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ИРИДОИДЛАРНИНГ ГЕПАТОПРОТЕКТОРЛИК ФАОЛЛИГИНИ МИҚДОРИЙ НИСБАТ ТУЗИЛИШИ ФАОЛЛИГИ (МНТФ) УСУЛИ АСОСИДА ЎРГАНИШ

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Аннотация. *Мазкур тадқиқот иши миқдорий нисбат тузилиши фаоллигини (МНТФ) қўллаш орқали 10 та иридоиднинг гепатопротекторлик фаоллигини коррелация ва башорат қилишни ўрганишга бағишланган. Иридоидлар ўсимликнинг турли қисмларида учрайдиган монотерпеноидларнинг энг катта синфи ҳисобланади. Квант-кимёвий дискрипторлар ярим эмперик RM1 усулини қўллаш орқали ҳисобланди. Олинган модель иридоидларнинг гепатоҳимоя фаоллигини ёритиш учун фойдали ва уни янги иридоидларнинг гепатопротекторлик фаоллигига баҳо беришда қўлласа бўлади. Тадқиқотлар натижасида олинган модель нафақат яхши статистик кўрсаткич, балки яхши башорат қилиш қобилиятини ҳам кўрсатди. Моделнинг башорат қилиш кўрсаткичи (r^2test) 0,99 ни ташкил қилади.*

Таянч тушунчалар: *иридоидлар, гепатопротекторлик, МНТФ, башорат қилиш модели, квант-кимёвий ҳисоб.*

ИЗУЧЕНИЕ ГЕПАТОПРОТЕКТИВНОЙ АКТИВНОСТИ ИРИДОИДОВ С ПРИМЕНЕНИЕМ МЕТОДА КОЛИЧЕСТВЕННОГО СООТНОШЕНИЯ СТРУКТУРНОЙ АКТИВНОСТИ (КССА)

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Аннотация. *Данная статья посвящена исследованию 10 иридоидов с применением метода количественного соотношения структурной активности (КССА) для корреляции и прогнозирования гепатопротекторной активности иридоидов. Они относятся к самому большому классу*

монотерпеноидов, представляют собой широко распространенную группу веществ, встречающихся в различных растительных организмах. Квантово-химические дескрипторы были рассчитаны с помощью полуэмпирического подхода RM1. Полученная модель полезна для описания гепатозащитной активности иридоидов и может быть использована для оценки гепатозащитной активности новых иридоидов. Модель, полученная в нашем исследовании, продемонстрировала не только статистическую значимость, но и превосходную прогностическую способность. Предполагаемая прогностическая способность модели (r^2test) для внешнего набора составляет 0,99.

Ключевые слова: *иридоиды, гепатопротекторная активность, КССА; прогнозная модель, квантово-химические расчеты.*

A QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIP (QSAR) STUDY OF THE HEPATOPROTECTIVE ACTIVITY OF IRIDOIDS

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Abstract. *This study is devoted to investigation of 10 iridoids applying quantitative structure-activity relationship analysis (QSAR) to correlate and predict their hepatoprotective activity. Iridoids, the largest class of monoterpenoids, are widespread group of substances occurring in various plant organisms. Quantum-chemical descriptors were calculated by semi-empirical RM1 approach. The obtained model is useful for description of iridoids hepatoprotective activity and can be used to estimate the hepatoprotective activity of new substituted iridoids. The model obtained in our study shows not only statistical significance, but also an excellent predictive ability. The estimated predictive ability (r^2_{test}) of the model for the external set is 0.99.*

Keywords: *iridoids, hepatoprotective, QSAR, predictive model, quantum-chemical calculations.*

Introduction

Iridoids represent a large and still expanding group of cyclo-peanta[*c*] pyran monoterpenoids found in a number of folk medicinal plants used as bitter tonics, sedatives, hypotensives, anti-pyretics, cough medicines, and remedies for wound sand skin disorders [1]. This fact encouraged to investigate the bioactivities of these phytochemicals. Intensive studies revealed that iridoids exhibit a wide range of bioactivity: neuroprotective, antitumor, anti-inflammatory, antioxidant, cardiovascular, antihepatotoxic, choleretic, hypoglycemic, hypolipidemic, antispasmodic, antiviral, antimicrobial, immunomodulator, anti-allergic, anti-leishmanial and molluscicidal effects[2]. Naturally occurring iridoid compounds have been classified into different

subgroups on the basis of their demonstrated or postulated biosynthesis as well as on the basis of chemical properties. According to Hegnauer's classification[3], natural iridoids in the broadest sense are represented by nine structural groups, consisting of cyclopentanoid monoterpenes and secoiridoids, in general, characterised by the structural feature of a 7,8-seco ring including pseudoalkaloids as well as complex indole- and isochinoline-type alkaloids. Only iridoid glycosides have been summarized [4], usually but not necessarily containing glucose, secoiridoid glucosides and non-glycosidic compounds and omitting all nit-

rogen-containing iridoids. Simple pseudoalkaloids have been considered as artefacts formed by replacement of oxygen by nitrogen in genuine iridoids upon ammonia treatment during extraction.

Oxidative stress, chronic liver inflamemation from viral and chemical toxicity, and accumulation of fats in liver from insulin resistance are the key factors for liver diseases. Several pro-inflammatory cytokines such as TNF-a, IL-1b, and IL-6 and endothelial growth factors are over-expressed by liver kupffer cells in the inflamemationsite, which in turn initiate inflamemation cascade to produce TGF-b1 and other growth factors and chemokines for remedial measure. The growth factorTGF-b1 induces the activation of hepatic stellate cells for transformation into myofibroblasts, which initiate apoptosis of hepatocytes in liver tissues. The pro-inflammatory genes, TNF-a, IL-1b, IL-6, IL-8, and IL-17 are considered as key players to elevate obesity and fat-related inflammation in liver [5, 6, 7]. Therefore, design of new effective medicinal compounds for hepatology is an important task.

Sum of iridoids from *P.scandensvar tomentosa* possessed incapable hepatoprotective activity mainly via decreasing oxidetive stress level in liver tissues. TG can therefore be regarded as a promising candidate agent for protecting stacuteorchronic liver injury [8].

The iridoids, seco-iridoids and analog glycosides from a Gentianaceae herb gentian may be responsible for the hepatoprotective effect of this kind of food additive or medicine. The regulation of the expression levels of hepatic CYP450 systems and improvement of mitochondrial functions are the potential hepatoprotective mechanisms. Molecular docking analysis provides useful information on structure–activity relationships between CYPs and the naturally found iridoids, seco-iridoids and analog glycosides. Further experimental validation of the hepatoprotective effect of amarogentin on aconitine-induced stress in HepG2 cells reveals a functional relationship between amarogentin and the CYP3A4 enzyme [9].

Picroliv has been shown to have a marked hepatoprotective activity against many hepatotoxic compounds such as alcohol, aflatoxin B1 and oxytetracycline [10, 11, 12]. This effect has been attributed to a stabilizing action on the cell membrane of the hepatocytes, which was possibly related to the ability of picroliv to act as an oxygen free-radical scavenger that limits lipid-peroxidation involved in membrane damage elicited by hepatotoxins. The heaptoprotective activity of picroliv to provide protection against the biochemical alterations produced by CCl4 and *E. histolytica* was also evaluated [13].

For the last decade, iridoids have been the object of considerable interest for quantitative structure-activity relationship (QSAR) investigations since there is a growing need for more effective hepatoprotective drugs. This work is the first QSAR analyses of iridoids with hepatoprotective activity. The present work is devoted to the SAR study of a set of 10 iridoids isolated from different kinds of plants. The main goal of this work is the investigation of structural features responsible for hepatoprotective activity and development of the QSAR model for further design of a potent and specific hepatoprotective agent based on iridoid structure.

Materials and methods

The dataset for the present study has been collected from several experimental studies [14] for a series of 10 compounds with hepatoprotective activity (HA) data. All original activity data has been converted into molar log(HA) response variables. The structures of the compounds that were used in the analysis and experimental values related to log(IC_{50}) activity are shown in Table 1.

Computational part

All molecular models were built using the HyperChem 8.0.10 software package [15]. The molecular geometries of target molecules were optimized using semi-

empirical RM1 [16]. Aiming to understand better the experimental results, the following properties were calculated: energies of the HOMO (highest occupied molecular orbital, a measure of nucleophilicity), and LUMO (lowest unoccupied molecular orbital, a measure of electrophilicity), dipole moment (and its *X, Y, Z* components), total energies, LogP (measure of lipophilicity), refractivity, polarizability and charges of the compounds, which were used as quantum-chemical descriptors. Numerical values of the quantum-chemical descriptors are summarized in Table 2.

Cheminformatics structure-activity modelling

Model development and selection were performed by means of combined approach of genetic algorithm (GA) and multiple linear regression analysis (MLRA), GA-MLRA [17, 18] technique, as implemented in the QSARINS v2.2.3 [19, 20] program. This approach allows selection of the models with the following characteristics for the better performance: high squared regression coefficient r^2, low standard deviation s, and the least number of descriptors involved. Thus, the high Fisher coefficient F and non-collinear descriptors served as additional selection parameters. A final set of QSARs was identified by applying the "leave-one-out" technique with its predicting ability being evaluated and confirmed by cross-validation coefficient q^2 based on predictive error sum of squares. Constitutional, topological and molecular descriptors were calculated using the DRAGON software [21]. A set of 384 different molecular descriptors was used to describe the chemical diversity of the compounds.

Table 1

№	Compound, training set, *n* = 10	Log[IC50]	Log[IC50] calc for 3-desc. model	Residual
1	Aucubine	2.6202	2.5949	-0.0253
2	Catalpole	2.6704	2.6746	0.0042
3	Catalposide	2.8080	2.7822	-0.0257
4	Geksaasetat catalposide	2.9880	2.9916	0.0036
5	Lamiide	2.6811	2.7095	0.0284
6	Flomozide A	2.6520	2.6632	0.0112
7	Stansiozide	2.5451	2.5535	0.0085
8	7-O-Benzoyltecomozide	2.8045	2.8084	0.0039
9	Garpagid	2.6223	2.6534	0.0311
10	8-O-Acetylgarpagid	2.6674	2.6869	0.0195

List of compounds with experimental and predicted values of hepatoprotective activity for the 2-variable model 977030992

The descriptor typologies include: (i) functional groups, (ii) atom-centered fragments, (iii) molecular walk counts [22]. The cross-correlation for all pair of descriptors was used to identify highly correlated descriptors and to detect redundancy in the data set. Any type of redundancy might lead to an overexploitation of a chemical property in the explanation of the dependent variable. Hence, some highly correlated and constant descriptors (with r^2 value more than 0.9) were removed from the further consideration. Moreover, descriptors with cross-correlation coefficients values more than 0.6 have been avoided during the model buildings.

Results

The whole set of 10 compounds was divided into the training set consisted of 8 compounds and a test set (predicting set) of two compounds. GA-MLRA technique has identified three top models and one significant model for the training set as the best

one predicting HA of the iridoids. Statistical characteristics with one-and two descriptors variables models are shown in Table 3.

Table 2

Statistical characteristics of the one- and two-variable models

Model, no. of descriptors	Training set, *n*=8				Predict set, n=2	
	r^2	S	F	q^2	r^2	s
1 (1 descr-s)	0.9613	0.0297	149.1633	0.9263	0.99	1.2379
2 (2 descr-s)	0.9859	0.0196	175.3266	0.9699	0.99	0.0298

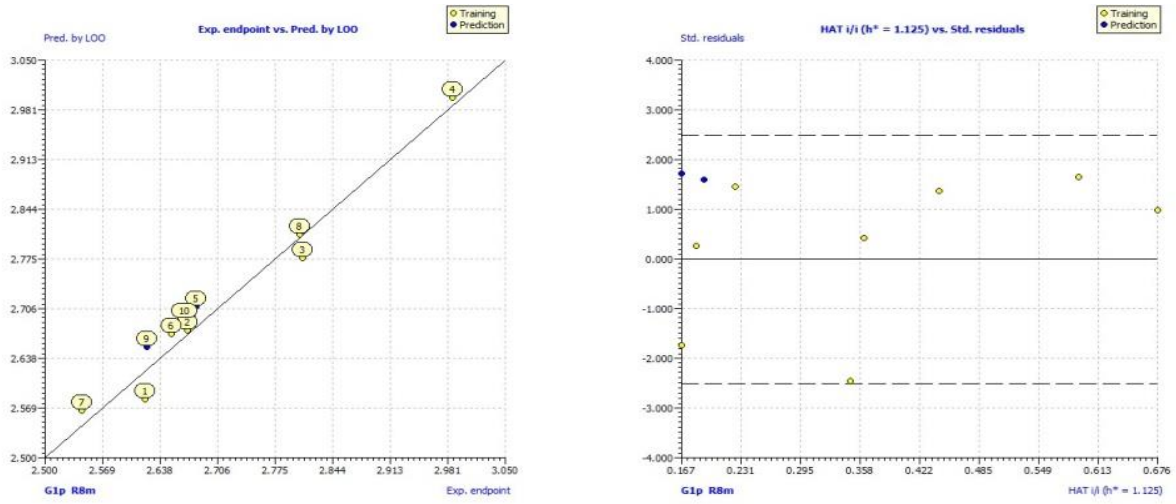
The following equation represent one-variable model:

Log[HA] = -8.3466(±1.9377) G1p + 0.9496 (±0.1942) R8m +3.6013(±0.3517)
n=10; r^2=0.9859; *s*=0.0196; *F*=175.3266; RMSEtr= 0.0155; q^2=0.9699 (training set);
n=2; r^2ext=0.99; *s* = 0.0298(test set) (1)

This model shows the best r^2 and q^2 values for the training set, and the best predictive potential for the test set for HA. Graphical representations of the model are shown in Figure 1. Experimental and predicted values of log(HA), according to Eq. (1) are shown in Table 1.

Discussion

As it was indicated in the Results section, the following descriptors constitute the best models: G1p (1st component symmetry directional WHIM index / weighted by polarizability, WHIM descriptors), R8m (R autocorrelation of lag 8 / weighted by mass, GETAWAY des-criptors). Model 2 provides the best perfor-mance with two variables.



a **b**

Figure 1. **Graphical representation of statistical performance of the best model: (a) Observed vs Predicted correlation plot; (b) Williams plot, shows that all compounds' values are within the applicability domain**

In general, the best model shows a very good predictive ability and has a transparent nature, which allows explaining the factors influencing IC_{50} index (hepatoprotective activity) of the investigated compounds.

Conclusions

A QSAR study has been performed for the set of 10 iridoid compounds to analyze and predict IC_{50}values related to hepatoprotective activity. QSAR analysis was performed using machine-learning methods, such as GA for variable selection among generated and calculated descriptors and MLRA.

Quantum-chemical calculations have been applied for electronic properties calculations.

One mathematical model to predict IC_{50}values related to hepatoprotective activity is proposed. The best overall performance is achieved by three-descriptor QSAR model, where r^2 values for the training and test sets are 0.9859 and 0.99, respectively. The significant molecular descriptors related to the compounds with hepatoprotective activity are: G1p - 1st component symmetry directional WHIM index / weighted by polarizability, WHIM descriptors, R8m - R autocorrelation of lag 8 / weighted by mass, GETAWAY descriptors). Obtained model can be used to estimate the hepatoprotective activities of new substituted iridoids or their derivatives.

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