Test purchase, synthesis and characterization of 3-fluorophenmetrazine (3-FPM) and its ortho- and para-substituted isomers

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Introduction

Over the past number of years in Europe, there has been an unprecedented increase in the number, types and seizures of chemicals frequently referred to as new psychoactive substances (NPS). There was no change to this trend in 2015 as a total of 100 new substances was detected and reported for the first time by the European Union Early Warning System, which brings the total number of substances being monitored by European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) to more than 560.1 The nature of substances available for purchase is not limited to compounds derived from illicit drugs as increasing numbers of compounds derived from medicinal products have also joined the catalogs of NPS suppliers.2

Phephmetrazine & Fluorophenmetrazine

Fluorophenmetrazine (3-methyl-2-phenylmorphine) is a synthetic morphine derivative of amphetamine that includes a phenothiazine skeleton where the terminal amine is incorporated into a morphine ring.3 In the 1950s, phenmetrazine and its N-methyl derivative phendimetrazine (3,4-dimethyl-2-phenylmorphine) were developed within the pharmaceutical setting as sympathomimetic weight-control medications considered to show less abuse liability compared to other amphetamine anorexiants (Figure 1).4

Phenmetrazine is a potent substrate for noradrenaline and dopamine transporters and displays stimulant properties similar to those of amphetamine, whereas phendimetrazine is classified as a pro-drug and exerts its pharmacological effect through biotransformation to methamphetamine.5 The nature of substances available for purchase is not limited to compounds derived from illicit drugs as increasing numbers of compounds derived from medicinal products have also joined the catalogs of NPS suppliers.2

Synthesis

The synthesis procedure (Figure 2) employed for the preparations of 2-, 3- and 4-FPM was selected to give high resolution mass spectra with acceptable mass accuracies consistent with the proposed structures (Figure 3A). It was encouraging to observe that thin layer chromatography (TLC) analysis also facilitated successful separations of the three isomers as evidenced by distinct retardation factors of 0.65, 0.51 and 0.43 for 2-, 3- and 4-FPM, respectively (Figure 3B). This served as a valuable reminder that seemingly basic separation technique should not be discounted when faced with the challenge of dealing with the presence of isomers, particularly when operating within a forensic context where time and financial constraints can be significant. Pharmacological evaluation of the FPM compounds concluded that all three isomers are substrate-like releasing agents at monoamine transporters.5

Characterization

Initial analysis of the underivatized isomers by Gas Chromatography-Mass Spectrometry (GC-MS) failed to obtain separation between meta- and para-substituted 3- and 4-FPM isomers although separation from the 2-FPM isomer was feasible. Derivatization with trifluoroacetic anhydride (TFAA) improved the chromatography results and provided mass spectra with diagnostically useful information. The spectra obtained for FPM-TFAA isomers although separation from the 2-FPM isomer was feasible. The spectra obtained for FPM-TFAA isomers although separation from the 2-FPM isomer was feasible.

The molecular ion at m/z 291 was detectable in all three mass spectra, however an additional ion at m/z 290 was observed in the spectrum of 3-FPM-TFAA. The detection of this ion was rationalized by a possible rearrangement that might have involved the loss of a hydrogen radical and the formation of a thermodynamically more stable mercuric ion. In a study it was shown that FPM isomer may have formed between the carbon at the ortho position of the phenyl ring and the methyl group on the phenyl ring (Figure 3B). The proposed fragmentation pattern for the FPM-TFAA isomers is outlined in Figure 3B. Two dominant fragments were noticed at m/z 70 and m/z 167. The m/z 70 indicates a partial loss of the methyl substituted phenyl ring and the m/z 167 is due to the expulsion of a dissociated methyl group from the molecular ion.2

The product ion spectra obtained from in-source collision induced dissociation (CID) at 3.25 eV for the FPM-TFAA isomers provided elemental compositions with acceptable mass accuracies consistent with the proposed structures (Figure 5A).

Conclusion

The release of new psychoactive substances onto the recreational drug market continues to challenge the drug testing laboratories and academic institutions when attempting to actively engage in the challenges linked to the NPS phenomenon. It is envisaged that thin layer chromatography (TLC) analysis also facilitated successful separations of the three isomers as evidenced by distinct retardation factors of 0.65, 0.51 and 0.43 for 2-, 3- and 4-FPM, respectively (Figure 3B). This served as a valuable reminder that seemingly basic separation technique should not be discounted when faced with the challenge of dealing with the presence of isomers, particularly when operating within a forensic context where time and financial constraints can be significant. Pharmacological evaluation of the FPM compounds concluded that all three isomers are substrate-like releasing agents at monoamine transporters.5

References

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