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SHORT COMMUNICATION

Analytical and behavioral characterization of *N*-ethyl-*N*-isopropyllysergamide (EIPLA), an isomer of N^6–ethylnorlysergic acid *N*,*N*-diethylamide (ETH-LAD)

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Abstract

Preclinical investigations have shown that *N*-ethyl-*N*-isopropyllysergamide (EIPLA) exhibits lysergic acid diethylamide (LSD)-like properties, which suggests that it might show psychoactive effects in humans. EIPLA is also an isomer of N^6-ethylnorlysergic acid *N*,*N*-diethylamide (ETH-LAD), a lysergamide known to produce psychedelic effects in humans that emerged as a research chemical. EIPLA was subjected to analysis by various forms of mass spectrometry, chromatography (GC, LC), nuclear magnetic resonance (NMR) spectroscopy, and GC condensed-phase infrared spectroscopy. The most straightforward differentiation between EIPLA and ETH-LAD included the evaluation of mass spectral features that reflected the structural differences (EIPLA: N^6-methyl and *N*-ethyl-*N*-isopropylamide group; ETH-LAD: N^6-ethyl and *N*,*N*-diethylamide group). Proton NMR analysis of blotter extracts suggested that EIPLA was detected as the base instead of a salt, and two blotter extracts suspected to contain EIPLA revealed the detection of 96.9 ± 0.5 μg (RSD: 0.6%) and 85.8 ± 2.8 μg base equivalents based on LC–MS analysis. The in vivo activity of EIPLA was evaluated using the mouse head-twitch response (HTR) assay. Similar to LSD and other serotonergic psychedelics, EIPLA induced the HTR (ED_{50} = 234.6 nmol/kg), which was about half the potency of LSD (ED_{50} = 132.8 nmol/kg). These findings are consistent with the results of previous studies demonstrating that EIPLA can mimic the effects of known psychedelic drugs in rodent behavioral models. The dissemination of analytical data for EIPLA was deemed justifiable to aid future forensic and clinical investigations.

KEYWORDS
blotters, LSD, new psychoactive substances, psychedelics

1 | INTRODUCTION

Since its discovery by Dr. Albert Hofmann eight decades ago, (+lysergic acid diethylamide (LSD, Figure 1) has been the focus of intense interest due to its popularity as a recreational drug and its use as a tool in medical and scientific investigations.[1–4] Furthermore, the exploration of LSD and other lysergamides provides insight into the structural features involved in their interactions with the 5-HT_{2A} receptor, which is thought to be the key site of action in the brain for LSD and other classical psychedelic drugs. The interaction of LSD with the 5-HT_{2A} receptor is dependent on the configuration of the *N*,*N*-diethylamide moiety in LSD, and most other substitution patterns lead to considerable reductions in potency and activity.[3,5,6] In the published cryoelectron microscopy structure of LSD bound to the 5-HT_{2A} receptor, the diethylamide moiety projects into a region between TM2, TM7, and ECL2, and the two ethyl groups are in contact with non-polar residues including W151, I152, and L362,[7] interactions that are sensitive to the substitution pattern.[8]

In addition to LSD, many other mono- and dialkyllysergamides have been synthesized. One example is the *N*-methyl-*N*-isopropyl isomer of LSD (MIPLA, Figure 1). MIPLA was first synthesized by Dr. Albert Hofmann[9] and was later found to show LSD-like activity in humans but with lower potency.[5,6,10–15] It appears that MIPLA is available on the research chemicals market based on its reported detection in blotter paper samples ("blotters").[16,17] 1-(Cyclopropanecarbonyl)-MIPLA (1cP-MIPLA), a potential prodrug for MIPLA, has also been detected in blotter paper products distributed on the research chemicals market.[18]

N-Ethyl-6-methyl-*N*-(propan-2-yl)-9,10-didehydroergoline-8β-carboxamide (*N*-ethyl-*N*-isopropyllysergamide, EIPLA, Figure 1) is a MIPLA homolog that shows LSD-like properties both in vivo and in vitro.[3,10,11] EIPLA produced full substitution in rats trained to discriminate 0.08 mg/kg LSD from saline, although LSD had three-fold higher potency than EIPLA.[10] According to anecdotal reports, EIPLA produces psychedelic effects in humans.[19–21] The extent to which EIPLA is currently circulating in the research chemicals market is unknown, although there is some indication that it was available in the Netherlands a few years ago.[22]

Analytical data obtained from EIPLA could not be identified in the existing literature, which is an oversight given the potential need for information about the drug to support clinical and forensic investigations. EIPLA is also an isomer of N^6-ethylnorlysergic acid *N*,*N*-diethylamide (ETH-LAD), another lysergamide with psychedelic effects that has been distributed on the recreational market.[23,24] Hence, there is a need to compare the analytical features of EIPLA and ETH-LAD to facilitate their differentiation. Blotters suspected to contain EIPLA were also analyzed to confirm the presence of EIPLA and determine the amount of drug in single dosage units being distributed for recreational use.

In addition, the in vivo activity of EIPLA was assessed using the mouse head-twitch response (HTR), a 5-HT_{2A} receptor-mediated head movement that serves as a behavioral proxy in rodents for hallucinogenic effects in humans.[15,25–27] Because MIPLA, *N*-ethyl-*N*-cyclopropyllysergamide (ECPLA), and *N*-methyl-*N*-propyllysergamide (LAMPA) were reported to induce the HTR,[6] it was hypothesized that EIPLA would also induce the response.

2 | EXPERIMENTAL

2.1 | Materials

Formic acid (HCOOH, Rotipuran® ≥ 98%, p.a.) and potassium hydrogen phosphate (≥99%, p.a.) were obtained from Carl Roth (Karlsruhe, Germany); acetonitrile (ACN) (LC–MS grade), ammonium formate 10 M (99.995%), and potassium hydroxide (puriss. p.a. ≥ 86% [T] pellets) from Sigma-Aldrich (Steinheim, Germany). Other chemicals and solvents were of analytical or HPLC grade and obtained from Aldrich (Dorset, UK). A powdered sample of EIPLA tartrate (95%) (identified as a 3:2 salt based on ^{1}H NMR) was provided by Synex Synthetics BV, Maastricht, The Netherlands. Blotters suspected to contain EIPLA originated from a vendor.

2.2 | Instrumentation

2.2.1 | Gas chromatography–mass spectrometry (GC–MS)

For electron ionization mass spectrometry (EI-MS), a Finnigan TSQ 8000 Evo triple stage quadrupole mass spectrometer coupled to a gas chromatograph (Trace GC 1310, Thermo Electron, Dreieich, Germany) was used, whereas for chemical ionization MS (CI-MS), a Finnigan TSQ 7000 triple stage quadrupole mass spectrometer coupled to a gas chromatograph (Trace GC Ultra, Thermo Electron, Dreieich, Germany) was employed. A Triplus RSH (Thermo Scientific for TSQ 8000 Evo) and a CTC CombiPAL (CTC Analytics, Zwingen, Switzerland for TSQ 7000) autosampler were employed for sample

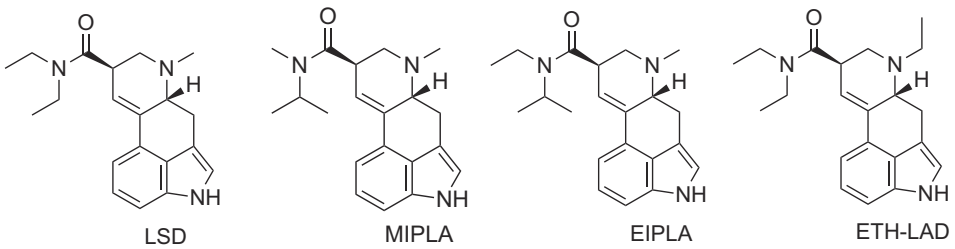


FIGURE 1 Chemical structures of lysergic acid diethylamide (LSD) and closely related isomers and homologs.

introduction. Mass spectra were recorded at 70 eV electron ionization energy. The ion source temperature was set at 175°C and the emission current was 50 μA (TSQ 8000 Evo) and 400 μA (TSQ 7000). For recordings of EI mass spectra, the scan time was 1 s spanning a scan range between *m/z* 29–600 and samples were injected in splitless mode (EI-MS and CI-MS). For CI, the reagent gas was methane and the source pressure was 1.5 mTorr (0.2 Pa). The scan time was 0.5 s and the scan range was *m/z* 50–600.

Separation was achieved using a fused silica capillary DB-1 column (30 m × 0.25 mm, film thickness 0.25 μm). The temperature program consisted of an initial temperature of 80°C, held for 2 min, followed by a ramp to 280°C at 15°C/min. The final temperature was held for 20 min. The injector temperature was 280°C (TSQ 8000) and 220°C (TSQ 7000), respectively. The transfer line temperature was set at 280°C and the carrier gas was helium in constant flow mode at a flow rate of 1.2 mL/min. Kovats retention indices (RI) were calculated from the measurement of retention times obtained from the constituents of an *n*-alkane mixture (temperature program specified above). For calculation, logarithmic interpolation was applied between two consecutive *n*-alkanes.

For the analysis of the EIPLA base, the powdered tartrate salt (2 mg) was dissolved in 2 mL demineralized water and made alkaline with one drop of NaOH (5% w/w). The solution was extracted with 2 mL diethyl ether, and the ethereal phase was transferred into a new vial and subjected to GC–MS and GC-solid-phase-infrared analysis (GC-sIR).

2.2.2 | Infrared spectroscopy (IR)

The powdered sample was analyzed directly using attenuated total reflection (ATR) FT-IR, and the EIPLA base was analyzed by GC-sIR. Instrumental details and conditions have been added as Supporting Information.

2.2.3 | Liquid chromatography-electrospray ionization single quadrupole mass spectrometry (LC-Q-MS)

Liquid chromatography/single quadrupole mass spectrometry (LC-Q-MS) was performed on an Agilent 1100 LC-MSD system (Agilent Technologies, Cork, Ireland) using a Restek (Bellefonte, PA, USA) Allure PFPP column (5 μm, 50 mm × 2.1 mm). The aqueous mobile phase A consisted of 0.1% formic acid, whereas the mobile phase B consisted of 0.1% formic acid in ACN. The following gradient elution program was used: 0–2 min 2% B, followed by an increase to 60% within 15 min, then up to 80% within 20 min, returning to 2% within 25 min. The MSD settings were as follows: positive electrospray mode, capillary voltage 3500 V, drying gas (N_2) 12 L/min at 350°C, nebulizer gas (N_2) pressure 50 psig scan mode *m/z* 70–500, and fragmentor voltage used for in-source collision-induced dissociation (is-CID) was 150 V. The sample was dissolved in ACN/water (1:1, containing 0.1% formic acid) at a concentration of 10 μg/mL. The injection volume was 10 μL, and the flow rate was 0.80 mL/min. The mass spectrometer was tuned according to the manufacturer's instructions using ESI Tuning Mix G2421A (Agilent Technologies, Cork, Ireland). The LC-Q-MS method used for semi-quantitative estimations of blotter extracts has been added as Supporting Information.

2.2.4 | High performance liquid chromatography-electrospray ionization-quadrupole time-of-flight mass spectrometry (HPLC-ESI-QTOF-MS)

HPLC-ESI-QTOF-MS analysis was performed on an impact II™ QTOF instrument coupled with an Elute HPLC system (both from Bruker Daltonik, Bremen, Germany). Chromatographic separation was achieved on a Kinetex® Biphenyl column (100 mm × 2.1 mm, 2.6 μm particle size, Phenomenex, Aschaffenburg, Germany) equipped with a corresponding guard column (SecurityGuard™ ULTRA Cartridges UHPLC Biphenyl for 2.1 mm ID columns, Phenomenex, Aschaffenburg, Germany). Mobile phases A (1% v/v ACN, 0.1% v/v HCOOH, 2 mM ammonium formate in water) and B (0.1% v/v HCOOH, 2 mM ammonium formate in ACN) were freshly prepared prior to analysis and varied in a linear program (T_{min}/A:B; T_0/99:1; T_3/70:30; T_{25}/5:95; T_{26}/5:95; $T_{26.5}$/95:5; T_{28}/95:5) with LC flow set at 0.3 mL/min and column oven temperature at 40°C. The autosampler was cooled down to 5°C. The injection volume was 10 μL. HyStar™ version 3.2 and DataAnalysis version 4.2 (both from Bruker Daltonik) were used for data acquisition and processing, respectively. The QTOF-MS was operated in positive electrospray ionization mode, acquiring spectra in the range of *m/z* 30–500 Da (acquisition rate of 4.0 Hz). Acquisition was performed in full scan/bbCID mode and in a second run in full scan/AutoMS/MS mode to obtain cleaner fragment spectra. The collision energy applied for bbCID and Auto-MS/MS was 30 ± 6 eV. The dry gas temperature was set to 200°C with a dry gas flow of 8.0 L/min. The nebulizer's gas pressure was 200 kPa. Nitrogen was used as a collision gas. The voltages for the capillary and end plate offset were 2500 and 500 V, respectively. External and internal mass calibrations were performed using sodium formate/acetate clusters and high precision calibration (HPC) mode.

2.2.5 | Nuclear magnetic resonance (NMR) spectroscopy

NMR spectra (^{1}H at 600 MHz; ^{13}C at 150 MHz) of the powdered sample (10 mg/0.75 mL solvent) were recorded using a Bruker AVANCE III 600 MHz spectrometer (Bruker UK Ltd., Coventry, UK) both in DMSO-d_6 and MeOH-d_4. Experiments were carried out at 298 K using a 5 mm PA BBO probe with a z-gradient. Spectra were referenced to residual solvent, and assignments were supported by both 1D and 2D experiments. For proton NMR experiments (zg30 pulse sequence, 16 scans), relaxation delay and acquisition time were 1.0000 and 3.6351 s, respectively. For the analysis of blotter extracts

in MeOH-d_4, the proton NMR spectral acquisition involved a suppression experiment (noesygppr1d pulse sequence, 16 scans; relaxation delay and acquisition time were 4.0000 and 2.6564 s, respectively).

2.3 | Extraction of blotters

For LC-Q-MS analysis, two individual absorbent paper samples (9 mm × 9 mm, also known as blotters with perforated edges) were extracted with ACN/water/formic acid (50/50/0.1) (AWFA) (4 mL × 2 mL, rolling for 5 min). The extracts were combined and made up to 10 mL with AWFA. This solution (50 µL) was diluted with 550 µL AWFA and analyzed by LC-Q-MS. Six concentration levels (0.078125–2.5 µg/mL) were prepared using the powdered EIPLA tartrate salt ($y = 9E{+}07 + 2E{+}06$; $R^2 = 0.9985$) and used for semi-quantitative estimation. For NMR analysis, five blotters were cut into small pieces and extracted three times with 0.5 mL deuterated methanol using a vortex mixer for 1 min. The volume was reduced under reduced pressure to 0.6 mL and subjected to proton NMR analysis.

2.4 | Animal pharmacology

Male C57BL/6J mice (6–8 weeks old) were obtained from Jackson Laboratories (Bar Harbor, ME, USA) and housed up to four per cage with a reversed light cycle (lights on at 1900 h, off at 0700 h). Food and water were provided ad libitum, except during behavioral testing. Testing was conducted between 1000 and 1830 h. All animal experiments were carried out in accordance with NIH guidelines and were approved by the University of California San Diego (UCSD) animal care committee. The HTR was assessed using a head-mounted magnet and a magnetometer detection coil.[27] Mice were anesthetized, a small incision was made in the scalp, and a small neodymium magnet was attached to the dorsal surface of the cranium using dental cement. Following a 2-week recovery period, HTR experiments were carried out in a well-lit room with at least 7 days between sessions to avoid carryover effects. Mice received intraperitoneal (IP) vehicle (saline) or EIPLA (0.1, 0.2, 0.4, or 0.8 mg/kg), and then activity was recorded in a glass cylinder surrounded by a magnetometer coil for 30 min. The injection volume was 5 mL/kg. Coil voltage was low-pass filtered (2 kHz cutoff frequency), amplified, digitized (40 kHz sampling rate, 16-bit ADC resolution), and saved to disk using a PowerLab 8/35 data acquisition system with LabChart software ver. 8.1.16 (ADInstruments, Colorado Springs, CO, USA). To detect head twitches, events in the recordings were transformed to scalograms, deep features were extracted using the deep convolutional neural network ResNet-50, and then the images were classified using a support vector machine (SVM).[28] Head twitch counts were analyzed using a one-way ANOVA. *Post-hoc* comparisons were made using Dunnett's comparisons test. Significance was demonstrated by surpassing an α-level of 0.05. ED_{50} values and 95% confidence intervals were calculated using nonlinear regression.

3 | RESULTS AND DISCUSSION

3.1 | Gas chromatography–mass spectrometry (GC–MS)

Analysis of a powdered EIPLA sample by GC–MS revealed the detection of five chromatographic peaks in total (Figure 2a), and further inspection uncovered that all detected peaks were isomeric in nature based on similarities in the EI mass spectra and molecular ions (Supporting Information). Further analysis by LC–MS (below) indicated the detection of one peak, which suggested that the four isomeric peaks might have been formed artificially during GC-based analysis. Interestingly, during the GC–MS analysis of ETH-LAD reported previously, three isomeric degradation products were also detected that did not appear under LC–MS conditions.[23]

Similar to ETH-LAD,[23] EIPLA also showed a distinctive molecular ion at *m/z* 337 under EI conditions (Figure 2b), which reflected an increased mass of 14 Da compared with LSD. Correspondingly, both ETH-LAD and EIPLA could be considered higher homologs of LSD; however, their structural differences were also reflected in their mass spectral features that enabled their differentiation. Because ETH-LAD (N^6-ethyl) retained the *N*,*N*-diethylamide group also found in LSD, a recognizable fragment was the iminium ion at *m/z* 72,[23] whereas the analogous iminium ion in EIPLA was detected at *m/z* 86 because this moiety reflected the increased mass (Figure 2c; Supporting Information for proposed fragmentation pathways).

As indicated by the mass spectral differences seen in Figure 2b,c, the identity of the N^6-alkyl substituents (ethyl with ETH-LAD, methyl with EIPLA) had a noticeable impact on the EI mass spectra, with two distinguishing fragments at *m/z* 294 (ETH-LAD: *m/z* 280[23]) and 221 (ETH-LAD: *m/z* 235[23]). In the first case, and similar to other N^6-methyl substituted lysergamides (e.g., LSD), a neutral loss of 43 Da (*N*-methylmethanimine) involving a retro-Diels–Alder (RDA) mechanism gave rise to *m/z* 294, whereas the equivalent fragment was detected at *m/z* 280 following the loss of 57 Da (*N*-ethylmethanimine). The *m/z* 221 detected in the mass spectrum of EIPLA formed part of a fragment cluster (*m/z* 219–224) frequently observed with other lysergamides, resulting in the N^6-methyl substituted ergoline-type ring following the loss of *N*-ethyl-*N*-isopropylformamide and a hydrogen radical to give the even-electron species at *m/z* 221 (Supporting Information). The EI mass spectrum of ETH-LAD revealed the detection of the equivalent species (loss of *N*,*N*-diethylformamide and hydrogen radical) at *m/z* 235. The mass increase of 14 Da reflected the presence of the N^6-ethyl group (Figure 2c).[23] The remaining fragment clusters detected in the EI mass spectrum of EIPLA (*m/z* 150–155, *m/z* 163–168, *m/z* 177–183, m/z 205–210) were reminiscent of other lysergamides, which all share the same ergoline backbone. A partial mass spectrum of another EIPLA isomer (*N*-ethyl-*N*-propyllysergamide, EPLA) (reported scan range above *m/z* 150) was reported 5 decades ago, which also showed the formation of the RDA fragment *m/z* 294, together with similar fragment clusters[29] (interestingly, it appears that EPLA was also included in pharmacological evaluations at the Sandoz Research Laboratories[9]).

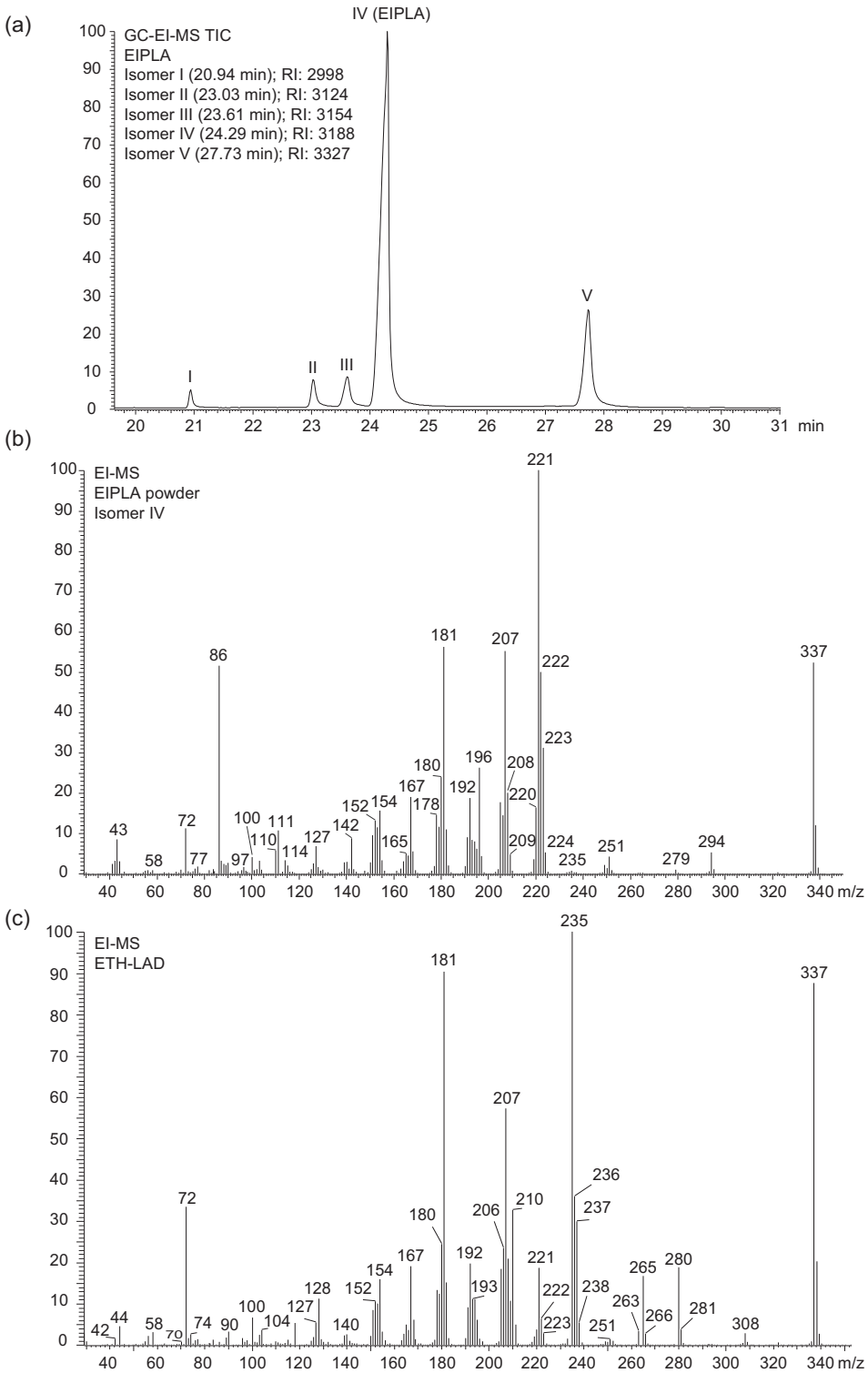


FIGURE 2 (a) Gas chromatographic analysis of EIPLA powder including GC-induced formation of artifacts. (b) Electron ionization mass spectrum of EIPLA. (c) Electron ionization mass spectrum of ETH-LAD available from a previous study.[23]

The EI mass spectra of EPLA and EIPLA might be expected to be more similar than those of EIPLA versus ETH-LAD (see above, Figure 2b,c), given that the structural differences are less pronounced and concentrated on the amide group. By analogy, EI mass spectral differences encountered during the analysis of isomers involving the amide group MIPLA, LAMPA, and LSD were reported to be subtle.[17,30] Interestingly, a fragment at *m/z* 72 was also detectable in the mass spectrum of EIPLA, although it was not possible to compare the formation of iminium ions in the EI mass spectrum reported for EPLA because it was below the reported scan range.[29] Potential alternative mechanisms involved in formations at *m/z* 86 and 72 (e.g., alkene loss from a transient oxonium ion) have been included as Supporting Information. The chemical ionization mass spectrum (Supporting Information) confirmed the detection of the protonated molecule at *m/z*

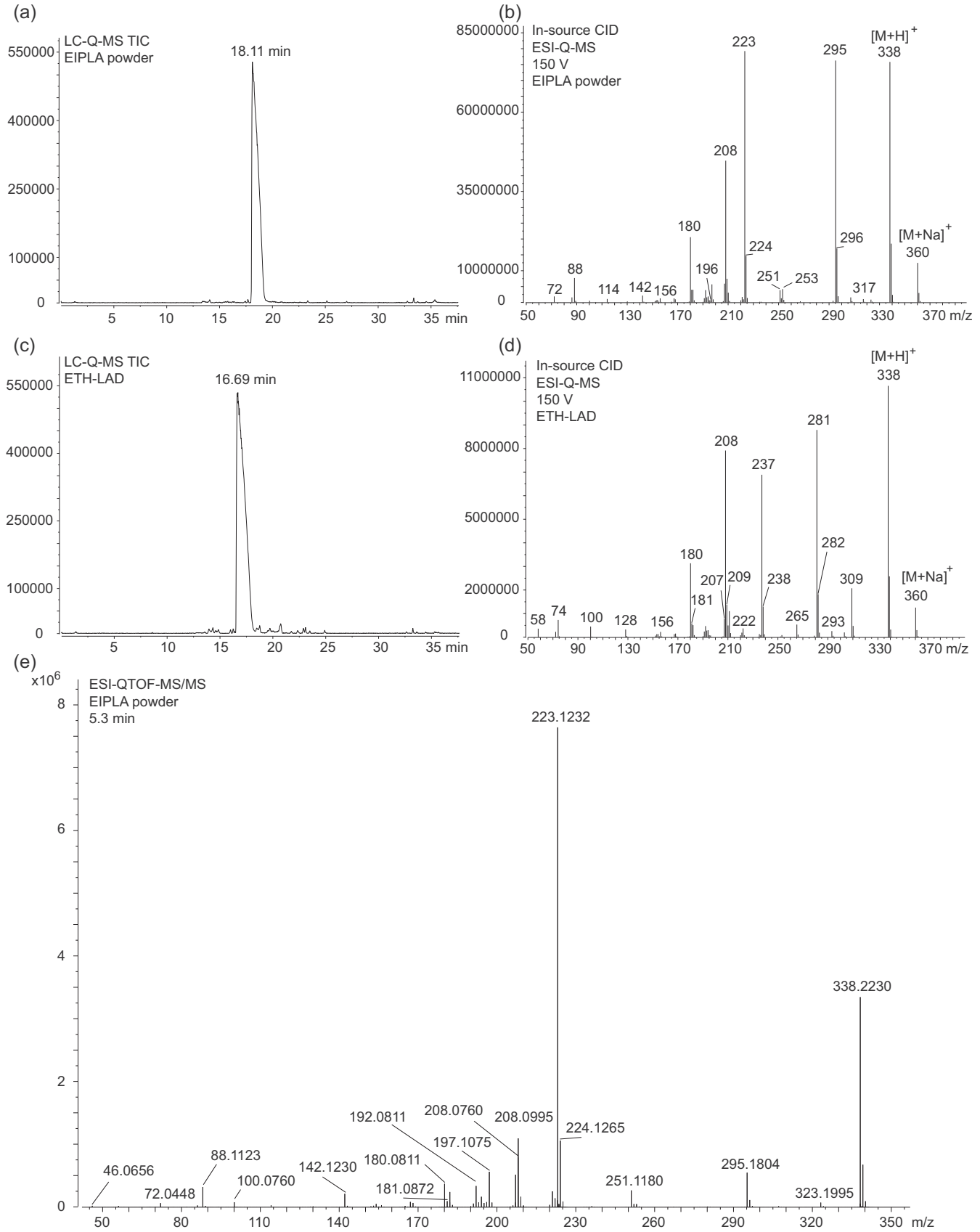


FIGURE 3 (a) Liquid chromatography electrospray ionization single quadrupole mass spectrometry (LC-Q-MS) trace of EIPLA powder in full scan mode. (b) In-source collision-induced dissociation (is-CID) mass spectrum of EIPLA. (c) LC-Q-MS trace of ETH-LAD in full scan mode available from a previous study.[23] (d) is-CID mass spectrum of ETH-LAD. (e). LC-QTOF tandem mass spectrum of EIPLA.

338 together with the formation of *m/z* 295 and another noticeable ion at *m/z* 323, which could have reflected N^6-demethylation.

All EI mass spectra reflecting the remaining chromatographic peaks have been included as Supporting Information. The identity could not be established unambiguously because of the lack of reference material, but some suggestions have been included based on mass spectral considerations. These should be viewed as speculative. Interestingly, the mass spectrum representing the chromatographic peak 3 (isomer III, 23.61 min, RI: 3154, Figure 2a) was very similar to the mass spectrum of EIPLA (Supporting Information), which suggested the potential presence of the 8–epimer iso-EIPLA. Under LC–MS conditions, however (see below), a second peak was not detected, so it was hypothesized that it might have been formed as a GC-induced artifact.

3.2 | Liquid chromatography–mass spectrometry (LC–MS)

When the powdered sample of EIPLA was subjected to analysis by liquid chromatography electrospray ionization single quadrupole mass spectrometry (LC-Q-MS), no additional chromatographic peaks were detected (Figure 3a), which provided further indications that the isomeric species detected by GC–MS could potentially be induced artificially. A sample of EIPLA was also subjected to analysis by LC-ESI-QTOF-MS. As shown in the Supporting Information, the extracted ion chromatogram using the mass of the protonated molecule also indicated that other isomers were not detectable under these conditions.

When implementing LC-Q-MS, increasing the fragmentor voltage facilitated the recording of mass spectra involving is-CID, as shown in Figure 3b. The protonated molecule was detected at *m/z* 338, together with a sodiated adduct at *m/z* 360 of lower abundance. A chromatographic and mass spectral comparison with ETH-LAD (Figure 3c,d) confirmed that the differentiation between both isomers was possible. Similar to observations reported above under EI mass spectral conditions, the structural differences between the two isomers (N^6-alkyl substituents and amide groups) directed the formation of distinct product ions under is-CID conditions as well (Figure 3b,d). For example, EIPLA displayed *m/z* 295 (ETH-LAD: *m/z* 281), *m/z* 223 (ETH-LAD: *m/z* 237), and *m/z* 88 (ETH-LAD: *m/z* 74). In addition, the is-CID mass spectrum of ETH-LAD showed a perceptible *m/z* 309 species indicative of N^6-dealkylation[23] that was evidently less favored in the mass spectrum of EIPLA (N^6-methyl), where this ion (*m/z* 323) was not detected to any significant extent (Figure 3b). It is interesting to note that in addition to ETH-LAD (N^6-ethyl), noticeable N^6-dealkylations have also been observed with other lysergamides where the N^6-substituent was more elongated, including those with an N^6-allyl group (e.g., AL-LAD,[31] 1P-AL-LAD,[32] or 1cP-AL-LAD[33]). Another fragment of lower abundance that might have reflected the presence of *m/z* 251 in the mass spectrum of EIPLA shifted to *m/z* 265 in ETH-LAD, possibly accounting for the presence of the N^6-ethyl group. The ESI-QTOF tandem mass spectrum of EIPLA is shown in Figure 3e, and the accurate masses detected were consistent with the low-resolution product ions generated under is-CID conditions using single quadrupole MS (Figure 3b). Differentiation between EIPLA and ETH-LAD involved the same ions discussed above, and proposed fragmentation pathways can be found as Supporting Information.

As can also be seen in the Supporting Information section, analysis of powdered EIPLA by ESI-QTOF-MS showed only one peak in the extracted ion chromatogram, which was consistent with the detection of only one epimer, suggesting that the epimeric iso-form was not detectable under these conditions. The physico-chemical properties of the 8–epimer are normally significantly different to render their detection by HPLC-based methods possible.[18]

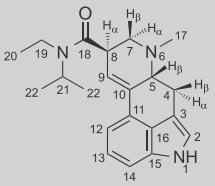
Two blotter samples suspected to contain EIPLA were extracted and analyzed by LC-Q-MS (for a representative chromatogram, see Supporting Information). Chromatographic and mass spectral analysis confirmed the presence of EIPLA, and duplicate analysis of each extract revealed the detection of 125.8 ± 0.7 μg (RSD: 0.6%) and 111.4 ± 3.7 μg (RSD: 3.3%) per blotter based on the EIPLA tartrate standard. However, proton NMR analysis of a deuterated methanol extract obtained from five blotter samples suggested that EIPLA extracted from the blotter matrix was the base instead of the tartrate salt given that the singlet related to the tartrate expected to resonate at 4.20 ppm was not detected (Supporting Information). This meant that the amount detected per blotter had to be adjusted to the base equivalent because the salt was used for semi-quantitative estimation. Based on the adjusted approximately 3:2 EIPLA/tartrate ratio (see NMR results and Supporting Information), the base constituent was estimated to reflect 77.04% of the salt, therefore leading to 96.9 ± 0.5 μg (RSD: 0.6%) and 85.8 ± 2.8 μg (RSD: 3.3%) base equivalent per blotter. These individual pieces of absorbent paper squares (9 mm × 9 mm), also known as blotters with perforated edges, originated from a larger paper sheet.

Information on the intended drug loading on the blotters was not available to facilitate a comparison with the amount detected, though anecdotal reports indicate that at least some products available on the research chemicals market were claimed to contain 200 μg EIPLA per blotter.[19,21] Anecdotal reports[19–21] and information available from pre-clinical investigations[10] suggest that EIPLA is less potent than LSD, which might explain the higher blotter strength compared with some other lysergamides available on the research chemicals market.

3.3 | Infrared spectroscopy (IR)

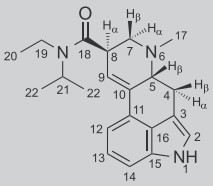
Spectral data are supplied in the Supporting Information section. A GC-sIR spectrum obtained from EIPLA base was recorded directly from a gas chromatographic peak. Using this approach, the analytes of interest were deposited cryogenically onto an IR-transparent disk, which meant that the resulting IR spectra were based on an amorphous base. As such, the resulting spectra would be identical to the base form analyzed by ATR-IR devices. Standard spectra can be collected under such conditions because spectral recordings are independent of any salt forms. A comparison with the spectrum obtained from ETH-LAD[23] revealed some similarities but also minor

TABLE 1 ^{1}H and ^{13}C NMR data for EIPLA tartrate (3:2) in DMSO-d_6 at 600/150 MHz referenced to residual solvent.



No.	^{13}C [δ/ppm]	^{1}H [δ/ppm]	
1	–	10.73 (s, 1H)	
2	119.42	7.08–7.03 (m, 1H) * Overlapping with H-12 (1H) and H-13 (1H)	
3	108.53, 108.46	–	
4	26.44, 26.36	3.53–3.50 (m, H-4β, 1H) 2.58–2.52 (m, H-4α, 1H) * Overlapping with H-17 (3H)	
5	62.70, 62.60	3.22–3.17 (m, H-5β, 1H) * Partially overlapping with H-19 (1H)	
6	–	–	
7	55.54, 55.40	3.08–3.02 (m, H-7α, 1H) 2.76–2.70 (m, H-7β, 1H)	
8	39.34	3.80–3.79 (m, 8α)	1H
	39.13	3.92–3.90 (m, 8α)	
9	119.71 and 119.96	6.25 (s)	1H
		6.24 (s)	
10	134.68, 134.62	–	
11	126.98, 126.88	–	
12	111.15, 111.02	7.08–7.03 (m, 1H) * Overlapping with H-2 (1H) and H-13 (1H)	
13	122.36, 122.32	7.08–7.03 (m, 1H) * Overlapping with H-2 (1H) and H-12 (1H)	
14	109.96	7.20 (d, $J = 7.5$ Hz, 1H)	
15	133.84	–	
16	125.79, 125.74	–	
17	43.12, 43.05	2.58–2.52 (m, H-17, 3H) * Overlapping with H-4α (1H)	
18	170.86, 170.03	–	
19	37.07	3.40–3.35 (m); possibly including impurity	2H
	34.88	3.22–3.17 (m, 1H) * Partially overlapping with H-5β	
20	17.14	1.20–1.19 (m) * Overlapping with H-22	3H
	14.80	1.08 (t, $J = 7.0$ Hz) or 1.09 ($J = 7.0$ Hz); possibly including impurity	
21	47.80	4.25 (sep, $J = 6.7$ Hz)	1H
	45.03	4.52 (sep, $J = 6.5$ Hz)	
22	21.31 and 21.24	1.24 (d, $J = 6.5$ Hz)	3H
		1.20–1.19 (m) * Overlapping with H-20	
	20.59 and 20.54	1.15 (d, $J = 6.8$ Hz)	3H
		1.12 (d, $J = 6.8$ Hz)	

TABLE 1 (Continued)



No.	^{13}C [δ/ppm]	^{1}H [δ/ppm]
TA[a]	173.44	–
TA[a]	71.94	4.20 (s, 1.3H)

[a]TA: Tartaric acid

differences. The carbonyl signal associated with the amide groups was detected at 1625 cm^{-1} (EIPLA) or 1627 cm^{-1} (ETH-LAD). Indole N−H and C−H stretches above 3000 cm^{-1} were also observed, though they did not provide any distinguishing information as expected. However, some differences could also be observed. For example, distinct bands could be observed for EIPLA at 1428, 1343, 1216, and 1407 cm^{-1}, whereas ETH-LAD showed distinctive features at 1074, 952, and 887 cm^{-1}. Similarly, some of these differences extended to the infrared spectra recorded from the tartrate salts by ATR-IR (Supporting Information).

3.4 | NMR spectroscopy

^{1}H and ^{13}C NMR data obtained from 1D and 2D experiments (full spectra recorded in DMSO-d_6 and MeOH-d_4 available as Supporting Information) were consistent with the structure of EIPLA as summarized in Table 1 (DMSO-d_6), though some interesting features were also noticed in the spectra. For example, the H-9 proton (typically observed as a singlet in closely related lysergamides) was detected as two overlapping singlets in DMSO-d_6 with a combined integral of one proton. During the analysis of lysergamides such as LSD, the appearance of a second H-9 singlet is typically associated with the detection of the epimeric form.[34] However, the use of solvents and/or the presence of specific amide groups might have had an impact. For example, in the proton NMR spectrum reported for the *N*-methyl-*N*-propyl isomer of LSD (LAMPA), two singlets could be identified for H-9 in a standard reference material, suggesting the presence of two rotamer species instead of epimers.[35]

Correspondingly, the available data suggest that the presence of the *N*-isopropyl group in EIPLA could have led to the formation of additional resonances in the spectra as a consequence of rotamer isomers. For example, the presence of the *iso*-EIPLA epimer was not detected under LC–MS conditions. Interestingly, when dissolved in MeOH-d_4 (Supporting Information and Table S1), H-9 was detected as a singlet as expected, consistent with the absence of the *iso*-form, though two separate C-9 resonances were detectable (Supporting Information). The presence of the *N*-isopropyl group also appeared to have an impact on resonances that extended beyond H-9. For C-22, the methyl groups in the *iso*-propyl group of each rotamer appeared to be non-equivalent, and thus a pair of doublets was observed for each rotamer. Similarly, the proton and carbon signals observed for the CH-group labeled as position 21 were also split into two resonances. As summarized in Table 1, the duplication of some carbon resonances extended beyond the confines of the amide group and included the ring system, overall suggesting an influence of the bulky nature of the *N*-isopropyl group and its impact on the changes in chemical shifts. On inspection of proton NMR spectra and integrals, it appeared that the two rotamer populations were not evenly distributed (see also Supporting Information). For example, when examining the integrals for H-9 and H-8α (in DMSO-d_6), the distribution was estimated at 55:45, which suggested a slight preference over a 50:50 mixture. Presumably, this reflected the steric differences found between the *N*-ethyl and *N*-isopropyl groups. A two-dimensional ^{1}H/^{1}H NOESY experiment (Supporting Information) was also employed to probe spatial relationships, which indicated some in-phase cross-matches for the rotamer species, including δ 4.52/4.25 ppm (H-19), 3.89/3.77 ppm (H-8α), 3.37/3.22 ppm (H-19), 1.24/1.12 ppm (H-22), and 1.20/1.07 ppm (H-20).[36] Overall, spectral data recorded for EIPLA were distinct from those reported for ETH-LAD,[23] which should allow for unambiguous differentiation.

In a study investigating preferred conformations, electron densities, and frontier orbitals involving computational methods (molecular dynamics and quantum mechanics), EIPLA only slightly affected the directionality of the carbonyl group of the amide, which led the authors to conclude that changes in the substitution of the alkylamide group did not affect the structure of the ring, though it was hypothesized that small variations in the orientation could affect binding.[37]

Typically, a 1:1 ratio between the H-9 integral and the tartaric acid singlet at 4.20 ppm indicates a ratio of two molecules of lysergamide to one molecule of tartaric acid, thus giving rise to a hemitartrate salt (2:1). As shown in Table 1 and the Supporting Information, proton NMR analysis of the EIPLA powder showed an integral of 1.34 protons instead of 1.0 (possibly excess tartaric acid) for the tartaric acid singlet, which resulted in an estimated EIPLA:tartrate mole ratio of

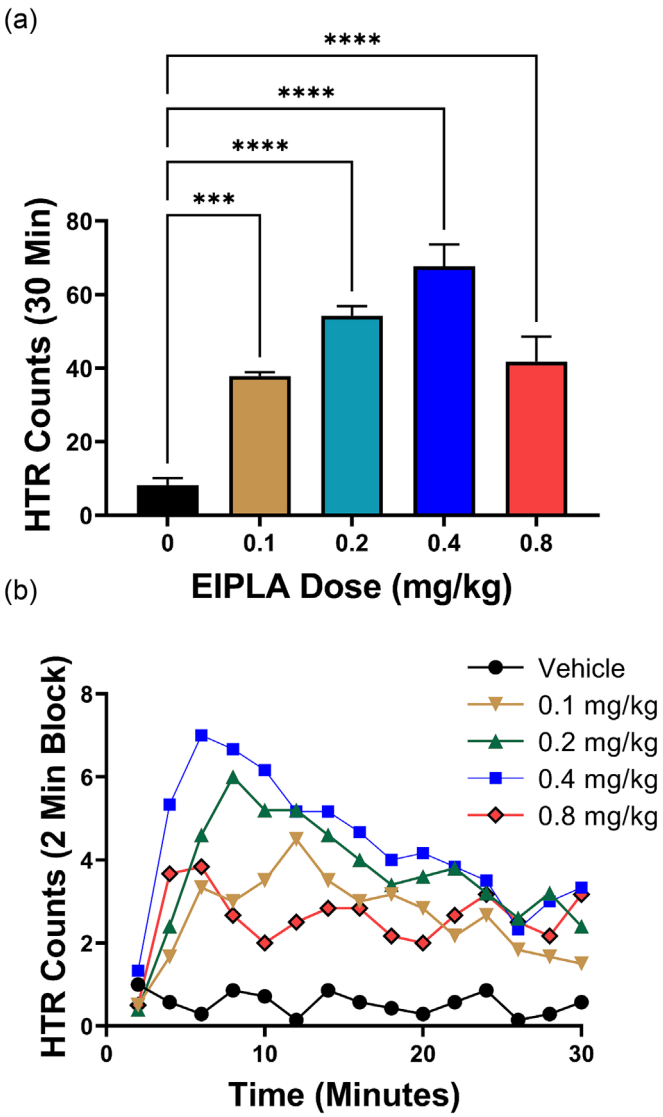


FIGURE 4 (a) Effect of EIPLA on the head-twitch response (HTR). Data are presented as group means ± SEM for the entire 30-min test session. ***$p < 0.001$, ****$p < 0.0001$, significant difference from vehicle control group (Tukey's test). (b) Time-course of the HTR induced by EIPLA. Data are presented as group means during 2-min time blocks.

1.00/0.67, that is, approximately 3:2 instead of 2:1 (Supporting Information).

3.5 | Head–twitch response (HTR)

Based on the H-9 and tartrate singlet ratios detected in the ^{1}H NMR spectrum, the EIPLA/acid ratio was estimated at 1.000/0.645, resulting in an adjusted molecular weight of 434.27 g/mol (equivalent to 77.71% EIPLA base per mole).

EIPLA was tested in the mouse HTR assay to assess whether it activates the 5-HT$_{2A}$ receptor and induces LSD-like effects in vivo. Male C57BL6J mice were used for the experiments because previous studies have shown that there is a robust correlation between HTR data collected in those animals and activity in humans and in rat drug discrimination studies performed with psychedelic drugs.[15] Administration of EIPLA induced a dose-dependent increase in HTR counts (F (4,21) = 27.69, $p < 0.0001$) (Figure 4). Similar to LSD and other serotonergic psychedelics,[15,38] the dose–response curve for EIPLA in the HTR assay was biphasic, with ascending and descending phases. The median effective dose (ED$_{50}$) for EIPLA was 101.9 (95% CI: 79.6–130.4) μg/kg, which was equivalent to 234.6 nmol/kg. This conversion was based on the adjusted molecular weight of 434.27 g/mol (see section 3.4). When tested under similar experimental conditions, LSD induced the HTR with an ED$_{50}$ of 132.8 nmol/kg,[27] so EIPLA had about half the potency of LSD. Interestingly, EIPLA has also been tested in rats trained to discriminate 0.08 mg/kg LSD from saline and was found to have about one-third of the potency of LSD, which was very similar to the potency relationship in HTR.[10] Although EIPLA was not as potent as LSD in the HTR assay, it showed a higher potency compared with the *N*-methyl-*N*-propyl (LAMPA, ED$_{50}$ = 358.3 nmol/kg), *N*-methyl-*N*-isopropyl (MIPLA, ED$_{50}$ = 421.7 nmol/kg), and *N*-ethyl-*N*-cyclopropyl (ECPLA, ED$_{50}$ = 317.2 nmol/kg) homologs.[6] Overall, it appears that a *N*,*N*-diethyl substitution pattern is optimal for the potency of *N*,*N*-disubstituted lysergamides in mice and any deviation from this pattern is detrimental for activity.

4 | CONCLUSION

The analytical profile of EIPLA established in this study might be useful to scientists interested in the multidisciplinary field of psychoactive drug research. The differentiation from its isomer ETH-LAD was straightforward. The most practical approach to differentiate between EIPLA and ETH-LAD was based on mass spectral features that reflected the structural differences (EIPLA: N^6-methyl and *N*-ethyl-*N*-isopropylamide group; ETH-LAD: N^6-ethyl and *N*,*N*-diethylamide group). Results from the HTR assay in mice confirmed that EIPLA produces behavioral effects that are closely reminiscent of LSD and other serotonergic psychedelics. Further testing in clinical studies is warranted to evaluate its abuse potential and determine the qualitative nature of its effects.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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