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Microwave-accelerated preparation and analytical characterization of 5-ethoxy-*N*,*N*-dialkyl-[α,α,β,β-H_4]- and [α,α,β,β-D_4]-tryptamines

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The increased interest in *N*,*N*-dialkyl tryptamines is a reflection of their diverse range of biologically active properties. Deuterated derivatives are of interest for use as internal standards in bioanalytical or pharmacological assays. The present study reports on the synthesis of twelve novel 5-ethoxy-*N*,*N*-dialkyl-[α,α,β,β-H_4]-tryptamines and their [α,α,β,β-D_4]-counterparts following the Speeter and Anthony procedure. The normally time-consuming reduction step was carried out in 5 min under microwave-accelerated conditions. Good yields were obtained using tetrahydrofuran as the solvent at 150 °C. The resulting 24 tryptamines have been characterized by 1D/2D nuclear magnetic resonance spectroscopy and gas chromatography ion trap mass spectrometry. Differential fragmentation of side-chain-related iminium ions has been observed as a key principle. Because many *N*,*N*-dialkyltryptamines are available outside of traditional pharmaceutical supply chains as so-called 'research chemicals', the availability, as standards, of these new *N*,*N*-dialkyltryptamines will aid in identifiying novel tryptamines arising from these other souces. They should therefore be of immediate value within forensic, research, and public health contexts.

Keywords: tryptamines; microwaves; forensic; clinical; deuteration; mass spectrometry

Introduction

Serotonin (5-hydroxytryptamine, 5-HT; Figure 1) plays a fundamental role in the modulation of many physiological processes in the central nervous system (CNS), the cardiovascular system, and the gastrointestinal tract. Structural alterations to the serotonin nucleus give rise to a plethora of bioactive molecules of medicinal interest. A common form of modification involves the addition of alkyl groups to the ethylamine side chain nitrogen. The *N*,*N*-dimethyltryptamine template is present in several structurally simple, but pharmacologically diverse, derivatives. For example, sumatriptan, the prototype of the so-called 'triptan' antimigraine drugs, is an *N*,*N*-dimethyltryptamine carrying a sulfonamide group at the 5-position of the indole ring, while the second-generation triptan rizatriptan carries a 1,2,4-triazolmethyl group at the 5-position. A number of closely related *N*,*N*-dimethyltryptamines, such as MS-245, PMDT (BGC20-761) and EMDT (Figure 1) have been studied extensively as ligands for 5-HT_6 receptors that are thought to be involved in a variety of CNS-related dysfunctions.[1–6] *N*,*N*-Dimethyltryptamine (DMT) and its 5-methoxy derivative (5-MeO-DMT), on the other hand, show powerful psychoactive and hallucinogenic activity in humans and are abundantly available in nature.[7,8] A related tryptamine, one of the main constituents of 'magic' mushrooms (i.e. *Psilocybe mexicana, P. cubensis*), is the *O*-phosphoryl-4-hydroxy derivative of DMT called psilocybin. While psilocybian mushrooms have been used for millenia for spiritual or ceremonial purposes by native populations,[7] psilocybin itself has been reported to produce mystical-type experiences in drug-naïve volunteers.[9,10] In the UK, it has been estimated that 337 000 users, aged 16–59, used 'magic' mushrooms recreationally in the year of 2004/2005.[11] There are also reports that this substance has potential for the treatment of cluster headaches[12,13] and obsessive-compulsive disorder.[14] In addition, there is increasing evidence that classical hallucinogens, such as psilocybin, show impressive potential for the treatment of a variety of mood disorders.[15]

Chain elongation of the *N*,*N*-dialkyl groups produces derivatives with a wide range of psychoactive effects. The variety of psychoactive effects are a consequence of diverse interactions with 5-HT receptors, alpha-adrenergic receptors, histamine H_1 receptors, sigma-1 receptors, several dopaminergic receptors,

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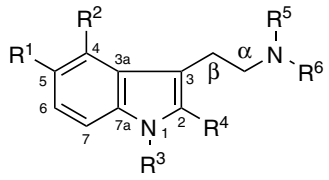


R^1 = HO; R^2 = R^3 = R^4 = R^5 = R^6 = H: Serotonin
R^1 = $CH_2SO_2NHCH_3$; R^2 = R^3 = R^4 = H; R^5 = R^6 = CH_3: Sumatriptan
R^1 = CH_3O; R^2 = R^4 = H; R^3 = $SO_2C_6H_5$; R^5 = R^6 = CH_3: MS-245
R^1 = CH_3O; R^2 = R^3 = H; R^4 = C_6H_5; R^5 = R^6 = CH_3: PMDT, BGC20-761
R^1 = CH_3O; R^2 = R^3 = H; R^4 = C_2H_5; R^5 = R^6 = CH_3: EMDT
R^1 = R^2 = R^3 = R^4 = H;R^5 = R^6 = CH_3: DMT
R^1 = CH_3O; R^2 = R^3 = R^4 = H; R^5 = R^6 = CH_3: 5-MeO-DMT
R^1 = H; R^2 = H_2O_3PO; R^3 = R^4 = H; R^5 = R^6 = CH_3: Psilocybin
R^1 = CH_3O; R^2 = R^3 = R^4 = H; R^5 = R^6 = $CH(CH_3)_2$: 5-MeO-DIPT, *Foxy*

Figure 1. Typical representatives of *N*,*N*-dialkylated tryptamines that show a variety of bio- and psychoactive properties.

and monoamine uptake transporters.[16–23] Knowledge about psychopharmacological properties of several naturally occurring *N*,*N*-dimethyl derivatives has been expanded throughout recent years[24] but less is known about their synthetic analogues. Most of the clinical and human pharmacological properties of synthetic *N*,*N*-dialkyl compounds are still to be investigated in detail. One of the few examples to appear in the literature was 5-methoxy-*N*,*N*-diisopropyltryptamine (5-MeO-DIPT, *Foxy*) (Figure 1), which has been linked to a number of toxic and fatal responses.[25–31]

The availability of novel tryptamines as drug standards and as investigatory tools is desired within forensic, clinical, research, and public health contexts, especially since many *N*,*N*-dialkyl tryptamines are available in the recreational drug market. In case of an overdose or other untoward reaction, effective treatment demands rapid and accurate identification of new compounds as they appear. Furthermore, structurally diverse tryptamines labelled with deuterium are also desirable as internal standards for pharmacokinetic and other bioanalytical studies.[32,33] To address these needs, the present study describes a rapid microwave-accelerated preparation of twelve 5-ethoxy-*N*,*N*-dialkyl-[α,α,β,β-H_4]-tryptamines and twelve 5-ethoxy-*N*,*N*-dialkyl-[α,α,β,β-D_4]-tryptamines. The analytical characterization of these previously unreported compounds was carried out by 1D/2D nuclear magnetic resonance spectroscopy (NMR) and gas chromatography ion trap mass spectrometry (GC-IT-MS). Both electron ionization (EI-IT-MS) and chemical ionization ion trap tandem mass spectrometry (CI-IT-MS-MS), with internal ionization using methanol as the chemical ionization reagent, were employed.

Experimental

Materials

Dimethylamine (aqueous, 60%), dipropylamine (98%), diisopropylamine (98%), N-ethylisopropylamine 98%) and oxalyl chloride (99%) were from Fluka and diethylamine (≥99%) was from Riedel-de Haën. Diallylamine (99%), N-methylpropylamine (96%), N-isopropylmethylamine (98%), N-ethyl-2-methylallylamine (98%), and *N*-allylcyclohexylamine (98%) were obtained from Aldrich (Dorset, UK). *N*-Ethylmethylamine (98%) and *N*-ethylpropylamine (98%) were from Alfa Aesar (Heysham, UK). 5-Hydroxyindole was purchased from Biosynth AG (Staad, Switzerland). All other solvents, reagents, and lithium aluminium deuteride (98 atom %) were also purchased from Aldrich (Dorset, UK) and were of analytical grade or equivalent.

Instrumentation

NMR spectra were recorded using a Bruker Avance 300 spectrometer at 300.1 MHz (^{1}H NMR) or 75.5 MHz (^{13}C NMR). Tryptamine spectra were taken in $CDCl_3$ and chemical shifts are reported relative to TMS at $\delta = 0$ ppm. NMR spectra were obtained by ^{1}H, proton decoupled ^{13}C, DEPT-135 and DEPT-90, HSQC and HMBC experiments. When d_6-DMSO was used, chemical shifts were determined relative to the residual solvent peak at $\delta = 2.51$ (^{1}H NMR) and $\delta = 39.6$ ppm (^{13}C NMR).

Microwave-accelerated syntheses were carried out using a monomode CEM Explorer (Buckingham, UK) microwave system. Operation settings were: microwave power 250 W, temperature 150 °C, maximum pressure 280 psi, ramp time 5 min, hold time 5 min. Reactions were performed in glass microwave tubes, closed with *Intellivent* caps (CEM) and contents of the vessel were continuously stirred by a Teflon-coated magnetic stir bar (10 × 3 mm). Temperature, pressure, and power profiles were monitored using the ChemDriver software version 3.6.0.

Samples were subjected to MS using both electron ionization (EI) and chemical ionization (CI) modes. Both EI and CI mass spectra (scan range *m/z* 40–*m/z* 500) were obtained on a Varian 220-MS ion trap MS equipped with a Varian 450-GC gas chromatograph and a Varian 8400 autosampler. Data handling was carried out using the Workstation, Version 6.91 software. The carrier gas was helium at a flow rate of 1 mL/min using the EFC constant flow mode. A CP-1177 injector (275 °C) was used in split mode (1 : 20). Transfer line, manifold and ion trap temperatures were set at 280, 80 and 220 °C, respectively. HPLC-grade methanol was used as the liquid CI reagent. CI ionization parameters (0.5 s/scan): CI storage level 19.0 *m/z*; ejection amplitude 15.0 *m/z*; background mass 55 *m/z*; maximum ionization time 2000 µs; maximum reaction time 40 ms; target TIC 5000 counts. The number of ions in the trap was controlled by an automatic gain control function. CI-IT-MS/MS spectra were obtained by collision-induced dissociation (CID) of the protonated molecule $[M + H]^+$ within the ion trap, using helium, by application of a CID waveform excitation amplitude set at 21 V in the non-resonant mode. Excitation storage level was set to 48.0 m/z. Separations were carried out using a 30 m × 0.25 mm (0.25 µm film thickness) Factor Four capillary column (VF-5 ms, Varian). The column temperature was programmed as follows: 100 °C held for 1 min, then heated at 20 °C/min to 280 °C and held constant for 10 min; total run time was 20 min.

Syntheses

5-Ethoxyindole (**b**)

A mixture of 5-hydroxyindole (**a**) (0.50 g, 3.8 mmol) and K_2CO_3 (1.52 g, 11.0 mmol), dissolved in 10 mL ethanol, was heated at reflux and followed by the addition of iodoethane (0.77 g, 4.9 mmol). The reaction was left at reflux for 2 h and the mixture was concentrated under reduce pressure. Water (20 ml) was added and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layer was dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography using 5% ethyl acetate/hexane (v/v) as eluent.

Yield: 0.53 g (3.3 mmol, 87%); colorless crystals; mp 36–38 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (1H, br s, N*H*), 7.26 (1H, d, J = 8.8 Hz, *H*-7), 7.14 (1H, t, J = 2.4 Hz, *H*-2), 7.06 (1H, d, J = 2.4 Hz, *H*-4), 6.86 (1H, dd, J = 8.8, 2.4 Hz, *H*-6), 6.46 (1H, m, *H*-3), 4.07 (2H, q, J = 7.0 Hz, OCH_2CH_3), 1.43 (3H, t, J = 7.0 Hz, OCH_2CH_3). ^{13}C NMR ($CDCl_3$) δ 153.4 (*C*-5), 130.9 (*C*-7a), 128.3 (*C*-3a), 124.8 (*C*-2), 113.0 (*C*-6), 111.7 (*C*-7), 103.5 (*C*-4), 102.4 (*C*-3), 64.2 (OCH_2CH_3), 15.1 (OCH_2CH_3). HRESIMS theory $[M + H]^+$: 162.0919; observed: 162.0917.

*5-Ethoxyindole-3-yl-glyoxalyl chloride (**c**)*

5-Ethoxyindole (**b**) (0.78 g, 3.1 mmol) was dissolved in 5 mL anhydrous diethyl ether and stirred on ice for 10 min. Oxalyl chloride (1.05 g, 8.3 mmol) was added dropwise and stirred on ice for 3 h. The crystalline product was filtered, washed with cold diethyl ether and dried in vacuo for 3 h at room temperature to give the product.

Yield: 0.61 g (2.6 mmol, 84%); yellow crystals; mp 128–130 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.20 (1H, br s, N*H*), 8.31 (1H, d, J = 3.4 Hz, *H*-4), 7.67 (1H, d, J = 2.4 Hz, *H*-2), 7.43 (1H, d, J = 8.9 Hz, *H*-7), 6.87 (1H, dd, J = 8.9, 2.4 Hz, *H*-6), 4.06 (2H, q, J = 7.0 Hz, OCH_2CH_3), 1.36 (3H, t, J = 7.0 Hz, OCH_2CH_3). ^{13}C NMR (DMSO-d_6) δ 180.5 (*CO*-β), 165.2 (*CO*-α), 155.2 (*C*-5), 137.7 (*C*-2), 131.3 (*C*-7a), 126.5 (*C*-3a), 113.6 (*C*-6), 113.3 (*C*-7), 112.2 (*C*-3), 103.9 (*C*-4), 63.3 (OCH_2CH_3), 14.7 (OCH_2CH_3). HRESIMS data was obtained from the sodiated adduct of the methyl ester derivative. Theory $[M + Na]^+$: 270.0742; observed: 270.0731.

*General procedure for 5-Ethoxyindole-3-yl-N,N-dialkyl glyoxalyl-amide precursors (**1**–**12**)*

5-Ethoxyindole-3-yl-glyoxalyl chloride (**c**) (0.78 g, 3.1 mmol) was dissolved in diethyl ether (5 mL). The appropriate amine (7 mmol) was added and the mixture was stirred for 2 h, then filtered and washed with 30 mL water. The crude product was recrystallized from MeOH/CH_2Cl_2 to give the corresponding amide.

*5-Ethoxyindole-3-yl-N,N-dimethylglyoxalylamide (**1**)*

Yield: 0.5 g (1.9 mmol, 61%); white crystals; mp 190–192 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.42 (1H, br s, N*H*), 7.81 (1H, d, J = 2.4 Hz, *H*-4), 7.76 (1H, d, J = 3.3 Hz, *H*-2), 7.25 (1H, d, J = 8.3 Hz, *H*-7), 6.91 (1H, dd, J = 8.9, 2.5 Hz, *H*-6), 4.12 (2H, q, J = 7.0 Hz, OCH_2CH_3), 3.09 (3H, s, NCH_3), 3.05 (3H, s, NCH_3), 1.43 (3H, t, J = 7.0 Hz, OCH_2CH_3). ^{13}C NMR ($CDCl_3$) δ 185.3 (*CO*-β), 167.8 (*CO*-α), 156.1 (*C*-5), 135.4 (*C*-2), 131.2 (*C*-7a), 126.3 (*C*-3a), 115.2 (*C*-6), 114.5 (*C*-3), 112.5 (*C*-7), 104.3 (*C*-4), 64.0 (OCH_2CH_3), 37.5 (NCH_3), 34.4 (NCH_3), 14.9 (OCH_2CH_3). HRESIMS theory $[M + Na]^+$: 283.1059; observed: 283.1054.

*5-Ethoxyindole-3-yl-N,N-diethylglyoxalylamide (**2**)*

Yield: 0.37 g (1.3 mmol, 42%); white crystals; mp 136–138 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.59 (1H, br s, N*H*), 7.79 (1H, d, J = 2.3 Hz, *H*-4), 7.67 (1H, d, J = 3.2 Hz, *H*-2), 7.22 (1H, d, J = 8.8 Hz, *H*-7), 6.89 (1H, dd, J = 8.9, 2.5 Hz, *H*-6), 4.11 (2H, q, J = 7.0 Hz, OCH_2CH_3), 3.53 (2H, q, J = 7.0 Hz, NCH_2CH_3), 3.52 (2H, q, J = 7.0 Hz, NCH_2CH_3), 1.44 (3H, t, J = 7.0 Hz, OCH_2CH_3), 1.25 (3H, t, J = 7.1 Hz, NCH_2CH_3), 1.18 (3H, t, J = 7.1 Hz, NCH_2CH_3). ^{13}C NMR ($CDCl_3$) δ 186.2 (*CO*-β), 167.7 (*CO*-α), 156.0 (*C*-5), 135.2 (*C*-2), 131.2 (*C*-7a), 126.2 (*C*-3a), 115.0 (*C*-6), 114.4 (*C*-3), 112.6 (*C*-7), 104.2 (*C*-4), 64.0 (OCH_2CH_3), 42.4 (NCH_2CH_3), 39.1 (NCH_2CH_3), 14.9 (OCH_2CH_3), 14.3 (NCH_2CH_3), 12.8 (NCH_2CH_3). HRESIMS theory $[M + Na]^+$: 311.1372; observed: 311.1369.

*5-Ethoxyindole-3-yl-N,N-dipropylglyoxalylamide (**3**)*

Yield: 0.66 g (2.1 mmol, 68%); white crystals; mp 102–104 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.91 (1H, br s, N*H*), 7.79 (1H, d, J = 2.4 Hz, *H*-4), 7.67 (1H, s, *H*-2), 7.24 (1H, d, J = 8.9 Hz, *H*-7), 6.88 (1H, dd, J = 8.9, 2.6 Hz, *H*-6), 4.11 (2H, q, J = 7.0 Hz, OCH_2CH_3), 3.43 (2H, t, J = 7.4 Hz, $NCH_2CH_2CH_3$), 3.25 (2H, t, J = 7.4 Hz, $NCH_2CH_2CH_3$), 1.76-1.53 (4H, m, 2 × $NCH_2CH_2CH_3$), 1.44 (3H, t, J = 7.0 Hz, OCH_2CH_3), 0.98 (3H, t, J = 7.4 Hz, $NCH_2CH_2CH_3$), 0.79 (3H, t, J = 7.4 Hz, $NCH_2CH_2CH_3$). ^{13}C NMR ($CDCl_3$) δ 186.2 (*CO*-β), 168.2 (*CO*-α), 156.0 (*C*-5), 135.3 (*C*-2), 131.4 (*C*-7a), 126.2 (*C*-3a), 115.0 (*C*-6), 114.4 (*C*-3), 112.7 (*C*-7), 104.3 (*C*-4), 64.0 (OCH_2CH_3), 49.6 ($NCH_2CH_2CH_3$), 46.2 ($NCH_2CH_2CH_3$), 21.9 ($NCH_2CH_2CH_3$), 20.6 ($NCH_2CH_2CH_3$), 14.9 (OCH_2CH_3), 14.4 ($NCH_2CH_2CH_3$), 11.1 ($NCH_2CH_2CH_3$). HRESIMS theory $[M + Na]^+$: 339.1685; observed: 339.1678.

*5-Ethoxyindole-3-yl-N,N-diisopropylglyoxalylamide (**4**)*

Yield: 0.36 g (1.1 mmol, 35%); white crystals; mp 160–163 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.10 (1H, br s, N*H*), 7.76 (1H, d, J = 2.2 Hz, *H*-4), 7.57 (1H, d, J = 2.8 Hz, *H*-2), 7.26 (1H, d, J = 8.9 Hz, *H*-7), 6.87 (1H, dd, J = 8.9, 2.4 Hz, *H*-6), 4.10 (2H, q, J = 7.0 Hz, OCH_2CH_3), 3.95 (1H, sep, J = 6.7 Hz, NC*H*), 3.55 (1H, sep, J = 6.7 Hz, NC*H*), 1.53 (6H, d, J = 6.7 Hz, 2 × CH_3), 1.45 (6H, d, J = 6.7 Hz, 2 × CH_3), 1.44 (3H, t, J = 7.0 Hz, OCH_2CH_3). ^{13}C NMR ($CDCl_3$) δ 186.3 (*CO*-β), 168.2 (*CO*-α), 155.9 (*C*-5), 134.8 (*C*-2), 131.6 (*C*-7a), 126.1 (*C*-3a), 114.9 (*C*-6), 113.9 (*C*-3), 112.9 (*C*-7), 104.0 (*C*-4), 64.0 (OCH_2CH_3), 50.4 (NCH), 45.9 (NCH), 20.6 (CH_3), 20.3 (CH_3), 14.9 (OCH_2CH_3). HRESIMS theory $[M + Na]^+$: 339.1685; observed: 339.1696.

*5-Ethoxyindole-3-yl-N,N-diallylglyoxalylamide (**5**)*

Yield: 0.61g (2.0 mmol, 65%); white crystals; mp 138–140 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.67 (1H, br s, N*H*), 7.79 (1H, d, J = 2.3 Hz, *H*-4), 7.69 (1H, d, J = 3.0 Hz, *H*-2), 7.22 (1H, d, J = 8.8 Hz, *H*-7), 6.88 (1H, dd, J = 8.9, 2.5 Hz, *H*-6), 5.81 (2H, m, 2 × C*H*=CH_2), 5.23 (4H, m, 2 × CH=CH_2), 4.10 (4H, q, J = 7.0 Hz, OCH_2CH_3, NCH_2), 3.93 (2H, d, J = 5.8 Hz, NCH_2), 1.43 (3H, t, J = 7.0 Hz, OCH_2CH_3). ^{13}C NMR ($CDCl_3$) δ 185.5 (*CO*-β), 167.9 (*CO*-α), 156.1 (*C*-5), 135.5 (*C*-2), 132.8 (*CH*=CH_2), 131.9 (*CH*=CH_2), 131.3 (*C*-7a), 126.2 (*C*-3a), 118.9 (CH=CH_2), 118.2 (CH=CH_2), 115.1 (*C*-6), 114.3 (*C*-3), 112.7 (*C*-7), 104.2 (*C*-4), 64.0 (OCH_2CH_3), 49.9 (NCH_2), 46.6 (NCH_2), 14.9 (OCH_2CH_3). HRESIMS theory $[M + Na]^+$: 335.1372; observed: 335.1377.

*5-Ethoxyindole-3-yl-N-methyl-N-propylglyoxalylamide (**6**)*

Yield: 0.66 g (2.3 mmol, 74%); white crystals; mp 98–100 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.36 (0.6H, br s, N*H*), 9.25 (0.4H, br s, N*H*), 7.80 (0.6H, d, J = 2.3 Hz, *H*-4), 7.48 (0.4H, d, J = 2.3 Hz, *H*-4), 7.65 (0.4H, d, J = 3.0 Hz, *H*-2), 7.58 (0.6H, d, J = 3.0 Hz, *H*-2), 7.27 (1H, d, J = 9.2 Hz, *H*-7), 6.89 (1H, dd, J = 8.9, 2.3 Hz, *H*-6), 4.12 (2H, q, J = 7.0 Hz, OCH_2CH_3), 3.46 (0.8H, t, J = 7.5 Hz, $NCH_2CH_2CH_3$), 3.28 (1.2H, t, J = 7.5 Hz, $NCH_2CH_2CH_3$), 3.04 (1.8H, s, NCH_3), 3.01 (1.2H, s, NCH_3), 1.74-1.55 (2H, m, $NCH_2CH_2CH_3$), 1.45 (3H, t, J = 7.0 Hz, OCH_2CH_3), 0.99 (1.2H, t, J = 7.3 Hz, $NCH_2CH_2CH_3$), 0.81 (1.8H, t, J = 7.3 Hz, $NCH_2CH_2CH_3$). ^{13}C NMR ($CDCl_3$) δ 186.1 (*CO*-β), 185.6 (*CO*-β), 168.6 (*CO*-α), 156.1 (*C*-5), 135.6 (*C*-2), 131.5 (*C*-7a), 126.2 (*C*-3a), 114.9 (*C*-6), 114.1 (*C*-3), 112.9 (*C*-7), 104.3 (*C*-4), 64.0 (OCH_2CH_3), 51.8 ($NCH_2CH_2CH_3$), 48.5 ($NCH_2CH_2CH_3$), 35.4 (NCH_3), 32.0 (NCH_3), 21.3 ($NCH_2CH_2CH_3$), 20.1 ($NCH_2CH_2CH_3$), 14.9 (OCH_2CH_3), 11.2 ($NCH_2CH_2CH_3$), 10.9 ($NCH_2CH_2CH_3$). HRESIMS theory $[M + Na]^+$: 311.1372; observed: 311.1384

*5-Ethoxyindole-3-yl-N-methyl-N-isopropylglyoxalylamide (**7**)*

Yield: 0.41 g (1.4 mmol, 45%); white crystals; mp 68–70 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.06 (0.7H, br s, N*H*), 9.90 (0.3H, br s, N*H*), 7.78 (1H, s, *H*-4), 7.64 (0.3H, d, J = 3.2 Hz, *H*-2), 7.52 (0.7H, d, J = 3.2 Hz, *H*-2), 7.21 (1H, d, J = 8.9 Hz, *H*-7), 6.87 (1H, dd, J = 8.9, 2.4 Hz, *H*-6), 4.89 (1H, m, NC*H*), 4.10 (2H, q, J = 7.0 Hz, OCH_2CH_3), 2.92 (2.1H, s, NCH_3), 2.86 (0.9H, s, NCH_3), 1.43 (3H, t, J = 7.0 Hz, OCH_2CH_3), 1.22 (1.8H, d, J = 7.0 Hz, 2 × CH_3), 1.16 (4.2H, d, J = 6.6 Hz, 2 × CH_3). ^{13}C NMR ($CDCl_3$) δ 186.3 (*C*O-β), 168.1 (*C*O-α), 156.1 (*C*-5), 135.2 (*C*-2), 131.5 (*C*-7a), 126.1 (*C*-3a), 115.1 (*C*-6), 114.3 (*C*-3), 112.8 (*C*-7), 104.1 (*C*-4), 64.0 (OCH_2CH_3), 49.3 (NCH), 44.2 (NCH), 28.9 (NCH_3), 25.1 (NCH_3), 20.3 (CH_3), 19.2 (CH_3), 14.9 (OCH_2CH_3). HRESIMS theory $[M + Na]^+$: 311.1372; observed: 311.1356.

*5-Ethoxyindole-3-yl-N-ethyl-N-isopropylglyoxalylamide (**8**)*

Yield: 0.70 g (2.3 mmol, 74%); white crystals; mp 124–126 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.48 (0.3H, br s, N*H*), 10.40 (0.7H, br s, N*H*), 7.78 (1H, d, J = 2.3 Hz, *H*-4), 7.55 (0.3H, d, J = 2.8 Hz, *H*-2), 7.45 (0.7H, d, J = 2.8 Hz, *H*-2), 7.17 (0.7H, d, J = 8.8 Hz, *H*-7), 7.15 (0.3H, d, J = 8.8 Hz, *H*-7), 6.83 (1H, dd, J = 8.8, 2.3 Hz, *H*-6), 4.57 (1H, m, NC*H*), 4.09 (2H, q, J = 7.0 Hz, OCH_2CH_3), 3.39 (1.4H, q, J = 7.0 Hz, NCH_2CH_3), 3.31 (0.6H, q, J = 7.1 Hz, NCH_2CH_3), 1.42 (3H, t, J = 7.0 Hz, OCH_2CH_3), 1.30 (3H, t, J = 7.0 Hz, NCH_2CH_3), 1.12 (6H, d, J = 6.8 Hz, 2 × CH_3). ^{13}C NMR ($CDCl_3$) δ 186.4 (*C*O-β), 168.5 (*C*O-α), 168.1 (*C*O-α), 156.0 (*C*-5), 135.2 (*C*-2), 131.6 (*C*-7a), 126.1 (*C*-3a), 115.0 (*C*-6), 114.8 (*C*-6), 114.1 (*C*-3), 113.0 (*C*-7), 112.9 (*C*-7), 104.1 (*C*-4), 64.0 (OCH_2CH_3), 49.9 (NCH), 46.6 (NCH), 39.3 (NCH_2CH_3), 35.2 (NCH_2CH_3), 21.1 (CH_3), 20.3 (CH_3), 16.6 (NCH_2CH_3), 14.9 (OCH_2CH_3), 14.6 (NCH_2CH_3). HRESIMS theory $[M + Na]^+$: 325.1528; observed: 325.1534.

*5-Ethoxyindole-3-yl-N-ethyl-N-methylglyoxalylamide (**9**)*

Yield: 0.51 g (1.9 mmol, 61%); white crystals; mp 98–100 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.50 (0.6H, br s, N*H*), 9.24 (0.4H, br s, N*H*), 7.76 (1H, s, *H*-4), 7.64 (0.4H, d, J = 3.2 Hz, *H*-2), 7.58 (0.6H, d, J = 3.2 Hz, *H*-2), 7.26 (1H, d, J = 8.8 Hz, *H*-7), 6.87 (1H, dd, J = 8.8, 2.4 Hz, *H*-6), 4.10 (2H, q, J = 7.0 Hz, OCH_2CH_3), 3.35 (0.8H, q, J = 7.2 Hz, NCH_2CH_3), 3.33 (1.2H, q, J = 7.2 Hz, NCH_2CH_3), 3.02 (1.8H, s, NCH_3), 2.99 (1.2H, s, NCH_3), 1.43 (3H, t, J = 7.0 Hz, OCH_2CH_3), 1.22 (1.8H, t, J = 7.2 Hz, NCH_2CH_3), 1.16 (1.2H, t, J = 7.2 Hz, NCH_2CH_3). ^{13}C NMR ($CDCl_3$) δ 186.0 (*C*O-β), 185.9 (*C*O-β), 168.4 (*C*O-α), 167.8 (*C*O-α), 156.1 (*C*-5), 135.7 (*C*-2), 131.6 (*C*-7a), 126.1 (*C*-3a), 115.0 (*C*-6), 113.9 (*C*-3), 113.0 (*C*-7), 104.2 (*C*-4), 64.0 (OCH_2CH_3), 45.1 (NCH_2CH_3), 41.8 (NCH_2CH_3), 34.9 (NCH_3), 31.5 (NCH_3), 14.9 (OCH_2CH_3), 11.9 (NCH_2CH_3), 13.6 (NCH_2CH_3). HRESIMS theory $[M + Na]^+$: 297.1200; observed: 297.1202.

*5-Ethoxyindole-3-yl-N-ethyl-N-propylglyoxalylamide (**10**)*

Yield: 0.74g (2.4 mmol, 77%); white crystals; mp 100–102 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.65 (1H, br s, N*H*), 7.76 (1H, s, *H*-4), 7.50 (1H, d, J = 2.7 Hz, *H*-2), 7.16 (1H, d, J = 8.9 Hz, *H*-7), 6.83 (1H, dd, J = 8.9, 1.9 Hz, *H*-6), 4.08 (2H, q, J = 7.0 Hz, OCH_2CH_3), 3.49 (0.8H, q, J = 7.2 Hz, NCH_2CH_3), 3.40 (1.2H, t, J = 7.2 Hz, $NCH_2CH_2CH_3$), 3.33 (1.2H, q, J = 7.2 Hz, NCH_2CH_3), 3.23 (0.8H, t, J = 7.2 Hz, $NCH_2CH_2CH_3$), 1.65 (1.2H, m, $NCH_2CH_2CH_3$), 1.59 (0.8H, m, $NCH_2CH_2CH_3$), 1.42 (3H, t, J = 7.0 Hz, OCH_2CH_3), 1.22 (1.8H, t, J = 7.2 Hz, NCH_2CH_3), 1.14 (1.2H, t, J = 7.2 Hz, NCH_2CH_3), 0.99 (1.8H, t, J = 7.3 Hz, $NCH_2CH_2CH_3$), 0.77 (1.2H, t, J = 7.3 Hz, $NCH_2CH_2CH_3$). ^{13}C NMR ($CDCl_3$) δ 186.0 (*C*O-β), 168.4 (*C*O-α), 168.3 (*C*O-α), 156.0 (*C*-5), 135.5 (*C*-2), 131.6 (*C*-7a), 126.1 (*C*-3a), 114.9 (*C*-6), 114.0 (*C*-3), 113.0 (*C*-7), 104.1 (*C*-4), 64.0 (OCH_2CH_3), 49.5 ($NCH_2CH_2CH_3$), 45.8 ($NCH_2CH_2CH_3$), 42.8 (NCH_2CH_3), 39.6 (NCH_2CH_3), 22.0 ($NCH_2CH_2CH_3$), 20.7 ($NCH_2CH_2CH_3$), 14.9 (OCH_2CH_3), 14.2 (NCH_2CH_3), 12.7 (NCH_2CH_3), 11.4 ($NCH_2CH_2CH_3$), 11.1 ($NCH_2CH_2CH_3$). HRESIMS theory $[M + Na]^+$: 325.1528; observed: 325.1530.

*5-Ethoxyindole-3-yl-N-ethyl-N-(2-methylallyl)glyoxalylamide (**11**)*

Yield: 0.66 g (2.1 mmol, 68%); white crystals; mp 128–130 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (0.6H, br s, N*H*), 9.57 (0.4H, br s, N*H*), 7.80 (0.6H, d, J = 2.3 Hz, *H*-4), 7.78 (0.4H, d, J = 2.3 Hz, *H*-4), 7.66 (1H, m, *H*-2), 7.22 (0.4H, d, J = 8.8 Hz, *H*-7), 7.21 (0.6H, d, J = 8.8 Hz, *H*-7), 6.91 (1H, m, *H*-6), 4.95 (0.8H, s, C=CH_2), 4.85 (1.2H, s, C=CH_2), 4.15-4.08 (2H, m, OCH_2CH_3), 4.07 (1.2H, s, NCH_2), 3.91 (0.8H, s, NCH_2), 3.48 (0.8H, q, J = 7.2 Hz, NCH_2CH_3), 3.33 (1.2H, q, J = 7.1 Hz, NCH_2CH_3), 1.77 (1.8H, s, CH_3), 1.63 (1.2H, s, CH_3), 1.44 (1.8H, t, J = 7.0 Hz, OCH_2CH_3), 1.43 (1.2H, t, J = 7.0 Hz, OCH_2CH_3), 1.21 (1.2H, t, J = 7.1 Hz, NCH_2CH_3), 1.16 (1.8H, t, J = 7.1 Hz, NCH_2CH_3). ^{13}C NMR ($CDCl_3$) δ 185.9 (*C*O-β), 168.2 (*C*O-α), 156.1 (*C*-5), 140.0 (*C*=CH_2), 139.9 (*C*=CH_2), 135.3 (*C*-2), 131.4 (*C*-7a), 126.2 (*C*-3a), 115.1 (*C*-6), 113.9 (CH_2), 112.8 (CH_2), 114.4 (*C*-3), 112.7 (*C*-7), 104.2 (*C*-4), 64.0 (OCH_2CH_3), 53.2 (NCH_2), 48.9 (NCH_2), 42.0 (NCH_2CH_3), 38.9 (NCH_2CH_3), 20.1 (CH_3), 19.8 (CH_3), 14.9 (OCH_2CH_3), 13.8 (NCH_2CH_3), 12.1 (NCH_2CH_3). HRESIMS theory $[M + Na]^+$: 337.1528; observed: 337.1530.

*5-Ethoxyindole-3-yl-N-allyl-N-cyclohexylglyoxalylamide (**12**)*

Yield: 0.58g (1.6 mmol, 52%); white crystals; mp 72–74 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.90 (0.6H, br s, N*H*), 9.70 (0.4H, br s, N*H*), 7.78 (0.6H, d, J = 2.2 Hz, *H*-4), 7.76 (0.4H, d, J = 2.3 Hz, *H*-4), 7.64 (0.4H, d, J = 3.3 Hz, *H*-2), 7.55 (0.6H, d, J = 3.3 Hz, *H*-2), 7.21 (0.4H, d, J = 8.8 Hz, *H*-7), 7.19 (0.6H, d, J = 8.8 Hz, *H*-7), 6.89-6.84 (1H, m, *H*-6), 5.93 (0.6H, ddt, $^3J_{trans}$ = 17.2 Hz, $^3J_{cis}$ = 10.3 Hz, ^3J = 5.5 Hz, *C*H=CH_2), 5.78 (0.4H, ddt, $^3J_{trans}$ = 14.2 Hz, $^3J_{cis}$ = 10.2 Hz, ^3J = 5.9 Hz, *C*H=CH_2), 5.28 (0.6H, dd, J = 17.2, 1.3 Hz, CH=CH_{trans}), 5.18 (0.6H, dd, J = 10.3, 1.3 Hz, CH=CH_{cis}), 5.08 (0.4H, dd, J = 17.2, 1.1 Hz, CH=CH_{trans}), 5.00 (0.4H, dd, J = 10.2, 1.1 Hz, CH=CH_{cis}), 4.28 (0.4H, m, NC*H*), 4.11 (1.2H, q, J = 7.0 Hz, OCH_2CH_3), 4.09 (0.8H, q, J = 6.9 Hz, OCH_2CH_3), 4.03 (1.2H, d, J = 5.5 Hz, NCH_2), 3.93 (0.8H, d, J = 5.9 Hz, NCH_2), 3.61 (0.6H, m, NC*H*), 1.46-1.40 (3H, m, OCH_2CH_3), 1.90-1.10 (10H, m, 5 × CH_2). ^{13}C NMR ($CDCl_3$) δ 186.1 (*C*O-β), 168.3 (*C*O-α), 155.9 (*C*-5), 135.5 (*C*-2), 135.2 (CH=CH_2), 134.3 (CH=CH_2), 131.4 (*C*-7a), 126.2 (*C*-3a), 117.5 (CH=CH_2), 116.8 (CH=CH_2), 115.0 (*C*-6), 114.4 (*C*-3), 112.7 (*C*-7), 104.2 (*C*-4), 64.0 (OCH_2CH_3), 58.3 (NCH), 54.7 (NCH), 47.3 (NCH_2), 43.6 (NCH_2), 37.7 (CH_2), 30.6 (CH_2), 25.9 (CH_2), 25.5 (CH_2), 25.1 (CH_2), 14.9 (OCH_2CH_3). HRESIMS theory $[M + Na]^+$: 377.1841; observed: 377.1837.

General procedure for the microwave-accelerated synthesis of 5-ethoxy-N,N-dialkyltryptamine derivatives **1a**–**12a**

To a microwave tube were added a stirrer bar and the corresponding glyoxalylamide (0.3 mmol). Ice-cold THF (3 mL) was added and lithium aluminium hydride (LAH) (1.8 mmol) was added with vigorous stirring on ice. The tube was sealed and the reaction mixture was heated in the microwave system under the conditions described above. At the end of the reaction, the

excess hydride was destroyed by adding a few drops of water, followed by a few drops of 20% NaOH (*v*/*v*). The precipitated inorganic salts were removed by filtration and washed with 30 mL THF. The filtrate was evaporated under reduced pressure and the resulting oily residue was dissolved in 40 mL CH_2Cl_2. The CH_2Cl_2 solution was washed with 20% HCl (20 mL) and the aqueous layer was extracted with 20 mL CH_2Cl_2. The combined CH_2Cl_2 layer was dried over anhydrous Mg_2SO_4 and evaporated to dryness. The resulting product was recrystallized from CH_2Cl_2 and EtOAc to give the corresponding $\alpha,\alpha,\beta,\beta$-$H_4$-tryptamine hydrochloride salts. In cases where salt formation was unsuccessful, data of the free base products are reported.

*5-Ethoxy-N,N-dimethyltryptamine base (**1a**)*

Yield: 48.8 mg (0.21 mmol, 70%); yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (1H, br s, N*H*), 7.20 (1H, d, J = 8.8 Hz, *H*-7), 7.05 (1H, d, J = 2.4 Hz, *H*-4), 6.98 (1H, d, J = 2.4 Hz, *H*-2), 6.84 (1H, dd, J = 8.8, 2.4 Hz, *H*-6), 4.08 (2H, q, J = 7.0 Hz, OCH_2CH_3), 2.92 (3H, m, β-CH_2), 2.65 (3H, m, α-CH_2), 2.36 (6H, s, 2 × NCH_3), 1.43 (3H, t, J = 7.0 Hz, OCH_2CH_3). ^{13}C NMR ($CDCl_3$) δ 153.2 (*C*-5), 131.5 (*C*-7a), 127.9 (*C*-3a), 122.3 (*C*-2), 112.7 (*C*-6), 111.8 (*C*-7), 114.0 (*C*-3), 102.1 (*C*-4), 64.3 (OCH_2CH_3), 60.2 (α-CH_2), 45.4 (NCH_3), 23.7 (β-CH_2), 15.1 (OCH_2CH_3). HRESIMS theory $[M + H]^+$: 233.1654; observed: 233.1656.

*5-Ethoxy-N,N-diethyltryptamine HCl (**2a**)*

Yield: 63.3 mg (0.21 mmol, 70%); white crystals; mp 179–181 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.08 (1H, br s, N*H*Cl), 9.02 (1H, br s, N*H*), 7.28 (1H, d, J = 8.8 Hz, *H*-7), 7.04 (1H, d, J = 2.3 Hz, *H*-4), 7.01 (1H, s, *H*-2), 6.82 (1H, dd, J = 8.8, 2.3 Hz, *H*-6), 4.10 (2H, q, J = 7.0 Hz, OCH_2CH_3), 3.26-3.10 (8H, m, 2 × NCH_2CH_3, α-CH_2, β-CH_2), 1.42-1.36 (9H, m, 2 × NCH_2CH_3, OCH_2CH_3). ^{13}C NMR ($CDCl_3$) δ 153.4 (*C*-5), 131.5 (*C*-7a), 127.0 (*C*-3a), 123.3 (*C*-2), 112.8 (*C*-6), 112.4 (*C*-7), 109.3 (*C*-3), 101.3 (*C*-4), 64.4 (OCH_2CH_3), 51.7 (α-CH_2), 46.4 (NCH_2CH_3), 20.1 (β-CH_2), 15.1 (OCH_2CH_3), 8.6 (NCH_2CH_3). HRESIMS theory $[M + H]^+$: 261.1967; observed: 261.1963.

*5-Ethoxy-N,N-dipropyltryptamine HCl (**3a**)*

Yield: 65.0 mg (0.20 mmol, 67%); white crystals; mp 190–192 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.12 (1H, br s, N*H*Cl), 8.66 (1H, br s, N*H*), 7.31 (1H, d, J = 8.8 Hz, *H*-7), 7.06 (1H, d, J = 2.1 Hz, *H*-4), 7.00 (1H, s, *H*-2), 6.83 (1H, dd, J = 8.8, 2.4 Hz, *H*-6), 4.10 (2H, q, J = 7.0 Hz, OCH_2CH_3), 3.00 (4H, m, 2 × $NCH_2CH_2CH_3$), 3.21 (4H, m, α-CH_2, β-CH_2), 1.84 (4H, m, 2 × $NCH_2CH_2CH_3$), 1.42 (3H, t, J = 7.0 Hz, OCH_2CH_3), 0.89 (6H, t, J = 7.3 Hz, 2 × $NCH_2CH_2CH_3$). ^{13}C NMR ($CDCl_3$) δ 153.5 (*C*-5), 131.5 (*C*-7a), 127.1 (*C*-3a), 123.1 (*C*-2), 112.9 (*C*-6), 112.4 (*C*-7), 109.5 (*C*-3), 101.4 (*C*-4), 64.4 (OCH_2CH_3), 54.0 ($NCH_2CH_2CH_3$), 52.8 (α-CH_2), 20.1 (β-CH_2), 16.8 ($NCH_2CH_2CH_3$), 15.1 (OCH_2CH_3), 11.2 ($NCH_2CH_2CH_3$). HRESIMS theory $[M + H]^+$: 289.2280; observed: 289.2277.

*5-Ethoxy-N,N-diisopropyltryptamine HCl (**4a**)*

Yield: 77.9 mg (0.24 mmol, 80%); white crystals; mp 184–186 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.42 (1H, br s, N*H*Cl), 8.40 (1H, br s, N*H*), 7.30 (1H, d, J = 8.8 Hz, *H*-7), 7.09 (1H, s, *H*-4), 7.03 (1H, d, J = 2.3 Hz, *H*-2), 6.87 (1H, dd, J = 8.8, 2.3 Hz, *H*-6), 4.08 (2H, q, J = 7.0 Hz, OCH_2CH_3), 3.69 (2H, m, 2 × N*CH*), 3.42 (2H, m, β-CH_2), 3.17 (2H, m, α-CH_2), 1.59 (6H, d, J = 6.6 Hz, 2 × CH_3), 1.47 (6H, d, J = 6.6 Hz, 2 × CH_3), 1.42 (3H, m, OCH_2CH_3). ^{13}C NMR ($CDCl_3$) δ 153.4 (*C*-5), 131.6 (*C*-7a), 127.1 (*C*-3a), 123.4 (*C*-2), 112.8 (*C*-6), 112.3 (*C*-7), 110.3 (*C*-3), 101.4 (*C*-4), 64.4 (OCH_2CH_3), 54.5 (NCH), 48.1 (α-CH_2), 23.3 (β-CH_2), 18.7 (CH_3), 17.2 (CH_3), 15.1 (OCH_2CH_3). HRESIMS theory $[M + H]^+$: 289.2280; observed: 289.2283.

*5-Ethoxy-N,N-diallyltryptamine HCl (**5a**)*

Yield: 77.0 mg (0.24 mmol, 80%); white crystals; mp 176–178 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.80 (1H, br s, N*H*Cl), 8.37 (1H, br s, N*H*), 7.29 (1H, d, J = 8.9 Hz, *H*-7), 7.06 (2H, s, *H*-4), 7.41 (1H, d, J = 2.3 Hz, *H*-2), 6.87 (1H, dd, J = 8.9, 2.3 Hz, *H*-6), 6.25-6.11, (2H, m, 2 × CH=CH_2), 5.56 (2H, d, J = 10.2 Hz, 2 × CH=CH_{cis}), 5.48 (2H, d, J = 17.0 Hz, 2 × CH=CH_{trans}), 4.10 (2H, q, J = 7.0 Hz, OCH_2CH_3), 3.69 (4H, m, 2 × NCH_2), 3.32 (2H, m, β-CH_2) 3.20 (2H, m, α-CH_2), 1.44 (3H, t, J = 7.0 Hz, OCH_2CH_3). ^{13}C NMR ($CDCl_3$) δ 153.6 (*C*-5), 131.4 (*C*-7a), 127.1 (*C*-3a), 126.2 (CH=CH_2), 125.8 (CH=CH_2), 123.4 (*C*-2), 113.1 (*C*-6), 112.3 (*C*-7), 109.5 (*C*-3), 101.5 (*C*-4), 64.4 (OCH_2CH_3), 54.9 (NCH_2), 52.1 (α-CH_2), 20.4 (β-CH_2), 15.1 (OCH_2CH_3). HRESIMS theory $[M + H]^+$: 285.1967; observed: 285.1970.

*5-Ethoxy-N-methyl-N-propyltryptamine HCl (**6a**)*

Yield: 59.3 mg (0.20 mmol, 67%); white crystals; mp 124–126 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.34 (1H, br s, N*H*Cl), 8.56 (1H, br s, N*H*), 7.30 (1H, d, J = 8.7 Hz, *H*-7), 7.08 (1H, d, J = 2.1 Hz, *H*-4), 7.02 (1H, s, *H*-2), 6.87 (1H, dd, J = 8.7, 2.3 Hz, *H*-6), 4.11 (2H, q, J = 7.0 Hz, OCH_2CH_3), 3.33-3.22 (4H, m, α-CH_2, β-CH_2), 3.19-2.83 (2H, m, $NCH_2CH_2CH_3$), 2.78 (3H, d, J = 5.1 Hz, NCH_3), 2.00-1.76 (2H, m, $NCH_2CH_2CH_3$), 1.43 (3H, t, J = 7.0 Hz, OCH_2CH_3), 1.00 (3H, t, J = 7.3 Hz, $NCH_2CH_2CH_3$). ^{13}C NMR ($CDCl_3$) δ 153.6 (*C*-5), 131.5 (*C*-7a), 127.1 (*C*-3a), 123.2 (*C*-2), 113.0 (*C*-6), 112.3 (*C*-7), 109.4 (*C*-3), 101.5 (*C*-4), 64.5 (OCH_2CH_3), 57.6 ($NCH_2CH_2CH_3$), 56.0 (α-CH_2), 39.9 (NCH_3), 20.4 (β-CH_2), 17.2 ($NCH_2CH_2CH_3$), 15.1 (OCH_2CH_3), 11.1 ($NCH_2CH_2CH_3$). HRESIMS theory $[M + H]^+$: 261.1967; observed: 261.1981

*5-Ethoxy-N-methyl-N-isopropyltryptamine HCl (**7a**)*

Yield: 68.2 mg (0.23 mmol, 76%); white crystals; mp 112–114 °C. ^{1}H NMR (300 MHz, $CDCl_3$) 12.11 (1H, br s, N*H*Cl), 8.59 (1H, br s, N*H*), 7.30 (1H, d, J = 8.9 Hz, *H*-7), 7.11 (1H, d, J = 1.5 Hz, *H*-4), 7.05 (1H, s, *H*-2), 6.88 (1H, dd, J = 8.9, 1.9 Hz, *H*-6), 4.11 (2H, q, J = 7.0 Hz, OCH_2CH_3), 3.58 (1H, m, β-CH_2), 3.42 (1H, m, β-CH_2), 3.23 (2H, m, α-CH_2), 3.06 (1H, m, N*CH*), 2.69 (3H, s, NCH_3), 1.43 (3H, t, J = 7.0 Hz, OCH_2CH_3), 1.33 (6H, d, J = 6.4 Hz, 2 × CH_3). ^{13}C NMR ($CDCl_3$) δ 153.5 (*C*-5), 131.5 (*C*-7a), 127.1 (*C*-3a), 123.4 (*C*-2), 113.0 (*C*-6), 112.3 (*C*-7), 109.7 (*C*-3), 101.6 (*C*-4), 64.5 (OCH_2CH_3), 56.3 (NCH), 53.4 (α-CH_2), 35.0 (NCH_3), 20.8 (β-CH_2), 17.4 (CH_3), 15.1 (OCH_2CH_3). HRESIMS theory $[M + H]^+$: 261.1967; observed: 261.1961.

*5-Ethoxy-N-ethyl-N-isopropyltryptamine HCl (**8a**)*

Yield: 52.8 mg (0.17 mmol, 57%); white crystals; mp 108–110 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.82 (1H, br s, N*H*Cl), 8.70 (1H, br s, N*H*), 7.31 (1H, d, J = 8.8 Hz, *H*-7), 7.08 (1H, d, J = 2.4 Hz, *H*-4), 7.05 (1H, d, J = 2.3 Hz, *H*-2), 6.85 (1H, dd, J = 8.8, 2.3 Hz, *H*-6), 4.09 (2H, q, J = 7.0 Hz, OCH_2CH_3), 3.69 (1H, m, N*CH*), 3.40-3.15 (6H, m, α-CH_2, β-CH_2, NCH_2CH_3), 1.60-1.30 (12H, m, OCH_2CH_3, NCH_2CH_3, 2 × CH_3). ^{13}C NMR ($CDCl_3$) δ 153.5 (*C*-5), 131.5 (*C*-7a), 127.1 (*C*-3a), 123.4 (*C*-2), 112.8 (*C*-6), 112.4 (*C*-7), 109.8 (*C*-3), 101.5 (*C*-4), 64.4 (OCH_2CH_3), 53.8 (NCH), 49.5 (α-CH_2), 45.1 (NCH_2CH_3), 21.1 (β-CH_2), 17.0 (CH_3), 16.6 (CH_3), 15.1 (OCH_2CH_3), 10.0 (NCH_2CH_3). HRESIMS theory $[M + H]^+$: 275.2123; observed: 275.2122.

*5-Ethoxy-N-ethyl-N-methyltryptamine HCl (**9a**)*

Yield: 60.2 mg (0.21 mmol, 71%); white crystals; mp 138–140 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.28 (1H, br s, NHCl), 8.73 (1H, br s, NH), 7.32 (1H, d, J = 8.7 Hz, *H*-7), 7.07 (2H, d, J = 2.3 Hz, *H*-4), 7.00 (1H, s, *H*-2), 6.86 (1H, dd, J = 8.7, 2.3 Hz, *H*-6), 4.10 (2H, q, J = 7.0 Hz, OCH_2CH_3), 3.32-3.00 (6H, m, NCH_2CH_3, α-CH_2, β-CH_2), 2.75 (3H, s, NCH_3), 1.43 (6H, m, NCH_2CH_3, OCH_2CH_3). ^{13}C NMR ($CDCl_3$) δ 153.5 (*C*-5), 131.5 (*C*-7a), 127.1 (*C*-3a), 123.3 (*C*-2), 113.0 (*C*-6), 112.4 (*C*-7), 109.3 (*C*-3), 101.5 (*C*-4), 64.5 (OCH_2CH_3), 55.4 (NCH_2CH_3), 50.9 (α-CH_2), 39.2 (NCH_3), 20.4 (β-CH_2), 15.1 (OCH_2CH_3), 9.0 (NCH_2CH_3). HRESIMS theory $[M + H]^+$: 247.1810; observed: 247.1808.

*5-Ethoxy-N-ethyl-N-propyltryptamine HCl (**10a**)*

Yield: 74.6 mg (0.24 mmol, 80%); white crystals; mp 126–128 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.13 (1H, br s, NHCl), 8.59 (1H, br s, NH), 7.31 (1H, d, J = 8.8 Hz, *H*-7), 7.07 (1H, d, J = 2.3 Hz, *H*-4), 7.03 (1H, d, J = 2.4 Hz, *H*-2), 6.86 (1H, dd, J = 8.8, 2.3 Hz, *H*-6), 4.10 (2H, q, J = 7.0 Hz, OCH_2CH_3), 3.27-3.15 (6H, m, α-CH_2, β-CH_2, NCH_2CH_3), 3.00 (2H, m, $NCH_2CH_2CH_3$), 1.86 (2H, m, $NCH_2CH_2CH_3$), 1.44-1.41 (6H, m, NCH_2CH_3, OCH_2CH_3), 0.98 (3H, t, J = 7.3 Hz, $NCH_2CH_2CH_3$). ^{13}C NMR ($CDCl_3$) δ 153.5 (*C*-5), 131.5 (*C*-7a), 127.1 (*C*-3a), 123.2 (*C*-2), 113.0 (*C*-6), 112.3 (*C*-7), 109.6 (*C*-3), 101.5 (*C*-4), 64.5 (OCH_2CH_3), 53.4 ($NCH_2CH_2CH_3$), 52.3 (α-CH_2), 47.2 (NCH_2CH_3), 20.1 (β-CH_2), 16.9 ($NCH_2CH_2CH_3$), 15.1 (OCH_2CH_3), 11.3 (NCH_2CH_3), 8.6 ($NCH_2CH_2CH_3$). HRESIMS theory $[M + H]^+$: 275.2123; observed: 275.2127.

*5-Ethoxy-N-ethyl-N-(2-methylallyl)tryptamine HCl (**11a**)*

Yield: 83.9 mg (0.26 mmol, 88%); white crystals; mp 134–136 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.06 (1H, br s, NHCl), 8.65 (1H, br s, NH), 7.31 (1H, d, J = 8.7 Hz, *H*-7), 7.09 (1H, d, J = 1.9 Hz, *H*-4), 7.00 (1H, s, *H*-2), 6.85 (1H, dd, J = 8.7, 1.9 Hz, *H*-6), 5.28 (1H, s, C=CH_2), 5.24 (1H, s, C=CH_2), 4.10 (2H, q, J = 7.0 Hz, OCH_2CH_3), 3.58 (2H, m, NCH_2), 3.27-3.23 (6H, m, NCH_2CH_3, α-CH_2, β-CH_2), 2.11 (3H, s, =CCH_3), 1.46-1.41 (6H, m, OCH_2CH_3, NCH_2CH_3). ^{13}C NMR ($CDCl_3$) δ 153.5 (*C*-5), 135.3 (*C*=CH_2), 131.5 (*C*-7a), 127.1 (*C*-3a), 123.3 (*C*-2), 122.1 (C=CH_2), 113.0 (*C*-6), 112.3 (*C*-7), 109.5 (*C*-3), 101.5 (*C*-4), 64.4 (OCH_2CH_3), 58.6 (NCH_2), 52.2 (α-CH_2), 47.2 (NCH_2CH_3), 22.2 (=CCH_3), 20.0 (β-CH_2), 15.1 (OCH_2CH_3), 8.3 (NCH_2CH_3). HRESIMS theory $[M + H]^+$: 287.2123; observed: 287.2127.

*5-Ethoxy-N-allyl-N-cyclohexyltryptamine HCl (**12a**)*

Yield: 98.0 mg (0.27 mmol, 90%); white crystals; mp 184–186 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.14 (1H, br s, NHCl), 8.41 (1H, br s, NH), 7.29 (1H, d, J = 8.9 Hz, *H*-7), 7.07-7.05 (2H, m, *H*-4, *H*-2), 6.87 (1H, dd, J = 8.9, 2.5 Hz, *H*-6), 6.36 (1H, ddt, $^3J_{trans}$ 17.7 Hz, $^3J_{cis}$ 10.7 Hz, ^3J 6.8 Hz, CH=CH_2), 5.48 (1H, dd, J = 10.7, 0.9 Hz, CH=CH_{cis}), 5.43 (1H, dd, J = 17.7, 0.9 Hz, CH=CH_{trans}), 4.10 (2H, q, J = 7.0 Hz, OCH_2CH_3), 3.80-3.64 (2H, m, NCH_2), 3.45-3.00 (5H, m, NCH, α-CH_2, β-CH_2), 2.28-1.00 (13H, m, OCH_2CH_3, 5 × CH_2). ^{13}C NMR ($CDCl_3$) δ 153.5 (*C*-5), 131.5 (*C*-7a), 127.1 (*C*-3a), 127.9 (CH=CH_2), 124.2 (CH=CH_2), 123.4 (*C*-2), 113.0 (*C*-6), 112.3 (*C*-7), 110.1 (*C*-3), 110.6 (*C*-4), 64.4 (OCH_2CH_3), 62.3 (NCH), 53.3 (NCH_2), 49.9 (α-CH_2), 27.1 (CH_2), 26.6 (CH_2), 25.1 (CH_2), 21.1 (β-CH_2), 15.1 (OCH_2CH_3). HRESIMS theory $[M + H]^+$: 327.2436; observed: 327.2440.

General procedure for the microwave-accelerated synthesis of 5-ethoxy-N,N-dialkyl-[α,α,β,β-D4]-tryptamine derivatives **1b**–**12b**

The deuterated derivatives have been prepared according to the procedure described above for tryptamines **1a**–**12a** but LAH was replaced by lithium aluminium deuteride (LAD).

*5-Ethoxy-N,N-dimethyl-[α,α,β,β-D4]-tryptamine base (**1b**)*

Yield: 52.1 mg (0.22 mmol, 73%); yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (1H, br s, NH), 7.20 (1H, d, J = 8.8 Hz, *H*-7), 7.05 (1H, d, J = 2.3 Hz, *H*-4), 6.95 (1H, d, J = 2.3 Hz, *H*-2), 6.84 (1H, dd, J = 8.8, 2.3 Hz, *H*-6), 4.07 (2H, q, J = 7.0 Hz, OCH_2CH_3), 2.36 (6H, s, 2 × NCH_3), 1.43 (3H, t, J = 7.0 Hz, OCH_2CH_3). ^{13}C NMR ($CDCl_3$) δ 153.1 (*C*-5), 131.6 (*C*-7a), 127.9 (*C*-3a), 122.2 (*C*-2), 112.6 (*C*-6), 113.9 (*C*-3), 111.8 (*C*-7), 102.0 (*C*-4), 64.4 (OCH_2CH_3), 45.4 (NCH_3), 15.1 (OCH_2CH_3). HRESIMS theory $[M + H]^+$: 237.1905; observed: 237.1895.

*5-Ethoxy-N,N-diethyl-[α,α,β,β-D4]-tryptamine HCl (**2b**)*

Yield: 72.2 mg (0.24 mmol, 80%); white crystals; mp 166–168 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.26 (1H, br s, NHCl), 8.41 (1H, br s, NH), 7.30 (1H, d, J = 8.8 Hz, *H*-7), 7.09 (1H, d, J = 2.3 Hz, *H*-4), 7.06 (1H, d, J = 2.0 Hz, *H*-2), 6.88 (1H, dd, J = 8.8, 2.3 Hz, *H*-6), 4.11 (2H, q, J = 6.9 Hz, OCH_2CH_3), 3.18 (4H, m, 2 × NCH_2CH_3), 1.43 (9H, m, 2 × NCH_2CH_3, OCH_2CH_3). ^{13}C NMR ($CDCl_3$) δ 153.5 (*C*-5), 131.5(*C*-7a), 127.1 (*C*-3a), 123.2 (*C*-2), 113.0 (*C*-6), 112.3 (*C*-7), 109.5 (*C*-3), 101.4 (*C*-4), 64.4 (OCH_2CH_3), 46.4 (NCH_2CH_3), 15.8 (OCH_2CH_3), 8.6 (NCH_2CH_3). HRESIMS theory $[M + H]^+$: 265.2218; observed: 265.2219.

*5-Ethoxy-N,N-dipropyl-[α,α,β,β-D4]-tryptamine HCl (**3b**)*

Yield: 96.1 mg (0.21 mmol, 70%); pale yellow crystals; mp 190–192 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.12 (1H, br s, NHCl), 8.70 (1H, br s, NH), 7.33 (1H, d, J = 8.8 Hz, *H*-7), 7.06 (1H, s, *H*-4), 6.98 (1H, s, *H*-2), 6.87 (1H, dd, J = 8.8, 1.3 Hz, *H*-6), 4.10 (2H, m, OCH_2CH_3), 2.99 (4H, m, 2 × $NCH_2CH_2CH_3$), 1.86 (4H, m, 2 × $NCH_2CH_2CH_3$), 1.44 (3H, t, J = 6.9 Hz, OCH_2CH_3), 0.99 (6H, t, J = 7.3 Hz, 2 × $NCH_2CH_2CH_3$). ^{13}C NMR ($CDCl_3$) δ 153.4 (*C*-5), 131.5 (*C*-7a), 127.1 (*C*-3a), 123.1 (*C*-2), 112.9 (*C*-6), 112.3 (*C*-7), 109.3 (*C*-3), 101.4 (*C*-4), 64.4 (OCH_2CH_3), 53.9 ($NCH_2CH_2CH_3$), 16.8 ($NCH_2CH_2CH_3$), 15.1 (OCH_2CH_3), 11.2 ($NCH_2CH_2CH_3$). HRESIMS theory $[M + H]^+$: 293.2531; observed: 293.2529.

*5-Ethoxy-N,N-diisopropyl-[α,α,β,β-D4]-tryptamine HCl (**4b**)*

Yield: 75.6 mg (0.23 mmol, 77%); white crystals; mp 184–186 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.42 (1H, br s, NHCl), 8.40 (1H, br s, NH), 7.30 (1H, d, J = 8.8 Hz, *H*-7), 7.08 (1H, d, J = 2.5 Hz, *H*-4), 7.03 (1H, d, J = 2.3 Hz, *H*-2), 6.87 (1H, dd, J = 8.8, 2.3 Hz, *H*-6), 4.08 (2H, q, J = 7.0 Hz, OCH_2CH_3), 3.69 (2H, m, 2 × NCH), 1.59 (6H, d, J = 6.6 Hz, 2 × CH_3), 1.47 (6H, d, J = 6.3 Hz, 2 × CH_3), 1.44 (3H, m, OCH_2CH_3). ^{13}C NMR ($CDCl_3$) δ 153.5 (*C*-5), 131.5 (*C*-7a), 127.5 (*C*-3a), 123.3 (*C*-2), 112.9 (*C*-6), 112.3 (*C*-7), 110.3 (*C*-3), 101.5 (*C*-4), 64.4 (OCH_2CH_3), 54.4 (NCH), 18.7 (CH_3), 17.2 (CH_3), 15.1 (OCH_2CH_3). HRESIMS theory $[M + H]^+$: 293.2531; observed: 293.2527.

*5-Ethoxy-N,N-diallyl-[α,α,β,β-D$_4$]-tryptamine HCl (**5b**)*

Yield: 81.2 mg (0.25 mmol, 83%); white crystals; mp 178–180 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.68 (1H, br s, NHCl), 8.45 (1H, br s, NH), 7.31 (1H, d, J = 8.8 Hz, H-7), 7.04 (2H, m, H-4, H-2), 6.87 (1H, dd, J = 8.8, 2.3 Hz, H-6), 6.17 (2H, ddt, $^3J_{trans}$ = 17.0 Hz, $^3J_{cis}$ = 10.2 Hz, ^3J = 7.1 Hz, 2 × CH=CH_2), 5.57 (2H, dd, J = 10.2, 0.9 Hz, 2 × CH=CH_{cis}), 5.47 (2H, dd, J = 17.0, 0.9 Hz, 2 × CH=CH_{trans}), 4.10 (2H, q, J = 7.0 Hz, OCH_2CH$_3$), 3.68 (4H, m, 2 × NCH_2), 1.44 (3H, t, J = 7.0 Hz, OCH$_2$$CH_3$). ^{13}C NMR ($CDCl_3$) δ 153.5 (C-5), 131.4 (C-7a), 127.1 (C-3a), 126.2 (CH=CH_2), 125.8 (CH=CH_2), 123.3 (C-2), 113.1 (C-6), 112.3 (C-7), 109.5 (C-3), 101.4 (C-4), 64.4 (OCH_2CH$_3$), 54.8 (NCH_2), 15.1 (OCH$_2$$CH_3$). HRESIMS theory $[M + H]^+$: 289.2218; observed: 289.2214.

*5-Ethoxy-N-methyl-N-propyl-[α,α,β,β-D$_4$]-tryptamine HCl (**6b**)*

Yield: 75.8 mg (0.25 mmol, 83%); yellow oil. ^{1}H NMR (300 MHz, DMSO-d$_6$) δ 10.81 (1H, br s, NH), 10.70 (1H, br s, NHCl), 7.25 (1H, d, J = 8.8 Hz, H-7), 7.18 (1H, d, J = 2.3 Hz, H-2), 7.16 (1H, d, J = 2.3 Hz, H-4), 6.74 (1H, dd, J = 8.8, 2.3 Hz, H-6), 4.04 (2H, q, J = 7.0 Hz, OCH_2CH$_3$), 3.10-3.03 (2H, m, NCH_2CH$_2$CH$_3$), 2.79 (3H, s, NCH_3), 1.73 (2H, m, NCH$_2$$CH_2CH_3$), 1.34 (3H, t, J = 7.0 Hz, OCH$_2$$CH_3$), 0.92 (3H, t, J = 7.3 Hz, NCH$_2$CH$_2$$CH_3$). ^{13}C NMR (DMSO-d$_6$) δ 152.3 (C-5), 131.4 (C-7a), 127.1 (C-3a), 124.9 (C-2), 111.6 (C-6), 112.1 (C-7), 108.7 (C-3), 101.5 (C-4), 63.5 (OCH_2CH$_3$), 56.2 (NCH$_2$CH$_2$CH$_3$), 38.7 (NCH_3), 16.8 (NCH$_2$CH$_2$CH$_3$), 14.9 (OCH$_2$$CH_3$), 10.9 (NCH$_2CH_2$$CH_3$). HRESIMS theory $[M + H]^+$: 265.2218; observed: 265.2231.

*5-Ethoxy-N-methyl-N-isopropyl-[α,α,β,β-D$_4$]-tryptamine HCl (**7b**)*

Yield: 75.2 mg (0.25 mmol, 83%); yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.79 (1H, br s, NHCl), 9.00 (1H, br s, NH), 7.31 (1H, d, J = 8.7 Hz, H-7), 7.09 (1H, s, H-4), 6.98 (1H, s, H-2), 6.83 (1H, dd, J = 8.3 Hz, H-6), 4.10 (2H, q, J = 7.0 Hz, OCH_2CH$_3$), 3.53 (1H, m, NCH), 2.65 (3H, s, NCH_3), 1.42 (3H, m, OCH$_2$$CH_3$), 1.28 (6H, m, 2 × CH_3). ^{13}C NMR ($CDCl_3$) δ 153.4 (C-5), 131.5 (C-7a), 127.1 (C-3a), 123.6 (C-2), 112.8 (C-6), 112.4 (C-7), 109.2 (C-3), 101.5 (C-4), 64.5 (OCH_2CH$_3$), 56.3 (NCH), 35.1 (NCH_3), 17.5 (CH_3), 15.1 (OCH$_2$$CH_3$). HRESIMS theory $[M + H]^+$: 265.2218; observed: 265.2122.

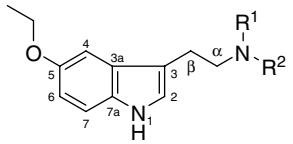
*5-Ethoxy-N-ethyl-N-isopropyl-[α,α,β,β-D$_4$]-tryptamine HCl (**8b**)*

Yield: 82.2 mg (0.26 mmol, 87%); yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.59 (1H, br s, NHCl), 9.00 (1H, br s, NH), 7.32 (1H, d, J = 8.8 Hz, H-7), 7.05 (1H, d, J = 2.4 Hz, H-4), 6.98 (1H, d, J = 2.1 Hz, H-2), 6.84 (1H, dd, J = 8.8, 2.4 Hz, H-6), 4.10 (2H, q, J = 7.0 Hz, OCH_2CH$_3$), 3.69 (1H, m, NCH), 3.14 (2H, q, J = 7.3 Hz, NCH_2CH$_3$), 1.51-1.40 (6H, m, OCH$_2$$CH_3$, NCH$_2$$CH_3$), 1.26 (6H, m, 2 × CH_3). ^{13}C NMR ($CDCl_3$) δ 153.4 (C-5), 131.6 (C-7a), 127.1 (C-3a), 123.5 (C-2), 112.7 (C-6), 112.5 (C-7), 109.5 (C-3), 101.4 (C-4), 64.4 (OCH$_2$CH$_3$), 53.8 (NCH), 45.1 (NCH$_2$CH$_3$), 17.0 (CH_3), 16.6 (CH_3), 15.1 (OCH$_2$$CH_3$), 9.9 (NCH$_2$$CH_3$). HRESIMS theory $[M + H]^+$: 279.2374; observed: 279.2370.

*5-Ethoxy-N-ethyl-N-methyl-[α,α,β,β-D$_4$]-tryptamine HCl (**9b**)*

Yield: 60.2 mg (0.21 mmol, 70%); white crystals; mp 146–148 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.42 (1H, br s, NHCl), 8.43 (1H, br s, NH), 7.30 (1H, d, J = 8.8 Hz, H-7), 7.07 (2H, m, H-4, H-2), 6.88 (1H, dd, J = 8.8, 1.9 Hz, H-6), 4.11 (2H, q, J = 7.0 Hz, OCH_2CH$_3$), 3.33-3.09 (2H, m, NCH_2CH$_3$), 2.78 (3H, s, NCH_3), 1.47-1.42 (6H, m, NCH$_2$$CH_3$, OCH$_2$$CH_3$), 1.00 (3H, t, J = 7.3 Hz, NCH$_2$CH$_2$$CH_3$). ^{13}C NMR ($CDCl_3$) δ 153.5 (C-5), 131.5 (C-7a), 127.1 (C-3a), 123.3 (C-2), 113.0 (C-6), 112.3 (C-7), 109.5 (C-3), 101.4 (C-4), 64.4 (OCH_2CH$_3$), 50.9 (NCH$_2$CH$_3$), 39.2 (NCH_3), 15.1 (OCH$_2$$CH_3$), 9.1 (NCH$_2$$CH_3$). HRESIMS theory $[M + H]^+$: 251.2061; observed: 251.2055.

Table 1. Structures of synthesized tryptamines 1a–12a and their [α,α,β,β-D$_4$] counterparts 1b–12b



No.	R^1	R^2	Name
1a	Me	Me	5-EtO-DMT
1b	Me	Me	5-EtO-D$_4$-DMT
2a	Et	Et	5-EtO-DET
2b	Et	Et	5-EtO-D$_4$-DET
3a	Pr	Pr	5-EtO-DPT
3b	Pr	Pr	5-EtO-D$_4$-DPT
4a	iPr	iPr	5-EtO-DIPT
4b	iPr	iPr	5-EtO-D$_4$-DIPT
5a	Allyl	Allyl	5-EtO-DALT
5b	Allyl	Ally	5-EtO-D$_4$-DALT
6a	Me	Pr	5-EtO-MPT
6b	Me	Pr	5-EtO-D$_4$-MPT
7a	Me	iPr	5-EtO-MIPT
7b	Me	iPr	5-EtO-D$_4$-MIPT
8a	Et	iPr	5-EtO-EIPT
8b	Et	iPr	5-EtO-d$_4$-EIPT
9a	Me	Et	5-EtO-MET
9b	Me	Et	5-EtO-d$_4$-MET
10a	Et	Pr	5-EtO-EPT
10b	Et	Pr	5-EtO-D$_4$-EPT
11a	2-Me-allyl	Et	5-EtO-2MALET
11b	2-Me-allyl	Et	5-EtO-D$_4$-2MALET
12a	Allyl	Cyclohexyl	5-EtO-ALCHT
12b	Allyl	Cyclohexyl	5-EtO-D$_4$-ALCHT

*5-Ethoxy-N-ethyl-N-propyl-[α,α,β,β-D$_4$]-tryptamine HCl (**10b**)*

Yield: 75.6 mg (0.24 mmol, 80%); white crystals; mp 140–142 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.21 (1H, br s, NHCl), 8.40 (1H, br s, NH), 7.31 (1H, d, J = 8.8 Hz, H-7), 7.08 (1H, d, J = 2.3 Hz, H-4), 7.05 (1H, d, J = 2.4 Hz, H-2), 6.88 (1H, dd, J = 8.8, 2.4 Hz, H-6), 4.11 (2H, q, J = 7.0 Hz, OCH_2CH$_3$), 3.18 (2H, m, NCH_2CH$_3$), 3.00 (2H, m, NCH_2CH$_2$CH$_3$), 1.89 (2H, m, NCH$_2$$CH_2CH_3$), 1.47-1.40 (6H, m, NCH$_2$$CH_3$, OCH$_2$$CH_3$), 1.00 (3H, t, J = 7.3 Hz, NCH$_2$CH$_2$$CH_3$). ^{13}C NMR ($CDCl_3$) δ 153.5 (C-5), 131.5(C-7a), 127.1 (C-3a), 123.2 (C-2), 113.0 (C-6), 112.3 (C-7), 109.4 (C-3), 101.4 (C-4), 64.4 (OCH_2CH$_3$), 53.5 (NCH$_2$CH$_2$CH$_3$), 47.1 (NCH$_2$CH$_3$), 16.8 (NCH$_2$CH$_2$CH$_3$), 15.1 (OCH$_2$$CH_3$), 11.3 (NCH$_2$$CH_3$), 8.6 (NCH$_2CH_2$$CH_3$). HRESIMS theory $[M + H]^+$: 279.2374; observed: 279.2376.

*5-Ethoxy-N-ethyl-N-(2-methylallyl)-[α,α,β,β-D$_4$]-tryptamine HCl (**11b**)*

Yield: 71.9 mg (0.22 mmol, 73%); pale yellow crystals; mp 132–134 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.12 (1H, br s, NHCl),

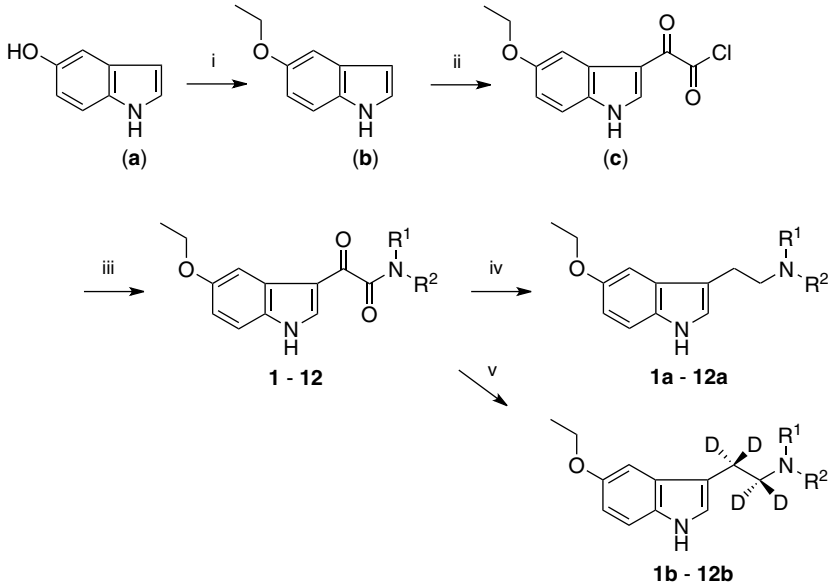


Figure 2. Preparation of deuterated tryptamines **1**–**12** following the route of Speeter and Anthony. i: K_2CO_3/CH_3CH_2I/EtOH; ii: $(COCl)_2/Et_2O$; iii: HNR^1R^2; iv: $LiAlH_4$/THF; v: $LiAlD_4$/THF.

8.50 (1H, br s, N*H*), 7.30 (1H, d, J = 8.8 Hz, *H*-7), 7.09 (1H, d, J = 2.1 Hz, *H*-4), 7.03 (1H, s, *H*-2), 6.87 (1H, dd, J = 8.8, 2.3 Hz, *H*-6), 5.28 (1H, s, C=CH_2), 5.24 (1H, s, C=CH_2), 4.09 (2H, q, J = 7.0 Hz, OCH_2CH$_3$), 3.59 (2H, m, NCH_2), 3.28-3.18 (2H, m, NCH_2CH$_3$), 2.12 (3H, s, CH_3), 1.46-1.42 (6H, m, OCH$_2$CH_3, NCH$_2$CH_3). ^{13}C NMR ($CDCl_3$) δ 153.5 (*C*-5), 135.3 (*C*=CH$_2$), 131.5 (*C*-7a), 127.1 (*C*-3a), 123.3 (*C*-2), 122.1 (CH$_2$), 113.0 (*C*-6), 112.3 (*C*-7), 109.4 (*C*-3), 101.4 (*C*-4), 64.4 (OCH$_2$CH$_3$), 58.5 (NCH$_2$), 47.1 (NCH$_2$CH$_3$), 22.1 (CH$_3$), 15.1 (OCH$_2$CH$_3$), 8.3 (NCH$_2$CH$_3$). HRESIMS theory $[M + H]^+$: 291.2374; observed: 291.2371.

5-Ethoxy-N-allyl-N-cyclohexyl-[α,α,β,β-D$_4$]-tryptamine HCl (**12b**)

Yield: 95.4 mg (0.26 mmol, 87%); white crystals; mp 183–184 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.11 (1H, br s, N*H*Cl), 8.37 (1H, br s, N*H*), 7.29 (1H, d, J = 8.8 Hz, *H*-7), 7.07 (2H, m, *H*-4, *H*-2), 6.87 (1H, dd, J = 8.8, 2.4 Hz, *H*-6), 6.37 (1H, ddt, $^3J_{trans}$ = 17.3 Hz, $^3J_{cis}$ = 11.2 Hz, ^3J = 7.1 Hz, C*H*=CH$_2$), 5.50 (1H, dd, J = 11.2, 0.9 Hz, CH=CH_{cis}), 5.44 (1H, dd, J = 17.3, 0.9 Hz, CH=CH_{trans}), 4.10 (2H, q, J = 7.0 Hz, OCH_2CH$_3$), 3.68–3.79 (2H, m, NCH_2), 3.28 (1H, m NC*H*), 2.36-1.07 (13H, m, OCH$_2$CH_3, 5 × CH_2). ^{13}C NMR ($CDCl_3$) δ 153.5 (*C*-5), 131.5 (*C*-7a), 127.1 (*C*-3a), 127.9 (CH=CH$_2$), 124.2 (CH=CH$_2$), 123.4 (*C*-2), 112.9 (*C*-6), 112.2 (*C*-7), 109.9 (*C*-3), 101.5 (*C*-4), 64.4 (OCH$_2$CH$_3$), 62.2 (NCH), 53.2 (NCH$_2$), 27.1 (CH$_2$), 26.5 (CH$_2$), 25.2 (CH$_2$), 15.1 (OCH$_2$CH$_3$). HRESIMS theory $[M + H]^+$: 331.2687; observed: 331.2687.

Results and discussion

Alkylation of 5-hydroxyindole (**a**) gave 5-ethoxyindole (**b**) as a common starting material. The procedure of Speeter and Anthony[34] provided convenient access to the tryptamine target compounds and the corresponding scheme is summarized in Figure 2. Acylation of 5-ethoxyindole (**b**) with oxalyl chloride gave the 5-ethoxyindole-3-yl-glyoxalyl chloride (**c**). This was followed by reaction with the appropriate amine to give the 5-ethoxyindole-3-yl-glyoxalylamides (**1**–**12**). Due to the partial double bond character of the amide bond, *N*,*N*-disubstituted glyoxalylamides displayed a duplication of side-chain related peaks in the ^{1}H and ^{13}C NMR spectra which was in agreement with derivatives reported previously.[35,36] Asymmetrically disubstituted glyoxalylamides showed the presence of major and minor rotamers, reflecting *anti*-periplanar and *syn*-periplanar conformations, which were indicated by unequal integrations in the ^{1}H NMR spectra. Implementation of electrospray ionization resulted in predominant formation of sodiated adducts which were used for high resolution measurements. Amides were then reduced with lithium aluminium hydride or lithium aluminium deuteride to yield the desired $\alpha,\alpha,\beta,\beta$-H$_4$ (**1a**–**12a**) and $\alpha,\alpha,\beta,\beta$-D$_4$ derivatives (**1b**–**12b**), respectively (Table 1).

Metal hydride or deuteride reductions are commonly carried out in solvents under reflux conditions. The boiling point of the solvent limits the reaction temperature and, as a consequence, reaction times between 2–16 h are typical.[18,35,37–42] Low-boiling-point solvents, such as diethyl ether, have been observed to result in significantly prolonged reaction times and incomplete reduction.[43] When using pressurized vessels under microwave conditions, a reaction temperature of 150 °C was rapidly obtained for the tetrahydrofuran solvent within 30 s, followed by product formation after 5 min. These findings were in agreement with previous work on the preparation of twenty-two 5-methoxy and unsubstituted *N*,*N*-dialkyl-[$\alpha,\alpha,\beta,\beta$-D$_4$]-tryptamines under similar conditions.[44]

GC-IT-MS retention times and electron ionization mass spectra for both proteo- and deutero amines are summarized in Table 2 and it can be seen that separations between derivatives was acceptable in most cases. An exception was observed for *N*-methyl-*N*-propyltryptamines (**6a**/**6b**) and *N*-methyl-*N*-isopropyltryptamines (**7a**/**7b**) where this was not the case. Differentiation between isomeric (**6a**/**7a**) and (**6b**/**7b**), however, was possible due to differential fragmentation of the iminium ion base peaks. A third isomeric pair, i.e. *N*,*N*-diethyltryptamines (**2a**/**2b**), could also be distinguished by their retention times. A graphical representation of differential fragmentation of the three isomeric pairs is shown in Figure 3.

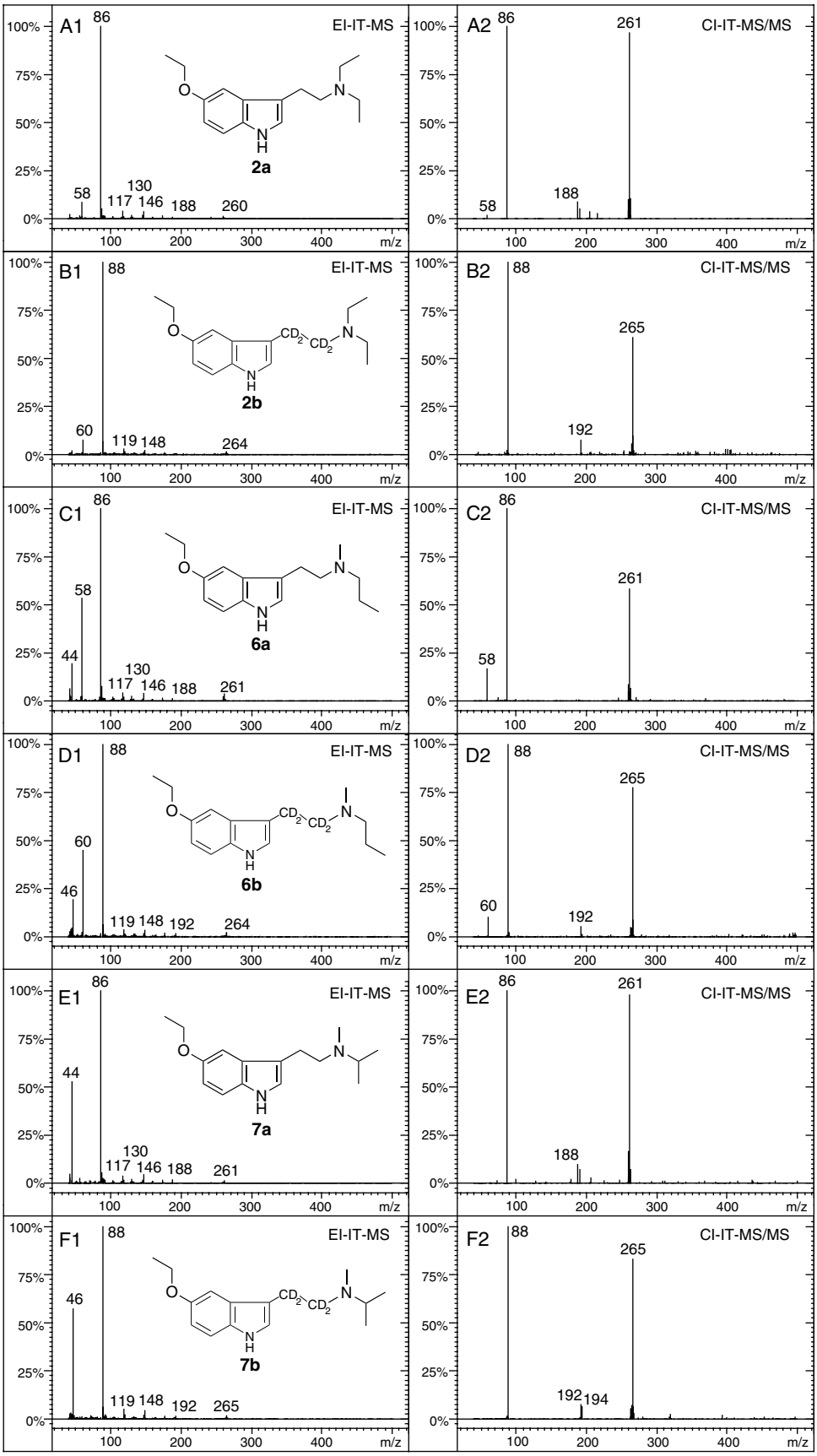


Figure 3. Representative EI-IT-MS and CI-IT-MS/MS spectra obtained from isomeric tryptamines **2a**, **6a**, **7a** and their deuterated counterparts **2b**, **6b** and **7b**, respectively. Mass spectral differentiation was observed due to secondary fragmentation of the iminium ions (see Figure 4 for details).

Table 2. EI-IT-MS spectra of tryptamines **1a**–**12b**

Relative intensity (%) of key fragments				
5-Ethoxy-*N*,*N*-dialkyl-[α,α,β,β-H_4]-tryptamines				
No.	T_R (min)	$M^{\bullet+}$/M + 1[a]	BP[b] *m/z*	Other key fragments *m/z* (%)[c]
1a	11.08	232	**58**	188 (1), 174 (1), 146 (4), 130 (2), 117 (4), 42 (7)
2a	11.86	260	**86**	188 (1), 174 (2), 146 (4), 130 (2), 117 (4), **58 (9)**, 42 (2)
3a	12.85	289[d]	**114**	188 (2), 174 (2), 146 (4), 130 (3), 117 (3), **86 (29)**, **58 (7)**, **44 (9)**
4a	12.72	289[d]	**114**	188 (1), 174 (2), 146 (4), 130 (1), 117 (3), **72 (15)**, 41 (4)
5a	12.88	284	**110**	188 (1), 174 (2), 146 (4), 130 (2), 117 (5), 68 (6), 41 (17)
6a	11.96	261[d]	**86**	188 (1), 174 (1), 146 (4), 130 (3), 117 (4), **58 (53), 44 (19)**, 42 (6)
7a	11.98	261[d]	**86**	188 (2), 174 (2), 146 (5), 130 (2), 117 (4), **44 (53)**, 42 (5)
8a	12.27	275[d]	**100**	188 (1), 174 (1), 146 (4), 130 (2), 117 (3), **58 (29)**, 42 (3)
9a	11.49	247[d]	**72**	188 (1), 174 (1), 146 (3), 130 (2), 117 (3), **44 (20)**, 42 (3)
10a	12.34	275[d]	**100**	188 (1), 174 (2), 146 (5), 130 (2), **72 (37), 58 (9)**, 42 (4)
11a	12.78	287[d]	**112**	188 (1), 174 (2), 146 (4), 130 (2), 117 (4), 110 (7), 97 (3), 55 (6)
12a	17.60	327[d]	**152**	188 (2), 187 (3), 174 (4), 146 (5), 130 (2), 117 (4), **70 (41)**, 55 (10), 41 (11)
5-Ethoxy-*N*,*N*-dialkyl-[α,α,β,β-D_4]-tryptamines				
No.	T_R (min)	$M^{\bullet+}$/M + 1[a]	BP[b]	Other key fragments *m/z* (%)[c]
1b	11.06	237[d]	**60**	192 (1), 176 (2), 148 (3), 119 (5)
2b	11.84	264	**88**	176 (1), 148 (2), 119 (3), 60 (7)
3b	12.83	293[d]	**116**	192 (1), 176 (1), 148 (3), 119 (2), **88 (24)**, **60 (5)**, **46 (7)**
4b	12.70	293[d]	**116**	192 (1), 176 (3), 148 (5), 119 (3), **74 (13)**, 41 (5)
5b	12.86	288	**112**	192 (1), 176 (3), 148 (5), 119 (4), 70 (3), 41 (12)
6b	11.93	264	**88**	192 (2), 176 (2), 148 (3), 119 (4), **60 (45)**, **46 (19)**, 41 (3)
7b	11.95	265[d]	**88**	192 (1), 176 (1), 148 (4), 119 (5), **46 (57)**, 41 (3)
8b	12.24	279[d]	**102**	192 (2), 176 (2), 148 (5), 119 (4), **60 (42)**, 41 (3)
9b	11.49	250	**74**	176 (1), 148 (1), 119 (3), **46 (17)**
10b	12.31	279[d]	**102**	192 (1), 176 (2), 148 (4), 119 (4), **74 (35)**, **60 (9)**, 41 (3)
11b	12.75	290	**114**	192 (1), 176 (3), 148 (5), 119 (4), 99 (5), 55 (8)
12b	17.56	231[d]	**154**	192 (1), 176 (3), 148 (3), 119 (2), **72 (30)**, 55 (7), 41 (9)

[a] In most cases both molecular ions ($M^{\bullet+}$) and M + 1 ions have been observed with very low intensity ranging between 1–3%, possibly due to ion-molecule interactions within the ion trap. The $M^{\bullet+}$ species is reported in cases where intensity was at least equal. One exception was observed with compound **9a** (5-EtO-MET) where the relative abundance of the molecular ion was 16%. [b] Base peak. Iminium ion base peaks are printed in bold. [c] Iminium ions derived from secondary fragmentation of the base peak species are printed in bold. [d] M + 1 species.

The EI-IT-MS spectra of the *N*,*N*-diethyl (**2a**) (Figure 3A1), *N*-methyl-*N*-propyl (**6a**) (Figure 3C1) and *N*-methyl-*N*-isopropyl derivative (**7a**) (Figure 3E1) showed a base peak at *m/z* 86, reflecting the $CH_2{=}N^+R^1R^2$ iminium ion ($C_nH_{2n+2}N^+$). Secondary fragmentation, presumably via neutral losses of the appropriate olefin, pointed towards the presence of the distinct isomer which was consistent with previously reported analysis of different *N*,*N*-dialkytryptamines.[35] Figure 4 summarizes the proposed differential fragmentation of the iminium base peaks. EI-induced fragmentation of their deuterated counterparts (**2b, 6b** and **7b**) (Figures 3B1, 3D1 and 3F1) displayed a 2 Da mass shift of the base peak reflecting the presence of 2 deuterium atoms in the iminium ion (Figure 4). Interestingly, co-elution of isomers (**6a**) and (**7a**) has also been described previously during the characterization of structurally related *N*-methyl-*N*-propyltryptamines and *N*-methyl-*N*-isopropyltryptamines[35] and attempts to achieve complete separation were also unsuccessful when changing the GC temperature profile.

Under EI-IT-MS conditions, an indole-specific fragmentation pattern was observed to yield low relative abundances where intensities rarely increased above 5% (Table 2). A characteristic series appeared to include a species at *m/z* 188, *m/z* 174, *m/z* 146, *m/z* 130 and *m/z* 117. On the other hand, previous EI-IT-MS analyses of 5-methoxy substituted *N*,*N*-dialkyltryptamines revealed a series of key fragments at *m/z* 174, *m/z* 160, *m/z* 145, *m/z* 130, *m/z* 117 and *m/z* 90 with relative abundancies of up to 16%.[35]

The low intensity of indole-related fragments observed for the 5-ethoxy derivatives (**1a**–**12b**) (Table 2), coupled with very low abundance or absence of molecular ions, led to the implementation to CI-IT-MS/MS analysis using internal ionization and methanol as the liquid CI reagent. The chosen excitation amplitude (non-resonant mode, 21 V) provided both the protonated molecule $[M + H]^+$ and structural information due to collision-induced dissociation using helium as damping and collision gas. All CI-IT-MS/MS spectra are summarized in Table 3.

Representative CI-IT-MS/MS spectra are shown for isomeric derivatives (**2a**/**b, 6a**/**b** and **7a**/**b**) displaying both molecular weight information and formation of iminium ions. As expected, chemical ionization procedures showed less intensive fragmentation, when compared to electron ionization, which resulted in reduced formation of secondary iminium ions. Inspection of all spectra (Table 3) indicated that differentiation between isomeric

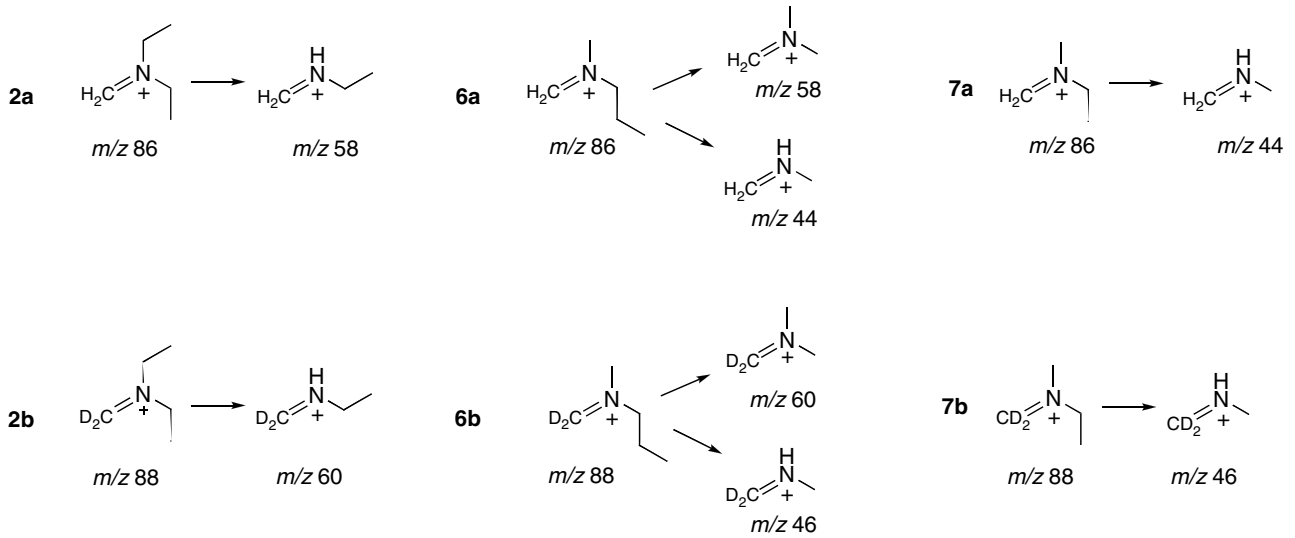


Figure 4. Proposed fragmentation pathway for the secondary fragmentation of the iminium base peak detected for three isomeric tryptamines (see Figure 3). The mass shift of 2 Da confirms incorporation of deuterium.

Table 3. CI-IT-MS/MS spectra of tryptamines **1a**–**12b** using an excitation amplitude of 21 V in non-resonant mode

Relative intensity (%) of key fragments			
5-Ethoxy-*N*,*N*-dialkyl-[α,α,β,β-H_4]-tryptamines			
No.	$[M + H]^+$ (%)	BP[a] *m/z*	Others *m/z* (%)[b]
1a	233 (1)[c]	**58**	188 (1), 56 (1)
2a	261 (97)	**86**	259 (10), 216 (3), 204 (4), 190 (5), 188 (9), **58 (2)**
3a	289 (71)	**114**	287 (10), 230 (1), 218 (2), 190 (3), 188 (4), **86 (7)**
4a	289 (47)	**114**	287 (9), 189 (1), 188 (1), **100 (8)**, **72 (1)**
5a	285 (100)	285	283 (5), 188 (10), **110 (34)**, 84 (1)
6a	261 (58)	**86**	259 (9), 188 (1), 74 (2), **58 (17)**
7a	261 (98)	**86**	259 (16), 247 (2), 205 (3), 190 (7), 188 (10), **100 (2)**, **72 (1)**
8a	275 (70)	**100**	216 (2), 188 (2)
9a	247 (82)	**72**	204 (3), 188 (7)
10a	275 (75)	**100**	230 (1), 216 (1), 204 (1), 202 (1), 190 (5), 188 (4), **72 (7)**
11a	287 (100)	287	240 (1), 230 (1), 203 (1), 188 (15), **112 (59)**, **72 (4)**
12a	327 (100)[c]	327	228 (1), 216 (1), 202 (1), 188 (7), **152 (64)**, 140 (6), 55 (38)
5-Ethoxy-*N*,*N*-dialkyl-[α,α,β,β-D_4]-tryptamines			
No.	$[M + H]^+$ (%)	BP[a] *m/z*	Others *m/z* (%)[b]
1b	237 (0)[c]	**60**	–
2b	265 (61)	**88**	192 (7)
3b	293 (100)	293	291 (8), 265 (10), **116 (82)**, **60 (12)**
4b	293 (49)	**116**	291 (2), 194 (9), 192 (5), **100 (16)**, **74 (2)**
5b	289 (100)	**289**	287 (2), 192 (5), **112 (39)**
6b	265 (74)	**88**	263 (8), 192 (9), **60 (13)**
7b	265 (93)	**88**	194 (8), 192 (9)
8b	279 (91)	**102**	277 (5), 194 (7), 192 (10),**86 (4)**, **60 (4)**
9b	251 (100)	251	206 (1), 192 (4), 74 (97)
10b	279 (66)	**102**	194 (6), 192 (9), 74 (12), 66 (1)
11b	291 (84)	**114**	232 (8), 206 (5), 204 (4), 192 (67), 180 (3), **74 (10)**
12b	331 (100)[c]	331	192 (2), 190 (3),**154 (77)**, 55 (52)

[a] Base peak. Iminium ion base peaks are printed in bold. [b] Iminium ions derived from secondary fragmentation of the base peak species are printed in bold. [c] Single stage MS spectrum without application of excitation amplitude due to sufficient dissociation.

derivatives was still possible. Under CI-IT-MS/MS conditions the presence of an ion at *m/z* 188 might have reflected the presence of the 5-ethoxy-3-ethylindole-type species which may have been in agreement with the fact that their deuterated counterparts displayed a prominent species at *m/z* 192 indicating retention of both methylene groups of the side chain (Table 3 and Figures 3A2–3F2). The presence of this indole related species might also be of assistance with the identification process when dealing with unknown derivatives. It has been reported previously that 5-methoxy-*N*,*N*-dialkyltryptamines would show a structurally related *m/z* 174 whereas derivatives unsubstituted at the benzene ring appeared to display a fragment at *m/z* 144 when employing CI-IT-MS/MS conditions.[45]

Conclusion

Twelve novel 5-ethoxy-*N*,*N*-dialkyl-[α,α,β,β-H_4]-tryptamines and twelve 5-ethoxy-*N*,*N*-dialkyl-[α,α,β,β-D_4]-tryptamines were prepared using the Speeter & Anthony procedure. Final products were obtained under microwave conditions within 5 min. This procedure resulted in good yields and showed that these tryptamines can be prepared quickly for forensic, clinical, and pharmacokinetic studies. A full analytical characterization using 1D/2D NMR and GC-IT-(EI/CI)-MS/MS was carried out and mass spectrometric analysis revealed the ability to differentiate between isomeric candidates. This set of analytical data should be of use to those who are concerned with frontline exposure to novel psychoactive substances and who rely on the availability of novel characterized compounds.

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