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Atom-based 3D-chiral quadratic indices. Part 3: prediction of the binding affinity of the stereoisomers of fenoterol to the β_2 adrenergic receptor

Juan A. Castillo-Garit,[a,b,c,d*] Ramón García-Domenech,[a] Yovani Marrero-Ponce,[d] Francisco Torrens[e] and Concepción Abad,[b]

[a]Unidad de Investigación de Diseño de Fármacos y Conectividad Molecular, Departamento de Química Física, Facultad de Farmacia, Universitat de València, València, Spain. [b]Departament de Bioquímica i Biologia Molecular, Universitat de València, E-46100 Burjassot, Spain. [c]Applied Chemistry Research Center. Universidad Central "Marta Abreu" de Las Villas, Santa Clara, 54830, Villa Clara, Cuba [d]Unit of Computer-Aided Molecular "Biosilico" Discovery and Bioinformatic Research (CAMD-BIR Unit), Faculty of Chemistry-Pharmacy. Universidad Central "Marta Abreu" de Las Villas, Santa Clara, 54830, Villa Clara, Cuba eInstitut Universitari de Ciència Molecular, Universitat de València, Edifici d'Instituts de Paterna, P. O. Box 22085, 46071 Valencia, Spain

Índices cuadráticos 3D-quirales basados en átomos. Parte 3: predicción de la afinidad de unión de estereoisómeros del fenoterol al receptor adrenérgico β_2.

Índex quadràtics 3D-quirals basats en atoms. Part 3: Predicció de l' afinitat d'unió d'estereoisòmers del fenoterol al receptor adrenèrgic β_2.

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RESUMEN

Los índices cuadráticos tridimensionales (3D)-quirales no-estocásticos y estocásticos basados en relaciones de átomos son aplicados para predecir la afinidad de unión de 26 estereoisómeros del fenoterol con el receptor adrenérgico β_2 (β_2-AR). La predicción de la afinidad de unión al β_2-AR de los estereoisómeros se realizó mediante le empleo de la regresión lineal múltiple. Dos modelos QSAR estadísticamente significativos son obtenidos cuando los índices 3D-quirales no-estocásticos (R^2 = 0.941 y s = 0.19) y estocásticos (R^2 = 0.947 y s = 0.18) son empleados. Ambos modelos mostraron un adecuado poder predictivo (evaluado por el procedimiento de validación cruzada *dejando-uno-fuera*), alcanzando valores de q^2 = 0.909 (s_{cv} = 0.219) y q^2 = 0.917 (s_{cv} = 0.208), respectivamente. Estos modelos fueron superiores a otro modelo 3D-QSAR obtenido previamente por otros investigadores empleando el método CoMFA (R^2 = 0.920, q^2 = 0.847 y s_{cv} = 0.309). Los resultados de nuestro trabajo demuestran la utilidad de nuestros descriptores topológicos para la predicción de la actividad biológica, incluso en los estudios en los cuales la configuración tridimensional de los compuestos juega un papel importante en la actividad biológica.

Palabras Claves: índices cuadráticos 3D-quirales no-estocásticos y estocásticos basados en relaciones de átomos, receptor adrenérgico-β_2, afinidad de unión, estereoisómeros del fenoterol, 3D-QSAR.

SUMMARY

The non-stochastic and stochastic atom-based three dimensional (3D)-chiral quadratic indices are applied to predict the binding affinities of 26 stereoisomers of fenoterol with the β_2-adrenoceptor (β_2-AR). The prediction of β_2-AR binding affinities of the stereoisomers is carried out by multiple linear regression analysis. Two statistically significant QSAR models are obtained when non-stochastic (R^2 = 0.941 and s = 0.19) and stochastic (R^2 = 0.947 and s = 0.18) 3D-chiral quadratic indices are used. These models show adequate predictive power (assessed by the leave-one-out cross-validation experiment), yielding values of q^2 = 0.909 (s_{cv} = 0.219) and q^2 = 0.917 (s_{cv} = 0.208), respectively. These models compare favorably with a 3D-QSAR equation obtained with the CoMFA method (R^2 = 0.920, q^2 = 0.847 and s_{cv} = 0.309). The results of our work demonstrate the usefulness of our topological approach for the prediction of biological activity, even in those studies in which the three-dimensional configuration of the chemicals play an important role in the bioactivity.

Keywords: non-stochastic and stochastic atom-based 3D-chiral quadratic indices, β_2-adrenoceptor, binding affinity, fenoterol stereoisomer, 3D-QSAR.

*Corresponding author:
Fax: 34.963543274; Phone: 34625033303;
jacgarit@yahoo.es or juancg.22@gmail.com

RESUM

Els índexs quadràtics tridimensionals (3D)-quirals no-estocàstics i estocàstics basats en relacions d'àtoms són aplicats per predir l'afinitat d'unió de 26 estereoisòmers del fenoterol amb el receptor adrenèrgic β_2 (β_2-AR). La predicció de l'afinitat d'unió a l'β_2-AR dels estereoisòmers es va realitzar mitjançant l'ús de la regressió lineal múltiple. Quan s'utilitzen els índexs 3D-quirals no-estocàstics (R^2 = 0941 i *s* = 0,19) i estocàstics (R^2 = 0947 i *s* = 0,18) s'obtenen dos models QSAR estadísticament significatius. Tots dos models van mostrar un poder predictiu adequat (avaluat pel procediment de validació creuada deixant-un-fora), assolint valors de q^2 = 0909 (S_{CV}= 0,219) i q^2 = 0917 (S_{CV} = 0,208), respectivament. Aquests models van ser superiors a un altre model 3D-QSAR obtingut prèviament per altres investigadors utilitzant el mètode COMFER (R^2 = 0.920, q^2 = 0847 i S_{CV}= 0,309). Els resultats del nostre treball demostren la utilitat dels nostres descriptors topològics per a la predicció de l'activitat biològica, fins i tot en els estudis en els quals la configuració tridimensional dels compostos juga un paper important en l'activitat biológica.

Paraules clau: índexs quadràtics 3D-quirals no-estocàstics i estocàstics basats en relacions d'àtoms, receptor adrenèrgic-β_2, afinitat d'unió, estereoisòmers del fenoterol, 3D-QSAR

INTRODUCTION

Fenoterol,5-[1-hydroxy-2-[[2-(4-hydroxyphenyl)-1-methylethyl]-amino]ethyl]-1,3-benzenediol, is a β_2-adrenoceptor (β_2-AR) agonist[1] that is used for the treatment of asthma[2] and may also be useful in the treatment of congestive heart failure.[3] This has been suggested by results from studies in cardiomyocytes from an animal model of congestive heart failure, the spontaneously hypertensive rat.[3, 4]

Fenoterol shows two chiral centers and exists as four stereoisomers. The clinically used drug, rac-fenoterol, is a racemic mixture of the (*R,R*) and (*S,S*) isomers of compound **1** (see Fig. 1).[5] In 1978, Kaiser and co-workers performed initial displacement binding studies using the separate enantiomers, in rat erythrocytes.[6] The data demonstrated that (*R,R*)-**1** displaced the marker ligand [^{3}H]-dihydroalprenolol with a K_d of 2.88x10^{-6} M, *rac*-**1** had a K_d of 5.79x10^{-5}M, and (*S,S*)-**1** had no measurable specific binding.[6] In a recent study Beigi *et al*. confirm the enantioselectivity of the β_2-AR; they also examined the pharmacological effects of (*R,R*)-**1** and (*S,S*)-**1** using cardiomyocyte contractility in freshly isolated adult rat cardiomyocytes.[7] In this model, (*R,R*)-**1** increased the maximum contractile response from (265±11.6%) to (306±11.8%) of resting cell length ($p < 0.05$) and reduced EC_{50} from (-7.0±0.27) to (-7.1±0.20) log [M] ($p < 0.05$), while (*S,S*)-**1** had no significant effect.

Moreover, another study was carried out recently by Jozwiak and co-workers.[5] They synthesized and characterized a series of derivatives of **1** (compounds **2**-**7** in Figure 1), to determine the effect of altering the 4-hydroxyphenyl moiety and of the removing of the second chiral center. Furthermore, they developed a QSAR model using comparative molecular field analysis (CoMFA). In this work, the authors concluded that the *R*-configuration is favored for functional activity at β-AR receptors, which is consistent with previous models and experimental data.[8-11] In this significant research, effort was made to find models of the relationship between the structure of β-adrenergic agonist and their binding affinities. Such models could assist researchers in understanding the structural basis for binding, as well as in providing a basis for the development of new compounds with β_2-AR selectivity, which could be tested for their use in the treatment of congestive heart failure.

Topological indices (TIs) have been extensively used in the past in drug design studies and in the modeling of many properties/activities. For example Bonchev *et al*. used TIs to model anticancer action in some works[12, 13] and Galvez *et al*. made use of TIs to select and design new active compounds in different therapeutical scopes, with a rather high efficiency level.[14, 15] Others studies were also performed to identify and design compounds with antimicrobial[16] and non-narcotic analgesic[17] action.

In recent times, a novel scheme in the rational –in silico- molecular design and to in QSAR/QSPR has been introduced by our research group TOMOCOMD (acronym of TOpological MOlecular COMputer Design). It calculates several new families of 2D, 3D-Chiral (2.5) and 3D (geometric and topographical) non-stochastic and stochastic atom- and bond-based molecular descriptors, based on algebraic theory and discrete mathematics. They are denoted quadratic, linear and bilinear indices and have been defined in analogy to the corresponding mathematical maps.[18-20] These approaches describe changes in the electron distribution with time throughout the molecular backbone, and they have been successfully employed in the prediction of several physical, physicochemical, chemical, biological, toxicological and pharmacokinetic properties of organic compounds.[21-27] Besides, these indices have been extended to consider three-dimensional features of small/medium-sized molecules based on the *trigonometric 3D-chirality correction factor approach*.[28-33] In earlier publications, we have obtained rather promising results when stochastic and non-stochastic atom-based 3D-chiral quadratic, linear and bilinear indices were applied to three of the chiral datasets most commonly used.[28-33] Taking into account the promissory results obtained with the atom-based 3D-chiral quadratic indices,[29, 30] the present report is written with two objectives in mind. First, to develop QSAR models, using the non-stochastic and stochastic atom-based 3D-chiral quadratic indices, in order to predict the binding affinities of the fenoterol stereoisomers with the β_2-AR receptor and, second, to compare our results with those previously obtained by other researchers using the CoMFA method.[5]

MATERIALS AND METHODS

The atom-based non-stochastic and stochastic quadratic indices has been explained elsewhere in some detail,[20, 29, 30] however here we are going to give a brief explanation about it. If a molecule consists of n atoms (*vector of* $\Re^n$), then the k^{th} total (whole) quadratic indices are calculated as quadratic forms on $\Re^n$ in a canonical basis set. Specifically, the k^{th} non-stochastic and stochastic atom-based quadratic indices for a molecule, $q_k(\bar{x})$ and ${}^s q_k(\bar{x})$, respectively, are computed from the following equations:

$$q_k(\bar{x}) = \sum_{i=1}^{n} \sum_{j=1}^{n} {}^k m_{ij} x_i x_j = [X]^t \mathbf{M}^k [X] \qquad (1)$$

$$ {}^{s}q_k(\bar{x}) = \sum_{i=1}^{n} \sum_{j=1}^{n} {}^{k}s_{ij}\, x_i x_j = [\mathrm{X}]^t \mathbf{S}^k [\mathrm{X}] \qquad (2) $$

where, n is the number of atoms of the molecule, and x_1 ,…,x_n are the coordinates or components of the "molecular vector" ($\bar{x}$) in a canonical ('natural') basis set of $\Re^n$. In this basis set, the coordinates of any vector $\bar{x}$, namely x_1,…,x_n, coincide with the components of this vector.[34, 35] Therefore, those coordinates can be considered as weights (atomic labels) of the vertices in the molecular pseudograph. The coefficients ${}^{k}m_{ij}$ and ${}^{k}s_{ij}$ are the elements of the k^{th} power of the matrices $\mathbf{M}(\mathrm{G})$ and $\mathbf{S}(\mathrm{G})$, correspondingly, in the molecular pseudograph.[20, 29, 30]

In addition to total quadratic indices, computed for the whole molecule, a local-fragment (atomic and atom type as well as group) formalism can be developed. These descriptors are termed local non-stochastic and stochastic quadratic indices, $q_{kL}(x)$ and ${}^{s}q_{kL}(x)$, correspondingly.[20, 29, 30] The definition of these descriptors is as follows:

$$ q_{kL}(\bar{x}) = \sum_{i=1}^{n} \sum_{j=1}^{n} {}^{k}m_{ijL}\, x_i x_j = [\mathrm{X}]^t \mathbf{M}^k{}_L [\mathrm{X}] \qquad (3) $$

$$ {}^{s}q_{kL}(\bar{x}) = \sum_{i=1}^{n} \sum_{j=1}^{n} {}^{k}s_{ijL}\, x_i x_j = [\mathrm{X}]^t \mathbf{S}^k{}_L [\mathrm{X}] \qquad (4) $$

where *n* is the number of atoms (atomic nuclei) in the fragment of interest and ${}^{k}m_{ijL}$ $[{}^{k}s_{ijL}]$ is the k^{th} element of the row "*i*" and column "*j*" of the local matrix $\mathbf{M}^k{}_L$ $[\mathbf{S}^k{}_L]$. This matrix is extracted from the $\mathbf{M}^k$ $[\mathbf{S}^k]$ matrix and contains information referred to the vertices (atomic nuclei) of the specific molecular fragments and also of the molecular environment in k steps. The matrix $\mathbf{M}^k{}_L$ $[\mathbf{S}^k{}_L]$ with elements ${}^{k}m_{ijL}$ $[{}^{k}\mathbf{s}_{ijL}]$ is defined as follows:

${}^{k}m_{ijL}$ $[{}^{k}\mathbf{s}_{ijL}]$ = ${}^{k}m_{ij}$ $[{}^{k}\mathbf{s}_{ijL}]$ if both v_i and v_j are atoms contained within the molecular fragment

= ${}^{1}/_{2}$ ${}^{k}m_{ij}$ $[{}^{k}s_{ijL}]$ if either v_i or v_j is an atom contained within the molecular fragment

= 0 otherwise

Moreover, the atom-type quadratic indices can also be calculated as local MDs. In the atom-type quadratic indices formalism, each atom in the molecule is classified into an atom type (fragment), such as –F, -OH, =O, -CH3, and so on. These local MDs can be calculated for a chemical (or functional) group in the molecule, such as heteroatoms (O, N and S in all valence states and including the number of attached H atoms), hydrogen bonding (H-bonding) to heteroatoms (O, N and S in all valence states), halogen atoms (F, Cl, Br and I), all aliphatic carbon chains (several atom types), all aromatic atoms (aromatic rings), and so on.[20, 29, 30]

Furthermore, due to that the total and local, non-stochastic and stochastic quadratic indices, as defined above, cannot codify any information about 3D molecular structure. In order to solve this problem we introduced a trigonometric 3D-chirality correction factor in the molecular vector $\bar{x}$, in previous works.29, 30 In these sense, a chirality molecular vector is obtained ($^{*}\bar{x}$), where the components of $\bar{x}$ (for instance, Mulliken electronegativity (xA) of the atom A) are substituted by the following term $\{x_A + \sin[(\omega_A + 4\Delta)\pi/2)]\}$. The trigonometric 3D-chirality correction factor uses a dummy variable, ω_A and an integer parameter, Δ:[28, 30]

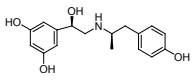
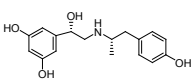
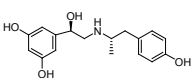
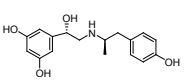
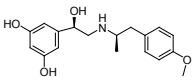
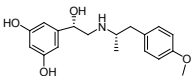
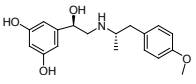
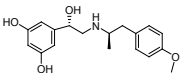
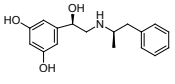
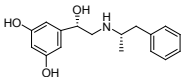
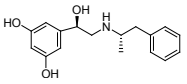
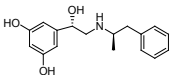
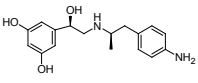
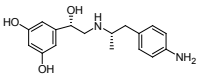
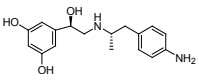
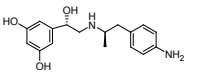
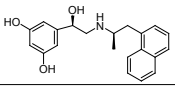
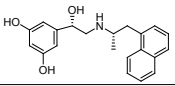
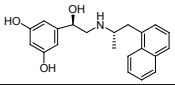
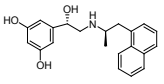
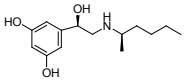
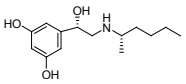
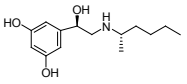
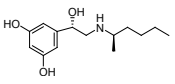
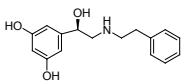
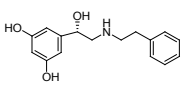
Compound	Stereoisomer			
	R,R	S,S	R,S	S,R
1				
2				
3				
4				
5				
6				
7				

Figure 1. *The structures of the stereoisomers of Fenoterol and compounds 2-7 synthesized and tested by Jozwiak et al.*[5]

ω_A = 1 and Δ is an odd number when A has R (rectus), E (entgegen), or a (axial) notation according to the Cahn-Ingold-Prelog (IUPAC) rules *(5)*
= 0, and Δ is an even number, if A does not have 3D specific enviroment,
= -1, and Δ is an odd number when A has S (sinister),Z (zusammen), or e (equatorial) notation according to Cahn-Ingold- Prelog rules.

Thus, this 3D-chirality factor $\sin[(\omega_A+4\Delta)\pi/2]$ takes different values in order to codify specific stereochemical information such as chirality, Z/E isomerism, and so on. This factor takes, therefore, values in the following order 1 > 0 > -1 for atoms that have specific 3D environments. A very interesting point is that the present 3D-chiral descriptor reduces to simple (2D) non-stochastic and stochastic quadratic indices, for molecules without specific 3D characteristics because $\sin[(0+4\Delta)\pi/2] = 0$, being Δ zero or any integer (particularly even) number. Therefore, when all the atoms in the molecule are not chiral, these chiral MDs do not change upon the introduction of this factor. This means that ${}^{*}\bar{x} = \bar{x}$ and, thus, ${}^{*}\boldsymbol{q}_k(\bar{x}) = \boldsymbol{q}_k(\bar{x})$.[28, 30]

On the other hand, the structures of the molecular set used in this study are depicted in Figure 1. This molecular dataset was recently introduced by Jozwiak and co-workers;[5] the respective binding affinities were also determined by these authors. The molecular structure of each compound was codified using the non-stochastic and stochastic atom-based 3D-chiral quadratic indices.[29, 30] In the present report, we characterized every atomic nucleus with the following parameters (weighting scheme): atomic mass (M), atomic polarizability (P), atomic Mulliken electronegativity (K), van der Waals atomic volume (V), plus the atomic electronegativity in Pauling scale (G).[36-39]

The following descriptors were calculated in this work:

(i) k^{th} total 3D-chiral quadratic indices, not considering and considering H atoms in the molecular pseudograph (G) [${}^{*}\boldsymbol{q}_k(x)$ and ${}^{*}\boldsymbol{q}_k{}^{\text{H}}(x)$, respectively].

(ii) k^{th} local (atom-type = heteroatoms: S, N, O) 3D-chiral quadratic indices, not considering and considering H atoms in the molecular pseudograph (G) [${}^{*}\boldsymbol{q}_{k\text{L}}(x_{\text{E}})$ and ${}^{*}\boldsymbol{q}_{k\text{L}}{}^{\text{H}}(x_{\text{E}})$, respectively]. These local descriptors are putative H-bonding acceptors.

(iii) k^{th} local (atom type = H atoms bonding to heteroatoms: S, N, O) 3D-chiral quadratic indices, considering H atoms in the molecular pseudograph (G) [${}^{*}q_{kL}{}^{\text{H}}(x_{\text{E-H}})$]. These local descriptors are putative H-bonding donors.

The k^{th} stochastic total [${}^{\$}q_k(x)$ and ${}^{\$}q_k{}^{\text{H}}(x)$] and local H)] 3D-chiral quadratic indices were also computed. All these molecular descriptors were calculated with the TOMOCOMD-CARDD software.40

Statistical analysis was carried out with the STATISTICA software.41 A multiple linear regression (MLR) was carried out to predict the binding affinity of the fenoterol stereoisomers data set. The quality of the models was determined examining the regression's statistical parameters. Namely, the quality of the models was determined by examining the determination coefficients (also known as square regression coefficients, R^2), Fisher-ratio's p-level [p(F)] and standard deviation of the regression (s).42 An important aspect of QSAR modeling is the development of tools for the validation of the model. Good direct statistical criteria to fit the dataset are not a guarantee that the model could make accurate predictions. The leave-one-out (LOO) press statistics (q^2, s_{cv})[43] have been used as a means of demonstrating predictive capability.

RESULTS AND DISCUSSION

The purpose of this study was to develop quantitative models which permit the prediction of the binding affinities of the fenoterol stereoisomers derivatives with the β_2-AR receptor from the molecular structure by using a combinatorial approach of atom-based 3D-chiral quadratic indices and multiple linear regression method. The experimental binding affinities of the fenoterol stereoisomer derivatives were taken from Jozwiak *et al*,[5] and Table 1 summarize the entire studied set with the observed and predicted binding affinities. The obtained QSAR models are given below together with their statistical parameters:

$$\mathbf{p}\boldsymbol{K}_{\mathbf{i}} = 1.06(\pm0.41) + 2.19\text{x}10^{-5}(\pm0.18\text{x}10^{-5})\ {}^{*\text{M}}\boldsymbol{q}_9{}^{\text{H}}(x) - 1.14\text{x}10^{-5}(\pm0.10\text{x}10^{-5})\ {}^{*\text{M}}\boldsymbol{q}_{10}{}^{\text{H}}(x) + 1.78\text{x}10^{-6}(\pm0.16\text{x}10^{-6})\ {}^{*\text{P}}\boldsymbol{q}_{11}{}^{\text{H}}(x) - 2.11\text{x}10^{-3}(\pm0.55\text{x}10^{-3})\ {}^{*\text{V}}\boldsymbol{q}_{1\text{L}}(x_{\text{E-H}}) \qquad (6)$$

N = 26 R = 0.970 R^2 = 0.941 F(4,21) = 83.996

s = 0.19 p< 0.0001 q^2= 0.909 S_{cv} = 0.219

$$\mathbf{p}\boldsymbol{K}_{\mathbf{i}} = 6.73\text{x}10^{-2}(\pm0.50) + 0.8601(\pm0.16)\ {}^{*\text{Ms}}\boldsymbol{q}_{14\text{L}}(x_{\text{E}}) - 0.90(\pm0.16)\ {}^{*\text{Ps}}\boldsymbol{q}_{12\text{L}}{}^{\text{H}}(x_{\text{E}}) + 2.79(\pm0.51)\ {}^{*\text{Ps}}\boldsymbol{q}_{11}{}^{\text{H}}(x) - 2.71(\pm0.52)\ {}^{*\text{Ps}}\boldsymbol{q}_{12}{}^{\text{H}}(x) \qquad (7)$$

N = 26 R = 0.973 R^2 = 0.947 F(4,21) = 94.688

s = 0.18 p< 0.0001 q^2= 0.917 S_{cv} = 0.208

where N is the size of the data set, R^2 is the square correlation coefficient (determination coefficient), s is the standard deviation of the regression, F is the Fischer ratio and q^2 (S_{cv}) is the square correlation coefficient (standard deviation) of the cross-validation performed by the LOO procedure. These statistics indicate that these models are appropriate for the description of the chemicals studied here. As can be seen, both models were developed with only four variables and they are able to explain more than 94% of the variance of the experimental binding affinity values, with low values of standard deviation s = 0.19 and s = 0.18 for models **6** and **7**, correspondingly. On the other hand, the model previously obtained by Jozwiak *et al*.[5], using CoMFA, explains only 92% of the experimental data with s = 0.223. The predictability and stability of the obtained models (Eqs. **6** and **7**) to data variation was carried out here by means of LOO cross-validation.

These models showed a cross-validation square correlation coefficient of 0.909 (S_{cv} = 0.219) and 0.917 (S_{cv} = 0.208), respectively, while the CoMFA model showed a q^2 value of 0.847 (S_{cv} =0.309). Notice that the results obtained with the present QSAR method, non-stochastic and stochastic atom-based 3D-chiral quadratic indices compare favourably to those previously achieved with CoMFA. The enantioselective binding preference for β_2-ARs, with the R-configuration at the stereogenic center containing the β-OH moiety, has been established in previous reports.[8-11] Therefore, a comparison between the R,R-isomers could be an important topic (see Table 1). The result of this comparison showed that (R,R)-**5** had the highest

Table 1. *The pK_i predicted with non-stochastic and stochastic atom-based 3D-chiral quadratic indices*

Compound	Observeda	Predicted Non-stochasticb	Residual	Predicted Stochastic c	Residual
R,R-1	6.460	5.979	0.481	6.127	0.333
S,S-1	4.560	4.764	-0.204	4.784	-0.224
R,S-1	5.430	5.541	-0.111	5.380	0.050
S,R-1	4.990	4.971	0.019	5.052	-0.062
R,R-2	6.320	6.168	0.152	6.354	-0.034
S,S-2	4.800	4.955	-0.155	5.033	-0.233
R,S-2	5.710	5.733	-0.023	5.629	0.081
S,R-2	5.280	5.161	0.119	5.281	-0.001
R,R-3	5.530	5.652	-0.122	5.774	-0.244
S,S-3	4.540	4.442	0.098	4.496	0.044
R,S-3	5.100	5.219	-0.119	5.093	0.007
S,R-3	4.640	4.645	-0.005	4.697	-0.057
R,R-4	5.730	5.684	0.046	5.764	-0.034
S,S-4	4.540	4.465	0.075	4.435	0.105
R,S-4	5.220	5.242	-0.022	5.033	0.187
S,R-4	4.510	4.677	-0.167	4.690	-0.180
R,R-5	6.620	6.805	-0.185	6.787	-0.167
S,S-5	5.600	5.528	0.072	5.520	0.080
R,S-5	6.470	6.305	0.165	6.129	0.341
S,R-5	5.750	5.798	-0.048	5.745	0.005
R,R-6	5.030	5.082	-0.052	5.189	-0.159
S,S-6	4.250	3.920	0.330	4.062	0.188
R,S-6	4.500	4.676	-0.176	4.380	0.120
S,R-6	4.000	4.093	-0.093	4.061	-0.061
R-7	4.980	5.268	-0.288	5.223	-0.243
S-7	4.690	4.478	0.212	4.531	0.159

[a]Observed β_2-AR binding affinity values taken from ref. [5] [b]Predicted binding affinity values from Eq.6. [c]Predicted binding affinity values from Eq.7.

relative affinity of the tested compounds, followed by (R,R)**-2** stereoisomer; these values are slightly greater than the predicted value for the (R,R)**-1**, although in experimental assays the order was **5** >**1** > **2** for these isomers. These results are quite similar to those obtained by Jozwiak *et al*.[5] According with the predicted and experimental values, isomers 5 and 2 can be proposed as new lead-compounds to develop new drugs with agonist action in the $\beta 2$-ARs. Studies of chemical optimization of these compounds should be carried out in the future.

Furthermore, we can see that for all the cases the predicted values for isomers (R,S) were lower than for the isomers (R,R); so, we can say that a change of the chirality from R to S in the second chiral atom causes a decay of the affinity of the chemical for the receptor. These results for the prediction are in completely agreement with the experimental results achieved by other researchers.

CONCLUSIONS

The drugs with β_2-AR agonist action are used in the treatment of asthma, but they may also be useful in the treatment of congestive heart failure. Therefore, this *in silico* method has been applied to predict the binding affinities of the fenoterol stereoisomers with the β_2-AR receptor. In this work, it has been shown that non-stochastic and stochastic atom-based 3D-ciral quadratic indices are quite versatile and can be applied in 3D-QSAR studies; the QSAR models obtained with our approach compare favourably with the CoMFA method. Although these are only preliminary results and more studies are necessary to design new β_2-AR agonists, the present work demonstrates in a straightforward way how 3D-chiral quadratic indices can be used to predict the affinity of a given chemical with the β_2-adrenoceptor.

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BIBLIOGRAPHY

1. O'Donnell, S. R. Eur. J. Pharmacol. 1970, 12, 35.
2. Heel, R. C.; Brogden, R. N.; Speight, T. M.; Avery, G. S. Drugs 1978, 15, 3.
3. Xiao, R.-P.; Zhang, S.-J.; Chakir, K.; Avdonin, P.; Zhu, W.; Bond, R. A.; Balke, C. W.; Lakatta, E. G.; Cheng, H. Circulation 2003, 108, 1633.
4. Xiao, R. P.; Zhu, W.; Zheng, M.; Chakir, K.; Bond, R.; Lakatta, E. G.; Cheng, H. Trends Pharmacol. Sci. 2004, 25, 358.
5. Jozwiak, K.; Khalid, C.; Tanga, M. J.; Berzetei-Gurske, I.; Jimenez, L.; Kozocas, J. A.; Woo, A.; Zhu, W.; Xiao, R.-P.; Abernethy, D. R.; Wainer, I. W. J Med Chem 2007, 50, 2903.
6. Kaiser, G.; Wiemer, G.; Kremer, G.; Dietz, J.; Palm, D. Naunyn-Schmiedeberg's Arch. Pharmacol. 1978, 305, 41.
7. Beigi, F.; Bertucci, C.; Zhu, W.; Chakir, K.; Wainer, I. W.; Xiao, R.-P.; Abernethy, D. R. Chirality 2006, 18, 822.
8. Eimerl, S.; Schramm, M.; Lok, S.; Goodman, M.; Khan, M.; Melmon, K. Biochem. Pharmacol. 1987, 36, 3523.
9. Wieland, K.; Zuurmond, H. M.; Krasel, C.; Ijzerman, A. P.; Lohse, M. J. Proc. Nat. Acad. Sci. U.S.A. 1996, 93, 9276.
10. Kikkawa, H.; Isogaya, M.; Nagao, T.; Kurose, H. Mol. Pharmacol. 1998, 53, 128.
11. Zuurmond, H. M.; Hessling, J.; Blüml, K.; Lohse, M.; Ijzerman, A. P. Mol. Pharmacol. 1999, 56, 909.
12. Bonchev, D.; Mountain, C. F.; Seitz, W. A.; Balaban, A. T. J Med Chem 1993, 36, 1562.
13. Bonchev, D.; Seitz, W. A.; Mountain, C. F.; Balaban, A. T. J Med Chem 1994, 37, 2300.
14. Galvez, J.; Garcia-Domenech, R.; de Julian-Ortiz, J. V.; Soler, R. J Chem Inf Comput Sci 1995, 35, 272.
15. Galvez, J.; Garcia-Domenech, R.; De Julian-Ortiz, V.; Soler, R. J Chem Inf Comput Sci 1994, 34, 1198.
16. Garcia-Domenech, R.; de Julian-Ortiz, J. V. J Chem Inf Comput Sci 1998, 38, 445.
17. Garcia-March, F. J.; Garcia-Domenech, R.; Galvez, J.; Anton-Fos, G. M.; de Julian-Ortiz, J. V.; Giner-Pons, R.; Recio-Iglesias, M. C. J Pharm Pharmacol 1997, 49, 10.
18. Marrero-Ponce, Y.; Khan, M. T. H.; Casañola-Martín, G. M.; Ather, A.; Sultankhodzhaev, M. N.; García-Domenech, R.; Torrens, F.; Rotondo, R. J Comput Aided Mol Des 2007, 21, 167.
19. Marrero-Ponce, Y.; Castillo-Garit, J. A.; Torrens, F.; Romero-Zaldivar, V.; Castro, E. Molecules 2004, 9, 1100.
20. Marrero-Ponce, Y.; Castillo-Garit, J. A.; Olazabal, E.; Serrano, H. S.; Morales, A.; Castanedo, N.; Ibarra-Velarde, F.; Huesca-Guillen, A.; Jorge, E.; del Valle, A.; Torrens, F.; Castro, E. A. J. Comput. Aided Mol. Des. 2004, 18, 615.
21. Marrero-Ponce, Y.; Castillo-Garit, J. A.; Olazabal, E.; Serrano, H. S.; Morales, A.; Castanedo, N.; Ibarra-Velarde, F.; Huesca-Guillen, A.; Sanchez, A. M.; Torrens, F.; Castro, E. A. Bioorg Med Chem 2005, 13, 1005.
22. Marrero Ponce, Y.; Meneses-Marcel, A.; Castillo Garit, J. A.; Machado-Tugores, Y.; Escario, J. A.; Barrio, A. G.; Pereira, D. M.; Nogal-Ruiz, J. J.; Arán, V. J.; Martínez-Fernández, A. R.; Torrens, F.; Rotondo, R.; Ibarra-Velarde, F.; Alvarado, Y. J. Bioorg Med Chem 2006, 14, 6502.
23. Castillo Garit, J. A.; Martinez-Santiago, O.; Marrero Ponce, Y.; Casañola-Martin, G. M.; Torrens, F. Chem. Phys. Lett. 2008, 464, 107.
24. Castillo-Garit, J. A.; Marrero-Ponce, Y.; Escobar, J.; Torrens, F.; Rotondo, R. Chemosphere 2008, 73, 415
25. Castillo-Garit, J. A.; Marrero-Ponce, Y.; Torrens, F.; García-Domenech, R. J. Pharm. Sci. 2008, 97, 1946.
26. Castillo-Garit, J. A.; Vega, M. C.; Rolón, M.; Marrero-Ponce, Y.; Gómez-Barrio, A.; Escario, J. A.; Bello, A. A.; Montero, A.; Torrens, F.; Pérez-Giménez, F.; Arán, V. J.; Abad, C. Europ. J. Med. Chem. 2011, 46, 3324.
27. Castillo-Garit, J. A.; Vega, M. C.; Rolon, M.; Marrero-Ponce, Y.; Kouznetsov, V.; Torres, D. F.; Gómez-Barrio, A.; Alvarez, A.; Montero, A.; Torrens, F.; Pérez-Giménez, F. Eur. J. Pharm. Sci. 2010, 39, 30.
28. Marrero-Ponce, Y.; Castillo-Garit, J. A. J. Comput.-Aided Mol. Design 2005, 19, 369.
29. Marrero-Ponce, Y.; Díaz, H. G.; Romero, V.; Torrens, F.; Castro, E. A. Bioorg. Med. Chem. 2004, 12, 5331.
30. Castillo-Garit, J. A.; Marrero-Ponce, Y.; Torrens, F. Bioorg Med Chem 2006, 14, 2398.
31. Castillo-Garit, J. A.; Marrero-Ponce, Y.; Torrens, F.; Rotondo, R. J Mol Graph Model 2007, 26, 32.
32. Castillo-Garit, J. A.; Marrero-Ponce, Y.; Torrens, F.; García-Domenech, R.; Romero-Zaldivar, V. J. Comput. Chem. 2008, 29, 2500
33. Castillo-Garit, J. A.; Marrero-Ponce, Y.; Torrens, F.; García-Domenech, R.; Rodríguez-Borges, J. E. QSAR & Comb. Sci. 2009, 28, 1465.
34. Axler, S. Linear Algebra Done Right.; New York: Springer-Verlag, 1996.
35. Browder, A. Mathematical Analysis. An Introduction.; New York: Springer-Verlag, 1996.

36. Pauling, L. The Nature of Chemical Bond; Ithaca, NY: Cornell University Press, 1939.
37. Todeschini, R.; Gramatica, P. Persp. Drug Disc. Des 1998, 9-11, 355.
38. Consonni, V.; Todeschini, R.; Pavan, M. J Chem Inf Comput Sci 2002, 42, 682.
39. Kier L., B.; Hall, L., H. Molecular Connectivity in Structure–Activity Analysis; Letchworth, U. K: Research Studies Press, 1986.
40. Marrero-Ponce, Y.; Romero, V.: Central University of Las Villas., 2002.
41. STATISTICA version. 6.0 Statsoft, I.: Tulsa, 2004.
42. Belsey, D. A.; Kuh, E.; Welsch, R. E. Regression Diagnostics; New York: Wiley, 1980.
43. Wold, S.; Erikson, L. In Chemometric Methods in Molecular Design; van de Waterbeemd, H., Ed.; VCH Publishers: Weinheim, 1995, 309.