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Novel 4-(substituted) pyrazolyl 5,6-dipyridylpyridazin-3(2H)-ones likely to possess antihypertensive and anti-inflammatory activities

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ABSTRACT

*Cyclocondensation of pyridilmonohydrazone and ethyl acetoacetate in refluxing sodium ethoxide/ethanol solution afforded 4-acetyl-5,6-dipyridylpyridazin-3(2H)-one **3** which on reaction with diethyl oxalate in refluxing sodium ethoxide/ethanol mixture gave ethyl 2,4-dioxo-4- (3-oxo-5,6- dipyridyl -2,3-dihydropyridazin4-yl) butanoate **4.** While on reaction of butanoate **4** with hydrazine hydrate in refluxing ethanol afforded ethyl 5-(3-oxo -5,6-dipyridyl -2,3-dihydro pyridazin 4-yl)-1H-pyrazole-3-carboxylate **5**. Reaction of the ester **4** with hydrazine hydrate in refluxing ethanol gave the acid hydrazide **6** .Hydrazide derivative **6** was considered as intermediate for synthesis different heterocyclic moieties attached to pyridazinones nucleus such as pyrazoles ,oxadiazoles,amino pyrazolones and methyl pyrazolone derivatives **12, 13,14** and **16** . The structure of all newly synthesized was confirmed from analytical and spectral data.*

Keywords: Pyridil–- pyridimonohydrazone - pyridazine – pyrazole –pyrazolone- oxadiazole- antihypertensive- anti-inflammatory.

INTRODUCTION

In continuation to our previous studies[1-2] on pyridylpyridazinone and pyrazole derivatives annulated with various five and six membered heterocycles and the considerable biological activity of each pyridazinone pyrazole moieties. .

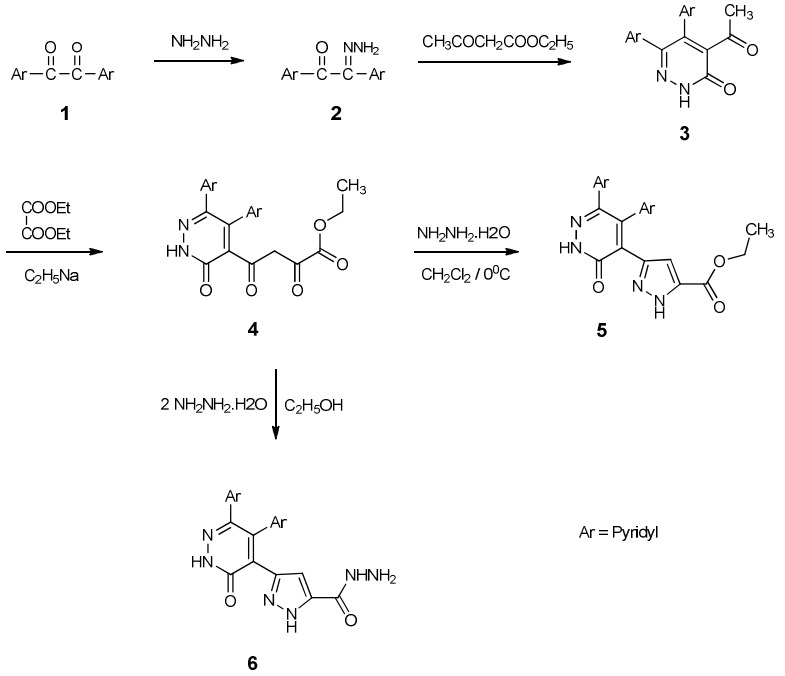
It has been reported that pyridazinones are considered as antihypertensive, anticancer, and H-IV activities[3]. Pyridazinones are platelet aggregation inhibitors and enhance phagocytes of leukocytes. On the other hand pyrazoles were reported to possess antipyretic, antipsychotic and antiplatelet aggregation, herbicidal and as food colorants in dyestuffs[4-6]. Also pyrazoles show analgesic, antinociceptive activity [7] . They are also used as drugs for treatment of pancytopenia, thrombocytopenia and erythropenia[8] .In addition it was reported that incorporation of pyrazole with other heterocyclic moieties enhances the anti-inflammatory activity[9] as they have a fewer gastric side effect in drugs used for rheumatic paints . This promoted us to synthesize of some new pyridazinones attached to pyrazole derivatives through cyclocondensation of pyridimonohydrazone and ethyl acetoacetate in refluxing sodium ethoxide/ethanol solution likely to possess antihypertensive and anti-inflammatory activities.

In the present work 3-acetyl-4,5dipyridylpyridazin-2(2H)-one **3** was prepared via the reaction of pyridilmono hydrazone with ethyl acetoacetate in the presence of sodium ethoxide/ ethanol solution which on reaction with diethyl oxalate in refluxing sodium ethoxide/ ethanol[10]mixture afforded ethyl 2,4-dioxo-4-(3-oxo-5,6- dipyridyl-2,3-dihydro pyridazin -4-yl) butanoate **4**. The structure of **4** was confirmed from its correct analytical and spectral data. IR

spectrum of **4** showed absorption bands at 3300(NH), 3105(Ar-H), 2975, 2910(C-H aliphatic), 1715(C=O ester), 1670, 1665(2C=O) and 1640(C=N). ^{1}HNMR spectrum of **4** showed signals at δ =1.2(t, 3H, CH_2-$\underline{CH_3}$) 4.0(q, 2H, $\underline{CH_2}$-CH_3), 5.5(s, 2H, CH_2-), 7.0(s, 1H, NH) and 7.3-7.8(m, 8H aromatic protons).

One of the most common methods for pyrazole synthesis was the reaction of 1, 3-diketones with hydrazine hydrate or its mono substituted derivatives. Thus, the reaction of the butanoate **4** with hydrazine hydrate (1:1 mole) in refluxing ethanol[11,12] afforded ethyl-5-(3-oxo-5,6- dipyridyl -2,3-dihydropyridazin-4-yl)-1*H*-pyrazole-3-carboxylate **5.**

Hydrazide derivatives were reported to exhibit different biological activity, analgesic and anti-inflammatory activity. Hence it was thought of interest in merging of both pyridazinones and acetic acid hydrazide moieties may enhance the drug activity. From this point of view, the objective of the present work is to prepare new hydrazide derivative as intermediate for synthesis different heterocyclic moieties attached to pyridazinones nucleus. Thus reaction of the butanoate **4** with hydrazine hydrate (1:2 moles) in refluxing ethanol gave -(3-oxo-5,6-dipyridyl-2,3-dihydropyridazin-4-yl)-1*H*-pyrazole-3- carbohydrazide **6** as shown in **Scheme 1.**.



Scheme 1

IR spectrum of **5** showed absorption bands at 3300, 3280(NH), 1725(C=O ester), 1655(C=O) and 1640(C=N). ^{1}H-NMR spectrum of **5** showed signals at δ = 1.4(t, 3H, CH_2-$\underline{CH_3}$) ,4.5(q, 2H, $\underline{CH_2}$-CH_3), 6.0(s,1H,CH-pyrazole) ,6.7(s, 1H, NH), 7.4-7.8 (m, 10H aromatic protons) and 11.0(s, 1H, NH pyrazole). While IR spectrum of **6** showed absorption bands at 3330, 3290(NH), 1675, 1660(2C=O) and 1445 (C=N). ^{1}H-NMR spectrum of **6** showed signals at δ = 4.1(s, 2H, NH_2), 6.2(s, 1H, CH-pyrazole), 7.1(s, 1H, NH), 7.5-7.9(m, 8H aromatic protons), 10.8(s, 1H, NH, CONH) and 12.6(s, 1H, NH pyrazole).Elemental analysis showed satisfied results for compounds **5** and **6**.

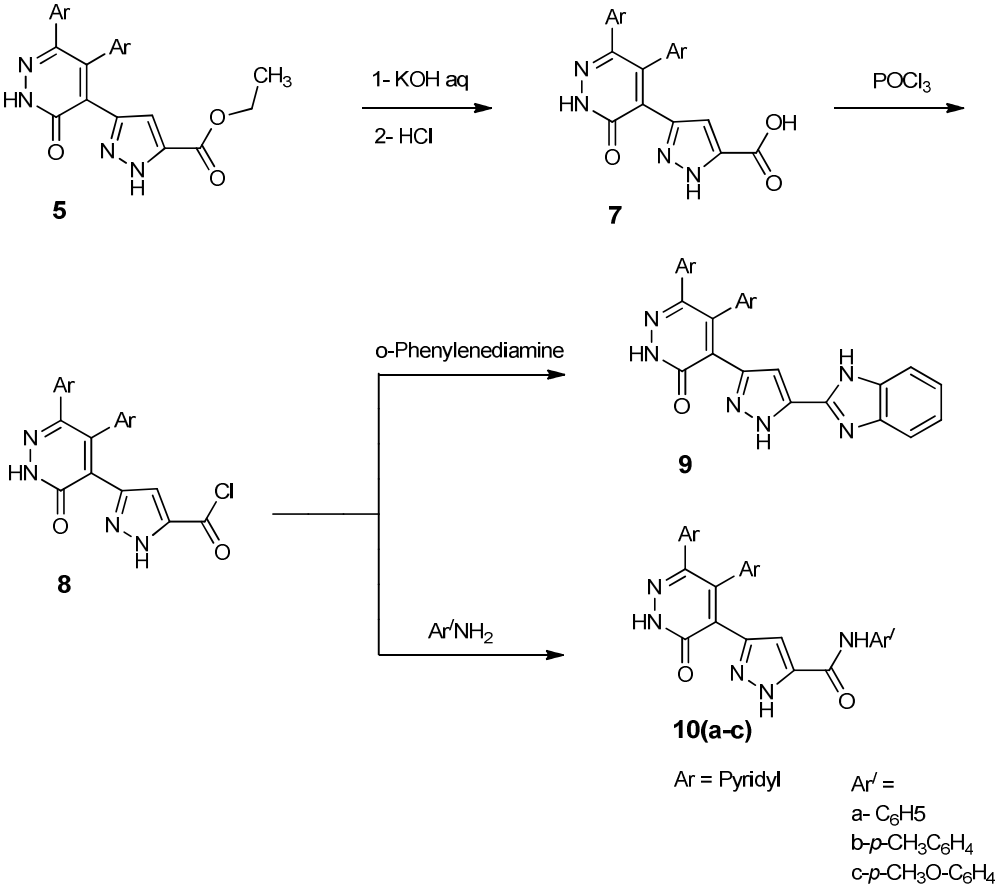
Acid chlorides are considered very active intermediate in organic chemistry to achieve transformation to new function groups so; we aimed to synthesis of acetic acid derivative 7 via hydrolysis of ester **5** with alkaline KOH to give the corresponding acid **7** which upon reaction with $POCl_3$ gave the acid chloride **8**. The structure of each acid and acid chloride **7** and **8** was established from their correct analytical and spectral data. IR spectra, the acid **7** showed absorption bands at 3350, 3255(NH) 2910, 2905(C-H aliphatic), 1670(C=O), 1660(C=O) and 1640(C=N), while IR of the acid chloride **8** showed absorption bands at 3250(NH), 3115(Ar-H), 2910, 2915(C-H aliphatic), 1725(C=O),1660(C=O) and 1615(C=N).

The synthesis of novel benzimidazole derivatives remains a main focus of medical research. Recent observations suggest that substituted benzimidazoles and heterocyclic are possess potential activity[13] with lower toxicities in the antihypertensive activity approach. Reaction of the acid chloride **8** with o-phenylenediamine in refluxing DMF in the presence of KCO_3 yielded 4-(5-(1H-benzo[d] imidazol-2-yl) -1H-pyrazol -3-yl) -5,6-dipyridyl pyridazin -3(2H)-one **9**. The structure of benzimidazol **9** was confirmed from its analytical and spectral data, IR spectrum of **9** showed absorption bands at 3340, 3115(NH), 1690(C=O) and 1635 cm^{-1} (C=N). ^{1}HNMR spectrum of **9** showed signals at δ = 5.3(s, 1H, CH pyrazole), 6.3(s, 1H, NH), 7.4-7.8(m, 12H aromatic protons), 11.3(s, 1H, NH benzimidazol) and 12.5 (s, 1H, NH pyrazole).

The amides **10a-c** were prepared via the reaction of acid chloride **8** with primary amines namely, aniline, p-toluidine and anisidine in the presence of DMF containing K_2CO_3[14] afforded the corresponding 5-(3-oxo-5,6-diphenyl-2,3-dihydropyridazin-4-yl)- N-P-Aryl-1*H*-pyrazole-3-carboxamide derivatives **10a-c** as shown in **Scheme 2** .

The structure of**10a-c** was established from their correct analytical and spectral data. IR spectrum of **10a** showed absorption bands at 3330(NH), 1675(C=O) and 1640 (CONH). ^{1}H-NMR spectrum of **10c** showed signals at δ = 3.1(s, 3H, CH3), 5.1(s, 1H, CH pyrazole), 7.0(s, 1H, NH), 7.5-8.1(m, 12H aromatic protons),10.2(s, 1H, NH amide) and 12.8(s, 1H, NH pyrazole).

Hydrazones **11a-c** were prepared via the reaction of the acid hydrazide **6** with appropriate aldehydes namely, benzaldehyde, p-chlorobenzaldehyde and p-nitrobenzaldehyde in refluxing ethanol/acetic acid mixture[15] . The structure of **11a-c** was confirmed from their correct analytical and spectral data, IR spectrum of **11a** showed bands at 3350, 3115(NH), 1670(C=O) and1645 cm^{-1} (C=N). While ^{1}H-NMR spectrum of **11c** showed signals at δ = 6.1(s, 1H, CH pyrazole), 7.0(s, 1H, NH), 7.5-8.1 (m, 12H aromatic protons), 10.5(s, 1H,CH=N), 11.2(s, 1H, NH amide) and 12.2 (s, 1H, NH pyrazole).



Scheme 2

In this study, when carboxylic acid hydrazide **6** was refluxed with acetyl acetone[16] in ethanol containing KOH gave 4-(5-(3,5-dimethyl-1H-pyrazole-1-carbonyl) -1H- pyrazol -3-yl) -5,6-diphenylpyridazin-3(2H)-one **12**. The structure of **12** was confirmed from its correct analytical data, its IR spectrum which, showed absorption bands at 3300, 3268(NH), 1665(C=O) and 1645cm^{-1} (C=N). Also, ^{1}H-NMR spectrum of **12** showed signals at **δ** = 2.3 (s, 3H, CH_3), 2.5 (s, 3H, CH_3) 6.3(s, 1H, CH pyrazole), 7.0(s, 1H, NH), 7.4-7.8(m, 8H aromatic protons) and 13.8(s, 1H, NH proton).

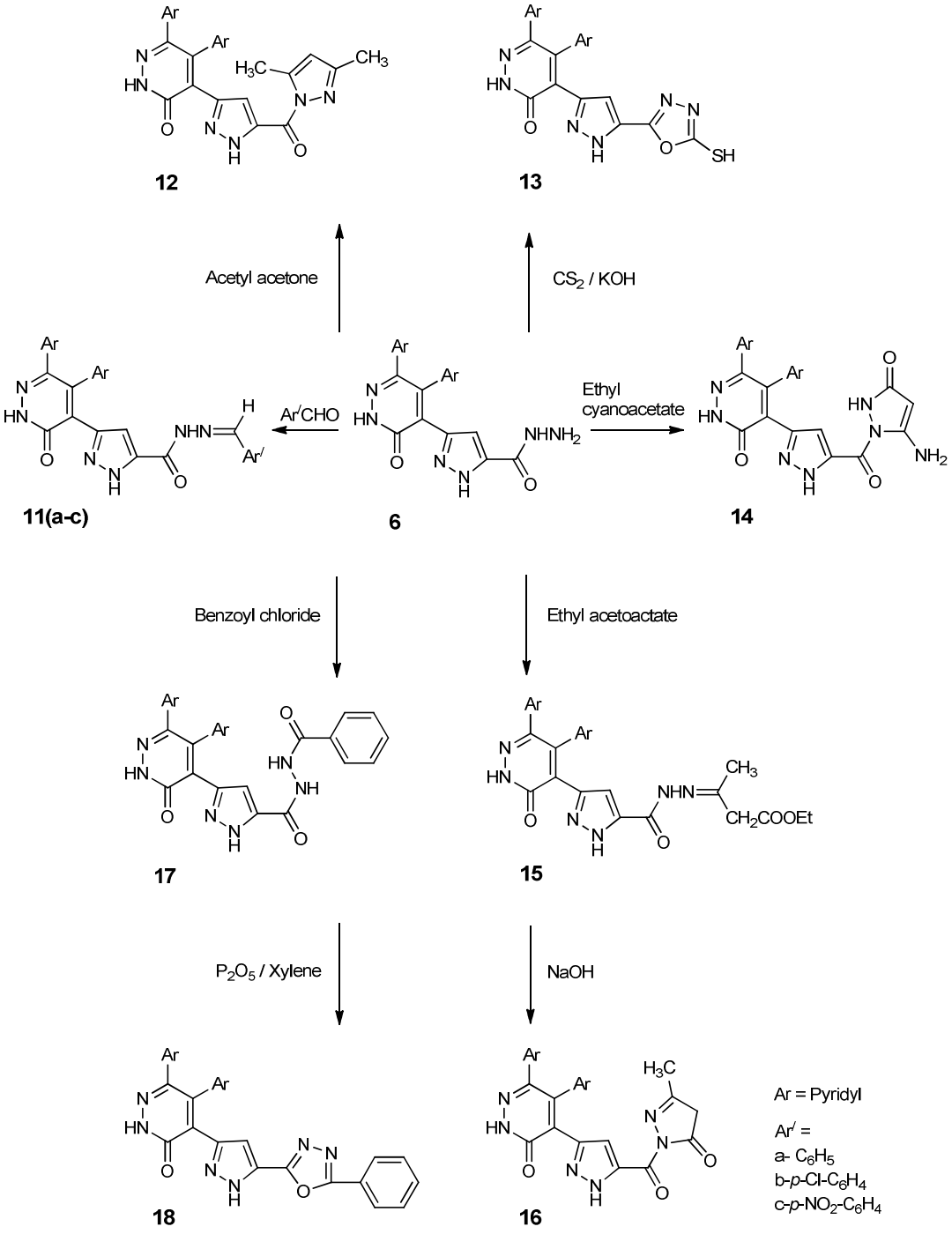
Reaction of the acid hydrazide **6** with carbon disulphide in ethanol containing KOH at room temperature gave potassium dithiocabazate derivative which undergo cyclative dehydrosulphorization via refluxing the reaction mixture for 12 hours to give 5,6-dipyridyl -4-[5-(5-sulfanyl-1,3,4-oxadiazol-2-yl)-1H -pyrazol-3-yl] pyridazin-3(2H)-one **13**. The structure of 1,3,4-oxadiazole **13** was confirmed from its correct analytical data and its IR spectrum which, showed absorption bands at 3330, 3290 (NH), 1690(C=O) and 1645cm^{-1} (C=N) .

Similarly 4-{5-[(5-amino-3-oxo-2,3-dihydro-1H-pyrazol-1-yl)carbonyl] -5,6-diphenyl pyridazin - 3(2H)-one **14** was obtained via the reaction of the carboxylic acid hydrazide **6** with ethyl cyanoacetate[17] in ethanol containing KOH under reflux . The structure of **14** was confirmed from its correct analytical data, its IR spectrum which showed absorption bands at 3281, 3268(NH), 1715(C=O ester), 1690(C=O) and 1645cm^{-1} (C=N). Also, ^{1}HNMR spectrum of **14** showed signals at δ = 4.1(s,1H,CH pyrazolone),5.2(s, 2H, NH_2), 6.3(s, 1H, CH pyrazole), 7.0(s, 1H, NH), 7.4-7.8(m, 8H aromatic protons) and 13.2 (s, 1H, NH proton).

On the other hand, reaction of carboxylic acid hydrazide **6** with ethyl acetoacetate[18] in ethanol containing NaOH under reflux followed by neutralization with dil.HCl gave(E) -ethyl3-(2-(5-(3-oxo-5,6-dipyridyl-2,3-dihydropyridazin -4-yl)-1H-pyrazole-3carbonyl) hydrazino)butanoate**15**. The structure of **15** was confirmed from its correct analytical data, its IR spectrum which showed absorption bands at 3320, 3110, 3270 (NH), 1725(C=O ester), 1690(C=O) and 1640 cm^{-1} (C=N). Also, ^{1}HNMR spectrum of **15** showed signals at δ = 1.2 (t, 3H, $CH_2\underline{CH_3}$), 1.9(s, CH_3), 2.6(s, 3H, CH2), 4.1(q, 2H, $\underline{CH_2}CH_3$), 7.0(s, 1H, NH), 7.4-7.8(m, 8H aromatic protons), 10.1(s, 1H, CONH) and 13.0(s, 1H, NH proton).

Cyclization of ethoxycarbonyl hydrazone **15** in aqueous NaOH afforded the corresponding 4-(5-(3-methyl-5-oxo- 4,5-dihydro-1H-pyrazole-1-carbonyl)-1H-pyrazo-3-yl) -5,6-diphenyl pyridazin-3(2H)-one**16.**The structure of **16** was confirmed from its correct analytical data, its IR spectrum which showed absorption bands at 3330, 3265(NH), 1675(C=O) and 1655cm^{-1} (C=N). Also, ^{1}HNMR spectrum of **16** showed signals at δ = 2.3(s, 3H, CH_3), 3.5(s, 2H, CH_2 pyrazolone), 6.1(s, 1H, CH pyrazole), 8.1(s, 1H, NH), 7.4-7.8(m, 8H aromatic protons) and 11.5(s, 1H, NH proton)

Benzoylation of the acid hydrazide **6** was succeeded via its reaction with benzoyl chloride in refluxing pyridine to give N-benzoyl-5-(3-oxo-5,6- dipyridyl- 2,3- dihydropyridazin- 4-yl)-1H-pyrazole-3-carbohydrazide **17** which under cyclocondensation in the presence of P_2O_5 in fluxing dry xylene afforded 5,6-dipyridyl-4-(5-(5-phenyl-1,3,4-oxadiazol-2-yl) -1H-pyrazol-3-yl)pyridazin- 3(2H)-one **18** as shown in **Scheme 3.**. The structure of **17** was confirmed from its correct analytical data, its IR spectrum which showed absorption bands at 3281, 3268 (NH), 1690(C=O) and 1645cm^{-1} (C=N). Also, ^{1}HNMR spectrum of **17** showed signals at **δ** = 6.3(s, 1H, CH pyrazole), 7.1(s, 1H, NH), 7.4-7.8(m, 13H aromatic protons) and 13.0(s, 1H, NH proton).


Acetyl acetone
CS2 / KOH
Ar/CHO
Ethyl cyanoacetate
Benzoyl chloride
Ethyl acetoactate
P2O5 / Xylene
NaOH
12
13
11(a-c)
6
14
17
15
18
16
Ar = Pyridyl
Ar/ =
a- C6H5
b-p-Cl-C6H4
c-p-NO2-C6H4

Scheme 3

Table 1: Characterization and physical data of the newly synthesized pyridazinones

Ser.	Yield (%)	M. p. (^{0}C)/	Mol. formula/ formula wt.	Analysis % calculated/ found		
				C	H	N
4	70	115	$C_{20}H_{16}N_6O_3$ (372.33)	64.45 64.40	4.29 4.27	22.56 22.51
5	65	135	$C_{20}H_{16}N_6O_3$ 388.38	61.85 61.80	4.15 4.10	21.64 21.60
6	68	295	$C_{18}H_{14}N_8O_2$ 374.36	57.75 57.71	3.77 3.71	29.93 29.84
9	70	285	$C_{24}H_{16}N_8O$ 432.44	66.66 66.60	3.73 3.65	25.91 25.84
10a	82	225	$C_{24}H_{17}N_7O_2$ 435.44	66.20 66.15	3.94 3.87	22.52 22.50
10b	74	245	$C_{25}H_{19}N_7O_2$ 449.46	66.81 66.75	4.26 4.15	21.81 21.74
10c	71	255	$C_{25}H_{19}N_7O_3$ 465.46	64.51 64.45	4.11 4.00	21.06 21.04
11a	66	276	$C_{25}H_{18}N_8O_2$ 462.46	64.93 64.85	3.92 3.89	24.23 24.17
11b	68	255	$C_{25}H_{17}ClN_8O_2$ 496.91	60.43 60.35	3.45 3.42	22.55 22.50
11c	71	287	$C_{25}H_{17}N_9O_4$ 507.46	59.17 59.14	3.38 3.33	24.84 24.74
12	65	198	$C_{23}H_{18}N_8O_2$ 438.44	63.01 62.89	4.14 4.11	25.56 25.51
13	66	282	$C_{19}H_{12}N_8O_2S$ 416.42	54.80 54.74	2.90 2.88	26.91 26.84
14	60	265	$C_{21}H_{15}N_9O_3$ 441.40	57.14 57.04	3.43 3.39	28.56 28.54
16	66	285	$C_{22}H_{16}N_8O_3$ 440.41	60.00 59.94	3.66 3.62	25.44 25.40
18	75	275	$C_{25}H_{16}N_8O_2$ 460.45	65.21 65.15	3.50 3.47	24.34 24.28

MATERIALS AND METHODS

All melting points were uncorrected. IR spectra were measured in KBr on a Brüker FT-IR ISS 25 spectrophotometer (ν_{max} in cm^{-1}). ^{1}H-NMR spectra (DMSO-d_6 and $CDCl_3$) were carried out on a Bruker Avance 300 MHz spectrometer using TMS as internal reference (chemical shifts in δ, ppm).

4-Acetyl-5,6-dipyridylpyridazin-3(2H)-one 3:
A mixture of sodium ethoxide solution (0.02 mole) (0.46 gm of sodium in 20ml ethanol) and pyridilmonohydrazone (0.02 mole), the reaction mixture was refluxed for 3-h, and then was left at room temperature overnight. The solution was neutralized with ice-cold dil HCl. Then the mixture was extracted with diethyl ether and the organic layer was collected, washed with water, dried and crystallized from benzene

Ethyl 2,4-dioxo-4-(3-oxo-5,6-dipyridyl -2,3-dihydropyridazin-4-yl) butanoate 4:
To a mixture of sodium ethoxide solution (0.02 mole) (0.46 gm of sodium in 20ml ethanol) and diethyl oxalate (0.02 mole), 4-Acetyl-5,6-dipyridylpyridazin-3(2H)-one **3** (0.02 mole) was added at 0°C. The reaction mixture was stirred at 0°C for 3-4h, and then was left at room temperature overnight. The solution was neutralized with ice-cold dil HCl. Then the mixture was extracted with diethyl ether and the organic layer was collected, washed with water, dried and crystallized from ethanol.

Ethyl 5-(3-oxo-5,6- dipyridyl -2,3-dihydropyridazin-4-yl)-1*H*-pyrazole-3-carboxylate 5:
To a solution of **4** (0.02 mole) in dichloroethane (20 ml) hydrazine hydrate (0.02 mole) was added. The reaction mixture was stirred at room temperature overnight, and then refluxed for 10h. The solvent was evaporated and the solid obtained was crystallizes from ethanol.

5-(3-oxo-5,6- dipyridyl -2,3-dihydropyridazin-4-yl)-1*H*-pyrazole-3-carbohydrazide 6:
To a solution of **4** (0.02 mole) in absolute ethanol (50 ml) hydrazine hydrate (0.04 mole) was added at 0°C. The reaction mixture refluxed for 5h. The solid obtained was crystallizes from acetic acid.

5-(3-oxo-5,6- dipyridyl -2,3-dihydropyridazin-4-yl)-1*H*-pyrazole-3-carboxylicacid 7:
A mixture of ester **5** (0.02 mole) and 10% NaOH solution (20ml) was refluxed for 2h ,then the reaction mixture was cooled, acidified with conc. HCl . The resulting solid was filtered washed with water, dried and crystallized from ethanol.

5-(3-oxo-5,6- dipyridyl -2,3-dihydropyridazin-4-yl)-1*H*-pyrazole-3-carbonyl chloride 8:
A suspension of the acid **7** (0.02 mole) and phosphorous oxychloride (20 ml) was refluxed for 2h .The excess $POCl_3$ was distilled under reduced pressure and the residual yellow fluid was poured onto ice-sodium carbonate solution. The resulting solid was filtered washed with water, dried and crystallized from toluene.

4-(5-(1H-benzo[d]imidazol-2-yl)-1H-pyrazol-3-yl)-5,6-dipyridylpyridazin-3(2H) -one 9:
To a solution of the acid chloride **8** (0.02 mole) in DMF (20 ml), o-phenylenediamine (0.02 mole) and K_2CO_3 were added. The reaction mixture refluxed for 24hs then cooled. After dilution with water the slid precipitated was filtered, dried and crystallized from DMF.

5-(3-oxo-5,6-dipyridyl-2,3-dihydropyridazin-4-yl)-N-P-Aryl-1*H*-pyrazole-3-carboxamide derivatives 10a-c:
To a solution of the acid chloride **8** (0.02 mol) in 30 ml DMF containing K_2CO_3, (0.02 mole) aromatic amines namely aniline, p-toluidine and anisidine was added. The reaction mixture was heated under reflux for 5 hrs, and then cooled to room temperature. The separated solids were filtered, dried and crystallized from ethanol.

(E)-N'-Benzylidene-3(3-oxo-5,6-dipyridyl-2,3-dihydropyridazin-4-yl)-1H-pyrazole-5-cabohydrazide derivatives 11a-c:
To a solution of the acid hyrazide **6** (0.01 mol) in 30 ml ethanol and few drops of acetic acid, (0.02 mole) of aromatic aldehydes namely benzaldehyde, p-chlorobenzaldehyde and p-nitrobenzaldehyde was added. The reaction mixture was heated under reflux for 5 hrs, and then cooled. The separated solids were filtered, dried and crystallized from acetic acid.

4-(5-(3,5-Dimethyl-1H-pyrazole-1-carbonyl)-1H-pyrazol-3-yl)-5,6-dipyridyl pyridazin-3(2H)-one 12:
A mixture of hydrazide **6** (0.02 mole) and acetyl acetone (0.02 mole) in glacial acetic acid 10 ml and few drops of DMF was stirred at room temperature overnight. After dilution with water the solid precipitated was filtered, dried and crystallized from acetic acid.

5,6-Dipyridyl-4-[5-(5-sulfanyl-1,3,4-oxadiazol-2-yl)-1H-pyrazol-3-yl] pyridazin-3(2H)-one 13:
Carbon disulfide (2 ml) was added drop wise to an ice cooled solution of KOH (2g) in ethanol (20 ml) containing the acid hydrazide **6** (0.02 mole), then the reaction mixture was stirred at room temperature 2h . After dilution with ethanol the solid precipitated was washed twice with ether. To the solid obtained (1 g), 10% KOH (20 ml) was added then the reaction mixture was refluxed for 10 h, cooled, acidified with conc. HCl. The resulting solid was filtered washed with water, dried and crystallized from DMF.

4-{5-[(5-Amino-3-oxo-2,3-dihydro-1H-pyrazol-1-yl)carbonyl]-5,6-dipyridyl pyridazin-3(2H)-one 14:
A mixture of acid hyrazide **6** (0.02 mole) in 10% KOH solution (10 ml) and ethyl cyanoacetate was refluxed in ethanol (20ml) for 10h, then the reaction mixture was cooled, diluted with water and acidified with conc. HCl. The resulting solid was filtered washed with water, dried and crystallized from ethanol.

(E)-Ethyl 3-(2-(5-(3-oxo-5,6- dipyridyl-2,3-dihydropyridazin-4-yl)-1H-pyrazole- 3-carbonyl) hydrazono) butanoate 15:
A mixture of hydrazide **6** (0.02 mole) and ethyl acetoacetate (10ml) was refluxed for 5h. The reaction mixture was diluted with pet. ether (60-80) and the resulting solid was filtered washed with water, dried and crystallized from acetic acid .

4-(5-(3-Methyl-5-oxo-4,5-dihydro-1H-pyrazole-1-carbonyl)-1H-pyrazol-3-yl)-5,6dipyridyl -pyridazin-3 (2H)-one 16:
A solution of ester **15** (0.02 mole) on 2M NaOH (20ml) was refluxed for 5h, and then the reaction mixture was cooled, acidified with conc. HCl. The resulting solid was filtered washed with water, dried and crystallized from acetic acid.

N-Benzoyl-5-(3-oxo-5,6-dipyridyl-2,3-dihydropyridazin-4-yl)-1H-pyrazole-3-carbohydrazide 17:
A mixture of hydrazide **6**(0.02 mole) and benzoyl chloride (0.02 mole) in pyridine (20 ml) for 24h , then the reaction mixture was cooled, diluted with water and acidified with dil. HCl. The resulting solid was filtered washed with water, dried and crystallized from ethanol.

5,6-Dipyridyl -4-(5-(5-phenyl-1,3,4-oxadiazol-2-yl)-1H-pyrazol-3-yl)pyridazin-3(2H)-one 18 :
A mixture of compound **17** (0.02 mole) in dry xylene (20 ml) and phosphorous pentoxide (0.5g) was refluxed for 12h, then the reaction mixture was cooled, diluted with water and neutralized with ammonia. The solid separated was filtered washed with water, dried and crystallized from acetic acid.

REFERENCES

[1] A. F. Seleim, *Der Pharma Chemica*; **(2013),** 5(3), 1-7.
[2] A. F. Seleim, *Der Pharma Chemica;***(2012)** , 4(3), 860-866.
[3] M. Kopp, J. Lancelot, P. Dallemagne and S. Rault*; J. Heter.Chem*; **(2001),** 38, 1045.
[4] E.Vinge and S.Bjorkman; *Acta pharmacol.et toxicol.;* (**1986**), 59, 165.
[5] Y .S .R. Reddy,T.Sosamma mani, G .V .S. Rama Sarma and B. Suresh *Indian J. pharma Sci.;* **(1999),** 61, 25.
[6] N .K. Satti, K .A. Suri and O. P. Suri; *Indian Drugs*; **(1987),** 24(10), 492.
[7] D. Libermann, N. Rist, F. Grumback, S. Cals, M. Moyeux and A. Rouaix; *Bull. Soc. Chim. France*; **(1958),** 687. C.A; **(1958**), 52, 20147g.
[8]L.Brockunier, J. Guo, R. Liang, E. Parmee, S. Raghavan, G. Tria and Y. Xiong; **(2006),** *PCT/US 2005/025541* . *WO 014618* p. 26.
[9]M .M. Ismail and H .M. Mohamed; *Biannual Conference on Chemistry*; (2004), 21.
[10]M. F.A.Yassin, *J.UltraChemistry* ; **(2008)** ,(4), 271-278.
[11]M. Kamal El-Dean and A. Geies; *J. Chem. Research (S)*; **(2005)**, 352,.
[12]H.Suzuli and N. Nonoyama; *J. Chem.Research (S);* **(1996)** , 244.
[13]M .S .K. Youssef, Kh. M. hassan, F. H., Atta and M.S. Abbady; *J. Heter. Chem*; **(1984),** 21, 1565.
[14]A. A. El-sayed and F. A. Atta; *Bull. Chem. Soc. Japan*; **(1973),** 46, 942.
[15]A. Weissberger and H.D. Porter; *J. Amer. Chem. Soc*; **(1944),** 66, 1849.
[16]R H. Wiely and P. Wiely "*Pyrazolones, Pyrazolidones and their Derivatives*" Jon Wiely and sons, NY; **(1946),** p. 132. 133.
[17]Rigo and D. Couturier; *J. Heter. Chem*; **(1985)**, 22, 925.
[18]F.A.Yassin *Journal of Microbiology and Antimicrobials;* **(2010)**, 2(7), 93-99.