Synthesis of target cathinones and preliminary study of cholinergic effects

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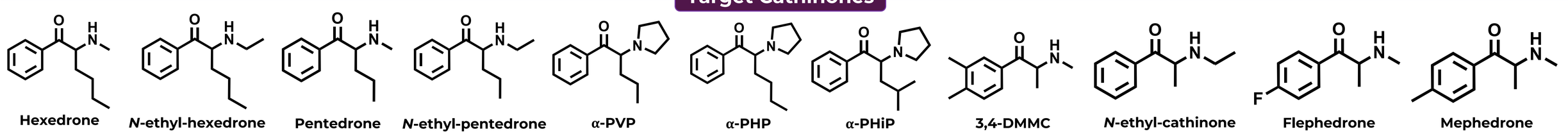
Introduction

Synthetic cathinones are one of the major classes of New Psychoactive Substances (NPS) commonly found on the illicit drug market. These substances are synthetic analogues of cathinone, the main psychoactive compound found in the leaves of *Catha Edulis* (khat), and act as central nervous system stimulants through interaction with monoamine receptors, similarly to amphetamines, such as Methamphetamine and MDMA[1]. To date, more than 204 synthetic cathinones have been reported on the illicit drug market, often synthesized to circumvent international legal control. However, the health consequences and outcomes associated with structural features emerging cathinones remain largely unknown, with severe cases of toxicity and death frequently reported. Several cathinones have been shown to inhibit the enzyme acetylcholinesterase (AChE)[2] with potential effects on the cholinergic system. Nevertheless, for most cathinones currently under drug surveillance, the effects on the cholinergic system is unclear, even though reports describe paralysis and convulsions, symptoms that may be linked to alterations, particularly through AChE inhibition.

Objectives

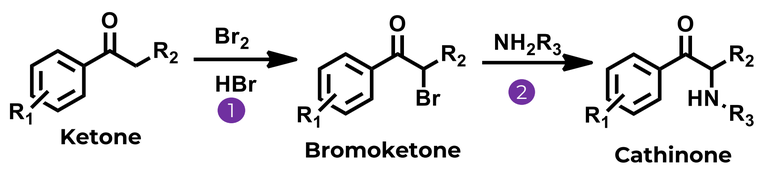
- To synthesize and characterize five target cathinones.
- To study of the effect of eleven target cathinones on the inhibition of acetylcholinesterase (AChE).

Target Cathinones



Methodology

Synthesis



1 α-Bromination of Ketone

2 Amination of Bromoketone

Figure 1: General synthesis procedure of target cathinones

Structural Analysis

The analytical techniques of Gas Chromatography coupled to Mass Spectrometry (GC-MS) and Nuclear Magnetic Resonance spectroscopy (NMR) were used to characterized the target cathinones.

AChE Inhibition

The Ellman's assay[3] was used to determine acetylcholinesterase (AChE) enzyme activity. AChE inhibition (%) was determined for the target cathinones at a concentration of 2 mM.

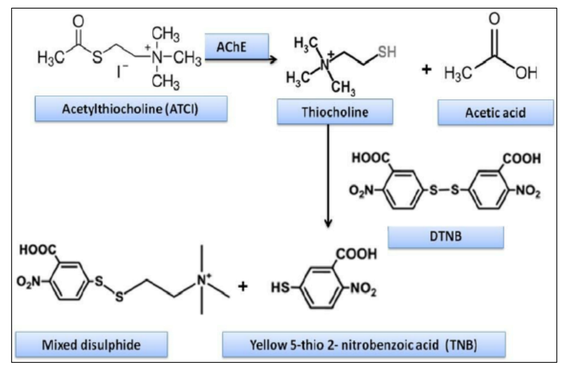
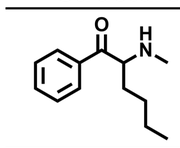
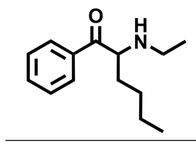
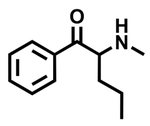
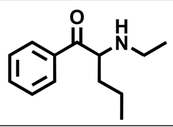
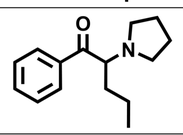


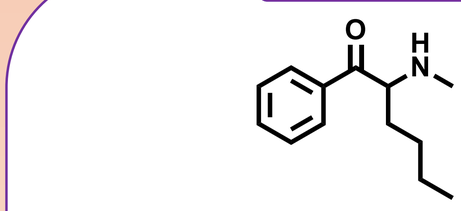
Figure 2: Reaction scheme of Ellman's method of AChE activity determination

Preliminary Results

Synthesis

Structure	Compound	Yield (%)
	Hexedrone	76
	*N*-Ethyl-Hexedrone	56
	Pentedrone	61
	*N*-Ethyl-Pentedrone	35
	Alpha-PVP	34

Characterization



Hexedrone

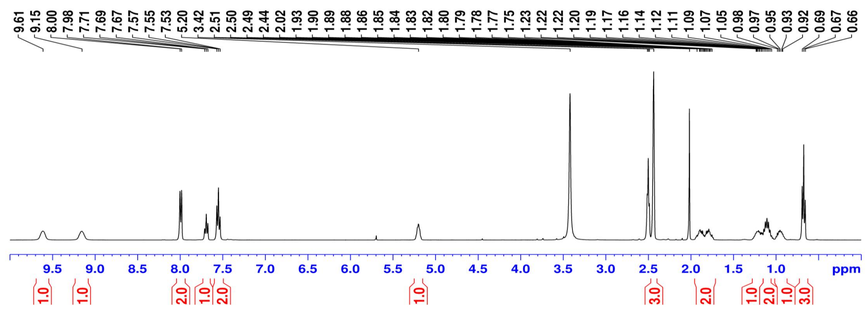


Figure 3: ^{1}H-NMR (400 MHz, DMSO-d_6) spectrum of Hexedrone.

Enzymatic Studies

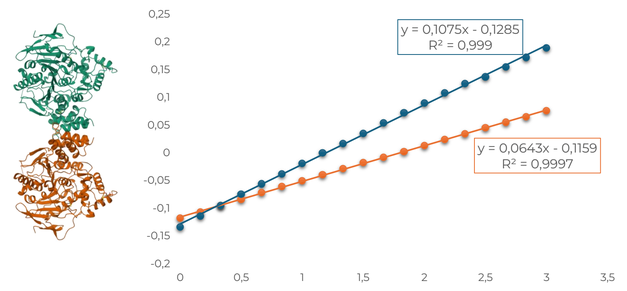


Figure 4: AChE inhibition (%) over time of *N*-ethyl-cathinone (2 mM). Blue: Control; Orange: Cathinone

Compound	AChE % Inhibition (2 mM)
Mephedrone	64
3,4-DMMC	**91**
Flephedrone	49
N-ethyl-cathinone	45

Preliminary Conclusions and ongoing work:

The five target cathinones were successfully synthesized, giving between 1,9 and 3,2 g with good yields (34 to 76%). All compounds were characterized by ^{1}H NMR. Additionally structural analyses are still in progress.

3,4-DMMC and Mephedrone showed higher AChE inhibition at 2 mM compared with Flephedrone and *N*-ethyl-cathinone, suggesting that methyl substituents on the aromatic ring could enhance AChE inhibition. Determination of IC_{50} values (concentration showing 50 % inhibition) for the most active cathinones is also ongoing. Continuing AChE inhibition assays for the remaining could clarify structure–activity relationships to understand the toxicity profiles of these eleven synthetic cathinones currently under surveillance.

References

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