Supplementary Information for

Novel Chelators Based on Adamantane-Derived Semicarbazones and Hydrazones that Target Multiple Hallmarks of Alzheimer's Disease

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General Procedure for the Preparation of Copper Complexes of the ASC Ligands

To a hot methanolic (5 mL) solution of the ASC ligand (1 mmol), copper chloride dihydrate (179 mg, 1.05 mmol) was added and refluxed for 2 h. The precipitate formed was cooled to room temperature and collected by vacuum filtration, washed with diethyl ether and dried in air.

[Cu(1)Cl_2]·1.5H_2O

Light green solid (0.32 g). Yield: 65%. ESI-MS in CH_3CN: found mass: 460.60 (100%), Calc. mass for $CuC_{21}H_{28}N_5O_3$: 461.16 $[M-2Cl^--H^++CH_3CN]^+$. Anal. Calc. for $CuC_{19}H_{25}N_4O_3Cl\cdot HCl\cdot 1.5H_2O$ (%): C 43.89, H 5.62, N 10.78. Found (%): C 43.58, H 5.49, N 10.63.

[Cu(2-H)Cl]·0.5CH_3OH

Yellow-green solid (0.28 g). Yield: 68%. ESI-MS in CH_3CN: found mass: 415.73 (100%), Calc. mass for $CuC_{20}H_{25}N_4O_2$: 416.14 $[M-Cl^-+CH_3CN]^+$. Anal. Calc. for $CuC_{18}H_{22}N_3O_2Cl\cdot 0.5CH_3OH$ (%): C 51.99, H 5.66, N 9.83. Found (%): C 52.04, H 5.48, N 10.02.

[Cu(3-H)Cl]·0.5CH_3OH

Light brown solid (0.24 g). Yield: 52%. ESI-MS in CH_3CN: found mass: 465.80 (100%), Calc. mass for $CuC_{24}H_{27}N_4O_2$: 466.15 $[M-Cl^-+CH_3CN]^+$. Anal. Calc. for $CuC_{22}H_{24}N_3O_2Cl\cdot 0.5CH_3OH$ (%): C 56.60, H 5.49, N 8.80. Found (%): C 56.69, H 5.19, N 8.85.

[Cu(4-H)Cl]·HCl

Green solid (0.22 g). Yield: 51%. ESI-MS in CH_3CN: found mass: 395.93 (100%), Calc. mass for $CuC_{17}H_{22}N_4OCl$: 396.09 $[M+H^+]^+$. Anal. Calc. for $CuC_{17}H_{21}N_4OCl\cdot HCl$ (%): C 47.33, H 5.14, N 12.99. Found (%): C 47.22, H 5.04, N 12.95.

[Cu(5-H)Cl]·HCl

Dark brown solid (0.29 g). Yield: 63%. ESI-MS in CH_3CN: found mass: 426.00 (100%), Calc. mass for $CuC_{21}H_{23}N_4O_2$: 426.12 $[M-2Cl^- - H^+]^+$. Anal. Calc. for $CuC_{21}H_{23}N_4O_2Cl \cdot HCl$ (%): C 50.56, H 4.85, N 11.23. Found (%): C 50.30, H 4.40, N 11.09.

[Cu(6-H)Cl]·2CH_3OH

Dark brown solid (0.24 g). Yield: 56%. ESI-MS in CH_3CN: found mass: 431.80 (80%), Calc. mass for $CuC_{20}H_{25}N_4O_3$: 432.13 $[M-Cl^- + CH_3CN]^+$, found mass: 422.73 (100%), Calc. mass for $CuC_{19}H_{26}N_3O_4$: 423.13 $[M-Cl^- + CH_3OH]^+$. Anal. Calc. for $CuC_{18}H_{22}N_3O_3Cl \cdot 2CH_3OH$ (%): C 48.88, H 6.15, N 8.55. Found (%): C 49.00, H 5.62, N 8.55.

General Procedure for the Preparation of Copper Complexes of the ABH Ligands

Copper complexes of the ABH ligands were prepared by following the procedure outlined for the preparation of the copper complexes of the ASC ligands above. The only exception to this protocol was that 0.5 mmol of the ABH ligand was refluxed with copper chloride dihydrate (90 mg, 0.53 mmol).

[Cu(7)Cl_2]

Light green solid (0.28 g). Yield: 94%. ESI-MS (negative mode) in CH_3CN: found mass: 558.05 (100%), Calc. mass for $CuC_{26}H_{28}N_4O_4Cl$: 558.12 $[M-HCl-H^+]^-$. Anal. Calc. for $CuC_{26}H_{30}N_4O_4Cl_2$ (%): C 52.31, H 5.07, N 9.39. Found (%): C 52.72, H 5.37, N 9.42.

[Cu(8-H)Cl]·H_2O

Green solid (0.26 g). Yield: 97%. ESI-MS (negative mode) in CH_3CN: found mass: 513.04 (100%), Calc. mass for $CuC_{25}H_{25}N_3O_3Cl$: 513.09 $[M-H^+]^-$. Anal. Calc. for $CuC_{25}H_{26}N_3O_3Cl\cdot H_2O$ (%): C 56.28, H 5.29, N 7.88. Found (%): C 56.57, H 5.49, N 7.58.

[Cu(9-H)Cl]·$3H_2O$

Grayish-green brown solid (0.30 g). Yield: 97%. ESI-MS (negative mode) in CH_3CN: found mass: 563.10 (100%), Calc. mass for $CuC_{29}H_{27}N_3O_3Cl$: 563.11 $[M-H^+]^-$. Anal. Calc. for $CuC_{29}H_{28}N_3O_3Cl\cdot 3H_2O$ (%): C 56.22, H 5.53, N 6.78. Found (%): C 56.22, H 5.46, N 6.73.

[Cu(10)Cl_2]

Yellowish green solid (0.25 g). Yield: 93%. ESI-MS in CH_3CN: found mass: 522.04 (100%), Calc. mass for $CuC_{24}H_{25}N_4O_2ClNa$: 522.09 $[M-HCl+Na^+]^+$. Anal. Calc. for $CuC_{24}H_{26}N_4O_2Cl_2$ (%): C 53.69, H 4.88, N 10.43. Found (%): C 53.82, H 4.86, N 10.42.

[Cu(11)Cl_2]·H_2O

Grey-yellow solid (0.23 g). Yield: 72%. ESI-MS (negative mode) in CH_3CN: found mass: 564.06 (40%), Calc. mass for $CuC_{28}H_{26}N_4O_3Cl$: 564.11 $[M-2H^+-Cl^-]^-$. Anal. Calc. for $CuC_{28}H_{28}N_4O_3Cl_2\cdot H_2O$ (%): C 54.15, H 4.87, N 9.02. Found (%): C 54.28, H 4.87, N 9.03.

[Cu(12)Cl_2]·CH_3OH

Grey solid (0.25 g). Yield: 42%. ESI-MS (negative mode) in CH_3CN: found mass: 529.07 (100%), Calc. mass for $CuC_{25}H_{25}N_3O_4Cl$: 529.09 $[M-2H^+-Cl^-]^-$. Anal. Calc. for $CuC_{25}H_{27}N_3O_4Cl_2\cdot CH_3OH$ (%): C 52.05, H 5.21, N 7.00. Found (%): C 51.71, H 5.01, N 7.10.

General Procedure for the Preparation of Iron Complexes of the ASC and ABH Ligands

The ligand (0.5 mmol; except for **10**) was dissolved in ethanol (10 mL) with heating. If not completely soluble, a few millilitres of acetonitrile was added to completely dissolve the ligands. Ferric perchlorate hexahydrate (115 mg, 0.25 mmol) was added and refluxed for 1 h. The solution was concentrated and poured into diethyl ether to precipitate the product, which was filtered, washed with adequate amounts of diethyl ether and dried in air.

As described previously, the Fe^{II} complex of **10** was prepared by an alternative procedure due to the inability to isolate a pure complex by the method above and because of the known preference of pyridine-derived hydrazones to form Fe^{II} complexes.[1] Briefly, **10** (0.25 mmol) was suspended in acetonitrile (10 mL) and triethylamine (5 mmol) was added. The resulting solution was degassed under nitrogen. Ferrous perchlorate hexahydrate (45 mg, 0.12 mmol) dissolved in degassed acetonitrile (5 mL) was added drop wise to the ligand solution under reflux and the reaction mixture was refluxed for 3 h. The precipitate formed was collected by filtration, washed with methanol and air dried.

$[Fe(1\text{-}H)_2]ClO_4 \cdot H_2O$

Dark brown solid (0.18 g). Yield: 41%. ESI-MS (negative mode) in CH_3OH: found mass: 768.37 (100%), Calc. mass for $FeC_{38}H_{48}N_8O_6$: 768.30 $[M-2H^+-ClO_4^-]^-$. ESI-MS (positive mode) in CH_3OH: found mass: 770.34 (100%), Calc. mass for $FeC_{38}H_{50}N_8O_6$: 770.32 $[M-ClO_4^-]^+$. Anal. Calc. for $FeC_{38}H_{50}N_8O_{10}Cl \cdot H_2O$ (%): C 51.39, H 5.90, N 12.62. Found (%): C 51.29, H 6.04, N 12.54. IR (cm^{-1}) 2904 (m), 2849 (w), 1623 (s), 1558 (m), 1390 (m), 1302 (m), 1248 (m), 1196 (m), 1091 (vs ClO_4^-), 1064 (vs), 923 (w), 662 (w), 613 (m), 567 (m).

[Fe(2-H)$_2$]ClO$_4$·0.5H$_2$O

Black solid (0.20 g). Yield: 51%. ESI-MS (negative mode) in CH_3OH: found mass: 678.32 (100%), Calc. mass for $FeC_{36}H_{42}N_6O_4$: 678.26 $[M-2H^+-ClO_4^-]^-$. ESI-MS (positive mode) in CH_3OH: found mass: 680.27 (100%), Calc. mass for $FeC_{36}H_{44}N_6O_4$: 680.28 $[M-ClO_4^-]^+$. Anal. Calc. for $FeC_{36}H_{44}N_6O_8Cl·0.5H_2O$ (%): C 54.80, H 5.75, N 10.65. Found (%): C 54.76, H 5.96, N 10.42. IR (cm^{-1}) 3312 (m), 2904 (m), 2851 (w), 1617 (s), 1564 (s), 1468 (m), 1375 (m), 1303 (m), 1208 (m), 1086 (vs, ClO_4^-), 1064 (vs), 831 (w), 752 (s), 621 (s), 420 (s).

[Fe(3-H)$_2$]ClO$_4$

Dark green solid (0.22 g). Yield: 50%. ESI-MS (negative mode) in CH_3OH: found mass: 778.38 (100%), Calc. mass for $FeC_{44}H_{46}N_6O_4$: 778.29 $[M-2H^+-ClO_4^-]^-$. ESI-MS (positive mode) in CH_3OH: found mass: 780.33 (100%), Calc. mass for $FeC_{44}H_{48}N_6O_4$: 780.31 $[M-ClO_4^-]^+$. Anal. Calc. for $FeC_{44}H_{48}N_6O_8Cl$ (%): C 60.04, H 5.50, N 9.55. Found (%): C 60.15, H 5.67, N 9.88. IR (cm^{-1}) 2906 (m), 1618 (s), 1575 (s), 1466 (m), 1318 (m), 1241 (m), 1182 (w), 1083 (s, ClO_4^-), 1029 (s), 954 (w), 831 (m), 786 (m), 750 (vs), 622 (s), 419 (s).

[Fe(4)(4-H)]ClO$_4$·0.5C$_2$H$_5$OH

Dark green solid (0.20 g). Yield: 44%. ESI-MS (positive mode) in CH_3OH: found mass: 651.24 (35%), Calc. mass for $FeC_{34}H_{43}N_8O_2$: 651.29 $[M-ClO_4^-]^+$. Anal. Calc. for $FeC_{34}H_{43}N_8O_6Cl·0.5C_2H_5OH$ (%): C 54.31, H 5.99, N 14.48. Found (%): C 54.23, H 6.15, N 14.53. IR (cm^{-1}) 2908 (m, CH), 2852 (m, CH), 1650 (m, C=O), 1551 (s, C=N), 1468 (m), 1360 (m), 1303 (m), 1245 (w), 1088 (vs, ClO_4^-), 920 (w), 774 (m), 620 (s), 517 (m), 425 (m).

$[Fe(5\text{-}H)_2]ClO_4 \cdot 0.75H_2O$

Dark brown solid (0.27 g). Yield: 61%. ESI-MS (negative mode) in CH_3OH: found mass: 780.53 (100%), Calc. mass for $FeC_{42}H_{44}N_8O_4$: 780.29 $[M-2H^+-ClO_4^-]^-$. ESI-MS (positive mode) in CH_3OH: found mass: 782.31 (100%), Calc. mass for $FeC_{42}H_{46}N_8O_4$: 782.30 $[M-ClO_4^-]^+$. Anal. Calc. for $FeC_{42}H_{46}N_8O_8Cl \cdot 0.75H_2O$ (%): C 56.32, H 5.35, N 12.51. Found (%): C 56.05, H 5.38, N 13.18. IR (cm^{-1}) 3246 (w), 2905 (m), 2848 (m) 1634 (s), 1541 (s), 1448 (s), 1338 (s), 1299 (m), 1183 (w), 1090 (vs, ClO_4^-), 1061 (vs), 908 (m), 835 (m), 742 (s), 622 (s), 495 (s).

$[Fe(6\text{-}H)_2]ClO_4 \cdot C_2H_5OH$

Dark brown solid (0.19 g). Yield: 47%. ESI-MS (positive mode) in CH_3OH: found mass: 712.26 (50%), Calc. mass for $FeC_{36}H_{44}N_6O_6$: 712.27 $[M-ClO_4^-]^+$. Anal. Calc. for $FeC_{36}H_{44}N_6O_{10}Cl \cdot C_2H_5OH$ (%): C 53.19, H 5.87, N 9.79. Found (%): C 52.97, H 6.09, N 9.90. IR (cm^{-1}) 3325 (w), 2906 (m), 2851 (m) 1619 (s), 1568 (s), 1448 (m), 1377 (m), 1302 (s), 1227 (m), 1071 (vs, ClO_4^-), 926 (m), 868 (m), 739 (s), 621 (s), 436 (s).

$[Fe(7\text{-}H)_2]ClO_4 \cdot 4H_2O$

Dark brown solid (0.28 g). Yield: 52%. ESI-MS (negative mode) in CH_3OH: found mass: 976.53 (100%), Calc. mass for $FeC_{52}H_{56}N_8O_8$: 976.36 $[M-2H^+-ClO_4^-]^-$. ESI-MS (positive mode) in CH_3OH: found mass: 1000.40 (25%), Calc. mass for $FeC_{52}H_{57}N_8O_8Na$: 1000.36 $[M-H^++Na^+-ClO_4^-]^+$. Anal. Calc. for $FeC_{52}H_{58}N_8O_{12}Cl \cdot 4H_2O$ (%): C 54.29, H 5.78, N 9.74. Found (%): C 54.01, H 5.78, N 9.72. IR (cm^{-1}) 3271 (w), 2905 (m), 2850 (m), 1657 (m), 1639 (m), 1583 (m), 1456 (m), 1379 (s), 1304 (m), 1085 (vs, ClO_4^-), 1059 (vs), 867 (m), 727 (m), 621 (s).

$[Fe(8\text{-}H)_2]ClO_4 \cdot (C_2H_5)_3N \cdot 0.25H_2O$

Black solid (0.33 g). Yield: 67%. ESI-MS (negative mode) in CH_3OH: found mass: 886.43 (100%), Calc. mass for $FeC_{50}H_{50}N_6O_6$: 886.32 $[M-2H^+-ClO_4^-]^-$. ESI-MS (positive mode) in CH_3OH: found mass: 932.33 (60%), Calc. mass for $FeC_{50}H_{50}N_6O_6Na_2$: 932.30 $[M-2H^++2Na^+-ClO_4^-]^+$. Anal. Calc. for $FeC_{50}H_{52}N_6O_{10}Cl \cdot (C_2H_5)_3N \cdot 0.25H_2O$ (%): C 61.48, H 6.22, N 8.96. Found (%): C 61.76, H 6.11, N 8.55. IR (cm^{-1}) 3256 (w), 2905 (s), 2850 (m), 1588 (s), 1537 (s), 1493 (m), 1439 (m), 1384 (m), 1298 (s), 1202 (m), 1084 (s, ClO_4^-), 894 (m), 867 (m), 757 (m), 607 (s).

$[Fe(9\text{-}H)_2]ClO_4 \cdot 6.5H_2O$

Black solid (0.29 g). Yield: 53%. ESI-MS (negative mode) in CH_3OH: found mass: 986.62 (100%), Calc. mass for $FeC_{58}H_{54}N_6O_6$: 986.35 $[M-2H^+-ClO_4^-]^-$. ESI-MS (positive mode) in CH_3OH: found mass: 1032.41 (100%), Calc. mass for $FeC_{58}H_{54}N_6O_6Na_2$: 1032.33 $[M-2H^++2Na^+-ClO_4^-]^+$. Anal. Calc. for $FeC_{58}H_{56}N_6O_{10}Cl \cdot 6.5H_2O$ (%): C 57.79, H 5.77, N 6.97. Found (%): C 57.80, H 5.39, N 6.97. IR (cm^{-1}) 2906 (s), 2851 (m), 1578 (s), 1526 (s), 1380 (m), 1359 (s), 1301 (s), 1198 (m), 1090 (s, ClO_4^-), 976 (m), 826 (m), 781 (m), 652 (s), 523 (s).

$[Fe(10\text{-}H)_2] \cdot 1.25H_2O$

Dark green solid (0.1 g). Yield: 46%. ESI-MS (positive mode) in CH_3OH: found mass: 881.35 (40%), Calc. mass for $FeC_{48}H_{50}N_8O_4Na$: 881.32 $[M+Na^+]^+$; found mass: 859.42 (13%), Calc. mass for $FeC_{48}H_{51}N_8O_4$: 859.81 $[M+H^+]^+$. Anal. Calc. for $FeC_{48}H_{50}N_8O_4 \cdot 1.25H_2O$ (%): C 65.41, H 6.00, N 12.71. Found (%): C 65.41, H 5.89, N 12.60. IR (cm^{-1}) 3337 (w), 2905 (m), 2849 (m), 1643 (s), 1531 (s), 1452 (s), 1358 (s), 1304 (s), 1142 (m), 1061 (m) 864 (m), 712 (m).

[Fe(11-H)$_2$]ClO$_4$·H$_2$O

Greenish brown solid (0.25 g). Yield: 46%. ESI-MS (negative mode) in CH_3OH: found mass: 988.35 (100%), Calc. mass for $FeC_{56}H_{52}N_8O_6$: 988.34 $[M-2H^+-ClO_4^-]^-$. Anal. Calc. for $FeC_{56}H_{54}N_8O_{10}Cl\cdot H_2O$ (%): C 60.68, H 5.09, N 10.11. Found (%): C 60.42, H 5.22, N 10.11. IR (cm^{-1}) 2906 (m), 2850 (w), 1639 (m), 1543 (m), 1451 (m), 1343 (m), 1300 (m), 1241 (m), 1091 (vs, ClO_4^-), 1061 (vs), 922 (m), 838 (m), 750 (m), 621 (s).

[Fe(12-H)$_2$]ClO$_4$·H$_2$O

Black solid (0.24 g). Yield: 47%. ESI-MS (negative mode) in CH_3OH: found mass: 918.49 (100%), Calc. mass for $FeC_{50}H_{50}N_6O_8$: 918.31 $[M-2H^+-ClO_4^-]^-$. Anal. Calc. for $FeC_{50}H_{52}N_6O_{12}Cl\cdot H_2O$ (%): C 59.44, H 5.60, N 8.50. Found (%): C 59.39, H 5.60, N 8.27. IR (cm^{-1}) 3320 (s), 2907 (m), 2851 (w), 1620 (m), 1566 (), 1448 (m), 1375 (m), 1346 (m), 1227 (m), 1071 (vs, ClO_4^-), 924 (m), 736 (s), 621 (s), 487 (s).

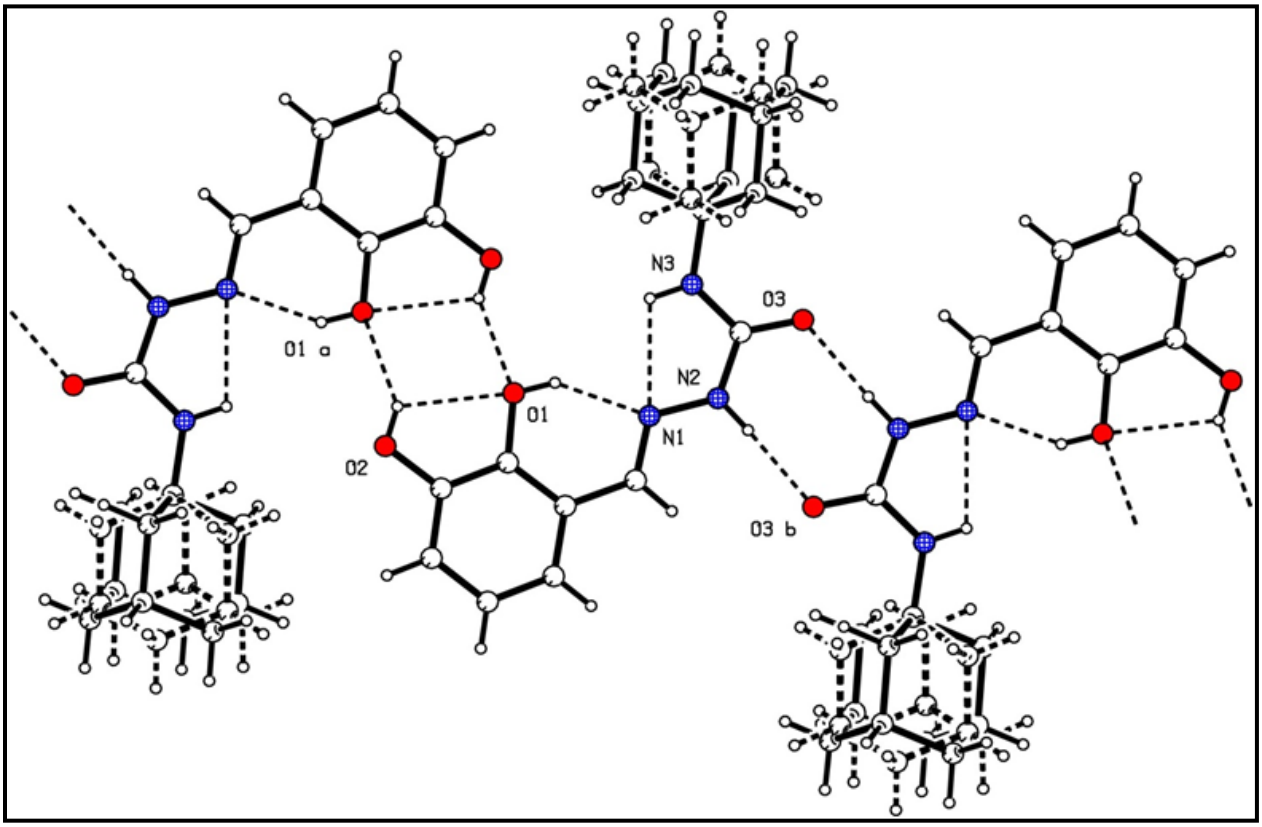

Figure S1. Inter- and intra-molecular hydrogen bond interactions in **6**.

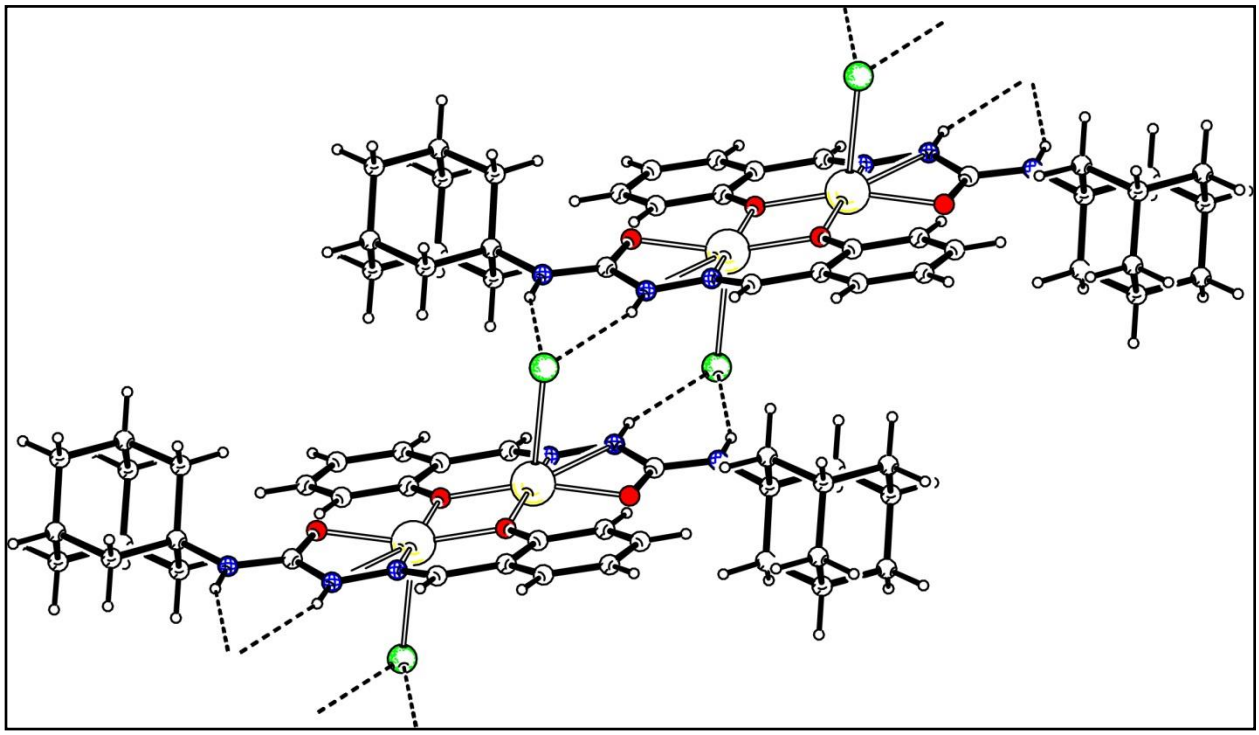

Figure S2. Inter- and intra-molecular hydrogen bond interactions in [Cu(**2**)Cl]$_2$.

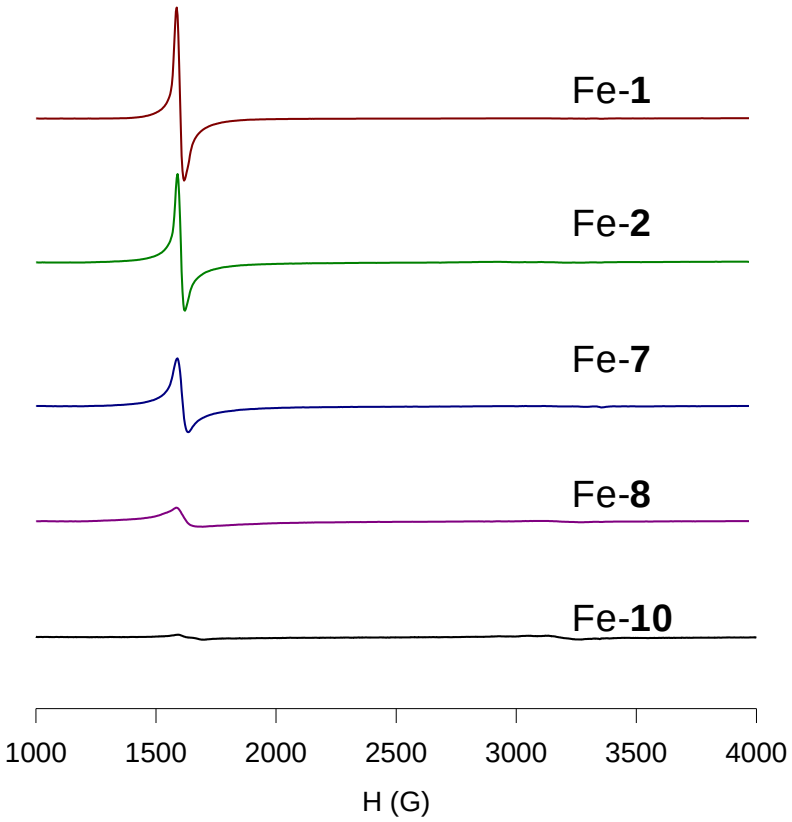

Figure S3. X-band (9.37448 GHz) EPR spectra of Fe complexes of selected semicarbazones and hydrazones (130 K, 1-3 mM in DMF:tris buffer 2:1).

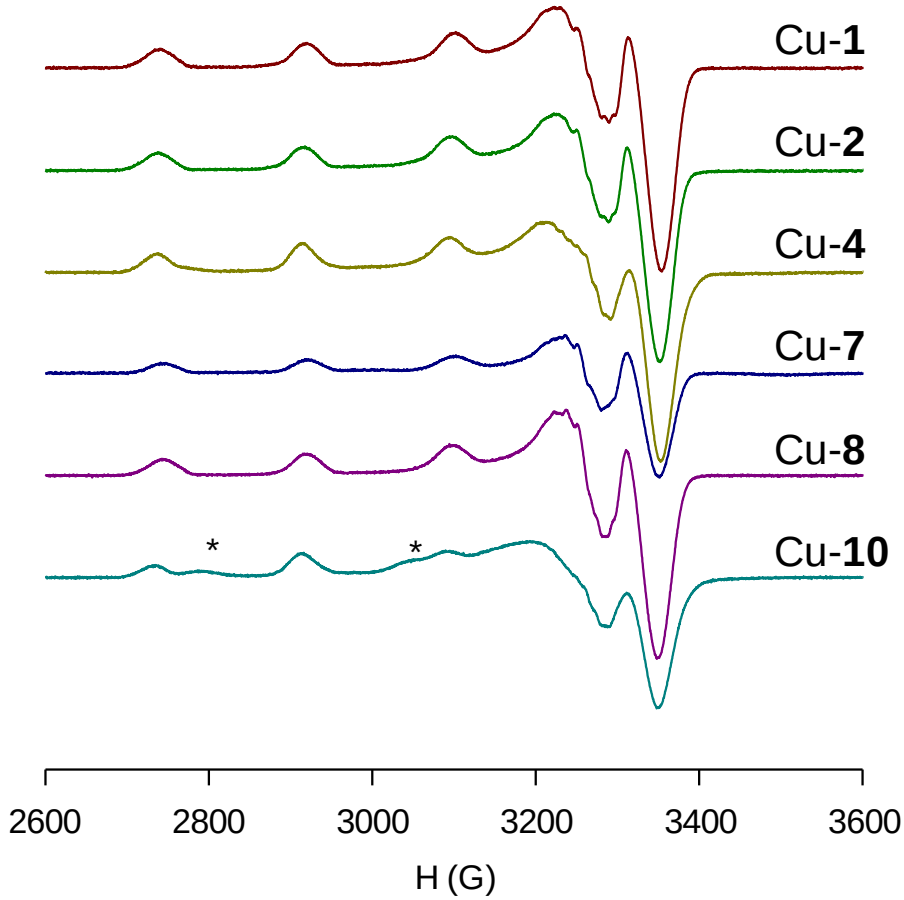

Figure S4. X-band (9.37448 GHz) EPR spectra of Cu^{II} complexes of selected semicarbazones and hydrazones (130 K, DMF:tris buffer 2:1). Asterisks denote a minor 1:2 Cu:L complex species.

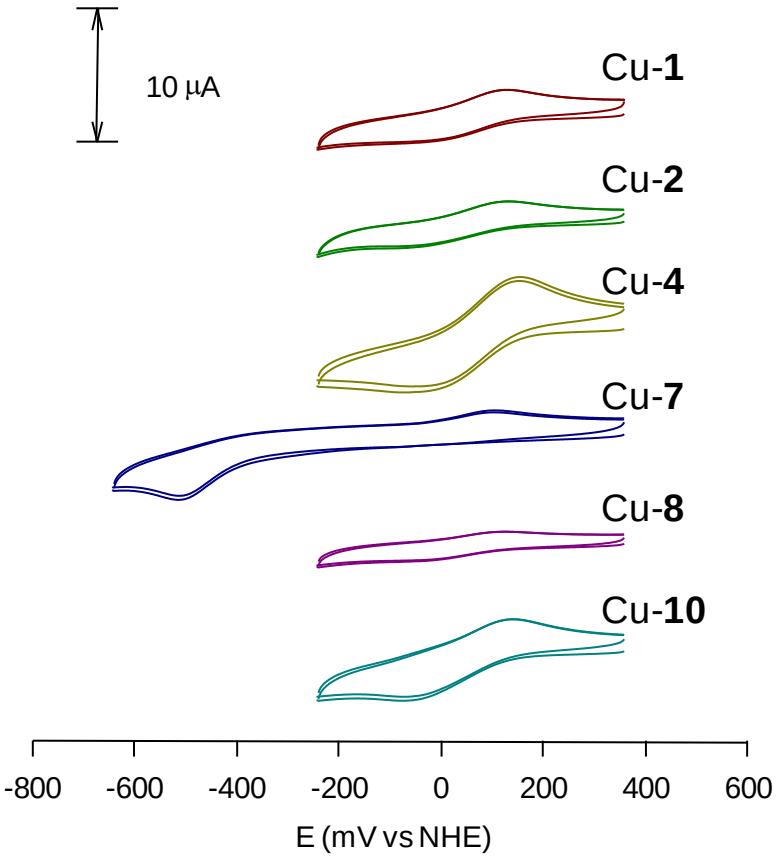

Figure S5. Cyclic voltammograms of selected Cu complexes (1-3 mM in DMF:Tris buffer 2:1 and 0.1 M Et_4NClO_4). Sweep rate: 100 mV s^{-1}.

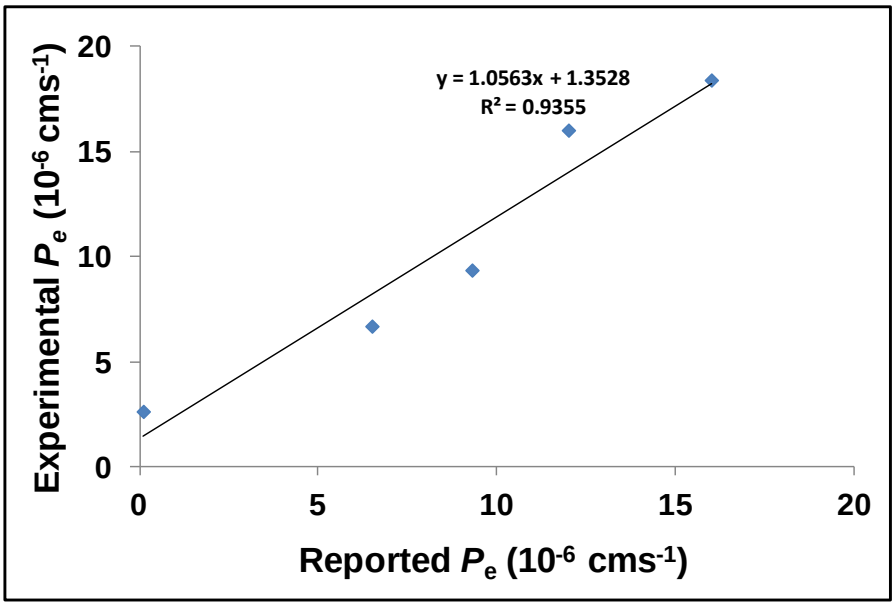

Figure S6. Linear relationship between the experimental and reported effective permeability coefficients (P_e) determined by PAMPA-BBB. P_e(exp) = 1.0563 P_e(ref) + 1.3528. Results are presented as the mean of quadruplicate repeats examined in ≥3 experiments.

Table S1. Effective permeability coefficients (P_e) of reference agents used for the validation of the PAMPA-BBB experiment.

Reference Agent	P_e (10^{-6} cm s^{-1})	
	Reference value	Experimental value
Theophylline	0.1[2]	2.63 ± 0.05
Verapamil	16[2]	18.42 ± 3.04
Progesterone	9.3[2]	9.36 ± 1.00
Chlorpromazine	6.5[2]	6.69 ± 0.53
Donepezil	12[3]	16.04 ± 4.20

Table S2. Classification of effective permeability coefficients (P_e) determined by the PAMPA-BBB (P_e, 10^{-6} cm s^{-1}).[4]

Compounds with predicted high BBB permeation (CNS+)	$P_e > 5.578$
Compounds with uncertain BBB permeation (CNS+/-)	$5.578 > P_e > 3.46$
Compounds with predicted low BBB permeation (CNS-)	$P_e < 3.46$

References

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