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Abstract

Quantitative structure–activity relationships (QSAR) models for the bone resorption inhibition of 29 aryl–substituted bisphosphonates (ABP) were established with the CODESSA program. The QSAR models for the ABP bone resorption inhibition are obtained by selecting descriptors from a wide diversity of constitutional, topological, electrostatic and quantum structural indices. Standard quantum chemistry packages are used for optimizing the molecular geometry and for semi–empirical quantum computations at the AM1 level. A heuristic algorithm selects the best multiple linear regression equation according to the highest statistical indices; the predictive power of each QSAR model is estimated with the leave–one–out (LOO) cross–validation method. For the whole set of 29 compounds, the best QSAR model (r^2 = 0.8328, r^2_{LOO} = 0.7479, s^2 = 0.251, F = 29.88) is obtained with four quantum descriptors (minimum total interaction for a C–P bond, maximum valency of a N atom, minimum total interaction for a C–C bond, and hydrogen–acceptors surface area). A significant improvement of the statistical indices is obtained by deleting three outliers, when a fairly good QSAR is obtained (r^2 = 0.8827, r^2_{LOO} = 0.8231, s^2 = 0.118, F = 39.51) also with four quantum descriptors (minimum electron–electron repulsion for a H–N bond, minimum coulombic interaction for a C–P bond, maximum one–electron reactivity index for a N atom, and minimum total interaction for a H–O bond). These results demonstrate the ability of AM1 quantum indices in modeling the bone resorption inhibition of aryl–substituted bisphosphonates.

Keywords. QSAR; quantitative structure–activity relationships; aryl–substituted bisphosphonates; bone resorption inhibition; CODESSA.

1 INTRODUCTION

The bone resorption inhibition activity of geminal bisphosphonates makes them important compounds for the treatment of patients with postmenopausal osteoporosis, osteolytic bone metastases arising from breast cancer or multiple myeloma, tumor–induced hypercalcemia, and for Paget's disease of bone [1–5]. Bisphosphonates contribute up to $5 billion to the global

[#] Dedicated to Professor Haruo Hosoya on the occasion of the 65th birthday.

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pharmaceutical market, and the design of new bone resorption inhibitors with improved potency is an active field of investigation.

In this paper we develop quantitative structure–activity relationships (QSAR) models for the bone resorption inhibition of aryl–substituted bisphosphonates (ABP). The relationships between ABP chemical structures and their activity in inhibiting bone resorption were established by selecting the structural descriptors for the multilinear regression equation from a wide range of topological, geometrical, electrostatic, and quantum indices.

2 MATERIALS AND METHODS

The success of the QSAR approach can be explained by the insight offered into the structural determination of chemical properties, and the possibility to estimate the properties of new chemical compounds without the need to synthesize and test them. The main QSAR hypothesis is that all properties (physical, chemical, and biological) of a chemical substance are statistically related to its molecular structure.

Table 1. Compound Number (See Figure 1 for Structure), Number from Ref. [4], Experimental ED_{50} (μg/kg) [4], and pIC_{50} Experimental and Computed with Eq. (2)

No	Ref. [4]	ED_{50}	$pIC_{50\ exp}$	$pIC_{50\ Eq.\ (2)}$
1	**5r**	0.33	9.209	9.099
2	**4j**	0.4	8.979	8.422
3	**5d**	0.5	8.885	8.397
4	**5f**	0.6	8.835	8.348
5	**4g**	0.7	8.778	8.223
6	**5p**	0.7	8.741	8.417
7	**4d**	1	8.586	8.178
8	**4i**	1.0	8.565	7.964
9	**5c**	1.2	8.488	8.156
10	**5h**	1.2	8.546	8.814
11	**5g**	1.3	8.506	8.534
12	**4b**	1.4	8.407	8.259
13	**4f**	1.5	8.405	8.104
14	**5a**	1.5	8.402	8.605
15	**5b**	1.7	8.385	8.563
16	**5e**	1.7	8.369	8.307
17	**5l**	4	7.997	8.162
18	**5q**	7	7.741	7.903
19	**5s**	7.8	7.745	8.426
20	**5j**	10	7.624	7.697
21	**4e**	15	7.405	7.537
22	**4c**	20	7.253	8.023
23	**4k**	20	7.306	8.136
24	**5i**	20	7.142	8.070
25	**5n**	100	6.609	6.434
26	**4a**	300	6.053	6.168
27	**5k**	500	5.930	5.203
28	**4l**	1500	5.436	5.374
29	**5m**	7500	4.754	5.557

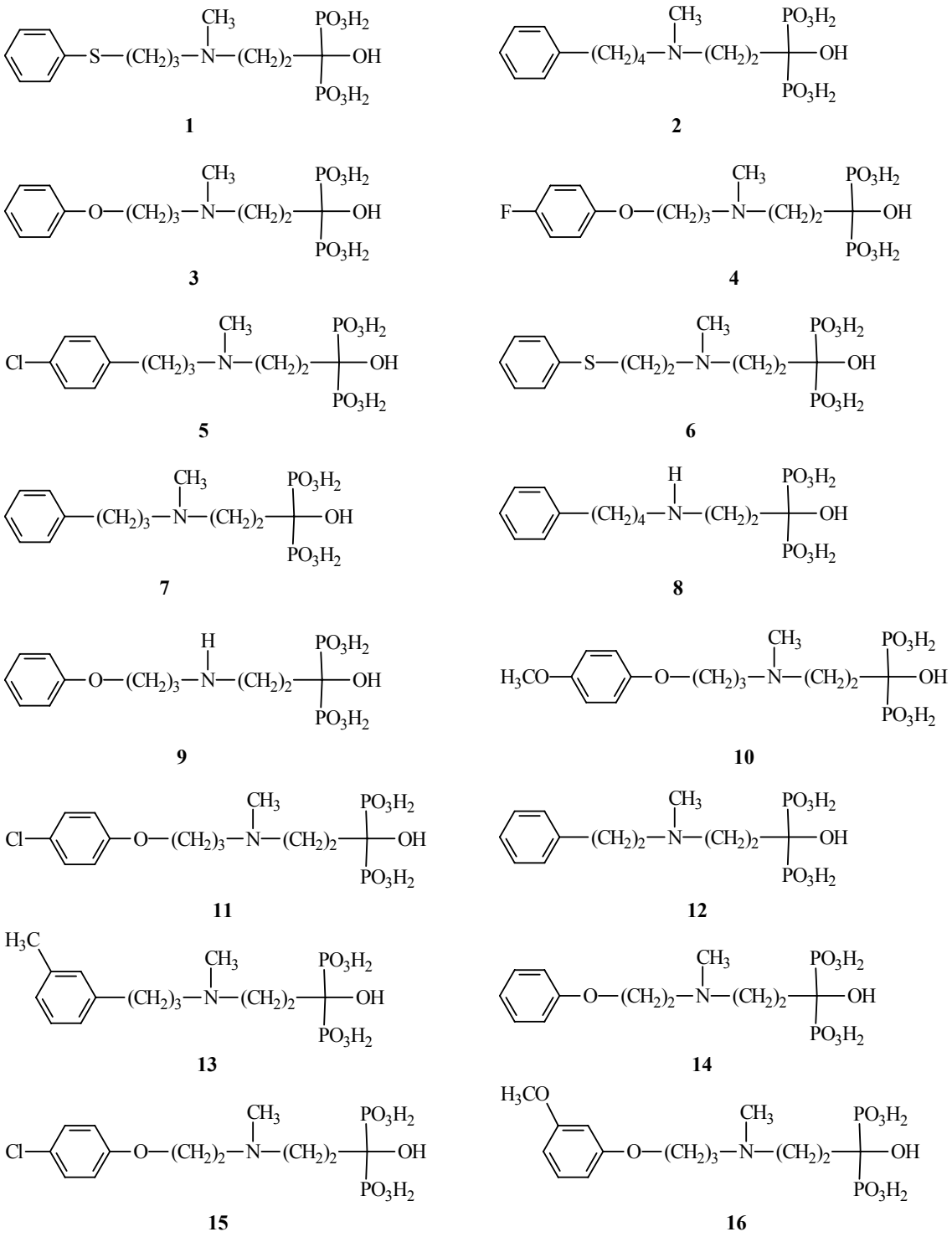
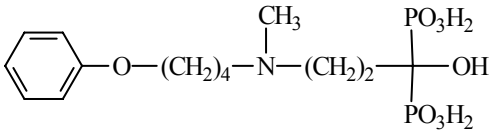


Figure 1. Structures of the 29 Aryl–Substituted Bisphosphonates [4].

The investigation of large and diverse molecular databases was made possible by the advent of general QSAR programs which integrate the computation of structural descriptors with the generation of structure–property models. CODESSA [6–8] is a widely used QSAR software [9–12] that describes numerically the chemical structure with more than one thousand structural descriptors from five classes: constitutional, graph theoretic and topological indices, geometrical, electrostatic,

and quantum–chemical descriptors. Using statistical methods, such as multiple linear regression (MLR) or PCA, the best descriptors are selected in the final structure–activity model. The bone resorption inhibition QSAR equations from this study were developed with CODESSA.



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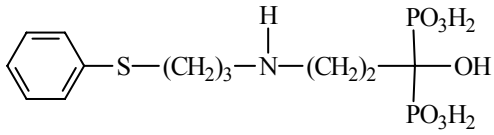

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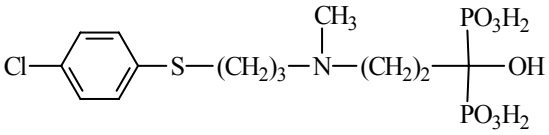

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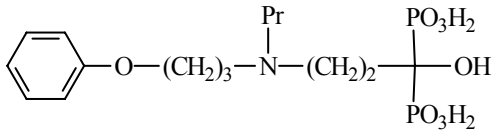

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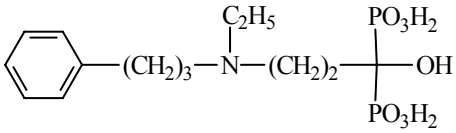

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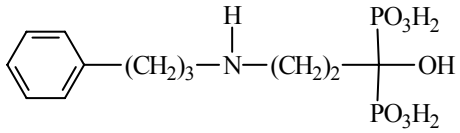

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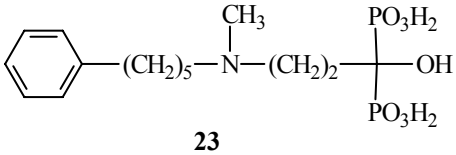

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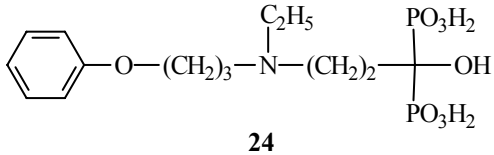

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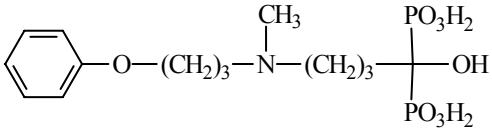

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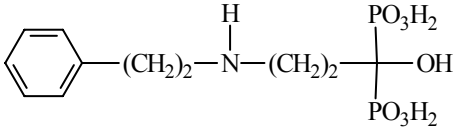

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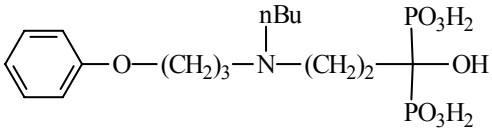

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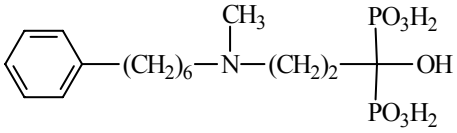

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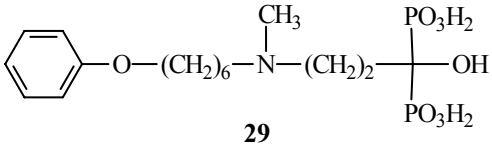

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Figure 1. (Continued).

2.1 Chemical Data

The experimental values for the bone resorption inhibition of 29 aryl–substituted bisphosphonates (Figure 1) taken from the literature [4] are presented in Table 1.

2.2 Previous QSAR Models

Using the Cerius^2 molecular field analysis QSAR, Kotsikorou and Oldfield [5] obtained a fairly good model for the set of 29 ABP:

$$pIC_{50} = 5.137 - 0.021\ H^+/326 + 0.052\ CH_3/335 - 0.073\ H^+/514 - 0.041\ H^+/564$$
$$n = 29 \quad r^2 = 0.900 \quad F = 54.28 \quad r^2_{LOO} = 0.799 \qquad (1)$$

where H^+/i represents the interaction energy between a proton probe and the molecule at the grid point i, and CH_3/j represents the interaction energy between a methyl probe and the molecule at the grid point j.

2.3 Molecular Modeling

In the present investigation, the chemical structures were generated with HyperChem [13], the geometry optimization was performed with MOPAC [14] using the semiempirical quantum method AM1 [15] and the QSPR models were computed with CODESSA [16].

2.4 Structural Descriptors

The HyperChem structure files and the MOPAC output files were used by CODESSA to calculate 603 descriptors. CODESSA computes five classes of structural descriptors: constitutional (number of various types of atoms and bonds, number of rings, molecular weight); topological (Wiener index, Randić connectivity indices, Kier shape indices, information theory indices); geometrical (principal moments of inertia, shadow indices, molecular volume and surface area); electrostatic (when atomic charges are computed on the basis of atomic electronegativity: minimum and maximum partial charges, polarity parameter, charged partial surface area descriptors, hydrogen bond donor and acceptor surface indices); quantum (minimum and maximum partial charges, Fukui reactivity indices, dipole moment, HOMO and LUMO energies, molecular polarizability, minimum/maximum valency of an atom, minimum/maximum electron–electron repulsion for an atom, minimum/maximum exchange energy for a chemical bond, etc).

2.5 Multiple Linear Regression Model

From the whole set of 603 descriptors generated with CODESSA we have discarded descriptors with a constant value for all molecules in the data set. Descriptors for which values were not available for every molecule were assigned a zero value for the missing position. In the next step the number of descriptors was reduced by eliminating those with F–test values less than 1, t–test values less than 0.1 or correlation coefficients with pIC_{50} less than 0.1; as a result of this descriptor

selection procedure, 348 descriptors remained for the 29 aryl–substituted bisphosphonates. CODESSA develops MLR models by a heuristic method that includes the following steps: (*a*) All quasi–orthogonal pairs of structural descriptors are selected from the initial set. Two descriptors are considered orthogonal if their intercorrelation coefficient r_{ij} is lower than 0.1. (*b*) CODESSA uses the pairs of orthogonal descriptors to compute the biparametric regression equations. The most significant 10 pairs of molecular descriptors are used in the third step. (*c*) To an MLR model containing *n* descriptors a new descriptor is added to generate a model with *n*+1 descriptors if the new descriptor is not significantly correlated with the previous *n* descriptors (intercorrelation coefficient lower than 0.8). Step (*c*) is repeated until MLR models with a given maximum number of descriptors are obtained.

2.6 Model Validation

QSPR correlations can be observed not only because a causal relationship exists between a set of descriptors and a property, but also due to statistical bias resulting from errors in determining structural descriptors, experimental errors in measuring the property, or even due to chance alone. Model validation techniques are needed in order to distinguish between true and random correlations and to estimate the predictive power of the model. Although the QSAR equations developed with CODESSA are obtained by selection of descriptors from a large pool, several descriptor selection techniques are used in order to minimize the possibility of chance correlations. In a first step, from the initial pool of descriptors, CODESSA eliminates descriptors that do not correlate with pIC_{50}, thus greatly reducing the dimensionality of the problem.

Table 2. Notation of the CODESSA Descriptors Involved in the QSAR Models

Notation	Descriptor
SD1	Maximum partial charge for a C atom (electrostatic)
SD2	Maximum partial charge for a O atom (electrostatic)
SD3	Maximum partial charge for a P atom (electrostatic)
SD4	Minimum total interaction for a C–P bond
SD5	Maximum valency of a N atom
SD6	Maximum electron–electron repulsion for a C atom
SD7	Maximum atomic state energy for a N atom
SD8	Minimum total interaction for a C–C bond
SD9	HASA H–acceptors surface area (quantum)
SD10	HBCA H–bonding charged surface area (quantum)
SD11	HBSA H–bonding surface area (quantum)
SD12	Minimum electron–electron repulsion for a H–N bond
SD13	Minimum coulombic interaction for a C–P bond
SD14	Minimum exchange energy for a C–N bond
SD15	Maximum one–electron reactivity index for a N atom
SD16	HA dependent HDSA–2/SQRT(TMSA) (electrostatic)
SD17	Minimum total interaction for a H–O bond
SD18	FPSA–3 Fractional PPSA (PPSA–3/TMSA) (electrostatic)

Then, as described in the previous section, a heuristic algorithm selects only quasi–orthogonal groups of descriptors that are tested for correlation with pIC_{50} of aryl–substituted bisphosphonates. This selection algorithm ensures that the probability of obtaining a chance correlation is low, and maintains a reasonable searching time. Finally, the leave–one–out (LOO) cross–validation procedure is applied to each MLR equation in order to estimate the prediction power of bone resorption inhibition QSAR.

3 RESULTS AND DISCUSSION

Table 2 presents the notation and a short description of the structural descriptors involved in the QSAR models reported in this investigation; more complete definitions of the descriptors can be found in the CODESSA manuals [16]. In Table 3 we present the descriptors and correlation coefficients for the best three QSAR models with one and two descriptors and with 29 and 26 compounds, respectively. For the whole set of 29 ABP, the best descriptors in monoparametric models are the electronegativity–based maximum partial charge for a C, O, and P atom, respectively. An improvement of r is obtained in QSAR models two descriptors, when r^2 is between 0.7324 and 0.7431. All four descriptors involved in the biparametric QSAR are quantum–based, namely: minimum total interaction for a C–P bond, maximum valency of a N atom, maximum electron–electron repulsion for a C atom, and maximum atomic state energy for a N atom.

Table 3. Descriptors and Correlation Coefficients for the Best Three QSAR Models with One and Two Descriptors and with 29 and 26 Compounds, Respectively

$n = 29$			$n = 26$		
x_1	x_2	r^2	x_1	x_2	r^2
SD1		0.5899	**SD1**		0.4143
SD2		0.5899	**SD2**		0.4143
SD3		0.5899	**SD3**		0.4143
SD4	**SD5**	0.7431	**SD6**	**SD12**	0.7784
SD6	**SD5**	0.7327	**SD13**	**SD12**	0.7741
SD6	**SD7**	0.7324	**SD13**	**SD14**	0.7594

The QSAR statistics increase further in equations with three and four descriptors. Because adding more descriptors does not significantly improve the statistical indices, we have selected the QSAR with four descriptors as the best for the 29 ABP. The best three such QSAR models are:

$$pIC_{50} = -357.35 + 2.903\ \mathbf{SD4} + 74.89\ \mathbf{SD5} + 3.894\ \mathbf{SD8} + 1.867 \cdot 10^{-2}\ \mathbf{SD9}$$
$$n = 29 \quad r^2 = 0.8328 \quad s^2 = 0.251 \quad F = 29.88 \quad r^2_{LOO} = 0.7479 \tag{2}$$

$$pIC_{50} = -381.83 + 3.145\ \mathbf{SD4} + 79.49\ \mathbf{SD5} + 4.038\ \mathbf{SD8} + 2.630 \cdot 10^{-2}\ \mathbf{SD10}$$
$$n = 29 \quad r^2 = 0.8313 \quad s^2 = 0.253 \quad F = 29.56 \quad r^2_{LOO} = 0.7374 \tag{3}$$

$$pIC_{50} = -351.95 + 2.921\ \mathbf{SD4} + 73.07\ \mathbf{SD5} + 3.691\ \mathbf{SD8} + 1.773 \cdot 10^{-2}\ \mathbf{SD11}$$
$$n = 29 \quad r^2 = 0.8296 \quad s^2 = 0.255 \quad F = 29.22 \quad r^2_{LOO} = 0.7428 \tag{4}$$

Eqs. (1)–(3) shows that starting with a large selection of structural descriptors it is possible to find

several combinations of descriptors that provide models with similar good statistics. Moreover, owing to the errors in the experimental data, small statistical differences between QSRR equations are not significant, and it is almost impossible to select a "best" modeling equation in such cases. The plot of experimental *vs*. calculated pIC_{50} for Eq. (2) is presented in Figure 2, and the pIC_{50} calculated with Eq. (2) can be found in Table 1, column 5. Four quantum descriptors computed with the AM1 method are used in the QSAR model from Eq. (2), namely the minimum total interaction for a C–P bond, maximum valency of a N atom, minimum total interaction for a C–C bond, and hydrogen–acceptors surface area.

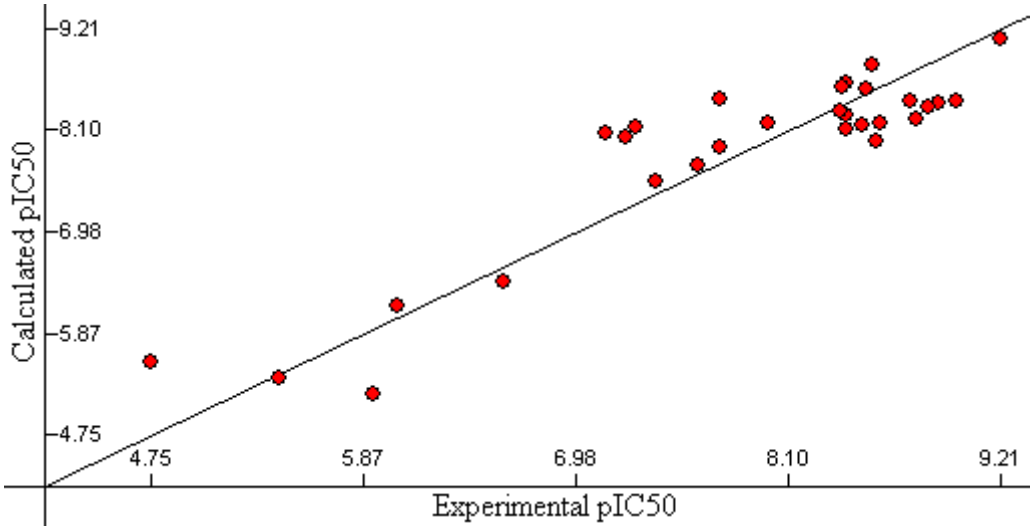

Figure 2. Experimental *vs*. calculated pIC_{50} for Eq. (2).

Because the pIC_{50} calculated with Eq. (2) for compounds **24**, **27**, and **29** have large deviations from the experimental values, we have removed these compounds and developed QSAR models with 26 ABP. In Table 3 we present the descriptors and correlation coefficients for the best three QSAR models with one and two descriptors, respectively. The best three QSAR models for the 26 ABP are:

$$pIC_{50} = -59.18 + 3.172\ \mathbf{SD13} - 5.608\cdot10^{-2}\ \mathbf{SD12} - 1.081\cdot10^{3}\ \mathbf{SD15} + 4.985\ \mathbf{SD16}$$
$$n = 26 \quad r^2 = 0.8860 \quad s^2 = 0.115 \quad F = 40.79 \quad r^2_{LOO} = 0.8055 \qquad (5)$$

$$pIC_{50} = 1.214\cdot10^{2} + 2.839\ \mathbf{SD13} - 5.240\cdot10^{-2}\ \mathbf{SD12} - 9.812\cdot10^{2}\ \mathbf{SD15} - 13.07\ \mathbf{SD17}$$
$$n = 26 \quad r^2 = 0.8827 \quad s^2 = 0.118 \quad F = 39.51 \quad r^2_{LOO} = 0.8231 \qquad (6)$$

$$pIC_{50} = -5.636\cdot10^{-1} + 3.099\ \mathbf{SD13} - 5.500\cdot10^{-2}\ \mathbf{SD12} - 1.073\cdot10^{3}\ \mathbf{SD15} + 1.341\cdot10^{2}\ \mathbf{SD18}$$
$$n = 26 \quad r^2 = 0.8816 \quad s^2 = 0.120 \quad F = 39.09 \quad r^2_{LOO} = 0.8221 \qquad (7)$$

Compared with the QSAR obtained with 29 ABP, both calibration and LOO cross–validation *r* are significantly improved in Eqs. (5)–(7). Because r^2_{LOO} has a maximum value for Eq. (6), in Figure 3 we present the plot of experimental *vs*. calculated pIC_{50} for Eq. (6). Four quantum descriptors computed with the AM1 method are used in the QSAR model from Eq. (6), namely the minimum electron–electron repulsion for a H–N bond, minimum coulombic interaction for a C–P

bond, maximum one–electron reactivity index for a N atom, and minimum total interaction for a H–O bond. Starting from a large collection of 603 constitutional, graph theoretic and topological indices, geometrical, electrostatic, and quantum–chemical descriptors, only electronic indices were selected in the best QSAR models, as can be seen from Table 2. These electronic indices, either based on the AM1 calculations or electronegativity–derived, offer good models for the ABP bone resorption inhibition. All these results suggest that electronic factors that control the molecular structure and inter–molecular interactions are the main factors that determine the bone resorption inhibition of aryl–substituted bisphosphonates.

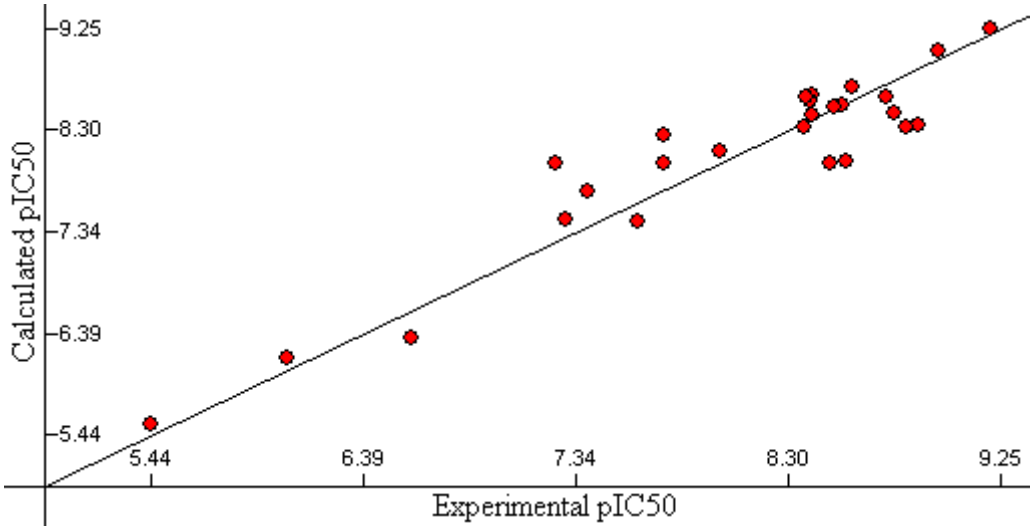

Figure 3. Experimental *vs*. calculated pIC_{50} for Eq. (6).

4 CONCLUSIONS

Quantitative structure–activity relationships (QSAR) models for the bone resorption inhibition of 29 aryl–substituted bisphosphonates were established with the CODESSA program. The QSAR models for the ABP bone resorption inhibition are obtained by selecting descriptors from a wide diversity of constitutional, topological, electrostatic and quantum structural indices. Standard quantum chemistry packages are used for optimizing the molecular geometry and for semi–empirical quantum computations at the AM1 level. A heuristic algorithm selects the best multiple linear regression equation according to the highest statistical indices; the predictive power of each QSAR model is estimated with the leave–one–out (LOO) cross–validation method. For the whole set of 29 compounds, the best QSAR model (r^2 = 0.8328, r^2_{LOO} = 0.7479, s^2 = 0.251, F = 29.88) is obtained with four quantum descriptors (minimum total interaction for a C–P bond, maximum valency of a N atom, minimum total interaction for a C–C bond, and hydrogen–acceptors surface area). A significant improvement of the statistical indices is obtained by deleting three outliers, when a fairly good QSAR is obtained (r^2 = 0.8827, r^2_{LOO} = 0.8231, s^2 = 0.118, F = 39.51) also with four quantum descriptors (minimum electron–electron repulsion for a H–N bond, minimum

coulombic interaction for a C–P bond, maximum one–electron reactivity index for a N atom, and minimum total interaction for a H–O bond). These results demonstrate the ability of AM1 quantum indices in modeling the bone resorption inhibition of aryl–substituted bisphosphonates. Together with the QSAR models proposed in this study, these three descriptors could be used to estimate the bone resorption inhibition for not yet synthesized or laboratory tested aryl–substituted bisphosphonates.

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