Analytical profiles of the piperazines

Over the past few months (Autumn 2006) members of LTG have become aware of an increasing number of piperazine compounds sold on websites as “herbal ecstasy”. They are often promoted as a legal alternative to MDMA, and sometimes as a “harm minimisation” strategy. The health consequences of their widespread availability are beginning to emerge with reports of hospitalisations and involvement in road accidents.

None of the compounds are licensed medicines or have been evaluated for their safety. The aryl piperazines were investigated as potential anthelminthic agents, but only unsubstituted piperazine is licensed for this purpose in the EU. Piperazine itself is available in the UK in Pripsen® sachets (piperazine phosphate 4g sennosides 15.3g) for the treatment of threadworms and roundworms.

The aryl piperazines are not directly related to any common psychoactive substance, although one of the compounds (mCPP) is a metabolite of legitimate medicines. The structures are shown below; there are no stereoisomers. The benzyl derivatives tend to behave as stimulants (especially BZP) while the substituted phenyl derivatives (for example mCPP) may be mild hallucinogens and have weak MDMA-like effects.

The free bases are liquids, but they are normally used as the hydrochloride or the dihydrochloride salts which are solids. The compounds described here are all synthetic with no known natural sources. Erroneous claims that 1-benzylpiperazine (BZP) and other piperazines are natural products derived from the pepper plant may arise from confusion with the unrelated substance - piperine, a constituent of *Piper nigrum*. We have found piperine in drugs sold for recreational purposes - although it does not gas chromatograph easily.

There are no reports of the illicit synthesis of the compounds, probably because they are available at low cost from chemical suppliers as intermediates in the production of chemicals and pharmaceuticals. m-Chlorophenylpiperazine (mCPP) is a known metabolite of trazodone and nefazodone and probably also of etoperidone and mepiprazole (once used in Spain).

Pharmacology

Studies in the rat have shown that BZP elevates serotonin and dopamine neurotransmitters in the brain by blocking the reuptake of the transmitters at the synapse. TFMPP which is commonly combined with BZP, was also found to be a selective releaser of serotonin in the rat brain. Compare this with MDMA which acts as a substrate for dopamine and serotonin transporters in brain tissue, elevating synaptic serotonin and dopamine levels. BZP and TFMPP are less potent individually than MDMA as they do not stimulate monoamine release to the same extent as MDMA.

Despite its non-specific pharmacology mCPP has been used in various neurochemical research projects, but the risk associated with the use of mCPP in humans has not been determined. It has been used extensively in psychiatric

research to test the sensitivity of the serotonin system in the brain. mCPP is of interest because it has 5-HT2C agonistic and 5-HT2A antagonistic properties as well as behavioural effects that are consistent with 5-HT agonistic properties such as anxiogenesis and anorexia in animals and humans.

There seems to be a wide range of opinions and 'recommendations' regarding the dosage and effects of mCPP for recreational use.

Users' experiences
The majority of published data concentrates on the effects of BZP, the most commonly used piperazine. It produces euphoria, wakefulness and increased vigilance, but can also cause nausea, vomiting, insomnia, anxiety, hallucinations and paranoia. Ecstasy users' comment that BZP is not as good as MDMA, as it does not give such a marked euphoric effect, with greater insomnia and hangover. Observations from hospital admissions in New Zealand, and a handful in the UK, have given further insight into the immediate effects of BZP.

Toxicity
There have been no reported deaths as a direct result of BZP or other piperazines. BZP seems to have some toxic effects; symptoms include insomnia, anxiety, nausea, vomiting, palpitations, dystonia and urinary retention. More seriously, toxic seizures occurred in 15 out of 80 cases seen in a study of A&E presentations in New Zealand, two were life-threatening status epilepticus with severe respiratory and metabolic acidosis.

Piperazines should be avoided by people with health problems such as a history of seizure disorders or coronary disease. Even Spiritual Highs' website describes how BZP long term effects "could put a stress on the heart due to increased blood pressure".

Dosage
A study of A&E presentations in New Zealand in 2005 showed that adverse effects occurred in patients taking an average of 4.5 tablets. Dosage of piperazines is certainly seen as an issue by the suppliers - package labeling usually warns that users should only take one capsule and not exceed the stated dosage. Typical dosage is 60mg-200mg BZP but some capsules claim to contain 1000mg of BZP.

A dose of 20-100 mg BZP produces euphoria, wakefulness and improved vigilance. At high doses BZP has the same psychoactive effects as amphetamine (100 mg BZP is thought to be equivalent to about 10 mg amphetamine). Users may experience various negative symptoms such as anxiety, vomiting, headache, palpitations, confusion, collapse and seizures. Some symptoms may persist for up to 24 hours.

Although "legal high" tablet and capsule packaging usually states that alcohol should not be taken with BZP – alcohol and other illicit drugs, are commonly seen in cases of BZP toxicity.

Piperazines are found in tablets bearing logos (e.g. Versace, Mitsubishi, Lacoste, Rolls Royce) similar to those found on ecstasy tablets. They are referred to on the streets as “legal ecstasy” or “herbal ecstasy” and it seems likely that they are passed off as MDMA. Tablets containing both mCPP and MDMA have been seen.

Legal Status

Doseage forms containing piperazines could be considered as unlicensed medicinal products and therefore subject to the UK Medicines Act. However no piperazine derivatives are currently controlled under the specific or generic provisions of the UK Misuse of Drugs Act (1971) or its amendments. BZP is controlled in Australia, USA, Belgium, Denmark, Greece, Malta and Sweden. New Zealand has introduced legislation to enforce age related restrictions on sale.

Analytical data

This monograph presents brief analytical profiles of the piperazine derivatives found in “illicit” tablets and capsules in the UK. Not all the compounds listed have been found in products but are presented because they are positional isomers of those that have. Isomers that are not resolved by GC/MS may be differentiated by HPLC with UV diode array detection because the UV absorption spectra vary.

Analytical standards of all the compounds are available commercially from Sigma Aldrich, the catalogue numbers are provided in the table. Some compounds are only available as free bases, for others the hydrochloride salts are also available.

Some immunoassays that target methylamfetamine also detect some of the piperazines. Dilutions of a 1mg/mL solution of the compounds in methanol were made in water for the evaluations of the immunoassay unit test devices. Thanks are due to Alan Freke of Dade Behring for donation of the Syva RapidTest d.a.u. devices.

Only one compound (oMeOPP) reacts with the Marquis reagent (very weak pink).

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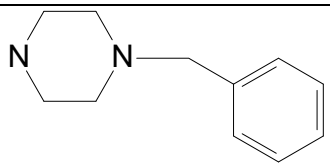
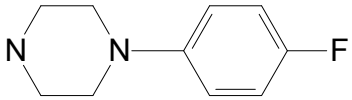
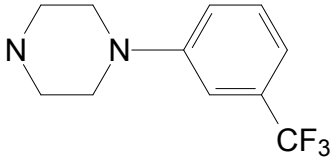
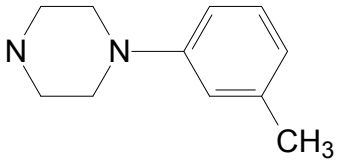
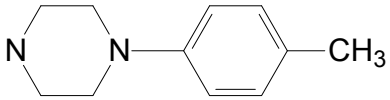
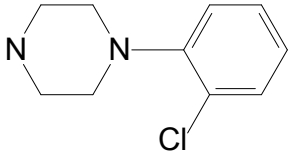
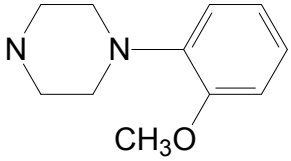
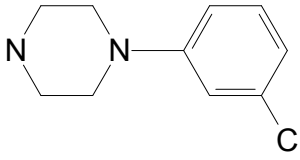
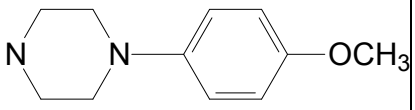
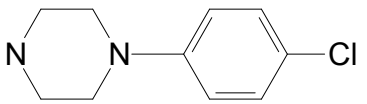
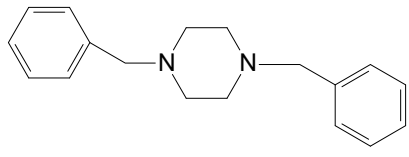
The compounds

A	1-benzylpiperazine $C_{11}H_{16}N_2$ mw 176 Sigma Aldrich 13815-25G-F	BZP	
B	1-(4-fluorophenyl)piperazine $C_{10}H_{13}FN_2$ mw 180 Sigma Aldrich 19133-7	pFPP	
C	1-(3-trifluoromethylphenyl) piperazine m-trifluoromethylphenylpiperazine $C_{11}H_{13}F_3N_2$ mw 230 1-(α,α,α-trifluoro-m-tolyl)piperazine Sigma Aldrich T8948 (HCl)	TFMPP	
D	1-(3-methylphenyl)piperazine $C_{11}H_{16}N_2$ mw 176 Sigma Aldrich R435376 (diHCl)	mMPP	
E	1-(4-methylphenyl)piperazine $C_{11}H_{16}N_2$ mw 176 Sigma Aldrich 71868-5G-F	pMPP	
F	1-(2-chlorophenyl)piperazine $C_{10}H_{13}ClN_2$ mw 196.5 Sigma Aldrich C67605 (HCl)	oCPP	
G	1-(2-methoxyphenyl)piperazine $C_{11}H_{16}N_2O$ mw 192 Sigma Aldrich M22601-5G (HCl)	oMeOPP	
H	1-(3-chlorophenyl)piperazine $C_{10}H_{13}ClN_2$ mw 196.5 Sigma Aldrich 125180-5G (HCl)	mCPP	
I	1-(4-methoxyphenyl)piperazine $C_{11}H_{16}N_2O$ mw 192 Sigma Aldrich 571415-1G (diHCl)	pMeOPP	
J	1-(4-chlorophenyl)piperazine $C_{10}H_{13}ClN_2$ mw 196.5 Sigma Aldrich C68008	pCPP	
K	1,4-dibenzylpiperazine $C_{18}H_{22}N_2$ mw 266 Sigma Aldrich S383937-1EA (diHCl)	DBZP	

GC/MS

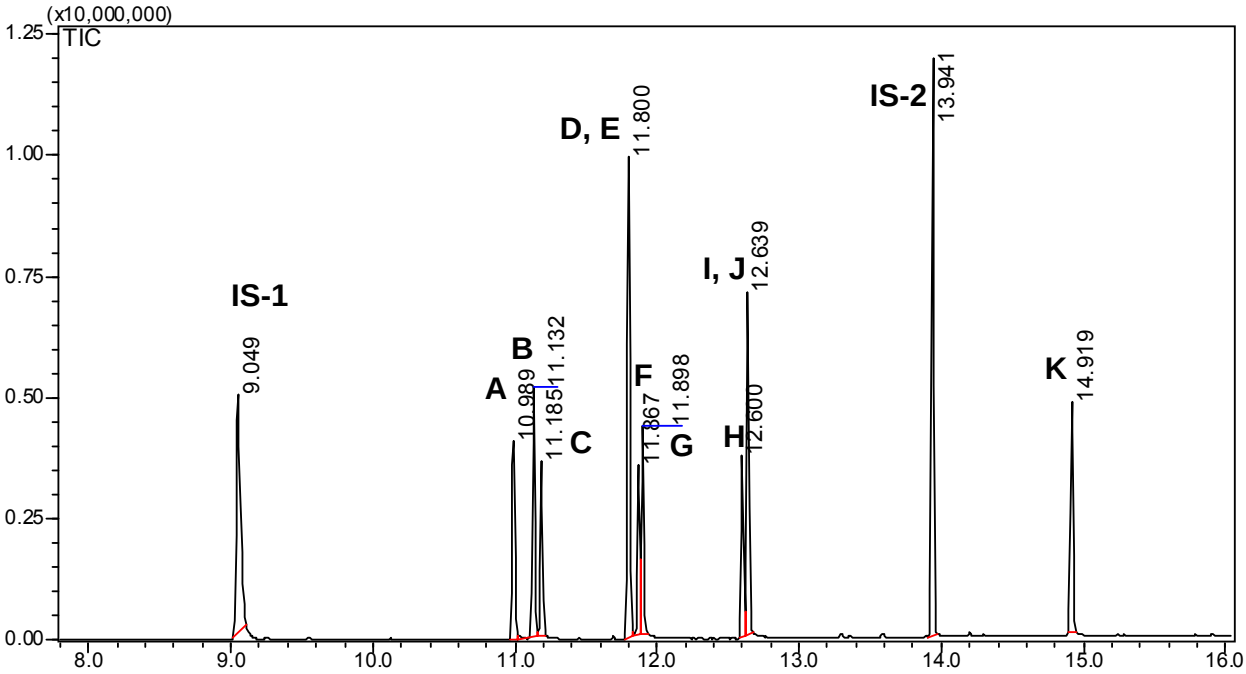
Samples were analysed on a Shimadzu QP2010 gas chromatograph mass spectrometer with an HP5MS column (30m x 0.25mm, 0.50µm).

Column oven temperature	80°C
Injection temperature	225°C
Injection mode	Splitless
Carrier gas	Helium
Flow rate	1.0 ml/min
Pressure	9.5 psi
Ion source temperature	200°C
Interface temperature	250°C

Column oven temperature programme:

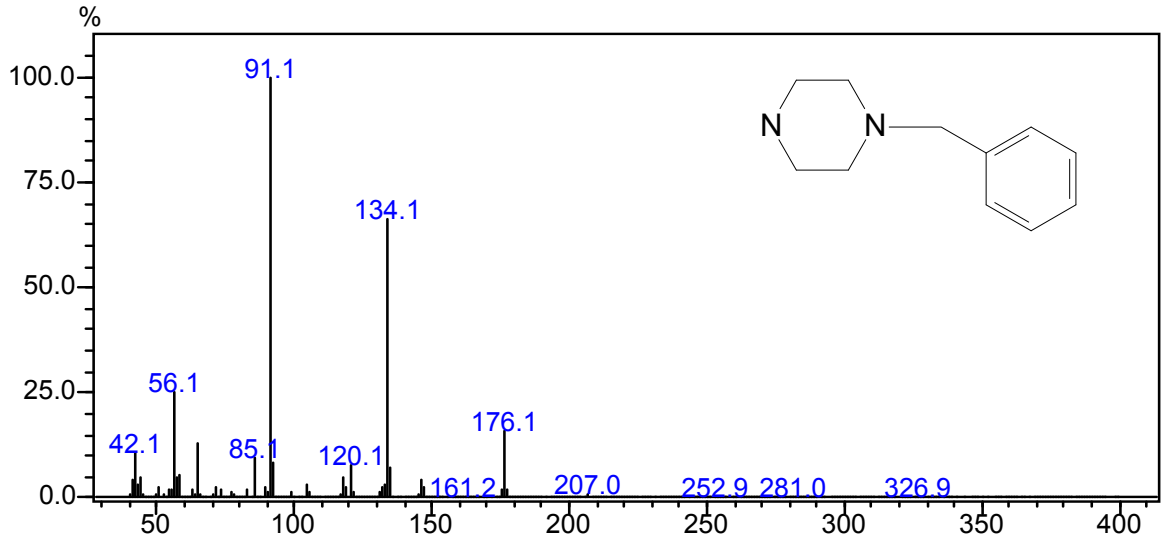
Rate	Final temperature	Hold time
-	80°C	4 minutes
20.00°C/min	280°C	8 minutes
20.00°C/min	290°C	11.5 minutes

Chromatogram:-

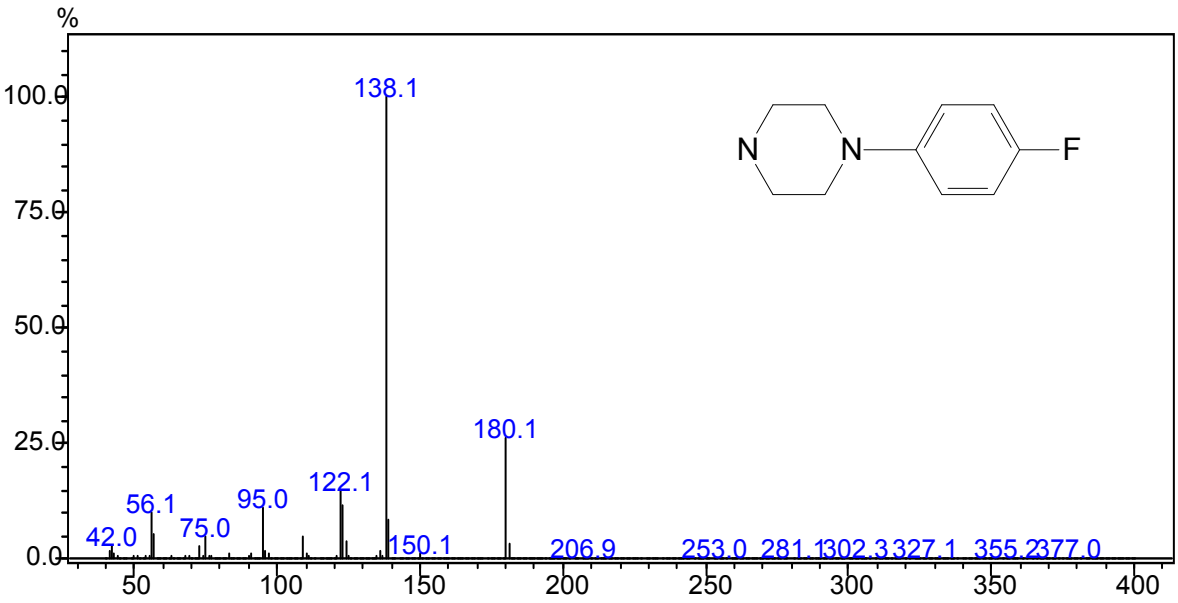


ID	Compound Name	Abbreviations	Retention time (mins.)
IS-1	Quinoline	IS-1	9.049
A	Benzylpiperazine	BZP	10.989
B	1-(4-fluorophenyl)piperazine	pFPP	11.132
C	m-trifluoromethylphenylpiperazine	TFMPP	11.185
D	1-(3-methylphenyl)piperazine	mMPP	11.800
E	1-(4-methylphenyl)piperazine	pMPP	11.800
F	1-(2-chlorophenyl)piperazine	oCPP	11.867
G	1-(2-methoxyphenyl)piperazine	oMeOPP	11.861
H	1-(3-chlorophenyl)piperazine	mCPP	12.600
I	1-(4-methoxyphenyl)piperazine	pMeOPP	12.639
J	1-(4-chlorophenyl)piperazine	pCPP	12.639
IS-2	Pyribenzamine (tripelenamine)	IS-2	13.941
K	1,4-dibenzylpiperazine	DBZP	14.919

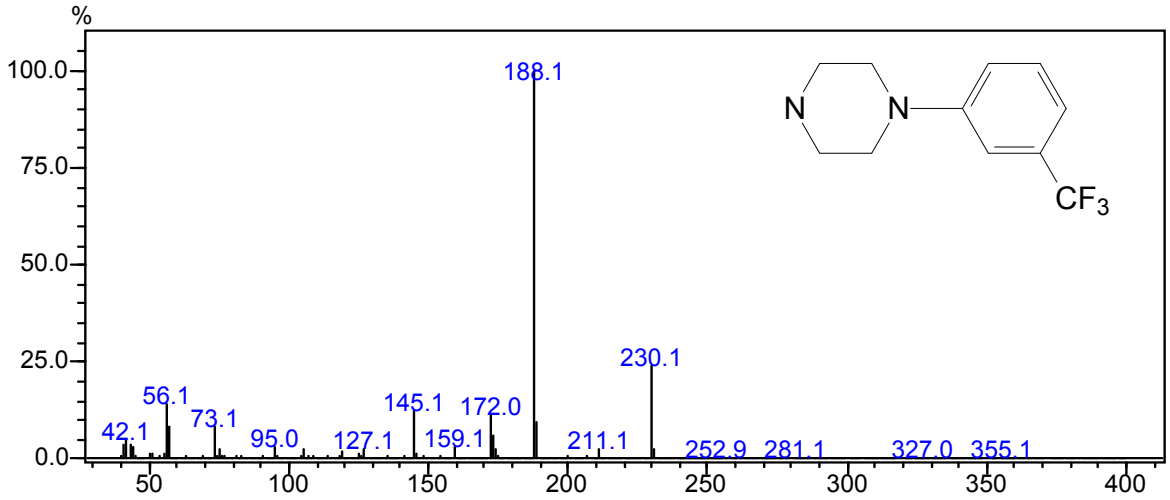
(A) BENZYLPIPERAZINE (BZP)



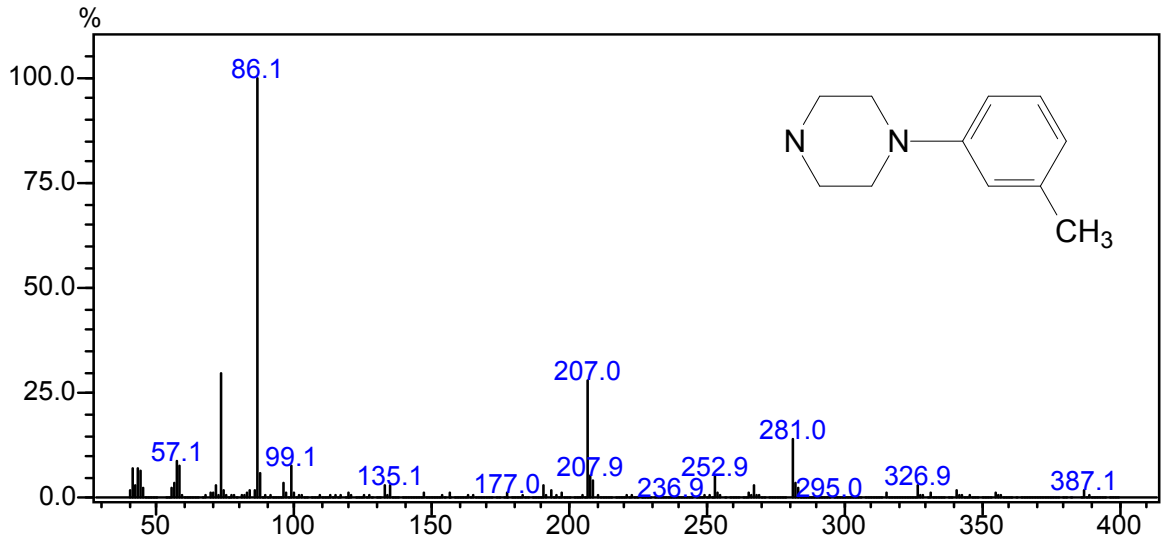
(B) 1-(4-FLUOROPHENYL)PIPERAZINE (pFPP)



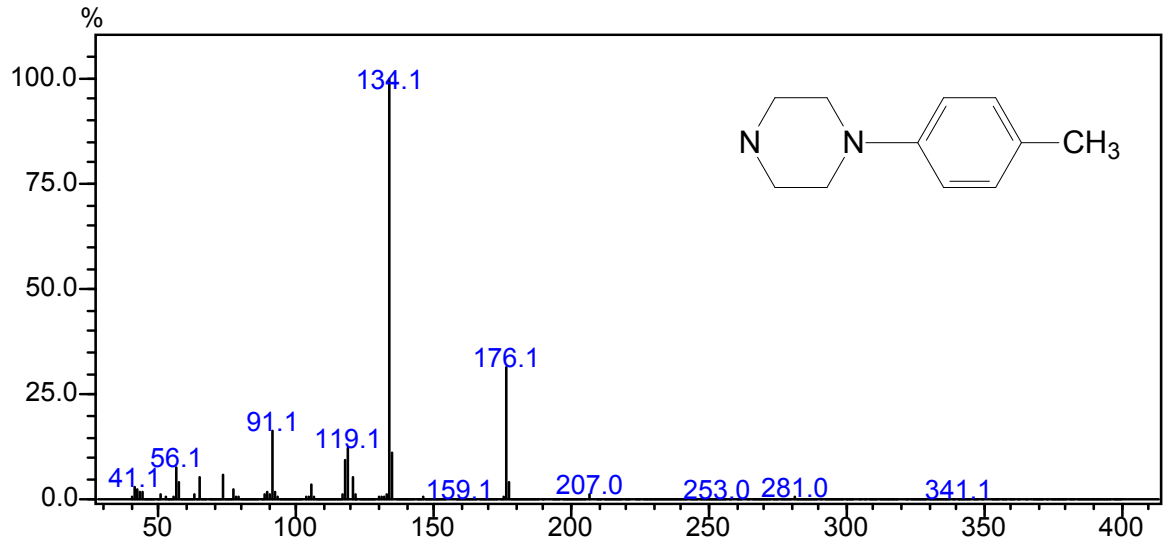
(C) m-TRIFLUOROMETHYLPHENYLPIPERAZINE (TFMPP)



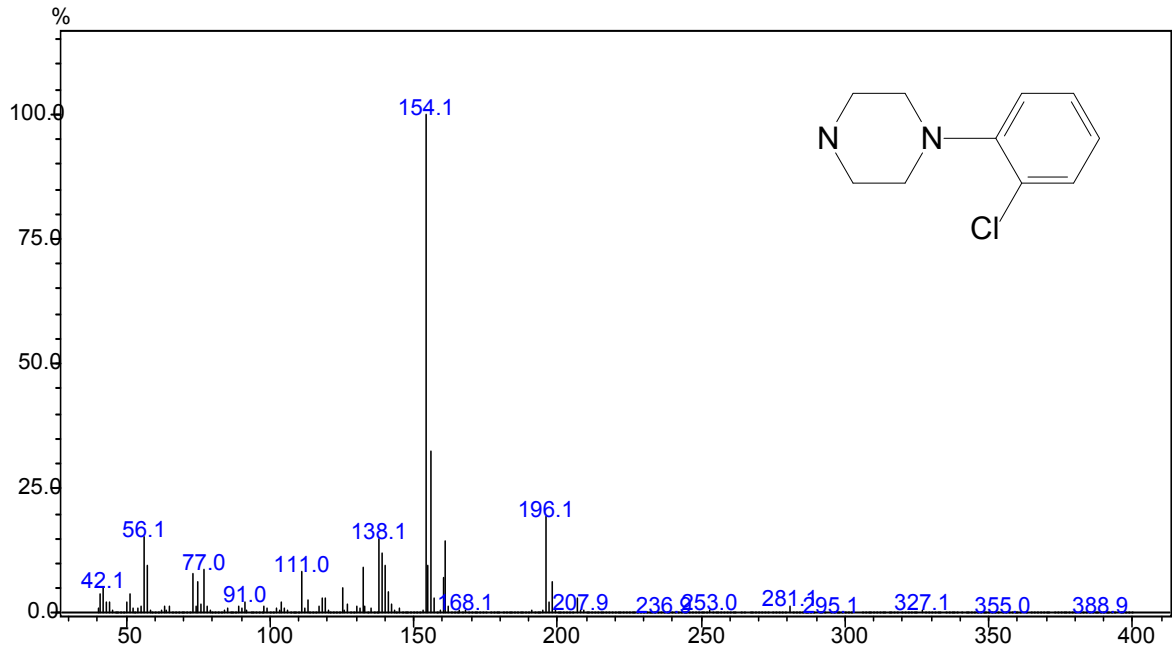
(D) 1-(3-METHYLPHENYL)PIPERAZINE (mMPP)



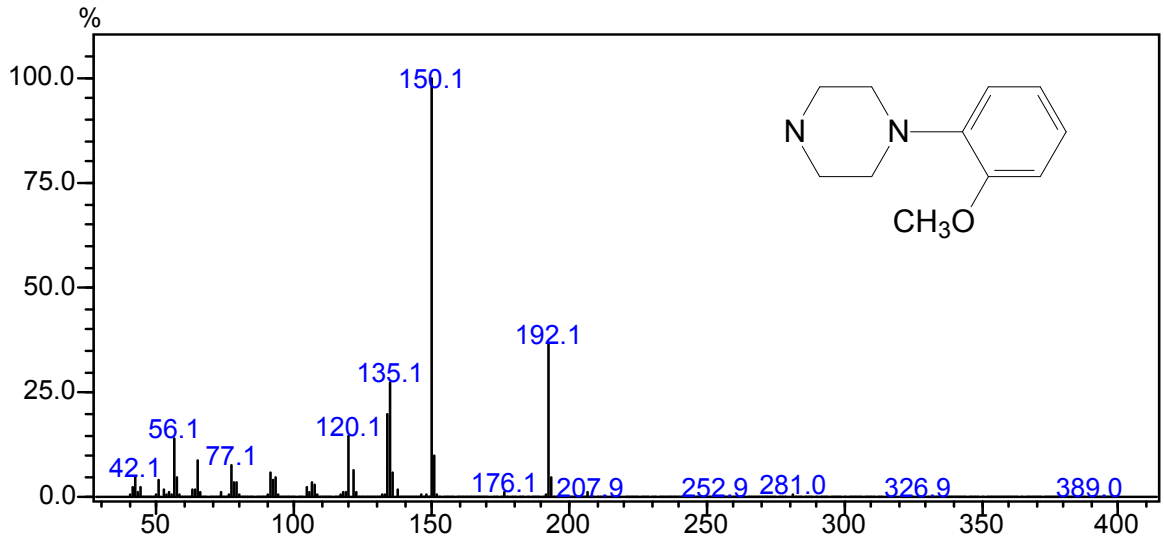
(E) 1-(4-METHYLPHENYL)PIPERAZINE (pMPP)



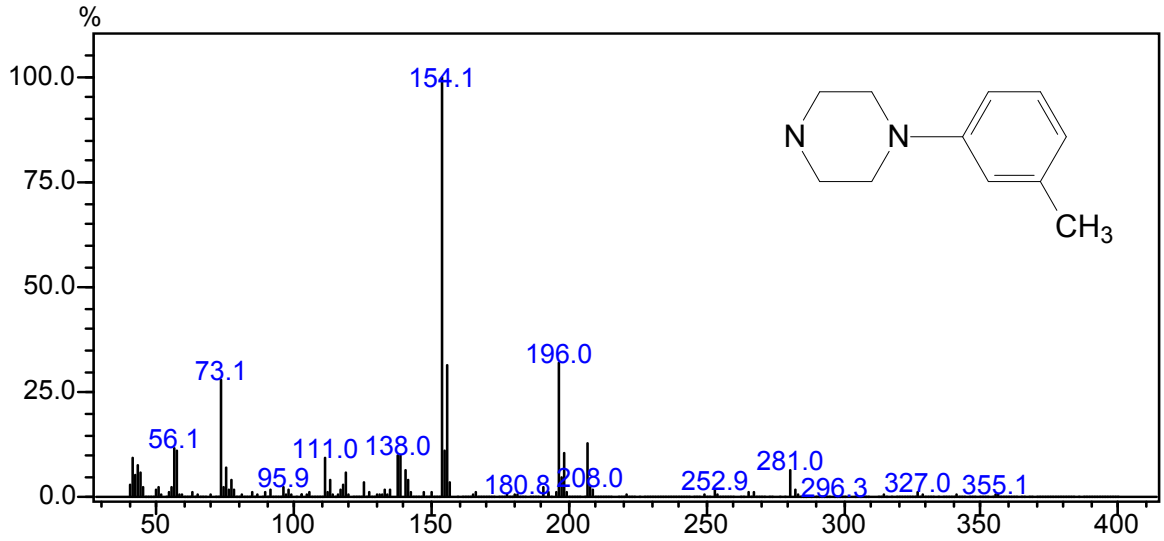
(F) 1-(2-CHLOROPHENYL)PIPERAZINE (oCPP)



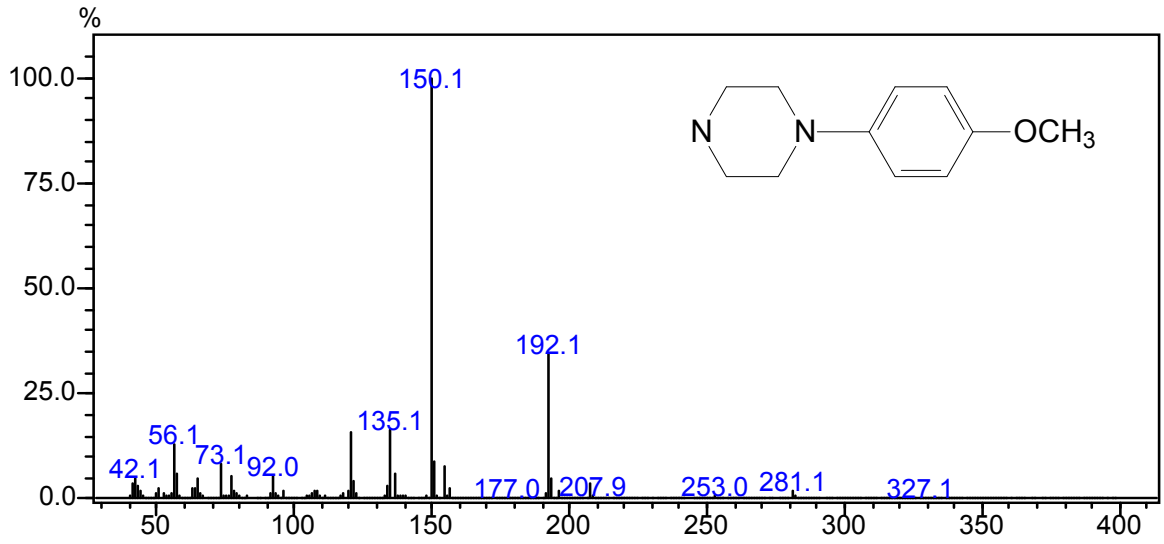
(G) 1-(2-METHOXYPHENYL)PIPERAZINE (oMeOPP)



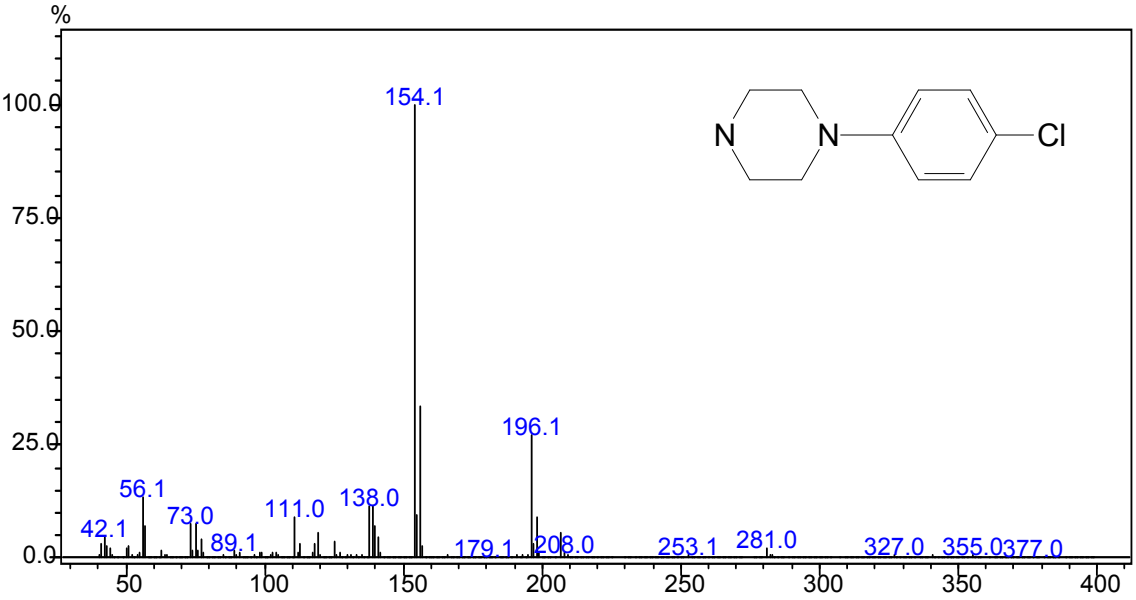
(H) 1-(3-CHLOROPHENYL)PIPERAZINE (mCPP)



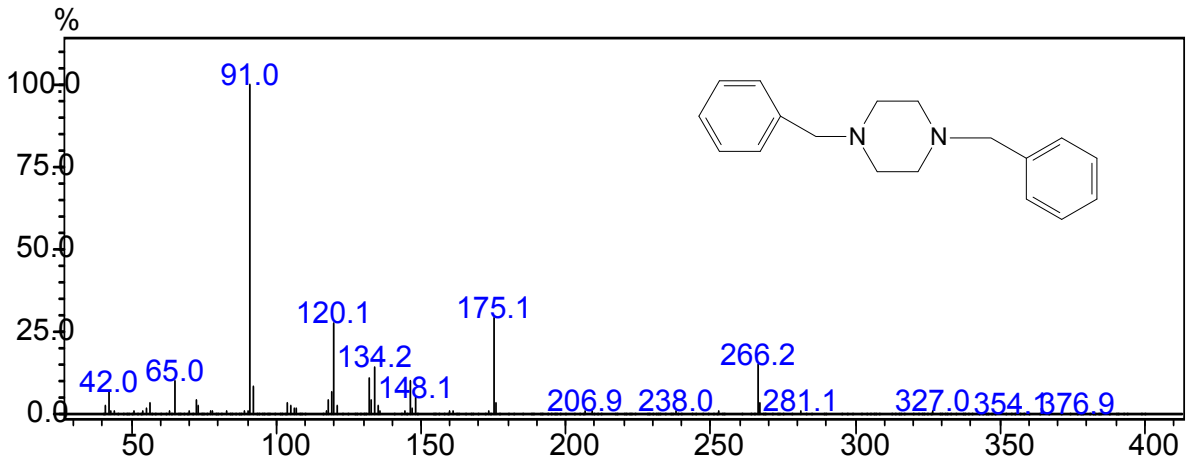
(I) 1-(4-METHOXYPHENYL)PIPERAZINE (pMeOPP)



(J) 1-(4-CHLOROPHENYL)PIPERAZINE (pCPP)



(K) 1,4-DIBENZYLPIPERAZINE (DBZP)



IMMUNOASSAY

		100 micrograms / ml			10 micrograms / ml		1 microgram / ml
		mAMP	**AMP**	**MET**	**mAMP**	**MET**	**mAMP**
A	**BZP**	P	N	N	P	N	?P
B	**pFPP**	P	N	N	P	N	?P
C	**TFMPP**	N	N	N	N	N	N
D	**mMPP**	P	N	N	P	N	N
E	**pMPP**	P	N	N	P	N	P
F	**oCPP**	P	N	?N	P	?N	N
G	**oMeOPP**	N	N	N	N	N	N
H	**mCPP**	?P	N	N	N	N	N
I	**pMeOPP**	P	N	N	P	N	P
J	**pCPP**	P	N	N	P	N	N
K	**DBZP**	N	N	N	N	N	N

Test		**Cutoff**
mAMP	Syva RapidTest d.a.u. Methylamphetamine	1 microgram / ml
AMP	Syva RapidTest d.a.u. Amphetamine	1 microgram / ml
MET	Acon Methylamphetamine	1 microgram / ml

P	positive
N	negative
-	not tested

Occurrence of the compounds in products found in UK

		in UK tablets/capsules
A	**BZP**	Yes
B	**pFPP**	Yes
C	**TFMPP**	Yes
D	**mMPP**	No
E	**pMPP**	No
F	**oCPP**	No
G	**oMeOPP**	No
H	**mCPP**	Yes
I	**pMeOPP**	Yes
J	**pCPP**	?
K	**DBZP**	Yes

Reaction with Marquis Reagent

		Marquis reagent
A	**BZP**	N
B	**pFPP**	N
C	**TFMPP**	N
D	**mMPP**	N
E	**pMPP**	N
F	**oCPP**	N
G	**oMeOPP**	very pale pink
H	**mCPP**	N
I	**pMeOPP**	N
J	**pCPP**	N
K	**DBZP**	O

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