The 13th Edition of the Symposium
NEW TRENDS AND STRATEGIES IN THE CHEMISTRY OF ADVANCED MATERIALS WITH RELEVANCE IN BIOLOGICAL SYSTEMS, TECHNIQUE AND ENVIRONMENTAL PROTECTION
ONLINE EVENT, October 07 -08, 2021 Timisoara, ROMANIA

EXPLORATION OF MAO-B INHIBITORS AS POTENTIAL ANTI-DIABETIC DRUGS

Daniela ISTRATE*, Luminița CRIȘAN, Alina BORA

"Coriolan Drăgulescu" Institute of Chemistry, 24 Mihai Viteazu, 300223 Timișoara, Romania; e-mail: istrate.dana@acad-icht.tm.edu.ro

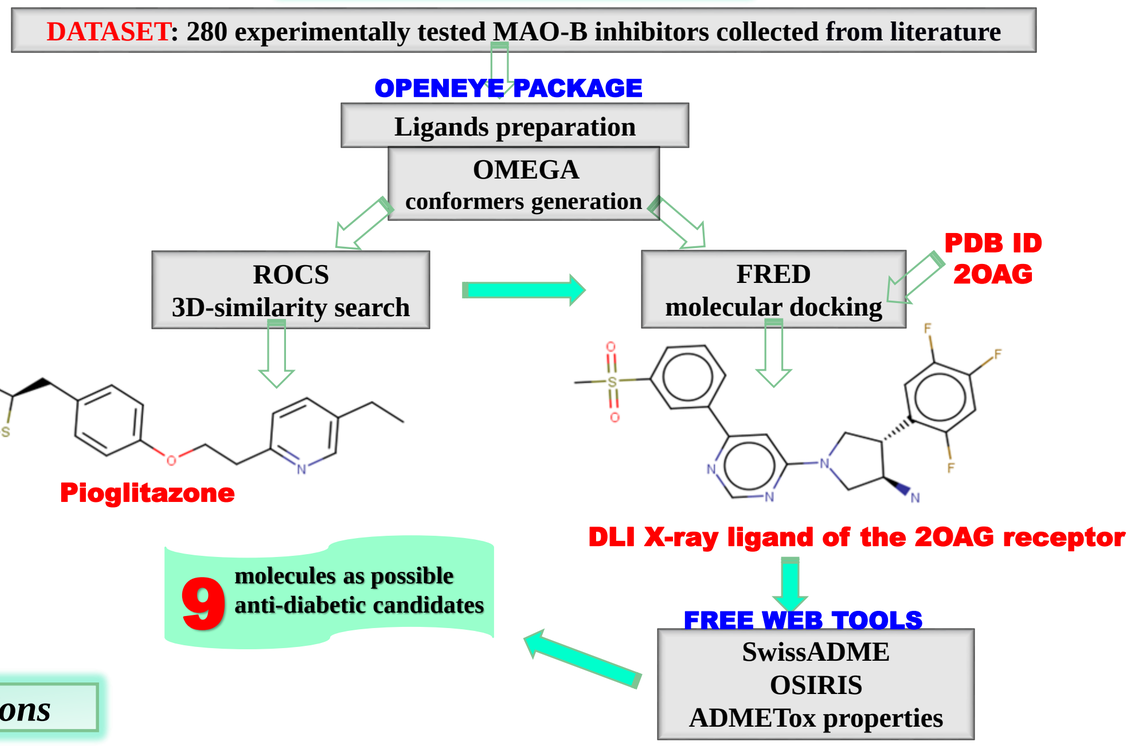
Overview

In recent years, an alarming increase in people with diabetes mellitus type 2 (T2DM), has been monitored. This disease affects also children and teens. Diabetes worsens over time, so there is a stringent need to develop new efficient therapy, adequate preventive measures and a new medicine with an improved profile and fewer side-effects to control the illness.
Pioglitazone (a diabetes drug of thiazolidinedione-type, also called "glitazones") is used adjunctively with diet and exercise to normalize glycemic levels in adults with type 2 diabetes mellitus.

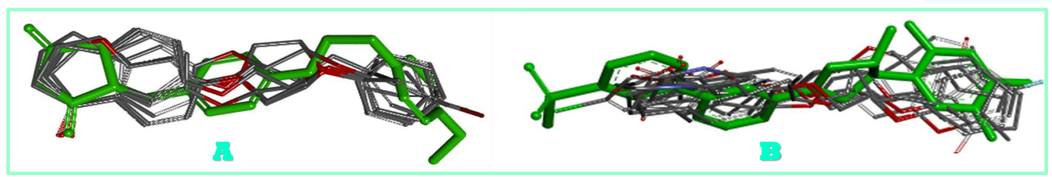
Aim: The commercial drug, pioglitazone, a specific inhibitor of human monoamine oxidase B (MAO-B), was used as a reference molecule to search a compiled set of 280 experimentally tested MAO-B inhibitors and select new compounds with potential anti-diabetic effects.

Methods: To reach the goal, 3D similarity search, toxicity related risks profiles, and ADME parameters were applied. According to ROCS similarity coefficients, toxicity and ADME profiles, nine MAO-B inhibitors were prioritized and further analyzed by molecular docking in the active site of dipeptidyl peptidase 4 enzyme (PDB ID: 2OAG), which is related to the pathophysiology of T2DM.

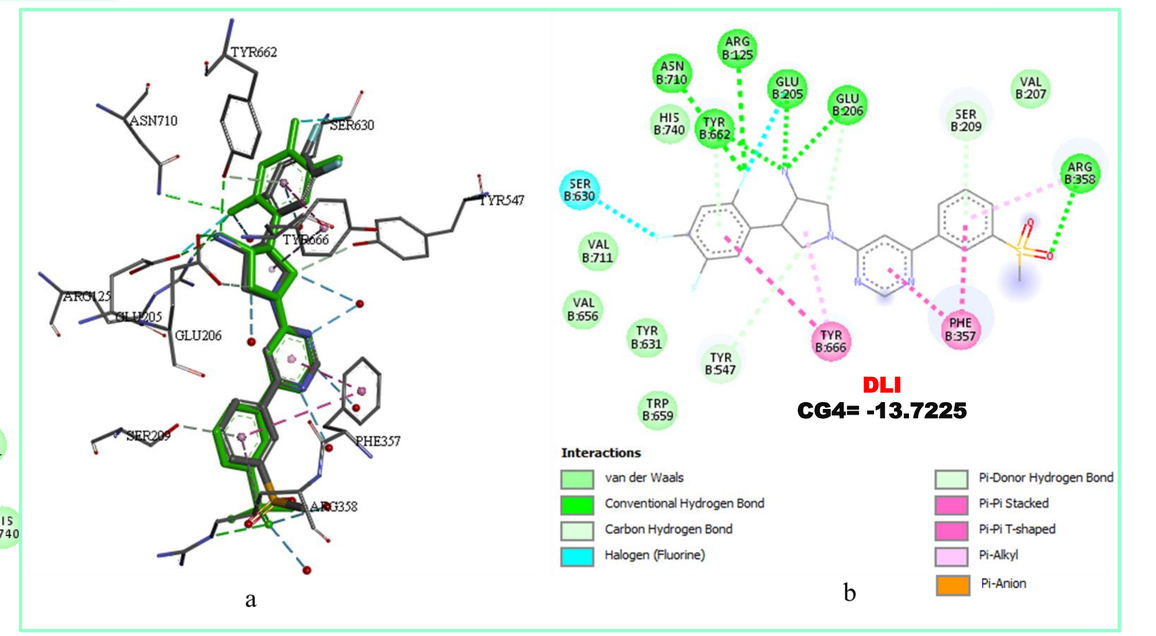
Methodology



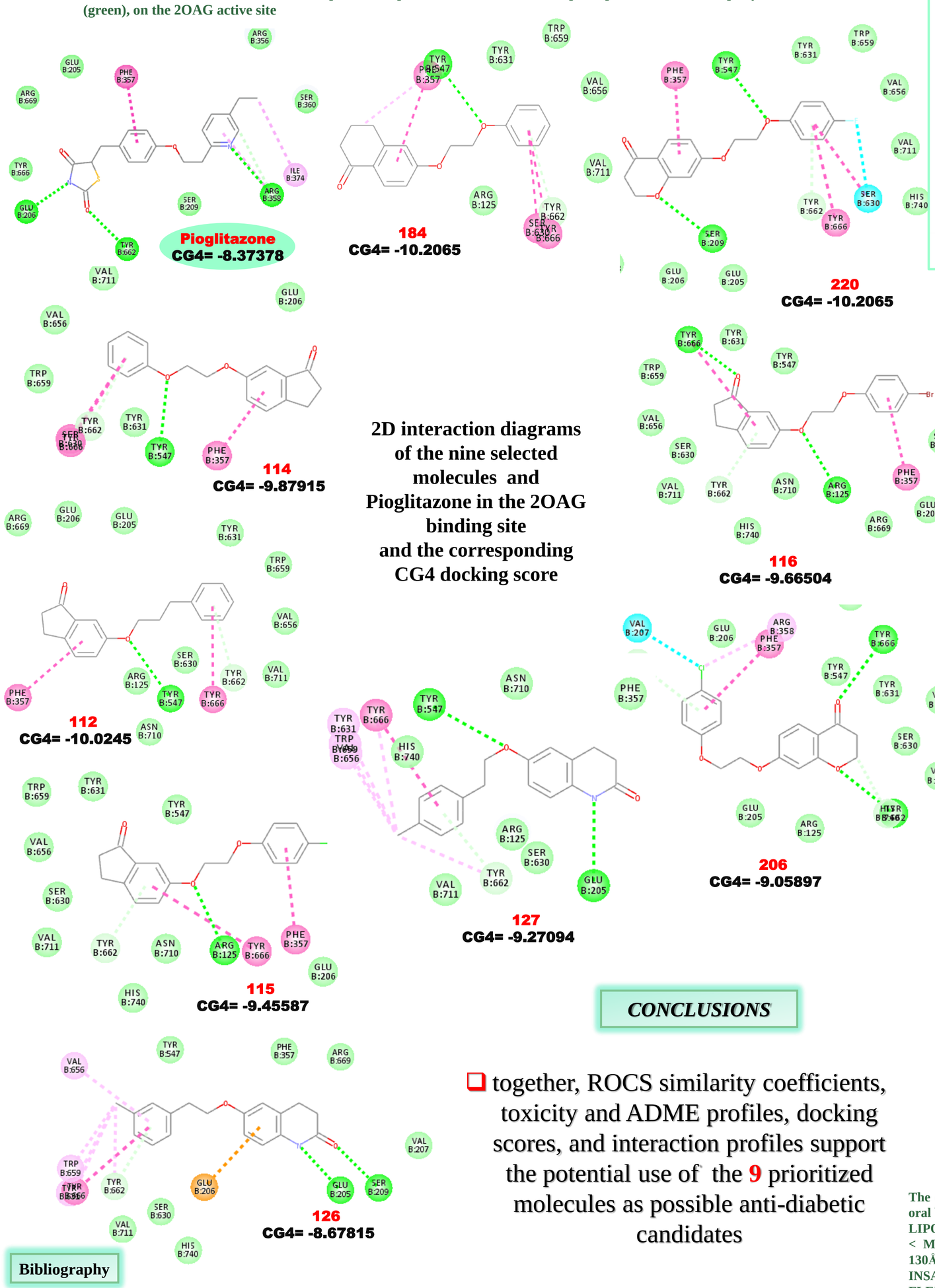
Results and Discussions



A - ROCS overly of the top ten MAO-B inhibitors (dark grey) against the Pioglitazone query (green) ordered by TanimotoCombo; B - the best docked poses of top ten MAO-B inhibitors superimposed on the DLI query (green), on the 2OAG active site



The 3D (a) and 2D (b) protein-ligand interaction of DLI with 2OAG receptor active site; the DLI X-ray structure is depicted in dark grey and the re-docked pose of DLI is shown in green (the RMSD value of 0.861 validated the docking protocol quality)

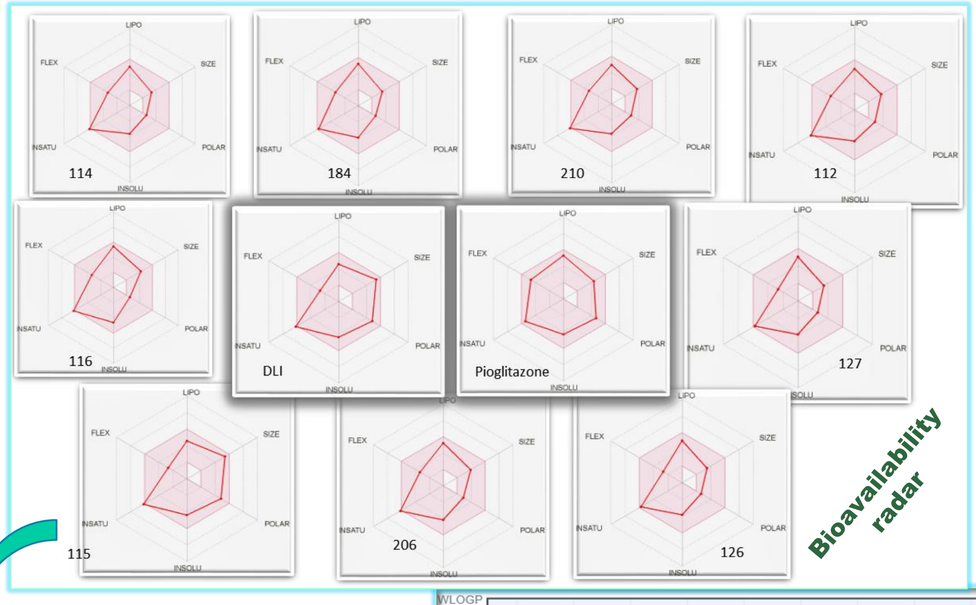


2D interaction diagrams of the nine selected molecules and Pioglitazone in the 2OAG binding site and the corresponding CG4 docking score

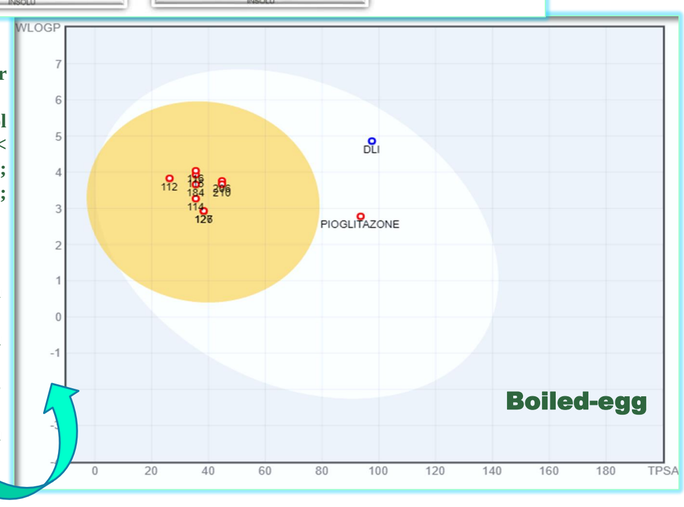
Toxicity related risks and pharmaceutical profiles of the first nine MAO-B inhibitors

ID Molecule	Toxicity risk*				MW	RBN	MR	TPSA	XLOGP3	WLOGP	GI absorption	BBB permeant	Role of Five	LogS (ESOL)	Fraction Csp3
	M	T	I	RE											
184	●	●	●	●	282.33	5	81.61	35.53	3.66	3.66	High	Yes	0	-3.99	0.28
210	●	●	●	●	302.3	5	78.28	44.76	3.11	3.67	High	Yes	0	-3.75	0.24
112	●	●	●	●	266.33	5	80.08	26.3	3.95	3.83	High	Yes	0	-4.09	0.28
114	●	●	●	●	268.31	5	76.8	35.53	3.3	3.27	High	Yes	0	-3.70	0.24
116	●	●	●	●	347.2	5	84.5	35.53	3.99	4.04	High	Yes	0	-4.60	0.24
115	●	●	●	●	302.75	5	81.81	35.53	3.93	3.93	High	Yes	0	-4.29	0.24
127	●	●	●	●	281.35	4	87.29	38.33	3.36	2.93	High	Yes	0	-3.86	0.28
206	●	●	●	●	318.75	5	83.34	44.76	3.64	3.76	High	Yes	0	-4.18	0.24
126	●	●	●	●	281.35	4	87.29	38.33	3.36	2.93	High	Yes	0	-3.86	0.28
Pioglita-zone	●	●	●	●	356.44	7	102.17	93.59	3.75	2.78	High	No	0	-4.31	0.32
X-ray Ligand DLI	●	●	●	●	448.46	4	112.27	97.56	2.51	4.86	High	No	0	-4.37	0.24

*M-Mutagenic; T-Tumorigenic; I-Irritant; RE-Reproductive Effective; ● - indicate drug-like conforming behavior; ●- designate properties with high risks of undesired effects like reproductive effect; MW: Molecular weight; RBN: Number of rotatable bonds; MR: Molar Refractivity; TPSA: Topological Polar Surface Area; XLOGP3; WLOGP; GI absorption: Gastrointestinal absorption; BBB permanent: Blood-Brain Barrier permeate; Role of Five: Number of violations of Lipinski's rule of five; LogS(ESOL) – Insolubility (Class solubility: moderately < -4, soluble <-2); Fraction Csp3 – Insaturation.



The colored zone is a suitable physicochemical space for oral bioavailability.
LIPO(Lipophilicity): -0.7< XLOGP3< +5; SIZE: 150g/mol < MW < 500g/mol; POLAR(Polarity): 20Å < TPSA < 130Å; INSOLU(Insolubility): 0 < Log S(ESOL) < 6; INSATU(Insaturation): 0.25 < Fraction Csp3 < 1; FLEX(Flexibility): 0 < Num.rotatable bond < 9



- **The molecules plotted in the yellow ellipse have a high probability of a good BBB crossing;**
- **The molecules plotted in the white ellipse have a high probability of good HIA;**
- **The red dots ● indicate molecules predicted as non-substrate of P-glycoprotein (PGP-);**
- **The blue dots ● indicate molecules predicted as a substrate of P-glycoprotein (PGP +);**

CONCLUSIONS

- together, ROCS similarity coefficients, toxicity and ADME profiles, docking scores, and interaction profiles support the potential use of the **9** prioritized molecules as possible anti-diabetic candidates

This study was financially supported by the Project No. 1.2/2021 of the "Coriolan Dragulescu" Institute of Chemistry, Timisioara. The authors are indebted to OpenEye Ltd for providing us academic license (dr. Simona Funar-Timofei laboratory).

Bibliography

Binda C., Aldeco M., Geldenhuys W.J., Tortorici M., Mattevi M., Edmondson D.E., ACS Med. Chem. Lett. 3 (2012) 39−42.
Backes B.J., Longenecker K., Hamilton G.L., Stewart K., Lai C., Kopecka H., von Geldern T.W., Madar D.J., Pei Z., Lubben T.H., Zinker B.A., Tian Z., Ballaron S.J., Stashko M.A., Mika A.K., Beno D.W., Kempf-Grote A.J., Black-Schaefer C., Sham H.L., Trevillyan J.M., Bioorg Med Chem Lett 17 (2007) 2005-2012.
MarvinSketch (2020) version 20.19.0 ChemAxon. http://www. chemaxon.com.
https://www.rcsb.org/structure/4A79
https://www.rcsb.org/structure/2OAG
MakeReceptor Version 3.5.0.4 OpenEye Scientific Software Inc. Santa Fe NM, USA www.eyesopen.com.
Schrödinger Release 2021-2: Maestro Version 12.8.117 for acdemic used only.
OMEGA Version 4.0.0.4 OpenEye Scientific Software Inc. Santa Fe NM, USA www.eyesopen.com.
Hawkins P.C.D., Nicholls A., J. Chem. Inf. Model. 52 (2012) 2919-2936.
ROCS Version 3.4.0.4 OpenEye Scientific Software Inc Santa Fe NM, USA www.eyesopencom.
Rush T.S., Grant, J.A., Mosyak L., Nicholls A., J. Med. Chem. 2005, 48, 1489–1495.
Hawkins P.C.D., Skillman A.G., Nicholls A., J. Med. Chem. 50 (2007) 74-82.
FRED Version 3.5.0.4 OpenEye Scientific Software Inc. Santa Fe NM, USA www.eyesopen.com.
McGann M., J. Chem. Inf. Model. 51 (2011) 578-596.
Osiris. Osiris Property Explorer. Available online: http://www.organic-chemistry.org/prog/peo/.
Daina A., Michielin O., Zoete V., Sci. Rep. 7 (2017) 42717.