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.

\[
[Cu(1)\text{Cl}_2]\cdot1.5\text{H}_2\text{O}
\]

Light green solid (0.32 g). Yield: 65%. ESI-MS in CH\text{3}CN: found mass: 460.60 (100%), Calc. mass for CuC\text{21}H\text{28}N\text{5}O\text{3}: 461.16 [M−2\text{Cl}−\text{H}^+\text{+CH}_3\text{CN}]^+. Anal. Calc. for CuC\text{19}H\text{25}N\text{4}O\text{3}\text{Cl}\cdot\text{HCl}\cdot1.5\text{H}_2\text{O} (%): C 43.89, H 5.62, N 10.78. Found (%): C 43.58, H 5.49, N 10.63.

\[
[Cu(2-\text{H})\text{Cl}]\cdot0.5\text{CH}_3\text{OH}
\]

Yellow-green solid (0.28 g). Yield: 68%. ESI-MS in CH\text{3}CN: found mass: 415.73 (100%), Calc. mass for CuC\text{20}H\text{25}N\text{4}O\text{2}: 416.14 [M−\text{Cl}−\text{+CH}_3\text{CN}]^+. Anal. Calc. for CuC\text{18}H\text{22}N\text{3}O\text{2}\text{Cl}\cdot0.5\text{CH}_3\text{OH} (%): C 51.99, H 5.66, N 9.83. Found (%): C 52.04, H 5.48, N 10.02.

\[
[Cu(3-\text{H})\text{Cl}]\cdot0.5\text{CH}_3\text{OH}
\]

Light brown solid (0.24 g). Yield: 52%. ESI-MS in CH\text{3}CN: found mass: 465.80 (100%), Calc. mass for CuC\text{24}H\text{27}N\text{4}O\text{2}: 466.15 [M−\text{Cl}−\text{+CH}_3\text{CN}]^+. Anal. Calc. for CuC\text{22}H\text{24}N\text{3}O\text{2}\text{Cl}\cdot0.5\text{CH}_3\text{OH} (%): C 56.60, H 5.49, N 8.80. Found (%): C 56.69, H 5.19, N 8.85.

\[
[Cu(4-\text{H})\text{Cl}]\cdot\text{HCl}
\]

Green solid (0.22 g). Yield: 51%. ESI-MS in CH\text{3}CN: found mass: 395.93 (100%), Calc. mass for CuC\text{17}H\text{22}N\text{4}O\text{Cl}: 396.09 [M+\text{H}^+]^+. Anal. Calc. for CuC\text{17}H\text{21}N\text{4}O\text{Cl}\cdot\text{HCl} (%): C 47.33, H 5.14, N 12.99. Found (%): C 47.22, H 5.04, N 12.95.
[\text{Cu(5-H)}\text{Cl}\cdot\text{HCl}]

Dark brown solid (0.29 g). Yield: 63%. ESI-MS in CH$_3$CN: found mass: 426.00 (100%), Calc. mass for CuC$_{21}$H$_{23}$N$_4$O$_2$: 426.12 [M$-2\text{Cl}^-\text{−H}^+$]^+. Anal. Calc. for CuC$_{21}$H$_{23}$N$_4$O$_2$Cl·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$_3$OH

Dark brown solid (0.24 g). Yield: 56%. ESI-MS in CH$_3$CN: found mass: 431.80 (80%), Calc. mass for CuC$_{20}$H$_{25}$N$_4$O$_3$: 432.13 [M$-\text{Cl}^-$+CH$_3$CN]^+, found mass: 422.73 (100%), Calc. mass for CuC$_{19}$H$_{26}$N$_3$O$_4$: 423.13 [M$-\text{Cl}^-$+CH$_3$OH]^+. Anal. Calc. for CuC$_{18}$H$_{22}$N$_3$O$_3$Cl·2CH$_3$OH (%): 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$_3$CN: found mass: 558.05 (100%), Calc. mass for CuC$_{26}$H$_{28}$N$_4$O$_4$Cl: 558.12 [M$-\text{HCl}^-\text{H}^+$]^−. Anal. Calc. for CuC$_{26}$H$_{30}$N$_4$O$_4$Cl$_2$ (%): C 52.31, H 5.07, N 9.39. Found (%): C 52.72, H 5.37, N 9.42.
[Cu(8-H)Cl]·H₂O
Green solid (0.26 g). Yield: 97%. ESI-MS (negative mode) in CH₃CN: found mass: 513.04 (100%), Calc. mass for CuC₂₅H₂₅N₅O₅Cl: 513.09 [M−H⁺]−. Anal. Calc. for CuC₂₅H₂₂N₅O₅Cl·H₂O (%): C 56.28, H 5.29, N 7.88. Found (%): C 56.57, H 5.49, N 7.58.

[Cu(9-H)Cl]·3H₂O
Grayish-green brown solid (0.30 g). Yield: 97%. ESI-MS (negative mode) in CH₃CN: found mass: 563.10 (100%), Calc. mass for CuC₂₉H₂₇N₃O₃Cl: 563.11 [M−H⁺]−. Anal. Calc. for CuC₂₉H₂₈N₃O₃Cl·3H₂O (%): C 56.22, H 5.53, N 6.78. Found (%): C 56.22, H 5.46, N 6.73.

[Cu(10)Cl₂]
Yellowish green solid (0.25 g). Yield: 93%. ESI-MS in CH₃CN: found mass: 522.04 (100%), Calc. mass for CuC₂₄H₂₅N₄O₂ClNa: 522.09 [M−HCl+Na⁺]. Anal. Calc. for CuC₂₄H₂₆N₄O₂Cl₂ (%): C 53.69, H 4.87, N 10.43. Found (%): C 53.82, H 4.86, N 10.42.

[Cu(11)Cl₂]·H₂O
Grey-yellow solid (0.23 g). Yield: 72%. ESI-MS (negative mode) in CH₃CN: found mass: 564.06 (40%), Calc. mass for CuC₂₈H₂₆N₄O₃Cl: 564.11 [M−2H⁺−Cl⁻]−. Anal. Calc. for CuC₂₈H₂₇N₄O₃Cl₂·H₂O (%): C 54.15, H 4.87, N 9.02. Found (%): C 54.28, H 4.87, N 9.03.

[Cu(12)Cl₂]·CH₃OH
Grey solid (0.25 g). Yield: 42%. ESI-MS (negative mode) in CH₃CN: found mass: 529.07 (100%), Calc. mass for CuC₂₅H₂₅N₃O₄Cl: 529.09 [M−2H⁺−Cl⁻]−. Anal. Calc. for CuC₂₅H₂₇N₃O₄Cl₂·CH₃OH (%): 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\textsuperscript{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\textsuperscript{II} complexes.\textsuperscript{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-H)\textsubscript{2}]ClO\textsubscript{4}·H\textsubscript{2}O**

Dark brown solid (0.18 g). Yield: 41%. ESI-MS (negative mode) in CH\textsubscript{3}OH: found mass: 768.37 (100%), Calc. mass for FeC\textsubscript{38}H\textsubscript{48}N\textsubscript{8}O\textsubscript{6}: 768.30 [M–2H\textsuperscript{2+}–ClO\textsubscript{4}\textsuperscript{−}]. ESI-MS (positive mode) in CH\textsubscript{3}OH: found mass: 770.34 (100%), Calc. mass for FeC\textsubscript{38}H\textsubscript{50}N\textsubscript{8}O\textsubscript{6}: 770.32 [M–ClO\textsubscript{4}\textsuperscript{−}]\textsuperscript{+}. Anal. Calc. for FeC\textsubscript{38}H\textsubscript{50}N\textsubscript{8}O\textsubscript{10}Cl·H\textsubscript{2}O (%): C 51.39, H 5.90, N 12.62. Found (%): C 51.29, H 6.04, N 12.54. IR (cm\textsuperscript{-1}) 2904 (m), 2849 (w), 1623 (s), 1558 (m), 1390 (m), 1302 (m), 1248 (m), 1196 (m), 1091 (vs ClO\textsubscript{4}\textsuperscript{−}), 1064 (vs), 923 (w), 662 (w), 613 (m), 567 (m).
[Fe(2-H)\textsubscript{2}]ClO\textsubscript{4}·0.5H\textsubscript{2}O

Black solid (0.20 g). Yield: 51%. ESI-MS (negative mode) in CH\textsubscript{3}OH: found mass: 678.32 (100%), Calc. mass for FeC\textsubscript{36}H\textsubscript{42}N\textsubscript{6}O\textsubscript{4}: 678.26 [M−2H\textsuperscript{+}−ClO\textsubscript{4}\textsuperscript{−}]\textsuperscript{−}. ESI-MS (positive mode) in CH\textsubscript{3}OH: found mass: 680.27 (100%), Calc. mass for FeC\textsubscript{36}H\textsubscript{44}N\textsubscript{6}O\textsubscript{4}: 680.28 [M−ClO\textsubscript{4}\textsuperscript{−}]\textsuperscript{+}. Anal. Calc. for FeC\textsubscript{36}H\textsubscript{44}N\textsubscript{6}O\textsubscript{8}Cl·0.5H\textsubscript{2}O (%): C 54.80, H 5.75, N 10.65. Found (%): C 54.76, H 5.96, N 10.42. IR (cm\textsuperscript{−1}) 3312 (m), 2904 (m), 2851 (w), 1617 (s), 1564 (s), 1468 (m), 1375 (m), 1303 (m), 1208 (m), 1086 (vs, ClO\textsubscript{4}−), 1064 (vs), 831 (w), 752 (s), 621 (s), 420 (s).

[Fe(3-H)\textsubscript{2}]ClO\textsubscript{4}

Dark green solid (0.22 g). Yield: 50%. ESI-MS (negative mode) in CH\textsubscript{3}OH: found mass: 778.38 (100%), Calc. mass for FeC\textsubscript{44}H\textsubscript{46}N\textsubscript{6}O\textsubscript{4}: 778.29 [M−2H\textsuperscript{+}−ClO\textsubscript{4}\textsuperscript{−}]\textsuperscript{−}. ESI-MS (positive mode) in CH\textsubscript{3}OH: found mass: 780.33 (100%), Calc. mass for FeC\textsubscript{44}H\textsubscript{48}N\textsubscript{6}O\textsubscript{4}: 780.31 [M−ClO\textsubscript{4}−]\textsuperscript{+}. Anal. Calc. for FeC\textsubscript{44}H\textsubscript{48}N\textsubscript{6}O\textsubscript{8}Cl·0.5H\textsubscript{2}O (%): C 54.80, H 5.50, N 9.55. Found (%): C 60.15, H 5.67, N 9.88. IR (cm\textsuperscript{−1}) 2906 (m), 1618 (s), 1575 (s), 1466 (m), 1318 (m), 1241 (m), 1182 (w), 1083 (s, ClO\textsubscript{4}−), 1029 (s), 954 (w), 831 (m), 786 (m), 750 (vs), 622 (s), 419 (s).

[Fe(4)(4-H)]ClO\textsubscript{4}·0.5C\textsubscript{2}H\textsubscript{5}OH

Dark green solid (0.20 g). Yield: 44%. ESI-MS (positive mode) in CH\textsubscript{3}OH: found mass: 651.24 (35%), Calc. mass for FeC\textsubscript{34}H\textsubscript{43}N\textsubscript{8}O\textsubscript{2}: 651.29 [M−ClO\textsubscript{4}−]\textsuperscript{+}. Anal. Calc. for FeC\textsubscript{34}H\textsubscript{43}N\textsubscript{8}O\textsubscript{6}Cl·0.5C\textsubscript{2}H\textsubscript{5}OH (%): C 54.31, H 5.99, N 14.48. Found (%): C 54.23, H 6.15, N 14.53. IR (cm\textsuperscript{−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\textsubscript{4}−), 920 (w), 774 (m), 620 (s), 517 (m), 425 (m).
**[Fe(5-H)$_2$]ClO$_4$·0.75H$_2$O**

Dark brown solid (0.27 g). Yield: 61%. ESI-MS (negative mode) in CH$_3$OH: found mass: 780.53 (100%), Calc. mass for FeC$_{42}$H$_{44}$N$_8$O$_4$: 780.29 [M−2H$^+$−ClO$_4^−$]. ESI-MS (positive mode) in CH$_3$OH: found mass: 782.31 (100%), Calc. mass for FeC$_{42}$H$_{46}$N$_8$O$_4$: 782.30 [M−ClO$_4^+$]. Anal. Calc. for FeC$_{42}$H$_{46}$N$_8$O$_4$: 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-H)$_2$]ClO$_4$·C$_2$H$_5$OH**

Dark brown solid (0.19 g). Yield: 47%. ESI-MS (positive mode) in CH$_3$OH: found mass: 712.26 (50%), Calc. mass for FeC$_{36}$H$_{44}$N$_6$O$_6$: 712.27 [M−ClO$_4^+$]. Anal. Calc. for FeC$_{36}$H$_{44}$N$_6$O$_6$: 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-H)$_2$]ClO$_4$·4H$_2$O**

Dark brown solid (0.28 g). Yield: 52%. ESI-MS (negative mode) in CH$_3$OH: found mass: 976.53 (100%), Calc. mass for FeC$_{52}$H$_{56}$N$_8$O$_8$: 976.36 [M−2H$^+$−ClO$_4^−$]. ESI-MS (positive mode) in CH$_3$OH: found mass: 1000.40 (25%), Calc. mass for FeC$_{52}$H$_{57}$N$_8$O$_8$Na: 1000.36 [M−H$^+$+Na$^+$−ClO$_4^+$]. Anal. Calc. for FeC$_{52}$H$_{58}$N$_8$O$_{12}$Cl·4H$_2$O (%): 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-H)2]ClO4·(C2H5)3N·0.25H2O

Black solid (0.33 g). Yield: 67%. ESI-MS (negative mode) in CH3OH: found mass: 886.43 (100%), Calc. mass for FeC50H50N6O6: 886.32 [M−2H+−ClO4−]. ESI-MS (positive mode) in CH3OH: found mass: 932.33 (60%), Calc. mass for FeC50H50N6O6Na2: 932.30 [M−2H+2Na+−ClO4−]. Anal. Calc. for FeC50H50N6O6Cl·(C2H5)3N·0.25H2O (%): 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, ClO4−), 894 (m), 867 (m), 757 (m), 607 (s).

[Fe(9-H)2]ClO4·6.5H2O

Black solid (0.29 g). Yield: 53%. ESI-MS (negative mode) in CH3OH: found mass: 986.62 (100%), Calc. mass for FeC58H54N6O6: 986.35 [M−2H+−ClO4−]. ESI-MS (positive mode) in CH3OH: found mass: 1032.41 (100%), Calc. mass for FeC58H54N6O6Na2: 1032.33 [M−2H+2Na+−ClO4−]. Anal. Calc. for FeC58H54N6O6Cl·6.5H2O (%): 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, ClO4−), 976 (m), 826 (m), 781 (m), 652 (s), 523 (s).

[Fe(10-H)2]·1.25H2O

Dark green solid (0.1 g). Yield: 46%. ESI-MS (positive mode) in CH3OH: found mass: 881.35 (40%), Calc. mass for FeC48H50N8O4Na: 881.32 [M+Na+]++; found mass: 859.42 (13%), Calc. mass for FeC48H51N8O4·1.25H2O (%): 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)₂ClO₄·H₂O]

Greenish brown solid (0.25 g). Yield: 46%. ESI-MS (negative mode) in CH₃OH: found mass: 988.35 (100%). Calc. mass for FeC₅₆H₅₂N₈O₆: 988.34 [M–2H⁺–ClO₄⁻]⁻. Anal. Calc. for FeC₅₆H₅₄N₈O₁₀Cl·H₂O (%): 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), 1541 (m), 1451 (m), 1300 (m), 1241 (m), 1091 (vs, ClO₄⁻), 1061 (vs), 922 (m), 838 (m), 750 (m), 621 (s).

[Fe(12-H)₂ClO₄·H₂O]

Black solid (0.24 g). Yield: 47%. ESI-MS (negative mode) in CH₃OH: found mass: 918.49 (100%), Calc. mass for FeC₅₀H₅₀N₆O₈: 918.31 [M–2H⁺–ClO₄⁻]⁻. Anal. Calc. for FeC₅₀H₅₂N₆O₁₂Cl·H₂O (%): 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, ClO₄⁻), 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 Et₄NClO₄). Sweep rate: 100 mV s⁻¹.
Figure S6. Linear relationship between the experimental and reported effective permeability coefficients ($P_e$) determined by PAMPA-BBB. $P_e(\text{exp}) = 1.0563 \times P_e(\text{ref}) + 1.3528$. Results are presented as the mean of quadruplicate repeats examined in $\geq 3$ experiments.
Table S1. Effective permeability coefficients ($P_e$) of reference agents used for the validation of the PAMPA-BBB experiment.

<table>
<thead>
<tr>
<th>Reference Agent</th>
<th>$P_e (10^{-6} \text{ cm s}^{-1})$</th>
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<tbody>
<tr>
<td></td>
<td>Reference value</td>
</tr>
<tr>
<td>Theophylline</td>
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</tr>
<tr>
<td>Verapamil</td>
<td>$16^2$</td>
</tr>
<tr>
<td>Progesterone</td>
<td>$9.3^2$</td>
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<tr>
<td>Chlorpromazine</td>
<td>$6.5^2$</td>
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<tr>
<td>Donepezil</td>
<td>$12^3$</td>
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Table S2. Classification of effective permeability coefficients ($P_e$) determined by the PAMPA-BBB ($P_e, 10^{-6} \text{ cm s}^{-1}$).

<table>
<thead>
<tr>
<th>Classification of BBB permeation</th>
<th>$P_e$ condition</th>
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<tr>
<td>Compounds with predicted high BBB permeation (CNS+)</td>
<td>$P_e &gt; 5.578$</td>
</tr>
<tr>
<td>Compounds with uncertain BBB permeation (CNS+/-)</td>
<td>$5.578 &gt; P_e &gt; 3.46$</td>
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<tr>
<td>Compounds with predicted low BBB permeation (CNS-)</td>
<td>$P_e &lt; 3.46$</td>
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References