Analysis of Synthetic Cannabinoids in Botanical Material: A Review of Analytical Methods and Findings

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1042-7201/25-1&2/March 2013/27–46/$20.00 •

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REFERENCE: Presley BC, Jansen-Varnum SA, Logan BK: Analysis of synthetic cannabinoids in botanical material: A review of analytical methods and findings; *Forensic Sci Rev* 25:27; 2013.

ABSTRACT: Synthetic cannabinoid analogs have gained a great deal of attention from the forensic community within the last four years. The compounds found to be of most interest to forensic practitioners include those of the following series: JWH, CP, HU, AM, WIN, RCS, and most recently, XLR and UR. Structurally the HU compounds are most similar in structure to Δ^9-tetrahydrocannabinol (THC), the main psychoactive component of marijuana. The novel compounds include cyclohexylphenols, naphthoylindoles, naphthylmethylindoles, naphthylmethylindenes, benzoylindoles, naphthoylpyrroles, phenylacetylindoles, adamantoylindoles, and tetramethylcyclopropylindoles. Many of these compounds are cannabinoid receptor agonists and were originally synthesized for medical research purposes but have recently been appropriated into the illicit drug market. Their psychoactive effects, mimicking those of marijuana, as well as their indeterminate legal status, have made them popular for recreational use. Solutions of the compounds dissolved in organic solvents are sprayed onto botanical material and sold as "herbal incense" products via the Internet, and in smoke shops, convenience stores, and gas stations around the world. Many of the products are labeled "Not for human consumption" in an attempt to circumvent legislation that bans the sale and manufacture of certain compounds and their analogs for human use. The compounds that were first detected following forensic analysis of botanical materials included JWH-018, JWH-073, and CP 47,497 (C7 and C8 homologs). However, in the four years since their appearance the number of compounds has grown, and additional diverse classes of compounds have been detected. Governments worldwide have taken action in an attempt to control those compounds that have become widespread in their regions. This article discusses the history of synthetic cannabinoids and how they have been detected in the illicit drug market. It also discusses the analytical methods and techniques used by forensic scientists to analyze botanical products obtained via the Internet or from law enforcement investigations and arrests.

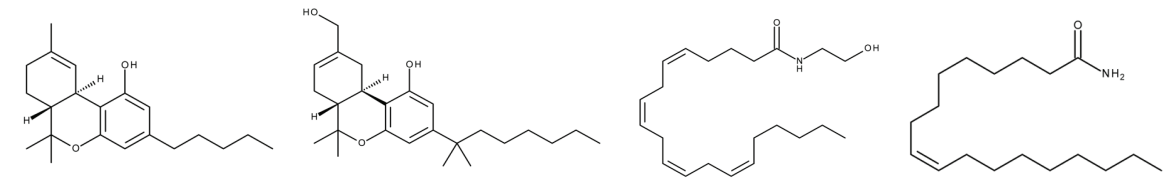
KEY WORDS: Analytical methodology, designer drugs, synthetic cannabinoids, synthetic drug scheduling.

INTRODUCTION

Natural and Endogenous Cannabinoids

In 1964, the chemical structure of Δ^9-tetrahydrocannabinol (THC) (**Structure 1**), the main psychoactive component of marijuana, was elucidated by researchers Raphael Mechoulam (Daniel Sieff Research Institute) and Yechiel Gaoni (Weizmann Institute of Science) in Rehovoth, Israel [31]. The compound was extracted from hashish provided by Israeli law enforcement and analyzed using several means of molecular identification, most importantly nuclear magnetic resonance (NMR) spectroscopy. This structural determination was a significant breakthrough, as the components of cannabis had been long studied, but until this point no definitive structure or full characterization of the major psychoactive component had been determined. With the characterization of THC, new insights began to develop in the study of what would be known as cannabinoids [7].

During the next 24 years, more findings related to cannabinoid compounds emerged. In 1988, a research group published data describing a G protein-coupled receptor in the brain that bound natural cannabinoids including THC and cannabinol. These studies were performed in conjunction with a research group at Pfizer Inc. The study also included analysis of CP 55,940 (**Structure 2**), which was synthesized by Pfizer and proved to exhibit cannabinoid receptor-binding activity [9]. Pfizer also synthesized CP 47,497 (Structure 2), another compound with significant cannabinoid receptor binding [54]. This work sparked more interest in cannabinoid receptor research and in 1990, an article was released that identified the structure and activity of the CB_1 cannabinoid receptor [30]. Soon after the CB_1 receptor discovery, in 1992 Devane et al. identified



Δ^9-Tetrahydrocannabinol (THC) HU-210 Anandamide Oleamide

Structure 1. Classical Compounds — Structures of THC, HU-210, anandamide, and oleamide.

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Brandon C. Presley earned his bachelor's degree in chemistry in 2010 from Temple University (Philadelphia, PA). He is currently a Ph.D. candidate studying analytical chemistry at Temple University (Philadelphia, PA). Mr. Presley is also employed as a forensic chemist at NMS Labs (Willow Grove, PA) performing analyses of drug evidence to identify substances contained therein.

During his tenure as an undergraduate Mr. Presley conducted several research projects in analytical, organic, and inorganic chemistry. These research projects included the analysis of prostaglandins and thromboxanes as inflammatory biomarkers for rheumatoid arthritis; synthesis of heterocyclic indole derivatives for use as inhibitors in disease modeling, and synthesis and characterization of transition metal complexes using benzenedithiol for use in scintillators. In 2009, he joined Intertek Testing Services in Essington, PA, and began working as a chemist performing analyses of various petrochemical products. He has worked in the clinical and forensic toxicology laboratory at NMS Labs, performing analyses of biological specimens for pharmaceuticals and illicit substances; he has also participated in a drug diversion study to determine the ease of tamperability and abuse of pharmaceutical preparations by drug users.

Mr. Presley has given a number of research presentations on his findings at various locations including Drexel University, the Eastern Analytical Symposium, American Chemical Society national meetings, and the Pennsylvania Senate and House of Representatives.

Susan A. Jansen-Varnum received her bachelor's and Ph.D. degrees from the University of Missouri – St. Louis (St. Louis, MO). Upon graduating in 1985, she was awarded a postdoctoral fellowship at Cornell University working with Nobel Prize-winning chemist Roald Hoffmann. She is currently a professor in the Department of Chemistry, Temple University (Philadelphia, PA).

Dr. Jansen-Varnum's research during her fellowship entailed computational modeling applied to catalytic surfaces. At Temple University, she has instructed many courses in general, analytical, physical, and inorganic chemistry and has also served as Ph.D. advisor to a host of students. Dr. Jansen-Varnum has over 120 publications in the scientific literature. Her research interests include the application of experimental and computational tools to understand structure/activity relationships in complex materials and pharmaceuticals; analysis of inflammatory biomarkers for determination of disease states related to hypertension and cardiovascular risk, and analysis of various pharmaceutical preparations in biological specimens for determination of metabolism and use in disease modeling. Experimental applications of Dr. Jansen-Varnum's work includes analytical tools such as LC-MS, GC-MS, and magnetic resonance techniques.

Since 1998 Dr. Jansen-Varnum has also served as science advisor for the Philadelphia branch of the Food and Drug Administration. She has worked on a number of directed research projects concerning drug safety and drug assays. Additionally, she has done consulting work for several organizations including the Eastern Division of the NHRA, Orthovita Inc., Dentsply Caulk, and Integra LifeSciences.

Barry K. Logan earned his bachelor's degree (1982) in chemistry and Ph.D. (1986) degree in forensic toxicology from the University of Glasgow (Glasgow, UK). Dr. Logan is currently director of forensic and toxicological services for NMS Labs (Willow Grove, PA), a leading US provider of esoteric toxicological testing services, specializing in new drug detection and forensic analysis for criminal justice and death-investigation agencies.

Dr. Logan has over 80 publications in toxicology and analytical chemistry, including treatises on the effects of methamphetamine, cocaine, marijuana, alcohol, hallucinogens, and depressant drugs on drivers; postmortem redistribution of drugs, and synthetic drug analysis. Since 2010, Dr. Logan has served as executive director at the Center for Forensic Science Research and Education at the Fredric Rieders Family Renaissance Foundation in suburban Philadelphia. The Center supports educational programs in the forensic sciences for high school and graduate students, and continuing professional education for forensic science professionals.

Dr. Logan is board certified by the American Board of Forensic Toxicologists (ABFT). In recognition of his work and contributions, Dr. Logan has received the American Academy of Forensic Sciences (AAFS) Rolla N. Harger Award and the National Safety Council's Robert F. Borkenstein Award. He currently serves as president-elect of the AAFS.