Synthesis of novel inhibitors of electron transport

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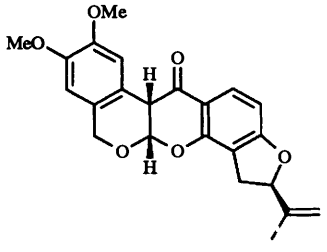
Molecular modelling comparisons of several known natural and synthetic inhibitors of electron transport, *e.g.* rotenone, papaverine, and piericidin A, suggested new 'hybrid' structures **8–12**, and relatives, as potential new inhibitors. Synthetic routes to these targets, some of which display significant biological activity, are outlined.

Control of insect pests remains a high priority for the agricultural and foodstuffs industries, since a substantial fraction of the world's vegetable crops is consumed by insects either in the field or in storage. Although synthetic pyrethroids currently dominate the insecticide market, there is evidence that insect resistance to these compounds is growing.[1] Also, the pyrethroids act as blockers of neurotransmission, and there appears to be increasing difficulty in licensing further new nerve agents for widespread application. Thus, there is a resurgence of interest in insecticidal compounds with a different biological action, such as inhibitors of electron transport.[2]

Rotenone **1**[3] and piericidin A **2**[4] are natural products with a



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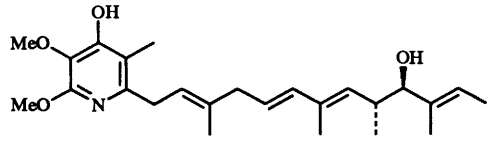

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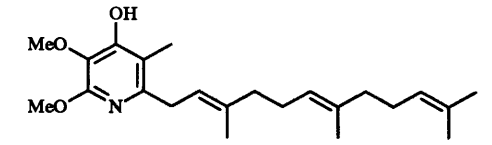
venerable history in crop protection and as tools in the elucidation of the biochemical mechanism of mitochondrial electron transport. Both compounds have been shown to block at complex I of the respiratory chain, specifically at NADH-ubiquinone dehydrogenase.[5] However their practical value as insecticides is limited by various disadvantages, such as rapid environmental breakdown, some adverse toxicology, and problems of supply from natural sources. Several studies of structure–activity relationships within the rotenoid group have been made using the available natural compounds and their transformation products,[6] and recently Crombie *et al.* have studied the activity of some synthetic variants on the core tetracyclic system of the rotenoids.[7] The area of synthesis of rotenoid analogues has been limited until recently[8] by the lack of short and versatile routes to the range of compounds necessary to clarify structure–activity relationships. The structural relationship between piericidin A and ubiquinone was noted by Jeng *et al.*,[5b] and aspects of the structural requirements for activity have been investigated.[9] The piericidin side chain could be replaced by a prenyl chain (forming the 'ubicidins' *e.g.* **3**) with little effect on overall activity. None of this work has so far proved fruitful in generating significant new insecticides for practical applications.

In order to make progress in this area, we looked for inspiration in structural comparisons between rotenone, piericidin A, and other compounds known or strongly suspected to act at the same location, including myxalamide D **4**,[10] papaverine **5**,[11] and the synthetic benzoimidazole **6**,[12] related to the ubicidins. In the first instance we used Dreiding models to seek structural connections and common features within this group, and it became clear that good correspondence with the A ring and the D/E rings of rotenone was possible, with rather loose contact in the B/C region. Tetrahydropapaverine **7** appeared to be a closer fit than the parent alkaloid, a relatively weak inhibitor. It was inferred that the ends of each inhibitor slotted into the active site with the central section acting as a spacer, holding the correct distance and orientation. Taking this as a working hypothesis we devised new 'hybrid' molecules with potential as electron transport inhibitors. These targets included the set of benzoimidazole–rotenone hybrids, **8–11** and the tetrahydropapaverine–rotenone hybrid **12**.

We then examined these structures more rigorously, carrying out molecular modelling studies using the SYBYL package.[13] Rotenone has the least conformational freedom of the group we wished to examine, and X-ray analysis has shown that it can exist in the crystalline state in two conformations differing in the B/C rings such that one form is approximately planar overall,[14] while the other bent along the line of the 6a,12a bond. This second form is adopted in solution, as is shown by NMR measurements.[15] Thus, we took rotenone minimised in the 'bent' conformation, and used a multifit routine to overlay potential inhibitors. In each case the energy of distortion, from the minimum energy conformation, required to achieve the best fit was measured. Since inhibitor receptor binding energies typically reach a maximum of 10 kcal mol^{-1},† we considered that distortion energies of less than 10 kcal mol^{-1} indicated a viable fit; values in the range 3.8–9.0 kcal mol^{-1} were calculated for **9–12** (5*S*,2*R*). The results of these studies are exemplifed in Figs. 1 and 2 which show the best fits between rotenone and benzoimidazole hybrid **9**, and between rotenone and the tetrahydropapaverine hybrid **12**, respectively. Encouraged by this analysis we embarked on the synthesis of the benzoimidazole set **8–11**, and of the tetrahydroisoquinoline **12**. In the latter case no substantial distinction between the four stereoisomers emerged from calculations, and so we decided not to plan a stereoselective route in the initial work, in the search for biological activity. In this paper we present the synthesis of these compounds, which were in the event all shown to have

† 1 cal = 4.184 J.



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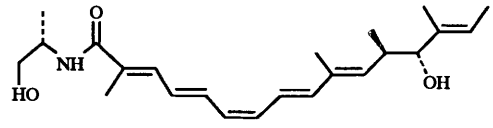

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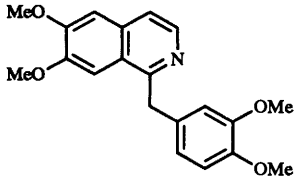

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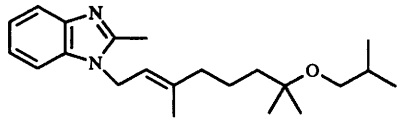

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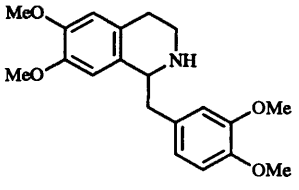

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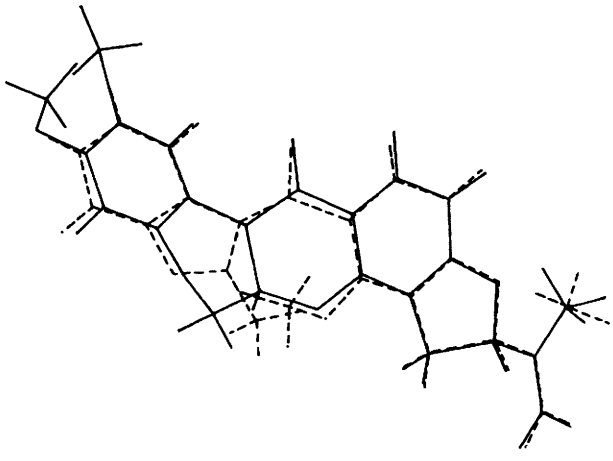


Fig. 1 Overlay of minimised rotenone **1** (——) with the benzoimidazole **9** (– – –), using the SYBYL software package [13]

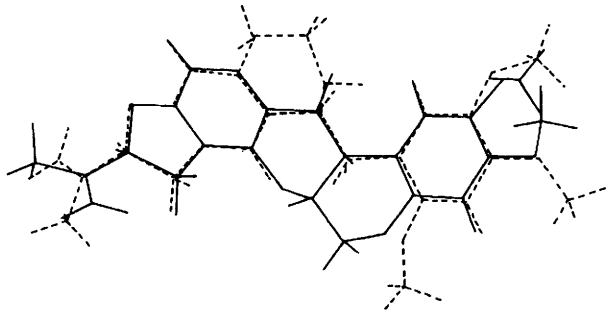
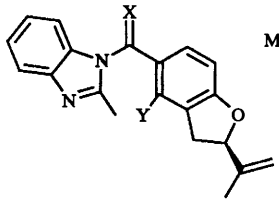
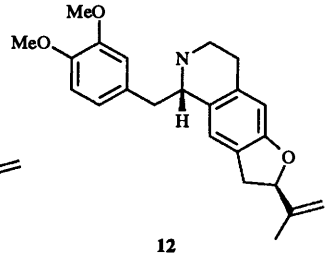


Fig. 2 Overlay of minimised rotenone **1** (——) with the tetrahydroisoquinoline **12** (– – –) using the SYBYL software package [13]



8 X = O, Y = OMe
9 X = H_2, Y = OMe
10 X = O, Y = H
11 X = H_2, Y = H



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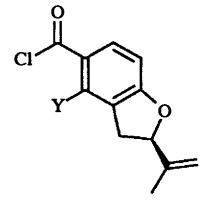
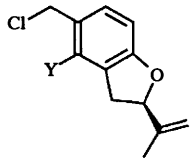
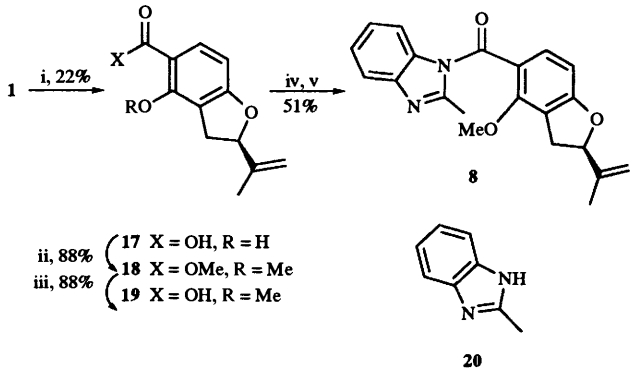


13 Y = OMe
14 Y = H



15 Y = OMe
16 Y = H

from commercial timbo resin) under alkaline conditions [17] in rather poor yield, but in one step and as a single enantiomer. Bis-*O*-methylation gave the ester **18**, as in Scheme 1, and



Scheme 1 *Reagents and conditions:* i, KOH, EtOH, 78 °C, 48 h; ii, MeI, K_2CO_3, MeCOMe, 56 °C, 20 h; iii, NaOH, EtOH, H_2O, 80 °C, 2 h; iv, $(COCl)_2$, DMF, DCM, 25 °C, 2 h; v, **20**, $CHCl_3$, 60 °C, 1 h

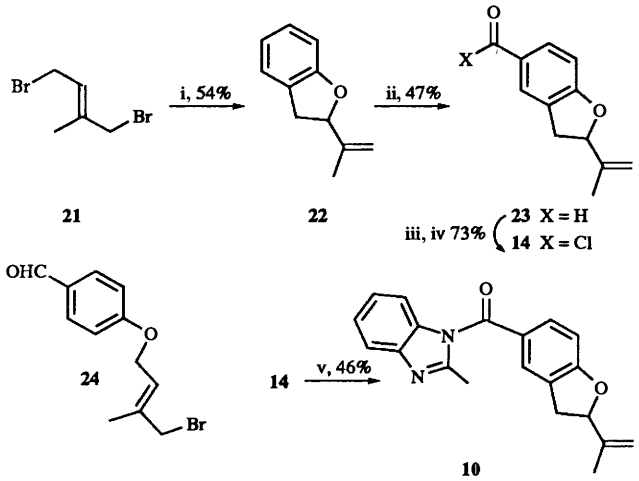
inhibitory action on mitochondrial electron transport; the biochemical aspects of this programme have been outlined elsewhere.[16]

Synthesis of *N*-aroyl- and *N*-arylmethyl-benzoimidazole targets

To synthesise the benzoimidazoles **8**–**11**, the acid chlorides **13** and **14**, and the related benzyl chlorides **15** and **16**, or their corresponding alcohols, were required. A convenient entry to the *o*-hydroxy acid set is tubaic acid **17**, available through oxidative degradation of rotenone **1** (isolated by crystallisation

ester hydrolysis formed the methoxy acid **19**. The corresponding acid chloride was formed in standard fashion and coupled with 2-methylbenzoimidazole **20** in chloroform at 60 °C, to afford the first required amide **8** in reasonable yield.

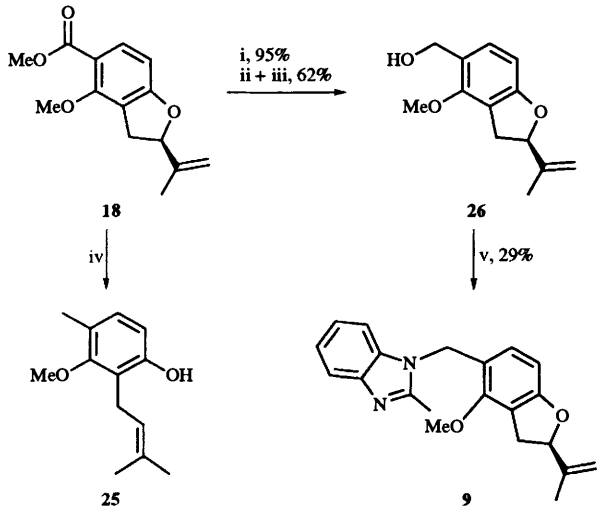
The 2-isopropenylbenzofuran acid chloride **14**, needed for the preparation of the amide **10**, was synthesised in racemic form as illustrated in Scheme 2. Lithium phenolate was treated with 1,4-dibromo-2-methylbut-2-ene **21**, using a variant on the conditions of the Nickl reaction,[18] to provide 2-isopropenyl-



Scheme 2 *Reagents and conditions:* i, PhOH, BuLi, Bu^{t}OH, PhMe, 100 °C, 22 h; ii, Ph(Me)NCHO, $POCl_3$, 90 °C, 1 h; iii, Ag_2O, H_2O, NaOH, 45 °C, 2 h; iv, $(COCl)_2$, DMF, DCM, 25 °C, 2 h; v, **20**, $CHCl_3$, 60 °C, 1 h

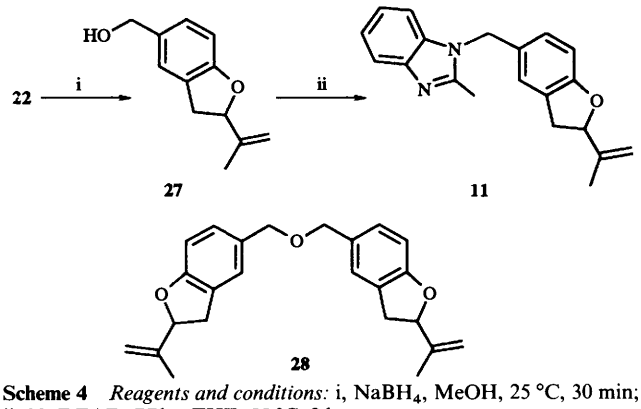
benzofuran **22**; this compound has been made by a different and low yielding method during synthesis of tremetone.[19] Vilsmeier formylation, following the procedure of Yamaguchi and co-workers[20] yielded the aldehyde **23** (fommanoxin), which was then oxidised with silver oxide to the desired acid. The derived acid chloride **14** was then treated with 2-methylbenzoimidazole to afford the second amide **10**, again in satisfactory yield. The Nickl reaction with *p*-hydroxybenzaldehyde was also investigated, to shorten the route, but although the desired benzofuran aldehyde **23** was formed it was accompanied by similar quantities of the *O*-alkylated material **24**, and conditions could not be found to eliminate this unwanted product.

The *N*-arylmethylbenzoimidazoles **9** and **11** of the planned set were readily accessed as shown in Schemes 3 and 4, although



Scheme 3 *Reagents and conditions:* i, NaOH, H_2O, EtOH, 80 °C, 2 h; ii, $ClCH{=}N^+Me_2Cl$; iii, $NaBH_4$, DMF, −60 °C, 30 min; iv, $LiAlH_4$, THF, 2 h, 0 °C; v, **20**, DEAD, PPh_3, THF, 55 °C, 21 h

not without some surprises. Thus, Scheme 3, reduction of the ester **18** with lithium aluminium hydride failed to give the expected alcohol **26**, but formed, as major product in a messy reaction, the furan cleaved phenol **25**, with the ester function fully reduced to methyl. A quinone methide intermediate is implicated. Lithium borohydride–diethyl ether–methanol gave similar results, and eventual success was achieved through hydrolysis of the ester to the acid **19**; activation of the acid

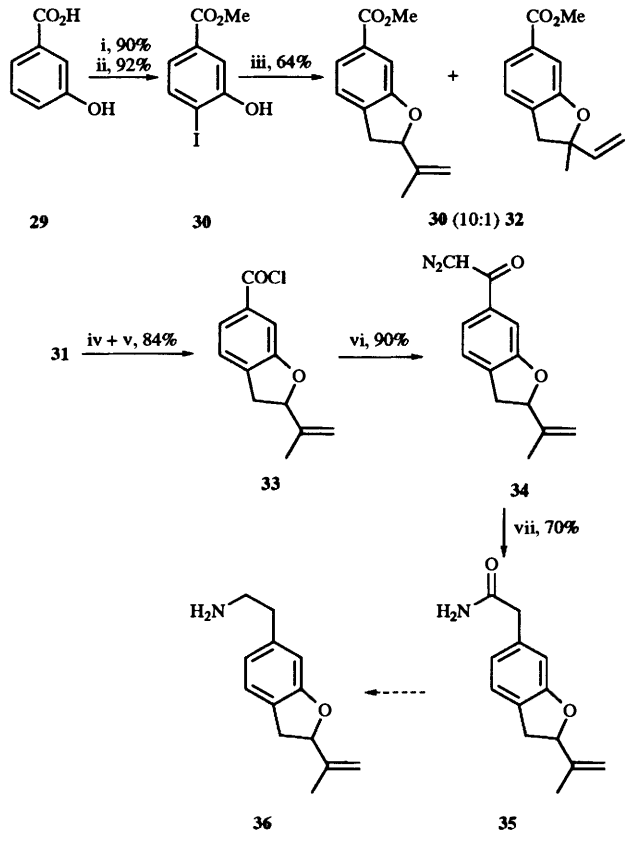


Scheme 4 *Reagents and conditions:* i, $NaBH_4$, MeOH, 25 °C, 30 min; ii, **20**, DEAD, PPh_3, THF, 55 °C, 2 h

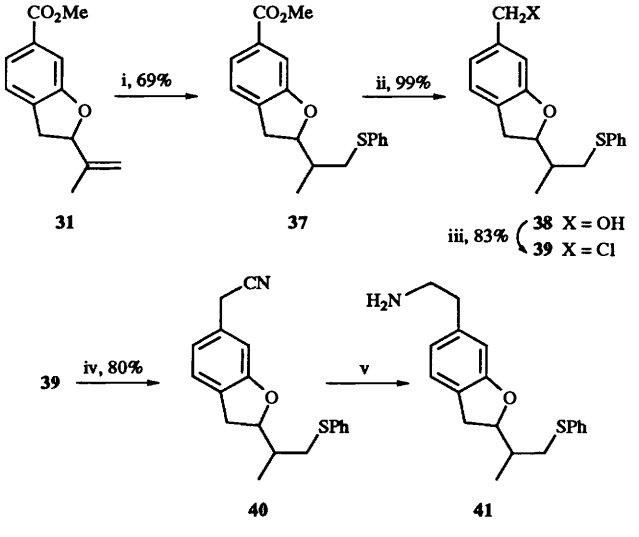
with (chloromethylidene)dimethylammonium chloride[21] then permitted reduction with sodium borohydride at −35 °C, providing alcohol **26** in good yield. The sensitivity of this alcohol to acid conditions made efforts to form the corresponding benzyl chloride unprofitable, and finally alkylation of 2-methylbenzoimidazole was effected directly with the benzyl alcohol **26** using Mitsunobu conditions, to deliver the required product **9** in modest yield. The analogous amine **11** was prepared similarly, using the benzyl alcohol **27**, obtained by reduction of the benzofuran aldehyde **22**. The latter reaction had to be carried out using excess sodium borohydride (20 equiv.) added in one portion; slow addition of portions of the reducing agent lead to formation of the dimer **28** in surprisingly high yield (up to 85%).

Synthesis of the furoisoquinoline targets

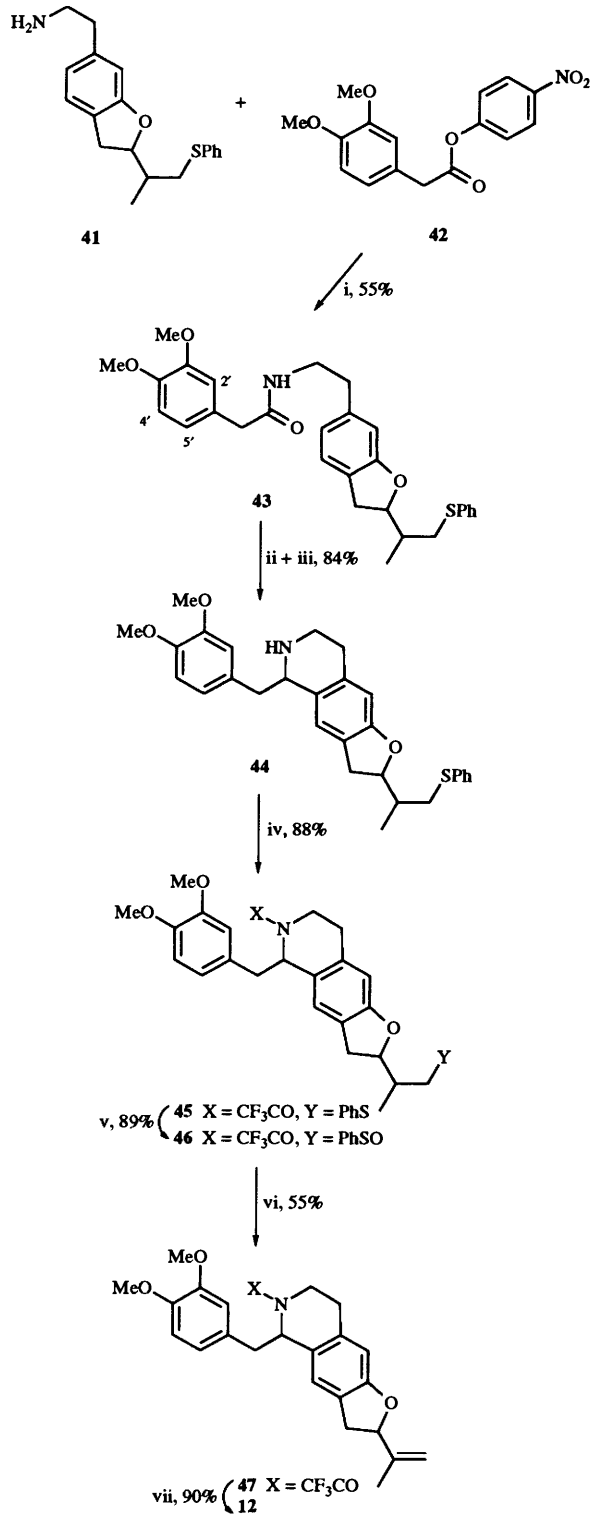
A more lengthy synthetic exploration was needed to access the furoisoquinoline **12**, and congeners. As stated above no attempt was made to design a stereospecific synthesis in the first instance. Our initial route was focussed on the arylethylamine **35**, Scheme 5, on which classical isoquinoline construction could be based. The approach work proceeded smoothly. Thus, iodination of 3-hydroxybenzoic acid **29** gave the desired 4-iodo acid in high yield. The corresponding ester **30** was treated with isoprene and palladium acetate, under the conditions devised by Larock *et al.*,[22] to produce the benzofuran **31** as the major regioisomer. Hydrolysis of the ester group in **31**, was followed by formation of the diazo ketone **34**, *via* the acid chloride **33** using standard methods. Wolff rearrangement with silver nitrate in ammonia afforded the arylacetamide **35** in good overall yield. However various attempts at reduction of the amide to the amine **36** were frustrated by the sensitivity of the allylic ether moiety to hydride transfer reagents with Lewis acidity, as noted above. It was eventually deemed necessary to protect the carbon–carbon double bond in the isopropenyl unit, and to this end the ester **31** was irradiated with benzenethiol and diphenyl disulfide to yield the sulfide **37** as a mixture of diastereoisomers. The ester group was then converted into the acetonitrile **40** through a conventional sequence, Scheme 6, starting with reduction of alcohol **38**, formation of the benzyl chloride **39**, and substitution by cyanide ion. Reduction of nitrile **40** by lithium aluminium hydride and aluminium chloride was complicated only by the relative instability of the amine **41**, and this product was treated, without further purification, with the *p*-nitrophenyl ester **42** to yield the amide **43**, Scheme 7, Bischler–Napierialski closure of the *N*-heterocyclic ring was effected with phosphorus oxychloride, the imine intermediate being then reduced *in situ* with borohydride to provide the furoisoquinoline **44**. The isoprenyl group was then regenerated through oxidation of the sulfide function to sulfoxide, after trifluoroacetylation of the secondary amine,



Scheme 5 *Reagents and conditions:* i, KI, I_2, NH_4OH, 10 min, 25 °C; ii, MeOH, H^+, 65 °C, 20 h; iii, isoprene, $Pd(OAc)_2$, NaOAc, DMF, 11 h, 100 °C; iv, Na_2CO_3, MeOH, 25 °C, 16 h; v, $SOCl_2$, 25 °C, 12 h; vi, CH_2N_2, Et_2O, 25 °C, 16 h; vii, $AgNO_3$, NH_4OH, 100 °C, 4 h



Scheme 6 *Reagents and conditions:* i, PhSH, PhSSPh, PhH, *hν*, 70 °C, 10 h; ii, $LiAlH_2$, Et_2O, 25 °C, 30 min; iii, $SOCl_2$, 70 °C, 30 min; iv, KCN, KI, MeCN, 60 °C; v, $LiAlH_4$, $AlCl_3$, Et_2O, 25 °C, 12 h



Scheme 7 *Reagents and conditions:* i, DBU, DCM, 25 °C, 12 h; ii, $POCl_3$, PhMe, 100 °C, 1 h; iii, $NaBH_4$, MeOH, 25 °C, 1 h; iv, TFAA, Py, DCM, 25 °C, 1 h; v, $NaIO_4$, MeOH, H_2O, 25 °C, 12 h; vi, PhMe, 100 °C, 72 h; vii, Na_2CO_3, MeOH, H_2O, 25 °C, 4 h

pyrolysis, and final deacylation to afford the required heterocycle for testing *i.e.* **44** ⟶ **45** ⟶ **46** ⟶ **47** ⟶ **12**.

The compounds described above, and some synthetic intermediates, were shown to be effective inhibitors of NADH dehydrogenase in a preparation of submitochondrial particles obtained from blow fly flight muscle, and these results have been reported.[16] Further, limited tests on the cytochrome *bf* complex in the photosynthetic apparatus have been carried out, and the furoisoquinoline sulfide **44** (FIQ) has been demonstrated to have the most powerful action known to date on the Qi site of this complex, completely without effect on the photosystems, the first example of such valuable specificity.[23] These results are of considerable significance in the study of the mechanism of photosynthesis, and clearly require the synthesis of single stereoisomers of FIQ, and of further relatives. This work is in progress.

Experimental

The following general procedures apply to all experiments unless stated otherwise. Melting points were determined on a Kofler hot stage microscope and are uncorrected. Optical rotations were determined at ambient temperatures using an Optical Activities AA-10 polarimeter and are given in units of 10^{-1} deg cm^2 g^{-1}; concentration (g cm^{-3}) and solvent are recorded in parentheses. Elemental analyses were determined using a Perkin-Elmer 240B elemental analyser. Mass spectra were recorded on a AE1 MS902 using electron impact (EI). Infra-red spectra were recorded on a Perkin-Elmer 1720X spectrometer and calibrated with polystyrene film. Nuclear magnetic resonance spectra were recorded using a 400 MHz Bruker AM400, a 270 MHz JEOL JNM EX270, a 250 MHz Bruker WM250, a 80 MHz Bruker WP80SY, a 90 MHz Perkin-Elmer R32 or a 90 MHz JEOL FX 90Q PFT spectrometer. The operating frequency and deuteriated solvent are recorded before chemical shift values which are quoted in parts per million (ppm), relative to tetramethylsilane (TMS). Observed coupling constants (J) are recorded in Hz with multiplicities designated as follows: s, singlet, d, doublet, t, triplet, q, quartet, m, multiplet and b, broad. For ^{13}C NMR, designations were determined by DEPT pulse sequences in conjunction with broad-band decoupling. Analytical thin-layer chromatography was undertaken on Merck Kieselguhr 60 F254 or aluminium oxide 60 F254, plates were visualised under UV (254 nm), or with iodine, or potassium permanganate or acidic anisaldehyde solutions. 'Drying' refers to the use of magnesium sulfate or sodium sulfate, and 'evaporation' implies rotary evaporation under reduced pressure.

(2*R*)-4-Hydroxy-2-isopropenyl-2,3-dihydrobenzofuran-5-carboxylic acid 17

To a hot solution of potassium hydroxide (20.0 g, 0.36 mol) in ethanol (120 cm^3) was added rotenone **1** (mp 166–167 °C, isolated from Derris resin) (10.5 g, 27 mmol), and the solution was refluxed at 78 °C for 48 h with vigorous mechanical stirring. The cooled solution was then poured into water (400 cm^3) and carbon dioxide was bubbled through for 1.5 h. The brown suspension was filtered off and the filtrate was acidified with hydrochloric acid (2 mol dm^{-3}) to congo red. The resulting precipitate was extracted with diethyl ether (2 × 200 cm^3), shaken with decolourising charcoal, dried and evaporated to dryness. Crystallisation from light petroleum (bp 40–60 °C) yielded the title compound (1.31 g, 22%) as a white solid, mp 128–129 °C (lit.,[17] mp 129 °C) (Found: C, 65.65; H, 5.6. $C_{12}H_{12}O_4$ requires C, 65.45; H, 5.45%) [Found: 220.074 (M^+, 28%). $C_{12}H_{12}O_4$ requires M, 220.074]; ν_{max}(KBr disc)/cm^{-1} 3427, 2980, 1657, 1626, 1466, 1306, 1252, 1180, 723 and 607; δ_H(80 MHz; $CDCl_3$) 1.78 (3 H, s, CH_3C=C), 2.98 (1 H, dd, J 7.8 and 16.0, 3-CHH), 3.38 (1 H, dd, J 9.5 and 15.9, 3-CHH), 4.94 (1 H, s, C=CHH), 5.09 (1 H, s, C=CHH), 5.32 (1 H, t, J 9.3, 2-CH), 6.43 (1 H, d, J 8.8, 7-H), 7.80 (1 H, d, J 8.7, 6-H) and 10.60 (1 H, s, ArOH).

Methyl (2*R*)-2-Isopropenyl-4-methoxy-2,3-dihydrobenzofuran-5-carboxylate 18

Methyl iodide (10 cm^3, 0.16 mol) was added to a solution of (2*R*)-4-hydroxy-2-isopropenyl-2,3-dihydrobenzofuran-5-carboxylic acid **17** (4.15 g, 18.9 mmol) and potassium carbonate (35.0 g, 0.25 mol) in dry acetone (300 cm^3), and the solution was refluxed for 24 h under nitrogen. Once cool the acetone was removed under reduced pressure and the residue was taken up into dichloromethane (100 cm^3). The solution was filtered and the filtrate was evaporated to dryness to yield the title compound (4.14 g, 88%) as a pale yellow oil (Found: C, 68.0; H, 6.7. $C_{14}H_{16}O_4$ requires C, 67.74; H, 6.45%) [Found: 248.103 (M^+, 100%). $C_{14}H_{16}O_4$ requires M, 248.105]; ν_{max}(film)/cm^{-1} 2950, 1722, 1602, 1466, 1323, 1265, 966 and 785; δ_H(250 MHz; $CDCl_3$) 1.76 (3 H, s, CH_3C=C), 3.16 (1 H, dd, J 7.9 and 15.8, C-CHH), 3.44 (1 H, dd, J 9.7 and 15.8, 3-CHH), 3.86 (3 H, s, OCH_3), 3.89 (3 H, s, CO_2CH_3), 4.93 (1 H, d, J 1.1, C=CHH), 5.11 (1 H, d, J 1.1, C=CHH), 5.25 (1 H, bt, J 9, 2-CH), 6.57 (1 H, d, J 8.5, 7-H) and 7.73 (1 H, d, J 8.4, 6-H); δ_C(22.5 MHz; $CDCl_3$) 17.3 (CH_3), 32.6 (CH_2), 51.8 (CH_3), 60.7 (CH_3), 87.2 (CH), 104.9 (CH), 112.6 (CH_2), 116.2 (C), 119.1 (C), 133.5 (CH), 143.5 (C), 158.0 (C), 165.1 (C) and 166.3 (C).

(2*R*)-2-Isopropenyl-4-methoxy-2,3-dihydrobenzofuran-5-carboxylic acid 19

A solution of methyl (2*R*)-2-isoprenyl-4-methoxy-2,3-dihydrobenzofuran-5-carboxylate **18** (0.71 g, 2.86 mmol) and sodium hydroxide (2.2 g, 55 mmol) in water (10 cm^3) and ethanol (10 cm^3) was refluxed for 45 min with stirring. Once cool the ethanol was removed under reduced pressure and the aqueous phase was acidified with hydrochloric acid (2 mol dm^{-3}, 50 cm^3). This mixture was then extracted with diethyl ether (3 × 30 cm^3), and the extracts were dried, and evaporated to dryness. Chromatography on flash silica with ethyl acetate–light petroleum (bp 40–60 °C) (1:4) as eluent yielded the *title compound* (0.64 g, 95%) as a white solid, mp 78–79 °C (Found: C, 67.1; H, 6.2. $C_{13}H_{14}O_4$ requires C, 66.66; H, 5.98%) [Found: 234.089 (M^+, 100%). $C_{13}H_{14}O_4$ requires M, 234.089]; ν_{max}(KBr disc)/cm^{-1} 3430, 2983, 1676, 1598, 1422, 1245, 1075, 907 and 782; δ_H(250 MHz; $CDCl_3$) 1.79 (3 H, s, CH_3C=C), 3.19 (1 H, dd, J 8.0 and 15.5, 3-CHH), 3.54 (1 H, dd, J 9.6 and 15.5, 3-CHH), 4.08 (3 H, s, OCH_3), 4.97 (1 H, d, J 1.0, C=CHH), 5.11 (1 H, d, J 1.0, C=CHH), 5.30 (1 H, bt, J 9, 2-CH), 6.67 (1 H, d, J 8.6, 7-H) and 8.02 (1 H, d, J 8.6, 6-H); δ_C(22.5 MHz; $CDCl_3$) 17.3 (CH_3), 33.4 (CH_2), 60.7 (CH_3), 87.4 (CH), 106.1 (CH), 113.2 (CH_2), 113.5 (C), 116.6 (C), 135.3 (CH), 143.1 (C), 156.9 (C), 166.5 (C) and 166.7 (C).

(2*R*)-(2-Isopropenyl-4-methoxy-2,3-dihydrobenzofuran-5-yl)-(2-methyl-1*H*-benzoimidazol-1-yl)methanone 8

Oxalyl chloride (0.14 cm^3, 1.16 mmol) and DMF (1 drop) were added to a solution of 2-isopropenyl-4-methoxy-2,3-dihydrobenzofuran-5-carboxylic acid **19** (0.16 g, 0.68 mmol) in dichloromethane (10 cm^3) at 0 °C and then stirred for 16 h at 25 °C under nitrogen. The dichloromethane was then removed under reduced pressure to yield the desired benzoyl chloride (0.16 g, 92%), which was dissolved in dry chloroform (15 cm^3) with 2-methyl-1*H*-benzoimidazole (0.08 g, 0.63 mmol) and refluxed at 62 °C for 1 h under nitrogen. The organic phase was then washed with saturated aqueous sodium hydrogencarbonate (2 × 10 cm^3) and brine (10 cm^3), then dried and evaporated to dryness. Chromatography on flash silica with ethyl acetate–dichloromethane (3:17) as eluent yielded the *title compound* (0.11 g, 51%) as a pale yellow oil [Found: 348.145 (M^+, 4%). $C_{21}H_{20}N_2O_3$ requires M, 348.147]; ν_{max}(film)/cm^{-1} 2924, 1701, 1598, 1455, 1314, 907 and 858; δ_H(80 MHz; $CDCl_3$) 1.80 (3 H, s, CH_3C=C), 2.69 (3 H, s, CH_3CN), 3.11 (1 H, dd, J 8.0 and 15.6, 3-CHH), 3.51 (1 H, dd, J 9.4 and 15.6, 3-CHH), 3.57 (3 H, s, OCH_3), 4.97 (1 H, s, C=CHH), 5.12 (1 H, s, C=CHH), 5.30 (1 H, bt, J 9, 2-CH), 6.65 (1 H, d, J 8.3, 7-H) and 6.88 (5 H, m, 5 × ArH); δ_C(100 MHz; $CDCl_3$) 17.1 (CH_3), 17.2 (CH_3), 33.2 (CH_2), 59.7 (CH_3), 86.7 (CH), 104.9 (CH), 113.0 (CH_2), 113.0 (CH), 116.2 (C), 119.1 (C), 119.2 (CH), 123.7 (CH), 123.9 (CH), 132.0 (CH), 133.64 (C), 142.2 (C), 142.9 (C), 153.1 (C), 156.0 (C), 165.9 (C) and 166.6 (C).

2-Isopropenyl-2,3-dihydrobenzofuran 22

Lithium hydride (2.4 g, 0.3 mol) was added to a solution of phenol (8.2 g, 0.1 mol) in toluene (120 cm^3) and stirred at 70 °C under nitrogen for 2 h. Then 1,4-dibromo-2-methylbut-2-ene (22.8 g, 0.1 mmol) was added and the mixture was refluxed at

110 °C for 18 h. The cooled reaction mixture was quenched with sulfuric acid (4 mol dm^{-3}, 50 cm^3) and the organic layer was collected and washed with water (2 × 50 cm^3), aqueous sodium hydroxide (2 mol dm^{-3}; 2 × 50 cm^3) and brine (20 cm^3), dried and then evaporated to dryness. Chromatography on flash silica with ethyl acetate–light petroleum (bp 40–60 °C) (1 : 99) yielded the *title compound* (8.64 g, 54%) as a colourless oil [Found: 160.086 (M^+, 84%). $C_{11}H_{12}O$ requires *M*, 160.089]; ν_{max}(film)/cm^{-1} 2918, 1595, 1480, 1461, 1230 and 749; δ_H(400 MHz; $CDCl_3$) 1.77 (3 H, s, CH_3C=C), 3.03 (1 H, dd, *J* 8.3 and 15.6, C-C*H*H), 3.33 (1 H, dd, *J* 9.5 and 15.6, 3-CH*H*), 4.91 (1 H, s, C=C*H*H), 5.09 (1 H, s, C=CH*H*), 5.16 (1 H, bt, *J* 8, 2-CH), 6.79–6.85 (2 H, m, 2 × ArH) and 7.09–7.16 (2 H, m, 2 × ArH); δ_C(100 MHz; $CDCl_3$) 17.2 (CH_3), 34.7 (CH_2), 85.6 (CH), 109.2 (CH), 112.0 (CH_2), 120.3 (CH), 124.8 (CH), 126.6 (C), 128.0 (CH), 144.0 (C) and 159.7 (C).

2-Isopropenyl-2,3-dihydrobenzofuran-5-carbaldehyde 23

(*a*) 2-Isopropenyl-2,3-dihydrobenzofuran **22** (1.50 g, 9.4 mmol) was added to *N*-methylformanilide (2.54 g, 18.8 mmol) and phosphorus oxychloride (2.88 g, 18.8 mmol) and the mixture was heated at 90 °C with stirring for 1 h. The cooled reaction mixture was added to dichloromethane (30 cm^3) and aqueous sodium hydroxide (2.5 mol dm^{-3}; 20 cm^3) and refluxed for 2 min. The volatiles were then removed under reduced pressure and the residue was taken up in diethyl ether (30 cm^3). The organic phase was then washed with hydrochloric acid (2 mol dm^{-3}; 2 × 20 cm^3), aqueous sodium hydroxide (2 mol dm^{-3}; 2 × 20 cm^3) and brine (10 cm^3) then dried and evaporated to dryness. Chromatography on flash silica with ethyl acetate–light petroleum (bp 40–60 °C) (1 : 19) as eluent yielded the *title compound* (0.84 g, 47%) as a colourless oil [Found: 188.082 (M^+, 100%). $C_{12}H_{12}O_2$ requires *M*, 188.084]; ν_{max}(film)/cm^{-1} 2919, 1684, 1605, 1484, 1246, 1105 and 943; δ_H(80 MHz; $CDCl_3$) 1.76 (3 H, s, CH_3C=C), 3.04 (1 H, dd, *J* 8.1 and 15.9, 3-C*H*H), 3.41 (1 H, dd, *J* 9.3 and 15.9, 3-CH*H*), 4.93 (1 H, s, C=C*H*H), 5.09 (1 H, s, C=CH*H*), 5.28 (1 H, bt, *J* 9, 2-CH), 6.86 (1 H, d, *J* 8.8, 7-H), 7.65 (1 H, d, *J* 8.8, 6-H), 7.70 (1 H, s, 4-H) and 9.80 (1 H, s, CHO); δ_C(22.5 MHz; $CDCl_3$) 17.0 (CH_3), 33.6 (CH_2), 87.1 (CH), 109.4 (CH), 112.5 (CH_2), 125.8 (CH), 128.1 (C), 130.6 (C), 132.8 (CH), 143.1 (C), 165.1 (C) and 190.2 (C).

(*b*) A solution of 3-iodo-4-hydroxybenzaldehyde (2.0 g, 8.1 mmol), palladium(II) acetate (14 mg, 0.32 mmol), sodium acetate (2.32 g, 28.4 mmol), tetrabutylammonium chloride (2.25 g, 8.1 mmol) and isoprene (11.26 g, 45 mmol) in dry DMF (20 cm^3) was heated at 100 °C for 96 h with stirring under nitrogen. When cool, diethyl ether (50 cm^3) was added and then the organic phase was washed with water (3 × 20 cm^3), aqueous sodium hydroxide (2 mol dm^{-3}; 2 × 20 cm^3), hydrochloric acid (2 mol dm^{-3}; 2 × 20 cm^3) and brine (20 cm^3), and then dried and evaporated to dryness to yield the title compound (0.60 g, 39%) as a colourless oil, spectroscopically and chromatographically indistinguishable from the sample above.

2-Isopropenyl-2,3-dihydrobenzofuran-5-carboxylic acid

Aqueous sodium hydroxide (8 cm^3) was added to a solution of silver nitrate (2.65 g, 15.6 mmol) in water (8 cm^3) and stirred for 5 min. The precipitated silver(I) oxide was then filtered off, washed with water, and then taken up as a suspension of water (26 cm^3). Sodium hydroxide (0.94 g, 23.4 mmol) was then added and the solution was stirred vigorously. Finally 2-isopropenyl-2,3-dihydrobenzofuran-5-carbaldehyde **23** (0.80 g, 3.9 mmol) was added in one portion and the reaction heated to 45 °C for 1 h. The suspension was then filtered and the filtrate was acidified with hydrochloric acid (2 mol dm^{-3}, 50 cm^3). The aqueous phase was then saturated with sodium chloride and extracted with diethyl ether (3 × 30 cm^3). The combined organic phases were then dried and evaporated to dryness to yield the title compound (0.58 g, 73%) as a white solid, mp 141–142 °C (lit.,[20a] 140.5–142.5 °C) (Found: C, 70.7; H, 5.9. $C_{12}H_{12}O_3$ requires C, 70.60; H, 5.88%) [Found: 204.078 (M^+, 100%). $C_{12}H_{12}O_3$ requires *M*, 204.079]; ν_{max}(KBr disc)/cm^{-1} 3443, 2938, 1673, 1609, 1592 and 1490; δ_H(250 MHz; $CDCl_3$) 1.77 (3 H, s, CH_3C=C), 3.07 (1 H, dd, *J* 7.9 and 15.8, 3-C*H*H), 3.40 (1 H, dd, *J* 9.7 and 15.8, 3-CH*H*), 4.95 (1 H, s, C=C*H*H), 5.10 (1 H, s, C=CH*H*), 5.28 (1 H, bt, *J* 8, 2-CH), 6.85 (1 H, d, *J* 8.3, 7-H), 7.93 (1 H, s, 4-H) and 7.96 (1 H, d, *J* 8.3, 6-H); δ_C(22.5 MHz; $CDCl_3$) 23.3 (CH_3), 38.5 (CH_2), 86.2 (CH), 106.1 (CH), 109.2 (CH_2), 112.0 (C), 117.5 (C), 122.5 (CH), 126.8 (CH), 136.9 (C), 156.1 (C) and 162.5 (C).

(2-Isopropenyl-2,3-dihydrobenzofuran-5-yl)(2-methylbenzimidazol-1-yl)methanone 10

Oxalyl chloride (0.64 g, 4.4 mmol) and dimethylformamide (DMF) (2 drops) were added to a solution of 2-isopropenyl-2,3-dihydrobenzofuran-5-carboxylic acid (0.40 g, 2.0 mmol) in dichloromethane (15 cm^3) at 0 °C, then stirred for 2 h at 25 °C under nitrogen. The dichloromethane was then removed under reduced pressure to yield the desired aroyl chloride **14**. This product was dissolved in dry chloroform (50 cm^3) with 2-methyl-1*H*-benzoimidazole (0.26 g. 2.0 mmol) and the solution was refluxed at 62 °C for 2 h under nitrogen. The cooled organic phase was then washed with hydrochloric acid (2 mol dm^{-3}, 2 × 20 cm^3), saturated aqueous sodium hydrogencarbonate (2 × 20 cm^3) and brine (20 cm^3), then dried and evaporated to dryness. Chromatography on flash silica with chloroform–methanol (49 : 1) as eluent, then chromatography on flash silica with ethyl acetate–dichloromethane (1 : 9) as eluent, yielded the *title compound* (0.16 g, 25%) as a pale yellow oil [Found: 318.138 (M^+, 8%). $C_{20}H_{18}N_2O_2$ requires *M*, 318.137]; ν_{max}(film)/cm^{-1} 2921, 1675, 1609, 1459, 1294, 1244, 1115 and 753; δ_H(250 MHz; $CDCl_3$) 1.79 (3 H, s, CH_3C=C), 2.72 (3 H, s, CH_3C=N), 3.08 (1 H, dd, *J* 8.1 and 16.0, 3-C*H*H), 3.40 (1 H, dd, *J* 9.5 and 15.9, 3-CH*H*), 4.97 (1 H, s, C=C*H*H), 5.12 (1 H, s, C=CH*H*), 5.34 (1 H, bt, *J* 9, 2-CH), 6.83 (1 H, d, 8.4, ArH), 6.95 (1 H, d, *J* 8.0, ArH), 7.12 (1 H, t, *J* 7.3, ArH), 7.26 (1 H, t, *J* 8.0, ArH), 7.60 (1 H, d, *J* 8.4, ArH), 7.66 (1 H, s, ArH) and 7.70 (1 H, d, *J* 7.6, ArH); δ_C(62.5 MHz; $CDCl_3$) 16.6 (CH_3), 17.1 (CH_3), 33.8 (CH_2), 87.3 (CH), 109.5 (CH), 112.9 (CH), 113.1 (CH), 119.3 (CH), 123.4 (CH), 123.6 (CH), 125.2 (C), 127.7 (CH), 128.2 (C), 132.8 (C), 134.1 (C), 142.3 (C), 142.9 (C), 153.1 (C), 165.2 (C) and 167.8 (C).

(2*R*)-5-Hydroxymethyl-2-isopropenyl-4-methoxy-2,3-dihydrobenzofuran 26

(2*R*)-2-Isopropenyl-4-methoxy-2,3-dihydrobenzofuran-5-carboxylic acid **19** (0.37 g, 1.7 mmol) was added to a solution of (chloromethylidene)dimethylammonium chloride (0.22 g, 1.7 mmol) in dry acetonitrile (5 cm^3) and dry THF (10 cm^3) at −10 °C under nitrogen and the mixture was stirred for 1 h. The solution was then cooled to −35 °C and a solution of sodium borohydride (0.16 g, 4.3 mmol) in DMF (3 cm^3) was added followed by stirring at −5 °C for 2 h. The reaction was then washed with hydrochloric acid (2 mol dm^{-3}, 20 cm^3) and water (2 × 10 cm^3), dried and then evaporated to dryness. Chromatography on flash silica with ethyl acetate–light petroleum (bp 40–60 °C) (7 : 13) as eluent yielded the *title compound* (0.23 g, 62%) as a pale yellow oil [Found: 220.108 (M^+, 100%). $C_{13}H_{16}O_3$ requires *M*, 220.110]; ν_{max}(film)/cm^{-1} 3397, 2945, 1606, 1426, 1236, 1073, 966, 906 and 812; δ_H(400 MHz; $CDCl_3$) 1.78 (3 H, s, CH_3C=C), 2.28 (1 H, s, OH), 3.14 (1 H, dd, *J* 8.1 and 15.4, 3-C*H*H), 3.48 (1 H, dd, *J* 9.4 and 15.3, 3-CH*H*), 3.90 (3 H, s, OCH_3), 4.56 (2 H, s, CH_2OH), 4.91 (1 H, d, *J* 1.4, C=C*H*H), 5.08 (1 H, d, *J* 1.4, C=CH*H*), 5.16 (1 H, bt, *J*, 9, 2-CH), 6.48 (1 H, d, *J* 8.0, 7-H) and 7.03 (1 H, d, *J* 8.0, 6-H); δ_C(100 MHz; $CDCl_3$) 17.1 (CH_3), 33.6 (CH_2),

59.3 (CH_3), 61.5 (CH_2), 86.0 (CH), 103.8 (CH), 112.3 (CH_2), 115.3 (C), 124.4 (C), 129.5 (CH), 143.7 (C), 154.9 (C) and 161.7 (C).

(2*R*)-(2-Isopropenyl-4-methoxy-2,3-dihydrobenzofuran-5-yl)-(2'-methyl-1'*H*-benzoimidazol-1'-yl)methane 9

A solution of 2-methyl-1*H*-benzoimidazole (0.12 g, 0.91 mmol), triphenylphosphine (0.36 g, 1.36 mmol) and 5-hydroxymethyl-2-isopropenyl-4-methoxy-2,3-dihydrobenzofuran **26** (0.20 g, 0.91 mmol) in THF (6 cm^3) was stirred at 25 °C under nitrogen. Diethyl azodicarboxylate (0.24 g, 1.36 mmol) was then added dropwise and the solution was warmed at 55 °C for 21 h under nitrogen. The reaction mixture was then extracted with hydrochloric acid (2 mol dm^{-3}, 2 × 50 cm^3) and this was brought to pH 7 with aqueous sodium hydroxide (2 mol dm^{-3}). The neutral aqueous layer was then extracted with diethyl ether (3 × 30 cm^3), and the extracts were dried and evaporated to dryness. Chromatography on neutral alumina with dichloromethane as eluent yielded the *title compound* (97 mg, 32%) as a yellow oil [Found: 334.168 (M^+, 14%). $C_{21}H_{22}N_2O_2$ requires *M*, 334.168]; ν_{max}(film)/cm^{-1} 2932, 1734, 1607, 1463 and 743; δ_H(250 MHz; $CDCl_3$) 1.76 (3 H, s, CH_3C=C), 2.60 (3 H, s, CH_3C=N), 3.15 (1 H, dd, *J* 8.2 and 15.4, 3-C*H*H), 3.49 (1 H, dd, *J* 9.4 and 15.4, 3-CH*H*), 3.77 (3 H, s, OCH_3), 4.92 (1 H, s, C=C*H*H), 5.08 (1 H, s, C=CH*H*), 5.15 (1 H, bt, *J* 9, 2-CH), 5.20 (2 H, s, CH_2N), 6.40 (1 H, d, *J* 8.2, ArH), 6.60 (1 H, d, *J* 8.2, ArH), 7.16–7.28 (3 H, m, 3 × ArH) and 7.68–7.71 (1 H, m, ArH); δ_C(62.5 MHz; $CDCl_3$) 14.9 (CH_3), 17.2 (CH_3), 33.9 (CH_2), 43.2 (CH_2), 58.7 (CH_3), 86.0 (CH), 103.8 (CH), 109.8 (CH), 112.3 (CH_2), 115.2 (C), 118.9 (CH), 121.7 (CH), 122.0 (CH), 128.3 (CH), 133.3 (C), 135.6 (C), 142.6 (C), 143.5 (C), 152.1 (C), 154.4 (C) and 161.9 (C).

5-Hydroxymethyl-2-isopropenyl-2,3-dihydrobenzofuran 27

A solution of 2-isopropenyl-2,3-dihydrobenzofuran-5-carbaldehyde **23** (0.32 g, 1.7 mmol) in THF (10 cm^3) was added dropwise to a solution of sodium borohydride (0.034 g, 0.9 mmol) in THF (15 cm^3) and water (3 cm^3) and stirred for 1 h at 25 °C. The THF was removed under reduced pressure and the residue was acidified with hydrochloric acid (2 mol dm^{-3}, 15 cm^3). This aqueous layer was then extracted with dichloromethane (2 × 50 cm^3). The extracts were dried and evaporated to dryness. Chromatography on flash silica with ethyl acetate–light petroleum (bp 40–60 °C) (1:99, 1:49, 1:24, 1:10) as eluent yielded the *title compound* (0.23 g, 70%) as a colourless oil [Found: 190.101 (M^+, 15%). $C_{12}H_{14}O_2$ requires *M*, 190.099]; ν_{max}(film)/cm^{-1} 3359, 2921, 1613, 1490, 1246, 1018, 904 and 757; δ_H(80 MHz; $CDCl_3$) 1.76 (3 H, s, CH_3C=C), 2.05 (1 H, s, OH), 2.97 (1 H, dd, *J* 8.4 and 15.6, 3-C*H*H), 3.34 (1 H, dd, *J* 9.3 and 15.5, 3-CH*H*), 4.55 (2 H, s, CH_2OH), 4.90 (1 H, d, *J* 1.3, C=C*H*H), 5.06 (1 H, d, *J* 1.3, C=CH*H*), 5.16 (1 H, bt, *J* 9, 2-CH), 6.74 (1 H, d, *J* 7.9, 7-H), 7.09 (1 H, d, *J* 7.9, H) and 7.14 (1 H, s, 4-H); δ_C(22.5 MHz; $CDCl_3$) 17.3 (CH_3), 34.8 (CH_2), 65.3 (CH_2), 86.0 (CH), 109.1 (CH), 112.0 (CH_2), 124.3 (CH), 127.1 (C), 127.6 (CH), 133.3 (C), 144.1 (C) and 159.6 (C).

5,5'-(*Oxydimethylene*)*bis*(2-*isopropenyl*-2,3-*dihydrobenzofuran*) **28** (92 mg, 30%) was also isolated as a pale yellow oil [Found: 362.188 (M^+, 41%). $C_{24}H_{26}O_3$ requires *M*, 362.188]; ν_{max}(film)/cm^{-1} 2856, 1490, 1244, 1110, 909 and 733; δ_H(250 MHz; $CDCl_3$) 1.76 (6 H, s, 2 × CH_3C=C), 2.99 (2 H, dd, *J* 8.3 and 15.6, 2 × 3-C*H*H), 3.34 (2 H, dd, *J* 9.4 and 15.6, 2 × 3-CH*H*), 4.43 (4 H, s, CH_2OCH_2), 4.89 (2 H, d, *J* 1.3, 2 × C=C*H*H), 5.06 (2 H, d, *J* 1.3, 2 × C=CH*H*), 5.16 (2 H, bt, *J* 9, 2 × 2-CH), 6.74 (2 H, d, *J* 8.0, 2 × 7-H), 7.10 (2 H, d, *J* 8.0, 2 × 6-H) and 7.15 (2 H, s, 2 × 4-H); δ_C(22.5 MHz; $CDCl_3$) 17.3 (CH_3), 34.8 (CH_2), 72.1 (CH_2), 85.9 (CH), 108.9 (CH), 112.0 (CH_2), 125.0 (CH), 127.0 (C), 128.3 (CH), 130.7 (C), 144.2 (C) and 159.6 (C).

(2-Isopropenyl-2,3-dihydrobenzofuran-5-yl)(2-methyl-1*H*-benzoimidazol-1-yl)methane 11

A solution of 2-methyl-1*H*-benzoimidazole (45 mg, 0.34 mmol), triphenylphosphine (134 mg, 0.51 mmol) and 5-hydroxymethyl-2-isopropenyl-2,3-dihydrobenzofuran **27** (65 mg, 0.34 mmol) in THF (3.4 cm^3) was stirred for 30 min at 25 °C under nitrogen. Diethyl azodicarboxylate (89 mg, 0.51 mmol) was then added dropwise and the solution was warmed at 55 °C for 16 h under nitrogen. The reaction was then extracted with hydrochloric acid (2 mol dm^{-3}, 2 × 50 cm^3) and this was brought to pH 7 with aqueous sodium hydroxide (2 mol dm^{-3}). The neutral aqueous layer was then extracted with diethyl ether (3 × 30 cm^3), and the extracts were dried and then evaporated to dryness. Chromatography on neutral alumina with dichloromethane as eluent yielded the *title compound* (30 mg, 29%) as a pale yellow oil [Found: 304.158 (M^+, 22%). $C_{20}H_{20}N_2O$ requires *M*, 304.158]; ν_{max}(film)/cm^{-1} 2922, 1615 and 1491; δ_H(250 MHz; $CDCl_3$) 1.73 (3 H, s, CH_3C=C), 2.58 (3 H, s, CH_3C=N), 2.93 (1 H, dd, *J* 8.2 and 15.9, 3-C*H*H), 3.23 (1 H, dd, *J* 9.6 and 15.9, 3-CH*H*), 4.89 (1 H, s, C=C*H*H), 5.05 (1 H, s, C=CH*H*), 5.14 (1 H, bt, *J* 9, 2-CH), 5.23 (2 H, s, CH_2N), 6.72 (1 H, d, *J* 8.2, ArH), 6.79 (1 H, s, ArH), 6.89 (1 H, d, *J* 8.2, ArH), 7.19–7.29 (3 H, m, 3 × ArH) and 7.70–7.74 (1 H, m, ArH); δ_C(62.5 MHz; $CDCl_3$) 14.1 (CH_3), 17.2 (CH_3), 34.5 (CH_2), 47.0 (CH_2), 86.1 (CH), 109.3 (CH), 109.5 (CH), 112.2 (CH_2), 119.0 (CH), 122.0 (CH), 122.3 (CH), 122.9 (CH), 126.6 (CH), 127.8 (C), 127.9 (C), 135.4 (C), 142.4 (C), 143.7 (C), 151.8 (C) and 159.6 (C).

Methyl 3-hydroxy-4-iodobenzoate 30

A solution of iodine (23.4 g, 92 mmol) and potassium iodide (18.2 g, 110 mmol) in water (100 cm^3) was added dropwise to a stirred solution of 3-hydroxybenzoic acid (13.8 g, 0.1 mol) in aqueous ammonia (200 cm^3) at 25 °C. After stirring the resulting green solution for 10 min, conc. hydrochloric acid (180 cm^3) was added, yielding a thick white precipitate. The precipitate was filtered off and crystallised from water–ethanol (5:1) to yield 3-hydroxy-4-iodobenzoic acid (23.8 g, 90%) as a white crystalline solid, mp 224–225 °C (lit.,[24] 226 °C). Thionyl chloride (35 cm^3) was added to a stirred solution of this acid (13.6 g, 51.5 mmol) in methanol (200 cm^3) and the system was then refluxed for 20 h. Once cool the volatiles were removed under reduced pressure and the residue was taken up in dichloromethane (100 cm^3). The organic layer was washed with saturated aqueous sodium hydrogencarbonate (3 × 50 cm^3) and water (50 cm^3), dried and evaporated to dryness to yield the *title compound* (13.1 g, 92%), mp 145–148 °C [Found: 277.944 (M^+, 100%). $C_8H_7IO_3$ requires *M*, 277.944]; ν_{max}(film)/cm^{-1} 3210, 2962, 1719, 1581, 1486, 1438, 1286, 1088, 919 and 766; δ_H(250 MHz; $CDCl_3$) 3.17 (1 H, bs, OH), 3.71 (3 H, s, CH_3), 7.06 (1 H, dd, *J* 2.2 and 8.1, 6-H), 7.43 (1 H, d, *J* 2.1, 2-H) and 7.72 (1 H, d, *J* 8.2, 5-H); δ_C(62.5 MHz; $CDCl_3$) 52.4 (CH_3), 90.8 (C), 115.8 (CH), 122.7 (CH), 132.6 (C), 140.4 (CH), 157.6 (C) and 166.6 (C).

2-Isopropenyl-2,3-dihydrobenzofuran-6-carboxylic acid

A solution of methyl 3-hydroxy-4-iodobenzoate **30** (13.0 g, 46.8 mmol), palladium(II) acetate (520 mg, 2.1 mmol), sodium acetate (13.4 g, 164 mmol) and tetrabutylammonium chloride (13.0 g, 46.8 mmol) in DMF (100 cm^3) was treated with isoprene (15.9 g, 234 mmol) and the mixture was refluxed for 24 h under nitrogen with stirring. When cool, dichloromethane (100 cm^3) was added and the solution was filtered through Kieselguhr. The filtrate was then washed with water (6 × 100 cm^3) and the organic layer dried and evaporated to dryness. Chromatography on flash silica with dichloromethane–light petroleum (bp 40–60 °C) (1:9, 3:7) as eluent yielded the esters **31** and **32** (10:1, by ^1H NMR) (6.6 g, 64%) as a light yellow oil [Found: 218.095

(M^+, 100%). $C_{13}H_{14}O_3$ requires *M*, 218.094]. A solution of the esters (0.15 g, 0.54 mmol) and sodium carbonate (0.57 g, 5.4 mmol) in methanol (5 cm^3) and water (5 cm^3) was refluxed for 24 h with stirring. Once cool the reaction mixture was acidified with hydrochloric acid (2 mol dm^{-3}, 5 cm^3) and the methanol removed under reduced pressure. The residue was taken up into diethyl ether (3 × 30 cm^3) which was then extracted with saturated aqueous sodium hydrogen carbonate solution (2 × 30 cm^3). The basic aqueous layer was then acidified with hydrochloric acid (2 mol dm^{-3}, 20 cm^3) and extracted with diethyl ether (3 × 20 cm^3). The organic phase was then dried and evaporated to yield the *title compound* (0.12 g, 84%) as a white solid, mp 128–129 °C [Found: 204.078 (M^+, 100%). $C_{12}H_{12}O_3$ requires *M*, 204.079]; ν_{max}(KBr disc)/cm^{-1} 3510, 2924, 1680, 1589, 1442 and 1303; δ_H(250 MHz; $CDCl_3$) 1.78 (3 H, s, CH_3C=C), 3.09 (1 H, dd, *J* 7.8 and 16.5, 3-C*H*H), 3.41 (1 H, dd, *J* 9.2 and 16.5, 3-CH*H*), 4.94 (1 H, d, *J* 0.5, C=C*H*H), 5.10 (1 H, d, *J* 0.5, C=CH*H*), 5.25 (1 H, bt, *J* 9, 2-CH), 7.24 (1 H, d, *J* 7.9, 4-H), 7.49 (1 H, d, *J* 1.2, 7-H) and 7.65 (1 H, dd, *J* 1.2 and 7.7, 5-H); δ_C(22.5 MHz; $CDCl_3$) 18.7 (CH_3), 36.4 (CH_2), 87.7 (CH), 112.0 (CH), 113.9 (CH_2), 124.8 (CH), 126.2 (CH), 131.3 (C), 135.0 (C), 145.1 (C), 161.7 (C) and 173.6 (C).

2-Diazo-1-(2-isopropenyl-2,3-dihydrobenzofuran-6-yl)ethanone 34

Thionyl chloride (23.5 g, 0.20 mol) was added dropwise to a solution of 2-isopropenyl-2,3-dihydrobenzofuran-6-carboxylic acid (0.40 g, 1.96 mmol) and stirred for 15 h at 25 °C under nitrogen. The volatiles were removed under reduced pressure and the resulting acid chloride **33** was dissolved in diethyl ether (10 cm^3) and added to excess ethereal diazomethane. The solution was set aside for 16 h, after which the residual diazomethane and the ether were distilled off. Chromatography on flash silica with ethyl acetate–light petroleum (bp 40–60 °C) (1:9) as eluent yielded the *title compound* (0.40 g, 90%) as a yellow solid, mp 108–110 °C [Found: 228.090 (M^+, 100%). $C_{13}H_{12}N_2O_2$ requires *M*, 228.090]; ν_{max}(KBr disc)/cm^{-1} 3091, 2103, 1651, 1603, 1578, 1435, 1362, 1343, 1253, 962 and 836; δ_H(400 MHz; $CDCl_3$) 1.76 (3 H, s, CH_3C=C), 3.06 (1 H, ddd, *J* 1.0, 8.0 and 16.3, 3-C*H*H), 3.37 (1 H, dd, *J* 9.5 and 17.0, 3-CH*H*), 4.92 (1 H, d, *J* 0.9, C=C*H*H), 5.09 (1 H, d, *J* 0.9, C=CH*H*), 5.22 (1 H, bt, *J* 9, 2-CH), 5.83 (1 H, s, CHN_2), 7.17 (1 H, d, *J* 1.3, 7-H), 7.19 (1 H, d, *J* 7.7, 4-H) and 7.25 (1 H, dd, *J* 1.3 and 7.8, 5-H); δ_C(100 MHz; $CDCl_3$) 17.2 (CH_3), 34.7 (CH_2), 54.1 (CH), 86.2 (CH), 107.3 (CH), 112.4 (CH_2), 119.5 (CH), 124.8 (CH), 132.1 (C), 137.4 (C), 143.6 (C), 160.3 (C) and 186.0 (C).

2-(2-Isopropenyl-2,3-dihydrobenzofuran-6-yl)acetamide 35

A solution of 2-diazo-1-(2-isopropenyl-2,3-dihydrobenzofuran-6-yl)ethanone **34** (0.12 g, 0.55 mmol) in 1,4-dioxane (2.0 cm^3) was treated with aqueous ammonia (0.9 sg, 1.0 cm^3) and 10% aqueous silver nitrate (0.3 cm^3) at 60 °C. The reaction mixture was refluxed at 100 °C for 4 h and then the volatiles were removed under reduced pressure. The organic residue was then taken up in dichloromethane (10 cm^3) and washed with water (2 × 10 cm^3). The organic phase was then dried and evaporated to dryness. Chromatography on flash silica with ethyl acetate–light petroleum (bp 40–60 °C) (4:1) as eluent yielded the *title compound* (83 mg, 70%) as a colourless oil [Found: 217.105 (M^+, 100%). $C_{13}H_{15}NO_2$ requires *M*, 217.110]; ν_{max}(KBr disc)/cm^{-1} 3372, 3190, 1657, 1594, 1499, 1437, 1416, 1246, 900 and 786; δ_H(270 MHz; $CDCl_3$) 1.77 (3 H, s, CH_3C=C), 3.02 (1 H, dd, *J* 7.9 and 15.5, 3-C*H*H), 3.22 (1 H, dd, *J*. 9.4 and 15.5, 3-CH*H*), 3.52 (2 H, s, CH_3CON), 4.92 (1 H, d, *J* 0.6, C=C*H*H), 5.09 (1 H, d, *J* 0.6, C=CH*H*), 5.18 (1 H, bt, *J* 9, 2-CH), 5.53 (1 H, s, N*H*H), 5.93 (1 H, s, NH*H*), 6.71 (1 H, s, 7-H), 6.74 (1 H, d, *J* 7.5, 4-H) and 7.12 (1 H, d, *J* 7.4, 5-H); δ_C(67.5 MHz; $CDCl_3$) 17.2 (CH_3), 34.3 (CH_2), 43.3 (CH_2), 86.1 (CH), 110.1 (CH), 112.1 (CH_2), 121.4 (CH), 125.2 (CH), 126.0 (C), 135.0 (C), 143.7 (C), 160.4 (C) and 173.8 (C).

Methyl 2-(1-methyl-2-phenylsulfanylethyl)-2,3-dihydrobenzofuran-6-carboxylate 37

A solution of methyl 2-isopropenyl-2,3-dihydrobenzofuran-6-carboxylate **31** (4.40 g, 20 mmol) in benzene (20 cm^3) was treated with benzenethiol (16.0 g, 145 mmol) and stirred for 0.5 h under nitrogen. This mixture was then irradiated with a sunlamp whilst a solution of diphenyl disulfide (6.61 g, 30 mmol) in benzene (20 cm^3) was slowly added, *via* a syringe pump, over 10 h. After the addition was complete the solution was irradiated for a further 24 h. Once cool the benzene was removed under reduced pressure and the residue was taken up in diethyl ether (50 cm^3). This solution was washed with aqueous sodium hydroxide (2 mol dm^{-3}, 3 × 50 cm^3) and brine (50 cm^3), then dried and evaporated to dryness. Chromatography on flash silica with ethyl acetate–light petroleum (bp 40–60 °C) (1:99, 2:98, 3:97) as eluent yielded the *title compound* (4.54 g, 69%) as a light yellow oil and mixture of two diastereoisomers [Found: 328.112 (M^+, 31%). $C_{19}H_{20}O_3S$ requires *M*, 328.1113]; ν_{max}(film)/cm^{-1} 2950, 1724, 1588, 1495, 1441, 1289, 1219, 1083, 990 and 761; δ_H(270 MHz; $CDCl_3$) 1.05 and 1.06 (3 H, d, *J* 6.9 and d, *J* 7.0, CH_3CHCH_2S), 1.93–2.22 (1 H, m, $CHCH_2S$), 2.72–3.37 (4 H, m, 3-CH_2 and CH_2S), 3.85 (3 H, s, CO_2CH_3), 4.68 and 4.92 (1 H, dd, *J* 8.6 and 16.7 and ddd, *J* 4.3, 8.4 and 9.4, 2-CH) and 7.09–7.56 (8 H, m, 8 × ArH); δ_C(67.5 MHz; $CDCl_3$) 13.5 and 14.5 (CH_3), 32.6 and 32.8 (CH_2), 36.4 and 36.6 (CH_2), 37.9 and 38.1 (CH), 51.8 (CH_3), 84.9 and 86.2 (CH), 109.6 and 109.7 (CH), 122.11 and 122.14 (CH), 124.28 and 124.33 (CH), 125.6 and 125.8 (CH), 128.6 and 128.73 (CH), 128.77 and 128.81 (CH), 130.2 (C), 132.3 (C), 136.3 and 136.5 (C), 159.5 and 159.8 (C) and 166.7 (C).

6-Hydroxymethyl-2-(1-methyl-2-phenylsulfanylethyl)-2,3-dihydrobenzofuran 38

A solution of 2-(1-methyl-2-phenylsulfanylethyl)-2,3-dihydrobenzofuran-6-carboxylate **37** (0.22 g, 0.67 mmol) in dry diethyl ether (15 cm^3) was added dropwise over 10 min to a stirred solution of lithium aluminium hydride (0.10 g, 2.7 mmol) in dry diethyl ether (15 cm^3), under nitrogen. After 0.5 h the reaction was quenched by the addition of ethyl acetate (10 cm^3) and the precipitate was filtered off. The filtrate was then acidified with hydrochloric acid (2 mol dm^{-3}, 5 cm^3) and the organic layer was separated, dried and then evaporated to dryness. Chromatography on flash silica with ethyl acetate–light petroleum (bp 40–60 °C) (1:9–1:1) as eluent yielded the *title compound* (0.20 g, 99%) as a pale yellow oil and mixture of two diastereoisomers [Found: 300.117 (M^+, 100%). $C_{18}H_{20}O_2S$ requires *M*, 100.118]; ν_{max}(film)/cm^{-1} 3240, 2940, 1595, 1486, 1286 and 731; δ_H(250 MHz; $CDCl_3$) 1.070 and 1.076 (3 H, d, *J* 6.8 and d, 6.8, CH_3CHCH_2S), 2.02 (1 H, s, OH), 1.95–2.18 (1 H, m, $CHCH_2S$), 2.78–3.45 (4 H, m, 3-CH_2 and CH_2S), 4.57 (2 H, s, CH_2OH), 4.67 and 4.91 (1 H, dd, *J* 8.7 and 16.4 and ddd, *J* 4.3, 6.6 and 12.4, 2-CH), 6.76 (1 H, d, *J* 1.4, 7-H), 6.79 (1 H, d, *J* 7.5, 5-H) and 7.07–7.36 (6 H, m, 6 × ArH); δ_C(67.5 MHz; $CDCl_3$) 13.7 and 14.7 (CH_3), 32.4 and 32.7 (CH_2), 36.7 and 36.8 (CH_2), 38.0 and 38.1 (CH), 65.2 (CH_2), 85.0 and 86.3 (CH), 107.7 and 107.8 (CH), 118.90 and 118.96 (CH), 124.65 and 124.69 (CH), 125.7 and 125.9 (CH), 126.02 and 126.06 (C), 128.79 and 128.84 (CH), 128.88 and 128.95 (CH), 136.5 and 136.7 (C), 141.37 (C) and 159.9 and 160.2 (C).

6-Chloromethyl-2-(1-methyl-2-phenylsulfanylethyl)-2,3-dihydrobenzofuran 39

A solution of 6-hydroxymethyl-2-(1-methyl-2-phenylsulfanyl-

ethyl)-2,3-dihydrobenzofuran **38** (1.24 g, 4.13 mmol) was refluxed for 0.5 h with freshly distilled thionyl chloride (6.60 cm^3, 82.6 mmol). The volatiles were removed under reduced pressure (2 mmHg), and chromatography on neutral alumina with dichloromethane–light petroleum (bp 40–60 °C) (1 : 1) as eluent yielded the *title compound* (1.10 g, 83%) as a pale yellow oil and a mixture of two diastereoisomers [Found: 318.078 (M^+, 68%). $C_{18}H_{19}ClOS$ requires *M*, 318.086]; δ_H(270 MHz; $CDCl_3$) 1.08 (3 H, d, *J* 6.6, CH_3CHCH_2S), 1.98–2.14 (1 H, m, $CHCH_2S$), 2.75–3.40 (4 H, m, CH_2S), 4.52 (2 H, s, CH_2Cl), 4.69 and 4.91 (1 H, dd, *J* 8.6 and 16.5 and ddd, *J* 4.3, 6.8 and 9.6, 2-CH), 6.80 (1 H, d, *J* 2.6, 7-H), 6.83 (1 H, dd, *J* 1.6 and 7.6, 5-H) and 7.08–7.36 (6 H, m, 6 × ArH); δ_C(67.5 MHz; $CDCl_3$) 14.3 and 15.3 (CH_3), 33.0 and 33.3 (CH_2), 37.2 and 37.4 (CH_2), 38.5 and 38.7 (CH), 46.9 (CH_2), 85.7 and 87.0 (CH), 109.7 and 109.9 (CH), 121.1 and 121.2 (CH), 125.3 and 125.4 (CH), 126.3 and 126.4 (CH), 129.1 (C), 129.36 and 129.40 (CH), 129.5 and 129.8 (CH), 137.1 (C), 138.1 (C) and 160.4 and 160.7 (C).

2-[(1-Methyl-2-phenylsulfanylethyl)-2,3-dihydrobenzofuran-6-yl]acetonitrile 40

A suspension of potassium cyanide (2.81 g, 43.2 mmol) and 18-crown-6 (0.25 g) in acetonitrile (25 cm^3) was added dropwise over 10 min to a solution of 6-chloromethyl-2-(1-methyl-2-phenylsulfanylethyl)-2,3-dihydrobenzofuran **39** (4.61 g, 14.4 mmol), potassium iodide (0.25 g, 1.45 mmol) and tetrabutylammonium chloride (0.25 g, 0.90 mmol) in acetonitrile (30 cm^3). This mixture was then refluxed at 82 °C for 6 h under nitrogen with stirring. Once cool the acetonitrile was removed under reduced pressure. Chromatography on flash silica with dichloromethane–light petroleum (bp 40–60 °C) (3 : 7) as eluent yielded the *title compound* (3.62 g, 80%) as a pale yellow oil and as a mixture of two diastereoisomers [Found: 309.119 (M^+, 68%). $C_{19}H_{19}NOS$ requires *M*, 309.119]; ν_{max}(film)/cm^{-1} 2929, 2250, 1593, 1496, 1439, 1246, 983 and 740; δ_H(270 MHz; $CDCl_3$) 1.07 and 1.08 (3 H, d, *J* 6.6 and d, *J* 6.9, CH_3CHCH_2S), 1.97–2.17 (1 H, m, $CHCH_2S$), 2.75–3.38 (4 H, m, 3-CH_2 and CH_2S), 3.66 (2 H, s, CH_2CN), 4.70 and 4.93 (1 H, dd, *J* 8.5 and 16.5 and ddd, *J* 4.3, 6.8 and 9.6, 2-CH), 6.71 (1 H, s, 7-H), 6.77 (1 H, d, *J* 7.6, 5-H) and 7.09–7.37 (6 H, m, 6 × ArH); δ_C(67.5 MHz; $CDCl_3$) 13.7 and 14.7 (CH_3), 23.5 (CH_2), 32.3 and 32.6 (CH_2), 36.6 and 36.8 (CH_2), 38.0 and 38.2 (CH), 85.3 and 86.6 (CH), 108.6 and 108.8 (CH), 117.9 (C), 119.7 and 119.8 (CH), 125.18 and 125.23 (CH), 125.8 and 125.9 (CH), 126.72 and 126.75 (C), 128.82 and 128.86 (CH), 128.90 and 129.0 (CH), 129.9 (C), 136.4 and 136.6 (C) and 160.2 and 160.5 (C).

4-Nitrophenyl 3,4-dimethoxyphenylacetate 42

4-Nitrophenol (8.3 g, 60 mmol) was added in one portion to a solution of 3,4-dimethoxyphenylacetic acid (9.8 g, 50 mmol) in ethyl acetate (100 cm^3). Dicyclohexylcarbodiimide (10.3 g, 50 mmol) was then added at 0 °C and the solution was stirred for 0.5 h. The organic phase was then washed with aqueous sodium hydroxide (2 mol dm^{-3}, 3 × 50 cm^3), dried and then evaporated to dryness. Crystallisation from light petroleum (bp 40–60 °C)–ethyl acetate yielded the *title compound* (14.4 g, 91%) as a white crystalline solid, mp 126–128 °C [Found: 317.093 (M^+, 55%). $C_{16}H_{15}NO_6$ requires *M*, 317.090]; ν_{max}(KBr disc)/cm^{-1} 2937, 1752, 1614, 1593, 1510, 1487, 1466, 1348, 1245, 1125 and 1028; δ_H(250 MHz; $CDCl_3$) 3.85 (2 H, s, CH_2CO_2), 3.89 (3 H, s, OCH_3), 3.90 (3 H, s, OCH_3), 6.82–6.95 (3 H, m, 3 × ArH), 7.26 (2 H, d, *J* 8.4, ArH) and 8.27 (2 H, d, *J* 8.4, ArH); δ_C(67.5 MHz; $CDCl_3$) 40.8 (CH_2), 55.9 (CH_3), 56.0 (CH_3), 111.3 (CH), 112.3 (CH), 121.5 (CH), 122.3 (CH), 124.9 (C), 125.2 (CH), 145.3 (C), 148.5 (C), 149.1 (C), 155.4 (C) and 169.3 (C).

2-(3′,4′-Dimethoxyphenyl)-*N*-{2-[(1-methyl-2-phenylsulfanylethyl)-2,3-dihydrobenzofuran-6-yl]ethyl}acetamide 43

A solution of aluminium chloride (1.40 g, 10.5 mmol) in dry diethyl ether (50 cm^3) was carefully added to a stirred suspension of lithium aluminium hydride (0.40 g, 10.5 mmol) in dry diethyl ether (50 cm^3) under nitrogen and stirring was continued for 15 min. To this solution was added a solution of the nitrile **40** (0.97 g, 3.1 mmol) in dry diethyl ether (50 cm^3) dropwise over 10 min and the mixture was set aside at 25 °C for 4 h. An additional portion of lithium aluminium hydride (0.30 g, 7.9 mmol) was then added and the solution was stirred for a further 16 h. The solution was then cooled to 0 °C and water (15 cm^3) was added dropwise over 5 min. The organic phase was then separated off and the aqueous layer was extracted with diethyl ether (2 × 30 cm^3). The aqueous layer was then stirred for 15 min with aqueous ammonia (15 cm^3) and diethyl ether (15 cm^3) and the resulting precipitate was filtered off. The diethyl ether layer was then separated off and the aqueous ammonia layer was re-extracted with diethyl ether (2 × 30 cm^3). All the diethyl ether fractions were then combined and extracted with aqueous hydrochloric acid (2 mol dm^{-3}, 30 cm^3). This acidic layer was then basidified with aqueous sodium hydroxide (5 mol dm^{-3}) and then re-extracted with diethyl ether (2 × 50 cm^3). The combined organic layers were then dried and evaporated to dryness to leave crude arylethylamine **41** as a light brown oil (0.65 g).

The 4-nitrophenyl ester **42** (0.66 g, 2.1 mmol) in dichloromethane (10 cm^3) was added to a solution of the amine **41** (0.65 g, 2.1 mmol) in dichloromethane (10 cm^3) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.32 g, 2.1 mmol), and the reaction mixture was stirred for 16 h under nitrogen. The dichloromethane was removed under reduced pressure and the residue was taken up in diethyl ether (20 cm^3). This solution was washed with aqueous sodium hydroxide (2 mol dm^{-3}, 10 cm^3), brine (10 cm^3), hydrochloric acid (2 mol dm^{-3}, 10 cm^3) and brine (10 cm^3) and then dried and evaporated to dryness. Chromatography on flash silica with dichloromethane as eluent followed by chromatography on flash silica with ethyl acetate as eluent yielded the *title compound* (0.84 g, 55%) as a pale yellow oil and the mixture of two diastereoisomers [Found: 491.203 (M^+, 59%). $C_{29}H_{33}NO_4S$ requires *M*, 491.213]; δ_H(270 MHz; $CDCl_3$) 1.09 (3 H, d, *J* 6.6, CH_3CHCH_2S), 1.95–2.15 (1 H, m, $CHCH_2S$), 2.64 (2 H, t, *J* 6.4, CH_2CH_2N), 2.65–3.16 (4 H, m, 3-CH_2 and CH_2S), 3.40 (2 H, dt, *J* 6.4, CH_2N), 3.45 (2 H, s, CH_2CON), 3.82 (3 H, s, OCH_3), 3.86 (3 H, s, OCH_3), 4.64 and 4.82 (1 H, dd, *J* 8.4 and 16.2 and ddd, *J* 4.3, 6.3 and 9.7, 2-CH), 5.59 (1 H, t, *J* 6.4, NH), 6.47 (1 H, d, *J* 7.6, 5′-H), 6.50 (1 H, s, 2′-H), 6.70 (1 H, s, 7-H), 6.73 (1 H, d, *J* 8.4, 5-H), 6.80 (1 H, d, *J* 8.3, 4-H), 6.92 (1 H, d, *J* 7.8, 6′-H) and 7.06–7.38 (5 H, m, 5 × ArH); δ_C(67.5 MHz; $CDCl_3$) 13.8 and 14.7 (CH_3), 32.4 and 32.7 (CH_2), 35.3 (CH_2), 36.6 and 36.7 (CH_2), 37.9 and 38.2 (CH), 40.6 (CH_2), 43.2 (CH_2), 55.7 (CH_3), 55.8 (CH_3), 85.0 and 86.2 (CH), 109.1 and 109.3 (CH), 111.3 (CH), 112.3 (CH), 120.5 and 120.6 (CH), 121.5 (CH), 124.5 (CH), 124.7 and 124.8 (C), 125.7 and 125.8 (CH), 127.3 (C), 128.6 and 128.81 (CH), 128.84 and 128.86 (CH), 136.5 and 136.7 (C), 138.9 (C), 148.1 (C), 149.0 (C), 159.8 and 160.1 (C) and 171.1 (C).

5-(3,4-Dimethoxybenzyl)-2-isopropenyl-6-trifluoroacetyl-2,3,5,6,7,8-hexahydrofuro[2,3-*g*]isoquinoline 47

(i) A solution of the acetamide **43** (0.84 g, 1.7 mmol) and phosphorus oxychloride (1.53 g, 10.0 mmol) in dry toluene (20 cm^3) was refluxed at 100 °C for 1 h under nitrogen with stirring. Once cool, volatiles were removed under reduced pressure (0.5 mmHg) and the residue taken up in dichloromethane, washed with 5% aqueous ammonia (30 cm^3) and brine (20 cm^3), dried and then evaporated to dryness. The crude imine was dissolved in methanol (20 cm^3) and sodium borohydride (1.0 g, 26.3 mmol) was carefully added. The solution was stirred for 1 h at 25 °C. The volatiles were then removed under reduced pressure

and the residue taken up in diethyl ether (20 cm^3). Water (10 cm^3) was added and the mixture was basified with 5% aqueous ammonia (10 cm^3). The aqueous layer was then extracted with diethyl ether (3 × 75 cm^3) and the combined organic layers were dried and evaporated to dryness to yield the isoquinoline **44** (0.68 g, 84%) as a pale yellow oil and a mixture of four diastereoisomers.

(ii) Dry pyridine (0.08 cm^3, 1.0 mmol) and trifluoroacetic anhydride (0.43 cm^3, 3.1 mmol) were added to a solution of the isoquinoline **44** (0.38 g, 0.80 mmol) in dry dichloromethane (20 cm^3) and stirred for 14 h under nitrogen. Additional portions of pyridine (0.08 cm^3, 1.0 mmol) and trifluoroacetic anhydride (0.43 cm^3, 3.1 mmol) were added and the solution was stirred for a further 6 h. The organic layer was then washed with saturated aqueous sodium hydrogen carbonate (2 × 20 cm^3), brine (10 cm^3), hydrochloric acid (2 mol dm^{-3}, 2 × 20 cm^3) and brine (10 cm^3) then dried and evaporated to dryness to yield the N-*trifluoroacetylisoquinoline* **45** (0.40 g, 88%) as a yellow oil and a mixture of four diastereoisomers [Found: 420.125 ($M^+ - C_9H_{11}O_2$, 81%). $C_{22}H_{21}F_3NO_2S$ requires *M*, 420.125].

(iii) To a solution of sodium periodate (0.18 g, 0.84 mmol) in water (8 cm^3) and methanol (8 cm^3) was added a solution of the *N*-trifluoroacetylisoquinoline **45** (0.24 g, 0.42 mmol) in methanol (28 cm^3) and this was stirred at 25 °C for 15 h. The methanol was removed under reduced pressure and the residue was taken up into diethyl ether (20 cm^3). This solution was then washed with brine (15 cm^3), dried and then evaporated to dryness. Chromatography on flash silica with ethyl acetate–light petroleum (bp 40–60 °C) (50:50–80:20) as eluent yielded the *sulfoxide* **46** (0.22 g, 89%) as a pale yellow oil. This product was dissolved in toluene (25 cm^3) and refluxed for 3 days. Once cool the organic phase was washed with saturated aqueous sodium hydrogen carbonate (2 × 20 cm^3) then dried and evaporated to dryness. Chromatography on flash silica with ethyl acetate–light petroleum (bp 40–60 °C) (1:1) as eluent yielded the *title compound* **47** (0.10 g, 55%) as a colourless oil and a mixture of two diastereoisomers [Found: 310.1061 ($M^+ - C_9H_{11}O_2$, 100%). $C_{16}H_{15}F_3NO_2$ requires *M*, 310.1055]; ν_{max}(film)/cm^{-1} 2938, 1687, 1516, 1492, 1466, 1264, 1200, 1143 and 756; δ_H(400 MHz; $CDCl_3$) 1.74 and 1.77 (3 H, s and s, $CH_3C{=}C$), 2.57–3.50 (8 H, m, 3-CH_2, 7-CH_2, 8-CH_2 and CH_2CHN), 3.72 and 3.77 (3 H, s, and s, OCH_3), 3.85 (3 H, s, OCH_3), 4.90 (1 H, d, *J* 2.8, C=C*H*H), 5.06 (1 H, d, *J* 2.8, C=CH*H*), 5.13 and 5.16 (1 H, t, *J* 8.5 and t, *J* 8.7, 2-CH), 5.55 (1 H, t, 4.6, 5-CH), 6.39–6.59 (3 H, m, 3 × ArH) and 6.72–6.77 (2 H, m, 2 × ArH); δ_C(100 MHz; $CDCl_3$) 17.1 and 17.2 (CH_3), 29.2 (CH_2), 34.4 (CH_2), 40.7 (CH_2), 41.6 and 41.7 (CH_2), 55.6 (CH_3), 55.7 (CH_3), 55.8 and 55.9 (CH), 85.8 and 86.0 (CH), 108.5 (CH), 111.0 (CH), 112.0 and 112.2 (CH_2), 112.7 (CH), 121.8 (CH), 123.9 (CH), 125.5 (C), 126.0 (C), 126.7 (C), 129.4 (C), 133.3 (C), 143.8 (C), 147.9 (C), 148.7 (C), 155.9 (q, *J* 35.7, CF_3) and 159.0 (C).

5-(3,4-Dimethoxybenzyl)-2-isopropenyl-2,3,5,6,7,8-hexahydrofuro[2,3-*g*]isoquinoline 12

To a solution of the furoisoquinoline **47** (43 mg, 0.09 mmol) in methanol (5 cm^3) was added saturated aqueous potassium carbonate (5 cm^3) and the mixture was stirred for 12 h at 25 °C. The methanol was then removed under reduced pressure and the organic residue was taken up in dichloromethane (10 cm^3). The organic layer was then washed with water (2 × 10 cm^3), dried and then evaporated to dryness to leave the *title compound* (30 mg, 90%) as a pale yellow oil and as a mixture of two diastereoisomers [Found: 214.108 ($M^+ - C_9H_{11}O_2$, 6%). $C_{14}H_{16}NO$ requires *M*, 214.113]; ν_{max}(film)/cm^{-1} 2924, 1515, 1490, 1464, 1262, 1236, 1157, 1140, 1029 and 732; δ_H(250 MHz; $CDCl_3$) 1.765 and 1.773 (3 H, s and s, $CH_3C{=}C$), 2.46 (1 H, s, NH), 2.73–3.34 (8 H, m, 3-CH_2, 7-CH_2, 8-CH_2 and CH_2CHN), 3.83 and 3.86 (3 H, s and s, OCH_3), 3.87 (3 H, s, OCH_3), 4.15 (1 H, dd, *J* 3.7 and 9.4, 5-CH), 4.90 (1 H, d, *J* 1.4, C=C*H*H), 5.08 (1 H, d, *J* 1.4, C=CH*H*), 5.14 (1 H, dd, *J* 8.8 and 8.6, 2-CH), 6.54 (1 H, s, ArH), 6.74 (1 H, dd, *J* 1.8 and 12.5, ArH), 6.78–6.84 (2 H, m, 2 × ArH) and 7.02 (1 H, s, ArH); δ_C(62.5 MHz; $CDCl_3$) 17.18 and 17.23 (CH_3), 30.4 (CH_2), 34.6 (CH_2), 40.8 (CH_2), 42.3 and 42.4 (CH_2), 55.79 and 55.83 (CH_3), 55.88 (CH_3), 57.12 and 57.16 (CH), 85.7 (CH), 109.1 (CH), 111.3 (CH), 111.93 and 111.98 (CH_2), 112.4 (CH), 121.30 and 121.35 (CH), 122.5 (CH), 124.5 (C), 130.4 (C), 131.46 and 131.50 (C), 135.2 (C), 144.1 (C), 147.6 (C), 148.9 (C) and 158.2 (C).

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