Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

A Convenient Chemical-Microbial Method for Developing Fluorinated Pharmaceuticals

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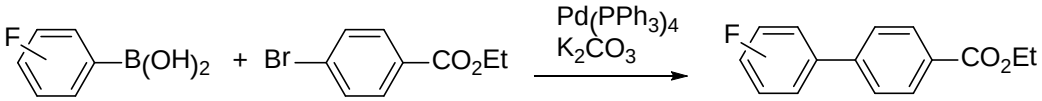
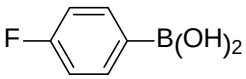
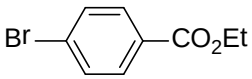
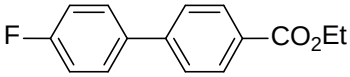
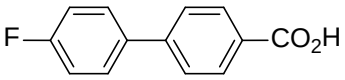
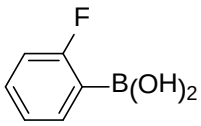
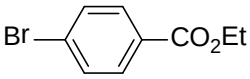
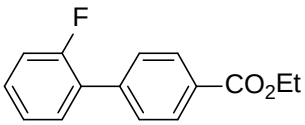
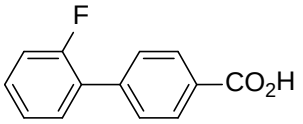
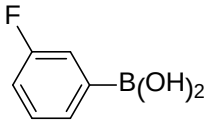
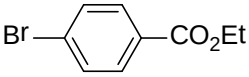
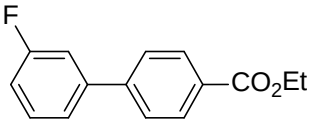
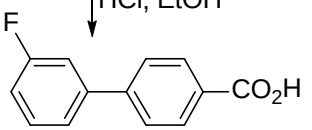
SUPPORTING INFORMATION

Proton, carbon and fluorine nuclear magnetic resonance spectra (^{1}H NMR, ^{13}C NMR and ^{19}F NMR) were recorded (^{1}H NMR, 500 MHz; ^{13}C NMR, 126 MHz; ^{19}F NMR, 470 MHz or ^{1}H NMR, 700 MHz; ^{13}C NMR, 176 MHz; ^{19}F NMR, 658 MHz) using solvent resonance as the internal standard (^{1}H NMR, $CHCl_3$ at 7.26 ppm; ^{13}C NMR, $CDCl_3$ at 77.36 ppm; ^{19}F NMR, $CFCl_3$ at 0.00 ppm). ^{1}H, ^{13}C and ^{19}F spectroscopic data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constants (Hz), and assignment. Melting points were measured at atmospheric pressure and are uncorrected. Unless otherwise stated, commercially available reagents were used without

purification. Flash column chromatography was carried out using Fluorochem Silica gel LC60A (40-63 micron).

Table S1. Synthesis of fluorobiphenyl carboxylic acid derivatives



Fluoroarene	Haloarene	Product (%)
		 62%
		HCl, EtOH
		 66%
		 62%
		HCl, EtOH
		 66%
		 62%
		HCl, EtOH
		 66%

***2'-Fluorobiphenyl-4-carboxylic acid* 1d**

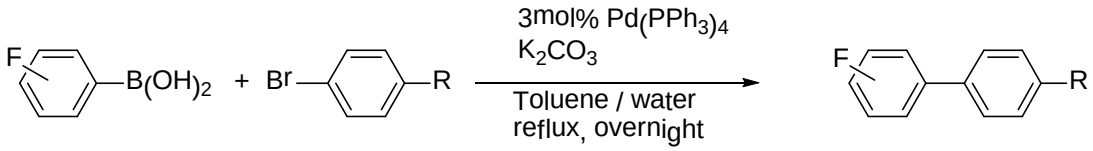
2-Fluorobenzene boronic acid (0.861g, 7mmol), potassium carbonate (1.312 g, 9.5mmol), $Pd(PPh_3)_4$ (0.248 g, 2.14 mmol), ethyl-4-bromobenzoate (0.76 mL, 4.65mmol), ethanol (20 mL) and water (20 mL), were stirred at room temperature for 30 minutes, washed with brine

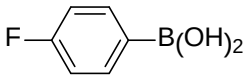
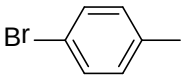
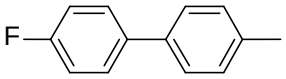
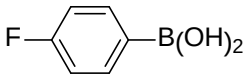
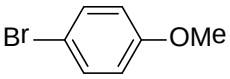
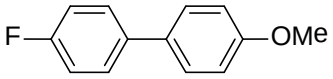
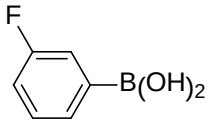
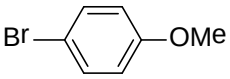
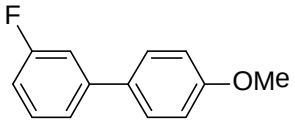
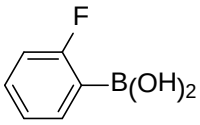
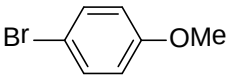
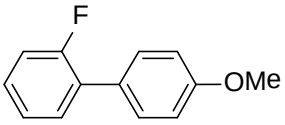
and extracted using diethyl ether to yield crude 2'-fluorobiphenyl-4-carboxylic acid ethyl ester. Hydrolysis was carried out (2M NaOH, 2M HCl) to give *2'-fluorobiphenyl-4-carboxylic acid* **1d** (0.41g, 66%) as a white solid; m.p. 241.1 - 242.1 ^{o}C (lit.,[1] 232 – 233 ^{o}C); δ_H7.26-7.30 (1H, m, ArH),7.48-7.52 (1H, m, ArH), 7.70-7.74 (1H, m, ArH), 7.77-7.82 (1H, m, ArH), 7.85 (2H, m, ArH), 8.10 (2H, m, ArH); δ_F -120.9 (s); *m/z*(ASAP$^+$) 216 ([MH]$^+$, 100%).

***3'-Fluorobiphenyl-4-carboxylic acid* 1c**

3-Fluorobenzene boronic acid (0.861g, 7mmol), potassium carbonate (1.312 g, 9.5mmol), $Pd(PPh_3)_4$ (0.248 g, 2.14 mmol), ethyl-4-bromobenzoate (0.76 mL, 4.65mmol), ethanol (20 mL) and water (20 mL), were stirred at room temperature for 30 minutes, washed with brine and extracted using diethyl ether to yield ethyl 3'-fluorobiphenyl-4-carboxylate. Hydrolysis was carried out (2M NaOH, 2M HCl) to give *3'-fluoro-4-carboxylic acid* **1c** (0.41 g, 66%) as a white solid; m.p. 244.1 - 246.1 ^{o}C (lit.,[1] 240 – 242 ^{o}C); δ_H 7.16-7.22 (1H, m, ArH), 7.46-7.51 (1H, m, ArH), 7.28-7.31 (1H, m, ArH), 7.50-7.54 (1H, m, ArH), 7.80 – 7.90 (2H, m, ArH), 8.05 – 8.10 (2H, m, ArH); δ_F -116.5 (s); *m/z*(ASAP$^+$) 216 ([MH]+, 100%).

Table S2. Synthesis of fluorobiphenyl derivatives



Fluoroarene	Haloarene	Product (%)	
			61%
			27%
			35%
			44%

***4-Fluoro-4'-methylbiphenyl* 1f**

1-Bromotoluene (1.37 g, 8 mmol), 4-fluorobenzene boronic acid (1.12 g, 8 mmol), potassium carbonate (2.21 g, 16 mmol), $PdCl_2$ (4.0 mg, 0.024 mmol) and *iso*propanol (20 mL), after recrystallisation from ethanol, gave *4-fluoro-4'-methylbiphenyl* **1f** (0.90 g, 61 %) as a white crystalline solid; mp 78.3-74.4 °C (lit.,[2] 74 - 77 °C); (Found: C, 83.7; H, 6.0. $C_{13}H_{11}$Frequires: C, 83.8; H, 5.9%); ν_{max}(cm^{-1}) 2924, 1499, 1225, 811; δ_H2.41 (3H, s, CH_3), 7.17- 7.09 (2H, m, ArH),7.28 – 7.23 (2H, m, ArH), 7.48 – 7.43 (2H, m, ArH), 7.57-7.50 (2H, m, ArH); δ_C21.05 (CH_3), 115.52 (d, $^2J_{CF}$ 21.4, C-3),126.84 (C-2'),128.44 (d, $^3J_{CF}$ 8.0, C-2),129.52 (C-3'),137.01 (C-4'),137.26 (d, $^4J_{CF}$ 3.3, C-1),137.38 (C-1'),162.29 (d, $^1J_{CF}$ 245.9, C-4); δ_F -116.81 (s); *m/z* (ASAP$^+$) 186 ([M]$^+$, 100%).

***2-Fluoro-4'-methoxy-biphenyl* 1j**

2-Fluorobenzene boronic acid (1.00 g, 7.15 mmol), potassium carbonate (1.78 g, 12.9 mmol), $Pd(PPh_3)_4$ (0.248 g, 0.21 mmol), 4-bromoanisole (0.8 mL, 6.43 mmol), toluene (25 mL) and

water (0.5 mL), after column chromatography on silica gel using hexane:DCM(4:1) as elutant, gave *2-fluoro-4'-methoxy-biphenyl*[3] **1j** (0.57 g, 44 %) as a white solid; mp 47.3-47.9 °C; (Found: C, 77.0; H, 5.5. $C_{13}H_{11}FO$ requires: C, 77.2; H, 5.5%); ν_{max}(cm^{-1}) 3042, 2938, 2842, 1608, 1482, 1248 (-COR); δ_H3.86 (3H, s, OCH_3), 6.95 - 7.21 (3H, m, ArH), 7.26 - 7.31 (1H, m, ArH), 7.40 -7.44 (2H, m, ArH), 7.49 - 7.52 (2H, m, ArH); δ_C55.29 (OCH_3), 113.91 (C-3'),116.03 (d, $^2J_{CF}$ 22.9, C-3), 124.28 (d, $^4J_{CF}$ 3.7, C-5),128.17 (C-2'),128.38 (d, $^3J_{CF}$ 8.1, C-4),128.69 (d, $^2J_{CF}$ 13.3, C-1),130.12 (d, $^3J_{CF}$ 3.1, C-6),130.48 (d, $^3J_{CF}$ 3.6, C-1'),159.22 (C-4'),159.74 (d, $^1J_{CF}$ 247.0, C-2); δ_F -118.73 (s); *m/z* (ASAP$^+$)202 ($[M]^+$, 100%).

3-Fluoro-4'-methoxybiphenyl **1i**

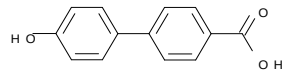
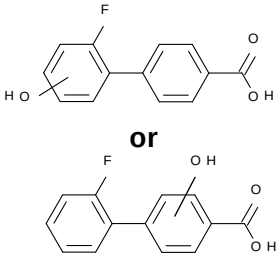
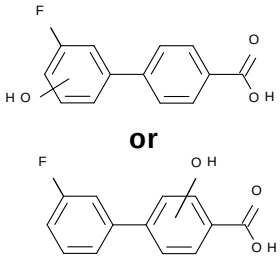
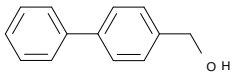
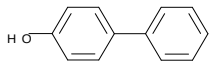
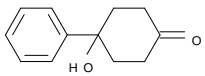
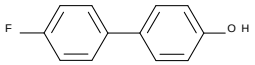
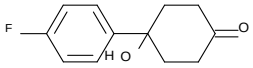
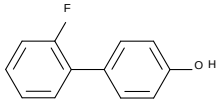
3-Fluorobenzene boronic acid (1 g, 7.15 mmol), potassium carbonate (1.78 g, 12.9 mmol), $Pd(PPh_3)_4$ (0.248 g, 0.214 mmol), 4-bromoanisole (0.8 mL, 6.43 mmol), toluene (25 mL) and water (0.5 mL), after column chromatography on silica gel using hexane:ethyl acetate (9:1) as elutant, gave *3-fluoro-4'-methoxybiphenyl* **1i** (0.685 g, 53 %) as a white solid; mp 64.5-66.1 °C (lit.,[4] 67.0 – 67.5 ^oC; (Found: C, 77.2; H, 5.5. $C_{13}H_{11}FO$ requires: C, 77.2; H, 5.5%); ν_{max}(cm^{-1}) 3016, 2937, 1587, 1185; δ_H3.85 (3H, s, OCH_3), 6.94 - 7.03 (3H, m, ArH),7.22 - 7.28 (1H, m, ArH), 7.29 -7.41 (2H, m, ArH), 7.48 - 7.56 (2H, m, ArH); δ_C55.32 (OCH_3), 113.03 (d, $^2J_{CF}$ 21.6, C-4), 113.42 (d, $^2J_{CF}$ 19.0, C-2),114.29 (C-3'), 122.25 (d, $^4J_{CF}$ 2.8, C-6),128.11 (C-2'),130.12 (d, $^3J_{CF}$ 8.5, C-5),132.41 (d, $^4J_{CF}$ 2.3, C-1'),143.09 (d, $^3J_{CF}$ 7.8, C-1),159.55 (C-4'),163.22 (d, $^1J_{CF}$245.3, C-3); δ_F -113.79 (s); *m/z* (ASAP$^+$) 202 ($[M]^+$, 100%).

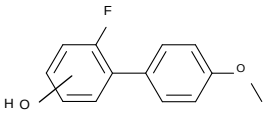
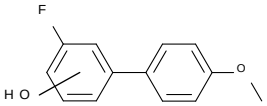
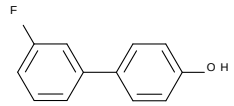
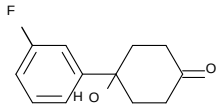
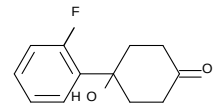
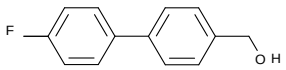
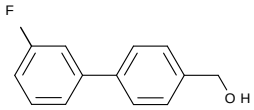
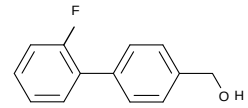
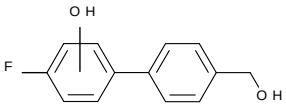
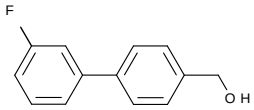
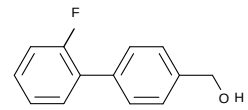
4-Fluoro-4'- methoxybiphenyl **1h**

4-Fluorobenzene boronic acid (1 g, 7.15 mmol), potassium carbonate (1.78 g, 12.9 mmol), $Pd(PPh_3)_4$ (0.248 g, 0.214 mmol), 4-bromoanisole (0.8 mL, 6.43 mmol), toluene (25 mL) and water (0.5 mL), after by column chromatography on silica gel using hexane:ethyl acetate(9:1) as elutant, gave *4-fluoro-4'-methoxybiphenyl* **1h** (0.36 g, 27 %) as a white solid; mp 89.7-

92.1 °C lit.,[2] 86 – 88 °C); (Found: C, 77.2; H, 5.35. $C_{13}H_{11}FO$ requires: C, 77.2; H, 5.5%); ν_{max}(cm^{-1})3017, 1600, 1493; δ_H3.85 (3H, s, OCH_3), 6.90 - 7.01 (2H, m, ArH), 7.06 - 7.15 (2H, m, ArH),7.43-7.53 (4H, m, ArH); δ_C 55.32 (s, OCH_3),114.24 (C-3'),115.50 (d, $^2J_{CF}$ 21.4, C-3),128.00 (C-2'),128.19 (d, $^3J_{CF}$7.9, C-2),132.81 (C-1'),136.95 (d, $^4J_{CF}$ 3.2, C-1),159.11 (C-4'),162.08 (d, $^1J_{CF}$ 245.5, C-4); δ_F -117.17 (s); *m/z* ($ASAP^+$) 202 ($[M]^+$, 100%).

Table S3. GC-MS data of metabolites produced by *C. elegans* and *S. griseus*

		m/z (relative intensity) of:	
Compound	tR (min)	M+	Fragment ions
1a 	12.72	214(100)	197(47), 91(17), 115(17), 139(17)
2b 	12.54	232(100)	215(50), 170(14), 159(13), 139(11), 86(9)
2c 	11.54	232(100)	215(48), 139(24), 69(14), 157(8)
2d 	8.22	184(100)	155(81), 152(49), 77(39), 165(28)
2e 	7.40	170(65)	128(100), 86(26), 70(25), 113(23), 141(23), 99(20)
2f 	7.69	190(31)	133(100), 105(69), 77(39), 120(68),
2g 	7.36	188(100)	159(29), 133(19), 94(10)
2h 	7.77	208(25)	151(100), 123(82), 138(42), 95(30),
2l 	7.22	188(100)	159(30), 133(18), 94(10), 139(10)

2m 	10.11	218(100)	203(62), 175(59), 146(19)
2j 	9.05	218(100)	203(64), 175(45), 127(14), 146(7)
2i 	7.48	188(100)	128(27), 159(25), 139(7)
2k 	7.74	208(69)	151(100), , 123(65), 138(64), 188(38)
2n 	7.43	208(36)	151(100), 123(75), 138(48), 208(36), 109(19)
3c 	8.32	202(100)	153(65), 173(39), 183(30)
3b 	8.40	202(100)	153(58), 173(38), 183(32)
3a 	8.35	202(100)	153(63), 173(40), 183(33)
4c 	11.71	218(40)	91(100), 127(18), 55(16), 73(13)
4b 	10.65	218(100)	201(39), 189(30), 169(28), 141(28)
4a 	11.89	218(100)	189(40), 201(30), 170(28), 141(23)

References

1. D.J. Byron, G.W. Gray, R.C. Wilson, J. Chem. Soc. (C), 1966, 840-844.

2. L.R. Moore, E.C. Western, R. Craciun, J.M. Spruell, D.A. Dixon, K.P. O'Halloran, K.H. Shaughnessy, Organometallics, 2008, 27, 576-593.

3. S.M. Raders, J.V. Kingston, J.G. Verkade, J. Org. Chem., 2010, 75, 1744-1747.

4. A. Gavryushin, C. Kofink, G. Manolikakes, P. Knockel, Tetrahedron, 2006, 62, 7521-7533.