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NOVEL SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 3-AMINO PHENYL-5-METHYL PYRAZOLES AND ITS DERIVATIVES

Priti Warbhe and Reshal Deshmukh*

Department of Chemistry, Shri Shivaji Science College, Congress Nagar, Nagpur – 440012, M.S., India.

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Heterocyclic Compounds, Pyrazoles, Nitroso and Benzoyl Derivatives, Antibacterial Activity

Correspondence to Author:
Reshal Deshmukh

Associate professor
Shri Shivaji Science College,
Congress Nagar, Nagpur - 440012
M.S., India.

E-mail: priti.warbhe@rediffmail.com

ABSTRACT: Pyrazoles and fused heterocyclic pyrazoles derivatives constitute an interesting class of heterocyclic compounds due to their synthetic versatility and effective biological activity in the field of pharmaceutical science, agriculture etc. In the present study, new substituted pyrazoles were prepared by condensation of substituted primary amine and ethyl acetoacetate at 140^0C to form analides as intermediate. These intermediates on further reaction with hydrazine hydrate using ethanol as solvent and converted into pyrazoles. The synthesized compounds were characterised by their physical properties, IR, NMR and elemental analysis techniques. The purity of the compounds and completion of reaction was tested by TLC Technique using ethyl acetate and petroleum ether as an eluent (6:4). The antimicrobial activity of synthesized pyrazoles was assessed by Disk diffusion method using gram positive and gram negative strains. The benzoyl and nitroso derivatives were also prepared to confirm the formation of new compounds. The derivative of these compounds also shows good antimicrobial activity.

INTRODUCTION: The chemistry of heterocyclic compounds is one of the most complex and important stream of organic chemistry. Because of the diverse properties, easily accessible path and the wide range of biological activities, these are centre of attraction for organic chemist to synthesise various heterocyclic compounds [1-3]. The literature survey reveals the importance of pyrazole derivatives as an intermediate in the medicinal chemistry [4-6]. Pyrazoles and their substituted derivatives are interesting potential pharmaceuticals. They exhibit wide variety of biological and pharmaceutical activities. Therefore, they play important role in medicinal chemistry [7].

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The pyrazoles nucleus has been reported to possess a wide spectrum of biological properties such as anti-inflammatory [8], antibacterial [9], analgesic [10], antifungal [11], antiviral [12], antibacterial [13], CNS depressant, antitumor, potent local anaesthetics etc [14]. Keeping in view, the importance of heterocyclic compounds were synthesised according to Paal-Knorr Synthesis and its nitroso derivatives and benzoyl derivatives were prepared [15-16]. The newly synthesised compounds were screened for their antimicrobial activity against Gram +ve and Gram –ve strains.

MATERIALS AND METHODS: All chemicals used for the synthesis were of analytical grade. H NMR spectra were recorded on Bruker Avance II 400 NMR Spectrometer. IR spectra were recorded by using Affinity-1 FTIR Spectrophotometer. Melting points were determined by using INDO Melting Point M-AB-92 apparatus and were uncorrected. All the reactions were monitored by thin layer chromatography (TLC). The crude

compounds were purified by recrystallization from ethanol. Mass spectra were also recorded.

Experimental:

Section A: Synthesis of 1-(N-phenyl-carboxamido)-propan-2-one: An equimolar (0.01 mol) of the mixture of substituted primary amine and ethyl acetoacetate in ethanol (99% pure ethanol) ml was refluxed for 6-8 hrs. Reaction mixture was cooled and poured onto crushed ice while stirring continuously. Resultant solid was filtered, washed thoroughly with cold water, dried and purified by recrystalisation with [17] ethanol to form **Ia**. Similarly **(Ib – If)** were synthesised by above method.

NMR: **[Ia]** Ar-H=δ (7.03 to 7.26ppm), NH=δ (9.21ppm), CH_2= δ (3.59ppm),-CH_3=δ (2.33ppm), OCH_3=δ (3.87ppm) NMR Ar-H=δ(7.03 to 7.26ppm), NH=δ(9.21ppm), CH_2= δ(3.59ppm),-CH_3=δ(2.33ppm), OCH_3=δ(3.87ppm) IR N-H Str.=3282.02 cm^{-1} C=O Str. =1676 cm^{-1} C-N Str. =1459.21 cm^{-1}

[Ie] Ar-H= δ (6.72 to 7.46ppm), NH=δ (9.832ppm), CH_2= δ (3.328ppm), -CH_3=δ (2.25ppm), OH=δ (11.33ppm) NMR Ar-H=δ(6.72 to 7.46ppm), NH=δ(9.832ppm), CH_2= δ(3.328ppm), -CH_3=δ(2.25ppm), OH=δ(11.33ppm) IR N-H Str.=3172.02 cm^{-1} C=O Str. =1683.51 cm^{-1} C-N Str. =1376.01 cm^{-1}

Section B: Synthesis of 3-amino phenyl-5-methyl pyrazoles: 1-(N-phenyl-carboxamido)-propan-2-one (Ia) (0.01M) was then refluxed with hydrazine hydrate (0.01M) in methanol as a solvent for 2-3 hrs. After refluxing the reaction mixture was allowed to distill off. A shiny crystal of pyrazoles (IIa) is obtained. These were recrystallised with ethanol [18-20]. Similarly compounds (IIb – IIf) were synthesised.

Section C: Derivatives of pyrazoles:

a) Nitroso derivative of pyrazoles: 3-amino phenyl-5-methyl pyrazoles **(**IIa- IIf) was made into solution with conc. HCl. Cool this solution at 0-5° C. To this acidic solution 5ml of 20% sodium nitrite was added with continuous stirring. The reaction mixture was allowed to stand for half an hrs for completion of reaction. It was filtered through Buchner funnel and washed with water. Recrystalised with ethanol to form IIIa –IIIf.

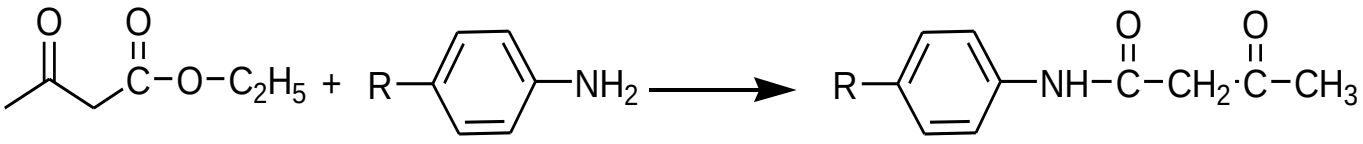
b) Benzoyl derivative of pyrazoles: 3-amino phenyl-5-methyl pyrazoles **(**IIa- IIf) of compound was mixed with NaOH solution .The reaction mixture was cooled on ice bath. Approximately 2ml Benzoyl Chloride was added drop wise and shake [21-22]. Allow the reaction mixture to settle down. Filter the mixture. Recrystallised with ethanol to form IVa – IVf.

Section D: Antimicrobial Activity:

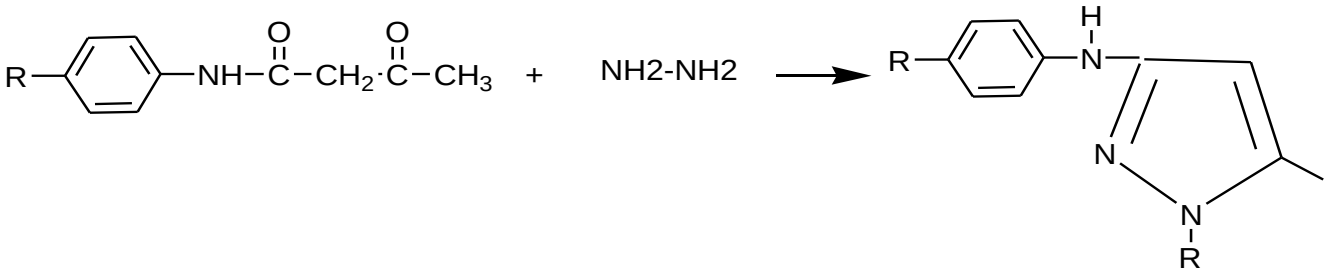
Preparation of sample: 0.001 g/ 1 mg 3-amino phenyl-5-methyl pyrazoles **(**IIa- IIf) was taken and dissolved in 1 ml of DMSO.

Preparation of inoculums: Stock cultures were maintained at 4^{o}C on slants of nutrient agar. Active cultures of experiment were prepared by transferring a loop full of cells from the stock cultures to test tube of Muller-Hinton broth (MHB) for bacteria that were incubated for 24 hrs at 37^{o}C.

Screening of Bacteria: The disk diffusion method was used for antimicrobial activity. The nutrient agar were poured in Petri plates and allowed it to solidify. The above prepared microbial culture was spread uniformly on the surface of the agar. The diffused disks of each sample are placed on the agar. Plates were then incubated at 37°C for 24hrs [23-24].



1-(N-phenyl-carboxamido)-propan-2-one
(Ia –If)



3-[2-Methoxy Phenyl amino] 5-Methyl Pyrazole
(IIa –IIf)

R= -OCH_3 at ortho, meta and para position
-OH at ortho, meta and para position

FIG. 1: REACTION SCHEME

RESULT AND DISCUSSION: Pyrazoles and substituted pyrazoles were important moiety present in most of the drugs and medicines. It shows good antimicrobial activity against gram positive and gram negative strains.

In present study3-amino phenyl-5-methyl pyrazoles **(**IIa- IIf) have been synthesised using different primary amines, acetoacetic ester and hydrazine hydrate by applying simple and green chemistry method and characterised them. These compounds have been synthesised in good yield.

(IIa): 3-[2-Methoxy Phenyl amino] 5-Methyl Pyrazole, $C_{11}H_{13}N_3O$, 210^0C, 74%, C= 64.72 (65.02), H= 6.13(6.40), N=18.95(20.68), O= 7.35 (7.88) **NMR** Ar-H=δ(7.71 to 7.74ppm), NH=δ (9.84ppm), CH_2= δ(3.33ppm),-CH_3=δ (2.60ppm), OCH_3=δ(3.31ppm) **IR** N-H Str.=3282.02 cm^{-1} C=N Str. =1532.51 cm^{-1} C-N Str. =1329.01 cm^{-1} N-N Str. = 1174 cm^{-1}

(IIb): 3-[3-Methoxy Phenyl amino] 5-Methyl Pyrazole, $C_{11}H_{13}N_3O$, 208^0C, 68%, C= 63.80 (65.02), H= 6.30(6.40), N=19.09(20.68), O= 7.48 (7.88) **NMR** Ar-H=δ(7.64 to 7.83ppm), NH=δ (9.81ppm), CH_2= δ(3.36ppm),-CH_3=δ (2.66ppm), OCH_3=δ(3.32ppm) IR N-H Str.=3272.42 cm^{-1} C=N Str. =1509.84 cm^{-1} C-N Str. =1310.51 cm^{-1} N-N Str. = 1116 cm^{-1}

(IIc): 3-[4-Methoxy Phenyl amino] 5-Methyl Pyrazole, $C_{11}H_{13}N_3O$, $>300^0$C, 82, C= 64.87 (65.02), H= 5.90(6.40), N=20.40(20.68), O= 6.79 (7.88) NMR Ar-H=δ(7.71 to 7.74ppm), NH=δ (9.88ppm), CH_2= δ(3.33ppm),-CH_3= δ (2.60ppm), OCH_3=δ(3.31ppm) IR N-H Str. =3304.20 cm^{-1} C=N Str. =1497.21 cm^{-1} C-N Str. =1304.11 cm^{-1} N-N Str. = 1204 cm^{-1}

(IId): 3-[2-hydroxy Phenyl amino] 5-Methyl Pyrazole, $C_{10}H_{11}N_3O$, 168^0C, 61%, C= 61.50 (63.49), H= 6.00(5.82), N=22.04(22.22), O= 8.32 (8.46) NMR Ar-H=δ(7.47 to 7.71ppm), NH=δ (9.68ppm), CH_2= δ(3.18ppm),-CH_3=δ(2.50ppm), OH=δ(11.28ppm) IR N-H Str.=3180.90 cm^{-1} C=N Str. =1650.80 cm^{-1} C-N Str. =1285.41 cm^{-1} N-N Str. = 1198 cm^{-1}

(IIe): 3-[3-hydroxy Phenyl amino] 5-Methyl Pyrazole, $C_{10}H_{11}N_3O$, $>300^0$C, 90%, C= 62.00 (63.49), H= 5.45(5.82), N=20.96(22.22), O= 8.12(8.46) NMR Ar-H=δ(7.47 to 6.71ppm), NH=δ (9.88ppm), CH_2= δ(3.33ppm),-CH_3=δ(2.52ppm), OH=δ(11.34ppm) IR N-H Str.=3234.20 cm^{-1} C=N Str. =1577.80 cm^{-1} C-N Str. =1322.48 cm^{-1} N-N Str. = 1212 cm^{-1}

(IIf): 3-[4-hydroxy Phenyl amino] 5-Methyl Pyrazole, $C_{10}H_{11}N_3O$, 156^0C, 85%, C= 61.87 (63.49), H= 5.73(5.82), N=21.54(22.22), O= 7.92 (8.46) NMR Ar-H=δ(7.21 to 7.52ppm), NH= δ(9.54ppm), CH_2= δ(3.12ppm),-CH_3=δ(2.45ppm), OH=δ(11.04ppm) IR N-H Str.=3374.12 cm^{-1} C=N Str. =1457.81 cm^{-1} C-N Str. =1298.45 cm^{-1} N-N Str. = 1204 cm^{-1}

3-amino phenyl-5-methyl pyrazoles **(IIa- IIf)** have free H-atom present at nitrogen atom, so its nitroso derivatives (**IIIa-IIIf):**

(IIIa) 3-[2-Methoxy Phenyl amino] 5-Methyl 1-Nitroso Pyrazole, $C_{11}H_{12}N_4O_2$, 216^0C, C= 56.56

(56.89), H= 5.02(5.17), N=24.00(24.13), O= 13.12(13.79) NMR Ar-H=δ(7.10 to 7.22ppm), NH=δ(9.34ppm), CH_2= δ(3.31ppm),-CH_3=δ (2.35ppm), OCH_3=δ(3.04ppm) IR N-H Str.= 3134.12 cm^{-1} C=N Str. =1523.81 cm^{-1} C-N Str. =1298.45 cm^{-1}N-N Str. = 1265 cm^{-1} N=O Str.= 1432cm-1

(IIIb) 3-[3-Methoxy Phenyl amino] 5-Methyl 1-Nitroso Pyrazole, $C_{11}H_{12}N_4O_2$, 220^{0}C, C= 55.87 (56.89), H= 5.13(5.17), N=23.72(24.13), O= 13.65 (13.79) NMR Ar-H=δ(7.18 to 7.32ppm), NH=δ (9.21ppm), CH_2= δ(3.28ppm),-CH_3=δ(2.48ppm), OCH_3=δ(3.18ppm)

(IIIc) 3-[4-Methoxy Phenyl amino] 5-Methyl 1-Nitroso Pyrazole, $C_{11}H_{12}N_4O_2$, 205^{0}C, C= 56.52 (56.89), H= 5.34(5.17), N=23.58(24.13), O= 12.94 (13.79) NMR Ar-H=δ(6.97 to 7.25ppm), NH=δ (9.07ppm), CH_2= δ(3.39ppm),-CH_3=δ (2.78ppm), OCH_3=δ(3.23ppm)

(IIId) 3-[2-hydroxy Phenyl amino] 5-Methyl 1-Nitroso Pyrazole, $C_{10}H_{10}N_4O_2$, 124^{0}C, C= 55.48 (55.04), H= 4.12(4.58), N=24.95(25.68), O= 14.34 (14.67) NMR Ar-H=δ(6.89 to 7.22ppm), NH=δ (9.30ppm), CH_2= δ(3.33ppm),-CH_3=δ (2.54ppm), OH =δ(11.71ppm) IR N-H Str.=3321.7 cm^{-1} C=N Str. =1603.84 cm^{-1} C-N Str. =1243.45 cm^{-1} N-N Str.=1207.65 cm^{-1} N=O Str.= 1444cm^{-1}

(IIIe) 3-[3-hydroxy Phenyl amino] 5-Methyl 1-Nitroso Pyrazole, $C_{10}H_{10}N_4O_2$, 196^{0}C, C= 54.59 (55.04), H= 4.47(4.58), N=25.09(25.68), O= 14.22 (14.67) NMR Ar-H=δ(7.13 to 7.24ppm), NH=δ (9.38ppm), CH_2= δ(3.38ppm),-CH_3=δ (2.41ppm), OH =δ(11.57ppm)

(IIIf) 3-[4-hydroxy Phenyl amino] 5-Methyl 1-Nitroso Pyrazole, $C_{10}H_{10}N_4O_2$, 164^{0}C, C= 54.09 (55.04), H= 4.24(4.58), N=24.65(25.68), O= 13.65 (14.67) NMR Ar-H=δ(7.04 to 7.18ppm), NH=δ (9.12ppm), CH_2= δ(3.22ppm),-CH_3=δ (2.61ppm), OH =δ(11.23ppm)

Benzoyl derivatives (IVa- IVf) were formed easily. These derivatives also having important place in medicinal chemistry.

(IVa) 3-[2-Methoxy Phenyl amino] 5-Methyl 1-Benzoyl Pyrazole, $C_{18}H_{17}N_3O_2$, 216^{0}C, C= 56.56 (56.89), H= 5.02(5.17), N=24.00(24.13), O= 13.12(13.79) NMR Ar-H=δ(7.50 to 7.92ppm), NH=δ (12.20ppm), CH_2= δ(3.82ppm),-CH_3=δ (2.50ppm), OCH_3=δ(3.31ppm)

IR N-H Str. = 3244.12 cm^{-1} C=N Str. =1493.65 cm^{-1} C-N Str. =1206.85 cm^{-1} N-N Str. = 1212 cm^{-1} C=O Str. = 1694cm-1

(IVb) 3-[3-Methoxy Phenyl amino] 5-Methyl 1-Benzoyl Pyrazole, $C_{18}H_{17}N_3O_2$, 220^{0}C, C= 55.87 (56.89), H= 5.13(5.17), N=23.72(24.13), O= 13.65 (13.79) NMR Ar-H=δ(6.78. to 7.28ppm), NH=δ (11.94ppm), CH_2= δ(3.45ppm),-CH_3=δ (2.34ppm), OCH_3=δ(3.28ppm)

(IVc) 3-[4-Methoxy Phenyl amino] 5-Methyl 1-Benzoyl Pyrazole, $C_{18}H_{17}N_3O_2$, 205^{0}C, C= 56.52 (56.89), H= 5.34(5.17), N=23.58(24.13), O= 12.94 (13.79) NMR Ar-H=δ(7.23 to 7.82ppm), NH=δ (12.43ppm), CH_2= δ(3.56ppm),-CH_3=δ (2.42ppm), OCH_3=δ(3.09ppm)

(IVd) 3-[2-hydroxy Phenyl amino] 5-Methyl 1-Benzoyl Pyrazole, $C_{17}H_{16}N_3O_2$, 124^{0}C, C= 55.48 (55.04), H= 4.12(4.58), N=24.95(25.68), O= 14.34 (14.67) NMR Ar-H=δ(7.54 to 7.91ppm), NH=δ (9.3ppm), CH_2= δ(3.28ppm),-CH_3=δ (2.37ppm), OH=δ(11.56ppm) IR N-H Str.=3334.12 cm^{-1} C=N Str. =1523.81 cm^{-1} C-N Str. =1273.5 cm^{-1} N-N Str. = 1208.67 cm^{-1} C=O Str.= 1639cm-1

(IVe) 3-[3-hydroxy Phenyl amino] 5-Methyl 1-Benzoyl Pyrazole, $C_{17}H_{16}N_3O_2$, 196^{0}C, C= 54.59 (55.04), H= 4.47(4.58), N=25.09(25.68), O= 14.22 (14.67) NMR Ar-H=δ(7.68 to 7.90ppm), NH=δ (9.4ppm), CH_2= δ(3.42ppm),-CH_3=δ (2.66ppm), OH=δ(11.91ppm)

(IVf) 3-[4-hydroxy Phenyl amino] 5-Methyl 1-Benzoyl Pyrazole, $C_{17}H_{16}N_3O_2$, 164^{0}C, C= 54.09 (55.04), H= 4.24(4.58), N=24.65(25.68), O= 13.65 (14.67) NMR Ar-H=δ(7.08 to 7.43ppm), NH=δ (8.7ppm), CH_2= δ(3.73ppm),-CH_3=δ (2.48ppm), OH=δ(11.62ppm).

Antimicrobial activity results of all synthesised compounds (IIa – IIf) shows satisfactory zone of inhibition and active against all the strains. Highest inhibition activities were seen with compounds IId and IIf for all the strains. Similarly compound IIa,

IIc and IIe showed good activity with *E.coli.* Results have been shown in **Table 1**.

TABLE 1`: RESULTS OF ANTIMICROBIAL ANALYSIS

Name of Organism	Zone of Inhibition in mm					
	IIa	IIb	IIc	IId	IIe	IIf
Eichersia coli	22	10	24	20	22	16
Salmonella typhi	-	16	20	22	-	22
Staphylococcus aureous	12	20	16	20	12	24
Bacillus subtilis	10	17	14	24	10	24
Klebsiella shigella	-	12	-	14	12	22

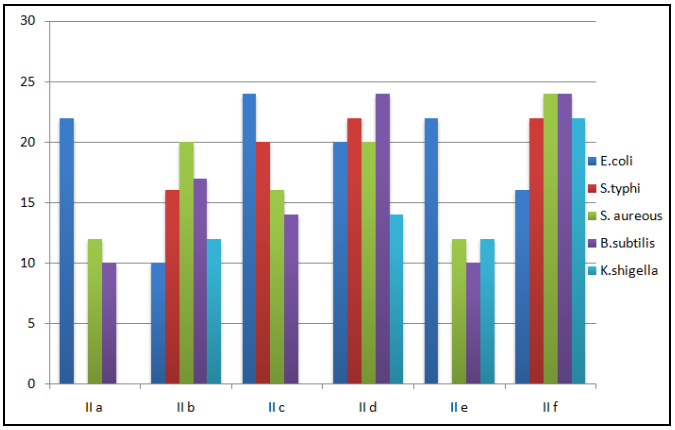


FIG. 2: ANTIMICROBIAL ACTIVITY OF COMPOUNDS WITH DIFFERENT ORGANISMS

CONCLUSION: In this study, we synthesised 3-amino phenyl-5-methyl pyrazoles and its nitroso and benzoyl derivatives by simple condensation method. All these compounds were ecofriendly, non-hazardous and biologically active. Antimicrobial results reveal that, these substituted pyrazoles were most useful in medicinal chemistry and further studies in pharmaceutical and microbiological studies.

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