Kazius-Bursi Salmonella Mutagenicity and Carcinogenicity Predicted by the Base of Acute Toxicity in Quantitative SAR (QSAR)-Analysis, by MLR and PNN Applied to 13-Thiophosphonates Pesticides

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Abstract

In this paper, the acute toxicity, the carcinogenicity potential, and the **Kazius-Bursi Salmonella mutagenicity** of thirteen compounds were predicted *in silico* technology by ToxPredict software, for *rodent's species*, in a quantitative SAR (QSAR) – analysis. The obtained models demonstrated the dependence of **Kazius –Bursi Salmonella** mutagenicity and carcinogenicity potential with physical-chemical parameters by MLR (multiple linear regression) and PNN (probabilistic neural network).

Introduction

This approach has its origins in the work of Meyer [1] and Overton [2], from the end of last century and the beginning of our century. Thus, they successfully demonstrated for the first time dependence of bioactivity by physical-chemical parameter, namely, partition coefficient, or lipophilicity by Hansch [3] which is a function of a molecular structure.

Thus, the biological response caused by a bioactive structure with L configuration is determined by its intrinsic activity and its ability to reach a certain receptor, respectively, at a certain site thereof. But if the intrinsic activity of L depends on a number of physicochemical properties and the geometry of molecules, bioactive compound permeability is thought to be the result of a process of passive transport is influenced only by the character of the lipophilic compound.

Therefore, a similar series in which the biological activity must depend, through a simple functional relationship, lipophilicity. And, indeed, was found a linear relationship between biological activity, A, and hydrophobicity, as:

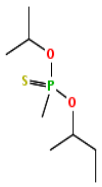
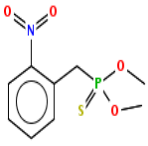
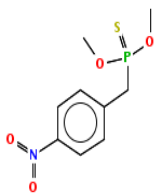
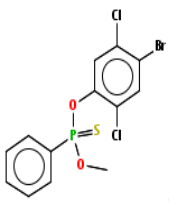
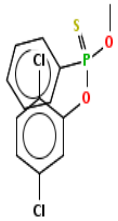
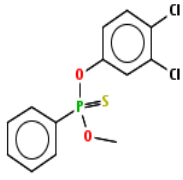
$A = \log (1 / C) = a_0 + a_1 \cdot \log P$ (1) (equation by Hammett, first equation in QSAR)[4]

where C is the molar concentration or dose, which causes a constant biological response, for example; LC50- the concentration required to kill 50% of population that been tested;

and log P represent the logarithmic expression of the partition coefficient between 1-octanol and water, namely hydrophobicity after Hansch [3].

Experimental

The case study was conducted on a series of 13 thiophosphonates, shown below in figure 1:

1. 
2. 
3. 
4. 
5. 
6. 

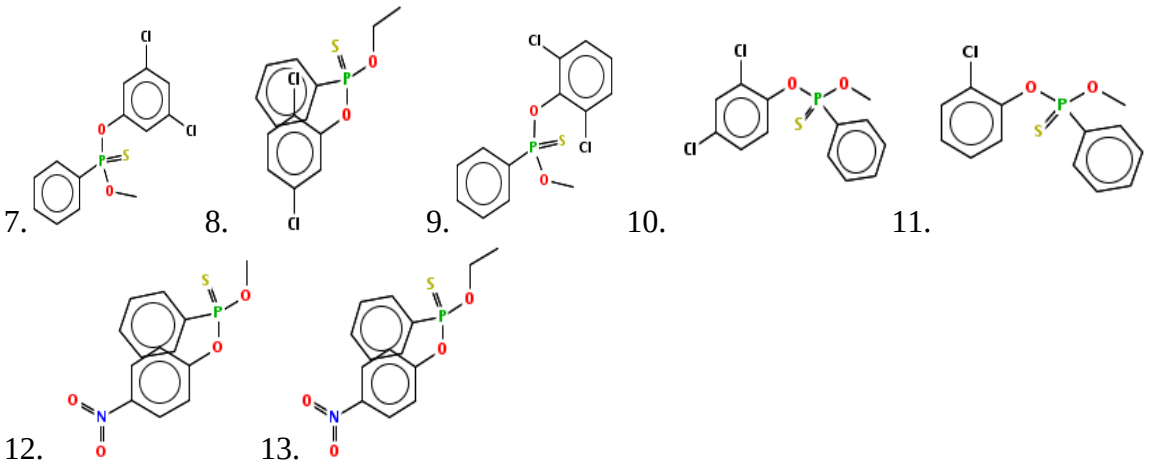


Figure1. Structures of thiophosphonates: **1**: o-butan 2-yl o-propan 2-yl methylphosphonothioate; **2**: AC1LD4KQ ; **3**: AC1LBDMI; **4:** Leptophos; **5:** Debromoleptophos**; 6:** BRN 2865560 ; 7: BRN 2865559; **8**: BRN 2877455; **9:** BRN 2873148 ;**10.** BRN 2871980 ;**11.** BRN 2858294 ; **12**. BRN 2947387; **13.** EPN(O-Ethyl O-(4-nitrophenyl) phenylphosphonothioate) .

The predictions of toxicity, carcinogenicity and mutagenicity were achieved by ToxPredict software [5]. ToxPredict is a web-based interface for predicting toxicity of individual chemicals facilitated by David Gallagher and Barry Hardy[6], and were performed by QSAR modeling, based on the **principle of similarity** between structure and properties, saying that chemicals that have the same structure, generates the same activity [7]. Consequently, biological and toxicological effects of new chemical substances are often derived from existing similar chemical properties. Otherwise, quantitative analysis SAR (QSAR) is based on mathematical algorithms and quantum using physical properties (molecular weight, solubility, melting point, and ionization energy) and chemical properties (such as steric effects, the presence or absence of fragments or functional groups, last orbital energy level: HOMO, and the first orbital energy level: LUMO, and electrophilicity) [8]. The physical chemical properties are obtain by semi-empirical methods, used HyperChem Professional software 7, accessed in 20.08.2015. (Table 2) [9]:

Table 2.The values of the descriptors use in the software ToxPredict

Entry	**LC50 predicted (mmol)**	**A= -Log (1/LC 50)**	**DSS Tox Single CellCall**	**DSS Tox Multi CellCall**	**DSS Tox Rat**	**DSS Tox Mouse**	**DSSTox MGe**	Log P	tPSA	MW	V	HOMO	LUMO
1	0.436	0.36	0.028	0.087	0.068	0.143	0.063	3.37	18.4	210.3	201.1	-9.0929	-1.2433
2.	0.302	0.519	0.046	0.019	0.011	0.0026	0.115	2.90	64.3	261.2	212.5	-9.4326	-1.6643
3.	0.349	0.457	0.067	0.056	0.011	0.052	0.145	2.95	64.3	261.2	212.5	-9.5624	-1.7809
4.	0.179	0.747	0.033	0.020	0.0037	0.0275	0.096	6.81	18.5	412.1	272.2	-9.0344	-1.6017
5.	0.179	0.747	0.033	0.020	0.00368	0.028	0.095	6.07	18.5	333.2	254.3	-9.0545	-1.5044
6.	0.175	0.756	0.015	0.016	0.00368	0.027	0.095	6.07	18.5	333.2	254.3	-9.0023	-1.5207
7.	0.179	0.747	0.055	0.015	0.00367	0.0275	0.124	6.07	18.5	333.2	254.3	-9.2518	-1.5353
8.	0.179	0.747	0.045	0.035	0.00564	0.0275	0.066	6.45	18.5	347.2	271.1	-9.028	-1.4915
9.	0.179	0.747	0.033	0.021	0.00368	0.0275	0.124	6.05	18.5	333.2	254.3	-8.2786	-1.6327
10	0.178	0.749	0.034	0.020	0.00368	0.0275	0.124	6.07	18.5	333.2	254.3	-9.0520	-1.5385
11	0.184	0.735	0.034	0.020	0.00368	0.0277	0.095	5.42	18.5	298.8	240.7	-9.1063	-1.4566
12	0.191	0.719	0.019	0.032	0.419	0.028	0.152	4.75	64.3	309.3	250.5	-9.6330	-1.8934
13	3.6136	0.55	0.017	0.050	0.373	0.027	0.134	5.12	64.3	323.3	267.3	-9.5314	-1.8294

Entry	GPCR ligand	Ion channel	GSK-3	PPARα	Enzyme Inhibitor	Entry	GPCR ligand	Ion channel	GSK-3	PPARα	Enzyme Inhibitor
1	-0.54	-0.37	-1.33	-1.16	0.06	8	-0.13	-0.18	-0.10	-0.03	0.11
2	-0.39	-0.11	-0.87	-0.92	-0.05	9	-0.10	-0.11	-0.11	-0.20	0.12
3	-0.35	-0.02	-0.80	-0.97	0.05	10	-0.12	-0.14	-0.16	-0.24	0.13
4	-0.32	-0.35	-0.31	-0.50	0.1	11	-0.19	-0.16	-0.21	-0.29	0.13
5	-0.12	-0.17	-0.16	-0.20	0.15	12	-0.20	-0.22	-0.17	-0.17	0.04
6	-0.03	-0.19	-0.07	-0.07	0.14	13	-0.21	-0.23	-0.12	-0.02	-0.0
7	-0.02	-0.17	-0.05	-0.08	0.15						

Results and discussion

PNN results. This procedure uses a probabilistic neural network (PNN) [10] to classify cases according to different ligand, and showed Kasius-Bursi Salmonella Mutagenicity based on 5 input variables (biological parameters), like in the Table 3:

Table 3.The values of the descriptors use in the software PNN

Of the 13 cases in the training set, 92.3077 % were correctly classified by the network.

MLR (multiple linear regression) results.

Dose response modeling of toxicity pathways involves the integration of mechanism and dosimetric information about the toxicity of a chemical into descriptive mathematical formulas to provide a quantitative model that allows dose extrapolation by MLR.

This response is shown in the Figure 2.

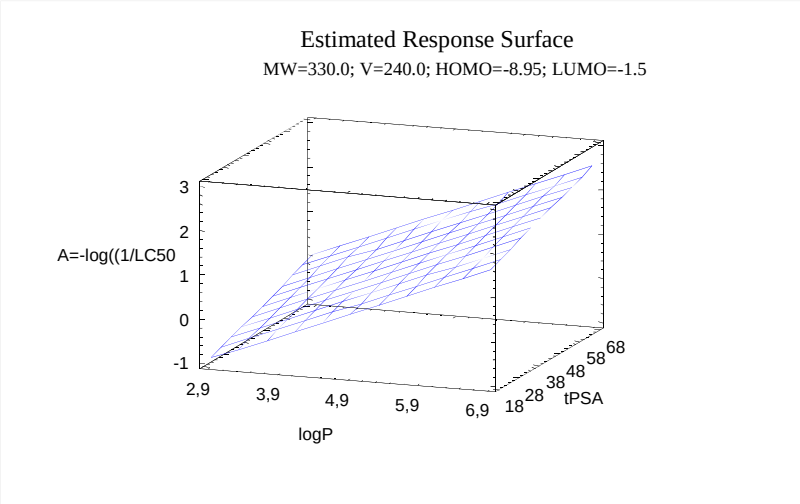


Figure 2. The chart of the estimated response surface of the physico-chemical parameters

We conducted several experiments correlation on quantitative models SAR (QSAR), as predicted data program ToxPredict namely: correlation values quantified according to equation (1) acute toxicity (LC50), the carcinogenicity potential (DSSTox) in mice and rats predicted by a single cell and multi-cell, and mutagenicity potential (DSSToxMGe) to Salmonella, with descriptors of molecular 2D/ 3D obtained through optimization HyperChem: log P (log partition coefficient 1-octanol-water) tPSA (topological area surface), MW (molecular mass) V (molar volume), HOMO and LUMO. The equations (2-4) of the fitted models in MLR, by StatGraphicsCenturion software [10], are:

$$A = -\log(1/LC50) = 3.4575 + 0.6246 \cdot logP + 0.01939 \cdot tPSA - 0.00063 \cdot MW - 0.020681 \cdot V + 0.06465 \cdot HOMO + 0.5159 \cdot LUMO \quad (2)$$

$R^2 = 0.927121$; R^2 (adjusted for d.f.) = 0.854; SEE =0.05254; MAE = 0.0278**,** Durbin-Watson statistic = 1.8151(p = 0.1468)

DSSTox = -1.17072 - 0.1673▪logP - 0.007▪tPSA - 0.00021▪MW + 0.00637▪V - 0.03751▪HOMO - 0.2901▪LUMO (3)

R^2=0.849; R^2 (adjusted for d.f.) = 0.698; SEE =0.01159; MAE= 0.006838; Durbin-Watson statistic = 1.56568 (p = 0.0607)

DSSToxMGe=-0.1538 + 0.0319▪logP- 0.0006▪ tPSA- 0.0003▪MW - 0.00159▪V - 0.01693▪HOMO - 0.2839▪LUMO (4)

R^2 = 0.9089; R^2(adjusted for d.f.) = 0.81; SEE= 0.0118091; MSE = 0.00657923; Durbin-Watson statistic = 2.62439 (p =0.7107)

Where: R^2-coefficient of the correlation; SEE-standard error of the estimate; MSE-mean error

The Durbin-Watson (DW) statistic tests the residuals to determine if there is any significant correlation based on the order in which they occur in your data file.

Conclusion

From ToxPredict software, we obtained the following results: twelve carcinogenic compounds (2÷13), three mutagenic compounds (2, 3, and 13) and eight toxic compounds (4÷12). SAR (QSAR) models were validated in MLR, by R^2 =0.9271, for acute toxicity, R^2 = 0.849, for carninogenicity potential, R^2=0.9089, for mutagenicity potential, meaning a connection between carcinogenicity potential, mutagenicity, acute toxicity and the physico-chemical properties.

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