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The Development of Radiolabelled Peripheral Benzodiazepine Receptor Ligands for Imaging Cancer and Neurodegenerative Disorders

Taryn P Homes

B. Med. Chem. Hons.

A thesis submitted in fulfilment of the requirements

for the award of the degree

Doctor of Philosophy

from

University of Wollongong

Department of Chemistry

December 2007

Certification

I, Taryn P. Homes, declare that this thesis, submitted in fulfilment of the requirements for the award of Doctor of Philosophy, in the Department of Chemistry, University of Wollongong, is wholly my own work unless otherwise referenced or acknowledged. The document has not been submitted for qualifications at any other academic institute.

Taryn P. Homes

December 2007

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List of Abbreviations

^{13}C NMR	Carbon Nuclear Magnetic Resonance
^{1}H NMR	Proton Nuclear Magnetic Resonance
ACN	Acetonitrile
AcOH	Acetic Acid
AIBN	Azobisisobutyronitrile
ANT	Adenine Nucleotide Translocase
Ar	Aryl
bs	Broad singlet
CAT	Chloramine-T
CBR	Central Benzodiazepine Receptor
CI	Chemical Ionisation
CNS	Central Nervous System
DBI	Diazepam Binding Inhibitor
DCM	Dichloromethane
dd	Doublet of doublets
ddd	Doublet of doublets of doublets
DEPT	Distortionless Enhancement by Polarisation Transfer
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
dt	Doublet of triplets
EAE	Experimental Autoimmune Encephalomyelitis
EI	Electron Impact

ES	Electrospray
FDG	Fluorodeoxyglucose
GABA	Gamma-aminobutyric Acid
GIT	Gastrointestinal Tract
h	Hour
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
Hz	Hertz
IC_{50}	Inhibition Constant at 50%
ID/g	Injected dose per gram
IMM	Inner mitochondrial membrane
LE	Lupus Erythmatosus
M	Molar
m	Multiplet
MBq	Megabequerel
min	Minute
mL	Millilitre
mmol	Milli mol
mp.	Melting Point
MS	Mass Spectometry
m/z	Mass/charge ratio
NBS	*N*-Bromosuccinimide
OMM	Outer mitochondrial membrane
PBR	Peripheral Benzodiazepine Receptor
PE	Petroleum Ether

PET	Positron Emission Tomography
PPA	Polyphosphoric Acid
q	Quartet
qC	Quaternary Carbon
RCY	Radiochemical Yield
RT	Room Temperature
s	Singlet
SAR	Structure-Activity Relationship
SPECT	Single Photon Emission Computed Tomography
StAR	Steroidogenic acute regulatory protein
t	Triplet
TFA	Trifluoroacetic Acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
Tris	Tris(Hydroxymethyl)aminomethane
UV	Ultraviolet
VDAC	Voltage Dependent Anion Channel

Publications/Presentations

Publications

- **Homes, T.P**., Keller, P.A., Katsifis, A., Mattner, F. (2006); Synthesis and in vitro binding of *N,N*-dialkyl-2-phenylindol-3-ylglyoxylamides for the peripheral benzodiazepine binding sites; Bioorganic and Medicinal Chemistry; 14; 3938-3946
- **Homes, T.P**. Mattner, F. Keller, P.A, Katsifis, A. (2007); Synthesis and in vivo evaluation of a novel [^{123}I] indolglyoxylamide for the Peripheral Benzodiazepine Binding Sites; Journal of Labelled Compounds and Radiopharmaceuticals; 50; S307
- **Homes, T.P**., Mattner, F., Keller, P.A., Katsifis, A. In vivo evaluation of ^{123}I- *N,N*-diethyl-[5-chloro-2-(4-iodophenyl)indol-3-yl]glyoxylamide for the peripheral benzodiazepine binding sites. To be submitted to Nuclear Medicine and Biology.

Oral Presentations

- **Homes, T.P.**, Keller, P.A., Katsifis, A. Synthesis and peripheral and central benzodiazepine receptor binding affinity of *N,N*-dialkyl-2-phenylindol-3-ylglyoxylamides. RACI Young Chemist's Symposium, 3rd July 2005, University of Sydney
- **Homes, T.P.**, Keller, P.A., Katsifis, A., Mattner, F. Development of radiolabelled peripheral benzodiazepine receptor ligands. University of Wollongong Department of Chemistry Annual Conference. 24-25th October, 2005, ANU Kialoa coastal campus.

Poster Presentations

- **Homes, T.P**., Keller, P.A., Katsifis, A., Mattner, F. (2006); Synthesis and evaluation of *N,N*-dialkyl-2-phenylindol-3-ylglyoxylamides for the study of peripheral benzodiazepine binding sites; 4th France – Australia Symposium on Nuclear Medicine, Melbourne
- **Homes, T.P**., Mattner, F., Keller, P.A., Katsifis, A. (2007); Synthesis and in vivo evaluation of a novel [^{123}I] indolglyoxylamide for the peripheral benzodiazepine binding sites; 17th International Symposium on Radiopharmaceutical Science, 29th April-3rd May, Aachen, Germany

Abstract

Three classes of compounds were chosen for investigation to find a high affinity and selective iodinated peripheral benzodiazepine receptor (PBR) ligand; indol-3-ylglyoxylamides, pyrazolopyrimidines, and pyridopyrrolooxazepines and pyrrolobenzoxazepines. These compounds were chosen from a literature search for their high PBR affinity and selectivity, ease of synthesis, and the potential for radioiodination.

Fifteen new halogenated *N,N*-dialkylindol-3-ylglyoxylamides were synthesised and tested for their PBR and central benzodiazepine receptor (CBR) affinity. The compounds IC_{50} values for the PBR ranged from 7.8 – 618 nM, and a structure activity relationship (SAR) was determined. Brominated compounds had higher binding affinities than their iodinated analogues, and indoles with a chloro substituent on position 5 had higher binding affinities than the non-chlorinated compounds. The optimum alkyl chain length was found to be two carbons. The highest affinity iodinated ligand, with a PBR IC_{50} of 8.2 nM, was radiolabelled with ^{123}I in 55-60% radiochemical yield and evaluated *in vivo* in Sprague-Dawley rats. Biodistribution studies revealed high uptake of the radiotracer in organs known to contain PBR, such as the kidneys, adrenals, heart, liver and lungs. Drug competition studies showed that the PBR drugs PK11195 and Ro5-4864, when injected into the rat 5 min prior to injection of the radiotracer, significantly decreased uptake of radiotracer into those organs. The CBR drug, flumazenil, did not decrease the uptake of the radiotracer. Metabolite studies showed that the radiotracer was > 95% intact in the heart, kidneys, adrenals, and brain after 3 h and was 65% intact in the plasma. This compound is the first radiolabelled

PBR ligand of this class, and is an excellent candidate for future studies and may lead to a clinically useful imaging agent.

Three pyrazolopyrimidines were synthesised, with lengths of the alkyl chains being methyl, ethyl, or propyl groups. The highest affinity ligand, with the propyl groups, displayed an IC_{50} of 7.9 nM, however, only the compound with ethyl groups displaying an IC_{50} of 11.7 nM was radiolabelled with ^{123}I in 95% radiochemical yield, and evaluated *in vivo* in rats. This compound showed high uptake into organs known to contain PBR, and also showed an interesting result in which pre-administration of Ro5-4864 did not cause any significant decrease of uptake of radiotracer in the kidney or heart, however PK11195 did cause of significant decrease in these organs. This compound provides the first radioiodinated PBR ligand of this class.

Two pyrrolopyridooxazepines and two pyrrolobenzoxazepines were synthesised and tested. One of the compounds was found to be inactive, while the others had moderate PBR IC_{50} values of 24-39 nM. The moderate binding affinity for these compounds would unlikely lead to a successful imaging agent.

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