Structure-Affinity Relationships (SARs) and Structure-Kinetics Relationships (SKRs) of K_v11.1 Blockers

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Supporting Information

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3-(*P*-tolyl)prop-2-yn-1-ol (S13). To a solution of 4-iodotoluene (5.45 g, 25 mmol) in THF (33 mL) and Et_3N (7.3 mL) were added $PdCl_2(PPh_3)_2$ (35 mg, 0.5 mmol) and CuI (327 mg, 1.7 mmol). The mixture was stirred for 30 minutes and a solution of propargyl alcohol (1.48 mL, 25 mmol) in THF (10 mL) was added dropwise. The mixture was stirred at r.t. for 12 hours and filtered on Celite. The solvents were evaporated and the crude residue was purified by flash chromatography on silica gel (33% EtOAc-Petroleum ether) to afford pure **S13** (2.54 g, 70%) as an oil. Spectral data were in agreement with literature.[1]

3-(*P*-tolyl)prop-2-yn-1-yl 4-methylbenzenesulfonate (S14). To a stirred solution of **S13** (1 g, 6.8 mmol) in diethylether (45 mL) at 0 °C was added tosyl chloride (1.6 g, 8.2 mmol) followed, portionwise, by freshly powdered KOH (3.8 g, 68 mmol). After the addition was complete, the reaction mixture was stirred at room temperature for 3.5 h and then poured into water (90 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 × 40 mL). The combined organic extract was dried, filtered, concentrated *in vacuo* and chromatographed (25% EtOAc - Petroleum ether) to obtain the title compound **S14** (1.9 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.17 (d, *J* = 8.1 Hz, 2H), 7.11 (d, *J* = 8.1 Hz, 2H), 4.97 (s, 2H), 2.42 (s, 3H), 2.36 (s, 3H) ppm.

General Sonogashira coupling procedure (S23a-e).

$PdCl_2(PPh_3)_2$ (148 mg, 0.21 mmol, 0.05 eq.) and CuI (121 mg, 0.63 mmol, 0.15 eq.) was added to a solution of 2,6-dibromopyridine (1000 mg, 4.22 mmol, 1.0 eq.) in Et_3N (10 mL) and stirred for 30 min under a nitrogen atmosphere. The appropriate alkyne (10.1 mmol, 2.4 eq.) was added drop wise, and the mixture was stirred overnight at room temperature after which full conversion was shown by TLC. The reaction mixture was adsorbed on silica and purification by FCC yielded the desired compound **2,6-di(hex-1-ynyl)pyridine (S23a)**.

Prepared from hex-1-yne. FCC (petroleum ether: ethyl acetate 60:1 to 20:1) gave the desired product in a yield of (635 mg) 63%; ^{1}H NMR (400MHz, $CDCl_3$): δ 7.52 (t, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 2H), 2.42 (t, *J* = 7.0 Hz, 4H), 1.64-1.56 (m, 4H), 1.52-1.42 (m, 4H), 0.93 (t, *J* = 7.4 Hz, 6H).

2,6-Di(hept-1-ynyl)pyridine (S23b). Prepared from hept-1-yne. FCC (petroleum ether:dichloromethane 4:1 tot 2:1) gave the desired product in a yield of (241 mg) 21%. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.53 (t, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 7.6 Hz, 2H), 2.41 (t, *J* = 6.8 Hz, 4H), 1.64-1.60 (m, 4H), 1.44-1.31 (m, 8H), 0.91 (t, *J* = 7.2 Hz, 6H).

2,6-Di(non-1-ynyl)pyridine (S23c). Prepared from non-1-yne. FCC (petroleum ether:dichloromethane 30:1 tot 4:1) gave the desired product in a yield of (247 mg) 18%. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.52 (t, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 2H), 2.41 (t, *J* = 7.2 Hz, 4H), 1.65-1.57 (m, 4H), 1.45-1.39 (m, 4H), 1.35-1.26 (m, 12H), 0.89 (t, *J* = 6.4 Hz, 6H).

2,6-Di(dec-1-ynyl)pyridine (S23d). Prepared from dec-1-yne. FCC (petroleum ether:dichloromethane 5:1 to 3:1) gave the desired product in a yield of (210 mg) 14%. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.53 (t, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 7.6 Hz, 2H), 2.41 (t, *J* = 7.2, 4H), 1.65-1.57 (m, 4H), 1.45-1.39 (m, 4H), 1.30-1.24 (m, 16H), 0.88 (t, *J* = 6.8 Hz, 6H).

2,6-Di(dodec-1-ynyl)pyridine (S23e). Prepared from dodec-1-yne. FCC (petroleum ether : dichloromethane 5:1 to 2:1) gave the desired product in a yield of 79% (1131 mg). ^{1}H NMR (400MHz, $CDCl_3$): δ 7.53 (t, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 2H), 2.41 (t, *J* = 7.2 Hz, 4H), 1.64-1.57 (m, 4H), 1.44-1.39 (m, 4H), 1.32-1.26 (m, 24H), 0.88 (t, *J* = 6.4 Hz, 6H).

General procedure for reduction of pyridine alkynes (S24a-e).

The appropriate alkyne (**S23a**) (600 mg, 2.52 mmol) was dissolved in THF (3 mL) and MeOH (3 mL) under a N_2 atmosphere. 10% Pd/C (120 mg, 1.14 mmol) was added and H_2 was introduced via a balloon. The mixture was stirred overnight at r.t. after which the reaction

mixture was filtered over Celite. The filtrate were concentrated under reduced pressure and FCC (petroleum ether:ethyl acetate 20:1) gave the desired compound.

2,6-Dihexylpyridine (S24a). Prepared from **S23a** and purified by FCC (petroleum ether:ethyl acetate 20:1) which gave the desired product in a yield of (469 mg) 75%. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.48 (t, *J* = 7.6 Hz, 1H), 6.94 (d, *J* = 7.6 Hz, 2H), 2.75 (t, *J* = 7.6 Hz, 4H), 1.73-1.65 (m, 4H), 1.39-1.26 (m, 12H), 0.88 (t, *J* = 6.8 Hz, 6H).

2,6-Diheptylpyridine (S24b). Prepared from **S23b** and purified by FCC (petroleum ether:dichloromethane 4:1 to 1:2) which gave the desired product in a yield of (106 mg) 43%. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.47 (t, *J* = 7.6 Hz, 1H), 6.93 (d, *J* = 7.6 Hz, 2H), 2.75 (t, *J* = 7.6 Hz, 4H), 1.71-1.66 (m, 4H), 1.34-1.23 (m, 16H), 0.87 (t, *J* = 6.8 Hz, 6H).

2,6-Dinonylpyridine (S24c). Prepared from **S23c** and purified by FCC (petroleum ether:dichloromethane 4:1 to 1:2) which gave the desired product in a yield of (91 mg) 78%. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.47 (t, *J* = 7.6 Hz, 1H), 6.93 (d, *J* = 7.6 Hz, 2H), 2.75 (t, *J* = 8.0 Hz, 4H), 1.73-1.65 (m, 4H), 1.36-1.16 (m, 24H), 0.86 (t, *J* = 4.4 Hz, 6H).

2,6-Didecylpyridine (S24d). Prepared from **S23d** and purified by FCC (petroleum ether:dichloromethane 3:1 to 1:1) which gave the desired product in a yield of (153 mg) 71%. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.48 (t, *J* = 7.6 Hz, 1H), 6.94 (d, *J* = 7.6 Hz, 2H), 2.74 (t, *J* = 8.0 Hz, 4H), 1.73-1.65 (m, 4H), 1.32-1.25 (m, 28H), 0.88 (t, *J* = 6.8 Hz, 6H).

2,6-Didodecylpyridine (S24e). Prepared from **S23e** and purified by FCC (petroleum ether:dichloromethane 4:1 to 1:1) which gave the desired product in a yield of (440 mg) 86%. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.48 (t, *J* = 7.6 Hz, 1H), 6.94 (d, *J* = 7.6 Hz, 2H), 2.75 (t, *J* = 7.6 Hz, 4H), 1.73-1.65 (m, 4H), 1.35-1.25 (m, 36H), 0.88 (t, *J* = 6.8 Hz, 6H).

2,6-Bis((trimethylsilyl)ethynyl)pyridine (S32). 2,6-dibromopyridine (9.00 g, 38.0 mmol), $Pd(PPh_3)_4$ (2.20 g, 1.90 mmol), CuI (361 mg, 1.90 mmol), diisopropylamine (9 mL) and

toluene (100 mL) were stirred at r.t. and trimethylsilylacetylene (13.0 mL, 91.2 mmol) was added. The mixture was stirred overnight followed by filtration over Celite using CH_2Cl_2. The filtrate was concentrated under reduced pressure, dissolved in CH_2Cl_2, and washed with an 1M aqueous NH_4Cl solution. The organic layer was dried over $MgSO_4$, filtered and evaporated to dryness. Yield quantitative and used in the next step without further purification. ^{1}H NMR ($CDCl_3$): δ 7.61 (t, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 7.6 Hz, 2H), 0.25 (s, 18H).

2,6-Bis((4-bromophenyl)ethynyl)pyridine (S33). To a solution of CuCl (346 mg, 3.50 mmol), PPh_3 (918 mg, 3.50 mmol) and potassium benzoate (11.3 g, 70.7 mmol) in 38 mL DMI (1,3-dimethyl-2-imidazolidinone) were added compound **S32** (9.60 g, 35.4 mmol) and 1-bromo-4-iodobenzene (20.0 g, 70.7 mmol) at r.t. The mixture was stirred at 120 °C for 4 h after which full consumption of **S32** was seen. The mixture was cooled down, quenched with a 3M HCl (aq.) solution. The organics were extracted with CH_2Cl_2, and washed with subsequently $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and the solvents were evaporated under vacuum. FCC (petroleum ether:dichloromethane 10:1 to 2:1) gave the desired product. Yield (4.44 g) 29%; ^{1}H NMR ($CDCl_3$): δ 7.70 (t, *J* = 8.0 Hz, 1H), 7.52-7.45 (m, 10H).

General Suzuki reaction procedure yielding compounds S34a-e. Compound **S33** (0.2 mmol, 1.0 eq.), the respective substituted-phenylboronic acid (0.4 mmol, 2.0 eq.), 2M K_2CO_3 (10 eq.) (aq.) were dissolved in a mixture of 3 mL toluene and 0.4 mL of ethanol. $Pd(PPh_3)_4$ (0.02 mmol, 0.1 eq.) were added and the mixture was heated in the microwave at 100 °C under a nitrogen atmosphere for 24 h. After cooling down to room temperature, EtOAc was

added and a precipitate was formed (**S34b-e**). The precipitate was collected by filtration, resulting in the desired products.

2,6-Bis((2'-methylbiphenyl-4-yl)ethynyl)pyridine (S34a). Prepared from 2-methylphenyl boronic acid according to the general procedure, but a precipitate was not formed after addition of EtOAc. The organic layer was washed with a 2 × 0.5 M NaOH solution, dried over $MgSO_4$, filtered and the solvents were evaporated *in vacuo*. Used this as a crude mixture in the next reaction. Yield (37 mg) 50%. ESI-MS: 460.2 $[M+H]^+$.

2,6-Bis((3'-methylbiphenyl-4-yl)ethynyl)pyridine (S34b). Prepared from 3-methylphenyl boronic acid according to the general procedure. Yield (17 mg) 16%; ^{1}H NMR ($CDCl_3$): δ 7.72-7.67 (m, 5H), 7.60 (d, *J* = 8.4 Hz, 4H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.42 (d, J = 8.8 Hz, 4H), 7.35 (t, *J* = 7.2 Hz, 2H), 7.19 (d, *J* = 7.2 Hz, 2H), 2.43 (s, 6H).

2,6-Bis((4'-methylbiphenyl-4-yl)ethynyl)pyridine (S34c) was obtained as a white solid. Yield (13 mg) 18%; ^{1}H NMR ($CDCl_3$): δ 7.72-7.70 (m, 5H), 7.59 (d, *J* = 8.0 Hz, 4H), 7.52-7.49 (m, 6H), 7.30-7.24 (m, H), 2.41 (s, 6H).

2,6-Bis((4'-methoxybiphenyl-4-yl)ethynyl)pyridine (S34d). Prepared from 4-methoxyphenyl-boronic acid according to the general procedure. Yield (55 mg) 49%; ^{1}H NMR ($CDCl_3$): δ 7.72-7.64 (m, 5H), 7.57-7.45 (m, 9H), 7.00 (d, *J* = 8.0 Hz, 4H), 7.30-7.24 (m, H), 2.41 (s, 6H).

2,6-Bis((4'-chlorobiphenyl-4-yl)ethynyl)pyridine (S34e). Prepared from 4-chlorophenyl boronic acid according to the general procedure. Yield (56 mg) 49%; ^{1}H NMR ($CDCl_3$): δ 7.74-7.65 (m, 5H), 7.59-7.47 (m, 10H), 7.43 (d, J = 8.4 Hz, 4H).

4'-Bromo-3-methoxybiphenyl (S43a). Palladium acetate (40.0 mg, 0.18 mmol) was added to

mixture of 1-bromo-4-iodobenze (500 mg, 1,77 mmol), 3-methoxy-phenylboronic acid (269 mg, 1.77 mmol), triphenylphosphine (139 mg, 0.53 mmol), a 2M K_2CO_3 aqueous solution (5 mL) in toluene (15 mL) and EtOH (2 mL). This mixture was heated at 50 °C for 24 h., after which it was cooled to room temperature and partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated. FCC (petroleum ether:ethyl acetate 1:0 to 4:1) gave the desired product. Yield (126 mg) 27%; ^{1}H NMR ($CDCl_3$): δ 7.55 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 8.8 Hz, 2H), 7.36 (t, *J* = 8.0 Hz, 1H), 7.15-7.13 (m, 1H), 7.08 (t, *J* = 2.4 Hz, 1H), 6.93-6.90 (m, 1H), 3.86 (s, 3H).

4'-Bromo-3-chlorobiphenyl (S43b). Prepared from 1-bromo-4-iodobenzene and 3-chloro-phenylboronic following the procedure of 4-bromo-3-methoxybiphenyl (**S43a**). The reaction was performed at 80° C for 20 h. FCC (petroleum ether) gave the compound 190 mg, 40%. ^{1}H NMR ($CDCl_3$): δ 7.56 (d, *J* = 8.4 Hz, 2H), 7.53 (t, *J* = 1.6 Hz, 1H), 7.47-7.43 (m, 3H), 7.36 (t, *J* = 8.0 Hz, 1H), 7.34-7.31 (m, 1H).

General procedure for Sonogashira coupling between 4‘-bromo-3-*substituted*-biphenyl and ethynyltrimethylsilane. Compound **S43a** (126 mg, 0.48 mmol), $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol), CuI (4.0 mg, 0.02 mmol), PPh_3 (5.0 mg, 0.02 mmol) and trimethylsilylacetylene (123 μL, 0.86 mmol) were dissolved in THF (1 mL) and piperidine (200 μl) was added. This was heated in the microwave at 120 °C for 12 min. The mixture was extracted with diethyl ether and washed with aq. H_2SO_4 (10%), water and brine. The organic layer was dried over $MgSO_4$, filtered and evaporated. FCC (petroleum ether:ethyl acetate 1:0 to 10:1) gave the desired **((3'-Methoxybiphenyl-4-yl)ethynyl)trimethylsilane (S44a).** Yield (104 mg) 78%. ^{1}H NMR ($CDCl_3$): δ 7.53 (s, 4H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.18-7.15 (m, 1H), 7.12-7.00 (m, 1H), 6.90 (dd, J^1 = 8.0 Hz, J^2 = 2.8 Hz, 1H), 3.86 (s, 3H), 0.27 (s, 9H).

((3'-Chlorobiphenyl-4-yl)ethynyl)trimethylsilane (S44b). Following the procedure of **S44a** starting from **S43b**. Yield (49 mg) 64%.^{1}H NMR ($CDCl_3$): δ 7.56 (t, J = 2.0 Hz, 1H), 7.53 (d, J = 8.4 Hz, 2H), 7.50 (d, *J* = 8.8 Hz, 2H), 7.45 (dt, J^1 = 7.6 Hz, J^2 = 1.6 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.32 (dt, J^1 = 8.0 Hz, J^2 = 2.0 Hz, 1H), 0.27 (s, 9H).

4'-Ethynyl-3-methoxybiphenyl (S45). To a solution of **S44a** (104 mg, 0.37 mmol) in diethyl ether (3 mL) was added methanol (3 mL) and 2M NaOH (1 mL). After 10 min of stirring at room temperature the mixture was neutralized with 2M HCl (aq.). The layers were separated and the organic layer was washed with brine and water, dried, filtered over $MgSO_4$ and concentrated. The product was used without further purification.

2,6-Bis((2'-methoxybiphenyl-4-yl)ethynyl)pyridine (S46). Reaction conditions according to the general Sonogashira coupling procedure (**S23a-e**), starting from **S45** and **S21**. Purified by FCC (petroleum ether:ethyl acetate 4:1 to 1:1). Yield (23 mg) 25%. ^{1}H NMR ($CDCl_3$): δ 7.72-7.65 (m, 5H), 7.60 (d, *J* = 8.4 Hz, 4H), 7.51 (d, *J* = 7.6 Hz, 2H), 7.38 (t, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.14 (s, 2H), 6.93 (dd, J^1 = 8.2 Hz, J^2 = 2.0 Hz, 2H), 3.88 (s, 6H).

2,6-Bis((2'-chlorobiphenyl-4-yl)ethynyl)pyridine (S47). Starting from compounds **S21** and **S44b**. FCC (petroleum ether:dichloromethane 20:1 to 1:2). Yield (16 mg) 19%. ^{1}H NMR ($CDCl_3$): δ 7.70-7.66 (m, 4H), 7.59-7.55 (m, 6H), 7.53 (d, *J* = 5.2 Hz, 1H), 7.50-7.44 (m, 4H), 7.39 (t, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H).

References

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