Structure-Activity Relationships for Serotonin Transporter and Dopamine Receptor Selectivity

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Abstract: Antipsychotic medications have a diverse pharmacology with affinity for serotonergic, dopaminergic, adrenergic, histaminergic and cholinergic receptors. Their clinical use now also includes the treatment of mood disorders, thought to be mediated by serotonergic receptor activity. The aim of our study was to characterise the molecular properties of antipsychotic agents, and to develop a model that would indicate molecular specificity for the dopamine (D_2) receptor and the serotonin (5-HT) transporter.

Back-propagation artificial neural networks (ANNs) were trained on a dataset of 47 ligands categorically assigned antidepressant or antipsychotic utility. The structure of each compound was encoded with 63 calculated molecular descriptors. ANN parameters including hidden neurons and input descriptors were optimised based on sensitivity analyses, with optimum models containing between four and 14 descriptors.

Predicted binding preferences were in excellent agreement with clinical antipsychotic or antidepressant utility. Validated models were further tested by use of an external prediction set of five drugs with unknown mechanism of action. The SAR models developed revealed the importance of simple molecular characteristics for differential binding to the D_2 receptor and the 5-HT transporter. These included molecular size and shape, solubility parameters, hydrogen donating potential, electrostatic parameters, stereochemistry and presence of nitrogen.

The developed models and techniques employed are expected to be useful in the rational design of future therapeutic agents.

Key Words: Theoretical descriptors, ANN, QSAR, 5-HT transporter, SERT, D_2 receptor.

INTRODUCTION

The Global Burden of Disease study found that depression was the fourth leading cause of disease burden in the world [1, 2] representing a major public health problem affecting individuals and society. Over the past number of decades large advances have been made in both our understanding of the central nervous system and in the pathophysiology of major psychiatric disorders. It is generally accepted that the monoamine neurotransmitters play a critical role in depression and, as such, have been the primary target for antidepressant medication. However, since the exact pathophysiology of depression remains as yet unclear, several antidepressant treatments have been developed which target one neurotransmitter system over another.

The neurotransmitter dopamine is strongly implicated in the pathophysiology of schizophrenia and it has been demonstrated that dopamine agonists cause worsening of symptoms [3]. Since the discovery of the antipsychotic action of chlorpromazine, many effective antipsychotic drugs have been developed. Today, antipsychotics are divided into two major groups. The typical antipsychotics, also known as the first generation, include a variety of phenothiazine and butyrophenone compounds. The principal pharmacological action of both groups is antagonism at the dopamine D_2 receptor. However, extrapyramidal side effects (EPS), autonomic and endocrine side effects, and poor efficacy against negative symptoms and cognitive disturbances have considerably limited the therapeutic usefulness of the typical antipsychotics. The increased understanding of the pathophysiology of psychotic illness has resulted in a change of focus from the traditional D_2 antagonism of the butyrophenone and phenothiazine groups, to the "atypical" antipsychotics, typified by clozapine. Newer, atypical antipsychotics have a more diverse pharmacology, with no or little EPS at doses showing antipsychotic activity [4-7].

The role of serotonin in depression has also been well documented, and the affinity of atypical antipsychotics for the serotonin transporter as well as post-synaptic serotonin receptors suggests a role for this neurotransmitter [8]. The neurotransmitter transporters have proved to be very important targets for CNS drug discovery, particularly for antidepressant drugs. Virtually all of the modern generations of antidepressants act as inhibitors of one or other of the monoamine transporters.

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It is likely that atypicality of a neuroleptic drug is explained by its affinity for more than one receptor subtype. However, no single hypothesis effectively explains atypical character. Clozapine is arguably the most effective atypical antipsychotic agent and the only drug that has demonstrated clinical effectiveness in refractory schizophrenia [9]. The pharmacology of clozapine is complex, having affinity for serotonergic, dopaminergic, adrenergic, histaminergic and cholinergic receptors [10]. The varied pharmacology of the atypical antipsychotics has led to their use in non-psychotic illnesses such as depression and bipolar disorder. More recently anti-epileptic drugs have been used in the treatment of mood disorders, despite the lack of detailed pharmacological knowledge of their mode of action.

The aim of our study was to characterize the molecular properties of antipsychotic agents, and to develop a model that would indicate molecular specificity for the D_2 receptor and serotonin transporter. We then wished to test several anti-epileptic drugs that are currently being used in mood disorders using this model to evaluate theoretical affinity for either the D_2 receptor or the serotonin transporter.

METHOD

The affinity values (dissociation constants, K_i) of 41 compounds at the human cloned D_2 receptor or 5-HT transporter were taken from the literature [11] and are given in Table **1**. The 3D structures of all compounds were generated and optimised using the MM2 (full molecular mechanics) procedure in Molecular Modeling Pro 5.1 [12]. MM2 is the standard geometry minimization procedure that ascribes optimum values for bond lengths, bond angles and torsional bond angles. Full MM2 preserves the stereochemistry of the molecule while calculating the local minimum for the current conformation. From the optimised structures 63 calculated molecular descriptors were then generated for each compound that described 2D and 3D structural information as well as molecular physicochemical properties. These included size and shape parameters (molecular weight, surface area, volume, kappa shape, connectivity indices), electrostatic parameters (dipole moment, valence indices 0-3, CIM indices), lipophilicity parameters (water solubility, polarity, percent hydrophilic surface, hydrophilic-lipophilic balance), hydrogen bonding potential, cyclic components, and specific substitution. Molecular descriptors were used as inputs and relative binding affinities as the outputs to build the ANN model.

The total number of compounds in the present study was 46. Of these, 41 compounds were used either as antipsychotics or antidepressants, and had defined Ki values for the D_2 receptor or 5-HT transporter. All 41 compounds were randomly divided into training (27 compounds), testing (7 compounds) and validation (7 compounds) subsets before each training cycle. The remaining five compounds, carbamazepine, gabapentin, lamotrigine, valproic acid and vigabatrin are licensed anti-epileptic drugs, and did not have binding data available for D_2 or 5-HT. We tested this additional independent set of compounds using the QSAR models developed for prediction of 5-HT transporter and D_2 receptor relative binding preference.

Back-propagation artificial neural networks (ANNs) were trained using commercial software [13] on a dataset of 41 ligands. These compounds were assigned categorical values of 1 or -1 depending on their use as an antipsychotic or antidepressant and their preferential binding to 5-HT or D_2 receptors. An antidepressant would therefore be coded as +1 (5-HT) and -1 (D_2). The number of inputs, transfer function and the number of hidden neurons were optimized using the ANN program internal algorithms. Connections or units were eliminated during training based on a sensitivity report. Following a sensitivity analysis [14] the number of inputs was reduced from 63 to between 14, 13, and 4.

RESULTS AND DISCUSSION

The QSAR models developed revealed the importance of simple molecular characteristics essential for antidepressant or antipsychotic activity and their differential binding to the D_2 receptor and the 5-HT transporter. These included molecular size and shape (bulkiness), lipophilicity (solubility parameters, hydrogen donating potential, clogP, Crippen), electrostatic parameters, stereochemistry and presence of nitrogen. Once the network was established during training and testing, the QSAR model was validated. The validated model was then used to evaluate categorical binding affinities for selected anti-epileptic drugs currently used in the treatment of mood disorders (carbamazepine, gabapentin, lamotrigine, valproic acid and vigabatrin,).

Three models with 100% accuracy in classifying training, internal testing, and validation with the external set of compounds (Table **2**). They all categorized the external set of compounds (carbamazepine, gabapentin, lamotrigine, valproic acid and vigabatrin) as antidepressants. The simplest of these was a 3-layer ANN with only four descriptors as inputs and four hidden neurons (Table **3**). All models had calculated log *P* (clogP) and valence connectivity index 2 ($^2\chi^v$) in common, while substituted double ($R{=}CR_2$) bond was present in the first and third model, and the number of nitrogens next to another nitrogen (NN) was common for the second and third model. It has been shown that introduction of a double bond specifically influences D_2 receptor affinity [15], while NN influences binding to 5-HT [16].

Log *P*, the octanol–water partition coefficient, is a well established parameter describing lipophilicity in biological systems and has been frequently used in quantitative structure–activity/property relationships [17]. However, *P* is a ratio and a compound with low solubility in both octanol and water could have the same log *P* as a compound with solubilities 100 times higher in both solvents. Additional descriptors are therefore required in QSAR to account for other binding and transport properties [18].

Molecular connectivity (χ) is a method of quantitatively characterizing skeletal variation in a molecule, in which weighted counts of substructure fragments are incorporated into numerical indices. The second order χ index encodes specific information about skeletal branching which may indicate the amount of structural flexibility. Inclusion of second order valence connectivity index ($^2\chi^v$) in the optimum models may be necessary to account for heteroatom substitution and positioning at the receptor binding site. The aim of

Table 1. Dataset of 5-HT Transporter and D_2 Receptor Ligands with Experimental Binding Affinities and Categorical Values [11]

Compound	Ki Values (nM)		Categorical Values	
	5-HT Transporter	D_2	Antidepressant	Antipsychotic
amoxapine	58	-	1	-1
amitriptyline	22.71	-	1	-1
aripiprazole	-	2.33	-1	1
chlorpromazine	-	3.53	-1	1
citalopram	5.95	-	1	-1
clomipramine	0.28	-	1	-1
clozapine	-	140.75	-1	1
cocaine	236.5	-	1	-1
desipramine	112.12	-	1	-1
domperidone	-	0.94	-1	1
doxepin	68	-	1	-1
duloxetine	1.22	-	1	-1
escitalopram	1.8	-	1	-1
fenfluramine	667	-	1	-1
fluoxetine	5.92	-	1	-1
flupenthixol	-	0.77	-1	1
fluphenazine	-	0.65	-1	1
fluvoxamine	6.22	-	1	-1
haloperidol	-	1.86	-1	1
imipramine	10.43	-	1	-1
metoclopramide	-	64	-1	1
mirtazepine	100 000	-	1	-1
nefazodone	402.67	-	1	-1
olanzapine	-	36.72	-1	1
paroxetine	0.29	-	1	-1
perphenazine	-	0.56	-1	1
pimozide	-	2.47	-1	1
prochlorperazine	-	1.89	-1	1
promazine	-	300	-1	1
quetiapine	-	429.7	-1	1
reboxetine	273.5	-	1	-1
reserpine	-	586	-1	1
risperidone	-	3.86	-1	1
sertraline	1.28	-	1	-1
sulpiride	-	57.45	-1	1
thioridazine	-	8.75	-1	1

(Table 1. Cond….)

Compound	Ki Values (nM)		Categorical Values	
	5-HT Transporter	D_2	Antidepressant	Antipsychotic
trazodone	367.33	-	1	-1
trifluoperazine	-	2.83	-1	1
trimipramine	149	-	1	-1
venlafaxine	63.89	-	1	-1
ziprasidone	-	5.35	-1	1
Model predictions for the data set with unknown binding affinities				
carbamazepine	-	-	1	-1
gabapentin	-	-	1	-1
lamotrigine	-	-	1	-1
valproic acid	-	-	1	-1
vigabatrin	-	-	1	-1

Table 2. Models Performance and Predictions

MLP Profile	4-4-2	13-5-8-2	14-18-13-2
Train Error	0.00005	0.068	0.0022
Select Error	0.00004	0.057	0.1381
Test Error	0.00004	0.003	0.0020

Table 3. Descriptors in Optimum ANN Models [14]

Model Profile[a]	14-*18*-*13*-1	13-*5*-*8*-1	4-*4*-1[c]
Descriptors[b]	CHRRR	**NN**	$^{2}\chi^{v}$
	$^{0}\chi$	$^{2}\chi^{v}$	**clogP**
	dipole moment from	solubility parameter	**R=CRR**
	clogP	$^{3}\chi^{v}$	**NN**
	molecular width	**clogP**	
	N–aromatic	$^{1}\chi^{v}$	
	parachor	CHRRR	
	R=CRR	R=N	
	surface area	LUMO	
	$^{0}\chi^{v}$	Hansen H-bond	
	$^{2}\chi^{v}$	H-bond donor from	
	$^{3}\chi^{v}$	Hansen dispersion	
	water solubility	Hansen polarity	
	CHRRR		

[a]number of artificial neurons in input-*hidden1*-*hiddens*-output layer.

[b]rank order according to external validation.

[c] descriptors in common are given in bold.

this study was not to extensively analyze the importance of individual descriptors, however further information is available elsewhere [14, 19].

Stereochemistry and other geometrical factors (shape of the molecule) are significant in determining the type of psychotic activity. The structures of typical tricyclic antidepressants (TCA) contain rigid ring systems with a conformationally restrained dopamine moiety fused within. A rigid tricyclic system yields optimal D_2 activity. This suggests that D_2 receptor pocket more readily accommodates a flatter molecule. Three main types of internal conformational mobility are possible for TCA drugs. These include ring inversion of the tricyclic moiety, flexing bridge ($-CH_2-CH_2$ or CH_2-X-) in the central seven-membered ring, and flexibility of the alkyl side chain [20]. All of these types can result in substantial changes in either the overall shape of the molecules or in the local environments of individual sites within them. One of the structural differences between the TCAs and other central nervous system active drugs is the lack of coplanarity in the TCA structures due to the twisted central seven-membered ring system and greater deal of flexibility. Consequently, the angle between the two phenyl planes is different when compared with antipsychotic drugs. This lack of coplanarity contrasts to the limited degree of internal mobility of the two aromatic rings in antipsychotic drugs where a central six-membered ring is present. Thus, molecular dynamics should be an additional factor considered when trying to understand the mode of action of this clinically important family of molecules. Modification of the tricyclic moiety has major functional implications. For instance, modifications in amitriptyline are marked by changes in neuronal specificity and side effects. Inclusion of an oxygen heteroatom gives rise to doxepin, a drug with less selectivity for serotonin uptake and fewer cardiotoxic effects, whereas addition of a chlorine substituent on the aromatic ring of imipramine gives clomipramine, a drug useful in the treatment of obsessional neurosis. Studies relating the effects of alteration of the sidechain or tricyclic nucleus structure on the pharmacological activity of the TCA drugs have been reviewed [21].

A large number of dopamine antagonists have been developed, with greater structural variety present than for dopamine agonists. A pharmacophoric model for D_2 antagonism can be summarized as a lipophilic aromatic area located about 6Å from a basic nitrogen atom [22, 23]. Further away (7.5Å) from this centre, there is a flat aromatic region with a lipophilic substituent. The ethylamino side chain is structurally flexible which lends to small variations in the intramolecular distance between the center of the aromatic ring and the nitrogen atom (5.091Å – 5.166Å). The region near the nitrogen favours the presence of bulky substituents yielding high affinity for the D_2 receptor.

Only a small number of pharmacophoric models of serotonin transporter (SERT) ligands have been published [24-26]. In most cases only one aromatic ring had been included in the pharmacophore and placed at a distance from the basic nitrogen, comparable to the distance in serotonin itself [27-32]. One study described a secondary phenyl ring as an additional pharmacophoric feature [25]. The central rings in molecules showing preferential affinity for the 5-HT_2 subtype of serotonin receptor are more flexible, comprising a twisted structure that holds two aromatic rings in a skewed arrangement (Fig. **1**). As pharmacophoric features, the centers of the two aromatic rings and a side chain with nitrogen at a distance of 2.8Å from the basic nitrogen in the direction of the lone pair have been defined [25]. The distance between the two aromatic rings is approximately 4.6Å – 5.2Å. The distance between the first aromatic ring and nitrogen in the side chain is in the range of 7.4Å – 8.3Å, and the distance between the second aromatic ring and nitrogen in the side chain is in the range of 6.2Å – 6.9Å. The two pharmacophoric aromatic rings are perpendicular to each other.

The SERT pharmacophore, reported recently [33], is characterized by a basic nitrogen atom, a lipophilic aromatic region at 6.1Å, and a second lipophilic part (second aromatic ring). The space around the basic nitrogen atom is sterically restricted. The presence of the same features in both pharmacophores for D_2 and SERT may account for the possibility and existence of bifunctional molecules, although none of the features appeared to overlap properly in three-dimensional space.

Binding of serotonin to the 5-HT receptor occupies two subpockets within the active site: a relatively wide lipophilic part into which the indole skeleton is located, and a narrow channel occupied by the ethylamino group. Binding of a ligand, such as escitalopram, occupies three separate subpockets in the receptor protein by fitting the dimethylamino-

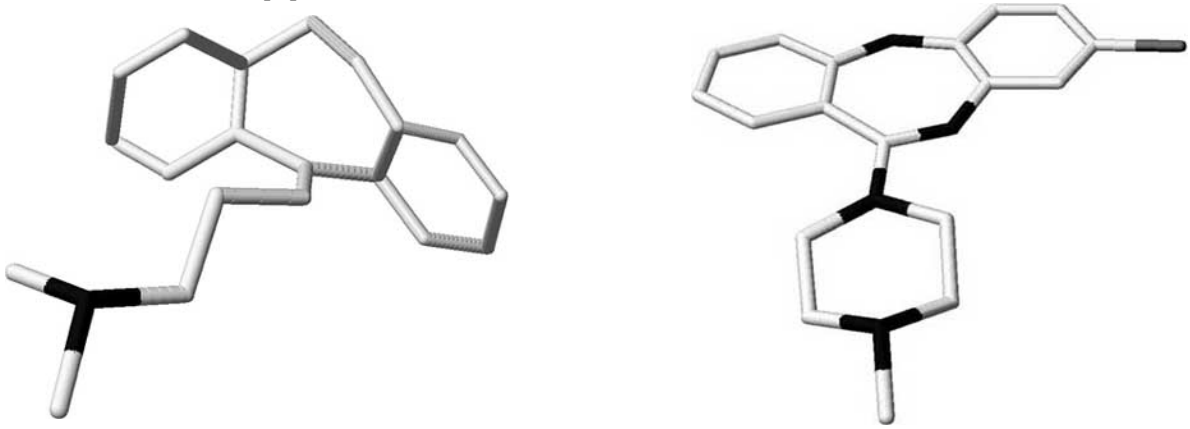

Fig. (1). Flexibility of the central ring; molecular structures of (a) amitriptyline and (b) clozapine.

propyl chain (side chain), the fluorophenyl group (aromatic ring), and the cyanophthalane skeleton (aromatic ring with substituent) (Fig. **2**). Thus, the subpocket occupied by the indole skeleton of 5-HT corresponds to the subpocket occupied by the cyanophthalane skeleton, whereas the narrow channel-like pocket occupied by the ethylamine side chain of 5-HT shares similarities with the dimethylaminopropyl pocket.

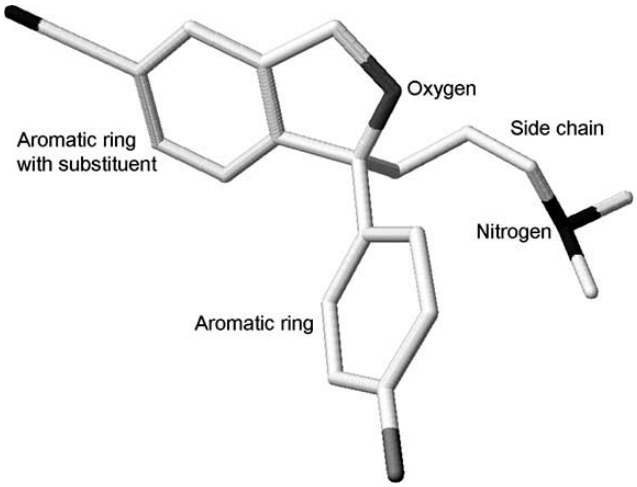

Fig. (2). *(S)*-citalopram pharmacophore.

Most neuroleptic drugs are extremely lipophilic molecules, bind extensively to proteins, and tend to accumulate in highly perfused tissues. After long-term treatment and drug administration is stopped, therapeutic effects may outlast significant blood concentrations by days or weeks. This may result from tight binding of parent drug or its active metabolites in the brain. It has been found that the chromatpgraphic retention of antidepressants measured by micellar chromatography can describe the inhibitory activity of antidepressants [34]. In micellar liquid chromatography solutes are separated mainly on the basis of differences in their polarities. Chromatographic retention generally depends on the same interactions that influence drug activity (lipophilic, electronic and steric contributions). Since most antidepressants possess similar electronic features, differences observed in retention are explained by means of molecular shape and overall lipophilic contributions.

Many currently used antidepressants are chiral drugs, some of which are administered as racemates (mianserin, mirtazepine, fluoxetine, reboxetine, venlafaxine, citalopram) while others are given as single isomers (paroxetine and sertraline) [35, 36]. Current evidence suggests that functional differences between the enantiomers and the racemate could have important clinical implications [37]. The relative benefits of the enantiomers of antidepressants vary greatly. When the therapeutic properties of the enantiomers are complementary (for example, mianserin) then use of the racemate is an advantage. However, if there are qualitative, but not quantitative, similarities, then it would be beneficial to develop the active isomer. For instance, the *S*-enantiomer of citalopram (escitalopram) is over 100 times more potent in inhibiting the 5-HT transporter than the *R*-form, and lacks significant activity at other neurotransmitter receptors. Racemic citalopram shows additional affinity for histamine receptors and causes sedation. Knowledge of the stereochemistry of psychotropic drugs will thus help in the development of new and more effective molecules in the near future.

Although carbamazepine, valproate, and, most recently, lamotrigine [38, 39] are the only antiepileptic drugs with a Food and Drug Administration (FDA) indication for the treatment of a psychiatric disorder, virtually every other new antiepileptic drug has received claims of efficacy for a range of psychiatric illnesses. The use of antiepileptic drugs in psychiatric illness is also based on the belief that there are shared biological mechanisms involved in epilepsy and these disorders.

The antiepileptic drugs with established psychotropic effects (carbamazepine, valproate, and lamotrigine) have been found to cause an increase in synaptic 5-HT [40-42]. One of the most recognized hypothesis of depression focuses on alteration of the serotonergic function. Recent evidence suggests that serotonergic involvement in depression may be modulated by the action of gamma-hydroxybutyric acid (GABA). The GABA system regulates many physiological and psychological processes and its dysfunction is implicated in the pathophysiology of several neuropsychiatric disorders, including anxiety and depression [43]. There is strong evidence for interactions between the GABAergic system and the serotonergic system. Experimental data suggest that $GABA_B$ receptor antagonists display antidepressant-like properties *via* an interaction with the serotonergic system [44]. $GABA_B$ receptors play a major role in the modulation of behaviours relevant to anxiety and suggest that positive modulation is a novel approach to probe a role for $GABA_B$ receptors in behavioral processes.

Gabapentin, designed as a precursor of GABA, easily crosses the blood-brain barrier, increasing synaptic levels of GABA [45]. Preclinical studies have suggested that gabapentin increases brain and intracellular GABA by an amino acid active transporter at the blood-brain barrier and multiple enzymatic regulatory mechanisms, respectively. Vigabatrin is an anticonvulsant that inhibits the catabolism of GABA, thereby increasing the amount of GABA available synaptically. Vigabatrin exerts its effects by irreversible inhibition of GABA transaminase [46].

All predictions of activity of these antiepileptic drugs were for binding at the 5-HT transporter rather than the D_2 receptor, in keeping with the above discussion. The lack of knowledge of the precise mechanism of action has not prevented their use in an increasing range of psychiatric conditions.

CONCLUSION

It is apparent that the molecules, pathways, and systems thought to be involved in anxiety and depression are interconnected. The pharmacological profiles of psychoactive drugs are complex and, since they interact with many receptor sites, they often result in numerous side effects. There is a lack of understanding of the pharmacological mode of action of most psychoactive drugs. Many have similar 3D structures which make it difficult to rationalize their differing relative potency in different clinical settings. However, significantly

different degrees of internal mobility suggests that molecular dynamics should be an additional factor considered when trying to understand the mode of action of this clinically important family of molecules.

REFERENCES

[1] Murray, C.J.; Lopez, A.D. Regional patterns of disability-free life expectancy and disability-adjusted life expectancy: global Burden of Disease Study. *Lancet,* **1997**, *349*, 1347-52.

[2] Ustun, T.B.; Ayuso-Mateos, J.L.; Chatterji, S.; Mathers, C.; Murray, C.J. Global burden of depressive disorders in the year 2000. *Br. J. Psychiatry,* **2004**, *184*, 386-92.

[3] Davis, K.L.; Kahn, R.S.; Ko, G.; Davidson, M. Dopamine in schizophrenia: a review and reconceptualization. *Am. J. Psychiatry,* **1991**, *148*, 1474-86.

[4] Meltzer, H.Y.; Matsubara, S.; Lee, J.C. Classification of typical and atypical antipsychotic drugs on the basis of dopamine D-1, D-2 and serotonin2 pKi values. *J. Pharmacol. Exp. Ther.,* **1989**, *251*, 238-46.

[5] Nyberg, S.; Nakashima, Y.; Nordstrom, A.L.; Halldin, C.; Farde, L. Positron emission tomography of in-vivo binding characteristics of atypical antipsychotic drugs. Review of D2 and 5-HT2 receptor occupancy studies and clinical response. *Br. J. Psychiatry Suppl.,* **1996**, *29*, 40-4.

[6] Remington, G. Understanding antipsychotic "atypicality": a clinical and pharmacological moving target. *J. Psychiatry Neurosci.,* **2003**, *28*, 275-84.

[7] Seeman, P.; Corbett, R.; van Tol, H.H. Atypical neuroleptics have low affinity for dopamine D2 receptors or are selective for D4 receptors. *Neuropsychopharmacology,* **1997**, *16*, 93-110.

[8] Roth, B.L.; Sheffler, D.; Potkin, S.G. Atypical antipsychotic drug actions: unitary or multiple mechanisms for 'atypicality'? *Clin. Neurosci. Res.,* **2003**, *3*, 108-17.

[9] Taylor, D.M.; Duncan-McConnell, D. Refractory schizophrenia and atypical antipsychotics. *J. Psychopharmacol.,* **2000**, *14*, 409-18.

[10] Coward, D.M. General pharmacology of clozapine. *Br. J. Psychiatry Suppl.,* **1992**, *17*, 5-11.

[11] Roth, B. NIMH Psychoactive Drug Screening Program. http://pdsp.med.unc.edu (14 October 2007).

[12] ChemSW *Molecular Modeling Pro*, 5.1; ChemSW: Fairfield, **2003**.

[13] StatSoft Inc *Statistica Neural Networks*, 7.1; StatSoft Inc,: Tulsa, USA, **2005**.

[14] Turner, J.V.; Maddalena, D.J.; Agatonovic-Kustrin, S. Bioavailability prediction based on molecular structure for a diverse series of drugs. *Pharm. Res.,* **2004**, *21*, 68-82.

[15] 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*, 143-57.

[16] Talik, P.; Pawłowski, M.; Lasocha, W. The structure of Azo-Analogs of 8-Styrylxanthines- X-Ray and Molecular Modelling Studies. In *V Multidyscyplinarna Konferencja Nauki o Leku*, Darłówko, **2006**.

[17] Mager, D.E. Quantitative structure-pharmacokinetic/pharmacodynamic relationships. *Adv. Drug Deliv. Rev.,* **2006**, *58*, 1326-56.

[18] Raevsky, O.A. Physicochemical descriptors in property-based drug design. *Mini Rev. Med. Chem.,* **2004**, *4*, 1041-52.

[19] Turner, J.V.; Maddalena, D.J.; Cutler, D.J. Pharmacokinetic parameter prediction from drug structure using artificial neural networks. *Int. J. Pharm.,* **2004**, *270*, 209-19.

[20] Casarotto, M.G.; Craik, D.J. Ring flexibility within tricyclic antidepressant drugs. *J. Pharm. Sci.,* **2001**, *90*, 713-21.

[21] Kaiser, C.; Setler, P. In *Burgers Medicinal Chemistry*, Wolff, M.; Ed.: Wiley: New York, **1981**; vol. *4*, p. 997.

[22] Hackling, A.; Ghosh, R.; Perachon, S.; Mann, A.; Holtje, H.D.; Wermuth, C.G.; Schwartz, J.C.; Sippl, W.; Sokoloff, P.; Stark, H. N-(omega-(4-(2-methoxyphenyl)piperazin-1-yl)alkyl)carboxamides as dopamine D2 and D3 receptor ligands. *J. Med. Chem.,* **2003**, *46*, 3883-99.

[23] Smid, P.; Coolen, H.K.; Keizer, H.G.; van Hes, R.; de Moes, J.P.; den Hartog, A.P.; Stork, B.; Plekkenpol, R.H.; Niemann, L.C.; Stroomer, C.N.; Tulp, M.T.; van Stuivenberg, H.H.; McCreary, A.C.; Hesselink, M.B.; Herremans, A.H.; Kruse, C.G. Synthesis, structure-activity relationships, and biological properties of 1-heteroaryl-4-[omega-(1H-indol-3-yl)alkyl]piperazines, novel potential antipsychotics combining potent dopamine D2 receptor antagonism with potent serotonin reuptake inhibition. *J. Med. Chem.,* **2005**, *48*, 6855-69.

[24] Rupp, A.; Kovar, K.A.; Beuerle, G.; Ruf, C.; Folkers, G. A new pharmophoric model for 5-HT reuptake-inhibitors: differentiation of amphetamine analogues. *Pharm. Acta Helv.,* **1994**, *68*, 235-44.

[25] Gundertofte, K.; Bjornholm, B. Pharmacophore mapping of the serotonin reuptake site. *Abstr. Pap. Am. Chem. Soc.,* **1997**, *213*, 9.

[26] Gundertofte, K.; Bogeso, K.P. Development of a pharmacophoric model of the serotonin reuptake site. *Abstr. Pap. Am. Chem. Soc.,* **1994**, *27*, 163.

[27] Bradley, A.L.; Izenwasser, S.; Wade, D.; Klein-Stevens, C.; Zhu, N.; Trudell, M.L. Synthesis and dopamine transporter binding affinities of 3alpha-benzyl-8-(diarylmethoxyethyl)-8-azabicyclo[3.2.1] octanes. *Bioorg. Med. Chem. Lett.,* **2002**, *12*, 2387-90.

[28] Chang, A.S.; Chang, S.M.; Starnes, D.M. Structure-activity relationships of serotonin transport: relevance to nontricyclic antidepressant interactions. *Eur. J. Pharmacol.,* **1993**, *247*, 239-48.

[29] Lindberg, U.H.; Thorberg, S. O.; Bengtsson, S.; Renyi, A.L.; Ross, S.B.; Ogren, S.O. Inhibitors of neuronal monoamine uptake. 2. Selective inhibition of 5-hydroxytryptamine uptake by alpha-amino acid esters of phenethyl alcohols. *J. Med. Chem.,* **1978**, *21*, 448-56.

[30] Smith, D.F. The stereoselectivity of serotonin uptake in brain tissue and blood platelets: the topography of the serotonin uptake area. *Neurosci. Biobehav. Rev.,* **1986**, *10*, 37-46.

[31] Xu, L.; Izenwasser, S.; Katz, J.L.; Kopajtic, T.; Klein-Stevens, C.; Zhu, N.; Lomenzo, S.A.; Winfield, L.; Trudell, M.L. Synthesis and biological evaluation of 2-substituted 3beta-tolyltropane derivatives at dopamine, serotonin, and norepinephrine transporters. *J. Med. Chem.,* **2002**, *45*, 1203-10.

[32] Humber, L.G.; Lee, D.; Rakhit, S.; Treasurywala, A.M. Computer-assisted investigation of structure-activity relationships in serotonin-uptake blockers. *J. Mol. Graph.,* **1985**, *3*, 84-89.

[33] Bureau, R.; Daveu, C.; Lancelot, J.C.; Rault, S. Molecular design based on 3D-pharmacophore. Application to 5-HT subtypes receptors. *J. Chem. Inf. Comput. Sci.,* **2002**, *42*, 429-36.

[34] Quinones-Torrelo, C.; Sagrado, S.; Villanueva-Camanas, R.M.; Medina-Hernandez, M.J. Efficiency of antidepressant drugs as monoamine reuptake inhibitors: analysis of the hydrophobicity influence using biopartitioning micellar chromatographic data. *Biomed. Chromatogr.,* **2004**, *18*, 427-35.

[35] Baumann, P.; Eap, C.B. Enantiomeric antidepressant drugs should be considered on individual merit. *Hum. Psychopharmacol.,* **2001**, *16*, S85-S92.

[36] Lane, R.M.; Baker, G.B. Chirality and drugs used in psychiatry: nice to know or need to know? *Cell. Mol. Neurobiol.,* **1999**, *19*, 355-72.

[37] Baker, G.B.; Prior, T.I. Stereochemistry and drug efficacy and development: relevance of chirality to antidepressant and antipsychotic drugs. *Ann. Med.,* **2002**, *34*, 537-43.

[38] Ballenger, J.C.; Post, R.M. Carbamazepine in manic-depressive illness: a new treatment. *Am. J. Psychiatry,* **1980**, *137*, 782-90.

[39] Goodnick, P.J. Anticonvulsants in the treatment of bipolar mania. *Expert Opin. Pharmacother.,* **2006**, *7*, 401-10.

[40] Dailey, J.W.; Reith, M.E.; Yan, Q.S.; Li, M.Y.; Jobe, P.C. Anticonvulsant doses of carbamazepine increase hippocampal extracellular serotonin in genetically epilepsy-prone rats: dose response relationships. *Neurosci. Lett.,* **1997**, *227*, 13-6.

[41] Southam, E.; Kirkby, D.; Higgins, G.A.; Hagan, R.M. Lamotrigine inhibits monoamine uptake *in vitro* and modulates 5-hydroxytryptamine uptake in rats. *Eur. J. Pharmacol.,* **1998**, *358*, 19-24.

[42] Whitton, P.S.; Fowler, L.J. The effect of valproic acid on 5-hydroxytryptamine and 5-hydroxyindoleacetic acid concentration in hippocampal dialysates *in vivo*. *Eur. J. Pharmacol.,* **1991**, *200*, 167-9.

[43] Cryan, J.F.; Kaupmann, K. Don't worry 'B' happy!: a role for GABA(B) receptors in anxiety and depression. *Trends Pharmacol. Sci.,* **2005**, *26*, 36-43.

[44] Slattery, D.A.; Desrayaud, S.; Cryan, J.F. GABAB receptor antagonist-mediated antidepressant-like behavior is serotonin-dependent. *J. Pharmacol. Exp. Ther.,* **2005**, *312*, 290-6.

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[45] Taylor, C.P. Mechanisms of action of gabapentin. *Rev. Neurol. (Paris),* **1997**, *153*, S39-45.

[46] Gram, L.; Larsson, O.M.; Johnsen, A.; Schousboe, A. Experimental studies of the influence of vigabatrin on the GABA system. *Br. J. Clin. Pharmacol.,* **1989**, *27*, 13S-17S.