Current Scenario of 1,4-Diazepines as Potent Biomolecules-A Mini Review

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Abstract: The aim of this review is precisely to give a comprehensive account of the large volume of work carried out on 1,4-diazepines regardless of the degree of unsaturation in the diazepine system. This review mainly emphasizes recent work on the diazepines also including earlier work.

Key Words: Benzodiazepines, monocyclic diazepines, multifarious activity.

INTRODUCTION

The history of benzodiazepines as pharmacologically important agents started in 1960 when one of them, chlordiazepoxide (**1**), was introduced as a tranquilizer under the trade name Librium® [1]. Extensive structural modifications of this prototype compound resulted in numerous clinically effective and potent CNS depressants displaying superior pharmacological properties, for example, diazepam (**2**) [2]. Later, some interesting developments [3-7] in the area of benzodiazepines took place like, an additional heterocyclic ring fused to the different faces of the benzodiazepine ring nucleus as in alprazolam (**3**), oxazolazepam (**4**) and the replacement of the benzene ring by naphthalene [8] and different heterocycles (**5**) like thiophene [9-11], pyrrole [12-13], furan [14], imidazole [15], pyrazole [16-19], thiazole [20], furazan [21], pyridine [22-25], pyrimidine [26-27], pyrazine [28], indane [29], indole [30-31] and flavone[32]. In 1969 Hofmann and Safir had the interest to study the CNS depressant properties of monocyclic 1,3-dihydro-2*H*-1,4-diazepin-2-ones (**6, 7**) which are closely related to the benzodiazepines [33]. They found that none of the monocyclic diazepine compounds showed CNS depressant activity (Fig. **1**).

CHIRAL SYNTHESIS OF 1,4-BENZODIAZEPINES

The discovery of benzodiazepine receptors in mammalian brain tissue in 1977 led to a useful screening procedure for identifying compounds that interact with the receptor [34, 35]. Although the benzodiazepine ring exists as a pair of enantiomers, in case of diazepam it proved impossible to resolve the isomers. Gilman *et al.* were successful in resolving the enantiomers when the *N*-methyl group in diazepam was replaced by N^1-tert-butyl group (**8, 9**). These compounds represent the first example of optically active 1,4-benzodiazepines whose asymmetry is due only to conformational elements [36]. Herrero *et al.* reported new highly functionalized chiral 1,4-benzodiazepine derivatives (**10-13**) from amino acid-derived amino nitriles to obtain a variety of scaffolds of potential use in the search for peptidomimetics [37] (Fig. **2**).

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COMBINATORIAL SYNTHESIS OF 1,4-BENZODIAZEPINES

Researchers recognized the importance of 1,4-benzodiazepines in the arena of therapeutics after the entry of high throughput screening (HTS), a powerful screening technique to identify potential hits among large number of compounds in short time with the support of combinatorial chemistry to generate remarkable libraries of compounds. In 1992 Bunin and Ellman reported an expedient solid-phase synthesis of 1,4-benzodiazepine derivatives which is a critical step in the combinatorial synthesis of such compounds (Scheme **1**) [38]. This was followed by the Stille coupling reaction, a slightly modified solid-phase synthesis, to obtain variously substituted 1,4-benzodiazepines by Plunkett and Ellman in 1995 [39] (Scheme **2**). The limitation of commercially available 2-aminoarylketones was overcome in this method thus providing a plethora of 1,4-benzodiazepines. The technique of solid-phase synthesis was further exploited to generate a library of 1,4-benzodiazepine-2,5-diones and also for generalizing the synthesis of such compounds by Boojamra *et al.* in 1997 [40]. 1,4-Benzodiazepine-2,5-dione shows similar kind of pharmacological activity as observed for 1,4-benzodiazepine-2-one analogs. Earlier benzodiazepine libraries have limited diversity on the benzene ring, since the earlier library synthesis was achieved by the benzene moiety linked to the resin or the benzene moiety was introduced in building blocks such as anthranilic acids to give diversity [41]. Im *et al.* reported a successful parallel solid-phase synthesis of a tetrahydrobenzo[*e*][1,4]diazepin-2-one library with three points of diversity, namely N-1, C-3 and C-7 position as β-turn peptidomimetics (Scheme **3**) [42]. The β-turn has been implicated as an important conformation for biological recognition of peptides or proteins.

A last decade reports of benzodiazepines shows different pharmacological activity when a battery of diazepine compounds was screened for diverse pharmacological activities which were given below as subheads:

DIAZEPINES FROM NATURAL SOURCES

Liposidomycins (**14**) are a family of novel lipid containing nucleoside antibiotics that were found in the culture filtrate and mycelia of *Streptomyces griseosporous* [43, 44]. These classes of compounds have unique biological activity

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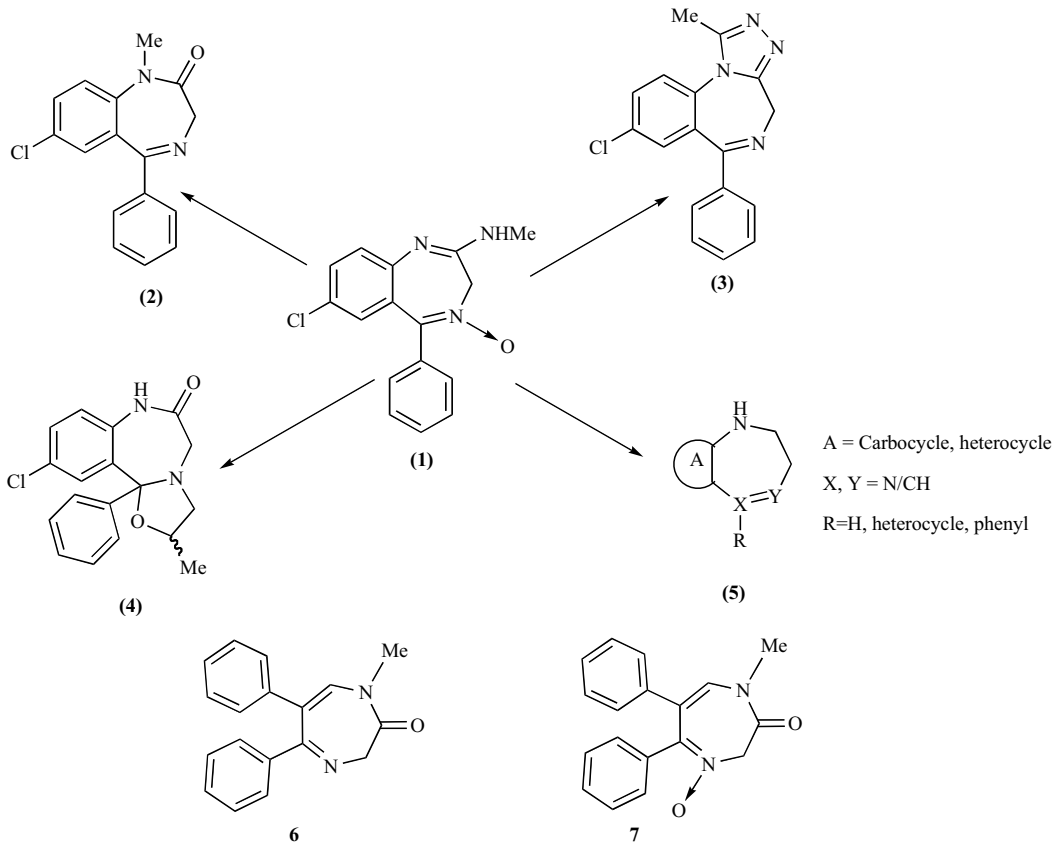


Fig. (1).

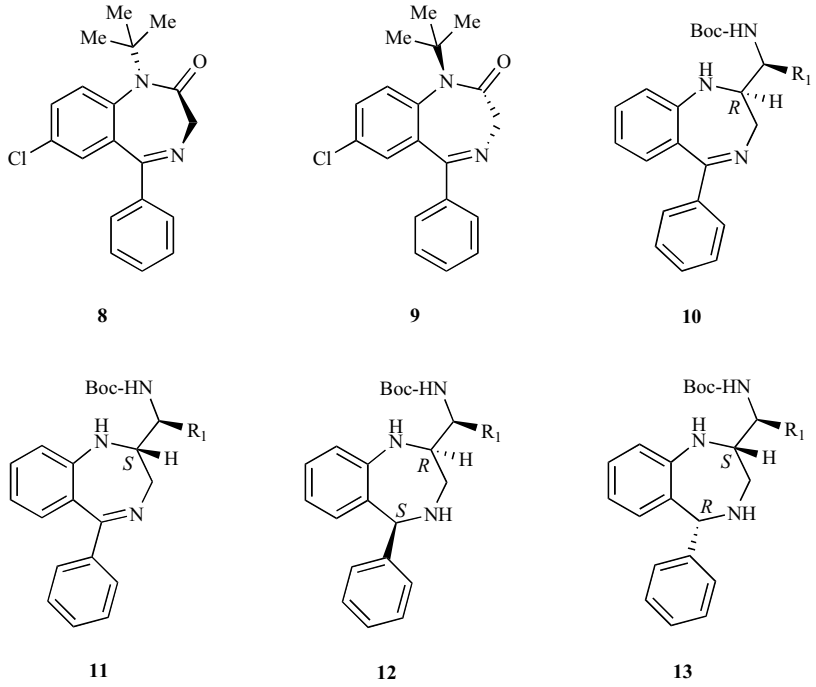
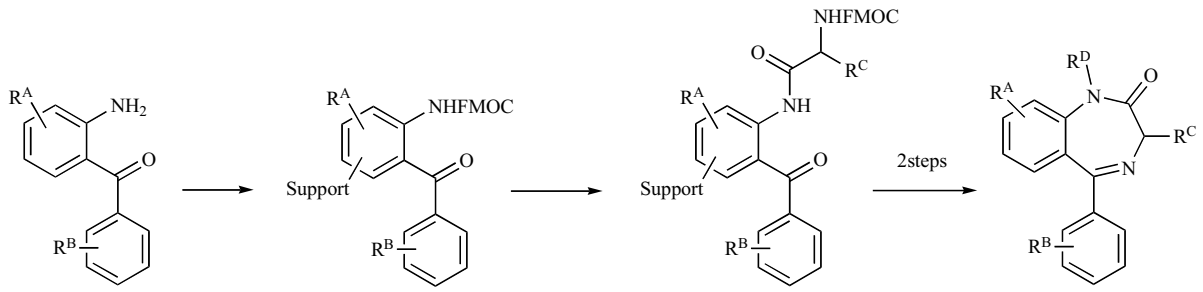
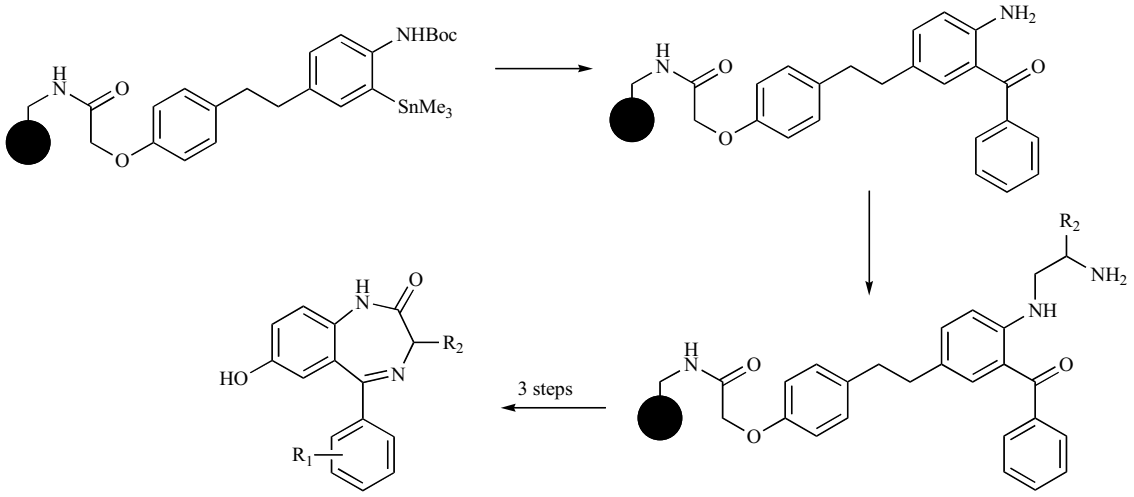


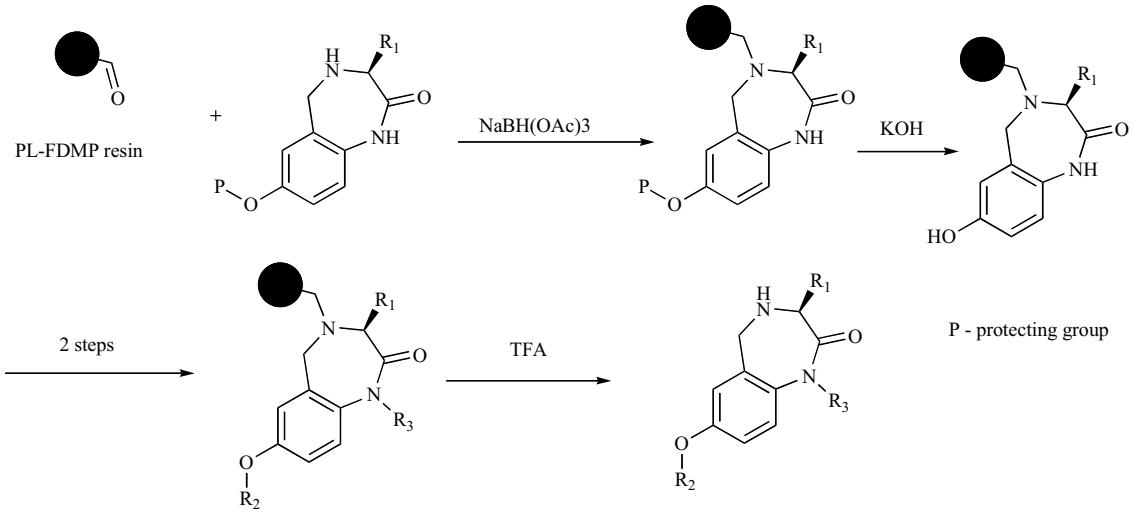
Fig. (2).



Scheme (1).



Scheme (2).



Scheme (3).

and structures; inhibit the formation of the lipid intermediate in bacterial peptidoglycan synthesis with three fold greater activity than tunicamycin including extremely high specificity. Asmarines A (**15**) and B (**16**) are marine alkaloids which are isolated from sponge Raspalila sp. [45], with an unique tertrahydro[1,4]diazepino-[1,2,3-g,h] purine structure. These alkaloids are cytotoxic to tumor cells like leukemic, brain tumor cells etc. Asperlicin (**17**) is a cholecystokinin receptor antagonist [46]. It is the first natural nonpeptide compound extracted from microbial source, *Aspergillus alliaceus*. The total synthesis of quinazolinodiazepine residue required for the CCK-A receptor agonist was reported by Szabo *et al.*

[47]. Benzomalvin A (**18**) isolated from a fungus culture of *Penicillium* sp, showed inhibitory activity against substance phospholipids of the guinea pig, rat and human neurokinin-1 (NK-1) receptors, respectively [48]. Sclerotigenin (**19**) was recently isolated from organic extracts of sclerotia of *Penicillium sclerotigenum*, a potential antiinsectan benzodiazepine alkaloid [49]. Recently, a new metabolite Circumadatin G (**20**) has been isolated from the fungus *Aspergillus ochracues*, which is an analog of Circumadatin F (**21**) and C (**22**) [50] (Fig. **3**).

DIAZEPINES AS NON NUCLEIC ACID INHIBITORS OF PROTEIN-DNA INTERACTIONS

Binding of antibodies to single- and double-stranded DNA present in the serum of systemic lupus erythematosus (SLE) patients leads to inflammatory response in kidney tissue (glomerulonephritis) often resulting in renal damage. Identification of DNA adherent to the glomerular basement membrane can anchor pathogenic anti-DNA to glomeruli, the sites of injury within kidney tissue [51]. Stevens *et al.* reported 1,4-benzodiazepine (anti-DNA monoclonal antibody) as a non nucleic acid inhibitor that blocks DNA recognition [52]. They used their combinatorial small- molecule library to identify inhibitors of a protein without precise knowledge either of the natural ligand or other known inhibitors. Among the library of compounds, compound (**23**) (Fig. **4**) showed 60% inhibition at 20 μM by the ELISA test.

1,4-DIAZEPINE AS NEURO PROTECTIVE AGENTS

Novel benzodiazepine derivatives of general structure (**24**) bearing a *Z exo* α, β-unsaturated side chain at position C-5, were designed using the lead compound GV 150526 A

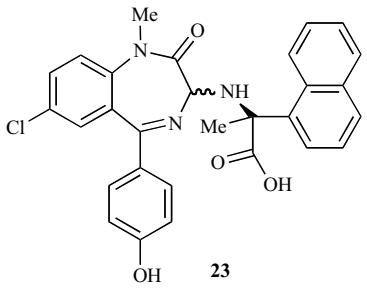


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Fig. (4).

(**25**) by receptor mapping techniques based on the known pharmacophore model of the glycine binding study [53]. The lead compound (**25**) reached phase III clinical trials in man as a potential anti-stroke agent. Zhou *et al.* reported *N, N'*-disubstituted piperazine and homopiperazine derivatives with the objective of developing high-affinity polyamine site ligands that either facilitate or reduce activity at *N*-methyl-D-aspartate (NMDA) receptors. The homopiperazine compounds (**26**) showed polyamine-like actions by enhancing [^{3}H]MK-801 binding to NMDA receptors which are greater than compounds (**27**) [54]. The activation of NMDA receptors required for the induction of long-term potentiation in hippocampus, a process involved with learning and memory [55]. Excessive activation of NMDA receptors contributes to neuronal cell death resulting from cerebral ischemia and other neurodegenerative disorders [56]. Uehata *et al.* reported fasudil (**28**) and hydroxyl fasudil (**29**) as the first small-molecule ROCK inhibitors [57]. Rho-Kinase (ROCK) inhibitors were identified for the potential treatment of vari-

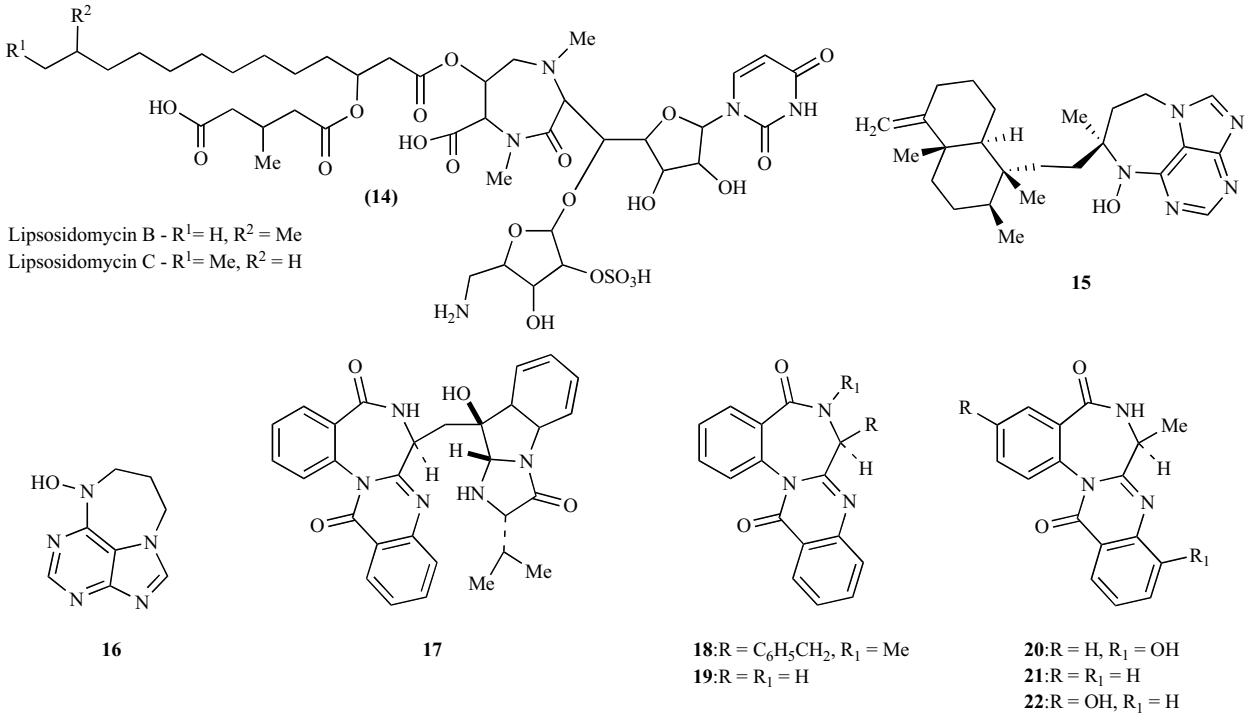

Fig. (3).

ous neurological disorders [58]. Dimethyl-fasudil (**30**) is the one of the most potent ROCK inhibitors emerged out from the optimization of the above fasudil derivatives. These compounds act as NMDA receptor antagonists in an excitotoxicity rat model. Originally, their mode of action was classified as intracellular calcium antagonism. Merour *et al.* reported pyrrolidobenzodiazepines (**31**) as pyrologlutamic derivatives which have potential in the treatment of diseases associated with cholinergic deficits as in the case of Alzheimer's disease [59] (Fig. **5**).

DIAZEPINES AS SELECTIVE NON-IMIDAZOLE HISTAMINE H_3-RECEPTOR ANTAGONIST

The H_3-receptor has been proposed to be a potential therapeutic target for cognitive disorders like attention deficit hyperactivity disorder and Alzheimer's disease [60]. Research is recently focused on the development of highly selective non-imidazole histamine H_3-receptor antagonists mainly because of the unfavorable drug-drug interactions involving imidazole compounds in multidrug therapy. Curtis *et al.* reported the selective non-imidazole H_3-receptor antagonists by incorporating the D-amino acid amides (**33**) into a potent biaryl homopiperazine motif (**32**) (Scheme **4**), a potent lead of H_3-receptor antagonists [61].

DIAZEPINES AS MMP INHIBITORS

The matrix metalloproteinases (MMP) are a family of zinc containing enzymes that have been implicated in the etiology of a wide variety of disease states including atherosclerosis, rheumatoid arthritis, osteoarthritis and cancer [62]. The present need is to synthesize small molecules as inhibitors of MMP which also have the advantage of being orally bioavailable. Levin and coworkers found the conformationally constrained hydroxamic acid MMP inhibitors (**34**) which encompass diazepine ring system [63] (Fig. **6**).

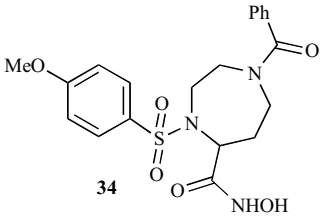

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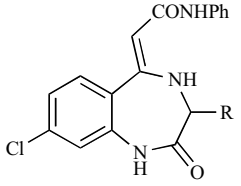
Fig. (6).

DIAZEPINES AS $5HT_3$-ANTAGONISTS

$5HT_3$-antagonists are clinically used as antiemetics in cancer chemotherapy. DAT-582 (**35**) is the most potent $5HT_3$-



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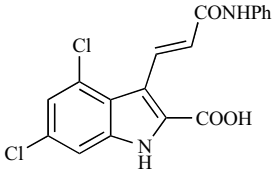

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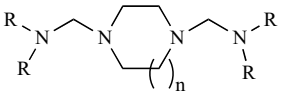
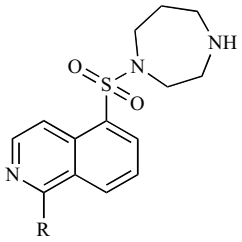
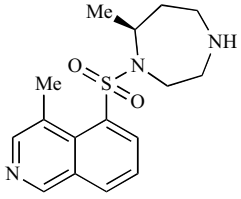


26: n = 2, **27**: n= 1
R = H, alkyl



28: R = H, **29** : R = OH



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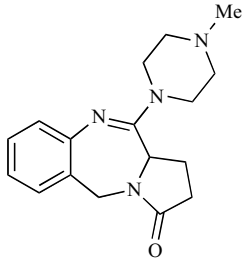

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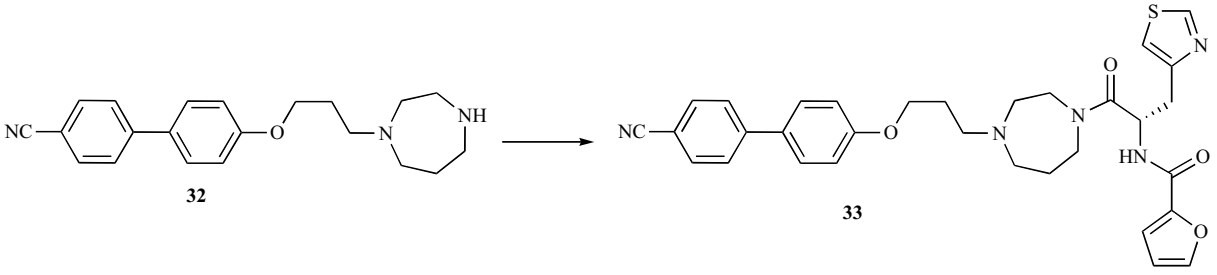
Fig. (5).



Scheme (4).

receptor antagonist and is selected as a promising candidate for potential clinical use [64]. Recent reports from the same laboratory show that by keeping the homopiperazine ring (**36**) constant and replacing the heterocyclic core by different aryl/hetero aryl system produced potential serotonin $5HT_3$ and dopamine D_2 receptor antagonits. These are effective against cisplatin induced emesis in ferrets and morphine induced emesis in dogs [65]. Liegeois *et al.* reported new pyridobenzodiazepines (**37**) with variation of basic chain at C-6 position and evaluated them for their binding to dopamine (D_2) and serotonin (5-HT_{2A}) receptors [66] (Fig. **7**).

DIAZEPINES WITH TRYPANOCIDAL ACTIVITY

A series of conformationally restricted congeners of pentamidine in which the flexible pentyl bridge of pentamidine was replaced by trans-1,2-bismethylene cyclopropyl, phenyl, pyridinyl, piperazinyl, piperidiny and homopiperazinyl groups were reported (Fig. **8**). The compounds were evaluated for trypanocidal activity. The nature of the linker influenced the DNA binding affinity as well as the trypanocidal activity of the compounds. Among the different linkers, homopiperazine linker containing compound N,N-Bis(4-amidinophenyl) homopiperazine (**38g**) was the most potent trypanocide [67]. Human African trypanosomiasis or sleeping sickness is caused by a subspecies of the parasitic hemoflagellate *Trypanosoma brucei*.

DIAZEPINES AS CHOLECYSTOKININ (CCK-A & B) RECEPTOR AGONISTS/ANTAGONISTS

Researchers believed that the benzodiazepine fragment of asperlicin contributes to the development of cholecystokinin receptor agonists. As a result, numerous CCK compounds encompassing the benzodiazepine analogues are available in literature. Bock and coworkers isolated the 3-(*S*)(-)-Amino-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4- benzodiazepine-2-one

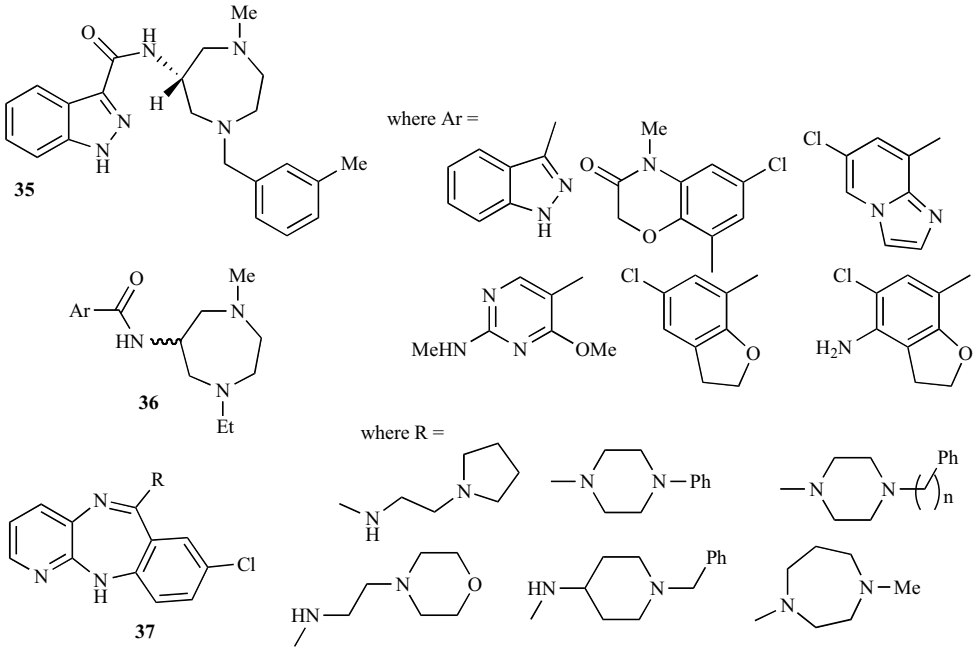


Fig. (7).

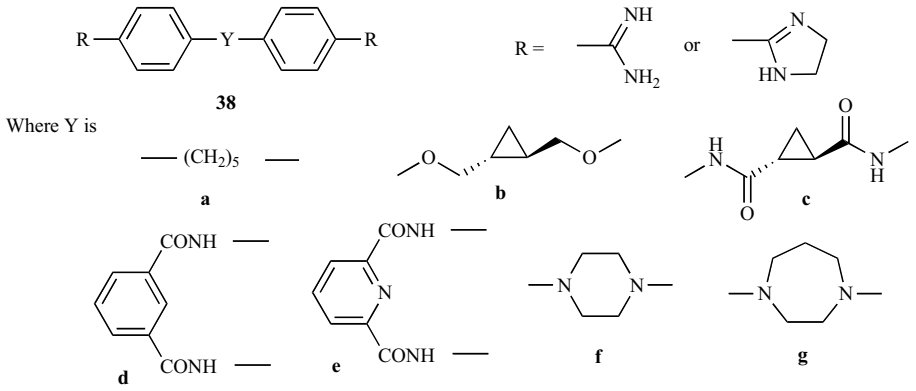


Fig. (8).

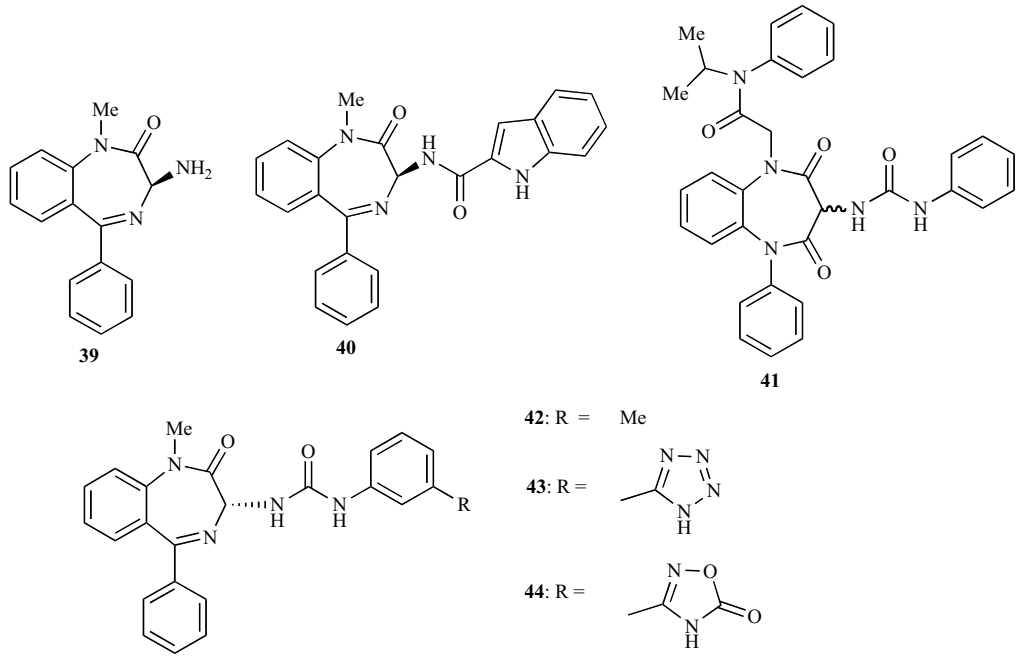


Fig. (9).

isomer (**39**), the key intermediate for the syntheses of specific nonpeptide cholecystokinin antagonist (**40**) [68]. Aquino and co-workers reported the compound (**41**) as a CCK-A agonist on the isolated guinea pig gallbladder [69]. CCK-A (alimentary) receptors are primarily located in the gut where they mediate pancreatic enzyme secretion, gallbladder contraction, gastric emptying and intestinal motility [70]. Some of 1,4-benzodiazepines are also reported as CCK-B receptor antagonists. CCK-B (brain) receptors are widely distributed in the CNS and they are thought to be involved in the modulation of anxiety, panic disorder, depression, nociception and satiety [71]. L-36526 (**42**) has been reported among the first generation of CCK-B receptor antagonists. The second generation CCK-B receptor antagonist has high selectivity towards CCK-B receptor derived by incorporating acidic or basic solubilizing functionalities in the phenyl ring [72]. Compounds containing tetrazole (**43**) and 1,2,4-oxadiazolone (**44**) (Fig. **9**) showed excellent potency, selectivity and solubility to cross the blood-brain barrier.

DIAZEPINES AS ANALGESIC AGENTS

The earlier diazepine analog, tifluadom (**45**) had negligible effects upon classical central benzodiazepine receptors, but showed high affinity for the κ-opioid receptor and caused antinociception in several animal models [73]. Unfortunately tifluadom is also a cholecystokinin (CCK) antagonist and several studies indicate that agonists and antagonists of the CCK receptors can interfere with the actions of opioids [74]. Recent studies available in literature were to separate the various opioid and CCK components in tifluadom analogs. As a result, compound (**46**) with lower affinity for the CCK receptors, exhibits a greater CCK-A/κ selectivity ratio [75]. Recently, Toma and co-workers synthesized pyridazinylhomopiperazine derivative (**47**) (Fig. **10**) as a nicotinic agent, which is selective as a neuronal nicotinic acetylcholine receptor agonist (nAChR) [76]. These agents are useful in the treatment of both acute and chronic pain without the side effects of drug dependence.

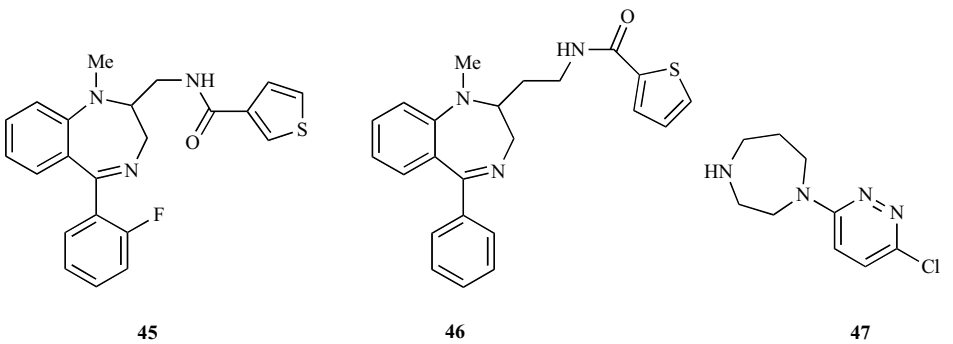


Fig. (10).

INDOLODIAZEPINES

A considerable proportion of diazepines with condensed indole systems as compared to any other heterocycles are available in literature. These compounds were reported to be useful for various CNS disorders and as muscle relaxants [77-79]. Hiremath *et al.* synthesized a series of indolo[3,2-*b*][1,4]-benzodiazepines (**48**). The compounds were screened for antimicrobial activity against *E.coli* and *Staphylococcus aureus*. These compounds depicted moderate activity against both organisms with 14-20 mm and 12-20 mm inhibition, respectively [80]. Hendi *et al.* reported 2,3,4,5-tetrahydro-1*H*-1,4-diazepinoindoles as serotonin antagonists (**50**). These compounds emerged out because of their interest to study the effect of 1-(3-aminopropyl)indoles (**49**) as antimicrobial agents [81]. Brzechffa *et al.* found the benefit of indolodiazepines as starting material to synthesize new analogs of diaza heterocycles (**51**) *via* β-elimination reaction [82]. Duncan and coworkers investigated some novel ring systems which resulted in benzodiazepine type structures (**52**) for CNS activity [83]. Garcia *et al.* reported the synthesis of indolo-1,4-diazepine-2,5-diones (**53**) [84] which are analogs of benzodiazepine-2,5-dione (Fig. **11**).

Glycogen Synthase Kinase-3 (GSK-3) Inhibitors

GSK3 is an attractive target for the potential treatment of Type 2 or noninsulin-dependent diabetes mellitus (NIDDM) [85]. The inhibitors of GSK3 would be expected to have some of the common effects of insulin, such as its ability to activate glycogen synthase and stimulate the conversion of glucose to glycogen, thereby lowering plasma glucose. Compound (**54**) is the most potent of the series with an IC_{50} value of 0.0011μM against GSK-3β kinase [86] (Fig. **12**).

Selective Phospodiesterase Type 4 Inhibitors (PDE4)

PDE4 is a potential molecular target for the development of new antiasthmatic and antiinflammatory drugs. Burnouf *et al.* found some diazepinoindole derivatives (**55, 56**) (Fig. **13**) as anti-inflammatory and antiasthmatic agents with reduced side effects by high-throughput screening in PDE4 isoenzyme mixture obtained from the U937 human cell line [87].

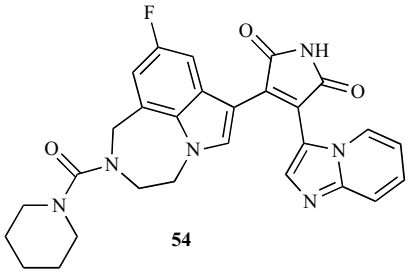


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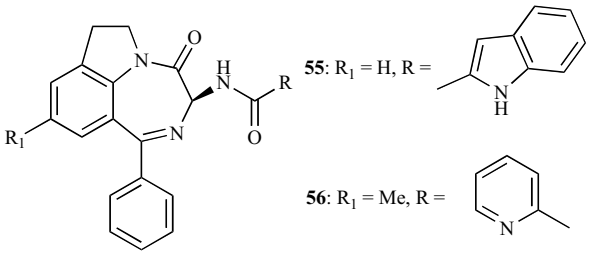
Fig. (12).



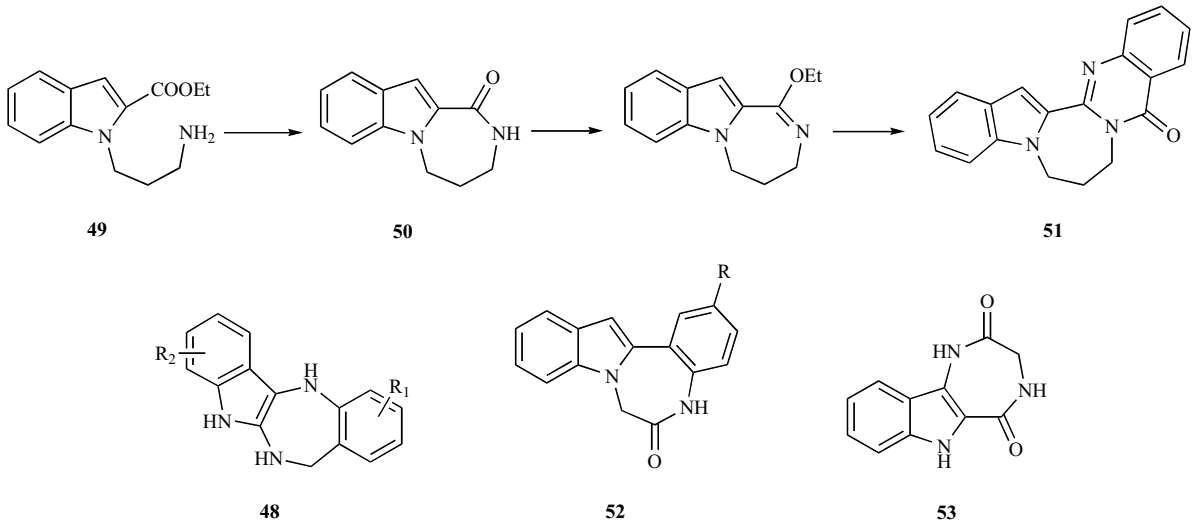
55: R_1 = H, R =

56: R_1 = Me, R =

Fig. (13).

IMIDAZODIAZEPINES AS ADENOSINE RECEPTOR ANTAGONISTS

The prototypic xanthines, theophyline, theobromine and caffeine are not particularly potent adenosine receptor antagonists. But their cyclic homologs, the imidazodiazepinediones (**57**) (Fig. **14**) have potent adenosine receptor antagonist activity and show selectivity for A_1 adenosine receptor [88]. Also, they have low affinity for brain benzodiazepine receptors.



49 **50** **51**

48 **52** **53**

Fig. (11).

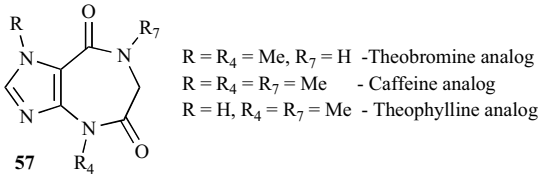


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Fig. (14).

DIAZEPINES AS ANTIPROLIFERATIVE AGENTS ACTING BY VARIOUS MECHANISMS

By Activation of p53

A very recent report among the 2,5-benzodiazepinediones (**58, 59**) is low-molecular weight antagonists of HDM2. p53 is a transcription factor that regulates genes which can induce either cycle arrest or apoptosis [89]. In human cells, p53 activity is normally modulated by HDM2; the homologue of murine MDM2. HDM2 binds to and blocks the p53 transactivation domain, preventing the transcription of p53 target genes [90]. Researchers found benzodiazepinedione to be a potential hit by screening a library of 38,000 compounds by high-throughput screening. The X-ray crystal structure of improved antagonists bound to HDM2 mimicked by neutralizing antibodies and p53 peptides. The optimized molecules increase the transcription of p53 target genes and decrease proliferation of tumor cells expressing wild-type p53. Raboisson *et al.* reported 1,4-diazepine-2,5-dione (**60**) (Fig. **15**), as bioisosters of benzodiazepine-2,5-dione scaffold, mimicking the α-helix of the natural p53 protein with respect to the HDM2 binding interaction [91].

Regulation of Retinoidal Actions by Diazepinylbenzoic Acids

Retinoids have potential chemopreventive and therapeutic applications in the field of dermatology and oncology [92]. The recent reports show that the diazepinylbenzoic acid derivatives can exhibit either antagonist or synergistic effects on the differentiation–inducing activities of natural or synthetic retenoids in human HL-60 promyelocytic leukemia cells. The activity is depending largely on the nature of the substituents on the diazepine ring. Compound (**61**) and (**62**)) showed antagonistic and synergistic activity, respectively [93] (Fig. **16**).

Diazepine as Peptidomimetic Inhibitor of Caspase- 3

To date, eleven (11) human caspases have been identified. Among them, Caspase-3 is reported to play the role of a major executioner in cell death by a variety of pro-apoptotic stimuli [94].

The development of small molecule inhibitors of caspases as therapeutic agents has been a target of intense research [95]. The researchers adopted the diazepine nucleus for the construction of the peptidomimetic agents (**63**) (Fig. **17**).

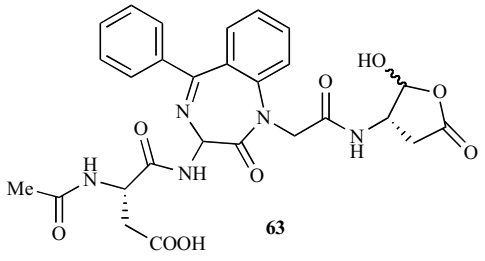

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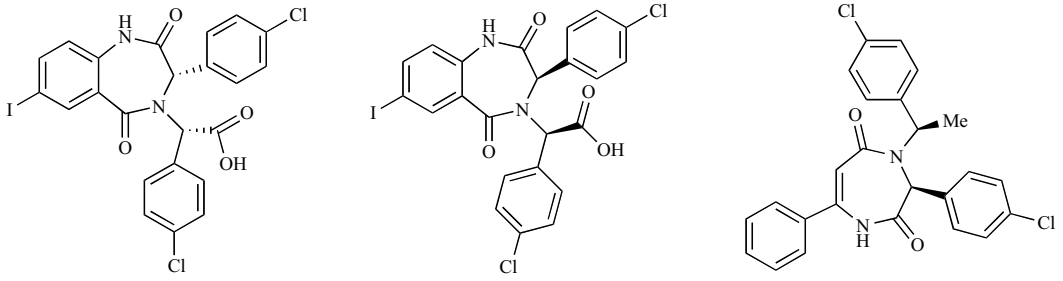
Fig. (17).

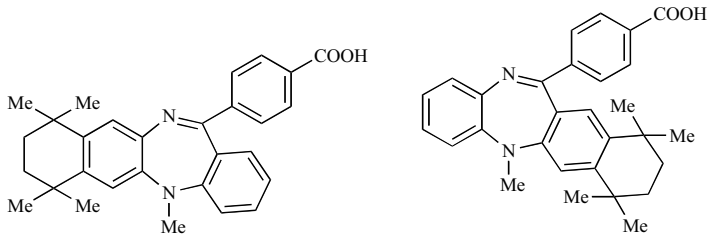
PBD Analogs as Antitumoral Agents

Pyrrolobenzodiazepine (PBD) types of antitumor antibiotics are produced by various *Streptomyces* species with



58 **59** **60**

Fig. (15).



61 **62**

Fig. (16).

family members including tomaymycin (**64**), anthramycin (**65**), sibiromycin (**66**), neothramycins A (**67**) and B (**68**) and DC-81 (**69**) [96] (Fig. **18**). PBDs are of considerable current interest due to their ability to recognize and subsequently form covalent bonds to specific base sequences of double-stranded DNA [97]. Such monofunctional alkylating compounds have potential therapeutic application in cancer treatment and as selective anti-infective agents [98]. Extensive studies have been carried out on PBDs and their antitumor activity has been established (Fig. **19**). Lisowski *et al.* reported new aromatic pyrrolobenzodiazepines (**70, 71**) which showed antiproliferative activity against the L1210 leukemia cell lines at 0.35 μM [99]. The earlier reports from the same laboratory reported some other analogs of pyrrolothienodiazepine (**72, 73**) for the same activity [100, 101]. The thiophene ring of pyrrolothienodiazepine was replaced by a furan ring (**74**) [102]. They extend their molecular manipulation on PBD analog by replacing the pyrrole ring of pyrrolo benzodiazepines (PBD) with a thiazole (**75**). The authors also reported tetracyclic diazepine derivative of thiazolobenzodiazepine (**76**) for the same therapeutic purpose [103]. In 2002, Shafiee *et al.* synthesized a series of compounds by replacing the benzene ring of PBD by a thiazole ring (**77-79**) [104]. Clerici *et al.* synthesized some new heterocycle containing PBD analogs by replacing the benzene with an indole (**80**) and a benzofuran (**81**) [105].

A very recent outcome of PBDs analogs is the synthesis of some heterocycles like pyrimidine and indole linked–PBD conjugates. These compounds are prepared with varying degrees of linker length in order to probe the structural requirements for optimal *in vitro* antitumor activity. The pyrimidine linked-PBD conjugates (**82**) with four carbon spacer exhibited promising *in vitro* anticancer activity in comparison to other analogues [106]. The PBD hybrids linked with indolecarboxylates (**83**) is described by Wang *et al.* [107]. These compounds were prepared by linking C-8 of (DC-81) with an indole 2-carbonyl moiety through carbon chain linkers to afford PBD hybrid agents. Preliminary *in vivo* tests show that these hybrid agents have potent antitumor activity. The cytotoxic studies of the hybrid agents on human melanoma A2058 cells indicate most of the hybrids induced higher cytotoxicity and better DNA binding ability than the parent compound DC-81 (**69**).

Tetrahydrobenzodiazepine as Farnesyltransferase (FT) Inhibitors

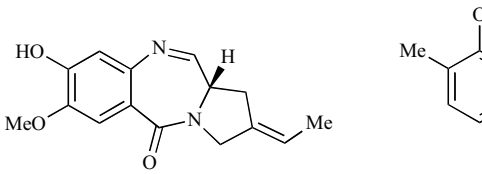
The farnesylation of Ras by the enzyme protein farnesyl transferase inhibitors (FT) has been focused on with a great deal of attention on interrupting this enzymatic transformation for potential anticancer therapy [108]. The importance of imidazole functionality in potent FT inhibitors of imidazole based tetrapeptide FT inhibitors was found by the Merck researchers. Later, the imidazole was attached through various linkers to a tetrapeptide framework. Ding *et al.* found the tetrahydrobenzodiazepine, a privileged structure because it serves as the template for a variety of small molecules which are biologically active against diverse protein targets [109]. Compound (**84**) (Fig. **20**) showed a FT IC_{50} value of 24 nM.

Pyridodiazepine as Antiproliferative Agents

Various substituted pyridodiazepines were synthesized and evaluated for antiproliferative activity *in vitro* against different human cancer cell lines MES-SA (uterine carcinoma), SW707 and LS-180 (colon adenocarcinoma) HepG2 (hepatoma), Molt-4 (lymphatic leukemia); using the MTT technique. Compound (**85d**) (Fig. **20**) was active only against the cells of both human leukemia and bladder cancer cell lines [110].

Pyrimidobenzodiazepines as Tyrosine Kinase Inhibitors

Smith *et al.* identified and studied the structure–activity relationships of a novel series of non-quinazoline compounds containing a diazepine ring system (**86**) as tyrosine kinase inhibitors [111] (Fig. **21**). Tyrosine kinase inhibitors are used in controlling proliferation of cancerous cells. The



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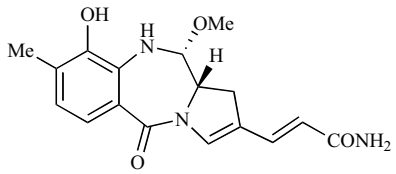

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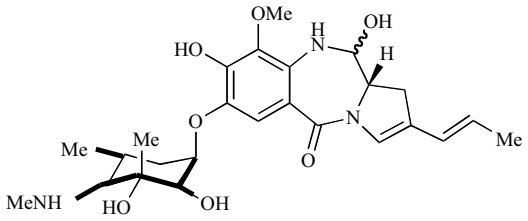

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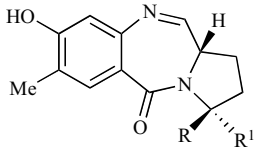
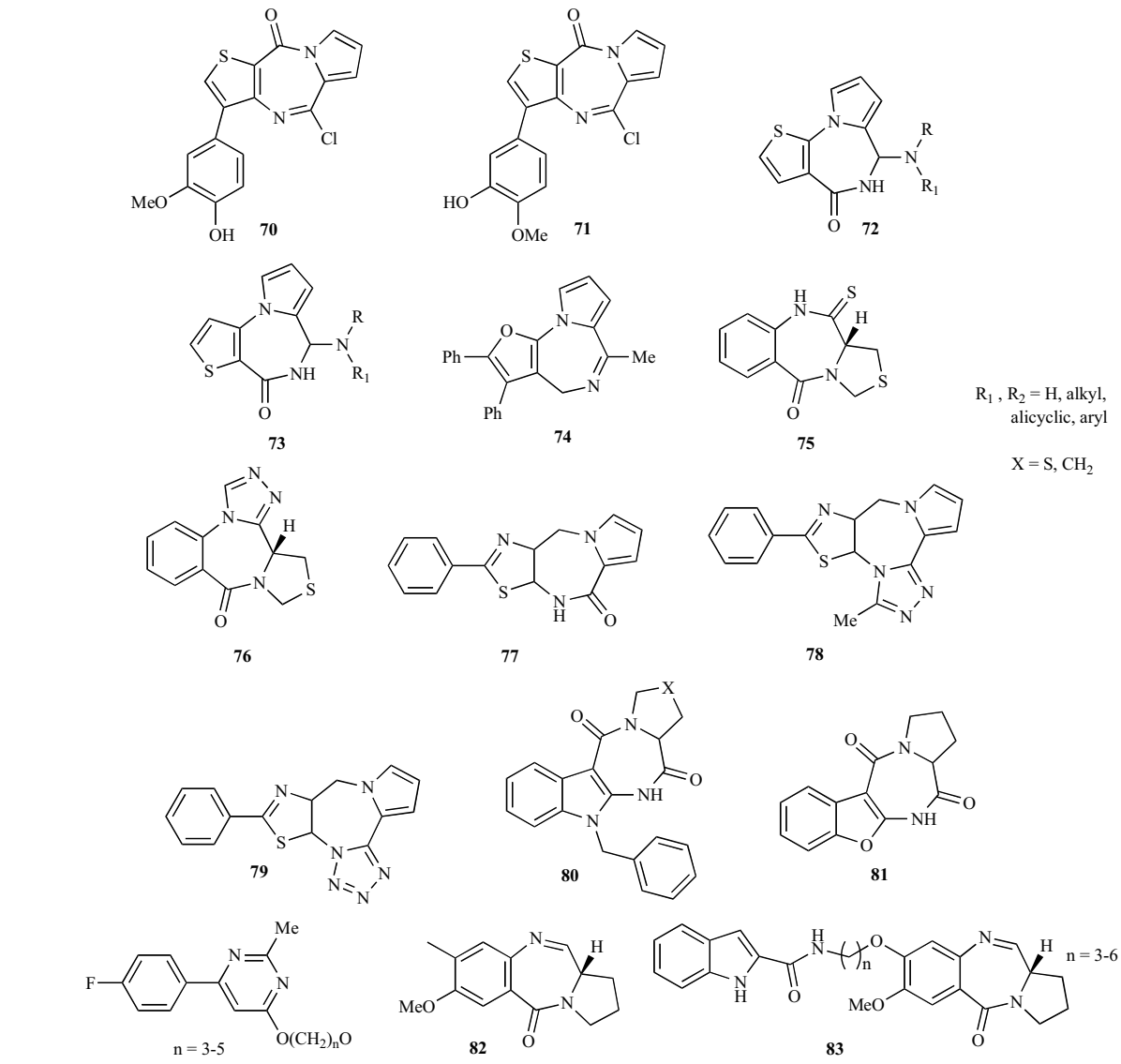


67: R = H, R^1 = OH
68: R = OH, R^1 = H
69: R = R^1 = H

Fig. (18).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71
72
73
74
75
R1 , R2 = H, alkyl, alicyclic, aryl
X = S, CH2
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79
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n = 3-5
82
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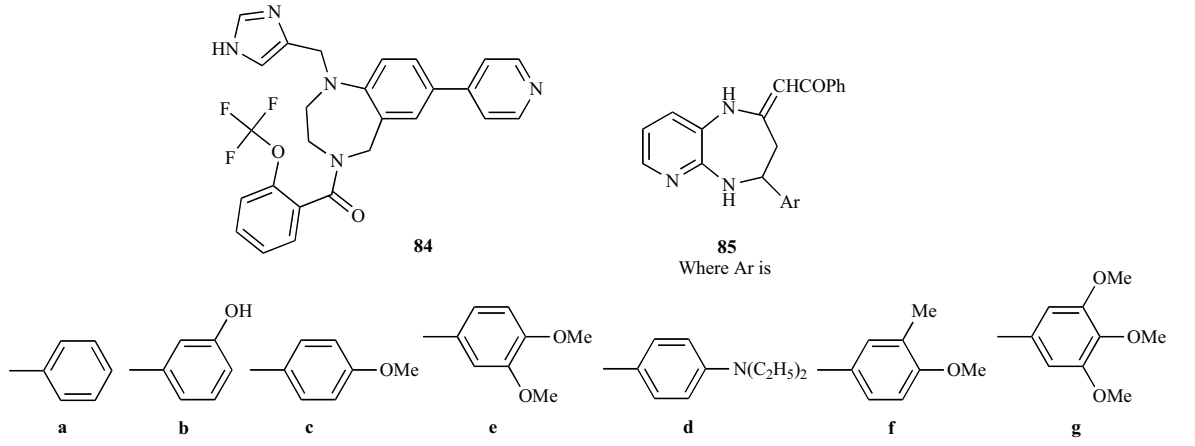
n = 3-6

Fig. (19).


84
85
Where Ar is
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e
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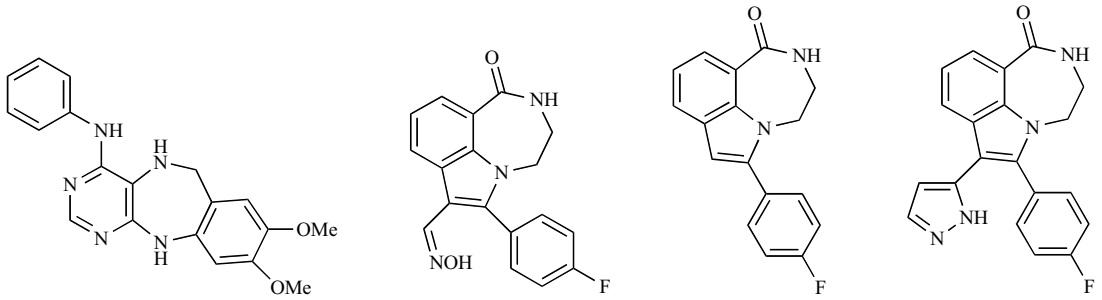
g

Fig. (20).



86 **87** **88** **89**

Fig. (21).

diazepines showed moderate inhibition at 2-5μM. Furthermore, these diazepines demonstrated significant ability to inhibit cell-based phosphorylation in DiFi cells at single-digit micromolar to submicromolar range.

Indolodiazepines as Poly (ADP-Ribose) Polymerase Inhibitors (PARP)

PARPs are nuclear enzymes which are responsible for the formation of the protein-bound linear and branched homo-ADP-ribose polymers. The activation of PARP and formation of poly (ADP-ribose) are the result of DNA strand breaking induced from exposure to certain chemotherapeutics, ionizing radiation, and oxygen free radicals or nitric oxide. PARPs may indirectly contribute to the resistance that often develops to various types of cancer therapies through its role in repairing DNA strand breaks caused by radiotherapy or chemotherapy [112]. PARP-1 is one of the enzymes involved in maintaining DNA integrity. Consequently, the inhibition of PARP-1 may retard intracellular DNA repair and thereby enhance and prolong the antitumor effects of certain anticancer therapies. Enzyme inhibition assays showed that indolodiazepine (**87-89**) acts as PARP inhibitors (Fig. **21**) and potentiate the effects of ionizing radiation or cytotoxic agents and, therefore, may serve as effective adjuncts in cancer chemotherapy [113, 114].

Diazepines as DNA Breakers

Nobuko *et al.* reported 1,4-diazepines (**90a-c**) with DNA strand breaking activity (Fig. **22**) using covalently closed circular duplex DNA (ccc-DNA) of plasmid pBR322 in the presence of cupric ion [115]. The DNA strand breaking activity was remarkably accelerated by the addition of cupric ion, which possibly stimulates the production of active radicals, resulting in DNA strand damage and subsequently arresting cell division [116]. Only a couple of reports dealing with the syntheses of 2,3-diaryl-6,7-dihydro-5*H*-1,4-diazepine obtained by reacting cheaply available benzil and 1,3-propanediamine. This system was almost unexplored and this diaryl diazepines (**90c**) system was explored by Ramajayam *et al.* [117]. Some of the compounds synthesized were found to be moderately active against various leukemic cell lines. The results of the biological activity are yet to be published. Senthilkumar *et al.* used the monocyclic diazepine for the syntheses of cyclic *N*-nitroso compounds (**91**) which are found to be effective anticancer agents [118]. The α-carbons of nitroso compounds undergo enzymatic hydroxylation followed by oxidative cleavage leading to the formation of alkyldiazo hydroxides, alkyldiazonium ions and alkyl cations. These cations are postulated to initiate the process of carcinogenesis in some cases by alkylating the bases of DNA [119].

2,3-dihydro-1,4-diazepines

This class of monocyclic diazepines have received less biological attention although they are chemically well explored than the 6,7-dihydro-5*H*-1,4-diazepines mentioned above [120]. During our work on monocyclic diazepines we developed the interest to study the effect of diaryl positions and the saturation of monocyclic diazepine for anticancer activity. Hence, we synthesized some 5,7-substituteddiaryl-2,3-dihydro-1,4-diazepines as anticancer agents[1] which were found to be more potent than the 2,3-diaryl-6,7-dihydro-5*H*-1,4-diazepine analogs. Pathak and co-workers reported that some of the 5,7-diaryl-2,3-dihydro-1,4-diazepine derivatives (**92**) exhibit appreciable antiulcer activity [121] (Fig. **22**).

BENZODIAZEPINES AS NONPEPTIDE SCAFFOLDS/BUILDING BLOCKS

In the design of peptidomimetics, incorporation of nonpeptide scaffolds into bioactive molecules has been the focus of extensive research over the last years. Advantages are limiting the number of conformations available to a peptide which results in increased potency, selectivity and stability by active conformation with unwanted biological responses [122]. Earlier caspase-3 inhibitor was discussed in this review as one of the example. In addition few examples were given here for some other activity.

Lauffer *et al.* found that the potency and stability of the dipeptide mimetic (**93**), as caspase-1 inhibitor, was improved when diazepine is used as scaffold over previously reported scaffolds [123]. Caspase-1 inhibitor blocks interleukin-1β converting enzyme (ICE) which is an important mediator of inflammation and infectious diseases. Holzgrabe and coworkers selected the diazepines as a scaffold due to their rigid structure for the construction of novel compounds. AFDX-384 (**94**), one of the compound being a subtype-prevalent as a muscarinic M_2 receptor antagonists, was built using pyrido-1,4-benzodiazepine as a building block [124]. AFDX-384 is an analog of pirenzepine (**95**) which acts se-

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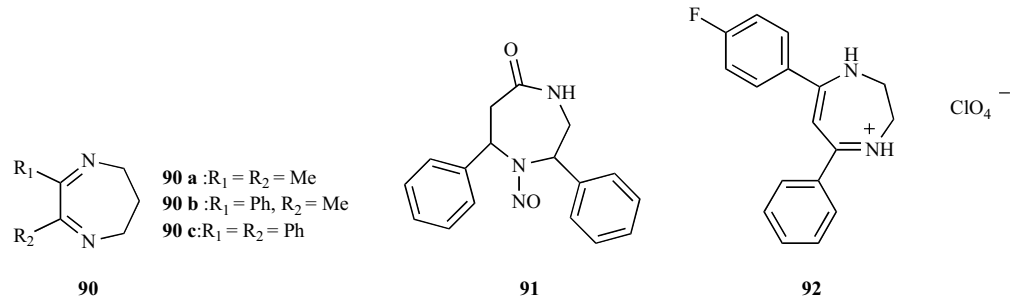


Fig. (22).

lectively as a muscarinic (M_1) receptor antagonist [125] (Fig. **23**). The first synthesis of spiro-1,4-diazepine-2,5-dione heterocycles (**96**) at the anomeric position of furano sugars were reported [126]. Currently they are exploring the use of these compounds as biological tools and as peptidomimetic scaffolds (Fig. **24**). Iris *et al.* reported the synthesis of a trisubstituted 1,4-diazepine-3-one (**97**) based as a novel dipeptidomimetic molecular scaffold [127].

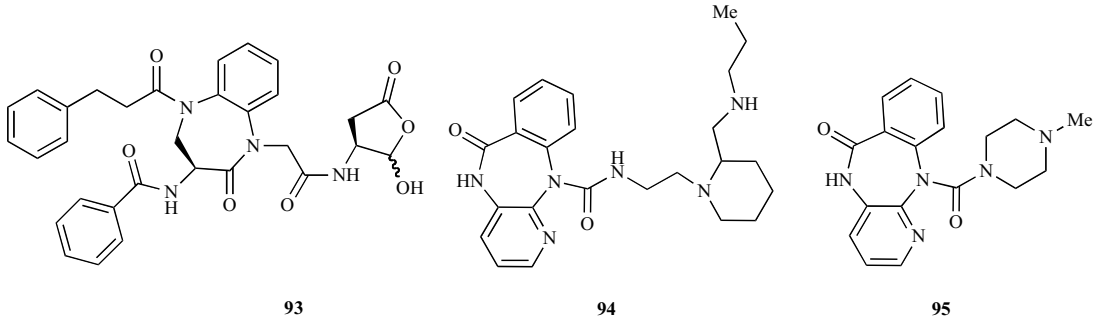


Fig. (23).

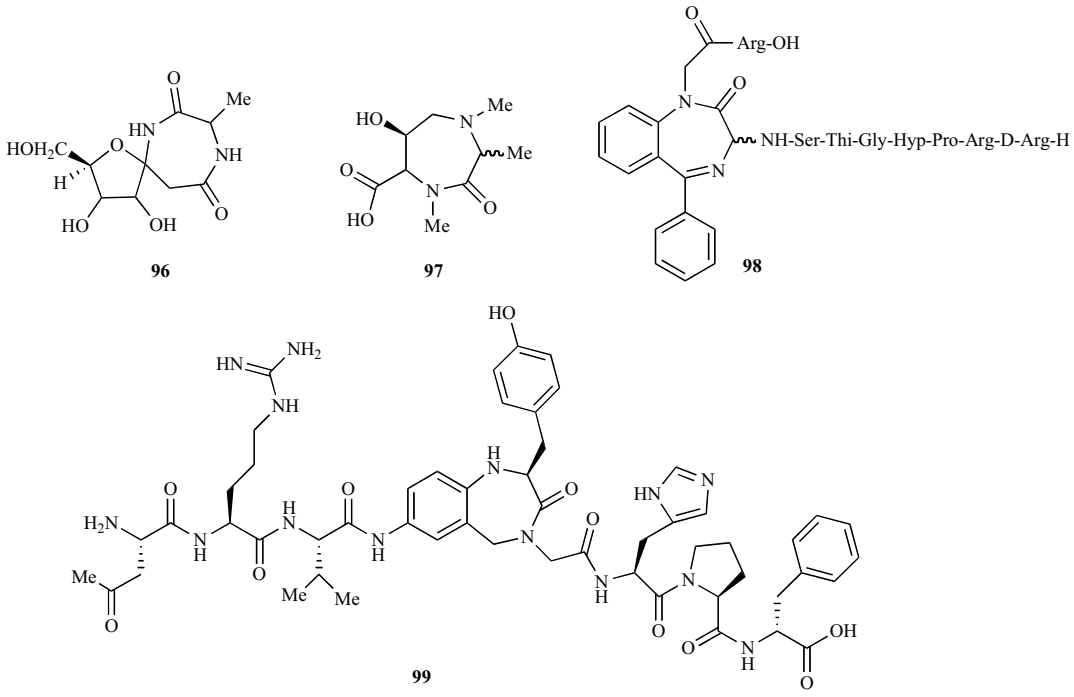
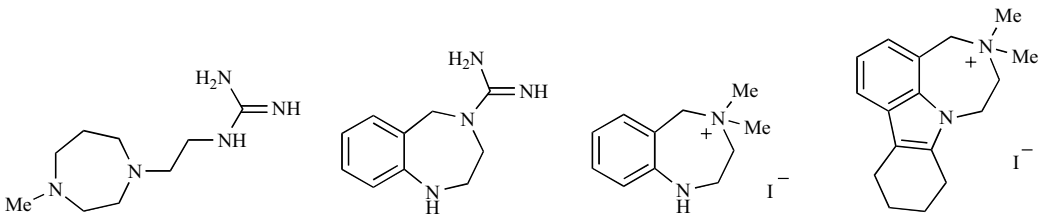


Fig. (24).



100 **101** **102** **103**

Fig. (25).

Benzodiazepines as Bradykinin B_2 Receptor Antagonists

The replacement of D-Tic[7]-Oic[8]- dipeptide of bradykinin antagonist HOE 140, (H-D-Arg[0]-Arg[1]-Pro[2]-Hyp[3]-Gly[4]-Thi[5]-Ser[6]-D-Tic[7]-Oic[8]-Arg[9]-OH), resulted in potent bradykinin agonist action. Amblard *et al.* synthesized a series of HOE 140 analogues by replacement of the dipeptide -D-Tic[7]-Oic[8]- of HOE 140 by various nonpeptide moieties including benzodiazepine (**98**) and benzothiazepine [128] (Fig. **24**).

Benzodiazepine in Angiotensin II AT_2 Antagonists

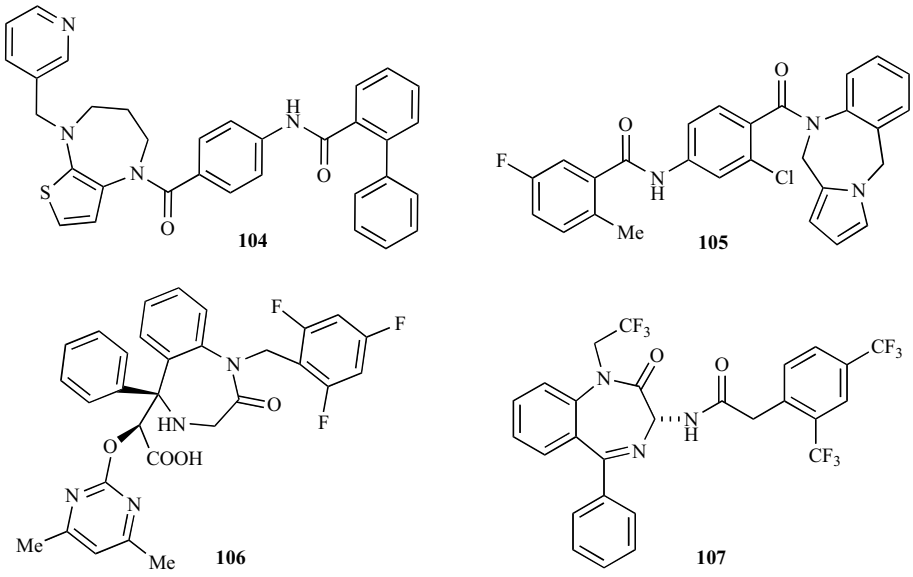
Rosenstrom and co-workers adopted the above strategy and synthesized three angiotensin II (AngII) analogues encompassing a benzodiazepine-based γ-turn like scaffold [129] (Fig. **24**). One of these compounds (**99**) displayed considerable affinity to the pig uterus AT_2 receptor (K_i = 3.0 nM).

DIAZEPINES AS POTENT ANTIHYPERTENSIVE AGENTS

It was believed that the attachment of guanidine with a large membered heterocyclic system possesses antihypertensive activity [130,131] (Fig. **25**). Mull *et al.* synthesized homopiperazine possessing the ethylguanidine side chain (**100**) [132]. The compound was found to have cardiovascular properties. Kim incorporated the guanidino group into the tetrahydro-1,4-benzodiazepine nucleus (**101**) for potential antihypertensive action. The quaternary salts of the tetrahydro-1,4-benzodiazepine (**102**) showed antihypertensive properties through ganglion blockade [133]. Kim also reported 1,4-diazepino carbazole (**103**) ring system, in which benzodiazepine is fused to indole [134].

DIAZEPINE AS ARGININE VASOPRESSIN (AVP) ANTAGONISTS

AVP is a neurohypophyseal nonapeptide that has a wide variety of physiological activity in mammals. It plays an important role in regulating water and solute excretion by the kidneys and also participates in other physiological functions such as blood pressure control, regulation of platelet aggregation and ACTH secretion [135]. Some derivatives of thienodiazepine (**104**) showed antihypertensive activity against AVP-induced hypertension [136]. Another 1,4-benzodiazepine derivative (**105**) has been reported for orally active arginine vasopressin antagonist with selectivity for V_2 receptor [137] (Fig. **26**). The blockade of V_2 receptors may be useful in treating diseases characterized by excess renal reabsorption of free water. V_2 antagonists correct the fluid retention in congestive heart failure, liver cirrhosis, lung disease and hyponatremia [138].



104 **105** **106** **107**

Fig. (26).

DIAZEPINES AS ENDOTHELIN (ET) RECEPTOR ANTAGONISTS

The three highly active vasoactive peptides ET-1, ET-2 and ET-3 act with different binding affinities to two closely related G-protein-coupled receptors ET_A and ET_B. During pathophysiology the ET-1 peptides bind with ET_A receptor and causes renal failure, heart failure, hypertension, atherosclerosis, acute myocardial infarction and cerebral vasospasm. So researchers believed such disorders can be prevented or treated by endothelin receptor antagonists [139]. Recently, the diazepine compound (**106**) has been reported as ET-1 antagonist and efficiently reduced arterial blood pressure after oral administration to Dahl salt sensitive rats [140] (Fig. **26**).

DIAZEPINES WITH ANTIARRHYTHMIC ACTIVITY

Compound (107) was reported as a potent antiarrhythmic agent (Fig. **26**) both *in vitro* and *in vivo*. It was found to have selectivity with long duration of action after oral dosing [141].

DIAZEPINES AS PLATELET ACTIVATING FACTOR (PFA) ANTAGONISTS

The triazolothienodiazepines have emerged as one of the important series of PAF antagonists (Fig. **27**) because of their selectivity, potency and bioavailability [142]. These factors are essential to assess the clinical utility of PAF antagonists in allergic and inflammatory diseases. Walser and co-workers reported that compounds (**108**) and (**109**) have good oral potency and a long duration of action [143]. Kawakami and co-workers reported that the length of alkyl or arylalkyl side chain at the 2-position of compound 110 was responsible for enhancing the affinity for the PAF receptor. Simultaneous substitution at both 2- and 6-positions resulted in successful separation of affinity for the PAF and benzodiazepine receptors [144]. Among the series of the compounds, compound (**110**) showed to be a specific antagonist for PAF receptor and is currently under clinical trials. Blackburn and co-workers reported 1,4-benzodiazepine-2,5-dione (**111**) as a non-peptidal class of GPIIbIIIa antagonists. GPIIbIIIa antagonists inhibit the adhesive and aggregatory function of platelets by binding to platelet receptor GPIIbIIIa [145]. Askew and co-workers reported pyrazolodiazepinine (**112**), a potent selective fibrinogen receptor antagonist that displays an extremely long pharmacodynamic profile following intravenous or oral administration in dogs [146]. Recently Glaxo SmithKline pharmaceuticals introduced Lotrafiban® (**113**), a potent nonpeptidic glycoprotein IIb/IIIa antagonist for antiplatelet aggregation. The molecule has (*S*)-stereochemistry and only this enantiomer is active. Unfortunately this molecule was suspended during phase III clinical trials, when assessing whether this agent would be useful in the management of heart attack or stroke as it caused severe hemorrhage [147,148]. Many structurally related analogs have been reported to possess antiplatelet activity [149-153].

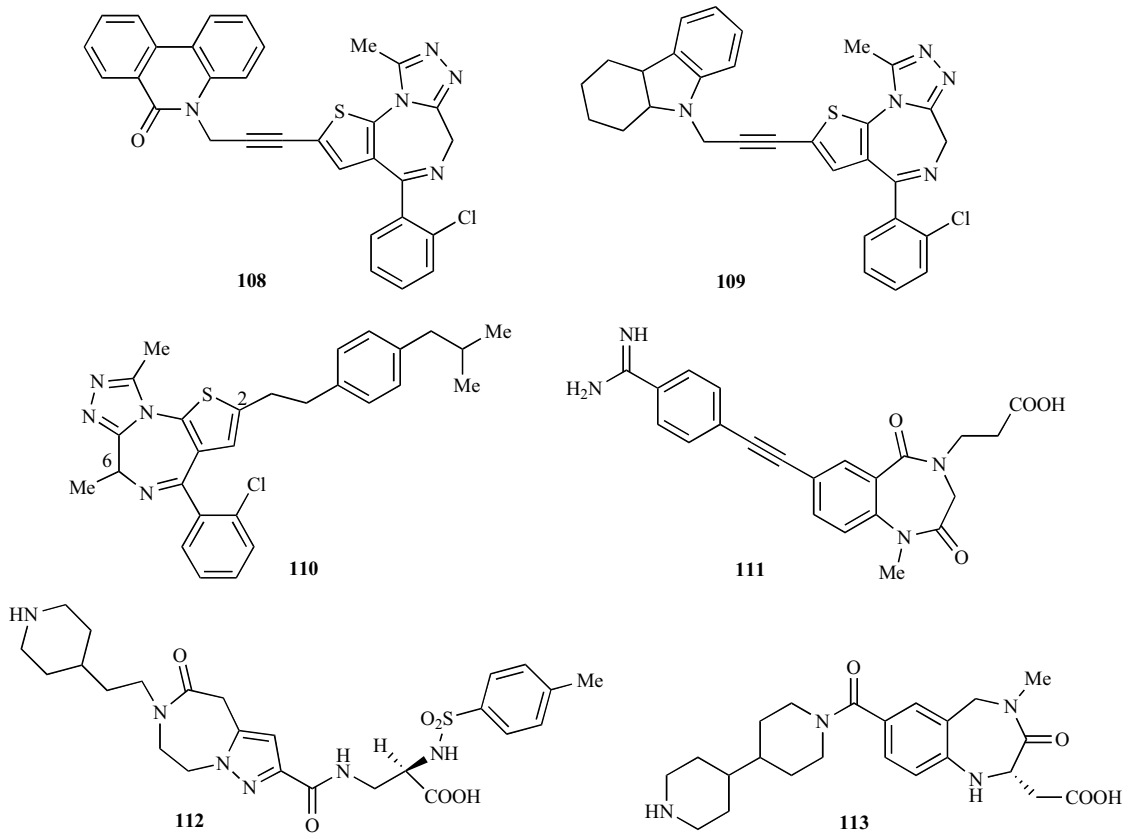
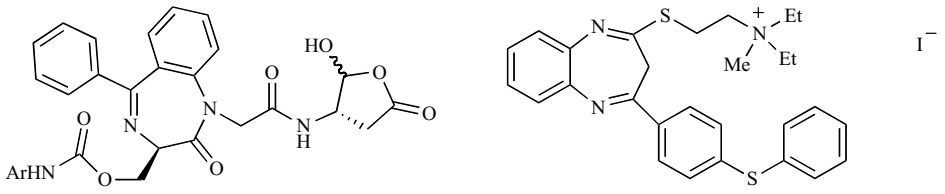


Fig. (27).



114 **115**

Fig. (28).

DIAZEPINES AS ANTIMALARIAL AGENTS

Micale *et al.* designed new Falcipain-2 (FP-2) inhibitors (Fig. **28**) based on a 1,4-benzodiazepine scaffold (**114**) introduced internally to a peptide sequence, which mimics the fragment D-Ser-Gly, and on a C-terminal aspartyl aldehyde building block, which inhibits the enzyme by forming a reversible covalent bond at the active site [154].

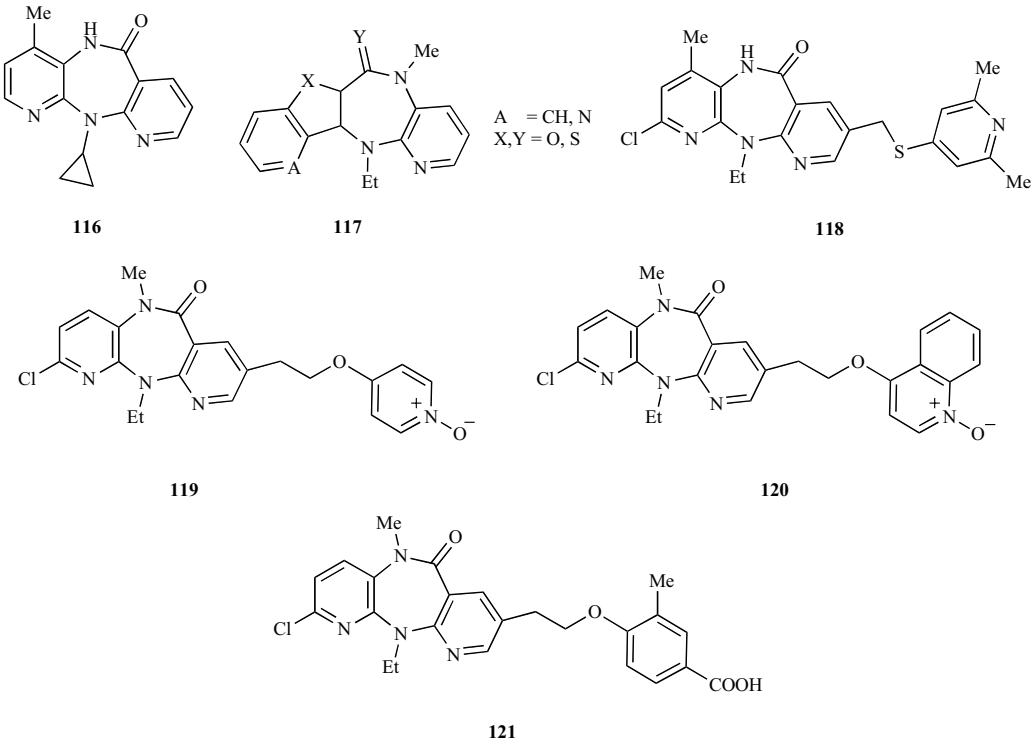
DIAZEPINES AS ANTIBACTERIAL AGENTS

Tibenzonium iodide (**115**) is an example of a benzodiazepine with antibacterial activity against *Streptococus pyogenes* A88 also possessing virucidal activity [155] (Fig. **28**).

DIAZEPINES AS ANTI-VIRAL AGENTS

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) Containing Diazepine Motifs- Nevirapine and TIBO Series

More than 30 different families of NNRTI's have been identified as specifically inhibitory to the replication of human immunodifficiecy virus-1 (HIV-1) and that are targeted at a specific, allosteric (i.e., nonsubstrate binding) site of the reverse transcriptase [156-158]. Nevirapine (**116**), a dipyrido-1,4-diazepine compound (Fig. **29**), is the one of the NNRTI among the three NNRTIs, approved by Food and Drug Administration (FDA) for the treatment of HIV-1 infections. Bellorosa *et al.* reported on arylpyridodiazepine (**117**) and it was found to inhibit human immunodeficiency virus type I [HIV-1(IIIB)] replication at a concentration of 0.003-0.04 μM without being cytotoxic at a 3,000-15,000 fold higher concentration [159]. A series of novel 8-substituted dipyridodiazepinone-based inhibitors (**118-121**) were investigated for their antiviral activity against wild type HIV-1 and the clinically prevalent K103N/Y181C mutant virus. These conjugates show the combination of good antiviral potency, a broad spectrum of activity, and an excellent pharmacokinetic profile in the treatment for wild type and NNRTI-resistant HIV-1 infection [160]. In 1987 Janssen Pharmaceutica and Co, Belgium entered into the area of HIV research by screening 600 molecules with two decisive factors: (1) they cov-

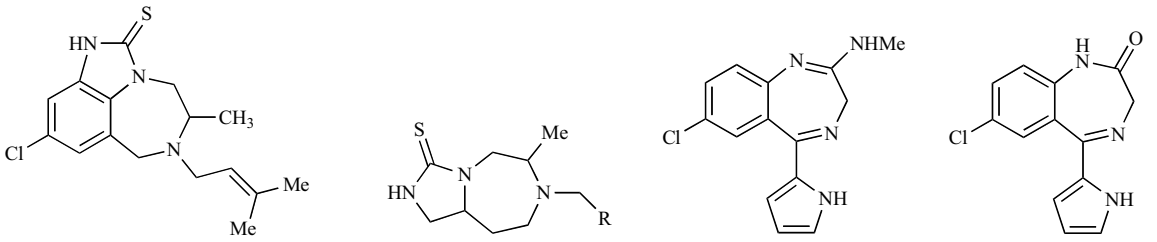


116 **117** **118**

119 **120**

121

Fig. (29).



122 **123** R = Ph, $CH=C(CH_3)_2$ **124** **125**

Fig. (30).

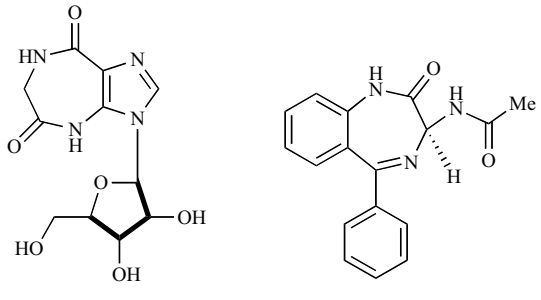
ered a wide range of chemical diversity and (2) they did not show significant biological activity in a battery of unrelated pharmacological assays. A lead compound 4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-*jk*](1,4)-benzodiazepin-2-(1*H*)-one (TIBO) (**122**) (Fig. **30**) was discovered as a potent NNRTI during antiviral screening although the molecular target was not known precisely. SAR studies of TIBO molecule were further carried out [161-164]. The molecular docking studies revealed that the phenyl ring in the TIBO makes unfavorable binding within the allosteric pocket of reverse transcriptase enzyme [165]. So Janin *et al.* synthesized some imidazo-1,4-diazepines (**123**) as TIBO analogs lacking phenyl ring, as anti-HIV agents [166].

Diazepines Tat Inhibitors

HIV transcription is controlled primarily by the *trans*-activator protein (Tat) [167]. The best known Tat inhibitors (Fig. **30**) of diazepine derivatives Ro5-3335 (**124**) and Ro24-7429 (**125**) are reported by Cupelli *et al.* [168]. These compounds inhibit the initiation of HIV transcription but do not specifically interfere with Tat. Ro24-7429 had entered into Phase I clinical trials. Unfortunately, the trial has been abandoned due to severe CNS side effects. The lack of antiviral activity may be due to extensive binding of the drug to human plasma proteins.

Miscellaneous Antiviral Agents

Hosmane *et al.* reported imidazo-1,4-diazepine (**126**) (Fig. **31**), the ring-expanded xanthosine analogue as an antiviral agent against murine leukemia virus (MuLV) in tissue culture system [169]. Carter *et al.* found the 1,4-benzodiazepine as respiratory syncytial virus (RSV) inhibitors during their investigation of 20,000- member diverse molecule screen against RSV in a whole cell assay. They found the antiviral activity was solely by 3-(*S*) enantiomer benzodiazepine [170]. Compound (**127**) displayed antiviral activity with virtually no associated cell toxicity.



126 **127**

Fig. (31).

CONCLUSION

Since the discovery of benzodiazepines about five decades ago as CNS active drugs several studies have been undertaken to understand the SAR profile of 1,4-diazepines. Ring systems having fusion of carbo/heterocyclic rings to 1,4-diazepine at various positions and isolated 1,4-diazepines having different types of substituents at different positions have been synthesized and biologically evaluated. These compounds have shown activities ranging from CNS disorders, antibiotics, neuroprotective, H_3-receptor antagonists, MMP inhibitors, 5-HT_3 receptor antagonists, trypanocidal activity, CCK agonists/antagonists, analgesics, antidiabetic, antiasthmatic and anti-inflammatory, anti-proliferative, CVS disorders, PAF antagonists, antimalarial, anti-HIV, peptidomimetic and as biological tools. The multifarious activities of the diazepines are mainly governed by the position of the nitrogen atom atoms in the ring and the types of additional rings and substituents present in the seven membered ring. But it would not be safe to make any generalization as far as the bioactivity of 1,4-diazepines are concerned. The application of combinatorial approach to develop libraries of closely related analogs has hastened the process of discovery of compounds. Comparatively, reports on monocyclic diazepines are scarce particularly with respect to biological activity. Looking to the various types of biological activities as mentioned above we can conclude that the monocyclic diazepine motif provides a useful avenue for the development of small drug-like molecules.

ACKNOWLEDGEMENTS

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