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Regioisomeric bromodimethoxy benzyl piperazines related to the designer substance 4-bromo-2,5-dimethoxybenzylpiperazine: GC–MS and FTIR analysis

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ABSTRACT

A series of seven regioisomeric bromodimethoxy benzyl piperazines including the designer benzylpiperazine (4-bromo-2,5-dimethoxybenzylpiperazine) were synthesized and their analytical profiles evaluated using GC–MS and FT-IR. The mass spectra for the seven regioisomeric bromodimethoxy benzyl piperazines are almost identical with only the two 2,3-dimethoxy isomers showing one unique major fragment ion at *m/z* 214/216. Thus, mass spectrometry alone does not provide for the confirmation of identity of any one of the seven compounds to the exclusion of the other isomers. Perfluoroacylation of the secondary amine nitrogen for each of the seven regioisomers gave mass spectra showing some differences in the relative abundance of fragment ions without the appearance of any unique fragments for specific confirmation of structure. Attenuated total reflection infrared spectroscopy provides direct confirmatory data for differentiation between the seven regioisomeric aromatic ring substituted bromodimethoxy benzyl piperazines. Mixtures of the seven piperazine PFP derivatives were successfully resolved via capillary gas chromatography using a relatively polar stationary phase composed of 100% trifluoropropyl methyl polysiloxane.

1. Introduction

Structural modifications of drugs of abuse are well known for the amphetamine-derived designer drugs. The most common variations involve the introduction of a methylenedioxy, dimethoxy or bromo moiety into the aromatic ring of amphetamine leading to compounds such as 3,4-methylenedioxyamphetamine (MDA), 2,5-dimethoxyamphetamine (2,5-DMA) and 4-bromo-2,5-dimethoxyamphetamine (DOB), repectively. In addition to the amphetamines, a series of piperazine-derived compounds have recently entered the illicit drug market and represent a new group of designer drugs. Many of these piperazines are reported to bind to serotonin receptors of the human central nervous system [1]. The 1-aryl-piperazines show good binding affinity to serotonin receptors [1] and the affinity is made more selective with the appropriate aromatic ring substituents [2]. It appears that *N*-benzylpiperazine and 3-trifluoromethylphenyl piperazine (3-TFMPP) are among the most commonly abused compounds of this group [3].

Structural modifications similar to those found in the amphetamines are also encountered in the piperazine compounds. 1-(3,4-methylenedioxybenzyl)-piperazine (3,4-MDBP) is the methylenedioxy analogue of *N*-benzylpiperazine (BZP), a scheduled compound in the USA [4]. Recently, 3,4-MDBP has been described as producing psychoactive effects similar to those of 3,4-methylenedioxymethamphetamine (MDMA) [5–7]. Furthermore, 4-bromo-2,5-dimethoxy-benzylpiperazine (2C-B-BZP) is a psychoactive compound of the piperazine chemical class which has been sold as a "designer drug" [8,9] and is reported to produce stimulant effects similar to those of benzylpiperazine (BZP) [9]. A clandestine sample of 4-bromo-2,5-dimethoxybenzylpiperazine was identified in a street drug sample in Germany in 2006 [8]. The analytical structure elucidation and differentiation of 4-bromo-2,5-dimethoxybenzylpiperazine and one of its regioisomers 2-bromo-4,5-dimethoxybenzylpiperazine was reported using gas chromatography–mass spectroscopy (GC–MS), product ion spectroscopy (GC–MS/MS), and nuclear magnetic resonance (NMR) spectroscopy [8].

The most likely method for the synthesis of (2C-B-BZP) is via the reductive amination of piperazine with 4-bromo-2,5-

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dimethoxybenzaldehyde under reducing conditions. Several regioisomeric bromodimethoxybenzaldehydes are commercially available and uncontrolled, thus a number of monobrominated dimethoxybenzylpiperazines can be prepared by the same synthetic methodology from readily available precursors. The pharmacological effects for the other regioisomers have not been extensively described. Thus, analytical differentiation among the brominated derivatives of these regioisomeric dimethoxybenzylpiperazines is an important issue in forensic drug chemistry.

Gas chromatography–mass spectrometry (GC–MS) is the most widely used technique in the analysis of controlled substances in forensic laboratories [10–21]. The regioisomer issue is extremely important when some of these molecules are legally controlled drugs or controlled precursor substances [10–15]. This study is concerned with the differentiation of the seven monobrominated products resulting from the six possible regioisomeric dimethoxybenzylpiperazines. Such compounds have mass spectral equivalency and similar chromatographic elution properties. Those substances co-eluting in the chromatographic system and having common mass spectra could be misidentified. The ability to distinguish between these regioisomers directly enhances the specificity of the analysis for the target molecules.

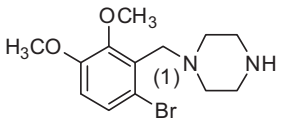
Previous studies [11–14] have shown that chemical derivatization methods (primarily acylation) can be used to add analytical specificity to the analysis of regioisomeric primary and secondary amines of varying side-chain structure. Derivatization can alter major fragmentation pathways often providing additional structural information about an individual isomer as well as altered chromatographic properties [11–14]. However, amine acylation is less successful for the identification of regioisomeric aromatic ring substitution patterns and is not useful for tertiary amines that do not form stable acylation products.

This group of seven compounds represents the complete set of monobromonated products of all possible regioisomeric dimethoxybenzylpiperazines. Analytical differentiation of the regioisomeric bromodimethoxy benzyl piperazines (compounds 1–7 in Fig. 1) can be a significant issue since all these isomers represent likely designer analogues in this series and methods to differentiate them have not been reported. The aim of this study is to evaluate analytical methods using GC–MS and infrared spectroscopy (FTIR) to characterize and differentiate among this set of ring regioisomeric compounds.

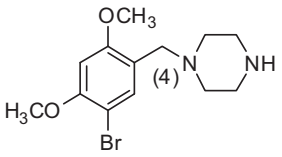
2. Experimental

2.1. Instrumentation

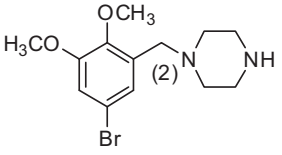
GC–MS analysis was performed using an Agilent Technologies (Santa Clara, CA) 7890A gas chromatograph and an Agilent 7683B auto injector coupled with a 5975C VL Agilent mass selective detector. The mass spectral scan rate was 2.86 scans/s. The GC was operated in splitless mode with a helium (grade 5) flow rate of 0.7 mL/min and a column head pressure of 10 psi. The MS was operated in the electron impact (EI) mode using an ionization voltage of 70 eV and a source temperature of 230 °C. The GC injector was maintained at 250 °C and the transfer line at 280 °C.



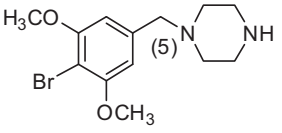
(1) 6-Br-2,3-DMBP
6-Bromo-2,3-Dimethoxybenzylpiperazine



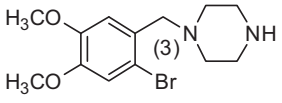
(4) 5-Br-2,4-DMBP
5-Bromo-2,4-Dimethoxybenzylpiperazine



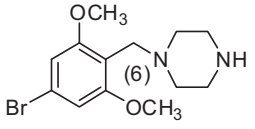
(2) 5-Br-2,3-DMBP
5-Bromo-2,3-Dimethoxybenzylpiperazine



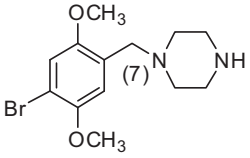
(5) 4-Br-3,5-DMBP
4-Bromo-3,5-Dimethoxybenzylpiperazine



(3) 2-Br-4,5-DMBP
2-Bromo-4,5-Dimethoxybenzylpiperazine



(6) 4-Br-2,6-DMBP
4-Bromo-2,6-Dimethoxybenzylpiperazine



(7) 4-Br-2,5-DMBP
4-Bromo-2,5-Dimethoxybenzylpiperazine
(2C-B-BZP)

Fig. 1. Structures of the seven bromodimethoxy benzyl piperazines in this study.