Quinolinone and pyridopyrimidinone inhibitors of DNA-dependent protein kinase†

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8-Substituted 2-morpholin-4-yl-quinolin-4-ones and 9-substituted 2-morpholin-4-yl-pyrido[1,2-*a*]pyrimidin-4-ones with selected aryl and heteroaryl groups as the substituent have been synthesised as potential inhibitors of DNA-dependent protein kinase. A multiple-parallel approach, employing Suzuki cross-coupling methodology, was utilised in the preparation of 8-substituted 2-morpholin-4-yl-quinolin-4-ones. For this purpose 8-bromo-2-morpholin-4-yl-quinolin-4-one was required as an intermediate. This compound was obtained by adapting a literature route in which thermal cyclocondensation of (2-bromoanilino)-morpholin-4-yl-5-methylene-2,2-dimethyl[1,3]dioxane-4,6-dione afforded 8-bromo-2-morpholin-4-yl-quinolin-4-one. A multiple-parallel approach, employing Suzuki cross-coupling methodology, was also utilised to prepare 9-substituted 2-morpholin-4-yl-pyrido[1,2-*a*]pyrimidin-4-ones using 9-hydroxy-2-morpholin-4-yl-pyrido[1,2-*a*]pyrimidin-4-one *O*-trifluoromethanesulfonate as an intermediate. 8-Substituted 2-morpholin-4-yl-quinolin-4-ones and 9-substituted 2-morpholin-4-yl-pyrido[1,2-*a*]pyrimidin-4-ones were both inhibitors of DNA-dependent protein kinase. When the substituent was dibenzothiophen-4-yl, dibenzofuran-4-yl or biphen-3-yl, IC_{50} values in the low nanomolar range were observed. Interestingly, the pyridopyrimidinones and quinolinones were essentially equipotent with the corresponding 8-substituted 2-morpholin-4-yl-chromen-4-ones previously reported (I. R. Hardcastle, X. Cockcroft, N. J. Curtin, M. Desage El-Murr, J. J. J. Leahy, M. Stockley, B. T. Golding, L. Rigoreau, C. Richardson, G. C. M. Smith and R. J. Griffin, *J. Med. Chem.*, 2005, **48**, 7829–7846).

Introduction

DNA-dependent protein kinase (DNA-PK), a member of the phosphatidyl inositol (PI3)-kinase related kinase (PIKK) family, is a multi-component serine/threonine protein kinase that plays a key role in the repair of mammalian DNA double-strand breaks (DSBs).[1] Selective DNA-PK inhibitors could be useful for defining the role of DNA-PK. In addition, by impeding DNA DSB repair, DNA-PK inhibitors have potential application as radio- and chemo-potentiators in the treatment of cancer. 8-Aryl-substituted 2-morpholin-4-yl-chromenones (*e.g.* **1a–1g**) have been shown to be potent and selective inhibitors of DNA-PK.[2] Structure–activity studies and homology modelling have shown the importance of the morpholinyl oxygen atom and chromenone carbonyl oxygen as hydrogen bond donors to specific groups in the protein target.[2,3] To probe whether alterations to the core heterocycle at positions other than the carbonyl group would be tolerated we have synthesised 8-substituted 2-morpholin-4-yl-quinolin-4-ones **2a–2g** and 9-substituted 2-morpholin-4-yl-pyrido[1,2-*a*]pyrimidin-4-ones **3a–3f**. The 8-substituent in **2a–2g** and the 9-substituent in **3a–3f** are selected aryl and heteroaryl groups, some of which are known to confer high potency in 8-substituted 2-morpholin-4-yl-chromenones. We show that the 8-substituted 2-morpholin-4-yl-quinolin-4-ones **2a–2g** and 9-substituted 2-morpholin-4-yl-pyrido[1,2-*a*]pyrimidin-4-ones **3a–3f** are equipotent with the corresponding 8-aryl 2-morpholin-4-yl-chromen-4-ones (**1a–1g**).[2]

Results and discussion

Synthesis of 8-substituted 2-morpholin-4-yl-quinolin-4-ones

Previous investigators[4,5] have demonstrated the synthesis of 2,6-disubstituted quinolin-4-ones from 5-(bis-methylsulfanyl-methylene)-2,2-dimethyl[1,3]dioxane-4,6-dione **4**, which is easily prepared from Meldrum's acid (2,2-dimethyl[1,3]dioxane-4,6-dione).[6] Sequential displacement of the methylsulfanyl groups of **4** with amines, one of which was *p*-bromoaniline, to give *e.g.* **5**, followed by heating of this intermediate in diphenyl ether or polyphosphoric acid gave 2,6-disubstituted quinolin-4-ones, *e.g.* **6**. The mechanism of the cyclisation step in this remarkable sequence was proposed to involve an imidoylketene.[7] To access 8-substituted 2-morpholin-4-yl-quinolin-4-ones **2a–2g** we envisaged using 8-bromo-2-morpholin-4-yl-quinolin-4-one **7** as an intermediate for

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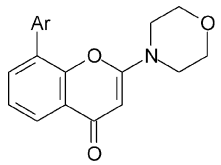
† Electronic supplementary information (ESI) available: Experimental procedures for compounds **2b–2g** and **3b–3f** and crystal structures of compounds **10a** and **16**. See DOI: 10.1039/b705095j



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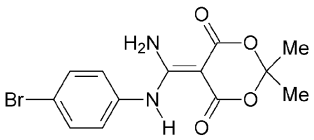

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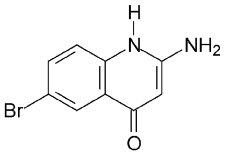

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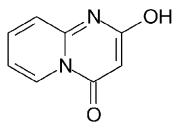

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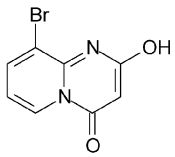

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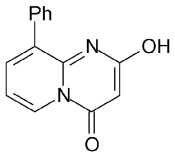

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Suzuki couplings, with **7** being derived from **4** in an analogous manner to that described[3,4] for 2,6-disubstituted quinolin-4-ones.

We have found an improved methodology leading to substituted quinolin-4-ones from **4** and have uncovered some further mechanistic features. Reaction of **4** with 2-bromoaniline proceeded smoothly in 2,2,2-trifluoroethanol (TFE) solvent at reflux giving 5-[2-bromoanilino-(methylthio)-methylene]-2,2-dimethyl-4,6-dione **8** in 88% yield. This step was accomplished even more efficiently by prior oxidation of **4** with 3-chloroperbenzoic acid (*m*CPBA), which enabled reaction with 2-bromoaniline in TFE to occur at room temperature. Reaction of **8** with 2 mole equiv. of morpholine in TFE at reflux gave (2-bromoanilino)-morpholin-4-yl-5-methylene-2,2-dimethyl[1,3]dioxane-4,6-dione **9** (64%). In an analogous manner to that described for *e.g.* **5**,[3,4,8] heating **9** at reflux in diphenyl ether gave 8-bromo-2-morpholin-4-yl-quinolin-4-one **7** (84%). A one-pot conversion of **8** into **7** was achieved by initial heating of **8** with 2 mole equivalents of morpholine in diphenyl ether at 90 °C for 18 hours, followed by raising the temperature to 260 °C for 3 hours.[8] In an attempt to conduct this sequence at lower temperature we found that heating **8** with 2 mole equiv. of morpholine at 90 °C for 18 hours and then at 200 °C for 1 hour led to a different product, which was identified as 3-(2-bromoanilino)-3-morpholin-4-yl-propionamide morpholinamide **10a** by crystal structure analysis‡ (Fig. 1, Supplementary Information†). Heating **10a** in diphenyl ether at 250 °C gave **7** (47%).

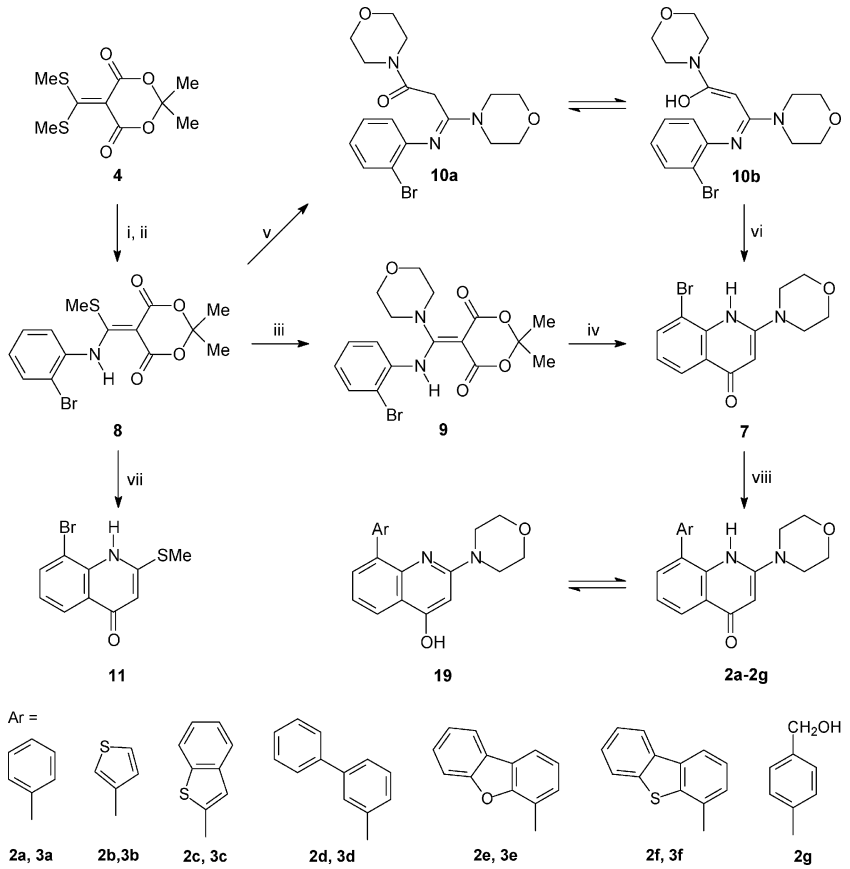
These experiments show that whilst **7** can undoubtedly be derived directly from **9** without addition of further morpholine,[3,4,8] there is an alternative pathway to **7** *via* **10a**. The latter may proceed *via* an electrocyclic process, involving the tautomer **10b**, which leads to an intermediate that expels morpholine. The fact that **7** can also arise by thermolysis of **10a**/**10b** raises the question as to whether the precursor of **7** in the one-pot reaction described using 2 mole equivalents of morpholine is **9** or **10a**/**10b**. Actually, heating **8** with 1 mole equivalent of morpholine in diphenyl ether at 100 °C gave **9**, from which **7** was derived by raising the temperature to 250 °C. However, under these conditions a by-product was **11**. Monitoring a one-pot reaction by HPLC showed that **8** with 2 mole equivalents of morpholine at 100 °C gave exclusively **9** after 1 hour. Heating the mixture at 150 °C for 16 hours afforded **10a**. When the temperature was raised from 100 °C to 200 °C **10a** was obtained within 30 minutes. Finally heating at 250 °C for 3 hours gave **7**. The experiments performed (summarised in Scheme 1) show that efficient formation of **7** from **8** in a one-pot system occurs better with 2 mole equiv. rather than 1 mole equiv. of morpholine and that although **9** is an intermediate, the immediate precursor of **7** is **10a**/**10b**.

Suzuki reactions were performed on compound **7** leading to 8-substituted 2-morpholin-4-yl-quinolin-4-ones **2a–2g**. The couplings were optimised using a 24-reaction GreenHouse™, which led to the selection of potassium carbonate as base with tetrakis(triphenylphosphine)palladium(0) as catalyst in dioxane solvent.

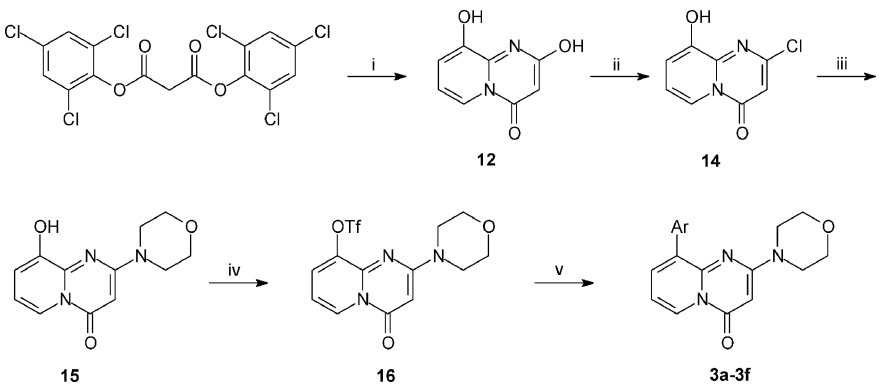
Synthesis of 9-substituted 2-morpholin-4-yl-pyrido[1,2-*a*]pyrimidin-4-ones

A key intermediate for the synthesis of 9-substituted 2-morpholin-4-yl-pyrido[1,2-*a*]pyrimidin-4-ones **3a–3f** was 2,9-dihydroxypyrido[1,2-*a*]pyrimidin-4-one **12**, which was prepared by heating 2-amino-3-hydroxypyridine with either diethyl malonate or di-(2,4,6-trichlorophenyl) malonate (Scheme 2).[9,10] This method followed closely the published syntheses of **12**, the parent 2-hydroxypyrido[1,2-*a*]pyrimidin-4-one **13** and related compounds.[9,11,12] The 2-hydroxyl group of **12** was selectively chlorinated by reaction with an excess of phosphorus oxychloride to afford 2-chloro-9-hydroxypyrido[1,2-*a*]pyrimidin-4-one **14**. Displacement of the chloro function of **14** with morpholine gave 9-hydroxy-2-morpholin-4-yl-pyrido[1,2-*a*]pyrimidin-4-one **15**, quantitatively. Compound **15** has been reported in the patent literature as a precursor to inhibitors of phosphoinositol 3-kinase, but without details of its preparation.[13] Finally, **15** was converted into the corresponding 9-*O*-triflate **16** by reaction with trifluoromethanesulfonic (triflic) anhydride. The structure of **16** was unambiguously determined as 9-hydroxy-2-morpholin-4-yl-pyrido[1,2-*a*]pyrimidin-4-one *O*-trifluoromethanesulfonate by an X-ray crystal structure analysis‡ (Figs. 2 and 3, Supplementary Information†). 9-Substituted 2-morpholin-4-yl-pyrido[1,2-*a*]pyrimidin-4-ones **3a–3f** were obtained from **16** by Suzuki reactions employing the same optimised combination of base, catalyst and solvent [K_2CO_3, tetrakis(triphenylphosphine)palladium(0) and dioxane], as described above for the preparation of **2a–2g**.

‡ CCDC reference numbers 647931 and 647932. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b705095j



Scheme 1 *Reagents and conditions*: (i) *m*CPBA, DCM, rt; (ii) 2-bromoaniline, TFE, rt; (iii) morpholine (2 equiv.), TFE or Ph_2O, 90 °C; (iv) Ph_2O, 260 °C; (v) morpholine (2 equiv.), Ph_2O, 200 °C; (vi) Ph_2O, 250 °C; (vii) polyphosphoric acid, 130 °C; (viii) cat. $Pd(PPh_3)_4$, K_2CO_3, $ArB(OH)_2$, dioxane, 90 °C.



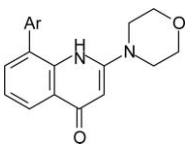
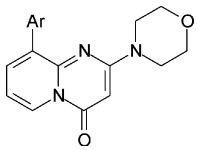
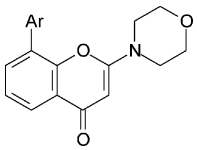
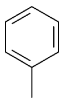
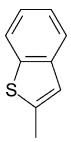
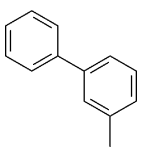
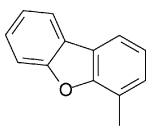
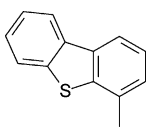
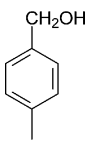
Scheme 2 *Reagents and conditions*: (i) 3-hydroxy-2-aminopyridine, PhBr, reflux; (ii) $POCl_3$, reflux; (iii) morpholine, ethanol, reflux; (iv) Tf_2O, NEt_3, DCM, −78 °C; (v) $ArB(OH)_2$, K_2CO_3, cat. $Pd(PPh_3)_4$, dioxane, 90 °C (see Scheme 1 for definition of Ar groups in **3a–3f**).

An alternative route to **3a–3f** was explored *via* 9-bromo-2-hydroxypyrido[1,2-*a*]pyrimidin-4-one **17**. 2-Amino-3-bromopyridine was prepared from 2-aminopyridine as described.[14] However, reaction of 2-amino-3-bromopyridine with diethyl malonate gave only 10% yield of **17**. In another approach 2-phenylacetonitrile was converted into 2-amino-3-phenylpyridine in the manner described.[15] Heating this compound with diethyl malonate gave only 21% 2-hydroxy-9-phenylpyrido[1,2-*a*]pyrimidin-4-one **18** and so this route was also discontinued.

Inhibition of DNA-dependent protein kinase by 8-substituted 2-morpholin-4-yl-quinolin-4-ones and 9-substituted 2-morpholin-4-yl-pyrido[1,2-*a*]pyrimidin-4-ones

Compounds **2a–2g** and **3a–3f** were evaluated as inhibitors of DNA-PK using the published assay,[16] and the results are summarised in Table 1. The DNA-PK inhibitory activities of the analogous 8-substituted chromen-4-ones are included for comparison. The results show that replacing the 1-oxygen of

Table 1 Inhibition of DNA-PK by 8-substituted 2-morpholin-4-yl-quinolin-4-ones (**2a–2g**) and 9-substituted 2-morpholin-4-yl-pyrido[1,2-*a*]pyrimidin-4-ones (**3a–3f**)

	DNA-PK inhibitory activity (IC_{50})/nM[a]					
						
Ar						
	**2a**	4900	**3a**	733	**1a**[b]	1600
	**2b**	1200	**3b**	390	**1b**	300
	**2c**	1260	**3c**	1420	**1c**	800
	**2d**	49	**3d**	89	**1d**	176
	**2e**	28	**3e**	59	**1e**	40
	**2f**	28	**3f**	13	**1f**	12
	**2g**	2430	—	—	**1g**	600

[a] DNA-PK inhibitory activity was determined as described in reference 16. The values for the 8-substituted chromenones are taken from reference 2. [b] LY294002.

8-aryl-2-morpholin-4-yl-chromenones with NH (**2a–2g**) does not significantly affect the biological activity, indicating that neither the 1-oxygen nor 1-NH make significant productive hydrogen bonding interactions with DNA-PK. This analysis assumes that the tautomer indicated for the 8-substituted 2-morpholin-4-yl-quinolin-4-ones **2a–2g** is preferred over the alternative **19**. This statement is based on analogy with quinolin-4-one[17] and similar heterocycles[18] for which the pyridone-like tautomer is preferred in polar solvents, although the population of the enol tautomer may be increased by appropriate hydrogen bonding interactions.[19] Replacing the 5-C of 8-aryl-2-morpholin-4-yl-chromenones with N (**3a–3f**) also had no significant effect on the biological activity. As with the 8-aryl-2-morpholin-4-yl-chromenones, the optimum 8- or 9-substituents were dibenzothiophen-4-yl, dibenzofuran-4-yl and biphen-3-yl, all of which gave IC_{50} values in the low nanomolar range.

Conclusions

This paper presents efficient methods for preparing a variety of 8-substituted 2-morpholin-4-yl-quinolin-4-ones and 9-substituted 2-morpholin-4-yl-pyrido[1,2-*a*]pyrimidin-4-ones using the Suzuki

reaction on the readily available precursors 8-bromo-2-morpholin-4-yl-quinolin-4-one and 9-hydroxy-2-morpholin-4-yl-pyrido[1,2-*a*]pyrimidin-4-one *O*-trifluoromethanesulfonate, respectively. Quinolin-4-ones **2a–2g** and pyrido[1,2-*a*]pyrimidin-4-ones **3a–3f** with 8-/9-substituents dibenzothiophen-4-yl, dibenzofuran-4-yl and biphen-3-yl were especially potent against DNA-dependent protein kinase. These and previous results[2,3,16,18] indicate that *three* structural motifs are principally associated with low nanomolar (IC_{50}) potency against DNA-PK: i) a bicyclic heterocyclic core containing a carbonyl group; ii) a morpholin-4-yl substituent on the core and iii) a bulky aromatic/heteroaromatic system (*e.g.* dibenzothiophen-4-yl) attached to the core. There is an optimum substitution pattern: 2-morpholinyl and 4-one in all cases; 8-aryl (or heteroaryl) for chromenones **1** and quinolinones **2** {or the corresponding 9-aryl (or heteroaryl) for pyrido[1,2-*a*]pyrimidinones **3**}. Remarkably, there is little difference in potency between the three structurally distinct heterocyclic cores described in this paper. We are continuing our studies with the aim of obtaining a clinical candidate from the structural types studied or closely related analogues or derivatives thereof.

Experimental

Materials and methods

Chemicals and solvents were obtained from reputable suppliers (for further details see ref. 20). Solvents were either dried by standard techniques or purchased as anhydrous. Triethylamine was dried by distillation from calcium hydride and stored over potassium hydroxide, under nitrogen. Chromatography, spectroscopy and combustion analyses were performed as described.[2,3,16,20] Where the inclusion of dichloromethane (DCM) was necessary to obtain a good agreement between calculated and found values for C, H and N, the requisite amount of DCM was observed in the ^{1}H NMR spectrum of the compound concerned. A GreenHouse™ 24-position reactor (Radley's, Cambridge, UK) was used for Suzuki reactions, which were all run under an argon atmosphere.

5-(Bis-methylsulfanylmethylene)-2,2-dimethyl[1,3]dioxane-4,6-dione (5)

To 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) (4.09 g, 28.4 mmol) in DMSO (14 mL) were added triethylamine (7.9 mL, 56.8 mmol) and carbon disulfide (1.7 mL, 28.4 mmol) in quick succession. The mixture was stirred vigorously at room temperature for 1 h. After cooling (ice-bath), iodomethane (3.5 mL, 56.8 mmol) was slowly added to the reaction mixture. When the addition was complete the mixture was allowed to warm up to room temperature and was stirred for a further 4 h before being diluted with ice-cold water (25 mL). Trituration of the mixture precipitated the product, which was filtered off and washed with petrol. The crude product (2.76 g, 45%) was obtained as a yellow solid that was pure enough for use in subsequent reactions: mp: 118 °C (lit.[6] 116–118 °C); IR (cm^{-1}) 3728, 1668, 1373, 1302, 1264, 1199; ^{1}H NMR, (300 MHz, $CDCl_3$) δ 1.54 (6H, s, 2 × CH_3); 2.58 (6H, s, 2 × CH_3S); ^{13}C NMR, (75 MHz, $CDCl_3$) δ 21.9; 27.2; 103.3; 160.3; 194.0.

8-Bromo-2-morpholin-4-yl-1*H*-quinolin-4-one (7)

Method A. A solution of 5-[(2-bromoanilino)morpholin-4-yl-methylene]-2,2-dimethyl[1,3]dioxane-4,6-dione (103 mg, 0.25 mmol) in diphenyl ether (0.7 mL) was stirred and heated at reflux for 3 h. After cooling, petrol was added and the precipitated product was collected by suction. The crude product was purified by medium pressure chromatography using DCM–methanol (95 : 5 v/v) as eluent. The title compound was obtained as a brown solid (65 mg, 84%).

Method B. A solution of 5-[2-bromoanilino(methylthio)-methylene]-2,2-dimethyl-4,6-dione (163 mg, 0.44 mmol) and morpholine (40 μL, 0.44 mmol) in diphenyl ether (2.5 mL) was stirred and heated at 90 °C for 18 h. The temperature was raised to 260 °C over 3 h. After cooling, petrol was added and the product was collected by suction. The crude product was purified by chromatography (see Method A) to give the title compound as a brown solid (87 mg, 65%).

Method C. A solution of 3-(2-bromophenylimino)-1,3-dimorpholin-4-yl-propan-1-one (200 mg, 0.50 mmol) in diphenyl ether (1 mL) was stirred and heated to 250 °C for 1 h. After work-up as described in Method A the title compound was obtained as a brown solid (84 mg, 54%): R_f = 0.25 (MeOH–DCM 1 : 19); mp: 96 °C; IR (cm^{-1}) 3395, 2959, 2849, 1617, 1577, 1487, 1421, 1384, 1327, 1263, 1229, 1188, 1152, 1111, 1066, 999, 902, 785; ^{1}H NMR, (300 MHz, $CDCl_3$) δ 3.72 (4H, t, J = 5.0 Hz, 2 × CH_2N-morpholine), 3.75 (4H, t, J = 5.0 Hz, 2 × CH_2O–morpholine), 5.95 (1H, s, H-3), 7.04 (1H, dd, J = 8.0 and 8.0 Hz, H-6), 7.69 (1H, dd, J = 1.3 and 8.0 Hz, H-7), 8.09 (1H, dd, J = 1.3 and 8.0 Hz, H-5); ^{13}C NMR, (75 MHz, $CDCl_3$) δ 46.4, 66.6, 92.5, 114.5, 123.0, 123.5, 124.7, 134.5, 138.0, 156.1, 172.6; MS (ES+) m/z 308.98, 310.98. HRMS calcd for $C_{13}H_{13}{}^{79}BrN_2O_2$ $[M + H]^+$ 309.0233, found 309.0233.

5-[2-Bromoanilino(methylthio)methylene]-2,2-dimethyl-4,6-dione (8)

Method A. A solution of 5-(bis-methylsulfanylmethylene)-2,2-dimethyl[1,3]dioxane-4,6-dione (900 mg, 3.6 mmol) and 2-bromoaniline (624 mg, 3.6 mmol) in 2,2,2-trifluoroethanol (3.6 mL) was stirred and heated at reflux for 18 h. After cooling, the solvent was removed to afford crude product that was recrystallised from methanol to yield the title compound (1.19 g, 88%) as white crystals.

Method B. A solution of 5-(bis-methylsulfanylmethylene)-2,2-dimethyl[1,3]dioxane-4,6-dione (100 mg, 0.40 mmol) and *m*CPBA (75% pure, 102 mg, 0.44 mmol) in DCM (2 mL) was stirred at room temperature for 1 h. The solvent was removed and the residual solid was taken up in TFE (2 mL). 2-Bromoaniline (45 μL, 0.4 mmol) was added and the mixture was stirred at room temperature for 1.5 h. The solvent was removed and the residue was taken up in DCM. The resulting solution was washed with an aqueous saturated sodium bicarbonate solution, dried ($MgSO_4$), and the DCM was removed. The crude product was purified by medium pressure chromatography using DCM as eluent. The title compound was obtained as a white solid (145 mg, 98%): R_f = 0.31 (DCM); mp: 159 °C; IR (cm^{-1}) 2990, 1706, 1653, 1535, 1370, 1199; ^{1}H NMR, (300 MHz, $CDCl_3$) δ 1.69 (6H, s, 2 × CH_3), 2.15 (3H, s,

CH_3S), 7.18 (1H, ddd, $J = 2.0$, 8.0 and 8.0 Hz, H-4′), 7.35 (2H, m, H-5′ and H-6′), 7.61 (1H, dd, $J = 2.0$ and 8.0 Hz, H-3′), 12.51 (1H, s, NH); ^{13}C NMR, (75 MHz, $CDCl_3$) δ 18.8, 26.9, 87.5, 103.3, 120.5, 127.8, 128.5, 129.9, 133.6, 136.9, 163.9, 178.7; MS (ES−) m/z 369.97, 371.98; HRMS calcd for $C_{14}H_{14}{}^{79}BrNO_4S$ $[M + H]^+$ 371.9900, found 371.9903.

5-[(2-Bromoanilino)morpholin-4-yl-methylene]-2,2-dimethyl[1,3]dioxane-4,6-dione (9)

A solution of 5-[2-bromoanilino(methylthio)methylene]-2,2-dimethyl-4,6-dione (234 mg, 0.6 mmol) and morpholine (110 μL, 1.3 mmol) in 2,2,2-trifluoroethanol (1 mL) was stirred and heated at reflux for 18 h. After cooling, the solvent and excess of morpholine were removed. The residual solid was recrystallised from methanol to yield the title compound as white crystals (158 mg, 64%): $R_f = 0.05$ (DCM); mp: 212–213 °C; IR (cm^{-1}) 1627, 1342, 1305, 1100, 1022, 934; ^{1}H NMR, (300 MHz, $CDCl_3$) δ 1.77 (6H, s, 2 × CH_3), 3.24 (4H, dd, $J = 4.5$ and 4.9 Hz, 2 × CH_2N-morpholine), 3.66 (4H, dd, $J = 4.5$ and 4.9 Hz, 2 × CH_2O-morpholine), 7.18 (2H, m, H-4′ and H-6′), 7.40 (1H, dd, $J = 8.0$ and 8.0 Hz, H-5′), 7.69 (1H, dd, $J = 1.4$ and 8.0 Hz, H-3′), 9.62 (1H, s, NH); ^{13}C NMR, (75 MHz, $CDCl_3$) δ 26.8, 51.1, 65.6, 87.5, 102.8, 120.5, 127.2, 128.9, 129.0, 134.9, 138.5, 164.9, 178.7; MS (ES−) m/z 409.01, 411.01.

3-(2-Bromophenylimino)-1,3-dimorpholin-4-yl-propan-1-one (10a)

A solution of 5-[2-bromoanilino(methylthio)methylene]-2,2-dimethyl-4,6-dione (8.86 g, 23.8 mmol) and morpholine (4.15 mL, 47.6 mmol) in diphenyl ether (40 mL) was stirred and heated at 90 °C for 18 h. The temperature was raised to 200 °C over 1 hour. After cooling, petrol was added and the precipitated solid was collected by suction. The crude product was purified by medium pressure chromatography using DCM–methanol (95 : 5, v/v) as eluent to give the title compound as white crystals (5.09 g, 54%): $R_f = 0.27$ (MeOH–DCM 1 : 19); mp: 159–160 °C; IR (cm^{-1}) 2950, 2901, 2854, 1631, 1600, 1448, 1413, 1358, 1298, 1253, 1222, 1166, 1105, 1064, 1024, 964, 950, 912; ^{1}H NMR, (300 MHz, $CDCl_3$) δ 2.98 (2H, m, CH_2-morpholine), 3.18 (2H, m, CH_2-morpholine), 3.31 (2H, m, CH_2-morpholine), 3.45 (2H, m, CH_2-morpholine), 3.53 (6H, m, 2 × CH_2-morpholine and CH_2), 3.71 (4H, m, 2 × CH_2 morpholine), 6.70 (1H, dd, $J = 7.8$ Hz and 1.5 Hz, H-6), 6.77 (1H, ddd, $J = 7.5$, 7.5 and 1.5 Hz, H-4), 7.11 (1H, ddd, $J = 7.8$, 7.5 and 1.4 Hz, H-5), 7.45 (1H, dd, $J = 7.5$ Hz and 1.4 Hz, H-3); ^{13}C NMR, (75 MHz, $CDCl_3$) δ 33.7, 42.7, 46.4, 46.4, 66.6, 67.0, 67.1, 117.5, 123.8, 123.9, 128.4, 133.1, 149.4, 154.9, 166.4; MS (ES+) m/z 396.01, 398.01; HRMS calcd for $C_{17}H_{22}{}^{79}BrN_3O_3$ $[M + H]^+$ 396.0917, found 396.0914.

8-Bromo-2-methylsulfanyl-1*H*-quinolin-4-one (11)

To polyphosphoric acid (160 mg, 1.13 mmol) stirred at 130 °C was added 5-[2-bromoanilino(methylthio)methylene]-2,2-dimethyl-4,6-dione (191 mg, 0.54 mmol). Work-up as in method B for the preparation of 8-bromo-2-morpholin-4-yl-1*H*-quinolin-4-one gave the title compound as a yellow solid (118 mg, 0.44 mmol, 82%): $R_f = 0.34$ (MeOH–DCM 1 : 19); mp: 108–110 °C; IR (cm^{-1}) 3356, 2167, 2021, 1616, 1551, 1492, 1426, 1334, 1097, 933; ^{1}H NMR, (300 MHz, $CDCl_3$) δ 2.53 (3H, s, CH_3), 6.21 (1H, s, H-3), 7.12 (1H, dd, $J = 8.0$ and 7.9 Hz, H-6), 7.73 (1H, d, $J = 7.9$ Hz, H-7), 8.17 (1H, d, $J = 8.0$ Hz, H-5), 8.46 (1H, s, NH); ^{13}C NMR, (75 MHz, $CDCl_3$) δ 15.0, 106.7, 112.0, 124.7, 124.8, 125.9, 135.2, 138.0, 168.0, 173.0; MS (ES+) m/z 269.91, 271.91; HRMS calcd for $C_{10}H_8{}^{79}BrNOS$ $[M + H]^+$ 269.9583, found 269.9582.

2,9-Dihydroxypyrido[1,2-*a*]pyrimidin-4-one (12)

Method A. A mixture of di-(2,4,6-trichlorophenyl) malonate[21] (17.3 g, 37.5 mmol) and 3-hydroxy-2-aminopyridine (4.12 g, 37.5 mmol) in bromobenzene (37 mL) was heated at reflux for 3 h. After cooling, the mixture was filtered and the resulting solid was washed with ethanol. The solid was solubilised in a 1 M sodium hydroxide solution and acetic acid was added to precipitate the product (6.53 g, 98%) as a pale yellow solid.

Method B. To 3-hydroxy-2-aminopyridine (5.21 g, 47.3 mmol) in *o*-xylene (16 mL) was added diethyl malonate (10.8 mL, 71 mmol) and the mixture was heated at 170 °C for 18 h. The reaction was worked up as described in Method A to give the product (6.0 g, 82%) as a pale yellow solid: $R_f = 0.11$ (MeOH–DCM, 3 : 17); mp: 320 °C (dec.) (lit.[9]: 310 °C); λ_{max} (EtOH)/nm 252; IR (cm^{-1}) 2862, 1688, 1564, 1374, 1295, 1102, 783; ^{1}H NMR, (300 MHz, DMSO) δ 5.22 (1H, s, H-3), 7.12 (1H, t, $J = 7$ Hz, H-7), 7.27 (1H, d, $J = 8$ Hz, H-8), 8.43 (1H, d, $J = 7$ Hz, H-6); ^{13}C NMR, (75 MHz, DMSO) δ 103.3, 116.5, 117.1, 119.0, 144.0, 148.8, 157.3, 157.5; MS (ES+) m/z 179.02.

2-Chloro-9-hydroxypyrido[1,2-*a*]pyrimidin-4-one (14)

Method A. 2,9-Dihydroxypyrido[1,2-*a*]pyrimidin-4-one (1.071 g, 6.02 mmol) was cautiously dissolved in phosphorus(III) oxychloride (7.5 mL, 80.4 mmol) to give a solution that was heated at reflux for 48 h. After cooling, the reaction mixture was poured carefully into ice-cold water (100 mL) and the pH was adjusted to 7 by addition of a saturated solution of sodium carbonate. The aqueous layer was extracted with DCM. The combined organic layers were dried ($MgSO_4$) and the solvent was removed to yield a brown solid. The crude product was purified by medium pressure chromatography using DCM as eluent to furnish the title compound as a white solid (712 mg, 60%).

Method B. 3-Hydroxy-2-aminopyridine (444 mg, 4.03 mmol) and di-(2,4,6-trichlorophenyl) malonate (1.865 g, 4.03 mmol) were cautiously dissolved in phosphorus(III) oxychloride (3.2 mL, 34.3 mmol). The reaction was continued as described in Method A to give crude product that was purified by medium pressure chromatography using DCM–methanol (98 : 2 v/v) as eluent. The title compound was obtained as a white solid (251 mg, 32%): $R_f =$ 0.34 (MeOH–DCM, 1 : 19); mp: 162 °C; IR (cm^{-1}) 3103, 1684, 1630, 1511, 1458, 1297, 1105; ^{1}H NMR, (300 MHz, $CDCl_3$) δ 6.4 (1H, s, H-3), 7.11 (1H, dd, $J = 7.3$ and 7.4 Hz, H-7), 7.25 (1H, d, $J = 7.4$ Hz, H-8), 8.51 (1H, d, $J = 7.3$ Hz, H-6); ^{13}C NMR, (75 MHz, $CDCl_3$) δ 103.3, 116.5, 117.1, 119.0, 144.0, 148.8, 157.3, 157.5; MS (ES+) m/z 196.93 M^+; HRMS calcd for $C_8H_5ClN_2O_2$ $[M + H]^+$ 197.0112, found 197.0114.

9-Hydroxy-2-morpholin-4-yl-pyrido[1,2-*a*]pyrimidin-4-one (15)

2-Chloro-9-hydroxypyrido[1,2-*a*]pyrimidin-4-one (142 mg, 0.72 mmol) and morpholine (315 μL, 3.6 mmol) were taken

up in ethanol (5 mL) and the resulting solution was heated at reflux for 18 h with vigorous stirring. The solvent was removed to give a yellow solid that was recrystallised from ethanol to afford the title compound as white crystals (174 mg, 97%): R_f = 0.27 (MeOH–DCM 1 : 19); mp: 245 °C; λ_{max} (EtOH)/nm 267; IR (cm^{-1}) 3302, 1690, 1644, 1551, 1427, 1224, 1110; ^{1}H NMR, (500 MHz, $CDCl_3$) δ 3.56 (4H, m, 2 × NCH_2-morpholine), 3.75 (4H, m, 2 × OCH_2-morpholine), 5.55 (1H, s, H-3), 6.80 (1H, dd, J = 7.0 and 7.0 Hz, H-7), 7.02 (1H, dd, J = 7.0 Hz and 1.3 Hz, H-8), 7.33 (1H, s, OH), 8.37 (1H, dd, J = 7.0 Hz and 1.3 Hz, H-6); ^{13}C NMR, (125 MHz, $CDCl_3$) δ 45.3, 67.0, 82.2, 113.5, 114.2, 119.1, 143.0, 147.5, 159.0, 161.0; MS (ES+) m/z 248.08; Anal. Calcd for 0.8 mol $C_{12}H_{12}N_3O_3$ + 0.2 mol H_2O: C, 57.25, H, 5.40, N, 16.69. Found: C, 57.58, H, 5.12, N, 16.58.

9-Hydroxy-2-morpholin-4-yl-pyrido[1,2-*a*]pyrimidin-4-one 9-*O*-triflate (16)

A 3-necked flask equipped with a thermometer, addition funnel and magnetic stirrer, was charged with 9-hydroxy-2-morpholin-4-yl-pyrido[1,2-*a*]pyrimidin-4-one (2.11 g, 8.5 mmol) in DCM (70 mL). The mixture was cooled to −30 °C and triethylamine (3.6 mL, 25.6 mmol) was added. After 5 min, trifluoromethanesulfonic anhydride (2.1 mL, 12.8 mmol) in DCM (10 mL) was added dropwise to the reaction mixture, *via* the funnel. The addition took place over 30 min, and the temperature of the reaction mixture was kept below −20 °C during this time. After 3 h, the reaction mixture was washed with a saturated solution of sodium carbonate (50 mL) and extracted with DCM (3 × 30 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was removed to yield a brown solid. The crude product was purified by medium pressure chromatography using DCM as eluent to furnish the title compound as an orange solid (2.91 g, 90%): R_f = 0.42 (MeOH–DCM, 1 : 19); mp: 146–147 °C; λ_{max} (EtOH)/nm 271; IR (cm^{-1}) 1705, 1644, 1551, 1189, 1112, 939, 769; ^{1}H NMR, (300 MHz, $CDCl_3$) δ 3.56 (4H, m, 2 × NCH_2-morpholine), 3.71 (4H, m, 2 × OCH_2-morpholine), 5.53 (1H, s, H-3), 6.80 (1H, dd, J = 8.0 and 7.0 Hz, H-7), 7.46 (1H, dd, J = 8.0 Hz and 1.3 Hz, H-8), 8.79 (1H, dd, J = 7.0 Hz and 1.3 Hz, H-6); ^{13}C NMR, (75 MHz, $CDCl_3$) δ 45.2, 66.9, 81.8, 110.2, 112.6, 116.9, 121.1, 125.3, 127.9, 128.1, 141.5, 145.8, 158.1, 160.4; MS (ES+) m/z 380.16; Anal. Calcd for $C_{13}H_{12}F_3N_3O_5S$: C, 41.16, H, 3.19, N, 11.08. Found: C, 41.29, H, 2.88, N, 10.93%.

8-Substituted 2-morpholin-4-yl-quinolin-4-ones (2a–2g)

Typical procedure. The arylboronic acid (1 mol equiv.) and potassium carbonate (1.9 mol equiv.) were dispersed in dioxane (4 mL per mmol boronic acid). Concurrently, 8-bromo-2-morpholin-4-yl-1*H*-quinolin-4-one (0.67 mol equiv.) and tetrakis-(triphenylphosphine)palladium (3 mol%) were taken up in dioxane (6 mL per mmol bromo compound). Argon was bubbled into both mixtures, which were sonicated for 15 min. The mixtures were combined, stirred and heated at 95 °C for 48 h. After cooling, DCM (10 mL per mmol boronic acid) was added. The resulting solution was washed with water and brine (10 mL each per mmol boronic acid), dried ($MgSO_4$), and the solvent was removed. The crude product was purified as described below for compound **2a** and in the Supplementary Information† for compounds **2b–2g**.

2-Morpholin-4-yl-8-phenyl-4-yl-1*H*-quinolin-4-one (2a). Phenylboronic acid (59 mg, 0.49 mmol) and 8-bromo-2-morpholin-4-yl-1*H*-quinolin-4-one (100 mg; 0.32 mmol) gave crude product that was purified by medium pressure chromatography using ethyl acetate–methanol (98 : 2 v/v) as eluent. Further purification was achieved by HPLC (aqueous methanol as eluent) to afford the title compound as a cream solid (65 mg, 65%): R_f = 0.11 (EtOAc); mp: 109–110 °C (dec.); λ_{max} (EtOH)/nm 251; IR (cm^{-1}) 3410, 2954, 2846, 1613, 1576, 1488, 1422, 1364, 1227, 1111, 996, 903, 800, 700; ^{1}H NMR, (300 MHz, $CDCl_3$) δ 3.05 (4H, m, 2 × NCH_2-morpholine), 3.68 (4H, m, 2 × OCH_2-morpholine), 5.68 (1H, s, H-3), 7.26 (1H, dd, J = 7.0 and 7.0 Hz, H-6), 7.40 (3H, m), 7.51 (2H, m), 7.82 (1H, m, H-7), 8.23 (1H, d, J = 7.0 Hz, H-5); ^{13}C NMR, (75 MHz, $CDCl_3$) δ 46.7, 66.4, 92.9, 123.4, 125.8, 129.6, 132.5, 135.6, 137.0, 154.3, 178.9; MS (ES+) m/z 307.13; Anal. Calcd for 0.73 mol $C_{19}H_{18}N_2O_2$ + 0.27 mol DCM: C, 69.21, H, 5.73, N, 8.18. Found: C, 69.21, H, 5.60, N, 8.58%.

9-Substituted 2-morpholin-4-yl-pyrido[1,2-*a*]pyrimidin-4-ones (3a–3f)

Typical procedure. A similar procedure to that detailed above for 8-substituted 2-morpholin-4-yl-quinolin-4-ones was also used for reactions of arylboronic acids with 9-hydroxy-2-morpholin-4-yl-pyrido[1,2-*a*]pyrimidin-4-one 9-*O*-triflate. The crude product was purified as described below for compound **3a** and in the Supplementary Information† for compounds **3b–3f**.

2-Morpholin-4-yl-9-phenyl-4-yl-pyrido[1,2-*a*]pyrimidin-4-one (3a). Phenylboronic acid (36 mg, 0.26 mmol) and 9-hydroxy-2-morpholin-4-yl-pyrido[1,2-*a*]pyrimidin-4-one 9-*O*-triflate (100 mg, 0.26 mmol) gave crude product that was recrystallised from ethyl acetate. The title compound was obtained as a brown solid (71 mg, 88%): R_f = 0.22 (MeOH–DCM 1 : 19); mp: 187–188 °C; λ_{max} (EtOH)/nm 275; IR (cm^{-1}) 2862, 1681, 1539, 1494, 1427, 1219, 1106, 756; ^{1}H NMR, (300 MHz, $CDCl_3$) δ 3.47 (4H, m, 2 × NCH_2-morpholine), 3.65 (4H, m, 2 × OCH_2-morpholine), 5.57 (1H, s, H-3), 6.91 (1H, dd, J = 7.0 and 7.1 Hz, H-7), 7.33–7.41 (3H, m), 7.55–7.59 (3H, m), 8.90 (1H, dd, J = 7.0 Hz and 1.6 Hz, H-6); ^{13}C NMR, (75 MHz, $CDCl_3$) δ 44.9, 66.9, 81.3, 112.9, 127.5, 128.3, 128.6, 130.2, 136.0, 136.7, 137.2, 149.5, 159.5, 160.9; MS (ES+) m/z 308.14; Anal. Calcd for 2.0 mol $C_{19}H_{18}N_2O_2S$ + 0.1 mol H_2O: C, 68.34, H, 5.73, N, 13.28. Found: C, 68.72, H, 5.17, N, 13.08%.

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