Preparation of the I_3 Imidazoline Receptor Antagonist KU14R and Related 2,3-Dihydrobenzo[*b*]furan Derivatives

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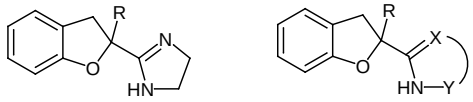
Abstract: The preparation and characterisation of a series of novel analogues of the imidazoline insulin secretagogue efaroxan, including the I_3-receptor antagonist KU14R, are described. Replacement of the imidazoline ring of efaroxan by selected functional groups leads either to loss of activity or to very weak I_3-agonist activity in insulin secretion studies. The imidazole analogue KU14R was found to be an I_3-antagonist in this assay and useful as a biological tool.

Key words: imidazoline, efaroxan, I_3-receptor, imidazole, antagonist, tetrazole, insulin

It is well known that some imidazoline-containing ligands have an affinity for binding sites distinct from α-adrenoceptors[1] and two discrete imidazoline receptors (designated I_1 and I_2) are well characterised.[2] Recent work in our laboratories at Keele[3] has identified a third imidazoline binding site (putatively designated I_3) in pancreatic β-cells and this receptor is associated with control of insulin secretion. An endogenous ligand has not been identified but the imidazoline derivative efaroxan (**1**) is a selective agonist [EC_{50} 100 μM] at the I_3 receptor (versus I_1 and I_2).



1 (R=Et)(efaroxan)
2 (R=H)(RX801080)

3

Figure 1 Structure of efaroxan (**1**) and related analogues **2** and **3**

Insulin secretagogue activity mediated by imidazoline agonists is known to be associated with closure of ATP-sensitive potassium (K_{ATP}) channels, leading to membrane depolarisation and Ca^{2+} influx, but the relationship between binding site and channel has not yet been established.[4] Indeed, recent evidence suggests that the I_3 receptor may also control secretary events at a site distal to the channel.[5] Work on the characterisation of the binding site(s) is limited by the lack of sufficiently potent ligands. We have therefore initiated an investigation of novel compounds related to efaroxan (**1**) with the objective of mapping the I_3 receptor pharmacophore and identifying more potent ligands. As part of this work we prepared the imidazole derivative **14** (KU14R) and have shown that in both insulin secretion[6] and electrophysiological studies[7] KU14R behaves as an antagonist [EC_{50} 30 μM] at the I_3 imidazoline binding site, although it is important to note that KU14R also displays weak channel blocking activity in the absence of efaroxan (**1**).[7] KU14R (**14**) has proved to be a useful biological tool for the study of insulin secretion mechanisms and further evaluation is in hand. In this paper we describe the preparation and chemical characterisation of KU14R and closely related compounds relevant to mapping the receptor binding requirements.

Our initial studies have focused on the preparation of efaroxan analogues having the general structure **3** (Figure 1). The simplest analogues of this type are the amides **8** and **9** which were prepared from the known carboxylic acids **4** and **5**.[8] Using similar procedures the secondary and tertiary amides **6** and **7** were also prepared (Scheme 1). The amides **6** and **7** did not show I_3-agonist activity in insulin secretion studies although amides **8** and **9** displayed weak activity. Treatment of the amide **8** with Lawesson's reagent[9] gave the thioamide **10** (Scheme 1). This product appeared to inhibit insulin secretion in response to glucose by a mechanism that was unrelated to the I_3-receptor and was not studied further.

The urea **13** was prepared from the amide **8** in modest yield by treatment with (diacetoxyiodo)benzene (DAIB) in hot toluene. We believe that this product is formed via oxidative rearrangement of the amide **8** to the isocyanate **17**, which adds to a second molecule of the amide **8** to give the acylurea **18** (Scheme 2). The intermediate **18** then reacts with the acetic acid formed in the first step to give the urea **13**. Although we have not detected the intermediate **18**, a similar oxidation of furan-2-carboxamide gave the corresponding acylurea as the major product (57%).[10] The urea **13** retained weak I_3-agonism in insulin secretion studies but was not sufficiently active to merit further evaluation.

The amides **8** and **9** were converted into the corresponding nitriles **11** and **12** using phosphorus oxychloride in hot pyridine. Treatment of the nitrile **11** with methanolic sodium methoxide to generate the imidate followed by aminoacetaldehyde diethylacetal [$H_2NCH_2CH(OEt)_2$] and acetic acid at reflux temperature[11] gave the imidazole **14**

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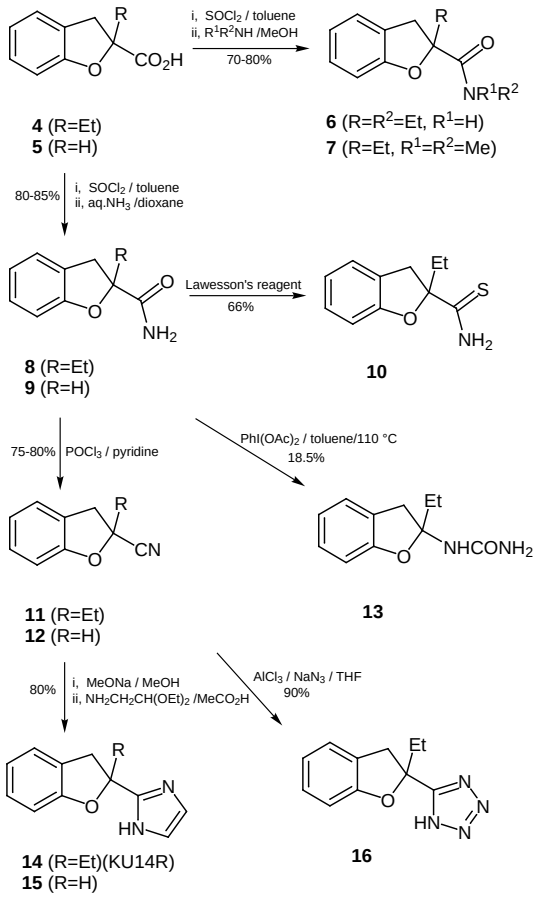
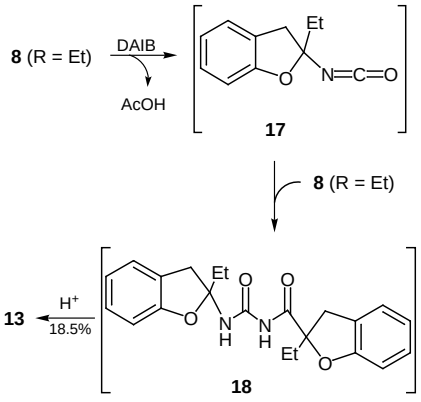


Scheme 1

(KU14R) in good yield. The structure of compound **14** is fully supported by its spectroscopic properties and elemental analysis. In the ^{1}H NMR spectrum, the benzylic protons are non-equivalent and appear as doublets (J = 15.9 Hz) centered at δ = 3.39 and 3.77. Similarly, the methylene protons of the ethyl substituent are non-equivalent and appear as a multiplet at δ = 2.15. The imidazole CH protons appear as two very broad singlets, due to imidazole tautomerism, among the other aromatic protons in the range δ = 6.8–7.3. In the ^{13}C NMR spectrum



Scheme 2

no signals are observed for the imidazole CH carbon atoms and we also attribute this to broadening as a result of tautomerism. All other aspects of the ^{13}C NMR spectrum are in agreement with the structure **14**. The mass spectrum shows a strong molecular ion [*m/z* = 214 (40%)] with the base peak at *m/z* = 185 corresponding to loss of the ethyl substituent.

We have previously described the preparation of the benzimidazole analogue **20** from the *N*-phenylamidine **19** (Figure 2) as part of a study of the oxidation of amidines by I(III) reagents.[12] In contrast to the imidazole **14**, the benzimidazole **20** showed no activity at the I_3 receptor, possibly due to steric hindrance at the receptor. Like the amides **6** and **7** and the thioamide **10**, the amidine **19** was also biologically inactive in the imidazoline receptor assay.

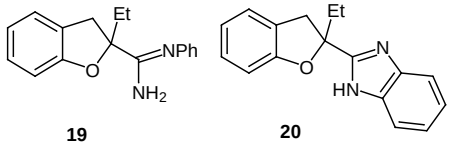


Figure 2

The imidazoline **2** (Figure 1) (RX801080)[13] is the only other compound known to be an antagonist [EC_{50} 40 μM] of the I_3 receptor. Since substituent contributions to biological activity at different positions of a molecule are often found to be additive (the Free-Wilson model),[14] we also prepared and evaluated the imidazoline derivative **15** which has the structural features of both antagonists. Thus, treatment of the nitrile **12** with aminoacetaldehyde diethylacetal gave the imidazole **15** in good yield. Although this product is an I_3-antagonist it did not show enhanced activity over KU14R.

Finally, we have prepared the tetrazole derivative **16** for direct comparison with the isoconjugate imidazole **14**. Treatment of the nitrile **11** with a mixture of aluminium chloride and sodium azide[15] gave the tetrazole **16** in high yield. The assigned structure was fully supported by elemental analysis and spectroscopic properties, which were very similar to those of compound **14**. The mass spectrum shows a molecular ion and a fragment ion corresponding to loss of HN_3. In contrast to the imidazole **14**, the more acidic tetrazole **16** had no properties of biological interest. We conclude from these studies that the binding requirements for the imidazoline fragment of efaroxan (**1**) and the imidazole fragment of KU14 R are highly specific and closely related structures show complete loss of activity. All compounds described in this study were prepared and tested as racemates. Products of special interest, e.g. KU14R, have been resolved and the properties of enantiomers will be described elsewhere.

The ^{1}H NMR spectra were recorded on a Bruker Advance DPX300 NMR spectrometer; IR spectra on a Perkin-Elmer Paragon 1000 FT-IR spectrophotometer, mass spectra on a Hitachi-Perkin-Elmer

MSI 12 spectrometer and microanalyses on a Perkin-Elmer 240 elemental analyzer. Unless otherwise state, IR spectra were measured as thin films (liquids) or KBr discs (solids) and 300 MHz NMR spectra in $CDCl_3$ (tetramethylsilane as internal standard). Only significant bands for the IR spectra are quoted. Melting points were determined on a Kofler block and are uncorrected. Chromatotron chromatography was performed on plates prepared using silica gel 60 PF_{254} containing $CaSO_4$. Petroleum ether used refers to the fraction boiling at 60–80 °C.

2,3-Dihydro-2-ethylbenzo[*b*]furan-2-carboxamide (8); Typical Procedure

$SOCl_2$ (5.37 g, 45 mmol) was added to a suspension of the acid **4**[8] (4.44 g, 23 mmol) in anhyd toluene (150 mL). The mixture was heated with stirring at 90–100 °C until all the carboxylic acid was in solution (25 min). The solvent and excess $SOCl_2$ were then removed under diminished pressure to give the acid chloride as an oil. The crude product was dissolved in anhyd dioxane (18 mL) and the solution was added dropwise with stirring to aq ammonia (SG 0.88, 27.0 mL) at 0 °C. After the addition was complete, the mixture was allowed to warm to r.t. and H_2O (120 mL) was added. The solid product was recrystallised from EtOAc–petroleum ether and identified as the amide **8** (3.70 g, 85%); tiny colourless crystals; mp 96–97 °C.

IR (KBr): ν = 3459, 3192, 2972, 2914, 1637, 1484, 1462, 1438, 1327, 1277, 1233, 1145, 1073, 1019, 960, 892, 865, 788, 757 cm^{-1}.

^1H NMR ($CDCl_3$/TMS): δ = 1.00 (2 H, t, *J* = 7.3 Hz, CH_2CH_3), 1.92 (1 H, m, $CH_aH_bCH_3$), 2.09 (1 H, m, $CH_aH_bCH_3$), 3.16 (1 H, d, *J* = 16.6 Hz, $ArCH_aH_b$), 3.56 (1 H, d, *J* = 16.6 Hz, $ArCH_aH_b$), 6.68 (2 H, br s, NH_2), 6.81–7.15 (4 H, m, arom H).

^{13}C NMR ($CDCl_3$/TMS): δ = 8.05 (q), 31.43 (t), 39.12 (t), 91.36 (s), 109.58 (d), 121.39 (d), 125.09 (d), 125.76 (s), 128.14 (d), 158.15 (s), 177.32 (s).

MS (EI): *m*/*z* = 191 (M^+).

Anal. Calcd for $C_{11}H_{13}NO_2$ (191.2): C, 69.09; H, 6.85; N, 7.32. Found: C, 68.97; H, 6.89; N, 7.18.

2,3-Dihydrobenzo[*b*]furan-2-carboxamide (9)

Following the method described for compound **8**, the title compound was obtained from the carboxylic acid **5**[8] (7.5 g, 46 mmol); yield: 6.0 g (80%); colourless platelets from EtOAc; mp 158–159 °C.

IR (KBr): ν = 3410, 3204, 1635, 1484, 1465, 1228, 1107, 1010, 873, 745 cm^{-1}.

^1H NMR ($CDCl_3$/TMS): δ = 3.45 (1 H, m, CH_aH_b), 3.56 (1 H, m, CH_aH_b), 5.12 (1 H, dd, *J* = 6.6, 10.8 Hz, $CHCH_2$), 6.2 (1 H, br s, CONH), 6.6 (1 H, br s, CONH), 6.85–7.25 (4 H, m, arom H).

MS (EI): *m*/*z* = 163 (M^+), 146, 119, 91 (100%).

Anal. Calcd for $C_9H_9NO_2$ (163.2): C, 66.25; H, 5.56; N, 8.58. Found: C, 66.31; H, 5.47; N, 8.29.

2,3-Dihydro-2-ethylbenzo[*b*]furan-2-thiocarboxamide (10)

A mixture of the amide **8** (1.91 g, 10 mmol) and Lawesson's reagent (4.40 g, 10 mmol) in toluene (75 mL) was heated under reflux (5 h). The solvent was removed under vacuum and the residue purified by chromatotron chromatography (EtOAc–petroleum ether). Recrystallisation from EtOAc–petroleum ether gave the thioamide **10** (1.37 g, 66%); fine colourless needles; mp 135–137 °C.

IR (KBr): ν = 3378, 3261, 3155, 2971, 1618, 1482, 1446, 1311, 1233, 1141, 1115, 1093, 1064, 1023, 962, 893, 872, 850, 752, 688, 664 cm^{-1}.

^1H NMR ($CDCl_3$/TMS): δ = 0.99 (2 H, t, *J* = 7.3 Hz, CH_2CH_3), 2.10 (1 H, m, $CH_aH_bCH_3$), 2.34 (1 H, m, $CH_aH_bCH_3$), 3.36 (1 H, d, *J* = 16.6 Hz, $ArCH_aH_b$), 3.89 (1 H, d, *J* = 16.6 Hz, $ArCH_aH_b$), 6.81–7.16 (4 H, m, arom H), 7.85 (1 H, br s, CSNH), 8.20 (1 H, br s, CSNH).

^{13}C NMR ($CDCl_3$/TMS): δ = 7.98 (q), 34.43 (t), 42.55 (t), 96.84 (s), 109.54 (d), 121.59 (d), 125.03 (d), 125.73 (s), 128.12 (d), 157.44 (s), 210.35 (s).

MS (EI): *m*/*z* = 207 (M^+), 174 (100%), 163, 146.

Anal. Calcd for $C_{11}H_{13}NOS$ (207.3): C, 63.74; H, 6.32; N, 6.76. Found: C, 63.52; H, 6.58; N, 6.59.

***N*-(2,3-Dihydro-2-ethylbenzo[*b*]furan-2-yl)urea (13)**

To a stirred solution of (diacetoxyiodo)benzene (DAIB) (1.68 g, 5.3 mmol) in anhyd toluene (40 mL) heated at 110 °C was added dropwise a solution of the amide **8** (1.0 g, 3 mmol) in toluene (10 mL). After stirring (30 min), the solvent was removed and the residue heated under vacuum (50 °C at 0.001 Torr) for 30 min. The residue was then purified by chromatotron chromatography (EtOAc–petroleum ether) and, after recrystallisation from EtOAc, identified as the urea **13** (0.20 g, 18.5%); colourless crystals; mp 117–118 °C.

IR (KBr): ν = 3507, 3361, 3306, 1658, 1607, 1566, 1484, 1463, 1355, 1335, 1257, 1230, 942, 872, 761 cm^{-1}.

^1H NMR (DMSO-d_6/TMS): δ = 0.88 (3 H, t, *J* = 7.4 Hz, CCH_2CH_3), 1.82 (1 H, m, $CH_aH_bCH_3$), 2.03 (1 H, m, $CH_aH_bCH_3$), 3.02 (1 H, d, *J* = 16.2 Hz, $ArCH_aH_b$), 3.55 (1 H, d, *J* = 16.2 Hz, $ArCH_aH_b$), 5.60 (2 H, s, NH_2), 6.60–7.15 (5 H, m, 4 arom H + NH).

MS (EI): *m*/*z* = 207 (MH^+).

Anal. Calcd for $C_{11}H_{14}N_2O_2$ (206.2): C, 64.06; H, 6.84; N, 13.58. Found: C, 64.31; H, 6.97; N, 13.70.

***N*-Ethyl-2,3-dihydro-2-ethylbenzo[*b*]furan-2-carboxamide (6)**

Following the method described for compound **8**, the title compound was obtained from the carboxylic acid **4** (4.44 g, 23 mmol) and methanolic ethylamine (2 M); yield: 3.63 g (72%); hygroscopic plates; mp 38–39 °C.

IR (KBr): ν = 2974, 1660, 1597, 1526, 1482, 1463, 1240, 959, 870, 750 cm^{-1}.

^1H NMR ($CDCl_3$/TMS): δ = 0.97 (3 H, t, *J* = 7.3 Hz, CCH_2CH_3), 1.14 (3 H, t, *J* = 7.3 Hz, NCH_2CH_3), 1.91 (1 H, m, $CCH_aH_bCH_3$), 2.09 (1 H, m, $CCH_aH_bCH_3$), 3.15 (1 H, d, *J* = 16.1 Hz, $ArCH_aH_b$), 3.20 (1 H, m, $NCH_aH_bCH_3$), 3.37 (1 H, m, $NCH_aH_bCH_3$), 3.55 (1 H, d, *J* = 16.1 Hz, $ArCH_aH_b$), 6.74 (1 H, br s, CONH), 6.82–7.16 (4 H, m, arom H).

^{13}C NMR ($CDCl_3$/TMS): δ = 8.08 (q), 14.83 (q), 31.69 (t), 34.07 (t), 39.24 (t), 91.47 (s), 109.55 (d), 121.29 (d), 125.11 (d), 125.89 (s), 128.03 (d), 158.09 (s), 173.19 (s).

MS (EI): *m*/*z* = 219 (M^+), 190, 174, 131, 119, 91 (100%).

Anal. Calcd for $C_{13}H_{17}NO_2$ (219.3): C, 71.21; H, 7.81; N, 6.39. Found: C, 71.29; H, 7.77; N, 6.21.

***N*,*N*-Dimethyl-2,3-dihydro-2-ethylbenzo[*b*]furan-2-carboxamide (7)**

Following the method described for compound **8**, the title compound was obtained from the carboxylic acid **4** (4.44 g, 23 mmol) and methanolic dimethylamine (2 M); yield: 3.93 g (78%); pale cream crystals; mp 51–52 °C.

IR (KBr): ν = 1625, 1483, 1397, 1242, 1171, 1088, 1014, 957, 871, 749, 671 cm^{-1}.

^1H NMR ($CDCl_3$/TMS): δ = 0.96 (3 H, t, *J* = 7.3 Hz, CH_2CH_3), 1.97 (1 H, m, $CH_aH_bCH_3$), 2.06 (1 H, m, $CH_aH_bCH_3$), 2.97 (3 H, s, NCH_3), 3.12 (1 H, d, *J* = 16.6 Hz, $ArCH_aH_b$), 3.27 (3 H, s, NCH_3), 3.93 (1 H, d, *J* = 16.6 Hz, $ArCH_aH_b$), 6.77–7.17 (4 H, m, arom H).

^{13}C NMR ($CDCl_3$/TMS): δ = 8.02 (q), 31.66 (t), 37.70 (q), 38.10(q), 39.08 (t), 93.03 (s), 109.10 (d), 120.90 (d), 124.72 (d), 126.07 (s), 127.84 (d), 158.24 (s), 171.75 (s).

MS (EI): *m*/*z* = 219 (M^+), 190, 175, 146, 131, 119, 91 (100%).

Anal. Calcd for $C_{13}H_{17}NO_2$ (219.3): C, 71.21; H, 7.81; N, 6.39. Found: C, 70.99; H, 8.05; N, 6.21.

Dihydro-2-ethylbenzo[*b*]furan-2-carbonitrile (11)
A solution of the amide **8** (1.44 g, 7.5 mmol) in anhyd pyridine (30 mL) was cooled to 0°C. $POCl_3$ (3.63 g, 7.8 mmol) was added with stirring and the resulting solution was heated under reflux (2.5 h). The solvent was then removed under vacuum and the residue partitioned between dil. HCl (60 mL) and CH_2Cl_2 (3 × 60 mL). The combined organic extracts were washed with brine (60 mL), dried (Na_2SO_4) and evaporated to give the nitrile **11** as a yellow oil (1.09 g, 76%) that was shown to be pure by NMR and was used without further purification.

^{1}H NMR ($CDCl_3$/TMS): δ = 1.22 (3 H, t, *J* = 7.4 Hz, CH_2CH_3), 2.09 (2 H, m, CH_2CH_3), 3.30 (1 H, d, *J* = 15.9 Hz, $ArCH_aH_b$), 3.61 (1 H, d, *J* = 15.9 Hz, $ArCH_aH_b$), 6.80–7.21 (4 H, m, arom H).

MS (EI): *m*/*z* = 173 (M^+).

Dihydrobenzo[*b*]furan-2-carbonitrile (12)
A solution of the amide **9** (5.5 g, 337 mmol) in anhyd pyridine was cooled to 0°C and $POCl_3$ (16.5 g) was added with stirring. The solution was then heated under reflux (2.5 h). The solvent was removed under reduced pressure and the residue partitioned between CH_2Cl_2 and dil. HCl. The organic phase was washed with 10% aq NaCl solution, dried ($MgSO_4$) and evaporated to give the nitrile **12** as a yellow oil (4.0 g, 82%) that was shown to be pure by NMR and was used without further purification.

IR (KBr): ν = 2220 (w), 1733, 1596, 1480, 1463, 1325, 1240, 1224, 1154, 1095, 1002, 967, 852, 753 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS): δ = 3.35–3.60 (2 H, m, $ArCH_2CH$), 5.25 (1 H, dd, *J* = 5.7, 9.8 Hz, $ArCH_2CH$), 6.80–7.20 (4 H, m, arom H).

^{13}C NMR ($CDCl_3$/TMS): δ = 35.42 (t), 68.01 (d), 110.23 (d), 118.15 (s), 122.29 (d), 123.56 (s), 124.98 (d), 128.93 (d), 157.70 (s).

MS (EI): *m*/*z* = 145 (100%, M^+), 118, 90.

2-(2,3-Dihydro-2-ethylbenzo[*b*]furan-2-yl)-1*H*-imidazole (KU14R) (14); Typical Procedure
A solution of NaOMe (1 M in MeOH, 3.0 mL) was added with stirring to a solution of the nitrile **11** (2.0 g, 11.6 mmol) in MeOH (40 mL). After stirring at r.t. (18 h), the solution was cooled to 0 ° C and aminoacetaldehyde diethylacetal (1.54 g, 11.6 mmol) and AcOH (1.4 g, 23.0 mmol) were added and the mixture heated under reflux (3 h).[13] After cooling to r.t., 5 M HCl (9.0 mL) was added and the mixture boiled under reflux (30 min.). H_2O (100 mL) was added to the cooled mixture, which was then evaporated to dryness under reduced pressure. The residue was taken up in water, basified with NaOH solution and extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4) and evaporated to give a buff solid that was recrystallised from EtOAc–petroleum ether and identified as compound **14**, (2.01 g, 81%); colourless needles; mp 136–136.5°C.

IR (KBr): ν = 2600–3100 (br), 1597, 1550, 1485, 1461, 1436, 1384, 1330, 1241, 1190, 1098, 1016, 950, 874, 750, 735 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS): δ = 0.91 (3 H, t, *J* = 7.3 Hz, CH_2CH_3), 2.15 (2 H, m, CH_2CH_3), 3.39 (1 H, d, *J* = 15.9 Hz, CH_aH_b), 3.77 (1 H, d, *J* = 15.9 Hz, CH_aH_b), 6.79–7.26 (6 H, m, arom H), 9.87 (1 H, br s, NH).

^{13}C NMR ($CDCl_3$/TMS): δ = 8.3 (q), 34.0 (t), 40.8 (t), 89.2 (s), 109.5 (d), 121.0 (d), 125.2 (d), 126.5 (s), 127.7 (d), 150.9 (s), 158.5 (s).

MS (EI): *m*/*z* = 214 (M^+), 213, 197, 185 (100%), 169, 156, 131.

Anal. Calcd for $C_{13}H_{14}N_2O$ (214.3): C, 72.87; H, 6.59; N, 13.07. Found: C, 72.60; H, 6.74; N, 13.26.

2-(2,3-Dihydrobenzo[*b*]furan-2-yl)-1*H*-imidazole (15)
Following the method described for compound **14**, the title compound was obtained from the nitrile **12** (1.67 g. 11.5 mmol); yield: 1.7 g (79%); colourless crystals from EtOAc–petroleum ether; mp 195–196°C.

IR (KBr): ν = 2300–3850 (br), 1597, 1480, 1459, 1406, 1234, 1165, 1107, 1016, 997, 950, 926, 856, 770, 750 cm^{-1}.

^{1}H NMR (acetone-d_6/TMS): δ = 3.55 (1 H, m, CH_aH_b), 3.75 (1 H, m, CH_aH_b), 5.81 (1 H, dd, *J* = 7.7, 9.5 Hz, $CHCH_2$), 6.70–7.20 (6 H, m, arom H), 11.51 (1 H, br s, NH).

MS (EI): *m*/*z* = 186 (M^+), 169 (100%), 156, 128, 118.

Anal. Calcd for $C_{11}H_{10}N_2O$ (186.2): C, 70.95; H, 5.41; N, 15.04. Found: C, 70.69; H, 5.42; N, 15.18.

5-(2,3-Dihydro-2-ethylbenzo[*b*]furan-2-yl)-1*H*-tetrazole (16)
Anhyd $AlCl_3$ (2.84 g, 22 mmol) was carefully added to cold, anhyd THF (35 mL). When all the material had dissolved, NaN_3 (4.14 g, 64 mmol) was added with vigorous stirring followed by the nitrile **11** (1.2 g, 7 mmol). The mixture was then heated under reflux (24 h) and poured onto a mixture of ice (75 g) and concd HCl (20 mL). The product was extracted into Et_2O and the ethereal solution dried ($MgSO_4$). Evaporation gave the crude product (1.75 g) as a yellow oil that was purified by chromatotron chromatography (EtOAc–petroleum ether and identified as the tetrazole **16** (1.35 g, 90%); colourless crystals; mp 96–97°C.

IR (KBr): ν = 2600–3100 (br), 1597, 1545, 1481, 1464, 1441, 1423, 1410, 1382, 1326, 1300, 1278, 1236, 1188, 1151, 1121, 1083, 1051, 1016, 984, 951, 874, 754 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS): δ = 0.95 (3 H, t, *J* = 7.3 Hz, CH_2CH_3), 2.25 (2 H, dq, CH_2CH_3), 3.54 (1 H, d, *J* = 16.1 Hz, CH_aH_b), 3.73 (1 H, d, *J* = 16.1 Hz, CH_aH_b), 6.77–7.15 (4 H, m, arom H), 13.3 (1 H, v br s, NH).

MS (EI): *m*/*z* = 216 (M^+), 173, 146, 43 (100%).

Anal. Calcd for $C_{11}H_{12}N_4O$ (216.2): C, 61.10; H, 5.59; N, 25.91. Found: C, 61.30; H, 5.65; N, 26.17.

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