Allosteric Modulation of 'Reproductive' GPCRs : a case for the GnRH and LH receptors

Heitman, L.H.

Allosteric Modulation of ‘Reproductive’ GPCRs

A Case for the Human GnRH and LH Receptors

Allosteric Modulation of 'Reproductive' GPCRs

A Case for the Human GnRH and LH Receptors

Proefschrift

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden
op gezag van Rector Magnificus Prof. Mr. P.F. van der Heijden,
volgens besluit van het College voor Promoties
te verdedigen op woensdag 22 april 2009
klokke 16.15 uur

door

Laura Helena Heitman
geboren te Alphen aan den Rijn
in 1981

PROMOTIECOMMISSIE

Promotor:	Prof. Dr. A. P. IJzerman
Overige Leden:	Prof. Dr. A. Christopoulos (University of Melbourne, Australia)
	Dr. M. W. Beukers
	Prof. Dr. R. Leurs
	Prof. Dr. C. A. A. van Boeckel
	Prof. Dr. M. Danhof

This research described in this thesis was performed at the Division of Medicinal Chemistry of Leiden/Amsterdam Center for Drug Research, Leiden University (Leiden, The Netherlands) in collaboration with Schering Plough Research Institute (Oss, The Netherlands), as part of the TI Pharma consortium. The project has been financially supported by TI Pharma (project number D1-105).

This thesis was printed by Wöhrmann Print Service (Zutphen, The Netherlands).

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

7-TM	Seven-transmembrane
AID	Assay identifier number in PubChem data repository
AMP	Adenosine-5'-monophosphate
ATP	adenosine 5'-triphosphate
δ	Cooperativity factor of two allosteric modulators
B_{max}	Maximal specific radioligand binding
BSA	Bovine serum albumin
cAMP	Cyclic adenosine-5'-monophosphate
CHO	Chinese hamster ovary
CID	Compound identifier number in PubChem data repository
DCM	Dichloromethane
DMEM	Dulbecco's Modified Eagle's Medium
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
EDAC	N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride
EDTA	Ethylene diamine tetraacetic acid
EC_{50}	Half-maximal effective concentration (potency)
E_{max}	Maximal effect (efficacy)
EtOAc	Ethyl acetate
FD-1	5-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-furan-2-carboxylic acid (2,4,6-trimethoxy-pyrimidin-5-yl)-amide
FSH	Follicle-stimulating hormone
GnRH	Gonadotropin-releasing hormone
GPCR(s)	G protein-coupled receptor(s)
GTP	Guanosine-5'-triphosphate
hCG	Human chorionic gonadotropin
HMA	5-(N,N-hexamethylene)amiloride
HMW	High molecular weight
HOBt	1-hydroxybenzotriazole
IC_{50}	Half-maximal inhibitory concentration (affinity);

K_D	Equilibrium dissociation constant
K_i	Equilibrium inhibition constant (absolute affinity)
K_M	Substrate concentration at half maximal reaction rate
K_{off}	Dissociation rate
K_{on}	Association rate
LMW	Low molecular weight
logD	Logarithm of octanol-water distribution coefficient
LUF5419	4-Chloro-N-(4-pyridin-2-yl-thiazol-2-yl)-benzamide
LUF5771	Cyclopentyl-carbamic acid [1,1';3',1"]terphenyl-5'-yl ester
MIBA	5-(N-methyl-N-isobutyl)amiloride
NFAT-luc	Nuclear Factor Activated T-cell luciferase reporter gene
Org 43553	5-Amino-2-methylsulfanyl-4-[3-(2-morpholin-4-yl-acetylamino)-phenyl]-thieno[2,3-d]pyrimidine-6-carboxylic acid tert-butylamide
PBS	Phosphate-buffered saline
$(Ph_3P)4Pd$	Tetrakis(triphenylphosphine)palladium
rec-hCG	Recombinant human chorionic gonadotropin
recLH	Recombinant luteinizing hormone
RMSD	Root mean square deviation
SAR	Structure-activity relationship
SEM	Standard error of the mean
TLC	Thin-layer chromatography
TSH	Thyroid-stimulating hormone
V_{max}	Maximal reaction rate