One-pot strategy to synthesize seven–membered 1,4-diazepine heterocyclic scaffolds assisted by zinc oxide nanoparticles as heterogeneous catalytic support system

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| CHRONICLE	ABSTRACT
	The present paper elicits the zinc oxide nanoparticles-assisted synthesis of a new series of seven-membered 1,4-diazepine heterocyclic compounds as potent lead scaffolds. Structures of synthesized compounds were corroborated using spectroanalytical techniques viz, FT-IR, 1H, ^{13}C NMR, Mass, and elemental analysis. Also, Field emission scanning electron microscopy (FE-SEM), Transmission electron microscopy (TEM), Energy dispersive x-ray analysis (EDAX), powder X-ray diffraction (PXRD), and Fourier transform infrared spectroscopy (FT-IR) were used to establish the structure and morphology of the synthesized nanocatalyst. The clean workup procedure, high to excellent yields, relatively short reaction times, and high atom economy are the incredible advantages associated with the protocol.

1. Introduction

Heterocyclic compounds constitute the largest diversity of organic molecules of chemical, biomedical, and industrial significance. The dominance of polymerized organic compounds as an eloquent factor in the discrete area is conventional. Heterocyclic constituents depict a significant part of human life, on account of their biological eminence, under the stress of pathogens. Heterocyclic compounds have a predominant disparity of praxis in medicine and fertilizer processing, and their unconventional predominant requisition beforehand for these compounds came to be proclaimed beforehand. Heterocyclic compounds acquired the center of attention on the leading edge because of their extensive biological activities. The fusion of an operating platform in the composition of heterocyclic compounds reinforces valuables aligned with them.[1-10] Diazepines are considered the biologically active epitope antigenic determinant and the useful building blocks in the construction of various pharmaceutically significant lead molecules.[11] Their derivatives are imperious types of compounds that have been widely explored for pharmacological activities such as antibacterial, antiviral, antioxidant, anticancer, antitumor[12-13], antiparasitic[14], antiemetic, antihistaminic, spasolytic[15], antagonistic, anticonvulsive, anti-inflammatory and anti-fungicidal.[14-16] Some of them are an integral component of antimalarial drug therapy, anti-HIV, and other various pharmaceutical applications.[17] Certain drugs embracing azepine nucleus are used for the treatment of Parkinson's and Alzheimer's disease since they exhibit anticonvulsant activity and may be used as tranquilizers.[18] Moreover a number of 1,4 azepine derivatives find their utility as dyes for acrylic fibers,[19] as valuable intermediates for the synthesis of fused hetero- diazepine compounds bearing triazole,[20]oxadiazole,[21]oxazine,[22] and Furano-nuclei.[23]

Therefore, keeping in view such a wide range of pharmaceutical profiles and industrial applications associated with such an important seven-membered aza-scaffold, the development of mild and efficient protocols for their preparation continues to be a challenging endeavor for synthetic organic chemists.[24-25] Some commonly reported literature methods include cycloaddition reactions, [26]imino-annulation, [27] ring-closing metatheses [RCM], [28,] and coupling reactions.[29-31] However a large number of methods reported in the literature suffer from several bottlenecks viz the use of drastic conditions, lesser yields, and typical product isolation procedures. Though certain improvements have been proposed to overcome the shortcomings of existing methods by incorporating ionic liquids, [32]silica-supported acids,[33] metal triflates,[34]HY-zeolites,[35] and boronic acids,[36] L-proline,[37] TMSCI/NaI,[38] InCl3,[39] and DBU,[40] in synthetic protocols. Also, the use of microwave,[41] ultrasound - radiation,[42,] and aqueous media,[43] have also been reported to achieve the improvement in their synthetic outcomes to some extent. Hence, buoyed from these findings vis-à-vis to overcome the shortcomings of the existing synthetic strategies, it was thought worthwhile to develop an efficient, cost-effective, eco-savy, neat protocol for synthesizing 1,4-azepine derivatives 5,7-dimethyl-6-(phenyldiazenyl)-3,6-dihydro-2H-1,4-diazepine derivatives 5(a-e) and 2,4-dimethyl-3-(phenyldiazenyl)-3H-benzo 6(a-e) as medicinally potent heterocyclic scaffolds. The role of zinc oxide nanoparticles (ZnO NPs) was corroborated in the synthetic strategy (Scheme 1) as the heterogenous support catalytic system. It is known that the surface of zinc oxide possesses both Lewis acidic and basic sites.[44-47] Therefore, ZnO nanoparticles were synthesized using the precipitation process, considering a modified literature-based protocol. This single-step process to scale up the production without unwanted impurities is desirable for the cost-effective preparation of ZnO nanocrystals. Moreover, ease of separation of catalyst, reusability, recyclability, and waste-free protocol are the attributes to place the strategy as green and environmentally benign. An overview of the synthetic strategy to develop a series of 1,4 –diazepines is elicited in scheme 1.

Scheme 1. Synthesis of substituted-1,4 diazepine derivatives
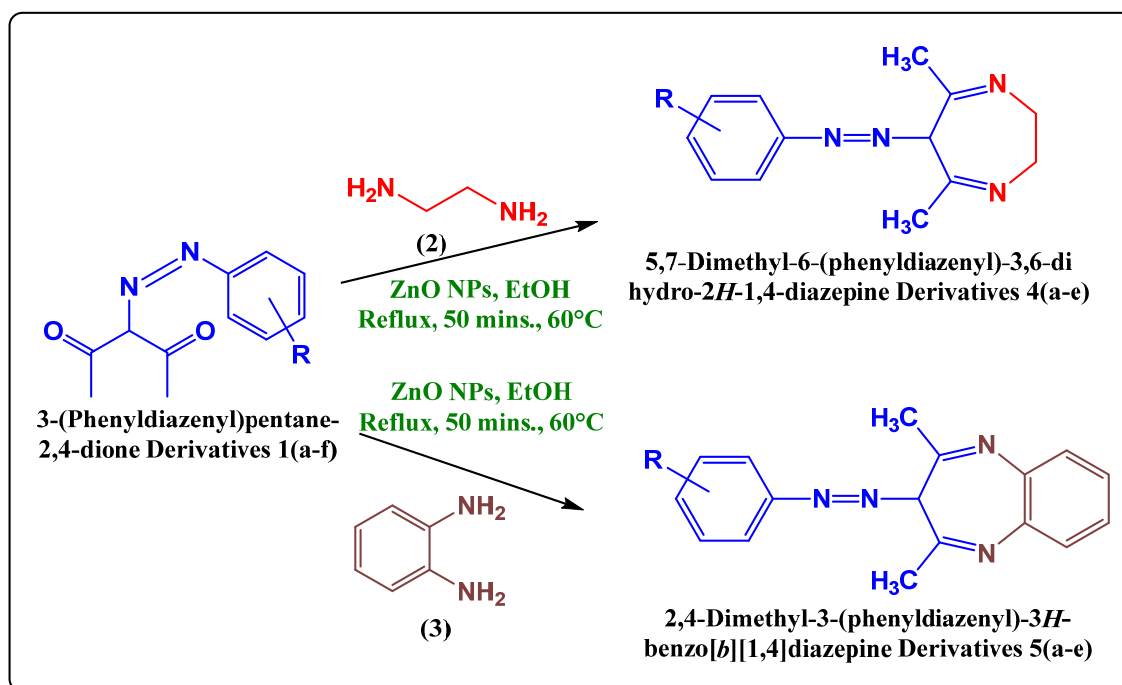
Initially, a series of aryldiazonium compounds coupled to pentane-2,4-dione 1(a-f) was prepared as per the method reported in the literature. [48] The 1(a-f) was treated with ethylene diamine (EDA) (2)/ ortho phenylene diamine (OPD) (3) to yield the desired 1,4-diazepine derivatives 5,7-dimethyl-6-(phenyldiazenyl)-3,6-dihydro-2H-1,4-diazepine derivatives 4(a-e) and 2,4-dimethyl-3-(phenyldiazenyl)-3H-benzo 5(a-e), respectively after being assisted by ZnO NPS as the heterogeneous catalyst.

2. Results and discussion

2.1 Characterization of Catalyst

The optical and nanostructured characteristics of the produced ZnO nanoparticles were screened. **Fig. 1** displays an X-ray diffraction pattern with large peaks centred at 31.7°, 34.4°, 36.2°, 47.5°, 56.6°, 62.9°, 66.4°, 67.9°, 69.1°, 76.9°, which correspond to the presence of (100), (002), (101), (102), (110), (013), (200), (112), (201), (202) indices, respectively.[49]
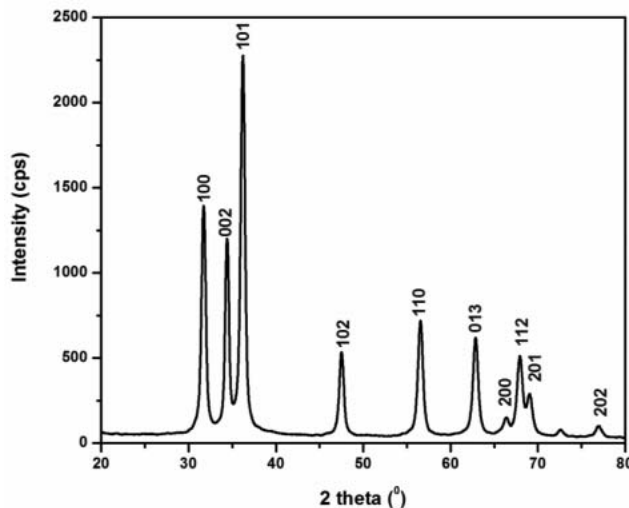
Fig. 1. PXRD pattern of zinc oxide nanoparticles

All of the diffraction peaks were attributed to the pure zincite hexagonal phase of ZnO (space group p63mc), with lattice parameters a = 3.25 and c = 5.21, which are consistent with JCPDS card no.96-900-4180. There were no characterization peaks for any other phase of ZnO, indicating that the produced material was pure. The sharpness of the peaks revealed the catalyst's crystalline form. The existence of many peaks implies that the crystallites are oriented randomly (**Fig. 1**). The Debye-Scherrer formula (equation 1) was used to compute the average crystallite size.

$$D = \frac{K\lambda}{\beta Cos\theta} \tag{1}$$

where, D denotes crystallite size, K = Scherrer constant (shape factor) = 0.9, λ = 0.154nm is the wavelength of the incident CuKα radiation, β represents full-width at half maximum of the corresponding peak, and is the Bragg diffraction angle. The equation determined that the average crystallite size was 21.3 nm. SEM and TEM investigations were used to further establish the catalyst's morphology (**Fig. 2**). [49] The SEM pictures of ZnO nanoparticles at various magnifications are shown in **Fig. 2A** and **Fig. B**. The generation of ZnO nanoparticles is confirmed by these flower-like images. The XRD pattern confirmed the crystalline structure of the zinc oxide flower. The diameter of the flower-like structure is estimated to be between 1-2 μm.
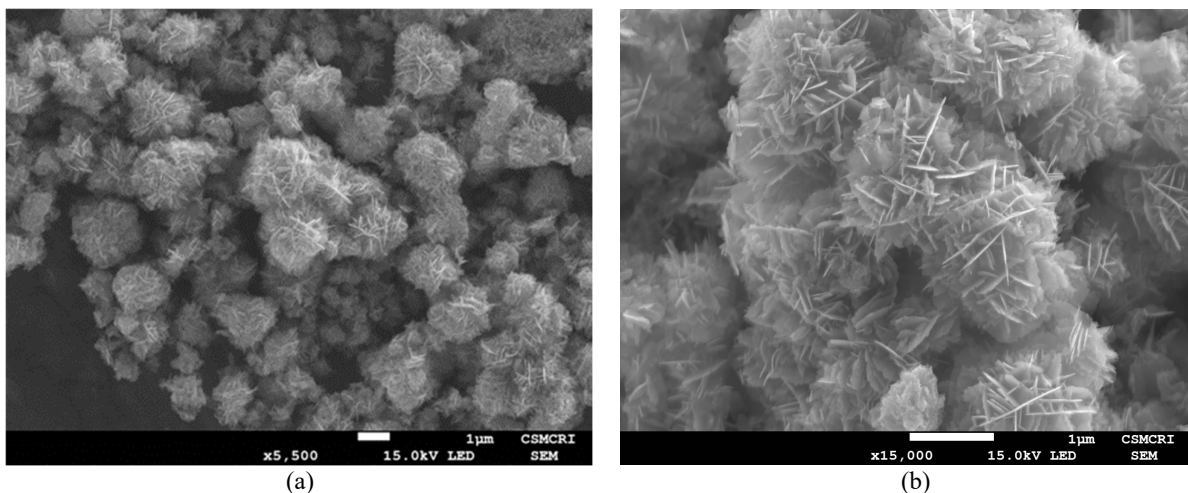

(a)   (b)

Fig. 2. SEM images of zinc oxide nanoparticles

Fig. 3A and Fig. **3B** depict TEM pictures of the catalyst's development into a flower-like structure. The sample's single-crystalline structure was shown by the TEM picture, which showed distinct lattice fringes. The lattice spacing is 0.45 nm as observed. Only zinc and oxygen are present in the sample, according to the EDX analysis shown in **Fig. 4**, with no other contaminants.[49]
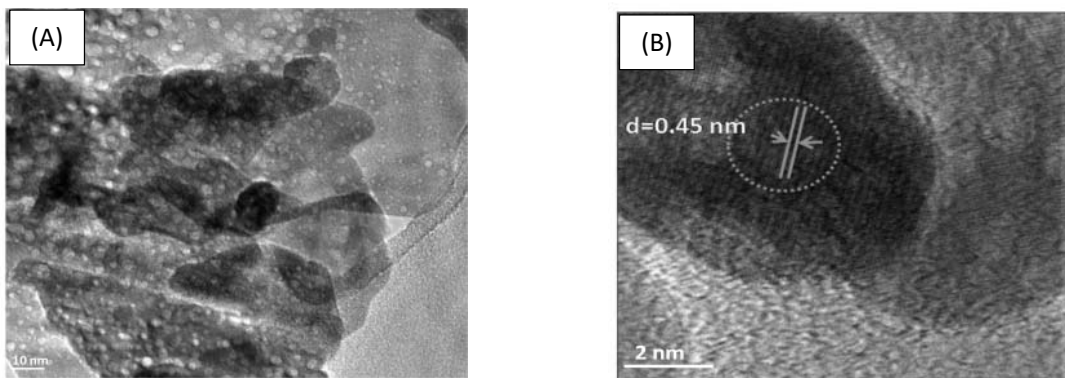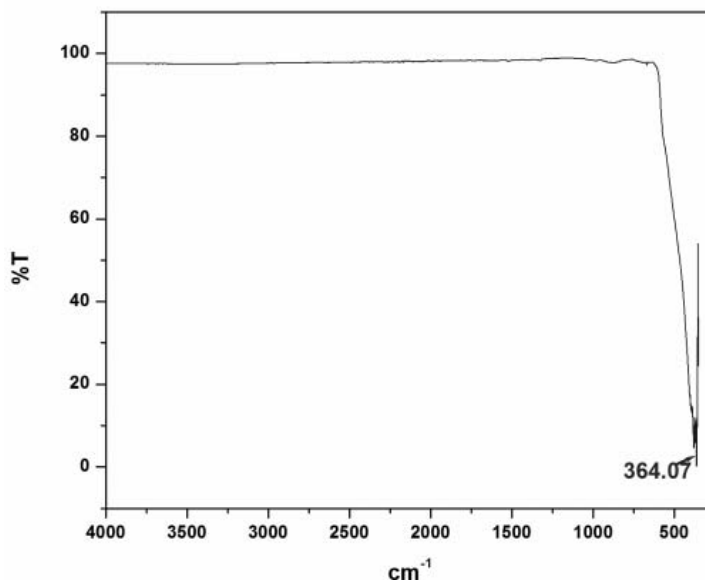
Fig. 3. TEM pattern of zinc oxide nanoparticles
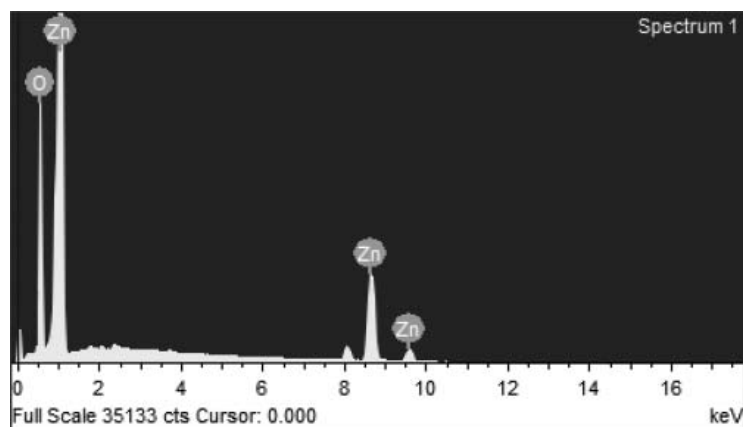
Fig. 4. EDAX pattern of zinc oxide nanoparticles

Similarly, the appearance of a strong peak in the FT-IR spectrum at 364.07 cm 1 in **Fig. 5** indicated the presence of a Zn-O vibrational peak in the produced ZnO NPs. The absence of any additional IR frequency peak validates the produced catalyst's structural purity. [49]

Fig. 5. FT-IR spectrum of zinc oxide nanoparticles

Under ethanolic conditions, the role of zinc oxide NPs as catalytic support for the synthesis of aryl azo diazepine derivatives was investigated. Condensing 3-(phenyl diazinyl) pentane-2,4-dione 1(a) and ethane-1, 2diamines (2) in the presence of a variable catalytic quantity of ZnO NPs was used to conduct optimization experiments (5-20 mole %).

Table 1. Optimization of catalyst concentration for the model reaction
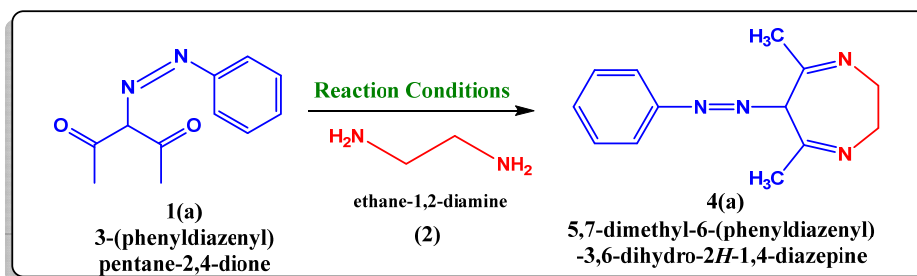
Entry	Without Catalyst	ZnO NPs	ZnO NPs	ZnO NPs	ZnO NPs	ZnO (Bulk)	ZnO (Bulk)
Catalyst (mole %)	-	5	10	**15**	20	15	20
Time [b] (mins.)	90	80	60	**50**	80	90	90
Temperature (°C)	80	60	70	**60**	80	70	80
Yield [c] (%)	38	70	83	**92**	90	66	65

[a]**Reaction Conditions**: The mixture of 3-(phenyl diazenyl)pentane-2,4-dione 1(a) (2mmole) and Ethane–1, 2 diamines (2) (2mmole) with or without different concentrations of catalysts was heated at different temperatures.
[b] Progress of the reactions was monitored by TLC.
[c] Isolated Yields.
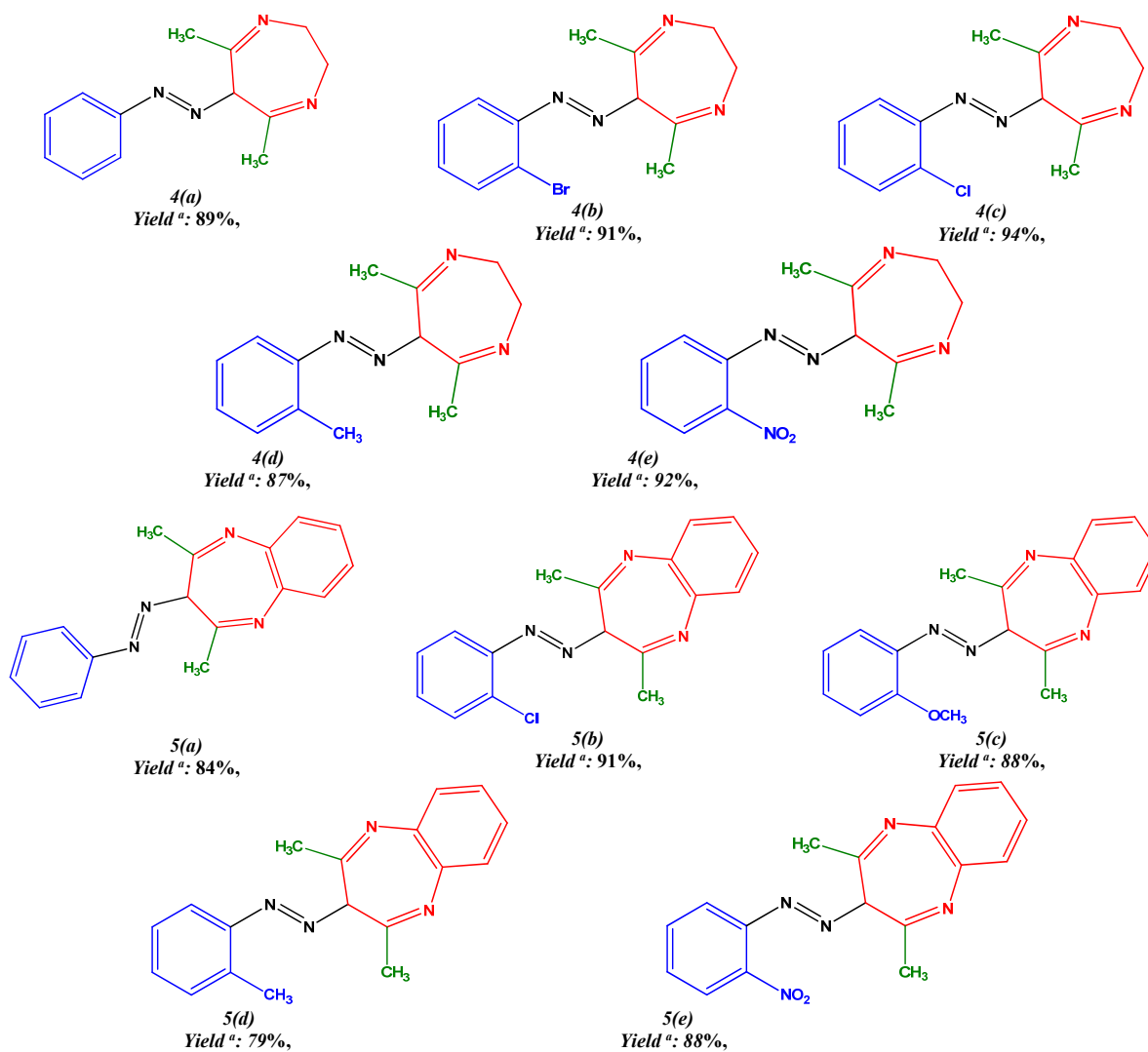
Fig. 6. A library of synthesized 1,4-diazepines

[a]Isolated Yields.

Initially, the reaction was carried out under ambient conditions using 5 mole% of catalyst loading in solvent-free media. An unsatisfactory yield was obtained after the elapse of 4 hrs. reaction time. No remarkable change took place on even increasing the reaction time up to 8 hrs. It was observed that upon using 15 mole% of ZnO at 60°C. The yield of desired product; 5,7–dimethyl 1-6(phenyl diazenyl)–3,6-dihydro–2H-1,4-Diazepine derivative is 92% which is the maximum. The use of ZnO in comparison to bulk ZnO reduces the reaction time by a factor of two with higher yields. This may be assigned to the nano size of the catalyst particles with enhancement in the surface area.[50, 51]

The ^{1}H NMR spectrum of compound (4a) showed an up field singlet resonance at δ 1.95 ppm as characteristic of the two adjacent methyl groups (C-10', 15'). A singlet at δ 3.68 confirms the presence of two methyl groups on the azepine ring. A one proton singlet at δ 5.28 justifies the presence of C-6 proton, whereas phenyl ring protons, delineated a multiplet at δ 7.48 – 7.65. Likewise, the FT-IR bands at 3070 cm^{-1} and 3004 cm^{-1} correspond to the sp^2 and sp^3 hybridized C-H stretching vibrations, respectively. The azo group (N=N) exhibits a peak at 1795 cm^{-1}, while the stretching frequency at 11632, 1542, and 1411 cm^{-1} corresponds to the C-C ring vibrations. A typical band around 1660 cm for the C=C/C=N group indicates at 1688 and 1667 cm^{-1} indicates the presence of C=C/C=N functional groups.

The protocol was validated for reactions of structurally different substrates using the optimum reaction conditions for the model system, as indicated in **Fig. 6**. A wide range of substituted anilines with both electron-withdrawing and electron-donating groups can be tolerated by the reaction. The reaction time and yields were affected by steric hindrance. [52] Chloro-substituted molecules outperformed all other substituted anilines in terms of the yield of the products. (**Fig. 6**, entries 4(c) and 5(b)).
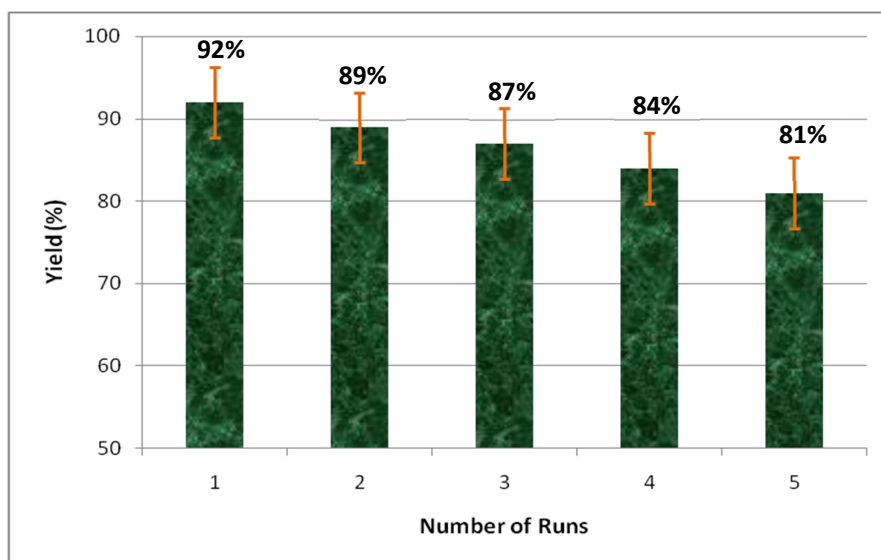
Fig. 7. Reusability of the synthesized catalyst

3. Conclusion

A simple, efficient, and environmentally friendly method for obtaining 1,4 diazepine scaffolds was developed and reported herein. The intermediacy of ZnO NPS as a heterogeneous catalytic system aided the development of the protocol, which resulted in the desired synthesis of 5,7-dimethyl-6-(phenyldiazenyl)-3,6-dihydro-2H-1,4-diazepine derivatives 4(a-e) and 2,4-dimethyl-3-(phenyldiazenyl)-3H-benzo 5(a-e). The facile recovery and reusability of the catalyst are elicited by this one-pot synthesis approach. Furthermore, the established protocol's clean conditions, short reaction time, high yields, and ease of workup are among the notable benefits that make this strategy for inclusion in green chemistry tenets.

4. Experimental section

All chemicals were procured from Sigma Aldrich and Merck India and were not purified further. The reactions were carried out in an aerobic environment with no special precautions taken. FrontierPerkin-ElmerFT-IRSP10STD was used to record Fourier Transform Infrared (FT-IR) spectra as ATR spectra in the range of 4000–350 cm^{-1}. The ^{1}H and ^{13}CNMR spectra of the produced compounds were recorded at 400 MHz in chloroform (CDCl$_3$) solvent using a Bruker Advance II 400 NMR spectrometer, and chemical shifts were represented in parts per million. Using electrospray ionization (ESI) in positive mode, mass analysis was performed on a quadrupole-time-of-flight (Q-TOF) mass spectrometer (MICROMASS). CuK-alpha radiations of 0.154 nm were used in the XRD experiments using a Bruker D8 Advance X-ray diffractometer. A Jeol (Jem-2100) electron microscope was used to capture transmission electron microscopy (TEM) pictures at a 200 kV

acceleration voltage. Scanning Electron Microscopic (SEM) images and their corresponding Electron Dispersive X-ray analysis (EDX) data were recorded by Jeol microscope (JSM7100F). Elemental analyses were performed on Thermo Scientific (Flash 2000) CHN Elemental Analyzer. Thin-layer chromatography (TLC) was performed using precoated aluminum sheets with silica gel 60F254.[53-56]

4.1 Synthesis of Zinc Oxide Nanoparticles (ZnO NPs) as Heterogeneous Catalyst

The hydrothermal chemical precipitation approach was used to synthesize the catalyst.[49] A 25 mL aqueous solution of zinc acetate dihydrate (0.5 M or 2.29 gm) (A) was prepared at room temperature for 15 minutes with steady stirring. A homogeneous solution (B) was made in another round-bottomed flask by dissolving (1.25 M or 1.29 gm) sodium hydroxide in 25 ml distilled water using a magnetic stirrer at room temperature for 15 minutes. Now, the zinc acetate solution (A) was added dropwise to the sodium hydroxide solution (B) for about 10 minutes. The resultant solution was stirred continuously for two hours at room temperature, yielding zinc hydroxide in the form of a white precipitate. The precipitate was filtered and washed with ethanol and distilled water. The precipitate was dried in the air at around 80°C before being ground to a fine powder. Finally, the product was calcined for 12 hours at 300°C in a muffle furnace. A yield of 1.5 gm was obtained.

4.2 General procedure for One-Pot Synthesis of 1,4-Diazepines 4(a-e) and 5(a-e)

In a 250 cc round-bottomed flask, compound 1(a-f) (1mmole), ethane-1,2-diamine (EDA) (2) or benzene-1,2-diamine (OPD) (3) (1mmole), ethyl alcohol (20 ml) were taken. Now the catalytic amount of ZnO NPs (15 mole%) was added to the flask and then the contents were refluxed at 60°C with constant stirring for 30 minutes. The progress of the reaction was monitored by TLC (on aluminum sheets precoated with silica) using n-hexane/ethyl acetate (4:1), (v/v) as the eluting system. On completion, the reaction mixture was cooled to room temperature and dissolved in 15ml of ethanol. The catalyst was separated by filtration and the solvent was removed under reduced pressure using a rotatory evaporator. Further. purification of the product was achieved by column chromatography over silica gel using n-hexane /EtOAc (4:1) (v/v) as the eluting system yielding the pure products 4 *(a-e)* and 5 *(a-e)* in good yields.

4.2 The physical analyses data for substituted 1,4-diazepine derivatives 4(a-e) and 5(a-e) are given below:

Compound (4a): 5,7-dimethyl-6-(phenyldiazenyl)-3,6-dihydro-2H-1,4-diazepine *(4a)* Compound was synthesized using 3-(phenyldiazenyl)pentane-2,4-dione (1a) and ethane-1,2-diamine (EDA) (2).

Color: Yellowish Orange; M.P.: 110−112°C; Yield: 89%

FT-IR (ATR, υ, cm^{-1}): 3070 (C−H, sp^2), 3004 (C−H, sp^3), 1795 (N=N), 1688, 1667 (C=C/C=N), 1632, 1542, 1411 (C$\cdots$C ring str.), 723 (CH$_2$);

^{1}H NMR (400 MHz, CDCl$_3$): d 1.95 (6H, s, CH$_3$), 3.68 (4H, s, CH$_2$), 5.28 (1H, s, CH), 7.43-7.65 (5H, m, CH).

^{13}C NMR (400 MHz, CDCl$_3$): δ 14.5 (*C*−5', 7'), 50.3 (*C*−2, 3), 56.6 (*C*−6), 122.2 (*C*−11,15), 127.8 (*C*−13), 128.2 (*C*−12, 14), 149.5 (*C*−10), 151.7 (*C*−5,7).

HRMS (ESI) *m/z*: 229.1407[M+H]$^+$; Anal. Cald. for C$_{13}$H$_{16}$N$_4$: C, 68.39; H, 7.06; N, 24.54 %. Found: C, 68.32; H, 7.04; N, 24.48 %.

Compound (4b): 6-((2-bromophenyl)diazenyl)-5,7-dimethyl-3,6-dihydro-2H-1,4-diazepine (4b)

Compound was synthesized using 3-((2-bromophenyl)diazenyl)pentane-2,4-dione (1b) and ethane-1,2-diamine (EDA) (2).

Color: Orangish Brown; M.P.: 113−115°C; Yield: 91%

FT-IR (ATR, υ, cm^{-1}): 3074 (C−H, sp^2), 3014 (C−H, sp^3), 1789 (N=N), 1661 (C=C/C=N), 1632, 1546, 1417 (C$\cdots$C ring str.), 726 (CH$_2$), 674 (C-Br);

^{1}H NMR(400 MHz, CDCl$_3$): δ 1.93 (6H, s, CH$_3$), 3.66 (4H, s, CH$_2$), 5.23 (1H, s, CH), 7.24 (1H, d ,*J* = 8.0, CH), 7.52 (1H, d, *J* = 7.9, CH). 7.62-7.77 (2H, d, *J* = 8.0, CH).

^{13}C NMR (400 MHz, CDCl$_3$): δ 14.5 (*C*−5', 7'), 50.3 (*C*−2, 3), 56.6 (*C*−6), 113.62 (*C*−11), 117.7 (*C*−15), 128.2 (*C*−13, 14), 133.0 (*C*−12), 139.5 (*C*−10), 151.7 (*C*−5,7).

HRMS (ESI) *m/z*: 307.0537[M+H]$^+$; Anal. Cald. for C$_{13}$H$_{15}$BrN$_4$: C, 50.83; H, 4.92; N, 26.01 %. Found: C, 50.78; H, 4.88; N, 25.99 %.

Compound (4c): 6-((2-chlorophenyl)diazenyl)-5,7-dimethyl-3,6-dihydro-2H-1,4-diazepine (4c)

Compound was synthesized using 3-((2-chlorophenyl)diazenyl)pentane-2,4-dione (1c) and ethane-1,2-diamine (EDA) (2). Color: Creamish Yellow; M.P.: 116−115°C; Yield: 94%

FT-IR (ATR, υ, cm^{-1}): 3068 (C−H, sp^2), 3024 (C−H, sp^3), 1791 (N=N), 1673 (C=C/C=N), 1636, 1548, 1421 (C⁼C ring str.), 787 (C-Cl), 716 (CH$_2$);

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.97 (6H, s, CH$_3$), 3.69 (4H, s, CH$_2$), 5.27 (1H, s, CH), 7.37 (1H, d,J = 7.9, CH), 7.49-7.70 (2H, d,J = 8.0, CH), 7.79 (1H, d,J = 8.2, CH).

^{13}C NMR (400 MHz, CDCl$_3$): δ 14.5 (C−5', 7'), 50.3 (C−2, 3), 56.6 (C−6), 117.7 (C−15), 122.1 (C−11), 128.2 (C−13), 128.3 (C−14), 129.2 (C−12), 151.7 (C−5,7) 152.4 (C−10).

HRMS (ESI) m/z: 263.1069[M+H]$^+$; Anal. Cald. for C$_{13}$H$_{15}$ClN$_4$: C, 59.43; H, 5.75; N, 21.32 %. Found: C, 59.40; H, 5.71; N, 21.28 %.

Compound (4*d*): 5,7-dimethyl-6-(o-tolyldiazenyl)-3,6-dihydro-2H-1,4-diazepine (4*d*)

Compound was synthesized using 3-(*o*-tolyldiazenyl)pentane-2,4-dione (1d) and ethane-1,2-diamine (EDA) (2).

Color: Reddish Orange; M.P.: 121−123°C; Yield: 87%

FT-IR (ATR, υ, cm^{-1}): 3074 (C−H, sp^2), 3037 (C−H, sp^3), 1787 (N=N), 1666 (C=C/C=N), 1634, 1546, 1416 (C⁼C ring str.), 731 (CH$_2$);

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.93 (6H, s, CH$_3$), 2.24 (3H, s, CH$_3$), 3.63 (4H, s, CH$_2$), 5.29 (1H, s, CH), 7.05-7.21 (2H, d,J = 8.2, CH), 7.42-7.56 (2H, d,J = 8.3, CH),

^{13}C NMR (400 MHz, CDCl$_3$): δ 14.5 (C−5', 7'), 17.7 (C−11'), 50.3 (C−2, 3), 56.6 (C−6), 119.1 (C−15), 128.0 (C−11), 128.2 (C−14), 128.4 (C−13), 129.0 (C−12), 150.5 (C−10) 151.7 (C−5,7).

HRMS (ESI) m/z: 244.1508[M+H]$^+$; Anal. Cald. for C$_{14}$H$_{18}$N$_4$: C, 69.39; H, 7.49; N, 23.12 %. Found: C, 69.31; H, 7.44; N, 23.08 %.

Compound (4*e*): 5,7-dimethyl-6-((2-nitrophenyl)diazenyl)-3,6-dihydro-2H-1,4-diazepine (4*e*)

Compound was synthesized using 3-((2-nitrophenyl)diazenyl)pentane-2,4-dione (1e) and ethane-1,2-diamine (EDA) (2).

Color: Reddish Orange; M.P.: 119−121°C; Yield: 92%

FT-IR (ATR, υ, cm^{-1}): 3071 (C−H, sp^2), 3024 (C−H, sp^3), 1792 (N=N), 1669 (C=C/C=N), 1652 (NO$_2$), 1628, 1549, 1419 (C⁼C ring str.), 727 (CH$_2$);

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.93 (6H, s, CH$_3$), 3.61 (4H, s, CH$_2$), 5.30 (1H, s, CH), 7.58-7.85 (3H, d,J = 8.3, CH), 8.12 (1H, d,J = 8.2, CH),

^{13}C NMR (400 MHz, CDCl$_3$): δ 14.5 (C−5', 7'), 50.3 (C−2, 3), 56.6 (C−6), 117.7 (C−12), 123.8 (C−15), 128.2 (C−14), 128.4 (C−13), 129.4 (C−10), 151.7 (C−5,7), 154.8 (C−11).

HRMS (ESI) m/z: 274.1231[M+H]$^+$; Anal. Cald. for C$_{13}$H$_{15}$N$_5$O$_2$: C, 57.13; H, 5.53; N, 23.63 %. Found: C, 57.09; H, 5.50; N, 23.58 %.

Compound (5*a*): 2,4-dimethyl-3-(phenyldiazenyl)-3H-benzo[b][1,4]diazepine *(5a)*

Compound was synthesized using 3-(phenyldiazenyl)pentane-2,4-dione (1a) and benzene- 1,2- diamine (OPD) (3).

Color: Orange; M.P.: 117−119°C; Yield: 84%

FT-IR (ATR, υ, cm^{-1}): 3068 (C−H, sp^2), 3018 (C−H, sp^3), 1788 (N=N), 1671, 1662 (C=C/C=N), 1631, 1528, 1407 (C⁼C ring str.), 721 (CH$_2$);

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.09 (6H, s), 5.06 (1H, s), 7.34 (2H, d, J = 8.3 Hz, CH), 7.42-7.66 (7H, d, J = 8.1 Hz, CH).

^{13}C NMR (400 MHz, CDCl$_3$): δ 14.5 (C−5', 7'), 56.6 (C−6), 122.2 (C−11,15), 127.8 (C−13), 128.1 (C−16, 16'), 128.2 (C−12, 14, 17, 17'), 137.7 (C−2, 3), 149.5 (C−10), 151.7 (C−5,7).

HRMS (ESI) m/z: 277.1405[M+H]$^+$; Anal. Cald. for C$_{17}$H$_{16}$N$_4$: C, 73.89; H, 5.84; N, 20.27 %. Found: C, 73.82; H, 5.79; N, 20.21 %.

Compound (5*b*): 3-((2-chlorophenyl)diazenyl)-2,4-dimethyl-3H-benzo[b][1,4]diazepine (5*b*)

Compound was synthesized using 3-((2-chlorophenyl)diazenyl)pentane-2,4-dione (1c) and benzene- 1,2- diamine (OPD) (3).   Color: Yellow; M.P.: 112−114°C; Yield: 91%

FT-IR (ATR, υ, cm$^{−1}$): 3073 (C−H, sp^2), 3022 (C−H, sp^3), 1789 (N=N), 1674 (C=C/C=N), 1641, 1544, 1417 (C$^{···}$C ring str.), 776 (C-Cl), 718 (CH$_2$);

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.09 (6H, s), 4.95 (1H, s), 7.28-7.44 (3H, d, J = 8.3 Hz, CH), 7.49-7.70 (4H, d, J = 7.9 Hz, CH), 7.79 (1H, d, J = 8.2 Hz, CH)

^{13}C NMR (400 MHz, CDCl$_3$): δ 14.5 (C−5', 7'), 56.6 (C−6), 117.7 (C−15), 122.2 (C−11), 128.1 (C−16, 16'), 128.2 (C−14, 17, 17'), 128.3 (C−13), 129.2 (C−12), 137.7 (C−2, 3),151.7 (C−5,7) 152.4 (C−10).

HRMS (ESI) m/z: 311.1071[M+H]$^+$; Anal. Cald. for C$_{17}$H$_{15}$ClN$_4$: C, 65.70; H, 11.41; N, 18.03 %. Found: C, 65.68 ; H, 11.38; N, 18.01 %.

Compound (5c): 3-((2-methoxyphenyl)diazenyl)-2,4-dimethyl-3H-benzo[b][1,4]diazepine *(5c)*

Compound was synthesized using 3-((2-methoxyphenyl)diazenyl)pentane-2,4-dione (1f) and benzene- 1,2- diamine (OPD) (3).

Color: Dark Orange; M.P.: 119−121°C; Yield: 88%

FT-IR (ATR, υ, cm$^{−1}$): 3071 (C−H, sp^2), 3022 (C−H, sp^3), 1784 (N=N), 1675, 1669 (C=C/C=N), 1638, 1521, 1409 (C$^{···}$C ring str.), 1082 (C-O), 724 (CH$_2$);

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.09 (6H, s), 3.84 (3H, s), 5.00 (1H, s), 7.13-7.41 (4H, d, J = 8.0 Hz, CH), 7.51-7.75 (3H, d, J = 8.3 Hz, CH), 7.87 (1H, d, J = 8.0 Hz, CH).

^{13}C NMR (400 MHz, CDCl$_3$): δ 14.5 (C−5', 7'), 56.0 (C−11'), 56.6 (C−6), 114.3 (C−12), 117.7 (C−15), 128.1 (C−16, 16'), 128.2 (C−14, 17, 17'), 129.4 (C−13), 132.7 (C−10), 137.7 (C−2, 3), 146.3 (C−11), 151.7 (C−5,7).

HRMS (ESI) m/z: 307.1501[M+H]$^+$; Anal. Cald. for C$_{18}$H$_{18}$N$_4$O: C, 70.57; H, 5.92; N, 18.29 %. Found: C, 70.54; H, 5.87; N, 18.21 %.

Compound (5d): 2,4-dimethyl-3-(o-tolyldiazenyl)-3H-benzo[b][1,4]diazepine (5d)

Compound was synthesized using 3-(*o*-tolyldiazenyl)pentane-2,4-dione (1d) and benzene- 1,2- diamine (OPD) (3).

Color: Yellowish Brown; M.P.: 128−130°C; Yield: 79%

FT-IR (ATR, υ, cm$^{−1}$): 3082 (C−H, sp^2), 3031 (C−H, sp^3), 1793 (N=N), 1673 (C=C/C=N), 1626, 1553, 1418 (C$^{···}$C ring str.), 716 (CH$_2$);

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.09 (6H, s), 2.24 (3H, s), 5.01 (1H, s), 7.05-7.21 (2H, d, J = 8.3 Hz, CH), 7.34 (2H, d, J = 8.3 Hz, CH), 7.42-7.66 (4H, d, J = 8.2 Hz, CH).

^{13}C NMR (400 MHz, CDCl$_3$): δ 14.5 (C−5', 7'), 17.7 (C−11'), 56.6 (C−6), 119.1 (C−15), 128.0 (C−11), 128.1 (C−16, 16'),128.2 (C−14, 17, 17'), 128.3 (C−11), 129.0 (C−12), 137.7 (C−2,3), 150.5 (C−10), 151.7 (C−5,7).

HRMS (ESI) m/z: 290.1561[M+H]$^+$; Anal. Cald. for C$_{18}$H$_{18}$N$_4$: C, 74.46; H, 6.25; N, 19.30 %. Found: C, 74.42; H, 6.21; N, 19.28 %.

Compound (5e): 2,4-dimethyl-3-((2-nitrophenyl)diazenyl)-3H-benzo[b][1,4]diazepine (5e)

Compound was synthesized using 3-((2-nitrophenyl)diazenyl)pentane-2,4-dione (1e) and benzene- 1,2- diamine (OPD) (3).Color: Yellowish Orange; M.P.: 126−128°C; Yield: 88%

FT-IR (ATR, υ, cm$^{−1}$): 3083 (C−H, sp^2), 3027 (C−H, sp^3), 1787 (N=N), 1667 (C=C/C=N), 1662 (NO$_2$), 1632, 1542, 1421 (C$^{···}$C ring str.), 723 (CH$_2$);

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.09 (6H, s CH$_3$), 5.02 (1H, s, CH), 7.34 (2H, ddd, J = 8.3 Hz, CH), 7.51-7.58 (2H, m, CH), 7.65-7.85 (3H, m, CH), 8.12 (1H, d, J = 8.3 Hz, CH).

^{13}C NMR (400 MHz, CDCl$_3$): δ 14.5 (C−5', 7'), 56.6 (C−6), 117.7 (C−12), 123.8 (C−15), 128.1 (C−16, 16'), 128.2 (C−2, 3, 13, 14), 129.4 (C−10), 137.7 (C−14), 151.7 (C−5,7), 154.8 (C−11).

HRMS (ESI) m/z: 322.1249[M+H]$^+$; Anal. Cald. for C$_{17}$H$_{15}$N$_5$O$_2$: C, 63.54; H, 4.71; N, 21.79 %. Found: C, 63.51; H, 4.68; N, 21.75 %.

Conflicts of interest

The authors declare no conflicts of interest.

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References

1. O. Elhady, E. Mansour, M. Elwassimy, S. Zawam, A. Drar, S. A. Raheem, (**2022**) Selective synthesis, characterization, and toxicological activity screening of some furan compounds as pesticidal agents, *Curr. Chem. Lett.,* 11 (3), 285-290.
2. M.S. Tolba, M. Sayed, A.M. Kamal El-dean, R. Hassanien, S.A. Abdel-Raheem, M. Ahmed, (**2021**) Design, synthesis and antimicrobial screening of some new thienopyrimidines, *Org. Commun.*, 14(4), 334-345.
3. S.A.A. Abdel-Raheema, A.M.K. El-Deanb, M.A. Abdul-Malikc, R. Hassaniend, M.E.A. El-Sayeda, A.A. Abd-Ellae, S.A. Zawamf, M.S. Tolba, (**2022**) Synthesis of new distyrylpyridine analogs bearing amide substructure as effective insecticidal agents, *Curr. Chem. Lett.,* 11 (1), 23-28.
4. S.A.A. Raheem, A.M. Kamal, E. Dean, R. Hassanien, M.E.A. El-Sayed, A.A. Abd-Ella, (**2021**) Synthesis and characterization of some distyryl-derivatives for agricultural uses, *Eur. Chem. Bull.*, 10(1): 35-38.
5. M.S. Tolba, A.M. Kamal El-Dean, M. Ahmed, R. Hassanien, M.S.R. Melad, S.K. Mohamed, S.A. Zawam, S.A.A. Abdel-Raheem, (**2022**) Synthesis, reactions, and applications of pyrimidine derivatives, *Curr. Chem. Lett.*, 11(1), 121-138.
6. M.S. Tolba, M.A.A. Ul-Malik, A.M.K. El-Dean, A.A. Geies, S.M. Radwan, R.M. Zaki, M. Sayed, S.K. Mohamed, S.A.A. Abdel-Raheem, (**2021**) An overview on synthesis and reactions of coumarin-based compounds, *Curr. Chem. Lett.*, 11(1), 29-42.
7. A.A. Abd-Ella, S.A. Metwally, M.A. Abdul-Malik, Y.A. El-Ossaily, F.M. Abd Elrazek, S.A. Aref, Y.A. Naffea, (**2022**) A review on recent advances for the synthesis of bioactive pyrazolinone and pyrazolidinedione derivatives, *Curr. Chem. Lett.,* 11(2), 157-172.
8. S.A.A. Abdel-Raheem, A.M.K. El-Dean, M.A. Abdul-Malik, A.A. Abd-Ella, E. Altaifi, R. Hassanien, M.E.A. Elsayed, S.K. Mohamed, S.A. Zawam, Y.A. Naffea, E. Bakhite,

S.A.A. Abdel-Raheem, (**2022**) A concise review on some synthetic routes and applications of pyridine scaffold compounds, *Curr. Chem. Lett.,* 10(4), 337-362.
9. A. Abdelhamid, A. Elsaghiera, S. Aref, M. Gad, N. Ahmed, S. Abdel-Raheem, (**2022**) Preparation and biological activity evaluation of some benzoyl thiourea and benzoylurea compounds, *Curr. Chem. Lett.,* 10(4), 371-376.
10. M.A. Gad, S.A. Aref, A.A. Abdelhamid, M.M. Elwassimy, S.A.A. Abdel-Raheem, (**2021**) Biologically active organic compounds as insect growth regulators (IGRs): introduction, mode of action, and some synthetic methods, *Curr. Chem. Lett.,* 10 (4) 393-412.
11. R.M. Ghalib, S.H. Mehdi, A.M. Malla, G.A. Bogdanović, (2**020**) Synthesis of new seven-member heterocyclic rings: An easy access to Indeno-benzo[1,4]diazepines, *Arabian Journal of Chemistry*, 13(10), 7338-7345.
12. M.A. Rashid, A. Ashraf, S.S. Rehman, S.A. Shahid, A. Mahmood, M. Faruq, (**2019**) 1,4-Diazepines: A Review on Synthesis, Reactions and Biological Significance, *Current Organic Chemistry*, 16(5), 709-729.
13. M.E. Haimer, M. Palkó, M. Haukka, M. Gajdács, I. Zupkó, F. Fülöp, (**2021**) Synthesis and biological evaluation of the new ring system benzo[*f*]pyrimido[1,2-*d*][1,2,3]triazolo[1,5-*a*][1,4]diazepine and its cycloalkane and cycloalkene condensed analogs, *RSC Advances*, 11(12), 6952-6957.
14. M.A. Rashid, A. Ashraf, S.S. Rehman, S.A. Shahid, A. Mahmood, M. Faruq, (**2019**) 1,4-Diazepines: A Review on Synthesis, Reactions and Biological Significance, *Curr Org Synth*., 16(5),709-729.
15. Y. Malki, L.T. Maillard, N. Masurier, (2021) 1,3-Diazepine Derivatives: Strategies for Synthesis, *Eur. J. Org. Chem..*, https://doi.org/10.1002/ejoc.202100492
16. F. Křemen, M. Gazvoda, S. Kafka, K. Proisl, A. Srholcová, A. Klásek, Damijana Urankar, and Janez Kosmrlj (**2017**) Synthesis of 1,4-Benzodiazepine-2,5-diones by Base Promoted Ring Expansion of 3-Aminoquinoline-2,4-diones, *J. Org. Chem.*, 82, 1, 715–722.
17. M.P. Sadashiva, Basappa, N. Swamy, F. Li, K.A. Manu, M. Sengottuvelan, D.S. Prasanna, N.C. Anilkumar, G. Sethi, K. Sugahara, K.S. Rangappa. (**2012**) Anti-cancer activity of novel dibenzo[b,f]azepine tethered isoxazoline derivatives. *BMC Chem Biol.*, 12(5), 1-11.
18. E Esposito , S Cuzzocrea, New therapeutic strategy for Parkinson's and Alzheimer's disease, *Curr Med Chem.*, 17(25), 2764-2774.
19. Tawfik A. Khattab, Mohamed Rehan, (**2018**) A Review on Synthesis of Nitrogen-Containing Heterocyclic Dyes for Textile Fibers - Part 2: Fused Heterocycles, *Egyptian Journal of Chemistry*, 61(6), 989-1018.
20. A. Shafie, M.M. Khanaposhtani, M. Asadi, N. Rahimi, P. R. Ranjbar, J.B. Ghasemi, B. Larijani, M. Mahdavi, H. Shafaroodi, A.R. Dehpour, (**2020**) Novel fused 1,2,3-triazolo-benzodiazepine derivatives as potent anticonvulsant agents: design, synthesis, in vivo, and in silico evaluations, *Mol Divers,* 24(1), 179-189.
21. A. Chimirri, S. Grasso, R. Ottanà, G. Romeo, M. Zappala, (**1990**) Synthesis and stereochemistry of novel [1,2,4]oxadiazolo[4,5-a][1,5]benzodiazepine derivatives, *Journal of Heterocyclic Chemistry*, 27(2), 371-374.
22. P. Kralova, M. Malon, M. Soural, (**2017**) Stereoselective Synthesis of Benzo[e][1,4]oxazino[4,3-a][1,4]diazepine-6,12-diones with Two Diversity Positions, *ACS Comb. Sci.*, 19(12), 770–774.
23. G. Varvounis, (**2016**) An Update on the Synthesis of Pyrrolo[1,4]benzodiazepines, *Molecules*, 21(2), 154-210.
24. M.A. Rashid, A.Ashraf, S.S. Rehman, S.A. Shahid, A. Mahmood, M. Faruq, (**2019**)1,4-Diazepines: A Review on Synthesis, Reactions and Biological Significance, *Curr Org Synth*, 16(5), 709-729.
25. Nicholas E. Calcaterra, James C. Barrow, (**2014**) Classics in Chemical Neuroscience: Diazepam (Valium), *ACS Chem Neurosci.,* 5(4), 253–260.

26. Dong Jin Lee, Hong Sik Han, Jinhwan Shin, and Eun Jeong Yoo, **(2014)** Multicomponent [5 + 2] Cycloaddition Reaction for the Synthesis of 1,4-Diazepines: Isolation and Reactivity of Azomethine Ylides, *J. Am. Chem. Soc.*, 136(33), 11606–11609.

27. Chang Guo, Basudev Sahoo, Constantin G. Daniliuc, and Frank Glorius, **(2014)** N-Heterocyclic Carbene Catalyzed Switchable Reactions of Enals with Azoalkenes: Formal [4 + 3] and [4 + 1] Annulations for the Synthesis of 1,2-Diazepines and Pyrazoles, *J. Am. Chem. Soc.*, 136(50), 17402–17405.

28. S. Tao, Q. Bu, Q. Shi, D. Wei, B. Dai, N. Liu, **(2020)** Synthesis of Benzodiazepines Through Ring Opening/Ring Closure of Benzimidazole Salts, *Chemistry – A European Journal*, 26,(15), 3252-3258.

29. M.J. Plunkett, J.A. Ellman, **(1995)** Solid-Phase Synthesis of Structurally Diverse 1,4-Benzodiazepine Derivatives Using the Stille Coupling Reaction, *J. Am. Chem. Soc.*, 117(11), 3306–3307.

30. I.R. Siddiqui, S. Shamim, D. Kumar, Shireena, M.A. Waseema, **(2012)** Tandem imino-pinacol coupling-aza-Michael reaction promoted by Zn/InCl3: a novel multicomponent strategy for diastereoselective synthesis of monocyclic 1,4-diazepine in water, *New J. Chem.*, 36(11), 2209-2214.

31. M.A. Ghasemzadeh, N.G. Seresht, **(2015)** Facile and efficient synthesis of benzo[b][1,5]diazepines by three-component coupling of aromatic diamines, Meldrum's acid, and isocyanides catalyzed by Fe3O4 nanoparticles, *Research on Chemical Intermediates*, 41(11), 8625–8636.

32. D.V. Jarikote, S. Siddiqui, R Rajagopal, T. Daniel, R. J Lahoti, K. V Srinivasan, **(2003)** Room Temperature Ionic Liquid Promoted Synthesis of 1,5-Benzodiazepine Derivatives under Ambient Conditions, *ChemInform*, 44(9), 1835-1838.

33. D. Shobha, M.A. Chari, M. Khagga, K.H. Ahn, **(2009)** Silica gel-supported sulfuric acid-catalyzed synthesis of 1,5-benzodiazepine derivatives, *Journal of Heterocyclic Chemistry*, 46(5), 1028 - 1033.

34. S. De, R. Gibbs, **(2005)** Scandium(III) Triflate as an Efficient and Reusable Catalyst for Synthesis of 1,5-Benzodiazepine Derivatives, *Tetrahedron Letters*, 46(11), 1811-1813.

35. M. Jeganathan, K. Pitchumani, **(2014)** Solvent-Free Syntheses of 1,5-Benzodiazepines Using HY Zeolite as a Green Solid Acid Catalyst, *ACS Sustainable Chem. Eng.*, 2(5), 1169–1176.

36. S.V. Goswami, P.B. Thorat, S.R. Bhusare, **(2013)** Phenylboronic Acid Catalyzed Synthesis of 1,5-Benzodiazepines via Cyclocondensation of o-Phenylenediamine and Ketones, *Journal of Chemical Sciences*, 125(4), 745-749.

37. S. Vajiravelu, K. Deepa, M. Palanichamy, V. Murugesan, **(2011)** [(L)Proline]2Zn Catalysed Synthesis of 1,5-Benzodiazepine Derivatives Under Solvent-Free Condition, *Synthetic Communications*, 34(21), 3833-3846.

38. A. Kamal, E. Laxman, N. Laxman, N.V. Rao, **(2000)** Synthesis of pyrrolo[2,1-c[1,4]benzodiazepines via reductive cyclization of omega-azido carbonyl compounds by TMSI: an efficient preparation of antibiotic DC-81 and its dimers, *Bioorg Med Chem Lett*, 10(20), 2311-2313.

39. S.K. Mahato, C. Acharya, K.W. Wellington, P. Bhattacharjee, P. Jaisankar, **(2020)** InCl3: A Versatile Catalyst for Synthesizing a Broad Spectrum of Heterocycles, *ACS Omega*, 5(6), 2503–2519.

40. O.A. Shemyakina, O.G. Volostnykh, A.V. Stepanov, A.G. Mal'kina, I.A. Ushakov, K. Apartsin, V.V. Kireeva, B. Trofimov, **(2018)** DBU as a scaffold for the synthesis of [1,3]oxazolo[2',3':2,3]pyrimido-[1,2-a]azepines: annulation with aromatic cyanopropargylic alcohols, *Mendeleev Communications*, 28(2), 128-130.

41. J.S. Yadav, Y. Srivastava, **(2020)** An efficient microwave-assisted synthesis of some novel 1, 4 diazepine derivatives as possible antimicrobial agents, *Rasayan Journal of Chemistry*, 3(4),726-730.

42. S.K. Maury, D. Kumar, A. Kamal, H.K. Singh, S. Kumari, S. Singh, **(2021)** A facile and efficient multicomponent ultrasound-assisted "on water" synthesis of benzodiazepine ring, *Mol Divers.*, 25(1), 131-142.

43. N. Kausar, P. Mukherjee, A.R. Das, **(2016)** Practical carbocatalysis by graphene oxide nanosheets in aqueous medium towards the synthesis of diversified dibenzo[1,4]diazepine scaffolds, *RSC Adv.*, 91(6), 88904-88910

44. A.M. Berrada, D. Grondin, S. Bennicia, A. Auroux, **(2012)** Design of amphoteric mixed oxides of zinc and Group 3 elements (Al, Ga, In): migration effects on basic features, *Phys. Chem. Chem. Phys.*,14(12), 4155-4161.

45. B.V. Kumar, H.S.B. Naik, D.K. Girija, **(2011)** ZnO nanoparticle as catalyst for efficient green one-pot synthesis of coumarins through Knoevenagel condensation, *Journal of Chemical Sciences*, 123(5), 615-621.

46. B. Banerjee, **(2017)** Recent developments on nano-ZnO catalyzed synthesis of bioactive heterocycles, *J Nanostruct Chem.*, 7, 389–413.

47. R. Tayebee, A.H Nasr, S. Rabiee, E. Adibi, **(2013)** Zinc Oxide as a Useful and Recyclable Catalyst for the One-Pot Synthesis of 2,4,6-Trisubstituted-1,3,5-trioxanes under Solvent-Free Conditions, *Ind. Eng. Chem. Res.*, 52(28), 9538–9543.

48. H.C. Yao, **(1964)** Azohydrazone Conversion. II. The Coupling of Diazonium Ion with β-Diketones, J. Org. Chem., 29 (10), 2959–2963.

49. G.K. Reen, M. Ahuja, A. Kumar, R. Patidar, P. Sharma, **(2017)** ZnO Nanoparticle-Catalyzed Multicomponent Reaction for the Synthesis of 1,4-Diaryl Dihydropyridines, *Organic Preparations, and Procedures International*, 49(3), 273-286.

50. H. Sachdeva, R. Saroj, **(2013)** ZnO Nanoparticles as an Efficient, Heterogeneous, Reusable, and Ecofriendly Catalyst for Four-Component One-Pot Green Synthesis of Pyranopyrazole Derivatives in Water, Sci. World J., 1-8.

51. I. Khan, K. Saeed, I. Khan, **(2019)** Nanoparticles: Properties, applications and toxicities, *Arab. J. Chem.*, 12, 908-931.

52. L. Zhengyi, Y. Zhaozhuo, L. Xiaoxiang, L. Chuanhui, W. Hongguo, Z. Wenfeng, L. Hu, Y. Song Ya, **(2020)** Recent advances in liquid hydrosilane-mediated catalytic N-formylation of amines with CO_2, *RSC Adv.*, 10, 33972-34005.

53. D. Geedkar, A. Kumar, K. Kumar, P. Sharma, **(2021)** Hydromagnesite sheets impregnated with cobalt–ferrite magnetic nanoparticles as heterogeneous catalytic system for the synthesis of imidazo[1,2- a]pyridine scaffolds, *RSC Advances*, 11(38), 23207-23220.

54. D. Geedkar, A. Kumar, P. Sharma, **(2020)** Multiwalled carbon nanotubes crowned with nickel-ferrite magnetic nanoparticles assisted heterogeneous catalytic strategy for the synthesis of benzo[*d*]imidazo[2,1-*b*]thiazole scaffolds, *Journal of Heterocyclic Chemistry*, 57(12), 4331-4347.

55. D. Geedkar, A. Kumar, G.K. Reen, P. Sharma, **(2020)** Titania-silica nanoparticles ensembles assisted heterogeneous catalytic strategy for the synthesis of pharmacologically significant 2,3-diaryl-3,4-dihydroimidazo[4,5-b]indole scaffolds, *Journal of Heterocyclic Chemistry*, 57(4), 1963-1973.

56. D. Geedkar, A. Kumar, G.K. Reen, P. Sharma, **(2022)** Molecular Iodine-Catalyzed Synthesis of Imidazo[1,2-a]Pyridines: Screening of Their In Silico Selectivity, Binding Affinity to Biological Targets, and Density Functional Theory Studies Insight, *ACS Omega*, 7, 22421-22439.