WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 7, Issue 7, 1640-1656. Research Article ISSN 2277– 7105

GREENER APPROACH OF SYNTHESIS OF AZO DERIVATIVES AND BIS- PYRAZOLE DERIVATIVES ALONG WITH ANTIMICROBIAL SCREENING

Prashant P. Chaudhari[1]* and Shankarsing S. Rajput[2]

[1]Department of Engineering Science, Dr. D Y Patil School of Engineering, Dr. D Y Patil Knowledge City, Charoli (Bk), Lohegaon, Pune (412105) Maharashtra, India.

[2]Department of Chemistry, SVS's Dadasaheb Rawal College, Dondaicha (425408), Maharashtra, India.

Article Received on
19 February 2018,
Revised on 11 March 2018,
Accepted on 01 April 2018,
DOI: 10.20959/wjpr20187-11613

***Corresponding Author**
Prashant P. Chaudhari
Department of Engineering Science, Dr. D Y Patil School of Engineering, Dr. D Y Patil Knowledge City, Charoli (Bk), Lohegaon, Pune (412105) Maharashtra, India.

ABSTRACT

A clean, efficient and solvent free method for the synthesis of Azo compounds was carried out with the help of PbO nanoparticles. They have been synthesized by the reaction between 1-(N-methylpyridin-2-yl)pyrrolidine/ piperidine -2,5/6-dione and propionaldehyde at room temperature with the help of green chemistry. PbO nanoparticles employed as an efficient catalytic tool due to efficient, renewable and eco-friendly heterogeneous characteristics. The bis pyrazoles are synthesized by a simple eco-friendly microwave instigated solvent free synthesis. It was carried out by the reaction of corresponding bis-chalcones : 3,4/5-bis((E)-2-chlorobenzylidene)-1-(N-methylpyridin-2-yl)pyrrolidine/ piperidine -2,5/6-dione with hydrazine hydrate in presence of neutral Alumina. This method furnished various advantages, such as straight forward work-up procedure, environmentally benevolent, neutral condition and high yield. All the derivatives were characterized and interpreted for antimicrobial activities.

KEYWORDS: Green Chemistry, clean, Solvent free, pyrrolidine-2,5-dione, piperidine-2,6-dione, propionaldehyde, hydrazine hydrate.

INTRODUCTION

It is recognized that multi-functionalized benzopyrans and their derivatives are a very important class compounds. They have been broadly applicable as medicine intermediates

because their synergetic pharmacological and biological properties, such as anticoagulant, antibacterial, anticancer, spasmolytic, diuretic, hypnotic and insecticide.[1-7] Generally, substituted pyrazole and their derivatives are synthesized in organic solvents[8-10] which can be used as important pharmaceuticals and agricultural chemicals. Additionally, multi-substitution benzopyrans can contribute a structural unit for a group of natural products[11-13] and some of them along with their derivatives were signed up as photo-active materials.[14]

In recent years Pyrazoles are established as important class of heterocyclic community and have attractive achievements in both in organic synthesis and medicinal chemistry.[15-20] Pyrazoles are a very propitious synthetic intermediate which is source of an important pharmacophore exist in a variety of biologically active and potential therapeutic commixtures.[21-23] These admixtures have been mostly used in sententious antibacterial[24-28], antipyretic[29-32], antidepressant[33], antiviral[34], antitumor[35-38], anti-inflammatory.[39-41] In addition various pyrazoles have been considered as the extracting and chelating reagents for different metal ions[42,43] and few of the pyrazolone derivatives are used in several marketable drugs for myocardial and brain ischemia.[44,45] Now a days research is focused on eco-friendly, solvent free efficient greener synthesis. In line of this few catalyst are invented for the synthesis of pyrazoles like heteropolyacids[46, 47], acetic acid or piperidine[48], Na^+-MMT-[pmim]HSO_4[49], cesium fluoride (CsF)[50], 3-aminopropylated silica gel[51], 1,3,5-tris(hydrogensulfato) benzene (THSB)[52], sodium dodecyl sulfate (SDS)[53], $ZnAl_2O_4$ nanoparticles[54], silica-bonded S-sulfonic acid (SBSSA)[55], $LiOH{\cdot}H_2O$[56], [Cu(3,4-tmtppa)]$(MeSO_4)_4$[57] ceric ammonium nitrate (CAN), benzyltriethylammonium chloride[58] and so on. However, it is well-known that several of the methods reported above faces challenges like strong basic or acidic conditions, difficulty in handling and separation of catalyst, use of costly catalysts long reaction time and huge solvent consumption. These transactions include possibility of side reactions which restrict their usage in practical applications. Wherefore, it is very important to ponder and develop novel eco-friendly efficient and scalable synthetic routes which are able to construct pyrazolone derivatives in high yields.

The current trends of research are focused on the applications of the solid support Al_2O_3 and silica gel SiO_2. They have pulled out much attention as not only they could be used as a catalyst for many organic transactions which providing high yields but also cheaper and non-

toxic. Also, It is found that Al_2O_3 and SiO_2 have greatly simplified the workup in a solvent-free procedures.[59,60]

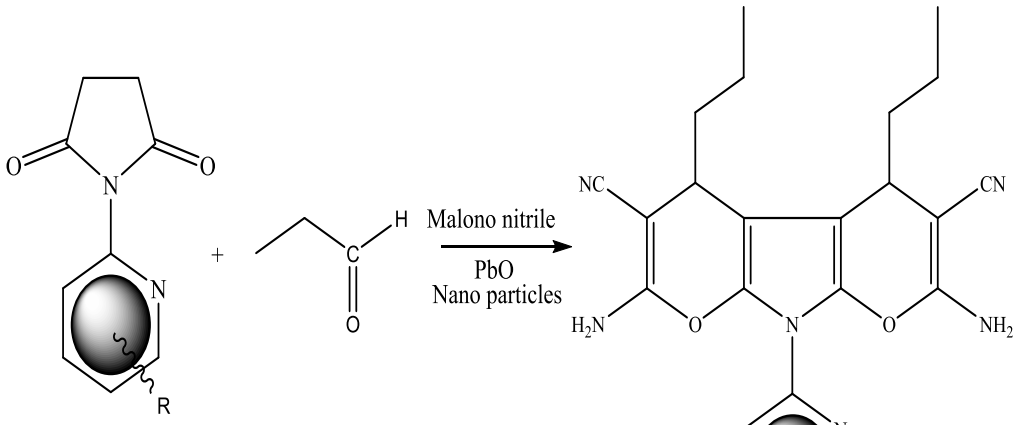
EXPERIMENTAL

MATERIAL METHODS

Melting points were recorded in open glass capillaries and were uncorrected. The chemical structures of the obtained compounds were confirmed by spectral analyses. IR spectra in KBr pallets were obtained on Simadzu and ATR Brucker alpha FT-IR spectrophotometer. ^1H NMR spectra were obtained on and 500.13 MHz by Brucker spectrophotometer. The chemical shifts were reported as parts per million (ppm) with $(CH_3)_4Si$ (TMS) as an internal standard. Signal multiplicities are represented by: s (singlet), d (doublet), t (triplet), m (multiplet). The purity of compound was checked by thin layer chromatography which was performed by using pre-coated silica gel aluminium plates with mixture of diethyl ether and ethyl acetate 7:3 proportion. Anti-microbial and Anti-fungal activities were carried out by Agar diffusion assay (Disk diffusion method, Disk size 6 mm). PbO nanoparticle were synthesized by taking a mixture of 10 ml of 0.1N sodium hydroxide and 0.025 mole citric acid in distilled water was added to methanolic solution of 0.02 mole lead nitrate. The reaction mixture was continuously stirred with the help of magnetic stirrer for 2 hours at room temperature. The white polycrystalline product was obtained which is filtered, washed with distilled water and dried at110ºC for 2 hours. The dried solid product was calcinized at 500 ºC for 2 hours. During this process, the PbO nanoparticle which has white colour earlier turned to pale yellow colour. All the compounds (7a-f and 10a-f) were synthesized from the corresponding Succinic and Glutaric Anhydride derivatives and commercially purchased propionaldehyde, neutral alumina (Al_2O_3) and ethanol.

General Procedure of synthesis

Preparation of Azo derivatives: 2,7-diamino-9-(N-methylpyridin-2-yl)-4,5-dipropyl-5,9-dihydro-4H-dipyrano[2,3-b:3',2'-d]pyrrole-3,6-dicarbonitrile (7a-c): A mixture of 0.01 mole N-phenyl pyrrolidine-2,5-dione, 0.02 mole propionaldehyde, 0.02 mole malononitrile and 100 mg PbO nanoparticles were ground at a room temperature with a mortar and pestle. The reaction was monitored by thin layer chromatography (TLC). After completion of reaction, the product was washed with distilled water. The novel developed compounds were dried and recrystallized from ethanol to afford pure compounds with high yield **(Scheme – I)**.

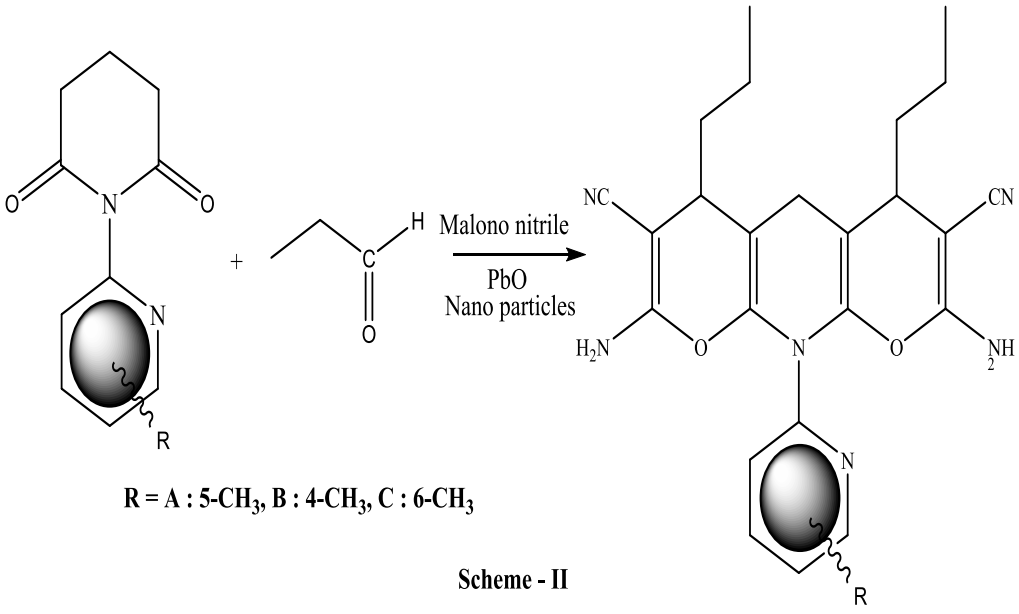


R = A : 5-CH_3, B : 4-CH_3, C : 6-CH_3

Scheme - I

Preparation of Azo (Dipyrano): 2,8-diamino-10-(N-methylpyridin-2-yl)-4,6-dipropyl-6,10-dihydro-4H,5H-dipyrano[2,3-b:3',2'-e]pyridine-3,7-dicarbonitrile (7d-f)

A mixture of 0.01 mole N-phenyl piperidine-2,6-dione, 0.02 mole propionaldehyde, 0.02 mole malononitrile and 100 mg PbO nanoparticles were ground at a room temperature with a mortar and pestle. The reaction was monitored by thin layer chromatography (TLC). After completion of reaction, the product was washed with distilled water. The novel developed compounds were dried and recrystallized from ethanol to afford pure compounds with high yield **(Scheme – II)**.



R = A : 5-CH_3, B : 4-CH_3, C : 6-CH_3

Scheme - II

Physicochemical and analytical data for compounds 7a-f

2,7-diamino-9-(5-methylpyridin-2-yl)-4,5-dipropyl-5,9-dihydro-4H-dipyrano[2,3-b:3',2'-d]pyrrole-3,6-dicarbonitrile (7a)

Yellow Orange Solid, Yield (82.14%), M. P. 268-70ºC, M.F. $C_{24}H_{26}O_2N_6$ M.W.430.50, Composition: C (66.29%) H (6.35%) N (19.28%); IR (KBr): C≡N:2137.50; -N-H: 3334.46; aromatic ring: 683.60; -CH_3: 3214.75; C-N (Aliphatic): 1154.36; C-N (Aromatic): 1222.63; -C-C- Stretch in a ring(2-Peaks): 1637.43, 1539.22; -CH_3 bend: 1492.79, 1384.71 cm^{-1}. ^1H NMR (500.13 MHz, DMSO, δ ppm): 0.90 (d, 6H), 1.22 (t, 4H, Methylene), 1.51 (t,4H, Methylene), 2.12 (s,2H, methine),6.86 (s, 4H,-NH_2), 7.30-8.49 (m, 3H, aromatic), 2.37 (s, 3H, CH_3-pyridine).

2,7-diamino-9-(4-methylpyridin-2-yl)-4,5-dipropyl-5,9-dihydro-4H-dipyrano[2,3-b:3',2'-d]pyrrole-3,6-dicarbonitrile (7b)

Yellow Orange Solid, Yield (78.15%), M. P. 312-14ºC, M.F. $C_{24}H_{26}O_2N_6$ M.W.430.50, Composition: C (66.39%) H (6.26%) N (19.41%); IR (KBr): C≡N:2141.96; -N-H: 3330.28; aromatic ring: 683.41; -CH_3: 2921.49; C-N (Aliphatic): 1048.07; C-N (Aromatic): 1222.07; -C-C- Stretch in a ring(2-Peaks): 1620.98, 1539.73; -CH_3 bend: 1492.99, 1383.42 cm^{-1}. ^1H NMR (500.13 MHz, DMSO, δ ppm): 0.94 (d, 6H), 1.24 (t,4H, Methylene), 1.52 (t,4H, Methylene), 2.12 (s,2H, methine),6.80 (s, 4H,-NH_2), 7.34-8.54 (m, 3H, aromatic), 2.37 (s, 3H, CH_3-pyridine).

2,7-diamino-9-(6-methylpyridin-2-yl)-4,5-dipropyl-5,9-dihydro-4H-dipyrano[2,3-b:3',2'-d]pyrrole-3,6-dicarbonitrile (7c)

Yellow Orange Solid, Yield (78.72%), M. P. 188-90ºC, M.F. $C_{24}H_{26}O_2N_6$ M.W.430.50, Composition: C (66.62%) H (6.19%) N (19.37%); IR (KBr): C≡N: 2164.50; -N-H: 3337.62; aromatic ring: 687.72; -CH_3: 2968.39; C-N (Aliphatic): 1058.76; C-N (Aromatic): 1228.01 -C-C- Stretch in a ring(2-Peaks): 1646.36, 1495.52; -CH_3 bend: 1457.24, 1384.24 cm^{-1}. ^1H NMR (500.13 MHz, DMSO, δ ppm): 0.90 (d, 6H), 1.27 (t,4H, Methylene), 1.54 (t,4H, Methylene), 2.12 (s,2H, methine),6.91 (s, 4H,-NH_2), 7.04-7.79 (m, 3H, aromatic), 2.64 (s, 3H, CH_3-pyridine).

2,8-diamino-10-(5-methylpyridin-2-yl)-4,6-dipropyl-6,10-dihydro-4H,5H-dipyrano[2,3-b:3',2'-e]pyridine-3,7-dicarbonitrile (7d)

Yellow Orange Color Solid, Yield (78.49%), M. P. 184-86ºC, M.F. $C_{25}H_{28}O_2N_6$ M.W.444.52, Composition: C (67.02%) H (6.89%) N (18.26%); IR (KBr): C≡N:2135.17; -N-H: 3332.09;

aromatic ring: 684.53; -CH_2: 3001.18; -CH_3: 2927.33; C-N (Aliphatic): 1153.27; C-N (Aromatic): 1298.31; -C-C- Stretch in a ring(2-Peaks): 1730.05, 1532.34; -CH_3 bend: 1451.66; -CH_2 bend: 1380.28 cm^{-1}. ^1H NMR (500.13 MHz, DMSO, δ ppm): 0.89 (d, 6H), 1.17 (t,4H, Methylene), 2.44 (t,4H, Methylene), 2.56 (s,2H, methine), 3.53 (s, 2H, -CH_2), 6.56 (s, 4H,-NH_2), 7.19-7.75 (m, 3H, aromatic), 2.51 (s, 3H, CH_3-pyridine).

2,8-diamino-10-(4-methylpyridin-2-yl)-4,6-dipropyl-6,10-dihydro-4H,5H-dipyrano[2,3-b:3',2'-e]pyridine-3,7-dicarbonitrile (7e)

Yellow Orange Color Solid, Yield (72.41%), M. P. 166-68ºC, M.F. $C_{25}H_{28}O_2N_6$ M.W.444.52, Composition: C (67.19%) H (6.93%) N (18.06%); IR (KBr): C≡N:2140.5; -N-H: 3331.19; aromatic ring: 685.88; -CH_2: 3003.54; -CH_3: 2928.51; C-N (Aliphatic): 1050.34; C-N (Aromatic): 1290.18; -C-C- Stretch in a ring(2-Peaks): 1740.22, 1531.94; -CH_3 bend: 1453.53; -CH_2 bend: 1379.36 cm^{-1}. ^1H NMR (500.13 MHz, DMSO, δ ppm): 0.91 (d, 6H), 1.20 (t,4H, Methylene), 2.39 (t,4H, Methylene), 2.35 (s,2H, methine), 3.53 (s, 2H, -CH_2), 6.60 (s, 4H,-NH_2), 7.22-7.35 (m, 3H, aromatic), 2.33 (s, 3H, CH_3-pyridine).

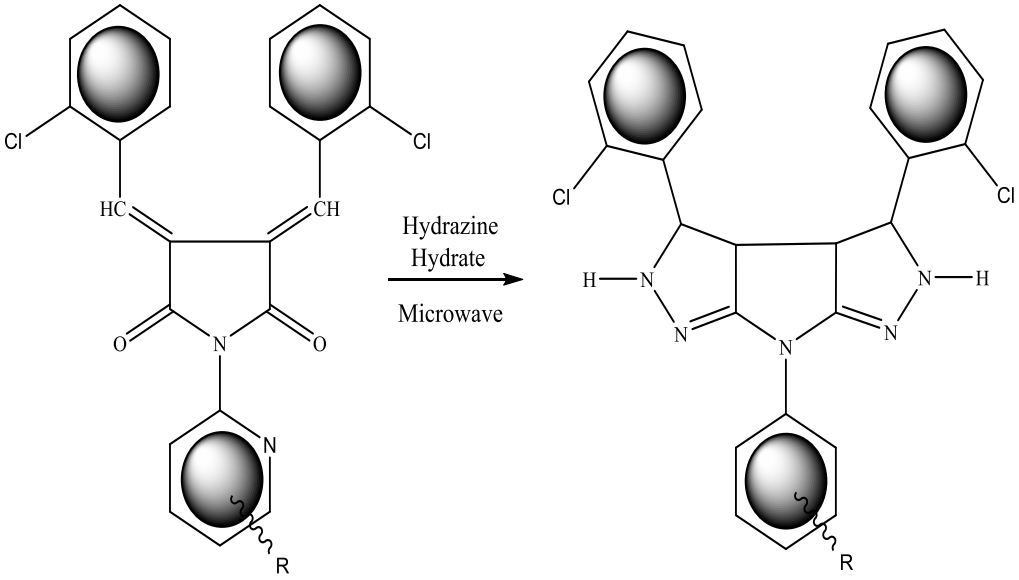
2,8-diamino-10-(6-methylpyridin-2-yl)-4,6-dipropyl-6,10-dihydro-4H,5H-dipyrano[2,3-b:3',2'-e]pyridine-3,7-dicarbonitrile (7f)

Pastel Orange Solid, Yield (78.22%), M. P. 240-42ºC, M.F. $C_{25}H_{28}O_2N_6$ M.W.444.52, Composition: C (66.98%) H (6.11%) N (18.19%); IR (KBr): C≡N:2137.05; -N-H: 3327.75; aromatic ring: 683.34; -CH_2: 3002.44; -CH_3: 2925.64; C-N (Aliphatic): 1156.90; C-N (Aromatic): 1300.21; -C-C- Stretch in a ring(2-Peaks): 1744.42, 1496.28; -CH_3 bend: 1452.13; -CH_2 bend: 1388.53 cm^{-1}. ^1H NMR (500.13 MHz, DMSO, δ ppm): 0.94 (d, 6H), 1.15 (t,4H, Methylene), 2.40 (t,4H, Methylene), 2.64 (s,2H, methine), 3.59 (s, 2H, -CH_2), 6.69 (s, 4H,-NH_2), 7.25-7.64 (m, 3H, aromatic), 2.45 (s, 3H, CH_3-pyridine).

General Procedure of Synthesis

Preparation of Pyrazole: 3,4-bis(2-chlorophenyl)-7-(N-methylpyridin-2-yl)-3,3a,3b,4,5,7-hexahydro-2H-pyrrolo[2,3-c:5,4-c']dipyrazole (13a-c)

The bis-pyrazole (13a-c) derivatives were synthesized by the mixture of 0.01 mole of N-phenyl pyrrolidine-2, 5-dione and 0.02 mole of aromatic aldehyde in 1 gm of neutral Al_2O_3 with the help of microwave irradiations. This mixture is maintained in microwave at 800W power for 4-6 minutes in solvent free condition. The novel developed compounds were recrystallized from ethanol (Scheme – III).

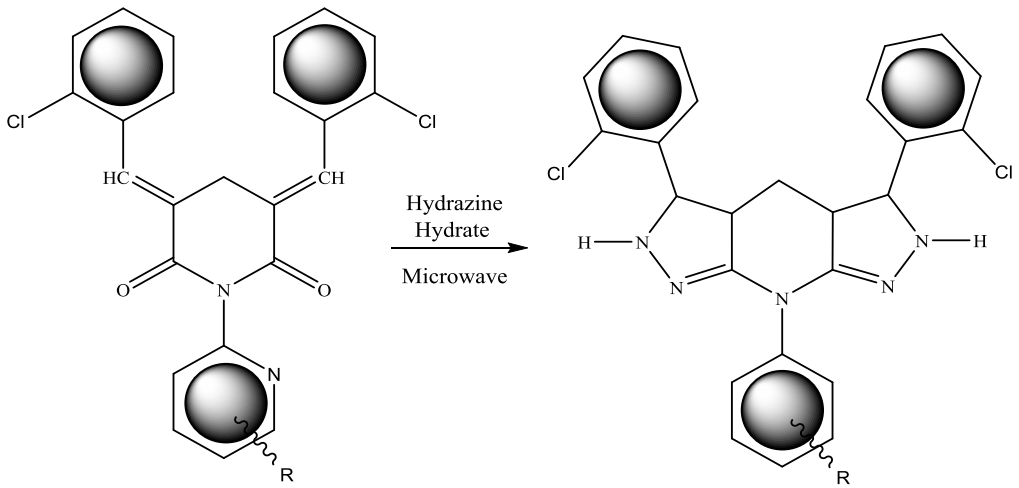


R = A : 5-CH_3, B : 4-CH_3, C : 6-CH_3

Scheme - III

Preparation of Pyrazole: 3,5-bis(2-chlorophenyl)-8-(N-methylpyridin-2-yl)-2,3,3a,4,4a,5,6,8-octahydrodipyrazolo[3,4-b:4',3'-e]pyridine (13d-f)

The bis-pyrazole (13d-f) derivatives were synthesized by the mixture of 0.01 moles of N-phenyl piperidine-2,6-dione and 0.02 mole of aromatic aldehyde in 1 gm of neutral Al_2O_3 with the help of microwave irradiations. This mixture is maintained in microwave at 800W power for 5-8 minutes in solvent free condition. The novel developed compounds were recrystallized from ethanol (Scheme – IV).



R = A : 5-CH_3, B : 4-CH_3, C : 6-CH_3

Scheme - IV

Physicochemical and analytical data for compounds 13a-f

3,4-bis(2-chlorophenyl)-7-(5-methylpyridin-2-yl)-3,3a,3b,4,5,7-hexahydro-2H-pyrrolo[2,3-c:5,4-c']dipyrazole (13a)

Green Brown Solid, Yield (71.33%), M. P. 136-38ºC, M.F. $C_{24}H_{20}N_6Cl_2$ M.W.463.36, Composition: C (63.25%) H (3.81%) N (14.47%); IR (KBr): -C-Cl:645.06; -N-H: 3177.50; >C=N: 1655.70; aromatic ring (2-Peaks): 3063.07, 824.28; -CH_3: 3004.38; C-N (Aliphatic): 1209.99; C-N (Aromatic): 1274.57; -C-C- Stretch in a ring(2-Peaks): 1564.02, 1506.82; -CH_3 bend: 1467.09, 1371.66 cm^{-1}. ^1H NMR (500.13 MHz, DMSO, δ ppm): 2.20 (t, 2H, Methine), 3.40 (d, 2H, Methine), 9.85 (s, 2H,-N-H), 6.64-7.88 (m, 11H, aromatic), 2.28 (s, 3H, CH_3-pyridine).

3,4-bis(2-chlorophenyl)-7-(4-methylpyridin-2-yl)-3,3a,3b,4,5,7-hexahydro-2H-pyrrolo[2,3-c:5,4-c']dipyrazole (13b)

Faint Clay Brown Solid, Yield (76.24%), M. P. 194-96ºC, M.F. $C_{24}H_{20}N_6Cl_2$ M.W.463.36, Composition: C (63.30%) H (3.37%) N (14.55%); IR (KBr): -C-Cl:644.71; -N-H: 3150.16; >C=N: 1655.17; aromatic ring (2-Peaks): 3051.27, 825.15; -CH_3: 3003.82; C-N (Aliphatic): 1211.31; C-N (Aromatic): 1271.43; -C-C- Stretch in a ring(2-Peaks): 1566.17, 1528.29; -CH_3 bend: 1465.26, 1373.61 cm^{-1}. ^1H NMR (500.13 MHz, DMSO, δ ppm): 2.28 (t, 2H, Methine), 3.47 (d, 2H, Methine), 9.96 (s, 2H,-N-H), 6.57-7.95 (m, 11H, aromatic), 2.29 (s, 3H, CH_3-pyridine).

3,4-bis(2-chlorophenyl)-7-(6-methylpyridin-2-yl)-3,3a,3b,4,5,7-hexahydro-2H-pyrrolo[2,3-c:5,4-c']dipyrazole (13c)

Saffron Yellow Solid, Yield (63.20%), M. P. 326-28ºC, M.F. $C_{24}H_{20}N_6Cl_2$ M.W.463.36, Composition: C (63.61%) H (3.76%) N (14.39%); IR (KBr): -C-Cl:643.26; -N-H: 3165.52; >C=N: 1664.68; aromatic ring (2-Peaks): 3048.18, 823.25; -CH_3: 3001.55; C-N (Aliphatic): 1212.44; C-N (Aromatic): 1275.36; -C-C- Stretch in a ring(2-Peaks): 1532.77, 1572.25; -CH_3 bend: 1461.12, 1372.45 cm^{-1}. ^1H NMR (500.13 MHz, DMSO, δ ppm): 2.17 (t, 2H, Methine), 3.08 (d, 2H, Methine), 9.95 (s, 2H,-N-H), 6.27-7.45 (m, 11H, aromatic), 2.36 (s, 3H, CH_3-pyridine).

3,5-bis(2-chlorophenyl)-8-(5-methylpyridin-2-yl)-2,3,3a,4,4a,5,6,8-octahydrodipyrazolo[3,4-b:4',3'-e]pyridine (13d)

Honey Yellow Solid, Yield (77.38%), M. P. 332-34ºC, M.F. $C_{25}H_{22}N_6Cl_2$ M.W.477.38, Composition: C (63.05%) H (4.91%) N (17.21%); IR (KBr): -C-Cl:643.64; -N-H: 3176.69;

>C=N: 1654.66; aromatic ring (2-Peaks): 3002.00, 856.72; -CH_3: 2856.80; -CH_2: 2827.62; C-N (Aliphatic): 1210.84; C-N (Aromatic): 1275.79; -C-C- Stretch in a ring(2-Peaks): 1594.73, 1563.93; -CH_3 bend: 1436.03, 1365.69; -CH_2 bend: 1466.81 cm^{-1}. ^1H NMR (500.13 MHz, DMSO, δ ppm): 2.26 (m, 2H, methine), 3.79 (m, 2H, methine), 1.69 (m, 2H, methylene), 9.94 (s, 2H,-N-H), 6.51-7.83 (m, 11H, aromatic), 2.14 (s, 3H, CH_3-pyridine).

3,5-bis(2-chlorophenyl)-8-(4-methylpyridin-2-yl)-2,3,3a,4,4a,5,6,8-octahydrodipyrazolo[3,4-b:4',3'-e]pyridine (13e)

Clay Brown Solid, Yield (65.74%), M. P. 278-80ºC, M.F. $C_{25}H_{22}N_6Cl_2$ M.W.477.38, Composition: C (62.09%) H (4.21%) N (17.18%); IR (KBr): -C-Cl:641.28; -N-H: 3210.31; >C=N: 1655.41; aromatic ring (2-Peaks): 3001.98, 855.33; -CH_3: 2879.28; -CH_2: 2825.19; C-N (Aliphatic): 1209.75; C-N (Aromatic): 1274.39; -C-C- Stretch in a ring(2-Peaks): 1580.29, 1565.74; -CH_3 bend: 1434.28, 1365.47; -CH_2 bend: 1463.08 cm^{-1}. ^1H NMR (500.13 MHz, DMSO, δ ppm): 2.21 (m, 2H, methine), 3.77 (m, 2H, methine), 1.75 (m, 2H, methylene), 9.93 (s, 2H,-N-H), 6.49-7.86 (m, 11H, aromatic), 2.16 (s, 3H, CH_3-pyridine).

3,5-bis(2-chlorophenyl)-8-(6-methylpyridin-2-yl)-2,3,3a,4,4a,5,6,8-octahydrodipyrazolo[3,4-b:4',3'-e]pyridine (13f)

Deep Orange Solid, Yield (75.61%), M. P. 334-36ºC, M.F. $C_{25}H_{22}N_6Cl_2$ M.W.477.38, Composition: C (62.18%) H (4.22%) N (17.01%); IR (KBr): -C-Cl:640.65; -N-H: 3202.88; >C=N: 1657.50; aromatic ring (2-Peaks): 3004.91, 858.21; -CH_3: 2949.15; -CH_2: 2926.74; C-N (Aliphatic): 1208.87; C-N (Aromatic): 1273.11; -C-C- Stretch in a ring(2-Peaks): 1587.44, 1568.37; -CH_3 bend: 1435.39, 1373.13; -CH_2 bend: 1463.94 cm^{-1}. ^1H NMR (500.13 MHz, DMSO, δ ppm): 2.37 (m, 2H, methine), 3.86 (m, 2H, methine), 1.71 (m, 2H, methylene), 9.91 (s, 2H,-N-H), 6.32-7.62 (m, 11H, aromatic), 2.21 (s, 3H, CH_3-pyridine).

RESULTS AND DISCUSSION

Chemistry

The series of Azo derivatives 7a-f were synthesized by the reaction of 1-(N-methylpyridin-2-yl)pyrrolidine/ piperidine -2,5/6-dione, propionaldehyde and malononitrile with the help of PbO nanoparticles. The formation of Azo derivatives was confirmed by IR, ^{13}C NMR and ^1H NMR and elemental analysis. The series of bis-pyrazole derivatives 13a-f were synthesized by the reaction of bis chalcones 3,4/5-bis((E)-2-chlorobenzylidene)-1-(N-methylpyridin-2-yl)pyrrolidine/ piperidine -2,5/6-dione and hydrazine hydrate in presence of neutral Al_2O_3

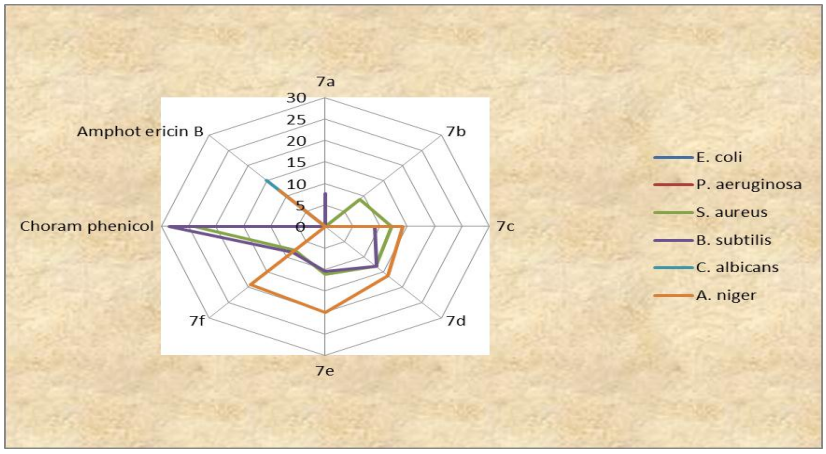
with the help of microwave irradiations. The formation of bis-pyrazoles was confirmed by IR, ^{13}C NMR and ^{1}H NMR and elemental analysis.

Antimicrobial Activities

All the synthesized Azo derivatives 7a-f and bis-pyrazole derivatives 13a-f were screened for their antibacterial activity against gram positive bacteria *Staphylococcus aureus* (NCIM 2079), *Bacillus subtilis* (NCIM 2250) and gram negative bacteria *Escherichia coli* (NCIM 2109), *Pseudomonas aeruginosa* (NCIM 2036) using DMSO solvent. All these novel synthesized compounds were screened against Fungi (Yeast) *Candida albicans* (NCIM 3471) and *Aspergillus niger* (NCIM 545). The bacterial cultures were purchased from NCIM: National Collection of Industrial Microorganisms, National Chemical Laboratory (NCL), Pune 411008 [India]. Some of the compound showed moderate to good activities against gram positive bacteria *S. aureus* and synergetic activities against Fungi *A. niger* as shown in the Table –I, II and Graph –I, II.

Table-I: Antimicrobial activities of Azo derivatives 7a-f.

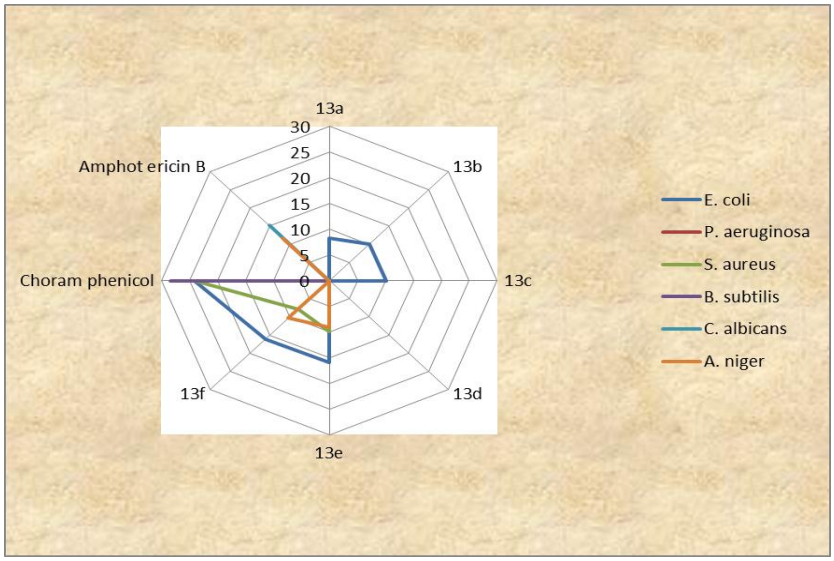
Sr. No.	Sample	*E. coli*	*P. aeruginosa*	*S. aureus*	*B. subtilis*	*C. albicans*	*A. niger*
		Mean±SD	***Mean ±SD***	***Mean ±SD***	***Mean ±SD***	***Mean ±SD***	***Mean ±SD***
1	7a	- - -	- - -		7.66±0.20	- - -	- - -
2	7b	- - -	- - -	8.96±0.09	- - -	- - -	- - -
3	7c	- - -	- - -	12.06±0.07	9.05±0.13	- - -	14.2±0.07
4	7d	- - -	- - -	13.09±0.02	13.19±0.06	- - -	16.2±0.01
5	7e	- - -	- - -	11.09±0.14	10.49±0.05	- - -	20±0.12
6	7f	- - -	- - -	7.86±0.11	8.40±0.06	- - -	19.2±0.11
	Choram phenicol	**24.09±0.10**	**14.39±0.07**	**23.92±0.17**	**28.43±0.29**	NA	NA
	Amphot ericin B	NA	NA	NA	NA	**15.21±0.15**	**11.8±0.08**



Graph-I: Antimicrobial activities of Azo derivatives 7a-f.

Table-II: Antimicrobial activities of bis pyrazole derivatives 13a-f.

Sr. No.	Sample	*E. coli*	*P. aeruginosa*	*S. aureus*	*B. subtilis*	*C. albicans*	*A. niger*
		Mean±SD	***Mean ±SD***	***Mean ±SD***	***Mean ±SD***	***Mean ±SD***	***Mean ±SD***
1	13a	8.28±0.09	- - -	- - -	- - -	- - -	- - -
2	13b	10.01±0.18	- - -	- - -	- - -	- - -	- - -
3	13c	10.08±0.13	- - -	- - -	- - -	- - -	- - -
4	13d	- - -	- - -	- - -	- - -	- - -	- - -
5	13e	15.93±0.14	- - -	9.85±0.15	- - -	- - -	9.11±0.04
6	13f	16.1±0.18	- - -	7.82±0.03	- - -	- - -	10.3±0.16
	Choram phenicol	**24.09±0.10**	**14.39±0.07**	**23.92±0.17**	**28.43±0.29**	NA	NA
	Amphot ericin B	NA	NA	NA	NA	**15.21±0.15**	**11.8±0.08**



Graph-II: Antimicrobial activities of bis pyrazole derivatives 13a-f.

CONCLUSION

The greener path used catalyst PbO nanoparticle which is solvent-free and produced sensible yield. 13e and 13f have showed ameliorate activities against *S. aureus.* Also, the series of compounds 13a-c reveals excellent and congenial activities against *A. niger* strain.

ACKNOWLEDGMENT

I wish to express my profound gratitude to Hon'ble Dr Ajeenkya DY Patil, President of Ajeenkya DY Patil University and Chairman of Ajeenkya DY Patil Group on promoting me to contribute a quality work by allowing all facilities. I wish to express my insightful gratitude to Hon'ble Mr. Jaykumar Rawal, Minister, Employment Guarantee Scheme and Tourism Development, Government of Maharashtra. With deep sense of regards I express my thanks to Dr Nilesh Vishanath, Director, DYPKC, Mr. Sushant Patil, Advisor, DYPKC. I am

equally grateful for I express my thanks to Dr. S. S. Sonavane, Director – TC, Prof. A. P. Deshmukh, Dean Academics and Dr. S. M. Khairnar, Head, Dept. of Engineering Science, Dr. D. Y. Patil School of Engineering, Pune. I would like to extend my appreciation to Dr. Ravindra S. Dhivare, Assistant Professor, Sangola College, Sangola, Kadlas road, State Highway 71, Sangola, 413307, Maharashatra, India for valuable advice and discussion during research work. I express my sincere thanks to the Director, Central Instrumentation Facility, Savitribai Phule Pune University, Pune. I am grateful to Ms. Snehal Dhokale, Mr. Datta Ukale, Mr. Umesh Kasabe and Mr. Ritesh Walecha, Project Assistant of NMR and HRMS spectroscopy in Savitribai Phule Pune University, Maharashtra.

REFERENCES

1. Witte EC, Neubert P, Roesch A. (7-(Piperazinylpropoxy)-2H-1-benzopyran-2-ones). Ger Offen DE, 1986; 3427985; Chem Abstr, 1986; 104: 224915f.
2. Bonsignore L, Loy G, Secci, D, Calignano A. (Synthesis and pharmacological activity of 2-oxo-(2H) 1-benzopyran-3-carboxamide derivatives). Eur J Med Chem., 1993; 28(6): 517-520.
3. Foye WO, Thomas L. Foye's Principles of medicinal chemistry, 2007; 6: 754.
4. El-Agrody AM, Emam HA, El-Hakim MH, AbdEl-latif MS, Fakery AH, (Activated Nitriles in Heterocyclic Synthesis: Synthesis of Pyrano [2,3-d]pyrimidine and Pyrano [3,2-e][1,2,4] triazolo [1,5-c]pyrimidine Derivatives), J Chem Res (S), 1997; 320-321.
5. Adreani LL, Lapi E. (Aspects and Orientations of Modern Pharmacognosy). Boll Chim Farm, 1960; (99): 583-586; Chem Abstr, 1961; 55: 2668d.
6. Wang JL, Liu D, Zhang ZJ, Shan S, Han X, Srinivasula SM, Croce CM, Alnemri ES, Huang Z. (Structure-based discovery of an organic compound that binds Bel-2 protein and induces apoptosis of tumour cells). Proc Natl Acad Sci USA, 2000; 97(13): 7124.
7. Zhang YL, Chen BZ, Zheng KQ, Xu ML, Lei XH. (Chemotherapeutic Studies on Schistosomiasis XXV Derivatives of Substituted Coumarin-3-Carboxylic Esters and Amides). Chinese Acta Pharmaceutica Sinica, 1982; (1): 17; Chem Abstr, 1982; 96: 135383e.
8. Kamaljit S, Jasbi S, Harjit S. (A Synthetic Entry into Fused Pyran Derivatives through Carbon Transfer Reactions of 1, 3-Oxazinanes and Oxazolidines with Carbon Nucleophiles). Tetrahedron, 1996; 52(45): 14273-14280.
9. Zhou JF, Tu SJ, Gao Y, Qi M. (One pot synthesis of pyrans and pyrano[2,3-c]pyrazole derivatives under microwave irradiation). Chinese J Org Chem., 2001; 21(10): 742.

10. Shi DQ, Mou J, Zhuang QY, Niu, LH, Wu N, Wang XS. (Three-Component One-Pot Synthesis of 1,4- Dihydropyrano[2,3-c]pyrazole Derivatives in Aqueous Media). Synth Commun, 2004; 34(24): 4557-4563.
11. Jin TS, Zhao RQ, Li TS. (An One-Pot Three-Component Process for the Synthesis of 6-amino-4-aryl-5-cyano-3-methyl-1-phenyl-1, 4- dihydropyrano [2, 3-c] Pyrazoles in Aqueous Media). ARKIVOC, 2006; xi: 176-182.
12. Hatakeyama S, Ochi N, Numata H, Takano SJ. (A New Route to Substituted 3-Methoxycarbonyldihydropyrans; Enantioselective Synthesis of (-)-Methyl Elenolate). Chem Soc, Chem Commun, 1988; 1202.
13. Ciller JA, Martin N, Seoane C, Soto JJ. (Ring Transformation of Isoxazoles into Furan and Pyran Derivatives). Chem Soc, Perkin Trans 1, 1985; 202.
14. Armetso D, Horspool WM, Martin N, Ramos A, Seaone C. (Synthesis of Cyclobutenes by the Novel Photochemical Ring Contraction of 4-substituted 2-amino-3, 5-dicyano-6-phenyl-4H-pyrans). J Org Chem., 1989; 54(13): 3069-3072.
15. Pirrung MC, Tumey LN, Raetz CRH, Jackman JE, Snehalatha K. (Inhibition of the Antibacterial Target UDP-(3-O-acyl)-Nacetylglucosamine Deacetylase (LpxC): Isoxazoline Zinc Amidase Inhibitors Bearing Diverse Metal Binding Groups). J Med Chem., 2002; 45: 4359–4370.
16. Jadhav SY, Shirame SP, Kulkarni SD, Patil SB, Pasale SK, Bhosale RB. (PEG Mediated Synthesis and Pharmacological Evaluation of Some Fluoro Substituted Pyrazoline Derivatives as Antiinflammatory and Analgesic Agents). Bioorg Med Chem Lett., 2013; 23: 2575–2578.
17. Kalaria PN, Satasia SP, Raval DK. (L-Proline promoted green and regioselective synthesis of a novel pyrazole based trifluoromethylated fused thiazolopyran scaffold and its biological evaluation). RSC Adv., 2014; 4: 32353–32362.
18. Barbachyn MR, Cleek GJ, Dolak LA, Garmon SA, Morris J, Seest EP, Thomas RC, Toops DS, Watt W, Wishka DG, Ford CW, Zurenko GE, Hamel JC, Schaadt RD, Stapert D, Yagi BH, Adams WJ, Friis JM, Slatter JG, Sams JP, Oien NL, Zaya MJ, Wienkers LC, Wynalda MA. (Identification of Phenylisoxazolines as Novel and Viable Antibacterial Agents Active against Gram-Positive Pathogens). Med Chem., 2003; 46(2): 284–302.
19. Tantawy AS, Nasr MNA, El-Sayed MAA, Tawfik SS. (Synthesis And Antiviral Activity of New 3-methyl-1, 5-diphenyl-1H-pyrazole Derivatives). Med Chem Res., 2012; 21: 4139–4149.

20. Harigae R, Moriyama K, Togo H. (Preparation of 3, 5-disubstituted Pyrazoles and Isoxazoles from Terminal Alkynes, Aldehydes, Hydrazines and Hydroxylamine). J Org Chem., 2014; 79: 2049−2058.
21. Wei F, Zhao BX, Huang B, Zhang L, Sun CH, Dong WL, Shin DS, Miao JY. (Design, Synthesis and Preliminary Biological Evaluation of Novel ethyl 1-(2′-hydroxy-3′-aroxypropyl)-3-aryl-1H-pyrazole-5-carboxylate). Bioorg Med Chem Lett., 2006; 16(24): 6342–6347.
22. Kalaria PN, Satasia SP, Raval DK. (Synthesis, Identification and in vitro Biological Evaluation of Some Novel 5-Imidazopyrazole Incorporated Pyrazoline and Isoxazoline Derivatives). New J Chem., 2014; 38: 2902–2910.
23. Abbasi-Tarighat M, Shahbazi E, Niknam K. (Simultaneous Determination of Mn^{2+} and Fe^{3+} as 4, 4′[(4-cholorophenyl) methylene] bis (3-methyl-1-. phenyl-1 Hpyrazol-5-ol) Complexes in Some Foods, Vegetable and Water Samples by Artificial Neural Networks). Food Chem, 2013; 138: 991–997.
24. Bhavanarushi S, Kanakaiah V, Bharath G, Gangagnirao A, Rani JV. (Synthesis and Antibacterial Activity of 4, 4′-(aryl or alkyl methylene)-bis (1H-pyrazol-5-ol) Derivatives). Med Chem Res, 2014; 23: 158–167.
25. Chaudhari PP, Rajput SS. (Clean Synthesis and Antimicrobial Interpretation of Azo (Dipyrano) and Bis- Chalcones Derivatives from N-Phenyl Pyrrolidine-2, 5-Dione and N-Phenyl Piperidine-2, 6-Dione). Heterocyclic Letters, 2018; 8(1): 133–144.
26. Rajput AP, Rajput SS. (Synthesis and Microbial Screening of Seven Membered Heterocyclic Ring Compounds from 1, 2-diaminobenzene). International Journal of PharmTech Research, 2009; 1(3): 900-904.
27. Chaudhari PP, Rajput SS. (One Pot Synthesis and Antimicrobial Evaluation of Some Novel Chalcones and Pyrazoles from Cyclic Imides under Microwave Irradiation). World Journal of Pharmaceutical Research, 2016; 5(8): 1301-1313.
28. Rajput SS. (Synthesis and Characterization of Bis-Heteroyclic Derivatives of 1-(3-Chlorophenyl)-Pyrrolidine-2, 5-Dione), International Journal of Advances in Pharmacy, Biology and Chemistry, 2012; 1(2): 242-246.
29. Uramaru N, Shigematsu H, Toda A, Eyanagi R, Kitamura S, Ohta S. (Design, Synthesis and Pharmacological Activity of Non Allergenic Pyrazolone Type Antipyretic Analgesics). J Med Chem., 2010; 53: 8727–8733.

30. Dhivare RS, Rajput SS. (Microwave Supported Synthesis and Antimicrobial Evaluation of Bispyrazole Derivatives from N-Phenyl Glutarimides). International Letters of Chemistry, Physics and Astronomy, 2016; (65): 53-63.
31. Chaudhari PP, Rajput SS. (Synthesis, Characterization and Antimicrobial Evaluation of Novel Five and Six Membered cyclic Imide derivatives of 2-Amino 5-Methyl, 2-Amino 4-Methyl, 2-Amino 6-Methyl Pyridine). International Journal of Current Research, 2016; 8(11): 41647–41551.
32. Dhivare RS, Rajput SS. (Microwave Assisted Solvent Free Synthesis and Antifungal Evaluation of 3, 5-bis-(4-hydroxy-3-methoxybenzylidene)-Nphenylpiperidine-2, 6-dionederived from N-Phenyl Glutarimides). International Journal of Chem Tech Research, 2016; 9(3): 325-331.
33. Bailey DM, Hansen PE, Hlavac AG, Baizman ER, Pearl J, Defelice AF, Feigenson ME. (3,4-Diphenyl-1H-pyrazole-1-propanamine Antidepressants). J Med Chem, 1985; 28: 256–260.
34. Sujatha K, Shanthi G, Selvam NP, Manoharan S, Perumal PT, Rajendran M. (Synthesis and Antiviral Activity of 4,4'-(arylmethylene)bis(1H-pyrazol-5-ols) against Peste Des Petits Ruminant Virus (PPRV)). Bioorg Med Chem Lett, 2009; 19(15): 4501–4503.
35. Dhivare RS, Chaudhari PP, Rajput SS. (Synthesis of Pyridine and Phenyl Succinimides by Green Pathway and Their Antimicrobial Assay). American Journal of Heterocyclic Chemistry, 2018; 4(1): 26-29.
36. Lin Z, Zhang W, Wang L, Yu H, Wu C. (Mechanism of the Synergistic Toxicity of malononitrile and p -nitrobenzaldehyde with photobacterium phosphoreum). Toxicology mechanism and methods, 2003; 13(4): 241-245.
37. Dhivare RS, Rajput SS. (Malononitrile: A Versatile Active Methylene Group). International Letters of Chemistry, Physics and Astronomy, 2015; 57: 126-144.
38. Zou S, Meng X, Meng Y, Liu J, Liu B, Zhang S, Ding W, Wu J, Zhou J. (Microarray analysis of anti-cancer effects of docosahexaenoic acid on human colon cancer model in nude mice). Int J Clin Exp Med., 2015; 8: 5075–5084.
39. Sugiura S, Ohno S, Ohtani O, Izumi K, Kitamikado T, Asai H, Kato K, Hori M, Fujimura H. (Syntheses and Anti-inflammatory and Hypnotic Activity of 5- alkoxy-3-(N-substituted carbamoyl)-1-phenylpyrazoles). J Med Chem., 1977; 20: 80–85.
40. Chaudhari PP, Rajput SS. (Synthesis and Antimicrobial Evaluation of Some Novel Chalcones and Pyrazoles from Cyclic Imides under microwave irradiation). International Journal of Chemistry and Pharmaceutical Sciences, 2016; 4(6): 286–291.

41. Rajput AP, Girase PD. (Synthesis, Characterization and Microbial Screening of Pyrazoline Derivatives of 2, 6-Dichloro-1-(N-Substituted Phenyl)-1, 4-Dihydropyridine-3, 5-Dicarbaldehyde). International Journal of Pharmacy and Pharmaceutical Sciences, 2011; 3(4): 214-218.
42. Wisniewski MZ, Surga WJ, Opozda EM. (Palladium (II) methylpyrazole Complexes Transition). Transit Met Chem, 1994; 19: 353–354.
43. Modi CK, Jani DH. (Mn(III) Mixed-Ligand Complexes with Bis-Pyrazolones and Ciprofloxacin Drug: Synthesis, Characterization and Antibacterial Activities). Appl Organometal Chem., 2011; (25): 429–436.
44. Kessler P, Aybek T, Neidhart G, Dogan S, Bremerich DH, Lischke V, Byhahan C. (Comparison of Three Anesthetic Techniques for Off-Pump Coronary Artery Bypass Grafting: General Anesthesia, Combined General and High Thoracic Epidural Anesthesia or High Thoracic Epidural Anesthesia Alone). J Cardiothorac Vasc Anesth, 2005; (19): 32−39.
45. Nakagawa H, Ohyama R, Kimata A, Suzuki T, Miyata N. (Hydroxyl Radical Scavenging by Edaravone Derivatives: Efficient Scavenging by 3-methyl-1-(pyridin-2-yl)-5-pyrazolone with an Intramolecular Base). Bioorg Med Chem Lett 2006; 16(23): 5939−5942.
46. Asieh V, Abolghasem D, Mehdi P, Bozorgmehr MR. (An Efficient and High-Yielding One-Pot Synthesis of 1H-pyrazolo [1,2-b]phthalazine-5,10-Diones Catalyzed by Sodium Hydrogen Carbonate under Solvent-Free Conditions). Res Chem Intermed., 2015; 31(4): 2153-2158.
47. Phatangare KR, Padalkar VS, Gupta VD, Patil VS, Umape PG, Sekar N. (Phosphomolybdic Acid: An Efficient and Recyclable Solid Acid Catalyst for the Synthesis of 4,4′-(Arylmethylene)bis(1H-pyrazol-5-ols)). Synth Commun, 2012; 42(9): 1349–1358.
48. Soleimani E, Ghorbani S, Taran M, Sarvary ACR. (Synthesis of 4,4′-(arylmethylene)bis(3-methyl-1H-pyrazol-5-ol) Derivatives in Water). Chim., 2012; 15(11-12): 955–961.
49. Shirini F, Seddighi M, Mazloumi M, Makhsous M, Abedini M. (One-pot Synthesis of 4,4 -(arylmethylene)-bis-(3-methyl-1-phenyl-1H-pyrazol-5-ols) Catalyzed by Bronsted Acidic Ionic Liquid Supported on Nanoporous Na^+-montmorillonite). J Mol Liq, 2015; 208: 291–297.

50. Khan KM, Muhammad MT, Khan I, Perveen S, Voelter W. (Rapid Cesium Fluoride-Catalyzed Knoevenagel Condensation for the Synthesis of Highly Functionalized 4, 4'-(arylmethylene) bis (1H-pyrazol-5-ol) Derivatives). Monatshefte Chem-Chem, 2015; 146: 1587–1590.
51. Sobhani S, Hasaninejad A, Maleki MF, Parizi ZP. (Knoevenagel–Michael Reaction of 1-Phenyl-3 methyl-5-pyrazo-lone with Aldehydes using 3-Aminopropylated Silica Gel as an Efficient and Reusable Heterogeneous Catalyst). Synth Commun, 2012; (42): 2245–2255.
52. Karimi-Jaberi Z, Pooladian B, Moradi M, Ghasemi E. (1,3,5-tris(hydrogensulfato) Benzene: A New and Efficient Catalyst for Synthesis of 4,4′-(arylmethylene)bis(1H-pyrazol-5-ol) Derivatives). Chin J Catal, 2012; 33(11-12): 1945–1949.
53. Wang W, Wang SX, Qin XY, Li JT. (Reaction of Aldehydes and Pyrazolones in the Presence of Sodium Dodecyl Sulfate in Aqueous Media). Synth Commun, 2005; 35(9): 1263–1269.
54. Safaei-Ghom J, Khojastehbakht-Koopaei B, Shahbazi-Alavi H. (Pseudo Five Component Process for the Synthesis of 4,4'-(arylmethylene)bis(3-methyl-1H-pyrazol-5-ol) Derivatives using $ZnAl_2O_4$ nanoparticles in aqueous media). RSC Adv., 2014; 4: 46106–46113.
55. Niknam K, Saberi D, Sadegheyan M, Deris A. (Silica-bonded S-sulfonic Acid: An Efficient And Recyclable Solid Acid Catalyst for the Synthesis of 4,4′-(arylmethylene)bis(1H-pyrazol-5-ols)). Tetrahedron Lett., 2010; 51(4): 692−694.
56. Gouda MA, Abu-Hashem AA. (An Eco-Friendly Procedure for the Efficient Synthesis of arylidinemalononitriles and 4,4′-(arylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ols) in Aqueous Media). Green Chem Lett Rev., 2012; 5(2): 203–209.
57. Sobhani S, Safaei E, Hasaninejad AR, Rezazadeh SJ. (An Eco-Friendly Procedure for the Efficient Synthesis of bis(indolyl)methanes in Aqueous Media). Organomet Chem., 2009; 694(18): 3027–3031.