Template-Based Alignment Modeling of the Structure-Activity Relationships of CB2R Ligands

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Introduction

Cannabinoid receptors (CBRs) are a type of G-protein-couple receptors (GPCRs) with two subtypes known, CB1R and CB2R. CB1R is mainly expressed in the central nervous system, while the CB2R mainly in the immune system and in hematopoietic cells.

CB2R is upregulated on microglial cells at the early stage of neurodegeneration, which makes CB2R a promising target for the early diagnosis and treatment of a variety of neurodegenerative disorders, including Alzheimer's disease, Parkinson disease, and others. To date a large number of CB2R ligands with diverse scaffolds have been reported.

Template-based alignment modeling (TAM) is an innovative SAR-modeling approach developed recently in our studies on opioid ligands. (Wu and Hruby, *ACS Omega*, Oct. **2019**). In this study, by applying TAM, we investigated the structural correlations as well as the structure-activity relationships (SARs) of a variety of CBR ligands. Herein, we will first show how an artificial template of CB ligands was constructed. And we will then demonstrate how to utilize the template to understand the SARs of various CBR ligands with respect to their structural correlations and the structural features of CB2-selectivity as well as CB-ligand antagonism.

Cannabinoids

There exist three major groups of CB ligands, including endocannabinoids, phytocannabinoids, and synthetic cannabinoids.

Endocannabinoids & analogs

Anandamide

2-AG

Noladin ether

Phytocannabinoids & derivatives

Δ^8 -THC

11'-DMH- Δ^8 -THC

Cannabidiol

HU-308

Synthetic cannabinoids

WIN 55212-2

A-796260

High structural diversity of synthetic cannabinoids

Han, S.; Thatte, J.; Buzard, D. J.; Jones, R. M., Therapeutic utility of cannabinoid receptor type 2 (CB₂) selective agonists. *J Med Chem* **2013**, 56, (21), 8224-56.

Results and Discussion

1) Basic strategy for the CB-ligand template construction (with CB2- or nonselective CB-ligands as building blocks)

However, the initial trying was hampered, due to the lipid-like nature of CB ligands - most of the scaffolds were flat or flexible, which made hard to validate the ligand alignment.

2) Assisted with the crystal structures of CB ligands

The binding conformations as revealed with the crystal structures of CB ligands provided critical information for the structural correlations between phyto- and synthetic cannabinoids, which in turn helped for the construction of the CB-ligand template.

Features of the template:

- A flat and rigid scaffold with a 5-C aliphatic side chain perpendicular to the template scaffold
- A/B rings: for alignment of the major scaffolds of most of synthetic CB-ligands
- C/D/E rings: for alignment of the major scaffolds of phytocannabinoids
- A1 ring: for certain CB antagonists.

3) Alignment for structural correlations

Phytocannabinoids

Tetrahydrocannabinol

CP-55,940

Endocannabinoids

Anandamide ($r_{1/2}=0.25$)

Ashton, 2008 (CB2-selective)

The other natural products_{Ref}

Savinorin A
(CB1-ago)

Curcumin
(CB1-antg/CB2-ago)

Euphol
(CB1/2-ago)

Rutamarin
(CB2-ligand)

Ref. Gertsch, J.; Pertwee, R. G.; Di Marzo, V., Phytocannabinoids beyond the Cannabis plant - do they exist? *Br J Pharmacol* **2010**, 160, (3), 523-9.

Alignment of synthetic cannabinoids

CHEMBL306529

Win55212-2

UR-144

Ashton2008-38

BDBM50402874

Spinelli2017-6

Ashton2008-39

Ashton2008-41

Han2013-99

Morales2016-38

MDA7

Morales2016-32

(Note: as the template is still in refinement process, most of the current alignments are putative and will need further validation).

4) SARs interpretation

Two major alignment patterns were revealed by TAM modeling, which in turn helped to address the basic issues regarding the structural correlations of CB ligands: (1) how phyto- and synthetic-CB ligands are correlated; (2) how the diverse CB ligands are correlated.

(1)

(2)

5) The CB2-binding features (...maybe scaffold-dependent and still in validation)

6) CB-antagonists/Inverse-agonists

JTE-907 (CB2 inv-ago)

Ref-1

Lucchesi2014-23 (CB2-inv ago)

Ref-2

AM10257 (CB2-antg)

Ref-3

Ref-4

Ref-5

Ref-1: Iwamura, H.; et al., *The Journal of pharmacology and experimental therapeutics* 2001, 296, (2), 420-425. **Ref-2.** Lucchesi, V.; et al., *J Med Chem* **2014**, 57, (21), 8777-91. **Ref-3.** Li, X.; et al., *Cell* **2019**, 176, (3), 459-467 e13; **Ref-4:** Lucchesi, V.; et al., *J Med Chem* **2014**, 57, (21), 8777-91; **Ref-5:** Pasquini, S. et al., *J Med Chem* **2010**, 53, (16), 5915-28.

Conclusions

1. A preliminary template of CB-ligand was constructed based on the innovative template-alignment modeling (TAM).
2. TAM helped for the structural correlations as well as the SAR interpretations of various CB ligands.
3. Continued template refinement is in progress in order to further define the structural features with respect to the CB2-binding selectivity and the antagonism, as well as the more complete ligand binding space, of the template.

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