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Prediction of the Binding Affinity between Fenoterol Derivatives and the β_2-Adrenergic Receptor Using Atom-Based 3D-Chiral Linear Indices

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ABSTRACT

The non-stochastic and stochastic atom-based 3D-chiral quadratic indices were applied to the study of the β_2-adrenoceptor (β_2-AR) agonist effect (binding affinities) between a set of 26 stereoisomers of fenoterol, reported with this activity. Linear multiple regression analysis was carried out to predict the β_2-AR binding affinities of the stereoisomers. Two statistically significant QSAR models, able to describe more than the 92% of the variance of the experimental binding affinities, were obtained using non-stochastic (R^2 = 0.924 and s = 0.21) and stochastic (R^2 = 0.92 and s = 0.22) 3D-chiral linear indices, respectively. The predictability and stability (robustness) of the obtained models (assessed by the leave-one-out cross-validation experiment) yielded values of q^2 = 0.893 (s_{cv} = 0.237) and q^2 = 0.886 (s_{cv} = 0.245), respectively. The results obtained with our approach were slightly better than the results of a 3D-QSAR model, 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 drug discovery of new lead compounds, even in those studies in which the three-dimensional configuration of the chemicals play an important role in the biological activity.

KEYWORDS: *non-stochastic and stochastic atom-based 3D-chiral linear index, binding affinity, β_2-adrenoceptor, fenoterol stereoisomer, 3D-QSAR.*

RESUMEN

Los índices lineales 3D-quirales no-estocásticos y estocásticos basados en relaciones de átomos son aplicados al estudio del efecto agonista (afinidad de unión) sobre el receptor adrenérgico β_2 (β_2-AR) entre una serie de 26 estereoisómeros del fenoterol, a los cuales se les ha reportado esta actividad. Una regresión lineal múltiple es llevada a cabo para predecir la afinidad de unión β_2-AR de los estereoisómeros. Se obtienen dos modelos QSAR estadísticamente significativos, capaces de describir más del 92 % de la varianza experimental de las afinidades de unión, empleando los índices lineales 3D-quirales no-estocásticos (R^2 = 0.924 y s = 0.21) y estocásticos (R^2 = 0.92 y s = 0.22) respectivamente. El poder predictivo y la robustez de los modelos obtenidos (comprobados mediante una validación cruzada *dejando-uno-fuera*) alcanzan valores de q^2 = 0.893 (s_{cv} = 0.237) y q^2 = 0.886 (s_{cv} = 0.245), correspondientemente. Los resultados obtenidos con nuestro enfoque fueron ligeramente superiores a aquellos resultados obtenidos previamente con un modelo 3D-QSAR, 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 nuestro enfoque topológico para el descubrimiento de nuevos compuestos líderes candidatos a fármacos, incluso para estudios en los cuales las conformaciones tridimensionales de los compuestos juegan un rol fundamental en la actividad biológica.

PALABRAS CLAVE: *Aíndice lineal 3D-quiral no-estocástico y estocástico basado en relación de átomos, afinidad de unión, receptor adrenérgico β_2, estereoisómero del fenoterol, 3D-QSAR.*

INTRODUCTION

G-protein-coupled receptors (GPCRs) comprise a superfamily of proteins that play a key role in signal transduction in many cells; they are implicated in control or regulation of a wide array of biological functions. Thus, these receptors are important therapeutic targets in a variety of disease states. The structural basis of GPCR activation by agonists has been the focus of much experimental research and has inspired the generation of numerous kinetic and molecular models (Furse and Lybrand, 2003; Kobilka, 2004). The β-adrenoceptors (β-ARs) are prototypical G-protein-coupled receptor (GPCRs) coupled to the classic Gs–adenylyl cyclase–cAMP–protein kinase A signalling pathway, resulting in the phosphorylation of an array of proteins involved in metabolic regulation, growth control, muscle contraction and cell survival or death. In the heart, β-adrenoceptor stimulation provides the most powerful mechanisms to augment cardiac contractility in response to a 'fight-or-flight' situation (Xiao et al., 2004).

On the other hand, chronic heart failure (CHF), which is caused by varied aetiologies, is characterized by high levels of circulating catecholamines, a concurrent reduction in β- adrenoceptors density, and desensitization of the remaining β-ARs, causing a markedly blunted β-adrenoceptor-mediated contractile response (Xiao et al., 2004). Several studies, carried out some years ago, demonstrated that coexisting cardiac β-AR subtypes, mainly β_1-adrenoceptors and β_2-adrenoceptors, activate different signalling pathways and fulfil strikingly distinct, sometimes even opposing, physiological and pathological roles in the heart. Particularly interesting are the opposing roles of β_1- and β_2-ARs in the regulation of cardiomyocyte survival and death (Xiao et al., 2004; Rohrer et al., 1999; Chesley et al., 2000; Zhu et al., 2001). These studies demonstrated that the stimulation of β_1-adrenoceptors leads to cardiac apoptosis, whereas the stimulation of β_2-adrenoceptors protects cardiac myocytes against a wide range of apoptotic insults, including enhanced β_1-adrenoceptor signalling, hypoxia and reactive oxygen species. Furthermore, other studies have also established that selective β_2-adrenoceptors activation *in vivo* is cardio-protective, whereas β_1-adrenoceptors activation is cardiotoxic (Patterson et al., 2004).

In a recent report, Liapakis *et al.* have provided new mechanistic insight with an elegantly simple set of studies, on a well-characterized experimental system, the β_2-AR (Liapakis et al., 2004). Therefore, fenoterol, 5-[1-hydroxy-2-[[2-(4-hydroxyphenyl)-1-methylethyl]-amino]ethyl]-1,3-benzenediol, is a β_2-adrenoceptor agonist (O'Donnell, 1970), which is used for the treatment of asthma (Heel et al., 1978) and may also be useful in the treatment of congestive heart failure (Xiao et al., 2003). This has been suggested by the results from studies in cardiomyocytes from an animal model of congestive heart failure, i.e., the spontaneously hypertensive rat (Xiao et al., 2003; Xiao et al., 2004). Fenoterol contains two chiral centres and exists as four stereoisomers. The clinically used drug, rac-Fenoterol, is a racemic mixture of the isomers (*R,R*) and (*S,S*) of compound **1** (see Fig. 1). A rather recent study has been carried out by Jozwiak *et al*. in which they synthesized and characterized a series of derivatives of compound **1** (compounds **2**-**7** in Figure 1), in order to determine the effect of altering the 4-hydroxyphenyl moiety and the removing of the second chiral centre (Jozwiak et al., 2007). In addition, they developed a QSAR model using comparative molecular field analysis (CoMFA), in order to predict the respective binding affinities of the stereoisomers derived from fenoterol. In that work, the authors concluded that the *R*-configuration is favoured for functional activity at β-AR receptors, which is consistent with previous models and experimental data (Eimerl et al., 1987; Wieland et al., 1996; Kikkawa et al., 1998; Zuurmond et al., 1999). In this significant research effort, there is a need to find models of the relationship between the structures of β-adrenergic agonists and their binding affinities. Such models can assist researchers in understanding the structural basis for binding, as well as in providing a foundation for the development of new compounds with β_2-AR selectivity, which can be tested with regard to their use in the treatment of congestive heart failure.

Recently, a novel scheme to the rational –*in silico*- molecular design and to QSAR/QSPR has been introduced by our research group: ***TOMOCOMD*** (acronym of ***TO***pological ***MO***lecular ***COM***puter ***D***esign). 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 by analogy with quadratic, linear and bilinear mathematical maps (Marrero-Ponce, 2003; Marrero-Ponce, 2004; Marrero-Ponce and Torrens, 2006; Casanola-Martin et al., 2007; Marrero-Ponce et al., 2007). 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 and pharmacokinetic properties of organic compounds (Marrero-Ponce et al., 2006; Marrero-Ponce et al., 2005c; Marrero-Ponce et al., 2005b; Marrero-Ponce et al., 2005a; Montero-Torres et al., 2005; Montero-Torres et al., 2006; Casañola-Martin et al., 2006; Castillo-Garit et al., 2008; Marrero Ponce et al., 2006). 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* (Marrero-Ponce and Castillo-Garit, 2005; Marrero-Ponce et al., 2004; Castillo-Garit et al., 2006; Castillo-Garit et al., 2007). In recent studies we obtained rather

promising results when stochastic and non-stochastic atom-based 3D-chiral quadratic, linear and bilinear indices were applied to three of the most commonly used chiral data-sets (Marrero-Ponce and Castillo-Garit, 2005; Marrero-Ponce et al., 2004; Castillo-Garit et al., 2006; Castillo-Garit et al., 2007). Taking into account these results, 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 linear indices, in order to predict the binding affinities of the fenoterol-derivative stereoisomers with the β_2-AR receptor and, second, to compare with the results previously reported by other researchers using the CoMFA method (Jozwiak et al., 2007).

COMPUTATIONAL AND EXPERIMENTAL PROCEDURES

Computational Strategies

Molecular fingerprints were generated by using the 'in house' TOMOCOMD software (Marrero-Ponce and Romero, 2002). It is an interactive program for molecular design and bioinformatics research consisting of four subprograms: CARDD (Computed-Aided Rational Drug Design), CAMPS (Computed-Aided Modelling in Protein Science), CANAR (Computed-Aided Nucleic Acid Research), and CABPD (Computed-Aided Bio-Polymers Docking). Every one of them allows both drawing the structures (drawing mode) and calculating molecular 2D/3D descriptors (calculation mode). In the present report, we outline salient features concerned with only one of these subprograms, CARDD, and with the calculation of non-stochastic and stochastic atom-based linear indices, considering and not considering H-atoms in the molecular pseudograph (G). The non-stochastic and stochastic atom-based 3D-chiral linear indices have been explained in some detail in the literature (Marrero-Ponce and Castillo-Garit, 2005).

The main steps, for the application of the present method in QSAR/QSPR and drug design, can be summarized briefly in the following algorithm:

1. Draw the molecular structure for each molecule in the data-set, by using the software drawing mode. This procedure is performed by a selection of the active atomic symbol in the corresponding group of the periodic table of the elements;

2. Use appropriate weights in order to differentiate the atoms in the molecule. The weights used in this study are those previously proposed for the calculation of the DRAGON descriptors (Todeschini and Gramatica, 1998; Consonni et al., 2002; Kier L. and Hall, 1986), i.e., atomic mass (M), atomic polarizability (P), van der Waals atomic volume (V), Mulliken electronegativity (K) plus the atomic electronegativity in Pauling scale (G). The values of these atomic labels are shown in Table 1 (Pauling, 1939; Todeschini and Gramatica, 1998; Consonni et al., 2002; Kier L. and Hall, 1986).

3. Compute the total and local (atomic, group and atom-type) non-stochastic and stochastic linear indices. This can be carried out in the software calculation mode, where one can select the atomic properties and the descriptor family before calculating the molecular indices. This software generates a table in which the rows correspond to the compounds, and columns correspond to the atom-based 3D-chiral linear maps or other Molecular Descriptor (MD) family implemented in this program;

Table 1. Values of the Atomic Weights Used for ***TOMOCOMD-CARDD*** MDs (Pauling, 1939; Kier L. and Hall, 1986; Todeschini and Gramatica, 1998; Consonni et al., 2002).

ID	Atomic Mass (g/mol)	VdW[a] Volume (Å^3)	Polarizability (Å^3)	Mulliken Electronegativity	Pauling Electronegativity
H	1.01	6.709	0.667	2.592	2.20
B	10.81	17.875	3.030	2.275	2.04
C	12.01	22.449	1.760	2.746	2.55
N	14.01	15.599	1.100	3.194	3.04
O	16.00	11.494	0.802	3.654	3.44
F	19.00	9.203	0.557	4.000	3.98
S	32.07	24.429	2.900	2.957	2.58
Cl	35.45	23.228	2.180	3.475	3.16
Br	79.90	31.059	3.050	3.219	2.96
I	126.90	38.792	5.350	2.778	2.66

[a] VdW: van der Waals

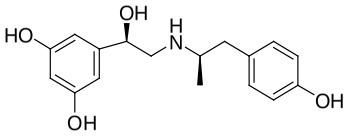
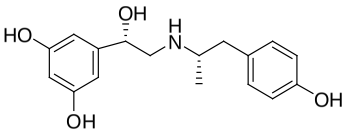
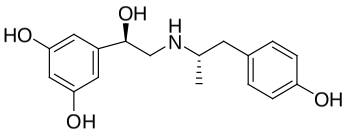
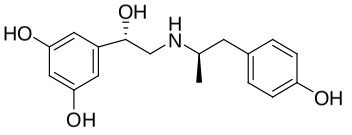
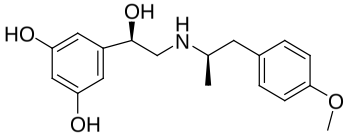
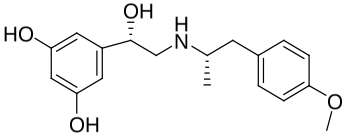
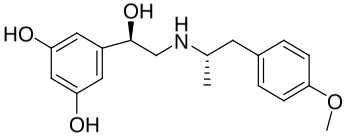
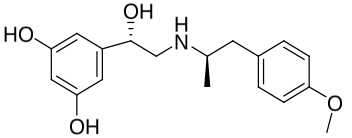
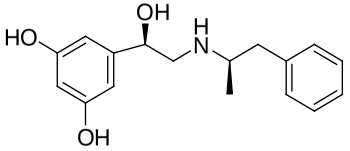
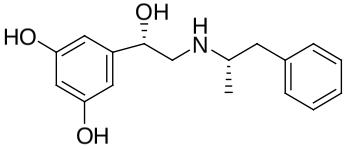
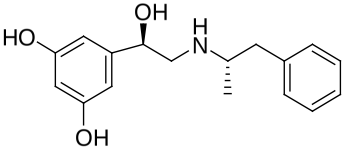
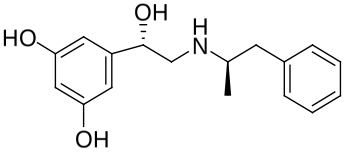
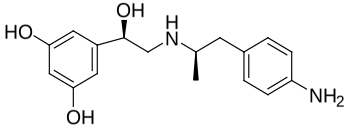
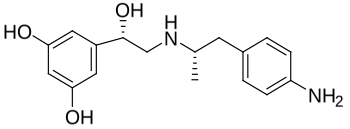
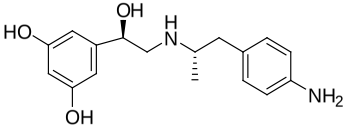
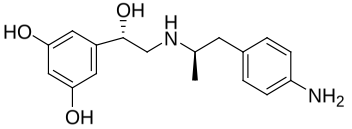
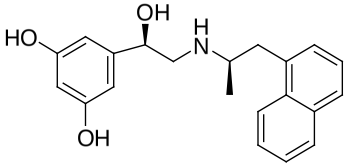
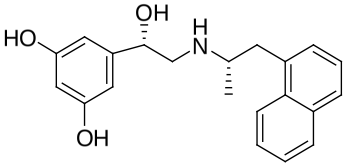
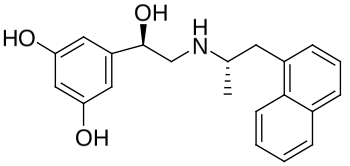
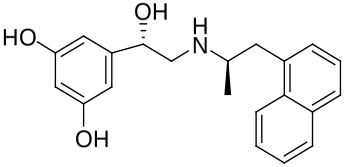
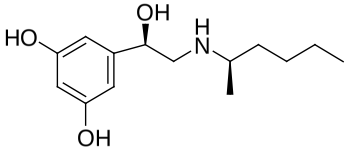
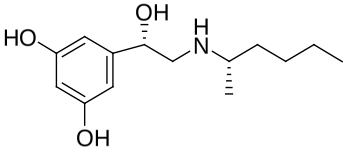
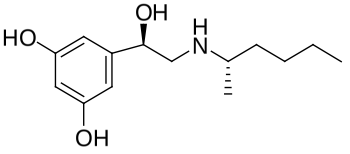
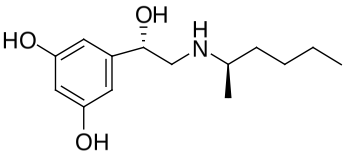
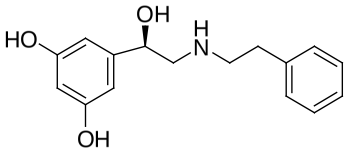
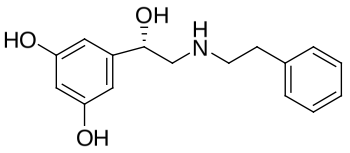
Compound	Stereoisomer			
	R,R	*S,S*	*R,S*	*S,R*
1				
2				
3				
4				
5				
6				
7				

Figure 1. The structures of the stereoisomers of Fenoterol and compounds 2-7 synthesized and tested by Jozwiak *et al.* (Jozwiak et al. 2007)

4. Find a QSPR/QSAR equation by using several multivariate analytical techniques, such as multilinear regression analysis (MRA), neural networks, linear discrimination analysis, and so on. Therefore, one can find a quantitative relation between a property P and the linear fingerprints having, for instance, the following appearance,

$$\boldsymbol{P} = a_0\boldsymbol{f}_0(x) + a_1\boldsymbol{f}_1(x) + a_2\boldsymbol{f}_2(x) + \ldots + a_k\boldsymbol{f}_k(x) + c \quad (\mathbf{1})$$

where P is the measure of the property, $f_k(x)$ is the kth total linear index and the a_k's and c are the fitting coefficients obtained by MRA.

5. Test the robustness and predictive power of the QSPR/QSAR equation, by using internal (cross-validation) and external validation techniques.

The descriptors calculated in this work were the following:

i) ${}^*\boldsymbol{f}_k(x)$ and ${}^*\boldsymbol{f}_k^{H}(x)$ are the k^{th} non-stochastic atom-based 3D-chiral total linear indices, considering and not considering H-atoms, respectively, in the molecule.

ii) ${}^*\boldsymbol{f}_{kL}(x_E)$ and ${}^*\boldsymbol{f}_{kL}{}^{H}(x_E)$ are the k^{th} non-stochastic atom-based 3D-chiral local (atom-type = heteroatoms: S, N, O) linear indices, considering and not considering H-atoms, respectively, in the molecule.

iii) ${}^*\boldsymbol{f}_{kL}{}^{H}(x_{E\text{-}H})$ are the k^{th} non-stochastic atom-based 3D-chiral local (atom-type = H-atoms bonding to heteroatoms: S, N, O) linear indices, considering H-atoms in the molecular pseudograph (G).

The k^{th} stochastic atom-based 3D-chiral total [${}^{*s}\boldsymbol{f}_k(x)$ and ${}^{*s}\boldsymbol{f}_k^{H}(x)$], as well as local [${}^{*s}\boldsymbol{f}_k(x_E)$, ${}^{*s}\boldsymbol{f}_k^{H}(x_E)$ and ${}^{s}\boldsymbol{f}_{kL}{}^{H}(x_{E\text{-}H})$] linear indices were also computed.

Molecular Data-Set

The molecular set used in this study was recently introduced by Jozwiak *et al.* (Jozwiak et al., 2007); the synthetic approach can be seen in that work, as well as details about the experimental assays to determinate the respective binding affinities of the 26 stereoisomers. The structures of the molecular set used in this study are depicted in Figure 1.

Chemometric Analysis

Statistical analysis was carried out with the STATISTICA software (STATISTICA version 6.0, Statsoft, 2004). The considered tolerance parameter (proportion of variance that is unique to the respective variable) was the default value for minimum acceptable tolerance, which is 0.01. Forward stepwise procedure was fixed as the strategy for variable selection. The principle of maximal parsimony (Occam's razor) was taken into account as the strategy for model selection. Therefore, the model with the highest statistical significance, but having as few parameters (a_k) as possible was selected.

Multiple linear regression (MLR) was carried out to predict the binding affinity of the fenoterol stereoisomer data-set. The quality of the models was determined by examining the regression statistic parameters. Namely, the quality of models was determined by examining the determination coefficients (also known as square regression coefficients, R^2), Fisher-ratio *p*-levels [*p*(F)] and standard deviations of the regression (*s*) (Belsey et al., 1980). An important aspect of QSAR modelling is the development of means to validate the model. Good direct statistical criteria to fit the data-set are not a guarantee that the model could make accurate predictions. The leave-*one*-out (LOO) press statistics (q^2, s_{cv}) (Wold and Erikson, 1995) were 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 stereoisomer derivatives with the β_2-AR receptor from the molecular structure, by using a combinatorial approach of atom-based 3D-chiral linear indices and multiple linear regression method. As was previously pointed out, the data set was taken from Jozwiak *et al.* (Jozwiak et al., 2007). The models obtained by using non-stochastic and stochastic atom-based 3D-chiral linear indices, with their statistical parameters, are given bellow:

$$\mathbf{p}\boldsymbol{Ki} = 0.673(\pm 0.386) + 3.32\text{x}10^{-7}(\pm 0.217\text{x}10^{-7})^{*M}\boldsymbol{f}_{14L}{}^{H}(x_E) + 7.70\text{x}10^{-4}(\pm 0.97\text{x}10^{-4})^{*K}\boldsymbol{f}_{7L}{}^{H}(x_E) - 7.48\text{x}10^{-6}(\pm 0.47\text{x}10^{-6})^{*V}\boldsymbol{f}_{11L}{}^{H}(x_E) \quad (\mathbf{2})$$

N = 26 R = 0.961 R^2 = 0.924 q^2 = 0.893 s_{cv} = 0.237 F(4,21) = 89.26 s = 0.21 p< 0.0001

$$\mathbf{p}\boldsymbol{Ki} = -1.034(\pm 0.547) + 2.08\text{x}10^{-2}(\pm 0.176\text{x}10^{-2})^{*Ms}\boldsymbol{f}_{0}{}^{H}(x) + 0.583(\pm 0.057)^{*Vs}\boldsymbol{f}_{1L}(x_E) - 0.613(\pm 0.059)^{*Vs}\boldsymbol{f}_{5L}(x_E) \quad (\mathbf{3})$$

N = 26 R = 0.959 R^2 = 0.919 q^2 = 0.886 s_{cv} = 0.245 F(4,21) = 83.56 s = 0.22 p< 0.0001

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. The experimental binding affinities and the results predicted by the multiple linear regression models for the data-set are listed in Table 2.

Table 2. The pK_i predicted with non-stochastic and stochastic atom-based 3D-chiral linear indices.

Compound	Observed[a]	Predicted Non-stochastic[b]	Residual	Predicted Stochastic[c]	Residual	Predicted CoMFA[d]	Residual
R,R-1	6.460	6.069	0.391	5.860	0.600	5.84	0.620
S,S-1	4.560	4.820	-0.260	4.681	-0.121	4.66	-0.100
R,S-1	5.430	5.686	-0.256	5.546	-0.116	5.48	-0.050
S,R-1	4.990	5.203	-0.213	4.995	-0.005	5.02	-0.030
R,R-2	6.320	6.072	0.248	6.165	0.155	6.17	0.150
S,S-2	4.800	4.821	-0.021	4.987	-0.187	4.99	-0.190
R,S-2	5.710	5.687	0.023	5.851	-0.141	5.80	-0.090
S,R-2	5.280	5.206	0.074	5.301	-0.021	5.34	-0.060
R,R-3	5.530	5.613	-0.083	5.624	-0.094	5.57	-0.040
S,S-3	4.540	4.437	0.103	4.446	0.094	4.39	0.150
R,S-3	5.100	5.301	-0.201	5.311	-0.211	5.21	-0.110
S,R-3	4.640	4.750	-0.110	4.760	-0.120	4.75	-0.110
R,R-4	5.730	5.628	0.102	5.630	0.100	5.58	0.150
S,S-4	4.540	4.371	0.169	4.451	0.089	4.43	0.110
R,S-4	5.220	5.237	-0.017	5.316	-0.096	5.25	-0.030
S,R-4	4.510	4.762	-0.252	4.765	-0.255	4.75	-0.240
R,R-5	6.620	6.655	-0.035	6.662	-0.042	6.72	-0.100
S,S-5	5.600	5.478	0.122	5.478	0.122	5.54	0.060
R,S-5	6.470	6.342	0.128	6.343	0.127	6.36	0.110
S,R-5	5.750	5.792	-0.042	5.797	-0.047	5.90	-0.150
R,R-6	5.030	4.981	0.049	4.969	0.061	5.01	0.020
S,S-6	4.250	3.836	0.414	3.839	0.411	3.84	0.410
R,S-6	4.500	4.700	-0.200	4.701	-0.201	4.66	-0.160
S,R-6	4.000	4.118	-0.118	4.108	-0.108	4.19	-0.190
R-7	4.980	5.271	-0.291	5.260	-0.280	5.33	-0.350
S-7	4.690	4.414	0.276	4.403	0.287	4.51	0.180

[a] Observed β_2-AR binding affinities values taken from the literature (Jozwiak et al., 2007). [b] Predicted binding affinity values from Eq.2. [c] Predicted binding affinity values from Eq.3. [d] Predicted binding affinity values obtained with CoMFA method, these values were taken form the literature (Jozwiak et al., 2007).

Table 3. Statistical parameters of the QSAR models obtained using different molecular descriptors to predict the binding affinities of fenoterol stereoisomer derivatives.

Index	***N***	**R**	**R^2**	***s***	**q^2**	**s_{cv}**	**F**
Non-Stochastic 3D-chiral Linear Indices (Eq. 2)	26	0.961	0.924	0.21	0.893	0.237	89.26
Stochastic 3D-chiral Linear Indices (Eq. 3)	26	0.959	0.92	0.22	0.886	0.245	83.56
CoMFA[a]	26	0.959	0.92	*	0.847	0.309	60.38

[a] Model developed by Jozwiak *et al.* (Jozwiak et al., 2007) *Values are not reported in the literature

As can be seen, both models, with only three variables, explain about the 92% of the variance of the experimental binding affinities with low values of standard deviation, $s = 0.21$ and $s = 0.22$ for models **2** and **3**, respectively. These results are rather similar to those previously obtained by Jozwiak *et al.* (Jozwiak et al., 2007) using CoMFA (see also Table 2), which also explain 92% of the experimental data with $s = 0.223$. Predictability and stability (robustness) of the obtained models (Eqs. **2** and **3**), with regard to data variation, was carried out by means of LOO cross-validation. Our models showed cross-validation square correlation coefficients of 0.893 ($s_{cv} = 0.237$) and 0.886 ($s_{cv} = 0.245$), respectively, while the CoMFA model showed a q^2 value of 0.847 ($s_{cv} = 0.309$). Notice that the result obtained for the LOO procedure with the present QSAR method, non-stochastic and stochastic atom-based 3D-chiral linear indices, compares favourably to the results previously achieved with CoMFA. The best model, from the statistical point of view, was the model developed with atom-based non-stochastic 3D-chiral linear indices. All these results are summarized in Table 3, where a comparison with the CoMFA method can be more easily performed.

Previous reports have established the enantioselective binding preference for β_2-ARs, with the *R*-configuration at the stereogenic centre containing the β-OH moiety (Eimerl et al., 1987; Wieland et al., 1996; Kikkawa et al., 1998; Zuurmond et al., 1999). Consequently, a comparison between the *R*,*R*-isomers should be an important topic. It was shown that (*R*,*R*)-**5** had the highest relative affinity of the tested compounds, followed by the (*R*,*R*)-**2** stereoisomer; these values are slightly greater than the predicted value for (*R*,*R*)-**1**, although in experimental values the order was **5** > **1** > **2** for these isomers. That behaviour is mainly because of the fact of the residual value of isomer (*R*,*R*)-**1** for the obtained models (0.39 for non-stochastic and 0.60 for stochastic). This result is quite similar to the one obtained by Jozwiak *et al*, in which the residual value was 0.62 for isomer (*R*,*R*)-**1** (Jozwiak et al., 2007). According to the predicted and experimental values, isomers **5** and **2** can be proposed as new lead compounds, in order to develop novel drugs with agonist action in the β_2-ARs. Studies of chemical optimization of these compounds should be carried out in the future.

On the other hand, the predicted values for isomers (*R*,*S*) turned out to be lower than for the isomers (*R*,*R*); so, we can conclude that the structural change of the chirality in the second chiral atom, from R to S, produces a decay in the affinity of the chemicals for the receptor. These theoretical results, obtained in our study, agree with the experimental results obtained by other researchers (Jozwiak et al., 2007).

CONCLUSIONS

The principal medical use of the drugs with β_2-AR agonist action is the treatment of asthma, but they may also be useful in the treatment of congestive heart failure. For this reason, ***TOMOCOMD-CARDD*** molecular descriptors were applied, in order to develop QSAR models to predict the binding affinities of the fenoterol stereoisomers with the β_2-AR receptor. In this report, it has been shown that non-stochastic and stochastic atom-based 3D-chiral linear indices result is quite versatile and can be applied in 3D-QSAR studies; the QSAR models obtained with our approach achieve results comparable to, or even slightly better than those previously obtained with the CoMFA method. Although these are only preliminary results and more studies are necessary to design new β_2-AR agonists, this work demonstrates the straightforward way in which 3D-chiral linear indices can be used to predict the affinity between organic compounds and the β_2-adrenoceptor.

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