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Differentiation of methylenedioxybenzylpiperazines (MDBPs) and methoxymethylbenzylpiperazines (MMBPs) By GC-IRD and GC–MS

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ABSTRACT

The substituted benzylpiperazines, 3,4-methylenedioxybenzylpiperazine (3,4-MDBP), its regioisomer 2,3-methylenedioxybenzylpiperazine (2,3-MDBP) and four isobaric ring substituted methoxymethylbenzylpiperazines (MMBP) have almost identical mass spectra. Perfluoroacylation of the secondary amine nitrogen of these isomeric piperazines gave mass spectra with differences in relative abundance of some fragment ions. However, the spectra did not yield any unique fragments for specific identification of one isomer to the exclusion of the other compounds.

Gas chromatography coupled with infrared detection (GC-IRD) provides direct confirmatory data for the structural differentiation between the six isomers. The mass spectra in combination with the vapor phase infrared spectra provide for specific confirmation of each of the isomeric piperazines. The underivatized and perfluoroacyl derivative forms of the ring substituted benzylpiperazines were resolved on the polar stationary phase Rtx-200.

1. Introduction

Several compounds of the 1-arylpiperazine type are known to have good binding affinity for serotonin receptors of the human central nervous system [1]. This affinity is made more selective with the appropriate aromatic ring substituents [2]. This new class of potential designer drugs includes a variety of benzylpiperazine substitution patterns such as N-benzylpiperazine, 1-(3,4-methylenedioxybenzyl)-piperazine and phenylpiperazines such as 1-(3-trifluoromethyl-phenyl)piperazine, 1-(3-chlorophenyl)piperazine and 1-(4-methoxyphenyl)piperazine [3]. The most commonly abused compounds of this group are N-benzylpiperazine and 3-trifluoromethylphenylpiperazine (3-TFMPP) [3]. Both N-benzylpiperazine and 3-trifluoromethylphenylpiperazine (3-TFMPP) were placed into Schedule 1 of the United States Controlled Substance Act in September 2002 [4]. Recently, 3,4-methylenedioxybenzylpiperazine (3,4-MDBP) has been described as producing psychoactive effects similar to those of 3,4-methylenedioxymethamphetamine (MDMA) [5–7]. Some of these piperazine compounds are commercially available and are not yet under specific legal control [8].

The 3,4-methylenedioxybenzylpiperazine has been reported as a potential drug of abuse while the pharmacology of its 2,3 regioisomer has not yet been reported. Indeed the analysis of 3,4-MDBP in biological and forensic samples has been the focus of several studies in recent years [9–12]. A recent report [13] showed that 3,4-MDBP cannot be differentiated from its 2,3 regioisomer using mass spectrometry even after chemical derivatization. However, GC-IRD provided for discrimination between these two compounds based on differences in position and intensity in IR bands. Gas chromatography mass spectrometry (GC–MS) is the most commonly employed technique in the analysis of controlled substances in forensic laboratories [14–19].

The identification of psychoactive drugs in a number of chemical categories is complicated by the existence of regioisomeric and isobaric substances related to the target drug [9–15]. These isomeric substances are a challenge to forensic analyses that must depend heavily on mass spectrometry for confirmation level data. Regioisomeric and isobaric substances have the same nominal mass and many of these molecules yield essentially identical mass spectra. Previous studies [10,15] have shown that chemical derivatization methods (primarily perfluoroacylation) can be successfully applied to discriminate among many isomeric compounds. Derivatization can alter major fragmentation pathways often providing additional structural information about an individual isomer as well as altered chromatographic properties [10–12,14,15]. However, in some cases,

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derivatization does not yield characteristic mass spectral fragment ions for individual isomers [12].

Infrared spectroscopy is considered a confirmation method for the identification of organic compounds due to the uniqueness of infrared spectra for very similar organic molecules. Gas chromatography with infrared detection (GC-IRD) is characterized by scanning quickly enough to obtain vapor phase IR spectra of compounds eluting directly from capillary GC columns. This technique has been successfully used in the identification of amphetamine isomers [20] as well as side chain regioisomers of methamphetamine and phentermine [21]. Recently, GC-IRD studies have been described for the differentiation of ring and side chain substituted ethoxyphenethylamines, methoxymethcathinones and methylenedioxymethamphetamines [22] as well as ring substituted phenylacetones [23].

The methoxymethylbenzylpiperazines have an isobaric relationship with 2,3 and 3,4-MDBP. Isobaric compounds are those with the same nominal mass but with different elemental composition. Substitution of the methoxy and methyl groups at the 2,3 and 3,4 positions of the aromatic ring gives four possible compounds that mimic the positions of the 2,3 and 3,4-methylenedioxy group on the aromatic ring. These compounds produce almost identical mass spectra to the substance of abuse 3,4-MDBP and its 2,3 regioisomer. While accurate mass measurements using gas chromatography coupled with time-of-flight mass spectrometry can differentiate between isobaric compounds, this technique does not distinguish between isomeric substances. The lack of analytical reference standards of these compounds makes their identification and discrimination a significant challenge to forensic drug chemistry. This report will describe GC-IRD and GC–MS studies on the two regioisomeric ring substituted methylenedioxybenzylpiperazines and their isobaric ring substituted methoxymethylbenzylpiperazines in an effort to offer methods for discrimination among these compounds.

2. Experimental

2.1. Instrumentation

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

Chromatographic separation was carried out using a capillary column (30 m × 0.25 mm i.d.) coated with 0.50 μm film of 100% trifluoropropyl methyl polysiloxane (Rtx-200). The temperature program consisted of an initial temperature of 100 °C for 1 min, ramped up to 180 °C at a rate of 12 °C/min followed by a hold at 180 °C for 2 min then ramped up to 200 °C at a rate of 10 °C/min and held at 200 °C for 5.0 min.

GC-IRD studies were carried out using a Hewlett–Packard 5890 Series II gas chromatograph and a Hewlett–Packard 7673 auto-injector coupled with an IRD-II

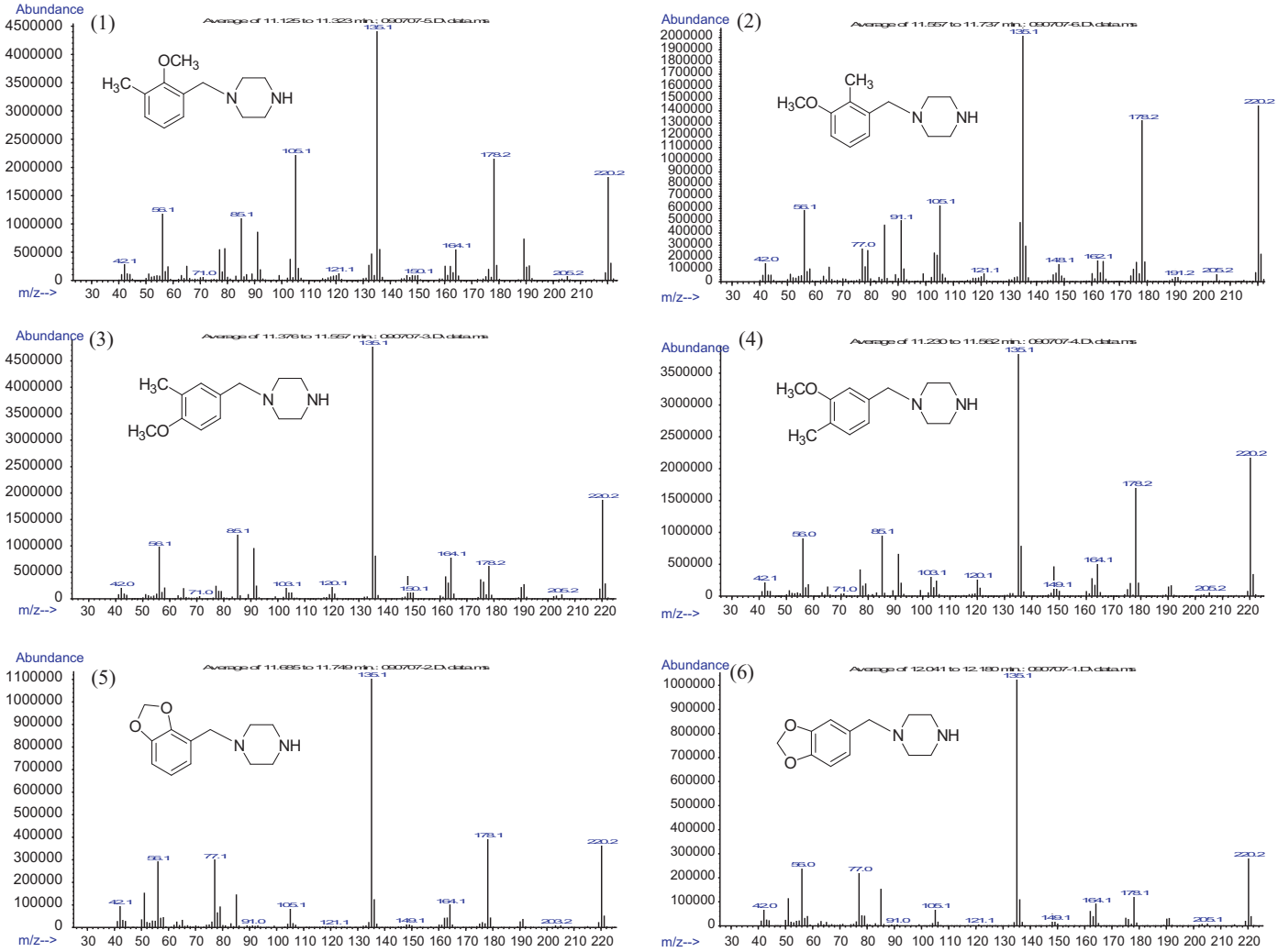

Fig. 1. EI mass spectra of the six methylenedioxy and methoxymethylbenzylpiperazines.