DESIGN, SYNTHESIS AND BIOLOGICAL ACTIVITIES OF PYRROLYLETHANONEAMINE DERIVATIVES, A NOVEL CLASS OF MAO INHIBITORS

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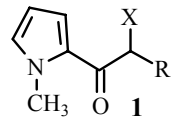
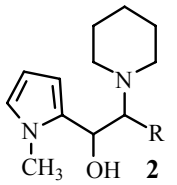
Mitochondrial monoamine oxidases (MAOs) are flavin-containing enzymes that catalyze the oxidative deamination of neurotransmitters and exogenous aryl-alkylamines. In mammals, two different types of MAOs are present in most tissues, namely MAO-A and MAO-B. MAO-A preferentially deaminates aromatic monoamines, such as the neurotransmitters serotonin, noradrenaline and adrenaline, while MAO-B oxidizes β-phenylethylamines (PEA) and benzylamines. Selective MAO-A inhibitors are currently used for treating neurological disorders, such as anxiety or depression, while selective anti-MAO-B agents (e.g., selegiline) are administered alone or together with *L*-DOPA for the treatment of Parkinson's syndrome or Alzheimer's disease. Actually, the studies on new MAO inhibitors have been focused on reversible and selective agents. In fact, irreversible and/or non-selective inhibitors showed shortcomings including cumulative effects, loss of selectivity after chronic treatment, and interaction with tyramine-containing foods (cheese effect) [1].



1

R = H, CH_3, Ph;
X = aliphatic and alicyclic amines



2

R = H, Ph

Pursuing our studies on pyrrole analogs of cathinone [2-4], we synthesized and tested against MAO-A and MAO-B isoenzymes a series of pyrrolylethanoneamine derivatives **1** and **2** which share chemical features similar to that of moclobemide, brofaromine, toloxatone and other reversible MAO inhibitors used in clinical practice.
In general, aminoketones **1** were found to be potent and selective A-inhibitors. In particular, derivative (-)-(*R*)-**1a** (X = 1-pyrrolidinyl, R = Ph) was more potent (K_i(MAO-A) = 0.0035 μM) and selective (A-selectivity 200000) against A isoenzyme than toloxatone and moclobemide used as reference drugs. Interestingly, aminoalcohol (+)-**2a** selectively inhibited MAO-B enzyme (K_i(MAO-B) = 1.24 μM; K_i(MAO-A) = 7 μM).

[1] Wouters, J. *Current Med. Chem.* **1998**, *5*, 137.
[2] R. Di Santo, et al. *Arch. Phar.* (Weinheim) **1992**, *325*, 403-409.
[3] F. La Torre, R. Costi, R. Di Santo, et al. *Chromatographia*, **2004**, *60*, 171-178.
[4] R. Di Santo, R. Costi, A. Roux, et al. *J. Med. Chem.* submitted.