1, 5-Benzodiazepines: A Review Update

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Abstract
1,5-benzodiazepines are the most studied group of diazepines, which are a class of drugs prescribed against psychotic disorders. An immense literature is continually produced from the research work carried out about the synthesis and pharmacological activities of 1,5-benzodiazepine, two recent reviews in 2013 outlined the importance of this privileged pharmacophore. Due to their wide range of biological properties the benzodiazepine nucleus has continued to attract many investigators to synthesize and screen their analogues for all possible activities. This current review article describes the literature relating to 1,5-benzodiazepines synthetic strategies and provides highlights of the different pharmacological activities accomplished since 2013.

Keywords: 1,5-Benzodiazepines, Anxiolytic, Synthesis, o-Phenylenediamine, Ketones, Catalyst, Solvent-free

1. Introduction
Benzodiazepines are an important pharmacophore due to their pharmacotherapeutic properties and various pharmacopeial information. The 1,5-benzodiazepine nucleus is a privileged scaffold that is a core structure of medicinal drugs and has received great attention of medicinal research searching for new derivatives with enhanced pharmacological activities [1, 2, 3]. The bicyclic, tricyclic, tetracyclic and fused polycyclic 1,5-benzodiazepines exist in literature [4]. The benzodiazepines have revolutionized the treatment of anxiety and insomnia since the 1950s with the introduction of chlordiazepoxide [5] largely due to their anxiolytic and sedative-hypnotic effects [6].

The 1,5-benzodiazepine have retained attention due to their pharmacological activities and immense literature exist on the benzodiazepine nucleus. Barival and co-workers [7]. Reviewed the pharmacological profiles of structurally enhanced 1,5-benzodiazepines. Salvi and Mali [3] review article reported on the various synthetic routes, solvents and catalysts used towards 1,5-benzodiazepines and their different pharmacological activities, while another recent review by Aastha and co-workers [1]. Provided an overview of the biological properties and synthetic schemes for 1,5-benzodiazepine. Casher and co-workers [8]. have described benzodiazepines as versatile clinical tools and a review showing the compendium on genotoxicity and carcinogenicity data for benzodiazepine drugs appeared in 2007 [9].

Post the 2013 [1] reviews a significant number of articles have appeared in literature reporting on the synthesis and screening of 1,5-benzodiazepine analogues for all possible activities. Therefore, this review describes the synthesis of 1,5-benzodiazepine analogues and highlights the different pharmacological activities from the last two years (2013-2015).

2. Discussion
2.1 The ring system
The IUPAC ring numbering of the simplest form of 1,5-benzodiazepine (2, 3-dihydro-1H-1, 5 benzodiazepine) is shown in Figure 1. The structure has two nitrogen atoms at positions 1 and 5 in a seven membered diazepine ring fused to a benzene ring. The ring system occurs in the diimine forms where there is conjugation between the two imino groups and the benzene ring, which bring stability to the system [10-13].

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2.2 Pharmacological properties

Psychiatrists use benzodiazepines to treat anxiety, sleep disorders and alcohol withdrawal. Benzodiazepines provide relief at lower sedation levels compared to the barbiturates. They are safer than both barbiturates and dicarbamates [14, 15]. Benzodiazepines are sedative, hypnotic central nervous system (CNS) depressants and work with the γ-aminobutyric acid (GABA) receptors of the CNS. GABA is a neurotransmitter stored in the nerve cells and released by the brain to calm the body. In state of anxiety, polypeptides stimulate the nerve cells and suppress the release of GABA. Benzodiazepines interact with receptors to allow its release. Once GABA is released, the stimulation by the polypeptides stops and the state of anxiety ends [8, 16, 17]. Benzodiazepines abuse can lead to unintentional drug overdose and dependence. Benzodiazepines are not FDA (Food and Drug Administration) approved for long term use and are approved only for the short-term use for several conditions [3]. Therefore they should be used at low doses and for a short term. Benzodiazepines withdrawal effects are mainly anxiety symptoms, autonomic stability, insomnia and seizures in serious cases [18]. Benzodiazepines and analogues exhibit muscle relaxant, anti-anxiety, anticonvulsant, anti-HIV-1, anticoagulant, antiobesity, calcium channel blockers, cholecystokinin antagonists, thrombopoietin receptor agonist, anti-leukemic, anti-epileptic, anti-cancer, antiviral, antifungal, antibacterial, analgesic, anti-inflammatory, antihelminthic, antipyretic and antiulcer properties [3, 7, 19-23]. The 1,5-benzodiazepine based drugs in clinical applications against psychotic disorders are shown in Figure 2.

2.3 Synthesis

The 1,5-benzodiazepine synthetic strategies are mostly based upon coupling diamines with α,β-unsaturated ketone, aliphatic ketones, β-diketones, β-ketoesters in acid or base. The inorganic catalyst have also been employed as promoters of the reactions to achieve higher yield and stereospecificity. Recently green methodologies have appeared in literature. The various reported reactions are described in the following text. 4-naphtho [2,1-b] furan-2-yl-2(phenyl)-2, 5-dihydro-1H-1,5-benzodiazepines 4 have been prepared through the reaction of chalcones and α-phenylenediamine (α-PDAs) in presence of a base as shown in Scheme 1. The benzodiazepines exhibited good antibacterial, antifungal, anti-inflammatory, diuretic, antihelminthic and antipyretic activities. The electron withdrawing and methoxy groups resulted in enhanced activities [22].

The condensation of α-phenylenediamine and substituted chalcones under microwave irradiation afforded a series of 2, 4-disubstituted-1,5-benzodiazepine 6 in Scheme 2.

Benzodiazepine bearing a 1, 2, 3-triazole moiety 12 were prepared from the reaction of α-phenylenediamine and α,β-unsaturated ketones as described in Scheme 3 [24]. Some GABA receptor modulating 8-chloro-6-phenyl-4H-[1,2,4] triazolo [4, 3-a, 1, 5] benzodiazepin-5(6H)-ones 14 have been synthesized starting from 8-chloro-4-(dimethylamino)-1,3-dihydro-1-phenyl-2H-1,5-benzodiazepin-2-one 13 utilizing a eutectic solvent under microwave irradiation as depicted in Scheme 4. The (4-methyl-1, 5-dihydro, 1, 5-benzodiazepin-2-ylidene)-aryl-arnines 16 synthesis was accomplished through the condensation of α-phenylenediamine and acetooacetilide catalyzed by CdCl2 under thermal and microwave irradiation (Scheme 5). The microwave irradiation was effective in the reduction of reaction times but had a non-significant effect on the yields. The derivatives of compound 16 showed moderate to good antimicrobial activities [21]. The microwave irradiation of α-phenylenediamine and isophthalic acid 17 in the presence of acetone afforded a salt of the isophthalate ion and 2, 2, 4-trimethyl-2, 3-dihydro-1H-1, 5-benzodiazepin-5-ium ion 18 in Scheme 6.
Some cytogenetic active enamino-1,5-benzodiazepines 20 were prepared by the condensation of 1, 3, 5-triketones with \( \sigma \)-PDAs through a microwave assisted reaction \[^2\] as shown in Scheme 7. 1,5-benzodiazepines 22 were synthesized in one step from the reaction of \( \sigma \)-phenylenediamine with 2-oxoketenedithioacetal 21. The benzodiazepines were further linked to oxadiazole 26 and imidazole 28 rings \[^26\] as described in Scheme 8 and 9. A recent one-pot condensation reaction of thiophene aldehydes, \( \sigma \)-PDAs and ethyl acetoacetate using phosphomolybdic acid (PMA: \( H_3PMo_{12}O_{40} \)) catalyst yielded 1,5-benzodiazepines 31 \[^27\] shown in Scheme 10.

The condensation of arylamines with ketones yielded diazepine 33 using \( BF_3-H_2O \), which acted as a non-oxidizing Brønsted acid catalyst as well as a solvent making the reaction environmentally friendly \[^28\] (Scheme 11). This reaction worked only with acetone, but a protocol that worked with different types of ketones 34 utilized phenylboronic acid \[^29\]. The ketones used were aliphatic ketones, arylketones, and cyclic ketones as shown in Scheme 12. The advantages of these methods are easy mild reaction condition, experimental work up, excellent yields and versatility. Similar reactions were also reported using boron sulfonic acid (BSA), which was also an efficient catalyst \[^30\].

\[^{13} \text{R} = \text{CH}_2\text{CH}_2\text{Me}, \text{CH}_2\text{Ph, CH}_2\text{CO}_2\text{Et, pClPh, Ph, m-OMePh, C}_5\text{H}_5\text{N, CH}_2\text{N(CH}_2\text{CH}_2)_2\text{O}}

\[^{14} \text{Scheme 4} \]

\[^{15} \text{R} = \sigma-\text{OMe, p-OMe, o-Me, m-Me, p-Cl, m-Cl, p-Br, H} \]

\[^{16} \text{Scheme 5} \]

\[^{17} \text{Scheme 6} \]

\[^{18} \text{Scheme 7} \]

\[^{19} \text{o-PDAs also from 2,3-diaminonaphthalene and 2,3-diaminopyridine} \]

\[^{20} \text{Scheme 8} \]

\[^{21} \text{R} = \text{CHO, COMe} \]

\[^{22} \text{Scheme 9} \]

\[^{23} \text{Scheme 10} \]

\[^{24} \text{R} = \text{CHO, COMe} \]

\[^{25} \text{Scheme 11} \]

\[^{26} \text{Scheme 12} \]

\[^{27} \text{Scheme 13} \]

\[^{28} \text{Scheme 14} \]

\[^{29} \text{Scheme 15} \]

\[^{30} \text{Scheme 16} \]

\[^{31} \text{Scheme 17} \]
Another efficient protocol for the synthesis of 1,5-benzodiazepines by the reaction of o-phenylenediamine with ketones was demonstrated using a re-usable protic pyridinium ionic liquid [2-MPyH] OTf catalyst (IL-1) in aqueous mixture \[^{[31]}\] as shown in Scheme 13. An ionic liquid has also been employed under solvent free condition to prepare 1,5-benzodiazepines by the condensation of o-phenylenediamine with ketones. The cationic liquid, tetraethylene glycol-bis (3-methylimidazolium) diacetate ([tetraEG (mim) 2] [OAc] \[^{[2]}\] : IL-2) and the heterogeneous silver salt of silicotungstic acid (AgSTA), showed high reactant conversion rates and reduced reaction times \[^{[32, 33]}\]. Similarly, chloroacetic acid catalyzed the synthesis of 1,5-benzodiazepines under solvent free conditions \[^{[34]}\]. Other acids such as malonic, cinnamic, succinic, oxalic, formic and tartaric acid also resulted in excellent yields. ZnO was efficiently employed under solvent free conditions to effect the condensation of o-phenylenediamine with aliphatic and aryl-ketones \[^{[35]}\], while silica supported heterogeneous catalyst FeCl\(_3\)-SiO\(_2\) promoted the three component reactions of o-phenylenediamine, \(\beta\)-ketoesters, and arylaldehydes. The 2-pyridinecarboxaldehyde was regioselective towards the \(\alpha\)-products 42 \[^{[36]}\] shown in Scheme 14. Several green catalysts have been employed as catalyst for the cyclocondensation of o-phenylenediamine, \(\beta\)-ketoesters or ketones, and arylaldehydes using green methodologies. These catalysts include HY zeolites, sulfamic acid, YbCl\(_3\), Yb(OPf\(_3\)), K-10 montmorillonite clay, ambeylist-15 \[^{[7]}\], silica gel using ultrasound \[^{[30]}\], AlCl\(_3\) \[^{[31]}\], silicotungstic acid, phosphotungstic acid, FeCl\(_3\) and pTsOH \[^{[36]}\]. The organocatalyst 2, 6-pyridinedicarboxylic acid (2,6-PDCA) catalyzed the regioselective synthesis of 1,5-benzodiazepine derivatives from o-phenylenediamine, \(\beta\)-ketoesters, and arylaldehydes in a three-component reaction, Scheme 14 and 15. Only the \(\gamma\)-products 41 were formed by the C–C bond formation at the \(\gamma\)-position of \(\beta\)-ketoesters \[^{[39]}\].
1,5-benzodiazepines 48 were synthesized from the reaction of alk-3-yn-1-ones with \( o \)-phenylenediamines assisted by microwave irradiation (Scheme 16) and devoid of catalysts. Novel potential anticancer agents were synthesized using a one-pot three-component reaction of diamides, Meldrum’s acid, and benzyl isocyanide as shown in Scheme 17. The benzodiazepines exhibited moderate to potent \textit{in vitro} antitumor activities against human lung carcinoma (A549), human breast epithelial carcinoma (MCF-7), human colon carcinoma (HCT116), human cervical carcinoma (Hela) and Lewis lung carcinoma (2LL). The preparation of dihydroquinazolino [3, 2-a] [1, 5] benzodiazepinones 56 was accomplished via the benzoylation of 1, 5-benzodiazepinones with 2-nitrobenzoyl chloride in the presence of 4-dimethylaminopyridine (DMAP) and N,N-diisopropylethylamine (DIPEA) as depicted in Scheme 18.

3. Conclusion
1,5-benzodiazepines are the most studied group of diazepines, which are a class of drugs prescribed against psychotic disorders. Due to their wide range of biological properties the benzodiazepine nucleus has continued to attract many investigators to synthesize and screen their analogues for all possible activities. This current review article describes the literature relating to 1,5-benzodiazepines synthetic strategies and provides highlights of the different pharmacological activities accomplished since 2013. 1,5-benzodiazepine synthetic strategies are based upon coupling diamines with \( \alpha,\beta \)-unsaturated ketone, aliphatic ketones, \( \beta \)-diketones, \( \beta \)-ketoesters in acid or base. Inorganic catalyst have been reported as promoters of the reactions to achieve higher yields and stereospecificity. Green methodologies devoid of catalyst were also reported.
4. Acknowledgment
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