channel blockers:-2, 5-dihydro-4-methyl-2-phenyl-1, 5-benzothiazepine-3-carboxylacid esters (197, x = S) and 2, 5-dihydro-4-methyl-2-phenyl-1, 5-benzo-diazepine-3-carboxylic acid esters (X = N).



(197)

Anti-inflammatory agents

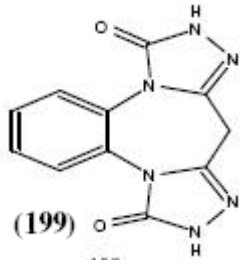
a. Herbert J. Brabander et al[87] synthesized derivatives of 1,2,3,4-tetrahydro-5H- pyrrolo [2, l-c][1, 4]ben-zodiazepine-5,11(10H)–dione **(198)** as anti-inflam-matory agents.



(198)

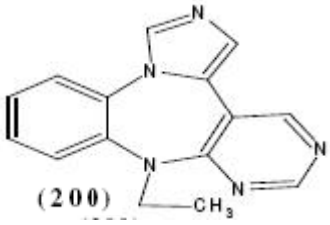
Anti-HIV-1-activity

a. Flavio Rocco et al[88] synthesized 9H-bis (1,2,4,7-triazolo)(1,5) benzodiazepine **(199)** and evaluated there HIV-1 reverse transcriptase inhibitor activity.



(199)

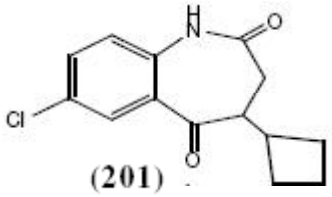
b. Laura Vargiu et al[89] reported HIV-1-protease in-hibitory activity of tricyclic and tetracyclic -1, 5- ben-zodiazepine derivatives **(200)**.



(200)

Herbicidal activity

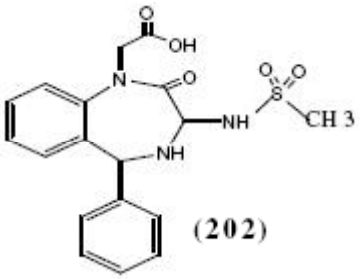
a. Pierre Marc et al[90] synthesized 1, 4-Benzodiaz-epine-2, 5-diones **(201)** and reported its herbicidal activity.



(201)

Anticoagulant agents

a. Daniel Dumas et al[91] synthesized a new 3-[(sulfo-nyl aryl)-amino]-1,4-benzodiazepine-2-one **(202)** derivatives as -thrombin inhibitor.



(202)

Microreview

Biological screening

- Antidepressant and anxiolytic activity .
- Anticonvulsant activity .

Antideppressant and anxiolytic activity

Animals required: Male albino Swiss mice 25-30 g (despair test)
Male Sprague-Dawley rats 200-250 g (social interaction test)

(a) Despair Test

As described by Porsolt et al[92,93] the animals were forced to swim inside a plexiglass cylinder containing water, and the total duration of immobility in a period of 5 min test was recorded. Antidepressants decreased the duration of immobility. Test compounds were injected intraperitoneally (i. p.) 1hr before evaluation of the mice, and repeated administration once a day for 1 week.

(b) Social interaction test

The method was based as described by File et al[94,95]. The tests are consisted of a white open-topped box (55 ×55 30 cm^3) with a 100 W lamp 50 cm above the box floor. The behavior of pairs of rats was observed over a 10 min test period, and the time spent in social interaction (following, sniffing, crawling, tumbling, boxing, grooming) was recorded. Such increases in social interaction are considered to be predictive of anxiolytic activity. The compounds were administered i. p. 1h before the test.

(c) Rotorod test

The activity of the drug interfering with motor coordination is checked by this Rotarod test[96]. In this test, mice (20-25 gm) are trained to stay on the rotating rod. Rod is rotated by 10 rotations/ min, at its diameter of 3.2 cm. Only those mice are taken for the test, which can stay on the revolving rod for at least one minute. Then test compounds are injected intraperitonialy at a dose of 25 mg/kg. Neurotoxicity is indicated by the inability of the animal to maintain equilibration on the rod for at least 1 min.

(d) Elevated plus-maze apparatus

Elevated plus-maze apparatus is a simple apparatus to study anxiolytic response of almost all type of antianxiety agents. Exposure of the animals to the novel maze alley evokes an approach-avoidance conflict, which is stronger in open arm as compared to enclosed arm. When the animal is placed on the maze they show a preference for the enclosed arms the animals enter open arm, showing anxiety, then freezing, become immobile, defecation and show fear-like movements on entering the open arms[97].

Ethanol potentiation test

Mice are treated with the test compound (2.5 g/kg i.p) and 1h later with ethanol. This dose of ethanol did not induce lateral position in the control animals. The number of mice that were in the lateral position after receiving ethanol in each group was determined[98,99].

Anticonvulsant activity

Maximal electroshock seizure method

The solution of standard drug and test compounds are prepared in propylene glycol. Phenytoin 25mg/kg) and test compounds (25mg/kg) are then administered intraperitonially.

Standard drugs and test compounds

Phenytoin 25mg/kg i.p.
Test compounds 25mg/kg i.p.

Equipment: Electroconvulsiometer.

Methodology: MES test method (Maximal electroshock seizure method) is employed for anticonvulsant activity of the synthesized compounds[100]. The compounds are screened for their anticonvulsant activity by electroshock seizure method, and subjected to supra maximal electroshock of 50mA, 60Hz alternating current from a convulsiometer for 0.2 sec through a pair of electrodes attached to each ear. The duration of the tonic hind limb extensor phase, clonic phase and the number of animals protected from convulsions were noted.Phenytoin (20mg/ kg) is used as standard drug.

(b) PTZ animal model

Pentylene tetrazole (PTZ) produces clonic convulsions in rats or mice, which are prevented by drugs effective in absences seizures activity. In this model, represent action on seizures focuses itself. PTZ (Sigma Chemicals, USA) was used to produce convulsion and diazepam (Ranbaxy Laboratories, India) was used as

a standard drugs dissolved in 2% gum acacia suspension[101].

Convulsion was induced 1 hour after the administration of the standard drug or the test compounds by i.p. injection (80mg/kg) dissolved in saline to a volume of 0.1ml/10gm body weight. The time needed for the development of unequivocal sustained clonic seizure activity involving the limbs (isolated myoclonic jerks or other preconvulsion chewing behavior is not counted) was carefully noted. Duration of seizure was also noted. Seizure free duration for a period of 1hr was taken as protection. The number of animals protected in each group was recorded and percent protection was calculated[102].

Other methods by which, one can check the anticonvulsant activity-:

a. Subcutaneous Metrazole threshold test.
b. Subcutaneous Picrotoxin threshold test.
c. Subcutaneous Strychnine threshold test.
d. Subcutaneous Bicucullline threshold test.

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