Synthesis and Characterisation of Novel Phenanthroline Quinone Derivatives and their Evaluation as Alzheimer's Disease Therapeutic Active Ingredients

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CERTIFICATE OF AUTHORSHIP/ORIGINALITY

I, Seta Tosonyan, certify that the work in this thesis has not been previously submitted for a degree nor has it been submitted as part of requirements for a degree.

I also certify that the thesis has been written by myself. Any assistance that I have received in my research work and the preparation of the thesis itself has been acknowledged. Furthermore, I certify that all information sources and literature used are indicated in the thesis.

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Seta Tosonyan

February 2018

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ABSTRACT

The study is based on the synthesis, characterisation and biological evaluation of series of new derivatives of phen-5,6-dione potentially could act as inhibitors for acetylcholinesterase (AChE) from electric eel and butyrylcholinesterase (BuChE) from equus horse serum and as an active pharmacophore inhibitors of acetylcholinesterase and butyrylcholinesterase.

Twenty four derivatives of phen-5,6-dione were prepared including imine-Schiff based of phen-5,6-dione and 2-amino phenol as mono and di substituted active ingredient, condensation products of phen-5,6-dione with thiosemicarbazide, semicarbazide hydrochloride, hydroxylamine hydrochloride, aminoguanidine hydrochloride, aminoguanidine bicarbonate, 4-methyl-3-thiosemicarbazide, 2-methyl-3-thiosemicarbazide, 4-methyl-3-thiosemicarbazide, 4,4-di methyl-3-thiosemicarbazide, 4-ethyl-3-thiosemicarbazide, 4-phenyl-3-Thiosemicarbazide, ethylenediamine, hydrazine sulfate, o-nitro anline, diethylamine carbamyl chloride, o-phenylenediamine and benzyl amine. All the prepared compounds were characterised by various advanced techniques: ^{1}H NMR,^{13}C NMR, FT-IR, ATR and HRMS and digital melting point.

Ellman Assays were performed with acetylthiocoline iodide (ATCI) and s-butyrylthiocholine iodide (BTCI) as the substrate, using Galantamine and Tacrine, well-known AChE and BuChE inhibitors as the positive controls. IC_{50} for the prepared compounds were determined. The study includes determination of several important kinetic parameters such as type of inhibition (Competitive) and Inhibition constant (Ki). The inhibition mechanism for determination of the activity of both AChE and BuChE inhibitors were extracted from Lineweaver- Burk plots and Dixon plots.

Furthermore the drug-like properties were assessed based on Lipinski five rules and by utilising ADMET properties such as Aqueous solubility, Blood-brain barrier (BBB), CYP2D6 binding, Hepatotoxicity, Intestinal Absorption and PPB descriptors for each of studied compounds. Furthermore all the prepared active ingredients were sent for screening at QLD University.

The simulation studies for molecular modelling of the obtained experimental results were assimilated with implementing Accelrys Discovery Studio 4.5 suite. The obtained data from the docking study were used for analysing the biological properties obtained in this study and some suggestions are stated.

We found ability of the prepared compounds as active ingredient as chelating ligands to form complexes with Cu^{+2} and Zn^{+2} were investigated using UV–Vis spectroscopy. Similarities in absorption spectra including π–π*intra ligand transitions and a strong metal –ligand charge transfer (MLCT) in the visible region were observed. The obtained results support the idea that the phen-5,6-dione structure and electronic properties of these ligands incorporate features of both diamine and quinone ligands. These characteristics may be beneficial in decreasing the rate of cognitive decline in moderate to severe AD patients.

This technique may provide useful information to investigators with relation to chemical profiling of drug seizures, however its use should be limited to that of a screening method.

This technique demonstrate that a rational structure based on phen-5,6-dione derivatives can generate a molecules that can target modulate multiple factors, and provide a new tool to investigate Alzheimer's disease.

List of Abbreviations

$[M+H]^+$	Protonated molecular ion
2D-NMR	2 Dimensional Nuclear Magnetic Resonance
3D	3 Dimensional structure
ACh	Acetylcholine
AChE	Acetylcholinesterase
AChEIs	Acetylcholinesterase inhibitors
AD	Alzheimer's disease
APP	Amyloid precursor protein
Ar	Aromatic
Aβ	Amyloid beta
ATCI	Acetylthiocoline iodide
BBB	Blood-brain barrier
BTCI	S-butyrylthiocholine iodide
BuCHE	Butyrylcholinesterase
CAS	Catalytic active site
$CDCl_3$	Deuterated chloroform
ChE	Cholinesterase
ChEI	Cholinesterase inhibitor
CNS	Central nervous system
CT	Cerebral tomography
dd	Doublet of doublets (NMR)
d	Doublet (NMR)
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DMSO-d6	Deuterated Dimethyl sulfoxide
FDA	Food and Drug Administration
HRMS	High resolution mass spectroscopy
Hz	Hertz
IR	Infrared
J	coupling constant (NMR)

m	Multiplet (NMR)
m.p.	Melting point
m/z	Mass to charge ratio
MAO	Monoamine oxidase
mg	Milligrams
mL	Millilitre
ML	Multifunctional Ligand
mmol	Millimol
MTDLs	Multi-target-directed ligands
MW	Molecular weight
NMR	Nuclear Magnetic Resonance
phen	1,10-phenanthroline
PAS	Peripheral anionic site
phen-5,6-dione	1,10-phenanthroline-5,6-dione
R	Alkyl
Ar	Aryl
ROS	Reactive oxygen species
τ	Tau protein
TcAChE	Torpedo California Acetylcholinesterase
TLC	Thin layer chromatography
δ	Chemical Shift (NMR)
FDA	Food and drug administration
kD	kilo Dalton
q	Quartet
t	Triplet

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