

New Metal Chelators for Chelation Therapy in Neurodegenerative Diseases

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Thesis submitted in fulfilment of the requirements for
the degree of

Doctor of Philosophy

under the supervision of
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March 2021

CERTIFICATE OF ORIGINAL AUTHORSHIP

I, *Mahmoud El Safadi* declare that this thesis, is submitted in fulfilment of the requirements for the award of *Doctor of Philosophy*, in the *School of Mathematical and Physical Sciences* at the University of Technology Sydney.

This thesis is wholly my own work unless otherwise referenced or acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

This document has not been submitted for qualifications at any other academic institution.

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ACKNOWLEDGEMENT

In the year of this thesis, 2020, the world experienced a life-threatening situation due to the Covid-19 pandemic leading governments to implement extreme measures such as quarantines and lockdowns. I have faced many difficulties in the last year of my PhD journey. I sincerely thank all the people mentioned below for their exceptional efforts and support during this unpredictable time.

Firstly, I would like to thank Associated Professor Andrew McDonagh for the continuing support of my PhD and related research, for his patience, inspiration and huge knowledge. His guidance helped me throughout my research and writing this thesis. I could not have imagined a better PhD research advisor and mentor.

Also, I would like to thank my Co-supervisor Dr Tristan Rawling, for his informative feedback and motivation, as well as for the hard question that led me to extend my study from different perspectives.

I would also like to thank Dr Ronald Shimmon, who gave access to the laboratory and research facilities. Without his precious encouragement, this work would not be possible.

I take this opportunity to express my deepest gratitude to Dr. Adam Southon, for his support and valuable discussions in the cell culture biological study.

I want to thank the University of Technology Sydney for allowing following my passion for chemistry research and give me access to the facilities I needed to finish my PhD.

A special thanks to my family. Words cannot express how grateful I am to my mother Mouminah Taha, and father Nasser El Safadi for all of the sacrifices that you have made on my behalf. Your prayer for me was what sustained me thus far. I would also like to thank all of my friends, especially Susan Shimmon, who incited me to strive towards my goal.

In the end, I would like to express appreciation to my beloved wife Hanan El Wardani who spent sleepless nights with and was always my support in the moments when there was no one to answer my queries.

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List of Abbreviations

Å: Angstrom

δ: Chemical Shift (NMR)

λ: Wavelength

ν_{\max} : Maximum absorbance

[M]⁺: Molecular ion

[M+H]⁺: Protonated molecular ion

8-HQ: 8-Hydroxyquinoline

Aβ: Amyloid-beta

AD: Alzheimer's disease

ADMET: Absorption, Distribution, Metabolism, Excretion, and Toxicity

AICD: APP intracellular domain

ALA: Alanine

AMPA: 2- amino- 3- (3-hydroxy 5-methyl- isoxazol-4-yl propanoic acid

APP: Amyloid precursor protein

ASP: Aspartic acid

ATP: Adenosine triphosphate

BBB: Blood-brain barrier

BCA: Bicinchoninic acid assay

BSA: Bovine Serum Albumin

CDCl₃: Deuterated chloroform

CNS: Central nervous system

COX17: Cytochrome oxidase copper chaperone

CQ: Clioquinol

CTR1: Copper transport protein

Cyclam: 1,4,8,11-Tetraazacyclotetradecane or 14 ane- N4

Cyclen: 1, 4, 7, 10-tetraazacyclododecane or 12 ane- N4

d: Doublet (NMR)

dd: Doublet of doublets (NMR)

DA: Dopamine

DAT: Dopamine transporter

DFP: Deferiprone
DPPH: 2,2-diphenyl-1-picrylhydrazyl
DMSO: Dimethyl sulfoxide
DNA: Deoxyribonucleic acid
FTIR: Fourier transform infrared spectroscopy
GABA: Gamma-amino butyric acid
GC: Gas chromatography
GLU: Glutamic acid
HIS: Histidine
HRMS: High resolution mass spectroscopy
Hz: Hertz
IC50: The half maximal inhibitory concentration
ITC: Isothermal titration calorimetry
J: Coupling constant (NMR)
M: Multiplet (NMR)
 m/z : Mass to charge ratio
MAO: Monoamine oxidase inhibitory
mg: Milligrams
mL: Millilitre
mmol: Millimole
MLCT: Metal ligand charge transfer
MS: Mass spectroscopy
MTF: Membrane- bound transferrin
MTT: Microculture Tetrazolium Assay
NMDA: N-Methyl-D-aspartic acid
NMR: Nuclear magnetic resonance
NTBI: Non transferrin-bound iron
ORTEP: Oak Ridge Thermal Ellipsoid Plot Program
PBS: Phosphate-buffered saline
PD: Parkinson's Disease
PEAs: Phenylethylamines

PSA: Polar surface area
q: quartet (NMR)
Q-TOF: Quadrupole Time-of-Flight
R_f: Retention factor
RNA: Ribonucleic acid
ROS: Reactive oxygen species
SERT: Serotonin transporter
SFN: Small fibre neuropathy
s: Singlet (NMR)
SOD: Superoxide dismutase
SN: Substantia nigra
TETA: Triethylenetetramine
TF-Fe³⁺: Iron-bound transferrin
TLC: Thin layer chromatography
Tyr: Tyrosinase
UV: Ultraviolet

Publications from This Thesis

M. E Safadi, M. Bhadbhade, R. Shimmon, A. T. Baker, A. M. McDonagh.

Cyclen-based chelators for the inhibition of A β aggregation: Synthesis, antioxidant and aggregation evaluation.

Inorganica Chimica Acta, 467, **2017** 343-350. <https://doi.org/10.1016/j.ica.2017.07.060>.

ABSTRACT

In this thesis, a series of four new metal chelating compounds (**MS1-4**) based on the cyclen macrocycle that bear pendant arms to modify the molecules' properties are evaluated as candidate drugs for Alzheimer's disease. These compounds have been designed to bind to the misregulated metals associated with Alzheimer's disease. The corresponding Cu^{2+} , Zn^{2+} and Ni^{2+} complexes were synthesized and characterized to examine the ability of the chelators to bind to the metal centres. $\text{A}\beta_{40}$ de-aggregation by the cyclen compounds was assessed using turbidometry, and the re-solubilization of $\text{A}\beta_{40}$ was also examined. The results show that the cyclen compounds have the ability to effectively chelate Cu^{2+} and Zn^{2+} metal ions and de-aggregate $\text{A}\beta_{40}$ that has been aggregated due to the presence of these ions. The antioxidant properties of the cyclen compounds were tested using the DPPH scavenging assay, and the results show that some of the compounds can decrease oxidative stress especially MS1 with IC_{50} equals to $71 \mu\text{M}$. Molecular modelling studies revealed the behaviour of the cyclen compounds within the E2 domain of APP and its interaction with Cu and Zn. Pharmacokinetics parameters were also promising for the compounds. Overall, these compounds exhibit promising properties as candidates for the treatment of Alzheimer's disease.

A study of drug candidates for Parkinson's disease investigated a series of new iron chelating compounds based on deferiprone and 8-hydroxyquinoline that have amphetamine-like structures. This work addresses a significant problem in Parkinson's disease research, the issue of targeted delivery of chelating compounds into dopaminergic cells where iron may accumulate. The corresponding Fe^{2+} complexes were synthesised and characterised to examine the ability of the chelators to bind to metal centres. Thermodynamic parameters between the chelators and iron were calculated by using Isothermal titration calorimetry.

The results show that 8-hydroxyquinoline-based compounds are more potent chelators than deferiprone-based compounds. N27 dopaminergic cell culture study was conducted to investigate whether the chelators can be transported within cells to prevent dopaminergic cell death caused by iron toxicity. The 8-hydroxyquinoline-based compounds showed the most promising results to rescue dopaminergic cells from iron-induced stress. The antioxidant properties of the compounds were tested using the DPPH scavenging assay, and the results show that 8-hydroxyquinoline-based compounds were superior in decreasing oxidative stress compared to the deferiprone-based compounds. Overall, 8-hydroxyquinoline-based compounds showed favourable properties as candidates for future Parkinson's disease research.