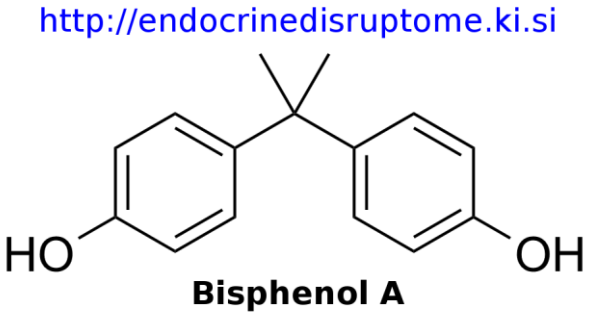
An Open Source Prediction Tool for Assessing Endocrine Disruption Potential through Nuclear Receptors Binding

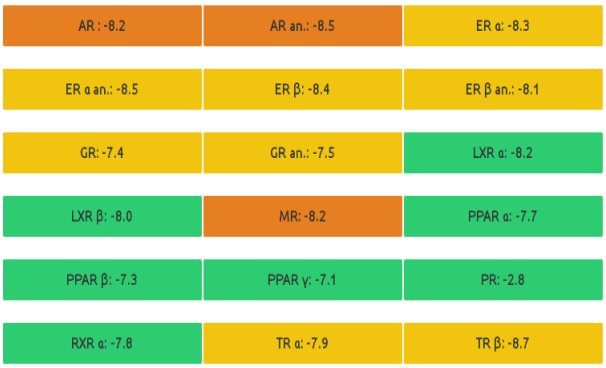
Katra Kolšek,[1,2] Janez Mavri,[2] Marija Sollner Dolenc,[1] Stanislav Gobec[1] and Samo Turk[3]

[1]*Faculty of Pharmacy, University of Ljubljana, Aškerčeva 7, 1000 Ljubljana, Slovenia*

[2]*Laboratory for Biocomputing and Bioinformatics, National Institute of Chemistry, Hajdrihova 19, 1000 Ljubljana, Slovenia*

[3]*BioMed X Innovation Center, Im Neuenheimer Feld 583, 69120 Heidelberg, Germany*





Endocrine disrupting chemicals (EDCs) are substances which can interfere with the production, release, transport, metabolism, binding, action, or elimination of the natural hormone in both humans and wildlife. A wide range of substances were identified to cause endocrine disruption, ranging from manmade chemicals, including pharmaceuticals, DDT and other pesticides, bisphenol A, and plasticizers such as phthalates, to natural chemicals for instance phytoestrogens [1]. These EDCs can be serious health threat by leading and/or contributing to major diseases [2]. Therefore identification and safety assessment of EDCs is at most utter importance [3].

Traditionally QSAR was used for prediction of endocrine disrupting potential of chemicals. Although QSAR can be very accurate it has its limitations especially because it is mostly limited to structurally related compounds [4]. Our aim was to develop a method that would work on any type of chemical and that would be well validated. We chose 14 nuclear receptors and more than 100 crystal structures of those receptors. Additionally we selected up to 600 active compounds for each receptor and generated up to 30,000 decoys (compounds assumed to be inactive). We used all this data to check the performance of all the crystal structures. The results enabled us to finally select 1 or 2 structures per receptor with the best results.

All data was then integrated in DoTS (Docking interface for Target Systems) which is an open source web platform that enables docking of chemicals to multiple structures at once. DoTS with integrated best performing crystal structures of nuclear receptors forms Endocrine Disruptome.

DoTS source code is available on GitHub (https://github.com/katrakolsek/DoTS) and Endocrine Disruptome can be accessed via http://endocrinedisruptome.ki.si

[1] T. Colborn et al., *Environ Health Perspect*, **1993**, 101(5), 378-84.
[2] E. Diamanti-Kandarakis et al., *Endocr Rev*, **2009**, 30(4), 293-342
[3] Endocrine Disruptor Screening Program for the 21st Century. http://www.epa.gov/endo/pubs/edsp21_work_plan_summary%20_overview_final.pdf
[4] J. Devillers et al., *SAR QSAR Environ Res*, **2006,** 17(4), 393-412.