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Synthesis and characterization of 5-methoxy-2-methyl-*N*,*N*-dialkylated tryptamines

Simon D. Brandt,[a]* Ruchanok Tearavarich,[b] Nicola Dempster,[a] Nicholas V. Cozzi[c] and Paul F. Daley[d]

The absence of reference material is a commonly experienced difficulty among medical and forensic professionals tasked with identifying new psychoactive substances that are encountered for the first time. The identification of newly emerging substances lies at the heart of forensic and clinical analysis, and a proactive public health policy calls for a thorough analysis of the properties of new psychoactive substances before they appear in the emergency clinic, where they may be noticed because of adverse reactions or toxicity. For example, a wide range of *N*,*N*-dialkyltryptamines show psychoactive properties in humans and these tryptamines are sometimes encountered as intoxicants. However, most of the existing reference data on new psychoactive tryptamines have been obtained retrospectively, after reports of acute toxicities. To address the need for reference standards for new tryptamines, thirteen 5-methoxy-2-methyl-*N*,*N*-dialkyltryptamines were prepared. Analytical characterization was based on ^{1}H and ^{13}C nuclear magnetic resonance (NMR), gas chromatography-electron ionization ion-trap mass spectrometry (GC-EI-IT-MS) and chemical ionization-ion-trap tandem mass spectrometry (CI-IT-MS/MS), respectively. Differentiation among isomers was feasible by NMR and MS. In addition to the expected iminium ion base peak, indole-related key ions were detected under EI-IT-MS conditions at *m/z* 174, 159, 131, 130, and 103. CI-IT-MS/MS analysis of the 5-methoxy-2-methyl derivatives revealed the presence of *m/z* 188 in addition to $[M+H]^+$ and the iminium species. This study served as an extension from previous work on isomeric 5-ethoxylated counterparts and confirmed the ability to differentiate between the two groups. The data provided here add to the existing body of literature and aim to serve both forensic and clinical communities. Copyright © 2012 John Wiley & Sons, Ltd.

Keywords: tryptamines; microwave; psychoactive; receptor probes; nuclear magnetic resonance; mass spectrometry

Introduction

5-Methoxy-2-methyl-*N*,*N*-dimethyltryptamine (5-MeO-2-Me-DMT, MMDT) **1** and its 2-ethyl homologue (EMDT) (Figure 1) have been shown to be h5-HT_6-selective agents with K_i values of 16 and 60 nM ([^{3}H]LSD as radioligand), respectively.[1] In recent years, the 5-HT_6 receptor subtype has been the target of intensive research activities in the attempt to find effective strategies for the treatment of central nervous system (CNS) related diseases.[2–4] Functional studies using the cAMP assay revealed that both **1** and EMDT behaved as agonists whereas 5-methoxy-2-phenyl-*N*,*N*-dimethyltryptamine (PMDT) (K_i = 20 nM) exhibited antagonist character.[1] In addition, the pyrrolidine derivative of EMDT (EMDT-A) displayed stereoselective binding (*8R* K_i = 1.8 and *8S* K_i = 220 nM).[5] On the other hand, the closely related 5-methoxy-*N*,*N*-dimethyltryptamine (5-MeO-DMT, Fig. 1) (K_i = 13 nM[6]) shows powerful psychoactive/hallucinogenic effects in humans[7,8] which exemplifies the need to understand the delicate interactions involved between medicinal and psychoactive drugs and their molecular targets. Indeed, many *N*,*N*-dialkylated tryptamines, such as *N*,*N*-dimethyltryptamine (DMT, Figure 1) show psychoactive properties in humans and while several *N*,*N*-dimethyl derivatives are abundantly available in nature, most of the currently known derivatives are of synthetic origin that display a pharmacologically rich profile of receptor interactions.[7,9–13]

While it can be appreciated that structural modifications of biologically active templates form the basis of any form of drug discovery, it has also become obvious that many psychoactive derivatives have appeared on the recreational drug market, for example, in the form of so-called research chemicals.[14] A wide range of compound classes have emerged in recent years which extended beyond the tryptamine nucleus[15] and increasing availability raises concerns about uncontrolled patterns of consumption in a recreational and non-clinical context. Developing effective and efficient responses to new psychoactive substances is a major challenge to public health. This is particularly apparent in an increasingly globalized market where the Internet is playing an important role in supply.[14,16]

The identification and characterization of newly emerging substances lies at the heart of forensic and clinical analysis and a proactive public health policy calls for a thorough analysis of the properties of new psychoactive substances before they

* *Correspondence to: Simon Brandt, School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Byrom Street, Liverpool, L3 3AF, UK. E-mail: s.brandt@ljmu.ac.uk*

a *School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Liverpool, UK*

b *Department of Chemistry, Faculty of Engineering, Rajamangala University of Technology Isan, Khon Kaen Campus, Khon Kaen 40000, Thailand*

c *Neuropharmacology Laboratory, Department of Cell and Regenerative Biology, University of Wisconsin School of Medicine and Public Health, 1300 University Avenue, Madison, WI 53706, USA*

d *Alexander Shulgin Research Institute, 1483 Shulgin Road, Lafayette, Lafayette, CA 94549, USA*

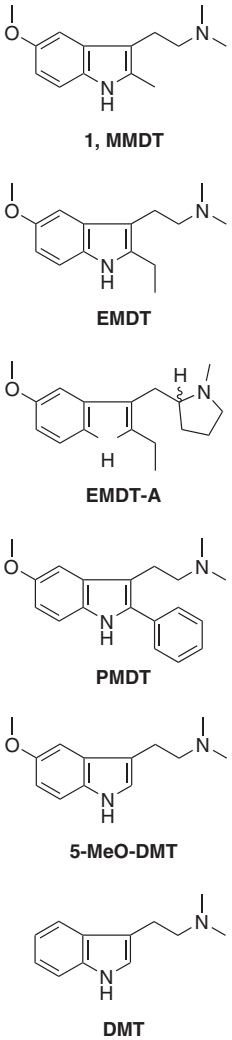


Figure 1. Representative *N,N*-dialkylated tryptamines. MMDT: 5-methoxy-2-methyl-*N,N*-dimethyltryptamine; EMDT: 5-methoxy-2-ethyl-*N,N*-dimethyltryptamine; EMDT-A: 2-ethyl-5-methoxy-3-[(1-methylpyrrolidin-2-yl)methyl]-1,*H*-indole; PMDT: 5-methoxy-2-phenyl-*N,N*-dimethyltryptamine; 5-MeO-DMT: 5-methoxy-*N,N*-dimethyltryptamine; DMT: *N,N*-dimethyltryptamine. While the latter two derivatives are typical representatives with hallucinogenic properties the first four candidates have been explored as h5-HT_6 ligands.

appear in the emergency clinic, where they may be noticed because of adverse reactions or toxicity. The lack of suitable reference materials makes unambiguous identification difficult and the need for appropriate data is especially felt when exposed to the need to differentiate among stereo or positional isomers. To address this need, the present study describes the preparation and analytical characterization of thirteen 5-methoxy-2-methyl-*N,N*-dialkyltryptamines which extends previous investigations on their isomeric 5-ethoxy counterparts.[17] Their effect on humans is currently unknown but there appears to be some indication that MMDT **1** may be orally active in humans at the 75–150 mg level.[7] In addition to nuclear magnetic resonance (NMR) spectroscopy, gas chromatography ion-trap mass spectrometry (GC-IT-MS) was employed using electron ionization (EI) and chemical ionization (CI) modes. In order to increase the information content beyond the $[M+H]^+$ the CI-MS/MS option was chosen.

Experimental

The use and origin of solvents and reagents, and details on instrumentation, i.e. 1D/2D NMR, GC-EI-MS, and GC-CI-MS/MS, have been described previously.[17,18] However, 5-methoxy-2-methylindole (99%) and *N*-allylmethylamine (96%) were purchased from Aldrich (Dorset, UK) and GC separations were carried out using a 30 m × 0.25 mm (0.25 μm film thickness) DB1ms column (J&W). Temperature, pressure settings, and power profiles involved during the microwave-accelerated $LiAlH_4$ reduction of glyoxalylamide precursors (**1a–13a**) were monitored using the SYNERGY software version 1.5.

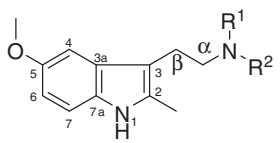
Syntheses

Synthesis procedures of all 13 precursors and tryptamine products were adapted from previous work.[17,18] This was based on the Speeter and Anthony approach[19] that provides convenient access to a large variety of simple tryptamines. In the present study, 5-methoxy-2-methylindole was acylated with oxalyl chloride to yield the glyoxalyl chloride intermediate **a** followed by reaction with the corresponding amine. The resulting glyoxalylamide precursors **1a – 13a** were then reduced with lithium aluminium hydride to give the *N,N*-dialkylated tryptamines **1–13** summarized in Table 1.

*5-Methoxy-2-methylindole-3-yl-glyoxalyl chloride (**a**)*

Yield: 2.32 g (9.2 mmol, 74%) starting from 5-methoxy-2-methylindole (2.00 g, 12.4 mmol). ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.30 (1H, br s, N*H*), 7.49 (1H, d, *J* = 2.4 Hz, *H*-4), 7.32 (1H, dd, *J* = 8.7, 0.5 Hz, *H*-7), 6.83 (1H, dd, *J* = 8.7, 2.4 Hz, *H*-6), 3.77 (3H, s, OCH_3), 2.58 (3H, s, 2-CH_3). ^{13}C NMR: δ 183.1 (*C*O-β), 168.3 (*C*O-α), 155.6 (*C*-5), 147.1 (*C*-2), 129.8 (*C*-7a), 127.4 (*C*-3a), 112.3 (*C*-7), 111.7 (*C*-6), 108.2 (*C*-3), 102.7 (*C*-4), 55.3 (OCH_3), 13.3 (2-CH_3). HRESIMS data were obtained as the sodiated adduct of the methyl ester derivative. Theory $[M+Na]^+$: 270.0742; observed: 270.0750.

Table 1. Structures of synthesized tryptamines **1–13**.



No.	R^1	R^2	Abbreviation
1	Me	Me	5-MeO-2-Me-DMT*
2	Et	Et	5-MeO-2-Me-DET
3	Pr	Pr	5-MeO-2-Me-DPT
4	iPr	iPr	5-MeO-2-Me-DIPT
5	Allyl	Allyl	5-MeO-2-Me-DALT
6	Me	Pr	5-MeO-2-Me-MPT
7	Me	iPr	5-MeO-2-Me-MIPT
8	Et	iPr	5-MeO-2-Me-EIPT
9	Me	Et	5-MeO-2-Me-MET
10	Et	Pr	5-MeO-2-Me-EPT
11	2-Me-allyl	Et	5-MeO-2-Me-2MALET
12	Allyl	Cyclohexyl	5-MeO-2-Me-ALCHT
13	Me	Allyl	5-MeO-2-Me-MALT

* Also known as 5-MeO-TMT, Indapex and MMDT.

Data for 5-methoxy-2-methylindole-3-yl-*N*,*N*-dialkyl glyoxalylamide precursors (**1a – 13a**) starting from 5-methoxy-2-methylindole-3-yl-glyoxalyl chloride (**a**) (1.00 g, 4.0 mmol).

*5-Methoxy-2-methylindole-3-yl-N,N-dimethylglyoxalylamide (**1a**)*

Yield: 676 mg (2.6 mmol, 65%): ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.08 (1H, br s, N*H*), 7.43 (1H, br s, *H*-4), 7.31 (1H, d, *J* = 8.7 Hz, *H*-7), 6.82 (1H, dd, *J* = 8.7, 2.5 Hz, *H*-6), 3.77 (3H, s, OCH_3), 2.99 (3H, s, NCH_3), 2.90 (3H, s, NCH_3), 2.51 (3H, s, 2-CH_3, overlapping with residual solvent). ^{13}C NMR: δ 186.5 (*C*O-β), 168.3 (*C*O-α), 155.1 (*C*-5), 146.1 (*C*-2), 129.8 (*C*-7a), 127.3 (*C*-3a), 112.2 (*C*-7), 111.8 (*C*-6), 109.3 (*C*-3), 102.4 (*C*-4), 55.2 (OCH_3), 36.2 (NCH_3), 33.0 (NCH_3), 13.2 (2-CH_3). HRESIMS theory [M+Na]$^+$: 283.1059; observed: 283.1053.

*5-Methoxy-2-methylindole-3-yl-N,N-diethylglyoxalylamide (**2a**)*

Yield: 634 mg (2.2 mmol, 55%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.90 (1H, br s, N*H*), 7.56 (1H, br s, *H*-4), 7.06 (1H, d, *J* = 8.9 Hz, *H*-7), 6.75 (1H, dd, *J* = 8.9, 2.4 Hz, *H*-6), 3.85 (3H, s, OCH_3), 3.60 (2H, q, *J* = 7.2 Hz, NCH_2CH$_3$), 3.37 (2H, q, *J* = 7.1 Hz, NCH_2CH$_3$), 2.36 (3H, s, 2-CH_3), 1.32 (3H, t, *J* = 7.2 Hz, NCH$_2$CH_3), 1.19 (3H, t, *J* = 7.1 Hz, NCH$_2$CH_3). ^{13}C NMR: δ 186.3 (*C*O-β), 169.1 (*C*O-α), 156.3 (*C*-5), 146.8 (*C*-2), 129.8 (*C*-7a), 127.6 (*C*-3a), 112.7 (*C*-6), 112.0 (*C*-7), 110.3 (*C*-3), 103.0 (*C*-4), 55.8 (OCH_3), 42.3 (NCH_2CH$_3$), 38.8 (NCH_2CH$_3$), 13.9 (2-CH_3), 13.9 (NCH$_2$CH_3), 12.6 (NCH$_2$CH_3). HRESIMS theory [M+Na]$^+$: 311.1372; observed: 311.1365.

*5-Methoxy-2-methylindole-3-yl-N,N-dipropylglyoxalylamide (**3a**)*

Yield: 771 mg (2.4 mmol, 60%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.36 (1H, br s, N*H*), 7.55 (1H, br s, *H*-4), 7.00 (1H, d, *J* = 8.9 Hz, *H*-7), 6.71 (1H, dd, *J* = 8.8, 2.3 Hz, *H*-6), 3.84 (3H, s, OCH_3), 3.48 (2H, t, *J* = 7.7 Hz, NCH_2CH$_2$CH$_3$), 3.25 (2H, t, *J* = 7.7 Hz, NCH_2CH$_2$CH$_3$), 2.28 (3H, s, 2-CH_3), 1.75 (2H, sext, *J* = 7.6 Hz, NCH$_2$CH_2CH$_3$), 1.63 (2H, sext, *J* = 7.6 Hz, NCH$_2$CH_2CH$_3$), 1.02 (3H, t, *J* = 7.4 Hz, NCH$_2$CH$_2$CH_3), 0.80 (3H, t, *J* = 7.3 Hz, NCH$_2$CH$_2$CH_3). ^{13}C NMR: δ 186.1 (*C*O-β), 169.7 (*C*O-α), 156.2 (*C*-5), 147.1 (*C*-2), 130.0 (*C*-7a), 127.6 (*C*-3a), 112.5 (*C*-6), 112.1 (*C*-7), 110.2 (*C*-3), 103.0 (*C*-4), 55.8 (OCH_3), 49.9 (NCH_2CH$_2$CH$_3$), 46.4 (NCH_2CH$_2$CH$_3$), 21.7 (NCH$_2$CH_2CH$_3$), 20.6 (NCH$_2$CH_2CH$_3$), 13.7 (2-CH_3), 11.5 (NCH$_2$CH$_2$CH_3), 11.2 (NCH$_2$CH$_2$CH_3). HRESIMS theory [M+Na]$^+$: 339.1685; observed: 339.1686.

*5-Methoxy-2-methylindole-3-yl-N,N-diisopropylglyoxalylamide (**4a**)*

Yield: 664 mg (2.1 mmol, 53%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.49 (1H, br s, N*H*), 7.62 (1H, s, *H*-4), 6.93 (1H, d, *J* = 8.9 Hz, *H*-7), 6.67 (1H, dd, *J* = 8.8, 2.5 Hz, *H*-6), 3.96 (1H, sep, *J* = 6.6 Hz, NC*H*), 3.84 (3H, s, OCH_3), 3.61 (1H, sep, *J* = 6.9 Hz, NC*H*), 2.26 (3H, s, 2-CH_3), 1.61 (6H, d, *J* = 6.8 Hz, 2 × CH_3), 1.22 (6H, d, *J* = 6.6 Hz, 2 × CH_3). ^{13}C NMR: δ 185.9 (*C*O-β), 169.4 (*C*O-α), 156.2 (*C*-5), 147.1 (*C*-2), 130.1 (*C*-7a), 127.7 (*C*-3a), 112.5 (*C*-6), 112.1 (*C*-7), 110.0 (*C*-3), 102.9 (*C*-4), 55.8 (OCH_3), 50.8 (NCH), 45.9 (NCH), 20.6 (2 × CH_3), 20.2 (2 × CH_3), 13.7 2-CH_3). HRESIMS theory [M+Na]$^+$: 339.1685; observed: 339.1680.

*5-Methoxy-2-methylindole-3-yl-N,N-diallylglyoxalylamide (**5a**)*

Yield: 810 mg (2.6 mmol, 65%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.64 (1H, br s, N*H*), 7.56 (1H, s, *H*-4), 7.06 (1H, d, *J* = 8.9 Hz, *H*-7), 6.75 (1H, dd, *J* = 8.8, 2.5 Hz, *H*-6), 5.86 (1H, ddt, $^{3}J_{trans}$ = 17.1 Hz, $^{3}J_{cis}$ = 10.0 Hz, ^{3}J = 6.1 Hz, C*H*=CH$_2$), 5.75 (1H, ddt, $^{3}J_{trans}$ = 17.0 Hz, $^{3}J_{cis}$ = 9.3 Hz, ^{3}J = 6.2 Hz, C*H*=CH$_2$), 5.35–5.27 (2H, m, CH=CH_2), 5.20–5.14 (2H, m, CH=CH_2), 4.15 (2H, d, *J* = 6.2 Hz, NCH_2), 3.90 (2H, d, *J* = 6.2 Hz, NCH_2), 3.83 (3H, s, OCH_3), 2.39 (3H, s, 2-CH$_3$). ^{13}C NMR: δ 185.7 (*C*O-β), 169.2 (*C*O-α), 156.4 (*C*-5), 146.9 (*C*-2), 132.2 (*C*H=CH$_2$), 131.6 (CH=CH$_2$), 129.8 (*C*-7a), 127.6 (*C*-3a), 119.6 (CH=CH$_2$), 119.2 (CH=CH$_2$), 112.8 (*C*-6), 111.9 (*C*-7), 110.4 (*C*-3), 103.0 (*C*-4), 55.8 (OCH$_3$), 49.8 (NCH$_2$), 45.8 (NCH$_2$), 14.1 (2-CH$_3$). HRESIMS theory [M+Na]$^+$: 335.1372; observed: 335.1376.

*5-Methoxy-2-methylindole-3-yl-N-methyl-N-propylglyoxalylamide (**6a**)*

Yield: 623 mg (2.2 mmol, 55%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.33 (0.5H, br s, N*H*), 10.30 (0.5H, br s, N*H*), 7.52 (0.5H, s, *H*-4), 7.47 (0.5H, s, *H*-4), 7.04 (1H, dd, *J* = 8.8, 2.9 Hz, *H*-7), 6.71 (1H, dt, *J* = 8.7, 2.4 Hz, *H*-6), 3.82 (3H, s, OCH_3), 3.49 (1H, t, *J* = 7.6 Hz, NCH_2CH$_2$CH$_3$), 3.25 (1H, t, *J* = 7.5 Hz, NCH_2CH$_2$CH$_3$), 3.11 (1.5H, s, NCH_3), 2.97 (1.5H, s, NCH_3), 2.30 (3H, s, 2-CH_3), 1.76–1.56 (2H, m, NCH$_2$CH_2CH$_3$), 1.00 (1.5H, t, *J* = 7.4 Hz, NCH$_2$CH$_2$CH_3), 0.81 (1.5H, t, *J* = 7.3 Hz, NCH$_2$CH$_2$CH_3). ^{13}C NMR: δ 186.3 (*C*O-β), 186.0 (*C*O-β), 169.7 (*C*O-α), 169.5 (*C*O-α), 156.4 (*C*-5), 156.3 (*C*-5), 147.2 (*C*-2), 130.01 (*C*-7a), 130.00 (*C*-7a), 127.57 (*C*-3a), 127.53 (*C*-3a), 112.53 (*C*-6), 112.45 (*C*-6), 112.2 (*C*-7), 110.16 (*C*-3), 110.06 (*C*-3), 102.9 (*C*-4), 55.74 (OCH$_3$), 55.72 (OCH$_3$), 51.7 (NCH$_2$CH$_2$CH$_3$), 48.4 (NCH$_2$CH$_2$CH$_3$), 35.1 (NCH$_3$), 31.7 (NCH$_3$), 21.2 (NCH$_2$CH$_2$CH$_3$), 20.0 (NCH$_2$CH$_2$CH$_3$), 13.7 (2-CH$_3$), 11.3 (NCH$_2$CH$_2$CH$_3$), 11.0 (NCH$_2$CH$_2$CH$_3$). HRESIMS theory [M+Na]$^+$: 311.1372; observed: 311.1371.

*5-Methoxy-2-methylindole-3-yl-N-isopropyl-N-methyl-glyoxalylamide (**7a**)*

Yield: 850 mg (2.9 mmol, 73%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.17 (1H, br s, N*H*), 7.55 (0.4H, s, *H*-4), 7.49 (0.6H, s, *H*-4), 7.05 (1H, dd, *J* = 8.7, 3.9 Hz, *H*-7), 6.75–6.70 (1H, m, *H*-6), 4.92 (0.4H, sep, *J* = 6.8 Hz, NC*H*), 4.03 (0.6H, sep, *J* = 6.5 Hz, NC*H*), 3.82 (3H, s, OCH_3), 3.00 (1.8H, s, NCH_3), 2.84 (1.2H, s, NCH_3), 2.31 (3H, s, 2-CH_3), 1.24 (2.4H, d, *J* = 6.8 Hz, CH_3), 1.18 (3.6H, d, *J* = 6.6 Hz, CH_3). ^{13}C NMR: δ 186.4 (*C*O-β), 186.1 (*C*O-β), 169.3 (*C*O-α), 169.1 (*C*O-α), 156.4 (*C*-5), 156.3 (*C*-5), 146.9 (*C*-2), 129.9 (*C*-7a), 127.5 (*C*-3a), 112.6 (*C*-6), 112.1 (*C*-7), 110.2 (*C*-3), 103.0 (*C*-4), 102.7 (*C*-4), 55.76 (OCH$_3$), 55.71 (OCH$_3$), 49.5 (NCH), 43.9 (NCH), 28.5 (NCH$_3$), 25.0 (NCH$_3$), 20.3 (CH$_3$), 19.0 (CH$_3$), 13.7 (2-CH$_3$). HRESIMS theory [M+Na]$^+$: 311.1372; observed: 311.1365.

*5-Methoxy-2-methylindole-3-yl-N-ethyl-N-isopropylglyoxalylamide (**8a**)*

Yield: 551 mg (1.8 mmol, 45%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.12 (0.7H, br s, N*H*), 10.07 (0.3H, br s, N*H*), 7.56 (1H, br s, *H*-4), 7.03 (1H, d, *J* = 8.9 Hz, *H*-7), 6.73 (1H, dd, *J* = 8.9, 2.4 Hz, *H*-6), 4.61 (0.3H, sep, *J* = 6.9 Hz, NC*H*), 4.03 (0.7H, sep, *J* = 6.6 Hz, NC*H*), 3.84 (3H, s, OCH_3), 3.49 (1.5H, q, *J* = 7.0 Hz, NCH_2CH$_3$), 3.35 (0.5H, q, *J* = 7.2 Hz, NCH_2CH$_3$), 2.34 (3H, s, 2-CH_3), 1.40–1.36 (4H, m, overlapping d and t, CH_3), 1.24–1.19 (5H, m, overlapping d and t, CH_3). ^{13}C NMR: δ 186.3 (*C*O-β), 186.2 (*C*O-β), 169.6 (*C*O-α), 169.2 (*C*O-α), 156.29 (*C*-5), 156.25 (*C*-5), 147.0 (*C*-2), 129.9 (*C*-7a), 127.6 (*C*-3a), 112.7 (*C*-6), 112.5 (*C*-6), 112.1 (*C*-7), 112.0 (*C*-7), 110.3 (*C*-3), 110.2 (C-3), 103.0 (*C*-4), 102.8 (*C*-4), 55.8 (OCH$_3$), 50.1 (NCH), 46.4 (NCH), 39.3 (NCH$_2$CH$_3$), 35.3 (NCH$_2$CH$_3$), 21.2 (CH$_3$), 20.3 (CH$_3$), 16.1 (NCH$_2$CH$_3$), 14.4 NCH$_2$CH$_3$, 13.9 (2-CH$_3$). HRESIMS theory [M+Na]$^+$: 325.1528; observed: 325.1519.

*5-Methoxy-2-methylindole-3-yl-N-ethyl-N-methylglyoxalylamide (**9a**)*

Yield: 900 mg (3.3 mmol, 83%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.40 (1H, br s, N*H*), 7.52 (0.6H, s, *H*-4), 7.48 (0.4H, s, *H*-4), 7.03 (1H, dd, *J* = 8.9, 2.8 Hz, *H*-7), 6.70 (1H, dt, *J* = 8.9, 2.5 Hz, *H*-6), 3.81 (3H, s, OCH_3), 3.58 (0.8H, q, *J* = 7.2 Hz, NCH_2CH$_3$), 3.35 (1.2H, q, *J* = 7.0 Hz, NCH_2CH$_3$), 3.10 (1.8H, s, NCH_3), 2.96 (1.2H, s, NCH_3), 2.30 (3H, s, 2-CH_3), 1.25 (1.2H, t, *J* = 7.2 Hz, NCH$_2$CH_3), 1.16 (1.8H, t, *J* = 7.0 Hz, NCH$_2$CH_3). ^{13}C NMR: δ 186.1 (*C*O-β), 169.5 (*C*O-α), 169.2 (*C*O-α), 156.4 (*C*-5), 147.2 (*C*-2), 130.0 (*C*-7a), 127.6 (*C*-3a), 112.6 (*C*-6), 112.2 (*C*-7), 110.1 (*C*-3), 102.9 (*C*-4),

55.7 (OCH_3), 44.8 (NCH_2CH_3), 41.3 (NCH_2CH_3), 34.4 (NCH_3), 31.1 (NCH_3), 13.7 (2-CH_3), 13.3 (NCH_2CH_3), 11.8 (NCH_2CH_3). HRESIMS theory $[M+Na]^+$: 297.1215; observed: 297.1207.

*5-Methoxy-2-methylindole-3-yl-N-ethyl-N-propylglyoxalylamide (**10a**)*

Yield: 633 mg (2.1 mmol, 53 %): ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.12 (1H, br s, N*H*), 7.56 (1H, br s, *H*-4), 7.03 (1H, d, *J* = 8.9 Hz, *H*-7), 6.73 (1H, dd, *J* = 8.7, 2.4 Hz, *H*-6), 3.84 (3H, s, OCH_3), 3.60 (1H, q, *J* = 7.2 Hz, NCH_2CH_3), 3.51–3.45 (1H, m, $NCH_2CH_2CH_3$), 3.37 (1H, q, *J* = 7.2 Hz, NCH_2CH_3), 3.27–3.22 (1H, m, $NCH_2CH_2CH_3$), 2.32 (3H, d, *J* = 1.7 Hz, 2-CH_3), 1.75 (2H, sext, *J* = 7.6 Hz, $NCH_2CH_2CH_3$), 1.64 (2H, sext, *J* = 7.6 Hz, $NCH_2CH_2CH_3$), 1.31 (1.5H, t, *J* = 7.2 Hz, NCH_2CH_3), 1.18 (1.5H, t, *J* = 7.1 Hz, NCH_2CH_3), 1.03 (1.5H, t, *J* = 7.3 Hz, $NCH_2CH_2CH_3$), 0.82 (1.5H, t, *J* = 7.3 Hz, $NCH_2CH_2CH_3$). ^{13}C NMR: δ 186.2 (CO-β), 186.1 (CO-β), 169.5 (CO-α), 169.4 (CO-α), 156.3 (*C*-5), 146.9 (*C*-2), 129.9 (*C*-7a), 127.6 (*C*-3a), 112.6 (*C*-6), 112.1 (*C*-7), 110.3 (*C*-3), 110.2 (*C*-3), 103.0 (*C*-4), 55.8 (OCH_3), 49.4 ($NCH_2CH_2CH_3$), 45.8 ($NCH_2CH_2CH_3$), 42.7 (NCH_2CH_3), 39.4 (NCH_2CH_3), 21.8 ($NCH_2CH_2CH_3$), 20.7 ($NCH_2CH_2CH_3$), 13.8 (2-CH_3), 13.8 (NCH_2CH_3), 12.5 (NCH_2CH_3), 11.5 ($NCH_2CH_2CH_3$), 11.1 ($NCH_2CH_2CH_3$). HRESIMS theory $[M+Na]^+$: 325.1528; observed: 325.1519.

*5-Methoxy-2-methylindole-3-yl-N-ethyl-N-(2-methylallyl)glyoxalylamide (**11a**)*

Yield: 940 mg (3.0 mmol, 75%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.28 (1H, br s, N*H*), 7.55 (1H, br s, *H*-4), 7.00 (1H, dd, *J* = 8.7, 2.5 Hz, *H*-7), 6.70 (1H, dt, *J* = 8.7, 2.5 Hz, *H*-7), 4.98 (1.2H, s, CH=CH_2), 4.93 (0.8H, s, CH=CH_2), 4.15 (1.2H, s, NCH_2), 3.85 (0.8H, s, NCH_2), 3.81 (3H, s, OCH_3), 3.54 (0.8H, q, *J* = 7.1 Hz, NCH_2CH_3), 3.35 (1.2H, q, *J* = 7.0 Hz, NCH_2CH_3), 2.29 (3H, d, *J* = 1.7 Hz, 2-CH_3), 1.79 (1.8H, s, CH_3), 1.67 (1.2H, s, CH_3), 1.25 (1.2H, t, *J* = 7.2 Hz, NCH_2CH_3), 1.12 (1.8H, t, *J* = 7.1 Hz, NCH_2CH_3). ^{13}C NMR: δ 185.8 (CO-β), 185.7 (CO-β), 169.8 (CO-α), 169.7 (CO-α), 156.3 (*C*-5), 147.2 (*C*-2), 139.7 (*C*=CH_2), 139.6 (*C*=CH_2), 130.0 (*C*-7a), 127.6 (*C*-3a), 127.5 (*C*-3a), 114.6 (C=CH_2), 113.6 (C=CH_2), 112.5 (*C*-6), 112.2 (*C*-7), 110.4 (*C*-3), 110.1 (*C*-3), 103.1 (*C*-4), 55.7 (OCH_3), 53.2 (NCH_2), 48.7 (NCH_2), 42.0 (NCH_2CH_3), 38.5 (NCH_2CH_3), 20.3 (CH_3), 19.9 (CH_3), 13.9 (2-CH_3), 13.8 (2-CH_3), 13.4 (NCH_2CH_3), 11.9 (NCH_2CH_3). HRESIMS theory $[M+Na]^+$: 337.1528; observed: 337.1535.

*5-Methoxy-2-methylindole-3-yl-N-allyl-N-cyclohexyl-glyoxalylamide (**12a**)*

Yield: 740 mg (2.1 mmol, 53%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.99 (0.6H, br s, N*H*), 9.85 (0.4H, br s, N*H*), 7.55 (1H, br s, *H*-4), 7.01 (1H, dd, *J* = 8.7, 1.1 Hz, *H*-7), 6.71 (1H, dd, *J* = 8.8, 2.4 Hz, *H*-6), 5.98 (0.6H, ddt, $^3J_{trans}$ = 17.3 Hz, ^3J = 10.4 Hz, ^3J = 5.9 Hz, C*H*=CH_2), 5.79 (0.4H, ddt, $^3J_{trans}$ = 17.0 Hz, ^3J = 10.1 Hz, ^3J = 5.6 Hz, C*H*=CH_2), 5.35 (0.7H, dd, ^3J = 15.8 Hz, ^2J = 1.3 Hz, CH=CH_{trans}), 5.20 (0.7H, dd, ^3J = 8.9 Hz, ^2J = 1.3 Hz, CH=CH_{cis}), 5.08 (0.3H, dd, ^3J = 16.2 Hz, ^2J = 1.2 Hz, CH=CH_{trans}), 5.02 (0.3H, dd, ^3J = 9.2 Hz, ^2J = 1.1 Hz, CH=CH_{cis}), 4.28–4.19 (0.4H, m, N*CH*), 4.09 (1.3H, d, *J* = 6.0 Hz, NCH_2), 3.91 (0.7H, d, *J* = 6.0 Hz, NCH_2), 3.83 (3H, s, OCH_3), 3.62–3.52 (0.6H, m, N*CH*), 2.32 (1.2H, s, 2-CH_3), 2.30 (1.8H, s, 2-CH_3), 1.88–1.00 (10H, m, 5 × CH_2). ^{13}C NMR: δ 186.0 (CO-β), 169.5 (CO-α), 156.3 (*C*-5), 147.0 (*C*-2), 135.0 (*C*H=CH_2), 134.0 (*C*H=CH_2), 129.9 (*C*-7a), 127.7 (*C*-3a), 117.9 (CH=CH_2), 117.7 (CH=CH_2), 112.7 (*C*-6), 112.6 (*C*-6), 112.1 (*C*-7), 112.0 (*C*-7), 110.3 (*C*-3), 102.9 (*C*-4), 58.8 (NCH), 55.8 (OCH_3), 54.8 (NCH), 47.8 (NCH_2), 43.8 (NCH_2), 31.7 (CH_2), 30.5 (CH_2), 25.9 (CH_2), 25.5 (CH_2), 25.1 (CH_2), 14.0 (2-CH_3). HRESIMS theory $[M+Na]^+$: 377.1841; observed: 377.1843.

*5-Methoxy-2-methylindole-3-yl-N-allyl-N-methyl-glyoxalylamide (**13a**)*

Yield: 701 mg (2.4 mmol, 60%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.39 (1H, br s, N*H*), 7.53 (0.5H, br s, *H*-4), 7.48 (0.5H, br s, *H*-4), 7.06 (1H, dd, *J* = 8.9, 2.3 Hz, *H*-7), 6.73 (1H, dt, *J* = 8.7, 2.4 Hz, *H*-6), 5.85 (0.5H, ddt, $^3J_{trans}$ = 17.3 Hz, ^3J = 10.0 Hz, ^3J = 6.2 Hz, C*H*=CH_2), 5.74 (0.5H, ddt, $^3J_{trans}$ = 17.3 Hz, ^3J = 10.0 Hz, ^3J = 6.1 Hz, C*H*=CH_2), 5.37–519 (2H, m, CH=CH_2), 4.16 (1H, d, *J* = 6.2 Hz, NCH_2), 3.90 (1H, d, *J* = 6.1 Hz, NCH_2), 3.83 (3H, d, *J* = 1.3 Hz, OCH_3), 3.08 (1.5H, s, NCH_3), 2.96 (1.5H, s, NCH_3), 2.34 (3H, d, *J* = 1.1 Hz, 2-CH_3). ^{13}C NMR: δ 186.0 (CO-β), 185.9 (CO-β), 169.7 (CO-α), 169.4 (CO-α), 156.4 (*C*-5), 156.3 (*C*-5), 147.4 (*C*-2), 131.9 (*C*H=CH_2), 131.2 (*C*H=CH_2), 130.0 (*C*-7a), 127.5 (*C*-3a), 119.6 (CH=CH_2), 119.2 (CH=CH_2), 112.6 (*C*-6), 112.58 (*C*-6), 112.51 (*C*-6), 112.2 (*C*-7), 110.1 (*C*-3), 110.0 (*C*-3), 102.8 (*C*-4), 55.8 (OCH_3), 55.7 (OCH_3), 52.7 (NCH_2), 48.9 (NCH_2), 34.5 (NCH_3), 31.3 (NCH_3), 13.8 (2-CH_3). HRESIMS theory $[M+Na]^+$: 309.1215; observed: 303.1227.

Data for 5-methoxy-2-methyl-*N*,*N*-dialkyltryptamine derivatives (**1–13**) starting from the appropriate amide precursor (0.3 mmol).

*5-Methoxy-2-methyl-N,N-dimethyltryptamine base (**1**)*

Yield: 60 mg (0.26 mmol, 87%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 (1H, br s, N*H*), 7.12 (1H, d, *J* = 8.7 Hz, *H*-7), 6.96 (1H, d, *J* = 2.4 Hz, *H*-4), 6.75 (1H, dd, *J* = 8.7, 2.4 Hz, *H*-6), 3.84 (3H, s, OCH_3), 2.87–2.81 (2H, m, β-CH_2), 2.52–2.46 (2H, m, α-CH_2), 2.35 (6H, s, NCH_3), 2.34 (3H, s, 2-CH_3). ^{13}C NMR: δ 153.9 (*C*-5), 132.1 (*C*-2), 130.4 (*C*-7a), 129.1 (*C*-3a), 110.8 (*C*-7), 110.4 (*C*-6), 109.5 (*C*-3), 100.3 (*C*-4), 60.2 (α-CH_2), 56.0 (OCH_3), 45.5 (NCH_3), 22.9 (β-CH_2), 11.7 (2-CH_3). HRESIMS theory $[M+H]^+$: 233.1654; observed: 233.1657.

*5-Methoxy-2-methyl-N,N-diethyltryptamine HCl (**2**)*

Yield: 61 mg (0.21 mmol, 70%): ^{1}H NMR (300 MHz, D_2O): δ 7.37 (1H, d, *J* = 8.7 Hz, *H*-7), 7.07 (1H, d, *J* = 2.3 Hz, *H*-4), 6.89 (1H, dd, *J* = 8.9, 2.4 Hz, *H*-6), 3.89 (3H, s, OCH_3), 3.33–3.24 (6H, m, overlapping α-CH_2 and NCH_2CH_3), 3.08 (2H, t, *J* = 7.8 Hz, β-CH_2), 2.39 (3H, s, 2-CH_3), 1.30 (6H, t, *J* = 7.3 Hz, NCH_2CH_3). ^{13}C NMR: δ 153.0 (*C*-5), 135.5 (*C*-2), 130.7 (*C*-7a), 127.8 (*C*-3a), 112.0 (*C*-7), 110.3 (*C*-6), 103.9 (*C*-3), 100.3 (*C*-4), 56.3 (OCH_3), 50.9 (α-CH_2), 47.4 (NCH_2CH_3), 18.5 (β-CH_2), 10.5 (2-CH_3), 8.2 (NCH_2CH_3). HRESIMS theory $[M+H]^+$: 261.1967; observed: 261.1964.

*5-Methoxy-2-methyl-N,N-dipropyltryptamine HCl (**3**)*

Yield: 67 mg (0.21 mmol, 70%): ^{1}H NMR (300 MHz, D_2O): δ 7.37 (1H, d, *J* = 8.7 Hz, *H*-7), 7.02 (1H, d, *J* = 2.3 Hz, *H*-4), 6.88 (1H, dd, *J* = 8.7, 2.4 Hz, *H*-6), 3.89 (3H, s, OCH_3), 3.27 (2H, t, *J* = 7.8 Hz, α-CH_2), 3.15–3.10 (4H, m, $NCH_2CH_2CH_3$), 3.02 (2H, t, *J* = 7.8 Hz, β-CH_2), 2.38 (3H, s, 2-CH_3), 1.76–1.63 (4H, m, $NCH_2CH_2CH_3$), 0.96 (6H, t, *J* = 7.3 Hz, $NCH_2CH_2CH_3$). ^{13}C NMR: δ 153.0 (*C*-5), 135.4 (*C*-2), 130.7 (*C*-7a), 127.8 (*C*-3a), 112.0 (*C*-7), 110.3 (*C*-6), 104.0 (*C*-3), 100.1 (*C*-4), 56.2 OCH_3, 54.5 ($NCH_2CH_2CH_3$), 51.8 (α-CH_2), 18.3 (β-CH_2), 16.9 ($NCH_2CH_2CH_3$), 10.5 (2-CH_3), 10.1 ($NCH_2CH_2CH_3$). HRESIMS theory $[M+H]^+$: HRESIMS theory $[M+H]^+$: 289.2280; observed: 289.2260.

*5-Methoxy-2-methyl-N,N-diisopropyltryptamine HCl (**4**)*

Yield: 63 mg (0.19 mmol, 63%): ^{1}H NMR (300 MHz, d_6-DMSO): δ 10.76 (1H, s, N*H*Cl), 10.10 (1H, s, N*H*), 7.15 (1H, d, *J* = 8.7 Hz, *H*-7), 6.97 (1H, d, *J* = 2.3 Hz, *H*-4), 6.66 (1H, dd, *J* = 8.7, 2.4 Hz, *H*-6), 3.76 (3H, s, OCH_3), 3.76–3.66 (2H, m, N*CH*), 3.14–3.04 (4H, m, α- and β-CH_2), 2.34 (3H, s, 2-CH_3), 1.42 (6H, d, *J* = 6.6 Hz, 2 × CH_3), 1.36 (6H, d, *J* = 6.6 Hz, 2 × CH_3). ^{13}C NMR: δ 153.1 (*C*-5), 133.4 (*C*-2), 130.2 (*C*-7a), 128.0 (*C*-3a), 111.2 (*C*-7), 109.6 (*C*-6), 105.3 (*C*-3),

99.7 (*C*-4), 55.3 (OCH_3), 53.7 (NCH), 46.7 (α-CH_2), 21.8 (β-CH_2), 18.0 (CH_3), 16.8 (CH_3), 11.3 (2-CH_3). HRESIMS theory $[M+H]^+$: 289.2280; observed: 289.2265.

*5-Methoxy-2-methyl-N,N-diallyltryptamine HCl (**5**)*

Yield: 83 mg (0.26 mmol, 86%): ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.22 (1H, br s, N*H*Cl), 10.70 (1H, br s, N*H*), 7.14 (1H, d, J = 8.7 Hz, *H*-7), 6.98 (1H, d, J = 2.4 Hz, *H*-4), 6.64 (1H, dd, J = 8.7, 2.4 Hz, *H*-6), 6.09 (2H, ddt, $^3J_{trans}$ = 17.1 Hz, ^3J = 10.2 Hz, ^3J = 7.0 Hz, C*H*=CH_2), 5.65 (2H, dd, J = 15.6, 1.4 Hz, 2 × CH=CH_{trans}), 5.55 (2H, dd, J = 8.7, 1.6 Hz, 2 × CH=CH_{cis}), 3.87–3.83 (4H, m, 2 × NCH_2), 3.76 (3H, s, OCH_3), 3.12–3.00 (4H, m, α-CH_2, β-CH_2), 2.31 (3H, s, 2-CH_3). ^{13}C NMR: δ 153.1 (*C*-5), 133.4 (*C*-2), 130.3 (*C*-7a), 128.1 (*C*-3a), 127.5 (*C*H=CH_2), 124.8 (CH=*C*H_2), 111.1 (*C*-7), 109.7 (*C*-6), 104.6 (*C*-3), 99.8 (*C*-4), 55.4 (OCH_3), 53.8 (NCH_2), 50.8 (α-CH_2), 18.2 (β-CH_2), 11.2 (2-CH_3). HRESIMS theory $[M+H]^+$: 285.1967; observed: 285.1963.

*5-Methoxy-2-methyl-N-methyl-N-propyltryptamine HCl (**6**)*

Yield: 70 mg (0.24 mmol, 80%): ^{1}H NMR (300 MHz, D_2O): δ 7.37 (1H, d, J = 8.7 Hz, *H*-7), 7.08 (1H, d, J = 2.3 Hz, *H*-4), 6.88 (1H, dd, J = 8.9, 2.4 Hz, *H*-6), 3.90 (3H, s, OCH_3), 3.33 (2H, t, J = 7.7 Hz, $NCH_2CH_2CH_3$), 3.15–3.07 (4H, m, overlapping triplets, α-CH_2 and β-CH_2), 2.91 (3H, s, NCH_3), 2.39 (3H, s, 2-CH_3), 1.69 (2H, sext, J = 7.7 Hz, $NCH_2CH_2CH_3$), 0.94 (3H, t, J = 7.4 Hz, $NCH_2CH_2CH_3$). ^{13}C NMR: δ 153.0 (*C*-5), 135.5 (*C*-2), 130.7 (*C*-7a), 127.7 (*C*-3a), 112.0 (*C*-7), 110.3 (*C*-6), 103.8 (*C*-3), 100.3 (*C*-4), 57.4 (α-CH_2), 56.3 (OCH_3), 55.0 ($NCH_2CH_2CH_3$), 40.0 (NCH_3), 18.7 (β-CH_2), 17.2 ($NCH_2CH_2CH_3$), 10.5 (2-CH_3), 10.0 ($NCH_2CH_2CH_3$). HRESIMS theory $[M+H]^+$: 261.1967; observed: 261.1972.

*5-Methoxy-2-methyl-N-isopropyl-methyl-tryptamine HCl (**7**)*

Yield: 71 mg (0.24 mmol, 80%): ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.68 (1H, br s, N*H*Cl), 10.62 (1H, br s, N*H*), 7.15–7.12 (2H, m, *H*-7, *H*-4), 6.65 (1H, dd, J = 8.7, 2.1 Hz, *H*-6), 3.77 (3H, s, OCH_3), 3.68–3.58 (1H, m, NC*H*), 3.14–2.98 (4H, m, α-CH_2 and β-CH_2), 2.73 (3H, d, J = 4.3 Hz, NCH_3), 2.34 (3H, s, 2-CH_3), 1.31 (3H, d, J = 6.6 Hz, CH_3), 1.23 (3H, d, J = 6.6 Hz, CH_3). ^{13}C NMR: δ 153.1 (*C*-5), 133.4 (*C*-2), 130.3 (*C*-7a), 128.2 (*C*-3a), 111.0 (*C*-7), 109.6 (*C*-6), 104.8 (*C*-3), 100.3 (*C*-4), 55.5 (OCH_3 and NCH), 52.1 (α-CH_2), 33.9 (NCH_3), 19.2 (β-CH_2), 16.9 (CH_3), 14.9 (CH_3), 11.2 (2-CH_3). HR ESIMS theory $[M+H]^+$: 261.1967; observed: 261.1963.

*5-Methoxy-2-methyl-N-ethyl-N-isopropyltryptamine HCl (**8**)*

Yield: 60 mg (0.19 mmol, 63%): ^{1}H NMR (300 MHz, D_2O): δ 7.37 (1H, d, J = 8.9 Hz, *H*-7), 7.04 (1H, d, J = 2.3 Hz, *H*-4), 6.88 (1H, dd, J = 8.9, 2.4 Hz, *H*-6), 3.89 (3H, s, OCH_3), 3.76 (1H, sep, J = 6.8 Hz, NC*H*), 3.30–3.20 (4H, m, overlapping q and t, NCH_2CH_3 and β-CH_2), 3.06 (2H, t, J = 7.9 Hz, α-CH_2), 2.39 (3H, s, 2-CH_3), 1.33–1.29 (9H, m, overlapping NCH_2CH_3 and 2 × CH_3). ^{13}C NMR: δ 153.0 (*C*-5), 135.5 (*C*-2), 130.7 (*C*-7a), 127.8 (*C*-3a), 112.0 (*C*-7), 110.3 (*C*-6), 104.0 (*C*-3), 100.2 (*C*-4), 56.2 (OCH_3), 54.5 (NCH), 48.7 (β-CH_2), 45.4 (NCH_2CH_3), 19.5 (α-CH_2), 15.7 (NCH_2CH_3), 10.5 (2-CH_3), 9.5 (CH_3). HRESIMS theory $[M+H]^+$: 275.2123; observed: 275.2113.

*5-Methoxy-2-methyl-N-ethyl-N-methyltryptamine HCl (**9**)*

Yield: 52 mg (0.18 mmol, 60%): ^{1}H NMR (300 MHz, CD_3OD): δ 10.18 (1H, br s, N*H*Cl), 7.16 (1H, d, J = 8.9 Hz, *H*-7), 7.02 (1H, d, J = 2.3 Hz, *H*-4) 6.70 (1H, dd, J = 8.7, 2.3 Hz, *H*-6), 3.82 (3H, s, OCH_3), 3.29–3.07 (4H, m, NCH_2CH_3 and α-CH_2), 3.11 (2H, t, J = 7.6 Hz, β-CH_2), 2.90 (3H, s, NCH_3), 2.38 (3H, s, 2-CH_3), 1.33 (3H, t, J = 7.7 Hz, NCH_2CH_3). ^{13}C NMR: δ 155.3 (*C*-5), 135.0 (*C*-2), 132.4 (*C*-7a), 129.6 (*C*-3a), 112.3 (*C*-7), 111.4 (*C*-6), 105.2 (*C*-3), 101.0 (*C*-4), 56.6 (OCH_3), 56.5 (NCH_2CH_3), 52.3 (α-CH_2), 39.9 (NCH_3), 20.6 (β-CH_2), 11.5 (2-CH_3), 9.7 (NCH_2CH_3). HRESIMS theory $[M+H]^+$: 247.1810; observed: 247.1808.

*5-Methoxy-2-methyl-N-ethyl-N-propyltryptamine HCl (**10**)*

Yield: 61 mg (0.2 mmol, 67%): ^{1}H NMR (300 MHz, D_2O): δ 7.36 (1H, d, J = 8.9 Hz, *H*-7), 7.01 (1H, d, J = 2.4 Hz, *H*-4), 6.87 (1H, dd, J = 8.9, 2.4 Hz, *H*-6), 3.89 (3H, s, OCH_3), 3.29–3.20 (4H, m, overlapping q and t, NCH_2CH_3 and α-CH_2), 3.13–3.08 (2H, m, N$CH_2CH_2CH_3$), 2.99 (2H, t, J = 7.9 Hz, β-CH_2), 2.37 (3H, s, 2-CH_3), 1.74–1.61 (2H, m, $NCH_2CH_2CH_3$), 1.30 (3H, t, J = 7.3 Hz, NCH_2CH_3), 0.96 (3H, t, J = 7.3 Hz, $NCH_2CH_2CH_3$). ^{13}C NMR: δ 153.0 (*C*-5), 135.4 (*C*-2), 130.7 (*C*-7a), 127.8 (*C*-3a), 112.0 (*C*-7), 110.3 (*C*-6), 104.0 (*C*-3), 100.1 (*C*-4), 56.2 (OCH_3), 53.8 (α-CH_2), 51.2 ($NCH_2CH_2CH_3$), 48. 0 (NCH_2CH_3), 18.4 (β-CH_2), 17.0 ($NCH_2CH_2CH_3$), 10.5 (2-CH_3), 10.1 ($NCH_2CH_2CH_3$), 8.2 (NCH_2CH_3). HRESIMS theory $[M+H]^+$: 275.2123; observed: 275.2112.

*5-Methoxy-2-methyl-N-ethyl-N-(2-methylallyl)tryptamine HCl (**11**)*

Yield: 65 mg (0.20 mmol, 67%): ^{1}H NMR (300 MHz, CD_3OD): δ 10.19 (1H, br s, N*H*Cl), 7.16 (1H, d, J = 8.7 Hz, *H*-7), 6.97 (1H, d, J = 2.3 Hz, *H*-4), 6.70 (1H, dd, J = 8.7, 2.4 Hz, *H*-6), 5.34–5.31 (2H, m, C = CH_2), 3.83 (2H, s, NCH_2), 3.82 (3H, s, OCH_3), 3.35 (2H, q, J = 7.2 Hz, NCH_2CH_3), 3.23–3.20 (2H, m, α-CH_2), 3.15–3.09 (2H, m, β-CH_2), 2.38 (3H, s, 2-CH_3), 1.92 (3H, s, CH_3), 1.92 (3H, s, CH_3), 1.39 (3H, t, J = 7.8 Hz, NCH_2CH_3). ^{13}C NMR: δ 155.3 (*C*-5), 136.8 (*C*=CH_2), 134.9 (*C*-2), 132.4 (*C*-7a), 129.6 (*C*-3a), 122.3 (C=CH_2), 112.4 (*C*-7), 111.5 (*C*-6), 105.3 (*C*-3), 100.8 (*C*-4), 59.9 (NCH_2), 56.5 (OCH_3), 52.9 (β-CH_2), 49.2 (NCH_2CH_3), 21.1 (CH_3), 19.9 (α-CH_2), 11.5 (2-CH_3), 9.1 (NCH_2CH_3). HRESIMS theory $[M+H]^+$: 287.2123; observed: 287.2125.

*5-Methoxy-2-methyl-N-allyl-N-cyclohexyltryptamine HCl (**12**)*

Yield: 74 mg (0.20 mmol, 67%): ^{1}H NMR (300 MHz, CD_3OD): δ 10.20 (1H, br s, N*HCl*), 7.16 (1H, d, J = 8.9 Hz, *H*-7), 6.94 (1H, d, J = 2.4 Hz, *H*-4), 6.71 (1H, dd, J = 8.7, 2.3 Hz, *H*-6), 6.13–6.00 (1H, m, C*H*=CH_2), 5.66 (1H, dt, J = 15.8, 1.1 Hz, CH=CH_{trans}), 5.62 (1H, dt, J = 10.2, 1.1 Hz, CH=CH_{cis}), 3.91 (2H, br d, J = 6.4 Hz, NCH_2), 3.82 (3H, s, OCH_3), 3.43 (1H, tt, J = 11.7, 3.3 Hz, NC*H*), 3.32–3.26 (2H, m, overlapping solvent and α-CH_2), 3.12 (2H, t, J = 8.3 Hz, β-CH_2), 2.38 (3H, s, 2-CH_3), 2.11–2.07 (2H, m, CH_2), 1.94–1.90 (2H, m, CH_2), 1.72–1.68 (1H, m, 0.5 × CH_2), 1.62–1.49 (2H, m, CH_2), 1.42–1.19 (3H, m, 1.5 × CH_2). ^{13}C NMR: δ 155.3 (*C*-5), 134.9 (*C*-2), 132.4 (*C*-7a), 129.5 (*C*-3a), 129.0 (CH=CH_2), 126.0 (CH=CH_2), 112.4 (*C*-7), 111.4 (*C*-6), 105.4 (*C*-3), 100.8 (*C*-4), 64.2 (NCH), 56.5 (OCH_3), 54.3 (NCH_2), 51.0 (α-CH_2), 28.0 (2 × CH_2), 26.1 (3 × CH_2), 21.4 (β-CH_2), 11.5 (2-CH_3). HRESIMS theory $[M+H]^+$: 327.2436; observed: 327.2440.

*5-Methoxy-2-methyl-N-allyl-N-methyltryptamine free base (**13**)*

Yield: 71 mg (0.27 mmol, 90%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (1H, br s, N*H*), 7.12 (1H, d, J = 8.7 Hz, *H*-7), 6.96 (1H, d, J = 2.4 Hz, *H*-4), 6.75 (1H, dd, J = 8.7, 2.4 Hz, *H*-6), 5.94 (1H, ddt, $^3J_{trans}$ = 17.0 Hz, $^3J_{cis}$ = 10.2 Hz, ^3J = 6.6 Hz, C*H*=CH_2), 5.21 (1H, dm, J_{trans} = 18.1 Hz, CH=C*H*), 5.16 (1H, dm, J_{cis} = 11.4 Hz, CH = C*H*), 3.84 (3H, s, OCH_3), 3.12 (3H, dt, J = 6.6, 1.1 Hz, NCH_2), 2.87–2.82 (2H, m, β-CH_2), 2.60–2.55 (2H, m, α-CH_2), 2.73 (3H, s, NCH_3), 2.34 (3H, s, 2-CH_3). ^{13}C NMR: δ 153.9 (*C*-5), 135.7 (*C*H=CH_2), 132.1 (*C*-2), 130.4 (*C*-7a), 129.2 (*C*-3a), 117.6 (CH=CH_2), 110.8 (*C*-7), 110.4 (*C*-6), 109.6 (*C*-3), 100.6 (*C*-4), 60.8 (NCH_2), 57.6 (α-CH_2), 56.0

(OCH_3), 42.1 (NCH_3), 22.4 (β-CH_2), 11.7 (2-CH_3). HRESIMS theory $[M+H]^+$: 259.1810; observed: 259.1796.

Results and discussion

Few data are available in the published literature about the preparation and characterization of 5-methoxy-2-methyl-*N*,*N*-dialkylated tryptamines **1–13**. Exceptions include the synthesis of 5-methoxy-2-methyl-*N*,*N*-dimethyltryptamine **1** that was reported for the first time in 1955. In this particular case, 2-methyl-5-methoxy-3-indoleacetic acid was prepared *via* a Fischer procedure using methyl 4-oxopentanoate and *p*-methoxyphenylhydrazine. Conversion to the indole-*N*,*N*-dimethylacetamide precursor was achieved using tetramethylurea and then followed by lithium aluminium hydride (LAH) reduction to give the DMT derivative.[20] A variation of the theme was offered by Shulgin and Shulgin who started from indomethacin, i.e. 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetic acid, followed by conversion to 1-(*p*-chlorobenzoyl)-5-methoxy-2,*N*,*N*-trimethylindole-3-acetamide using oxalyl chloride and dimethylamine. Alkaline hydrolysis afforded 5-methoxy-2,*N*,*N*-trimethylindole-3-acetamide that was then reduced by LAH.[7] DMT **1** has also been prepared by reductive amination using aqueous formaldehyde and the corresponding primary amine starting material[21,22] whereas a one-pot approach was also provided using *p*-methoxyphenylhydrazine and 5-(dimethylamino) pentan-2-one.[23] The DET derivative **2**, on the other hand, was detected during an arynic cyclization reaction involving a halogenated aryl imine intermediate.[24] A Fischer cylization was also employed for the synthesis of *N*,*N*-dipropyltryptamine **3** using *p*-methoxyphenylhydrazine and 5-(dipropylamino)pentan-2-one[25] whereas 2-(diisopropylamino)-4-pentanone ethylene glycol

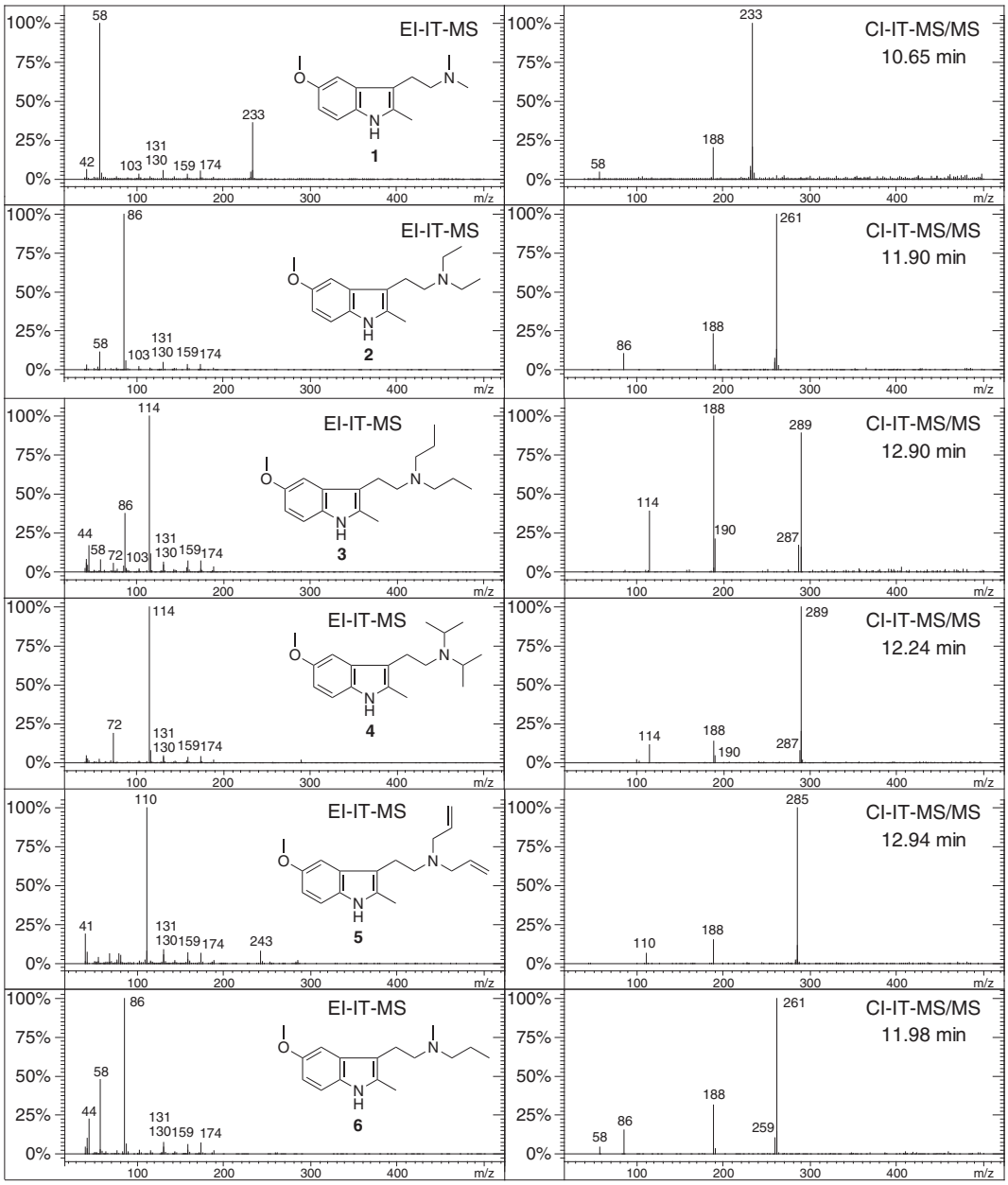


Figure 2. EI-IT-MS and CI-IT-MS/MS spectra obtained from 5-methoxy-2-methyl-N,N-dialkyltryptamines isomeric tryptamines 1–6.

ketal was successfully used to provide the DIPT **4** derivative.[26] Interestingly, this compound was used as a precursor to give 1-benzoyl-**4** that was then evaluated for its anti-inflammatory properties using the carrageenan edema (CE) and adjuvant arthritic (AA) tests. Reduced inflammation was expressed in terms of percent inhibition, i.e. CE 61% at 0.324 μM/kg and AA 53% at 0.08 μM/kg, respectively.[26]

Restricted rotation in indole-3-yl-*N*,*N*-dialkyl glyoxalylamides results in the detection of syn-periplanar and anti-periplanar rotamers leading to two sets of side chain related peaks when using NMR spectroscopy. In addition, asymmetrically disubstituted glyoxalylamides have previously been shown to display predominant peaks that corresponded to one of the rotamers.[17,18,27,28] As far as 5-methoxy-2-methylindole-3-yl-*N*,*N*-dialkyl glyoxalylamides

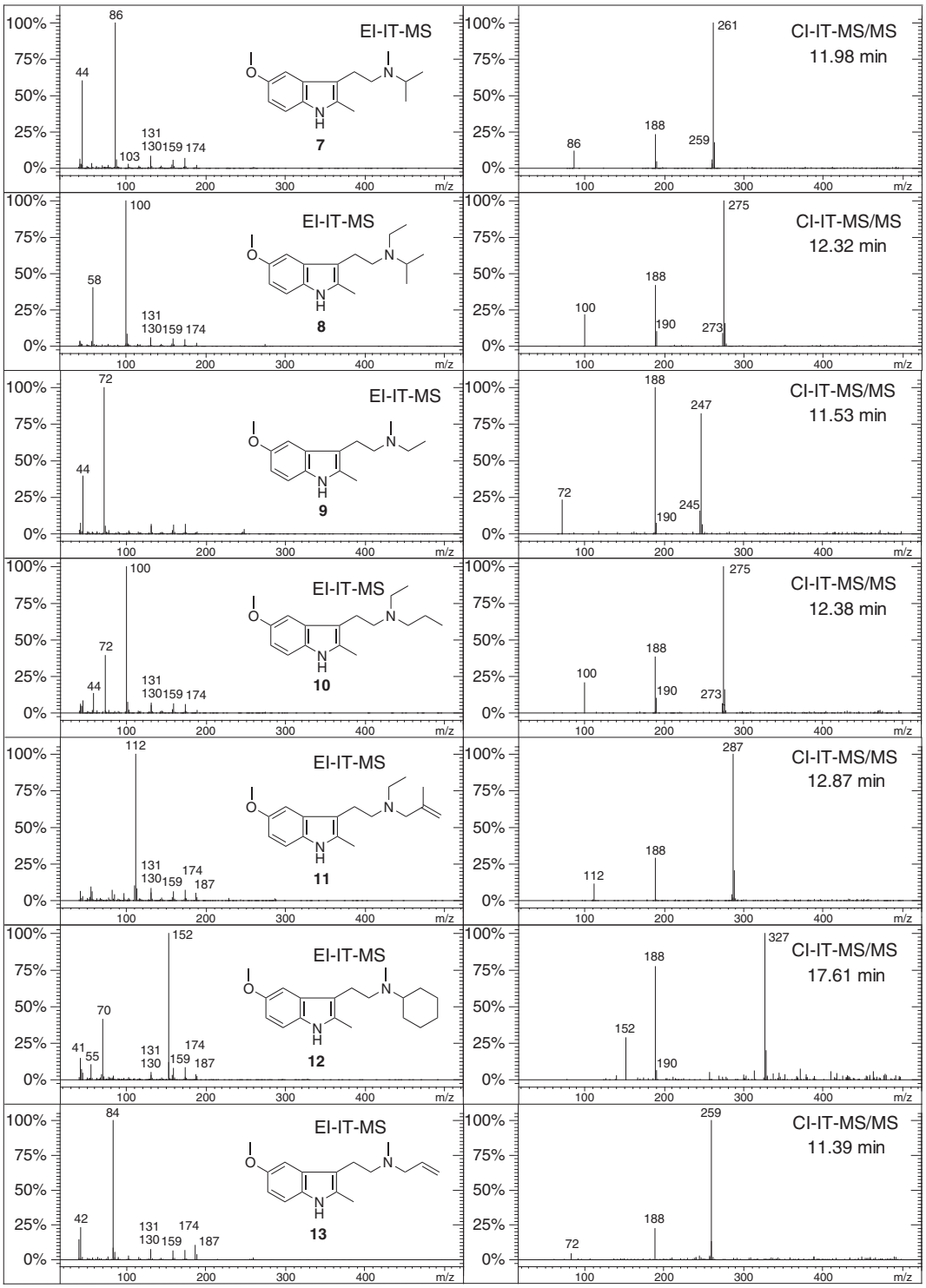


Figure 3. EI-IT-MS and CI-IT-MS/MS spectra obtained from 5-methoxy-2-methyl-N,N-dialkyltryptamines isomeric tryptamines 7–13.

were concerned two sets of rotamers were also detected and the extent to which this occurred is reflected in unequal proton integrals reported in the NMR section.

One of the key tools involved in forensic and clinical analysis involves the implementation of GC-MS, particularly in cases where NMR analysis is not an option. The absence of reference standards is also a common experience especially when dealing with new psychoactive substances that are encountered for the first time. All 13 EI-IT-MS and CI-IT-MS/MS data and GC retention times are shown in Figures 2 and 3.

Under EI conditions, base peaks reflected the presence of $CH_2{=}N^+R^1R^2$ iminium ions ($C_nH_{2n+2}N^+$) that are typically found for tryptamines.[27] For example, the *N*-ethyl-*N*-isopropyl (EIPT) derivative **8** (Figure 3) displayed its base peak at *m/z* 100 representing the $CH_2{=}N^+(C_2H_5)CH(CH_3)_2$ species. Correspondingly, the *m/z* 100 also formed the base peak when investigating the *N*-ethyl-*N*-propyl isomer (EPT) **10** (Figure 3). However, differentiation between both isomers was possible due to secondary fragmentation (loss of olefin) yielding further fragmentation of *m/z* 100 to *m/z* 58 (**8**) and *m/z* 100 to *m/z* 72 and *m/z* 44 (**10**), respectively. CI-IT-MS/MS analysis allowed for the determination of $[M+H]^+$, for example, *m/z* 275 for tryptamines **8** and **10** (Figure 3), but also provided further fragments such as iminium ions and a species at *m/z* 188 in all cases. Differentiation between isomers was not always possible under CI-IT-MS/MS conditions but the complementary key feature was the ability to determine the molecular mass which could normally not be obtained under EI conditions due to extensive fragmentation of the $M^{\bullet+}$ ion. Overall, EI-IT-MS displayed key ions at *m/z* 174, 159, 131, 130, and 103 that corresponded to fragmentations associated with the indole nucleus. On the other hand, previous work on a series of 5-ethoxy-*N*,*N*-dialkyltryptamines presented the corresponding indole ion series at *m/z* 188, 146, 130 and 117[17] which confirmed the ability to distinguish them for their isomeric 5-methoxy-2-methyl counterparts described here.

In addition to the indication that **1** may be orally active in humans, further research should shed more light on this aspect including the extent to which tryptamines **2–13** show psychoactive properties as well. In any case, the possibility that these derivatives might be encountered within the recreational context cannot be excluded.

Conclusion

The emergence of new psychoactive drugs on the recreational drug market is often complicated by the inability to determine their identity due to the lack of suitable reference material. A simple preparation of thirteen 5-methoxy-2-methyl-*N*,*N*-dialkyltryptamines provided access to a range of molecules that might be useful for pharmacological studies to determine their psychoactivity, if any, as well as their biological targets. More importantly, the analytical procedures implemented here confirmed that it was possible to differentiate them from a range of isomeric candidates. This will be useful for forensic, clinical, and public health providers if these substances become widely available.

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