2-(3-Arylhydrazono-3-formyl-2-oxopropyl)-1*H*-isoindole-1,3(2*H*)-dione in heterocyclic synthesis. Novel derivatives of pyridazin-6(1*H*)-one, pyridazin-6(1*H*)-imine, and pyrazolo[5,1-c][1,2,4]triazine incorporating an *N*-(2-oxoethyl)phthalimide moiety

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A novel series of 2-(3-arylhydrazono-3-formyl-2-oxopropyl)-1*H*-isoindole-1,3-(2*H*)-diones has been prepared and their utility as building blocks in the synthesis of novel derivatives of pyridazin-6(1*H*)-ones, pyridazin-6(1*H*)-imines, and pyrazolo[5,1-c][1,2,4]triazines incorporating a *N*-(2-oxoethyl)phthalimide moiety is investigated.

Keywords: hydrazones, pyridazinones, pyridazinimines, fused pyrazoles, fused 1,2,4-triazines, *N*-acetonylphthalimide

Pyridazinones form a very interesting class of heteroaromatic compounds on account of their significant biological and pharmaceutical properties.[1-3] *N*-Alkylphthalimide derivatives also exhibit a broad spectrum of biological activities.[4-7] Several publications have pointed out that these derivatives also have value as intermediates in synthetic and polymer chemistry.[8,9] We have developed several novel and efficient synthesis of pyridazine derivatives from the readily obtainable 2-arylhydrazononitriles,[10] 2-arylhydrazonoaldehydes,[11,12] and 2-arylhydrazonoketones.[13-15] In continuation of our recent interest in the synthesis of polyfunctionally substituted heteroaromatic compounds incorporating the *N*-alkylphthalimide moiety as potential pharmaceuticals,[16,17] it was thought worthwhile to construct a novel series of pyridazin-6-ones, pyridazin-6-imines, and pyrazolo[5,1-*c*][1,2,4]triazine derivatives incorporating the *N*-(2-oxoethyl) phthalimide moiety, in the hope of obtaining compounds that may have some pharmaceutical application. We now report a new series of 2-(3-arylhydrazono-3-formyl-2-oxopropyl)-1*H*-isoindole-1,3(2*H*)-diones as building blocks in the synthesis of the required compounds.

Results and discussion

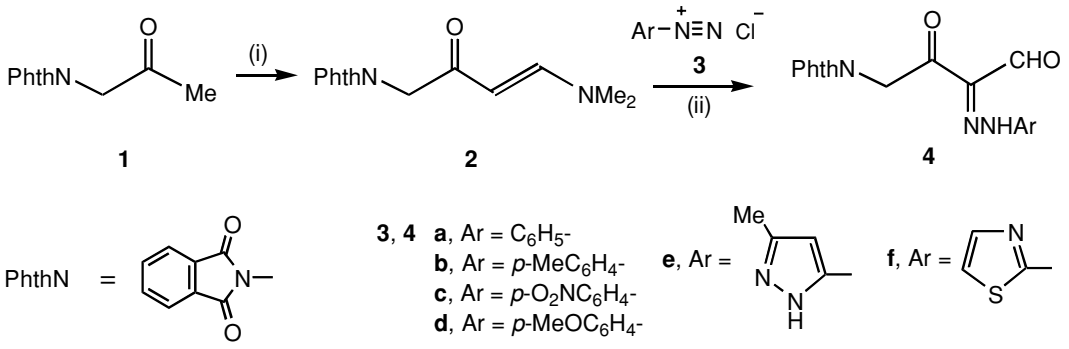
Treatment of phthalimidoacetone (**1**) with dimethylformamide dimethylacetal (DMFDMA) in xylene at reflux temperature afforded the enaminone **2**.[17] The latter compound readily undergoes coupling with aromatic and heterocyclic diazonium salts **3a–f** in the presence of sodium hydroxide to yield the 2-(3-arylhydrazono-3-formyl-2-oxopropyl)-1*H*-isoindole-1,3(2*H*)-diones **4a–f** in good yields (Scheme 1).

The reactivity of compounds **4** towards active methylene carbonitriles was investigated. Compounds **4a–c** readily condensed with malononitrile in the presence of a catalytic amount of piperidine gave the corresponding pyridazin-6(1*H*)-imines **5a–c**. The structure of **5a–c** were established on the basis of their elemental analysis and spectral data. Their IR spectra showed a strong absorption band at ν_{max} *ca* 2195 cm^{-1} corresponding to the nitrile functional group. The ^1H NMR spectra also indicated the disappearance of both hydrazone NH and aldehydic protons (Scheme 2).

Arylhydrazone derivative **4c** also condensed with ethyl (1*H*-benzotriazol-1-yl)acetate in anhydrous pyridine at reflux temperature to afford the pyridazin-6(1*H*)-one derivative **6a**, while the condensation of **4c** with (1*H*-benzotriazol-1-yl) acetonitrile in a mixture of dioxan and dimethylformamide at reflux afforded the pyridazin-6(1*H*)-imine derivative **6b**. The spectral data of compounds **6a,b** were in complete agreement with proposed structures.

On the other hand, condensation of hydrazones **4b,c** with diethyl malonate **7a** and ethyl cyanoacetate **7b** in ethanol and the presence of a catalytic amount of piperidine afforded the pyridazin-6(1*H*)-one and pyridazin-6(1*H*)-imine derivatives **8a–c** in good yield. The structures of the isolated products **8a–c** were confirmed on the basis of their elemental analysis and spectral data. The ^1H NMR spectra in each case revealed a triplet and quartet at δ_H 1.20 and 4.29 ppm characteristic of the methyl and OCH_2 protons of the ester function.

Treatment of **4a–c** with hippuric acid in refluxing acetic anhydride afforded yellow crystalline products identified as the 2-[2'-(1-aryl-5-benzamido-1,6-dihydro-6-oxopyridazin-3-yl)-2'-oxoethyl]-1*H* isoindole-1,3(2*H*)-dione **9a–c** on the basis of the spectral data (Scheme 2). The mass spectrum of **9c** revealed a molecular ion peak at *m/z* 523 [M^+]. The ^1H NMR spectrum showed, in addition to aromatic signals, singlet signals for methylene, pyridazine H-4 and NH at δ_H 5.19, 8.61



Scheme 1 Reagents: (i) DMFDMA / xylene; (ii) EtOH / NaOH

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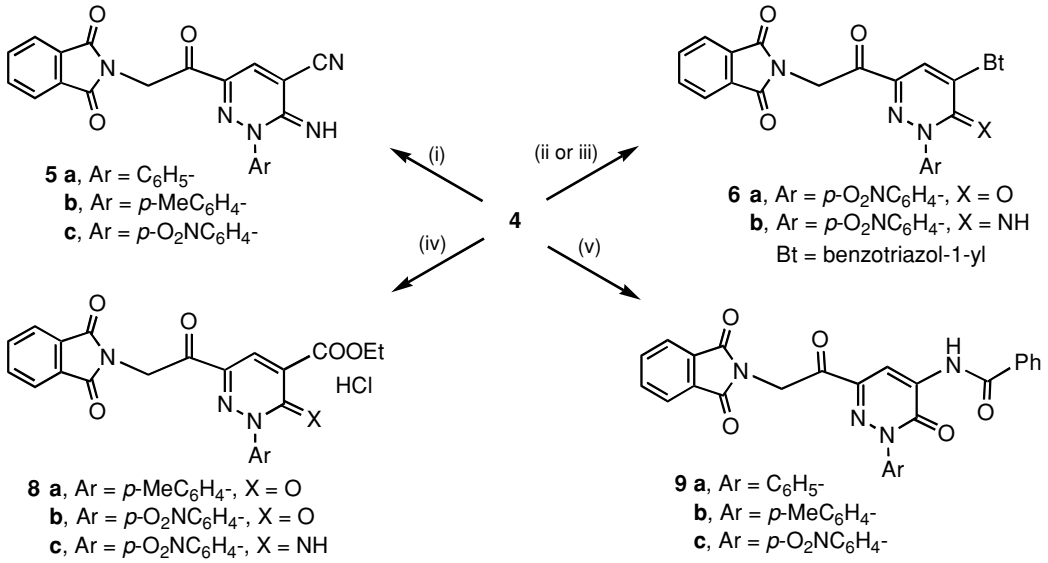


Scheme 2 Reagents: (i) $CH_2(CN)_2$, EtOH/piperidine; (ii) $BtCH_2COOEt$/pyridine, reflux; (iii) $BtCH_2CN$/dioxan/DMF, NaH, reflux; (iv) XCH_2COOEt (7a, X = COOEt, 7b, X = CN)/EtOH/piperidine; (v) $PhCONHCH_2COOH$/AcOH. reflux

and 10.10 ppm, respectively. The last signal underwent ready H/D exchange upon addition of deuterium oxide.

It was found that the arylhydrazone **4e** cyclised easily in boiling ethanol in the presence of catalytic piperidine to give the pyrazolo[5,1-*c*][1,2,4]triazine hydrochloride derivative **10** (Scheme 3). The mass spectrum revealed a molecular ion peak with *m/z* 321 [M^+ -HCl]. The ^{1}H NMR spectrum of compound **10** was free from the aldehydic and hydrazone NH protons of **4e**. Treatment of compound **4e** with malononitrile in refluxing ethanol and the presence of a catalytic amount of piperidine gave the 2-butenamide derivative **11**. The IR spectrum of **11** shows NH_2 and nitrile absorption bands in region of 3330, 3224 and 2190 cm^{-1} respectively in addition to three characteristic bands for the carbonyl groups at ν_{max} 1774, 1714 and 1630 cm^{-1}. Condensation of **10** with malononitrile also afforded **11**; (the product was identical in all respects (m.p., spectra) with that obtained previously from the reaction of **4e** with malononitrile (Scheme 3).

Experimental

The IR spectra (KBr) were recorded on a Shimadzu 2000 FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer with DMSO-d_6 or $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal standard; chemical shifts are reported as δ units (ppm). Mass spectra were measured on a GS/MS INCOL XL Finningan MAT instrument. Microanalyses were performed on a Leco CHNS 932 analyser. Compound **2** was prepared according to a recent report.[17]

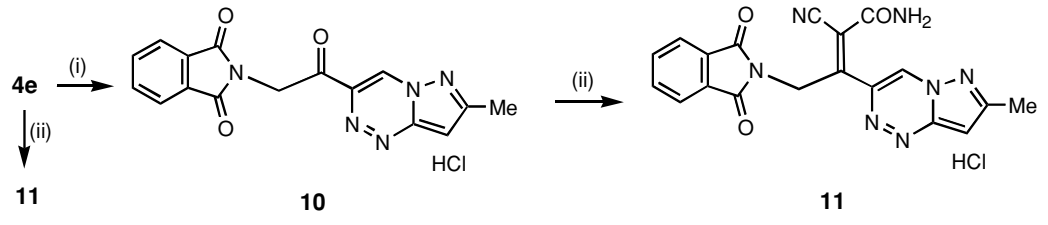
General procedure for the preparation of arylhydrazones **4a–f**
A cold solution of aryldiazonium salt **3a–f** (10 mmol) was prepared by adding a solution of sodium nitrile (0.65 g into 10 ml H_2O) to a cold solution of arylamine hydrochloride or heterocyclic hydrochloride amine (10 mmol of arylamine in 3 ml HCl) with stirring as described earlier.[13] The resulting solution of the aryldiazonium salt was then added to cold solution of the enaminone **2** (2.58 g, 10 mmol) in EtOH (30 ml) containing sodium hydroxide (0.60 g). The reaction mixture was stirred at room temperature for 1 h. The solid products so formed were collected by filtration and recrystallised from ethanol.

2-[3-Formyl-2-oxo-3-(phenylhydrazono)propyl]-1H-isoindole-1,3(2H)-dione (**4a**): Yellow crystals, yield 2.44 g (73%), m.p. 101–102 °C. IR: ν_{max}: 3448 (NH), 1773 and 1719 (phthalimide CO), 1686 (keto CO), 1638 cm^{-1} (ald. CO). ^{1}H NMR (DMSO-d_6): δ 5.06 (s, 2*H*, CH_2), 7.30–7.97 (m, 9H, Ar–H), 9.85 (s, 1*H*, CHO), 14.22 (bs, 1*H*, NH). MS (EI): *m/z* 335 [M^+]. Found: C, 64.22; H, 4.06; N, 12.54. $C_{18}H_{13}N_3O_4$ (335.31) requires C, 64.47; H, 3.91; N, 12.53 %.

2-[3-Formyl-3-(p-methylphenylhydrazono)-2-oxopropyl]-1H-isoindole-1,3(2H)-dione (**4b**): Brown crystals, yield 2.89 g (83%), m.p. 160–162 °C. IR: ν_{max}: 3335 (NH), 1773 and 1718 (phthalimide CO), 1676 (keto CO), 1649 (ald. CO). ^{1}H NMR (DMSO-d_6): δ 2.45 (s, 3H, Me), 5.05 (s, 2*H*, CH_2), 7.16–8.50 (m, 8H, Ar–H), 9.83 (s, 1*H*, CHO), 14.30 (bs, 1*H*, NH, D_2O exchangeable). Found: C, 65.23; H, 4.17; N, 11.92. $C_{19}H_{15}N_3O_4$ (349.33) requires C, 65.32; H, 4.33; N, 12.03 %.

2-[3-Formyl-3-(p-nitrophenylhydrazono)-2-oxopropyl]-1H-isoindole-1,3(2H)-dione (**4c**): Brown crystals, yield 3.26 g (86%), m.p. 122–123 °C. IR: ν_{max} 3433 (NH), 1777 and 1717 (phthalimide CO), 1661 (keto CO) and 1638 (ald. CO). ^{1}H NMR (DMSO-d_6): δ 5.10 (s, 2*H*, CH_2), 7.47–8.30 (m, 8H, Ar–H), 10.40 (s, 1*H*, CHO), 14.00 (bs, 1*H*, NH, D_2O exchangeable). MS (EI): *m/z* 380 [M^+]. Found: C, 57.02; H, 3.38; N, 14.73. $C_{18}H_{12}N_4O_6$ (380.31) requires C, 56.84; H, 3.18; N, 14.74 %.

2-[3-Formyl-3-(p-methoxyphenylhydrazono)-2-oxopropyl]-1H-isoindole-1,3(2H)-dione (**4d**): Brown crystals, yield 2.99 g (82%), m.p. 126–128 °C. IR: ν_{max} 3445 (NH), 1773 and 1716 (phthalimide CO), 1674 (keto CO), 1653 (ald. CO). ^{1}H NMR (DMSO-d_6): δ 3.82 (s, 3H, OMe), 5.12 (s, 2*H*, CH_2), 6.91–7.99 (m, 8H, Ar–H), 9.97 (s, 1*H*, CHO), 14.35 (bs, 1*H*, NH). ^{13}C NMR (DMSO-d_6): δ_C 193.2 (C-2), 190.0 (C-4), 168.2 (phthalimide CO), 159.3 (*ipso*-NO_2), 155.8(C-3), 142.6 (*ipso*-NH), 135.7, 132.7, 124.4 (phthalimide carbons), 130.1 (C-2',6'), 115.8 (C-3',5'), 65.1 (OMe) and 45.6 (CH_2). Found: C, 62.38; H, 4.04; N, 11.55. $C_{19}H_{15}N_3O_5$ (365.33) required C, 62.46; H, 4.14; N, 11.50 %.



Scheme 3 Reagents: (i) EtOH/piperidine, reflux; (ii) $CH_2(CN)_2$/EtOH/piperidine

2-[3-Formyl-3-(3'-methylpyrazol-5'-ylhydrazono)-2-oxopropyl]-1H-isoindole-1,3(2H)-dione (**4e**): Yellow crystals, yield 2.67 g (79%), m.p. 182–184 °C. IR: ν_{max} 3381 (2NH); 1774 and 1714 (phthalimide CO), 1688 (keto CO), 1611 (ald CO). ^{1}H NMR (DMSO-d_6): δ 2.20 (s, 3H, Me), 5.32 (s, 2*H*, CH_2); 5.81 (s, 1*H*, pyrazole 4'-H), 7.23–8.02 (m, 5H, ArH and NH), 9.64 (s, 1*H*, CHO), 13.59 (bs, 1*H*, NH). Found: C, 56.69; H, 4.09; N, 20.73. $C_{16}H_{13}N_5O_4$ (339.30) requires C, 56.63; H, 3.86; N, 20.64 %.

2-[3-Formyl-2-oxo-3-(2'-thiazolylhydrazono)propyl]-1H-isoindole-1,3(2H)-dione (**4f**): Brown crystals, yield: 2.49 g (73%), m.p. 205–207 °C. IR: ν_{max} 3320 (NH), 1772 and 1716 (phthalimide CO); 1685 (keto CO), 1635 (ald. CO). ^{1}H NMR (DMSO-d_6): δ 4.87 (s, 2*H*, CH_2), 6.55 (d, 1*H*, *J* = 2.9 Hz, thiazolyl 5'-H), 6.99 (d, 1*H*, *J* = 2.9 Hz, H-4', thiazolyl-H), 7.09–7.90 (m, 4H, Ar–H), 9.53 (s, 1*H*, CHO) and 13.31 ppm (bs, 1*H*, NH, D_2O-exchangeable). ^{13}C NMR (DMSO-d_6): δ 194.8 (C-2), 190.9 (C-4); 172.7 (thiazolyl C-2'); 168.1 (phthalimide CO), 154.7 (C-3), 140.5 (thiazolyl C-4'), 135.8, 133.9, 124.2 (phthalimide carbons), 110.9 (thiazolyl C-5') and 47.9 (CH_2). Found: 52.46; H, 3.09; N, 16.13. $C_{15}H_{10}N_4O_4S$ (342.26) requires C, 52.64; H, 2.95; N, 16.37 %.

General procedure for the preparation of iminopyridazinecarbonitriles **5a–c**

To a suspension of **4a–c** (10 mmol) in ethanol malononitrile (0.66 g, 10 mmol) and a few drops of piperidine were added. The mixture was refluxed for 15 minutes, left to cool to room temperature, then poured into ice-cold water and neutralised with 10% hydrochloric acid. The solid products so formed were collected by filtration and recrystallised from ethanol.

2-[2'-(5-Cyano-1,6-dihydro-6-imino-1-phenylpyridazin-3-yl)-2'-oxoethyl]-1H-isoindole-1,3(2H)-dione (**5a**): Brown crystals, yield 2.48 g (65%), m.p 189–190 °C. IR: ν_{max} 3438 (NH), 2187 (CN), 1776 and 1720 (phthalimide CO), 1691 (keto CO). ^{1}H NMR (DMSO-d_6); δ 5.00 (s, 2*H*, CH_2), 6.89–8.10 (m, 10H, Ar–H and H-4 pyridazine-H) and 8.28 (bs, 1*H*, NH, D_2O-exchangeable). ^{13}C NMR (DMSO-d_6); δ 191.4 (keto CO), 168.0 (phthalimide CO), 167.7 (C-3), 153.1 (C-6), 140.5, 135.8, 132.4, 131.9, 130.3, 127.1, 126.5, 124.3, 120.6 (aromatic carbons), 115.2 (CN), 45.4 (CH_2). MS (EI): *m/z* 383 [M^+]. Found: C, 65.82, H, 3.18; N, 18.31. $C_{21}H_{13}N_5O_3$ (383.35) requires C, 65.79; H, 3.42, N, 18.27 %.

2-[2'-(5-Cyano-1,6-dihydro-6-imino-1-(p-methylphenyl)-pyridazin-3-yl)-2'-oxoethyl]-1H-isoindole-1,3(2H)-dione hydrochloride (**5b**): Brown crystals, yield 2.90 g (67%), m.p. 135–137 °C. IR: ν_{max} 3440 (NH), 2197 (CN), 1775 and 1720 (phthalimide CO) and 1680 (keto CO); ^{1}H NMR (DMSO-d_6): δ 2.25 (s, 3H, Me), 4.98 (s, 2*H*, CH_2), 7.01–8.01 (m, 9H, Ar–H and H-4 pyridazine-H), 11.10 (bs, 1*H*, NH). Found: C, 61.01; H, 3.92; N, 16.36. $C_{22}H_{16}ClN_5O_3$ (433.84) requires C, 60.91; H, 3.72; N, 16.14 %.

2-[2'-(5-Cyano-1,6-dihydro-6-imino-1-(p-nitrophenyl)-pyridazin-3-yl]-2'-oxoethyl]-1H-isoindole-1,3(2H)-dione (**5c**): Brown crystals, yield 2.27 g (71%), m.p 162–164 °C. IR: ν_{max} 3355 (NH), 2190 (CN), 1774 and 1716 (phthalimide CO), 1680 (keto CO). ^{1}H NMR (DMSO-d_6): δ 5.19 (s, 2*H*, CH_2), 7.48–8.27 (m, 9H, Ar–H and H-4 pyridazine-H) and 11.69 (bs, 1*H*, NH, D_2O-exchangeable). ^{13}C NMR (DMSO-d_6): δ 191.5 (keto CO), 168.4 (phthalimide CO), 166.9 (C-3), 148.9, 143.0, 136.3, 132.9, 130.2, 129.0, 127.9, 126.9, 125.2 (aromatic carbons), 116.3 (CN), 109.2 (C-5), 45.9 (CH_2). Found: C, 58.99; H, 2.85; N, 19.41. $C_{21}H_{12}N_6O_5$ (428.34): C, 58.88; H, 2.82, N, 19.61 %.

2-[2'-(5-(Benzotriazol-1-yl)-1,6-dihydro-1-(p-nitrophenyl)-6-oxopyridazin-3-yl)-2-oxoethyl]-1H-isoindole-1,3(2H)-dione (**6a**): A suspension of **4c** (3.80 g, 10 mmol) in anhydrous pyridine (20 ml) was treated with ethyl benzotriazol-1-ylacetate (2.03 g, 10 mmol). The reaction mixture was refluxed for 8 h, then poured onto ice-cold water and neutralised with hydrochloric acid (10%). The solid product so formed was collected by filtration and recrystallised from EtOH/DMF (2 : 1) as brown crystals, yield 3.90 g (75%), m.p. 173–175 °C. IR: ν_{max} 1718 and 1772 (phthalimide CO), 1684 (keto CO), 1635 cm^{-1} (ring CO). ^{1}H NMR (DMSO-d_6): δ 5.01 (s, 2*H*, CH_2), 7.41–8.44 (m, 12*H*, Ar–H), 8.54 ppm (s, 1*H*, H-4 pyridazine-H). ^{13}C NMR (DMSO-d_6): δ 191.30 (keto CO), 168.7 (phthalimde CO), 163.4 (ring CO), 147.6 (*ipso*-NO_2), 145.3, 135.8, 133.8, 132.2, 132.4, 131.5, 130.1, 127.4, 125.4, 125.8, 124.3, 124.1, 120.0, 118.4, 113.4 (aromatic carbons), 44.5 (CH_2). Found: C, 59.76; H, 3.08; N, 18.70. $C_{26}H_{15}N_7O_6$ (521.43) requires C, 59.89; H, 2.89; N, 18.80 %.

2-[2'-(5-(Benzotriazol-1-yl)-1,6-dihydro-6-imino-1-(p-nitrophenyl)-pyridazin-3-yl)-2-oxoethyl]-1H-isoindole-1,3(2H)-dione hydrochloride (**6b**): A suspension of **4c** (3.80 g, 10 mmol) in a mixture of dioxan (20 ml) and DMF (20 ml) was treated with benzotriazol-1-ylacetonitrile (1.58 g, 10 mmol) and sodium hydride (0.8 g). The reaction mixture was refluxed for 3 h, then poured onto ice-cold water and neutralised with hydrochloric acid (10%). The solid product so formed was collected by filtration and recrystallised from EtOH/DMF (2 : 1) as brown crystals, yield: 4.22 g (78%), m.p. 190–192 °C. IR: ν_{max} 3383 (NH), 1773 and 1718 (phthalimide CO), 1685 (keto CO). ^{1}H NMR (DMSO-d_6): δ 5.05 (s, 2*H*, CH_2), 7.48–8.35 (m, 12H, Ar–H), 8.47 (s, 1*H*, H-4 pyridazine-H), 9.58 (bs, 1*H*, NH, D_2O-exchangeable). Found: C, 57.41; H, 3.03; N, 17.87. $C_{26}H_{17}ClN_7O_5$ (542.83) requires C, 57.51; H, 3.15; N, 18.05 %.

General procedure for the preparation of the pyridazine esters **8a–c**

A mixture of each of **4b,c** (10 mmol) and diethyl malonate (**7a**) (10 mmol) or ethyl cyanoacetate (**7b**) (1.13 g, 10 mmol) in ethanol (20 ml) containing a few drops of piperidine was refluxed for 30 minutes, then poured onto ice-cold water and neutralised with hydrochloric acid (10%). Each of the solid products was collected by filtration and recrystallised from ethanol.

2-[2'-(5-Ethoxycarbonyl-1,6-dihydro-1-(p-methylphenyl)-6-oxopyridazin-3-yl)-2'-oxoethyl]-1H-isoindole-1,3(2H)-dione hydrochloride (**8a**): Brown crystals, yield 3.12 g (65%), m.p. 135–137 °C. IR: ν_{max} 1775 and 1721 (phthalimide and ester CO), 1685 (keto CO), 1653 (ring CO). ^{1}H NMR (DMSO-d_6): δ 1.20 (t, 3H, *J* = 7Hz, Me); 2.25 (s, 3H, Me), 4.29 (q, 2*H*, *J* = 7Hz, OCH_2), 5.17 (s, 2*H*, CH_2), 6.87–8.11 (m, 9H, Ar–H and H-4 pyridazine-H). Found: C, 60.01; H, 4.02; N, 8.94. $C_{24}H_{20}ClN_3O_6$ (481.88) requires C, 59.86; H, 4.18; N, 8.72 %.

2-[2'-(5-Ethoxycarbonyl-1,6-dihydro-1-(p-nitrophenyl)-6-oxopyridazin-3-yl)-2'-oxoethyl]-1H-isoindole-1,3(2H)-dione hydrochloride (**8b**): Brown crystals, yield 3.32 g (65%), m.p. 183–185 °C. IR: ν_{max} 1776, 1721 (phthalimide CO and ester CO), 1678 (keto CO) and 1653 (ring CO); ^{1}H NMR (DMSO-d_6): δ_H 1.20 (t, 3H, *J* = Hz, Me); 4.26 (q, 2*H*, *J* = 8Hz, OCH_2), 5.10 (s, 2*H*, CH_2), 7.25–8.25 (m, 9H, Ar–H and H-4 pyridazine-H). Found: C, 54.04; H, 3.25; N, 10.47. $C_{23}H_{17}ClN_4O_8$ (512.83) requires C, 53.86; H, 3.14; N, 10.76 %.

2-[2'-(5-Ethoxycarbonyl-1,6-dihydro-6-imino-1-(p-nitrophenyl) pyridazin-3-yl)-2'-oxoethyl]-1H-isoindole-1,3(2H)-dione hydrochloride (**8c**): Brown crystals, yield: 3.62 g (71%), m.p. 198–200 °C. IR: ν_{max} 3425 (NH), 1772 and 1718 (phthalimide CO); 1695 (ester CO), 1669 (keto CO). ^{1}H NMR (DMSO-d_6): δ 1.21 (t, 3H, *J* = 8Hz, Me); 4.15 (q, 2*H*, *J* = 8Hz, OCH_2), 5.18 (s, 2*H*, CH_2), 6.58–8.19 ppm (m, 9H, Ar–H and H-4 pyridazine-H); 8.42 (bs, 1*H*, NH); ^{13}C NMR (DMSO-d_6): δ 193.6 (keto CO); 167.9 (phthalimide CO); 167.8 (ester CO); 160.0 (C-3), 156.7 (C-6), 147.8, 142.5, 135.8, 132.3, 131.5, 129.4, 128.9, 127.5, 126.8 (aromatic carbons), 63.0 (OCH_2), 44.7 (CH_2), 14.7 (Me). Found: C, 54.05; H, 3.64, N, 13.82. $C_{23}H_{18}ClN_5O_7$ (511.87) requires C, 53.97; H, 3.54; N, 13.68 %.

General procedure for the synthesis of the benzamidopyridazinones **9a–c**

A solution of **4a–c** (10 mmol) in acetic anhydride (10 ml) was treated with hippuric acid (1.79 g, 10 mmol). The reaction mixture was refluxed for 2 h, then poured onto ice cold water. Each of the solid products so formed was recrystallised from ethanol.

2-[2'-(5-Benzamido-1,6-dihydro-1-phenyl-6-oxopyridazin-3-yl)-2'-oxoethyl]-1H-isoindole-1,3(2H)-dione (**9a**): Yellow crystals, 3.20 g (67%), m.p. 310–312 °C. IR: ν_{max} 3388 (NH) 1773 and 1712 (phthalimide CO), 1685 (keto CO), 1648 (ring CO), 1629 (amide CO). ^{1}H NMR (DMSO-d_6): δ 5.15 (s, 2*H*, CH_2), 7.54–7.98 (m, 14H, Ar–H), 8.61 (s, 1*H*, H-4, pyridazine-H), 9.95 (bs, 1*H*, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6): δ_C 191.2 (keto CO), 172.4 (amide CO), 168.6 (phthalimide CO), 167.4 (ring CO), 142.2, 135.8, 135.8, 133.9, 132.5, 130.2, 129.9, 129.5, 128.8, 127.6, 126.8, 124.4, 118.3, 109.1 (aromatic carbons), 47.1 (CH_2). Found: C, 67.98; H, 3.83; N, 11.57. $C_{27}H_{18}N_4O_5$ (478.45) requires C, 67.78; H, 3.79; N, 11.71 %.

2-[2'-(5-Benzamido-1,6-dihydro-1-(p-methylphenyl)-6-oxopyridazin-3-yl)-2'-oxoethyl]-1H-isoindole-1,3(2H)-dione hydrochloride (**9b**): Brown crystals; yield: 3.764 g (69%), m.p. 133–135 °C. IR: ν_{max} 3363 (NH), 1774 and 1721 (phthalimide CO), 1685 (keto CO), 1677 (ring CO), 1643 (amide CO). ^{1}H NMR (DMSO-d_6): δ 1.91 (s, 3H, Me); 5.15 (s, 2*H*, CH_2), 6.96–8.01 (m, 13H, Ar–H), 8.60 (s, 1*H*, H-4', pyridazine-H), 9.90 (bs, 1*H*, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6), δ 190.8 (keto CO), 173.0 (amide CO), 168.6 (phthalimide CO), 167.4 (ring CO), 160.3, 156.7, 142.38, 137.0, 135.0, 133.8, 132.1, 130.2, 129.5, 128.8, 125.2, 124.4, 116.9, 109.0 (aromatic carbons), 44.1 (CH_2), 25.1 (Me). Found: C, 63.78;

H, 4.29; N, 10.42. $C_{28}H_{21}N_4O_5Cl$ (528.93) requires C, 63.58; H, 4.00; N, 10.59 %.

2-[2'-(5-Benzoamido-1,6-dihydro-1-(p-nitrophenyl)-6-oxo-pyridazin-3-yl)-2'-oxoethyl]-1H-isoindole-1,3(2H)-dione (**9c**): Yellow crystals, yield 4.23 g (81%), m.p. 180–182 °C. IR: ν_{max} 3373 (NH), 1774 and 1716 (phthalimide CO), 1692 (keto CO), 1661 (ring CO), 1620 (amide CO). ^{1}H NMR (DMSO-d_6): δ 5.19 (s, 2*H*, CH_2), 7.56–8.47 (m, 13H, Ar–H), 8.61 (s, 1*H*, H-4', pyridazine-H), 10.10 (bs, 1*H*, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6), δ 191.6 (keto CO), 170.8 (amide CO), 168.6 (phthalimide CO); 166.9 (ring CO), 156.6, 147.9, 136.3, 135.8, 133.7, 129.8, 128.9, 127.9, 126.9, 125.2, 124.4, 119.5, 115.5, 109.2 (aromatic carbons), 44.2 (CH_2). MS(EI) *m/z* 523 [M^+]. Found: C, 61.84; H, 3.35; N, 13.33. $C_{27}H_{17}N_5O_7$ (523.44) requires C, 61.95; H, 3.27; N, 13.37 %.

2-[2'-(7-Methylpyrazolo[5,1-c][1,2,4]triazin-3-yl)-2'-oxoethyl]-1H-isoindole-1,3(2H)-dione hydrochloride (**10**): A solution of **4e** (3.39 g, 10 mmol) in ethanol (20 ml) with a few drops of piperidine was refluxed for 15 minutes. The reaction mixture was left to cool at room temperature, then poured onto ice-cold water and neutralised with hydrochloric acid (10%). The solid product so formed was collected by filtration and recrystallised from ethanol as yellow crystals, yield 82%, m.p 250–252 °C. IR: ν_{max} 1774 and 1717 (phthalimide CO); 1685 cm^{-1} (keto CO); ^{1}H NMR (DMSO-d_6): δ 2.20 (s, 3H, Me), 5.41 (s, 2*H*, CH_2), 6.30 (s, 1*H*, H-8 pyrazole-H), 7.44–7,97 (m, 5H, phthalimide-H and H-4 triazine-H). MS (EI): *m/z* 321 [M^+-HCl]. Found: C, 53.51; H, 3.63; N, 19.57. $C_{16}H_{12}ClN_5O_3$ (357.82) requires C, 53.71; H, 3.38; N, 19.57 %.

2-Cyano-3-(7'-methylpyrazolo[5,1-c][1,2,4]triazin-3'-yl)-4-(2'-phthalimido)-2-butenamide hydrochloride (**11**): A suspension of **4e** or **10** (10 mmol) in of ethanol (20 ml), in the presence of few drops of piperidine, was treated with malononitrile (0.66 g, 10 mmol). The reaction mixture was refluxed for 15 minutes then poured onto ice-cold water and neutralised with hydrochloric acid (10%). The solid product so formed was collected by filtration and recrystallised from ethanol as brown crystals, yield 3.34 g (79%), m.p. 220–222 °C. IR: ν_{max} 3566, 3451 (NH_2), 2190 (CN), 1774 and1714 (phthalimido CO); 1630 (amide CO). ^{1}H NMR (DMSO-d_6): δ 2.20 (s, 3H, Me), 5.22 (s, 2*H*, CH_2), 6.28 (s, 1*H*, H-8' pyrazole-H); 7.18–7.97 (m, 5H, phthalimide-H and H-4' triazine-H), 8.92 (bs, 2*H*, NH_2, D_2O exchangeable). ^{13}C NMR (DMSO-d_6); δ 169.7 (amide CO), 168.3 (phthalimide CO), 156.7, 141.3, 137.3, 136.5, 135.1, 132.4, 130.2, 129.38, 124.4, 116.2, 101.2 (aromatic C and CN), 44.5 (CH_2), 11.7 (Me). Found: C, 53.96; H, 3.48; N, 23.31. $C_{19}H_{14}ClN_7O_3$ (423.84) requires C, 53.84; H, 3.32; N, 23.13 %.

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