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Tryptophanol-derived oxazolopiperidone lactams: Identification of a hit compound as NMDA receptor antagonist

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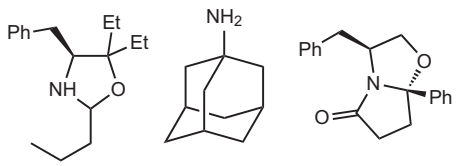
ABSTRACT

N-Methyl-D-aspartate receptors (NMDAR) exacerbated activation leads to neuron death through a phenomenon called excitotoxicity. These receptors are implicated in several neurological diseases (e.g., Alzheimer and Parkinson) and thus represent an important therapeutic target. We herein describe the study of enantiopure tryptophanol-derived oxazolopiperidone lactams as NMDA receptor antagonists. The most active hit exhibited an IC_{50} of 63.4 μM in cultured rat cerebellar granule neurons thus being 1.5 fold more active than clinically approved NMDA antagonist amantadine (IC_{50} = 92 μM).

Neurodegenerative pathologies represent a challenge for modern medicines especially in developed countries where life expectancy is higher. Patients suffering from Alzheimer's and Parkinson's diseases are confronted with the lack of adequate therapies that can provide a partial or complete reversal of neural death.[1] In this context, new therapeutical targets or new treatment strategies to fight mental dementia have attracted much research efforts from both academia and pharmaceutical companies in the recent years.[2] The neurotransmitter glutamate plays a pivotal role in the synaptic plasticity since its accumulation in the synaptic cleft activates the *N*-Methyl-D-aspartate receptor (NMDAR), a subtype of ionotropic glutamate receptors (iGluR).[3] The NMDAR allows the influx of calcium ions (Ca^{2+}) to the neuron, thus reestablishing the membrane potential after the synapse. However, if there is a rapid increase in intracellular Ca^{2+} levels, it can lead to neuronal death trough mitochondrial dysfunction, a process that has been named excitotoxicity.[4] These neuronal receptors are heteromers formed by the assembly of different combinations of three or four NR1, NR2A-NR2D and NR3A-NR3B subunits which form Ca^{2+} permeable transmembrane channels. At the NR1 subunits is where the NMDAR co-agonist glycine will bind. On the other hand glutamate will bind to the NR2 subunits. Besides the need for the simultaneous binding of two agonists other unique features of NMDAR activation are its voltage-dependence and when resting its ion pore is permanently blocked by extracellular Mg^{2+}.[5]

In fact, the development of biologically active compounds that block NMDAR excessive activity and simultaneously maintain their physiological role unharmed is incredibly challenging due to the complex pharmacology and molecular architecture of these receptors. For this reason, blocking NMDARs completely with high affinity antagonists has already been shown not to be therapeutically useful.

In the last decades, several types of NMDAR antagonists with a wide range of action mechanisms have been reported but unfortunately only few exhibited proper pharmacokinetics and tolerable side effects in human trials.[6] A successful example is



1 Amantadine 2

Figure 1. Known *N*-methyl-D-aspartate receptor antagonists.

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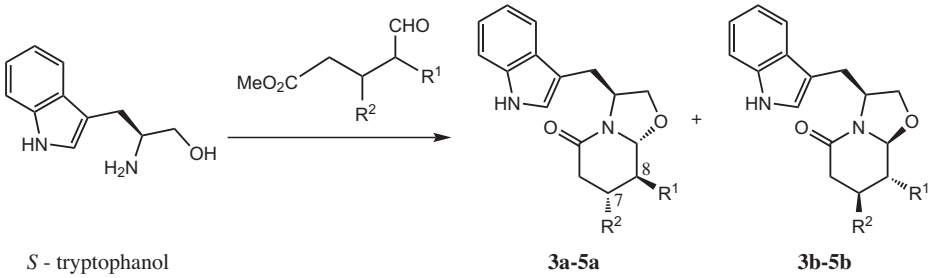


Scheme 1. Synthesis of *S*-tryptophanol-derived oxazolopiperidones. Reagents and conditions: 1.1 equiv of δ-oxo-esters, toluene, 16 h Δ, inert atmosphere and Dean–Stark apparatus.

Table 1
NMDAR antagonist activity of compounds **3a**–**5a** and **3b**–**5b**

Compound	R^1	R^2	NMDA (100 μM) IC_{50} (μM) [a]
3a	H	H	429.2 ± 142.4
3b	H	H	305.1 ± 37.0
4a	Ethyl	H	>450
4b	Ethyl	H	>450
5a	H	CH_2CO_2Me	>450
5b	H	CH_2CO_2Me	>450
Amantadine	—	—	92.0 ± 29.1

[a] Results are the mean of three independent experiments.

Table 2
NMDA antagonistic activity of compounds **6a**–**8a** and **6b**–**8b**

Compound yield	R^1	R^2	NMDA (100 μM) IC_{50} (μM) [a]
6a (11%)	H	H	63.4 ± 9.0
6b (49%)	H	H	>450
7a (12%)	Ethyl	H	>450
7b (58%)	Ethyl	H	>450
8a (13%)	H	CH_2CO_2Me	>450
8b (57%)	H	CH_2CO_2Me	>450
Amantadine	—	—	92.0 ± 29.1

[a] Results are the mean of three independent experiments.

amantadine, a low-affinity NMDA channel blocker, currently used to mitigate levodopa-induced dyskinesia in Parkinson's disease.[7]

In 2009, a group of oxazolidines **1** was described as NMDAR antagonists by preventing the binding of NMDAR ligands through a yet unknown mechanism of action.[8] Based on this information, we decided to test a small library of phenylalaninol-derived oxazolopyrrolidones, which contain an oxazolidine ring but have a more rigid structure than compounds **1**. In fact, we discovered a hit compound **2** with an IC_{50} of 62 μM in cultured cerebellar granule neurons (Fig. 1).[9] Following our first encouraging results in the development of novel chemotypes of NMDAR antagonists, we have decided to explore if related derivatives have enhanced activity.

Here, we present our biological activity screening results with a series of tryptophanol-derived oxazolopiperidones. These compounds can be synthesized through chiral-induced cyclocondensation reactions between enantiopure tryptophanol and racemic or prochiral δ-oxo-esters in moderate to good yields.[10] Compounds **3**–**5** were synthesized by cyclocondensation reaction of *S*-tryptophanol and the appropriate δ-oxo-esters in yields up to 81% (Scheme 1).[11]

The NMDA receptor blocking activity of compounds **3a**–**5a** and **3b**–**5b** was evaluated by measuring the compounds ability to inhibit the intracellular calcium increase, induced by NMDA, in in vitro cultures of neurons (Table 1).[12] In our first screening of *S*-tryptophanol-derived oxazolopiperidones, only compounds without any substituent in the piperidine ring, compounds **3a** and **3b**, exhibited some activity. Compounds **4a**–**5a** and **4b**–**5b** were inactive (IC_{50} >450 μM) pointing out the receptor intolerance for methylene-ester and ethyl chains at C-7 and C-8, respectively.

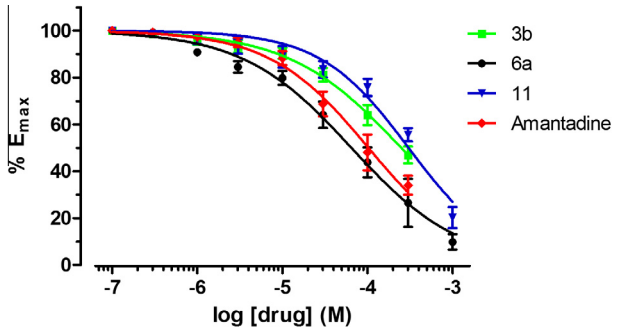
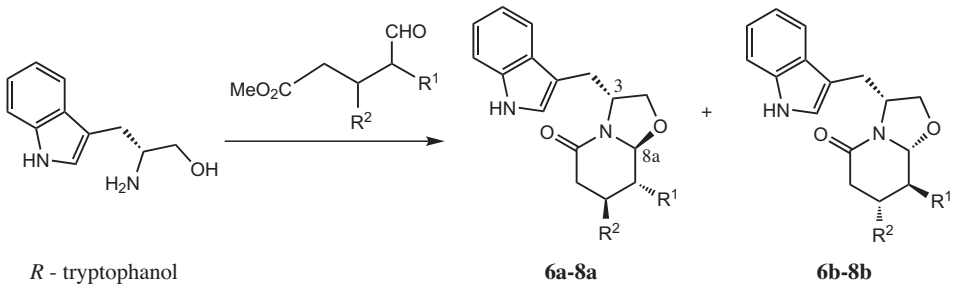


Figure 2. Inhibitory effect of compounds **3b**, **6a**, **11**, and amantadine on NMDA-induced intracellular calcium increase in cultured cerebellar granule neurons.



Scheme 2. Synthesis of *R*-tryptophanol-derived oxazolopiperidones. Reagents and conditions: 1,1 equiv of δ-oxo-esters, toluene, 16 h Δ, inert atmosphere and Dean–Stark apparatus.