Original Article

Pyrolysis of UR-144, a synthetic cannabinoid, augments an affinity to human CB₁ receptor and cannabimimetic effects in mice

Asuka Kaizaki-Mitsumoto¹, Kyoko Hataoka¹, Masahiko Funada², Yuki Odanaka³,
Hiroki Kumamoto⁴ and Satoshi Numazawa¹

¹Division of Toxicology, Department of Pharmacology, Toxicology and Therapeutics, Showa University School of Pharmacy,
1-5-8 Hatanodai, Shinagawa-ku, Tokyo, 142-8555 Japan

²National Institute of Mental Health, National Center of Neurology and Psychiatry,
4-1-1 Ogawa-higashi, Kodaira, Tokyo, 187-8553 Japan

³Center for Instrumental Analysis, Showa University School of Pharmacy,
1-5-8 Hatanodai, Shinagawa-ku, Tokyo, 142-8555 Japan

⁴Department of Medicinal and Industrial Chemistry, Showa University School of Pharmacy,
1-5-8 Hatanodai, Shinagawa-ku, Tokyo, 142-8555 Japan

(Received December 21, 2016; Accepted March 11, 2017)

ABSTRACT — Drug abusers most often smoke ‘herbal incense’ as a cigarette or inhale it using a smoking tool. Smoking may cause pyrolysis of the drug and produce decomposed products of which biological effect has never been investigated. The synthetic cannabinoid UR-144 is known to undergo thermal degradation, giving a ring-opened isomer, so-called UR-144 degradant. The present study demonstrates by using UR-144 as a model drug that the smoke of burned UR-144 contains the UR-144 degradant. The UR-144 degradant showed approximately four fold higher agonist activity to human CB₁ receptor and augmented hypothermic and akinetic actions in mice compared to UR-144. These results indicate that smoking behavior may increase psychological actions of the certain synthetic cannabinoids.

Key words: UR-144, Synthetic cannabinoid, Smoking, UR-144 degradant, CB₁ receptor

INTRODUCTION

In recent times, recreational drugs that have been gaining increasing popularity in the Japanese market are characterized by ‘herbal incense’, in which the main active chemicals, so-called synthetic cannabinoids, are mixed and absorbed in the dried leaves. Drug abusers most often smoke these drugs as a cigarette or inhale them using a smoking tool. It is possible that the smoking behavior makes the start-up hurdle abusing illicit drugs lower (Kurti *et al.*, 2016). On the other hand, smoking may cause pyrolysis of the drug, the biological effects of which have not been determined. Therefore, it is necessary to consider the biochemical action of pyrolyzed chemicals to elucidate the psychiatric effects of such recreational drugs.

UR-144 [(1-pentyl-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone] is a synthetic cannabi-

noid, which has been detected in several herbal drugs (Numazawa, 2013) and thus has been assigned as a ‘designated substance’ by the Pharmaceutical and Medical Devices Act (2012) in Japan. Although UR-144 induces hypothermia and reduces locomotor activity in experimental animals (Wiley *et al.*, 2013; Gatch and Forster, 2015; Banister *et al.*, 2015), the effects are weaker than other typical synthetic cannabinoids such as JWH-018 and AM-2201 (Banister *et al.*, 2015). It is possible that these phenomena are explained by receptor selectivity of UR-144, as its *K_i* values are 150 nM and 1.8 nM for CB₁ and CB₂, respectively (Frost *et al.*, 2010). On the other hand, UR-144 and its fluoro derivative XLR-11 [(1-(5-fluoropentyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone] contain a cyclopropyl ring (Fig. 1). It has been reported that the cyclopropyl ring of these compounds undergoes thermal rearrangement giving two peaks with similar mass spectra in gas chromatography-

Fig. 1. Chemical structure of UR-144 (A), XLR-11 (B), UR-144 degradant (C), XLR-11 degradant (D).

mass spectrometry (GC-MS) analysis (SWGDRUG Website [UR-144], 2014; SWGDRUG Website [XLR-11], 2014). These experimental observations prompted us to investigate the biological actions of the pyrolyzed compound which may be produced during smoking.

The present study demonstrated that pyrolysis of UR-144 increased in its agonist activity to the human CB₁ receptor and thereby caused stronger psychiatric effects, such as hyperreflexia, in mice. These results suggest that heating the certain drugs by smoking causes a switch to so-called ‘harder drugs’.

MATERIALS AND METHODS

Materials

The research collaborator obtained UR-144, intended for use as an ingredient in the recreational drug product, from a recreational drug vendor in April 2012 before assigned to the designated substance. Chemical structure of the compound was confirmed by GC-MS with SWGDRUG MS library, high resolution mass spectrometry and nuclear magnetic resonance (NMR) analyses. Purity of the compound was evaluated to be more than 95% by high-performance liquid chromatography (HPLC) and NMR. A 50 mg portion of UR-144 was dis-

solved in acetone and mix with 1 g of cut mint leaf. The solvent was evaporated to dryness to make ‘UR-144 herb’ containing 5% UR-144. The UR-144 degradant was made by heating UR-144 in the sealed glass tube at 300°C for 10 min.

Measurement of chemicals in the smoke of UR-144 herb

A 0.5 g portion of UR-144 herb was burned and the resulting smoke was introduced into an animal chamber (7018 cm³) by suctioning air. After 60 sec, 10 mL of chamber air was collected using gastight syringe and absorbed in 1 mL methanol with shaking in a hermetically sealed vial for 10 min. The solvent was evaporated to dryness under nitrogen stream, and the residue was dissolved in 100 µL methanol. A 20 µL portion of the methanol solution was analyzed by HPLC equipped with a photodiode array detector SPD-M10A (Shimadzu Co., Kyoto, Japan) at 300 nm and a Prodigy 5u ODS column (150 x 4.6 mm, 5 µm particle size, Phenomenex, Torrance, CA, USA). Gradient elution was performed with (A) 10 mM ammonium acetate and (B) acetonitrile at a flow rate of 1 mL/min. The initial eluent condition was set at 50% B, the condition was changed to 100% B in 20 min and held for 10 min.

Nuclear magnetic resonance (NMR) analysis

A 5 mg portion of the sample was dissolved in 1 mL DMSO-d₆ (99.9%). NMR spectra were measured using ECX-500 (JEOL RESONANCE Inc., Tokyo, Japan) at 500 MHz for ¹H and 125 MHz for ¹³C. The signals were assigned on the basis of 2D NMR experiments, which involved CORrelated Spectroscopy (COSY), Distorsionless Enhancement by Polarization Transfer (DEPT135), Heteronuclear Multiple Quantum Coherence (HMQC) and Heteronuclear Multiple-Bond Coherence (HMBC) spectral analysis.

Animals

Male Balb/c mice (8 weeks old) were purchased from Sankyo Lab Service Corporation (Tokyo, Japan). Mice were housed in plastic cages in a temperature controlled room (22 ± 1°C) and maintained on a 12-hr light-dark cycle with free access to food and water. All procedures for animal care were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committee at the Showa University. Every effort was made to minimize the number of animals used and their suffering.

Drug treatment

The toxicity of cannabinoids is characterized by hypothermia, analgesia, akinesia/catalepsy and suppression of locomotor activity. To evaluate these symptoms, three kinds of animal experiments were conducted.

A mouse was placed in an activity chamber (W200 mm x D200 mm x H250 mm) for 30 min prior to drug administration to habituate the environment. UR-144 or UR-144 degradant was dissolved in a 1:1 mixture of ethanol and Kolliphor ELP (BASF Japan, Tokyo, Japan) and diluted with saline to make the vehicle ratio of ethanol: Kolliphor ELP: saline (1:1:48). Vehicle (10 mL/kg), UR-144 (15 mg/kg) or UR-144 degradant (15 mg/kg) were injected to the mice intraperitoneally (i.p.).

Nano-Tag (Kissei Comtec Co., Nagano, Japan), an apparatus measuring the locomotor activity, were implanted in the back of mice. The mice were allowed to recover for at least 20 hr before experiments. Measurement of locomotor activity was started 5 min prior to and ended 10 min after administration. Locomotor activity was analyzed using the Nano-Tag viewer program (Kissei Comtec Co.).

The body temperature was employed to measure the grade of hypothermia. Rectal temperature as an index of total body heat was measured before and 5, 30 and 60 min after treatment using a small animal warmer and thermometer BWT-100A (Bio Research Center Co., Nagoya, Japan).

The bar test was employed to measure the grade of akinesia/catalepsy, a time needed to initiate a movement. Gently placing both the forepaws of the mouse over a metal bar (6 mm diameter) suspended 3.5 cm above the tabletop. The intensity of akinesia/catalepsy was assessed by counting time in seconds until the mouse brought both forepaws down to the tabletop, with a maximum cutoff time of 60 sec. The bar test was performed before and 15, 30 and 60 min after treatment.

Calcium mobilization assays

Chinese hamster ovary cells, expressing human CB₁ receptor G_{α16} and mitochondrial apo-aequorin protein (CHO-CB₁ cells, Perkin Elmer, Santa Clara, CA, USA) were maintained in Ham's-F12 medium with 10% fetal bovine serum (FBS), 2 mM L-glutamine, 400 mg/mL G418 and 250 mg/mL Zeocin (Invitrogen, Burlington, ON, Canada).

Cells were plated in 100 μ L culture medium on 96-well black/clear bottom plates (Corning, Life Sciences, Kennebunk, ME, USA) at 50,000 cells. The next day, 50 μ L of 3 μ M Fluo-4 was added to each well and cells were incubated for 1 hr at 37°C. Intracellular calcium con-

centration was measured in terms of relative fluorescence units (RFUs) using a Flexstation-3 microplate reader (Molecular Devices). Samples were excited at 488 nm, and emission spectra were recorded at 525 nm by using SOFTMAX PRO software (Ver. 5.4.5., Molecular Devices, Sunnyvale, CA, USA). The basal intracellular calcium levels were measured for the first 20 sec, and then the appropriate concentration of ligands was added by the built-in 8-channel pipette of Flexstation-3, and calcium readout continued for another 120 sec.

MAM-2201 obtained from Cayman Chemical (Ann Arbor, MI, USA) was used as a positive control. To get the absolute fluorescence units (AFUs), the basal RFU before adding the ligand (Min) was deducted from the peak RFU (Max) obtained after stimulating with the ligand (AFUs = Max - Min). EC₅₀ values were calculated by using PRISM Ver. 6 software (GraphPad, San Diego, CA, USA).

Statistical analysis

The rectal temperature and locomotor activity data were analyzed by ANOVA followed by Tukey's test. The bar test data were analyzed by Mann-Whitney test.

RESULTS

Smoke of UR-144 herb contains UR-144 and UR-144 degradant

UR-144 subjected to heating at 300°C for 10 min was analyzed by HPLC (Fig. 2B). UR-144 pyrolyzed almost completely into a single component under these conditions. NMR analysis indicated that the obtained compound was identical to a UR-144 degradant in which the cyclopropyl ring was opened, as reported previously (Kavanagh *et al.*, 2013) (Table 1). Therefore, the pyrolyzed UR-144 was used in the following experiments as the UR-144 degradant.

Smoke produced by burning UR-144 herb was absorbed into methanol and subjected to HPLC analysis. A novel peak (peak A) was observed in addition to a peak originating from UR-144 (peak B). Retention time (Fig. 2A and C) and UV-spectrum (data not shown) of peak A were almost identical to those of the UR-144 degradant. Peak intensities of UR-144 (100 ng) and its degradant (100 ng) were 297×10^3 , and 128×10^3 , respectively, indicating that UV sensitivity of UR-144 degradant at 300 nm was obviously lower than UR-144. On the other hand, the intensity of peaks A (UR-144 degradant) and B (UR-144) were 289×10^3 and 214×10^3 , respectively. These results indicate that the smoke of burned UR-144 contains the UR-144 degradant at levels higher than the parent compound (Fig. 2).

Table 1. NMR data for UR-144 and heated-UR-144.

Compound	NMR	Data
UR-144		¹ H δ; 0.84 (t, J = 8.0 Hz, 3H, H-5''), 1.21-1.35 (m, 4H, H-3'', H-4''), 1.25 (s, 12H, CH ₃ ×4), 1.76-1.82 (m, 2H, H-2''), 2.19 (s, 1H, H-2), 4.22 (t, J = 7.4 Hz, 1H, H-1''), 7.14-7.17 (m, 1H, H-5'), 7.20-7.23 (m, 1H, H-6'), 7.53 (d, J = 8.0 Hz, 1H, H-7'), 8.22 (d, J = 7.3 Hz, 1H, H-4'), 8.29 (s, 1H, H-2').
	¹³ C	δ; 13.9 (C-5''), 16.7 (CH ₃ ×2), 23.6 (CH ₃ ×2), 21.7 (C-4''), 28.7 (C-3''), 29.3 (C-2''), 30.7 (C-3×2), 39.7 (C-2), 46.0 (C-1''), 110.4 (C-7'), 118.4 (C-3'), 121.6 (C-5'), 121.8 (C-4'), 122.5 (C-6'), 125.8 (C-9'), 135.7 (C-2'), 136.3 (N-C-8'), 193.5 (C-1).
	HMBC	1_2, 2_3-CH ₃ , 3_2,3-CH ₃ , 2'_1'', 3'_2', 4'_6', 5'_7', 7'_5', 6', 1''_2'', 2''_1'', 5''_4'', 3-CH ₃ _2, 9'_2', 5', 7', 8'_2', 4', 6'.
UR-144 degradant		¹ H δ; 0.82 (t, J = 7.4 Hz, 3H, H-5''), 1.17-1.23 (m, 2H, H-3''), 1.24-1.33 (m, 2H, H-4''), 1.15 (s, 6H, CH ₃ ×2), 1.76-1.82 (m, 2H, H-2''), 1.78 (s, 3H, H-4-CH ₃), 2.85 (s, 2H, H-2), 4.22 (t, J=7.1 Hz, 2H, H-1''), 4.65-4.66 and 4.70-4.70 (each as m, 2H, H-5), 7.16 (m, 1H, H-5'), 7.21-7.25 (m, 1H, H-6'), 7.55 (d, J=8.5 Hz, 1H, H-7'), 8.20 (d, J = 7.4 Hz, 1H, H-4'), 8.39 (s, 1H, H-2').
	¹³ C	δ; 13.9 (C-5''), 19.8 (C-4-CH ₃), 21.6 (C-4''), 28.3 (C-3''), 27.4 (C-3-CH ₃ ×2), 29.1 (C-2''), 38.6 (C-3), 46.0 (C-1''), 48.4 (C-2), 109.0 (C-5), 110.6 (C-7'), 116.9 (C-3'), 121.8 (C-4' and C-5'), 122.7 (C-6'), 126.0 (C-9'), 136.5 (C-8'), 137.1 (C-2'), 152.0 (C-4), 193.9 (C-1).
	HMBC	1_2, 2_3-CH ₃ , 3_4-CH ₃ , 5, 3-CH ₃ _2, 4_2, 4-CH ₃ , 2'_1'', 3'_2', 6'_4', 7'_5', 1''_2'', 3''_2'', 5'', 4''_2'', 5'', 5''_3'', 4'', 5_4-CH ₃ , 9'_2', 5', 7', 8'_2', 4', 6'.

Effects of UR-144 degradant on body temperature and behavior

Psychotropic effects of the UR-144 degradant were evaluated in mice and compared with those of the parent compound. The UR-144 at a dose of 15 mg/kg, i.p. induced a decrease in core body temperature in a time-dependent manner (Fig. 3A). A significant effect on the body temperature caused by UR-144 was observed as early as 5 min after the treatment and body temperature further decreased thereafter. Such an effect of UR-144 was observed in a dose-dependent manner (data not shown). The UR-144 degradant induced hypothermia more profoundly than the same dose of UR-144 observed 30 and 60 min after the treatment (Fig. 3A).

UR-144 treatment induced akinesia in mice as demonstrated by the bar test. The effect reached its peak 30 min and diminished 60 min after the treatment (Fig. 3B). On the other hand, the UR-144 degradant induced akinesia lasted at least up to 60 min. There was a significant difference in the mean immobility time between UR-144 and its degradant observed 60 min after treatment. Mice treat-

ed with UR-144 degradant showed ramping and jumping for the first few minutes after the treatment. These effects were monitored by the Nano-Tag implanted device (Fig. 3C), which can detect movements in the vertical direction. A significant increase in locomotor activity was observed as early as 1 min and persisted until 4 min after the UR-144 degradant treatment, whereas UR-144 showed no effect on such activity.

CB₁ receptor agonist activity of UR-144 degradant

Results obtained from *in vivo* experiments suggest that the UR-144 degradant has more potent activity in inducing capability of hypothermia and catalepsy, which have been known as typical CB₁-mediated physiological responses. Therefore, further experiments were conducted to determine CB₁ receptor agonist activity of the UR-144 degradant *in vitro*. CHO-CB₁ cells, in which intracellular Ca²⁺ concentration increases upon human CB₁ receptor ligation, were used for these experiments. The dose-response curves of UR-144 and MAM-2201 used as a

Pyrolysis of UR-144 augments cannabinimimetic effects

Fig. 2. HPLC chromatograms for UR-144 (A), pyrolyzed-UR-144 (B) and smoke of UR-144 herb (C). A 20 μ L portion of the UR-144 (5 ng/ μ L), heated-UR-144 (5 ng/ μ L) and smoke of UR-144 herb dissolved in methanol were analyzed by HPLC.

Fig. 3. Effects of UR-144 and UR-144 degradant on rectal temperature (A), bar test (B), and locomotor activity (C). A) Rectal temperature was measured before and 5, 30 and 60 min after treatment. 'Time 0' on the X axis in the figure means before treatment. B) The intensity of akinesia was assessed by bar test which was performed before and 15, 30 and 60 min after treatment. 'Time 0' on the X axis in the figure means before treatment. C) Measurement of locomotor activity was started 5 min prior to and ended 10 min after administration. Values represent the mean $\pm$ S.E.M (n = 6). Statistical analysis was performed with ANOVA followed by Tukey test (A and C) or Mann-Whitney test (B). *P < 0.05, **P < 0.01 compared with vehicle treated group. #P < 0.05, ##P < 0.01 compared with UR-144 treated group.

Fig. 4. The dose-response curves of UR-144, UR-144 degradant and MAM-2201. Intracellular calcium concentration was measured in terms of relative fluorescence units (RFUs). Values represent the percent of AFUs (peak RFU - basal RFU). EC₅₀ values were calculated by using PRISM Ver. 6 software.

positive control indicated a typical sigmoidal pattern, and ED₅₀ values of these compounds were calculated to be 401 nM and 18.7 nM, respectively (Fig. 4). The dose-response curve of the UR-144 degradant was observed between the curves of UR-144 and MAM-2201, and its ED₅₀ was calculated to be 111 nM. These results indicate that the agonistic activity of UR-144 degradant for the human CB₁ receptor is approximately four times greater than that of UR-144.

DISCUSSION

The herb-type recreational drugs are often abused by smoking. The psychotropic and physiological effects of such drugs have been experimentally characterized by the systemic administration to animals, such as orally and intraperitoneally. Heat-labile synthetic cannabinoids reported previously may decompose and undergo chemical structural changes during smoking. Therefore, it is important to know the biological effect of pyrolyzed components to understand in detail the psychoactivity of chemical drugs.

In the present study, UR-144 was used as a model drug because it can be decomposed into the open ring formation. We also confirmed that burning UR-144 produces a degradant in the resulting smoke (Fig. 2). It is suggested

that the UR-144 degradant is heat-stable because UR-144 changed almost completely to its degradant by heating at 300°C for 10 min (Fig. 2B, Table 1). Such a physicochemical property of the UR-144 degradant made it easy to obtain useful amounts of this compound.

In mice, the UR-144 degradant exerted potent effects on hypothermia and has a longer duration of the action than UR-144 (Fig. 3A). UR-144 degradant also induced akinesia with a duration longer than the parent compound (Fig. 3B). The well-known features of cannabinoid-mediated pharmacology, such as hypothermia, suppression of spontaneous activity, and catalepsy, act through the CB₁ receptor (Wiley and Martin, 2003). To investigate the binding activity of the UR-144 degradant to the CB₁ receptor, we utilized calcium mobilization assays in which ligand ligation increases intracellular Ca²⁺ level. The UR-144 degradant displayed approximately four-fold higher agonistic activity for the CB₁ receptor compared with UR-144 (Fig. 4). These results indicate that the pyrolysis of UR-144 causes increased agonistic activity for the CB₁ receptor, resulting in stronger effect on body temperature and locomotor activity. Therefore, smoking the synthetic cannabinoid may lead to more profound pharmacological effects than expected.

During the course of *in vivo* experiments, we found that the UR-144 degradant induces excitation behavior such as ramping and jumping in the initial time period. To monitor the hypersthenia-like behavior in which mice moved in the vertical direction, a biotelemetry system composed of an acceleration sensor was employed. The UR-144 degradant-induced transient excitation was successfully scored using this system. Similar transient hypersthenia was also observed in mice treated with MAM-2201 (5 mg/kg, i.p.). Synthetic cannabinoid-induced excitatory action in experimental animals has not been investigated in detail. However, such an excitatory action seems to resemble the behavior of drug abusers using synthetic cannabinoids, such as agitation, aggression and tachycardia (Lonati *et al.*, 2014). Although the precise mechanism of the action is not clear, it is reported that synthetic cannabinoids cause serotonin syndrome-like symptoms (Lough and Freeman, 2014). The excitatory actions appearing after the treatment with synthetic cannabinoids were suppressed significantly by the CB₁ receptor inverse agonist AM251 (data not shown). Therefore, it is possible that forced CB₁ receptor activation is linked with the excitatory action induced by synthetic cannabinoids in mice.

In conclusion, the present study demonstrates that pyrolysis of synthetic cannabinoids caused by smoking increases the effects on the central nervous system. Smok-

Pyrolysis of UR-144 augments cannabimimetic effects

ing chemical drugs may thus produce unexpected behavioral outcomes.

ACKNOWLEDGEMENTS

This work was supported by JSPS KAKENHI Grant Number JP15K18908.

Conflict of interest---- The authors declare that there is no conflict of interest.

REFERENCES

- Banister, S.D., Stuart, J., Kevin, R.C., Edington, A., Longworth, M., Wilkinson, S.M., Beinat, C., Buchanan, A.S., Hibbs, D.E., Glass, M., Connor, M., McGregor, I.S. and Kassiou, M. (2015): Effects of bioisosteric fluorine in synthetic cannabinoid designer drugs JWH-018, AM-2201, UR-144, XLR-11, PB-22, 5F-PB-22, API-CA, and STS-135. *ACS Chem. Neurosci.*, **6**, 1445-1458.
- Frost, J.M., Dart, M.J., Tietje, K.R., Garrison, T.R., Grayson, G.K., Daza, A.V., El-Kouhen, O.F., Yao, B.B., Hsieh, G.C., Pai, M., Zhu, C.Z., Chandran, P. and Meyer, M.D. (2010): Indol-3-ylcycloalkyl ketones: effects of N1 substituted indole side chain variations on CB(2) cannabinoid receptor activity. *J. Med. Chem.*, **53**, 295-315.
- Gatch, M.B. and Forster, M.J. (2015): Δ^9 -Tetrahydrocannabinol-like effects of novel synthetic cannabinoids found on the gray market. *Behav. Pharmacol.*, **26**, 460-468.
- Kavanagh, P., Grigoryev, A., Savchuk, S., Mikhura, I. and Formanovsky, A. (2013): UR-144 in products sold via the Internet: identification of related compounds and characterization of pyrolysis products. *Drug Test Anal.*, **5**, 683-692.
- Kurti, A.N., Keith, D.R., Noble, A., Priest, J.S., Sprague, B. and Higgins, S.T. (2016): Characterizing the intersection of Co-occurring risk factors for illicit drug abuse and dependence in a U.S. nationally representative sample. *Prev. Med.*, **92**, 118-125.
- Lonati, D., Buscaglia, E., Papa, P., Valli, A., Coccini, T., Giampreti, A., Petrolini, V.M., Vecchio, S., Serpelloni, G. and Locatelli, CA. (2014): MAM-2201 (analytically confirmed) intoxication after "Synthacaine" consumption. *Ann Emerg Med.*, **64**, 629-632.
- Louh, I.K. and Freeman, W.D. (2014): A 'spicy' encephalopathy: synthetic cannabinoids as cause of encephalopathy and seizure. *Crit. Care*, **18**, 553.
- Numazawa, S. (2013): The forefront of drug abuse-Recent trends in illegal drug markets in Japan, 2012-. *The Showa Univ. J. Pharmaceut. Sci.*, **4**, 13-25.
- Scientific Working Group for the Analysis of Seized Drugs (SWGDRUG) Website. <http://www.swgdrug.org/Monographs/UR144.pdf> (Latest Revision: 1/7/2014)
- Scientific Working Group for the Analysis of Seized Drugs (SWGDRUG) Website. <http://www.swgdrug.org/Monographs/XLR11.pdf> (Latest Revision: 1/22/2014)
- Wiley, J.L. and Martin B.R. (2003): Cannabinoid pharmacological properties common to other centrally acting drugs. *Eur. J. Pharmacol.*, **471**, 185-193.
- Wiley, J.L., Marusich, J.A., Lefever, T.W., Grabenauer, M., Moore, K.N. and Thomas, B.F. (2013): Cannabinoids in disguise: Δ^9 -tetrahydrocannabinol-like effects of tetramethylcyclopropyl ketone indoles. *Neuropharmacology*, **75**, 145-154.