Synthesis and Structure–Activity Relationships of 4-Pyridones as Potential Antimalarials

Clive L. Yeates,*[,†] John F. Batchelor,[†] Edward C. Capon,[†] Neil J. Cheesman,[†] Mitch Fry,[†] Alan T. Hudson,[†] Mary Pudney,[†] Helen Trimming,[†] James Woolven,[†] José M. Bueno,*[,‡] Jesús Chicharro,[‡] Esther Fernández,[‡] José M. Fiandor,[‡] Domingo Gargallo-Viola,[‡] Federico Gómez de las Heras,[‡] Esperanza Herreros,[‡] and María L. León[‡]

Wellcome Research Laboratories, Langley Court, Beckenham, Kent, U.K., and Centre for Diseases of the Developing World, GlaxoSmithKline R&D, 28760 Tres Cantos, Spain

Received May 17, 2007

A series of diaryl ether substituted 4-pyridones have been identified as having potent antimalarial activity superior to that of chloroquine against *Plasmodium falciparum* in vitro and murine *Plasmodium yoelii* in vivo. These were derived from the anticoccidial drug clopidol through a systematic study of the effects of varying the side chain on activity. Relative to clopidol the most active compounds show >500-fold improvement in IC_{50} for inhibition of *P. falciparum* in vitro and about 100-fold improvement with respect to ED_{50} against *P. yoelii* in mice. These compounds have been shown elsewhere to act selectively by inhibition of mitochondrial electron transport at the cytochrome bc_1 complex.

Introduction

Malaria remains a major infective disease in man, with over 40% of the world's population exposed to the risk of infection and an estimated hundred million clinical cases every year. The spread of chloroquine- and multidrug-resistant *P. falciparum*[a]-malaria[1] has led to renewed efforts to find new drugs for both treatment and prophylaxis.[2,3] The respiratory chain of *P. falciparum* makes an attractive target for chemotherapy because it differs from the analogous mammalian system in a number of ways.[4–6] This concept has already borne fruit with atovaquone (Figure 1), introduced in 1997 as a combination with proguanil, used in treating multidrug-resistant malaria and for prophylaxis in areas with chloroquine resistance.[7,8] Atovaquone acts by inhibition of mitochondrial respiration through the cytochrome bc_1 complex;[9] recent studies with bacterial and yeast cyt bc_1 have shown that it binds to the ubiquinol oxidation pocket (Q_P or Q_O site) and the Rieske iron−sulfur protein.[10–12] Despite the effectiveness of the atovaquone/proguanil combination, its high cost has proved a hurdle to widespread use in disease-endemic areas, especially sub-Saharan Africa.

In our efforts to exploit other inhibitors of parasite respiration as potential drugs, we focused our attention on a series of 4(1*H*)-pyridones related to the anticoccidial drug clopidol (Figure 1). In studies carried out under the aegis of the Walter Reed Army Institute of Research in the late 1960s clopidol was shown to have activity against *Plasmodium* sp., including chloroquine-resistant strains, in a number of animal models.[13] Clinical trials in man confirmed activity against chloroquine-resistant *P. falciparum*, although this was not sufficient to warrant further development. Attempts at the time to improve activity through a range of simple derivatives were not successful. Evidence subsequently emerged indicating the mode of action of clopidol involved inhibition of mitochondrial respiration.[14] Furthermore, clopidol was shown to potentiate the antimalarial activity of hydroxynaphthoquinones, in vitro and in vivo, and retained activity against an atovaquone-resistant strain.[15] This raised the prospect that clopidol was acting by a novel mechanism, and its simple structure clearly offered some scope for manipulation to improve antimalarial activity.

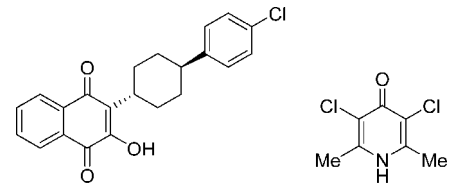


Figure 1

We report here part of our investigation into the relationship between structure and antimalarial activity of 4-pyridones, the aim of which was to identify compounds with significantly improved activity over clopidol against *P. falciparum* in vitro and murine *P. yoelii* in vivo, with potential for the treatment of malaria.

Chemistry

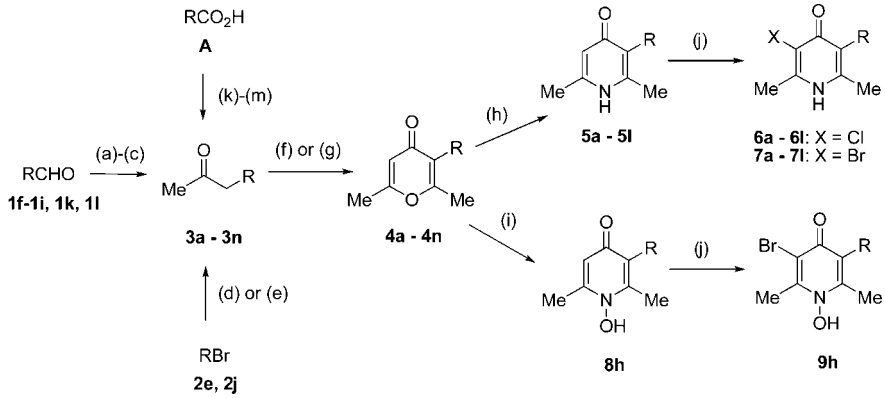
On the assumption that clopidol could be acting as a ubiquinone antagonist, part of our strategy to improve the antimalarial activity was to introduce a lipophilic side chain at C-5 (i.e., replacing the 5-Cl substituent). 2,6-Dimethyl-4-pyridones with a 5-alkyl or aryl substituent were prepared according to Scheme 1. The intermediate pyrones (**4**) were accessible from the corresponding methyl ketones (**3**) using a modification of the procedure described by Letsinger;[16] the substitution of acetic anhydride for the acetic acid originally used allows a lower reaction temperature (80–100 °C, compared to 140–150 °C). Subsequently Eaton's reagent (phosphorus pentoxide in methanesulfonic acid) was found to provide a convenient substitute for polyphosphoric acid, with advantages in ease of handling, aqueous workup and in lower reaction temperature (~50 °C). The intermediate pyrones also provide access to *N*-hydroxy-4-pyridones (**8h**).[17] Those precursor ketones (**3e**−**n**) not available commercially were prepared from the corresponding benzaldehydes (**1**) or bromides (**2**) by adaptation of published procedures;[18–20] ketone **3d**, required for incorporation of the atovaquone side chain, was prepared from the commercially available acid **A** (Scheme 1). For the *o*- and *m*-phenoxyaryl derivatives (**7o**, **7p**) it was found convenient to

* To whom correspondence should be addressed. For C.L.Y.: phone, +44 1438 718933; e-mail, cly@inpharma.co.uk. For J.M.B., phone, +34 918 070616; fax, +34 918 070550; e-mail, jose.m.bueno@gsk.com.
† Wellcome Research Laboratories.
‡ GlaxoSmithKline R&D.

[a] Abbreviations: GSK Tres Cantos, GlaxoSmithkline R&D, Tres Cantos, Spain; *P. falciparum*, *Plasmodium falciparum*; *P. yoelii*, *Plasmodium yoelii*.

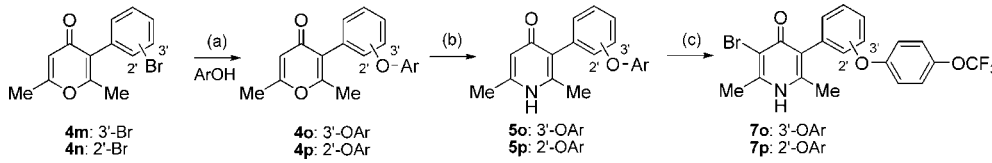
10.1021/jm0705760 CCC: $40.75
Published on Web 04/09/2008

Scheme 1. Synthesis of Pyridones[a]



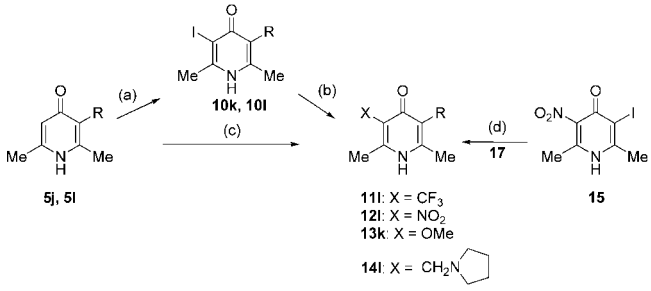
[a] Reagents and conditions: (a) *n*-$BuNH_2$, toluene; (b) $EtNO_2$, AcOH; (c) Fe, aqueous AcOH; (d) isopropenyl acetate, *n*-Bu_3SnOMe, $Cl_2Pd(P(o\text{-tolyl})_3)_2$, toluene, 100 °C; (e) $KCH(COMe)_2$, CuI, DMF, 100 °C, 24 h; (f) Ac_2O, PPA, 80 °C, 30 min; (g) Ac_2O, P_2O_5, $MeSO_3H$, 50 °C, 1 h; (h) aqueous NH_3, 150 °C; (i) $NH_2OH \cdot HCl$, NaOAc, aqueous EtOH, 100 °C; (j) X = Cl, *N*-chlorosuccinimide, AcOH, 100 °C, or X = Br, Br_2, AcOH; (k) $BH_3 \cdot Me_2S$, Et_2O; (l) 48% HBr, concentrated H_2SO_4; (m) (i) Mg, Et_2O; (ii) Ac_2O, −70 °C. Substituent R is as defined in Tables 1, 2, and 6.

Scheme 2. Synthesis of Isomeric Phenoxy Derivatives[a]



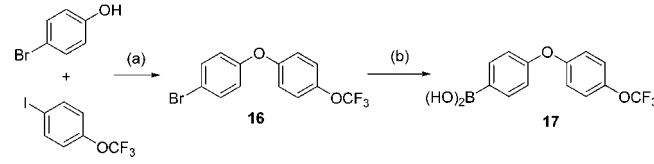
[a] Reagents and conditions: (a) $CsCO_3$, CuCl, 2,4-pentanedione, NMP, 120 °C, 48 h; (b) aqueous NH_3, 140 °C; (c) *N*-bromosuccinimide, CH_2Cl_2, MeOH, room temp, 3 h.

Scheme 3. Synthesis of 3-CF_3, Alkoxy, and Amino Derivatives[a]



[a] Reagents and conditions: (a) *N*-iodosuccinimide, AcOH, 2 h; (b) X = CF_3, CuI, $FSO_2CF_2CO_2Me$, DMF, 70 °C, 6 h, or X = OMe, NaOMe, MeOH, CuI, 110 °C, 8 h; (c) pyrrolidine, $(CH_2O)_n$, EtOH, reflux, 24 h; (d) K_2CO_3, tris(dibenzylideneacetone)dipalladium(0), 110 °C, 24 h. Substituent R is as defined in Table 3.

Scheme 4. Synthesis of Boronic Acid Intermediate[a]



[a] Reagents and conditions: (a) 2,2,6,6-tetramethyl-3,5-heptanedione, $CsCO_3$, CuCl, 100 °C, 5 h; (b) (i) $(i\text{-PrO})_3B$, THF, *n*-BuLi, −75 °C, 3 h; (ii) 6 M HCl, 18 h.

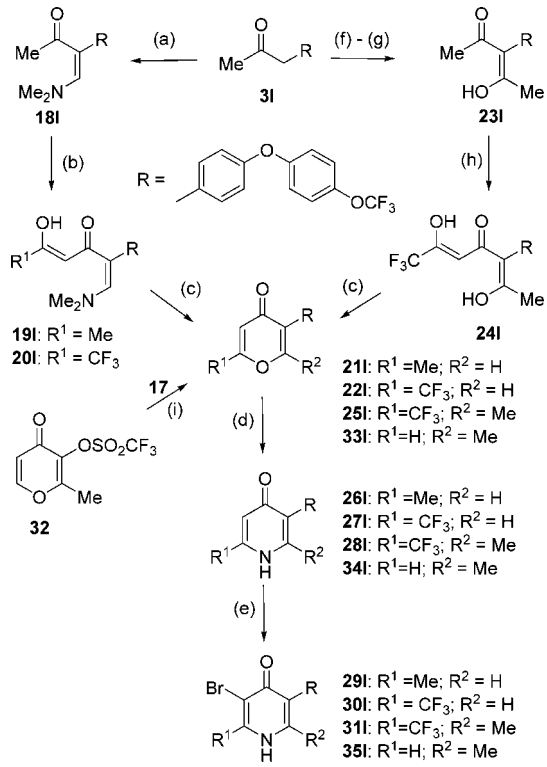
elaborate the corresponding bromophenyl pyrone intermediates (Scheme 2). Further derivatives covering a variety of substituents at C-5 were prepared according to Scheme 3. Notable is the facile boronic acid coupling used in the preparation of the 3-NO_2 derivative **12l**; the synthesis of the requisite boronic acid is outlined in Scheme 4. Analogues of some of the most active pyridones in which either the 2- or 6- methyl was removed (**29l**, **35l**) or the 2-methyl replaced with CF_3 (**31l**) were accessible from the corresponding pyranones, prepared through acid-catalyzed cyclization of the enamino-1,3-diketones **19l** and **20l**, triketone **24l**, or through boronic acid coupling with the triflate **32** (Scheme 5). There is precedence for the synthesis of 2-trifluoromethyl pyrones through the metalation and subsequent acylation of enaminones analogous to **18l**.[21]

Results and Discussion

All compounds were evaluated for antimalarial activity in vitro against *P. falciparum* (T9-96 or 3D7A strains). In vivo efficacy was determined in a mouse *P. yoelii* model, administering test samples in seven oral doses by gavage over 4 days. Some of the compounds were also evaluated when given as a single oral dose. The in vivo data is expressed as ED_{50} (mg/kg) values, representing the dose (estimated from the dose–response curve) for parasite reduction of 50% relative to untreated controls.

The antimalarial activity of a cross section of the initial series of 4-pyridones synthesized is summarized in Table 1. The 3-octyl derivative **6a** had enhanced activity over clopidol in vitro but was inactive in vivo. The phenyl and 4′-chlorophenyl analogues **6b** and **6c** showed some improvement in activity relative to clopidol in vitro and in vivo, although further simple variation in the aryl substitution pattern (4-F, 3,4-Cl_2, 2,4-Cl_2, 4-CF_3, 4-MeO; details not shown) failed to improve on this. On the assumption that the loss of in vivo activity with **6a** was due to metabolic degradation of the side-chain, the *trans*-(4-chlorophenyl)cyclohexyl side chain of atovaquone, known to be resistant to metabolism, was introduced, resulting in a dramatic increase in efficacy in vivo (**6d**). Analogues with a biaryl (**6e**) or 4′-phenoxyaryl side-chain (**6 h**) were also highly active, superior to chloroquine in the murine *P. yoelii* assay. The introduction of a similar series of side chains at the 2-position on clopidol gave no improvement in activity (details

Scheme 5. Synthesis of 2- or 6-H and CF_3 Derivatives[a]



[a] Reagents and conditions: (a) Me_2 $NCH(OMe)_2$, toluene, reflux, 8 h; (b) R^1 = Me: LiHMDS, AcCl, THF, −78 °C to reflux or $R^1 = CF_3$: *t*-BuOK, CF_3CO_2Me, THF, 0 °C to reflux; (c) 5 M HCl, *i*-PrOH, room temp, 4 h; (d) 30% aqueous NH_3, *i*-PrOH, reflux; (e) NBS, CH_2Cl_2, MeOH; (f) Ac_2O, $BF_3.OEt_2$, room temp, 4 h; (g) NaOAc, MeOH, reflux, 2 h; (h) *t*-BuOK, CF_3CO_2Me, THF, 0 °C to reflux, 24 h; (i) $Pd(PPh_3)_4$, toluene, EtOH, 90 °C, 1.5 h.

not shown).[22] Further exploration of the SAR focused on derivatives with a 3-(4′-phenoxy)phenyl side chain. The following observations on the SAR can be made:

(1) In all cases halogenation at C-3 increased activity in vitro (by about 10-fold on IC_{50}) and in vivo relative to the 5-H derivatives (Table 2). In many cases there was little difference between the 3-Br and 3-Cl analogues. Other electronegative substituents (CF_3, NO_2) provided no improvement in activity, while electron-donating substituents (OMe, aminoalkyl) result in a significant drop in activity relative to the 5-H derivatives (Table 3).

(2) Variation in the substitution on the phenoxyaryl side chain had relatively little effect on in vitro activity, although there appeared to be a significant impact on in vivo efficacy (Table 2).

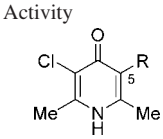
(3) Regarding the effect of variation in the orientation of the phenoxy side chain (Table 4), activity is retained in the 3′-isomer (**7o**) but much reduced in the 2′- analogue (**7p**) compared to the 4′- derivative (**7l**).

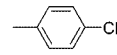
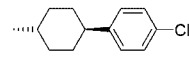
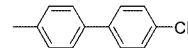
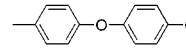
(4) Removal of either 2- or 6-methyl results in a >10× drop in activity in vitro, exacerbated by replacement with CF_3 (Table 5).

(5) The *N*-hydroxy derivative (**9h**; Table 6) was about 10-fold less active (by IC_{50}) in vitro compared to the corresponding pyridone (**7h**) but retained a degree of in vivo activity.

An important aspect to be taken into account in interpreting these SAR studies is pyridone/pyridinol tautomerism; 2,6-dimethyl substituted 4-pyridones would be expected to adopt predominantly the pyridone tautomer in the solid state and in aqueous solution.[23] This is confirmed in the crystal structure of clopidol.[24] In solution solvent polarity has a significant effect, with the less polar pyridinol tautomer predicted to be progressively more favored as the dielectric constant decreases. Electronegative substituents at C-2 would be predicted to stabilize the pyridinol tautomer;[23] this may explain the loss of activity on substituting CF_3 for methyl (compare **7l** and **31l**, Table 5). 3-Substitution is predicted to have comparatively little effect on the tautomerism. 4-Pyridone *N*-oxides are depicted as the N−OH pyridone tautomer, although the pyridone/pyridinol tautomerism is probably more finely balanced than with the NH compounds.

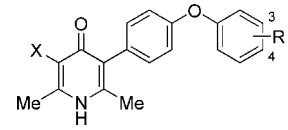
Table 1. 4(1*H*)-Pyridones: Influence of Side Chain at C-5 on in Vitro and in Vivo Antimalarial Activity



Compound	R	*P. falciparum* T9-96 IC_{50} (μM)	*P. yoelii* YM in vivo[a] ED_{50} (mg/kg)
Clopidol	Cl	20	40
6a	n-C_8H_{17}	4	>60
6b	Ph	11	22
6c		2.5	20
6d		0.05	0.6
6e		0.4	0.7
6h		0.06	0.6
Atovaquone		0.003	0.03
Chloroquine		0.07	1.8-2.2

[a] Seven doses po over 4 days.

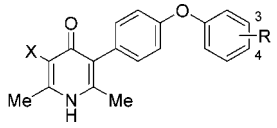
Table 2. In Vitro and in Vivo Antimalarial Activity of Phenoxyaryl-4(1*H*)-pyridones



compd	X	R	*P. falciparum* T9-96, IC_{50} (μM)	*P. yoelii* YM in vivo,[a] ED_{50} (mg/kg)
7f	Br	H	0.15	4
7g	Br	4-F	0.04	0.6
5h	H	4-Cl	0.25	2.5
6h	Cl	4-Cl	0.06	1.7
7h	Br	4-Cl	0.04	0.3 (5)
6i	Cl	3-Cl	0.03	>5
7i	Br	3-Cl	0.03	3.9
5j	H	4-CF_3	0.5	1.3
6j	Cl	4-CF_3	0.06	0.6
7j	Br	4-CF_3	0.03	0.3 (1.1)
6k	Cl	3-CF_3	0.03	0.2 (0.2–0.6)
7k	Br	3-CF_3	0.03	0.6 (3.6)
5l	H	4-OCF_3	0.16	>5
6l	Cl	4-OCF_3	0.03	0.2 (0.4–1.3)
7l	Br	4-OCF_3	0.03	0.3 (0.2–0.5)

[a] Seven doses po over 4 days. Figures in parentheses are for a single dose po; where a range is quoted, the figures given are results from different experiments.

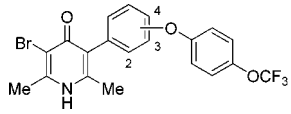
Table 3. Influence of 3-Substitution on in Vitro Antimalarial Activity



Compd	X	R	*P. falciparum* 3D7A IC_{50} (μM)[a]
5l	H	4-OCF_3	0.16
7l	Br	4-OCF_3	0.008
6l	Cl	4-OCF_3	0.005
11l	CF_3	4-OCF_3	0.03
12l	NO2	4-OCF_3	0.03
13k	OMe	3-CF_3	0.3
14l		4-OCF_3	1.29

[a] Data from GSK Tres Cantos.

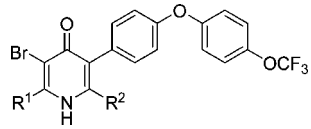
Table 4. Effect of Side Chain Orientation on in Vitro Antimalarial Activity



compd	isomer	*P. falciparum* 3D7A, IC_{50} (μM)[a]
7l	4-OAr	0.008
7o	3-OAr	0.007
7p	2-OAr	0.4

[a] Data from GSK Tres Cantos.

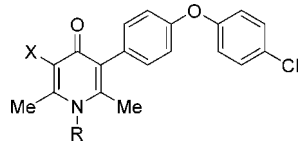
Table 5. Influence of 2- or 6-Substitution on in Vitro Antimalarial Activity



compd	R^1	R^2	*P. falciparum* 3D7A, IC_{50} (μM)[a]
7l	Me	Me	0.008
29l	Me	H	0.2
35l	H	Me	0.11
31l	CF_3	Me	>1
30l	CF_3	H	>1

[a] Data from GSK Tres Cantos.

Table 6. Antimalarial Activity of *N*-Hydroxy-4-pyridones in Vitro and in Vivo



compd	R	X	*P. falciparum* T9-96, IC_{50} (μM)	*P. yoelii* YM in vivo,[a] ED_{50} (mg/kg)
7h	H	Br	0.04	0.3
9h	OH	Br	0.45	~1.0
8h	OH	H	2.2	>1.0

[a] Seven doses po over 4 days.

On the basis of their potent activity against *P. yoelii* in mice, **6l** and **7l** were evaluated in *Aotus* monkeys infected with *P. falciparum*, the closest primate model available for human malaria; both compounds administered orally at 10 mg/kg/day × 7 were completely curative.[25] Further evaluation of the antimalarial potential of the 4(1*H*)-pyridones has focused on **6k** (GW308678) and **6l** (GW844520),[26–32] which show significant differences in ADME profiles.[33–36] Studies using isolated mitochondria from *P. falciparum* and *P. yoelii* indicate that the 4(1*H*)-pyridones inhibit respiration through the cyt bc_1 complex (complex **III**) at concentrations similar to the levels required for activity against whole *P. falciparum* in vitro and show a high degree of selectivity (>100-fold) for inhibition of respiration in isolated mitochondria from *Plasmodia* sp. relative to that isolated from yeast or mammalian sources.[37–40] There is some evidence to indicate that the molecular target for the 4(1*H*)-pyridones lies in the quinone binding site (Qo).[38,41] However, no significant cross-resistance with atovaquone has been found in studies with pyridones across a number of atovaquone-resistant strains of *P. falciparum* and the frequency at which pyridone-resistant parasites arise in vitro appears significantly lower compared to atovaquone.[42] Comparative data for the atovaquone-sensitive *P. falciparum* 3D7A and an atovaquone/chloroquine-resistant clone FCR3-A (derived from FCR3) are provided in Table 7. In addition to potent activity against the erythrocytic stages of malaria, pyridones also show activity in vitro and in vivo against liver stages,[43] indicating potential for causal prophylaxis.

Table 7. In Vitro Activity of Pyridones against a *P. falciparum* Atovaquone-Resistant Strain

	IC_{50} (μM)	
	P. falciparum 3D7A	*P. falciparum* FCR3-A[a]
6l	0.005	0.001
6k	0.005	0.0025
atovaquone	0.00027	1.36
chloroquine diphosphate	0.031	0.3

[a] Atovaquone and chloroquine-resistant strain. Contains G399C and G839A mutations in cytochrome *b*.

Conclusions

The introduction of a lipophilic side chain at C-5 on clopidol has been found to lead to a significant improvement in activity both in vitro against *P. falciparum* and orally in vivo against murine *P. yoelii*, yielding a number of derivatives with antimalarial activity in these assays comparable to current drugs. Additional studies on two of the compounds described here, **6k** and **6l**, which have been reported elsewhere, encourage the further exploration of this series as potential antimalarials.

Experimental Section

Chemistry. Melting points were determined using an Electrothermal capillary melting point apparatus and are uncorrected. Column chromatography was performed on silica gel, Merck 40–63 μm (230–400 mesh). NMR spectra were determined on a Bruker AC200 spectrometer (200 MHz) or Varian Unity spectrometer (300 MHz). Chemical shifts are reported as δ values (ppm) downfield from tetramethylsilane, used as an internal standard in the solvent indicated. ESIMS (electron spray ionization mass spectra) were recorded on a Waters ZMD 2000.

3-[4-(4-Chlorophenoxy)phenyl]-2,6-dimethyl-4*H*-pyran-4-one (4h). A solution of 1-[4-(4-chlorophenoxy)phenyl]propan-2-one (**3h**, 26 g, 115 mmol) in acetic anhydride (100 mL, 1.06 M) was added over 5 min to a vigorously stirred mixture of polyphosphoric acid (200 g) and acetic anhydride (100 mL, 1.06 M) at 80 °C. After being stirred for 30 min, the mixture was poured into water (1 L) and extracted with toluene (2 × 500 mL). The combined extracts were washed with water and aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated to leave an oil. Trituration with diethyl ether followed by recrystallization from carbon tetrachloride afforded **4h** (14.64 g, 39%) as white crystals, mp 150–152 °C. ^{1}H

NMR (200 MHz, $CDCl_3$): δ 6.95–7.4 (m, 8H), 6.2 (s, 1H), 2.3 (s, 3H), 2.2 (s, 3H).

4a–l were prepared in a similar manner to **4h** from the appropriate ketones.

3-(3-Bromophenyl)-2,6-dimethyl-4*H*-pyran-4-one (4m). A solution of 1-(3-bromophenyl)-2-propanone (1g, 4.7 mmol) in acetic anhydride (2.6 mL, 27.5 mmol) was added to a solution of Eaton's reagent (5 mL, 7.7 wt % P_2O_5 in methanesulfonic acid; Aldrich) and acetic anhydride (2 mL, 27.5 mmol) and the mixture heated at 50 °C for 1 h. Water and diethyl ether were added, and the organic phase was separated, dried (Na_2SO_4), and evaporated under reduced pressure. Chromatography of the residue on silica gel (10:1 CH_2Cl_2/MeOH eluant) gave **4m** (640 mg, 49%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50–7.46 (m, 1H), 7.38 (t, 1H), 7.28 (t, 1H), 7.16 (dt, 1H), 6.21 (s, 1H), 2.29 (s, 3H), 2.18 (s, 3H).

4n was prepared in a similar manner to **4m** from 1-(2-bromophenyl)-2-propanone.

2,6-Dimethyl-3-{3-[4-(trifluoromethoxy)phenoxy]phenyl}-4*H*-pyran-4-one (4o). A mixture of **4m** (240 mg, 0.86 mmol), cesium carbonate (560 mg, 1.72 mmol), 2,4-pentanedione (36 μL, 0.34 mmol), 4-(trifluoromethoxy)phenol (306 mg, 1.72 mmol), and CuCl (43 mg, 0.43 mmol) in *N*-methylpyrrolidine (5 mL) was heated under argon at 120 °C for 48 h. Diethyl ether was added and the mixture filtered to remove a black residue. The filtrate was washed with 1 M aqueous HCl, 1 M NaOH, and brine and concentrated under reduced pressure. The residue was chromatographed on silica gel (6:1 hexane/ethyl acetate eluant) to give **4o** (82 mg, 25%) as a colorless oil.

4p was prepared from **4n** in a similar manner to **4o**.

3-[4-(4-Chlorophenoxy)phenyl]-2,6-dimethylpyridin-4(1*H*)-one (5h). The pyrone **4h** (10 g, 30.6 mmol) was heated at 150 °C with 30% aqueous ammonia (200 mL, ~3 M) in an autoclave for 18 h. The precipitate was filtered off, washed with water, dried, and recrystallized from DMF to afford **5h** (6.6 g, 66%) as white crystals, mp 271–273 °C. R_f (silica gel, 9:1 $CHCl_3$/MeOH) = 0.2. ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.42 (m, 2H), 7.18 (m, 2H), 6.95–7.1 (m, 4H), 5.95 (s, 1H), 2.2 (s, 3H), 2.1 (s, 3H). Anal. ($C_{19}H_{16}ClNO_2$) C, H, N.

5a−l,o,p were prepared in a similar manner to **5h** from the appropriate pyrones (**4a−l,o,p**).

3-Chloro-5-[4-(4-chlorophenoxy)phenyl]-2,6-dimethylpyridin-4(1*H*)-one (6h). To a stirred solution of **5h** (0.8g, 2.45 mmol) in acetic acid (10 mL) was added *N*-chlorosuccinimide (0.39 g, 2.9 mmol). The mixture was heated at 100 °C for 30 min and cooled to room temperature, and the precipitate was filtered and dried in vacuo to afford **6h** (0.33 g, 37%) as white crystals, mp 340–343 °C. R_f (silica gel, 9:1 $CHCl_3$/MeOH) = 0.36. ^{1}H NMR (200 MHz, DMSO-d_6): δ 11.3 (br s, 1H), 7.42 (m, 2H), 7.2 (m, 2H), 6.95–7.12 (m, 4H), 2.4 (s, 3H), 2.1 (s, 3H). Anal. ($C_{19}H_{15}Cl_2NO_2$) C, H, N.

Choro derivatives **6a−l** were prepared in a similar manner to **6h** from the corresponding pyridones (**5a−l**).

3-Bromo-5-[4-(4-chlorophenoxy)phenyl]-2,6-dimethylpyridin-4(1*H*)-one (7h). To a stirred solution of **5h** (6.5 g, 20 mmol) in acetic acid (50 mL) was added dropwise, over 30 min, a solution of bromine (1.2 mL, 23.3 mmol) in acetic acid (10 mL). After 3 h the mixture was poured into 1% aqueous sodium sulfite (250 mL) and the precipitate filtered, washed with water, dried in air, and recrystallized from DMF to afford **7h** (6.6 g, 81.5%) as white crystals, mp 306–308 °C. R_f (silica gel, 9:1 $CHCl_3$/MeOH) = 0.37. ^{1}H NMR (200 MHz, DMSO-d_6): δ 11.3 (br s, 1H), 7.42 (m, 2H), 7.2 (m, 2H), 6.95–7.12 (m, 4H), 2.42 (s, 3H), 2.1 (s, 3H). Anal. ($C_{19}H_{15}BrClNO_2$) C, H, N.

Bromo derivatives **7f−l** were prepared in a similar manner to **7h** from the corresponding pyridones (**5f−l**).

3-Bromo-2,6-dimethyl-5-{3-[4-(trifluoromethoxy)phenoxy]-phenyl}pyridin-4(1*H*)-one (7o). To a stirred solution of **5o** (50 mg, 0.13 mmol) in CH_2Cl_2 (1 mL) and MeOH (0.25 mL) was added in portions *N*-bromosuccinimide (30 mg, 0.13 mmol). After 3 h the solvent was evaporated and the residue chromatographed on silica gel (10:1 CH_2Cl_2/MeOH eluant) to afford **7o** (37 mg, 63%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.60 (s, 1H), 7.44–7.36 (m, 3H), 7.11 (d, 2H), 7.01–6.97 (m, 2H), 6.87 (t, 1H), 2.40 (s, 3H), 2.08 (s, 3H).

Bromo derivative **7p** was prepared in a similar manner to **7o** from **5p.**

3-[4-(4-Chlorophenoxy)phenyl]-1-hydroxy-2,6-dimethylpyridin-4(1*H*)-one (8h). A mixture of the pyrone **4h** (1.0 g, 3 mmol), hydroxylamine hydrochloride (1.06 g, 15.2 mmol), sodium acetate (1.25 g, 15.2 mmol), water (5 mL), and ethanol (10 mL) was heated to reflux for 3 days. After the mixture was cooled to room temperature, water (20 mL) was added and the precipitate collected by filtration, washed with ethyl acetate, and recrystallized from DMF to afford **8h** (0.2 g, 22%) as white crystals, mp 232–236 °C. ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.5–7.4 (d, J = 8.0 Hz, 2H), 7.3–7.2 (d, J = 8.0 Hz, 2H), 7.15–7.0 (m, 4H), 6.75 (s, 1H), 2.35 (s, 3H), 2.15 (s, 3H).

3-Bromo-5-[4-(4-chlorophenoxy)phenyl]-1-hydroxy-2,6-dimethylpyridin-4(1*H*)-one (9h). To a stirred solution of the pyridone **8h** (0.5 g, 1.6 mmol) in acetic acid (10 mL) was added dropwise a solution of bromine (0.08 mL, 1.6 mmol) in acetic acid (1 mL). After 1.5 h a few drops of a saturated aqueous sodium sulfite solution was added to discharge excess bromine. The mixture was diluted with water and the precipitate filtered, washed with water, dried, and recrystallized from DMF to afford **9h** (0.32 g, 52%) as white crystals, mp 246–250 °C dec. ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.5–7.4 (d, J = 8.0 Hz, 2H). 7.25–7.15 (d, J = 8.0 Hz, 2H), 7.15–7.0 (m, 4H), 2.6 (s, 3H), 2.1 (s, 3H).

3-Iodo-2,6-dimethyl-5-{4-[4-(trifluoromethoxy)phenoxy]phenyl}-pyridin-4(1*H*)-one (10l). To a stirred solution of the pyridone **5l** (0.775 g, 2.06 mmol) in glacial acetic acid (15 mL) at room temperature was added portionwise *N*-iodosuccinimide (0.473 g, 2.1 mmol). After the mixture was stirred for 2 h, the precipitate was filtered, washed with acetic acid and then acetonitrile, and dried in vacuo to provide **10l** (0.75 g, 73%) as a white powder. ^{1}H NMR (200 MHz, DMSO-d_6): δ 11.61 (bs, 1H), 7.40 (m, 2H), 7.20 (m, 2H), 7.13 (m, 2H), 7.03 (m, 2H), 2.49 (m, 3H + DMSO-d_6), 2.09 (s, 3H).

Iodo derivative **10k** was prepared in a similar manner to **10l** from **5k.**

2,6-Dimethyl-3-{4-[4-(trifluoromethoxy)phenoxy]phenyl}-5-(trifluoromethyl)pyridin-4(1*H*)-one (11l). A mixture of the iodo derivative **10l** (0.526 g, 1.04 mmol) and CuI (0.247 g, 1.3 mmol) in dry DMF (10 mL) was stirred and heated to 70 °C, and hexamethylphosphoramide (0.913 mL, 5.2 mmol) was added, followed by methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (0.668 mL, 5.2 mmol; Aldrich). The mixture was stirred and heated for a further 6 h and allowed to cool. Then 1 M aqueous NH_4Cl was added. The resulting precipitate was isolated by filtration, washed with 30% aqueous ammonia and then water, dried in air, then dissolved in acetone and the solution filtered through Celite and concentrated. The residual pale-brown solid was dissolved in MeOH and treated with activated charcoal; filtration, evaporation, and trituration with ethyl acetate provided **11l** (0.195 g, 41%) as a white crystalline solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.42 (bs, 1H), 7.39 (m, 2H), 7.20 (m, 2H), 7.13 (m, 2H), 7.04 (m, 2H), 2.41 (q, 3H), 2.10 (s, 3H).

3-Methoxy-2,6-dimethyl-5-{4-[3-(trifluoromethyl)phenoxy]-phenyl}pyridin-4(1*H*)-one (13k). To a solution of sodium methoxide prepared from sodium (0.048 g, 2.1 mmol) and MeOH (1 mL) were added the iodo derivative **10k** (0.266 g, 0.55 mmol) and CuI (0.015 g, 0.08 mmol). The mixture was heated at 110 °C for 18 h and cooled, and 1 M aqueous NH_4Cl was added. The resulting precipitate was recovered by filtration, washed with water, and subjected to chromatography on silica gel (75:1 to 20:1 CH_2Cl_2/MeOH eluant) to afford **13k** (0.088 g, 41%) as a white powder. ^{1}H NMR (300 MHz, CD_3OD): δ 7.54 (m, 1H), 7.39 (m, 1H), 7.30–7.24 (m, 4H), 7.10 (m, 2H), 3.78 (s, 3H), 2.36 (q, 3H), 2.16 (s, 3H). ESIMS *m/z*: 390 (MH^+), 388 (MH^-).

2,6-Dimethyl-3-nitro-5-{4-[4-(trifluoromethoxy)phenoxy]phenyl}-pyridin-4(1*H*)-one (12l). To a solution of 3-iodo-2,6-dimethyl-5-nitropyridin-4(1*H*)-one[44] (0.735 g, 2.5 mmol) in dry DMF (40 mL) were added the boronic acid **17** (1.15 g, 3.9 mmol) and powdered

potassium carbonate (2.07 g, 15 mmol). The suspension was deoxygenated by bubbling argon for 15 min. Then tris(dibenzylideneacetone)dipalladium(0) (0.25 g, 0.27 mmol) was added and the mixture stirred at 110 °C under argon for 24 h. After cooling to room temperature, the mixture was diluted with a 2:1 mixture of CH_2Cl_2/MeOH (90 mL) and filtered through a pad of Celite. The filter cake was washed with more of the CH_2Cl_2/MeOH mixture (3 × 30 mL). The combined washings were concentrated under reduced pressure, and the residue was suspended in water and acidified with 1 M aqueous HCl to pH 5. The resulting precipitate was collected by filtration, washed with water, dried, and purified by chromatography on silica gel (75:1 to 30:1 CH_2Cl_2/MeOH eluant) to give a slightly colored solid, which was triturated with ethyl acetate (20 mL) to afford **12l** (0.55 g, 52%) as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.91 (bs, 1H), 7.44–7.36 (m, 2H), 7.28–7.20 (m, 2H), 7.19–7.11 (m, 2H), 7.1–7.03 (m, 2H), 2.33 (s, 3H), 2.13 (s, 3H). ESIMS *m*/*z*: 421 (MH^+), 419 (MH^-).

2,6-Dimethyl-3-(pyrrolidin-1-ylmethyl)-5-{4-[4-(trifluoromethoxy)-phenoxy]phenyl}pyridin-4(1*H*)-one (14l). A mixture of the pyridone **5l** (0.1 g, 0.266 mmol), solid paraformaldehyde (0.15 g, 5 mmol), and pyrrolidine (1.5 mL, 18 mmol) in dry ethanol (10 mL) was heated under reflux for 24 h. After the mixture had cooled, the solvent was evaporated under reduced pressure and the resulting residue dissolved in ethyl acetate (50 mL) and washed with water (3 × 50 mL). The organic layer was extracted with 1 M aqueous HCl (3 × 5 mL), the aqueous acidic extracts were combined, and 4 M NaOH was added to adjust to pH > 9. The resulting precipitate was filtered, washed with water, and dried in vacuo to give **14l** (110 mg, 90%) as a white powder. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.94 (bs, 1H), 7.38 (m, 2H), 7.20 (m, 2H), 7.12 (m, 2H), 7.03 (m, 2H), 2.40 (bs, 4H), 2.30 (s, 3H), 2.07 (s,3H), 1.61 (bs, 4H). ESIMS *m*/*z*: 459 (MH^+).

(3*Z*)-4-(Dimethylamino)-3-{4-[4-(trifluoromethoxy)phenoxy]-phenyl}but-3-en-2-one (18l). To a solution of **3l** (300 mg, 0.97 mmol) in anhydrous toluene (6 mL) under a nitrogen atmosphere was added dropwise *N,N*-dimethylformamide dimethyl acetal (161 μL, 1.21 mmol, 1.25 equiv). The mixture was heated under reflux for 6 h after which further *N,N*-dimethylformamide dimethyl acetal (161 μL, 1.21 mmol, 1.25 equiv) added and heating under reflux continued for a further 2 h. After the mixture was cooled, the solvent was evaporated under reduced pressure and the residue coevaporated (2×) with MeOH. The residue was dried in vacuo to afford **18l** (364 mg, ∼100%) as an orange oil, used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (s, 1H), 7.15–7.21 (m, 4H), 6.95–7.04 (m, 4H), 2.73 (br s, 6H), 1.98 (s, 3H).

(1*Z*,4*Z*)-1-(Dimethylamino)-5-hydroxy-2-{4-[4-(trifluoromethoxy)-phenoxy]phenyl}hexa-1,4-dien-3-one (19l). To a solution of 1 M lithium bis(trimethylsilyl)amide in anhydrous THF (0.41 mL, 0.41 mmol, 1 equiv) at −78 °C under nitrogen atmosphere was added dropwise a solution of **18l** (150 mg, 0.41 mmol, 1 equiv) in anhydrous THF (1.5 mL). The mixture was stirred at −78 °C for 20 min and acetyl chloride (14.5 μL, 0.205 mmol, 0.5 equiv) in anhydrous THF (2 mL) added dropwise. The mixture was stirred and allowed to warm to room temperature over 18 h. Then 1 M aqueous NH_4Cl and ethyl acetate were added and the organic phase was separated, washed with brine, and dried ($MgSO_4$). The solvent was evaporated in vacuo and the residue subjected to column chromatography on silica gel (hexane/ethyl acetate eluant) to afford **19l** (57 mg, 68%) as a yellow oil consisting of a 65:45 mixture of the keto–enol and diketone tautomers, respectively. ^{1}H NMR (300 MHz, $CDCl_3$): δ 16.94 (br s, 1H, keto–enol), 7.67 (s, 1H), 7.13–7.23 (m, 4H), 6.95–7.07 (m, 4H), 4.94 (s, 1H, keto–enol), 3.42 (s, 2H, diketone), 2.75 (m, 6H), 2.13 (s, 3H, diketone), 1.89 (s, 3H, keto–enol).

(1*Z*,4*Z*)-1-(Dimethylamino)-6,6,6-trifluoro-5-hydroxy-2-(4-(4-(trifluoromethoxy)phenoxy)phenyl)hexa-1,4-dien-3-one (20l). To a suspension of potassium *tert*-butoxide (95 mg, 0.84 mmol, 2 equiv) in anhydrous THF (6 mL) at 0 °C under a nitrogen atmosphere was added a solution of **18l** (154 mg, 0.42 mmol) and methyl trifluoroacetate (74 μL, 0.74 mmol, 1.75 equiv) in anhydrous THF (3 mL). The resulting suspension was heated at reflux for 6 h, cooled in an ice bath, acidified with acetic acid (a few drops) and water added. The aqueous phase was separated and extracted with ethyl acetate, and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ and dried ($MgSO_4$). The solvent was evaporated to afford **20l** (190 mg, 90%) as an orange oil used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87 (s, 1H), 7.15–7.24 (m, 4H), 6.97–7.08 (m, 4H), 5.28 (s, 1H), 2.49–3.29 (m, 6H).

5-{4-[4-(Trifluoromethoxy)phenoxy]phenyl}-2-(trifluoromethyl)-4*H*-pyran-4-one (22l). A solution of **20l** (190 mg, 0.41 mmol) in 2-propanol (1 mL) and 1 M aqueous HCl (0.5 mL) was stirred at room temperature for 4 h. The mixture was partitioned between ethyl acetate and brine, the organic phase separated and dried ($MgSO_4$), and the solvent evaporated to afford **22l** (114 mg, 67%) as a yellow solid used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96 (s, 1H), 7.47–7.52 (m, 2H), 7.20–7.23 (m, 2H), 7.03–7.09 (m, 4H), 6.87 (s, 1H).

2-Methyl-5-{4-[4-(trifluoromethoxy)phenoxy]phenyl}-4*H*-pyran-4-one (21l). 21l was obtained from **19l** in a similar manner to **22l**, as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83 (s, 1H), 7.48–7.53 (m, 2H), 7.16–7.21 (m, 2H), 7.01–7.07 (m, 4H), 6.29 (s, 1H), 2.32 (s, 3H).

5-{4-[4-(Trifluoromethoxy)phenoxy]phenyl}-2-(trifluoromethyl)pyridin-4(1*H*)-one (27l). To a suspension of **22l** (109 mg, 0.26 mmol) in of 2-propanol (1 mL) was added 30% aqueous ammonia (25 μL, 0.39 mmol, 1.5 equiv), and the solution was heated under reflux for 48 h. Over the course of the reaction further 30% aqueous ammonia was added intermittently (0.78 mL, 12.2 mmol, 47 equiv). After cooling, the mixture was diluted with CH_2Cl_2 and the organic phase separated, washed with water (2×) and brine, dried ($MgSO_4$) and the solvent evaporated to afford **27l** (93 mg, 85%) as a yellow solid used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.42 (s, 1H), 7.52–7.57 (m, 2H), 7.15–7.20 (m, 3H), 7.01–7.09 (m, 4H). ESIMS *m*/*z*: 416.1 (MH^+).

26l was prepared in a similar manner to **27l** from **21l**.

Bromo derivatives **29l** and **30l** were prepared from **26l** and **27l**, respectively, following the procedure described for **7o**.

(3*Z*)-4-Hydroxy-3-{4-[4-(trifluoromethoxy)phenoxy]phenyl}-pent-3-en-2-one (23l). To a solution of **3l** (200 mg, 0.65 mmol) in acetic anhydride (3.2 mL, 34.2 mmol, 53 equiv), cooled on an ice bath under a nitrogen atmosphere, was added dropwise boron trifluoride diethyl etherate (515 μL, 4.06 mmol, 6.3 equiv). The solution was stirred at room temperature for 4 h and the solvent then evaporated under reduced pressure. The residue was dissolved in MeOH (5 mL), saturated aqueous sodium acetate (0.5 mL) added, and the mixture heated under reflux for 2 h. The solvent was evaporated and residue partitioned between ethyl acetate and water. The organic phase was separated, dried ($MgSO_4$), and evaporated to afford **23l** (208 mg, 92%) as an orange oil used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 16.67 (s, 1H), 7.13–7.23 (m, 4H), 6.99–7.08 (m, 4H), 1.92 (s, 6H).

2-Methyl-3-{4-[4-(trifluoromethoxy)phenoxy]phenyl}-6-(trifluoromethyl)-4*H*-pyran-4-one (25l). A solution of **23l** (128 mg, 0.36 mmol) and methyl trifluoroacetate (87 μL, 0.73 mmol, 2 equiv) in anhydrous THF (1.5 mL) was added to a suspension of potassium *tert*-butoxide (122 mg, 1.09 mmol, 3 equiv) in anhydrous THF (2.5 mL) at 0 °C under a nitrogen atmosphere. The mixture was heated at reflux for 5 h and cooled, and further potassium *tert*-butoxide (122 mg, 1.09 mmol, 3 equiv) and methyl trifluoroacetate (87 μL, 0.73 mmol, 2 equiv) were added. After heating under reflux for a further 24 h, the mixture was cooled on ice, acidified with acetic acid (a few drops), and diluted with water. The organic phase was separated and the aqueous residue extracted with ethyl acetate. The combined organic extracts were washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated under reduced pressure to afford (2*Z*,5*Z*)-1,1,1-trifluoro-2,6-dihydroxy-5-{4-[4(trifluoromethoxy)phenoxy]phenyl}hepta-2,5-dien-4-one (**24l**) (163 mg) as an orange oil, which was used in the next step without further purification. To a solution of **24l** (163 mg, 0.36 mmol) in 2-propanol (2 mL) was added 5 M HCl (2 mL). After being stirred at room temperature for 24 h, the mixture was partitioned between ethyl

acetate and water and the organic phase separated, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane/ethyl acetate eluant) to afford **25l** (19 mg, 12% overall) as a yellow oil used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19–7.23 (m, 4H), 7.03–7.10 (m, 4H), 6.80 (s, 1H), 2.32 (s, 3H). ESIMS *m/z*: 431.1 (MH^+).

28l was prepared from **25l** following the procedure described for **27l** and converted to the bromo derivative **31l** following the procedure described for **7o**.

2-Methyl-4-oxo-4*H*-pyran-3-yl Trifluoromethanesulfonate (32). K_2CO_3 (0.98 g, 7.1 mmol, 3 equiv) was added to a solution of 3-hydroxy-2-methyl-4*H*-pyran-4-one (300 mg, 2.4 mmol; Aldrich) in DMF (20 mL). After the mixture was stirred for 5 min, *N*-phenylbis(trifluoromethanesulfonimide) (850 mg, 2.4 mmol; Aldrich) was added. After being stirred for 30 min, the mixture was diluted with ethyl acetate and washed with 1 M aqueous NH_4Cl followed by 1 M NaOH. Evaporation afforded **32** (516 mg, 84%) as a white solid, used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71 (d, 1H, J = 5.9 Hz), 6.4 (d, 1H, J = 5.9 Hz), 2.44 (s, 3H). ESIMS *m/z*: 259.00 (MH^+).

2-Methyl-3-{4-[4-(trifluoromethoxy)phenoxy]phenyl}-4*H*-pyran-4-one (33l). To a mixture of **32** (100 mg, 0.4 mmol), 2 M aqueous Na_2CO_3 (1 mL), and tetrakis(triphenylphosphine)palladium(0) (27 mg, 0.02 mmol) in toluene (0.8 mL) was added a solution of the boronic acid **17** (150 mg, 0.5 mmol) in EtOH (0.8 mL). The mixture was stirred and heated at 90 °C for 90 min, cooled, diluted with diethyl ether, and washed with water. After evaporation the residue was chromatographed on silica gel (hexane/ethyl acetate eluant) to afford **33l** (95 mg, 68%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72 (d, 1H, J = 5.9 Hz), 7.24–7.19 (m, 4H), 7.09–7.02 (m, 4H), 6.29 (d, 1H, J = 5.9 Hz), 2.23 (s, 3H). ESIMS: *m/z* 363.10 (MH^+).

33l was converted to the pyridone derivative **34l** following the procedure described for **5o**. **34l** was converted to the bromo derivative **35l** following the procedure described for **7o**.

***P. falciparum* Inhibition in Vitro.** The activity of the test compounds against *P. falciparum* in vitro was determined using a modification of the semiautomated microdilution technique of Desjardins.[45] The following details relate to the procedure used at the Wellcome Laboratories using *P. falciparum* T9-96; in vitro data for *P. falciparum* 3D7A and FCR3-A were from a similar assay run at GSK Tres Cantos (see Supporting Information for details).

Compounds were dissolved in DMSO and subsequently diluted in culture medium (RPMI 1640) supplemented with 10% v/v human plasma. Serial 1:2 drug dilutions were prepared in triplicate on microtiter plates. To these were added culture medium supplemented with 10% v/v human plasma and type A Rhesus positive human erythrocytes infected with *P. falciparum* T9-96 to yield a hemocrit of 3% and a parasitemia of 0.25–0.55%. [^{3}H]Hypoxanthine was added to give a final concentration of 12.5–16 μCi/mL of culture. The plates were incubated at 37 °C in a modular incubator flushed with a mixture of 5% oxygen, 3% carbon dioxide, and 92% nitrogen. After incubation for 48 h particulate matter was harvested on fiber-glass strips and hypoxanthine incorporation determined by scintillation spectrophotometry. From the concentration–response curves, analyzed by nonlinear regression, the 50% inhibitory concentrations (IC_{50}) for each test compound could be calculated.

In Vivo Antimalarial Activity against *P. yoelii*. The blood schizontocidal activity of test compounds was determined using a modified 4-day suppressive assay. Mice (CD1) were infected intraperitoneally with about 3×10^6 *P. yoelii* (YM strain) parasitized erythrocytes. Drugs were formulated by ball milling overnight in 0.25% Celacol to form a fine suspension, which was kept at 4 °C. The test compounds were administered orally in seven doses over 4 days. On day 5 blood films were prepared and the extent of parasitemia was determined by microscopy; the degree of inhibition of parasitemia relative to control animals was calculated, and analysis of the dose–response curve yielded an ED_{50} (mg/kg) value.

Acknowledgment. We thank Drs. W. E. Gutteridge, D. J. Linstead, and V. S. Latter for their help and advice in the early phase of the work at Wellcome, and we thank Drs. A. P. Hill and E. Rahr for physical chemistry input. We also thank J. Pearce and L. Jones for their contributions in carrying out the antimalarial assays at Wellcome. The work at GSK Tres Cantos was supported by the Medicines for Malaria Venture.

Supporting Information Available: Additional experimental details, with spectroscopic and combustion analysis data for selected compounds and details of the procedure used for the in vitro *P. falciparum* assay at GSK Tres Cantos. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Talisuna, A. O.; Bloland, P.; D'Alessandro, U. History, Dynamics, and Public Health Importance of Malaria Parasite Resistance. *Clin. Microbiol. Rev.* **2004**, *17*, 235–254.
(2) Rosenthal, P. J. Antimalarial Drug Discovery: Old and New Approaches. *J. Exp. Biol.* **2003**, *206*, 3735–3744.
(3) Wiesner, J.; Ortmann, R.; Jomaa, H.; Schlitzer, M. New Antimalarial Drugs. *Angew. Chem., Int. Ed.* **2003**, *42*, 5274–5293.
(4) Mather, M. W.; Henry, K. W.; Vaidya, A. B. Mitochondrial Drug Targets in Apicomplexan Parasites. *Curr. Drug Targets* **2007**, *8*, 49–60.
(5) Painter, H. J.; Morrisey, J. M.; Mather, M. W.; Vaidya, A. B. Specific Role of Mitochondrial Electron Transport in Blood-Stage *Plasmodium falciparum*. *Nature* **2007**, *446*, 88–91.
(6) Mi-Ichi, F.; Takeo, S.; Takashima, E.; Kobayashi, T.; Kim, H. S.; Wataya, Y.; Matsuda, A.; Torrii, M.; Tsuboi, T.; Kita, K. Unique Properties of Respiratory Chain in *Plasmodium falciparum* Mitochondria. *Adv. Exp. Med. Biol.* **2003**, *531*, 117–133.
(7) Hudson, A. T.; Dickins, M.; Ginger, C. D.; Gutteridge, W. E.; Holdich, T.; Hutchinson, D. B.; Pudney, M.; Randall, A. W.; Latter, V. S. 566C80: A Potent Broad Spectrum Anti-Infective Agent with Activity against Malaria and Opportunistic Infections in AIDS Patients. *Drugs Exp. Clin. Res.* **1991**, *17*, 427–435.
(8) Looareesuwan, S.; Chulay, J. D.; Canfield, C. J.; Hutchinson, D. B. Malarone (Atovaquone and Proguanil Hydrochloride): A Review of Its Clinical Development for Treatment of Malaria. Malarone Clinical Trials Study Group. *Am. J. Trop. Med. Hyg.* **1999**, *60*, 533–541.
(9) Fry, M.; Pudney, M. Site of Action of the Antimalarial Hydroxynaphthoquinone, 2-[*trans*-4-(4′-Chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone (566C80). *Biochem. Pharmacol.* **1992**, *43*, 1545–1553.
(10) Kessl, J. J.; Meshnick, S. R.; Trumpower, B. L. Modeling the Molecular Basis of Atovaquone Resistance in Parasites and Pathogenic Fungi. *Trends Parasitol.* **2007**, *23*, 494–501.
(11) Mather, M. W.; Darrouzet, E.; Valkova-Valchanova, M.; Cooley, J. W.; McIntosh, M. T.; Daldal, F.; Vaidya, A. B. Uncovering the Molecular Mode of Action of the Antimalarial Drug Atovaquone Using a Bacterial System. *J. Biol. Chem.* **2005**, *280*, 27458–27465.
(12) Kessl, J. J.; Lange, B. B.; Merbitz-Zahradnik, T.; Zwicker, K.; Hill, P.; Meunier, B.; Palsdottir, H.; Hunte, C.; Meshnick, S.; Trumpower, B. L. Molecular Basis for Atovaquone Binding to the Cytochrome *bc1* Complex. *J. Biol. Chem.* **2003**, *278*, 31312–31318.
(13) Markley, L. D.; Van Heertum, J. C.; Doorenbos, H. E. Antimalarial Activity of Clopidol, 3,5-Dichloro-2,6-dimethyl-4-pyridinol, and Its Esters, Carbonates, and Sulfonates. *J. Med. Chem.* **1972**, *15*, 1188–1189.
(14) Fry, M.; Williams, R. B. Effects of Decoquinate and Clopidol on Electron Transport in Mitochondria of *Eimeria tenella* (Apicomplexa: Coccidia). *Biochem. Pharmacol.* **1984**, *33*, 229–240.
(15) Latter, V. S.; Hudson, A. T.; Richards, W. H. G.; Randall, A. W. Antiprotozoal Agents. U.S. Patent 5,053,418, 1991.
(16) Letsinger, R. L.; Jamison, J. D. Synthesis of Pyranones and Benzofluorenones from Ketones and Carboxylic Acids. *J. Am. Chem. Soc.* **1961**, *83*, 193–198.
(17) Soliman, G.; El-Sayed El-Kholy, I. The Pyrone Series. Part I. 2:6-Diaryl-4-pyrones. *J. Chem. Soc.* **1954**, 1755–1760.
(18) Heinzelman, R. V. *o*-Methoxyphenylacetone [2-Propanone, 1-(*o*-methoxyphenyl)-]. In *Organic Syntheses*; Rabjohn, N., Ed.; Wiley & Sons: New York, 1963; Collect. Vol. IV, pp 573–576.
(19) Kosugi, M.; Hagiwara, I.; Sumiya, T.; Migita, T. Arylation and 1-Alkenylation on α-Position of Ketones via Tributyltin Enolates Catalyzed by Palladium Complex. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 242–246.
(20) Sugai, S.; Ikawa, H.; Okazaki, T.; Akaboshi, S.; Ikegami, S. A Versatile Synthesis of Arylacetones from Aryl Halides and Acetylacetonate. *Chem. Lett.* **1982**, *11*, 597–600.

(21) Tyvorskii, V. I.; Bobrov, D. N.; Kulinkovich, O. G.; Aelterman, W.; De Kimpe, N. Synthesis of 3-(Trifluoromethyl)benzo[*c*][1,6]-naphthyridines from Substituted 4*H*-Pyran-4-ones via 4-Amino-5-aryl-2-(trifluoromethyl)pyridines. *Tetrahedron* **2000**, *56*, 7313–7318.

(22) Yeates, C. L. Wellcome Research Laboratories, U.K. Unpublished work, 1992.

(23) Katritsky, A. R.; Karelson, M.; Harris, P. A. Prototropic Tautomerism of Heteroaromatic Compounds. *Heterocycles* **1991**, *22*, 329–367.

(24) Boer, F. P. The Crystal Structure of Clopidol (3,5-Dichloro-2,6-Dimethyl-4-Pyridinol). *Acta Crystallogr.* **1972**, *28*, 3200–3206.

(25) Pudney, M.; Yeates, C.; Pearce, J.; Jones, L.; Fry, M. New 4-Pyridone Antimalarials Which Potentiate the Activity of Atovaquone (566C80). In *Abstracts and Programme*, Proceedings of the 13th International Congress for Tropical Medicine and Malaria, Pattaya, Thailand, Nov 29 through Dec 4, 1992; Tharavanij, S., Ed.; Mahidol University: Bangkok, Thailand, 1992; Vol. 2, p 149.

(26) Herreros, E.; Vidal, J.; Almela, M. J.; Roncalés, M.; Torres, P.; Lozano, S.; del-Reino, P.; Gómez de las Heras, F.; Gargallo-Viola, D. In Vitro Pharmacodynamics of Pyridone Derivatives. *Am. J. Trop. Med. Hyg.* **2006**, *75* (Suppl. 5), 50 (Program and Abstracts of the 55th Annual Meeting of the ASTMH).

(27) Jiménez-Diaz, M. B.; Mulet, T.; Gómez, V.; Viera, S.; Angulo-Barturen, I.; Jiménez, M.; Gargallo-Viola, D. *In Vivo* Antimalarial Efficacy against *P. yoelii* and *P. falciparum*of a 4(1*H*)-Pyridone Candidate for Clinical Development. *Am. J. Trop. Med. Hyg.* **2006**, *75* (Suppl. 5), 154. (Program and Abstracts of the 55th Annual Meeting of the ASTMH).

(28) Angulo-Barturen, I.; Jiménez-Diaz, M. B.; Castañeda, P.; Rullas, J.; Pinel, G.; Mulet, T.; Martínez, A.; Gómez de las Heras, F. M.; Pompliano, D. L.; Gargallo-Viola, D. Therapeutic Efficacy of 4(1*H*)-Pyridones in a *Plasmodium yoelii* Murine Model of Malaria, Preliminary Toxicity and Therapeutic Window in Mice. *Am. J. Trop. Med. Hyg.* **2005**, *73* (Suppl. 6), 117. (Program and Abstracts of the 54th Annual Meeting of the ASTMH).

(29) Ferrer, S.; Huss, S.; García, A.; Rodríguez, B.; Maraschiello, C.; Vilageliu, J.; Xiang, H.; Davis, C.; Gómez de las Heras, F. M.; Pompliano, D. L.; Gargallo-Viola, D. Single-Dose Pharmacokinetic Characterization Studies in Mice and Beagle Dogs of a New Family of Antimalarial Agents. *Am. J. Trop. Med. Hyg.* **2005**, *73* (Suppl. 6), 118. (Program and Abstracts of the 54th Annual Meeting of the ASTMH).

(30) Herreros, E.; Almela, M. J.; Roncalés, M.; Lozano, S.; Gómez de las Heras, F. M.; Pompliano, D. L.; Gargallo-Viola, D. Combination Studies of 4(1*H*)-Pyridone Derivatives with other Antimalarial Drugs. *Am. J. Trop. Med. Hyg.* **2005**, *73* (Suppl. 6), 118. (Program and Abstracts of the 54th Annual Meeting of the ASTMH).

(31) Herreros, E.; Roncales, M. C.; Almela, M. J.; Lozano, S.; Torres, P.; López, C.; Dei-Cas, E.; Gómez de las Heras, F. M.; Gargallo-Viola, D. Stage Specific Effects of Antimalarial 4(1*H*)-Pyridones. *Am. J. Trop. Med. Hyg.* **2005**, *73* (Suppl. 6), 118. (Program and Abstracts of the 54th Annual Meeting of the ASTMH).

(32) Herreros, E.; Almela, M. J.; Lozano, S.; Roncales, M. C.; Torres, P.; Gut, J.; Rosenthal, P. J.; Gómez de las Heras, F. M.; Pompliano, D. L.; Gargallo-Viola, D. In Vitro Antimalarial Activity of 4(1*H*)-Pyridone Derivatives. *Am. J. Trop. Med. Hyg.* **2005**, *73* (Suppl. 6), 117. (Program and Abstracts of the 54th Annual Meeting of the ASTMH).

(33) García-Perez, A.; Jiménez-Diaz, B.; Rodríguez, B.; Alvarez, A.; Mulet, T.; Viera, S.; Gómez, V.; Garuti, H.; Fernández, A.; Romanos, E.; Angulo-Barturen, I.; Ferrer, S.; Gargallo-Viola, D. Preliminary Pharmacokinetic/Pharmacodynamic Study of 4(1*H*)-Pyridone GW308678 in a Murine *Plasmodium yoelii* Model of Malaria. *Am. J. Trop. Med. Hyg.* **2007**, *77* (Suppl. 5), 147. (Program and Abstracts of the 56th Annual Meeting of the ASTMH).

(34) Ferrer, S.; García, A.; Jiménez-Diaz, M. B.; Rodríguez, B.; Romanos, E.; Mulet, T.; Viera, S.; Gomez, V.; Angulo-Barturen, I.; Sparrowe, J.; Xiang, H.; Davis, C.; Gómez de las Heras, F.; Pompliano, D. L.; Gargallo-Viola, D. Comparative Multi-Dose Pharmacokinetic Modelling and Determination of Nonrecrudescence Level for *Plasmodium yoelii* Infection in Mouse of Antimalarial 4(1*H*)-Pyridones. *Am. J. Trop. Med. Hyg.* **2006**, *75* (Suppl. 5), 155. (Program and Abstracts of the 55th Annual Meeting of the ASTMH).

(35) Xiang, H.; McSurdy-Freed, J.; Subbanagounder, G.; Hugger, E.; Han, C.; Bambal, R.; Ferrer, S.; Gargallo-Viola, D.; Davis, C. B. Preclinical Pharmacokinetics and Metabolism of GW308678, a Second Generation 4(1*H*)-Pyridone Anti-Malarial Mitochondrial Electron Transport Inhibitor. *Am. J. Trop. Med. Hyg.* **2006**, *75* (Suppl. 5), 248. (Program and Abstracts of the 55th Annual Meeting of the ASTMH).

(36) Xiang, H.; Surdy-Freed, J.; Moorthy, G. S.; Hugger, E.; Bambal, R.; Han, C.; Ferrer, S.; Gargallo-Viola, D.; Davis, C. B. Preclinical Drug Metabolism and Pharmacokinetic Evaluation of GW844520, a Novel Anti-Malarial Mitochondrial Electron Transport Inhibitor. *J. Pharm. Sci.* **2006**, *95*, 2657–2672.

(37) Gamo, F.-J.; Lafuente, M. J.; de Cozar, C.; Sanz, L. M.; Llergo, J. L.; Jimenez, L.; Gómez de las Heras, F. M.; Pompliano, D. L.; Vaidya, A. B.; García-Bustos, J. F. Antimalarial 4(1*H*)-Pyridones Selectively Inhibit Ubiquinol:Cytochrome *c* reductase (Respiratory Complex III) from Plasmodia. *Am. J. Trop. Med. Hyg.* **2005**, *73* (Suppl. 6), 272. . (Program and Abstracts of the 54th Annual Meeting of the ASTMH).

(38) Gamo, F.-J.; Sanz, L. M.; Mendoza, A.; Llergo, J. L.; Lopez, E. M.; Gómez de las Heras, F. M.; Pompliano, D. L.; Vaidya, A. B.; García-Bustos, J. F. Cytochrome *b* is the Primary Target of Antimalarial 4(1*H*)-Pyridones. *Am. J. Trop. Med. Hyg.* **2005**, *73* (Suppl. 6), 272. (Program and Abstracts of the 54th Annual Meeting of the ASTMH).

(39) Mendoza, A.; Gomez-Lorenzo, M.; Martínez-Hoyos, M.; Talavante, A.; Gómez de las Heras, F. M.; Pompliano, D. L.; Vaidya, A. B.; García-Bustos, J. F. Antimalarial 4(1*H*)-Pyridones Depolarize the Mitochondrial Membrane and Inhibit Oxygen Consumption in *Plasmodium yoelii*. *Am. J. Trop. Med. Hyg.* **2005**, *73* (Suppl. 6), 266. (Program and Abstracts of the 54th Annual Meeting of the ASTMH).

(40) Fry, M. Wellcome Research Laboratories, Beckenham, Kent, U.K. Unpublished work, 1992.

(41) Gamo, F.-J.; Sanz, L. M.; Lafuente, M. J.; Mendoza, A.; de Cozar, C.; Rodríguez, A.; Llergo, J. L.; Lopez, E. M.; Gómez de las Heras, F.; García-Bustos, J. F. Isolated Mitochondria from *Plasmodium falciparum* with Cytochrome *b* Mutations Present an Altered Sensitivity to Antimalarial 4(1*H*)-Pyridones. *Am. J. Trop. Med. Hyg.* **2007**, *77* (Suppl. 5), 49–50. (Program and Abstracts of the 56th Annual Meeting of the ASTMH).

(42) Morrisey, J. M.; Painter, H. J.; Gamo, F.-J.; García-Bustos, J. F.; Vaidya, A. B. Comparing Atovaquone and 4(1*H*)-pyridones, Antimalarial Compounds That Selectively Target the Parasite Mitochondrion. *Am. J. Trop. Med. Hyg.* **2005**, *73* (Suppl. 6), 31. (Program and Abstracts of the 54th Annual Meeting of the ASTMH).

(43) Hez-Deroubaix, S.; Bentchikou, E.; Blanc, C.; Gripon, P.; Belghiti, J.; Sauerwein, R. W.; Bourgouin, C.; Angulo-Barturen, I.; Ferrer, S.; Gargallo-Viola, D.; Druilhe, P. Strong Anti-Liver Stage Activity of a Novel 4(1*H*)-Pyridone Antimalarial Compound. *Am. J. Trop. Med. Hyg.* **2005**, *73* (Suppl. 6), 30. (Program and Abstracts of the 54th Annual Meeting of the ASTMH).

(44) Nantka-Namirski, P. Graebe−Ullmann Method in the Synthesis of Carbolines. II. Synthesis of 2,4-Dimethyl-alpha-carboline Derivatives. *Acta Pol. Pharm.* **1961**, *18*, 449–460.

(45) Desjardins, R. E.; Canfield, C. J.; Haynes, J. D.; Chulay, J. D. Quantitative Assessment of Antimalarial Activity in Vitro by a Semiautomated Microdilution Technique. *Antimicrob. Agents Chemother.* **1979**, *16*, 710–718.

JM0705760