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Synthesis and biological activity of pyrazole and 1,2,3-triazole containing heterocyclic compounds

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ABSTRACT

As heterocyclic compounds show good biological activity, we have synthesized nitrogen containing compounds among them **9a**, **9c**, **9e** and **9f** have shown very good antimicrobial activity with remarkable inhibition zones. N'-((5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene)-5-methyl-1-phenyl-1*H*-1,2,3-triazole-4-carbohydrazide **(9a-i, 10)** was synthesized from 5-(aryloxy)-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde and 5-methyl-1-phenyl-1*H*-1,2,3-triazole-4-carbohydrazide by condensation in acidic media. 5-(aryloxy)-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde and 5-methyl-1-phenyl-1*H*-1,2,3-triazole-4-carbohydrazide were synthesized from phenyl hydrazine and substituted anilines respectively. All intermediates and final compounds were confirmed by ^{1}H-NMR, ^{13}C-NMR, Mass Spectroscopy methods and compound **9c** was confirmed by single XRD analysis.

***Keywords*:** hydrazones, azides, pyrazol, triazole, XRD crystal, antibacterial

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1. INTRODUCTION

The compound having biological activity are most probably contain heterocycles like pyrazole, thiazole, quinolins, triazoles, oxadiazole, tetrazole, coumarin etc. this work is planed basically on pyrazole and triazole containing molecules because these heterocycles show different types of biological activity like, antimicrobial [1-3,12], antitubercular [4,5], antioxidant [6] anti-TMV activity [7], antibacterial [8], Antiproliferative Activity [9,14], anti-allergenic [10], anti-HIV [11], cytostatic, anti-depressant, gastric secretion stimulatory, and anti-filarial agents.

As pyrazole [15,16] and 1,2,3-triazole [17,19] are mostly water soluble so that they can be used in different prospect of life due to different kind of biological activity . The pyrazole ring is found within a variety of pesticides as fungicides, insecticides and herbicides, including chlorfenapyr, fenpyroximate, fipronil, tebufenpyrad [20-23].

As pyrazole and triazoles are very useful compounds in drug synthesis and there is lots of work done on this scaffolds that is why synthesis of this intermediates is quite easy. There are different methods available for synthesis and among them one was selected here. Phenylhydrazine was converted into pyrazolone with simple reaction with ethyl acetoacetate, then well-known reaction villsmer hack was used to introducing aldehyde and chloro groups which is intermediate-**1**.

Different derivatives of intermediate-2 were synthesized by taking different substituted anilines. Aniline was diazotized to give diazonium salt which was converted into triazole by cyclisation. This triazoles were further reacted with hydrazinehydrate to give intermediate-**2**.

The final product was synthesized by the reaction of 1 and 2 in presence of acidic media. All final products were confirmed by ^{1}H NMR, ^{13}C NMR, and Mass spectroscopy. The structure of 3d was supported by XRD [24-26].

The structure was solved by direct methods and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model.

The final cycle of full-matrix least-squares refinement on F was based on 6272 observed reflections and 334 variable parameters and converged (largest parameter shift was 0.97 times its esd) with unweighted and weighted agreement factors.

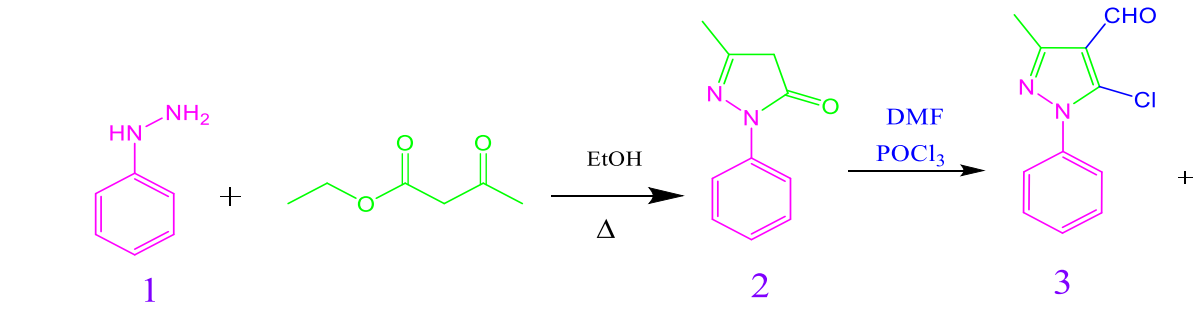
2. EXPERIMENTAL PROCEDURE

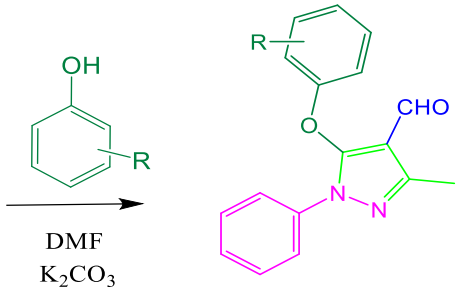
A) General introduction

For all these conversions, progress of reaction was carried out on TLC plate silica gel GF^{254} and the melting points were recorded by open capillary method.

Mass spectra were recorded on Shimadzu GCMS-QP-2010 model using Direct Injection Probe technique. ^{1}H NMR was determined in $CDCl_3$/DMSO solution on a Bruker AVANCE II 400 MHz.

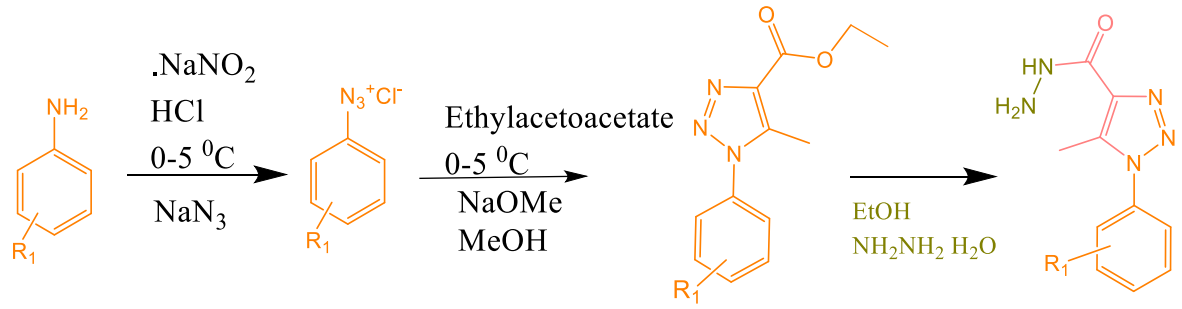
B) General method of synthesis





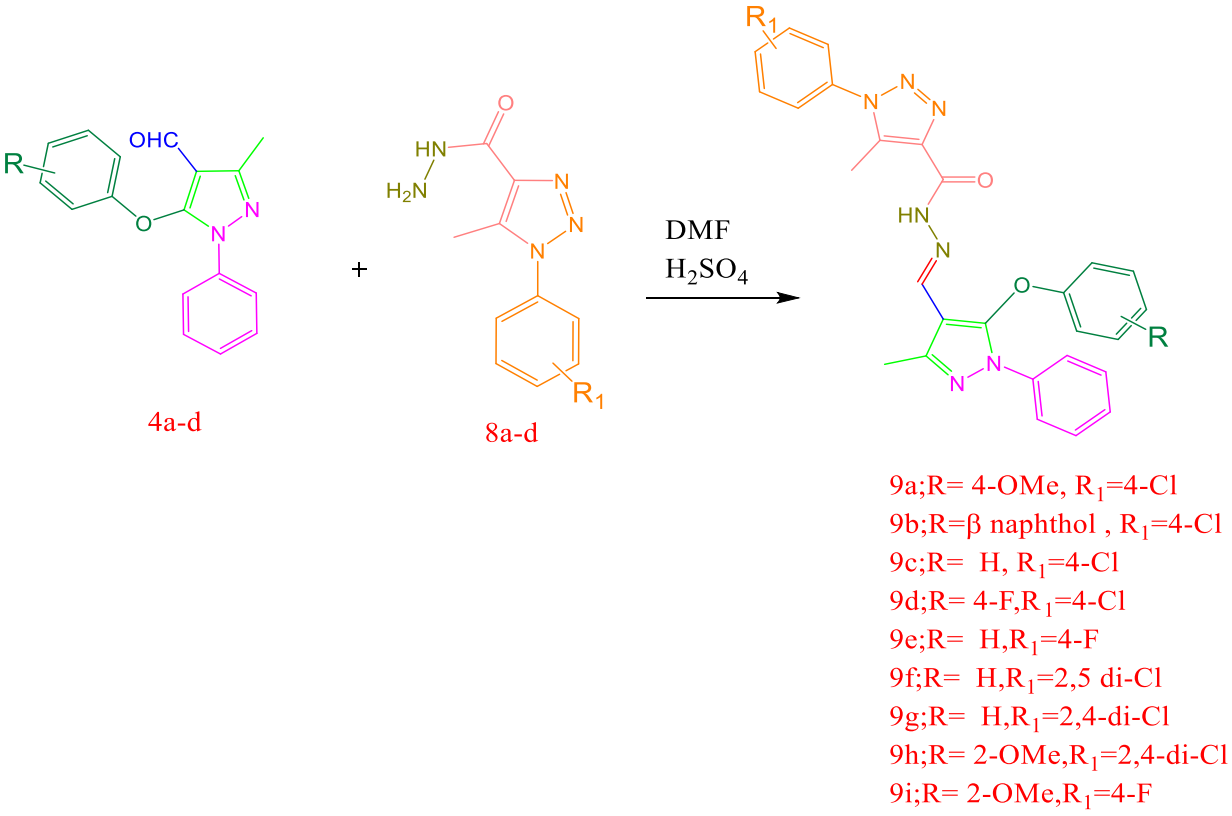
4a;R= 2-OMe
4b;R= β naphthol
4c;R= H
4d;R= 4-F

Scheme 1. Rout of synthesis for compounds 3 and 4a-d.

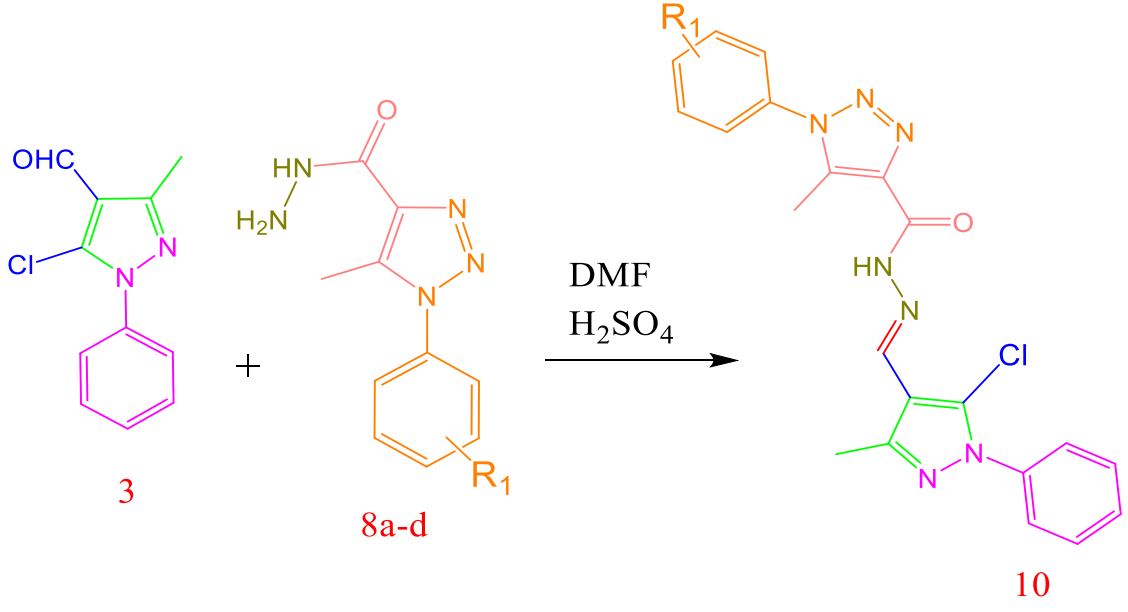


5a; R_1 = 4- Cl	6a; R_1 = 4- Cl	7a; R_1 = 4- Cl	8a ; R_1= 4- Cl
5b; R_1 = 4- F	6b; R_1 = 4- F	7b; R_1= 4- F	8b; R_1 = 4- F
5c; R_1 = 2,4 di Cl	6c; R_1 = 2,4 di Cl	7c; R_1 = 2,4 di Cl	8c; R_1 = 2,4 di Cl
5d; R_1 = 2,4 di Cl	6d ; R_1= 2,4 di Cl	7d ; R_1= 2,4 di Cl	8d; R_1 = 2,4 di Cl

Scheme 2. Rout of synthesis for compounds 8a-d.



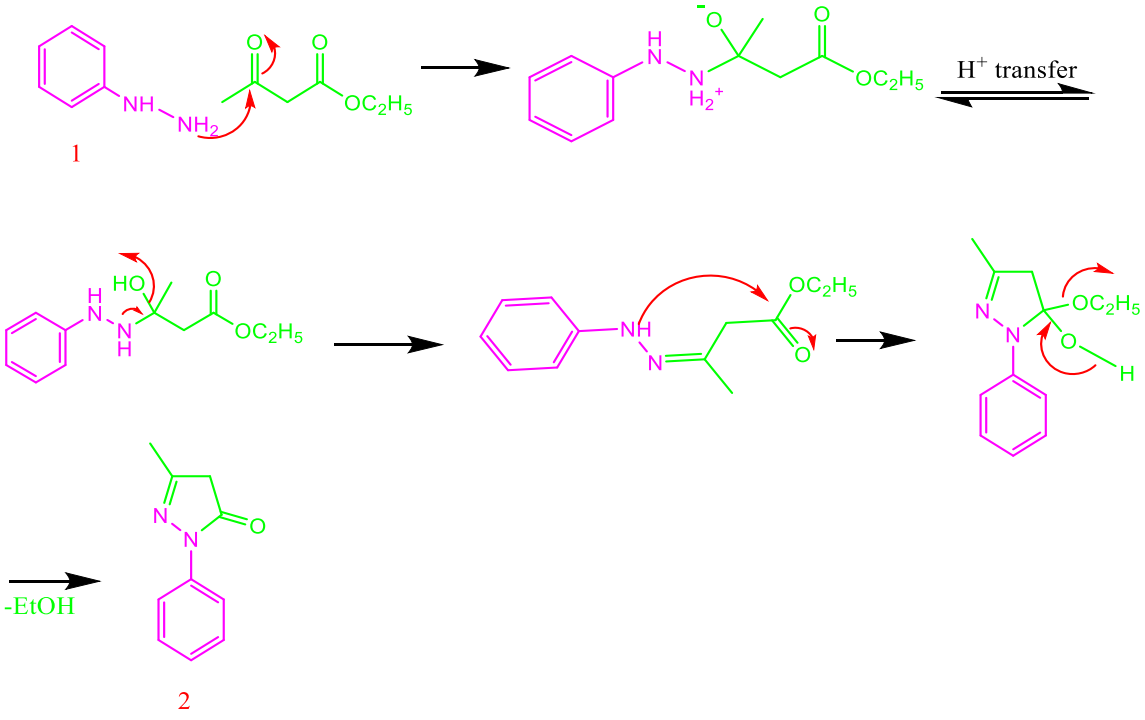
Scheme 3. Rout of synthesis for compounds 9a-i.



Scheme 4. Rout of synthesis for compounds 10.

2. 1. Mechanism

Step 1



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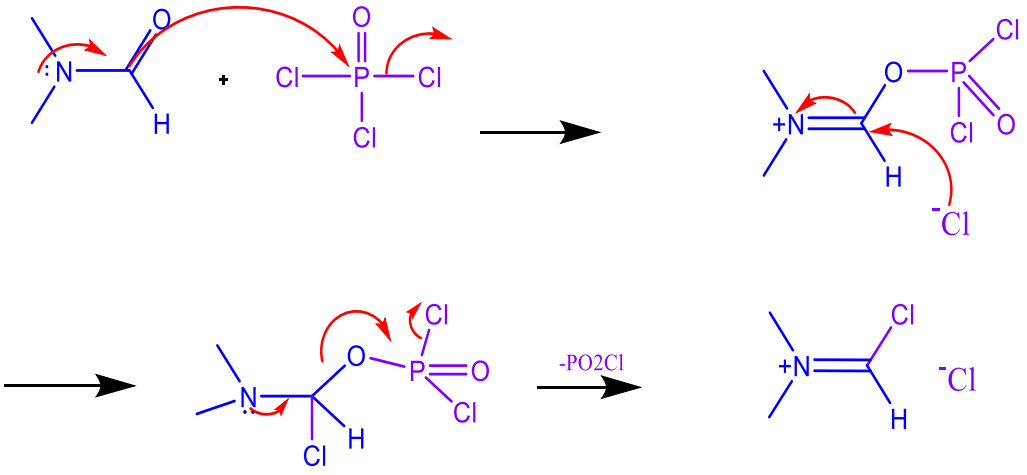
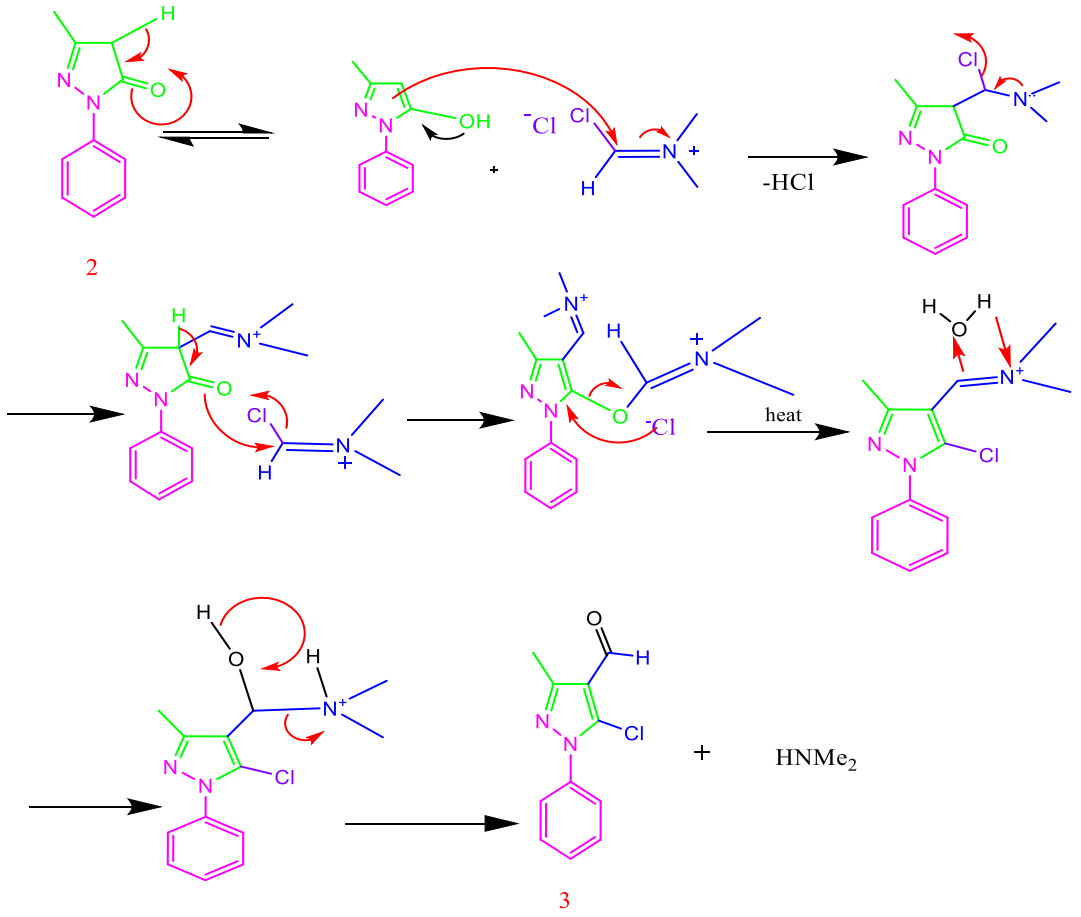


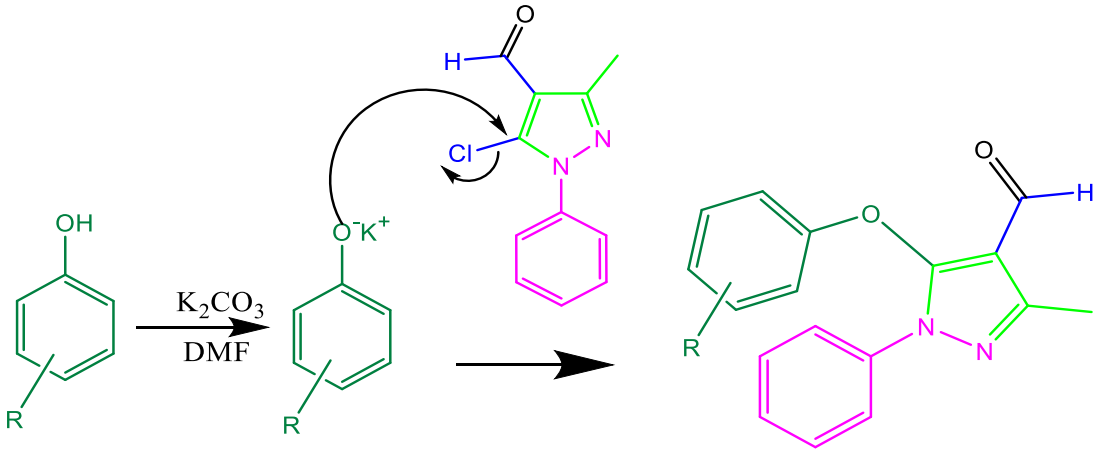
Step 3



2

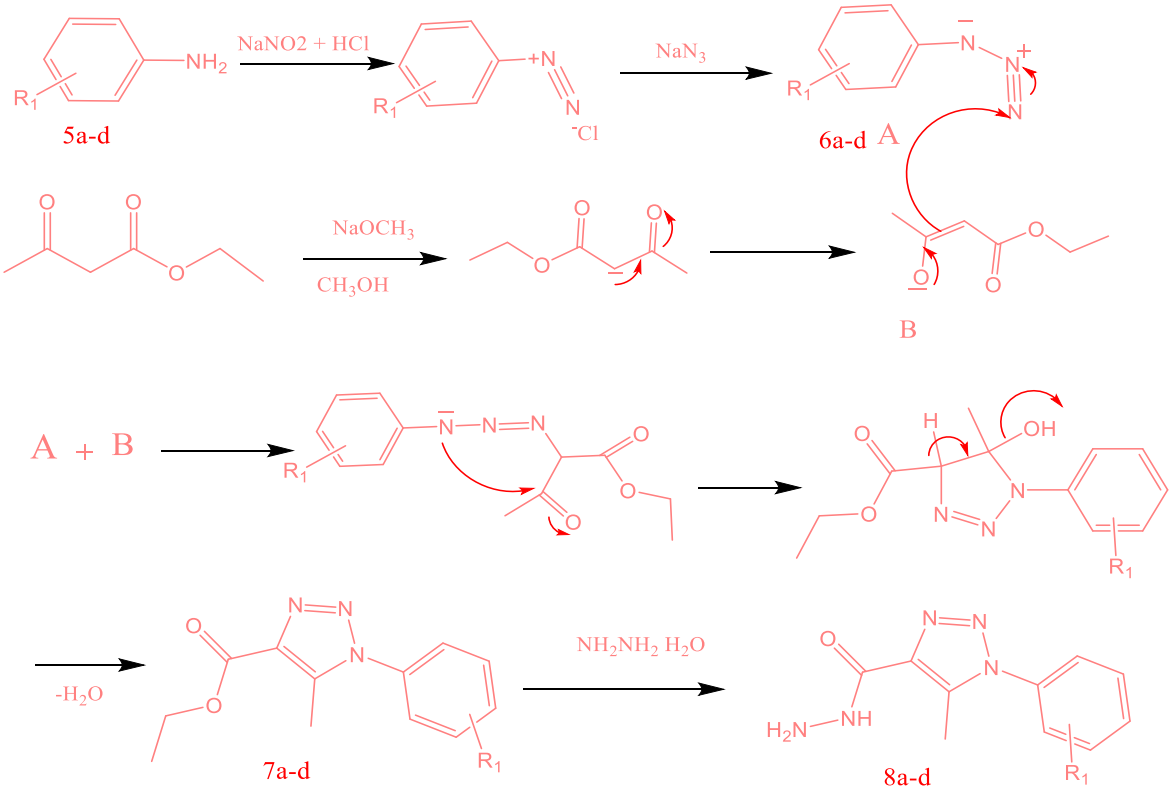
3

Step 4

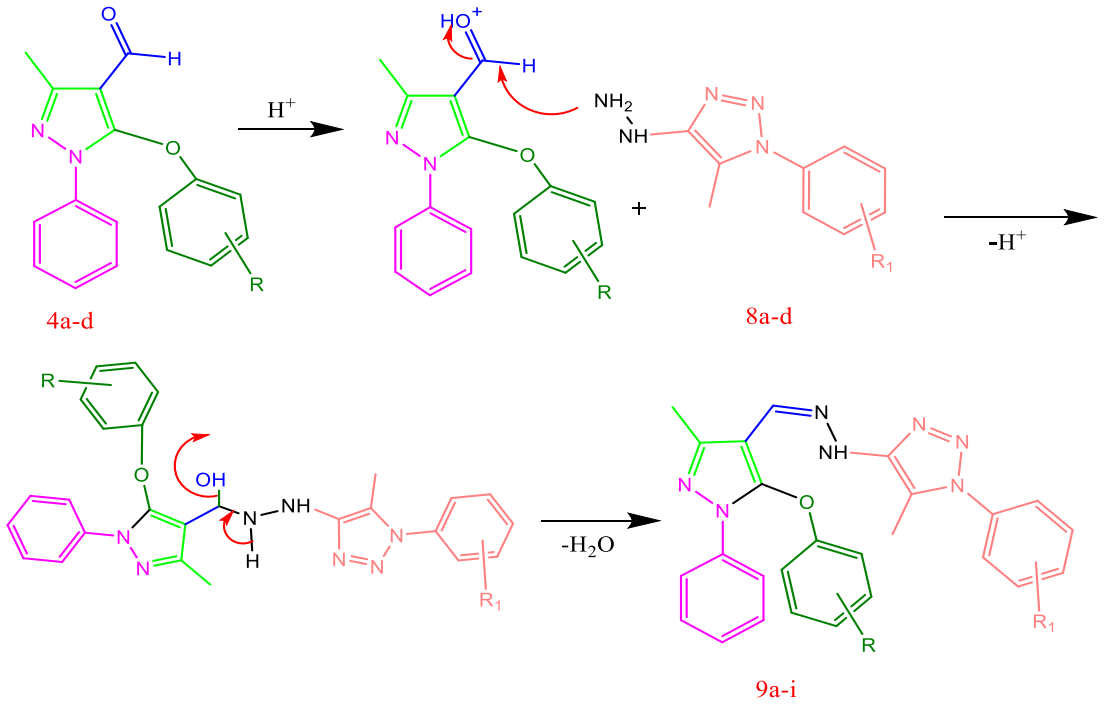


4a-d

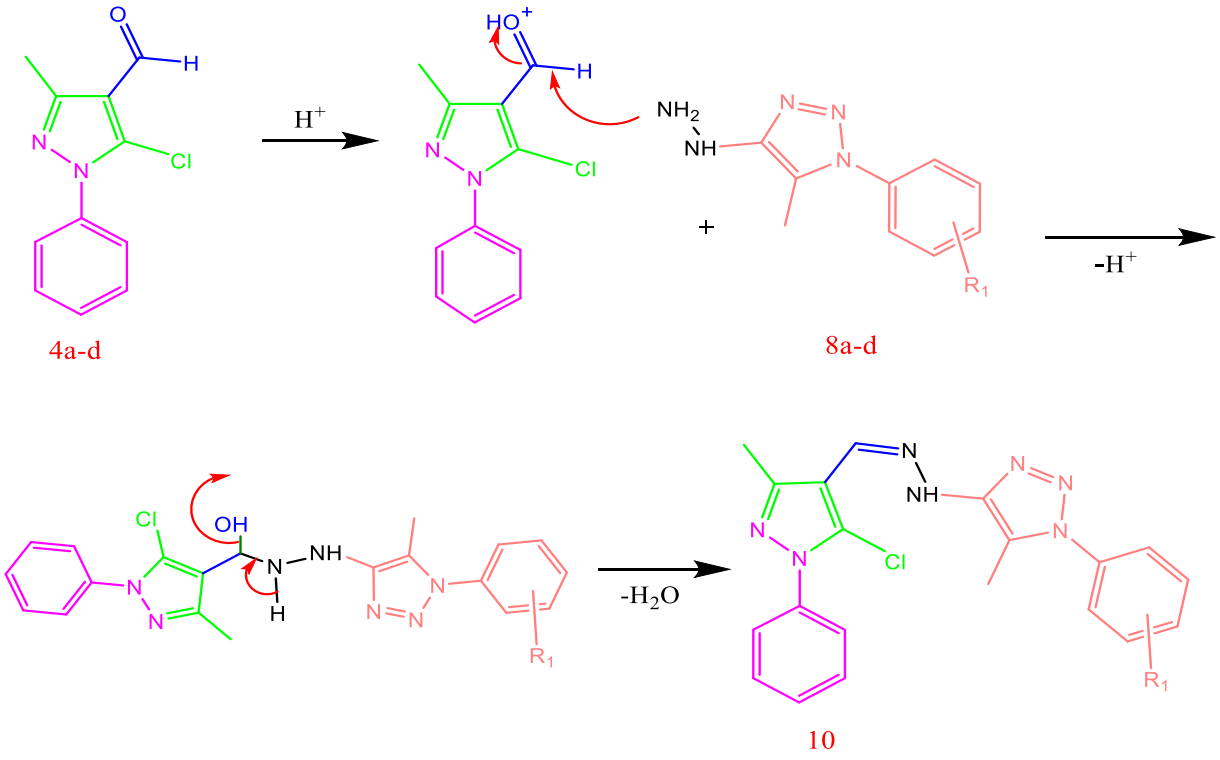
Step 5


NaNO2 + HCl
NaN3
5a-d
6a-d
A
NaOCH3
CH3OH
B
A + B
-H2O
7a-d
NH2NH2 H2O
8a-d

Step 6


H+
4a-d
8a-d
-H+
-H2O
9a-i

Step 7



2. 2. Antibacterial activity

Table 1. Antibacterial/fungal activity table [microgramme/ml]

MINIMAL INHIBITION CONCENTRATION						
S. No	CODE	*E. coli*	*P. aeruginosa*	*KL. pneumoniae*	*S. aureus*	*P. marneffei*
		MTCC 443	MTCC 1688	MTCC 109	MTCC 96	WILD STAIN
1	(10) (AZ1)	25	50	100	50	500
2	(9a) (AZ2)	12.5	25	25	100	100
3	(9b) (AZ3)	50	50	100	25	250
4	(9c) (AZ4)	100	25	50	50	100
5	(9d) (AZ5)	25	50	100	25	50

6	(9e) (AZ6)	12.5	50	25	100	50
7	(9f) (AZ7)	50	50	25	50	100
8	(9g) (AZ8)	25	12.5	25	100	250
9	(9h) (AZ9)	100	25	100	50	250
10	(9i) (AZ10)	50	12.5	25	100	50
11	Furacin	25	25	50	50	-
12	Itracon ozole	-	-	-	-	100

The antibacterial activity of N'-((5-substituted-3-methyl-1-phenyl-1H-pyrazol-4-yl)methylene)-5-methyl-1-phenyl-1H-1,2,3-triazole-4-carbohydrazide (9a-i,10) was appraised against *E. coli, P. aeruginosa, Kl. Pneumoniae, S. aureus, P. marneffei* (antifungal bacteria) using Furacin and ltraconozoleas standard drugs. Minimum bacterial inhibitory concentration (MIC) values were resolved by Broth dilution technique.

Dimethyl sulfoxide was used as diluent. MIC values of the appraised compounds are recorded in (Table 1). Majority of the prepared compounds displayed less activity than standard drug Furacin and ltraconozole against *E. coli, P. aeruginosa, Kl. pneumoniae, S. aureus, P. marneffei.* Compound with one methoxy group at 2nd position of phenoxide ring along with Chloro substitution at 4th position of 1,2,3-triazole ring (9a) and Compound with only phenoxide ring (no substitution) along with Chloro substitution at 4th position of 1,2,3-triazole ring (9c) showed encouraging antibacterial activity.

2. 3. XRD crystal study

Single crystal X-ray analysis of compound 9c was performed with a Rigaku SCX mini diffractometer with using graphite monochromated Mo-Kα radiation. (λ = 0.71075 Å) and operating at 50 kV and 30 mA at 20.0 ºC temperature. A single crystal was isolated and was mounted loop with protective oil and placed under a flow of nitrogen gas at 20 ±1 ºC to a maximum 2θ value of 55.0º.

A total of 540 oscillation images were collected. Structure solution of the structure was solved by direct methods and expanded using fourier techniques. Non-hydrogen atoms and hydrogen atoms were refined by anisotropically and riding model respectively. The observed reflection 6272 and variable parameters 334 were used for the least squares refinement and full-matrix final cycle and converged (largest parameter shift was 0.97 times its esd) with using un-weighted and weighted agreement factors.

The observation of unit weight of standard deviation was 2.38 unit weights were used and the maximum and minimum peaks on the final difference Fourier map to 2.21 and -0.44 $e^{-}/Å^{3}$, respectively. The software SHELXL-97 was used for calculations to derive crystal structure **(CCDC Number: 1873263)**.

Table 2. Crystal and Experimental data of compound 9c(AZ4).

Compound ID	**9c**
CCDC Deposition Number	**1873263**
Empirical Formula	$C_{27}H_{22}ClN_7O_2$
Formula Weight	511.97
Crystal Color, Habit	colorless, chip
Crystal Dimensions	0.500 × 0.200 × 0.170 mm
Crystal System	monoclinic
Lattice Type	I-centered
Lattice Parameters	a = 18.538(3) Å
	b = 10.915(2) Å
	c = 27.341(4) Å
	β = 96.157(8)º
	V = 5500(2) $Å^3$
Space Group	I2/a (#15)
Z value	8
D_{calc}	1.236 g/cm^3
F_{000}	2128.00
μ(MoK α)	1.750 cm^{-1}
ω oscillation Range	-120.0 - 60.0º
Exposure Rate	10.0 sec./º
Detector Position	52.00 mm
2Θ max	55.0º
No. of Reflections Measured	Total: 6272 Unique: 6272
R_{int}	0.0000
R1 (I>2.00 σ(I))	0.1336

R (All reflections)	0.1777
wR2 (All reflections)	0.3957
Goodness of Fit Indicator	2.385
Max Shift/Error in Final Cycle	0.967
Maximum peak in Final Diff. Map	2.21 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.44 $e^-/Å^3$

2. 4. Crystal preparation

In an oven dried conical flask pure compound 9c was taken in 5.0 ml Dimethylformamide, and was heated it up to 60-65 °C for 15-20 minutes till it dissolved completely. The hot solution was filtered out, allowed to cool gradually and was kept in a stoppered conical flask. The crystals were grown due to thin layer evaporation. The ORTEP diagram and crystallographic data for the representative compound was shown in Figure 1.

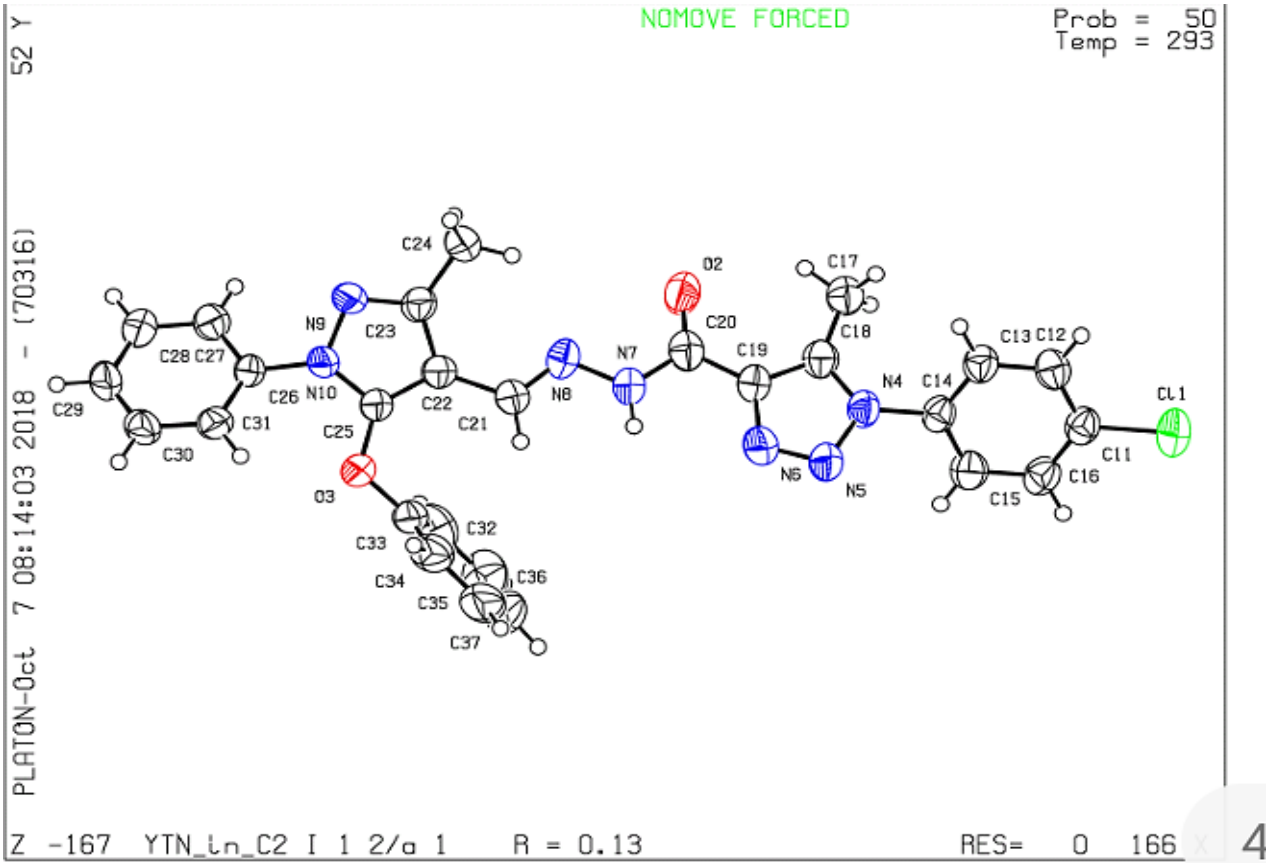


Figure 1. Medicinal important hydrazone derivatives have been synthesized, characterized and biologically evaluated.

2. 5. Experimental Section

5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one(2)
Phenyl hydrazine **(1)** (5.0 g, 0.046 mol) and ethylacetoacetate (9.02 g, 0.069 mol) was taken in evaporating dish, the reaction mixture was heated at 80 ºC in water bath with continues stirring. After formation of solid mass reaction mixture was cooled at room temperature and washed with diethyl ether and dried under reduced pressure to obtain white solid product (7.5 g, 93 % yeild) (mp-126-128 ºC).

5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde (3)
$POCl_3$ (13 ml) was taken in 250 mL RBF, cooled at 0-5 ºC and Dimethylformamide (6 ml) was added drop wise. The reaction mixture was allowed to stir at same temperature for 10-15 min and 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (7.5 g, 0.043 mol) was added to it. The reaction mixture was allowed to stir at room temperature and heated at reflux temperature for 5 to 6 hrs. The reaction was monitored by TLC. After completion of reaction, mass was poured to cold water and filtered off, washed with cold water and dried under reduced pressure at 80-90 ºC to obtained pure product (6.5g, 68.56 % yield)

3-methyl-5-phenoxy-1-phenyl-1H-pyrazole-4-carbaldehyde (4a-d)
The 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde (6.5g, 0.0295 mol) was dissolved in Dimethylformamide (30 ml) and K_2CO_3 (8.15g, 0.059 mol) Phenol derivatives (2.77g, 0.0295 mol) was added to it and allowed to stir at reflux temperature for 4-5 hrs. The reaction was monitored by TLC. After completion, the reaction mixture was poured to water and extracted by ethyl acetate. The organic layer was washed with cold water and dried over Na_2SO_4, concentrated under reduced pressure to obtained pure product (7.2g, 87.69 %),

Synthesis of Various azide derivatives of Aniline (6a-d)
For the formation of various azide derivatives, HCl (6ml) and water (20ml) were placed in three necked round bottom flask. The solution was cooled at 0 ºC. Then anilinederivatives (5.0g, 0.053 mol) was added drop wise and temperature kept constant between 0-5 ºC then sodium nitrite solution (3.65g, 0.053 mol) and sodium azide (3.44 g, 0.053 mol) was added dropwise at 0-5 ºC. Then allow the reaction mass to stirred for 30 min. after the completion of reaction the residue extracted using chloroform and washed with waterto give 5a-d (4.2g, 70.42%) .

Synthesis of ethyl 5-methyl-1-phenyl-1H-1,2,3-triazole-4-carboxylate (7a-d)
The formation of ethyl 5-methyl-1-phenyl-1H-1,2,3-triazole-4-carboxylate derivatives azide (4.2g, 0.035 mol) derivatives treated with ethyl acetoacetate (9.1g, 0.07 mol) then reaction mixture cooled at 0 ºC and then sodium methoxide (3.78g,0.07 mol) was added under inert atmosphere in methanol as a solvent. The reaction mixture was stirred at ambient temperature and the progress of the reaction was monitored using TLC. after the completion of reaction the reaction mass was poured into the ice cold water, the residue obtained are dry and separated and washed with water and recrystallalized from ethanol to give 7a-d (6.2g, 76.68%).

Synthesis of 5-methyl-1-phenyl-1H-1,2,3-triazole-4-carbohydrazide (8a-d)
The carbohydrazide derivatives prepared by dissolveng ethyl 5-methyl-1-phenyl-1H-1,2,3-triazole-4-carboxylate (6g, 0.0259 mol) into ethanol (30 ml) and then hydrazine hydrate was

added dropwise and refluxe the reaction mass for 6 hr at 80 ºC. After the completion of reaction, the reaction mass was colled and residue was separated are filtered and washed with water to give 8a-d (5g, 88.80%).

Synthesis of N'-((5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)methylene)-5-methyl-1-phenyl-1H-1,2,3-triazole-4-carbohydrazide (9a-i, 10)

5-methyl-1-phenyl-1H-1,2,3-triazole-4-carbohydrazide (0.902g, 0.0036 mol) dissolve in DMF (5 ml) and ethanol (5 ml) mixture. Add pyrazole aldehyde (1g, 0.0036 mol) and 2-3 drops of conc. Sulphuric acid. Reflux the reaction for two hours. The solid product is filtered, collected and dry it. Product is recrystalized from DMF to give 9c (1.5g, 81.52%)

(E)-N'-((5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)methylene)-1-(4-chlorophenyl)-5-methyl-1H-1,2,3-triazole-4-carbohydrazide(10) (AZ1)

White coloured, Yield: 82% m.p.: 182-184 ºC ^{1}H NMR: (400MHz, $CDCl_3$-d), δ 10.177 (s, 1H, NH), δ 8.255 (s, 1H, imine proton), 7.596-7.561 (m, 4H), 7.525-7.434 (m, 3H), 2.702 (s, 3H, triazole), 2.651 (s, 3H, pyrazol), LC mass m/z: 452.9 (M.F: $C_{21}H_{17}Cl_2N_7O$)

E-N'-((5-(2-methoxyphenoxy)-3-methyl-1-phenyl-1H-pyrazol-4-yl)methylene)-1-(4-chlorophenyl)-5-methyl-1H-1,2,3-triazole-4-carbohydrazide (9a) (AZ2)

White coloured ,Yield: 77% compound, m.p: 173-175 ºC, ^{13}C NMR (101 MHz, CDCl3) δ 156.58 (s), 149.07 (d, J = 10.8 Hz), 145.85 (s), 139.52 (s), 137.72 (d, J = 12.5 Hz), 136.30 (s), 133.85 (s), 130.00 (s), 129.05 (s), 127.10 (s), 126.44 (s), 124.95 (s), 122.21 (s), 121.04 (s), 116.24 (s), 112.97 (s), 103.32 (s), 77.37 (s), 77.05 (s), 76.73 (s), 56.08 (s), 29.71 (s), 15.63 (s), 9.76 (s), 0.01 (s). ^{1}H NMR: (400MHz, $CDCl_3$-d),δ 9.854 (s, 1H,NH) 7.809 (s, 1H, imine proton), 7.696-7.674 (m, 2H), 7.582-7.547 (m, 2H) 7.439-7.355 (m, 4H), 7.271-7.234 (m, 1H), 7.099-7.056 (m, 1H), 6.999-6.977 (d, 1H, J = 8Hz), 6.829-6.797 (m, 2H), 3.914 (s, 3H), 2.668-2.663 (s, 6H, triazole and pyrazol). LC mass m/z: 540.8 (M.F $C_{28}H_{24}ClN_7O_3$)

(E)-1-(4-chlorophenyl)-5-methyl-N'-((3-methyl-5-(naphthalen-3-yloxy)-1-phenyl-1H-pyrazol-4-yl)methylene)-1H-1,2,3-triazole-4-carbohydrazide (9b) (AZ3)

Yellow coloured, Yield: 72% m.p: 192-194 ºC, ^{13}C NMR (101 MHz, CDCl3), δ 156.65 (s), 154.87 (s), 149.31 (s), 148.06 (s), 139.34 (s), 138.19-137.35 (m), 133.89 (d, J = 15.7 Hz), 130.68 (s), 130.36 (s), 129.96 (s), 129.20 (s), 127.81 (s), 127.32 (s), 127.10 (s), 126.41 (s), 125.22 (s), 122.10 (s), 116.75 (s), 110.45 (s), 104.20 (s), 77.37 (s), 77.05 (s), 76.74 (s), 15.56 (s), 9.74 (s). ^{1}H NMR: (400MHz, $CDCl_3$-d), δ 9.906 (s, 1H, NH) 7.937 (s, 1H, imine proton), 7.851-7.792 (m, 2H), 7.699-7.650 (m, 3H) 7.549-7.521 (m, 2H), 7.459-7.336 (m, 6H, triazole and pyrazol), 7.294-7.223 (m, 3H), 2.950-2.629 (s, 6H). LC mass m/z: 560.8, (M.F $C_{31}H_{24}ClN_7O_2$)

(E)-1-(4-chlorophenyl)-5-methyl-N'-((3-methyl-5-phenoxy-1-phenyl-1H-pyrazol-4-yl) methylene)-1H-1,2,3-triazole-4-carbohydrazide (9c) (AZ4)

White coloured, Yield: 85% m.p: 181-184 ºC, ^{1}H NMR: (400MHz, $CDCl_3$-d), δ 9.946 (s, 1H, NH), 7.887 (s, 1H, imine proton), 7.643-7.574 (m, 2H), 7.588-7.540 (m, 2H), 7.434-7.354 (m, 4H), 7.329-7.240 (m, 3H), 6.987-6.980 (t, 1H, 2.8Hz), 6.965-6.963 (m, 2H), 2.681-2.659 (s, 6H, triazole and pyrazol). LC mass m/z: 510.7 (M.F $C_{27}H_{22}ClN_7O_2$)

(E)-1-(4-chlorophenyl)-N'-((5-(4-fluorophenoxy)-3-methyl-1-phenyl-1H-pyrazol-4-yl) methylene)-5-methyl-1H-1,2,3-triazole-4-carbohydrazide (9d) (AZ5)
Yellow coloured, Yield: 85% m.p: 170-172 ºC, ^{1}H NMR: (400MHz, $CDCl_3$-d), δ 10.042 (s, 1H, NH), 7.946 (s, 1H, imine proton), 7.626-7.607 (d, 2H, J = 7.6Hz), 7.565-7.543 (d, 2H, J = 8.8 Hz), 7.430-7.363 (m, 4H),7.290-7.271 (m, 1H), 6.996-6.919 (m, 4H), 2.685-2.650 (s, 6H, triazole and pyrazol). LC mass m/z: 528.6 (M.F $C_{27}H_{21}ClFN_7O_2$)

3. CONCLUSIONS

All the final compounds 9a-I, 10 were successfully synthesized, purified by Column chromatography and characterized by different spectroscopicaltechniques like ^{1}H NMR, ^{13}C NMR and MS analysis, crystal structure of 9c was determined by XRD analysis. The details of XRD report is given in supplementary martial, more ever all the compounds were carried out for their antibacterial and anti-fungal activity using 2 gram positive and 2 gram negative bacterias as well as one fungal stain, from this study we came to know that all the compounds emerged out as potent antibacterial and anti-fungal agents expect 9b and 9h.

Acknowledgements

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