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S. A. Andronati[a]
[a] A. V. Bogatsky Physico-Chemical Institute of the National Academy of Sciences of Ukraine 86 Lustdorfskaya doroga, Odessa, Ukraine

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Structure-Functions Relationships of the Benzodiazepine and Serotonine Receptors Ligands

S.A. ANDRONATI*

A.V. Bogatsky Physico-Chemical Institute of the National Academy of Sciences of Ukraine 86 Lustdorfskaya doroga, 270080 Odessa, Ukraine

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States of anxiety and fear are controlled in organism by GABA-ergic and serotonine- ergic systems. Concepts about the structure and functions of $GABA_A$ receptor channel, benzodiazepine and serotonine receptors have been considered. Structural and conformational peculiarities of ligands of these receptors determine their role (agonists, antagonists, inverse agonists, partial agonists, partial inverse agonists) at the formation of supramolecular complexes "ligand-receptor" and, as a result, pharmacological effects of ligands.

Keywords: GABA, benzodiazepines, serotonine, receptors, structure, conformation, affinity, properties

The 1,4-benzodiazepine derivatives are the most used psychotropic agents in medical practice. The pharmacological spectrum of these agents includes the anxiolytic, anticonvulsive, hypnotic, sedative and miorelaxant effects. In the early 70s it was shown that psychopharmacological effects of 1,4-benzodiazepines realized through the system of the main inhibiting mediator of the central nervous system – γ-aminobutyric acid (GABA).

Most of biological processes depend on the ability of molecules to discriminate and bind between themselves. The ability to form supramolecular complexes is usual in reactions among biological macromolecules and another biological active compounds (neurotransmitters, hormones, drugs etc.)

Since 1977 the molecular mechanisms of action of these agents are the subject for numerous investigations. It became possible due to the discovery of highly sensitive binding sites of 1,4-benzodiazepines (benzodiazepine receptors, BDR) in the mammalians brain. It became soon known that GABA (GABA R) and benzodiazepine receptors (BDR) have interdependence. Furthermore, the binding sites of GABA and BD are located on the subunits of receptor-ionophoric assemblyes – $GABA_A$ – receptor channel often called simply as $GABA_A$ receptor. The latter is the ligand operated anionic channel related to the class of ionotropic receptors.

Structure and functions of the given supramolecular assembly are the subject for investigations in different scientific centres. Now there is the following idea on the architecture and functions of this assembly [1].

$GABA_A$ receptor is heteropentameric assembly penetrating the biological membrane and forming the anionic (for the Cl^- and HCO_3^-) channel (Fig. 1). It includes the α-, β-, γ-, δ- and

* Corresponding Author.

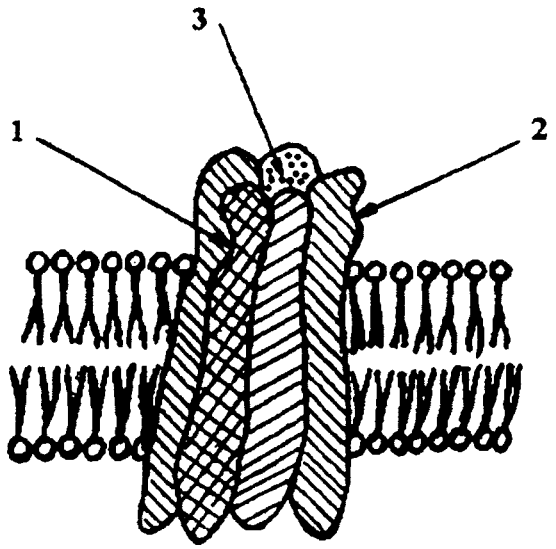


FIGURE 1 Scheme of $GABA_A$ Receptor channel. 1.BD binding site 2.GABA binding site 3.Anion channel

ε-types of subunits. The α-, β- and γ-types, in their turn, could be expressed in some variants (isoforms). Probably, the total number of the subunit variants included in $GABA_A$ receptor approximates to 20.

$GABA_AR$ subunit conformations at the absence of GABA are such that anionic channel is closed. At the interaction of GABA with its binding sites the change of conformations of the subunit domains is realized. Thereat the assembly architecture provides with the ionic current through the channel.

The $GABA_AR$, besides the GABA binding sites, has the binding sites for different substances, which could act as izosteric ligands, activators or blockers of ionic channel as well as allosteric modulators. These are the binding sites of barbiturates, pycrotoxine, alcohols, steroids, 1,4-benzodiazepines, etc.

The binding sites of 1,4-benzodiazepines are located on the α-subunit of the $GABA_AR$. Ligands of the given receptors act as the allosteric modulators of the $GABA_AR$. Probably, the BDR interaction with its ligands leads up to the conformation transition of the $GABA_AR$ that favours (in case of positive modulation) or prevents (in case of negative modulation) to its binding with the GABA.

The BDR ligands depending on their action are subdivided into agonists, antagonists, inverse agonists, partial agonists and partial inverse agonists.

It is supposed that domains with the benzodiazepine binding sites have two conformations. One of them favours to the opening of ionic channel (conformation of positive modulation), but another – prevents (conformation of negative modulation). These conformations are in the equilibrium state.

The BDR agonists could selectively bind with conformation of negative modulation and to shift equilibrium to the side of positive modulation conformation. Ligands selectively binding with the conformation of positive modulation shift the equilibrium to the side of negative modulation conformation. Such ligands act as inverse agonists of BDR. Ligands with the equal affinity for both conformations do not influence on the equilibrium and, as a result, on the state of ionic channel. These ligands are the BDR antagonists as they prevent to the interaction with the binding sites of agonists and inverse agonists. The intermediate positions between described variants have place in the case of partial agonists and partial inverse agonists.

An attempts of molecular modelling of recognition ligands by benzodiazepine receptors were undertaken in different scientific centers [2].

For example, correlation between dipole moments of 1,4-benzodiazepines and their sedation and taming activity have been established by Blair and Webb [3]. In another model obtained by semiempirical quantum-mechanical calculations [2], recognition and receptor activation centers are two strong proton-acceptor fragments on the distance 3.5 Å and highly lipophilic area. Value of angle between proton-acceptor and lipophilic fragment is 140–150° for agonists,

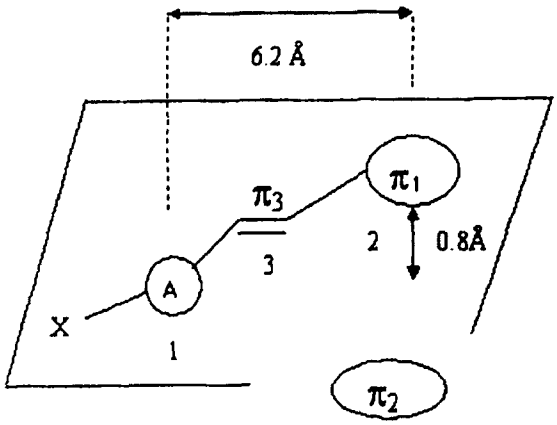


FIGURE 2 Model of binding centers of benzodiazepine receptor ligands

100–120° for antagonists and approximately 90° for inverse agonists.

The dependencies of pharmacological activity and affinity for BDR of the benzodiazepine derivatives on their structure and physico-chemical properties have been investigated in our works [4–6].

For example, we demonstrated that position of the hallogen atoms did not influence essentially on the physico-chemical properties of 5-(halogenophenyl)benzodiazepinones, whereas the affinity of these compounds changed dramatically [4].

Model of binding centres which are responsible for the ligands recognition by benzodiazepine receptors has been proposed on the base of X-ray analysis data [7] (Fig. 2).

Model includes aromatic ring A, π_1-system on the distance 6.2Å from the ring centre, π_1-system is located on approximate distance 0.8Å from the plane of ring A, π_3-system connects ring A and π_1-system. The electron withdrawing substituent X is no fixed in the p-position. π_2-System is undefined in terms of position or geometry.

In many works have been demonstrated that the 1,4-benzodiazepines affinity for BDR very well correlates with their anticonvulsive activity in pentylenetetrazole test [8]. Thereby in many cases it is possible to evaluate the affinity of substances for BDR by their anticonvulsive activity using the given test. However, such approach is incorrect at the comparison of substances which essentially differ by their pharmacokinetic characteristics and metabolic pathways [9].

It is known that subtle differences in the substrates spatial structure could be very important at the "substrate-receptor" interaction.

It is coincidence that problems of the benzodiazepines stereochemistry as well as their conformation analysis are interesting for researchers.

Molecules of 1,2-dihydro-3H-1,4-benzodiazepine-2-ones have pseudo-boat conformation and they are in the inverse state [10, 11].

Conclusions on the conformation of pseudo-boat of 1,4-benzodiazepinones in solutions have been confirmed by the methods of IR spectroscopy and dipole moments in our works [12].

It has been established in the series of investigations of crystal and molecular structure of 1,4-benzodiazepine-ones that all investigated compounds in solid phase have the pseudo-boat form [13–16].

Hamor and Martin had attempted to consider the influence of geometric parameters of the 1,4-benzodiazepine molecules on their psychotropic properties [17]. The deviation of 7-member ring form from the ideal boat conformation has been described with the asymmetry (ΔGs) parameters introduced by Duax. The substances activity was evaluated by the values of effective dozes (ED_{50}), using the anticonvulsive pentylenetetrazole test. The satisfactory correlation between ΔGs and ED_{50} were not found.

Thus, the boat conformation of 1,4-benzodiazepinones in crystal form as well as in solutions was ascertained in the mentioned publications based on the spectral and X-ray crystal structure analysis.

We have established the existence of two non-equivalent 1,4- benzodiazepine-2-ones conformations in the gas phase by the methods of

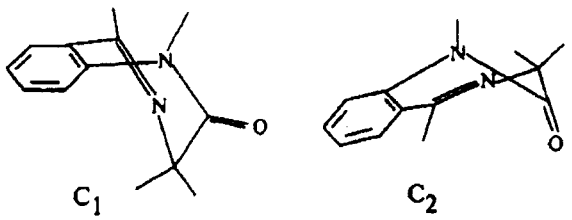


FIGURE 3 Pseudo-boat conformation (C_1) and flattened form with anticlinal conformation of the amide group (C_2) of 1,2-dihydro-3H-1,4-benzodiazepinones

ERC mass-spectrometry and photo-electronic spectroscopy [18].

The data of IR-spectroscopy confirm the existence of two non-equivalent conformations in the benzodiazepinone solutions [19].

Analysis of benzodiazepine molecular models suggests the possible existence of two conformers of the 7-membered ring a pseudo-boat form with the cis-conformation of the amide group C_1, and the flattened form with anticlinal conformation of the amide group C_2. The value of the torsion angle NR-CO is the important characteristic of these conformers.

The first conformation corresponds to the known pseudo-boat conformation of 1,4-benzodiazepines. The conclusion on the existence of the other conformer was suggested during our investigation. Quantum-chemical calculations of the conformers C_1 and C_2 by the MNDO method using the known geometric parameters from the X-ray structural analysis of 1,4-benzodiazepines proved the possibility of the existence of the second conformer – a flattened form with the anticlinal conformation of the amide group (Fig. 3).

The full energies of the first and second conformers are differed by 0.5 eV. According to the data of ERC mass spectrometry and photoelectron spectroscopy the more active compounds of the series have preferred conformation C_1 (pseudo-boat), while not active members of this series have the preferred conformation C_2 (the flattened one with the anticlinal conformation of the amide group).

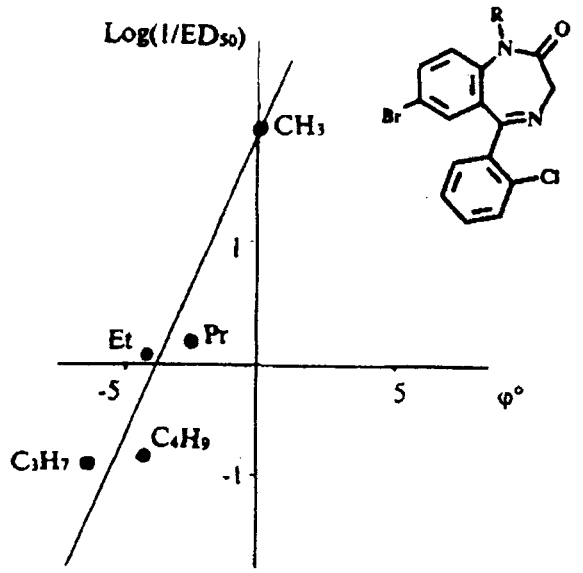


FIGURE 4 Relationship between the anticonvulsive activity (antipentilentetrazole test) and the torsion angle NR-CO of the 1-substituted benzodiazepines

Now there is a question: if the different conformers of 1,4-benzodiazepinones exist not only in the gaseous phase and in solution but also in crystalline state?

The geometry of the series of 1,4-benzodiazepinones in crystalline state was investigated by the X-ray analysis [6]. All investigated compounds as well as 1,4-benzodiazepinones described in literature previously, have the pseudo-boat conformation. The essential differences of the deformation of the boat are measured by the asymmetry index ΔG_s. At the comparison of torsion angles (φ) of amide group of 1-substituted benzodiazepinones one can see that the differences in values of angle φ reach up 23°. The above-stated testifies for that in the solid phase the 1,2-dihydro-3-H-1,4-benzodiazepinones could have essential different conformations.

It is interesting to note that comparison of values of torsion angles NR-CO of the 1-substituted 1,2-dihydro-3-H-1,4-benzodiazepine-2-ones and

the corresponding values of effective doses of these substances has demonstrated that their relationship could be presented by the linear dependence Fig. 4 [5].

These results allow to suppose that the diazepine ring conformation of dihydro-1,4-benzodiazepinones have important significance in process of their interaction with the BDR: the deviation of the ring form from the ideal pseudo-boat conformation (or increase of the torsion angle NR-CO) favours to decrease of the compound affinity for BDR, and decrease of the psychotropic activity.

The discovery of anxiolytic properties of buspirone has resulted in new direction in the creation and investigation of anxiolytics [20]. Buspirone and its analogues have been synthesized and patented as potential sedative and neuroleptical agents by Wu and his colleagues in the late sixties [21]. Antiaggressive properties of buspirone were discovered only in 1980 [22]. Buspirone and related compounds by the range of psychopharmacological properties are differed from 1,4-benzodiazepine anxiolytics. In particular, anticonvulsant and miorelaxant properties are not typical for buspirone and its analogues. One more aspect in the progress of anxiety in humans and animals has been elucidated thanks to the discovery of anxiolytic properties of buspirone, which depends on the serotoninergic system activity. There is the idea that control for anxiety from the GABA-ergic system is realized via serotoninergic system.

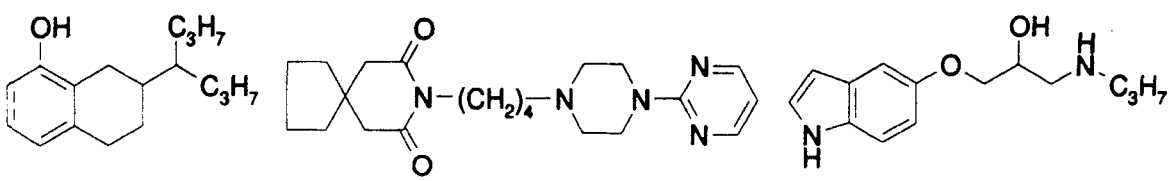
Serotonine is the neuromediator and epiphysis hormon that is formed in the organism from triptophane. Memory, sleep, anxiety, depression, hallucinations, sexual behaviour, thermoregulation and appetite are dependant on the serotonine action. Design and synthesis of ligands of different populations of serotonine receptors are perspective for the directed creation of medicinal agents for treatment of various human deseases. There are six types of serotonine receptors. The heterogenity of the receptors of 5-HT_1group has been established. This type of receptors is divided into 6 subtypes: 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1DA}, 5-HT_{1DB}, 5-HT_{1E} and 5-HT_{1F}, receptors [23]. Buspirone is the partial agonist of 5-HT_{1A}-receptors, 8-OH-DPAT is the selective agonist of these receptors, pindolol is the antagonist.

Anxiolytic effect of buspirone and buspirone analogs is caused by their interaction with the 5-HT_{1A} receptors.

5-HT_{1A}R is the polypeptide molecule with the molecular mass 55 kD [24], it contains 421 amino acidic residues [24, 25]. The transmembrane part of molecule is formed from seven helices penetrating biomembrane (Fig. 5).

Possible variants of interaction between ligands and 5-HT_{1A} receptors are investigated by the methods of computer molecular modelling [23].

It is supposed that agonists and antagonists of 5-HT_{1A} R interact with the different binding sites. Thus, according to the model by Kuipers et al. [26], in case of serotonine (agonist) the ionic bond between basic nitrogen atom of serotonine and carboxyl group Asp116 on helix III is formed. Two hydrogen bonds joint 5-OH group and indole nitrogen of serotonine with Thr200 and Ser 199 on helix V.



8-OH-DPAT BUSPIRONE PINDOLOL

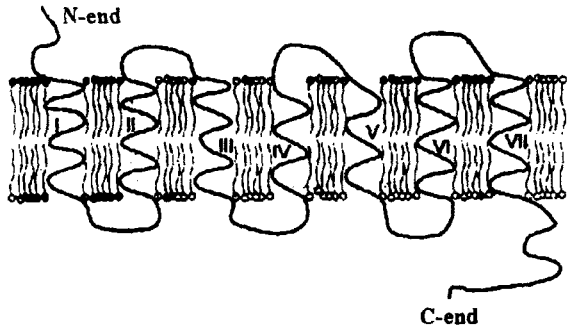
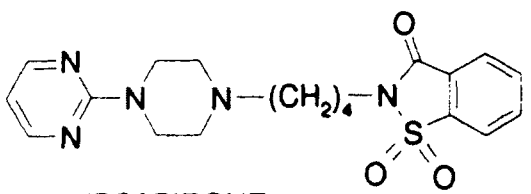
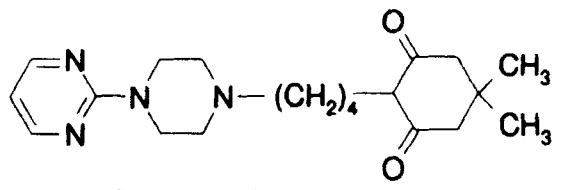


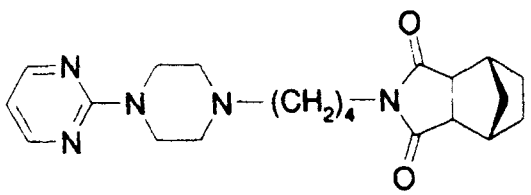
FIGURE 5 Model of 5-HT_{1A} receptor

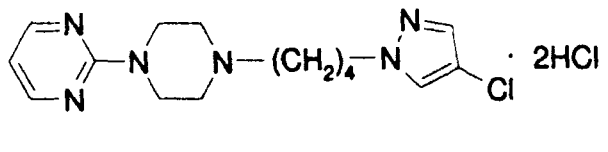
It has been established that various modifications of the buspirone structure could resulted in pharmacologically perspective substances. Series of the buspirone analogs (hepiron, ipsapiron and others) with the high affinity for 5-HT_{1A}receptors have been established. Some of them are on the different stages of clinical trials.

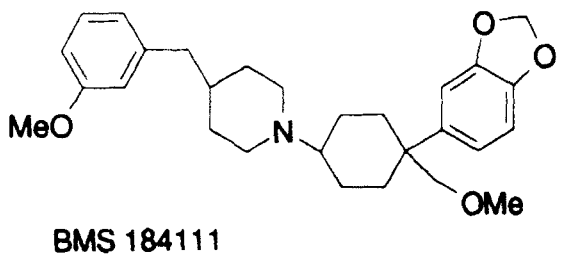
Aryl(hetaryl)piperazinylalkylphthalimides and -naphthalimides, phenylpiperazinylalkylheterocyclic compounds (benzodiazepines, indazoles and barbituric acids) have been synthesized in our Institute as a potential ligands of 5-HT_{1A} – receptors.





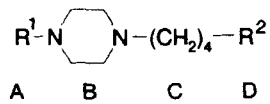


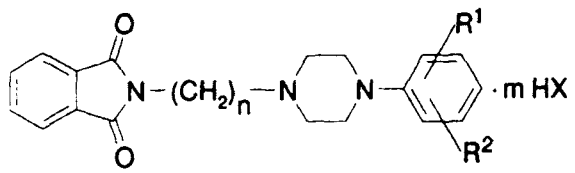


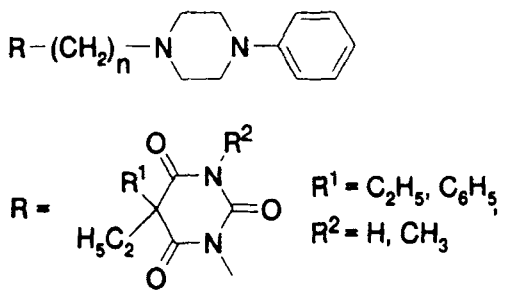


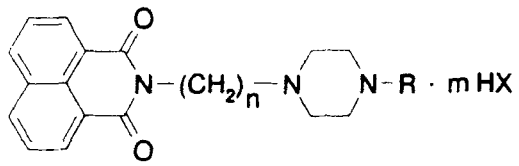
The obtained compounds have a linear form in the crystal state [27–31]. However, the claw conformation may be realized in solution. This conclusion have been made on the base of values of the Nuclear Overhauser effect by computer modelling [32].

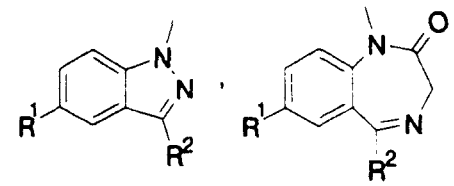
Molecules of buspirone-like substances contain 4 fragments – A, B, C and D.

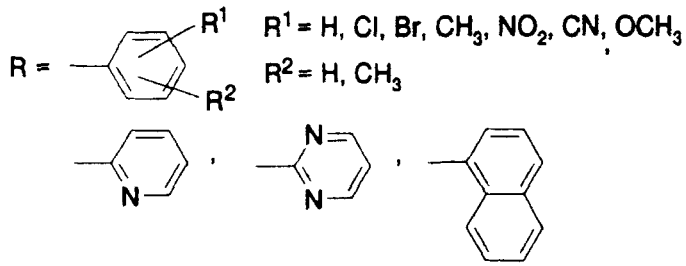












Role each of fragments was investigated in the numerous works. It has been established that A and B fragments play the main role. Compounds without C and D fragments could possess the high affinity. Aromatic or hetero-aromatic nuclei usually play the role of R^1 radical.

Fundamental role of an aromatic ring and nitrogen atom in the interaction of psychotropic agents with their binding sites in the central nervous system is evident. Three-dimensional two-points model of pharmacophore of ligands 5-HT_{1A}R was proposed by Hibert [33]. Aromatic nucleus and basic nitrogen atom are elements of this pharmacophore (Fig. 6).

Distance between centroide of aromatic nucleus and nitrogen atom should be 5.6 Å. Deviation of the nitrogen atom from the plane of aromatic nucleus is 0.2 Å for agonists and 1.6 Å – for antagonists of 5-HT_{1A} R.

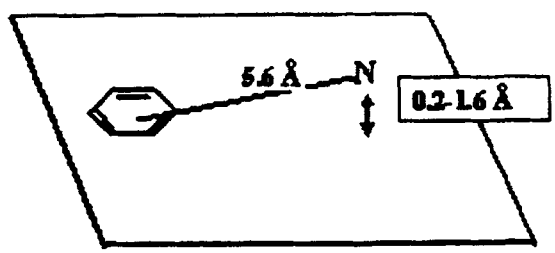
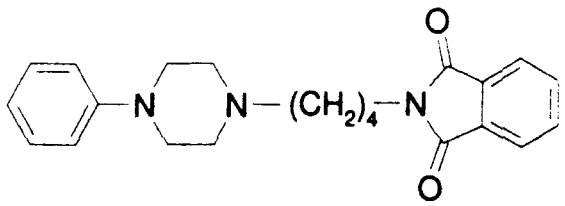
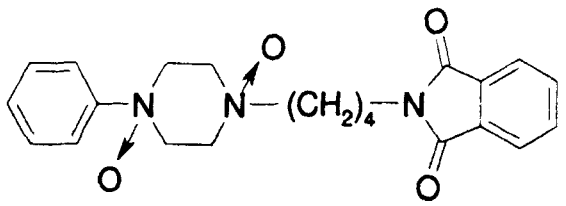


FIGURE 6 Two-points model of the pharmacophore for binding buspirone analogs at $5HT_{1A}$ receptor

The role of basic nitrogen atom in the interaction of ligands with 5-HT_{1A} receptor have been confirmed by the following fact. Oxidation of



Active



Unactive

nitrogen atoms of piperazine nucleus of highly affinitive phenylpiperazinylbutylphthalimide leads to the appropriate dioxide, which is not recognized by 5-HT_{1A} receptors and it does not possess the anxiolytic activity [30].

The affinity of the obtained compounds for serotonine (5-HT_{1A}) receptors have been determined by their ability to inhibit specific binding of [^{3}H]-8-OH-DPAT to brain synaptic membranes fractions, contained above mentioned receptors.

Data in the Table I testify for substantial influence of the nature and position of the substituents in aromatic ring of fragment D to the affinity of the compounds for 5-HT_{1A} receptors.

However, this influence is different for phthalimide and naphthalimide derivatives.

In series of phthalimide derivatives (n=4–6) the highest affinity for 5-HT_{1A} – receptors has been demonstrated by the unsubstituted in A ring and ortho-subsdtituted derivatives.

Metha- and para-substitution resulted in substantially lower affinity for receptors of these compounds.

The fact that influence of ortho- and para-substitution on compounds affinity is opposed suggests that in case of *o*-substituted compounds the increase of affinity is connected with more content of pharmacologically active conformation.

TABLE I The affinity of phthalimide and naphthalimide derivatives for 5-HT_{1A} receptors

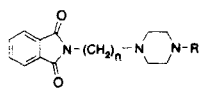
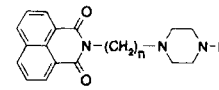
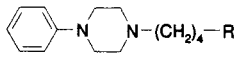
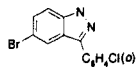
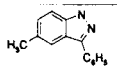
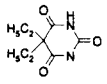
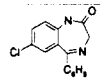
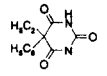
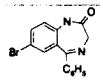
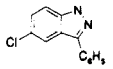
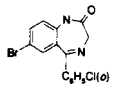
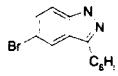
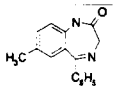
Comp.			*K_i, nM*	*NoNo Comp.*			*K_i, nM*
	n	*R*			*n*	*R*	
1	1	C_6H_5	30000	11	3	C_6H_5	53.8
2	2	C_6H_5	9600	12	3	*o*-Cl C_6H_4	72.6
3	4	C_6H_5	10	13	3	*o*-CH_3 C_6H_4	2440
4	4	*o*-Cl C_6H_4	5.20	14	4	C_6H_5	3.5
5	5	*o*-Cl C_6H_4 6.8		15	4	*o*-Cl C_6H_4	25.9
6	5	*o*-CH_3 C_6H_4	13.1	16	4	*m*-CH_3 C_6H_4	30.5
7	5	*m*-CH_3 C_6H_4	152	17		4 *p*-CH_3 C_6H_4	38.7
8	5	*p*-CH_3 C_6H_4	163.4	18	4	*o*-CH_3 C_6H_4	1280
9	6	*o*-Cl C_6H_4	14.0	19	5	C_6H_5	43.4

TABLE II Lipophilicity and affinity for 5-HT_{1A} receptors of piperazinylbutyl derivatives of heterocyclic compounds



No Comp.	*R*	*logP*	K_i, *nM*	*No Comp.*	*R*	*logP*	K_i, *nM*
3		3.97 ± 0.43	10.0	25		7.44 ± 0.61	6100
14		5.20 ± 0.43	2.9	26		5.02 ± 0.57	447
21		3.50 ± 0.41	144 ± 11	27		5.38 ± 0.59	2200
22		2.29 ± 0.74	96 ± 7	28		5.84 ± 0.69	1680
23		6.79 ± 0.54	2800	29		6.01 ± 0.64	890
24		5.77 ± 0.64	5500	30		4.90 ± 0.58	1500

The high affinity for 5-HT_{1A} receptors in series of naphthalimide derivatives (n=4–6) have been manifested by the compounds with unsubstituted D ring. Compound shows the highest affinity for 5-HT_{1A} receptors exceeded than that of buspirone.

The affinity of indazole derivatives is substantially lower.

Polymethylene chain adds some more flexibility of the molecule to built on to the binding site. Usually the number of methylene groups spacer is 4. However, there are more long chains (penta – and hexamethylene chains). The role of fragment R^2 is subject for discussion. From the one point of view this fragment plays the role of hydrophobic anchor. Another point of view is that this fragment is the third binding site of ligand with receptor.

Comparison of lipophilicity (values log P) of our compounds with their affinity for 5-HT_{1A}R has demonstrated that there is no correlation between the given values (Table II).

These results do not correspond to the opinion that character of the interaction between fragment A and 5-HT_{1A} receptors is hydrophobic. Apparently this interaction could be polar.

Possibility for the additional ligands binding through the hydrogen bonds or donor-acceptor relationships of fragment D with 5-HT_{1A}R has been discussed by J. Mokrosz, Z. Chilmonczyk and co-authors [34,35].

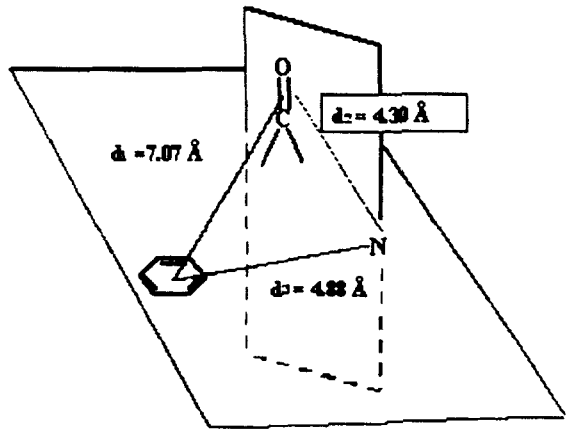


FIGURE 7 Three-point model of the pharmacophore for binding buspirone analogs at $5HT_{1A}$ receptor

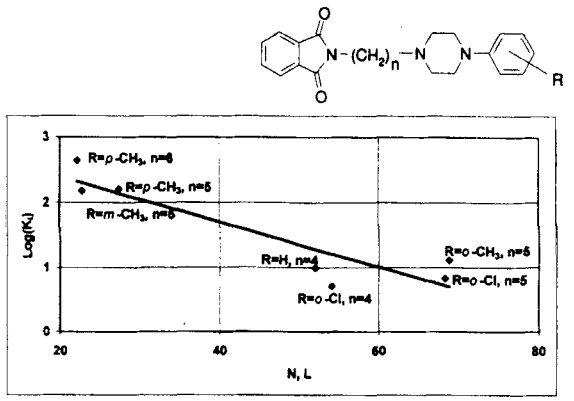


FIGURE 8 Relationship between the anxiolytic activity (conflict situation test) and affinity for 5-HT_{1A} receptors of arylpiperazinylalkylphthalimides. N,L-number of licks (consumption of water)

Three-dimensional model of pharmacophore of 5-HT_{1A} receptors ligands has been proposed by Dr. Chilmonczyk and co-authors [34]. In this model the carbonyl group of amide or imide fragment C plays the role of the third point of interaction (Fig. 7).

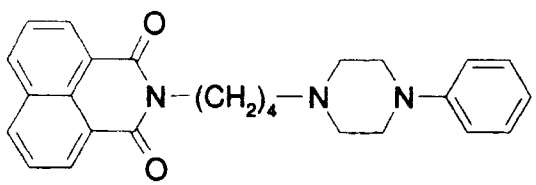
Many of the investigated compounds possess the anxiolytic activity. The anxiolytic effect substantially dependent on the structure of the compounds. Phthalimide derivatives as a whole are more active than naphthalimide derivatives.

Study of affinity – anxiolytic activity relationships for arylpiperazinylalkylphthalimides shows the satisfactory correlation between these indices (Fig. 8).

Ligands with the high-affinity were obtained in different scientific centers on the base of the large information about the relationships between structure and affinity for 5-HT_{1A}R their ligands. In particular, compounds BD-1207 and BD-1194 were obtained in our laboratory.

The naphthalimide derivative BD-1207, with higher affinity for 5-HT_{1a}R than buspiron [36], is antagonist of these receptors.

Pirazolopyrimidine BD-1194 in experiments with animals has demonstrated the high activity in the conflict situation test and made a special interest as potential anxiolitic of a new group of 5-HT_{1A} R ligands.



BD – 1207 K_i for 5-HT_{1A} R 3.5±1.0 nM

BUSPIRONE K_i for 5-HT_{1A} R 5.1±1.6 nM

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