Synthesis and spectral characterisation of some phthalazinone derivatives

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1,2,4-Triazol-3-yl, 1,3,4-oxadiazol-2-yl, 1,3-dioxoisoindolin-2-yl, 1*H*-pyrazol-4-yl, phthalazin-1(2*H*)one, 5*H*-2,3-benzodiazepine-1,4-dione and pyridazine-1,4-dione derivatives were prepared via the reaction of the readily obtainable starting material 1-oxo-1,2-dihydrophthalazin-4-carbohydrazide with one carbon donor like phenyl isothiocyanate, phenyl isocyanate, triethylorthoformate, formic acid and different electrophilic reagents such as anhydrides, chromen-1,3-dione, chloroacetyl chloride, acetic anhydride, arylidene malononitrile, ethoxymethylene malononitrile and ethyl acetoacetate.

Keywords: phthalazinone, carbohydrazide, oxadiazole, triazole, pyrazole

Hypertension is one of the most common cardiovascular diseases that can cause coronary disease, myocardial infarction, kidney failure, stroke and sudden death.[1] Hence, great efforts are continuously being made to find novel antihypertensive agents acting through different mechanisms.[2,3]

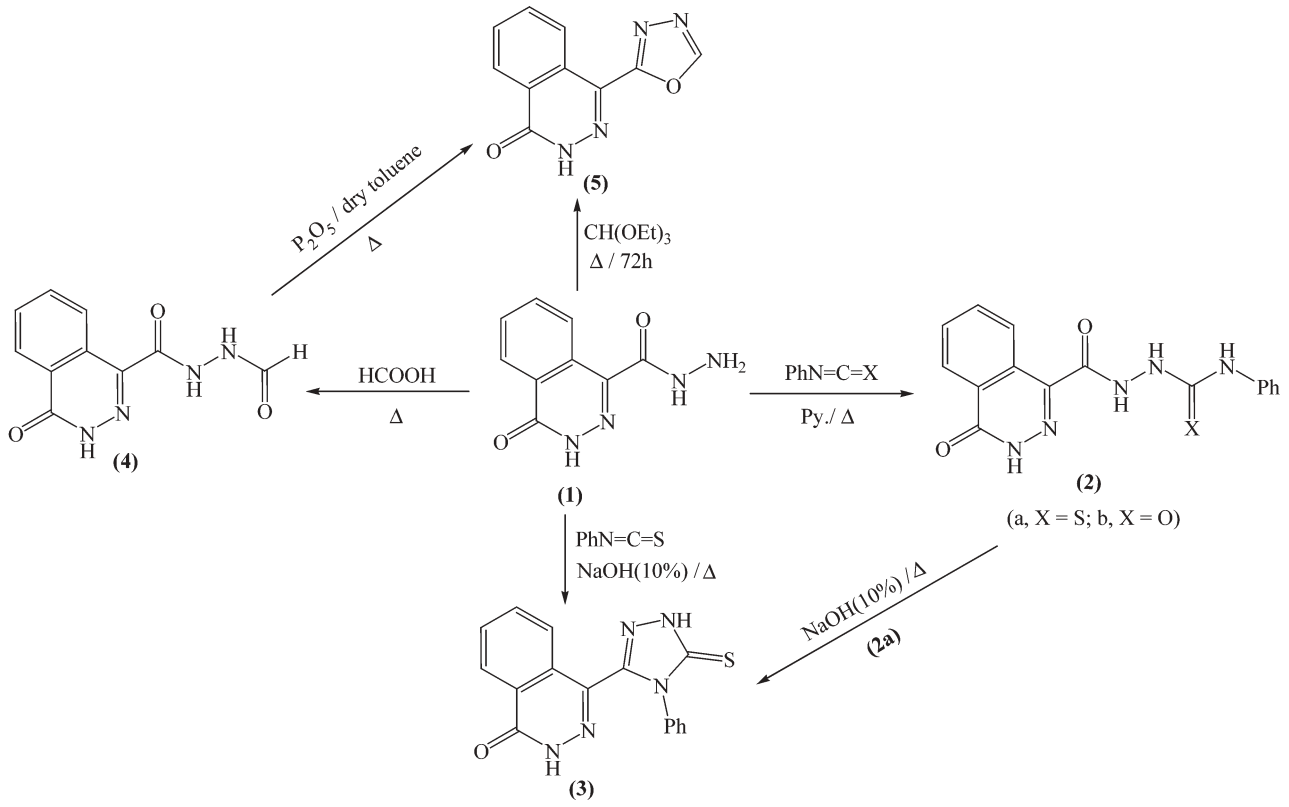
Hydralazine (1-hydrazinophthalazine), was one of the first antihypertensive agents developed in the 1950s, which has attracted much attention in the last decade because of its direct vasodilator action.[4] Structural modification of hydralazine led to the discovery of some pyridazinones and other phthalazine derivatives with a broad spectrum of action on the cardiovascular system,[5,6] including antihypertensive effects,[7,8] inhibition of platelet aggregation[9,10] and of phosphodiesterases.[11,12] Some of them also displayed antiasthmatic,[13,14] antipsychotic,[15] antidiabetic,[16] anticonvulsant,[17] antineoplastic,[18] antimicrobial,[19] antifungal[20] and antiparasitic [21,22] activities.

These reported diverse biological activities initiated our interest to utilise the phthalazine hydrazide derivative **1** for the synthesis of some phthalazine derivatives bearing another heterocycles have a broad spectrum of biological activities like pyrazole, triazole and oxadiazole.

Results and discussion

The hydrazide **1** was previously prepared by our research group.[23] Refluxing the hydrazide **1** with phenylisothiocyanate or phenylisocyanate in boiling pyridine gave 1-(1-oxo-1,2-dihydrophthalazine-4-carbonyl)-4-phenylthiosemicarbazide **2a** and 1-(1-oxo-1,2-dihydrophthalazine-4-carbonyl)-4-phenylsemicarbazide **2b**, respectively. The structure **2** was deduced from the analytical and spectroscopic data.

On the other hand, when compound **1** was allowed to react with phenylisothiocyanate in sodium hydroxide (10%) followed by acidification gave 4-[4-phenyl-5-thioxo-1*H*-1,2,4-triazol-3-yl]phthalazin-1-(2*H*)-one **3**. Moreover, when compound **2a** was allowed to react with sodium hydroxide (10%)



Scheme 1

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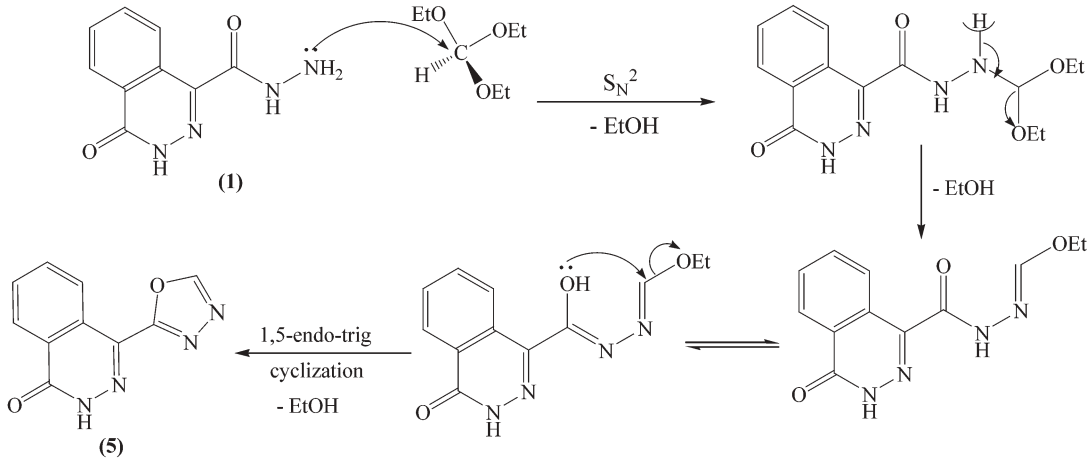
produced the same compound **3** (identify by m.p, mixed m.p and TLC). The structure of **3** was confirmed by the correct analytical and spectroscopic data. Refluxing the hydrazide **1** with formic acid for 10 h yielded *N*-formyl-4-oxo-3,4-dihydrophthalazine-1-carbonyl hydrazide **4** which easily cyclised through dehydration upon heating with phosphorus pentaoxide in dry toluene to give 4-(1,3,4-oxadiazol-2-yl)phthalazin-1(2*H*)-one **5** (Scheme 1).

Compound **5** was obtained as the sole product in fairly good yield upon refluxing compound **1** with one carbon donor such as triethylorthoformate for three days which consider another clue for the structure **5**. The reaction of the carbohydrazide **1** with triethyl orthoformate could be postulated as follows (Scheme 2).

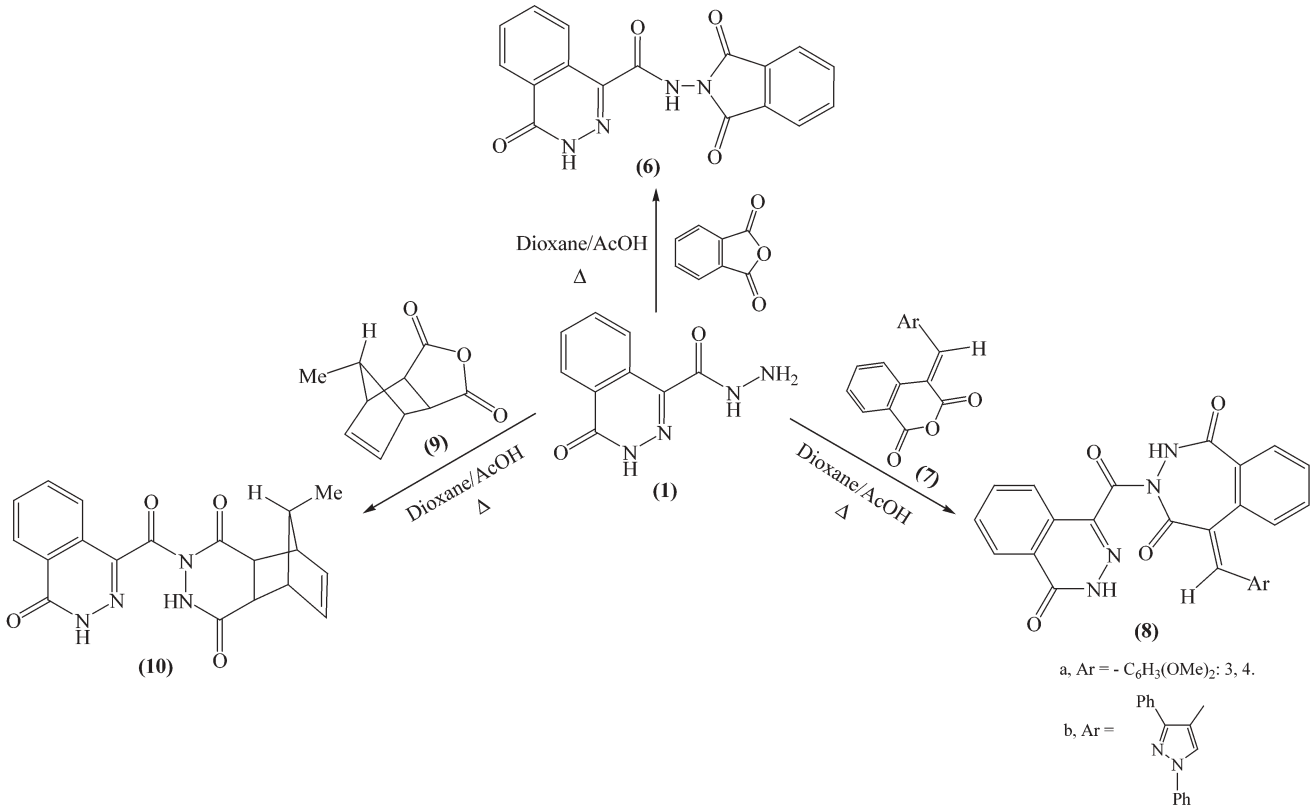
It has been reported that the reaction of hydrazide and hydrazine derivative with phthalic anhydride yielded the *N*-phthalimide or phthalazine derivatives.[24] We now report the reaction of the hydrazide derivative **1** with phthalic anhydride in refluxing dioxane in acetic acid which gave *N*-(1,3-dioxoisoindolin-2-yl)-4-oxo-3,4-dihydrophthalazine-1-carboxamide **6**. The reaction of **1** with isochromene-1,3-dione derivatives **7a,b** under the same conditions gave 5-(3,4-dimethoxybenzylidene)-3-(1-oxo-1,2-dihydrophthalazine-4-carbonyl)-2,3-dihydro-5*H*-2,3-benzodiazepine-1,4-dione **8a** and 5-[(1,3-diphenyl-1*H*-pyrazol-4-yl)methylene]-3-(1-oxo-1,2-dihydrophthalazine-4-carbonyl)-2,3-dihydro-5*H*-2,3-benzodiazepine-1,4-dione **8b** (Scheme 3). The structure of compounds **6** and **8 a,b** were substituted from the analytical and spectroscopic data.

The conversion of **1** to compounds **6** and **8a,b** via the reaction with phthalic anhydride and chromen-1,3-dione derivative can be visualised as shown in Scheme 4.

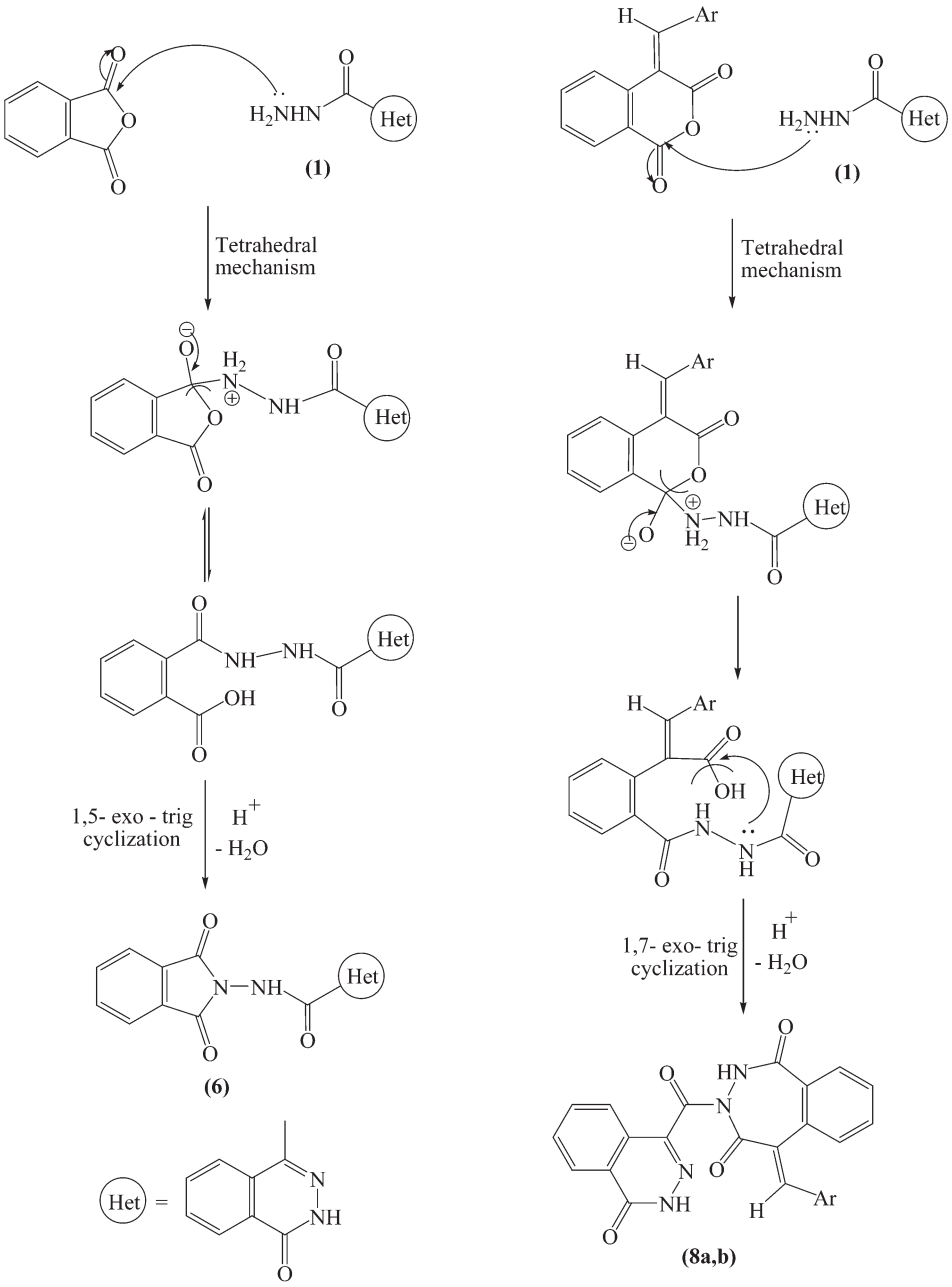
Furthermore, the reaction of the hydrazide **1** with norbornene dicarboxylic acid anhydride derivative **9** in boiling dioxane



Scheme 2



Scheme 3



Scheme 4

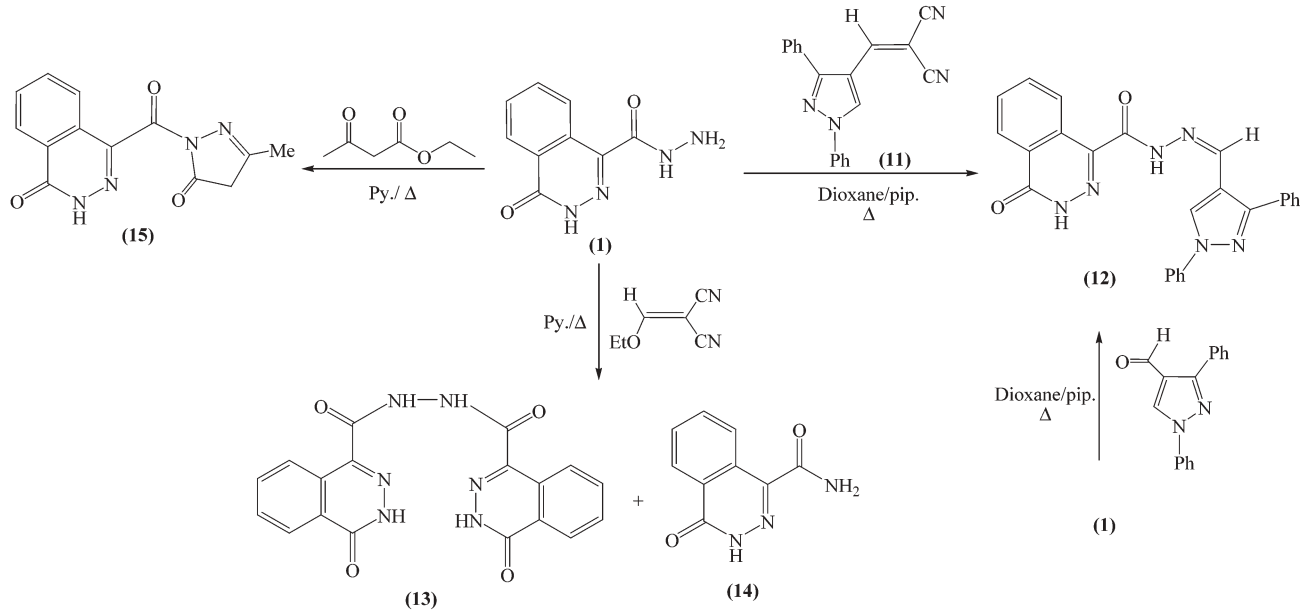
gave the pyridazine-1,4-dione derivative **10**. The IR spectrum of the product is devoid of the absorption bands characteristic of the symmetric and antisymmetric stretching vibrational coupling. The formation of **10** could took place through the nucleophilic addition by the nitrogen nucleophile of the hydrazide on the carbonyl group of the anhydride leading to ring opening followed by cyclisation with elimination of the water molecule.

When compound **1** was allowed to react with activated nitrile such as 1,3-diphenyl pyrazol-4-yl methylene malononitrile **11** in refluxing dioxane in the presence of a catalytic amount of piperidine it gave the Shiff's like base *N*-[(1, 3-diphenyl-1*H*-pyrazol-4-yl)-methylene]-4-oxo-3,4-dihydrophthalazine-1-carbohydrazide **12**. This was confirmed by spectroscopic data and comparison with an authentic sample prepared from the condensation of the acid hydrazide **1** with 1,3-diphenylpyrazole-4-carboxaldehyde,[25] in refluxing dioxane in a catalytic amount of piperidine (Scheme 5).

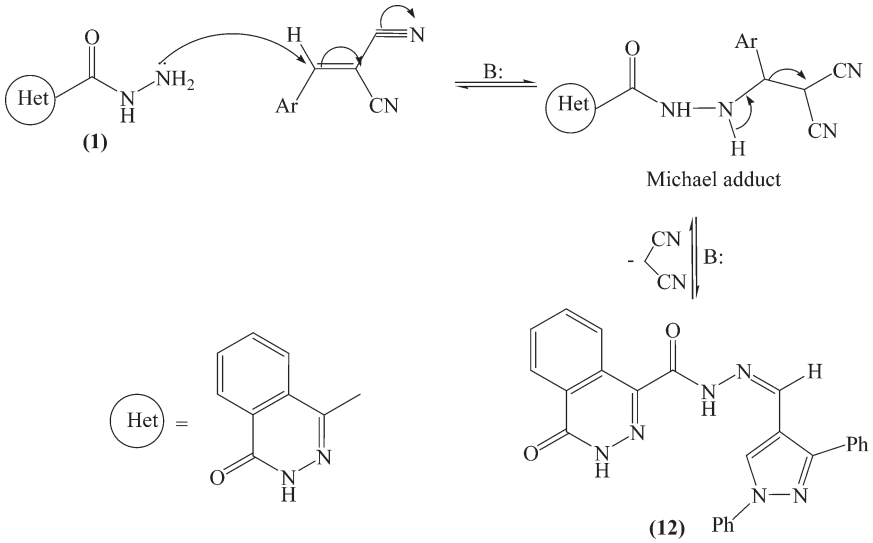
The formation of **12** can be visualised as shown in Scheme 6.

Reaction of the hydrazide **1** with ethoxymethylenemalononitrile[26] in boiling pyridine gave the pale yellow solid product with molecular formula $C_{18}H_{12}N_6O_4$ [M^+ = 376 (23.8%)] which was analysed and assigned as 4-oxo-*N*-(1-oxo-1,2-dihydrophthalazine-4-carbonyl)-3,4-dihydrophthalazine-1-carbohydrazide **13**. Evaporation of the excess solvent after acidification of the filtrate left 4-oxo-3,4-dihydrophthalazine-1-carboxamide **14**. The formation of compounds **14** and **15** can be postulated as shown in Scheme 7.

It has been reported[27] that the hydrazine or hydrazide derivative reacted with a β-ketoester such as ethyl acetoacetate in refluxing ethanol gave the pyrazolone derivative. The reaction of compound **1** with ethyl acetoacetate in refluxing pyridine gave 4-(3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-1-carbonyl) phthalazin-1(2*H*)-one **15** (Scheme 5). Acylation of the hydrazide **1** using chloroacetyl chloride in DMF in the cold for one hour gave the chloroacetyl derivative **16** which is easily cyclised through dehydration upon heating in pyridine to give 4-(5-(chloro-methyl)-1,3,4-oxadiazol-2-yl)phthalazin-1(2*H*)-one **17** (Scheme 8).



Scheme 5



Scheme 6

The nucleophilic substitution reaction takes place through the tetrahedral mechanism shown in Scheme 9.

Acylation of **1** using freshly distilled acetic anhydride at different times afforded mono- , di- and tri-acetylated products **18–20**. Isatin and benzil condensed with the hydrazide derivative **1** in boiling dioxane to give the corresponding condensation product **21** and **22** respectively (Scheme 9).

Experimental

Melting points were measured on an electrothermal melting point apparatus. Elemental analyses were performed using a Heraeus CHN Rapid analyser at the Microanalytical unit, Cairo University. IR Spectra were measured on a Unicam SP-1200 spectrophotometer using KBr Wafer technique. ^{1}H NMR spectra were measured in DMSO-d_6 on a Varian plus instrument (300 MHz). Mass spectra were recorded on a Shimadzu GC-MS QP1000 EX instrument operating at 70 eV in EI mode.

Reaction of the hydrazide **1** *with phenylisothiocyanate and phenylisocyanate; general procedure*

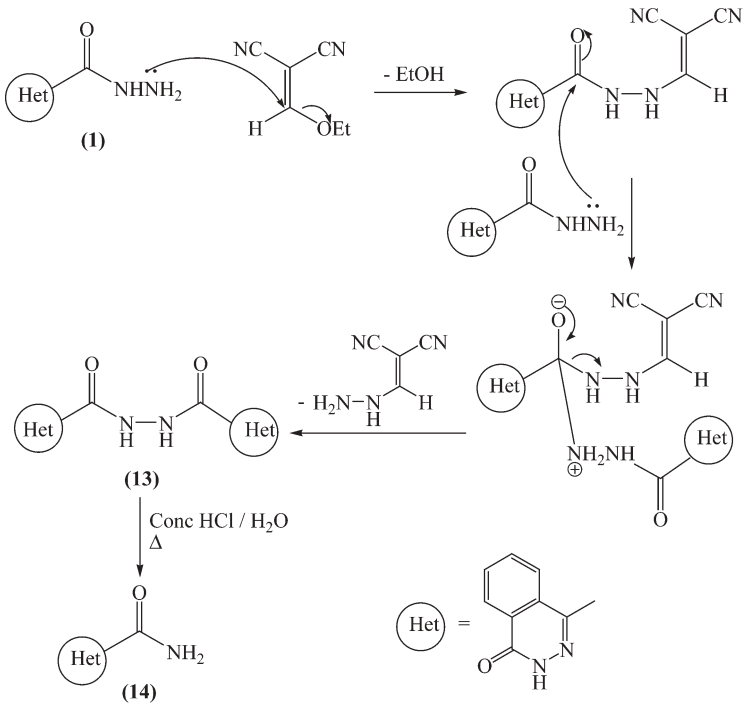
A mixture of **1** (1 g, 4.9 mmole) and phenylisothiocyanate (0.8 mL, 4.9 mmole) or phenylisocyanate (0.5 mL, 4.9 mmole) in pyridine (20 mL) was refluxed for 6 h. The reaction mixture was allowed to cool and then acidified with cold dilute hydrochloric acid. The residue was filtered off and then recrystallised from dioxane to give **2a** and **2b** respectively.

1-(1-Oxo-1,2-dihydrophthalazine-4-carbonyl)-4-phenylthiosemicarbazide (**2a**): Yellow crystals; m.p. 280–283 °C, yield 55%. IR (KBr) (υ_{max}, cm^{-1}): 3465(w), 3237(br.) (NH), 1666 (C=O). ^{1}H NMR (DMSO-d_6): δ_H (ppm) 7.15–8.65 (m, 9H$_{arom.}$), 9.8 (br.s, 2H, 2NH, exchangeable with D_2O), 10.57 (s, 1H, NH, exchangeable with D_2O), 13.07 (s, 1H, NH, NHCO$_{phth}$, exchangeable with D_2O). MS, *m/z* (%): 339 (M$^+$, 1.75), 285 (2.3), 245 (5.6),173 (2.48), 129 (31.9), 70(100). Anal. Calcd for $C_{16}H_{13}N_5O_2S$ (339): C, 56.63; H, 3.86; N, 20.64; S, 9.45. Found: C, 56.42; H, 3.53; N, 20.76; S, 9.60%.

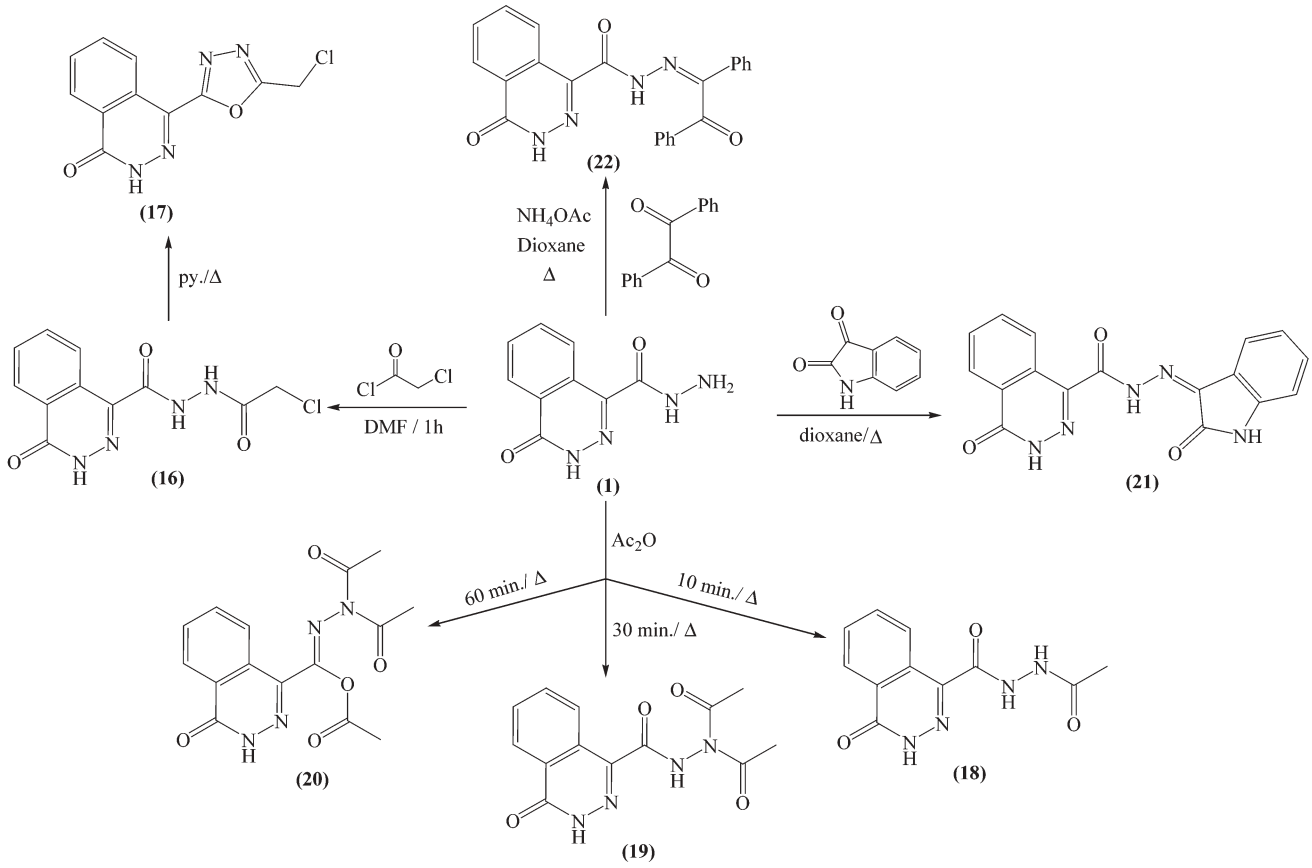
1-(1-Oxo-1,2-dihydrophthalazine-4-carbonyl)-4-phenylsemicarbazide (**2b**): Colourless crystals; m.p > 300 °C, yield 50%. IR (KBr) (υ_{max}, cm^{-1}): 3417 (br.), 3171(br.) (NH), 1666 (C=O). MS, *m/z* (%): 323 (M$^+$, 1.11), 204 (52.36), 173 (68.8),145 (65.12), 117 (41), 102 (29.9), 90 (68.4), 79 (100). Anal. Calcd for $C_{16}H_{13}N_5O_3$ (323): C, 59.44; H, 4.05; N, 21.66. Found: C, 59.12; H, 3.93; N, 21.73%.

4-(4-Phenyl-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)phthalazin-1(2H)-one (**3**)

Method 1: A mixture of **1** (2.04 g, 10 mmole) and phenylisothiocyanate (1.6 mL, 10 mmole) in (10%) sodium hydroxide (20 mL) was



Scheme 7

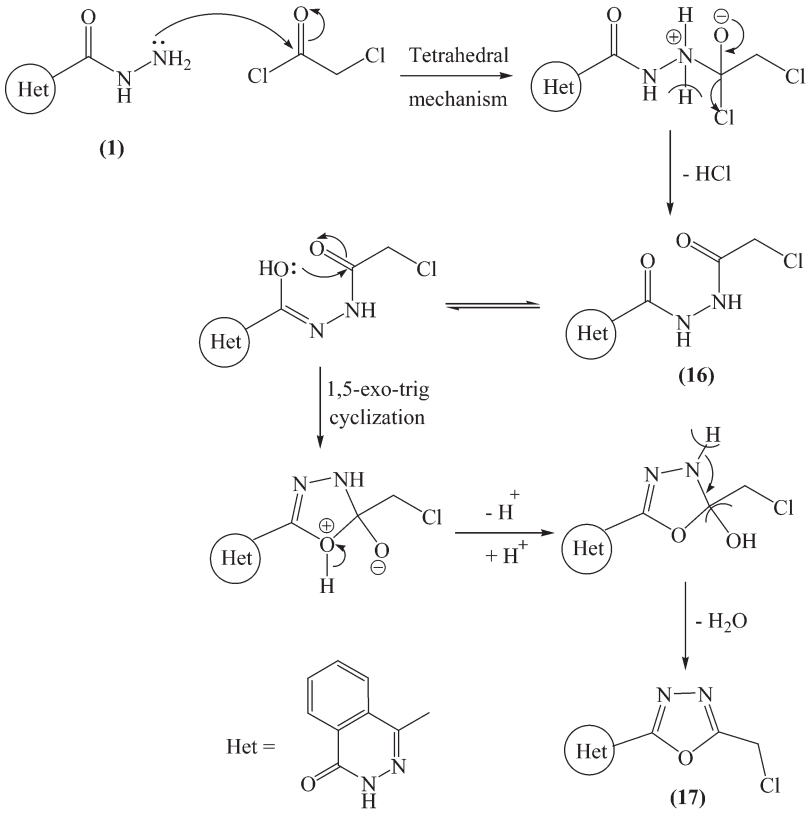


Scheme 8

refluxed for 3 h. The reaction mixture was allowed to cool and then acidified with cold dilute hydrochloric acid. The deposited solid was filtered off, washed several times with cold water, dried and then recrystallised from dioxane to give **3**.

Method 2: Compound **2a** (3.39 g, 10 mmole) was heated under reflux with (10%) sodium hydroxide (20 mL) for 3 h. The reaction mixture was allowed to cool and then acidified with cold dilute hydrochloric acid. The deposited solid was filtered off, washed several times with cold water, dried and then recrystallised from dioxane to give **3**.

4-(4-Phenyl-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)phthalazin-1(2H)-one **(3)**: Colourless crystals; m.p. 220–222 °C, yield 30%. IR (KBr) (υ_{max}, cm^{-1}): 3325, 3285, 3195, 3132 (NH), 1650 (C=O). ^{1}H NMR (DMSO-d_6): δ_H (ppm) 6.9–8.8 (m, 9$H_{arom.}$), 9.8 (s, 1H, NH,



Scheme 9

exchangeable with D_2O), 12.98 (s, 1H, NH, $NHCO_{phth}$, exchangeable with D_2O). MS, *m/z* (%): 321 (M^+, 76.3), 259 (16.3), 219 (23.8), 173 (16.3), 102 (36.3), 51 (100). Anal. Calcd for $C_{16}H_{11}N_5OS$ (321): C, 59.80; H, 3.45; N, 21.79; S, 9.98. Found: C, 59.62; H, 3.73; N, 21.73; S, 9.67%.

Reaction of **1** *with formic acid; synthesis of N-formyl-4-oxo-3,4-dihydro-phthalazine-1-carbohydrazide* **4**

A solution of **1** (1 g, 4.9 mmole) in formic acid (10 mL) was heated under reflux. The deposited solid during heating after 7 h was filtered off, washed several times with water, dried and then recrystallised from dioxane to give **4**. Colourless crystals; m.p. 262–264 °C, yield 55%. IR (KBr) (υ_{max}, cm^{-1}): 3428, 3295, 3171(NH), 1702(C = O_{formyl}), 1662 (C = $O_{hydrazide}$). ^1H NMR (DMSO-d_6): δ_H (ppm) 7.89–8.4 (m, 5H, $4H_{arom.}$ + aldehydic protone CHO), 10.1 (s, 1H, NH, NHCHO, exchangeable with D_2O), 10.5 (s, 1H, NH, NHCO, exchangeable with D_2O), 13.03 (s, 1H, NH, $NHCO_{phth}$, exchangeable with D_2O). MS, *m/z* (%): 232 (M^+, 9.9), 204 (53.8), 173 (81.9), 145 (100), 117 (35.2), 90 (91.2). Anal. Calcd for $C_{10}H_8N_4O_3$ (232): C, 51.73; H, 3.47; N, 24.13. Found: C, 51.47; H, 3.73; N, 24.37%.

4-(1,3,4-Oxadiazol-2-yl)phthalazin-1(2H)-one **(5)**: A mixture of compound **4** (1 g, 4.3 mmole) and phosphorus pentaoxide (1 g) in dry toluene (20 mL) was refluxed for 8 h. The deposited solid during reflux was filtered off, washed several times with water, dried and then recrystallised from ethanol/dioxane mixture to give **5**. The same product **5** formed when a mixture of the acid hydrazide **1** (1 g, 4.9 mmole) and triethylorthoformate (10 mL) was heated under reflux for 72 h. After cooling, the solid deposited was filtered off and recrystallised from ethanol/dioxane mixture to give **5** (identity m.p., mixed m.p., IR, MS and TLC comparison). Pale yellow powder; m.p > 300 °C, yield 60%. IR (KBr) (υ_{max}, cm^{-1}): 3438, 3216(w), 3166(w) (NH), 1671 (CO). MS, *m/z* (%): 214 (M^+, 67.4), 171 (8.4), 145 (20.2), 129 (100), 117 (14), 102 (30.4), 88 (41.1). Anal. Calcd for $C_{10}H_6N_4O_2$ (214): C, 56.08; H, 2.82; N, 26.16. Found: C, 56.37; H, 2.73; N, 26.37%.

N-(1,3-Dioxoisoindolin-2-yl)-4-oxo-3,4-dihydrophthalazine-1-carboxamide **(6)**: A mixture of **1** (1 g, 4.9 mmole) and phthalic anhydride (0.72 g, 4.9 mmole) in dioxane (30 mL) in the presence of glacial acetic acid (1 mL) was refluxed for 6 h. The excess solvent was removed under reduced pressure, the deposited solid was filtered off, dried and then recrystallised from dioxane/DMF mixture to give **6**. Colourless crystals; m.p 312–314 °C, yield 63%. IR (KBr) (υ_{max}, cm^{-1}): 3373, 3168 (NH), 1796, 1739 (coupling bands), 1707, 1667 (CO). ^1H NMR (DMSO-d_6): δ_H (ppm) 7.9–8.5 (m, $8H_{arom.}$), 11.36 (s, 1H, NH, NHCHO, exchangeable with D_2O), 13.27 (s, 1H, NH, $NHCO_{phth}$, exchangeable with D_2O). MS, *m/z* (%): 334 (M^+, 21.2), 173 (100), 145 (65.8). Anal. Calcd for $C_{17}H_{10}N_4O_4$ (334): C, 61.08; H, 3.02; N, 16.76. Found: C, 61.37; H, 3.23; N, 16.37%.

5-(3,4-Dimethoxybenzylidene)-3-(1-oxo-1,2-dihydrophthalazine-4-carbonyl)-2,3-dihydro-5H-2,3-benzodiazepine-1,4-dione **(8a)**: A mixture of **1** (1 g, 4.9 mmole) and 4-(3,4-dimethoxybenzylidene)-4*H*-isochromene-1,3-dione **7a** (1.5 g, 4.9 mmole) in dioxane (30 mL) in the presence of glacial acetic acid (1 mL) was refluxed for 5 h. The excess solvent was removed under reduced pressure, the obtained yellow solid was filtered off, dried and then recrystallised from ethanol/dioxane mixture to give **8a**. Yellow crystals; m.p 310–312 °C, yield 52%. IR (KBr) (υ_{max}, cm^{-1}): 3444, 3222 (NH), 1682, 1662 (CO). MS, *m/z* (%): 496 (M^+, 17.2), 360 (24.1), 266 (34.5), 189 (34.5), 163 (100), 120 (48.3), 103 (20.7). Anal. Calcd for $C_{27}H_{20}N_4O_6$ (496): C, 65.32; H, 4.06; N, 11.29. Found: C, 65.27; H, 3.83; N, 11.37%.

5-((1,3-Diphenyl-1H-pyrazol-4-yl)methylene)-3-(1-oxo-1,2-dihydrophthalazine-4-carbonyl)-2,3-dihydro-5H-2,3-benzodiazepine-1,4-dione **(8b)**: A mixture of **1** (1 g, 4.9 mmole) and 4-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)isochromen-1,3-dione **7b** (1.9 g, 4.9 mmole) in dioxane (30 mL) in the presence of glacial acetic acid (1 mL) was refluxed for 5 h. The excess solvent was removed under reduced pressure. The deposited solid was collected by filtration, dried and then recrystallised from dioxane/DMF mixture to give **8b** as yellow crystals; m.p. 286–288 °C, yield 45%. IR (KBr) (υ_{max}, cm^{-1}): br.3182 (NH), 1680 (CO). MS, *m/z* (%): 578 (M^+, 11.1), 334 (16.2), 189 (17.7), 173 (34.8), 145 (36.9), 77(100) . Anal. Calcd for $C_{34}H_{22}N_6O_4$ (578): C, 70.58; H, 3.83; N, 14.53. Found: C, 70.37; H, 3.53; N, 14.25%.

Reaction of the acid hydrazide 1 with norbornenedicarboxylic acid anhydride derivative; synthesis of the pyridazine-1,4-dione derivative **10**

A mixture of the acid hydrazide **1** (1 g, 4.9 mmole) and norbornenedicarboxylic acid anhydride derivative **9** (0.4 mL, 4.9 mmole) in dioxane (20 mL) in the presence of glacial acetic acid (1 mL) was

heated under reflux for 5 h. Evaporation of excess solvent left the solid product which recrystallised from benzene/ethanol mixture to give **10**. Colourless crystals; m.p. 160–162 °C, yield 50%. IR (KBr) (υ_{max}, cm^{-1}): br.3268 (NH), 1725, 1673 (CO). MS, *m/z* (%): 364 (M^+, 9.3), 284 (13), 173 (57.4), 145 (33.0), 90 (36.9), 80 (100). Anal. Calcd for $C_{19}H_{16}N_4O_4$ (364): C, 62.63; H, 4.43; N, 15.38. Found: C, 62.41; H, 4.55; N, 15.26%.

*Reaction of **1** with activated nitrile; synthesis of N-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)-4-oxo-3,4-dihydro-phthalazine-1-carbohydrazide* **12**

A mixture of **1**(1 g, 4.9 mmole) and 2-[(1,3-diphenyl-1*H*-pyrazol-4-yl) methylene] malononitrile **11** (1.5 g, 4.9 mmole) in dioxane (30 mL) in the presence of piperidine (1 mL) was heated under reflux for 3 h. The reaction mixture was allowed to cool and then acidified with cold dilute hydrochloric acid. The precipitated was collected by filtration, washed several times with water, dried and then recrystallised from dioxane/DMF mixture to give **12**. Colourless crystals; m.p. 296–298 °C, yield 54%. IR (KBr) (υ_{max}, cm^{-1}): br.3442, 3230 (OH, NH), 1671 (CO). ^{1}H NMR (DMSO-d_6): δ_H (ppm) 7.5–8.6 (m, 15$H_{arom.}$), 9.03 (s, 1H, N = CH), 12.01 (s, 1H, NH, NHCO, exchangeable with D_2O), 13.07 (s, 1H, NH, $NHCO_{phth}$, exchangeable with D_2O). MS, *m/z* (%): 434 (M^+, 46.98), 245 (100), 189 (30.54), 173 (11.83), 145 (16.15), 117 (15.56), 104 (25.50), 90 (28.71). Anal. Calcd for $C_{25}H_{18}N_6O_2$ (434): C, 69.11; H, 4.18; N, 19.34. Found: C, 69.32; H, 4.23; N, 19.11%.

Synthesis of authentic sample **12**

To a solution of the hydrazide **1** (1 g, 4.9 mmole) in dioxane (20 mL), 1,3-diphenyl-1H-pyrazole-4-carbaldehyde (1.2 g, 4.9 mmole) and piperidine (1 mL) were added and the whole mixture was heated under reflux for 3 h. Evaporation of excess solvent left the solid product which recrystallised from dioxane to give **12** (identity m.p., mixed m.p., IR and TLC).

*Reaction of the acid hydrazide **1** with ethoxymethylene malononitrile; synthesis of 4-oxo-N-(1-oxo-1,2-dihydro-phthalazine-4-carbonyl)-3,4-dihydrophthalazine-1-carbohydrazide 13 and 4-oxo-3,4-dihydrophthalazine-1-carboxamide* **14**

A mixture of **1**(1 g, 4.9 mmole) and ethoxymethylene malononitrile (0.6 g, 4.9 mmole) in pyridine (15 mL) was refluxed for 1 h. The solid precipitated during heating was filtered off and recrystallised from DMF to give **13**. Acidification of the filtrate with cold dilute hydrochloric acid followed by evaporation of the excess solvent left beige precipitate which recrystallised from ethanol/dioxane mixture to give **14**.

4-Oxo-N-(1-oxo-1,2-dihydrophthalazine-4-carbonyl)-3,4-dihydrophthalazine-1-carbohydrazide (**13**): Pale yellow crystals m.p. 326–327 °C, yield 40%. IR (KBr) (υ_{max}, cm^{-1}): 3398, 3241, 3169 (NH), 1673 (CO). MS, *m/z* (%): 376 (M^+, 23.8), 173 (100), 145 (60), 117 (27.9), 90 (44.1). Anal. Calcd for $C_{18}H_{12}N_6O_4$ (376): C, 57.45; H, 3.21; N, 22.33. Found: C, 57.23; H, 3.45; N, 22.19%.

4-Oxo-3,4-dihydrophthalazine-1-carboxamide (**14**): Beige crystals. m.p. 240–242 °C, yield 37%. IR (KBr) (υ_{max}, cm^{-1}): 3228, 3162 (NH_2, NH), 1666 (CO), 1629 (C = N). MS, *m/z* (%): 189 (M^+, 77.8), 173 (40), 145 (26.7), 130 (68.9), 117 (66.7), 103 (42.2), 88 (100). Anal. Calcd for $C_9H_7N_3O_2$ (189): C, 57.14; H, 3.73; N, 22.21. Found: C, 57.33; H, 3.45; N, 22.43%.

4-(3-Methyl-5-oxo-4,5-dihydro-1H-pyrazole-1-carbonyl) phthalazin-1(2H)-one (**15**): A mixture of **1** (1 g, 4.9 mmole) and ethyl acetoacetate (0.6 mL, 4.9 mmole) in pyridine (15 mL) was refluxed for 3 h. The deposited solid during reflux was filtered off, dried and then recrystallised from dioxane/DMF mixture to give **15**. Pale yellow crystals; m.p 306–308 °C, yield 57 %. IR (KBr) (υ_{max}, cm^{-1}): 3225, 3170 (NH), br.1673 (CO). MS, *m/z* (%): 268 (M-2, 28), 173 (44), 145 (100), 103 (48), 90 (76). Anal. Calcd for $C_{13}H_{10}N_4O_3$ (270): C, 57.78; H, 3.73; N, 20.73. Found: C, 57.53; H, 3.56; N, 20.44%.

Acylation of 1 using chloroacetyl chloride; synthesis of N-(2-chloroacetyl)-4-oxo-3,4-dihydrophthalazine-1-carbohydrazide **16**

A mixture of the hydrazide **1** (1 g, 4.9 mmole) and chloroacetyl chloride (0.5 mL, 4.9 mmole) in DMF (15 ml) was stirred at room temperature for 1 h. The reaction mixture was poured on water, the obtained solid precipitate was collected by filtration, dried and then recrystallised from dioxane to give **16**. Colourless powder; m.p. 284–286 °C, yield 72%. IR (KBr) (υ_{max}, cm^{-1}): 3342, 3297 (NH), 1699, 1674 (CO). MS, *m/z* (%): 280 (M^+, 10.9), 173 (100), 145 (61.1), 114 (22.2), 90 (44.2). Anal. Calcd for $C_{11}H_9ClN_4O_3$ (280.5): C, 47.04; H, 3.23; Cl, 12.63; N, 19.96. Found: C, 47.33; H, 3.46; Cl, 12.49; N, 19.74%.

*Cyclisation of **16**; synthesis of 4-(5-(chloromethyl)-1,3,4-oxadiazol-2-yl) phthalazin-1(2H)-one* **18**

Solution of the chloroacetyl derivative **16** (1 g, 3.5 mmole) in pyridine (15 mL) was heated under reflux for 6 h. The solid precipitated during heating was filtered off and recrystallised from DMF to give **17**. Colourless powder; m.p. 306–308 °C, yield 80%. IR (KBr) (υ_{max}, cm^{-1}): 3247 (NH), 1665 (CO), 1635 (C = N). MS, *m/z* (%): 263 (M^+, 1.2), 213 (3.5), 171 (4.1), 145 (5.2), 129 (11.3), 117 (2.9), 102 (1.7), 90 (7.4), 52 (100). Anal. Calcd for $C_{11}H_7ClN_4O_2$ (262.5): C, 50.30; H, 2.69; Cl, 13.50; N, 21.33. Found: C, 50.15; H, 2.48; Cl, 13.21; N, 21.27%.

*Acetylation of **1**; general procedure*

A mixture of **1** (1 g, 4.9 mmole) and freshly distilled acetic anhydride (10 mL) was heated under reflux for different times 10 min., 30 min. and 60 min. The excess solvent was removed under reduced pressure, the obtained solid was collected by filtration and then recrystallised from ethanol/dioxane mixture to give the mono-, di-, and tri-acetylated products **18–20** respectively.

N-Acetyl-4-oxo-3,4-dihydrophthalazine-1-carbohydrazide (**18**): Colourless crystals; m.p; 296–298 °C, yield 42%. IR (KBr) (υ_{max}, cm^{-1}): 3321 (NH), 1714, 1683 (CO). ^{1}H NMR (DMSO-d_6): δ_H (ppm) 1.88 (s, 3H, CH_3), 7.8–8.4 (m, 4$H_{arom.}$), 9.99 (s, 1H, NH, $NHCOCH_3$, exchangeable with D_2O), 10.3 (s, 1H, NH, NHCO, exchangeable with D_2O), 12.99 (s, 1H, NH, $NHCO_{phth}$, exchangeable with D_2O). MS, *m/z* (%): 246 (M^+, 12.7), 204 (70.7), 173 (100), 145 (64.7), 117 (20.7), 90 (52), 63 (38). Anal. Calcd for $C_{11}H_{10}N_4O_3$ (246): C, 53.66; H, 4.09; N, 22.75. Found: C, 53.37; H, 4.23; N, 22.47%.

N,N-diacetyl-4-oxo-3,4-dihydrophthalazine-1-carbohydrazide (**19**): Colourless crystals; m.p. 240–242 °C, yield 30%. IR (KBr) (υ_{max}, cm^{-1}): 3375, 3303, 3168 (NH), 1729, 1714, 1617 (CO). ^{1}H NMR (DMSO-d_6): δ_H (ppm) 2.37 (s, 6H, $N(COCH_3)_2$), 7.9–8.5 (m, 4$H_{arom.}$), 11.1 (s, 1H, NH, NHCO, exchangeable with D_2O), 13.19 (s, 1H, NH, $NHCO_{phth}$, exchangeable with D_2O). MS, *m/z* (%): 288 (M^+, 3.7), 246 (40.7), 204 (100), 173 (72.2), 145 (50.9), 117 (21.3), 90 (58.3), 63 (29.6). Anal. Calcd for $C_{13}H_{12}N_4O_4$ (288): C, 54.17; H, 4.20; N, 19.44. Found: C, 54.35; H, 4.53; N, 19.21%.

N,N,O-Triacetyl-4-oxo-3,4-dihydrophthalazine-1-carbohydrazide (**20**): Colourless crystals; m.p. 198–200 °C, yield 51%. IR (KBr) (υ_{max}, cm^{-1}): 3167 (NH), 1736 (CO_{ester}), 1686 (CO_{phth}), 1671 (CO_{amide}). ^{1}H NMR (DMSO-d_6): δ_H (ppm) 2.372 (s, 9H, 3 $COCH_3$), 7.815–7.817 (d, 1$H_{arom.}$, H = 0.6Hz), 7.91–7.99 (m, 2$H_{arom.}$), 8.321–8.326 (d, 1$H_{arom.}$, H = 1.5Hz), 13.09 (s, 1H, NH, exchangeable with D_2O). Anal. Calcd for $C_{15}H_{14}N_4O_5$ (330): C, 54.55; H, 4.27; N, 16.96. Found: C, 54.25; H, 4.53; N, 16.77%.

Reaction of the hydrazide 1 with isatin; synthesis of 4-oxo-N-(2-oxoindolin-3-ylidene)-3,4-dihydrophthalazine-1-carbohydrazide **21**

A mixture of the hydrazide **1** (1 g, 4.9 mmole) and isatin (0.7 g, 4.9 mmole) in dioxane (20 mL) was heated under reflux for 2 h. The deposited solid during reflux was filtered off, dried and then recrystallised from DMF to give **21**. Yellow powder; m.p > 300 °C, yield 65%. IR (KBr) (υ_{max}, cm^{-1}): 3226(w), 3165(w), 3109 (NH), 1713 ($CO_{phthalazinone}$), 1683 ($CO_{hydrazide}$) MS, *m/z* (%):334 (M+1, 52.2%), 333 (30.4), 159 (82.6), 132 (100), 104 (48.8), 77 (88.9). Anal. Calcd for $C_{17}H_{11}N_5O_3$ (333): C, 61.26; H, 3.33; N, 21.01. Found: C, 61.34; H, 3.76; N, 21.25%.

*Reaction of the hydrazide **1** with benzyl; synthesis of 4-oxo-N-(2-oxo-1,2-diphenylethylidene)-3,4-dihydro-phthalazine-1-carbohydrazide* **22**

A mixture of the hydrazide **1** (1 g, 4.9 mmole), benzil (1 g, 4.9 mmole) and ammonium acetate (1 g) in dioxane (25 mL) was heated under reflux for 6 h (TLC). Evaporation of excess solvent left a solid product which washed with water, dried and then recrystallised from ethanol/dioxane mixture to give **22**. Pale yellow powder; m.p. 160–163 °C, yield 70%. IR (KBr) (υ_{max}, cm^{-1}): 3307, 3162 (NH), 1714, 1688, 1647 (CO). MS, *m/z* (%): 396 (M^+, 0.6), 291 (74), 204 (85.6), 173 (84.8), 145 (87.3), 102 (25.9), 90 (100). Anal. Calcd for $C_{23}H_{16}N_4O_3$ (396): C, 69.69; H, 4.07; N, 14.13. Found: C, 69.33; H, 3.86; N, 14.24%.

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