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Simultaneous determination of five naphthoylindole-based synthetic cannabinoids and metabolites and their deposition in human and rat hair

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ABSTRACT

The continuing appearance of new synthetic cannabinoids has been a major issue in the field of forensic and clinical toxicology. In response to that, analytical methods for synthetic cannabinoids have been increasingly established in a variety of biological matrices. Since most of synthetic cannabinoids with structure similarity share some enzymatic metabolites, making the interpretation of analytical results and the discovery of the parent drug actually ingested very complicated, the investigation on metabolites of the first generation of synthetic cannabinoids with their relatively short side chains in chemical structure could be more important. Therefore, in the present study, we developed the analytical method for AM-2201, JWH-122 and MAM-2201 with JWH-018 as a precursor and their monohydroxylated metabolites in hair matrix. Also, using a rat model, AM-2201 and its monohydroxylated metabolites were identified and then the ratios of metabolite-to-parent drug were estimated to be used as criteria on external contamination. All analytes were extracted with methanol from washed and cut hair samples and the extracts were injected into LC–MS/MS with electrospray ion source in the positive ionization mode. Matrix effect and recovery were evaluated in hair matrices and no significant variations were observed. The validation results for precision and accuracy were satisfactory in both human and rat hair. The LOD and LOQ were 0.5 pg/10 mg and 1.0 pg/10 mg in human hair and 0.5 pg/20 mg and 1.0 pg/20 mg in pigmented and non-pigmented rat hair, respectively. Additionally, as a result of the animal study, there were not significant differences in the effect of pigmentation on the distribution of AM-2201 and its monohydroxylated metabolites in hair. Wide variations were observed for the concentrations of the naphthoylindole-based synthetic cannabinoids and metabolites in authentic hair samples from nine cases; those were 0.4–59.2 pg/mg for JWH-018, 0.1–0.8 pg/mg for JWH-073, 1.7–739.0 pg/mg for AM-2201, 0.1–402.0 pg/mg for JWH-122, 0.2–276.0 pg/mg for MAM-2201, 0.2–1.1 pg/mg for JWH-018 N-COOH, 0.3–37.2 pg/mg for JWH-018 N-5-OH, 0.3 pg/mg for JWH-073 N-COOH, 0.4 pg/mg for AM-2201 N-4-OH, 0.2–3.1 pg/mg for AM-2201 N-6-OHindole and 0.1–3.5 pg/mg for JWH-122 N-5-OH. This quantitative LC–MS/MS analytical method for five naphthoylindole-based synthetic cannabinoids and their metabolites was very useful to be applied to authentic hair samples, of which their analytical results suggested the incorporation of synthetic cannabinoids in the hair matrix and provided the information on ingested parent drugs.

1. Introduction

The continuing appearance of new synthetic cannabinoids has been a major issue in the field of forensic and clinical toxicology. In pharmacological aspects of synthetic cannabinoids, they have psychoactive effects similar to those of strong cannabinoid type 1 (CB_1) and/or type 2 (CB_2) receptor agonists like

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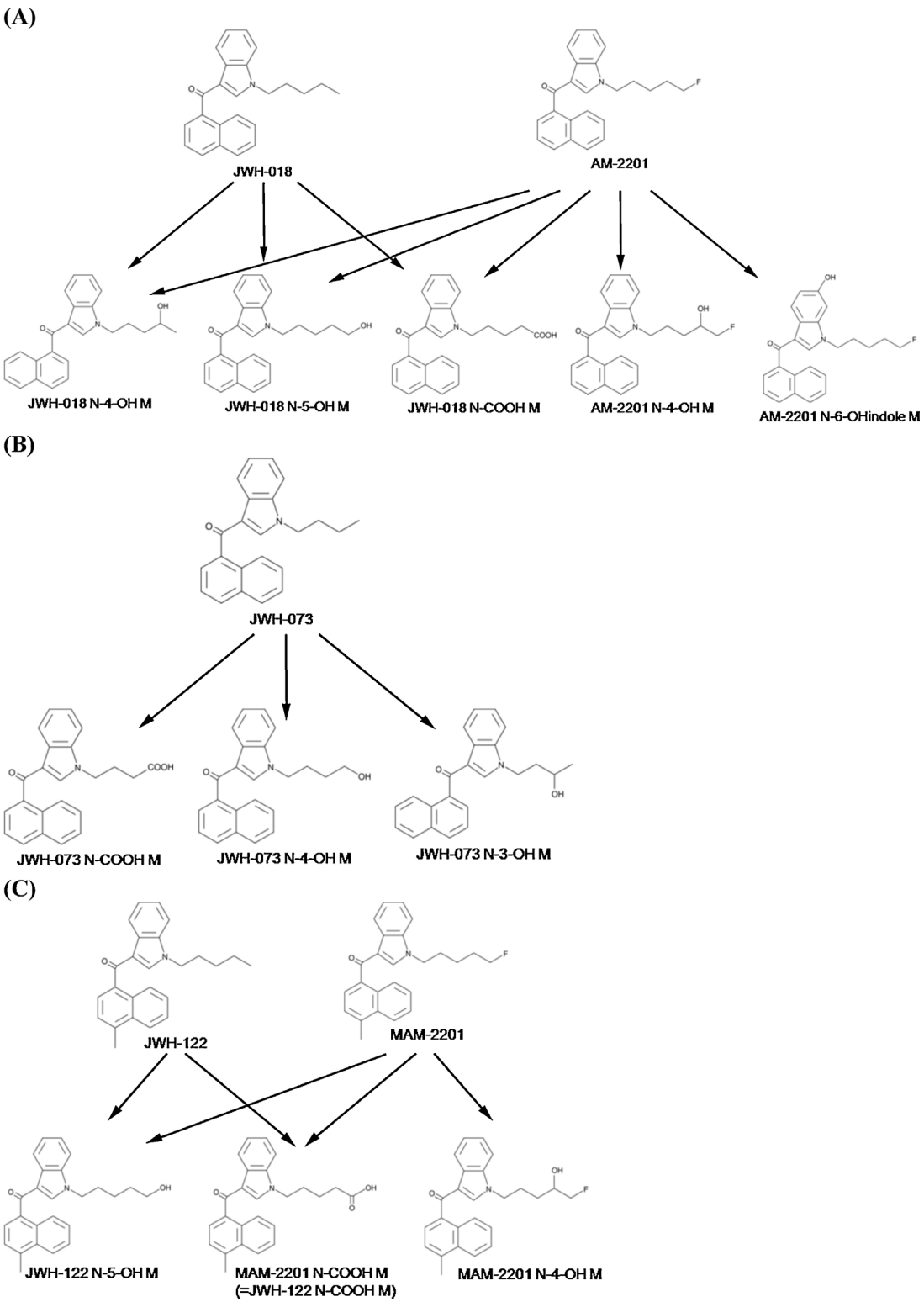

Fig. 1. Proposed phase 1-metabolic pathways of five naphthoylindole-based synthetic cannabinoids: (A) JWH-018, AM-2201 and their metabolites, (B) JWH-073 and its metabolites, and (C) JWH-122, MAM-2201 and their metabolites.

delta-9-tetrahydrocannabinol (Δ^9-THC), a natural constituent of cannabis. On the other hand, it was reported that the ingestion of synthetic cannabinoids can induce disorders such as psychosis, seizures, anxiety, tachycardia, tachyarrhythmia, cardiotoxicity, nausea, vomiting and so on in the central, cardiovascular, gastrointestinal and other systems [1,2]. Some fatal cases were also reported related to synthetic cannabinoids such as AM-2201 (naphthalene-1-yl-[1-[(1-methylpiperidine-2-yl)methyl]-1*H*-indol-3-yl]methanone) and MAM-2201 (4-methylnaphthalen-1-yl-[1-(5-fluoro-pentyl)-1*H*-indol-3-yl]methanone) [3–7]. The chronic administration of aminoalkylindoles may cause carcinogenesis associated to their naphthyl moiety as though naphthalenes have an oncogenic potential [8]. Furthermore, synthetic cannabinoids were biotransformed to be active metabolites