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Structure-Hepatoprotective Activity Relationship Study of Iridoids: A QSAR Analysis

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ABSTRACT

Iridoids, the largest class of monoterpenoids, are widespread group of substances present in various plant organisms. This study is devoted to investigation of the hepatoprotective activity of a series of iridoid compounds with application of a quantitative structure-activity relationship (QSAR) analysis. The investigated activity was based on in vitro experimental data, where iridoids' effects on CCl_4-induced hepatocytes' damage were obtained. The QSAR analysis was carried out using a combination of genetic algorithm for variable selection and multiple linear regression analysis. A set of calculated descriptors was used for modeling, including quantum-chemical descriptors. Several high-performance models were developed and the best model describing the hepatoprotective activity of iridoids is proposed. The model obtained in this study shows not only a statistical significance, but also excellent predictive ability. The obtained model can be used to estimate the hepatoprotective activity of new substituted iridoids.

KEYWORDS

Hepatoprotective Activity, In Vitro, Iridoids, Natural Compounds, Predictive Model, QSAR, Quantum-Chemical Descriptors, Structure-Activity Relationship

1. INTRODUCTION

Iridoids represent a large group of cyclopenta[*c*]pyran monoterpenoids found in a number of folk medicinal plants and used as hypotensives, cough medicines, bitter tonics, sedatives, antipyretics, remedies for wound sand skin disorders (Tietze et al., 1983). This fact encouraged scientists to investigate the bioactivities of these plant compounds. Additional studies during recent years revealed that iridoids exhibit a wide range of bioactivity: neuroprotective, antitumor, anti-inflammatory, antioxidant, cardiovascular, antihepatotoxic, choleretic, hypoglycemic, hypolipidemic, antispasmodic,

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antiviral, antimicrobial, immunomodulator, antiallergic, anti-leishmanial and molluscicidal effects (Ghisalberti et al., 1998, Usmanov et al., 2019). Naturally occurring iridoid compounds were classified into different sub-groups on the basis of their demonstrated or postulated biosynthesis pathway as well as on the basis of chemical properties. According to Hegnauer's classification (Hegnauer, 1986), natural iridoids in the broadest sense are represented by nine structural groups, consisting of cyclopentanoid monoterpenes and secoiridoids in general characterized by the structural feature of a 7,8-seco ring including pseudo alkaloids, as well as complex indole- and isoquinoline-type alkaloids. In another study, the iridoid glycosides were summarized (El-Naggar et al., 1980), which are mainly containing a glucose, secoiridoid glucosides and non-glycosidic compounds, while all nitrogen-containing iridoids were omitted. Also, simple pseudoalkaloids were considered as artefacts, where they were formed by replacement of oxygen by nitrogen in iridoids, during ammonia treatment at extraction.

Oxidative stress, chronic liver inflammation 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 inflammation site, which in turn initiate an inflammation cascade to produce TGF-b1 and other growth factors and chemokines for remedial measure. The growth factor TGF-b1 induces the activation of hepatic stellate cells for transformation into myfibroblasts, 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 (Andrade et al., 2015; Czaja et al., 2014; Tilg et al., 2010). Therefore, search for new effective medicinal compounds with hepatoprotective properties is an important task. Pathology and functional disorders of the liver are almost always combined with pathology of the gallbladder and biliary tract, and therefore the most successful therapy is aimed at improving the metabolic processes in the liver, increasing its resistance to pathogenic effects, accelerating the recovery of its functions during various injuries and to eliminate dysfunctional disorders of the biliary tract.

Some of iridoids from *P. scandensvar tomentosa* possess a notable hepatoprotective activity, mainly via the process of decreasing the oxidative stress level in liver tissues. Total sum of iridoid glycosides can therefore be regarded as a promising candidate agent for protecting again stacuteorchronic liver injury (Peng et al., 2015). The iridoids, secoiridoids 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. Among computational methods, molecular docking analysis provides useful information on structure–activity relationships between CYPs and the naturally found iridoids, secoiridoids 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 (Dai et al., 2018). Such iridoid as picroliv has been shown to have a pronounced hepatoprotective activity against many hepatotoxic compounds such as alcohol, aflatoxin B1 and oxytetracycline (Saraswat et al., 1997; Rastogi et al., 2000; Rastogi et al., 2001). 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 the lipid-peroxidation involved in membrane damage elicited by hepatotoxins. The hepatoprotective activity of picroliv to provide protection against the biochemical alterations produced by CCl_4 and *E. histolytica* was also previously evaluated (Singh et al., 2005).

For the last decade, iridoids have been the objects of considerable interest for quantitative structure-activity relationship (QSAR) investigations since there is a growing need for more effective hepatoprotective drugs. There are limited number of publications available that report QSAR studies to predict hepatoprotective activity (Jaqua et al., 2005; Paukku et al., 2009; Bartalis et al., 2011; Vinholes et al, 2014; Kondeva-Burdina et al., 2019). These QSAR models were developed for other class of compounds, such as sesquiterpenes (Paukku et al., 2009; Vinholes et al, 2014), cucurbitacin

(Jaqua et al., 2005; Bartalis et al., 2011), and flavonoids (Kondeva-Burdina et al., 2019), but not for iridoids. This work is the first QSAR analysis of the hepatoprotective activity of iridoids. The present work is devoted to analysis of a set of 18 iridoid compounds isolated from different kinds of plants. The main goal of this work is investigation of structural features responsible for hepatoprotective activity and development of a QSAR model for further design of a potent and specific hepatoprotective agent based on iridoid structure.

2. MATERIALS AND METHODS

2.1. Biological Data

The dataset for the present study was collected from several experimental studies (Wang et al., 2006; Zhang et al., 2018; Wu et al., 2018; Tang et al., 2016; Chen et al., 2016; Singh et al., 2014; Liu et al., 2018). In total, a series of 18 iridoid compounds (see Figure 1) with IC_{50} data was collected. All original activity data were converted into the molar $Log(1/IC_{50})$ response variable. The structures of the compounds that were used in the analysis and experimental values related to $Log(1/IC_{50})$ activity are shown in Figure 1 and Table 1, respectively.

Figure 1. Structures of the studied compounds

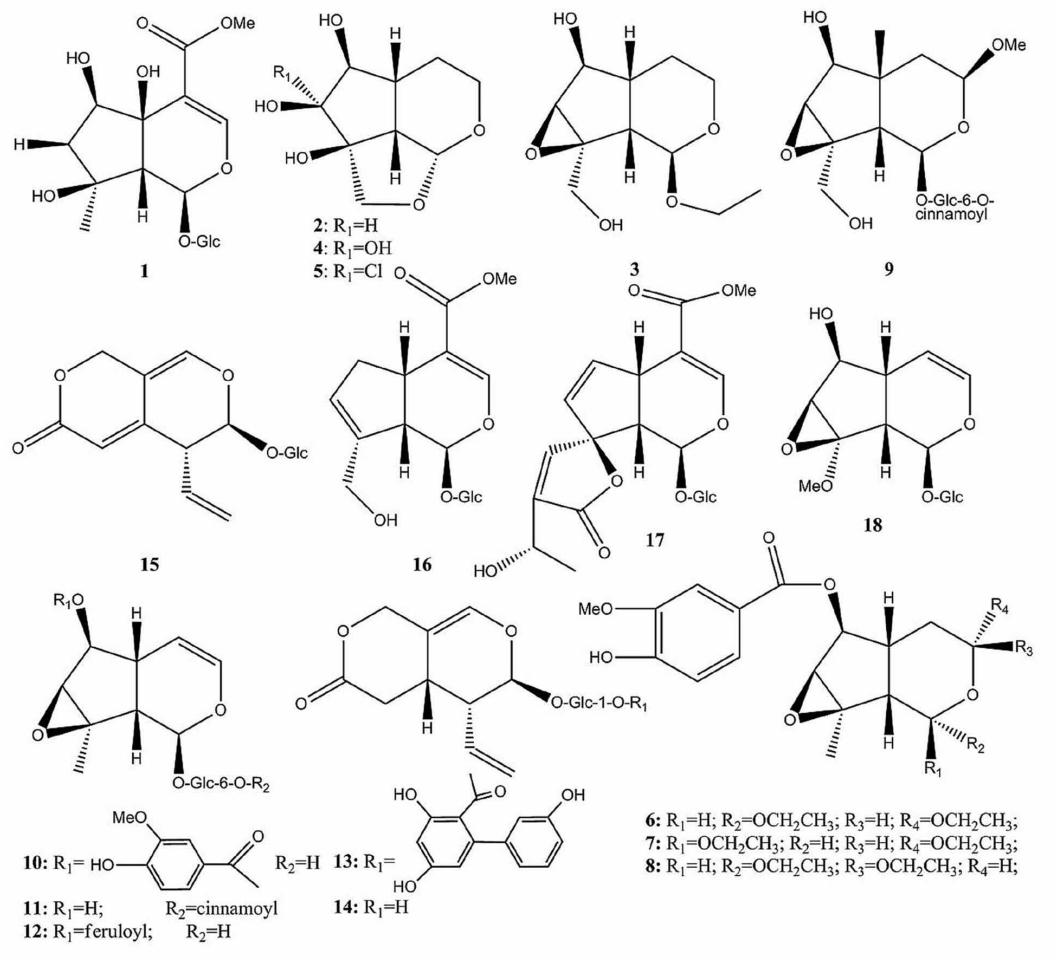


Table 1. List of investigated compounds, experimental IC_{50} values of hepatoprotective activity, experimental and predicted values of Log[1/IC_{50}]

Nº	Compound	Exp. IC_{50}, mg/kg	Exp. Log[1/IC_{50}]	Calc. Log [1/IC_{50}] for 3-desc. Model	Residual
1*	Lamiide	25	0.2365	0.2416	0.0051
2	Piscrocin D	64	0.2857	0.3039	0.0182
3	Piscrocin E	29	0.2564	0.3529	0.0965
4	Rehmaglutin A	475	0.3846	0.3106	-0.0740
5	Rehmaglutin D	2000	0.5000	0.4974	-0.0026
6	3'-methaxyspecinonin	8400	0.5882	0.5659	-0.0223
7	Piscrocin F	1350	0.4000	0.3968	-0.0032
8	Piscrocin G	1050	0.3846	0.3955	0.0109
9	Piscroside B	0.025	0.1370	0.1548	0.0179
10*	Piscroside II	10	0.2128	0.2741	0.0614
11	Piscroside I	0.0025	0.1205	0.1071	-0.0134
12	Piscroside III	0.75	0.1695	0.1636	-0.0059
13	Amarogentin	100	0.2654	0.2704	0.0051
14	Swertiamarin	100	0.2799	0.2850	0.0051
15	Gentiopicroside	130	0.2909	0.2718	-0.0191
16	Geniposide	400	0.3348	0.2761	-0.0586
17	Plumieride	20	0.2288	0.2744	0.0457
18*	Catalpol	40	0.2527	0.1890	-0.0637

* - test set compounds

2.2. Computational Part

To find properties responsible for hepatoprotective activity in the investigated set of iridoids a computational study was performed. In this regard, all molecular models were built using the HyperChem 8 software package (HyperCube Inc., Gainesville, USA; http://www.hyper.com/). The molecular geometries of target molecules were optimized using semi-empirical RM1 (Rocha et al., 2006). Aiming to understand better the experimental results, the following quantum-chemical and physico-chemical 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 μ (and its *X, Y, Z* components), total energy (E), heat of formation (Hf), LogP (measure of lipophilicity), refractivity (Refc), polarizability (Pola) and charges of the compounds. The numerical values of the calculated quantum-chemical descriptors are summarized in Table 2.

2.3. Quantitative Structure-Activity Relationship Modeling

QSAR model development and selection were performed by combined genetic algorithm (GA) and multiple linear regression analysis (MLRA) approach, GA-MLRA (Davis et al., 1991; Devillers et al., 1996; Turabekova et al, 2008; Turabekova et al., 2010; Toropova et al., 2012; Juretic et al., 2014), as implemented in the QSARINS v2.2.3 (Gramatica et al., 2013; Gramatica et al., 2014) software.

Table 2. Numerical values of calculated quantum-chemical and physico-chemical descriptors

	E	Hf	LogP	Refc	Pola	HOMO	LUMO	μ	μ_x	μ_y	μ_z
1	-5505.89	-23.10	-3.76	88.96	36.55	-10.2096	-0.1294	2.4843	1.9845	1.0479	-1.0656
2	-2753.79	-12.51	-1.29	44.68	18.15	-10.3520	2.1777	3.0107	-1.6514	-0.1877	2.5104
3	-3305.51	-9.83	-0.67	54.18	21.82	-10.5657	2.0352	4.3931	-2.0068	-1.5441	3.5899
4	-2752.94	-12.56	-1.29	44.68	18.15	-10.2681	2.2253	3.6222	-2.8297	0.7403	2.1356
5	-2636.03	-8.60	-0.15	47.74	19.44	-10.4660	-0.0056	3.6722	-2.2517	-1.4834	2.4928
6	-5912.05	-14.38	-1.10	106.27	40.82	-9.4943	-0.2554	4.1377	3.2405	-0.7409	2.4639
7	-5915.67	-14.92	-1.10	106.27	40.82	-9.2509	-0.1786	3.3031	-2.0679	-1.6320	1.9926
8	-5915.69	-14.92	-1.10	106.27	40.82	-9.2488	-0.1685	3.3266	-2.0075	-1.6228	2.0982
9	-6766.04	-23.19	-0.51	122.54	47.18	-9.1956	0.1393	5.3373	-4.8715	-2.0768	0.6641
10	-6648.16	-31.44	-3.48	118.4	46.07	-9.4286	-0.4036	2.7426	-1.0871	1.6965	1.8606
11	-6600.62	-21.63	-1.06	120.66	46.44	-9.4613	-0.1404	4.0658	0.5421	-2.1176	3.4282
12	-7077.13	-31.43	-3.07	128.64	49.55	-9.1007	-0.2632	2.3005	0.7781	-0.4411	-2.1195
13	-7789.61	-30.52	-2.26	148.01	55.76	-9.1666	-0.6753	5.8268	4.5069	0.2695	3.6839
14	-4892.52	-22.11	-1.98	82.33	33.25	-10.1867	0.0048	5.3272	4.2775	3.0357	0.9306
15	-4659.55	-20.72	-1.37	81.91	32.42	-9.3179	-0.3278	4.9301	2.6959	1.1573	-3.9622
16	-5161.64	-19.89	-1.99	88.27	35.08	-9.4052	0.2588	3.0432	-2.7142	1.0583	-0.8800
17	-6128.61	-20.78	-1.89	106.79	42.18	-9.8453	-0.2686	2.8021	-2.2171	0.7214	-1.5542
18	-4696.77	-26.12	-2.74	76.95	31.38	-9.7581	0.7564	3.8969	2.3249	3.1086	-0.3425

This approach allows developing GA-MLRA models, with several variables, followed by strong validation. The selection of the models is performed with the subsequent characteristics for the higher performance: high square regression coefficient r^2, low variance s, and also the least number of descriptors involved in the model. Thus, the high Fisher ratio F and noncollinear descriptors served as extra choice parameters. A final set of QSARs was selected by applying the "leave-one-out" technique with their predicting ability being evaluated and confirmed by cross-validation q^2 parameter, based on error sum of squares. Constitutional, topological and molecular descriptors were calculated by the DRAGON code (Todeschini et al., 2004). A final set of 384 different molecular descriptors selected from the initial set of 4500 descriptors was used to describe the chemical diversity of investigated compounds.

The descriptor typologies include: (i) functional groups, (ii) atom-centered fragments, (iii) molecular walk counts (Todeschini et al., 2000). The cross-correlation for all pairs of descriptors was used to establish highly correlated descriptors and to find redundancy within the dataset. Any sort of redundancy may lead to overexploitation of a property within the explanation of the dependent variable. Hence, some extremely correlated and constant descriptors (with r^2 values over 0.9) were removed from the further analysis. Moreover, descriptors with cross-correlation coefficients values over 0.6 are avoided throughout the model development.

3. RESULTS

To investigate the hepatoprotective activity by application of the QSAR approach a set of 18 compounds was divided into a training set consisted of fifteen (15) compounds and a test set (predicting set) of three (3) compounds. The GA-MLRA technique has identified top three models and one model for

the training set as the best one predicting IC_{50} values for the iridoids. Statistical characteristics with one-, two-, and three-descriptors variable models are shown in Table 3.

The following equation represents the developed best three-variable model:

$$\text{Log}[1/IC_{50}] = -1.028(\pm 0.369)\ \text{GATS2p} - 0.015(\pm 0.005)\ \text{RDF060m} + 1.14(\pm 0.647)\ \text{H8v} + 1.562(\pm 0.427) \quad (1)$$

n=15; r^2=0.904; $RMSEtr$= 0.412 (training set);
n=3; r^2_{ext}=0.941 (test set);
Q^2_{LOO}=0.846; Q^2_{LMO}=0.826

Table 3. Statistical characteristics of the one-, two-, and three-variable models

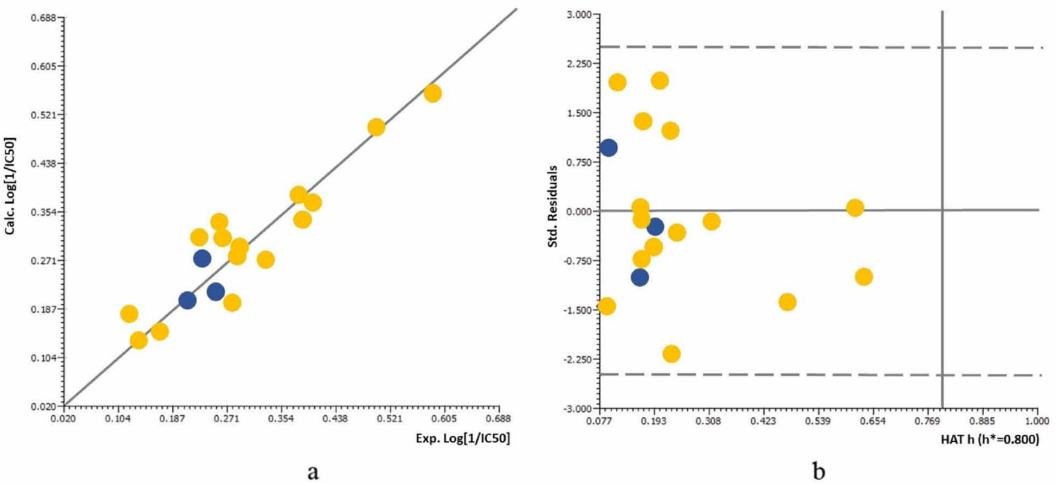
Model, No. of Descriptors	Training Set, n=15				Test Set, n=3	
	r^2	s	F	q^2	r^2	s
1 (1 descr)	0.639	0.080	23.065	0.519	0.865	0.100
2 (2 descr-s)	0.812	0.060	25.966	0.721	0.993	0.050
3 (3 descr-s)	0.904	0.045	34.651	0.846	0.941	0.051

The selected model shows the best r^2 and q^2 values for the training set and for the test set, predicting IC_{50} values. Graphical representations of the model are shown in Figure 2. The experimental and predicted values of $\text{Log}(1/IC_{50})$, according to Equation (1) are shown in Table 1.

4. DISCUSSION

As it was indicated in the Results section, the following descriptors constitute the best 1- to 3-variable models: GATS2p (Geary autocorrelation lag2 / weighted by polarizabilities), RDF060m (Radial

Figure 2. A graphical representation of statistical performance of the best model: (a) Observed vs. Predicted correlation plot; (b) Williams plot shows all compounds' values are within the applicability domain. Yellow dots – training set, blue dots – test set.



a b

Distribution Function - 060 / weighted by mass), H8v (H autocorrelation of lag 8 / weighted by atomic van der Waals volumes). Model 3 provides the best performance with three variables. All models with number of descriptors of 1-3 show a good correlation coefficient for the training set, while the best r^2 value for the test set is shown by the model 3 (Equation 1).

All three descriptors that were selected by GA algorithm are structure-based descriptors. The first descriptor is GATS2p (Geary autocorrelation lag2 / weighted by polarizabilities) is an autocorrelation descriptor (Todeschini and Consonni, 2000). Autocorrelation descriptors of chemical compounds can be represented at the atomic level or molecular surface level or else, which reflect molecular topology structural features and atomic properties (i.e., van der Waals volume, carbon-scaled atomic polarizability and intrinsic state). The negative sign of GATS2p indicates that an increase in this descriptor causes decrease in $\text{Log}(1/\text{IC}_{50})$ value, which is in consonance with the positive sign for IC_{50}.

RDF060m is a Radial Distribution Function-6.0/weighted by atomic mass. Radial distribution function (RDF) (Todeschini et al., 2004) encodes geometrical and atomic features of chemical structures in 3D space according to atomic pair properties A_i and A_j, which in this work corresponds to the atomic mass. Equation 2 describes in general the RDF descriptors as a distance function:

$$RDF\left(r\right) = f\sum_{i=1}^{N-1}\sum_{j=i-1}^{N} A_i A_j e^{-B\left(r-r_{ij}\right)^2} \tag{2}$$

where f is a scaling factor, N the number of atoms i and j and r_{ij} the interatomic distances. A smoothing parameter, B, defines the probability distribution of individual distances of the atoms which may be regarded as their vibrations in the molecule. According to the equation, the RDF descriptor can be interpreted as the probability distribution to find an atom in a spherical volume of radius r. Based on this definition, it is plausible to presume that RDF060m encodes a partial contribution to the iridoid's bioactivity; the encoded information is of the fragments that have size with $r = 6.0$Å from the geometrical center of each fragment. According to the developed model (1), the RDF060m descriptor has a negative effect on IC_{50}, i.e. with increasing the value of this descriptor, the $-\log\text{IC}_{50}$ value of hepatoprotective activity decreases.

The final descriptor of the GA-MLRA model is the H autocorrelation of lag 8/weighted by atomic van der Waals volumes (H8v). This descriptor belongs to GETAWAY type of descriptors; it is related to the atomic van der Waals volume, the size, and the location of the atom in the molecule. The GETAWAY (Geometry, Topology, and Atom-Weights AssemblY) descriptors are proposed as three-dimensional chemical structure descriptors, encoding structural and stereochemical information (Consonni et al., 2002). The molecular structural representation is defined as Molecular Influence Matrix (MIM) denoted by H in Equation 3:

$$H = M \cdot \left(M^T \cdot M\right)^{-1} \cdot M^T \tag{3}$$

where M is a molecular matrix and the superscript T refers to the transposed matrix.

The greater the atomic van der Waals volume, the atom size, and the distance between the atom and the center of the molecule, the greater is the descriptor value (Todeschini and Consonni, 2000). This descriptor has a positive influence on the IC_{50} values.

Thus, statistically model 3 showed a very good performance, having r^2 for the training set equal to 0.904, as well as a high cross-validation coefficient - q^2=0.846. In addition, the predictive performance was confirmed by a high value of the external $r^2_{ext} = 0.941$. The model revealed that a combination of structural (GATS2p, RDF060m) and physico-chemical properties (H8v) affecting on the hepatoprotective activity.

In overall, based on the available largest to date dataset of iridioid's compounds a QSAR model predicting the hepatoprotective activity of investigated compounds is developed. The best model is transparent and shows a very good predictive ability, which allows to explain factors influencing the -logIC_{50} (hepatoprotective activity) of the investigated compounds.

5. CONCLUSION

A QSAR study was performed on the largest to date a set of 18 iridoid compounds to analyze and predict -logIC_{50} values related to hepatoprotective activity. QSAR analysis was performed using a combination of machine learning methods, such as GA for variable selection and MLRA. Quantum-chemical calculations were performed to assess the electronic properties of investigated iridoids and used as additional physico-chemical descriptors.

A transparent model to predict -logIC_{50} values related to hepatoprotective activity is proposed. The best overall performance is achieved by three-variable QSAR model, where r^2 values for the training and test sets are 0.904 and 0.941, respectively. The selected significant molecular descriptors related to the compounds with hepatoprotective activity are: GATS2p - Geary autocorrelation lag2 / weighted by polarizabilities is an autocorrelation descriptor, RDF060m is a Radial Distribution Function-6.0/weighted by atomic mass and H8v - H autocorrelation of lag 8/weighted by atomic van der Waals volumes. These variables are able to mechanistically explain the potency of compounds with hepatoprotective activity on basis of geometrical fragments and electronic contributions. The obtained model can be used to estimate the hepatoprotective activities of new iridoids and their derivatives.

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