5F-PB-22
Critical Review Report
Agenda Item 4.12

Expert Committee on Drug Dependence
Thirty-ninth Meeting
Geneva, 6-10 November 2017
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Acknowledgements

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WHO would like to thank the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) for providing information on AB-CHMINACA from the European Union Early Warning System, which includes data reported by the Reitox National Focal Points in the EU Member States, Turkey, and Norway.
Summary

5F-PB-22 (quinolin-8-yl 1-(5-fluoropentyl)-1H-indole-3-carboxylate) is a synthetic cannabinoid receptor agonist (SCRA) that had no history in the scientific literature until its detection emerged in 2013. This substance has been encountered as a synthetic constituent found in herbal smoking mixtures that are sold under a variety of brand names. It is common for retailers to purchase bulk quantities of the synthetic substance and add the synthetic material to plant matter that is then distributed onto the market. However, 5F-PB-22 is also available in powdered form as a “research chemical”. Various UN Member States reported the identification of 5F-PB-22 first in 2013 and data obtained from law enforcement suggest that 5F-PB-22 emerged and peaked in 2013 and 2014 in the United States of America, which then dropped in the following years.

A small number of in vitro and in vivo studies are currently available but the data indicate that 5F-PB-22 binds to and activates human CB₁ and CB₂ receptors at low nanomolar concentrations, and that it induces a number of biological responses also triggered by the naturally occurring phytocannabinoid Δ⁹-THC. In some in vitro assays, 5F-PB-22 acted as a full at both cannabinoid receptors. 5F-PB-22 also fully substituted for Δ⁹-THC in the drug discrimination paradigm and was ~22 times more potent than the training drug, which suggests that 5F-PB-22 may have abuse liability similar to Δ⁹-THC and/or other internationally controlled synthetic cannabinoid receptor agonists.

Reports indicate an increasing trend for SCRAs being implicated in mini epidemics that have been associated with severe adverse drug effects including deaths. Reported adverse drug reactions associated with a range of SCRAs frequently include gastrointestinal (e.g. nausea/hyperemesis), neurological (e.g. hallucination, agitation, anxiety, paranoia, confusion, delusions, catatonia, lethargy, psychosis (including susceptible individuals)), cardiovascular (e.g. tachycardia, hypertension) and renal (e.g. acute kidney failure) features.

The total number of cases reported in the scientific literature that make a causal link with 5F-PB-22 is very small. Intoxications and deaths associated with 5F-PB-22 have been reported but very few details are available. ‘Driving Under the Influence’ cases linked to 5F-PB-22 intoxication revealed significant impairment.

Although not specific to 5F-PB-22, there are indications that socially vulnerable and stigmatized drug users for example found in homeless and prison populations, are increasingly associated with problematic use of SCRA products. Heavy use of SCRAs has been associated with problematic withdrawal symptoms and further research is needed to investigate the underlying mechanisms. Epidemiological data, such as prevalence of use, abuse and dependence information specifically related to 5F-PB-22 could not be identified.
1. Substance identification

A. International Nonproprietary Name (INN)
   Not available.

B. Chemical Abstract Service (CAS) Registry Number
   1400742-41-7 (free base)

C. Other Chemical Names
   1-(5-Fluoropentyl)-1H-indole-3-carboxylic acid 8-quinolinyl ester;
   8-Quinolinyl ester-1-(5-fluoropentyl)-1H-indole-3-carboxylic acid

D. Trade Names
   Not available.

E. Street Names
   5F-PB-22; 5-fluoro-PB-22; 5F-QUPIC; QCBL-2201; PB-22F; MN-25F; QUPIC
   N-(5-fluoropentyl) analog.

F. Physical Appearance
   5F-PB-22 has been described as a crystalline solid, white powder and off-
   white/tan crystalline solid.

G. WHO Review History
   5F-PB-22 has not been previously pre-reviewed or critically reviewed. A direct
   critical review is proposed based on information brought to WHO’s attention that
   5F-PB-22 is clandestinely manufactured, of especially serious risk to public health
   and society, and of no recognized therapeutic use by any party. Preliminary data
   collected from literature and different countries indicated that this substance may
   cause substantial harm and that it has no medical use.

2. Chemistry

A. Chemical Name
   IUPAC Name: Quinolin-8-yl 1-(5-fluoropentyl)-1H-indole-3-carboxylate
   CA Index Name: 1H-Indole-3-carboxylic acid, 1-(5-fluoropentyl)-, 8-
   quinolinyl ester
B. Chemical Structure

Free base:

Molecular Formula: C\(_{23}\)H\(_{21}\)FN\(_2\)O\(_2\)
Molecular Weight: 376.43 g/mol

C. Stereoisomers

Not applicable.

D. Methods and Ease of Illicit Manufacturing

The preparation of 5F-PB-22 is straightforward and follows standard procedures starting from indole (1). Indole N-alkylation followed by indole acylation and saponification provides the carboxylic acid intermediate (2). Conversion to the acid chloride intermediate (3) is then followed by reaction with 8-hydroxyquinoline to yield the ester product 5F-PB-22 (4).\(^4\)

(a) NaH (2.0 equiv), Br(CH\(_2\))\(_4\)F, DMF, 0 °C to rt, then (CF\(_3\))\(_2\)O, 0 °C to rt, 1 h; next step: KOH, MeOH, PhMe, reflux, 2 h; (b) (f) (COCl)\(_2\), DMF (cat.), CH\(_2\)Cl\(_2\), rt, 1 h; (c) 8-hydroxyquinoline, Et\(_3\)N, CH\(_2\)Cl\(_2\), rt, 24 h.\(^4\)

E. Chemical Properties

Melting point: 117.4 °C;\(^3\) 116–117 °C\(^4\)

Boiling point: Information could not be identified.

Solubility: ~0.25 mg/mL in dimethylformamide/phosphate buffered saline (1:3; pH 7.2); ~11 mg/mL in dimethylsulfoxide; ~16 mg/mL in dimethylformamide.\(^2\)


3. Ease of Convertibility Into Controlled Substances
   No information has been found. However, 5F-PB-22 can be easily converted back to the carboxylic acid intermediate (Section 2D, compound (2)), which can then be transformed into many other synthetic cannabinoid receptor agonists (SCRAs). It seems conceivable that the carboxylic acid intermediate might also be convertible into a ketone function, found for example in AM-2201, i.e. [1-(5-fluoropentyl)-1H-indole-3-yl](naphthalen-1-yl)methanone, which is listed in Schedule II of the Convention on Psychotropic Substances 1971.

4. General Pharmacology
   A. Routes of administration and dosage
      5F-PB-22, in its pure form but mostly as a synthetic constituent added to a plant matrix (e.g. damiana (Turnera diffusa) or marshmallow (Althaea officinalis)), is normally smoked but reliable data about dosage are unavailable. The variations in drug composition and quantities frequently observed with many smoking mixtures (e.g.6, 7) make such estimation impossible for users despite of information may be displayed on a product label. Speculative doses (presumably based on smoking/inhalation) have been suggested: 1 mg (threshold); 1-3 mg (light); 3-5 mg (common); 5-8 mg (strong).8

   B. Pharmacokinetics
      Information from clinical studies in humans is not available. A number of reports have been published that describe the biotransformation of 5F-PB-22 under in vitro conditions, either using human liver microsomes,9 pooled cryopreserved human hepatocytes,10 recombinant human carboxylesterases,11 or incubation studies using the fungus Cunninghamella elegans.12 The incubation with human hepatocytes resulted in the detection of 22 phase I and phase II metabolites with the ester hydrolysis product (1-(5-fluoropentyl)-1H-indole-3-carboxylic acid, 5F-PI-COOH) being the most dominant species, which has also been observed during an incubation study with human liver microsomes.9 Other transformations, either
alone or in combination, included hydroxylation and dihydroxylation, oxidative defluorination, carboxylation, epoxide hydrolysis and conjugation with glucuronic acid or cysteine. In addition to 5F-PI-COOH, two other major metabolites that originated via ester hydrolysis included 5F-PI-COOH-glucuronide indole hydroxylated 5F-PI-COOH. One major species still retaining the ester function originated from oxidative defluorination (to carboxylic acid at the terminal 5’-carbon of the pentyl chain) whereas another was identified as the 5’-OH-PB-22-glucuronide. It was also demonstrated that some of the 5F-PB-22 metabolites were identical to the products arising from metabolism of the defluorinated analog (PB-22). The ester hydrolysis product 5F-PI-COOH has also been detected in smoke condensates, which reflects pyrolysis-induced formation although it is unclear whether this carboxylic acid derivative would enter the brain for eliciting psychoactive effects. Interestingly, it has also been demonstrated that the detection of both 5F-PI-COOH and 5’-OH-PB-22 in human hair samples can result from external contamination rather than ingestion. An incubation of 5F-BB-22 (10 μM) with human recombinant carboxylesterases (CES1b/CES1A1 and CES2) in human serum (37 °C, 10 min) confirmed that these enzymes facilitated the ester hydrolysis. The correct identification of the parent molecule associated with drug intake can be challenging if one considers that structurally related metabolites might also show seemingly similar analytical features depending on the procedures used for their detection and identification. An example of this has recently been described where metabolites originally thought to originate from 5F-PB-22 were confirmed to arise from methyl 2-[[1-(5-fluoropentyl)-1H-indole-3-carbonyl]amino]-3,3-dimethylbutanoate (5F-MDMB-PICA) instead. The identification of metabolites is also important to evaluate the question whether these could play a role in mediating the biological effects. It was recently reported that the 5F-PB-22 metabolite 5’-OH-PB-22 maintained the ability to activate both hCB1 and hCB2 receptors. Under the investigated in vitro conditions (Table 1), the 5’-COOH-PB-22 metabolite also displayed some activation (hCB1: 25.8%; hCB2: 43.5%) whereas the hydrolyzed 5F-PI-COOH metabolite was inactive.  

C. Pharmacodynamics

A number of in vitro and in vivo studies have been carried out, which suggest that 5F-PB-22, a SCRA, binds to and activates CB1 and CB2 receptors, and that it induces a number of biological responses that are also triggered by the naturally occurring phytocannabinoid Δ9-THC and other internationally controlled SCRA (Tables 1 and 2).  

In vitro data:  

5F-PB-22 was more potent than Δ9-THC in the ability to activate G-protein-gated inwardly rectifying K+ channels (GIRKs) in mouse AtT20 neuroblastoma cells transfected with human CB1 and CB1 receptors. 5F-PB-22 was 101 times (hCB1) and 5.6 times (hCB2) more potent than WIN-55,212-2 and showed similar efficacy as a full agonist. In comparison to Δ9-THC, 5F-PB22 was 89 times more potent (hCB1). As a partial agonist, Δ9-THC only elicited 51% activation (hCB1) compared to a 13% efficacy (hCB2) that could only be achieved at a concentration of 10 μM. In this assay, the full agonist JWH-018 was 2.8 times more potent (hCB1) than
WIN-55,212-2 (similar efficacy) although the latter was 2 times more potent than the former (hCB2) with comparable efficacy (Table 1).3

When using the $[^{35}\text{S}]$GTP$\gamma$S turnover assay, it was reported that 5F-PB-22 acted as an agonist at the CB$_1$ receptor (rat/mouse cortical homogenates). This compound was 5.5 times (rat CB$_1$) and 9.5 times (mouse CB$_1$) more potent than JWH-018. Relative to basal levels, 5F-PB-22 was also more effective than JWH-018 (Table 1). Activation was absent in CB$_1$ knockout mice and also abolished following co-incubation with CB$_1$ receptor antagonist/inverse agonist AM-251.18

A G-protein coupled receptor activation assay, operating via drug-induced β-arrestin 2/CB$_1$/CB$_2$ interaction, revealed that 5F-PB-22 was 45.5 times (hCB$_1$) and 18.3 time (hCB$_2$) more potent than JWH-018. Furthermore, 5F-PB-22 was also 2.8 times (hCB$_1$) and 1.32 time (hCB$_2$) more effective. In this study, it was also demonstrated that two main 5F-PB-22 metabolites, namely the ester hydrolysis product 1-(5-fluoropentyl)-1H-indole-3-carboxylic acid (5F-PI-COOH) and quinolin-8-yl 1-(5-hydroxypentyl)-1H-indole-3-carboxylate (5'-OH-PB-22) retained activity (Table 1).15 Recently published data showed that 5F-PB-22 had sub-nanomolar affinity toward hCB$_1$ and that its potency to activate the hCB$_1$ receptor was 416 times higher than that measured for the internationally controlled SCRA XLR-11.* 16

Agonist-mediated inhibition of forskolin stimulated cAMP levels monitored in HEK-293 cells expressing the hCB$_1$ receptor and compared relative to WIN-55,212-2, 5F-PB-22 was determined to be a full agonist together with the SCRA JWH-018 and XLR-11 whereas CP-55,940 and HU-210 were identified as partial agonists. 5F-PB-22 was 2 times more potent than WIN-55,212-2; 100 times more potent than XLR-11 and 6.3 times more potent than JWH-018. Under these assay conditions, JWH-073 was inactive (Table 1).17 From the perspective of evaluating living cellular functional responses to drug administration, hCB$_1$-induced suppression of Ca$^{2+}$ spiking was investigated in cultured rat hippocampal neurons (fluorescence detection and multi-electrode experiments). 5F-PB-22 induced significant overall suppression of Ca$^{2+}$ spiking together with other SCRA. HU-210 did not produce a suppression using the same concentration.17 In multi-electrode experiments, 5F-PB-22 caused significant suppression at 10 μM and overall at 1 μM; effects were partially reversed by rimonabant.19

*XLR-11: [1-(5-Fluoropentyl)-1H-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone.
Table 1. 5F-PB-22 in-vitro data

<table>
<thead>
<tr>
<th>Functional activity:</th>
<th>Ref</th>
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<tbody>
<tr>
<td>5F-PB-22 at hCB1: EC50 = 2.8 nM (E_{max} = 108%); hCB2: EC50 = 11 nM (E_{max} = 101%)</td>
<td>Banister et al.⁴</td>
</tr>
<tr>
<td>WIN-55,212-2 at hCB1: EC50 = 284 nM (E_{max} = 100%); hCB2: EC50 = 62 nM (E_{max} = 100%)</td>
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<tr>
<td>Δ²-THC at hCB1: EC50 = 250 nM (E_{max} = 51%); hCB2: EC50 = 1157 nM (E_{max} = 13% at 10,000 nM)</td>
<td></td>
</tr>
<tr>
<td>JWH-018 at hCB1: EC50 = 102 nM (E_{max} = 107%); hCB2: EC50 = 133 nM (E_{max} = 95%)</td>
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<table>
<thead>
<tr>
<th>Receptor binding:</th>
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<tbody>
<tr>
<td>5F-PB-22 at hCB1: IC50/Ki = 0.27 nM</td>
<td>Gatch et al.¹⁶</td>
</tr>
<tr>
<td>XLR-11 at hCB1: IC50/Ki = 7.92 nM</td>
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<tr>
<td>UR-144 at hCB1: IC50/Ki = 578.5 nM</td>
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<tr>
<th>Functional activity:</th>
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<tbody>
<tr>
<td>5F-PB-22 at hCB1: EC50 = 0.95 nM (E_{max} = 98.31%)</td>
<td>Cannaert et al.¹⁵</td>
</tr>
<tr>
<td>XLR-11 at hCB1: EC50 = 359 nM (E_{max} = 104.95%)</td>
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</tr>
<tr>
<td>UR-144 at hCB1: EC50 = 1295 nM (E_{max} = 95.28%)</td>
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<tr>
<th>Functional activity:</th>
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<tbody>
<tr>
<td>CB reporter assay</td>
<td>Costain et al.¹⁷</td>
</tr>
<tr>
<td>5F-PB-22 at hCB1: EC50 = 0.84 nM (E_{max} = 278.8%); hCB2: EC50 = 0.70 nM (E_{max} = 131.9%)</td>
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<tr>
<td>JWH-018 at hCB1: EC50 = 38.2 nM (E_{max} = 100%); hCB2: EC50 = 12.8 nM (E_{max} = 100%)</td>
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<tr>
<td>JWH-122 at hCB1: EC50 = 71.7 nM (E_{max} = 173.4%); hCB2: EC50 = 9.2 nM (E_{max} = 94.0%)</td>
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<tr>
<td>MAM-2201 at hCB1: EC50 = 60.5 nM (E_{max} = 174.7%); hCB2: EC50 = 2.7 nM (E_{max} = 97.4%)</td>
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Activation of 5F-PB-22 metabolites: 5F-PI-COOH at hCB1: E_{max} = 3.1%; hCB2: E_{max} = 4.6% (not significantly different from basal levels) 5'-OH-PB-22 at hCB1: E_{max} = 171.0%; hCB2: E_{max} = 142.3% 5'-COOH-PB-22 at hCB1: E_{max} = 25.8%; hCB2: E_{max} = 43.5%

<table>
<thead>
<tr>
<th>Functional activity (hCB1):</th>
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<tr>
<td>Inhibition of forskolin stimulated cAMP levels:</td>
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<tr>
<td>Efficacy relative to WIN-55,212-2: EC50 = 79 nM (E_{max} = 65%).</td>
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<thead>
<tr>
<th>Inhibition of forskolin stimulated cAMP levels:</th>
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<tbody>
<tr>
<td>5F-PB-22: EC50 = 39.8 nM (E_{max} = 67%), full agonist.</td>
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</tr>
<tr>
<td>CP-55,940: EC50 = 316 nM (E_{max} = 47%), partial agonist.</td>
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</tr>
<tr>
<td>HU-210: EC50 = 1585 nM (E_{max} = 35%), partial agonist.</td>
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<tr>
<td>JWH-018: EC50 = 251 nM (E_{max} = 55%), full agonist.</td>
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<tr>
<td>JWH-073: no activity.</td>
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<tr>
<td>XLR-11: EC50 = 3981 nM (E_{max} = 65%), full agonist.</td>
<td></td>
</tr>
<tr>
<td>AB-PINACA: EC50 = 79 nM (E_{max} = 69%), full agonist.</td>
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hCB1-induced suppression of Ca²⁺ spiking in cultured rat hippocampal neurons: Compared to addition of blank.

<table>
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<tr>
<th>hCB1-induced suppression of Ca²⁺ spiking in cultured rat hippocampal neurons:</th>
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<tbody>
<tr>
<td>5F-PB-22: significant suppression of Ca²⁺ spiking at 10 μM.</td>
<td></td>
</tr>
<tr>
<td>WIN-55,212-2: significant suppression at 10 μM.</td>
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</tr>
<tr>
<td>CP-55,940: significant suppression at 10 μM.</td>
<td></td>
</tr>
<tr>
<td>HU-210: no suppression at 10 μM.</td>
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</tr>
<tr>
<td>XLR-11: significant suppression at 1 μM and 10 μM (significant more suppression than AB-PINACA)</td>
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<tr>
<td>AB-PINACA: significant suppression at 10 μM.</td>
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<tr>
<th>Receptor binding/hCB1 (³H)CP-55,940):</th>
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<tbody>
<tr>
<td>5F-PB-22: Kᵢ = 0.13 nM</td>
<td>De Luca et al.¹⁸</td>
</tr>
<tr>
<td>5F-AKB-48: Kᵢ = 0.87 nM</td>
<td></td>
</tr>
<tr>
<td>JWH-018: Kᵢ = 3.38 nM</td>
<td></td>
</tr>
</tbody>
</table>
5F-PB-22: rCB1; EC$_{50}$ = 3.7 nM (E$_{max}$ = 203%); mouse cortex CB1; EC$_{50}$ = 4 nM (E$_{max}$ = 183%)
5F-AKB-48: rCB1; EC$_{50}$ = 31 nM (E$_{max}$ = 190%); mouse cortex CB1; EC$_{50}$ = 28 nM (E$_{max}$ = 167%)
JWH-018: rCB1; EC$_{50}$ = 20.2 nM (E$_{max}$ = 163%); mouse cortex CB1; EC$_{50}$ = 38 nM (E$_{max}$ = 158%)

Activation of G-proteins absent in CB$_1$-KO mice; response also abolished when test drugs co-incubated with CB$_1$ receptor antagonist/inverse agonist AM-251.

**Functional activity (hCB1):**

hCB1-induced suppression of Ca$_{2+}$ spiking in cultured rat hippocampal neurons (multi-electrode experiments):

Percent change in number of spontaneous spikes before and after addition of 0.1% DMSO. 5F-PB-22 (10 μM) caused significant decrease in spontaneous activity at all time points at 10 μM; overall decrease at 1 μM. Rimonabant (5 μM) significantly reversed 5F-PB-22-induced suppression (10 μM) at the first three time-matched recordings and overall. WIN-55,212-2 (10 μM), WIN-55,212-3 (10 μM), HU-210 (10 μM), CP-55,940 (10 μM) suppressed overall activity, JWH-018 (10 μM and 1 μM), XLR-11(10 μM), JWH-250 (10 μM), and MAM-2201 (10 μM and 1 μM) suppressed overall activity. AB-PINACA caused significant suppression overall at both 10 μM and 1 μM but not at all investigated time points. “Overall” suppression determined at the end of the recording time. For some compounds, suppression was not always considered significant at a number of earlier time points, thus, indicating suppression occurring at longer incubation times.

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*Ref:* 19

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**[^S]GTPγS turnover:**

[^S]GTPγS binding assay: rat cortical homogenates; membranes incubated with[^3H]CP-55,940 (0.5 nM) for 1 h at 30 °C;[^3S]GTPγS binding assay: rat and mouse cortical membranes used; mouse and rat brain membranes incubated with test drugs at 30 °C in assay buffer containing 0.1% BSA in the presence of 0.05 nM[^3S]GTPγS and 30 μM GDP; final volume of 1 mL and incubation for 60 min; stimulation expressed relative to basal levels. For stimulation experiments test drugs (1 μM) added alone or in combination with CB$_1$ receptor antagonist/inverse agonist AM-251 (0.1 μM).

**[^S]GTPγS turnover:**

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**[^S]GTPγS turnover:**

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**In vivo data:**

Currently available data suggest that 5F-PB-22 induces responses in animals that are also seen with Δ⁹-THC and other SCRs, such as suppression of locomotor activity and decreased body temperature. 5F-PB-22 was 45 times more potent than Δ⁹-THC; 41 times more potent than XLR-11 and 31 times more potent than UR-144† in resulting in decreased locomotor activity (Table 2). Furthermore, 5F-PB-22 was found to fully substitute for Δ⁹-THC using the drug discrimination paradigm in mice where it was found to be 22 times more potent than the training drug. Microdialysis studies (nucleus accumbens shell) in male Sprague–Dawley rats revealed a modest increase in extracellular dopamine levels (~150%) (Table 2).†

<table>
<thead>
<tr>
<th>Table 2. In vivo assay data for 5F-PB-22</th>
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<tr>
<td><strong>Behavior / physiology / neurochemistry</strong></td>
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<td><strong>Body temperature:</strong> a</td>
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<tr>
<td>5F-PB-22: hypothermic effect (0.3-3 mg/kg) (&gt; 1.5 °C) was observed. Maximum drop in body temperature observed with in the first hour of the 6 h monitoring period. Mean maximal hypothermia (at 3 mg/kg) was comparable to that induced by JWH-018. Rimonabant partially reversed hypothermic effects but CB₂ receptor antagonist SR-144528 had only negligible effects on drug-induced hypothermia.</td>
</tr>
<tr>
<td><strong>Heart rate:</strong> a</td>
</tr>
<tr>
<td>5F-PB-22: significant decrease in heart rate but more variable than body temperature data, possibly reflecting multiple determinants.</td>
</tr>
<tr>
<td><strong>Locomotor activity:</strong> b</td>
</tr>
<tr>
<td>5F-PB-22 (ED₅₀ = 0.25 mg/kg), Δ⁹-THC (ED₅₀ = 11.14 mg/kg), XLR-11 (ED₅₀ = 10.29 mg/kg), and UR-144 (ED₅₀ = 7.68 mg/kg) decreased locomotor activity as dose increased. Depressant effects of 5F-PB-22 (0.5 and 1.0 mg/kg) occurred within 10 min after injection and lasted 140 min. Maximal depressant effects were observed 0-30 min. Depressant effects of Δ⁹-THC occurred within 10-50 min after injection and lasted 90-140 min. Maximal depressant effects were observed 30-60 min after 10 and 30 mg/kg. Depressant effects of XLR-11 occurred within 10 min after administration and lasted 40-60 min. Maximal depressant effects of 10 and 30 mg/kg occurred 10-40 min after injection. Depressant effects of UR-144 occurred within 10 min after administration and lasted 60-90 min. Maximal depressant effects of 10 and 30 mg/kg occurred 10-40 min after injection.</td>
</tr>
<tr>
<td><strong>Drug discrimination:</strong> c</td>
</tr>
<tr>
<td>5F-PB-22 (ED₅₀ = 0.039 mg/kg), Δ⁹-THC (ED₅₀ = 0.85 mg/kg), XLR-11 (ED₅₀ = 0.18 mg/kg), and UR-144 (ED₅₀ = 0.45 mg/kg), amongst other synthetic cannabinoids tested, fully substituted for the discriminative stimulus effect of Δ⁹-THC (3 mg/kg). 5F-PB-22 (0.5 mg/kg) fully substituted from 30 to 60 min after administration, and drug-appropriate responding was attenuated at the 120 min point; rates of responding decreased at 5, 15, 30 and 60 min with marked suppression at 15 min after administration. XLR-11 (1 mg/kg) fully substituted from 5 to 15 min after administration, and drug-appropriate</td>
</tr>
</tbody>
</table>

† UR-144: (1-Pentyl-1H-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone
responding was nearly absent by 60 min. No effect of UR-144 on the response rate was observed.

UR-144 (2.5 mg/kg) fully substituted at 15 and 60 min after administration, and drug-appropriate responding was diminished to <40% after 4 h. No effect of UR-144 on the response rate was observed.

No other adverse effects were observed at the doses and time points tested.

**In vivo microdialysis:**

5F-PB-22 administration (0.01 mg/kg, i.v.) led to a moderate but significant increase in extracellular dopamine levels in the nucleus accumbens shell dialysate at the 30 min (~145%) and 40 min (~150%) point (relative to basal levels). In comparison, 5F-AKB-48 induced comparable increases at the 60, 10 and 150 min time point.

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**5. Toxicology**

5F-PB-22, XLR-11 (1-500 μM, 24 h) and their pyrolysis products (10 mg of test drug burned and pyrolysis products isolated by solid phase extraction) were studied for exposure to SH-SY5Y, HepG2 and H9c2 cell lines and cell viability was assessed by the MTT and sulforhodamine B assay (SRB). 5F-PB-22 was found to reduce viability of cardiac and neuronal cells whereas XLR-11 decreased viability of all three cell lines tested at lower concentrations. The pyrolysis products arising from 5F-PB-22 were stated to be more toxic than 5F-PB-22 and affected all assessed cell types. The XLR-11 pyrolysis products were stated to be less toxic than XLR-11 in the three cell lines. Any other information related to acute and chronic preclinical toxicology could not be identified.

**6. Adverse Reactions in Humans**

Reports associated with the presence of 5F-PB-22 in drug products and biofluids is summarized in Table 3. The total number of cases reported in the scientific literature that make a specific causal link with 5F-PB-22 is small.
appearing quite ill and diaphoretic’. Patient confirmed history of seizures. Blood biochemistry was normal – except for potassium of 3.3 mM.

One of four death cases analyzed between July and October 2013; arrived at emergency room ‘appearing quite ill and diaphoretic’. Patient confirmed history of marijuana use of several times per week. Evaluation indicated severe liver injury, severe coagulopathy, acute kidney injury, acute respiratory failure, hypoxemia, severe anion gap, metabolic and lactic acidosis; clinical condition deteriorated over the next 12 h; progressed to critically ill status due to circulatory failure, respiratory failure, central nervous system failure, renal failure and severe metabolic derangement. Autopsy revealed cause of death to be fulminant liver failure in the setting of THC (marijuana) and 5F-PB-22 (synthetic cannabinoid) exposure. The manner of death was certified as undetermined. Toxicology findings: a pair of hospital serum specimens obtained a day before death (~9.5 h apart) indicated presence of THCCOOH (246 and 176 ng/mL); piperacillin, levofloxacin (presumably reflecting treatment) also detected. A different serum specimen, collected ~7 h before death revealed 5F-PB-22 at 1.3 ng/mL and lorazepam (19.5 ng/mL) (presumably reflecting treatment).

One of four death cases analyzed between July and October 2013; pronounced dead at home following a night of partying; reported to have consumed numerous beers, mixed alcoholic beverages and smoked synthetic marijuana (K2/Spice); later discovered unresponsive, not breathing, cool to the touch and pulseless; autopsy: bilateral pulmonary vasocongestion and congestion in the abdominal organs (liver, spleen and kidneys); concentration of 1.5 ng/mL 5F-PB-22 determined in iliac blood; cause of death was attributed to sudden death, in association with synthetic cannabinoid use; manner of death classified as accident.

One of four death cases analyzed between July and October 2013; was found dead after returning from a party. Autopsy: included bilateral pulmonary edema, necrotizing granulomatous inflammation with histoplasma microorganisms and congestion of viscera. Toxicology findings: 5F-PB-22 at 1.5 ng/mL in superior vena cava blood; stated cause of death was suspected acute drug intoxication using the synthetic cannabinoid 5F-PB-22. The manner of death was accident.

Seventeen-year-old male’s cause of death listed “5F-PB-22 intoxication,” Autopsy findings of 18 year old male reported as a fatal cardiac arrhythmia and/or fatal seizure in association with 5F-PB-22 use. Three separate postmortem cases stated to be under investigation. Whether any of these cases are similar to the ones published by Behonick et al. is not clear.

Recreationally smoked a synthetic cannabinoid cigarette (trade name K2) at home and 6 h later suffered what his wife described as generalized tonic–clonic seizure activity, including urinary incontinence and tongue lacerations; presented later at emergency department with nausea, dry mouth, and vomiting. Neurologic and cardiopulmonary examination was normal; patient experienced second episode of seizure activity three h after discharge. Use history: smoking synthetic cannabinoids more or less daily for the previous several years with no history of seizures. Blood biochemistry was normal except for potassium of 3.3 mM.

Two plasma samples were taken (5.5 and 8.3 h after the last exposure) and analyzed. 5.5 h / 8.3 h samples (pg/mL): BB-22 (97/94), AM-2233 (148/125); PB-22 (75.84); 5F-
<table>
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<tr>
<th>Year</th>
<th>Age</th>
<th>Sex</th>
<th>Reports</th>
<th>Adverse effects</th>
<th>Toxicology findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016</td>
<td>1</td>
<td>F, 19</td>
<td>Reported to have purchased three products from a headshop: two new psychoactive substances (sachets of “cannabis tea” and “mushroom tea”) as well as two LSD blotters. After the “cannabis tea” was smoked and the two LSD blotters and “mushroom tea” were ingested, the patient became tachycardic (HR 128), developed seizures, agitation, visual hallucinations as well as suspected serotoninergic toxicity (sustained ankle clonus 20-30 beats) 1-2 hours after use. Patient was treated with 1 mg of intravenous midazolam and symptoms/signs resolved within 13 h. Patient had medical history of depression, treated with fluoxetine and citalopram. Samples collected from patient at 5 h (plasma) and 17 h (blood and urine) post exposure.</td>
<td>Toxicology findings: initial plasma sample (5 h) contained 5F-PB-22 (200 pg/mL) and two 5F-AKB-48 metabolites (5F-AKB-48 adamantyl hydroxy (900 pg/mL) and 5F-AKB-48 desfluoro hydroxypentyl (5000 pg/mL)), citalopram (10-20 ng/mL), diazepam 10-20 ng/mL and fluoxetine metabolites. Seventeen hours: 5F-PB-22 (40 pg/mL), two 5F-AKB-48 metabolites (150 pg/mL and 800 pg/mL), citalopram (10-20 ng/mL), fluoxetine (20-30 ng/mL) and diazepam (40-50 ng/mL). Urine sample (17 h) contained metabolites of 5F-AKB-48 (1-5 ng/mL range), citalopram (approx. 250 ng/mL), fluoxetine 40 ng/mL and diazepam metabolites (oxazepam 200 ng/mL, temazepam 100 ng/mL) and zolpidem metabolites (10-50 ng/mL). The detection of diazepam and zolpidem might have indicated potential adulteration of drugs (not given during treatment and not reported by user).</td>
<td></td>
</tr>
<tr>
<td>2017</td>
<td>1</td>
<td>M, 22</td>
<td>Presenting at emergency department between January-July 2015. Self reported use: &quot;Herbal A&quot; and alcohol. Observations at admission: heart rate: 52 bpm; temp: 35.8 °C; Glasgow coma scale: 14; length of stay: 1.7 h. Serum analysis (ng/mL): 5F-AKB-48: 2 and 6.8 for metabolites; BB-22: 0.06; 5F-PB-22: 0.4.</td>
<td>Abouchedid et al.</td>
<td></td>
</tr>
<tr>
<td>2017</td>
<td>1</td>
<td>M, 18</td>
<td>Presenting at emergency department between January-July 2015. Self reported use: Unknown. Observations at admission: heart rate: 74 bpm; temp: 36.4 °C; Glasgow coma scale: 15; length of stay: 2.5 h. Serum analysis (ng/mL): 5F-AKB-48: 0.4 and 2.4 for metabolites; 5F-PB-22: 0.36.</td>
<td>Abouchedid et al.</td>
<td></td>
</tr>
<tr>
<td>2017</td>
<td>1</td>
<td>M, 38</td>
<td>Presenting at emergency department between January-July 2015. Self reported use: Unknown. Observations at admission: heart rate: 96 bpm; temp: 35.4 °C; Glasgow coma scale: 15; length of stay: 7.8 h. Serum analysis (ng/mL): 5F-AKB-48: 0.08 and 0.4 for metabolites; 5F-PB-22: 0.03. Other drug detected: carbamazepine.</td>
<td>Abouchedid et al.</td>
<td></td>
</tr>
<tr>
<td>2017</td>
<td>1</td>
<td>F, 24</td>
<td>Presenting at emergency department between January-July 2015. Self reported use: white powder. Observations at admission: heart rate: 79 bpm; temp: 35.5 °C; Glasgow coma scale: 15; chest pain; length of stay: 2.3 h. Serum analysis (ng/mL): main drugs detected: ethylphenidate and methiopropamine; also levamisole/tetramisole; 5F-AKB-48: 0.4 and 0.6 for metabolites; 5F-PB-22: 0.08.</td>
<td>Abouchedid et al.</td>
<td></td>
</tr>
</tbody>
</table>
7. Dependence Potential
   
   A. Animal Studies

   No information available.

   B. Human Studies

   Three male (aged 17-38 years) and three female (aged 20-42 years) dependent users (included based on the Severity of Dependence Screener) of herbal mixtures containing 5F-AKB-48‡ and 5F-PB-22 were interviewed following a structured interview guide. Users reported agitation, suicidal ideation and self-harm ideologies, and incidences of sibling and peer suicide during times of withdrawal and when attempted to restricted use or self-detoxify. The urge to re-dose has been reported by the users. However, it was not reported whether 5F-PB-22 was present in the herbal mixtures and biofluids.

8. Abuse Potential
   
   A. Animal Studies

   As summarized in Tables 1 and 2 (Section 4C), 5F-PB-22 was shown to share some cannabinoid-like properties, such as binding to and activation of CB1 and CB2 receptors and depression of locomotor activity. A moderate increase in extracellular dopamine levels have been identified in an in vivo microdialysis study (nucleus accumbens shell) using conscious rats. One drug discrimination study revealed that 5F-PB-22 (more potently) substituted fully for Δ9-THC although a decrease in response rates was also observed (Table 2). These data indicate that 5F-PB-22 may have abuse liability and further studies are warranted to investigate this further.

   B. Human Studies

   See 7B.

‡ 5F-AKB-48: N-(Adamantan-1-yl)-1-(5-fluoropentyl)-1H-indazole-3-carboxamide

a It appears that some of the case data were also published by Bottei in an abstract form.
b NR: not reported.
9. Therapeutic Applications and Extent of Therapeutic Use and Epidemiology of Medical Use
   5F-PB-22 is not known to have any therapeutic applications.

10. Listing on the WHO Model List of Essential Medicines
    5F-PB-22 is not listed on the WHO Model List of Essential Medicines (20th List) or the WHO Model List of Essential Medicines for Children (6th List).

11. Marketing Authorizations (as a Medicinal Product)
    5F-PB-22 is not marketed as a medicine.

12. Industrial Use
    5F-PB-22 has no reported industrial use.

13. Non-Medical Use, Abuse and Dependence
    Household or subpopulation surveys that specifically probe for prevalence of 5F-PB-22 could not be identified in the currently available literature. Epidemiological data, such as prevalence of use, abuse and dependence information, are not available specifically for 5F-PB-22. However, heavy use of synthetic cannabinoid receptor agonists has been associated with problematic withdrawal symptoms (e.g.,29-31) and further research is needed to investigate the underlying mechanisms.

    Also see Annex 1: Report on WHO questionnaire for review of psychoactive substances.

    The majority of available synthetic cannabinoid products (including those containing 5F-PB-22) is sold in the form of herbal mixtures, and designed for smoking purposes. It is common for retailers to purchase bulk quantities of the synthetic substance and to add the synthetic material to a variety of vegetable matter as the plant base. Products sold as herbal smoking mixtures frequently change in drug composition and quantity, often without indications on product labels, which results in challenges to unambiguously correlate harms to public health with a specific drug such as 5F-PB-22.

    The consumption of these products might be attractive to a variety of users, such as regular users of cannabis and those who might wish to avoid drug-testing procedures resulting in positive cannabis findings. Ease of access, and perceived lack of control might equally be of interest to some users. The high potency associated with many synthetic cannabinoids carries the risk of accidental overdose and potentially severe adverse events but information specific to 5F-PB-22 is limited. As highlighted in Section 6 (Table 3), the ingestion of 5F-PB-22 products has been implicated in cases of impaired driving and motor
It also adds a public health dimension. Although not specific to 5F-PB-22, there are indications that socially vulnerable and stigmatized drug users, for example found in homeless and prison populations, are increasingly associated with problematic use of synthetic cannabinoid receptor agonist products.32-35

Also see Annex 1: Report on WHO questionnaire for review of psychoactive substances.

15. **Licit Production, Consumption and International Trade**

5F-PB-22 is available as standard reference material and produced for scientific research by a number of commercial suppliers. Other uses could not be identified.

16. **Illicit Manufacture and Traffic and Related Information**

Reports have been received from the European Early-Warning System on new psychoactive substances that 5F-PB-22 (first detected in 2013) was encountered in seizures and collected specimen (herbal mixtures or powders) in Belgium, Sweden, Latvia, Germany, Denmark, United Kingdom, Romania, Turkey, Lithuania, Croatia, Luxembourg, France, Hungary, Norway, Italy, Czech Republic, Bulgaria and Spain.36

5F-PB-22 detections started to appear and peaked in United States of America (USA) in 2013. The National Forensic Laboratory Information System (NFLIS), which is dedicated to the collection of drug cases submitted by State and local laboratories in the USA, registered a drop in reports from 2015 onward (Table 4), presumably as a consequence of issuing an order to temporarily schedule 5F-PB-22 into Schedule I of the Controlled Substances Act.37-39 5F-PB-22 has also been seized in kilogram quantities.22

| Year  
| Numbers | XLR-11 | MDMA | Meth \(^b\) | Ref |
|--------|--------|-------|-------|--------|-----|
| 2013 (MY) | 544 | 11,273 | 2,423 | 100,045 | NFLIS\(^{40}\) |
| 2013 (AR) | 1,952 | 19,243 | 4,798 | 206,784 | NFLIS\(^{41}\) |
| 2014 (MY) \(^c\) | 708 | 6,316 | 2,224 | 117,318 | NFLIS\(^{42}\) |
| 2014 (AR) | 1,067 | 11,001 | 4,902 | 236,175 | NFLIS\(^{43}\) |
| 2015 (MY) | 184 | 3,769 | 2,421 | 133,374 | NFLIS\(^{44}\) |
| 2015 (AR) | 408 | 6,973 | 5,188 | 277,823 | NFLIS\(^{45}\) |
| 2016 (MY) | NR \(^d\) | 1,409 | 2,901 | 155,535 | NFLIS\(^{46}\) |

\(^{a}\)MY: mid-year report (January to June); AR: annual report (January to December).

\(^{b}\)Meth: methamphetamine.

\(^{c}\)Revised March 2016.

\(^{d}\)Not reported but 5F-PB-22 related numbers might have been covered under the item “other synthetic cannabinoids”.

Detections of 5F-PB-22 have also been reported to UNODC’s Early Warning Advisory on New Psychoactive Substances.47 5F-PB-22 was reported by 28 countries in 2013, 27 countries in 2014, 29 countries in 2015, and 7 countries in 2016 (as of 08 August 2017).
17. **Current International Controls and Their Impact**
   5F-PB-22 is not controlled under the 1961, 1971 or 1988 United Nation Conventions.

18. **Current and Past National Controls**
   Refer to Annex 1: Report on WHO questionnaire for review of psychoactive substances.

19. **Other Medical and Scientific Matters Relevant for a Recommendation on the Scheduling of the Substance**
   Not applicable.
References


Please refer to separate Annex 1 document published on ECDD website
Annex 2: Studies associated with the detection and chemical analysis of 5F-PB-22 (amongst other substances) published in the scientific literature.

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<th>Comment</th>
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<td>Characterization of seized/collected compounds.</td>
<td>Shevyrin et al.\textsuperscript{1,2}</td>
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<td>Melting point, \textsuperscript{1}H-NMR, GC-MS, ATR-FT-IR</td>
<td>Characterization of reference material.</td>
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<td>Analysis of reference material and method application to samples.</td>
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<td>Watanabe et al.\textsuperscript{26}</td>
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\textsuperscript{a} GC: gas chromatography; MS: mass spectrometry; MS/MS: tandem mass spectrometry; HR: high resolution; LC: liquid chromatography (various forms); Q: quadrupole; TOF: time-of-flight; NMR: nuclear magnetic resonance spectroscopy; FT-IR: Fourier transform infrared spectroscopy; ATR: attenuated total reflectance; QqQ: triple quadrupole; ESI: electrospray ionization; DART: direct analysis in real time; PDA: photo diode array detector.


