International Scholars Journals

Advanced Journal of Microbiology Research ISSN 2241-9837 Vol. 12 (6), pp. 001-007, June, 2018. Available online at www.internationalscholarsjournals.org © International Scholars Journals

Author(s) retain the copyright of this article.

Full Length Research Paper

Novel pyrazolyl pyridazine derivatives likely to possess anti- inflammatory activity

F. A. Yassin

Chemistry Department, Faculty of Science, Zagazig University, Zagazig, Egypt. E-mail: fathy_yassin@yahoo.co.uk.

Accepted 14 pril, 2018

Reaction of 4-acetyl-5,6-diphenylpyridazin-3(2H)-one (1) with diethyl oxalate in refluxing sodium ethoxide/ethanol mixture afforded ethyl 2,4-dioxo -4-(3-oxo- 5,6-diphenyl-2,3-dihydropyridazin4-yl)butanoate (2) which with hydrazine hydrate (1:1 mol) in refluxing ethanol afforded ethyl5- (3-oxo-5,6-diphenyl-2,3-dihydropyridazin 4- yl)-1H-pyrazole-3-carboxylate (3) while reaction of 2 with hydrazine hydrate (1:2 moles) in refluxing ethanol gave the corresponding acid hydrazide (4) . Reaction of acid chloride (6) with primary amines namely, aniline, p-toluidine and anisidine in the presence of DMF containing K_2CO_3 afforded the corresponding amide derivatives (7a – c). Hydrazones (9a – c) were prepared via the reaction of the acid hydrazide (4) with appropriate aldehydes namely, benzaldehyde, p-chlorobenzaldehyde and p-nitrobenzaldehyde in refluxing ethanol/acetic acid mixture. Reaction of carboxylic acid hydrazide (4) with each of ethyl acetoacetate, acetylacetone and ethyl cyanoacetate gave the corresponding pyrazolone and pyrazole derivatives 11, 12 and 13 respectively.

Key words: Benzilmonohydrazone, pyridazine, pyrazole, ethyl acetoacetate, diethyl oxalate, acetylacetone, ethyl cyanoacetate, antihypertensive, anti-inflammatory.

INTRODUCTION

In continuation of previous works (Yassin, 2009, 2005, 2004) on pyridazine derivatives annulated with various five and six membered heterocycles and the considerable biological activity of pyridazinone derivatives as antihypertensive, anticancer, and H-IV activities, the synthesis of several pyridazines containing heterocyclic moieties such as pyrazoles had been outlined. These later compounds were reported to possess antipyretic, antipsychotic, antiplatelet aggregation, herbicidal activities and are used as food colorants (Vinge and Bjorkman, 1986; Reddy, 1999; Satti et al., 1987) in dyestuffs. In addition, it was reported that incorporation of pyrazole with other heterocyclic moieties enhances anti-inflammatory activity (Libermann et al., 1958; Brockunier et al., 2006; Ismail and Mohamed, 2004) as they have fewer gastric side effect in drugs used for rheumatic patients. Based on these considerations, it deemed on interest to synthesize of several newly pyrazolyl pyridazine derivatives.

In this work 3-acetyl-4,5-diphenylpyridazin-2(2H)-one (1) was prepared via the reaction of benzilmonohydrazone with ethyl acetoacetate in the presence of sodium ethoxide/ethanol solution which on reaction with diethyl oxalate in refluxing sodium ethoxide/ethanol (Kopp et al., 2001) mixture afforded ethyl 2,4-dioxo- 4-(3- oxo-5,6-diphenyl-2,3-dihydropyridazin-4-yl)butanoate (2). The structure of 2 was confirmed from its correct analytical and spectral data. IR spectrum of 2 showed absorption bands at 3300 (NH), 3105 (Ar-H), 2980, 2930 (C- H aliphatic), 1725(C=O ester), 1675, 1660(2C=O) and 1645(C=N). ^{1}HNMR spectrum of 2 showed signals at 1.3 (t, 3H, CH_2-$\underline{CH_3}$) 4.3 (q, 2H, $\underline{CH_2}$- CH_3), 5.1 (s, 2H, CH_2-), 7.0 (s, 1H, NH) and 7.3 - 7.8 (m, 10H aromatic protons).

One of the most common methods for pyrazole synthesis was the reaction of 1, 3-diketones with hydrazine hydrate or its monosubstituted derivatives. Thus, the reaction of 2 with hydrazine hydrate (1:1 mole) in refluxing ethanol (Rigo and Lagrenee, 1999; Kamal and Geies, 2005) afforded ethyl-5-(3-oxo-5,6-diphenyl-2,3-dihydropyridazin-4-yl)-1*H*-pyrazole-3 carboxylate (3) without hydrazinolysis of the ester function, while reaction of 2 with hydrazine hydrate (1:2 mol) in refluxing ethanol gave the corresponding 5-(3-oxo-5,6-diphenyl-2,3-

dihydropyridazin-4-yl)-1*H*-pyrazole-3-carbohydrazide 4 which can also be obtained by fusion of 2 with hydrazine hydrate. The structure of 3 was confirmed from its correct analytical and spectral data, IR spectrum of 3 showed absorption bands at 3330, 3290 (NH), 1715 (C=O ester), 1665 (C=O) and 1645 (C=N). ^{1}H-NMR spectrum of 3 showed signals at 1.2 (t, 3H, CH_2- CH_3), 4.1 (q, 2H, CH_2-CH_3), 6.3 (s,1H,CH-pyrazole), 7.1 (s, 1H, NH), 7.4 - 7.8 (m, 10H aromatic protons) and 13.1 (s, 1H, NH pyrazole). While 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 = 4.4 (s, 2H, NH_2), 6.3 (s, 1H, CH-pyrazole), 7.1 (s, 1H, NH), 7.4 - 7.8 (m, 10H aromatic protons), 9.8 (s, 1H, NH, CONH) and 13.6 (s, 1H, NH pyrazole).

The reaction of ester 3 with primary amines in order to obtain amides 7a - c failed due to the week electrophilicity of the carbonyl group as a result of +M effect of both lone pair of electron of nitrogen and oxygen atoms of the alcohol part of the ester, while amides 7a - c were prepared via the hydrolysis of ester 3 with alkaline KOH to give the corresponding acid 5 which upon reaction with $POCl_3$ gave the acid chloride (6). The structure of each acid and acid chloride 5 and 6 was established from their correct analytical and spectral data (Scheme 1).

In IR spectra, the acid 5 showed absorption bands at 3340, 3285 (NH) 2930, 2905 (C-H aliphatic), 1690 (C=O), 1660 (C=O) and 1645 (C=N), while IR of the acid chloride 6 showed absorption bands at 3290 (NH), 3105 (Ar-H), 2930, 2905 (C-H aliphatic), 1727 (C=O),1665 (C=O) and 1645(C=N).

Reaction of acid chloride 6 with primary amines (Suzuli and Nonoyama, 1996; Youssef et al., 1984) namely, aniline, p-toluidine and anisidine in the presence of DMF containing K_2CO_3 afforded the corresponding 5-(3-oxo-5,6-diphenyl-2,3-dihydropyridazin-4-yl)-N-*p*-Aryl-1*H*-pyrazole-3-carboxamide derivatives 7a - c. IR spectrum of 7a showed absorption bands at 3310 (NH), 1660 (C=O) and 1640 (CONH). ^{1}H-NMR spectrum of 7c showed signals at 3.2 (s, 3H, CH3), 6.1 (s, 1H, CH pyrazole), 7.0 (s, 1H, NH), 7.5 - 8.1 (m, 14H aromatic protons), 9.2 (s, 1H, NH amide) and 13.8 (s, 1H, NH pyrazole).

Also, reaction of the acid chloride 6 with o-phenylenediamine (El-Sayed and Atta,1973) in refluxing DMF in the presence of KCO_3 yielded 4-(5-(1H-benzo[d]imidazol-2-yl)-1H-pyrazol-3-yl)-5,6-diphenylpyridazin-3(2H)-one (8). The structure of benzimidazole 8 was confirmed from its analytical and spectral data; IR spectrum of 8 showed absorption bands at 3371, 3207 (NH), 1690 (C=O) and 1605 cm^{-1} (C=N). ^{1}HNMR spectrum of 8 showed signals at 6.3 (s, 1H, CH pyrazole), 7.1 (s, 1H, NH), 7.4 - 7.8 (m, 14H aromatic protons), 12.0 (s, 1H, NH benzimidazole) and 13.0 (s, 1H, NH pyrazole) (Scheme 2).

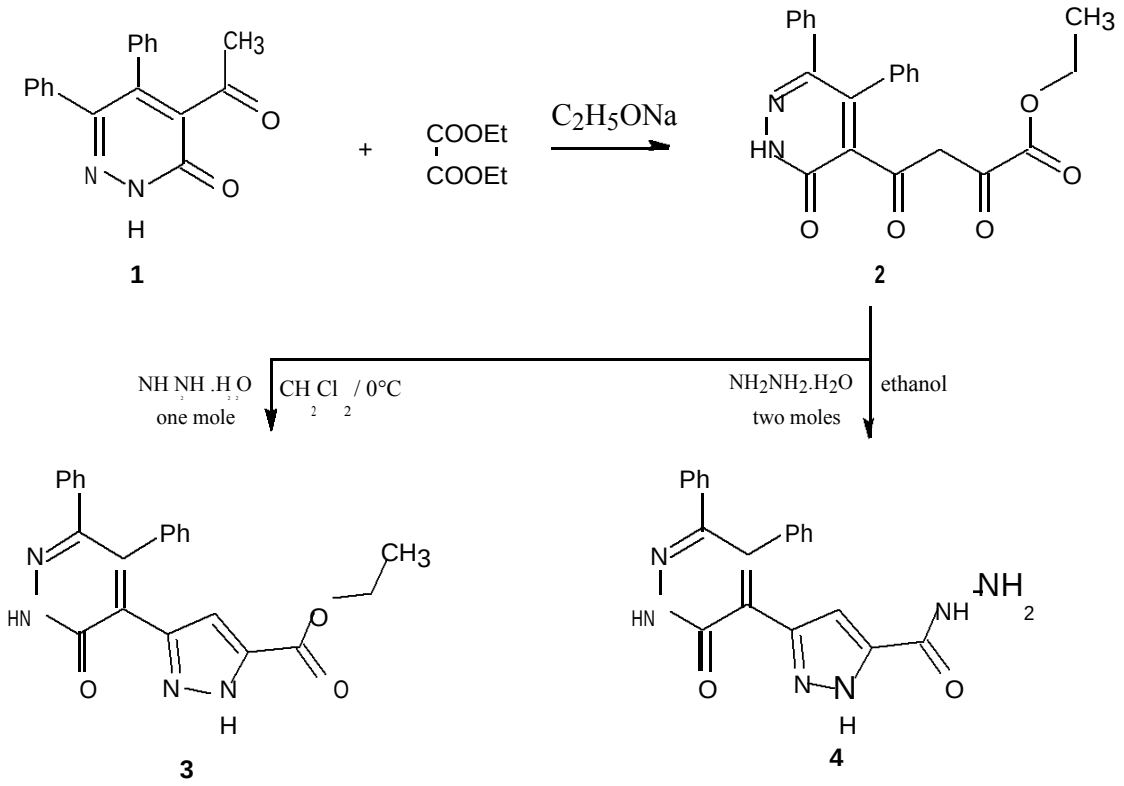
Hydrazones 9a - c were prepared via the reaction of the acid hydrazide 4 with appropriate aldehydes namely, benzaldehyde, p-chlorobenzaldehyde and p-nitrobenzaldehyde in refluxing ethanol/acetic acid mixture. The structure of 9a - c was confirmed from their correct analytical and spectral data, IR spectrum of 9a showed bands at 3320, 3215 (NH), 1690 (C=O) and1605 cm^{-1} (C=N). While ^{1}H-NMR spectrum of 9c showed signals at 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).

On the other hand, reaction of carboxylic acid hydrazide 4 with ethyl acetoacetate (Weissberger and Porter, 1944) in ethanol containing NaOH under reflux followed by neutralization with diluated. HCl gave(E)-ethyl3-(2-(5-(3-oxo-5,6-diphenyl-2,3-dihydropyridazin-4-yl)-1H-pyrazole-3- carbonyl)hydrazono)butanoate (10). The structure of 10 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 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 hydrazonebutanoate (10) in aqueous NaOH afforded the corresponding4-(5-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazole-1-carbonyl)-1H-pyrazol-3-yl)-5,6-diphenylpyridazin-3(2H)-one (11). The structure of 11 was confirmed from its correct analytical data, its IR spectrum which showed absorption bands at 3290, 3265 (NH), 1660 (C=O) and 1645 cm^{-1} (C=N) (Scheme 3).

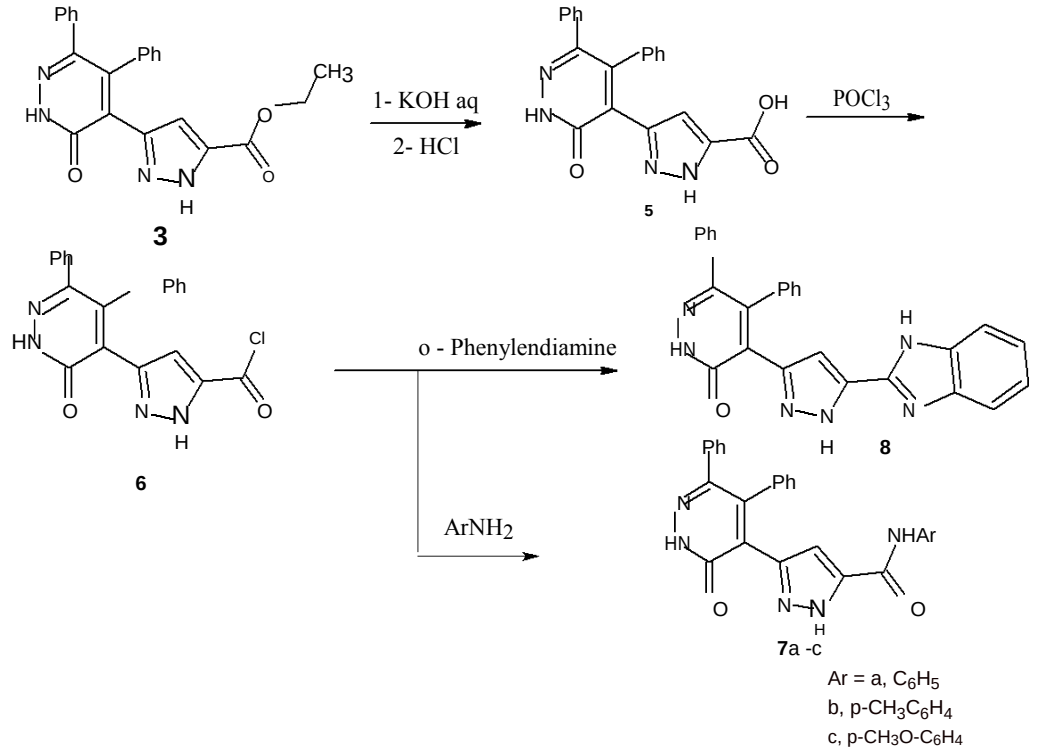
Also, ^{1}HNMR spectrum (solvent: DMSO-d_6) of 11 showed signals at = 1.9 (s, 3H, CH_3), 2.5 (s, 2H, CH_2 pyrazolone), 6.3 (s, 1H, CH pyrazole), 7.0 (s, 1H, NH), 7.4 - 7.8 (m, 10H aromatic protons) and 13.5 (s, 1H, NH proton).

In this investigation, when carboxylic acid hydrazide (4) was refluxed with acetylacetone (Wiely and Wiely, 1946) in ethanol containing KOH, which gave 4-(5-(3,5-dimethyl-1H-pyrazole-1-carbonyl)-1H-pyrazol-3-yl)-5,6-diphenylpyridazin-3(2H)-one (12). Compound 12 was also obtained by fusion of the acid hydrazide (4) with acetylacetone in an oil bath. 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 1645 cm^{-1} (C=N). Also, ^{1}H-NMR spectrum of 12 showed signals at 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, 10H aromatic protons) and 13.8 (s, 1H, NH proton) (Scheme 4).

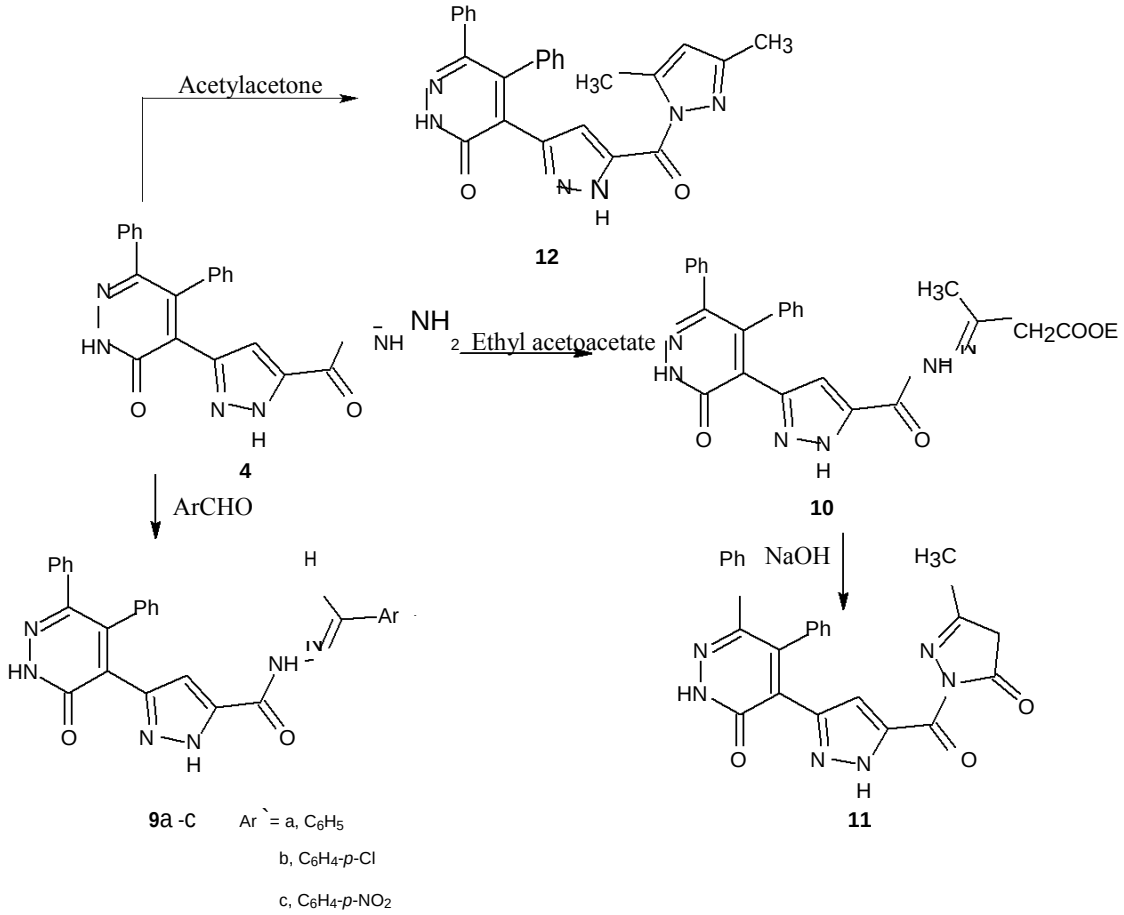
Similarly, 4-{5-[(5-amino-3-oxo-2,3-dihydro-1H-pyrazol-1-yl)carbonyl] pyrazol-3-yl-5,6-diphenyl pyridazin-3(2H)-one (13) was obtained via the reaction of the carboxylic acid hydrazide (4) with ethyl cyanoacetate (Rigo and Couturier, 1985) in ethanol containing KOH under reflux. The structure of 13 was confirmed from its correct analytical data, its IR spectrum which showed absorption



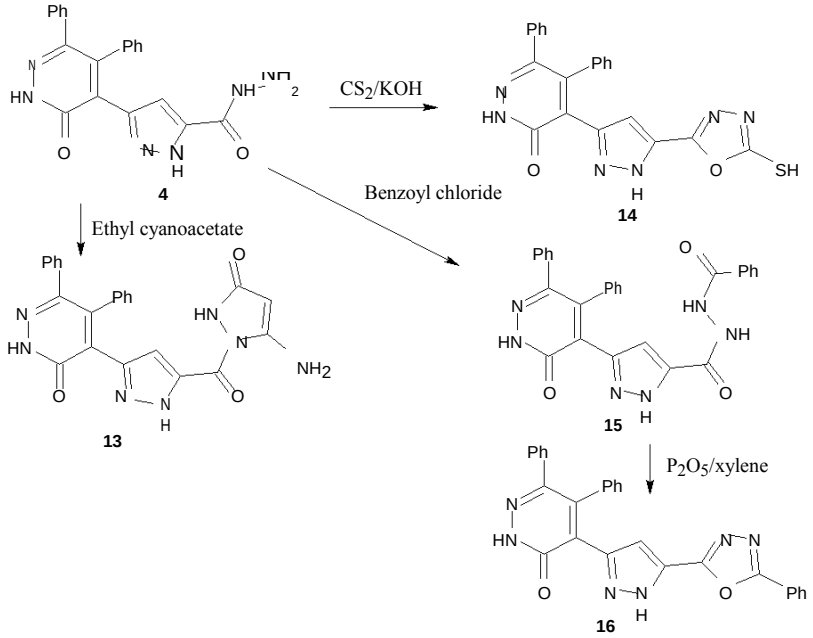
Scheme 1. synthesis of the acid hydrazide 4 as starting material.



Scheme 2. Synthesis of imidazole and pyrazole derivatives.



Scheme 3. Synthesis of imidazole and pyrazole derivatives.Synthesis of hydrazone and pyrazolone derivatives



Scheme 4. Synthesis of oxadiazine derivatives.

bands at 3281, 3268 (NH), 1715 (C=O ester), 1690 (C=O) and 1645 cm^{-1} (C=N) . Also, ^{1}HNMR spectrum of 13 showed signals at 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, 10H aromatic protons) and 13.2 (s, 1H, NH proton).

Reaction of the acid hydrazide (4) 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 h to give 5,6-diphenyl-4-[5-(5-sulfanyl-1,3,4-oxadiazol-2-yl)-1H-pyrazol-3-yl]pyridazin-3(2H)-one (14). The structure of 1,3,4-oxadiazole (14) 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) .

Benzoylation (Tobe et al., 1998) of the carboxylic acid hydrazide 4 was succeeded via its reaction with benzoyl chloride in refluxing pyridine to give N-benzoyl-5-(3-oxo-5,6-diphenyl-2,3-dihydropyridazin-4-yl)-1H-pyrazole-3-carbohydrazide (15) which under cyclocondensation in the presence of P_2O_5 in refluxing dry xylene afforded 5,6-diphenyl-4-(5-(5-phenyl-1,3,4-oxadiazol-2-yl)-1H- pyrazol-3-yl)pyridazin-3(2H)-one (16). The structure of 16 was confirmed from its correct analytical data, its IR spectrum which showed absorption bands at 3281, 3268 (NH), 1690 (C=O) and 1645 cm^{-1} (C=N). Also, ^{1}HNMR spectrum of 16 showed signals at 6.3 (s, 1H, CH pyrazole), 7.1 (s, 1H, NH), 7.4 - 7.8 (m, 15H aromatic protons) and 13.0 (s, 1H, NH proton).

EXPERIMENTAL

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 200 MHz spectrometer using TMS as internal reference (chemical shifts in δ, ppm). Microanalysis was preformed at the microanalytical center, Cairo University, Cairo, Egypt

Ethyl 2,4-dioxo-4-(3- oxo-5,6-diphenyl-2,3-dihydropyridazin-4-yl) butanoate (2)

To a mixture of sodium ethoxide solution (0.02 mol) (0.46 mg of sodium in 20 ml ethanol) and diethyl oxalate (0.02 mol), 4-Acetyl-5,6- diphenylpyridazin-3(2H)-one (1) (0.02 mol) was added at 0°C. The reaction mixture was stirred at 0°C for 3 – 4 h, and was then left at room temperature overnight. The solution was neutralized with ice-cold diluated HCl. Then the mixture was extracted with diethyl ether and the organic layer was collected, washed with water, dried and crystallized from benzene:

M.P.= 95°C, yield 80%.
Analysis: $C_{22}H_{18}N_2O_5$ (390.38).
Calcd.: C = 67.69; H = 4.65; N = 7.18.
Found: C = 67.5; H = 4.61; N = 7.00.

Ethyl 5-(3-oxo-5,6-diphenyl-2,3-dihydropyridazin-4-yl)-1*H*-pyrazole-3-carboxylate (3)

To a solution of 2 (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 10 h. The solvent was evaporated and the solid obtained was crystallized from ethanol:

M.P. = 145°C, yield 75%.
Analysis: $C_{22}H_{18}N_4O_3$ (386.40).
Calcd.: C = 68.38; H = 4.70; N = 14.50.
Found: C = 68.20; H = 4.67; N = 14.34.

5-(3-oxo-5,6-diphenyl-2,3-dihydropyridazin-4-yl)-1*H*-pyrazole-3-carbohydrazide (4)

To a solution of 2 (0.02 mol) in absolute ethanol, (50 ml) hydrazine hydrate (0.04 mol) was added at 0 °C. The reaction mixture refluxed for 5 h. The solid obtained was crystallized from acetic acid:

M.P. = 295°C, yield 66%.
Analysis: $C_{20}H_{16}N_6O_2$ (372.38).
Calcd.: C = 64.51; H = 4.33; N = 22.57.
Found: C = 64.20; H = 4.21; N = 22.34.

5-(3-oxo-5,6-diphenyl- 2,3-dihydropyridazin-4-yl)-1*H*-pyrazole-3-carboxylic acid (5)

A mixture of ester 3 (0.02 mol) and 10% NaOH solution (20 ml) was refluxed for 2 h, the reaction mixture was then cooled, acidified with conc. HCl. The resulting solid was filtered, washed with water, dried and crystallized from ethanol:

M. P. < 300 °C, yield 71%.
Analysis: $C_{20}H_{14}N_4O_3$ (358.35).
Calcd.: C = 67.03; H = 3.94; N = 15.63.
Found: C = 66.90; H = 3.87; N = 15.33.

5-(3-oxo-5,6-diphenyl-2,3-dihydropyridazin-4-yl)-1*H*-pyrazole-3-carbonyl chloride (6)

A suspension of the acid 5 (0.02 mol) and phosphorus oxychloride (20 ml) was refluxed for 2 h. 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:

M. P. < 300°C, yield 66%.
Analysis: $C_{20}H_{13}ClN_4O_2$ (376.79).
Calcd.: C = 63.75; H = 3.48; N = 14.87.
Found: C = 63.66; H = 3.41; N = 14.64.

5-(3-oxo-5,6-diphenyl-2,3-dihydropyridazin-4-yl)-N -P-Aryl-1*H*-pyrazole-3-carboxamide derivatives (7a – c)

To a solution of the acid chloride 6 (0.02 mol) in 30 ml DMF containing K_2CO_3, (0.02 mol), aromatic amines namely aniline, p-toluidine and anisidine was added. The reaction mixture was heated under reflux for 5 h, and then cooled to room temperature. The separated solids were filtered, dried and crystallized from ethanol:

M. P. 7a: 275°C; 7b: 255°C and 7c: 287°C yield 70, 65 and 61%, respectively.
Analysis: 7a: $C_{26}H_{19}N_5O_2$ (433.46); 7b: $C_{27}H_{21}N_5O_2$ (447.48), and 7c: $C_{27}H_{21}N_5O_3$ (463.16).
Calcd.: 7a, Calcd.: C = 72.04; H = 4.42; N = 16.16.
Found: C = 71.98; H = 4.40; N = 16.00. 7b Calcd.: C = 72.47; H = 4.73; N = 15.65. Found: C = 72.38; H = 4.66; N = 15.50. 7c, Calcd.: C = 69.97; H = 4.57; N = 15.11.
Found: C = 69.88; H = 4.51; N = 15.00.

4-(5-(1H-benzo[d]imidazol-2- yl)-1H-pyrazol-3-yl)-5,6-diphenylpyridazin-3(2H)-one (8)

To a solution of the acid chloride (6) (0.02 mol) in DMF (20 ml), o-phenylenediamine (0.02 mol) and K_2CO_3 were added. The reaction mixture refluxed for 24 h and then cooled. After dilution with water, the solid precipitated was filtered, dried and crystallized from DMF:

M. P. 245°C, yield 66%.
Analysis: $C_{26}H_{18}N_6O$ (430.46).
Calcd.: C = 72.55; H = 4.21; N = 19.52.
Found: C = 72.45; H = 4.11; N = 19.30.

(E)-N'-Benzylidene-3(3-oxo-5,6-diphenyl-2,3-dihydropyridazin -4-yl)-1H-pyrazole-5-cabohydrazide derivatives (9a – c)

To a solution of the acid hyrazide (4) (0.01 mol) in 30 ml ethanol and few drops of acetic acid, (0.02 mol) of aromatic aldehydes namely benzaldehyde, p-chlorobenzaldehyde and p-nitrobenzaldehyde was added. The reaction mixture was heated under reflux for 5 h, and then cooled. The separated solids were filtered, dried and crystallized from acetic acid:

M.P. 9a: 275°C; 9b: 255°C, and 9c: 287°C, yield 70, 65 and 61%, respectively.

Analysis: 9a: $C_{27}H_{20}N_6O_2$ (460.49); 9b: $C_{27}H_{19}ClN_6O_2$ (494.93), and 9c: $C_{27}H_{19}N_7O_3$ (489.46).
Calcd.: 9a Calcd. C = 70.42; H = 4.38; N = 18.25. Found: C = 70.38; H = 4.31; N = 18.00. 9b Calcd.: C = 65.52; H = 3.87; N = 16.98. Found: C = 65.48; H = 3.76; N = 16.80. 9c Calcd.: C = 66.19; H = 3.88; N = 20.02. Found: C = 66.08; H = 3.71; N = 19.80.

(E)-Ethyl 3-(2-(5-(3-oxo-5,6-diphenyl-2,3-dihydropyridazin-4-yl)-1H-pyrazole- 3-carbonyl)hydrazono)butanoate (10)

A mixture of hydrazide (4) (0.02 mol) and ethyl acetoacetate (10 ml) was refluxed for 5 h. The reaction mixture was diluted with petroleum ether (60 - 80) and the resulting solid was filtered, washed with water, dried and crystallized from acetic acid:

M. P. 195°C, yield 73%.
Analysis: $C_{26}H_{24}N_6O_4$ (484.51).
Calcd.: C = 64.45; H = 4.99; N = 17.35.
Found: C = 64.37; H = 4.91;N = 17.30.

4-(5-(3-Methyl-5-oxo-4,5-dihydro-1H-pyrazole-1-carbonyl)- 1H-pyrazol-3-yl)-5,6-diphenylpyridazin-3(2H)-one (11)

A solution of ester 10 (0.02 mol) on 2 M KOH (20 ml) was refluxed for 5 h, and the reaction mixture was then cooled, acidified with conc. HCl. The resulting solid was filtered, washed with water, dried and crystallized from acetic acid:

M. P. < 300°C, yield 62%.
Analysis: $C_{24}H_{18}N_6O_3$ (438.43).
Calcd.: C = 65.75; H = 4.14; N = 19.17.
Found: C = 65.65; H = 4.11; N = 19.10.

4-(5-(3,5-Dimethyl-1H-pyrazole-1-carbonyl)-1H-pyrazol-3-yl)-5,6-diphenylpyridazin-3(2H)-one (12)

A mixture of hydrazide (4) (0.02 mol) and acetyl acetone (0.02 mol) 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:

M. P. 282°C, yield 66%.
Analysis: $C_{25}H_{20}N_6O_2$ (436.46).
Calcd.: C = 68.80: H = 4.62: N = 19.25.
Found: C = 68.65; H = 4.56; N = 19.00.

4-{5-[(5-Amino-3-oxo-2,3-dihydro-1H-pyrazol- 1-yl)carbonyl]-5,6-diphenylpyridazin-3(2H)-one (13)

A mixture of acid hyrazide (4) (0.02 mol) in 10% KOH

solution (10 ml) and ethyl cyanoacetate was refluxed in ethanol (20 ml) for 10 h, the reaction mixture was then cooled, diluted with water and acidified with conc. HCl. The resulting solid was filtered, washed with water, dried and crystallized from ethanol;

M. P. 265°C, yield 76%.
Analysis: $C_{23}H_{17}N_7O_3$ (438.43).
Calcd.: C = 62.87; H = 3.90; N = 22.31.
Found: C = 62.65; H = 3.81; N = 22.10.

5,6-Diphenyl-4-[5-(5-sulfanyl-1,3,4-oxadiazol-2-yl)-1H-pyrazol-3-yl]pyridazin-3(2H)-one (14)

Carbon disulfide (2 ml) was added drop wise to an ice cooled solution of KOH (2 g) in ethanol (20 ml) containing the acid hydrazide (4) (0.02 mol), the reaction mixture was then stirred at room temperature 2 h. 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:

M. P. 275°C, yield 61%.
Analysis: $C_{21}H_{14}N_6O_2S$ (438.43).
Calcd.: C = 60.86; H = 3.40; N = 20.28; S = 7.47.
Found: C = 60.75; H = 3.36; N = 22.10; S = 7.41.

N-Benzoyl-5-(3-oxo-5,6-diphenyl-2,3-dihydropyridazin-4-yl)-1H-pyrazole-3-carbohydrazide (15)

A mixture of hydrazide (4) (0.02 mol) and benzoyl chloride (0.02 mol) in pyridine (20 ml) for 24 h, then the reaction mixture was then cooled, diluted with water and acidified with dil. HCl. The resulting solid was filtered, washed with water, dried and crystallized from ethanol:

M. P. 285°C, yield 56%.
Analysis: $C_{27}H_{20}N_6O_3$ (476.48).
Calcd.: C = 68.06; H = 4.23; N = 17.64.
Found: C = 67.95; H = 4.15; N = 17.50.

5,6-Diphenyl-4-(5-(5-phenyl-1,3,4-oxadiazol-2-yl)-1H-pyrazol-3-yl)pyridazin-3(2H)-one (16)

A mixture of compound 15 (0.02 mol) in dry xylene (20 ml) and phosphorus pentoxide (0.5 g) was refluxed for 12 h, the reaction mixture was then cooled, diluted with water and neutralized with ammonia. The solid separated was filtered, washed with water, dried and crystallized from acetic acid:

M. P. <300°C, yield 60%.
Analysis: $C_{27}H_{18}N_6O_2$ (458.47).
Calcd.: C = 70.73; H = 3.96; N = 18.33.
Found: C = 70.65; H = 3.85; N = 18.00.

REFERENCES

Brockunier L, Guo J, Liang R, Parmee E, Raghavan S, Tria G, Xiong Y (2006). Annual Reports in Medicinal Chemistry. PCT/US 2005/02554. WO 014618, p. 26.

El-Sayed AA, Atta FA (1973). Bull. Chem. Soc. Japan. 46: 942.

Ismail MM, Mohamed HM (2004). Biannual Conference on Chemistry, p. 21.

Kamal EM, Geies A (2005). Synthesis of Some Pyrimidothienopyrimidine. J. Chem. Res. (S), p. 352.

Kopp M, Lancelot J, Dallemagne P, Rault S (2001). Synthesis of novel pyrazolopyrrolopyrazines, potential analogs of sildenafil. J. Heterocyclic Chem., 38: 1045.

Libermann D, Rist N, Grumback F, Cals S, Moyeux M, Rouaix A (1958). Strategies for Organic Drug Synthesis and Design. Bull. Soc. Chim. France, 687. C.A. 52, 20147g.

Reddy YSR, Sosamma MT, Rama SGVS, Suresh B (1999). Indian J. pharm. Sci., 61: 25.

Rigo A, Couturier D (1985). Studies on pyrrolidinones. Synthesis of N-benzhydrylpyroglutamic. J. Heterocycl. Chem., 22: 925.

Rigo A, Lagrenee M (1999). A simple and e cient procedure for synthesis of optically active 1,3,4-oxadiazole derivatives containing L-amino acid moieties. J. Heterocycl. Chem., 36: 1029.

Satti NK, Suri KA, Suri OP (1987). Synthesis and biological activities of new anti-inflammatory 4,5-dihydro-1H- pyrazoles. Indian Drugs, 24(10): 492-493.

Suzuli H, Nonoyama N (1996). Heterocyclic Chemistry. J. Chem. Res. (S), p. 244.

Tobe Y, Sasaki S, Mizuno M (1998). Novel Self-Assembly of m-Xylylene Type Dithioureas by Head-to-Tail Hydrogen Bonding. J. Org. Chem., 63: 7481.

Vinge E, Bjorkman S (1986). Compared effects of the two antiinflammatory drugs indoprofen and Lonazolac. Acta Pharmacol. Toxicol., 59: 165.

Weissberger A, Porter HD (1944). Synthesis, structure and inhibitory effects on cyclooxygenase. J. Am. Chem. Soc., 66: 1849.

Wiely RH, Wiely P (1946). "Pyrazolones, Pyrazolidones and their Derivatives" Jon Wiely and sons, NY., 132: 133.

Yassin FA (2004). Informations sur le ou les traducteurs. Egypt. J. Chem., 47(4): 427.

Yassin FA (2005). Synthesis of New Thieno- and Pyrazolo-pyridazine Derivatives. J. Chem. Res., 270-273.

Yassin FA (2009). Chem. Heterocycl. Comp., 45(8): 997-1003.

Youssef MSK, Hassan KHM, Atta FH, Abbady MS (1984). Advances in Heterocyclic Chemistry. J. Heterocycl. Chem., 21: 1565.