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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. Bariwal 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 benzodiazepines 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].

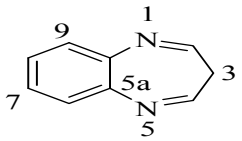


Figure 1

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 [8]. 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, anthelmintic, antipyretic and antiulcer properties [1-3, 7, 19-23]. The 1,5-benzodiazepines 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 withα,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-1*H*-1,5-benzodiazepines 4 have been prepared through the reaction of chalcones and *o*-phenylenediamine (*o*-PDAs) in presence of a base as shown in Scheme 1. The benzodiazepines exhibited good antibacterial, antifungal, anti-inflammatory, diuretic, anthelmintic and antipyretic activities. The electron withdrawing and methoxy groups resulted in enhanced activities [22].

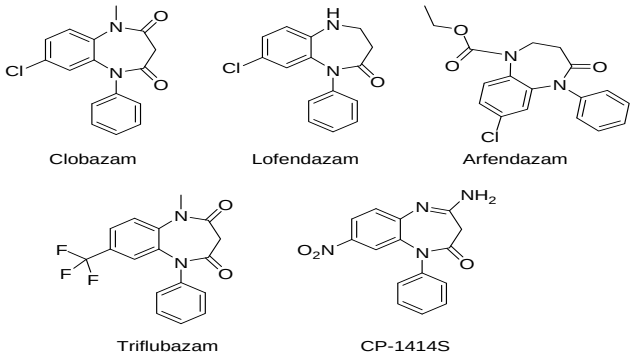
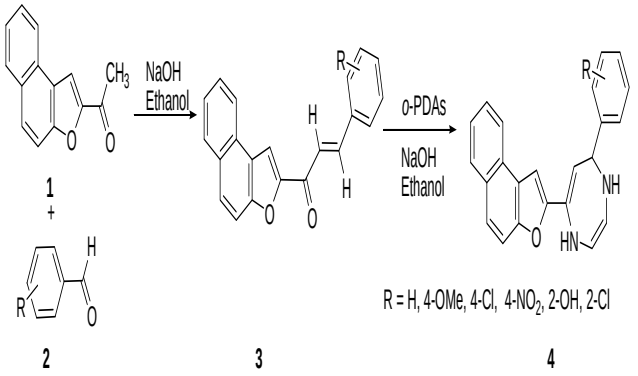


Figure 2

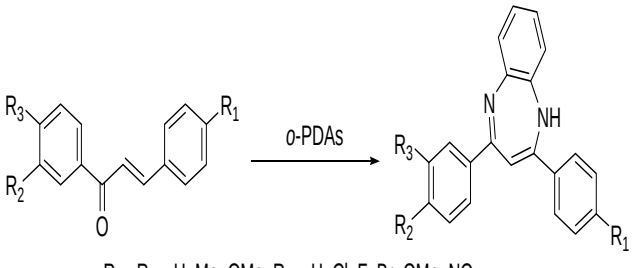
The condensation of *o*-phenylenediamine and substituted chalcones under microwave irradiation afforded a series of 2, 4-disubstituted-1,5-benzodiazepine 6 [4] in Scheme 2. Benzodiazepine bearing a 1, 2, 3-triazole moiety 12 were prepared from the reaction of *o*-phenylenediamine andα,β-unsaturated ketones as described in Scheme 3 [24].

Some $GABA_a$ 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 [23] utilizing a eutectic solvent under microwave irradiation as depicted in Scheme 4.

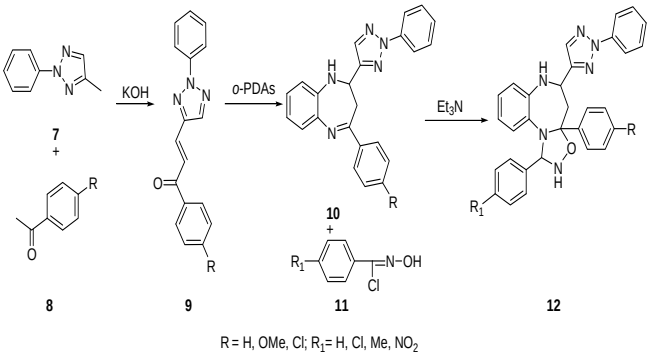
The (4-methyl-1, 5-dihydro, 1, 5-benzodiazepin-2-ylidene)-aryl-amines 16 synthesis was accomplished through the condensation of *o*-phenylenediamine and acetoacetanilide catalyzed by $CdCl_2$ under thermal and microwave irradiation (Scheme 5). The microwave irradiation was effective in the reduction 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 *o*-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-1*H*-1, 5-benzodiazepin-5-ium ion 18 [25] in Scheme 6.



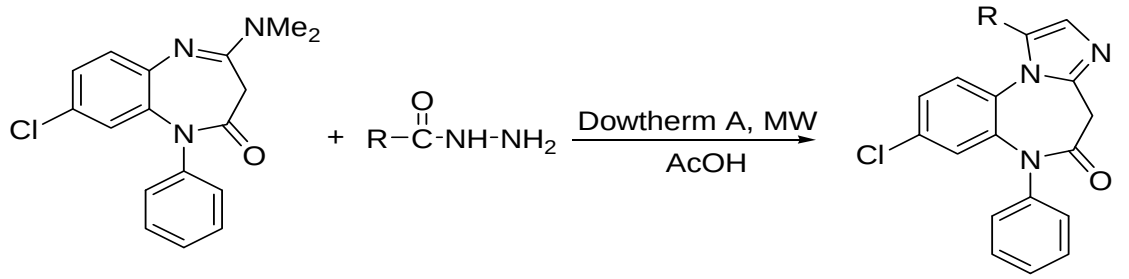
Scheme 1



Scheme 2

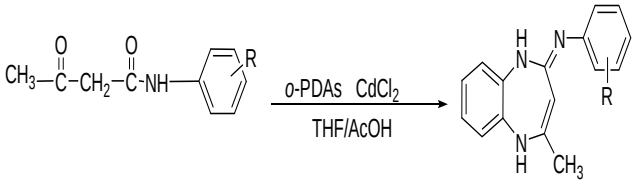


Scheme 3



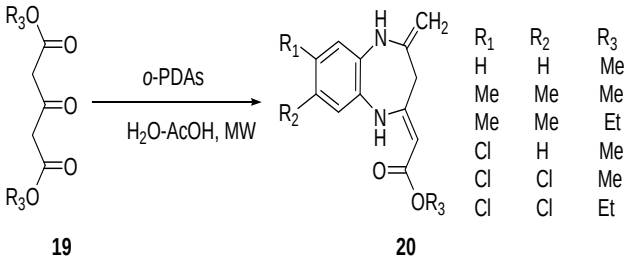
R = CH_2CH_2Me, CH_2Ph, CH_2CO_2Et, *p*ClPh, Ph, *m*-OMePh, C_5H_5N, $CH_2N(CH_2CH_2)_2O$

Scheme 4



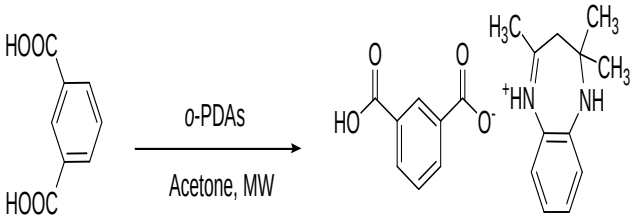
R= *o*-OMe, *p*-OMe, *o*-Me, *m*-Me, *p*-Me, *o*-Cl, *m*-Cl, *p*-Cl, *p*-Br, H

Scheme 5

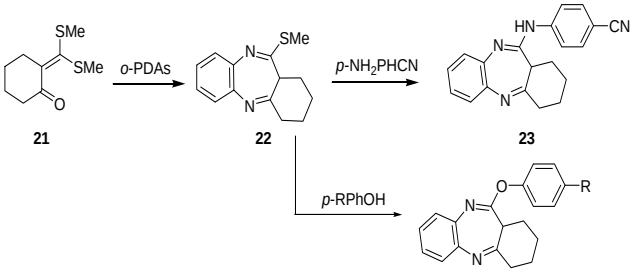


Scheme 7

*o*PDAs also from 2,3-diaminonaphthalene and 2,3-diaminopyridine



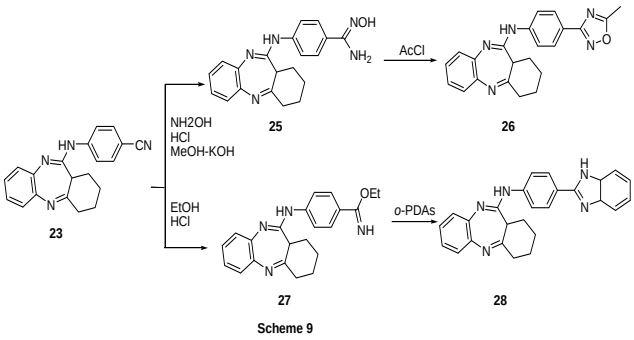
Scheme 6



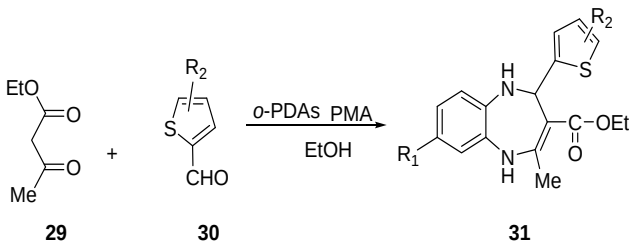
Scheme 8

Some cytogenetic active enamino-1,5-benzodiazepines 20 were prepared by the condensation of 1, 3, 5-triketones with *o*-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 *o*-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, *o*-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].

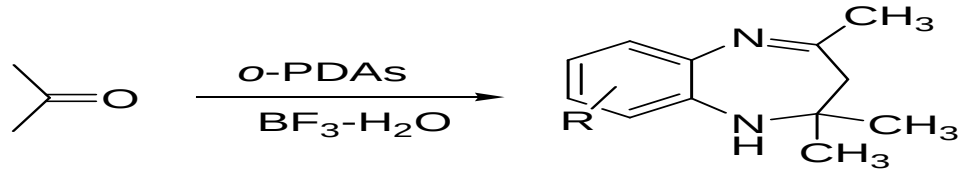


Scheme 9



R_1= H, Me, Br; R_2 = H, 3-Me, 4-Me, 3-Br, 4-Br, 5-Br

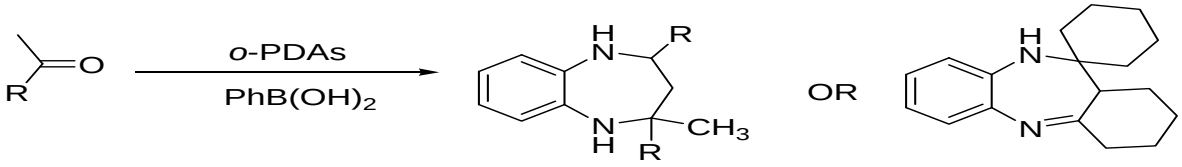
Scheme 10



32 **33**

R = Me, F, CF_3

Scheme 11

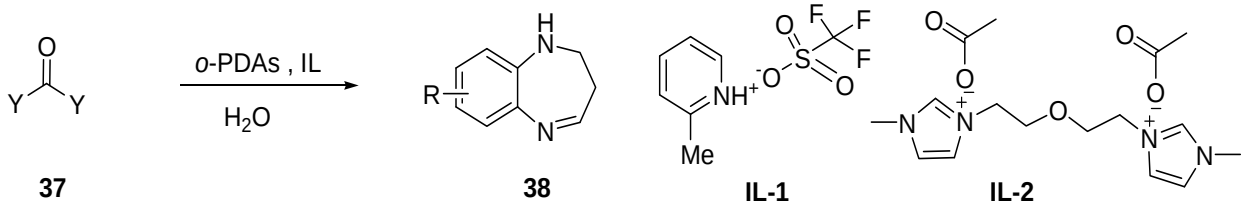


34 **35** **36**

R = Me, Et, *p*BrPh, *p*MePh, *p*BrPh, *p*OHPh, *p*OMePh, *p*NO_2Ph for cyclicketones

Scheme 12

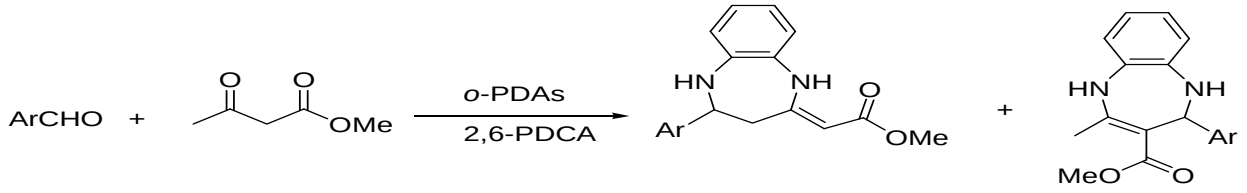
Another efficient protocol for the synthesis of 1,5-benzodiazepines by the reaction of *o*-phenylenediamine with ketones was demonstrated using a re-usable protic pyridinium ionic liquid [2-MPyH] OTf catalyst (IL-1) in aqueous mixture [31] as shown in Scheme 13. An ionic liquid has also been employed under solvent free condition to prepare 1,5-benzodiazepines by the condensation of *o*-phenylenediamine with ketones. The cationic ionic 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, β-ketoesters, and arylaldehydes. The 2-pyridinecarboxaldehyde was regioselective towards the α-products 42 [36] shown in Scheme 14. Several green catalysts have been employed as catalyst for the cyclocondensation of *o*-phenylenediamine, β-ketoesters or ketones, and arylaldehydes using green methodologies. These catalysts include HY zeolites, sulfamic acid, $YbCl_3$, $Yb(OPf)_3$, K-10 montmorollonite clay, ambeylist-15 [37], silica gel using ultrasound [38], $AlCl_4$ [33], silicotungstic acid, phosphotungstic acid, $FeCl_3$ and *p*TsOH [36]. The organocatalyst 2, 6-pyridinedicarboxylic acid (2, 6-PDCA) catalyzed the regioselective synthesis of 1,5-benzodiazepine derivatives from *o*-phenylenediamine, β-ketoesters, and arylaldehydes in a three-component reaction, Scheme 14 and 15. Only the γ–products 41 were formed by the C–C bond formation at the γ-position of β-ketoesters [39].



37 **38** **IL-1** **IL-2**

37 = Acetone, 2-butanone, 2-pentanone, 3-pentanone, 3-Methylbutan-2-one, Acetophenone, cyclopentanone, cyclohexanone, 6-Methyl-5-heptan-2-one, R=H, 4-Me, 4,5-diMe, 4-NO_2

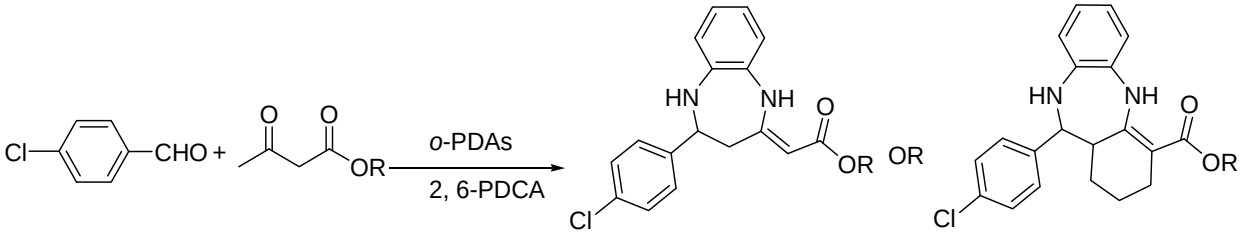
Scheme 13



39 **40** **41** γ-prdt **42** α-prdt

Ar = Ph, *p*ClPh, *p*MePh, *p*OMePh, *p*NO_2Ph, *o*NO_2Ph, *p*BrPh, *p*OHPh, *o*BrPh, *p*OHPh, furan, pyrrole, 3-methylthiophene, Indole

Scheme 14

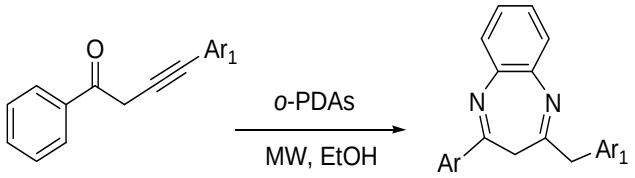


43 **44** **45** **46**

R = Et, $C(CH_3)_3$, CH_2CHCH_2 from cyclicketones

Scheme 15

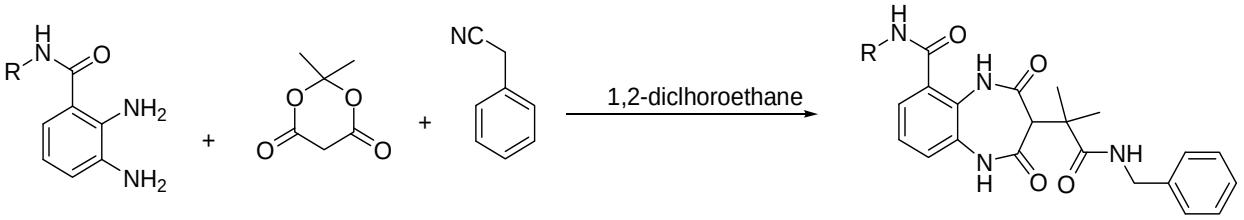
1,5-benzodiazepines 48 were synthesized from the reaction of alk-3-yn-1-ones with *o*-phenylenediamines assisted by microwave irradiation (Scheme 16) and devoid of catalysts [40]. Novel potential anticancer agents were synthesized using a one-pot three-component reaction of diamides, Meldrum's acid, and benzyl isocyanide as shown in Scheme 17. The benzodiazepines exhibited moderate to potent *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) [19]. 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 [41].



47 **48**

Ar= Et, Ph, *p*-BrPh, *p*-ClPh; Ar_1= Ph, *p*-MePh, *p*-*t*-BuPh

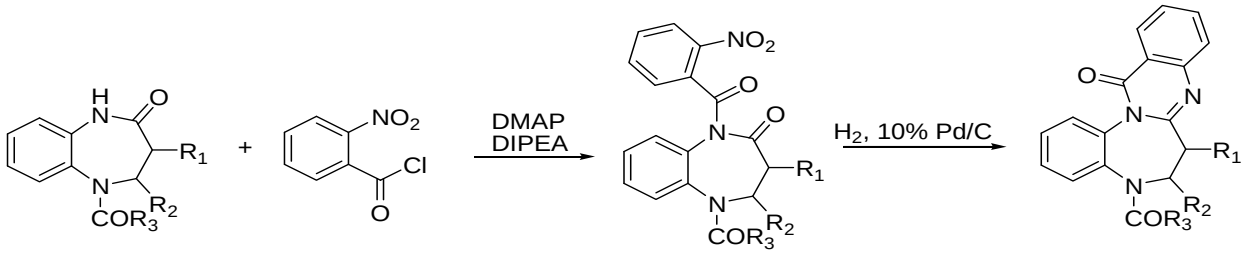
Scheme 16



49 **50** **51** **52**

R = Isopropyl, benzyl, 3-(trifluoromethyl)benzyl, 3-chloro-4-fluorobenzyl, pyridin-2-ylmethyl, 3-(trifluoromethyl)phenyl, 3-chlorophenyl, 4-(trifluoromethyl)phenyl, phenyl, cyclopropyl

Scheme 17



R_1=R_2 = H, Me; R_3= H, Me, OEt, CF_3

53 **54** **55** **56**

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 withα,β-unsaturated ketone, aliphatic ketones, β-diketones, β-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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5. References

1. Aastha P, Navneet K, Anushu A, Pratima S, Dharma K. 1, 5- Benzodiazepines: Overview of properties and synthetic aspects. Res J Chem Sci. 2013; 3:90-103.
2. Eleftheriadis N, Neochoritis CG, Tsoleridis CA, Stephanidou-Stephanatou J, Iakovidou-Kristi Z. One-pot microwave assisted synthesis of new 2-alkoxycarbonylmethylene-4-oxo-1,5-benzo-,naphtha-and pyridodiazepines and assessment of their cytogenic activity. European J Med Chem. 2013; 67:302-309.
3. Salve PS, Mali DS. 1,5-benzodiazepine: A versatile pharmacophore. Int J Pharma Bio Sci. 2013; 43(11):345-370.
4. Salve PS, Mali DS. An expenditious and efficient microwave assisted synthesis of 1,5-benzodiazepine derivatives. J Chem Pharma Res. 2013; 5(2):158-161.
5. Sternbach H, Montclair UNI 1, 4-benzodiazepine-4-oxides. US Patent 2893992, 1959.
6. Mihic SJ, Harris RA. Hypnotics and sedatives, in: Brunton LL, Chabner BA, Knollmann BC, (Eds.), Goodman & Gilman's the pharmacological basis of therapeutics. McGraw Hill and Company, New York 2011, 457-480.
7. Bariwal JB, Upadhyay KD, Manvar AT, Trivedi JC, Singh JS, Jain KS *et al*. 1, 5-Benzothiazepine, a versatile pharmacophore: a review. Eur J Med Chem. 2008; 43(11):2279-2290.
8. Casher MI, Botswick JR, Yasugi S. Benzodiazepines: a versatile clinical tool. Current Psychiatry 2012; 11(4):55-63.
9. Brambilla G, Carrozzino R, Martelli A. Genotoxicity and carcinogenicity studies of denzodiazepines. Pharmacol Res 2007; 56(6):443-458.
10. Claramunt RM, Alkorta I, Elgureo J. A theoretical study of the conformation and dynamic properties of 1,5-benzodiazepines and their derivatives. Comput Theor Chem 2013; 1019:108-115.
11. Kurasawa Y, Okamoto Y, Ogura K, Takada A. Facile synthesis of novel 3-quinoxalinyl-1,5-benzodiazepines *via* ring transformation. Stable tautomers in the 1, 5-benzodiazepin-2-one ring system. J Heterocycl Chem. 1995; 22(3):661-664.
12. Rabahi A, Hamdi SM, Rachedi Y, Hamdi M, Talhi O, Paz FAA, *et al*. X-ray crystallography and theoretical studies of the reaction mechanism for the synthesis of 1,5-benzodiazepines from dehydroacetic acid derivatives and o-phenylenediamine. J Mol Struct. 2014; 1061:97-103.
13. Steffan RJ, Failli AA. Pyrrolobenzodiazepine carboxyamide vasopressin agonists. European Patent, EP 2000; 1(149):104B1.
14. Kester M, Karpa DK, Vrana EK. Elsevier's Integrated Review Pharmacology, 2nd ed Elsevier, Amsterdam, 2012.
15. Pagel JF, Parnes BL. Medications for the treatment of sleep disorders: An overview. J Clin Psychiatry. 2001; 3(3):18-125.
16. Malcolm, R.J. GABA systems, benzodiazepines and substance dependence. J Clin Psychiatry. 2003; 64(3):36-40.
17. Nemeroff CB. The role of GABA in the pathophysiology and treatment of anxiety disorders. Psychopharmacol Bull 2003; 37(4):133-46.
18. Lance P, Longo MD, Johnson B. Addiction: Part I. Benzodiazepines-side effects, abuse risk and alternatives. Am Fam Physician 2000; 61(7):2121-2128.
19. Chen Y, Le V, Xu X, Shao X, Liu J, Li Z. Discovery of novel 1,5-benzodiazepine-2,4-dione derivatives as potential anticancer agents. Bioorg Med Chem Lett 2014; 24(16):3948-3951.
20. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2013. http://www.emcdda.europa.eu/publications/drug-profiles/benzodiazepine. Accessed 05 Nov. 2014.
21. Ilango SS, Remya PU, Ponnuswamy S. Synthesis and antimicrobial activity of novel 1,5-benzodiazepines. Indian J Chem. 2013; 52B:136-140.
22. Kumaraswamy MN, Vaidya VP, Chandrashekhar C, Parthima-Mathias DA, Shivakumar H, Mahadevan KM. Synthesis of novel 2, 5-dihydro-1H-1,5-benzodiazepines encompassing naphtha [2, 1-B] furan and evaluation of their pharmacological activities. Inter J Pharm Chem Bio Sci. 2013; 3(2):281-287.
23. Nikas P, Gatta E, Cupello A, Di Braccio M, Grossi G, Pellistri F *et al*. Modulation of native $GABA_A$ receptor activity by triazolo 1,5-benzodiazepines. Neuroscience 2013; 243:158-164.
24. Dong ZQ, Shi H, Chen SL, Chen HX, Jiang WB, Liu FM, *et al*. Synthesis of 1,5-benzodiazepine derivatives containing 1,2,3-triazole moiety *via* 1, 3-dipolar cycloaddition reaction J Heterocycl Chem. 2014. DOI: 10.1002/jhet.1733.
25. Odame F, Kleyi P, Hosten E, Betz R, Lobb K, Tshentu Z. The formation of 2, 2, 4-trimethyl-2, 3-dihydro-1H-1,5-benzodiazepine from 1, 2-diaminibenzene in the presence of acetone. Molecules 2013; 18(11):14293-14305.
26. Sharma P, Kumar N. Synthesis of amidine, imidates esters, oxadiazoles, imidazoles banzimidazole derivatives of face 'C' annulated 1,5-benzodiazepines. Inter J Pharma Bio-Sci. 2014; 5(1):278-284.
27. Li XQ, Wang LZ. Highly efficient one-pot, three-component synthesis of 1,5-benzodiazepine derivatives. Chin Chem Lett 2014; 25(2):327-332.
28. Prakash GKS, Paknia F, Narayan A, Mathew T, Olah GA. Synthesis of perimidine and 1,5-benzodiazepine derivatives using tamed Bronsted acid, BF_3-H_2O. J Fluorine Chem. 2013; 152:99-105.
29. Goswami SV, Throat PB, Bhusare SR. Phenylboronic acid catalysed synthesis of 1,5-benzodiazepines via condensation of o-phenylenediamine and ketones, J Chem Sci. 2013; 125(4):745-749.
30. Sajjadifar S, Rezayati S. A simple and new method for the synthesis of 1,5-benzodiazepine derivatives catalyzed by boron sulfonic acid in solvent H_2O/EtOH. Inter J ChemTech Res. 2013; 5(4):1964-1968.
31. Alinezhad H, Tajbakhsh M, Norouzi M, Baghery S. An efficient and green protocol for The Synthesis of 1,5-benzodiazepine and quinoxaline derivatives using protic pyridinum ionic liquid as a catalyst. World Appl Sci J. 2013; 22(12):1711-1717.
32. Jadhav AH, Kim H. Solvent free synthesis of 1,5-benzodiazepine derivatives over the heterogeneous silver salt of silicotungstic acid under ambient conditions. RSC Adv 2013; 3:5131-5133.

33. Jadhav HA, Chinnappan A, Patil HR, Kostjuk VS, Kim H. Short oligo ethylene glycolic tailor-made ionic liquids as highly efficient and reusable catalyst for one-pot synthesis of 1,5-benzodiazepine derivatives under solvent free condition. Chem Eng J. 2014; 240:228-234.
34. Sandhar A, Singh RK, Rapid and efficient synthesis of 2, 3-dihydro-1H-1,5-benzodiazepines catalyzed by chloroacetic acid screened among various aliphatic acids under solvent free conditions. Chem Sci Tran 2013; 2(1):176-180.
35. Langade M, Pachpinde A. One pot solvent-free synthesis of 1,5-benzodiazepine derivatives. J Chem Pharm Res. 2013; 5(5):37-40.
36. An YS, Li XQ, An XR, Wang LZ. $FeCl_3$–SiO_2 promoted one-pot, three-component synthesis of novel 1,5-benzodiazepine derivatives. Monatshefte für Chemie 2014; DOI: 10.1007/s00706-014-1275-9.
37. Jeganathan M, Pitchumani K. Solvent-free syntheses of 1,5-benzodiazepines using HY zeolite as a green solid acid catalyst. ACS Sustainable Chem Eng 2014; 2(5):1169-1176.
38. Chikhale VR, Khedekar BP. Ultrasound assisted one-pot synthesis of some 1,5-benzodiazepine derivatives. Current Catalysis 2014; 3(3):111-115.
39. Lal M, Basha S, Sarkar S, Khan AT. 2, 6-Pyridinedicarboxylic acid as organocatalyst for the synthesis of 1,5-benzodiazepines through one pot reaction. Tetrahedron Lett 2013; 54(32):4264-4272.
40. Solan A, Nişanci B, Belcher M, Young J, Schäfer C, Wheeler AK, *et al*. Catalyst-free chemo-/regio-/stereo-selective amination of alk-3-ynones. Synthesis of 1,5-benzodiazepines and 3-amino-2-alkenones, Green Chem 2014; 16:1120-1124.
41. Janciene R, Mikulskiene G, Javorskis T, Vektariene A, Vektaris G, Kosychova L. Dihydroquinazolino [3, 2-a] [1,5] benzodiazepines: Synthesis and computational study of reductive N-heterocyclization of N-(2-nitrobenzoyl)-1, 5-benzodiazepin-2-ones, J Heterocycl Chem. 2014; DOI: 10.1002/jhet.2038.