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# Ifenprodil-like NMDA receptor modulator based on the biphenyl scaffold

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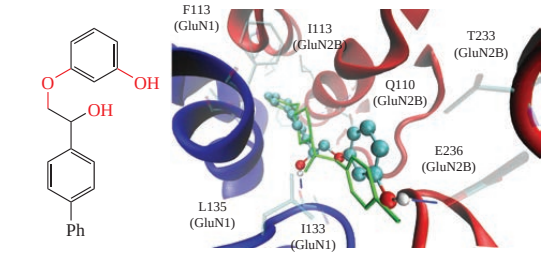
**Ifenprodil-like NMDA receptor negative allosteric modulator based on the biphenyl scaffold has been identified using virtual screening. Docking approach demonstrated that the modulator maintains some characteristic interactions with protein similar to ifenprodil. Electrophysiological and radioligand investigations demonstrated the concentration-dependent NMDA/Gly-induced currents inhibition with $IC_{50}$ = 5 μM and significant displacement of [$H^3$]ifenprodil with $EC_{50}$ = = 30 μM, respectively.**




$IC_{50}$(NMDA/Gly) = 5 μM

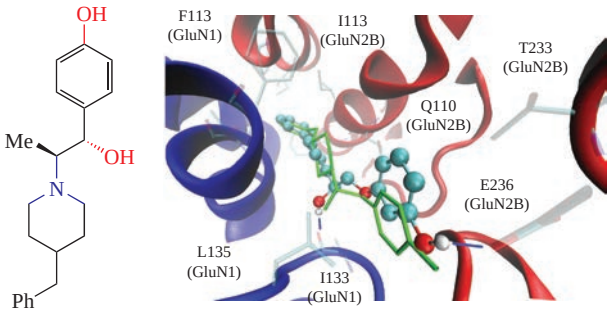
*Keywords*: NMDA receptors, negative allosteric modulator, docking, biphenyl scaffold, electrophysiological investigations.

*N*-Methyl-D-aspartate (NMDA) receptors are ligand-gated cationic channels expressed in brain tissue and naturally activated by the simultaneous action of glutamate and glycine. These receptors are considered to be involved in learning and memory formation.[1] Being permeable to calcium ions, NMDA receptors can cause the death of neurons as a result of the receptor hyperactivation.[2] However, their strong inhibition typically leads to a psychotomimetic effect accompanied by the organic changes in the brain tissue after long-term consumption.[3] Despite this fact, the weak nonselective NMDA receptor blocker memantine is employed to slow down the progression of Alzheimer disease *via* a decrease in neuronal cell death induced by excitotoxicity.

It was demonstrated[4] that the NMDA receptor non-selective blocker ketamine produced a rapid antidepressant effect in animal models, and in 2019 (*S*)-ketamine was approved by Food and Drug Administration (USA) for the treatment of Major Depressive Disorder. One of the proposed mechanisms explains its antidepressant action by the direct blockage of GluN2B-containing NMDA receptors by ketamine, which leads to inhibition of GABAergic inhibitory interneurons in turn inducing the increase in glutamate level in the prefrontal cortex.[5]

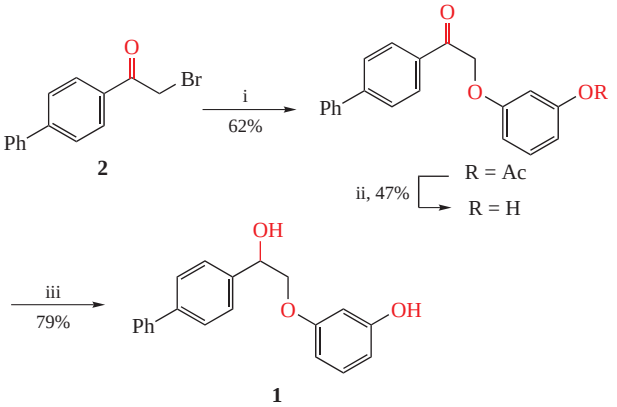
Note that the selective inhibitors of GluN2B-containing NMDA-receptors are currently known, and their administration can prevent some off-target effects. Ifenprodil represents the most investigated inhibitor with the mentioned properties, which binds to the Amino Terminal Domains (ATDs) of NMDA receptors. A set of X-ray structures for the NMDA receptor ATDs with different ligands have been published and can be applied to the structure-based drug design.[6–8] The local effect of ifenprodil-like ligands consists in maintaining of the GluN2B ATD in its closed form. The absence of ifenprodil leads to the GluN2B opening[9] and internal mutual rotation of two GluN2B ATD subunits.[10] A set of other ATD binders had been found earlier.[11–13]

Unfortunately, the ifenprodil structure contains 2-phenylethylamine moiety and therefore possesses a high affinity to a range of targets like α-adrenergic, σ- and serotonin receptors.[14] As well, the clinical trials revealed potential elongation of the QT-interval due to the inhibition of hERG by ifenprodil.[15] Typical high-affinity hERG inhibitors represent elongated molecules composed of three basic pharmacophoric features, namely a positively charged group in the center of the molecule and two bulky hydrophobic fragments at its ends (Figure 1),[16] and elimination of the positively charged group significantly decreases the inhibitory effect. Therefore, we performed molecular modeling, namely virtual screening of our in-house chemical library towards the structure of




(*S*,*S*)-ifenprodil

**Figure 1** Possible binding mode of compound **1** in the ifenprodil binding site; ifenprodil is marked by green color, blue lines correspond to hydrogen bonds.




**Scheme 1** *Reagents and conditions*: i, 3-$AcOC_6H_4OH$, $K_2CO_3$, DMF, 20 °C, 24 h; ii, $K_2CO_3$, MeOH, 20 °C, 6 h; iii, $LiAlH_4$, $Et_2O$, THF, reflux, 2 h.

GluN1/GluN2B ATD (PDB code 5EWJ) to transform the ifenprodil scaffold into a neutral molecule while retaining the specific interactions with inhibitor binding site in the NMDA ATD.

Biphenyl based compound **1** (Scheme 1) was selected according to the docking score using Autodock Vina[17] for screening of the in-house library. Note, that biphenyl-containing scaffolds have been widely used in medicinal chemistry, for example in diflunisal, which is an anti-inflammatory agent, or losartan as an antihypertensive drug. The binding mode of compound **1** along with that of ifenprodil obtained *via* molecular docking is shown in Figure 1. Both compounds maintain a hydrogen bond with E236 residue in GluN2B, and the distal phenyl ring occupies the hydrophobic pocket formed by T110, F113 and A75 residues in GluN1 as well as I82, I111 and F114 residues in GluN2B. At the same time, the protonated amino group of ifenprodil forms a hydrogen bond with Q110 in GluN2B, in contrast to compound **1**. Note, that aliphatic hydroxyl group of the latter maintains a hydrogen bond with I133 residue in GluN1.

The synthesis of biphenyl derivative **1** was accomplished in three steps starting from commercially available 1-biphenyl-4-yl-2-bromoethan-2-one **2** (see Scheme 1).

Both radioligand and electrophysiological investigations were performed for the synthesized compound **1**. [$H^3$]Ifenprodil substitution experiments demonstrated, that compound **1** competed with ifenprodil for the binding site [Figure 2(*a*)] with $EC_{50}$ equal to 30 μM. It is known, that the inhibition of wild type NMDA receptors by ifenprodil leads to approximately 60% decrease[18] in the NMDA-receptors currents due to binding to the GluN2B subunit. Thus, the approximation of the inhibition curve was carried out using the Hill equation with maximal effect set to 62%. The electrophysiological experiments demonstrated the significant inhibition of the NMDA/Gly-induced currents in the whole-cell configuration by compound **1** with $IC_{50} = 5 \pm 2$ μM [Figure 2(*b*)].

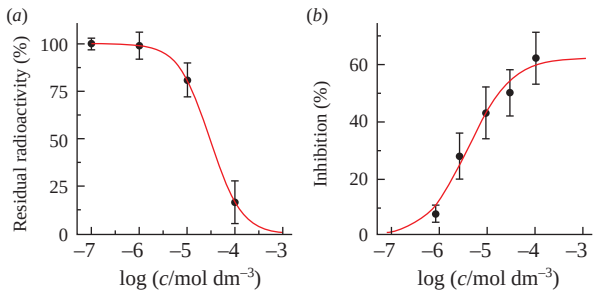



**Figure 2** (*a*) Substitution of radiolabeled [$H^3$]ifenprodil by compound **1** in homogenized brain tissue. (*b*) Concentration dependence of the inhibitory effect of compound **1** on the NMDA/Gly-induced currents.

The absence of protonated amine moiety in compound **1** can reduce its affinity to major ifenprodil targets, namely α-adrenergic, σ and serotonin receptors. The predicted[19] hERG $pIC_{50}$ for compound **1** equal to 6.2 is relatively low and can be further optimized.

In summary, we report a negative allosteric NMDA-receptor modulator, which interacts with the ifenprodil binding site as a potential lead compound for the development of new antidepressant drugs.

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*Online Supplementary Materials*

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.05.027.

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