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Preliminary communication

Quantitative structure activity relationship of benzoxazinone derivatives as neuropeptide Y Y5 receptor antagonists

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Abstract

Quantitative structure activity relationship (QSAR) has been established for 30 benzoxazinone derivatives acting as neuropeptide Y Y5 receptor antagonists. The genetic algorithm and multiple linear regression were used to generate the relationship between biological activity and calculated descriptors. Model with good statistical qualities was developed using four descriptors from topological, thermodynamic, spatial and electrotopological class. The validation of the model was done by cross validation, randomization and external test set prediction.

Keywords: QSAR; Neuropeptide Y Y5 receptor antagonists; Obesity; Genetic function approximation

1. Introduction

Obesity has emerged as an epidemic in last several decades especially in the developed countries. In a recent study it was found that more than 1 billion peoples in world are overweight and at least 300 million of them are obese [1]. The cause of its high prevalence in developed countries might be the changing life style of the peoples in these countries i.e. increased consumption of high-energy diet in combination with lack of physical exercise. Although the molecular mechanism underneath is not clearly understood number of pathophysiological alterations associated with obesity are documented. Based on these studies therapeutic interventions are designed and being designed. Some of the agents which are in use or are under investigation for intervention of obesity are central nervous system agents, neuropeptide Y and agouti-related peptide antagonists, gastrointestinal–neural pathway agents like cholecystokinin enhancers and glucagon-like peptide-1 activity enhancers, resting metabolic rate promoters and agents like melanin concentrating hormone antagonists [2]. Obesity it self is not life threatening however it can significantly increase the risk of life threatening diseases like cardiovascular disease, neurological disorders, respiratory disorders, musculoskeletal disorders, endocrine disorders, gastrointestinal disorders, genitourinary disorders and psychological disorders [3,4]. Therefore it is necessary to develop effective and safe antiobesity drugs to reduce the worldwide obesity epidemic.

Neuropeptide Y is a 36 amino acid peptide and belongs to a large family of peptides, which also include peptide YY and pancreatic polypeptide [5]. It is widely distributed in central [6] as well as peripheral nervous system [7] and is found to be associated with several diseases like diabetes mellitus [8], cardiovascular disorders [9], depression [10], anxiety [10], seizures [11], asthma [12], inflammatory diseases [12] and immune system disorders [13]. It has been observed that NPY is a strong feeding stimulant and its administration reduces energy expenditure [14–16]. Though various biological functions of NPY are mediated by five receptor subtypes i.e. Y1, Y2, Y4, Y5 and Y6, the regulation of feeding behavior is mainly mediated via Y1 and Y5 receptor subtypes [17]. In a number of pharmacological studies it has been established that NPY Y5 antagonists are potential antiobese agents [18]. So development of NPY Y5 antagonists can offer effective antiobese drugs.

Quantitative structure activity relationship (QSAR) is a useful method for the design of bioactive compounds and the prediction of activity from the parameters calculated from chemical structure of compound. There are many examples available in literature where QSAR models have been used for screening of compounds from the chemical databases [19–22]. The

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QSAR models can be developed by linearly correlating the biological activity to the descriptors or the non-linear regression methods such as artificial neural network (ANN) can be used [23]. In present study we carried out a quantitative structure NPY Y5 receptor inhibitory activity relationship of a series of benzoxazinone derivatives using genetic function approximation (GFA) method for variable selection. The objective of study is to develop a model which can be used to screen the compounds for NPY Y5 receptor inhibitory activity from the available chemical databases. The model can be used for virtual screening by applying Lipinski's rule filters for initial screening and then predicting the activity by QSAR model.

2. Materials and methods

2.1. Data set

The inhibitory activity of the benzoxazinone derivatives was taken from literature in terms of IC_{50} values [24]. The IC_{50} values were converted to pIC_{50} to get the linear relationship in the equation using following formula

$$pIC_{50} = -\log IC_{50} \quad (1)$$

Total set of 30 compounds was divided in training and test set of 24 and six compounds randomly. In the original article the IC_{50} values were given in nM values. To make the interpretation easy, before conversion to pIC_{50}, IC_{50} values were changed to μM unit, so that the pIC_{50} values become in the positive range only. The structures of compounds used in the study along with observed IC_{50} values are provided in Table 1.

2.2. Molecular modeling

All computational work was performed on Silicon Graphics Fuel Work station. The compounds were built using build model program in the Sybyl 6.9 software package [25]. The energy minimization calculations were performed using AM1 method [26] in MOPAC 6.0. The following specific software options were employed while performing AM1 studies: convergence = normal, optimization = full, state = singlet, net charge = 0 e.u., time limit = 3600 s, keyword = mmok.

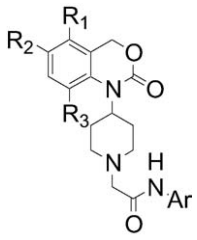
2.3. Descriptor calculation

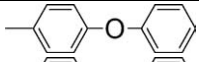
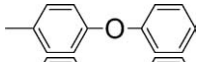
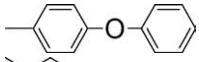
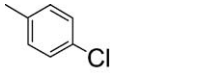
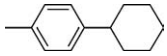
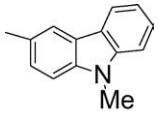
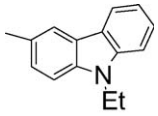
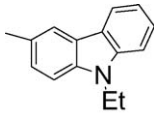
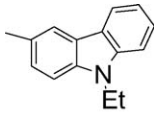
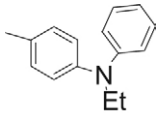
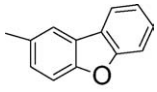
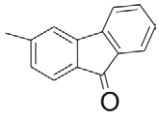
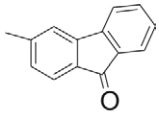
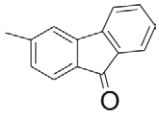
A total of more than 100 descriptors were calculated using Cerius^2 4.10 software package [27]. A brief description of descriptors used which include topological descriptors, spatial descriptors, E-state indices, thermodynamic, electronic and structural descriptors is provided in Table 2.

2.4. Regression analysis

From the total calculated descriptors some of the descriptors e.g. Atype_Br_91, Atype_Br_92, Atype_I_96, Atype_I_97, Atype_I_98, Atype_S_106, Atype_S_107 Atype_P_115, Aty-

Table 1
Structure and observed IC_{50} of the compounds used for study



Compounds	R1	R2	R3	Ar	IC_{50} (nM)
1	H	H	H		20
2	H	Me	H		104
3	H	Cl	H		60.7
4	H	H	H		300
5	H	Cl	H		112.4
6	H	H	H		9.6
7	Cl	H	H		54.6
8	H	Cl	H		100
9	H	H	Me		50
10	H	H	OMe		765.1
11	H	H	OMe		55.7
12	H	H	H		23.3
13	H	H	Me		50
14	H	Cl	H		25

(continued)