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Synthesis & antibacterial activities of 1-phenyl-5-(1H-pyrrol-1yl)-1H-pyrazole-4-carboxilic acid N' -acyl hydrazides

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ABSTRACT

A Novel series of 1-phenyl-5-(1H-pyrrol-1yl)-1H-pyrazole-4-carboxilic acid hydrazide derivatives were prepared by a 4 step course of action starting with Phenyl Hydrazine and 2-(1-ethoxyethylidine)malononitrile, with good yields and simple reaction condition. Synthesized compounds were test for their antibacterial activities. The structures were confirmed by ES-MS, NMR analysis.

Keywords: phenyl hydrazine, pyrazole-4-carboxilic acid, Clauson-Kass procedure, hydrazide, antibacterial activity,

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INTRODUCTION

Pyrazoles or azoles are five member ring heterocyclic compound having two adjacent nitrogen atoms[1]. The best described property of pyrazole is in the treatment of inflammation associated disorders, such as arthris [2]. Pyrazole derivatives are the subject of many research studies because of their potential to exhibit biological activities such as antimicrobial [3], antitumor [4,] antihistaminic [5], antiviral [6], fungicides [7], insecticides [8].Substituted pyrazoles and its analogs have been used as precursors for synthesis of different biologically active molecules. Taking into consideration the importance of biological activities of pyrazoles, we have decided to synthesize some novel substituted pyrazoles and studied their antimicrobial and antifungal activities.

MATERIALS AND METHODS

Melting points were measured by melting point apparatus in open capillaries and are uncorrected. 1H NMR spectra were taken on Bruker advance spectrophotometer working at 400 MHz. DMSO-d6 and CDCl3 was used as a solvents and TMS as an internal standard. Mass spectra were recorded on an LCMS-QP2010A instrument by direct injection method. All other analytical grade chemicals and solvents were obtained from commercial sources and as received standard procedure. The organisms employed in vitro testing of the compounds were *S. aureus* (Gram Positive), *S albus* (Gram Positive) *S. faecalis* (Gram Positive), *Bacillus sp.* (Gram Positive) *Pseudomonas aeruginosa* (Gram Negative), *sp. Proteus sp.* (Gram Negative) *Klebsiella sp.* (Gram Negative) *Escherichia coli* (Gram Negative).

Chemistry

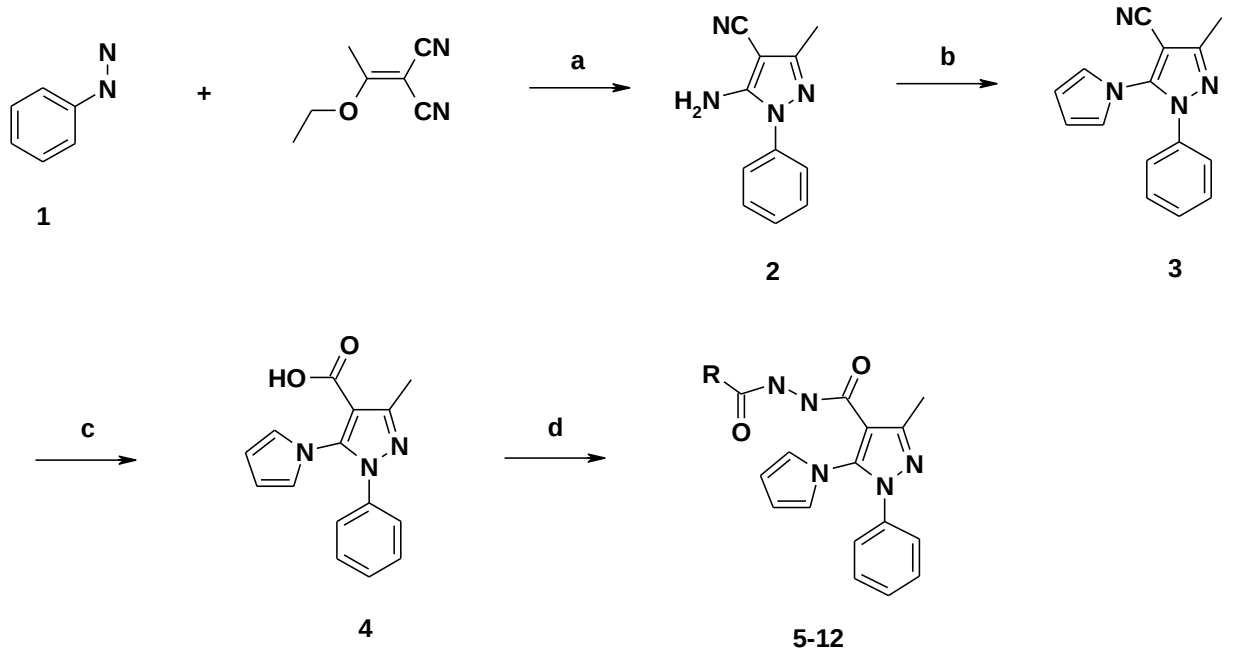
As a part of our ongoing research program on the application of substituted Pyrazole, we herein report the synthesis of novel 1-phenyl-5-(1H-pyrrol-1yl)-1H-pyrazole-4-carboxilic acid hydrazide (**5-12**) . Synthesis of novel hydrazides derivative was prepared as depicted in **Scheme 1.** Reaction of Phenyl hydrazine **1** with 2-(1-ethoxyethylidine) malononitrile in ethanol under reflux condition gave 5-amino-1-(4-phenyl)-3-methyl-1*H*-pyrazole-4-carbonitrile **2** , which was transformed into the corresponding pyrrol derivative **3** by reaction with 2,5 dimethoxytetrahydrofuran in glacial acetic acid according to Clauson-Kaas procedure [9]. Transformation of nitrile intermediate **3** into the acid intermediate **4** was achieved by alkaline hydrolysis using sodium hydroxide in refluxing ethylene glycol [10]. At last step, pyrazole 4-carboxilic acid N' -acyl hydrazides **5-12** were obtained through coupling of acid intermediate **4** with selected hydrazide side chains.

General Procedure for the preparation of new substituted pyrazoles (5-12)

3-methyl-1-phenyl-5-pyrro1-yl-1H-pyrazole-4-carboxylic acid (500mg, 1.87 mmol)was taken in

DMF (5ml) and was added EDC.HCl (542 mg, 2.80 mmol) , Acetic acid hydrazide (280 mg, 2.07mmol), HOBt (253mg, 1.87mmol and TEA (787 µL , 5.61 mmol) under nitrogen. Stirred the reaction mixture for 6h. TLC shows completion of reaction. Water was added (50ml), solid was comes out was filtered, dried and washed with diethyl ether to gave compound **5 (**520mg, 72%).

Scheme 1



Scheme 1. Reagents and solvents:- **a)** Ethanol, reflux, 3h **b)** 2,5 dimethoxytetrahydrofuran in glacial acetic acid, reflux 2h **c)** 3N NaOH, ethylene glycol, reflux, 24h, **d)** hydrazide, N,N dimethylformamide, EDC.HCl/ HOBt, TEA, room temp. 60-70%

RESULTS AND DISCUSSIONS

5-Amino-3-methyl-1-phenyl-1H-pyrazole-4-carbonitrile (2)

2-(1-ethoxyethylidine) malononitrile (10g, 0.072 mmol) and phenyl hydrazine **1** (7.76g, 0.072 mmol) was taken in ethanol (50ml) and refluxed the reaction mixture for 3h. Cooled the content to room temperature resulted into solid formation, which was collected by filtration, and washed with cold ethanol (10ml) to yield 8.54g of intermediate **2.** Yield = 60%, MP= 172-175^{0}C MF= $C_{11}H_{10}N_4$, MW= 198.23

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33-7.35 (m, 3H), 7.03-7.6(m, 2H), 4.58 (br s, 2H), 2.34 (s, 3H),

3-methyl-1-phenyl-5-pyrro1-yl-1H-pyrazole-4-carbonitrile (3)

Intermediate **2** (8.54g, 0.043 mmol) was taken in glacial acetic acid (85ml) was added 2, 5 dimethoxytetrahydrofuran (6.83 g, 0.051 mmol). The reaction mixture was refluxed for 2h. After cooling little water was added, volatiles was removed under vacuum to obtained residue was then

taken in Ethyl acetate and washed with saturated sodium bicarbonate. Collected organic layer was dried over sodium sulfate and removed under vacuum to crude intermediate which was purified by column chromatography (chloroform as eluent) to furnish 7.5 g of intermediate **3**. Yield = 70%, MP= 142-146^{0}C MF= $C_{15}H_{12}N_4$, MW= 248.29

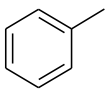
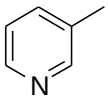
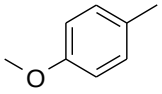
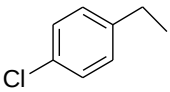
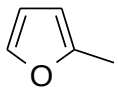
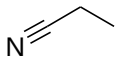
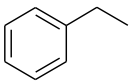
^{1}H NMR (DMSO-d6, 400 MHz): δ 7.33-7.35 (m, 3H), 7.03-7.6 (m, 2H), 6.73 (t, 2H), 6.37 (t, 2H), 2.49(s, 3H),

3-methyl-1-phenyl-5-pyrro1-yl-1H-pyrazole-4-carboxilic acid (4)

Intermediate **3** (7.5 g, 0.030 mmol), 3N NaOH (45ml) and ethylene glycol (150 ml) was refluxed for 24 h. After cooling reaction was quenched with water and made acidic with 6N HCl until PH 2. The mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried. The evaporation of the organic layer under vacuum furnishes (6.0g) intermediate acid core **4.** Yield = 75%, MP= 232-235^{0}C MF= $C_{15}H_{13}N_3O_2$, MW= 267.29

^{1}H NMR (DMSO-d6, 400 MHz): δ 12.36 (br, s, 1H), 7.33-7.35 (m, 3H), 7.08 (d, 2H), 6.83 (s, 2H), 6.1 (s, 2H), 2.46 (s, 3H),

Table1: Examples of Novel pyrazole 4-carboxilic acid N'-acyl hydrazides 5-12

Entry	R	MF	MW	MP in ^{0}C	% Yield
5.	CH_3	$C_{17}H_{17}N_5O_2$	323.36	132-134	72
6.		$C_{22}H_{19}N_5O_2$	385.43	145-147	68
7.		$C_{21}H_{18}N_6O_2$	386.42	153-155	58
8.		$C_{23}H_{21}N_5O_3$	415.46	151-153	72
9.		$C_{23}H_{20}ClN_5O_2$	433.90	168-169	70
10.		$C_{20}H_{17}N_5O_3$	375.39	137-139	63
11.		$C_{18}H_{16}N_6O_2$	348.37	127-129	56
12.		$C_{23}H_{21}N_5O_2$	399.46	161-163	64

The target compounds (**5-12**) were prepared as outlined in **scheme 1**.

3-Methyl-1-phenyl-5-pyrrol-1-1H-pyrazole-4-carboxylic acid N'-acetyl-hydrazide (5)

Mol. Formula: $C_{17}H_{17}N_5O_2$; MW= 323.36; Mp= 132-134^{0}C ES-MS: m/z 324.2 $(M+H)^+$

^{1}H NMR (DMSO-d6, 400 MHz) δ 9.87 (s, 1H), 9.44 (s, 1H), 7.33-7.35 (m, 3H), 7.03-7.6(m, 2H), 6.84-6.85 (m,2H), 6.16-6.17 (m, 2H),2.38 (s, 3H),1.83 (s, 3H)

Benzoic acid N'-(3-methyl-1-phenyl-5-pyrrol-1-1H-pyrazole-4-carbonyl)- hydrazide (6)

Mol. Formula: $C_{22}H_{19}N_5O_2$; MW= 385.43; Mp=145-147^{0}C ES-MS: m/z 386.1 $(M+H)^+$

^{1}H NMR (DMSO-d6, 400 MHz) δ 10.89 (s, 1H), 9.74 (s, 1H),7.88-7.89 (m, 2H), 7.46-7.56(m, 3H), 7.32-7.36 (m,3H), 7.05 (d, 2H), 6.89 (d, 2H), 6.19 (d, 2H), 2.48 (s,3H)

Nicotinic acid N' -(3-methyl-1-phenyl-5-pyrrol-1-1H-pyrazole-4-carbonyl)- hydrazide (7)

Mol. Formula: $C_{21}H_{18}N_6O_2$; MW= 387.2; Mp= 153-155^{0}C ES-MS: m/z 386.1 $(M+H)^+$

^{1}H NMR (DMSO-d6, 400 MHz) δ 10.59 (s, 1H), 9.72 (s, 1H),9.22 (1H,s), 8.35-7.85 (m, 2H), 7.63 (m, 1H), 7.34-7.36 (m,3H), 7.05 (d, 2H), 6.87 (d, 2H), 6.20 (d, 2H), 2.48 (s,3H)

4-Methoxy-benzoic acid N'-(3-methyl-1-phenyl-5-pyrrol-1-1H-pyrazole-4-carbonyl) hydrazide (8)

Mol. Formula: $C_{23}H_{21}N_5O_3$; MW= 415.46; Mp= 151-153^{0}C ES-MS: m/z 416.4 $(M+H)^+$

^{1}H NMR (DMSO-d6, 400 MHz) δ 10.34 (s, 1H), 9.66 (s, 1H), 7.86-7.88 (d, 2H), 7.34-7.35 (m, 3H), 7.05-7.07 (d,2H), 6.99-7.01 (d, 2H), 6.88 (s, 2H), 6.18 (s, 2H), 3.80 (s, 3H), 2.48 (s,3H)

3-Methyl-1-phenyl-5-pyrrol-1-yl-1H-pyrazole-4-carboxylic acid N' -(2-(4-chloro-phenyl)-acetyl]-hydrazide (9)

Mol. Formula: $C_{23}H_{20}ClN_5O_2$; MW= 433.9; Mp= 168-169^{0}C ES-MS: m/z 434.3 $(M+H)^+$

^{1}H NMR (DMSO-d6, 400 MHz) δ 10.18 (s, 1H), 9.60 (s, 1H), 7.28-7.36 (m,6H), 7.03-7.04 (d, 3H), 6.83-6.84 (m,2H), 6.17 (s, 2H), 3.46 (s, 2H), 2.37 (s, 3H),

Furan-2-carboxylic acid N'-(3-methyl-1-phenyl-5-pyrrol-1-1H-pyrazole-4-carbonyl)-hydrazide (10)

Mol. Formula: $C_{20}H_{17}N_5O_3$; MW= 375.39; Mp= 137-139^{0}C ES-MS: m/z 434.3 $(M+H)^+$

^{1}H NMR (DMSO-d6, 400 MHz) δ 10.38 (s, 1H), 9.71 (s, 1H), 7.88 (s,1H), 7.33-7.35 (m, 3H), 7.22-7.23 (m,1H), 7.04-7.06 (m, 2H), 6.85-6.87 (m, 2H), 6.63-6.64 (m, 1H),6.17-6.18 (m, 2H), 2.46 (s, 3H)

3-Methyl-1-phenyl-5-pyrrol-1-1H-pyrazole-4-carboxylic acid N'-(2-cyno-acetyl)-hydrazide (11)

Mol. Formula: $C_{18}H_{16}N_6O_2$; MW= 348.37; Mp= 127-129^{0}C ES-MS: m/z 434.3 $(M+H)^+$

^{1}H NMR (DMSO-d6, 400 MHz) δ 10.38 (s, 1H), 9.71 (s, 1H), 7.22-7.23 (m,1H), 7.04-7.06 (m, 3H), 6.85-6.87 (m, 2H), 6.63-6.64 (m, 1H),6.17-6.18 (m, 2H),3.48(s, 2H) 2.46 (s, 3H)

3-Methyl-1-phenyl-5-pyrrol-1-1H-pyrazole-4-carboxylic acid N' -(phenyl acetyl)-hydrazide (12)

Mol. Formula: $C_{23}H_{21}N_5O_2$; MW= 399.46; Mp= 161-163^{0}C ES-MS: m/z 400.3 $(M+H)^+$

^{1}H NMR (DMSO-d6, 400 MHz) δ 10.20 (s, 1H), 9.63 (s, 1H), 7.28-7.36 (m,6H), 7.03-7.04 (d, 3H), 6.83-6.84 (m,3H), 6.17 (s, 2H), 3.46 (s, 2H), 2.37 (s, 3H),

Antimicrobial activity

The evaluation of the synthesized compounds (**5-12**) for antibacterial activity was carried out by standard literature procedure using agar diffusion method by finding the zone of inhibition of the drug sample against the standard drugs. The organisms employed in vitro testing of the compounds were *S. aureus* (Gram Positive), *S albus* (Gram Positive) *S. faecalis* (Gram Positive), *Bacillus sp.* (Gram Positive) *Pseudomonas aeruginosa* (Gram Negative), *sp. Proteus sp.* (Gram Negative) *Klebsiella sp.* (Gram Negative) *Escherichia coli* (Gram Negative). All the cultures were maintained on Nutrient agar (Microbiology) grade, Hi Media) medium by periodic sub culturing. Ciprofloxacin was used as reference compound for antibacterial activity. The compounds were tested at a concentration of a 100µg/ml were prepared in Dimethylsulphoxide.

Code No	Gram Positive Bacteria	Code No	Gram Negative Bacteria
A	*Staphylococcus aureus*	**E**	*Pseudomonas sp.*
B	*Staphylococcus albus*	**F**	*Proteus sp.*
C	*Staphylococcus faecalis*	**G**	*Klebsiella sp.*
D	*Bacillus species*	**H**	*Escherichia coli*

Following are the antimicrobial activity Results of compound 5-12

Sr. No.	Compound No.	Inhibition Zone Diameter (mm)				Inhibition Zone Diameter (mm)			
		Gram Positive Bacteria				Gram Negative Bacteria			
		A	**B**	**C**	**D**	**E**	**F**	**G**	**H**
1	**5**	16	19	18	22	22	18	27	25
2	**6**	18	24	22	24	20	19	30	28
3	**7**	21	26	24	24	19	22	29	26
4	**8**	23	31	19	21	25	22	28	27
5	**9**	17	28	21	23	18	23	33	21
6	**10**	13	24	17	19	26	25	27	29
7	**11**	15	22	19	20	19	27	25	33
8	**12**	19	31	23	24	22	28	35	32
9	***Ciprofloxacin***	***19***	***20***	***14***	***13***	***17***	***17***	***20***	***22***

Graphical representation of Antibacterial activity

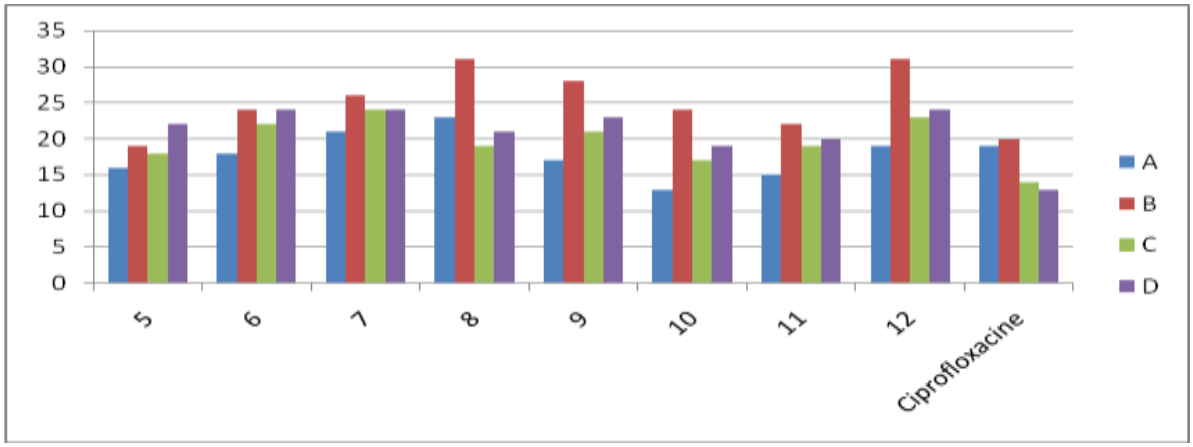


Figure 1: Graph of antibacterial activity against *Gram positive* bacteria

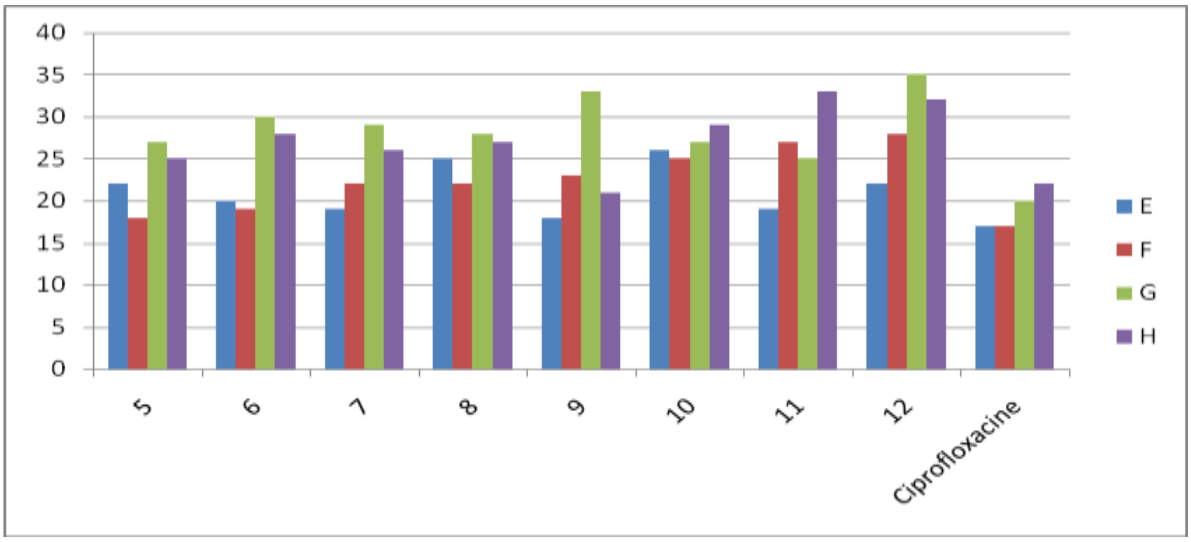


Figure 2: Graph of antibacterial activity against *Gram negative* bacteria

CONCLUSION

In this study, the syntheses of some substituted pyrazole derivatives (**5-12**) were synthesized and their structures were confirmed by ^{1}H NMR, Mass spectroscopic techniques. In addition, the newly synthesized compounds were screened for their antibacterial activities. Some of them found to posses good antibacterial activities.

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