



Synthesis, Structural Elucidation, Spectral Studies and Antimicrobial Activity of Pyrano-Pyrazole Derivatives

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ABSTRACT

The emergence of multidrug-resistant pathogens have posed a major challenge to the treatment strategies for infectious diseases. In this study, a panel of eight novel pyrano-pyrazole heterocyclic moiety were prepared by multi-component one-pot reactions. In the first step Pyrano-pyrazole moiety prepared by single pot multicomponent condensation of Ethyl 3-oxobutanoate, pyridine-4-carbohydrazide, Propanedinitrile, and substituted benzaldehydes. In the second step above synthesized pyrano-pyrazole derivative react with different substituted phenyl amino-acetyl chloride derivative to give final compound. All the compounds were obtained in reasonable yields bearing their characteristic structure as inferred from the spectral analysis. All the synthesized compounds were screened for antimicrobial activity. Product B-1, B-5 and B-8 is found to have remarkable antibacterial activity. Products B-4 and B-7 are moderately active and compound B-5 and B-6 are found to have remarkable Antifungal activity.

Keywords: Synthesis, Spectral, Pyrazole, Antimicrobial activity, Derivatives.

INTRODUCTION

The Pyrano-pyrazole moiety is a fascinating template in the pharmaceutical industry, and it is responsible for the molecule's vast range of biological activity. Compound containing pyrano-pyrazole moiety can act as antimicrobial¹, analgesic², vasodilator³, anticancer⁴, anti-inflammatory⁵, inhibitors of human Chk1 kinase⁶, antifungicidal⁷ and also as

biodegradable agrochemicals⁸. Different methods of one pot multicomponent reactions (MCRs) known for the preparation of pyrano [2,3-c] pyrazole structures, either in two-, three-, or four-component reactions⁹⁻¹⁴.

In this study, we aimed to synthesis the substituted pyrano-pyrazole derivatives having biological activity as anti-bacterial and anti-fungal activities.



EXPERIMENTAL

Materials

All the compounds were synthesized using a high purity grade chemical, reagents, and solvents purchased from S. D. Fine chem and Merck Chemical Co. Aluminum precoated sheets (Merck Kieselgel 60 GF254) were used for TLC, which was observed using an ultraviolet lamp (254 and 365 nm).

Instrumentation

Melting point observed by a Veergo Melting point Instrument sand uncorrected. ¹H NMR spectral data was obtained through Bruker (300 MHz) spectrophotometer at Sophisticated Analytical Instrumentation Facility (SAIF), Punjab. Mass spectra recorded with Waters Micromass and Fourier Transform Infrared spectroscopy was measured on Shimadzu Spectrophotometer.

Procedure

PART-A: [6-Amino-4-(4-chloro-phenyl)-5-cyano-3-methyl-4H-pyrano[2,3-c]pyrazol-1-yl]-pyridin-4-yl-methanone

A mixture of P-chloro aldehyde (0.01M), pyridine-4-carbohydrazide(0.01M), Ethyl 3-oxobutanoate (0.01M), Propanedinitrile (0.01M) and sodium benzoate (5 mol%) was stirred in absolute Ethanol (10 mL) for 5-10 min at room temperature. After getting the solid, the crude product was filtered using Whatman filter paper. Pure product was obtained by recrystallizing the crude product from ethanol.

PART-B: (substituted phenyl amino)-acetyl chloride

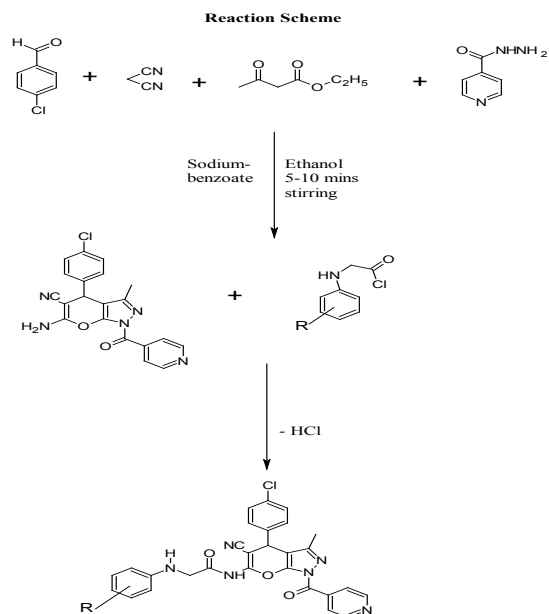
4-nitro-aniline (0.01M) was dissolved in glacial acetic (15 mL) containing 15 mL of saturated solution of sodium acetate. If substance not dissolved completely, the mixture was then warmed at 60 to 70°C in water bath and subsequently it was cooled in ice-bath with continuous stirring. To avoid vigorous reaction, Chloro acetyl chloride (1 mL) was added drop wise. The white product was separated out and filtered after 30 minutes. The yield was washed with cooled H₂O and was purify by recrystallization from ethanol.

PART-C: N-[4-(4-Chloro-phenyl)-5-cyano-3-methyl-1-(pyridine-4-carbonyl)-1,4-dihydro-pyrano [2,3-c]pyrazol-6-yl]-2-(substituted phenylamino)-acetamide

A mixture of products from Part-A (0.04M) and Part-B (0.04M) was taken in 25 mL of absolute

alcohol and refluxed for 4 h at 65 to 70°C. TLC was used to monitor the reaction's conclusion. The reaction mass was put into pieces of ice and filtered when it was finished.

To get the pure yield, the product was purify with recrystallization from hot ethanol.



Mechanism

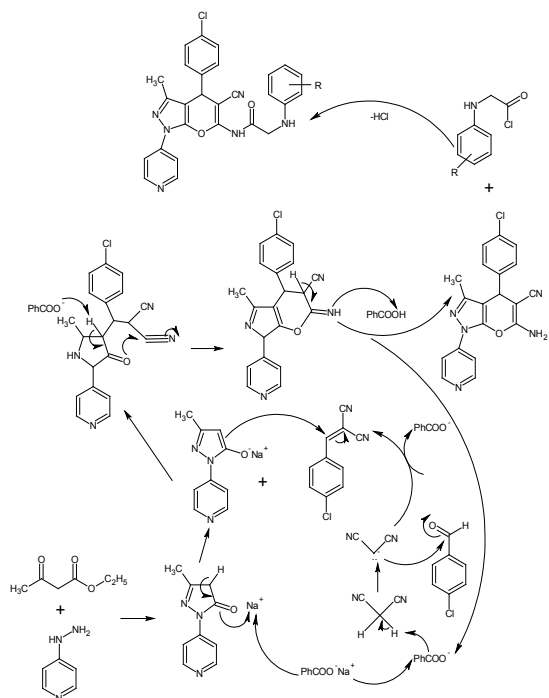


Table 1: Structure of all final synthesized compounds

Compound B1	
Compound B2	
Compound B3	
Compound B4	
Compound B5	
Compound B6	
Compound B7	
Compound B8	

Compound B1-

Yield B1 got as solid (69%). Melting Point 125.6. Ft-IR spectra, ν , cm^{-1} : 1426, 1623 (C=C str. Aromatic), 3034 (C-H Aromatic), 1684, 1726 (Ar-C=O, C=O), 2242 (CN), 3379 (N-H), 1495 (-CH₂), 3034 (-CH₃), 1523 (-NO₂), 742 (-Cl).

PMR(300 MHz, DMSO):2.54 (s, 3H), 3.42

(s, 2H), 4.21(s, 1H), 4.61(s, 1H), 7.39 to 8.44 (m, 13H), 8.51 (s, 1H). $m/z=569.96$. Anal. Calc. (%) for C₂₈H₂₀ClN₅O₅ C 59.00, H 3.54. N 17.20 Instrument Value C 58.99, H 3.51, N 17.19.

Compound B2 -

Yield B2 got as solid (66%). Melting Point 135.9. Ft-IR spectra, ν , cm^{-1} : 1431, 1634 (C=C str. Aromatic), 3039 (C-H Aromatic), 1690,1728 (Ar-C=O, C=O), 2248 (CN), 3384 (N-H), 1499(-CH₂), 3029 (-CH₃), 1534 (-NO₂), 748 (-Cl).

PMR (300 MHz, DMSO):2.35 (s, 3H), 3.63 (s, 2H), 4.29 (s, 1H), 4.68(s, 1H), 7.44 to 8.99 (m, 13H), 8.45 (s, 1H). $m/z=569.96$. Anal. Calc. (%) for C₂₈H₂₀ClN₅O₅ C 59.00, H 3.92. N 17.27 Instrument Value C 58.99, H 3.90, N 17.26.

Compound B3 -

Yield B3 got as solid (66%). Melting Point 139.8 Ft-IR spectra, ν , cm^{-1} : 1419, 1633 (C=C str. Aromatic), 3038 (C-H Aromatic), 1674,1729 (Ar-C=O, C=O), 2252 (CN), 3383 (N-H), 1479 (-CH₂), 3044 (-CH₃), 785 (-Cl).

PMR(300 MHz, DMSO):2.59 (s, 3H), 3.48 (s, 2H), 4.29 (s, 1H), 4.73(s, 1H), 7.45 to 8.88 (m, 13H), 8.65 (s, 1H). $m/z=559.40$, Analytical Calculation (%) C₂₈H₂₂Cl₂N₆O₃ C 60.12, H 3.60. N 15.02 Instrument value C 60.10, H 3.58, N 14.99.

Compound B4 -

Yield B4 was got as solid (71%). Melting Point 143.8. Ft-IR spectra, ν , cm^{-1} : 1418, 1638 (C=C str. Aromatic), 3053 (C-H Aromatic), 1699,1739 (Ar-C=O, C=O), 2263 (CN), 3364 (N-H), 1488 (-CH₂), 3039 (-CH₃), 1530 (-NO₂), 746 (-Cl).

PMR (300 MHz, DMSO) : 2.67 (s, 3H), 3.31 (s, 2H), 4.11(s, 1H), 4.55(s, 1H), 7.49 to 8.91 (m, 13H), 8.66 (s, 1H). $m/z=569.96$. Anal. Calc. (%) for C₂₈H₂₀ClN₅O₅ C 59.00, H 3.54. N 17.20 Found C 58.98, H 3.52, N 17.17.

Compound B5 -

Yield B5 was got as solid (63 %). Melting Point 110.5. Ft-IR spectra, ν , cm^{-1} : 1446, 1635 (C=C str. Aromatic), 3039 (C-H Aromatic), 1689,1741 (Ar-C=O, C=O), 2235 (CN), 3366 (N-H), 1489 (-CH₂), 3039 (-CH₃), 749 (-Cl). ¹H NMR (300 MHz, DMSO) : 2.34 (s, 3H), 3.48 (s, 2H), 4.23 (s, 1H), 4.66 (s, 1H), 7.35

to 8.49 (m, 13H), 8.55 (s, 1H). $m/z=538.98$, Analytical Calculation (%) for $C_{29}H_{23}ClN_6O_3$ C 64.62, H 4.30. N 15.59. Instrument Value C 64.59, H 4.29, N 15.58.

Compound B6 -

Yield B6 was got as solid (70 %). Melting Point 125.7. Ft-IR spectra, ν, cm^{-1} : 1429, 1625 (C=C str. Aromatic), 3033 (C-H Aromatic), 1682, 1728 (Ar-C=O, C=O), 2245 (CN), 3381 (N-H), 1498 (-CH₂), 2968 (-CH₃), 745 (-Cl).

PMR(300 MHz, DMSO):2.52 (s, 3H), 3.44 (s, 2H), 4.23 (s, 1H), 4.65(s, 1H), 7.40 to 8.43 (m, 13H), 8.49 (s, 1H). $m/z=538.98$, Analytical Calculation (%) for $C_{29}H_{23}ClN_6O_3$ C 64.62, H 4.30. N 15.59 Instrument Value C 64.60, H 4.28, N 15.56.

Compound B7 -

Yield, B7 was got as solid (64 %). Melting Point 113.2. Ft-IR spectrum, ν, cm^{-1} : 1427, 1638 (C=C str. Aromatic), 3038 (C-H Aromatic), 1685, 1729 (Ar-C=O, C=O), 2249 (CN), 3372 (N-H), 1499 (-CH₂), 2925 (-CH₃), 745 (-Cl).

PMR(300 MHz, DMSO):2.58 (s, 3H), 3.45 (s, 2H), 4.25 (s, 1H), 4.66 (s, 1H), 7.44 to 8.49 (m, 13H), 8.55 (s, 1H). $m/z=538.98$, Analytical Calculation (%) for $C_{29}H_{23}ClN_6O_3$ C 64.62, H 4.30. N 15.59 Instrument Value C 64.61, H 4.28, N 15.57.

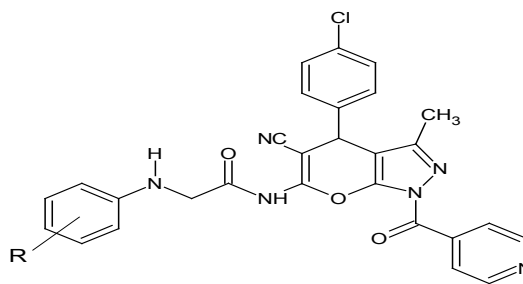
Compound B8 -

Yield B8 got as solid (65 %). Melting Point

161.8. Ft-IR spectrav, cm^{-1} : 1427, 1622 (C=C str. Aromatic), 3033 (C-H Aromatic), 1685, 1725 (Ar-C=O, C=O), 2244 (CN), 3384 (N-H), 1497(-CH₂), 3038 (-CH₃), 747 (-Cl). PMR (300 MHz, DMSO) : 2.59 (s, 3H), 3.46(s, 2H), 4.25 (s, 1H), 4.66 (s, 1H), 7.44 to 8.54 (m, 13H), 8.55 (s, 1H). $m/z=524.96$, Analytical Calculation (%) for $C_{28}H_{21}ClN_6O_3$ C 64.06, H 4.03. N 16.01 Instrument Value C 64.02, H 4.01, N 16.00.

RESULTS AND DISCUSSION

First synthesis of [2,3-c]pyrazole type derivatives were prepared by Gein *et al.*, via one-pot reaction manners¹⁵. In Present work, one-pot design of pyrano[2,3-c]pyrazole derivatives through MCR of Ethyl 3-oxobutanoate, pyridine-4-carbohydrazide, Propanedinitrile, and substituted benzaldehydes. Here, we performed antimicrobial study of synthesized pyrano[2,3-c]pyrazoleheterocyclic derivatives.



Where R=Ortho Nitro, Meta Nitro, Pera Nitro, Ortho Methyl, Meta Methyl, Pera Methyl, PeraChloro, Hydrogen

Table 2: Antibacterial activity of synthesized compounds

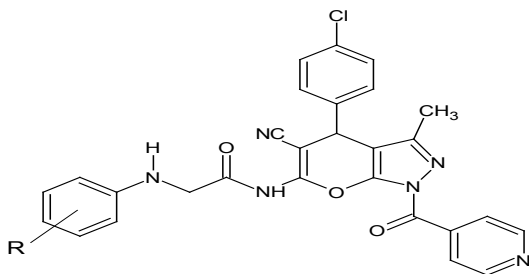
Compound	Gram+ve		Gram-ve	
	MTCC 96 <i>S. aureus</i>	MTCC 442 <i>S. pyogenus</i>	MTCC 433 <i>E. coli</i>	MTCC 1688 <i>P. aeruginosa</i>
B-1	100	62.5	125	125
B-2	250	500	250	200
B-3	250	250	250	250
B-4	125	200	125	100
B-5	62.5	200	50	100
B-6	125	250	250	500
B-7	250	100	100	125
B-8	50	100	62.5	25

Antibacterial activity

Antibacterial activity shown that compound B-1 is good active against *S. pyogenus*. B-5 is good active against *S. aures* and *E. coli* and B-8 is good active against *S. aureus*, *E. coli* and very good activity on *P. aeruginosa*.

Antifungal activity

Antifungal activity shown that Product B-4 and B-7 are moderately reactive against *C. albicans*. Product B-6 is better reactive against *C. albicans*, *A. niger* and compound B-5 good active against *A. clavatus*.



Where R=2-Nitro, 3-Nitro, 4-Nitro, 2-Methyl, 3-Methyl, 4-Methyl, 4-Chloro, Hydrogen

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Conflicts of Interests

The authors declare that there are no conflict of interest regarding this research paper.

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