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New tricyclic cage compound as allosteric modulator of the glutamatergic system: synthesis and biological activity

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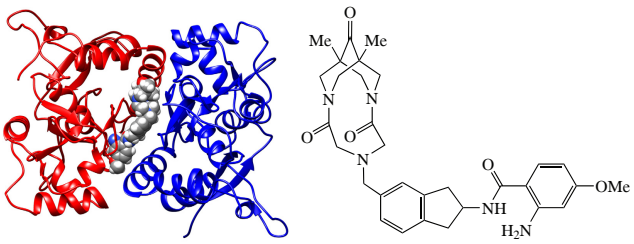
A new tricyclic derivative of 1,5-dimethyl-3,7-diazabicyclo[3.3.1]nonane was synthesized in three steps using 2-aminoindane-5-carbonitrile. A positive modulatory activity of this compound towards the glutamatergic system in a wide range of nanomolar and subnanomolar concentrations has been demonstrated in electrophysiological studies *in vitro* using patch clamp technique. A putative binding mode of this compound has been revealed by means of molecular docking and molecular dynamics simulations.



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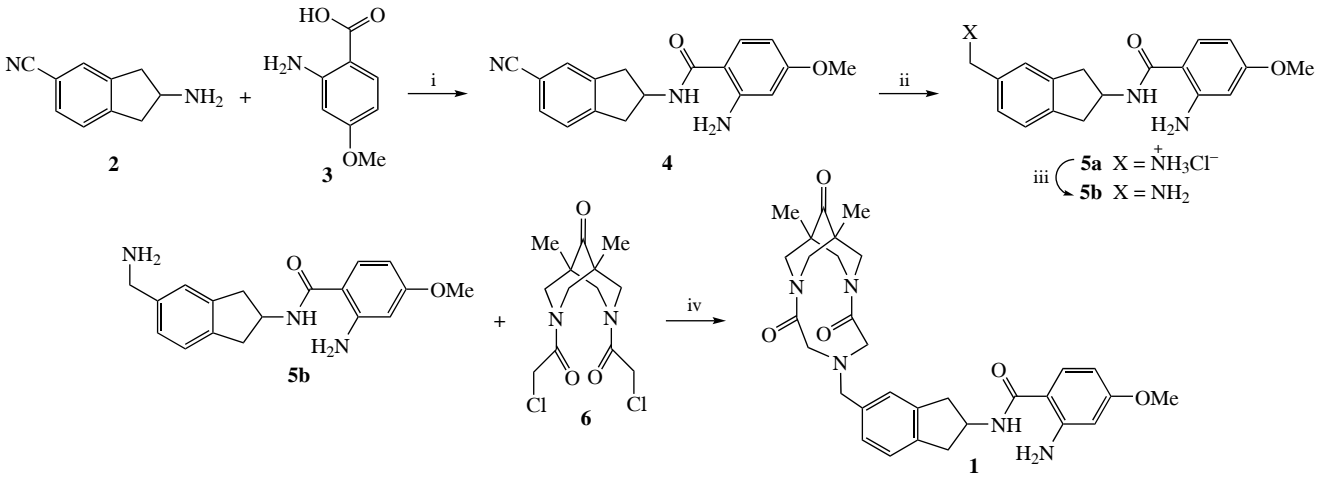
L-Glutamate is one of the essential neurotransmitters in the mammalian central nervous system. Glutamate receptors are divided into two families: metabotropic glutamate receptors are classified as G protein-coupled receptors (GPCRs), while ionotropic glutamate receptors are ligand-gated ion channels.[1,2] The latter mediate fast excitatory synaptic neurotransmission, being very important for cognition, memory, mood, and motor functions. Ionotropic glutamate receptors, in their turn, are presented by three subtypes: NMDA (*N*-methyl-D-aspartate), AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid), and kainate receptors. AMPA receptors are of great interest because they are most abundant in mammalian brain and play a crucial role in cognitive functions and memory formation.[3–6]

There are many compounds that, unlike the endogenous glutamate ligand, bind at the allosteric sites of AMPA receptor and subtly modulate its activity, thereby fine-tuning the receptor functions.[7,8] Therapeutic potential of the positive allosteric modulators (PAMs) of AMPA receptor is based on their ability to enhance synaptic plasticity, one of the memory formation mechanisms, as well as increase the expression of neurotrophic factors (BDNF, NGF), thereby providing neuroprotective effects and regeneration of nerve tissue.[9–11] Therefore, such compounds are promising candidates for the treatment of neurodegenerative and psychoneurological diseases, such as schizophrenia, depression, Alzheimer's disease, Parkinson's disease, ADHD, and soft cognitive disorders.[9–13]

AMPA receptor PAMs are mainly represented by four classical chemotypes: benzamides, benzothiadiazines, biarylalkylsulfonamides, and trifluoromethylpyrazoles.[2,9,14] Earlier, we have developed a new class of AMPA receptor allosteric modulators based on the 1,5-dimethyl-3,7-diazabicyclo[3.3.1]-nonane scaffold.[15–17] Many of these compounds demonstrated high positive modulatory activity in a wide range of nanomolar and subnanomolar concentrations; some of them have shown anti-amnestic, nootropic, and neuroprotective effects *in vivo*. Several compounds have passed preclinical trials.

Recently, we have reported a series of tricyclic derivatives of 1,5-dimethyl-3,7-diazabicyclo[3.3.1]nonane containing indane moiety.[18,19] In this work, we have further developed this chemotype by varying amide substituent. A new tricyclic compound **1** has been synthesized and its biological activity has been evaluated in electrophysiological assay *in vitro*.

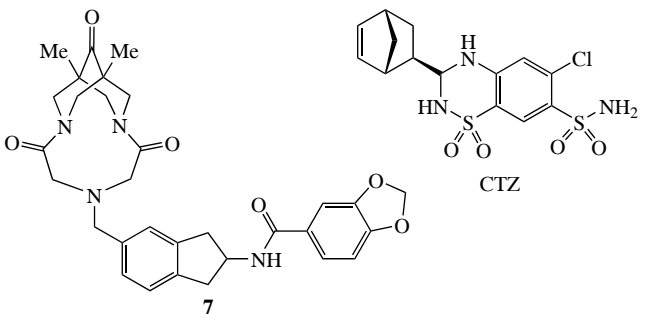
The target compound **1** was obtained in three steps from 2-aminoindane-5-carbonitrile **2** (Scheme 1) that was prepared by the approach developed previously.[19] First, reaction between 2-aminoindane-5-carbonitrile **2** and 2-amino-4-methoxybenzoic acid **3** was carried out using CDI as a carbonyl-activating agent, that provided amide **4**. Despite the literature data[20] describing the side reaction of CDI with similar substrates (2-aminobenzoic acid and 2-amino-5-chlorobenzoic acid), in this case the procedure gave good results. Then, amine **5** was obtained by reduction of cyano group in compound **4**. The previously developed[18,19] technique of heterogeneous hydrogenation in an autoclave using 10% Pd/C as a catalyst and adding concentrated HCl provided the amine in the form of hydrochloride **5a** in a high yield. Further treatment with KOH made it possible to isolate amine **5b** as a free base. Finally, the target compound **1** was synthesized by double alkylation of amine **5b** with dichloro derivative **6** that was obtained using a modified procedure of 5,7-dimethyl-1,3-diazaadamantan-6-one acylation in a two-phase system $CHCl_3/H_2O$, described previously.[17] Potassium carbonate and *N*-methyl-2-pyrrolidone were used as a base and a solvent, respectively, because those conditions had been shown previously to be beneficial for the synthesis of similar



Scheme 1 *Reagents and conditions*: i, CDI, MeCN, 50 °C; ii, H_2, Pd/C, HCl_{conc}, EtOH; iii, KOH, H_2O; iv, K_2CO_3, NMP, 70 °C.

tricyclic compounds.[18,19] An overall yield of compound **1** was 33%.

The action of the target compound **1** on AMPA receptors was investigated in the electrophysiological assay by means of the patch clamp technique on freshly isolated Purkinje neurons of Wistar rats. The addition of the AMPA receptor partial agonist, kainic acid, was used to activate the receptor, as described earlier.[15] Compound **1** demonstrated significant positive modulation of AMPA receptors in a wide range of concentrations down to nano- and subnanomolar ones. Receptor potentiation was observed from 10^{-12} to 10^{-7} M with a maximum (current amplitude 154±7%) at 10^{-10} M concentration (Table 1). The results are comparable to the data obtained previously for related compounds such as **7**.[14,18] Notably, compound **1** demonstrates a significant potentiating effect at much lower concentrations than a well-known AMPA receptor PAM cyclothiazide (CTZ).



CTZ

7

The interaction of the positive modulator **1** with the GluA2 AMPA receptor was modelled by means of molecular docking using AutoDock Vina 1.1.2 software[21] and molecular dynamics simulations using the CHARMM36/CGenFF 4.6 force field[22,23] in the GROMACS 2024.3 software[24] following the previously published[17] computational workflow. Two enantiomers with the protonated tertiary amine moiety in the tricyclic system were considered, and the binding of the *S* form was found to be most favorable in terms of stability and strength. The ligand shifted from the initial docking-based pose, and then its binding mode in the PAM binding site at the interface between the dimeric ligand-binding domains remained stable over the entire course of the simulation [100 ns, see root mean squared deviation (RMSD) plots in Figure S1, Online Supplementary Materials]. Roughly similar to the predicted binding mode for a closely related tricyclic modulator,[18] the modulator molecule was located in the central subpocket of the symmetrical PAM binding site (Figure 1). The binding is primarily stabilized by steric fit and hydrophobic interactions. The binding free energies calculated using the MM/GBSA (molecular mechanics, generalized Born, surface area) method in the optimal binding modes were –55.3±0.3 kcal mol^{-1} for the *S* enantiomer and –46.7±0.5 kcal mol^{-1} for the *R* enantiomer.

Computational evaluation of the physicochemical, ADMET, and PAINS profiles for compound **1** included the predictions of its lipophilicity and aqueous solubility,[25] human intestinal absorption,[26] blood–brain barrier permeability,[27] and hERG-mediated cardiac toxicity risk,[28] as well as calculation of

Table 1 Effects of various concentrations of compound **1** and reference compounds on the kainate-induced AMPA receptor currents in rat cerebellum Purkinje cells measured as current amplitude (% to control±SD); the number of neurons is 4.

Compound	Effects (%) for concentrations/M						
	10^{-12}	10^{-11}	10^{-10}	10^{-9}	10^{-8}	10^{-7}	10^{-6}
1	111±6	143±6	154±7	144±5	122±6	105±4	100±2
7 (ref. 18)	111±3	145±4	152±5	165±5	120±3	96±3	
CTZ						100±3	145±11

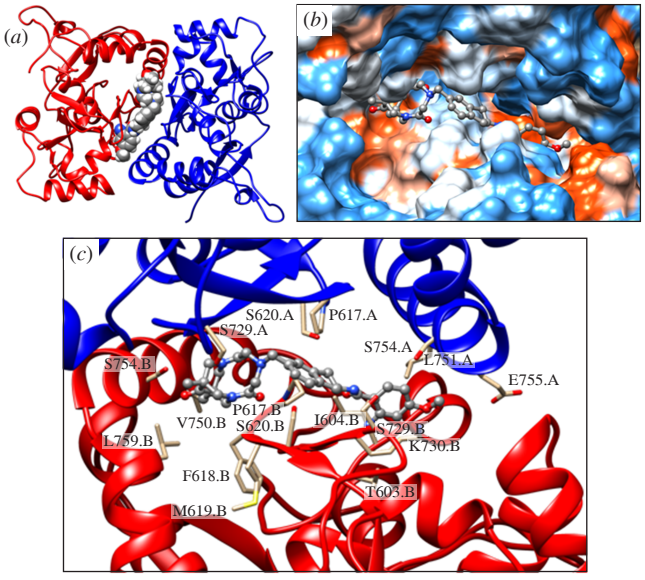


Figure 1 Binding mode of the PAM **1** (*S* isomer), refined using molecular dynamics simulation (100 ns). (*a*) General view of the dimeric ligand binding domain of AMPA receptor (GluA2) and location of the binding site. (*b*) Binding pockets in the protein molecular surface colored by local hydrophobicity (brown for hydrophobic and blue for hydrophilic). (*c*) Detailed view of the binding site. The ligand is represented by a grey ball-and-stick model, the amino acid residues located within 3 Å of it are represented by beige stick models.

Table 2 Predicted physicochemical and ADMET profiles of compounds **1** and **7**.

Compound	LogP_{ow} [a]	pS_{aq} [b]	LogBB [c]	HIA [d] (%)	hERG pK_i [e]	hERG pIC_{50} [f]	QED [g]
1	0.67	2.35	–1.66	26	5.11	3.32	0.53
7	1.00	2.85	–1.47	48	5.82	3.77	0.60

[a] LogP_{ow} is octanol–water partition coefficient. [b] pS_{aq} is aqueous solubility [–log(M)]. [c] LogBB is blood–brain barrier permeability. [d] HIA is human intestinal absorption (%). [e] hERG pK_i is hERG potassium channel affinity [–log(M)]. [f] hERG pIC_{50} is hERG potassium channel inhibitory activity [–log(M)]. [g] QED is quantitative estimate of drug-likeness.

quantitative estimate of drug-likeness[29] and pan-assay interference compounds (PAINS) alert check using RDKit version 2020.03.4 software.[30] The results (see Table 2) were similar to those for compound **7** and quite acceptable for a potential lead compound at the early drug development stages, although additional checks and structure optimization would likely be required.

To summarize, compound **1** has demonstrated significant positive modulation of the AMPA receptor *in vitro* in a wide range of nano- and subnanomolar concentrations. Molecular modeling has revealed a presumed binding mode of this compound in the binding site of the AMPA receptors PAMs. These results, along with the previously published data,[18,19] inspire the hope that tricyclic derivatives of 1,5-dimethyl-3,7-diazabicyclo[3.3.1]nonane with indane moiety can be a new promising class of the AMPA receptors allosteric modulators. We expect that further *in vitro* and *in vivo* studies will allow us to develop new compounds of this class with optimized characteristics for the treatment of neurodegenerative and psychoneurological diseases.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7654.

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