Metabolism of the new synthetic cannabinoid MDMB-FUBICA and analysis of authentic forensic case samples

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Introduction and Aims

Synthetic cannabinoids (SCs) are firmly established as cannabis alternative and offered worldwide via the Internet as so called 'legal highs'. Within the newly emerging compounds, substances like AB-FUBINACA (Fig. 3.2) or MDMB-FUBINACA (Fig. 3.3) have shown extraordinarily high prevalence and were associated with numerous cases of severe intoxications[1]. Recently, a new SC was seized by the Swedish and the Hungarian federal police, named MDMB-FUBICA (Fig. 3.1), representing the indole derivative of MDMB-FUBINACA.[1] To facilitate a reliable detection of this compound in urine samples, we aimed to identify the *in vivo* phase I main metabolites of MDMB-FUBICA.

Methods

Authentic urine (n=12) and serum (n=2) samples were received in the context of forensic case work at the National Institute of Forensic Toxicology in Hungary. Seized MDMB-FUBICA material was used as reference standard. The *in vivo* metabolic profile of MDMB-FUBICA was investigated using LC-ESI-MS/MS (Fig. 3.30) and LC-ESI-Q-ToF-MS (Fig. 3.31) analyses. In order to provide positive control samples, a pooled human liver microsome (pHLM) assay was applied.[2] A semi-quantitative LC-ESI-MS/MS method (Fig. 3.32) was established and integrated into an existing SC screening method to measure MDMB-FUBICA serum concentrations. Serum concentrations were approximately 0.37 ng/mL and 1.7 ng/mL.

Results and Discussion

In total, 26 *in vivo* metabolites were detected (Fig. 1 and 2). The hydrolysis product of the methyl ester (M23) was the most predominant metabolite in all urine samples and should be used when maximum sensitivity is required, e.g. in terms of abstinence control. Identified metabolites were ranked according to their relative abundance (Fig. 1).

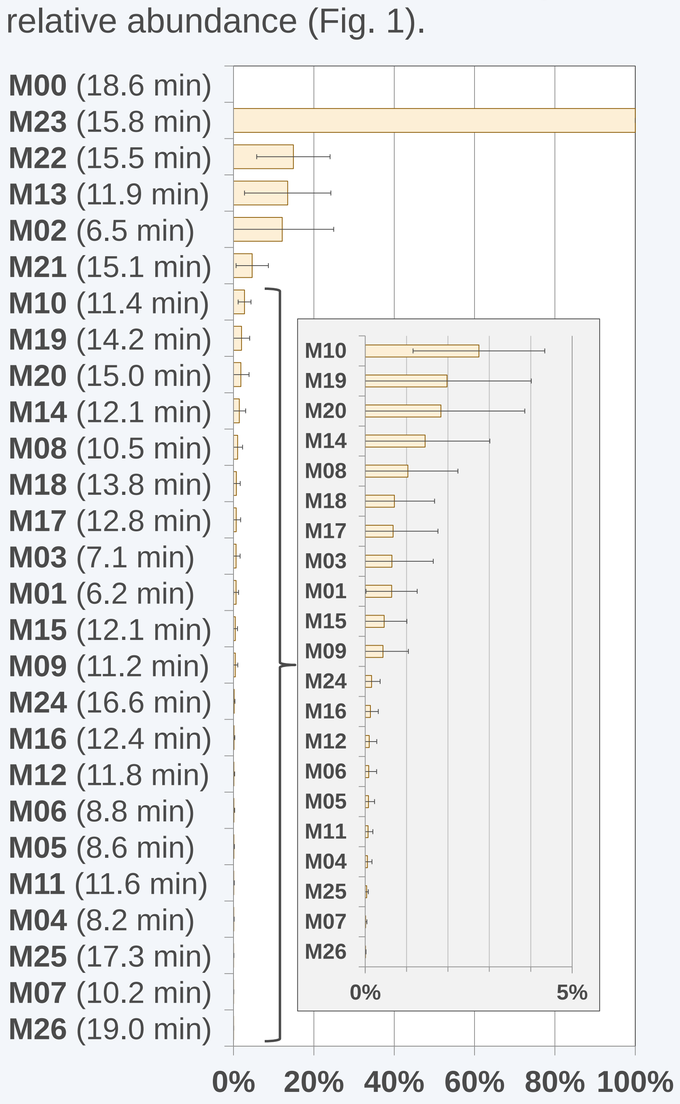

Fig. 1: Ranking of the detected *in vivo* phase I metabolites of MDMB-FUBICA according to their relative abundance in 12 authentic urine samples. Error bars show the RSDs as an indicator for the variation of the rank position within the investigated collective.

Furthermore, oxidations of the *tert*-butyl side chain and the indole ring were observed as preferred metabolic reactions, leading to hydroxy metabolites of MDMB-FUBICA (M00) and its ester hydrolysis product (M23) (Fig. 2).

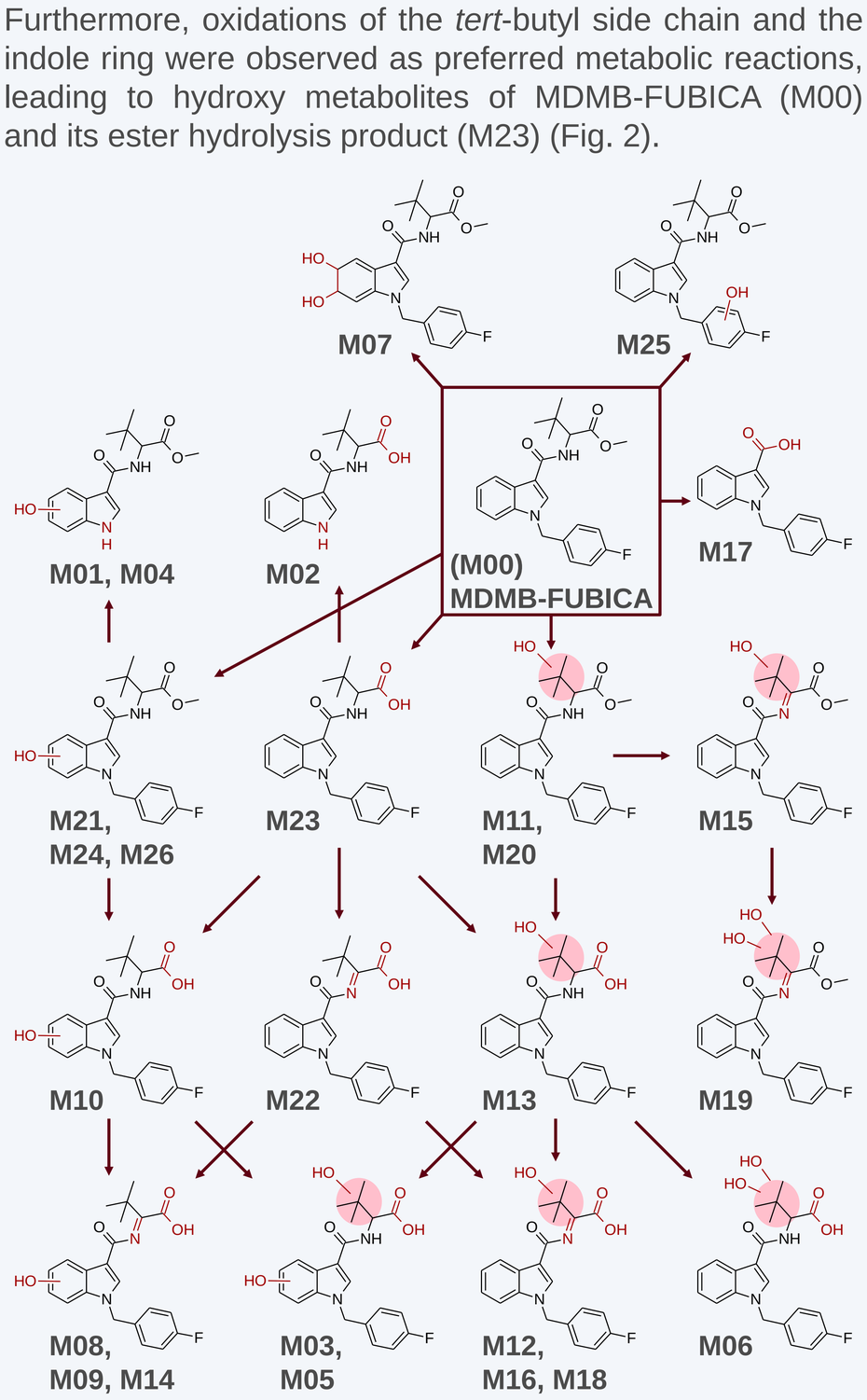

Fig. 2: Postulated phase I metabolic pathway of MDMB-FUBICA *in vivo*.

Interestingly, no pronounced formation of dihydrodiol metabolites was detected for MDMB-FUBICA, although these were described as *in vivo* main metabolites for AB-FUBINACA[3]. This might be due to the differences in the chemical properties of the indole and indazole core structures.

Flip chart

Fig. 3: Please scroll for more details on the discussed parent compounds (3.1-3.3), metabolites (3.4-3.29) and methods (3.30-3.32).

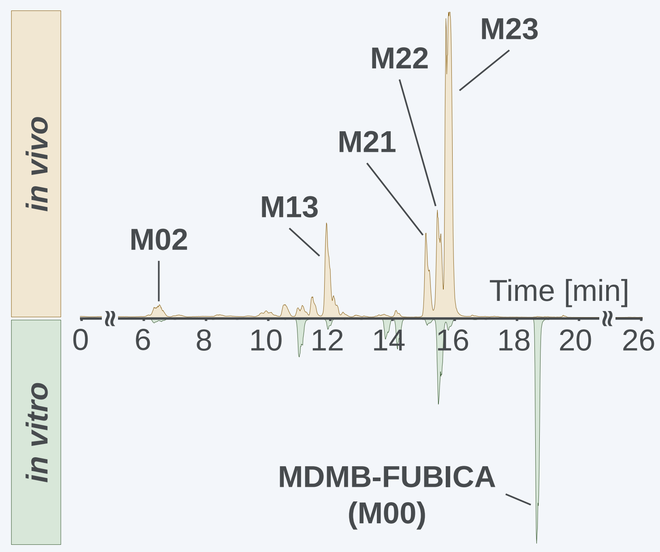

Fig. 4: Total ion chromatogram of the detected phase I metabolic profile of MDMB-FUBICA (M00) *in vivo* (recorded from urine sample 6) and *in vitro* (pHLM assay).

Conclusion

The identified main metabolites can serve as target analytes for a reliable detection of an MDMB-FUBICA uptake. Comparison of the biotransformation of MDMB-FUBICA and AB-FUBINACA shows high similarity, except for the formation of dihydrodiol metabolites[3]. Since ester hydrolysis can lead to metabolites identical to the methyl-valine amide analog ADB-FUBICA, it is recommended to use the MDMB-FUBICA-specific hydroxy metabolites (e.g. M21) for discrimination. Assessing structure-metabolism relationships facilitates postulation of main metabolites of new emerging SCs, and therefore increases the accuracy of predictions for structurally related compounds.

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