ベンゾジアゼピン系薬物における急性毒性のモデリング

Acute Toxicity Modeling of Benzodiazepine Drugs

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Abstract

Benzodiazepines are well known drugs used as hypnotics, anxiolytics, tranquillizers and anticonvulsants. Multiple linear regression (MLR) has been previously applied to a series of 54 benzodiazepines to model their toxicity, expressed as the lethal oral dose for mouse, yielding robust models with predictive power. This paper presents a comparison of principal component regression analysis applied to the same series of drugs with the previous MLR ones. Structural descriptors were derived from the optimized structures obtained by molecular mechanics and the semiempirical RM1 approach. They were correlated to the logarithm of the lethal dose by MLR. Several models were selected based on the genetic algorithm. The variables included in the final MLR models, having best goodness of fit and prediction results, were further used in principal component regression (PCR) analysis. Similar statistical results with those of the best MLR model were obtained. More information on structural factors which influence the benzodiazepine toxicity was obtained by PCR in comparison to the MLR model.

Keywords: benzodiazepine, quantitative structure-toxicity relationships (QSTR), multiple linear regression (MLR), genetic algorithm, principal component regression (PCR)

1. Introduction

Quantitative structure-activity relationships (QSARs) are employed as scientifically-credible tools for predicting the acute toxicity of chemicals when few, or no, empirical data are available (Schultz et al, 2003). There are two basic aims of toxicologically-based QSAR analyses. The first aim is to determine, as accurately as possible, the limits of variation in molecular structure that are consistent with the production of a specific toxic effect. The second aim is to define the ways in which alterations in structure, and thereby the overall properties of a compound, influence potency.

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Many chemical agents having potential negative effects on human health and environment have been used (Benfenati and Gini, 1997). Besides, most agents undergo transformations during their life, generating new molecules, which means that new information must be obtained about the toxicity of the transformation products.

Several times published toxicity value as a definitive (high quality) datum point are considered in structure-toxicity studies (Cronin and Schultz, 2003). There are many such toxicological databases which are compilations of data for many species from different sources. One of the best-known and most widely utilised database for mammalian toxicity is the Registry of Toxic Effects of Chemical Substances (RTECS). This database, like others, are similar in that they comprise compilations of data from various sources, from a number of laboratories, often employing different protocols, being subject to considerable variation.

Toxicological endpoints can very often be the result of more than one physicochemical interaction of the compound with the model system of interest (Soffers et al, 2001). Therefore, the description of quantitative structure-toxicity relationships (QSTR) often does not follow a one-descriptor mechanistic approach. In this field researchers rather start from the other end, describing QSARs by multi-parameter approaches using multiple linear regression or multivariate techniques such as principal component analysis (PCA) or partial least square (PLS) analysis. Multivariate techniques such as PLS have the advantage that they allow the application of several descriptors. The starting point of the multivariate approach is the idea that a single descriptor will not contain enough information to capture the dominant features of a given biological phenomenon and that the characterization of chemicals should be multivariate.

Breggin (1998) indicated in his work that benzodiazepines have been recognized in the literature and clinical practice for their capacity to cause mental and behavioral abnormalities. Neurophysiologic studies show that the benzodiazepines potentate the neuronal inhibitory activity of GABA (γ-aminobutyric acid). Some high-potency benzodiazepines bind especially tightly to the receptor sites in the cerebral cortex. This may increase their tendency to produce more intense sedation and hypnosis and also more severe cognitive deficits, behavioral abnormality, rebound and withdrawal. Some advocates of the benzodiazepines have argued for a specific antianxiety effect separately from the general sedative effect, but there was not found any substantial evidence for this. Benzodiazepines can cause paradoxical excitement with irritability, hyperactive or aggressive behavior and exacerbation of seizures in epileptics. Increased aggression, hostility and impulsivity occur in some subjects and may result in attacks of rage and violent actions.

Few quantitative structure-activity relationships (QSARs) of benzodiazepines were concerned with molecular structure-receptor affinity (Borea, 1983; Hadjipavlou-Litina and Hansch, 1994; Loew et al, 1994; Maddalena and Johnston, 1995; Debnath et al,

2004).

This paper presents a structure – toxicity study applied to a series of 54 benzodiazepine derivatives, in order to model the benzodiazepine derivative toxicity by statistical methods. Multiple linear regression was applied to correlated structural descriptors derived from benzodiazepine molecular structure with their toxicity, expressed by the logarithm of LD_{50} values. Descriptors chosen by the genetic algorithm in these models were further used in principal regression analysis, to derive structural parameters which influence the benzodiazepine toxicity.

2. Materials and Methods

Definition of target property and molecular structures

In this study 54 benzodiazepines derivatives (Figure 1) with toxicity, expressed as the logarithm of the lethal oral dose for mouse LD_{50} in mg/Kg (Table 1) , were employed for the QSAR study. The data were retrieved from the RTECS database (RTECS Database, MDL Information Systems, Inc. 14600 Catalina Street San Leandro, California U.S.A. 94577, http://www.ntis.gov/products/types/databases/rtecs.asp).

The molecular structure of the benzodiazepine derivatives was built by the ChemOffice package (ChemOffice 6.0, CambridgeSoft.Com, Cambridge, MA, U.S.A) and energetically optimized using molecular mechanics method and quantum chemical calculations (RM1 hamiltonian (Rocha et al, 2006)). To the lowest energy conformations obtained by molecular mechanics calculations the MOPAC 2007 (Stewart, 2007) semiempirical molecular orbital program was applied to finally optimize the structures.

Twenty-two types of descriptors were calculated by the Dragon software (Dragon Professional 5.5/2007, Talete S.R.L., Milano, Italy), like: constitutional (nR09-number of 9-membered rings), functional groups counts (like: nCt – number of total tertiary C (sp^3), nCrt -number of ring tertiary C (sp^3), nN=C-N< – number of amidine derivatives, nRNR2 – number of tertiary amines (aliphatic), nC=N-N< – number of hydrazones, nROR – number of ethers (aliphatic), nThiophenes – number of Thiophenes), topological descriptors, Burden eigenvalues, eigenvalue-based indices, Galvez descriptors (topological charge indicies), Randic descriptors (Randic molecular profiles), RDF (radial distribution function) descriptors, MWC (Molecular walk counts path counts – atomic and molecular descriptors) and 3D-MoRSE (Mor21u – 3D-MoRSE – signal 21 / unweighted; Mor30e – 3D-MoRSE – signal 30 / weighted by atomic Sanderson electronegativities), atom-centred fragments, information indices, edge adjacency indices (ESpm07r – spectral moment 07 from edge adj. matrix weighted by resonance integrals), topological charge indices, connectivity indices, 2D-autocorrelations, molecular properties, 2D binary fingerprints, and 2D frequency fingerprints. The descriptors included in the final MLR and PCR models are presented in Table 1.

Multiple linear regression (MLR)

A multiple linear regression treatment between the experimental variable y_k (dependent variable) and a set of structural descriptors (independent variables) x_i is expressed by the following equation (Wold and Dunn, 1983):

$$y_k = b_0 + \sum_i b_i \cdot x_{ik} + e_k \quad (1)$$

where b represents regression coefficients and e the deviations and residuals. MLR calculations were performed by the STATISTICA (STATISTICA 7.1, Tulsa, StatSoft Inc, OK, USA) and MobyDigs (Todeschini et al, 2003) programs.

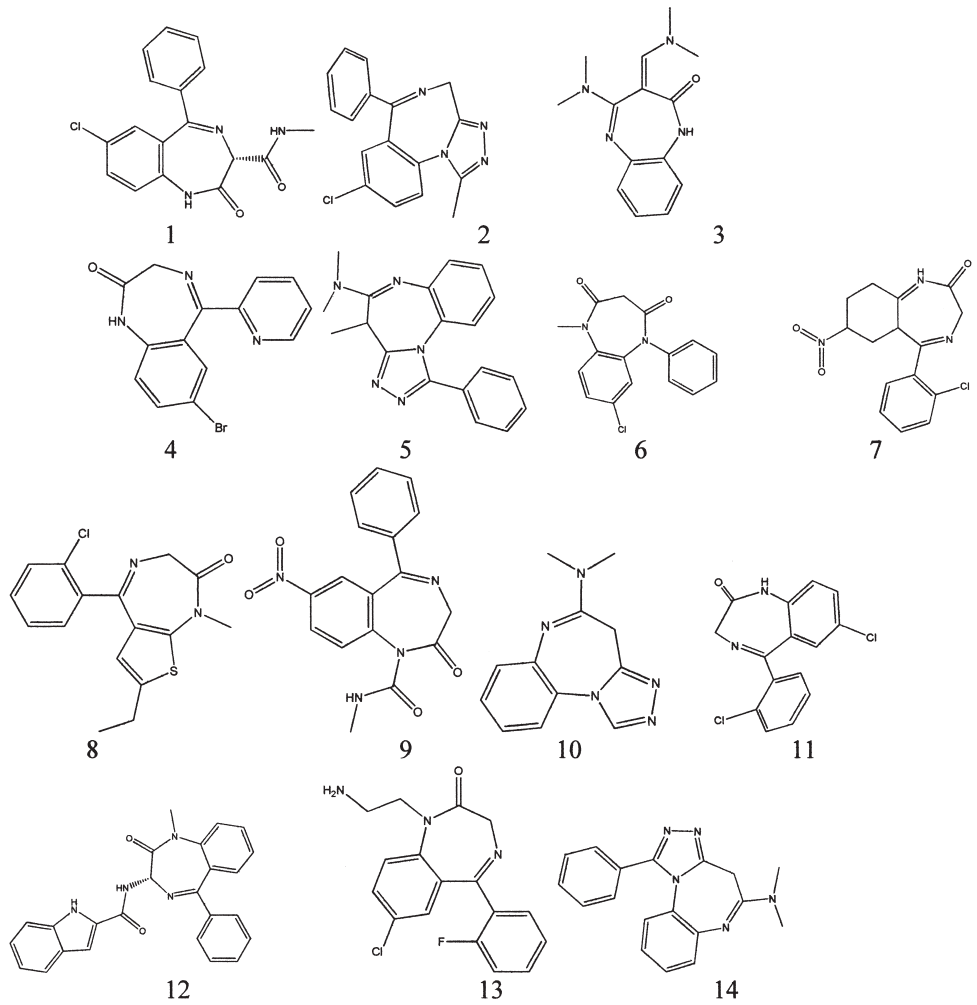

Fig 1. Benzodiazepine structure

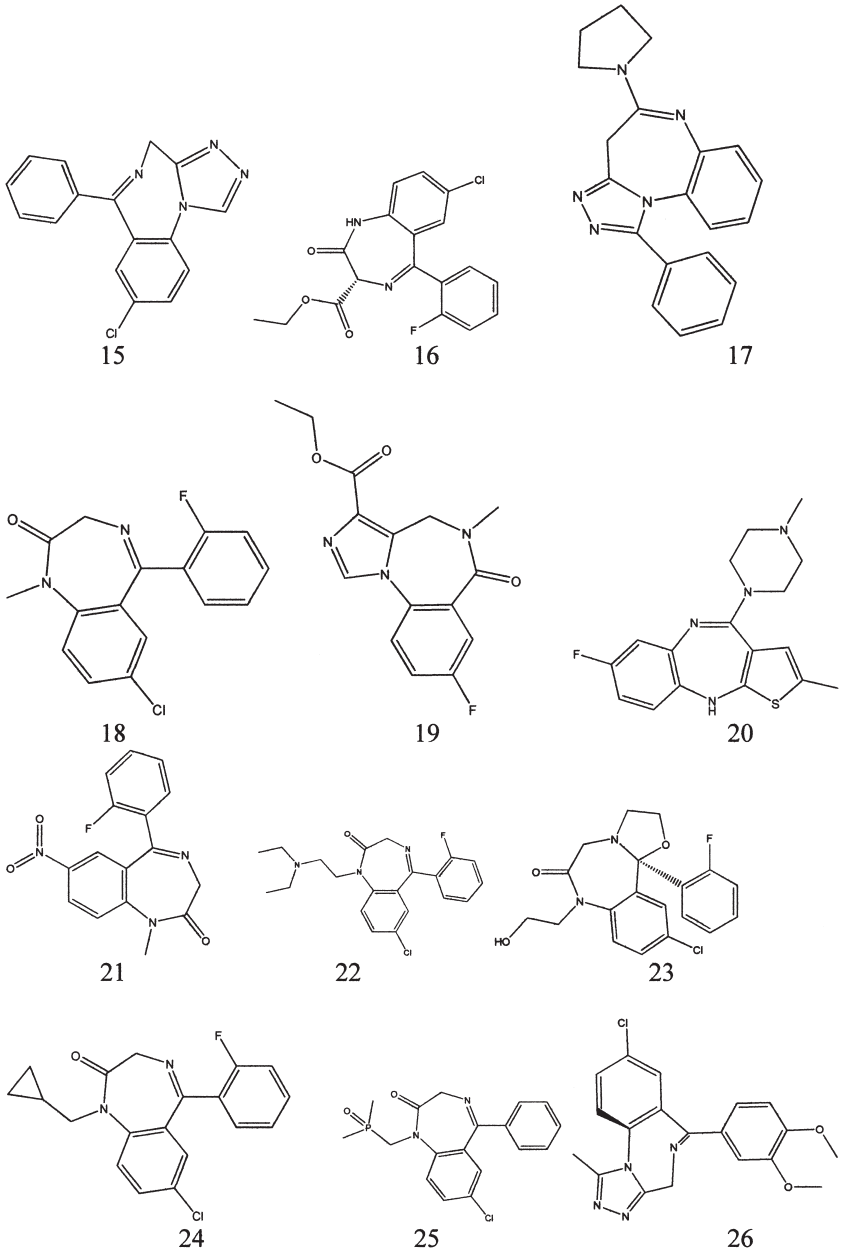

Fig 1. (continued)

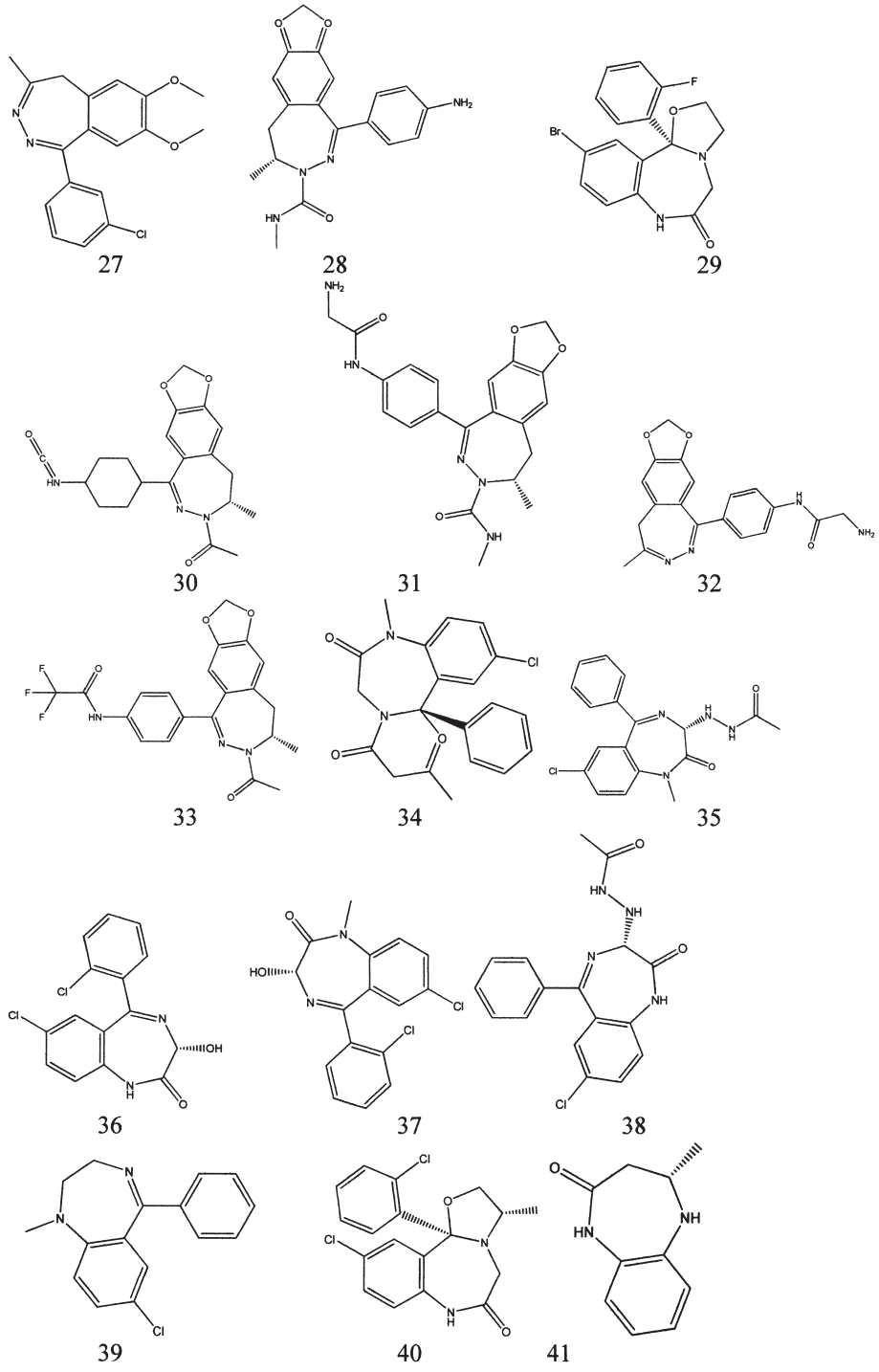

Fig 1. (continued)

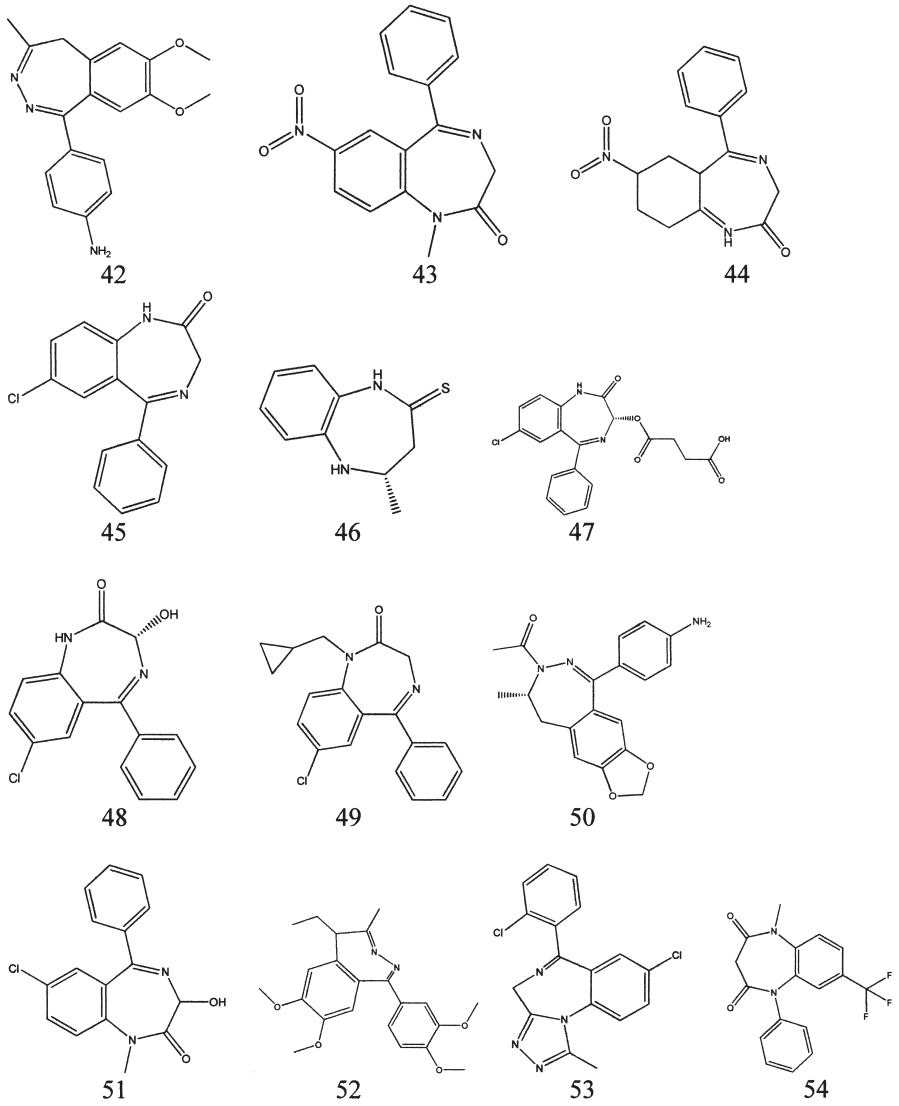

Fig 1. (continued)

Principal component regression (PCR)

The first step in carrying out PCR is the application of the principal component analysis (PCA) method. This last approach produces new variables created by a linear combination of the original variables or descriptors. The utility of PCA is the dimension reduction. Thus, this method is based upon a spectral decomposition of the correlation matrix (H) of the regressors X_i (i = 1,2,...,c) (the physicochemical parameters) (Mager and Rothe, 1990; Mager, 1994). On the basis of this orthogonal transformation, principal components of the original variables are estimated and used instead

Table 1. The logarithm of the lethal oral dose for mouse LD_{50} and descriptors included in the final MLR and PCR models*

No.	nR09	ESpm07r	Mor21u	Mor30e	nCt	nCrt	nN=C-N<	nRNR2	nC=N-N<	nROR	nThiophenes
1	0	10.762	−1.299	0.13	0	0	0	0	0	0	0
2	0	10.793	−1.374	0.324	0	0	0	0	0	0	0
3	0	10.504	−1.119	0.192	0	0	1	2	0	0	0
4	0	10.458	−0.578	0.215	0	0	0	0	0	0	0
5	0	10.921	−1.837	0.562	1	1	1	1	0	0	0
6	0	10.728	−1.143	0.399	0	0	0	0	0	0	0
7	0	10.721	−0.974	0.226	0	0	0	0	0	0	0
8	0	10.725	−0.962	0.121	0	0	0	0	0	0	1
9	0	10.893	−1.289	−0.061	0	0	0	0	0	0	0
10	0	10.444	−0.8	0.362	0	0	1	1	0	0	0
11	0	10.581	−0.555	0.233	0	0	0	0	0	0	0
12	1	11.145	−1.36	−0.003	0	0	0	0	0	0	0
13	0	10.765	−0.778	0.101	0	0	0	0	0	0	0
14	0	10.794	−1.266	0.317	0	0	1	1	0	0	0
15	0	10.689	−0.961	0.106	0	0	0	0	0	0	0
16	0	10.853	−0.708	0.398	0	0	0	0	0	0	0
17	0	10.866	−1.637	0.872	0	0	1	1	0	0	0
18	0	10.732	−1.087	0.106	0	0	0	0	0	0	0
19	0	10.857	−0.501	0.399	0	0	0	0	0	0	0
20	0	10.763	−1.849	0.265	0	0	1	2	0	0	1
21	0	10.853	−1.204	0.074	0	0	0	0	0	0	0
22	0	10.857	−1.605	0.366	0	0	0	1	0	0	0
23	0	11.316	−1.397	0.412	0	0	0	1	0	1	0
24	0	10.924	−0.663	0.154	1	1	0	0	0	0	0
25	0	11.029	−1.275	0.251	0	0	0	0	0	0	0
26	0	10.973	−1.174	0.588	0	0	0	0	0	0	0
27	0	10.718	−1.171	0.303	0	0	0	0	0	0	0
28	1	10.974	−1.229	−0.055	0	0	0	0	1	0	0
29	0	11.22	−0.837	0.095	0	0	0	1	0	1	0
30	1	10.986	−1.41	0.234	0	0	0	0	1	0	0

Table 1. (continued)

No.	nR09	ESpm07r	Mor21u	Mor30e	nCt	nCrt	nN=C-N<	nRNR2	nC=N-N<	nROR	nThiophenes
31	1	11.065	−1.252	0.08	0	0	0	0	1	0	0
32	1	10.875	−0.816	0.427	0	0	0	0	0	0	0
33	1	11.288	−1.498	0.168	0	0	0	0	1	0	0
34	0	11.347	−1.349	0.262	0	0	0	0	0	1	0
35	0	10.837	−1.354	0.135	0	0	0	0	0	0	0
36	0	10.687	−0.675	0.187	0	0	0	0	0	0	0
37	0	10.814	−0.966	0.389	0	0	0	0	0	0	0
38	0	10.713	−1.118	0.282	0	0	0	0	0	0	0
39	0	10.492	−1.34	0.271	0	0	0	0	0	0	0
40	0	11.279	−1.051	0.104	0	0	0	1	0	1	0
41	0	9.975	−0.874	0.186	0	0	0	0	0	0	0
42	0	10.734	−1.338	0.353	0	0	0	0	0	0	0
43	0	10.762	−1.352	0.188	0	0	0	0	0	0	0
44	0	10.629	−1.154	0.176	0	0	0	0	0	0	0
45	0	10.475	−0.949	0.27	0	0	0	0	0	0	0
46	0	9.926	−0.985	0.286	0	0	0	0	0	0	0
47	0	10.794	−1.016	0.289	0	0	0	0	0	0	0
48	0	10.593	−0.854	0.26	0	0	0	0	0	0	0
49	0	10.84	−1.022	0.331	1	1	0	0	0	0	0
50	1	10.96	−1.416	0.336	0	0	0	0	1	0	0
51	0	10.732	−1.237	0.305	0	0	0	0	0	0	0
52	0	11.003	−1.213	0.903	1	1	0	0	0	0	0
53	0	10.871	−1.232	0.304	0	0	0	0	0	0	0
54	0	11.075	−1.676	0.571	0	0	0	0	0	0	0

* nR09: number of 9-membered rings, ESpm07r: spectral moment 07 from edge adjacency matrix weighted by resonance integrals, Mor21u: 3D-MoRSE-signal 21/unweighted, Mor30e: 3D-MoRSE-signal 30/weighted by atomic Sanderson electronegativities

of the original variables. In PCR the multiple linear regression is applied to estimate the regression matrix of the regressands Y_i (i = 1,2,....,N) and component regressors Z_f (f = 1,2,...., s≤c) and finally, a re-transformation (rectification) yields the desired estimators (nonleast-squares regression). The general PCR equation is given by:

$$Y = h_O + Z \cdot H \tag{2}$$

where $h_O = \bar{y}$ is the intercept vector, which is equal to the vector $\bar{y}$ of mean values of the regressands Y_i, and Z is the matrix of the principal components. The PCR calculations were performed by the MobyDigs package (Todeschini et al, 2003)

Model validity

All the statistical tests were performed at a significance level of 5 % or less. In MLR calculations outliers were tested by estimating the standardized residuals of less than −2.5 or more than +2.5 (Frank and Althoen, 1995) and by the value of residual greater than three times the value of standard error in calculation (Todeschini and Consonni, 2000), as implemented in the MobyDigs program (Todeschini et al, 2003).

The goodness of prediction of the MLR models was checked by the Akaike Information Criterion (AIC) (Gentleman and Wilk, 1975), Y-scrambling (Lindgren et al, 1996) and bootstrapping (Efron, 1982). All these calculations were performed by the MobyDigs software. The leave-one out cross-validation (in MLR and PCR calculations) procedure (Efron , 1983; Stone, 1974; Wold, 1978) was, also, employed.

The overall performance of MLR and PCR models was evaluated in terms of the root-mean-square error (RMS):

$$RMS = \sqrt{\frac{\sum_{n=1}^{n} (y_i - y_i^{fit})^2}{n}} \tag{3}$$

where y_i is the experimental target value for the ith compound (logLD50) and y_i^{fit} represents the predicted target values calculated by the models.

3. Results and Discussion

In a previous MLR analysis (Funar-Timofei et al, 2010) a training set of 45 compounds (three outliers were found: 12, 41 and 46 and omitted from the final models) and a test set of the following 6 compounds: 5, 7, 21, 24, 36, 45 were considered (see Figure 1).

In this paper, several MLR models were found from the correlation with the toxicity, based on the variable selection by genetic algorithm (GA) included in the MobyDigs program (Todeschini et al, 2003), using the RQK fitness function (Todeschini et al, 2004), with squared multiple correlation coefficient as constrained function to be opti-

Table 2. MLR results*

Models	Descriptors	R^2	Q^2	Q^2_{boot}	a(R^2)	a(Q^2)	AIC	SDEP	F	s
1	nR09 ESpm07r Mor21u Mor30e	0.800	0.744	0.705	0.159	−0.061	0.05	0.214	40.04	0.2
2	nCt nRNR2 nC=N-N< nROR	0.667	0.600	0.557	0.121	−0.144	0.084	0.267	19.99	0.259
3	nR09 ESpm07r Mor30e	0.646	0.586	0.562	0.09	−0.102	0.083	0.272	24.98	0.263
4	nR09 Mor21u Mor30e	0.636	0.571	0.525	0.111	−0.077	0.085	0.277	23.92	0.267
5	nR09 ESpm07r	0.619	0.568	0.548	0.122	−0.058	0.083	0.278	34.16	0.27
6	nRNR2 nC=N-N< nROR nThiophenes	0.632	0.568	0.527	0.117	−0.147	0.093	0.278	17.17	0.272
7	nRNR2 nC=N-N< nROR	0.619	0.554	0.511	0.114	−0.081	0.089	0.282	22.18	0.274
8	nCt nC=N-N< nROR	0.595	0.548	0.507	0.054	−0.155	0.095	0.284	20.11	0.282
9	nCrt nC=N-N< nROR	0.595	0.548	0.512	0.049	−0.167	0.095	0.284	20.11	0.282
10	nCrt nN=C-N< nC=N-N< nThiophenes	0.609	0.530	0.500	0.086	−0.244	0.098	0.29	15.58	0.28

* R^2 – squared multiple regression coefficient, Q^2 – leave-one-out cross-validated R^2, Q^2_{boot} – bootstrapping Q^2, Y-scrambling parameters (Lindgren et al., 1996) (a(R^2), a(Q^2)), AIC- the Akaike Information Criterion; SDEP- standard deviation error in prediction, F- Fischer test, s- standard deviation

mised, a crossover/mutation trade-off parameter T = 0.5 and a model population size P = 50. The final MLR models are presented in Table 2. Model 1, with best statistical results, gave a RMS error of 0.213 log LD_{50} units for the training set and of 0.194 for the test set.

Table 3. PCR results of the model with four principal components (PCs)

Components	PC1	PC2	PC3	PC4
Eigenvalues	2.51	2.32	1.95	1.59
Explained Variance (%)	22.8	21.1	17.7	14.5
nR09	−0.5	0.055	0.182	−0.335
ESpm07r	−0.299	0.125	0.46	0.386
Mor21u	0.065	0.108	−0.473	0.167
Mor30e	0.296	0.238	0.233	−0.088
nCt	0.232	0.543	0.205	−0.097
nCrt	0.232	0.543	0.205	−0.097
nN=C-N<	0.324	−0.341	0.278	−0.287
nRNR2	0.271	−0.376	0.404	0.016
nC=N-N<	−0.507	0.041	0.212	−0.336
nROR	−0.068	−0.068	0.292	0.673
nThiophenes	0.147	−0.241	0.153	−0.19

Table 4. Regression coefficients obtained by PCR calculations for the first principal component

Intercept	−3.449
nR09*	−0.412
ESpm07r*	0.107
Mor21u*	0.255
Mor30e*	0.17
nCt*	0.236
nCrt*	0.236
nN=C-N<*	−0.175
nRNR2*	−0.022
nC=N-N<*	−0.458
nROR*	0.366
nThiophenes*	−0.221

*Dragon [23] descriptors

The PCR calculations were performed on variables chosen by the final MLR models presented in Table 2, by using the Q^2 leave-one-out as fitness parameter. The most correlated PCs to the *Y* response variable were selected by GA.

Four principal components were found to be significant (R^2 = 0.742, Q^2 = 0.688, SDEP = 0.236). These results are slightly poorer in comparison to the MLR model 1

ones. The PCR results are presented in Table 3 and the regression coefficients in Table 4. The RMS values were of 0.215 for the training set, 0.194 for the test set, close to the RMS values of the MLR model.

Benzodiazepine having increased number of 9-membered rings, number of amidine derivatives, number of aliphatic tertiary amines, number of hydrazone and of number of thiophene moieties are expected to have high toxicity. Higher number of total tertiary C (sp^3), number of ring tertiary C (sp^3) and of number of aliphatic ethers yield low toxicity.

4. Conclusion

Quantitative structure – toxicity relationship (QSTR) models were developed for a series of 54 benzodiazepines by MLR and PCR approaches. It was found that benzodiazepine structures including 9-membered rings, and increased number of amidine derivatives, aliphatic tertiary amines, hydrazone and of thiophene moieties would be expected to be toxic. Inclusion in the benzodiazepine molecules of total tertiary C (sp^3) groups, of ring tertiary C (sp^3) and of aliphatic ethers leads less toxic compounds.

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要　旨

ベンゾジアゼピン系薬物における急性毒性のモデリング

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ベンゾジアゼピン系薬物は、3つの環構造のベンゾジアゼビン骨格を有する化合物である。鎮静・催眠作用、抗不安作用、中枢性筋弛緩作用などの広い薬理学的作用を示す。本研究では、54種類のベンゾジアゼビン系薬物の化学構造とマウスに対する経口急性毒性試験結果との定量的な関係を見出すため、主成分回帰分析（PCR）を適用した急性毒性のモデル化を試みた。先ず、分子力学法と半経験的RM1法によって最適化した分子構造から、種々の構造記述子を計算し、急性毒性試験結果との相関を検討した。遺伝的アルゴリズムを適用して最適なPCRモデルを得たところ、重回帰モデル（MLR）の結果と比較し、ベンゾジアゼビン系薬物の毒性に影響を与える構造因子についてより詳細な知見を得ることができた。