Molecular Quantum Similarity-Based QSARs for Binding Affinities of Several Steroid Sets

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The application of Molecular Quantum Similarity Measures (MQSM) to correlate biological activities for three different sets of steroids is reported. A general protocol for the generation of descriptors is detailed, thus covering molecular superposition, electronic density fitting, and quantum similarity calculation issues. Satisfactory Quantitative Structure−Activity Relationship (QSAR) models ($r^2 \in [0.69,0.94]$ and $q^2 \in [0.59,0.73]$), comparable to previous studies, are obtained in all cases, where steroid binding affinities to different enzymes are studied. In this work, MQSM, properly scaled using Carbó Index, are related to activity using a Partial Least Squares routine.

INTRODUCTION

One of the most promising subjects in present day computational chemistry is the characterization and quantification of molecular properties and biological activities by means of structure-based descriptors, generated from theoretical development and computationally based methodologies. Given a molecular set and a relevant molecular property or biological activity, a quantitative structure−property or −activity relationship (QSPR/QSAR)[1,2] model can be constructed by derivation of molecular structure descriptors, which will be related to a molecular feature by some statistical procedure.

First started by Cross in 1863,[3] observing that toxicity of alcohols to mammals increased as water solubility of such alcohols decreased, QSPR/QSAR techniques have been largely developed using a large variety of parameters as descriptors of molecular structural characteristics. For example, Hammett sigma values[4] are often used as electronic parameters or the octanol/water partition coefficient[5] for lipophilicity description. Other frameworks have been devised to account for the shape, size, polarizability, and many other molecular structural features. In addition, the recent and fast development of computer architectures has increased the computational power to stages that allow the application of the quantum theory to regular organic molecules at fairly accurate computational levels (semiempirical or ab initio methods with appropriate basis sets) within reasonable time limits and affordable costs. A number of reviews have been published,[1,2,6] concerning the historical development, generation of descriptors, and different methodologies in the QSPR/QSAR fields.

Arising from the quantum point of view of a molecule and according to the postulate that its density function contains all accessible information contained within this molecule, Molecular Quantum Similarity Measures (MQSM)[7−13] stand as a general efficient tool to solve actual chemical problems. MQSM methodology has been successfully applied within pharmacological[14−19] and toxicological[20−22] problems. MQSM are based on the concept of molecular similarity[23,24] and are related to a self-evident molecular similarity principle: "the more similar two molecules are, the more similar properties will possess". This last statement requires a procedure to compare the molecules, and MQSM easily establish the degree of similarity based on the electronic distribution, namely first-order density functions (DF), of the molecular structures.

In this work, it is intended to use the MQSM methodology to correlate binding affinities of three sets of steroids, each related to a different enzyme, possessing diverse biological responses. For this purpose, this paper is structured as follows: a brief description of the proposed protocol is given first, next the presentation of the molecular sets as well as the results achieved are described, and the concluding remarks are finally given.

MATERIAL AND METHODS

MQSM and Carbó Indices. Up to date, the practical application of MQSM lays on the use of first-order density functions. These functions are quantum-mechanical observable elements producing information on the molecular electron distribution. Within this framework, two molecular structures are considered to be similar if their electron distributions are. Thus, among other possibilities,[9] quantitative measures of the similarity between two molecules can be defined as the direct volume integral between their density functions, expressed as

$$Z_{AB} = \int \int \rho_A(\mathbf{r}_1)\, \delta(\mathbf{r}_1 - \mathbf{r}_2) \rho_B(\mathbf{r}_2) d\mathbf{r}_1 d\mathbf{r}_2 \qquad (1)$$

where $\rho_A(\mathbf{r})$ and $\rho_B(\mathbf{r})$ are the first-order electron density functions of molecules *A* and *B*, respectively, $\delta(\mathbf{r}_1 - \mathbf{r}_2)$ is Dirac's Delta function, and Z_{AB} is the resulting quantum

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similarity measure, in this case known as *Overlap* similarity measure, which simplifies eq 1 to

$$Z_{AB} = \int \rho_A(\mathbf{r})\rho_B(\mathbf{r})d\mathbf{r} \tag{2}$$

As MQSM depend on the relative position of both compared objects in space, a molecular alignment procedure is required. When studied molecular sets share common structural features, like the four rings structure present in all steroids, Topo-Geometrical Superposition Algorithm (TGSA)[25] is used, as it performs pairwise superpositions according to the molecular backbone coincidence. Once superposed, the overall set of MQSM for a series of N molecules are computed and collected in the way of a ($N\times N$) similarity matrix form, which can be used to extract the appropriate correlation information and build QSPR/QSAR descriptors. Once the similarity matrix has been computed, a possible scaling of the MQSM can be done by means Carbó Index,[7] as in eq 3

$$C_{ij} = Z_{ij}(Z_{ii}Z_{jj})^{-1/2} \tag{3}$$

providing a weighted similarity measure inside the open interval (0,1]. Within this scope, the closest the value to unity, the higher is the degree of similarity between both analyzed molecules, and vice versa otherwise. A singular case consists of $C_{ij} = 1$, indicating that both molecular structures are the same.

Promolecular Atomic Shell Approximation (ASA). To avoid expensive theoretical calculations, the promolecular atomic shell approximation (ASA)[27−29] has been used here to construct molecular first-order electron density. Within ASA the molecular density is expressed as a sum of discrete atomic density contributions, which are taken as a superposition of 1*S* Gaussian functions and fitted to atomic ab initio ones. Once the overall atomic densities are built, each molecular density function can be constructed by adding as appropriate these elementary atomic building blocks. Since it has been proved that the MQSM from fitted densities built in this way differ by up to a 2% from the ab initio ones,[28] their use is clearly justified.

Molecular Alignment. MQSM are dependent on the relative position of the molecules under comparison. In this way, the Topo-Geometrical Approach (TGSA)[25] has been used to perform the needed pairwise molecular alignments. This molecular superposition method overlays the involved molecules, considered as rigid bodies, according to the maximal common substructure shared by the analyzed compounds. As an illustrative example of TGSA results, a pairwise superposition between two steroids (both compounds of the first studied molecular set) is presented in Figure 1.

Molecular Modeling. All molecules have been sketched and cleaned using Weblab Viewer 4.0.[30] The geometry optimization of the resulting structures has been carried out in gas phase with Mopac 6.0[31] software package at the AM1[32] computational level. Molecular electronic DF has been constructed using the ASA approach, as described above, using parameters fitted to Huzinaga basis set.[29]

Treatment of Quantum Similarity Matrices and Model Building. Common chemometric tools may be applied to deal with similarity matrices. Particularly, Partial Least Squares (PLS)[33,34] stands as an ideal technique to obtain a generalized regression to model the association between the matrices **X** (descriptors) and **Y** (responses). In computational chemistry, its main use is to model the relationship between computed variables, which together characterize the structural variation of a set of N compounds and any property of interest measured on those N substances.[35−37] This variation of the molecular skeleton is condensed into the matrix **X**, whereas the analyzed properties are recorded into **Y**. In PLS, the matrix **X** is commonly built up from nonindependent data, as it uses to have more columns than rows; hence it is not called the *independent* matrix but predictor or descriptor matrix. A good review as well as its practical application in QSAR is found in ref 38 and a detailed tutorial in ref 39.

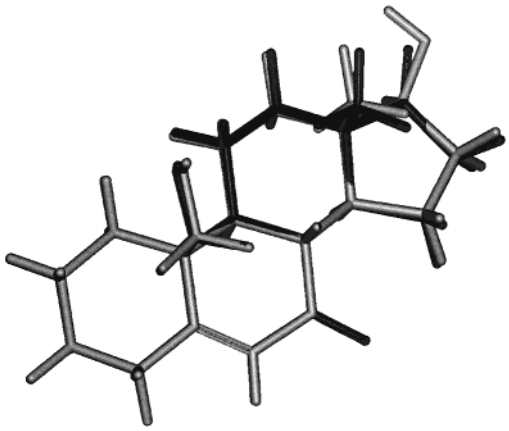


Figure 1. Pairwise superposition of two steroids according to the TGSA superposition procedure.

Unlike regression, PLS is not based on the assumption of independent and precise **X** variables, but it is rather based on the more realistic assumption that **X** contains more or less collinear and noisy parameters. PLS summarizes these **X** variables by means of a few orthogonal score vectors ($\boldsymbol{t}_a \in \mathbf{T}$), and the matrix **Y** is also resumed in few score vectors ($\boldsymbol{u}_a \in \mathbf{U}$) which are not orthogonal. Plots of columns from **T** and **U** provide visual representation of the configuration of the observations in the **X** or **Y** spaces, respectively. The PLS procedure allows to derive a number of *factors* and *weights*, which are used to describe the desired properties. QSPR models are built up from these factors and weights.

In this work, all obtained models are evaluated by commonly used statistical parameters: goodness-on fit (r^2),[40] root-mean-square error between experimental and predicted values (s)[40] by *leave-one-out*[41] and predictive capacity (q^2).[40] In addition and in order to avoid chance correlations and excess of parameters, models are submitted to random tests, where the properties are randomly permuted in their positions and the entire modeling procedure is repeated a number of times, a thousand in our case. If satisfactory correlations are found within the random test, the model obtained should not be trusted, as the methodology used may be potentially capable to correlate any kind of data.

RESULTS AND DISCUSSION

In this section, it is intended to prove the usefulness of the proposed procedure with three molecular sets constituted by steroids, where in each case the associated biological response is related to the binding activity of the involved

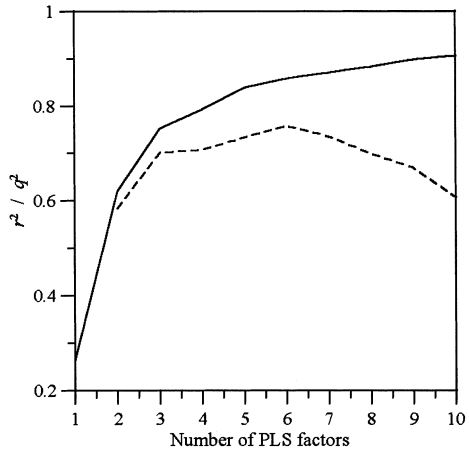


Figure 2. Evolution of r^2 (continuous line) and q^2 (dashed line) versus the number of PLS factors involved in the construction of the QSAR model for a set of 50 steroids.[42]

molecules to an enzyme. The first example is composed by 50 steroids, and the studied activity is the binding affinity to aromatase enzyme.[42] The second example, built up from 93 6-azasteroids, the studied properties are related to both binding affinity to 5α-reductase (type I) and 3β-hydroxy-Δ^5-steroid dehydrogenase/3-keto-Δ^5-steroid isomerase (3-BHSD), and selectivity to bind to 3-BHSD relative to 5α-reductase (type I).[43] The last steroid set is the widely studied Crammer's 31 steroid set, where the corticosteroid binding affinity is studied for such molecular series.[44,45]

Steroid Binding to Aromatase Enzyme. The importance of an aromatase enzyme, which consists of a cytochrome P450 complex that plays a role in the conversion of androgens to estrogens, lies on its implication on breast cancer.[46] Since this enzyme catalyzes the testosterone to estradiol, a typical estrogen, conversion, its activity is directly involved in the evolution and development of estrogen-dependent tumors, such as breast cancer.[46,47] Designing inhibitors of this enzyme may lead to therapeutically useful drugs able to control or avow the development of affected cells. For this purpose, a set of 50 steroids,[42] inhibitors of aromatase enzymes, with experimentally determined binding affinity have been studied with MQSM. All data regarding molecular structures and binding activity of the compounds are summarized in Table 1.

As stated in the methodological section, the PLS technique is used to create QSAR models for this molecular set from descriptors derived from quantum similarity measures. Models have been created up to 10 descriptors, and the optimal number of parameters to be used in the final model, which in this case it has been fixed to 5 PLS factors, has been chosen from the evolution of both correlation (r^2) and predictivity (q^2), as presented in Figure 2.

As observed in Figure 2, a sharp increase in the predictive capacity occurs up to the third PLS factor, and a slow increase until the sixth one. A further increase in the number of parameters results, in despite of the expected increase of r^2, in a decrease of the predictive power of the generated model. In this way, the chosen number of PLS factors used was 5, as the results provide the optimal balance between predictivity and descriptors applied, and a further increase does not lead to noticeable improved results and could lead to overfitted models. Thus, the final equation and statistical

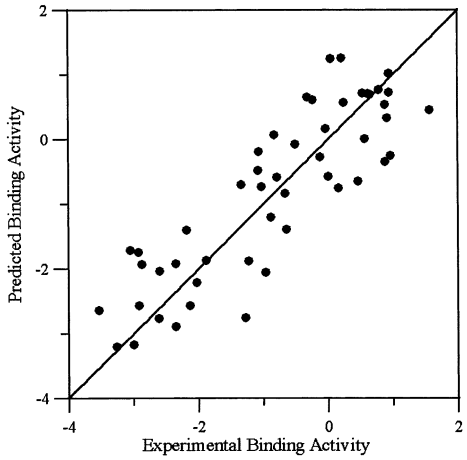


Figure 3. Experimental versus predicted binding activity for a set of 50 steroids.

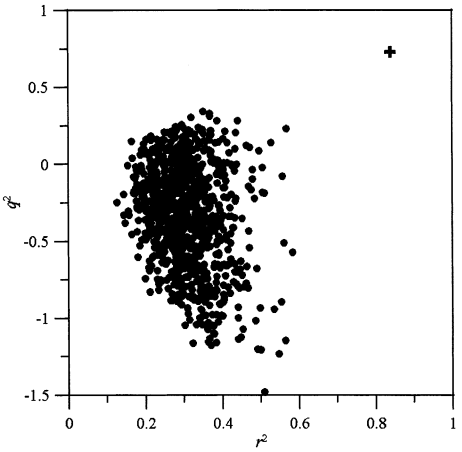


Figure 4. Random test results after permuting the binding activity values for a set of 50 steroids 1000 times. The real value is labeled with a cross.

results for this molecular set are

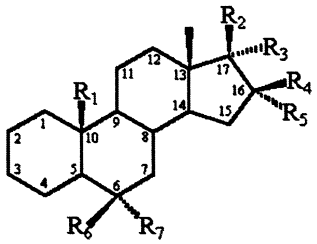
$$\text{binding activity} = 0.132\cdot\mathbf{f}_1 + 6.141\cdot\mathbf{f}_2 + 6.440\cdot\mathbf{f}_3 + 4.510\cdot\mathbf{f}_4 + 6.721\cdot\mathbf{f}_5$$

$$r^2 = 0.839 \qquad q^2 = 0.734 \qquad s = 0.710$$

The results are also graphically presented by plotting the experimental binding activities, versus the predicted ones from the PLS procedure, as shown in Figure 3. In addition, the random test was carried out permuting 1000 times the activity values and reconstructing the QSAR model each time. The results are graphically compiled in Figure 4, where each point represents the values of r^2 and q^2 achieved in each permutation.

As seen from the statistical and graphical results, satisfactory results are obtained for this molecular set. Most of the compounds are correctly predicted, within a close margin, even a few deviations are present, as displayed in Figure 3. The random test shows a clear separation between the original point (+) and the permuted ones (●). The results of the previously published work[42] are comparable, yielding to a range of results $r^2 \in [0.73,1.0]$ and $q^2 \in [0.66,0.75]$, using from 5 to 87 parameters based on ^{13}C spectrometric data.

Table 1. Structures and Binding Activities to Aromatase for a Set of 50 Steroids[42]

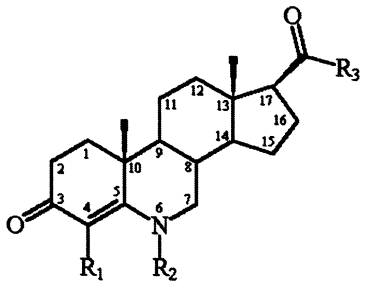


no.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	=O in 3	=O in 7	other	activity
1	CH_2OH	=O		H	H	H		no	yes	Δ^5	−2.92
2	CH_2OH	OH	H	H	H	H		no	yes	Δ^5	−3.54
3	CHO	=O		H	H	H		no	yes	Δ^5	−3.00
4	H	=O		H	H	H		no	yes	Δ^5	−3.26
5	CH_3	OH	H	H	H	H		no	yes	Δ^5	−2.62
6	CH_2OH	=O		H	H	H		no	yes	Δ^3, Δ^5	−3.06
7	CHO	=O		H	H	H		no	yes	Δ^3, Δ^5	−2.14
8	H	=O		H	H	H		no	yes	Δ^3, Δ^5	−2.36
9	CH_2OH	=O		H	H	H		no	no	Δ^5	−1.89
10	CH_2OH	OH	H	H	H	H		no	no	Δ^5	−2.88
11	CHO	=O		H	H	H		no	no	Δ^5	−2.03
12	CH_3	=O		H	H	H		no	no	Δ^5	−0.97
13	CH_3	=O		H	Br	H		no	no	Δ^5	−2.93
14	CH_3	=O		H	H	H		no	yes	Δ^5	−1.28
15	CH_3	=O		H	H	H		no	yes	Δ^3, Δ^5	−1.23
16	CH_3	OH	H	H	H	H		no	yes	Δ^3, Δ^5	−2.61
17	CH_3	OH	H	H	H	H		no	no	Δ^5	−2.36
18	CH_3	=O		H	H	H		no	no	Δ^3, Δ^5	−0.65
19	CH_3	OH	H	H	H	H		no	no	Δ^3, Δ^5	−2.19
20	H	=O		H	H	H	H	yes	no	Δ^4	−1.03
21	CH_3	=O		H	H	H	H	no	no	Δ^4	0.00
22	CH_2OH	=O		H	H	H	H	no	no	Δ^4	0.46
23	CH_2OH	=O		H	H	H	H	yes	no	Δ^4	−0.84
24	CH_3	=O		H	H	=O		yes	no	Δ^4	0.15
25	CH_3	=O		H	H	see other		yes	no	Δ^4, 6,7-α-CF_2	−0.13
26	CH_3	=O		H	H	see other		no	no	Δ^4, 6,7-α-CH_2	0.87
27	CH_3	OH	H	H	H	see other		no	no	Δ^4, 6,7-α-CH_2	−0.51
28	CH_3	OH	H	H	H	H	H	no	no	Δ^4	−1.35
29	CH_2OH	OH	H	H	H	H	H	no	no	Δ^4	−0.67
30	$CH_2OC(O)CH_3$	=O		H	H	H	H	no	no	Δ^4	−0.89
31	CH_3	=O		H	Br	H	H	no	no	Δ^4	−0.79
32	CH_3	=O		H	H	H	H	no	no	Δ^4	−1.09
33	CF_3	=O		H	H	H	H	no	no	Δ^4	−1.08
34	CH_3	=O		H	H	CH_3	H	yes	no	Δ^4	0.56
35	CH_3	=O		H	H	H	CH_3	yes	no	Δ^4	0.87
35	CH_3	=O		H	H	CH_2CH_3	H	yes	no	Δ^4	1.56
37	CH_3	=O		H	H	H	CH_2CH_3	yes	no	Δ^4	0.94
38	CH_3	=O		H	H	$(CH_2)_2CH_3$	H	yes	no	Δ^4	0.94
39	CH_3	=O		H	H	H	$(CH_2)_2CH_3$	yes	no	Δ^4	0.78
40	CH_3	=O		H	H	$(CH_2)_3CH_3$	H	yes	no	Δ^4	0.65
41	CH_3	=O		H	H	H	$(CH_2)_3CH_3$	yes	no	Δ^4	0.53
42	CH_3	=O		H	H	$CH(CH_3)_2$	H	yes	no	Δ^4	0.21
43	CH_3	=O		H	H	H	$CH(CH_3)_2$	yes	no	Δ^4	0.04
44	CH_3	=O		H	H	C_6H_5	H	yes	no	Δ^4	−0.04
45	CH_3	=O		H	H	H	C_6H_5	yes	no	Δ^4	0.24
46	CH_3	=O		H	H	$CH_2C_6H_5$	H	yes	no	Δ^4	−0.24
47	CH_3	=O		H	H	H	$CH_2C_6H_5$	yes	no	Δ^4	0.61
48	CH_3	=O		H	H	$CH{=}CH_2$	H	yes	no	Δ^4	0.91
49	CH_3	=O		H	H	H	$CH{=}CH_2$	yes	no	Δ^4	−0.32
50	CH_3	=O		H	H	$=CHCH_3$		yes	no	Δ^4	0.96

Steroid Binding and Selectivity to 5α-Reductase. 5α-Reductase is responsible for the biological conversion of testosterone into androgen dihydrotestosterone (DHT). Since DHT is related to increased body hair, hair line recession, prostatic enlargement, and, at high concentration levels, DHT is also associated with several disorders, like prostatic cancer, male baldness, and acne, several investigations have pointed their attention to 5α-reductase,[48−62] due to the fact that it has been detected at higher levels in those affected areas. Therefore, inhibition of this enzyme becomes a faithful therapeutically efficient treatment for disorders caused by high levels of DHT. Also, it has been proved that, for an optimal treatment, inhibition rate should be complemented with selectivity to other enzymes.[60,61] In this way, ideal inhibitors should possess low binding affinity to 5α -reductase and a high one to 3-BHSD.

For this molecular set, composed of 93 azasteroids, two QSAR models have been developed to correlate the two relevant properties: the necessary nanomolar concentration to inhibit a sample of 5α-reductase (expressed as log K_i)[43]

Table 2. Structures, Binding Affinities (log K_i) to 5α-Reductase, and Selectivities (log S_i) to 3-BHSD[43]



no.	R_1	R_2	R_3	other	log K_i	log S_i
1	H	H	NH_2		2.38	−1.38
2	H	H	2-$C(CH_3)_3$−Ph-NH		1.43	0.50
3	H	H	5-Cl,2-$C(CH_3)_3$−Ph-NH		0.88	2.01
4	H	H	5-Br,2-$C(CH_3)_3$−Ph-NH		0.62	2.29
5	H	H	4-Br,2-$C(CH_3)_3$−Ph-NH		0.72	1.87
6	H	H	2,5-bis($C(CH_3)_3$)-Ph-NH		0.70	2.00
7	H	H	2-$C(CH_3)_3$,5-Ph-Ph-NH		0.66	2.26
8	H	H	2-$C(CH_3)_3$,5-CF_3−Ph-NH		0.94	2.26
9	H	H	2-$C(CH_3)_3$,5-(4-Cl−Ph)-Ph-NH		0.53	2.55
10	H	H	2-$C(CH_3)_3$,5-(4-$C(CH_3)_3$−Ph)-Ph-NH		0.11	3.84
11	H	H	2,5-bis(CF_3)-Ph-NH		0.60	1.88
12	H	H	2-(4-$C(CH_3)_3$−Ph),5-CF_3−Ph-NH		3.04	−1.76
13	H	H	3,5-bis(CF_3)-Ph-NH		1.41	0.35
14	H	H	3,5-bis($C(CH_3)_3$)-Ph-NH		0.90	−0.01
15	H	H	4-Cl−Ph-$C(CH_2)_4$−NH		0.83	2.37
16	H	H	4-Cl−Ph-$C(CH_2)_5$−NH		0.49	2.76
17	H	H	2,4-di-Cl−Ph-$C(CH_2)_2$−NH		0.83	1.29
18	H	H	4-$C(CH_3)_3$−Ph-$C(CH_2)_4$−NH		0.48	2.70
19	H	H	4-$C(CH_3)_3$−Ph-$C(CH_2)_5$−NH		0.18	3.17
20	H	H	4-$C(CH_3)_3$−Ph-$C(CH_2)_6$−NH		0.56	2.62
21	CH_3	H	2-$C(CH_3)_3$,5-CF_3−Ph-NH		−0.30	2.60
22	Cl	H	2-$C(CH_3)_3$,5-CF_3−Ph-NH		−0.22	2.79
23	CH_3	H	2,5-bis(CF_3)-Ph-NH		−0.70	1.98
24	Cl	H	2,5-bis(CF_3)-Ph-NH		−0.70	2.98
25	CH_3	H	(1-(4-Cl−Ph)c-pentyl)NH		−0.52	2.73
26	Cl	H	(1-(4-Cl−Ph)c-pentyl)NH		−0.22	2.91
27	H	H	$N(CH_2CH_3)_2$		2.88	−1.10
28	H	H	$N(CH_2CH_3)_2$	Δ^1	3.76	−1.86
29	H	H	$N(CH_2CH_3)_2$	1,2-α-CH_2	4.15	−2.17
30	H	H	$N(CH_2CH_3)_2$	2-α,β-CH_3	3.54	−0.84
31	H	$COCH_3$	$N(CH_2CH_3)_2$		4.60	−0.07
32	H	CN	$N(CH_2CH_3)_2$		3.92	−0.74
33	H	CH_2CO_2H	$N(CH_2CH_3)_2$		4.00	−1.74
34	H	CH_3	$N(CH_2CH_3)_2$		2.26	−1.70
35	H	CH_2CH_3	$N(CH_2CH_3)_2$		3.11	−1.42
36	H	$CH_2CH_2CH_3$	$N(CH_2CH_3)_2$		4.38	−1.66
37	H	i-Pr	$N(CH_2CH_3)_2$		3.53	−0.49
38	H	$(CH_2)_3CH_3$	$N(CH_2CH_3)_2$		3.89	−0.34
39	H	$(CH_2)_5CH_3$	$N(CH_2CH_3)_2$		3.77	0.27
40	H	CH_2Ph	$N(CH_2CH_3)_2$		4.00	0.20
41	H	CH_3	$N(CH_2CH_3)_2$	Δ^1	3.11	−1.77
42	H	CH_3	$N(CH_2CH_3)_2$		4.00	−3.00
43	Cl	H	$N(CH_2CH_3)_2$		1.71	−0.28
44	Br	H	$N(CH_2CH_3)_2$		1.99	−0.87
45	I	H	$N(CH_2CH_3)_2$		2.84	−1.66
46	$CH_2N(CH_3)_2$	H	$N(CH_2CH_3)_2$		4.00	−0.92
47	CH_3	H	$N(CH_2CH_3)_2$		1.60	−0.35
48	CH_3	H	$N(CH_2CH_3)_2$	Δ^1	2.45	−0.49
49	CH_2CH_3	H	$N(CH_2CH_3)_2$		3.61	−1.94
50	CH_3	CH_3	$N(CH_2CH_3)_2$		1.91	−0.87
51	H	H	$NHC(CH_3)_3$		2.91	−0.74
52	H	H	$NHC(CH_3)_3$	Δ^1	3.38	−0.04
53	H	H	$NHC(CH_3)_3$	1,2-α-CH_2	4.69	−2.21
54	H	CH_3	$NHC(CH_3)_3$		1.94	−1.12
55	H	CH_3	$NHC(CH_3)_3$		3.15	−1.35
56	CH_3	H	$NHC(CH_3)_3$		1.08	−0.12
57	CH_3	CH_3	$NHC(CH_3)_3$		1.78	−0.42
58	H	H	i-But		0.95	0.05
59	H	CH_3	i-But		0.49	−0.45
60	Br	H	i-But		0.51	−0.14
61	CH_3	H	i-But		−0.40	0.48

Table 2 (Continued)

no.	R_1	R_2	R_3	other	log K_i	log S_i
62	H	H	NH-1-Ad		1.04	0.85
63	H	H	NH-1-Ad	Δ^1	1.87	1.13
64	H	CH_3	NH-1-Ad		0.93	−0.50
65	H	CH_3	NH-1-Ad	Δ^1	2.45	−0.65
66	Br	H	NH-1-Ad		0.65	0.46
67	CH_3	H	NH-1-Ad		0.04	0.91
68	Br	CH_3	NH-1-Ad		0.93	−0.02
69	CH_3	CH_3	NH-1-Ad		0.79	0.46
70	H	H	$NHCHPh_2$		1.48	0.70
71	H	H	$NHCHPh_2$	Δ^1	0.68	1.31
72	H	CH_3	$NHCHPh_2$		0.81	0.24
73	H	$(CH_2)_2CH_3$	$NHCHPh_2$	Δ^1	2.53	−0.28
74	CH_3	H	$NHCHPh_2$		0.56	0.70
75	H	H	OCH_3		2.18	−1.10
76	H	H	O-2-Ad		0.84	1.42
77	H	H	$N(CH_3)OCH_3$		3.36	−1.66
78	H	H	piperazine		3.93	−1.59
79	H	H	morpholine		3.34	−1.06
80	H	H	thiomorpholine		2.76	−1.26
81	H	H	piperidine		1.93	0.11
82	H	H	$NHCH(4\text{-}F{-}Ph)_2$		1.30	1.20
83	H	H	$NHCH(4\text{-}Cl{-}Ph)_2$		1.30	1.41
84	H	H	$NHNPh_2$		1.15	1.06
85	H	H	$N(OH)C(CH_3)_3$		1.58	0.21
86	H	H	$NHCH(c\text{-}Hex)_2$		1.30	2.30
87	H	H	$NHCPh_3$		0.91	1.09
88	H	H	$(CH_2)_2CH_3$		1.08	−0.04
89	H	H	$(CH_2)_7CH_3$		0.00	0.88
90	H	H	CH_2-c-Hex		0.60	0.60
91	H	H	2,6-difluorophenyl		1.59	−0.55
92	H	H	1-naphthyl		1.18	−0.28
93	H	H	2,4,6-triisopropylphenyl		2.45	0.83

and the ability to selectively inhibit 5α-reductase relative to 3-BHSD, denoted as S_i, which is the ratio of K_i for 3-BHSD and K_i for 5α-reductase (expressed as log S_i).[43] All data for this molecular set are summarized in Table 2.

Following the previous exposed protocol, the optimal QSAR models are fixed to five PLS factors, whose results are presented below for log K_i

$$\log K_i = 0.221\cdot\mathbf{f}_1 + 2.351\cdot\mathbf{f}_2 + 3.829\cdot\mathbf{f}_3 + 2.367\cdot\mathbf{f}_4 + 2.747\cdot\mathbf{f}_5$$

$$r^2 = 0.688 \qquad q^2 = 0.594 \qquad s = 0.888$$

and log S_i

$$\log S_i = 0.034\cdot\mathbf{f}_1 + 2.982\cdot\mathbf{f}_2 + 3.719\cdot\mathbf{f}_3 + 2.353\cdot\mathbf{f}_4 + 2.179\cdot\mathbf{f}_5$$

$$r^2 = 0.699 \qquad q^2 = 0.600 \qquad s = 0.959$$

As seen from the statistical results, acceptable relationships with valuable predictive capacity are obtained. These predictive capacities can be visually observed in Figures 5 and 6, where experimental versus predicted values are represented for log K_i and log S_i, respectively.

As seen in Figures 5 and 6, accurate predictions are obtained for both activities for most of the compounds present in the set. Even if a few deviations are present, the proposed model can still be used for classification or discriminant analysis, allowing to order the compounds by discrete ranges of predicted activity. Also, satisfactory results arise from the random test, where after 1000 permutations were carried out. In the log K_i case, the highest values of r^2 and q^2 were 0.406 and 0.236, whereas the mean values were 0.205 and −0.211, respectively. When analyzing log S_i, the maximum values were 0.373 and 0.245, and the mean values were 0.203 and −0.232, respectively. Since both activities are quite correlated, $r^2 = 0.612$, it is not a coincidence that the statistical results as well as the slopes of the proposed models become similar. The previous study[43] also obtained similar results when using simple statistical tools, like linear regression, PLS or PCR, to correlate the activities, selecting a small set of optimal descriptors from a bunch of 224 parameters (topological, geometric, electronic, and hybrid ones). However, the usage of neural networks considerably improved the results, yielding to high predicitive capacity.

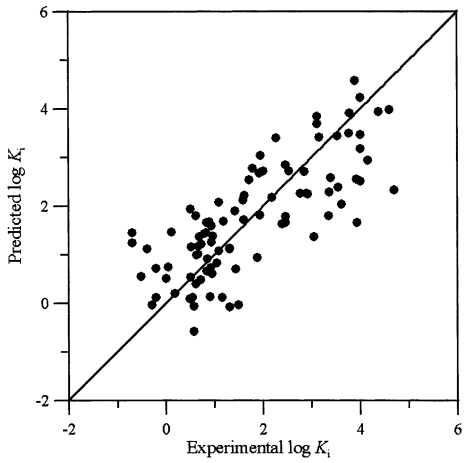


Figure 5. Experimental versus predicted log K_i for a set of 93 azasteroids.

Steroid Binding Affinity to Corticosteroid Binding Globulin. The importance of corticosteroids rests on their

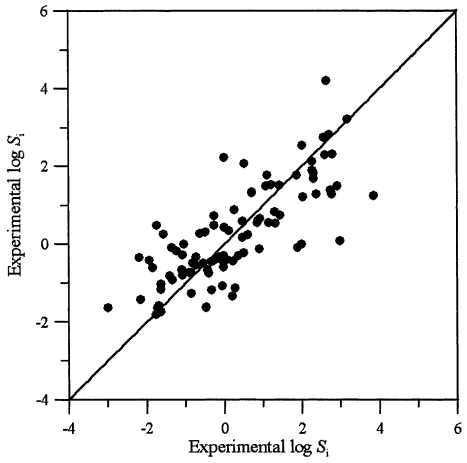


Figure 6. Experimental versus predicted log S_i for a set of 93 azasteroids.

role played in human physiology. Depending on the side group of the binding enzyme, its action ranges from nutrient metabolism regulation to electrolyte balance. In addition, and properly activated, several therapeutical applications have been found, such as treatments for rheumatoid arthritis, allergies, Crohn's disease, uveitis, or minimization of the complications associated with premature births.[63−67] Consequently, many research efforts[16,18,44,45,68] have been devoted to obtain significant models for these kinds of compounds.

The exposed protocol is applied to this molecular set composed by 31 steroids, whose binding affinity is expressed in terms of p*K*. All data regarding the structures is summarized in Table 3. The optimal QSAR model using MQSM is composed of four PLS factors, whose results are presented below:

$$pK = 1.237 \cdot \mathbf{f}_1 + 4.795 \cdot \mathbf{f}_2 + 5.255 \cdot \mathbf{f}_3 + 5.591 \cdot \mathbf{f}_4$$

$$r^2 = 0.751 \qquad q^2 = 0.654 \qquad s = 0.636$$

As seen from the previous statistical results, a satisfactory QSAR model is found with a remarkable predictive capacity, as judged from the q^2 value achieved. A clearer picture of the obtained results can be seen by browsing Figure 7, where the experimental p*K* are plotted versus the predicted ones. As seen in Figure 7, most of the compounds are correctly predicted, except for four ones, which are overestimated, one being the 31st structure (fluorine-substituted), which is commonly overpredicted.[16,18,44,45,68] The random test is satisfactorily overcome, yielding to mean values of 0.281 and −0.322 for r^2 and q^2, respectively, whereas the maximum values were 0.596 and 0.326 after 1000 permutations of the p*K* data.

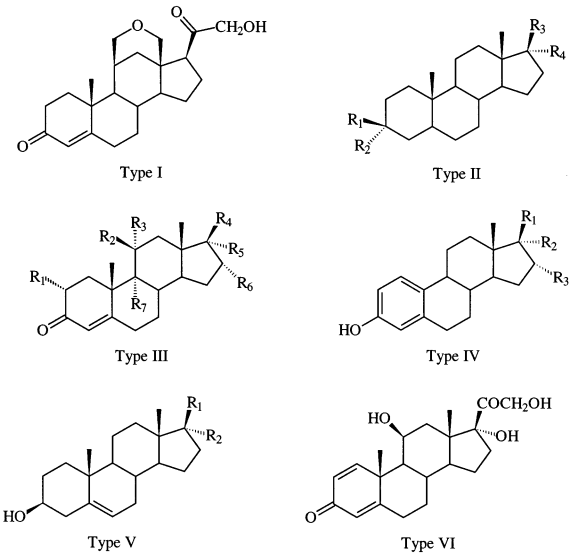
According to literature,[18,45] the obtained results with the proposed model are within the range covered by previous works, where a variety of both molecular descriptor generation and numerical data treatment were used.

CONCLUSIONS

A general protocol for the QSAR model generation for steroids using Molecular Quantum Similarity Measures has been presented, where different molecular activities related to binding activity of these compounds to different enzymes have been tested for correlation search. In all three application examples, satisfactory correlations were obtained using a relative small number of molecular descriptors.

Even if other methodologies may provide better results, it must be emphasized that the procedure used along this work as well as the generation of molecular descriptors has been kept untouched. In other words, the exposed QSAR protocol consists of a methodological pathway made of unbiased and universal MQSM descriptors able to characterize different molecular activities for steroids without introducing further information than those provided by quantum similarity based on electronic density functions. Additional refinements or statistical tools may be applied to the procedure in order to improve the results according to each

Table 3. Structures and Binding Affinities to Corticosteroid Binding Globulin for a Set of 31 Steroids[44,45]



no.	type	R_1	R_2	R_3	R_4	R_5	R_6	R_7	p*K*
1	I								6.279
2	II	OH	H	OH	H				5.000
3	V	OH	H						5.000
4	III	H	H	H		=O	H	H	5.763
5	II	H	OH		=O				5.613
6	III	H	OH	H	$COCH_2OH$	H	H	H	7.881
7	III	H	OH	H	$COCH_2OH$	OH	H	H	7.881
8	III	H	=O		$COCH_2OH$	OH	H	H	6.892
9	V	=O							5.000
10	III	H	H	H	$COCH_2OH$	H	H	H	7.653
11	III	H	H	H	$COCH_2OH$	OH	H	H	7.881
12	II	=O		OH	H				5.919
13	IV	OH	H	H					5.000
14	IV	OH	H	OH					5.000
15	IV	=O	H						5.000
16	II	OH	H	=O					5.225
17	V	$COCH_3$	H						5.225
18	V	$COCH_3$	OH						5.000
19	III	H	H	H	$COCH_3$	H	H	H	7.380
20	III	H	H	H	$COCH_3$	OH	H	H	7.740
21	III	H	H	H	OH	H	H	H	6.724
22	VI								7.512
23	III	H	OH	H	$COCH_2OCOCH_3$	OH	H	H	7.553
24	III	H	=O		$COCH_3$	H	H	H	6.779
25	III	H	H	OH	$COCH_2OH$	H	H	H	7.200
26	III	H	H	H	OH	H	H	H	6.144
27	III	H	H	H	$COCH_3$	OH	OH	H	6.247
28	III	H	H	H	$COCH_3$	H	CH_3	H	7.120
29	III	H	H	H	$COCH_3$	H	H	H	6.817
30	III	CH_3	OH	H	$COCH_2OH$	OH	H	H	7.688
31	III	CH_3	OH	H	$COCH_2OH$	OH	H	F	5.797

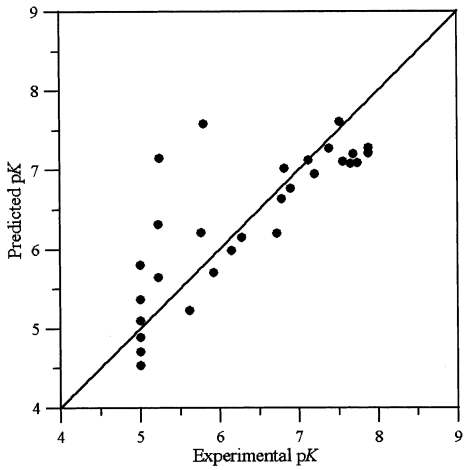


Figure 7. Experimental versus predicted p*K* for a set of 31 steroids.

molecular set under study; however, the exposed protocol may constitute an excellent starting point for subsequent research.

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