



The 8th International Electronic Conference on Medicinal Chemistry (ECMC 2022)

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A Chemical Strategy to Improve Bioavailability of Glypromate Peptide-Conjugates

Chaired by **DR. ALFREDO BERZAL-HERRANZ**;
Co-Chaired by **PROF. DR. MARIA EMÍLIA SOUSA**



pharmaceuticals



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¹ LAQV/REQUIMTE, Department of Chemistry and Biochemistry, Faculty of Science, University of Porto, Portugal;

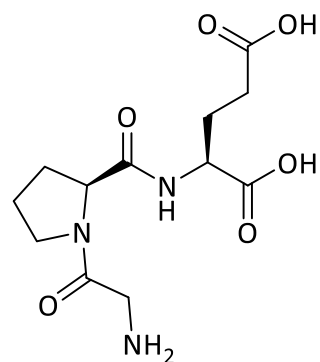
² UCIBIO-Applied Molecular Biosciences Unit, REQUIMTE, Laboratory of Toxicology, Department of Biological Sciences, Faculty of Pharmacy, University of Porto, Porto, Portugal.

³ Associate Laboratory i4HB – Institute for Health and Bioeconomy, Faculty of Pharmacy, University of Porto, Porto, Portugal

⁴ Department of Organic Chemistry, Faculty of Pharmacy, University of Santiago de Compostela, Santiago de Compostela, Spain.

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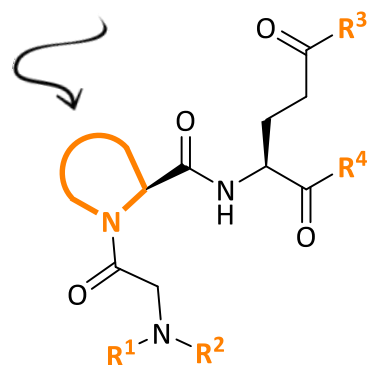
A Chemical Strategy to Improve Bioavailability of Glypromate Peptide-Conjugates



Glypromate

Peptide Conjugation

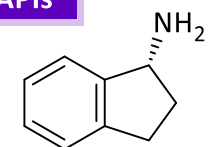
**Constrained
Prolines**



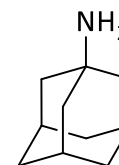
Glypromate conjugates

$R^1, R^2 = -H \text{ or } -CH_3$
 $R^3, R^4 = -OCH_3 \text{ or API}$

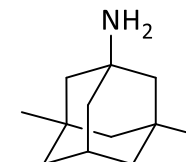
APIs



(R)-Aminoindane



Amantadine



Memantine

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Abstract:

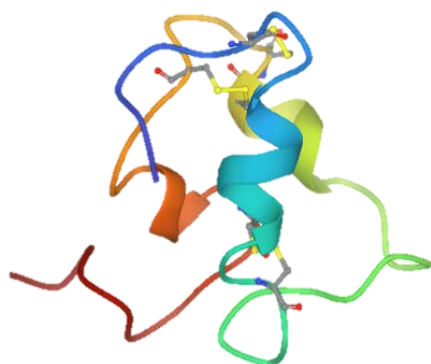
Alzheimer (AD) and Parkinson (PD) diseases are the main neurodegenerative disorders of the central nervous system, affecting millions of people worldwide. The absence of effective and curative therapies to slow down the progression of neurodegenerative processes constitutes a serious medical concern. In this sense, the development of new neuroprotective therapies becomes imperative. Glypromate is an endogenous neuropeptide with sequence of Gly-Pro-Glu which displays evidences of neuroprotective activity in many in vitro models of AD and PD. Despite its neuroprotective potential use in the clinical, this neuropeptide exhibits low intestinal absorption, liability towards enzymatic proteolysis, and reduced blood-brain barrier permeability. In fact, clinical trials led by Neuren Pharmaceuticals with Glypromate failed in phase III. The use of constrained proline mimetics and capping strategies have been employed in the assembly of bioactive Glypromate analogues to improve lipophilicity and enhance enzymatic stability. Considering this rationale, the NeuroPro project aims at the design, synthesis, and biological evaluation of novel constrained Glypromate analogues. NeuroPro also explores the chemical conjugation of these constrained peptidomimetics with relevant active pharmaceutical ingredients (APIs) used in AD and PD therapy. This approach is expected to deliver new neuroprotective hits with higher metabolic resistance while exploring synergism between Glypromate analogues and APIs. In this work, the synthesis of 54 new Glypromate conjugates with Amantadine, Memantine, and Aminoindane is disclosed. These peptide-conjugates are currently undergoing biological evaluation to assess their cytotoxicity in human differentiated SH-SY5Y cells. The conjugates with lowest cytotoxicity will be selected to proceed with neuroprotection studies.

Keywords: Active Pharmaceutical Ingredients; Neurodegenerative diseases; Peptide-Conjugates.

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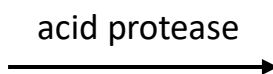
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Introduction

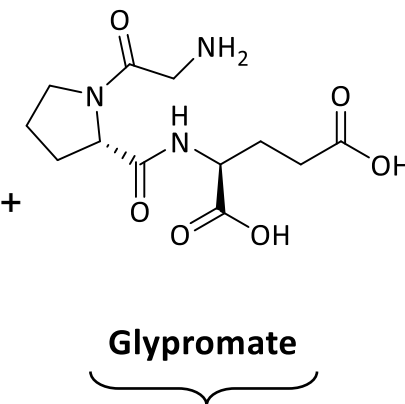


IGF-1

(PDB: 1B9G)



des-IGF-1



Neuroprotective effects (animal models)

Huntington's; Parkinson's; Alzheimer's

- Possible interaction with the *N*-methyl-D-aspartate (NMDA) receptors.
- Stimulates the release of potassium-induced **acetylcholine** in the cerebral cortex and **dopamine** in the striatum.

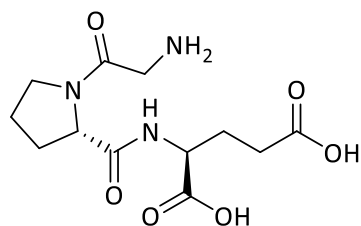
Ivo E. Sampaio-Dias, Miguel Santejo, Sara C. Silva-Reis, Márcia A. Liz, Cristina Alcoholado, Manuel Algarra, Xerardo García-Mera, and José E. Rodríguez-Borges, *ACS Chem. Neurosci.*, **2021**, *12*, 19, 3615–3624.

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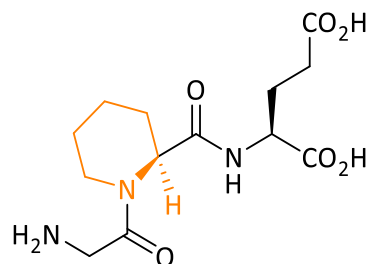
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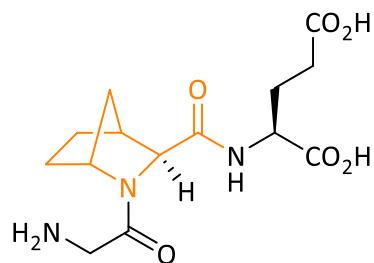
Introduction



Glypromate



L-pipecolic acid derivative

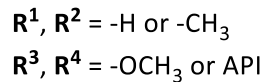
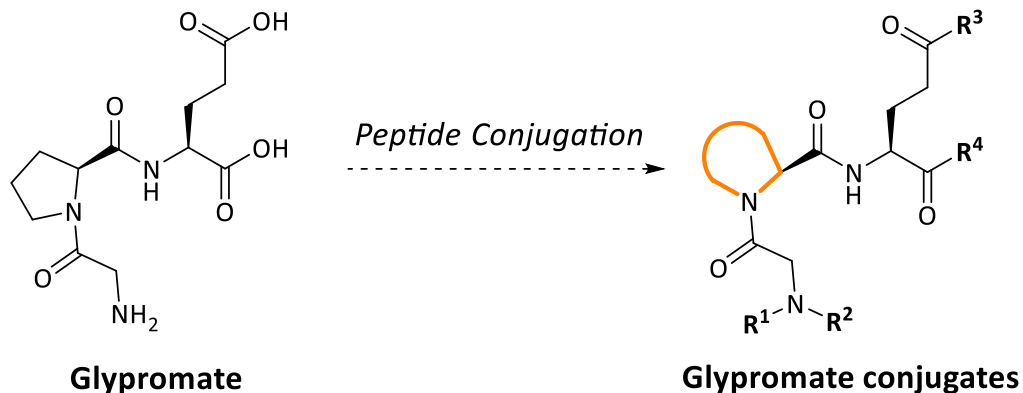


Glypromate Bicyclic Analogues

Constrained proline mimetics:

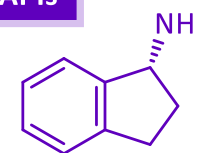
- ✓ **Increase potency** either by promoting a better fitting in a target molecule or by inducing an optimal conformation;
- ✓ **Improve biochemical stability** toward enzymatic systems;
- ✓ **Increase specificity** for a particular molecular target.

Results and discussion

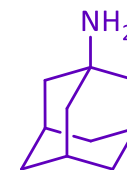


Synthesis of conjugates:
Glypromate analogues with APIs

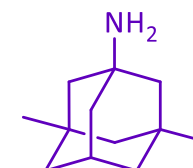
APIs



(R)-Aminoindane

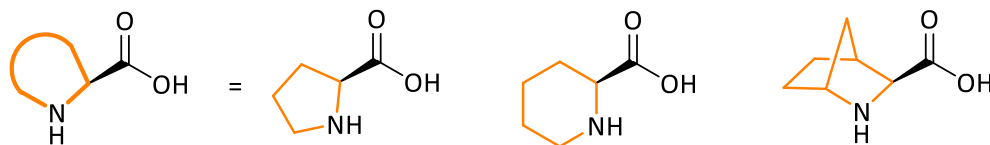


Amantadine



Memantine

Constrained Prolines



L-proline

L-pipecolic acid

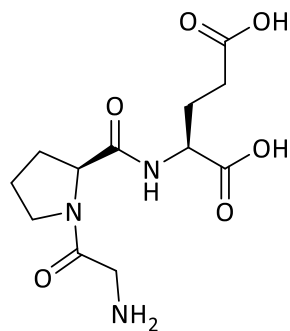
Bicyclic proline

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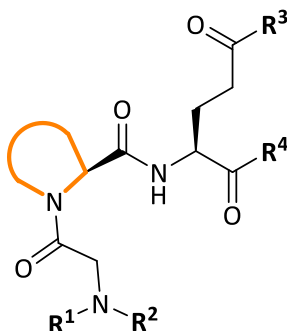
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Results and discussion



Glypromate

Peptide Conjugation

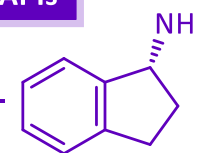


Glypromate conjugates

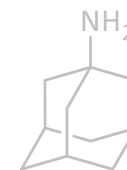
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Synthesis of conjugates:
Glypromate analogues with APIs

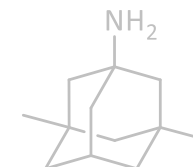
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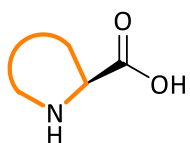


Amantadine

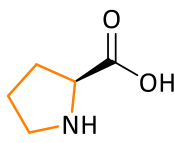


Memantine

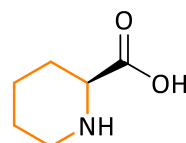
Constrained Prolines



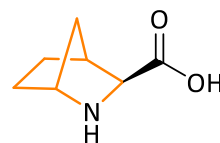
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L-proline



L-pipecolic acid



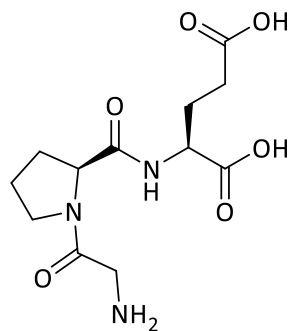
Bicyclic proline

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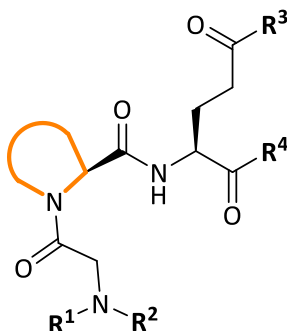
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Results and discussion



Glypromate

Peptide Conjugation

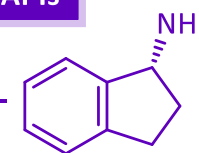


Glypromate conjugates

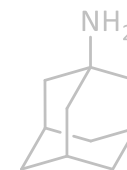
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Synthesis of conjugates:
Glypromate analogues with APIs

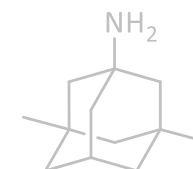
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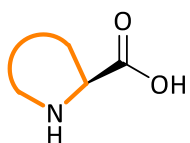


Amantadine

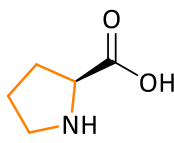


Memantine

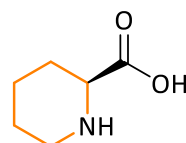
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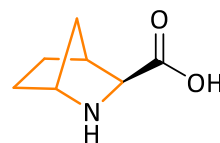
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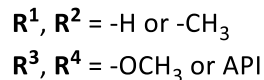
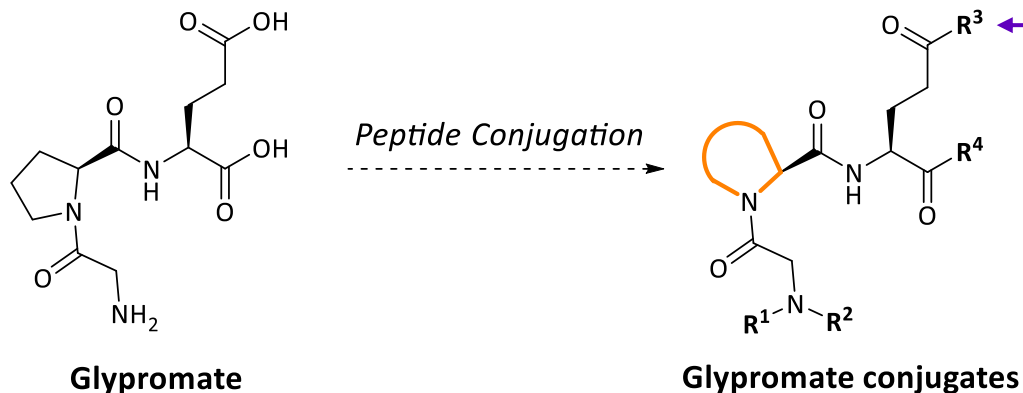


Bicyclic proline

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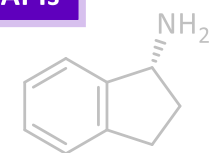
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Results and discussion

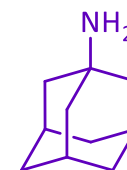


Synthesis of conjugates:
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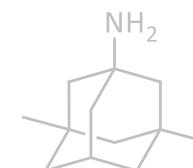
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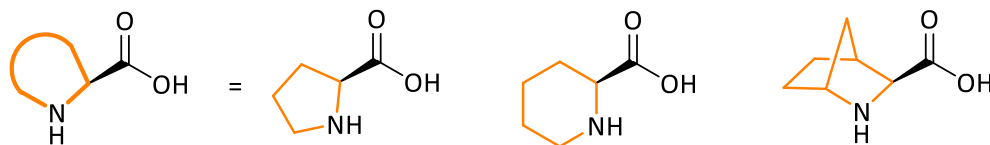


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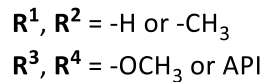
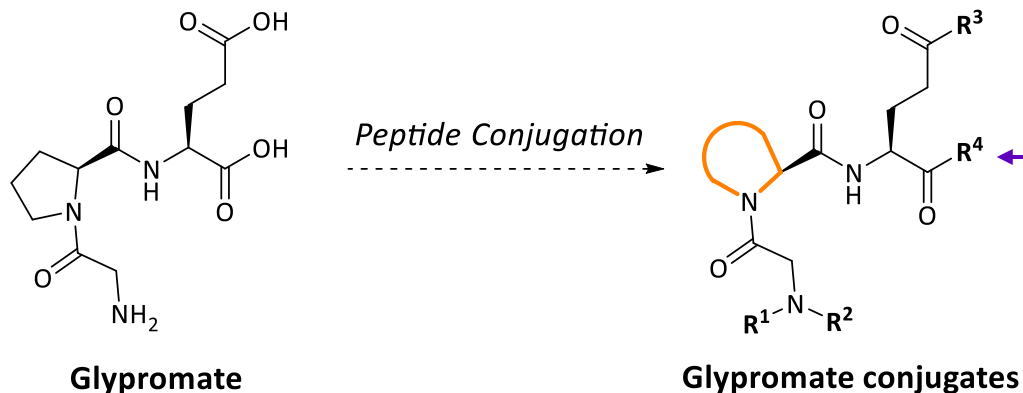
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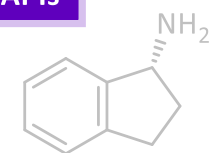


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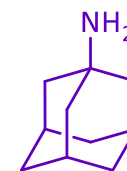


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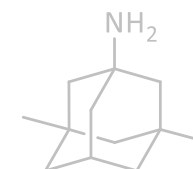
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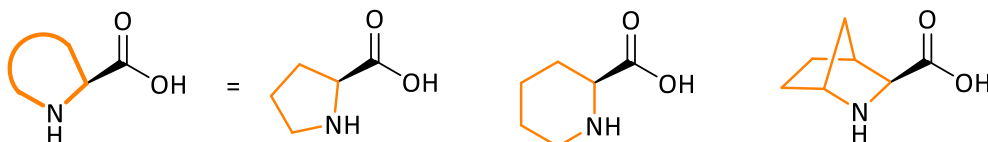


Amantadine



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Constrained Prolines



L-proline

L-pipecolic acid

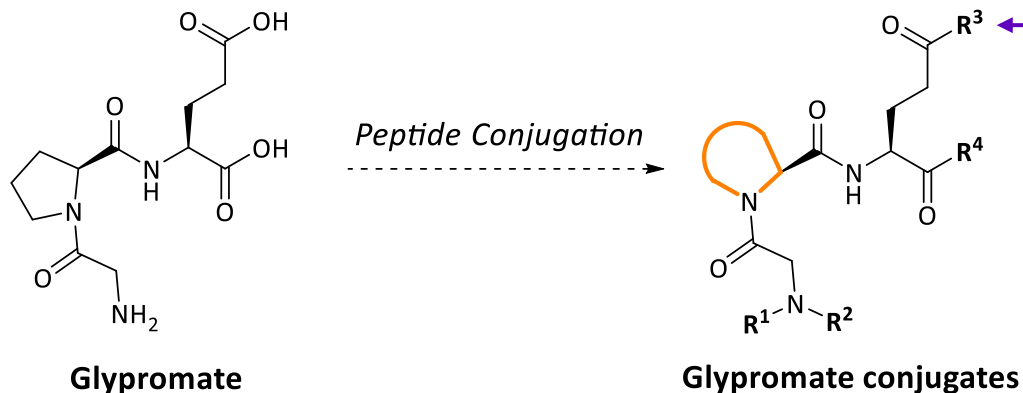
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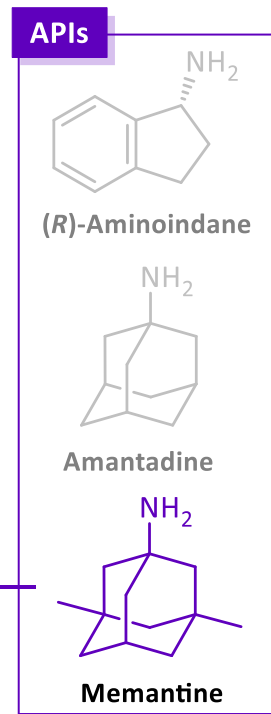


Results and discussion

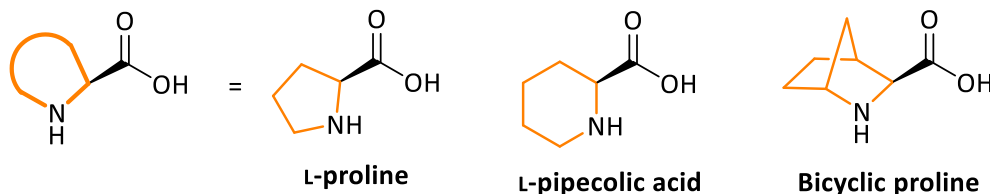


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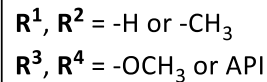
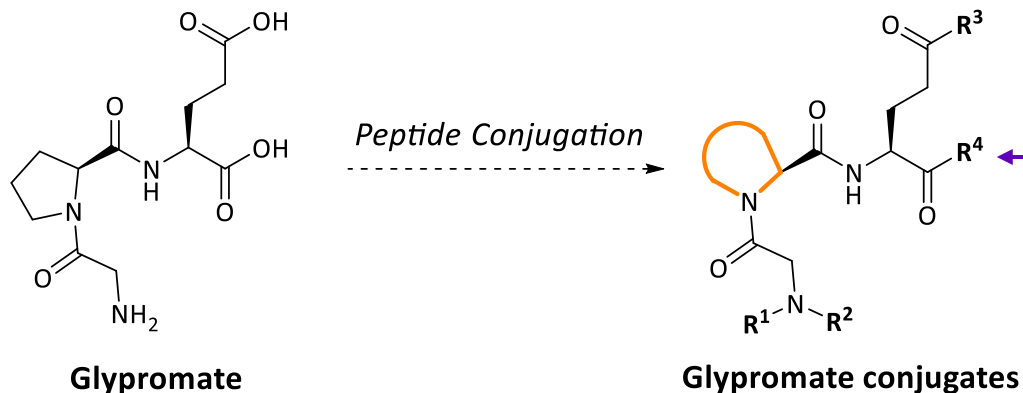
**Synthesis of conjugates:
Glypromate analogues with APIs**



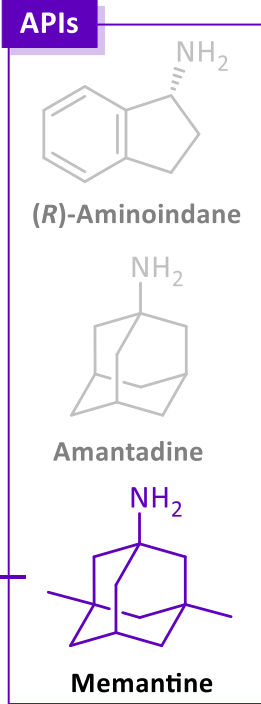
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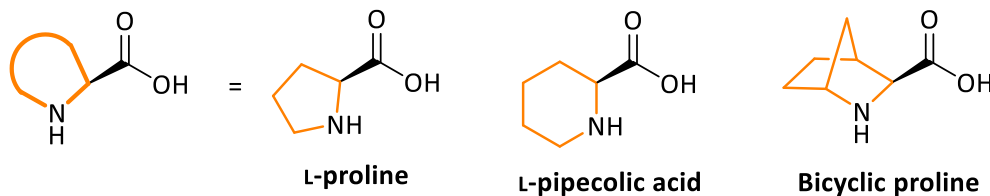
Results and discussion



Synthesis of conjugates:
Glypromate analogues with APIs



Constrained Prolines

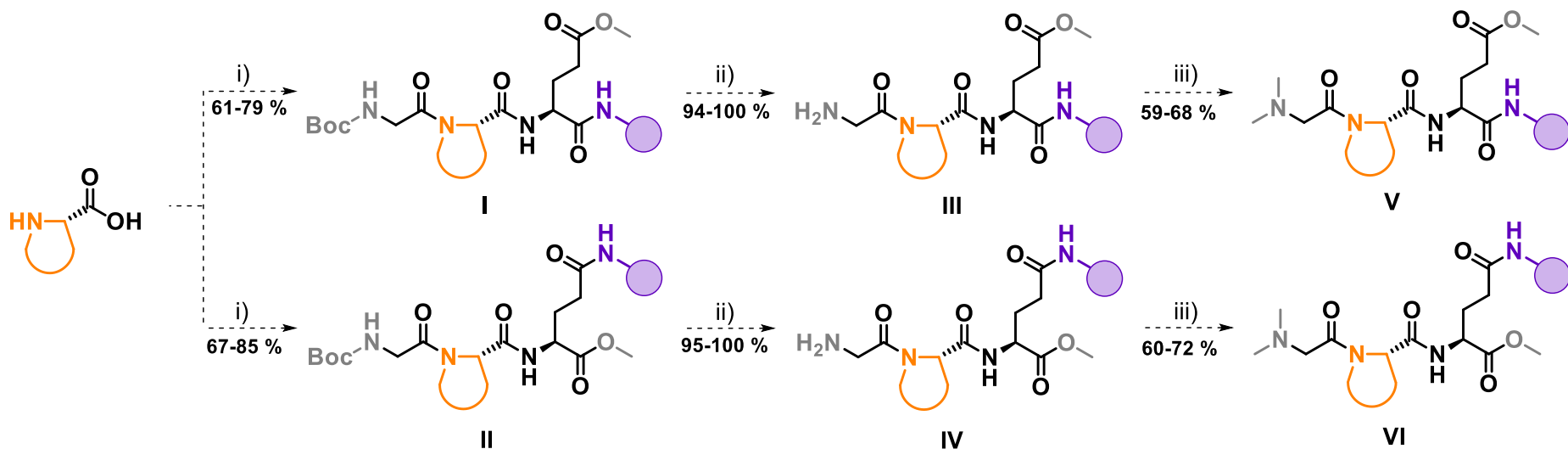


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Conditions and Reagents:

- i) Boc-Gly-OSu, Et₃N, TBTU, Functionalized glutamates, CH₂Cl₂;
- ii) TFA, CH₂Cl₂;
- iii) CH₂O, NaBH(OAc)₃, 1,2-dichloroethane.

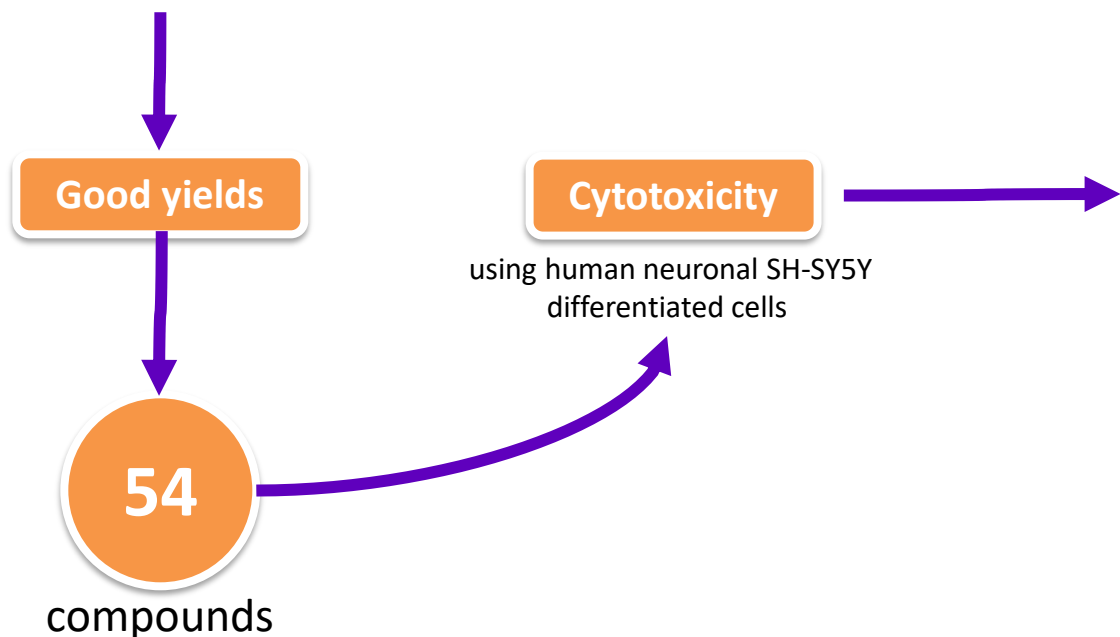
Conclusions

Glypromate analogues

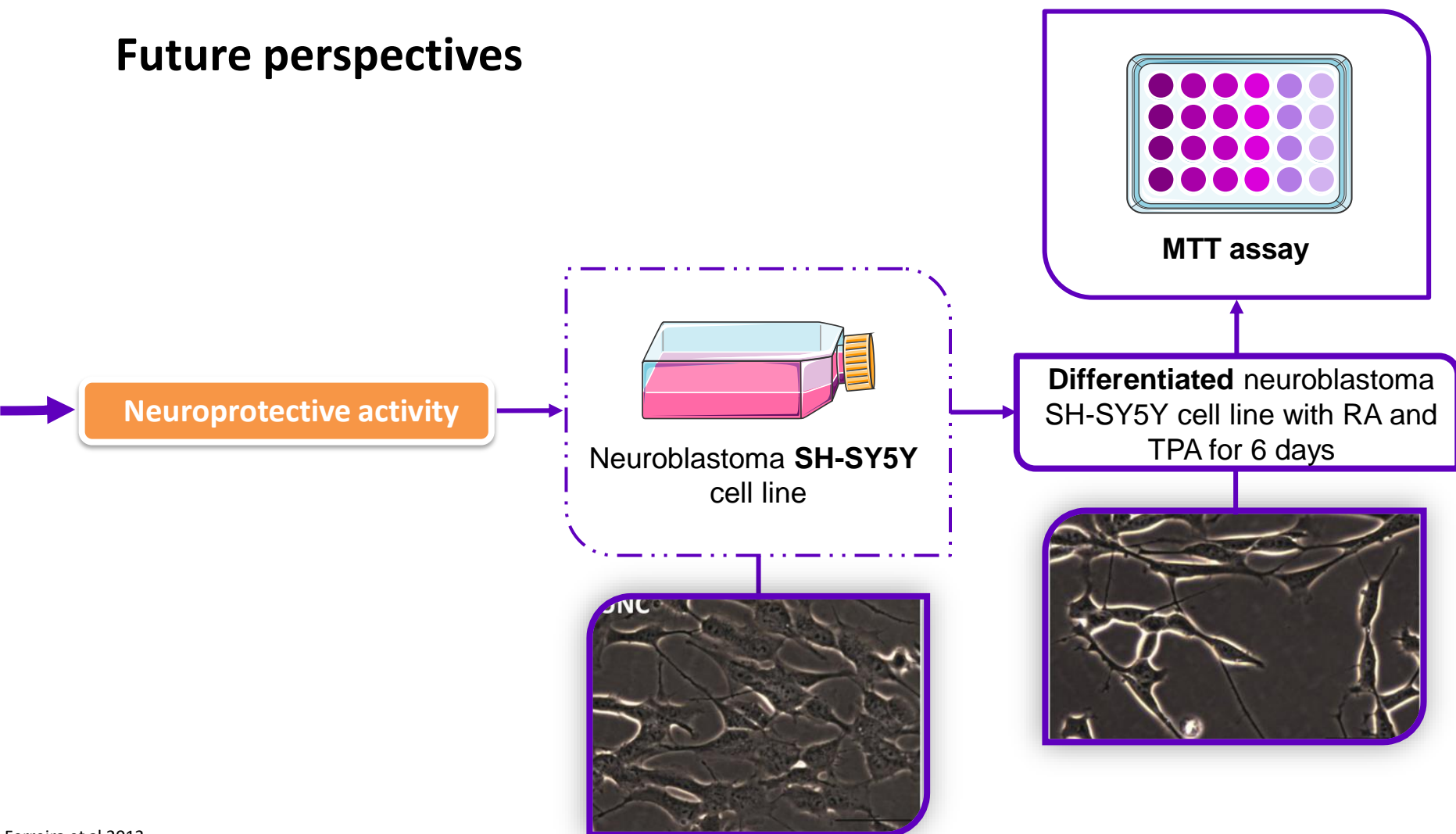
Incorporating L-proline, L-pipecolic acid and chiral bicyclic construct.

Glypromate conjugates

Using the Glypromate analogues was coupled 3 APIs in 2 positions.



Future perspectives



Ferreira et al 2013

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Acknowledgments

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