Evaluation of the Pharmacological Descriptors Related to the Induction of Antidepressant Activity and its Prediction by QSAR/QRAR Methods

S. Avram*[,1], C. Buiu[1,2], D. Duda-Seiman[3], C. Duda-Seiman[4], F. Borcan[5] and D. Mihailescu[1]

[1]*University of Bucharest, Faculty of Biology, Dept. of Anatomy, Animal Physiology and Biophysics, 91-95 Spl. Independentei, Bucharest-076201, Romania*

[2]*"Politehnica" University of Bucharest, Faculty of Control and Computers, 313 Spl. Independentei, Bucharest-060042, Romania*

[3]*University of Medicine and Pharmacy "Victor Babes" Timisoara, Clinic of Preventive Cardiology and Cardiovascular Rehabilitation, 49 Loga Bvd, Timisoara-300020, Romania*

[4]*West University Timisoara, Faculty of Chemistry, Biology and Geography, Chemistry Dept., 16 Pestalozzi Str., Timisoara-300115, Romania*

[5]*University of Medicine and Pharmacy "Victor Babes" Timisoara, Biochemistry Dept., 2 E. Murgu Sq., Timisoara-300041, Romania*

Abstract: Antidepressants are psychiatric agents used for the treatment of different types of depression, being at present amongst the most commonly prescribed drugs, while their effectiveness and adverse effects are still the subject of many studies. To reduce the inefficiency of known antidepressants caused by their side-effects, many research efforts have recently focused on the development of improved strategies for new antidepressants drug design. For this reason it is necessary to apply very fast and precise techniques, such as QSAR (Quantitative Structure-Activity Relationships) and QRAR (Quantitative Retention-Activity Relationship), which are capable to analyze and predict the biological activity for these structures, taking in account the possible changes of the molecular structures and chromatographic parameters. We discuss the pharmaceutical descriptors (van der Waals, electrostatic, hydrophobicity, hydrogen donor/acceptor bond, Verloop's parameters, polar area) involved in QSAR and also chromatographic parameters involved in QRAR studies of antidepressants. Antidepressant activities of alkanol piperazine, acetamides, arylpiperazines, thienopyrimidinone derivatives (as preclinical antidepressants) and also the antidepressants already used in clinical practice are mentioned.

Keywords: Antidepressants, drug design, membrane receptors, QSAR, QRAR, pharmaceutical descriptors.

DEPRESSION, MAJOR DEPRESSIVE DISORDER – GENERAL ASPECTS

Humans cross several mood patterns in a day, in response to environmental factors, situations and inter-human relationships. When normal emotions that express sadness become a constant and augmented expression in life, without an object, or with a past and not anymore valid cause-effect relation, a depressive disorder should be taken into consideration. This distinct change of mood must last at least two weeks to speak about a major depressive disorder, being accompanied by some disturbances of normal psychological and functional features (sleep and appetite disorders, crying, experiencing no pleasure interacting with environmental components, slow reactions, and suicidal thoughts) [1]. In order to define a major depressive episode, five or more symptoms have to be present almost daily for two weeks [2, 3].

*Address correspondence to this author at the Dept. of Anatomy, Animal Physiology and Biophysics, University of Bucharest, Faculty of Biology, 91-95 Spl. Independentei, Bucharest-076201, Romania; Tel: +40213181573; Fax: +40213181573; E-mail: speranta.avram@gmail.com

It is a fact that an illness appears as a result of an interaction between local factors (genetic factors) and external influences. A published meta-analysis [4] concluded that major depression is a complex disorder resulting from both genetic and environmental influences. Scientists have hypothesized that predisposing genes and stress affect neuronal bio-anatomy and physiological neuronal processes [5].

Being a real public health problem, depression requires several therapy approaches with the main goal to regain the patients' baseline level of functioning. Recent guidelines [6] recommend initiating appropriate treatment in patients with mild to moderate major depressive disorder and definitely in those with severe acute major depressive disorder, unless electroconvulsive therapy is planned. Specific pharmaco-therapy has to be provided in the continuation, as well as in the maintenance phase. Also, patients with depression have a higher risk to develop other comorbidity than those with no depression [5, 7]. A new hypothesis affirms that both cardiovascular conditions and depression have common underlying pathophysiological processes [8].

1875-5607/12 $58.00+.00

Table 1. Classes of Antidepressants Acting on Cellular Targets

Classes of antidepressants	Antidepressants
selective serotonin reuptake inhibitors (SSRIs)	sertraline, paroxetine, fluvoxamine, escitalopram
serotonin norepinephrine reuptake inhibitors (SNRIs)	venlafaxine, desvenlafaxine, duloxetine
dopamine norepinephrine reuptake inhibitor	bupropion
norepinephrine-serotonin modulator	mirtazapine
serotonin modulators	nefazodone, trazodone
tricyclic antidepressants (TCAs)	amitriptyline, nortriptyline, protriptyline, doxepin
monoamine oxidase inhibitors (MAOIs)	phenelzine, tranylcypromine, moclobemide

CLASSIFICATION OF ANTIDEPRESSANT AGENTS BY THEIR MECHANISM OF ACTION

The "first-generation" antidepressants were introduced in the late 1950s, comprising the tricyclics and monoamine oxidase inhibitors. New classes of drugs to treat major depression have been developed since then (see Table **1**) [9]. There are also under development new antidepressants, like triple reuptake inhibitors, dual-acting serotonin reuptake inhibitors, histamine agonists, etc. [10].

Actual guidelines from the American Psychiatric Association [6] for the treatment of major depressive disorders consider the following classes of antidepressants, selected and presented in Table **1**.

ANTIDEPRESSANTS – CLINICAL EVIDENCE

There is still a debate if all antidepressants show similar effectiveness rates. Most comparisons regarded the differences, if any, between TCAs and SSRIs. Results favored mostly TCAs in respect of benefits, especially discussing the case of severe depression when treatment was addressed to in-patients. Thus, Parker *et al.,* [11] found that effectiveness rates were distinctly higher for TCAs than for SSRIs in patients meeting the melancholia criteria, but were quite similar for both drug classes in patients with milder depressions. This tendency was observed in a meta-analysis cited by Parker [12]. Some study [13, 14] show that newer antidepressants were more effective than placebo in several depression forms, with no differences among newer agents, but also with no significant difference in terms of effectiveness between older and newer antidepressants.

Anderson [15] showed in his meta-analysis that SSRIs are generally as effective as TCAs, and SSRIs are better tolerated than TCAs. Both conclusions are labeled as findings with higher confidence.

The American College of Physicians (ACP) stated recently [16], based on published data, that there are no significant differences among second-generation antidepressants in terms of efficacy and effectiveness; the choice of medication within this class of drugs is made considering the time to onset of action of certain compound and the potential adverse effects. ACP elaborated recommendations in order to use antidepressants [17, 18]. A major benefit in using antidepressants would be the impact on mortality by decreasing it. Almeida *et al.,* [19] showed in their study that antidepressants don't reduce mortality rates of elderly men with persistent depression symptoms.

Pigott *et al.,* [20], after examining the current state of efficacy and effectiveness of used antidepressants, concluded that there is needed a reconsideration of the standards that define the depression management.

GENERAL OVERVIEW OF DESCRIPTORS USED IN QSAR TO PREDICT BIOLOGICAL ACTIVITY IN PSYCHIATRIC DISEASES AND 2D-QSAR METHODS

At present, QSAR studies using both the classical quantitative structure-activity relationship (2D-QSAR) [21-23] and also 3D-QSAR approaches [24-31] enhanced our knowledge about psychiatric drugs and their interactions with different membrane receptors. Considering the severe side-effects of antidepressants [32-34] and, also, the large number of membrane receptors involved into (e.g., dopamine, serotonin, epinephrine receptors) the real interest of pharmacological industry is to develop new, more potent antidepressants. When the antidepressants mechanisms are discussed, frequently serotonin [35, 36], epinephrine [37, 38] and dopamine [39, 40] receptors are considered. Although 3D structures of these membrane receptors have not been experimentally resolved, there are few studies [41-43] attempting the modeling of D2 dopamine and serotonin receptors. Unfortunately, this is not enough, because the interactions between antidepressants and membrane receptors involved not only membrane receptors presented above, but many other receptors for which the 3D structures are also not available. In these conditions, the QSAR methods remain the only option, being useful when the 3D structures of the receptors or proteins are unknown.

Basically, all QSAR methods consider that the macroscopic properties are induced by the molecular structure and every change into molecular structure leads to modification of these properties [44, 45]. A major QSAR goal is to generate the pharmacophore, represented as an ensemble of steric and electronic characteristics that are necessary to obtain the optimal interactions with a specific biological target (membrane receptors) and to trigger its biological response. The resulting model can be used either to search 3D databases for new molecules that contain a combination of these structural features or to understand

structure–activity relationships within series of biologically active molecules, in order to guide medicinal chemistry efforts in the design of novel compounds having improved affinity and potency [46].

In many QSAR studies, the reciprocal logarithm of the constant of inhibition, K_i [47, 48], is correlated with physicochemical descriptors like Verloop Sterimol parameters [49], van der Waals volume and surface [50] or Connolly surface area [51], electrostatic [52-54], hydrophobic coefficient [55], or Hansch aromatic fragment [56].

At present are available a huge number of molecular descriptors computed by dedicated software packages (MOE [57], SYBYL [58], Cerius [59], etc). These can be classified in 2D molecular descriptors [57-65] and 3D molecular descriptors (potential energy descriptors as well as conformation-dependent charge descriptors [57-59, 66]. A short description of few molecular descriptors available in MOE and Sybyl software is illustrated in Table **2**.

GENERAL OVERVIEW OF 3D-QSAR METHODS APPLIED TO MEDICINAL CHEMISTRY

3D-QSAR methods consider that the interactions between the biological target and ligands are taking place in a three-dimensional space. In 3D-QSAR approaches, quantitative models are constructed relating biological activities of small molecules with their 3D properties. The aim of 3D-QSAR methods is to identify the spatial properties represented by the similarity or dissimilarity, respectively, between energetic force fields of biological target and their inhibitors, respectively.

Some alignment-dependent 3D-QSAR methods (Comparative Molecular Field Analyses (CoMFA) [67, 68] and Comparative Molecular Similarity Indices (CoMSIA) [69] and alignment-independent 3D-QSAR-ALMOND are frequently used [70].

CoMFA considers that the steric and electrostatic descriptors are the most important for interaction between ligands and cellular targets while supplementary, CoMSIA used hydrophobic and hydrogen donor/acceptor bond properties. Also, supplementary, 3D-QSAR-ALMOND considers the interaction with different specious of ions (sodium, potassium, calcium, iron, etc).

The multivariate statistics methods such as partial least squares (PLS) [67], is used to extract the orthogonal principal components of QSAR matrix [67, 68]. Statistical parameters which validate the QSAR model are represented by SD (standard deviation), q^2 (cross-validate r^2), R^2 correlation factor, SEE (standard error of estimate) and F (Fisher) [67].

DEVELOPMENT OF PREDICTIVE QUANTITATIVE RETENTION-ACTIVITY RELATIONSHIP MODELS (QRAR)

As many others drugs, psychiatric drugs are provided also as pills and, in this case, it is considered the intestinal absorption of drugs [71] involves the number and strength of the hydrogen bonds which are formed between drugs and water molecules and appropriate affinity of the drugs to membrane lipids [72]. The distribution of many drugs to the brain is a more selective process than the distribution to other organs. This fact is a consequence of the blood-brain barrier (BBB) action which allows only a restricted distribution from blood to brain. The distribution of tricyclic antidepressants from plasma to brain, where these drugs exert their main clinical action and other organs is related to transport events across the cell membranes of the different tissues. It could be expected that all the molecular features that condition the transport processes (mainly hydrophobicity and molar total charge) also control the pharmacokinetic and biochemical behavior [72].

The application of chromatographic parameters in QSAR generated a new field, quantitative retention-activity relationship (QRAR) [72-74]. Basically, QRAR considers that the same intermolecular interactions determine the behavior of chemical compounds in both biological and chromatographic environments. A great deal of efforts have been made to develop biological chromatographic models such as immobilized artificial membranes chromatography [75], immobilized liposomes chromatography [76], micellar liquid chromatography (MLC) [72, 77, 78] or biopartioning micellar chromatography (BMC) [72, 73] which is a mode of micellar liquid chromatography useful to simulate the drug's passive absorption and the transport in biological systems.

APPLICATION OF QSAR AND QRAR METHODS FOR DEVELOPING NEW ANTIDEPRESSANT DRUGS

The lack of knowledge regarding the three-dimensional structures of the membrane receptors and the high costs of antidepressants synthesis [32] can be real obstacles for

Table 2. Selected Molecular Descriptors Useful for Psychopharmacological Studies Available in MOE and SYBYL Software

Descriptors	Description	software
Refractivity descriptor (SMR_VSA)	denotes the contribution to molar refractivity for atom *i* as calculated in the SMR descriptor	MOE
Hydrogen donor/acceptor bond character	number of acceptor/donor atoms	SYBYL
Hydrophobicity	number of hydrophobic centers	SYBYL
Dipole moment	descriptors based on dipole moment are calculated as total dipole moment and its X, Y, and Z components	SYBYL
Polar surface area (PSA)	includes all O, N, and S atoms, as well as hydrogens covalently bonded to these atoms.	SYBYL

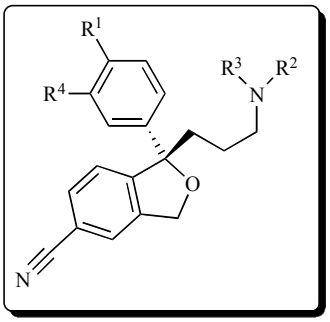
psycho-pharmaceutical studies.

Recently, many research groups have applied QSAR techniques to develop new, more potent antidepressant drugs. The most important aims of these studies were to explain, by using QRAR and QSAR, the regulation mechanisms induced by antidepressants at the membrane receptors. To give a complete image of the depression mechanisms, the QSAR studies were applied also to the autoreceptors [72, 79], which are also involved in this disease. Here we present QSAR and QRAR studies applied to piperazine [80], acetamide [81], arylpiperazine [82-84], thienopyrimidinone [85] derivatives proposed as possible antidepressants and also QSAR/QRAR studied involved the antidepressants already used in depression treatment are discussed [72, 79].

A study by C. Quinones-Torrelo *et al.,* [72] established by using QRAR the relationships between the micellar liquid chromatography retention data (MLC) and some pharmacokinetic parameters of tricyclic antidepressants (half-life time, volume of distribution (Vd), plasma clearance (CLM) and therapeutic plasma level (TPL)). Also, using QSAR allowed to obtain the correlation between observed and predicted antidepressant activity, express as IC_{50} (concentration for 50% inhibition) of 15 tricyclic antidepressants at reuptake noradrenaline (NA) and serotonin (5-HT) receptors and adrenergic (α1) and histaminic (H1 and H2) receptors. Also, the inhibition constant K_i of same antidepressants at brain adenylate cyclase localized in hippocampus and neocortex were take in account for QSAR studies. Analysis of retention behavior of antidepressants shows that it depends not only on the hydrophobic interactions but also on the molar total charge and steric properties of the compounds. The best correlation between retention behavior (log k) and hydrophobic coefficient, log P, was obtained when the molar total charge of compounds was included into the model (i.e., fitted correlation parameter $R^2 = 0.91$) and were proved that retention data (log k) and pharmacokinetic parameters are into polynomial correlation.

Some observations were made when the relationships between the of tricyclic antidepressants for NA and 5-HT reuptake in rat brain and the logarithm of retention data has been studied: (i) in both cases the polynomial model was applied; (ii) the coefficients in the QRAR model for the blockade of NA reuptake were statistically significant (R^2= 0.97) but the corresponding values to the blockade of 5-HT reuptake were statistically non-significant; (iii) the relationships between log IC_{50} values for NA and 5-HT reuptake and log *k* values were statistically significant at the 95% confidence level. All results of study lead to conclusions that the quantitative retention- activity relationships (QRAR) is a preferable alternative (and sometimes an unique option) to QSAR models in order to obtain estimation or at least useful qualitative information about drug activity.

Avram *et al.,* [79] established by using 3D-QSAR-ALMOND the membrane ions' contributions supplied by donor/acceptor hydrogen bond and electrostatic properties of 18 antidepresants at the SERT active site. Significant cross-validated correlation q^2 (0.5–0.6) and the fitted correlation coefficient R^2 (0.7–0.82) were obtained indicating that the proposed QSAR models can predict the antidepressant activity of selected compounds. During this study, significant 3D-QSAR models were developed in the following manner: (i) combination of atom probes sodium and phenyl-OH ($q^2 = 0.60$; $R^2 = 0.80$), (ii) combination of atom probes potassium and phenyl-OH ($q^2 = 0.56$; $R^2 = 0.81$); (iii) combination of atom probes calcium and phenyl-OH ($q^2 =0.60$; $R^2 =0.80$). In this study, authors suggested a number of 24 new escitalopram derivatives as possible antidepressants and their affinity to SERT was predicted in accordance with estimated 3D-QSAR models. The skeleton structure of escitalopram derivative is presented below.

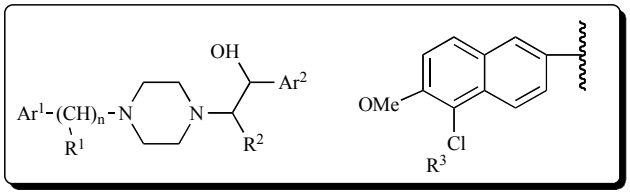


A real improvement of escitalopram's predicted activity within the SERT were reported for derivative 20 (R_1=F, R_2= ethyl, R_3= ethyl, R_4=H; the biological activity of derivative differences to the parent biological activity = 0.43), derivative 21 (R_1=F, R_2= propyl, R_3= propyl, R_4=H, the biological activity of derivative differences to the parent biological activity = 0.41) and derivative 23 (R_1=F, R_2= ethyl, R_3= ethyl, R_4=F, the biological activity of derivative differences to the parent biological activity = 0.50).

In their aim to predict in a judicious manner the antidepressants activity of new escitalopram derivatives at SERT, authors suggested some conclusions. First, the simultaneous presence of diethyl groups at the amine tail and two fluorine atoms at the phenyl ring increased the antidepressant activity while the antidepressant activity is the drastically decrease by the presence of dimethyl or dibutyl group linked by the amine tail or by the presence of primary amine. Secondly, the results indicated that the judicious modulations of the physicochemical properties, particularly hydrophobic and electronic are able to increase antidepressants' effects. Binding affinity of an antidepressant can be influenced by the simultaneous presence of the cations and of the hydroxyl anion, while the simultaneous presence of water atoms and of the cations can modified the binding affinity, but certainly in a weaker manner than the presence of hydroxyl.

In 2009, Chen KX *et al.,* [80] developed a very complex 2D, respective 3D-QSAR, models which predicted the antagonism activity of 32 aryl alkanol piperazine derivatives at 5-hydroxytryptamine (5-HT) reuptake and noradrenaline (NA) reuptake receptors. More, the robust 2D/3D-models were applied to predict the antagonism activities of 15 newly designed molecules as possible antagonists of 5-HT reuptake and NA reuptake receptors. The skeleton structures of aryl

alkanol piperazine derivative proposed in this study are presented below.



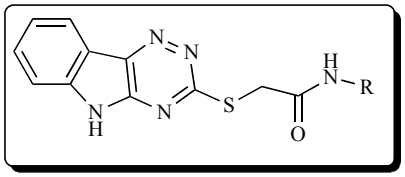
The statistically significant 2D-QSAR models (fitted correlation R^2 >0.924, cross-validated correlation q^2 > 0.870) were developed using genetic function approximation (GFA) when the number of descriptors in equation was set to four. In this study the results of the 2D-QSAR models were further compared with 3D-QSAR models generated by molecular field analysis (MFA), investigating the useful information in the characterization of specific inhibition of aryl alkanol piperazine derivatives at serotonin and noradrenaline receptors mentioned above.

In this study, a large number of molecular descriptors with nonzero values were taken into account but at the end just eight of they were kept. These descriptors and chemical and physical considerations on the descriptors are presented in Table **3**.

The results of 2D-QSAR study shown that Atype_C_6, Dipole-mag, S_sssCH and Jurs-PNSA-3 mainly influence the antagonism activity of alkanol piperazine derivatives at 5-HT reuptake receptor (q^2 = 0.879; R^2 = 0.926) while HOMO, PMI-mag, S_sssN and Shadow-XZ are important for antagonism activity of alkanol piperazine derivatives at NA reuptake receptor (q^2 = 0.871; R^2 = 0.925).

Conclusions of the study about the antagonism of alkanol piperazine derivatives at 5-HT reuptake receptor show that the compounds having larger dipole moment may show less antidepressant activity while increasing Jurs-PNSA-3 value in a molecule could increase antidepressant activity (derivative 11, Ar^1= 2-OMe-Ph, Ar^2=R3, R^1= H, R^2= CH_3, n= 0 $pK_{i\ residual\ value}$= -0.040) and 13(Ar^1= 2,3-Me_2-Ph, Ar^2= R3 R^1= H, R^2= CH_3, n= 0, $pK_{i\ residual\ value}$=0.226). Also, by increasing the presence of S_sssCH it would be possible to reduce the 5-HT reuptake inhibition. About the antagonism of alkanol piperazine derivatives at NA reuptake receptor, it was possible to notice that the presence of HOMO and S_sssN mainly controlled the NA reuptake inhibition. Also, the results show that the increased of S_sssN lead to more NA reuptake inhibition while decreased Shadow-XZ a great pK_i NA reuptake receptor was obtained.

Shelke. S *et al.,* [81] synthesized a series of 2-(5*H*-[1,2,4]triazino[5,6-*b*]indol-3-ylthio)-*N* acetamides namely compound **(3a-r)** and identified these derivatives as potential antidepressants by using QSAR. The skeleton structure of acetamides derivative is presented below.



Based on structural variation and antidepressant activity, measured in terms of percentage decrease in immobility duration (%DID), compounds were divided into a training set (thirteen compounds) and a test set (four compounds). The best QSAR model was selected on the basis of statistical parameters like squared correlation coefficient (R^2), standard deviation (SD), Fisher's value (F) and cross-validated correlation q^2. Biological activity of selected compounds, expressed as log (%DID) was correlated with descriptors like: dipole moment, solvent accessible surface area (SASA), hydrophobic component of the solvent accessible surface area (FOSA), hydrophilic component of the SASA (FISA), π (carbon and attached hydrogen) component of the SASA (PISA), globularity descriptor (glob), total solvent accessible volume, predicted brain/blood partition coefficient (QP log BB). The best correlation between observed and predicted biological activity was obtained (q^2 = 0.8713, R^2 = 0.9287) when FOSA, PISA and globularity were included into QSAR equation. From this model it can be

Table 3. Significant Descriptors and Chemical and Physical Considerations of them

Descriptors	Chemical and physical considerations of descriptors
Atype _C_6	C in CH_2RX where X represents any heteroatom
Dipole-mag	electronic descriptor involved in ligand–receptor interactions
S_sssCH	type of the E-state indices stands for the carbon bonded to one hydrogen atom and three non-hydrogen atoms in the alkane. E-state indices encode information about both the topological environment and the electronic interaction of an atom due to all other atoms in the molecule
Jurs-PNSA-3	sum of the product of solvent-accessible surface area X partial charge for all negatively charged atoms
HOMO	highest occupied molecular orbital
PMI-mag	calculates the principal moments of inertia about the principal axes of a molecule
S_sssN	the sum of the atom level E-state values for all nitrogen atoms with three single bonds in the molecule
Shadow-XZ	area of molecular shadow in the XZ plane (Sxz), which can be calculated by projecting the molecular surface on mutually perpendicular XZ plane

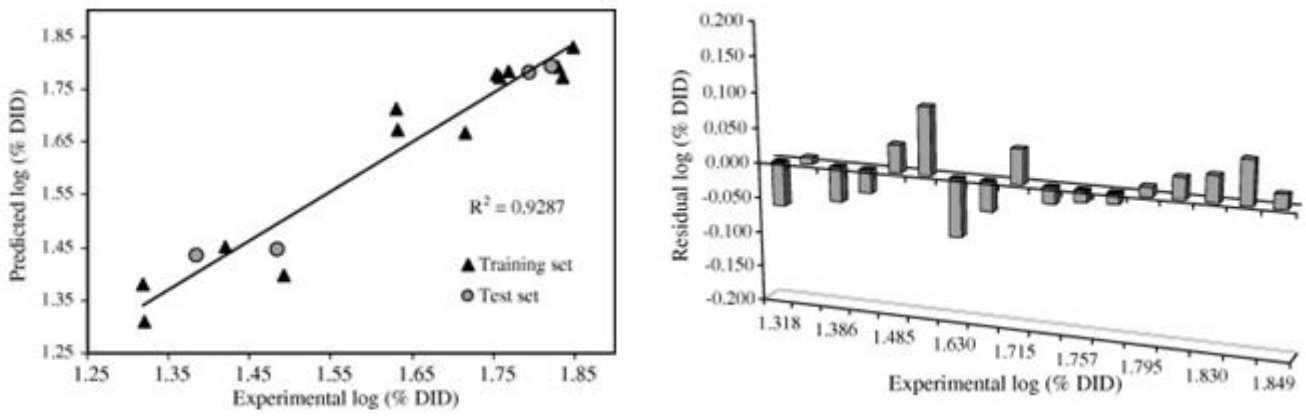


Fig. (1). (**a**) Plot of predicted log (%DID) against experimental log (%DID) for training and test set compounds and (**b**) Plot of residual log (%DID) against experimental log (%DID) (original after Shelke. S *et al.,* [81])

seen that two parameters, FOSA and globularity descriptors negatively correlate with log (%DID), while PISA correlates positively.

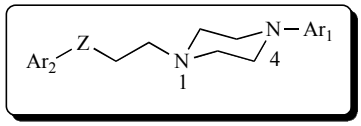
The results led to certain conclusions: (i) as FOSA is negatively correlated with log (%DID), any aliphatic substituent in the molecule which increases FOSA, will decrease biological activity; (ii) because PISA is positively correlated with log (%DID), any substitution which decreases aromatic hydrophobic makeup of the molecule will shrink its activity. The statistical results are supported by plots representing (a) plot of predicted log (%DID) against experimental log (%DID) for training and test set compounds and (b) plot of residual log (%DID) against experimental log (%DID) (Fig. **1**).

In the same study, authors noticed that any substituent on the phenyl ring diminished the activity of parent compound **3a (**R= Phenyl) and presence of bulky non-polar groups on phenyl ring as in compound **3b (**R= 2-Methylphenyl) and compound **3c (**R= 2-Methoxyphenyl) tended to lessen the activity drastically. Also, it was shown that changing of phenyl by benzyl in compound **3q** (R= Benzyl) shrunk the activity to some extent. It was noticed that replacing phenyl by cyclohexyl in compound **3r** (R= Cyclohexyl) reduced the antidepressant activity. A suitable conclusion with preclinical relevance was that compounds **3a**, **3n** (R= 4-Chlorophenyl**)**, **3o** (R= 4-Bromophenyl**)**, **3j** (R= 3-Bromophenyl**)** and **3p** (R= 4-Nitrophenyl**)** exhibited activity very comparable to standard antidepressant drugs moclobemide, imipramine and fluoxetine.

Interesting QSAR studies [82-85] explored the antagonism of thienopyrimidinone and arylpiperazines derivatives at 5HT receptors [82-85].

These antagonists were studied in special by Weber *et al.,* [82-84]. In one of study [84] 52 selected arylpiperazines derivatives were used to validated a robust QSAR model ($q^2 = 0.76$, $r^2 = 0.83$). In this study, the chemometric methods HCA, PCA, KNN, SIMCA and PLS were employed in order to obtain SAR and QSAR models relating the structures of arylpiperazine compounds to their 5-HT_{1A} receptor affinities. It was confirmed that the steric descriptors are critically for antagonism activity at 5HT1A receptor.

The skeleton chemical structure used by Weber in his study is presented below.

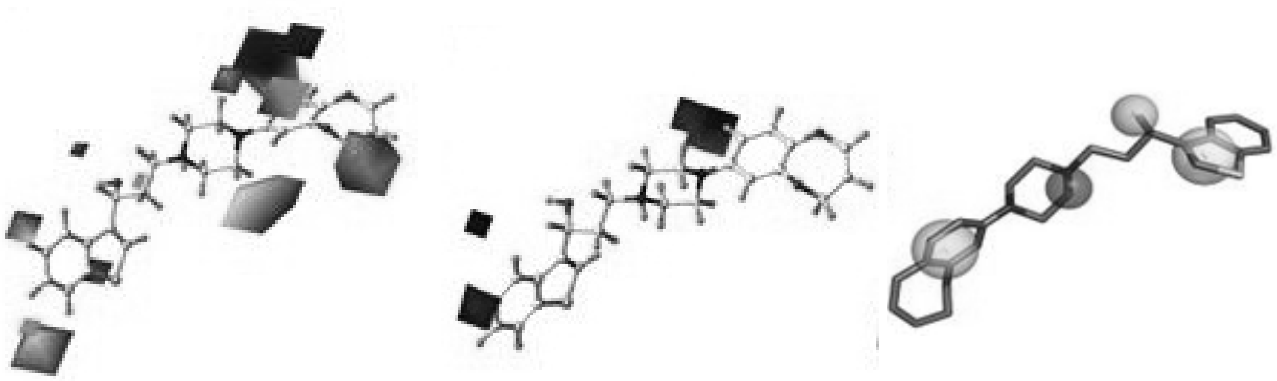


In other study, Weber *et al.,* developed a 3D-QSAR CoMFA study [83] on a large set of arylpiperazines (70 compounds in the training set and the other 18 compounds as members of the test set for external model validation) in order to generate a new pharmacophore model with potential antidepressant character.

The external predictive ability of the CoMFA model derived using the 70 training set molecules ($R^2 = 0.87$, SEE = 0.37, $q^2 = 0.75$) was assessed by predicting pK_i values for 18 test set molecules which were not included in the training set for model generation.

In this study, by visualization of unfavorable (gray) and favorable (black) steric regions and regions where electronegative substituents may increase the biological activity (black) was possible to notice that (Fig. **2a**, **b**): (i) bulky groups can be accommodated and are related to increasing binding affinity, however, the benzothiophene moiety is surrounded by unfavorable steric contours, which suggests that bulkier groups would cause a decrease in 5-HT_{1A} receptor affinity; (ii) the unfavorable steric contours surrounding this region possibly delimit a receptor pocket that would not permit the accommodation of these groups.

Additionally, the pharmacophore model developed was studied for the development of new arylpiperazines with improving 5-HT_{1A} binding affinity (Fig. **2c**). The structural



a **b** **c**

Fig. (2). CoMFA (**a**) steric, (**b**) electrostatic contour maps, **c**. final pharmacophore model for a series of 5-HT_{1A} receptor ligands, containing one acceptor center (white-little ball), one positive center (black), one aromatic ring (white-big ball down) and one hydrophobic center (white-big ball up) (after Weber *et al.,* [83]).

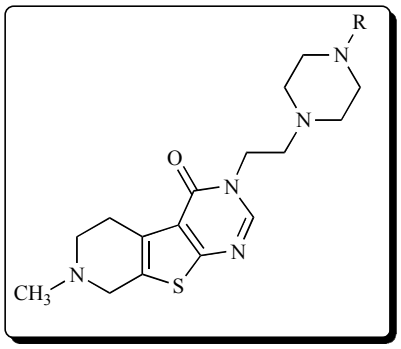
analyses of the pharmacophore model suggested that: (i) the basic nitrogen and the aromatic ring attached to the arylpiperazine moiety, in addition to the hydrophobic center and the hydrogen bond acceptor group are highlighted as key pharmacophore elements in determining binding affinity, (ii) the black sphere around the basic nitrogen of the piperazine ring can be related to the interaction between the protonated atom of the ligand and active site of the 5-HT_{1A} receptor, (iii) confirm the importance of the hydrophobic center represented by the white-big ball up on the benzothiophenyl group.

This study led to a robust 3D QSAR model of the 5-HT_{1A} binding affinity of arylpiperazines, possessing high internal and external consistency and substantial predictive power, was developed employing a pharmacophore-based alignment strategy. The CoMFA methodology was successfully applied to provide useful insights into the chemical and structural requirements for biological activity in this series of arylpiperazines. In addition, the contour maps emphasized important regions in 3D space where modifications of steric and electrostatic fields would be strongly associated with concomitant changes in the observed binding affinity. The pharmacophore model developed in this study is possible to be applied into future virtual screening studies and, along with the 3D QSAR model generated, can be a useful tool to guide further ligand-based design studies for the development of new arylpiperazines having improved 5-HT_{1A} binding affinity.

N. Dessalew [85] has studied thienopyrimidinone derivatives as antagonists of serotonin receptors $5HT_{1A}$ and $5HT_{1B}$. The skeleton structure of thienopyrimidinone derivatives is represented below.

The QSAR models developed in this study show a good ability to predicte antidepressant activity (as pKi) of thienopyrimidinone derivatives at 5-HT1A receptor (q^2 = 0.780, R^2 = 0.824) and also at 5-HT1B receptor (q^2 = 0.638 and r^2 = 0.745) when Verloop's steric parameters (L and B1) are involved as descriptors.

When antagonism of thienopyrimidinone derivatives at 5HT1A receptor was analyzed by authors, it was noticed that the substituents with high Verloop B1 parameter are more negatively correlated with the prediction of antagonist activity of selected compounds (e.g. predicted antagonism of compounds 3, 4, 5, 7 and 9 at 5HT1A receptor in comparison with the antagonism of compounds 10 and 8 at some receptor (see in comparison the residual values (observed



Compound	Residual value $_{5HT1A}$	Residual value $_{5HT1B}$
3	0.1	-
4	-0.3	-
5	-0.4	-
6	-	-0.4
7	0.2	-
8	0.01	-0. 13
9	0.1	-
10	0.01	-
19	-	-0.36
20	-	-0.5
26	-	-0.01

pK_i-predicted pK_i)). In a similar manner, different antagonism of thienopyrimidinone derivatives at 5HT1B is explain by the negatively correlation of Verloop B1 parameter with antidepressant activity. This appears to explain the better antagonist activity of compounds 8 and 26 in comparison with compounds 6, 20 or 19.

This study has shown that the QSAR analysis using 31 thienopyrimidinone derivatives was successfully carried out to build statistically significant models possessing a good correlative and predictive capabilities for the antagonism of both 5-HT1A and 5-HT1B receptors. The comparative investigation provided structural insights on how modulation of the steric bulk of the substituents could be usefully made to optimize the antidepressant activity. The study provided useful clues about the structural requirement for effective antagonist-autoreceptor binding chemistry and hence for the improvement of the observed biological activity. The important conclusions of this study were that the dual autoreceptor antagonistic activity observed is predominantly explained by the steric factors of substituents, and by the comparative investigation was proved how the steric bulk of the substituents could be usefully made to optimize the antidepressant activity.

CONCLUSIONS

The understanding of molecular determinants of ligand binding is critical in drug design, especially when the crystal structure of the target protein in complex with a ligand is unknown. In such situations, QSAR approaches can be useful to investigate the possible intermolecular interactions between biological receptors and small molecule ligands. Considering the important side-effects of antidepressants, the actual trend aims at developing new antidepressants. The objective of this review was to show that 3D- and also 2D-QSAR methods will continue to give important information about antidepressants drug design. Many substances, such as alkanol piperazine, acetamides, arylpiperazines thienopyrimidinone derivatives are potential candidates as antidepressants. The steric, topological, hydrogen donor or acceptor, the electrostatic or steric fields used as molecular descriptors can improve the global information about membrane receptors affinity of antidepressants. A useful approach is to separate the contributions of steric, electrostatic or lipophylic fields to the antidepressants affinity for membrane receptors. This is possible by using 3D-QSAR techniques like CoMFA, CoMSIA, ALMOND. The CoMFA methodology was successfully applied to provide useful insights into the chemical and structural requirements for biological activity in this series of arylpiperazines. The contour maps emphasized important regions in 3D space where modifications of steric and electrostatic fields would be strongly associated with concomitant changes in the observed binding affinity. Supplementary, an analysis of QSAR-ALMOND on antidepressants interactions with SERT brings up a number of points of interest.

In QSAR studies, biological membrane ions sodium, chlorine, potassium, and calcium, were critical for antidepressants activity. Also, in 2D-QSAR approaches, the selected descriptors, which encode useful information about several aspects of molecular structure, have shown to be closely related to antidepressants affinities to membrane receptors. Here, we can give importance to sterical properties well represented by the topological indices and also the electronic features of the compounds that may be involved in ligand binding to the receptor. This review provided useful information about the structural requirement for effective antagonist-autoreceptor binding chemistry and hence for the improvement of the observed biological activity. This analysis could be of help in the rational design of potential drug candidates with enhanced antagonist potency.

CONFLICT OF INTEREST

None declared.

ACKNOWLEDGEMENTS

We acknowledge the financial support of CNMP PNII 62-061/2008.

REFERENCES

[1] Belmaker, R.H.; Agam G. Mechanisms of disease: Major depressive disorder. *N Engl J Med.,* **2008**, *358*, 55-68.

[2] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed.; APA: Washington DC, **1994**.

[3] Spigset, O.; Mårtensson B. Drug treatment of depression. *BMJ*., **1999**, *318*, 1188-1191.

[4] Sullivan, P.F.; Neale, M.C.; Kendler, K.S. Genetic epidemiology of major depression: review and meta-analysis. *Am J Psychiatry,* **2000**, *157*, 1552-1562.

[5] Mann, J.J. The medical management of depression. *N Engl J Med.,* **2005**, *353*, 1819-1834.

[6] American Psychiatric Association. Work Group on Major Depressive Disorder. Practice Guideline for the Treatment of Patients with Major Depressive Disorder. 3rd ed.; **2010**.

[7] Jiang, W.; Krishnan, R.R.; O'Connor, C.M. Depression and heart disease: evidence of a link, and its therapeutic implications. *CNS Drugs,* **2002**, *16*, 111-127.

[8] Paz-Filho, G., Licinio, J., Wong, M.L. Pathophysiological basis of cardiovascular disease and depression: a chicken-and-egg dilemma. *Revista Brasileira de Psiquiatria,* **2010**, *32*, 181-191.

[9] Shelton, R.C. Classification of antidepressants and their clinical implications. *Primary Care Companion J Clin Psychiatry,* **2003**, *5[suppl 7]*, 27-32.

[10] Perović, B.; Jovanović, M.; Miljković, B.; Vezmar, S. Getting the balance right: established and emerging therapies for major depressive disorders. *Neuropsychiatric Disease and Treatment,* **2010**, *6*, 343-364.

[11] Parker, G., Mitchell, P., Wilhelm, K., Menkes, D., Snowdon, J., Schweitzer, I., Grounds, D., Skerritt, P., Roy, K., Hadzi-Pavlovic, D. Are the new antidepressant drugs as effective as established physical treatments? Results from an Australian clinical panel review. *Australian and New Zeeland Journal of Psychiatry,* **1999**, *33*, 874-881.

[12] Parker, G. 'New' and 'old' antidepressants: all equal in the eyes of the lore? *British Journal of Psychiatry*, **2001**, *179*, 95-96.

[13] Williams, J.W.; Mulrow, C.D.; Chiquette, E.; Noël, P.; Aguilar, C.; Cornell, J. A systematic review of newer pharmacotherapies for depression in adults: evidence report summary. Clinical Guideline, Part 2. *Ann Intern Med,* **2000**, *132*(9), 743-756.

[14] Arroll, B.; Macgillivray, S.; Ogston, S.; Reid, I.; Sullivan, F.; Williams, B.; Crombie, I. Efficacy and tolerability of tricyclic antidepressants and SSRIs compared with placebo for treatment of depression in primary care: a meta-analysis. *Ann Fam Med*, **2005**, *3*, 449-456.

[15] Anderson, I.M. Meta-analytical studies on new antidepressants. *British Medical Bulletin*, **2001**, *57*, 161-178.

[16] Gartlehner, G.; Gaynes, B.N.; Hansen, R.A.; Thleda, P.; De Veaugh-Gelss, A.; Krebs, E.E.; Moore, C.G.; Morgan, L.; Lohr, K.N. Comparative benefits and harms of second-generation antidepressants: background paper for the American College of

Physicians. Clinical Guidelines. *Ann Intern Med*, **2008**, *149*, 734-750.

[17] Quaseem, A.; Snow, V.; Denberg, T.D.; Forciea, M.A.; Owens, D.K. Using second-generation antidepressants to treat depressive disorders: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*., **2008**, *149*(10), 725-733.

[18] Gartlehner, G.; Gaynes, B.N. Are all antidepressants equal? *Evid Based Mental Health*, **2009**, *12*, 98-100.

[19] Almeida, O.P.; Alfonso, H.; Hankey, G.J.; Flicker, L. Depression, antidepressant use and mortality in later life: The Health in Men Study. *PLoS ONE*, **2010**, *5*(6), e11266.

[20] Pigott, H.E.; Leventhal, A.M.; Alter, G.S.; Boren, J.J. Efficacy and effectiveness of antidepressants: current status of research. *Psychother Psychosom.,* **2010**, *79*, 267-279.

[21] Campiani, G.; Butini, S.; Fattorusso, C.; Trotta, F.; Gemma, S.; Catalanotti, B.; Nacci, V.; Fiorini, I.; Cagnotto, A.; Mereghetti, I.; Mennini, T.; Minetti, P.; Di Cesare, M. A.; Stasi, M. A.; Di Serio, S.; Ghirardi, O.; Tinti, O.; Carminati, P. Novel atypical antipsychotic agents: rational design, an efficient palladium-catalyzed route, and pharmacological studies. *J. Med. Chem*., **2005,** *48*, 1705-1708.

[22] Campiani, G.; Butini, S.; Fattorusso, C.; Catalanotti, B.; Gemma, S.; Nacci, V.; Morelli, E.; Cagnotto, A.; Mereghetti, I.; Mennini, T.; Carli, M.; Minetti, P.; Di Cesare, M. A.; Mastroianni, D.; Scafetta, N.; Galletti, B.; Stasi, M. A.; Castorina, M.; Pacifici, L.; Vertechy, M.; Di Serio, S.; Ghirardi, O.; Tinti, O.; Carminati, P. Pyrrolo[1,3]benzothiazepine-based serotonin and dopamine receptor antagonists. Molecular modeling, further structure-activity relationship studies, and identification of novel atypical antipsychotic agents. *J. Med. Chem*., **2004**, *47*, 143-157.

[23] Campiani, G.; Butini, S.; Gemma, S.; Nacci, V.; Fattorusso, C.; Catalanotti, B.; Giorgi, G.; Cagnotto, A.; Goegan, M.; Mennini, T.; Minetti, P.; Di Cesare, M. A.; Mastroianni, D.; Scafetta, N.; Galletti, B.; Stasi, M. A.; Castorina, M.; Pacifici, L.; Ghirardi, O.; Tinti, O.; Carminati, P. Pyrrolo[1,3]benzothiazepine-based atypical antipsychotic agents. Synthesis, structure-activity relationship, molecular modeling, and biological studies. *J. Med. Chem*., **2002**, *45*, 344-359.

[24] Nilsson, J.; Wikstrom, H.; Smilde, A.; Glase, S.; Pugsley, T.; Cruciani, G.; Pastor, M.; Clementi, S. GRID/GOLPE 3D quantitative structure-activity relationship study on a set of benzamides and naphthamides, with affinity for the dopamine D3 receptor subtype. *J. Med. Chem.,* **1997**, *40*, 833-840.

[25] Balle, T.; Andersen, K.; Soby, K. K.; Liljefors, T. Alpha(1) adrenoceptor subtype selectivity. 3D-QSAR models for a new class of alpha(1) adrenoceptor antagonists derived from the novel antipsychotic sertindole. *J. Mol. Graph. Model.,* **2003**, *21*, 523-534.

[26] Lanig, H.; Utz, W.; Gmeiner, P. Comparative molecular field analysis of dopamine D4 receptor antagonists including 3-[4-(4-chlorophenyl)piperazin-1-ylmethyl]pyrazolo[1,5-a]pyridine (FAUC 113), 3-[4-(4-chlorophenyl)piperazin-1-ylmethyl]-1H-pyrrolo-[2,3-b]pyridine (L-745,870), and clozapine. *J. Med. Chem.,* **2001**, *44*, 1151-1157.

[27] Bostrom, J.; Bohm, M.; Gundertofte, K.; Klebe, G. A 3D QSAR study on a set of dopamine D4 receptor antagonists. *J. Chem. Inf. Comput. Sci.*, **2003**, *43*, 1020-1027.

[28] Bostrom, J.; Gundertofte, K.; Liljeforsa, T. A pharmacophore model for dopamine D4 receptor antagonists. *J. Comput. Aided. Mol. Des.,* **2000**, *14*, 769-786.

[29] Audouze, K.; Nielsen, E. O.; Peters, D. New series of morpholine and 1,4-oxazepane derivatives as dopamine D4 receptor ligands: synthesis and 3D-QSAR model. *J. Med. Chem.,* **2004**, *47*, 3089-3104.

[30] Tehan, B. G.; Lloyd, E. J.; Wong, M. G. Molecular field analysis of clozapine analogs in the development of a pharmacophore model of antipsychotic drug action. *J. Mol. Graph. Model.,* **2001**, *19*, 417-426.

[31] Ravina, E.; Negreira, J.; Cid, J.; Masaguer, C. P.; Rosa, E.; Rivas, M. E.; Fontenla, J. A.; Loza, M. I.; Tristan, H.; Cadavid, M. I.; Sanz, F.; Lozoya, E.; Carotti, A.; Carrieri, A. Conformationally constrained butyrophenones with mixed dopaminergic (D(2)) and serotoninergic (5-HT(2A), 5-HT(2C)) affinities: synthesis, pharmacology, 3D-QSAR, and molecular modeling of (aminoalkyl)benzo- and -thienocycloalkanones as putative atypical antipsychotics. *J. Med. Chem.,* **1999**, *42*, 2774-2797.

[32] Schellander, R.; Donnerer, J. Antidepressants: Clinically Relevant Drug Interactions to Be Considered. *Pharmacology*. **2010**, *86*(4), 203-215.

[33] Neri, S.; Bertino, G.; Petralia, A.; Giancarlo, C.; Rizzotto, A.; Calvagno, G.S.; Mauceri, B.; Abate, G.; Boemi, P.; Di Pino, A.; Ignaccolo, L.; Vadalà, G.; Misseri, M.; Maiorca, D.; Mastrosimone, G.; Judica, A.; Palermo, F. A multidisciplinary therapeutic approach for reducing the risk of psychiatric side effects in patients with chronic hepatitis C treated with pegylated interferon α and ribavirin. *J Clin Gastroenterol.*, **2010**, *44*(9), e210-217.

[34] Haskett, R.F.; Loo, C. Adjunctive psychotropic medications during electroconvulsive therapy in the treatment of depression, mania, and schizophrenia. *J ECT*., **2010**, *26*(3), 196-201.

[35] Macgillivray, L.; Lagrou, L.M.; Reynolds, K.B.; Rosebush, P.I.; Mazurek, M.F. Role of serotonin transporter inhibition in the regulation of tryptophan hydroxylase in brainstem raphe nuclei: time course and regional specificity. Neuroscience, **2010**, *171*(2), 407-420.

[36] Hajjo, R.; Grulke, C.M.; Golbraikh, A.; Setola, V.; Huang, X.P.; Roth, B.L.; Tropsha, A. Development, Validation, and Use of Quantitative Structure-Activity Relationship Models of 5-Hydroxytryptamine (2B) Receptor Ligands to Identify Novel Receptor Binders and Putative Valvulopathic Compounds among Common Drugs. *J Med Chem.*, **2010**, *53*(21), 7573-7586.

[37] Brea, J.; Rodrigo, J.; Carrieri, A.; Sanz, F.; Cadavid, M.I.; Enguix, M.J.; Villazón, M.; Mengod, G.; Caro, Y.; Masaguer, C.F.; Raviña, E.; Centeno, N.B.; Carotti, A.; Loza, M.I. New serotonin 5-HT(2A), 5-HT(2B), and 5-HT(2C) receptor antagonists: synthesis, pharmacology, 3D-QSAR, and molecular modeling of (aminoalkyl)benzo and heterocycloalkanones. *Med Chem.*, **2002**, *45*(1), 54-71.

[38] Jesse, C.R.; Wilhelm, E.A.; Bortolatto, C.F.; Nogueira, C.W. Evidence for the involvement of the noradrenergic system, dopaminergic and imidazoline receptors in the antidepressant-like effect of tramadol in mice. *Pharmacol Biochem Behav.*, **2010**, *95*(3), 344-350.

[39] Manta, S.; Dong, J.; Debonnel, G.; Blier, P. Enhancement of the function of rat serotonin and norepinephrine neurons by sustained vagus nerve stimulation. *J Psychiatry Neurosci.*, **2009**, *34*(4), 272-280.

[40] Jhaveri, D.J.; Mackay, E.W.; Hamlin, A.S.; Marathe, S.V.; Nandam, L.S.; Vaidya, V.A.; Bartlett, P.F. Norepinephrine directly activates adult hippocampal precursors *via* beta3-adrenergic receptors. *J Neurosci.*, **2010**, *30*(7), 2795-2806.

[41] López, L.; Selent, J.; Ortega, R.; Masaguer, C.F.; Domínguez, E.; Areias, F.; Brea, J.; Loza, M.I.; Sanz, F.; Pastor, M. Synthesis, 3D-QSAR, and structural modeling of benzolactam derivatives with binding affinity for the D(2) and D(3) receptors. *Med Chem.*, **2010**, *5*(8), 1300-1317.

[42] de Graaf, C.; Foata, N.; Engkvist, O.; Rognan, D. Molecular modeling of the second extracellular loop of G-protein coupled receptors and its implication on structure-based virtual screening. *Proteins,* **2008**, *71*(2), 599-620.

[43] Teeter, M.M.; Froimowitz, M.; Stec, B.; DuRand, C. J. Homology nodeling of the dopamine D_2 receptor and its testing by docking of agonists and tricyclic antagonists. *J. Med. Chem.,* **1994**, *37*, 2874-2888.

[44] Andrade, C.H.; Salum, L.B.; Pasqualoto, K.F.M.; Ferreir, E.I.; Andricopulo, A.D. Three-Dimensional Quantitative Structure-Activity Relationships for a Large Series of Potent Antitubercular Agents. *Lett. Drug Des. Discov.*, **2008**, *5*, 377-387.

[45] Akamatsu, M. Current state and perspectives of 3D-QSAR. *Curr. Top. Med. Chem.,* **2002**, *2*, 1381-1394.

[46] Frederic, C.; Cristine Ada, C.; Erwan, A.; David, A.; Cecile, D.; Michael, F.; Jean-Francois, H.; Martinez, J.; Solveig, L.J.; Philippe, M.; Andrea, P.; Agnes, P.; Christopher, P.; Philippe, R.; Peter, S.G.; Sherwin, W. JLK inhibitors: isocoumarin compounds as putative probes to selectively target the gamma-secretase pathway. *Curr. Alzheimer Res.*, **2005**, *2*, 327-334.

[47] Garg, A.; Tewari, R.; Raghava, G.P. KiDoQ: using docking based energy scores to develop ligand based model for predicting antibacterials. *BMC Bioinformatics*, **2010**, *11*, 125.

[48] Gundersen, E.; Fan, K.; Haas, K.; Huryn, D.; Steven Jacobsen, J.; Kreft, A.; Martone, R.; Mayer, S.; Sonnenberg-Reines, J.; Sun, S.C.; Zhou, H. Molecular-modeling based design, synthesis, and

activity of substituted piperidines as gamma-secretase inhibitors. *Bioorg. Med. Chem. Lett.*, **2005**, *15*, 1891-1894.

[49] Prasad, C.V.; Vig, S.; Smith, D.W.; Gao, Q.; Polson, C.T.; Corsa, J.A.; Guss, V.L.; Loo, A.; Barten, D.M.; Zheng, M.; Felsenstein, K.M.; Roberts, S.B. 2,3-Benzodiazepin-1,4-diones as peptidomimetic inhibitors of gamma-secretase. *Bioorg. Med. Chem. Lett.*, **2004**, *14*, 3535-3538.

[50] Park, H.; Lee, S. Determination of the active site protonation state of beta-secretase from molecular dynamics simulation and docking experiment: implications for structure-based inhibitor design. *J. Am. Chem. Soc.*, **2003**, *125*, 16416-16422.

[51] Hu, J.; Cwi, C.L.; Smiley, D.L.; Timm, D.; Erickson, J.A.; McGee, J.E.; Yang, H.C.; Mendel, D.; May, P.C.; Shapiro, M.; McCarthy, J.R. Design and synthesis of statine-containing BACE inhibitors. *Bioorg. Med. Chem. Lett.*, **2003**, *13*, 4335-4339.

[52] Ghosh, A.K.; Devasamudram, T.; Hong, L.; DeZutter, C.; Xu, X.; Weerasena, V.; Koelsch, G.; Bilcer, G.; Tang, J. Structure-based design of cycloamide-urethane-derived novel inhibitors of human brain memapsin 2 (beta-secretase). *Bioorg. Med. Chem. Lett.*, **2005**, *15*, 15-20.

[53] Snyder, R.D.; Hendry, L.B. Toward a greater appreciation of noncovalent chemical/DNA interactions: application of biological and computational approaches. *Environ. Mol. Mutagen.*, **2005**, *45*, 100-105.

[54] Zuo, Z.; Luo, X.; Zhu, W.; Shen, J.; Shen, X.; Jiang, H.; Chen, K. Molecular docking and 3D-QSAR studies on the binding mechanism of statine-based peptidomimetics with beta-secretase. *Bioorg. Med. Chem.*, **2005**, *13*, 2121-2131.

[55] Hayashi, Y.; Sakaguchi, K.; Kobayashi, M.; Kikuchi, Y.; Ichiishi, E. Molecular evaluation using in silico protein interaction profiles. *Bioinformatics*, **2003**, *19*, 1514-1523.

[56] Oprea, T.I.; Waller, C.L.; Marshall, G.R. Three-dimensional quantitative structure-activity relationship of human immunodeficiency virus (I) protease inhibitors. 2. Predictive power using limited exploration of alternate binding modes. *J. Med. Chem.,* **1994**, *37*, 2206-2215.

[57] Chemical Computing Group. http://www.chemcomp.com (Accessed November 13, 2010).

[58] Sybyl Basic Ligand-Based Design Manual, Tripos Associates Inc.: St. Louis, **1988**.

[59] The Laboratory for Molecular Simulation. http://lms.chem.tamu.edu/cerius2.html (Accessed November 13, 2010).

[60] Avram, S.; Berner, H.; Milac, A.L.; Wolschann, P. Quantitative structure-activity relationship studies on membrane receptors inhibition by antipsychotic drugs. Application to new schizophrenia. *Chemical Monthly*, **2008**, *139*, 407.

[61] Catana, C.; Gao, H.; Orrenius, C.; Stouten P.F.W. Linear and nonlinear methods in modeling the aqueous solubility of organic compounds. *J. Chem. Inf. Model.,* **2005**, *45,* 170-176.

[62] Kier, L.B.; Hall, L.H. Intermolecular accessibility: the meaning of molecular connectivity. *J. Chem. Inf. Comput. Sci.,* **2000**, *40*, 792-795.

[63] Kier, L.B. Inclusion of symmetry as a shape attribute in kappa-index analysis. *Quant. Struct-Act. Relat.,* **1987**, *6*, 8-12.

[64] Petitjean, M. Applications of the radius-diameter diagram to the classification of topological and geometrical shapes of chemical compounds. *J. Chem. Inf. Comput. Sci.,* **1992**, *32*, 331-337

[65] Gasteiger, J.; Marsili, M. Iterative partial equalization of orbital electronegativity – a rapid access to atomic charges. *Tetrahedron,* **1980**, *36*, 3219-3228.

[66] Stanton, D.; Jurs, P. Development and use of the charged partial surface area structural descriptors in computer-assisted quantitative structure-property relationship studies. *Anal. Chem*., **1990**, *62*, 2323-2329.

[67] Cramer, R.D.3rd; Patterson, D.E.; Bunce, J.D. Recent advances in comparative molecular field analysis (CoMFA). *Prog. Clin. Biol. Res.*, **1989**, *291*, 161-165.

[68] Khedkar, S.A.; Malde, A.K.; Coutinho, E.C. CoMFA study of distamycin analogs binding to the minor-groove of DNA: a unified model for broad-spectrum activity. *J Mol Model.*, **2007**, *13*(10), 1099-1108.

[69] Klebe, G.; Abraham, U.; Mietzner, T. Molecular similarity indices in a comparative analysis (CoMSIA) of drug molecules to correlate and predict their biological activity. *J. Med. Chem.*, **1994**, *37*, 4130-4146.

[70] Carosati, E.; Lemoine, H.; Spogli, R.; Grittner, D.; Mannhold, R.; Tabarrini, O.; Sabatini, S.; Cecchetti, V. Binding studies and GRIND/ALMOND-based 3D QSAR analysis of benzothiazine type K(ATP)-channel openers. *Bioorg. Med. Chem.,* **2005**, *13*, 5581-5591.

[71] Clark, D.E. Prediction of Intestinal Absorption and Blood-Brain Barrier Penetration by Computational Methods. *Comb. Chem. High Throughput Screen,* **2001**, *4*, 477-496.

[72] Quiñones-Torrelo, C.; Sagrado, S.; Villanueva-Camañas, R.M.; Medina-Hernández, M.J. Development of predictive retention-activity relationship models of tricyclic antidepressants by micellar liquid chromatography, *J Med Chem.*, **1999**, *42*(16), 3154-3162.

[73] Wang, S.R.; Chen, Y.; Wu, L.P.; Miao, W.J.; Xiong, M.J.; Chen, C.; Zhong, Z.R.; Ye, L.M. Development of predictive quantitative retention-activity relationship models of HMG-CoA reductase inhibitors by biopartitioning micellar chromatography, *J Pharm Biomed Anal.*, **2008**, *46*(2), 243-249.

[74] Wang, S.R.; Chen, Y.; Xiong, M.J.; Wu, L.P.; Ye, L.M. Quantitative retention-activity relationship models of angiotensin converting enzyme inhibitors using biopartitioning micellar chromatography, *J Chromatogr Sci.,***2010,** *48*(2), 134-139.

[75] Pidgeon, C.; Ong, S.; Liu, H.; Qiu, X.; Pidgeon, M.; Dantzig, A.H.; Munroe, J.; Hornback, W.J.; Kasher, J.S.; Glunz, L.; Szczerba, T. IAM chromatography: an *in vitro* screen for predicting drug membrane permeability. *J. Med. Chem.,* 1995, *38*, 590–594.

[76] Balon, K.; Riebesehl, B.U., Muller, B.W. Drug liposome partitioning as a tool for the prediction of human passive intestinal absorption. *Pharm. Res.,* 1999, *16*, 882–888.

[77] Lundqvist, A.; Lundahl, P. Chromatography on Cells and Biomolecular Assemblies. *J. Chromatogr. B* **1997**, *699*, 209-220.

[78] Berthod, A.; Girard, I.; Gomet, C. Micellar Liquid Chromatography. Adsorption Isotherms of Two Ioninc Surfactants on Five Stationary Phases. *Anal. Chem.,* **1986**, *58*, 1356-1358.

[79] Avram, S.; Buiu, C.; Duda-Seiman, D.M.; Duda-Seiman, C.; Mihailescu, D. Design of new escitalopram derivatives for the treatment of major depressive disorder by 3D-QSAR, *Sci Pharm.*, **2010**, *78*, 233-248.

[80] Chen, K.X.; Li, Z.G.; Xie, H.Y.; Gao, J.R.; Zou, J.W. Quantitative structure-activity relationship analysis of aryl alkanol piperazine derivatives with antidepressant activities. *Eur J Med Chem.*, **2009**, *44*(11), 4367-4375.

[81] Shelke, S.M; Bhosale, S.H. Synthesis, antidepressant evaluation and QSAR studies of novel 2-(5*H*-[1,2,4]triazino[5,6-*b*]indol-3-ylthio)-*N*-(substituted phenyl)acetamides. *Bioorganic & Medicinal Chemistry Letters*, **2010**, *20*(15), 4661-4664.

[82] Weber, K.C.; Honório, K.M.; Andricopulo, A.D.; Da Silva, A.B. Two-dimensional QSAR studies on arylpiperazines as high-affinity 5-HT(1A) receptor ligands. *Med Chem.*, **2008**, *4*(4), 328-335.

[83] Weber, K.C.; Salum, L.B.; Honório, K.M. Pharmacophore-based 3D QSAR studies on a series of high affinity 5-HT_{1A} receptor ligands. *European Journal of Medicinal Chemistry*, **2010**, *45*(4), 1508-1514.

[84] Weber, K.C.; da Silva, A.B. A chemometric study of the 5-HT_{1A} receptor affinities presented by arylpiperazine compounds. *European Journal of Medicinal Chemistry*, **2008**, *43*(2), 364-372.

[85] Dessalew, N. QSAR Study on Dual 5-HT1Aand 5-HT1B Antagonists: An Insight into the Structural Requirement for Antidepressant Activity. *Arch. Pharm. Chem. Life Sci.*, **2008**, *341*, 314-322.

Received: November 25, 2010 Revised: August 17, 2011 Accepted: August 17, 2011