

Supporting information

First Structure-Activity Relationship of 17 β -Hydroxysteroid Dehydrogenase Type 14

Nonsteroidal Inhibitors and Crystal Structures in Complex with the Enzyme

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1. Chemistry

1.1. Chemical methods

Chemical names follow IUPAC nomenclature.

Starting materials were purchased from Acros Organics, Alfa Aesar, Combi-Blocks, Roth and Sigma Aldrich and were used without further purification. Anhydrous THF was freshly distilled from sodium benzophenone ketyl.

Microwave irradiation experiments were carried out in a CEM-Discover apparatus.

Column chromatography was performed on silica gel (0.04-0.063 mm, Macherey-Nagel) and reaction progress was monitored by TLC on aluminium sheets (Silicagel 60 F254, Merck). Visualization was accomplished with UV light at 254 nm and 366 nm, respectively.

Preparative HPLC was performed with a Varian PrepStar 218 gradient system using a ProStar 320 detector. A ProntoSIL C18 column (5.0 μ m, 120 Å, 250-32 mm) was used as stationary phase with an acetonitrile/water gradient containing 0.1% TFA at a flow rate of 20 ml/min. All solvents were HPLC grade. Detection was performed at a wavelength of 254 nm.

Mass spectrometry was performed on a Q-Trap 2000 (Applied Biosystems) equipped with an electrospray interface (ESI).

^1H and ^{13}C NMR spectra were measured on a JEOL ECX-400 spectrometer (at 400 MHz and 100 MHz, respectively). Chemical shifts are reported in δ (parts per million: ppm), using residual peaks for the deuterated solvents as internal standard: ^1H 2.05 ppm (^1H NMR), 29.8 ppm and 206.3 ppm (^{13}C NMR), acetone- d_6 ; 7.26 ppm (^1H NMR), 77.2 ppm (^{13}C NMR), CDCl_3 ; 2.50 ppm (^1H NMR), 39.5 ppm (^{13}C NMR), DMSO- d_6 . Signals are described as s, bs, d, t, q, dd, ddd, dt and m for singlet, broad signal, doublet, triplet, doublet of doublets, doublet of doublet of doublets, doublet of triplets and multiplet, respectively. All coupling constants (J) are given in Hertz (Hz).

Infrared spectroscopy was performed on a Bruker ALPHA FT-IR spectrometer as neat sample.

All tested compounds have $\geq 95\%$ chemical purity as evaluated by HPLC. The Shimadzu[®]-system consisted of a LC-20AT pump, an SIL-20A autosampler and a SPD-M20A PDA detector. The system was operated by the standard software LCsolution[®]. A RP C18 NUCLEODUR[®] (125 mm x 4 mm, 5 μ m) column (Macherey-Nagel) was used as stationary phase. All solvents were HPLC grade. In a gradient run the percentage of acetonitrile in water was increased from initial concentration of 30% at 0 min to 90% at 15 min and kept at 90% for 5 min. The injection volume was 20 μ l at a flow rate of 1.00 ml/min. UV spectra were recorded at a wavelength of 254 nm.

Marvin sketch was used for the calculation of the pKa data (Marvin 15.9.14, 2015, Chemaxon (<http://www.chemaxon.com>)).

The following compounds were prepared according to previously described procedures: (**1a**),² (**1**),² (**10g**),³ (**10f**),⁴ (**15d**),⁵ (**31f**),⁶ (**33f**),⁷ (using commercial POBr_3 , max. temp: 150 °C), (**33e**).⁷

1.2. General procedures

General procedures for alcohol formation

Method A1

A solution of *n*-BuLi (1.0 eq, 2.5 M in hexane), was diluted with anhydrous THF (0.8 M) and arylbromide (1.0 eq) in anhydrous THF was slowly added at -80 °C under argon. The resulting solution was stirred for 15 min at -80 °C, then the appropriate aldehyde (1.0 eq) was added and the reaction solution was stirred for additional 15 min at -80 °C followed by room temperature for 2 h. The mixture was quenched with saturated NH₄Cl and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The product was purified by column chromatography.

Method A2

A mixture of arylbromide (1.0 eq), magnesium turnings (1.1 eq) and a catalytic amount of iodine in anhydrous THF was stirred for 2 h at 60 °C under argon. A solution of the appropriate aldehyde in anhydrous THF was added and the reaction mixture was stirred at 80 °C. The end of the reaction was monitored by TLC. The mixture was quenched with brine and extracted with ethyl acetate. The combined organic layer was dried over magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The product was purified by column chromatography.

General procedure for alcohol oxidation

Method B

2-Iodoxybenzoic acid (1.2 eq) was added to a solution of alcohol derivative (1.0 eq) in THF and the reaction mixture was stirred at 60 °C. After the end of the reaction (monitored by TLC) the mixture was cooled to room temperature, quenched with saturated Na₂S₂O₃ and extracted with ethyl acetate. The combined organic layer was washed with water and saturated sodium bicarbonate, dried over magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The product was purified by column chromatography.

General procedures for Suzuki coupling

Method C1

A mixture of arylbromide (1.0 eq), boronic acid (1.2 eq), cesium carbonate (4.0 eq) and tetrakis(triphenylphosphine)palladium (0.02 eq) was solved in DME/water (2:1) and degassed with argon. The mixture was stirred overnight at 80 °C. The reaction mixture was cooled to room temperature, quenched with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The product was purified by column chromatography.

Method C2

A mixture of arylbromide (1.0 eq), boronic acid (1.2 eq), sodium carbonate (2.0 eq) and tetrakis(triphenylphosphine)palladium (0.02 eq) was solved in DME/water (2:1) and degassed with argon. The mixture was exposed to microwave irradiation (60 min, 150 W, 150 °C) and quenched with water after reaching room temperature. The mixture was extracted with ethyl acetate and the combined organic layer was washed with brine, dried over magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The product was purified by column chromatography.

General procedure for amination of bromopyridine

Method D

A mixture of bromopyridine (1.0 eq), appropriate *N*-heterocycle (1.1 eq) and potassium phosphate (4.0 eq) in 1,4-dioxane was stirred at 100 °C. At the end of the reaction (monitored by TLC) the mixture was cooled to room temperature, quenched with 1 M sodium hydroxide and extracted with ethyl acetate. The combined organic layer was dried over magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The product was purified by column chromatography.

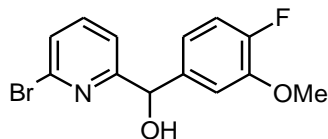
General procedure for ether cleavage

Method E

A solution of methoxy derivative (1.0 eq) in dry dichloromethane was cooled to -80 °C and boron tribromide (1 M in dichloromethane, 5 eq per methoxy function) was slowly added under argon. The reaction mixture was stirred at -80 °C for 1 h and then allowed to warm to room temperature overnight. The mixture was cooled in an ice bath, quenched with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The product was purified by column chromatography.

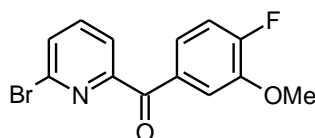
1.3. Detailed synthesis procedures and compounds characterization

(6-Bromopyridin-2-yl)(4-fluoro-3-methoxyphenyl)methanol (**1c**).



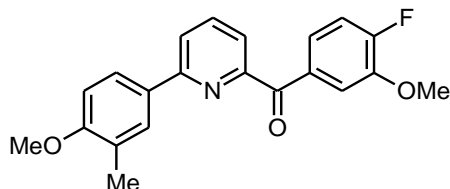
According to method A1 the title compound was prepared by reaction of 2,6-dibromopyridine (**1d**) (1.18 g, 5.0 mmol, 1.0 eq) with 4-fluoro-3-methoxybenzaldehyde (0.77 g, 5.0 mmol, 1.0 eq). The product was used in the next step without further purification. $C_{13}H_{11}BrFNO_2$; MW: 312; 1H NMR ($CDCl_3$, 400 MHz): δ 7.49 (t, J = 7.7 Hz, 1H), 7.39 (t, J = 7.8 Hz, 1H), 7.12 (d, J = 7.6 Hz, 1H), 7.02 (d, J = 8.2 Hz, 1H), 7.02 (dd, J = 13.9 Hz, 8.2 Hz, 1H), 6.88 (ddd, J = 8.2 Hz, 4.3 Hz, 2.1 Hz, 1H), 5.68 (d, J = 3.9 Hz, 1H), 4.56 (d, J = 4.1 Hz, 1H), 3.85 (s, 3H); MS (ESI): 312, 314 ($M+H$) $^+$.

(6-Bromopyridin-2-yl)(4-fluoro-3-methoxyphenyl)methanone (**1b**).



According to method B the title compound was prepared by reaction of the previously obtained (6-bromopyridin-2-yl)(4-fluoro-3-methoxyphenyl)methanol (**1c**) with 2-iodoxybenzoic acid (1.68 g, 6.0 mmol, 1.2 eq) for 2 h. The product was purified by column chromatography (cyclohexane/ethyl acetate 8:1) to give 1.17 g (3.7 mmol/ 75%, two steps) of the analytically pure compound. $C_{13}H_9BrFNO_2$; MW 310; 1H NMR ($CDCl_3$, 400 MHz): δ 8.01 (dd, J = 7.5 Hz, 1.0 Hz, 1H), 7.92 (dd, J = 8.4 Hz, 2.1 Hz, 1H), 7.80-7.74 (m, 2H), 7.69 (dd, J = 8.0 Hz, 1.0 Hz, 1H), 7.18 (dd, J = 10.7 Hz, 8.5 Hz, 1H), 3.97 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 189.7, 155.9 (d, J = 256.3 Hz), 155.6, 147.7 (d, J = 10.8 Hz), 140.7, 139.6, 132.1 (d, J = 3.5 Hz), 131.0, 125.9 (d, J = 8.0 Hz), 123.7, 115.9 (d, J = 8.7 Hz), 115.8 (d, J = 6.8 Hz), 56.4; MS (ESI): 310, 312 ($M+H$) $^+$.

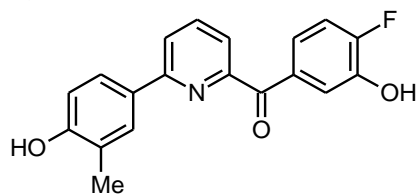
(4-Fluoro-3-methoxyphenyl)[6-(4-methoxy-3-methylphenyl)pyridin-2-yl]methanone (**6a**).



According to method C1 the title compound was prepared by reaction of (6-bromopyridin-2-yl)(4-fluoro-3-methoxyphenyl)methanone (**1b**) (123 mg, 0.40 mmol, 1.0 eq) with 4-methoxy-3-methylphenylboronic acid (79 mg, 0.48 mmol, 1.2 eq) in DME/water (6.0 ml). The product was purified by column chromatography (cyclohexane/ethyl acetate 10:1) to give 131 mg (0.38 mmol/ 95%) of the analytically pure compound. $C_{21}H_{18}FNO_3$; MW: 351; 1H NMR ($CDCl_3$, 400 MHz): δ 8.00 (dd, J = 8.5 Hz, 2.0 Hz, 1H), 7.95-7.82 (m, 6H), 7.18 (dd, J = 10.8 Hz, 8.5 Hz, 1H), 6.91 (d,

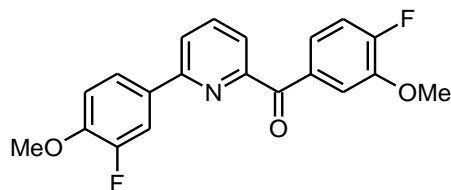
$J = 8.4$ Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 192.0, 159.2, 155.9, 155.6 (d, $J = 254.9$ Hz), 154.6, 147.5 (d, $J = 11.0$ Hz), 137.9, 133.0 (d, $J = 3.5$ Hz), 130.5, 129.2, 127.2, 126.1 (d, $J = 7.8$ Hz), 125.8, 122.3, 121.9, 116.1 (d, $J = 3.2$ Hz), 115.6 (d, $J = 18.9$ Hz), 110.2, 56.4, 55.6, 16.6; MS (ESI): 352 ($\text{M}+\text{H}$) $^+$.

(4-Fluoro-3-hydroxyphenyl)[6-(4-hydroxy-3-methylphenyl)pyridin-2-yl]methanone hydrochloride salt (6).



According to method E the title compound was prepared by reaction of (4-fluoro-3-methoxyphenyl)[6-(4-methoxy-3-methylphenyl)pyridin-2-yl]methanone (**6a**) (110 mg, 0.31 mmol, 1.0 eq) with boron tribromide (3.1 ml, 3.1 mmol, 10 eq) in dichloromethane (6.0 ml). The crude product was purified by column chromatography (cyclohexane/ethyl acetate 3:1) and the hydrochloride salt was prepared by means of 2 M hydrogen chloride solution in ether to give 85 mg (0.24 mmol/ 75%) of the analytically pure compound. $\text{C}_{19}\text{H}_{14}\text{FNO}_3 \cdot \text{HCl}$; MW: 360; mp: 194-195 $^\circ\text{C}$; ^1H NMR ($\text{DMSO}-d_6$, 400 MHz): δ 10.29 (bs, 1H), 9.71 (bs, 1H), 8.12-7.96 (m, 2H), 7.85-7.81 (m, 1H), 7.79-7.73 (m, 1H), 7.71 (dd, $J = 8.8$ Hz, 2.2 Hz, 1H), 7.56 (ddd, $J = 8.4$ Hz, 4.5 Hz, 2.1 Hz, 1H), 7.33 (dd, $J = 11.0$ Hz, 8.5 Hz, 1H), 6.89 (d, $J = 8.4$ Hz, 1H), 2.18 (s, 3H); ^{13}C NMR ($\text{DMSO}-d_6$, 100 MHz): δ 191.9, 157.1, 155.4, 154.2 (d, $J = 248.2$ Hz), 154.1, 144.8 (d, $J = 12.5$ Hz), 138.3, 132.7 (d, $J = 3.1$ Hz), 129.3, 128.5, 125.6, 124.2, 123.2 (d, $J = 7.8$ Hz), 121.7, 121.3, 120.0 (d, $J = 4.4$ Hz), 116.0 (d, $J = 19.1$ Hz), 114.9, 16.2; IR: 3390, 1661, 1611, 1597, 1583, 1526, 1510, 1427, 1235, 1119, 756 cm^{-1} ; MS (ESI): 324 ($\text{M}+\text{H}$) $^+$.

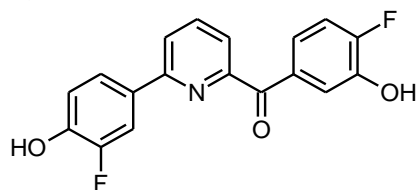
(4-Fluoro-3-methoxyphenyl)[6-(3-fluoro-4-methoxyphenyl)pyridin-2-yl]methanone (8a).



According to method C1 the title compound was prepared by reaction of (6-bromopyridin-2-yl)(4-fluoro-3-methoxyphenyl)methanone (**1b**) (151 mg, 0.49 mmol, 1.0 eq) with 3-fluoro-4-methoxyphenylboronic acid (100 mg, 0.59 mmol, 1.2 eq) DME/water (6.0 ml). The product was purified by column chromatography (cyclohexane/ethyl acetate 5:1) to give 160 mg (0.45 mmol/ 92%) of the analytically pure compound. $\text{C}_{20}\text{H}_{15}\text{F}_2\text{NO}_3$; MW: 355; ^1H NMR (CDCl_3 , 400 MHz): δ 7.99-7.93 (m, 3H), 7.90-7.76 (m, 4H), 7.19 (dd, $J = 10.7$ Hz, 8.5 Hz, 1H), 7.05 (t, $J = 8.5$ Hz, 1H), 3.95 (s, 6H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 191.8, 155.7 (d, $J = 258.2$ Hz), 154.8, 154.5, 152.8 (d, $J = 245.7$ Hz), 149.0 (d, $J = 10.8$ Hz), 147.6 (d, $J = 10.9$ Hz), 138.2, 132.9 (d, $J = 3.6$ Hz), 131.6 (d, $J = 6.3$ Hz),

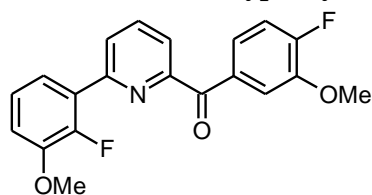
126.0 (d, $J = 7.9$ Hz), 122.9, 122.9 (d, $J = 3.5$ Hz), 121.9, 115.9 (d, $J = 3.2$ Hz), 115.7 (d, $J = 19.0$ Hz), 114.7 (d, $J = 19.9$ Hz), 113.4 (d, $J = 2.1$ Hz), 56.4; MS (ESI): 356 (M+H)⁺.

(4-Fluoro-3-hydroxyphenyl)[6-(3-fluoro-4-hydroxyphenyl)pyridin-2-yl]methanone hydrochloride salt (8).



According to method E the title compound was prepared by reaction of (4-fluoro-3-methoxyphenyl)[6-(3-fluoro-methoxyphenyl)pyridin-2-yl]methanone (**8a**) (148 mg, 0.42 mmol, 1.0 eq) with boron tribromide (4.2 ml, 4.2 mmol, 10 eq) in dichloromethane (8.0 ml). The crude product was purified by column chromatography (cyclohexane/ethyl acetate 2:1) and the hydrochloride salt was prepared by means of 2 M hydrogen chloride solution in ether to give 92 mg (0.25 mmol/ 61 %) of the analytically pure compound. C₁₈H₁₁F₂NO₃·HCl; MW: 364; mp: 206-207 °C; ¹H NMR (acetone-*d*₆, 400 MHz): δ 8.16 (dd, $J = 8.1$ Hz, 1.2 Hz, 1H), 8.11 (dd, $J = 8.0$ Hz, 7.5 Hz, 1H), 7.93 (dd, $J = 8.5$ Hz, 1.7 Hz, 1H), 7.90 (dd, $J = 3.2$ Hz, 1.7 Hz, 1H), 7.88-7.82 (m, 2H), 7.72 (ddd, $J = 8.5$ Hz, 4.5 Hz, 2.1 Hz, 1H), 7.31 (dd, $J = 10.8$ Hz, 8.5 Hz, 1H), 7.13 (t, $J = 8.7$ Hz, 1H); ¹³C NMR (acetone-*d*₆, 100 MHz): δ 192.3, 155.6, 155.4 (d, $J = 249.3$ Hz), 155.2 (d, $J = 2.35$ Hz), 152.6 (d, $J = 240.0$ Hz), 147.2 (d, $J = 12.9$ Hz), 145.5 (d, $J = 13.3$ Hz), 139.3, 134.2 (d, $J = 3.3$ Hz), 131.6 (d, $J = 5.9$ Hz), 124.8 (d, $J = 7.47$ Hz), 124.11 (d, $J = 3.2$ Hz), 123.0, 122.6, 121.3 (d, $J = 4.2$ Hz), 118.9 (d, $J = 3.0$ Hz), 116.6 (d, $J = 19.2$ Hz), 115.3 (d, $J = 20.0$ Hz); IR: 3380, 1660, 1598, 1582, 1524, 1430, 1235, 754 cm⁻¹; MS (ESI): 328 (M+H)⁺.

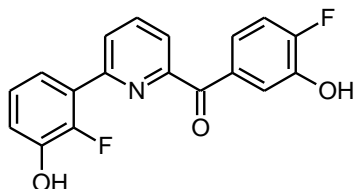
(4-Fluoro-3-methoxyphenyl)[6-(2-fluoro-3-methoxyphenyl)pyridin-2-yl]methanone (9a).



According to method C1 the title compound was prepared by reaction of (6-bromopyridin-2-yl)(4-fluoro-3-methoxyphenyl)methanone (**1b**) (152 mg, 0.49 mmol, 1.0 eq) with 2-fluoro-3-methoxyphenylboronic acid (100 mg, 0.59 mmol, 1.2 eq) in DME/water (6.0 ml). The product was purified by column chromatography (cyclohexane/ethyl acetate 9:1) to give 165 mg (0.46 mmol/ 95%) of the analytically pure compound. C₂₀H₁₅F₂NO₃; MW: 355; ¹H NMR (CDCl₃, 400 MHz): δ 8.06-7.93 (m, 4H), 7.85 (ddd, $J = 8.4$ Hz, 4.5 Hz, 2.0 Hz, 1H), 7.51 (ddd, $J = 8.2$ Hz, 6.7 Hz, 1.6 Hz, 1H), 7.17 (dd, $J = 10.8$ Hz, 8.5 Hz, 1H), 7.16 (dt, $J = 8.1$ Hz, 1.4 Hz, 1H), 7.04 (dt, $J = 8.0$ Hz, 1.5 Hz, 1H), 3.94 (s, 3H), 3.94 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 191.6, 155.7 (d, $J = 255.2$ Hz), 154.9, 152.2 (d, $J = 1.9$ Hz), 150.9 (d, $J = 250.6$ Hz), 148.5 (d, $J = 10.1$ Hz), 147.6 (d, $J = 11.0$ Hz), 137.9, 132.8 (d,

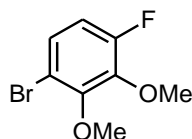
$J = 3.5$ Hz), 127.5 (d, $J = 9.0$ Hz), 127.1 (d, $J = 9.9$ Hz), 126.0 (d, $J = 8.0$ Hz), 124.3 (d, $J = 4.8$ Hz), 123.5, 122.0 (d, $J = 1.8$ Hz), 115.9 (d, $J = 3.2$ Hz), 115.7, 114.0 (d, $J = 2.1$ Hz), 56.6, 56.4; MS (ESI): 356 (M+H)⁺.

(4-Fluoro-3-hydroxyphenyl)[6-(2-fluoro-3-hydroxyphenyl)pyridin-2-yl]methanone hydrochloride salt (9).



According to method E the title compound was prepared by reaction of (4-fluoro-3-methoxyphenyl)[6-(2-fluoro-3-methoxyphenyl)pyridin-2-yl]methanone (**9a**) (126 mg, 0.35 mmol, 1.0 eq) with boron tribromide (3.5 ml, 3.5 mmol, 10 eq) dichloromethane (6.0 ml). The crude product was purified by column chromatography (cyclohexane/ethyl acetate 2:1) and the hydrochloride salt was prepared by means of 2 M hydrogen chloride solution in ether to give 117 mg (0.32 mmol/ 92%) of the analytically pure compound. C₁₈H₁₁F₂NO₃·HCl; MW: 364; mp: 198-199 °C; ¹H NMR (DMSO-*d*₆, 400 MHz): δ 8.15 (t, $J = 7.8$ Hz, 1H), 8.00 (ddd, $J = 7.9$ Hz, 2.1 Hz, 0.9 Hz, 1H), 7.92 (dd, $J = 7.7$ Hz, 1.0 Hz, 1H), 7.70-7.64 (m, 1H), 7.55 (ddd, $J = 8.5$ Hz, 4.5 Hz, 2.2 Hz, 1H), 7.31 (dd, $J = 11.0$ Hz, 8.5 Hz, 1H), 7.29-7.22 (m, 1H), 7.12-7.04 (m, 2H); ¹³C NMR (DMSO-*d*₆, 100 MHz): δ 191.7, 154.6, 154.3 (d, $J = 125.5$ Hz), 151.9, 149.2 (d, $J = 146.2$ Hz), 145.6 (d, $J = 12.6$ Hz), 144.9 (d, $J = 12.4$ Hz), 138.4, 132.5, 127.3 (d, $J = 9.1$ Hz), 126.7 (d, $J = 8.1$ Hz), 124.4 (d, $J = 4.1$ Hz), 123.3 (d, $J = 7.5$ Hz), 122.9, 120.2, 119.8 (d, $J = 4.5$ Hz), 118.5 (d, $J = 3.2$ Hz), 116.0 (d, $J = 19.3$ Hz); IR: 3155, 1655, 1593, 1481, 1293, 1225, 750 cm⁻¹; MS (ESI): 328 (M+H)⁺.

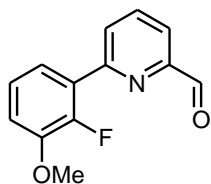
1-Bromo-4-fluoro-2,3-dimethoxybenzene (10e).



A mixture of 3-bromo-6-fluorobenzene-1,2-diol (**10f**) (785 mg, 3.79 mmol, 1.0 eq), methyl iodide (0.70 ml, 11.4 mmol, 3.0 eq) and potassium carbonate (1.57 g, 11.4 mmol, 3.0 eq) in DMF (10 ml) was stirred at room temperature overnight. The mixture was acidified with 1 M HCl and extracted with ethyl acetate. The combined organic layer was washed with saturated sodium bicarbonate and brine, dried over magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The product was used in the next step without further purification. C₈H₈BrFO₂; MW: 235; ¹H NMR (CDCl₃, 400 MHz): δ 7.19 (ddd, $J = 9.0$ Hz, 5.5 Hz, 1.1 Hz, 1H), 6.78 (ddd, $J = 10.1$ Hz, 9.0 Hz, 1.0 Hz, 1H), 3.96 (t, $J = 1.1$ Hz, 3H), 3.91 (d, $J = 0.9$ Hz, 3H). ¹³C NMR (CDCl₃, 100 MHz): δ 155.8

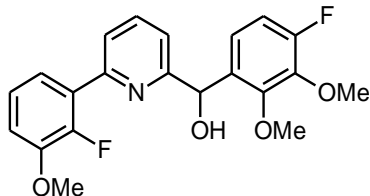
(d, $J = 248.0$ Hz), 151.4 (d, $J = 4.2$ Hz), 142.7 (d, $J = 12.5$ Hz), 126.5 (d, $J = 8.8$ Hz), 113.0 (d, $J = 20.6$ Hz), 112.1 (d, $J = 3.5$ Hz), 61.8 (d, $J = 4.2$ Hz), 61.3; MS (ESI): 235, 237 ($M+H$)⁺.

6-(2-Fluoro-3-methoxyphenyl)pyridine-2-carbaldehyde (10c).



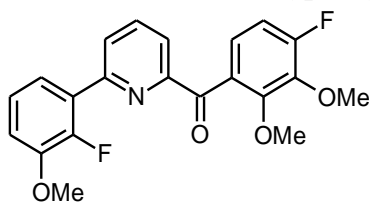
According to method C1 the title compound was prepared by reaction of 6-bromopyridine-2-carbaldehyde (**10d**) (372 mg, 2.0 mmol, 1.0 eq) with 2-fluoro-3-methoxyphenylboronic acid (408 mg, 2.5 mmol, 1.2 eq) in DME/water (24 ml). The product was purified by column chromatography (cyclohexane/ethyl acetate 9:1) to give 367 mg (1.59 mmol/ 79%) of the analytically pure compound. $C_{13}H_{10}FNO_2$; MW: 231; 1H NMR ($CDCl_3$, 400 MHz): δ 10.15 (s, 1H), 8.04-7.99 (m, 1H), 7.97-7.91 (m, 2H), 7.63 (ddd, $J = 8.1$ Hz, 6.7 Hz, 1.6 Hz, 1H), 7.23 (dt, $J = 8.1$ Hz, 1.5 Hz, 1H), 7.07 (dt, $J = 8.1$ Hz, 1.6 Hz, 1H), 3.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.8, 154.0 (d, $J = 1.6$ Hz), 152.9, 150.8 (d, $J = 250.5$ Hz), 148.4 (d, $J = 11.2$ Hz), 137.7, 128.9 (d, $J = 9.6$ Hz), 127.2 (d, $J = 9.0$ Hz), 124.5 (d, $J = 4.8$ Hz), 122.1 (d, $J = 1.7$ Hz), 120.3, 114.3 (d, $J = 2.0$ Hz), 56.6; MS (ESI): 264 ($M+H$)⁺.

(4-Fluoro-2,3-dimethoxyphenyl)[6-(2-fluoro-3-methoxyphenyl)pyridin-2-yl]methanol (10b).



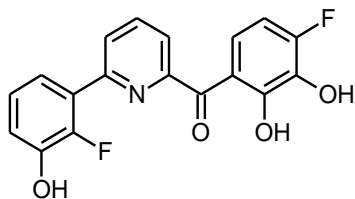
According to method A1 the title compound was prepared by reaction of 6-(2-fluoro-3-methoxyphenyl)pyridine-2-carbaldehyde (**10c**) (169 mg, 0.73 mmol, 1.0 eq) with 1-bromo-4-fluoro-2,3-dimethoxybenzene (**10e**) (171 mg, 0.73 mmol, 1.0 eq). The product was purified by column chromatography (cyclohexane/ethyl acetate 9:1) to give 76 mg (0.20 mmol/ 27%) of the analytically pure compound. $C_{21}H_{19}F_2NO_4$; MW: 387; 1H NMR ($CDCl_3$, 400 MHz): δ 7.74-7.67 (m, 2H), 7.57 (ddd, $J = 8.1$ Hz, 6.7 Hz, 1.6 Hz, 1H), 7.24-7.16 (m, 2H), 7.05 (dt, $J = 8.0$ Hz, 1.5 Hz, 1H), 6.99 (dd, $J = 8.8$ Hz, 6.0 Hz, 1H), 6.82 (dd, $J = 10.5$ Hz, 8.8 Hz, 1H), 6.10 (s, 1H), 3.97 (d, $J = 1.2$ Hz, 3H), 3.95 (s, 3H), 3.91 (s, 3H); MS (ESI): 388 ($M+H$)⁺.

(4-Fluoro-2,3-dimethoxyphenyl)[6-(2-fluoro-3-methoxyphenyl)pyridin-2-yl]methanone (10a).



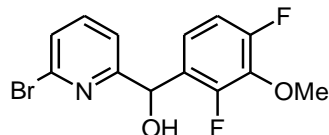
According to method B the title compound was prepared by reaction of (4-fluoro-2,3-dimethoxyphenyl)[6-(2-fluoro-3-methoxyphenyl)pyridin-2-yl]methanol (**10b**) (76 mg, 0.20 mmol, 1.0 eq) with 2-iodoxybenzoic acid (67 mg, 0.24 mmol, 1.2 eq) for 3 h. The product was purified by column chromatography (cyclohexane/ethyl acetate 19:1) to give 54 mg (0.14 mmol/ 70%) of the analytically pure compound. $C_{21}H_{17}F_2NO_4$; MW: 385; 1H NMR ($CDCl_3$, 400 MHz): δ 8.03-7.92 (m, 3H), 7.42 (ddd, J = 8.1 Hz, 6.7 Hz, 1.7 Hz, 1H), 7.30 (dd, J = 8.7 Hz, 6.0 Hz, 1H), 7.09 (dt, J = 8.1 Hz, 1.4 Hz, 1H), 6.99 (dt, J = 8.0 Hz, 1.6 Hz, 1H), 6.94 (dd, J = 10.1 Hz, 8.7 Hz, 1H), 3.93 (d, J = 1.0 Hz, 3H), 3.92 (s, 3H), 3.65 (s, 3H); MS (ESI): 386 (M+H) $^+$.

(4-Fluoro-2,3-dihydroxyphenyl)[6-(2-fluoro-3-hydroxyphenyl)pyridin-2-yl]methanone (10).



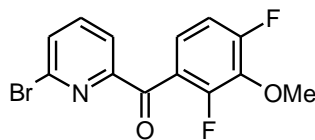
According to method E the title compound was prepared by reaction of (4-fluoro-2,3-dimethoxyphenyl)[6-(2-fluoro-3-methoxyphenyl)pyridin-2-yl]methanone (**10a**) (69 mg, 0.18 mmol, 1.0 eq) with boron tribromide (2.7 ml, 2.7 mmol, 15 eq) in dichloromethane (4.0 ml). The product was purified by column chromatography (cyclohexane/ethyl acetate 3:1, 3% acetic acid) to give 50 mg (0.15 mmol/ 81%) of the analytically pure compound. $C_{18}H_{11}F_2NO_4$; MW: 343; mp: 174-175 $^{\circ}C$; 1H NMR (acetone- d_6 , 400 MHz): δ 12.91 (bs, 1H), 8.89 (bs, 1H), 8.42 (bs, 1H), 8.22 (t, J = 7.9 Hz, 1H), 8.09 (ddd, J = 8.0 Hz, 2.0 Hz, 1.0 Hz, 1H), 8.02 (dd, J = 7.7 Hz, 1.0 Hz, 1H), 7.89 (dd, J = 9.2 Hz, 6.1 Hz, 1H), 7.41 (ddd, J = 7.4 Hz, 6.4 Hz, 2.8 Hz, 1H), 7.18-7.10 (m, 2H), 6.77 (dd, J = 10.2 Hz, 9.2 Hz, 1H); ^{13}C NMR (acetone- d_6 , 100 MHz): δ 197.0, 156.0 (d, J = 249.0 Hz), 155.0 (d, J = 8.2 Hz), 153.1 (d, J = 1.8 Hz), 150.6 (d, J = 245.3 Hz), 146.5 (d, J = 13.6 Hz), 139.5, 135.0 (d, J = 13.2 Hz), 128.1 (d, J = 9.2 Hz), 127.9 (d, J = 8.5 Hz), 126.4 (d, J = 10.0 Hz), 125.4 (d, J = 4.6 Hz), 124.2, 122.0 (d, J = 1.2 Hz), 119.6 (d, J = 2.9 Hz), 117.3 (d, J = 2.1 Hz), 108.2, 108.0; IR: 3447, 3368, 1630, 1582, 1510, 1480, 1434, 1307, 1248, 990, 765, 743 cm^{-1} ; MS (ESI): 344 (M+H) $^+$.

(6-Bromopyridin-2-yl)(2,4-difluoro-3-methoxyphenyl)methanol (11c).



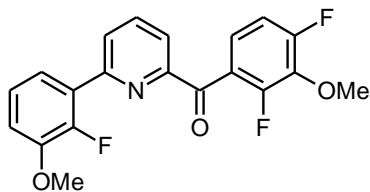
According to method A1 the title compound was prepared by reaction of 2,6-dibromopyridine (**1d**) (1.18 g, 5.00 mmol, 1.0 eq) with 2,4-difluoro-3-methoxybenzaldehyde (0.86 g, 5.00 mmol, 1.0 eq). The product was used in the next step without further purification. $C_{13}H_{10}BrF_2NO_2$; MW: 330; MS (ESI): 330, 332 (M+H) $^+$.

(6-Bromopyridin-2-yl)(2,4-difluoro-3-methoxyphenyl)methanone (11b).



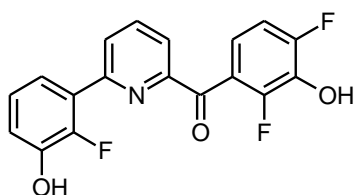
According to method B the title compound was prepared by reaction of (6-bromopyridin-2-yl)(2,4-difluoro-3-methoxyphenyl)methanol (**11c**) with 2-iodoxybenzoic acid (1.68 g, 6.0 mmol, 1.2 eq) for 2 h. The product was purified by column chromatography (cyclohexane/ethyl acetate 19:1) to give 1.01 g (3.08 mmol/ 62%, two steps) of the analytically pure compound. $C_{13}H_8BrF_2NO_2$; MW 328; 1H NMR ($CDCl_3$, 400 MHz): δ 7.99 (dd, $J = 7.5$ Hz, 1.0 Hz, 1H), 7.76 (t, $J = 7.9$ Hz, 1H), 7.68 (dd, $J = 8.3$ Hz, 1H), 7.39 (ddd, $J = 8.6$ Hz, 7.2 Hz, 5.9 Hz, 1H), 7.01 (dd, $J = 10.5$ Hz, 3.2 Hz, 1H), 4.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.2 (d, $J = 2.6$ Hz), 158.8 (dd, $J = 253.7$ Hz, 3.9 Hz), 155.5 (dd, $J = 257.0$ Hz, 6.1 Hz), 154.95, 141.4, 139.4, 136.9 (t, $J = 15.3$ Hz), 131.8, 125.1 (dd, $J = 10.0$ Hz, 3.9 Hz), 122.9 (dd, $J = 12.1$ Hz, 3.6 Hz), 122.4, 62.3 (t, $J = 3.5$ Hz); MS (ESI): 328, 330 ($M+H$) $^+$.

(2,4-Difluoro-3-methoxyphenyl)[6-(2-fluoro-3-methoxyphenyl)pyridin-2-yl]methanone (11a).



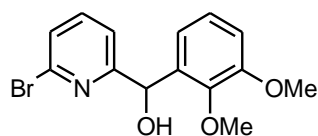
According to method C2 the title compound was prepared by reaction of (6-bromopyridin-2-yl)(2,4-difluoro-3-methoxyphenyl)methanone (**11b**) (164 mg, 0.50 mmol, 1.0 eq) with 2-fluoro-3-methoxyphenylboronic acid (102 mg, 0.60 mmol, 1.2 eq) in DME/water (6.0 ml). The product was purified by column chromatography (cyclohexane/ethyl acetate 9:1) to give 167 mg (0.45 mmol/ 89%) of the analytically pure compound. $C_{20}H_{14}F_3NO_3$; MW: 373; 1H NMR ($CDCl_3$, 400 MHz): δ 8.06 (d, $J = 7.3$ Hz, 1H), 8.04-8.00 (m, 1H), 8.00-7.95 (m, 1H), 7.47-7.40 (m, 2H), 7.11 (t, $J = 8.1$ Hz, 1H), 7.05-6.97 (m, 2H), 4.02 (s, 3H), 3.92 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.9 (dd, $J = 2.4$ Hz, 0.7 Hz), 158.5 (dd, $J = 254.1$ Hz, 5.2 Hz), 155.3 (dd, $J = 256.1$ Hz, 5.7 Hz), 153.7, 152.6 (d, $J = 2.0$ Hz), 150.9 (d, $J = 250.7$ Hz), 148.3 (d, $J = 11.3$ Hz), 137.7, 136.8 (t, $J = 14.4$ Hz), 128.0 (d, $J = 10.3$ Hz), 127.3 (d, $J = 8.9$ Hz), 125.3 (dd, $J = 9.9$ Hz, 4.1 Hz), 124.2 (d, $J = 4.9$ Hz), 123.8 (dd, $J = 12.7$ Hz, 3.7 Hz), 122.2, 122.0 (d, $J = 2.1$ Hz), 114.0 (d, $J = 2.4$ Hz), 112.1 (dd, $J = 19.9$ Hz, 3.7 Hz), 62.2 (t, $J = 3.4$ Hz), 56.6; MS (ESI): 374 ($M+H$) $^+$.

(2,4-Difluoro-3-hydroxyphenyl)[6-(2-fluoro-3-hydroxyphenyl)pyridin-2-yl]methanone (11).



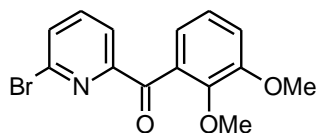
According to method E the title compound was prepared by reaction of (2,4-difluoro-3-methoxyphenyl)[6-(2-fluoro-3-methoxyphenyl)pyridin-2-yl]methanone (**11a**) (112 mg, 0.30 mmol, 1.0 eq) with boron tribromide 3.0 ml, 3.0 mmol, 10 eq) in dichloromethane (6.0 ml). The product was purified by column chromatography (cyclohexane/ethyl acetate 4:1, 3% acetic acid) and preparative HPLC (gradient water/acetonitrile/trifluoroacetic acid 30:70:0.1→10:90:0.1, in 160 min) to give 62 mg (0.18 mmol/ 60%) of the analytically pure compound. C₁₈H₁₀F₃NO₃; MW: 345; mp: 144-145 °C; ¹H NMR (acetone-*d*₆, 400 MHz): δ 8.16 (t, *J* = 7.8 Hz, 1H), 8.10-8.01 (m, 2H), 7.32 (ddd, *J* = 10.4 Hz, 7.9 Hz, 3.8 Hz, 1H), 7.26 (ddd, *J* = 8.8 Hz, 7.0 Hz, 6.0 Hz, 1H), 7.14 (ddd, *J* = 10.1 Hz, 8.8 Hz, 1.8 Hz, 1H), 7.09-7.02 (m, 2H); ¹³C NMR (acetone-*d*₆, 100 MHz): δ 192.5 (dd, *J* = 2.5 Hz, 1.1 Hz), 155.5 (dd, *J* = 247.4 Hz, 5.6 Hz), 155.0, 153.6 (d, *J* = 2.1 Hz), 150.7 (d, *J* = 248.6 Hz), 146.4 (d, *J* = 13.8 Hz), 138.9, 134.9, 128.5 (d, *J* = 9.6 Hz), 128.3 (d, *J* = 9.2 Hz), 125.2 (d, *J* = 6.1 Hz), 124.4 (dd, *J* = 12.4 Hz, 3.6 Hz), 122.5, 121.9 (d, *J* = 1.7 Hz), 121.5 (dd, *J* = 9.3 Hz, 3.7 Hz), 119.4 (d, *J* = 3.2 Hz), 112.3 (dd, *J* = 19.4 Hz, 3.5 Hz), 112.3 (dd, *J* = 19.4 Hz, 3.5 Hz); IR: 3289, 1665, 1618, 1596, 1465, 1449, 1319, 1273, 1071, 991, 765 cm⁻¹; MS (ESI): 346 (M+H)⁺.

(6-Bromopyridin-2-yl)(2,3-dimethoxyphenyl)methanol (12c**).**



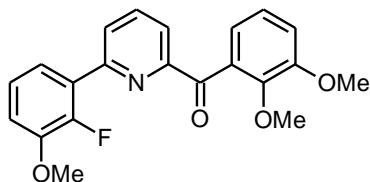
According to method A1 the title compound was prepared by reaction of 2,6-dibromopyridine (**1d**) (474 mg, 2.0 mmol, 1.0 eq) with 2,3-dimethoxybenzaldehyde (332 mg, 2.0 mmol, 1.0 eq). The product was purified by column chromatography (cyclohexane/ethyl acetate 5:1) to give 538 mg (1.66 mmol/ 83%) of the analytically pure compound. C₁₄H₁₄BrNO₃; MW: 323; ¹H NMR (CDCl₃, 400 MHz): δ 7.46 (t, *J* = 7.7 Hz, 1H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 7.6 Hz, 1H), 7.04 (t, *J* = 8.0 Hz, 1H), 6.92 (dd, *J* = 7.9 Hz, 1.5 Hz, 1H), 6.86 (d, *J* = 1.5 Hz, 1H), 6.10 (s, 1H), 3.87 (s, 3H), 3.86 (s, 3H); MS (ESI): 324, 326 (M+H)⁺.

(6-Bromopyridin-2-yl)(2,3-dimethoxyphenyl)methanone (12b).



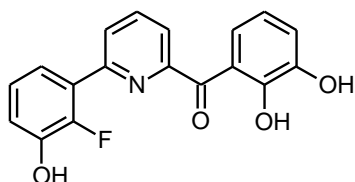
According to method B the title compound was prepared by reaction of (6-bromopyridin-2-yl)(2,3-dimethoxyphenyl)methanol (**12c**) (520 mg, 1.60 mmol, 1.0 eq) with 2-iodoxybenzoic acid (532 mg, 1.90 mmol, 1.2 eq) for 2 h. The product was purified by column chromatography (cyclohexane/ethyl acetate 7:1) to give 380 mg (1.18 mmol/ 74 %) of the analytically pure compound. $C_{14}H_{12}BrNO_3$; MW: 322; 1H NMR ($CDCl_3$, 400 MHz): δ 7.92 (dd, $J = 7.5$ Hz, 0.9 Hz, 1H), 7.72 (t, $J = 7.7$ Hz, 1H), 7.62 (dd, $J = 7.9$ Hz, 0.9 Hz, 1H), 7.16-7.06 (m, 3H), 3.89 (s, 3H), 3.67 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 194.7, 156.4, 152.6, 148.3, 141.4, 139.2, 132.1, 131.1, 123.9, 122.2, 121.8, 116.0, 61.4, 56.1; MS (ESI): 322, 324 ($M+H$) $^+$.

(2,3-Dimethoxyphenyl)[6-(2-fluoro-3-methoxyphenyl)pyridin-2-yl]methanone (12a).



According to method C1 the title compound was prepared by reaction of (6-bromopyridin-2-yl)(2,3-dimethoxyphenyl)methanone (**12b**) (165 mg, 0.51 mmol, 1.0 eq) with 2-fluoro-3-methoxyphenylboronic acid (102 mg, 0.60 mmol, 1.2 eq) in DME/water (6.0 ml). The product was purified by column chromatography (cyclohexane/ethyl acetate 5:1) to give 174 mg (0.47 mmol/ 93%) of the analytically pure compound. $C_{21}H_{18}FNO_4$; MW: 367; 1H NMR ($CDCl_3$, 400 MHz): δ 8.00-7.89 (m, 3H), 7.46-7.40 (m, 1H), 7.16-7.11 (m, 2H), 7.10-7.04 (m, 2H), 7.00-6.93 (m, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 3.61 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.2, 155.2, 152.6, 152.4 (d, $J = 1.8$ Hz), 150.9 (d, $J = 250.3$ Hz), 148.3, 148.2, 137.4, 133.5, 127.4 (d, $J = 8.8$ Hz), 127.3 (d, $J = 10.9$ Hz), 124.2 (d, $J = 4.7$ Hz), 123.7, 122.4 (d, $J = 1.6$ Hz), 122.0, 121.8, 115.4, 113.8 (d, $J = 1.9$ Hz), 61.5, 56.6, 56.2; MS (ESI): 368 ($M+H$) $^+$.

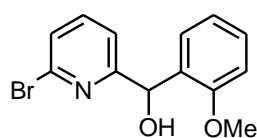
(2,3-Dihydroxyphenyl)[6-(2-fluoro-3-hydroxyphenyl)pyridin-2-yl]methanone (12).



According to method E the title compound was prepared by reaction of (2,3-dimethoxyphenyl)[6-(2-fluoro-3-methoxyphenyl)pyridin-2-yl]methanone (**12a**) (110 mg, 0.30 mmol, 1.0 eq) with boron tribromide (4.5 ml, 4.5 mmol, 15 eq) in dichloromethane (6.0 ml). The product was purified by column chromatography (cyclohexane/ethyl acetate 3:1, 3% acetic acid) to give 77 mg (0.24 mmol/

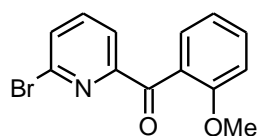
79%) of the analytically pure compound. $C_{18}H_{12}FNO_4$; MW: 325; mp: 193-194 °C; 1H NMR (acetone- d_6 , 400 MHz): δ 8.21 (t, J = 7.9 Hz, 1H), 8.08 (ddd, J = 8.0 Hz, 1.9 Hz, 0.9 Hz, 1H), 7.99 (dd, J = 7.7 Hz, 0.9 Hz, 1H), 7.70 (dd, J = 8.2 Hz, 1.5 Hz, 1H), 7.45-7.40 (m, 1H), 7.18-7.09 (m, 3H), 6.83 (t, J = 8.0 Hz, 1H); ^{13}C NMR (acetone- d_6 , 100 MHz): δ 198.3, 156.1, 153.1 (d, J = 1.8 Hz), 152.1, 150.6 (d, J = 245.3 Hz), 147.3, 146.5 (d, J = 13.7 Hz), 139.4, 128.2 (d, J = 9.1 Hz), 127.7 (d, J = 8.6 Hz), 125.7, 125.4 (d, J = 4.5 Hz), 123.9, 122.0, 121.9 (d, J = 1.5 Hz), 120.6, 119.6 (d, J = 3.0 Hz), 119.5; IR: 3352, 3085, 1624, 1604, 1591, 1580, 1478, 1459, 1445, 1340, 1278, 1228, 1044, 706 cm^{-1} ; MS (ESI): 326 (M+H) $^+$.

(6-Bromopyridin-2-yl)(2-methoxyphenyl)methanol (13c).



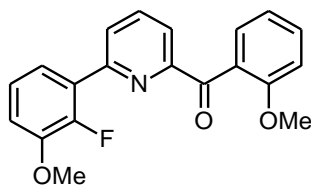
According to method A1 the title compound was prepared by reaction of 2,6-dibromopyridine (**1d**) (1.18 g, 5.0 mmol, 1.0 eq) with 2-methoxybenzaldehyde (680 mg, 5.0 mmol, 1.0 eq). The product was purified by column chromatography (cyclohexane/ethyl acetate 7:1) to give 1.20 g (4.08 mmol/ 82%) of the analytically pure compound. $C_{13}H_{12}BrNO_2$; MW: 294; 1H NMR ($CDCl_3$, 400 MHz): δ 7.46 (t, J = 7.7 Hz, 1H), 7.37-7.33 (m, 1H), 7.31 (dd, J = 7.6 Hz, 2.0 Hz, 1H), 7.29-7.22 (m, 2H), 6.95 (dt, J = 7.4 Hz, 0.9 Hz, 1H), 6.90 (dd, J = 8.2 Hz, 0.8 Hz, 1H), 6.15 (s, 1H), 3.85 (s, 3H); MS (ESI): 294, 296 (M+H) $^+$.

(6-Bromopyridin-2-yl)(2-methoxyphenyl)methanone (13b).



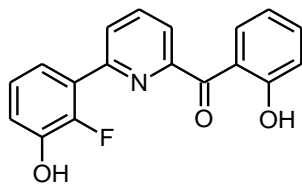
According to method B the title compound was prepared by reaction of (6-bromopyridin-2-yl)(2-dimethoxyphenyl)methanol (**13c**) (1.18 g, 4.05 mmol, 1.0 eq) with 2-iodoxybenzoic acid (1.36 g, 4.86 mmol, 1.2 eq) for 2 h. The product was purified by column chromatography (cyclohexane/ethyl acetate 5:1) to give 1.04 g (3.56 mmol/ 88%) of the analytically pure compound. $C_{13}H_{10}BrNO_2$; MW: 292; 1H NMR ($CDCl_3$, 400 MHz): δ 7.89 (dd, J = 7.5 Hz, 1.0 Hz, 1H), 7.70 (t, J = 7.7 Hz, 1H), 7.60 (dd, J = 7.9 Hz, 1.0 Hz, 1H), 7.59-7.55 (m, 1H), 7.51 (ddd, J = 8.4 Hz, 7.4 Hz, 1.8 Hz, 1H), 7.06 (dt, J = 7.5 Hz, 0.9 Hz, 1H), 6.98 (d, J = 8.2 Hz, 1H), 3.67 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 194.3, 159.0, 156.4, 141.2, 139.1, 133.6, 131.0, 130.8, 127.3, 122.1, 120.8, 112.1, 55.9; MS (ESI): 292, 294 (M+H) $^+$.

[6-(2-Fluoro-3-methoxyphenyl)pyridin-2-yl](2-methoxyphenyl)methanone (13a).



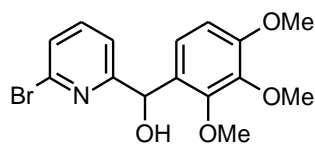
According to method C1 the title compound was prepared by reaction of (6-bromopyridin-2-yl)(2-methoxyphenyl)methanone (**13b**) (146 mg, 0.50 mmol, 1.0 eq) with 2-fluoro-3-methoxyphenylboronic acid (104 mg, 0.60 mmol, 1.2 eq) in DME/water (6.0 ml). The product was purified by column chromatography (cyclohexane/ethyl acetate 7:1) to give 156 mg (0.46 mmol/ 92%) of the analytically pure compound. $C_{20}H_{16}FNO_3$; MW: 337; 1H NMR ($CDCl_3$, 400 MHz): δ 8.00-7.88 (m, 3H), 7.61 (dd, J = 7.5 Hz, 1.8 Hz, 1H), 7.50 (ddd, J = 8.3 Hz, 7.5 Hz, 1.8 Hz, 1H), 7.38 (ddd, J = 8.4 Hz, 6.7 Hz, 1.7 Hz, 1H), 7.12-7.02 (m, 2H), 7.01-6.93 (m, 2H), 3.91 (s, 3H), 3.65 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.1, 158.7, 155.2, 152.3 (d, J = 2.1 Hz), 150.9 (d, J = 250.3 Hz), 148.3 (d, J = 11.5 Hz), 137.3, 132.7, 130.9, 128.3, 127.6 (d, J = 8.9 Hz), 127.1 (d, J = 10.7 Hz), 124.1 (d, J = 4.9 Hz), 122.2 (d, J = 2.2 Hz), 121.9, 120.4, 113.8 (d, J = 2.3 Hz), 111.5, 56.5, 55.7; MS (ESI): 338 (M+H) $^+$.

[6-(2-Fluoro-3-hydroxyphenyl)pyridin-2-yl](2-hydroxyphenyl)methanone (13).



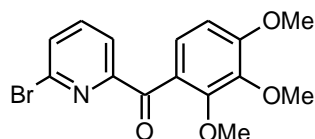
According to method E the title compound was prepared by reaction of [6-(2-fluoro-3-methoxyphenyl)pyridin-2-yl](2-methoxyphenyl)methanone (**13a**) (140 mg, 0.42 mmol, 1.0 eq) with boron tribromide (4.2 ml, 4.2 mmol, 10 eq) in dichloromethane (8.0 ml). The product was purified by column chromatography (cyclohexane/ethyl acetate 5:1) to give 70 mg (0.23 mmol/ 54%) of the analytically pure compound. $C_{18}H_{12}FNO_3$; MW: 309; mp: 140-141 $^{\circ}C$; 1H NMR (acetone- d_6 , 400 MHz): δ 12.19 (s, 1H), 8.88 (s, 1H), 8.30-8.24 (m, 1H), 8.20 (t, J = 7.85 Hz, 1H), 8.08 (ddd, J = 8.0 Hz, 2.1 Hz, 1.0 Hz, 1H), 7.98 (dd, J = 7.7 Hz, 1.0 Hz, 1H), 7.59 (ddd, J = 8.4 Hz, 7.2 Hz, 1.7 Hz, 1H), 7.42 (ddd, J = 7.4 Hz, 6.3 Hz, 2.9 Hz, 1H), 7.17-7.08 (m, 2H), 7.07-7.01 (m, 1H), 6.96 (ddd, J = 8.2 Hz, 7.2 Hz, 1.2 Hz, 1H); ^{13}C NMR (acetone- d_6 , 100 MHz): δ 198.5, 164.3, 156.1, 153.1 (d, J = 1.8 Hz), 150.7 (d, J = 245.2 Hz), 146.5 (d, J = 13.6 Hz), 139.3, 137.6, 135.6, 128.3 (d, J = 9.1 Hz), 127.6 (d, J = 8.9 Hz), 125.4 (d, J = 4.7 Hz), 123.9, 121.9 (d, J = 1.6 Hz), 119.9, 119.7, 119.5 (d, J = 3.2 Hz), 118.8; IR: 3389, 1626, 1606, 1587, 1565, 1510, 1411, 1349, 747, 716 cm^{-1} ; MS (ESI): 310 (M+H) $^+$.

(6-Bromopyridin-2-yl)(2,3,4-trimethoxyphenyl)methanol (14c).



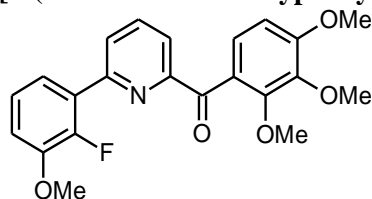
According to method A1 the title compound was prepared by reaction of 2,6-dibromopyridine (**1d**) (1.18 g, 5.0 mmol, 1.0 eq) with 2,3,4-trimethoxybenzaldehyde (0.98 g, 5.0 mmol, 1.0 eq). The product was purified by column chromatography (cyclohexane/ethyl acetate 5:1) to give 1.45 g (4.09 mmol/ 82%) of the analytically pure compound. $C_{15}H_{16}BrNO_4$; MW: 354; 1H NMR ($CDCl_3$, 400 MHz): δ 7.48 (t, $J = 7.7$ Hz, 1H), 7.36 (d, $J = 7.8$ Hz, 1H), 7.23 (d, $J = 7.6$ Hz, 1H), 6.96 (d, $J = 8.7$ Hz, 1H), 6.64 (d, $J = 8.7$ Hz, 1H), 5.97 (s, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H); MS (ESI): 354, 356 ($M+H$) $^+$.

(6-Bromopyridin-2-yl)(2,3,4-trimethoxyphenyl)methanone (14b).



According to method B the title compound was prepared by reaction of (6-bromopyridin-2-yl)(2,3,4-trimethoxyphenyl)methanol (**14c**) (1.04 g, 2.94 mmol, 1.0 eq) with 2-iodoxybenzoic acid (1.00 g, 3.57 mmol, 1.2 eq) for 2 h. The product was purified by column chromatography (cyclohexane/ethyl acetate 5:1) to give 760 mg (2.16 mmol/ 73%) of the analytically pure compound. $C_{15}H_{14}BrNO_4$; MW: 352; 1H NMR ($CDCl_3$, 400 MHz): δ 7.86 (dd, $J = 7.5$ Hz, 1.0 Hz, 1H), 7.71 (t, $J = 7.7$ Hz, 1H), 7.60 (dd, $J = 7.9$ Hz, 1.0 Hz, 1H), 7.39 (d, $J = 8.7$ Hz, 1H), 6.75 (d, $J = 8.8$ Hz, 1H), 3.93 (s, 3H), 3.82 (s, 3H), 3.72 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.3, 157.8, 157.4, 153.9, 141.6, 141.0, 139.2, 130.6, 126.6, 124.6, 121.9, 107.0, 61.4, 60.8, 56.3; MS (ESI): 352, 354 ($M+H$) $^+$.

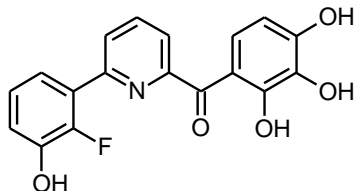
[6-(2-Fluoro-3-methoxyphenyl)pyridin-2-yl](2,3,4-trimethoxyphenyl)methanone (14a).



According to method C1 the title compound was prepared by reaction of (6-bromopyridin-2-yl)(2,3,4-dimethoxyphenyl)methanone (**14b**) (352 mg, 1.00 mmol, 1.0 eq) with 3-fluoro-4-methoxyphenylboronic acid (205 mg, 1.20 mmol, 1.2 eq) in DME/water (6.0 ml). The product was purified by column chromatography (cyclohexane/ethyl acetate 5:1) to give 373 mg (0.94 mmol/ 94%) of the analytically pure compound. $C_{22}H_{20}FNO_5$; MW: 397; 1H NMR ($CDCl_3$, 400 MHz): δ 8.00-7.89 (m, 3H), 7.51-7.45 (m, 1H), 7.44 (d, $J = 8.7$ Hz, 1H), 7.08 (dt, $J = 8.1$ Hz, 1.4 Hz, 1H), 6.98 (dt, $J = 8.0$ Hz, 1.7 Hz, 1H), 6.76 (d, $J = 8.7$ Hz, 1H), 3.94 (s, 3H), 3.92 (s, 3H), 3.85 (s, 3H), 3.62 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.0, 157.2, 156.1, 154.0, 152.0, 150.9 (d, $J = 250.4$ Hz), 148.3,

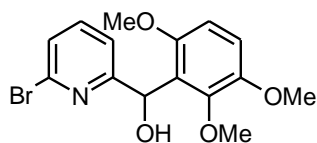
148.2, 141.7, 137.5, 127.5 (d, $J = 8.8$ Hz), 126.9 (d, $J = 10.8$ Hz), 126.6, 125.7, 124.1 (d, $J = 4.8$ Hz), 122.3 (d, $J = 1.9$ Hz), 113.8 (d, $J = 2.0$ Hz), 106.7, 61.5, 60.9, 56.6, 56.3; MS (ESI): 398 (M+H)⁺.

[6-(2-Fluoro-3-hydroxyphenyl)pyridin-2-yl](2,3,4-trihydroxyphenyl)methanone (14).



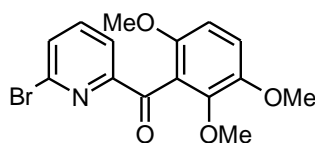
According to method E the title compound was prepared by reaction of (2,3,4-trimethoxyphenyl)[(6-(2-fluoro-3-methoxyphenyl)pyridin-2-yl)methanone (**14a**) (119 mg, 0.30 mmol, 1.0 eq) with boron tribromide (9.0 ml, 9.0 mmol, 30 eq) in dichloromethane (6.0 ml). The product was purified by column chromatography (cyclohexane/ethyl acetate 2:1, 3% acetic acid) and preparative HPLC (gradient water/acetonitrile/trifluoroacetic acid 80:20:0.1→0:100:0.1, in 160 min) to give 33 mg (0.10 mmol/ 32%) of the analytically pure compound. C₁₈H₁₂FNO₅; MW: 341; mp: 137-138 °C; ¹H NMR (acetone-*d*₆, 400 MHz): δ 12.79 (s, 1H), 9.20 (bs, 3H), 8.15 (t, $J = 7.8$ Hz, 1H), 8.03 (ddd, $J = 8.0$ Hz, 2.0 Hz, 1.0 Hz, 1H), 7.89 (dd, $J = 7.7$ Hz, 0.7 Hz, 1H), 7.75 (d, $J = 9.0$ Hz, 1H), 7.43 (dt, $J = 6.6$ Hz, 3.3 Hz, 1H), 7.17-7.09 (m, 2H), 6.51 (d, $J = 9.0$ Hz, 1H); ¹³C NMR (acetone-*d*₆, 100 MHz): δ 197.0, 156.8, 154.2, 153.4, 153.1 (d, $J = 2.2$ Hz), 150.7 (d, $J = 245.5$ Hz), 146.5 (d, $J = 13.7$ Hz), 139.0, 133.1, 128.5 (d, $J = 10.4$ Hz), 128.0, 127.0 (d, $J = 9.0$ Hz), 125.3 (d, $J = 4.7$ Hz), 123.6, 121.8 (d, $J = 1.7$ Hz), 119.4 (d, $J = 3.2$ Hz), 113.4, 108.6; IR: 3323, 1629, 1569, 1509, 1478, 1436, 1286, 1246, 1190, 1159, 1001, 991, 768 cm⁻¹; MS (ESI): 342 (M+H)⁺.

(6-Bromopyridin-2-yl)(2,3,6-trimethoxyphenyl)methanol (15c)



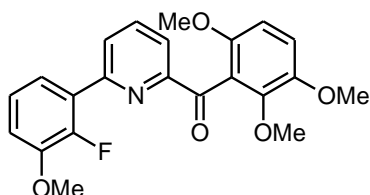
According to method A1 the title compound was prepared by reaction of 2,6-dibromopyridine (**1d**) (1.18 g, 5.00 mmol, 1.0 eq) with 2,3,6-trimethoxybenzaldehyde (**15d**) (0.98 g, 5.00 mmol, 1.0 eq). The product was used in the next step without further purification. C₁₅H₁₆BrNO₄; MW: 354; ¹H NMR (CDCl₃, 400 MHz): δ 7.44 (t, $J = 7.7$ Hz, 1H), 7.30 (dt, $J = 7.8$ Hz, 0.8 Hz, 1H), 7.22 (dt, $J = 7.6$ Hz, 0.8 Hz, 1H), 6.81 (d, $J = 9.0$ Hz, 1H), 6.57 (d, $J = 9.0$ Hz, 1H), 6.26 (s, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 3.71 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 164.3, 151.9, 148.2, 147.4, 140.9, 138.6, 126.0, 125.0, 119.3, 112.5, 106.6, 68.4, 61.3, 56.4, 56.3; MS (ESI): 354, 356 (M+H)⁺.

(6-Bromopyridin-2-yl)(2,3,6-trimethoxyphenyl)methanone (15b).



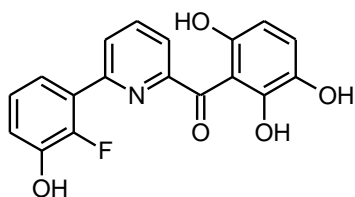
According to method B the title compound was prepared by reaction of (6-bromopyridin-2-yl)(2,3,6-trimethoxyphenyl)methanol (**15c**) with 2-iodoxybenzoic acid (1.46 g, 6.0 mmol, 1.2 eq) for 2 h. The product was purified by column chromatography (cyclohexane/ethyl acetate 7:1) to give 1.10 g (3.12 mmol/ 72%, two steps) of the analytically pure compound. $C_{15}H_{14}BrNO_4$; MW: 352; 1H NMR ($CDCl_3$, 400 MHz): δ 7.99 (dd, $J = 7.5$ Hz, 1.0 Hz, 1H), 7.69 (dd, $J = 8.1$ Hz, 7.6 Hz, 1H), 7.61 (dd, $J = 7.9$ Hz, 1.0 Hz, 1H), 6.94 (d, $J = 9.0$ Hz, 1H), 6.63 (d, $J = 9.0$ Hz, 1H), 3.84 (s, 3H), 3.73 (s, 3H), 3.66 (s, 3H); MS (ESI): 352, 354 ($M+H$) $^+$.

[6-(2-Fluoro-3-methoxyphenyl)pyridin-2-yl](2,3,6-trimethoxyphenyl)methanone (15a).



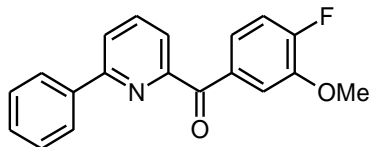
According to method C1 the title compound was prepared by reaction of (6-bromopyridin-2-yl)(2,3,6-trimethoxyphenyl)methanone (**15b**) (176 mg, 0.50 mmol, 1.0 eq) with 2-fluoro-3-methoxyphenylboronic acid (102 mg, 0.60 mmol, 1.2 eq) in DME/water (6.0 ml). The product was purified by column chromatography (cyclohexane/ethyl acetate 5:1) to give 160 mg (0.40 mmol/ 81%) of the analytically pure compound. $C_{22}H_{20}FNO_5$; MW: 397; 1H NMR ($CDCl_3$, 400 MHz): δ 8.04 (dd, $J = 7.6$ Hz, 1.1 Hz, 1H), 7.99 (ddd, $J = 7.9$ Hz, 1.9 Hz, 1.2 Hz, 1H), 7.91 (t, $J = 7.7$ Hz, 1H), 7.39 (ddd, $J = 8.1$ Hz, 6.8 Hz, 1.7 Hz, 1H), 7.05 (dt, $J = 8.1$ Hz, 1.4 Hz, 1H), 6.96 (dt, $J = 8.0$ Hz, 1.6 Hz, 1H), 6.94 (d, $J = 9.0$ Hz, 1H), 6.63 (d, $J = 9.0$ Hz, 1H), 3.90 (s, 3H), 3.85 (s, 3H), 3.70 (s, 3H), 3.64 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.3, 154.1, 152.6 (d, $J = 2.2$ Hz), 151.6, 151.0 (d, $J = 250.3$ Hz), 148.2 (d, $J = 11.5$ Hz), 147.5, 146.9, 137.4, 127.7 (d, $J = 11.4$ Hz), 127.4 (d, $J = 8.8$ Hz), 124.6, 124.0 (d, $J = 4.9$ Hz), 122.4 (d, $J = 2.3$ Hz), 121.7, 114.3, 113.7 (d, $J = 2.3$ Hz), 106.2, 61.5, 56.8, 56.5, 56.4; MS (ESI): 398 ($M+H$) $^+$.

[6-(2-Fluoro-3-hydroxyphenyl)pyridin-2-yl](2,3,6-trihydroxyphenyl)methanone (15)



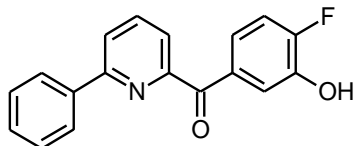
According to method E the title compound was prepared by reaction of [6-(2-fluoro-3-methoxyphenyl)pyridin-2-yl](2,3,6-trimethoxyphenyl)methanone (**15a**) (117 mg, 0.29 mmol, 1.0 eq) with boron tribromide (6.0 ml, 6.0 mmol, 20 eq) in dichloromethane (6.0 ml). The product was purified by column chromatography (cyclohexane/ethyl acetate 3:1, 3% acetic acid) and preparative HPLC (gradient water/acetonitrile/trifluoroacetic acid 80:20:0.1→50:50:0.1, in 150 min) to give 47 mg (0.14 mmol/ 48%) of the analytically pure compound. C₁₈H₁₂FNO₅; MW: 341; mp: 204-205 °C; ¹H NMR (acetone-*d*₆, 400 MHz): δ 12.45 (s, 1H), 11.18 (s, 1H), 8.94 (d, *J* = 1.5 Hz, 1H), 8.28 (t, *J* = 7.9 Hz, 1H), 8.14 (dd, *J* = 7.9 Hz, 0.9 Hz, 1H), 8.10 (ddd, *J* = 7.9 Hz, 2.3 Hz, 0.6 Hz, 1H), 7.37-7.32 (m, 1H), 7.31 (s, 1H), 7.19-7.12 (m, 2H), 7.02 (d, *J* = 8.7 Hz, 1H), 6.33 (d, *J* = 8.7 Hz, 1H); ¹³C NMR (acetone-*d*₆, 100 MHz): δ 197.1, 156.5, 155.6, 152.2 (d, *J* = 1.6 Hz), 150.3 (d, *J* = 245.2 Hz), 149.1, 146.5 (d, *J* = 13.5 Hz), 140.3, 139.4, 128.8 (d, *J* = 7.8 Hz), 127.4 (d, *J* = 9.8 Hz), 125.6 (d, *J* = 4.7 Hz), 124.4, 123.6, 121.9 (d, *J* = 1.4 Hz), 119.9 (d, *J* = 3.3 Hz), 112.7, 107.5; IR: 3356, 1638, 1575, 1508, 1463, 1202, 1168, 775 cm⁻¹; MS (ESI): 342 (M+H)⁺.

(4-Fluoro-3-methoxyphenyl)[6-phenylpyridin-2-yl]methanone (16a).



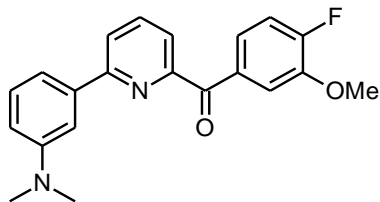
According to method C2 the title compound was prepared by reaction of (6-bromopyridin-2-yl)(4-fluoro-3-methoxyphenyl)methanone (**1b**) (155 mg, 0.50 mmol, 1.0 eq) with phenylboronic acid (73 mg, 0.60 mmol, 1.2 eq) in DME/water (6.0 ml). The product was purified by column chromatography (cyclohexane/ethyl acetate 10:1) to give 137 mg (0.45 mmol/ 89%) of the analytically pure compound. C₁₉H₁₄FNO₂; MW: 307; mp: 122-123 °C; ¹H NMR (CDCl₃, 400 MHz): δ 8.07-8.03 (m, 2H), 8.02-7.95 (m, 4H), 7.88 (ddd, *J* = 8.5 Hz, 4.6 Hz, 2.0 Hz, 1H), 7.52-7.42 (m, 3H), 7.19 (dd, *J* = 10.8 Hz, 8.5 Hz, 1H), 3.95 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 191.9, 155.9, 155.7 (d, *J* = 255.2 Hz), 154.8, 147.6 (d, *J* = 11.0 Hz), 138.4, 138.1, 132.9 (d, *J* = 3.5 Hz), 129.7, 129.1, 127.0, 126.1 (d, *J* = 8.0 Hz), 123.2, 122.7, 116.0 (d, *J* = 3.2 Hz), 115.6 (d, *J* = 18.9 Hz), 56.4; IR: 1665, 1604, 1580, 1518, 1447, 1414, 1322, 1272, 1219, 1140, 1227, 750 cm⁻¹; MS (ESI): 308 (M+H)⁺.

(4-Fluoro-3-hydroxyphenyl)[6-phenylpyridin-2-yl]methanone (16).



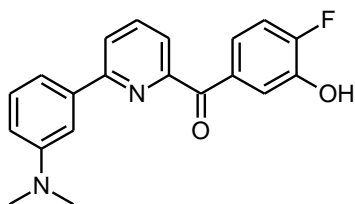
According to method E the title compound was prepared by reaction of (4-fluoro-3-methoxyphenyl)[6-phenylpyridin-2-yl]methanone (**16a**) (92 mg, 0.30 mmol, 1.0 eq) with boron tribromide (1.5 ml, 1.5 mmol, 5.0 eq) in dichloromethane (6.0 ml). The product was purified by column chromatography (cyclohexane/ethyl acetate 8:1) to give 73 mg (0.25 mmol/ 83%) of the analytically pure compound. $C_{18}H_{12}FNO_2$; MW: 293; mp: 181-182 °C; 1H NMR (DMSO- d_6 , 400 MHz): δ 10.32 (bs, 1H), 8.23 (d, J = 8.0 Hz, 1H), 8.14 (t, J = 7.8 Hz, 1H), 8.09 (d, J = 7.3 Hz, 2H), 7.90 (d, J = 7.6 Hz, 1H), 7.71 (dd, J = 8.7 Hz, 2.1 Hz, 1H), 7.57 (ddd, J = 8.4 Hz, 4.4 Hz, 2.1 Hz, 1H), 7.55-7.43 (m, 3H), 7.34 (dd, J = 10.9 Hz, 8.6 Hz, 1H); ^{13}C NMR (DMSO- d_6 , 100 MHz): δ 191.9, 155.0, 154.4, 154.3 (d, J = 250.3 Hz), 144.9 (d, J = 12.3 Hz), 138.8, 137.8, 132.6 (d, J = 3.2 Hz), 129.6, 129.0, 126.9, 123.3 (d, J = 7.8 Hz), 123.0, 122.8, 119.9 (d, J = 4.5 Hz), 116.2 (d, J = 19.0 Hz); IR: 3385, 1658, 1598, 1580, 1528, 1431, 1322, 1233, 1192, 747 cm^{-1} ; MS (ESI): 294 (M+H) $^+$.

[6-(3-(*N,N*-Dimethylamino)-phenyl)pyridin-2-yl](4-fluoro-3-methoxyphenyl)methanone (17a).



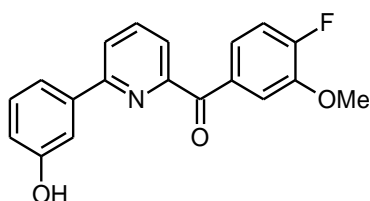
According to method C1 the title compound was prepared by reaction of (6-bromopyridin-2-yl)(4-fluoro-3-methoxyphenyl)methanone (**1b**) (155 mg, 0.50 mmol, 1.0 eq) with 3-(*N,N*-dimethylamino)-phenylboronic acid (100 mg, 0.60 mmol, 1.2 eq) in DME/water (6.0 ml). The product was purified by column chromatography (cyclohexane/ethyl acetate 7:1) to give 152 mg (0.43 mmol/ 87%) of the analytically pure compound. $C_{21}H_{19}FN_2O_2$; MW: 350; 1H NMR (CDCl $_3$, 400 MHz): δ 8.01 (dd, J = 6.0 Hz, 2.8 Hz, 1H), 7.99-7.92 (m, 4H), 7.57-7.44 (m, 1H), 7.42-7.30 (m, 2H), 7.16 (dd, J = 10.9 Hz, 8.5 Hz, 1H), 6.91-6.78 (m, 1H), 3.95 (s, 3H), 3.01 (s, 6H); ^{13}C NMR (CDCl $_3$, 100 MHz): δ 191.9, 155.6 (d, J = 254.9 Hz), 154.5, 147.5 (d, J = 11.0 Hz), 138.0, 133.1 (d, J = 3.5 Hz), 129.7, 126.3 (d, J = 7.8 Hz), 123.0, 122.9, 116.0 (d, J = 3.2 Hz), 115.3 (d, J = 18.8 Hz), 56.4; MS (ESI): 351 (M+H) $^+$.

[6-(3-(*N,N*-Dimethylamino)-phenyl)pyridin-2-yl](4-fluoro-3-hydroxyphenyl)methanone trifluoroacetate salt (17**).**



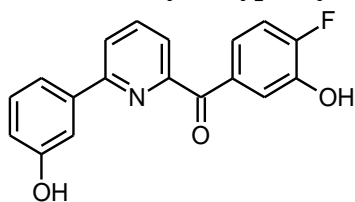
According to method E the title compound was prepared by reaction of [6-(3-(*N,N*-dimethylamino)-phenyl)pyridin-2-yl](4-fluoro-3-methoxyphenyl)methanone (**17a**) (105 mg, 0.30 mmol, 1.0 eq) with boron tribromide (1.5 ml, 1.5 mmol, 5 eq) in dichloromethane (4.0 ml). The crude product was purified by column chromatography (cyclohexane/ethyl acetate 5:1) and preparative HPLC (gradient water/acetonitrile/trifluoroacetic acid 80:20:0.1→35:65:0.1, in 120 min) to give 75 mg (0.22 mmol/ 74%) of the analytically pure compound. C₂₀H₁₇FN₂O₂·TFA; MW: 450; mp: 146-147 °C; ¹H NMR (acetone-*d*₆, 400 MHz)*: δ 9.06 (s, 1H), 8.17 (dd, *J* = 8.0 Hz, 1.0 Hz, 1H), 8.09 (t, *J* = 7.8 Hz, 1H), 8.00-7.92 (m, 2H), 7.82 (ddd, *J* = 8.5 Hz, 4.6 Hz, 2.1 Hz, 1H), 7.61 (dd, *J* = 2.5 Hz, 1.7 Hz, 1H), 7.40 (ddd, *J* = 7.7 Hz, 1.5 Hz, 0.9 Hz, 1H), 7.35-7.26 (m, 2H), 6.85 (ddd, *J* = 8.2 Hz, 2.7 Hz, 0.8 Hz, 1H), 2.99 (s, 6H); ¹³C NMR (acetone-*d*₆, 100 MHz)*: δ 192.1, 157.1, 155.3, 155.3 (d, *J* = 249.3 Hz), 152.1, 145.4, (d, *J* = 13.0 Hz), 139.6, 139.1, 134.3 (d, *J* = 3.4 Hz), 130.2, 124.9 (d, *J* = 7.6 Hz), 123.5, 123.3, 121.6 (d, *J* = 4.3 Hz), 116.5 (d, *J* = 19.2 Hz), 115.7, 114.5, 111.7, 40.6; IR: 3400, 1657, 1594, 1529, 1504, 1580, 1434, 764 cm⁻¹; MS (ESI): 337 (M+H)⁺; *measured as base.

(4-Fluoro-3-methoxyphenyl)[6-(3-hydroxyphenyl)pyridin-2-yl]methanone (18a**).**



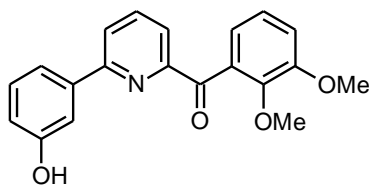
According to method C1 the title compound was prepared by reaction of (6-bromopyridin-2-yl)(4-fluoro-3-methoxyphenyl)methanone (**1b**) (155 mg, 0.50 mmol, 1.0 eq) with 3-hydroxyphenylboronic acid (83 mg, 0.60 mmol, 1.2 eq) in DME/water (6.0 ml). The product was purified by column chromatography (cyclohexane/ethyl acetate 15:1→10:1→5:1→2:1) to give 147 mg (0.46 mmol/ 76%) of the analytically pure compound. C₁₉H₁₄FO₃; MW: 323; ¹H NMR (acetone-*d*₆, 400 MHz): δ 8.56 (bs, 1H), 8.19-8.09 (m, 2H), 8.06 (d, *J* = 8.6 Hz, 1H), 7.98 (d, *J* = 7.4 Hz, 1H), 7.85 (ddd, *J* = 8.5 Hz, 4.5 Hz, 2.0 Hz, 1H), 7.68 (d, *J* = 1.5 Hz, 1H), 7.62 (dd, *J* = 7.8 Hz, 0.9 Hz, 1H), 7.37-7.28 (m, 2H), 6.97-6.92 (m, 1H), 3.96 (s, 3H); ¹³C NMR (acetone-*d*₆, 100 MHz): δ 191.9, 158.9, 156.3, 156.1 (d, *J* = 253.3 Hz), 155.5, 148.3 (d, *J* = 11.0 Hz), 140.6, 139.3, 134.1 (d, *J* = 3.6 Hz), 130.8, 126.1 (d, *J* = 7.9 Hz), 123.7, 123.5, 118.9, 117.5, 116.8 (d, *J* = 3.2 Hz), 116.4 (d, *J* = 18.9 Hz), 114.5, 56.5; MS (ESI): 324 (M+H)⁺.

(4-Fluoro-3-hydroxyphenyl)[6-(3-hydroxyphenyl)pyridin-2-yl]methanone (18).



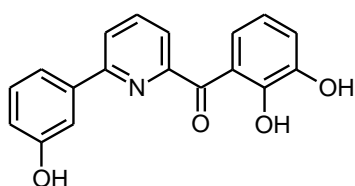
According to method E the title compound was prepared by reaction of (4-fluoro-3-methoxyphenyl)[6-(3-hydroxyphenyl)pyridin-2-yl]methanone (**18a**) (97 mg, 0.30 mmol, 1.0 eq) with boron tribromide (3.0 ml, 3.0 mmol, 10 eq) in dichloromethane (6.0 ml). The product was purified by column chromatography (cyclohexane/ethyl acetate 2:1) to give 91 mg (0.24 mmol/ 98%) of the analytically pure compound. $C_{18}H_{12}FNO_3$; MW: 309; mp: 218-219 °C; 1H NMR (acetone- d_6 , 400 MHz): δ 8.75 (bs, 2H), 8.18-8.08 (m, 2H), 7.93 (dd, $J = 7.3$ Hz, 1.3 Hz, 1H), 7.86 (dd, $J = 8.7$ Hz, 2.1 Hz, 1H), 7.75 (ddd, $J = 8.5$ Hz, 4.6 Hz, 2.2 Hz, 1H), 7.67-7.63 (m, 1H), 7.61 (ddd, $J = 7.7$ Hz, 1.7 Hz, 1.0 Hz, 1H), 7.33 (t, $J = 7.9$ Hz, 1H), 7.29 (dd, $J = 10.8$ Hz, 8.5 Hz, 1H), 6.94 (ddd, $J = 8.1$ Hz, 2.5 Hz, 0.9 Hz, 1H); ^{13}C NMR (acetone- d_6 , 100 MHz): δ 192.3, 158.8, 156.3, 155.8, 155.4 (d, $J = 249.5$ Hz), 145.6 (d, $J = 13.0$ Hz), 140.7, 139.2, 134.1 (d, $J = 3.4$ Hz), 130.8, 124.9 (d, $J = 7.6$ Hz), 123.5, 123.4, 121.3 (d, $J = 4.1$ Hz), 118.9, 117.4, 116.6 (d, $J = 19.2$ Hz), 114.6; IR: 3394, 1659, 1598, 1580, 1459, 1431, 1237, 755 cm^{-1} ; MS (ESI): 310 (M+H) $^+$.

(2,3-Dimethoxyphenyl)[6-(3-hydroxyphenyl)pyridin-2-yl]methanone (19a).



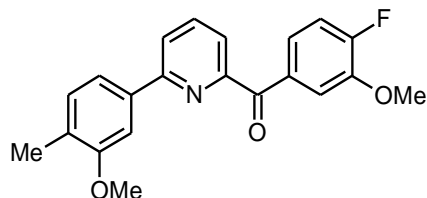
According to method C1 the title compound was prepared by reaction of (6-bromopyridin-2-yl)(2,3-dimethoxyphenyl)methanone (**12b**) (135 mg, 0.42 mmol, 1.0 eq) with 3-hydroxyphenylboronic acid (70 mg, 0.50 mmol, 1.2 eq) in DME/water (6.0 ml). The product was purified by column chromatography (cyclohexane/ethyl acetate 4:1) to give 136 mg (0.41 mmol/ 97%) of the analytically pure compound. $C_{20}H_{17}NO_4$; MW: 335; 1H NMR ($CDCl_3$, 400 MHz): δ 7.95-7.83 (m, 3H), 7.47-7.40 (m, 2H), 7.28-7.21 (m, 1H), 7.16-7.08 (m, 2H), 7.04 (dt, $J = 7.5$ Hz, 2.6 Hz, 1H), 6.84 (dd, $J = 8.0$ Hz, 2.3 Hz, 1H), 3.85 (s, 3H), 3.60 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.5, 156.4, 156.1, 154.9, 152.6, 148.1, 139.9, 137.8, 133.4, 130.0, 123.8, 123.2, 122.0, 121.8, 119.1, 116.6, 115.4, 114.2, 61.5, 56.1; MS (ESI): 336 (M+H) $^+$.

(2,3-Dihydroxyphenyl)[6-(3-hydroxyphenyl)pyridin-2-yl]methanone (19).



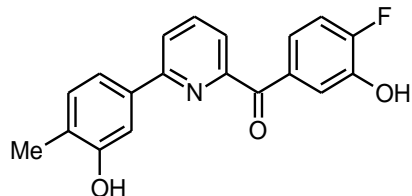
According to method E the title compound was prepared by reaction of (2,3-dimethoxyphenyl)[6-(3-methoxyphenyl)pyridin-2-yl]methanone (**19a**) (101 mg, 0.37 mmol, 1.0 eq) with boron tribromide (3.7 ml, 3.7 mmol, 10 eq) in dichloromethane (6.0 ml). The product was purified by column chromatography (cyclohexane/ethyl acetate 4:1, 3% acetic acid) to give 68 mg (0.22 mmol/ 60%) of the analytically pure compound. C₁₈H₁₃NO₄; MW: 307; mp: 149-150 °C; ¹H NMR (acetone-*d*₆, 400 MHz): δ 12.6 (s, 1H), 8.59 (s, 1H), 8.20-8.13 (m, 2H), 8.04 (s, 1H), 7.96-7.89 (m, 1H), 7.70 (dt, *J* = 8.2 Hz, 1.7 Hz, 1H), 7.67-7.63 (m, 1H), 7.63-7.58 (m, 1H), 7.35 (dt, *J* = 8.0 Hz, 1.8 Hz, 1H), 7.20-7.14 (m, 1H), 6.99-6.94 (m, 1H), 6.84 (dt, *J* = 2.0 Hz, 8.2 Hz, 1H); ¹³C NMR (acetone-*d*₆, 100 MHz): δ 198.5, 158.9, 156.4, 155.9, 152.1, 147.3, 140.3, 139.7, 130.9, 125.7, 123.8, 123.6, 121.9, 120.6, 119.6, 119.1, 117.6, 114.6; IR: 3354, 1614, 1582, 1457, 1224, 1207, 733 cm⁻¹; MS (ESI): 308 (M+H)⁺.

(4-Fluoro-3-methoxyphenyl)[6-(3-methoxy-4-methylphenyl)pyridin-2-yl]methanone (20a).



According to method C1 the title compound was prepared by reaction of (6-bromopyridin-2-yl)(4-fluoro-3-methoxyphenyl)methanone (**1b**) (155 mg, 0.50 mmol, 1.0 eq) with 3-methoxy-4-methylphenylboronic acid (100 mg, 0.60 mmol, 1.2 eq) in DME/water (6.0 ml). The product was purified by column chromatography (cyclohexane/ethyl acetate 10:1→5:1) to give 156 mg (0.44 mmol/ 74 %) of the analytically pure compound. C₂₁H₁₈FNO₃; MW: 351; ¹H NMR (acetone-*d*₆, 400 MHz): δ 8.21 (dd, *J* = 8.0 Hz, 1.0 Hz, 1H), 8.11 (t, *J* = 7.8 Hz, 1H), 8.01-7.96 (m, 2H), 7.94 (ddd, *J* = 8.4 Hz, 4.6 Hz, 2.0 Hz, 1H), 7.74 (d, *J* = 1.4 Hz, 1H), 7.67-7.62 (m, 1H), 7.34 (dd, *J* = 11.0 Hz, 8.4 Hz, 1H), 7.28-7.23 (m, 1H), 3.96 (s, 3H), 3.89 (s, 3H), 2.22 (s, 3H); ¹³C NMR (acetone-*d*₆, 100 MHz): δ 192.0, 159.1, 156.4, 156.1 (d, *J* = 252.0 Hz), 155.3, 148.3 (d, *J* = 10.9 Hz), 139.3, 138.2, 134.2, (d, *J* = 3.7 Hz), 131.6, 129.8, 126.4 (d, *J* = 7.9 Hz), 123.4, 123.3, 119.5, 116.7 (d, *J* = 3.2 Hz), 116.1 (d, *J* = 19.0 Hz), 109.1, 56.6, 55.6, 16.2; MS (ESI): 352 (M+H)⁺.

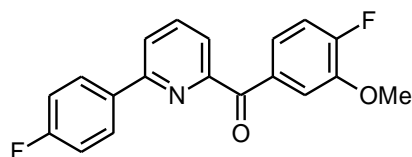
(4-Fluoro-3-hydroxyphenyl)[6-(3-hydroxy-4-methylphenyl)pyridin-2-yl]methanone (20).



According to method E the title compound was prepared by reaction of (4-fluoro-3-methoxyphenyl)[6-(3-methoxy-4-methylphenyl)pyridin-2-yl]methanone (**20a**) (105 mg, 0.30 mmol, 1.0 eq) with boron tribromide (3.0 ml, 3.0 mmol, 10 eq) in dichloromethane (6.0 ml). The product was purified by column chromatography (cyclohexane/ethyl acetate 3:1) to give 95 mg (0.24 mmol/ 98%) of the analytically pure compound. C₁₉H₁₄FNO₃; MW: 323; 224-225 °C; ¹H NMR (acetone-*d*₆, 400 MHz): δ

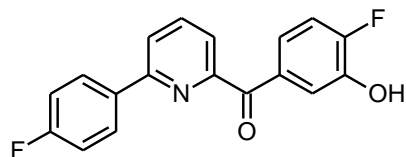
8.66 (bs, 2H), 8.12-8.05 (m, 2H), 7.88 (dd, $J = 4.7$ Hz, 2.1 Hz, 1H), 7.86 (dd, $J = 6.6$ Hz, 2.0 Hz, 1H), 7.76 (ddd, $J = 8.5$ Hz, 4.6 Hz, 2.2 Hz, 1H), 7.65 (d, $J = 1.8$ Hz, 1H), 7.53 (dd, $J = 7.8$ Hz, 1.8 Hz, 1H), 7.29 (dd, $J = 10.8$ Hz, 8.5 Hz, 1H), 7.24-7.19 (m, 1H), 2.25 (s, 3H); ^{13}C NMR (acetone- d_6 , 100 MHz): δ 192.3, 156.7, 156.4, 155.8, 155.4 (d, $J = 249.5$ Hz), 145.6 (d, $J = 12.9$ Hz), 139.1, 138.1, 134.1 (d, $J = 3.4$ Hz), 132.0, 127.0, 124.9 (d, $J = 7.6$ Hz), 123.2, 123.0, 121.3 (d, $J = 4.2$ Hz), 118.8, 116.7 (d, $J = 19.2$ Hz), 113.8, 16.1; IR: 3386, 1659, 1599, 1580, 1456, 1431, 1237, 756 cm^{-1} ; MS (ESI): 324 (M+H) $^{+}$.

(4-Fluoro-3-methoxyphenyl)[6-(4-fluorophenyl)pyridin-2-yl]methanone (21a).



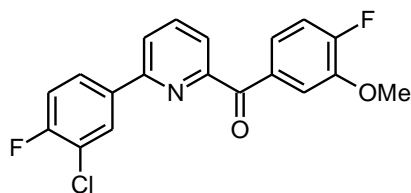
According to method C2 the title compound was prepared by reaction of (6-bromopyridin-2-yl)(4-fluoro-3-methoxyphenyl)methanone (**1b**) (156 mg, 0.50 mmol, 1.0 eq) with 4-fluorophenylboronic acid (85 mg, 0.60 mmol, 1.2 eq) in DME/water (6.0 ml). The product was purified by column chromatography (cyclohexane/ethyl acetate 9:1 \rightarrow 7:1) to give 128 mg (0.33 mmol/ 78 %) of the analytically pure compound. $\text{C}_{19}\text{H}_{13}\text{F}_2\text{NO}_2$; MW: 325; ^1H NMR (CDCl_3 , 400 MHz): δ 8.04 (dd, $J = 9.1$ Hz, 5.4 Hz, 2H), 8.00-7.96 (m, 2H), 7.96-7.90 (m, 2H), 7.84 (ddd, $J = 8.5$ Hz, 4.6 Hz, 2.0 Hz, 1H), 7.21-7.12 (m, 3H), 3.94 (s, 3H); MS (ESI): 326 (M+H) $^{+}$.

(4-Fluoro-3-hydroxyphenyl)[6-(4-fluorophenyl)pyridin-2-yl]methanone (21).



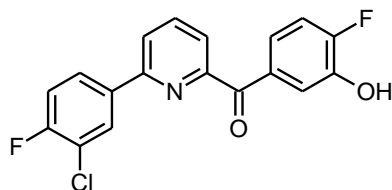
According to method E the title compound was prepared by reaction of (4-fluoro-3-methoxyphenyl)[6-(4-fluorophenyl)pyridin-2-yl]methanone (**21a**) (120 mg, 0.37 mmol, 1.0 eq) with boron tribromide (1.9 ml, 1.90 mmol, 5.0 eq) in dichloromethane (7.0 ml). The product was purified by column chromatography (cyclohexane/ethyl acetate 3:1) to give 101 mg (0.32 mmol/ 88%) of the analytically pure compound. $\text{C}_{18}\text{H}_{11}\text{F}_2\text{NO}_2$; MW: 311; mp: 207-208 $^{\circ}\text{C}$; ^1H NMR (acetone- d_6 , 400 MHz): δ 9.07 (s, 1H), 8.23-8.16 (m, 3H), 8.16-8.09 (m, 1H), 7.94 (d, $J = 7.5$ Hz, 1H), 7.85 (dd, $J = 8.7$ Hz, 2.1 Hz, 1H), 7.73 (ddd, $J = 8.5$ Hz, 4.5 Hz, 2.2 Hz, 1H), 7.34-7.20 (m, 3H); ^{13}C NMR (acetone- d_6 , 100 MHz): δ 192.3 (d, $J = 1.0$ Hz), 164.6 (d, $J = 244.8$ Hz), 155.8, 155.4 (d, $J = 249.5$ Hz), 155.3, 145.5 (d, $J = 13.1$ Hz), 139.4, 135.6 (d, $J = 3.2$ Hz), 134.1 (d, $J = 3.4$ Hz), 129.9 (d, $J = 8.6$ Hz), 124.9 (d, $J = 7.7$ Hz), 123.3 (d, $J = 19.9$ Hz), 121.2 (d, $J = 4.3$ Hz), 116.6 (d, $J = 19.4$ Hz), 116.6, 116.4; IR: 3391, 1657, 1598, 1584, 1513, 1434, 1300, 1232, 758 cm^{-1} ; MS (ESI): 312 (M+H) $^{+}$.

[6-(3-Chloro-4-fluorophenyl)pyridin-2-yl](4-fluoro-3-methoxyphenyl)methanone (22a).



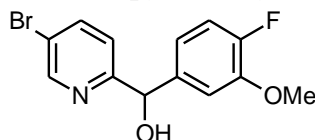
According to method C1 the title compound was prepared by reaction of (6-bromopyridin-2-yl)(4-fluoro-3-methoxyphenyl)methanone (**1b**) (154 mg, 0.50 mmol, 1.0 eq) with 3-chloro-4-fluoroboronic acid (104 mg, 0.60 mmol, 1.2 eq) in DME/water (6.0 ml). The product was purified by column chromatography (cyclohexane/ethyl acetate 9:1) to give 158 mg (0.44 mmol/ 88 %) of the analytically pure compound. $C_{19}H_{12}ClF_2NO_2$; MW: 360; 1H NMR ($CDCl_3$, 400 MHz): δ 8.12 (dd, $J = 7.1$ Hz, 2.3 Hz, 1H), 8.04-7.88 (m, 5H), 7.81 (ddd, $J = 8.4$ Hz, 4.5 Hz, 2.0 Hz, 1H), 7.25 (t, $J = 8.6$ Hz, 1H), 7.19 (dd, $J = 10.7$ Hz, 8.5 Hz, 1H), 3.96 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.6, 159.1 (d, $J = 252.1$ Hz), 155.8 (d, $J = 255.6$ Hz), 155.0, 153.7 (d, $J = 1.0$ Hz), 147.7 (d, $J = 10.8$ Hz), 138.4, 135.6 (d, $J = 3.9$ Hz), 132.7 (d, $J = 3.5$ Hz), 129.4, 126.8 (d, $J = 7.6$ Hz), 126.0 (d, $J = 7.9$ Hz), 123.6, 122.4, 121.9, 117.2 (d, $J = 21.3$ Hz), 115.9 (d, $J = 3.3$ Hz), 115.7 (d, $J = 18.9$ Hz), 56.5; MS (ESI): 360, 362 ($M+H$) $^+$.

[6-(3-Chloro-4-fluorophenyl)pyridin-2-yl](4-fluoro-3-hydroxyphenyl)methanone (22).



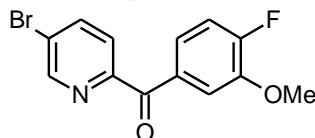
According to method E the title compound was prepared by reaction of [6-(3-chloro-4-fluorophenyl)pyridin-2-yl](4-fluoro-3-methoxyphenyl)methanone (**22a**) (115 mg, 0.32 mmol, 1.0 eq) with boron tribromide (1.6 ml, 1.6 mmol, 5.0 eq) in dichloromethane (6.0 ml). The crude product was purified by column chromatography (cyclohexane/ethyl acetate 3:1) to give 105 mg (0.30 mmol/ 95%) of the analytically pure compound. $C_{18}H_{10}ClF_2NO_2$; MW: 346; mp: 208-209 $^{\circ}C$; 1H NMR (acetone- d_6 , 400 MHz): δ 9.09 (d, $J = 1.2$ Hz, 1H), 8.29 (dd, $J = 7.2$ Hz, 2.2 Hz, 1H), 8.27 (dd, $J = 8.0$ Hz, 1.0 Hz, 1H), 8.20-8.13 (m, 2H), 7.98 (dd, $J = 7.0$ Hz, 1.0 Hz, 1H), 7.85 (dd, $J = 8.7$ Hz, 2.1 Hz, 1H), 7.71 (ddd, $J = 8.5$ Hz, 4.5 Hz, 2.2 Hz, 1H), 7.46 (dd, $J = 13.4$ Hz, 4.5 Hz, 1H), 7.30 (dd, $J = 10.8$ Hz, 8.5 Hz, 1H); ^{13}C NMR (acetone- d_6 , 100 MHz): δ 192.2, 159.6 (d, $J = 150.0$ Hz), 155.8, 155.5 (d, $J = 249.6$ Hz), 154.0 (d, $J = 1.3$ Hz), 145.6 (d, $J = 13.1$ Hz), 139.7, 136.9 (d, $J = 3.6$ Hz), 134.0 (d, $J = 3.3$ Hz), 130.0, 128.3 (d, $J = 7.7$ Hz), 124.8 (d, $J = 7.6$ Hz), 124.0, 123.5, 121.8 (d, $J = 18.1$ Hz), 121.2 (d, $J = 4.2$ Hz), 118.0 (d, $J = 21.4$ Hz), 116.7 (d, $J = 19.2$ Hz); IR: 3410, 1657, 1596, 1583, 1506, 1453, 1432, 1236, 755 cm^{-1} ; MS (ESI): 346, 348 ($M+H$) $^+$.

(5-Bromopyridin-2-yl)(4-fluoro-3-methoxyphenyl)methanol (23c).



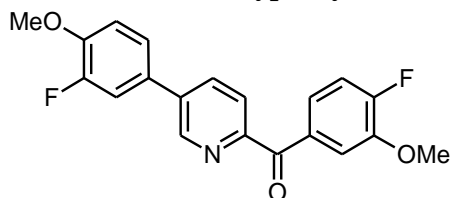
According to method A2 the title compound was prepared by reaction of 4-bromo-1-fluoro-2-methoxybenzene (**23e**) (417 mg, 2.0 mmol, 1.0 eq), magnesium turnings (49 mg, 2.0 mmol, 1.0 eq) and 5-bromopyridine-2-carbaldehyde (**23d**) (417 mg, 1.1 mmol, 2.2 eq). The product was purified by column chromatography (cyclohexane/ethyl acetate 7:1→5:1→3:1) to give 315 mg (1.0 mmol/ 50%) of the analytically pure compound. C₁₃H₁₁BrFNO₂; MW: 312; ¹H NMR (CDCl₃, 400 MHz): δ 8.63 (dd, *J* = 2.0 Hz, 1.6 Hz, 1H), 7.77 (ddd, *J* = 8.4 Hz, 2.3 Hz, 0.9 Hz, 1H), 7.08 (d, *J* = 8.4 Hz, 1H), 7.03 (dd, *J* = 11.0 Hz, 8.3 Hz, 1H), 6.97 (dd, *J* = 8.1 Hz, 2.0 Hz, 1H), 6.87 (ddd, *J* = 7.7 Hz, 4.2 Hz, 1.9 Hz, 1H), 5.67 (s, 1H), 4.79 (s, 1H), 3.85 (s, 3H); MS (ESI): 312, 314 (M+H)⁺.

(5-Bromopyridin-2-yl)(4-fluoro-3-methoxyphenyl)methanone (23b).



According to method B the title compound was prepared by reaction of (5-bromopyridin-2-yl)(4-fluoro-3-methoxyphenyl)methanol (**23c**) (296 mg, 0.95 mmol, 1.0 eq) with 2-iodoxybenzoic acid (531 mg, 1.90 mmol, 2.0 eq) for 4 h. The product was purified by column chromatography (cyclohexane/ethyl acetate 20:1) to give 211 mg (0.68 mmol/ 72 %) of the analytically pure compound. C₁₃H₉BrFNO₂; MW: 310; ¹H NMR (CDCl₃, 400 MHz): δ 8.79-8.74 (m, 1H); 8.05 (dd, *J* = 8.4 Hz, 2.3 Hz, 1H), 7.98-7.91 (m, 1H), 7.77 (dd, *J* = 8.3 Hz, 1.9 Hz, 1H), 7.71 (ddd, *J* = 8.4 Hz, 4.5 Hz, 2.0 Hz, 1H), 7.15 (dd, *J* = 10.7 Hz, 8.5 Hz, 1H), 3.95 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 191.1, 155.9 (d, *J* = 255.9 Hz), 153.3, 149.7, 147.9 (d, *J* = 11.0 Hz), 140.1, 132.4 (d, *J* = 3.5 Hz), 126.2, 125.8 (d, *J* = 8.0 Hz), 124.6, 115.8 (d, *J* = 19.0 Hz), 115.5 (d, *J* = 3.4 Hz), 56.4; MS (ESI): 310, 312 (M+H)⁺.

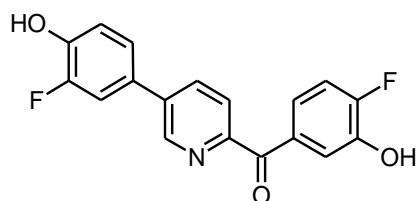
(4-Fluoro-3-methoxyphenyl)[5-(3-fluoro-4-methoxyphenyl)pyridin-2-yl]methanone (23a).



According to method C1 the title compound was prepared by reaction of (5-bromopyridin-2-yl)(4-fluoro-3-methoxyphenyl)methanone (**23b**) (157 mg, 0.51 mmol, 1.0 eq) with 3-fluoro-4-methoxyphenylboronic acid (104 mg, 0.61 mmol, 1.2 eq) in DME/water (6.0 ml). The product was purified by column chromatography (cyclohexane/ethyl acetate 7:1) to give 169 mg (0.48 mmol/ 94%) of the analytically pure compound. C₂₀H₁₅F₂NO₃; MW: 355; mp: 153-154 °C; ¹H NMR (CDCl₃, 400 MHz): δ 8.89 (dd, *J* = 2.2 Hz, 0.7 Hz, 1H), 8.12 (dd, *J* = 8.2 Hz, 0.7 Hz, 1H), 8.03 (dd, *J* = 8.2 Hz,

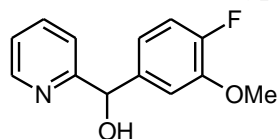
2.3 Hz, 1H), 7.82 (dd, $J = 8.4$ Hz, 2.0 Hz, 1H), 7.77 (ddd, $J = 8.3$ Hz, 4.5 Hz, 2.0 Hz, 1H), 7.45-7.40 (m, 1H), 7.40-7.38 (m, 1H), 7.17 (dd, $J = 10.7$ Hz, 8.4 Hz, 1H), 7.11 (t, $J = 8.6$ Hz, 1H), 3.97 (s, 6H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 191.8, 155.7 (d, $J = 255.3$ Hz), 153.5, 152.9 (d, $J = 247.2$ Hz), 148.6 (d, $J = 10.8$ Hz), 147.8 (d, $J = 10.9$ Hz), 146.6, 137.8 (d, $J = 1.9$ Hz), 134.8, 133.0 (d, $J = 3.7$ Hz), 129.7 (d, $J = 6.7$ Hz), 125.8 (d, $J = 7.8$ Hz), 125.1, 123.4 (d, $J = 3.6$ Hz), 115.7 (d, $J = 19.1$ Hz), 115.6 (d, $J = 3.3$ Hz), 115.1 (d, $J = 19.4$ Hz), 114.1 (d, $J = 2.3$ Hz), 56.5, 56.5; IR: 1652, 1605, 1583, 1513, 1412, 1303, 1266, 1148, 1122, 885 cm^{-1} ; MS (ESI): 356 ($\text{M}+\text{H}$) $^+$.

(4-Fluoro-3-hydroxyphenyl)[5-(3-fluoro-4-hydroxyphenyl)pyridin-2-yl]methanone hydrochloride salt (23).



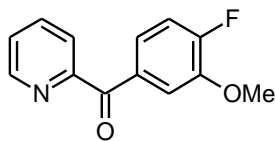
According to method E the title compound was prepared by reaction of (4-fluoro-3-methoxyphenyl)[5-(3-fluoro-4-methoxyphenyl)pyridin-2-yl]methanone (**23a**) (124 mg, 0.35 mmol, 1.0 eq) with boron tribromide (3.5 ml, 3.5 mmol, 10 eq) in dichloromethane (7.0 ml). The crude product was purified by column chromatography (cyclohexane/ethyl acetate 2:1) and the hydrochloride salt was prepared by means of 2 M hydrogen chloride solution in ether to give 113 mg (0.31 mmol/ 89%) of the analytically pure compound. $\text{C}_{18}\text{H}_{11}\text{F}_2\text{NO}_3\cdot\text{HCl}$; MW: 364; mp: 240-241 $^\circ\text{C}$; ^1H NMR ($\text{DMSO}-d_6$, 400 MHz): δ 10.28 (bs, 2H), 9.02 (d, $J = 2.0$ Hz, 1H), 8.30 (dd, $J = 8.2$ Hz, 2.3 Hz, 1H), 8.00 (d, $J = 8.2$ Hz, 1H), 7.73 (dd, $J = 12.6$ Hz, 2.0 Hz, 1H), 7.68 (dd, $J = 8.7$ Hz, 2.1 Hz, 1H), 7.58-7.47 (m, 2H), 7.30 (dd, $J = 10.9$ Hz, 8.6 Hz, 1H), 7.12 (t, $J = 8.8$ Hz, 1H); ^{13}C NMR ($\text{DMSO}-d_6$, 100 MHz): δ 191.3, 154.1 (d, $J = 250.0$ Hz), 152.6, 151.5 (d, $J = 241.3$ Hz), 146.0 (d, $J = 12.1$ Hz), 145.9, 144.8 (d, $J = 12.4$ Hz), 136.8, 134.5, 132.8 (d, $J = 3.2$ Hz), 127.2 (d, $J = 6.4$ Hz), 124.4, 123.6 (d, $J = 2.9$ Hz), 123.2 (d, $J = 7.6$ Hz), 119.9 (d, $J = 4.6$ Hz), 118.5 (d, $J = 3.5$ Hz), 115.9 (d, $J = 19.0$ Hz), 114.9 (d, $J = 19.3$ Hz); IR: 3393, 3063, 1646, 1585, 1511, 1429, 1298, 1226, 1115 cm^{-1} ; MS (ESI): 328 ($\text{M}+\text{H}$) $^+$.

(4-Fluoro-3-methoxyphenyl)(pyridin-2-yl)methanol (24b).



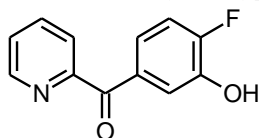
According to method A2 the title compound was prepared by reaction of 4-bromo-1-fluoro-2-methoxybenzene (**23e**) (205 mg, 1.0 mmol, 1.0 eq), magnesium turnings (26 mg, 1.05 mmol, 1.05 eq) and pyridine-2-carbaldehyde (**24c**) (121 mg, 1.1 mmol, 1.1 eq). The product was used in the next step without further purification. $\text{C}_{13}\text{H}_{12}\text{FNO}_2$; MW: 233; MS (ESI): 234 ($\text{M}+\text{H}$) $^+$.

(4-Fluoro-3-methoxyphenyl)(pyridin-2-yl)methanone (24a).



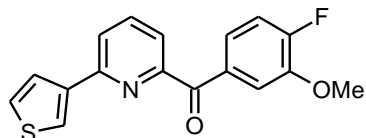
According to method B the title compound was prepared by reaction of (4-fluoro-3-methoxyphenyl)(pyridin-2-yl)methanol (**24b**) with 2-iodoxybenzoic acid (560 mg, 2.0 mmol, 2.0 eq) for 4 h. The product was purified by column chromatography (cyclohexane/ethyl acetate 8:1) to give 106 mg (0.46 mmol/ 46 %, two steps) of the analytically pure compound. $C_{13}H_{10}FNO_2$; MW: 231; 1H NMR ($CDCl_3$, 400 MHz): δ 8.74-8.70 (m, 1H), 8.05-8.01 (m, 1H), 7.94-7.88 (m, 1H), 7.79 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 7.71 (ddd, J = 8.4 Hz, 4.5 Hz, 2.0 Hz, 1H), 7.53-7.48 (m, 1H), 7.15 (dd, J = 10.7 Hz, 8.5 Hz, 1H), 3.95 (s, 3H); MS (ESI): 232 ($M+H$) $^+$.

(4-Fluoro-3-hydroxyphenyl)(pyridin-2-yl)methanone (24).



According to method E the title compound was prepared by reaction of (4-fluoro-3-methoxyphenyl)(pyridin-2-yl)methanone (**24a**) (92 mg, 0.40 mmol, 1.0 eq) with boron tribromide (2.0 ml, 2.0 mmol, 5.0 eq) in dichloromethane (8.0 ml). The product was purified by column chromatography (cyclohexane/ethyl acetate 2:1) to give 23 mg (0.11 mmol/ 26%) of the analytically pure compound. $C_{12}H_8FNO_2$; MW: 217; mp: 140-141 $^{\circ}C$; 1H NMR (acetone- d_6 , 400 MHz): δ 9.05 (bs, 1H), 8.74-8.69 (m, 1H), 8.08-8.02 (m, 1H), 7.99 (dd, J = 7.8 Hz, 1.0 Hz, 1H), 7.82 (dd, J = 8.7 Hz, 2.1 Hz, 1H), 7.67 (ddd, J = 8.6 Hz, 4.6 Hz, 2.2 Hz, 1H), 7.65-7.61 (m, 1H), 7.25 (dd, J = 10.8 Hz, 8.5 Hz, 1H); ^{13}C NMR (acetone- d_6 , 100 MHz): δ 192.3 (d, J = 1.0 Hz), 156.1, 155.4 (d, J = 249.2 Hz), 149.2, 145.4 (d, J = 13.2 Hz), 138.2, 134.1 (d, J = 1.5 Hz), 127.2, 125.0, 124.8 (d, J = 7.7 Hz), 121.3 (d, J = 4.4 Hz), 116.5 (d, J = 20.4 Hz); IR: 3016, 1669, 1589, 1506, 1318, 1288, 749, 197, 599 cm^{-1} ; MS (ESI): 218 ($M+H$) $^+$.

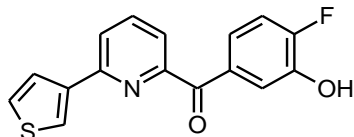
(4-Fluoro-3-methoxyphenyl)[6-(thiophen-3-yl)pyridin-2-yl]methanone (25a).



According to method C1 the title compound was prepared by reaction of (6-bromopyridin-2-yl)(4-fluoro-3-methoxyphenyl)methanone (**1b**) (115 mg, 0.37 mmol, 1.0 eq) with 3-thiophenylboronic acid (50 mg, 0.45 mmol, 1.2 eq) in DME/water (6.0 ml). The product was purified by column chromatography (cyclohexane/ethyl acetate 7:1) to give 109 mg (0.35 mmol/ 94%) of the analytically pure compound. $C_{17}H_{12}FNO_2S$; MW: 313; 1H NMR ($CDCl_3$, 400 MHz): δ 7.96-7.85 (m, 5H), 7.82 (dd, J = 6.0 Hz, 3.0 Hz, 1H), 7.68 (dd, J = 5.1 Hz, 1.3 Hz, 1H), 7.41 (dd, J = 5.1 Hz, 3.0 Hz, 1H), 7.18 (dd,

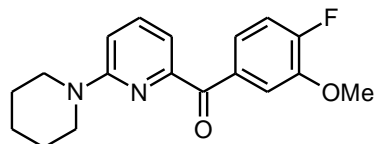
$J = 10.8$ Hz, 8.4 Hz, 1H), 3.95 (s, 3H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 191.8 , 155.6 (d, $J = 255.2$ Hz), 154.7 , 152.1 , 147.5 (d, $J = 11.0$ Hz), 141.5 , 138.0 , 132.9 (d, $J = 3.5$ Hz), 126.8 , 126.2 , 126.0 (d, $J = 7.9$ Hz), 124.4 , 122.7 , 122.5 , 115.9 (d, $J = 3.3$ Hz), 115.5 (d, $J = 18.9$ Hz), 56.4 ; MS (ESI): 314 ($\text{M}+\text{H}$) $^+$.

(4-Fluoro-3-hydroxyphenyl)[6-(thiophen-3-yl)pyridin-2-yl]methanone hydrochloride salt (25).



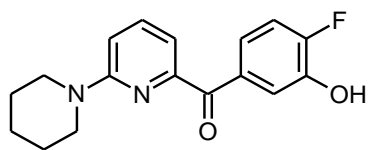
According to method E the title compound was prepared by reaction of (4-fluoro-3-methoxyphenyl)[6-(thiophen-3-yl)pyridin-2-yl]methanone (**25a**) (62 mg, 0.20 mmol, 1.0 eq) with boron tribromide (1.0 ml, 1.0 mmol, 5 eq) in dichloromethane (4.0 ml). The crude product was purified by column chromatography (cyclohexane/ethyl acetate $5:1$) and the hydrochloride salt was prepared by means of 2 M hydrogen chloride solution in ether to give 22 mg (0.07 mmol/ 33%) of the analytically pure compound. $\text{C}_{16}\text{H}_{10}\text{FNO}_2\text{S}\cdot\text{HCl}$; MW: 336 ; mp: 208 - 209 $^\circ\text{C}$; ^1H NMR (acetone- d_6 , 400 MHz): δ 8.99 (bs, 1H), 8.16 (dd, $J = 3.0$ Hz, 1.3 Hz, 1H), 8.11 - 8.04 (m, 2H), 7.89 (dd, $J = 8.7$ Hz, 2.1 Hz, 1H), 7.89 (dd, $J = 6.6$ Hz, 2.1 Hz, 1H), 7.79 (dd, $J = 5.1$ Hz, 1.3 Hz, 1H), 7.77 (ddd, $J = 8.5$ Hz, 4.0 Hz, 2.1 Hz, 1H), 7.58 (dd, $J = 5.1$ Hz, 3.0 Hz, 1H), 7.29 (dd, $J = 10.8$ Hz, 8.5 Hz, 1H); ^{13}C NMR (acetone- d_6 , 100 MHz): δ 192.2 , 155.8 , 155.5 (d, $J = 249.4$ Hz), 153.0 , 145.5 (d, $J = 13.0$ Hz), 142.6 , 139.2 , 134.2 (d, $J = 3.4$ Hz), 127.6 , 127.3 , 125.4 , 124.9 (d, $J = 7.6$ Hz), 123.4 , 123.1 , 121.4 (d, $J = 4.0$ Hz), 116.6 (d, $J = 19.2$ Hz); IR: 3376 , 1655 , 1596 , 1583 , 1525 , 1439 , 1424 , 751 cm^{-1} ; MS (ESI): 300 ($\text{M}+\text{H}$) $^+$.

(4-Fluoro-3-methoxyphenyl)[6-(piperidin-1-yl)pyridin-2-yl]methanone (26a).



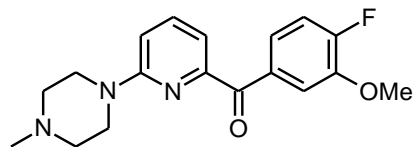
According to method D the title compound was prepared by reaction of (6-bromopyridin-2-yl)(4-fluoro-3-methoxyphenyl)methanone (**1b**) (155 mg, 0.50 mmol, 1.0 eq) with piperidine (59 μl , 0.6 mmol, 1.2 eq) in 1,4-dioxane (2.0 ml). The product was purified by column chromatography (n -pentane/ diethyl ether $7:1$) to give 114 mg (0.36 mmol/ 73%) of the analytically pure compound. $\text{C}_{18}\text{H}_{19}\text{FN}_2\text{O}_2$; MW: 314 ; ^1H NMR (CDCl_3 , 400 MHz): δ 7.84 (dd, $J = 8.5$ Hz, 2.0 Hz, 1H), 7.78 (ddd, $J = 8.5$ Hz, 4.6 Hz, 2.1 Hz, 1H), 7.62 (dd, $J = 8.6$ Hz, 7.3 Hz, 1H), 7.28 (dd, $J = 7.3$ Hz, 0.7 Hz, 1H), 7.12 (dd, $J = 10.8$ Hz, 8.5 Hz, 1H), 6.83 (d, $J = 8.6$ Hz, 1H), 3.94 (s, 3H), 3.60 - 3.47 (m, 4H), 1.71 - 1.58 (m, 6H); MS (ESI): 315 ($\text{M}+\text{H}$) $^+$.

(4-Fluoro-3-hydroxyphenyl)[6-(piperidin-1-yl)pyridin-2-yl]methanone hydrochloride salt (26).



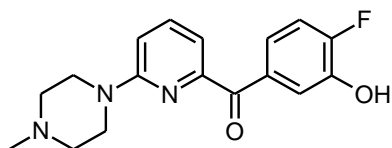
According to method E the title compound was prepared by reaction of (4-fluoro-3-methoxyphenyl)[6-(piperidin-1-yl)pyridin-2-yl]methanone (**26a**) (95 mg, 0.30 mmol, 1.0 eq) with boron tribromide (4.5 ml, 4.5 mmol, 15 eq) in dichloromethane (6.0 ml). The crude product was purified by column chromatography (cyclohexane/ethyl acetate 5:1) and the hydrochloride salt was prepared by means of 2 M hydrogen chloride solution in ether to give 40 mg (0.12 mmol/ 40 %) of the analytically pure compound. $C_{17}H_{17}FN_2O_2 \cdot HCl$; MW: 337; mp: 100-101 °C; 1H NMR (acetone- d_6 , 400 MHz)*: δ 8.93 (bs, 1H), 7.80 (dd, J = 8.8 Hz, 2.1 Hz, 1H), 7.70 (dd, J = 8.7 Hz, 7.3 Hz, 1H), 7.66 (ddd, J = 8.5 Hz, 4.6 Hz, 2.2 Hz, 1H), 7.22 (dd, J = 10.8 Hz, 8.5 Hz, 1H), 7.18 (dd, J = 7.3 Hz, 0.6 Hz, 1H), 7.01 (dd, J = 8.7 Hz, 0.6 Hz, 1H), 3.65-3.51 (m, 4H), 1.70-1.61 (m, 2H), 1.63-1.52 (m, 4H); ^{13}C NMR (acetone- d_6 , 100 MHz)*: δ 192.7 (d, J = 1.1 Hz), 158.9, 155.1 (d, J = 248.7 Hz), 154.0, 145.3 (d, J = 13.1 Hz), 139.1, 134.6 (d, J = 3.5 Hz), 124.6 (d, J = 7.5 Hz), 121.2 (d, J = 4.2 Hz), 116.3 (d, J = 19.1 Hz), 113.1, 110.5, 46.7, 26.1, 25.4; IR*: 3276, 2936, 2856, 1645, 1588, 1486, 1462, 1447, 1418, 1255, 1236, 758 cm^{-1} ; MS (ESI): 301 (M+H) $^+$; *measured as base.

(4-Fluoro-3-methoxyphenyl)[6-(4-methylpiperazin-1-yl)pyridin-2-yl]methanone (27a).



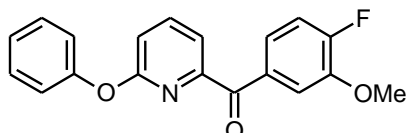
According to method D the title compound was prepared by reaction of (6-bromopyridin-2-yl)(4-fluoro-3-methoxyphenyl)methanone (**1b**) (155 mg, 0.50 mmol, 1.0 eq) with 1-methylpiperazine (60 mg, 0.6 mmol, 1.2 eq) in 1,4-dioxane (2.0 ml). The product was purified by column chromatography (ethyl acetate, 3% triethylamine) to give 90 mg (0.27 mmol/ 55 %) of the analytically pure compound. $C_{18}H_{20}FN_3O_2$; MW: 329; 1H NMR ($CDCl_3$, 400 MHz): δ 7.82 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 7.75 (ddd, J = 8.5 Hz, 4.6 Hz, 2.0 Hz, 1H), 7.66 (dd, J = 8.5 Hz, 7.4 Hz, 1H), 7.34 (d, J = 7.3 Hz, 1H), 7.13 (dd, J = 10.8 Hz, 8.5 Hz, 1H), 6.84 (d, J = 8.6 Hz, 1H), 3.94 (s, 3H), 3.64-3.52 (m, 4H), 2.57-2.45 (m, 4H), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.5 (d, J = 1.2 Hz), 158.1, 155.4 (d, J = 254.4 Hz), 153.1, 147.4 (d, J = 10.3 Hz), 138.5, 133.3 (d, J = 3.9 Hz), 125.6 (d, J = 8.2 Hz), 115.8 (d, J = 3.6 Hz), 115.4 (d, J = 18.9 Hz), 114.2, 109.8, 56.4, 54.9, 46.4, 45.1; MS (ESI): 330 (M+H) $^+$.

(4-Fluoro-3-hydroxyphenyl)[6-(4-methylpiperazin-1-yl)pyridin-2-yl]methanone dihydrochloride salt (27).



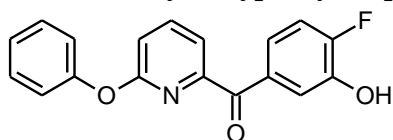
According to method E the title compound was prepared by reaction of (4-fluoro-3-methoxyphenyl)[6-(4-methylpiperazin-1-yl)pyridin-2-yl]methanone (**27a**) (90 mg, 0.27 mmol, 1.0 eq) with boron tribromide (2.7 ml, 2.7 mmol, 10 eq) dichloromethane (5.0 ml). The crude product was purified by column chromatography (cyclohexane/ethyl acetate 1:1) and the hydrochloride salt was prepared by means of 2 M hydrogen chloride solution in ether to give 98 mg (0.25 mmol/ 93%) of the analytically pure compound. $C_{17}H_{18}FN_3O_2 \cdot 2HCl$; MW: 388; mp: 216-217 °C; 1H NMR (acetone- d_6 , 400 MHz)*: δ 8.99 (bs, 1H), 7.87 (dd, J = 8.6 Hz, 7.4 Hz, 1H), 7.78 (dd, J = 8.8 Hz, 2.1 Hz, 1H), 7.68 (ddd, J = 8.5 Hz, 4.6 Hz, 2.2 Hz, 1H), 7.39 (d, J = 7.3 Hz, 1H), 7.27-7.20 (m, 2H), 4.51-4.39 (m, 2H), 4.05-3.94 (m, 2H), 3.76-3.66 (m, 2H), 3.65-3.52 (m, 2H), 3.32 (s, 3H); ^{13}C NMR (acetone- d_6 , 100 MHz)*: δ 192.3 (d, J = 0.9 Hz), 158.2, 155.2 (d, J = 248.9 Hz), 153.9, 145.4 (d, J = 13.2 Hz), 139.7, 134.3 (d, J = 3.5 Hz), 124.7 (d, J = 7.6 Hz), 120.9 (d, J = 4.2 Hz), 116.4 (d, J = 19.2 Hz), 115.5, 111.5, 54.8, 40.5, 39.9; IR*: 3374, 2926, 2853, 1696, 1588, 1459, 1438, 1420, 1402, 1277, 1256, 1238, 759, 671 cm^{-1} ; MS (ESI): 316 (M+H) $^+$; * measured as base.

(4-Fluoro-3-methoxyphenyl)(6-phenoxy pyridin-2-yl)methanone (28a).



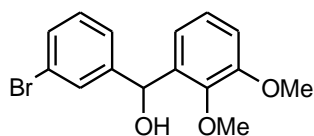
A mixture of copper(I) iodide (10 mg, 0.05 mmol, 0.1 eq), picolinic acid (12 mg, 0.10 mmol, 0.2 eq), tripotassium phosphate (212 mg, 1.00 mmol, 2.0 eq), (6-bromopyridin-2-yl)(4-fluoro-3-methoxyphenyl)methanone (**1b**) (155 mg, 0.50 mmol, 1.0 eq) and phenol (56 mg, 0.60 mmol, 1.2 eq) in dry dimethyl sulfoxide (1.0 ml) was stirred for 3 d at 80 °C under argon atmosphere. The reaction mixture was cooled to room temperature, diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The product was purified by column chromatography (*n*-pentane/diethyl ether 10:1) to give 48 mg (0.15 mmol/ 30%) of the analytically pure compound. $C_{19}H_{14}FNO_3$; MW: 323; 1H NMR ($CDCl_3$, 400 MHz): δ 7.89 (t, J = 7.8 Hz, 1H), 7.84 (d, J = 7.4 Hz, 1H), 7.79-7.71 (m, 2H), 7.40 (t, J = 7.7 Hz, 2H), 7.23 (t, J = 7.4 Hz, 1H), 7.20-7.10 (m, 3H), 6.91 (dd, J = 10.7 Hz, 8.4 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.0, 162.5, 155.6 (d, J = 255.2 Hz), 154.0, 152.8, 147.5 (d, J = 11.0 Hz), 140.5, 132.6 (d, J = 3.6 Hz), 129.8, 126.3 (d, J = 1.8 Hz), 125.2, 121.7, 119.7, 115.6 (d, J = 3.3 Hz), 115.2 (d, J = 18.8 Hz), 114.8, 56.3; MS (ESI): 324 (M+H) $^+$.

(4-Fluoro-3-hydroxyphenyl)(6-phenoxy-pyridin-2-yl)methanone (28).



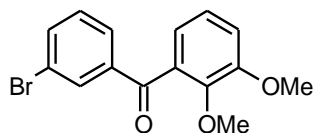
According to method E the title compound was prepared by reaction of (4-fluoro-3-methoxyphenyl)(6-phenoxy-pyridin-2-yl)methanone (**28a**) (48 mg, 0.15 mmol, 1.0 eq) with boron tribromide (1.5 ml, 1.5 mmol, 10 eq) in dichloromethane (3.0 ml). The crude product was purified by column chromatography (cyclohexane/ethyl acetate 5:1) to give 41 mg (0.13 mmol/ 89%) of the analytically pure compound. $C_{18}H_{12}FNO_3$; MW: 309; mp: 94-95 °C; 1H NMR (acetone- d_6 , 400 MHz): δ 8.89 (bs, 1H), 8.08 (dd, J = 8.3 Hz, 7.4 Hz, 1H), 7.76 (dd, J = 7.4 Hz, 0.8 Hz, 1H), 7.66 (dd, J = 8.7 Hz, 2.1 Hz, 1H), 7.60 (ddd, J = 8.5 Hz, 4.6 Hz, 2.2 Hz, 1H), 7.49-7.38 (m, 2H), 7.28 (dd, J = 8.3 Hz, 0.8 Hz, 1H), 7.26-7.17 (m, 3H), 7.03 (dd, J = 10.8 Hz, 8.6 Hz, 1H); ^{13}C NMR (acetone- d_6 , 100 MHz): δ 190.7, 163.3, 155.3 (d, J = 249.5 Hz), 154.9, 153.6, 145.3 (d, J = 13.1 Hz), 141.9, 133.8 (d, J = 3.2 Hz), 130.5, 125.7, 125.3 (d, J = 7.6 Hz), 122.4, 120.8 (d, J = 4.2 Hz), 120.0, 116.1 (d, J = 19.0 Hz), 115.6; IR: 3390, 1647, 1595, 1574, 1523, 1492, 1445, 1428, 1235, 754 cm^{-1} , MS (ESI): 310 (M+H) $^+$.

(3-Bromophenyl)(2,3-dimethoxyphenyl)methanol (29c).



According to method A1 the title compound was prepared by reaction of 1,3-dibromobenzene (**29d**) (1.18 g, 5.0 mmol, 1.0 eq) with 2,3-dimethoxybenzaldehyde (0.83 g, 5.0 mmol, 1.0 eq). The product was purified by column chromatography (cyclohexane/ethyl acetate 9:1) to give 1.25 g (3.87 mmol/ 77%) of the analytically pure compound. $C_{15}H_{15}BrO_3$; MW: 323; 1H NMR ($CDCl_3$, 400 MHz): δ 7.58-7.56 (m, 1H), 7.38-7.35 (m, 1H); 7.32-7.29 (m, 1H), 7.18 (t, J = 7.8 Hz, 1H), 7.06 (t, J = 8.0 Hz, 1H), 6.91 (ddd, J = 7.9 Hz, 1.6 Hz, 0.6 Hz, 1H), 6.89 (dd, J = 8.2 Hz, 1.4 Hz, 1H), 5.95 (s, 1H), 3.86 (s, 3H), 3.62 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.8, 146.5, 146.4, 136.9, 130.3, 129.9, 129.5, 125.1, 124.4, 122.6, 119.8, 112.3, 72.1, 60.7, 55.9; MS (ESI): 323, 325 (M+H) $^+$.

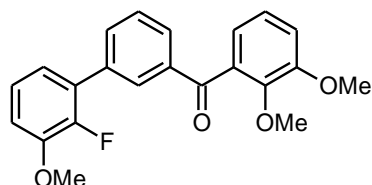
(3-Bromophenyl)(2,3-dimethoxyphenyl)methanone (29b)



According to method B the title compound was prepared by reaction of (3-bromophenyl)(2,3-dimethoxyphenyl)methanol (**29c**) with 2-iodoxybenzoic acid (1.26 g, 4.49 mmol, 1.2 eq) for 2 h. The product was purified by column chromatography (cyclohexane/ethyl acetate 9:1) to give 1.09 g (3.40 mmol/ 91%) of the analytically pure compound. $C_{15}H_{13}BrO_3$; MW: 321; 1H NMR ($CDCl_3$,

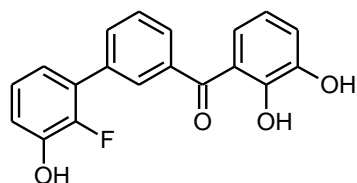
400 MHz): δ 7.96 (t, J = 1.6 Hz, 1H), 7.72 (ddd, J = 7.8 Hz, 1.6 Hz, 1.0 Hz, 1H), 7.68 (ddd, J = 8.0 Hz, 2.0 Hz, 1.0 Hz, 1H), 7.31 (t, J = 7.9 Hz, 1H), 7.19-7.12 (m, 1H), 7.07 (dd, J = 8.2 Hz, 1.6 Hz, 1H), 6.92 (dd, J = 7.5 Hz, 1.6 Hz, 1H), 3.91 (s, 3H), 3.71 (s, 3H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 195.0, 152.9, 147.1, 139.6, 136.1, 133.5, 132.6, 130.0, 128.7, 124.3, 122.7, 120.6, 114.9, 61.8, 56.1; MS (ESI): 321, 323 ($\text{M}+\text{H}$) $^+$.

(2,3-Dimethoxyphenyl)(2'-fluoro-3'-methoxybiphenyl-3-yl)methanone (29a)



According to method C1 the title compound was prepared by reaction of (3-bromophenyl)(2,3-dimethoxyphenyl)methanone (**29b**) (161 mg, 0.5 mmol, 1.0 eq) with 2-fluoro-3-methoxyphenylboronic acid (102 mg, 0.60 mmol, 1.2 eq) in DME/water (6.0 ml). The product was purified by column chromatography (cyclohexane/ethyl acetate 7:1) to give 163 mg (0.44 mmol/ 89%) of the analytically pure compound. $\text{C}_{22}\text{H}_{19}\text{FO}_4$; MW: 366; ^1H NMR (CDCl_3 , 400 MHz): δ 8.02-7.97 (m, 1H), 7.84 (ddd, J = 7.8 Hz, 2.9 Hz, 1.2 Hz, 1H), 7.75 (ddd, J = 7.1 Hz, 2.7 Hz, 1.5 Hz, 1H), 7.52 (dt, J = 7.7 Hz, 0.5 Hz, 1H), 7.16-7.10 (m, 2H), 7.07-7.03 (m, 1H), 7.02-6.93 (m, 3H), 3.92 (s, 3H), 3.91 (s, 3H), 3.73 (s, 3H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 196.2, 152.9, 152.2 (d, J = 250.9 Hz), 148.3 (d, J = 11.3 Hz), 147.1, 138.0, 136.0, 134.2, 134.0 (d, J = 3.8 Hz), 130.5 (d, J = 2.8 Hz), 129.4, 129.0 (d, J = 11.0 Hz), 128.6, 124.2 (d, J = 4.9 Hz), 124.1, 122.1 (d, J = 2.5 Hz), 120.6, 114.5, 112.7 (d, J = 1.9 Hz), 61.9, 56.5, 56.1; MS (ESI): 367 ($\text{M}+\text{H}$) $^+$.

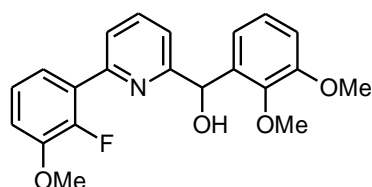
(2,3-Dihydroxyphenyl)(2'-fluoro-3'-hydroxybiphenyl-3-yl)methanone (29).



According to method E the title compound was prepared by reaction of (2,3-dimethoxyphenyl)(2'-fluoro-3'-methoxybiphenyl-3-yl)methanone (**29a**) (110 mg, 0.30 mmol, 1.0 eq) with boron tribromide (4.5 ml, 4.5 mmol, 15 eq) in dichloromethane (6.0 ml). The product was purified by column chromatography (cyclohexane/ethyl acetate 5:1, 3% acetic acid) to give 61 mg (0.19 mmol/ 63%) of the analytically pure compound. $\text{C}_{19}\text{H}_{13}\text{FO}_4$; MW: 324; mp: 147-148 $^{\circ}\text{C}$; ^1H NMR (acetone- d_6 , 400 MHz): δ 11.90 (d, J = 2.4 Hz, 1H), 8.81 (s, 1H), 8.17 (s, 1H), 7.92-7.88 (m, 1H), 7.88-7.83 (m, 1H), 7.79-7.74 (m, 1H); 7.69 (dt, J = 7.8 Hz, 4.6 Hz, 1H), 7.22-7.14 (m, 2H), 7.12 (dd, J = 7.6 Hz, 3.8 Hz, 1H), 7.09-6.99 (m, 2H), 6.85 (dt, J = 8.0 Hz, 4.8 Hz, 1H); ^{13}C NMR (acetone- d_6 , 100 MHz): δ

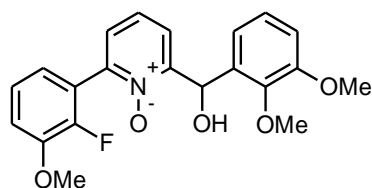
202.2, 151.8, 149.6 (d, $J = 241.3$ Hz), 147.4, 146.5 (d, $J = 14.7$ Hz), 139.1 (d, $J = 1.0$ Hz), 136.9, 133.3 (d, $J = 4.0$ Hz), 130.4 (d, $J = 3.9$ Hz), 129.6 (d, $J = 12.0$ Hz), 129.6 (d, $J = 0.7$ Hz), 129.3, 125.5 (d, $J = 5.7$ Hz), 124.7, 122.1 (d, $J = 0.6$ Hz), 121.6 (d, $J = 2.6$ Hz), 120.5 (d, $J = 1.1$ Hz), 119.7 (d, $J = 0.8$ Hz), 118.3 (d, $J = 3.6$ Hz); IR: 3434, 1630, 1451, 1324, 1281, 1234, 1196, 1166, 749 cm^{-1} ; MS (ESI): 325 (M+H)⁺.

(2,3-Dimethoxyphenyl)[6-(2-fluoro-3-methoxyphenyl)pyridin-2-yl]methanol (30c).



According to method C1 the title compound was prepared by reaction of (6-bromopyridin-2-yl)(2,3-dimethoxyphenyl)methanol (**12c**) (259 mg, 0.8 mmol, 1.0 eq) with 2-fluoro-3-methoxyphenylboronic acid (163 mg, 0.96 mmol, 1.2 eq) in DME/water (7.0 ml). The product was purified by column chromatography (cyclohexane/ethyl acetate 10:1 \rightarrow 1:1) to give 272 mg (0.74 mmol/ 92%) of the analytically pure compound. $\text{C}_{21}\text{H}_{20}\text{FNO}_4$; MW: 369; ^1H NMR (CDCl_3 , 400 MHz): δ 7.70-7.64 (m, 2H), 7.58 (ddd, $J = 8.1$ Hz, 6.7 Hz, 1.6 Hz, 1H), 7.27-7.23 (m, 1H), 7.21 (dt, $J = 8.1$ Hz, 1.5 Hz, 1H), 7.04 (ddd, $J = 9.5$ Hz, 7.1 Hz, 2.3 Hz, 1H), 7.02 (d, $J = 7.9$ Hz, 1H), 6.95 (dd, $J = 7.9$ Hz, 1.2 Hz, 1H), 6.84 (dd, $J = 8.0$ Hz, 1.4 Hz, 1H), 6.22 (s, 1H), 3.95 (s, 3H); 3.91 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 160.6, 152.7, 150.9 (d, $J = 2.0$ Hz), 150.7 (d, $J = 250.6$ Hz), 148.4 (d, $J = 12.8$ Hz), 146.6, 137.7, 137.1, 124.5, 124.1 (d, $J = 5.0$ Hz), 123.3 (d, $J = 9.5$ Hz), 122.1 (d, $J = 2.2$ Hz), 120.5, 119.7, 113.8 (d, $J = 2.3$ Hz), 111.7, 69.0, 61.1, 56.6, 55.9; MS (ESI): 370 (M+H)⁺.

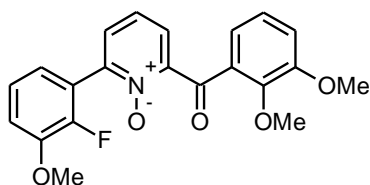
(2,3-Dimethoxyphenyl)[6-(2-fluoro-3-methoxyphenyl)-1-oxidopyridin-2-yl]methanol (30b).



A solution of (2,3-dimethoxyphenyl)[6-(2-fluoro-3-methoxyphenyl)pyridin-2-yl]methanol (**30c**) (258 mg, 0.70 mmol, 1.0 eq) in dry dichloromethane was cooled to 0 °C and *m*CPBA (77%) (314 mg, 1.40 mmol, 2.0 eq) was added. The reaction mixture was stirred at room temperature for 18 h. The mixture was diluted with dichloromethane, washed with 6 M KOH, dried over magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The product was purified by column chromatography (dichloromethane/methanol 20:1) to give 178 mg (0.46 mmol/ 66%) of the analytically pure compound. $\text{C}_{21}\text{H}_{20}\text{FNO}_5$, MW: 385; ^1H NMR (CDCl_3 , 400 MHz): δ 7.38 (dd, $J = 7.7$ Hz, 1.5 Hz, 1H), 7.33 (dd, $J = 7.9$ Hz, 1.4 Hz, 1H), 7.31 (t, $J = 7.8$ Hz, 1H), 7.21 (dt,

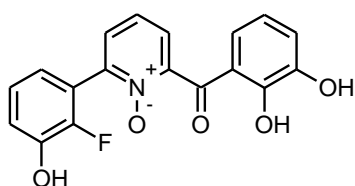
$J = 7.9$ Hz, 1.2 Hz, 1H), 7.18 (d, $J = 7.9$ Hz, 1H), 7.16-7.07 (m, 2H), 6.99 (dd, $J = 7.8$ Hz, 2.1 Hz, 1H), 6.95 (dd, $J = 8.2$ Hz, 1.4 Hz, 1H), 6.44 (s, 1H), 3.93 (s, 3H), 3.89 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 152.5, 150.1 (d, $J = 250.9$ Hz), 148.2 (d, $J = 10.5$ Hz), 146.2, 145.4, 132.5, 127.2 (d, $J = 2.2$ Hz), 124.9, 124.6, 124.2 (d, $J = 5.0$ Hz), 122.3 (d, $J = 1.7$ Hz), 119.8, 115.0 (d, $J = 2.2$ Hz), 112.4, 67.6, 60.8, 56.6, 55.9; MS (ESI): 386 ($\text{M}+\text{H}$) $^+$.

(2,3-Dimethoxyphenyl)[6-(2-fluoro-3-methoxyphenyl)-1-oxidopyridin-2-yl]methanone (30a).



According to method B the title compound was prepared by reaction of (2,3-dimethoxyphenyl)[6-(2-fluoro-3-methoxyphenyl)-1-oxidopyridin-2-yl]methanol (**30b**) (166 mg, 0.43 mmol, 1.0 eq) with 2-iodoxybenzoic acid (145 mg, 0.52 mmol, 1.2 eq) for 2 h. The product was purified by column chromatography (dichloromethane/methanol 40:1 \rightarrow 20:1) to give 99 mg (0.26 mmol/ 60%) of the analytically pure compound. $\text{C}_{21}\text{H}_{18}\text{FNO}_5$; MW: 383; ^1H NMR (CDCl_3 , 400 MHz): δ 7.48 (ddd, $J = 7.1$ Hz, 2.5 Hz, 1.2 Hz, 1H), 7.48-7.43 (m, 2H), 7.41 (dd, $J = 8.0$ Hz, 7.2 Hz, 1H), 7.17-7.08 (m, 3H), 7.07-6.99 (m, 2H), 3.89 (s, 3H), 3.82 (s, 3H), 3.62 (s, 3H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 189.1, 152.3, 151.3, 149.6 (d, $J = 152.5$ Hz), 149.0, 148.2 (d, $J = 10.7$ Hz), 144.5, 131.3, 128.8 (d, $J = 2.6$ Hz), 125.3, 124.4, 124.2, 124.0 (d, $J = 4.8$ Hz), 122.5 (d, $J = 1.6$ Hz), 121.5, 120.8 (d, $J = 11.8$ Hz), 117.2, 114.7 (d, $J = 2.5$ Hz), 61.2 (d, $J = 2.1$ Hz), 56.5, 56.1; MS (ESI): 384 ($\text{M}+\text{H}$) $^+$.

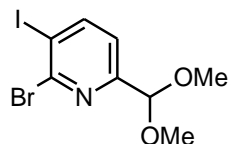
(2,3-Dihydroxyphenyl)[6-(2-fluoro-3-hydroxyphenyl)-1-oxidopyridin-2-yl]methanone (30).



To a solution of (2,3-dimethoxyphenyl)[6-(2-fluoro-3-methoxyphenyl)-1-oxidopyridin-2-yl]methanone (**30a**) (99 mg, 0.26 mmol, 1.0 eq) in dry dichloromethane (3.0 ml), boron trifluoride dimethylsulfide complex (3.0 ml, 27 mmol, 105 eq) was slowly added. The reaction mixture was stirred at room temperature for 18 h. The mixture was quenched with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The product was purified by column chromatography (dichloromethane/methanol 20:1 \rightarrow 15:1, 3% acetic acid) and preparative HPLC (gradient water/acetonitrile/trifluoroacetic acid 85:15:0.1 \rightarrow 5:95:0.1, in 160 min) to give 54 mg (0.16 mmol, 61%) of the analytically pure compound. $\text{C}_{18}\text{H}_{12}\text{FNO}_5$; MW: 341; mp: 244 $^{\circ}\text{C}$ (decomposition); ^1H NMR ($\text{DMSO}-d_6$, 400 MHz): δ 10.38 (bs, 1H), 9.99 (bs, 1H), 9.60 (bs, 1H), 7.69

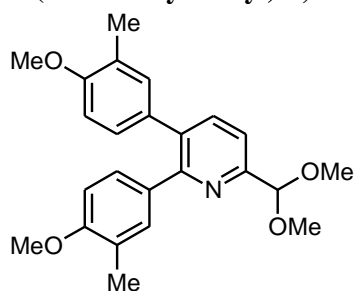
(dd, $J = 7.7$ Hz, 2.1 Hz, 1H), 7.66 (dd, $J = 7.9$ Hz, 2.1 Hz, 1H), 7.55 (t, $J = 7.8$ Hz, 1H), 7.13-7.02 (m, 3H), 6.98-6.88 (m, 2H), 6.74 (t, $J = 7.9$ Hz, 1H); ^{13}C NMR (DMSO- d_6 , 100 MHz): δ 191.5, 149.5, 148.9 (d, $J = 246.2$ Hz), 147.4, 146.2, 145.1 (d, $J = 12.0$ Hz), 144.7, 129.0, 125.6, 124.0, 124.2 (d, $J = 4.4$ Hz), 121.3, 121.2 (d, $J = 12.3$ Hz), 121.1, 120.9, 120.8, 119.2, 119.1 (d, $J = 3.7$ Hz); IR: 3086, 1637, 1470, 1388, 1349, 1255, 1231, 1201, 1177, 1134, 722, 658 cm^{-1} ; MS (ESI): 342 ($\text{M}+\text{H}$) $^+$.

2-Bromo-6-(dimethoxymethyl)-3-iodopyridine (**31e**).



A 2.5 M solution of *n*-BuLi in hexane (0.8 ml, 2.0 mmol, 1.0 eq) was added at -80 $^{\circ}\text{C}$ to a solution of diisopropylamine (0.31 ml, 2.2 mmol, 1.1 eq) in dry THF (5.0 ml), under argon. The solution was allowed to warm up to -40 $^{\circ}\text{C}$ for 0.5 h. 2-Bromo-6-(dimethoxymethyl)pyridine (**31f**) (464 mg, 2.0 mmol, 1.0 eq) in dry THF (2.0 ml) was added at -80 $^{\circ}\text{C}$ to the in situ prepared LDA and the mixture was stirred at this temperature for 3 h. A solution of iodine (508 mg, 2.0 mmol, 1.0 eq) in dry THF (1.0 ml) was added and the reaction mixture was stirred at room temperature. The end of the reaction was monitored by TLC. The mixture was quenched with saturated NH_4Cl and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The crude product was purified by column chromatography (cyclohexane/ethyl acetate 5:1) to give 171 mg (0.48 mmol/ 24 %) of the analytically pure compound. $\text{C}_8\text{H}_9\text{BrINO}_2$; MW: 358; ^1H NMR (CDCl_3 , 400 MHz): δ 8.13 (d, $J = 8.0$ Hz, 1H), 7.24 (d, $J = 8.0$ Hz, 1H), 5.25 (s, 1H), 3.40 (s, 6H).

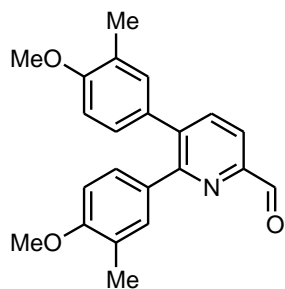
6-(Dimethoxymethyl)-2,3-bis(4-methoxy-3-methylphenyl)pyridine (**31d**).



A mixture of 2-bromo-6-(dimethoxymethyl)-3-iodopyridine (**31e**) (170 mg, 0.50 mmol, 1.0 eq), 4-methoxy-3-methylphenylboronic acid (199 mg, 1.2 mmol, 2.4 eq), cesium carbonate (1.30 g, 8.0 mmol, 4 eq) and tetrakis(triphenylphosphine)palladium (23 mg, 0.02 mmol, 0.04 eq) was solved in DME/water (2:1, 6 ml) and degassed with argon. The mixture was heated to 80 $^{\circ}\text{C}$ and stirred overnight at 80 $^{\circ}\text{C}$. The reaction mixture was cooled to room temperature, quenched with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The product was purified by column chromatography (cyclohexane/ethyl acetate 5:1) to give 202 mg (0.50 mmol/

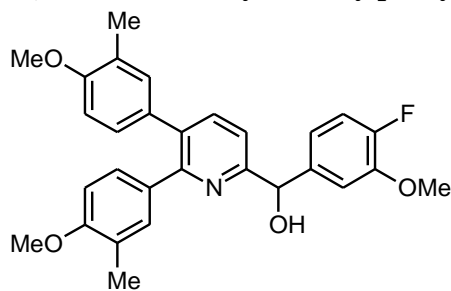
100%) of the analytically pure compound. $C_{24}H_{27}NO_4$; MW: 393; 1H NMR ($CDCl_3$, 400 MHz): δ 7.71 (d, J = 7.2 Hz, 1H), 7.51 (d, J = 7.9 Hz, 1H), 7.31 (s, 1H), 7.06 (d, J = 8.8 Hz, 1H), 7.02-6.96 (m, 1H), 6.90 (d, J = 8.1 Hz, 1H), 6.70 (d, J = 8.3 Hz, 1H), 6.63 (d, J = 8.5 Hz, 1H), 5.46 (bs, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.49 (s, 6H), 2.16 (s, 3H), 2.15 (s, 3H).

5,6-Bis-(4-methoxy-3-methylphenyl)pyridine-2-carbaldehyde (31c).



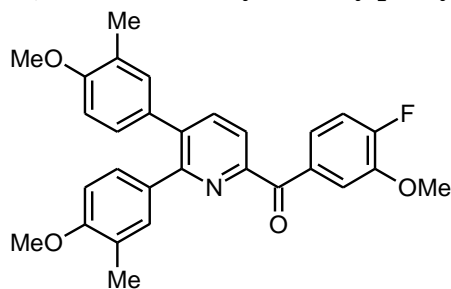
6-(Dimethoxymethyl)-2,3-bis(4-methoxy-3-methylphenyl)pyridine (**31d**) (197 mg, 0.50 mmol, 1.0 eq) was refluxed for 2 h in a mixture of water (1.5 ml) and acetic acid (1.0 ml). The mixture was quenched with saturated sodium bicarbonate and extracted with ethyl acetate. The combined organic layer was dried over magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The crude product was purified by column chromatography (cyclohexane/ethyl acetate 1:1) to give 149 mg (0.43 mmol/ 86%) of the analytically pure compound. $C_{22}H_{21}NO_3$; MW: 347; 1H NMR ($CDCl_3$, 400 MHz): δ 10.17 (s, 1H), 7.91 (d, J = 7.9 Hz, 1H), 7.82 (d, J = 7.9 Hz, 1H), 7.37-7.34 (m, 1H), 7.11 (dd, J = 8.5 Hz, 2.3 Hz, 1H), 7.07-7.03 (m, 1H), 6.96 (dd, J = 8.4 Hz, 2.4 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 6.68 (d, J = 8.5 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 2.18 (s, 6H); MS (ESI): 348 (M+H) $^+$.

(5,6-Bis-(4-methoxy-3-methylphenyl)pyridin-2-yl)(4-fluoro-3-methoxyphenyl)methanol (31b).



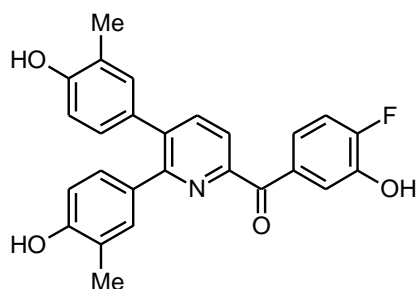
According to method A2 the title compound was prepared by reaction of 4-bromo-1-fluoro-2-methoxybenzene (**23e**) (119 mg, 0.58 mmol, 1.0 eq), magnesium turnings (14 mg, 0.58 mmol, 1.0 eq) and 5,6-bis-(4-methoxy-3-methylphenyl)pyridine-2-carbaldehyde (**31c**) (222 mg, 0.64 mmol, 1.1 eq). The product was used in the next step without further purification. $C_{29}H_{28}FNO_4$; MW: 474; MS (ESI): 474 (M+H) $^+$.

(5,6-Bis-(4-methoxy-3-methylphenyl)pyridin-2-yl)(4-fluoro-3-methoxyphenyl)methanone (31a).



According to method B the title compound was prepared by reaction of (5,6-bis-(4-methoxy-3-methylphenyl)pyridine-2-yl)(4-fluoro-3-methoxyphenyl)methanol (**31b**) (283 mg, 0.60 mmol, 1.0 eq) with 2-iodoxybenzoic acid (252 mg, 0.90 mmol, 1.5 eq) for 3 h. The product was purified by column chromatography (cyclohexane/ethyl acetate 5:1) to give 158 mg (0.34 mmol/ 56 %) of the analytically pure compound. $C_{29}H_{26}FNO_4$; MW: 472; 1H NMR ($CDCl_3$, 400 MHz): δ 8.09 (dd, J = 8.5 Hz, 1.9 Hz, 1H), 8.01 (d, J = 7.93 Hz, 1H), 7.93 (ddd, J = 8.5 Hz, 4.5 Hz, 2.0 Hz, 1H), 7.85 (d, J = 7.9 Hz, 1H), 7.32 (d, J = 2.1 Hz, 1H), 7.17 (dd, J = 10.8 Hz, 8.5 Hz, 1H), 7.08-7.15 (m, 2H), 7.01 (dd, J = 8.5 Hz, 2.2 Hz, 1H), 6.75 (d, J = 8.4 Hz, 1H), 6.65 (d, J = 8.5 Hz, 1H), 3.95 (s, 3H), 3.84 (s, 3H), 3.80 (s, 3H), 2.19 (s, 3H), 2.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.4, 157.9, 157.6, 157.4, 155.6 (d, J = 254.8 Hz), 155.5, 152.8, 152.8, 147.5 (d, J = 10.6 Hz), 139.7, 138.3, 133.2 (d, J = 3.5 Hz), 132.3, 131.6, 129.0, 128.1, 127.0, 126.2, 126.1 (d, J = 7.7 Hz), 122.5, 116.3 (d, J = 3.3 Hz), 115.5 (d, J = 19.0 Hz), 109.9, 109.3, 56.4, 55.5, 55.4, 16.44, 16.41; MS (ESI): 472 ($M+H$) $^+$.

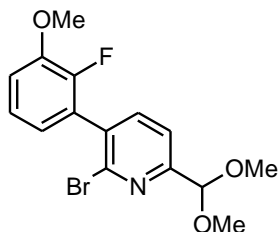
(5,6-Bis-(4-hydroxy-3-methylphenyl)pyridine-2-yl)(4-fluoro-3-hydroxyphenyl)methanone (31).



According to method E the title compound was prepared by reaction of (5,6-bis-(4-methoxy-3-methylphenyl)pyridine-2-yl)(4-fluoro-3-methoxyphenyl)methanone (**31a**) (145 mg, 0.30 mmol, 1.0 eq) with boron tribromide (4.5 ml, 4.5 mmol, 15 eq) in dichloromethane (6.0 ml). The product was purified by column chromatography (cyclohexane/ethyl acetate 3:1) to give 100 mg (0.23 mmol/ 76%) of the analytically pure compound. $C_{26}H_{20}FNO_4$; MW: 429; mp: 112 °C (decomposition); 1H NMR (acetone- d_6 , 400 MHz): δ 9.04 (s, 1H), 8.45 (s, 1H), 8.40 (s, 1H), 7.88-8.01 (m, 3H), 7.82 (ddd, J = 8.4 Hz, 4.6 Hz, 2.1 Hz, 1H), 7.33 (d, J = 1.6 Hz, 1H), 7.28 (dd, J = 10.8 Hz, 8.6 Hz, 1H), 7.11 (d, J = 1.7 Hz, 1H), 7.05 (dd, J = 8.3 Hz, 2.2 Hz, 1H), 6.91 (dd, J = 8.2 Hz, 2.2 Hz, 1H), 6.79 (d, J = 8.2 Hz, 1H), 6.66 (d, J = 8.3 Hz, 1H), 2.18 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (acetone- d_6 , 100 MHz): δ 191.9 (d, J = 1.0 Hz), 156.4, 156.3, 156.1, 155.3 (d, J = 249.3 Hz), 153.6, 145.4 (d, J = 13.3 Hz), 140.4, 139.0, 134.4 (d, J = 3.4 Hz), 133.6, 132.6, 132.1, 131.7, 129.6, 128.8, 125.4, 124.9 (d,

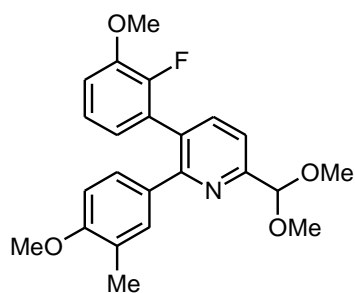
$J = 8.0$ Hz), 124.4, 122.6, 121.5 (d, $J = 4.3$ Hz), 116.4 (d, $J = 19.1$ Hz), 115.5, 114.6, 16.3, 16.2; IR: 3303, 1653, 1596, 1507, 1427, 1271, 1199, 1112, 762 cm^{-1} ; MS (ESI): 430 ($\text{M}+\text{H}$) $^{+}$.

2-Bromo-6-(dimethoxymethyl)-3-(2-fluoro-3-methoxyphenyl)pyridine (32e).



A mixture of 2-bromo-6-(dimethoxymethyl)-3-iodopyridine (**31e**) (201 mg, 0.56 mmol, 1.0 eq), 2-fluoro-3-methoxyphenylboronic acid (229 mg, 1.35 mmol, 2.4 eq), cesium carbonate (1.30 g, 8.0 mmol, 4 eq) and tetrakis(triphenylphosphine)palladium (23 mg, 0.02 mmol, 0.04 eq) was solved in DME/water (2:1, 6.0 ml) and degassed with argon. The mixture was heated to 80 °C and stirred overnight at 80 °C under argon. The reaction mixture was cooled to room temperature, quenched with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The product was purified by column chromatography (cyclohexane/ethyl acetate 10:1) to give 168 mg (0.47 mmol/ 84%) of the analytically pure compound. $\text{C}_{15}\text{H}_{15}\text{BrFNO}_3$; MW: 356; ^1H NMR (CDCl_3 , 400 MHz): δ 7.66 (d, $J = 7.8$ Hz, 1H), 7.60 (d, $J = 7.7$ Hz, 1H), 7.15 (ddd, $J = 8.2$ Hz, 7.8 Hz, 1.4 Hz, 1H), 7.05 (dt, $J = 8.1$ Hz, 1.6 Hz, 1H), 6.86 (ddd, $J = 7.8$ Hz, 6.1 Hz, 1.6 Hz, 1H), 5.36 (s, 1H), 3.94 (s, 3H), 3.46 (s, 6H).

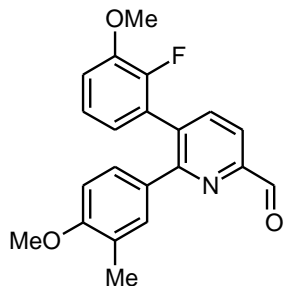
6-(Dimethoxymethyl)-3-(2-fluoro-3-methoxyphenyl)-2-(4-methoxy-3-methylphenyl)pyridine (32d).



According to method C1 the title compound was prepared by reaction of 2-bromo-6-(dimethoxymethyl)-3-(2-fluoro-3-methoxyphenyl)pyridine (**32e**) (168 mg, 0.47 mmol, 1.0 eq) with 4-methoxy-3-methylphenylboronic acid (94 mg, 0.57 mmol, 1.2 eq) in DME/water (6.0 ml). The product was purified by column chromatography (cyclohexane/ethyl acetate 5:1) to give 183 mg (0.46 mmol/ 81%) of the analytically pure compound. $\text{C}_{23}\text{H}_{24}\text{FNO}_4$; MW: 397; ^1H NMR (CDCl_3 , 400 MHz): δ 7.73 (d, $J = 7.9$ Hz, 1H), 7.54 (d, $J = 7.9$ Hz, 1H), 7.11 (dd, $J = 8.5$ Hz, 2.2 Hz, 1H), 6.98 (dt, $J = 7.8$ Hz,

1.1 Hz, 1H), 6.90 (dt, $J = 8.2$ Hz, 1.7 Hz, 1H), 6.54-6.72 (m, 3H), 5.47 (s, 1H), 3.86 (s, 3H), 3.77 (s, 3H), 3.50 (s, 6H), 2.11 (s, 3H).

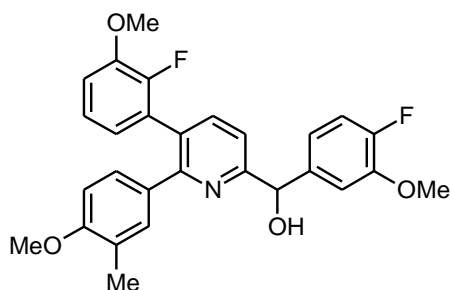
5-(2-Fluoro-3-methoxyphenyl)-6-(4-methoxy-3-methylphenyl)pyridine-2-carbaldehyde (32c).



6-(Dimethoxymethyl)-3-(2-fluoro-3-methoxyphenyl)-2-(4-methoxy-3-methylphenyl)pyridine (32d)

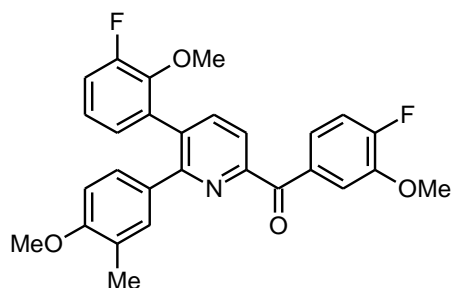
(173 mg, 0.44 mmol, 1.0 eq) was refluxed for 2 h in a mixture of water (6.0 ml) and acetic acid (4.0 ml). The mixture was quenched with saturated sodium bicarbonate and extracted with ethyl acetate. The combined organic layer was dried over magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The product was used in the next step without further purification. $C_{21}H_{18}FNO_3$; MW: 351; MS (ESI): 352 ($M+H$)⁺.

(4-Fluoro-3-methoxyphenyl)[5-(2-fluoro-3-methoxyphenyl)-6-(4-methoxy-3-methylphenyl)pyridine-2-yl]methanol (32b).



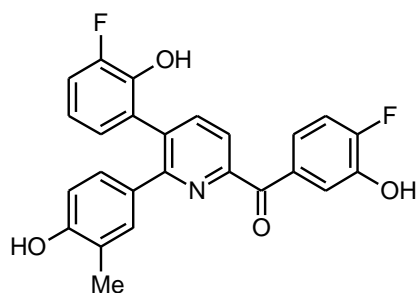
According to method A1 the title compound was prepared by reaction of 4-bromo-1-fluoro-2-methoxybenzene (**23e**) (89 mg, 0.44 mmol, 1.0 eq) and 5-(2-fluoro-3-methoxyphenyl)-6-(4-methoxy-3-methylphenyl)pyridine-2-carbaldehyde (**32c**) (153 mg, 0.44 mmol, 1.0 eq). The product was purified by column chromatography (cyclohexane/ethyl acetate 10:1 → 5:1 → 2:1) to give 75 mg (0.16 mmol/36%) of the title compound. $C_{28}H_{25}F_2NO_4$; MW: 478; MS (ESI): 478 ($M+H$)⁺.

(4-Fluoro-3-methoxyphenyl)[5-(2-fluoro-3-methoxyphenyl)-6-(4-methoxy-3-methylphenyl)pyridin-2-yl]methanone (32a).



According to method B the title compound was prepared by reaction of (4-fluoro-3-methoxyphenyl)[5-(2-fluoro-3-methoxyphenyl)-6-(4-methoxy-3-methylphenyl)pyridin-2-yl]methanol (**32b**) (75 mg, 0.16 mmol, 1.0 eq) with 2-iodoxybenzoic acid (66 mg, 0.24 mmol, 1.5 eq) for 2 h. The product was purified by column chromatography (cyclohexane/ethyl acetate 10:1) to give 54 mg (0.11 mmol/ 73%) of the analytically pure compound. $C_{28}H_{23}F_2NO_4$; MW: 475; 1H NMR ($CDCl_3$, 400 MHz): δ 8.09 (dd, $J = 8.5$ Hz, 2.0 Hz, 1H), 8.03 (d, $J = 7.9$ Hz, 1H), 7.94 (ddd, $J = 8.5$ Hz, 4.6 Hz, 2.0 Hz, 1H), 7.88 (dd, $J = 7.9$ Hz, 0.9 Hz, 1H), 7.29-7.26 (m, 1H), 7.21-7.14 (m, 2H), 7.08-7.02 (m, 1H), 6.96 (dt, $J = 8.1$ Hz, 1.5 Hz, 1H), 6.77 (ddd, $J = 7.8$ Hz, 6.3 Hz, 1.6 Hz, 1H), 6.64 (d, $J = 8.5$ Hz, 1H), 3.94 (s, 3H), 3.88 (s, 3H), 3.78 (s, 3H), 2.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.3, 158.2, 156.4, 155.7 (d, $J = 255.1$ Hz), 154.1, 149.5 (d, $J = 247.4$ Hz), 148.2 (d, $J = 11.1$ Hz), 147.5 (d, $J = 9.5$ Hz), 140.5 (d, $J = 1.6$ Hz), 133.0 (d, $J = 3.7$ Hz), 132.0, 131.7, 131.4, 128.4 (d, $J = 12.8$ Hz), 128.2, 126.1 (d, $J = 7.9$ Hz), 124.2 (d, $J = 5.0$ Hz), 122.8 (d, $J = 2.3$ Hz), 122.0, 116.3 (d, $J = 3.5$ Hz), 115.6 (d, $J = 19.0$ Hz), 113.3, 109.3, 56.5, 56.4, 55.4, 16.4; MS (ESI): 476 ($M+H$) $^+$.

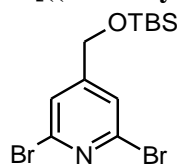
(4-Fluoro-3-hydroxyphenyl)[5-(2-fluoro-3-hydroxyphenyl)-6-(4-hydroxy-3-methylphenyl)pyridin-2-yl]methanone (32).



According to method E the title compound was prepared by reaction of (4-fluoro-3-methoxyphenyl)[5-(2-fluoro-3-methoxyphenyl)-6-(4-methoxy-3-methylphenyl)pyridin-2-yl]methanone (**32a**) (54 mg, 0.11 mmol, 1.0 eq) with boron tribromide (1.7 ml, 1.70 mmol, 15 eq) in dichloromethane (6.0 ml). The product was purified by column chromatography (cyclohexane/ethyl acetate 2:1) to give 34 mg (0.08 mmol/ 69%) of the analytically pure compound. $C_{25}H_{17}F_2NO_4$; MW: 433; mp: 145-146 $^{\circ}C$; 1H NMR (acetone- d_6 , 400 MHz): δ 9.07 (bs, 1H), 8.70 (bs, 1H), 8.43 (bs, 1H), 8.00-7.96 (m, 2H), 7.94 (dd, $J = 8.7$ Hz, 2.1 Hz, 1H), 7.81 (ddd, $J = 8.5$ Hz, 4.6 Hz, 2.2 Hz, 1H), 7.33-7.27 (m, 2H), 7.10-6.99

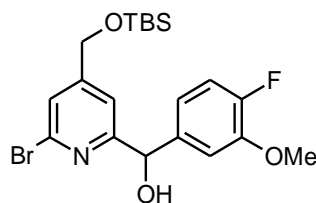
(m, 3H), 6.83 (ddd, $J = 7.5$ Hz, 6.3 Hz, 2.0 Hz, 1H), 6.66 (d, $J = 8.4$ Hz, 1H), 2.09 (s, 3H); ^{13}C NMR (acetone- d_6 , 100 MHz): δ 192.0 (d, $J = 1.0$ Hz), 157.1, 156.7, 155.4 (d, $J = 249.2$ Hz), 155.0, 149.2 (d, $J = 241.5$ Hz), 146.2 (d, $J = 13.4$ Hz), 145.5 (d, $J = 13.2$ Hz), 141.3 (d, $J = 1.4$ Hz), 134.2 (d, $J = 3.4$ Hz), 132.9, 132.8, 131.8 (d, $J = 1.3$ Hz), 129.4 (d, $J = 13.1$ Hz), 125.5 (d, $J = 4.7$ Hz), 124.9 (d, $J = 7.7$ Hz), 124.5, 122.4 (d, $J = 1.9$ Hz), 122.2, 121.4 (d, $J = 4.3$ Hz), 118.5 (d, $J = 3.0$ Hz), 116.6 (d, $J = 19.2$ Hz), 114.8, 16.2; IR: 3313, 2961, 2929, 2855, 1653, 1610, 1596, 1509, 1475, 1430, 1317, 1280, 1263, 1201, 1110, 1095, 818, 803, 778, 762 cm^{-1} ; MS (ESI): 434 ($\text{M}+\text{H}$) $^{+}$.

4-[[*tert*-Butyl(dimethyl)silyl]oxy)methyl]-2,6-dibromopyridine (**33d**).



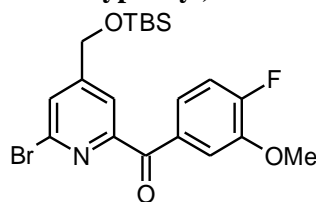
A mixture of (2,6-dibromopyridin-4-yl)methanol (**33e**) (534 mg, 2.0 mmol, 1.0 eq), TBSCl (392 mg, 2.6 mmol, 1.3 eq) and imidazole (340 mg, 5.0 mmol, 2.5 eq) was dissolved in dry DMF (2.0 ml). The reaction mixture was stirred for 18 h under argon atmosphere. The mixture was diluted with water and extracted with *n*-pentane. The combined organic layer was washed with brine, dried over magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The product was purified by column chromatography (cyclohexane/ethyl acetate 10:1) to give 614 mg (1.6 mmol/ 81%) of the analytically pure compound. $\text{C}_{12}\text{H}_{19}\text{Br}_2\text{NOSi}$; MW: 381; ^1H NMR (CDCl_3 , 400 MHz): δ 7.40 (t, $J = 0.8$ Hz, 2H), 4.68 (t, $J = 0.9$ Hz, 2H), 0.94 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 156.3, 140.8, 124.1, 62.6, 26.0, 18.4, 5.3; MS (ESI): 380, 382, 384 ($\text{M}+\text{H}$) $^{+}$.

[6-Bromo-(4-[[*tert*-butyl(dimethyl)silyl]oxy)methyl])pyridin-2-yl](4-fluoro-3-methoxyphenyl)methanol (**33c**).



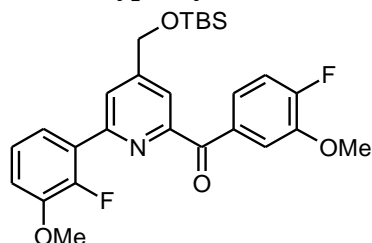
According to method A1 the title compound was prepared by reaction of 4-[[*tert*-butyl(dimethyl)silyl]oxy)methyl]-2,6-dibromopyridine (**33d**) (600 mg, 1.57 mmol, 1.0 eq) with 4-fluoro-3-methoxybenzaldehyde (242 mg, 1.57 mmol, 1.0 eq). The product was used in the next step without further purification. $\text{C}_{20}\text{H}_{27}\text{BrFNO}_3\text{Si}$; MW: 456; MS (ESI): 456, 458 ($\text{M}+\text{H}$) $^{+}$.

[6-Bromo-4-(((*tert*-butyl(dimethyl)silyl)oxy)methyl))pyridin-2-yl](4-fluoro-3-methoxyphenyl)methanone (33b).



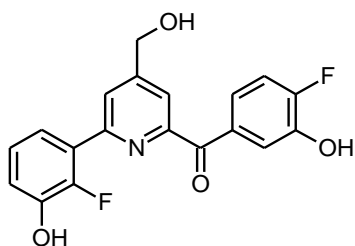
According to method B the title compound was prepared by reaction of [6-bromo-4-(((*tert*-butyl(dimethyl)silyl)oxy)methyl))pyridin-2-yl](4-fluoro-3-methoxyphenyl)methanol (**33c**) with 2-iodoxybenzoic acid (661 mg, 2.36 mmol, 1.5 eq). The product was purified by column chromatography (cyclohexane/ethyl acetate 15:1) to give 520 mg (1.14 mmol/ 73%, two steps) of the analytically pure compound. $C_{20}H_{25}BrFNO_3Si$; MW: 454; 1H NMR ($CDCl_3$, 400 MHz): δ 7.93-7.87 (m, 2H), 7.76 (ddd, J = 8.5 Hz, 4.5 Hz, 2.1 Hz, 1H), 7.69 (dd, J = 2.2 Hz, 1.0 Hz, 1H), 7.17 (dd, J = 10.7 Hz, 8.5 Hz, 1H), 4.82-4.78 (m, 2H), 3.96 (s, 3H), 0.97 (s, 9H), 0.14 (s, 6H); ^{13}C NMR ($CDCl_3$): 190.0 (d, J = 1.3 Hz), 155.9 (d, J = 256.2 Hz), 155.3, 155.3, 147.7 (d, J = 11.0 Hz), 141.0, 132.2 (J = 3.7 Hz), 127.7, 125.9 (J = 8.2 Hz), 120.9, 115.9 (d, J = 7.1 Hz), 115.8 (d, J = 8.5 Hz), 63.1, 56.4, 26.0, 18.5, -5.3; MS (ESI): 454, 456 ($M+H$) $^+$.

[(4-(((*tert*-Butyl(dimethyl)silyl)oxy)methyl))-6-(2-fluoro-3-methoxyphenyl)pyridin-2-yl](4-fluoro-3-methoxyphenyl)methanone (33a).



According to method C1 the title compound was prepared by reaction of [6-bromo-4-(((*tert*-butyl(dimethyl)silyl)oxy)methyl))pyridin-2-yl](4-fluoro-3-methoxyphenyl)methanone (**33b**) (227 mg, 0.50 mmol, 1.0 eq) with 2-fluoro-3-methoxyphenylboronic acid (102 mg, 0.60 mmol, 1.2 eq) in DME/water (6.0 ml). The product was purified by column chromatography (cyclohexane/ethyl acetate 8:1) to give 195 mg (0.39 mmol/ 78%) of the analytically pure compound. $C_{27}H_{31}F_2NO_4Si$; MW: 500; 1H NMR ($CDCl_3$, 400 MHz): δ 8.01-7.98 (m, 1H), 7.98-7.93 (m, 2H), 7.84 (ddd, J = 8.5 Hz, 4.5 Hz, 2.0 Hz, 1H), 7.50 (ddd, J = 8.2 Hz, 6.6 Hz, 1.6 Hz, 1H), 7.19-7.12 (m, 2H), 7.03 (dt, J = 8.0 Hz, 1.6 Hz, 1H), 4.89 (s, 2H), 3.94 (s, 3H), 3.93 (s, 3H), 0.97 (s, 9H), 0.15 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.9 (d, J = 1.3 Hz), 155.7 (d, J = 255.3 Hz), 154.7, 153.0, 152.3 (d, J = 2.2 Hz), 150.9 (d, J = 250.8 Hz), 148.5 (d, J = 11.4 Hz), 147.6 (d, J = 10.9 Hz), 132.9 (d, J = 3.6 Hz), 127.7 (d, J = 10.2 Hz), 126.0 (d, J = 7.9 Hz), 124.2 (d, J = 5.0 Hz), 124.0 (d, J = 9.7 Hz), 122.1 (d, J = 2.1 Hz), 120.6, 115.9 (d, J = 3.5 Hz), 115.6 (d, J = 18.9 Hz), 113.9 (d, J = 2.4 Hz), 63.8, 56.6, 56.4, 26.0, 18.5, -5.2; MS (ESI): 500 ($M+H$) $^+$.

(4-Fluoro-3-hydroxyphenyl)[6-(2-fluoro-3-hydroxyphenyl)-4-(hydroxymethyl)pyridin-2-yl]methanone (33).



According to method E the title compound was prepared by reaction of [(4-(((tert-butyl(dimethyl)silyl)oxy)methyl))-6-(2-fluoro-3-methoxyphenyl)pyridin-2-yl](4-fluoro-3-methoxyphenyl)methanone (**33a**) (184 mg, 0.37 mmol, 1.0 eq) with boron tribromide (5.5 ml, 5.5 mmol, 15 eq) in dichloromethane (6.0 ml). The product was purified by column chromatography (cyclohexane/ethyl acetate 4:3) to give 91 mg (0.26 mmol/ 70%) of the analytically pure compound. $C_{19}H_{13}F_2NO_4$; MW: 357; mp: 225-226 °C; 1H NMR (acetone- d_6 , 400 MHz): δ 9.04 (s, 1H), 8.83 (d, J = 1.3 Hz, 1H), 8.07-8.02 (m, 1H), 8.00-7.95 (m, 1H), 7.85 (dd, J = 8.7 Hz, 2.1 Hz, 1H), 7.75 (ddd, J = 8.5 Hz, 4.6 Hz, 2.2 Hz, 1H), 7.42 (ddd, J = 7.4 Hz, 6.4 Hz, 2.9 Hz, 1H), 7.26 (dd, J = 10.8 Hz, 8.5 Hz, 1H), 7.14-7.06 (m, 1H), 4.90 (d, J = 5.7 Hz, 1H), 4.79 (t, J = 5.8 Hz, 1H); ^{13}C NMR (acetone- d_6 , 100 MHz): δ 192.4 (d, J = 1.2 Hz), 155.9, 155.4 (d, J = 249.4 Hz), 154.9, 153.1 (d, J = 2.2 Hz), 150.7 (d, J = 245.0 Hz), 146.4 (d, J = 13.8 Hz), 145.5 (d, J = 13.2 Hz), 134.2 (d, J = 3.4 Hz), 128.7 (d, J = 9.2 Hz), 125.2 (d, J = 4.7 Hz), 124.9 (d, J = 7.7 Hz), 124.6 (d, J = 9.1 Hz), 122.0 (d, J = 1.7 Hz), 121.2 (d, J = 4.3 Hz), 121.1, 119.2 (d, J = 4.2 Hz), 116.5 (d, J = 19.2 Hz), 63.2; IR: 3390, 1651, 1599, 1483, 1441, 1429, 1407, 1301, 1235, 1195 cm^{-1} ; MS (ESI): 358 (M+H) $^+$.

1.4. Purity as evaluated by HPLC (Table 1)

#	Retention time (min)	HPLC purity (%)
1	8.98	99.1
6	12.29	97.6
8	11.63	98.8
9	10.82	98.4
10	11.46	99.5
11	11.62	99.7
12	10.77	98.8
13	13.83	98.0
14	8.99	99.9
15	8.58	99.5
16a	17.26	98.4
16	14.45	98.9
17	14.62	98.9
18	11.08	99.7
19	10.50	99.7
20	12.84	97.3
21	14.74	99.3
22	16.20	96.2
23a	16.71	99.6
23	10.28	95.4
24	4.74	99.8
25	13.90	99.4
26	14.81	95.1
27	15.47	97.7
28	14.10	97.9
29	12.73	99.6
30	3.38	99.2
31	13.23	96.5
32	12.46	95.5
33	7.64	97.6

Gradient run: the percentage of acetonitrile in water was increased from initial concentration of 30% at 0 min to 90% at 15 min and kept at 90% for 5 min. Injection volume: 20 µl; flow rate: 1.00 ml/min; wavelength: 254 nm.

2. Crystallography

2.1. Data collection and processing

The data for the structures protein-inhibitor complex structure containing **10** and (PDB ID: 5L7W) were collected at Elettra Sincrotrone at beamline XRD1 in Trieste, Italy. The data collection was achieved at a wavelength of 1 Å and a temperature of 100 K on a DECTRIS Pilatus 2M pixel detector. The diffraction data of **6** and **9**, were obtained at beamline P13 at a wavelength of 0.8 Å and a temperature of 100 K (PDB ID: 5L7T and PDB ID: 5L7Y, respectively) and **12** at beamline P14 at a wavelength of 0.9763 Å and a temperature of 291 K (PDB ID: 5EN4) at PETRA III (EMBL/DESY) in Hamburg, Germany, on a silicon Pilatus 6M pixel detector. All datasets were indexed, processed and scaled with XDS.⁸

2.2. Crystallographic table (Table 2)

Data collection and refinement statistic for the crystal structures.

PDB ID code ^a	Complex with 6, 5L7T	Complex with 9, 5L7Y	Complex with 10, 5L7W	Complex with 12, 5EN4
(A) Data collection and processing				
space group	<i>I</i> 422	<i>I</i> 422	<i>I</i> 422	<i>I</i> 422
unit cell parameters <i>a</i> , <i>b</i> , <i>c</i> (Å)	91.2, 91.2, 131.4	91.6, 91.6, 132.5	91.0, 91.0, 132.2	91.7, 91.7, 135.0
Matthews coefficient ^b (Å ³ /Da)	2.4	2.4	2.4	2.5
solvent content ^b (%)	48.5	49.3	48.5	50.4
(B) Diffraction data				
resolution range (Å)	50-1.98 (2.10- 1.98)	50-1.91 (2.03- 1.91)	50-1.76 (1.86- 1.76)	50-1.52 (1.61- 1.52)
unique reflections	19413 (3002)	21943 (3336)	27439 (4039)	44532 (7097)
<i>R</i> (<i>I</i>) _{sym} (%)	8.2 (48.4)	8.8 (49.7)	8.4 (49.8)	5.3 (47.3)
Wilson <i>B</i> factor (Å ²)	26.0	21.7	20.6	19.5
completeness (%)	98.9 (97.1)	98.9	97.6 (90.3)	99.9 (99.6)
redundancy	7.2 (6.7)	7.2 (6.6)	9.3 (8.5)	14.6 (14.6)
<i><I/σ(I)></i>	17.8 (3.5)	16.8 (3.7)	17.1 (3.7)	28.4 (6.6)
(C) Refinement				
resolution range (Å)	46.05-1.98	46.31-1.91	39.7-1.76	46.8-1.52
reflections used in refinement (work/free)	19413 (18442/971)	21943 (20845/1098)	27439 (26067/1372)	44532 (42305/2227)
final <i>R</i> value for all reflections (work/free) (%)	0.15/0.19	0.14/0.16	0.15/0.19	0.11/0.13
protein residues	256	256	254	251
water molecules	172	188	204	99
RMSD from ideality: bond lengths (Å)	0.007	0.009	0.009	0.008
RMSD from ideality: bond angles (°)	0.850	0.993	1.066	1.062
<i>Ramachandran plot:</i> ^c				
residues in most favored regions (%)	92.3	93.3	91.8	93.2
residues in additionally allowed regions (%)	7.7	6.7	8.2	6.8
residues in generously allowed regions (%)	0	0	0	0
residues in disallowed regions (%)	0	0	0	0
Mean <i>B</i> factor protein (Å ²) ^d	22.2	20.3	24.6	22.9
Mean <i>B</i> factor ligand (Å ²) ^d	31.3	27.3 (interface) 35.1 (binding pocket)	26.9	31.6
Mean <i>B</i> factor water molecules (Å ²) ^d	29.9	27.9	34.8	33.7

^a Values in parenthesis describe the highest resolution shell. ^b Calculated with Matthews_coef program from CCP4 suite version 6.4.0.⁹ ^c Calculated with PROCHECK.¹⁰ ^d Mean *B* factors were calculated with MOLEMAN.¹¹

2.3. Structure determination and refinement

The structures were determined by molecular replacement with the program PHASER MR¹² from the CCP4 suit.⁹ The structure 5EN4 was determined using 1YDE¹³ as starting point for the molecular replacement search. For the remaining structures, 5EN4 was used as a search model. A subset that corresponds to 5% of the reflections was used for the calculation of R_{free} and consequently was omitted from the refinement. The model was built in Coot¹⁴ and refined using PHENIX.refine version 1.10.1-2155.¹⁵ The ligands were energetically minimized and their restraints were generated using Grade Web Server¹⁶ and eLBOW¹⁵ based on the SMILES codes obtained with Molinspiration v2014.11.¹⁷ As first refinement step, for all the structures, a Cartesian simulated annealing was performed using default parameters. The final models were built in Coot with alternating structural modification and refinement of XYZ coordinates, occupancies and individual B-factors in Phenix. With exception of 5L7T, hydrogens were included in the models of the structures. For 5EN4, the temperature factors of all atoms, except hydrogen atoms and solvent molecules, were refined anisotropically. For 5L7W, TLS refinement was performed with TLS groups selected from the TLSMD web server.^{18,19} For 5L7T and 5L7Y, the temperature factors were refined isotropically.

Hydrogen bonds and van der Waals contacts between the protein 17 β -HSD14 and the inhibitors were assigned with the aid of the program CONTACTSYM.^{20,21} The buried surfaces of the inhibitors in the binding pocket were calculated using the program MS.^{22,23}

3. Physico-chemical properties table of the inhibitors - Table 3

Cmpd	MW ^a	clogP ^a	cpKa ^b	tPSA ^a	solubility	Rotat. bonds ^a	HD ^a	HA ^a
1	325	3.02	1.85 (N) 7.71(O/C _{ring}) 12.19(4-O/A _{ring}) 8.74(3-O/A _{ring})	90.65	≥ 200 μM	3	3	5
6	323	4.35	1.94(N) 7.76 (O/ C _{ring}) 9.92 (O/A _{ring})	70.42	100-200 μM	3	2	4
8	327	3.86	1.82(N) 7.58 (O/C _{ring}) 8.23 (O/A _{ring})	70.42	100-200 μM	3	2	4
9	327	3.83	0.78(N) 7.46 (O/C _{ring}) 8.07 (O/A _{ring})	70.42	≥ 200 μM	3	2	4
10	343	3.54	0.69 (N) 6.30(2-O/C _{ring}) 10.83(3-O/C _{ring}) 7.76(O/A _{ring})	90.65	≥ 200 μM	3	3	5
11	345	3.93	0.67 (N) 6.95(O/C _{ring}) 7.84(O/A _{ring})	70.42	-	3	2	4
12	325	3.20	0.69 (N) 7.12(2-O/C _{ring}) 11.84(3-O/C _{ring}) 7.88(O/A _{ring})	90.65	≥ 200 μM	3	3	5
13	309	3.90	0.70 (N) 6.95(O/C _{ring}) 7.84(O/A _{ring})	70.42	25-50 μM	3	2	4
14	341	2.93	0.70 (N) 7.09(2-O/C _{ring}) 12.94(3-O/C _{ring}) 8.81(4-O/C _{ring}) 7.83(O/A _{ring})	110.88	≥ 200 μM	3	4	6
15	341	3.14	0.60 (N) 7.06(2-O/C _{ring}) 13.57(3-O/C _{ring}) 8.52(4-O/C _{ring}) 7.78(O/A _{ring})	110.88	≥ 200 μM	3	6	4
16a	307	4.26	1.82 (N)	39.20	< 3,13 μM	4	0	3
16	293	3.99	1.82 (N) 7.76(O/C _{ring})	50.19	25-50 μM	3	1	3
17	336	4.06	1.41 (N) 7.76(O/C _{ring}) 4.85(N/A _{ring})	53.43	25-50 μM	4	1	4
18	309	3.48	1.73 (N) 7.75(O/C _{ring}) 9.24(O/A _{ring})	70.42	100-200 μM	3	2	4
19	307	2.85	1.64 (N) 7.22(2-O/C _{ring}) 11.84(3-O/C _{ring}) 9.23(O/A _{ring})	90.65	≥ 200 μM	3	3	5

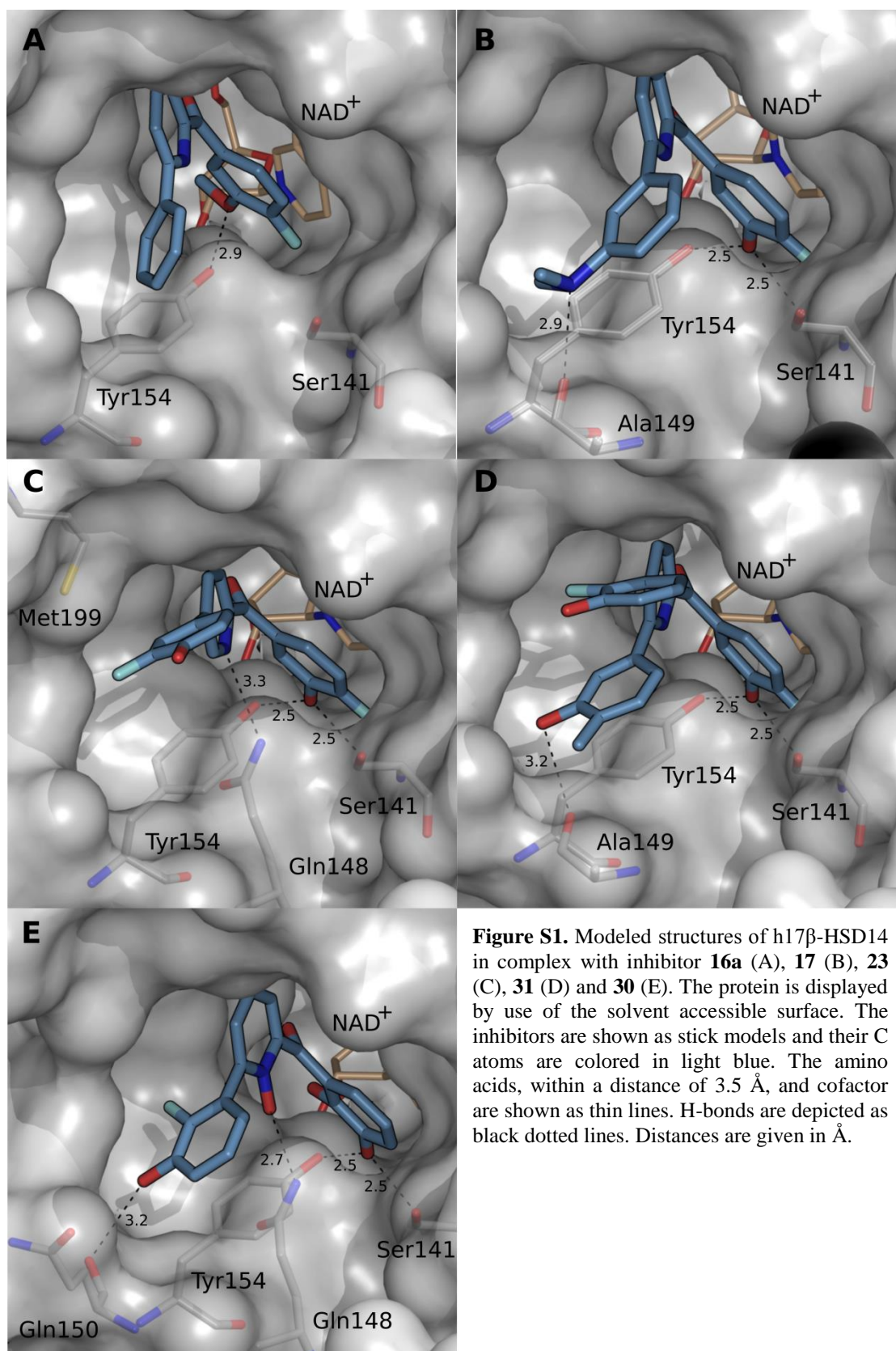
20	323	4.35	1.81 (N) 7.75(O/C _{-ring}) 9.59(O/A _{-ring})	70.42	50-100 μM	3	2	4
21	311	4.15	1.88 (N) 7.76(O/C _{-ring})	50.19	< 3,13 μM	3	1	3
22	346	4.75	1.82 (N) 7.76(O/C _{-ring})	50.19	< 3,13 μM	3	1	3
23a	335	4.48	2.03(N)	48.43	< 3,13 μM	5	0	4
23	327	3.93	2.04(N) 7.48 (O/C _{-ring}) 8.08 (O/A _{-ring})	70.42	100-200 μM	3	2	4
24	217	2.10	2.46(N) 7.76 (O/C _{-ring})	50,19	≥ 200 μM	2	1	3
25	299	3.57	1.54 (N) 7.76(O/C _{-ring})	50.19	6,25-12,5 μM	3	1	3
26	300	3.45	3.82 (N) 7.76(O/C _{-ring})	53.43	100-200 μM	3	1	4
27	315	2.43	2.54 (N) 6.72(O/C _{-ring}) 7.80(O/A _{-ring})	56.67	25-50 μM	3	1	5
28	309	4.19	7.76(O/C _{-ring})	59.42	100-200 μM	4	1	4
29	324	4.25	7.26(2-O/C _{-ring}) 11.88(3-O/C _{-ring}) 8.05(O/A _{-ring})	77.75	50-100 μM	3	3	4
30	341	1.57	6.95(2-O/C _{-ring}) 11.77(3-O/C _{-ring}) 7.71(O/A _{-ring})	103.2	≥ 200 μM	3	3	6
31	429	6.46	1.68 (N) 7.75(O/C _{-ring}) 10.08(O/A _{-ring}) 9.45(O/D _{-ring})	90.65	100-200 μM	4	3	5
32	433	5.95	1.52 (N) 7.65(O/C _{-ring}) 9.87(O/A _{-ring}) 8.39(O/D _{-ring})	90.65	≥ 200 μM	4	3	5
33	357	3.51	0.69 (N) 7.46(O/C _{-ring}) 8.06(O/A _{-ring}) 14.60(O-CH ₂ -)	90.65	≥ 200 μM	4	3	5

^acalculated with Molinspiration¹⁷

^bcalculated with Marvin Sketch 15.9.14

4. MOE models

The inhibitors **16a**, **17**, **23**, **30** and **31** were modeled inside the crystal structure of **12** and minimized with MOE.²⁴ During the minimization, the protein and the C-ring of the ligands were fixed with the exception of **16a** where the full ligand was set free to move.



5. Morrison equation²⁵

$$\frac{v_i}{v_0} = 1 - \frac{([E] + [I] + K_i^{app}) - \sqrt{([E] + [I] + K_i^{app})^2 - 4[E][I]}}{2[E]}$$

v_i : initial rate observed in the presence of the inhibitor; v_0 : initial rate observed in the absence of the inhibitor; $[E]$: total concentration of the enzyme; $[I]$ total concentration of the inhibitor; K_i^{app} : apparent inhibition constant at the used substrate concentration.

$$K_i^{app} = K_i \left(1 + \frac{[S]}{K_m} \right)$$

K_i : inhibition constant; $[S]$: total concentration of the substrate; K_m : Michaelis constant.

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