MICROWAVE-ASSISTED SYNTHESIS AND *IN SILICO* ADMET PROPERTIS OF BILE ACIDS LACTONES

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INTRODUCTION:

In modern synthetic chemistry, alternative energy sources are increasingly relevant, and one of them are microwaves. The use of microwave energy is considered an acceptable technique in the principles of "green chemistry", but it is also a useful approach to syntheses because it enables more efficient and selective reactions. Baeyer-Villiger oxidation is the most commonly used method for converting ketones to lactones by oxidizing agents. In our previous work, we synthesized a series of bile acids with lactone function in the steroid skeleton and examined their hydrophobicity and self-association properties (micellization).[1] The aim of this work is to modify the conventional method of Baeyer-Villiger oxidation used for synthesis of lactones (Figure 1). We performed the reaction in a Discover Bench Mate microwave reactor (CEM), in a closed system under pressure, with significantly shortened duration of the reaction. We tested *in silico* ADMET properties of compounds **1–4**. *In silico* ADMET profiles were predicted using SwissADME and ProTox-II online tools.

RESULTS:

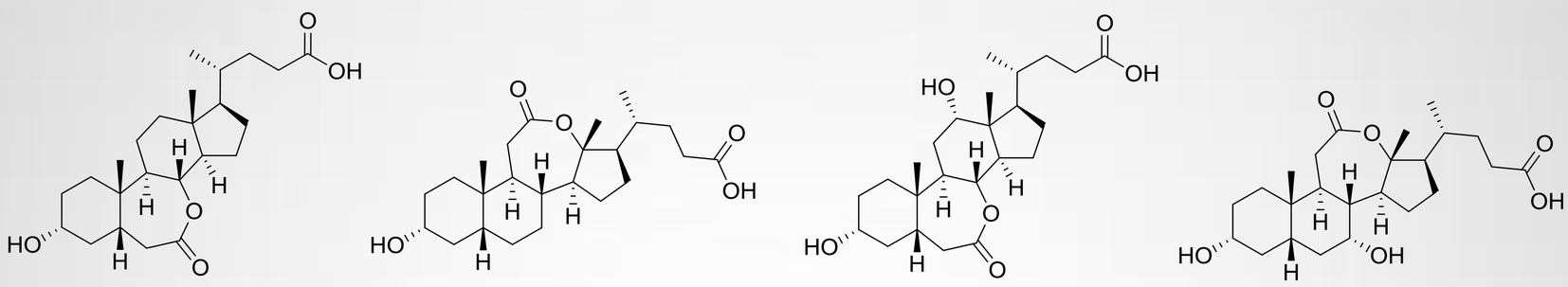

Figure 1. Structures of compounds **1–4**.

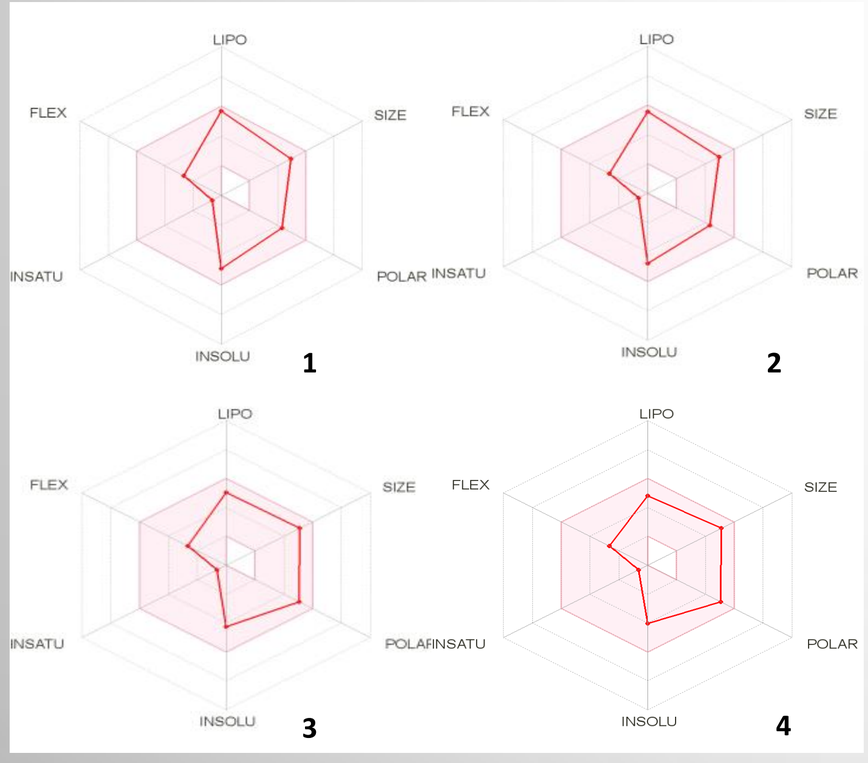

Figure 2. SwissADME The Bioavailability Radars of synthesized compounds. The pink area represents the optimal range for each properties.

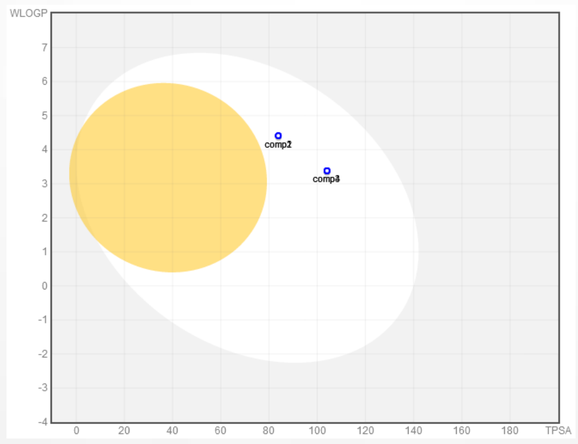

Figure 3. SwissADME the BOILED-Egg predictive model for intestine and brain permeation of synthesized compounds 1-4.

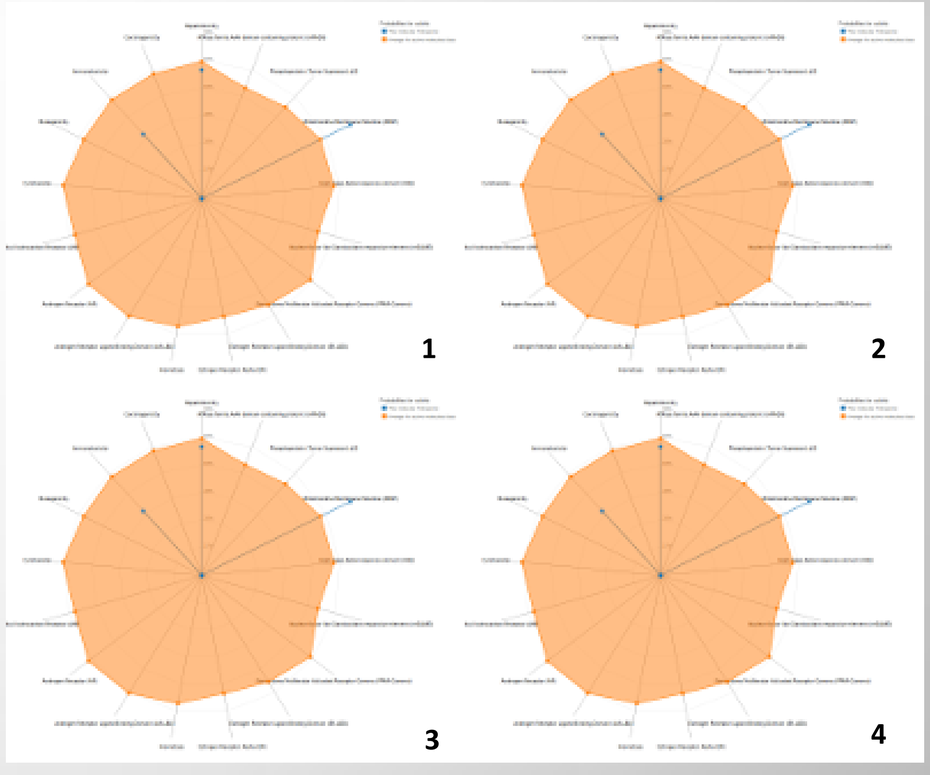

Figure 4. The toxicity radar chart of synthesized compounds

Table 1. SwissADME Calculate molecular properties

Compounds	MF	MW	HBD	HBA	LogP	nrotb	TPSA	MR	No rings
1	$C_{25}H_{40}O_5$	420.29	2	5	3.87	4	83.83	112.72	4
2	$C_{25}H_{40}O_5$	420.29	2	5	3.81	4	83.83	113.2	4
3	$C_{25}H_{40}O_6$	436.59	3	6	3.00	4	104.06	113.89	4
4	$C_{25}H_{40}O_6$	436.59	3	6	2.95	4	104.06	114.18	4

MF: molecular formula; MW: molecular weight ($gmol^{-1}$; <500); HBD: Num. H-bond donors (<5); HBA: Num. H-bond Acceptors (<10); LogP: logarithm of compound partition coefficient between n-octanol and water (<5); nrotb: number of rotatable bonds (<12); TPSA: topological polar surface area (Å2; <140); MR: molar refractivity

The Baeyer-Villiger oxidation of oxo derivatives of bile acids performed in a microwave reactor is up to 300 times faster compared to the same reaction that use conventional methods of heating. The syntheses were performed on a small scale, using the pressure of 20 mbar and temperature 120 °C. In the case of compound 2, the yield is increased. Based on the values of molecular descriptors of oral radar for bioavailability (Figure 2.), it can be seen that all tested compounds meet all the stated empirical criteria without deviations, ie. to fulfill the theoretical precondition for adequate bioavailability in the organism, and thus to possess appropriate biological potential. The BOILED-Egg model (Figure 3.) indicated that these compounds could be absorbable by the human intestine but couldn't penetrate the brain barrier. Toxicity prediction results (Figure 4.) showed that compounds **1–4** do not possess mutagenic, carcinogenic and cytotoxic potential. *In silico* ADMET analysis showed that all synthesized lactone derivatives of bile acids (1–4) possess desirable drug-like properties.

References: [1] Poša M., Tepavčević V., Grbović Lj., Mikulić M., Pavlović K., *Journal of Physical Organic Chemistry* **34** (2021) 4133.

The authors acknowledge financial support of the Ministry of Education, Science and Technological Development of the Republic of Serbia (Grant No. 451-03-68/2020-14/ 200125)