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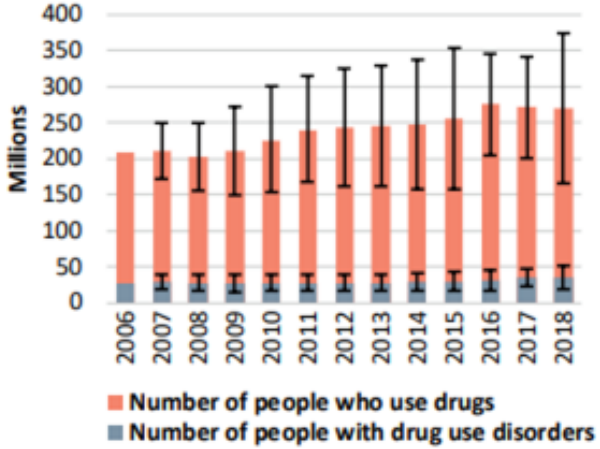
Facultat de Farmàcia i Ciències de l'Alimentació

Neuropharmacology of novel designer drugs: Effect of structural modifications of synthetic cathinones on their mechanism of action, psychostimulant and rewarding properties

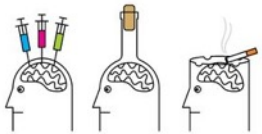
Núria Nadal Gratacós
Directors: Dr. Raúl López Arnau & Dr. Xavier Batllori Aguilá
June 2021

INTRODUCTION

Why is it important to study addiction?



Global number of people who use drugs and people with drug use disorders between 2006 and 2018. Source: World Drug Report 2020



1 in 5

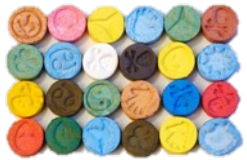
1 in 5 children grow up in a home affected by addiction

Source: American Academy of Pediatrics

NEW PSYCHOACTIVE SUBSTANCES

NPS are analogues of traditionally abused drugs that are not included in the Single Convention on Narcotic Drugs of 1961.

- Drugs that have been designed in order to mimic the effect of already considered illicit drugs.
- New chemical entities are developed in order to replace the molecular structure of those that have been banned.
- Attempt to avoid the law.



Public Health Threat.
Monitoring of their effect.
Wide understanding and control of synthetic drugs and its precursors

NEW PSYCHOACTIVE SUBSTANCES

Source: World Drug Report 2020

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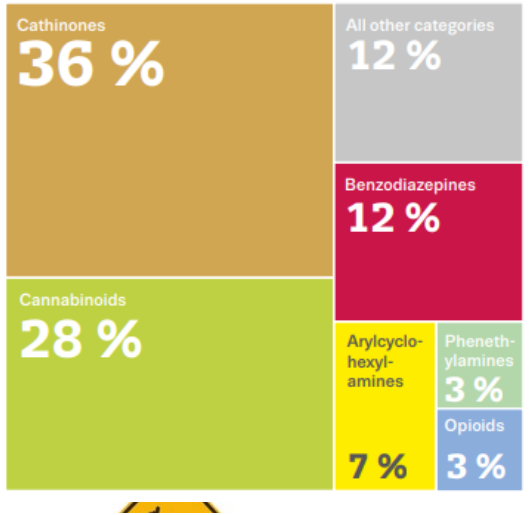
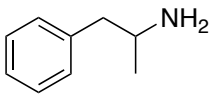
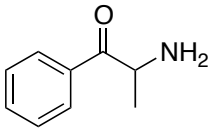


Number of seizures of new psychoactive substances reported to the EU early warning system by category.
Source: World Drug Report 2020

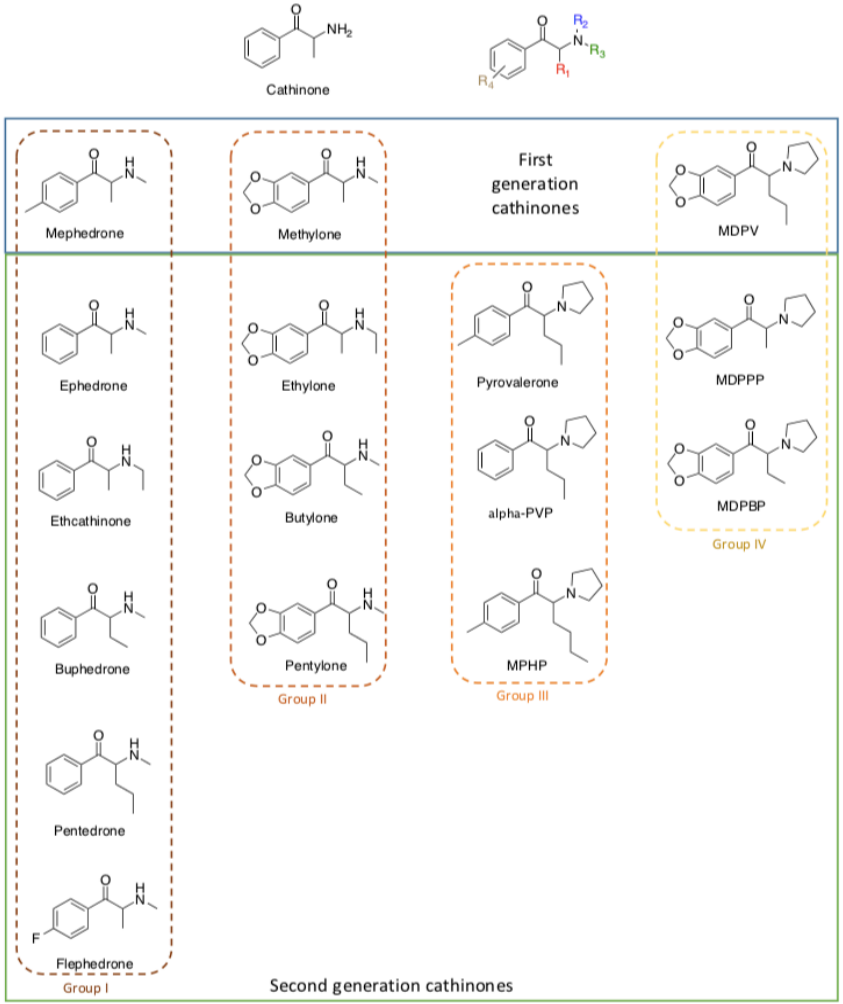
SYNTHETIC CATHINONES

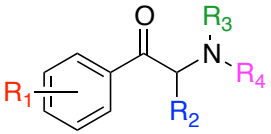


amphetamine



cathinone





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Role of amino terminal substitutions in the pharmacological, rewarding and psychostimulant profiles of novel synthetic cathinones

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New psychoactive substances
Synthetic cathinones
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Dopamine transporter

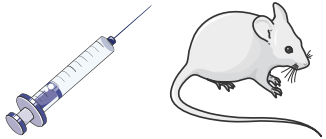
ABSTRACT

The emergence of new synthetic cathinones continues to be a matter of public health concern. In fact, they are quickly replaced by new structurally related alternatives. The main goal of the present study was to characterize the pharmacological profile, the psychostimulant and rewarding properties of novel cathinones (pentedrone, N-ethyl-pentedrone, α-PVP, N,N-diethyl-pentedrone and α-PpVP) which only differs in their amino terminal substitution.

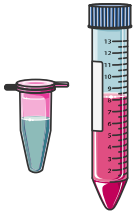
Rat synaptosomes were used for [^{3}H]dopamine uptake experiments. HEK293 transfected cells (hDAT, hSERT, hOCT; human dopamine, serotonin and organic cation transporter) were also used for [^{3}H]monoamine uptake and transporter binding assays. Molecular docking was used to investigate the effect of the amino substitutions on the biological activity. Hyperlocomotion and conditioned place preference paradigm were used in order to

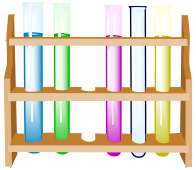
Study the effects of drugs that have recently appeared on the illicit market.

Prediction of the effects of drugs that may appear in the future.

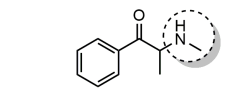


RESEARCH STRATEGY

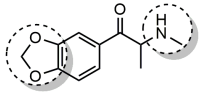




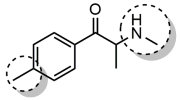
Define the Structure-activity relationship (SAR) of Novel Psychoactive Substances (NPS).



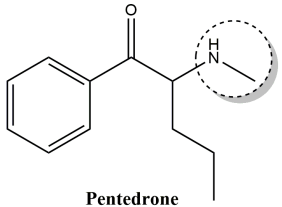
Methcathinone



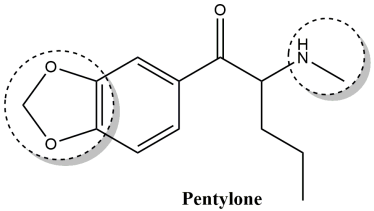
Methylone



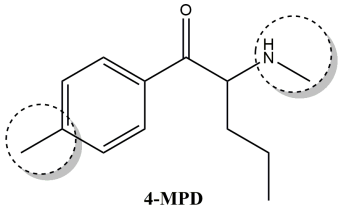
Mephedrone



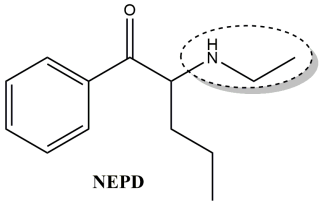
Pentedrone



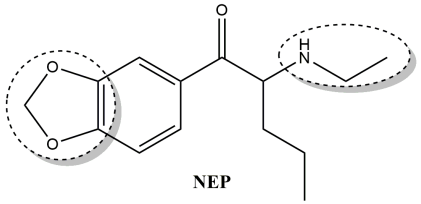
Pentylone



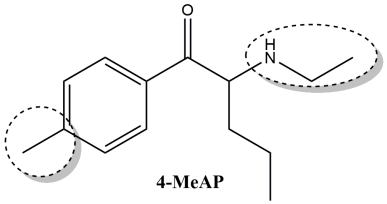
4-MPD



NEPD

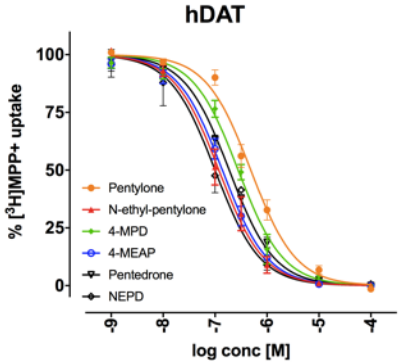


NEP



4-MeAP

UPTAKE INHIBITION ASSAYS IN HEK293 CELLS



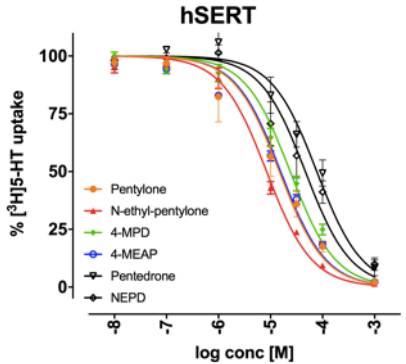
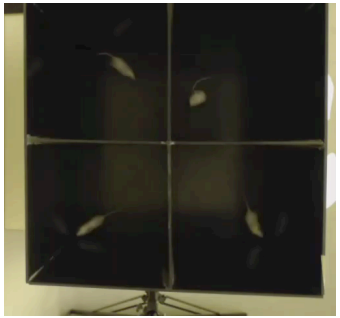
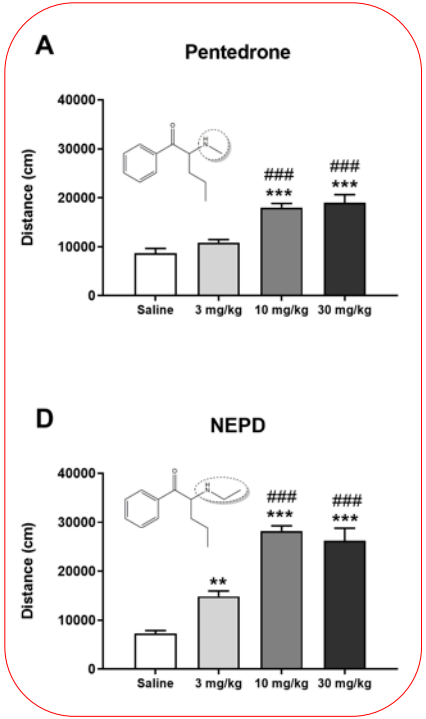


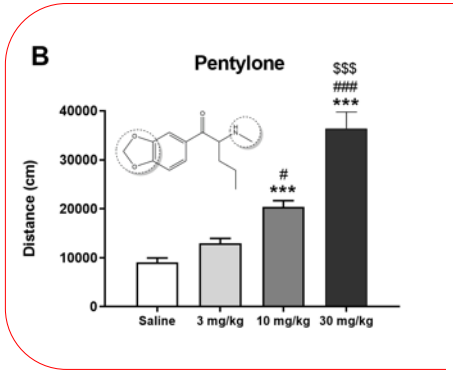
Table I. Potency of substituted cathinones and standard compounds at monoamine transporters. Monoamine uptake-1 and uptake-2 inhibition: values are IC_{50} given as µM (mean ± SEM).

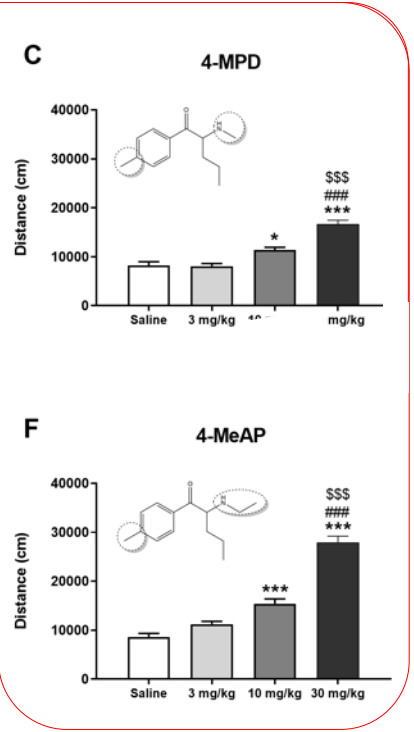
Compound	Monoamine uptake inhibition Transfected HEK293 cells Uptake-1 [^{3}H]MPP$^+$ uptake at hDAT	[^{3}H]5-HT uptake at hSERT	hDAT/hSERT ratio
Pentedrone	0.21 ± 0.02	137,9 ± 26.8	666
Pentylone	0.51 ± 0.07	23,2 ± 4,64	45
4-MPD	0.29 ± 0.05	30,88 ± 10,8	108
N-ethyl-pentedrone	0.10 ± 0.03	127,1 ± 8,91	>1000
N-ethyl-pentylone	0.13 ± 0.01	6,37 ± 0.156	51
4-MeAP	0.14 ± 0.02	13,27 ± 1.54	93
Cocaine[a]	0.23 ± 0.01	1.82 ± 0.10	7.84

HORIZONTAL LOCOMOTOR ACTIVITY (HLA)

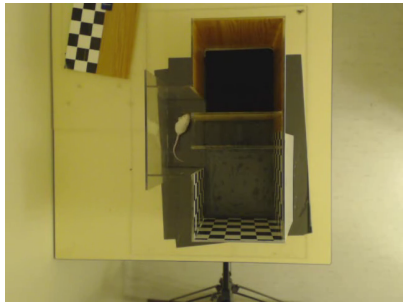


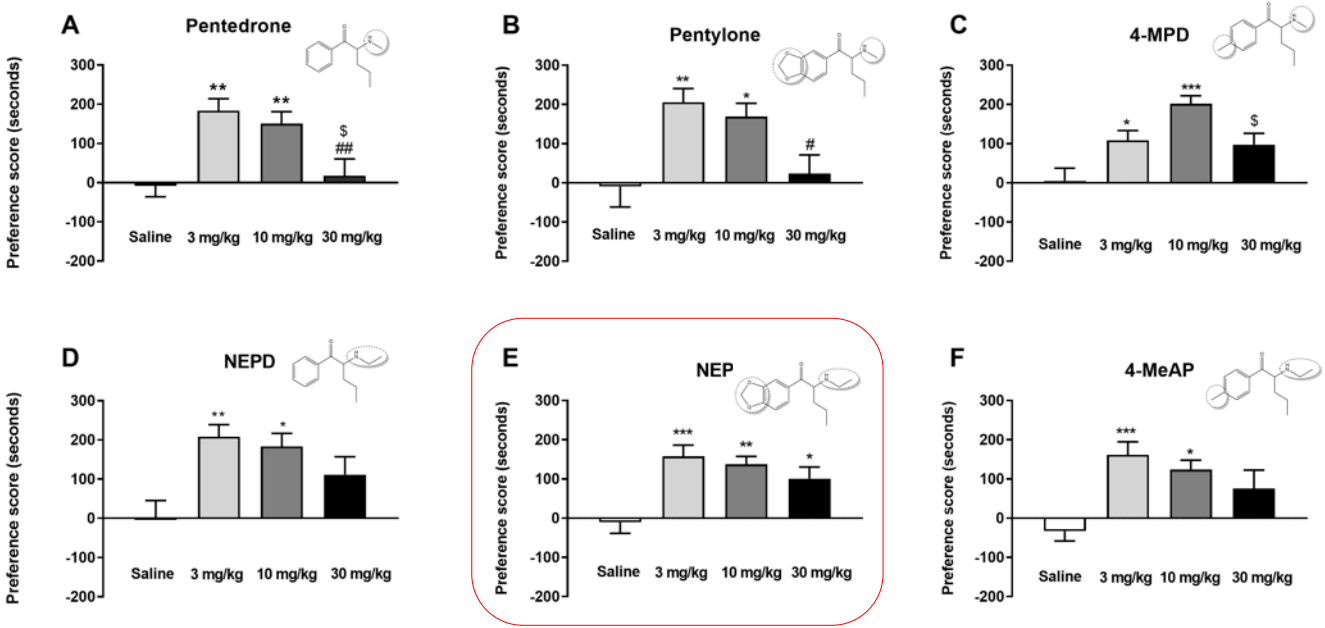






CONDITIONED PLACE PREFERENCE (CPP)





CONCLUSIONS

- All of the synthetic cathinones studied act as **potent DA uptake inhibitors** with a potency similar to that of cocaine.
- Increasing the length of the amino group from a methyl to **an ethyl group increases the potency in inhibiting dopamine uptake** (⇣IC_{50}).
- **Ring-substituted cathinones show a higher potency at inhibiting 5-HT uptake** than their non-substituted analogues.
- All the cathinones showed a **higher DAT/SERT ratio than cocaine,** suggesting their abuse liability.
- Pentedrone, NEPD, Pentylone, NEP, 4-MPD and 4-MeAP are **able to induce psychostimulant and rewarding effects in mice**, which is in accordance with what is expected for molecules with a high DAT/SERT ratio.

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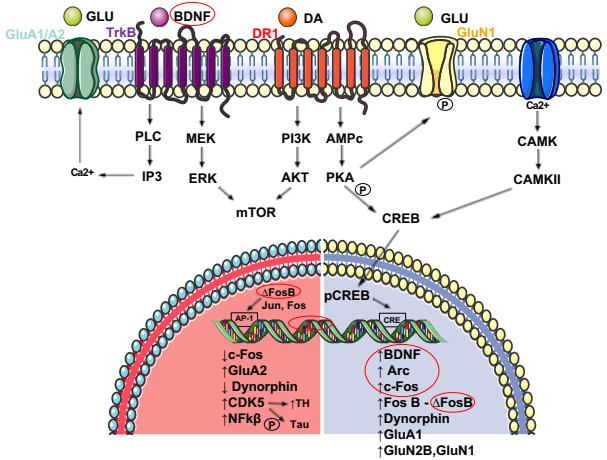
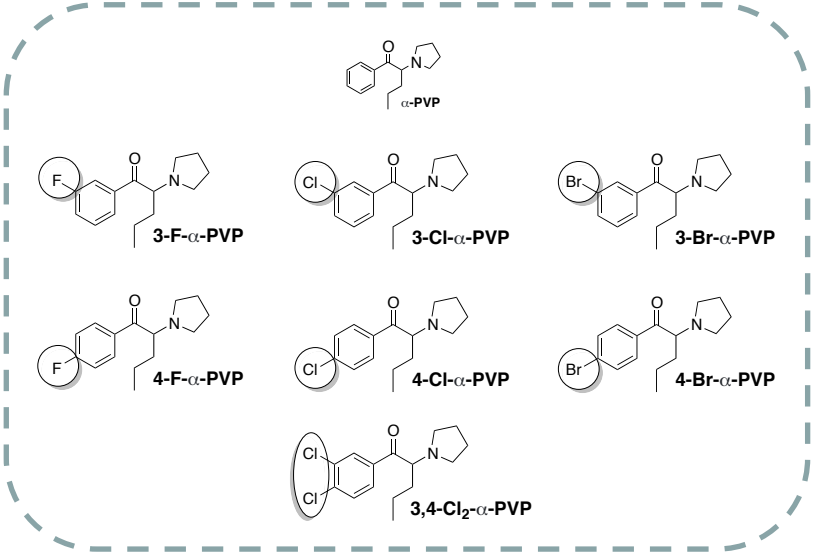
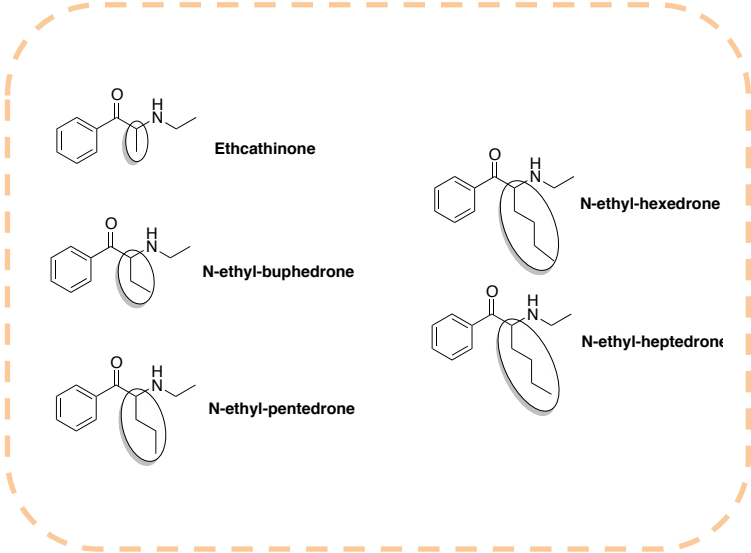
OTHER STUDIES



Results:

↑Arc
↑c-Fos
↑ BDNF (NEP)





Neuropsicofarmacologia dels derivats amfetamínics

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