

Supporting Information

Discovery of Imidazo[1,2-*b*][1,2,4]triazines as GABA_A α 2/3 Subtype Selective Agonists for the Treatment of Anxiety

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Full experimental details and data for all final compounds

Squirrel monkey RPI lever pressing assay

Elemental analyses and HPLC data

General Methods. Melting points were obtained on a Leica Galen III hot stage and are uncorrected. Proton NMR spectra were obtained using either a Bruker AM360 or a Bruker DPX-400 spectrometer. Mass spectra were recorded on a Waters Micromass ZMD or ZQ operating in an electrospray (ES) mode. (Note that only the strongest peaks from the mass spectra are reported below.) Elemental analysis for carbon, hydrogen, and nitrogen were performed by Butterworth Laboratories Ltd. Unless otherwise stated, high performance liquid chromatography (HPLC) analysis was performed on a Hewlett Packard HP1100 instrument using a Supelcosil™ ABZ+Plus 15 cm × 4.6 mm, 5µm column, eluting with acetonitrile/water (containing 0.1% trifluoroacetic acid). Analytical thin-layer chromatography (TLC) was conducted on precoated silica gel 60 F₂₅₄ plates (Merck). Visualisation of the plates was accomplished by using UV light and/or iodine and/or aqueous potassium permanganate solution. Chromatography was conducted on silica gel 60, 220-440 mesh (Fluka) under low pressure. Solutions were evaporated on a Büchi rotary evaporator under reduced pressure. All starting materials were obtained from commercial sources and used as received unless otherwise indicated.

3-Bromo-7-methyl-imidazo[1,2-*b*]pyridazine (13). To a stirred solution of 7-methyl-imidazo[1,2-*b*]pyridazine (30.1 mg, 0.226 mmol) (prepared as described by Pollak et al. *Tetrahedron* **1968**, 24, 2623) and sodium acetate (27.4 mg, 0.334 mmol) in glacial acetic acid (1 mL) was added dropwise, over 2 min, bromine (12.2 µL, 0.237 mmol). The mixture was stirred at room temperature for 20 min, then partitioned carefully between saturated aqueous NaHCO₃ (15 mL) and ethyl acetate (20 mL). The aqueous layer, which had a pH of 9, was extracted further with ethyl acetate (2 x 20 mL). The combined organic extracts were dried (Na₂SO₄) and evaporated. The residue was purified by flash chromatography (silica gel, ethyl acetate) to leave 47.3 mg (99%) of **13**: ¹H NMR (400 MHz, CDCl₃) δ 2.45 (3H, s), 7.70 (2H, s), 8.30 (1H, s).

3'-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-biphenyl-2-carbonitrile (18a). A mixture of 2-bromobenzonitrile (9.1 g, 50 mmol), 3-aminobenzeneboronic acid monohydrate (11.6 g, 75 mmol) and tetrakis(triphenylphosphine)palladium(0) (1.73 g, 1.5 mmol) in dimethoxyethane (50 mL) and 2 M aqueous sodium carbonate (25 mL) was heated at 80 °C for 20 h. After cooling to ambient temperature the reaction was partitioned between ethyl acetate (400 mL) and water (400 mL). The organic layer was washed with brine (400 mL), dried (Na₂SO₄), and evaporated. Purification of the residue by flash chromatography (silica gel, 0-25% EtOAc/isohexane) gave 9.5 g (98%) of 3'-aminobiphenyl-2-carbonitrile as a colourless oil that solidified on standing to afford a white solid: ¹H NMR (400 MHz, CDCl₃) δ 3.79 (2 H, br), 6.75 (1 H, ddd, *J* 8, 3 and 1 Hz), 6.84 (1 H, dd, *J* 3 and 3 Hz), 6.92 (1 H, dd, *J* 8 and 3 Hz), 7.25 (1 H, dd, *J* 8 and 8 Hz), 7.40 (1 H, ddd, *J* 8, 8 and 1 Hz), 7.50 (1 H, dd, *J* 8 and 1 Hz), 7.62 (1 H, ddd, *J* 8, 8 and 1 Hz), 7.73 (1 H, dd, *J* 8 and 1 Hz).

A solution of 3'-aminobiphenyl-2-carbonitrile (10.9 g, 56 mmol) in 1,4-dioxane (30 mL) was treated with a solution of 25% aqueous sulphuric acid (150 mL). The resulting suspension was cooled to 0 °C before being treated dropwise over 10 minutes with a solution of sodium nitrite (4.6 g, 67 mmol) in water (10 mL). After stirring at 0 °C for 30 minutes the reaction was poured into hot (70 °C) water (500 mL). On cooling to ambient temperature the product was extracted into ethyl acetate (500 mL), the organic layer was washed with water (300 mL), brine (300 mL) and dried (Na₂SO₄). Filtration and concentration afforded 7.1 g (65%) of 3'-hydroxybiphenyl-2-carbonitrile as a dark oil: ¹H NMR (400 MHz, CDCl₃) δ 5.40 (1

H, br), 6.92 (1 H, ddd, *J* 8, 3 and 1 Hz), 7.04 (1 H, dd, *J* 3 and 3 Hz), 7.11 (1 H, ddd, *J* 8, 3 and 1 Hz), 7.35 (1 H, dd, *J* 8 and 8 Hz), 7.44 (1 H, ddd, *J* 8, 8 and 1 Hz), 7.51 (1 H, dd, *J* 8 and 1 Hz), 7.64 (1 H, ddd, *J* 8, 8 and 1 Hz), 7.75 (1 H, dd, *J* 8 and 1 Hz).

3'-Hydroxybiphenyl-2-carbonitrile (0.48 g, 2.47 mmol) and dry pyridine (0.98 g, 12.35 mmol) were dissolved in dichloromethane (7 mL) and cooled to 0 °C before the dropwise addition of trifluoromethane sulfonic anhydride (1.04 g, 3.70 mmol) over 5 min. The mixture was stirred at 0 °C for 10 min at then at 25 °C for 1 h. The solvent was evaporated *in vacuo* and the residue was partitioned between ethyl acetate (200 mL) and water (150 mL). The organic layer was washed with brine (150 mL), dried (Na₂SO₄) and evaporated to give a brown oil. Purification by chromatography (silica gel, 0-30% EtOAc/isohehexane) gave 544 mg (67%) of trifluoromethanesulfonic acid 2'-cyanobiphenyl-3-yl ester as a yellow oil: ¹H NMR (400 MHz, CDCl₃) δ 7.37 (1 H, ddd, *J* 8, 3 and 1 Hz), 7.39 (1 H, dd, *J* 3 and 3 Hz), 7.50-7.60 (2 H, m), 7.61-7.65 (2 H, m), 7.64 (1 H, td, *J* 8 and 1 Hz), 7.80 (1 H, dd, *J* 8 and 1 Hz).

Trifluoromethanesulfonic acid 2'-cyanobiphenyl-3-yl ester (0.55 g, 1.66 mmol), potassium acetate (0.49 g, 4.98 mmol) and bis(pinacolato)diboron (0.55 g, 2.16 mmol) were dissolved in 1,4-dioxane (10 mL) and the mixture degassed with nitrogen for 15 min. Dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct (41 mg, 0.05 mmol) and 1,1'-bis-(diphenylphosphino)ferrocene (28 mg, 0.05 mmol) were then added and the mixture heated at 85 °C for 18 h. The mixture was cooled to ambient temperature and partitioned between ethyl acetate (150 mL) and water (50 mL). The organic layer was washed with brine (50 mL), dried (Na₂SO₄), and evaporated to give 0.51 g (100%) of **18a** as a black oil. This oil was dissolved in sufficient *N,N*-dimethylacetamide to give a 0.5 M stock solution.

3'-(7-Methyl-imidazo[1,2-*b*]pyridazin-3-yl)-biphenyl-2-carbonitrile (5). A stirred mixture of **13** (43.7 mg, 0.206 mmol) dried potassium phosphate (88.0 mg, 0.415 mmol), and a 0.5 M solution of **18a** in *N,N*-dimethylacetamide (0.82 mL, 0.41 mmol) was degassed by evacuation and refilling with nitrogen three times. Tetrakis(triphenylphosphine)palladium(0) (12.5 mg, 0.0108 mmol) was then added and the mixture was degassed with two more evacuation-refilling cycles before heating at 80 °C under nitrogen for 21 h. The mixture was diluted with ethyl acetate and filtered through glass fibre filter paper, washing solid with more ethyl acetate. The combined filtrates were washed with saturated aqueous NaCl (15 mL), and the aqueous layer was further extracted with ethyl acetate (20 mL). The combined organic extracts were dried (Na₂SO₄) and evaporated. The residue was purified by flash chromatography (silica gel, EtOAc) to give 57.7 mg (90%) of **5** as a yellow solid: mp 164-166 °C (CH₂Cl₂-EtOAc-isohehexane); ¹H NMR (400 MHz, CDCl₃) δ 2.46 (3H, s), 7.48 (1H, td, *J* 7.6, 1.3 Hz), 7.57 (1H, dt, *J* 7.8, 1.6 Hz), 7.60-7.64 (2H, m), 7.69 (1H, td, *J* 7.6, 1.3 Hz), 7.78 (1H, fine m), 7.81 (1H, dd, *J* 7.8, 1.2 Hz), 8.04 (1H, s), 8.13 (1H, dd, *J* 7.7, 1.5 Hz), 8.26 (1H, fine m), 8.29 (1H, fine m); MS (ES⁺) *m/z* 311 [M+H]⁺; Anal. (C₂₀H₁₄N₄•0.03C₄H₈O₂•0.04CH₂Cl₂•0.1H₂O) C, H, N.

2- and 3-Methyl-imidazo[1,2-*b*][1,2,4]triazine (16c). A stirred mixture of bromoacetaldehyde diethyl acetal (5.10 mL, 32.9 mmol) in concentrated hydrobromic acid (1.62 mL) and water (1.62 mL) was heated at reflux for 2 h, then poured into ethanol (54 mL). The solution was neutralised to pH 7 with solid sodium hydrogen carbonate, then filtered. To the filtrate was added a 1:1 mixture of 3-amino-5-methyl-1,2,4-triazine and 3-amino-6-methyl-1,2,4-triazine (1.5210 g, 13.8 mmol) (prepared from pyruvic aldehyde and aminoguanidine bicarbonate as described by Daunis, J. et

al. *Bull. Soc. Chim. Fr.* **1969**, *10*, 3675) and the mixture was stirred at 60 °C for 18 h. After allowing to cool, silica gel was added to the mixture, the solvent was removed and the residue was introduced onto a flash column (silica gel, 2% MeOH/CH₂Cl₂) to give 0.2887 g (16%) of the title compounds as a 71:29 mixture: ¹H NMR (360 MHz, CDCl₃) δ 2.64 and 2.69 (3H, two s), 7.86 (1H, two m), 7.89 and 7.92 (1H, two d, *J* 1.1 Hz), 8.24 and 8.33 (1H, two s); MS (ES⁺) *m/z* 135 [M+H]⁺.

7-Bromo-2-methyl-imidazo[1,2-*b*][1,2,4]triazine and 7-bromo-3-methyl-imidazo[1,2-*b*][1,2,4]triazine (17c). To a solution of the 71:29 mixture of 2- and 3-methyl-imidazo[1,2-*b*][1,2,4]triazine (0.256 g, 1.91 mmol) in acetic acid (3 mL) was added sodium acetate (0.252 g, 3.07 mmol), then, dropwise over 3 min, bromine (109 μL, 2.12 mmol). The solution was stirred at room temperature for 15 min, then partitioned between saturated aqueous NaHCO₃ (135 mL) and ethyl acetate (150 mL). The aqueous layer (pH 8) was further extracted with ethyl acetate (150 mL), and the combined organic extracts were dried (Na₂SO₄) and evaporated. The residue was purified by flash chromatography (silica gel, EtOAc) to afford 0.2623 g (66%) of the title compounds as a 74:26 mixture: ¹H NMR (360 MHz, CDCl₃) δ 2.72 (3H, s), 7.86 (1H, two m), 7.89 and 7.93 (1H, two s), 8.35 and 8.36 (1H, two s); MS (ES⁺) *m/z* 213/215 [M+H]⁺.

3'-(3-Methyl-imidazo[1,2-*b*][1,2,4]triazin-7-yl)biphenyl-2-carbonitrile (8). A stirred 74:26 mixture of 7-bromo-2-methyl-imidazo[1,2-*b*][1,2,4]triazine and 7-bromo-3-methyl-imidazo[1,2-*b*][1,2,4]triazine (0.2623 g, 1.23 mmol), dried potassium phosphate (0.52 g, 2.46 mmol), and a 0.5 M solution of **18a** in *N,N*-dimethylacetamide (4.92 mL, 2.46 mmol) was degassed by evacuation and refilling with nitrogen three times. Tetrakis(triphenylphosphine)palladium(0) (70 mg, 0.061 mmol) was then added and the mixture was degassed with two more evacuation-refilling cycles before heating at 80 °C under nitrogen for 24 h. The residue was purified by flash chromatography (silica gel, EtOAc) to give 0.1551 g (41%) of a mixture of two isomers. These could be separated by preparative HPLC on a ABZ+ plus column (250 x 21 mm i.d.) eluting with 40% MeCN/H₂O (+ 0.1% TFA) at 20 mL/min. Data for **11**: mp 211-216 °C (CH₂Cl₂-EtOAc-isohexane); ¹H NMR (400 MHz, CDCl₃) δ 2.73 (3H, s), 7.50 (1H, td, *J* 7.6, 1.3 Hz), 7.59-7.66 (3H, m), 7.70 (1H, td, *J* 7.7, 1.4 Hz), 7.82 (1H, dd, *J* 7.8, 1.4 Hz), 8.10 (1H, dt, *J* 7.6, 1.5 Hz), 8.29 (2H, t, *J* 1.4 Hz), 8.26 (1H, s), 8.36 (1H, s); HRMS (ES⁺) found *m/z* 312.1225 mDa [M+H]⁺; Required for C₁₉H₁₄N₅: 312.1249 mDa.

3-Amino-5-trifluoromethyl-1,2,4-triazine (15a). To a stirred solution of sodium acetate trihydrate (22.62 g, 166.2 mmol) in water (80 mL) was added 1,1-dibromo-3,3,3-trifluoroacetone (21.57 g, 79.9 mmol). The solution was heated at reflux under nitrogen for 30 min, then allowed to cool to room temperature before adding solid aminoguanidine bicarbonate (10.88 g, 79.9 mmol). The resulting pale yellow solution (pH 5) was stirred at room temperature for 3 h, then 4 N aqueous NaOH solution (40 mL, 160 mmol) was added causing a precipitate to appear. The mixture (pH 10) was stirred under nitrogen for a further 39 h. The solid was collected by filtration, washed with water and dried at 60 °C under vacuum to give 6.96 g of a mixture of two isomers in a 28:72 ratio. This was further purified by flash chromatography (silica gel, 30% EtOAc/isohexane), then recrystallised from ethanol to afford 3.53 g (27%) of **15a**: ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.00 (2H, br s), 9.08 (1H, s).

3-Trifluoromethyl-imidazo[1,2-*b*][1,2,4]triazine (16a). A stirred mixture of bromoacetaldehyde diethyl acetal (2.30 mL, 14.8 mmol) in concentrated hydrobromic acid (0.73 mL) and water (0.73 mL) was heated at reflux for 2 h, then poured into

ethanol (25 mL). The solution was neutralised to pH 7 with solid sodium hydrogen carbonate, then filtered. To the filtrate was added **15a** (1.0079 g, 6.14 mmol) and the mixture was stirred at 60 °C for 20 h, then 80 °C for 23 h. The mixture was evaporated and the residue was purified by flash chromatography (silica gel, 35-50% EtOAc/isoohexane) to give 0.2593 g (22%) of **16a**: ¹H NMR (360 MHz, CDCl₃) δ 8.20 (1H, d, *J* 0.8 Hz), 8.30 (1H, d, *J* 0.9 Hz), 8.73 (1H, s).

7-Bromo-3-trifluoromethyl-imidazo[1,2-*b*][1,2,4]triazine (17a). To a solution of **16a** (0.2211 g, 1.18 mmol) in acetic acid (6 mL) was added sodium acetate (0.1470 g, 1.79 mmol), then bromine (90.8 µL, 1.76 mmol). The solution was stirred at room temperature for 6 h, then partitioned between saturated aqueous NaHCO₃ (100 mL) and ethyl acetate (100 mL). The aqueous layer (pH 9) was further extracted with ethyl acetate (100 mL), and the combined organic extracts were dried (Na₂SO₄) and evaporated. The residue was purified by flash chromatography (silica gel, 25% EtOAc/isoohexane) to afford 0.2073 g (66%) of **17a**: ¹H NMR (360 MHz, CDCl₃) δ 8.30 (1H, s), 8.83 (1H, s).

2',4-Difluoro-5'-[3-(trifluoromethyl)imidazo[1,2-*b*][1,2,4]triazin-7-yl]biphenyl-2-carbonitrile (9). A stirred mixture of **17a** (0.100 g, 0.375 mmol) and 4,2'-difluoro-5'-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-biphenyl-2-carbonitrile (**18b**) (0.192 g, 0.563 mmol) in THF (5 mL) and 2 M aqueous Na₂CO₃ (0.561 mL, 1.12 mmol) was degassed by bubbling through nitrogen for 20 min. Tetrakis(triphenylphosphine)palladium(0) (21.6 mg, 0.019 mmol) was then added and the mixture was degassed for a further 10 min, then stirred at 70 °C for 16 h under nitrogen. The mixture was partitioned between dichloromethane (30 mL) and water (10 mL) and the aqueous phase was extracted further with dichloromethane (2 x 30 mL). The organic extracts were combined, dried (MgSO₄) and evaporated. The residue was purified by flash chromatography (silica gel, 10-20% EtOAc/isoohexane) to yield 0.092 g (61%) of the title compound as a yellow solid: (EtOAc/isoohexane); ¹H NMR (400 MHz, CDCl₃) δ 7.41-7.47 (2H, m), 7.55 (1H, dd, *J* 7.9, 2.6 Hz), 7.59 (1H, m), 8.16-8.22 (2H, m), 8.62 (1H, s), 8.80 (1H, s); HRMS (ES⁺) found *m/z* 402.0765 mDa [M+H]⁺. Required for C₁₉H₉N₅O₅: 402.0778 mDa.

1,1-Dibromo-3-hydroxy-3-methyl-butan-2-one (14b). A solution of 3-hydroxy-3-methyl-2-butanone (450 g, 4.41 mol), 4-dimethylaminopyridine (26.9 g, 0.22 mol) and triethylamine (921 mL, 6.61 mol) in dichloromethane (2.25 L) was cooled in an ice-bath and treated with acetic anhydride (521 mL, 5.51 mol) at such a rate that the reaction temperature did not exceed 25 °C. The reaction mixture was stirred at ambient temperature for 14 h. After this time, the reaction mixture was cooled in an ice-bath and methanol (450 mL) was added with vigorous stirring at such a rate that the temperature did not exceed 25 °C. 2 M Hydrochloric acid (1 L) was then added with vigorous stirring at such a rate that the temperature did not exceed 25 °C. The phases were separated and the dichloromethane layer was washed with water (900 mL) and saturated sodium hydrogen carbonate solution (450 mL), then dried (MgSO₄), filtered and concentrated in vacuo at 40 °C to give the required product. Distillation of the residue at reduced pressure afforded 550 g (87%) of 3-acetoxy-3-methyl-2-butanone as a colourless liquid: bp (25 mmHg) 68-72 °C; δ (400 MHz, CDCl₃) 1.46 (6 H, s), 2.09 (3 H, s), 2.12 (3 H, s). In later runs, the crude product was used successfully in the next step, obviating the need for distillation.

To a mechanically stirred slurry of pyridine hydrobromide perbromide (1.11 kg, 3.468 mol) in dichloromethane (200 mL) was added 3-acetoxy-3-methyl-2-butanone (200 g, 1.387 mol) and methanol (200 mL), and the reaction mixture was stirred for 24 h at room temperature. After this time, dissolution was complete and

the reaction mixture was washed with 2 M hydrochloric acid (2 x 400 mL), and the combined acidic layers were back-extracted with dichloromethane (3 x 400 mL). The combined organic layers were washed with 10% w/v sodium hydrogen sulfite solution and saturated brine (400 mL), then dried (MgSO₄), filtered and concentrated in vacuo at 40 °C to give 351.6 g (98%) of **14b** as a brown liquid: δ (360 MHz, CDCl₃) 1.54 (6 H, s), 2.45 (1 H, br s), 6.62 (1 H, s).

2-(3-Amino-[1,2,4]triazin-5-yl)-propan-2-ol (15b) and 2-(3-Amino-[1,2,4]triazin-6-yl)-propan-2-ol. To a stirred solution of sodium acetate trihydrate (387 g, 2.835 mol) in water (1.05 L) was added **14b** (351.6 g, 1.35 mol). The solution was heated at 90 °C for 30 min, then allowed to cool to 50 °C before adding solid aminoguanidine bicarbonate (184.1 g, 1.35 mol) and solid potassium hydrogen carbonate (392.6 g, 2.835 mol). An immediate darkening of the reaction mixture, followed by a gradual exotherm to 60 °C, was observed over the next 10 minutes. The reaction mixture was allowed to cool to room temperature over 1.5 h, then solid sodium chloride (175 g) was added and stirring continued for 0.5 h. The slurry was filtered through a filter cloth and the solid was washed with water (2 x 175 mL). The filtrate was extracted with ethyl acetate (5 x 1L), dried (MgSO₄), filtered and concentrated in vacuo at 40 °C to give 139.1 g (67%) of an approximately 1:1 mixture of **15b** and its isomer as a brown solid: δ (360 MHz, DMSO-d₆) 1.38 and 1.47 (6H, s), 5.30 and 5.43 (1H, br s), 7.01 and 7.06 (2H, br s), 8.43 and 8.80 (1H, s); MS (ES⁺) m/z 155 [M+H]⁺.

2-(Imidazo[1,2-b][1,2,4]triazin-3-yl)-propan-2-ol (16b). A stirred mixture of bromoacetaldehyde diethyl acetal (191 mL, 1.268 mol) in concentrated hydrobromic acid (62.4 mL, 0.55 mol) and water (62.4 mL) was heated at 90 °C for 25 min, then cooled to room temperature, poured into ethanol (1.7 L) and basified with the careful addition of solid sodium hydrogen carbonate (120 g). The slurry was filtered and to the filtrate was added **15b** (85 g, 0.55 mol, [1:1 mixture with isomer]) and the mixture was stirred at 50 °C for 28 h. The reaction mixture was evaporated in vacuo at 40 °C and the residue was diluted with water (425 mL) and extracted with dichloromethane (250 mL). The organic phase was washed with 2 M hydrochloric acid (2 x 170 mL), the combined aqueous acidic phases were basified to pH 7/8 using solid potassium carbonate (90 g) and extracted with ethyl acetate (4 x 425 mL), then dried (MgSO₄), filtered and concentrated in vacuo at 40 °C to give a red/brown liquid (73.7 g). The crude product was purified by chromatography on a Biotage flash 75L system using 4% isopropanol/dichloromethane as eluent to give, after azeotrope with toluene, 22.7 g (23%) of **16b** as a yellow solid: δ (360 MHz, CDCl₃) 1.69 (6H, s), 3.69 (1H, br s), 7.93 (2H, s), 8.70 (1H, s).

2-(7-Bromo-imidazo[1,2-b][1,2,4]triazin-3-yl)-propan-2-ol (17b). To a solution of **16b** (5.55 g, 31.1 mmol) in acetic acid (112 mL) was added sodium acetate (3.83 g, 46.7 mmol), then bromine (1.77 mL, 34.4 mmol). The solution was stirred at room temperature for 25 min, then partitioned carefully between saturated aqueous NaHCO₃ (2 L) and ethyl acetate (1 L). The aqueous layer (pH 7) was further extracted with ethyl acetate (1 L), and the combined organic extracts were dried (Na₂SO₄) and evaporated. The residue was purified by flash chromatography (silica gel, 2% MeOH/CH₂Cl₂) to afford 6.17 g (77%) of **17b**: ¹H NMR (360 MHz, CDCl₃) δ 1.70 (6H, s), 3.12 (1H, br s), 7.95 (1H, s), 8.80 (1H, s).

4,2'-Difluoro-5'-[3-(1-hydroxy-1-methyl-ethyl)imidazo[1,2-b][1,2,4]triazin-7-yl]-biphenyl-2-carbonitrile (10). This was prepared from 5'-(5,5-dimethyl-[1,3,2]dioxaborinan-2-yl)-4,2'-difluoro-biphenyl-2-carbonitrile (**18d**)¹² and **17b** in 54% yield, using a similar procedure to that described for **9**, to give **10** as a

yellow solid: mp 215 °C; ¹H NMR (360 MHz, CDCl₃) δ 1.71 (6H, s), 3.27 (1H, br s), 7.35-7.59 (4H, m), 8.09-8.15 (2H, m), 8.26 (1H, s), 8.78 (1H, s); MS (ES⁺) *m/z* 392 [M+H]⁺. Anal. (C₂₁H₁₅F₂N₅O) C, H, N.

5'-(5,5-Dimethyl-[1,3,2]dioxaborinan-2-yl)-6,2'-difluorobiphenyl-2-carbonitrile (18e). A mechanically stirred mixture of 4-nitro-fluorobenzene (**8**, 28.2 g, 200 mmol) and potassium sulfate (350 mg, 2 mmol) in 50% sulphuric acid (400 mL) was heated to 65 °C (internal temperature). The mixture was stirred vigorously whilst sodium bromate (31 g, 205 mmol) was added, in portions, over 2.5 h (maximum internal temp. 72 °C). After the last of the sodium bromate had been added, stirring at 65 °C was continued for a further 1 h before pouring the reaction mixture into water (2.5 L). The resulting solid was collected by filtration, triturated with water and dried at atmospheric pressure over phosphorus pentoxide. Recrystallization from toluene gave 33 g (75%) of 1-bromo-2-fluoro-5-nitrobenzene as a pale yellow crystalline solid: δ (360 MHz, DMSO-*d*₆) 7.68 (1 H, dd, *J* 9 and 8 Hz), 8.30-8.35 (1 H, m), 8.59 (1 H, dd, *J* 6 and 3 Hz).

A mixture of 1-bromo-2-fluoro-5-nitrobenzene (66 g, 300 mmol), potassium acetate (58.9 g, 600 mmol), bis(pinacolato)diboron (83.8 g, 330 mmol) and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct (7.35 g, 9 mmol) in 1,4-dioxane (900 mL containing 18 mL dimethyl sulfoxide) was degassed with nitrogen for 1h, then heated at 90 °C for 14 h. The reaction mixture was cooled to ambient temperature, filtered and the filter-cake was washed with diethyl ether. The combined filtrate was concentrated, the residue was stirred with 2N sodium hydroxide solution (1 L) for 45 min and then filtered. The filtrate was extracted with diethyl ether (2 x 750 mL) and the organic layers were discarded. The aqueous component was cooled to 0 °C, then treated with 36% hydrochloric acid (175 mL), added dropwise over 15 min, until pH 5 was attained. After standing at 0 °C for 2 h, the resulting precipitate was collected by filtration, washed with ice-cold water and then dried under vacuum (300 mmHg) over phosphorus pentoxide to give 76.1 g (95%) of 2-(2-fluoro-5-nitrophenyl)-4,4,5,5-tetramethyl[1,3,2]dioxaborolane as a light brown solid: ¹H NMR (400 MHz, CDCl₃) δ 1.38 (12 H, s), 7.17 (1 H, dd, *J* 9 and 9 Hz), 8.32 (1 H, ddd, *J* 9, 5 and 3 Hz), 8.64 (1 H, dd, *J* 5 and 3 Hz).

A solution of 2,3-difluorobenzonitrile (22.4 g, 161 mmol) in ethanol saturated with ammonia (250 mL) was heated at 140 °C in a pressure reactor for 16 h during which time the pressure rose to a maximum of 170 psi. The mixture was allowed to cool to room temperature and the solvent was removed. The residual solid was taken up in water (400 mL) and washed with diethyl ether (2 x 250 mL). The combined organic layers were washed with water (1 x 300 mL), then dried (MgSO₄) and concentrated. The residue was triturated with isohexane and dried, yielding 18.2 g (83%) of 2-amino-3-fluorobenzonitrile an orange solid: ¹H NMR (360 MHz, CDCl₃) δ 4.48 (2 H, br s), 6.65-6.71 (1 H, m), 7.14-7.21 (2 H, m).

To a hot solution of 2-amino-3-fluorobenzonitrile (12.1 g, 88.7 mmol) in 1,4-dioxane (20 mL) was added 48% hydrobromic acid (160 mL), and the resulting mixture was cooled to 0 °C. A solution of sodium nitrite (7.04 g, 102 mmol) in water (20 mL) was added dropwise with stirring over 45 min, maintaining the temperature of the mixture below 3 °C throughout the addition. The thick slurry was stirred at 0 °C for a further 2 h, and was then poured cautiously into a solution of copper(I) bromide (12.7 g, 88.7 mmol) in 48% hydrobromic acid (80 mL). The reaction mixture was heated slowly to 50 °C and was stirred at this temperature for 20 min. After cooling to room temperature, the reaction mixture was diluted with water (1 L)

and washed with diethyl ether (2 x 500 mL). The combined organic layers were washed with 10% aqueous ammonia (1 x 500 mL), water (1 x 500 mL), saturated sodium chloride solution (1 x 500 mL), and then dried (MgSO₄), filtered and concentrated, to give 11.2 g (63%) of 2-bromo-3-fluorobenzonitrile as a dark brown oil which solidified upon standing: ¹H NMR (400 MHz, CDCl₃) δ 7.34-7.45 (2H, m), 7.48-7.51 (1H, m).

A mixture of 2-bromo-3-fluorobenzonitrile (13.1 g, 65.5 mmol), 2-(2-fluoro-5-nitrophenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (26.2 g, 98.2 mmol), potassium fluoride (12.6 g) and water (10 mL) in THF (260 mL) was degassed by bubbling nitrogen through with stirring for 30 min. After this time tris(dibenzylideneacetone)dipalladium(0) (600 mg, 0.655 mmol) and tri-*tert*-butylphosphine (6.55 mL of a 0.2 M solution in 1,4-dioxane, 1.31 mmol) were added and the slurry was stirred at room temperature for 15 min, then at 50 °C for 2 h under nitrogen. The mixture was allowed to cool to room temperature, then was poured into water (3 L) and stirred vigorously for 2 h. The solid that precipitated was collected by filtration, washed with water (250 mL) and iso-hexane (250 mL) then dried at room temperature in a dessicator over phosphorus pentoxide to give 16.4 g (96%) of 6,2'-difluoro-5'-nitrobiphenyl-2-carbonitrile as a dark solid: ¹H NMR (360 MHz, CDCl₃) δ 7.40-7.44 (2H, m), 7.49 (2H, dt, *J* 8.6 and 1.3 Hz), 8.37-8.44 (2H, m). A mixture of 6,2'-difluoro-5'-nitrobiphenyl-2-carbonitrile (16.4 g, 63.0 mmol) and tin(II) chloride dihydrate (49.8 g, 221 mmol) in ethanol (100 mL) and THF (100 mL) was stirred at room temperature for 24 h. The solvent was removed, and the residual material was taken up in 2 M sodium hydroxide solution (300 mL) and stirred at room temperature for 90 min. The suspension was filtered and the filtrate was washed with dichloromethane (3 x 300 mL). The combined organic layers were washed with saturated brine (1 x 300 mL), then dried (MgSO₄), filtered and concentrated. 5'-Amino-6,2'-difluorobiphenyl-2-carbonitrile was isolated as a brown solid (13.8 g, 95%) and used without further purification: ¹H NMR (360 MHz, CDCl₃) δ 3.65 (2 H, s), 6.68 (1 H, dd, *J* 3.0 and 5.8 Hz), 6.73-6.77 (1 H, m), 7.01 (1 H, t, *J* 9.0 Hz), 7.37-7.50 (2 H, m), 7.56-7.59 (1 H, m).

To 5'-amino-6,2'-difluorobiphenyl-2-carbonitrile (13.6 g, 59.7 mmol) in hot 1,4-dioxane (20 mL) was added 48% hydrobromic acid (190 mL). The mixture was cooled to 0 °C and a solution of sodium nitrite (4.12 g, 59.7 mmol) in water (7 mL) was added drop-wise over 20 min, maintaining the temperature between 0 °C and 2 °C throughout the addition. The resulting slurry was stirred at 0 °C for 1 h, and then poured cautiously into a solution of copper(I) bromide (12.8 g, 89.6 mmol) in hydrobromic acid (100 mL) at 0 °C (effervescence was observed). The mixture was stirred at 0 °C for 10 min, then heated slowly to 50 °C and heated at that temperature for a further 20 min (further effervescence was observed upon heating). The mixture was diluted with water (1 L) and washed with diethyl ether (2 x 500 mL). The combined organic layers were washed with 10% aqueous ammonia (1 x 500 mL), water (1 x 500 mL) and saturated brine (1 x 500 mL), then dried (MgSO₄) and concentrated. The crude product was purified by flash chromatography (silica gel, 2-6% ethyl acetate/iso-hexane) (the material was loaded onto the column in the minimum amount of dichloromethane) to give 10.9 g (62%) of 5'-bromo-6,2'-difluorobiphenyl-2-carbonitrile as a pale yellow solid: ¹H NMR (400 MHz, CDCl₃) δ 7.14 (1 H, t, *J* 9.0 Hz), 7.44 (1 H, dt, *J* 9.0 and 1.2 Hz), 7.50-7.55 (2 H, m), 7.58-7.62 (2H, m).

A mixture of 5'-bromo-6,2'-difluorobiphenyl-2-carbonitrile (10.8 g, 36.7 mmol), bis(neopentylglycolato)diboron (12.2 g, 54.0 mmol), potassium acetate (10.9

g, 111 mmol) and DMSO (3.4 mL) in 1,4-dioxane (170 mL) was degassed by bubbling nitrogen through with stirring for 40 min. [1,1'-Bis(diphenylphosphino)ferrocene]-dichloropalladium(II) dichloromethane complex (604 mg, 0.74 mmol) was added and the mixture was stirred at 85 °C under nitrogen for 16 h. The mixture was cooled to room temperature and diluted with diethyl ether (210 mL), then was filtered through glass fibre filter paper. The filtrate was concentrated, then the crude product was taken up in diethyl ether (425 mL) and was washed with 1 M sodium hydroxide solution (2 x 200 mL). Concentrated hydrochloric acid was added to the combined aqueous layers until pH ~5 and the acidic mixture washed with diethyl ether (2 x 400 mL). The combined organic layers were washed with water (1 x 200 mL) and saturated brine (1 x 200 mL), then were dried (MgSO₄), filtered and concentrated to give 12.2 g (100%) of **18e** as a pale brown solid which was used without further purification: ¹H NMR (360 MHz, CDCl₃) δ 1.02 (6 H, s), 3.76 (4 H, s), 7.21 (1 H, dd, *J* 8.4 and 9.8 Hz), 7.37-7.50 (2 H, m), 7.58 (1 H, dd, *J* 1.1 and 7.0 Hz), 7.85 (1 H, dd, *J* 1.4 and 8.1 Hz), 7.89-7.93 (1 H, m).

6,2'-Difluoro-5'-[3-(1-hydroxy-1-methylethyl)imidazo[1,2-*b*][1,2,4]triazin-7-yl]biphenyl-2-carbonitrile (11). A mixture of **17b** (5.55 g, 21.6 mmol), **18e** (9.28 g, 28.4 mmol) and 2 M sodium carbonate solution (28.3 mL, 56.7 mmol) in DME (115 mL) was degassed by bubbling nitrogen through with stirring for 15 min. Tetrakis(triphenyl-phosphine)palladium (0) (1.26 g, 1.09 mmol) was added and the mixture was degassed as before for a further 5 min, then stirred at 80 °C under nitrogen for 16 h. The reaction mixture was allowed to cool to room temperature, then diluted with water (500 mL) and was washed with ethyl acetate (2 x 300 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo* and the residual material was purified by flash chromatography on silica gel, eluting with 0-2% methanol in dichloromethane (the crude product was dry-loaded onto the silica gel). Trace impurities were removed by recrystallization from toluene followed by a second recrystallization from ethyl acetate to give 5.4 g (64%) of **11** as a bright yellow solid: mp 212-214 °C; ¹H NMR (400 MHz, CDCl₃) δ 1.71 (6 H, s), 3.28 (1 H, s), 7.40 (1 H, t, *J* 9.2 Hz), 7.45-7.58 (2 H, m), 7.66 (1 H, dd, *J* 1.0 and 8.0 Hz), 8.13-8.17 (2 H, m), 8.26 (1 H, s), 8.78 (1 H, s). MS (ES⁺) *m/z* 392 [M+H]⁺. Anal. (C₂₁H₁₅F₂N₅O) C, H, N.

2',4,6-Trifluoro-5'-[3-(1-hydroxy-1-methylethyl)imidazo[1,2-*b*][1,2,4]triazin-7-yl]biphenyl-2-carbonitrile (12). This was prepared from **17b** and 4,6,2'-trifluoro-5'-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-biphenyl-2-carbonitrile (**18c**) using the same procedure as that described for **9** to give a yellow solid: mp 202-204 °C (EtOAc-CH₂Cl₂-isohexane); ¹H NMR (400 MHz, CDCl₃) δ 1.71 (6H, s), 3.22 (1H, s), 7.25 (1H, m), 7.38-7.42 (2H, m), 8.14-8.17 (2H, m), 8.26 (1H, s), 8.78 (1H, s); HRMS (ES⁺) found *m/z* 410.1238 mDa [M+H]⁺. Required for C₂₁H₁₅F₃N₅O: 410.1229 mDa.

Squirrel Monkey RPI Lever Pressing Assay. Nine adult male squirrel monkeys (*Saimiri sciureus*, 0.7-1.2 kg) were placed in a standard Plexiglas primate chair. Monkeys were trained to press a lever to obtain a fruit juice reward on a fixed reinforcement (FR) schedule prior to being transferred to a Regulated Probability Interval schedule (RPI30) under which they received a reinforcer, on average, every 30 s. An experimental session was initiated by the extension of the lever into the operant chamber and the illumination of the house light. After 30 min. the end of the session was signalled by turning off the houselight and retracting the response lever.

Animals were dosed with vehicle (0.5% w/v) methyl cellulose; 2 mL/kg) or compound **11** (1, 3 or 10 mg/kg po) 30 min prior to testing. The experiment used a pseudo-Latin square design in which each animal received vehicle and each dose of **11**. Lever pressing rates on days monkeys received **11** or vehicle expressed as a percentage of the lever presses rates recorded on the day prior to drug administration were subjected to one way analysis of variance with repeated measures followed, where appropriate, by paired Student t-tests.

Elemental Analyses Data

No.	Formula	Calculated			Found		
		C	H	N	C	H	N
5	$\text{C}_{20}\text{H}_{14}\text{N}_4 \bullet 0.03\text{C}_4\text{H}_8\text{O}_2$ $\bullet 0.04\text{CH}_2\text{Cl}_2 \bullet 0.1\text{H}_2\text{O}$	76.10	4.60	17.61	75.89	4.62	17.38
10	$\text{C}_{21}\text{H}_{15}\text{F}_2\text{N}_5\text{O}$	64.45	3.86	17.89	64.38	3.88	17.66
11	$\text{C}_{21}\text{H}_{15}\text{F}_2\text{N}_5\text{O}$	64.45	3.86	17.89	64.29	3.61	17.54

HPLC Data

No.	Purity	Retention Time/min	% MeCN
8	>99.5%	6.79	40
9	>99.5%	4.75	60
12	>99.5%	9.30	40