RECEPTOR BASED RADIOLIGANDS FOR NEUROIMAGING

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DEPARTMENT OF CHEMISTRY

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RECEPTOR BASED RADIOLIGANDS FOR NEUROIMAGING

by

PREETI JHA

Department of Chemistry

Submitted

in the fulfillment of the requirements of the degree of Doctor of Philosophy

to the

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CERTIFICATE

This is to certify that the thesis entitled, **"RECEPTOR BASED RADIOLIGANDS FOR NEUROIMAGING"** being submitted by **Ms. PREETI JHA** to the Indian Institute of Technology Delhi, for the award of the degree of **Doctorate of Philosophy** in Chemistry, is an authentic record of research work carried by her. She has worked under my guidance and supervision. She has fulfilled the requirements for the submission of this thesis, which to my knowledge has reached the requisite standards.

The work and results embodied in this thesis have not been submitted, in part or in full, to any other institute or university for the award of any degree or diploma.

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PhD is all about learning. The more you fail, the more you gain and the more you are challenged, the more you explore. The best lesson of being a Research Scholar is to learn to apply the basic concepts of life into Science and Development. Many ingredients of healthy living are inculcated during the entire training of PhD, especially perseverance, determination, dedication and preeminent of all the broad vision to convert the feeling of "cannot do this" to "did it". Certainly, PhD Scholar has to strive hard and is awarded with the degree of Doctor of Philosophy, yet I believe that, it is the conclusion of cumulative efforts made by Supervisors, Mentors, Well-wishers, Friends and Family.

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Last but not the least, I devote all my achievements to the "GOD: the origin of life".

Preeti Jha

ABSTRACT

Chapter 1: An overview of the need of neuroimaging and the importance of CADD for neuroreceptor specific drug development have been elucidated. Implications of 5-HT_{1A} and 5-HT_7 neuroreceptors in neurological disorders and the utilization of radioligands for early diagnostics have also been discussed.

Chapter 2: A brief description of computational methodology and various techniques employed to accomplish the entitled work have been provided.

Chapter 3: The 3D homology models of monomeric 5-HT_{1A} and 5-HT_7 receptors have been generated and validated. Mono-template methodology was conceived for developing 5-HT_{1A} receptor homology models, while multi-template approach was utilized for building the homology models of 5-HT_7 receptors. 3D4S derived mono-template models were found most promising and efficient for drug design and development.

Chapter 4: The 3D-structure of homodimeric 5-HT_{1A}-5-HT_{1A}, 5-HT_7-5-HT_7 and 5-HT_{1A}-5-HT_7 heterodimeric receptors have been generated using protein-protein docking and validated successfully. The dimer interface 1 (TM1/TM2/TM7/H8-ECL1) was found most stable and conserved for homo and heterodimerization of 5-HT_{1A} and 5-HT_7 receptors.

Chapter 5: Mixed affinity based monovalent and bivalent neuroimaging probes were designed by employing the SBDD approach of CADD. Receptor targeting ability of newly designed probes were predicted using Docking studies and analysed by investigating the receptor-ligand interactions at the recognition sites of monomeric dimeric receptor models. Drugability and dynamic stability at physiological conditions have also been studied.

Chapter 6: Synthesis, radiolabelling studies and pre-clinical bio-evaluations of the designed neuroimaging probes have been discussed in this chapter. Biocompatibility, *in vitro* stability, BBB permeation, non-invasive *in vivo* imaging and blood kinetics evaluations were performed to predict the applicability for medical imaging purposes. The *ex vivo* biodistribution and

regional brain uptake studies were also investigated to determine the organ distribution and specific localization of developed radioligands in the receptor-rich regions of brain.

Chapter 7: Leading outcomes of the entitled thesis, limitations and solutions, failure and merit, the future aspects and the scope of the thesis have been summarised.

सार

अध्याय 1: न्यूरोइमेजिंग की आवश्यकता का अवलोकन और न्यूरोरेसेप्टर विशिष्ट दवा विकास के लिए CADD के महत्व को स्पष्ट किया गया है। न्यूरोलॉजिकल विकारों में 5-HT1A और 5-HT7 न्यूरोरेसेप्टर्स के कार्यान्वयन और शुरुआती निदान के लिए रेडिओलिगैंड्स के उपयोग पर भी चर्चा की गई है।

अध्याय 2: कम्प्यूटेशनल कार्यप्रणाली और आवश्यक कार्य को पूरा करने के लिए नियोजित विभिन्न तकनीकों का संक्षिप्त विवरण प्रदान किया गया है।

अध्याय 3: मोनोमेरिक 5-HT1A और 5-HT7 रिसेप्टर्स के 3D होमोलॉजी मॉडल उत्पन्न और मान्य किए गए हैं। 5-HT1A रिसेप्टर होमोलॉजी मॉडल विकसित करने के लिए मोनो-टेम्पलेट दृष्टिकोण की कल्पना की गई थी, जबकि 5-HT7 रिसेप्टर्स के होमोलॉजी मॉडल के निर्माण के लिए मल्टी-टेम्पलेट दृष्टिकोण का उपयोग किया गया था। 3D4S व्युत्पन्न मोनो-टेम्पलेट मॉडल दवा डिजाइन और विकास के लिए सबसे आशाजनक और कुशल पाए गए।

अध्याय 4: होमोडायमेरिक 5-HT1A-5-HT1A, 5-HT7-5-HT7 और 5-HT1A-5-HT7 हेटेरोडायमेरिक रिसेप्टर्स की 3 डी संरचना प्रोटीन-प्रोटीन डॉकिंग का उपयोग करके उत्पन्न की गई है और सफलतापूर्वक सत्यापित की गई है। डायमर इंटरफ़ेस 1 (TM1 / TM2 / TM7 / H8-ECL1) को सबसे अधिक स्थिर और 5-HT1A और 5-HT7 रिसेप्टर्स के होमो और विषमकरण के लिए संरक्षित किया गया था।

अध्याय 5: मिश्रित आत्मीयता पर आधारित मोनोवैलेन्ट और बाइवेलेंट न्यूरोइमेजिंग प्रोब को CADD के SBDD दृष्टिकोण को नियोजित करके डिजाइन किया गया था। नए डिज़ाइन किए गए प्रोब की रिसेप्टर लक्ष्यीकरण क्षमता की भविष्यवाणी डॉकिंग अध्ययनों का उपयोग करके की गई थी और मोनोमेरिक डायमेरिक रिसेप्टर मॉडल के मान्यता स्थलों पर रिसेप्टर-लिगैंड इंटरैक्शन की जांच करके इसका विश्लेषण किया गया था। शारीरिक स्थितियों में दवा की क्षमता और गतिशील स्थिरता का भी अध्ययन किया गया है।

अध्याय 6: इस अध्याय में सिंथेसिस, रेडियोलेबलिंग अध्ययन और डिज़ाइन किए गए न्यूरोइमेजिंग एजेंटों के पूर्व-नैदानिक जैव मूल्यांकन पर चर्चा की गई है। जैव इमेजिंग, इन विट्रो स्थिरता, बीबीबी पारगम्यता, गैर-इनवेसिव इन-विवो इमेजिंग और रक्त काइनेटिक्स मूल्यांकन चिकित्सा इमेजिंग उद्देश्यों के लिए प्रयोज्यता की भविष्यवाणी करने के लिए किए गए थे। मस्तिष्क के रिसेप्टर-समृद्ध क्षेत्रों में विकसित रेडियोलिगैंड्स के वितरण और विशिष्ट स्थानीयकरण का निर्धारण करने के लिए पूर्व विवो बायोडिस्ट्रिएशन और क्षेत्रीय मस्तिष्क उत्थान अध्ययनों की भी जांच की गई थी।

अध्याय 7: हकदार थीसिस, सीमाओं और समाधान, विफलता और योग्यता के प्रमुख परिणामों, भविष्य के पहलुओं और थीसिस के दायरे को संक्षेप में प्रस्तुत किया गया है।

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GLOSSARY OF SYMBOLS AND ABBREVIATIONS

β^+	Positron
γ	Gamma
KeV	Kilo Electron Volt
MeV	Mega Electron Volt
°	Degree (unit of Angle)
˚C	Degree Celsius (unit of Temperature)
$t_{½}$	Half-life
p	Proton
α	Alpha particle
n	Neutron
d	Deuteron
m_e	Mass of electron (9.109×10^{-31} kilograms)
c	Speed of light ($2.998\ 10^8$ m / s)
min	Minute
h	Hour
mm	Millimetre
M	mol L^{-1} (Unit of concentration, Molarity)
N	equivalents/L (Unit of concentration, Normality)
mM	Millmolar
nM	Nanomolar
pM	Picomolar
K_i	Inhibition Constant
pK_i	$-\log_{10}K_i$

vdW	Van der Waals
Å	Ångström (10^{-10} meter)
ns	Nanosecond
MHz	Mega Hertz
δ	Delta
ppm	Parts per million
J	Coupling Constant
K	Kelvin (Unit of temperature)
Cα	Alpha-position of protein backbone
λ	Wavelength
nm	Nanometre (10^{-9} m)
µm	Micrometre (10^{-6} m)
v/v/v or v/v	Volume ratio
mL	Millilitre
g	Gram
L	Litre
g/l	Gram per litre
rpm	Revolutions per minute
i.v.	Intravenous
i.p.	Intraperitoneal
MBq	Megabecquerel (SI unit of radioactivity, 1 Bq = 1 s^{-1})
mCi	Millicurie (non-SI unit of radioactivity, 1 mCi = 3.7×10^{16} decays per second or Bq)
pH	Logarithmic scale of acidity or basicity in aqueous solution ($-\log_{10}[H^+]$)
R_f	Retention factor

$G_{\alpha i}$, $G_{\alpha o}$, $G_{\alpha q}$, $G_{\alpha s}$	GDP-bound conformations of G-protein
Na^{+}/K^{+}	Sodium-Potassium pump
^{11}B, ^{14}N, ^{15}O	Naturally occurring Boron, Nitrogen, Oxygen
^{11}C, ^{18}F	Radioactive isotope of Carbon, Fluorine
^{99m}Tc	Radioactive metastable isotope of Technetium
^{111}In, ^{90}Y, ^{201}Tl	Radioactive isotope of Indium, Yttrium, Thallium
^{123}I, ^{131}I	Radioactive isotopes of Iodine
^{99}Mo, ^{177}Lu, ^{188}Rh	Radioactive isotope of Molybdenum, Lutetium, Rhodium
^{235}U, ^{68}Ga	Radioactive isotope of Uranium, Gallium
Kr	Krypton
Nu	Nucleophile
$LiAlH_4$	Lithium aluminium hydride
CH_3OTf	Methyl Triflate
Al_2O_3	Aluminium oxide
TcO_4^{-}	Pertechnetate
$NaBH_4$	Sodium borohydride
HCl	Hydrochloric acid
$SnCl_2$	Stannous chloride
NaI	Sodium iodide
SER	Serotonin Hydrochloride
MPP	2-Methoxyphenylpiperazine
BTZ	Benzothiazolone
$CHCl_3$	Chloroform
$CDCl_3$	Deuterated chloroform
MeOH	Methanol

DMF	Dimethylformamide
TEA	Triethylamine
TFA	Triflouro acetic acid
TBAOH	Tetrabutylammonium Hydroxide
DMSO	Dimethyl sulfoxide
NaOH	Sodium hydroxide
Na_2CO_3	Sodium carbonate
SG	Silica gel
NaCl	Sodium chloride
CO_2	Carbon dioxide
XP	Extra Precision
2D	Two-Dimensional
3D	Three-Dimensional
CNS	Central Nervous System
WHO	World Health Organisation
GBD	Global Burden of Disease
CT	Computed Tomography
MRI	Magnetic Resonance Imaging
PET	Positron Emission Tomography
SPECT	Single Photon Emission Computed Tomography
PMTs	Photomultiplier tubes
BBB	Blood Brain Barrier
AD	Alzheimer's Disease
CADD	Computer Aided Drug Design
LBDD	Ligand Based Drug Design

SBDD	Structure Based Drug Design
QSAR	Quantitative Structure-Activity Relationship
NMR	Nuclear Magnetic Resonance
SSRIs	Selective Serotonin Reuptake Inhibitors
COX-2	Cyclooxygenase-2
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
HIV	Human Immunodeficiency Virus
HM	Homology Modeling
FASTA	Text-based representation of protein sequences by using single letter codes
BLAST	Basic Local Alignment Search Tool
PSI-BLAST	Position-Specific Iterative BLAST
G-protein	Guanine Nucleotide-Binding Protein
GPCRs	G-protein Coupled Receptors
MDs	Molecular Dynamic simulations
LGICs	Ligand-Gated Ion Channels
GABA	γ-Aminobutyric acid
TM	Transmembrane
TMD	Transmembrane Domain
TMH	Transmembrane Helix
ICL	Intracellular Loop
ECL	Extracellular Loop
5-HT	Serotonin
DA	Dopamine
NE	Norepinephrine

AC	Adenylate cyclase
cAMP	Cyclic adenosine monophosphate or 3',5'-cyclic adenosine monophosphate
5-HTRs	Serotonin receptors
h5-HT_{1A}R	human 5-HT_{1A} receptor
h5-HT_7R	human 5-HT_7 receptor
5-HT_1	Serotonin receptor subtype - 1
5-HT_{1A}R	Serotonin receptor subtype - 1A
5-HT_{1B}R	Serotonin receptor subtype - 1B
5-HT_{1D}R	Serotonin receptor subtype - 1D
5-HT_{1E}R	Serotonin receptor subtype - 1E
5-HT_{1F}R	Serotonin receptor subtype - 1F
5-HT_{2A}R	Serotonin receptor subtype - 2A
5-HT_{2B}R	Serotonin receptor subtype - 2B
5-HT_{2C}R	Serotonin receptor subtype - 2C
5-HT_3R	Serotonin receptor subtype - 3
5-HT_4R	Serotonin receptor subtype - 4
5-HT_5Rs	Serotonin receptor subtype - 5
5-HT_{5A}R	Serotonin receptor subtype - 5A
5-HT_{5B}R	Serotonin receptor subtype - 5B
5-HT_6R	Serotonin receptor subtype - 6
5-HT_7 or 5-HT_7R	Serotonin receptor subtype - 7
5-HT_{1A}-5-HT_{1A}	Homodimer of serotonin receptor subtype - 1A
5-HT_7-5-HT_7	Homodimer of serotonin receptor subtype - 7
5-HT_{1A}-5-HT_7	Heterodimer of serotonin receptor subtypes - 1A and 7

D_2	Dopamine receptor 2
mGluR5	Metabotropic glutamate receptor 5
β_2AR, β_1AR	human β_2-adrenergic receptor, β_1-adrenergic receptor
hA_{2A}R	human A_{2A} crystal structure
CBRs	Cannabinoid receptors
CCM	Consensus Cholesterol Binding Motif
4GPO	Oligomeic Turkey Beta1-Adrenergic G Protein-Coupled Receptor
1N3M	Theoretical model of Rhodopsin Oligomer
ADME	Adsorption, Distribution, Metabolism and Excretion
3D4S	Cholesterol bound human β_2-Adrenergic Receptor
2RH1	human β_2-adrenergic receptor
1F88	Bovine Rhodopsin
CA	cornu Ammon
CA1	cornu Ammon 1
CA3	cornu Ammon 3
Lys	Lysine
Cys	Cysteine
D, Asp	Aspartic acid
E, Glu	Glutamic acid
R, Arg	Arginine
Y, Tyr	Tyrosine
W, Trp	Tryptophan
P, Pro	Proline
N, Asn	Asparagine

Phe	Phenylalanine
Val	Valine
Thr	Threonine
Ile	Isoleucine
Ser	Serine
Gln	Glutamine
MAOI	Monoamine Oxidase Inhibitor
TCA	Tricyclic Antidepressant
FDA	Food and Development Administration
ADHD	Attention Deficit Hyperactivity Disorder
OCD	Obsessive Compulsive Disorder
MDD	Major Depressive Disorders
DAS	Depression, Anxiety and Stress
HPA	Hypothalamic-Pituitary-Adrenal
DSM	Diagnostic and Statistical Manual
PTSD	Post-Traumatic Stress Disorder
GAD	Generalized Anxiety Disorder
ACTH	Adrenocorticotropic Hormone
CRF	Corticotropic-Releasing Factors
CRH	Corticotropic-Releasing Hormone
DST	Dexamethasone Suppression Test
mRNA	Messenger Ribonucleic Acid
CORT	Corticosterone
TH	Tyrosine Hydroxylase
FST	Forced Swim Test

TST	Tail Suspension Test
FT	Filed Test
PMT	Plus Maze Test
BM	Biomolecule
EMA	European Medicines Agency
BFCs	Bifunctional Chelating Agents
DTPA	Diethylenetriamine Pentaacetic Acid
EDTA	Ethylenediaminetetraacetic Acid
DFO	Desferrioxamine
H_2DEDPA	6,6'-((ethane-1,2-diylbis(azanediyl))bis(methylene))dipicolinic acid
AAZTA	2,2'-((1,4-bis(carboxymethyl)-6-methyl-1,4-diazepan-6-yl)azanediyl)diacetic acid
DOTA	2,2',2'',2'''-(1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrayl)tetraacetic acid
TETA	2,2',2'',2'''-(1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetrayl)tetraacetic acid
NOTA	2,2',2''-(1,4,7-triazonane-1,4,7-triyl)triacetic acid
THF	Tetrahydrofuran
CH_3OTf	Trifluoromethanesulfonate or triflate
SB-269970	3-[(2R)-2-[2-(4-Methylpiperidin-1-yl)ethyl]pyrrolidin-1-yl]sulfonylphenol
LATUDA	Trade name of Lurasidone
^{11}C-PIB	N-Methyl-[11C]-2-(4'-methylaminophenyl)-6-hydroxybenzothiasole
^{11}C-PMP	1-[^{11}C]methylpiperidin-4-yl propionate
^{11}C-NMSP	3-N-[^{11}C]Methylspiperone

^{11}C-WAY100635	[^{11}C]N-(2-(4-(2-methoxyphenyl)-1-piperazin-1-yl)ethyl)-N-(2-pyridyl)cyclohexanecarboxamide
^{11}C-MPEP	2-[^{11}C]Methyl-6-(2-phenylethynyl)pyridine
15R-^{11}C-TIC	(15R)-16-m-[^{11}C]tolyl-17,18,19,20-tetranorisocarbacyclin methyl ester
^{11}C-85380	3-[2(S)-2-Azetidinylmethoxy]pyridine
8-OH-DPAT	7-(Dipropylamino)-5,6,7,8-tetrahydronaphthalen-1-ol
DR-4004	1-[4-(4-Phenyl-3,6-dihydro-2H-pyridin-1-yl)-butyl]-2a,3,4,5-tetrahydro-1H-benzo[cd]indol-2-one
SB-269970	(*R*)-3-[2-[2-(4-Methylpiperidin-1-yl)ethyl]pyrrolidine-1-sulfonyl]phenol hydrochloride
SB-258741	R-(+)-1-(toluene-3-sulfonyl)-2-[2-(4-methylpiperidin-1-yl)ethyl]pyrrolidine
SB-656104	6-((R)-2-{2-[4-(4-Chloro-phenoxy)-piperidin-1-yl]-ethyl}-pyrrolidine-1-sulphonyl)-1H-indole hydrochloride
LP-44	4-[2-(Methylthio)phenyl]-*N*-(1,2,3,4-tetrahydro-1-naphthalenyl)-1-piperazinehexanamide hydrochloride
NAN-190	1-(2-methoxyphenyl)-4(4-(2-phtalimido)butyl)piperazine
F-15599	3-chloro-4-fluorophenyl-(4-fluoro-4([(5-methyl-pyrimidin-2-ylmethyl)-amino]-methyl)-piperidin-1-yl)-methanone
F-13640	(3-chloro-4-fluoro-phenyl)-[4-fluoro-4-{[(5-methyl-pyridin-2-ylmethyl)-amino]-methyl}piperidin-1-yl]methanone
F-13714	3-Chloro-4-fluorophenyl-(4-fluoro-4-[[((5-methyl-4-methylamino-pyridin-2-ylmethyl)-amino]-methyl]-piperidin-1-yl)methanone
PRX-00023	N-[3-[4-[4-(cyclohexylmethylsulfonylamino)butyl]piperazin-1-yl]phenyl]acetamide
WAY-101405	(R)-N-(2-methyl-(4-indolyl-1-piperazinyl)ethyl)-N-(2-pyridinyl)-cyclohexane carboxamide
WAY-100135	3-[4-(2-Methoxyphenyl)piperazin-1-yl]-2-phenyl-N-tert-butyl-propanamide dihydrochloride

SRA-333	4-cyano-N-[(2R)-2-[4-(2,3-dihydro-1,4-benzodioxin-5-yl)piperazin-1-yl]propyl]-N-pyridin-2-ylbenzamide;hydrochloride
p-MPPF	4-Fluoro-N-(2-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl)-N-2-pyridinylbenzamide
p-MPPI	4-Iodo-N-[2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]-N-pyridin-2-ylbenzamide
NAN-190	1-(2-Methoxyphenyl)-4-(4-phthalimidobutyl)piperazine hydrobromide
NAD-299	(3*R*)-3-(Dicyclobutylamino)-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrochloride
LY-426965	(2S)-1-Cyclohexyl-4-[4-(2-methoxyphenyl)-1-piperazinyl]-2-methyl-2-phenyl-1-butanon
MP-3022	4-(3-(Benzotriazol-1-yl)propyl)-1-(2-methoxyphenyl)piperazine
(S)-UH-301	(S)-5-fluoro-8-hydroxy-2-(dipropylamino)-tetralin [(S)-UH-301
BMY-7378	8-[2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]-8-azaspiro[4.5]decane-7,9-dione
LP-211	N-[(4-cyanophenyl)methyl]-6-[4-(2-phenylphenyl)piperazin-1-yl]hexanamide
UCM-5600	1-[5-(4-phenylpiperazin-1-yl)pentyl]benzo[cd]indol-2-one
LP-12	6-[4-(2-phenylphenyl)piperazin-1-yl]-N-(1,2,3,4-tetrahydronaphthalen-1-yl)hexanamide
CW	ClustalW
PSTA	Prime-Single Template Alignment
KB	Knowledge Based
EB	Energy Based
SGB	Surface Generalized Born
PDB	Protein Data Bank
LIDs	Ligand Interaction Diagrams

RMSD	Root Mean Square Deviation
RMSF	Root Mean Square Fluctuation
SSEs	Secondary Structure Elements
TMS	Tetramethylsilane
MBAE	Multi-Ligand Bimolecular Association with Energetics
NVT	Constant Temperature and Volume
NPT	Constant Temperature and Pressure
ITLC	Instant Thin Layer Chromatography
HPLC	High Performance Liquid Chromatography
MTT	3-(4,5-Dimethylthiazol-2-Yl)-2,5-Diphenyltetrazolium Bromide
PAW	Pyridine/Acetic acid/Water
DMEM	Dulbecco's Modified Eagle's Medium
HEPES	2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanesulfonic acid
α-MEM	Minimum Essential Medium
PBS	Phosphate Buffer Saline
FBS	Fetal Bovine Serum
HEK-293	Human Embryonic Kidney Cells
RBCs	Red blood cells
OD	Optical Density
BALB/c	Albino, Laboratory-bred strain of the house mouse
CPCSEA	Committee for the Purpose of Control and Supervision of Experiments on Animals
IAEC	Institutional Animal Ethics Committee
BRIT	Board of Radiation and Isotope Technology
DAE	Department of Atomic Energy