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Mendeleev Commun., 2021, **31**, 219–220

Mendeleev Communications

New nanomolar negative modulators of AMPA receptors

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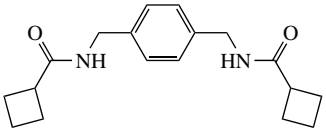
DOI: 10.1016/j.mencom.2021.03.024

Bisamides of 1,4-bis(aminomethyl)benzene with cyclopropane-, cyclobutane- and cyclopentanecarboxylic acids reveal the negative modulation of kainate-induced currents in rat Purkinje neurons observed using patch clamp technique. The most pronounced effect has been found for the bisamide of cyclobutanecarboxylic acid, which blocks the currents by 41 and 49% at concentrations of 1×10^{-10} and 1×10^{-9} mol dm^{-3}, respectively.



49% negative AMPA receptor modulation at 1 nM

Keywords: AMPA receptor, negative modulator, patch clamp, Purkinje neurons, cycloalkanecarboxamide, 1,4-bis(aminomethyl)benzene.

Glutamate receptors play an important role in the functioning of mammalian central nervous system.[1] The ionotropic glutamate receptors, which have an ion channel able to be activated by glutamate binding, are further subdivided into α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, which consist of four subunits forming the transmembrane ligand-gated ion channel as well as four extracellular ligand binding domains and four further extracellular N-terminal domains.[2] These receptors are involved in the formation of memory and cognitive functions.[3,4] Positive allosteric modulators of the AMPA receptors[5,6] improve learning and memory formation, which makes them promising drug candidates for the treatment of dementia and cognitive disorders, including early stages of Alzheimer's disease,[7,8] as well as other pathologies of the central nervous system.[9–11] On the other hand, negative modulators of AMPA receptors can be employed for the treatment of epilepsy[12,13] and provide other beneficial effects including anticonvulsant activity.[14] Thus, the search for new positive and negative modulators for AMPA receptors is considered as an important and promising challenge.

Predictive QSAR and pharmacophore models were developed in our work[15] for molecular design of the positive modulators including compounds that increased the kainate-induced currents in subnanomolar concentrations, improved cognitive impairment in animal models and were among the most active positive AMPA receptor modulators known.[16,17] As well, a number of negative AMPA receptor modulators were found based on two different scaffolds.[18,19]

In this work, we synthesized three new negative modulators of AMPA receptors, namely bisamides **1**–**3** based on one more scaffold, and investigated them by an electrophysiological method. The new compounds are structurally similar to positive allosteric modulator **4**, found in our recent work, for which 40% potentiation of AMPA receptors at concentration of 1 nmol dm^{-3} has been detected.[20]

Compounds **1**–**3** were synthesized by acylation of 1,4-bis(aminomethyl)benzene with appropriate carboxylic acid chlorides in the presence of a base, and their structures were confirmed by spectral and analytical data (for details, see Online Supplementary Materials).

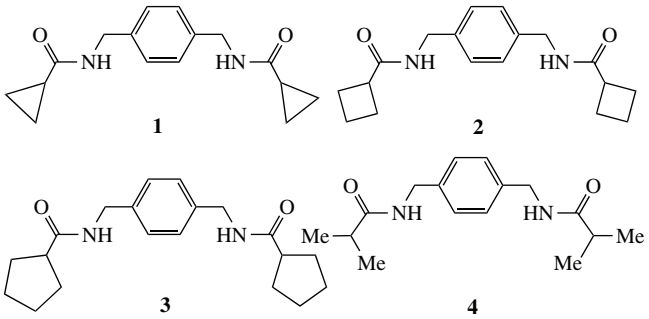


Table 1 The effect of compounds **1**–**3** at various concentrations *C* on the kainate-induced AMPA receptor currents in Purkinje neurons (number of the cells $n = 5$), the current amplitude for control is taken as 100%.

Compound	Current amplitude (%)					
	$C = 1\times10^{-11}$ mol dm^{-3}	$C = 1\times10^{-10}$ mol dm^{-3}	$C = 1\times10^{-9}$ mol dm^{-3}	$C = 1\times10^{-8}$ mol dm^{-3}	$C = 1\times10^{-7}$ mol dm^{-3}	$C = 1\times10^{-6}$ mol dm^{-3}
1	87±8	89±6	78±10	81±8	94±6	96±5
2	73±6	59±5	51±5	48±5	42±6	52±6
3	70±10	68±11	61±9	73±10	87±7	93±6

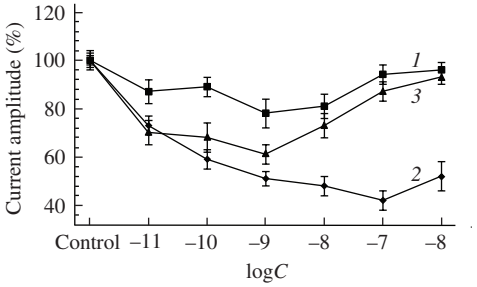


Figure 1 The effect of compounds (*1*) **1**, (*2*) **2** and (*3*) **3** on the kainate-induced AMPA receptor currents, where *C* represents the compound concentration in mol dm^{-3} and the current amplitude for control is taken as 100%.

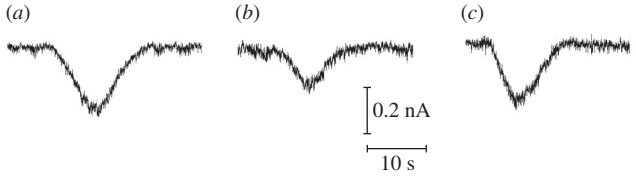


Figure 2 Kainate-induced currents: (*a*) for control, (*b*) after addition of compound **2** at 1 nmol dm^{-3} concentration and (*c*) after subsequent washout.

The electrophysiological evaluation of the bisamides obtained was carried out using the patch clamp technique with freshly isolated rat Purkinje neurons as described.[17] Compounds **1**, **2** and **3** induced a concentration-dependent decrease in the kainate-induced AMPA receptor currents (Table 1 and Figure 1). The most pronounced effect was observed for bisamide **2**, which blocked the current by 41, 49 and 58% at concentrations of 1×10^{-10}, 1×10^{-9} and 1×10^{-7} mol dm^{-3}, respectively. Figure 2 demonstrates the change of the kainate-induced currents after addition of compound **2** at 1 nmol dm^{-3} concentration and after subsequent washout, both compared with control.

It is not quite clear at present, why the effect of compounds **1**, **2** and **3** differs so much from that of structurally similar bisamide **4**. Besides, the docking results for this type of structures can hardly be related to the positive or negative modulation. However, we hope that further optimization of this structural series with its simple synthetic scheme and available starting materials as well as subsequent *in vitro* and *in vivo* investigations will allow one to develop more potent and safe negative AMPA receptor modulators applicable as antiepileptics and anticonvulsants.

This work was supported by the Russian Science Foundation (grant no. 17-15-01455). The development of general technique for the electrophysiological investigation of AMPA receptor modulators was supported by the State Target of the Institute of Physiologically Active Compounds, Russian Academy of Sciences (topic no. 0090_2019_0005).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.03.024.

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Received: 23rd November 2020; Com. 20/6378