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Anti-inflammatory oxicam / cyclodextrin supramolecular systems: molecular modeling and docking experiments

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Abstract

The paper presents a theoretical study among molecular modeling of the main non-steroidal thiazine anti-inflammatory drugs and the possibility of obtaining supramolecular systems formulations based on natural cyclodextrin complexes. The main anti-inflammatory compounds, *guest* structures – piroxicam, meloxicam, tenoxicam, and isoxicam – were builded, molecular modeled, and conformationally analyzed; the natural α- and β-cyclodextrin structures – *host* structures – were studied in the same way. For both structure types the most stable conformations were used in *host-guest* interaction analysis (docking experiments), which could conduct to pharmaceutical formulations with controlled release properties. Further, quantitative structure – activity relationships were obtained in the anti-inflammatory benzothiazine class.

Keywords: natural cyclodextrins, thiazine anti-inflammatory compounds, oxicams, supramolecular systems, molecular modelling, QSAR, docking

1. Introduction

Anti-inflammatory properties of drugs have a unique mechanism of action. Both antipyretic and anti-inflammatory compounds act by inhibition of the synthesis and release of prostaglandins (tissue hormones, derived enzymatically from fatty acids and arachidonic acid), which are responsible for inflammations. The biosynthesis of prostaglandins imply an oxidation in the presence of a peroxidase – cyclooxygenase (COX). COX-1 is responsible for the baseline levels of prostaglandins (generating gastritis and nausea), while COX-2 produces prostaglandins through stimulation; as a result, the prostaglandin levels are increased by COX-2 in the case of inflammations. A lot of classes of compounds which inhibit cyclooxygenases (more or less selective) exist: pyrazolones, pyrazolidin-diones, salicylic derivatives, *p*-aminophenols, aryl-anthranyl and aryl-acetic acids, sulfonamides, all with non-steroidal structures [1]. From the last class, piroxicam, meloxicam, and tenoxicam were approved as drugs after 1980 and have more or less selective COX inhibitory activity [2-7].

These drugs are used for acute and long-term therapy for the relief of symptoms of osteoarthritis and rheumatoid arthritis, as well as for the treatment of the acute gout. They are metabolized mostly *via* hydroxylation and excreted in the urine [1]. All oxicams have acidic properties due to the presence of enolic hydroxyl groups and this properties is corroborated with the inhibitory activity also against COX-1; this observations conduct to a secondary effects of oxicams, *i.e.* gastric damage [8].

The secondary effects of oxicams could be reduced by molecular encapsulation in cyclodextrins, which help also to enhancing water solubility, protect against degradation, and furnish formulations with controlled release properties [9,10]. Cyclodextrins are cyclic oligosaccharides consist of 6-8

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glucopyranose moieties in the case of natural α-, β-, and γ-cyclodextrin [9,11,12]. They have structures such as truncated cone with an outer part having primary (face A) and secondary (face B) hydroxyl groups which furnish water solubility; the inner cavity consist of pyranose rings which conduct to hydrophobic properties and further, van der Waals interactions could appear with the geometric compatible hydrophobic molecules or moieties, such as oxicams [11].

In this paper a theoretical study among molecular modeling of the main non-steroidal thiazine anti-inflammatory drugs and the possibility of obtaining supramolecular systems formulations based on natural cyclodextrin complexes were investigated. Further, quantitative structure – activity relationships (QSARs) were obtained in the anti-inflammatory benzothiazine class.

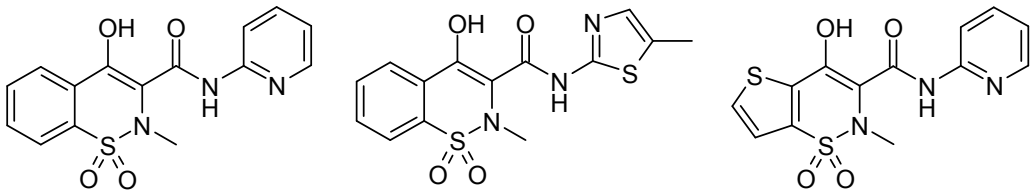


Figure 1. The main structures of non-steroidal oxicams anti-inflammatory drugs

2. Materials and methods

Structures and biological activities. The series of 24 compounds with anti-inflammatory activity, (revealed by the cyclooxygenase – COX – inhibition), from the 4-hydroxy-1,1-dioxo-1,2-dihydro-benzo[e][1,2]thiazin-3-carboxylic acid amide class, have structural variations especially at amidic and sulfonamidic groups, as well as at benzene ring (Table 1) [3]. The anti-inflammatory activities were grouped as inhibition percent ranges (% *Inhibition*) for an established inhibitory molar concentration (*IC*) as follows:

$$A = \log\left(\frac{1}{IC_{50-100}}\right)$$

for the inhibition domain of [50-100]%.

Structure skeleton for the anti-inflammatory selected compounds is presented in Figure 1 and the specific structures and biological activities are presented in Table 1.

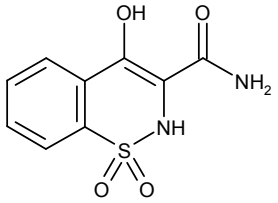


Figure 1. General structure of benzothiazine derivatives with anti-inflammatory activity

Molecular modeling. Molecular modeling of natural cyclodextrins and oxicam anti-inflammatory compounds was performed by using the molecular mechanics MM+ program from the HyperChem 5.1; a RMS of 0.05 kcal/mole and a Polak-Ribiere algorithm were used in the molecular modeling process.

Conformational analysis. The number of torsion angles from oxicam structures was low due to the rigid structures of these compounds. The flexible bonds in cyclodextrins were only those corresponding to the hydroxymethyl from C^5 position of glucopyranose unit; the flexible rings were all glucopyranose rings and the corresponding macrocyclic ring. In order to find the most stable conformations of these *hosts* and *guests* compounds,

a conformational analysis program (*Conformational Search* program, HyperChem 5.1) was used. The following conditions were set up for conformational search: variation of the flexible torsion angles ±60º ÷ ±180º, energy criterion for acceptance of the conformation 4 kcal/mole above minimum, all conformations with atomic distances lower than 0.5 Å and differences between torsion angles lower than 15º were not considered as well as conformations with energy differences lower than 0.05 kcal/mole (duplicates); the maximum number of optimization and iterative calculations was 250 and maximum 20 conformations were retained. The hydrogen atoms were neglected.

Table 1. Structures and anti-inflammatory activity of benzothiazine derivatives

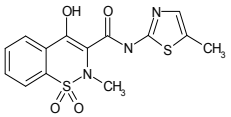
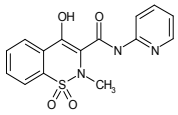
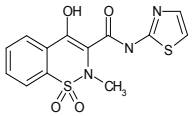
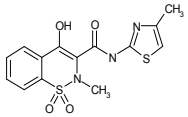
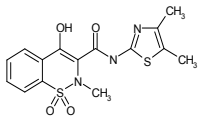
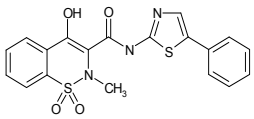
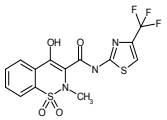
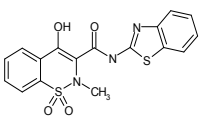
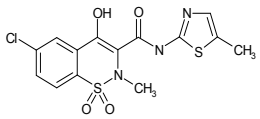
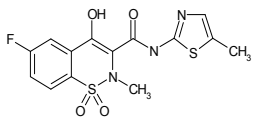
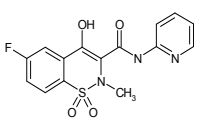
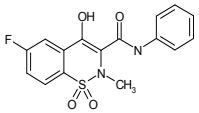
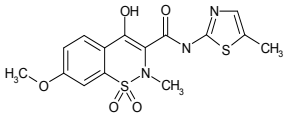
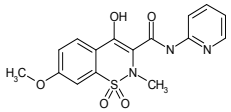
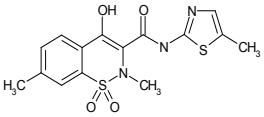
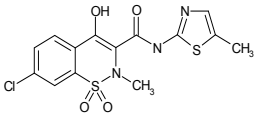
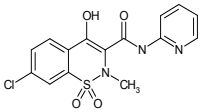
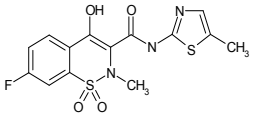
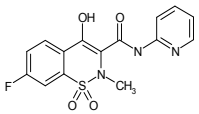
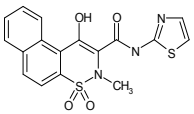
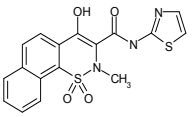
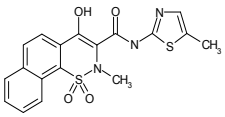
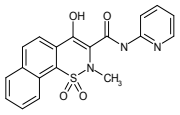
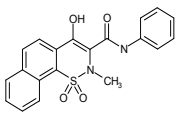
No	Structure	log(1/IC_{50-100})	*Inhibition* (%)
1 (meloxicam)		@4.5458	77
2 (piroxicam)		@4.5203	62
3		@4.5281	51
4		@4.5458	71
5		@4.5628	74
6		@4.6165	97
7		@4.6079	72
8		@4.5882	95
9		@4.5864	76
10		@4.5675	72
11		@4.5433	58

Table 1. (continued)

No	Structure	log(1/IC_{50-100})	*Inhibition* (%)
12		@4.5420	61
13		@4.5814	70
14		@4.5580	51
15		@4.5628	68
16		@4.5864	66
17		@4.5632	72
18		@4.5632	72
19		@4.5433	62
20		@4.5882	69
21		@6.5884	75
22		@4.6036	67
23		@5.5814	78
24		@4.5803	88

Docking of oxicams in cyclodextrins. The docking of the more stable conformations of oxicams (piroxicam, meloxicam, tenoxicam, and isoxicam) in α- and β-cyclodextrin was realized by using the molecular mechanics interactions of the *host-guest* molecules in vacuum [12-16]. The oxicam and cyclodextrin structures in minimal energy conformations were set up at distances of ~8Å between the gravity centres of the *host-guest* molecules, and the oxicam structure was oriented with the benzothiazine moiety in the front of the primary (A) or secondary (B) face of cyclodextrin (the principal axis corresponding to the biocompound was perpendicular to the A or B plan of cyclodextrin). The complex was modeled in absence of water molecules by using the same MM+ program and the interaction was stopped when the RMS gradient was lower than 0.005 kcal/mole. The oxicam-cyclodextrin interaction energy was evaluated as the difference between the the overall energies of these two molecules and the complex energy.

Structural parameters. A large number of structural descriptors were performed by using different *in house* programs and *QSAR Properties* program from HyperChem 5.1 package (total or polar/non-polar molecular surface and volume, hydration energy, log*P*, refractivity, polarizability). The other descriptor classes were following: constitutional (including total number of atoms, bonds, independent rings, flexible bonds, rigid bonds, heteroatoms, non-polar atoms, positive/negative ionization atoms, H-donor and H-acceptor atoms), topological, molecular walk, *BCUT* (descriptors derived from Burden matrix), *Galvez* (topological charge indices), 2D autocorrelation (autocorrelation descriptors, derived from topological descriptors), charge, aromaticity indices, *RDF* (radial distribution function descriptors), *3D-MoRSE*, *WHIM*, *Getaway*, functional groups, atom-centered fragments, empirical, and molecular property descriptors (Clog*P*, water solubility, log*Wsol* etc.) [17,18]. The minimum energy conformation for every compound was used for these determinations.

QSAR analysis. For the quantitative structure – activity relationships (QSAR) analysis in the oxicam anti-inflammatory derivative class the following mono- and bilinear mathematical models were used [12-15,17,19-22]:

$$\log(1/IC_{50})_i = a_0 + \sum_j b_{ij} \cdot P_{ij}$$

where P_{ij} represents the j parameter of the structure i, a_0 and b_{ij} are coefficients of the model.

3. Results and discussion

Docking of oxicams in natural cyclodextrins. In order to evaluate the possibility of encapsulation of the main oxicams with anti-inflammatory properties in natural cyclodextrins the molecular modeling and docking studies were performed. The oxicam/cyclodextrin complexes could have enhanced properties such as: controlled release properties, stability against degradation, reduced acidity. Molecular modeling was performed by using only molecular mechanics method, MM+, because the semi-empirical methods (*e.g. AM1* and *PM3* methods) not conduct to a significant increasing of the quality of results.

Molecular modeling and conformational analysis of α- and β-cyclodextrin revealed conformations resembling to truncated cone, with dimensions which have small variations on values determined along different axes. The van der Waals radii of hydrogen atoms, calculated by Bondi [16,23], were considered in order to evaluate the correct diameters of A and B faces of cyclodextrins in minimal energy conformations. Thus, the A (with primary hydroxyl groups) and B (with secondary hydroxyl groups) faces of α-cyclodextrin have outer diameters of 11.5-11.6Å and 14.6-14.8Å, respectively; the inner diameter of the secondary face was 5.4-5.5Å, while for the primary face this diameter was much smaller (<1Å). For the corresponding β-cyclodextrin these values were: 17.5-18.3Å and ~12.9Å for the outer diameters of A and B face, respectively; the inner diameter of the secondary face of β-cyclodextrin was ~5.5Å. The most stable conformations of α- and β-cyclodextrin (obtained by molecular mechanics and conformational analysis) in vacuum are presented in Figure 2. The internal energies of these conformations were 71.5 kcal/mole and 82.7 kcal/mole for α- and β-cyclodextrin, respectively.

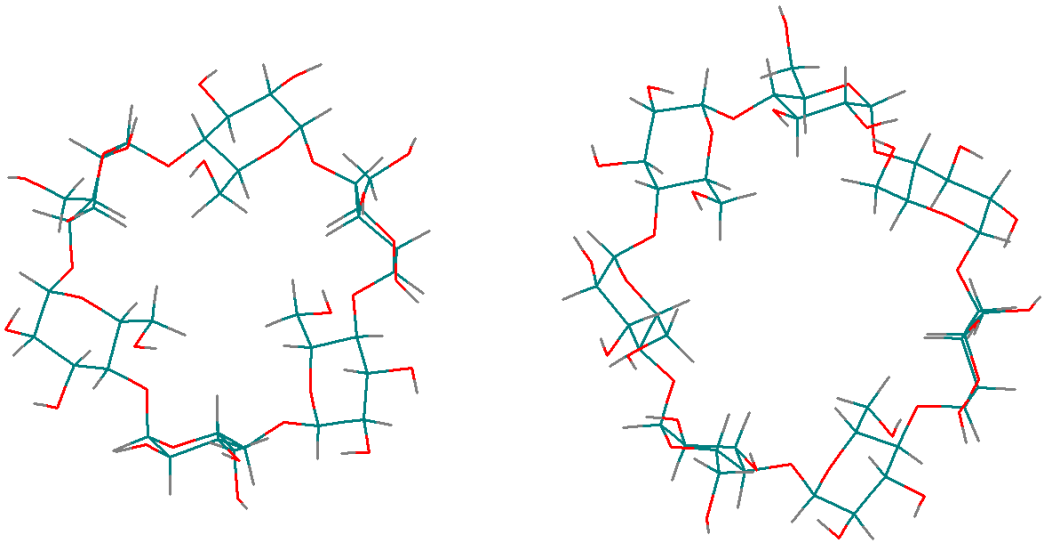


Figure 2. Minimum energy conformations for α- and β-cyclodextrin

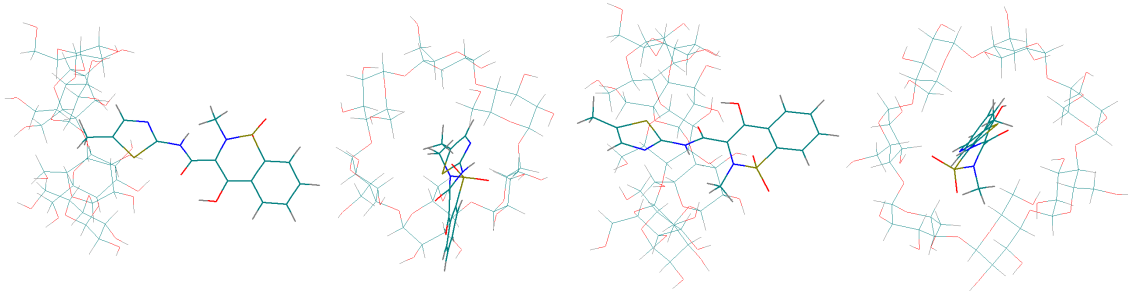
All oxicams are accomodated better in the β-cyclodextrin cavity, in comparison with α-cyclodextrin case; even the secondary face of cyclodextrins was used in docking experiment. In the case of α-cyclodextrin molecular encapsulation, the study indicates especially a van der Waals interaction between oxicam moieties (even bicyclic or *N*-amide heterocyclic moiety) and the inner cavity of cyclodextrin. Oxicam/α-cyclodextrin interaction energies were obtained in vacuum for all four anti-inflammatory compound studied as the difference between the sum of potential energies of *guest* and *host* compounds in most stable conformations (calculated in vacuum) and the energy of the *host-guest* complex evaluated in the same conditions (Table 2). Thus, meloxicam and isoxicam interact better with the inner cavity of α-cyclodextrin (~13.5 kcal/mole), while only meloxicam has an appropriate interaction with β-cyclodextrin (24.5 kcal/mole); further, tenoxicam and piroxicam have important interactions with β-cyclodextrin (23.5 kcal/mole and 21 kcal/mole, respectively). The worst interaction with β-cyclodextrin is the isoxicam case, with interaction energy of 17.8 kcal/mole.

Table 2. Interaction energies for the main anti-inflammatory thiazines / α- and β-cyclodextrin supramolecular systems

No	Code	E_{CD} (kcal/mole)	E_{oxicam} (kcal/mole)	$E_{CD+oxicam}$ (kcal/mole)	$E_{complex}$ (kcal/mole)	$E_{interaction}$ (kcal/mole)
1	aCD-P	71.49	19.3	90.79	80.7	10.09
2	aCD-P*	71.49	19.3	90.79	76.5	14.29
3	aCD-M	71.49	21.9	93.39	80.1	13.29
4	aCD-T	71.49	30.6	102.09	92.3	9.79
5	aCD-I	71.49	18.1	89.59	76	13.59
6	bCD-P	82.70	19.3	102	80.6	21.4
7	bCD-P*	82.70	19.3	102	81	21
8	bCD-M	82.70	21.9	104.6	80.1	24.5
9	bCD-T	82.70	30.6	113.3	89.8	23.5
10	bCD-I	82.70	18.1	100.8	83	17.8

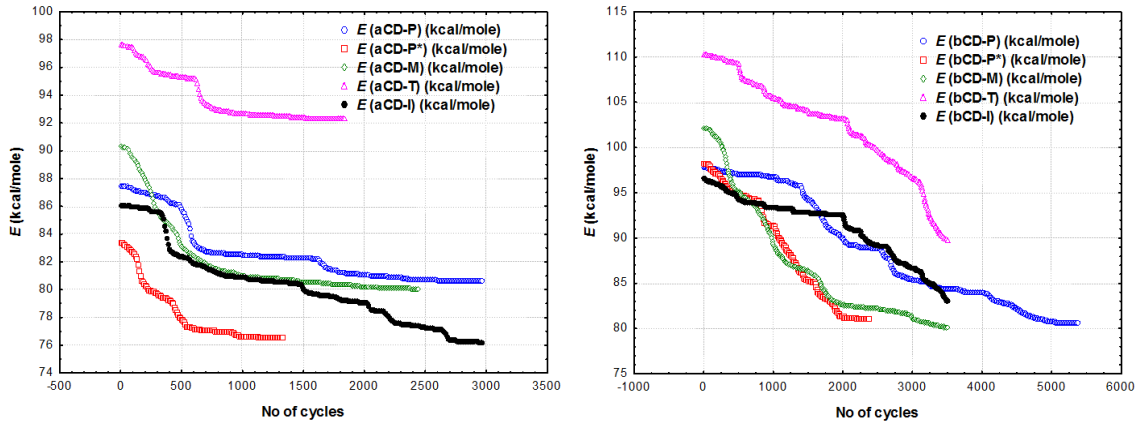
* Piroxicam-cyclodextrin interaction with the benzothiazine moiety oriented to the secondary face of cyclodextrin

The molecular encapsulation of oxicams in α-cyclodextrin is not completely from the steric point of view (Figure 3a); neither *N*-aromatic ring nor bicyclic moiety is completely encapsulated until stabilization of the complex (considering a gradient of 0.005 kcal/mole for molecular mechanics optimization) (Figure 4a). In the case of β-cyclodextrin complexes, a better encapsulation of the oxicams is observed, especially in the case of meloxicam and tenoxicam (Figure 3b); this fact is revealed also by the variation of the interaction energies among the encapsulation process (Figure 4b).



(a) (b)

Figure 3. Meloxicam / α-cyclodextrin (a) and meloxicam / β-cyclodextrin (b) supramolecular systems, obtained by molecular mechanics docking experiments



(a) (b)

Figure 4. Variation of the interaction energy between oxicams (*P* – piroxicam, *M* – meloxicam, *T* – tenoxicam, *I* – isoxicam) and α-cyclodextrin (a) or β-cyclodextrin (b)

QSARs in the benzothiazine anti-inflammatory compounds class. The main oxicams (piroxicam and meloxicam, in comparison with isoxicam and tenoxicam) with anti-inflammatory activity have stable conformations which are very good superposition in the case of atoms from the main skeleton – thiazine ring and amide group (Figure 5). Molecular modeling and conformational analysis of all twenty four oxicam structures studied indicate that these structures have a low number of conformations with higher stability due to a low number of flexible bonds. The main structures, used as standard non-steroidal anti-inflammatory drugs (piroxicam and meloxicam), have only three flexible bonds (the lowest number in the studied series) corresponding to the likage between benzothiazine and *N*-amide ring moieties. Generally, the most stable conformations of these compounds have the *N*-amide ring oriented even to the *C*4-OH group or to the *N*2-Me group of the thiazine ring, but most of the stable confomations from all compounds studied are from the first class; this fact is probably due to the steric hindrance of the *N*2-Me group, more important in comparison with the *C*4-OH group case.

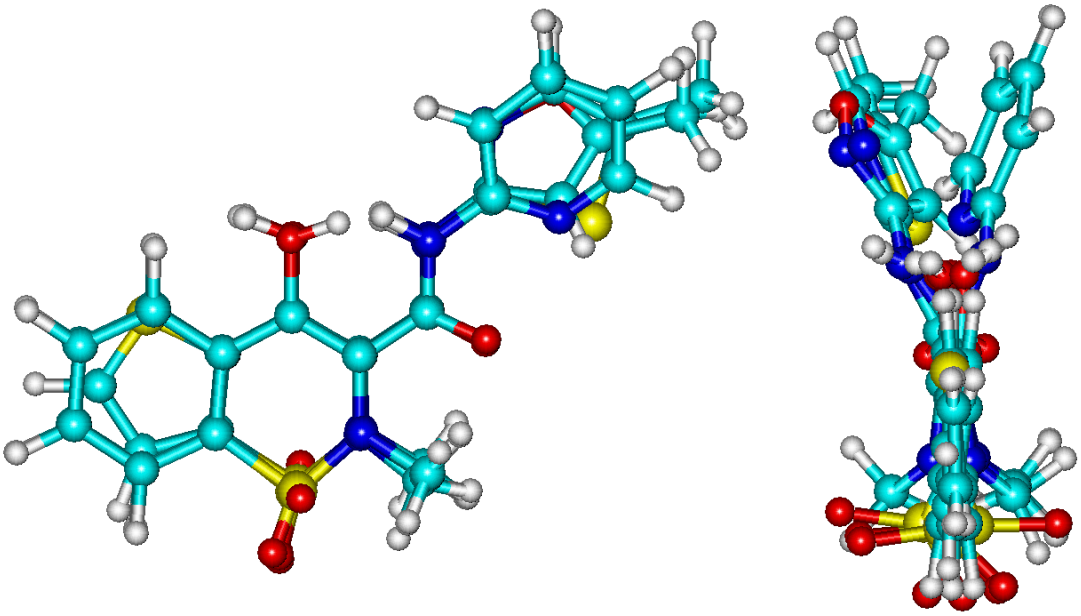


Figure 5. Superposition of the most stable conformations of the main non-steroidal anti-inflammatory drugs (piroxicam, meloxican, tenoxicam, and isoxicam)

The attempt to find statistically significant mathematical models (QSAR equations) in the thiazine anti-inflammatory compounds class, an exhaustive determination of structural descriptors from various classes was performed. The best results were obtained in the case of *BCUT* and *RDF* descriptors for monolinear regression, the correlation coefficients being statistically significant for many descriptors from these two classes (Eq. 1), especially for the second class, where *r* was higher than 0.7 in many cases. A better model was obtained by using two descriptors from these classes, which are not intercorrelated, the correlation coefficient being >0.8 (Eq. 2). Even if the correlation coefficient is statistically significant, no predictive power (low q^2) could be obtained for these QSARs.

(Eq. 1)

$$A_i = 3.86(\pm 0.16) + 0.07(\pm 0.01) \cdot (RDF045m)_i$$

$n = 24$; $r = 0.760$; $s = 0.30$; $F = 30.1$; $q^2 < 0.4$

(Eq. 2)

$$A_i = -199.7(\pm 99) + 43.65(\pm 21.23) \cdot (BEHm1)_i + \\ + 0.06(\pm 0.01) \cdot (RDF045m)_i$$

$n = 24$; $r = 0.805$; $s = 0.28$; $F = 19.4$; $q^2 < 0.4$

4. Conclusion

The following conclusions can be drawn among the molecular modeling, conformational analysis, quantitative structure-activity relationships study, and cyclodextrin docking of non-steroidal oxicams with anti-inflammatory activity: (1) theoretical docking of the main oxicam non-steroidal drugs with non-selective anti-inflammatory activity (piroxicam, meloxicam, tenoxicam, and isoxicam) in natural α- and β-cyclodextrin allow the evaluate the possibility of obtaining of useful complexes by means of the sterical compatibility of the *host-guest* supramolecular system and the interaction energy (which allow to evaluate the stability of the complex); these oxicams could be encapsulated better in β-cyclodextrin, in comparison with the α-cyclodextrin case, where the interaction is not very appropriate (incomplete molecular encapsulation and low interaction energy); (2) meloxicam and tenoxicam are better encapsulated in natural cyclodextrins, the best interaction being with the *N*-amide homo- or heterocyclic ring moiety; (3) the most stable conformations of these oxicams (which have been used in cyclodextrin nanoencapsualtion) have the amide substituent oriented to the hydroxyl group from the thiazine heterocycle; (4) the attempt to obtain QSARs in the anti-inflammatory

benzothiazine class conduct to statistically significant equations, but without predictive power for designing new non-steroidal anti-inflammatory benzothiazine compounds.

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