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To the 1. Dzial Obslugi Rady ds. Nauki I Doktorantow of the Medical University of Warsaw and 2. Ecole doctorale de l'Institut Polytechnique de Paris (ED 626)

Evaluation report on the thesis submitted by Ms Anna Mazurek, for her PhD at the Medical University of Warsaw and at the Institut Polytechnique de Paris

The thesis presented by Ms Anna Mazurek is entitled "a study of selected endocrine disrupting chemicals and their binding to host molecules with molecular modeling" The work was carried out under the direction of Prof. Thomas Simonson, Ecole Polytechnique and Prof. Lucasz Szeleszczuk, Medical University of Warsaw.

The first part of the manuscript consists in a short introduction where Ms Anna Mazurek briefly presents the different molecular systems studied during the thesis. She then describes the different force-fields (polarizable AMOEBA and classical additive CHARMM and AMBER) and simulation methods (MD, MMGBSA and DFT) used for her studies. Ms Anna Mazurek then outlines the results obtained that are then discussed and put into perspective with relevance. This part is particularly enjoyable to read, very well written and documented. There are a total of 10 publications/manuscripts and 2 review articles which is

The first manuscript describes a successful use of the AMOEBA Force-field to derive force field parameters for selected EDCs (estradiol, progesterone, bisphenol A) and β-Cyclodextrin. The results are compared with quantum mechanics (QM) data and CHARMM FF. The choice of the AMOEBA force-field is clearly appropriate for modeling these complex systems. The paper is completed by an analysis of a 10ns MD trajectory of the ER/Estradiol complex. The first manuscript is currently under evaluation in J Comput Chem.

The second publication describes the determination of the crystal structure of the estradiol / β-cyclodextrin complex. Various approaches were conducted to achieve both crystalline and amorphous systems. The complex was analyzed using a range of experimental techniques such as SCXRD, PXRD, 13C CP MAS ssNMR, FT-IR, TGA, DSC, Cryo-SEM, as well as molecular modelling approaches like periodic DFT calculations and NMR parameters calculation. The second paper has been published in Molecules in 2023.

The third publication describes the analysis of the Estradiol-β-cyclodextrin complex in an aqueous solution with different techniques. HRMS was used to analyze the structure of the complex and determine its molar ratio. The phase solubility studies provided the complex stability constant, which enabled the calculation of the experimental ΔG Gibbs free energy of the EST-βCD complex. The system was subjected to DFT and semi-empirical computational

approaches using Gaussian. The impact of different computational QM-based parameters (functional, water models etc) has been evaluated on the energy and thermodynamic properties prediction. The third paper has been published in J Mol Struct in 2024.

Overall, the amount of work produced is admirable. The candidate has successfully applied a wide range of computational techniques (DFT, polarizable MD, classical MD) on very challenging systems. The results obtained are discussed with relevance, which demonstrates the good scientific maturity of Ms Anna Mazurek. The work has resulted in 2 major publications (plus one under review), 2 review articles and 7 additional publications. Ms Anna Mazurek is the first author of 9 of them which is outstanding.

In conclusion, the submitted thesis has already resulted in 2 published scientific articles and 2 reviews in international journals completed by 7 additional publications, which testifies to an excellent thesis work. The writing skills and discussions of the results highlight the very good scientific maturity of the candidate, which fully justifies that Ms Anna Mazurek defends her doctoral thesis at Institut Polytechnique de Paris and at Medical University of Warsaw on the proposed date.

Paris, the 31st of july, 2024

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