

INDEX

Contents	Page No.
List of Figures	xi
List of Tables	xvi
Abbreviations and Symbols	xvii
Preface	xxi
CHAPTER 1. INTRODUCTION	1
1.1 Alzheimer's disease	1
1.2 Pathophysiological mechanisms involved in AD	2
1.2.1 Cholinergic hypothesis	2
1.2.2 A β hypothesis	4
1.2.3 Excitotoxic hypothesis	6
1.2.4 Oxidative stress hypothesis	6
1.2.5 Tau hypothesis	7
1.2.6 APO ϵ 4 hypothesis	9
1.2.7 CREB signaling pathways	10
1.3 Available neurotherapeutics for the treatment of AD	11
1.4 Novel therapeutic strategies for the development and discovery of compounds for the treatment of AD	11
1.4.1 Multitarget approach	12
1.4.2 Computer-aided drug design approach	13
1.4.3 Molecular hybridization	14
1.5 Design hypothesis in the present study	14
CHAPTER 2. REVIEW OF LITERATURE	16
2.1. <i>N</i> -Benzylpiperidines: Development as multitargeted ligands in AD	16
2.2. 1,3,4-Oxadiazoles: Development as multitargeted ligands in AD	26
CHAPTER 3. RATIONALE, OBJECTIVES AND PLAN OF WORK	31
3.1. Rationale and objectives	31
3.1.1 Designing of Part-I (Series I) ligands	32
3.1.2 Designing of Part-II (Series II–V) ligands	33
3.2. Plan of work	35
CHAPTER 4. EXPERIMENTAL	37
4.1 Computational studies	37
4.1.1 Pharmacophore modeling	37
4.1.2 Virtual screening and docking-post processing (DPP)	37
4.1.3 MM-GBSA	38
4.1.4 Molecular docking study	38
4.1.5 Molecular dynamics simulations study	38

Contents	Page No.
4.2 Synthesis	39
4.2.1 Chemicals and reagents	39
4.2.2 Series I: <i>N</i> -Benzylpiperidine analogs with substituted phenyl methanimines/ methanamines	39
4.2.2.1 General procedure for synthesis of compounds (S_I3a–o)	39
4.2.2.2 General procedure for synthesis of compounds (S_I4a–o)	40
4.2.3 Series II: <i>N</i> -Benzylpiperidine and substituted benzylidenehydrazine-1-carboxamides and Series III: 5-Phenyl-1,3,4-oxadiazoles tethered with an —NH linker	40
4.2.3.1 General procedure for synthesis of compounds (S_{II}7)	41
4.2.3.2 General procedure for synthesis of compounds (S_{II}8)	41
4.2.3.3 General procedure for synthesis of compounds Series II (S_{II}9a–h)	41
4.2.3.4 General procedure for synthesis of compounds Series III (S_{III}10a–c)	42
4.2.3.5 General procedure for synthesis of compounds Series III (S_{III}10d–h)	42
4.2.4 Series IV: <i>N</i> -Benzylpiperidine and substituted 5-phenyl-1,3,4-oxadiazoles tethered with the —NHCH ₂ linker	42
4.2.4.1 General procedure for synthesis of compounds (S_{IV}12–h)	43
4.2.4.2 General procedure for synthesis of compounds (S_{IV}13–h)	43
4.2.4.3 General procedure for synthesis of compounds Series IV (S_{IV}14–h)	43
4.2.5 Series V: <i>N</i> -Benzylpiperidine and substituted 5-phenyl-1,3,4-oxadiazoles tethered without linker	44
4.2.5.1 General procedure for synthesis of compounds (S_V16a–h and S_V17a–h)	44
4.3 Characterization of the synthesized compounds	45
4.3.1 Melting point	45
4.3.2 TLC (R _f value)	45
4.3.3 FT-IR	45
4.3.4 ¹ H NMR and ¹³ C NMR	45
4.3.5 Mass spectra	46
4.3.6 Determination of percentage purity by HPLC	46
4.4 Biological Evaluation	46
4.4.1 <i>In vitro</i> studies	46
4.4.1.1 Cholinesterase inhibition by Ellman assay	46
4.4.1.2 Enzyme kinetics study	47
4.4.1.3 BACE-1 inhibition assay	47

Contents	Page No.
4.4.1.4 Propidium iodide displacement assay	48
4.4.1.5 Parallel artificial membrane permeation assay (PAMPA)	49
4.4.1.6 A β aggregation (self- and AChE-induced) inhibition by thioflavin T assay	49
4.4.1.7 AFM study	50
4.4.1.8 Neurotoxic liabilities against SH-SY5Y cell lines by MTT assay	51
4.4.2 <i>In vivo</i> and <i>ex vivo</i> studies	51
4.4.2.1 Animals	51
4.4.2.2 Acute oral toxicity study	51
4.4.2.3 Scopolamine-induced amnesia model: Y-maze test	52
4.4.2.4 <i>Ex vivo</i> studies: AChE estimation and antioxidant activity	53
4.4.2.5 A β -induced AD phenotypic model: Morris water maze test	54
4.4.2.6 Western-blot analysis	55
4.4.2.7 Immunohistochemical analysis	56
4.4.3 Pharmacokinetic studies	57
CHAPTER 5. RESULTS AND DISCUSSION	58
5.1 PART-I: SERIES I	58
5.1.1 Computational studies and designing considerations	58
5.1.1.1 Pharmacophore modeling	58
5.1.1.2 Virtual screening and docking-post processing (DPP)	59
5.1.1.3 MM-GBSA	60
5.1.1.4 Molecular docking study	61
5.1.1.5 Molecular dynamics simulations study	63
5.1.2 Chemistry	67
5.1.2.1 Synthesis of Series I: <i>N</i> -Benzylpiperidine with substituted phenyl methanimines/methanamines	67
5.1.2.2 Characterization of the synthesized compounds (Series I)	68
5.1.3 Biological evaluation	80
5.1.3.1 <i>In vitro</i> studies	80
5.1.3.2 <i>In vivo</i> and <i>ex vivo</i> studies	80
5.1.3.3 Pharmacokinetic studies	89
5.2 PART-II: SERIES II–V	93
5.2.1 Chemistry	94
5.2.1.1 Synthesis of Series II (S_{II}9a–h) and III (S_{III}10a–h): <i>N</i> -Benzylpiperidine with substituted benzylidenehydrazine-1-carboxamides and substituted 5-phenyl-1,3,4-oxadiazoles tethered with —NH linker	94

Contents	Page No.
5.2.1.2 Characterization of the synthesized compounds (Series II and III)	95
5.2.1.3 Synthesis of Series IV (S_{IV}14a-h): <i>N</i> -Benzylpiperidine and substituted 5-phenyl-1,3,4-oxadiazoles tethered with —NHCH ₂ linker	103
5.2.1.4 Characterization of the synthesized compounds (Series IV)	104
5.2.1.5 Synthesis of Series V (S_V17a-h): <i>N</i> -Benzylpiperidine and substituted 5-phenyl-1,3,4-oxadiazoles tethered without linker	111
5.2.1.6 Characterization of the synthesized compounds (Series V)	112
5.2.2 Biological evaluation	115
5.2.2.1 <i>In vitro</i> studies	115
5.2.2.2 <i>In vivo</i> and <i>ex vivo</i> studies	126
5.2.2.3 Pharmacokinetic studies	132
5.2.3 Computational studies	133
5.2.3.1 Molecular docking study	133
5.2.3.2 Molecular dynamics simulations study	135
CHAPTER 6. SUMMARY AND CONCLUSION	140
6.1. Scope and future directions	143
CHAPTER 7. REFERENCES	145
CHAPTER 8. APPENDIX	161
8.1. ¹ H and ¹³ C spectra of representative synthesized compounds	161
8.2. Mass spectra of representative synthesized compounds	188
8.3 HPLC chromatograms of representative synthesized compounds	190
LIST OF PUBLICATIONS	197

LIST OF FIGURES

Fig. No.	Figure Legends	Page No.
1.1	Synthesis of ACh and cholinergic neurotransmission.	4
1.2	Amyloidogenic (β -secretase) and non-amyloidogenic (α -secretase) pathways.	5
1.3	The process of tau aggregation, formation of NFTs, and neurodegeneration.	9
2.1	Schematic structural representation of (<i>R,S</i>)-1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl]methylpiperidine.	16
2.2	Structures of donepezil analogs with modification of benzyl and piperidine moieties.	17
2.3	Structures of minaprine and its most potent analog.	18
2.4	Structures of <i>N</i> -benzylpiperidine analogs tethered with variably substituted indole moieties.	19
2.5	The cyclopentathiophene substituted analogs of donepezil.	19
2.6	The <i>N</i> -benzylpiperidine and indolylpropargylamine tethered multitargeted hybrid.	20
2.7	Molecular hybrids of <i>N</i> -benzylpiperidine and 2-aminopyridine-3,5-dicarbonitrile.	20
2.8	The <i>N</i> -benzylpiperidine and indole molecular hybrid with multitargeted activities against AD.	21
2.9	Ferulic acid-based <i>N</i> -benzylpiperidine hybrids.	22
2.10	A molecular hybrid of <i>N</i> -benzylpiperidine and diarylthiazole as potential multitargeted ligand against AD.	23
2.11	A molecular hybrid of <i>N</i> -benzylpiperidine moiety of donepezil and coumarin.	23
2.12	Umbelic and caffeic acid-based molecular hybrids of <i>N</i> -benzylpiperidine.	24
2.13	Donepezil-like multitargeted compounds as AChE and BACE-1 inhibitors.	25
2.14	Donepezil-based hybrids of <i>N</i> -benzylpiperidine/benzylpiperazine moiety with benzimidazole or benzofuran.	25
2.15	Novel <i>N</i> -benzylpiperidine carboxamide derivatives.	26
2.16	1,3,4-Oxadiazole as GSK-3 β and CDK-5 inhibitor.	26
2.17	1,3,4-Oxadiazoles as ChE and LOX inhibitors.	27
2.18	1,3,4-Oxadiazole analogs with AChE inhibitory potential from the library of (<i>E</i>)-2-aryl-5-(3,4,5-trimethoxystyryl)-1,3,4-oxadiazoles and (<i>E</i>)-2-aryl-5-(2-benzo[d][1,3]diox-ol-5-yl)vinyl)-1,3,4-oxadiazoles.	27
2.19	Novel benzothiazole tethered 1,3,4-oxadiazole hybrids.	28
2.20	3-Piperidinyl-1,3,4-oxadiazole hybrid with AChE inhibitory activity.	28

Fig. No.	Figure Legends	Page No.
2.21	A multifunctional hybrid with 2-aminopyrimidine linked 1,3,4-oxadiazole to treat AD.	29
2.22	A molecular hybrid of 4-aminopyridine and 1,3,4-oxadiazole.	29
2.23	Molecular hybrids of 4-aminopyridine and 1,3,4-oxadiazole.	30
3.1	Design strategy for Part-I (Series I) ligands.	33
3.2	Design strategy for Part-II (Series II–V) ligands.	34
5.1	Favored binding sites in generated e-pharmacophore models. [A] AChE (PDB code: 4EY7) [B] BACE-1 (PDB code: 2ZJM).	58
5.2	3D Structures of cocrystallized ligands depicting numbering of favored residues. [A] AChE (PDB code: 4EY7) [B] BACE-1 (PDB code: 2ZJM).	59
5.3	Structures of common identified hits. [A] SEW06622 [B] AW01119 [C] PD00698.	60
5.4	Superimpose representation. [A] Donepezil redocked (green) and cocrystallized pose (blue) on AChE (RMSD: 0.4227 Å) [B] F1M redocked (green) and cocrystallized pose (blue) on BACE-1 (RMSD: 1.9161 Å).	62
5.5	Binding pattern of SEW06622 (S₁3a) depicted in orange colored ligand binding surface at the active pocket. [A] AChE (4EY7) [B] BACE-1 (2ZJM).	62
5.6	Binding pattern of S₁3j depicted in green colored ligand binding surface at the active pocket. [A] AChE (4EY7) [B] BACE-1 (2ZJM).	62
5.7	Binding pattern of S₁4j depicted in golden colored ligand binding surface at the active pocket. [A] AChE (4EY7) [B] BACE-1 (2ZJM).	62
5.8	Molecular dynamics studies of SEW06622 (S₁3a)-AChE (4EY7) docked complex. [A] Histogram [B] Graphical representation showing percentage interactions with active site residues [C] Timeline representation showing interactions at each time frame.	64
5.9	Molecular dynamics studies of S₁3j -AChE (4EY7) docked complex. [A] Histogram [B] Graphical representation showing percentage interactions with active site residues [C] Timeline representation showing interactions at each time frame.	64
5.10	Molecular dynamics studies of S₁4j -AChE (4EY7) docked complex. [A] Histogram [B] Graphical representation showing percentage interactions with active site residues [C] Timeline representation showing interactions at each time frame.	65
5.11	Molecular dynamics studies of SEW06622 (S₁3a)-BACE-1 (2ZJM) docked complex. [A] Histogram [B] Graphical representation showing percentage interactions with active site residues [C] Timeline representation showing interactions at each time frame.	65

Fig. No.	Figure Legends	Page No.
5.12	Molecular dynamics studies of S₁3j -BACE-1 (2ZJM) docked complex. [A] Histogram [B] Graphical representation showing percentage interactions with active site residues [C] Timeline representation showing interactions at each time frame.	66
5.13	Molecular dynamics studies of S₁4j -BACE-1 (2ZJM) docked complex. [A] Histogram [B] Graphical representation showing percentage interactions with active site residues [C] Timeline representation showing interactions at each time frame.	66
5.14	Lineweaver-Burk plot for the kinetic study of hAChE inhibition by compound S₁4j .	82
5.15	Dixon plot of compound S₁4j at three different concentrations (0.03, 0.15, and 0.30 μ M) showing K_i value of inhibitor as the negative intersection at the x-axis.	83
5.16	Effect of test compounds on A β aggregation inhibition. [A] Self-induced and [B] AChE-induced experiments.	87
5.17	Effect of test compounds on A β aggregation. [A] Self-induced and [B] AChE-induced A β aggregation.	87
5.18	AFM images of A β ₁₋₄₂ aggregates (10 μ M) incubated with or without inhibitor (S₁4j) at different time intervals (0, 3, 5, and 7 days).	88
5.19	Cell viability assay on neuroblastoma SH-SY5Y cell lines with increasing concentrations of S₁4i and S₁4j .	89
5.20	Effect of compounds S₁4i , S₁4j , and donepezil on scopolamine-induced cognition and memory improvement. [A] Spontaneous alternations (%) and [B] Total number of arm entries in the Y-maze experiment.	91
5.21	Results of <i>ex vivo</i> studies. [A] AChE activity- rate of substrate hydrolyzed [B] TBARS assay- levels of MDA [C] Superoxide dismutase assay- levels of SOD units.	92
5.22	Effect of compound S₁4j in spatial memory improvement on ICV A β ₁₋₄₂ -induced model [A] Escape latency time (ELT) [B] Number of platform crossings in target quadrant during the last 5 days of trials by Morris water maze experiment.	93
5.23	Lineweaver-Burk double reciprocal plot showing the mechanism of enzyme inhibition by compound S_{III}10g [A] hAChE inhibition with acetylthiocholine iodide (ATCI) as substrate [B] hBChE inhibition with butyrylthiocholine iodide (BTCl) as substrate.	120
5.24	The Dixon plots of compound S_{III}10g between Lineweaver-Burk double reciprocal slope and inhibitor concentrations. [A] Dissociation constant $K_i = 0.026 \mu$ M for hAChE and [B] Dissociation constant $K_i = 0.115 \mu$ M for hBChE.	120
5.25	Effect of test compounds on A β aggregation inhibition. [A] Self-induced and [B] AChE-induced experiments.	124
5.26	Effect of test compounds on A β aggregation. [A] Self-induced and [B] AChE-induced A β aggregation.	124

Fig. No.	Figure Legends	Page No.
5.27	AFM images of A β ₁₋₄₂ aggregates (10 μ M) incubated with or without inhibitor (S_{III}10g) at different time intervals (on days 0, 4, 7, and 10).	125
5.28	Cell viability assay on neuroblastoma SH-SY5Y cell lines with increasing concentrations of [A] S_{III}10g and [B] S_{IV}14f .	126
5.29	Effect of compounds S_{III}10g , S_{IV}14f , and donepezil on scopolamine-induced cognition and memory improvement. [A] Spontaneous alternations (%) and [B] Total number of arm entries in the Y-maze experiment.	128
5.30	Results of <i>ex vivo</i> studies. [A] AChE activity- rate of substrate hydrolyzed [B] TBARS assay- levels of MDA and [C] Superoxide dismutase assay- levels of SOD units.	129
5.31	Effect of compound S_{III}10g in spatial memory improvement on ICV A β ₁₋₄₂ -induced model [A] Escape latency time (ELT) [B] Number of platform crossings in target quadrant during the last 5 days of trials by Morris water maze experiment.	131
5.32	Effect of S_{III}10g on <i>in vivo</i> expression of A β and BACE-1 levels in the hippocampal region of the rat brain. [A] Representative bands in the Western blot analysis [B] Densitometric quantification showing attenuated levels of A β and [C] BACE-1, which were elevated with ICV administration of A β ; [D] Immunostaining showing attenuated levels of A β and BACE-expression by S_{III}10g at 10 \times magnification after staining; [E & F] Quantification analysis of immunostains showing changes in burden (% area) of A β and BACE-1 levels, respectively.	132
5.33	Docking poses of ligands in the active site of AChE (4EY7). [A] S_{III}10g and [B] S_{IV}14f .	135
5.34	Docking poses of ligands in the active site of BACE-1 (2ZJM). [A] S_{III}10g and [B] S_{IV}14f .	135
5.35	Results of molecular dynamics simulation run of 100 ns for S_{III}10g -AChE (4EY7) docked complex. [A] Ligand-protein RMSD relative to protein backbone structure [B] Histogram showing interaction fractions and [C] Time-line graphical representation showing interaction with individual residues in each trajectory frame.	137
5.36	Results of molecular dynamics simulation run of 100 ns for S_{IV}14f -AChE (4EY7) docked complex. [A] Ligand-protein RMSD relative to protein backbone structure [B] Histogram showing interaction fractions and [C] Time-line graphical representation showing interaction with individual residues in each trajectory frame.	137
5.37	Results of molecular dynamics simulation run of 100 ns for S_{III}10g -BACE-1 (2ZJM) docked complex. [A] Ligand-protein RMSD relative to protein backbone structure [B] Histogram showing interaction fractions and [C] Time-line graphical representation showing interaction with individual residues in each trajectory frame.	138

Fig. No.	Figure Legends	Page No.
5.38	Results of molecular dynamics simulation run of 100 ns for S_{IV}14f -BACE-1 (2ZJM) docked complex. [A] Ligand-protein RMSD relative to protein backbone structure [B] Histogram showing interaction fractions and [C] Time-line graphical representation showing interaction with individual residues in each trajectory frame.	138
5.39	2D graphical representation of active site interactions in 100 ns molecular dynamics simulations runs. [A] S_{III}10g -AChE [B] S_{IV}14f -AChE [C] S_{III}10g -BACE-1 and [D] S_{IV}14f -BACE-1.	139

LIST OF SCHEMES

Scheme No.	Scheme Legends	Page No.
1	Synthesis of compounds from Series I (S_I3a–o and S_I4a–o).	39
2	Synthesis of compounds from Series II (S_{II}9a–h) and Series III (S_{III}10a–h).	40
3	Synthesis of compounds from Series IV (S_{IV}14a–h).	42
4	Synthesis of compounds from Series V (S_V17a–h).	44

LIST OF TABLES

Table No.	Table Captions	Page No.
1.1	Chemical structures, mechanism, and adverse effects of USFDA approved drugs for the treatment of AD.	11
5.1	Glide score, interacting residues, and MM-GBSA ΔG binding free energy of identified hits (SEW06622, AW01119, and PD00698) against AChE and BACE-1.	60
5.2	Cholinesterases (hAChE and hBChE) and hBACE-1 inhibition activity and selectivity index of compounds (Series I).	81
5.3	Propidium iodide displacement and predicted BBB permeability (Series I).	85
5.4	Pharmacokinetic evaluation after an oral administration of S_I4j (10 mg/kg, p.o.)	94
5.5	Cholinesterases (hAChE and hBChE) and hBACE-1 inhibition activity and selectivity index of compounds (Series II-V).	118
5.6	Propidium iodide displacement and predicted BBB permeability (Series II-V).	123
5.7	Pharmacokinetic evaluation after an oral administration of S_{III}10g (10 mg/kg, p.o.)	133

ABBREVIATIONS & SYMBOLS

ACh	Acetylcholine
AChE	Acetylcholinesterase
AD	Alzheimer's disease
AFM	Atomic force microscopy
AMP	Adenosine monophosphate
AMPK	AMP-activated protein kinase
AP	Anterior – Posterior
ApoE	Apolipoprotein E
A β	Amyloid beta
APP	Amyloid precursor protein
ATCI	Acetylthiocholine iodide
ATR	Attenuated total reflectance
BACE-1	Beta amyloid cleaving enzyme 1
BBB	Blood-brain barrier
BChE	Butyrylcholinesterase
BSA	Bovine serum albumin
BTCI	Butyrylthiocholine iodide
CADD	Computer-aided drug design
CaMK	Ca ²⁺ /calmodulin dependent kinase
CAS	Catalytic anionic site
CAT	Choline acetyltransferase
CDCl ₃	Deuteriochloroform
CDK-5	Cyclin dependent kinase-5
ChE	Cholinesterase
CNS	Central nervous system
CoA	Coenzyme A
CoMFA	Comparative molecular field analysis
CoMSIA	Comparative molecular similarity indices analysis
COX	Cyclooxygenase
CREB	Cyclic-AMP-response element-binding protein
CST	Conjugated secondary antibody
CYP	Cytochrome P
DMSO	Dimethyl sulfoxide
DPP	Docking-post processing
DTNB	5,5-Dithio-bis-(2-nitrobenzoic acid)
DV	Dorsal - Ventral
Dyrk1A	Dual specificity tyrosine- phosphorylation-regulated kinase-1 A
EDGs	Electron donating groups
EDTA	Ethylenediaminetetraacetic acid

ELT	Escape latency time
ERK	Extracellular signal-regulated protein kinases
ESI	Electrospray ionization
EtOH	Ethanol
EWGs	Electron withdrawing groups
FDA	Food and drug administration
FRET	Fluorescence resonance energy transfer
FT-IR	Fourier-transform infrared spectroscopy
GSK-3 β	Glycogen synthase kinase-3 β
hAChE	Human AChE
hBChE	Human BChE
HPLC	High performance liquid chromatography
HTVS	High throughput virtual screening
i.p.	Intraperitoneal
ICV	Intracerebroventricular
JNK	Janus kinase
LBDD	Ligand-based drug design
MAO-B	Monoamine oxidase-B
MAPK	Mitogen activated protein kinase
MARK	Microtubule affinity-regulating kinase
MDA	Malondialdehyde
ML	Medial – Lateral
MM-GBSA	Molecular mechanics generalized Born surface area
MnSOD	Manganese superoxide dismutase
mp	Melting point
MPO	Myeloperoxidase
MTT	3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide
Na-CMC	Sodium carboxymethyl cellulose
NADPH	Reduce form of nicotinamide adenine dinucleotide phosphate
NFI	Normalized fluorescence intensity
NFTs	Neurofibrillary tangles
NMDAR	<i>N</i> -Methyl-D-aspartate receptor
NMR	Nuclear magnetic resonance spectroscopy
NOS	Nitric oxide synthase
NOx	NADPH oxidase
NPT	Normality, pressure and temperature
OECD	Organisation for economic co-operation and development
OPLS	Optimized potential for liquid simulations
p.o.	Per oral
PAMPA	Parallel artificial membrane permeation assay

PAS	Peripheral anionic site
PBL	Porcine brain lipid
PBS	Phosphate buffered saline
PBST	Phosphate buffered saline with Tween 20
PDB	Protein data bank
PDE	Phosphodiesterase
PHFs	Paired helical fibrils
PI	Propidium iodide
PKA	Protein kinase-A
PPs	Protein phosphatases
PTPA	Protein tyrosine phosphatase-A
QSAR	Quantitative structure-activity relationship
RIPA	Radioimmunoprecipitation assay
RMSD	Root mean square deviation
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
SBDD	Structure-based drug design
SFKs	Src family non-receptor tyrosine kinases
SOD	Superoxide dismutase
SP	Standard precision
TBARS	Thiobarbituric acid reactive substances
TBST	Tris-buffered saline with Tween 20
TLC	Thin layer chromatography
TPKI	Tau protein kinase-I
TRITC	Tetramethylrhodamine isothiocyanate
UV	Ultraviolet spectroscopy
VSGB	Variable surface generalized Born
WHO	World Health Organization
XO	Xanthine oxidase
XP	Extra precision
XRD	X-ray diffraction

SYMBOLS & UNITS

× g	Relative centrifugal force
°C	Degree Celsius
μL	Microliter
μm	Micrometer
μM	Micromolar
Å	Angstrom
α	Alpha
β	Beta

γ	Gamma
ν	Wavenumber
AUC	Area under curve
cm	Centimeter
C_{\max}	Maximal plasma concentration
d	Doublet
dd	Doublet of doublets
ddd	Doublet of doublets of doublets
equiv	Equivalent
g	Gram
h	Hour
Hz	Hertz
J -value	Spin-spin coupling constant
K	Kelvin
kg	Kilogram
KHz	Kilohertz
m	Multiplet
mg	Milligram
min	Minute
mL	Milliliter
mM	Millimolar
MRT	Mean residence time
N/m	Newton per meter
ng	Nanogram
nm	Nanometer
ppm	Parts per million
q	Quartet
RH	Relative humidity
rpm	Rotations per minute
s	Seconds/Singlet
t	Triplet
$t_{1/2}$	Elimination half-life
td	Triplet of doublets
T_{\max}	Time to reach maximum plasma concentration
U/mL	Units per milliliter
v/v	Volume by volume
w/v	Weight by volume