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Supporting Information

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The Art of Filling Protein Pockets Efficiently with Octahedral Metal Complexes**

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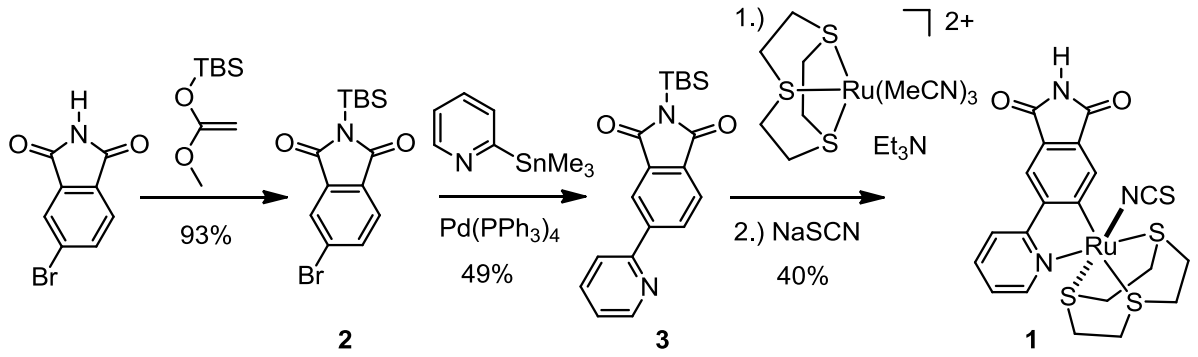
Content:

I.) Synthesis

General methods:

All reactions were carried out using oven-dried glassware and conducted under a positive pressure of nitrogen unless specified otherwise. Chemicals were used as received from standard suppliers. 4-Bromophthalic anhydride,[1] 4-bromophthalimide,[1] TBS-methoxyethene,[2] 2-(trimethylstannyl)pyridine,[3] $[Pd(PPh_3)_4]$,[4] and $[Ru(MeCN)_3([9]aneS_3)](CF_3SO_3)_2$[5] were prepared according to literature procedures. All solvents were distilled prior to use. Acetonitrile and DMF were dried by common methods and freshly distilled prior to use. NMR spectra were recorded on an Avance 300 (300 MHz), Avance 500 (500 MHz), or DPX-250 (250 MHz) spectrometer. Infrared spectra were recorded on a Bruker Alpha FTIR. High resolution mass spectra were obtained with a Finnigan LTQ-FT instrument using either APCI or ESI.

Synthesis of ruthenium complex 1:



Scheme S1. Synthesis of racemic ruthenium complex **1**.

***N*-(*tert*-Butyldimethylsilyl)-4-bromophthalimide (2).** 4-Bromophthalimide (4.00 g, 17.7 mmol) was suspended in 100 mL acetonitrile, TBS-methoxyethene (6.16 mL, 28.3 mmol) was added and the suspension heated to reflux for 5 h. The solvent was removed and the crude product subjected to silica gel chromatography with CH_2Cl_2. The combined

product eluents were dried *in vacuo* and *N*-(*tert*-butyldimethylsilyl)-4-bromophthalimide (**2**) was obtained as white solid (5.59 g, 93%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 7.93 (d, *J* = 0.9 Hz, 1H), 7.83 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.67 (d, *J* = 8.1 Hz, 1H) 0.97 (s, 9H), 0.51 (s, 6H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) = 172.8, 172.3, 136.9, 135.7, 132.6, 128.8, 126.4, 124.4, 26.3, 19.0, –4.3. IR (film) ν (cm^{-1}) 2955, 2932, 2857, 1757, 1700, 1599, 1464, 1414, 1331, 1293, 1255, 1167, 1068, 885, 834, 792, 746, 705, 672. HRMS calcd for $C_{14}H_{19}BrNO_2Si$ $(M+H)^+$ 340.0363, found 340.0365.

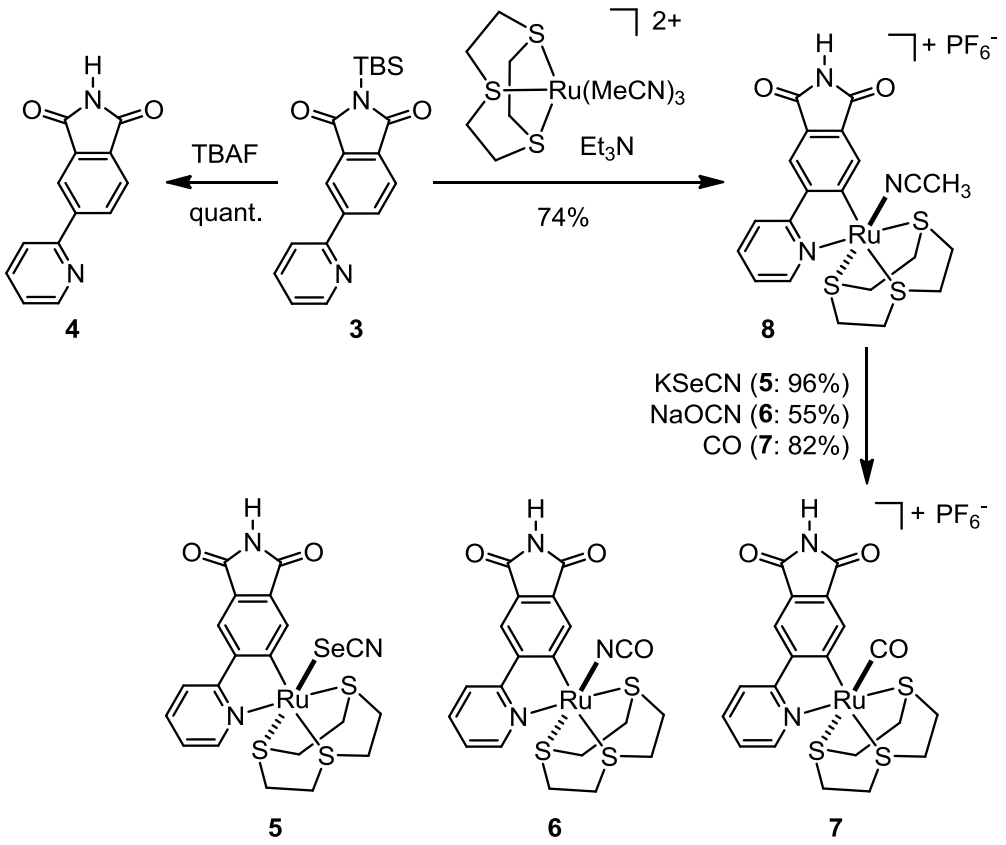
***N*-(*tert*-Butyldimethylsilyl)-4-(pyridin-2-yl)phthalimide (3).** *N*-(*tert*-Butyldimethylsilyl)-4-bromophthalimide (**2**) (1.10 g, 2.98 mmol) and 2-(trimethylstannyl)pyridine (0.74 g, 3.06 mmol) were dissolved in 10 mL *m*-xylene and the solution was purged with nitrogen for 20 minutes. Tetrakis(triphenylphosphine)palladium(0) (40 mg, 35 µmol) was added and the solution was heated to reflux under nitrogen for 48 h. The solution was cooled to ambient temperature, water (50 mL) was added, the organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 twice. The combined organic layers were washed with brine, dried using Na_2SO_4, filtered and the solvent removed *in vacuo*. The crude product was subjected to silica gel chromatography with first CH_2Cl_2 and then CH_2Cl_2-MeOH (50:1). The combined product eluents were dried in *vacuo* and *N*-(*tert*-butyldimethylsilyl)-4-(pyridin-2-yl)phthalimide (**3**) was obtained as light yellow solid (490 mg, 49%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 8.75 (dt, *J* = 4.8, 1.3 Hz, 1H), 8.43 (dd, *J* = 7.8, 1.5 Hz, 1H), 8.37-8.38 (m, 1H), 7.90 (dd, *J* = 7.8, 0.6 Hz, 1H), 7.81-7.84 (m, 2H), 7.31-7.35 (m, 1H), 1.00 (s, 9H), 0.55 (s, 6H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) = 173.71, 173.67, 155.5, 150.3, 145.4, 137.3, 135.0, 134.1, 132.8, 123.6, 123.5, 121.5, 121.2, 26.5, 19.2, –4.1. IR (film) ν (cm^{-1}) 2951, 2926, 2880, 2854, 1759, 1693, 1620, 1585, 1465, 1418, 1350, 1296, 1249, 1155, 1057, 849, 838, 787, 746, 673. HRMS calcd for $C_{19}H_{23}N_2O_2Si$ $(M+H)^+$ 339.1523, found 339.1516.

Ruthenium complex 1. *N*-(*tert*-Butyldimethylsilyl)-4-(pyridin-2-yl)phthalimide (**3**) (50 mg, 151 µmol) and $[Ru(MeCN)_3([9]aneS_3)](CF_3SO_3)_2$ (156 mg, 222 µmol) were dissolved in 5 mL DMF and purged with nitrogen for 15 minutes. Triethylamine (26.8 µL, 192 µmol) was added and the solution was heated to 90 °C for 16 h. NaSCN (18 mg, 222 µmol) in water (300 µL) was added and the solution was further heated for 3 h to 90 °C. The solvent was removed *in vacuo* and the crude product subjected to silica gel chromatography with CH_2Cl_2-MeOH (35:1 to 10:1). The combined product eluents were dried *in vacuo* and the N-bound isomer was obtained as a red solid (35 mg, 40%). The S-bound isomer was obtained as a purple solid (7 mg, 8%).

N-bound isomer: ^{1}H-NMR (300 MHz, DMSO-d_6): δ (ppm) 10.88 (s, 1H), 8.79 (d, J = 5.1 Hz, 1H), 8.42 (d, J = 8.1 Hz, 1H), 8.20 (s, 1H), 8.18 (s, 1H), 7.91 (t, J = 7.2 Hz, 1H), 7.33 (t, J = 6.3 Hz, 1H), 2.79-3.02 (m, 4H), 2.42-2.68 (m, 7H), 2.01-2.10 (m, 1H). ^{13}C-NMR (75 MHz, DMSO-d_6): δ (ppm) = 201.5, 170.9, 170.2, 164.4, 152.8, 151.3, 136.8, 132.5, 132.1, 130.1, 125.2, 123.7, 120.2, 116.5, 34.7, 34.5, 33.5, 30.9, 30.4, 27.8. IR (film) ν (cm^{-1}) 2961, 2922, 2099, 1752, 1706, 1591, 1558, 1474, 1339, 1305, 1210, 1128, 1035, 820, 790, 722. HRMS calcd for $C_{20}H_{19}N_3O_2RuS_4Na$ $(M+Na)^+$ 585.9297, found 585.9296.

S-bound isomer: ^{1}H-NMR (300 MHz, DMSO-d_6): δ (ppm) 10.85 (s, 1H), 8.72 (dd, J = 5.7, 0.9 Hz, 1H), 8.39 (d, J = 8.1 Hz, 1H), 8.17 (s, 1H), 8.08 (s, 1H), 7.84-7.90 (m, 1H), 7.30 (ddd, J = 7.5, 5.7, 1.2 Hz, 1H), 2.62-2.93 (m, 11H), 2.07-2.14 (m, 1H). HRMS calcd for $C_{20}H_{19}N_3O_2RuS_4Na$ $(M+Na)^+$ 585.9297, found 585.9293.

Synthesis of ligand 4 and the ruthenium complexes 5-7:



Scheme S2. Synthesis of 4-(pyridin-2-yl)phthalimide (**4**) and the racemic ruthenium complexes **5**-**7**.

4-(Pyridin-2-yl)phthalimide (4). *N*-(*tert*-Butyldimethylsilyl)-4-(pyridin-2-yl)phthalimide (**3**) (30 mg, 89 µmol) was dissolved in CH_2Cl_2, TBAF (1 M in hexane, 106 µL, 106 µmol) was added and the solution was stirred at room temperature for 5 minutes. The solvent was removed and the crude product subjected to silica gel chromatography with CH_2Cl_2-MeOH (35:1). The combined product eluents were dried *in vacuo* to provide 4-(pyridin-2-yl)phthalimide (**4**) as a white solid (20 mg, quant.). ^{1}H-NMR (300 MHz, DMSO-d_6): δ (ppm) 11.43 (s, 1H), 8.74 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 8.54 (dd, *J* = 7.9, 1.5 Hz, 1H), 8.47 (dd, *J* = 1.5, 0.6 Hz, 1H), 8.19 (dt, *J* = 8.0, 0.9 Hz, 1H), 7.98 (td, *J* = 7.7, 1.8 Hz, 1H), 7.93 (dd, *J* = 7.8, 0.6 Hz, 1H), 7.47 (ddd, *J* = 7.5, 4.8, 1.0 Hz, 1H). ^{13}C-NMR (63 MHz,

DMSO-d_6): δ (ppm) = 168.94, 168.91, 153.9, 149.8, 144.3, 137.6, 133.5, 132.6, 132.2, 123.9, 123.4, 121.3, 120.6. IR (film) ν (cm^{-1}) 2926, 2722, 1717, 1655, 1587, 1430, 1351, 1303, 1177, 1141, 1102, 1059, 996, 833, 783, 737, 687, 634. HRMS calcd for $C_{13}H_9N_2O_2$ $(M+H)^+$ 225.0659, found 225.0659.

Ruthenium complex 8. *N*-(*tert*-Butyldimethylsilyl)-4-(pyridin-2-yl)phthalimide (**3**) (50 mg, 148 µmol) and $[Ru(MeCN)_3([9]aneS_3)](CF_3SO_3)_2$ (156 mg, 222 µmol) were dissolved in 5 mL DMF and purged with nitrogen for 15 minutes. Triethylamine (26.8 µL, 192 µmol) was added and the solution was heated to 90 °C for 16 h. The solvent was removed and the crude product subjected to silica gel chromatography with first acetonitrile and then acetonitrile/water/sat. KNO_3 solution (50:3:1). The combined product eluents were dried *in vacuo*, dissolved in a minimal amount of acetonitrile-water and NH_4PF_6 was added. The solution was centrifuged, the resulting orange filter cake washed three times with water and dried *in vacuo* to provide the monoacetonitrile complex **8** as a light orange solid (75 mg, 74%). ^{1}H-NMR (500 MHz, CD_3CN): δ (ppm) = 8.75 (ddd, *J* = 5.6, 1.5, 0.7 Hz, 1H), 8.60 (s, 1H), 8.28 (s, 1H), 8.24 (d, *J* = 8.1 Hz, 1H), 8.17 (s, 1H), 7.92 (ddd, *J* = 8.1, 6.7, 1.5 Hz, 1H), 7.30 (ddd, *J* = 7.4, 5.6, 1.4 Hz, 1H), 2.92-3.06 (m, 3H), 2.83-2.88 (m, 1H), 2.59-2.74 (m, 3H), 2.45-2.50 (m, 1H), 2.33-2.39 (m, 1H), 2.25-2.31 (m, 2H), 2.10-2.16 (m, 1H). ^{13}C-NMR (63 MHz, CD_3CN): δ (ppm) 196.0 169.7, 169.1, 164.4, 152.9, 151.4, 137.2, 132.7, 130.7, 126.5, 123.8, 122.8, 120.3, 116.4, 35.0, 33.9, 33.3, 31.3, 30.2, 27.7, 2.8. IR (film) ν (cm^{-1}) 3185, 3059, 1755, 1704, 1590, 1476, 1444, 1411, 1339, 1307, 1211, 1131, 1044, 835, 747, 677, 645. HRMS calcd for $C_{21}H_{22}N_3O_2RuS_3$ $(M-PF_6)^+$ 545.9916, found 545.9911.

Ruthenium complex 5. Monoacetonitrile complex **8** (13 mg, 19 µmol) was dissolved in 3 mL DMF, KeSCN (4 mg, 28 µmol) in 300 µL water was added and the solution was heated to 90 °C for 5 h. The solvent was removed and the crude product subjected to silica gel

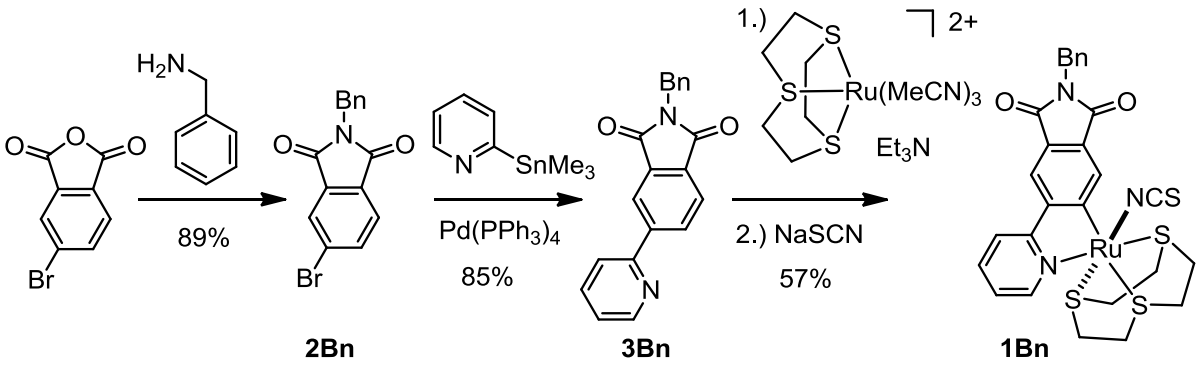
chromatography with CH_2Cl_2-MeOH (35:1→10:1). The combined product eluents were dried *in vacuo* to provide the selenocyanate complex **5** as a red solid (11 mg, 96%). ^{1}H-NMR (500 MHz, DMSO-d_6): δ (ppm) 10.83 (s, 1H), 8.72 (d, J = 5.0 Hz, 1H), 8.38 (d, J = 8.1 Hz, 1H), 8.17 (s, 1H), 8.08 (s, 1H), 7.84-7.87 (m, 1H), 7.27-7.30 (m, 1H), 2.86-2.93 (m, 2H), 2.75-2.84 (m, 3H), 2.66-2.74 (m, 1H), 2.44-2.54 (m, 5H), 2.06-2.12 (m, 1H). ^{13}C-NMR (125 MHz, DMSO-d_6): δ (ppm) = 201.8, 171.4, 170.7, 164.6, 153.2, 151.6, 136.7, 132.8, 130.6, 125.6, 124.0, 120.8, 116.9, 108.2, 35.3, 34.7, 33.4, 33.3, 32.4, 28.7. IR (film) ν (cm^{-1}) 3121, 3053, 2920, 2719, 2098, 1749, 1708, 1590, 1473, 1442, 1406, 1336, 1304, 1208, 1139, 1039, 1012, 949, 899, 817, 744. HRMS calcd for $C_{20}H_{19}N_3O_2RuS_3SeNa$ $(M+Na)^+$ 633.8747, found 633.8734.

Ruthenium complex 6. Monoacetonitrile complex **8** (23 mg, 33 µmol) was dissolved in 3 mL DMF, NaOCN (3 mg, 50 µmol) in 300 µL water was added and the solution was heated to 95 °C for 3 h. The solvent was removed and the crude product subjected to silica gel chromatography with CH_2Cl_2-MeOH (35:1→10:1). The combined product eluents were dried *in vacuo* to provide the isocyanate complex **6** as a red solid (10 mg, 55%). ^{1}H-NMR (300 MHz, DMSO-d_6): δ (ppm) 10.82 (s, 1H), 8.80 (dd, J = 5.6, 0.8 Hz, 1H), 8.37 (d, J = 8.3 Hz, 1H), 8.19 (s, 1H), 8.15 (s, 1H), 7.84-7.90 (m, 1H), 7.27-7.31 (m, 1H), 2.73-2.95 (m, 5H), 2.56-2.64 (m, 3H), 2.34-2.45 (m, 3H), 1.99-2.08 (m, 1H). ^{13}C-NMR (125 MHz, DMSO-d_6): δ (ppm) = 205.4, 171.6, 170.8, 164.9, 153.1, 151.8, 136.8, 132.9, 130.3, 125.0, 123.9, 120.4, 116.8, 35.4, 34.8, 34.3, 31.2, 30.7, 28.0. IR (film) ν (cm^{-1}) 3436, 3154, 3052, 2181, 1751, 1700, 1620, 1587, 1473, 1405, 1338, 1306, 1037, 898, 816, 743. HRMS calcd for $C_{20}H_{19}N_3O_3RuS_3Na$ $(M+Na)^+$ 569.9526, found 569.9520.

Ruthenium complex 7. Monoacetonitrile complex **8** (15 mg, 22 µmol) was dissolved in 3 mL DMF, purged with CO gas for 30 sec and heated under a CO atmosphere to 95 °C for 3 h. The

solvent was removed and the crude product subjected to silica gel chromatography with first acetonitrile and then acetonitrile/water/sat. KNO_3 solution (50:3:1). The combined product eluents were dried *in vacuo*, dissolved in a minimal amount of acetonitrile-water and NH_4PF_6 was added. The solution was centrifuged, the resulting orange filter cake washed three times with water and dried *in vacuo* to provide the carbonyl complex **7** as an orange solid (12 mg, 82%). ^{1}H-NMR (500 MHz, CD_3CN): δ (ppm) = 8.81 (s, 1H), 8.55 (ddd, *J* = 5.6, 1.5, 0.8 Hz, 1H), 8.34 (dd, *J* = 7.3, 0.7 Hz, 1H), 8.29 (s, 1H), 8.09 (s, 1H), 8.06 (ddd, *J* = 8.1, 7.6, 1.5 Hz, 1H), 7.39 (ddd, *J* = 7.5, 5.6, 1.4 Hz, 1H), 3.29-3.34 (m, 1H), 3.11-3.21 (m, 3H), 2.91-2.96 (m, 1H), 2.82-2.90 (m, 2H), 2.71-2.79 (m, 2H), 2.57-2.64 (m, 2H), 2.39-2.45 (m, 1H). ^{13}C-NMR (125 MHz, CD_3CN): δ (ppm) 194.3, 179.6, 169.1, 169.0, 163.9, 153.7, 151.1, 139.3, 132.7, 132.3, 129.3, 125.2, 122.0, 117.9, 36.9, 34.9, 34.8, 33.2, 32.3, 29.8. IR (film) ν (cm^{-1}) 3223, 1970, 1765, 1713, 1560, 1480, 1450, 1408, 1343, 1307, 1221, 1171, 1133, 1042, 831, 745, 645. HRMS calcd for $C_{20}H_{19}N_2O_3RuS_3$ $(M\text{-}PF_6)^+$ 532.9596, found 532.9606.

Synthesis of ruthenium complex 1Bn:



Scheme S3. Synthesis of the racemic ruthenium complex **1Bn**.

***N*-Benzyl-4-bromophthalimide (2Bn).** 4-Bromophthalic anhydride (5.00 g, 22.0 mmol) was dissolved in 50 mL glacial acetic acid. Benzylamine (2.40 mL, 22.0 mmol) was added and the solution was heated to 130 °C for 4 h. The hot solution was carefully poured into 200 mL ice-

cold water, the resulting solid filtered off, washed with 100 mL water and dried *in vacuo* to provide *N*-benzyl-4-bromophthalimide as a beige solid (6.22 g, 89%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) . 7.97 (dd, *J* = 1.6, 0.3 Hz, 1H), 7.84 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.69-7.72 (m, 1H), 7.40-7.43 (m, 2H), 7.27-7.35 (m, 3H), 4.83 (s, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$): 167.2, 166.7, 137.0, 136.0, 133.7, 130.6, 128.9, 128.7, 128.6, 128.0, 126.7, 124.7, 41.8. δ (ppm) =. IR (film) ν (cm^{-1}) 3065, 3033, 1772, 1710, 1607, 1430, 1418, 1387, 1345, 1186, 1170, 1102, 1068, 942, 739, 714, 398. HRMS calcd for $C_{15}H_{11}BrNO_2$ $(M+H)^+$ 317.9949, found 317.9950.

***N*-Benzyl-4-(pyridin-2-yl)phthalimide (3Bn).** *N*-Benzyl-4-bromophthalimide (**2Bn**) (1.28 g, 4.04 mmol) and 2-pyridyltrimethylstannane (0.90 g, 3.69 mmol) were dissolved in 35 mL *m*-xylene and the solution was purged with nitrogen for 20 minutes. Tetrakis-(triphenylphosphine)palladium(0) (473 mg, 0.41 mmol) was added and the solution was heated to reflux under nitrogen for 48 h. The solution was cooled to ambient temperature, water (50 mL) was added, the organic phase was separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were washed with brine, dried using Na_2SO_4, filtered and the solvent removed *in vacuo*. The crude product was subjected to silica gel chromatography with first CH_2Cl_2 then CH_2Cl_2-MeOH (75:1). The combined product eluents were dried in *vacuo* and *N*-benzyl-4-(pyridin-2-yl)phthalimide (**3Bn**) was obtained as a light yellow solid (980 mg, 85%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 8.74 (dt, *J* = 4.8, 1.4 Hz, 1H), 8.44-8.45 (m, 1H), 8.41 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.93 (dd, *J* = 7.8, 0.6 Hz, 1H), 7.81-7.83 (m, 2H), 7.44-7.47 (m, 2H), 7.27-7.35 (m, 4H), 4.88 (s, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) = 167.8, 155.1, 150.1, 145.3, 137.1, 136.4, 132.9, 132.5, 132.0, 128.7, 128.6, 127.8, 123.8, 123.5, 121.7, 121.0, 41.7. IR (film) ν (cm^{-1}) 3029, 2930, 1766, 1699, 1617, 1584, 1422, 1387, 1341, 1304, 1155, 1106, 1067, 949, 786, 740, 695, 623. HRMS calcd for $C_{20}H_{15}N_2O_2$ $(M+H)^+$ 315.1128, found 315.1124.

Ruthenium complex 1Bn. A solution of *N*-benzyl-4-(pyridin-2-yl)phthalimide (**3Bn**) (70.3 mg, 223 μmol), $[Ru(MeCN)_3([9]aneS_3)](CF_3SO_3)_2$ (140 mg, 200 μmol) and triethylamine (30 μL, 223 μmol) in 11 mL DMF was heated to 90 °C for 21 h. Following the addition of NaSCN (30.5 mg, 376 μmol) the solution was heated for an additional 1 h to 90 °C. The solvent was removed *in vacuo* and the crude product subjected to silica gel chromatography with CH_2Cl_2-MeOH (20:1). The combined product eluents were dried *in vacuo* and the N-bound isomer was obtained as a red solid (61 mg, 57%). Small amounts of the purple S-bound isomer were also obtained (15 mg, 12%).

N-bound isomer: ^{1}H-NMR (300 MHz, DMSO-d_6): δ (ppm) 8.80 (d, *J* = 4.7 Hz, 1H), 8.45 (d, *J* = 8.1 Hz, 1H), 8.28 (s, 1H), 8.25 (s, 1H), 7.95-7.89 (m, 1H), 7.38-7.23 (m, 6H), 4.76 (s, 2H), 3.03-2.40 (m, 12H). ^{13}C-NMR (75 MHz, DMSO-d_6): δ (ppm) = 202.7, 169.3, 168.7, 164.3, 152.8, 151.5, 137.2, 136.8, 132.7, 132.20, 132.17, 128.9, 128.5, 127.2, 123.9, 123.8, 120.3, 116.7, 54.9, 34.7, 34.5, 33.6, 30.9, 30.5, 27.8. IR (film) ν (cm^{-1}) 2919, 2851, 2107, 2088, 1753, 1694, 1591, 1571, 1555, 1476, 1396, 1380, 1365, 1333, 1271, 1209, 1158, 1108, 1062, 1018, 962, 906, 875, 817, 788, 749, 733, 622, 592. HRMS calcd for $C_{27}H_{25}N_3O_2RuS_4Na$ $(M+Na)^+$ 675.9765, found 675.9776.

S-bound isomer: ^{1}H-NMR (300 MHz, DMSO-d_6): δ (ppm) 8.73 (d, *J* = 4.7 Hz, 1H), 8.42 (d, *J* = 8.1 Hz, 1H), 8.25 (s, 1H), 8.15 (s, 1H), 7.87 (dt, *J* = 8.1, 1.4 Hz, 1H), 7.36-7.23 (m, 6H), 4.74 (s, 2H), 2.95-2.54 (m, 10H), 2.06-2.18 (m, 2H). IR (film) ν (cm^{-1}) 3425, 3029, 2921, 2088, 1753, 1693, 1592, 1566, 1475, 1381, 1338, 1271, 1204, 1112, 959, 904, 875, 787, 746, 700. HRMS calcd for $C_{27}H_{25}N_3O_2RuS_4Na$ $(M+Na)^+$ 675.9765, found 675.9774.

II.) Proof of Purity of Complex 1

Complex **1** was eluted with a normal phase silica gel column (Merck Purospher STAR, LiChroCART 250 x 4.6 mm, Si, 5 µm) on an Agilent 1200 Series HPLC system with a quaternary pump. Flow rate: 0.75 mL/min; UV-detection at 470 nm; isocratic: 30 min dichloromethane/methanol 95:5. Result: Purity of complex **1** ≥ 98%.

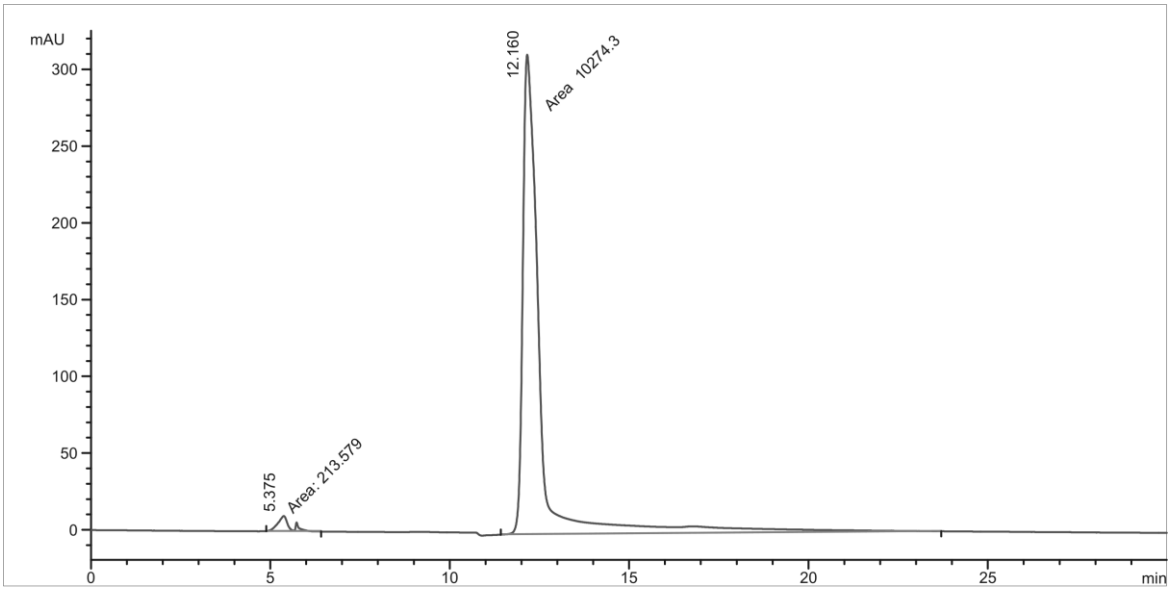


Figure S1. HPLC trace of complex **1**.

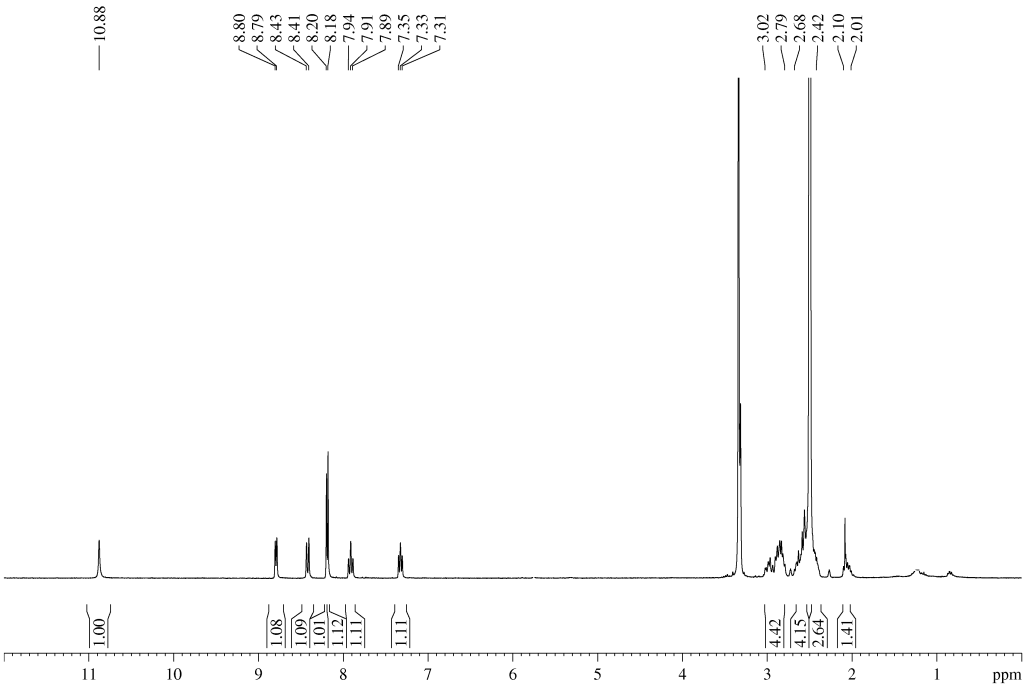


Figure S2. ^{1}H-NMR of complex **1** (300 MHz, DMSO-d_6).

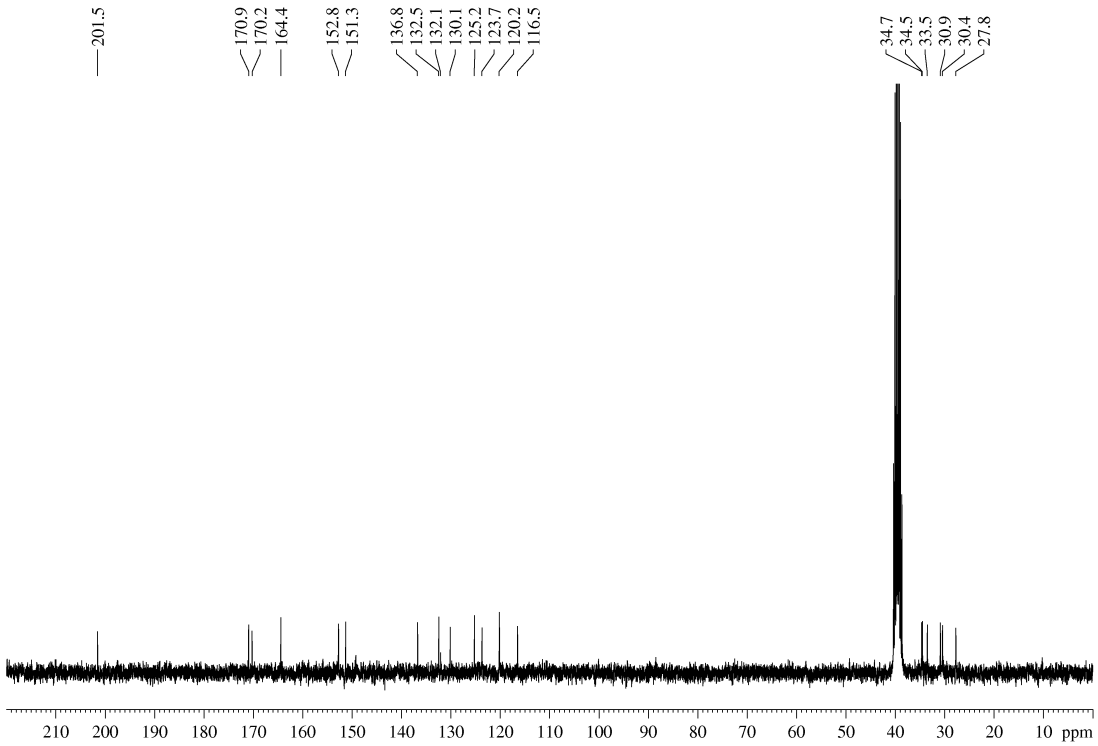


Figure S3. ^{13}C-NMR of complex **1** (75 MHz, DMSO-d_6).

III.) Single Crystal X-Ray Diffraction Study with 1Bn

Single crystals of complex **1Bn** were obtained upon slow diffusion of diethylether into dichloromethane at 6 °C. The intensity data were collected at 100 K using a STOE IPDS-2T system. The data were corrected for absorption effects using indexed faces.[6] The structure was solved using direct methods (SIR-92)[7] and refined using the full matrix least squares procedure implemented in SHELX-97.[8] Hydrogen atoms were included at calculated positions.

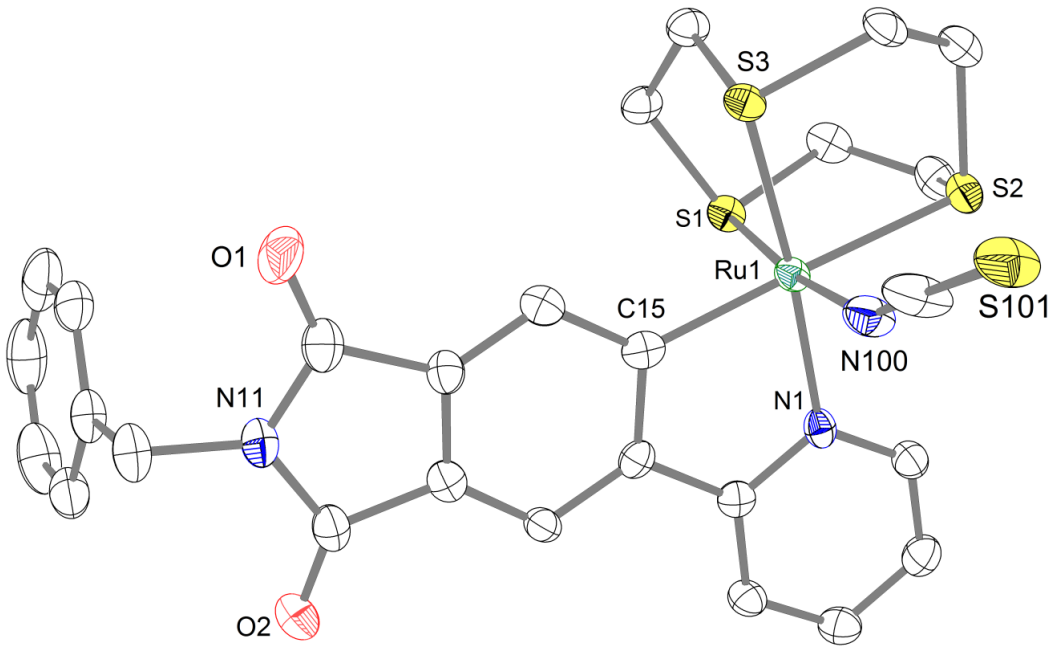


Figure S4. Structure of the *N*-benzylated derivative of complex **1** (**1Bn**). Disordered solvent and a disordered position of S101 are not shown. ORTEP drawing with 50% probability thermal ellipsoids.

Table S1. Crystallographic data for complex **1Bn**.[a]

	1Bn
formula	$C_{28}H_{27}Cl_2N_3O_2RuS_4$
fw	737.74
a(Å)	14.6619(6)
b(Å)	13.2660(4)
c(Å)	15.5860(7)
α(°)	90
β(°)	98.519(4)
γ(°)	90
V(Å^3)	2998.1(2)
Z	4
space group	$P2_1/n$
d_{calcd}(Mg/m^3)	1.634
μ(mm^{-1})	1.012
θ range(°)	4.60 – 25.0
no. of indep. reflections	5246
no. of parameters	399
wR2 (all data)[b]	0.0699
R1 (I > 2σ(I))[b]	0.0350
CCDC no.[c]	855528

[a]MoKα radiation (λ = 0.71073 Å). [b]R1 = Σ||F_o| - |F_c||/Σ|F_o|; wR2=[w(F_o^2 – F_c^2)^2/ Σw(F_o^2)^2]$^{1/2}$. [c]Crystallographic data (excluding structure factors) have been deposited in the Cambridge Crystallographic Data Center. CIF files can be obtained from the CCDC free of charge via http://www.ccdc.cam.ac.uk/data_request/cif.

IV.) Protein Crystallography

PAK1 expression and purification.[9] PAK1 kinase domain (residues 249 to 545, mutation Lys299Arg) was cloned into a pET-TOPO vector with an N-terminal 6-His tag and expressed in BL21(DE3) *E. coli* cells. The kinase domain contained the inactivating mutation Lys299Arg. Cells were grown at 37 °C until they reached an OD_{600} of 0.6 and protein expression was induced by adding 1 mM IPTG and carried on for 6 hours at 28 °C. Cells were harvested and lysed by sonication in 50 mM HEPES pH 7.0, 500 mM NaCl and 5 mM DTT (lysis buffer). The lysate was cleared by centrifugation and applied to a Ni-NTA affinity column. The protein was eluted from the column with increasing concentration of imidazole in lysis buffer (20 mM to 250 mM) and treated overnight with TEV protease to cleave the His_6-tag. The protein was further purified by passage through Mono-Q and a size–exclusion Superdex 200 column equilibrated with 20 mM Tris pH 8.0, 125 mM NaCl. Purified protein was concentrated to 9 mg/ml in a buffer containing 20 mM Tris pH 8.0, 125 mM NaCl and used for crystallization.

Crystallization and data collections. Crystals of apo-PAK1 were obtained using hanging drop vapor diffusion by mixing 1 μL of PAK1 (9 mg/ml) with 1 μL of crystallization solution (0.1 M HEPES pH 7.5, 1 M NaCl, 25% PEG 4000, 10 mM DTT) at 4°C. Crystals were subjected to soaking with 1 mM of the racemic complex **1** overnight. Crystals were cryoprotected, flash frozen in liquid nitrogen and yielded X-ray diffraction to 2.0 Å at The National Synchrotron Light Source, Brookhaven National Laboratory, X6A beam line. Collected data were integrated and scaled using the program HKL2000.[10]

Structure determination and refinement. The PAK1/inhibitor structure was solved by molecular replacement using the program PHASER[11] with the structure of PAK1 (249-545,

Lys299Arg) in complex with Λ-**FL172** (PDB code 3FXZ)[9] as a search model. Iterative cycles of refinement and manual rebuilding of the initial model were performed using the programs REFMAC5[12] and COOT[13], respectively. Inhibitor models were manually fitted into calculated F_o-F_c maps. The validity of each step of refinement and rebuilding was monitored by the R_{work} and R_{free}. See Table S2 for data collection and refinement statistics. Coordinates of the structure have been deposited in the Protein Data Bank (PDB ID: 4DAW).

Table S2. Data collection and refinement statistics for the complex PAK1/**1**.

Data Collection	
Space Group	$C222_1$
Cell Dimension [Å,°]	a = 51.676 b = 103.549 c = 122.790 $\alpha = \beta = \gamma = 90$
Resolution [Å]	50.0-2.0
Reflections total, unique	166063, 22771
R_{merge} [a]	0.137 (0.587)
I/σ	15.2 (3.4)
Completeness [%]	99.8 (98.5)
Redundancy	7.3 (7.2)
Refinement	
R_{work}/R_{free} [%]	20.3/ 23.8
Ramachandran[%] favoured/allowed/disallowed	91.5/ 8.5/ 0
R.m.s.d.[b]	
Bond lengths [Å]	0.009
Bond angles [°]	1.373

[a] Data for highest resolution shell in parentheses. [b] R.m.s.d = root-mean-square-deviation.

V.) Determination of IC_{50}-Values

Various concentrations of the ruthenium complexes **1**, **5-7** or the ligand **4** were incubated at room temperature in 20 mM MOPS, 30 mM $Mg(OAc)_2$, 0.8 µg/µL BSA, 5% DMSO (resulting from the inhibitor stock solution), pH 7.0 in the presence of substrate MBP (10 µM) and human PAK1 (2.9 nM). After 30 min, the reaction was initiated by adding ATP to a final concentration of 1 µM and approximately 0.1 µCi/µL $^{[\gamma\text{-}33P]}$ATP. Reactions were performed in a total volume of 25 µL. After 45 min, the reaction was terminated by spotting 15 µL on a circular P81 phosphocellulose paper (2.1 cm diameter, Whatman), followed by washing three times with 0.75% phosphoric acid and once with acetone. The dried P81 papers were transferred to a scintillation vial, 5 mL of scintillation cocktail was added, the counts per minute (CPM) were measured with a Beckmann Coulter^{TM} LS6500 Multi-Purpose Scintillation Counter and corrected by the background CPM. The IC_{50} values were determined in triplicate from sigmoidal curve fits.

VI.) Supplementary Kinase Selectivity Data

The protein kinase selectivity profile of racemic complex **1** at an assay concentration of 10 μM was derived from an active-site-directed affinity screening against 442 protein kinases (KINOMEscan, DiscoveRx).[14]

Table S3. KINOME*scan* Binding Data for Complex **1** (10 μM).

Ambit Gene Symbol	Entrez Gene Symbol	Percent Control
AAK1	AAK1	91
ABL1(E255K)-phosphorylated	ABL1	16
ABL1(F317I)-nonphosphorylated	ABL1	100
ABL1(F317I)-phosphorylated	ABL1	71
ABL1(F317L)-nonphosphorylated	ABL1	48
ABL1(F317L)-phosphorylated	ABL1	23
ABL1(H396P)-nonphosphorylated	ABL1	3.3
ABL1(H396P)-phosphorylated	ABL1	27
ABL1(M351T)-phosphorylated	ABL1	28
ABL1(Q252H)-nonphosphorylated	ABL1	13
ABL1(Q252H)-phosphorylated	ABL1	54
ABL1(T315I)-nonphosphorylated	ABL1	3.1
ABL1(T315I)-phosphorylated	ABL1	1.6
ABL1(Y253F)-phosphorylated	ABL1	40
ABL1-nonphosphorylated	ABL1	27
ABL1-phosphorylated	ABL1	35
ABL2	ABL2	67
ACVR1	ACVR1	100
ACVR1B	ACVR1B	95
ACVR2A	ACVR2A	100
ACVR2B	ACVR2B	93
ACVRL1	ACVRL1	100
ADCK3	CABC1	88

ADCK4	ADCK4	90
AKT1	AKT1	0.7
AKT2	AKT2	35
AKT3	AKT3	8.7
ALK	ALK	30
AMPK-alpha1	PRKAA1	1.4
AMPK-alpha2	PRKAA2	7.4
ANKK1	ANKK1	100
ARK5	NUAK1	16
ASK1	MAP3K5	100
ASK2	MAP3K6	63
AURKA	AURKA	23
AURKB	AURKB	16
AURKC	AURKC	31
AXL	AXL	8.3
BIKE	BMP2K	62
BLK	BLK	1.2
BMPR1A	BMPR1A	98
BMPR1B	BMPR1B	100
BMPR2	BMPR2	15
BMX	BMX	76
BRAF	BRAF	100
BRAF(V600E)	BRAF	100
BRK	PTK6	100
BRSK1	BRSK1	100
BRSK2	BRSK2	100
BTK	BTK	0.1
CAMK1	CAMK1	41
CAMK1D	CAMK1D	2.3
CAMK1G	CAMK1G	45
CAMK2A	CAMK2A	30
CAMK2B	CAMK2B	35
CAMK2D	CAMK2D	65
CAMK2G	CAMK2G	43

CAMK4	CAMK4	1.3
CAMKK1	CAMKK1	0.9
CAMKK2	CAMKK2	0.95
CASK	CASK	100
CDC2L1	CDC2L1	100
CDC2L2	CDC2L2	100
CDC2L5	CDC2L5	100
CDK11	CDC2L6	98
CDK2	CDK2	32
CDK3	CDK3	72
CDK4-cyclinD1	CDK4	100
CDK4-cyclinD3	CDK4	99
CDK5	CDK5	100
CDK7	CDK7	7
CDK8	CDK8	100
CDK9	CDK9	100
CDKL1	CDKL1	100
CDKL2	CDKL2	100
CDKL3	CDKL3	100
CDKL5	CDKL5	100
CHEK1	CHEK1	41
CHEK2	CHEK2	2
CIT	CIT	100
CLK1	CLK1	38
CLK2	CLK2	1.4
CLK3	CLK3	5.2
CLK4	CLK4	84
CSF1R	CSF1R	71
CSK	CSK	77
CSNK1A1	CSNK1A1	100
CSNK1A1L	CSNK1A1L	100
CSNK1D	CSNK1D	100
CSNK1E	CSNK1E	92
CSNK1G1	CSNK1G1	100

CSNK1G2	CSNK1G2	100
CSNK1G3	CSNK1G3	100
CSNK2A1	CSNK2A1	98
CSNK2A2	CSNK2A2	80
CTK	MATK	93
DAPK1	DAPK1	61
DAPK2	DAPK2	76
DAPK3	DAPK3	68
DCAMKL1	DCLK1	7.8
DCAMKL2	DCLK2	4
DCAMKL3	DCLK3	25
DDR1	DDR1	53
DDR2	DDR2	53
DLK	MAP3K12	54
DMPK	DMPK	73
DMPK2	CDC42BPG	60
DRAK1	STK17A	100
DRAK2	STK17B	100
DYRK1A	DYRK1A	82
DYRK1B	DYRK1B	82
DYRK2	DYRK2	100
EGFR	EGFR	100
EGFR(E746-A750del)	EGFR	100
EGFR(G719C)	EGFR	100
EGFR(G719S)	EGFR	100
EGFR(L747-E749del, A750P)	EGFR	92
EGFR(L747-S752del, P753S)	EGFR	100
EGFR(L747-T751del,Sins)	EGFR	100
EGFR(L858R)	EGFR	100
EGFR(L858R,T790M)	EGFR	65
EGFR(L861Q)	EGFR	84
EGFR(S752-I759del)	EGFR	100
EGFR(T790M)	EGFR	24
EIF2AK1	EIF2AK1	100

EPHA1	EPHA1	100
EPHA2	EPHA2	93
EPHA3	EPHA3	29
EPHA4	EPHA4	79
EPHA5	EPHA5	94
EPHA6	EPHA6	74
EPHA7	EPHA7	89
EPHA8	EPHA8	65
EPHB1	EPHB1	100
EPHB2	EPHB2	100
EPHB3	EPHB3	84
EPHB4	EPHB4	100
EPHB6	EPHB6	76
ERBB2	ERBB2	84
ERBB3	ERBB3	100
ERBB4	ERBB4	95
ERK1	MAPK3	15
ERK2	MAPK1	19
ERK3	MAPK6	95
ERK4	MAPK4	100
ERK5	MAPK7	2.5
ERK8	MAPK15	49
ERN1	ERN1	64
FAK	PTK2	8.5
FER	FER	2.9
FES	FES	54
FGFR1	FGFR1	12
FGFR2	FGFR2	30
FGFR3	FGFR3	47
FGFR3(G697C)	FGFR3	54
FGFR4	FGFR4	29
FGR	FGR	24
FLT1	FLT1	86
FLT3	FLT3	29

FLT3(D835H)	FLT3	12
FLT3(D835Y)	FLT3	50
FLT3(ITD)	FLT3	44
FLT3(K663Q)	FLT3	12
FLT3(N841I)	FLT3	2.7
FLT3(R834Q)	FLT3	18
FLT4	FLT4	66
FRK	FRK	36
FYN	FYN	23
GAK	GAK	5.6
GCN2(Kin.Dom.2,S808G)	EIF2AK4	98
GRK1	GRK1	1.6
GRK4	GRK4	100
GRK7	GRK7	1
GSK3A	GSK3A	3.6
GSK3B	GSK3B	1.2
HCK	HCK	22
HIPK1	HIPK1	88
HIPK2	HIPK2	45
HIPK3	HIPK3	65
HIPK4	HIPK4	100
HPK1	MAP4K1	38
HUNK	HUNK	100
ICK	ICK	4.9
IGF1R	IGF1R	16
IKK-alpha	CHUK	100
IKK-beta	IKBKB	100
IKK-epsilon	IKBKE	100
INSR	INSR	11
INSRR	INSRR	26
IRAK1	IRAK1	78
IRAK3	IRAK3	51
IRAK4	IRAK4	1.3
ITK	ITK	14

JAK1(JH1domain-catalytic)	JAK1	95
JAK1(JH2domain-pseudokinase)	JAK1	73
JAK2(JH1domain-catalytic)	JAK2	31
JAK3(JH1domain-catalytic)	JAK3	4.8
JNK1	MAPK8	100
JNK2	MAPK9	100
JNK3	MAPK10	75
KIT	KIT	64
KIT(A829P)	KIT	63
KIT(D816H)	KIT	92
KIT(D816V)	KIT	73
KIT(L576P)	KIT	42
KIT(V559D)	KIT	62
KIT(V559D,T670I)	KIT	87
KIT(V559D,V654A)	KIT	87
LATS1	LATS1	74
LATS2	LATS2	7.4
LCK	LCK	3.8
LIMK1	LIMK1	92
LIMK2	LIMK2	100
LKB1	STK11	81
LOK	STK10	65
LRRK2	LRRK2	100
LRRK2(G2019S)	LRRK2	78
LTK	LTK	5.8
LYN	LYN	49
LZK	MAP3K13	46
MAK	MAK	100
MAP3K1	MAP3K1	71
MAP3K15	MAP3K15	100
MAP3K2	MAP3K2	28
MAP3K3	MAP3K3	17
MAP3K4	MAP3K4	100
MAP4K2	MAP4K2	100

MAP4K3	MAP4K3	0.85
MAP4K4	MAP4K4	76
MAP4K5	MAP4K5	9
MAPKAPK2	MAPKAPK2	100
MAPKAPK5	MAPKAPK5	100
MARK1	MARK1	42
MARK2	MARK2	4.8
MARK3	MARK3	24
MARK4	MARK4	47
MAST1	MAST1	81
MEK1	MAP2K1	5.2
MEK2	MAP2K2	10
MEK3	MAP2K3	0
MEK4	MAP2K4	5.8
MEK5	MAP2K5	5.8
MEK6	MAP2K6	85
MELK	MELK	100
MERTK	MERTK	5.4
MET	MET	33
MET(M1250T)	MET	16
MET(Y1235D)	MET	31
MINK	MINK1	12
MKK7	MAP2K7	14
MKNK1	MKNK1	100
MKNK2	MKNK2	0.6
MLCK	MYLK3	99
MLK1	MAP3K9	29
MLK2	MAP3K10	66
MLK3	MAP3K11	26
MRCKA	CDC42BPA	78
MRCKB	CDC42BPB	46
MST1	STK4	4.9
MST1R	MST1R	64
MST2	STK3	50

MST3	STK24	3
MST4	MST4	0.2
MTOR	FRAP1	100
MUSK	MUSK	100
MYLK	MYLK	15
MYLK2	MYLK2	100
MYLK4	MYLK4	85
MYO3A	MYO3A	2.1
MYO3B	MYO3B	23
NDR1	STK38	7.8
NDR2	STK38L	14
NEK1	NEK1	74
NEK11	NEK11	100
NEK2	NEK2	63
NEK3	NEK3	56
NEK4	NEK4	100
NEK5	NEK5	95
NEK6	NEK6	100
NEK7	NEK7	100
NEK9	NEK9	100
NIM1	MGC42105	100
NLK	NLK	77
OSR1	OXSR1	30
p38-alpha	MAPK14	99
p38-beta	MAPK11	72
p38-delta	MAPK13	54
p38-gamma	MAPK12	70
PAK1	PAK1	0.8
PAK2	PAK2	12
PAK3	PAK3	25
PAK4	PAK4	14
PAK6	PAK6	13
PAK7	PAK7	0.55
PCTK1	PCTK1	17

PCTK2	PCTK2	52
PCTK3	PCTK3	100
PDGFRA	PDGFRA	79
PDGFRB	PDGFRB	39
PDPK1	PDPK1	62
PFCDPK1(P.falciparum)	PFB0815w	100
PFPK5(P.falciparum)	MAL13P1.279	37
PFTAIRE2	PFTK2	4.4
PFTK1	PFTK1	39
PHKG1	PHKG1	75
PHKG2	PHKG2	7.8
PIK3C2B	PIK3C2B	100
PIK3C2G	PIK3C2G	100
PIK3CA	PIK3CA	100
PIK3CA(C420R)	PIK3CA	100
PIK3CA(E542K)	PIK3CA	97
PIK3CA(E545A)	PIK3CA	88
PIK3CA(E545K)	PIK3CA	100
PIK3CA(H1047L)	PIK3CA	100
PIK3CA(H1047Y)	PIK3CA	100
PIK3CA(I800L)	PIK3CA	73
PIK3CA(M1043I)	PIK3CA	100
PIK3CA(Q546K)	PIK3CA	100
PIK3CB	PIK3CB	84
PIK3CD	PIK3CD	93
PIK3CG	PIK3CG	77
PIK4CB	PI4KB	4.7
PIM1	PIM1	22
PIM2	PIM2	79
PIM3	PIM3	39
PIP5K1A	PIP5K1A	100
PIP5K1C	PIP5K1C	49
PIP5K2B	PIP4K2B	100
PIP5K2C	PIP4K2C	100

PKAC-alpha	PRKACA	1.4
PKAC-beta	PRKACB	2
PKMYT1	PKMYT1	58
PKN1	PKN1	4.3
PKN2	PKN2	35
PKNB(M.tuberculosis)	pknB	38
PLK1	PLK1	97
PLK2	PLK2	100
PLK3	PLK3	72
PLK4	PLK4	0.95
PRKCD	PRKCD	85
PRKCE	PRKCE	4.4
PRKCH	PRKCH	40
PRKCI	PRKCI	31
PRKCQ	PRKCQ	1
PRKD1	PRKD1	58
PRKD2	PRKD2	67
PRKD3	PRKD3	25
PRKG1	PRKG1	53
PRKG2	PRKG2	100
PRKR	EIF2AK2	58
PRKX	PRKX	21
PRP4	PRPF4B	100
PYK2	PTK2B	32
QSK	KIAA0999	100
RAF1	RAF1	77
RET	RET	2.4
RET(M918T)	RET	2
RET(V804L)	RET	4.8
RET(V804M)	RET	6.9
RIOK1	RIOK1	65
RIOK2	RIOK2	100
RIOK3	RIOK3	98
RIPK1	RIPK1	100

RIPK2	RIPK2	100
RIPK4	RIPK4	100
RIPK5	DSTKY	5.4
ROCK1	ROCK1	1.4
ROCK2	ROCK2	3.6
ROS1	ROS1	90
RPS6KA4(Kin.Dom.1-N-terminal)	RPS6KA4	2.8
RPS6KA4(Kin.Dom.2-C-terminal)	RPS6KA4	100
RPS6KA5(Kin.Dom.1-N-terminal)	RPS6KA5	17
RPS6KA5(Kin.Dom.2-C-terminal)	RPS6KA5	100
RSK1(Kin.Dom.1-N-terminal)	RPS6KA1	7.2
RSK1(Kin.Dom.2-C-terminal)	RPS6KA1	3.9
RSK2(Kin.Dom.1-N-terminal)	RPS6KA3	0.3
RSK3(Kin.Dom.1-N-terminal)	RPS6KA2	4.4
RSK3(Kin.Dom.2-C-terminal)	RPS6KA2	51
RSK4(Kin.Dom.1-N-terminal)	RPS6KA6	3
RSK4(Kin.Dom.2-C-terminal)	RPS6KA6	14
S6K1	RPS6KB1	11
SBK1	SBK1	100
SgK110	SgK110	100
SGK3	SGK3	44
SIK	SIK1	29
SIK2	SIK2	66
SLK	SLK	34
SNARK	NUAK2	13
SNRK	SNRK	100
SRC	SRC	2
SRMS	SRMS	60
SRPK1	SRPK1	100
SRPK2	SRPK2	100
SRPK3	SRPK3	100
STK16	STK16	60
STK33	STK33	9
STK35	STK35	36

STK36	STK36	84
STK39	STK39	98
SYK	SYK	100
TAK1	MAP3K7	69
TAOK1	TAOK1	11
TAOK2	TAOK2	76
TAOK3	TAOK3	60
TBK1	TBK1	45
TEC	TEC	19
TESK1	TESK1	100
TGFBR1	TGFBR1	100
TGFBR2	TGFBR2	100
TIE1	TIE1	46
TIE2	TEK	51
TLK1	TLK1	31
TLK2	TLK2	81
TNIK	TNIK	12
TNK1	TNK1	56
TNK2	TNK2	50
TNNI3K	TNNI3K	86
TRKA	NTRK1	0.25
TRKB	NTRK2	1.4
TRKC	NTRK3	2.3
TRPM6	TRPM6	75
TSSK1B	TSSK1B	100
TTK	TTK	64
TXK	TXK	90
TYK2(JH1domain-catalytic)	TYK2	9.4
TYK2(JH2domain-pseudokinase)	TYK2	100
TYRO3	TYRO3	84
ULK1	ULK1	11
ULK2	ULK2	4.3
ULK3	ULK3	0.3
VEGFR2	KDR	69

VRK2	VRK2	0.75
WEE1	WEE1	100
WEE2	WEE2	67
YANK1	STK32A	21
YANK2	STK32B	44
YANK3	STK32C	65
YES	YES1	13
YSK1	STK25	28
YSK4	YSK4	52
ZAK	ZAK	100
ZAP70	ZAP70	85

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