QSAR models applied to the anti-depression activity of hexahydro-pyrrolo-isoquinoline

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INTRODUCTION

According to World Health Organization, millions of people worldwide suffer from depression[1]. The current medications have been associated with some drawbacks like slow onset of action, undesirable side effects and poor efficacy. In this sense, Apodaca and coworkers developed hexahydro-pyrrolo-isoquinoline compounds (Figure 1) that block serotonin receptors[2]. In this work, a quantitative structure-activity relationship study in four dimension (4D-QSAR)[3] was performed on serotonin inhibitors in order to identify characteristics that enhance the activity of these compounds.

METHODS

The RM1 optimized structures were used as starting point in the 4D-QSAR analysis. Molecular dynamics simulation was performed to construct the conformational ensemble profile of each ligand. After that they were aligned inside a cubic box using the atoms 4-7-10, Figure 1. The interaction pharmacophore elements (descriptors) were calculated and genetic function approximation (GFA) analysis were performed to generate the mathematical models.

RESULTS AND DISCUSSION

The models were valuated according to the statistic measures and the best model from Alignment 1 is outlined below:

MODEL 1

pKi = 8.5569 - 7.2674**(GC1_any)** + 4.8241**(GC2_np)** + 37.2096**(GC3_np)** - 17.8005**(GC4_arom)** - 3.2314**(GC5_any)**

n=86; r^2=0.73; q^2=0.70; r^2_{test}=0.62; LSE=0.150; LOF=0.173

GC = grid cells
Interactions: np=non polar; arom=aromatic; any=any type

The model has five descriptors, three of them with negative value coefficients and two with positive value coefficients (Figure 2). The descriptors GC1, GC2 and GC3 indicated that compounds with substituent at position R_1 have lower activity than those at position R_3. Furthermore, non-polar interactions in this position favor the activity.

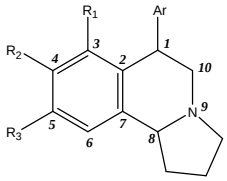

Figure 1. General structure of the hexahydro-pyrrolo-isoquinoline compounds[3].

GC4 and GC5 have negative value coefficients suggesting that when the substituent at position *Ar* is *trans* or *para*-substituted the biological activity of the compounds decreases.

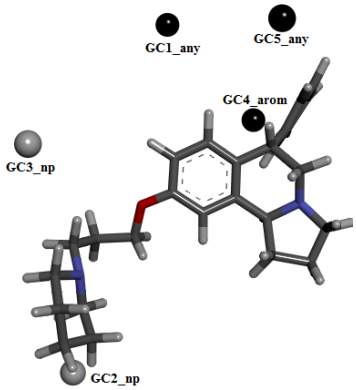

Figure 2. Descriptors of Model 1 represented in the most active compound.

CONCLUSIONS

Model 1 presents descriptors with important pharmacophore groups for serotonin inhibitors suggesting structural modification towards the synthesis of new compounds.

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[1] L. Yu et al., J. Med. Chem., 57, 8204-8223, (2014).
[2] R. Apodaca et al., (2012) US2012/0321559A1
[3] A. J. Hopfinger et al., J. Am. Chem. Soc., 119, 10509-10524, (1997).