ORIGINAL ARTICLE

A C G publications

Org. Commun. 7:2 (2014) 68-76

organic communications

Eco-friendly synthesis of novel indeno-pyrazole derivatives and their *in-vitro* antimicrobial screening

Ashok P. Acharya[1], Rahul D. Kamble[1], Shrikant V. Hese[1], Shuddhodan N. Kadam[1], Rajesh N. Gacche[2] and Bhaskar S. Dawane[*1]

[1]Organic Research Laboratory, School of Chemical Sciences, Swami Ramanand Teerth Marathwada University, Nanded (MS) India. 431606.

[2]School of Life Sciences, Swami RamanandTeerthMarathwada University, Nanded (MS) India. 431606.

(Received January 5, 2014; Revised March 29, 2014; Accepted June 9, 2014)

Abstract: In the present communication a series of novel indeno-pyrazole derivatives were synthesized by the reaction of α, β-unsaturated ketones with phenyl hydrazine in polyethylene glycol-400 (PEG-400) and few drop of acetic acid. The newly synthesized compounds were characterized and confirmed by IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral data. The results obtained indicate the significance of indeno-pyrazole derivatives as potent scaffold for designing novel and broad spectrum antimicrobials.

Keywords: Indeno-Pyrazole derivatives, bleaching earth clay (pH12.5), Polyethylene glycol-400(PEG-400), Antimicrobial activity.

1. Introduction

The emergence of bacterial resistance towards available antibiotics is rapidly becoming a major worldwide problem, thus limiting the usage of currently available therapeutic modalities. The design and development of new antimicrobials has remained a focal research area in the midst of growing multiple drug resistant (MDR) pathogenic strains. Despite the stratified and tailored efforts towards the development of several new antibacterial agents, their clinical value is limited towards treating an increasing array of life threatening systemic infections because of their relatively high risk of toxicity, emergence of multiple drug resistant (MDR) strains, pharmacokinetic differences, and inefficacy in their activity. Nevertheless the economic constraint is another limiting factor in the usage of currently available effective antimicrobials. Therefore, there is a resurgence of interest in developing novel, effective, safe and economically affordable antimicrobials for the amelioration of infectious diseases.

Enormous interest in the chemistry of pyrazoles is reflected by the design of new synthetic approaches due to their significant biological and therapeutic value. A plethora of literature has accumulated in the recent years linking the immense biological potential of pyrazoles derivatives as antitumor, anti-HIV, anti-inflammatory and antimicrobial activities.[1-7]

Many heterocyclic compounds containing pyrazole moiety are biological significant and possessing a wide range of target-oriented bioactivities. The pyrazole derivatives make up the core structure of various biologically active compounds. Molecules of many modern drugs, such as

[*] Corresponding author: E-mail: bhaskardawane@rediffmail.com

The article was published by Academy of Chemistry of Globe Publications
www.acgpubs.org/OC/index.htm © Published 06/19/2014 EISSN:1307-6175

antiphlogistic[8], antidiabetic[9], analgesic[10], etc., as well as of insect acaricides used in practice, contain the pyrazole ring as structural moiety (**figure 1**).[11-12] Recently pyrazoles and its derivatives have been proven to be an extremely useful intermediate for the synthesis of new biologically active compounds.[13-14] Pyrazole derivatives have attracted great attention due to widespread applications in pharmaceutical[15] and agrochemical industries.[16-18]

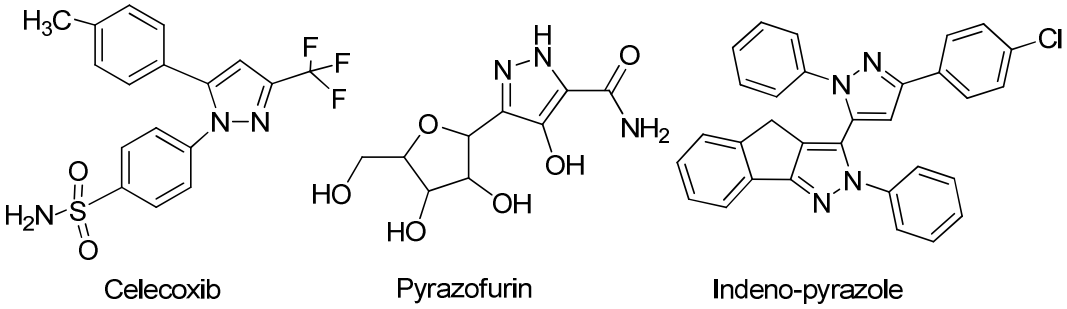


Figure 1. Some biological active drugs containing pyrazole nucleus.

The use of 'green' solvents and environmentally benign catalysts is one of the prime goals of 'green' chemistry. Liquid polymers have recently emerged as alternative green solvent systems[19] with unique properties such as thermal stability, commercial availability, non-volatility, immiscibility with a number of organic solvents and recyclability. Previously, we have assessed the potential of Polyethylene glycols as one of the green solvents.[20-21] Recently bleaching earth clay has been described to possess unique physical and chemical properties such as shape selectivity, acidic, basic nature and thermal stability. It is used in refining of vegetable oilfats, greases[22] and as a catalyst[23] in chemical reactions[24]. Keeping the view of these observations and under the framework of "Green Chemistry", herein we report an environmentally benign synthesis of some novel indeno-pyrazole derivatives using polyethylene glycol (PEG)-400 as a 'green' solvent and the evaluation them for their antibacterial and antifungal activities.

2. Results and discussion

2.1. Chemistry

As part of our ongoing research program, we have reported greener synthesis of some novel indeno-pyrazole derivatives. A new series of pyrazole derivatives were synthesized from cyclic α, β-unsaturated ketones. These cyclic α, β-unsaturated ketones were synthesized by Claisen-Schmidt Condensation of indan-1-one with different het/araldehydes[25] in the presence of a catalytic amount of bleaching earth (10 mol% of pH 12.5) and PEG-400 as green reaction solvent.[26] The reaction time, yield and melting point of α,ß-Unsturated ketones (**2a-j**) are presented in Table 1.

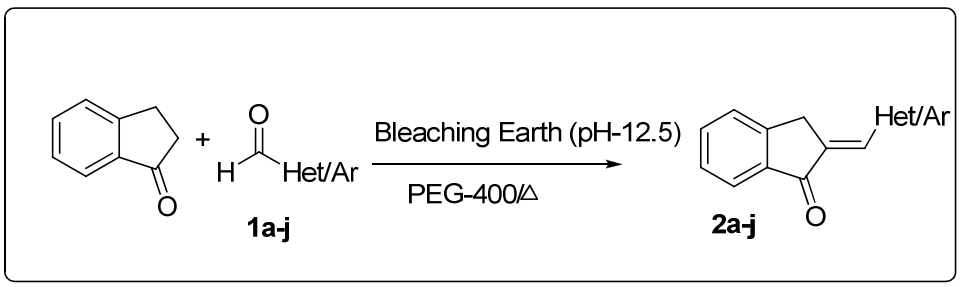


Figure 2. Green protocol for synthesis of α, ß-unsaturated ketones

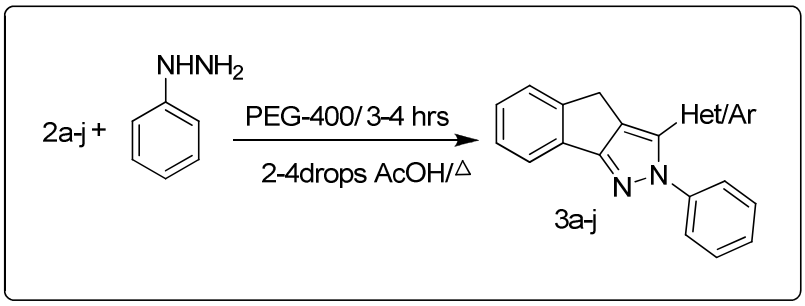
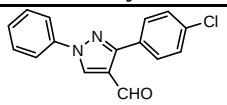
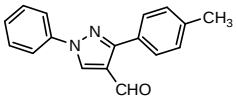
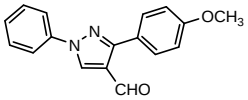
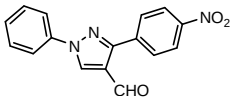
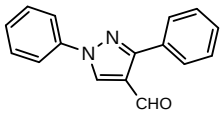
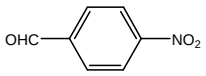
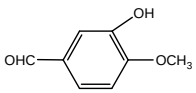
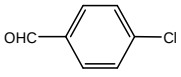
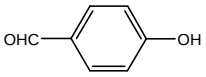
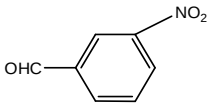


Figure 3. Synthesis of indeno-pyrazole derivatives **(3a-j)** using PEG-400.

Table 1. Bleaching Earth Clay pH 12.5 catalysed synthesis of α,ß-Unsturated ketones (2a-j)

Entry	Aldehyde	Product	Time (min)	Yield (%)
1		**2a**	135	84
2		**2b**	120	78
3		**2c**	150	90
4		**2d**	125	89
5		**2e**	205	75
6		**2f**	130	85
7		**2g**	140	80
8		**2h**	165	92
9		**2i**	140	87
10		**2j**	120	84

Focusing on our aim to find the optimal reaction conditions to synthesize these indeno-pyrazole derivatives using catalytic amount of bleaching earth pH-12.5 (10 weight %) and

PEG-400 as green solvent.[27] The condensations occur smoothly followed by the Michael addition of phenyl hydrazine to corresponding product shown in Figure 3. Highly pure product can be obtained simply by recrystallization from aqueous acetic acid (Figure 3), without using any chromatographic technique. The reaction time, yield and melting point of indeno-pyrazole derivatives **(3a-j)** are presented in Table 2.

Table 2. Synthesis of indeno-pyrazole derivatives **(3a-j)** using PEG-400.

Entry	Reactant	Product	Time (min)	Yield (%)
1	**2a**	**3a**	180	95
2	**2b**	**3b**	200	88
3	**2c**	**3c**	195	92
4	**2d**	**3d**	225	94
5	**2e**	**3e**	215	90
6	**2f**	**3f**	230	92
7	**2g**	**3g**	220	85
8	**2h**	**3h**	185	90
9	**2i**	**3i**	240	78
10	**2j**	**3j**	210	88

3. Antibacterial activity

All the synthesized compounds of the series were screened for their antibacterial and antifungal activities. The results of these studies in terms of zone of inhibition (ZOI) and minimum inhibitory concentrations (MICs) are summarized in Table 2. In comparison with a standard antibacterial penicillin-V, the compounds **3a, 3c** and **3e** showed good zone of inhibition against *Escherichia Coli* and *Staphylococcus aureus*, whereas compounds **3d, 3f, 3h** and **3j** showed significant antibacterial activity against the selected bacterial strains namely, *Escherichia coli, Proteus vulgaris, Bacillus subtilis,* and *Staphylococcusaureus*. However, the compounds **3b** and **3i** were less active against almost all selected bacterial strains.

The results of *in vitro* antifungal activities are summarized in comparison with the standard antifungal, nystatin, (Table 2), the compounds **3a, 3d, 3f, 3h** and **3j** exhibited significant antifungal activities against all tested fungi such as *Aspergillus niger, Aspergillus flavus* and *Penicillium chrysogenum.* The compounds **3c** and **3e** showed good zones of inhibition against, *Aspergillus flavus* and *Penicillium chrysogenum*. The compounds **3b** and **3i** exhibited less antifungal activity against all the selected fungi.

It is observed that the enhanced antibacterial and antifungal activity of the synthesized compounds may be due to the presence of –OH, -Cl or -NO_2 groups present in the pyrazole compounds.The ZOI and the related MICs shown in Table-3 for the present antimicrobial studies signifies the importance of synthesized indeno-pyrazole derivatives as potential antimicrobial agents.

Table 3. Antimicrobial activity of synthesized indeno-pyrazole derivatives **(3a-j)**

Sr.No.	Products	Bacteria				Fungi		
		ZOI in mm (MIC in µg/ml)				ZOI in mm (MIC in µg/ml)		
		Ec	Pv	Bs	Sa	An	Af	Pc
1	**3a**	15(50)	12(50)	11(100)	16(50)	16(50)	12(50)	14(100)
2	**3b**	10(100)	09(100)	-	12(100)	-	11(100)	10(100)
3	**3c**	14(50)	10(100)	11(50)	15(50)	12(100)	14(50)	15(50)
4	**3d**	17(50)	13(50)	14(50)	20(50)	18(50)	12(100)	15(50)
5	**3e**	13(100)	09(100)	10(100)	14(50)	10(50)	13(50)	12(100)
6	**3f**	15(50)	14(50)	15(50)	18(50)	16(100)	139(50)	15(50)
7	**3g**	12(100)	14(50)	13(100)	14(50)	14(50)	10(100)	12(50)
8	**3h**	14(50)	13(50)	16(50)	17(50)	14(50)	12(50)	13(50)
9	**3i**	10(100)	08(100)	09(100)	12(100)	11(100)	10(100)	-
10	**3j**	16(50)	13(50)	15(50)	17(50)	15(50)	12(100)	14(50)
11	Penicillin	20(50)	18(50)	1(50)	23(50)	NA	NA	NA
12	Nystatin	NA	NA	NA	N A	20(50)	16(50)	18(50)

Ec-Escherichia coli;Pv-Proteus vulgaris; Bs-Bacillus subtilis; Sa-Staphylococcus aureus; An-Aspergillusniger; Af-Aspergillusflavus; Pc-Penicilliumchrysogenum; MIC-Minimum inhibitory concentration shown in bracket;(-)- MIC>100 µg /L^{-1} ;*NA: Not applicable*

4. Experimental Section

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 as KBr pellets on FTIR Shimadzu spectrophotometer (8400s). ^{1}H NMR and ^{13}C NMR (70 MHz) spectra were recorded in DMSO-*d6* with an Avance spectrometer (Bruker, Germany) at 400-MHz frequency using TMS as an internal standard. Mass spectra were recorded by an EI-Shimadzu QP 2010 PLUS GC-MS system (Shimadzu, Japan). Elemental analyses were performed using a Carlo Erba 106 Perkin-Elmer model 240 analyzer (Perkin-Elmer, USA).

4.1. General procedure for the synthesis of α, β-unsaturated ketones derivatives (2a-j):

A mixture of indan-1-one (1 mmol), substituted Het/Ar aldehyde (1 mmol), and a catalytic amount of bleaching earth clay pH 12.5 (10 weight %) in PEG-400 (20 ml). The reaction mixture was heated for 2 to 4 hours at 60-65 °C. The progress of reaction was monitored by thin layer chromatography (TLC). After completion of reaction, the mixture 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 solid product obtained was filtered, washed using water (2 x 20 ml). It was then dried and recrystallized from aqueous acetic acid to afford the desired α, β-unsaturated ketones i.e. 2-[3-(substituted phenyl)-1-phenyl-1H-pyrazol-4-ylmethylene]-indan-1-ones **(2a-j)** as product.

4.1.1. 2-[3-(4-Chloro-phenyl)-1-phenyl-1H-pyrazolylmethylene]-indan-1-one (2a): Yellow solid; mp.154-156 ^{o}C; IR (KBr, ν, cm^{-1}): 3059 (Ar-H), 2924 (-C-H), 1705 (-C=O) 1599 (C=N of pyrazole ring), 1500-1542 (Aromatic C=C), 1230 (C-N), 754 (C-Cl) ; ^{1}HNMR (400 MHz, DMSO-d_6) (δ,ppm): 4.3 (s, 2H,CH_2), 6.9-8.9 (m,15H,Ar-H); ^{13}C-NMR (70 MHz, DMSO-d_6) (δ,ppm): 33 (-CH_2), 113-142 (CH, Aromatic rings), 141-152 (C, pyrazole rings) 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%

4.2. Synthesis of 3-[3-(Substituted-phenyl)-1-phenyl-1H-pyrazol-4-yl]-2-phenyl-2, 4-dihydro-indeno[1, 2-c] pyrazole. (3a-j):

A mixture of α, β-unsaturated ketones (IIa-f), (1 mmol), phenyl hydrazine (1 mmol), PEG-400 (20 ml) and 3-4 drops of acetic acid was heated for 3 to 4 hours at 60°C to 80°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 3-[3-(Substituted-phenyl)-1-phenyl-1H-pyrazol-4-yl]-2-phenyl-2,4-dihydro-indeno [1, 2-c] pyrazole. (3a-j) The PEG-400 was recovered from water by direct distillation and reused for second run by charging the same substrates.

4.2.1. 3-[3-(4-Chloro-phenyl)-1-phenyl-1H-pyrazol-4-yl]-2phenyl-2, 4-dihydro-indeno [1, 2-c]pyrazole (3a): Pale yellow Solid; mp.188-190 ^{o}C; IR (KBr, ν, cm-^{1}): 3048, 2917 (Ar-H), 1596 (C=N of pyrazole ring), 1500-1600 (Aromatic C=C), 1240 (C-N), 753 (C-Cl) ; ^{1}HNMR (400 MHz, DMSO-d_6) (δ, ppm): 4.1(s, 2H,CH_2), 6.8-8.8 (m,18H,Ar-H), 9.7 (s,1H,pyrazole) ; ^{13}C-NMR (70 MHz, DMSO-d_6) (δ, ppm): 32 (-CH_2), 120-142 (CH, Aromatic rings), 145-152 (C, pyrazole rings) 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,11.52%

4.2.2. 2-Phenyl-3-(1-phenyl-3-p-tolyl-1H-pyrazol-4-yl)-2, 4 dihydro-indeno[1,2-c] pyrazole (3b): Pale yellow solid; mp. 156-158 ^{o}C; IR (KBr, ν, cm^{-1}): 3043 (Ar-H), 2918 (C-H aliphatic), 1597 (C=N of pyrazole ring), 1480-1600 (Aromatic C=C), 1242 (C-N) ; ^{1}HNMR (400 MHz, DMSO-d_6) (δ, ppm): 2.3 (s,3H,CH_3) 4.0 (s, 2H,CH_2), 6.7-8.8 (m,18H,Ar-H), 9.6 (s,1H,pyrazole); ^{13}C-NMR (70 MHz, DMSO-d_6) (δ, ppm): 20.8 (-CH_3), 36 (-CH_2), 115-140 (CH, Aromatic rings), 145-150 (C, pyrazole rings)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%

4.2.3.3-[3-(4-Methoxy-phenyl)-1-phenyl-1H-pyrazol-4-yl]-phenyl-2,4-dihydro-indeno[1,2c] Pyrazole (3c): Yellow solid; mp. 172-174 ^{o}C; IR (KBr, ν, cm^{-1}): 3080 (Ar-H), 2920 (C-H aliphatic) 1605 (C=N of pyrazole ring), 1510-1605 (Aromatic C=C), 1250 (C-N), 1210 (C-O) ; ^{1}HNMR (400 MHz, DMSO-d_6) (δ, ppm): 3.7 (s,3H,OCH_3), 4.2 (s, 2H,CH_2), 6.6-8.8 (m,18H,Ar-H), 9.5 (s, 1H, pyrazole) ; ^{13}C-NMR (70 MHz, DMSO-d_6) (δ, ppm): 53.6 (-OCH_3), 30 (-CH_2), 116-145 (CH, Aromatic rings), 135-155 (C, pyrazole rings)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,76.97,H, 5.04, N,11.63,O,3.32%

4.2.4. 3-[3-(4-Nitro-phenyl)-1-phenyl-1H-pyrazol-4-yl]-2-phenyl-2, 4-dihydro-indeno [1, 2-c]Pyrazole (3d): Yellow solid; mp. 203-205 ^{o}C; IR (KBr, ν, cm^{-1}): 3050 (Ar-H), 1595 (C=N of pyrazole ring), 1515-1608 (Aromatic C=C), 1535 (-N-O), 1270 (C-N) ; ^{1}HNMR (400 MHz, DMSO-d_6) (δ, ppm): 4.3 (s,2H,CH_2), 6.8-8.5 (m,18H,Ar-H), 9.6 (s,1H, pyrazole) ; ^{13}C-NMR (70 MHz, DMSO-d_6) (δ, ppm): 28.6 (-CH_2), 114-144 (CH, Aromatic rings), 140-154 (C, pyrazole rings)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, 75.15, H, 4.25, N, 14.15, O, 6.43%

4.2.5. 3-(1,3-Diphenyl-1H-pyrazol-4-yl)-2-phenyl-2,4-dihydro-indeno[1,2-c]pyrazole (3e): Yellow soilid; mp. 158-160 ^{o}C; IR (KBr, ν, cm^{-1}): 3050 (Ar-H), 1595 (C=N of pyrazole ring), 1510-

1604 (Aromatic C=C), 1530 (-N-O), 1260 (C-N) ; ^{1}HNMR (400 MHz, DMSO-d_6) (δ, ppm): 4.1 (s, 2H, CH_2), 6.8-8.4 (m, 19H, Ar-H), 9.3 (s,1H,pyrazole) ; ^{13}C-NMR (70 MHz, DMSO-d_6) (δ, ppm): 33 (-CH_2), 115-142 (CH, Aromatic rings), 143-150 (C, pyrazole rings)EIMS (m/z): 450(M^+) ; Anal. Calcd. For $C_{31}H_{22}N_4$: C, 82.64; H, 4.92; N, 12.44% Found; C, 82.66, H, 4.95, N, 12.50,%

4.2.6. 3-(4-nitro-phenyl)-2-phenyl-2, 4-dihydro-indeno [1, 2-c] pyrazole (3f): Yellow solid; mp. 142-144 ^{o}C; IR(KBr, ν, cm^{-1}): 3040 (Ar-H), 1608 (C=N of pyrazole), 1520-1604 (Aromatic C=C)1530 (-N-O),; ^{1}HNMR (400 MHz, DMSO-d_6) (δ, ppm): 4.1 (s, 2H, CH_2), 6.6-8.2 (m,13H, Ar-H), 9.6 (s 1H, pyrazole) ; ^{13}C-NMR (70 MHz, DMSO-d_6) (δ, ppm): 31.5 (-CH_2), 112-140 (CH, Aromatic rings), 142-153 (C, pyrazole rings);EIMS (m/z): 353 (M^+) ; Anal. Calcd. For $C_{22}H_{15}N_3O2$:C; 74.78; H, 4.28; N, 11.89; O, 9.06% Found; C,74.30, H, 4.43, N,11.78; O, 9.03%

4.2.7. 2-Methoxy-4-(2-phenyl-2,4-dihydro-indeno[1,2-c]pyrazol-3-yl)-phenol (3g): Pale yellow solid; mp. 166-168 ^{o}C; IR (KBr, ν, cm^{-1}): 3301 (-OH), 2994 (Ar-H), 2933 (C-H,aliphatic) 1603 (C=N of pyrazole ring), 1570-1602 (Aromatic C=C), 1260 (C-O) ; ^{1}HNMR (400 MHz, DMSO-d_6) (δ,ppm): 3.8 (s, 3H, OCH_3), 4.1 (s, 2H, CH_2), 6.8-7.7 (m,12H,Ar-H), 9.3 (s 1H,pyrazole) 9.7 (s,1H,-OH) ; ^{13}C-NMR (70 MHz, DMSO-d_6) (δ,ppm): 54.4 (-OCH_3), 35 (-CH_2), 118-143 (CH, Aromatic rings), 138-151 (C, pyrazole rings);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%

4.2.8. 3-(4-Chloro-phenyl)-2-phenyl-2, 4-dihydro-indeno [1, 2-c] pyrazole (3h): Yellow solid; mp. 145-147^{o}C IR (KBr, ν, cm-^{1}): 3080 (Ar-H), 1602 (C=N of pyrazole), 1510-1600 (Aromatic C=C), 730 (C-Cl) ; ^{1}HNMR (400 MHz, DMSO-d_6) (δ, ppm): 4.0 (s, 2H, CH_2), 6.7-8.1 (m,13H, Ar-H), 9.4 (s 1H, pyrazole) ; ^{13}C-NMR (70 MHz, DMSO-d_6) (δ, ppm): 31.8 (-CH_2), 113-145 (CH, Aromatic rings), 143-154 (C, pyrazole rings);EIMS (m/z): 342 (M^+) ; Anal. Calcd. For $C_{22}H_{15}ClN_2$:C, 77.08; H, 4.41; Cl, 10.34; N, 8.17% Found; C,77.06,H, 4.43,Cl, 10.33,N,8.18%

4.2.9. 4-(2-Phenyl-2,4-dihydro-indeno[1,2-c]pyrazol-3-yl)-phenol (3i): Yellow solid; mp. 150-152 ^{o}C; IR (KBr, ν, cm-^{1}): 3440 (-OH), 3025 (Ar-H), 1610 (C=N of pyrazole ring), 1520-1605 (Aromatic C=C), 1210 (C-O) ; ^{1}HNMR (400 MHz, DMSO-d_6) (δ, ppm): 4.2 (s, 2H, CH_2), 6.6-8.4 (m,13H,Ar-H), 9.1(s,1H, pyrazole), 9.8 (s, 1H,-OH) ; EIMS (m/z): 324 (M^+) ; Anal. Calcd. For $C_{22}H_{16}N_2O$:C, 81.46; H, 4.97; N, 8.64; O, 4.93% Found; C,81.44,H, 4.95, N,8.62, O,4.91%

2.10. 3-(3-Nitro-phenyl)-2-phenyl-2, 4-dihydro-indeno [1, 2-c] pyrazole (3j): Yellow solid; mp. 160-162 ^{o}C; IR (KBr, ν, cm-^{1}): 3046 (Ar-H), 1604 (C=N of pyrazole ring), 1515-1600 (Aromatic C=C), 1535 (-N-O), 1210 (C-N) ; ^{1}HNMR (400 MHz, DMSO-d_6) (δ, ppm): 4.1 (s, 2H, CH_2), 6.6-8.6 (m,13H, Ar-H), 9.1 (s,1H, pyrazole) ; ^{13}C-NMR (70 MHz, DMSO-d_6) (δ, ppm): 34 (-CH_2), 116-143 (CH, Aromatic rings), 145-155 (C, pyrazole rings);EIMS (m/z): 353(M^+) ; Anal. Calcd. For $C_{22}H_{15}N_3O_2$: C, 74.78; H, 4.28; N, 11.89; O, 9.06% Found; C, 74.75, H, 4.30, N, 11.86, O, 9.07%

5. Conclusion

In summary, in the present investigation we have described a simple and green method for the synthesis of a novel series of substituted pyrazole derivatives. The structures of these compounds were confirmed by spectral analysis and evaluated for their antimicrobial activity. The results reveal that most of the synthesized pyrazole derivatives can be considered as a scaffold for the development of novel and effective antibacterial and antifungal agents.

Acknowledgement

Authors are thankful to UGC SAP Award No (F.3-36/2011 (SAP-II). Author APA is thankful to UGC for a teaching fellowship under the FDP scheme. RDK is thankful to the CSIR New Delhi for

JRF. Authors gratefully acknowledge the Director, School of Chemical Sciences SRTMU, IICT and Vishnu chemicals, Hyderabad for spectral analysis.

References

[1] Prakash, O.; Kumar, R.; Sehrawat, R.Synthesis and antibacterial activity of some new 2,3-dimethoxy-3-hydroxy-2-(1-phenyl-3-aryl-pyrazolyl) chromanones. *Eur. J. Med. Chem.* **2009,** 44,1763-1769.

[2] Maggio, B.; Daidone, G.; Raffa, D.; Plescia, S.; Mantione, L.; Cutuli, V. M. C.; Mangano, N.G.; Caruso, A. Synthesis and Pharmacological study of ethyl 1-methyl-5-(substituted3,4-dihydro-4-oxoquinazolin.. *Eur. J. Med. Chem.***2001,** 36, 737-742.

[3] Lange, J. H. M.; Kruse, C. G. Medicinal chemistry strategies to CB1 cannabinoid receptor antagonists. *Drug Discovery Today* **2005**, 10, 693-702.

[4] Bailey, D. M.; Hansen, P. E.; Hlavac, A. G.; Baizman, E. R.; Pearl, J.; Defelice, A. F.; Feigenson, M. E. 3,4-Diphenyl-1H-pyrazole-1-propanamine antidepressants.*J. Med. Chem.* **1985,** 28, 256-260.

[5] Bernardino, A. M. R.; Gomez, A. O.; Charret, K. S.; Freitas, A. C. C.; Machado, G. M. C.; Canto-Cavalheiro, M. M.; Leon, L. L.; Amaral, V. F. Synthesis and leishmanicidalactivities of 1- (4-X-phenyl)-N′-[(4-phenyl)methylene]-1H-pyrazole-4-carbohydrazides. *Eur. J. Med. Chem.* **2006**, 41,80-87.

[6] Jia, Z. Z.; Wu, Y. H.; Huang, W. R.; Zhang, P. L.; Song, Y. H.; Woolfrey, J.; Sinha, U.; Arfsten, A. E.; Edwards, S.T.; Hutchaleelaha, A.; Hollennbach, S. J.; Lambing, J. L.; Scarborough, R. M.; Zhu, B. Y. 1-(2-Naphthyl)-1H-pyrazole-5-carboxylamides as potent factor Xa inhibitors. Part 3: Design, synthesis and SAR of orally bioavailable benzamidine-P4 inhibitors. *Bioorg. Med. Chem. Lett.* **2004**, 14, 1229-1234.

[7] Choi, W. K.; El-Gamal, M. I; Choi, H. S.; Baek, D. New diarylureas and diarylamides containing 1,3,4-triarylpyrazole scaffold: Synthesis, antiproliferative evaluation against melanoma cell lines, ERK kinase inhibition,and molecular docking studies. *Eur. J. Med. Chem.* **2011**, 46, 5754-5762.

[8] Pereira, A. L.; Barreiro, A. C. C.; Freitas, C. J. C. Correa & Gomes, L. N. L. F. Investigation of the Lipophilicity of Antiphlogistic Pyrazole Derivatives: Relationships Between Log Kw and Log P Values of 5-Arylamino and Arylhydrazono-3-Methyl-4-Nitro-1-Phenylpyrazoles, *J. Liq. Chroma.* **1991,** 14, 1161-1171.

[9] Cottineau, B.; Toto, P.; Marot, C.; Pipaud, A.; Chenault, J. Synthesis and hypoglycemic evaluation of substituted pyrazole-4-carboxylic acids. *Bioorg. & Med. Chem. Lett.* **2002,** 12, 2105–2108.

[10] Jayanna, N. D.; Vagdevi, H. M.; Dharshan, J. C.; Raghavendra, R.; Telkar, S. B. Synthesis, antimicrobial, analgesic activity, and molecular docking studies of novel 1-(5,7-dichloro-1,3-benzoxazol-2-yl)-3-phenyl-1Hpyrazole-4-carbaldehyde derivatives, *Med. Chem. Res.*, **2013**, 22, 5814-5822.

[11] Elguero, J.; Goya, P.; Jagerovic, N.; Silva, A.M.S.;Targets in Heterocyclic Systems, Chemistry and Properties.*Italian Soc.Chem.* **2002**, 6, 52-98.

[12] Grapov, A. F.New insecticides and acaricides. *Usp. Khim*. **1999,** 68,773-784.

[13] Gioiello, A.; Khamidullina, V.; Fulco, M. C.; Venturoni, F.; Zlotsky, S.; Pellicciari, R. New one-pot synthesis of pyrazole-5-carboxylates by 1, 3-dipole cycloadditions of ethyl diazoacetate with α-methylene carbonyl compounds. *Tetrahedron Lett.* **2009**, 50, 5978-5980.

[14] Ouyang, G.;Cai, X. J.; Chen, Z.; Song, B. A.; Bhadury, P. S.; Yang, S.; Jin, L. H.; Xue, W.; Hu, D. Y.; Zeng, S. J. Synthesis and antiviral activities of pyrazole derivatives containing an oxime moiety. *Agric. Food Chem.* **2008**, 56, 10160-10167.

[15] Dias, L. R. S.; Salvador, R. R. S.; Pyrazole Carbohydrazide Derivatives of Pharmaceutical Interest. *Pharmaceuticals (Basel)* **2012**, 5, 317–324.

[16] Machado, P.; Lima, G. R.; Rotta, M.; Bonacorso, H.G.; Zanatta, N.; Martins, M. A. Efficient and highly regioselective synthesis of ethyl 1-(2,4-dichlorophenyl)-1*H*-pyrazole-3-carboxylates under ultrasound irradiation. *Ultrason. Sonochem.* **2010**, 18, 293-299.

[17] Matsumoto, H. Mode of Action of Pyrazole Herbicides Pyrazolate and Pyrazoxyfen: HPPD Inhibition by the Common Metabolite.*New Discoveries in Agrochem.* **2004**, 161-171.

[18] Sherman, T. D. ; Duke, M. V.; Clark, R. D.; Sanders, E. F.; Matsumoto, H.; Duke, S.O. Pyrazole phenyl ether herbicides inhibit protoporphyrinogen oxidase. *Pestic. Biochem. Physiol.* **1991**, 40, 236-245.

[19] Ballini, R.; Bosica, G.; Maggi, R.; Ricciutelli, M.; Righi, P.; Sartori, G. and Sartorio, R. Clay-catalysedsolventless synthesis of *trans*-chalcones. *Green Chem.* **2001**, 3, 178-180.

[20] Dawane, B. S.; Shaikh, B. M.; Khandare, N. T.; Kamble, V. T.; Chobe, S. S.; Konda, S. G. Eco-friendly polyethylene glycol-400: a rapid and efficient Recyclable reaction medium for the synthesis of thiazole derivatives. *Green Chem. Lett. and Rev.* **2010,** 3, 205-208.

[21] Dawane, B. S.; Konda, S. G.; Mandawad, G. G.; Shaikh, B. M. Poly(ethylene glycol)(PEG-400) as an Alternative Reaction Solvent for the Synthesis of Some New 1-(4-(4'-Chlorophenyl-2-thiazolyl)-3-aryl-5-(2-butyl-4-chloro-1H imidazol5yl)pyraz-olines and their in vitro Antimicrobial Evaluation. *Eur. J. Med. Chem.* **2010,** 45, 387-392.
[22] Arthur, W.; Brownlee, W. H. Refining of Oils Dawkins. *British Patent* GB, 1077557, **1970**.
[23] Schuchardt, J. L. Preparation of oxetane polyether polyols using a bleaching earth catalyst. *US Patent*, 4970295,**1990**.
[24] Acharya A. P., Kamble R. D., Patil S. D., Hese S. V., Yemul O. S ., Patil S. G ., Halale S. N ., Dawane B. S. "Green synthesis" of benzothiazepine library of indeno analogues and their in vitro antimicrobial activity, *Chem. Papers*, **2014**, 68, 4, 719-724.
[25] Kira, M. A.; Abdel-Rahman, M.O.; Gadalla, K. Z.The Vilsmeier reaction-III, cyclization of hydrazones to pyrazoles.*Tetrahedron Lett.***1969**, 10, 109-110.
[26] Mandawad, G. G.; Chobe, S. S.; Yemul, O. S.; Dawane, B. S. An efficient green synthesis of some novel hetero chalcones as potent antimicrobial agents, *J. Pharm. Res.*, **2011**, 4, 3360-3363.
[27] Acharya A. P., Kamble R. D., Patil S. D., Hese S. V., Dawane B. S. An efficient and green synthesis of some novel benzodiazepine derivatives and their antimicrobial screening, *Der Chem. Sin.*, **2013**, 4, 189-193.