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, 1H-pyrazol-4-yl, phthalazin-1(2H)-one, 5H-2,3-benzodiazepine-1,4-dione and pyrimidine-1,4-dione derivatives were prepared via the reaction of the readily obtainable starting material 1-oxo-1,2-dihydropthalazin-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. Hence, great efforts are continuously being made to find novel antihypertensive agents acting through different mechanisms. 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. 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, including antihypertensive effects, inhibition of platelet aggregation and of phosphodiesterases. Some of them also displayed antiasthmatic, antipsychotic, antidiabetic, anticonvulsant, antineoplastic, antimicrobial, antifungal and antiparasitic 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. Refluxing the hydrazide 1 with phenylisothiocyanate or phenylisocyanate in boiling pyridine gave 1-(1-oxo-1,2-dihydropthalazin-4-carbonyl)-4-phenylthiosemicarbazide 2a and 1-(1-oxo-1,2-dihydropthalazin-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-1H,1,2,4-triazol-3-yl]phthalazin-1-(2H)-one 3. Moreover, when compound 2a was allowed to react with sodium hydroxide (10%)
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(2H)-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-dioxoisooindolin-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-5H-2,3-benzodiazepine-1,4-dione 8a and 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 (Scheme 3). The structure of compounds 6 and 8 a,b were substituted from the analytical and spectroscopic data.

Furthermore, the reaction of the hydrazide 1 with norbornene dicarboxylic acid anhydride derivative 9 in boiling dioxane...
Reaction of the hydrazide 1 with ethoxymethylenemalononitriile in boiling pyridine gave the pale yellow solid product with molecular formula C$_{18}$H$_{12}$N$_6$O$_4$ [M$^+$ = 376 (23.8%)] which was analysed and assigned as 4-oxo-N-(1-oxo-1,2-dihydrophthalazine-4-carbonyl)-3,4-dihydrophthalazine-1-carboxydrazide. Evaporation of the excess solvent after acidification of the filtrate left 4-oxo-3,4-dihydrophthalazine-1-carboxamide. The formation of compounds 14 and 15 can be postulated as shown in Scheme 7.

It has been reported that the hydrazine or hydrazide derivative reacted with a $\beta$-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-1H-pyrazole-1-carbonyl)phthalazin-1(2H)-one (Scheme 5). Acylation of the hydrazide 1 with chloroacetyl chloride in DMF in the cold for one hour gave the chloroacetyl derivative which is easily cyclised through dehydration upon heating in pyridine to give 4-(5-(chloro-methyl)-1,3,4-oxadiazol-2-yl)phthalazin-1(2H)-one.

The formation of 12 can be visualised as shown in 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. 1H NMR spectra were measured in DMSO-d6 on a Varian plus instrument (300 MHz). Mass spectra were recorded on a Shimadzu GC-MS QP1000 EX instrument operating at 70 eV in El 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, cm⁻¹): 3465(w), 3237(br.) (NH), 1666 (C=O). 1H NMR (DMSO-d6): δH (ppm) 7.15–8.65 (m, 9H arom.), 9.8 (brs, 2H, 2NH, exchangeable with D₂O), 10.57 (s, 1H, NH, exchangeable with D₂O), 13.07 (s, 1H, NH, NHCO phth, exchangeable with D₂O). MS, m/z (%): 339 (M⁺, 1.75), 285 (2.3), 245 (5.6), 173 (2.48), 129 (31.9), 70(100). Anal. Calcd for C₁₆H₁₃N₅O₂S (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, cm⁻¹): 3417 (br.), 3171(br.) (NH), 1666 (C=O). MS, m/z (%): 323 (M⁺, 1.11), 285 (2.5), 245 (5.6), 173 (2.48), 129 (31.9), 70(100). Anal. Calcd for C₁₆H₁₃N₅O₃ (323): 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%.

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
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)phthalazine-1(2H)-one (3): Colourless crystals; m.p. 220–222 °C, yield 30%. IR (KBr) (νmax cm−1): 3325, 3285, 3195, 3132 (NH), 1650 (C=O).

1H NMR (DMSO-d6): δH (ppm) 6.9–8.8 (m, 9H arom.), 9.8 (s, 1H, NH,
exchangeable with D,O), 12.98 (s, 1H, NH, NHCO phth, exchangeable with D,O). MS, m/z (%): 321 (M⁺, 76.3), 259 (16.3), 219 (23.8), 173 (16.3), 102 (36.3), 51 (100). Anal. Calc’d for C₆H₅NO₃ (321): C, 59.80; H, 3.45; N, 21.73; S, 9.67%.

Reaction of 1 with formic acid: synthesis of N-formyl-4-oxo-3,4-dihydro-phthalazine-1-carboxyhydrazide 4
A solution of 1 (1 g, 4.9 mmole) and triethylorthoformate (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 60%. IR (KBr) (υmax, cm⁻¹): 3428, 3295, 3171 (NH), 1702 (C = Oformyl), 10.5 (s, 1H, NH, NHCO, exchangeable with D,O). δH (ppm) 7.89–8.4 (m, 8H arom.), 11.36 (s, 1H, NH, NHCHO, exchangeable with D,O). 13.03 (s, 1H, NH, NHCO phth, exchangeable with D,O). MS, m/z (%): 232 (M⁺, 9.9), 204 (53.8), 173 (81.9), 145 (100), 117 (35.2), 90 (91.2). Anal. Calc’d for C₁⁶H₁₁N₅OS (321): C, 59.62; H, 3.73; N, 21.73; S, 9.98. Found: C, 59.67; H, 3.53; N, 21.73; S, 9.67%.

5-(3,4-Dimethoxybenzylidene)-1-(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)-4H-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. 312–314 °C. Yield 63%. IR (KBr) (υmax, cm⁻¹): 3444, 3222 (NH), 1682, 1662 (CO). δH (ppm) 7.9–8.5 (m, 8H arom.), 88 (41.1). Anal. Calc’d for C₂₇H₂₀N₄O₆ (496): C, 70.58; H, 3.83; N, 14.53. Found: C, 70.37; H, 3.53; N, 14.25%.

Scheme 9

N-(1-Dioxoisooindolin-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) (υmax, cm⁻¹): 3373, 3168 (NH), 1796, 1739 (coupling bands), 1707, 1667 (CO). δH (ppm) 7.89–8.4 (m, 8H arom.), 11.36 (s, 1H, NH, NHCHO, exchangeable with D,O). 13.27 (s, 1H, NH, NHCO phth, exchangeable with D,O). MS, m/z (%): 334 (M⁺, 21.2), 171 (100), 145 (65.8). Anal. Calc’d for C₁⁰H₆N₄O₂ (334): C, 61.37; H, 3.23; N, 16.76. Found: C, 61.37; H, 3.23; N, 16.37%.

5-(3,4-Dimethoxybenzylidene)-1-(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-(3,4-dimethoxybenzylidene)-4H-isochromene-1,3-dione 7a (1 g, 4.9 mmole) and 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 4-(3,4-dimethoxybenzylidene)-4H-isochromene-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 obtained yellow solid was filtered off, dried and then recrystallised from ethanol/dioxane mixture to give 8b. Yellow crystals; m.p. 310–312 °C. Yield 52%. IR (KBr) (υmax, cm⁻¹): 3444, 3222 (NH), 1682, 1662 (CO). MS, m/z (%): 496 (M⁺, 11.1), 334 (16.2), 189 (21.5), 163 (100), 120 (48.3), 103 (20.7). Anal. Calc’d for C₁₇H₁₀N₄O₄ (496): C, 65.32; H, 4.06; N, 11.29. Found: C, 65.27; H, 4.03; 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-1H-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) (υmax, cm⁻¹): 3182 (NH), 1680 (CO). MS, m/z (%): 578 (M⁺, 11.1), 334 (16.2), 189 (17.7), 173 (34.8), 156 (36.9), 77 (100). Anal. Calc’d for C₁₇H₁₀N₄O₄ (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) (\(\text{cm}^{-1}\)): 3268 (NH), 1725, 1673 (CO). MS, m/z (%): 364 (M⁺, 9), 283 (13), 173 (57.4), 145 (33.0), 90 (36.9), 80 (100). Anal. Calc. for C₁₃H₁₂N₄O₄ (338): C, 53.78; H, 3.94; N, 15.26%.

Reaction of 1 with activated nitrite; synthesis of N-(1,3-diphenyl-1H-pyrazol-4-yl)methylene)-4-oxo-3,4-dihydro-phthalazin-1-carboxylic acid 12
A mixture of 1 (1 g, 4.9 mmole) and 2-[(1,3-diphenyl-1H-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) (\(\text{cm}^{-1}\)): 3292, 3230 (OH, NH), 1671 (CO).'H NMR (DMSO-d₆): 8 2.87 (s, 6H, N(COCH₃)₂), 7.815–7.817 (d, 4H, H arom.), 7.9–8.5 (m, 4Harom.), 10.3 (s, 1H, NH, NHCO, exchangeable with D₂O). 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. Calc. for C₁₃H₁₂N₄O₄ (338): C, 54.17; H, 4.20; N, 19.44. Found: C, 54.35; H, 4.27; N, 19.21%.

4-Oxo-3,4-dihydrophthalazin-1-carboxylic acid 19:
Colourless crystals; m.p. 240–242 °C, yield 50%. IR (KBr) (\(\text{cm}^{-1}\)): 3393, 3307, 3162 (NH), 1729, 1714, 1617 (CO).'H NMR (DMSO-d₆): 8 2.37 (s, 3H, CH₃), 7.9–8.5 (m, 4H, H arom.), 10.3 (s, 1H, NH, NHCO, exchangeable with D₂O). MS, m/z (%): 288 (M⁺, 3.7), 246 (3.7), 204 (70.7), 173 (100), 145 (64.7), 117 (20.7), 90 (52.5), 63 (38). Anal. Calc. for C₁₃H₁₂N₄O₄ (338): C, 54.17; H, 4.20; N, 19.44. Found: C, 54.35; H, 4.27; N, 19.21%.

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 mono-, di- and tri-acetylated products 18–20 respectively.

4-Oxo-3,4-dihydrophthalazin-1-carboxylic acid 21
A mixture of 1 (1 g, 4.9 mmole) and isatin (1.5 g, 3.5 mmole) in pyridine (25 mL) was heated under reflux for 3 h. The solid precipitated during heating was filtered off and recrystallised from DMF to give 21. Colourless crystals; m.p. 284–286 °C, yield 72%. IR (KBr) (\(\text{cm}^{-1}\)): 3432, 3297 (NH), 1699, 1674 (CO). MS, m/z (%): 280 (M⁺, 10.9), 173 (100), 145 (61.1), 114 (22.2), 90 (44.2). Anal. Calc. for C₁₃H₁₁CINO₃ (280): 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. 308–308 °C, yield 80%. IR (KBr) (\(\text{cm}^{-1}\)): 3232 (NH), 1665 (CO), 1635 (C = N). MS, m/z (%): 263 (M⁺, 12.3), 213 (3.5), 171 (4.1), 145 (5.2), 129 (11.3), 117 (2.9), 102 (1.7), 90 (7.4), 52 (100). Anal. Calc. for C₁₃H₁₁CINO₃ (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 mono-, di- and tri-acetylated products 18–20 respectively.
References
