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Synthesis and reactions of 5-phenylpyrido-[3,2-d]-pyridazin-8(7*H*)-one derivatives

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ABSTRACT

*Reaction of picolinic acid anhydride with dry benzene under Friedl-Crafts conditions gave 3-benzoyl picolinic acid **1** which on reaction with hydrazine hydrate in boiling n- butanol afforded 5-phenylpyrido[3,2-d]pyridazine-8(7H)-one **2**. Reaction of pyridazinone **2** with ethyl chloroacetate in dry acetone and K_2CO_3 gave ethyl 2-(5-phenylpyrido[3,2-d]pyridazin—8-yloxyl)acetate **3** which on reaction with hydrazine hydrate in refluxing ethanol afforded 2-(5-phenylpyrido [3,2-d]pyridazin—8-yloxyl)acetohyrazide **4** .Cyclization of the acid hydrazide **4** with phenyl isothiocyante under different conditions afforded oxadiazole and thiadiazole derivatives **9** and **10**. Also, cyclization the acid hydrazide **4** with of CS_2 in alcoholic KOH and with benzoic acid in refluxing with $POCl_3$ gave oxadiazole derivatives **12** and **13** respectively . Hydrazones **14a,b** and **c** were prepared via the reaction of the acid hydrazide **4** with appropriate aldehydes flowed by treatment with thioglycolic acid gave thiazolidine **15a,b** and **c**, while on reaction of **14a** with ethyl chloroacetate flowed by refluxing in dichlorobenzene yielded pyrazole derivative **17**. The structure of new compounds was confirmed from its correct analytical and spectral data.*

Keywords: Pyridopyridazinone, thiazoles, oxadiazoles, thiadiazole, triazole, cardiovesclator, antihypertensive activity.

INTRODUCTION

Pyridazinones are reported to possess interesting pharmacological activities like antihypertensive, antihistaminic, analgesic, anti-inflammatory, anticancer, and anti-HIV[(1-9)]activities. In spite of various pyridopyridazinones derivatives attached to thiazole, oxadiazole, thiadiazole and triazole moieties having been prepared and studied. The starting material 5-phenylpyrido [3,2-d]pyridazin-8(7*H*)-one **2** was synthesized from reaction of picolinic acid anhydride with dry benzene in the presence of $AlCl_3$ under Friedl-Crafts conditions gave 3-benzoyl picolinic acid **1** followed by cyclization with hydrazine hydrate in boiling n- butanol The title compounds were synthesized by the cyclocondensation of 2-(5-phenylpyrido [2, 3-d] pyridazin-8-yloxyl)acetohydrazide **4** with different reagents. The chemical structures of the synthesized compounds were confirmed on the basis of their spectral and the purity was ascertained by microanalysis. Characterization and physical data are listed in table 1.

MATERIALS AND METHODS

All melting points (M.P.) were uncorrected. IR spectra were measured using KBr diske plate technique with a Bruker FT-IR ISS 25 spectrophotometer (ν_{max} in cm^{-1}). ^{1}HNMR spectra (DMSO-d_6 and $CDCl_3$) were carried out with a Bruker Avance 200 MHz spectrometer using TMS as internal reference (chemical shifts in δ, ppm).

5-Phenylpyrido-[3,2-d]pyridazin-8(7H)-one 2:
A mixture of 3-benzoyl picolinic acid **1** (0.01 mole) in *n*-butanol (20 ml) and hydrazine hydrate (0.01 mole) was refluxed for 3 h. The reaction mixture was cooled; the separated solid was filtered, dried and recrystallized.

Ethyl 2-(5-phenylpyrido [2,3-d]pyridazin-8-yloxyl)acetate 3:
A mixture of 5-phenylpyrido-[3,2-d]pyridazin-8(7H)-one **2** (0.01 mole) and ethyl chloroacetate (0.01 mole) in the presence of K_2CO_3 (0.04 mole) was refluxed in dry acetone (30 ml) for 24 h, then the solvent was evaporated and the residue was dissolved , and the solid separated was filtered, dried and recrystallized.

2-(5-Phenylpyrido [2, 3-d] pyridazin-8-yloxyl)acetatohydrazide 4:
A mixture of the ester **3** (0.01mol) and hydrazine hydrate(0.01mol) in absolute ethanol (30 ml) was heated under reflux for 5 hours , the reaction mixture was left to cool . The precipitate was collected and recrystallized.

8-Chlolo-5-phenylpyrido [2, 3-d] pyridazine 5:
A mixture of 5-Phenylpyrido-[3,2-d]pyridazin-8(7H)-one **2** (0.01 mol) with excess phosphorous oxychloride (30 ml) was refluxed for 4 hours. The reaction mixture was left to cool; the excess $POCL_3$ was evaporated under vacuum the precipitate was washed several times with water the filtered and recrystallized .

8-Hydrazinyl-5-phenylpyrido [2, 3-d] pyridazine 6:
To a solution of 3-chloro-4,5,6- triphenylpyridazine **5** (0.01 mol.) in *n*- butanol (10 ml), hydrazine hydrate (3 ml) was added. The reaction mixture was refluxed for 12h. The precipitated product was filtered, dried and recrystallized.

5-Phenylpyrido [3,2-d]pyridazin-8(7H)-thione 7**.**
A mixture of compound **2** (0.01 mol) and P_2S_5 (0.02mole) , was refluxed for 6 hours in dry xylene (20ml) . The solid precipitated was washed with xylene and recrystallized.

N-phenyl-2-(2-(5-phenylpyrido[3,2-d]-8-yloxyl)acetyl) hydrazine carbothioamide 8 :
A mixture of the acid hydrazide **4**(0.01 mol) and phenylisocyanate (0.01mol) in absolute ethanaol (30 ml) was heated under reflux for 5 hours , the reaction mixture was left to cool . The precipitate was collected and recrystallized**.**

N-phenyl-5-((5-phenylpyrido[3,2-d]-8-yloxyl)methyl)-1,3,4-oxadiazole-2-amine 9:
To a mixture of compound **8** (0.01 mol) in 20 ml of (4N) NaOH , I_2/KI solution was added until the colour of I_2 disappeared then, the reaction mixture was refluxed for 6 h. The mixture was cooled and poured in ice-cold water; the solid precipitated was washed several times with water, filtered and recrystallized.

N-phenyl-5-((5-phenylpyrido[3,2-d]-8-yloxyl)methyl)-1,3,4-thiadiazole-2-amine 10:
2- Aniline oxadiazole **9** (0.01 mole) was dissolved in cold concentrated H_2SO_4 acid (2ml) .The mixture was stirred at room temperature for 3 h, then poured upon crushed ice . The solid separated was washed several times with water, filtered and recrystallized.

4-Phenyl-5-((5-phenylpyrido[3,2-d]-8-yloxyl)methyl)- 4*H*-1,2,4-triazole-3-thiol 11.
A mixture of the acid hydrazide **4**(0.01 mol) and phenylisocyanate (0.01mol) in absolute ethanaol (30 ml) and (20ml) of 10% NaOH solution was heated under reflux for 5 hours , the reaction mixture was left to cool . The precipitate was collected and recrystallized.

5-((5-phenylpyrido [3,2-d]-8-yloxyl)methyl)- 1,3,4-oxadiazole -2-thiol 12:
Carbon disulfide (2 ml) was added drop wise to an ice cooled solution of KOH (2g) in ethanol (20 ml) containing the acid hydrazide **4** (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.

2-Phenyl-5-((5-phenylpyrido[3,2-d]-8-yloxyl)methyl)- 1,3,4-oxadiazole 13:
To a solution of aminotriazole **12** (0.02 mole) in phosphorus oxychloride (0.02 mole), benzoic acid (0.01 mol) was added. The reaction mixture was refluxed for 2h on a water bath, and then the reaction mixture was slowly poured into crushed ice with stirring and neutralized with sodium bicarbonate. The precipitate obtained was filtered off, washed with water, dried and recrystallized.

N- Arylidene 2- (5-phenylpyrido[3,2-d]-8-yloxyl)acetohydrazide derivatives 14a,b and c: To a solution of the acid hydrazide 4 (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*-methoxybenzaldehyde was added. The reaction mixture was heated under reflux for 5 h , and then cooled. The separated solids were filtered, dried and recrystallized.

4-(Substituted) phenyl-3-(2-(5-phenylpyrido[3,2-d]pyridazin-8-yloxyl)acetyl) thiazolidin-2-ones 15a-c.
To a solution of the N- arylidenes **14a,b and c** (0.01 mol) in dry benzene (50 ml) thioglycolic acid (0.01 mol) was added, the mixture was refluxed for 5h. The excess benzene was evaporated and the residue obtained was dried and recrystallized.

(E)-ethyl-3-(2-(5-(3-oxo-5,6-diphenyl-2,3-dihydropyridazin-4-yl)-1H-pyrazole-3-carbonyl)hydrazino) butanoate16:
A mixture of acid hydrazide **4** (0.02 mole) and ethyl chloroacetate (0.02 mole) in n- butanol (20ml) was refluxed with stirring for 5 h ,then the reaction mixture was cooled. The resulting solid was filtered washed with ethanol, dried and crystallized.

4-(5-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazole-1-carbonyl)-1H-pyrazol-3-yl)-5,6-diphenylpyridazin-3(2H)-one 17:
A mixture of acid hydrazide **4** (0.02 mole) and ethyl chloroacetate (0.02 mole) and n- butanol (20ml) in presence of 10 ml of 10% NaOH solution was refluxed with stirring for 5 h ,then the reaction mixture was cooled, neutralized with dil. HCl solution . The resulting solid was filtered washed with water, dried and recrystallized.

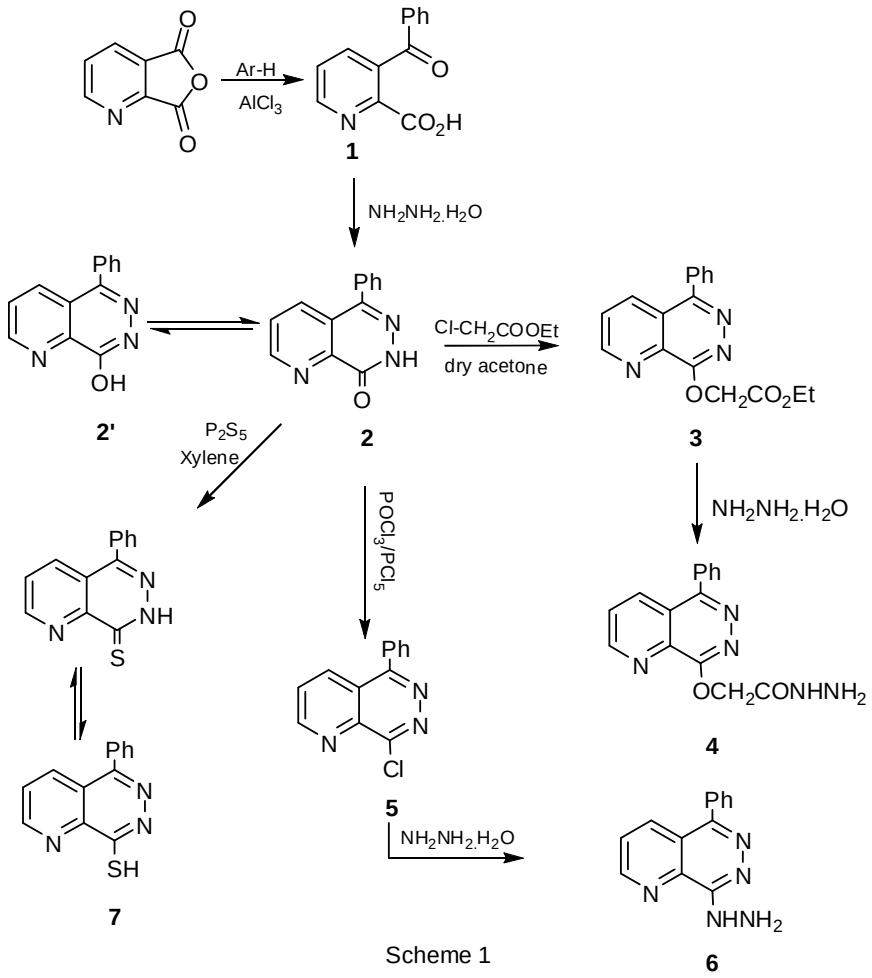
RESULTS AND DISCUSSION

In previous studies we reported the synthesis of different *o*-aroyl aromatic acids via reaction of phthalic anhydride with different aromatic hydrocarbons under Friedl-Crafts conditions, followed by cyclization with hydrazines to give the corresponding benzopyridazinone derivatives. In this study reaction picolinic acid anhydride with dry benzene In the presence of $AlCl_3$ under Friedl-Crafts conditions gave 3-benzoyl picolinic acid **1** which on cyclization with hydrazine hydrate in boiling n- butanol afforded 5-phenylpyrido [3,2-d]pyridazin-8(7*H*)-one **2**.The structure of **2** was confirmed from its analytical and spectral data .IR spectrum of **2** exhibits absorption bands at 1660, 3200 and 3400 attributable to C=O, OH and NH groups, this illustrate that pyridopyridazinone **2** exists in lactam – lactim dynamic equilibrium .The presence of **2** in lactim form was confirmed from its reaction with ethyl chloroacetate in the presence of K_2CO_3 in dry acetone [(10)] gave ethyl 2-(5-phenylpyrido [2,3-d]pyridazin-8-yloxyl)acetate **3**. No N- alkyl derivative was obtained due to the rapid intercoversion under this condition of the lactam form (CO-NH) to lactim form (HO-C=N). The structure of **3** was confirmed from its correct analytical and spectral data. IR spectrum of **3** showed absorption bands at 1725(C=O ester), 1665(C=O) and1645 (C=N). ^{1}HNMR spectrum of **3** showed signals at δ =1.3(t, 3H, CH2-CH_3) 4.3(q, 2H, CH_2-CH_3), 5.1(s, 2H, CH_2-), and 7.3-7.8 (m, 7H aromatic protons).

Chemically, the structure of the ester **3** was confirmed through its reaction with hydrazine hydrate to give 2-(5-phenylpyrido [2, 3-d] pyridazin-8-yloxyl)aceto hydrazide **4** . The structure of the acid hydrazide **4** was established from its spectral and analytical data. IR spectrum of **4** showed absorption bands at 3385, 3290(NH), 1690, 1665(2C=O) and 1645 (C=N). ^{1}H-NMR spectrum of **4** showed signals at δ = 4.4(s, 2H, NH_2), 7.1(s, 1H, NH), 7.4-7.8(m, 7H aromatic protons), 9.8(s, 1H, NH, CONH).scheme 1.

The lactime form of the pyridopyridazinone **2** has been supported via its reaction with $POCl_3/PCl_5$ mixture [(14)] afforded the corresponding 8-chlolo5-phenylpyrido [2, 3-d] pyridazine **5** which on reaction with hydrazine hydrate in boiling n-butanol gave 8-hydrazinyl-5-phenylpyrido [2, 3-d] pyridazine **6**.The structure of the hydrazino pyridazine derivative **6** was established from its analytical and spectral data. The lactam form of **2** has been confirmed via its reaction with P_2S_5 in boiling dray xylene afforded the corresponding 5-phenylpyrido [3,2-d]pyridazin-8(7*H*)-thione **7**. The structure of **7** was confirmed from its analytical and spectral data .IR spectrum of **3** exhibits absorption bands at 1660, 3200 and 3400 attributable to C=O, OH and NH groups confirming that pyridopyridazine thion **7** is presence in the phenomena of thioamid ====== iminothiol dynamic equilibrium. In the present work, the acid hydrazid **4** was considered as the starting material for preparing different heterocyclic moieties attached to pyridopyridazine ring with the hope of obtaining high biological and pharmaceutical activities.
It has been reported that, 1, 3, 4- oxadiazoles exhibit a wide therapeutic activities as anti-inflammatory activity, this promoted us to prepare novel oxadizole derivatives through the reaction of the acid hyrazide **4** with phenyl isothiocyanate in refluxing ethanol [(11)] afforded N-phenyl-2-(2-(5-phenylpyrido[3,2-d]-8-yloxyl)acetyl)-hydrazine carbothioamide **8** which on treatment with KI/I_2 in NaOH solution gave the corresponding N-phenyl-5-((5-phenylpyrido[3,2-d]-8-yloxyl)methyl)-1,3,4-oxadiazole-2-amine **9** . On the other hand reaction of carbothioamide derivative **8** with conc. H_2SO_4 at room temperature[(15)] yielded the corresponding N- phenyl-5-((5-phenylpyrido[3,2-

d]-8-yloxyl)methyl)-1,3,4-thiadiazole-2-amine **10**, while on cyclization of **8** in refluxing NaOH afforded 4-phenyl-5-((5-phenylpyrido[3,2-d]-8-yloxyl)methyl)- 4*H*-1,2,4-triazole-3-thiol **11**. scheme2

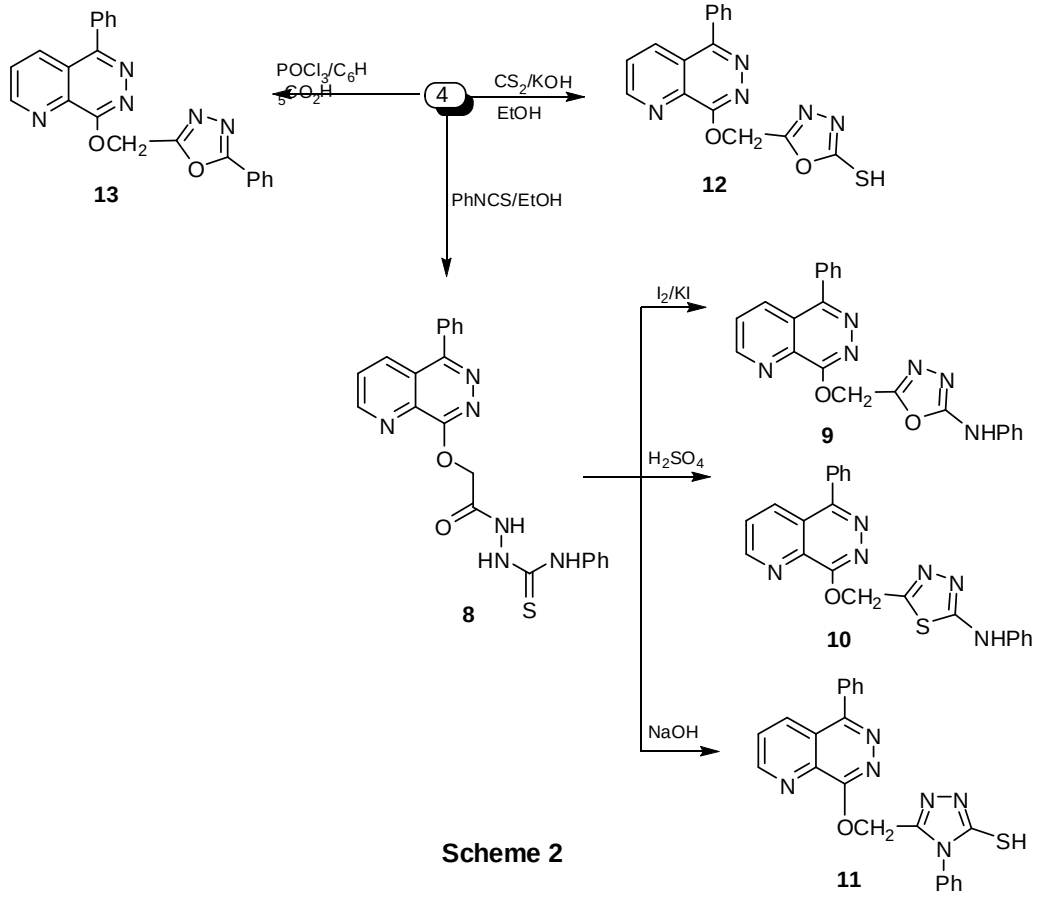


Scheme 1

Reaction of the acid hydrazide **4** with carbon disulphide[12] in ethanol containing KOH at room temperature gave potassium dithiocabazate derivative which undergo cyclative dehydrosulphorization via refluxing the reaction mixture overnight gave 5-((5-phenylpyrido[3,2-d]-8-yloxyl)methyl)- 1,3,4-oxadiazole -2-thiol **12.**

It has been reported that, 1, 3, 4- oxadiazoles exhibit a wide therapeutic activities such as anti-inflammatory activity. Hence, in this investigation,2-phenyl-5-((5-phenyl pyrido[3,2-d]-8-yloxyl)methyl)- 1,3,4-oxadiazole **13** was synthesized through the reaction of the acid hydrazide **4** with benzoic acid [13] in the presence of $POCl_3$ .The structure of oxadiazole **13** was confirmed from its correct analytical and spectral data.

N- Arylidene 2- (5-phenylpyrido [3,2-d]-8-yloxyl)acetohydrazide derivatives **14a,b** and **c** were prepared via the reaction of the acid hydrazide **4** with appropriate aldehydes namely, benzaldehyde, p-chlorobenzaldehyde and *p*-methoxybenzaldehyde in refluxing ethanol/acetic acid mixture. The structure of **14a-c** was confirmed from their correct analytical and spectral data, IR spectrum of **14a** showed bands at 3320, 3215(NH), 1690(C=O) and1605 cm^{-1} (C=N). While ^{1}H-NMR spectrum of **14c** showed signals at δ = 6.8(s, 1H, CH pyrazole), 7.2(s, 1H, NH), 7.5-8.1 (m, 14H aromatic protons), 9.5(s, 1H, CH=N), 11.2(s, 1H, NH amide) and 13.2 (s, 1H, NH pyrazole). Chemically , on reaction of N- Arylidene derivatives **14a,b** and **c** with thioglycollic acid in refluxing benzene yielded 4-substituted phenyl3-(2-(5-phenylpyrido[3,2-d]pyridazin-8-yloxyl)acetyl) thiazolidin-2-ones **15a,b** and **c**.On the other hand, reaction of carboxylic acid hydrazide **4** with ethyl acetoacetate[17] in ethanol containing NaOH under reflux followed by neutralization with dil. HCl gave(E)-ethyl-3-(2-(5-(3-oxo-5,6-diphenyl-2,3-dihydropyridazin-4-yl)-1H-pyrazole-3-carbonyl) hydrazino) butanoate**16**.



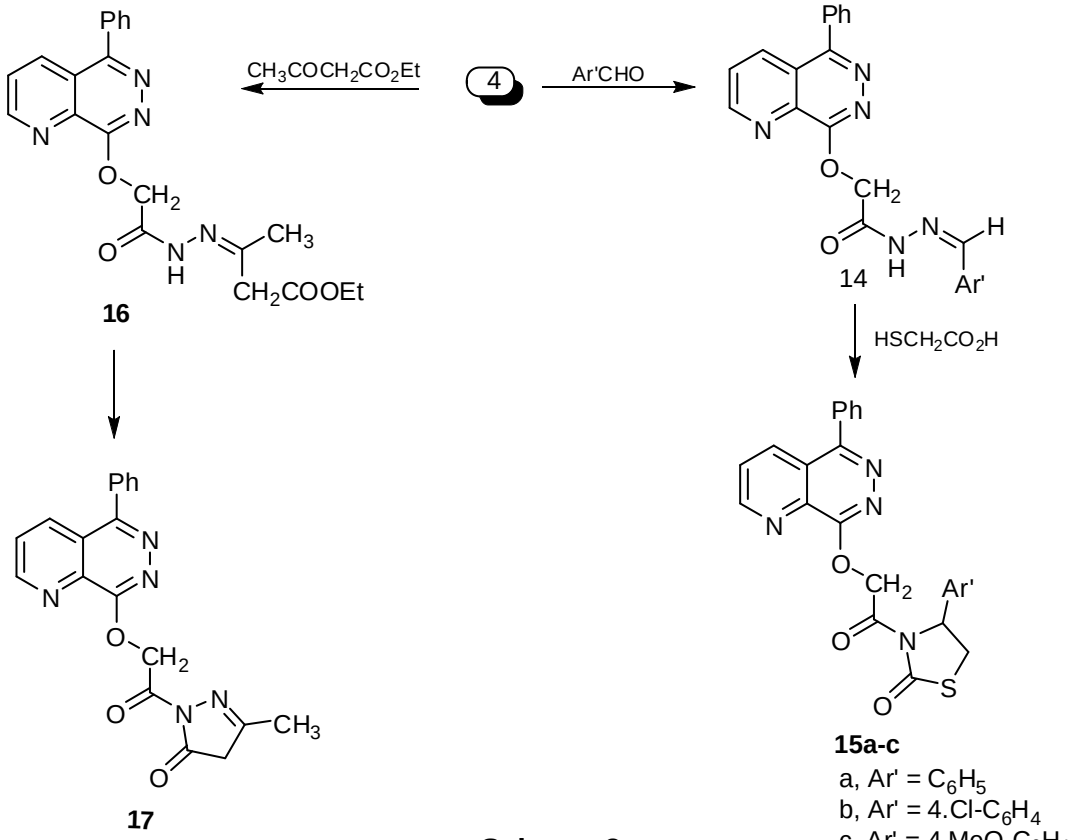
Scheme 2

Table (1): Charactization and physical data

Compd.	M.P. °C Solvent	Yield%	Mol. Formula /M.Wt	Analyses Calcd/Found (%)			
				C	H	N	S
1	225 E	75	$C_{13}H_9NO_3$ (227.22)	68.72 68.69	3.99 3.95	6.16 6.10	
2	275 E	87	$C_{13}H_9N_3O$ (223.23)	64.96 64.90	4.84 4.69	11.96 11.54	
3	145 Pet.	65	$C_{17}H_{15}N_3O_3$ (309.32)	66.01 65.91	4.89 4.83	13.58 13.40	
4	265 E	69	$C_{15}H_{13}N_5O_2$ (295.30)	61.01 65.90	4.44 4.40	23.72 23.50	
5	286 B	75	$C_{13}H_8ClN_3$ (241.68)	64.61 64.50	3.34 3.10	17.39 17.26	
6	175 M	60	$C_{13}H_{11}N_5$ (237.10)	65.81 65.60	4.67 4.55	29.52 29.46	
7	280 X	65	$C_{13}H_9N_3S$ (239.30)	65.25 65.11	3.79 3.71	17.56 17.50	13.40 13.22
8	235 E	70	$C_{22}H_{18}N_6O_2S$ (430.48)	61.38 61.10	4.21 4.15	19.52 19.41	7.45 7.44
9	255 E	66	$C_{22}H_{16}N_6O_2$ (396.40)	66.66 66.59	4.07 4.00	21.20 21.17	
10	240 E	63	$C_{22}H_{16}N_6OS$ (412.47)	64.06 64.00	3.91 3.86	20.38 20.20	
11	260 B	70	$C_{22}H_{16}N_6OS$ (412.47)	64.06 64.01	3.91 3.88	20.38 20.20	7.77 7.71
12	226 E	72	$C_{16}H_{11}N_5O_2S$ (337.36)	56.96 56.86	3.29 3.20	20.76 20.70	9.50 9.40
13	245 E	80	$C_{22}H_{15}N_5O_2$ (381.39)	69.28 69.11	3.96 3.90	18.36 18.22	
14a	160 E	69	$C_{22}H_{17}N_5O_2$ (383.40)	68.92 68.70	4.47 4.44	18.27 18.20	
15a	185 E	70	$C_{24}H_{18}N_4O_3S$ (442.49)	65.14 65.10	4.10 4.00	12.66 12.60	
17	E B	72	$C_{19}H_{15}N_5O_3$ (361.35)	54.94 54.90	4.16 4.11	17.48 17.41	

E=ethanol, B= Benzene, Bu= Butanol, Pet. =petroleum ether, M =Methanol, X=Xylene

The structure of **16** was confirmed from its correct analytical data, its IR spectrum which showed absorption bands at 3330, 3281, 3268 (NH), 1715(C=O ester), 1690(C=O) and 1645 cm^{-1} (C=N). Also, ^{1}HNMR spectrum of **10** showed signals at δ = 1.3 (t, 3H, CH_2CH_3), 1.9(s, CH_3), 2.5(s, 3H, CH2), 4.2(q, 2H, CH_2CH_3), 7.1(s, 1H, NH), 7.4-7.8(m, 10H aromatic protons), 10.2(s, 1H, CONH) and 13.0(s, 1H, NH proton). Cyclization of ethoxycarbonyl hydrazone **17** in aqueous NaOH[18] afforded the corresponding 4-(5-(3-methyl-5-oxo-4, 5-dihydro-1H-pyrazole-1-carbonyl)-1H-pyrazol-3-yl)-5, 6-diphenylpyridazin-3(2H)-one **17.** The structure of **17** was confirmed from its correct analytical data, its IR spectrum which showed absorption bands at 3290, 3265(NH), 1660(C=O) and 1645cm^{-1} (C=N). scheme3.



Scheme 3

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