Hesham Haffez et al., Med chem 2015, 5:10
http://dx.doi.org/10.4172/2161-0444.C1.015

OMICS International
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4th International Conference on
Medicinal Chemistry & Computer Aided Drug Designing
November 02-04, 2015 Atlanta, USA

Investigating the molecular interactions between novel synthetic retinoids and the ligand-binding domains of retinoic acid receptors

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All-Trans Retinoic Acid (ATRA) is widely used to direct differentiation of cultured stem cells and pluripotent Embryonal Carcinoma (ECs) stem cell lines into neuronal cells. EC23 and EC19 are synthetic analogues of Retinoic Acid (RA) differing from each other with respect to the position of the carboxylic acid group. EC23 has been shown to be a more potent inducer of neuronal differentiation than either EC19 or ATRA. In order to investigate the molecular basis of the functional difference, binding assays to RA Receptors (RAR α, β and γ, respectively) and molecular modeling studies were performed. EC50 values for EC23 are generally lower than for EC19 or ATRA on RAR-α and-β, indicating a higher binding affinity and co-activator recruitment. *In silico* molecular docking studies confirmed these differences in binding interactions, and showed that the carboxylic acid group of EC23 in the para-substitution creates the best fit to the ligand binding site with minimal steric hindrance, favoring the downstream binding of transcriptional co-activators. For EC19, the meta-substitution of the carboxylic acid group points away from a favorable interaction with Arg278 (RAR-γ) or create steric clashes with RAR-α/-β, resulting in interference with downstream co-activator binding activity. In comparison, ATRA shows similar protein-ligand interactions to EC23, supporting the notion that ATRA and EC23 possess similar molecular activation mechanisms. This study was able to combine chemical structures, receptor binding assay and molecular docking tools to shed light on the reported biological activity of these synthetic retinoids.

Biography

Hesham Haffez has completed his Master's degree in 2011 from Pharmacy College, Helwan University, Cairo, Egypt. Now, he is pursuing his PhD degree in Medicinal Chemistry from Durham University, United Kingdom.

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