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An efficient and green synthesis of some novel benzodiazepine derivatives and their antimicrobial screening

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ABSTRACT

In present communication a novel series of benzodiazepine derivatives were synthesized from α, β-unsaturated ketones and evaluated for their antimicrobial activities. The α, β-unsaturated ketones were prepared by Claisen-Schimidt Condensation of Indan-1-one with different aldehydes in presence bleaching earth clay and PEG-400 as Greener reaction solvent. A novel benzodiazepine derivatives were synthesized by the reaction of α,β-unsaturated ketones with o-phenylenediamine in Polyethylene glycol (PEG-400) and few drop of acetic acid. The chemical structures of the newly synthesized compounds were confirmed by IR, ^{1}H NMR and Mass spectral data. All compounds of the series have been screened for their antimicrobial activity studies. The result revealed that most of the compounds showed moderate to significant antimicrobial activity.

Keywords: benzo[b] indeno [1, 2e] diazepine, bleaching earth clay (pH12.5), Polyethylene glycol -400(PEG-400), antimicrobial activity.

INTRODUCTION

The heterocyclic scaffolds containing benzodiazepines moiety have been investigated extensively because of their significant biological applications such as anti-convulsant, anti-anxiety, analgesic, sedative, anti-depressive, and hypnotic activities in the central nervous system [1] and also as anti-inflammatory agents [2]. Due to their broad spectrum of biological activity benzodiazepines shows potent antibacterial and antifungal activity[3-5]. Beside that some benzodiazepine derivatives are also used in industry, such as in photography (as dyes for acrylic fibers)[6].

The reaction of aromatic or heteroaromatic 1,2-diamines with α, β-unsaturated ketones (chalcones) is a useful method for the preparation of condensed 1,4-diazepine systems [7,8]. Generally, benzodiazepines are synthesized by the condensation of o-phenylenediamines with unsaturated carbonyl compounds, haloketones or with ketones. Many reagents have been reported in the literature for this condensation including BF_3–etherate[9], polyphosphoric acid[10], $NaBH_4$[11], SiO_2,MgO/$POCl_3$[12], Yb$(OTf)_3$[13] and acetic acid under microwave conditions[14]. Recently, these condensations have been reported even in anionic liquid medium [15, 16]. However, many of these synthetic pathways are associated with several shortcomings such as long reaction times, hazardous reaction condition, low product yields, occurrence of several side products, and difficulty in recovery and reusability of the catalysts and solvent.

Recently, bleaching earth has unique physical and chemical properties such as shape selectivity, acidic, basic nature and thermal stability. It is used in refining of vegetable oil [17] fats, greases and as a catalyst in reactions [18]. Liquid polymers or low melting polymers have recently emerged as alternative green solvent systems with unique properties such as thermal stability, commercial availability, non-volatility, immiscibility with a

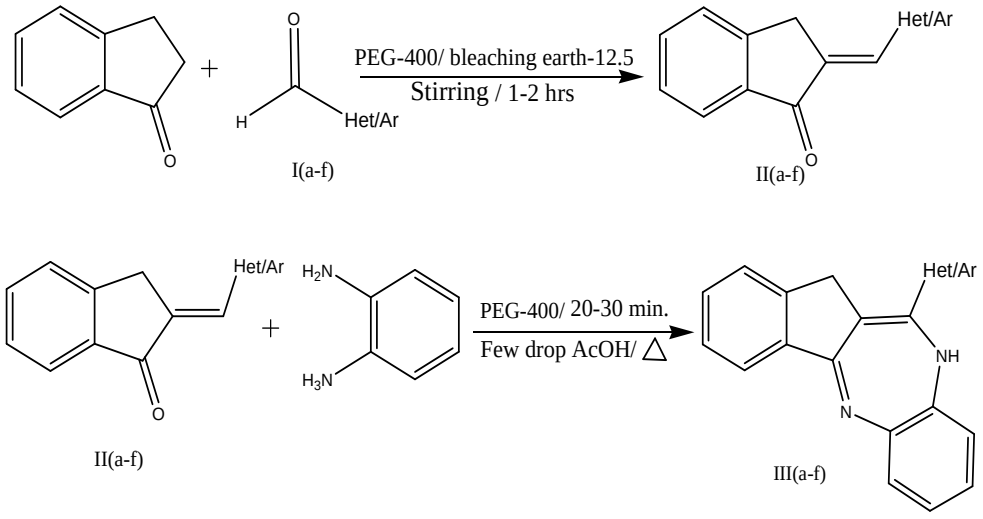
number of organic solvents and recyclability. Polyethylene glycols [19-21] are among the one of green solvents. Keeping the view of these observations and under the framework of "Green Chemistry," polyethylene glycol (PEG-400) prompted reactions [22-24] have attracted the attention of organic chemists due to their versatile advantages such as solvating ability, aptitude to act as a phase transfer catalyst, negligible vapors pressure, easy recyclability, ease of work-up, and eco-friendly nature. Prompting that we herein report an environmentally benign synthesis of some novel benzodiazepine derivatives using polyethylene glycol PEG-400 as greener solvent and screen them for their antibacterial and antifungal activity.

MATERIALS AND METHODS

All the melting points were uncorrected and determined in an open capillary tube. The chemicals and solvents used were of laboratory grade and were purified. Completion of the reaction was monitored by thin layer chromatography on precoated sheets of silica gel-G (Merck, Germany) using iodine vapour for detection. IR spectra were recorded in KBr pallets on FTIR Schimadzu spectrophotometer. ^{1}H NMR spectra were recorded in DMSO-d^6 with an Avance spectrometer (Bruker, Germany) at 400-MHz frequency using TMS as an internal standard. Mass spectra were recorded on an EI-Shimadzu QP 2010 PLUS GC-MS system (Shimadzu, Japan). Elemental analyses were performed on a Carlo Erba 106 Perkin-Elmer model 240 analyzer (Perkin-Elmer, USA).

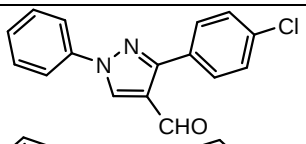
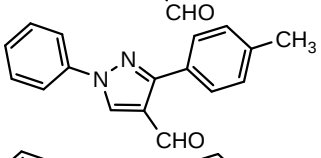
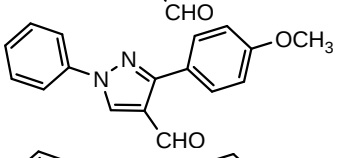
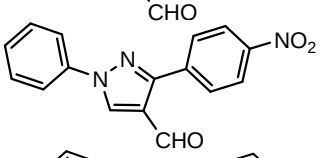
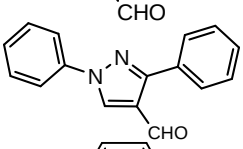
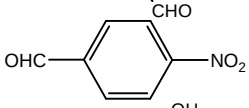
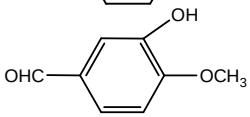
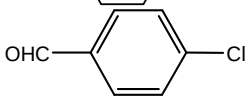
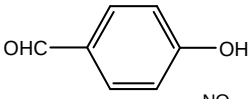
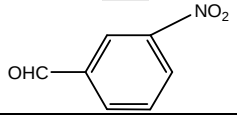
General procedure for the synthesis of α, β-unsaturated ketones derivatives (IIa-f):
A mixture of indan-1-one (1 mmol), substituted Het/Ar aldehyde (1 mmol), and catalytic amount of bleaching earth (10 mol% of pH 12.5) was taken in of polyethylene glycol-400 (PEG-400) (20 mL). The reaction mixture was stirred for 1 to 2 hours at 60-65 °C. The progress of reaction was monitored by thin layer chromatography (TLC) time to time. After completion of reaction, it was filtered to separate the solid catalyst powder. The filtrate was then poured into a beaker containing ice cold water (100 ml) with stirring. The obtained solid product was filtered, washed using water (2 X 20 ml). It was then dried and recrystallized from ethanol afford corresponding α, β-unsaturated ketones i.e. 2-[3-(substituted phenyl)-1-phenyl-1H-pyrazol-4-ylmethylene]-indan-1-one **(IIa-f)** as product.

General procedure for synthesis of -benzo[b] indeno [1, 2e] diazepine (IIIa-f):
A mixture of α,β-unsaturated ketones (IIa-f), (1 mmol), o-phenylenediamine (1 mmol), PEG-400 (20 mL) and 3-4 drops of acetic acid was heated for 20 to 30 minutes at 60^{0}C to 80^{0}C temperature in the appropriate time (Table-1). After completion of reaction (monitored by TLC), the reaction mixture was cooled and poured into ice-cold water (100 mL).The obtained solid product was filtered and washed with 2 x 5 mL water and recrystallized by aqueous acetic acid to give pure product (11-[(substituted-phenyl)-1-phenyl-1H-pyrazol-4-yl]-dihydro-benzo[b] indeno [1, 2e] diazepine **(IIIa-f).** The PEG-400 was recovered from water by direct distillation and reused for second run by charging the same substrates.



Scheme1: Synthesis of α, β-unsaturated ketones (IIa-f) and benzo[b]indeno [1, 2-e] diazepine (IIIa-f).

Table1: Synthesis of 11-[3-(4-Chloro-phenyl)-1-phenyl-1H-pyrazol-4-yl]-10, 12-dihydro-benzo[b]indeno[1,2-e]diazepine(IIIa-j) using PEG-400.

Sr.No.	Product	Het/Ar	Time in min	Yield	M.P in °C
1	**IIIa**		20	92	212-215
2	**IIIb**		28	88	198-200
3	**IIIc**		25	90	204-208
4	**IIId**		22	95	210-213
5	**IIIe**		20	94	196-198
6	**IIIf**		23	95	170-173
7	**IIIg**		24	90	190-195
8	**IIIh**		27	96	148-150
9	**IIIi**		30	85	142-144
10	**IIIj**		25	91	180-184

Spectroscopic data of selected compounds:

2-[3-(4-Chloro-phenyl)-1-phenyl-1H-pyrazol-4-ylmethylene]-indan-1-one **(IIa):):** IR (KBr, ν, cm-^{1}): 3059 (Ar-H), 2924 (-C-H), 1705 (-C=O) 1599 (C=N of diazepine ring), 1500-1542 (Aromatic C=C), 1230 (C-N), 754 (C-Cl) ; ^{1}HNMR (400 MHz, DMSO-d_6) (δ,ppm): 4.3(dd,2H,CH_2), 6.9-8.9 (m,15H,Ar-H); EIMS (*m/z*): 396 (M^+) ; Anal. Calcd. For $C_{25}H_{17}ClN_2O$: C, 75.66; H, 4.32; Cl, 8.93; N, 7.06; O, 4.03 % Found; C,75.63,H, 4.30,Cl, 8.95,N,7.07,O, 4.01%

11-[3-(4-Chloro-phenyl)-1-phenyl-1H-pyrazol-4-yl]-4b, 5, 10, 12-tetrahydro benzo[b]indeno-[1, 2-e] diazepine **(IIIa):** IR (KBr, ν, cm-^{1}): 3440(-N-H), 3080 (Ar-H), 1610 (C=N of diazepine ring), 1581-1600 (Aromatic C=C), 1250 (C-N), 737 (C-Cl) ; ^{1}HNMR (400 MHz, DMSO-d_6) (δ,ppm): 4.1(dd,2H,CH_2), 7.1-8.0 (m,18H,Ar-H), 8.7 (S,1H,N-H) ; EIMS (*m/z*): 484 (M^+) ; Anal. Calcd. For $C_{31}H_{21}ClN_4$: C, 76.77; H, 4.36; Cl, 7.31; N, 11.55% Found; C,76.68,H, 4.34,Cl, 7.32,N,11.72%

11-(1-Phenyl-3-p-tolyl-1H-pyrazol-4-yl)-4b, 5, 10, 12-tetrahydro-benzo[b] indeno [1,2e] diazepine **(IIIb):** IR (KBr, ν, cm-^{1}): 3430 (-N-H), 3095 (Ar-H), 2930 (C-H aliphatic), 1632 (C=N of diazepine ring), 1580-1600 (Aromatic C=C), 1240 (C-N) ; ^{1}HNMR (400 MHz, DMSO-d_6) (δ,ppm): 1.7 (s,3H,CH_3) 4.3(dd,2H,CH_2), 6.5-7.9 (m,18H,Ar-H), 8.6 (S,1H,N-H); EIMS (*m/z*): 464 (M^+) ; Anal. Calcd. For $C_{32}H_{24}N_4$: C, 82.73; H, 5.21; Cl; N, 12.06% Found; C,82.69,H, 5.24,N,11.98%

11-[3-(4-Methoxy-phenyl)-1-phenyl-1H-pyrazol-4-yl]-4b, 5, 10, 12-tetrahydro-benzo[b] indeno [1, 2-e]diazepine **(IIIc):** IR (KBr, ν, cm-$^{-1}$): 3440(-N-H), 3080 (Ar-H), 1610 (C=N of diazepine ring), 1581-1600 (Aromatic C=C), 1250 (C-N) ; ^{1}HNMR (400 MHz, DMSO-d_6) (δ,ppm): 3.7 (s,3H,OCH_3), 4.2 (dd,2H,CH_2), 7.2-8.1 (m,18H,Ar-H), 8.9 (S,1H,N-H) ; EIMS (*m/z*): 480 (M^+) ; Anal. Calcd. For $C_{32}H_{24}N_4O$: C, 79.98; H, 5.03; N, 11.66; O, 3.33% Found; C,76.96,H, 5.2, N,11.63,O,3.36%

11-[3-(4-Nitro-phenyl)-1-phenyl-1H-pyrazol-4-yl]-4b, 5, 10, 12-tetrahydro-benzo [b]indeno [1, 2-e]diazepine **(IIId):** IR (KBr, ν, cm-$^{-1}$): 3405(-N-H), 3080 (Ar-H), 1630 (C=N of diazepine ring), 1585-1608 (Aromatic C=C), 1535 (-NO2), 1270 (C-N) ; ^{1}HNMR (400 MHz, DMSO-d_6) (δ,ppm): 4.4 (dd,2H,CH_2), 7.0-8.2 (m,18H,Ar-H), 8.6 (S,1H,N-H) ; EIMS (*m/z*): 495(M^+) ; Anal. Calcd. For $C_{31}H_{21}N_5O_2$: C, 75.14; H, 4.27; N, 14.13; O, 6.46 % Found; C, 75.18, H, 4.30, N, 14.15, O, 6.44%

2-Methoxy-5-(10, 11, 11a, 12-tetrahydro-benzo[b] indeno [1, 2-e] diazepin-11-yl)-phenol **(IIIe):** IR (KBr, ν, cm-$^{-1}$): 3460 (-OH), 3376 (-N-H), 3080 (Ar-H),2930 (C-H,aliphatic) 1615 (C=N of diazepine ring), 1570-1602 (Aromatic C=C), 1230 (C-O) ; ^{1}HNMR (400 MHz, DMSO-d_6) (δ,ppm): 3.8 (s,3H,OCH_3), 4.1 (dd,2H,CH_2), 7.2-7.8 (m,11H,Ar-H&1H,-NH), 9.7 (S,1H,-O H) ; EIMS (*m/z*): 354 (M^+) ; Anal. Calcd. For $C_{23}H_{18}N_2O_2$: C, 77.95; H, 5.12; N, 7.90; O, 9.03% Found; C,77.96,H, 5.10, N,7.8,O,9.2%

MATERIALS AND METHODS

In the course of our research and as part of our program we herein report an environmentally benign synthesis of some novel benzodiazepine derivatives focusing on our desired aim to find the optimal reaction conditions to synthesize these derivatives using bleach Earth clay and polyethylene glycol PEG-400 as greener solvent. The synthesized compounds has screened for their antibacterial and antifungal activity.

The IR spectral interpretation of all newly synthesized benzodiazepine derivatives showed that presence of -N-H stretching frequency at 3350 cm^{-1} to 3440 cm^{-1} and -C=N at 1610 cm^{-1} to 1650 cm^{-1} as well as absence of (–C=O at 1670 cm^{-1} to 1695 cm^{-1}) carbonyl stretching frequency fully indicates cyclization of α, β-unsaturated ketones with o-phenylenediamine to seven member benzodiazepine ring. The ^{1}HNMR spectral analysis of all newly synthesized benzodiazepine derivatives mentioned above including deshielded singlet of 1H of –N-H signal at 8.1 to 8.4 δppm. The EIMS (*m/z*) represents corresponding acurate molecular ion peak (M^+) ie molecular weight of all synthesised benzodiazepine derivative.Thus all above spectral information have immensly support to decide correct structural identification of newly synthesised compounds.

MICROBIOLOGY

The antimicrobial activities of the synthesized compounds **III(a-j)** were determined by agar diffusion method. The compounds were evaluated for antibacterial activity against *Escherichia coli, Proteus vulgaris, Bacillus subtilis, Staphylococcus aureus.* The antifungal activity was studied against *Aspergillus niger, Aspergillus flavus, Penicillium chrysogenum* and all results are represented in table-2.

Table2: Antimicrobial activity of benzodiazepines derivatives (IIIa-j)

Sr. No.	Compounds	Bacteria				Fungi		
		Zone of inhibition in mm				Zone of inhibition in mm		
		Ec	Pv	Bs	Sa	An	Af	Pc
1	**IIIa**	14	11	10	16	15	13	12
2	**IIIb**	11	08	-	10	-	11	11
3	**IIIc**	13	10	11	14	10	14	15
4	**IIId**	14	13	13	13	14	12	15
5	**IIIe**	12	09	10	14	08	13	12
6	**IIIf**	14	13	15	18	16	13	15
7	**IIIg**	11	14	13	14	14	10	09
8	**IIIh**	13	12	15	17	13	12	14
9	**IIIi**	11	07	09	12	10	11	-
10	**IIIj**	14	12	15	17	13	12	15
11	Penicillin	18	16	19	22	NA	NA	NA
12	Nystatin	NA	NA	NA	NA	20	16	18

Ec-Escherichia coli;Pv-Proteus vulgaris; Bs-Bacillus subtilis; Sa-Staphylococcus aureus; An-Aspergillus niger; Af-Aspergillus flavus; Pc-Penicillium chrysogenum NA: Not applicable

All the compounds of the series have been screened for their antibacterial and antifungal activity studies. The results of antibacterial studies are given in Table-2. In comparison with standard antibacterial penicillin, the compounds **IIIa, IIIc** and **IIIe** were showed good zone of inhibition against *Escherichia Coli* and *Staphylocous aureus*,

where compound **IIId, IIIf, IIIh** and **IIIj** were showed significant antibacterial activity against all *Escherichia coli, Proteus vulgaris, Bacillus subtilis,* and *Staphylococcus.* The compounds **IIIb** and **IIIi** were less active against almost all bacteria.

The results of *in vitro* antifungal activities are summarized in comparison with standard antifungal nyststin, the compounds **IIIa, IIId, IIIf, IIIh, IIIj** and **IIIp** were exhibited significant antifungal activities against all tested fungi viz. *Aspergillus niger*, *Aspergillus flavus* and *Penicillium chrysogenum.* The compounds activities of **IIIc** and **IIIe** were showed good zone of inhibition against, *Aspergillus flavus* and *Penicillium chrysogenum*. The compounds **IIIb** and **IIIi** exhibits less active against all selected fungus.

The antibacterial and antifungal activity enhanced due to –OH, -Cl and $–NO_2$ group present in the compounds. Thus almost all synthesized benzodiazepines derivatives were exhibits good to moderate antibacterial and antifungal activity.

CONCLUSION

In summary, we have described a simple and green method for the synthesis of substituted novel series of Benzodiazepine derivatives. The newly synthesized compounds were confirmed by the spectral analysis and further evaluated for their antimicrobial activity. The results reveal that most of the synthesized benzodiazepines derivatives were exhibits good to moderate antibacterial and antifungal activity.

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