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Supporting Information

for

Fluorine Interactions at the Thrombin Active Site: Protein Backbone Fragments H-C_α-C=O Comprise a Favorable C-F Environment and Interactions of C–F with Electrophiles

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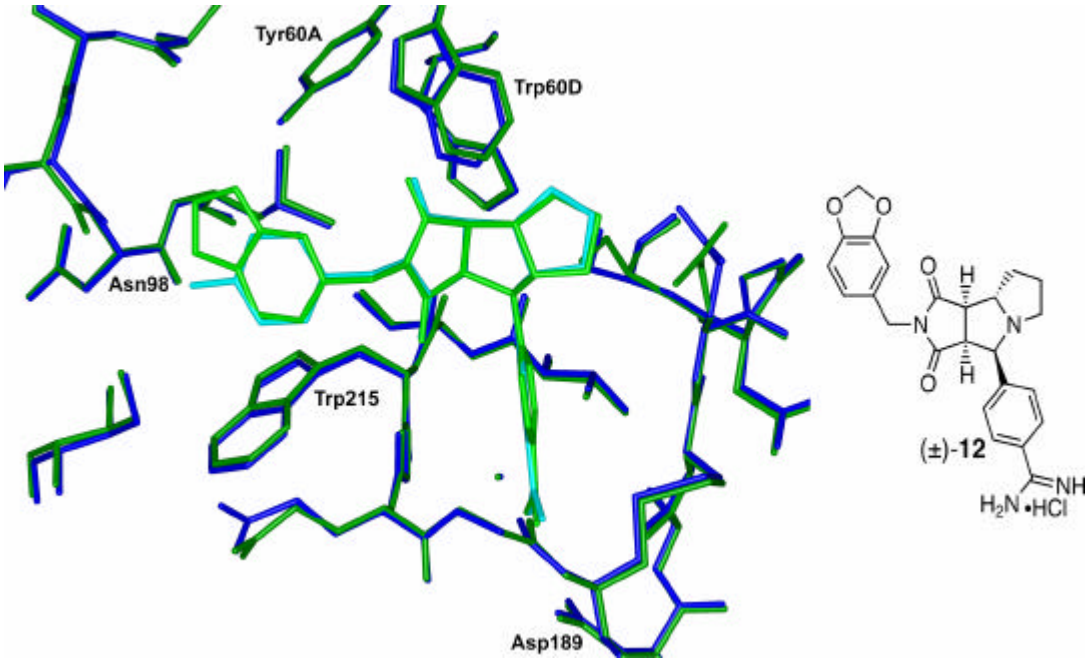


Figure 9 (SI). Least-square superimposition of the crystal structures of inhibitors (±)-**4d** and (±)-**12**[1] bound to thrombin.

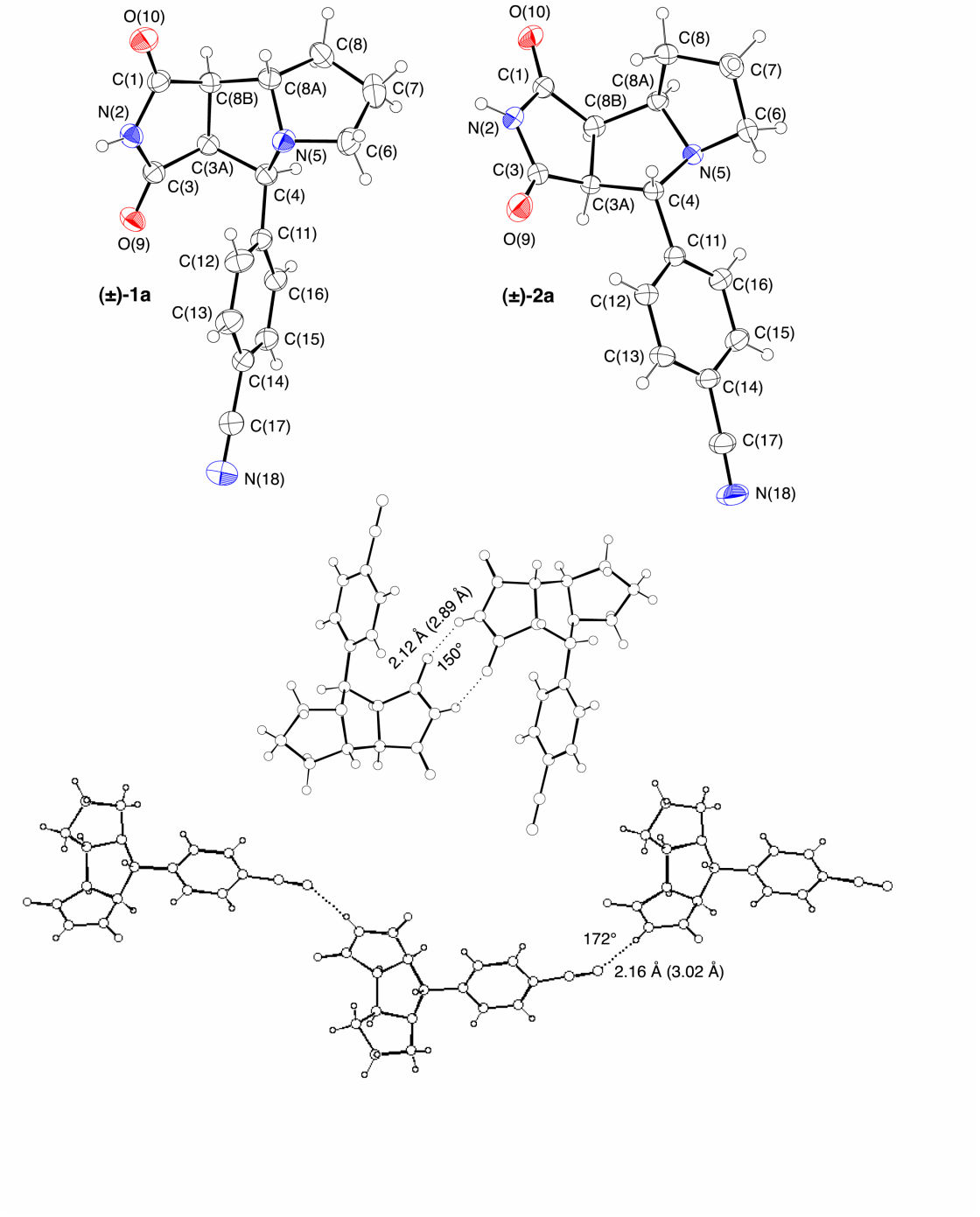
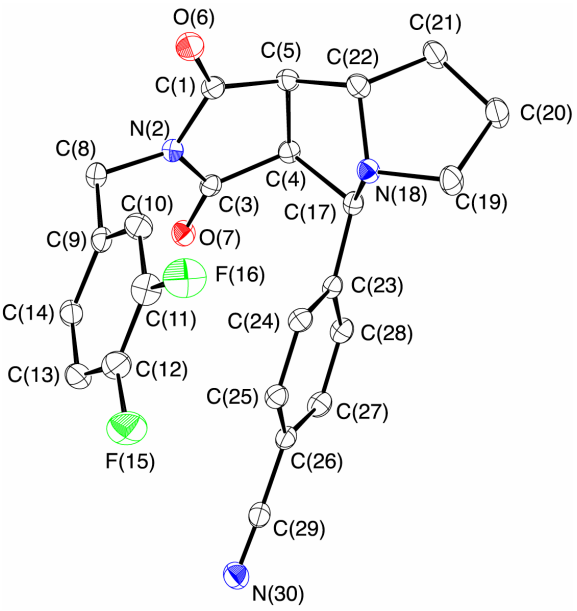


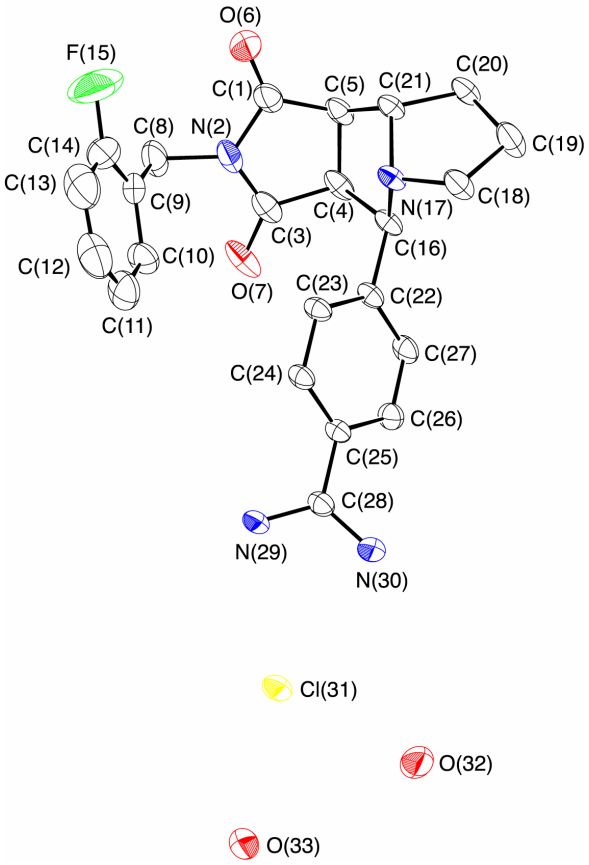
Figure 10 (SI). ORTEP representation of the X-ray crystal structures of (±)-**1a**[3] and (±)-**2a.**[4] The H-bonding pattern observed in the crystal packing of (±)-**1a** (up) and in the crystal packing of (±)-**2a** (down).



F	Y	$d_{F...Y}$	$d_{F...H-Y}$[2]
F15	F16	3.31	-
F15	C19	3.40	2.58 (H19B)
F15	O6	3.60	-
F15	N18	3.64	-
F15	C22	3.69	3.27 (H22A)
F15	C5	3.72	3.22 (H5A)
F15	C21	3.83	3.20 (H21B)
F15	C28	3.83	3.62 (H28A)

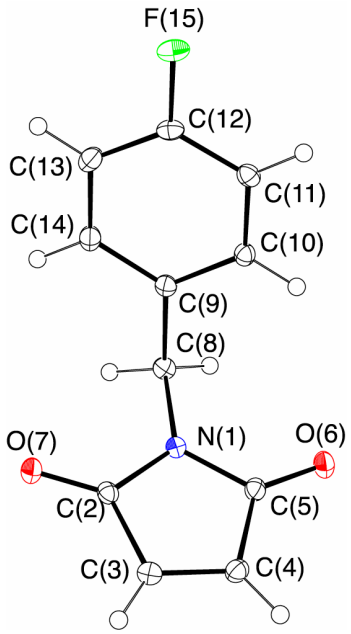
F	Y	$d_{F...Y}$	$d_{F...H-Y}$[2]
F16	F16	2.98	-
F16	C25	3.23	2.72 (H25A)
F16	C11	3.25	-
F16	C24	3.26	2.77 (H24A)
F16	F15	3.31	-
F16	C12	3.42	-
F16	C20	3.77	2.91 (H20B)
F16	C21	3.95	3.01 (H21B)

Figure 11 (SI). Analysis of the X-ray crystal structure of (±)-**3g.**[5] ORTEP representation. Tables of all intermolecular F-contacts to other atoms (Y) < 4.0 Å observed in the crystal packing of (±)-**3g.**



F	Y	$d_{F...Y}$	$d_{F...H-Y}$[2]
F15	C18	3.24	2.38 (H18)
F15	C19	3.50	2.91 (H19)
F15	C12	3.62	3.56 (H12)
F15	C11	3.84	3.94 (H11)
F15	O6	3.98	-

Figure 9 (SI). Analysis of the crystal structure of compound (±)-**4b**.[6] ORTEP representation and table of all intermolecular F-contacts to other atoms (Y) < 4.0 Å observed in the crystal packing of (±)-**4b**.



F	Y	$d_{F...Y}$	$d_{F...H-Y}$[2]
F15''	C3	3.12	3.06 (H3A)
F15''	C2	3.18	-
F15''	C4''	3.22	2.57 (H4A'')
F15''	O6'	3.24	-
F15''	O7	3.25	-
F15''	C3''	3.39	2.94 (H3A'')
F15''	C11	3.72	2.97 (H11A)
F15''	C4	3.91	4.41 (H4A)
F15''	O7	3.93	-

F	Y	$d_{F...Y}$	$d_{F...H-Y}$[2]
F15	C3''	3.01	3.10 (H3A'')
F15	C2''	3.11	-
F15	C3	3.12	2.55 (H3)
F15	C4	3.17	2.67 (H4A)
F15	O7	3.29	-
F15	O7''	3.37	-
F15	C10''	3.59	2.82 (H10A'')
F15	C4''	3.60	4.09 (H4A'')
F15	N1''	3.76	-
F15	O6	3.94	-

F	Y	$d_{F...Y}$	$d_{F...H-Y}$[2]
F15'	C5'	2.94	-
F15'	C4'	2.97	3.07 (H4A')
F15'	O6'	3.13	-
F15'	C3'	3.23	2.68 (H3A')
F15'	C4'	3.25	2.71 (H4A')
F15'	O7''	3.58	-
F15'	N1'	3.63	-
F15'	C3'	3.63	4.18 (H3A')
F15'	O6''	3.82	-
F15'	C14'	3.94	3.64 (H14A')
F15'	C13''	3.95	3.10 (H13A'')

Figure 10 (SI). Analysis of the crystal structure of *N*-(4-fluorobenzyl)maleimide **6**.[7] ORTEP representation and tables of all intermolecular F-contacts to other atoms (Y) < 4.0 Å observed in the crystal packing.

Experimental Part (SI)

(3a*SR*,4*RS*,8a*SR*,8b*RS*)-4-(4-Bromophenyl)perhydropyrrolo[3,4-*a*]pyrrolizine-1,3-dione ((±)-1b) and (3a*SR*,4*SR*,8a*RS*,8b*RS*)-4-(4-Bromophenyl)perhydropyrrolo[3,4-*a*]pyrrolizine-1,3-dione ((±)-2b). A solution of maleimide (291 mg, 3.0 mmol) maleimide, 4-bromobenzaldehyde (583 mg, 3.15 mmol) 4, and L-proline (363 mg, 3.15 mmol) in MeCN (9 mL) was heated to reflux for 16 h. The solvent was removed *in vacuo* and (±)-**1b** and (±)-**2b** separated by CC (CH_2Cl_2/EtOAc 65:35). (±)-**1b**: Yield: 182 mg (19 %, colorless needles). M.p. 173-175 °C. IR (KBr): 1763, 1699, 1482, 1345, 1192, 1081. ^{1}H NMR (300 MHz, $CDCl_3$):*?d?*= 1.62-1.84 (*m*, 2H), 1.96-2.20 (*m*, 2H), 2.63-2.74 (*m*, 1H, H-C(6)), 2.82-2.94 (*m*, 1H, H-C(6)), 3.33 (*d*, *J* = 8.1, 1H, H-C(8b)), 3.52 (*t*, *J* = 8.3, 1H, H-C(3a)), 3.79 (*dd*, *J* = 9.9 and 7.5, 1H, H-C(8a)), 4.03 (*d*, *J* = 8.7, 1H, H-C(4)), 7.26, 7,46 (*AA'BB'*, *J* = 8.3, 4H, Ar), 7.68 (br s, 1H, NH). ^{13}C NMR (75 MHz, $(CD_3)_2SO$):*?d??*= 23.1, 29.0, 49.9, 50.3, 51.4, 67.1, 67.3, 119.9, 130.1, 138.5, 176.9, 179.8. HRMS: calcd for $C_{15}H_{16}BrN_2O_2$ $[MH]^+$, 335.0395; found 335.0395 and 337.0369. (±)-**2b**: Yield: 335 mg (33 %, colorless needles). M.p. 177-178 °C. IR (KBr): 1780, 1698, 1489, 1357, 1344, 1183, 1073. ^{1}H NMR (300 MHz, $CDCl_3$):*?d?*= 1.70-1.91 (*m*, 2H), 1.96-2.12 (*m*, 2H), 2.64-2.74 (*m*, 1H, H-C(6)), 2.95-3.05 (*m*, 1H, H-C(6)), 3.34 (*dd*, *J* = 9.0 and 6.6, 1H, H-C(3a)), 3.65 (*t*, *J* = 9.0, 1H, H-C(8b)), 3.87 (*dd*, *J* = 8.7 and 6.6, 1H, H-C(8a)), 4.07 (*d*, *J* = 6.6, 1H, H-C(4)), 7.37, 7,49 (*AA'BB'*, *J* = 8.4, 4H, Ar), 7.83 (br s, 1H, NH)). ^{13}C NMR (75 MHz, $(CD_3)_2SO$):*?d?*= 24.2, 26.5, 48.5, 50.9, 56.3, 67.9, 120.1, 129.4, 131.1, 142.0, 178.3, 179.2. HRMS: calcd for $C_{15}H_{16}BrN_2O_2$ $[MH]^+$, 335.0395; found 335.0393 and 337.0367.

(3a*SR*,4*RS*,8a*SR*,8b*RS*)-4-(2-(2-Fluorobenzyl)-1,3-dioxodecahydropyrrolo[3,4-*a*]pyrrolizin-4-yl)benzonitrile ((±)-3b). Compound (±)-**3b** was synthesized according to the

procedure described for compound (±)-**3d**. Yield: 113 mg (58%, colorless prism). M.p. 200-202 °C (EtOAc/hexane). IR (KBr): 2224, 1778, 1705, 1491, 1457, 1420, 1400, 1344, 1184, 1175. ^{1}H NMR (300 MHz, $CDCl_3$):*?d??*= 1.60-1.88 (*m*, 2H), 1.96-2.24 (*m*, 2H), 2.56-2.68 (*m*, 1H, H-C(6)), 2.84-2.97 (*m*, 1H, H-C(6)), 3.35 (*d*, *J* = 8.1, 1H, H-C(8b)), 3.56 (*t*, *J* = 8.4, 1H, H-C(3a)), 3.81 (*dd*, *J* = 9.8 and 7.4, 1H, H-C(8a)), 4.13 (*d*, *J* = 8.7, 1H, H-C(4)), 4.58 and 4.65 (AB, *J* = 15.0, 2H, CHH'-N(5)), 6.99-7.12 (*m*, 2H, Ar(F)), 7.17-7.31 (*m*, 2H, Ar(F)), 7.34, 7.48 (*AA'BB'*, *J* = 8.5, 4H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$):*?d??*= 23.4, 29.7, 36.1, 48.9, 50.5, 50.8, 68.0, 68.3, 111.2, 115.3 (*d*, *J* = 21.4), 118.7, 122.1 (*d*, *J* = 14.6), 123.8 (*d*, *J* = 3.7), 128.5, 129.5 (*d*, *J* = 7.9), 130.1 (*d*, *J* = 3.6), 131.7, 143.4 160.4 (*d*, *J* = 247.9), 174.5, 177.2. ^{19}F NMR (282 MHz, $CDCl_3$ + $CFCl_3$):*?d??*= -116.4 (*m*). HRMS: calcd for $C_{23}H_{21}FN_3O_2$ $[MH]^+$, 390.1618; found 390.1609.

(3a*SR*,4*RS*,8a*SR*,8b*RS*)-4-(2-(3-Fluorobenzyl)-1,3-dioxodecahydropyrrolo[3,4-*a*]pyrrolizin-4-yl)benzonitrile ((±)-3c). Compound ((±)-**3c** was synthesized according to the procedure described for compound (±)-**3d**. Yield: 161 mg (83%, colorless crystals). M.p. 181-182°C (EtOAc/hexane). IR (KBr): 2223, 1779, 1704, 1617, 1593, 1488, 1451, 1423, 1398, 1359, 1342, 1273, 1232, 1183, 1143. ^{1}H NMR (300 MHz, $CDCl_3$):*?d??*= 1.60-1.88 (*m*, 2H), 1.96-2.22 (*m*, 2H), 2.55-2.66 (*m*, 1H, H-C(6)), 2.82-2,95 (*m*, 1H, H-C(6)), 3.33 (*d*, *J* = 8.1, 1H, H-C(8b)), 3.55 (*t*, *J* = 8.3, 1H, H-C(3a)), 3.78 (dd, *J* = 10.1 and 7.1, 1H, H-C(8a)), 4.12 (*d*, *J* = 8.7, 1H, H-C(4)), 4.47 and 4.53 (AB, *J* = 14.4, 2H, CHH'-N(5)), 6.92-7.08 (*m*, 3H, Ar(F)), 7.20-7.31 (*m*, 1H, Ar(F)), 7.33, 7.52 (*AA'BB'*, *J* = 8.3, 4H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$):*?d??*= 23.4, 29.7, 41.9, 49.0, 50.5, 50.8, 68.0, 68.3, 111.4, 114.8 (*d*, *J* = 20.7), 115.5 (*d*, *J* = 22.0), 118.7, 124.3, 128.6, 129.9 (*d*, *J* = 7.9), 131.8, 137.6 (*d*, *J* = 7.3), 143.4, 162.5 (*d*, *J* = 246.0), 174.6, 177.3. ^{19}F NMR (282

MHz, $CDCl_3$ + $CFCl_3$):*?d??*= -112.2 (*td*, *J* = 9.2 and 5.6). HRMS: calcd for $C_{23}H_{21}FN_3O_2$ $[MH]^+$, 390.1618; found 390.1609.

(3a*SR*,4*RS*,8a*SR*,8b*RS*)-4-(2-(2,3-Difluorobenzyl)-1,3-dioxodecahydropyrrolo[3,4-*a*]pyrrolizin-4-yl)benzonitrile ((±)-3e). Compound (±)-**3e** was synthesized according to the procedure described for compound (±)-**3d**. Yield: 165 mg (81%, colorless crystals). M.p. 160-161 °C (EtOAc/hexane). IR (KBr): 2224, 1776, 1710, 1494, 1433, 1400, 1349, 1339, 1278, 1175, 1162. ^{1}H NMR (300 MHz, $CDCl_3$):*?d??*= 1.60-1.89 (*m*, 2H, H-C(7), H-C(8)), 1.96-2.24 (*m*, 2H, H-C(7), H-C(8)), 2.58-2.68 (*m*, 1H, H-C(6)), 2.86-2,97 (*m*, 1H, H-C(6)), 3.32 (*dd*, *J* = 8.1 and 0.9, 1H, H-C(8b)), 3.58 (*t*, *J* = 8.4, 1H, H-C(3a)), 3.81 (dd, *J* = 9.6 and 7.2, 1H, H-C(8a)), 4.15 (*d*, *J* = 8.4, 1H, H-C(4)), 4.59 (*dd*, *J* = 14.7 and 0.9, 1H, CHH'-N(5)), 4.65 (*dd*, *J* = 14.7 and 0.9, 1H, CHH'-N(5)), 6.93-7.16 (*m*, 3H, Ar(F)), 7.37, 7.52 (*AA′BB′*, *J* = 8.1, 4H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$):*?d??*= 23.4, 29.7, 35.9, 48.9, 50.5, 50.8, 68.0, 68.3, 111.4, 116.7 (*d*, *J* = 17.1), 118.7, 123.8 (*dd*, *J* = 6.7 and 4.9), 124.5 (*d*, *J* = 11.6), 124.7 (*t*, *J* = 2.6), 128.5, 131.8, 148.5 (*dd*, *J* = 249.6 and 13.1), 150.2 (*dd*, *J* = 248.4 and 12.5), 174.3, 177.0. ^{19}F NMR (282 MHz, $CDCl_3$ + $CFCl_3$):*?d??*= - 137.4 (*ddd*, *J* = 20.3, 10.7 and 4.2, 1F), -141.1 (*dt*, *J* = 21.5 and 6.5, 1F). HRMS: calcd for $C_{23}H_{20}F_2N_3O_2$ $[MH]^+$, 408.1524; found 408.1519. Anal. calcd for $C_{23}H_{19}F_2N_3O_2$: C 67.81, H 4.70, F 9.33, N 10.31; found: C 67.81, H 4.89, F 9.29, N 10.19.

(3a*SR*,4*RS*,8a*SR*,8b*RS*)-4-(2-(2,6-Difluorobenzyl)-1,3-dioxodecahydropyrrolo[3,4-*a*]pyrrolizin-4-yl)benzonitrile ((±)-3f). Compound (±)-**3f** was synthesized according to the procedure described for compound (±)-**3d**. Yield: 176 mg (86%, colorless crystals). M.p. 211-212 °C (EtOAc/hexane). IR (KBr): 2225, 1776, 1710, 1624, 1473, 1451, 1433, 1398, 1352, 1293, 1270, 1238, 1176. ^{1}H NMR

(300 MHz, $CDCl_3$):*?d??*= 1.59-1.87 (*m*, 2H, H-C(7)), H-C(8)), 1.95-2.22 (*m*, 2H, H-C(7)), H-C(8)), 2.55-2.65 (*m*, 1H, H-C(6)), 2.83-2.95 (*m*, 1H, H-C(6)), 3.32 (*d*, *J* = 8.1, 1H, H-C(8b)), 3.53 (*t*, *J* = 8.3, 1H, H-C(3a)), 3.79 (dd, *J* = 10.1 and 7.4, 1H, H-C(8a)), 4.11 (*d*, *J* = 8.7, 1H, H-C(4)), 4.59, 4.68 (*AB*, *J* = 14.6, 2H, CHH'-N(5)), 6.80-6.92 (*m*, 2H, Ar(F)), 7.20-7.31 (*m*, 1 H, Ar(F)), 7.34, 7.47 (*AA'BB'*, *J* = 8.6, 4H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$):*?d??*= 23.5, 29.8, 30.1, 49.0, 50.4, 50.9, 68.0, 68.4, 110.8 (*t*, *J* = 20.0), 111.2, 111.2 (*d*, *J* = 18.9), 118.8, 128.5, 129.6 (*t*, *J* = 10.4), 131.7, 143.6, 161.3 (*dd*, *J* = 250.9 and 7.3), 173.9, 176.7. ^{19}F NMR (282 MHz, $CDCl_3$ + $CFCl_3$):*?d??*= -112.9 (*t*, *J* = 6.5). HRMS: calcd for $C_{23}H_{20}F_2N_3O_2$ $[MH]^+$, 408.1524; found 408.1515.

(3a*SR*,4*RS*,8a*SR*,8b*RS*)-4-(2-(3,4-Difluorobenzyl)-1,3-dioxodecahydropyrrolo[3,4-*a*]pyrrolizin-4-yl)benzonitrile ((±)-3g). Compound (±)-**3g** was synthesized according to the procedure described for compound (±)-**3d**. Yield: 159 mg (78%, colorless crystals). M.p. 150-151 °C (EtOAc/hexane). IR (KBr): 2223, 1773, 1712, 1608, 1518, 1440, 1429, 1397, 1348, 1336, 1286, 1212, 1170, 1120. ^1H NMR (300 MHz, $CDCl_3$):*?d??*= 1.60-1.89 (*m*, 2H, H-C(7)), H-C(8)), 1.96-2.22 (*m*, 2H, H-C(7), H-C(8)), 2.56-2.66 (*m*, 1H, H-C(6)), 2.83-2.95 (*m*, 1H, H-C(6)), 3.32 (*d*, *J* = 8.1 and 0.6, 1H, H-C(8b)), 3.55 (*t*, *J* = 8.4, 1H, H-C(3a)), 3.77 (dd, *J* = 10.5 and 7.2, 1H, H-C(8a)), 4.13 (*d*, *J* = 8.4, 1H, H-C(4)), 4.46 (*s*, 2H, CH_2-N(5)), 6.98-7.14 (*m*, 3H, Ar(F)), 7.34, 7.56 (*AA'BB'*, *J* = 8.4, 4H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$):*?d??*= 23.4, 29.6, 41.4, 48.8, 50.5, 50.7, 67.9, 68.2, 111.5, 117.2 (*d*, *J* = 17.7), 117.8 (*d*, *J* = 17.7), 118.7, 125.0 (*dd*, *J* = 6.0 and 3.7), 128.6, 131.8, 132.2 (*dd*, *J* = 5.5 and 4.2), 143.4, 149.8 (*d*, *J* = 248.4), 150.0 (*d*, *J* = 247.1), 177.2, 174.5. ^{19}F NMR (282 MHz, $CDCl_3$ + $CFCl_3$):*?d??*= -136.5 (*ddd*, *J* = 21.5, 11.9, and 7.6, 1F), -137.8 (*m*, 1F). HRMS: calcd for $C_{23}H_{20}F_2N_3O_2$ $[MH]^+$, 408.1524;

found 408.1522. Anal. calcd for $C_{23}H_{19}F_2N_3O_2$: C 67.81, H 4.70, F 9.33, N 10.31; found: C 67.76, H 4.92, F 9.28, N 10.23. X-ray.

(3a*SR*,4*RS*,8a*SR*,8b*RS*)-4-(2-(3,5-Difluorobenzyl)-1,3-dioxodecahydropyrrolo[3,4-*a*]pyrrolizin-4-yl)benzonitrile ((±)-3h). Compound **3h** was synthesized according to the procedure described for compound **3d**. Yield: 154 mg (76%, colorless prism). M.p. 168-170 °C (EtOAc/hexane). IR (KBr): 2223, 1774, 1711, 1622, 1608, 1595, 1465, 1437, 1397, 1335, 1319, 1166, 1119. ^{1}H NMR (300 MHz, $CDCl_3$):*?d??*= 1.60-1.88 (*m*, 2H), 1.96-2.22 (*m*, 2H), 2.58-2.68 (*m*, 1H, H-C(6)), 2.86-2.97 (*m*, 1H, H-C(6)), 3.35 (*d*, *J* = 8.1, 1H, H-C(8b)), 3.58 (*t*, *J* = 8.4, 1H, H-C(3a)), 3.79 (dd, *J* = 9.6 and 7.2, 1H, H-C(8a)), 4.15 (*d*, *J* = 8.9, 1H, H-C(4)), 4.49 (*s*, 2H, CH_2-N(5)), 6.70-6.81 (*m*, 3H, Ar(F)), 7.37, 7.57 (*AA′BB′*, *J* = 8.3, 4H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$):*?d??*= 23.4, 29.7, 41,6, 48.9, 50.5, 50.8, 68.0, 68.3, 103.4 (*t*, *J* = 25.3), 111.3 (*dd*, *J* = 18.0 and 7.9), 111.5, 118.7, 128.6, 131.9, 138.7 (*t*, *J* = 9.2), 143.2, 162.8 (*dd*, *J* = 248.7 and 12.5), 174.5, 177.2. ^{19}F NMR (282 MHz, $CDCl_3$ + $CFCl_3$):*?d??*= - 108.8 (*t*, *J* = 7.9). HRMS: calcd for $C_{23}H_{20}F_2N_3O_2$ $[MH]^+$, 408.1524; found 408.1510.

(3a*SR*,4*RS*,8a*SR*,8b*RS*)-4-(2-(2,3,4,5,6-Pentafluorbenzyl)-1,3-dioxodecahydro-pyrrolo[3,4-*a*]pyrrolizin-4-yl)benzonitrile ((±)-3i). Compound (±)-**3i** was synthesized according to the procedure described for compound ((±)-**3d**. Yield: 179 mg (78%, colorless needles). M.p. 160-161 °C (EtOAc/hexane). IR (KBr): 2231, 1779, 1713, 1520, 1508, 1398, 1344, 1329, 1176. ^{1}H NMR (300 MHz, $CDCl_3$):*d??*= 1.60-1.88 (*m*, 2H), 1.96-2.24 (*m*, 2H), 2.57-2.68 (*m*, 1H, H-C(6)), 2.85-2.97 (*m*, 1H, H-C(6)), 3.33 (*d*, *J* = 7.8, 1H, H-C(8b)), 3.57 (*t*, *J* = 8.4, 1H, H-C(3a)), 3.76 (*dd*, *J* = 9.8 and 7.4, 1H, H-C(8a)), 4.17 (*d*, *J* = 8.7, 1H, H-C(4)), 4.60, 4.65 (*AB*, *J* = 15.8, 2H, CHH'-N(5)), (7.42, 7.59 (*AA′BB′*, *J* = 8.3, 4H, Ar). ^{13}C

NMR (75 MHz, $CDCl_3$): *?d??*= 23.4, 29.7, 30.6, 48.7, 50.5, 50.8, 67.8, 68.2, 108.3 (*td*, *J* = 16.7 and 3.9), 111.4, 118.7, 128.5, 131.7, 137.1 (*dm*, *J* = 252.7), 140.9 (*dm*, *J* = 255.2), 143.3, 146.2 (*dm*, *J* = 250.3), 173.6, 176.5. ^{19}F NMR (282 MHz, $CDCl_3$ + $CFCl_3$): *d??*= -140.6 (*dd*, *J* = 22.5 and 8.6, 2F), -153.1 (*t*, *J* = 20.9, 1F), -161.1 (*m*, 2F). HRMS: calcd for $C_{23}H_{17}F_5N_3O_2$ $[MH]^+$, 462.1241; found 462.1230. Anal. calc. for $C_{23}H_{16}F_5N_3O_2$: C 59.87, H 3.50, F 20.59, N 9.11; found: C 59.82, H 3.70, F 20.72, N 9.06. X-ray.[8]

(3a*SR*,4*RS*,8a*SR*,8b*RS*)-4-(2-(4-Chlorobenzyl)-1,3-dioxodecahydropyrrolo[3,4-*a*]pyrrolizin-4-yl)benzonitrile ((±)-3j). Compound (±)-**3j** was synthesized according to the procedure described for compound (±)-**3d**. Yield: 174 mg (86%, colorless crystals). M.p. 184-185 °C (EtOAc/hexane). IR (KBr): 2223, 1772, 1706, 1607, 1493, 1432, 1395, 1334, 1299, 1230, 1168. ^{1}H NMR (300 MHz, $CDCl_3$): *d??*= 1.60-1.88 (*m*, 2H), 1.96-2.21 (*m*, 2H), 2.54-2.65 (*m*, 1H, H-C(6)), 2.81-2.93 (*m*, 1H, H-C(6)), 3.31 (*dd*, *J* = 7.8 and 0.6, 1H, H-C(8b)), 3.52 (*t*, *J* = 8.4, 1H, H-C(3a)), 3.77 (dd, *J* = 10.2 and 7.5, 1H, H-C(8a)), 4.10 (*d*, *J* = 8.7, 1H, H-C(4)), 4.44, 4.51 (*AB*, *J* = 14.1, 2H, CHH'-N(5)), 7.21, 7.28 (*AA'BB'*, *J* = 8.4, 4H, Ar(Cl)), 7.30, 7.51 (*AA'BB'*, *J* = 8.4, 4H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): *?d??*= 23.4, 29.6, 41.8, 48.9, 50.5, 50.8, 68.0, 68.3, 111.4, 118.7, 128.6, 130.2, 131.8, 133.8, 133.9, 143.4, 174.5, 177.3. HRMS: calcd for $C_{23}H_{21}ClN_3O_2$ $[MH]^+$, 406.1324; found 406.1316. Anal. calcd for $C_{23}H_{20}ClN_3O_2$: C 68.06, H 4.97, Cl 8.73, N 10.35; found: C 68.06, H 5.02, Cl 8.80, N 10.26.

(3a*SR*,4*RS*,8a*SR*,8b*RS*)-4-(2-(2-Fluorobenzyl)-1,3-dioxodecahydropyrrolo[3,4-*a*]pyrrolizin-4-yl)benzamidine Hydrochloride ((±)-4b). Compound (±)-**4b** was synthesized according to the procedure described for compound (±)-**4d**. Yield: 75 mg (56%, colorless solid)). M.p. > 210 °C (dec.). IR (KBr): 3468, 3267, 2958, 1776, 1710, 1669,

1490, 1430, 1399, 1351, 1339, 1174. ^{1}H NMR (300 MHz, CD_3OD): *d??*= 1.72-1.92 (*m*, 2H), 2.02-2.20 (*m*, 2H), 2.59-2.69 (*m*, 1H, H-C(6)), 2.84-2.96 (*m*, 1H, H-C(6)), 3.48 (*d*, *J* = 8.1, 1H, H-C(8b)), 3.70-3.80 (m, 2H, H-C(3a) and H-C(8a)), 4.32 (*d*, *J* = 8.4, 1H, H-C(4)), 4.55 and 4.61 (*AB*, *J* = 15.5, 2H, CHH'-N(5), 7.02-7.10 (m, 1H, ArF), 7.13 (td, *J* = 7.4 and 0.9, 1H, ArF), 7.13 (td, *J* = 7.6 and 1.8, 1H, ArF), 7.26-7.36 (m, 1H, ArF), 7.51, 7.63 (*AA'BB'*, *J* = 8.6, 4H, Ar). ^{13}C NMR (75 MHz, CD_3OD): *?d??*= 24.3, 30.5, 36.8, 50.2, 51.8, 52.1, 69.3, 69.6, 116.2 (*d*, *J* = 21.4), 123.8 (*d*, *J* = 14.7), 125.2, 128.2, 128.4, 130.2, 130.6, 146.7, 161.6 (*d*, *J* = 246.0), 167.9, 176.8, 179.7. ^{19}F NMR (282 MHz, CD_3OD + $CFCl_3$): *?d??*= -117.0 (*m*). HRMS: calcd for $C_{23}H_{24}FN_4O_2$ $[MH]^+$, 407.1883; found 407.1872. X-ray.

(3a*SR*,4*RS*,8a*SR*,8b*RS*)-4-(2-(3-Fluorobenzyl)-1,3-dioxodecahydropyrrolo[3,4-a]pyrrolizin-4-yl)benzamidine Hydrochloride ((±)-4c). Compound (±)-**4c** was synthesized according to the procedure described for compound (±)-**4d**. Yield: 101 mg (76%, light yellow solid)). M.p. > 160°C (dec.). IR (KBr): 3333, 3062, 1775, 1699, 1676, 1615, 1591, 1489, 1399, 1340, 1176. ^{1}H NMR (300 MHz, CD_3OD): *?d??*= 1.72-1.90 (*m*, 2H), 2.01-2.18 (*m*, 2H), 2.58-2.68 (*m*, 1H, H-C(6)), 2.82-2.93 (*m*, 1H, H-C(6)), 3.48 (*d*, *J* = 8.1, 1H, H-C(8b)), 3.69-3.80 (m, 2H, H-C(3a) and H-C(8a)), 4.31 (*d*, *J* = 8.7, 1H, H-C(4)), 4.48 and 4.54 (*AB*, *J* = 14.7, 2H, CHH'-N(5)), 6.92-7.09 (*m*, 3H, Ar-F)), 7.33 (*td*, *J* = 8.3 and 5.7, 1H, Ar-F)), 7.48, 7.64 (*AA'BB'*, *J* = 8.3, 4 H, Ar). ^{13}C NMR (75 MHz, CD_3OD): *?d??*= 24.4, 30.5, 42,5, 50.3, 51.8, 52.0, 69.3, 69.5, 115.4 (*d*, *J* = 21.3), 115.8 (*d*, *J* = 22.0), 124.9, 128.2, 128.4, 130.2, 131.2 (*d*, *J* = 7.9), 139.7 (*d*, *J* = 6.7), 146.7, 163.9 (*d*, *J* = 244.2), 168.0, 177.0, 179.8. ^{19}F NMR (282 MHz, CD_3OD + $CFCl_3$): *?d??*= -112.6 (*td*, *J* = 9.0 and 5.6). HRMS: calcd for $C_{23}H_{24}FN_4O_2$ $[MH]^+$, 407.1883; found 407.1875.

(3a*SR*,4*RS*,8a*SR*,8b*RS*)-4-(2-(2,3-Difluorobenzyl)-1,3-dioxodecahydropyrrolo[3,4-*a*]pyrrolizin-4-yl)benzamidine Hydrochloride ((±)-4e). Compound (±)-**4e** was synthesized according to the procedure described for compound (±)-**4d**. Yield: 68 mg (59%, colorless solid). M.p. > 180 °C (dec.). IR (KBr): 3105, 1776, 1703, 1615, 1492, 1437, 1431, 1403, 1344, 1175. ^{1}H NMR (300 MHz, CD_3OD):*?d??*= 1.73-1.92 (*m*, 2H, H-C(7), H-C(8)), 2.02-2.20 (*m*, 2H, H-C(7), H-C(8)), 2.60-2.70 (*m*, 1H, H-C(6)), 2.85-2.97 (*m*, 1H, H-C(6)), 3.50 (*d*, *J* = 8.1, 1H, H-C(8b)), 3.70-3.82 (*m*, 2H, H-C(3a) and H-C(8b)), 4.33 (*d*, *J* = 8.7, 1H, H-C(4)), 4.61 (*s*, 2H, CHH'-N(5)), 7.01-7.27 (*m*, 3H, Ar(F)), 7.52, 7.65 (*AA′BB′*, *J* = 8.4, 4H, Ar). ^{13}C NMR (75 MHz, CD_3OD):*?d??*= 24.2, 30.5, 36.3, 50.2, 51.9, 52.1, 69.3, 69.6, 117.7 (*d*, *J* = 17.1), 125.5 (*dd*, *J* = 6.7 and 4.9), 125.9; 126.6 (*d*, *J* = 11.6), 128.5, 128.6, 130.3, 146.9, 149.8 (*dd*, *J* = 248.4 and 13.4), 151.7 (*dd*, *J* = 246.6 and 12.8), 168.2, 177.0, 179.8. ^{19}F NMR (282 MHz, CD_3OD + $CFCl_3$):*?d??*= -138.3 (m, 1F), -142.1 (ddd, *J* = 20.3, 6.5 and 6.2 1F). HRMS: calcd for $C_{23}H_{23}F_2N_4O_2$ $[MH]^+$, 425.1789; found 425.1794.

(3a*SR*,4*RS*,8a*SR*,8b*RS*)-4-(2-(2,6-Difluorobenzyl)-1,3-dioxodecahydropyrrolo[3,4-*a*]pyrrolizin-4-yl)benzamidine Hydrochloride ((±)-4f). Compound (±)-**4f** was synthesized according to the procedure described for compound (±)-**4d**. Yield: 103 mg (75%, colorless solid). M.p. > 162°C (dec.). IR (KBr): 3369, 3051, 1773, 1700, 1626, 1509, 1481, 1437, 1401, 1347, 1119, 1176. ^{1}H NMR (300 MHz, CD_3OD):*?d??*= 1.70-1.88 (*m*, 2H, H-C(7), H-C(8)), 2.00-2.22 (*m*, 2H, H-C(7), H-C(8)), 2.56-2.66 (*m*, 1H, H-C(6)), 2.81-2.93 (*m*, 1H, H-C(6)), 3.44 (*d*, *J* = 8.4, 1H, H-C(8b)), 3.70 (*t*, *J* = 8.3, 2H, H-C(3a) and H-C(8b)), 4.28 (*d*, *J* = 8.4, 1H, H-C(4)), 4.58 and 4.65 (*AB*, *J* = 14.9, 2H, CHH'-N(5)), 6.89-7.00 (*m*, 2H, Ar(F)), 7.36 (*tt*, *J* = 8.4 and 6.6, 1H, Ar(F)), 7.49, 7.62 (*AA′BB′*, *J* = 8.3, 4H, Ar). ^{13}C NMR (125 MHz, CD_3OD):*?d??*= 24.3, 30.6, 31.7 (*t*, *J* = 4.2), 50.3, 51.9,

52.0, 69.5, 69.6, 112.3 (*dd*, *J* = 20.2 and 5.5), 112.5 (*t*, *J* = 18.4), 128.4, 128.5, 131.3 (*t*, *J* = 10.4), 147.0, 163.0 (*dd*, *J* = 249.8 and 7.6), 168.4, 176.7, 179.3. ^{19}F NMR (282 MHz, CD_3OD + $CFCl_3$):*?d* = -113.3 (m). HRMS: calcd for $C_{23}H_{23}F_2N_4O_2$ $[MH]^+$, 425.1789; found 425.1781.

(3a*SR*,4*RS*,8a*SR*,8b*RS*)-4-(2-(3,4-Difluorobenzyl)-1,3-dioxodecahydropyrrolo[3,4-*a*]pyrrolizin-4-yl)benzamidine Hydrochloride ((±)-4g). Compound (±)-**4g** was synthesized according to the procedure described for compound (±)-**4d**. Yield: 103 mg (75%, colorless solid). M.p. > 180 °C (dec.). IR (KBr): 3354, 3126, 1774, 1699, 1613, 1519, 1486, 1439, 1401, 1342, 1285, 1210, 1176, 1118. ^{1}H NMR (300 MHz, CD_3OD):*?d?*= 1.74-1.92 (*m*, 2H, H-C(7), H-C(8)), 2.00-2.20 (*m*, 2H, H-C(7), H-C(8)), 2.58-2.69 (*m*, 1H, H-C(6)), 2.83-2.94 (*m*, 1H, H-C(6)), 3.48 (*d*, *J* = 8.1, 1H, H-C(8b)), 3.69 (*m*, 2H, H-C(3a) and H-C(8b)), 4.32 (*d*, *J* = 8.7, 1H, H-C(4)), 4.45 and 4.51 (*AB*, *J* = 14.7, 2H, CHH'-N(5)), 7.04-7.28 (*m*, 3H, Ar(F)), 7.48, 7.67 (*AA′BB′*, *J* = 8.4, 4H, Ar). ^{13}C NMR (75 MHz, CD_3OD):*?d??*= 24.2, 30.5, 42.1, 50.3, 51.9, 52.0, 69.3, 69.5, 118.3 (*d*, *J* = 18.3), 125.9 (*dd*, *J* = 6.7 and 3.6), 128.3, 128.4, 130.2, 134.6 (*dd*, *J* = 5.5 and 4.3), 146.7, 150.9 (*dd*, *J* = 246.0 and 14.0), 151.1 (*dd*, *J* = 246.6 and 12.8), 168.0, 176.9, 179.7. ^{19}F NMR (282 MHz, CD_3OD + $CFCl_3$):*?d??*= -137.5 (*ddd*, *J* = 22.6, 9.6 and 7.6, 1F), -137.8 (*m*, 1F). HRMS: calcd for $C_{23}H_{23}F_2N_4O_2$ $[MH]^+$, 425.1789; found 425.1559.

(3a*SR*,4*RS*,8a*SR*,8b*RS*)-4-(2-(3,5-Difluorobenzyl)-1,3-dioxodecahydropyrrolo[3,4-*a*]pyrrolizin-4-yl)benzamidine Hydrochloride ((±)-**4h**). Compound ((±)-**4h** was synthesized according to the procedure described for compound (±)-**4d**. Yield: 56 mg (40%, colorless solid). M.p. > 150 °C. IR (KBr): 3383, 3096, 1772, 1700, 1675, 1624, 1598, 1487, 1465, 1430, 1399, 1343, 1176. ^{1}H NMR (300 MHz, CD_3OD):*?d??*= 1.73-1.90 (*m*, 2H), 2.00-2.20 (*m*, 2H), 2.59-2.70 (*m*, 1H, H-

C(6)), 2.84-2.96 (*m*, 1H, H-C(6)), 3.49 (*d*, *J* = 8.1, 1H, H-C(8b)), 3.70-3.81 (m, 2H, H-C(3a) and H-C(8a)), 4.33 (*d*, *J* = 8.7, 1H, H-C(4)), 4.47 and 4.54 (*AB*, *J* = 15.0, 2H, CHH'-N(5)), 6.80-6.94 (*m*, 3H, Ar-F)), 7.50, 7.66 (*AA′BB′*, *J* = 8.3, 4H, Ar). ^{13}C NMR (75 MHz, CD_3OD):*?d??*= 24.2, 30.5, 42,3, 50.3, 51.9, 52.0, 69.3, 69.6, 103.8 (*t*, *J* = 25.4), 111.9 (*dd*, *J* = 18.0 and 7.9), 128.4, 128.5, 130.1, 141.4 (*t*, *J* = 9.2), 146.7, 164.3 (*dd*, *J* = 247.2 and 12.2), 168.1, 176.9, 179.7. ^{19}F NMR (282 MHz, CD_3OD + $CFCl_3$):*d?*= -109.0 (*t*, *J* = 8.6). HRMS: calcd for $C_{23}H_{23}F_2N_4O_2$ $[MH]^+$, 425.1789; found 425.1780.

(3a*SR*,4*RS*,8a*SR*,8b*RS*)-4-(2-(2,3,4,5,6-Pentafluorobenzyl)-1,3-dioxodecahydro-pyrrolo[3,4-*a*]pyrrolizin-4-yl)benzamidine Hydrochloride ((±)-4i). Compound ((±)-**4i** was synthesized according to the procedure described for compound (±)-**4d**. Yield: 111 mg (73%, colorless needles). M.p. > 220 °C (dec., Et_2O/EtOH). IR (KBr): 3356, 3060, 1775, 1713, 1674, 1520, 1511, 1506, 1490, 1395, 1345, 1178. ^{1}H NMR (300 MHz, CD_3OD):*d* = 1.70-1.90 (*m*, 2H), 2.00-2.18 (*m*, 2H), 2.58-2.68 (*m*, 1H, H-C(6)), 2.84-2.95 (*m*, 1H, H-C(6)), 3.45 (dd, *J* = 8.1 and 0.9, 1H, H-C(8b)), 3.66-3.75 (*m*, 2H, H-C(3a) and H-C(8a)), 4.31 (*d*, *J* = 8.7, 1H, H-C(4)), 4.58 and 4.65 (*AB*, *J* = 14.7, 2H, CHH'-N(5)), 7.52, 7.66 (*AA′BB′*, *J* = 8.3, 4H, Ar). ^{13}C NMR (75 MHz, CD_3OD):*d?* = 24.3, 30.6, 31.2, 50.3, 51.9, 52.0, 69.3, 69.4, 110.7 (*tt*, J, *J* = 18.2 and 4.3), 128.4, 130.0, 146.6, 168.0, 176.1, 178.8. ^{19}F NMR (282 MHz, CD_3OD + $CFCl_3$):*?d??*= -140.0 (*dd*, *J* = 21.4 and 7.3, 2F), -155.3 (*t*, *J* = 20.3, 1F), -162.8 (m, 2F). HRMS: calcd for $C_{23}H_{20}F_5N_4O_2$ $[MH]^+$, 479.1506; found 479.1493.

(3a*SR*,4*RS*,8a*SR*,8b*RS*)-4-(2-(4-Chlorobenzyl)-1,3-dioxodecahydropyrrolo[3,4-*a*]pyrrolizin-4-yl)benzamidine Hydrochloride ((±)-4j). Compound (±)-**4j** was synthesized according to the procedure described for compound (±)-**4d**.

Yield: 61 mg (53%, colorless solid). M.p. > 165 °C (dec.). IR (KBr): 3349, 3104, 1773, 1703, 1675, 1613, 1536, 1492, 1431, 1400, 1343, 1174. ^{1}H NMR (300 MHz, CD_3OD): *?d?*= 1.72-1.90 (*m*, 2H), 2.00-2.18 (*m*, 2H), 2.56-2.67 (*m*, 1H, H-C(6)), 2.81-2.93 (*m*, 1H, H-C(6)), 3.47 (*d*, *J* = 8.1, 1H, H-C(8b)), 3.69-3.79 (m, 2H, H-C(3a) and H-C(8a)), 4.30 (*d*, *J* = 8.7, 1H, H-C(4)), 4.45 and 4.52 (*AB*, *J* = 14.4, 2H, CHH'-N(5)), 7.22 and 7.32 (*AA'BB'*, *J* = 8.4, 4H, Ar(Cl)), 7.45, 7.63 (*AA'BB'*, *J* = 8.7, 4H, Ar). ^{13}C NMR (75 MHz, CD_3OD): *?d?*= 24.3, 30.5, 42.5, 50.4, 51.9, 52.0, 69.4, 69.5, 128.3, 128.4, 129.5, 130.2, 130.9, 134.5, 135.9, 146.8, 168.0, 177.0, 179.8. HRMS: calcd for $C_{23}H_{24}ClN_4O_2$ $[MH]^+$, 425.1789; found 425.1794.

***N*-(4-Fluorobenzyl)maleimide (6)**. Compound **6** was synthesized from (4-fluorobenzyl)amine (12.8 g, 102 mmol) maleic anhydride (10.0 g, 102 mmol) according to a literature procedure for the corresponding benzyl derivative.[9] Yield: 8.9 g (42%, colorless crystals). M.p. 88-89 °C. IR (KBr): 1699, 1602, 1511, 1436, 1408, 1350, 1222, 1158, 1140. ^{1}H NMR (300 MHz, $CDCl_3$): *?d?*= 4.64 (s, 2H, NCH_2), 6.71 (s, 2H, CHCH), 6.94-7.03 (m, 2H, Ar), 7.29-7.36 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): *?d* = 40.7, 115.4 (*d*, *J* = 21.9), 130.2 (*d*, *J* = 8.5), 131.9 (*d*, *J* = 3.7), 134.0, 162.1 (*d*, *J* = 245.0), 170.1. ^{19}F NMR (282 MHz, $CDCl_3$ + $CFCl_3$): *?d?*= -113.9 (*m*). MS: calcd for $C_{11}H_8FNO_2$ $[M]^+$, 205.05; found 204.96. X-ray.

References

[1] a) U. Obst, D. W. Banner, L. Weber, F. Diederich, *Chem. Biol.* **1997**, *4*, 287-295; b) U. Obst, P. Betschmann, C. Lerner, P. Seiler, F. Diederich, V. Gramlich, L. Weber, D. W. Banner, P. Schönholzer, *Helv. Chim. Acta* **2000**, *83*, 855-909;

[2] The H positions were obtained from X-ray crystal structure refinement in which the C-H distances are characteristically too short (~ 0.1 Å). As a result the distances $d_{F\cdots H\text{-}Y}$ in the table are too long.

[3] X-ray crystal data for (±)-**1a** at 295 K ($C_{16}H_{15}N_3O_2$, M_r = 281.31): Monoclinic, space group $P2_1/c$, D_c= 1.340 g cm^{-3}, Z = 4, a = 9.305(2), b = 16.216(4), c = 9.240(2) Å, b = 90.83(2), V = 1394.1(5) Å^3. Nonius CAD4 diffractometer, CuK_α radiation, l = 1.5418 Å. A single crystal with linear dimensions of ca. 0.25 x 0.22 x 0.20 mm, which crystallized out from EtOAc/Et_2O after CC was used. The structure was solved by direct methods[10] and refined by full-matrix least-squares analysis[11] including an isotropic extincton correction. All heavy atoms were refined anisotropically (H-atoms isotropic, whereby H-positions are based on stereochemical considerations). Final $R(F)$ = 0.0383, $wR(F^2)$= 0.1112 for 206 parameters and 1972 reflections with $I > 2\sigma(I)$ and q < 66.91°. CCDC-226080.

[4] X-ray crystal data for (±)-**2a** at 295 K ($C_{16}H_{15}N_3O_2$, M_r = 281.31): Monoclinic space group $P2_1/c$, D_c= 1.356 g cm^{-3}, Z = 4, a = 5.073 (1), b = 13.424(2), c = 20.244(5) Å, b = 92.12(2), V = 1377.7(5) Å^3. Nonius CAD4 diffractometer, CuK_α radiation, l = 1.5418 Å. A single crystal with linear dimensions of ca. 0.32 x 0.30 x 0.27 mm, which crystallized out from EtOAc/Et_2O after CC was used. The structure was solved by direct methods[10] and refined by full-matrix least-squares analysis[11] including an isotropic extinction correction. All heavy atoms were refined anisotropically (H-atoms isotropic, whereby H-positions are based on stereochemical considerations). Final $R(F)$ = 0.0388, $wR(F^2)$= 0.1093 for 206 parameters and 2245 reflections with $I > 2\sigma(I)$ and q < 66.95°. CCDC-226079.

[5] X-ray crystal data for (±)-**3g** at 173 K ($C_{23}H_{19}F_2N_3O_2$, M_r = 407.41): Monoclinic, space group $P\bar{1}$, D_c= 1.416 g cm^{-3}, Z = 2, a = 9.4643(2), b = 10.2137(2), c = 11.1334(4) Å, a = 94.110 (1), b = 94.603 (1), g = 116.206(1) °, V = 955.55(4) Å^3. Bruker-Nonius Kappa-CCD diffractometer, MoK_α radiation, l = 0.7107 Å. A single crystal with linear dimensions of ca. 0.25 x 0.25 x 0.20 mm, grown by vapor phase diffusion of hexane into an EtOAc solution at r.t. was used. The structure was solved by direct methods[10] and refined by full-matrix least-squares analysis[11] including an isotropic extincton correction. All heavy atoms were refined anisotropically (H-atoms isotropic, whereby H-positions are based on stereochemical considerations). Final $R(F)$ = 0.0400, $wR(F^2)$= 0.0978 for 291 parameters and 3584 reflections with $I > 2\sigma(I)$ and q < 27.44°. CCDC-226082.

[6] X-ray crystal data for (±)-**4b** at 203 K ($C_{23}H_{24}ClFN_4O_2$, 2 H_2O, M_r = 478.94): Monoclinic, space group $P2_1/c$, D_c= 1.372 g cm^{-3}, Z = 4, a = 15.9963(6), b = 14.4021(5), c = 10.0665(3) Å, b = 90.945 (1)°, V = 2318.81(14) Å^3. Bruker-Nonius Kappa-CCD diffractometer, MoK_α radiation, l = 0.7107 Å. A single crystal with linear dimensions of ca. 0.20 x 0.18 x 0.16 mm, grown by slow evaporation of a MeOH:CH_2Cl_2 solution at r.t. was used. The structure was solved by direct methods[10] and refined by full-matrix least-squares analysis[11] including an isotropic extincton correction. All heavy atoms were refined anisotropically (H-atoms isotropic, whereby H-positions are based on stereochemical considerations). Final $R(F)$ = 0.0771, $wR(F^2)$= 0.1896 for 323 parameters and 4499 reflections with $I > 2\sigma(I)$ and q < 26.04°. CCDC-226083.

[7] X-ray crystal data for (±)-**6** at 100 K ($C_{11}H_8FNO_2$, M_r = 205.18): Triclinic, space group $P\bar{1}$, D_c= 1.450 g cm^{-3}, Z = 6, a = 10.4112(2), b = 11.4529(3), c = 12.6696(3)

Å, a = 72.734 (1), b = 78.112 (1), g = 89.319(1) °, V = 1409.72(6) Å^3. Bruker-Nonius Kappa-CCD diffractometer, MoK_α radiation, l = 0.7107 Å. A single crystal with linear dimensions of ca. 0.20 x 0.18 x 0.16 mm, grown by slow evaporation of an EtOAc solution at r.t. was used. The structure was solved by direct methods[10] and refined by full-matrix least-squares analysis[11] including an isotropic extinction correction. All heavy atoms were refined anisotropically (H-atoms isotropic, whereby H-positions are based on stereochemical considerations). Final $R(F)$ = 0.0383 $wR(F^2)$= 0.0973 for 431 parameters and 5373 reflections with $I > 2\sigma(I)$ and q < 27.48°. CCDC-226082.

Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Center as supplementary publication with the CCDC number indicated in refs. [3-7]. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk.

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