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Molecular modelling of central nervous system receptors

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The molecular models of ionotropic and metabotropic glutamate receptors, ionotropic γ-aminobutyric acid receptors, adenosine and melatonin receptors are discussed; the developed models were used in the design of new neuroprotective compounds.

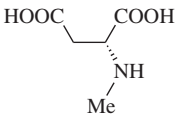
The functioning of central nervous system (CNS) involves the activation of numerous receptors. In the case of neurodegenerative diseases, usually, some corrections of that activation are necessary. For this purpose, the selective agonists and antagonists, as well as the positive and negative modulators of receptors, could be considered as drug candidates. For their efficient design as potential drugs, the detailed knowledge of the 3D structure of CNS receptors is necessary. However, despite a great amount of X-ray data available for various proteins, the 3D structure of the majority of CNS receptors can currently be obtained only using molecular modelling.[1]

Here, we consider the molecular modelling of ionotropic and metabotropic glutamate receptors, ionotropic g-aminobutyric acid (GABA) receptors, adenosine and melatonin receptors.

Ionotropic glutamate receptors

The glutamatergic system is of vital importance for learning and memory functioning.[2,3] It includes both metabotropic glutamate receptors $mGluR_{1\text{-}8}$ and ligand-gated ionotropic receptors, which are subdivided into several types: NMDA receptors, AMPA receptors and KA receptors (or kainate receptors) named after their agonists *N*-methyl-D-aspartate **1**, 2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid **2** and kainic acid **3**, respectively. The kainate receptors are often considered as a subtype of AMPA receptors.

NMDA receptors are involved in neuronal signalling processes, memory consolidation and synaptic plasticity. NMDA receptor hyperactivation induces neurotoxic effects leading to a number of pathological conditions including neurodegenerative diseases. Thus, NMDA receptor antagonists or reversible ion channel blockers could be used for the cure of such diseases.



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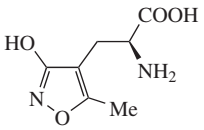

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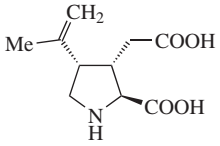

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Professor **Nikolay S. Zefirov**† graduated from M. V. Lomonosov Moscow State University (MSU) in 1958. For more than 50 years, he holds various positions at the Department of Chemistry of the MSU; since 1994, he is the head of Organic Chemistry Division. He received PhD and Dr. Sci. degrees in 1961 and 1966, respectively. Professor Zefirov was elected a corresponding member and a full member of the USSR Academy of Sciences in 1981 and 1987, respectively. Since 1987, he is the head of the Laboratory of Mathematical Chemistry and Computer-Assisted Synthesis at the N. D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences (RAS). In 1989–2006, he was the director of the Institute of Physiologically Active Compounds of the RAS; in 2006, he was appointed as a scientific supervisor at this institute. Professor Zefirov was awarded the Prize of the Government of the Soviet Union (1989) and Russia (2001). He received the Lomonosov Award (1983) and Butlerov Award (1994). Professor Zefirov is a member of the International Academy of Mathematical Chemistry. In 1974–1991, he headed the Division of Organic Chemistry at the D. I. Mendeleev USSR Chemical Society; currently, he is the president of the Medicinal Chemistry Section of D. I. Mendeleev Russian Chemical Society. His research interests cover theoretical and synthetic organic chemistry, medicinal chemistry, mathematical chemistry and computer-aided molecular design.

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† The Editorial Board and Staff of Mendeleev Communications take an opportunity to congratulate Academician N. S. Zefirov on the occasion of his 75th birthday and wish him all the very best.

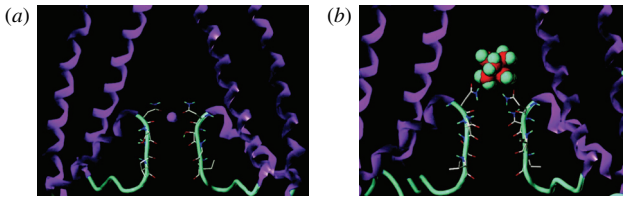
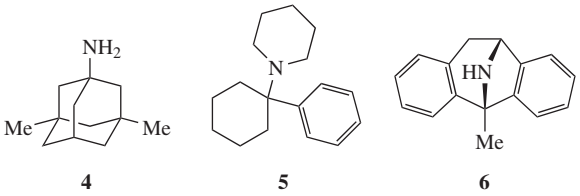


Figure 1 (*a*) Model of Ca^{2+} ion transport through the NMDA receptor ion channel, and (*b*) channel blocking by the hydrated Mg^{2+} ion.

An NMDA receptor is composed of two NR1 and two NR2 subunits. Each NR2 subunit belongs to one of its four subtypes, NR2A–NR2D, leading to the heterogeneity of the wild-type NMDA receptors. NR1 and all NR2 subunits have similar four domain structures: (*a*) the N-terminal extracellular modulatory domain, (*b*) the agonist/coagonist binding domain, which holds the glycine (or D-serine) binding site in an NR1 subunit and the glutamate binding site in an NR2 subunit, (*c*) the transmembrane channel-forming region, which hosts several binding sites, and (*d*) the C-terminal intracellular regulatory domain.

The NMDA receptor ion channel is an important target for compounds exhibiting neuroprotective properties. The reversible channel blockers decreasing the Ca^{2+} influx into neurons could be used for the cure of neurodegenerative diseases. However, the 3D molecular structure of the channel was not considered in the literature before our modelling studies. The first 3D model of a closed form of NMDA receptor ion channel was constructed[4] on the basis of its homology with the potassium channel KscA.[5] For the construction[6] of the open form of the channel, the X-ray data on the potassium channel of *Methanothermobacter* were used. The latter model is important as far as it was demonstrated[7] that the ion channel blockers influence the receptor in the presence of its agonists; that is, they interact with the open form of the channel. The channel consists of four subunits surrounding a pore having a narrow neck with carbonyl groups involved in the intermediate binding of the cations passing through the channel. The carbonyl group of an asparagine side chain at the neck inlet should be involved in the dehydration of Ca^{2+} cations [Figure 1(*a*)]. The hydrated magnesium ion binds with this asparagine residue and serves as a natural channel blocker [Figure 1(*b*)]. The binding mode of memantine **4** (a drug used for the cure of neurodegenerative diseases) is somewhat similar to that of magnesium; its protonated form also should generate a hydrogen bond with asparagines (Figure 2). Thus, the ligand-bound asparagine cannot be involved in the cation dehydration, which is a necessary step for passing



4 **5** **6**

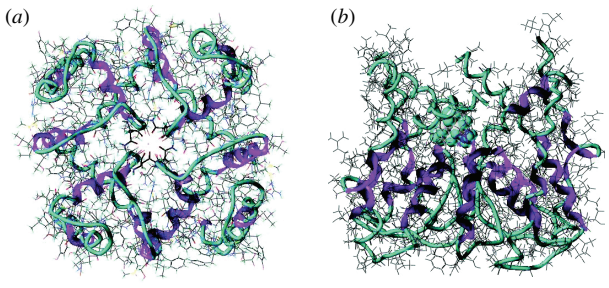


Figure 2 (*a*) NMDA receptor ion channel (top view), and (*b*) its blocking by memantine (side view).

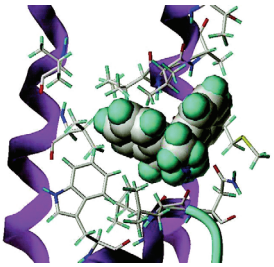
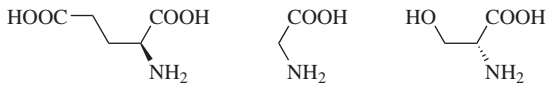


Figure 3 Docking of MK-801 into an NMDA receptor ion channel.

cations through the neck of the channel. Other known channel blockers like phencyclidine **5** or MK-801 **6** not only form a hydrogen bond with asparagine but also stick tightly to the hydrophobic walls of the channel and occupy the hydrophobic pocket (Figure 3). Thus, their binding becomes excessively high to cause serious side effects. The design of flexible analogs of MK-801 to decrease the binding could be a reasonable outcome.[4]

Extracellular agonist and co-agonist binding domains host the binding sites of a natural agonist (glutamic acid **7**) or a co-agonist (glycine **8** or D-serine **9**). The glutamate and glycine binding sites of the NMDA receptor have similar 3D structures and are localized in NR2 and NR1 subunits, respectively. The simultaneous binding of an agonist and a co-agonist together with membrane depolarization to relieve magnesium block leads to receptor activation[8,9] and opening of the ion channel as a result of conformational reorganization.



7 **8** **9**

The models of the glutamate binding site (in closed and open forms) of the NMDA receptor NR2B subunit have been constructed[10,11] on the basis of comparative modelling with the GluR2 ligand binding core.[12] These models allowed us to analyse the binding modes of agonists and antagonists (Figure 4) and to explain known structure–activity relationships for them like a switch between the agonist and antagonist activity of ligands upon lengthening the chain between the amino acid moiety and the distal anionic group, the preference for the D-configuration in some agonists (like NMDA) and antagonists, *etc*.

Interest in the glycine binding site of NMDA receptor significantly increased after the discovery of the fact that antagonists of this site may lack certain undesirable side effects observed for many noncompetitive and competitive antagonists. The modelling of the glycine binding site of NMDA receptor[13,14] was based on the same template as for the glutamate binding site. The docking of agonists and antagonists to the models (Figure 5) was used to analyse their binding modes and to explain structure–activity relationships. Note that, after the first publication of our model, X-ray data for the glycine binding site of NMDA receptor[15]

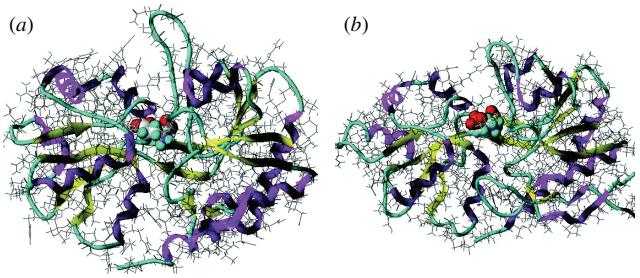


Figure 4 (*a*) Docking of agonist glutamate **7** into the closed form, and (*b*) docking of antagonist AP5 **10** into the open form of NMDA receptor glutamate binding domain.

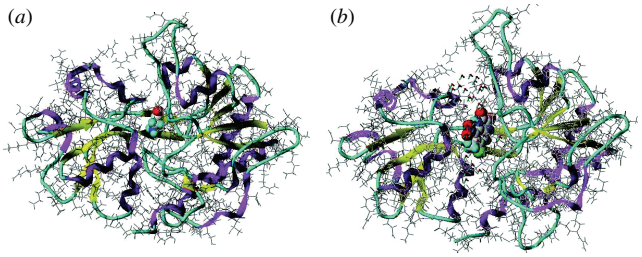
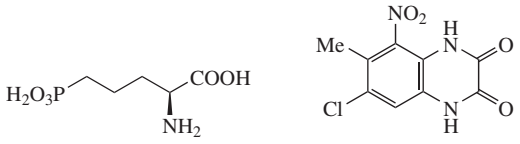


Figure 5 (*a*) Docking of agonist glycine **8** into the closed form, and (*b*) docking of antagonist **11** into the open form of NMDA receptor glycine binding domain.

with the same antagonist **11** as in our model were published. All main structural features in our model were confirmed experimentally including the binding mode of the antagonist.[15] Subsequently, we suggested the concept of selectivity fields, which was demonstrated using data on the binding of antagonists of the glycine site of NMDA receptor and glutamate site of AMPA receptor.[16]

NMDA receptor N-terminal domains are of considerable interest as potential targets for the treatment of neurodegenerative diseases: the binding sites for many pharmacologically significant compounds affecting CNS are localized in these domains. The modelling of the 3D structure of N-terminal domains of NR1 and NR2B subunits[17] was based on their homology with the N-terminal domain of metabotropic glutamate receptor $mGluR_1$.[18] The constructed models were used for the evaluation of putative binding sites of ifenprodil-like compounds. It was shown that, in the N-terminal domains of NR2B subunits, the side chains of the amino acid residues involved in binding of modulator ifenprodil **12** (according to site-directed mutagenesis data) are exposed to the space between globules while for NR1 subunit the amino acid residues important for ifenprodil binding are exposed to the outer surface of the globule and do not form a certain binding site. As far as ifenprodil-like compounds are considered as selective antagonists of the NR2B subunit of NMDA receptor, it can be supposed that the main binding site of ifenprodil is located in the N-terminal domain of the NR2B subunit, while the NR1 subunit is additionally involved in the binding process. The molecular models of NMDA receptor N-terminal domains together with 3D QSAR studies allowed us to evaluate the structural features of ifenprodil-like compounds important for binding to NMDA receptor.[17]



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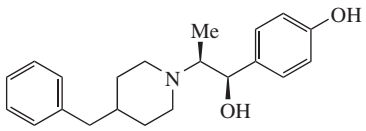

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The constructed models of NMDA receptor domains together with X-ray data for AMPA receptors and our QSAR studies for their ligands[16,19] allowed us to develop a virtual screening system for the design of ligands of NMDA and AMPA receptors.[20]

Recently, a model of the tetrameric structure of ionotropic GluR6 was built[21] and the crystal structure of the AMPA-sensitive, homotetrameric, rat GluA2 receptor at 3.6 Å resolution in complex with a competitive antagonist was reported,[22] which means a considerable success in the experimental studies of ionotropic glutamate receptors. The latter structure can serve as a good template for modelling a complete NMDA receptor structure.

The positive modulators of AMPA receptors could be effective as cognition enhancers. The docking studies[23] for a series of positive AMPA receptor modulators and a detailed analysis of their binding modes served as a basis for the design of new molecules optimally fitting to the modulator binding site. After the synthesis and biological studies, the compounds with picomolar activity were found,[24] which are significantly more potent than any other known positive modulators.

Metabotropic glutamate receptors

Metabotropic glutamate receptors[25] are considered as targets for the cure of various CNS disorders. Eight subtypes of metabotropic glutamate receptors are known ($mGluR_{1\text{-}8}$), which belong to type 3 G protein-coupled receptors (GPCRs). They may be divided into three groups with respect to the signal transduction mechanism, pharmacological properties and the amino acid sequence homology. The receptors of the first group ($mGluR_1$ and $mGluR_5$) activate phospholipase C, while the receptors of the second group ($mGluR_2$ and $mGluR_3$) and the third group ($mGluR_4$, $mGluR_6$, $mGluR_7$ and $mGluR_8$) inhibit adenylate cyclase but differ in pharmacological properties.[25] All mGluRs

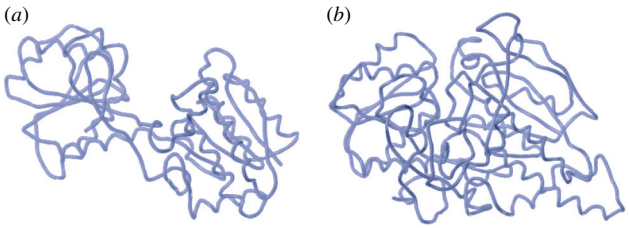


Figure 6 (*a*) Open and (*b*) closed forms of the $mGluR_1$ N-terminal domain.

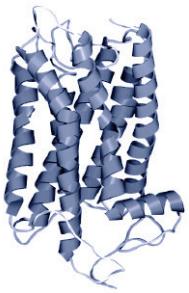


Figure 7 Molecular model of A_{2B} adenosine receptor.

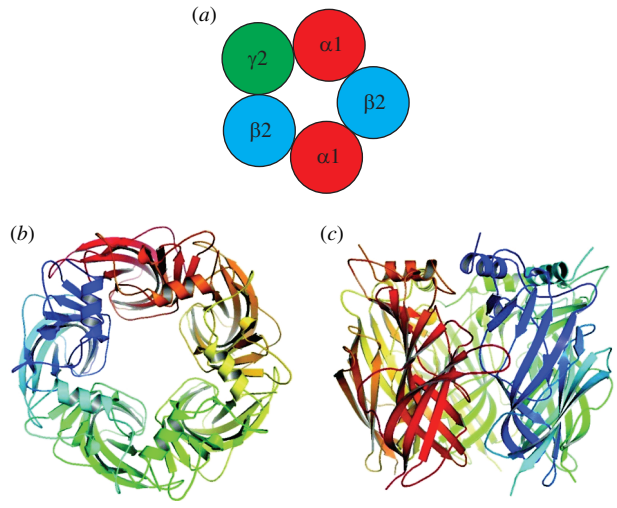


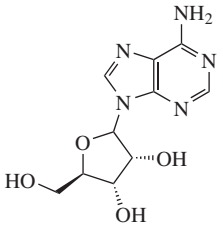
Figure 8 Extracellular domain of $GABA_A$ receptor: (*a*) arrangement of domains, (*b*) top view, and (*c*) side view.

function as dimeric structures, whose monomers incorporate N-terminal, cisteine-rich (CRD) and transmembrane domains. Agonists and competitive antagonists bind to N-terminal domain (to the glutamate binding site), while non-competitive antagonists bind to transmembrane domain. The first our model[26] of the open form of an N-terminal domain revealed the importance of Arg78 for ligand binding in the $mGluR_1$ subtype (unlike published modelling results). This hypothesis was confirmed experimentally[27] and later by an X-ray study of the N-terminal domain of $mGluR_1$.[18] The model for the closed form of $mGluR_1$ (Figure 6) was built by a threading method.[28] The earlier hypothesis of antagonist binding had also been corrected[29] as a result of our simulation. Using the $mGluR_1$ structure as a template, the models of other seven subtypes of mGluRs were constructed, the comparative analysis of structures for all subtypes of metabotropic glutamate receptors was carried out[30] and the results of their ligands docking were analysed.[31]

The transmembrane domain of mGluRs hosts the binding site of highly active non-competitive antagonists. The structure of this domain in $mGluR_1$ was constructed using the rhodopsin structure as a template.[32] The CRD is located between N-terminal and transmembrane domains, its fold type was estimated, the first 3D models were constructed and the role of CRD in receptor functioning was considered.[33]

Adenosine receptors

The adenosine receptors (A_1, A_{2A}, A_{2B} and A_3)[34,35] are activated by natural agonist adenosine **13** and have been classified as GPCRs of the rhodopsin family (type 1 GPCRs). They consist of seven transmembrane α-helices connected by three intracellular and three extracellular hydrophilic loops. Adenosine receptors are present in various tissues and involved in the regulation of various processes. The activation of A_1 and A_3 receptors decreases the cAMP level, while the activation of A_{2A} and A_{2B} receptors increases it. Adenosine A_1 receptor activation induces the inhibition of the dopamine D_1 receptors, and stimulation of the A_{2A} receptor leads to functional inhibition of the D_2 dopamine receptors. Antagonists of the A_{2A} receptor can be used to increase the effect of dopaminergic neurotransmission in the treatment of Parkinson's disease. Other adenosine receptor ligands could be used in treatment of Alzheimer's disease and schizophrenia. The antagonist of A_{2B} receptor theophylline **14** is a strong antiasthmatic drug. A_3 receptor agonists reduce myocardial ischemia/reperfusion injury.



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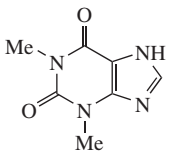

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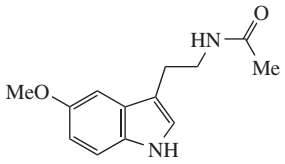
Our molecular models for all subtypes of adenosine receptors[36–41] were built using the bovine rhodopsin structure as a template. The structure of A_{2B} receptor is shown in Figure 7. The detailed analysis of docking results both for antagonists and for agonists (which are located between transmembrane α-helices) allowed us to evaluate the main features of the ligands structures responsible for the activity. Recently, after the publication of the A_{2A} receptor X-ray structure,[42] it has been shown that the crystallographic structure of A_{2A} receptor has been reasonably approximated using rhodopsin-based modelling,[43,44] though the ligand positions are most accurate when water molecules are taken into account or some constraints (like at least one H-bond) are applied. A comparison of the A_{2B} receptor models based on the X-ray structures of bovine rhodopsin, the β_2-adrenergic receptor and the human A_{2A} receptor was performed.[45]

Melatonin receptors

Melatonin **15**, the natural agonist of melatonin receptors,[46] is widely used to treat daily rhyme disorders, migraine and seasonal depressions. Melatonin receptors belong to the same family of GPCRs as adenosine receptors (type 1 GPCRs). Like other GPCRs, they consist of seven transmembrane α-helices linked by three extracellular and three intracellular hydrophilic loops. The models of two subtypes of melatonin receptors based on the bovine rhodopsin structure were published.[47–52] The binding site of melatonin is located between α-helices, the oxygen atom of the methoxy group, as well as the acetamido group of melatonin, form hydrogen bonds with the receptor. However, the results of the docking of melatonin and its analogues showed the absence of any direct interactions of the nitrogen atom in the indol fragment of melatonin with the receptor. It allows one to conclude that the indol fragment is not necessary for the manifestation of activity, and it may be replaced with other fragments. This conclusion is confirmed by the existence of a great number of ligands without the indol fragment. The results of modelling were used in the design of melatonin receptor ligands incorporating new scaffolds.[53]



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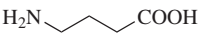
Receptors of γ-aminobutyric acid $GABA_A$ and $GABA_C$

γ-Aminobutyric acid (GABA) **16** is the main inhibitory neurotransmitter in the vertebrate CNS.[54–57] GABA activates three types of receptors, $GABA_A$, $GABA_B$, and $GABA_C$. The $GABA_C$ receptor is sometimes considered as a subtype of $GABA_A$ receptors, and it is designated as $GABA_{A0r}$.[54] The $GABA_B$ receptor belongs to the type 3 GPCR, and it will not be considered in this article. $GABA_A$ and $GABA_C$ receptors are pentameric ligand-gated ion channels belonging to a nicotinicoid (Cys-loop) family. Several drugs like benzodiazepines and barbiturates bind with $GABA_A$ receptors. New ligands affecting $GABA_A$ receptors may find application in the treatment of epilepsy, schizophrenia, Alzheimer's and Parkinson's diseases, *etc*.



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$GABA_A$ and $GABA_C$ receptors consist of five subunits forming the ion channel. Each subunit includes an N-terminal domain and four transmembrane α-helices. The extracellular domain consists of an α-helical region and a β-sandwich. Several types and subtypes of subunits composing the pentameric structure of $GABA_A$ receptors have been identified, the composition $\gamma_2\beta_2\alpha_1\beta_2\alpha_1$ [Figure 8(*a*)] is the most common in brain, and for this composition (as well as for a few other compositions with different α-subunit types) our modelling[58,59] was performed for open and closed forms of the receptor using acetylcholine-binding protein (AChBP) as a template. Similarly, the models of $GABA_C$ receptor consisting of ρ_1 subunits were built.[59–61] The picture of the model of extracellular domain of $GABA_A$

receptor is shown in Figure 8. This domain hosts the main binding sites for the neurotransmitter GABA (located between α and β subunits) and benzodiazepines (located between α and γ subunits). The analysis of the docking of GABA into the closed form of the receptor allowed us to suggest the mechanism of the receptor activation: GABA binds to the $GABA_A$ receptor and interacts with αArg120 and βGlu155 to weaken the salt bridge between βGlu155 and βArg207. Thus, the latter may interact with αGlu183 and αAsp184. This can lead to conformational rearrangements finally causing the channel opening. The detailed analysis of the GABA binding site allowed us to design new potent structures.

Our molecular modelling of $GABA_A$ and $GABA_C$ receptors and molecular dynamics simulation[58–61] together with other modelling studies[62–72] had revealed the receptor structures in different forms and putative binding modes of many known ligands.

The docking studies for the benzodiazepine-binding site in several $GABA_A$ receptor subtypes jointly with QSAR studies[73–76] have shown the ligand structural features responsible for the activity variation and selectivity with respect to those subtypes.

In conclusion, note that the molecular modelling of receptors and the detailed analysis of their binding sites is an important step in the design of new drugs. Dozens of receptors ligands computationally designed by our group had demonstrated exclusively high activity, and some of them are now at the preclinical stages of pharmacological studies.

References

1 I. I. Baskin, V. A. Palyulin and N. S. Zefirov, *Usp. Khim.*, 2009, **78**, 539 (*Russ. Chem. Rev.*, 2009, **78**, 495).
2 C. G. Parsons, W. Danysz and G. Quack, *Drug News Perspect*., 1998, **11**, 523.
3 N. S. Nakanishi, *Science*, 1992, **258**, 31.
4 S. Bachurin, S. Tkachenko, I. Baskin, N. Lermontova, T. Mukhina, L. Petrova, A. Ustinov, A. Proshin, V. Grigoriev, N. Lukoyanov, V. Palyulin and N. Zefirov, *Ann. New York Acad. Sci*., 2001, **931**, 219.
5 D. A. Doyle, J. M. Cabral, R. A. Pfuetzner, A. Kuo, J. M. Gulbis, S. L. Cohen, B. T. Chait and R. MacKinnon, *Science*, 1998, **280**, 69.
6 I. G. Tikhonova, I. I. Baskin, V. A. Palyulin and N. S. Zefirov, *Dokl. Akad. Nauk*, 2004, **396**, 551 [*Dokl. Biochem. Biophys*. (*Engl. Transl.*), 2004, **396**, 181].
7 K. Kashiwagi, T. Masuko, C. D. Nguyen, T. Kuno, I. Tanaka, K. Igarashi and K. Williams, *Mol. Pharmacol*., 2002, **61**, 533.
8 M. L. Mayer, G. L. Westbrook and P. B. Guthrie, *Nature*, 1984, **309**, 261.
9 J. W. Johnson and P. Ascher, *Nature*, 1987, **325**, 529.
10 I. G. Tikhonova, I. I. Baskin, V. A. Palyulin and N. S. Zefirov, *Dokl. Akad. Nauk*, 2002, **382**, 550 [*Dokl. Biochem. Biophys*. (*Engl. Transl.*), 2002, **382**, 38].
11 (*a*) I. G. Tikhonova, I. I. Baskin, V. A. Palyulin, N. S. Zefirov and S. O. Bachurin, *J. Med. Chem.*, 2002, **45**, 3836; (*b*) I. G. Tikhonova, I. I. Baskin, V. A. Palyulin, N. S. Zefirov and S. O. Bachurin, *J. Med. Chem.*, 2002, **45**, 5608.
12 N. Armstrong and E. Gouaux, *Neuron*, 2000, **28**, 165.
13 I. G. Tikhonova, I. I. Baskin, V. A. Palyulin and N. S. Zefirov, *Dokl. Akad. Nauk*, 2002, **382**, 840 [*Dokl. Biochem. Biophys*. (*Engl. Transl.*), 2002, **382**, 67].
14 I. G. Tikhonova, I. I. Baskin, V. A. Palyulin and N. S. Zefirov, *J. Med. Chem*., 2003, **46**, 1609.
15 H. Furukawa and E. Gouaux, *EMBO J*., 2003, **22**, 2873.
16 I. I. Baskin, I. G. Tikhonova, V. A. Palyulin and N. S. Zefirov, *J. Med. Chem*., 2003, **46**, 4063.
17 I. G. Tikhonova, I. I. Baskin, V. A. Palyulin and N. S. Zefirov, *Dokl. Akad. Nauk*, 2004, **397**, 549 [*Dokl. Biochem. Biophys*. (*Engl. Transl.*), 2004, **397**, 242].
18 N. Kunishima, Y. Shimada, Y. Tsuji, T. Sato, M. Yamamoto, S. Kumasaka, S. Nakanishi, H. Jingami and K. Morikawa, *Nature*, 2000, **407**, 971.
19 I. G. Tikhonova, I. I. Baskin, V. A. Palyulin and N. S. Zefirov, *Dokl. Akad. Nauk*, 2003, **389**, 123 [*Dokl. Biochem. Biophys*. (*Engl. Transl.*), 2003, **389**, 75].
20 I. G. Tikhonova, I. I. Baskin, V. A. Palyulin and N. S. Zefirov, *Izv. Akad. Nauk, Ser. Khim.*, 2004, 1282 (*Russ. Chem. Bull., Int. Ed*., 2004, **53**, 1335).
21 A. A. Kaczor, U. A. Kijkowska-Murak, C. Kronbach, K. Unverferth and D. Matosiuk, *J. Chem. Inf. Model*., 2009, **49**, 1094.
22 A. I. Sobolevsky, M. P. Rosconi and E. Gouaux, *Nature*, 2009, **462**, 745.
23 I. G. Tikhonova, M. I. Lavrov, V. A. Palyulin and N. S. Zefirov, *Dokl. Akad. Nauk*, 2004, **399**, 268 [*Dokl. Biochem. Biophys*. (*Engl. Transl.*), 2004, **399**, 351].
24 S. O. Bachurin, V. V. Grigor'ev, N. S. Zefirov, M. I. Lavrov, V. L. Lapteva and V. A. Palyulin, *RF Patent* RU 2333211, 2008.
25 D. D. Schoepp, D. E. Jane and J. A. Monn, *Neuropharmacology*, 1999, **38**, 1431.
26 I. I. Baskin, M. S. Belenikin, E. V. Ekimova, G. Costantino, V. A. Palyulin, R. Pellicciari and N. S. Zefirov, *Dokl. Akad. Nauk*, 2000, **374**, 347 [*Dokl. Chem.* (*Engl. Transl.*), 2000, **374**, 191].
27 A. A. Jensen, P. O. Sheppard, P. J. O'Hara, P. Krogsgaard-Larsen and H. Brauner-Osborne, *Eur. J. Pharmacol*., 2000, **397**, 247.
28 M. S. Belenikin, I. I. Baskin, V. A. Palyulin and N. S. Zefirov, *Dokl. Akad. Nauk*, 2002, **383**, 643 [*Dokl. Chem.* (*Engl. Transl.*), 2002, **383**, 97].
29 M. S. Belenikin, I. I. Baskin, V. A. Palyulin and N. S. Zefirov, *Dokl. Akad. Nauk*, 2002, **384**, 113 [*Dokl. Biochem. Biophys*. (*Engl. Transl.*), 2002, **384**, 131].
30 M. S. Belenikin, I. I. Baskin, G. Costantino, V. A. Palyulin, R. Pellicciari and N. S. Zefirov, *Dokl. Akad. Nauk*, 2002, **386**, 261 [*Dokl. Biochem. Biophys*. (*Engl. Transl.*), 2002, **386**, 251].
31 M. S. Belenikin, A. Macciarulo, G. Costantino, V. A. Palyulin, R. Pellicciari and N. S. Zefirov, *Vestn. Mosk. Univ., Ser. 2: Khim.*, 2002, **43**, 221 (in Russian).
32 M. S. Belenikin, G. Costantino, V. A. Palyulin, R. Pellicciari and N. S. Zefirov, *Dokl. Akad. Nauk*, 2003, **393**, 827 [*Dokl. Biochem. Biophys*. (*Engl. Transl.*), 2003, **393**, 341].
33 M. S. Belenikin, V. A. Palyulin and N. S. Zefirov, *Dokl. Akad. Nauk*, 2004, **394**, 259 [*Dokl. Biochem. Biophys*. (*Engl. Transl.*), 2004, **394**, 21].
34 B. B. Fredholm, J. F. Chen, S. A. Masino and J. M. Vaugeois, *Annu. Rev. Pharmacol. Toxicol*., 2005, **45**, 385.
35 B. B. Fredholm, A. P. IJzerman, K. A. Jacobson, K. N. Klotz and J. Linden, *Pharmacol. Rev*., 2001, **53**, 527.
36 A. A. Ivanov, V. A. Palyulin and N. S. Zefirov, *J. Mol. Graph. Model*., 2007, **25**, 740.
37 A. A. Ivanov, I. I. Baskin, V. A. Palyulin, P. G. Baraldi and N. S. Zefirov, *Mendeleev Commun*., 2002, 211.
38 A. A. Ivanov, I. I. Baskin, V. A. Palyulin, L. Piccagli, P. G. Baraldi and N. S. Zefirov, *J. Med. Chem*., 2005, **48**, 6813.
39 V. A. Palyulin, A. A. Ivanov, P. G. Baraldi and N. S. Zefirov, *Purinergic Signalling*, 2006, **2**, 262.
40 A. A. Ivanov, I. I. Baskin, V. A. Palyulin and N. S. Zefirov, *Dokl. Akad. Nauk*, 2002, **386**, 548 [*Dokl. Biochem. Biophys*. (*Engl. Transl.*), 2002, **386**, 271].
41 A. A. Ivanov, I. I. Baskin, V. A. Palyulin and N. S. Zefirov, *Dokl. Akad. Nauk*, 2003, **389**, 404 [*Dokl. Biochem. Biophys*. (*Engl. Transl.*), 2003, **389**, 94].
42 V.-P. Jaakola, M. T. Griffith, M. A. Hanson, V. Cherezov, E. Y. T. Chien, J. R. Lane, A. P. IJzerman and R. C. Stevens, *Science*, 2008, **322**, 1211.
43 A. A. Ivanov, D. Barak and K. A. Jacobson, *J. Med. Chem*., 2009, **52**, 3284.
44 S.-K. Kim, Z.-G. Gao, P. Van Rompaey, A. S. Gross, A. Chen, S. Van Calenbergh and K. A. Jacobson, *J. Med. Chem*., 2003, **46**, 4847.
45 F. F. Sherbiny, A. C. Schiedel, A. Maaß and C. E. Müller, *J. Comput. Aided Mol. Des*., 2009, **23**, 807.
46 R. Jockers, P. Maurice, J. A. Boutin and P. Delagrange, *Br. J. Pharmacol*., 2008, **154**, 1182.
47 A. A. Ivanov, A. E. Voronkov, I. I. Baskin, V. A. Palyulin and N. S. Zefirov, *Dokl. Akad. Nauk*, 2004, **394**, 822 [*Dokl. Biochem. Biophys*. (*Engl. Transl.*), 2004, **394**, 49].
48 A. E. Voronkov, A. A. Ivanov, I. I. Baskin, V. A. Palyulin and N. S. Zefirov, *Dokl. Akad. Nauk*, 2005, **403**, 409 [*Dokl. Biochem. Biophys*. (*Engl. Transl.*), 2005, **403**, 284].
49 (*a*) P. Mazna, V. Obsilova, I. Jelinkova, A. Balik, K. Berka, Z. Sovova, R. Ettrich, P. Svoboda, T. Obsil and J. Teisinger, *J. Neurochem*., 2004, **91**, 836; (*b*) P. Mazna, V. Obsilova, I. Jelinkova, A. Balik, K. Berka, Z. Sovova, R. Ettrich, P. Svoboda, T. Obsil and J. Teisinger, *J. Neurochem*., 2004, **91**, 1505.
50 S. Rivara, M. Mor, S. Lorenzi, A. Lodola, P. V. Plazzi, G. Spadoni, A. Bedini and G. Tarzia, *ARKIVOC*, 2006, Part 8, 8.
51 A. O. Chugunov, A. Farce, P. Chavatte and R. G. Efremov, *J. Biomol. Struct. Dyn*., 2006, **24** (2), 91.
52 A. Farce, A. O. Chugunov, C. Logé, A. Sabaouni, S. Yous, S. Dilly, N. Renault, G. Vergoten, R. G. Efremov, D. Lesieur and P. Chavatte, *Eur. J. Med. Chem*., 2008, **43**, 1926.

53 T. Yu. Baranova, O. N. Zefirova, N. V. Averina, V. V. Boyarskikh, G. S. Borisova, N. V. Zyk and N. S. Zefirov, *Zh. Org. Khim.*, 2007, **43**, 1201 (*Russ. J. Org. Chem.*, 2007, **43**, 1196).
54 G. Michels and S. J. Moss, *Crit. Rev. Biochem. Mol. Biol*., 2007, **42**, 3.
55 M. Chebib and G. A. Johnston, *J. Med. Chem*., 2000, **43**, 1427.
56 M. Chebib, *Clin. Exp. Pharmacol. Physiol*., 2004, **31**, 800.
57 C. D'Hulst, J. R. Atack and R. F. Kooy, *Drug Discov. Today*, 2009, **14**, 866.
58 V. I. Chupakhin, V. A. Palyulin and N. S. Zefirov, *Dokl. Akad. Nauk*, 2006, **408**, 693 [*Dokl. Biochem. Biophys*. (*Engl. Transl.*), 2006, **408**, 169].
59 D. I. Osolodkin, V. I. Chupakhin, V. A. Palyulin and N. S. Zefirov, *Dokl. Akad. Nauk*, 2007, **412**, 404 [*Dokl. Biochem. Biophys*. (*Engl. Transl.*), 2007, **412**, 25].
60 D. I. Osolodkin, V. I. Chupakhin, V. A. Palyulin and N. S. Zefirov, *J. Mol. Graph. Model*., 2009, **27**, 813.
61 V. I. Chupakhin, *PhD Thesis*, M. V. Lomonosov Moscow State University, 2010.
62 B. A. Cromer, C. J. Morton and M. W. Parker, *Trends Biochem. Sci*., 2002, **27**, 280.
63 M. Ernst, D. Brauchart, S. Boresch and W. Sieghart, *Neuroscience*, 2003, **119**, 933.
64 M. Ernst, D. Brauchart, S. Boresch and W. Sieghart, *Mol. Pharmacol*., 2005, **68**, 1291.
65 C. L. Padgett, A. P. Hanek, H. A. Lester, D. A. Dogherty and S. C. Lummis, *J. Neurosci*., 2007, **26**, 760.
66 Y. Mokrab, V. N. Bavro, K. Mizuguchi, N. P. Todorov, I. L. Martin, S. M. Dunn, S. L. Chan and P. L. Chau, *J. Mol. Graph. Model*., 2007, **26**, 760.
67 J. R. Trudell and E. Bertaccini, *Br. J. Anaesth*., 2002, **89**, 32.
68 V. Canpagna-Slater and D. F. Weaver, *J. Mol. Graph. Model*., 2007, **25**, 721.
69 M. O'Mara, B. Cromer, M. Parker and S. H. Chung, *Biophys. J*., 2005, **88**, 3286.
70 A. Sedelnikova, C. D. Smith, S. O. Zakharkin, D. Davis, D. S. Weiss and Y. Cheng, *J. Biol. Chem*., 2005, **280**, 1535.
71 N. J. Harrison and S. C. Lummis, *J. Mol. Model*., 2006, **12**, 317.
72 H. Abdel-Halim, J. R. Hanrahan, D. E. Hibbs, G. A. Johnston and M. A. Chebib, *Chem. Biol. Drug. Des*., 2008, **71**, 306.
73 V. I. Chupakhin, S. V. Bobrov, E. V. Radchenko, V. A. Palyulin and N. S. Zefirov, *Dokl. Akad. Nauk*, 2008, **422**, 204 [*Dokl. Chem.* (*Engl. Transl.*), 2008, **422**, 227].
74 E. V. Radchenko, V. A. Palyulin and N. S. Zefirov, in *Chemoinformatics Approach to Virtual Screening*, ed. A. Varnek and A. Tropsha, RSC, Cambridge, 2008, pp. 150–181.
75 V. A. Palyulin, E. V. Radchenko and N. S. Zefirov, *J. Chem. Inf. Comput. Sci*., 2000, **40**, 659.
76 E. V. Radchenko, V. A. Palyulin and N. S. Zefirov, *Zh. Khim. Ob-va im. D. I. Mendeleeva (Ross. Khim. Zh.)*, 2006, **50** (2), 76 (in Russian).

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