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In silico ADME and drug-likeness evaluation of a series of cytotoxic polyprenylated acylphloroglucinols, isolated from *Hypericum annulatum* Morris subsp. *annulatum*

Y. Ilieva[1, 2], Z. Kokanova-Nedialkova[1], P. Nedialkov[1], G. Momekov[2]*

[1] *Department of Pharmacognosy, Faculty of Pharmacy, Medical University of Sofia, Bulgaria*
[2] *Department of Pharmacology, Pharmacotherapy and Toxicology, Faculty of Pharmacy, Medical University of Sofia, Bulgaria*

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Eight polyprenylated acylphloroglucinols, isolated from *Hypericum annulatum* Moris subsp. *annulatum,* and characterized as cytotoxic agents against human cancer cells, were subjected to computational ADME, pharmacokinetic and drug-likeness evaluation, using the web tool SwissADME. The physicochemical parameters assessment shows significant lipophilicity, and low water solubility. The compounds are expected to have good oral bioavailability, and with the only exception of hyperatomarin are not considered to be P-glycoprotein substrates. The evaluation of their inhibitory effects profile in several cytochrome P450 isoforms indicate that all of them as CYP3A4 inhibitors, whereas the expected modulatory effects on other CYPs varied among the series. The drug-likeness evaluation employed five alternative rule-based filters and noteworthy all compounds complied with the Lipinski "rule of five". Taken together, the calculated ADME and pharmacokinetic parameters, give us reason to consider the polyprenylated acylphloroglucinols from *Hypericum annulatum* Moris subsp. *annulatum* as a perspective set of cytotoxic lead compounds for further more detailed oncopharmacological and toxicological evaluation.

Keywords: Polyprenylated acyl phloroglucinols, Anticancer agents, ADME, Drug-likeness.

INTRODUCTION

The exploration of the plant kingdom as a source of novel anticancer drugs comprises a research area of significant interest, driven by the clinical and commercial success of a variety of plant-derived drugs or their semisynthetic analogues, such as Vinca alkaloids, taxanes, epipodophyllotoxins, camptothecins, combretastatins, maytansionoids *etc*. [1, 2]. Moreover, the chemical diversity of the Plant Kingdom is an immense and generally unexplored source of structurally complex molecules, which virtually could not be generated in a chemical lab [1–3].

Among the numerous plant secondary metabolites the polyprenylated acyl phloroglucinols (PAP) comprise an important class of biologically active compounds, peculiar for the plants from the related families Hypericaceae and Clusiaceae (Guttiferae) [4, 5]. The complex substitution patterns involving different acyl and isoprenoid functionalizations, glycosylation, oxidation, or cyclization of the highly oxygenated phloroglucinol core structure affords the tremendous structural diversity of these fascinating compounds [4–7]. Not surprisingly, this chemical diversity is translated into pleiotropic pharmacological activities, incl. antibacterial, antiprotozoal, antifungal, psychotropic, anti-inflammatory, antiangiogenic, and noteworthy potent cytotoxicity against human cancer cell lines [8, 9].

Our natural phloroglucinol-based drug discovery program has been focused for years on Hypericum species characteristic for the Bulgarian flora [10, 11], and noteworthy on *Hypericum annulatum* Moris subsp. *annulatum* [12–15], an endemic species inhabiting Sardinia, the Balkan Peninsula, East Africa and Saudi Arabia [6, 16]. Phytochemical and bioactivity-guided fractionation has resulted in the identification and oncopharmacological evaluation of several potent cytotoxic agents from this plant [13–15]. Hyperatomarin (**1**), a bicyclic prenylated acylphloroglucinol is a very effective compound, capable of inhibiting the growth of cultured cancer cells and inducing apoptosis at very low micromo-

* To whom all correspondence should be sent:
E-mail: gmomekov@gmail.com

lar concentrations [14, 15]. More recently, a series of acylphloroglucinols (**2**–**8**) (Fig. 1) were isolated from the same plant and shown to exert cytotoxicity against human tumor cell lines [13].

The promising pharmacological activity however is not a solitary prerequisite for a successful pharmaceutical commercialization of a chemical entity, because it should be accompanied by suitable physicochemical and biopharmaceutical properties, translating in turn into the desired pharmacokinetic parameters [17]. As a high-throughput pre-screen aid in drug discovery a number of *in silico* approaches have been developed for prognosis and estimation of absorption, distribution, metabolism and elimination (ADME) profiles, and for assessment of the so-called drug-likeness, defined as a qualitative prediction of the feasibility for acceptable bioavailability and pharmacokinetics after oral intake [17–21]. The forerunner work of Lipinski *et al*. analysed a comprehensive number of orally active compounds and coined the notorious *Rule-of-five* as a merit of optimal range of the drug's physicochemical ranges to afford optimal pharmacokinetic behaviour after oral intake [22–24].

In order to elucidate the potential of the aforementioned series of prenylated acyl phloroglucinols for further development as antineoplastic agents we herein describe the computational analysis of their pharmacokinetic profile and drug-likeness, using a panel of filters, routinely utilized in the prescreen stage of drug development in the pharmaceutical companies.

EXPERIMENTAL

Target compounds and computational tools

The analysed compounds were isolated from the aerial parts of *Hypericum annulatum* Moris subsp. *annulatum*, collected during the flowering period. The detailed description of the extraction, isolation and identification of the tested compounds has been previously reported [13, 14]. Their structure was confirmed by means of spectral methods (UV, IR, ^{1}H- and ^{13}C-NMR, EI-MS) (Fig. 1, Table 1). The in silico ADMET screening and drug-likeness evaluation was performed using the free webtooll SwissADME, developed by the Swiss Institute of Bioinformatics, and freely available at http://www.swissadme.ch [20].

Hyperatomarin (**1**) is a bicyclic PAP, whereas the other compounds are monocyclic, aromatic PAPs. Compounds **4**–**7** contain a chroman ring system, which in case of **4** is fused with a cyclohexane

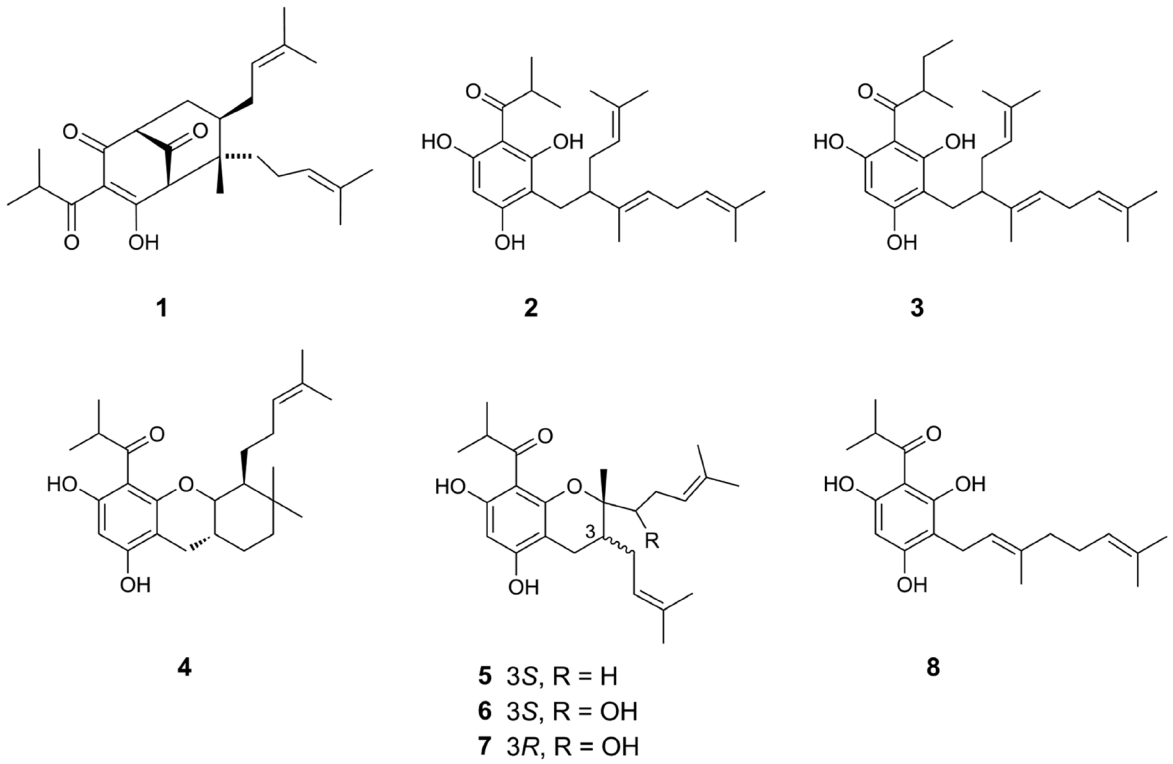

Fig. 1. Chemical structures of the target polyprenylated acylphloroglucinols from *Hypericum annulatum* Moris subsp. a*nnulatum.*

Table 1. Designation of the target compounds

Compound designation	Structure/nomenclature
1	(1R,5R,7R,8S)-4-Hydroxy-3-isobutyryl-8-methyl-7-(3-methyl-2-buten-1-yl)-8-(4-methyl-3-penten-1-yl) bicyclo[3.3.1]non-3-ene-2,9-dione
2	(*E*)-1-(3-(3,7-dimethyl-2-(3-methylbut-2-enyl) octa-3,6-dienyl)-2,4,6-trihydroxyphenyl)-2-methylpropan-1-one
3	(*E*)-1-(3-(3,7-dimethyl-2-(3-methylbut-2-enyl)octa-3,6-dienyl)-2,4,6-trihydroxyphenyl)-2-methylbutan-1-one
4	1-((4a*R*,9a*R*)-6,8-dihydroxy-3,3-dimethyl-4a-(4-methylpent-3-enyl)-2,3,4,4a,9,9a-hexahydro-1H-xanthen-5-yl)-2-methylpropan-1-one
5	1-[5,7-dihydroxy-2-methyl-3-(3-methyl-but-2-enyl)-2-(4-methyl-pent-3-enyl)-chroman-8-yl]-2-methyl-propan-1-one; hypercalyxone A
6*	1-((2*S*,3*S*)-5,7-dihydroxy-2-(1- hydroxy-4-methylpent-3-enyl)-2-methyl-3-(3-methylbut-2-enyl) chroman-8-yl)-2-methylpropan-1-one
7*	1-((2*S*,3*R*)-5,7-dihydroxy-2-(1-hydroxy-4-methylpent-3-enyl)-2-methyl-3-(3-methylbut-2- enyl) chroman-8-yl)-2-methylpropan-1-one
8	3-geranyl-1-(2′-methylpropanoyl)phloroglucinol

* Compounds 6 and 7 are OH-derivatives of **5** and are epimers.

ring. The agents **6** and **7** are hydroxylated derivatives of **5** and are epimers (Fig. 1).

Physiochemical properties and general computational methodology

The SMILES for each structure were generated by the structure file generator, available at the free online tool SwissADME web page. Using the web tool we calculated a number of simple molecular and physicochemical descriptors, such as the molecular weight (MW), molecular refractivity (MR), count of specific atom types and the topological polar surface area (TPSA), the latter proven as a useful descriptor in many models for estimation of membrane diffusion, ADME and pharmacokinetic behaviour. The lipophilicity was assessed by means of five alternative predictive models; i.e. XLOGP; WLOGP; MLOGP; SILICOS-IT, iLOGP, together with a consensus logP estimation, based on the average value of the different computational parameters [20, 25]. Conversely, the aqueous solubility was established, as well, using three alternative models [20].

ADME

The ADME/pharmacokinetics analysis aimed at estimation of core parameters such as gastro intestinal absorption, P-glycoprotein-mediated efflux, ability to penetrate the blood-brain barrier (BBB). Moreover, we analysed whether the target compounds are substrates of a battery of essential isoforms of the cytochrome P450 (CYP) family, namely CYP1A2, CYP2D6, CYP2C9, CYP2C19, and CYP3A4. To meet this objective the SwissADME tool is relying on a robust vector machine algorithm (SVM) with precisely cleaned comprehensive datasets of established inhibitors/non-inhibitors and substrates/non-substrates. The theoretic background, development and validation of these computational approaches have been described in detail elsewhere [20, 26].

Drug likeness estimation

The drug likeness analysis was carried out using the validated rules used as high-throughput screens filters in some of the leading pharmaceutical companies, as follows: Lipinski (*Pfizer*), Ghose (*Amgen*), Veber (*GSK*), Egan (*Pharmacia*) and Muegge (*Bayer*). The Abbott bioavailability score was calculated to predict the probability for a 10% oral bioavailability or Caco-2 diffusion. These filters have been developed to assess drug-likeness, i.e. to predict whether a chemical entity is likely to have useful pharmacokinetic properties, using calculations, based on parameters such as molecular weight, LogP, number of HPA and HBD [17–21]. Moreover the feasibility to explore the presented structures as starting scaffolds or lead compounds in a future synthetic drug discovery program was analysed using specific medicinal chemistry and lead-likeness filters [20].

RESULTS AND DISCUSSION

The basic physicochemical parameters are described in Table 2, whereas the lipophilicity and water solubility estimations are presented in Tables 3 and 4 respectively. Based on the calculated logP values all tested compounds proved to be lipophilic with consensus values ranging 4.25–5.98 (Table 3). These are considered as boundary values for most of the drug-likeness filters employed by the pharmaceutical industry. Conversely these findings were mirrored by the estimation of the water solubility showed that the target compounds are moderately to poorly soluble, depending both on the LogS estimation model and the tested compound (Table 4).

The main ADME parameters of the pharmacokinetic behaviour of the tested phloroglucinols are described in Table 5. With the only exception of compound **3** all agents are estimated to have high absorption in the gastrointestinal tract which is a highly favourable feature of a drug candidate, considering the undisputable advantages of the oral route of administration. With very few exceptions the phloroglucinols are not expected to act as inhibitors of CYP1A2, CYP2C19, CYP2D6, which mediate the biotransformation of a number of important classes of drugs [27]. All of the compounds from the tested series are expected to inhibit CYP3A4, which is a potentially disadvantageous feature, as this CYP isoform is implicated in the metabolism and elimination of the majority of clinically used drugs, such as calcium channel blockers, some statins, immunosuppressors, macrolides, atypical antipsychotics, among others [27, 31]. With the only exception of 6 and 7 the phloroglucinols are expected to act as CYP2C9 inhibitors, as well.

The computational data do not indicate the target compounds as capable of crossing the BBB. The latter feature is disadvantage if considering the possible CNS localization of malignant tumours or metastases thereof, but on the other hand it indicates low risk of CNS side effects, which are at least not impossible having into account the ability of PAP (including hyperatomarin, **1**) to modulate monoam-

Table 2. Basic physicochemical properties and computational descriptors of the tested compounds

Properties	**1**	**2**	**3**	**4**	**5**	**6**, **7**	**8**
Formula	$C_{25}H_{36}O_4$	$C_{25}H_{36}O_4$	$C_{26}H_{38}O_4$	$C_{25}H_{36}O_4$	$C_{25}H_{36}O_4$	$C_{25}H_{36}O_5$	$C_{20}H_{28}O_4$
Molecular weight	400.55 g/mol	400.55 g/mol	414.58 g/mol	400.55 g/mol	400.55 g/mol	416.55 g/mol	332.43 g/mol
Num. heavy atoms	29	29	30	29	29	30	24
Num. arom. heavy atoms	0	6	6	6	6	6	6
Fraction Csp3	0.64	0.48	0.50	0.64	0.56	0.56	0.45
Num. rotatable bonds	7	9	10	5	7	7	7
Num. H-bond acceptors	4	4	4	4	4	5	4
Num. H-bond donors	1	3	3	2	2	3	3
Molar Refractivity	118.55	123.16	127.97	119.28	121.22	122.38	99.60

Table 3. Lipophilicity of the tested compounds

Properties	**1**	**2**	**3**	**4**	**5**	**6**, **7**	**8**
Log $P_{o/w}$ (iLOGP)	4.01	4.17	4.09	3.36	3.88	3.71	2.80
Log $P_{o/w}$ (XLOGP3)	6.61	7.67	8.03	7.25	7.28	6.31	5.92
Log $P_{o/w}$ (WLOGP)	5.54	6.46	6.85	6.04	6.35	5.32	4.88
Log $P_{o/w}$ (MLOGP)	2.81	3.93	4.13	3.70	3.62	2.79	2.93
Log $P_{o/w}$ (SILICOS-IT)	5.80	6.35	6.78	5.60	6.30	5.54	4.73
Consensus Log $P_{o/w}$	4.95	5.72	5.98	5.19	5.49	4.73	4.25

Table 4. Water solubility prediction values, based on three alternative models [20, 25]

Properties	**1**	**2**	**3**	**4**	**5**	**6**, **7**	**8**
Log *S* (ESOL)	–6.03	–6.71	–6.96	–6.71	–6.60	–6.08	–5.35
Solubility	$3.78.10^{-4}$ mg/ml; $9.43.10^{-7}$ mol/l	$7.73.10^{-5}$ mg/ml; $1.93.10^{-7}$ mol/l	$4.57.10^{-5}$ mg/ml; $1.10.10^{-7}$ mol/l	$7.74.10^{-5}$ mg/ml; $1.93.10^{-7}$ mol/l	$1.00.10^{-4}$ mg/ml; $2.51.10^{-7}$ mol/l	$3.43.10^{-4}$ mg/ml; $8.24.10^{-7}$ mol/l	$1.47.10^{-3}$ mg/ml; $4.43.10^{-6}$ mol/l
Class	Poorly soluble	Poorly soluble	Poorly soluble	Poorly soluble	Poorly soluble	Poorly soluble	Moderately soluble
Log *S* (Ali)	–7.91	–9.14	–9.52	–8.48	–8.51	–7.93	–7.33
Solubility	$4.92.10^{-6}$ mg/ml; $1.23.10^{-8}$ mol/l	$2.88.10^{-7}$ mg/ml; $7.19.10^{-10}$ mol/l	$1.26.10^{-7}$ mg/ml; $3.04.10^{-10}$ mol/l	$1.34.10^{-6}$ mg/ml; $3.34.10^{-9}$ mol/l	$1.24.10^{-6}$ mg/ml; $3.11.10^{-9}$ mol/l	$4.94.10^{-6}$ mg/ml; $1.19.10^{-8}$ mol/l	$1.56.10^{-5}$ mg/ml; $4.71.10^{-8}$ mol/l
Class	Poorly soluble	Poorly soluble	Poorly soluble	Poorly soluble	Poorly soluble	Poorly soluble	Poorly soluble
Log *S* (SILICOS-IT)	–4.87	–4.83	–5.23	–5.37	–5.60	–4.65	–3.97
Solubility	$5.39.10^{-3}$ mg/ml; $1.35.10^{-5}$ mol/l	$5.86.10^{-3}$ mg/ml; $1.46.10^{-5}$ mol/l	$2.46.10^{-3}$ mg/ml; $5.93.10^{-6}$ mol/l	$1.72.10^{-3}$ mg/ml; $4.31.10^{-6}$ mol/l	$1.01.10^{-3}$ mg/ml; $2.51.10^{-6}$ mol/l	$9.24.10^{-3}$ mg/ml; $2.22.10^{-5}$ mol/l	$3.55.10^{-2}$ mg/ml; $1.07.10^{-4}$ mol/l
Class	Moderately soluble	Moderately soluble	Moderately soluble	Moderately soluble	Moderately soluble	Moderately soluble	Soluble

Table 5. Calculated ADME and pharmacokinetic parameters

Properties	**1**	**2**	**3**	**4**	**5**	**6**, **7**	**8**
GI absorption	High	High	Low	High	High	High	High
BBB permeant	No	No	No	No	No	No	No
P-gp substrate	Yes	No	No	No	No	No	No
CYP1A2 inhibitor	No	Yes	No	No	No	No	Yes
CYP2C19 inhibitor	Yes	No	No	No	No	No	No
CYP2C9 inhibitor	Yes	Yes	Yes	Yes	Yes	No	Yes
CYP2D6 inhibitor	Yes	No	No	No	No	No	No
CYP3A4 inhibitor	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Log K_p (skin permeation)	–4.05 cm/s	–3.30 cm/s	–3.13 cm/s	–3.60 cm/s	–3.57 cm/s	–4.36 cm/s	–4.12 cm/s

ine neurotransmission [8, 9, 28]. Another beneficial issue for all monocyclic PAPs is that the computational screening indicates them as non-P-gp substrates. This xenobiotic pump mediates the unilateral efflux of anticancer drugs out of cancer cells and hence its overexpression confers multi-drug resistance to a number of chemically and pharmacologically distinct antineoplastic agents [29, 30]. Thus, the findings indicating the target monocyclic PAPs as non-P-gp substrates is a prerequisite for activity against multidrug resistant cancer cells, overexpressing this drug transporter. On the contrary, the computational data for the bicyclic prenylated acyl phloroglucinol hyperatomarin indicate it as a P-gp substrate. Nevertheless, our pharmacological data from preceding studies shows that this compound is capable of eradicating multidrug resistant leukemic cells, which indirectly indicates that it is actually an inhibitor of the ATP-binding cassette transporters, such as P-gp.

The skin permeation ability of the tested compounds is expected to be very low, based on the calculated LogKp values.

The drug likeness evaluation is summarized in Table 6. All compounds proved to comply with the Lipinski rules, which comprise the pioneering drug

Table 6. Drug likeness, medicinal chemistry and lead-likeness parameters for the tested compounds

Properties	**1**	**2**	**3**	**4**	**5**	**6**, **7**	**8**
Lipinski	Yes; 0 violations	Yes; 0 violations	Yes; 0 violations	Yes; 0 violations	Yes; 0 violations	Yes; 0 violations	Yes; 0 violations
Ghose	Yes	No; 1 violation: WLOGP>5.6	No; 1 violation: WLOGP>5.6	No; 1 violation: WLOGP>5.6	No; 1 violation: WLOGP>5.6	Yes	Yes
Veber	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Egan	Yes	No; 1 violation: WLOGP>5.88	No; 1 violation: WLOGP>5.88	No; 1 violation: WLOGP>5.88	No; 1 violation: WLOGP>5.88	Yes	Yes
Muegge	No; 1 violation: XLOGP3>5	No; 1 violation: XLOGP3>5	No; 1 violation: XLOGP3>5	No; 1 violation: XLOGP3>5	No; 1 violation: XLOGP3>5	No; 1 violation: XLOGP3>5	No; 1 violation: XLOGP3>5
Bioavailability Score	0.56	0.55	0.55	0.55	0.55	0.55	0.55
Brenk	3 alerts: beta/keto/ anhydride, isolated alkene, Michael acceptor_4	1 alert: isolated alkene	1 alert: isolated alkene	1 alert: isolated alkene	1 alert: isolated alkene	1 alert: isolated alkene	1 alert: isolated alkene

candidate filter, implemented in the drug discovery screens of Pfizer and are considered the ultimate archetype of all drug-likeness tools. Conversely the tested phloroglucinols had no violations of the rules, implemented in the Veber filter, but had variable success rates in Ghose and Egan filters.

We also calculated the Abbot Bioavailability Score, which measures the probability of a compound to have at least 10% oral bioavailability in rat or measurable Caco-2 permeability [20]. Based on this semi-quantitative score, calculated on the basis of total charge, TPSA, and violation to the Lipinski filter the tested compounds are classified to four classes of compounds with probabilities of 11%, 17%, 56% or 85%. In line with the gastrointestinal absorption data from table 3 all tested compounds were classified as having 56% probability of attaining the aforementioned bioavailability end-points.

Due to their chemical complexity high molecular mass and lipophilicity the tested series generally failed to comply to the Muegge and Brent lead-likeness filters [20], which indicates that if they are to employed as starting scaffolds for a drug discovery programs the synthetic strategies should be focused on structure simplification, elimination of troublesome functionalities and decreased lipophilicity.

CONCLUSION

The global ADME and PK features of the target PAPs generally indicate that the main issue of concern is their significant lipophilicity and low water solubility, otherwise the analysed series of phloroglucinols have a suitable amalgam of physicochemical and biopharmaceutical properties, to afford plausible pharmacokinetic properties. This together with the promising antineoplastic effects give us reason to consider the PAP from *Hypericum annulatum* Moris subsp. *annulatum* as a perspective set of lead compounds for further more detailed pharmacological and toxicological evaluation.

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IN SILICO ОЦЕНКА НА ADME ПРОФИЛИТЕ И НА ЛЕКАРСТВЕНОТО ПОДОБИЕ НА СЕРИЯ ОТ ЦИТОТОКСИЧНИ ПОЛИПРЕНИЛИРАНИ АЦИЛФЛОРОГЛУЦИНОЛИ, ИЗОЛИРАНИ ОТ *HYPERICUM ANNULATUS* MORRIS SUBSP. *ANNULATUM*

Я. Илиева[1,2], З. Коканова-Недялкова[1], П. Недялков[1], Г. Момеков[2]

[1] Катедра по фармакогнозия, Фармацевтичен факултет, Медицински университет, София
[2] Катедра по фармакология, фармакотерапия и токсикология, Фармацевтичен факултет, Медицински университет, София

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(Резюме)

Осем цитотоксични полипренилирани ацилфлорфлуциноли, изолирани от *Hypericum annulatum* Moris subsp. *annulatum*, бяха подложени на виртуална оценка на ADME, фармакокинетиката и лекарственото подобие, с помощта на уеб платформата SwissADME. Оценката на физикохимичните параметри показва значителна липофилност и ниска водоразтворимост. Въз основа на получените данни се очаква съединенията да имат добра орална бионаличност и с изключение на хиператомарин да не са субстрат на P-гликопротеина. Оценката на техния профил на модулиращи ефекти спрямо някои изоформи на цитохром P450 показва, че всички те са инхибитори на CYP3A4, докато очакваните ефекти върху други CYP изоформи варират при отделните съединения. При оценката на лекарствено подобие бяха използвани пет алтернативни филтъра, при което всички съединения са в съответствие с правилото на Липински. В заключение, изчислените ADME и фармакокинетичните параметри ни дават основание да разглеждаме полипренилираните ацилфлорфлуциноли от *Hypericum annulatum* Moris subsp. *annulatum* като перспективна серия от цитотоксични лекарствени кандидати, заслужаващи по-задълбочена онкофармакологична и токсикологична оценка.