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CoMFA methodology in structure-activity analysis of hexahydro- and octahydropyrido[1,2-*c*]pyrimidine derivatives based on affinity towards 5-HT_{1A}, 5-HT_{2A} and α_1-adrenergic receptors

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Abstract

Structural features of the pyrido[1,2-*c*]pyrimidine derivatives with arylpiperazine moiety and their affinities towards 5-HT_{1A}, 5-HT_{2A} and α_1-adrenergic receptors were analyzed using the CoMFA procedure. On the basis of 3D-QSAR models for the 5-HT_{2A} and α_1-adrenergic receptors, four compounds with expected better affinity/selectivity were proposed and synthesized. The affinities obtained confirm experimentally the usefulness of CoMFA models. Our results suggest that active conformations adopted by the studied molecules when interacting with the receptors are neutral instead of the protonated ones.

Keywords: Hexahydro- and octahydropyrido[1,2-*c*]pyrimidines; CoMFA methodology

1. Introduction

The role of buspirone-like compounds as the potent partial agonists to the 5-HT_{1A} receptors is well established [1–6]. The various serotonin (5-HT) receptors are strongly implicated in neuropsychiatric diseases such as anxiety, depression and schizophrenia [7–9]. They are members of the superfamily of G protein-coupled receptors with seven transmembrane α-helices [10,11]. Their biological effects are dependent on the signalling pathways generated by different conformations of the receptor and ligands [12,13]. Buspirone-like ligands possess low selectivity and most of them also reveal high affinity towards α_1-adrenergic and 5-HT_{2A} receptors [14–16]. To circumvent this problem, we would like to establish the optimal shape for compounds of this type on the basis of their biological affinities towards 5-HT_{1A}, 5-HT_{2A} and α_1-adrenergic receptors provided by radioligand binding studies [17–19]. Most drug actions result from the non-covalent association to a specific binding site at the macromolecule, and the CoMFA (Comparative Molecular Fields Analysis) [20–22], a valuable tool in the field of ligand–protein interaction [23–25], could help us to rationalize the relationships between the active molecular conformations and the biological activities.

In this paper we report preliminary results of the 3D-QSAR investigations into the title compounds and their affinities towards α_1-adrenergic, 5-HT_{1A} and 5-HT_{2A} receptors (Table 1). We have employed a few steps of CoMFA methodology: two alignment methods, the protonated and non-protonated species, and computations at different levels of theory to find clues for selectivity of the designed compounds, defined as the difference in the $\log(1/IC_{50})$ values between affinities towards 5-HT_{1A}, 5-HT_{2A} and α_1-adrenergic receptors, respectively.

2. Material and methods

2.1. Receptor binding affinities

The title compounds were tested for their potency to inhibit binding of labeled ligands to serotonin 5-HT_{1A}, 5-HT_{2A} and to α_1-adrenergic receptors using in vitro radioligand binding assays in rat cerebral cortical tissue. The labeled [^{3}H]8-hydroxy-2-(dipropylamino)tetralin for 5-HT_{1A}, [^{3}H]Ketan-

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Table 1
The structures of the compounds **1–21** used in CoMFA training set

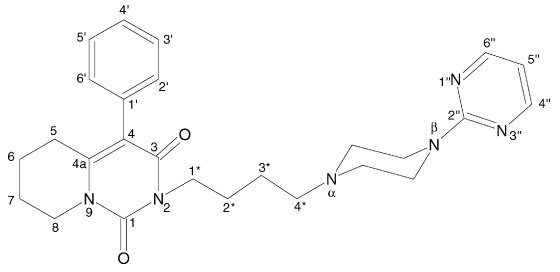
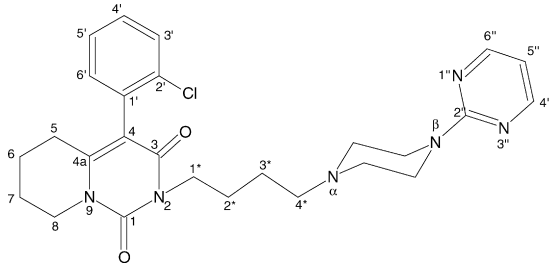
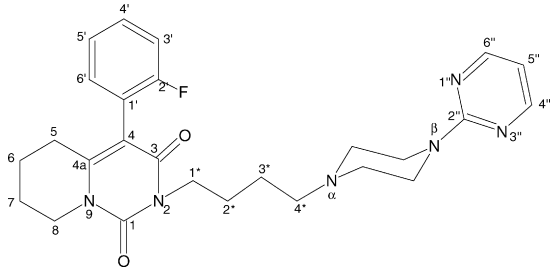
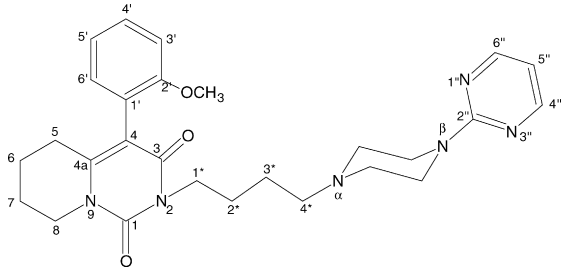
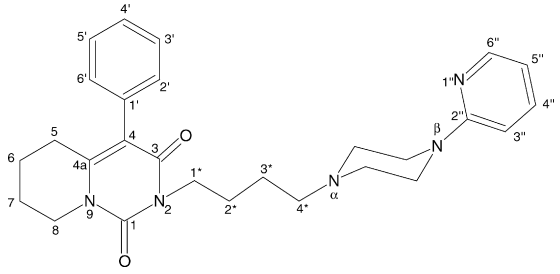
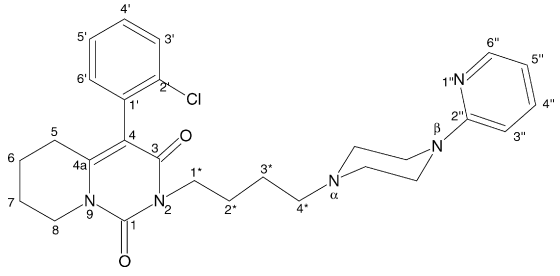
Compounds	Structure	pIC_{50}		
		$5-HT_{1A}$	$5-HT_{2A}$	α_1
1		7.095	6.173	5.677
2		6.859	5.916	5.950
3		6.914	6.126	5.887
4		7.003	5.759	5.554
5		6.856	6.692	6.783
6		7.231	7.204	6.700

Table 1 (*Continued*)

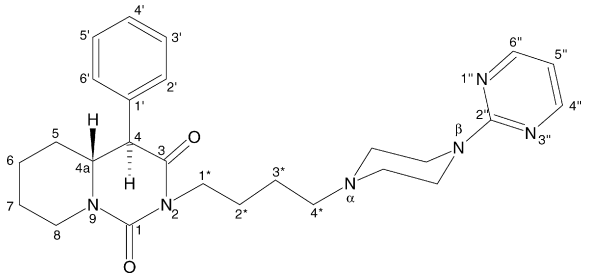
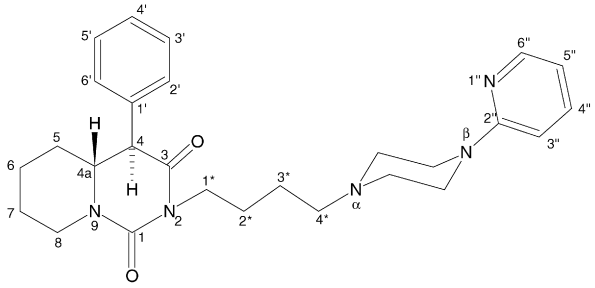
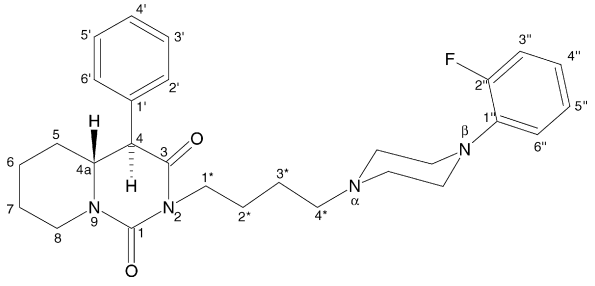
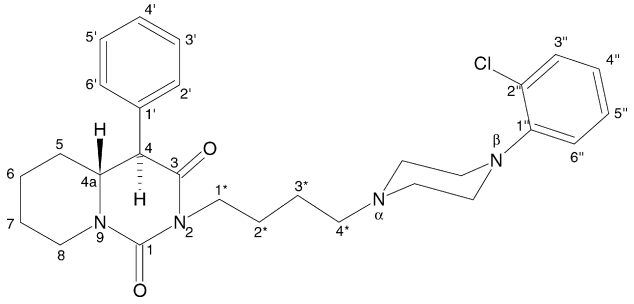
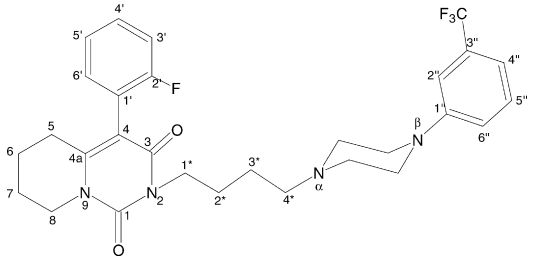
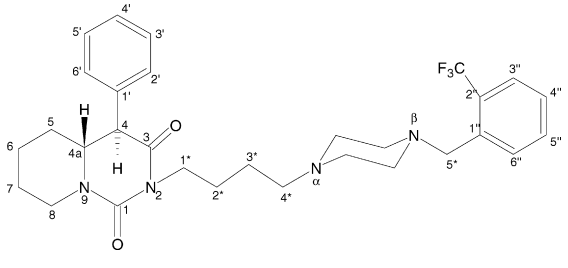
Compounds	Structure	pIC_{50}		
		$5-HT_{1A}$	$5-HT_{2A}$	α_1
7		6.755	6.357	6.010
8		7.319	6.856	6.921
9		7.176	6.632	7.444
10		7.164	7.144	7.509
11		6.896	6.362	5.311
12		6.192	6.038	5.583

Table 1 (*Continued*)

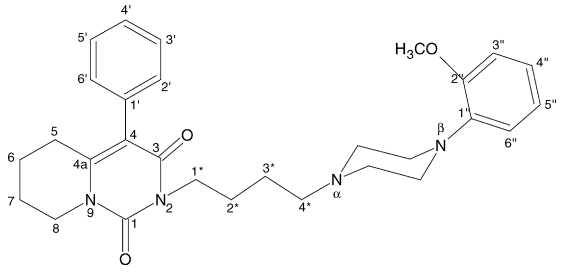
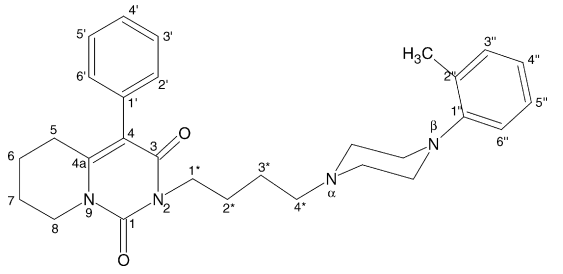
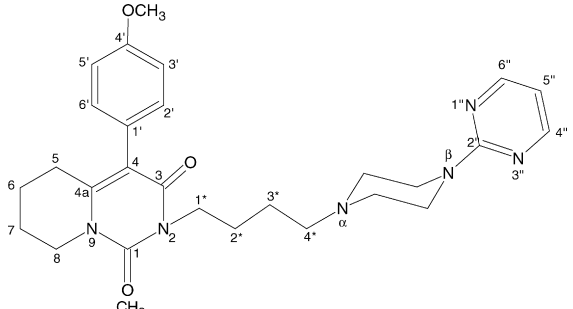
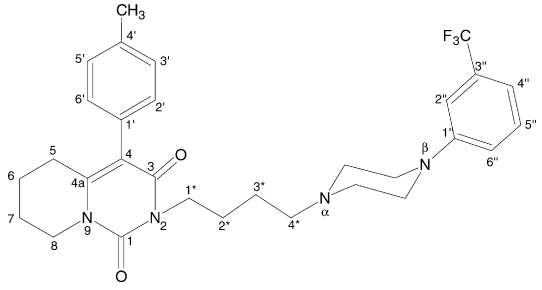
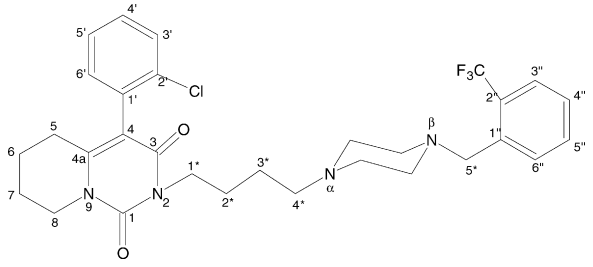
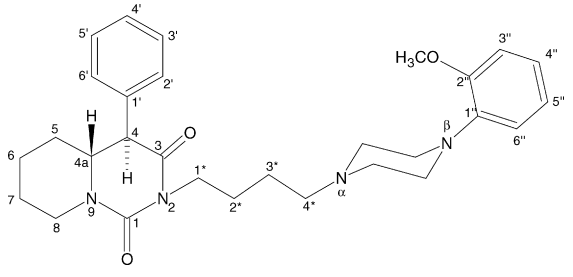
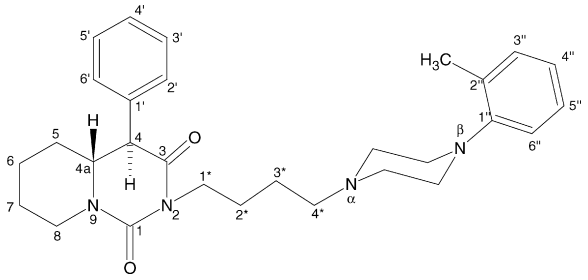
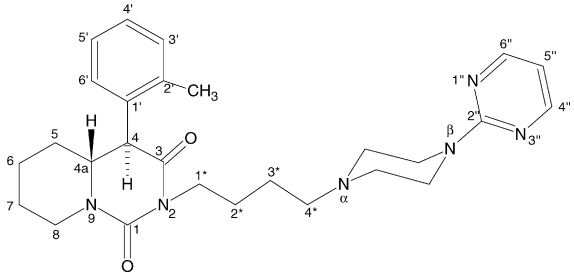
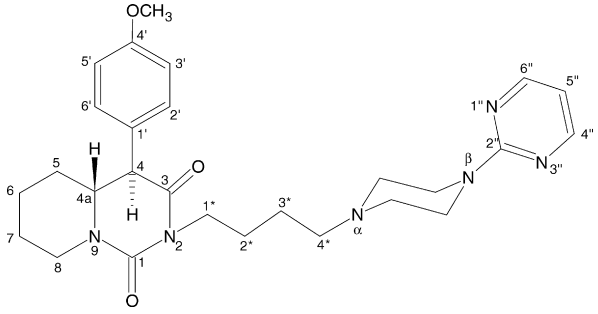
Compounds	Structure	pIC_{50}		
		$5-HT_{1A}$	$5-HT_{2A}$	α_1
13		6.899	6.584	7.578
14		6.526	6,325	7.323
15		6.801	5.824	5.951
16		6.083	5.965	6.588
17		6.272	5.799	6.460
18		6.592	6.536	7.870

Table 1 (*Continued*)

Compounds	Structure	pIC_{50}		
		$5-HT_{1A}$	$5-HT_{2A}$	α_1
19		6.549	6.627	7.745
20		7.305	6.193	5.924
21		6.997	6.050	6.110

serin for 5-HT_{2A} and [^{3}H]Prazosin for α_1-adrenergic receptors were used. More details are given in paper [17,18]. The observed IC_{50} (nM) were converted into $-\log IC_{50} = pIC_{50}$ and are reported in Table 1. The affinity values demonstrate the differences from $pIC_{50} = 7.870$ of **18** to $pIC_{50} = 5.311$ of **11**, both to α_1-adrenergic receptor.

2.2. Compounds

A series of 21 compounds **1**–**21** was used as a test set (Table 1). Twelve of them were hexahydropyrido[1,2-*c*]pyrimidine derivatives and nine of them were octahydropyrido[1,2-*c*]pyrimidine derivatives. We introduced various halogens and methoxy group into the phenyl rings of the studied molecules, expecting the changes in their lipophilicity. The octahydro derivatives contain the chiral atoms C4 and C4a. This pharmacophoric element is very important in the biological active substances and could change their affinity to the receptors. The pyrimidinyl and pyridyl substituents attached to N_β atom in piperazine ring should allow us to estimate a heteroaromatic ring effect. The test set of four compounds **22**–**25** (Table 3) was used to find out the predicting ability of the models.

2.3. Molecular modeling

The structures of the examined compounds were built using the tools implemented in Sybyl 7.0 programme [26]. The absolute configuration of the atoms C4 and C4a cannot be defined, but only established as *S,S* (*R,R*) [27], thus these atoms were arbitrarily oriented in the *S,S* configurations. The fully optimized geometries at PM3 level of theory and the point charges calculated by Mulliken population analysis were used as the first point within CoMFA methodology.

Many authors [22] but not all [28] claim that the CoMFA results are not sensitive to the method of the point charges calculations. However, the ESP charges (fitting point charges to the electrostatic potential using the Breneman model CHelpG) could be more proper, because they reflect the charges at the van der Waals surface, i.e. in close proximity of the points of the ligand–receptor interactions. Then we have calculated the fully optimized geometries at DFT level of theory with B3LYP functional and 6-311G(d,p) basis set, and ESP charges using Gaussian 98 package [29]. These geometries and charges were also considered within the CoMFA methodology. Since the theoretical calculations of the 5-HT_{1A} receptor [30] have indicated that the electrostatic potential is mainly negative

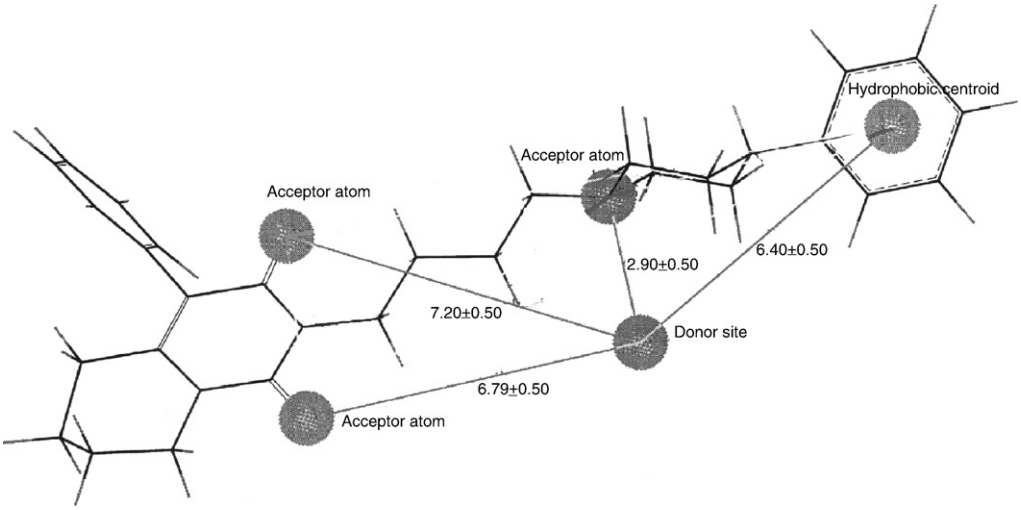


Fig. 1. View of the model of the pharmacophore based on DISCO results.

around the ligand binding site, the analysis was extended to the protonated molecules. In each case the piperazine nitrogen Nα atom attached to the *n*-butyl moiety was chosen as protonated on the basis of the DISCO model (Fig. 1) and single crystal X-ray diffraction analysis of buspirone analog hydrochlorides [31]. The fully optimized PM3 and DFT geometries of cations were calculated according to the methods mentioned above.

Next, the sets of 20 conformers for 10 compounds **1**–**10** were produced by Multisearch method within the energy differences 84 kJ/mol, according to a procedure accessible within Sybyl 7.0 package [26]. The DISCO models were generated to identify the possible active conformations (different from those corresponding to the local minimum of energy) and to develop the pharmacophore models given in literature. The DISCO method identified a number of potential pharmacophore elements (see Fig. 1): the oxygen atoms of carbonyl groups and the nitrogen atom of piperazine ring as H-bond acceptor atoms, the centroids of both aromatic rings as the hydrophobic centers (only one centroid is shown in Fig. 1). These elements were considered in several models suggested previously [31,32]. Visual inspection of the conformer bases, which are created during Multisearch procedure, revealed that all the derivatives occupy approximately equal conformational space.

The studied compounds were superimposed using the unsubstituted derivative **1** as an alignment template, and the pharmacophore elements of choice: (i) both carbonyl groups of the pyrimidine moiety, (ii) both piperazine nitrogen atoms, and (iii) the centroid of the benzene ring at the pyrimidine moiety (five-point pharmacophore) or two centroids of both single aromatic rings (six-point pharmacophore). The *ortho* substituents at the phenyl rings were chosen for optimal overlap with one another, under the assumption that they occupy the same cavity in the receptor. Compounds were aligned via point-by-point method optimized through a root means square (RMS) technique. In order to have a better insight into the modes of the receptor–ligand interaction we have analyzed two types of species: the neutral and protonated molecules adopting the 'extended' conformation, corresponding to the minimum of the energy.

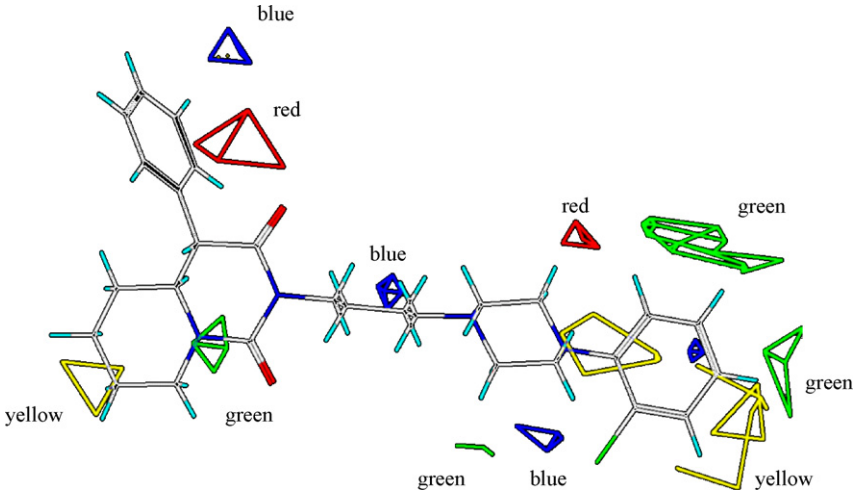


Fig. 2. Steric and electrostatic graphical results of CoMFA model **A1** with compound **10**. (Green: steric bulk – increased affinity; yellow: steric bulk – decreased affinity; red: high electron density – increased affinity; blue: low electron density – increased affinity.)

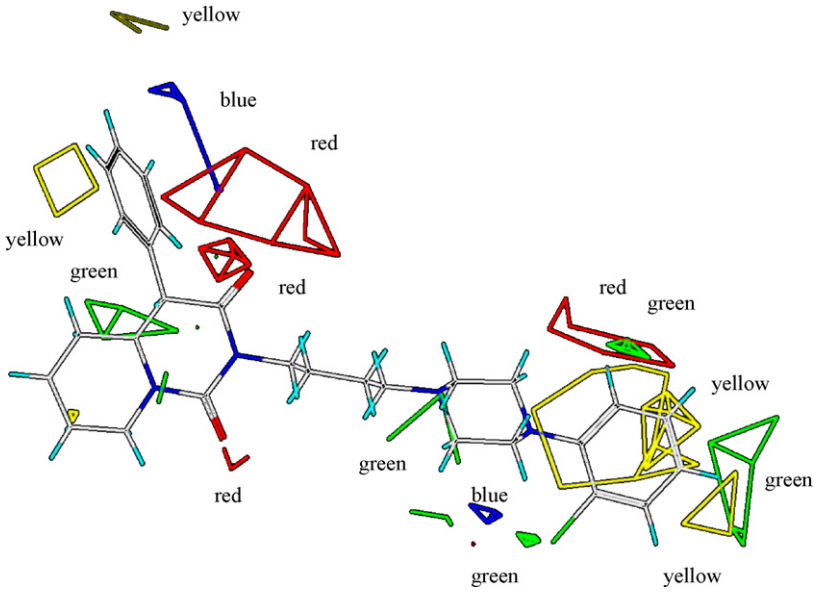


Fig. 3. Steric and electrostatic graphical results of CoMFA model **H2A** with compound **10**. (Green: steric bulk – increased affinity; yellow: steric bulk – decreased affinity; red: high electron density – increased affinity; blue: low electron density – increased affinity.)

2.4. CoMFA methodology

Each alignment was submitted to the CoMFA procedure for the combinations of the electrostatic and steric molecular fields. Since nearly all of the successful CoMFA analyses have been performed with default parameters suggested by the CoMFA module, we also used default settings in our analysis. The grid used in the study had a resolution of 2.0 Å and extended beyond the molecular dimensions by 4.0 Å in all directions. The steric and electrostatic probe–ligand interaction energies were calculated using a sp^3 carbon probe carrying a charge of +1.0. The QSAR table was built with three columns of dependent variables, pIC_{50} values towards 5-HT_{1A}, 5-HT_{2A} and α_1-adrenergic receptors and with CoMFA columns. The introduction of lipophilicity log P values did not improve the CoMFA models. The calculation of log P values was carried out using HyperChem 7.02 program [33] with atomic parameters derived by Ghose, Pritchett and Grippen [34].

The data matrix was analyzed by the partial least squares (PLS) method. The optimal number of the components was designated such that cross-validated r^2 was highest and standard error of prediction was lowest. The CoMFA results were visualized when the values of r^2 were higher than 0.5. From the models to the α_1 and 5-HT_{2A} receptors the 3D CoMFA color contour maps were derived (Figs. 2 and 3). The color code, used to characterize the isocontours, shows the green regions where steric bulk enhances the binding affinity, or the yellow ones where it reduces the binding affinity. The red

Table 2
Summary of CoMFA results

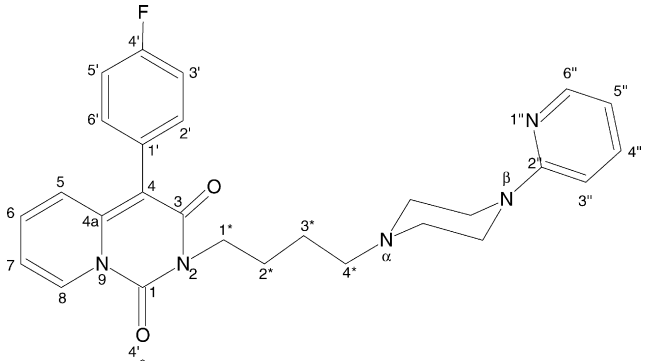
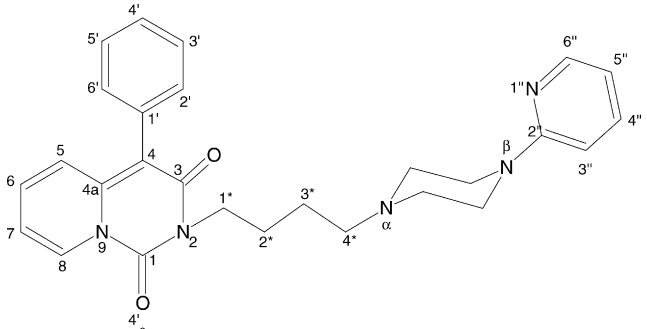
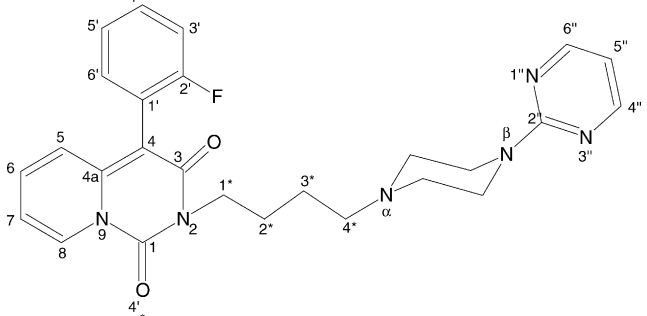
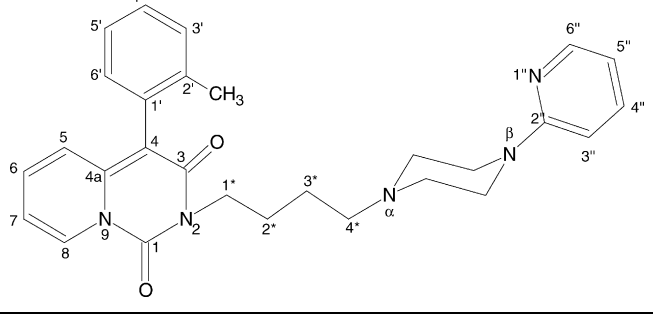
CoMFA models								
		Calculation	Receptor	Cross-validated, r^2	Number of components	R^2	Relative contribution (%) Steric field	Electrostatic field
Conformation "extended"	Neutral	PM3 (**21** compounds)	$5HT_{1A}$	−0.226	1	0.959	28.7 37.4 (HBOND)	34.0
			$5HT_{2A}$	0.097	1	0.979	31.9 29.5 (HBOND)	38.7
			α_1	**0.447**	3	0.984	37.9 30.3(HBOND)	31.8
	Protonated	PM3 (**21** compounds)	$5HT_{1A}$	−0.038	2	0.847	69.0	31.0
			$5HT_{2A}$	0.099	1	0.877	73.3	26.7
			α_1	**0.517**	2	0.818	73.3	26.7
Conformation "extended"	Neutral	DFT (**21** compounds) (PARABOLIC FIELDS)	$5HT_{1A}$	−0.052	2	0.815	72.9	27.1
			$5HT_{2A}$	**0.654**	3	0.940	68.6	31.4
			α_1	**0.652**	3	0.937	76.5	23.5
	Protonated	DFT (**21** compounds)	$5HT_{1A}$	−0.119	2	0.903	79.4	20.6
			$5HT_{2A}$	0.142	1	0.785	79.3	20.7
			α_1	**0.453**	3	0.952	82.1	17.9

regions denote a favorable influence of the high electron density, whereas the blue ones – an unfavorable influence.

3. Results and discussion

The summary of CoMFA results is given in Table 2. We have decided to analyze the initial affinity results obtained by us to verify our hypothesis that structural features of the synthesized compounds which could diversify their affinities (selectivity) towards 5-HT_{1A}, 5-HT_{2A} or α_1-adrenergic receptors could be identified. The first approach was developed, where the standard steps of the CoMFA methodology were taken into account for the fully PM3 optimized neutral molecules and both five-point and six-point pharmacophores. Surprisingly, the accuracy of prediction was even worse than in the case of no model at all ($r^2 \sim 0$) for the 5-HT and α_1-receptors and five-point pharmacophore, and was more optimistic for α_1-adrenoreceptor and six-point pharmacophore ($r^2 = 0.447$.) Assuming that ligand binding to 5-HT_{1A}, 5-HT_{2A} and α_1-adrenergic receptors is initiated by

Table 3
The structures of the compounds used in CoMFA testing set **22–25** and their experimental and calculated affinities

Compounds	Structure	pIC_{50}	
		5-HT_{2A}	α_1
22		6.281 cal. 6.365	7.620 cal. 7.013
23		6.026 cal. 6.375	7.284 cal. 7.753
24		7.587 cal. 7.092	6.655 cal. 6.167
25		7.943 cal. 7.998	6.960 cal. 6.828

electrostatic interaction of the negatively charged region of the receptor near the aspartic acid and the protonated amino group of the ligand (in our case at the piperazine Nα atom) we decided to continue the CoMFA methodology with a six-point pharmacophore and the protonated molecules. The geometries were optimized using the PM3 semi-empirical method and the structures corresponding to the minimum of energy were considered. Once more the CoMFA results displayed poor results ($r^2 \sim 0$) for 5-HT receptors and better ones for α_1-adrenoreceptor ($r^2 = 0.517$).

Taking into account the flexibility of the title compounds we have analyzed the conformational space by Multisearch method. We have found that the distortion necessary to bring both aromatic rings closer ('bent' conformation) is energetically unfavorable by more than 22 kJ/mol, and the respective structural changes could not be induced spontaneously. As a result, we have decided to perform again CoMFA analysis working with the 'extended' conformations of the neutral and protonated molecules using DFT optimized geometries and ESP charges, which could potentially improve predictability of the model. Finally, we have obtained two CoMFA models based on the neutral molecules: **A1** with $r^2 = 0.652$ to α_1-adrenoreceptor, and **H2A** to 5-HT_{2A} receptor with $r^2 = 0.654$ (see Table 2). CoMFA results shown in Table 2 suggested that the methods of charge and geometries computations affected the predictability of models in our case. However, the DFT calculations are time consuming and are too expensive for a long series of compounds. The CoMFA isocontour maps relative to **A1** and **H2A** models are presented in Figs. 2 and 3, respectively.

3.1. CoMFA models derived for α_1-adrenergic and 5-HT_{2A} receptors

On the basis of the alignment discussed above, two CoMFA models **A1** and **H2A** both with three components were selected, and Table 2 contains the statistics of these models. On the CoMFA contour map of **A1** presented in Fig. 2 the green contour above and on the right-hand side of the aromatic ring joined to the piperazine shows that the occupation of that region increases the affinity. The yellow region at *meta* position of this benzene ring shows that less bulky substituents are preferred in this area. The next yellow region located in the vicinity of hexahydropyridopyrimidine rings shows the area where a decrease of molecular volume is favorable. The red contours close to imide and piperazine moieties suggest that the substitution, which can increase the negative charge, could result in higher activity. On the basis of CoMFA contour map relevant to model **H2A**, presented in Fig. 3, we could define slightly different steric and electrostatic preferences as compared with model **A1**. The green contours are located in the proximity of *para* position in benzene ring joined to the piperazine ring in both models, and should not be a criterion for selectivity, but the lack of substituents in *ortho* position should increase the affinity to 5-HT_{2A} receptor. The next green zone located close to piperazine ring, shows the area where branched alkyl groups are favorable. The green contour at C4 in the imide moiety indicates that some substituents in its proximity should be favorable. The vast red contours close to imide and piperazine moieties suggest (much more strongly than in model **A1**) that the negative charge in these regions leads to an increase in affinity. We have proposed the synthesis of a few compounds with the aromatic ring instead of aliphatic one to change the electronegativity of this part of molecules, and four of them (**22**–**25**) are used as a testing set (see Table 3): two, 4-(4-fluorophenyl)-2-[4-[4-(2-pyridyl)-1-piperazinyl]-butyl]-2H-pyrido[1,2-*c*]pirimidine-1,3-dione **22** and 4-phenyl-2-[4-[4-(2-pyridyl)-1-piperazinyl]-butyl]-2H-pyrido[1,2-*c*]pirimidine-1,3-dione **23** with probably better affinity to α_1-adrenergic receptor and the other two, 4-(2-fluorophenyl)-2-[4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl]-2H-pyrido[1,2-*c*]pyrimidine-1,3-dione **24** and 4-(2-methylphenyl)-2-[4-[4-(2-pyridyl)-1-piperazinyl]butyl]-2H-pyrido[1,2-*c*]pyrimidine-1,3-dione **25** with the *ortho*-F and *ortho*-CH_3 substituent, respectively with probably better affinity to 5-HT_{2A} receptor. The calculated and experimental affinities for these four compounds are presented in Table 3. Indeed, it was found that compounds **22** and **23** have better affinity to the α_1-adrenergic receptor than to the 5-HT_{2A} receptor, and compounds **24** and **25** have better affinity to the HT_{2A} receptor than to the α_1-adrenergic receptor. The experimental differences in pIC_{50} values $|(pIC_{50}|$ to various receptors (which could be a measure of selectivity, calculated as $|pIC_{50(\alpha 1)} - pIC_{50(5-HT_{2A})}|$ are on the average 1.30 for **22** and **23**, and 0.95 for **24** and **25**, respectively.

4. Conclusions

Two satisfactory CoMFA models, **A1** to the α_1-adrenergic receptor and **H2A** to the 5-HT_{2A} receptor were obtained with the cross-validated r^2-value of 0.652 and 0.654, respectively. The effect of the electrostatic and steric fields around the aligned molecules on their activities was used successfully to introduce further structural modifications and synthesized more selective substances. In the analyzed case, the CoMFA models were affected by the method chosen for the computations of the geometries and the atomic charges.

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