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A new synthetic access to furo[3,2-*f*]chromene analogues of an antimycobacterial

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ABSTRACT

From the structure of 3,3-dimethyl-3*H*-benzofuro[3,2-*f*][1]-benzopyran, a selective in vitro inhibitor of mycobacterial growth, we have undertaken a structure–activity relationship investigation. We wish to report here our results on the use of [2+3] cycloadditions between 2-formylbenzoquinone and various enol derivatives to give various 4-formyl-5-hydroxy benzofurans. In the next step, an ytterbium triflate-catalysed reaction with 2-methylpropene allowed the preparation of various original furo[3,2-*f*]chromenes derivatives. Their biological evaluation on the growth of *Mycobacterium smegmatis* as well as *Mycobacterium tuberculosis* pointed out that some analogues were four times more active than the initial hit.

1. Introduction

As we previously reported, the dibenzofurans **1** and **2** were found out to be remarkably selective in vitro inhibitors of mycobacterial growth[1] (Fig. 1).

The first elements of structure–activity relationship were somewhat disappointing as the structural analogues made, bearing a benzofuro[3,2-*f*][1]-benzopyran ring system, had lower antimycobacterial activity or were also cytotoxic.[2] An attempt was also made to alleviate the high lipophilicity of compounds **1** and **2** by the preparation of an aza analogue, which met with some relative success.[3] In the course of preliminary work on the synthesis of tricyclic furo[3,2-*f*]chromenes analogues of **1**, we undertook the preparation of 2-aryl-6-hydroxybenzofuranes **5a**,**b** from the addition of the corresponding enamines **3a**,**b** on benzoquinone (**4**). However, if the preparation of **5a** was achieved by adapting a method previously reported[4] our attempt to extend this to the 4-pyridyl analogue **5b** met with some success although in a much lower 3.9% yield. This was followed by their alkylation with dimethylpropargylchloride to provide ethers **6a**,**b** which again proceeded in a low yield in the case of compound **6b**. These ethers were then thermally cyclized[5–7] to give the 2-phenyl and the 2-pyridyl analogues **7a** and **7b**. As described in the biological part of this manuscript, the level of antimycobacterial activity of the 4-pyridyl analogue **7b**, along with the very poor overall yield of this synthesis, drove us not only to study in depth this reaction but also to design better synthetic accesses to this compound and its analogues. From our work on the reaction of enamines with benzoquinone, we found out that the use of sodium metabisulfite was crucial as, in its absence, only minute amounts of **5b** were obtained along with quite intractable over-oxidized reaction products. Moreover, when using the more hindered enamine of 4-propionyl pyridine **3c**,[8] a far better 13.2% yield of the 2-pyridyl product **5c** was obtained. A very recent report describing the unprecedented addition of dihydrofurane on benzoquinone[9] catal-

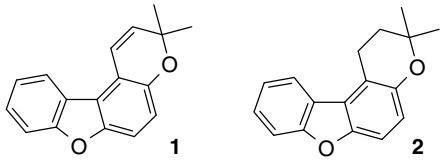

Figure 1.

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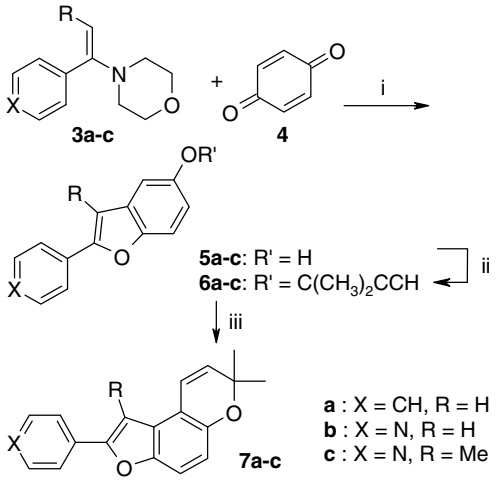
ysed by a remarkable boron-containing Lewis acid[10] would probably be of interest for further improvement of this particular reaction. Again, in the next step, the preparation of the propargylic ether only led to 45% of compound **6c**, which then provided the 3-methylated analogue **7c** in a 62% yield. In any case, the difficulties encountered in this study encouraged us even more to find alternative accesses to analogues of compounds **7a**–**c**.

As depicted in the Scheme 2, a different synthetic access was designed via a two-stage process. First, we investigated a [2+3] cycloaddition reaction between 2-formylbenzoquinone (**8**) and various enol ethers. This actually stemmed from the association of a report describing the reaction between many enolethers and 2-acetylbenzoquinone[11] along with more recent work illustrating the synthetic usefulness of 2-formylquinone.[12–14] From the ortho formylphenol-bearing cycloadducts arising from this reaction, we then made good use of our ytterbiumtriflate-catalysed addition of isobutene to *ortho*-quinonemethides.[15] This strategy allowed us to prepare many analogues of **7a**,**b**. Some of the scope of this reaction, along with the biological assays of the analogues prepared, are described in this paper.

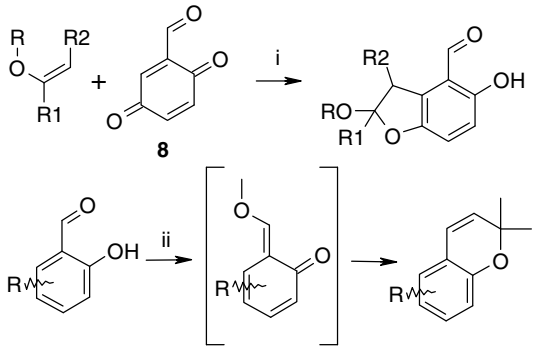
In order to prepare the 2-formylquinone (**8**), we used the reported DDQ oxidation of various 2,5-dihydrobenzaldehyde such as compound (**9**).[12,16] However, as the formylquinone **8** is not really stable,[17] we then directly added dihydropyran (**10**) in the reaction mixture. This procedure led to a 42% yield of the ortho formylphenol **11**. The study of the 1H NMR spectra of compound **11** shows that the value of $^3J_{HH}$ coupling constant between the hydrogens of carbons 4a and 9a is 6.1 Hz. This value is only compatible with a *cis* conformation, with a dihedral angle close to zero, which can result from a [2+3] cycloaddition.[10] Many trials were made to improve the reaction yield, and the following comments can be made from them. An excess of dihydropyran is important as only a 16% yield of **11** was obtained if only one equivalent was used. Trials in acetonitrile instead of ethyl acetate led to a similar yield of compound **11**. In this particular case, mixing DDQ and compound **8** followed by the immediate addition of dihydropyran (**10**) led to the same reaction yield. A small yield increase (56%) was achieved if the reaction was run under an inert atmosphere and if the cycloaddition step was allowed to run overnight. In any case, we then built the pyran ring of compound **12** in a 75% yield, using our ytterbiumtriflate-catalysed addition of isobutene on *ortho*-quinonemethides (Scheme 3).[15]



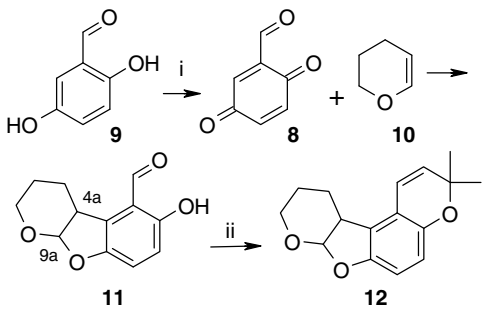
Scheme 1. Reagents and conditions: (i) a—EtOH; b—H_2O, $Na_2S_2O_5$; c—AcOH, reflux; (ii) $ClC(Me)_2CCH$, DBU, MeCN, $CuCl_2$; (iii) 1,3-dichlorobenzene, reflux.

The same route was investigated using other enol ethers. Extensive decomposition was the only result of the reaction between vinylethylether and formylbenzoquinone (**8**) generated in situ. This was unexpected as a cycloaddition between this ether and acetylbenzoquinone has been reported previously.[11] From tertbutylvinyl ether, traces of the expected compound were detected. From the more hindered 1-propenylethyl ether (**13**), an overall yield of 18% of the diastereoisomeric cycloadducts **14a** and **14b** was obtained. These diastereoisomers could actually be separated and their relative conformations could be assigned by their $^3J_{HH}$ coupling constants between the hydrogens of carbons 3 and 2. A small dihedral angle is reflected by the 6.1 Hz value for the *cis* isomer (**14a**) whereas a dihedral angle close to 90° leads to the 0.9 Hz value for the *trans* isomer (**14b**). In the next step, using the mixture of **14a** and **1b**, an unoptimised 11% yield of compound **15** was only obtained along with a diastereoisomeric mixture of compound **16** (27%) and the adduct **17** (11%). On the other hand, from 2-methoxypropene (**18**), the cycloaddition gave the cycloadduct **19** in a 46% yield, and the corresponding chromene-bearing analogue **20** was obtained in a 56% yield. When starting from diethoxyketene **21**, the crude cycloadduct **22** was obtained in a 78% yield (a pure sample could be obtained only after a recrystallisation with much loss). However, an extensive decomposition of this electron-rich benzofuran was the only thing observed at the next stage. Since the furan ring of **22** is far more reactive than isobutene, we suggest that an intermolecular addition on the intermediate quinonemethide takes place and leads to fairly complex polymeric material (Scheme 4).

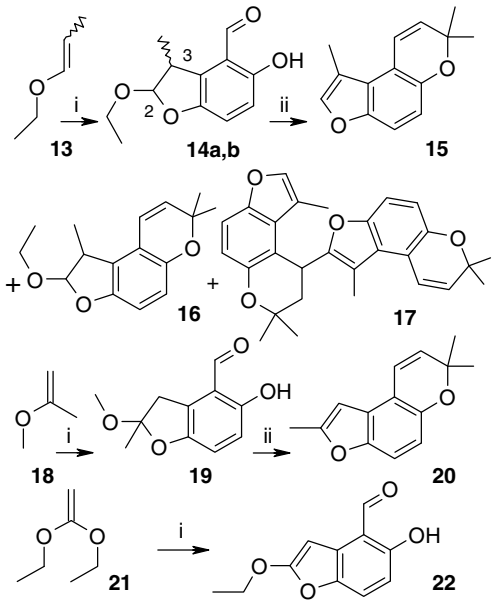
From a twofold excess of 1-(trimethylsiloxy)cyclohexene (**23**), a far better 37% overall yield of the previously[2] prepared compound **25** was obtained via the not so stable cycloadduct **24**, which was only partially purified before the next synthetic step. The use of the same procedure from the commercially available trimethyl(1-phenylvinyloxy)silane (**26**) led, again via the not fully purified cyc-



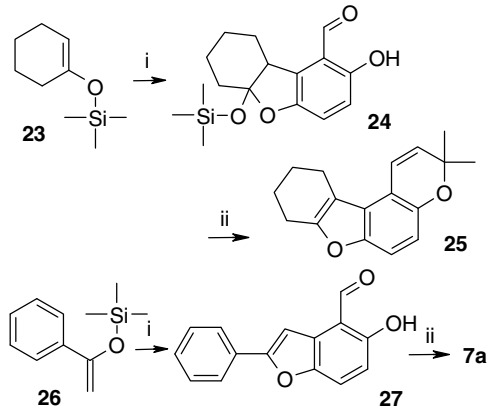
Scheme 2. Reagents and conditions: (i) see text below; (ii) 2-methylpropene, $Yb(OTf)_3$, $HC(OMe)_3$, dichloromethane, 25 °C, 60 h, then TSA, toluene, reflux, 1 h.



Scheme 3. Reagents and conditions: (i) DDQ, AcOEt, 25 °C, 1 h, then **10** overnight; (ii) 2-methylpropene, $Yb(OTf)_3$, $HC(OMe)_3$, dichloromethane, 25 °C, 60 h, then TSA, toluene, reflux, 1 h.



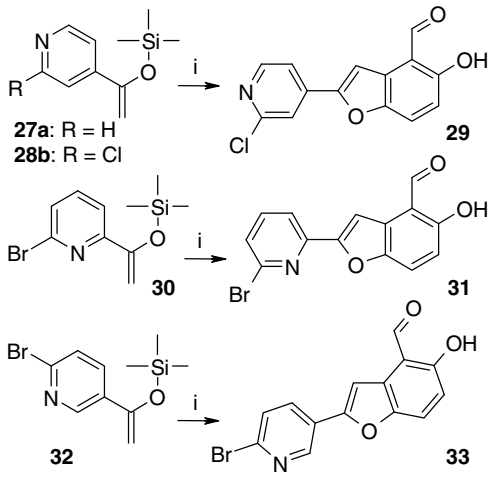
Scheme 4. Reagents and conditions: (i) a—compound **9**, DDQ, AcOEt, 2 h; b—enols; (ii) 2-methylpropene, $Yb(OTf)_3$, $HC(OMe)_3$, dichloromethane, 25 °C, 60 h, then TSA, toluene, reflux, 1 h.



Scheme 5. Reagents and conditions: (i) a—compound **9**, DDQ, AcOEt, 2 h; b—enols; (ii) 2-methylpropene, $Yb(OTf)_3$, $HC(OMe)_3$, dichloromethane, 25 °C, 60 h; then TSA, toluene, reflux, 1 h.

loadduct **27**, to the 2-aryl analogue **7a** in a 18% overall yield. This last unoptimized yield is actually identical with the one obtained using the synthetic path described in Schemes 1 and 5.

From this last result, we set out to prepare the silylenolether of 4-acetylpyridine which we obtained by altering a reported procedure.[18] Unexpectedly, from the resulting 4-pyridylsilylenolether (**28a**) or the enamine **3b**, despite repeated attempts, no cycloaddition reaction could be detected in the reaction mixture. On the other hand, we prepared the 2-chlorinated enolether (**28b**) and obtained the corresponding cycloaddition product **29** in a modest 8% yield. In view of this, we suggest that the nucleophilic nature of the pyridine ring may hamper the cycloaddition of **28a** via the occurrence of a Michael adduct,[19] which would block any other processes. This nucleophile nature would actually be lowered in the case of the 2-chlorine-bearing enolether **28b**. Moreover, from the more hindered bromine-bearing silylenolethers **30** and **32**, the cycloaddition reaction turned out to proceed much better, and the compounds **31** and **33** were obtained in 55% and 44% yield, respectively (Scheme 6).



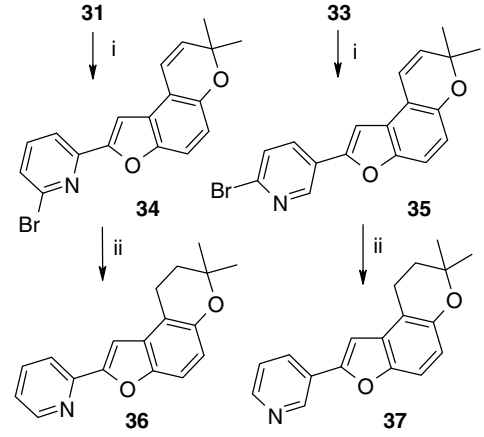
Scheme 6. Reagents and conditions: (i) a—compound **9**, DDQ, MeCN, 1 h; b—enols.

Unexpectedly, the construction of the pyran ring failed in the case of compound **29**. It appears that the highly insoluble property of this compound is at the source of this result. In fact, the NMR measurements of compound **29** had to be made in deuterated pyridine as it was only weakly soluble in DMSO. On the other hand, from the more soluble compounds **31**, the chromene-bearing analogue **34** was obtained in 55% yield. In the case of the compound **33**, the corresponding reaction product **35** was obtained in a 30% yield along with 44% of unreacted starting material. The reduction of compound **35** and **36** allowed us to obtain compounds **37** and **38**, the chromane-bearing isomers of compound **7b** (Scheme 7).

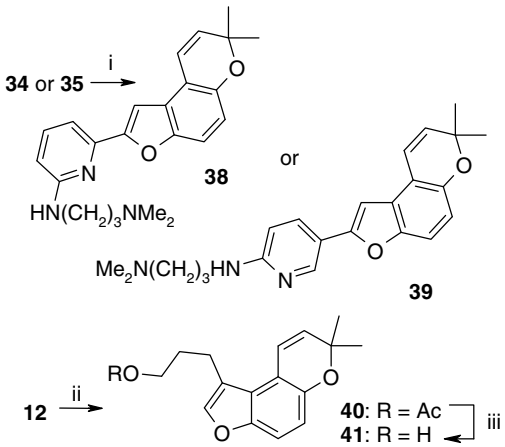
Further transformations were made. For instance, the bromine atom of compounds **34** or **35** could be displaced by amines to give compound such as the diaminated side-chain bearing analogue **38** and **39**. Moreover, the pyran ring of compound **12** could be opened thus providing an access to the tricyclic ester **40** and the corresponding alcohol **41** (Scheme 8).

2. Biological results and discussion

The antimycobacterial activity was screened on the fast growing saprophyte *Mycobacterium smegmatis* mc^2155 and on the virulent strain *Mycobacterium tuberculosis* H37Rv for all synthesised compounds, using the new Microdilution resazurin assay



Scheme 7. Reagents and conditions: (i) 2-methylpropene, $Yb(OTf)_3$, $HC(OMe)_3$, dichloromethane, 25 °C, 60 h, then TSA, toluene, reflux, 1 h; (ii) HCOOH, NH_3, Pd/C ethanol reflux.



Scheme 8. Reagents and conditions: (i) $H_2N(CH_2)_3NMe_2$, 120 °C; (ii) AcOH, HCl, reflux; (iii) MeONa, MeOH.

Table 1
In vitro biological assays

Compound	MIC_{95} (μg/mL) *M. smegmatis*	MIC_{95} (μg/mL) *M. tuberculosis*
Isoniazid	12	0.1
1	10	10
2	10	10
5a	8	125
5b	>50	>10
5c	>50	>10
6b	25	16
7a	>500	32
7b	3	2.5
7c	6.2	3
11	>125	125
12	125	250
20	>500	>500
25	>500	120
34	>50	>10
35	>50	>10
36	25	10
37	6.2	10
38	12.5	10
39	12.5	10
40	>500	>500
41	62	125

ND, not determined.

(MRA).[20] The minimal inhibitory concentration (MIC_{95}) is defined as the amount of compound required for >95% inhibition of bacterial growth (Table 1).

In conclusion, the design of an original synthetic access to furo[3,2-*f*]chromenes allowed easier preparations of compounds related to the 4-pyridyl derivative **7b**, which still displays the best antimycobacterial activity we have found so far.[1–3] Simple analogues featuring the core 7*H*-furo[3,2-*f*]chromen ring system, with substituents on carbon 2 or 3, have little or no activity. On the other hand, pyridyl-bearing compounds **36**–**39** have equal antimycobacterial activity although they are of a lesser interest or equal to the initial 2-pyridyl-bearing analogue **7b**. The bromopyridyl-bearing analogues **34** and **35** were of no interest although it is difficult to say whether it is due to their lack of solubility or their inherent lack of biological effect on mycobacteria. Aside from this, the replacement of this pyridyl by a phenyl (compound **7a**) or a methyl (compound **19**) as well as the introduction of an aliphatic side-chain on carbon 3 (compounds **40** and **41**) are disappointing. In conclusion, this work proved that it is possible to escape the most used propargylic ethers cyclization strategy to build chromene-bearing compounds. The use of a [2+3] cycloaddition between various enol ethers and formylbenzoquinone **8** allowed the positioning of a formyl moiety on the reaction products **11**, **14**, **19**, **24**, **27**, **31** and **33** perfectly set to ensure the regioselectivity of another (formal) [2+4] cycloaddition reaction with isobutene to build the pyran ring. However, this original synthetic access to furo[3,2-*f*]chromenes has inherent limits. This method requires mixing an oxidant (benzoquinone **8**) and enol ethers which are, as the initial reaction products, potential oxidation substrates. This aspect very likely explains the rather low yield we observed in the case of the compounds that are less inherently stable as compound **11**. The lack of solubility of some of the synthetic intermediates **29** pointed out a serious limitation of the second cycloaddition step used to build the pyran ring system. For these reasons, we then focused on the design of easier diversity-oriented synthesis of furo[3,2-*f*]chromenes-bearing analogues, which will be described in a forthcoming paper.

3. Experimental

^1H NMR and ^{13}C NMR spectra were recorded on a Bruker spectrometer at 400 and 100 MHz, respectively. Shifts (δ) are given in ppm with respect to the TMS signal and coupling constants (J) are given in Hertz. Column chromatography are performed over Merck silica gel 60 (0.035–0.070 mm), using a solvent pump operating at pressure between 2 and 7 bar (25–50 mL/mn), and an automated collecting system driven by a UV detector set to 254 nm unless stated otherwise (i.e., if ethylacetate was used then it would be set to 280 nm). Mass spectra were obtained on an Agilent 1100 serie LC/MSD system using an atmospheric electrospray ionisation system. High resolution mass spectroscopy (HRMS) was performed using a water Micromass Q-Tof with an electrospray ion source.

Biology

MIC determinations

MICs were determined using the new Microdilution Resazurin Assay (MRA).[20] Resazurin salt powder (Sigma) was prepared at 0.01% (wt/vol) in distilled water, sterilized by filtration through a 0.22 μm membrane and stored at 4 °C for a week. Drug stock solutions were prepared in dimethylsulfoxide (DMSO) at concentration of 50 mg/mL and frozen until used. The inocula were prepared from *M. tuberculosis* H37Rv and *M. smegmatis* mc^2155 strains grown in Dubos medium supplemented with 10% ADC enrichment (Difco). One microliter of twofold serial dilutions of each drug was prepared in 100 μL of Dubos medium directly in 96-well plates at concentrations from 500 to 0.9 μg/mL. Growth controls containing DMSO and isoniazid (from 1 μg/mL to 1 ng/mL) were also included. The plates were covered, sealed and incubated at 37 °C. After 48 h for *M. smegmatis* or 6 days for *M. tuberculosis*, 30 μL of resazurin solution was added to each well and plates were allowed to incubate at 37 °C for an additional 24 h. A change from blue to pink indicates reduction of resazurin and therefore bacterial growth. The MIC was defined as the lowest drug concentration that prevented this colour change.

2-Phenyl-benzofuran-5-ol (5a). To a solution of benzoquinone (**4**) (1.08 g, 10 mmol) in ethanol (15 mL, dried over 4 Å molecular sieves) enamine **3a** (1.89 g, 10 mmol), dissolved in ethanol (15 mL, dried over 4 Å molecular sieves), was added drop-wise. The reaction mixture was stirred at room temperature for 45 min. This was followed by the addition of water (50 mL) and then sodium metabisulfite (3 g, 15.8 mmol), the suspension was protected from air and stirred at room temperature overnight. The mixture was diluted with water and extracted with ethyl acetate (three times). The organic layer was dried over anhydrous so-

dium sulfate, filtered and evaporated to dryness. It was then dispersed in acetic acid (30 mL), and the suspension was heated at reflux for 1 h. The mixture was evaporated to dryness. Purification by chromatography of the residue over silica gel (dichloromethane) gave compound **5a** as an amorphous solid (0.58 g, 27.6%). Mp = 191 °C (lit.[4] = 189 °C). HRMS (ES) calcd for $C_{14}H_{10}O_2$: 211.0759, found: 211.0724. ^{1}H (DMSO): 6.76 (dd, 1H, *J* = 8.8 and 2.4), 6.95 (d, 1H, *J* = 2.4), 7.29 (s, 1H), 7.40 (m, 2H), 7.49 (m, 2H), 7.88 (m, 2H),9.24 (s, 1H). ^{13}C (DMSO-d_6): 102.8, 106.2, 112.2, 114.2, 125.3, 129.5, 129.8, 130.4, 130.8, 149.3, 154.3, 156.4.

2-(Pyridin-4-yl)benzofuran-5-ol(5b). To a solution of benzoquinone (**4**) (2.26 g, 20.9 mmol) in ethanol (30 mL, dried over 4 Å molecular sieves) enamine **3b**[21] (4 g, 20.2 mmol), dissolved in ethanol (30 mL, dried over 4 Å molecular sieves), was added drop-wise. The reaction was protected from air and stirred at room temperature for 45 min. This was followed by the addition of water (50 mL) and then sodium metabisulfite (4 g, 21.0 mmol). The suspension was protected from air and stirred at room temperature overnight before diluting in water and extracting it with ethyl acetate (three times). The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to dryness. It was then dispersed in acetic acid (100 mL) and the suspension was heated at reflux for 2.5 h. The mixture was evaporated to dryness. Purification by chromatography of the residue over silica gel (dichloromethane/ethanol, from 1% to 5%) gave the fluorescent compound **5b** as an amorphous solid (0.17 g, 3.9%). Mp >250 °C. HRMS (ES) calcd for $C_{13}H_9NO_2$: 212.0712, found: 212.0685. ^{1}H (DMSO-d_6): 6.85 (dd, 1H, *J* = 2.3 and 8.8), 7.00 (d, 1H, *J* = 2.3), 7.47 (d, 1H, *J* = 8.8), 7.61 (d, 1H, *J* = 0.8), 7.80 (dd, 2H, *J* = 1.6 and 4.6), 8.66 (dd, 2H, *J* = 1.6 and 4.6), 9.36 (s, 1H). ^{13}C (DMSO-d_6): 106.5, 106.6, 112.6, 115.8, 119.2, 129.9, 137.5, 149.8, 151.2, 153.7, 154.6.

2-(Pyridin-4-yl)benzofuran-5-ol (5c). Note: the following procedure can also be used with success for the synthesis of compound **5b**. To a solution of benzoquinone (**4**) (1.05 g, 9.7 mmol) in ethanol (30 mL, dried over 4 Å molecular sieves) enamine **3c**[8] (2 g, 9.7 mmol), dissolved in ethanol (20 mL, dried over 4 Å molecular sieves), was added. The reaction mixture was protected from air and stirred at room temperature for 1 h. Concentrated hydrochloric acid (1.37 mL, 14.55 mmol) was then added followed by water (15 mL). This was stirred for 10 min and neutralised with solid potassium carbonate (1.05 g, 7.6 mmol). More water (80 mL) was added along with sodium metabisulfite (3.72 g, 19.4 mmol). The suspension was protected from air and stirred at room temperature overnight before concentrating the ethanol under vacuum. The residue was diluted in water and extracted with ethyl acetate (three times). The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The resulting residue was then dispersed in acetic acid (100 mL), and the suspension was heated at reflux for 2.5 h. The mixture was evaporated to dryness. Purification by chromatography of the residue over silica gel (cyclohexane/ethyl acetate 2:3) gave the fluorescent compound **5b** as an amorphous solid, which was further purified by a recrystallisation in aqueous ethanol (0.29 g, 13.2%). Mp 229 °C. LC/MS (ES) *m/z* = 226 [M+H]$^+$. ^{1}H (DMSO-d_6): 2.46 (s, 3H), 6.91 (dd, 1H, *J* = 2.5 and 8.7), 7.42 (d, 1H, *J* = 8.7), 7.72 (m, 2H), 8.68 (m, 2H), 9.30 (s, 1H). ^{13}C (DMSO-d_6): 10.1, 105.1, 112.3, 115.9, 116.3, 120.6, 131.8, 138.4, 148.3, 149.5, 151.1, 154.4.

5-(2-Methylbut-3-yn-2-yloxy)-2-phenylbenzofuran (6a). 2-Phenyl-benzofuran-5-ol (**5a**) (0.57 g, 2.71 mmol) was dissolved in anhydrous acetonitrile (25 mL for 5.5 mmol; dried over 4A molecular sieves) under argon and cooled using an ice bath. To this solution were added DBU (0.63 mL, 4.2 mmol) and copper chloride dihydrate (4.6 mg, 0.027 mmol). The solution was maintained at 0 °C, and chlorobutyne (0.45 mL, 4.06 mmol) was added. After stirring for 5 h, the mixture was concentrated at reduced pressure, and the residue was partitioned between water and toluene. The organic fraction was washed with hydrochloric acid 1 N, sodium hydroxide 1 N, sodium hydrogenocarbonate 1 N and brine and dried over anhydrous sodium sulfate. Following a concentration to dryness, compound **6a** was obtained as a yellow amorphous solid (0.57 g, 77%) after purification by a chromatography over silica gel (cyclohexane/dichloromethane 1:1). Mp = 90 °C. LC/MS (ES) *m/z* = 277 [M+H]$^+$. ^{1}H (DMSO-d_6): 1.59 (s, 6H), 3.65 (s, 1H), 7.90 (dd, 2H, *J* = 0.9 and 8.5), 7.09 (dd, 1H, *J* = 2.4 and 8.8), 7.52 (m, 3H), 7.41 (m, 3H). ^{13}C (DMSO-d_6): 30.2, 73.6, 77.6, 87.0, 103.1, 111.8, 114.4, 120.6, 125.5, 129.7, 129.9, 130.0, 130.6, 151.5, 151.9, 156.9.

4-(5-(2-Methylbut-3-yn-2-yloxy)benzofuran-2-yl)pyridine (6b). This compound was obtained by following the procedure described for compound **6a** from compound **5b**. The resulting crude extract was purified by a chromatography over silica gel (dichloromethane/ethanol 100:0 then 98:2) to yield compound **6b** as a wax (33%). HRMS (ES) calcd for $C_{18}H_{16}NO_2$: 278.1181, found: 278.1154. ^{1}H (DMSO-d_6): 1.60 (s, 6H), 3.66 (s, 1H), 7.17 (dd, 1H, *J* = 2.4 and 8.9), 7.50 (d, 1H, *J* = 2.4), 7.61 (d, 1H, *J* = 8.9), 7.73 (s, 1H), 7.84 (dd, 2H, *J* = 1.6 and 4.5), 8.69 (dd, 2H, *J* = 1.6 and 4.5). ^{13}C (DMSO-d_6): 32.3, 75.8, 79.9, 89.0, 109.1, 114.5, 117.0, 121.5, 124.1, 131.5, 139.5, 153.4, 154.0, 154.2, 156.3.

4-(3-Methyl-5-(2-methylbut-3-yn-2-yloxy)benzofuran-2-yl)pyridine (6c). This compound was obtained by following the procedure described for compound **6a** from compound **5c**. The resulting crude extract was purified by a chromatography over silica gel (dichloromethane/ethanol 98:2 then 95:5) to yield compound **6c** as a wax (45%). HRMS (ES) calcd for $C_{14}H_{12}NO_2$: 226.0608, found: 226.0899. ^{1}H (DMSO-d_6): 1.60 (s, 6H), 2.48 (s, 3H), 3.63 (s, 1H), 7.31 (dd, 1H, *J* = 2.4 and 8.8), 7.46 (d, 1H, *J* = 2.4), 7.53 (d, 1H, *J* = 8.8), 7.76 (m (l), 2H), 8.71 (m (l), 2H). Note: upon heating, the ^{1}H pyridyl signals became much sharper. ^{13}C (DMSO-d_6): 10.1, 30.2, 73.8, 77.7, 87.0, 112.0, 113.7, 116.6, 121.1 (l), 122.1, 131.4, 138.0 (l), 148.9, 150.7, 151.0 (l), 151.9.

7,7-Dimethyl-2-phenyl-7*H*-furo[3,2-*f*]chromene (7a). Compound **6a** (0.53 g, 1.9 mmol) was heated to reflux in 1,2-dichlorobenzene (40 mL) for 12 h under an inert atmosphere. Purification of the residue, obtained after concentration to dryness, was made by a chromatography over silica gel (cyclohexane/dichloromethane 85:15) to give compound **7a** as a yellow amorphous solid (0.47 g, 89%). Mp = 82 °C. HRMS (ES) calcd for $C_{19}H_{16}O_2$: 277.1229, found: 277.1112. ^{1}H (DMSO-d_6): 1.39 (s, 6H), 5.85 (d, 1H, *J* = 9.8), 6.75 (dd, 2H, *J* = 16 and 9.8), 7.34 (dd, 1H, *J* = 0.6 and 8.7), 7.40 (m, 1H), 7.49 (m, 2H), 7.58 (d, 1H, *J* = 0.8), 7.89 (dd, 2H, *J* = 1.3 and 3.3). ^{13}C (DMSO-d_6): 28.1, 76.6, 101.1, 111.5, 113.6, 114.2, 119.9, 125.4, 126.7, 128.9, 129.7, 129.9, 130.7, 132.0, 150.2, 157.0.

4-(7,7-Dimethyl-7*H*-furo[3,2-*f*]chromen-2-yl)pyridine (7b). The same protocol used for compound **7a** was used with compound **6b**, and after a purification by chromatography over silica gel (dichloromethane/ethanol 95:5) compound **7b** was obtained as a wax (74%). HRMS (ES) calcd for $C_{18}H_{16}NO_2$: 278.1181, found: 278.1238. ^{1}H ($CDCl_3$): 1.49 (s, 6H), 5.74 (d, 1H, *J* = 9.8), 6.65 (dd, 1H, *J* = 0.3 and 9.8), 6.84 (d, 1H, *J* = 9.1), 7.24 (d, 1H, *J* = 0.9), 7.28 (m, 1H), 7.49 (m, 2H), 7.69 (m, 2H), 8.69 (m, 2H). ^{13}C ($CDCl_3$): 27.9, 76.5, 103.0, 111.3, 113.7, 115.7, 119.0, 119.4, 125.8, 131.6, 137.8, 149.1, 150.8, 150.9, 154.2.

4-(1,7,7-Trimethyl-7*H*-furo[3,2-*f*]chromen-2-yl)pyridine (7c). The same protocol used for compound **7a** was used with compound **6c**, and after a purification by chromatography over silica gel

(cyclohexane/ethyl acetate 3:1) compound **7c** was obtained as a solid (62%). Mp = 72 °C). HRMS (ES) calcd for $C_{19}H_{18}NO_2$: 292.1338, found: 292.1325. ^{1}H ($CDCl_3$): 1.48 (s, 6H), 2.63 (s, 3H), 5.72 (d, 1H, *J* = 9.9), 6.84 (d, 1H, *J* = 8.7), 6.96 (d, 1H, *J* = 8.7), 7.23 (d, 1H, *J* = 9.9), 7.63 (m, 2H), 8.70 (m, 2H). ^{13}C ($CDCl_3$): 12.3, 27.6, 75.6, 111.3, 115.1, 115.9, 116.1, 119.2, 121.3, 126.0, 131.4, 138.8, 149.1, 149.4, 150.1, 150.4.

6-Hydroxy-3,4,4a,9a-tetrahydro-2*H*-benzofuro[2,3-*b*]pyran-5-carbaldehyde (11). 2,5-Dihydroxybenzaldehyde (**9**) (0.5 g, 3.62 mmol) was dissolved in ethyl acetate (50 mL) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.82 g, 3.62 mmol) was added. The solution was protected from air and stirred for 4 h before the addition of dihydropyran (1.98 mL, 21.7 mmol). The mixture was stirred overnight, concentrated to dryness and the residue was purified by a chromatography over silica gel (dichloromethane/cyclohexane 1:1) to yield compound **11** (0.34 g, 42.7%) which was recrystallised in cyclohexane for analytical purposes. Mp = 134 °C). HRMS (ES) calcd for $C_{12}H_{15}O_4$: 221.0814, found: 221.0870. ^{1}H (DMSO): 1.22 (m, 1H), 1.51 (m, 2H), 2.12 (m, 1H), 3.49 (m, 1H), 3.71 (m, 1H), 5.81 (d, 1H, *J* = 6.1), 6.77 (d, 1H, *J* = 8.7), 7.01 (d, 1H, *J* = 8.7), 10.3 (s, 1H), 10.7 (s, 1H). ^{13}C (DMSO): 21.7, 25.3, 37.9, 62.0, 105.8, 116.9, 118.4, 119.8, 113.0, 150.0, 156.3, 191.8.

3,3-Dimethyl-9,10,11,11a-tetrahydro-3*H*,7a*H*-4,7,8-trioxa-benzo[*c*]fluorene (12). In a 60 mL round-bottomed thick glass tube fitted with a PTFE-faced screw-cap, compound **11** (0.15 g, 0.68 mmol) was dissolved in dichloromethane (40 mL). Trimethylorthoformate (0.111 mL, 1.02 mmol) and ytterbium triflate hydrate (0.021 g, 0.034 mmol) were then added. The resulting solution was cooled to 0 °C using an ice bath and 2-methylpropene was bubbled through the solution. The mass added was monitored by periodic weighting, thus 2-methylpropene (0.8 g, 14 mmol) was added. The glass tube was tightly closed and the solution was stirred at room temperature for 60 h. The resulting solution was cooled at 0 °C and this was diluted in dichloromethane and washed three times with a 1 N sodium hydrogen carbonate solution. The organic layer was dried over sodium sulfate and concentrated to dryness. The residue was dissolved in toluene (60 mL) and *p*-toluenesulfonic acid (0.002 g, 0.01 mmol) was added. This was heated to reflux for 1 h while allowing the methanol to distil from the reaction mixture by removing the water condenser four times (we suggest the much safer use of a distillation or a Dean-Stark apparatus for larger reaction scale). After concentration to dryness, the residue was purified by a chromatography over silica gel (dichloromethane/cyclohexane 7:3) to yield the compound **12** (0.17 g, 75%). Mp = 78 °C. HRMS (ES) calcd for $C_{16}H_{19}O_3$: 259.1334, found: 259.1299. ^{1}H ($CDCl_3$): 1.43 (s, 6H), 1.63 (m, 3H), 2.09 (m, 1H), 3.23 (m, 1H), 3.88 (m, 2H), 5.71 (d, 1H, *J* = 9.8), 5.88 (d, 1H, *J* = 6.4), 6.32 (d, 1H, *J* = 9.8), 6.60 (m, 2H). ^{13}C ($CDCl_3$): 21.1, 25.1, 27.8, 27.9, 37.4, 61.5, 75.7, 105.0, 109.7, 115.8, 118.4, 119.2, 126.9, 133.0, 147.2, 151.5.

2-Ethoxy-5-hydroxy-3-methyl-2,3-dihydrobenzofuran-4-carbaldehyde (14a,b). 2,5-Dihydroxybenzaldehyde (**9**) (1 g, 7.2 mmol) was dissolved in ethyl acetate (100 mL) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (1.64 g, 7.2 mmol) was added. The solution was protected from air and stirred for 2 h before the addition of ethyl-1-propenyl ether (4.78 mL, 43.2 mmol). The mixture was stirred overnight, concentrated to dryness and the residue was purified by a chromatography over silica gel (dichloromethane) to yield compounds **14a**,**b** (0.28 g, 17.5%) as a crude mixture of diastereoisomers. This was usually used directly in the next step leading to compounds **15**–**17**. In one instance we proceeded in their separation by a chromatography over silica gel (cyclohexane/dichloromethane 1:1), which led to pure compound **14a** (*cis* conformation) and compound **14b** (*trans* conformation) still containing about 5% of **14a**. Compound **14a**: ^{1}H ($CDCl_3$): 1.30 (d, 3H, *J* = 7.0), 1.43 (d, 3H, *J* = 7.2), 2.77 (m, 2H), 4.02 (m, 1H), 5.74 (d, 1H, *J* = 6.6), 6.78 (d, 1H, *J* = 8.8), 7.01 (d, 1H, *J* = 8.8), 10.17 (s, 1H), 10.85 (s, 1H). Compound **14b**: ^{1}H ($CDCl_3$): 1.24 (d, 3H, *J* = 7.1), 1.38 (d, 3H, *J* = 7.3), 3.65 (m, 2H), 3.92 (m, 1H), 5.34 (d, 1H, *J* = 0.9), 6.80 (d, 1H, *J* = 8.8), 7.04 (d, 1H, *J* = 8.8), 10.08 (s, 1H), 10.71 (s, 1H).

Preparation of compounds 15–17

The mixture of compounds **14a**,**b** was treated as described for the synthesis of compound **12**. Following a purification of the residue by a chromatography over silica (cyclohexane/dichloromethane, from 7:3 to 1:1), compounds **15**, **17** and **16** were obtained in that order of elution as described below.

1,7,7-Trimethyl-7*H*-furo[3,2-*f*]chromene (15). 11% as an oil. HRMS (ES) calcd for $C_{14}H_{15}O_2$: 215.1072, found: 215.1097. ^{1}H ($CDCl_3$): 1.47 (s, 6H), 2.37 (s, 3H), 5.69 (d, 1H, *J* = 9.9), 6.77 (d, 1H, *J* = 8.7), 6.89 (d, 1H, *J* = 9.9), 7.19 (d, 1H, *J* = 8.7), 7.35 (s, 1H). ^{13}C ($CDCl_3$): 10.0, 27.7, 75.7, 111.4, 114.1, 114.7, 116.2, 119.5, 124.6, 131.0, 143.2, 148.7, 151.3.

2,2′,7,7,7′,7′-Hexamethyl-8′,9′-dihydro-7*H*,7′*H*-1,9′-bifuro[3,2-*f*]-chromene (17). 11% as an oil. HRMS (ES) calcd for $C_{28}H_{29}O_4$: 429.2066, found: 429.2072. Extensive two dimensional NMR studies were undertaken to determine the structure of this compound. ^{1}H ($CDCl_3$): 1.38 (s, 6H), 1.42 (s, 3H), 1.44 (s, 3H), 1.71 (s, 3H), 1.89 (s, 3H), 2.13 (dd, 1H, *J* = 8.5 and 13.7), 2.31 (dd, 1H, *J* = 7.5 and 13.7), 4.79 (m, 1H), 5.62 (d, 1H, *J* = 9.9), 6.68 (d, 1H, *J* = 8.7), 6.81 (d, 1H, *J* = 9.9), 6.85 (d, 1H, *J* = 8.8), 7.08 (d, 1H, *J* = 8.7), 7.22 (s, 1H), 7.31 (d, 1H, *J* = 8.8). ^{13}C ($CDCl_3$): 9.9, 10.3, 25.4, 27.6, 27.9, 28.5, 32.0, 41.2, 73.9, 75.6, 110.6, 110.9, 112.1, 112.8, 113.3, 114.3, 115.9, 116.9, 119.4 126.3, 127.6, 130.6, 143.0, 148.8, 149.1, 150.2, 151.1, 157.6.

2-Ethoxy-1,7,7-trimethyl-2,7-dihydro-1*H*-furo[3,2-*f*]chromene (16). 27% as an oil; mixture of diastereoisomers. LC/MS (ES) *m*/*z* = 261 $[M+H]^+$ (no proper ionisation in HRMS). ^{1}H ($CDCl_3$): 1.24 (t, 3H, *J* = 7.1), 1.28 (t, 3H, *J* = 7.3), 1.40 (s, 6H), 3.27 (m, 1H), 3.63 (m, 1H), 3.93 (m, 1H), 5.16 (d, 0.2H, *J* = 1.1), 5.26 (d, 0.8H, *J* = 1.1), 5.66 (m, 1H), 6.34 (d, 1H, *J* = 9.8), 6.59 (m, 2H). ^{13}C ($CDCl_3$): 15.5, 18.6, 27.9, 27.95, 42.8, 64.3, 75.7, 109.6, 113.0, 115.8, 118.2, 119.3, 127.2, 132.7, 147.5, 152.0.

5-Hydroxy-2-methoxy-2-methyl-2,3-dihydrobenzofuran-4-carbaldehyde (19). 2,5-dihydroxybenzaldehyde (**9**) (0.25 g, 1.81 mmol) was dissolved in ethyl acetate (50 mL) and DDQ (0.41 g, 1.81 mmol) was added. The solution was protected from air and stirred for 90 min before the addition of 2-methoxypropene (**18**) (1 mL, 10.4 mmol). The mixture was stirred overnight, concentrated to dryness and the residue was purified by a chromatography over silica gel (dichloromethane/cyclohexane 4:6) to yield compound **19** (0.26 g, 68%) as an oil. LC/MS (ES): extensive decomposition. ^{1}H ($CDCl_3$): 1.74 (s, 3H), 3.36 (s, 3H), 3.37 (m, 1H), 3.52 (m, 1H), 6.80 (d, 1H, *J* = 8.8), 7.03 (d, 1H, *J* = 8.8), 10.00 (s, 1H), 10.66 (s, 1H). ^{13}C ($CDCl_3$): 23.9, 39.9, 50.3, 112.6, 117.0, 117.3, 119.4, 128.5, 151.9, 157.7, 194.1.

2,7,7-Trimethyl-7*H*-furo[3,2-*f*]chromene (20). The protocol described for compound **12** was used starting from **19** (0.24 g, 1.15 mmol), and the resulting residue was purified by a chromatography over silica gel (dichloromethane/cyclohexane 4:1) to yield compound **20** (0.14 g, 56%) as an oil %). HRMS (ES) calcd for $C_{14}H_{14}O_2$: 215.1072, found: 215.1089. ^{1}H ($CDCl_3$): 1.50 (s, 6H), 2.49 (s, 3H), 5.71 (d, 1H, *J* = 9.6), 6.41 (m, 1H), 6.59 (d, 1H, *J* = 9.6), 6.71 (d, 1H, *J* = 8.6), 7.17 (d, 1H, *J* = 8.6). ^{13}C ($CDCl_3$): 14.5, 27.9, 76.1, 100.8, 110.6, 112.5, 112.8, 120.0, 126.4, 130.8, 148.6, 150.3, 156.8.

2-Ethoxy-5-hydroxybenzofuran-4-carbaldehyde (22). 2,5-Dihydroxybenzaldehyde (**9**) (2 g, 14.5 mmol) was dissolved in ethyl acetate (100 mL) and DDQ (3.28 g, 14.5 mmol) was added. The solution was protected from air and stirred for 60 min before the addition of diethoxyketene (5.7 mL, 43.5 mmol). The mixture was stirred for 2 h, concentrated to dryness and the residue was purified by a chromatography (dichloromethane/cyclohexane 2:1) to yield compound **22** (2.35 g) as a crude solid which could be recrystallised in cyclohexane for analytical purposes. Mp = 89 °C. LC/MS (ES) m/z = 207 $[M+H]^+$ (no proper ionisation in HRMS). ^{1}H ($CDCl_3$): 1.54 (m, 3H), 4.33 (d, 2H, J = 7.2), 5.88 (s, 1H), 6.66 (d, 1H, J = 8.8), 7.72 (d, 1H, J = 8.8), 10.22 (s, 1H), 11.24 (s, 1H). ^{13}C ($CDCl_3$): 14.8, 67.8, 74.9, 110.1, 111.5, 119.3, 133.2, 142.6, 159.6, 166.2, 193.0.

3,3-Dimethyl-8,9,10,11-tetrahydro-3*H*-benzofuro[3,2-*f*]chromene (25). 2,5-Dihydroxybenzaldehyde (**9**) (0.1 g, 0.72 mmol) was dissolved in ethyl acetate (30 mL) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.16 g, 0.72 mmol) was added. The solution was protected from air and stirred for 45 min before the addition of 1-(trimethylsiloxy)cyclohexene (0.27 mL, 1.45 mmol). The mixture was stirred for two days, concentrated to dryness and the residue was purified by a chromatography over silica gel eluting with a dichloromethane and then dichloromethane/ethanol 98:2 to yield a mixture of compounds containing **24** and the product of the trimethylsilanol elimination (0.2 g). This chromatographic fraction was used without further purification following the protocol described for compound **12**. The resulting residue was purified by a chromatography over silica gel (dichloromethane/cyclohexane 15:85) to yield compound **25** (0.07 g, 37%) as a white solid with analytical data similar to the one we previously described[2] *Note*: by following the same protocol, 7,7-dimethyl-2-phenyl-7*H*-furo[3,2-*f*]chromene (**7a**) described above was obtained in a 18% overall yield via the partially purified compound **27**.

2-Chloro-4-(1-(trimethylsilyloxy)vinyl)pyridine (28b). A reaction tube (60 mL) was charged with 1-(2-chloropyridin-4-yl)ethanone[22] (3.1 g, 20.3 mmol), triethylamine (3.00 mL, 21.5 mmol) and dry toluene (30 mL) and sealed with a septum. To this was added drop-wise trimethylsilyl trifluoromethanesulfonate (4.0 mL, 22 mmol) via syringe. The mixture was heated at 80 °C for 5 h. After cooling, the upper toluene phase was isolated and volatiles were removed via rotary evaporation. The residue was distilled on a Kugelrohr apparatus under oil pump vacuum at 160 °C to give **28b** as a colourless liquid (3.79 g, 82% yield). ^{1}H ($CDCl_3$): 0.29 (s, 9H), 4.63 (d, 1H, J = 2.4), 5.10 (d, 1H, J = 2.4), 7.36 (d, 1H, J = 5.3), 7.47 (s, 1H), 8.33 (d, 1H, J = 5.3).

2-Bromo-6-(1-(trimethylsilyloxy)vinyl)pyridine (30). This compound was obtained from 1-(6-bromopyridin-2-yl)ethanone by following the procedure described for the preparation of compound **28**, to give **30** as a colourless liquid (92% yield). ^{1}H ($CDCl_3$): 0.30 (s, 9H), 4.62 (d, 1H, J = 1.1), 5.72 (d, 1H, J = 1.1), 7.37 (dd, 1H, J = 5.6, 3.1), 7.54 (d, 1H, J = 5.6), 7.55 (d, 1H, J = 3.1).

2-Bromo-5-(1-(trimethylsilyloxy)vinyl)pyridine (32). This compound was obtained from 1-(6-bromopyridin-3-yl)ethanone by following the procedure described for the preparation of compound **28**, to give **32** as a colourless liquid (6.44 g, 93% yield). ^{1}H ($CDCl_3$): 0.29 (s, 9H), 4.53 (d, 1H, J = 2.3), 4.95 (d, 1H, J = 2.3), 7.44 (d, 1H, J = 8.3), 7.71 (dd, 1H, J = 2.5, 8.3), 8.58 (d, 1H, J = 2.5).

2-(2-Chloropyridin-4-yl)-5-hydroxybenzofuran-4-carbaldehyde (29). A round-bottomed flask (100 mL) was charged with 2,5-dihydroxybenzaldehyde (0.75 g, 5.4 mmol) and dry acetonitrile (25 mL), and to this was added a solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (1.23 g, 5.4 mmol) in dry acetonitrile (25 mL). After 15 min, compound **28b** (1.23 g, 5.4 mmol) was added. After 5 h, volatiles were removed via rotary evaporation. Acetic acid (20 mL) was added to the residue, and the mixture was refluxed for 2 h. After cooling, volatiles were removed via rotary evaporation. Toluene (20 mL) was added, and again volatiles were removed via rotary evaporation. The residue was purified by a chromatography on silica gel (dichloromethane/ethanol 98:2). The resulting fraction was triturated in dichloromethane (20 mL) and filtered to give **29** as a bright yellow powder (0.12 g, 8% yield). Mp = 271 °C (decomp.). HRMS (ES) calcd for $C_{14}H_9{}^{35}ClNO_3$: 274.0271, found: 274.0251. ^{1}H (pyridine-d_5): 8.69 (d, 1H, J = 8.9), 9.17 (d, 1H, J = 5.2), 9.27 (d, 1H, J = 8.9), 9.40 (s, 1H), 9.85 (s, 1H), 10.01 (d, 1H, J = 5.2), 12.52 (s, 1H), 14.31 (s, 1H). ^{13}C (pyridine-d_5): one carbon signal probably occulted by the solvent signals, 108.8, 117.0, 118.4, 119.9, 121.2, 121.3, 129.9, 141.9, 152.5, 154.3, 156.3, 162.4, 192.5.

2-(6-Bromopyridin-2-yl)-5-hydroxybenzofuran-4-carbaldehyde (31). A round-bottomed flask (250 mL) was charged with 2,5-dihydroxybenzaldehyde (2.90 g, 20.1 mmol) and dry acetonitrile (75 mL), and to this was added a solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (4.76 g, 21.0 mmol) in dry acetonitrile (75 mL). After 15 min, compound **30** (5.71 g, 21.0 mmol) was added. After 12 h, volatiles were removed via rotary evaporation. Acetic acid (50 mL) was added to the residue, and the mixture was refluxed for 2 h. After cooling, volatiles were removed via rotary evaporation. Toluene (50 mL) was added, and again volatiles were removed via rotary evaporation. The residue was purified by a chromatography on silica gel (dichloromethane) to give **31** as a bright yellow powder (3.67 g, 55% yield). Mp = 179 °C. HRMS (ES) calcd for $C_{14}H_9{}^{79}BrNO_3$: 317.9766, found: 317.9779. ^{1}H (DMSO-d_6): 7.02 (d, 1H, J = 9.0), 7.62 (d, 1H, J = 7.7), 7.83 (d, 1H, J = 9.0), 7.86 (t, 1H, J = 7.7), 7.92 (d, 1H, J = 9.0), 7.94 (s, 1H), 10.50 (s, 1H), 10.81 (br s, 1H). ^{13}C (DMSO-d_6): 106.7, 114.8, 116.5, 120.0, 120.3, 127.8, 128.7, 141.3, 142.4, 149.5, 149.8, 156.7, 160.0, 191.0.

2-(6-Bromopyridin-3-yl)-5-hydroxybenzofuran-4-carbaldehyde (33). A round-bottomed flask (500 mL) was charged with 2,5-dihydroxybenzaldehyde (3.27 g, 23.7 mmol) and dry acetonitrile (75 mL), and to this was added a solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (5.38 g, 23.7 mmol) in dry acetonitrile (75 mL). After 15 min, compound **32** (6.44 g, 23.6 mmol) was added. After 12 h, volatiles were removed via rotary evaporation. Acetic acid (50 mL) was added to the residue, and the mixture was refluxed for 1 h. After cooling, volatiles were removed via rotary evaporation. Toluene (50 mL) was added, and again volatiles were removed via rotary evaporation. The residue was purified by a chromatography on silica gel (dichloromethane/ethanol 98:2). The resulting fraction was triturated in dichloromethane (20 mL) and filtered to give **33** as a bright yellow powder (3.29 g, 44% yield). Mp = 218 °C (decomp.). HRMS (ES) calcd for $C_{14}H_9{}^{79}BrNO_3$: 317.9766, found: 317.9793. ^{1}H (DMSO-d_6): 7.00 (d, 1 H, J = 8.9), 7.77 (d, 1H, J = 8.4), 7.82 (d, 1H, J = 8.9), 8.04 (s, 1H), 8.26 (d, 1H, J = 8.4), 8.96 (s, 1H), 10.51 (s, 1H), 10.74 (s, 1H). ^{13}C (DMSO-d_6): 105.3, 114.8, 115.8, 120.0, 126.1, 128.0, 129.3, 136.1, 142.2, 147.5, 149.5, 155.3, 160.0, 190.6.

2-Bromo-6-(7,7-dimethyl-7*H*-furo[3,2-*f*]chromen-2-yl)pyridine (34). A round-bottomed flask (250 mL) was charged with **33** (3.44 g, 10.8 mmol), trimethylorthoformate (6.00 mL, 54.8 mmol), ytterbium triflate hydrate (0.30 g, 0.48 mmol) and dry dichloromethane (150 mL, dried over 4 Å molecular sieves). After 30 min, the flask was cooled in an ice bath, and isobutylene (8.57 g, 153 mmol) was added to the solution. The flask was sealed with a rubber septum, and then the cold bath was removed. After

60 h, the solution was washed with sodium hydrogenocarbonate (150 mL, 1 M) and brine (150 mL) and dried over magnesium sulfate. After filtration, volatiles were removed via rotary evaporation. The residue was combined with dry toluene (30 mL) and *p*-toluene sulfonic acid (0.11 g) in a round-bottomed flask (100 mL), and heated at 115 °C for 1 h. After cooling, diethylether (100 mL) was added, and the mixture was washed with sodium hydrogenocarbonate (50 mL, 1 M) and brine (100 mL) and dried over magnesium sulfate. This was concentrated to dryness and the residue was purified by a chromatography on silica gel (dichloromethane/cyclohexane 1:1) to give compound **34** (1.98 g, 51% yield) as a colourless amorphous solid. Mp = 155–156 °C. HRMS (ES) calcd for $C_{18}H_{15}{}^{79}BrNO_2$: 356.0286, found: 356.0273. ^{1}H ($CDCl_3$): 1.43 (s, 6H), 5.67 (d, 1H, *J* = 9.8), 6.60 (d, 1H, *J* = 9.8), 6.77 (d, 1H, *J* = 8.8), 7.21 (d, 1H, *J* = 8.8), 7.35 (d, 1H, *J* = 7.8), 7.48 (s, 1H), 7.56 (t, 1H, *J* = 7.8), 7.76 (d, 1H, *J* = 7.8). ^{13}C ($CDCl_3$): 28.0, 76.4, 104.5, 111.3, 114.0, 115.6, 118.4, 119.5, 126.0, 127.3, 131.4, 139.3, 142.6, 149.1, 150.6, 151.1, 154.8.

2-Bromo-5-(7,7-dimethyl-7*H*-furo[3,2-*f*]chromen-2-yl)pyridine (35). A round-bottomed flask (500 mL) was charged with compound **33** (3.29 g, 10.3 mmol), trimethylorthoformate (6.00 mL, 54.8 mmol), ytterbium triflate hydrate (0.35 g, 0.57 mmol) and dry dichloromethane (300 mL, dried over 4 Å molecular sieves). After 30 min, the flask was cooled with an ice bath, and isobutylene (6.56 g, 117 mmol) was added to the solution. The flask was sealed with a rubber septum, and then the cold bath was removed. After 60 h, the mixture was filtered on a fritted funnel to recover some unreacted starting material (0.35 g). The filtrate was washed with sodium hydrogenocarbonate (200 mL, 1 M) and brine (200 mL) and dried over magnesium sulfate. After concentration to dryness, the residue was combined with dry toluene (40 mL) and *p*-toluene sulfonic acid (0.12 g) in a round-bottomed flask (250 mL), and heated at 115 °C for 1 h. After cooling, diethylether (100 mL) was added, and the mixture was washed with sodium hydrogenocarbonate (50 mL, 1 M) and brine (100 mL) and dried over magnesium sulfate. After a concentration to dryness, the residue was purified by a chromatography on silica gel (dichloromethane/ethanol from 100:0 to 98:2) to give, in order of elution, compound **35** (1.09 g, 30% yield) as a colourless amorphous solid, described below and more unreacted starting material (1.12 g). Mp = 159–160 °C. HRMS (ES) calcd for $C_{18}H_{15}{}^{79}BrNO_2$: 356.0286, found: 356.0286. ^{1}H NMR ($CDCl_3$): 1.48 (s, 6H), 5.73 (d, 1H, *J* = 9.8), 6.60 (d, 1H, *J* = 9.8), 6.81 (d, 1H, *J* = 8.8), 7.08 (s, 1H), 7.24 (d, 1H, *J* = 8.8), 7.54 (d, 1H, *J* = 8.3), 7.91 (dd, 1H, *J* = 2.1, 8.3), 8.80 (d, 1H, *J* = 2.1). ^{13}C NMR ($CDCl_3$): 27.9, 76.4, 101.5, 111.2, 113.6, 115.1, 119.4, 125.8, 126.3, 128.5, 131.5, 134.4, 141.7, 146.7, 149.2, 150.7, 152.9.

2-(7,7-Dimethyl-8,9-dihydro-7*H*-furo[3,2-*f*]chromen-2-yl)pyridine (36). A round-bottomed flask (25 mL) was charged with compound **34** (0.10 g, 0.29 mmol), ammonium formate (0.18 g, 2.8 mmol), 10% palladium over charcoal (0.0336 g, 0.0316 mmol) and ethanol (6 mL), and the mixture was refluxed for 4 h. Upon cooling, the mixture was filtered on a plug of Celite on a fritted funnel, and washed with dichloromethane (20 mL). The filtrate was concentrated to dryness and the residue purified by a chromatography on silica gel (ethylacetate/cyclohexane 1:3, UV monitoring at 280 nm) to give compound **36** (0.0422 g, 51% yield) as a colourless amorphous solid. Mp = 116–117 °C. HRMS (ES) calcd for $C_{18}H_{18}NO_2$: 280.1338, found: 280.1348. ^{1}H ($CDCl_3$): 1.39 (s, 6H), 1.90 (t, 2H, *J* = 6.8), 2.95 (t, 2H, *J* = 6.8), 6.82 (d, 1H, *J* = 8.8), 7.23 (m, 1H), 7.30 (d, 1H, *J* = 8.8), 7.43 (s, 1H), 7.77 (td, 1H, *J* = 1.7, 7.9), 7.89 (d, 1H, *J* = 7.9), 8.67 (d, 1H, *J* = 4.6). ^{13}C ($CDCl_3$): 20.4, 27.0, 32.7, 74.3, 103.7, 110.4, 113.0, 116.4, 120.0, 123.0, 128.7, 137.2, 149.8, 150.0, 150.1, 155.6 (one signal doubled).

3-(7,7-Dimethyl-8,9-dihydro-7*H*-furo[3,2-*f*]chromen-2-yl)pyridine (37). A round-bottomed flask (50 mL) was charged with **35** (0.076 g, 0.21 mmol), ammonium formate (0.048 g, 0.76 mmol), 10% palladium over charcoal (0.0220 g, 0.0207 mmol) and ethanol (10 mL), and the mixture was refluxed for 4 h. Upon cooling, the mixture was filtered on a plug of Celite on a fritted funnel, and washed with dichloromethane (20 mL). The filtrate was concentrated to dryness and the residue purified by a chromatography on silica gel (ethylacetate/cyclohexane 1:1, UV monitoring at 280 nm) to give compound **37** (0.0436 g, 73% yield) as a colourless amorphous solid. Mp = 129–130 °C. HRMS (ES) calcd for $C_{18}H_{18}NO_2$: 280.1338, found: 280.1356. ^{1}H ($CDCl_3$): 1.39 (s, 6H), 1.92 (t, 2H, *J* = 6.8), 2.94 (t, 2H, *J* = 6.8), 6.81 (d, 1H, *J* = 8.8), 7.06 (s, 1H), 7.28 (d, 1H, *J* = 8.8), 7.38 (dd, 1H, *J* = 4.0, 8.0), 8.12 (d, 1H, *J* = 8.0), 8.57 (d, 1H, *J* = 4.0), 9.11 (s, 1H). ^{13}C ($CDCl_3$): 20.4, 27.0, 32.7, 74.3, 101.5, 110.3, 112.6, 116.0, 124.0, 127.4, 128.6, 132.2, 146.5, 149.1, 149.8, 150.1, 153.4.

***N*^{1}-(6-(7,7-Dimethyl-7*H*-furo[3,2-*f*]chromen-2-yl)pyridin-2-yl)-*N*^{3},*N*^{3}-dimethylpropane-1,3-diamine (38).** A round-bottomed flask (5 mL) was charged with compound **34** (0.050 g, 0.14 mmol) and *N*^{1},*N*^{1}-dimethylpropane-1,3-diamine (0.30 mL, 2.4 mmol) and was heated at 120 °C for 60 h. After cooling, the residue was purified by a chromatography on a column of neutral alumina (1.2% wt/wt water, eluting with a dichloromethane/2 N ammonia in ethanol 95:5 mixture) to give compound **38** (0.051 g, 95% yield) as a wax. calcd HRMS (ES) calcd for $C_{23}H_{28}N_3O_2$: 378.2182, found: 378.2200. ^{1}H ($CDCl_3$): 1.47 (s, 6H), 1.84 (quintet, 2H, *J* = 6.9), 2.27 (s, 6H), 2.44 (t, 2H, *J* = 7.0), 3.41 (t, 2H, *J* = 6.7), 5.70 (d, 1H, *J* = 9.7), 6.37 (d, 1H, *J* = 8.3), 6.66 (d, 1H, *J* = 9.8), 6.77 (d, 1H, *J* = 8.8), 7.18 (d, 1H, *J* = 7.3), 7.25 (d, 1H, *J* = 8.7), 7.33 (d, 1H, *J* = 0.7), 7.49 (dd, 1H, *J* = 7.5, 8.1). ^{13}C ($CDCl_3$): 27.5, 27.9, 41.2, 45.8, 58.1, 76.3, 102.2, 107.0, 109.3, 111.2, 113.7, 114.4, 119.9, 126.2, 131.0, 138.2, 147.7, 148.8, 150.7, 157.4, 159.1.

***N*^{1}-(5-(7,7-Dimethyl-7*H*-furo[3,2-*f*]chromen-2-yl)pyridin-2-yl)-*N*^{3},*N*^{3}-dimethylpropane-1,3-diamine (39).** A round-bottomed flask (5 mL) was charged with **35** (0.083 g, 0.233 mmol) and *N*^{1},*N*^{1}-dimethylpropane-1,3-diamine (1 mL, 8 mmol) and was heated at 120 °C for 60 h. After cooling, the residue was purified by a chromatography on a column of neutral alumina (1.2% wt/wt water, eluting with a dichloromethane/2 N ammonia in ethanol 95:5 mixture) to give compound **39** (0.025 g, 28% yield) as a colourless amorphous solid. Mp >240 °C (decomp.) HRMS (ES) calcd for $C_{23}H_{28}N_3O_2$: 378.2182, found: 378.2167. ^{1}H NMR ($CDCl_3$): 1.47 (s, 6H), 1.84 (quintet, 2H, *J* = 6.6), 2.31 (s, 6H), 2.48 (t, 2H, *J* = 6.6), 3.43 (m, 2H), 5.69 (d, 1H, *J* = 9.7), 5.69 (m br, 1H), 6.46 (d, 1H, *J* = 8.7), 6.62 (d, 1H, *J* = 9.7), 6.71 (d, 1H, *J* = 8.6), 6.80 (s, 1H), 7.21 (d, 1H, *J* = 8.6), 7.83 (dd, 1H, *J* = 2.3, 8.7), 8.59 (d, 1H, *J* = 2.3). ^{13}C ($CDCl_3$): 26.9, 27.9, 41.5, 45.7, 58.3, 76.2, 96.8, 107.0, 110.7, 112.97, 113.02, 116.4, 119.9, 126.7, 130.8, 134.3, 145.9, 148.8, 150.1, 156.2, 159.0.

3-(7,7-Dimethyl-7*H*-furo[3,2-*f*]chromen-1-yl)propyl acetate (40). Compound **24** (0.3 g, 1.16 mmol) was dissolved in acetic acid (30 mL). Concentrated hydrochloric acid (1 mL) was added and this was heated to reflux for 1 h. The solution was concentred to dryness, and the residue was purified by a chromatography over silica gel (ethylacetate/cyclohexane 1:6, UV monitoring at 280 nm) to yield the compound **40** (0.32 g, 92%). Mp = 80 °C. LC/MS (ES) *m*/*z* = 318 $[M+NH_4]^+$. ^{1}H ($CDCl_3$): 1.47 (s, 6H), 2.04 (m, 2H), 2.10 (s, 3H), 2.85 (s, 3H), 2.85 (m, 2H), 4.20 (t, 2H, *J* = 6.3), 5.71 (d, 1H, *J* = 9.9), 6.70 (m, 2H), 7.20 (d, 1H, *J* = 8.7), 7.38 (s, 1H). ^{13}C ($CDCl_3$): 21.4, 22.3, 27.7, 28.7, 64.2, 75.7, 111.6, 114.3, 114.4, 119.5, 120.2, 123.7, 131.3, 142.9, 148.8, 151.4, 171.5.

3-(7,7-Dimethyl-7*H*-furo[3,2-*f*]chromen-1-yl)propan-1-ol(41). Compound **40** (0.15 g, 0.5 mmol) was dissolved in a 1 N solution of sodium methanolate in methanol (10 mL). This was stirred at 0 °C for 1 h and neutralized with a saturated solution of ammonium chloride and diluted in water. The aqueous phase was extracted with dichloromethane, the organic phase was washed with water, dried over sodium sulfate and concentrated to dryness to yield pure compound **41** (0.09 g, 70%) as an oil. LC/MS (ES). HRMS (ES) calcd for $C_{16}H_{19}O_3$: 259.1334, found: 259.1352. ^{1}H ($CDCl_3$): 1.47 (s, 6H), 2.00 (m, 2H), 2.88 (m, 2H), 3.80 (t, 2H, ***J*** = 6.2), 5.70 (d, 1H, ***J*** = 9.8), 6.78 (d, 1H, ***J*** = 8.7), 6.84 (d, 1H, ***J*** = 9.8), 7.20 (d, 1H, ***J*** = 8.7), 7.38 (s, 1H). ^{13}C ($CDCl_3$): 22.0, 27.7, 32.5, 62.6, 75.7, 111.5, 114.3, 114.4, 119.6, 120.7, 123.9, 131.2, 142.8, 148.8, 151.4.

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