GPCR Library

ChemDiv Inc.

2015
Knowledge Mining Sources

- PubChem Database
- Thomson Integrity
- SciFinder
- ChEMBL
- Pocketom
- BindingDB
- Protein Data Bank
- MOAD

Scientific publication & Patents (2010-2015)
Knowledge Progression & Selection

Learning

Reference Compounds
> 80K

Analysis

2D-clustering procedure
isosteric and bioisosteric morphing
singeltones assignment
outliers finding and exclusion

2D-Topological analogues
privileged hot-spot containing compounds
Kohonen-based modeling

CADD

Selection

Screening

GPCR Library
> 39.5K

>15K Templates Design
Focus on novel chemistry
Scaffold prioritization
MedChem Filters

FOCUS ON NOVEL CHEMISTRY

GPCR-active agents claimed since 2010
Reference Compounds (Examples)

Disclosed since 2010

GPR40 agonists
Takeda
WO 2015020184

selective inhibitors of the Dopamine D2 receptor
US Department of Health & Human Services
WO 2015017412

GnRH (LHRH) Antagonist
Bayer Schering Pharma AG
WO 2015007606

GnRH (LHRH) Antagonist
Ono Pharmaceutical Co., Ltd.
WO 2015005305

Melanin-Concentrating Hormone MCH Receptor Antagonist
Takeda Pharmaceutical Co., Ltd
WO 2015005489

CCR9 Receptor Antagonist
ChemoCentryx, Inc.
US 2014329803

CGRP Antagonist
Merck & Co., Inc.
US 2014256699

FSH Receptor Regulator
Merck Patent GmbH
WO 2014209978

D2 Receptor Ligand
KACST
2013 US 44826

CB2 Agonist
F. Hoffmann-La Roche AG
WO 2014198592

Prostanoid EP4 Antagonist
Kaken Pharmaceutical Co., Ltd.
WO 2014200075

muscarinic M1 Agonist
Heptares Therapeutics Ltd.
US 2014256699

D3 Receptor Ligand
AbbVie Inc.
US 201418356

CCR2 Antagonist
Janssen Pharmaceutica NV
US 2014018356

GLP-1 Receptor Ligand
Academia Sinica
US 2014350100

H3 Receptor Ligand
Sanofi
US 2014315923

CCR2 Antagonist
Janssen Pharmaceutica NV
US 2014018356

mgluR2 Agonist
Eli Lilly and Company
US 2011152334

mgluR2 Agonist
Eli Lilly and Company
US 2011152334

mgluR regulators
BrainCells, Inc.
US 2015025064

CB2 Agonist
Boehringer Ingelheim Pharma GmbH & Co.
US 2010331304
Methodology for Compound Selection

Kohonen-based *in silico* modeling

Of total: >63K training examples from the clusters (reported GPCR ligands)

Model 1

1.9K NOVEL GPCR ligands from 2010

av. classification power: 77%

Descriptors: LogP, Sp3, PEOE_VSA_POL, diameter, a_ICM, KierA1

Of total: 4.3K training examples - singeltones (reported GPCR ligands)

Model 2

1.9K NOVEL GPCR ligands from 2010

av. classification power: 79%
Descriptor Distributions (ref compounds)
Library Design

- **120K** Compounds selected based on 2D-Topology searching were tested using the developed *in silico* model.
- **39576** Compounds were classified as matched the neurons directly assigned to GPCR ligands reported from **2010**

*Points within the maps indicate the compounds classified as Virtual Hits*
Examples from different areas
Validation of GPCR Library
ChemDiv’s Design & Activity (PubMed Examples)

**PAR2 Antagonist**

Compound inhibited the increase in intracellular Ca\(^{2+}\) levels in trypsin-treated HEK293 cells by 90.5% at 10 \(\mu\)g/ml and decreased the production of PGE2 in human synovial SW 982 cells by 84% and 119%, respectively, at 0.25 \(\mu\)g/ml and 1 \(\mu\)g/ml.

**Endothelin Receptor Antagonist**

Mathiesen, J.M.; et al. 1 Record(s) Retrieved

Identification of indole derivatives exclusively interfering with a G protein-independent signaling pathway of the prostaglandin D2 receptor CRTH2

Mol Pharmacol 2005, 68(2): 393

**PAR1 Antagonist**

Displacement of \([3H]\)-thrombin receptor agonist peptide

\(K_i=19.1\) nM

**Cannabinoïd CB2 Agonist**

EK293 human embryonic kidney cells transfected with human receptor

Displacement of \([3H]\)-WIN-55212-2

\(IC_{50}=5.01\) µM

**OX1 Antagonist**

CHO Chinese hamster ovary cells transfected with human OX1 receptor

Fluorescent assay

\(IC_{50}<0.3\) µM

**GPR131 Ligand**

cAMP production, induction

HEK293 human embryonic kidney cells transfected with human GPBA (TGR5) receptor, cAMP accumulation assay

\(EC_{50}=0.10\) µM

**GPR131 Agonist**

cAMP production, induction

HEK293 human embryonic kidney cells transfected with human TSH receptor

cAMP accumulation assay

\(EC_{50}=0.66\pm0.06\) nM

**H1 Receptor Antagonist**

Clemizol

HCV NS4B Inhibitor

Malaria remission/reduction, IN VITRO

Erythrocytes, human, Fluorescent assay

\(IC_{50}=19\) nM

**TSHR Agonist**

cAMP production, induction

HEK293 human embryonic kidney cells transfected with human TSH receptor

cAMP accumulation assay

\(EC_{50}=0.660\) µM

**PAR1 Antagonist**

Displacement of \([125I]\)-endothelin-1

\(IC_{50}=0.6\) µM

**PTGDR2 Antagonist**

PKR1 Agonist

Compound induced PKR1 internalization and displayed angiogenic activity in endothelial H5V cells at 1, 10 and 100 nM in a GFR Matrigel assay.

**H1 Receptor Antagonist**

HCV NS4B Inhibitor

Malaria remission/reduction, IN VITRO

Erythrocytes, human, Fluorescent assay

\(IC_{50}=19\) nM
Validation of GPCR Library
ChemDiv’s Design & Activity (PubMed Examples)

- **Prostaglandin D2 receptor**
  - Displacement of [3H]PGD2 from human CRTH2 receptor expressed in 293 cells by scintillation counting in presence of 0.5% BSA
  - IC50=0.064 μM

- **5-hydroxytryptamine receptor 2A**
  - Luminescence-based cell-based HTS
  - EC50=8.393 μM
  - Peripheral myelin protein 22
  - S16 Schwann cell PMP22 intronic element firefly luciferase assay
  - IC50=22.8 μM

- **glp-1 receptor**
  - qHTS of GLP-1 Receptor Inverse Agonists
  - EC50=7.0795 μM
  - G-protein coupled receptor 183

- **D(1A) dopamine receptor isoform**
  - Antagonist of Human D 1 Dopamine Receptor: qHTS Activ
  - 8009-0249
  - glp-1 receptor
  - qHTS of GLP-1 Receptor Inverse Agonists
  - EC50=7.1 μM
  - G-protein coupled receptor 183
  - Active

- **neuropeptides B/W receptor 1**
  - Fluorescence-based primary cell-based HTS
  - Active
  - E015-1760

- **neuropeptides B/W receptor 1**
  - Fluorescence-based primary cell-based HTS
  - Active
  - E015-0273
GPCR Library Statistics

Diversity in Heterocycles: 700 unique heterocycles

Clusters (Tanimoto metrics, min cmpds per cluster - 10, similarity threshold 0.6): 970

Singeltones: 379

Av. structures in cluster: 40

Screens: 8691

Diversity: 0.76
Examples of Scaffolds
Examples of Compounds
Thank you