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Journal of Enzyme Inhibition and Medicinal Chemistry

ISSN: 1475-6366 (Print) 1475-6374 (Online) Journal homepage: informahealthcare.com/journals/ienz20

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To cite this article: Rolf W. Hartmann, Anja Palusczak, Fabrice Lacan, Giacomo Ricci & Renzo Ruzziconi (2004) CYP 17 and CYP 19 Inhibitors. Evaluation of Fluorine Effects on the Inhibiting Activity of Regioselectively Fluorinated 1-(Naphthalen-2-ylmethyl)imidazoles, Journal of Enzyme Inhibition and Medicinal Chemistry, 19:2, 145-155, DOI: 10.1080/1475636042000196222

To link to this article: https://doi.org/10.1080/1475636042000196222

Published online: 03 Oct 2008.

Journal of Enzyme Inhibition and Medicinal Chemistry, April 2004 Vol. 19 (2), pp. 145–155

CYP 17 and CYP 19 Inhibitors. Evaluation of Fluorine Effects on the Inhibiting Activity of Regioselectively Fluorinated 1-(Naphthalen-2-ylmethyl)imidazoles

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(Received 4 November 2003)

Regioselectively fluorinated 1-(naphth-2-ylmethyl)imidazoles 1a–h have been synthesized starting from the corresponding (naphth-2-yl)methanols (2). 2a–d have been obtained by $LiAlH_4$-promoted reduction of fluorinated 1-methyl-2-naphthaldehydes. The latter were easily prepared in fairly good overall yields by ceric ammonium nitrate (CAN)-promoted oxidative addition of the suitable 3-(fluoroaryl)-1-trimethylsilyloxy-1-butenes to ethyl vinyl ether in methanol followed by cyclization of the resulting acetals in strongly acidic medium in the presence of DDQ. 2e–h were prepared by $LiAlH_4$-promoted reduction of the corresponding fluorinated methyl 2-naphthoates. The latter were more profitably obtained by reacting the suitable benzyl bromide with the sodium salt of dimethyl 2-(2,2-dimethoxyethyl)malonate in DMF followed by demethoxycarbonylation and acid catalysed cyclization of the resulting acetals. Compared with the non-fluorinated parent compounds 1i–l, fluorinated 1-(naphth-2-yl)methylimidazoles 1a–h turned out to be potent inhibitors of CYP17 and CYP19 enzymes. The most active inhibitor of CYP17 is 1c, whereas CYP19 is strongly inhibited by 1b, 1e, and 1g. Interestingly, 1g is a potent dual inhibitor also being very active towards CYP19.

Keywords: Ceric ammonium nitrate; Oxidative addition; Electrophilic cyclization; Fluoronaphthalenes; Imidazoles; CYP17 and CYP19 inhibition

INTRODUCTION

P450 or CYP enzymes consist of a heme moiety and are involved in the metabolism of xenobiotics or the biosynthesis of endogenous compounds like steroids or eicosanoids. CYP 17 (17α-steroid-hydroxylase-C17, 20-lyase; $P450_{17\alpha}$) and CYP 19 (aromatase or estrogen synthase) catalyze the last step in androgen or estrogen biosynthesis, respectively. In a high percentage of breast and prostate cancer the growth depends on the corresponding sex hormone. Consequently selective inhibition of the enzymes responsible for the last synthetic step is an appropriate strategy to treat the tumours. Several steroidal[1,2] and non-steroidal[3] compounds have been previously reported as CYP 17 or CYP 19 inhibitors. Among the non-steroidal type, examples include tetrahydronaphthalene and di- or tetrahydroquinoline derivatives.[4,5]

Due to some surprising peculiarities of fluorine,[6] the only element capable of mimicking hydrogen in virtue of its comparable size, it is being used ever more frequently as a substituent in the synthesis of important pharmacologically active compounds.[7] Its electron withdrawing power combined with the high carbon-fluorine bond energy enhances significantly the metabolic stability of the host molecule and at the same time increases its lipophilic character facilitating cell-membrane permeation. With the aim of discovering new inhibitors, as well as of assessing the effect of fluorine on the inhibition activity, we are attracted by the introduction of a regioselectively fluorinated naphthyl group as a possible bioisosteric modification.

Here, we report the synthesis of several regioselectively fluorinated 1-[(naphth-2-yl)methyl]imidazoles **1** (Chart 1) as potential inhibitors of $P450_{17\alpha}$ enzyme, using regioselectively fluorinated 2-naphthaldehydes and methyl 2-naphthoates as building blocks.

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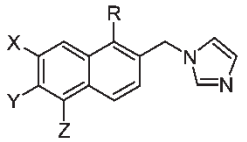
ISSN 1475-6366 print/ISSN 1475-6374 online
DOI: 10.1080/1475636042000196222



a: R = CH_3; X = F; Y = Z = H
b: R = CH_3; X = Z = F; Y = H
c: R = CH_3; X = F; Y = OMe; Z = H
d: R = CH_3; X = Z = F; Y = OMe
e: R = Y = Z = H; X = F
f: R = Y = H; X = Z = F
g: R = Z = H; X = F; Y =OMe
h: R = H; X = Z = F; Y = OMe
i: R = X = Z = H; Y = OMe
l: R = X = Y = Z = H

CHART 1 Synthesised imidazoles.

EXPERIMENTAL

^{1}H- and ^{13}C-NMR spectra were recorded in the presence of TMS as an internal standard, running frequency and solvent is specified for each experiment. IR spectra were recorded in KBr in the 4000–625 cm^{-1} range. *G.l.c.* analyses were performed on two capillary columns employing two different stationary phases: crosslinked 5% PH ME syloxane (HP-5MS) and polyethylene glycol (HP-Innowax). Mass spectra were recorded at 70 eV. Melting points are corrected after calibration performed with authentic standards.

Reagents and Solvents

7-Fluoro-1-methyl-2-naphthaldehyde (**7a**) and 5,7-difluoro-1-methyl-2-naphthaldehyde (**7b**), were available from a previous work.[8] 4-Bromo-2-fluoroanisole, 4-bromo-2,6-difluoroanisole, 3-fluorobenzyl bromide (**13a**), 3,5-difluorobenzyl bromide (**13b**), 3-fluoro-4-methoxybenzyl alcohol, 3,5-difluoro-4-methoxybenzaldehyde (Apollo) and (2-bromomethyl)naphthalene (**16l**), 2-bromo-6-methoxynaphthalene, dimethyl malonate, vinyl acetate (Aldrich), of the highest grade of purity, were used as received. **3-Fluoro-4-methoxybenzyl bromide (13g)** was prepared in 96% of yield by bromination of commercial benzyl alcohol with PBr_3-LiBr in DMF at room temperature: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.02 (m, 3 H), 4.44 (s, 2 H), 3.87 (s, 3 H). 3,5-Difluoro-4-methoxybenzyl bromide was prepared in 80% overall yield by reduction of 3,5-difluoro-4-methoxybenzaldehyde with $LiAlH_4$ in diethyl ether, followed by bromination of the resulting benzyl alcohol with PBr_3-LiBr in DMF. **3,5-Difluoro-4-methoxybenzyl alcohol (2h)**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.89 (m, AA′XX′ system, 2 H), 4.54 (s, 2 H), 3.95 (s, 3 H); **3,5-Difluoro-4-methoxybenzyl bromide (13h)**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.96 (d, J = 8.98, 2 H), 4.40 (s, 2 H), 4.03 (s, 3 H). Dimethyl 2-Methoxycarbonyl-4,4-dimethoxybutanoate was prepared in 77% yield by ceric ammonium nitrate-promoted oxidative addition of dimethyl malonate to vinyl acetate in methanol at room temperature according to the procedure reported in the literature. Tetrahydrofuran and diethyl ether were distilled from KOH in the presence of CuCl and redistilled from sodium wire in the presence of benzophenone.

7-Fluoro-6-methoxy-1-methyl-2-naphthaldehyde (7c) and **5,7-difluoro-6-methoxy-1-methyl-2-naphthaldehyde (7d)** were prepared from 4-bromo-2-fluoroanisole and 4-bromo-2,6-difluoroanisole, respectively, by the same procedure described for **7a** and **7b**.[8]

7c (25% from **3c**): mp 118–120°C (from hexane); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 10.59 (s, 1 H), 7.87 (d, J = 8.5 Hz, 1 H), 7.84 (d, J = 13.1 Hz, 1 H), 7.67 (d, J = 8.5 Hz, 1 H), 7.22 (d, J = 8.6 Hz, 1 H), 4.04 (s, 3 H), 2.96 (s, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 191.7, 152.7 (d, J = 249.2 Hz), 149.8 (d, J = 14.6 Hz), 143.2, 139.1, 134.0, 130.1, 125.4, 124.9, 110.3 (d, J = 19.0 Hz), 108.7, 56.1, 13.2; IR (KBr) 2938, 1674, 1631, 1480, 1275, 1185, 1156, 880, 860 cm^{-1}; MS (EI), m/z (%) 218 (M^+, 96), 217 (90), 189 (41), 174 (13), 157 (15), 146 (100), 120 (15). Calcd. for $C_{13}H_{11}FO_2$: C, 71.55; H, 5.08. Found: C, 71.35; H, 5.12%.

7d (28% from **3d**): mp 103–105°C (from hexane); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 10.61 (s, 1 H), 7.95 (dd, J = 9.0 and 0.4 Hz, 1 H), 7.92 (d, J = 9.0 Hz, 1 H), 7.69 (dd, J = 12.7 and 2.0 Hz, 1 H), 4.18 (s, 3 H), 2.95 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.6, 154.7 (d, J = 255.1 Hz), 149.7 (d, J = 251.0 Hz), 145.5, 138.9, 131.4, 124.7, 124.1, 118.4 (d, J = 5.6 Hz), 116.3, 106.2 (dd, J = 19.9 and 3.9 Hz), 61.9, 13.2; IR (KBr) 2955, 2915, 1639, 1606, 1508, 1190, 1096, 977, 907 cm^{-1}; MS (EI), m/z (%) 236 (M^+, 100), 235 (75), 207 (27), 193 (11), 164 (44). Calcd. for $C_{13}H_{10}F_2O_2$: C, 66.10; H, 4.27. Found: C, 66.31; H, 4.20%.

General Procedure for the Synthesis of Fluorinated Methyl 2-naphthoates (15e–h)

To a stirred solution of dimethyl (2,2-dimethoxyethyl)malonate (12.1 g, 55 mmol) in anhydrous DMF (60 mL), 80% oil dispersed NaH (2.2 g, 55 mmol) was slowly, added under N_2, at 0°C and the mixture was allowed to react at room temperature for 30 min. The appropriate benzyl bromide (**13e–h**) (50 mmol) in DMF (5 mL) was added dropwise and the stirring was continued overnight. The resulting suspension was cautiously poured into iced water (50 mL) and extracted with EtOAc (3 × 30 mL). The collected organic phase was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure leaving the crude methyl 2-fluoroaryl-2-methoxycarbonyl-4,4-dimethoxybutanoates (90%). To the crude product water (3.38 mL, 18.77 mmol), NaCl (3.65 g, 62.5 mmol) and DMSO (44 mL) were added and the mixture was heated at 180°C overnight. After addition of water (100 mL), the mixture was extracted with ethyl acetate (3 × 30 mL). The organic layer was dried with Na_2SO_4 and the solvent was evaporated under reduced pressure (15 mmHg) to

give crude methyl 2-fluoroaryl-4,4-dimethoxybutanoates. The latter was taken up in methanol (40 mL) and after addition of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (13.2 g, 58.1 mmol) the solution was added dropwise, over 30 min, to 80% aqueous sulfuric acid (300 mL) at 0°C. The ice bath was removed and stirring continued for 30 min. before the mixture was poured into iced water (500 mL) and extracted with Et_2O (4 × 200 mL). The collected organic phase was dried with Na_2SO_4, the solvent was evaporated under reduced pressure. The crude residue was dissolved in acetone (100 mL), SiO_2 (10 g) was added and the solvent removed at reduced pressure. The resulting powder was put on the top of a silica gel chromatographic column and eluted with 9:1 (v/v) petroleum ether/ethyl acetate to collect the fluorinated 2-naphthoates **(15e–h)**.

Methyl 7-fluoro-2-naphthoate (15e)

(21% from **13e**): mp 102–104°C (from hexane); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.54 (s, 1 H), 8.02 (dd, J = 8.6 and 1.6 Hz, 1 H), 7.88 (d, J = 8.6 Hz, 1 H), 7.87 (dd, J = 8.8 and 5.3 Hz, 1 H), 7.56 (dd, J = 9.5 and 2.5 Hz, 1 H), 7.37 (ddd, J = 9.2, 8.6 and 2.5 Hz, 1 H), 3.99 (s, 3 H); ^{13}C NMR (50 Hz, $CDCl_3$) δ 167.0, 160.9 (d, J = 246.5 Hz), 133.3 (d, J = 9.5 Hz), 132.4, 130.2, 130.1, 128.4, 128.1, 124.6, 118.6 (d, J = 25.3 Hz), 112.2 (d, J = 20.5 Hz), 52.3; IR (KBr) 3071, 3018, 2958, 1718, 1634, 1602, 1280, 1150, 1123, 964, 919, 850 cm^{-1}; MS (EI), m/z (%) 204 (M$^+$, 72), 173 (100), 145 (88), 125 (25). Calcd. for $C_{12}H_9FO_2$: C, 70.58; H, 4.44. Found: C, 70.43; H, 4.37%.

Methyl 5,7-difluoro-2-naphthoate (15f)

(25% from **13f**): mp 88–90°C (from AcOH/H_2O); ^{1}H NMR ($CDCl_3$, 400 MHz,) δ 8.54 (s, 1 H), 8.11 (d, J = 8.8 Hz, 1 H), 8.07 (dd, J = 8.8 and 1.4 Hz, 1 H), 7.39 (ddd, J = 9.1, 2.3 and 1.1 Hz, 1 H), 7.09 (ddd, J = 10.1, 8.8 and 2.3 Hz, 1 H), 3.99 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.6, 160.1 (dd, J = 247 and 12.1 Hz), 159.1 (dd, J = 255 and 13.0 Hz), 133.6 (dd, J = 10.8 and 5.7 Hz), 129.8 (dd, J = 5.8 and 3.3 Hz), 129.6 (t, J = 1.0 Hz), 124.9 (dd, J = 2.7 and 1.9 Hz), 122.8 (dd, J = 16.3 and 1.6 Hz), 121.3 (dd, J = 4.5 and 1.9 Hz), 108.3 (dd, J = 20.5 and 4.7 Hz), 103.7 (dd, J = 29.2 and 23.5), 52.4; IR (KBr) 3085, 2956, 1727, 1613, 1267, 1123, 972, 925, 842 cm^{-1}; MS (EI), m/z (%) 222 (M$^+$, 77), 191 (100), 163 (98), 143 (30). Calcd. for $C_{12}H_8F_2O_2$: C, 64.87; H, 3.63. Found: C, 65.02; H, 3.58%.

Methyl 7-fluoro-6-methoxy-2-naphthoate (15g)

(23% from **13g**): mp 156–158°C (from hexane); ^{1}H NMR ($CDCl_3$, 200 MHz,) δ 8.42 (s, 1 H), 7.99 (dd, J = 8.6 and 1.5 Hz, 1 H), 7.72 (d, J = 8.6 Hz, 1 H), 7.52 (d, J = 11.5 Hz, 1 H), 7.19 (d, J = 8.3 Hz, 1 H), 4.00 (s, 3 H), 3.96 (s, 3 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 167.4, 153.0 (d, J = 250.0 Hz), 150.0 (d, J = 13.6 Hz), 133.8, 130.2 (d, J = 5.3 Hz), 127.6 (d, J = 8.5 Hz), 127.0, 126.5, 125.6 (d, J = 1.7 Hz), 113.6 (d, J = 17.9 Hz), 108.1, 56.3, 52.5; IR (KBr) 3065, 2956, 1720, 1636, 1252, 1157, 1100, 972, 921, 859 cm^{-1}; MS (EI), m/z (%) 234 (M$^+$, 85), 203 (100), 175 (39), 160 (23), 132 (28). Calcd. for $C_{13}H_{11}FO_3$: C, 66.66; H, 4.73. Found: C, 66.81; H, 4.68%.

Methyl 5,7-difluoro-6-methoxy-2-naphthoate (15h)

(24% from **13h**): mp 106–108°C (from hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.48 (s, 1 H), 8.06 (dd, J = 8.8, 1.4 and 0.3 Hz, 1 H), 8.03 (d, J = 8.8 Hz, 1 H), 7.42 (dd, J = 10.9, and 1.9 Hz, 1 H), 4.16 (dd, J = 1.9 and 0.8 Hz, 3 H), 3.98 (s, 3 H); ^{13}C NMR ($CDCl_3$,100 Hz) δ 167.1, 155.2 (dd, J = 249.6 and 5.7 Hz), 150.1 (dd, J = 250.4 and 5.7 Hz), 136.5 (dd, J = 17 and 13 Hz), 130.0 (dd, J = 5.6 and 2.9 Hz), 128.4, 127.9 (dd, J = 15.5 and 5.2 Hz), 125.5 (t, J = 2.3 Hz), 124.2 (d, J = 15.7 Hz), 120.6 (dd, J = 5.4 and 2.1 Hz), 109.5 (dd, J = 19.0 and 4.2 Hz), 62.3 (dd, J = 4.9 and 2.5 Hz), 52.7; IR (KBr) 3016, 2959, 2841, 1724, 1654, 1255, 1165, 1099, 1057, 911, 850 cm^{-1}; MS (EI), m/z(%) 252 (M$^+$, 100), 237 (13), 221 (98), 193 (33), 178 (20), 150 (39). Calcd. for $C_{13}H_{10}F_2O_3$: C, 61.91; H, 4.00. Found: C, 61.78; H, 4.05%.

General Procedure for the Preparation of Poly-substituted (2-naphthyl)methanols 2a–h

To a solution of the aldehyde **7** or the ester **15** (2.5 mmol) in THF (25 mL) $LiAlH_4$ (0.114 g, 3 mmol) was slowly added in small portions at 0°C. When the reduction was completed (*tlc*), the mixture was poured into iced water, acidified with 10% aq. H_2SO_4 and extracted with AcOEt (3 × 30 mL). The collected organic phase was washed with water and brine, dried with Na_2SO_4 and the solvent was evaporated at reduced pressure. The resulting crude oil was allowed to crystallize by treatment with few drops of hexane.

(7-Fluoro-1-methyl-2-naphthyl)methanol (2a)

(92% from **7a**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, J = 8.9 and 6.0 Hz, 1 H), 7.70 (d, J = 8.4 Hz, 1 H), 7.67 (dd, J = 11.7 and 2.5 Hz, 1 H), 7.48 (d, J = 8.4 Hz, 1 H), 7.26 (td, J = 8.7 and 2.5 Hz, 1 H), 4.91 (s, 2 H), 2.64 (s, 3 H), 1.60 (broad, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9 (d, J = 243.7 Hz), 136.3, 133.9 (d, J = 12.0 Hz), 131.3, 130.8 (d, J = 9.1 Hz), 130.1, 126.2, 125.6, 115.8 (d, J = 25.1 Hz), 107.8 (d, J = 21.3 Hz), 64.0, 14.1; IR ($CDCl_3$) 3604, 3051, 2928, 1632, 1603, 1517, 1174, 1085 cm^{-1}; MS, m/z (%) 190 (M$^+$, 48), 172 (100), 159 (23), 146 (42), 133 (22).

Calcd. for $C_{12}H_{11}FO$: C, 75.77; H, 5.83. Found: C, 75.61; H, 5.89%.

(5,7-Difluoro-1-methyl-2-naphthyl)methanol (2b)

(75% from **7b**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, $J = 8.7$ Hz, 1 H), 7.52 (d, $J = 8.6$ Hz, 1 H), 7.46 (ddd, $J = 11.1$, 3.3 and 1.0 Hz, 1 H), 6.98 (ddd, $J = 10.2$, 8.7 and 2.3 Hz, 1 H), 4.89 (s, 2 H), 2.59 (s, 3 H), 1.64 (broad s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6 (dd, $J = 244$ and 12.8 Hz), 160.2 (dd, $J = 253$ and 13.8 Hz), 138.2, 134.9 (dd, $J = 8.9$ and 6.4 Hz), 132.0 (d, $J = 3.6$ Hz), 126.3, 121.2 (d, $J = 16.6$ Hz), 119.5 (d, $J = 5.0$ Hz), 104.5 (dd, $J = 21.3$ and 4.1 Hz), 101.6 (dd, $J = 29.1$ and 23.9 Hz), 64.6, 14.9; IR ($CHCl_3$) 3608, 3421, 3082, 3011, 2928, 1644, 1517, 1403, 1112, 988, 849; MS, m/z (%) 208 (M^+, 48), 190 (100), 177 (25), 164 (43), 151 (26). Calcd. for $C_{12}H_{10}F_2O$: C, 69.22; H, 4.84. Found: C, 69.31; H, 4.92%.

(7-Fluoro-6-methoxy-1-methyl-2-naphthyl)methanol (2c)

(81% from **7c**): mp 103–105°C (from hexane/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.71 (d, $J = 13.5$ Hz, 1 H), 7.60 (d, $J = 8.4$ Hz, 1 H), 7.44 (d, $J = 8.4$ Hz, 1 H), 7.19 (d, $J = 8.8$ Hz, 1 H), 4.87 (s, 2 H), 4.00 (s, 3 H), 2.62 (s, 3 H), 1.57 (broad, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.6 (d, $J = 247$ Hz), 147.5 (d, $J = 13.8$ Hz), 134.3, 131.7 (d, $J = 5.5$ Hz), 130.9, 128.1 (d, $J = 7.4$ Hz), 126.6 (d, $J = 2.5$ Hz), 125.0, 109.3 (d, $J = 18.7$ Hz), 108.7 (d, $J = 2.5$ Hz), 64.2, 56.2, 14.3; IR (KBr) 3362, 2925, 1636, 1266, 1150, 1088, 860, 808 cm^{-1}; MS, m/z (%) 220 (M^+, 100), 202 (92), 191 (25), 176 (32), 162 (40), 146 (39), 133 (42). Calcd. for $C_{13}H_{13}FO_2$: C, 70.90; H, 5.95. Found: C, 71.69; H, 6.02%.

(5,7-Difluoro-6-methoxy-1-methyl-2-naphthyl)methanol (2d)

(92%, from **7d**): mp 83–85°C (from cyclohexane); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.88 (d, $J = 8.7$ Hz, 1 H), 7.55–7.48 (m, 2 H), 4.88 (s, 2 H), 4.11 (s, 3 H), 2.59 (s, 3 H), 1.71 (broad, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2 (dd, $J = 245.0$ and 6.1 Hz), 150.8 (dd, $J = 247.7$ and 6.6 Hz), 138.8, 134.2, 131.2, 129.0 (dd, $J = 9.0$ and 5.4 Hz), 126.9, 121.6 (d, $J = 14.4$ Hz), 117.6 (d, $J = 5.0$ Hz), 105.4 (dd, $J = 19.8$ and 4.0 Hz), 62.8, 13.7; IR (KBr) 3312, 2952, 1607, 1498, 1264, 1072, 993, 835 cm^{-1}; MS, m/z (%) 238 (M^+, 100), 220 (95), 215 (30), 176 (32), 194 (22), 177 (27), 164 (49), 151 (43). Calcd. for $C_{13}H_{12}F_2O_2$: C, 65.54; H, 5.08. Found: C, 65.36; H., 5.13%.

(7-Fluoro-2-naphthyl)methanol (2e)

(88% from **15e**): mp 105–107°C (from diethyl ether); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.83–7.79 (m, 2 H), 7.75 (s, 1 H), 7.45–7.41 (m, 2 H), 7.25 (td, $J = 8.8$ and 2.6 Hz, 1 H), 4.85 (s, 2 H), 1.75 (broad, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9 (d, $J = 244.6$ Hz), 139.4, 134.1 (d, $J = 9.1$ Hz), 130.0 (d, $J = 9.0$ Hz), 129.9 (d, $J = 1.1$ Hz), 128.2 (d, $J = 1$ Hz), 124.6 (d, $J = 5.3$ Hz), 124.3 (d, $J = 2.7$ Hz), 116.2 (d, $J = 25$ Hz), 110.9 (d, $J = 20.4$ Hz), 65.2; IR (KBr) 3238 (broad), 2922, 2869, 1636, 1512, 1182, 1024, 900, 842, cm^{-1}; MS, m/z (%) 176 (M^+, 65), 159 (15), 147 (100), 127 (21). Calcd. for $C_{11}H_9FO$: C, 74.99; H, 5.15. Found: C, 74.75; H, 5.06%.

(5,7-Difluoro-2-naphthyl)methanol (2f)

(97% from **15f**): mp 78–80°C (from diethyl ether); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.04 (d, $J = 8.6$ Hz, 1 H), 7.75 (s, 1 H), 7.46 (dd, $J = 8.6$ and 1.3 Hz, 1 H), 7.25 (ddd, $J = 9.5$, 2.3 and 1.1 Hz, 1 H), 6.96 (ddd, $J = 10.4$, 8.9 and 2.3 Hz, 1 H), 4.86 (s, 2 H), 1.96 (broad, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.0 (dd, $J = 245.3$ and 12.4 Hz), 159.2 (dd, $J = 253.5$ and 13.2 Hz), 140.8, 134.5 (dd, $J = 10.8$ and 6.1 Hz), 124.5 (dd, $J = 2.5$ and 2.0 Hz), 124.2 (dd, $J = 5.6$ and 3.3 Hz), 121.2 (dd, $J = 4.6$ and 1.9 Hz), 120.2 (dd, $J = 16.2$ and 1.6 Hz), 106.9 (dd, $J = 20.4$ and 4.6 Hz), 101.4 (dd, $J = 29.2$ and 23.9 Hz), 65.0; IR (KBr) 3350, 3089, 2922, 1651, 1590, 1516, 1124, 1027, 898, 850, 824 cm^{-1}; MS, m/z (%) 194 (M^+, 67), 177 (15), 165 (100), 145 (26). Calcd. for $C_{11}H_8F_2O$: C, 68.04; H, 4.15. Found: C, 67.91; H, 4.12%.

(7-Fluoro-6-methoxy-2-naphthyl)methanol (2g)

(87% from **15g**): mp 122–124°C (from hexane/diethyl ether); ^{1}H NMR δ 7.77 (d, $J = 8.5$ Hz, 1 H), 7.74 (s, 1 H), 7.55 (d, $J = 12.3$ Hz, 1 H), 7.43 (d, $J = 8.6$ Hz, 2 H), 4.74 (s, 2 H), 3.97 (s, 3 H), 2.97 (s, 1 H) ^{13}C NMR δ 152.8 (d, $J = 246.6$ Hz), 147.9 (d, $J = 13.6$ Hz), 139.3, 130.8, 128.7 (d, $J = 8.1$ Hz), 127.1, 125.5 (d, $J = 1.5$ Hz), 124.4 (d, $J = 4.9$ Hz), 112.2 (d, $J = 17.7$ Hz), 108.8, 64.3, 55.9; IR (KBr) 3259, 2917, 2864, 1615, 1275, 1184, 1161, 1121, 1024, 896, 852 cm^{-1}; MS, m/z (%) 206 (M^+, 100), 189 (33), 177 (63), 162 (51), 146 (27), 133 (37), 115 (20). Calcd. for $C_{12}H_{11}FO_2$: C, 69.89; H, 5.38. Found: C, 69.91; H, 5.31%.

(5,7-Difluoro-6-methoxy-2-naphthyl)methanol (2h)

(99% from **15h**): mp 65–67°C (from diethyl ether); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.99 (d, $J = 8.6$ Hz, 1 H), 7.71 (s, 1 H), 7.47 (dd, $J = 8.7$ and 1.0 Hz, 1 H), 7.30 (dd, $J = 11.2$ and 1.8 Hz, 1 H), 4.85 (s, 2 H), 4.11 (s, 3 H), 1.84 (broad, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.8 (dd, $J = 248.1$and 5.7 Hz), 150.2 (dd, $J = 250.0$ and 6.1 Hz), 139.1, 128.7 (dd, $J = 10.0$ and 5.3 Hz), 124.9 (t, $J = 2.3$ Hz), 124.1 (dd, $J = 5.4$ and 3.0 Hz), 121.0 (dd, 14.0 and 1.9 Hz), 120.4 (dd, $J = 5.2$ and 2.1 Hz), 112.6 (dd, $J = 15.8$ and 6.0 Hz), 107.8 (dd, $J = 18.8$ and 4.2 Hz), 65.0, 62.1 (dd, $J = 4.3$ and 2.5 Hz); IR (KBr)

3330, 2958–2846, 1654, 1508, 1406, 1255, 993, 890 cm^{-1}; MS, m/z (%) 224 (M^+, 21), 195 (10), 180 (8), 164 (9), 133 (19), 89 (25), 45 (100). Calcd. for $C_{12}H_{10}F_2O_2$: C, 64.28; H, 4.50. Found: C, 64.15; H, 4.58%.

(6-methoxy-2-naphthyl)methanol (2i)

A solution of 2-bromo-6-methoxynaphthalene (5.0 g, 21 mmol) in THF (50 mL) was added dropwise to iodine activated magnesium chips in THF (20 mL) at 20°C. After the aryl bromide had completely reacted (3 h, *glc*), paraformaldehyde (1.26 g, 42 mmol) was added in small portions and the mixture was allowed to react for 5 h at 20°C. Sat. aq. NH_4Cl was added (50 mL) and the resulting suspension was extracted with diethyl ether (3 × 50 mL). The collected organic phase was washed with brine and dried with Na_2SO_4. Evaporation of the solvent at reduced pressure left the expected hydroxymethylnaphthalene as a waxy white solid which was re-crystallized from methanol and dried at 60°C under vacuum (4.6 g, 67%). M.p. 118–120; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.8–7.0 (m, 6 H), 4.81 (s, 2 H), 3.92 (s, 3 H), 1.73 (broad, 1 H).

General Procedure for the Preparation of Poly-substituted Bromomethylnaphthalenes 16a–l

To a solution of the alcohol **2** (2.0 mmol) and LiBr (0.19 g, 2.2 mmol) in DMF (8 mL) PBr_3 (0.67 g, 2.5 mmol) was added dropwise under nitrogen at 0°C and the mixture was stirred overnight at room temperature before it was poured with caution into iced aq. $NaHCO_3$ (20 mL) and extracted AcOEt (2 × 5 mL). The collected organic phase was washed with water and brine and dried with Na_2SO_4. After the solvent was evaporated under reduced pressure, the crude oil crystallised by treatment with a few drops of hexane. The product was used in the following reaction without further purification.

2-(Bromomethyl)-7-fluoro-1-methylnaphthalene (16a)

(71% from **2a**): ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.81 (dd, $J = 8.9$ and 5.9 Hz, 1 H), 7.69 (d, $J = 8.3$ Hz, 1 H), 7.68 (dd, $J = 11.9$ and 2.5 Hz, 1 H), 7.39 (d, $J = 8.4$ Hz, 1 H), 7.28 (ddd, $J = 8.9$, 8.1 and 2.5 Hz, 1 H), 4.68 (s, 2 H), 2.62 (s, 3 H); MS, m/z (%) 254 ($M^+ + 1$, 12), 252 ($M^+ - 1$, 12) 173 (100) 152 (11).

2-(Bromomethyl)-5,7-difluoro-1-methylnaphthalene (16b)

(75% from **2b**): ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.94 (d, $J = 8.6$ Hz, 1 H), 7.50 (d quint., $J = 11.0$ and 1.0 Hz, 1 H), 7.44 (d, $J = 8.6$ Hz, 1 H), 7.01 (ddd, $J = 10.2$, 8.6, 2.3 Hz, 1 H), 4.70 (s, 2 H), 2.63 (s, 3 H); MS, m/z (%) 272 ($M^+ + 1$, 10), 270 ($M^+ - 1$, 10), 191 (100), 170 (13), 151 (9).

2-(Bromomethyl)-7-fluoro-6-methoxy-1-methylnaphthalene (16c)

(78% from **2c**): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.70 (d, $J = 13.3$ Hz, 1 H), 7.60 (d, $J = 8.5$ Hz, 1 H), 7.43 (d, $J = 8.5$ Hz, 1 H), 7.18 (d, $J = 8.7$ Hz, 1 H), 4.68 (s, 2 H), 3.99 (s, 3 H), 2.65 (s, 3 H); MS, (70 eV) m/z (%), 284 (4), 282 (4), 203 (100), 188 (5), 159 (21), 133 (15).

2-(Bromomethyl)-5,7-difluoro-6-methoxy-1-methylnaphthalene (16d)

(80% from **2d**): ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 7.86 (d, $J = 8.7$ Hz, 1 H), 7.53 (dd, $J = 13.0$ and 2.0 Hz, 1 H), 7.41 (d, $J = 8.7$ Hz, 1 H), 4.69 (s, 2 H), 4.12 (s, 3 H), 2.62 (s, 3 H); MS, m/z (%), 302 (7), 300 (7), 221 (100), 206 (17), 177 (15).

2-(Bromomethyl)-7-fluoronaphthalene 16e

(75% from **2e**): mp 72–74°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, $J = 8.5$ Hz, 1 H), 7.81 (dd, $J = 8.4$ and 5.7 Hz, 1 H), 7.77 (s, 1 H), 7.46 (dd, $J = 8.5$ and 1.7 Hz, 1 H), 7.42 (dd, $J = 9.7$ and 2.5 Hz, 1 H), 7.27 (ddd, $J = 8.8$, 8.4 and 2.5 Hz, 1 H), 4.64 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0 (d, $J = 245$ Hz), 136.3, 133.9 (d, $J = 9.4$ Hz), 130.1 (d, $J = 9$ Hz), 130.0 (d, $J = 1$ Hz), 128.7 (d, $J = 1.1$ Hz), 127.1 (d, $J = 5.3$ Hz), 126.0 (d, $J = 2.3$ Hz), 116.9 (d, $J = 25.1$ Hz), 111.0 (d, $J = 20.5$ Hz), 33.5; IR (KBr) 3060, 2963, 2924, 1611, 1460, 1181, 1134, 1108, 968, 903, 842, cm^{-1}; MS, m/z (%) 240 ($M^+ + 1$, 13), 238 ($M^+ - 1$, 13), 159 (100), 133 (31).

2-(Bromomethyl)-5,7-difluoronaphthalene (16f)

(72% from **2f**): mp 95–97°C (from hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, $J = 8.7$ Hz, 1 H), 7.77 (s, 1 H), 7.51 (dd, $J = 8.7$ and 1.7 Hz, 1H), 7.25 (ddd, $J = 9.3$, 2.3 and 1.1 Hz, 1 H), 6.99 (ddd, $J = 10.3$, 8.9 and 2.3 Hz, 1 H), 4.62 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2 (dd, $J = 246.1$ and 12.3 Hz), 159.2 (dd, $J = 254$ and 13.1 Hz), 137.6 (dd, $J = 1.1$ and 1 Hz), 134.3 (dd, $J = 10.8$ and 5.9 Hz), 126.8 (dd, $J = 5.6$ and 3.3 Hz), 126.4 (dd, $J = 2.6$ and 1.8 Hz), 121.7 (dd, $J = 4.6$ and 1.8 Hz), 120.4 (dd, $J = 16.3$ and 1.6 Hz), 107.1 (dd, $J = 20.5$ and 4.6 Hz), 102.1 (dd, $J = 29.2$ and 23.7 Hz), 33; IR (KBr) 3085, 3034, 2921, 1589, 1160, 1124, 998, 950, 898, 847, cm^{-1}; MS, m/z (%) 258 ($M^+ + 1$, 10), 256 ($M^+ - 1$, 10), 177 (100), 151 (30).

2-(Bromomethyl)-7-fluoro-6-methoxynaphthalene (16g)

(76% from **2g**): ^{1}H NMR $CDCl_3$, 400 MHz) δ 7.63 (d, $J = 8.6$ Hz, 1 H), 7.61 (s, 1 H), 7.36 (dd, $J = 8.4$ and 1.6 Hz, 1 H), 7.34 (d, $J = 11.7$ Hz, 1 H), 7.11 (d, $J = 8.4$ Hz, 1 H), 4.55 (s, 2 H), 3.91 (s, 3 H); MS, m/z (%) 270 ($M^+ + 1$, 8), 268 ($M^+ - 1$, 8), 189 (100), 174 (10), 157 (5), 146 (16).

2-(Bromomethyl)-5,7-difluoro-6-methoxynaphthalene (16h)

(75% from **2h**): mp 91–93°C (from $AcOH/H_2O$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, $J = 8.7$ Hz, 1 H), 7.71 (s, 1 H), 7.50 (dd, $J = 8.7$ and 1.4 Hz, 1 H), 7.29 (dd, $J = 11.1$ and 1.7 Hz, 1 H), 4.62 (s, 2 H), 4.11 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7 (dd, $J = 248.8$ and 5.6 Hz), 150.5 (dd, $J = 250.6$ and 6 Hz), 136.3, 128.7 (dd, $J = 10.3$ and 5.6 Hz), 127.1, 127.0 (dd, $J = 5.5$ and 3 Hz), 121.5 (dd, $J = 14.7$ and 0.9 Hz), 121.3 (dd, $J = 5.4$ and 2.1 Hz), 108.3 (dd, $J = 19$ and 4.3 Hz), 62.4, 33.6; IR (KBr) 2962, 2922, 2847, 1654, 1583, 1404, 1101, 1059, 895, 802, cm^{-1}; MS, m/z (%) 288 ($M^+ + 1$, 14), 286 ($M^+ - 1$, 14), 207 (100), 192 (47), 164 (33).

2-(Bromomethyl)-6-methoxynaphthalene (16i)

(73% from **2i**): mp 80–82; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.80–7.65 (m, 3 H), 7.46 (dd, $J = 8.45$ Hz and 1.8 Hz, 1 H), 7.20–7.15 (m, 2 H), 4.65 (s, 2 H), 3.91 (s, 3 H); MS (EI), m/z (%) 252 ($M^+ + 1$, 9), 250 ($M^+ - 1$, 9), 171 (100), 128 (31).

General Procedure for the Preparation of Poly-substituted 1-[(naphth-2-yl)methyl]-1H-imidazoles 1a–l

To a solution of imidazole (2.4 mmol) in DMF (20 mL) NaH (0.058 g, 2.4 mmol) was added at 0°C. The mixture was stirred for 2 h at 20°C and the 2-bromomethylnaphthalene **16** (2 mmol) was cautiously added. After overnight stirring, the mixture was poured into ice water (50 mL) and extracted with ethyl acetate. The organic phase was washed with water and brine, dried with Na_2SO_4, and the solvent was evaporated at reduced pressure. The crude product solidified by trituration with few drops of hexane, it was re-crystallised from a suitable solvent.

1-[(7-Fluoro-1-methylnaphth-2-yl)methyl]-1H-imidazole (1a)

(54% from **16a**): mp 120–122°C (from cyclohexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1 H), 7.84 (dd, $J = 8.9$ and 6 Hz, 1 H), 7.72 (d, $J = 8.5$ Hz, 1 H), 7.66 (dd, $J = 11.3$ and 2.4 Hz, 1 H), 7.31 (ddd, $J = 8.9$, 8.1 and 2.4 Hz, 1 H), 7.17 (s, 1 H), 7.15 (d, $J = 8.5$ Hz, 1 H), 6.90 (s, 1 H), 5.42 (s, 2 H), 2.60 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2 (d, $J = 242$ Hz), 133.8, 132.2 (d, $J = 4.3$ Hz), 131.0 (d, $J = 9.1$ Hz), 130.4, 130.2, 127.2, 126.6, 125.7, 119.5, 116.7 (d, $J = 25.2$ Hz), 108.1 (d, $J = 21.7$ Hz), 50.2, 14.5; IR (KBr) 3115, 2936, 2363, 1628, 1601, 1452, 1280, 1254, 1080, 955, 905, 852, 814, cm^{-1}; MS (EI), m/z (%) 240 (M^+, 21), 173 (100), 152 (21), 146 (20), 133 (20). Calcd. for $C_{15}H_{13}FN_2$: C, 74.98; H, 5.45; N, 11.66. Found: C, 74.71; H, 5.51; N, 11.54%.

1-[(5,7-Difluoro-1-methylnaphth-2-yl)methyl]-1H-imidazole (1b)

(59% from **16b**): mp 127–129°C (from $AcOH/H_2O$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, $J = 9.1$ Hz, 1 H), 7.58 (s, 1H), 7.50 (ddd, $J = 11.4$, 2.2 and 1.1 Hz, 1 H), 7.14 (d, $J = 9.1$ Hz, 1 H), 7.12 (s, 1 H), 7.03 (ddd, $J = 10.2$, 8.6 and 2.2 Hz, 1 H), 6.88 (s, 1 H), 5.34 (s, 2 H), 2.59 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3 (dd, $J = 245$ and 12.9 Hz), 159.6 (dd, $J = 254$ and 13.1 Hz), 134.2 (t, $J = 8.3$ Hz), 132.8, 131.8, 129.9, 125.7, 120.8 (d, $J = 16.2$ Hz), 119.6 (d, $J = 5.2$ Hz), 104.2 (dd, $J = 21.7$ and 4.5 Hz), 101.6 (dd, $J = 29$ and 23.9 Hz), 49.3, 14.5; IR (KBr) 3108, 3066, 2920, 1643, 1605, 1513, 1403, 1233, 1108, 986, 909, 854, 816 cm^{-1}; MS (EI), m/z (%) 258 (M^+, 53), 231 (10), 170 (34), 151 (27). Calcd. for $C_{15}H_{12}F_2N_2$: C, 69.76; H, 4.68; N, 10.85. Found: C, 69.53; H, 4.72; N, 11.01%.

1-[(7-Fluoro-6-methoxy-1-methylnaphth-2-yl)methyl]-1H-imidazole (1c)

(60% from **16c**): mp 166–168°C (from CH_2Cl_2/cyclohexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, $J = 13.4$ Hz, 1 H), 7.60 (s, 1 H), 7.55 (d, $J = 8.1$ Hz, 1 H), 7.20 (d, $J = 8.7$ Hz, 1 H), 7.10 (d, $J = 8.1$ Hz, 1 H), 7.09 (s, 1 H), 6.87 (s, 1 H), 5.30 (s, 2 H), 4.01 (s, 3 H), 2.55 (s, 3 H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 152.7 (d, $J = 248.1$ Hz), 147.9 (d, $J = 13.7$ Hz), 131.8 (d, $J = 5.3$ Hz), 131.0, 129.1, 129.0, 127.9 (d, $J = 6.9$ Hz), 126.3, 125.6, 119.2, 109.3 (d, $J = 18.9$ Hz), 108.6, 56.0, 49.5, 14.4; IR (KBr) 3140, 3100, 2942, 1631, 1604, 1485, 1152, 1114, 941, 866, 810 cm^{-1}; MS (EI), m/z (%) 270 (M^+, 17), 203 (100), 159 (15). Calcd. for $C_{16}H_{15}FN_2O$: C, 71.10; H, 5.59; N, 10.36. Found: C, 70.81; H, 5.62; N, 10.03%.

1-[(5,7-Difluoro-6-methoxy-1-methylnaphth-2-yl)methyl]-1H-imidazole (1d)

(65% from 16d): mp 110–112°C (from hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87 (d, $J = 8.7$ Hz, 1 H), 7.54–7.50 (m, 2 H), 7.14 (d, $J = 8.7$ Hz, 1 H), 7.08 (s, 1 H), 6.86 (s, 1 H), 5.30 (s, 2 H), 4.12 (s, 3 H), 2.55 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8 (d, $J = 247.6$ Hz), 150.1 (d, $J = 243.5$ Hz), 137.2, 131.6 (d, $J = 7.8$ Hz), 131.1, 129.8, 129.6, 128.3 (dd, $J = 11.7$ and 7.8 Hz), 126.3, 125.5, 121.7 (d, $J = 14.9$ Hz), 119.1, 118.8 (d, $J = 5.2$ Hz), 105.0 (dd, $J = 20.0$ and 3.9 Hz), 49.3, 14.4; IR (KBr) cm^{-1}; 3100, 2956–2847, 1654, 1429, 1269, 1095, 809 cm^{-1};

MS, m/z (%) 288 (M^+, 22), 221 (100), 207 (11), 177 (10). Calcd. for $C_{16}H_{14}F_2N_2O$: C, 66.66; H, 4.89; N, 9.72. Found: C, 66.45; H, 4.91; N, 9.78%.

1-[(7-Fluoronaphth-2-yl)methyl]-1H-imidazole (1e)

(55% from **16e**): mp 91–93°C (from CH_2Cl_2/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, $J = 8.5$ Hz, 1 H), 7.81 (dd, $J = 9.0$ and 5.7 Hz, 1 H), 7.61 (s, 1 H), 7.52 (s, 1 H), 7.40 (dd, $J = 9.7$ and 2.5 Hz, 1 H), 7.27 (ddd, $J = 9.0$, 8.7 and 2.5 Hz, 1 H), 7.20 (dd, $J = 8.5$ and 1.7 Hz, 1 H), 7.12 (s, 1 H), 6.94 (s, 1 H), 5.27 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0 (d, $J = 245$ Hz), 134.7 (d, $J = 0.9$ Hz), 134.1 (d, $J = 9.3$ Hz), 130.1 (d, $J = 9.1$ Hz), 129.9, 129.9 (d, $J = 1.7$ Hz), 128.9 (d, $J = 1.1$ Hz), 125.5 (d, $J = 5.4$ Hz), 124.0 (d, $J = 2.6$ Hz), 119.3, 116.8 (d, $J = 22.8$ Hz), 110.9 (d, $J = 20.4$ Hz), 50.8; IR (KBr) 3099, 3067, 2924, 2852, 1635, 1509, 1232, 1443, 1183, 1104, 1072, 927, 897, 842 cm^{-1}; MS, m/z (%) 226 (M^+, 26), 159 (100), 133 (25). Calcd. for $C_{14}H_{11}FN_2$: C, 74.32; H, 4.90; N, 12.38. Found: C, 74.29; H, 4.78; N, 12.45%.

1-[(5,7-Difluoronaphth-2-yl)methyl]-1H-imidazole (1f)

(63% from **16f**): mp 90–92°C (from hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, $J = 8.7$ Hz, 1 H), 7.61 (s, 1 H), 7.50 (s, 1 H), 7.26 (dd, $J = 8.7$ and 1.6 Hz, 1 H), 7.23 (ddd, $J = 11$, 2.3 and 1.2 Hz, 1 H), 7.13 (s, 1 H), 7.00 (ddd, $J = 10.3$, 8.9 and 2.3, 1 H), 6.94 (s, 1 H), 5.28 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3 (dd, $J = 246.5$ and 12.3 Hz), 159.2 (dd, $J = 254.2$ and 13.2 Hz), 137.5, 136.2, 134.4 (dd, $J = 10.8$ and 5.9 Hz), 130.1, 125.1 (dd, $J = 5.6$ and 3.2 Hz), 124.3 (dd, $J = 2.6$ and 2.2 Hz), 122.0 (dd, $J = 4.5$ and 1.7 Hz), 120.4 (dd, $J = 16.2$ and 1.4 Hz), 119.3, 107.0 (dd, $J = 20.7$ and 4.6 Hz), 102.0 (dd, $J = 29.1$ and 23.5 Hz), 50.7; IR (KBr) 3130, 3094, 2921, 1649, 1586, 1517, 1433, 1232, 1127, 1070, 991, 860, 818, 763 cm^{-1}; MS, m/z (%) 244 (M^+, 31), 177 (100), 151 (30). Calcd. for $C_{14}H_{10}F_2N_2$: C, 68.85; H, 4.13; N, 11.47. Found: C, 68.91; H, 4.05; N, 11.54%.

1-[(7-Fluoro-6-methoxynaphth-2-yl)methyl]-1H-imidazole (1g)

(58% from **16g**): mp 124–126°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70 (d, $J = 8.5$ Hz, 1 H), 7.59 (s, 1 H), 7.44 (s, $J = 1$ H), 7.38 (d, $J = 11.8$ Hz, 1 H), 7.30–7.17 (m, 2 H), 7.12 (s, 1 H), 6.93 (s, 1 H), 5.21 (s, 2 H), 3.97 (s, 3 H); ^{13}C NMR ($CDCl_3$,100 MHz,) δ 152.6 (d, $J = 249.1$), 148.0 (d, $J = 13.5$), 137.3, 132.3, 130.3, 129.7, 128.0 (d $J = 8.5$ Hz), 127.4, 125.2 (d, $J = 5.0$ Hz), 124.6 (d, $J = 1.7$ Hz), 119.2, 111.9 (d, $J = 18$ Hz), 107.8, 55.8, 50.6; IR (KBr) 3135–3053, 2964–2368, 1618, 1517, 1490, 1158, 859 cm^{-1}; MS, m/z (%) 256 (M^+, 19), 207 (3), 189 (100), 174 (6), 146 (22). Calcd. for $C_{15}H_{13}FN_2O$: C, 70.30; H, 5.11; N, 10.93. Found: C, 70.11; H, 5.16; N, 11.01%.

1-[(5,7-Difluoro-6-methoxynaphth-2-yl)methyl]-1H-imidazole (1h)

(51% from **16h**): mp 80–82°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, $J = 8.7$ Hz, 1 H), 7.60 (s, 1 H), 7.44 (s, 1 H), 7.26 (d, $J = 9.5$ Hz, 1 H), 7.26 (d, $J = 8.7$ Hz, 1 H), 7.12 (s, 1 H), 6.93 (s, 1 H), 5.26 (s, 2 H), 4.11 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1 (dd, $J = 249.2$ and 5.8 Hz), 150.1 (dd, $J = 250.6$ and 6.0 Hz), 137.5, 134.5, 130.0, 128.5 (dd, $J = 10.3$ and 5.3 Hz), 124.9 (dd, $J = 5.4$ and 3 Hz), 124.6 (t, $J = 2.3$ Hz), 121.2 (dd, $J =$ 13.3 and ? Hz), 121.1 (dd, $J = 5.2$ and 2.1 Hz), 118.6, 111.9 (dd, $J = 15.3$ and 5.6 Hz), 107.8 (dd, $J = 19.2$ and 4.3 Hz), 62.1 (dd, $J = 4.5$ and 2.5 Hz), 50.6; IR (KBr) 3128, 3104, 2925, 2851, 1618, 1508, 1498, 1261, 1058, 921, 815 cm^{-1}; MS, m/z (%) 274 (M^+, 22), 207 (100), 192 (21), 175 (5), 164 (21). Calcd. for $C_{15}H_{12}F_2N_2O$: C, 65.69; H, 4.41; N, 10.21. Found: C, 65.61; H., 4.32; N, 10.00%.

1-[(6-Methoxynaphth-2-yl)methyl]-1H-imidazole (1i)

(71% from **16i**): m.p. 135–136°C (from cyclohexane/$CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.7–7.5 (m, 4 H), 7.2–7.0 (m, 4 H), 6.91 (s, 1 H), 5.19 (s, 2 H), 3.90 (s, 3 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 158.0, 137.3, 134.1, 131.1, 129.6, 129.2, 128.6, 127.6, 126.2, 125.4, 119.4, 119.2, 105.6, 55.2, 50.8; IR (KBr) 3145, 3106, 3093, 2967, 2939, 1609, 1506, 1227, 1029, 854 cm^{-1}; MS, m/z (%) 238 (M^+, 22), 171 (100), 128 (23). Calcd. for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.34; H, 5.87; N, 11.73%.

1-[(Naphth-2-yl)methyl]-1H-imidazole (1l)

(87% from **16l**): mp 104–105°C (from cyclohexane/$CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.9–7.2 (m, 8 H), 7.11 (d, $J = 1.0$ Hz, 1 H), 6.93 (d, $J = 1.2$ Hz, 1 H), 5.27 (s, 2 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 137.4, 133.5, 133.1, 132.9, 129.8, 128.8, 127.7, 127.6, 126.6, 126.4, 126.1, 124.7, 119.3, 50.8; IR (KBr) 3121, 3102, 3088, 1601, 1508, 1236, 1080, 818, cm^{-1}; MS, m/z (%) 208 (M^+, 26), 141 (100), 115 (23). Calcd. for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.42; H, 5.69; N, 13.37%.

Inhibition of Aromatase (CYP 19):

Human placental aromatase was prepared according to described methods.[12,13] The inhibitory activities of the compounds were determined *in vitro* according to Thompson and Siiteri,[12] with modifications.[13] Enzyme activity was monitored by measuring ^3H_2O formed during aromatization from [1β,2β-^{3}H]testosterone or [1β-^{3}H]androstenedione

(40–60 Ci/mmol or 15–30 Ci/mmol, respectively, PerkinElmer, NEN, Boston, MA). Each incubation tube contained 0.025 μCi of labeled substrate, 2.5 μM unlabeled substrate, 0.5 mM NADPH, 10 mM glucose 6-phosphate, 1 U glucose 6-phosphate dehydrogenase and inhibitor (0–250 μM) in 0.05 M phosphate buffer (pH 7.40). The test compounds had been dissolved in ethanol and diluted with buffer. The final ethanol concentration in each incubation tube was 2%.

Inhibition of 17α-Hydroxylase-C17,20-lyase (CYP 17):

The human enzyme was prepared according to Sergejew and Hartmann.[14] The enzyme assay was performed as described in the same publication with slight modifications: 50 μL of the microsomal enzyme fraction (800 μg protein) and a solution of 165 μL phosphate buffer (50 mM sodium phosphate, 1 mM $MgCl_2$, 0.1 mM EDTA, 0.1 mM dithiothreitol, pH 7.4) with 6.25 nmol progesterone (in 5 μL methanol), 150 nmol NADPH (in 25 μL of the above mentioned phosphate buffer) and inhibitor (in 5 μL DMSO) were preincubated separately at 37°C for 5 min. The reaction was started by addition of the enzyme and stopped after 40 min incubation (37°C) by adding 50 μL 1 N HCl. Steroid extraction and HPLC procedure was performed according to Sergejew and Hartmann.[14]

RESULTS AND DISCUSSION

Chemistry

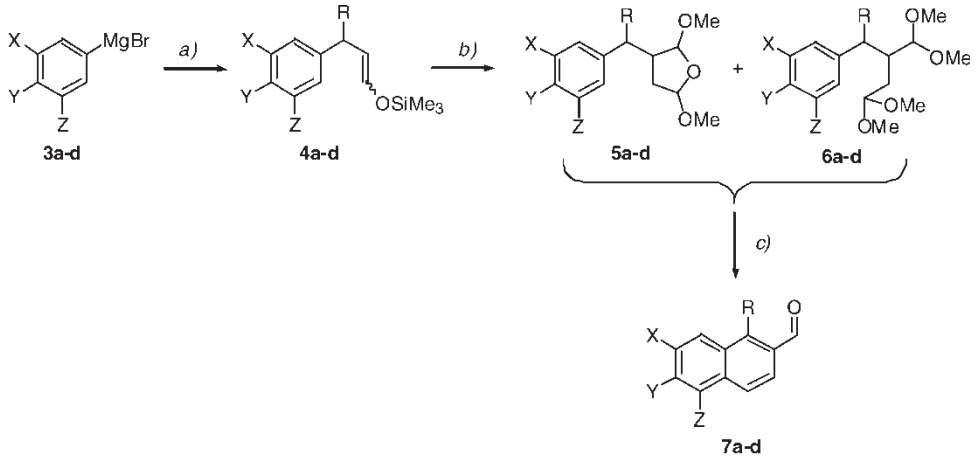
Regioselectively fluorinated (2-naphthyl)methanols (**2a–h**) and the non-fluorinated analogues (**2i–l**) were the selected precursors of the target imidazole derivatives **1a–l**.

The naphthaldeydes **7a–d**, precursors of the alcohols **2**(**a–d**), were prepared by a versatile method discovered during our investigation on the ceric ammonium nitrate (CAN)-promoted carbon-carbon bond forming reactions enabling the construction of selectively fluorinated polycyclic aromatic derivatives.[8]

The method is based on the CAN-promoted oxidative addition of easily accessible 3-(fluoroaryl)-1-(trimethylsilyloxy)alkenes[9] (**4a–d**) to ethyl vinyl ether (Scheme 1). The reaction occurs smoothly in methanol at ambient temperature affording cyclic (**5a–d**) and acyclic (**6a–d**) acetals.[10] According to the proposed mechanism reported (Scheme 2), the silyl enol ether **4** is oxidized by CAN to give the electrophilic α-carbonylalkyl radical **9**, probably through the transient radical cation **8**. In turn, the fast addition of **9** to ethyl vinyl ether generates an α-alkoxy radical **10**, a nucleophilic species, which is rapidly oxidized by CAN to give the cyclic carbocation **11** in equilibrium with its open chain isomer **12**. Finally the addition of a molecule of solvent lead to a thermodynamic mixture of the corresponding acetals **5** and **6**.

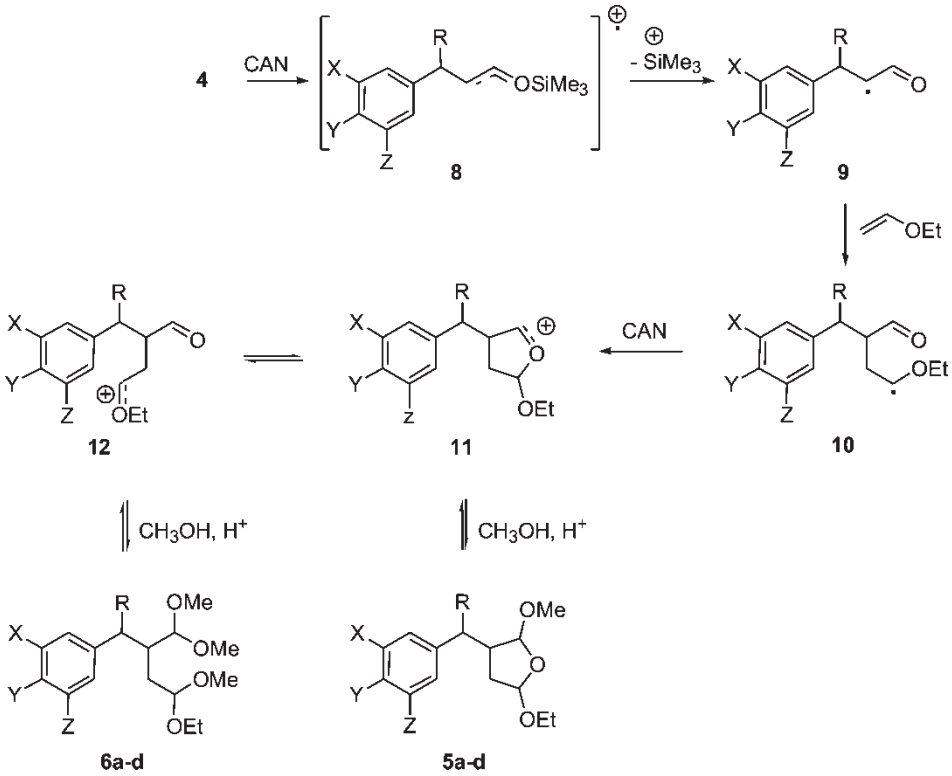
The latter mixture gives the expected aromatic aldehydes **7a–d** by cyclization under strongly acidic condition and in the presence of DDQ.

Owing to a substantial polymerisation following the conjugate addition of **3** to acrylic aldehyde, the above procedure showed itself unsuited to the synthesis of the non-methylated analogues **2f–h**. They required a substantially different strategy to be adopted. According to the Scheme 3 (R=H), the sodium salt of dimethyl (2,2-dimethoxyethyl)malonate,[11] was condensed with the suitable benzyl bromide **13** to give, after demethoxycarbonylation,

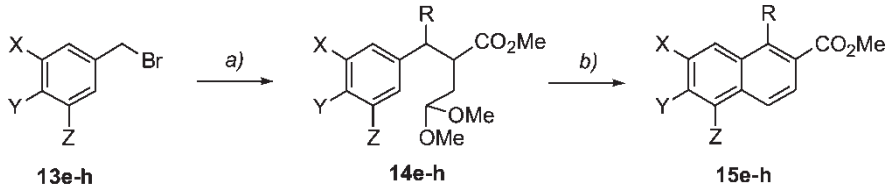


a) CuI-LiBr, $CH_3CH{=}CHCHO$, THF, -50°C, 91-95%; b) $CH_2{=}CHOEt$, CAN, MeOH, r.t.; c) 80%H_2SO_4, DDQ (1 eq.) 0°C, 45 min, 21-39% from **3**.

SCHEME 1 Synthesis of **7a–d**.



SCHEME 2 CAN-promoted oxidative mechanism.

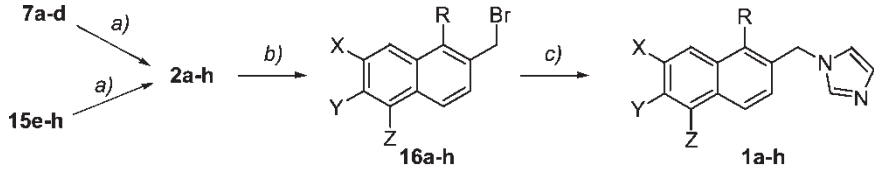


a) *1.* $[(H_3CO)_2CHCH_2C(CO_2CH_3)_2]^-Na^+$, DMF,r.t.; *2.* DMSO/NaCl/H_2O, 170°C.
b) 80%H_2SO_4, DDQ (1 eq.), 21-25% from **13**.

SCHEME 3 Synthesis of **15e–h**.

the acetals **14e–h**. Finally, the latter were converted into the expected methyl naphthoates (**15e–h**) by cyclization in H_2SO_4 in the presence of DDQ.

Both the aldeydes **7a–d** and the esters **15e–h** were transformed into the corresponding alcohols **2a–h** by reduction with $LiAlH_4$. Finally, bromination of the above alcohols with PBr_3-LiBr, followed by condensation of the resulting benzyl bromides **16a–h** with the sodium salt of imidazole (Scheme 4) provided the expected targets **1a–h** in satisfactory overall yield.



a) $LiAlH_4$, THF, O°C, 75-92% from **7** and 87-98% from **15**; b) PBr_3-LiBr, DMF, 0°C, 71-76%; c) Imidazole/NaH, then **16a-h**, DMF r.t. 51-87%

SCHEME 4 Synthesis of **1a–h**.

TABLE I Inhibition of CYP17 and CYP19 by the Fluorinated 1-[(Naphth-2-yl)methyl]-1*H*-imidazoles **1a–h** in Comparison with the Non-Fluorinated Parent Compounds **1i–l**

					Inhibition of CYP17 [a]			Inhibition of CYP19 [b]		
Compound	R	X	Y	Z	%	IC_{50} (μM)	RP	%	IC_{50} (μM)	RP
1a	CH_3	F	H	H	74	1.00	0.74	94	0.51	36
1b	CH_3	F	H	F	59	ND [c]	ND	96	0.18	103
1c	CH_3	F	OCH_3	H	88	0.27	2.70	95	0.57	32
1d	CH_3	F	OCH_3	F	79	0.50	1.50	93	0.96	19
1e	H	F	H	H	48	ND	ND	96	0.16	116
1f	H	F	H	F	35	ND	ND	96	0.36	51
1g	H	F	OCH_3	H	79	0.41	1.80	97	0.17	109
1h	H	F	OCH_3	F	70	1.00	0.74	94	0.76	24
1i	H	H	OCH_3	H	45	3.1	0.69	92	1.7	17
1l	H	H	H	H	18	ND	ND	96	0.97	31

[a] Substrate progesterone concentration: 25 μM; RP = Relative Potency (ketoconazole = 1). [b] Substrate ([1,2^{3}H]-testosterone) concentration: 4.4 pM + testosterone concentration: 2.5 μM; RP = Relative Potency (aminoglutethimide = 1). For **1i** and **1b**, 1β-^{3}H-androstenedione 0.5 μM. [c] ND = not determined.

For sake of comparison, non-fluorinated imidazole derivatives **1i** was prepared from the corresponding alcohol **2i**, in turn obtained by addition of 6-methoxy-2-naphthylmagnesium bromide to paraformaldehyde. **1l** was prepared in the same way from the commercially available 2-bromomethylnaphthalene (**16l**).

BIOLOGICAL RESULTS

Table I shows the inhibition towards CYP 17 and CYP 19 of the fluorinated compounds **1a–h** in comparison with the non-fluorinated parent compounds **1i–l**. The percent inhibition values at an inhibitor concentration of 2.5 μM are presented. For highly potent compounds the IC_{50} values are also given. The RP (relative potency) values indicate the potency of the corresponding compound compared to a well known reference, ketoconazole for CYP 17 and aminoglutethimide for CYP 19.

Both enzymes are strongly inhibited by the compounds. The most active inhibitor of CYP 17 is **1c**, whereas **1b**, **1e** and **1g** are the strongest inhibitors of CYP 19. Interestingly **1g** is a potent dual inhibitor also being very active towards CYP 19.

The finding that fluorination leads to an increase in inhibitory activity is very important. In the case of the non-fluorinated compounds **1i** and **1l** (RP values 17 and 31, respectively), inhibitory activity towards CYP 19 is dramatically enhanced by the introduction of one fluorine atom (**1g** and **1e**, RP values 109 and 116, respectively). A second fluorine atom, however, decreases potency (**1h** and **1f**, RP values 24 and 51, respectively) but the difluorinated compounds are still more potent than the non-fluorinated parent compounds. The only exception to this rule is the difluorinated compound **1b** (RP value of 103) which is more potent than the mono-fluorinated compound **1a** (RP value 36). In the case of CYP 17 the same tendency can be observed: the mono-fluorinated compounds are more active than the non- and difluorinated derivatives.

This finding is very interesting since in case of CYP 17 the fluorinated nucleus is supposed to mimic the steroidal A ring, whereas for CYP 19 the benzene nucleus most likely interacts with the steroidal D-ring binding site. The fact that fluorination leads to almost identical effects in both enzymes is an indication that both binding sites are very similar.

Acknowledgements

This work was carried out in the context of the COST D12 Action and the *Training and Mobility of Researchers* (TMR) European Project (Contract N° ERBFMRXCT970120). Thanks are due to the European Commission for financial support.

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