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R10. First in class (S,E)-11-[2-(arylmethylene)hydrazono]-PBD analogs as selective CB2 modulators targeting neurodegenerative disorders

Meirambek Ospanov
University of Mississippi, mospanov@olemiss.edu

David Mingle
East Tennessee State University

Mohamed O. Radwan
Kumamoto University, (Japan); National Research Centre, (Egypt)

Nicole M. Ashpole
University of Mississippi

Masami Otsuka
Kumamoto University, (Japan); National Research Centre, (Egypt)

See next page for additional authors

Authors

Meirambek Ospanov, David Mingle, Mohamed O. Radwan, Nicole M. Ashpole, Masami Otsuka, Samir A. Ross, Larry A. Walker, Abbas G. Shilabin, and Mohamed A. Ibrahim

First in class (S,E)-11-[2-(arylmethylene)hydrazono]-PBD analogs as selective CB2 modulators targeting neurodegenerative disorders

Meirambek Ospanov[1], David Mingle[2], Mohamed O. Radwan[3,4,5], Nicole Ashpole[6], Masami Otsuka[3,4], Samir A. Ross[1] , Larry A. Walker[1], Abbas G. Shilabin[2], Mohamed A. Ibrahim[1]

[1]National Center for Natural Products Research, Research Institute of Pharmaceutical Sciences, School of Pharmacy, The University of Mississippi, University, Mississippi 38677, USA; [2]Department of Chemistry, East Tennessee State University, Johnson City, TN 37614, USA; [3]Medicinal and Biological Chemistry Science Farm Joint Research Laboratory, Kumamoto University, Kumamoto 862-0973, Japan; [4]Department of Drug Discovery, Science Farm Ltd., Kumamoto 862-0976, Japan; [5]Chemistry of Natural Compounds Department, Pharmaceutical and Drug Industries Research Division, National Research Centre, Dokki, Cairo 12622, Egypt; [6]Department of BioMolecular Sciences, School of Pharmacy, University of Mississippi, University, MS 38677, USA

ABSTRACT

Newly designed pyrrolo[2,1-c][1,4]benzodiazepines tricyclic skeleton has shown potential clusters of cannabinoid receptors CB1/CB2 selective ligands. CB2 plays a critical role in microglial-derived neuroinflammation, where it modulates cell proliferation, migration, and differentiation into M1 or M2 phenotypes. Beginning with computer-based docking studies accounting the recently discovered X-ray crystal structure of CB2, we designed a series of PBD analogs as potential ligands of CB2 and tested their binding affinities. Interestingly, computational studies and theoretical binding affinities of several selected (S,E)-11-[2-(arylmethylene)hydrazono]-PBD analogs, have revealed the presence of potential selectivity in binding attraction toward CB1 and CB2. Reported here is the discovery of the first representatives of this series of selective binding to CB2. Preliminary data showed that this class of molecules display potential binding efficacy toward the cannabinoid receptors tested. Intriguingly, initial cannabinoid binding assay showed a selective binding affinity of 4g and 4h showed Ki of 0.49 and 4.7 µM toward CB2 receptors while no binding was observed to CB1. The designed leads have shown remarkable stability pattern at the physiological pH magnifying their therapeutic values. We hypothesize that the PBD tricyclic structure offers the molecule an appropriate three-dimensional conformation to fit snugly within the active site of CB2 receptors, giving them superiority over the reported CB2 agonists/inverse agonists. Our findings suggested that the attachment of heterocyclic ring through the condensation of diazepine hydrazone and S- or N-heterocyclic aldehydes enhances the selectivity of CB2 over CB1 [1].

SCHEME

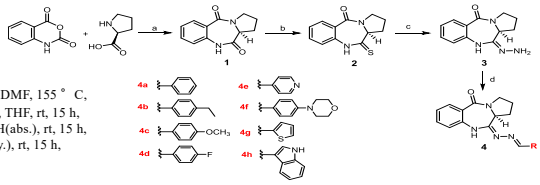

Fig. 1 Reagents and conditions: (a) DMF, 155 ° C, 5 h, 82.0%; (b) Lawesson's reagent, THF, rt, 15 h, 87.0%; (c) N2H4.H2O (98%), EtOH(abs.), rt, 15 h, 99.0%; (d) Aldehydes, MeOH (anhy.), rt, 15 h, 95.0%

MOLECULAR DOCKING

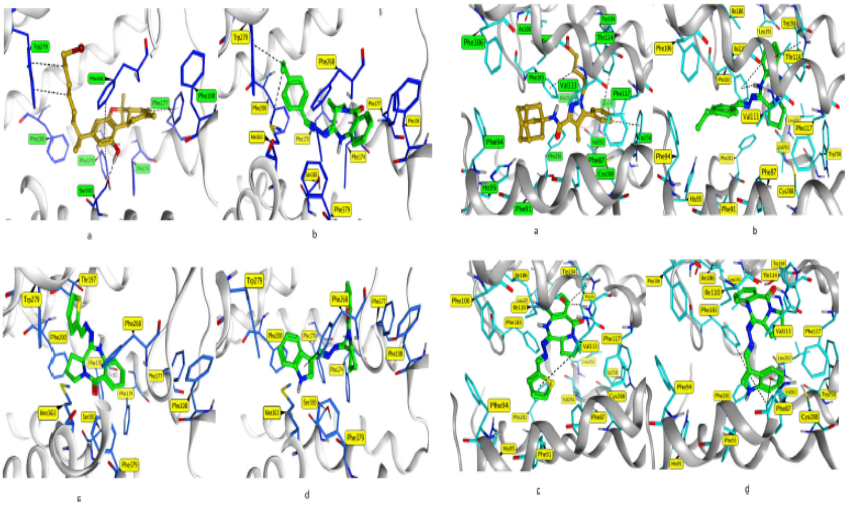

Fig. 2 Binding modes of selected compounds into CB1 orthosteric-binding pocket. (a) Native ligand **AM11542** (yellow sticks) **(b), (c)** and **(d) 4b, 4g**, and **4h** (green sticks), respectively. Key amino acid residues shown as blue sticks; non-Carbon atoms are colored by element. Settled intermolecular interactions (black dotted lines). Some amino acids were hidden for clarity

Fig. 3 Binding modes of selected compounds into CB2 orthosteric-binding pocket. (a) Native ligand **AM10257** (yellow sticks), **(b), (c)** and **(d) 4b, 4g,** and **4h** (green sticks), respectively. Key amino acid residues shown as cyan sticks; non-Carbon atoms are colored by element. Settled intermolecular interactions (black dotted lines). Some amino acids were hidden for clarity

ACTIVITY

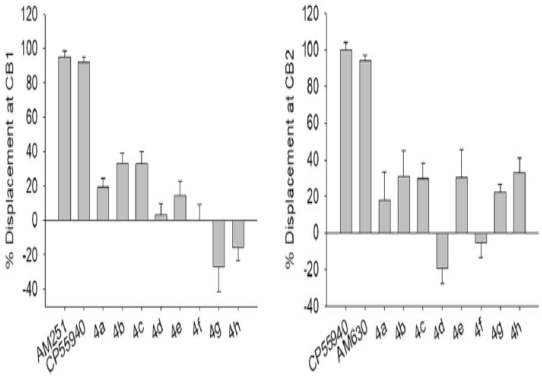

Fig. 4 Binding affinities of compounds 4a–h toward CB1 and CB2

CONCLUSION

This study highlights the design and synthesis of several (S,E)- 11-[2-(arylmethylene)hydrazono]-PBD derivatives through a structure-based rational design using a multi-step synthesis approach to establish potential clusters of selective CB2 ligands. Beginning with computer-based docking studies, calculation of ADMET, and physicochemical properties, considering the calculation of BBB filter and LogBB, we prepared a series of PBD analogs as potential CB2 ligands and tested their binding affinities toward CB1/CB2.

REFERENCES

1. Mingle, D., Ospanov, M., Radwan, M.O. *et al.* First in class (*S,E*)-11-[2-(arylmethylene)hydrazono]-PBD analogs as selective CB2 modulators targeting neurodegenerative disorders. *Med Chem Res* (2020). https://doi.org/10.1007/s00044-020-02640-2

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