Fourth generation of synthetic cannabinoid receptor agonists: a summary on the latest insights

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To the Editor,

New psychoactive substances (NPS) are continuously emerging onto the illicit drug market, and methods of detection for routine testing are often unsuitable, mostly due to the limited currently available information as to their structure and pharmacokinetics (1). Among the most abused NPS, synthetic cannabinoids are cannabinoid receptor agonists (SCRAs), also known as synthetic cannabinoids, and were created as unregulated alternatives to cannabis, mimicking the effect of the main psychotropic natural constituent Δ9-tetrahydrocannabinol (THC) on cannabinoid receptors in human body (2). The expected effects of SCRAs include disinhibition, euphoria, relaxation, and altered consciousness (2). However, adverse effects reported in association with SCRAs use involve neurological disorders (e.g., psychosis, agitation, irritability, paranoia, confusion, anxiety), psychiatric episodes (e.g., hallucinations, delusions, self-harm), other physical conditions (e.g., tachycardia, hypertension, arrhythmia, chest pain, tachypnea, gastrointestinal distress, acute kidney injury, nausea, vomiting, fever, hyperglycemia, hypokalemia, sedation) and deaths (2). Over the last twenty years, different chemical classes of SCRAs have been developed, presenting increasingly potent and toxic compounds, and thus posing a potential health threat to consumers. SCRAs were initially developed by academic chemists and pharmaceutical scientists as research tools to explore the endocannabinoid system or probe the specific mechanisms of action and related

health effects of cannabis in animal studies (2,3). The synthesis of selective SCRAs started at Pfizer in 1974 with CP 55940 (2-[(1r,2r,5r)-5-hydroxy-2-(3-hydroxypropyl)cyclohexyl]-5-(2-methyloctan-2-yl) phenol) and then CP-47,497 (cis-3-[2-hydroxy-4(1,1-dimethylheptyl)phenyl]-cyclohexan-1-ol) (4). Following structural leads from the pharmaceutical industry, such as pravadoline ((4-Methoxyphenyl)-[2-methyl-1-(2-morpholin-4-ylethyl)indol-3-yl] methanone or WIN 48,098), Huffman and coworkers from Clemson University, United States, synthesized indole SCRAs with potent cannabimimetic activity, including JWH-018 ((naphthalen-1-yl)(1-pentyl-1H-indol-3-yl)methanone).

Whereas initially synthesized for research purposes, several SCRAs were diverted onto the NPS market at the beginning of the century. For this purpose, several SCRAs started being synthesized in clandestine laboratories, mixed with dried herbal mixtures and introduced in the web market as legal alternatives to cannabis ("legal highs") (5). These preparations have been commonly sold as smokable herbal mixtures called "K2" (in North America), "Spice" (in Europe), "Youcatan", "Chill" or "Black Mamba, and allegedly safe for consumption.

Synthetic cannabinoids were synthesized based on previous SCRAs structures, having a four substructures pattern with an indole, indazole, or carbazol core surrounded by different N-substituents. Overall, new generations of SCRAs were introduced onto the drug market displaying psychoactive effects and anecdotal user reports suggested that it could

produce severe adverse effects such as increased heart rate, panic attacks and convulsions (6).

Eventually, new substances were introduced in the illicit market, as also known as the fourth generation of SCRAs. These substances were: Methyl 2-(1-(4-fluorobutyl)-1H-indazole-3-carboxamido)-3,3-dimethylbutanoate (4F-MDMB-BINACA), Methyl 2-{[1-(4-fluorobutyl)-1H-indole-3-yl]carbonyl} amino}-3,3-dimethylbutanoate (4F-MDMB-BICA), 5-(5-fluoropentyl)-2-(1-methyl-1-phenylethyl)-pyrido[4,3-b]indol-1-one (5F-CUMYL-PeGACLONE), Ethyl 2-[[1-(5-fluoropentyl) indole-3-carbonyl]amino]-3-methyl-butanoate (5F-EMB-PICA), (5-(Bicyclo[2.2.1]hept-2-yl)methyl)-2-(2-phenylpropan-2-yl)-2,5-dihydro-1H-pyrido[4,3-b]indol-1-one (CUMYL-BC-HPMeGACLONE-221), 1-(Cyclobutylmethyl)-N-(2-phenylpropan-2-yl)-1H-indazole-3-carboxamide (CUMYL-CBMINACA), 5-(Cyclobutylmethyl)-2-(1-methyl-1-phenyl-ethyl)pyrido[4,3-b]indol-1-one (CUMYL-CB-MeGACLONE), Methyl 3,3-dimethyl-2-(1-(pent-4-en-1-yl)-1H-indazole-3-carboxamido)butanoate (MDMB-4en-PINACA), N-(1-amino-1-oxobutan-2-yl)-1-(pent-4-en-1-yl)-1H-indazole-3-carboxamide (ABO-4en-PINACA), N-(adamantan-1-yl)-1-(4-fluorobutyl)-1H-indazole-3-carboxamide (4F-ABINACA), N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(4-cyanobutyl)-1H-indole-3-carboxamide (4CN-AB-BUTICA), Methyl-2-(1-(4-cyanobutyl)-1H-indazole-3carboxamido)-3-methylbutanoate (4CN-AMB-BUTINACA), Ethyl 2-(1-(5-fluoropentyl)-1H-indole-3-carboxamido)-3,3-dimethylbutanoate (5F-EDMB-PICA), 1-(5-Fluoropentyl)-3-(4-chloro-1-naphthoyl)indole (5F-JWH-398 or CL-2201), N-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-pentyl-1H-pyrrolo[2,3-b] pyridine-3-carboxamide(ADB-P7AICA),N-(1-amino-1-oxo-3-phenylpropan-2-yl)-1-butyl-1H-indazole-3-carboxamide (APP-BINACA), 1-(Bicyclo[2.2.1] heptan-2-ylmethyl)-N-(2-phenylpropan-2-yl)-1H-indole-3-carboxamide (CUMYL-NBMICA), N-({2-[1-(5-fluoropentyl)-1H-indol-3-yl]-1,3-thiazol-4-yl} methyl)-2-methoxy-N-methylethanamine (PTI-3) (see Figure 1 for chemical structure). Most of these new compounds present an indole or indazole core; an
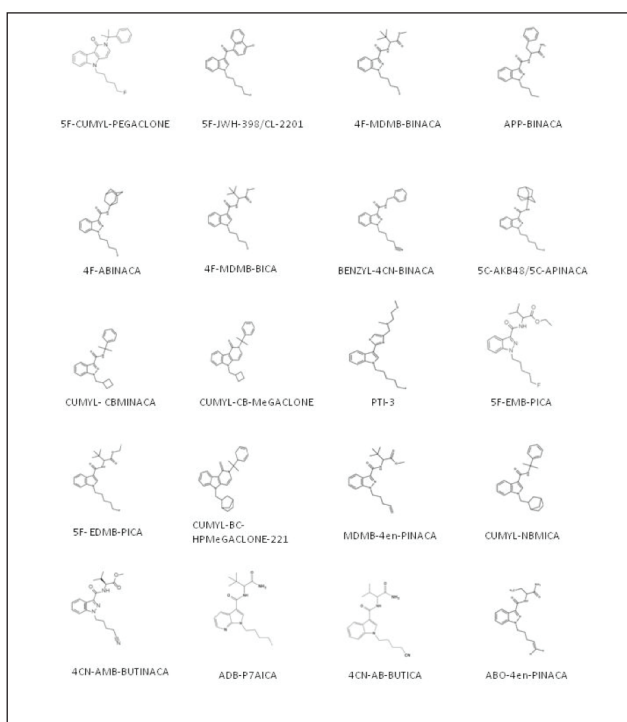

Figure 1. Chemical structure of the last generation of SCRAs.

ester, amide or ketone linker; a quinolinyl, naphthyl, adamantyl, tetramethylcyclopropyl or other moiety ring, and a hydrophobic side chain attached to the nitrogen atom of the indole or indazole core.

To date, there is no information available as to the pharmacokinetics of the last generation of SCRAs. Due the structural analogies with previous generations SCRAs, similar pharmacokinetics are expected, presenting a risk of stronger psychotropic and physiological effects. Because of the fact that SCRAs are not routinely searched in drug testing laboratories, the extent to which these drugs are contributing to morbidity and mortality is unclear. However, forensic scientists, public health officials, and others should be aware of its possible presence and impact (7,8). Toxicologists should incorporate new SCRAs in their detection methods, where possible. The issue that needs addressing lies in the fact that clinicians, lawmakers and the general public are still not fully aware of the potential for toxicity associated with the latest generation of synthetic cannabinoid use.

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Received: 1 October 2021
Accepted: 8 October 2021
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