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Synthesis, Characterization and Antimicrobial activity of Substituted Pyrazole based Heterocyclic compounds

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ABSTRACT

In the present study, a series of substituted pyrazole were synthesized from chalcones. The substituted pyrazole prepared from chalcones with substituted phenylhydrazine in acetic acid. The synthesized compounds were characterized by IR, ^{1}H and ^{13}C NMR and elemental analysis studies. The antimicrobial activity of all the compounds (CP01-CP04) showed significant activity against the selected bacteria and fungus used.

Key words: Chalcones, Furfural, Substituted Phenylhydrazine, Antimicrobial activity.

INTRODUCTION

Heterocyclic compounds are important to human life because their structural subunits exist in many natural products such as vitamins, hormones, antibiotics and pigments [1,2]. Pyrazoles are five member ring heterocyclic compounds having some structural features with two nitrogen atoms in adjacent position [3]. The best described property of almost are pyrazoles is in the treatment of inflammation and inflammation associated disorder, such as arthritis [4]. Pyrazole derivatives are the subject of many research studies due to their widespread potential biological activities such as antimicrobial [5, 6], antiviral [7], antioxidant [8], antitumor [9,10] , antihistaminic [11], antidepressant [12] and fungicides [13]. Several pyrazole derivatives have been found to possess significant activities such as ACE-inhibitor [14], anttiproliferative [15], anti-inflammatory [16] and antiprotozoal [17, 18] which render them valuable active ingredients of medicine and plant protecting agents. Further current literature indicates 1,2 -pyrazole derivatives to possess diverse biological activities [19]. These compounds are useful in the field of medicine and are used as a starting material for the synthesis of new drugs [20-29].

In view of these data we have undertaken the synthesis, characterization and antimicrobial evaluation of substituted pyrazoles. All the synthesized compounds were characterized on the basis of IR, ^{1}H & ^{13}C NMR spectral data and elemental analysis. The physical data of titled compounds are summarized and presented in the result and discussion part.

MATERIALS AND METHODS

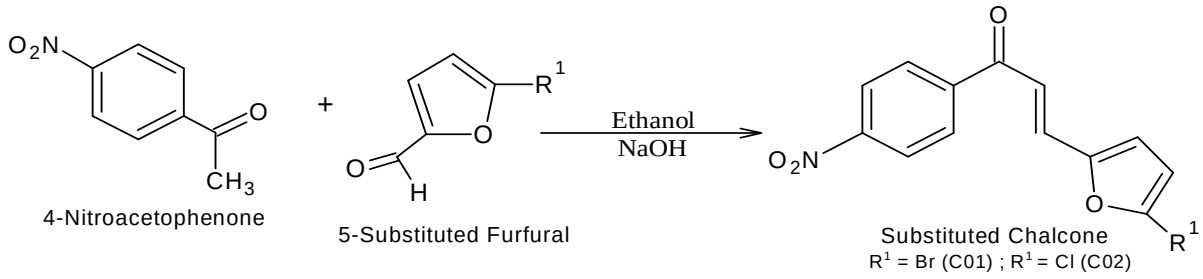
The melting points were carried out in the open capillary tube and were uncorrected. Thin layer chromatography was performed using silica gel coated on a glass plate and spots were visualized by exposure to iodine vapour. IR spectra of compounds were scanned on Shimadzu IR spectrophotometer using KBr disc and expressed in cm^{-1}. ^{1}H

and ^{13}C NMR spectra were recorded in DMSO-D_6 on BRUKER (400MHz) spectrometer using TMS as an internal standard (chemical shifts in δ, ppm). The elemental analysis for C, H, and N were in an agreement with the calculated values. The synthesis of the targeted compound was accomplished according to the reaction sequence illustrated in Scheme – 1 and Scheme – 2.

General method for Synthesis of chalcone

Synthesis of 3-(5-Bromofuran-2-yl)-1-(4-nitrophenyl)prop-2-en-1-one (C01)

A mixture of 4-nitroacetophenone (0.01 mol) and 5-bromofurfural (0.01 mol) is dissolved in ethanolic NaOH (20ml) was stirred for about 3 h with a mechanical stirrer and kept in a refrigerator for 24 h. The content is poured into crushed ice and acidified with HCl. The product formed was filtered washed with water and recrystallized from ethanol to give compound **C01.** Same procedure was adapted to synthesis compound **C02** from 5-Chlorofurfural.

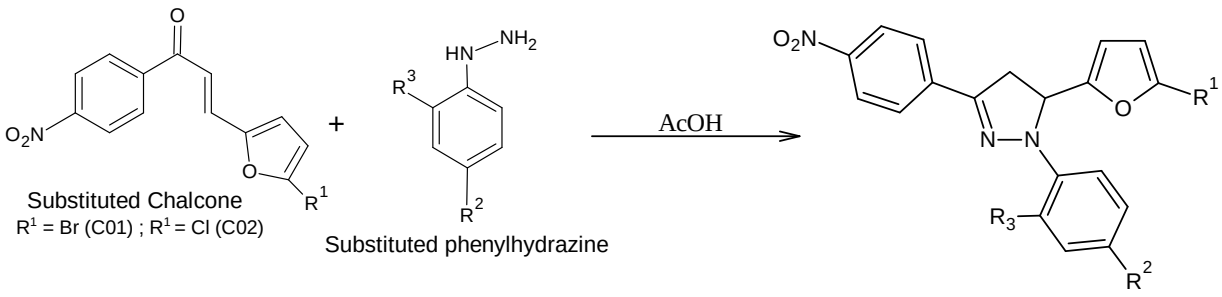


Scheme –1

Synthesis of substituted pyrazole

5-(5-Bromofuran-2-yl)-1,3-bis(4-nitrophenyl)-4,5-dihydro-1*H*-pyrazole (CP01)

A mixture of 3-(5-Bromofuran-2-yl)-1-(4-nitrophenyl)prop-2-en-1-one (0.005mol), 4-Nitrophenylhydrazine (0.005mol) and 25ml of glacial acetic acid was heated under reflux for 4 h, then the mixture was poured in to ice water(100ml). The precipitate obtained was filtered washed with water and recrystallized from absolute ethanol. Similarly other compounds **CP02–CP04** were synthesized using the same procedure.



Comp Code	R^1	R^2	R^3
CP01	Br	NO_2	H
CP02	Cl	NO_2	H
CP03	Br	NO_2	NO_2
CP04	Cl	NO_2	NO_2

Scheme – 2

RESULTS AND DISCUSSION

Synthesis of substituted chalcone was obtained by the scheme –1 and Synthesis of substituted pyrazole was obtained by the scheme –2. The required starting material substituted chalcone **(C01, C02)** was synthesed from 4-

Nitroacetophenone which on further treatment with 4-Nitrophenylhydrazine and 2,4-Dinitrophenylhydrazine yielded the substituted pyrazole **(CP01-CP04)**. Compounds were characterized by IR, ^{1}H and ^{13}C NMR spectral data.

3-(5-Bromofuran-2-yl)-1-(4-nitrophenyl)prop-2-en-1-one; (C01):
m.p**:** 204^{0}C**;** IR (KBr) λ_{max} in cm^{-1}: 3093 (aromatic C-H str), 2885 (aliphatic C-H str), 1728 (C=O), 1612 (aromatic C=C), 1427 (aliphatic C=C str), 1350 (NO_2 str); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 4.530 (d, 1H, aliphatic C-H), 4.329 (d, 1H, aliphatic C-H), 8.656-6.858 (m, 6H, Ar-H); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 187 (C=O), 148-121 (Ar-H, & HC=CH); Anal. Found: C, 64.96; H, 3.07; N, 7.21 (%). Calc. for ($C_{13}H_8BrNO_4$): C, 64.98; H, 3.09; N, 7.22 (%).

3-(5-Chlorofuran-2-yl)-1-(4-nitrophenyl)prop-2-en-1-one; (C02):
m.p**:** 198^{0}C**;** IR (KBr) λ_{max} in cm^{-1}: 3078 (aromatic C-H str), 2823 (aliphatic C-H str), 1722 (C=O), 1597 (aromatic C=C), 1496 (aliphatic C=C str), 1342 (NO_2 str); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 4.531(d, 1H, aliphatic C-H), 4.330 (d, 1H, aliphatic C-H), 8.637-6.858 (m, 6H, Ar-H); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 188 (C=O), 149-121 (Ar-H, & HC=CH); Anal. Found: C, 56.27; H, 2.94; N, 5.08 (%). Calc. for ($C_{13}H_8ClNO_4$): C, 56.23; H, 2.90; N, 5.04 (%).

5-(5-Bromofuran-2-yl)-1,3-bis(4-nitrophenyl)-4,5-dihydro-1*H*-pyrazole; (CP01):
m.p**:** 203^{0}C**;** IR (KBr) λ_{max} in cm^{-1}: 3086 (aromatic C-H str), 2823 (aliphatic C-H str), 1689 (C=N str), 1597 (aromatic C=C), 1481 (aliphatic C-C str), 1330 (NO_2 str); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 3.070-3.011 (dd, 1H, Pyrazole ring-H_A), 3.922-3.814 (dd, 1H, Pyrazole ring-H_M), 5.561 (dd, 1H, Pyrazole ring-H_X), 8.453-6.702 (m, 10H, Ar-H); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 167 (C=N), 148-111 (Ar-C), 62 (CH_2), 23 (CH); Anal. Found: C, 49.88; H, 2.84; N, 12.21 (%). Calc. for ($C_{19}H_{13}BrN_4O_5$): C, 49.91; H, 2.87; N, 12.25 (%).

5-(5-Chlorofuran-2-yl)-1,3-bis(4-nitrophenyl)-4,5-dihydro-1*H*-pyrazole; (CP02):
m.p**:** 217^{0}C**;** IR (KBr) λ_{max} in cm^{-1}: 3101 (aromatic C-H str), 2924 (aliphatic C-H str), 1604 (C=N str), 1527 (aromatic C=C), 1404 (aliphatic C-C str), 1350 (NO_2 str); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 3.070-3.011 (dd, 1H, Pyrazole ring-H_A), 3.888-3.814 (dd, 1H, Pyrazole ring-H_M), 5.143-5.161 (dd, 1H, Pyrazole ring-H_X), 8.453-6.702 (m, 10H, Ar-H); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 168 (C=N), 148-116 (Ar-C), 63 (CH_2), 23 (CH); Anal. Found: C, 55.25; H, 3.21; N, 13.62 (%). Calc. for ($C_{19}H_{13}ClN_4O_5$): C, 55.28; H, 3.17; N, 13.57 (%).

5-(5-Bromofuran-2-yl)-1-(2,4-dinitrophenyl)-3-(4-nitrophenyl)-4,5-dihydro-1*H*-pyrazole; (CP03):
m.p**:** 209^{0}C**;** IR (KBr) λ_{max} in cm^{-1}: 3024 (aromatic C-H str), 2954 (aliphatic C-H str), 1620 (C=N str), 1573 (aromatic C=C), 1450 (aliphatic C-C str), 1365 (NO_2 str); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 3.227-3.169 (dd, 1H, Pyrazole ring-H_A), 4.101-3.938 (dd, 1H, Pyrazole ring-H_M), 5.600-5.555 (dd, 1H, Pyrazole ring-H_X), 8.476-6.743 (m, 9H, Ar-H); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 162 (C=N), 148-105 (Ar-C), 62 (CH_2), 23 (CH); Anal. Found: C, 45.40; H, 2.44; N, 13.90 (%). Calc. for ($C_{19}H_{12}BrN_5O_7$): C, 45.44; H, 2.41; N, 13.94 (%).

5-(5-Chlorofuran-2-yl)-1-(2,4-dinitrophenyl)-3-(4-nitrophenyl)-4,5-dihydro-1*H*-pyrazole; (CP04):
m.p**:** 215^{0}C**;** IR (KBr) λ_{max} in cm^{-1}: 3105 (aromatic C-H str), 2903 (aliphatic C-H str), 1620 (C=N str), 1527 (aromatic C=C), 1442 (aliphatic C-C str), 1357 (NO_2 str); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 3.227-3.184 (dd, 1H, Pyrazole ring-H_A), 4.101-3.938 (dd, 1H, Pyrazole ring-H_M), 5.585-5.555 (dd, 1H, Pyrazole ring-H_X), 7.946-6.779 (m, 9H, Ar-H); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 158 (C=N), 150-112 (Ar-C), 62 (CH_2), 26 (CH); Anal. Found: C, 49.81; H, 2.68; N, 15.26 (%). Calc. for ($C_{19}H_{12}ClN_5O_7$): C, C, 49.85; H, 2.64; N, 15.30 (%).

Antimicrobial activity
In vitro antibacterial activity was determined by Kirby-Bauer disc diffusion method against bacteria such as *Staphylococcus aureus* and *Bacillus* (Gram +ve), *Salmonella typhi* and *Pseudomonas aeruginosa* (Gram -ve) using *Ampicilin* as standard a standard drug. The standard and test compounds were prepared in DMSO at different concentrations. The zone of inhibition was compared with standard drug after 24 hrs incubation at 35-37^{0}C.

Similarly antifungal activity was performed against *Candida albicans*, flucanazole was used as standard drug. The standard and test compounds were prepared in DMSO at different concentrations. The zone of inhibition was compared with standard drug after 48 hrs at 25^{0}C.

The results of antibacterial and antifungal activity are presented in Table –1.

Table –1. Antimicrobial activity of the synthesized compounds
Zone of inhibition (mm) of synthesized compounds

compound code	Anti-bacterial activity																Anti-fugal activity			
	Gram positive								Gram negative											
	Staphylococcus aureus				*Bacillus*				*Salmonella typhi*				*Pseudomonas aeruginosa*				*Candida albicans*			
	100 mcg	50 mcg	25 mcg	Std	100 mcg	50 mcg	25 mcg	Std	100 mcg	50 mcg	25 mcg	Std	100 mcg	50 mcg	25 mcg	Std	100 mcg	50 mcg	25 mcg	Std
CP01	6	4	3	10	6	3	-	11	3	2	-	9	6	5	3	9	8	-	-	18
CP02	6	4	2	8	7	5	-	8	4	2	-	5	9	8	6	10	6	5	4	14
CP03	7	5	4	9	7	5	4	9	7	5	3	10	9	7	5	10	7	6	3	17
CP04	8	6	5	11	12	8	6	10	6	5	3	10	8	6	4	10	8	6	4	20

The compounds of CP01, CP02, CP03 and CP04 showed significant activity against selected bacteria. Antifungal activity was performed on *Candida albicans*. All the compounds showed moderate activity against the fungus. The compound CP04 was more active among screened compounds.

CONCLUSION

The reaction profile explained in the present work is very efficient to synthesis, characterization and antimicrobial evaluation of 2-furyl based pyrazoles. The prepared compounds showed significant and moderate antimicrobial activities and these compounds will be taken for further pharmacological studies.

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