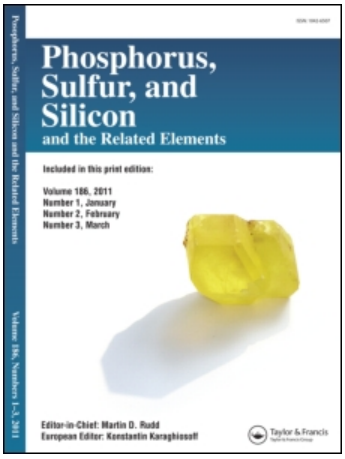

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POLYFUNCTIONALLY SUBSTITUTED HETEROCYCLES: SYNTHESIS OF NEW POLYFUNCTIONALLY SUBSTITUTED PHTHALAZINES, PYRIDO[3,4-C]PYRIDAZINES AND PYRAZOLO[3,4-C]PYRIDAZINES

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POLYFUNCTIONALLY SUBSTITUTED HETEROCYCLES: SYNTHESIS OF NEW POLYFUNCTIONALLY SUBSTITUTED PHTHALAZINES, PYRIDO[3,4-C]PYRIDAZINES AND PYRAZOLO[3,4-C]PYRIDAZINES

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Several new alkylpyridine and pyridazine derivatives have been synthesized. The reactivity of these alkylazines towards aromatic aldehydes and sulphur are reported. New syntheses of pyrido[3,4-C]pyridines and phthalazines were achieved.

Keywords: pyridazines; heterocycles; alkylpyridine; alkylazines

The discovery of the vasodilator action of hydralazine (phthalazin-1-yl-hydrazine); as well as some other pyridazinyl hydrazine derivatives; has promoted extensive work on synthesis and chemistry of pyridazines and condensed pyridazines1–3. Recently; we reported upon an efficient synthesis of **1** and showed that this compound can serve as an excellent starting material for the synthesis of substituted pyridazines and substituted phthalazines 3–6. It has been found that **1** reacts with hydrazine hydrate in ethanol to yield a product of condensation via ethanol elimination and forms the hydrazide **3**. Structure **3** could be readily established for this reaction product via its conversion into acid **5**. N-Aminopyridine **2** was obtained via reaction of **1** with hydrazine hydrate at

*Corresponding author.

100°C in the absence of solvent. Compound **2** was also formed from reaction of **3** with ethanolic sodium ethoxide. Formation of **2** by this way is assumed to proceed via opening of the pyridazine ring by ethoxide ion to yield intermediate **4** which then cyclises into **2** via ethanol elimination.

Compound **3** condensed with benzaldehyde to yield the benzylidene derivative **6** or **7**. Structure **7** was established based from ^{1}H NMR analysis which revealed signals for two CH_3 groups at δ = 2.3 and 3.2 ppm. Compound **7a** reacted with benzylidenemalononitrile **8** to yield the phthalazine **9**. Compound **9** is assumed to be formed via involvement of the methyl function in **7** with the activated double bond in **8**; then cyclized and aromatized via a sequence similar to that reported earlier by us2. Attempts to prepare **9** via reaction of **7** with benzaldehyde to give the styryl compound **10**; followed by reaction with malononitrile were failed. It gives the pyrido[3,4-C]pyridazine derivative **11** instead. The preparation of **11** could be generalized by using a variety of aldehydes as in form **11a–g**.

Compound **3** reacts also with 1-phenyl-3-chloro-5-methylpyrazole-4-aldehyde **12** to form a product of condensation via water and hydrochloric acid elimination. This product is assigned as the pyrazolo[3,4-C]pyrazol-1-yl-pyridazine derivative **14**. Compound **14** is assumed to be formed via **13** as an intermediate which cyclized during the reaction condition into the final isolable product **14**.

Compound **7** reacts with elemental sulfur to yield the thienopyridazine **15**. Compound **15** reacts with acrylonitrile and maleic anhydride to yield the phthalazines **16** and **17**; respectively. Formation of these products is assumed to proceed via [4 + 2] cycloadduct **18** which aromatize by H_2S elimination to yield the final isolable phthalazines.

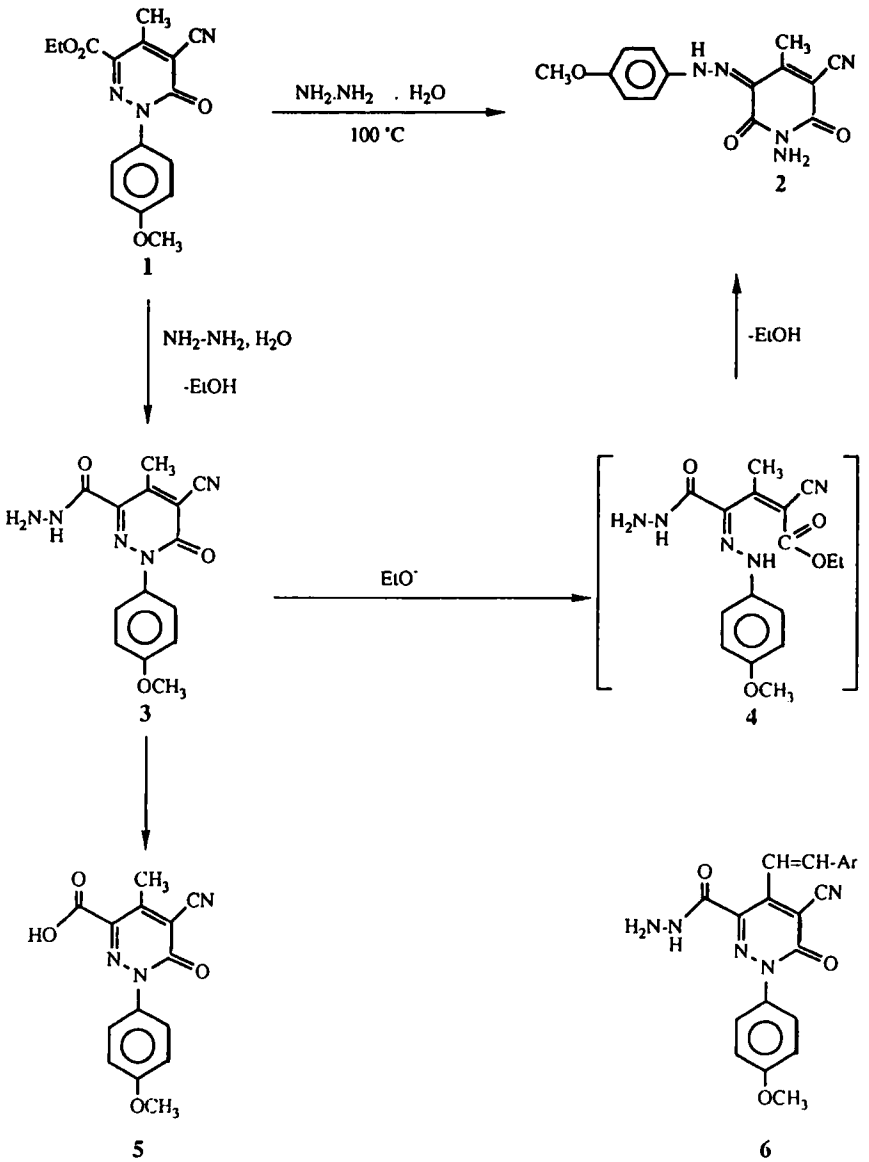
EXPERIMENTAL

All m.ps are uncorrected. IR spectra were recorded on a Pye-Unicam Spectrophotometer. ^{1}H-NMR spectra were measured on a Varian EM-390 spectrometer. Microanalyses were performed by the Microanalytical Data Unit at Cairo University.

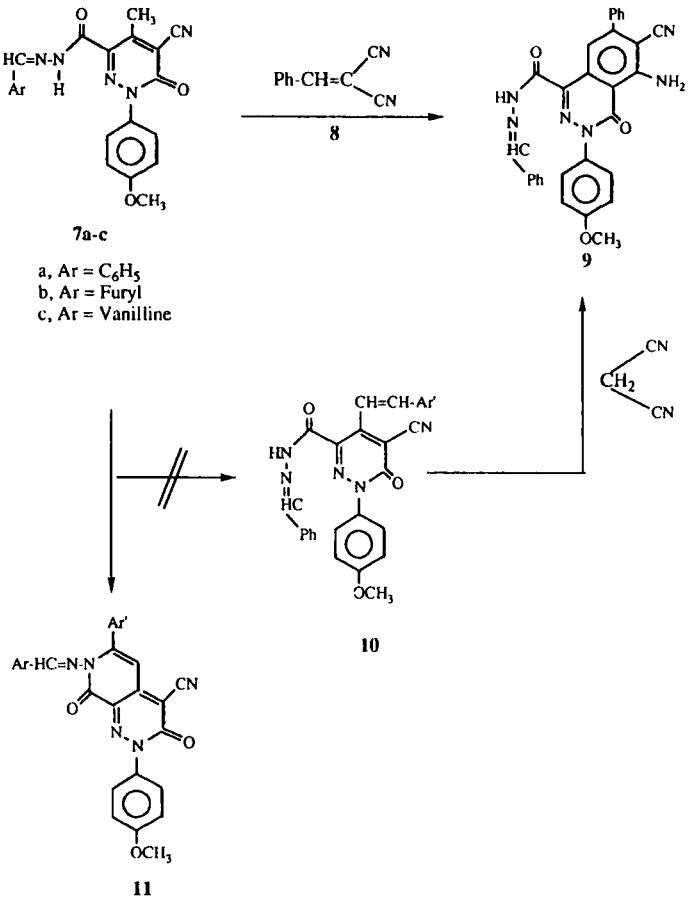
1-Amino-2,6-dioxo-4-methyl-1,2,5,6-tetrahydro-5-(*p*-anisyl)-hydrazonopyridine-3-carbonitrile (2)

Method A

A mixture of **1** (3.9 g%, 0.01 mol) and hydrazine hydrate (2.0 ml; 99%) was heated for 2 h at 100°C (water-bath temperature). The reaction product was then



triturated with water. The resulting solid product was collected by filtration and crystallized from ethanol as brown crystals (1.12g, 10%), m.p. 275°C. IR cm^{-1} 3450–3350 (NH, NH_2); 2220 (CN); 1690 (CO). ^1H NMR (DMSO-d_6): 2.41 (s, 3 H, CH_3); 3.60 (br, 2 H, NH_2); 6.70–7.12 (m, 4 H, aromatic H); 10.60 (br, 1 H, NH). (Found, C: 56.4; H, 4.3; N, 23.3. Calcd. for $C_{14}H_{13}N_5O_3$: C, 56.18, H, 4.34; N, 23.41%).



Method B

A solution of **3** (3.0 g; 0.01 mol) in ethanolic sodium ethoxide (0.03 g, 0.01 mol sodium dissolved in 30 ml of ethanol) was heated under reflux for 2 h and then evaporated in vacuo. The remaining product was triturated with water and acidified. The solid product so formed was collected by filtration and identified as **2** (1.7 g, 60%), m.p. 275°C.

5-Cyano-1,6-dihydro-4-methyl-6-oxo-1-(*p*-anisyl)pyridazine-3-carboxylic acid hydrazide (3)

A solution of **1** (3.1 g, 0.01 mol) in ethanol/DMF (5:1) mixture was treated with hydrazine hydrate (0.50 ml, 0.01 mol). The reaction mixture was refluxed for 30 min, and the solid product so formed was collected by filtration and crystallized

from dioxane as yellow crystals (1.5 g, 50%), m.p. 215°C. IR cm^{-1} (KBr): 3480–3380 (NH_2); 3250 (NH), 2220 (CN): 1690 (CO), 1670 (C=O). ^1H NMR (DMSO-d_6): 2.31 (s, 3 H, CH_3); 3.41 (s, 3 H, OCH_3); 3.69 (br, 2 H, NH_2); 6.71–7.12 (m, 4 H, aromatic protons); 10.5 (br, 1 H, NH). (Found, C: 56.1; H, 4.2; N, 23.2. Calcd. for $C_{14}H_{13}N_5O_3$: C, 56.18; H, 4.34; N, 23.41%).

5-Cyano-4-methyl-6-oxo-1-(*p*-anisyl)pyridazin-3-carboxylic acid (5)

A suspension of **3** (3.0 g, 0.01 mol) in acetic acid and hydrochloric acid (3:1 mixture) was refluxed for 1 h. The reaction mixture were left to cool at room temperature and then poured into cold water. The solid product so formed was collected by filtration and crystallized from ethanol as brown crystals, 1.7 g, 59.6%, m.p. 260°C. (Found: C, 58.7; H, 3.7; N, 14.6. Calcd. for $C_{14}H_{11}N_3O_4$: C, 58.94; H, 3.85; N, 14.73%)

N-Benzylidene-5-cyano-1,6-dihydro-4-methyl-6-oxo-1-(*p*-anisyl)-pyridazine-3-carboxylic acid hydrazide (7)

A suspension of **3** (3.0 g, 0.01 mol) in dioxane (20 ml) and a catalytic amount of piperidine was treated with appropriate aldehydes (0.01 mol). The reaction mixture was refluxed for 2 h. then poured into water. The solid product so formed was collected by filtration and crystallized from the proper solvent.

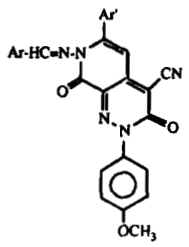
Compound **7a** formed as buff crystals from ethanol (1.7 g, 43%), m.p. 165°C. IR: cm^{-1} (KBr): 3200 (NH); 2220 (CN); 1700 (C=O) and 1670 (ring CO). ^1H NMR (DMSO-d_6): 2.31 (s, 3 H, CH_3); 3.22 (s, 3 H, OCH_3); 7.21–7.82 (m, 9 H, aromatic H); 8.30 (s, 1 H, CH); 13.0 (s, 1 H, NH); ms: m/z = 387 (M^+). (Found, C: 65.3; H, 4.2; N, 18.1. Calcd. for $C_{21}H_{17}N_5O_3$: C, 65.11; H, 4.39; N, 18.08%).

Compound **7b** formed as brown crystals from ethanol (1.7 g, 43%), m.p. 200°C. IR: cm^{-1} (KBr): 3320 (NH); 2221 (CN); 1690–1670 (C=O) (Found: C, 60.3; H, 4.0; N, 18.3. Calcd. for $C_{19}H_{15}N_5O_4$: C, 60.47; H, 3.97; N, 18.56%).

Compound **7c** formed as violet crystals from DMF (1.8 g, 41%), m.p. > 250°C. IR: cm^{-1} (KBr): 3330 (NH); 2221 (CN); 1700–1670 (C=O). (Found: C, 60.8; H, 4.2; N, 16.0. Calcd. for $C_{22}H_{19}N_5O_5$: C, 60.96; H, 4.38; N, 16.1%).

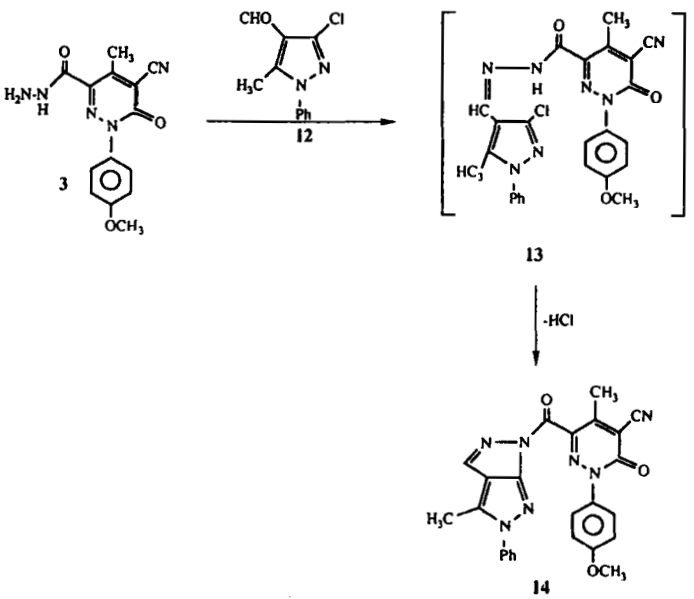
N-Benzylidene-5-amino-6-cyano-3,4-dihydro-7-phenyl-3-(*p*-anisyl)-phthalazine-1-carboxylic acid hydrazide (9)

A suspension of **7** (3.8 g, 0.01 mol) in DMF/dioxane (20 ml) was treated with benzylidenemalononitrile **8** (1.5 g, 0.01 mol). The reaction mixture was refluxed for 3 h and then left to cool at room temperature. The resulting solution was



11a-g

IIa, Ar = Ar' = C_6H_5
b, Ar = C_6H_5, Ar' = Furyl
c, Ar = C_6H_5, Ar' = Vanillinyl
d, Ar = Furyl, Ar' = C_6H_5
e, Ar = Furyl, Ar' = Vanillinyl
f, Ar = Vanillinyl, Ar' = C_6H_5
g, Ar = Vanillinyl, Ar' = Furyl



poured into water and the solid product so formed was collected by filtration and crystallized from dioxane as yellow crystals (1.9 g, 38%), m.p. > 300°C. IR: cm^{-1} (KBr): 3480–3340 cm^{-1} (NH_2), 3250 (NH); 2221 (CN), 1690 (CO). ^1H NMR (DMSO-d_6): 3.41 (s, 3 H, OCH_3); 4.00 (br, 2 H, NH_2); 6.71–7.42 (m, 16 H, aromatic protons); 12.2 (br, 1 H, NH). ms: m/z = 514 (M^+). (Found, C: 70.1; H, 4.3; N, 16.4%. Calcd. from $C_{30}H_{22}O_3$: C, 70.03; H, 4.28; N, 16.34%).

7-Benzylidenamino-2,3,7,8-tetrahydro-3-oxo-2-(*p*-anisyl)-6-phenyl-pyrido[3,4-C]pyridazine-3-carbonitrile (11)

A suspension of **7** (3.8 g, 0.01 mol) in dioxane (20 ml) and a catalytic amount of piperidine was treated with appropriate aldehydes (0.01 mol). The reaction mixture was refluxed for 2 h and then left to cool at room temperature. The reaction mixture was poured into water. The solid product so formed was collected by filtration and crystallized from the proper solvent.

Compound **11a** formed as yellow crystals from ethanol (3.9 g, 85%), m.p. 280°C. IR: cm^{-1} (KBr): 2220 (CN), 1680 (CO) and 1670 (ring carbonyl). ^1H NMR (DMSO-d_6): δ 3.30 (s, 3 H, OCH_3); 7.20–7.80 (m, 15 H, aromatic H and ring CH); 8.10 (s, 1 H, NH). ms: m/z = 473 (M^+). (Found, C: 71.1; H, 4.3; N, 14.7. Calcd. from $C_{28}H_{19}N_5O_3$: C, 71.03; H. 4.01, N. 14.79%).

Compound **11b** formed, as brown crystals from ethanol (1.7 g, 37%), m.p. 190°C. (Found: C, 67.2; H, 3.5; N, 15.1. Calcd. for $C_{26}H_{17}N_5O_4$: C, 67.3; H, 3.6; N, 15.1%).

Compound **11c** formed, as violet crystals from DMF (1.7 g, 50%), m.p. 230°C. (Found: C, 67.0; H, 4.2; N, 13.2. Calcd. for $C_{29}H_{21}N_5O_5$: C, 67.05; H, 4.04; N, 13.48%).

Compound **11d** formed, as brown crystals from ethanol (2.3 g, %), m.p. 210°C. (Found: C, 67.2; H, 3.5; N, 15.0. Calcd. for $C_{26}H_{17}N_5O_4$: C, 67.38; H, 3.67; N, 15.11%).

Compound **11e** formed, as violet crystals from DMF (2.3 g, 68%), m.p. 300°C. (Found: C, 63.9; H, 3.0; N, 13.7. Calcd. for $C_{27}H_{16}N_5O_6$: C, 64.03; H, 3.16; N, 13.83%).

Compound **11f** formed, as violet crystals from DMF (3.3 g, 65%), m.p. 205°C. (Found: C, 67.3; H, 3.3; N, 13.4. Calcd. for $C_{29}H_{19}N_5O_5$: C, 67.44; H, 3.48; N, 13.56%).

Compound **11g** formed, as brown crystals from ethanol (4.0 g, 78%), m.p. 225°C. (Found: C, 63.7; H, 3.0; N, 13.6. Calcd. for $C_{27}H_{16}N_5O_6$: C, 64.03; H, 3.16; N, 13.83%).

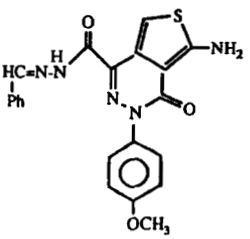
Reaction of 12 with 3

A suspension of **3** (3.0 g, 0.01 mol) in dioxane 20 ml and a catalytic amount of piperidine was treated with **12** (2.0 g, 0.01 mol). The reaction mixture was refluxed for 1 h and then left to cool. The resulting solution was poured into water and the solid product so formed was collected by filtration and crystallized from ethanols as yellow crystals of compound **14** (1.7 g, 37.0%), m.p. 250°C. IR: cm^{-1} (KBr): 2222 (CN), 1690–1675 (C=O). ^1H NMR (DMSO-d_6): δ 2.10

(s, 3 H, CH_3); 2.31 (s, 3 H, CH_3); 3.40 (s, 3 H, OCH_3); 6.71 (s, 1 H, pyrazole proton); 7.06–7.52 (m, 9 H, aromatic protons). ms: m/z = 465 (M^+). (Found, C: 64.2; H, 3.9; N, 21.07%). Calcd. for $C_{25}H_{19}N_7O_3$: C, 64.51; H, 4.08; N, 21.07%).

N-Benzylidene-5-amino-3,4-dihydro-3-(*p*-anisyl)thieno[3,4-d]-pyridazine-1-hydrazide (15).

A suspension of **6** (2.8 g, 0.01 mol) in dioxane (20 ml) and a catalytic amount of piperidine was treated with sulphur (0.32, 0.01 mol). The reaction mixture was refluxed for 2 h and then left to cool at room temperature and then was poured into water. The solid product so formed was collected by filtration and crystallized from dioxane as brown crystals (2.7 g, 85%), m.p. 220°C. IR: cm^{-1} (KBr): 3400–3380 (NH_2), 3280 (NH), 1690-1670 (C=O). ^1H NMR (DMSO-d_6): δ 3.20 (s, 3 H, OCH_3); 3.40 (s, 2 H, NH_2); 7.2–7.8 (m, 10 H, aromatic H and ring CH); 8.0 (s, 1 H, CH); 13.4 (s, 1 H, NH). ms: m/z = 419 (M^+). (Found, C: 59.9; H, 3.8; N, 16.6; S, 7.3. Calcd. for $C_{21}H_{17}N_5O_3S$: C, 60.14; H, 4.05; N, 16.70; S, 7.63%).



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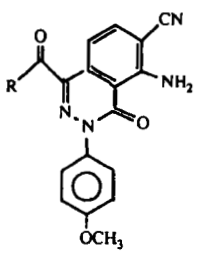

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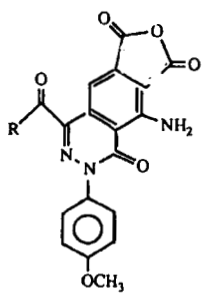
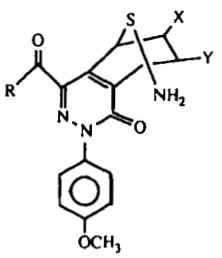


17



18

R=-NHN=CH-Ph

N-Benzylidene-5-amino-6-cyano-3,4-dihydro-3-(*p*-anisyl)-4-oxo-phthalazin-1-carboxylic acid hydrazide (16)

A suspension of **15** (4.07 g, 0.01 mol) in dioxane (20 ml) and acetic acid (2 ml) was treated with acrylonitrile (0.53 g, 0.01 mol). The reaction mixture was refluxed for 3 h after cooling to room temperature, the mixture was poured into water. The solid product so formed was collected by filtration and crystallized from dioxane as brown crystals (1.50 g, 34.3%), m.p. 250°C. IR: 3450-3360 (NH_2); 3250 (NH); 2200 (CN); 1680 (C=O). ^{1}H NMR (DMSO-d_6): 3.20 (s, 3 H, OCH_3); 3.30 (s, 2 H, NH_2); 7.2–7.8 (s, 11 H, aromatic H and ring CH); 8.50 (s, 1 H, CH); 13.3 (s, 1 H, NH). ms: m/z = 438 (M^+). (Found, C: 65.5; H, 3.8; N, 19.2. Calcd. from $C_{24}H_{18}N_6O_3$: C, 65.75; H, 4.10; N, 19.17%).

N-Benzylidene-5-amino-3,4-dihydro-3-(*p*-anisyl)-4,5,7-trioxofuro-[3,4-g]phthalazin-1-carboxylic acid hydrazide (17)

Compound **15** (4.07 g, 0.01 mol) was fused with maleic anhydride (0.98 g, 0.01 mol) for 1 h. The solid product so formed after dilution with ethanol/water was collected by filtration and crystallized from dioxane as brown crystals (1.80 g, 38.2%), m.p. > 300°C. IR: cm^{-1} (KBr): 3480–3350 (NH_2); 3250 (NH); 1680–1660 (C=O). ^{1}H NMR (DMSO-d_6): δ 3.20 (s, 3 H, CH_3); 6.20 (s, 2 H, NH_2); 7.00–7.90 (m, 11 H, aromatic H); 10.20 (s, 1 H, NH). ms: m/z = 483 (M^+). (Found, C: 62.0; H, 3.4; N, 14.3 for $C_{25}H_{17}N_5O_6$: C, 62.11; H, 3.51; N, 14.49%).

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