POSTER PRESENTATION



Open Access

Discovery of novel TLR modulators by Molecular Modeling and Virtual Screening

Manuela S Murgueitio^{1*}, Sandra Santos-Sierra², Gerhard Wolber¹

From 7th German Conference on Chemoinformatics: 25 CIC-Workshop Goslar, Germany. 6-8 November 2011

Toll-like receptors (TLRs) play a crucial role in the onset of innate immunity by distinguishing between endogenous and pathogen-associated molecular patterns. TLR2, in cooperation with TLR1 and TLR6, recognizes several microbial components such as lipoteichoic acids and lipoproteins [1]. Toll-like receptors have been broadly reported to contribute to several inflammatory chronic diseases and autoimmune diseases [2]. In this study we aim to discover new TLR2 modulating agents through computer-aided drug design.

Based on recently identified synthetic TLR2 agonists [3] and antagonists [4], a shape and chemical-feature based similarity search was performed against a library of 260.071 compounds provided by the National Cancer Institute (NCI) [5]. This led to several virtual hits, which were tested *in vitro* in a cell-based assay. Several compounds with biological activity on TLR2 signaling in general and TLR1 signaling specifically were identified.

To further optimize these biologically validated virtual hits, molecular interaction fields (MIFs) for the dimerization of TLR2 and TLR1 were developed. Featurebased MIFs allowed for the manual creation of virtual compounds that fulfill an optimized interaction pattern, which led to a 3D pharmacophore that was used for a second virtual screening to select compounds for biological testing.

Author details

¹Pharmaceutical Chemistry, Institute of Pharmacy, Freie Universität Berlin, Berlin, Berlin,14195, Germany. ²Institute of Biochemical Pharmacology, Medizinische Universität Innsbruck, A-6020, Austria.

Published: 1 May 2012

* Correspondence: m.murgueitio@fu-berlin.de

¹Pharmaceutical Chemistry, Institute of Pharmacy, Freie Universität Berlin, Berlin, Berlin, 14195, Germany

Full list of author information is available at the end of the article

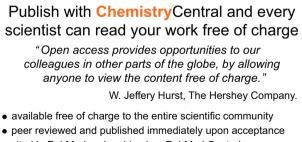


References

- Akira S, Takeda K: Toll-like Receptor Signalling. Nat Rev Immunol 2004, 4(7):499-511.
- Kawai T, Akira S: The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors. Nat Rev Immunol 2010, 11(5):373-384.
- Guan Y, et al: Identification of Novel Synthetic Toll-like Receptor 2 Agonists by High Throughput Screening. J Biol Chem 2010, 258(31):23755-23762.
- Zhou S, et al: Discovery of a novel TLR2 signaling inhibitor with anti-viral activity. Antiviral Res 2010, 87(3):295-306.
- 5. [http://cactus.nci.nih.gov/download/nci/].

doi:10.1186/1758-2946-4-S1-P58

Cite this article as: Murgueitio *et al.*: Discovery of novel TLR modulators by Molecular Modeling and Virtual Screening. *Journal of Cheminformatics* 2012 4(Suppl 1):P58.



ChemistryCentral

- cited in PubMed and archived on PubMed Central
- yours you keep the copyright

Submit your manuscript here: http://www.chemistrycentral.com/manuscript/

© 2012 Murgueitio et al; licensee BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.