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Research Article

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Prediction of Acute Toxicity of (Z) -N, N-Dimethyl-2- (perfluorophenyl) -2- (2-phenylhydrazinylidine)acetamide for Rats using the GUSAR Program

Askerova Ulviyya F.

Baku State University, st. Z. Khalilova 23, Az, 1148, Baku, Azerbaijan
Email: askerova.ulviyya.69@gmail.com

Abstract It is known that the determination of the values of half-lethal doses (LD_{50}) for rodents is a necessary stage of preclinical experimental studies for putative physiologically active substances. To calculate (*in silico*) the LD_{50} value for 4 methods of substance administration (oral, intraperitoneal, intravenous, subcutaneous), we used the GUSAR (General Unrestricted Structure-Activity Relationships) computer program as a web service. When making a forecast of the LD_{50} value for the analyzed compound, it is assessed that it falls within the range of applicability of the QSAR model used. A prediction of the LD_{50} value for (Z) -N, N-dimethyl-2- (perfluorophenyl) -2- (2-phenylhydrazinylidine) acetamide was obtained, and the possibilities of computerized prediction of acute toxicity were demonstrated.

Keywords Computer prediction LD_{50}, GUSAR program, Perfluorophenyl derivatives, Dimethylamino derivatives

Introduction

Experiments on animals are one of the most controversial issues in modern science. Experiments on animals are conducted for various purposes - research into the functioning of organisms, the development of methods for treating human diseases, as well as testing for the safety and quality of medicines and vaccines (which is very important at the present time). Proponents of animal testing point to advances in medicine that have been made possible by this type of experimentation. Opponents, however, consider them cruel and senseless, since the results of animal studies are not always applicable to humans.

In 1959, William Russell and Rex Birch, advocating a more humane approach to the use of animals in scientific research, in the published work Principles of Humane Experimental Technique, clearly formulated the so-called "Three R" Rule - Replacement, Reduction, Refinement, according to which, we are talking about replacing and reducing the use of animals in preclinical studies of pharmacologically active substances and, if possible, replacing them with improved and alternative methods [1]. Currently, about 29 million animals per year are subjected to experiments in the United States and the European Union (of which 80% are rats and mice). This is, of course, less than half of what it was in the mid-1970s. There is a decline and it has been observed in the last 10 years. Many scientists in their research adhere to the "three R" rule, and it is of course relevant both from the point of view of economics and ethics, because the study of the physiological activity of one compound requires a lot of time and resources, plus the factor of using laboratory animals.

Materials and Methods

One of the alternative methods for determining the physiological activity of the synthesized compounds and, in particular, for determining such an important parameter as the half-lethal dose (LD_{50}) for rodents is the computer program GUSAR [2].

This article presents a computer prediction of the half-lethal dose of LD_{50} for rats with 4 ways of administration of the synthesized substance based on the models of quantitative relationships "structure of acute toxicity" (QSAR models) constructed using the GUSAR program. Since the determination of LD_{50} values is carried out at the early stages of preclinical studies [3], computer assessments can significantly reduce the number of compounds studied, and, consequently, the number of laboratory animals used in the experiment.

For the first time, by means of a tandem reaction, under the conditions of a catalytic olefination reaction, we have synthesized (Z)-N,N-dimethyl-2-(perfluorophenyl)-2-(2-phenylhydrazinylidine)acetamide.

(Z)-N,N-dimethyl-2-(perfluorophenyl)-2-(2-phenylhydrazineylidene)acetamide

Full-scale studies have been carried out to determine (NMR, X-ray) and study the structural features of this compound [4]. Taking into account the latter, in particular the presence of 5 fluorine atoms, carbonyl, dimethylamine, hydrazone groups, it is assumed that this compound has a certain physiological activity.

Results and Discussion

Prediction of acute toxicity in rats using the GUSAR program

The GUSAR computer program is designed to construct models of quantitative relationships between the structure and various properties of organic molecules [5]. QSAR method for modeling acute toxicity for rats based on a combination of QNA (Quantitative Neighborhoods of Atoms) descriptors, PASS (Prediction of Activity Spectra for Substances) and self-consistent regression (SCR-Selective Catalytic Reduction) predictions. The proposed method was evaluated on a set of compounds tested for acute toxicity to rats after oral administration (7286 compounds) used to test the known QSAR methods in the TEST 3.0 (US EPA) program [6].

Using the GUSAR program, QSAR models of dependencies "structure of acute toxicity" were built with 4 modes of administration of a pharmacological substance (oral, intraperitoneal, intravenous, subcutaneous) for rats. The characteristics of the constructed models are given in table 1.

Table 1

Administration	N train	N test	N models	R^2	Q^2	R^2 test	RMSE test	Coverage, %
Oral	6280	2692	40	0.61	0.57	0.59	0.57	97.5
Intraperitoneal	2480	1065	68	0.66	0.56	0.57	0.57	96.1
Intravenous	920	394	50	0.73	0.66	0.63	0.62	99.2
Subcutaneous	759	325	7	0.69	0.59	0.50	0.69	92.0

Characteristics of QSAR models for rat ld_{50} values predictions

N train - number of compounds in the training set;

N test - number of compounds in the test set;

R^2 - average R^2 of the models calculated for the appropriate training set;

Q^2 - average Q^2 of the models calculated for the appropriate training set;

Coverage - % compounds from the test set in Applicability Domain.

According to the table 1, the statistical data characterizing the quality of the constructed dependences satisfy the requirements [7] and this allows them to be used to estimate the LD_{50} values based on the structural formulas of the analyzed substance.

It is also important that when predicting the LD50 value for the analyzed compound, an estimate of its falling into the Applicability Domain of the corresponding QSAR model was given. That is, the average similarity of the structural formula of this compound with the structural formulas of the 3 nearest neighbors in structure is calculated. In cases where this value exceeded 0.7, the compound corresponds to the scope of the model (in AD); otherwise, the compound does not correspond to the scope of the model (out of AD).

Using the example of assessing the acute toxicity of synthesized (Z)-N,N-dimethyl-2-(perfluorophenyl)-2-(2-phenylhydrazineylidene)acetamide, let us consider the possibilities of computer prediction.

The assessment of acute toxicity for mice was obtained by us using the local version of the GUSAR program.

Table 2

Rat IP LD_{50} Log10 (mmol/kg)	Rat IV LD_{50} log10 (mmol/kg)	Rat Oral LD_{50} log10 (mmol/kg)	Rat SC LD_{50} log10 (mmol/kg)
-0,022 in AD	-0,173 in AD	0,101 in AD	0,031 in AD
Rat IP LD_{50} (mg/kg)	Rat IV LD_{50} (mg/kg)	Rat Oral LD_{50} (mg/kg)	Rat SC LD_{50} (mg/kg)
339,700 in AD	239,900 in AD	450,500 in AD	384,000 in AD

Classification of chemicals for acute toxicity for rodents, developed by the OECD (Organization for Economic Co-operation and Development) project.

Table 3

Rat IP LD_{50} Классификация	Rat IV LD_{50} Классификация	Rat Oral LD_{50} Классификация	Rat SC LD_{50} Классификация
Класс 4 in AD	Класс 4 in AD	Класс 4 in AD	Класс 4 in AD

IP - Intraperitoneal route of administration
IV - Intravenous route of administration
Oral - Oral route of administration
SC - Subcutaneous route of administration
in AD - compound falls in applicability domain of models
out of AD - compound is out of applicability domain of models

According to the data presented in the tables, for all 4 ways of drug administration, the substance belongs to the 4th hazard class - "Moderately hazardous". In all cases, the results of assessing the compliance of the forecast results with the range of applicability of the corresponding models (in AD) are given [8].

Conclusion

Thus, on the basis of the GUSAR computer program, we implemented *in silico* an estimate of the LD_{50} value for (Z) -N, N, -dimethyl-2- (perfluorophenyl) -2- (fenildiazenyl) acetamide with 4 methods of administration of the substance (oral, intraperitoneal, intravenous , subcutaneously). Based on the above data, we can conclude that this compound certainly has a definite physiological activity and, which is important, is in the area of applicability (in AD). Using the capabilities of the program, we can continue our research and, without conducting preclinical studies on the basis of the GUSAR program, predict various pharmacotherapeutic properties. Because the GUSAR prediction is based on the analysis of quantitative relationships "structure – acute toxicity" for a heterogeneous training set; a similar approach can also be applied to various synthesized compounds. The use of computer prediction allows us to select the safest compounds among the substances we have synthesized that have the required pharmacological action, which will thus also reduce the number of experiments on laboratory animals.

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