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The determination of toxicities of sulphonylurea and phenylurea herbicides with quantitative structure–toxicity relationship (QSTR) studies

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ABSTRACT

Sulphonylurea and phenylurea herbicides are two groups of herbicides that are most commonly used worldwide. Quantitative structure–toxicity relationship models were derived for estimating the acute oral toxicity of these herbicides to male rats. The 20 chemicals of the training set and the seven compounds of external testing set were described by means of using descriptors for lipophilicity, polarity and molecular geometry, as well as the calculation of quantum chemical descriptors for energy. Model development to predict the toxicity of sulphonylurea and phenylurea herbicides in different matrices was carried out using multiple-linear regression. The model was validated internally and externally. In the present study, QSTR model was used for the first time to understand the inherent relationships between the sulphonyl and phenylurea-type herbicide molecules and their toxic behaviour. Such studies provide mechanistic insight about structure–toxicity relationships and assist in the design of less toxic herbicides.

1. Introduction

Pesticide compounds are found in significant quantities in the environment and foodstuffs worldwide due to their massive usage (every year an estimated 2.5 million tons of pesticides are applied to agricultural crops worldwide) making their toxicity an unresolved issue (Pimentel, 1995). Sulphonylureas are a family of herbicides which selectively control a range of undesirable plants, such as grasses, which interfere with the growth of foodcrops and vegetables. These herbicides have now been developed and commercialized worldwide for application with all major agronomic crops and for many specialty uses. Sulphonylureas represent a major advance in global crop protection technology and have revolutionized weed control by interfering with a key enzyme required for weed cell growth – acetolactate synthase. Their highly selective and specific mode of action means that these agents are compatible with the global trend toward post emergence weed control and integrated pest management.

Another family of herbicides are phenylurea herbicides. They are used for general weed control in agricultural monagricultural practices, for example, along railroads and industrial areas. Many more derivatives of this class of compounds have been marketed. The herbicidal action of these compounds is based on their ability to inhibit photosynthesis.

Abbreviations: QSTR, quantitative structure–toxicity relationship; LD_{50}, lethal dose; QSAR, quantitative structure–activity relationship; HOMO, highest occupied molecular orbital; LUMO, lowest unoccupied molecular orbital; AM1, austin model 1; PRESS, predicted residual sums of squares; SSY, sum of squares of Y.

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Toxicity has been quantified in terms of LD_{50}, which is the amount of a material, given all at once, which causes the death of 50% (one half) of a group of test animals. The LD_{50} is one way to measure the short-term poisoning potential (acute toxicity) of a material in experimental animals and in 1999, 2,607,349 animals on a total of 9,814,171 (Commission of the European Communities, 2003) were used in toxicity studies. The LD_{50} can be found for any route of entry or administration but dermal (applied to the skin) and oral (given by mouth) administration methods are the most common. The test is expensive, time consuming and ethically questionable and unfortunately alternative methods, such as QSAR models, are not numerous enough or sufficiently investigated to replace many animal tests (Tong et al., 2003).

As experimental determinations of toxicity are costly and time-consuming, it is preferred to develop mathematical equations which can be able to establish the relationships between the toxicity and structure of the toxic compound. The objective of structure–toxicity analyses is to predict toxic activity from information on molecular structure. Quantitative structure–toxicity relationship (QSTR) provides a relevant tool for toxicity evaluation and prediction, and can also give some insight into the mechanism of toxic actions (Schultz et al., 2003; Eriksson et al., 2003).

The aim of this study was to derive a QSTR model allowing us to simulate the acute oral toxicity of phenyl and sulphonylurea herbicides to rats. After calculating numerous molecular descriptors, most effective of them were selected via statistical method. Four descriptors reflecting the main characteristics of the sulphonyl and phenylurea-type herbicide molecules were found in this study. The best QSTR model was established on these four descriptors. The model was tested either internal or external test sets for the validation of the model equation. The test results indicate that the calculated QSTR model can be used with confidence for prediction of toxicity of phenylurea-type herbicide molecules.

2. Materials and methods

2.1. Toxicity data

The potency was defined as $\log 1/C$ where C was the molar lethal dose 50 (LD_{50}) values of the compounds. Before the calculations in this study, LD_{50} values (rat, male via oral) and the structural formulas of sulphonyl and phenylurea compounds were obtained from the literatures [1–51]. All this acute toxicity data being reported in mg/kg, for modelling purposes, they were first converted into mmol/kg and then translated to their negative logarithms (see Table 1).

2.2. Molecular descriptors

Before the calculations of molecular descriptors of the compounds, energetically stable molecular structures are needed. For this purpose, all compounds were optimized using MM+ (molecular mechanic) method for generating initial structures at the beginning of the calculations. In order to obtain minimum energy structures, second geometry optimization were performed with AM1 semi-empirical calculations. Geometry optimization calculations employ energy minimization algorithms to locate stable structures. Geometrically optimized structures were used for the calculations of molecular descriptors. Molecular descriptors consist of octanol/water partition coefficient ($\log P$), dipole moment, molar refractivity, polarizability, molar volume, hydration energy, surface area (grid and approximate), molecular mass, HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) energies (from AM1 semi-empirical single point calculation). Single-point calculations determine the molecular energy and properties for a given fixed geometry. HyperChem (TM) (Student Edition 8.0, Hypercube, Inc., 1115 NW 4th Street, Gainesville, FL 32,601, USA.) software was used for geometry optimizations and calculations of molecular descriptors except molecular mass.

The HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) energies are electronic molecular descriptors.

The steric effects were considered by means of surface areas and molar volume. Surface areas are estimated using a rapid, approximate method due to W.C. Still and co-workers or using a slower grid-based method. Molecular volumes, bounded by Van der Waals or solvent accessible surfaces, are calculated using a grid method (Hasel et al., 1988).

Specifically, the hydration energy and $\log P$ were considered as descriptors for hydrophobic effects. Hydration energy (for peptides and similar systems), using a method parameterized by Scheraga (Ooi et al., 1987), is predicted based on the approximate surface area calculation. The $\log P$ (the log of the octanol–water partition coefficient), a hydrophobicity indicator, using an atom fragment method developed by Ghose et al. (1988). For a sample of organic molecules, the method yields a correlation coefficient (r) with experimental values of 0.92 and a standard error of 0.36.

As polar descriptors, refractivity, dipole moment and polarizability were calculated. Refractivity is also computed using an atom-based fragment method due to Ghose and Grippen (1987). For a sample of organic molecules, the method yields a correlation coefficient (r) with experimental values of 0.995 and a standard error of 1.1. Polarizability, using an atom-based method due to Miller (1990). For a sample of organic molecules, the method yields a correlation coefficient (r) with experimental values of 0.991 and a standard error of 9.3. Molecular mass is calculated using a straightforward method.

2.3. Statistical analyses

In a first step, attempts were made to relate the LD_{50} data to the molecular descriptors by means of a linear statistical method. The multiple-linear regression method was selected due to its ability to derive robust model.

3. Results

The toxicity of some sulphonylurea and phenylurea herbicides were previously determined experimentally [1–51]. The toxicity data, LD_{50}, in the literature was converted to $\log 1/C$ as described above. Twenty training compounds were used for QSAR study (see Table 2). The quantitative structure–toxicity

Table 1 – The LD_{50} (mg/kg), MW (g/mol), C (mmol/kg) and log 1/C values of the herbicides.

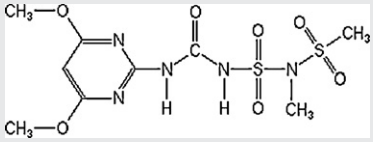
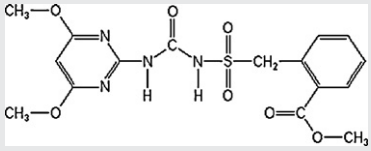
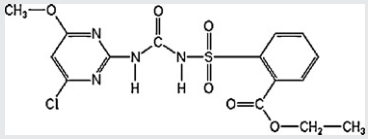
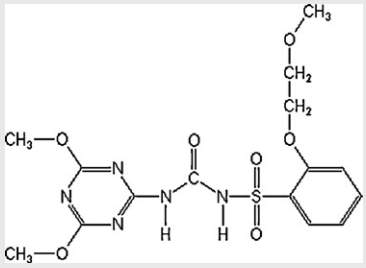
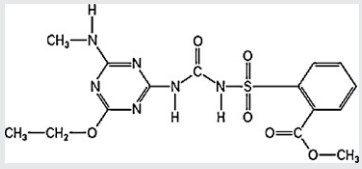
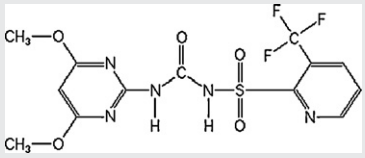
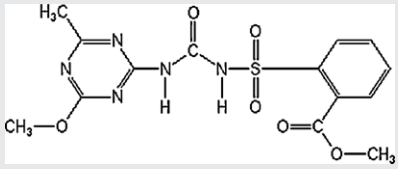
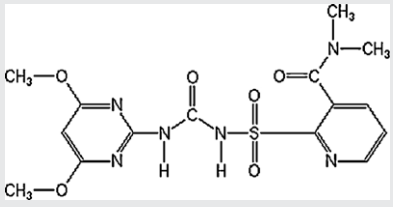
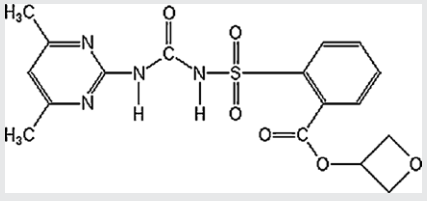
Name of compound	LD_{50} mg/kg [Ref. no.]	MW (g/mol)	C (mmol/kg)	log 1/C
Amidosulphuron	5000 [1]	355.340	0.0141	1.8517
Azimsulphuron	5000 [2]	424.394	0.0118	1.9288
Bensulphuron-methyl	5000 [3]	410.401	0.0122	1.9142
Chloromuron-ethyl	4102 [4]	414.820	0.0099	2.0049
Chlorsulphuron	3053 [5]	357.771	0.0085	2.0689
Cinosulphuron	4102 [6]	413.405	0.0099	2.0034
Cyclosulphamuron	5000 [7]	421.428	0.0119	1.9258
Ethametsulphuron-methyl	5000 [8]	410.404	0.0122	1.9142
Ethoxysulphuron	3270 [9]	398.390	0.0082	2.0858
Flazasulphuron	5000 [10]	407.324	0.0123	1.9110
Foramsulphuron	5000 [11]	452.442	0.0111	1.9566
Flupysulphuron-methyl	5000 [12]	465.361	0.0107	1.9688
Halosulphuron-methyl	1287 [13]	434.811	0.0030	2.5287
Imazosulphuron	5000 [14]	412.807	0.0121	1.9168
Iodosulphuron	2678 [15]	493.233	0.0054	2.2652
Metsulphuron-methyl	5000 [16]	381.363	0.0131	1.8824
Nicosulphuron	5000 [17]	410.404	0.0122	1.9142
Oxsasulphuron	5000 [18]	406.413	0.0123	1.9100
Pyrimsulphuron-methyl	5000 [19]	468.336	0.0107	1.9716
Prosulphuron	986 [20]	419.378	0.0024	2.6287
Pyrazosulphuron-ethyl	5000 [21]	413.428	0.0121	1.9174
Rimsulphuron	5000 [22]	430.474	0.0116	1.9350
Sulfometuron-methyl	5000 [23]	364.376	0.0137	1.8626
Sulfosulphuron	5000 [24]	470.475	0.0106	1.9736
Tifensulphuron-methyl	5000 [25]	387.385	0.0129	1.8892
Triasulphuron	5000 [26]	401.824	0.0124	1.9051
Tribenuron-methyl	5000 [27]	395.390	0.0126	1.8981
Trifloxysulphuron-Na	5000 [28]	437.350	0.0114	1.9419
Triflusulphuron-methyl	5000 [29]	492.429	0.0102	1.9934
Tritosulphuron	4700 [30]	445.296	0.0106	1.9766
Buturon	1791 [31]	236.701	0.0076	2.1211
Chlorbromuron	2150 [32]	293.548	0.0073	2.1352
Chlorotoluron	10,000 [33]	212.679	0.0470	1.3277
Chloroxuron	3700 [34]	290.749	0.0127	1.8953
Daimuron	5000 [35]	268.359	0.0186	1.7297
Difenoxuron	1000 [36]	286.330	0.0035	2.4569
Dimefuron	2000 [37]	356.809	0.0056	2.2514
Diuron	437 [38]	233.097	0.0019	2.7271
Fenuron	6400 [39]	164.207	0.0390	1.4092
Fluometuron	5000 [40]	232.205	0.0215	1.6669
Isoproturon	1826 [41]	206.288	0.0089	2.0530
Isouron	630 [42]	211.264	0.0030	2.5255
Linuron	1146 [43]	249.097	0.0046	2.3372
Methyldimron	3948 [44]	270.374	0.0146	1.8356
Metobenzuron	10,000 [45]	414.586	0.0241	1.6176
Metobromuron	10,000 [46]	259.103	0.0386	1.4135
Metoksuron	3200 [47]	228.678	0.0140	1.8541
Monolinuron	2100 [48]	252.120	0.0083	2.0794
Monuron	1053 [49]	198.652	0.0053	2.2757
Neburon	11,000 [50]	275.178	0.0400	1.3982
Siduron	7500 [51]	232.326	0.0323	1.4910

relationship (QSTR) model was calculated using multiple-linear regression method. The variables used as independent descriptors in the QSAR analysis were hydrophobic, electronic, polar, steric, and geometric parameters. Twelve molecular descriptors which are octanol–water partition coefficient (log P), dipole moment, molar refractivity, polarizability, molar volume, hydration energy, surface area (grid and approximate), molecular mass, HOMO and LUMO energies, were calculated for the training compounds (see Table 3).

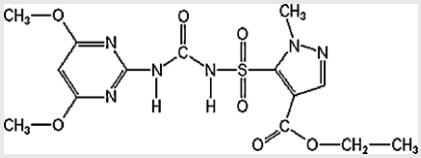
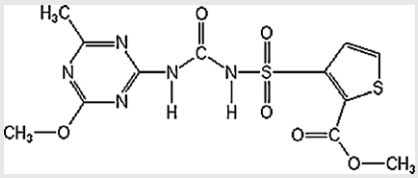
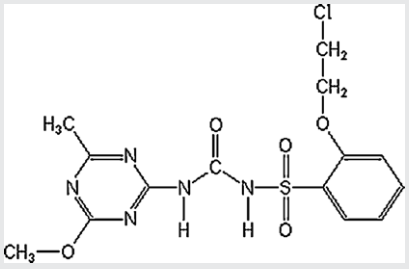
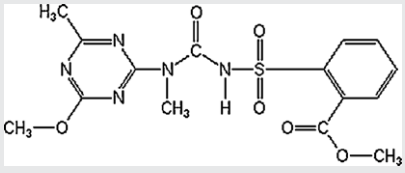
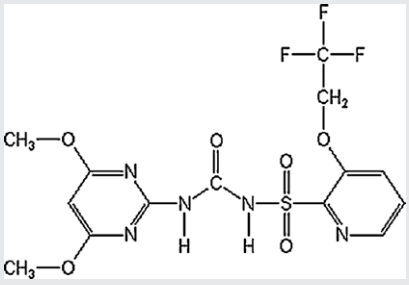
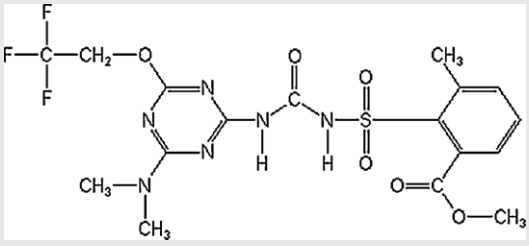
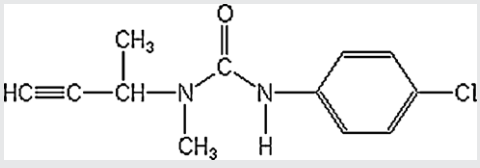
Stepwise regression analysis was used to select the most effective parameters on the toxicity of the sulphonylurea pesticides. According to stepwise regression, successive regression equations are derived in which parameters will be either added or removed until the r^2 and s values are optimized. The magnitude of the coefficients derived in this manner indicates the relative contribution of the associated parameter to toxicity. Among the twelve molecular descriptors, only four of them were taken placed in the model, as a result of stepwise regression analyses.

Results of QSAR model obtained by the multiple-linear regression analysis of the training set of compounds

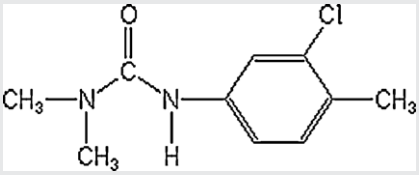
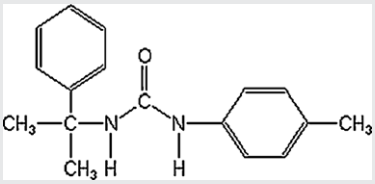
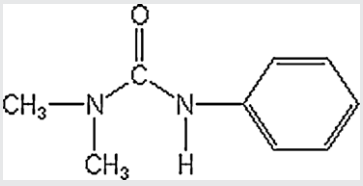
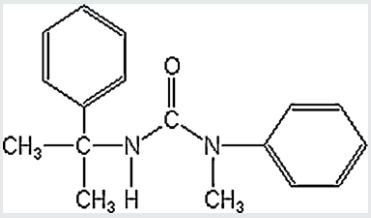
Table 2 – Structural formulas and codification of training compounds.

Compounds name	Structural formulas	Codification
Amidosulphuron		Tr01
Bensulphuron-methyl		Tr02
Chlorimuron-ethyl		Tr03
Cinosulphuron		Tr04
Ethametsulphuron-methyl		Tr05
Flazasulphuron		Tr06
Metsulphuron-methyl		Tr07
Nicosulphuron		Tr08
Oxasulphuron		Tr09

– Table 2 (*Continued*)

Compounds name	Structural formulas	Codification
Pyrazosulphuron-ethyl		Tr10
Thyfensulphuron-methyl		Tr11
Triasulphuron		Tr12
Tribenuron-methyl		Tr13
Trifloksisulphuron		Tr14
Triflusulphuron-methyl		Tr15
Buturon		Tr16

– Table 2 (*Continued*)

Compounds name	Structural formulas	Codification
Chlorotoluron		Tr17
Daimuron		Tr18
Fenuron		Tr19
Methyldimron		Tr20

(Tr01–Tr20), demonstrate that the equation (see Table 4), is statistically significant (see Table 5).

The equation is represents the best fitted model among the others which are not shown in this study. As can be deduced from Fig. 1, the goodness-of-fit of the equation is the most significant correlation models possessing a high r^2 (93.07%) and a small s (0.0557) with an overall F test value of 50.34 at the significant level of $p < 0.05$ (see Table 6).

From a statistical point of view, the equation has a sufficient number of DF (degrees of freedom DF = 15); that can be judged significant for overall F and t statistics at the 5% level of probability.

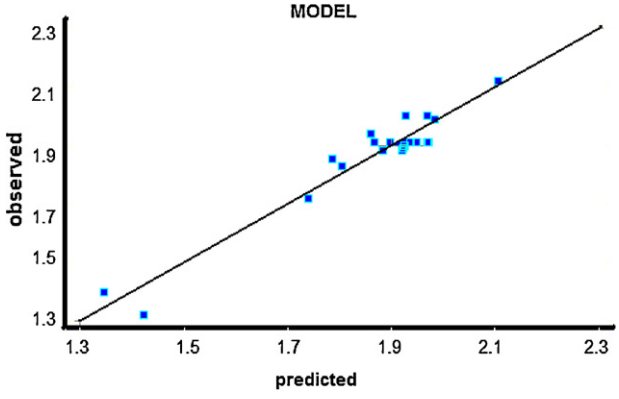


Fig. 1 – Plot of observed vs. calculated log 1/C values of the training set compounds obtained by using the equation.

In order to avoid the risk of chance correlation, some circumstances which were pointed out by Kubinyi et al. (1993), have been taken into consideration in the study. Cross-validation was applied to the original data set and the resulting PRESS was calculated. The calculated overall PRESS values for the equation is 0.0486, respectively that are found smaller than the SSY (sum of the squares of the response values of the total observations) values of the observed the equation, which is 0.672 (see Table 6). This proves that the developed model predict better than chance and can be considered statistically significant (Wold, 1991). The ratio PRESS/SSY for the equation, which is the approximate confidence interval for a prediction, is smaller than 0.4 and it also provides proof that the observed model is valid (Wold, 1991; Rawlings, 1988).

According to correlation matrix Table (see Table 7), there is no intercorrelation between physicochemical parameters. For validity of the model, the correlation constant value should be up to 0.7. In our model equation, the maximum intercorrelation constant value is obtained as 0.6029. It shows that the model does not consist of any chance correlation.

The good predictability of our QSTR model for the phenyl and sulphonylurea pesticides can be understood from the Table 8. The log 1/C value which obtained from model equation is close to experimental value of log 1/C.

Table 3 – QSAR study for training compounds.

Compounds	log 1/C	Dipole moment	HOMO	LUMO	Surface area (approx.)	Surface area (grid)	Volume	Hydration energy	Log P	Refractivity	Polarizability	Mass
Tr01	1.8517	2.91	−9.403	−1.798	513.685	533.849	863.306	−17.354	−0.102	72.599	24.045	355.34
Tr02	1.9142	5.417	−9.507	−1.026	541.664	618.977	1054.545	−13.678	0.704	100.177	35.609	410.401
Tr03	2.0049	5.246	−9.55	−1.179	528.78	603.769	1020.801	−10.533	0.968	99.85	35.065	414.82
Tr04	2.0034	5.262	−9.818	−0.98	535.635	598.429	1047.785	−13.383	0.464	100.579	35.451	413.405
Tr05	1.9142	5.259	−9.657	−1.178	527.099	620.817	1045.538	−11.616	1.064	100.627	35.614	410.404
Tr06	1.911	5.32	−9.53	−1.574	500.67	577.176	957.167	−13.149	1.424	86.284	30.234	407.324
Tr07	1.8824	3.867	−10.281	−1.104	497.673	583.191	967.438	−11.674	0.413	92.305	32.428	381.363
Tr08	1.9142	4.245	−9.355	−1.234	501.698	580.949	1027.253	−10.721	−0.133	98.684	35.614	410.404
Tr09	1.91	5.019	−9.573	−1.306	535.172	644.633	1070.438	−10.766	−0.245	103.512	36.033	406.413
Tr10	1.9174	4.427	−4.899	−0.734	601.847	656.65	1110.766	−13.018	0.476	98.838	36.261	413.428
Tr11	1.8892	5.004	−10.206	−1.386	493.756	569.189	942.694	−12.333	−0.976	89.601	31.95	470.475
Tr12	1.9051	3.89	−10	−0.977	508.187	594.23	999.004	−10.278	0.707	97.255	34.27	387.385
Tr13	1.8981	4.94	−9.972	−1.084	525.037	599.44	1013.729	−9.000	0.66	97.202	34.263	401.824
Tr14	1.9419	7.117	−9.44	−1.3	551.112	628.942	1042.318	−13.693	0.836	92.894	32.706	395.39
Tr15	1.9934	10.82	−9.832	−1.02	582.238	642.732	1141.871	−7.253	2.212	110.906	39.011	437.35
Tr16	2.1211	4.766	−8.7551	0.1163	455.38	444.83	720.131	−2.325	2.322	64.414	25.056	445.296
Tr17	1.3277	4.766	−8.6829	0.1564	427.331	412.517	652.137	−1.624	−0.142	61.418	22.49	212.679
Tr18	1.7297	3.133	−8.8842	0.118	428.602	497.135	836.711	−4.657	1.339	89.612	32.057	268.359
Tr19	1.4092	3.656	−8.6758	0.4626	356.938	367.296	562.334	−3.174	−0.073	52.42	18.727	164.207
Tr20	1.8356	2.243	−8.871	0.3229	434.182	495.971	848.365	−2.601	1.797	89.453	32.249	270.374

Table 4 – Model equation.

Equation			
Log 1/C = 1.03492–0.0266253 DM[a] + 0.0806626 log P + 0.00138922 Rf[b] + 0.00206901 mass			
R^2	Standard error of est.	Mean absolute error	Durbin–Watson statistic
93.068%	0.056	0.041	1.721

[a] DM: dipol moment.
[b] Rf (refractivity).

Table 5 – Multiple regression analyses of model.

Parameter	Estimate	Standard deviation	T statistic	p-Value
Constant	1.035	7.698×10^{-2}	13.444	0.0000
Refractivity	1.389×10^{-3}	1.111×10^{-3}	1.250	0.2303
Mass	2.069×10^{-3}	2.165×10^{-4}	9.557	0.0000
Dipol moment	-2.662×10^{-2}	8.596×10^{-3}	−3.097	0.0074
Log P	8.066×10^{-2}	1.577×10^{-2}	5.114	0.0001

Table 6 – Variance analyses of model.

Source	Sum of squares	Df	Mean square	F rate	p-Value
Model	0.626	4	0.156	50.34	0.0000
Residual	0.047	15	0.003		
Total (corr.)	0.672	19			

The model was also tested using with the external test set (see Table 9). Based on the structural diversity of the training set and toxicity data availability, seven different sulphonyl and phenylurea herbicides with their LD_{50} values on male rats (oral) were retrieved from literature [1–51] for constituting the external testing set which is useful for testing the predictive power of the quantitative structure–toxicity relationship (QSTR) model. The r^2 value was calculated as 0.682. It shows that the equation has the excellent determining capability of the sulphonylurea and phenylurea toxicity (see Table 10).

4. Discussion

As seen from the model, the most effective parameter on the toxicity is log P due to this parameter's highest constant value in the equation. Indeed, log P increased in a direct relationship with toxicity. This suggests that high lipophilicity is a strong predictor of toxicity with these herbicides. The inverse proportion between dipole moment and toxicity was predicted from the equation above. The compound which possesses the higher dipole moment, has lower toxicity (log 1/C value). There is a linear correlation between the dipole moment and polarity. The third effective parameter related to toxicity was calculated as mass of the compound. The effect of mass was less than that of dipole moment and log P according to the equation above. As in the effect of log P, the greater the mass of the compound, the toxicity was recorded. In our hands, the least effective parameter which describes toxicity was molar refractivity, which has a linear relationship with the molecular mass. There was a linear relationship between molar refractivity and increasing toxicity.

Table 7 – Correlation matrix table of model.

	Constant	Rf	Mass	DM	Log P
Constant	1.0000				
Rf	−0.6029	1.0000			
Mass	−0.1786	−0.5680	1.0000		
DM	−0.0098	−0.1702	−0.2605	1.0000	
Log P	0.0134	−0.0391	0.0441	−0.2752	1.0000

Table 8 – Observed and calculated log 1/C values with residuals obtained from the equation.

Compounds	Observed log 1/C	Calculated log 1/C	Residuals
Tr01	1.85	1.78	0.07
Tr02	1.91	1.93	−0.02
Tr19	1.4	1.34	0.06
Tr05	1.91	1.96	−0.05
Tr06	1.91	1.97	−0.06
Tr17	1.32	1.42	−0.1
Tr16	2.12	2.1	0.02
Tr07	1.88	1.88	0
Tr08	1.91	1.89	0.02
Tr09	1.91	1.86	0.05
Tr13	1.89	1.92	−0.03
Tr10	1.91	1.94	−0.03
Tr11	1.88	1.92	−0.04
Tr18	1.72	1.73	−0.01
Tr12	1.9	1.92	−0.02
Tr14	1.94	1.85	0.09
Tr15	1.99	1.98	0.01
Tr04	2	1.92	0.08
Tr20	1.83	1.8	0.03
Tr03	2	1.97	0.03

Table 9 – Structural formulas and codification of setting compounds.

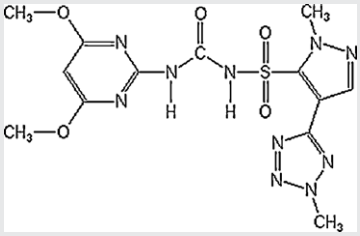
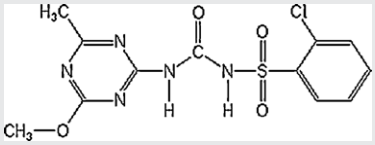
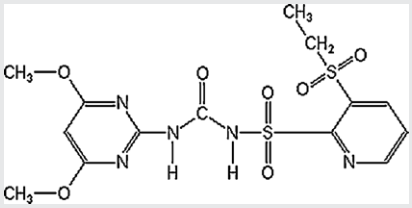
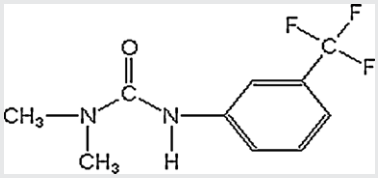
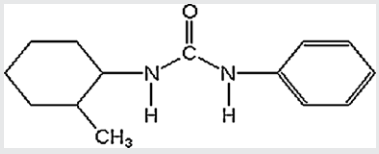
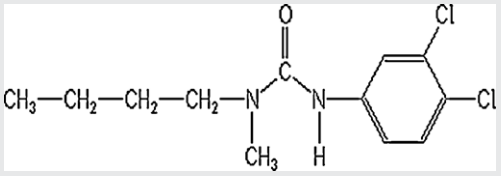
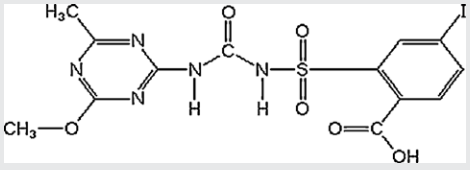
Compounds Name	Structural formulas	Codification
Azimsulphuron		Ts01
Chlorsulphuron		Ts02
Rimsulphuron		Ts03
Fluometuron		Ts04
Siduron		Ts05
Neburon		Ts06
Iodosulphuron		Ts07

Table 10 – Testing of model with using external test set that not used in modeling.

Compounds	Literature value of log 1/C	Calculated log 1/C with model equation	Residual
Ts01	1.92	2.08	0.16
Ts02	2.06	1.86	−0.2
Ts03	1.93	1.95	0.02
Ts04	1.66	1.44	−0.22
Ts05	1.49	1.66	0.17
Ts06	1.39	1.59	0.2
Ts07	2.26	2.18	−0.08

5. Conclusion

It can be concluded from this QSTR study that log *P*, dipole moment, molar refractivity and molecular mass are the effective parameters which describe sulphonylurea and phenylurea toxicity. For synthesizing less toxic sulphonylurea and phenylurea pesticides, the molecules should be highly polar, water-soluble, and having low molecular mass and refractivity, also. Quantitative structure–activity relationship models for LD_{50} value of phenylurea and sulphonylurea herbicides, suggest that if log *P* values, mass, and molar refractivity increase, herbicide toxicity also increases. However, there is an inverse proportion with toxicity and dipole moment. Researchers may use this model as part of the process of the design of less toxic sulphonylurea and phenylurea pesticides through the estmination of the LD_{50} values of new agents. It is hoped that animal usage materials, human labour and time can be saved through the application of this QSAR model.

Conflict of interest

None of the authors has any conflict of interest in this study.

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