K8 Fragmentation Pathways and Structural Characterization of Synthetic Cathinones Using Electrospray Ionization (ESI) and High Resolution Mass Spectrometry

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After attending this presentation, attendees will understand the importance of structural identification of fragment ions and be able to identify the common fragmentation pathways of synthetic cathinones.

This presentation will impact the forensic science community by increasing fundamental understanding of fragmentation pathways associated with the cathinone designer drugs.

Designer drugs continue to present a number of challenges to the forensic toxicology community. Synthetic cathinones are a growing class of psychostimulants that can be chemically characterized as beta-keto amphetamines. Although derived from cathinone (*Catha edulis*), these synthetic drugs are substituted at the phenyl ring, amino group, or propoanone terminus. The functional substituents greatly influence fragmentation pathways and ion formation in both Electron Impact (EI) and ESI. In addition to their low boiling points and volatility in the base (uncharged) form, several of the cathinones are thermally labile and degrade during Gas Chromatographic (GC) analysis. Many of the cathinones, particularly the tertiary amines (pyrrolidine derivatives), undergo extensive fragmentation in EI, yielding poorly specific mass spectra with a limited number of diagnostic ions for selected ion monitoring. Liquid Chromatography/ Mass Spectrometry (LC/MS)is advantageous from the standpoint of increased thermal stability and the ability to optimize the conditions during ionization to yield highly specific fragment ions using ESI. Moreover, high resolution mass spectrometry is a powerful tool for structural elucidation. This presentation describes the fragmentation pathways and structural characterization of synthetic cathinones using LC/quadrupole Time Of Flight/MS (LC/qTOF/MS).

A validated method for the determination of 22 synthetic cathinones in urine using LC/qTOF/MS has been previously reported. A total of nine isotopically labeled internal standards were used. The principal compounds of interest were: methcathinone; 3-Fluoromethcathinone (3-FMC); 4-Fluoromethcathinone (4-FMC); ethcathinone; ethylone;, methedrone;, buphedrone; butylone; mephedrone; eutylone; 4-Methylethcathinone (4-MEC) ; 3,4-Methylenedioxy-α-Pyrrolidinobutyrophenone (MDPBP); pentedrone; pentylone; 3,4-Dimethylmethcathinone (3,4-DMMC) ; α-Pyrrolidinopentiophenone (α-PVP); 4-Ethylmethcathinone (4-EMC); 4-Methyl-α-Pyrrolidinobutiophenone (MPBP); Methylenedioxypyrovalerone (MDPV); pyrovalerone; and naphyrone. The target compounds include a variety of secondary and tertiary amines, methylenedioxy derivatives, benzylic, and amino substituents. Following optimization of ionization conditions, fragmentation pathways were investigated.

In addition to the formation of stable immonium ions (that predominate EI spectra), other common fragmentation pathways involved neutral losses of water, amines and CH_4O_2. Although non-specific neutral losses (such as water) should be avoided during targeted analyses, formation of phenyloxazole and alkyldioxybenzoyloxonium cations arising from the loss of CH_4O_2 and amines in methylenedioxy derivatives provide improved structural specificity. Synthetic cathinones bearing a tertiary amine are also characterized by stable ions arising from the loss of pyrrolidine. In contrast to the secondary amines, water losses are not observed for the pyrrolidinyl derivatives due to the limited mobility of the hydrogen on the amino group. Many of the ring substituted and non-ring substituted secondary amine synthetic cathinones resulted in the formation of radical cations. Loss of the ketone with subsequent rearrangement to form a cyclic cation was prevalent among the secondary amines.

Tandem Mass Spectrometry (MS/MS) spectra arising from collision-induced dissociation should be evaluated carefully to enhance method specificity, as well as sensitivity. The selection of ions based on abundance alone is strongly discouraged. Structural characterization of fragments and optimization of their abundance during method development is important in terms of specificity and overall robustness of the method. Not only does this approach improve overall analytical performance, but these characteristic losses can also provide useful information for the identification of emerging or as-yet unidentified cathinone analogs and derivatives.

Synthetic Cathinones, Fragmentation, LC/qTOF

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