New Materials, Compounds and Applications
Vol.7, No.1, 2023, pp.50-56

PREDICTION OF ACUTE TOXICITY FOR (Z)-3-(2-PHENYLHYDRAZINYLIDENE)BENZOFURAN-2(3H)-ONE AND ITS DERIVATIVES FOR RATS USING GUSAR PROGRAM

Ulviyya F. Askerova*

Department of Organic Chemistry, Baku State University, Baku, Azerbaijan

Abstract. The value of half-lethal doses (LD50) for rodents is a necessary stage of preclinical experimental studies for compounds supposedly having a certain physiological activity. The GUSAR (General Unrestricted Structure-Activity Relationships) computer program is used to determine the LD50 value for the 4 methods of substance administration. A prediction of the LD50 value for (Z)-3-(2-phenylhydrazinylidene)benzofuran-2(3H)-one and its derivatives was gained, and thus the possibilities of computer prediction for acute toxicity were shown.

Keywords: *computer prediction LD50, GUSAR program, (Z)-3-(2-phenylhydrazinylidene) benzofuran-2(3H)-one derivatives*

Corresponding Author: *Ulviyya F. Askerova, Department of Organic Chemistry, Baku State University, Baku, Azerbaijan, e-mail: askerova.ulviyya.69@gmail.com*

Received: *31 December 2022;* ***Accepted:*** *16 February 2023;* ***Published:*** *17 April 2023.*

1. Introduction

Furanones are five-membered heterocycles, the presence of which in biologically active compounds of natural and synthetic origin has made it an indispensable pharmacophore for the design and development of new therapeutic agents. Compounds containing a furanone fragment can be classified into various therapeutic categories, namely: analgesic and anti-inflammatory, anticancer, anticonvulsant, antibacterial and antifungal, antioxidant, antiulcer and antituberculosis, etc.

The classic way to create drugs consists of several stages: the search for biologically active compounds, pharmacological and clinical trials. But this approach is associated with the involvement of a large amount of resources, time and is associated with some ethical aspects, i.e. with one of the most controversial issues in modern science - animal experiments. Scientists of the new generation in their research adhere to the "Rule of three R" - Replacement, Reduction, Refinement, formulated by William Russell and Rex Birch in 1959, which deals with substitution and reduction in preclinical animal studies and the use of alternative methods (Russell & Burch, 1959).

2. Materials and Methods

An alternative method path for determining the physiological activity of synthesized compounds and determining the half-lethal dose (LD50) for rodents is implementation the computer program GUSAR (Lagunin *et al.*, 2011)

How to cite (APA):
Askerova, U.F. (2023). Prediction of acute toxicity for (Z)-3-(2-phenylhydrazinylidene)benzofuran-2(3H)-one and its derivatives for rats using GUSAR program. *New Materials, Compounds and Applications*, *7*(1), 50-56.

This paper proposes a computer prediction of the half-lethal dose of LD50 for rats with 4 ways of administering the test substance based on models of quantitative relationships "structure - acute toxicity" (QSAR models) built using the GUSAR (Pozharitskaya *et al.,* 2019).

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 (.Zakharov *et al.,* 2006). 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 (http://www.pharmaexpert.ru/GUSAR/AcuToxPredict).

Through the GUSAR program, QSAR models of dependencies "structure - acute toxicity" were built with four 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. Characteristics of QSAR models for rat ld50 values predictions

Administration	N train	N test	N models	R2	Q2	R2 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

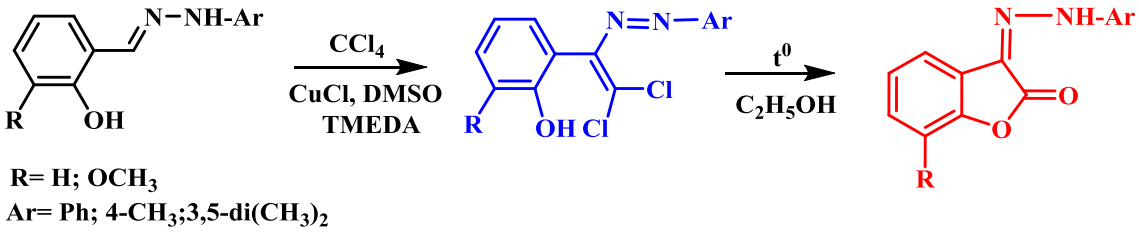
N train - number of compounds in the training set;
N test - number of compounds in the test set;
R2 - average R2 of the models calculated for the appropriate training set;
Q2 - average Q2 of the models calculated for the appropriate training set;
Coverage - % compounds from the test set in Applicability Domain.

According to the table 1, the statistical data characterizing the quality of the constructed dependences satisfy the requirements (Sukhachev *et al.,* 2019) and this allows them to be used to estimate the LD50 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).

3. Results and Discussion

We have carried out an economical synthesis of (Z) -3- (2-phenylhydrazone) ¬benzofuran-2(3H)-one of its derivatives. In the first, the corresponding fenlhydrazone of salicylic aldehyde was synthesized. Further, under standard COR (Catalytic olefination reaction) conditions, the corresponding dichlorodiazadienes were obtained. Then, by reaction of ethyl alcohol, the formation of crystals were observed. X-ray established the formation of (Z) -3- (2-phenylhydrazone)-benzofuran-2(3H)-one and its derivatives.



R= H; OCH_3
Ar= Ph; 4-CH_3;3,5-di(CH_3)$_2$

Scheme 1. Synthesis (Z) -3- (2-phenylhydrazone) ¬benzofuran-2(3H)-one of its derivatives

Full-scale studies have been carried out to determine (NMR, X-ray) and study the structural features of these compounds (Atioğlu *et al.*, 2021a; 2021b; Akkurt *et al.*, 2019; Asgarova *et al.*, 2019).

In this paper, we will consider acute toxicity estimates for (Z) -3- (2-phenylhydrazone) -benzofuran-2(3H) -one and its derivatives synthesized by us.

The assessment of acute toxicity for mice was obtained by us using the local version of the GUSAR program. The results of the forecast (in all cases there is a correspondence to the range of applicability of the models) are presented in Tables 2-9.

Rat acute toxicity predicted by GUSAR for (Z)-3-(2-phenylhydrazineylidene)benzofuran-2(3H)-one

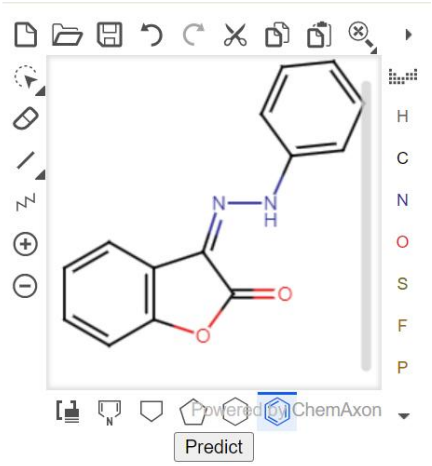


Fig. 1. Structural formula (Z)-3-(2-phenylhydrazineylidene)benzofuran-2(3H)-one

Table 2. Rat acute toxicity predicted by GUSAR for (Z)-3-(2-phenylhydrazineylidene) benzofuran-2(3H) – one

Rat IP LD50 Log10(mmol/kg)	Rat IV LD50 log10(mmol/kg)	Rat Oral LD50 log10(mmol/kg)	Rat SC LD50 log10(mmol/kg)
0,109 in AD	-0,388 in AD	0,642 in AD	0,679 in AD
Rat IP LD50 (mg/kg)	Rat IV LD50 (mg/kg)	Rat Oral LD50 (mg/kg)	Rat SC LD50 (mg/kg)
306,200 in AD	97,520 in AD	1044,000 in AD	1138,000 in AD

Table 3. Acute Rodent Toxicity Classification of Chemicals by OECD Project for (Z)-3-(2-phenylhydrazineylidene)benzofuran-2(3H)-one

Rat IP LD50 Classification	Rat IV LD50 Classification	Rat Oral LD50 Classification	Rat SC LD50 Classification
Class 4 in AD	Class 4 in AD	Class 4 in AD	Class 5 in AD

Rat acute toxicity predicted by GUSAR for (Z)-3-(2-(p-tolyl)hydrazineylidene) benzofuran- 2(3H)-one.

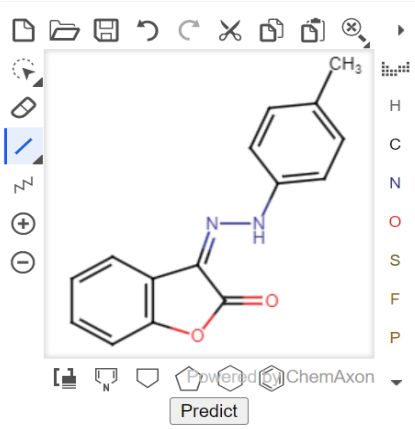


Fig. 2. Structural formula (Z)-3-(2-(p-tolyl)hydrazineylidene)benzofuran-2(3H)-one

Table 4. Rat acute toxicity predicted by GUSAR for (Z)-3-(2-(p-tolyl)hydrazineylidene) benzofuran- 2(3H)-one

Rat IP LD50 Log10(mmol/kg)	Rat IV LD50 log10(mmol/kg)	Rat Oral LD50 log10(mmol/kg)	Rat SC LD50 log10(mmol/kg)
0,316 in AD	-0,406 in AD	0,914 in AD	0,788 in AD
Rat IP LD50 (mg/kg)	Rat IV LD50 (mg/kg)	Rat Oral LD50 (mg/kg)	Rat SC LD50 (mg/kg)
522,300 in AD	99,060 in AD	2069,000 in AD	1549,000 in AD

Table 5. Acute Rodent Toxicity Classification of Chemicals by OECD Project for (Z)-3-(2-(p-tolyl)hydrazineylidene) benzofuran- 2(3H)-one

Rat IP LD50 Classification	Rat IV LD50 Classification	Rat Oral LD50 Classification	Rat SC LD50 Classification
Class 5 in AD	Class 4 in AD	Class 5 in AD	Class 5 in AD

Rat acute toxicity predicted by GUSAR for (Z)-3-(2-(3,5-dimethylphenyl) hydrazineylidene)benzofura-2(3H)-one

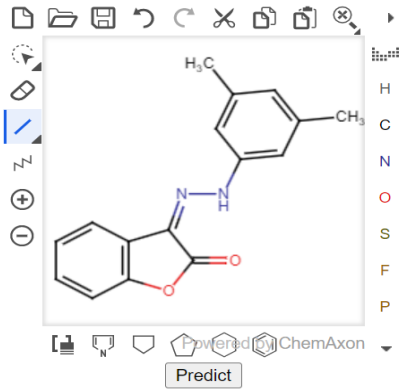


Fig. 3. Structural formula (Z)-3-(2-(3,5-dimethylphenyl)hydrazineylidene)benzofuran-2(3H)-one

Table 6. Rat acute toxicity predicted by GUSAR for (Z)-3-(2-(3,5-dimethylphenyl) hydrazineylidene)benzofura-2(3H)-one

Rat IP LD50 Log10(mmol/kg)	Rat IV LD50 log10(mmol/kg)	Rat Oral LD50 log10(mmol/kg)	Rat SC LD50 log10(mmol/kg)
-0,028 out of AD	-0,483 in AD	0,938 in AD	0,682 in AD
Rat IP LD50 (mg/kg)	Rat IV LD50 (mg/kg)	Rat Oral LD50 (mg/kg)	Rat SC LD50 (mg/kg)
249,500 out of AD	87,500 in AD	2310,000 in AD	1281,000 in AD

Table 7. Acute Rodent Toxicity Classification of Chemicals by OECD Project for (Z)-3-(2-(3,5-dimethylphenyl) hydrazineylidene)benzofura -2(3H)-one

Rat IP LD50 Classification	Rat IV LD50 Classification	Rat Oral LD50 Classification	Rat SC LD50 Classification
Class 4 out of AD	Class 4 in AD	Class 5 in AD	Class 5 in AD

Rat acute toxicity predicted by GUSAR for (Z)-7-methoxy-3-(2-phenylhydrazineylidene) benzofuran-2(3H)-one.

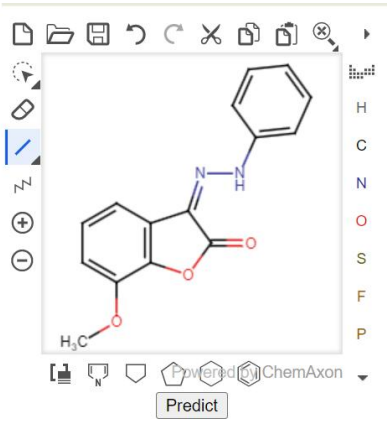


Fig. 4. Structural formula (Z)-7-methoxy-3-(2-phenylhydrazineylidene)benzofuran-2(3H)-one

Table 8. Rat acute toxicity predicted by GUSAR for (Z)-7-methoxy-3-(2-phenylhydrazineylidene) benzofuran-2(3H)-one

Rat IP LD50 Log10(mmol/kg)	Rat IV LD50 log10(mmol/kg)	Rat Oral LD50 log10(mmol/kg)	Rat SC LD50 log10(mmol/kg)
0,442 in AD	-0,371 in AD	0,639 in AD	0,688 in AD
Rat IP LD50 (mg/kg)	Rat IV LD50 (mg/kg)	Rat Oral LD50 (mg/kg)	Rat SC LD50 (mg/kg)
743,000 in AD	114,200 in AD	1167,000 in AD	1307,000 in AD

Table 9. Acute Rodent Toxicity Classification of Chemicals by OECD Project for (Z)-7-methoxy-3-(2-phenylhydrazineylidene) benzofuran-2(3H)-one

Rat IP LD50 Classification	Rat IV LD50 Classification	Rat Oral LD50 Classification	Rat SC LD50 Classification
Class 5 in AD	Class 4 in AD	Class 4 in AD	Class 5 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 4 in the 5th hazard class. These categories of chemicals have moderate and relatively low acute toxicity, respectively. 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 (https://www.ilo.org/legacy/english/protection/safework/ghs/ghsfinal/ghsc05.pdf).

4. Conclusion

Thus, on the basis of the GUSAR computer program, we implemented in silico an estimate of the LD50 value for (Z)-3-(2-phenylhydrazineylidene)benzofuran-2(3H)-one and its derivatives by 4 methods of administration of the substance (oral, intraperitoneal, intravenous , subcutaneously). Based on the above data, we can conclude that these compounds 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.

References

Akkurt, M., Shikhaliyev, N.Q., Suleymanova, G.T., Babayeva, G. V., Mammadova, G.Z., Niyazova, A.A., ... & Toze, F.A. (2019). Crystal structures and Hirshfeld surface analyses of the two isotypic compounds (E)-1-(4-bromophenyl)-2-[2, 2-dichloro-1-(4-nitrophenyl) ethenyl] diazene and (E)-1-(4-chlorophenyl)-2-[2, 2-dichloro-1-(4-nitrophenyl) ethenyl] diazene. *Acta Crystallographica Section E: Crystallographic Communications*, *75*(8), 1199-1204.

Asgarova, A.R., Khalilov, A.N., Brito, I., Maharramov, A.M., Shikhaliyev, N.G., Cisterna, J., ... & Mahmudov, K.T. (2019). Hydrogen and halogen bonding in the haloetherification products in chalcone. *Acta Crystallographica Section C: Structural Chemistry*, *75*(3), 342-347.

Atioğlu, Z., Akkurt, M., Askerova, U.F., Mukhtarova, S.H., Askerov, R.K., & Mlowe, S. (2021). Crystal structure and Hirshfeld surface analysis of (3Z)-7-methoxy-3-(2-phenylhydrazinylidene)-1-benzofuran-2 (3H)-one. *Acta Crystallographica Section E: Crystallographic Communications*, *77*(9), 907-911.

Atioğlu, Z., Akkurt, M., Shikhaliyev, N.Q., Askerova, U.F., Niyazova, A.A., & Mlowe, S. (2021). Crystal structure and Hirshfeld surface analysis of (2Z)-N, N-dimethyl-2-(pentafluorophenyl)-2-(2-phenylhydrazin-1-ylidene) acetamide. *Acta Crystallographica Section E: Crystallographic Communications*, *77*(8), 829-833.

Lagunin, A., Zakharov, A., Filimonov, D., & Poroikov, V. (2011). QSAR modelling of rat acute toxicity on the basis of PASS prediction. *Molecular informatics*, *30*(2-3), 241-250.

Pozharitskaya, O.N., Shikov, A.N., & Makarov, V.G. (2019). Toxicokinetics - methodological approaches. *Review article. Laboratory Animals for Scientific Research*. 1, 76–94. https://doi.org/10/29926/2618723X-2019-01-06

Russell, W.M.S., Burch, R.L. (1959). *The Principles of Humane Experimental Technique*. Methuen.

Sukhachev, V.S., Ivanov, S.M., Filimonov, D.A., & Poroikov, V.V. (2019). Alternative methods of studies. Computer-aided estimation of rodents acute toxicity. *Laboratory animals for science*, 4, 25-31.

Zakharov, A.B., Filimonov, D.A., Lagunin, A.A., & Poroikov, V.V. (2006). Certificate of official registration of the computer program GUSAR (General Unrestricted Structure Activity Relationships), №. 2006613591, Moscow, Federal Service for Intellectual Property, Patents and Trademarks.

http://www.pharmaexpert.ru/GUSAR/AcuToxPredict

https://www.ilo.org/legacy/english/protection/safework/ghs/ghsfinal/ghsc05.pdf