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ORIGINAL RESEARCH

Geometry optimization of steroid sulfatase inhibitors - the influence on the free binding energy with STS

Karolina Jagiello[1] · Anita Sosnowska[1] · Supratik Kar[2] · Sebastian Demkowicz[3] · Mateusz Daśko[3] · Jerzy Leszczynski[2] · Janusz Rachon[3] · Tomasz Puzyn[1]

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Abstract In the paper we review the application of two techniques (molecular mechanics and quantum mechanics) to study the influence of geometry optimization of the steroid sulfatase inhibitors on the values of descriptors coded their chemical structure and their free binding energy with the STS protein. We selected 22 STS-inhibitors and compared their structures optimized with MM+, PM7 and DFT B3LYP/6–31++G* approaches considering separately the bond lengths, angles, dihedral angles and total energies. We proved that different minimum energy conformers could be generated depending on the choice of the optimization method. However, the results indicated that selection of the geometry optimization method did not affect the optimal STS inhibitor coordinates, and hence the values of molecular descriptors which describe the 3D structure of the molecule. To study the interaction pattern of the STS inhibitors (optimized using different methods) with the target receptor we applied two strategies: AutoDock and PathDock. The docking studies point out that selection of software to docking simulation is one of the crucial factors determining the binding mode of STS inhibitors with their molecular target. Other factor is related to the ligand orientation in the binding pocket. Finally, obtained results indicate that MM+ and PM7 methods (faster and less expensive) could be successfully employed to geometry optimization of the STS inhibitors before their docking procedure as well as for molecular descriptors calculations.

Keywords Steroid sulfatase inhibitors · Geometry optimization · Molecular docking · Molecular mechanics · Quantum mechanics

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✉ Tomasz Puzyn
t.puzyn@qsar.eu.org

[1] Laboratory of Environmental Chemometrics, Faculty of Chemistry, University of Gdansk, Wita Stwosza 63, 80-308 Gdansk, Poland

[2] Interdisciplinary Nanotoxicity Center, Department of Chemistry and Biochemistry, Jackson State University, 1400 JR Lynch Street, Jackson, MS 39217-0510, USA

[3] Department of Organic Chemistry, Chemical Faculty, Gdansk University of Technology, Narutowicza 11/12, 80-233 Gdansk, Poland

Introduction

Over the past decades, numerous reports have suggested that the biologically active hormone precursors may affect on cellular proliferation in various cancers [1]. These compounds (including androgens and estrogens) play an important role in the development of many diseases, such as hormone-dependent breast cancer (HDBC) [1]. One approach for treatment of the HDBC involves inhibitors of enzymes responsible for the biosynthesis of estrogens in peripheral tissues, e.g., steroid sulfatase (STS) [1]. The STS catalyses the hydrolysis reaction of steroid sulphates to their active forms and therefore plays a crucial role in the formation of biologically active hormones. The STS hydrolyses, among other, estrone sulfate (E1S) and dehydroepiandrosteronesulfate (DHEAS) into estrone (E1) and dehydroepiandrosterone (DHEA), respectively. The detailed studies have shown that E1 and DHEA can act as precursors for the formation of the estrogenic steroids estradiol (E2) and androstenediol (Adiol) [2]. Furthermore, the wide distribution of the STS in various tissues indicates that the STS enzyme is involved in numerous physiological and pathological conditions [3].

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