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4F-PBP (4′-fluoro-α-pyrrolidinobutyrophenone), a new substance of abuse: Structural characterization and purity NMR profiling

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ABSTRACT

The rapidly growing problem of new psychoactive substances (NPS) makes the time management for international control a real challenge, with the traditional detection methods becoming increasingly inadequate. NPS screening technologies, such as NMR, which allows multiple substances to be detected, characterized and quantified simultaneously from a single sample, offers a rapid solution to this problem. This study describes the application of NMR to the simultaneous detection, characterization and quantification of samples of white powders seized by the Portuguese Police. 4F-PBP (4′-fluoro-α-pyrolidinobutyrophenone) a new synthetic psychoactive cathinone cut with *myo*-inositol was found in two seized products. The structural characterization of 4F-PBP was elucidated in the mixture, and confirmed after isolation from the matrix by ^{1}H, ^{13}C, ^{19}F NMR and MS. *Myo*-inositol was found for the first time as a cutting agent of cathinones. Furthermore another seized product was characterized as being MDPBP, with a high degree of purity, and its spectroscopic elucidation enabled the correction of ^{13}C NMR literature assignments.

1. Introduction

A "designer drug" is a synthetic compound that mimics the rising effects of an original illegal drug, but with a slightly altered chemical structure, to circumvent legislation restrictions against illegal substances [1]. Designer drugs include psychoactive substances that have been designated by the European Union [2] as new psychoactive substances (NPS), intended as "new narcotic or psychotropic drugs, that are not listed in the Single Convention on Narcotic Drugs of 1961[3] or the Convention on Psychotropic Substances of 1971, but which may pose a public health threat comparable to that posed by substances listed in those conventions" [4].

In recent years, on average, one NPS was detected every week in the EU and the numbers are expected to increase in the coming years. The rapid and unprecedented rate of evolution and spread of NPS makes the time management for international control a real challenge. The EU Early Warning System (EWS), a monitoring system administred by the European Monitoring Center for Drugs and Drug Addiction (EMCDDA) and EUROPOL was conceived, precisely, as a way to respond quickly to the increase of NPS in the European space. Since 1997, more than 350 substances were reported trough the EWS, and just between 2009 and 2013 the number of monitored NPS more than tripled [5].

Among these NPS, "synthetic cathinones" burst into the market at an explosive rate, with no signs of slowing. "Synthetic cathinones" are β-keto phenethylamines, the structural analogs of the natural occurring cathinone, the psychoactive stimulant found naturally in the khat plant (*Catha edulis*) [6]. These substances are sold as powders, tablets and capsules, masked as "bath salts" and "plant feeders" under different names. They are commercialized over the Internet and in retail establishments, such as "head shops" and "smartshops". Based on their amino groups, cathinones can be divided in two types: alkylamine and pyrrolidine cathinones [7]. Pyrrolidine cathinones (pyrrolidinophenones, also called pyrovalerones) are related to pyrovalerone, the first commercially available drug from the α-pyrrolidinophenones class, introduced in the market in the 1960s as a stimulant

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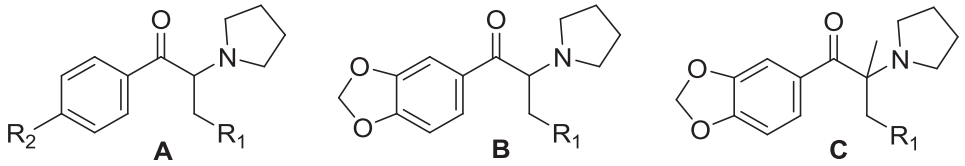
drug [8], having its clinical use being largely discontinued due to its association with risks of abuse and addiction. Alkylamine cathinones are structurally related to *N*-alkylamphetamines, differing only by the presence of β-keto group in the aliphatic chain. Synthetic cathinones made their largest first appearance on the market in the mid-2000s, with methylone (an analogue of MDMA, 3,4-methylenedioxy-methamphetamine, the scientific name of ecstasy) being the first one reported to the EMCDDA [9]. Since then, more than 50 different cathinones have appeared on the market [5]. In the EU, 22 pyrrolidinophenones were reported since 2004 [Table 1].

Pyrrolidinophenones found in the European Union can be grouped in three subclasses, according to the substitution pattern of the aryl moiety and the α-carbon substitution. In the first subclass, the aromatic ring is unsubstituted or *para* substituted with an alkyl group or halogen atom and the α-carbon is a tertiary one, with a C1 to C6 alkyl chain. A second class gathers compounds possessing a 3′,4′-methylenedioxyphenyl substitution, being the α-carbon, as well, a tertiary one with a C1 to C4 alkyl chain. Finally, the third class differs from the previous one on the fact that the α-carbon is quaternary holding an extra methyl group.

Few reports on the toxicity of synthetic cathinones exist to date, but it is known that cathinones, like many psychostimulants, exert their action interacting with monoamine neurons in the central nervous system (CNS) [10]. These neurons synthesize, store and release at least one of the neurotransmitters norepinephrine, dopamine and serotonin. The regulation of the extracellular concentration of these neurotransmitters is executed by the so-called monoamine transporters (MATs), integral plasma membrane proteins located outside the synaptic cleft, which transports

Table 1
Pyrrolidinophenones reported to EMCDDA as NPS, until December 2014.



Compound	Chemical name (common name, IUPAC name)	Molecular formula	Structure			EU	Portugal
				R_1	R_2		
PPP	α-pyrrolidinopropiophenone (*R,S*)-1-phenyl-2-(pyrrolidin-1-yl) propan-1-one	$C_{13}H_{17}NO$	**A**	H	H	Dec. 2008 Denmark	–
MPPP	4′-methyl-α-pyrrolidinopropiophenone (*R,S*)-2-(pyrrolidin-1-yl)-1-(*p*-tolyl)propan-1-one	$C_{14}H_{19}NO$	**A**	H	CH_3	Aug. 2010 UK	–
MOPPP	4′-methoxy-α-pyrrolidinopropiophenone (*R,S*)-1-(4-methoxyphenyl)-2-(pyrrolidin-1-yl)propan-1-one	$C_{14}H_{19}NO_2$	**A**	H	OCH_3	June 2004 Germany	–
ClPPP	4′-chloro-α-pyrrolidinopropiophenone (*R,S*)-1-(4-chlorophenyl)-2-(pyrrolidin-1-yl)propan-1-one	$C_{13}H_{16}ClNO$	**A**	H	Cl	Mar. 2013 Poland	–
MDPPP	3′,4′-methylenedioxy-α-pyrrolidinopropiophenone (*R,S*)-1-(benzo[*d*][1,3]dioxol-5-yl)-2-(pyrrolidin-1-yl)propan-1-one	$C_{14}H_{17}NO_3$	**B**	H	–	June 2004 Germany	–
MDMPP	3′,4′-methylenedioxy-α-methylpyrrolidinopropiophenone (*R,S*)-1-(benzo[*d*][1,3]dioxol-5-yl)-2-methyl-2-(pyrrolidin-1-yl)propan-1-one	$C_{15}H_{19}NO_3$	**C**	H	–	Aug. 2010 Switzerland	–
PBP	α-pyrrolidinobutiophenone (*R,S*)-1-phenyl-2-(pyrrolidin-1-yl)butan-1-one	$C_{14}H_{19}NO$	**A**	CH_3	H	Dec. 2011 Finland	Oct. 2014
MPBP	4′-methyl-α-pyrrolidinobutiophenone (*R,S*)-2-(pyrrolidin-1-yl)-1-(p-tolyl)butan-1-one	$C_{15}H_{21}NO$	**A**	CH_3	CH_3	July 2010 Bulgaria	–
MDPBP	3′,4′-methylenedioxy-α-pyrrolidinobutiophenone (*R,S*)-1-(benzo[*d*][1,3]dioxol-5-yl)-2-(pyrrolidin-1-yl)butan-1-one	$C_{15}H_{19}NO_3$	**B**	CH_3	–	May 2010 UK	Mar. 2013
MOPBP	4′-methoxy-α-pyrrolidinobutiophenone (*R,S*)-1-(4-methoxyphenyl)-2-(pyrrolidin-1-yl)butan-1-one	$C_{15}H_{21}NO_2$	**A**	CH_3	OCH_3	June 2014 Sweden	–
PVP	α-pyrrolidinovalerophenone (*R,S*)-1-phenyl-2-(pyrrolidin-1-yl)pentan-1-one	$C_{15}H_{21}NO$	**A**	C_2H_5	H	Feb. 2011 France	Mar. 2013
MOPVP	4′-methoxy-α-pyrrolidinovalerophenone (*R,S*)-1-(4-methoxyphenyl)-2-(pyrrolidin-1-yl)pentan-1-one	$C_{16}H_{23}NO_2$	**A**	C_2H_5	OCH_3	Dec. 2012 Finland	–
MDPV	3′,4′-methylenedioxy-α-pyrrovalerone (*R,S*)-1-(benzo[*d*][1,3]dioxol-5-yl)-2-(pyrrolidin-1-yl)pentan-1-one	$C_{16}H_{21}NO_3$	**B**	C_2H_5	–	Nov. 2008 UK/Finland	Feb. 2011
FPVP	4′-fluoro-α-pyrrolidinovalerophenone (*R,S*)-1-(4-fluorophenyl)-2-(pyrrolidin-1-yl)pentan-1-one	$C_{15}H_{20}FNO$	**A**	C_2H_5	F	Dec. 2013 Sweden	–
PHP	α-pyrrolidinohexanophenone (*R,S*)-1-phenyl-2-(pyrrolidin-1-yl)hexan-1-one	$C_{16}H_{23}NO$	**A**	C_3H_7	H	July 2013 Poland	–
MPHP	4′-methyl-α-pyrrolidinohexanophenone (*R,S*)-2-(pyrrolidin-1-yl)-1-(p-tolyl)hexan-1-one	$C_{17}H_{25}NO$	**A**	C_3H_7	CH_3	June 2004 Germany	Nov.2012
MDPHP	3,4-methylenedioxy-α-pyrrolidinohexiophenone (*R,S*)-1-(benzo[*d*][1,3]dioxol-5-yl)-2-(pyrrolidin-1-yl)hexan-1-one	$C_{17}H_{23}NO_3$	**B**	C_3H_7	–	Nov. 2014 Sweden	–
PHPP	α-pyrrolidinoheptanophenone (*R,S*)-1-phenyl-2-(pyrrolidin-1-yl)heptan-1-one	$C_{17}H_{25}NO$	**A**	C_4H_9	H	July 2013 Sweden	–
MOPEP	4-methoxy-α-pyrrolidinoenanthophenone (*R,S*)-1-(4-methoxyphenyl)-2-(pyrrolidin-1-yl)heptan-1-one	$C_{18}H_{27}NO_2$	**A**	C_4H_9	OCH_3	Nov. 2014 France	–
FPEP	4-fluoro-α-pyrrolidinoenanthophenone (*R,S*)-1-(4-fluorophenyl)-2-(pyrrolidin-1-yl)heptan-1-one	$C_{17}H_{24}FNO$	**A**	C_4H_9	F	Sept. 2014 Hungary	–
POP	α-pyrrolidinooctanophenone (*R,S*)-1-phenyl-2-(pyrrolidin-1-yl)octan-1-one	$C_{18}H_{27}NO$	**A**	C_5H_{11}	H	Sept. 2014 Germany	–
FPOP	4-fluoro-α-pyrrolidinooctanophenone (*R,S*)-1-(4-fluorophenyl)-2-(pyrrolidin-1-yl)octan-1-one	$C_{18}H_{26}FNO$	**A**	C_5H_{11}	F	Sept. 2014 Hungary	–