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Quantitative Analysis of Structure–Activity Relationships of Tetrahydro-2H-isoindole Cyclooxygenase-2 Inhibitors

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Abstract—Using the GUSAR program, structure–activity relationships on inhibition of cyclooxygenase-2 (COX-2) catalytic activity were quantitatively analyzed for twenty-six derivatives of 4,5,6,7-tetrahydro-2H-isoindole, 2,3-dihydro-1H-pyrrolyzine, and benzothiophene in the concentration range of 0.6-700 nmol/liter IC_{50} values. Six statistically significant consensus QSAR models for prediction of IC_{50} values were designed based on MNA- and QNA-descriptors and their combinations. These models demonstrated high accuracy in the prediction of IC_{50} values for structures of both training and test sets. Structural fragments of the COX-2 inhibitors capable of strengthening or weakening the desired property were determined using the same program. This information can be taken into consideration on molecular design of new COX-2 inhibitors. It was shown that in most cases, the influence of structural fragments on the inhibitory activity of the studied compounds revealed with the GUSAR program coincided with the results of expert evaluation of their effects based on known experimental data, and this can be used for optimization of structures to change the value of their biological activity.

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Key words: cyclooxygenase-2 inhibitors, GUSAR, QSAR models, QNA and MNA descriptors, analysis of structure–activity relationships

Cyclooxygenase is a heme-containing enzyme that catalyzes the conversion of arachidonic acid to prostaglandin H2 [1-7]. The enzyme contains two active centers: (i) a cyclooxygenase site where arachidonic acid is converted to prostaglandin G2; (ii) a heme having peroxidase activity and promoting the transformation of prostaglandin G2 into prostaglandin H2 [1, 2, 4, 5].

There are two 60% homologous isoforms of cyclooxygenase: cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) [1, 2, 4, 5]. COX-1 is a constitutive enzyme and therefore is present in tissues nearly everywhere [1, 2, 4, 5]. In platelets, it is responsible for the conversion of arachidonic acid to thromboxane [1, 4, 5]. On treatment with nonselective nonsteroidal antiinflammatory preparations, inhibition of the catalytic activity of COX-1 leads to damage of the stomach wall and development of ulcers [1, 3-7]. Under usual conditions, COX-2 is present in the brain and the cortex of kidneys [1, 2, 4, 5]. In other tissues, COX-2 is induced under conditions of inflammation [2, 5]. COX-2 has been experimentally shown to contribute to development of cancer of the intestine and mammary glands in animals treated with nonselective and selective inhibitors of COX-2 [2, 6, 7]. In particular, the COX-2 level is increased in more than 50% of patients with malignant tumors of mammary gland, prostate, etc. [6, 7]. Therefore, the search for efficient and selective inhibitors of COX-2 is an urgent task of medical chemistry and pharmacology.

Many experimental data have accumulated about the efficiency of inhibition of COX isoforms by various classes of biologically active compounds [1-7]. This allowed us to use virtual screening approaches based on analysis of

Abbreviations: COX-1(2), cyclooxygenase-1(2); GUSAR, General Unrestricted Structure–Activity Relationships; MNA, Multilevel Neighborhoods of Atoms; QSAR, Quantitative Structure–Activity Relationships.

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structure–activity relationships (Quantitative Structure–Activity Relationships (QSAR)) for purposeful searching for natural and synthetic heterocyclic compounds with pronounced selectivity relative to COX-2. The QSAR approaches allow quantitative prediction of the biological activity of potential pharmaceutical drugs even at the presynthetic stage of their creation [8-13]. Such studies are urgent because the modern pharmacological arsenal has thousands of different types of biological activity [12, 13]. Thus, experimental studies on pharmacological profiles of potential new pharmaceuticals in different model systems *in vitro* and *in vivo* is a problem that would require significant time and financial expenditures without attracting approaches of computerized chemistry [12]. Targeted molecular design of potential new inhibitors of COX-2 based on their structural analogs is another and similarly urgent task. This task can be rationally solved using structural analysis of biologically active compounds for detecting within them structural fragments associated with decrease or increase in biological activity. The creation of QSAR models describing and visualizing the contribution of different parts of molecules under study to changes in biological activity can become a basis for optimization and rational construction of new biologically active compounds, including inhibitors of COX-2. Methods of molecular modeling and 3D-QSAR are traditionally used in such studies [12, 13].

The purpose of the present work was to design and validate QSAR models of selective inhibitors of COX-2 for derivatives of tetrahydro-2H-isoindole, 2,3-dihydro-1H-pyrrolysine, and benzothiophene based on two-dimensional presentation of their structural formula and also to analyze the influence of atoms and structural groups on the efficiency of inhibition of the COX-2 catalytic activity using the created QSAR models.

MATERIALS AND METHODS

Structure–activity relationships of COX-2 inhibitors were quantitatively analyzed using the computer program GUSAR (General Unrestricted Structure–Activity Relationships) [13-18]. The approaches used in the GUSAR program are rather new in QSAR modeling. These approaches combine the ideas of both SAR and traditional 2D-QSAR methods. Therefore, to promote objective comprehension of results of the below-described studies, it is necessary to describe in brief the capabilities of this program and the concept of designing in it of quantitative structure–activity relationships.

Brief description of the GUSAR program. For designing (Q)SAR models in GUSAR, a self-consisted regression method is used [16]. The description of the structure and calculation of regression coefficients for further designing of QSAR models to predict quantitative values are based on two types of substructural descriptors of atomic neighborhoods: MNA (Multilevel Neighborhoods of Atoms) and QNA (Quantitative Neighborhoods of Atoms) [15, 16]. These descriptors are calculated automatically by the GUSAR program from structural formulas of chemical compounds with consideration of valence and partial charges of the atoms within them but without indicating the specificity of bond types. MNA descriptors are generated based on structural formulas of chemical compounds without using any previous list of structural fragments [11-13]. Based on the MNA descriptors and using B-statistics calculated by an algorithm realized in the PASS program (Prediction of Activity Spectra for Substances) the spectrum of biological activity of a chemical compound is predicted [11, 15, 16]. The prediction results presented as a list of biological activity types with the evaluation of probability of their manifestation are variables for calculation of regression coefficients. The regression equation based on MNA descriptors reflects the action specificity of the compound but does not clearly show physicochemical parameters of chemical compounds [15, 16].

QNA descriptors are calculated using the ionization potential and affinity for electrons of every atom of the molecule and on taking into account the bonds between all atoms of the structure. Thus, on one hand, QNA descriptors describe each atom of the molecule and, from the other hand, depend on the molecule structure as a whole [16]. Values of QNA descriptors are basic information for calculation of 2D Chebyshev polynomials, which are further used as variables for designing a regression equation that considers both the specificity and physicochemical properties of each atom in the training set [16]. It should be noted that the program can build QSAR models based either on one type of these descriptors or on their combination at the consensus approach [15, 16]. Based on the consensus approach ideology, models of the quantitative prediction of the biological activity are calculated independently for each type of descriptors. Ready QSAR models in GUSAR for predicting toxic effects of chemical compounds, which can be used, are exemplified on the Internet in the website http://www.way2drug.com/GUSAR.

In addition to the possibility of creating QSAR models, the GUSAR program allowed us to visualize the contribution of each atom to the predicted value [13, 15-18]. This possibility has been realized in QSAR models designed based on QNA descriptors and, respectively, in the consensus combination of QSAR models designed by different approaches. The program gives the possibility to determine "strong" and "weak" positions in molecules of biologically active compounds and, consequently, objectively conclude what fragments should be replaced on the molecular design for strengthening or weakening the targeted feature. It should be noted that this problem can be successfully solved also using other computerized programs and systems, e.g. with the computerized system

SARD-21 [19-21]. However, as discriminated from the possibility realized in the computerized system SARD-21, in the GUSAR program the contribution of atoms to the desired activity can be realized in a training set that includes a small number of structures (from 20 structures). No counter class of compounds, i.e. an alternative training set, all structures of which either lack the target feature or possess it to an insignificant extent, is required. By default, atoms not influencing the activity of the molecule are shown in green color. Atoms strengthening or weakening the activity under study are shown in red or blue color, respectively [13, 15-18].

Using the GUSAR program, QSAR models were designed in some stages.

Formation of the training and test sets. Structures of compounds of the training and test sets were created in the program MarvinSketch 5.9.1 [22] and converted into SDF format using the Discovery Studio Visualiser program [23].

The training set TS1 was formed based on 26 compounds studied as COX-2 inhibitors in work [24] (Table 1).

The training set (TS2) and test set (TeS) include, respectively, 20 and 6 structures of COX-2 inhibitors. These sets were obtained by separating TS1 that was previously sorted by increase in values of IC_{50} at ratio ~3 : 1, i.e. each fourth compound was excluded from TS1. Table 1 shows that structures of compounds in TS1, TS2, and TeS are characterized by a rather wide range of the 50% inhibitory concentration (IC_{50}). The inhibitory activity of these compounds was measured as binding by degree of decrease in the COX-2 catalytic activity of resident macrophages in male white mice and presented as a quantitative parameter IC_{50} expressed in nmol/liter. The chosen compounds are derivatives of 4,5,6,7-tetrahydro-2H-isoindole, 2,3-dihydro-1H-pyrrolysine, and benzothiophene. They were characterized by the presence in their structure of two benzene substituents bound with heterocyclic aromatic fragments. The abilities of these compounds to inhibit the catalytic activity of COX-2 were in the range 0.6-700.0 nmol/liter. To design QSAR models, these IC_{50} values in nmol/liter were expressed as mol/liter and then transformed into pIC_{50} values according to the formula:

$$pIC_{50} = -\log10(IC_{50}).$$

The activity ranges of compounds within the training sets TS1 and TS2 and in the test set TeS in pIC_{50} units were from 9.22 to 6.15 for TS1, from 9.22 to 6.15 for TS2, and from 8.96 to 6.30 for TeS.

QSAR modeling. QSAR models of quantitative prediction of inhibitory activity of COX-2 inhibitors were designed based on the MNA and QNA descriptors. The final regression models were a consensus of QSAR models designed independently on each other based on each descriptor type and characterized by a high predictive ability.

Assessment of quality and predictive ability of QSAR models. The predictive ability of the models M2, M4, and M6 design based on training set TS2 was assessed using the internal test set (TeS). The predictive ability of the M1, M3, and M5 models was assessed only by prediction results of numerical values of the training set TS1 activity. A sliding control with occasional twenty-fold exception of 20% of the training set was used as internal validation. Other parameters of GUSAR were used by default. Altogether, 360 models were created (180 for each descriptor type).

Assessment of atom contributions to target activity. The contribution of atoms to the activity of COX-2 inhibitors was assessed by consensus model M5, which contained 26 inhibitors of COX-2. As mentioned above, in the GUSAR program this procedure is realized automatically on designing QSAR models based on QNA descriptors and consensus models. To simplify comprehension of the illustrating data, the results of analysis of atom contributions to the target activity presented in the QSAR models by different colors were expressed as graphic symbols. Atoms not influencing the activity of COX-2 inhibitors are shown by squares, atoms increasing the activity of COX-2 inhibitors are shown by circles, and atoms lowering such activity are indicated by asterisks. The number of asterisks corresponds to value of the negative contribution of the atom under study to the target feature.

RESULTS AND DISCUSSION

The quantitative relationships between the structure and efficiency of inhibition of COX-2 catalytic activity by derivatives of 4,5,6,7-tetrahydro-2H-isoindole, 2,3-dihydro-1H-pyrrolysine, and benzothiophene included in the training sets TS1 and TS2 were modeled using a consensus approach (with averaging the prediction results by several models) realized in the GUSAR program. Finally, depending on the type of descriptors used in the calculations, three consensus models were obtained for each of the training sets (Table 2). The predictive ability of the final regression equations of consensus models M1-M6 was assessed on structures of training sets TS1 and TS2, respectively, at the sliding control with exclusion of 20% of the compounds. Additionally, the predictive abilities of models M2, M4, and M6 were tested in it independently of six isoindole derivatives from the test set TeS not included into training set TS1. Statistical parameters of the consensus models, as well as characteristics of the accuracy of the predicted pIC_{50} values for the COX-2 inhibitors, are presented in Table 2.

As follows from results presented in Table 2, to design QSAR models with acceptable statistical charac-

Table 1. Structures of COX-2 inhibitors included into the training and test sets TS1, TS2, and TeS with corresponding IC_{50} values as well as assessment of contribution of atoms to inhibitory activity evaluated by the consensus model

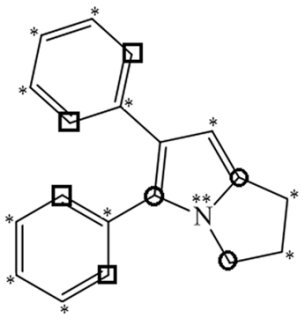
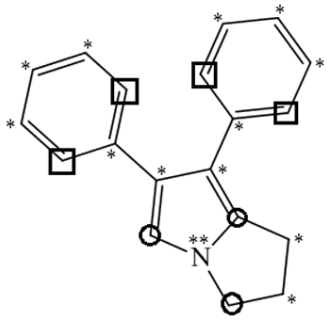
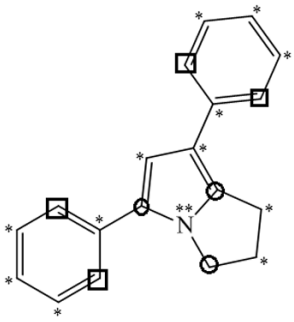
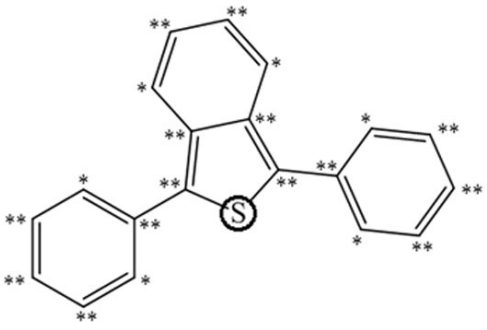
No.	Compound [24]	Structural formulas of compounds with corresponding contributions of atoms to activity	TS1	TS2	TeS	IC_{50}, nM [24]*
1	2	3	4	5	6	7
1	3		+	+	–	10.0
2	4		+	+	–	28.7
3	5		+	+	–	50.0
4	6		+	+	–	10.9

Table 1 (Contd.)

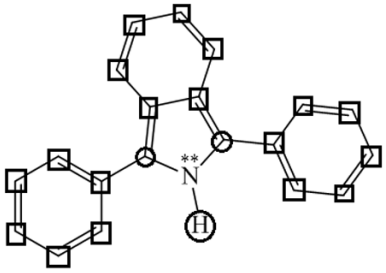
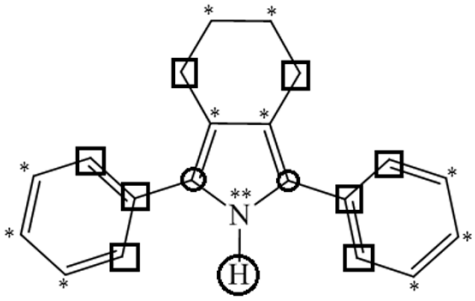
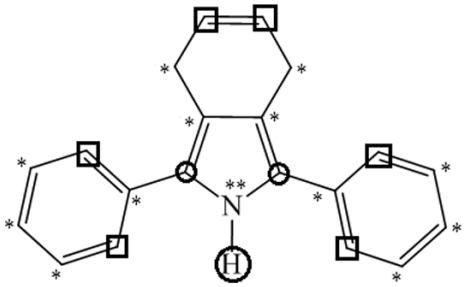
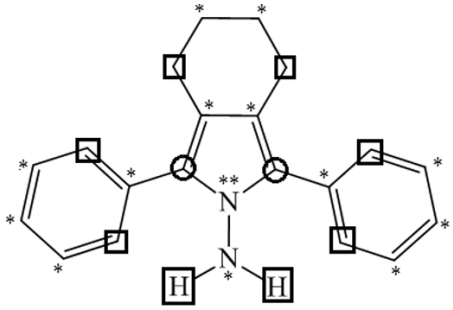
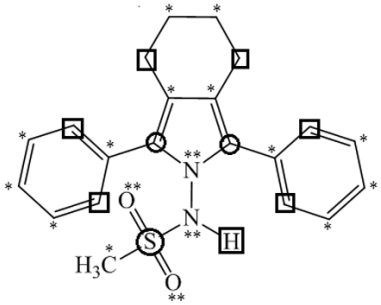
1	2	3	4	5	6	7
5	7		+	+	–	10.0
6	11		+	+	–	1.5
7	12		+	+	–	3.3
8	14		+	–	+	1.8
9	15		+	+	–	500.0

Table 1 (Contd.)

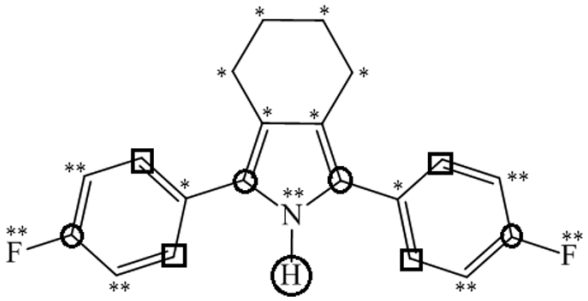
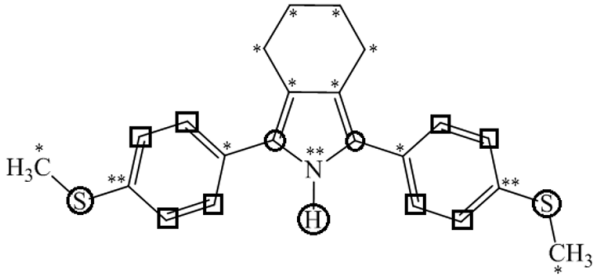
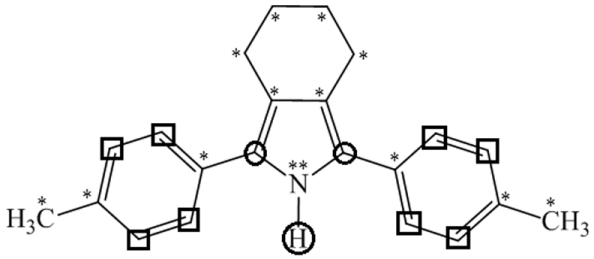
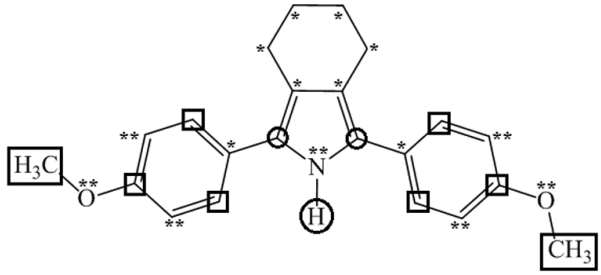
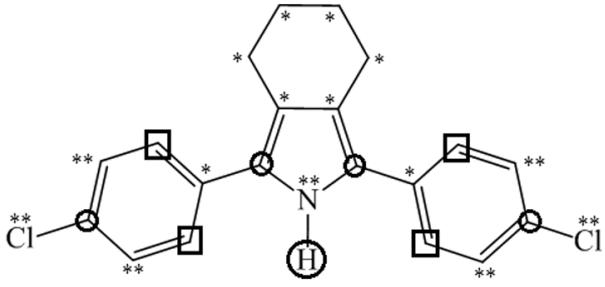
1	2	3	4	5	6	7
10	17		+	+	–	1.7
11	18		+	–	+	500.0
12	19		+	+	–	16.7
13	20		+	+	–	21.3
14	21		+	+	–	5.0

Table 1 (Contd.)

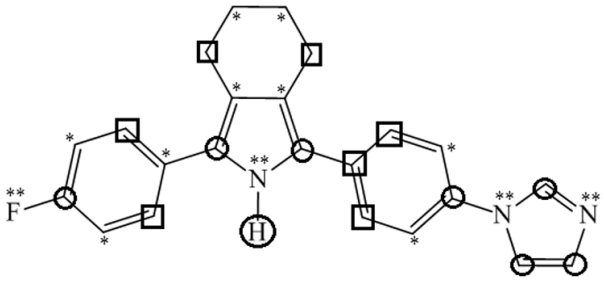
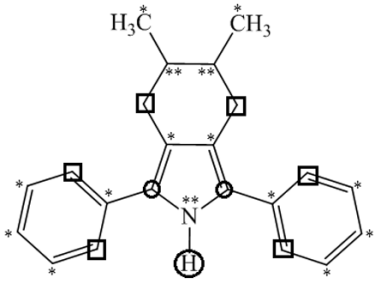
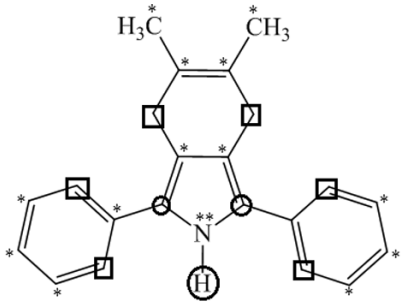
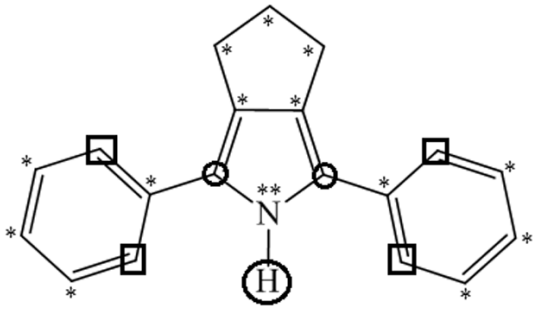
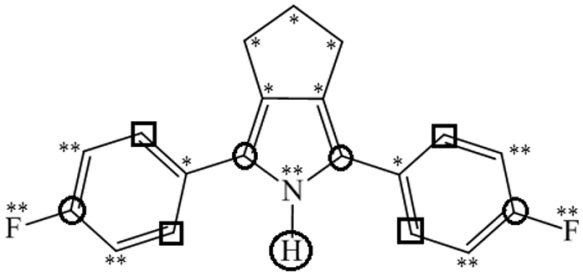
1	2	3	4	5	6	7
15	22		+	–	+	42.0
16	24		+	+	–	3.1
17	25		+	–	+	14.5
18	27		+	+	–	0.7
19	28		+	+	–	2.9

Table 1 (Contd.)

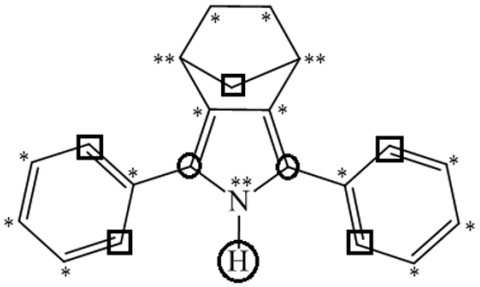
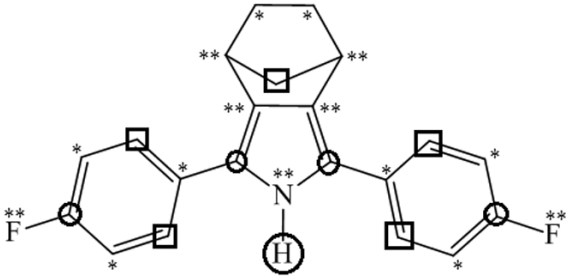
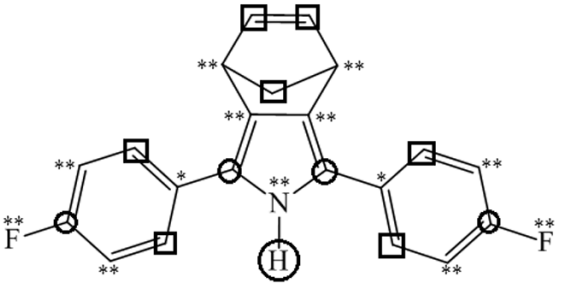
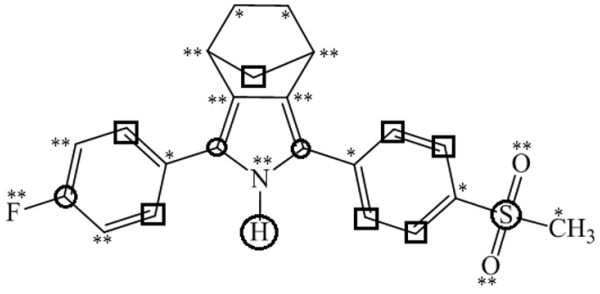
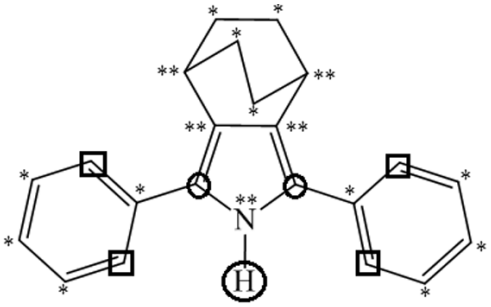
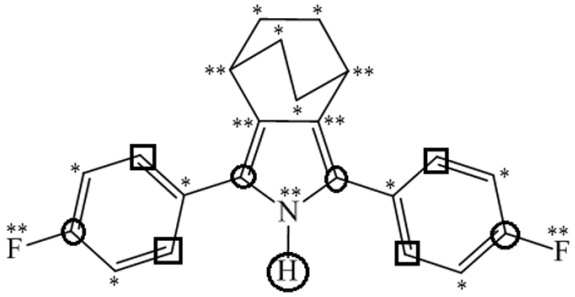
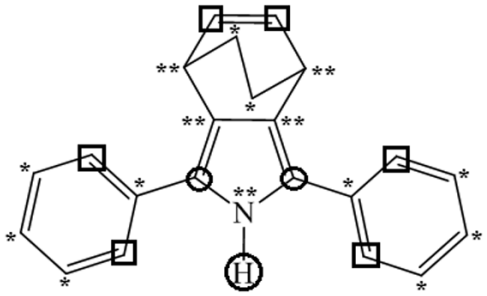
1	2	3	4	5	6	7
20	31		+	+	–	2.6
21	32		+	–	+	1.1
22	33		+	–	+	4.5
23	34		+	+	–	700.0
24	36		+	+	–	1.6

Table 1 (Contd.)

1	2	3	4	5	6	7
25	37		+	+	–	0.6
26	38		+	+	–	35.6

Note: Squares in structural formulas indicate atoms lacking influence on the activity of COX-2 inhibitors; circles indicate atoms increasing activity of COX-2 inhibitors; asterisks indicate atoms that lower the activity of COX-2 inhibitors, the number of asterisks corresponds to degree of down-regulatory influence of the atom under consideration.

* Data were obtained by Portevin et al. [24] in binding experiments from assessment of decrease in catalytic activity of COX-2 resident macrophages in male white mice.

teristics ($R^2 > 0.6$, $Q^2 > 0.5$) [15-18], consensus models can be used that combine QSAR models designed based on one or both types of descriptors (QNA or MNA). Insignificant difference between the statistical characteristics of the models predicting the pIC_{50} parameters for TS1 and TS2 design based on different descriptors indicates stability of these models (Table 2). Creation of QSAR models based on MNA descriptors helps obtain consensus models M1 and M2 with high values of R^2 and Q^2. However, the predictive ability of model M2 on compounds of the test set TeS, which are significantly similar in structure with compounds of the training set TS2, has low accuracy.

The consensus model M4 designed based on QNA descriptors is characterized by lower quality of prediction on compounds of training set TS1 (R^2_{TS} and Q^2 values) than model M1. However, it shows a high predictive ability on structures of test set TeS (R^2_{TeS}, Table 2).

Data presented in Table 2 show that using the consensus approach based on the combination of MNA and QNA descriptors for designing regression equations gave models M5 and M6 with high statistical parameters. In particular, model M6 is characterized by rather high predictive ability on compounds of both training set TS2 and compounds with similar structure of test set TeS. This conclusion is supported by results predicted by the consensus model in comparison with experimental values, which are presented in the figure.

The prediction results are in a good agreement with the literature data. It is known that using a consensus model, which averages results of prediction over separate models, decreases the variability of prediction results by separate models and thus obtains a more accurate result [25]. Moreover, the consensus approach in the generation of models provides a more accurate information on the contribution of different atoms to the studied activity. Therefore, models M5 and M6 based on the consensus approach were used for further analysis.

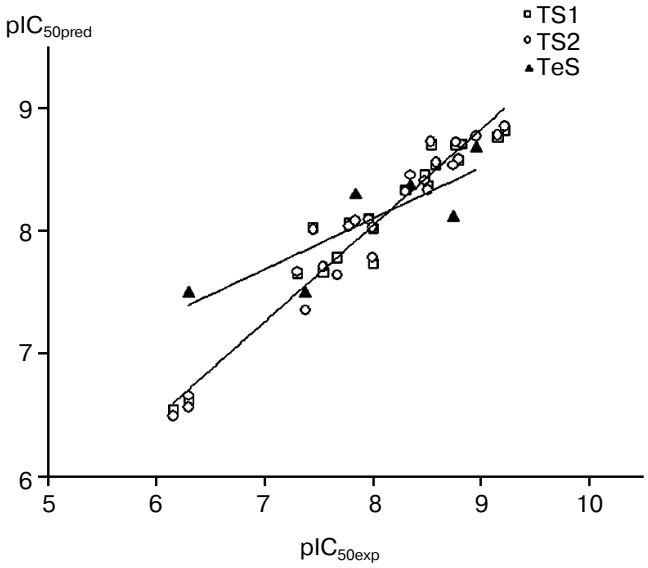
Then the contributions to COX-2 inhibition of atoms and functional groups including them in compounds of the TS1 set were analyzed using the GUSAR program. The analysis was performed on the M5 model, which contained 26 COX-2 inhibitors. Table 1 shows the contributions of atoms to the predicted activity of COX-2 inhibitors.

In particular, electron donating and electron accepting substituents ambiguously influenced the binding efficiency of isoindole derivatives with the active center of

COX-2. This could be due to different interaction mechanisms of the studied compounds with the COX-2 active center. A similar conclusion was made by authors of work [26] whose experimental data were used for the present theoretical investigation. The influence of halogen atoms on the efficiency of COX-2 inhibitors is also ambiguous. Comparison of structures S11, S17, S22, S27, S28, S33, and S34 shows that the fluorine atom bound with the 1,4-bisubstituted benzene weakens the activity of compounds that contain it. The compounds with codes S32 and S37 (Table 1) are exceptions: the substitution in them of the hydrogen atom by fluorine in the *para* position of the benzene fragment results in quite the opposite effect (Table 1). Introduction into the *para* position of benzene fragments of both fluorine atoms and sulfonic fragment combined with a methyl group results in a significant decrease in the activity of compound S34 that is obvious on comparing the efficiencies of compounds S31 and S34. These conclusions are also confirmed by visual analysis.

The discrepancy in the interpretation of the experimental data and the conclusions of the GUSAR program in the case of compounds S32 and S37 can be explained by another mechanism of their interaction with the COX-2 active center as compared to other known COX-2 inhibitors. It is known that sometimes even a slight structural modification of biologically active substances can lead to significant changes in their activity up to changes in the mechanism of their interaction with the active center of a studied enzyme. Such phenomena cannot be taken into account by any classical method of QSAR modeling, including approaches realized in the GUSAR program.

The comparative analysis of structures S18, S20, and S34 as well as of structures S14 and S15 revealed that a methyl group in combination with a sulfo-group, oxygen atom, or sulfur atom also negatively influenced the target property (Table 1). The oxygen atom within the sulfonic and methoxy groups decreases the activity of COX-2 inhibitors, while the sulfur atom within the same groups as well as within the thiomethyl group in the structures of COX-2 inhibitors promotes an increase in activity (Table 1). The sulfur atom within the heterocyclic aromatic fragments in structure S18 (Table 1) had a similar effect. Mono- and di-substituted benzene as well as fragments of



Comparison of experimental (pIC_{50exp}) values of pIC_{50} with predicted values (pIC_{50pred}) by models M5 and M6 for COX-2 inhibitors included in training sets TS1 and TS2 and test set TeS

Table 2. Statistical characteristics and assessment of prediction accuracy of pIC_{50} values for COX-2 inhibitors by consensus models M1-M6. The TS1 and TS2 structures are in the pIC_{50} activity range from 9.22 to 6.15

Training set	Model	N	R^2_{TS}	Q^2	R^2_{TeS}	F	S.D.	V
QSAR models based on MNA descriptors								
TS1	M1	26	0.865	0.818	–	19.626	0.320	5
TS2	M2	20	0.885	0.833	0.421	16.90	0.290	4
QSAR models based on QNA descriptors								
TS1	M3	26	0.826	0.731	–	14.996	0.357	5
TS2	M4	20	0.779	0.654	0.824	11.293	0.390	4
QSAR models based on QNA and MNA descriptors								
TS1	M5	26	0.889	0.837	–	15.301	0.316	5
TS2	M6	20	0.874	0.802	0.706	11.022	0.334	4

Note: N, number of structures in training set; R^2_{TS}, determination coefficient calculated for compounds from the training set; R^2_{TeS}, determination coefficient for compounds from the test set; Q^2, correlation coefficient calculated on the training set on sliding control with exception one by one; F, Fischer's test; S.D., standard deviation; V, number of variables in final regression equation.

Table 3. Influence of constants of Brown's *para* substituents in the benzene ring of compounds S11 and S17-S21 on efficiency of their inhibitory action toward COX-2

No.	Compound code in Table 1	4-R	σ^{+}_{para}	IC_{50}, nM
1	11	H	0.000	1.5
2	21	Cl	0.114	5.0
3	17	F	–0.073	1.7
4	19	CH_3	–0.311	16.7
5	18	SCH_3	–0.604	500.0
6	20	OCH_3	–0.778	21.3

Table 4. List of descriptors used for Hansh's approach in the work of Silakari et al. [26]

Type of descriptor	Symbol	Depiction of descriptor
Electronic	A_{pol}	summary of polarizability of atoms
Electronic	HOMO	energy of the highest occupied molecular orbital, eV
Structural	HBD	number of donors of hydrogen bond
Thermodynamic	F_{H_2O}	free energy of desolvation in water, kcal/mol
Spatial	S_{xyf}	projection of the molecule surface onto the plane within a rectangular produced by OX and OY axes
Spatial	S_{xzf}	projection of the molecule surface onto the plane within a rectangular produced by OX and OZ axes

Table 5. Comparison of statistical parameters of our models M5 and M6 with QSAR models of Silakari et al. [26]. Structures of sets TS1 and TS2 are in pIC_{50} activity range from 9.22 to 6.15

Model No.	N	R^2	Q^2	F	S.D.	V	Descriptor type
M5	20	0.873	0.803	11.411	0.335	4	QNA and MNA
M6	26	0.887	0.834	15.451	0.318	5	QNA and MNA
M (1)*	25	0.757	–	32.673	0.581	1	A_{pol}
M (2)*	25	0.817	–	29.819	0.516	2	A_{pol}, HBD
M (3)*	25	0.761	–	21.276	0.590	2	A_{pol}, HOMO
M (4)*	25	0.804	–	27.334	0.535	2	A_{pol}, F_{H_2O}
M (5)*	25	0.758	–	20.872	0.594	2	A_{pol}, S_{xyf}
M (6)*	25	0.764	–	21.530	0.587	2	A_{pol}, S_{xzf}

Note: N, number of structures in training set; R^2, determination coefficient calculated for compounds from the training set; Q^2, correlation coefficient calculated on the training set on sliding control with exception one by one; F, Fischer's test; S.D., standard deviation; V, number of variables in final regression equation.
* Literature data [26].

3,5-dimethyl-4-azatricyclo[5.2.1.0]deca-2,5-diene and 3,5-dimethyl-4-azatricyclo[5.2.2.0]undeca-2,5-diene display a weak negative influence on the studied activity in all compounds. The secondary nitrogen atom involved in heterocyclic fragments also decreases the inhibitory activity of compounds that contain it, whereas a hydrogen atom within this functional group acts on the activity of the compounds just oppositely. The tertiary nitrogen atom involved in the 2,3-dihydro-1H-pyrrolysine fragment decreases the efficiency of COX-2 inhibition. The primary amino group NH_2 negatively influences the target property in structure S14 (Table 1).

Electron-donating methyl and electron-accepting methoxyl groups, and well as an imidazole cycle located in *para* positions of benzene fragments, decrease by an order of magnitude the activity of compounds S19 and S20 as compared to compound S11 (Table 1). The introduction of an electron-accepting thiomethyl group into the *para* position of benzene fragments of compound S34 leads to a significant loss in inhibitory activity – virtually by two orders of magnitude (Table 1). On comparing structures of compounds S12 and S25, we can conclude that the introduction of methyl substituents into positions 5 and 6 of the 4,7-dihydro-2H-isoindole fragment decreases fourfold the activity of COX-2 inhibitors (Table 1). Thus, conclusions about the influence of structural fragments on COX-2 activity based on visual analysis with the GUSAR program do not contradict the experimental results.

To explain the ambiguous influence of electron-donating and electron-accepting groups on the activity of COX-2 inhibitors, we studied the influence of numerical values of constants of Brown's *para* substituents [27] on the activity of COX-2 inhibitors (Table 3).

Table 3 shows that functional groups with pronounced nucleophilic features decrease the activity of COX-2 inhibitors. Moreover, the substitution of hydrogen atoms in the *para* positions of benzene groups by functional groups incapable of generating hydrogen bonds with the COX-2 active site also decrease the inhibitory action on COX-2. Our conclusions about the influence of nucleophilicity and of capability of functional groups for formation of hydrogen bonds are in complete agreement with the conclusions of Silakari et al. [26]. Based on descriptors of four types (electronic, structural, thermodynamic, spatial) presented in Table 4, the authors of that work realized QSAR modeling of 25 compounds included in training sets TS1 and TS2 formed by us.

It should be noted that our models for predicting numerical values of IC_{50} for the COX-2 inhibitors are no less accurate than six QSAR models presented in work [26] when a genetic algorithm was used to form regression equations, which is confirmed by results of investigations presented in Table 5.

Thus, the influence of atom nature on the inhibitory activity of isoindole derivatives on COX-2 was ambiguous and often depended on the nature of the nearest structural fragments of the compound. Moreover, on analyzing the atom contributions to the activity it was necessary to take into account the functional group that included the studied atom. These results can be taken into consideration on the molecular design of acting substances in known nonsteroidal antiinflammatory drugs to increase the efficiency of their inhibitory action on COX-2.

1. Using the computer program GUSAR, structure–activity relationships have been analyzed for COX-2 inhibitors – derivatives of tetrahydro-2H-isoindole, 2,3-dihydro-1H-pyrrolysine, and benzothiophene.

2. On the basis of MNA and QNA descriptors as well as their consensus combination, six QSAR models were designed for prediction of numerical values of pIC_{50}. These models are characterized by good predictive abilities on structures of the training and test sets.

3. Functional groups responsible for modifying the activity of COX-2 inhibitors have been identified. *Para* substituents with pronounced nucleophilic features are shown to decrease the activity of COX-2 inhibitors.

4. The influence of atom nature on the efficiency of COX-2 inhibitors has been analyzed. During the structural analysis of COX-2 inhibitors included into model M5, atoms were detected that either decreased or increased the efficiency of the inhibitory action on COX-2. These data can be used for optimization of structures of biologically active substances to increase their inhibitory action on COX-2.

5. In the majority of cases, the dependences between atoms and structural fragments and the inhibitory activity of compounds identified based on QSAR models and their visualization in the GUSAR program were in agreement with the regularities found by expert assessment of experimental values of the studied compounds. This confirms that the GUSAR program can be used for optimization of structures of chemical compounds.

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