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**THE METABOLISM AND PHARMACOKINETICS OF BZP AND TFMP  
– ‘PARTY PILL’ DRUGS**

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**A THESIS SUBMITTED IN FULFILLMENT OF THE REQUIREMENTS  
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY,  
FACULTY OF MEDICAL AND HEALTH SCIENCES,  
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## Abstract

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Benzylpiperazine (BZP) and trifluoromethylphenylpiperazine (TFMPP) are recreational drugs and the major constituents of a number of 'party pills'. Previous studies of these drugs have indicated that they may be metabolised by hepatic enzymes of the cytochrome P450 (CYP) family. However, the metabolism, pharmacokinetic properties and drug interactions of these drugs are poorly understood. This thesis aimed to develop and apply an analytical method to the detection of these drugs, to investigate their *in vitro* and *in vivo* biotransformation, to describe their pharmacokinetic properties in humans and describe the potential for drug-drug interactions.

An analytical method consisting of a reversed phase HPLC system coupled with MS using an Agilent Zorbax C18 HPLC column (4.6 x 150 mm, 5 µm) with guard column (C18, 4.6 x 10 mm, 5 µm) at 20 °C and a mobile phase of ammonium formate buffer (pH 4.5, 0.01 M, solvent A) and acetonitrile (solvent B) with a phase gradient and total run time of 15 minutes was developed and validated for the detection of BZP and TFMPP plus three hydroxylated metabolites in plasma.

*In vitro* inhibition assays with human liver preparations were used to study the metabolism of these drugs. By using inhibitors quinidine, furafylline and troleandomycin it was found that CYP2D6, CYP1A2 and CYP3A4 metabolise both BZP and TFMPP. CYP2D6 poor metaboliser status was shown to compromise metabolism of TFMPP both *in vitro* and *in vivo*. For the human pharmacokinetic study, three groups of seven healthy human participants were dosed with either BZP HCl (200 mg) or TFMPP HCl (60 mg) or both drugs (100 mg of BZP HCl and 30 mg of TFMPP HCl). BZP and TFMPP reached maximum plasma concentrations of 262 ng/mL and 24.1 ng/mL at 75 minutes and 90 minutes respectively, and were cleared from the plasma of participants within 24 hr. *In vitro* and *in vivo* interactions were evident in this data, most notably the *in vivo* inhibition of the hydroxylation of each drug in the presence of the other.

In summary, this thesis presents the results of some of the first studies on the metabolism and pharmacokinetics of these drugs in humans and sets the stage for future studies on the pharmacology of these commonly-used recreational drugs.

**We shall not cease from exploration  
And the end of all our exploring  
Will be to arrive where we started  
And know the place for the first time.**

**-T. S. Eliot**

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## Abbreviations

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[S]	substrate concentration
$\lambda_{\max}$	wavelength demonstrating maximal absorbance
$\mu\text{m}$	micrometers/ microns
$\mu\text{g}$	microgram
$\mu\text{L}$	microlitres
$\mu\text{M}$	micromolar
3-OH BZP	3-hydroxyl benzylpiperazine
4-OH BZP	4-hydroxyl benzylpiperazine
4-OH TFMPP	4-hydroxyl trifluoromethylphenyl piperazine
5-HT	5-hydroxytryptamine (serotonin)
ACN	acetonitrile
ADHD	attention-deficit hyperactive disorder
Ae	amount of drug excreted
ANOVA	analysis of variance
AUC	area under curve
BMI	body mass index
BRUMS	Brunel Mood Scale
BSA	bovine serum albumin
BZP	1-benzylpiperazine
C.I.	confidence interval
CL	rate of clearance
CL/F	apparent clearance
$C_{\max}$	peak concentration
CNS	central nervous system
CYP	cytochrome P450
DA	dopamine
DDI	drug-drug interaction
DXM	dextromethorphan
EED	ethinylestradiol
EM	extensive metaboliser
ESI	electrospray ionisation
F	bioavailability
g	gravity
hr	hours
HPLC	high-performance liquid chromatography
kg	kilogram
$K_i$	inhibition constant
$K_m$	Michaelis constant
L	litres

LC	liquid chromatography
LSD	lysergic acid diethylamide
M	molar
m/z	mass/charge
mCPP	1-(3-chlorophenyl) piperazine
MBZP	4-methyl-1-benzyl piperazine
MDBP	1-(3,4-methylenedioxybenzyl) piperazine
MDEA	3,4-methylenedioxy-N-ethylamphetamine
MDMA	(3,4-methylenedioxy)methamphetamine
MeOH	methanol
MeOPP	1-(4-methoxyphenyl) piperazine
min	minute
mg	milligram
mL	millilitres
mm	millimetres
mM	millimolar
mol	mole
MPP <sup>+</sup>	1-methyl-4-phenylpyridinium
MR	metabolite ratio
MS	mass spectrometry
n	sample size
NA	noradrenaline
NADPH	nicotinamide adenine dinucleotide phosphate
ng	nanogram
nm	nanometres
nmol	nanomoles
NonMEM	non-linear mixed effects modelling
OPZ	omeprazole
PD	pharmacodynamic
PET	positron emission tomography
pFPP	1-(4-fluorophenyl) piperazine
PK	pharmacokinetic
PM	poor metaboliser
psig	pound-force per square inch gauge
R.S.D	relative standard deviation
R <sup>2</sup>	square of the correlation coefficient
S.D	standard deviation
SCX	strong cation exchange
SEM	standard error of the mean
SIM	single-ion monitoring
t <sub>½</sub>	half-life
TAO	troleandomycin

TBA	tolbutamide
TFMPP	1-(3-trifluoromethylphenyl) piperazine
THC	tetrahydrocannabinol
THF	tetrahydrofuran
TIC	total ion chromatogram
$T_{lag}$	lag time
TLC	thin-layer chromatography
$T_{max}$	time taken to reach peak concentration
UV	ultraviolet
V	voltage
V	reaction rate
V/F	volume of distribution/bioavailability
v/v	volume for volume
VAS	visual analogue scale
$V_{max}$	maximum reaction rate
w/v	weight for volume