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# One-pot multicomponent synthesis and antimicrobial evaluation of some novel pyrano-[*2,3-c*]- pyrazoles derivatives

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## ABSTRACT

*In the present communication a simple and efficient synthesis of some new Pyrano-[2,3-c]-Pyrazoles derivatives are described by the one-pot condensation of a mixture of 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one, substituted heterylaldehydes and malononitriles in Polyethylene glycol (PEG-400) as green reaction solvent, The chemical structure of the compounds was confirmed by IR,[1]H NMR and Mass spectral data. All the compounds of the series screened for their antimicrobial activity studies. The result revealed that most of the compounds showed good to moderate antimicrobial activity.*

**Key words:** Polyethylene glycol (PEG-400), 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one, Malononitrile, substituted heterylaldehydes and antimicrobial activity.

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## INTRODUCTION

Pyrano-Pyrazoles derivatives have occupied a unique position in medicinal chemistry due to their biological activities like analgesic, antipyretic, bacteriostatic, bactericidal and fungicidal activities [1-3]. Pyrazole and its synthetic analogues have been found to exhibit industrial, agricultural and some biological application [4-8]. The ring system plays an important role in many biological processes, and many therapeutic agents contain pyrazole moiety. For example some alkyl, aryl substituted pyrazoles have pronounced sedative action on the central nervous system [9]. These findings prompted us to prepare some new Pyrano-Pyrazoles derivatives and screen them for their antifungal activity. By knowing the chemical and pharmacological importance's of Pyrazoles derivatives it was planned to synthesize some novel Pyrano-Pyrazoles derivatives under the frame of green chemistry. In recent years, polyethylene glycol (PEG-400) prompted reactions [10-13] have attracted the attention of organic chemists due to their solvating

ability and aptitude to act as a phase transfer catalyst, negligible vapor pressure and easy recyclability, ease of work-up, eco-friendly nature and economical cost. PEG is non-toxic, non-halogenated, inexpensive potentially recyclable and water soluble which facilitate its removal from reaction product.

## MATERIALS AND METHODS

All the melting points were uncorrected and determined in an open capillary tube. The chemicals and solvents used were of laboratory grade and were purified. Completion of the reaction was monitored by thin layer chromatography on precoated sheets of silica gel-G (Merck, Germany) using iodine vapour for detection. IR spectra were recorded in KBr on a Shimadzu spectrometer (Japan). $^1$H NMR spectra were recorded in DMSO-*d6* with an Avance spectrometer (Bruker, Germany) at 300-MHz frequency using TMS as an internal standard. Mass spectra were recorded on an EI-Shimadzu QP 2010 PLUS GC-MS system (Shimadzu, Japan). Elemental analyses were performed on a Carlo Erba 106 Perkin-Elmer model 240 analyzer (Perkin-Elmer, USA).

**General procedure for preparation of substituted Pyrano-Pyrazoles derivatives:**

An equimolar mixture of 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (1 mmol), substituted heterylaldehydes (1 mmol), and malononitrile (1 mmol), was stirred in PEG-400 (15 mL) at 40°C for 2 hours. After completion of the reaction (monitored by TLC), the crude mixture was worked up in ice-cold water (100 mL). The product which separated out was filtered. The filtrate was evaporated to remove water leaving PEG behind. The same PEG was utilized to synthesize further derivatives.

**Spectroscopic data of selected compounds:**

**4a.6-amino-4-(3-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-1,4-dihydro-3-methylpyrano[2,3-c]pyrazole-5-carbonitrile.**

IR (KBr): 3350,3158,2215,1640,1535; $^1$H NMR (DMSO-*d6*): δ 2.13(s, 3H, $CH_3$), δ3.45(s,3H –$OCH_3$) δ5.41(brs, 2H –$NH_2$), δ6.9-7.89(m,15H, Ar-H+1H of pyranoring) M.S. (m/z): 500[M+]; Anal.Calcd for $C_{30}H_{24}O_2N_6$: C, 71.98; H, 4.83; N, 16.79 %. Found: C, 71.85; H, 4.76; N, 16.68%.

**4b.6-amino-4-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-1,4-dihydro-3-methylpyrano[2,3-c]pyrazole-5-carbonitrile.**

IR (KBr): 3365,3150,2210,1648,1532,786; $^1$H NMR (DMSO-*d6*): δ 2.10(s, 3H, $CH_3$), δ5.38(brs, 2H –$NH_2$), δ7.06-7.98(m,15H,Ar-H+1H of pyranoring) M.S. (m/z): 504[M+]; Anal.Calcd for $C_{29}H_{21}ClN_6O$: C, 68.98; H, 4.19; N, 16.64 %. Found: C, 68.92; H, 4.06; N, 16.72%.

**4c.6-amino-4-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-1,4-dihydro-3-methylpyrano[2,3-c]pyrazole-5-carbonitrile.**

IR (KBr): 3326,3165,2218,1665,1530,774; $^1$H NMR (DMSO-*d6*): δ 2.11(s, 3H, $CH_3$), δ5.40(brs, 2H –$NH_2$), δ7.15-7.80(m,15H,Ar-H+1H of pyranoring) M.S. (m/z): 488[M+]; Anal.Calcd for $C_{29}H_{21}FN_6O$: C, 71.30; H, 4.33; N, 17.20 %. Found: C, 71.18; H, 4.26; N, 17.12%.

**4d.6-amino-4-(3-(4-hydroxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-1,4-dihydro-3-methylpyrano[2,3-c]pyrazole-5-carbonitrile.**

IR (KBr): 3340,3039,2216,1645,1530; $^1$H NMR (DMSO-*d6*): δ 2.10(s, 3H, $CH_3$), δ5.38(brs, 2H –$NH_2$), δ7.05-7.89(m,15H,Ar-H+1H of pyranoring) M.S. (m/z): 486[M+]; Anal.Calcd for $C_{29}H_{22}N_6O_2$: C, 71.59; H, 4.56; N, 17.27 %. Found: C, 71.52; H, 4.48; N, 17.16%.

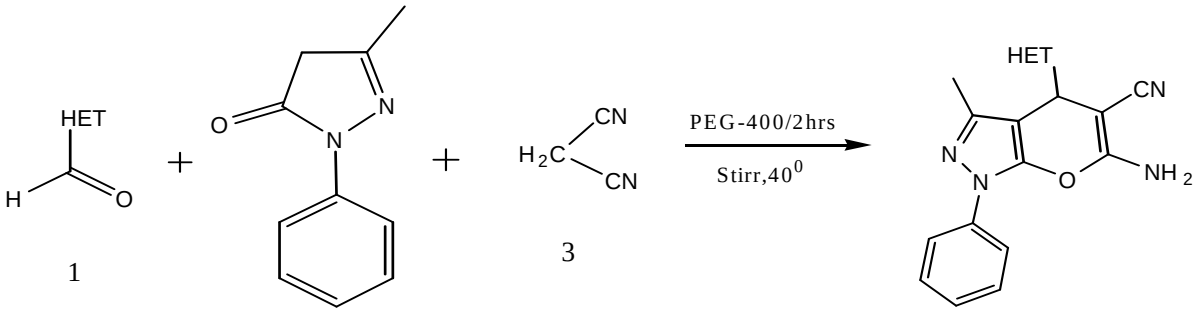
**4e.6-amino-4-(3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)-1,4-dihydro-3-methylpyrano[2,3-c]pyrazole-5-carbonitrile.**
IR (KBr): 3356,3085,2210,1642,1525,768; $^1$H NMR (DMSO-*d6*): δ 2.12(s, 3H, $CH_3$), δ5.45(brs, 2H $-NH_2$), δ7.05-8.15(m,15H,Ar-H+1H of pyranoring) M.S. (m/z): 515[M+]; Anal.Calcd for $C_{29}H_{21}N_7O_3$: C, 67.56; H, 4.11; N, 19.02 %. Found: C, 67.48; H, 4.06; N, 18.86%.

## RESULTS AND DISCUSSION

As part of our research programme, and in continuation of our work on the development of environmentally friendly methodologies using polyethylene glycol (PEG-400) as a reaction solvent for the preparation of biologically active compounds [14-16], herein we report an efficient synthesis of Pyrano-Pyrazoles derivatives. The one-pot condensation of substituted heterylaldehyde **(1)** 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one **(2)** and malononitrile **(3)** in polyethylene glycol (PEG-400) as reaction solvent to afford the corresponding Pyrano-Pyrazoles derivatives **4(a-h)** (Scheme-1) in good yield. The newly synthesized compounds were evaluated for their antibacterial and antifungal activity. The substitution of pyrazole, pyrano moiety attached to the further pyrazole, ring emerged as active in both antibacterial and antifungal evaluation and found to be excellent yield. The newly synthesized compounds confirmed by the spectral analysis.

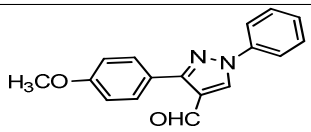
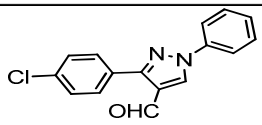
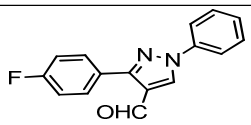
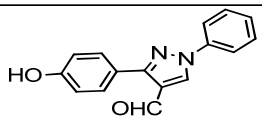
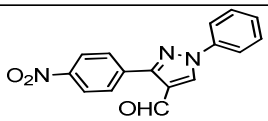
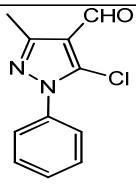
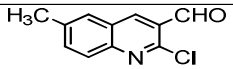
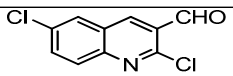
**Microbiology :**
The antimicrobial activities of the synthesized compounds **4(a-h)** were determined by agar diffusion method.[17] The compounds were evaluated for antibacterial activity against *Escherichia coli (MTCC 2939) St – Salmonella typhi (MTCC 98),Sa – Staphylococcus aureus (MTCC 96),Bs – Bacillus subtilis (MTCC 441.* The antifungal activity was studied against

*An – Aspergillus niger* (*MTCC 281*), and *Penicillium chrysogenum (MTCC 160)and Candida albicans (MTCC 183).* The antibiotic Penicillin (10 µg/mL) was used as reference drug for both antibacterial and antifungal activity for comparison. Dimethyl Sulphoxide (1%, DMSO) was used a control. The culture strains of bacteria were maintained on nutrient agar slant at 37±0.5 °C for 24 h. The antibacterial activity was evaluated using nutrient agar plate seeded with 0.1 mL of respective bacterial culture strain suspension prepared in sterile saline (0.85%) of 105 CFU/mL dilutions. The wells of 6 mm diameter were filled with 0.1 mL of compound solution at fixed concentration 10 µg/mL separately for each bacterial strain. All the plates were incubated at 37±0.5 °C for 24 h. Zone of inhibition of compounds in mm were noted. For antifungal activity, all the culture strains of fungi maintained on potato dextrose agar (PDA) slant at 27±0.2°C for 24-48 hrs, till sporulation. Spore of strains were transferred in to 5 mL of sterile distilled water containing 1% Tween-80 (to suspend the spore properly). The spores were counted by haemocytometer (106 CFU/mL). Sterile PDA plate was prepared containing 2% agar; 0.1 mL of each fungal spore suspension was spread on each plate and incubated at 27±0.2 °C for 12 hrs. After incubation well prepared using sterile cork borer and each agar well was filled with 0.1 mL of compound solution at fixed concentration 10 µg/mL. The plates were kept in refrigerator for 20 minutes for diffusion and then incubated at 27±0.2 °C for 24-28 hrs. After incubation, zone of inhibition of compounds were measured in mm, along with standard.




SCHEME-I

**Table-1: Physical data of Pyrano-Pyrazoles derivatives derivatives 4(a-h)**

| ENTRY | PRODUCT | HET | YIELDS (%) | TIME (min) | M.P (℃) |
|---|---|---|---|---|---|
| 1. | 4a |  | 86 | 90 | 145 |
| 2. | 4b |  | 90 | 85 | 160 |
| 3. | 4c |  | 85 | 100 | 168 |
| 4. | 4d |  | 82 | 110 | 156 |
| 5. | 4e |  | 86 | 95 | 148 |
| 6. | 4f |  | 88 | 92 | 140 |
| 7. | 4g |  | 80 | 98 | 150 |
| 8. | 4h |  | 83 | 106 | 158 |

The results of antimicrobial data are summarized in Table-2. In comparison with standard antibacterial penicillin, compounds **4b**, **4d**, found to be active against *Escherichia coli* (*MTCC 2939).* Compounds **4d**, **4e**, were also found to be active against *Staphylococcus aureus (MTCC 96)* Compounds **4a**, **4d**, **4g** showed good activity comparatively active against *Bacillus subtilis (MTCC 441).* As compared with standard antibacterial compounds **4a**, **4d**, **4e** were observed as active against *Salmonella typhi (MTCC 98)* On the other hand, compound **4c**, **4f**, **4h** were found to be reduced growth activity against *Aspergillus niger* (*MTCC 281*). Compounds **4d**, **4f** and **4h** were observed no fungal growth against *Candida albicans (MTCC 183).* Compounds **4a**, **4c**, **4e**, **4h** found to be reduced growth activity against *Penicillium chrysogenum(MTCC 160)*

**Table-2: The antimicrobial data of the synthesized novel Pyrano-[2,3-c]- Pyrazoles derivatives.**

| | Bacteria (Zone of inhibition in mm) | | | | Fungi (Growth) | | |
|---|---|---|---|---|---|---|---|
| Product | Ec | St | Sa | Bs | An | Ca | Pc |
| 4a | 12 | 14 | -- | 12 | +ve | +ve | RD |
| 4b | 13 | 12 | 10 | 11 | +ve | RD | -ve |
| 4c | 09 | 08 | 13 | 11 | RD | +ve | RD |
| 4d | 15 | 14 | 14 | 12 | +ve | -ve | +ve |
| 4e | 11 | 13 | 16 | O8 | +ve | RD | RD |
| 4f | 10 | 12 | 10 | 09 | RD | -ve | -ve |
| 4g | 12 | 11 | 07 | 12 | +ve | RD | +ve |
| 4h | 11 | 10 | 12 | 06 | RD | -ve | RD |
| Penicillin | 16 | 15 | 18 | 14 | NA | NA | NA |
| Nystatin | NA | NA | NA | NA | -ve | -ve | -ve |

.a Solvents: DMSO, water, *Escherichia coli (MTCC2939) St – Salmonella typhi (MTCC 98),Sa – Staphylococcus aureus (MTCC 96),Bs – Bacillus subtilis (MTCC 441), An – Aspergillus niger (MTCC 281),* and *Penicillium chrysogenum (MTCC 160), Candida albicans (MTCC 183).* -ve-No growth; +ve-Growth of fungi; RDReduced growth; NA-Not Applicable

## CONCLUSION

In summary, we have described a simple method for the synthesis of Substituted novel Pyrano-[2,3-c]- Pyrazoles derivatives. The newly synthesized compounds were confirmed by the spectral analysis and further evaluated for their antimicrobial activity. The antibacterial and antifungal activity revealed that most of the compounds showed moderate to good activity. The substitution presence of heteryl aldehydes with its Para position halo groups i.e.-Cl,F and pyrazolone aldehydes with its 2$^{nd}$ position of halo groups have emerged as active in both antibacterial and antifungal screening.

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