Towards the Development of a Benzylpiperazine Specific Molecular Imprinted Polymer

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Doctor of Philosophy (Chemistry)

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Signature: .................................................. Date: ............................
To

My Family and Peter

for all your love, support, encouragement and understanding.
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Abbreviations

$^{13}$C NMR  Carbon NMR
$^1$H NMR  Proton NMR
4VP  4-vinyl pyridine
6-MAM  6-monoacetylmorphine
AA  Acrylic acid
AAm  Acrylamide
AFM  Atomic force microscopy
AIBN  2,2’ Azob(isobutyronitrile)
AN  Acetonitrile
ATS  Amphetamine type substances
BET  Brunauer Emmett and Teller
BJH  Barret, Joyner and Halenda
BZP  Benzylpiperazine
CHCl$_3$  Chloroform
CNS  Central nervous system
CO  Cocaine
DEA  Drug Enforcement Administration
DMSO  Dimethyl sulfoxide
DSC  Differential scanning couliometry
DVB  Divinyl benzene
EGDMA  Ethylene glycol dimethacrylate
EPH  Ephedrine
EtOAc  Ethyl acetate
FM  Functional monomer
FT-IR  Furier transform-infrared
GC-MS  Gas chromatography - mass spectrometry
H₃PO₄  Phosphoric acid
HCl    Hydrochloric acid
HEM    2-Hydroxyethyl methacrylate
HMCA   7-Hydroxy-4-methylcoumarin acrylate
HPLC   High pressure liquid chromatography
IA     Itaconic acid
KCl    Potassium chloride
KH₂PO₄ Dihydrogen phosphate
KOH    Potassium hydroxide
LOD    Level of detection
LSD    Lysergic acid diethylamide
MAA    Methacrylic acid
MAAm   Methacrylamide
mCPP   1-(3-Chlorophenyl)piperazine
MDA    3,4-Methylenedioxymphetamine
MDBP   1-(3,4-Methylenedioxyphenyl)piperazine
MDMA   3,4-Methylenedioxy-N-methylamphetamine
MDMA   3,4-Methylenedioxymethamphetamine
MIP    Molecular imprinted polymer
MISPE  Molecular imprinted solid phase extraction
MO     Morphine
mTFMPP 1-(3-Trifluoromethylphenyl)piperazine
NaHCO₃ Sodium carbonate
NaOH   Sodium hydroxide
NC     Non-covalent
NDPSC  National Drugs and Poisons Scheduling Committee
NIP    Non-imprinted polymers
NMR    Nuclear magnetic resonance
NOBE   N,O-bis-methacryloyl ethanolamine
OMNiMIP One monomer molecularly imprinted polymer
PETA   Pentaerythritol triacrylate
PHP    Phenylpiperazine
pMeOPP 1-(4-Methoxyphenyl)piperazine
SC     Semi-covalent
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<td>SEM</td>
<td>Scanning electron microscopy</td>
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<tr>
<td>SNS</td>
<td>Sympathic nervous system</td>
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<td>STY</td>
<td>Styrene</td>
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<tr>
<td>SUSDP</td>
<td>Standard for the Uniform of Scheduling of Drugs and Poisons</td>
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<td>T</td>
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<tr>
<td>TEGDMA</td>
<td>Tetraethylene glycol dimethacrylate</td>
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<td>TGA</td>
<td>Therapeutic Goods Administration</td>
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<tr>
<td>TGA</td>
<td>Thermal gravitational analysis</td>
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<td>TRIM</td>
<td>Trimethylolpropane trimethacrylate</td>
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<td>VOC</td>
<td>Volatile organic compound</td>
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<tr>
<td>XL</td>
<td>Cross-linker</td>
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Abstract

Molecular imprinting has proved to be an effective technique for the creation of artificial recognition sites within a polymer matrix. These synthetic receptors known as MIPs, are cheap, are relatively simple to prepare and can be tailor made for potentially any target including large molecular-weight molecules. Two approaches, non-covalent (self assembly) and semi-covalent, have been employed to prepare MIPs for benzylpiperazine (BZP), a dominant bioactive compound in a new class of piperazine-base designer drugs. To the best of my knowledge, this is the first report on the synthesis of BZP MIPs via either approach.

Non-covalent MIPs were prepared in 1:1, 1:2 and 1:4 template:monomer ratios employing itaconic acid (IA), methacrylic acid (MAA) and acrylic acid (AA), identified through molecular modelling and NMR spectroscopy studies as favourable functional monomers, with two cross-linkers, ethyleneglycol dimethacrylate (EGDMA) and trimethylolpropane trimethacrylate (TRIM), shown to exhibit the lowest affinity to BZP, and using acetonitrile (AN) and chloroform (CHCl₃) as porogens. Of the 30 polymer formulations assessed, only MIPs prepared with MAA in 1:1 and 1:2 ratios in CHCl₃ exhibited moderate to impressive imprinting (I > 2).

The novel synthesis of benzylpiperazine (4-vinylphenyl) carbamate was required for the preparation of the semi-covalent MIPs. This was obtained through the multi-step synthesis of 4-vinylphenol with thiophosgene, the product of which was reacted with BZP, neat. Two polymers were prepared in CHCl₃ using EGDMA and TRIM as cross-linker.
The semi-covalent MIPs exhibited higher imprinting effect than the non-covalent MIPs. The highest imprinting factor obtained for the non-covalent polymers was 7.7 for the BZP:MAA 1:2 TRIM polymer bound in CHCl₃ while the semi-covalent polymer prepared with TRIM gave an imprinting factor of 28. For both non- and semi-covalent systems, BZP binding equilibrium was established with two hours or less. Rapid BZP up-take was observed for all polymers, with more than 80% of the equilibrium up-take occurring prior to 10 minutes. Quantitative analysis of the binding isotherm, Scatchard and Langmuir plots, showed the semi-covalent polymers to exhibit a stronger affinity to BZP and more homogeneous binding sites than the non-covalent polymers.

Cross-reactivity and selectivity experiments were carried out in non-competitive and binary competitive environments with morphine (MO), cocaine (CO), ephedrine (EHP) and phenylpiperazine (PHP). Low affinity was observed for MO and CO analytes, with high selectivity for BZP in these systems. For PHP an equivalent affinity was observed, while the polymers had a greater affinity for EPH. No selectivity was observed for EPH in the competitive system. Both non-covalent and semi-covalent MIPs exhibited high selectivity towards BZP in the presence of MO and CO analytes but equivalent affinity towards PHP and EPH.