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Bicyclic lactams as potential inhibitors of the NMDA receptor

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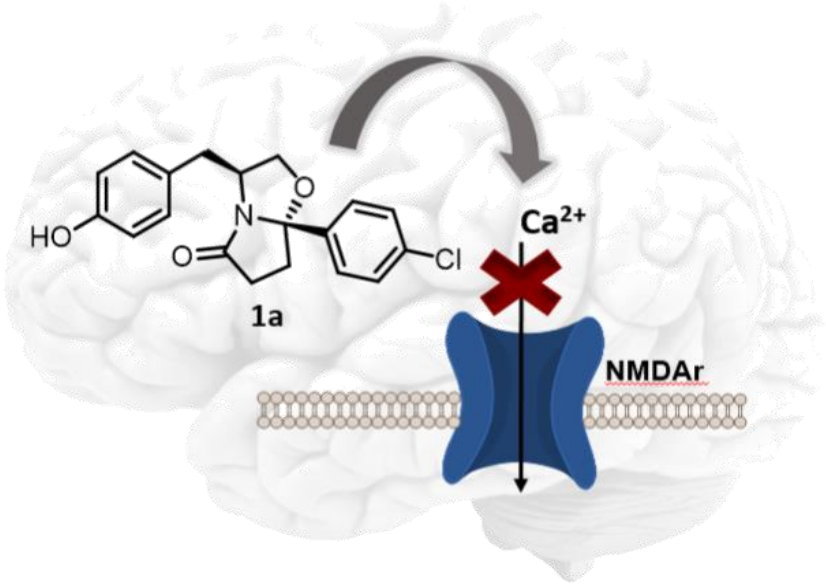
Bicyclic lactams as potential inhibitors of the NMDA receptor



Abstract:

The family of ionotropic glutamate receptors (iGluRs) is localized in the cell membrane of neurons and has crucial roles in the normal development of the central nervous system (CNS). Sustain healthy memory, learning, and cognitive processes are fundamental functions of these receptors. [1] N-Methyl-D-aspartate (NMDA) receptors belong to the family of iGluRs and its over-activation is associated to neuronal loss and, consequently, to major neurological disorders such as Parkinson and Alzheimer's diseases. Recently, targeting the NMDA receptor was considered a promising strategy in the medicinal chemistry field and the development of effective NMDA receptor antagonists become an attractive therapeutic approach. [2]

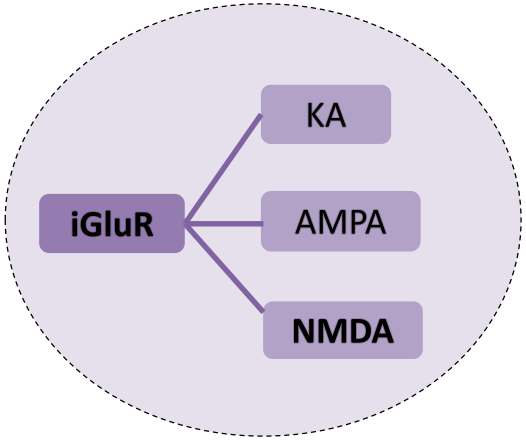
In the last years, Santos' group has been involved in the design and development of potent NMDA receptor antagonists, more precisely enantiopure bicyclic lactams. [3-5] To evaluate the activity of the potential NMDA receptor antagonists, was measured their capacity to inhibit NMDA-induced increase of intracellular Ca^{2+} levels in *in vitro* cultures of embryonary rat cortical neurons, using the Ca2+-sensitive fluorescent dye Fluo-4. The first molecule that showed some interesting results was a (S)-phenylalaninol oxazolopyrrolidone. [3] After, based on the oxazolopyrrolidone scaffold, a hit-to-lead optimization was carried out in the search for more potent NMDA receptor antagonists. A new library of enantiopure phenylalaninol bicyclic lactams was developed and most of the new compounds displayed NMDA receptor antagonism. It was even more interesting the significant difference in activities between the two enantiomers. The most promising compound showed an IC50 value of 27 µM, on the same order of magnitude as that of memantine (47 µM), an NMDA receptor antagonist in clinical use for the treatment of Alzheimer's disease. [5] More recently, we also extended our interest to more rigid molecules, also containing a bicyclic lactam core. Interestingly, this new family of compounds showed to be even more potent as NMDA receptor antagonists (4-fold more active than memantine). Additional biological tests indicated that the promising compounds can cross the blood-brain barrier (determined by an *in vitro* assay) and non-hepatotoxic, as well. Furthermore, the synthesis of the interesting aminoalchool-based libraries is easy to perform, resulting in moderate to good yields, and excellent stereoselectivities.

Keywords: NMDA receptor, neurological disorders, bicyclic lactams, antagonists

Introduction

N-Methyl-D-Aspartate (NMDA) receptors

- Belong to the family of ionotropic glutamate receptors and are localized in the cell membrane of neurons;
- These receptors are fundamental for the normal function of the central nervous system (CNS).



The over-activation of NMDA receptors

Associated with major neurological disorders: Parkinson's disease, Alzheimer's disease, schizophrenia, and epilepsy.

Calcium (Ca^{2+}) influx → Mithocondrial Dysfunction → Apoptosis or Necrosis of the nerve tissue

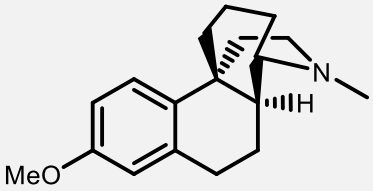
Development of effective NMDA receptor antagonists

Promising therapeutic approach to fight these diseases

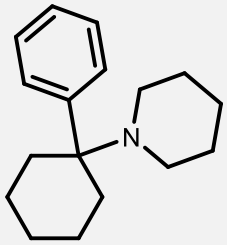
Introduction

State-of-the-art

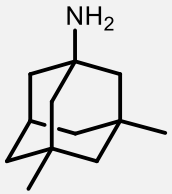
Examples of Channel Blockers



Dextromethorphan



Phencyclidine

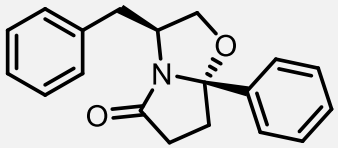


Memantine

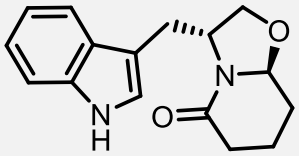
Used in the clinic in Alzheimer's patients

Figure 1. Representative channel Blockers in the literature.

Bicyclic lactams developed in Santos's group



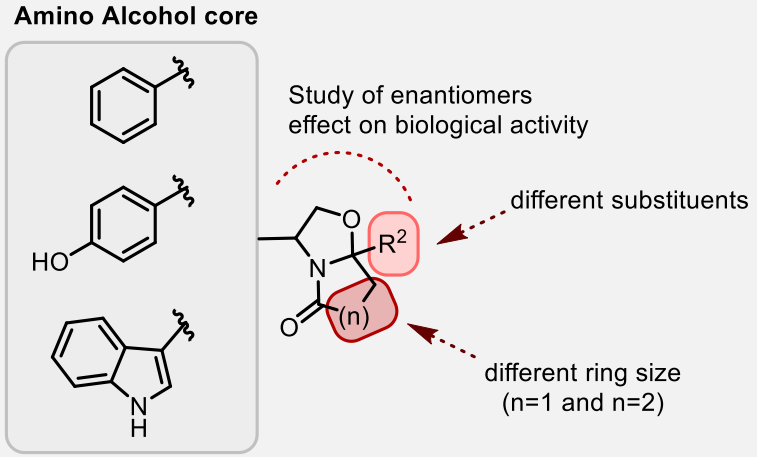
1a



2

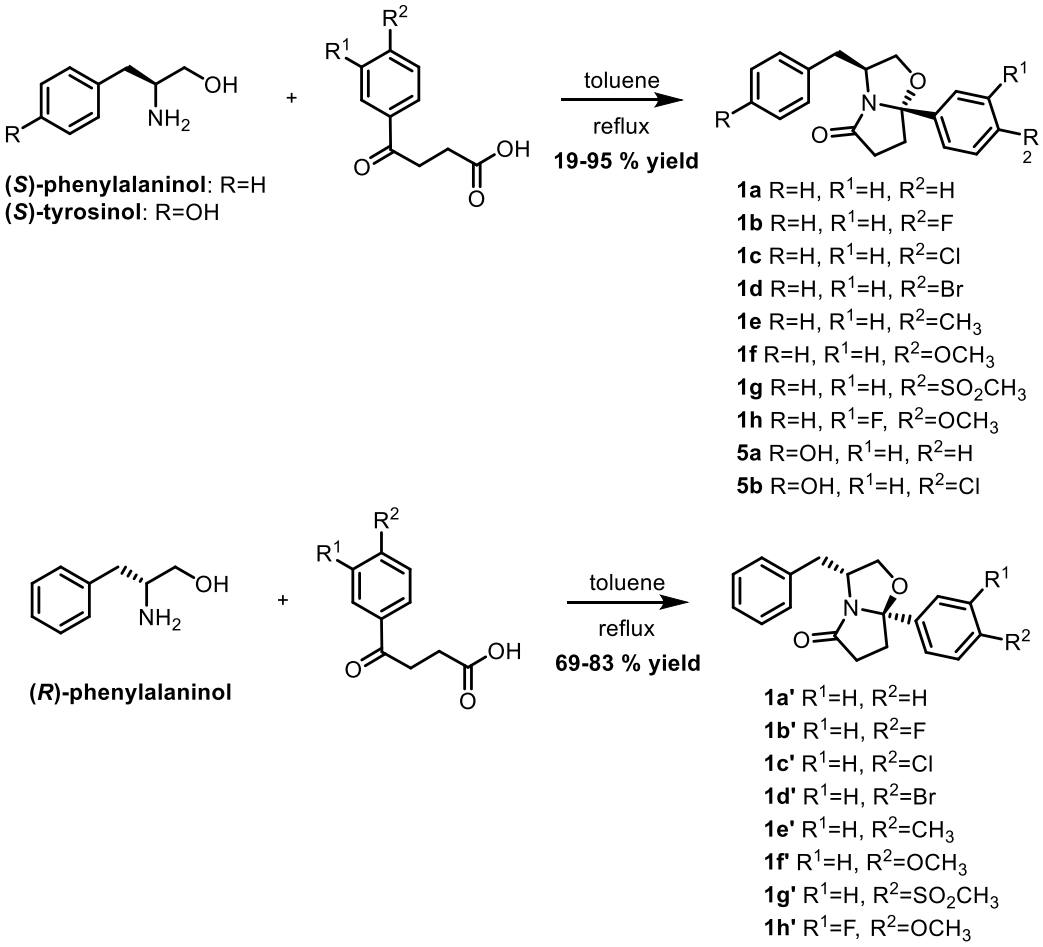
Figure 2. Previously novel chemical scaffolds reported by our group (*Monatsh. Chem.* **2013**, 144, 473-477 and *Bioorg. Med. Chem. Lett.* **2014**, 24, 3333-3336.

Current work: Optimization of bicyclic lactams



Results and discussion

Synthesis of enantiopure bicyclic lactams



Scheme 1. Synthesis of bicyclic lactams **1a-h** and **1a'-h'.**

- Twenty-two novel enantiopure bicyclic lactams were designed, synthesized, and evaluated as NMDA receptor antagonists.

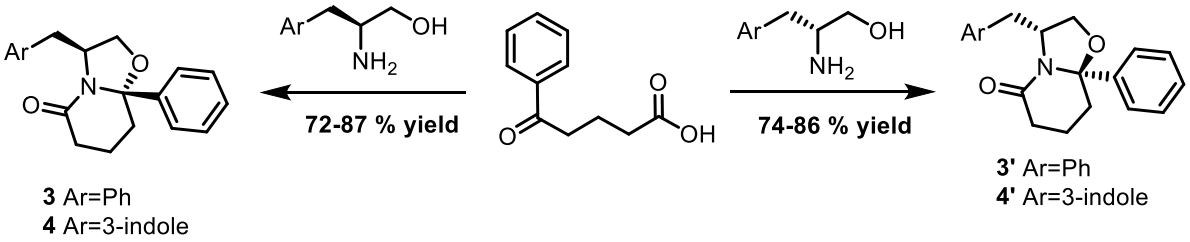
- All compounds are easily accessible by cyclocondensation reaction of the enantiopure amino-alcohol with the appropriate keto-acids (Schemes **1** and **2**) with moderate to excellent yields.

- Only one diastereoisomer was formed (confirmed by ^{1}H-NMR).

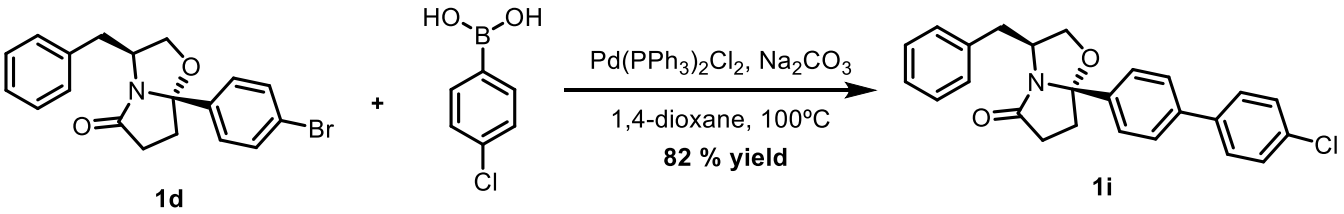
ChemMedChem **2017**, 144, 537-545

Results and discussion

Synthesis of enantiopure bicyclic lactams



Scheme 2. Synthesis of bicyclic lactams **3-4** and **3'-4'.**



Scheme 3. Synthesis of bicyclic lactam **1i.**

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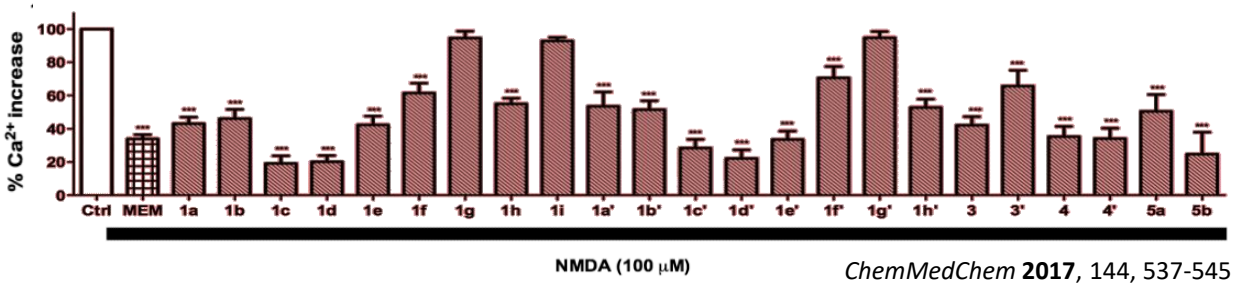
Results and discussion

Potential of the compounds as NMDA receptor antagonists

Measurement of their capacity to inhibit NMDA-induced increase of intracellular Ca^{2+} levels in *in vitro* cultures of embryonary rat cortical neurons



ChemMedChem **2017**, 144, 537-545

IC_{50} values and Blood–Brain Barrier Permeation

Compound	NMDA (100 μM)[a]	PAMPA-BBB assay[b]	
	IC_{50} (μM)	P_e (10^{-6} cm s^{-1})	CNS Prediction
1c	39 ± 8	66.2 ± 5.1	cns +
1d	36 ± 3	14.1 ± 0.7	cns +
5b	27 ± 1	24.5 ± 1.9	cns +
Memantine	47 ± 3	—	—

Table 1. IC_{50} values and permeability values from the PAMPA-BBB assay P_e (10^{-6} cm s^{-1}) of compounds **1c**-**d** and **5b**.

Oxazolopyrrolidone **5b**

IC_{50} value of 27 μM, **brain permeable** and **non-hepatotoxic**.

More active than memantine (47 μM), an NMDA receptor antagonist in clinical use for the treatment of Alzheimer's disease.

Results and discussion

Computational Studies: Docking

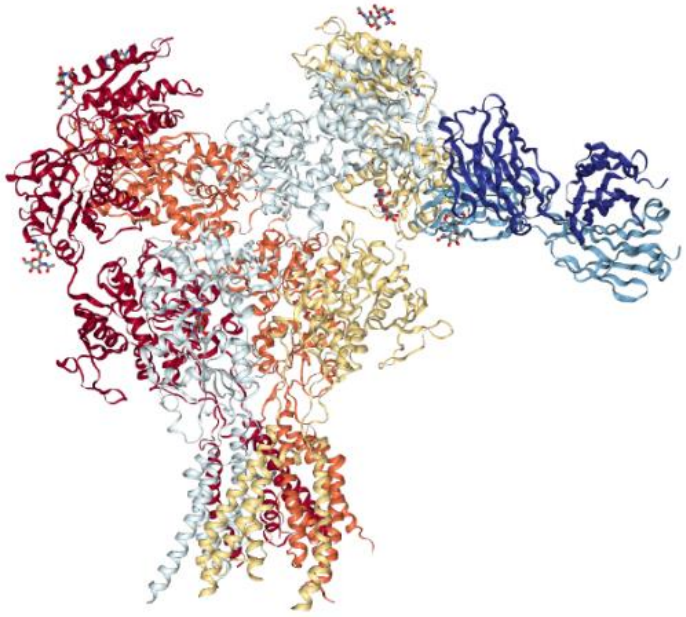


Figure 3 - NMDA receptor crystallographic estruture (PDB:5UOW) reported in 2017 (Science, 2017, 355, 6331). Source reference: https://www.rcsb.org/structure/5UOW

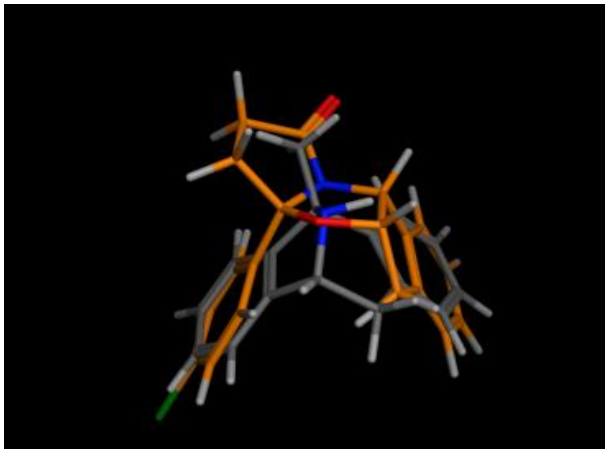


Figure 4 - Overlap of the MK-801 channel blocker with one of the oxazolopyrrolidones described by Santos's group.

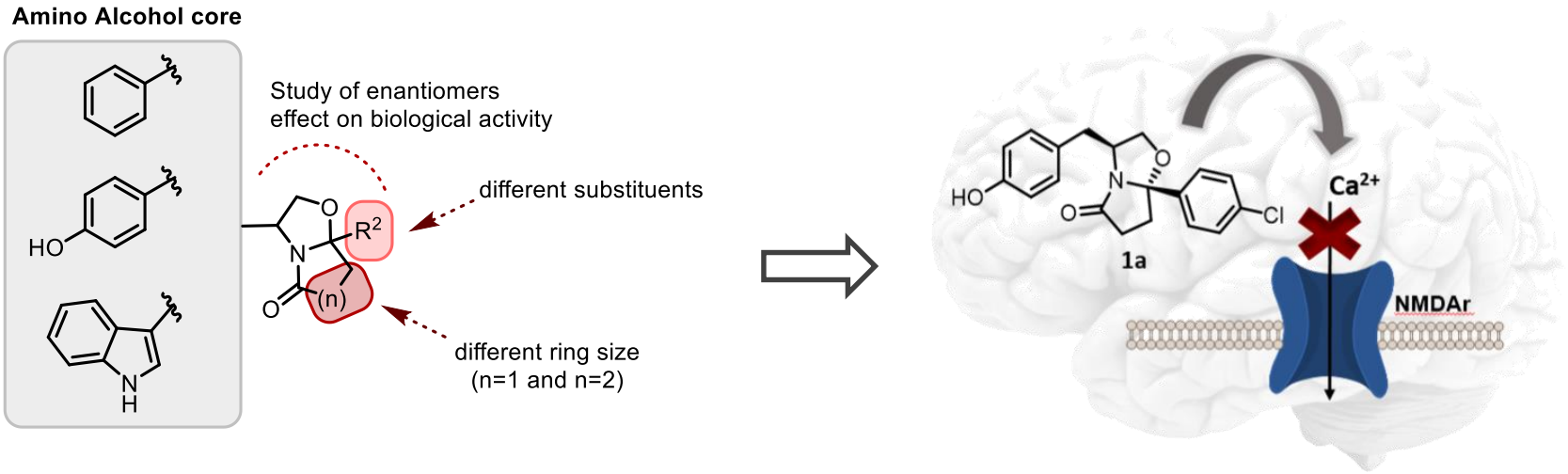
Current interest in our group:

Develop more rigid oxazolopyrrolidone derivatives in order to improve the potency as NMDA receptor antagonists

Preliminary studies revealed that less flexible structures are more active as NMDAr antagonists

Conclusions

- Therapeutic potential of bicyclic lactam **5b** in neurological diseases where NMDA receptors are over activated;
- Bicyclic lactam **5b** is brain permeable and non-hepatotoxic (in vitro assay);
- Preliminary studies with less flexible oxazolopyrrolidone derivatives **revealed an increase of potency** as NMDAr channel blocker.



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Chemical Libraries / Docking Studies

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MSc Student João Lopes

In vitro assays

Intracellular Ca^{2+} levels
Dr. Cristobal de los Rios
Hepatotoxicity assays
Dr. Lídia Gonçalves
PAMPA-BBB assays
Dr. María Rodríguez-Franco
MSc Clara Herrera- Arozamena

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