HETEROCYCLES, Vol. 81, No. 2, 2010, pp. 395 - 406. © The Japan Institute of Heterocyclic Chemistry
Received, 27th September, 2009, Accepted, 22nd December, 2009, Published online, 25th December, 2009
DOI: 10.3987/COM-09-11845

SYNTHESIS OF SOME NEW PYRIDAZINYLSPIROHETARYLINDOLES AND HETARYLPYRIDAZINE DERIVATIVES

Yassin Gabr,* Mohamed Abdel-Megid, Mohamed Abdel-Hamid Awas, and Naser Mohamed Abdel-Fatah

Department of Chemistry, Faculty of Education, Ain- Shams University, Roxy, Cairo 11757, Egypt

*Corresponding Author: E-mail: yasingabr@yahoo.com

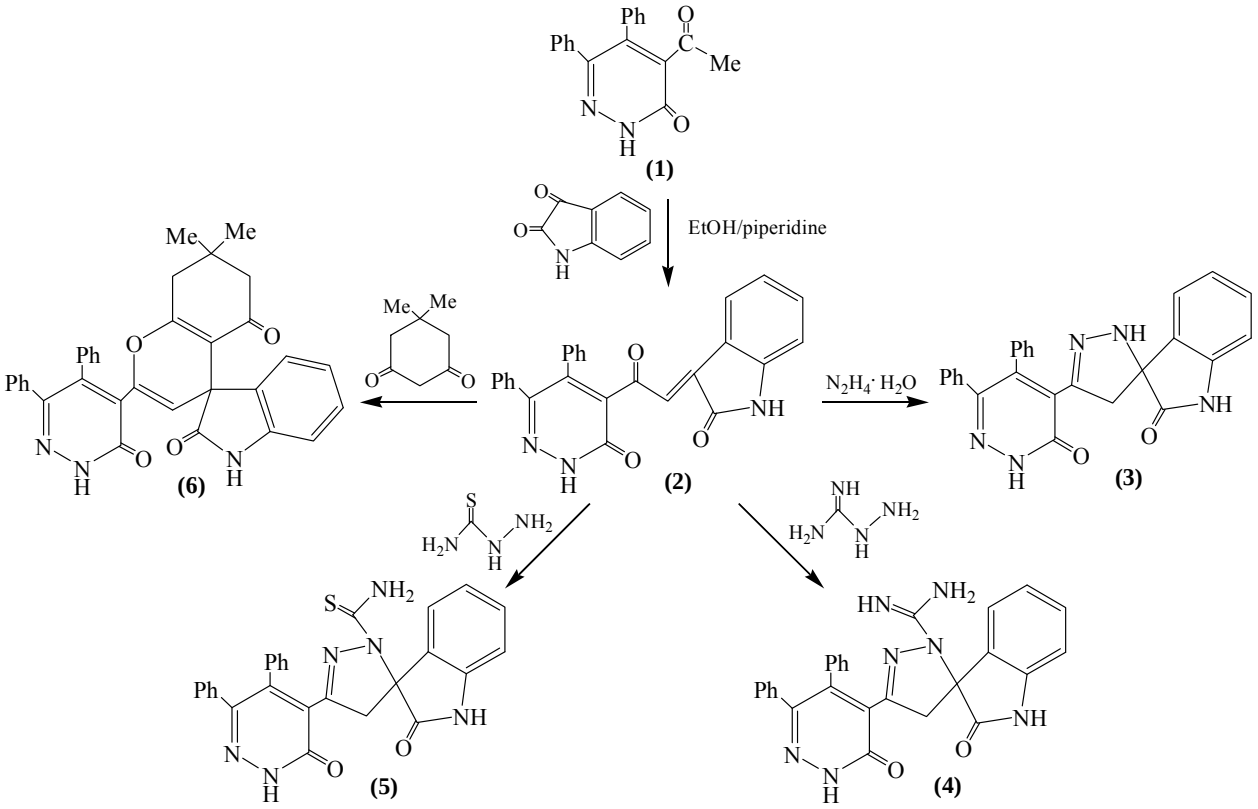
Abstract — Condensation of 4-acetyl-5,6-diphenylpyridazine-3(2*H*)-one (**1**) with 1*H*-indol-2,3-dione afforded the biheterocyclic enone **2**. Interaction of **2** with some bifunctional nitrogen nucleophiles and dimedone yielded some novel pyridazinyl spirohetarylindoles **3-6**. The reaction of 3-chloropyridazine derivative **7** with some heterocyclic compounds having vicinal amino and cyano groups gave hetarylaminopyridazines **9** and **13**. Treatment of acetylpyridazinone **1** with arylidenecyanoacetate and arylidenemalononitrile afforded pyridylpyridazines **16** and **19**, respectively. The effect of some active methylene compounds and thioacetamide on biheterocyclic enone **22** was also studied.

Pyridazines and indoles occupy a conspicuous place in domain of heterocyclic chemistry in view of their biological activities and medicinal importance. The pyridazine structure is found within a number of herbicides such as credazine, pyridafol and pyridate. It is also found within the structure of several pharmaceutical drugs such as cefozopran, cadralazine, minaprine, hydralazine, and cilazapril. There is also a recent article summarizing syntheses directed mainly to selected herbicidal, insecticidal and fungicidal pyridazines.[1] Moreover, pyridazines used as chemotherapeutics, antithrombotic, antisecretory and anti-ulcer agents, analgesic and anti-inflammatory agents as well as with various central nervous system stimulants and depressants.[2] On the other hand, Indole derivatives, formed during digestion of cruciferous vegetables, have been shown to have chemopreventative properties inhibiting human

papilloma virus (HPV) transcription and influencing oestrogen metabolism.[3] Furthermore, indole derivatives used as a chemoprotective agent in breast and prostate cancer,[4,5] In continuation of our studies on the synthesis of new substituted pyridazines[6,8] and indole[9] derivatives, the present investigation aimed to incorporate both pyridazine and indole in a molecular frame-work starting from 4-acetyl-5,6-diphenylpyridazine-3(2*H*)-one (**1**).[10]

One of our targets is the synthesis of some new spiro heterocyclic compounds having pyridazinone and indole moieties in their structures. For this purpose, 3-(3-oxo-5,6-diphenyl-2*H*-pyridazin-4-yloxoethylidene)-1,3-dihydro-2*H*-indol-2-one (**2**) was synthesized from compound **1** with 1*H*-indole-2,3-dione in boiling ethanol containing catalytic amount of piperidine. The structure of compound **2** was confirmed by its correct elemental analysis and spectroscopic data. IR spectrum showed three absorption vibration bands at 1717, 1680 and 1650 cm^{-1} due to carbonyl groups of enone, indole and pyridazinone respectively. Furthermore, its ^{1}H NMR spectrum (DMSO-d_6) exhibited signals at δ 2.31 attributed to ethylidene protons. Compound **2** is used as a suitable precursor for the synthesis of some novel spiro heterocyclic compounds having indolone moiety in their structures. Thus, 3'-(3-oxo-5,6-diphenyl-2*H*-pyridazin-4-yl)-1',4'-dihydrospiro[2-oxo-2,3-dihydroindole-3,5'-pyrazole] (**3**) was obtained from the reaction of compound **2** with hydrazine hydrate in boiling ethanol.[11] The mass spectrum of compound **3** showed a molecular ion peak at *m/z* 433. When compound **2** was allowed to react with aminoguanidine bicarbonate or thiosemicarbazide in boiling ethanol 3'-(3-oxo-5,6-diphenyl-2H-pyridazin-4-yl)-1'-(1-iminocarboxamido)-4'*H*-spiro[2-oxo-1*H*-indol-3,5'-pyrazole] (**4**) and 3'-(3-oxo-5,6-diphenyl-2*H*-pyridazin-4-yl)-1'-(1-thiocarboxamido-4'*H*-spiro[2-oxo-1*H*-indol-3,5'-pyrazole] (**5**) were obtained, respectively. The structure of compound **4** was established on the basis of its correct elemental analysis and spectroscopic data. The mass spectrum of compound **5** showed peak at *m/z* 476 for (M–16) indicating the loss of amino radical from the molecular ion peak.

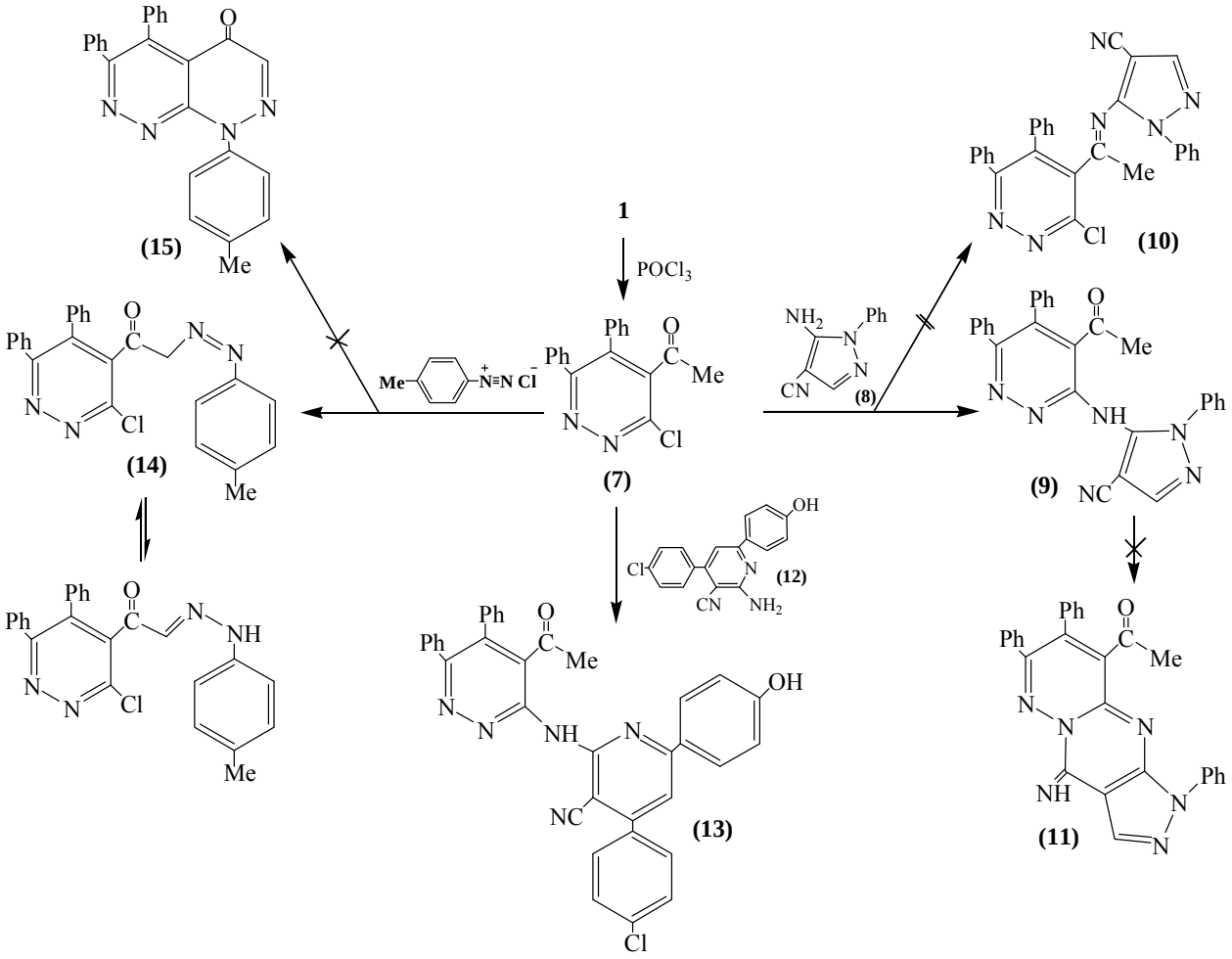
On the other hand, treatment of compound **2** with dimedone[12] in boiling ethanol containing catalytic amount of triethylamine, cyclocondensation took place giving 2'-(3-oxo-5,6-diphenyl-2*H*-pyridazin-4-yl)-5'-oxo-7',7'-dimethyl-6',8'-dihydrospiro[2-oxo-1*H*-indol-3,4'-chromen] (**6**). The structure of compound **6** was confirmed by mass spectrum which revealed the presence of molecular ion peak at *m/z* 541 (Scheme 1).



Scheme 1

Recently, it has been reported that, compound **1** was reacted with phosphorous oxychloride to give 4-acetyl-3-chloro-5,6-diphenylpyridazine (**7**).[13] The reaction of 3-chloropyridazine derivative **7** with some heterocyclic compounds having vicinal amino and cyano groups in their structures was studied. Thus, when compound **7** was subjected to react with 5-amino-1-phenylpyrazolo-4-carbonitrile (**8**) in boiling dimethylformamide two possible compounds **9** and **10** may be produced. Compound **9** is formed *via* direct nucleophilic displacement of chlorine atom yielding 4-acetyl-3-[(4-cyano-1-phenylpyrazol-5-yl)amino]-5,6-diphenylpyridazine (**9**), while compound **10** is formed *via* condensation of amino group with the carbonyl one. Compound **10** was ruled out based on the IR spectrum of the product which exhibited absorption band attributed to the carbonyl stretching frequency at 1708 cm^{-1} and element test showed the absence of chlorine atom. A trial was done to obtain a ring-chain tautomer of compound **9** was failed and the triheterocyclic compound **11** did not formed as IR spectrum of the product displayed absorption band at 2219 cm^{-1} which could be attributed to C≡N function. The structure of compound **9** was further supported by its mass spectrum which exhibited signals at 456 attributed to the molecular ion. Similarly, the interaction of chloropyridazine derivative **7** with 2-amino-4-(4-chlorophenyl)-3-cyanopyridine (**12**) yielded 4-acetyl-3-{[4-(4-chlorophenyl)-3-cyano-6-(4-hydroxyphenyl)pyridin-2-yl]amino}-5,6-diphenylpyridazine (**13**). The structure of compound **13** was confirmed *via* its mass spectrum which showed a peak at *m/z* 593 corresponding to the molecular ion.

Furthermore, treatment of chloropyridazine derivative **7** with 4-methylbenzenediazonium chloride afforded 3-chloro-4-[(4-methylphenyl)diazenylmethylcarbonyl]-5,6-diphenylpyridazine (**14**). The IR spectrum of compound **14** showed absorption bands at 1708 cm^{-1} which strongly support presence of conjugated carbonyl group. A trial to cyclized **14** to give pyridazinopyridazine **15** *via* removal of HCl was failed.

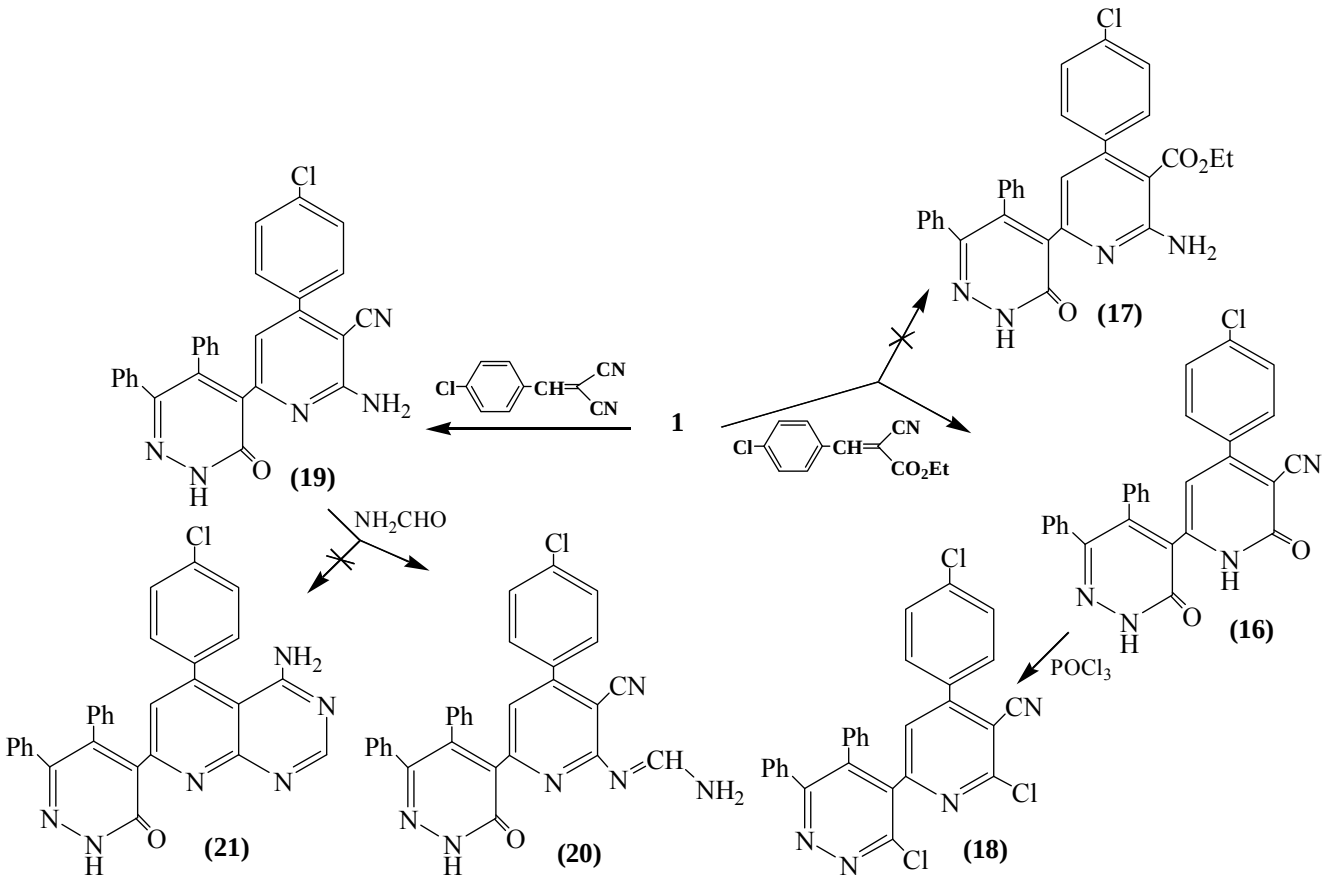


Scheme 2

Because of biological importance of pyridines,[14,15] it was of interest to use acetylpyridazine derivative **1** to synthesize some new pyridazines bearing pyridine moiety *via* interaction of acetylpyridazinone **1** with arylidenemalononitrile and arylidenecyanoacetate. Thus, when the acetylpyridazinone **1** was allowed to react with 4-chlorobenzylidene cayanoacetate in boiling ethanol containing ammonium acetate, 4-[4-(4-chlorophenyl)-3-cyano-2-oxo-1*H*-pyridin-6-yl]-5,6-diphenylpyridazin-3(2*H*)-one (**16)** was obtained, while 4-[2-amino-4-(4-chlorophenyl)-3-ethoxycarbonylpyridine-6-yl]-5,6-diphenylpyridazin-3(2*H*)-one (**17**) did not obtained based on the IR spectrum of the product which showed the presence of C≡N

function at 2218. Also, the structure of compound **16** was supported by its mass spectrum which exhibited a molecular ion peak at *m/z* 476. Treatment of compound **16** with phosphorous oxychloride yielded 3-chloro-4-[2-chloro-4-(4-chlorophenyl)-3-cyanopyridin-6-yl]-5,6-diphenylpyridazine (**18**).

On the other hand, the interaction of compound **1** with 4-chlorobenzylidene malononitrile in boiling ethanol afforded 4-[2-amino-4-(4-chlorophenyl)-3-cyanopyridin-6-yl]-5,6-diphenylpyridazin-3(2*H*)-one (**19**) which condensed with formamide to give 4-[4-(4-chlorophenyl)-3-cyano-2-(aminomethylideneimino)pyridin-6-yl]-5,6-diphenylpyridazin-3(2*H*)-one (**20**) not 8-amino-5-[3-oxo-5,6-diphenyl-2*H*-pyridazin-4-yl]-7-(4-chlorophenyl)pyrido[2,3-*d*]pyrimidine (**21**) (Scheme 3).



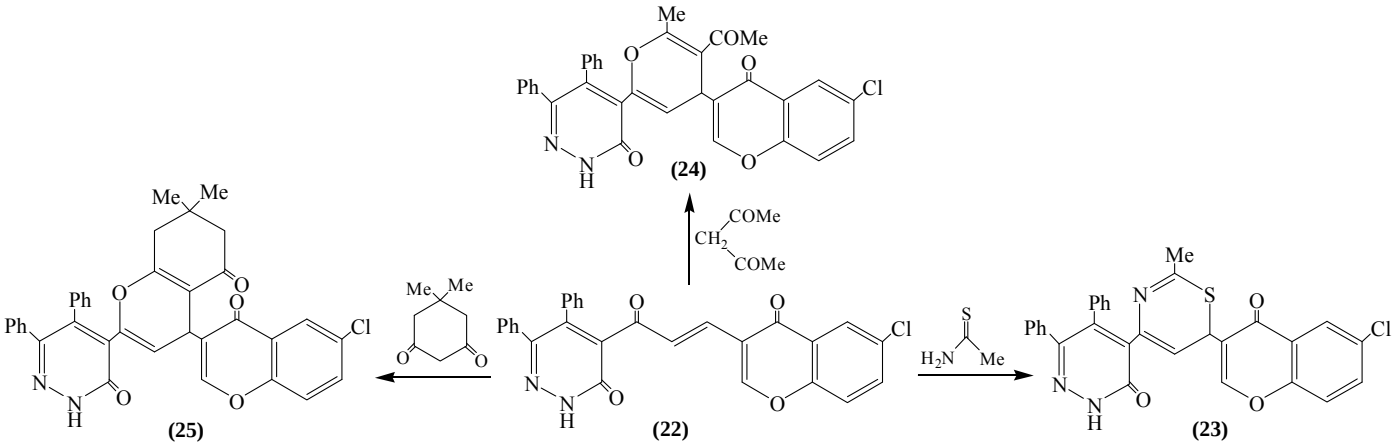
Scheme 3

Other goal of our interest is the use of acetylpyridazinone derivative **1** to synthesize some new pyridazines having thiazine and chromen moieties. For this purpose we previously synthesized the biheterocyclic enone **22** from interaction of equimolar amount of compound **1** with 3-formyl-6-chlorochromenone.[8]

2-Methyl-4-(3-oxo-5,6-diphenyl-2*H*-pyridazin-4-yl)-6-(6-chloro-4-oxochromen-3-yl)-6*H*-1,3-thiazine

(**23**) was obtained on treatment the enone **22** with thioacetamide in boiling ethanol containing catalytic amount of piperidine. Formation of compound **23** involves nucleophilic attack of sulphur in thioacetamide to the *β*-position of the enone. The mass spectrum of **23** exhibited peaks at *m/z* 522 due to loss of methyl radical from the parent ion peak.

The effect of active methylene compounds, namely acetylacetone and dimedone on the biheterocyclic enone **22** was also studied. Thus, treatment of compound **22** with acetylacetone in boiling ethanol containing catalytic amount of piperidine afforded 3-acetyl-2-methyl-6-(3-oxo-5,6-diphenyl-2*H*-pyridazin-4-yl)-4-(6-chloro-4-oxochromen-3-yl)-4*H*-pyran (**24**). While the reaction of compound **22** with dimedone in boiling ethanol containing catalytic amount of triethylamine as a base, afforded 7,7-dimethyl-2-(3-oxo-5,6-diphenyl-2*H*-pyridazin-4-yl)-4-(6-chloro-4-oxochromen-3-yl)-4,6,8-tetrahydro-chromen (**25**). Formation of compound **24** and **25** involves nucleophilic attack of methylidene anion, formed from action of base on active methylene compounds, to the *β*-position of the *α,β* unsaturated bond. The structure of compound **24** and **25** was established on the basis of elemental analysis and spectral data (Scheme 4).



Scheme 4

EXPERIMENTAL

Melting points were determined on a Stuart SMP10 apparatus. The IR spectra were recorded on FTIR Brücher Vector 22 spectrophotometer using KBr wafer technique. ^{1}H NMR spectra were measured on Varian Gemini spectrophotometer 200 MHz using TMS as internal standard. Mass spectra were obtained using Gas Chromatography Mass Spectrometry (GCMS) Hewlet packed 5988 Scheimadzu instrument at 70 eV. Elemental Analyses were done at microanalytical center, Cairo University.

4-Acetyl-5,6-diphenylpyridazin-3(2*H*)-one (1). This compound was prepared according to the reported method.[10]

3-(3-Oxo-5,6-diphenyl-2*H*-pyridazin-4-yloxoethylidene)-1,3-dihydro-2*H*-indol-2-one (2). A mixture of compound **1** (2.9 g, 10 mmol) and 1*H*-indol-2,3-dione (1.47 g, 10 mmol) in EtOH (50 mL) containing few drops of piperidine was heated under reflux for 8 h. The reaction mixture was cooled and poured gradually onto crushed ice. The solid so obtained was neutralized with very dilute hydrochloric acid to separate fine material, and was filtered off and recrystallized from EtOH-water to give compound **2** as red crystals (2.5 g, 58.5%): mp 94 ^{o}C; IR (ν cm^{-1}): 3189 (NH), 3058 (aromatic CH), 1717 (CO of enone), 1680 (CO of indole); 1652 (CO of pyridazinone), 1615 (C=N); ^{1}H NMR (DMSO-d_6) δ 2.31 (s, 1H, ethylidene H), 6.91–7.89 (m, 14H, aromatic H), 10.89 (s, 1H, NH indole), 13.70 (s, 1H, enolic OH pyridazinone); MS m/z (%): 418 [M–1] (0.1), 105 (100), 383 (1.9), 353 (2.0), 289 (30.0), 191 (16.6), 165 (20.8), 77 (76.93), 56 (5.62); *Anal.* Calcd for $C_{26}H_{17}N_3O_3$ (%): C, 74.46; H, 4.06; N, 10.02. Found: C, 74.23; H, 4.27; N, 10.41.

3'-(3-Oxo-5,6-diphenyl-2*H*-pyridazin-4-yl)-1',4'-dihydrospiro[2-oxo-1*H*-indol-3,5'-pyrazole] (3). To a solution of compound **2** (4.195 g, 10 mmol) in EtOH (10 mL) was added dropwise over 5 min, a solution of hydrazine hydrate (0.5 g, 10 mmol) in EtOH (10 mL) and the reaction mixture was refluxed for 8 h. After cooling, the reaction mixture was poured onto crushed ice. The solid so obtained was filtered off and recrystallized from EtOH-water to give compound **3** as yellow crystals (4.0 g, 93%): mp 143 ^{o}C; IR (ν cm^{-1}): 3260-3150 (br NH), 3059 (aromatic CH), 1680 (CO of indole), 1651 (CO of pyridazinone); ^{1}H NMR (DMSO-d_6) δ 3.08 (s, 2H, CH_2), 6.87–7.86 (m, 14H, aromatic H), 9.95 (s, 1H, NH pyrazole), 10.61 (s, 1H, NH indole), 13.64 (s, 1H, enolic OH pyridazinone); MS m/z (%): 432 [M–1] (0.1), 383 (4.1), 298 (32.9), 248 (9.4), 149 (8.27), 105 (88.0), 77 (100), 56 (7.1); *Anal.* Calcd for $C_{26}H_{19}N_5O_2$ (%): C, 72.05; H, 4.39; N, 16.17. Found: C, 71.91; H, 4.13; N, 15.91.

3'-(3-Oxo-5,6-diphenyl-2*H*-pyridazin-4-yl)-1'-(1-iminocarboxamido)-4'*H*-spiro[2-oxo-1*H*-indol-3,5'-pyrazole] (4). A mixture of compound **2** (4.195 g, 10 mmol) and aminoguanidine carbonate (0.74 g, 10 mmol) in EtOH (20 mL) was refluxed for 4 h. The reaction mixture was cooled and poured onto crushed ice. The solid obtained was filtered off and then dried and recrystallized from EtOH-water to give compound **4** as reddish crystals (3.5 g, 73.5%): mp 108–111 ^{o}C; IR (ν cm^{-1}): 3566–3195 (NH_2 and 3NH), 3059 (aromatic CH), 1685 and 1654 (2CO), 1599 (C=N and C=C); ^{1}H NMR (DMSO-d_6) δ 3.77 (s, 2H, CH_2), 5.2–6.1 (s, br, 3H, NH and NH_2), 6.85–7.81 (m, 14H, aromatic H), 10.71 (s, 1H, NH indole), 13.54 (s, 1H, enolic OH pyridazinone); MS m/z (%): 477 [M+2] (9.04); 476 [M+1] (16.5), 419 (11.2), 370 (7.5), 189 (24.5), 105 (88.3), 77 (100); *Anal.* Calcd for $C_{27}H_{21}N_7O_2$ (%): C, 68.21; H, 4.42; N, 20.63; Found: C, 68.50; H, 4.72; N, 20.99.

3'-(3-Oxo-5,6-diphenyl-2*H*-pyridazin-4-yl)-1'-(1-thiocarboxamido)-4'*H*-spiro[2-oxo-1*H*-in-dol-5,5'-

pyrazole] (5). To compound **2** (4.195 g, 10 mmol) in EtOH (10 mL) was added a solution of thiosemicarbazide (0.911 g, 10 mmol) in EtOH (10 mL) and the reaction mixture was refluxed for 4 h. Afterward, the reaction mixture was cooled and poured onto crushed ice. The solid given was collected by filtration, then dried and recrystallized from DMF–water to give compound **5** as brown crystals (3.90 g, 79%): mp 118–121 °C; IR (ν cm^{-1}): 3560–3184 (NH_2 and 2NH), 3058 (aromatic CH), 1683 and 1651 (2CO), 1599 (C=N), 1221 (C=S); ^{1}H NMR (DMSO-d_6) δ 3.85 (s, 2H, CH_2), 5.8–6.3 (s, br, 2H, NH_2), 6.80–7.87 (m, 14H, aromatic H), 10.61 (s, 1H, NH indole), 13.58 (s, 1H, enolic OH pyridazinone); MS m/z (%): 476 [M–16] (0.73), 383 (14.5), 178 (18.1), 105 (96.3), 77 (100), 55 (53.4); *Anal.* Calcd for $C_{27}H_{20}N_6O_2S$ (%): C, 65.85; H, 4.07; N, 17.07; S, 6.50. Found: C, 65.45; H, 4.21; N, 16.93; S, 6.99.

2'-(3-Oxo-5,6-diphenyl-2*H*-pyridazin-4-yl)-5'-oxo-7',7'-dimethyl-6',8'-dihydrospiro-[2-oxo-1*H*-indol-3,4'-chromen] (6). To a mixture of compound **2** (4.195 g, 10 mmol) and dimedone (1.40g, 10 mmol) in EtOH (20 mL) was added few drops of triethylamine. The reaction mixture was heated under reflux for 4 h. After cooling, the solid product so formed was collected and recrystallized from DMF-water to give compound **6** as dark brown crystals (3.83 g, 71%): mp 163 °C; IR (ν cm^{-1}): 3215 and 3150 (2NH), 3058 (aromatic CH), 2994 (aliphatic CH), 1682-1653 (3CO), 1583 (C=N), 1106 (C–O); ^{1}H NMR (DMSO-d_6) δ 1.59 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 3.03 (s, 2H, C_8–H), 3.36 (s, 2H, C_6–H), 4.26 (s, 1H, C_3–H), 6.94–8.05 (m, 14H, aromatic H), 10.06 (s, 1H, NH) and 13.67 (s, 1H, enolic OH pyridazinone); MS m/z (%): 539 [M–2] (1.12%), 491 (11.1), 476 (100), 419 (24.3), 208 (27.5), 126 (18.4), 77 (1.3), 60 (33.9), 55 (25.1); *Anal.* Calcd for $C_{34}H_{27}N_3O_4$ (%): C, 75.41; H, 4.99; N, 7.76. Found: C, 75.94; H, 4.61; N, 7.71.

4-Acetyl-3-chloro-5,6-diphenylpyridazine (7). This compound was prepared according to the reported method.[6]

4-Acetyl-3-[(4-cyano-1-phenylpyrazol-5-yl)amino]-5,6-diphenylpyridazine (9). A solution of 5-amino-1-phenylpyrazolo-4-carbonitrile **(8)** (1.86 g, 10 mmol) in DMF (10 mL) was added to a solution of compound **7** (3.09 g, 10 mmol) in DMF (10 mL) and the reaction mixture was heated under reflux for 6 h. The reaction mixture was cooled and poured gradually onto crushed ice. The solid obtained was collected by filtration, washed then dried and recrystallized from EtOH to give compound **9** as colorless crystals (3.90 g, 86%): mp 198–200 °C; IR (ν cm^{-1}): 3222 (NH), 3056 (aromatic CH), 2953 (aliphatic CH), 2219 (C≡N), 1708 (CO); ^{1}H NMR (DMSO-d_6) δ 2.19 (s, 3H, CH_3), 6.70 (s, 1H, C_3–H pyrazole), 7.22–7.52 (m, 15H, aromatic H) and 7.80 (s, 1H, NH); MS m/z (%): 456 [M^+] (1.36), 359 (1.8), 313 (8.1), 239 (7.8), 185 (5.3), 129 (18.2), 77 (7.83), 55 (100); *Anal.* Calcd for $C_{28}H_{20}N_6O$ (%): C, 73.68; H, 4.39; N, 18.42. Found: C, 73.91; H, 4.38; N, 18.00.

4-Acetyl-3-{[4-(4-chlorophenyl)-3-cyano-6-(4-hydroxyphenyl)pyridin-2-yl]amino}-5,6-diphenyl-pyridazine (13). To a solution of compound **7** (3.09 g, 10 mmol) in DMF (10 mL) was added dropwise a

solution of 2-amino-3-cyanopyridine derivative **12** (3.24 g, 10 mmol) in DMF (10 mL) and the reaction mixture was refluxed for 6 h. Afterwards, the reaction mixture was cooled and poured gradually onto crushed ice. The solid obtained was filtered off and recrystallized from EtOH-water to give **13** as pale yellow crystals (4.0 g, 68%): mp 228 °C; IR (ν cm^{-1}): 3469 (OH), 3362 (NH), 3064 (aromatic CH), 2959 (aliphatic CH), 2205 (CN), 1709 (CO); ^{1}H NMR (DMSO-d_6) δ 2.19 (s, 3H, CH_3), 6.84–8.04 (m, 20H, NH, aromatic H), 5.61 (s, 1H, C_5–H pyridine) and 9.95 (s, 1H, OH); MS m/z (%): 593 [M^+] (26.3), 595 [M+2] (8.8), 550 (10.4), 522 (53.0), 535 (10.2), 282 (8.90), 250 (17.4), 128 (42.8), 79 (7.2), 57 (100); *Anal.* Calcd for $C_{36}H_{24}N_5O_2Cl$ (%): C, 72.78; H, 4.04; N, 11.79; Cl, 5.98. Found: C, 73.00; H, 4.19; N, 11.31; Cl, 5.91.

3-Chloro-4-[(4-methylphenyl)diazenylmethylcarbonyl]-5,6-diphenylpyridazine (14). Sodium nitrite (0.69 g, 10 mmol) was dissolved in concentrated hydrochloric acid at room temperature, followed by the addition of 4-methylaniline (1.07 g, 10 mmol). The mixture was stirred at room temperature for 2 h then added to a cooled solution (0–5 °C) of compound **7** (3.09 g, 10 mmol) in alcoholic solution of sodium acetate and dropwise addition of concentrated hydrochloric acid. The mixture was stirred for 30 min; the precipitate product was collected and purified by column chromatography to give compound **14** as orange crystals (1.54 g, 36%): mp 223 °C. IR (ν cm^{-1}): 3058 (aromatic CH), 2954 (aliphatic CH), 1708 (CO); ^{1}H NMR (DMSO-d_6) δ 2.19 (s, 3H, CH_3), 3.35 (s, 2H, CH_2), 7.18–7.39 (m, 14H, aromatic H); MS m/z (%): 425 [M^+] (24.5), 427 [M+2] (8.0), 424 [M–1] (8.0), 339 (43.9), 313 (87.1), 262 (71.5), 207 (49.4), 144 (100), 98 (77.9), 84 (92.3), 77 (4.91); *Anal.* Calcd for $C_{25}H_{19}N_4OCl$ (%): C, 70.34; H, 4.46; N, 13.13; Cl, 8.32. Found: C, 70.33; H, 4.45; N, 13.10; Cl, 8.25.

4-[4-(4-Chlorophenyl)-3-cyano-2-oxo-1*H*-pyridin-6-yl]-5,6-diphenylpyridazin-3(2*H*)-one (16). In absolute EtOH containing ammonium acetate (4.7 g, 80 mmol), a mixture of compound **1** (2.9 g, 10 mmol) and arylidene cyanoacetate (2.36 g, 10 mmol) was heated under reflux for 6 h. The reaction mixture was cooled and the solid produced was filtered off and recrystallized to from petroleum ether 60–80 °C give compound **16** as yellowish crystals (3.30 g, 69.5%): mp 293 °C; IR (ν cm^{-1}): 3177 (NH), 3019 (aromatic CH), 2218 (CN), 1740 (CO pyridine), 1638 (CO pyridazinone); ^{1}H NMR (DMSO-d_6) δ 5.70 (s, 1H, C_5-H pyridine), 6.78–7.91 (m, 15H, aromatic H and NH pyridine), 13.78 (s, 1H, enolic OH pyridazinone); MS m/z (%): 476 [M^+] (16.5), 478 [M+2] (5.5), 288 (62.0), 215 (15.6), 189 (27.2), 105 (33.3), 77 (100); *Anal.* Calcd for $C_{28}H_{17}N_4O_2Cl$ (%): C, 70.51; H, 3.57; N, 11.75; 7.45; Cl, 7.45. Found: C, 70.47; H, 3.48; N, 11.43; Cl, 7.71.

3-Chloro-4-[2-chloro-4-(4-chlorophenyl)-3-cyanopyridin-6-yl]-5,6-diphenylpyridazine (18). A mixture of compound **16** (4.77g, 10 mmol) in phosphoryl chloride (30 mL) was warmed to 60 °C for 2 h. After cooling to room temperature, excess of phosphoryl chloride was removed under vacuum and then brought to pH 6 with sodium carbonate; the resulting oily product was solidified by stirring with water

and collected by fraction and recrystallized from water to give compound **18** as brown crystals (4.83 g, 94%): mp 289 °C; IR (ν cm^{-1}): 3058 (aromatic CH), 2222 (CN), 1654 (C=N); ^{1}H NMR (DMSO-d_6) δ 5.76 (s, 1H, C_5-H pyridine), 6.74–7.87 (m, 14H, aromatic H); MS m/z (%): 512 [M^+] (23.85), 514 [M+2] (12.8), 476 (22.7), 364 (26.9), 306 (51.9), 284 (98.5), 264 (100), 201 (57.9), 177 (45.9), 148 (30.0), 77 (28.2); *Anal.* Calcd for $C_{28}H_{15}N_4Cl_3$ (%): C, 65.43; H, 2.92; N, 10.91; Cl, 20.74. Found: C, 65.23; H, 3.10; N, 10.81; Cl, 20.93.

4-[2-Amino-4-(4-chlorophenyl)-3-cyanopyridin-6-yl]-5,6-diphenylpyridazin-3(2*H*)-one (19). In absolute ethanol (20 mL) containing ammonium acetate (4.7 g, 80 mmol), a mixture of compound **1** (2.9 g, 10 mmol) and arylidene malononitrile (1.89 g, 10 mmol) was heated under reflux for 6 h. The reaction mixture was cooled and the solid produced was filtered off and dried then recrystallized from EtOH to give compound **19** as brownish red crystals (3.43 g, 72%): mp 180 °C; IR (ν cm^{-1}): 3250 and 3190 (NH_2), 3118 (NH), 2208 (CN), 1656 (CO); ^{1}H NMR (DMSO-d_6) δ 5.21–5.61 (s, br, 2H, NH_2), 5.71 (s, 1H, C_5-H pyridine), 6.82–7.91 (m, 14H, aromatic H), 13.63 (s, 1H, enolic OH pyridazinone); MS m/z (%): 448 [M–HCN] (1.1), 414 (25.3), 344 (8.8), 330 (6.6), 311 (11.9), 269 (2.9), 178 (15.7), 105 (100), 104 (14.42), 77 (34.05); *Anal.* Calcd for $C_{28}H_{18}N_5OCl$ (%): C, 70.66; H, 3.79; N, 14.72; Cl, 7.47. Found: C, 70.99; H, 3.52; N, 14.50; Cl, 7.74.

4-[4-(4-Chlorophenyl)-3-cyano-2-(aminomethylideneimino)pyridin-6-yl]-5,6-diphenylpyridazin-3(2*H*)-one (20) A mixture of compound **19** (4.76 g, 10 mmol) and formamide (0.45 g, 10 mmol) was refluxed for 6 h at 100 °C and cooled. The solid obtained was filtered off and recrystallized from EtOH to give compound **20** as colorless crystals (3.27 g, 65%): mp 300 °C; IR (ν cm^{-1}): 3320 and 3250 (NH_2), 3196 (NH), 2208 (CN), 1686 (CO), 1648 (C=N); ^{1}H NMR (DMSO-d_6) δ 2.55 (s, 1H, N=CH), 4.61 (s, 2H, NH_2), 5.47 (s, 1H, H-5 pyridine), 6.93–7.97 (m, 14H, aromatic H), 13.55 (s, 1H, enolic OH pyridazinone); MS m/z (%): 502 [M^+] (12.0), 504 [M+2] (4.0), 409 (3.2), 383 (27.8), 289 (19.7), 236 (6.2), 178 (100), 151 (12.3), 105 (24.2); *Anal.* Calcd for $C_{29}H_{19}N_6OCl$ (%): C, 69.25; H, 3.78; N, 16.72; Cl, 7.06. Found: C, 69.22; H, 3.76; N, 16.21; Cl, 6.90.

2-Methyl-4-(3-oxo-5,6-diphenyl-2*H*-pyridazin-4-yl)-6-(6-chloro-4-oxochromen-3-yl)-6*H*-1,3-thiazine (23) A mixture of compound **22** (4.8 g, 10 mmol) and thioacetamide (0.75 g, 10 mmol) in DMF (30 mL) containing few drops of piperidine was heated under reflux for 4 h. The reaction mixture was cooled and poured onto crushed ice. The solid obtained was filtered off and recrystallized from EtOH to give compound **23** as deep yellow crystals (3.10 g, 57%): mp 192 °C; IR (ν cm^{-1}): 3337 (NH), 3067 (aromatic CH), 2924 (aliphatic CH), 1794 (CO pyrone), 1648 (CO pyridazinone), 1595 (C=N), 1150 (C–S); ^{1}H NMR (DMSO-d_6) δ 2.1 (s, 3H, CH_3), 6.55 (d, 1H, H-6 thiazine), 6.81 (d, 1H, H-5 thiazine), 7.08–7.89 (m, 13H, aromatic H), 8.02 (s, 1H, H-2 pyrone), 13.51 (s, 1H, enolic OH pyridazinone); MS m/z (%): 522 [M–CH_3] (8.1), 396 (8.4), 299 (10.6), 239 (23.8), 185 (27.4), 79 (20.2), 56 (31.6), 55 (100); *Anal.* Calcd

for $C_{30}H_{20}N_3O_3SCl$ (%): C, 66.98; H, 3.72; N, 7.81; Cl, 6.60. Found: C, 66.55; H, 3.52; N, 8.21; Cl, 7.13.

3-Acetyl-2-methyl-6-(3-oxo-5,6-diphenyl-2*H*-pyridazin-4-yl)-4-(6-chloro-4-oxochromen-3-yl)-4*H*-pyran (24). In dioxane (20 mL) containing few drops of piperidine, a mixture of compound **22** (4.8 g, 10 mmol) and acetylacetone (1 mL) was heated under reflux for 4 h and cooled. The solid obtained was filtered off, then dried and recrystallized from EtOH to give compound **24** as brownish red crystals (3.30 g, 59%): mp 220 °C; IR (ν cm^{-1}): 3185 (NH), 3055 (aromatic CH), 2931 (aliphatic CH), 1731 (CO pyrone), 1685 (CO acetyl), 1640 (CO pyridazinone), 1178 (C–O–C); ^{1}H NMR (DMSO-d_6) δ 1.95 (s, 3H, CH_3), 2.65 (s, 3H, $COCH_3$), 6.44 (d, 1H, H-4 pyran), 6.73 (d, 1H, H-5 pyran), 7.11–7.91 (m, 13H, aromatic H), 8.05 (s, 1H, H-2 pyrone), 13.58 (s, 1H, enolic OH pyridazinone); MS m/z (%): 562 [M^+] (0.4), 564 [M+2] (0.1), 290 (19.9), 289 (100), 275 (34.8), 264 (15.8), 190 (49.9), 164 (17.1), 129 (12.5), 77 (13.2), 55 (5.0); *Anal.* Calcd for $C_{33}H_{23}N_2O_5Cl$ (%): C, 70.40; H, 4.09; N, 4.98; Cl, 6.31. Found: C, 70.64; H, 4.59; N, 4.45; Cl, 6.11.

7,7-Dimethyl-2-(3-oxo-5,6-diphenyl-2*H*-pyridazin-4-yl)-4-(6-chloro-4-oxochromen-3-yl)-4,8-dihydrochrom-5(6H)-one (25) To a mixture of compound **22** (4.8 g, 10 mmol) and dimedone (1.4 g, 10 mmol) in EtOH (20 mL) was added few drops of piperidine and the reaction mixture was heated under reflux for 4 h. After cooling, the solid so formed, was collected and recrystallized from to give compound **25** as yellowish crystals (3.80 g 63%): mp 297 °C; IR (ν cm^{-1}): 3239 (NH), 3068 (aromatic CH), 2930 (aliphatic CH), 1775 (CO chromen), 1710 (CO benzopyran), 1632 (CO pyridazinone), 1155 (C–O–C); ^{1}H NMR (DMSO-d_6) δ 1.19 (s, 6H, $2CH_3$), 2.03 (s, 2H, C_8–H), 2.61 (s, 2H, C_6–H), 4.64 (d, 1H, C_3–H), 6.50 (d, 1H, H-4 pyran), 6.94–8.05 (m, 14H, aromatic H and C_2–H pyrone), 13.61 (s, 1H, enolic OH pyridazinone); MS m/z (%): 602 [M^+] (13.5), 604 [M+2] (4.5), 567 (6.1), 503 (6.3), 409 (7.8), 371 (16.2), 191 (12.6), 189 (49.0), 129 (22.9), 77 (47.0), 65 (16.0), 63 (100); *Anal.* Calcd for $C_{36}H_{27}N_2O_5Cl$ (%): C, 71.70; H, 4.48; N, 4.65; Cl, 5.89. Found: C, 71.68; H, 4.54; N, 4.25; Cl, 5.91.

REFERENCES

1. R. Schoenboeck, and E. Kloimstein, *Oesterr. Chem. Z.*, 1984, **85**, 185.
2. G. P. Ellis and G. B. West, *Progress in Medicinal Chemistry*, **27**, pp. 1-35, 1990, Elsevier Science Publishers B. V. (Biomedical Division).
3. G. C. Rieck and A. N. Fiander, *Molecular Nutrition & Food Research*, 2008, **52**, 105.
4. H. L. Bradlow, *In Vivo*, 2008, **22**, 441.
5. E. G. Rogan, *In Vivo*, 2006, **20**, 221.
6. M. Seada, M. M. Fawzy, H. Jahine, M. Abdel-Megid, and R. R. Saad, *J. Chin. Chem. Soc.*, 1989, **36**, 241.

7. M. Abdel-Megid, *Synth. Commun.*, 2007, **37**, 3211.
8. M. Abdel-Megid, Y. Gabr, M. A. A. Awas, and N. M. Abdel-Fatah, *Chemistry of Heterocyclic Compounds* (accepted).
9. M. Abdel-Megid, *International J. Chem*., 2006, **16**, 149.
10. P. Schmidt and J. Druey, *Helv. Chim. Acta*, 1954, **37**, 134.
11. F. Z. Macaev, O. M. Radul, I. N. Shterbet, S. I. Pogrebnoi, N. S. Sucman, S. T. Malinovskii, A. N. Barba, and M. Gdaniec, *Chem. Heterocycl. Compd.*, 2007, **43**, 298.
12. S. Ahadi, H. R. Khavasi, and A. Bazgir, *Chem. Pharm. Bull.*, 2008, **56**, 1328.
13. M. F. Ismail, S. S Fekria, A. Abdel Moemen, M. El-Khamry, A. Ali, and M. M. Mansour, *J. F. Prakt. Chemie Band*, 1989, 331, Heft. 3, S. **299**.
14. R. M. Weier, F. L. Lee, R. A. Partis, and F. G. Koszyk, PCT int. WO 9624, 584 (*Chem. Abstr.*, 1996**,** **125**, 247624h)
15. J. L. Zomocks and F. Devinsky, *Pharmazie*, 1994, **49**, 66.