Artículo de investigación científica

A quantitative structure – toxicity relationship of drugs on rat

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Summary

A quantitative structure toxicity relationship (QSTR) is proposed to correlate the toxicity of drugs on rat after intravenous administration. The computational descriptors of 319 drug molecules are calculated using HyperChem software and regressed against LD_{50} of drugs collected from the literature. Correlation coefficient (R), F value and average percentage deviation (APD) between calculated and experimental LD_{50} are used to evaluate the accuracy of the proposed QSTR model. The best QSTR model is:

$$LD_{50} = -639.254 + 3.773\ SAA - 4.786\ VOL - 21.050\ HE - 50.753\ \log P - 51.440\ REF + 121.219\ POL + 12.932\ MASS + 0.011\ TE - 95.494\ HOMO$$

$$N = 319\ ,\ R = 0.748,\ F = 43$$

where, SAA is surface area (approximate), VOL molar volume, HE hydration energy, log *P* is the logarithm of partition coefficient, REF molar refractivity, POL polarizability, MASS molecular weight, TE total energy and HOMO energy of the highest occupied molecular orbital. The APD of a number of drugs are very high and this resulted in high APD for the data set. These drugs include busulfan, calcitriol, epinephrine, triaziquone etc. and could be considered as outliers. After excluding these data points, the model is:

$$LD_{50} = -740.217 + 4.050\ SAA - 5.138\ VOL - 21.909\ HE - 50.713\ \log P$$
$$- 49.662\ REF + 120.843\ POL + 12.742\ MASS + 0.010\ TE - 106.513\ HOMO$$
$$N = 309,\ R = 0.751,\ F = 43.$$

Small changes in the model constants showed that the model is robust and could be considered as a predictive model. Because of various toxic mechanisms, high discrepancy in reported LD_{50} of some drugs from different references, high APD value could be justified. As an example, LD_{50}s of dixyrazine are 37.5 and 3.75 in different references. After excluding the outliers, APD reduces to 977%. The APD could be considered as acceptable over range if the experimental discrepancies between reported LD_{50} from different laboratories are kept in mind.

Key words: Quantitative structure-toxicity relationship, Rat, Drug, LD_{50}

Resumen

Una correlación cuantitativa entre la estructura molecular de fármacos y la toxicidad en ratas

En este trabajo se plantea una correlación cuantitativa entre la estructura molecular de fármacos y la toxicidad (QSTR) en ratas después de la administración intravenosa. Se calcularon los descriptores computacionales de la estructura molecular de 319 fármacos utilizando el programa HyperChem. Los descriptores computacionales fueron relacionados matemáticamente contra los respectivos valores LD_{50} tomados de la literatura. Para evaluar la precisión del modelo QSTR propuesto se utilizaron el coeficiente de correlación (R), el valor F y el porcentaje de desviación promedio (APD) entre los valores calculados y experimentales de LD_{50}. El mejor modelo QSTR es:

$$LD_{50} = -639{,}254 + 3{,}773\ SAA - 4{,}786\ VOL - 21{,}050\ HE - 50{,}753\ \log P - 51{,}440\ REF$$
$$+ 121{,}219\ POL + 12{,}32\ MASS + 0{,}011\ TE - 95{,}494\ HOMO$$
$$N = 319,\ R = 0{,}748,\ F = 43$$

Donde, SAA es el área superficial (aproximada), VOL es el volumen molar, HE es la energía de hidratación, log *P* es el logaritmo del coeficiente de reparto, REF es la refractividad molar, POL es la polarizabilidad, MASS es la masa molar, TE es la energía total y HOMO es la energía del orbital molecular más altamente ocupado. El valor de APD de un cierto número de fármacos es muy alto y esto incidió en un alto valor de APD para el total de compuestos estudiados. Estos fármacos incluyeron busulfán, calcitriol, epinefrina, triaziquona, entre otros, por lo que fueron considerados como descartables. Después de excluir estos puntos, el modelo obtenido es:

$$LD_{50} = -740{,}217 + 4{,}050\ SAA - 5{,}138\ VOL - 21{,}909\ HE - 50{,}713\ \log P - 49{,}662\ REF + 120{,}843\ POL + 12{,}742\ MASS + 0{,}010\ TE - 106{,}513\ HOMO$$
$$N = 309,\ R = 0{,}751,\ F = 43.$$

Con algunos pequeños cambios en las constantes el modelo demostró ser robusto y por lo tanto se consideró como altamente predictivo. El alto valor de APD obtenido podría justificarse gracias a los diferentes mecanismos de toxicidad y a la gran dispersión de los valores de LD_{50} presentados en la literatura. Como ejemplo podría citarse el caso de la dixirazina, para la cual se han reportado valores de LD_{50} de 37,5 y 3,75 según las diferentes fuentes bibliográficas. Después de excluir esos compuestos, el valor APD se reduce a 977%, el cual podría considerarse como aceptable si se tienen en cuenta las discrepancias experimentales encontradas en los valores de LD_{50} que han sido reportados por diferentes laboratorios.

Palabras clave: Correlaciones cuantitativas estructura-toxicidad, Ratas, Fármacos, LD_{50}.

Introduction

The first step in the development of a new drug is the synthesis of a potential new drug molecule or extraction of a candidate chemical compound from natural sources. The safety and efficacy of a drug have to be investigated before its marketing. These investigations start from *in vitro* studies and continue for most of the biologic effects of the molecule which should be characterized in animal studies before human drug trials. Human testing must then go forward in three conventional phases before the drug is considered for final approval of marketing. A fourth phase of data gathering follows after approval for general use.

Enormous costs, from 100 million to over 500 million USD, are involved in the development of a successful new drug. These costs are spent for searching new molecules and a huge number of candidates (5000-10000) may be synthesized for each successful drug, basic and clinical studies and promotion of the ultimate candidate molecule. It is primarily because of the economic investment and risks involved that most of the new drugs are now developed in the laboratories of pharmaceutical companies. At the same time, the incentives to succeed in drug development are equally enormous (1).

It is important to recognize the limitations of preclinical testing. These include the following: (A) Toxicity testing is time-consuming and expensive. During the last decade, the total cost of preclinical pharmacology and toxicology studies was estimated to be at least 41 million USD per a successful drug and 2-5 years to collect and analyze data.

(B) Large numbers of animals are used to obtain preclinical data and there are limitations for animal studies in some societies. Scientists are properly concerned about this situation, and progress has been made toward reducing the number of animals required while still obtaining valid data. *In vitro* methods such as cell and tissue cultures are increasingly being used, but their predictive capacity is still severely limited. (C) Extrapolation of toxicity data from animals to humans is not completely reliable. For any given compound, the total toxicity data from all species have a very high predictive value for it's toxicity in human. However, there are limitations on the extent of the available databases. (D) For statistical reasons, rare adverse effects are unlikely to be detected, just as in clinical trials (2).

Finding an active compound with maximal pharmacologic effects and minimal adverse and toxic effects is the most important goal of drug development investigations. Different mechanisms are involved in the toxicity of a compound and the tools on understanding such a complex phenomena are still very limited. Although different mechanisms are effective and different receptors are involved in toxic responses, but the outcomes of toxicity are death; disability and/or mutations.

The severe adverse and toxic effects result in decreasing the chance of further progress of introduction of the new drugs. In addition to the experimental investigations, the computational methods could also be employed in order to determining the safety and efficacy of the new candidates. By considering that drugs toxic effects result from their physico-chemical reactions with biological systems, basically, there must exist a relationship between physico-chemical characteristics of drugs and their toxic effects.

This relationship could be determined for the kinetic or dynamic effects of physico-chemical properties of drugs. Statistical analyses of drug data, for correlating toxicity with chemical structure and proposing mathematical models with ability of toxicity prediction, makes the drug discovery investigations faster and more cost-effective. These models could be applied for predicting toxicity of new compounds based on their structures (3).

Quantitative structure – activity (QSARs) and quantitative structure – toxicity (QSTRs) relationships have provided a valuable approach in research into the toxicity of organic chemicals in such studies (4).

One and two parameter QSTR equations were obtained to describe the cytotoxicity of isolated rat hepatocytes induced by 23 catechols in which LD_{50} represents the catechol concentration required to induce 50% toxicity after 2 h incubation. The reported QSTR equation was:

$$\log LD_{50}(\mu M) = 3.724(\pm 1.4) - 0.464(\pm 0.065)\log P \quad \text{(Eq. 1)}$$
$$N = 20,\ R = 0.710,\ S.E. = 0.372,\ p < 0.0005$$

where log *P* represents the logarithm of octanol/water partition coefficient.

Excluding three catechols from the original data set improved the QSTR equation between the catechols log LD_{50} (μM, 2h) and their log *P* values. The presence of outliers implies that factors or specific mechanisms other than log *P* are involved in their cytotoxicity. Therefore, they obtained the two–parameter QSTR equation in order to describe the correlation between the cytotoxicity of the various catechols, their lipophilicity (log *P*) and their degree of ionization (pK_{a1}) towards isolated rat hepatocytes:

$$\log LD_{50}(\mu M) = 4.389(\pm 0.350) - 0.343(\pm 0.058)\log P - 0.116(\pm 0.041)\, pK_{a_1} \quad \text{(Eq. 2)}$$
$$N = 22,\ R = 0.738,\ S.E. = 0.375,\ p < 0.01$$

Moridani *et al.* (5) excluded one catechol from the data set and improved the QSTR equation between the catechols log LD_{50} (μM, 2h), and physico–chemical properties log *P* and pK_{a1} values. QSTR models can be used as a powerful tool for understanding the toxic mechanisms that may be common among a group of similar compounds such as catechols. This is possible by first deriving the QSTR equations correlating different physico–chemical parameters to catechol toxicity. Then these QSTR equations can be applied to other biological endpoints that contribute to the toxic mechanisms; i.e., transport, metabolism, and target damage, so as to determine which endpoint is affected by the same catechol physico-chemical parameters that contribute to the toxicity. This information would be valuable to a research group that uses catechol functional groups for drug design and the optimization of a catechol molecule for a desired physico – chemical characteristic (5).

In another investigation on LD_{100} of some drugs in human subjects, the following relation was reported:

$$\log\left(\frac{1}{C}\right) = 0.83\ \log P + 0.13\ NVE + 1.26 \quad \text{(Eq. 3)}$$
$$N = 10,\quad R = 0.985,\quad S = 0.270$$

LD_{100} data of drugs were collected by measuring blood concentration of drugs obtained from the suicides victims. In Eq. 3 NVE is the number of valence electrons. To further improve Eq. 3, the toxicity data of 41 different drugs were applied and Eq. 4 was reported:

$$\log\left(\frac{1}{C}\right) = 0.61\ \log P + 0.017\ NVE + 1.44 \quad N = 36,\ R = 0.922,\ S = 0.438 \qquad \text{(Eq. 4)}$$

In this model, five drugs were considered as outliers and removed to improve the QSTR model between LD_{100}, NVE and log *P*. Drugs with Cl and Br substitutions fit well with this equation. In two recent models log *P* is one of the parameters that is determining the absorption of drugs from gastrointestinal tract and also drug penetration to the CNS (6).

The aim of the present study is to provide a model for prediction of drug toxicity based on acute toxicity data (LD_{50}) on rats and extend this model for toxicity evaluation of new drug candidates.

Materials and Methods

Toxicity data (LD_{50} mg/kg) of drugs (N=319) on rat after intravenous administration were collected from the literature (7-9). Then physico-chemical descriptors of the molecules were calculated using HyperChem® software (10). These descriptors were: surface area approximate (SAA), molecular weight (MASS), molar volume (VOL), total energy (TE), hydration energy (HE), molar refractivity (REF), logarithm of partition coefficient (log *P*), polarizability (POL), dipole moment (DM) and energy of the highest occupied molecular orbital (HOMO).

Details of the collected data including the drug name, LD_{50} values and the calculated descriptors are listed in Table 1. LD_{50} was used as dependent variable and other descriptors as independent variables and the best equation with consideration of correlation coefficient (*R*), percentage deviation (PD), *F* value and average percentage deviation (APD) was developed. The PD and APD were computed by Eqs. 5 and 6, respectively.

$$PD = 100\left(\frac{LD_{50}^{Calculated} - LD_{50}^{Observed}}{LD_{50}^{Observed}}\right) \qquad \text{(Eq. 5)}$$

$$APD = \frac{100}{N}\sum\left|\frac{LD_{50}^{Calculated} - LD_{50}^{Observed}}{LD_{50}^{Observed}}\right| = \frac{\sum|PD|}{N} \qquad \text{(Eq. 6)}$$

where, N is the number of data points. All calculations were carried out in SPSS (11) environment using the written programs through this project.

Table 1. List of studied drugs, their LD_{50} values in rat after intravenous administration and computational parameters calculated by HyperChem.

No.	Name	LD_{50}	SAA	VOL	HE	Log *P*	REF	POL	MW
1	Acarbose	7400.0	598.81	1492.52	−33.10	−5.36	134.09	54.57	631.58
2	Aceclidine	45.0	289.68	557.87	0.40	0.16	45.38	17.81	169.22
3	Acetylcycteine	1140.0	328.46	501.74	−8.24	−0.91	37.61	15.11	163.19
4	Aciclovir	910.0	334.75	649.21	−19.08	−1.45	54.54	20.99	225.21
5	Adiphenine	27.0	538.55	1006.14	−1.60	4.15	94.32	36.85	311.42
6	Ajmaline	26.0	303.17	883.79	−3.51	2.70	92.56	36.23	326.44
7	Alimemazine	35.0	439.45	897.49	−1.06	3.80	93.37	36.03	298.45
8	Aminocaproicacid	3300.0	340.38	496.13	−8.89	0.15	34.66	13.86	131.17
9	Aminophenazone	98.0	519.16	842.41	−1.08	−0.03	70.11	26.45	231.30
10	Ampicillin	6200.0	438.85	940.77	−13.19	0.14	87.43	35.18	349.40
11	Amrinone	75.0	287.52	566.77	−11.76	−2.96	56.65	20.53	187.20
12	Ancitabine	820.0	212.38	600.02	−12.85	−0.20	51.69	20.54	225.20
13	Astemizole	28.2	614.21	1322.88	−7.20	5.64	134.69	52.09	458.58
14	Atenolol	77.0	502.33	877.04	−11.47	0.56	73.50	29.18	266.34
15	Atropine	73.0	388.21	865.40	−6.14	1.71	80.81	31.76	289.37
16	Azapropazone	660.0	468.72	889.03	−1.99	3.09	83.63	32.39	300.36
17	Azelastine	36.0	513.30	1080.06	−1.29	4.05	110.02	42.55	381.90
18	Azosemide	252.0	329.85	836.20	−17.76	1.78	98.91	32.62	370.83
19	Aztreonam	2001.0	454.75	1000.14	−18.08	−0.53	95.13	35.12	435.43
20	Baclofen	78.0	345.75	627.62	−10.19	1.50	54.83	21.78	213.66
21	Bamethan	80.0	447.90	732.22	−11.86	2.12	60.84	24.07	209.29
22	Beclamide	770.0	445.86	728.76	−2.13	2.64	62.37	24.81	225.72
23	Bemegride	16.0	324.29	507.92	−2.28	0.48	40.51	16.20	155.20
24	Bendazac	304.0	377.36	811.94	−11.76	3.02	77.15	30.30	282.30
25	Benperidol	21.0	513.33	1081.21	−4.70	2.37	106.35	41.03	381.45
26	Bentiromide	485.0	572.55	1137.75	−19.76	3.37	109.68	43.16	404.42
27	Benzoctamine	36.0	310.45	772.99	−1.80	3.81	79.45	30.91	249.36

(*Continued*)

Table 1. List of studied drugs, their LD_{50} values in rat after intravenous administration and computational parameters calculated by HyperChem (*continuation*).

No.	Name	LD_{50}	SAA	VOL	HE	Log *P*	REF	POL	MW
28	Benzthiazide	422.0	530.39	1017.93	−13.21	−1.12	108.39	35.67	431.93
29	Benzyl alcohol	53.0	250.83	406.36	−6.21	1.51	32.87	12.91	108.14
30	Bevantolol	38.0	632.78	1106.75	−10.91	3.03	98.54	38.67	345.44
31	Bifonazole	63.0	425.06	955.39	−6.14	4.58	98.94	38.41	310.40
32	Binedaline	27.0	532.28	959.36	−1.28	2.26	93.39	36.03	293.41
33	Bromperidol	10.0	542.58	1063.73	−4.18	3.65	105.41	40.44	420.32
34	Budesonide	98.9	500.88	1149.25	−9.04	3.28	116.15	45.12	430.54
35	Budipine	28.0	450.41	929.06	−0.14	4.91	95.15	37.19	293.45
36	Bufetolol	59.4	531.61	1000.36	−5.20	1.85	89.73	35.58	323.43
37	Bupiracaine	5.6	472.84	934.92	0.61	3.82	88.41	34.47	288.43
38	Buperenorphine	31.0	481.70	1230.03	−5.75	3.96	131.47	51.89	467.65
39	Busulfan	1.8	527.53	680.54	−8.86	−0.11	50.31	15.33	246.29
40	Caffeine	105.0	337.43	569.16	−2.33	−1.06	50.01	18.87	194.19
41	Calcitriol	0.1	625.14	1287.88	−6.85	4.53	126.53	49.33	416.64
42	Captopril	554.0	364.23	645.63	−4.54	0.30	54.73	21.67	217.28
43	Carboquone	3.6	447.47	912.16	−5.68	−1.17	83.51	31.18	321.33
44	Carbromal	427.0	383.67	591.59	−6.62	1.03	48.70	19.12	237.10
45	Carbutamide	980.0	474.65	798.28	−10.32	0.96	69.93	24.89	271.33
46	Carbuterol	77.2	474.44	830.43	−17.71	0.33	72.53	28.69	267.33
47	Carisoprodol	450.0	515.21	837.41	−4.12	1.96	67.10	26.94	260.33
48	Carpipramine	37.0	522.43	1299.50	−3.61	3.37	136.14	52.62	446.64
49	Carvedilol	25.0	565.54	1190.58	−14.89	−2.39	128.52	45.24	406.48
50	Chenodeoxycholic acid	106.0	428.39	1099.29	−5.92	4.27	109.27	43.72	392.58
51	Chloramphenicol	171.0	465.84	806.44	−16.35	1.28	73.18	28.02	323.13
52	Chlorazanil	16.0	311.21	627.34	−13.85	2.85	58.05	22.60	221.65
53	Chlordiazepoxide	165.0	451.52	875.09	−4.62	5.26	88.91	34.27	313.79
54	Chlorhexidine	21.0	739.82	1475.30	−27.42	6.59	137.68	54.14	505.45
55	Chlorpyramine	32.5	497.46	887.11	−1.68	3.14	87.88	33.19	289.81
56	Chloroquine	60.0	591.61	1017.45	−2.31	2.53	97.62	36.96	299.46
57	Chlorothiazide	200.0	355.30	639.73	−13.84	−3.26	67.07	19.33	295.72

(*Continued*)

Table 1. List of studied drugs, their LD_{50} values in rat after intravenous administration and computational parameters calculated by HyperChem (*continuation*).

No.	Name	LD_{50}	SAA	VOL	HE	Log *P*	REF	POL	MW
58	Chlorphenesin carbamate	236.0	449.15	712.62	–7.22	2.69	59.45	23.63	265.09
59	Chlorpromazine	23.0	504.31	905.72	–1.27	3.82	93.76	36.13	318.86
60	Chlorpropamide	590.0	470.91	755.46	–6.49	1.87	65.43	23.63	276.74
61	Chlorteracycline	118.0	494.02	1118.49	–21.81	–1.69	118.13	45.16	478.89
62	Cimetidine	106.0	492.66	798.81	–15.34	–0.59	72.48	27.10	252.34
63	Cinnarizine	24.0	504.85	1127.92	–3.41	5.89	119.86	46.17	368.52
64	Cinoxacin	900.0	357.42	700.48	–11.71	–0.34	66.77	24.26	262.22
65	Ciprofloxacin	207.0	425.24	898.64	–6.98	0.67	87.15	32.88	331.35
66	Clebopride	39.0	478.24	1045.88	–8.27	2.36	105.57	40.70	373.88
67	Clobutinol	63.0	462.52	792.54	–1.28	2.96	74.04	29.03	255.79
68	Clorexolone	120.0	460.12	879.69	–4.77	–0.47	85.35	29.42	328.81
69	Cloricromen	10.0	665.51	1134.88	–2.80	2.79	104.81	40.52	395.88
70	Clozapine	41.6	434.30	925.09	–3.01	–0.73	103.53	36.47	326.83
71	Codeine	75.0	317.87	828.61	–4.15	1.57	84.60	32.43	299.37
72	Convallatoxin	15.2	548.66	1370.14	–14.26	0.28	136.78	54.42	550.65
73	Creatinolfosfate	1300.0	356.20	563.10	–25.12	0.29	42.10	14.62	197.13
74	Cyclobutyrol	1760.0	316.50	602.23	–4.83	1.74	49.12	19.71	186.25
75	Cyclophosphamide	148.0	385.46	677.38	–2.49	1.12	58.48	21.00	261.09
76	Dacarbazine	411.0	343.70	576.38	–14.40	–0.92	51.20	17.95	182.18
77	Daunorubicin	13.0	550.76	1306.79	–17.94	–2.40	137.10	51.37	527.53
78	Dehydrocholic acid	750.0	499.87	1089.67	–3.52	4.46	108.01	42.70	402.53
79	Deserpidine	15.0	728.50	1575.97	–8.93	1.65	155.39	60.20	578.66
80	Desipramine	29.0	430.98	868.60	–3.18	3.64	85.31	33.03	266.69
81	Dextromethrophan	16.3	342.36	820.17	–0.88	3.35	82.56	32.12	271.40
82	Dextromoramide	13.0	438.79	1101.81	–2.38	3.81	117.49	45.83	392.54
83	Dibenzepine	22.0	455.17	907.09	–0.82	3.40	90.46	34.95	294.40
84	Dichlorophen	17.0	365.58	713.74	–11.71	4.59	68.79	27.06	269.13
85	Dimetindene	27.0	466.14	942.17	–0.74	2.49	100.32	36.28	292.42
86	Dinoprost	106.0	577.70	1080.76	–14.52	3.10	100.47	38.95	354.49
87	Dinoprostone	59.5	626.83	1116.94	–8.23	3.67	99.43	38.40	352.47

(*Continued*)

Table 1. List of studied drugs, their LD_{50} values in rat after intravenous administration and computational parameters calculated by HyperChem (*continuation*).

No.	Name	LD_{50}	SAA	VOL	HE	Log *P*	REF	POL	MW
88	Diphenhydramine	42.0	485.89	860.33	−1.80	3.62	79.93	31.26	255.36
89	Diprophylline	860.0	406.14	714.68	−11.58	−1.88	62.26	23.82	254.25
90	Dipyridamole	195.0	613.97	1387.93	−20.12	2.09	139.51	53.21	504.63
91	Disopyramide	39.1	505.64	1041.41	−4.10	2.30	106.79	40.52	339.48
92	Dixyrazine	37.5	601.47	1231.36	−8.99	−0.86	136.19	48.89	427.60
93	Domperidone	41.7	485.04	1118.86	−7.30	−2.73	125.16	44.98	425.92
94	Doxepin	16.0	455.99	887.14	−2.06	3.57	89.07	33.96	279.38
95	Doxofylline	315.0	403.37	741.74	−4.22	−1.23	64.86	24.88	266.26
96	Doxorubicin	10.5	575.19	1321.78	−24.05	0.17	134.02	52.00	543.53
97	Doxycycline	228.0	461.24	1084.23	−21.47	−1.86	113.03	43.23	444.44
98	Epinephrine	0.2	346.74	587.50	−19.31	−1.61	52.62	19.20	183.21
99	Epirizole	214.0	395.42	716.43	−5.31	1.86	64.61	24.45	234.26
100	Ergotamine	80.0	540.48	1451.82	−8.10	0.24	163.75	61.89	581.67
101	Etamivan	17.0	317.39	695.02	−7.79	1.52	62.09	24.15	223.27
102	Ethinamate	157.0	328.94	558.72	−5.34	1.19	44.57	17.48	167.21
103	Ethylmorhine	62.0	363.24	879.67	−7.26	1.95	88.53	34.26	313.40
104	Etodroxizine	58.0	651.90	1235.17	−10.06	3.33	118.12	46.05	418.96
105	Etofenamate	139.0	574.32	997.91	−11.81	3.30	89.38	34.18	369.34
106	Etomidate	14.8	386.68	755.14	−2.99	1.31	70.73	27.16	244.29
107	Etoposide	75.0	638.50	1444.77	−22.89	1.27	138.73	55.15	588.56
108	Felodipine	5.4	535.56	1005.32	−2.53	1.81	99.49	37.95	384.26
109	Fencarbamide	30.0	551.08	1019.30	−1.39	4.46	99.40	38.73	328.47
110	Fentanyl	2.9	533.76	1070.16	−1.32	3.77	103.48	40.46	336.48
111	Fleroxacin	20.4	491.35	932.62	−5.32	−2.32	93.02	33.47	369.34
112	Floctafenine	160.0	507.55	1035.19	−16.33	2.10	100.96	37.82	406.36
113	Flopropione	246.0	305.94	543.12	−14.26	1.13	46.17	17.94	182.18
114	Fluanisone	20.0	536.07	1049.28	−1.86	3.50	102.57	39.17	356.44
115	Flufenamic acid	98.0	353.20	730.27	−8.55	3.88	67.28	25.56	281.23
116	Flumazenil	85.0	436.62	830.39	−3.11	0.23	79.96	29.56	303.29
117	Fluorouracil	245.0	234.76	356.26	−6.59	−1.78	26.20	9.93	130.08
118	Flurazepam	38.7	564.41	1092.61	−0.62	3.81	107.54	41.39	387.88

(*Continued*)

Table 1. List of studied drugs, their LD_{50} values in rat after intravenous administration and computational parameters calculated by HyperChem (*continuation*).

No.	Name	LD_{50}	SAA	VOL	HE	Log *P*	REF	POL	MW
119	Fosfestrol	425.0	579.69	1120.90	–28.81	5.62	103.84	36.65	428.32
120	Furosemide	800.0	433.99	813.52	–14.68	0.00	80.76	27.41	330.74
121	Gefarnate	2040.0	985.90	1464.24	5.38	7.25	131.77	50.08	400.64
122	Gliclazide	382.0	473.27	918.42	–6.01	1.90	83.88	30.68	323.41
123	Glisoxepide	196.0	499.89	1145.50	–12.52	1.67	116.80	42.67	449.52
124	Glyconiazide	1763.0	385.70	786.36	–20.97	–2.63	69.39	26.80	295.25
125	Griseofulvin	400.0	477.79	915.00	–6.00	1.18	87.58	33.53	352.77
126	Guaifenesin	360.0	366.36	631.93	–14.00	0.73	51.24	20.32	198.22
127	Haloperidol	15.0	553.08	1058.52	–4.09	3.38	102.59	39.75	375.87
128	Hexobendine	34.0	1003.16	1800.50	–9.27	1.92	157.75	61.09	592.69
129	Hydralazine	34.0	248.85	504.04	–17.29	1.87	48.23	17.90	160.18
130	Hydroxyzine	45.0	568.06	1130.91	–8.87	3.49	107.07	41.74	374.91
131	Ibudilast	42.5	377.75	731.77	–1.05	2.82	72.04	26.71	230.31
132	Ifosfamide	190.0	427.29	701.32	–3.02	1.12	58.48	21.00	261.09
133	Imipenem	1972.0	464.34	844.96	–18.04	–2.65	76.08	29.14	299.34
134	Imipramine	9.3	467.69	912.65	–0.01	4.01	90.61	34.87	280.41
135	Indecainide	10.0	470.46	973.06	–5.40	3.36	94.17	36.79	308.42
136	Indobufen	333.0	438.71	872.77	–5.90	3.37	83.25	32.49	295.34
137	Indometacin	21.0	500.18	958.41	–10.03	2.31	95.25	36.70	357.79
138	Inositol nicotinate	268.0	748.87	1914.86	–20.08	–3.28	215.21	80.06	810.73
139	Iocarmic acid	13300.0	967.86	1731.25	–20.14	7.64	200.65	79.48	1253.87
140	Iocetamic acid	700.0	510.31	913.42	–8.84	4.42	101.32	40.04	613.96
141	Iopanoic acid	280.0	467.98	836.93	–7.14	6.02	93.07	36.77	570.94
142	Iotroxic acid	4190.0	993.21	1743.20	–18.99	7.83	188.23	74.84	1215.82
143	Ioxaglic acid	13300.0	985.79	1759.22	–20.02	5.79	204.55	80.83	1268.89
144	Isoniazid	365.0	249.32	449.40	–14.68	–1.37	39.69	14.35	137.14
145	Isoprenaline	57.0	408.16	692.27	–17.54	1.39	57.82	22.87	211.26
146	Isosorbide mononitrate	1750.0	297.93	512.41	–14.63	–0.26	38.08	14.63	191.14
147	Isradipine	1.8	494.65	1021.85	–7.48	1.98	102.60	37.85	371.39
148	Itraconazole	40.0	850.24	1843.15	–8.43	7.59	189.98	73.26	705.64

(*Continued*)

Table 1. List of studied drugs, their LD_{50} values in rat after intravenous administration and computational parameters calculated by HyperChem (*continuation*).

No.	Name	LD_{50}	SAA	VOL	HE	Log *P*	REF	POL	MW
149	Kanamycin	437.0	357.10	1193.22	−32.11	−5.63	106.13	43.89	484.50
150	Kebuzone	315.0	467.31	942.31	−3.50	3.14	89.37	35.13	322.36
151	Ketobemidone	10.0	410.19	773.70	−6.40	2.98	72.84	28.25	247.34
152	Ketoconazole	86.0	630.23	1369.53	−5.03	3.55	139.07	54.11	531.44
153	Ketoprofen	350.0	399.05	768.53	−8.58	3.46	72.52	28.24	254.29
154	Khellin	34.4	368.03	725.10	−6.44	−3.33	72.86	25.82	260.25
155	Levamisole	24.0	303.11	625.84	−2.52	2.79	60.02	23.35	204.29
156	Lidocaine	18.0	355.85	782.43	−1.79	2.38	72.15	27.90	234.34
157	Lofexidine	13.0	366.23	708.83	−3.79	2.86	64.41	25.61	259.14
158	Loperamide	5.1	589.25	1309.10	−5.65	5.01	139.44	54.52	477.05
159	Loxapine	18.0	439.39	912.84	−4.27	3.62	92.60	35.76	327.81
160	Maprotiline	38.0	394.67	881.24	−2.59	4.00	91.60	34.77	279.43
161	Mefenamic acid	112.0	376.86	730.88	−5.19	3.93	71.39	27.67	241.29
162	Mefruside	500.0	517.46	923.15	−7.55	0.77	89.05	30.05	382.88
163	Melphalan	4.1	493.46	858.14	−9.73	2.82	78.23	30.56	305.20
164	Mephenesin	133.0	358.28	607.10	−12.47	1.45	49.82	19.68	182.22
165	Meprobamate	350.0	422.01	695.41	−8.57	0.96	53.04	21.44	218.25
166	Meproscillarin	5.8	584.50	1415.64	−9.51	2.51	144.84	56.98	544.69
167	Mercaptopurine	250.0	210.78	428.52	−12.60	−0.44	42.91	16.02	152.17
168	Methotrexate	14.0	582.62	1226.75	−28.45	0.53	116.88	45.06	454.45
169	Methylergometrine	23.0	480.54	1006.43	−9.83	0.39	99.87	38.19	339.44
170	Methylphenidate	48.0	371.86	748.11	−3.17	2.12	66.73	26.41	233.31
171	Methyprylon	380.0	329.98	588.51	−1.59	2.09	50.25	19.87	183.25
172	Meticrane	445.0	371.54	680.50	−7.43	0.92	66.11	20.63	275.34
173	Metoprolol	71.9	581.88	920.06	−7.92	1.79	76.70	30.21	267.37
174	Mexiletine	41.0	348.21	633.12	−2.42	2.35	54.97	21.60	179.26
175	Miconazole	105.0	558.06	1038.37	−4.87	4.81	104.07	40.77	416.13
176	midazolam	75.0	376.13	869.82	−3.18	3.41	91.20	34.42	325.77
177	Milrinone	73.0	357.72	632.12	−9.95	−1.49	63.86	22.87	211.22
178	Minoxidil	49.0	303.34	641.66	−12.56	2.23	57.30	22.10	209.25
179	Mitomycin	3.0	369.81	868.49	−11.49	−1.42	83.27	31.75	334.33

(*Continued*)

Table 1. List of studied drugs, their LD_{50} values in rat after intravenous administration and computational parameters calculated by HyperChem (*continuation*).

No.	Name	LD_{50}	SAA	VOL	HE	Log *P*	REF	POL	MW
180	Mizoribine	1500.0	272.75	665.58	–20.72	–2.57	56.75	22.46	259.22
181	Moracizine	11.0	523.59	1137.34	–5.85	–2.53	126.45	45.40	427.52
182	Morphine	140.0	288.45	776.75	–9.00	1.53	79.83	30.59	285.34
183	Mupirocin	1310.0	778.04	1462.83	–17.15	2.32	129.39	51.38	500.63
184	Nadolol	59.2	521.31	960.91	–14.76	1.27	85.52	33.74	309.41
185	Nalidixic acid	88.4	365.25	682.96	–5.36	0.33	64.85	23.76	232.24
186	Nalorphine	226.0	333.53	853.86	–12.63	2.27	89.00	34.07	311.38
187	Nemonapride	17.0	551.12	1106.09	–6.58	3.08	110.61	42.54	387.91
188	Netilmicin	25.2	544.16	1291.99	–19.73	–4.08	114.83	46.17	461.56
189	Nicergoline	42.0	562.12	1202.54	–3.61	0.39	125.81	47.41	484.39
190	Nikethamide	191.0	356.57	594.47	–1.65	–0.05	54.57	20.34	178.23
191	Nilvadipine	9.7	579.93	1045.08	–11.44	0.92	102.09	37.79	385.38
192	Nimodipine	5.0	595.49	1160.47	–7.37	0.97	112.67	42.08	418.45
193	Nipradilol	78.0	532.94	948.65	–15.02	2.01	82.80	31.91	326.35
194	Nisoldipine	1.1	481.75	1074.82	–3.76	1.60	106.20	39.60	388.42
195	Nitrendipine	12.6	527.58	979.60	–7.08	0.72	97.21	35.93	360.37
196	Nizatidine	301.0	617.91	978.65	–11.43	–1.00	90.52	34.46	331.45
197	Norfenefrine	17.4	284.15	516.19	–16.91	0.51	42.19	16.73	153.18
198	Norfloxacin	245.0	445.45	872.54	–7.47	0.62	84.68	31.81	319.34
199	Nortriptyline	22.0	426.22	865.42	–3.40	4.16	87.04	33.32	263.38
200	Oleandomycin	440.0	728.55	1696.72	–10.77	2.94	173.69	69.80	687.87
201	Opipramol	32.0	492.56	1103.11	–6.09	3.36	112.95	43.42	365.52
202	Orciprenaline	67.2	417.28	692.61	–17.95	1.39	57.82	22.87	211.26
203	Oxaprozin	82.0	440.91	875.94	–10.07	2.13	84.03	32.43	293.32
204	Oxatomide	29.0	511.15	1232.85	–5.81	4.21	129.16	50.21	426.56
205	Oxitriptan	27.0	330.44	652.59	–19.29	–0.23	58.19	22.70	220.23
206	Oxyphenbutazone	68.0	463.63	951.83	–9.47	3.94	90.45	35.68	324.38
207	Oxytetracycline	260.0	457.06	1091.59	–22.73	–2.98	114.54	43.87	460.44
208	Ozagrel	1150.0	378.31	667.13	–10.07	1.51	62.51	23.29	214.22
209	Pantethine	3410.0	942.20	1576.46	–25.11	–1.94	139.50	55.44	554.72
210	Papaverine	13.3	446.29	1096.29	–7.82	2.26	97.42	37.29	339.39

(*Continued*)

Table 1. List of studied drugs, their LD_{50} values in rat after intravenous administration and computational parameters calculated by HyperChem (*continuation*).

No.	Name	LD_{50}	SAA	VOL	HE	Log *P*	REF	POL	MW
211	Penbutolol	22.0	533.28	968.27	−3.27	3.36	86.60	34.30	291.43
212	Penicillamine	2000.0	289.16	464.57	−9.31	−0.24	37.22	15.02	149.21
213	Pentazocine	21.0	446.52	895.35	−4.69	4.28	89.51	34.54	285.43
214	Pentetrazol	45.0	245.42	452.75	−11.90	2.12	41.35	14.58	138.17
215	Pentoxifylline	231.0	503.55	840.05	−1.21	−0.14	73.70	28.13	278.31
216	Perazine	80.0	466.71	980.29	−1.65	3.10	105.00	40.28	339.50
217	Periciazine	35.0	482.59	1032.89	−9.59	2.89	108.41	41.42	365.49
218	Perlapine	60.0	405.98	891.20	−2.36	3.76	91.29	35.03	291.40
219	Perphenazine	34.0	552.77	1120.84	−7.40	3.18	116.10	44.68	403.97
220	Pethidine	22.5	406.54	784.21	−0.79	2.47	72.48	28.25	247.34
221	Phenobarbital	209.0	326.94	650.14	−7.34	1.56	59.75	23.63	232.24
222	Phenylbutazone	100.0	461.79	940.17	−2.50	4.22	88.76	35.04	308.38
223	Phenytoin	101.0	330.43	723.73	−7.53	2.26	69.98	27.70	252.27
224	Pilsicainide	18.0	386.24	837.41	−0.22	2.34	81.99	31.86	272.39
225	Pimobendan	72.0	484.26	982.19	−12.44	2.70	94.90	36.68	334.38
226	Pimozide	90.0	567.26	1272.37	−5.12	5.38	130.43	50.51	461.55
227	Pinacidil	155.0	362.27	763.47	−9.72	2.00	74.56	28.06	245.33
228	Pindolol	51.0	451.99	812.85	−11.09	1.01	72.52	28.12	248.32
229	Pipamperone	48.0	493.64	1071.90	−2.88	1.15	105.10	40.55	375.49
230	Pipemidic acide	529.0	423.88	851.01	−9.11	0.30	80.11	30.49	303.32
231	Piperidolate	100.0	492.16	1012.61	−2.01	4.21	96.78	37.91	323.43
232	Pipradrol	30.0	341.55	824.01	−4.24	3.50	81.58	32.32	267.37
233	Piretanide	700.0	572.93	1008.97	−12.47	2.65	94.37	33.69	362.40
234	Piritramide	13.0	527.13	1237.88	−7.56	3.49	129.31	50.23	430.59
235	Piromidic acid	158.0	409.97	824.06	−5.50	1.19	76.90	29.14	288.31
236	Pivampicillin	148.0	644.39	1270.78	−8.78	2.08	116.15	46.92	463.55
237	Plaunotol	120.0	420.56	948.93	−11.95	2.45	98.49	37.91	360.45
238	Procainamide	110.0	477.59	809.36	−5.59	1.01	71.75	27.42	235.33
239	Procaine	42.0	477.53	798.72	−4.60	1.66	69.80	26.70	236.31
240	Profenamine	15.0	421.81	936.93	−0.81	4.35	98.00	37.87	312.47
241	Promazine	14.5	466.96	861.70	−1.53	3.30	88.95	34.20	284.42

(*Continued*)

Table 1. List of studied drugs, their LD_{50} values in rat after intravenous administration and computational parameters calculated by HyperChem (*continuation*).

No.	Name	LD_{50}	SAA	VOL	HE	Log *P*	REF	POL	MW
242	Promethazine	45.0	426.13	831.88	–1.60	3.66	88.50	34.20	284.42
243	Propanidid	81.0	494.26	1071.38	–9.92	1.87	91.53	35.89	337.42
244	Propentofylline	180.0	563.86	944.53	–0.10	0.67	82.97	31.80	306.36
245	Propofol	42.0	358.50	637.27	–1.59	4.15	56.13	22.08	178.27
246	Propranolol	23.0	472.91	856.84	–7.11	1.76	80.00	30.25	259.35
247	Prosicllaridin	9.0	510.89	1350.47	–14.32	2.23	140.08	55.15	530.66
248	Prothipendyl	25.0	457.73	856.01	–2.23	–0.34	94.26	33.49	285.41
249	Protirelin	514.0	291.23	525.70	–15.98	–2.45	46.97	17.14	169.18
250	Proxyphylline	430.0	580.65	974.58	–3.24	2.22	85.54	32.85	294.39
251	Pyridoxine (vitamin B6)	657.0	291.23	525.70	–15.98	–2.45	46.97	17.14	169.18
252	Quazepam	2749.0	441.15	903.46	–3.03	5.24	93.76	35.59	386.79
253	Quinidine	23.0	404.99	942.51	–7.47	1.96	96.76	36.98	324.42
254	Ranimustine	31.8	406.58	824.94	–15.47	–0.78	70.05	27.46	327.72
255	Ranitidine	93.0	601.96	962.89	–11.30	–1.18	88.40	32.81	314.40
256	Rebamipide	700.0	488.64	978.63	–12.38	2.22	96.22	37.50	370.79
257	Reserpine	15.0	761.01	1622.98	–11.28	1.40	161.85	62.67	608.69
258	Riboflavin (Vit B2)	50.0	506.91	994.61	–18.27	1.51	93.63	36.36	376.37
259	Ribostamycin	535.0	384.14	1112.84	–28.98	–4.72	99.99	41.42	454.48
260	Risperidone	26.9	460.78	1109.07	–3.92	1.94	114.61	43.54	410.49
261	Salazosulfapyridine	1520.0	541.71	1041.18	–25.59	3.57	106.34	36.79	398.39
262	Salbutamol	57.1	468.72	778.27	–14.60	1.21	67.58	26.54	239.31
263	Secobarbital	80.0	360.39	627.54	–4.86	1.47	53.40	21.31	212.25
264	Sisomicin	32.0	473.05	1219.63	–20.90	–4.49	110.05	44.34	447.53
265	Sofalcone	105.0	828.31	1378.61	–8.03	4.95	130.59	49.76	450.53
266	Spiperone	14.0	516.48	1103.63	–4.72	3.02	111.19	42.87	395.48
267	Sulfadiazine	880.0	342.67	682.45	–13.46	0.64	65.38	22.52	250.27
268	Sulfaethidole	1300.0	425.21	757.69	–17.39	2.46	72.36	25.71	284.35
269	Sulfalene	1790.0	369.29	751.43	–12.54	0.55	70.67	24.99	280.30
270	Sulfamerazine	1100.0	378.71	736.52	–11.93	1.60	69.86	24.35	264.30
271	Sulfamethizole	2710.0	395.57	708.78	–17.17	1.83	67.73	23.87	270.32

(*Continued*)

Table 1. List of studied drugs, their LD_{50} values in rat after intravenous administration and computational parameters calculated by HyperChem (*continuation*).

No.	Name	LD_{50}	SAA	VOL	HE	Log *P*	REF	POL	MW
272	Sulfametoxy diazine	1000.0	404.73	759.26	−14.98	−0.23	71.83	24.99	280.30
273	Sulfanilamide	1400.0	267.85	490.49	−11.97	0.15	44.10	14.27	172.20
274	Sulfaphenazole	525.0	359.76	829.15	−11.68	2.09	85.93	30.76	314.36
275	Sulfathiazole	1370.0	342.83	664.68	−13.55	0.63	64.97	22.75	255.31
276	Sulforidazine	24.0	403.96	1010.43	−3.27	3.24	114.52	41.90	402.57
277	Sulpiride	40.0	471.31	933.26	−8.33	0.48	89.32	32.09	341.43
278	Suprofen	226.0	393.77	742.23	−6.45	1.31	73.95	27.76	260.31
279	Suxibuzone	305.0	591.56	1223.17	−8.85	3.81	115.08	45.66	438.48
280	Tacrine	20.0	274.01	630.89	−5.72	1.83	62.62	23.82	198.27
281	Talinolol	30.0	624.37	1156.93	−8.93	2.28	102.68	40.76	363.50
282	Tazanolast	1119.0	517.22	855.23	−19.57	3.20	78.04	29.01	289.29
283	Tegafur	685.0	290.94	540.38	−4.27	−1.24	44.53	17.13	200.17
284	Terbinafine	213.0	586.26	956.27	0.54	5.34	93.79	36.66	279.43
285	Tetracaine	6.0	605.21	918.92	−1.36	2.54	79.67	30.37	264.37
286	Tetracycline	129.0	473.96	1068.17	−19.12	−1.19	111.72	42.60	428.44
287	Tetroxoprim	300.0	489.77	980.56	−16.64	0.35	89.85	34.94	334.38
288	Thenalidine	42.0	373.87	840.81	−1.05	1.91	91.98	34.39	286.43
289	Thiamphenicol	339.0	511.14	877.58	−13.31	0.47	79.61	29.15	356.22
290	Thioctic acid	180.0	382.23	621.99	−5.26	1.78	54.29	21.40	206.32
291	Thioproperazine	25.0	586.75	1182.83	−2.41	2.12	126.95	46.44	446.63
292	Thioridazine	71.0	395.17	1037.76	−1.98	4.18	113.67	43.76	370.57
293	Thiotepa	9.4	317.28	599.45	0.58	−0.54	50.72	17.63	189.22
294	Ticlopidine	70.0	275.73	683.64	−1.56	1.54	78.11	29.46	263.78
295	Tiropramide	33.9	831.48	1487.52	−1.72	4.55	138.87	54.32	467.65
296	Tobramycin	104.0	388.21	1155.59	−31.65	−5.56	106.69	43.97	467.52
297	Todralazine	110.0	386.18	703.98	−12.94	2.47	62.98	24.13	232.24
298	Tofisopam	103.0	567.31	1101.11	−9.46	4.39	109.03	42.09	382.46
299	Tolbutamide	700.0	516.65	819.67	−5.17	2.21	70.27	25.37	270.35
300	Tranexamic acid	1200.0	271.20	524.32	−7.88	0.62	41.90	16.75	157.21
301	Trazodone	91.0	510.26	1056.31	−3.24	2.80	105.91	39.94	371.87

(*Continued*)

Table 1. List of studied drugs, their LD_{50} values in rat after intravenous administration and computational parameters calculated by HyperChem (*continuation*).

No.	Name	LD_{50}	SAA	VOL	HE	Log *P*	REF	POL	MW
302	Tretinoin	78.0	606.96	1004.69	–1.89	4.73	97.79	36.46	300.44
303	Triaziquone	0.5	329.44	702.26	0.03	–1.49	66.20	23.54	231.25
304	Trichlormethiazide	920.0	442.08	785.22	–12.21	1.23	78.62	25.44	380.65
305	Trifluperidol	14.0	566.44	1084.69	–4.32	3.74	103.76	39.38	409.42
306	Trifluridine	2946.0	331.56	686.60	–8.42	–0.87	56.38	21.90	296.20
307	Trofosfamide	90.0	483.45	819.17	–0.22	1.73	72.72	26.59	323.59
308	Urapidil	140.0	564.08	1116.27	–2.40	1.30	109.45	41.95	387.48
309	Verapamil	7.3	805.46	1403.45	–7.48	5.05	132.65	51.54	454.61
310	Vesnarinone	79.3	543.75	1158.45	–6.77	1.87	110.25	42.40	395.46
311	Vidarabine	302.0	371.37	841.12	–30.74	–1.34	73.70	26.89	347.22
312	Viloxazine	60.0	337.14	723.28	–4.53	1.23	65.20	25.77	237.30
313	Vinblastine	2.0	765.55	1991.61	–6.06	1.57	227.52	86.17	810.99
314	Vincristine	1.0	767.33	1989.23	–0.76	0.19	227.00	86.25	824.97
315	Vinpocetin	32.0	409.15	993.43	0.11	2.42	106.00	39.74	350.46
316	Zimeldine	50.0	475.39	861.28	–2.82	2.52	87.56	32.34	317.23
317	Zonisamide	672.0	290.47	567.18	–11.02	0.64	51.55	17.39	212.22
318	Zopiclone	280.0	491.48	1031.64	–4.23	–1.83	101.25	37.80	368.40
319	Zotepine	36.8	521.68	942.97	–9.92	3.49	97.34	37.05	331.86

Results and Discussion

Preliminary analysis was carried out employing all independent variables by backward regression command of SPSS software. The resulting equation was:

$$LD_{50} = -639.254 + 3.773\ SAA - 4.786\ VOL - 21.050\ HE - 50.753\ \log P - 51.440\ REF + 121.219\ POL + 12.932\ MASS + 0.011\ TE - 95.494\ HOMO \quad \text{(Eq. 7)}$$

$$N = 319,\ R = 0.748,\ F = 43,\ APD = 2686.$$

The above equation with applying 319 experimental data of different drugs was resulted. Relatively high correlation coefficient (R) and F value with the significance level of < 0.0005 reveal that, the model is able to fit the toxicity data of drugs on rat after intravenous administration. APD for some data points for Eq. 7 was high because

of existence of the outliers which were listed in Table 2. After excluding the outlier data points, the resulting equation was:

$$LD_{50} = -740.217 + 4.050\ SAA - 5.138\ VOL - 21.909\ HE - 50.713\ \log P - 49.662\ REF \quad \text{(Eq. 8)}$$
$$+120.843\ POL + 12.742\ MASS + 0.010\ TE - 106.513\ HOMO$$
$$N = 309,\ R = 0.751,\ F = 43,\ APD = 779$$

Table 2. Outlier points of the drugs, studied by Eq. 7.

Name	LD_{50}	PD
Epinephrine	0.2	348874
Calcitriol	0.1	−82404
Triaziquone	0.5	−63536
Busulfan	1.8	54368
Melphalan	4.1	16383
Vincristine	1.0	15766
Mitomycin	3.0	15317
Nisoldipine	1.1	−12165
Felodipine	5.4	10322
Doxorubicin	10.5	9709

For providing practical application of Eq. 8, Hodge and Sterner scale was applied. Based on this classification, drugs are divided into six groups from highly toxic to harmless (12). Table 3 shows the APD values for different groups and number of data in each group. Considering Table 3, with increasing toxicity of the drugs, predictive ability of the model is decreased. From statistical viewpoint, this limitation results from two factors: (A) Number of data in high toxic group is very small and (B) Effect of very small numerical values of high toxic drugs on the total LD_{50} mean is negligible and lead to the reduced accuracy of the equation.

Table 3. Toxicity classification of drugs, the number of them and APD values in each group.

Rating	LD_{50} (mg/kg)	N	APD	APD
High	<1	4	133093	-
regular	1-50	130	2517	75
Moderate	50-500	130	269	64
Low	500-5000	51	63	48
Very low	5000-15000	4	57	-
Harmless	>15000	0	-	-

In another numerical analysis, the proposed equation was trained by data of groups with higher than 50 data points (N>50) and then, the APD values were calculated and reported in Table 3. As shown, the overall APD reduces to ~ 60 %, however, one should be able to detect the class of the candidate concerning Hodge and Sterner classification and then to use this prediction method.

Any error in measuring or reporting the experimental toxicity data is another source of prediction error. In some cases, the numerical difference of the reported LD_{50} for a single drug, on a given animal and a common administration route is about 1500 folds. For example, LD_{50} of benzyl benzoate in rat after oral administration is 1.7 mg/Kg (7) and 2800 mg/Kg (9). The PD between two experimentally reported data is equal to 164600 %. Table 4 shows some of different data for LD_{50} of drugs in rat after intravenous administration.

Table 4. Differences in the LD50 amounts reported for intravenous administration of drugs on rat.

Drug	LD_{50} (7)	LD_{50} (9)	LD_{50} (8)
Atenolol	77	59	
Clozapine	118	58	
Dixyrazine	37.5	3.75	
Ergotamine	80		62
Fentanyl	2.91	6	
Imipramine	9.3	25	
Isoniazid	365		398
Methylphenidate	48	70	
Nalidixic acid	88.4	250	
Oxyphenbutazone	68		105
Phenylbutazone	100		150
Piperidolate	100		19
Promazine	14.5	32.5	
Tetracycline	129	160	

As a conclusion, a quantitative structure toxicity relationship (QSTR) was proposed to correlate toxicity of drugs on rat. The proposed model is robust and could be considered as a predictive model. Because of various toxic mechanisms, high discrepancy in reported LD_{50} of some of drugs from different references, high APD value could be justified. After excluding the outliers, APD reduces to 977%. The APD could be con-

sidered as acceptable error range if the experimental discrepancies between reported LD_{50} from different laboratories are kept in mind.

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