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Short communication

Biopartitioning micellar chromatography to predict mutagenicity of aromatic amines

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Abstract

Mutagenicity is a toxicity endpoint associated with the chronic exposure to chemicals. Aromatic amines have considerable industrial and environmental importance due to their widespread use in industry and their mutagenic capacity.

Biopartitioning micellar chromatography (BMC), a mode of micellar liquid chromatography that uses micellar mobile phases of Brij35 in adequate experimental conditions, has demonstrated to be useful in mimicking the drug partitioning process into biological systems. In this paper, the usefulness of BMC for predicting mutagenicity of aromatic amines is demonstrated. A multiple linear regression (MLR) model based on BMC retention data is proposed and compared with other ones reported in bibliography. The proposed model present better or similar descriptive and predictive capability.

Keywords: Mutagenicity; Biopartitioning micellar chromatography; Aromatic amines; Quantitative retention–activity relationships

1. Introduction

The advent of combinatorial chemistry has made possible to synthesize hundreds of new chemicals every year. The development of efficient and inexpensive technologies for testing and predicting the physical, chemical and biological properties of new compounds, which would enable the estimation of the potential dangers of old and new organic compounds, and allow effective risk assessment, is thus of major significance.

Carcinogenicity and mutagenicity are important toxicity parameters associated with the chronic exposure to chemicals. They are closely related, and ca. 70% of carcinogenic compounds are potential mutagens [1–3]. These toxicity parameters are of interest both for environmental pollutants and potential therapeutic agents. While the experimental assessment of carcinogenicity is complex and time consuming [4], several tests allow easy detection of mutagenicity [5]. Probably the most widely used is a bacterial test, based on the *Salmonella typhimurium* strain, introduced by Ames et al. [1,5,6].

Mutagenicity is used for screening of substances, potentially hazardous to human and environmental health. The importance of this endpoint and availability of high quality databases support the postulations of predictive structure–mutagenicity relationships. These studies are potentially suitable for investigating mechanisms of action and for estimating the toxicity of compounds lacking experimental determinations.

Quantitative structure–property relationships (QSPR) and quantitative structure–activity relationships (QSAR) have been used over the years to develop models to estimate/predict toxicity by relating it to chemical structure. Many different statistical models have been derived for the estimation and prediction of mutagenicity [7–9].

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Nomenclature

BMC	Biopartitioning micellar chromatography
E_{HOMO}	Energy of the highest occupied molecular orbital
E_{LUMO}	Energy of the lowest unoccupied molecular orbital
ln k	BMC chromatographic retention
ln R	Mutagenic potency
LV	Latent variable
MLR	Multiple linear regression
log P	Logarithm of the partition coefficient in the n-octanol/water system
MR	Molar refractivity
MP	Melting point
MW	Molecular weight
N_v	Number of descriptor variables
N	Number of compounds
PLS	Partial least squares analysis
pK_a	Acidity constant of conjugated acid
PSA	Polar surface area
QRAR	Quantitative retention–activity relationships
QSPR	Quantitative structure–property relationships
QSAR	Quantitative structure–activity relationships
WS	Water solubility

Aromatic and heteroaromatic amines are widespread chemicals with considerable industrial and environmental importance. Moreover, several types of aromatic and heteroaromatic amines are generated during cooking [10]. Owing to their hazard potential, aromatic amines have been the subject of many in vivo and in vitro experimental studies, both in terms of toxicological testing and of elucidation of their mechanisms of action.

Several QSAR studies are reported in the literature for this set of compounds. A well-studied set of chemical mutagens is the group of 95 aromatic amines collated by Debnath et al. [11]. They developed models on a subset of these compounds using an indicator variable, the logarithm of the partition coefficient in the n-octanol/water system (log P), energies of the highest occupied and lowest unoccupied molecular orbitals (E_{HOMO} and E_{LUMO}, respectively). Basak et al. in a series of studies employed topological, geometrical and quantum chemical descriptors [12,13]. Cash used electrotopological indices in comparison to calculate quantum chemical descriptors [14]. All these studies use linear techniques like multiple linear regression (MLR), principal component regression (PCR), partial least squares (PLS) and ridge regression. In an attempt to detect possible non-linear relationships between the structure and mutagenicity of these compounds some authors use artificial neural networks. Karelson et al. achieved substantial improvement of six-parameter linear model taking into account non-linear effects by using back propagation networks [15]. Vrako et al. used counter propagation neural network and different combinations of topological, geometrical and quantum descriptors [16]. Valkova et al. [17] studied how to select the minimal training set, which covers the information space efficiently using a sphere exclusion algorithm for rational division of the dataset into training and test sets.

Chromatography is a powerful technique for the measurement of physicochemical parameters. Chromatographic retention (expressed as k or its logarithmic form) obtained under the adequate experimental conditions has proven to be a good surrogate to log P measurements due to the higher accuracy and easier experimental performance. Biopartitioning micellar chromatography (BMC) is a liquid chromatographic system that uses polyoxyethylene (23) lauryl ether (Brij35) solutions as micellar mobile phases and C18 reversed stationary phases. BMC retention, obtained under the adequate experimental conditions (pH, temperature, ionic strength, etc), has been used to describe several biological activities [18,19] and ecotoxic parameters as lethal concentrations, bioconcentration factors and soil sorption coefficients of organic compounds [20–22]. The use of retention as predictor variable has generated the so called quantitative retention–activity relationships (QRAR). The usefulness of BMC in constructing good models could be attributed to the fact that the characteristics of the BMC systems are similar to biological barriers and extracellular fluids.

The aim of the present study was to investigate the use of the BMC chromatographic retention (ln k) as an in vitro/in silico approach for the mutagenic evaluation of aromatic and heteroaromatic amines, establishing a comparison with other in silico strategies.

2. Experimental

2.1. Instrumental and measurements

A Hewlett-Packard HP-1100 chromatograph with an isocratic pump and an UV–visible detector, a column thermostat and an autosampler with a 20 μL loop was used (Palo Alto, CA, USA). Data acquisition and processing were performed on an HP Vectra XM computer (Amsterdam, The Netherlands) equipped with HP-ChemStation software (A.07.01[682]© HP1999). A Kromasil octadecyl-silane C_{18} column (5 μm, 50 × 4.6 mm i.d.) (Scharlab, Barcelona, Spain) was used. The mobile phase flow rate was 1 mL/min. The detection was performed in UV region at the wavelength of 220 nm. All chromatographic runs were carried out at 36.5 °C.

Mobile phase solutions were degassed in an ultrasonic bath (JP Selecta, Barcelona, Spain). A Crison Micro pH 2000 pH meter from Crison Instruments (Barcelona, Spain) was employed to adjust the pH of solutions.

2.2. Reagents and standards

The chromatographic data of compounds listed in Table 1 were obtained using aqueous solutions of polyoxyethylene (23) lauryl ether (Brij35, Acros, Geel, Belgium) 0.04 and 0.02 M at pH 7.4 adjusted with 0.05 M phosphate buffer, prepared with sodium dihydrogenphosphate (analytical reagent, Panreac, Barcelona, Spain). In order to reproduce the osmotic

Table 1
Mutagenicity data (ln *R*) [16], logarithm of the retention factor in BMC in two mobile phases [0.02 M and 0.04 M Brij35 (ln *k*2 and ln *k*4)], and physicochemical and structural descriptor values of compounds tested for ln *R* modelling

Compound	ln *R*	ln *k*2 ± ts/$\sqrt{n}$	ln *k*4 ± ts/$\sqrt{n}$	log *P*	MP (°C)	MW (g/mol)	WS (g/l)	pK_a	PSA (cm^2)	Polarizability $\times 10^{24}$ (cm^3)	MR (cm^3)
4-Fluoroaniline	−3.32	2.55 ± 0.02	2.589 ± 0.002	1.15	−0.800	111.12	1.12×10^4	3.81	26.02	11.13	30.97
2-Chloroaniline	−3.00	3.368 ± 0.006	3.314 ± 0.004	1.9	−14.0	127.57	8.16×10^3	2.79	26.02	13.33	35.56
2-Amino-4-chlorophenol	−3.00	3.15 ± 0.04	3.013 ± 0.006	1.81	140	143.57	2.30×10^3	3.48	46.25	13.96	37.54
4-Bromoaniline	−2.70	3.40 ± 0.02	3.282 ± 0.006	2.26	66.4	172.02	707	3.83	26.02	14.26	38.38
4-Chloroaniline	−2.52	3.27 ± 0.04	3.185 ± 0.006	1.9	72.5	127.57	3.90×10^3	3.49	26.02	13.32	35.56
2,5-Xylidine	−2.40	3.230 ± 0.011	3.223 ± 0.002	1.83	15.5	121.18	5.60×10^3	4.55	26.02	15.03	40.84
p-Phenetidine	−2.30	2.481 ± 0.009	2.531 ± 0.002	1.24	2.4	137.18	7.51×10^3	5.13	35.25	15.83	41.97
2-Methoxy-5-methylaniline	−2.05	3.03 ± 0.02	3.050 ± 0.002	1.74	53	137.18	2.81×10^3	4.63	35.25	15.75	42.26
4,4′-Methylenedianiline	−1.60	2.98 ± 0.04	2.820 ± 0.004	1.59	92.5	198.27	1.00×10^3	4.83	52.04	24.01	65.2
8-Aminoquinoline	−1.14	3.048 ± 0.014	2.989 ± 0.002	1.79	70	144.18	8.22×10^3	4.20	38.91	18.17	44.68
2-Amino-α-α-α-trifluorotoluene	−0.80	3.77 ± 0.02	3.669 ± 0.010	2.41	35.5	161.13	592	2.15	26.02	12.66	36.73
2-Bromo-4,6-dinitroaniline	−0.54	3.593 ± 0.011	3.470 ± 0.012	2.73	153.5	261.90		12.5	117.66	18.53	53.03
3,3′-Dimethylbenzidine	0.01	3.10 ± 0.02	2.912 ± 0.008	2.34	131.5	212.29	1.30×10^3	4.48	52.04	27.2	70.68
3,3′-Dimethoxybenzidine	0.15	3.04 ± 0.05	2.864 ± 0.010	1.81	137	244.29	60.0	4.55	70.5	26.61	73.52
4-Phenoxyaniline	0.38	3.76 ± 0.06	3.605 ± 0.003	2.96	83	185.22	154	4.36	35.25	21.82	57
1-Aminoanthracene	1.18	3.87 ± 0.05	3.666 ± 0.010	3.69	116	193.25	2.59	4.07	26.02	26.81	63.66
1-Aminopyrene	1.43	3.81 ± 0.04	3.633 ± 0.009	4.99	116	217.27	0.576	3.97	26.02	31.04	71.42
2-Aminofluorene	1.93	3.69 ± 0.05	3.604 ± 0.009	3.14	129	181.24	8.78	4.29	26.02	23.6	59.57
2-Aminoanthracene	2.62	3.76 ± 0.02	3.584 ± 0.004	2.62	239	193.25	1.30	4.25	26.02	26.08	63.66
3-Aminofluoranthene	3.31	3.81 ± 0.007	3.630 ± 0.008	4.2	116	217.27	0.715	3.82	26.02	31.04	71.42

ts/$\sqrt{n}$, the confidence interval at 95% level; log *P*, logarithm of the partition coefficient in the *n*-octanol/water system of the neutral form of compounds studied; MP, melting point; MR, molar refractivity; pK_a, acidity constant of conjugated acid; MW, molecular weight; PSA, polar surface area; WS, water solubility.

pressure of biological fluids, NaCl (purisim, Panreac) was added to the micellar mobile phase (0.92%).

4-Fluoroaniline, 2-chloroaniline, 2-amino-4-chlorophenol, 4-bromoaniline, 4-chloroaniline, 2,5-xylidine, *p*-phenetidine, 2-methoxy-5-methylaniline, 4,4′-methylenedianiline, 8-aminoquinoline, 2-amino-α,α,α-trifluorotoluene, 2-bromo-4,6-dinitroaniline, 3,3′-dimethylbenzidine, 3,3′-dimethoxybenzidine, 4-phenoxyaniline, 1-aminopyrene, 2-aminofluorene, 2-aminoanthracene, and 3-aminofluoranthene were obtained from Acros (Gell, Belgium); 1-aminoanthracene and acetanilide from Fluka (Buchs, Switzerland), and propiophenone from Aldrich Chemicals (Milwaukee, WI, USA).

Barnstead E-pure, deionized water (Sybron, Boston, MA) was used throughout the assay. The mobile phases and the sample solutions were vacuum-filtered through 0.45 μm nylon membranes (Micron Separations, Westboro, MA, USA).

Stock standard solutions of 1 mg/mL were prepared by dissolving 10 mg of compound in 10 mL of methanol (Multisolvent, Scharlau Chemie S. A., Barcelona, Spain). Working solutions of 40 μg/mL were prepared by dilution of the stock standard solutions with mobile phase. The solutions were stored in the refrigerator at 4 °C.

2.3. Data sources, software, and data processing

Table 1 shows the set of 20 aromatic and heteroaromatic amines used in this study. The Mutagenic potency data were collected from the literature [11]. Mutagenic potency is expressed as natural logarithm of *R* (ln *R*), where *R* represents the number of revertants per nanomole in the strain *S. typhimurium* TA98+S9. Structural parameters [molar refractivity (MR), polarizability, polar surface area (PSA) and acidity constants (pK_a) of conjugated acid] were calculated using the ChemAxon Marvin software V. 4.0.6. This programme is integrated in the ChemID*plus* Advanced database available in the web site of the National Library of Medicine of United States [23]. The physical properties, melting point (MP) and water solubility (WS) and the values of molecular weight (MW) and log *P* are from ChemID*plus* Advanced database.

Microsoft® Excel 2000 software (Microsoft Corporation) and STATGRAPHICS (Statistical Graphics Cor. V. 2.1) were used to perform the statistical analysis of the regressions. The Unscrambler Version 7.6 by CAMO was used to perform multivariate analysis.

2.4. BMC data

The chromatographic data of the compounds listed in Table 1, ln *k*2 and ln *k*4 expressed as the natural logarithm of the retention factors, were obtained in our laboratory using micellar solutions of 0.02 and 0.04 M Brij35 at pH 7.4 as mobile phases and a C_{18} Kromasil column as stationary phase. All retention factor values were averages of at least triplicate determinations. The retention factor of compounds was estimated according to an approach described elsewhere [24].

$$k^{r2} = \frac{k_2(t_R^g - t_{R1}^g) + k_1(t_{R2}^g - t_R^g)}{t_{R2}^g - t_{R1}^g} \quad (1)$$

where k^{r2} is an estimate of *k* for the test compound, which besides its t_R^g, uses the gross retention times of the references R1 (acetanilide) and R2 (propiophenone) (t_{R1}^g and t_{R2}^g) injected

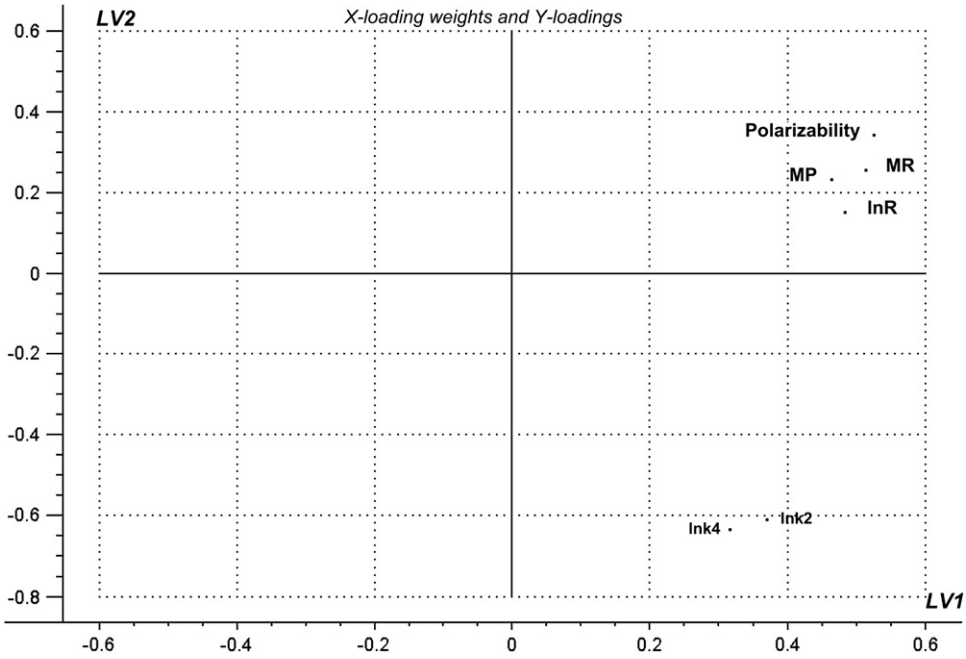

Fig. 1. PLS results: loading plot corresponding to the first two latent variables (LV1 and LV2).

during the working session. k_1 and k_2 are the retention factors of references, previously established for the experimental conditions assayed (surfactant concentration and temperature) and were considered constant. The use of this approach provides retention factor estimations more stable along time than the classical estimations based on the measurement of the dead time (actually the gross hold-up time).

3. Results and discussion

3.1. Mutagenic potency–retention relationships

Compounds included in this study (Table 1) were chosen in order to cover a broad range of mutagenic potency values ($\ln R$ ranged between −3.32 and 3.31). They are structurally unrelated amines with different hydrophobic properties ($\log P$ range between 1.15 and 4.2) and similar degrees of ionization at pH 7.4. At working pH all of the molecules are in their neutral form except 2-bromo-4,6-dinitroaniline which exist in the cationic form (p*K*a value of 12.5).

In order to study the importance of variables, shown in Table 1, in the construction of a regression model for predicting mutagenic potency ($\ln R$), a partial least squares analysis (PLS) was performed. The $\ln R$ values were used to construct the *y*-block and the variables: the $\ln k_{BMC}$ values obtained using Brij35 0.02 M ($\ln k2$) and Brij35 0.04 M ($\ln k4$) mobile phases, molecular weight (MW), molar refractivity (MR), polarizability, polar surface area (PSA) and the physical properties like

Table 2
Statistical characteristics of some of literature QSAR models

Model [year, Ref.]	Descriptor variables	Number of descriptor variables N_v	N	N/N_v	r^2	S.E.
Debnath et al. [1992, 11]	$\log P$, E_{LUMO}, E_{HOMO}, I_1	4	88	22	0.806	0.860
Basak et al. [1997, 25]	Topological and geometric	9	95	10	0.797	0.91
Basak et al. [1998, 12]	Topological, geometric and quantum chemical	9	95	10	0.790	0.92
Maran et al. [1999, 26]	Molecular descriptors	6	95	16	0.834	0.81
Basak et al. [2001, 13]	Topological, geometric and quantum chemical	9	95	10	0.794	0.912
		8	89	11	0.852	0.742
Cash [2001, 14]	Electrotopological	9	95	10	0.767	0.979
Vracko et al. [2004, 16]	Topostructural and topochemical	21	95	4	0.751	0.97
Valkova et al. [2004, 17]	Topostructural, topochemical, geometrical and quantum chemical descriptors	262	30	0.1	0.986	0.032
Bhat et al. [2005, 27]	Molecular descriptors ($\log P$, E_{LUMO}, E_{HOMO},…)	10	181	18	0.91	–
This work	Retention in BMC and polarizability	2	20	10	0.86	0.798

N_v is the number of descriptor variables and N, the number of compounds.

water solubility (WS) and melting point (MP), were used to construct the *X*-block. Descriptor variables (*X*-block) and response variable (*y*-block) were autoscaled before the PLS.

Two latent variables account for the 84% of the total variance of the original ln *R* data. The PLS-model regression coefficients together with their uncertainty limits for the two latent variables model were obtained. Non-significant variables were eliminated step by step, re-analyzing each time the PLS model. Fig. 1 shows the loading plot corresponding to the first two latent variables after the variable elimination. As can be seen, there are two groups of variables: polarizability, melting point, MR, which include steric and electronic information and retention data in BMC, ln *k*2 and ln *k*4, that informs about the hydrophobic character of compounds together with electronic and steric information. Finally a PLS model was obtained by selecting one variable of each group: ln *k*2 and polarizability. This model accounts for 80 and 78% of variance in calibration and cross-validation, respectively.

A multiple linear regression (MLR) analysis using non-scaled data was also performed using the selected variables by the PLS approach. The equation of the fitted MLR model, coefficient standard errors and statistical features were:

$$\ln \mathrm{R} = (-11.0 \pm 1.5) + (1.8 \pm 0.5)\ln k2 + (0.22 \pm 0.03)\ \text{polarizability}$$
$$N = 20;\ r^2 = 0.86;\ \text{S.E.} = 0.80;\ F = 52;\ P < 0.0001 \qquad (2)$$

The model explains 86% of variance in the data; this variability can be considered adequate taking into account the inherent difficulty in the mutagenecity estimation. In addition the uncertainty of experimental ln *R* values is unknown.

All the regression coefficients and the model were statistically significant at the 99% of confidence level ($P < 0.01$). The residual plot of the model showed a random distribution of the residuals with an average value practically equal to zero, which from a qualitative point of view suggests the adequacy of the model.

The analysis of the coefficients of the proposed model implies that most of the mutagenic aromatic amines are hydrophobic with high polarizability. The model derived is consistent with other reported models that indicate that mutagenic potency depends directly on the hydrophobic character of compounds which is directly related with retention in BMC.

3.2. Comparison with other QSAR approaches

As it has been indicated in Section 1 different mathematical approaches have been developed to estimate the mutagenic potency of aromatic and heteroaromatic amines. Table 2 summarizes the characteristics of some of the models reported in literature for estimation of compounds' mutagenicity together with the characteristics of the model proposed in the present paper. As can be observed, in computational approaches the number of descriptor variables, N_v, and compounds, N used to perform the models are more than in the BMC approach. However, the ratio N/N_v is an indication of the model consistency mainly when multiple linear regression of the proposed model is similar to or higher than other QSAR models proposed. The use of as few descriptors as possible has been recommended [28].

The *r*-squared statistic and standard error of estimated values are similar to those reported in literature (see Table 2).

Table 3
Experimental and predicted ln *R* [17] values using different proposed models

Compound number	Name	Experimental ln *R*	Predicted ln *R* values					
			Maran et al. [26]	Basak et al. [13]	Cash [14]	Vracko et al. [16]	Bhat et al. [27]	This work Eq. (2)
1	4-Fluoroaniline	−3.32	−2.15*	−3.28	−2.20*	−2.54	−2.10*	−3.97
2	2-Chloroaniline	−3.00	−2.44	−2.47	−2.12	−2.55	−2.10	−2.01
3	2-Amino-4-chlorophenol	−3.00	−2.69	−2.34	−2.41	−1.52*	−1.88*	−2.26
4	4-Bromoaniline	−2.70	−2.25	−1.98	−2.07	−2.56	−1.90	−1.75
5	4-Chloroaniline	−2.52	−2.22	−2.70	−1.95	−3.00	−1.91	−2.19
6	2,5-Xylidine	−2.40	−2.41	−1.57	−2.29	−1.78	−1.89	−1.88
7	*p*-Phenetidine	−2.30	−2.07	−3.97*	−2.36	−2.94	−1.83	−3.05
8	2-Methoxy-5-methylaniline	−2.05	−2.19	−2.84	−2.17	−2.97	−1.89	−2.07
9	4,4′-Methylenedianiline	−1.60	−1.50	−0.70	−0.34*	−0.95	−0.90	−0.35*
10	8-Aminoquinoline	−1.14	−2.15*	−2.54*	−1.10	−2.05	−0.03*	−1.52
11	2-Amino-α,α,α-trifluorotoluene	−0.80	−1.69	−1.85*	−0.76	−2.19*	−2.09*	−1.43
12	2-Bromo-4,6-dinitroaniline	−0.54	−2.22*	−0.99	−1.50	−1.98*	−1.95*	−0.46
13	3,3′-Dimethylbenzidine	0.01	−0.56	−0.66	−0.06	0.15	−0.15	0.56
14	3,3′-Dimethoxybenzidine	0.15	0.22	−0.63	0.36	1.10	−0.14	0.32
15	4-Phenoxyaniline	0.38	−0.39	−0.76*	−0.86*	0.25	−0.50	0.56
16	1-Aminoanthracene	1.18	1.99	1.24	1.07	2.79*	1.37	1.86
17	1-Aminopyrene	1.43	3.2*	3.44*	3.35*	3.08*	2.54*	2.68*
18	2-Aminofluorene	1.93	0.96	0.73*	1.43	0.93*	1.03	0.83*
19	2-Aminoanthracene	2.62	2.46	1.37*	1.16*	1.33*	1.16*	1.51*
20	3-Aminofluoranthene	3.31	2.32*	2.78	3.44	3.12	3.03	2.69
	MAE[a]		0.648	0.843	0.601	0.943	0.779	0.648

[a] Mean absolute error.

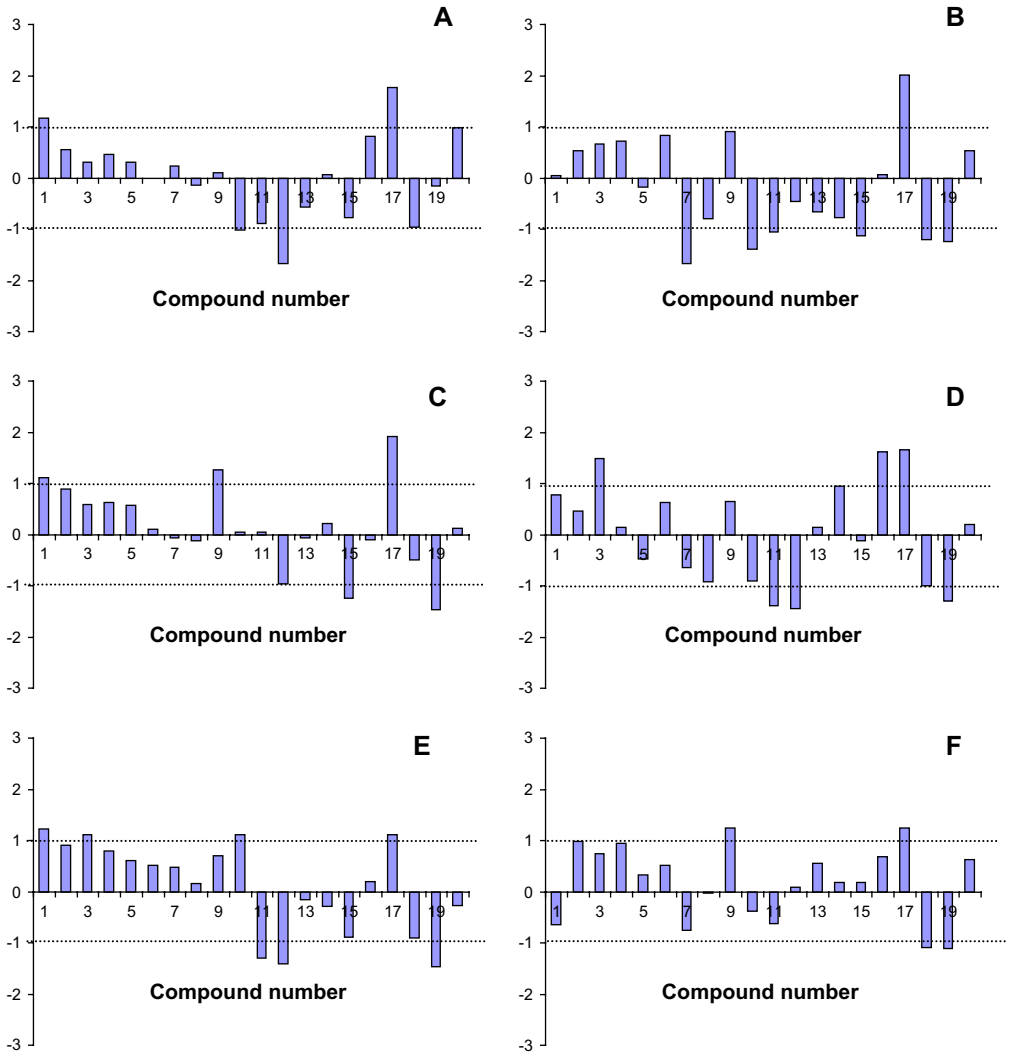

Fig. 2. Residual plots for compounds studied in this work obtained for different QSAR models. (A) Maran et al. [26], (B) Basak et al. [13], (C) Cash [14], (D) Vracko et al. [16], (E) Bhat et al. [27] and (F) BMC model Eq. (2). Compounds have been ordered according to their experimental ln *R* values (numbers in Table 3).

In Table 3, the predicted values obtained for the compounds used in this study using Eq. (2) and the values reported in literature using different QSAR models are shown. In the same table the mean absolute errors obtained for each proposed model are included. Fig. 2 shows the residual values; as can be observed that the proposed model based on BMC retention (Fig. 2F) shows better or at least comparable predictive ability than other reported QSAR models, with the advantage of its simplicity. This fact remarks the idea that the use of many descriptors does not warranty the improvement of the model prediction capability.

4. Conclusions

The results presented here indicate that the proposed model to estimate the mutagenicity of aromatic amines based on the retention of compounds in biopartitioning micellar chromatography, BMC, is capable of describing and predicting the toxicity values. The proposed MLR model indicates that hydrophobic amines with high polarizability present high mutagenic capacity and this model can be used for screening purposes at an early stage of the drug discovery process or in risk assessment studies. The comparison with other QSAR models proposed suggests that the MLR–BMC based model is better from a statistical point of view with the advantage of its simplicity. In addition, due to the larger number of parameters used to develop the QSAR models, the number of experimental data needed to obtain a statistical validated model is also large, mainly when multiple linear regression is used. The BMC methodology is less expensive than in vivo models and minimum experimentation is required.

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