Bioorganic & Medicinal Chemistry Letters 20 (2010) 7004–7010

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

3D-QSAR, homology modeling, and molecular docking studies on spiropiperidines analogues as agonists of nociceptin/orphanin FQ receptor

Ming Liu, Lin He, Xiaopeng Hu, Peiqing Liu, Hai-Bin Luo *

School of Pharmaceutical Sciences, Sun Yat-Sen University, Guangzhou 510006, PR China

ARTICLE INFO

Article history:
Received 3 May 2010
Revised 22 September 2010
Accepted 24 September 2010
Available online 29 September 2010

Keywords:
NOP
Agonist
3D-QSAR
CoMFA
Homology modeling
Molecular docking

ABSTRACT

The nociceptin/orphanin FQ receptor (NOP) has been implicated in a wide range of biological functions, including pain, anxiety, depression and drug abuse. Especially, its agonists have a great potential to be developed into anxiolytics. However, the crystal structure of NOP is still not available. In the present work, both structure-based and ligand-based modeling methods have been used to achieve a comprehensive understanding on 67 N-substituted spiropiperidine analogues as NOP agonists. The comparative molecular-field analysis method was performed to formulate a reasonable 3D-QSAR model (cross-validated coefficient $q^2 = 0.819$ and conventional $r^2 = 0.950$), whose robustness and predictability were further verified by leave-eight-out, Y-randomization, and external test-set validations. The excellent performance of CoMFA to the affinity differences among these compounds was attributed to the contributions of electrostatic/hydrogen-bonding and steric/hydrophobic interactions, which was supported by the Surflex-Dock and CDOCKER molecular-docking simulations based on the 3D model of NOP built by the homology modeling method. The CoMFA contour maps and the molecular docking simulations were integrated to propose a binding mode for the spiropiperidine analogues at the binding site of NOP.

© 2010 Elsevier Ltd. All rights reserved.

The nociceptin/orphanin FQ receptor (NOP), also known as ORL1, OP4, or LC132, is a deorphanized member of the G-protein coupled receptor (GPCR) superfamily. This receptor is distributed in the brain and periphery.[1] It shares considerable structural and localization features with other opioid receptors,[2] but it is classified as a non-opioid member of the opioid receptor family by the International Union of Basic and Clinical Pharmacology (IUPHAR). Its endogenous ligand, nociceptin (or orphanin FQ), which activates NOP, is a 17-amino acid neuropeptide isolated from the brain in 1995.[3,4] The neuropeptide acts as an inhibitive agent on synaptic transmission in the CNS, and reduces responsiveness to stress. The nociceptin-NOP system has been implicated in a wide range of biological functions, including pain, mood disorders, drug abuse, cardiovascular control, and immunity.[5–7] NOP is receiving considerable attention as a potential target for the treatment of anxiety and depression.

A number of drugs are used for the treatment of anxiety and depression. But they have some drawbacks due to their poor and/or variable efficacy, long run in to peak behavioral effect, and a wide range of side effects leading to tolerability and compliance problems.[8] Considerable evidences indicate that nociceptin and several non-peptide NOP agonists serve as anxiolytics with fewer side effects.[9–17]

Several different classes of NOP agonists have been reported. Among them, spiropiperidine analogues exhibit relatively higher NOP binding affinities,[18,19] however, there is not a QSAR (quantitative structure–activity relationship) or pharmacophore model reported in their work. In the present study, comparative molecular-field analysis (CoMFA) was performed to formulate 3D-QSAR models of 67 spiropiperidine analogues[19] as NOP agonists. Subsequently, a homology model was build based on the crystal structure of Beta2-Adrenergic G Protein-Coupled receptor (PDB code: 2RH1)[20] as a template. Finally, molecular docking simulations were performed to obtain a complete picture of the structural characteristics of the most active agonist **P67** within the putative active site of this protein. Results of the study not only support the use of spiropiperidine analogues as a potential therapeutic agent by targeting NOP, but also aid the rational design of novel and more effective NOP agonists as desired.

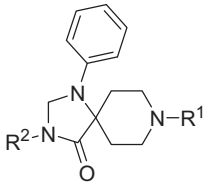
Sixty-seven N-substituted spiropiperidine analogues with human NOP binding affinities (K_i) determined from competition binding assays were collected from the literature.[19] The 67 molecules were divided into a training set of 57 compounds and a test set of 10 compounds, as shown in Table 1. The test set covers the range of biological activities and indicates a moderate diversity in their chemical structures. The experimental pK_i values ($-\log K_i$) were used for the 3D-QSAR analysis.

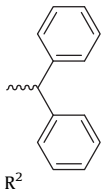
The three-dimensional structures were constructed using SYBYL programming package (version 7.3.5).[21] The MMFF94 force field and MMFF94 partial atomic charges were applied to these

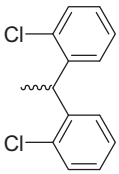
* Corresponding author. Tel.: +86 20 39943031.
E-mail address: luohb77@mail.sysu.edu.cn (H.-B. Luo).

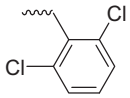
0960-894X/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2010.09.116

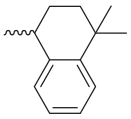
Table 1
Structures, experimental,[19] and CoMFA-predicted activities of spiropiperidines analogues as nociceptin/orphanin FQ receptor (NOP) agonists

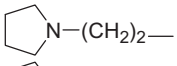
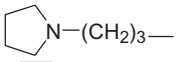
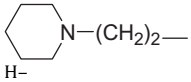
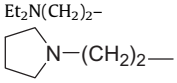


A


B


C


D


Compound	R^1	R^2	−log (K_i/nM)		
			Experimental	Predicted	Res
P09	A	H-	7.638	7.654	−0.016
P10[a]	A	Me	7.509	7.183	0.326
P11	A	Et	7.076	7.112	−0.036
P12	A	Pr	7.469	7.242	0.227
P13	A	Bu	7.244	7.344	−0.100
P14	A	*i*-Pr	7.180	7.242	−0.062
P15	A	*c*-PrCH$_2$	7.081	6.967	0.114
P16	A	*c*-BuCH$_2$	7.276	7.209	0.067
P17[a]	A	*c*-HexylCH$_2$	7.051	7.154	−0.103
P18	A	Propargyl	6.631	6.800	−0.169
P19	A	Allyl	6.693	6.750	−0.057
P02	B	H–	8.167	8.067	0.100
P20	B	Bu–	7.312	7.587	−0.275
P21	B	*i*-Amyl	7.252	7.476	−0.224
P22	B	CH$_3$OC(O)CH$_2$–	7.710	7.705	0.005
P23	B	HO(CH$_2$)$_2$	7.733	8.052	−0.319
P24	B	MeO(CH$_2$)$_2$	7.585	7.826	−0.241
P25[a]	B	NH$_2$(CH$_2$)$_2$–	7.321	7.621	−0.300
P26	B	CH$_3$NH(CH$_2$)$_2$–	8.393	8.274	0.119
P27	B	EtNH(CH$_2$)$_2$–	8.678	8.531	0.147
P28	B	*i*-PrNH(CH$_2$)$_2$–	8.593	8.376	0.217
P29	B	*c*-PentylNH(CH$_2$)$_2$–	8.063	8.395	−0.332
P30	B	*c*-HexylNH(CH$_2$)$_2$–	8.301	8.369	−0.068
P31	B	(CH$_3$)$_2$N(CH$_2$)$_2$–	8.456	8.138	0.318
P32	B	*c*-PrNH(CH$_2$)$_2$–	8.432	8.420	0.012
P33	B	(*i*-Pr)$_2$N(CH$_2$)$_2$–	7.917	7.802	0.115
P34[a]	B	BuNH(CH$_2$)$_2$–	8.668	8.662	0.006
P35	B	*i*-BuNH(CH$_2$)$_2$–	8.561	8.698	−0.137
P36	B	BuNH(CH$_2$)$_2$–	8.420	8.601	−0.181
P37	B		8.648	8.324	0.324
P38	B		8.495	8.288	0.207
P39	B		8.097	7.900	0.197
P40	C	H–	8.638	8.729	−0.091
P41	C	CH$_3$NH(CH$_2$)$_2$–	9.097	8.845	0.252
P42	C	EtNH(CH$_2$)$_2$–	9.155	9.167	−0.012
P43[a]	C	*i*-PrCH$_2$NH(CH$_2$)$_2$–	9.155	9.041	0.114
P44	C	*c*-PrCH$_2$NH(CH$_2$)$_2$–	9.301	9.470	−0.169
P45	C	*c*-BuNH(CH$_2$)$_2$–	9.301	9.048	0.262
P46	C	PrNH(CH$_2$)$_2$–	9.222	9.333	−0.111
P47	C	*i*-BuNH(CH$_2$)$_2$–	9.301	9.371	−0.070
P48	C	BuNH(CH$_2$)$_2$–	9.398	9.282	0.116
P49	C	Et$_2$N(CH$_2$)$_2$–	9.000	8.992	0.008
P50	C		8.638	8.939	−0.301
P03	D	H–	8.886	8.538	0.348
P51[a]	D	Pr–	8.268	8.132	0.136
P52	D	CH$_3$C(O)CH$_2$–	8.347	8.541	−0.194
P53	D	HO(CH$_2$)$_2$–	8.770	8.602	0.098
P54	D	CH$_3$NH(CH$_2$)$_2$–	8.678	8.702	−0.024
P55	D	EtNH(CH$_2$)$_2$–	8.796	9.029	−0.233
P56[a]	D	*i*-PrNH(CH$_2$)$_2$–	8.854	8.970	−0.116
P57	D	*c*-PentylNH(CH$_2$)$_2$–	9.046	8.965	0.081
P58	D	*c*-HexylNH(CH$_2$)$_2$–	9.046	9.016	0.030
P59	D	PrNH(CH$_2$)$_2$–	9.000	9.204	−0.204
P60	D	CH$_2$=CHCH$_2$NH(CH$_2$)$_2$–	9.046	9.090	−0.044
P61	D	*c*-BuNH(CH$_2$)$_2$–	8.824	8.910	−0.086
P62	D	*c*-PrCH$_2$NH(CH$_2$)$_2$–	9.097	9.123	−0.026
P63	D	*i*-BuNH(CH$_2$)$_2$–	9.301	9.237	0.064
P64[a]	D	(*i*Pr)$_2$-N-(CH$_2$)$_2$–	8.174	8.634	−0.460

(*continued on next page*)

Download English Version:

https://daneshyari.com/en/article/1362543

Download Persian Version:

https://daneshyari.com/article/1362543

Daneshyari.com