Forensic Toxicol
DOI 10.1007/s11419-015-0278-5

ORIGINAL ARTICLE

Identification of analogs of LY2183240 and the LY2183240 2′-isomer in herbal products

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Received: 16 January 2015 / Accepted: 31 March 2015

Abstract LY2183240 and the LY2183240 2′-isomer inhibit cellular reuptake and enzymatic hydrolysis of endocannabinoids. These compounds were detected in herbal blend products as designer drugs. Simultaneously, two analogs of LY2183240 and LY2183240 2′-isomer were also detected; (A) 5-[(biphenyl-4-yl)methyl]-1*H*-tetrazole and (B) 2-(*N*,*N*-dimethylamino)-5-[(biphenyl-4-yl)methyl]-1,3,4-oxadiazole. The structure of compound B was identified by nuclear magnetic resonance spectroscopy and X-ray crystallography. To reveal the mechanism of production of these compounds in herbal products, we analyzed the reference standard solution of LY2183240 or the LY2183240 2′-isomer after treatment under various conditions. Compound A was easily formed as a decomposition product of both LY2183240 and the LY2183240 2′-isomer under hydrolysis conditions. Compound B was only detected from the solution of the LY2183240 2′-isomer. These findings suggest that compound B was produced by elimination of N_2 from the tetrazole structure; LY2183240 and the LY2183240 2′-isomer may be decomposed at the step of producing herbal blend products, extraction procedure, and/or instrumental analysis. This is the first report to reveal the presence of two analogs of LY2183240 or the LY2183240 2′-isomer in herbal blend products.

Keywords LY2183240 · LY2183240 2′-isomer · New analogs · Herbal product · Decomposition product · Designer drug

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Introduction

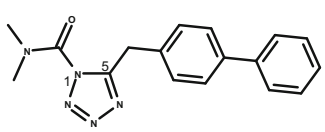
LY2183240 (*N*,*N*-dimethyl-5-[(biphenyl-4-yl)methyl]tetrazole-1-carboxamide, Fig. 1a) is a synthesized compound that strongly inhibits cellular reuptake and enzymatic hydrolysis of an endocannabinoid, anandamide [1]. The 2,5-regioisomer of LY2183240 (LY2183240 2′-isomer; *N*,*N*-dimethyl-5-[(biphenyl-4-yl)methyl]tetrazole-2-carboxamide, Fig. 1b) acts in a manner similar to LY2183240, although its pharmacological activity is relatively lower than that of LY2183240 [2]. Recently, LY2183240 and the LY2183240 2′-isomer were disclosed in an herbal blend product as designer drugs in Japan [3]. These designer drugs can be readily purchased at shops or over the Internet; the ease of accessibility is not only a major concern for human health, but also society. Recently, we confirmed the distribution of herbal blend products containing LY2183240 and the LY2183240 2′-isomer in Osaka Prefecture. In addition, two new compounds resembling LY2183240 and the LY2183240 2′-isomer were detected in herbal blend products. In the present study, we clarified the structures of the two analogs of LY2183240 and the LY2183240 2′-isomer by instrumental analyses and propose the mechanism of their production.

Materials and methods

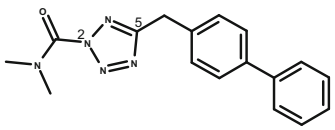
Chemicals and reagents

Acetonitrile, methanol, formic acid [liquid chromatography–mass spectrometry (LC–MS) grade], deuterated solvents for nuclear magnetic resonance (NMR), and all other chemicals for analysis were purchased from Wako Pure Chemical Industries (Osaka, Japan); reagents for synthesis

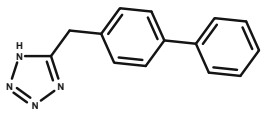
Published online: 19 April 2015



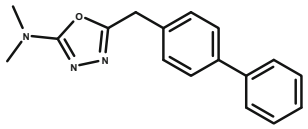
a LY2183240
Formula:$C_{17}H_{17}N_5O$
Exact mass:307.1433



b LY2183240 2′-isomer
Formula:$C_{17}H_{17}N_5O$
Exact mass:307.1433



c 5-[(Biphenyl-4-yl)methyl] -1*H*-tetrazole
Formula:$C_{14}H_{12}N_4$
Exact mass:236.1062



d 2-(*N*,*N*-Dimethylamino)-5-[(biphenyl-4-yl)methyl]-1,3,4-oxadiazole
Formula:$C_{17}H_{17}N_3O$
Exact mass:279.1372

Fig. 1 Structures of compounds to be dealt with in this study

from Tokyo Chemical Industry (Tokyo, Japan); LY2183240 from Santa Cruz Biotechnology (Dallas, TX, USA); LY2183240 2′-isomer, 5F-PB-22, and 5F-AMB from Cayman Chemical (Ann Arbor, MI, USA).

Preparation of standard solutions

The standard stock solution (100 ppm) of each compound was prepared by dissolving 1 mg of the compound in 10 ml of methanol. The standard solution for liquid chromatography–photodiode array (LC–PDA) detection (10 ppm) was prepared by adding 100 µl of each of the standard stock solutions to 900 µl of 50 % methanol in water. The standard solution (0.1 ppm) for LC–MS was prepared by adding 10 µl of each of the standard stock solutions to 990 µl of 0.1 % formic acid in water.

Preparation of test solutions for decomposition

The test solution (final 10 ppm) was prepared by adding 100 µl of each standard stock solution to 900 µl of 1 M hydrochloric acid solution, 28 % ammonia solution, or water. After incubation at 25 or 50 °C, the test solution for LC–MS (0.5 µg/ml) was prepared by adding 50 µl of each of the incubated test solutions to 950 µl of water.

Preparation of sample solutions from herbal blend products

Two herbal blend products (product 1, 3) were purchased at a head shop in Osaka Prefecture and the other one (product 2) was purchased via the Internet from August 2013 to May 2014. Sample stock solution was prepared by mixing each herbal blend product (50 mg) with methanol (2.5 ml) and stirring using a vortex mixer. The methanol extract was filtered through a 0.45-µm polyethersulfone filter (Dainippon Seiki, Kyoto, Japan). The test solution for LC–PDA was prepared by adding 100 µl of the sample stock solution to 900 µl of 50 % methanol in water. The test solution for LC–MS was prepared by adding 10 µl of the sample stock solution to 990 µl of 0.1 % formic acid in water.

Chemical synthesis of 5-[(biphenyl-4-yl)methyl]-1*H*-tetrazole (compound A) [2, 4]

A solution of tetrabutylammonium fluoride hydrate (0.4 g, 1.5 mmol), 4-phenoxyphenylacetonitrile (0.54 g, 3 mmol), and trimethylsilyl azide (0.6 ml, 4.5 mmol) in toluene (6 ml) was refluxed for 7 h. The mixture was purified by silica gel (35 g) chromatography with a stepwise gradient elution of *n*-hexane/ethyl acetate (4:1–1:2–1:0, v/v) to yield 5-[(biphenyl-4-yl)methyl]-1*H*-tetrazole (0.1 g, 14 %). ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.37 (2H, s), 7.35–7.66 (9H, m); ^{13}C NMR (100 MHz, DMSO-d_6): δ 28.5, 126.6, 127.0, 127.5, 128.9, 129.3, 135.2, 138.9, 139.7, and 155.3. High-resolution mass spectrometry (MS) [liquid chromatography–quadrupole time-of-flight-mass spectrometry (LC–QTOF-MS)]: Calcd for $C_{14}H_{13}N_4$ (MH^+) 237.1135, and found 237.1127.

Purification of compound B

After mixing ethyl acetate (40 ml) with an herbal blend product (product 2, 3 g) using a shaker for 5 min, the extract was filtered with a cotton plug. This process was repeated three times. The combined extract was evaporated under reduced pressure, and the residue was roughly purified by silica gel (25 g) chromatography with a stepwise

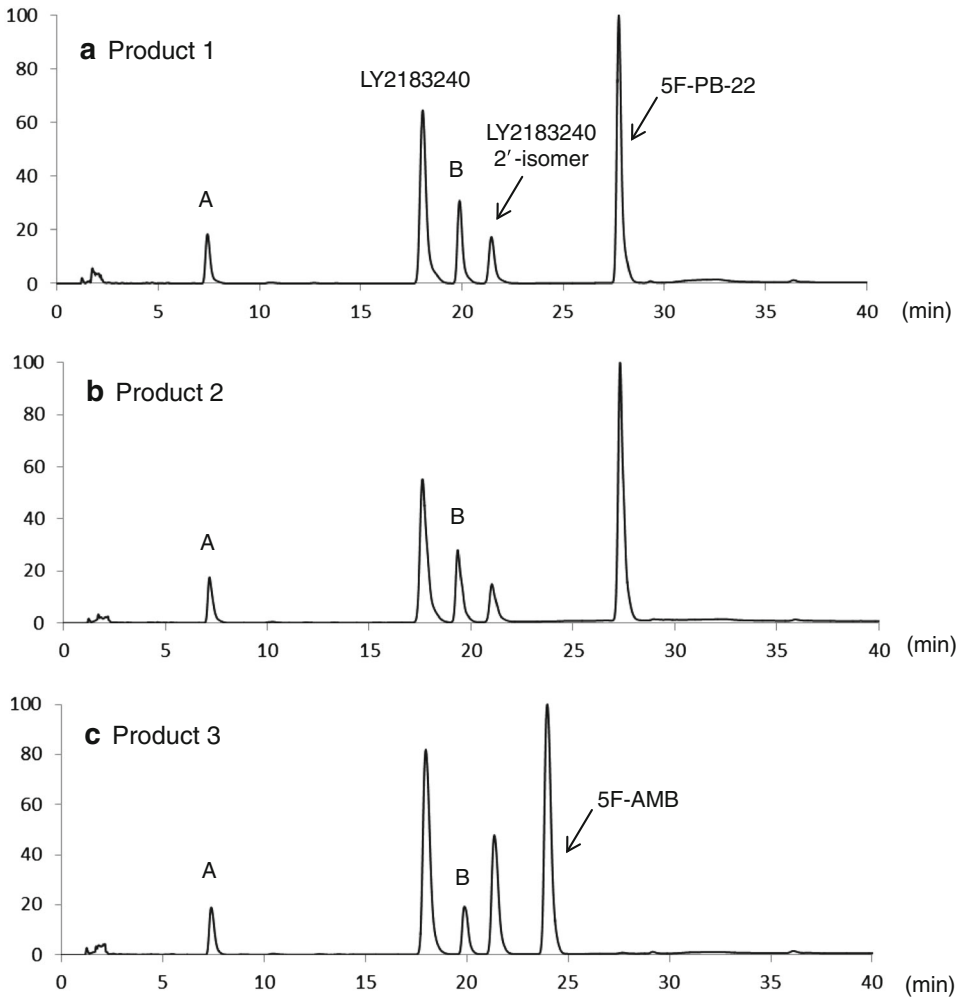


Fig. 2 Liquid chromatography–photodiode array (LC–PDA) chromatograms for the three herbal blend products

gradient elution of *n*-hexane/ethyl acetate (1:5–1:0, v/v). The crude product was further purified by preparative thin-layer chromatography (Merck PLC glass plate silica gel 60 F_{254} 2 mm) with a developing solvent of *n*-hexane/ethyl acetate (1:5, v/v) to yield compound B (20 mg).

Instrumental analyses

LC–PDA detection was performed on an Alliance e2695 (Waters, Milford, MA, USA). An L-column ODS (particle size 5 μm, 150 × 4.6 mm i.d.; Chemical Evaluation and Research Institute, Saitama, Japan) was used at 40 °C under linear gradient conditions with mobile phase (A) acetonitrile/water/phosphoric acid (300:700:1, v/v/v, containing 2.8 g/l of sodium dodecyl sulfate) and (B) acetonitrile/water/phosphoric acid (700:300:1, v/v/v, containing 2.8 g/l of sodium dodecyl sulfate) at a flow rate of 1 ml/min, and with an injected sample volume of 50 μl. The gradient program was started from 75 % A/25 % B and held for 10 min, linearly changed to 10 % A/90 % B over 20 min and held for 60 min. Ultraviolet (UV) spectra were recorded within the range of 200–400 nm.

LC separation connected to accurate MS was performed on a 6530 Accurate-Mass Q-TOF LC/MS instrument (Agilent Technologies, Santa Clara, CA, USA). LC conditions were as follows: an Aquity UPLC HSS T3 column (particle size 1.8 μm, 100 × 2.1 mm i.d., Waters) used at 40 °C; mobile phase, (A) 0.1 % formic acid in water and (B) 0.1 % formic acid in acetonitrile at a flow rate of 0.3 ml/min and an injected sample volume of 1 or 3 μl; gradient condition, started from 65 % A/35 % B, held for 4 min, linearly changed to 25 % A/75 % B over 12 min, changed to 10 % A/90 % B for at least 1 min and held for 5 min. (Q)TOF-MS (single-stage) conditions were as follows: interface, electrospray ionization in the positive mode; capillary voltage, 3000 V; drying gas flow, 10 l/min; drying temperature, 350 °C; fragmentor voltage, 150 V. QTOF-tandem mass spectrometry (MS-MS) conditions were as follows: the protonated ion used as a precursor ion; collision energy, 15 or 35 eV.

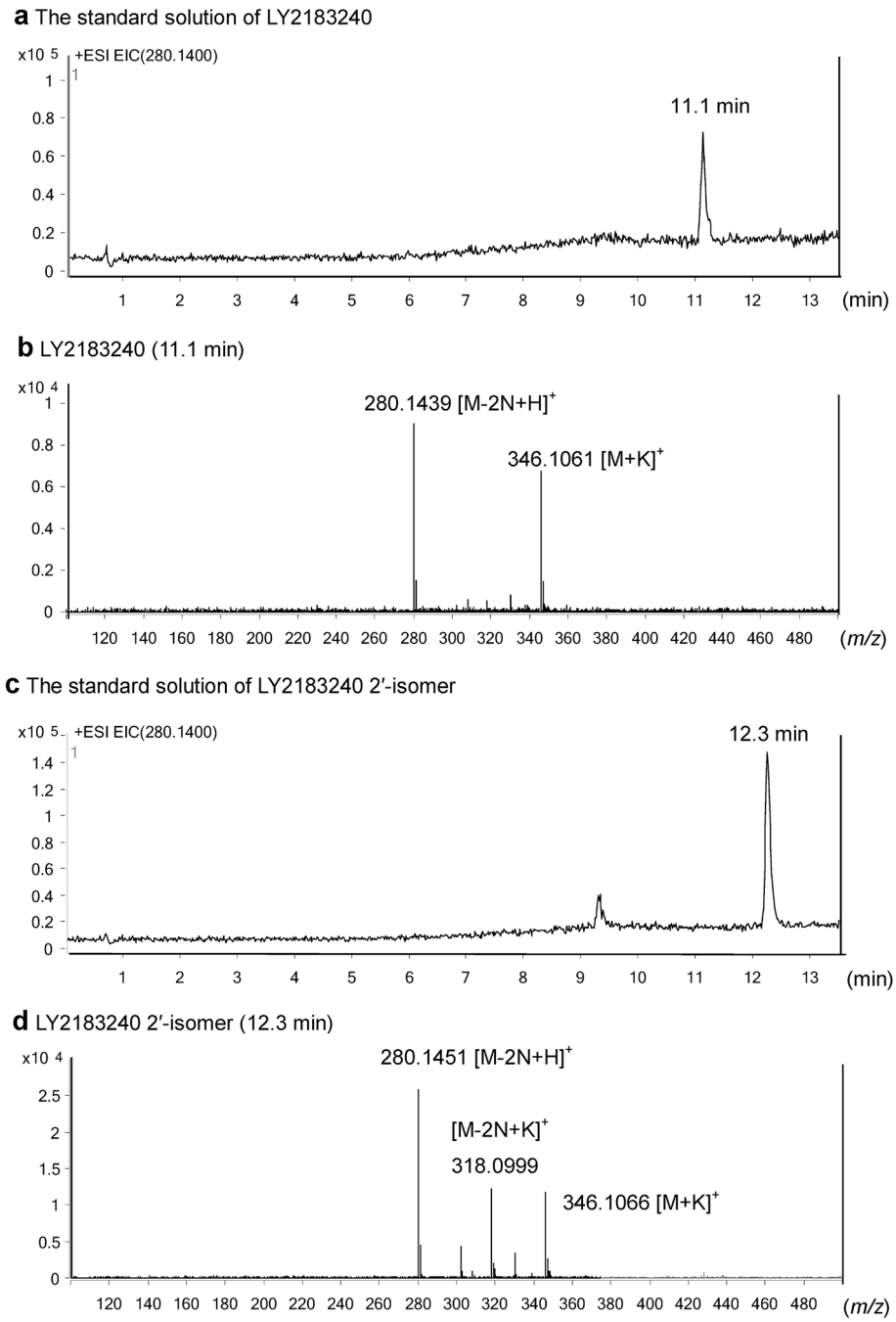


Fig. 3 **a** An extracted ion chromatogram of the standard solution of LY2183240 (monitored with a peak at *m*/*z* 280.14), **b** an electrospray ionization (ESI) mass spectrum for the peak at a retention time of 11.1 min, **c** an extracted ion chromatogram of the standard solution of the LY2183240 2′-isomer (monitored with a peak at *m*/*z* 280.14), and **d** an ESI mass spectrum for the peak at a retention time of 12.3 min all using liquid chromatography–quadrupole time-of-flight-mass spectrometry (LC–QTOF-MS) in the single-stage mode

NMR spectra of the synthesized compound were acquired on a JNM-ECS 400 instrument (JEOL Resonance, Tokyo, Japan) in 99.9 % dimethyl sulfoxide-d_6 containing 0.05 % (v/v) tetramethylsilane (TMS). NMR spectra of the purified compound were acquired on an AVANCE II 800US2 (Bruker Biospin K.K., Kanagawa, Japan) in 99.8 % methanol-d_4 containing 0.05 % (v/v) TMS.

Single crystal X-ray diffraction data was collected using a SuperNova, Dual, Cu at zero, AtlasS2 diffractometer (Agilent Technologies). The crystal was kept at 100.00(11) K during data collection. Using Olex2 [5], the structure was solved with the ShelXS [6] structure solution program using direct methods and refined with the ShelXL [6] refinement package using least square minimization.

Results and discussion

Figure 2 shows LC–PDA chromatograms for the three products purchased. Five major peaks were detected, including both LY2183240 and the LY2183240 2′-isomer, in all products. From the product containing LY2183240, the

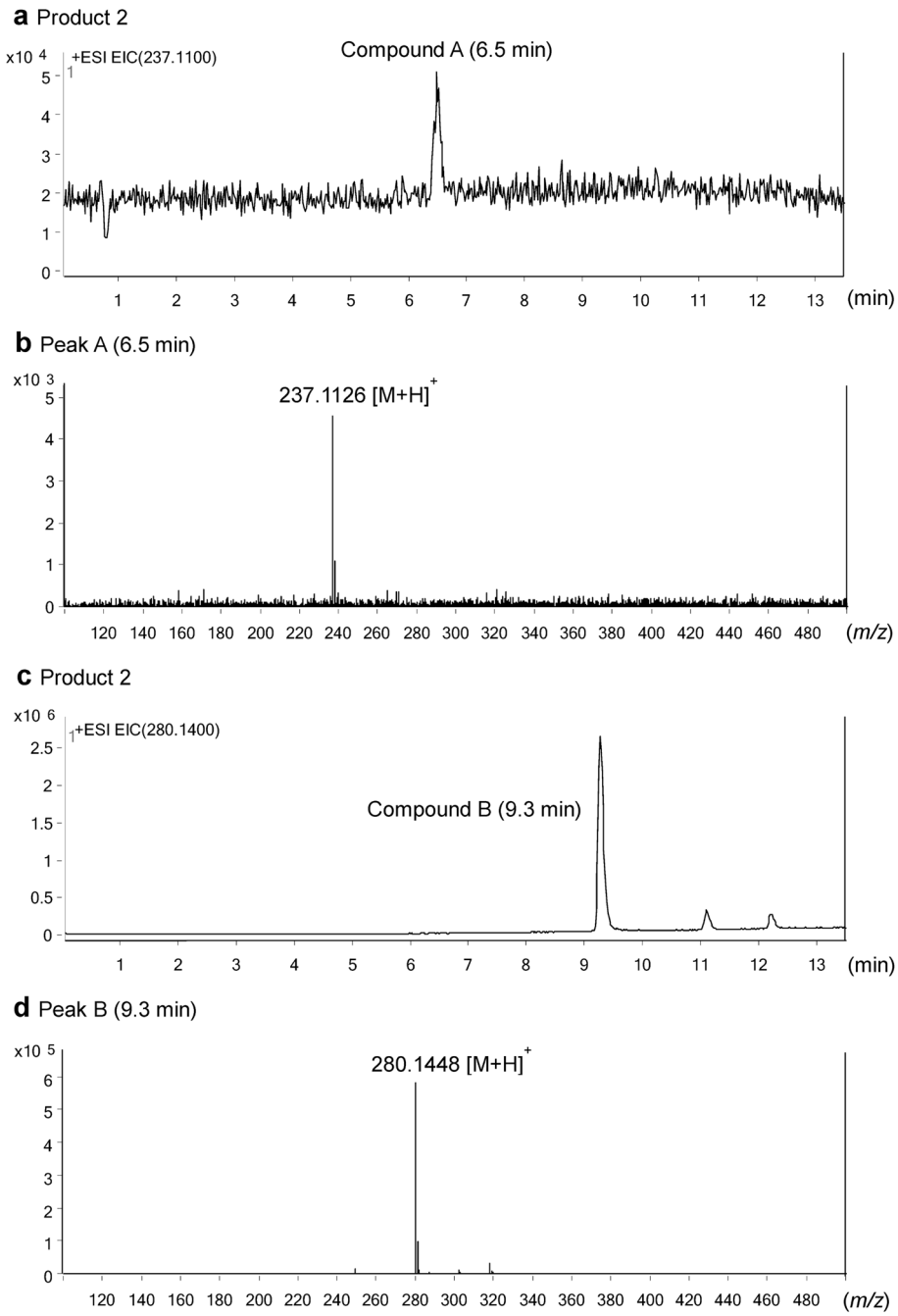


Fig. 4 **a** An extracted ion chromatogram of product 2 (monitored with a peak at *m/z* 237.11), and **b** an ESI mass spectrum for the unidentified compound A at a retention time of 6.5 min, **c** an extracted ion chromatogram of compound B (monitored with a peak at *m/z* 280.14), and **d** an ESI mass spectrum for the unidentified compound B at a retention time of 9.3 min all using LC–QTOF-MS in the single-stage mode

LY2183240 2′-isomer was detected without exceptions, which is in agreement with the result of the previous report [3]. Furthermore, 5F-PB-22 or 5F-AMB was detected in the products. Products 1 and 2, which contained 5F-PB-22 [7], had the same brand name labels, although their purchase season and methods of purchase (head shop or Internet) were different. Product 3 was sold after 5F-PB-22 was scheduled by the Pharmaceutical Affairs Law in Japan. Product 3, instead, contained 5F-AMB [8], which was not regulated at that time (5F-AMB regulated currently). The other peaks showed no matches with our in-house compound library.

The extracted ion chromatograms and accurate mass spectra measured by LC–QTOF-MS for LY2183240 and the LY2183240 2′-isomer in the standard solutions are shown in Fig. 3. In the case of LY2183240, an intense peak at *m/z* 346.1061 ($[M + K]^+$) appeared, whereas the ion peak of $[M + H]^+$ was hardly detected. In addition, the more intense peak appeared at *m/z* 280.1439 ($[M–2\ N + H]^+$). In the case of the LY2183240 2′-isomer, in

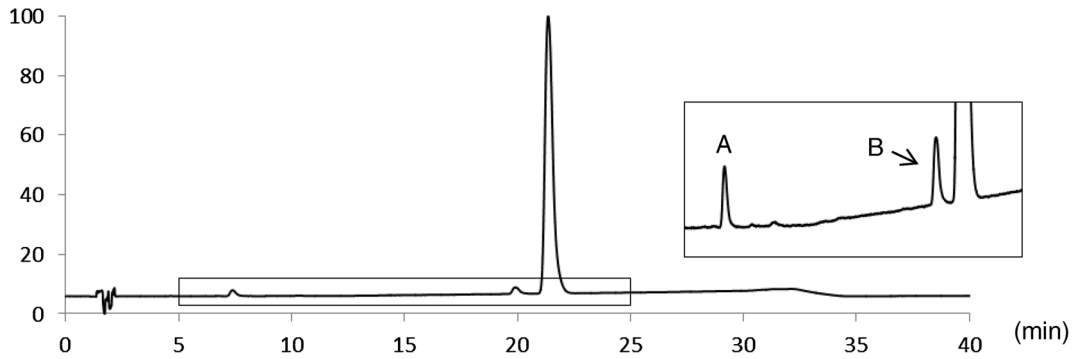


Fig. 5 LC–PDA chromatogram of the standard solution of the LY2183240 2′-isomer appearing as a *big peak*. The *inset* chromatogram showed the same one, in which the vertical axis was magnified and the horizontal axis was reduced. *A* the peak of compound A, *B* the peak of compound B

addition to the peak at *m/z* 346.1066 and 280.1451, a peak at *m/z* 318.0999 ($[M–2\ N + K]^+$) was detected. These profiles of the mass spectra were also observed during the analysis of the sample solutions, suggesting that LY2183240 and the LY2183240 2′-isomer have a tendency to lose easily two nitrogen atoms upon heating during ionization.

Then we analyzed the unidentified peaks by LC–QTOF-MS (Fig. 4). The accurate mass numbers obtained showed that compound A had a molecular formula of $C_{14}H_{12}N_4$, whereas compound B had a molecular formula of $C_{17}H_{17}N_3O$. In addition, an intense peak at *m/z* 167.0852 appeared in an MS-MS spectrum of compound A. Also, an intense peak at *m/z* 167.0848 was detected in the spectrum of the LY2183240 2′-isomer (data not shown). Thus, the MS-MS spectra showed that these compounds possessed a similar partial structure. The accurate mass of these peaks was highly similar to that of a biphenylmethyl group which was *m/z* 167.0855 ($[C_{13}H_{11}]^+$), suggesting that the unidentified compounds were analogs of LY2183240 or the LY2183240 2′-isomer (Fig. 1).

It should be mentioned that low levels of compounds A and B were detected in the standard solution of the LY2183240 2′-isomer, as analyzed by LC–PDA (Fig. 5). It was uncertain whether these compounds were already present as synthetic by-products at the time of purchase or if they were formed as decomposition products after synthesis of LY2183240 and its 2′-isomer. To clarify this, we analyzed standard solutions of LY2183240 and the LY2183240 2′-isomer at 0.5 μg/ml each by LC–QTOF-MS, after being kept under various conditions for 24 h (Figs. 6, 7). Compound A was detected in the standard solution of LY2183240 under basic conditions at room temperature (25 °C) (Fig. 6d); under acidic or neutral conditions, the production of compound A was promoted by heating (50 °C) (Fig. 7b, c). The LY2183240 2′-isomer was also decomposed to compound A within 24 h under acidic or basic conditions regardless of heating (Fig. 6g, h, 7e, f); however, it was unclear whether the production of compound B was promoted because the standard solution of the LY2183240 2′-isomer contained trace amounts of compound B at the start of the experiments.

Because the molecular formula of compound A was $C_{14}H_{12}N_4$ and it was produced under hydrolysis conditions, we deduced that compound A was 5-[(biphenyl-4-yl)methyl]-1*H*-tetrazole (Fig. 1c), which is the hydrolysate of LY2183240 or the LY2183240 2′-isomer. Also, it is the intermediate product during the synthesis of LY2183240 and the LY2183240 2′-isomer. We synthesized 5-[(biphenyl-4-yl)methyl]-1*H*-tetrazole [2] and confirmed that compound A was 5-[(biphenyl-4-yl)methyl]-1*H*-tetrazole.

Compound B was detected only from the standard solution of the LY2183240 2′-isomer. To confirm whether the compound B in the standard solution is synthetic by-product or decomposition product, we synthesized LY2183240 and the LY2183240 2′-isomer from 5-[(biphenyl-4-yl)methyl]-1*H*-tetrazole as described previously [2, 4]. Compound B was not observed by LC–QTOF-MS in the course of LY2183240 and the LY2183240 2′-isomer synthesis (data not shown), and it is most probable that compound B is the decomposition product of the LY2183240 2′-isomer. The molecular formula of compound B was $C_{17}H_{17}N_3O$, which suggested that two nitrogen atoms (probably N_2 gas) were eliminated from the LY2183240 2′-isomer. LY2183240 and the LY2183240 2′-isomer had a tendency to lose two nitrogen atoms with heating as discussed before. The reaction example of 2,5-substituted tetrazole compound has been previously reported [9, 10]. It was suggested that compound B was exclusively produced from the LY2183240 2′-isomer because LY2183240 was a 1,5-substituted tetrazole compound. Therefore, we estimated the structure of compound B, as described in Fig. 1d. The probable production mechanism of the estimated structure of compound B is

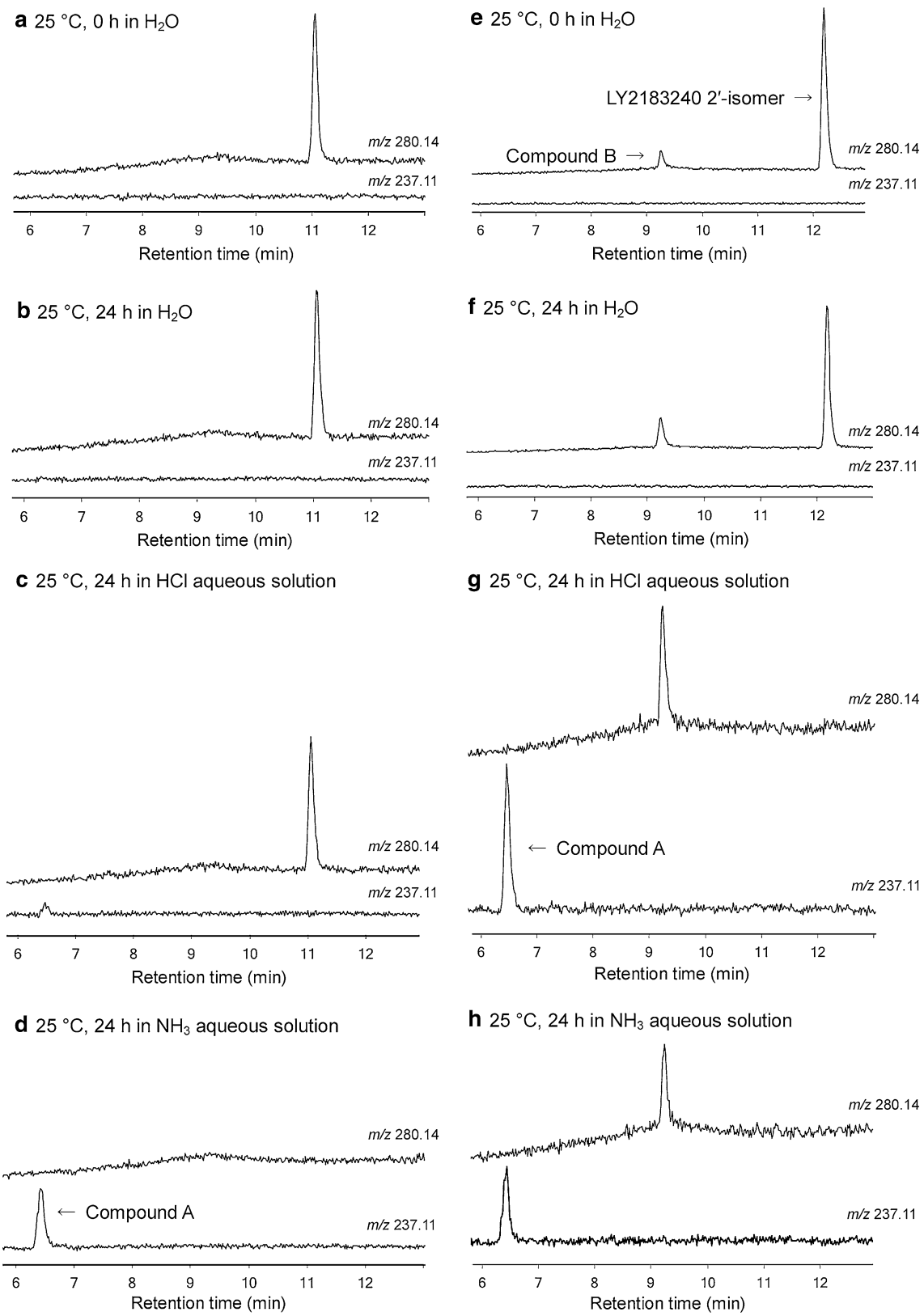


Fig. 6 Extracted ion chromatograms obtained from the standard solution of LY2183240 (**a**, **b**, **c**, **d**) or the LY2183240 2′-isomer (**e**, **f**, **g**, **h**) maintained at 25 °C under some medium conditions measured by LC–QTOF-MS in the single-stage mode

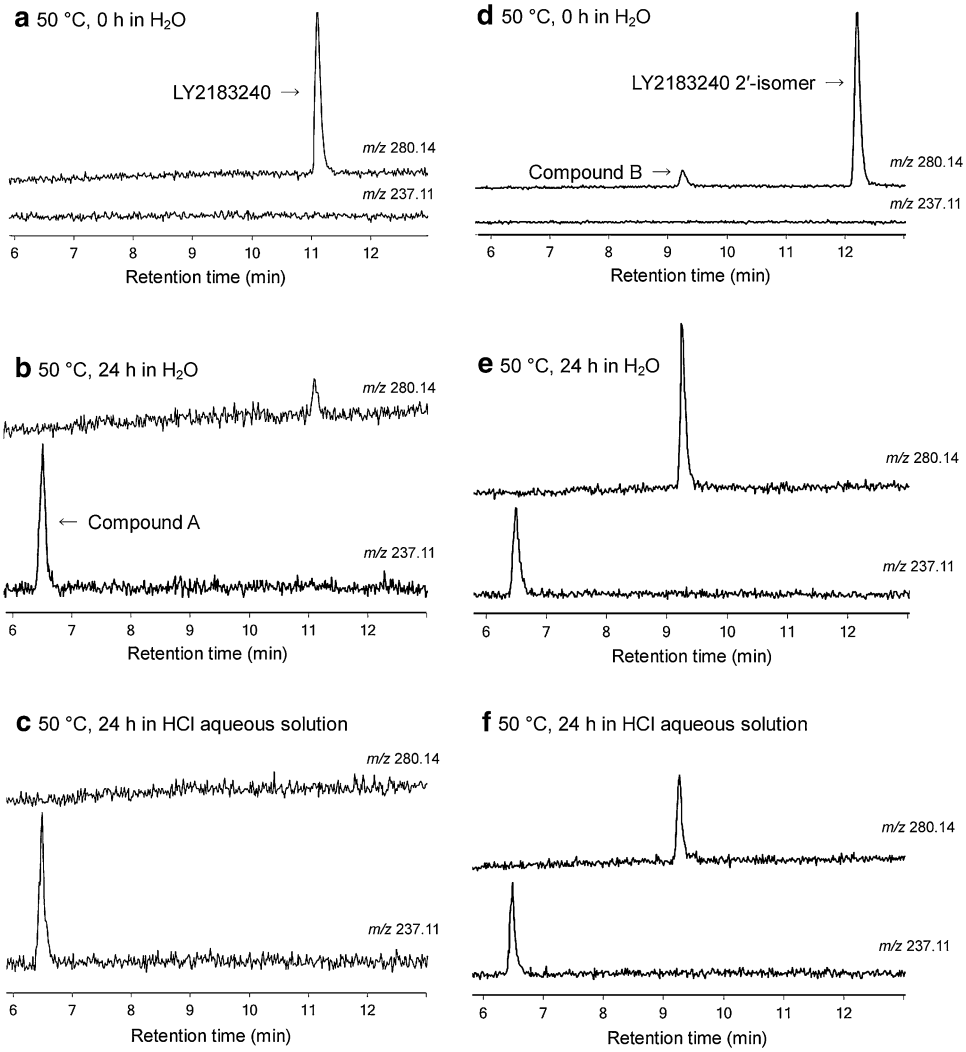


Fig. 7 Extracted ion chromatograms obtained from the standard solution of LY2183240 (**a**, **b**, **c**) or the LY2183240 2′-isomer (**d**, **e**, **f**) dissolved in water or HCl aqueous solution maintained at various conditions at 50 °C measured by LC–QTOF-MS in the single-stage mode

shown in Fig. 8; the eliminated N_2 was derived from the tetrazole, and then a five-membered ring (1,3,4-oxadiazole ring) was formed. However, we were unable to synthesize the target compound successfully. Therefore, we purified compound B and analyzed it by NMR spectroscopy.

The result of NMR for purified compound B was as follows: ^{1}H NMR (800 MHz, methanol-d_4): δ 3.03 (6 H, s), 4.11 (2 H, s), 7.33 (1H, t, $J = 7.5$ Hz), 7.38 (2H, d, $J = 8.0$ Hz), 7.42 (2H, t, $J = 7.5$ Hz), 7.60 (4H, d, $J = 8.0$ Hz); ^{13}C NMR (200 MHz, methanol-d_4): δ 32.1, 38.2, 128.0, 128.5, 128.5, 130.0, 130.3, 134.9, 141.8, 141.9, 161.2, and 166.6. The existence of a biphenyl structure was strongly suggested and the results of the analysis were consistent with the expected structure of compound B. However, the NMR data could not determine the location of the oxygen and nitrogen atoms in the oxadiazole ring. To determine the structure of compound B, X-ray crystallography was conducted. The structure of synthetic cannabinoid in herbal products was previously identified by X-ray crystallography [11]. X-Ray crystallography is very useful in determining the chemical and steric structure of compounds that consist of several heteroatoms. The size of the crystal was 0.001 × 0.001 × 0.001 mm, and its chemical structure was elucidated as shown in Fig. 9. The detailed data are as follows: $C_{17}H_{17}N_3O$, $M = 279.33$, monoclinic, $P2_1/n$, $a = 7.383(4)$ Å, $b = 6.144(2)$ Å, $c = 31.664(13)$ Å, $\beta = 94.64(4)^\circ$, $V = 1431.5(11)$ Å^3, $Z = 4$, $D_{calc} = 1.296$ g/cm^3, μ(CuKα) = 0.660 mm^{-1}, $T = 100.00(11)$ K, 8,827 measured reflections, independent reflections ($R_{int} = 0.2038$), 695 observed reflections with $I > 2\sigma$ (I), $R_1 = 7.34$ %, $wR_2 = 12.18$ % (observed data), $R_1 = 19.73$ %, $wR_2 = 16.57$ % (all data), $S = 0.984$.

The herbal products analyzed in the present study contained high amounts of compounds A and B, together with LY2183240 and the LY2183240 2′-isomer. In the previous study to synthesize LY2183240 and the LY2183240 2′-isomer from 5-[(biphenyl-4-yl)methyl]-1*H*-tetrazole, it was

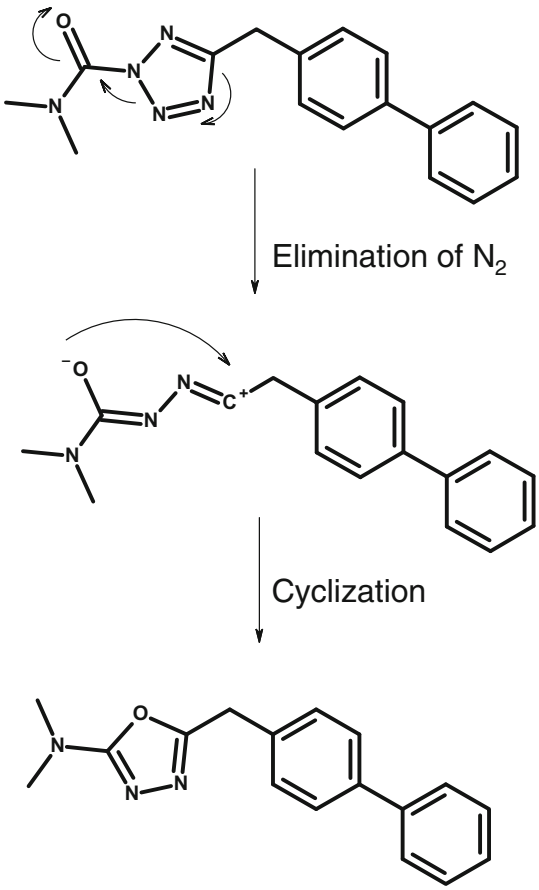


Fig. 8 Probable production mechanism of estimated compound B

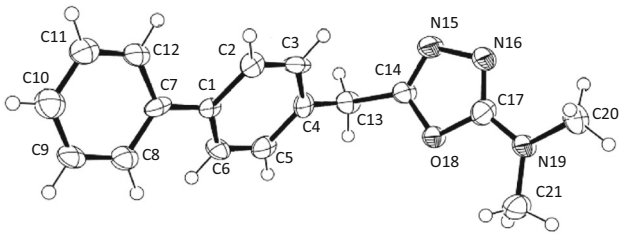


Fig. 9 Crystal structure of compound B elucidated by X-ray crystallography

shown that these compounds are given as the regioisomeric mixture [2]. Because of its tautomerization, introduction of the dimethyl carbamoyl group into the tetrazole ring of 5-[(biphenyl-4-yl)methyl]-1*H*-tetrazole likely occurs at both the 1′- and 2′-positions, and it seems to be difficult to synthesize LY2183240 or the LY2183240 2′-isomer separately. This suggests that the manufacturers added the synthetic compounds to the herbal blend products possibly without separation of the two isomers. In addition, these decomposition products were also detected in the standard solutions. The storage conditions of herbal products (e.g., temperature and humidity) may have an effect on the purity of LY2183240 and the LY2183240 2′-isomer, and also the production of the analogs may take place during the extraction procedure and/or instrumental analysis. Therefore, for accurate analysis, careful handling of herbal blend products containing LY2183240 and the LY2183240 2′-isomer or their standard solutions should be warranted.

Conclusions

In the present study, we identified two new compounds together with known LY2183240 and the LY2183240 2′-isomer in herbal blend products. The new compounds are probably decomposition products derived from LY2183240 and the LY2183240 2′-isomer. The pharmacological and toxic effects of these compounds in humans remains unclear; it is possible that herbal blend products containing these compounds can cause serious health problems.

Acknowledgements The present study received the support and encouragement of Dr. Takashi Sato (Agilent Technologies Japan, Ltd.). This study was partly supported by JSPS KAKENHI Grant No. 25860475.

Conflict of interest There are no financial or other relations that could lead to a conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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