Preparation of Analogues of Efaroxan and KU14R as Potential Imidazoline Receptor Subtype 3 Ligands

Richard D. Farn,[a] Noel G. Morgan[b+] and Christopher A. Ramsden[a*]

[a]Lennard-Jones Laboratories, Department of Chemistry, School of Physical and Geographical Sciences, Keele University, Keele, Staffordshire ST5 5BG, England
[b]School of Life Sciences, Keele University, Keele, Staffordshire ST5 5BG, England
+ Present address: Peninsula Medical School, John Bull Building, Research Way, Plymouth PL6 8BU, England

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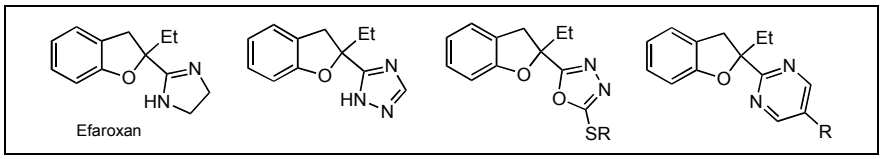

The preparation and characterization of new analogues of the imidazoline insulin secretagogue efaroxan **1** are described. These include 1,2,4-triazole, 1,3,4-oxadiazole, pyrimidine, 1,4,5,6-tetrahydropyrimidine and 1,2-dihydro-1,2,4,5-tetrazine analogues. Bromination of 2,3-dihydro-2-ethylbenzo[*b*]furan-2-carbonitrile **19** gives the 3,3-dibromo analogue **28**, which is readily hydrolysed to the corresponding ketone **29**. Reduction of this ketone gives the alcohol **31** as a mixture of diastereoisomers that is converted to the fluoride **32** using diethylaminosulfur trifluoride.

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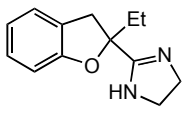
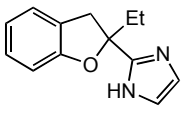
INTRODUCTION

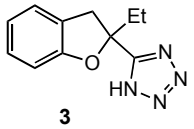
In previous studies we have shown that molecules based on the α_2-antagonist efaroxan **1** also interact with a separate class of binding sites known collectively as imidazoline receptors [1-3]. One member of this subclass, designated I_3, is expressed in pancreatic β-cells and is involved in regulating insulin secretion, leading to the proposal that novel I_3 agonists might be effective as insulin secretagogues in patients with type 2 diabetes [1-6]. A binding site for efaroxan **1** has been identified on the pore-forming subunit, Kir6.2, of ATP-sensitive potassium channels [2] but this is unlikely to represent the principal site involved in stimulation of insulin secretion [3,4]. In support of this, we have shown that structural modifications to the imidazoline ring of efaroxan lead to altered functional properties [1,7]. In particular, we described an imidazole derivative, KU14R **2** [7], that retains the ability of efaroxan to block ATP-sensitive potassium channels [1,8] and to raise intracellular Ca^{2+} [9] but which acts as a functional antagonist of efaroxan-induced insulin secretion in primary islets of Langerhans from rat and man [1,3,4,10], though possibly not in mouse [8,11]. KU14R **2** is likely to interact antagonistically at the I_3 receptor and may be of value for structural characterisation of this site. However, in order to progress further, a larger number of selective ligands are required. In this paper we describe the synthesis of additional molecules in the efaroxan series which were prepared as part of a search for new ligands for characterisation of the I_3 receptor.



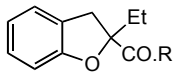
1 Efaroxan



2 KU14R



3



4 (R = OH)
5 (R = OMe)
6 (R = NH_2)
7 (R = NHnPr)

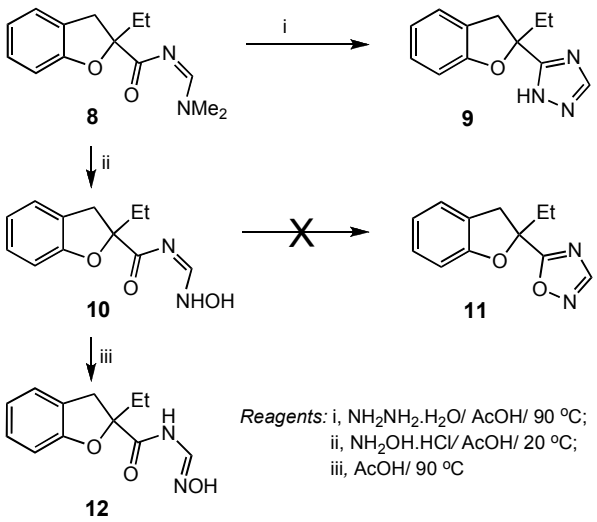
RESULTS AND DISCUSSION

Since the imidazole **2** is of interest but the tetrazole **3** is without significant biological activity [7], our first synthetic target was the 1,2,4-triazole **9** (Scheme 1). This synthesis was achieved by initially converting the amide **6** [7] to the *N*-acylamidine **8** using *N,N*-dimethylformamide dimethyl acetal in hot toluene, with removal of methanol as a distillate during the reaction. In this way the intermediate **8** was isolated as a crystalline solid in 80% yield. Reaction of this amidine **8** with hydrazine hydrate in hot acetic acid gave the triazole **9** as a crystalline solid (80%). The structure **9** was fully supported by elemental analysis and mass spectrometry ($M^{\bullet+}$ *m/z* 215). In the ^{1}H NMR spectrum the triazole proton appears at δ 8.04 and is significantly shifted relative to the amidine proton (δ 8.46) in the precursor **8**. In the ^{13}C NMR spectrum the C-7a and triazole C-5 carbon signals were too weak to be observed.

In common with our previous observations concerning the tetrazole **3** [7], it was found that the triazole **9** also lacks insulin secretagogue activity in

primary rat islets at concentrations up to 100 μM. In addition, it was also established that the triazole **9** failed to reproduce the antagonistic activity of KU14R **2** in rat islets.

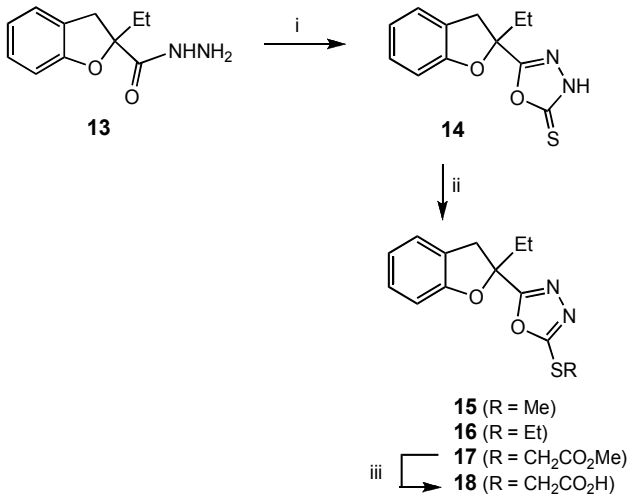
Scheme 1



The amidine intermediate **8** is a potential precursor of the 1,2,4-oxadiazole **11**. However, all attempts to achieve cyclisation using hydroxylamine in acetic acid at room temperature failed [12]. Regardless of the reaction time, a single product was obtained and this was identified as the *N*-hydroxyamidine **10** (67%, mp 108-109 °C). Elemental analysis confirmed the constitution $C_{12}H_{14}N_2O_3$ and the mass spectrum showed a molecular ion (*m/z* 234) with loss of •NHOH (*m/z* 202) and •NCHNHOH (*m/z* 175). When this product was heated in acetic acid under reflux a colourless solid (52%, mp 168-169 °C) was isolated. This product was isomeric with the precursor **10** and a carbonyl absorption (1720 cm^{-1}) indicated that the desired cyclisation had not occurred. The ^1H NMR spectra of product and precursor in $CDCl_3$ were quite distinct which eliminated the possibility of isomorphism. The spectroscopic evidence suggests that this product is the amidoxime tautomer **12**. In the mass spectrum the molecular ion (*m/z* 234) shows loss of •OH (*m/z* 217) but no loss of •NHOH, which is observed in the isomer **10**.

Attention was then directed to the preparation of 1,3,4-oxadiazole derivatives. The hydrazide **13** was readily obtained from the methyl ester **5** by treatment with hydrazine hydrate in hot ethanol. Reaction of the hydrazide **13** with carbon disulfide in hot ethanolic KOH gave the oxadiazole-2-thione **14** in 61% yield (Scheme 2). The presence of C=S (1509 and 1152 cm^{-1}) and NH (3142 cm^{-1}) absorptions in both the solid state and solution IR spectra indicates that this product exists predominantly as the thione tautomer **14**. A broad signal at δ 9.7 in the ^1H NMR spectrum corresponds to the N-3 proton. In the mass spectrum the molecular ion (*m/z* 248) shows loss of the oxadiazole ring (*m/z* 147).

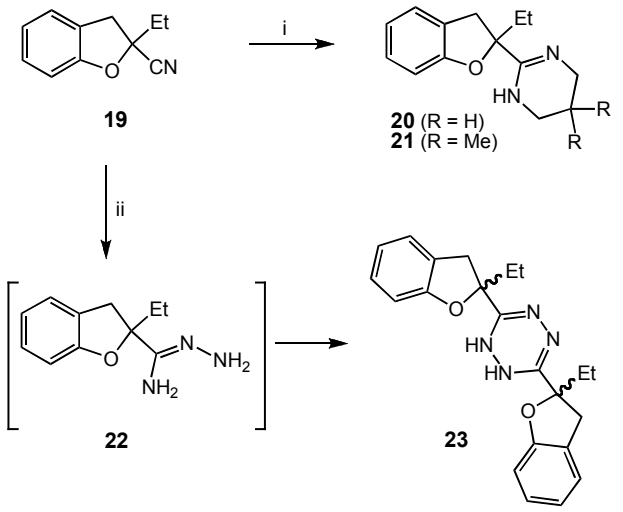
Scheme 2



The thione **14** was alkylated to give the derivatives **15** and **16** by treatment with the corresponding alkyl iodide in 0.1 *M* NaOH at room temperature. The ^1H and ^{13}C NMR spectra of these products were entirely consistent with S-alkylation. Attempts to prepare the acid derivative **18** by a similar treatment at 20–100 °C using chloroacetic acid were unsuccessful. In an alternative approach, the thione **14** was reacted with methyl bromoacetate in dry acetone in the presence of K_2CO_3 to give the ester **17** in 16% yield. This ester was then hydrolysed to the desired acid **18** using 2 *M* NaOH in hot methanol. Elemental analysis and spectroscopy fully support the proposed structures **15**-**18**.

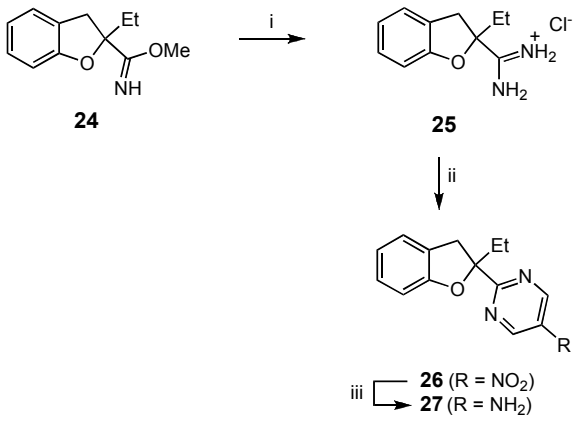
To investigate the effect of the modification of ring size on efaroxan activity we have prepared several pyrimidine and tetrahydropyrimidine analogues. Heating the nitrile **19** [7] with 1,3-diaminopropane and *p*-toluenesulfonic acid in ethylene glycol gave the crystalline tetrahydropyrimidine **20** (mp 93-94 °C) in moderate yield (Scheme 3). A similar procedure using 1,3-diamino-2,2-dimethylpropane gave compound **21**. The ^1H and ^{13}C NMR spectra of both products are in accord with ring formation. It is noteworthy that the N-1 proton in compound **21** appears as a broad singlet and the two NCH_2 groups are non-equivalent indicating that proton exchange is slow, in contrast to other efaroxan derivatives including compound **20**. Compound **20** stimulated insulin secretion from primary rat islets to a similar extent to efaroxan **1** and with similar potency.

Scheme 3



Reagents: i, $R_2C(CH_2NH_2)_2$/ heat; ii, $NH_2NH_2.H_2O$/ heat.

Scheme 4



Reagents: i, NH_4Cl/ MeOH; ii, $Na^{+-}C(NO_2)(CHO)_2$/ heat; iii, Pd/C/H_2

In an attempt to form the amidrazone **22**, which would be a convenient intermediate for several heterocyclic systems, the nitrile **19** was reacted with hydrazine hydrate. No reaction occurred without acid catalysis. In the presence of *p*-toluenesulfonic acid in hot ethanol a crystalline product had formed after twenty-four hours and this was identified as the dihydrotetrazine **23** (58%, mp 158-159 °C). The same product **23** was formed when the imidate **24** was reacted with hydrazine hydrate at room temperature and worked-up without heating. Presumably the initially formed amidrazone **22** undergoes self-condensation, even at room temperature, to give the product **23**. The mass spectrum ($M^{\bullet+}$ *m/z* 376), elemental analysis and the NMR spectra are entirely consistent with structure **23**. The IR spectrum shows NH stretching at 3321 cm^{-1}.

Reaction of the imidate **24** with ammonium chloride in methanol gave the amidine hydrochloride **25** (94%) as a hygroscopic solid. This product was reacted with sodium nitromalonaldehyde in aqueous solution to give after chromatography a low yield (13%) of the nitropyrimidine **26** (mp 76-77 °C) (Scheme 4). A second isolated product was identified as the amide **6**, formed by hydrolysis. The ^1H NMR spectrum of compound **26** showed a singlet at δ 9.51 attributable to the two pyrimidine protons and a strong molecular ion ($M^{\bullet+}$ *m/z* 271(95%)) confirmed the constitution. Reduction of the nitropyrimidine **26** in ethanol using 5% Pd/C as catalyst gave the amine **27** (90%, mp 133-134 °C). The ^1H NMR showed an NH_2 signal at δ 3.65 and, relative to the precursor **26**, the pyrimidine protons had moved up field to δ 8.20.

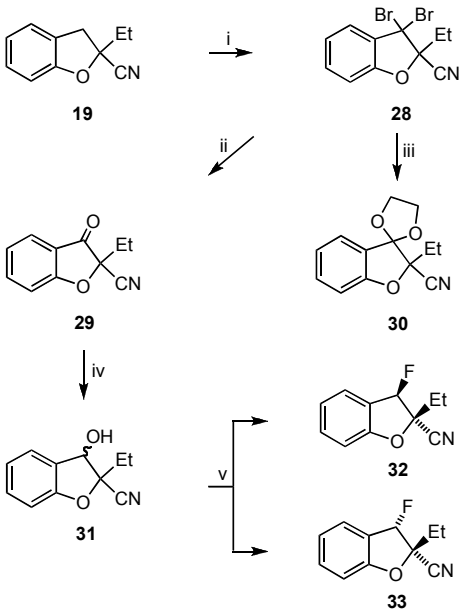
Attempts to prepare *N*-propylamidines from the amide **7** *via* the imidoyl chloride led only to complex mixtures of products.

With the objective of functionalising the tetrahydrofuran ring of efaroxan **1**, we investigated the bromination of the acid **4** [13] using *N*-bromosuccinimide in the presence of 2,2-azo*bis*isobutyronitrile (AIBN) as a radical initiator. This led to a complex mixture including products resulting from bromination of the ethyl sidechain. Multiple products probably arose from participation of the carboxyl group and we therefore directed our attention to bromination of the corresponding nitrile. Reaction of nitrile **19** [7] with *N*-bromosuccinimide and AIBN in carbon tetrachloride under reflux gave the crystalline dibromide **28** in 75% yield after column chromatography (Scheme 5). A small amount of a second product was also isolated and this was identified as the ketone **29**. All analytical and spectroscopic properties of the major product were in accord with structure **28** except that the mass spectrum did not show a molecular ion (*m/z* 331) or the presence of bromine. It transpired that the mass spectrometry samples were routinely dissolved in CH_2Cl_2/ MeOH and the obtained mass spectrum was that of the dimethylketal ($M^{\bullet+}$ *m/z* 233) indicating that the dibromide **28** readily undergoes substitution. We presume that the minor product **29** is formed by hydrolysis of the dibromide on the silica of the column.

Ketal formation was also observed when attempts were made to convert the nitrile **28** into an imidazoline using ethylenediamine in ethylene glycol solution. The only product isolated from this reaction was the cyclic ketal **30** (9%). We therefore decided to convert the dibromide to the ketone **29** and use this for further investigations.

We have found that the ketone **29** can be formed in 63% yield by reaction of the dibromide **28** with silver nitrate in hot aqueous ethanol. In this way the ketone was obtained as a colourless solid (mp 82-83 °C) that was fully characterized. The IR spectrum shows a carbonyl

Scheme 5



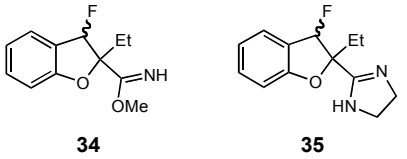
Reagents: i, NBS/ AIBN/ CCl_4/ heat; ii, aq EtOH/ $AgNO_3$; iii, $HOCH_2CH_2OH$/ H^+/ heat; iv, $NaBH_4$/ MeOH; v, DAST.

absorption at 1727 cm^{-1}. The mass spectrum shows a strong fragment ion (*m/z* 159) corresponding to loss of CO or ethylene (*via* a McLafferty rearrangement) from the molecular ion (*m/z* 187).

Reduction of the ketone **29** with sodium borohydride in methanol gave the mixture of secondary alcohols **31** (87%) as a 3:2 mixture of enantiomeric pairs that was not separated. In the ^{1}H NMR spectrum the diastereoisomers show two distinct furanyl C-3 protons (δ 5.10, *J* 9.9 Hz and δ 5.25, *J* 8.6 Hz) that are coupled to the adjacent alcohol protons (δ 2.36, *J* 9.9 Hz and δ 1.74, *J* 8.6 Hz). All other spectroscopic and analytical data support the alcohol structure.

Substitution of hydrogen by fluorine can result in useful modifications of biological properties and we therefore investigated the conversion of the alcohol **31** into the corresponding fluoride. Treatment of the alcohol **31** with diethylaminosulfur trifluoride (DAST) in dichloromethane at –78 °C gave a 63% yield of a mixture of the diastereomeric fluorides **32** and **33** in the ratio 3:1. Using column chromatography it was possible to separate the major diastereoisomer. ^{19}F NMR spectroscopy showed the presence of a fluorine atom coupled to an adjacent proton (δ -155.17, *J* 59.3 Hz). A Nuclear Overhauser Experiment (NOE) involving irradiation of the furanyl C-3 proton and the CH_2 protons indicated that the major enantiomeric pair has the structure **32** in which the fluoro and ethyl substituents have a *syn* relationship. A similar investigation of the diastereomeric mixture of alcohols **31** indicated that in the major enantiomeric pair the OH and ethyl substituents have an *anti* relationship. These results suggest that the fluorination using DAST occurs predominantly with inversion of configuration.

Attempts to convert the fluoronitriles **32/33** into the fluoro analogue of efaroxan **35** *via* the imidate **34** were unsuccessful. Both *in situ* imidate formation and isolation of the imidate were investigated under a variety of conditions. No product formation was observed, even under conditions identical to those that give efaroxan **1** from nitrile **19** [13,14].



EXPERIMENTAL

^{1}H and ^{13}C nmr spectra were recorded using a Bruker Advance DPX300 NMR spectrometer. IR spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrometer or a Thermo Nicolet Avatar 320 FT-IR spectrometer. All IR spectra were measured as thin films (liquids) or potassium bromide discs (solids) and all NMR spectra in $CDCl_3$ with tetramethylsilane as internal standard unless otherwise stated. Only significant bands for the IR spectra are quoted. Mass spectrometry was carried out by the EPSRC National Mass Spectrometry Service, Swansea and elemental analyses by the University of North London Elemental Analysis Service. Melting points were determined on a Kofler block or a Bibby Stuart Scientific SMP3 melting point apparatus and are uncorrected. Boiling points were determined using Gallenkamp melting point apparatus. Column chromatography was carried out using BDH silica gel (particle size 33-70 μm) and chromatatron chromatography was carried out using a LDC Analytical Consta Metric 3200 solvent delivery system and plates made using Merck silica gel 60 PF_{254} containing gypsum.

2,3-Dihydro-2-ethylbenzo[*b*]furan-2-carboxylic acid dimethylaminomethyleneamide (8). Dimethylformamide dimethyl acetal (0.95 mL, 7.2 mmol) was added to a solution of 2,3-dihydro-2-ethylbenzo[*b*]furan-2-carboxamide **6** (1.0 g, 5.2 mmol) [7] and dry toluene (6.0 mL) in a distillation flask. The mixture was heated at 120 °C during which time a small quantity of colourless liquid (bp 55-58 °C) was collected. The flask was cooled when distillation had ceased and the solvent was removed under reduced pressure to leave a green oil that crystallised on standing. The solid was recrystallised from ethyl acetate-petroleum ether and identified as the amidine **8** (0.74 g, 80%), colourless crystals, mp 66-67 °C; ir (KBr): 2974, 1667 and 1603 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 0.97 (t, 3H, *J* 7.4 Hz, CH_3CH_2), 2.08 (m, 2H, CH_3CH_2), 3.08 (s, 3H, NCH_3), 3.11 (s, 3H, NCH_3), 3.15 (d, 1H, *J* 16.2 Hz, $ArCH_aH_b$), 3.63 (d, 1H, *J* 16.2 Hz, $ArCH_aH_b$), 6.80 (m, 1H, arom H), 6.89 (d, 1H, *J* 7.9 Hz, arom H), 7.07-7.12 (m, 2H, arom H), 8.46 (s, 1H, N=C*H*N); ms: *m/z* 246(6%)($M^{\bullet+}$), 217(4), 174(2), 147(6), 131(17), 115(5), 99(100), 91 (26%), 77(6). *Anal.* Calcd. for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.50; H, 7.62; N, 11.20.

3-(2,3-Dihydro-2-ethylbenzo[*b*]furan-2-yl)-4*H*-[1,2,4]-triazole (9). To a mixture of hydrazine hydrate (0.22 mL, 4.5 mmol) and acetic acid (10.0 mL) was added the amidine **8** (1.04 g, 4.1 mmol). The mixture was stirred (1.5 h) at 90 °C before removal of solvent under reduced pressure. Diethyl ether (5 mL) was added and the mixture was cooled overnight to yield colourless crystals. Recrystallisation from chloroform gave the triazole **9** (0.88 g, 80%), colourless solid, mp 177-178 °C; ir (KBr): 3135, 1597, 1532, 1479, 1459, 1433 and 763cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 0.87 (t, 3H, *J* 7.4 Hz, C*H*$_3$CH$_2$), 2.09 (m, 2H, CH$_3$C*H*$_2$), 3.39 (d, 1H, *J* 16.0 Hz, C*H*$_a$H$_b$), 3.64 (d, 1H, *J* 16.0 Hz, CH$_a$*H*$_b$), 6.77-6.84 (m, 2H, arom H), 7.05-7.19 (m, 2H, arom H), 8.04 (s, 1H, NC*H*N); ^{13}C nmr ($CDCl_3$): δ 8.1 (*C*H$_3$CH$_2$), 33.5 (CH$_3$*C*H$_2$), 40.8 (*C*(3)), 88.5 (*C*(2)), 109.6 (*C*H), 121.4 (*C*H), 125.2 (*C*(3a), 125.8 (*C*H), 128.3 (*C*H), 158.2 (NC*H*N); ms: *m/z* 215(11%)(M$^{\bullet+}$), 198(100), 186(14), 146(15), 131(33), 115(10), 91(2), 85(34), 83.9(56), 77(24), 70(18), 63(11), 49(36). *Anal.* Calcd. for $C_{12}H_{13}N_3O$: C, 66.96; H, 6.09; N, 19.52. Found: C, 66.88; H, 6.12; N, 19.57.

2,3-Dihydro-2-ethylbenzo[*b*]furan-2-carboxylic acid hydroxyaminomethyleneamide (10). Hydroxylamine hydrochloride (0.34 g, 4.8 mmol) was added to the amidine **8** (1.0 g, 4.1 mmol) dissolved in a mixture of 5 *M* NaOH (1.0 mL) and 70% acetic acid (5.0 mL). The solution was stirred at room temperature (10 min) and water (3.0 mL) was then added. The reaction mixture was then cooled (ice bath), stirred at 0 °C (1 h) and extracted with CH_2Cl_2. The combined organic extracts were washed with water and dried ($MgSO_4$) before removal of the solvent under reduced pressure to yield a colourless oil that solidified on standing. This product was recrystallised from petroleum ether (bp 60-80 °C)/ ethyl acetate and identified as the *N*-hydroxyamidine **10** (0.28 g, 67%), colourless crystals, mp 108-109 °C; ir (KBr): 3378, 3212, 1718 and 1633 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 1.11 (t, 3H, *J* 7.4 Hz, C*H*$_3$CH$_2$), 2.01-2.29 (m, 2H, CH$_3$C*H*$_2$), 3.33 (d, 1H, *J* 16.4 Hz, ArC*H*$_a$H$_b$), 3.68 (d, 1H, *J* 16.4 Hz, ArCH$_a$*H*$_b$), 3.67 (br s, 1H, OH), 7.00 (d, 1H, *J* 8.6 Hz, arom H), 7.04 (dd, 2H, *J* 8.6 and 8.3 Hz, arom H), 7.27 (m, 2H, arom H), 7.80 (br d, 1H, NC*H*N), 9.53 (br d, 1H, NCHN*H*OH); ^{13}C nmr ($CDCl_3$): δ 7.95 (*C*H$_3$CH$_2$), 31.60 (CH$_3$*C*H$_2$), 38.95 (*C*(3)), 91.0 (*C*(2)), 110.09 (*C*H), 121.99 (*C*H), 124.86 (*C*(3a)), 125.03 (*C*H), 128.54 (*C*H), 152.90 (*C*(7a)), 157.36 (N*C*NHOH), 175.64 (*C*=O); ms: *m/z* 234(21%)(M$^{\bullet+}$), 216(3), 202(5), 175(13), 147(99), 131(21), 91(100), 77(18), 44(16). *Anal.* Calcd. for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.17; H, 5.56; N, 11.68.

2,3-Dihydro-2-ethylbenzo[*b*]furan-2-carboxylic acid hydroxyiminomethylamide (12). The *N*-hydroxyamidine **10** (0.6 g, 2.5 mmol) was dissolved in acetic acid (5.0 mL) and heated at 120 °C (2 h). After cooling the crude reaction mixture was diluted with water (8.0 mL) and chilled in an ice bath (2 h). The resultant colourless precipitate was collected, dried and after recrystallisation from ethyl acetate/ petroleum ether (bp 60-80 °C) identified as compound **12** (0.31 g, 52%), colourless crystals, mp 168-169 °C; ir (KBr): 3393, 3232, 1720, 1588, 1364 and 761 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 1.03 (t, 3H, *J* 7.4 Hz, CH$_2$C*H*$_3$), 1.94-2.19 (m, 2H, C*H*$_2$CH$_3$), 3.25 (d, 1H, *J* 16.5 Hz, ArC*H*$_a$H$_b$), 3.60 (d, 1H, *J* 16.5 Hz, ArCH$_a$*H*$_b$), 5.2 (s, 1H, NHC*H*N), 6.90 (d, 1H, *J* 7.9 Hz, arom H), 6.95 (dd, 1H, *J* 7.9 and 7.1 Hz, arom H), 7.17-7.22 (m, 2H, arom H), 8.11 (br s, 1H, OH), 8.64 (br s. 1H, NH); ms: *m/z* 234(37%)(M$^{\bullet+}$), 217(10), 205(17), 175(11), 174(55), 159(14), 148(42), 147(98), 131(89), 91(100), 77(59), 44(87). *Anal.* Calcd. for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.23; H, 5.66; N, 11.70.

Methyl 2,3-dihydro-2-ethylbenzo[*b*]furan-2-carboxylate (5). Methyl iodide (9.11 g, 64 mmol) and potassium carbonate (6.26 g, 45 mmol) were added to a solution of the carboxylic acid **4** (6.0 g, 31 mmol) [13] in DMF (125 mL). The mixture was stirred at room temperature overnight and then water (100 mL) was added and the aqueous solution extracted with chloroform (3 x 50 mL). The combined organic extracts were washed with saturated aqueous NaCl solution, water and dried ($MgSO_4$). Filtration followed by evaporation under reduced pressure gave the ester **5** (5.41 g, 84%), pale yellow oil, bp 274 ºC at 760 mm Hg; ir (film): 2952, 2360, 1736, 1482, 1241 and 751 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 1.00 (t, 3H, *J* 7.4 Hz, CH$_2$C*H*$_3$), 1.97-2.12 (m, 2H, C*H*$_2$CH$_3$), 3.19 (d, 1H, *J* 16.2 Hz, ArC*H*$_a$H$_b$), 3.58 (d, 1H, *J* 16.2 Hz, ArCH$_a$*H*$_b$), 3.80 (s, 3H, OC*H*$_3$), 6.85-6.90 (m, 2H, arom H), 7.12-7.15 (m, 2H, arom H); ^{13}C nmr ($CDCl_3$): δ 8.12 (*C*H$_3$CH$_2$), 31.53 (CH$_3$*C*H$_2$), 38.76 (*C*(3)), 52.68 (O*C*H$_3$), 90.31 (*C*(2)), 109.69 (*C*H), 120.95 (*C*H), 124.70 (*C*(3a)), 125.17 (*C*H), 128.28 (*C*H), 158.62 (*C*(7a)), 173.61 (*C*=O); ms: *m/z* 206(29%)(M$^{\bullet+}$), 174(11), 159(7), 147(99), 131(34), 119(11), 115(10), 91(100), 77(14), 59(11). *Anal.* Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.98; H, 6.90.

2,3-Dihydro-2-ethylbenzo[*b*]furan-2-carboxylic acid hydrazide (13). The ester **5** (1.0 g, 4.9 mmol) and hydrazine hydrate (0.31 g, 10 mmol) were heated under reflux (3 h) in ethanol solution. The reaction mixture was cooled and evaporated giving a solid product, which after recrystallisation from a mixture of ethyl acetate and petroleum ether (bp 60-80 °C) was identified as the hydrazide **13** (0.83 g, 81%), colourless crystals, mp 59-60.5 °C; ir (KBr): 3275, 2972, 1675, 1617, 1482, 1460, 1244, 956 and 750 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 0.97 (t, 3H, *J* 7.4 Hz, C*H*$_3$CH$_2$), 1.87-2.16 (m, 2H, CH$_3$C*H*$_2$), 3.20 (d, 1H, *J* 16.4 Hz, ArC*H*$_a$H$_b$), 3.55 (d, 1H, *J* 16.4 Hz, ArCH$_a$*H*$_b$), 6.83 (d, 1H, *J* 8.3 Hz, arom H), 6.90 (dd, 1H, *J* 7.3 and 7.4 Hz, arom H), 7.12-7.26 (m, 2H, arom H), 7.86 (br s, 1H, N*H*); ^{13}C nmr ($CDCl_3$): δ 8.03 (*C*H$_3$CH$_2$), 31.52 (CH$_3$*C*H$_2$), 39.19 (*C*(3)), 91.40 (*C*(2)), 109.64 (*C*H), 121.51 (*C*H), 125.11 (*C*(3a)), 125.52 (*C*H), 128.21 (*C*H), 157.81 (*C*(7a)), 173.911 (*C*=O); ms: *m/z* 206(9%)(M$^{\bullet+}$), 175(13), 147(35), 131(28), 115(10), 91(100), 89(14), 77(30). *Anal.* Calcd. for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 63.96; H, 6.85; N, 13.68.

5-(2,3-Dihydro-2-ethylbenzo[*b*]furan-2-yl)-3*H*-[1,3,4]-oxadiazole-2-thione (14). To a solution of the hydrazide **13** (2.89 g, 14 mmol) in 95% ethanol (56 mL) was added potassium hydroxide (0.79 g, 14 mmol) and carbon disulfide (1.52 g, 20 mmol). The mixture was heated under reflux (50 h) and then cooled and concentrated on a rotary evaporator. The residue was dissolved in water and poured onto a mixture of conc. HCl and ice to yield a brown precipitate, which turned to an oil upon filtration. The aqueous filtrate was extracted with CH_2Cl_2 and the organic extracts combined with the oil and the solvent removed to give crude oxadiazole as a brown oil. The product was dissolved in 0.25 *M* NaOH and the insoluble residue removed by decanting. Acidification of the aqueous phase precipitated a solid product that was identified as the oxadiazole **14** (2.12 g, 61%), colourless crystals, mp 83-84 ºC; ir (KBr): 3142, 2968, 2365, 1617, 1509, 1480, 1234, 1152, 961 and 754 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 0.95 (t, 3H, *J* 7.4 Hz, C*H*$_3$CH$_2$), 2.15 (q, 2H, *J* 7.4 Hz, CH$_3$C*H*$_2$), 3.28 (d, 1H, *J* 16.1 Hz, ArC*H*$_a$H$_b$), 3.66 (d, 1H, *J* 16.1 Hz, ArCH$_a$*H*$_b$), 6.78 (d, 1H, *J* 7.9 Hz, arom H), 6.86 (dd, 1H, *J* 7.4 and 6.7 Hz, arom H), 7.08-7.13 (m, 2H, arom

H), 9.74 (br s, 1H, NH); ^{13}C nmr ($CDCl_3$): δ 7.85 (*C*H_3CH$_2$), 30.83 (CH$_3$*C*H$_2$), 37.90 (*C*(3)), 85.52 (*C*(2)), 109.99 (*C*H), 121.68 (*C*H), 124.55 (*C*(3a)), 124.88 (*C*H), 128.72 (*C*H), 157.86 (*C*(7a)), 164.40 (O*C*N), 178.93 (*C*=S); ms: *m/z* 248(89%)(M$^{\bullet+}$), 187(10), 173(53), 159(12), 147(52), 131(50), 107(21), 91(100), 77(39). *Anal.* Calcd. for $C_{12}H_{12}N_2O_2S$: C, 58.05; H, 4.87; N, 11.28. Found: C, 58.19; H, 4.71; N, 11.20.

2-(2',3'-Dihydro-2'-ethylbenzo[*b*]furan-2'-yl)-5-methylsulfanyl-[1,3,4]oxadiazole (15). To a stirred solution of the oxadiazole **14** (0.25 g, 1 mmol) in 0.1 *M* NaOH (10.0 mL) was added iodomethane (0.14 g, 1 mmol) and the mixture was stirred at room temperature (18 h). The solution was then extracted with CH_2Cl_2 (x 3) and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution, water and dried ($MgSO_4$). Evaporation under reduced pressure gave the oxadiazole **15** (0.21 g, 80%), viscous brown oil; ir (film): 2973, 2936, 1597, 1480, 1329, 1239, 1145, 978, 872 and 751 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 1.00 (t, 3H, *J* 7.4 Hz, C*H*$_3$CH$_2$), 2.24 (q, 2H, *J* 7.4 Hz, CH$_3$C*H*$_2$), 2.70 (s, 3H, SCH$_3$), 3.38 (d, 1H, *J* 16.0 Hz, ArC*H*$_a$H$_b$), 3.95 (d, 1H, *J* 16.0 Hz, ArCH$_a$*H*$_b$), 6.82 (d, 1H, *J* 7.8 Hz, arom H), 6.91 (dd, 1H, *J* 7.3 and 7.7 Hz, arom H), 7.14 (t, 1H, *J* 7.7 and 7.8 Hz, arom H), 7.21 (d, 1H, *J* 7.3 Hz, arom H); ^{13}C nmr ($CDCl_3$): δ 6.89 (*C*H$_3$CH$_2$), 13.51 (S*C*H$_3$), 30.51 (CH$_3$*C*H$_2$), 37.15 (*C*(3)), 84.90 (*C*(2)), 108.61 (*C*H), 120.29 (*C*H), 123.89 (*C*(3a)), 124.24 (*C*H), 127.36 (*C*H), 156.93 (*C*(7a)), 16.44 (O*C*N), 167.08 (*C*=S); ms: *m/z* 262(18%)(M$^{\bullet+}$), 245(12), 233(8), 215(95), 187(6), 173(42), 158(13), 146(98), 131(75), 115(39), 107(12), 91(100), 77(44), 75(35), 63(25), 51(22). *Anal.* Calcd. for $C_{13}H_{14}N_2O_2S$: C, 59.52; H, 5.38; N, 10.68. Found: C, 59.59; H, 5.14; N, 10.50.

2-(2',3'-Dihydro-2'-ethylbenzo[*b*]furan-2'-yl)-5-ethylsulfanyl-[1,3,4]oxadiazole (16). Using ethyl iodide in a procedure otherwise identical to that described for compound **15** gave the oxadiazole **16** (0.15 g, 53%), viscous yellow oil; ir (film): 2972, 2935, 1597, 1480, 1329, 1239, 1143, 963, 872 and 751 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 1.00 (t, 3H, *J* 7.5 Hz, C*H*$_3$CH$_2$), 1.36 (t, 3H, *J* 7.4 Hz, SCH$_2$C*H*$_3$), 2.14 (q, 2H, *J* 7.5 Hz, CH$_3$C*H*$_2$), 3.14 (q, 2H, *J* 7.4 Hz, SC*H*$_2$CH$_3$), 3.28 (d, 1H, *J* 16.0 Hz, ArC*H*$_a$H$_b$), 3.85 (d, 1H, *J* 16.0 Hz, ArCH$_a$*H*$_b$), 6.72 (d, 1H, *J* 8.0 Hz, arom H), 6.80 (dd, 1H, *J* 7.3 and 7.4 Hz, arom H), 7.04 (dd, 1H, *J* 8.0 and 7.4 Hz, arom H), 7.11 (d, 1H, *J* 7.3 Hz, arom H); ^{13}C nmr ($CDCl_3$): δ 6.90 (*C*H$_3$CH$_2$), 13.59 (SCH$_2$*C*H$_3$), 25.88 (S*C*H$_2$CH$_3$), 30.53 (CH$_3$*C*H$_2$), 37.15 (*C*(3)), 84.79 (*C*(2)), 108.61 (*C*H), 120.27 (*C*H), 123.88 (*C*(3a)), 124.26 (*C*H), 127.35 (*C*H), 156.95 (*C*(7a)), 164.76 (O*C*N), 166.92 (*C*-S); ms: *m/z* 279(2%)(M$^{\bullet+}$), 248(5), 215(12), 173(30), 157(12), 146(52), 131(100), 107(42), 91(92), 77(48), 63(23), 51(28), 45(28). *Anal.* Calcd. for $C_{14}H_{16}N_2O_2S$: C, 60.85; H, 5.84; N, 10.14. Found: C, 60.69; H, 5.71; N, 10.06.

Methyl 2-[5-(2',3'-dihydro-2'-ethylbenzo[*b*]furan-2'-yl)-[1,3,4]-oxadiazol-2-ylsulfanyl]acetate (17). Methyl 2-bromoacetate (0.5 mL, 5.4 mmol) was added to a stirred solution of the oxadiazole **14** (1.2 g, 4.8 mmol) and anhydrous potassium carbonate (0.8 g, 5.8 mmol) in dry acetone (6.0 mL). The reaction mixture was heated to 60 °C with stirring (16 h) after which time no starting material was detected by tlc. The solvent and excess methyl 2-bromoacetate were removed under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate (3:1) as eluent) to give compound **17** (0.25 g, 16%), colourless crystals, mp 46-47 °C; ir (KBr): 2951, 2359, 1746, 1598, 1480, 1319, 1235, 1164, 1078, 871 and 758 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 0.99 (t, 3H, *J* 7.4 Hz, C*H*$_3$CH$_2$), 2.24 (q, 2H, *J* 7.4 Hz, CH$_3$C*H*$_2$), 3.38 (d, 1H, *J* 16.0 Hz, ArC*H*$_a$H$_b$), 3.77 (s, 3H, OC*H*$_3$), 3.93 (d, 1H, *J* 16.0 Hz, ArCH$_a$*H*$_b$), 4.05 (s, 2H, SC*H*$_2$), 6.82 (d, 1H, *J* 8.0 Hz, arom H), 6.91 (t, 1H, *J* 7.5 Hz, arom H), 7.15 (dd, 1H, *J* 8.0 and 7.5 Hz, arom H), 7.20 (d, 1H, *J* 7.5 Hz, arom H); ^{13}C nmr ($CDCl_3$): δ 8.30 (*C*H$_3$CH$_2$), 31.96 (CH$_3$*C*H$_2$), 34.43 (S*C*H$_2$), 38.64 (*C*(3)), 53.60 (O*C*H$_3$), 86.20 (*C*(2)), 110.11 (*C*H), 121.79 (*C*H), 125.33 (*C*(3a)), 125.59 (*C*H), 128.85 (*C*H), 158.34 (*C*(7a)), 164.73 (N*C*O), 168.25 (*C*-S), 168.95 (*C*O$_2$Me); ms: *m/z* 320(4%)(M$^{\bullet+}$), 303(4), 291(3), 215(32), 173(10), 147(22), 146(43), 131(32), 115(20), 103(10), 91(81), 89(20), 77(30), 59(100), 46(27), 45(41). *Anal.* Calcd. for $C_{15}H_{16}N_2O_4S$: C, 56.24; H, 5.03; N, 8.74. Found: C, 56.12; H, 4.97; N, 8.84.

2-[5-(2',3'-Dihydro-2'-ethylbenzo[*b*]furan-2'-yl)-[1,3,4]-oxadiazol-2-ylsulfanyl]acetic acid (18). To a solution of the ester **17** (0.54 g, 1.7 mmol) in methanol (10.0 mL) was added 2 *M* NaOH (2.0 mL) and the mixture was heated at 70 °C (3 days). The methanol was then evaporated, the residue treated with 2 *M* HCl (25.0 mL) and the acid solution extracted with CH_2Cl_2 (x 3). The combined organic extracts were washed with water, dried ($MgSO_4$) and evaporated to leave a yellow oil. This product was crystallised from ethyl acetate/petroleum ether (bp 60-80 °C) and identified as the carboxylic acid **18** (0.19 g, 38%), colourless crystals, m.p: 102-103 °C; ir (KBr): 2984, 1752, 1588, 1480, 1341, 1239, 1172, 963, 943, 877 and 759 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 0.92 (t, 3H, *J* 7.4 Hz, C*H*$_3$CH$_2$), 2.16 (q, 2H, *J* 7.4 Hz, CH$_3$C*H*$_2$), 3.31 (d, 1H, *J* 16.0 Hz, ArC*H*$_a$H$_b$), 3.83 (d, 1H, *J* 16.0 Hz, ArCH$_a$*H*$_b$), 3.99 (s, 2H, SC*H*$_2$CO), 6.75 (d, 1H, *J* 8.0 Hz, arom H), 6.83 (dd, 1H, *J* 7.6 and 7.3 Hz, arom H), 7.08 (dd, 1H, *J* 7.6 and 8.0 Hz, arom H), 7.13 (d, 1H, *J* 7.3 Hz, arom H); ^{13}C nmr ($CDCl_3$): δ 6.85 (*C*H$_3$CH$_2$), 30.51 (CH$_3$*C*H$_2$), 32.99 (S*C*H$_2$CO$_2$), 37.29 (*C*(3)), 84.77 (*C*(2)), 108.74 (*C*H), 120.45 (*C*H), 123.92 (*C*(3a)), 124.06 (*C*H), 127.48 (*C*H), 156.88 (*C*(7a)), 163.67 (O*C*N), 167.76 (*C*-S), 170.27 (*C*=O); ms: *m/z* 306(8%)(M$^{\bullet+}$), 289(7), 248(19), 215(50), 173(38), 158(12), 146(98), 131(80), 91(100), 77(32), 63(13), 51(14), 45(28). *Anal.* Calcd. for $C_{14}H_{14}N_2O_4S$: C, 54.89; H, 4.61; N, 9.14. Found: C, 54.69; H, 4.57; N, 9.17.

2-(2',3'-Dihydro-2'-ethylbenzo[*b*]furan-2'-yl)-1,4,5,6-tetrahydropyrimidine (20). A mixture of 2,3-dihydro-2-ethylbenzo-[*b*]furan-2-carbonitrile **19** (1.0 g, 5.8 mmol) [7], ethylene glycol (4.2 mL), 1,3-diaminopropane (0.65 mL, 7.7 mmol) and *p*-toluenesulfonic acid (0.68 g, 3.6 mmol) was heated with stirring (24 h). After removal of the solvent under reduced pressure, water (15.0 mL) was added with stirring followed by solid NaOH (0.35 g, 8.8 mmol). The mixture was extracted with CH_2Cl_2, dried ($MgSO_4$) and the solvent evaporated to leave a dark brown oil. This oil was mixed with hot petroleum ether (bp 60-80 °C). The solvent was then decanted and evaporated to yield an olive green oil which after drying under reduced pressure produced a pale orange solid. Recrystallisation from petroleum ether (bp 60-80 °C) yielded the tetrahydropyrimidine **20** (0.5 g, 38%), colourless solid, mp 93-94 °C; ir (KBr): 3401, 2972, 2924, 2854, 1634 and 1472 cm^{-1} ; ^{1}H nmr ($CDCl_3$): δ 0.82 (t, 3H, *J* 7.4 Hz, C*H*$_3$CH$_2$), 1.56-1.63 (m, 2H, CH$_2$C*H*$_2$CH$_2$), 1.72-1.84 (m, 1H, CH$_3$C*H*$_a$H$_b$), 1.89-2.00 (m, 1H, CH$_3$CH$_a$*H*$_b$), 3.05 (d, 1H, *J* 16.3 Hz, ArC*H*$_c$H$_d$), 3.16-3.28 (m, 4H, C*H*$_2$CH$_2$C*H*$_2$), 3.51 (d, 1H, *J* 16.3, ArCH$_c$*H*$_d$), 6.71-6.82 (m, 2H, arom H), 7.02-7.08 (m, 2H, arom H); ^{13}C nmr ($CDCl_3$): δ 6.75 (*C*H$_3$CH$_2$), 19.18 (CH$_3$*C*H$_2$), 32.02 (CH$_2$*C*H$_2$CH$_2$), 38.57 (*C*(3)), 89.90 (*C*(2)), 107.86 (*C*H), 119.44 (*C*H), 123.65 (*C*(3a)), 125.47 (*C*H), 126.36 (*C*H), 156.82 (*C*(7a)), 157.82 (N*C*N); ms: *m/z*

230(13%)($M^{\bullet+}$), 213(20), 201(100), 91(31). *Anal.* Calcd. for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16. Found: C, 72.96; H, 7.80; N, 11.99.

2-(2',3'-Dihydro-2'-ethylbenzo[*b*]furan-2'-yl)-5,5-dimethyl -1,4,5,6-tetrahydropyrimidine (21). A mixture of 2,3-dihydro-2-ethyl-benzo[*b*]furan-2-carbonitrile **19** (0.5 g, 2.9 mmol) [7], ethylene glycol (3.0 mL), 1,3-diamino-2,2-dimethylpropane (0.33 mL, 2.7 mmol) and *p*-toluenesulfonic acid (0.52 g, 2.7 mmol) was heated at 190 ºC with stirring (24 h). The solvent was then removed using a Kugelröhr micro-distillation apparatus. A solution of NaOH (0.18 g, 4.5 mmol) in water (15.0 mL) was added and the mixture stirred (10 min) at room temperature. The product was then extracted with CH_2Cl_2, dried ($MgSO_4$) and evaporated to a dark brown oil. The oil was mixed with hot petroleum ether (bp 60-80 °C). The solvent was then decanted and evaporated to yield a yellow oil, which after continued drying under reduced pressure produced a pale orange solid. Recrystallisation from petroleum ether (bp 60-80 ºC) gave the tetrahydropyrimidine **21** (0.1 g, 13%), colourless needles, mp 103.5-105 ºC; ir (KBr): 3194, 2970, 2947, 2359, 1634, 1513, 1278, 953 and 746 cm^{-1}; ^1H nmr ($CDCl_3$): δ 0.81 (s, 3H, C(5')CH_3), 0.87 (t, 3H, *J* 7.4 Hz, CH_3CH$_2$), 0.90 (s, 3H, C(5')CH_3), 1.78-2.08 (m, 2H, CH_2CH$_3$), 2.81 (m, 2H, CH_2C(CH$_3$)$_2$CH$_2$), 3.01 (m, 2H, CH$_2$C(CH$_3$)$_2$CH_2), 3.11 (d, 1H, *J* 16.2 Hz, ArCH_aH$_b$), 3.56 (d, 1H, *J* 16.2 Hz, ArCH$_a$$H_b$), 5.49 (s, 1H, N*H*), 6.74 (d, 1H, *J* 7.9 Hz, arom H), 6.79 (m, 1H, arom H), 7.30-7.36 (m, 2H, arom H); ^{13}C nmr ($CDCl_3$): δ 8.12 (*C*H$_3$CH$_2$), 25.10 (CH$_2$*C*(CH$_3$)$_2$CH$_2$), 26.32 (CH$_3$*C*H$_2$), 32.81 (CH$_2$*C*(CH$_3$)$_2$CH$_2$), 40.29 (*C*(3)), 50.77 (*C*(4')), 56.64 (C(6')), 91.32 (*C*(2)), 109.30 (*C*H), 120.86 (*C*H), 125.06 (*C*H), 126.87, (*C*(3a)), 127.78 (*C*H), 158.20 (*C*(7a)), 158.25 (*C*=N); ms: *m/z* 258(14%)($M^{\bullet+}$), 241(20), 229(100), 144(6), 131(9), 112(11), 91(30), 77(11). *Anal.* Calcd. for $C_{16}H_{22}N_2O$: C, 74.38; H, 8.58; N, 10.84. Found: C, 74.44; H, 8.62; N, 10.73.

3,6-Bis-(2',3'-dihydro-2'-ethylbenzo[*b*]furan-2'-yl)-1,2-dihydro-1,2,4,5-tetrazine (23). To a stirred solution of 2,3-dihydro-2-ethylbenzo[*b*]furan-2-carbonitrile **19** (1.5 g, 7.9 mmol) [7] in ethanol (8.0 mL) were added hydrazine hydrate (2.0 mL, 41 mmol) and *p*-toluenesulfonic acid monohydrate (0.2 g, 1.1 mmol). The mixture was heated under reflux (24 h), after which tlc showed no presence of the nitrile **19** and a colourless precipitate had formed. The reaction mixture was cooled to room temperature and the solid collected. This product was recrystallised from ethyl acetate and identified as the dihydrotetrazine **23** (0.86 g, 58%), colourless crystals, mp 158-159 °C; ir (KBr): 3221, 3030, 2359, 1649, 1594, 1479, 1458, 1361, 1233, 1175, 943 and 869 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.11 (t, 6H, *J* 7.4 Hz, CH_3CH$_2$), 2.03-2.16 (m, 4H, CH$_3$CH_2), 3.26 (d, 2H, *J* 16.0 Hz, ArCH_aH$_b$), 3.68 (d, 2H, *J* 16.0 Hz, ArCH$_a$$H_b$), 6.89 (d, 2H, *J* 8.1 Hz, arom H), 6.96 (t, 2H, *J* 7.40 Hz, arom H), 7.17-7.23 (m, 4H, arom H); ^{13}C nmr ($CDCl_3$): δ 8.49 (*C*H$_3$CH$_2$), 32.86 (CH$_3$*C*H$_2$), 39.68 (*C*(3)), 89.47 (*C*(2)), 110.05 (*C*H), 121.66 (*C*H), 125.36 (*C*(3a)), 126.36 (CH), 128.56 (CH), 152.86 (*C*(7a)), 158.30 (N*C*N); ms: *m/z* 376(50%)($M^{\bullet+}$), 359(11), 347(10), 229(3), 213(13), 188(9), 172(21), 159(8), 146 (21%), 131(50), 118(19), 107(60), 91(100), 89(20), 77(38), 65(10), 53(10). *Anal.* Calcd. for $C_{22}H_{24}N_4O_2$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.00; H, 6.36; N, 14.91.

Methyl 2,3-dihydro-2-ethylbenzo[*b*]furan-2-carboximidate (24). 2,3-Dihydro-2-ethylbenzo[*b*]furan-2-carbonitrile **19** (1.0 g, 5.8 mmol) [7] was added to a solution of sodium metal (0.02 g, 0.86 mmol) in methanol (12.0 mL). The flask was stoppered and allowed to stand at room temperature until no starting material could be detected by tlc (4 days). One drop of acetic acid was then added and the solvent was removed under reduced pressure to give a yellow oil. This residue was partitioned between CH_2Cl_2 and distilled water. The aqueous phase was extracted with two further portions of CH_2Cl_2 and the combined organic extracts were washed with water, dried ($MgSO_4$) and evaporated to give the imidate **24** (0.84 g, 71%), yellow oil, bp 154 °C 760 mm Hg; ir (film): 3324, 2975, 2942, 1661, 1598, 1482, 1463, 1329, 1089, 868 and 750cm^{-1}; ^1H nmr ($CDCl_3$): δ 0.93 (t, 3H, *J* 7.4 Hz, CH_3CH$_2$), 1.82-2.04 (m, 2H, CH$_2$CH$_3$), 3.59 (d, 1H, *J* 16.2 Hz, ArCH_aH$_b$), 3.39 (d, 1H, *J* 16.2 Hz, ArCH$_a$$H_b$), 3.80 (s, 3H, OMe), 6.85-6.89 (m, 2H, arom H), 7.10-7.16 (m, 2H, arom H), 7.83 (br s, 1H, NH); ^{13}C nmr ($CDCl_3$): δ 10.09 (*C*H$_3$CH$_2$), 33.22 (CH$_3$*C*H$_2$), 41.25 (*C*(3)), 55.53 (O*C*H$_3$), 91.49 (*C*(2)), 111.61 (*C*H), 123.04 (*C*H), 126.83 (*C*(3a)), 127.43 (*C*H), 130.11 (*C*H), 160.14 (*C*(7a)), 174.64 (*C*=N), ms: *m/z* 205(22%)($M^{\bullet+}$), 188(47), 176(48), 174(38), 147(15), 131(30), 115(14), 92(13), 91(100), 89(28), 77(48), 63(20).

2,3-Dihydro-2-ethylbenzo[*b*]furan-2-carboxamidine hydrochloride (25). Ammonium chloride (0.19 g, 3.5 mmol) was added to a solution of the imidate **24** (0.72 g, 3.5 mmol) in methanol (3.5 mL) and the mixture was stirred at room temperature (48 h). After evaporation the residue was partitioned between CH_2Cl_2 and water. The aqueous phase was washed with a further portion of CH_2Cl_2 and then evaporated *in vacuo* to yield the crude amidine hydrochloride **25** as a colourless oil that solidified on standing. The crude product was dissolved in water and filtered to remove insoluble impurities before evaporation under reduced pressure. Repetition of this purification procedure with chloroform as solvent yielded the pure amidine hydrochloride **25** (1.05 g, 94%), colourless hygroscopic solid, mp 173-174 °C, that quickly became an oily mass on exposure to air. The product was characterised and used without further purification; ir (KBr): 3390 (br), 2219, 1682, 1597, 1481, 1237, 1126, 1090, 969, 870 and 751cm^{-1}; ^1H nmr ($CDCl_3$): δ 0.88 (t, 3H, *J* 7.3 Hz, CH_3CH$_2$), 1.99-2.35 (m, 2H, CH$_3$CH_2), 3.51 (s, 2H, ArCH$_2$), 6.79-6.84 (m, 2H, arom H), 7.04-7.08 (m, 2H, arom H), 8.56 (s, 2H, N*H*), 9.18 (s, 2H, N*H*); ^{13}C nmr ($CDCl_3$): δ 5.52 (*C*H$_3$CH$_2$), 30.13 (CH$_3$*C*H$_2$), 38.56 (*C*(3)), 86.20 (*C*(2)), 107.95 (*C*H), 120.31 (*C*H), 122.50 (*C*(3a)), 123.16 (*C*H), 126.58 (*C*H), 154.72 (*C*(7a)), 170.86 (N*C*=N); ms: *m/z* 192(11%)($M^{\bullet+}$), 191(100), 174(23), 161(8), 147(32), 122 (8), 119 (12), 107 (5), 91 (18), 56 (7).

2-(2,3-Dihydro-2-ethylbenzo[*b*]furan-2-yl)-5-nitro-pyrimidine (26). The amidine hydrochloride **25** (1.05 g, 4.6 mmol) and sodium nitromalonaldehyde (0.72 g, 4.6 mmol) [15,16] were dissolved in distilled water (12.0 mL). A 40% aqueous solution of benzyltrimethylammonium hydroxide ('Triton B') (0.46 mL) was then added and the mixture heated to 65 °C (4 h). After chilling in a freezer overnight, the solid product was collected, dissolved in CH_2Cl_2, washed with water, and dried ($MgSO_4$). After evaporation, the crude product was purified by column chromatography (petroleum ether/ethyl acetate (9:1) as eluent) to give the nitropyrimidine **26** (0.15 g, 13%), yellow solid, mp 76-77 °C; ir (KBr): 3057, 2972, 2940, 1586, 1569, 1517, 1355, 1240, 1178, 956 and 753 cm^{-1}; ^1H nmr ($CDCl_3$): δ 0.92 (t, 3H, *J* 7.4 Hz, CH_3CH$_2$), 2.32-2.36 (m, 2H, CH$_3$CH_2), 3.51 (d, 1H, *J* 16.2 Hz, ArCH_aH$_b$), 3.87 (d, 1H, *J* 16.2 Hz, ArCH$_a$$H_b$), 6.88 (dd, 1H, *J* 7.4 and 7.3 Hz, arom H), 6.97 (d, 1H, *J* 8.2 Hz, arom H), 7.13-7.18 (m, 2H, arom H), 9.51 (s, 2H, pyrimidine *H*); ^{13}C nmr ($CDCl_3$): δ 8.16 (*C*H$_3$CH$_2$), 33.63 (CH$_3$*C*H$_2$), 40.04 (*C*(3)), 92.64 (*C*(2)), 109.79 (*C*H), 121.04 (*C*H), 124.77 (*C*(3a)), 125.59 (*C*H),

128.35 (*C*H), 140.90 (*C*NO_2), 152.68 (pyrimidine C*H*), 158.71 (*C*(7a)), 176.50 (N*C*N); ms: *m/z* 271(95%)($M^{\bullet+}$), 191(17), 190(100), 114(2), 91(1). *Anal*. Calcd. for $C_{14}H_{13}N_3O_3$: C, 61.99; H, 4.83. Found: C, 61.86; H, 4.64.

2-(2,3-Dihydro-2-ethylbenzo[*b*]furan-2-yl)-5-aminopyrimidine (27). The nitropyrimidine **26** (78 mg, 0.29 mmol) in absolute ethanol (5.0 mL) was hydrogenated with vigorous stirring using 5% palladium on charcoal as catalyst (2 h). The solvent was then removed under reduced pressure and the residue dissolved in boiling toluene and filtered through Celite. The residue was washed with CH_2Cl_2 to remove any remaining product and the combined extracts were evaporated to give a yellow oil. This product was crystallised from a mixture of ethyl acetate and petroleum ether (bp 60-80 °C) and identified as the aminopyrimidine **27** (62 mg, 90%), colourless solid, mp 133-134 °C; ir (KBr) 3456, 3057, 2972, 2940, 1300, 1240, 1178, 956 and 753 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 0.79 (t, 3H, *J* 7.4 Hz, CH_3CH$_2$), 2.12 (q, 2H, *J* 7.3 Hz, CH$_3$CH_2), 3.28 (d, 1H, *J* 15.9 Hz, ArCH_aH$_b$), 3.65 (br s, 2H, NH_2), 3.86 (d, 1H, *J* 15.9 Hz, ArCH$_a$$H_b$), 6.76 (dd, 1H, *J* 7.2 and 7.0, arom H), 6.84 (d, 1H, *J* 7.9 Hz, arom H), 7.10 (m, 2H, arom H), 8.20 (s, 2H, pyrimidine H); ^{13}C nmr ($CDCl_3$): δ 7.25 (*C*H$_3$CH$_2$), 32.66 (CH$_3$*C*H$_2$), 38.18 (*C*(3)), 91.53 (*C*(2)), 108.60 (*C*H), 119.24 (*C*H), 123.69 (*C*(3a)), 125.77 (*C*H), 126.83 (*C*H), 137.55 (*C*NH_2), 142.06 (pyrimidine *C*H), 158.03 (*C*(7a)), 160.23 (N-*C*=N); ms: *m/z* 241(19%)($M^{\bullet+}$), 225(20), 224(100), 212(33), 184(12), 134(13), 91(19), 77(21). *Anal*. Calcd. for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.27; N, 17.41. Found: C, 70.05; H, 6.64; N, 17.78.

2,3-Dihydro-2-ethylbenzo[*b*]furan-2-carboxylic acid propylamide (7). Thionyl chloride (3.3 mL, 4.5 mmol) was added to a stirred solution of the carboxylic acid **4** (1.5 g, 7.8 mmol) [13] in dry toluene (150 mL) and the mixture was heated at 95 °C (25 min). After cooling, the solution was evaporated under reduced pressure to yield the acid chloride as a pale yellow oil. The oil was dissolved in dry dioxane (2.0 mL) and the solution was slowly added to a stirred solution of propylamine (1.48 g, 25 mmol) in $CHCl_3$ (12.0 mL) cooled in an ice bath. The mixture was extracted with CH_2Cl_2 (3 x 50 mL) and the extracts combined and evaporated. The solid product was recrystallised from a mixture of ethyl acetate and petroleum ether (bp 60-80 °C) and identified as the amide **7** (0.38 g, 21%), colourless solid, mp 42-43 °C; ir (KBr): 3315, 3037, 2965, 2932, 1948, 1654, 1536, 1239, 955 and 757 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 0.89 (t, 3H, *J* 7.4 Hz, CH_3CH$_2$), 0.98 (t, 3H, *J* 7.4 Hz, NHCH$_2$CH$_2$CH_3), 1.52 (m, 2H, NHCH$_2$CH_2), 1.84-2.18 (m, 2H, CH$_3$CH_2), 3.06-3.38 (m, 2H, NCH_2), 3.17 (d, 1H, *J* 16.5 Hz, ArCH_aH$_b$), 3.55 (d, 1H, *J* 16.5 Hz, ArCH$_a$$H_b$), 6.15-6.91 (m, 2H, arom H), 7.11-7.17 (m, 2H, arom H); ^{13}C nmr ($CDCl_3$): δ 8.12 (*C*H$_3$CH$_2$), 11.28 (*C*H$_3$CH$_2$CH$_2$N), 22.83 (CH$_3$*C*H$_2$CH$_2$N), 31.61 (CH$_3$*C*H$_2$), 39.29 (*C*(3)), 40.86 (N*C*H$_2$), 91.70 (*C*(2)), 109.52 (*C*H), 121.35 (*C*H), 125.19 (*C*(3a)), 125.99 (*C*H), 128.05 (*C*H), 157.96 (*C*(7a)), 173.45 (C=O). *Anal*. Calcd. for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00%. Found: C, 71.89: H, 8.09; N, 5.85.

3,3-Dibromo-2,3-dihydro-2-ethylbenzo[*b*]furan-2-carbonitrile (28). To a stirred solution of 2,3-dihydro-2-ethylbenzo[*b*]furan-2-carbonitrile **19** (2.13 g, 12 mmol) [7] in CCl_4 (70 mL) was added *N*-bromosuccinimide (4.27 g, 24 mmol) and azo*bis*isobutyronitrile (0.2 g, 1.2 mmol). The reaction was heated at reflux until no starting material was detected by tlc (16 h) and after cooling was filtered to remove the succinimide by-product. After washing sequentially with $NaHCO_3$ and water, the filtrate was dried ($MgSO_4$), filtered and evaporated under reduced pressure to yield the crude dibromide as a viscous brown oil. Column chromatography eluting with a 7:1 mixture of petroleum ether (bp 60-80 °C) and ethyl acetate gave the pure dibromide **28** (3.12 g, 75%), colourless crystals, mp 57-58°C; ir (KBr): 1595, 1461, 1222, 902, 759, 699 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 1.57 (t, 3H, *J* 7.4 Hz, CH_3CH$_2$), 2.50-2.72 (m, 2H, CH$_3$CH_2), 7.05 (d, 1H, *J* 8.1 Hz, arom H), 7.29 (dd, 1H, *J* 7.5 Hz and 6.9 Hz, arom H), 7.45-7.51 (m, 1H, arom H), 7.73 (dd, 1H, *J* 7.8 Hz and 1.3 Hz, arom H); ^{13}C nmr ($CDCl_3$): δ 9.16 (CH$_2$*C*H$_3$), 30.21 (*C*H$_2$CH$_3$), 60.17 (*C*Br$_2$), 93.85 (*C*(2)), 112.04 (*C*H), 115.83 (*C*N), 124.21 (*C*H), 124.98 (*C*(3a)), 132.32 (*C*H), 132.62 (*C*H), 153.92 (*C*(7a)). *Anal*. Calcd. for $C_{11}H_9NOBr_2$: C, 39.92; H, 2.74; N, 4.23. Found: C, 39.98; H, 2.85; N, 4.13.

2,3-Dihydro-3-(1',3'-dioxalan-2'-yl)-2-ethylbenzo-[*b*]furan-2-carbonitrile (30). To a stirred mixture of 3,3-dibromo-2,3-dihydro-2-ethylbenzo[*b*]furan-2-carbonitrile **28** (0.2 g, 0.6 mmol) and *para*-toluenesulfonic acid (0.08 g, 0.4 mmol) in ethylene glycol (2.0 mL) was added ethylenediamine (0.1 mL, 1 mmol). The mixture was heated to 110 °C in an oil bath (30 min) after which no starting material remained (tlc). Water (10.0 mL) was added followed by solid NaOH (1 pellet) and the mixture was stirred at room temperature (15 min). The reaction mixture was extracted with CH_2Cl_2 (x 3), the combined extracts were washed with saturated aqueous $NaHCO_3$, saturated aqueous NaCl and water. The organic extracts were then dried ($MgSO_4$) and evaporated under reduced pressure to yield the crude product as a yellow oil. Column chromatography gave compound **30** (20 mg, 9%), colourless solid, mp 53-54.5 °C; ir (KBr): 2982, 2896, 1606, 1467, 1270, 1222, 1084, 952, 755, 734 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 1.20 (t, 3H, *J* 7.4 Hz, CH_3CH$_2$), 1.80-2.04 (m, 2H, CH$_3$CH_2), 4.02-4.13 (m, 2H, OCH_2CH$_2$O), 4.18-4.31 (m, 2H, OCH$_2$CH_2O), 6.83 (d, 1H, *J* 7.4 Hz, arom H), 6.97 (t, 1H, *J* 7.5 Hz, arom H), 7.23-7.32 (m, 2H, arom H); ^{13}C nmr ($CDCl_3$): δ 7.69 (*C*H$_3$CH$_2$), 26.30 (CH$_3$*C*H$_2$), 64.89 (O*C*H$_2$CH$_2$O), 65.59 (OCH$_2$*C*H$_2$O), 86.54 (*C*(3)), 110.55 (*C*H), 113.43 (*C*(2)), 115.74 (*C*H), 121.65 (*C*N), 123.26 (*C*(3a)), 123.36 (*C*H), 131.25 (*C*H), 156.74 (*C*(7a)); ms: *m/z* 231(12%)($M^{\bullet+}$), 202(12), 172(10), 148(100), 120(30), 104(75), 92(60), 76(38). *Anal*. Calcd. For $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.32; H, 5.37; N, 6.17.

2-Ethyl-3-oxo-2,3-dihydro-1-benzo[*b*]furan-2-carbonitrile (29). To a stirred solution of 3,3-dibromo-2,3-dihydro-2-ethylbenzo[*b*]furan-2-carbonitrile **28** (0.39 g, 1.2 mmol) in ethanol (9.0 mL) was added silver nitrate (0.42 g, 3.2 mmol) in hot water (2.0 mL). The mixture was heated under reflux (15 min), cooled to room temperature and concentrated HCl (3.0 mL) was added. After filtration to remove the insoluble salts, the filtrate was evaporated under reduced pressure and the residue treated with saturated aqueous $NaHCO_3$. The aqueous solution was extracted with dichloromethane and the combined organic extracts were washed with water, dried ($MgSO_4$) and evaporated in vacuo to yield the ketone **29** (0.14 g, 63%), colourless crystals, mp 82-83 °C; ir (KBr): 3435, 3090, 2977, 2935, 1990, 1727, 1613, 1475, 1382, 1329, 1231, 1141, 971, 881, 761, 686 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 1.10 (t, 3H, *J* 7.5 Hz, CH_3CH$_2$), 1.94-2.26 (m, 2H, CH$_3$CH_2), 7.12-7.19 (m, 2H, arom H), 7.63-7.69 (m, 2H, arom H); ^{13}C nmr ($CDCl_3$): δ 8.05 (*C*H$_3$CH$_2$), 29.99 (CH$_3$*C*H$_2$), 82.05 (*C*(2)), 114.20 (*C*H), 114.75 (*C*N), 118.69 (*C*H), 124.09 (*C*(3a)), 125.92 (*C*H), 139.94 (*C*H),

171.64 (*C*(7a)), 192.94 (*C*=O); ms: *m/z* 187(18%)($M^{\bullet+}$), 172(21), 159(72), 120(21), 104(96), 92(89), 76(100), 64(77), 63(99), 50(58). *Anal.* Calcd. for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.48; H, 4.71; N, 7.57.

2-Ethyl-3-hydroxy-2,3-dihydro-1-benzo[*b*]furan-2-carbonitrile (31). 2-Ethyl-3-oxo-2,3-dihydro-1-benzo[*b*]furan-2-carbonitrile **29** (0.75 g, 39 mmol) was dissolved in methanol (14.0 mL) and cooled in an ice bath. To the cooled stirred solution was added sodium borohydride powder (0.16 g, 43 mmol) in small portions. When addition was complete the reaction was allowed to warm to room temperature and stirred for a further 18 hours before evaporation under reduced pressure. The residue was partitioned between diethyl ether and 2 M aqueous hydrochloric acid and the organic layer separated. The aqueous phase was washed with diethyl ether (x 2) and the combined organic extracts were washed sequentially with saturated aqueous $NaHCO_3$ solution and water before drying ($MgSO_4$). Filtration and evaporation of the solvent under reduced pressure gave the alcohol **31** (0.65 g, 87%), yellow oil (3:2 mixture of enantiomeric pairs, not separated); ir (film) 3411, 1598, 1477, 1237 cm^{-1}; ^1H nmr ($CDCl_3$): δ1.18 (t, *J* 7.4 Hz, C*H*$_3$CH$_2$), 1.25 (t, *J* 7.4 Hz, C*H*$_3$CH$_2$), 1.74 (d, *J* 8.6 Hz, OH), 1.97 (m, CH$_3$C*H*$_2$), 2.09 (m, CH$_3$C*H*$_2$), 2.36 (d, *J* 9.9 Hz, OH), 5.10 (d, *J* 9.9 Hz, C*H*OH), 5.25 (d, *J* 8.6 Hz, C*H*OH), 6.83-6.90 (m, arom H), 6.96-7.02 (m, arom H), 7.24-7.42 (m, arom H); ^{13}C nmr ($CDCl_3$): δ 7.93 (*C*H$_3$), 24.31 (*C*H$_2$), 75.42(*C*HOH), 85.92 (*C*(2)), 110.27 (*C*H), 117.93 (*C*N), 121.78 (*C*H), 125.15 (*C*(3a)), 125.63 (*C*H), 130.63 (*C*H), 156.88 (*C*(7a)); ms: *m/z* 189(10%)($M^{\bullet+}$), 172(1), 163(5), 162(20), 156(10), 134(21), 133(89), 121(88), 115(20), 105(100), 93(20), 78(30), 77(98), 65(42). *Anal.* Calcd. for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 70.13; H, 5.86; N, 7.34.

2-Ethyl-3-fluoro-2,3-dihydro-1-benzo[*b*]furan-2-carbonitrile (32 + 33). A solution of 2-ethyl-3-hydroxy-2,3-dihydro-1-benzo[*b*]furan-2-carbonitrile **31** (0.35 g, 1.9 mmol) in dry dichloromethane (0.6 mL) was placed in a dry flask filled with argon and fitted with a rubber septum. The flask was cooled to –78 °C and diethylaminosulfur trifluoride (DAST) (0.24 mL, 1.9 mmol) in dichloromethane (1.0 mL) was injected through the septum. When addition was complete the flask was allowed to warm to room temperature and stirred until no starting material was detected (tlc). Water (1.0 mL) was added and the organic layer separated. The aqueous phase was extracted with dichloromethane and the extracts combined, washed with water and dried ($MgSO_4$) to give the fluoronitrile (0.23 g, 63 %), brown oil; ir (film): 2980, 2944, 2885, 1731, 1616, 1602, 1479, 1323, 1249, 1196, 1096, 1043, 946, 887, 754 cm^{-1}; ^1H nmr ($CDCl_3$): δ1.18 (t, 3H, *J* 7.4 Hz, C*H*$_3$CH$_2$), 1.84-2.11 (m, 2H, C*H*$_2$CH$_3$), 5.73 (d, 1H, *J* 59.3 Hz, ArC*H*F), 6.90 (d, 1H, *J* 8.2 Hz, arom H), 7.02 (dd, 1H, *J* 7.5 and 7.5 Hz, arom H), 7.36 (dd, 1H, *J* 7.5 and 8.2 Hz, arom H), 7.43 (d, 1H, *J* 7.5 Hz, arom H); ^{19}F nmr ($CDCl_3$): δ -155.17 (d, 1F, *J* 59.3 Hz, ArC*F*); ^{13}C nmr ($CDCl_3$): δ 8.50 (CH$_2$*C*H$_3$), 30.26 and 30.33 (*C*H$_2$CH$_3$), 86.38 and 86.61 (*C*(2)), 93.47 and 96.07 (*C*(3)), 111.66 and 111.70 (*C*H), 114.69 and 114.84 (*C*N), 121.25 and 121.50 (*C*H), 122.93 and 122.97 (*C*(3a)), 127.15 and 127.17 (*C*H), 133.40 and 133.45 (*C*H), 159.16 and 159.23 (*C*(7a)); ms: *m/z* 191(33%)($M^{\bullet+}$), 170(10), 157(10), 156(100), 134(15), 125(42), 124(50), 115(30), 107(80), 101(11), 96(90), 89(13), 77(25), 75(18), 70(14), 63(20), 51(11). *Anal.* Calcd. for $C_{11}H_{10}FNO$: C, 69.10; H, 5.27; N, 7.33. Found: C, 68.87; H, 5.12; N, 7.18. The mixture of diastereoisomers was separated by column chromatography (silica gel: petroleum ether (bp 60-90 °C)/ ethyl acetate as eluent) to give a pure sample of the major enantiomeric pair as a colourless oil.

2-Ethyl-3-fluoro-2,3-dihydro-benzo[*b*]furan-2-carboximidic acid methyl ester (34). 2-Ethyl-3-fluoro-2,3-dihydro-1-benzo[*b*]furan-2-carbonitrile **32** (0.22 g, 1.2 mmol) in methanol (1.6 mL) was added to a solution of metallic sodium (2.2 mg, 0.01 mmol) in methanol (1.0 mL) and the mixture was stirred at room temperature (16 h). The mixture was then cooled to 0 °C and ethylenediamine (0.072 g, 1.2 mmol) was added. The flask was allowed to warm to room temperature and after 15 minutes 1 mL of a methanolic solution of HCl (1.12 mL HCl in 10 mL MeOH) was added. The reaction was allowed to stand for 2 hours before being partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. The combined organic layers were washed with water, dried ($MgSO_4$) and evaporated. Column chromatography gave the fluoroimidate **34** as a mixture of diastereoisomers (0.04g, 15%): ir (film): 3350, 2982, 2945, 1670, 1604, 1245 cm^{-1}; ^1H nmr ($CDCl_3$): δ 0.85 (t, 3H, *J* 7.3 Hz, C*H*$_3$CH$_2$), 1.47-1.59 (m, 1H, CH$_3$C*H*$_a$H$_b$), 1.89-1.99 (m, 1H, CH$_3$CH$_a$*H*$_b$), 3.81 (s, 3H, OMe), 5.54 (d, 1H, *J* 58.6 Hz, ArCHF), 6.90-6.97 (m, 2H, arom H), 7.32 (dd, 1H, *J* 7.4 and 7.8 Hz, arom H), 7.38 (d, 1H, *J* 7.4 Hz, arom H), 7.98 (br s, 1H, N*H*); ^{13}C nmr ($CDCl_3$): δ 6.93 (*C*H$_3$CH$_2$), 26.44 and 26.54 (CH$_3$*C*H$_2$), 52.61 (O*C*H$_3$), 91.84 and 9.11 (*C*(2)), 92.68 and 95.20 (*C*F), 110.26 and 110.30 (*C*H), 120.84 and 120.88 (*C*H), 121.74 and 121.99 (*C*(3a)), 126.10 and 126.13 (*C*H), 131.50 and 131.56 (*C*H), 158.50 and 158.56 (*C*(7a)), 165.94 and 166.03 (*C*=N); ms: *m/z* 223(50%)($M^{\bullet+}$), 206(18), 194(30), 166(30), 146(55), 131(72), 115(40), 91(38), 77(39), 58(100), 51(30).

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