Heterocyclic Letters
Vol. 8| No.3|619-629|May-July|2018
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

MICROWAVE ASSISTED NEAT SYNTHESIS OF 1,2,3-TRIAZOLES BEARING PYRAZOLE MOIETY

Manju N[1], Balakrishna Kalluraya[1*], Asma[1] and Madan S Kumar[2]

[1]Department ofStudies in Chemistry, Mangalore University, Mangalagangothri-574199, Karnataka, India.
[2]PURSE Lab, Mangalore University, Mangalagangothri-574 199, Karnataka, India
Email: bkalluraya@gmail.com
Contact No.: 9448824075

ABSTRACT
A novel series of tri- heterocyclic compounds were synthesized by the condensation of chalcones carrying triazole and pyrazole moiety with hydrazine hydrate in presence of aliphatic acids using microwave irradiation method. The newly synthesized compounds were characterized by spectral, analytical and X-ray crystallographic study. The new hybrids were evaluated for their antioxidant activity. Some of the synthesized compounds showed moderateantioxidant activity.

KEYWORDS
1,3-Dipolar reaction, Pyrazole-triazole-pyrazoline hybrid, Antioxidant activity.

INTRODUCTION
Nitrogen-containing heterocycles are attracting the synthetic chemists because of the wide variety of biological properties associated with them such as antibacterial [I], analgesic [II], anticancer [III], anti-inflammatory [IV], anti-depressant [V], antioxidant [VI] etc. The Cu (I) catalyzed approach for the synthesis of 1,2,3-triazole by the reaction between azides and terminal alkynes is known as "click chemistry" which is very popular in the synthesis of 1,2,3-triazoles due to its reliability and regioselectivity. The 1,2,3- triazole core is highly stable towards acidic and basic hydrolysis as well as oxidative and reductive condition reflecting the stability of the ring. Due to its high dipole moment [VII] about 5D it is actively involved in hydrogen bonding as well as dipole interaction [VIII]. Review of literature indicated that heterocycles carrying a variety of bioactive moieties in one frame work further enhance the biological activity compared to single heterocycle[IX, X, XI]. Microwave-assisted synthesis receives several advantages over the conventional method by reducing the time [XII, XIII], eco-friendly and minimized byproducts with good yield compared to the conventional method. So here we report the synthesis of a novel series of pyrazoline hybrid carrying triazole-pyrazole moiety through microwave irradiation technique. Further, the newly synthesized compounds were screened for their antioxidant activities.

EXPERIMENTAL

MATERIALS AND METHOD

All the reagents and solvents were purchased from Sigma-Aldrich or Hi-Media and used after distillation/ recrystallization. ^{1}H NMR spectra were recorded on a 400MHz Bruker Avance II NMR spectrometer and all the chemical shift values were reported as δ (ppm), downfield from TMS and proton signals are indicated as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Coupling constant (J) values were expressed in Hertz (Hz). Mass spectra were recorded on LCMS (SHIMADZU LCMS-8030) operating at 70eV. The X-ray diffraction measurements were carried out in Rigaku Saturn724+ diffractometer.The microwave-assisted synthesis was carried out using catalyst system Microwave oven CATA R. Melting points of synthesized compounds were taken in open capillary method in Innovative DTC-967A digital melting point apparatus and are uncorrected. FT-IR spectra were recorded by dispersing the compounds in potassium bromide pellets on a Shimadzu FT-IR 157 spectrophotometer. The purity of the compounds was checked on silica gel plates (Merck) and visualized under an ultraviolet lamp using ethylacetate: hexane (3:7) as mobile phase.

General procedure for the synthesis of 1-(4-azidophenyl)-3-(3-methyl-5-aryloxy-1-phenyl-1*H*-pyrazol-4-yl)prop-2-en-1-one (3 a-c).

To a mixture of 3-methyl-5-phenoxy-1-phenyl-1H-pyrazole-4-carbaldehyde (**1 a-c**) (0.5 mmol) and p-azidoacetophenone (**2**) (0.5 mmol) in 25 mL of ethanol, potasium hydroxide(0.5g, 10 mmol) in 5 mL ethanol was added drop wise under ice bath, and the mixture was stirred for 4 hours. After the completion of the reaction (monitored by TLC), the solid product separated was filtered, washed with water, dried and recrystallized from ethanol: dimethylformamide mixture.

1-(4-Azidophenyl)-3-(3-methyl-1-phenyl-5-(p-tolyloxy)-1H-pyrazol-4-yl)prop-2-en-1-one(**3a**):(m.p=192^{o}C). CHN Analysis: C= 71.71 (71.68), H=4.86 (4.82), N= 16.08 (16.10)

1-(4-azidophenyl)-3-(5-(2,4-dichlorophenoxy)-3-methyl-1-phenyl-1H-pyrazol-4-yl)prop-2-en-1-one (**3b**): (m.p=234^{o}C).CHN Analysis: C= 61.24 (61.22), H=3.49 (3.52), N= 14.28 (14.30)

1-(4-azidophenyl)-3-(3-methyl-5-(naphthalen-2-yloxy)-1-phenyl-1H-pyrazol-4-yl)prop-2-en-1-one (**3c**): (m.p=265^{O}C).CHN Analysis: C= 73.87 (73.88), H=4.49 (4.52), N= 14.85 (14.86)

General procedure for the synthesis of 3-(3-methyl-5-aryloxy-1-phenyl-1*H*-pyrazol-4-yl)-1-(4-(4-phenyl-1*H*-1,2,3-triazol-1-yl)phenyl)prop-2-en-1-one (5 a-c).

Phenyl acetylene (0.5 mmol) (**4)** was dissolved in a mixture of 20 mL of t-butanol: water (1:1) at room temperature. Copper sulphate pentahydrate (0.5 mmol) was added, the reaction mixture turns light blue in colour. The contents were stirred for 10 minutes. Then sodium ascorbate (1 mmol) was added at once to the reaction mixture and stirred for another 20 minutes. The colour of the reaction mixture changed to dark yellow. 1-(4-Azidophenyl)-3-(3-methyl-5-aryloxy-1-phenyl-1*H*-pyrazol-4-yl) prop-2-en-1-one (0.5 mmol) (**3 a-c)** were then added, and further stirred at room temperature for 4 hours. After the completion of the reaction (monitored by TLC), the reaction mixture was quenched in water and extracted with dichloromethane. Combined organic layers were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain the compound **(5 a-c).**

3-(3-Methyl-1-phenyl-5-(p-tolyloxy)-1*H*-pyrazol-4-yl)-1-(4-(4-phenyl-1*H*-1,2,3-triazol-1-yl)phenyl)prop-2-en-1-one (5a)

Yellow crystals (64%), m.p:178-180 ^{o}C**:** ^{1}H NMR: 400 MHz, $CDCl_3$: δ: 2.2 (s, 3H, p-cresyl –CH_3), 2.4(s, 3H, Pyrazole –CH_3), 6.65 (d, J=7.56 Hz, 1H), 6.96 (d, J=15.76 Hz, 1H), 7.0 (m, 2H), 7.3 (m, 2H), 7.39 (m, 3H), 7.49 (t, J=7.32 Hz & J=15.04 Hz, 2H), 7.7 (d, J=7.7 Hz,

2H), 7.8 (d, J=8.68 Hz, 2H), 7.9 (d, J=7.24 Hz, 2H), 8.2 (s, 1H, triazole):LC-MS: m/z: 538 (M^++1), (M.F. $C_{34}H_{27}N_5O_2$).

3-(3-Methyl-1-phenyl-5-(2,4-dichlorophenoxy)-1*H*-pyrazol-4-yl)-1-(4-(4-phenyl-1*H* 1,2,3-triazol-1-yl)phenyl)prop-2-en-1-one (5b)

Brown flaks (72%), m.p: 216-217 ^oC:^1H NMR: 400 MHz, $CDCl_3$: δ: 2.1 (s, 3H, pyrazole –CH_3), 7.07-7.1 (m, 1H), 7.23 (t, J=7.4 Hz & J=14.76 Hz, 1H), 7.32-7.39 (m. 6H), 7.47-7.50 (m, 5H),7.76 (d, J=8.68 Hz, 2H), 7.96 (d, J=7.2 Hz, 2H), 8.02 (d, J=8.62 Hz, 2H), 9.27 (s, 1H, triazole): LC-MS: m/z: 593/595/597 (M^++1), (M^++3) (M^++5). (M.F. $C_{33}H_{23}Cl_2N_5O_2$).

3-(3-Methyl-1-phenyl-5-(naphthalen-2-yloxy)-1*H*-pyrazol-4-yl)-1-(4-(4-phenyl-1*H*-1,2,3-triazol-1-yl)phenyl)prop-2-en-1-one (5c)

Yellow amorphous solid (79%), m.p: 194-196 ^oC: ^1H NMR: 400 MHz, $CDCl_3$: δ: 1.98 (s, 3H, pyrazole –CH_3), 6.9 (m, 2H), 7.2 (t, J=19.2 Hz & J=14.4 Hz, 1H), 7.3-7.43(m, 5H), 7.51-7.57 (m, 5H), 7.6 (t, J=8.8 Hz & J= 17.6 Hz, 3H), 7.75-7.78 (m, 3H), 7.9 (d, J=8.4 Hz, 2H), 7.9 (d, J= 7.2 Hz, 2H), 9.3 (s, 1H, triazole): LC-MS: m/z: 574.2 (M^++1), (M.F. $C_{37}H_{27}N_5O_2$).

General procedure for the synthesis of 1-(5-(3-methyl-5-aryloxy-1-phenyl-1*H*-pyrazol-4-yl)-3-(4-(4-phenyl-1*H*-1, 2, 3-triazol-1-yl) phenyl)-4, 5-dihydropyrazol-1-yl) ethanone/propanone/carbaldehydes (6a-i)

3-(3-methyl-5-aryloxy-1-phenyl-1*H*-pyrazol-4-yl)-1-(4-(4-phenyl-1*H*-1,2,3-triazol-1-yl)phenyl)prop-2-en-1-one(**5 a-c)** (0.5 mmol) was treated with hydrazine hydrate (1 mmol) in the presence of aliphatic acids such as formic /acetic /propionic acid and subjected to microwave irradiation at 400 watts. After completion of the reaction (as monitored by TLC) the product was quenched with excess of crushed ice. The solid separated was collected by filtration, washed with water and recrystallized from ethanol + DMF mixture to give compound (**6a-i).**

1-(5-(3-Methyl-1-phenyl-5-(p-tolyloxy)-1*H*-pyrazol-4-yl)-3-(4-(4-phenyl-1*H*-1,2,3-triazol-1-yl)phenyl)-4,5-dihydropyrazol-1-yl)ethanone (6a)

IR (KBr) γ/cm^{-1}**:**1710 (C=O), 1587 (C=N),2920 (C-H),1255(C-O-C), 2920 (Ar-H),1500(C=C); ^1H NMR: 400 MHz, $CDCl_3$: δ: 2.05 (s, 3H, p-cresyl –CH_3), 2.2 (s, 3H, Pyrazole –CH_3), 2.3 (s, 3H, CO-CH_3), 3.46 (dd, J_{AX}= 5.2 Hz, J_{AB}=17.4 Hz, 1H, pyrazoline–CH_2), 3.78 (dd, J_{BX}= 12.32 Hz, J_{BA}=17.6 Hz, 1H, pyrazoline –CH_2), 5.2 (dd, J_{XA}= 4.8 Hz, J_{XB}=12.28 Hz, 1H, pyrazoline –CH), 7.05-7.9 (m, 18H Ar-H), 8.9(s, 1H, triazole);^{13}C NMR (100 MHz, DMSO, δ, ppm): 12.3, 23.6, 24.4, 42.2, 51.12, 120.2-151.8 (aromatic carbons), 168.3 (carbonyl carbon); LC-MS: m/z: 594.3 (M^++1), (M.F. $C_{36}H_{31}N_7O_2$).

1-(5-(3-Methyl-1-phenyl-5-(p-tolyloxy)-1*H*-pyrazol-4-yl)-3-(4-(4-phenyl-1*H*-1,2,3-triazol-1-yl)phenyl)-4,5-dihydropyrazol-1-yl)propan-1-one (6b)

IR (KBr) γ/cm^{-1}**:** 1696 (C=O), 1408 (C=N),2870 (C-H),1550 (C-O-C), 2844 (Ar-H),1664(C=C); ^1H NMR: 400 MHz, $CDCl_3$: δ: 1.1 (t, 3H, CH_2-$\underline{CH_3}$), 2.2 (q, 2H, $\underline{CH_2}$-CH_3), 2.21 (s, 3H, p-cresyl –CH_3), 2.28 (s, 3H, pyrazole -CH_3), 3.48 (dd, J_{AX}= 5.4 Hz, J_{AB} =17.4 Hz, 1H, pyrazoline -CH_2), 3.74 (dd, J_{BX} = 12.32 Hz, J_{BA}= 17.5 Hz, 1H, pyrazoline -CH_2), 5.4 (dd, J_{XA}= 5.32 Hz, J_{XB}= 12.24 Hz 1H, pyrazoline -CH), 7.05-7.9 (m, 18H, Ar-H), 8.9 (s, 1H, triazole);^{13}C NMR (100 MHz, DMSO, δ, ppm): 12.4, 21.3, 24.3, 29.8, 40.2, 51.2, 122.3-154.6 (aromatic carbons), 171.2 (carbonyl carbon);LC-MS: m/z: 608 (M^++1), (M.F. $C_{37}H_{33}N_7O_2$).

5-(3-Methyl-1-phenyl-5-(p-tolyloxy)-1*H*-pyrazol-4-yl)-3-(4-(4-phenyl-1*H*-1,2,3-triazol-1-yl)phenyl)-4,5-dihydropyrazole-1-carbaldehyde (6c)

IR (KBr) γ/cm^{-1}**:** 1702 (C=O), 1486 (C=N),2940 (C-H),1580 (C-O-C), 2884 (Ar-H),1540(C=C); ^1H NMR: 400 MHz, $CDCl_3$: δ: 2.1 (s, 3H, p-cresyl-CH_3), 2.32 (s, 3H, Pyrazole –CH_3) 3.5 (dd, J_{AX}= 5.2 Hz, J_{AB}=17.5 Hz, 1H, pyrazoline –CH_2), 3.8 (dd , J_{BX}= 12.2 Hz, J_{BA}=17.56 Hz, 1H, pyrazoline –CH_2), 5.2 (dd, J_{XA}=5.18 Hz, J_{XB}=12.32 Hz, 1H,

pyrazoline –CH), 7.1-7.9 (m, 18H Ar-H), 8.9 (s, 1H, carbaldehyde), 9.2 (s, 1H, triazole);^{13}C NMR (100 MHz, DMSO, δ, ppm): 14.4, 19.8, 42.2, 49.8, 121.3-152.6 (aromatic carbons), 166.2 (carbonyl carbon);LC-MS: m/z: 580 (M^++1), (M.F. $C_{35}H_{29}N_7O_2$).

1-(5-(5-(2,4-Dichlorophenoxy)-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-3-(4-(4-phenyl-1*H*-1,2,3-triazol-1-yl)phenyl)-4,5-dihydropyrazol-1-yl)ethanone (6d)

IR (KBr) γ/cm^{-1}: 1680 (C=O), 1528 (C=N),2876 (C-H),1540 (C-O-C), 2842 (Ar-H),1540(C=C); ^{1}H NMR: 400 MHz, $CDCl_3$: δ: 2.1 (s, 3H, Pyrazole –CH_3), 2.3 (s, 3H, CO-CH_3), 3.3 (dd, J_{AX}= 5.4 Hz, J_{AB}=17.88 Hz, 1H, pyrazoline–CH_2), δ , 3.82 (dd, J_{BX}= 12.4 Hz , J_{BA}=17.84 Hz, 1H, pyrazoline –CH_2), 5.28 (dd, J_{XA}= 5.34 Hz, J_{XB}=12.36 Hz, 1H, pyrazoline –CH), 6.5-8.03 (m, 17H Ar-H), 9.3 (s, 1H, triazole); ^{13}C NMR (100 MHz, DMSO, δ, ppm): 12.68, 18.20, 40.11, 52.38, 110.0-149.9 (aromatic carbons), 168.4 (carbonyl carbon);LC-MS: m/z: 649/651.2/653 (M^++1), (M^++3), (M^++5), (M.F. $C_{35}H_{27}Cl_2N_7O_2$).

1-(5-(5-(2,4-Dichlorophenoxy)-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-3-(4-(4-phenyl-1*H*-1,2,3-triazol-1-yl)phenyl)-4,5-dihydropyrazol-1-yl) propan-1-one (6e)

IR (KBr) γ/cm^{-1}**:** 1662 (C=O), 1544 (C=N),2948 (C-H),1470 (C-O-C), 2846 (Ar-H),1450(C=C),^{1}H NMR: 400 MHz, $CDCl_3$: δ: 1.1 (t, 3H, CH_2-$\underline{CH_3}$), 2.28 (q, 2H, $\underline{CH_2}$-CH_3), 2.31 (s, 3H, pyrazole -CH_3) 3.4 (dd, J_{AX}= 4.84 Hz, J_{AB}=17.82 Hz, 1H, pyrazoline -CH_2), 3.88 (dd, J_{BX}= 12.32 Hz, J_{BA}=17.80 Hz, 1H, pyrazoline -CH_2), 5.46 (dd, J_{XA}= 4.92 Hz, J_{XB}=12.38 Hz, 1H, pyrazoline -CH), 6.5-8.02 (m, 17H Ar-H), 8.9 (s, 1H, triazole); ^{13}C NMR (100 MHz, DMSO, δ, ppm): 14.1, 18.8, 24.8, 44.11, 55.20. 112.0-149.60 (aromatic carbons), 171.2 (carbonyl carbon);LC-MS: m/z: 664.5/656.2/658 (M^++1), (M^++3), (M^++5), (M.F. $C_{36}H_{29}Cl_2N_7O_2$).

5-(5-(2,4-Dichlorophenoxy)-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-3-(4-(4-phenyl-1*H*-1,2,3-triazol-1-yl)phenyl)-4,5-dihydropyrazole-1-carbaldehyde (6f)

IR (KBr) γ/cm^{-1}**:** 1670 (C=O), 1528 (C=N),3042 (C-H),1454 (C-O-C), 2872 (Ar-H),1356 (C=C); ^{1}H NMR: 400 MHz, $CDCl_3$: δ: 2.26 (s, 3H, Pyrazole –CH_3) 3.3 (dd, J_{AX}= 5.4 Hz, J_{AB}=17.8 Hz, 1H, pyrazoline –CH_2), 3.76 (dd , J_{BX}= 12.3 Hz, J_{BA}=17.74 Hz, 1H, pyrazoline –CH_2), 5.24 (dd, J_{XA}=5.3 Hz, J_{XB}=12.32 Hz, 1H, pyrazoline –CH), 6.7-7.8 (m, 17H Ar-H), 9.1 (s, 1H, carbaldehyde), 9.3 (s, 1H, triazole); ^{13}C NMR (100 MHz, DMSO, δ, ppm): 12.7, 42.11, 53.20. 112.0-149.60 (aromatic carbons), 167.4 (carbonyl carbon); LC-MS: m/z: 637.2/639/641 (M^++1), (M^++3), (M^++5), (M.F. $C_{34}H_{25}Cl_2N_7O_2$).

1-(5-(3-Methyl-5-(naphthalen-2-yloxy)-1-phenyl-1*H*-pyrazol-4-yl)-3-(4-(4-phenyl-1*H*-1,2,3-triazol-1-yl)phenyl)-4,5-dihydropyrazol-1-yl) ethanone (6g)

IR (KBr) γ/cm^{-1}**:** 1665 (C=O) , 1568 (C=N),2968 (C-H),1440 (C-O-C), 2849 (Ar-H),1470 (C=C); ^{1}H NMR: 400 MHz, $CDCl_3$: δ: 1.8 (s, 3H, pyrazole –CH_3), 2.3 (s, 3H, CO–CH_3), 3.4 (dd, J_{AX}= 5.1 Hz, J_{AB}=17.4 Hz, 1H, pyrazoline–CH_2), 3.7 (dd, J_{BX}= 12.8 Hz , J_{BA}=17.5, Hz, 1H, pyrazoline –CH_2), 5.47 (dd, J_{XA}= 5.2 Hz, J_{XB} 12.7 Hz, 1H, pyrazoline –CH), 6.9-7.9 (m, 21H Ar-H), 9.3 (s, 1H, triazole);^{13}C NMR (100 MHz, DMSO, δ, ppm): 14.2, 29.8, 42.11, 54.20. 112.0-149.60 (aromatic carbons), 167.4 (carbonyl carbon); LC-MS: m/z: 630.30 (M^++1), (M.F. $C_{39}H_{31}N_7O_2$).

1-(5-(3-Methyl-5-(naphthalen-2-yloxy)-1-phenyl-1*H*-pyrazol-4-yl)-3-(4-(4-phenyl-1*H*-1,2,3-triazol-1-yl)phenyl)-4,5-dihydropyrazol-1-yl)propan-1-one (6h)

IR (KBr) γ/cm^{-1}**:** 1672 (C=O), 1520 (C=N),2940 (C-H),1480(C-O-C), 2890 (Ar-H),1510(C=C); ^{1}H NMR: 400 MHz, $CDCl_3$: δ: 1.0 (t, 3H, CH_2–$\underline{CH_3}$), 2.2 (s, 3H, pyrazole -CH_3), 2.3 (q, 2H, $\underline{CH_2}$–CH_3), 3.8 (dd, J_{AX}= 4.9, Hz, J_{AB}=17.6 Hz, 1H, pyrazoline -CH_2), 4.1 (dd, J_{BX}= 12.2 Hz, J_{BA}=17.6 Hz, 1H, pyrazoline -CH_2), 5.44 (dd, J_{XA}=5.1 Hz, J_{XB}=12.3 Hz, 1H, pyrazoline -CH), 6.8-7.9 (m, 21H Ar-H), 9.1 (s, 1H, triazole); ^{13}C NMR (100 MHz, DMSO, δ, ppm): 14.2, 18.6, 29.8, 41.20, 52.20. 112.0-149.60 (aromatic carbons), 167.4 (carbonyl carbon); LC-MS: m/z: 645 (M^++1), (M.F. $C_{40}H_{33}N_7O_2$).

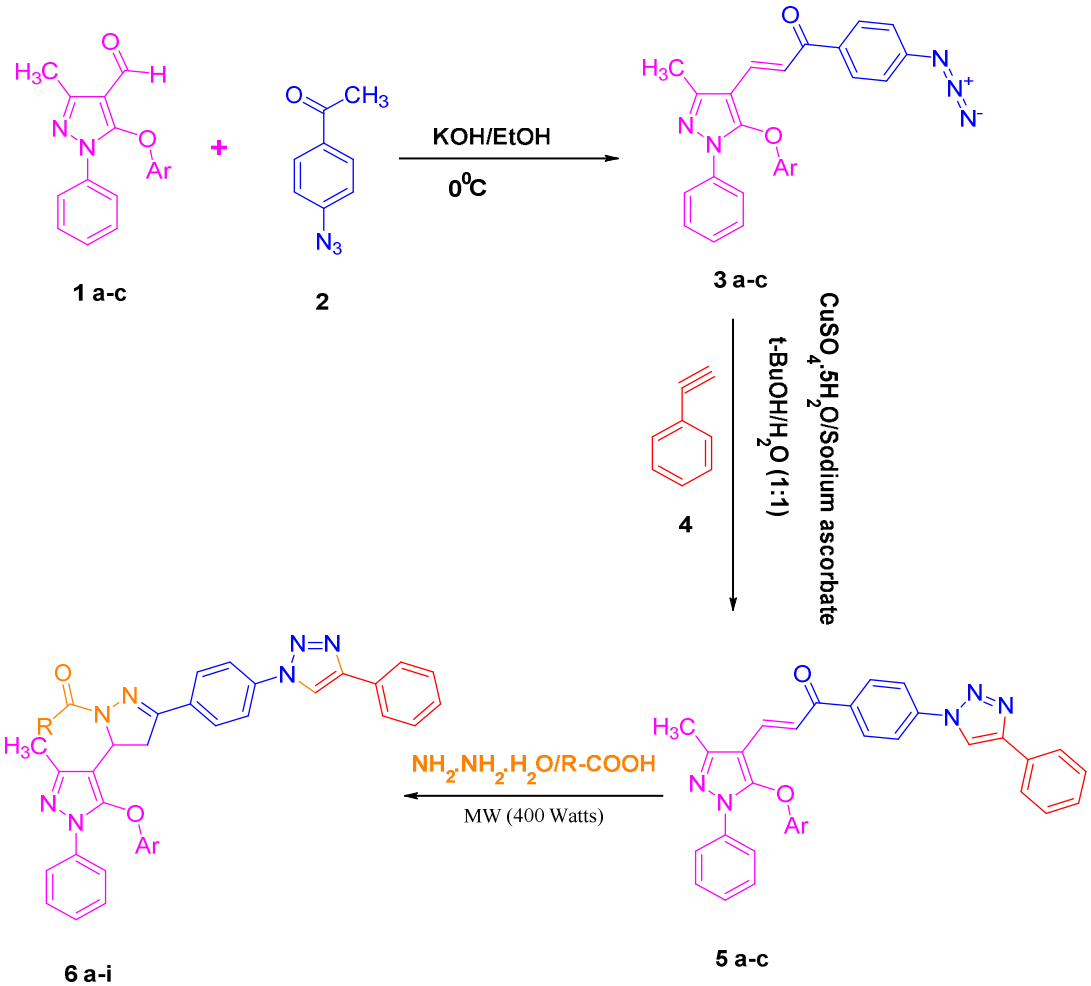
5-(3-Methyl-5-(naphthalen-2-yloxy)-1-phenyl-1*H*-pyrazol-4-yl)-3-(4-(4-phenyl-1*H*-1,2,3-triazol-1-yl)phenyl)-4,5-dihydropyrazole-1-carbaldehyde (6i)

IR (KBr) γ/cm^{-1}**:** 1678 (C=O), 1546 (C=N),2946 (C-H),1448 (C-O-C), 2980 (Ar-H),1556 (C=C); ^{1}H NMR: 400 MHz, $CDCl_3$: δ: 2.1 (s, 3H, Pyrazole –CH_3) 3.4 (dd, J_{AX}= 5.2 Hz, J_{AB}=18 Hz, 1H, pyrazoline –CH_2), 3.78 (dd , J_{BX}= 12 Hz, J_{BA}=18.2 Hz, 1H, pyrazoline –CH_2), 5.3 (dd, J_{XA}=5.2 Hz, J_{XB}=12.2 Hz, 1H, pyrazoline –CH), 6.8-7.9 (m, 21H Ar-H), 8.9 (s, 1H, carbaldehyde), 9.2 (s, 1H, triazole); ^{13}C NMR (100 MHz, DMSO, δ, ppm): 12.7, 42.11, 53.4. 112.0-149.60 (aromatic carbons), 167.4 (carbonyl carbon); LC-MS: m/z: 616.2 (M^++1), (M.F. $C_{38}H_{29}N_7O_2$).

RESULTS AND DISCUSSION

3-Methyl-5-aryloxy-1-phenyl-1H-pyrazole-4-carbaldehyde (**1 a-c)** was synthesized according to literature procedure[XIV]. It was further reacted with para-azido acetophenone **2** in a base catalysed Claised-Schimidt condensation reaction to give 1-(4-azidophenyl)-3-(3-methyl-5-aryloxy-1-phenyl-1*H*-pyrazol-4-yl) prop-2-en-1-one (**3a-c)**.

The reaction of compound (**3a-c)** with phenyl acetylene**4** under click chemistry condition afforded 3-(3-methyl-5-aryloxy-1-phenyl-1*H*-pyrazol-4-yl)-1-(4-(4-phenyl-1*H*-1, 2,3-triazol-1-yl)phenyl)prop-2-en-1-one (**5 a-c)**. Further reaction of chalcone **5 a-c** with hydrazine hydrate in the presence of aliphatic acids under microwave irradiation resulted in the formation of 1-(5-(3-methyl-5-aryloxy-1-phenyl-1*H*-pyrazol-4-yl)-3-(4-(4-phenyl-1*H*-1, 2, 3-triazol-1-yl) phenyl)-4, 5-dihydropyrazol-1-yl) ethanone/propanone/carbaldehyde (**6 a-i)** in good yield (**Scheme 1**). The structures of newly synthesized tri-heterocyclic derivatives were confirmed by recording their ^{1}H NMR, Mass, FT-IR spectra and Single crystal X-ray diffraction method. Characterization data of these compounds are given in **Table 1**. In the IR spectrum of compounds (**6a-i),** the carbonyl stretching band was observed around 1690-1715 cm^{-1}, while the C=N stretching band was seen around 1588-1618 cm^{-1}. The absorption band at 1390-1570 cm^{-1} corresponds to the ether linkage, while the aromatic C-H stretching band was observed at 2945-3058 cm^{-1}. In the ^{1}H-NMR spectra of compounds (**6a-i**) the stereogenic carbon (C-H) proton appeared as doublet of a doublet at δ 5.2-5.47, while the pro-chiral methylene protons appeared as two distinct doublet of a doublet at δ 3.3-4.2 indicating that these protons are magnetically non-equivalent. The acetyl (O=C-CH_3) protons appeared as a singlet at δ 2.3. In case of propyl derivative CH_3-CH_2 protons appeared as triplet and quartet in the range between δ 1.0 and 2.3. The carbaldehyde (O=C-H) proton appeared as a singlet at δ 8.9-9.1. Triazole ring proton resonated at higher value as a singlet at δ 9.3. In ^{13}C-NMR the peak at δ 40.2-44.11 are assigned to the methylene carbon and peak at δ 49.8-55.20 for chiral centered carbon. The mass spectrum of compounds **6** provided further evidence for the formation of tricyclic compounds. All the synthesized compounds showed M^+ + 1 peak thereby indicating the stability of the compounds.



Ar = p-cresyl, 2,4-dichlorophenyl, β-napthyl, R= H, CH_3, CH_2-CH_3

Table 1: Characterization data of 1-(5-(3-methyl-5-aryloxy-1-phenyl-1*H*-pyrazol-4-yl)-3-(4-(4-phenyl-1H-1, 2, 3-triazol-1-yl) phenyl)-4, 5-dihydropyrazol-1-yl) ethanone/ propanone/ carbaldehyde (**6 a-i**)

Com No.	Ar	R	m.p.°C Yield % and (Reaction time in min)	Molecular Formula (Mol. Wt)	% Analysis Found (Calculated)		
					C	H	N

Scheme 1: Synthetic route for the synthesis of tri-heterocyclic compounds (**6a-i)**

6a	p-cresyl	CH_3	212-214 65 (6)	$C_{36}H_{31}N_7O_2$ (593)	72.83 (72.78)	5.26 (5.24)	16.52 (16.52)
6b	p-cresyl	CH_2- CH_3	234-235 76 (9)	$C_{37}H_{33}N_7O_2$ (607)	73.13 (73.11)	5.47 (5.44)	16.13 (16.10)
6c	p-cresyl	H	190-194 68 (8)	$C_{35}H_{29}N_7O_2$ (579)	72.52 (72.50)	5.04 (5.02)	16.91 (16.88)
6d	2,4-di chloro phenyl	CH_3	265-266 81 (6.5)	$C_{35}H_{27}Cl_2N_7O_2$ (649)	64.82 (64.80)	4.20 (4.18)	15.12 (15.10)
6e	2,4-di chloro phenyl	CH_2- CH_3	226-228 74 (7)	$C_{36}H_{29}Cl_2N_7O_2$ (663)	65.26 (65.25)	4.41 (4.41)	14.80 (14.80)
6f	2,4-di chloro phenyl	H	246-248 72 (5)	$C_{36}H_{29}Cl_2N_7O_2$ (636)	64.36 (64.34)	3.97 (3.95)	15.45 (15.40)
6g	β-napthyl	CH_3	220-222 89 (8.5)	$C_{39}H_{31}N_7O_2$ (629)	74.39 (74.34)	4.96 (4.94)	15.57 (15.51)
6h	β-napthyl	CH_2- CH_3	204-205 76 (5)	$C_{40}H_{33}N_7O_2$ (645)	74.63 (74.61)	5.17 (5.12)	15.23 (15.20)
6i	β-napthyl	H	240-243 69 (7)	$C_{38}H_{29}N_7O_2$ (615)	74.13 (74.10)	4.75 (4.72)	15.92 (15.88)

SINGLE CRYSTAL X-RAY DIFFRACTION

The X-ray intensity data for compound **6e** is collected at temperature of 296 K on a Rigaku Saturn724 diffractometer using graphite monochromated Mo-Ka radiation.A complete data set was processed using Crystal Clear [XV]. The structure was solved by direct methods and refined by full-matrix least squares method on F^2 using SHELXS and SHELXL programs[XVI].All the non-hydrogen atoms were revealed in the first difference Fourier map itself.All the hydrogen atoms were positioned geometrically (C–H = 0.93Å) and refined using a riding model. After ten cycles of refinement, the final difference Fourier map showed peaks of no chemical significance. The ORTEP and packing diagrams were generated using the software MERCURY. The details of the crystal structure and data refinement are given in **Table 2.**

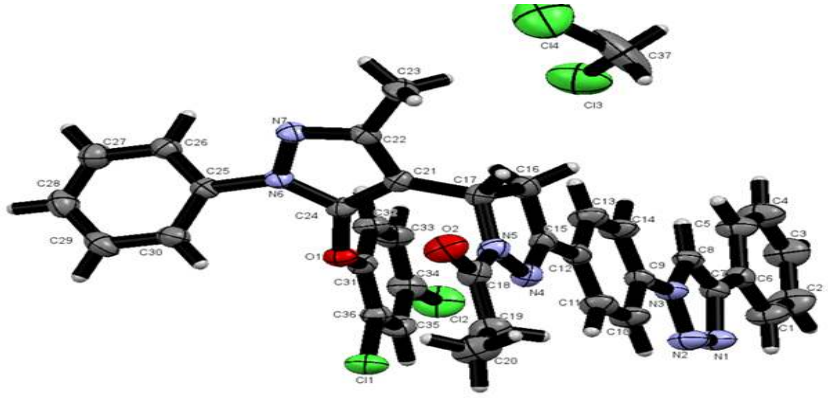


Fig. 1: Single crystal X-ray structure of compound **6e** associated with solvent dichloromethane, showing 50% probability displacement ellipsoids.

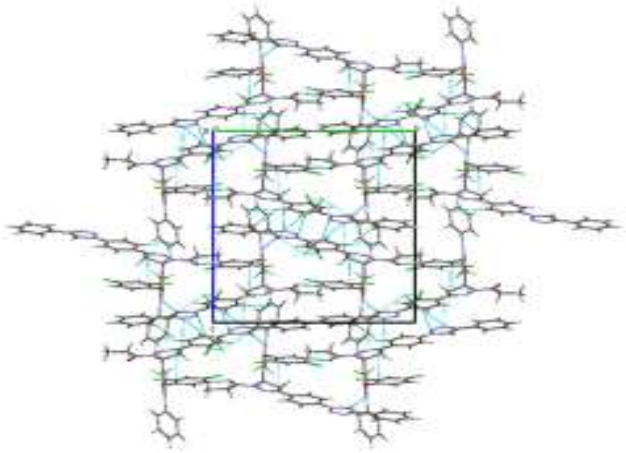


Fig. 2.Packing of the compounds: a view along *b* – axis. Dotted lines represent hydrogen bonding.

Table 2: Crystal Data and Structure Refinement details for **6e**.

Compound 6e	**6e**
CCDC number	1544854
Empirical formula	$C_{36}H_{29}Cl_2N_7O_2$, CH_2Cl_2
Formula weight	747.49
Temperature (K)	293(2)
Wavelength (Kα,Å)	0.71075
Crystal system, space group	monoclinic, *P21/n*
Unit cell dimensions (Å, º)	*a* = 11.8862(5) *b* = 16.1490(6) *c* = 18.5467(9) β = 92.525(4
Volume Å^3	3556.6(3)
Z,	4,
Calculated density (Mg/m^3)	1.396
Absorption coefficient (mm^{-1})	0.378
$F_{(000)}$	1544
Crystal size mm	0.21 x 0.23 x 0.32
Theta range for data collection (^{0})	1.7 to 50.0

Limiting indices	$-14 \leq h \leq 14$, $-19 \leq k \leq 19$, $-22 \leq l \leq 19$
Reflections collected / unique[R(int)]	35693/6267 [0.049]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4568 / 0 / 453
R value	0.0917
Goodness-of-fit on F^2	1.004
Largest diff. peak and hole (e. $Å^{-3}$)	0.57 and −0.87

CRYSTAL STRUCTURE OF (6e)

The unit cell consists of the title compound and the solvent molecule (Dichloromethane) and the ORTEP is shown in **Fig. 1** Intramolecular hydrogen bonds C1---H1…N1, C10---H10…N2 and C30---H30…O1 are observed.

In the crystal structure **Fig. 2** intermolecular hydrogen bonds C8---H8…N7, C13---H13…Cl13 and C33---H33…O2 connects the molecules (**Table 3**). In addition, short contacts, C11---H11…Cg6: C25-C30, exists with a distance (Cl1…Cg6) of 3.830 (2) Å [angle = 143^0, symmetry = 1/2+X,1/2-Y,1/2+Z] , C36---Cl1…Cg1:N1-N3/C7-C8, [C11…Cg1 = 3.830(2) Å, angle = 113.72 $(14)^0$, symmetry 3/2-X,-1/2+Y,1/2-Z] and C18---O2…Cg4:C1-C6 [O2…Cg4 = 3.981(5) Å, angle = $72.0(2)^0$, symmetry 1-X,1-Y,1-Z].

Table 3: Intermolecular and Intramolecular interactions

D---H...A	D-H	H...A	D....A	D---H...A
C1---H1...N1	0.93	2.60	2.919 (8)	100
C10---H10...N2	0.93	2.50	2.816 (7)	100
C30---H30…O1	0.93	2.56	3.024 (6)	111
C8---H8...N7 (i)	0.93	2.44	3.356 (5)	166
C13---H13...Cl3 (ii)	0.93	2.73	3.625(5)	162
C33---H33…O2 (i)	0.93	2.46	3.175(6)	134

(i) 1/2-x,1/2+y,1/2-z (ii) x, y, z

ANTIOXIDANT ACTIVITY

The newly synthesized compounds **(6 a-i)** were evaluated for their antioxidant property. The free radical scavenging activity of test sample was measured by DPPH scavenging assay and the results are given in **Table V**. The DPPH scavenging activity for tested compounds showed activity ranging from 57.1% to 8.56%, whereas standard drug BHA showed 88% inhibition. Compounds **6f**, **6b**and**6d** displayed moderate radical scavenging activity with 57.1%, 38.2%, and 31.0% DPPH inhibition respectively among the set of tested compounds.

Table V: DPPH radical assay of compounds **(6a-i)**

Comp. No.	**6a**	**6b**	**6c**	**6d**	**6e**
DPPH Assay in %	18.1	**38.2**	12.4	**31.0**	21.6

Comp. No.	**6f**	**6g**	**6h**	**6i**	**BHA**
DPPH Assay in %	**57.1**	8.56	11.12	7.12	**88.00**

PROCEDURE FOR THE ANTIOXIDANT ACTIVITY:

Free radical scavenging activity of the compounds were carried out based on the scavenging activity of DPPH. 150 µg/mL of each test sample and standard BHA was taken in different test tubes and the volume was adjusted to 1mL using MeOH. Freshly prepared 1mL of 0.1 mM DPPH solution was added to each test tube, vortexed thoroughly and left in dark for 30 min. The absorbance of stable DPPH radical was measured at 517 nm. The DPPH control (without sample) was prepared using the same procedure. Radical scavenging activity was expressed as the inhibition percentage and was calculated using the equation of DPPH radical scavenging activity[XVII].

$$\text{DPPH radical scavenging activiy (\%)} = \frac{(\text{Abs Control} - \text{Abs Sample})}{(\text{Abs Control})} \times 100$$

Where Abs Control is the absorbance of DPPH radical + solvent (Methanol); Abs Sample is the absorbance of DPPH radical + test sample/standard BHA.

CONCLUSION:

In this study, a series of tri heterocyclic hybrids carrying pyrazole, pyrazoline & triazole moiety are prepared using green protocol. The reactions complete in 5-9 minutes. Structures of the newly synthesized compounds were established by spectral, analytical and X-ray crystallographic study. In addition to this, short contacts were observed between C11---H11, C25-C30, C36---Cl1, C18---O2. The newly synthesized compounds were tested for their antioxidant activities. Some of the synthesised compounds exhibited moderate antioxidant activities.

ACKNOWLEDGMENT:

The authors are thankful to the Head, SAIF, Panjab University, Chandigarh and to Head, PURSE, Mangalore University, Mangalore, for spectral and analytical data.

REFERENCE:

[I] Asma, B. Kalluraya, N. Manju, Chandra, M. Mahendra. B. C. Revanasiddappa, J. Med. Chem. Drug. Des, 1, 6 (2018)

[II] Vijesh A.M, Isloor A M, Shetty P, Sundershan S, Fun H K, Eur. J. Med. Chem. 62, 410 (2013).

[III] Dawood K.M, Eldebs T M A, El-Zahabi H S A, Yousef M H, Metz P, Eur. J. Med. Chem. 70, 740 (2013)

[IV] Daidone G, Maggio B, Raffa D, Plescia S, Bajardi M L, Caruso A, Cutuli, V M C, Amico-Roxas M, Eur. J. Med. Chem. 36, 707 (1994).

[V] YeuJ P, Yeh J T, Chen T Y, Uang B J, Synthesis. 21, 1775 (2001)

[VI] Vidyashree Jois H S, Kalluraya B, and Girisha K S, J. Serb. Chem.Soc. 79, 1469 (2014)
[VII] Bourne Y, Kolb C, Radic Z, Sharpless K B, Taylor P, Proc. Natl. Acad. Sci. USA, 101 1449 (2004)
[VIII] Whiting M, Muldon J, Lin Y C, Silverman S M, Lindstron W, Olson A J, Kolb H C, Finn M G, Sharpless K B, Elder J H, Fokin V, Angew. Chem. Int. Ed. 45 118 (2006)
[IX] Sathish Rai N, and Balakrishna Kalluraya, Indian J. Chem, 46B, 375 (2007).
[X] Girisha K S, Balakrishna Kalluraya. Vijaya Naryana, Padmashree, Eur. J. Med. Chem. 45, 4640 (2010)
[XI] Chirag Sharma, Bhawana Thadhaney, Gangotri Pemawat and Talesara G L, Indian J. Chem. 47, 1892 (2008).
[XII] Kappe C O, Dallinger D, Nat. Rev. Drug Discovery. 5, 55 (2006)
[XIII] Leadbeater N E, Chem. Commun. 23, 2881 (2005)
[XIV] Asma, Balakrishna Kalluraya, Manju N, Der Pharma Chemica. 10, 50 (2017)
[XV] Rigaku CrystalClear SM Expert. Rigaku Corporation, Tokyo, Japan. (2011).
[XVI] Macrae C F, Bruno I J, Chisholm J A, Edgington P R, McCabe P, Pidcock E, Rodriguez-Monge L, Taylor R, van de Streek J, Wood PA, J Appl Cryst 41, 466 (2008)
[XVII] MensorL I, Menezes F S, LietaoG G, Reis A S, Don Santos T, Coube C S, Lietao S, Phytother. Res. 15, 127 (2001)

Received on July 20, 2018.