2-AMINONICOTINIC ACID-1-OXIDES INTERFERE WITH THE KYNURENINE PATHWAY OF TRYPTOPHAN METABOLISM AND INHIBIT QUINOLINIC ACID SYNTHESIS IN MAMMALIAN BRAIN

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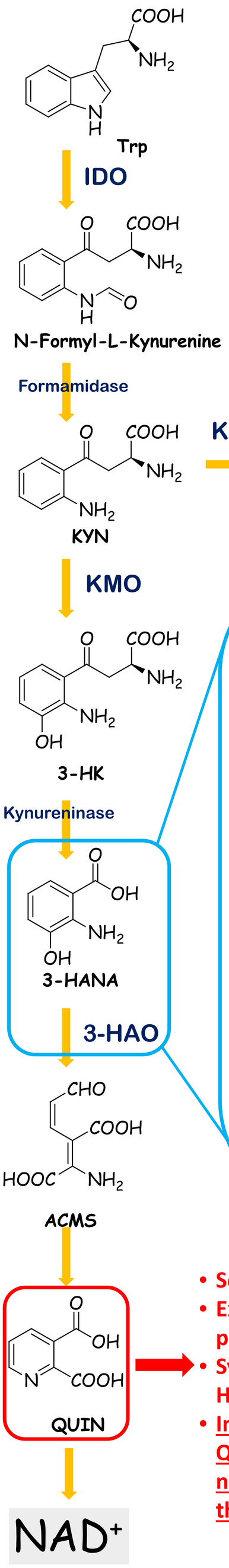
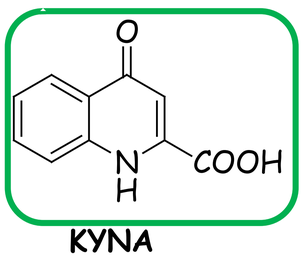
The kynurenine pathway (KP)



Introduction

Mammals degrade L-tryptophan through the so-called kynurenine pathway (KP). This metabolic cascade produces several KP metabolites that have distinct neuromodulatory properties and may be causally involved in the aetiology of acute and chronic brain diseases. An imbalance between neuroprotective [kynurenic acid (KYNA)] and neurotoxic [3-Hydroxykynurenine (3-HK) and quinolinic acid (QUIN)] KP metabolites has been tentatively linked to the onset and propagation of a number of severe neurological disorders, among which Huntington's disease (HD). Elevated brain levels of QUIN have been observed in HD, but the lack of suitable pharmacological tools makes further studies difficult. The rationally designed 2-aminonicotinic acid 1-oxides here reported provide a novel pharmacological tool for the study of the mechanisms underlying the onset and propagation of neurodegenerative diseases correlated to overproduction of QUIN, as in the case of HD.



- iGluRs antagonist
- α7nAChR negative allosteric modulator
- Free radical scavenger

Design of N-oxide derivatives

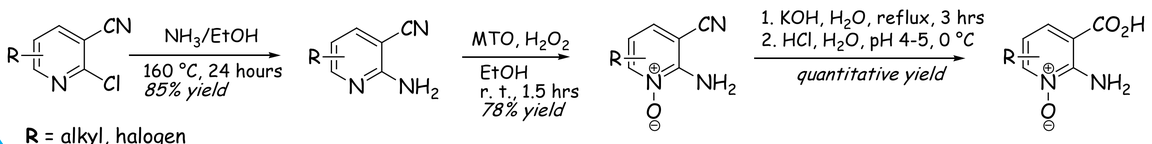
Modulation of the activity through aromatic substitution

2-Aminonicotinic acid 1-oxide nucleus escapes from the unstable O-aminophenol moiety of reported inhibitors

The 2-aminopyridine-N-oxide motif is expected to keep the Fe(II) chelating ability of the O-aminophenol ring

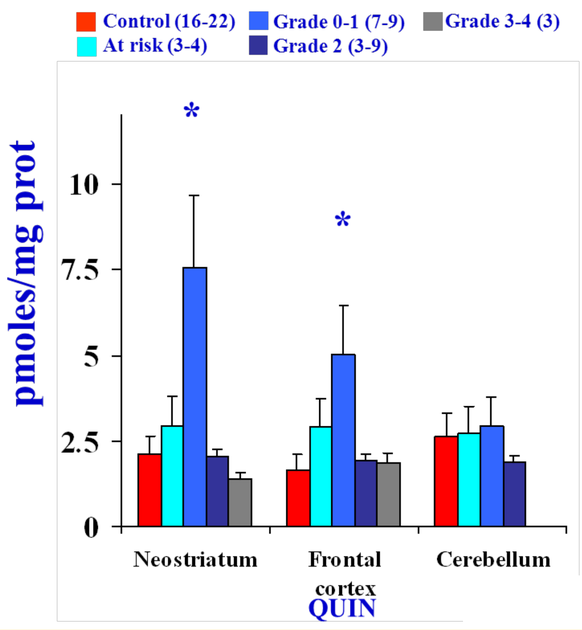
Retaining most of its relevant structural and electronic features.

Synthesis

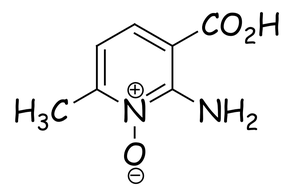


R = alkyl, halogen

- Selective NMDARs agonist
- Excitotoxic at non-physiological concentrations
- Synergistic toxicity with 3-HK
- Increased production of QUIN might contribute to neuronal degeneration in the early phases of HD



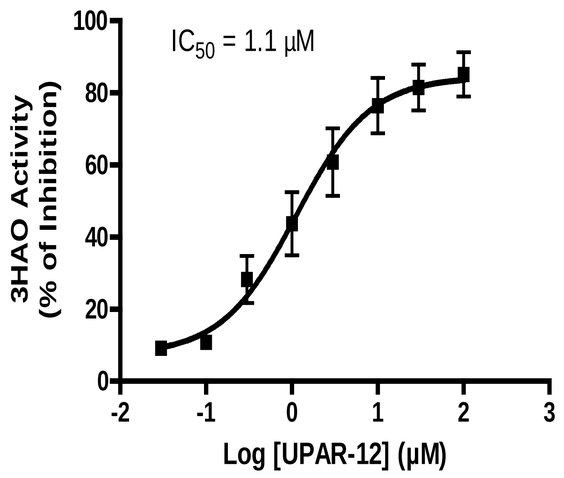
Results



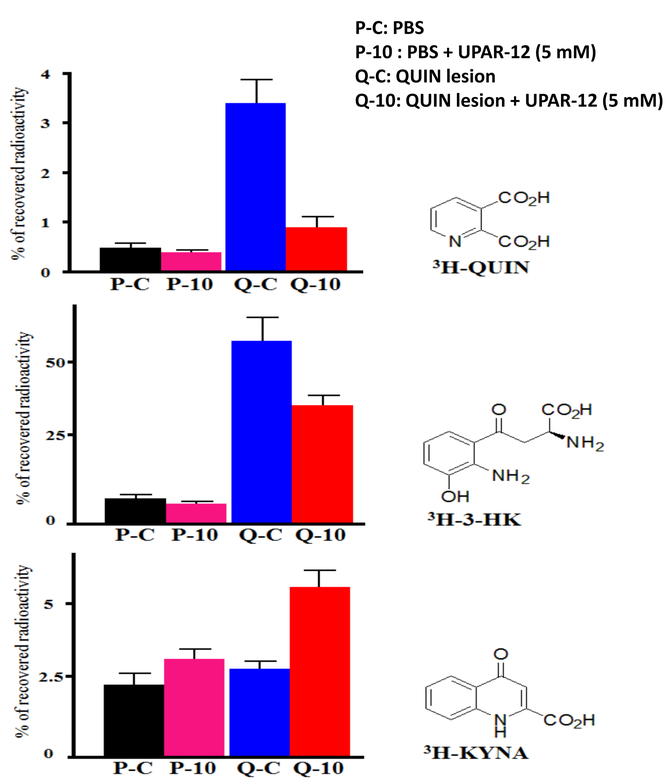
UPAR-12, IC_{50} 1.1 μM

a) UPAR-12 is a potent 3-HAO inhibitor

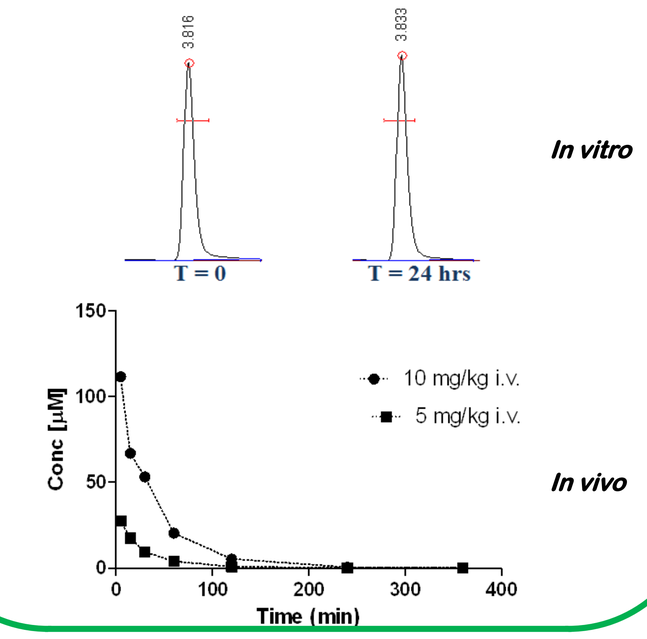
Effect of UPAR-12 in Human Brain on 3HAO Activity



b) UPAR-12 reduces the QUIN output after striatal lesion in vivo



c) UPAR-12 is stable in vitro and in vivo



Conclusions

- 2-Aminonicotinic acids 1-oxide are the first class of chemically stable 3-HAO inhibitors
- Hypothesis of the bioisosterism between 3-hydroxyanthranilate and 2-aminonicotinate is confirmed
- Neuroprotective activity *in vivo* after localized administration in QUIN model of neurodegeneration has been noticed

References:

Costantino G. et al. J.Med. Chem, 2013, 9482-95; Costantino G., Amori L., Schwarcz, R. PCT/EP2011/050670; Costantino G., Amori L.; Schwarcz, R. US 20130289081; Amori L. et al. *J Neurochem.*, 2009, 316-25; Guidetti P, et al. *Neurobiol Dis*. 2004, 455-461.