Supporting Information

Novel Pyridyl or Isoquinolinyl Substituted Indolines and Indoles as Potent and Selective CYP11B2 Inhibitors

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Contents

***tert*-Butyl 5-bromo-2,3-dihydro-1*H*-indole-1-carboxylate (3c).** To a solution of 5-bromoindoline (1.20 g, 6.10 mmol) in anhydrous THF (20 mL) and water (20 mL) was added $NaHCO_3$ (1.53g, 18.2 mmol). After being cooled down to 0 °C, to the reaction mixture was added Boc_2O (2.59 mL, 12.1 mmol) dropwise, and stirred at the same temperature for 30 min. Afterwards, the reaction was warmed to room temperature and stirred for additional 5 h. The resulting mixture was separated and the aqueous layer was extracted with EtOAc (3 x 20 mL), dried over $MgSO_4$ and concentrated in vacuo to give a grey solid (2.85 g), which was directly used in next step without further purification.

***tert*-Butyl 5-pyridin-3-yl-2,3-dihydro-1*H*-indole-1-carboxylate (3b).** The title compound were synthesized according to Method A using crude **1c** (2.85 g), pyridin-3-ylboronic acid (0.98 g, 7.93 mmol), sodium carbonate (3.23 g, 30.5 mmol) and tetrakis(triphenylphosphine)palladium (0) (0.35 g, 0.30 mmol) in dimethoxyethane (30 mL) and water (10 mL). The crude product was purified by flash column chromatography on silica gel (EtOAc/n-hexane, 1:100 to 1:2) to yield colorless crystals (1.42 g, 78% for two steps). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.58 (s, 9H), 3.16 (t, J = 8.7 Hz, 2H), 4.04 (t, J = 7.9 Hz, 2H), 7.32 (dd, J = 4.9, 7.9 Hz, 1H), 7.38 (m, 2H), 7.74 (s, 1H), 7.83 (dt, J = 2.0, 7.9 Hz, 1H), 8.54 (dd, J = 1.5, 4.8 Hz, 1H), 8.81 (d, J = 2.2 Hz, 1H).

***tert*-Butyl 5-isoquinolin-4-yl-2,3-dihydro-1*H*-indole-1-carboxylate (13b).** The title compound were synthesized according to Method A using crude **13c** (1.61 g), isoquinoline-4-ylboronic acid (0.73 g, 4.24 mmol), sodium carbonate (1.87 g, 17.6 mmol) and tetrakis(triphenylphosphine)palladium (0) (0.20 g, 0.18 mmol) in dimethoxyethane (30 mL) and water (10 mL). The crude product was used directly to next step without further purification.

1-Acetyl-5-bromo-2,3-dihydro-1*H*-indole (17b). The title compound were synthesized according to Method C using 5-bromoindoline (1.80 g, 9.09 mmol), acyl chloride (0.62 mL, 10.9 mmol), pyridine (1.10 mL, 13.6 mmol) and anhydrous THF (35 mL) to yield the crude product as grey solids. The crude product was used directly to next step without further purification.

1-(Cyclopropylcarbonyl)-5-pyridin-3-yl-2,3-dihydro-1*H*-indole (5). The title compound was synthesized according to Method C using **3a** (100 mg, 0.51 mmol), cyclopropanecarbonyl chloride (56 μL, 0.61 mmol) and pyridine (62 μL, 0.77 mmol) in anhydrous THF (5 mL). The crude product underwent flash column chromatography twice gave pale yellow crystals (103 mg, 76%). mp 158–161 °C, R_f = 0.07 (EtOAc/n-hexane, 1:1). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.91 (m, 2H), 1.15 (m, 2H), 1.78 (s, br, 1H), 3.30 (t, J = 8.3 Hz, 2H), 4.33 (t, J = 8.3 Hz, 2H), 7.34 (dd, J = 4.8, 7.8 Hz, 1H), 7.40 (m, 2H), 7.85 (dt, J = 2.0, 7.8 Hz, 1H), 8.26 (s, br, 1H), 8.55 (d, J = 4.6 Hz,1H), 8.82 (d, J = 1.8 Hz, 1H).^{13}C-NMR (125 MHz, $CDCl_3$): δ 8.3, 13.6, 27.9, 48.3, 117.3, 123.1, 123.5, 126.6, 132.2, 132.8, 134.1, 136.4, 143.4, 147.8, 171.9. MS (ESI) m/z = 265 $[M+H]^+$.

1-(2-Methylpropanoyl)-5-pyridin-3-yl-2,3-dihydro-1*H*-indole (6). The title compound was synthesized according to Method C using **3a** (100 mg, 0.51 mmol), isobutyryl chloride (64 μL, 0.61 mmol) and pyridine (62 μL, 0.77 mmol) in anhydrous THF (5 mL). The crude product underwent flash column chromatography twice gave pale yellow crystals (90 mg, 66%). mp 135–137 °C, R_f = 0.08 (EtOAc/n-hexane, 1:1). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.25 (d, J = 6.7 Hz, 6H), 2.80 (m, 1H), 3.27 (t, J = 7.8 Hz, 2H), 4.19 (t, J = 8.5 Hz, 2H), 7.34 (dd, J = 4.9, 7.7 Hz, 1H), 7.42 (m, 2H), 7.85 (dt, J = 2.0, 7.9 Hz, 1H), 8.36 (d, J = 7.5 Hz, 1H), 8.55 (dd, J = 0.9, 4.5 Hz, 1H), 8.82 (d, J = 1.9 Hz, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 19.1, 28.0, 33.5, 48.1, 117.7, 123.0, 123.5, 126.6, 132.3, 132.3, 133.0, 134.1, 136.4, 143.5, 147.9, 175.8. MS (ESI) m/z = 267 $[M+H]^+$.

1-(3-Chloropropanoyl)-5-pyridin-3-yl-2,3-dihydro-1*H*-indole (7). The title compound was

synthesized according to Method C using **3a** (80 mg, 0.41 mmol), 3-chloropropanoyl chloride (48 µL, 0.49 mmol) and pyridine (50 µL, 0.62 mmol) in anhydrous THF (3 mL). After flash column chromatography, recrystallization from THF gave pale yellow needles (95 mg, 81%). mp 157–159 °C, R_f = 0.10 (EtOAc/n-hexane, 1:1). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.95 (t, *J* = 6.8 Hz, 2H), 3.30 (t, *J* = 8.5 Hz, 2H), 3.93 (t, *J* = 6.8 Hz, 2H), 4.15 (t, *J* = 8.5 Hz, 2H), 7.34 (dd, *J* = 4.8, 7.8 Hz, 1H), 7.44 (m, 2H), 7.84 (dt, *J* = 1.9, 7.8 Hz, 1H), 8.31 (d, *J* = 8.2 Hz, 1H), 8.56 (d, *J* = 4.5 Hz,1H), 8.82 (d, *J* = 1.9 Hz, 1H).^{13}C-NMR (125 MHz, $CDCl_3$): δ 28.0, 38.7, 39.2, 48.2, 117.5, 123.2, 123.5, 126.7, 132.2, 133.6, 134.0, 136.2, 142.7, 148.1, 148.2, 168.9. MS (ESI) *m/z* = 287 $[M]^+$.

1-[(4-Fluorophenyl)carbonyl]-5-pyridin-3-yl-2,3-dihydro-1*H*-indole (8). The title compound was synthesized according to Method C using **3a** (80 mg, 0.41 mmol), 4-fluorobenzoyl chloride (60 µL, 0.49 mmol) and pyridine (50 µL, 0.62 mmol) in anhydrous THF (3 mL). After flash column chromatography, recrystallization from THF gave pale yellow crystals (102 mg, 78%). mp 161–162 °C, R_f = 0.09 (EtOAc/n-hexane, 1:1). ^{1}H-NMR (500 MHz, DMSO-d_6, 300K): δ 3.16 (t, *J* = 8.3 Hz, 2H), 4.07 (t, *J* = 8.3 Hz, 2H), 7.34 (m, 2H), 7.46 (dd, *J* = 4.8, 8.0 Hz, 1H), 7.56 (s, br, 1H), 7.67 (d, *J* = 0.9 Hz,1H), 7.70 (m, 2H), 8.05 (d, *J* = 8.0 Hz, 1H), 8.53 (dd, *J* = 1.5, 4.7 Hz, 1H), 8.87 (d, *J* = 1.8 Hz,1H). ^{1}H-NMR (500 MHz, DMSO-d_6, 373K): δ 3.19 (t, *J* = 8.3 Hz, 2H), 4.08 (t, *J* = 8.3 Hz, 2H), 7.31 (m, 2H), 7.43 (dd, *J* = 4.7, 7.9 Hz, 1H), 7.51 (d, *J* = 8.3 Hz, 1H), 7.63 (s, 1H), 7.68 (m, 2H), 7.73 (s, br, 1H), 8.01 (dt, *J* = 1.9, 7.9 Hz, 1H), 8.53 (dd, *J* = 1.4, 4.7 Hz, 1H), 8.85 (d, *J* = 2.0 Hz, 1H). ^{13}C-NMR (125 MHz, DMSO-d_6): δ 27.7, 50.5, 115.5 (d, $^2J_{C,F}$ = 22.0 Hz), 116.8, 123.4, 123.8, 125.6, 129.7 (d, $^3J_{C,F}$ = 8.8 Hz), 132.5, 133.3, 133.6, 133.9, 135.2, 142.7, 147.3, 148.0, 163.0 (d, $^1J_{C,F}$ = 247 Hz), 167.2. MS (ESI) *m/z* = 319 $[M+H]^+$.

1-[(4-Methoxyphenyl)carbonyl]-5-pyridin-3-yl-2,3-dihydro-1*H*-indole (9). The title compound was synthesized according to Method C using **3a** (80 mg, 0.41 mmol), 4-methoxybenzoyl chloride (70 µL, 0.49 mmol) and pyridine (50 µL, 0.62 mmol) in anhydrous THF (3 mL). After flash column chromatography (MeOH/CH_2Cl_2, 0 to 1:100), recrystallization from THF gave colorless crystals (106 mg, 78%). mp 177–179 °C, R_f = 0.07 (EtOAc/n-hexane, 1:1). ^{1}H-NMR (500 MHz, DMSO-d_6, 300K): δ 3.16 (t, *J* = 8.3 Hz, 2H), 3.83 (s, 3H), 4.11 (t, *J* = 8.3 Hz, 2H), 7.04 (m, 2H), 7.45 (dd, *J* = 4.8, 7.9 Hz, 1H), 7.54 (d, *J* = 7.7 Hz, 1H), 7.60 (m, 2H), 7.66 (s, 1H), 8.04 (dt, *J* = 2.0, 8.0 Hz, 1H), 8.52 (dd, *J* = 1.5, 4.7 Hz, 1H), 8.87 (d, *J* = 2.0 Hz, 1H). ^{1}H-NMR (500 MHz, DMSO-d_6, 373K): δ 3.18 (t, *J* = 8.3 Hz, 2H), 3.86 (s, 3H), 4.12 (t, *J* = 8.3 Hz, 2H), 7.04 (m, 2H), 7.42 (dd, *J* = 4.7, 7.9 Hz, 1H), 7.47 (dd, *J* = 1.7, 8.3 Hz, 1H), 7.57 (m, 2H), 7.60 (d, *J* = 0.9 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.98 (dt, *J* = 2.0, 7.9 Hz, 1H), 8.52 (dd, *J* = 1.5, 4.7 Hz, 1H), 8.84 (d, *J* = 2.4 Hz, 1H).^{13}C-NMR (125 MHz, $CDCl_3$): δ 28.2, 50.9, 55.4, 113.8, 117.2, 123.5, 126.3, 128.8, 129.4, 132.1, 133.3, 133.5, 133.9, 136.3, 143.1, 148.1, 148.2, 161.5, 168.9. MS (ESI) *m/z* = 331 $[M+H]^+$.

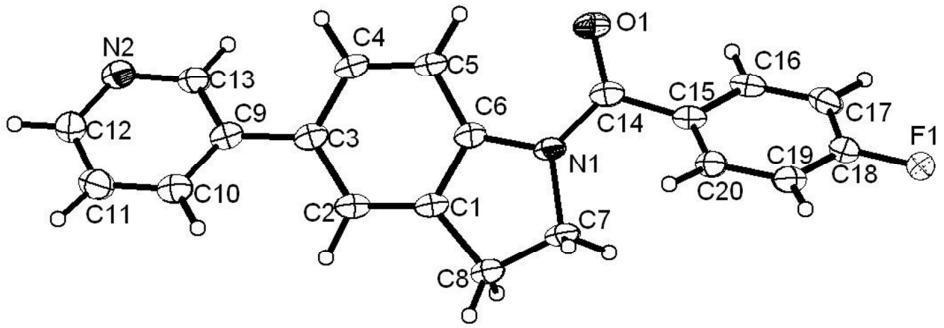
(3-Methoxyphenyl)(5-(pyridin-3-yl)indolin-1-yl)methanone (10). Synthesized using compound **3a** (130 mg, 0.66 mmol), 3-methoxybenzoyl chloride (0.28 mL, 1.99 mmol) and NaOH (66.0 mg, 1.65 mmol) according to Method B. Crude product was purified by flash chromatography on silica gel using a mixture of hexane/ethyl acetate (2:1) as eluent. White solid. Yield: 25 mg, 11%. Mp: 124–126 °C. ^{1}H NMR (DMSO-d_6, 500 MHz, 373K): δ_H (ppm) = 3.19 (t, *J* = 8.4 Hz, 2H), 3.84 (s, 3 H), 4.08 (t, *J* = 8.4 Hz, 2H), 7.07–7.11 (m, 1H), 7.11–7.16 (m, 2H), 7.38–7.45 (m, 2H), 7.48 (dd, *J* = 1.3, 8.5 Hz, 1H), 7.60 (s, 1H), 7.70 (d, *J* = 8.5 Hz, 1H), 7.99 (dt, *J* = 2.0, 8.0 Hz, 1H), 8.52 (dd, *J* = 1.3, 4.7 Hz, 1H), 8.85 (d, *J* = 2.2 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz, 373K): δ_C (ppm) = 27.6, 50.3, 55.5, 112.7, 116.1, 116.5, 119.0, 123.3, 123.5, 125.6, 129.7, 132.7, 133.5, 133.8, 135.5, 138.5, 142.9, 147.9, 147.9, 159.6, 167.9; MS (ESI): *m/z* = 331 $[M+H]^+$.

1-(Penylacetyl)-5-pyridin-3-yl-2,3-dihydro-1*H*-indole (11). The title compound was synthesized according to Method C using **3a** (80 mg, 0.41 mmol), phenylacetyl chloride (70 µL, 0.49 mmol) and pyridine (50 µL, 0.62 mmol) in anhydrous THF (3 mL). After flash column chromatography ($MeOH/CH_2Cl_2$, 0 to 1:100), recrystallization from THF gave pale yellow crystals (110 mg, 85%). mp 125–127 °C, R_f = 0.08 (EtOAc/n-hexane, 1:1). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.24 (t, *J* = 8.5 Hz, 2H), 3.84 (s, 2H), 4.13 (t, *J* = 8.5 Hz, 2H), 7.28 (m, 1H), 7.34 (m, 5H), 7.39 (s, 1H), 7.42 (d, *J* = 8.5 Hz,1H), 7.83 (dt, *J* = 1.8, 7.9 Hz, 1H), 8.36 (d, *J* = 8.4 Hz, 1H), 8.55 (d, *J* = 1.3, 4.7 Hz, 1H), 8.81 (d, *J* = 2.1 Hz, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 28.0, 43.5, 48.4, 117.6, 123.1, 123.5, 126.7, 127.1, 128.8, 129.0, 132.2, 133.4, 134.0, 134.0, 136.3, 143.2, 148.0, 148.1, 169.2. MS (ESI) *m/z* = 315 $[M+H]^+$.

5-Pyridin-3-yl-1-(thiophen-2-ylcarbonyl)-2,3-dihydro-1*H*-indole (12). The title compound was synthesized according to Method C using **3a** (80 mg, 0.41 mmol), thiophene-2-carbonyl chloride (50 µL, 0.49 mmol) and pyridine (50 µL, 0.62 mmol) in anhydrous THF (3 mL). Purification by flash column chromatography ($MeOH/CH_2Cl_2$, 0 to 1:100) gave pale yellow solids (101 mg, 80%). mp 160–162 °C, R_f = 0.08 (EtOAc/n-hexane, 1:1). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.30 (t, *J* = 8.3 Hz, 2H), 4.45 (t, *J* = 8.3 Hz, 2H), 7.13 (t, *J* = 8.3 Hz, 1H), 7.34 (dd, *J* = 4.8, 7.9 Hz, 1H), 7.44 (m, 2H), 7.56 (dd, *J* = 0.9, 5.0 Hz, 1H), 7.62 (dd, *J* = 0.8, 3.7 Hz, 1H), 7.83 (dt, *J* = 2.0, 7.9 Hz, 1H), 8.18 (s, br, 1H), 8.56 (dd, *J* = 1.5, 4.8 Hz, 1H), 8.83 (d, *J* = 2.0 Hz, 1H).^{13}C-NMR (125 MHz, $CDCl_3$): δ 28.7, 50.8, 118.2, 123.2, 123.5, 126.6, 127.3, 130.0, 130.4, 132.9, 133.8, 134.0, 136.2, 139.2, 143.3, 148.1, 148.2, 161.5. MS (ESI) *m/z* = 307 $[M+H]^+$.

X-ray crystal structure data:

Compound **8**:



Crystal data and structure refinement.		
Empirical formula	$C_{20}H_{15}FN_2O$	
Formula weight	318.34	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 9.3874(5) Å	□ α = 101.696(3)°.
	b = 11.5729(6) Å	□ β = 102.001(3)°.
	c = 16.2624(11) Å	□ γ = 111.851(2)°.
Volume	1525.71(15) $Å^3$	
Z	4	
Density (calculated)	1.386 mg/m^3	
Absorption coefficient	0.095 mm^{-1}	
F(000)	664	
Crystal size	0.43 x 0.38 x 0.25 mm^3	
Theta range for data collection	1.35 to 27.37°.	
Index ranges	-12<=h<=12, -14<=k<=14, -19<=l<=20	
Reflections collected	24262	
Independent reflections	6722 [R(int) = 0.0407]	
Completeness to theta = 27.37°	97.4 %	
Absorption correction	Multiscan	
Max. and min. transmission	0.9768 and 0.9600	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6722 / 0 / 553	

Goodness-of-fit on F^2	1.067
Final R indices [I>2sigma(I)]	R1 = 0.0505, wR2 = 0.1410
R indices (all data)	R1 = 0.0687, wR2 = 0.1547
Largest diff. peak and hole	0.332 and -0.276 e.$Å^{-3}$

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for Compound **8**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N(1)	4623(2)	6365(1)	1256(1)	27(1)
N(2)	6959(2)	488(2)	933(1)	35(1)
O(1)	1972(2)	5173(1)	1066(1)	37(1)
F(1)	1461(2)	10378(1)	948(1)	44(1)
C(1)	6629(2)	5696(2)	1180(1)	26(1)
C(2)	7356(2)	4860(2)	1197(1)	29(1)
C(3)	6564(2)	3647(2)	1326(1)	27(1)
C(4)	5040(2)	3331(2)	1443(1)	30(1)
C(5)	4300(2)	4162(2)	1436(1)	30(1)
C(6)	5109(2)	5352(2)	1297(1)	26(1)
C(7)	5994(3)	7516(2)	1214(2)	38(1)
C(8)	7195(2)	7000(2)	1016(2)	33(1)
C(9)	7307(2)	2728(2)	1340(1)	28(1)
C(10)	8952(2)	3148(2)	1755(1)	32(1)
C(11)	9571(3)	2242(2)	1763(1)	36(1)
C(12)	8537(3)	927(2)	1355(2)	35(1)
C(13)	6382(2)	1381(2)	931(1)	30(1)
C(14)	3077(2)	6224(2)	1132(1)	27(1)
C(15)	2732(2)	7371(2)	1090(1)	26(1)
C(16)	1287(2)	7138(2)	478(1)	29(1)
C(17)	848(2)	8136(2)	425(1)	31(1)
C(18)	1867(2)	9384(2)	1001(1)	31(1)
C(19)	3264(2)	9647(2)	1631(1)	30(1)
C(20)	3706(2)	8641(2)	1673(1)	28(1)
N(3)	3263(2)	5050(2)	3730(1)	26(1)
N(4)	6053(2)	-466(2)	4145(1)	37(1)
O(2)	975(2)	4146(1)	4091(1)	35(1)
F(2)	157(2)	9095(2)	3526(1)	60(1)
C(21)	5390(2)	4486(2)	3809(1)	25(1)
C(22)	6131(2)	3664(2)	3813(1)	26(1)
C(23)	5251(2)	2355(2)	3762(1)	25(1)
C(24)	3615(2)	1931(2)	3712(1)	28(1)
C(25)	2853(2)	2750(2)	3709(1)	28(1)
C(26)	3763(2)	4043(2)	3755(1)	25(1)
C(27)	4599(2)	6193(2)	3651(2)	33(1)
C(28)	6085(2)	5919(2)	3874(1)	30(1)
C(29)	6001(2)	1435(2)	3757(1)	25(1)

C(30)	7244(2)	1514(2)	3395(1)	29(1)
C(31)	7867(2)	610(2)	3413(1)	32(1)
C(32)	7237(3)	-364(2)	3788(1)	34(1)
C(33)	5470(2)	420(2)	4126(1)	31(1)
C(34)	1881(2)	5042(2)	3884(1)	26(1)
C(35)	1474(2)	6149(2)	3780(1)	27(1)
C(36)	805(2)	6622(2)	4378(1)	30(1)
C(37)	365(2)	7618(2)	4301(2)	35(1)
C(38)	578(2)	8106(2)	3605(2)	38(1)
C(39)	1161(2)	7628(2)	2982(2)	38(1)
C(40)	1631(2)	6651(2)	3076(1)	31(1)

Bond lengths [Å] and angles [°] for Compound **8**.

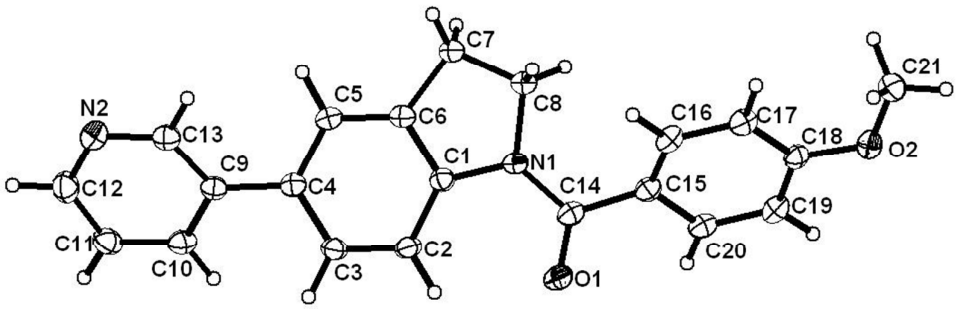
N(1)-C(14)	1.364(2)
N(1)-C(6)	1.416(2)
N(1)-C(7)	1.495(2)
N(2)-C(13)	1.333(3)
N(2)-C(12)	1.342(3)
O(1)-C(14)	1.236(2)
F(1)-C(18)	1.353(2)
C(1)-C(2)	1.377(3)
C(1)-C(6)	1.396(3)
C(1)-C(8)	1.502(3)
C(2)-C(3)	1.404(3)
C(3)-C(4)	1.403(3)
C(3)-C(9)	1.474(3)
C(4)-C(5)	1.381(3)
C(5)-C(6)	1.394(2)
C(7)-C(8)	1.519(3)
C(9)-C(10)	1.397(3)
C(9)-C(13)	1.400(3)
C(10)-C(11)	1.375(3)
C(11)-C(12)	1.386(3)
C(14)-C(15)	1.491(3)
C(15)-C(16)	1.400(3)
C(15)-C(20)	1.403(3)
C(16)-C(17)	1.376(3)
C(17)-C(18)	1.389(3)
C(18)-C(19)	1.372(3)
C(19)-C(20)	1.383(3)
N(3)-C(34)	1.369(2)
N(3)-C(26)	1.414(2)
N(3)-C(27)	1.497(2)
N(4)-C(33)	1.332(3)
N(4)-C(32)	1.335(3)

O(2)-C(34)	1.231(2)
F(2)-C(38)	1.363(2)
C(21)-C(22)	1.372(3)
C(21)-C(26)	1.395(2)
C(21)-C(28)	1.510(2)
C(22)-C(23)	1.405(2)
C(23)-C(24)	1.406(3)
C(23)-C(29)	1.478(3)
C(24)-C(25)	1.384(3)
C(25)-C(26)	1.397(2)
C(27)-C(28)	1.532(3)
C(29)-C(30)	1.394(3)
C(29)-C(33)	1.402(3)
C(30)-C(31)	1.377(3)
C(31)-C(32)	1.387(3)
C(34)-C(35)	1.496(3)
C(35)-C(36)	1.391(3)
C(35)-C(40)	1.394(3)
C(36)-C(37)	1.381(3)
C(37)-C(38)	1.381(3)
C(38)-C(39)	1.364(3)
C(39)-C(40)	1.382(3)
C(14)-N(1)-C(6)	124.57(15)
C(14)-N(1)-C(7)	125.66(16)
C(6)-N(1)-C(7)	109.00(15)
C(13)-N(2)-C(12)	116.98(18)
C(2)-C(1)-C(6)	120.45(16)
C(2)-C(1)-C(8)	129.73(17)
C(6)-C(1)-C(8)	109.78(17)
C(1)-C(2)-C(3)	120.02(17)
C(4)-C(3)-C(2)	118.19(18)
C(4)-C(3)-C(9)	120.56(16)
C(2)-C(3)-C(9)	121.25(17)
C(5)-C(4)-C(3)	122.55(17)
C(4)-C(5)-C(6)	117.87(18)
C(5)-C(6)-C(1)	120.90(18)
C(5)-C(6)-N(1)	129.16(17)
C(1)-C(6)-N(1)	109.94(15)
N(1)-C(7)-C(8)	104.94(16)
C(1)-C(8)-C(7)	104.40(16)
C(10)-C(9)-C(13)	116.68(19)
C(10)-C(9)-C(3)	122.29(17)
C(13)-C(9)-C(3)	121.03(17)
C(11)-C(10)-C(9)	119.69(19)
C(10)-C(11)-C(12)	118.8(2)
N(2)-C(12)-C(11)	123.3(2)
N(2)-C(13)-C(9)	124.52(19)

O(1)-C(14)-N(1)	121.32(18)
O(1)-C(14)-C(15)	119.80(17)
N(1)-C(14)-C(15)	118.87(15)
C(16)-C(15)-C(20)	118.67(18)
C(16)-C(15)-C(14)	117.52(17)
C(20)-C(15)-C(14)	123.60(17)
C(17)-C(16)-C(15)	121.03(18)
C(16)-C(17)-C(18)	118.38(18)
F(1)-C(18)-C(19)	118.55(18)
F(1)-C(18)-C(17)	118.98(18)
C(19)-C(18)-C(17)	122.47(19)
C(18)-C(19)-C(20)	118.77(18)
C(19)-C(20)-C(15)	120.62(18)
C(34)-N(3)-C(26)	124.77(15)
C(34)-N(3)-C(27)	125.69(16)
C(26)-N(3)-C(27)	108.89(15)
C(33)-N(4)-C(32)	116.96(17)
C(22)-C(21)-C(26)	120.94(16)
C(22)-C(21)-C(28)	129.56(17)
C(26)-C(21)-C(28)	109.48(16)
C(21)-C(22)-C(23)	120.07(17)
C(22)-C(23)-C(24)	118.01(17)
C(22)-C(23)-C(29)	121.73(16)
C(24)-C(23)-C(29)	120.26(16)
C(25)-C(24)-C(23)	122.54(17)
C(24)-C(25)-C(26)	117.86(17)
C(21)-C(26)-C(25)	120.58(17)
C(21)-C(26)-N(3)	110.51(15)
C(25)-C(26)-N(3)	128.88(17)
N(3)-C(27)-C(28)	104.69(15)
C(21)-C(28)-C(27)	103.94(15)
C(30)-C(29)-C(33)	116.46(18)
C(30)-C(29)-C(23)	123.27(16)
C(33)-C(29)-C(23)	120.27(17)
C(31)-C(30)-C(29)	119.49(17)
C(30)-C(31)-C(32)	119.14(19)
N(4)-C(32)-C(31)	123.1(2)
N(4)-C(33)-C(29)	124.83(19)
O(2)-C(34)-N(3)	121.54(18)
O(2)-C(34)-C(35)	120.30(17)
N(3)-C(34)-C(35)	118.14(15)
C(36)-C(35)-C(40)	119.28(19)
C(36)-C(35)-C(34)	117.87(17)
C(40)-C(35)-C(34)	122.68(17)
C(37)-C(36)-C(35)	120.55(19)
C(36)-C(37)-C(38)	118.1(2)
F(2)-C(38)-C(39)	118.3(2)

F(2)-C(38)-C(37)	118.5(2)
C(39)-C(38)-C(37)	123.1(2)
C(38)-C(39)-C(40)	118.3(2)
C(39)-C(40)-C(35)	120.6(2)

Compound **9**:



Crystal data and structure refinement.		
Empirical formula	$C_{21}H_{18}N_2O_2$	
Formula weight	330.37	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 19.5025(4) Å	α = 90°.
	b = 11.0639(2) Å	β = 109.506(2)°.
	c = 15.5364(4) Å	γ = 90°.
Volume	3159.94(12) $Å^3$	
Z	8	
Density (calculated)	1.389 mg/m^3	
Absorption coefficient	0.090 mm^{-1}	
F(000)	1392	
Crystal size	0.30 x 0.25 x 0.13 mm^3	
Theta range for data collection	2.15 to 27.90°.	
Index ranges	-18<=h<=25, -14<=k<=14, -20<=l<=20	
Reflections collected	15711	
Independent reflections	3782 [R(int) = 0.0356]	
Completeness to theta = 27.90°	99.8 %	
Absorption correction	Multiscan	
Max. and min. transmission	0.9883 and 0.9731	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3782 / 0 / 298	

Goodness-of-fit on F^2	1.029
Final R indices [I>2sigma(I)]	R1 = 0.0377, wR2 = 0.0887
R indices (all data)	R1 = 0.0547, wR2 = 0.0973
Largest diff. peak and hole	0.255 and -0.200 e.$Å^{-3}$

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for Compound **9**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N(1)	4633(1)	9286(1)	3532(1)	22(1)
N(2)	8676(1)	11194(1)	5779(1)	29(1)
O(1)	4446(1)	7294(1)	3703(1)	34(1)
O(2)	1150(1)	8388(1)	1616(1)	29(1)
C(1)	5388(1)	9273(1)	4038(1)	20(1)
C(2)	5856(1)	8296(1)	4337(1)	23(1)
C(3)	6576(1)	8530(1)	4856(1)	22(1)
C(4)	6842(1)	9706(1)	5066(1)	20(1)
C(5)	6360(1)	10674(1)	4748(1)	21(1)
C(6)	5640(1)	10454(1)	4246(1)	20(1)
C(7)	5028(1)	11342(1)	3895(1)	23(1)
C(8)	4386(1)	10561(1)	3327(1)	25(1)
C(9)	7619(1)	9933(1)	5585(1)	21(1)
C(10)	8033(1)	9186(1)	6292(1)	25(1)
C(11)	8758(1)	9456(1)	6732(1)	29(1)
C(12)	9055(1)	10457(1)	6455(1)	31(1)
C(13)	7977(1)	10918(1)	5368(1)	24(1)
C(14)	4194(1)	8286(1)	3401(1)	23(1)
C(15)	3397(1)	8411(1)	2902(1)	22(1)
C(16)	3085(1)	9146(1)	2147(1)	24(1)
C(17)	2338(1)	9163(1)	1699(1)	25(1)
C(18)	1887(1)	8434(1)	2005(1)	23(1)
C(19)	2194(1)	7672(1)	2753(1)	25(1)
C(20)	2936(1)	7656(1)	3184(1)	24(1)
C(21)	819(1)	9208(1)	877(1)	33(1)

Bond lengths [Å] and angles [°] for Compound **9**.

N(1)-C(14)	1.3726(15)
N(1)-C(1)	1.4184(15)
N(1)-C(8)	1.4907(15)
N(2)-C(13)	1.3343(16)
N(2)-C(12)	1.3394(18)
O(1)-C(14)	1.2295(15)
O(2)-C(18)	1.3614(15)
O(2)-C(21)	1.4360(17)

C(1)-C(2)	1.3906(17)
C(1)-C(6)	1.3953(16)
C(2)-C(3)	1.3905(18)
C(3)-C(4)	1.3986(17)
C(4)-C(5)	1.4022(17)
C(4)-C(9)	1.4808(17)
C(5)-C(6)	1.3796(17)
C(6)-C(7)	1.5018(17)
C(7)-C(8)	1.5337(18)
C(9)-C(13)	1.3944(17)
C(9)-C(10)	1.3952(17)
C(10)-C(11)	1.3817(18)
C(11)-C(12)	1.384(2)
C(14)-C(15)	1.4939(17)
C(15)-C(16)	1.3890(17)
C(15)-C(20)	1.3999(17)
C(16)-C(17)	1.3885(18)
C(17)-C(18)	1.3895(18)
C(18)-C(19)	1.3981(18)
C(19)-C(20)	1.3773(18)
C(14)-N(1)-C(1)	123.70(10)
C(14)-N(1)-C(8)	126.22(10)
C(1)-N(1)-C(8)	109.19(9)
C(13)-N(2)-C(12)	116.34(12)
C(18)-O(2)-C(21)	117.26(10)
C(2)-C(1)-C(6)	120.55(11)
C(2)-C(1)-N(1)	129.54(11)
C(6)-C(1)-N(1)	109.89(10)
C(3)-C(2)-C(1)	118.17(11)
C(2)-C(3)-C(4)	122.24(11)
C(3)-C(4)-C(5)	118.30(11)
C(3)-C(4)-C(9)	121.16(11)
C(5)-C(4)-C(9)	120.51(11)
C(6)-C(5)-C(4)	120.05(11)
C(5)-C(6)-C(1)	120.67(11)
C(5)-C(6)-C(7)	128.68(11)
C(1)-C(6)-C(7)	110.58(11)
C(6)-C(7)-C(8)	103.75(10)
N(1)-C(8)-C(7)	105.50(10)
C(13)-C(9)-C(10)	116.65(11)
C(13)-C(9)-C(4)	120.23(11)
C(10)-C(9)-C(4)	123.11(11)
C(11)-C(10)-C(9)	119.30(12)
C(10)-C(11)-C(12)	118.92(12)
N(2)-C(12)-C(11)	123.57(13)
N(2)-C(13)-C(9)	125.22(12)
O(1)-C(14)-N(1)	120.81(11)

O(1)-C(14)-C(15)	119.73(11)
N(1)-C(14)-C(15)	119.45(11)
C(16)-C(15)-C(20)	117.90(11)
C(16)-C(15)-C(14)	125.38(11)
C(20)-C(15)-C(14)	116.54(11)
C(17)-C(16)-C(15)	121.43(12)
C(16)-C(17)-C(18)	119.88(12)
O(2)-C(18)-C(17)	124.38(11)
O(2)-C(18)-C(19)	116.24(11)
C(17)-C(18)-C(19)	119.38(12)
C(20)-C(19)-C(18)	120.02(12)
C(19)-C(20)-C(15)	121.34(12)

HPLC Purity Control of Final Compounds

The Surveyor®-LC-system consisted of a pump, an autosampler, and a PDA detector. Mass spectrometry was performed on a TSQ® Quantum (Thermo Electron Corporation, Dreieich, Germany). The triple quadrupole mass spectrometer was equipped with an electrospray interface (ESI). The system was operated by the standard software Xcalibur®.

A RP C18 NUCLEODUR® 100-5 (125 × 3 mm) column (Macherey-Nagel GmbH, Duehren, Germany) was used as stationary phase. All solvents were HPLC grade.

In a gradient run the percentage of acetonitrile (containing 0.1% triflouro-acetic acid) in water was increased from an initial concentration of 3% at 0 min to 100% at 15 min and kept at 100% for 3 min.

The injection volume was 10 µl and flow rate was set to 350 µl/min. MS analysis was carried out at a spray voltage of 3800 V, a capillary temperature of 350 °C and a source CID of 10 V. Spectra were acquired in positive mode from 100 to 1000 m/z and full scan UV-mode. In some cases APC ionization had to be applied.

Comp.	RT (min)	Purity [%]
3	9.08	99.7%
4	7.79	99.9%
5	8.64	99.9%
6	8.93	99.9%
7	10.86	99.6%
8	10.33	99.9%
9	9.92	99.9%
10	11.65	99.5%
11	9.71	99.9%
12	10.44	99.9%
13	9.03	99.7%
14	12.26	99.7%
15	10.36	99.7%
16	10.61	99.9%
17	11.24	99.9%
18	11.17	99.9%
19	9.70	99.9%
20	8.35	99.4%
21	7.60	99.9%
22	11.05	99.7%
23	7.43	99.9%
24	10.65	98.5%
25	8.16	98.5%
26	11.95	99.3%
27	10.09	99.7%
28	11.23	99.6%
29	12.48	98.5%

Inhibition of selected compounds toward CYP17 and CYP19

Compd	CYP17	CYP19
	Inh.% @ 2 μM	Inh.% @ 500 nM
3	6.7	6.3
4	5.8	5.2
13	3.3	0.8
14	4.6	1.4
15	0.9	0
16	1.1	0.5
18	0	0
19	0	0.2
20	0	0
21	0	0
22	4.5	0
23	2.4	1.2
25	1.3	1.6
27	2.6	0