ARTICLE

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Analytical chemistry of synthetic routes to psychoactive tryptamines
Part I. Characterisation of the Speeter and Anthony synthetic route to 5-methoxy-*N*,*N*-diisopropyltryptamine using ESI-MS-MS and ESI-TOF-MS

Simon D. Brandt,[a] Sally Freeman,[b] Ian A. Fleet,[c] Peter McGagh[a] and John F. Alder*[a]

[a] *Department of Instrumentation and Analytical Science, UMIST, Manchester M60 1QD, UK. E-mail: fred.alder@umist.ac.uk; Fax: +44 161 200 4881; Tel: +44 161 200 4885*

[b] *School of Pharmacy and Pharmaceutical Sciences, University of Manchester, Oxford Road, Manchester M13 9PL, UK. E-mail: sally.freeman@man.ac.uk*

[c] *Deparment of Chemistry, UMIST, Manchester M60 1QD, UK. E-mail: ian.fleet@umist.ac.uk*

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5 Methoxy *N*,*N* diisopropyltryptamine (5 MeO DIPT), a new psychoactive tryptamine derivative, has been synthesised by the Speeter and Anthony procedure. This synthetic route was characterised by ESI MS MS, ESI TOF MS and NMR. Side products have been identified as 3 (2 *N*,*N* diisopropylamino ethyl) 1*H* indol 5 ol (**5**), 2 *N*,*N* diisopropylamino 1 (5 methoxy 1*H* indol 3 yl) ethanol (**6**), 2 (5 methoxy 1*H* indol 3 yl) ethanol (**7**) and 2 *N*,*N* diisopropylamino 1 (5 methoxy 1*H* indol 3 yl) ethanone (**8**).

Introduction

The psychoactive properties of 5 methoxy *N*,*N* diisopropyl tryptamine, 5 MeO DIPT (street names Foxy Methoxy or Foxy), were first published by Shulgin and Carter.[1] A second report on its ability to induce altered states of consciousness appeared in 1997.[2] 5 MeO DIPT appeares to be orally active at a 6 12 mg level, and its effects are short lived.[1,2] Users of 5 MeO DIPT may experience pleasant feelings and euphoria including perceptual changes and erotic enhancement. Visual and auditory hallucinogensis and physical discomfort have also been reported.[1 3] A recent hospital case report described an incident where 5 MeO DIPT had been ingested by a young man who complained about mild hallucinations and the inability to move his limbs.[4] Clare[5] calculated a quantitative structure activity relationship for 5 MeO DIPT based on molecular electronic properties and described its potency comparable to 50 mescaline units (MU) (3,4,5 trimethoxy phenethylamine). Using comparative molecular field analysis (CoMFA) and based on data published by Shulgin, Beuerle and coworkers calculated an activity equivalent to 33 MU.[6] In rats trained to discriminate a potent hallucinogen, DOM (2,5 dimethoxy 4 methylamphetamine),[7] it was found that 5 MeO DIPT was capable of producing an 85% DOM appropriate response at a dosage of 2 mg kg ^{1} indicating common drug receptor interactions.[8] Using dimethyltryptamine (DMT), a ''classical'' parenterally active hallucinogen as a reference point its potency has been compared to eight DMT equivalents at a range of 8 12 mg.[9] 5 MeO DIPT did not have any significant monoamineoxidase inhibition properties.[10]

Synthetic and analytical chemistry of 5-MeO-DIPT

The role of impurity profiling in drug research, development and production is indispensable,[11] especially in view of clinical research with injectable hallucinogenic substances where the drug needs to be of high purity.[12,13] There exists a variety of synthetic routes to psychotropic tryptamines[14 16] and the number of routes to indoles seems to be countless.[17 19] The synthetic route used by Speeter and Anthony[20] is considered to be one of the most important approaches to the production of tryptamine derivatives[15] (Scheme 1A). This method involves the acylation of 5 methoxyindole with oxalyl chloride and the formation of the 3 ylglyoxalylamide (**3a**). Reduction with lithium aluminium hydride afforded the desired tryptamine compound (**4a**). This reaction was also applied by Shulgin and Carter in 1980.[1] Apart from the synthesis of hallucinogenic derivatives this route is found to have a wide range of applica tions. For example, certain 5 alkyl and 5 thienyltryptamines synthesised by this method have been found to be potent agonists of cloned human 5 $HT_{1B/1D}$ receptors indicating potential in the treatment of migraine.[21,22]

Few data appear to be available on the analytical chemistry of 5 MeO DIPT. In the course of an investigation of amphetamine derivatives Katagi and coworkers[23] depicted the positive ion electron ionisation mass spectrometry (EI MS) and infrared spectrum of 5 MeO DIPT. Hugel and coworkers obtained an EI MS and IR of 5 MeO DIPT hydrochloride and freebase, respectively.[24] Gas chromatography mass spectro metry (GC MS) analysis of urine has been performed in a Canadian case study where after ingestion of 5 MeO DIPT, a man was observed in hospital for 2 h.[4] GC MS revealed the presence of 5 MeO DIPT and two additional compounds that were tentatively assigned to two urinary metabolites being 5 methoxy *N* isopropyltryptamine and 5 MeO DIPT 1 *N* oxide.[4]

The present work aimed to investigate the synthetic route of Speeter and Anthony to 5 MeO DIPT. A literature search has yielded no reference concerning the study of this synthetic route using electrospray ionisation tandem mass spectrometry (ESI MS MS). The use of liquid chromatography atmospheric pressure mass spectrometry (LC API MS) plays an important role in modern chemical analysis and is still developing.[25,26] Here flow injection analysis (FIA) *via* a HPLC pumping system combined with ESI MS MS, ESI TOF MS and NMR spectro scopy are used to identify several side products and to

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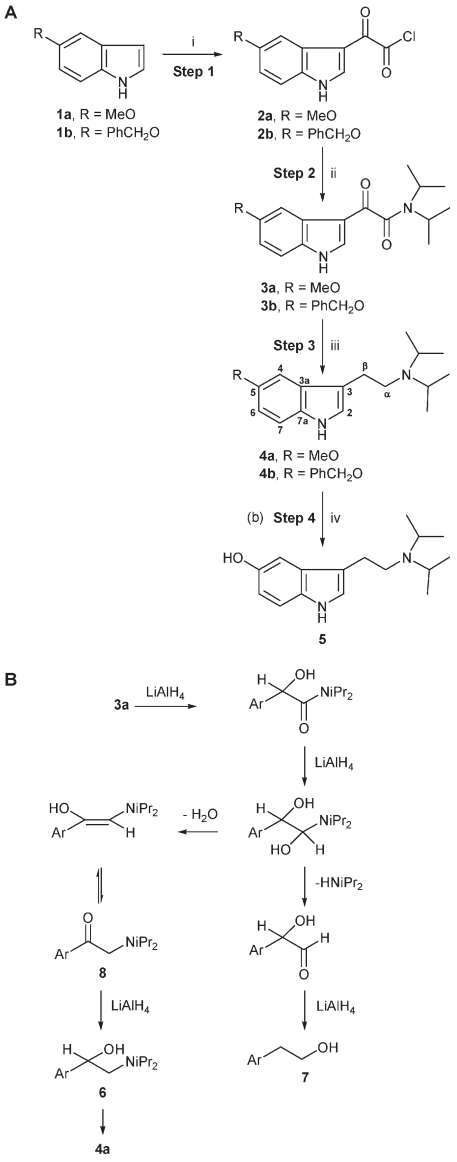

Scheme 1 1A Synthesis of 5 MeO DIPT and 5 HO DIPT *via* the synthetic route of Speeter and Anthony. i. oxalyl chloride; ii: diisopropylamine; iii: $LiAlH_4$; (b): iv: 10% Pd/C, H_2, rt. 1B A suggested route by which the observed impurities are formed during the reduction of glyoxalylamide **3a** during the synthetic route of Speeter and Anthony. Ar = 5 methoxyindole moiety.

characterise products and precursors. Such an approach will be of value to analysts in forensic laboratories, synthetic chemists developing new derivatives, clinicians and pathologists.

Experimental

Materials

Anhydrous ether (99.8%), 5 methoxyindole (99%), 5 benzylox yindole (95%), anhydrous THF (99.9%), diisopropylamine (99.5+%), $LiAlH_4$ (95%), 5 methoxytryptophol and Celite 545 were from Aldrich UK. Methanol (99.8%), CD_3OD (99.8%+), dichloromethane (99%), water (Chromanorm grade), acetoni trile (Chromanorm grade), isopropanol (Chromasolv), formic acid (98/100%), ethanol (Normapur grade), P_2O_5 (98%), silica gel (40 63 μm), and d_6 DMSO (Uvasol grade) were from VWR UK.

Instrumentation

Nuclear magnetic resonance (NMR) spectra were recorded using a Bruker DPX 400 MHz/100 MHz spectrometer (Coventry, UK), unless stated otherwise (Bruker DPX 300 MHz/75 MHz). The solvent used was d_6 DMSO and ^1H chemical shifts were calibrated on residual solvent at 2.51 ppm, unless stated otherwise. Melting points have been determined using a SMP3 melting point apparatus (Stuart Scientific, UK) and are uncorrected.

The LC ESI triple quadrupole MS MS (ESI TQ MS MS) system (Varian, USA) was controlled by the Varian MS Workstation version 6.30. A 1200 L triple quadrupole MS equipped with an ESI interface was used. The LC system provided the solvent system using two ProStar 210 solvent delivery modules. The solvent system consisted of (A) 0.1% v/v aqueous formic acid and (B) acetonitrile and was run isocra tically at 50% A and B. The flow rate was set to 20 μl min ^{1}. FIA was carried out with 10 μg ml ^{1} solution dissolved in the mobile phase. MS parameters: Drying and nebulizing gas was nitrogen at 20 psi and 350 °C, and 41 psi, respectively. The collision gas was argon and collision induced dissociation (CID) took place at 1.2 mTorr at 42 °C. The needle was held at 5000 V, shield at 600 V and the capillary voltage was 35 V. In source CID experiments were performed with a capillary voltage of 100 V unless stated otherwise. For tandem MS experiments quadrupole 1 (Q_1) was set for the appropriate protonated molecular ion $[M + H]^+$ and the collision energy of collision cell q_2 (rf only) was set to 0 eV. Fragmentation was induced by applying a potential, *i.e.* raising the collision energy until a satisfactory mass spectrum had been obtained. The individual collision energies varied between compounds and are shown in Table 1. The scan time was 1 s in positive mode (centroid) and the detector multiplier voltage was set to 1275 V.

A Micromass LCT orthogonal acceleration time of flight (TOF) mass spectrometer (Micromass, UK) equipped with an electrospray ionisation source, operating in positive mode, has been set up for open access use. Samples were presented as a batch to the LCT, using a flow injection method, *via* a Waters 2790 separation module autosampler. The instrument was tuned and calibrated in the mass range 100 to 1000 Da using 10 nl ml ^{1} PEG 300 + 10 nl ml ^{1} PEG 600 in 50 : 50 acetonitrile : water containing 2 mM ammonium acetate and 0.1% v/v formic acid. Exact mass measurements were carried out after instrument calibration using either caffeine (3 μg ml ^{1}) or leucine enkephaline (4 μg ml ^{1}) as lock mass standards. All electrospray data were obtained at sample concentrations of 5 μg ml ^{1}.

Procedures

Synthesis (Scheme 1A). The identity of the synthesised compounds was confirmed by exact mass measurements (see Table 2) and ^1H NMR. ^{13}C assignments were based on proton decoupled ^{13}C, distortionless enhancement polarisation transfer (DEPT 135) (pulse angle 135°) and ^1H ^{13}C COSY

Table 1 Collision energies used in positive mode to induce dissocia tion of the protonated molecular ion $[M + H]^+$

Compound	CE/−eV[a]	Figure[b]
1a	25	T[d]
1b	15	T[d]
2a[c]	30	T[d]
2b[c]	10	T[d]
3a	10	1B
3b	10	T[d]
4a	10	2B
4b	15	T[d]
5	15	4B
6	20	5B
7	10	6B
8	17.5	5D

[a] Collision energy. [b] Mass spectrum. [c] Observed as hydrolysed acid derivative only (see text). [d] Text only.

Table 2 Exact mass measurements of compounds 1 8 as $[M + H]^+$ and some of their fragments using positive ESI TOF

Compound	$[M + H]^+$	Product ions[a]	Theoretical	Observed	Error/ ppm
1a	148		148.0762		[c]
1b	224		224.1075	224.1069	−3.0
2a	220[b]		220.0610	220.0617	3.2
2b	296[b]		296.0923	296.0993	−23.6[c]
3a	303		303.1709	303.1710	0.4
		261	261.1239	261.1245	2.2
		174	174.0555	174.0547	−4.6
3b	379		379.2022	379.2035	3.6
		250	250.0868	250.0903	−14.0[c]
4a	275		275.2123	275.2112	−4.1
		174	174.0919	174.0923	2.4
4b	351		351.2436	351.2425	−3.4
5	261		261.1967	261.1957	−3.6
		160	160.0762	160.0771	5.1
6	291		291.2073	291.2070	−0.9
		273	273.1967	273.1968	0.4
7	192		192.1025	192.1015	−4.9
		174	174.0919	174.0916	−1.7
8	289		289.1916	289.1915	−0.3

[a] Exact mass measurement only for fragments ions resulting from destabilization (see text). [b] Observed as hydrolysed acid derivative (see text). [c] Refer to text.

heteronuclear multiple quantum coherence (HMQC) spectra. The indole ^{1}H NMR and ^{13}C NMR chemical shifts are given in Tables 3 and 4. All other chemical shifts are provided here.

*Step 1: 5 Methoxyindole 3 yl glyoxalylchloride (**2a**) and 5 benzyloxyindole 3 yl glyoxalylchloride (**2b**).* The appropri ate indole (5.44 mmol, **1a**: 800 mg, **1b**: 1.21 g) was dissolved in 150 ml anhydrous ether and stirred on ice for 30 min. Oxalyl chloride (2.071 g, 16.32 mmol) was added dropwise, stirred for 30 min on ice and kept at 20 °C for 4 h. The orange α oxo acid chlorides **2a** and **2b** were filtered and washed three times with 50 ml cold anhydrous ether and dried *in vacuo* for 3 h at room temperature to give a yield of 1.19 g (5.00 mmol, 92%) for **2a** and 1.36 g (4.33 mmol, 80%) for **2b**. Both were used for the next step without further purification.

Data for **2a**: mp 129 131 °C (dec.), lit.: 118 119 °C,[27] 123 126 °C,[28] 126 127 °C,[29] 127 128,[30] 130 °C,[31,32] 132 134 °C.[33] ^{1}H NMR: 3.80 (3 H, OCH_3, s). ^{13}C NMR: 180.6 (CO β), 165.3 (CO α), 55.3 (OCH_3).

Data for **2b**: mp 143 145 °C (dec.), lit.: 143 147 °C,[34] 146 150 °C.[20] ^{1}H NMR: 7.49 (2 H Ph, br d, 7.0 Hz), 7.41 (2 H Ph, m), 7.33 (1 H Ph, br t, *J* 7.3 Hz), 5.15 (2 H, OCH_2, s). ^{13}C NMR: (75 MHz) 180.8 (CO β), 165.5 (CO α), 138.3 (C_q Ph), 128.7 (C Ph), 128.0 (C Ph), 127.9 (C Ph), 70.0 (OCH_2).

Step 2: 5 Methoxyindole 3 yl N,N *diisopropylglyoxalyl amide (**3a**) and 5 benzyloxyindole 3 yl* N,N *diisopropylgly oxalylamide (**3b**).* Diisopropylamine (1.22 g, 12.09 mmol) was added dropwise to an ice cold solution of **2a** (718 mg, 3.02 mmol) or **2b** (945 mg, 3.02 mmol) dissolved in 50 ml anhydrous THF. The mixture was stirred on ice for 4 h. The solvent was evaporated under reduced pressure to give a crude yellow solid that was purified by flash chromatography (DCM MeOH, 9:1). Evaporation under reduced pressure gave pale yellow crystals **3a** (744 mg, 2.46 mmol, 81%) and **3b** (836 mg, 2.21 mmol, 73%).

Data for **3a**: mp 233 235 °C, recrystallised from EtOAc, lit.: 225 °C.[35] ^{1}H NMR: 3.80 (3 H, OCH_3, s), 3.76 (1 H, N CH, sept, *J* 6.6 Hz), 3.59 (1 H, N CH, sept, *J* 6.8 Hz), 1.47 (6 H, CH_3, d, *J* 6.8 Hz), 1.10 (6 H, CH_3, d, *J* 6.4 Hz). ^{13}C NMR: 186.4 (CO β), 167.3 (CO α), 55.3 (OCH_3), 49.8 (N CH), 44.7 (N CH), 20.1 (CH_3), 20.0 (CH_3).

Data for **3b**: mp 202 204 °C, recrystallised from EtOH. ^{1}H NMR: 7.50 (2 H Ph, br d, *J* 7.6 Hz), 7.41 (2 H Ph, br t, *J* 7.3 Hz), 7.34 (1 H Ph, br t, *J* 7.3 Hz), 5.14 (2 H, OCH_2, s), 3.75 (1 H, N CH, sept, *J* 6.5 Hz), 3.62 (1 H, N CH, sept, *J* 6.8 Hz), 1.48 (6 H, CH_3, d, *J* 6.6 Hz), 1.12 (6 H, CH_3, d, *J* 6.5 Hz). ^{13}C NMR: 186.8 (CO β), 167.6 (CO α), 137.7 (C_q Ph), 128.7 (C Ph), 128.1 (C Ph), 128.0 (C Ph), 70.0 (OCH_2), 50.2 (N CH), 45.1 (N CH), 20.5 (CH_3), 20.4 (CH_3).

Step 3: 5 Methoxy N,N *diisopropyltryptamine (**4a**) and 5 benzyloxy* N,N *diisopropyltryptamine (**4b**).* A solution of the glyoxalylamide (1.5 mmol; **3a**: 455 mg; **3b**: 568 mg), in 40 ml anhydrous THF, was added dropwise to a stirred, ice cold slurry of lithium aluminium hydride (570 mg, 15 mmol) in 100 ml anhydrous THF under nitrogen. This reaction mixture was refluxed for 15 h and then cooled on ice. The excess hydride was destroyed by the dropwise addition of 5 ml water, followed by 5 ml 20% NaOH and 5 ml of water. The precipitated inorganic salts were filtered and washed 3 times with 30 ml THF. The filtrate was evaporated under reduced pressure and the resulting oily residue was dissolved in 75 ml DCM and washed three times with water and once with saturated aq. NaCl. The organic phase was dried over anhydrous $MgSO_4$

Table 4 ^{13}C NMR chemical shifts (d_6 DMSO, unless otherwise stated) δ of the indolic carbons of the investigated compounds 2 6, 8 in ppm

Compound	C 2	C 3	C 3a	C 4	C 5	C 6	C 7	C 7a
2a	137.9	112.2	126.5	103.0	156.0	113.3	113.5	131.4
2b[a]	138.1	112.5	126.8	105.0	155.4	114.1	113.8	131.8
3a	135.9	112.8	125.8	102.6	155.8	113.3	113.5	131.6
3b	136.5	113.1	126.1	104.5	155.2	114.2	113.9	132.2
4a[a]	123.3	113.0	127.8	100.4	153.1	111.1	112.3	131.5
4a[ab]	124.1	109.4	127.0	100.0	153.2	111.2	112.3	131.3
4b[c]	124.3	114.6	129.4	103.8	154.3	113.4	113.7	134.0
5[ac]	124.4	113.4	129.7	103.9	151.5	112.7	113.1	133.5
6	123.4	117.3	126.7	101.6	153.0	111.2	112.4	132.0
8	136.6	112.1	126.5	103.3	156.3	113.4	113.8	131.8

[a] 75 MHz. [b] Hydrochloride salt. [c] In CD_3OD relative to TMS.

Table 3 ^{1}H NMR chemical shifts (d_6 DMSO, unless otherwise stated) δ of the indolic protons of the investigated compounds 2 6, 8 in ppm

Compound	NH 1, m[a]	H 2, m, *J*[b]	H 4, m, *J*	H 6, m, *J*	H 7, m, *J*
2a	12.28, br s	8.33, d, 3.4	7.67, d, 2.6	6.91, dd, 8.9, 2.5	7.44, d, 9.0
2b	12.32, br s	8.35, d, 3.0	7.77, d, 2.5	7.00, dd, 8.5, 2.5	7.46, d, 8.5
3a	12.09, br s	7.91, s	7.59, d, 2.3	6.90, dd, 8.7, 2.6	7.45, d, 9.0
3b	12.11, br s	7.92, s	7.70, br s	6.99, dd, 8.8, 2.3	7.46, d, 9.0
4a[c]	10.62, br s	7.09, s	6.92, d, 2.3	6.71, dd, 8.7, 2.3	7.22, d, 8.7
4a[cd]	9.92, br s	7.28, m	7.03, d, 1.9	6.75, dd, 8.7, 2.3	7.28, m
4b[de]		7.01, m	7.01, m	6.84, dd, 8.6, 2.3	7.22, d, 9.1
5[e]		6.89, s	6.80, d, 2.3	6.56, dd, 8.7, 2.3	7.05, d, 8.7
6	10.72, br s	7.20, d, 2.0	7.11, d, 2.5	6.72, dd, 8.5, 2.5	7.24, d, 9.0
8[c]	n/o[f]	8.51, s	7.63, d, 2.3	6.91, dd, 9.0, 2.3	7.45, d, 9.0

[a] Multiplicity. [b] Coupling constant in Hz. [c] 300 MHz. [d] Hydrochloride salt. [e] In CD_3OD relative to TMS. [f] Not observed.

and evaporated under reduced pressure. The resulting colour less transparent oils were dried overnight under vacuum over P_2O_5 to yield 359 mg of a beige solid base **4a** (1.31 mmol, 87%) and 431 mg of a light brown solid base **4b** (1.23 mmol, 82%).

Data for **4a**: mp HCl salt: 182 184 °C, recrystallised from isopropanol, lit.: 180 181 °C,[1,35] 181 182 °C.[2] ^{1}H NMR (300 MHz) base: 3.74 (3 H, OCH_3, s), 3.04 (2 H, N CH, sept, *J* 6.4 Hz), 2.69 (2 H, CH_2 β, m), 2.60 (2 H, CH_2 α, m), 1.00 (12 H, CH_3, d, *J* 6.4 Hz). ^{1}H NMR (300 MHz) hydrochloride salt: 10.90 (N+H, s), 3.76 (3 H, OCH_3, s), 3.69 (2 H, N CH, sept, *J* 6.8 Hz), 3.25 (2 H, CH_2 α, m), 3.10 (2 H, CH_2 β, m), 1.40 (6 H, CH_3, d, *J* 6.8 Hz), 1.35 (6 H, CH_3, d, *J* 6.4 Hz). ^{13}C NMR: (75 MHz) base: 55.6 (OCH_3), 48.6 (N CH), 46.3 (CH_2 α), 27.9 (CH_2 β), 20.9 (CH_3). ^{13}C NMR: (75 MHz) hydro chloride salt: 55.4 (OCH_3), 53.7 (N CH), 47.0 (CH_2 α), 22.7 (CH_2 β) 18.0 (CH_3), 16.8 (CH_3).

Data for **4b**: mp HCl salt: 217 218 °C, recrystallised from isopropanol. ^{1}H NMR (300 MHz, CD_3OD, relative to TMS) base: 7.43 (2 H Ph, br d, *J* 7.5 Hz), 7.35 (2 H Ph, br t, *J* 7.2 Hz), 7.28 (1 H Ph, br t, *J* 7.1 Hz), 5.09 (2 H, OCH_2, s), 3.11 (2 H, N CH, sept, *J* 6.5 Hz), 2.77 (2 H, CH_2 β, m), 2.66 (2 H, CH_2 α, m), 1.10 (12 H, CH_3, d, *J* 6.4 Hz). ^{13}C NMR (75 MHz, CD_3OD, relative to TMS) base: 139.9 (C_q Ph), 129.9 (C Ph), 129.1 (C Ph), 128.9 (C Ph), 72.5 (OCH_2), 51.4 (N CH), 49.0 (CH_2 α), 29.3 (CH_2 β), 21.0 (CH_3).

Step 4: 5 Hydroxy N,N *diisopropyltryptamine (**5**).* Com pound **4b** (395 mg, 1.13 mmol) was dissolved in 20 ml abs. ethanol. Pd/C (5 mg, 10%) was added and stirred at room temperature for 24 h under an atmosphere of hydrogen. The reaction mixture was filtered over a pad of Celite. The filtrate was evaporated under reduced pressure and dried *in vacuo* over P_2O_5 for 15 h. A greenish brown oil **5** was obtained that turned black (288 mg, 1.10 mmol, 97%).

Data for **5**: ^{1}H NMR (300 MHz, CD_3OD, relative to TMS): 3.09 (2 H, N CH, sept, *J* 6.5 Hz), 2.70 (2 H, CH_2 β, m), 2.68 (2 H, CH_2 α, m), 1.05 (12 H, CH_3, d, *J* 6.8 Hz), 8.60 (5 OH, s, in d_6 DMSO, ex D_2O). ^{13}C NMR (75 MHz, CD_3OD, relative to TMS): 52.2 (N CH), 49.2 (CH_2 α), 28.8 (CH_2 β), 20.6 (CH_3).

Synthesis of 2 N,N *diisopropylamino 1 (5 methoxy 1*H *indol 3 yl) ethanol (**6**).* The synthesis of this compound, representing an incompletely reduced amide, was synthesised as described above for step 3 using 1.6 g (5.29 mmol) **3a** and 2.0 g (52.7 mmol) $LiAlH_4$. The main difference was that the reduction step took place at room temperature for only 20 min. Quenching and workup was as described above. Isolation was by flash chromatography using a solvent system of MeOH:$CHCl_3$:NH_4OH (9:1:0.1). A pale yellow oil was obtained which was dried under vacuum and over P_2O_5 to give 365 mg beige solid **6** (1.26 mmol, 24%). Even after this short reaction time no glyoxalylamide could be detected.

Data for **6**: mp 97 99 °C. ^{1}H NMR: 4.74 (1 H, CH β, dd, *J* 8.0, 5.5 Hz), 4.36 (OH, br s, ex D_2O), 3.75 (3 H, OCH_3, s), 3.10 (2 H, N CH, sept, *J* 6.5 Hz), 2.71 (1 H, CH α, dd, 13.5, 5.5 Hz), 2.69 (CH α, dd, 13.5, 8.0 Hz), 1.06 (6 H, CH_3, d, *J* 6.5 Hz), 0.95 (6 H, CH_3, d, *J* 6.5 Hz). ^{13}C NMR: 65.3 (CH β), 55.5 (OCH_3), 51.8 (CH_2 α), 47.9 (N CH), 22.3 (CH_3), 20.2 (CH_3).

2 N,N *Diisopropylamino 1 (5 methoxy 1*H *indol 3 yl) etha none (**8**).* 5 MeO DIPT (898 mg, 3.27 mmol) free base (**4a**) was dissolved in 150 ml anhydrous ether. Dry gaseous HCl was passed through the solution. After filtration 875 mg of pink hydrochloride salt was obtained that was washed three times with 50 ml anhydrous ether and dried *in vacuo* for 3 h. Recrystallisation with isopropanol yielded colourless 5 MeO DIPT HCl crystals (mp, see above as described for **3a**). The filtrate was evaporated under reduced pressure and dried *in vacuo* over P_2O_5 overnight leaving 40 mg of a brown gum which was characterised as (**8**).

Data for **8**: ^{1}H NMR (300 MHz): 4.69 (2 H, CH_2, s), 3.77 (3 H, OCH_3, s), 3.67 (2 H, N CH, sept, 6.0 Hz), 1.28 (6 H, CH_3, d, *J* 6.4 Hz), 1.20 (6 H, CH_3, d, *J* 6.0 Hz). ^{13}C NMR: 186.2 (CO β), 56.3 (OCH_3), 55.6 (N CH), 52.8 (CH_2 α), 18.2 (CH_3), 16.6 (CH_3).

Results and discussion

The psychoactive 5 MeO DIPT (**4a**) and 5 HO DIPT (**5**) that represents one impurity, were synthesised by the route of Speeter and Anthony (Scheme 1A). The starting materials, intermediates, products and common impurities were subjected to ESI TQ MS MS and NMR spectroscopy in order to charac terise this synthetic route. The magnitude of side product formation under the experimental conditions used are esti mated to represent approximately 0.5 1.5% per impurity based on the free base product **4a**. Further work will provide detailed quantitative estimates of the abundance of the above impurities **5**, **6**, **7** and **8** in the free base product. A suggested route by which the product and impurities **6** **8** are formed from the reduction of the glyoxalylamide (**3a**) is given in Scheme 1B. The ketone is more reactive than the amide towards initial reduction. Reduction of a ketone typically gives an alcohol, whereas here complete reduction is observed. This is attributed to the unsubstituted indole nitrogen facilitating elimination of the β hydroxy group, with subsequent reduction to give the desired product (**4a**) and the impurity (**7**). Fragmentation patterns observed (*e.g.* loss of CH_3, CH_3O, and CO) were consistent with those reviewed by Smyth and coworkers on other drug classes.[36,37]

ESI-TQ-MS-MS characterisation

ESI MS MS allows a mixture of dissimilar protonated mole cular ions arising from pure and/or crude reaction mixtures to be studied without chromatographic separation. In the latter case, the molecular ion of interest can be selected in quadrupole Q_1 and its product ions are scanned in Q_3 after dissociation in the collision cell q_2. The collision energies used to induce collision induced dissociation CID are listed in Table 1. Examination of electrospray mass spectral data generated following product ion scanning experiments show compound specific ion transitions. Using a TOF instrument allows the empirical formula for many species to be assigned unambiguously based on exact mass measurement data. The poor resolving power of ESI TQ MS MS instrumentation, compared to TOF instrumentation, precludes its use for exact measurement of species generated under $Q_1q_2Q_3$ study. Although ESI is a soft ionization technique, strong binding between a proton and certain target molecules results in charge transfer to the molecule. Certain TOF spectra have yielded diagnostically useful fragment ions resulting from destabiliza tion of the molecule *via* charge transfer (Table 2). All com pounds (Scheme 1A and 1B) produce protonated molecular ions, $[M + H]^+$.

Analysis of synthetic step 1: Indole-3-yl-glyoxalylchlorides. The first step of this synthetic route is the acylation of **1a** with oxalyl chloride to give the α oxo acid chloride **2a** (Scheme 1A). The spectrum of 5 methoxyindole shows the protonated molecular ion $[M + H]^+$ at *m*/*z* 148. CID experiments give rise to a base peak of *m*/*z* 133 probably by expulsion of a methyl group. It is proposed that this $[MH\ CH_3]^+$ undergoes a further loss of CO to *m*/*z* 105. Interestingly, fragmentation of 5 methoxyindole **1a** also produces an *m*/*z* 121 ion that can be rationalised by the loss of HCN. The 5 methoxyindole

spectrum also yields a species at *m/z* 117 which has been assigned as $[M\ OCH_3]^+$. Exact mass measurement of com pound 5 methoxyindole, **1a**, has not been reported as the PEG calibration used had a limited number of data points in this region (refer to Table 2).

In spite of the relative stability of the acid chloride **2a** on storage, its direct detection especially using MS is impossible due to its reactivity in the electrospray interface. Compound **2a** undergoes hydrolysis into the corresponding α oxo acetic acid derivative yielding a $[M + H]^+$ at 220 Da. This $[M + H]^+$ has been confirmed by exact mass measurement, Table 2. In order to obtain a stable signal for further CID experiments com pound **2a** was dissolved in acetonitrile only, rather than in the water containing solvent system. The mass spectrum shows a fragmentation pattern of *m/z* 174, *m/z* 159, *m/z* 146 and *m/z* 131. It is believed that this pattern may be a typical representa tion of $[methoxyindole\ CO]^+$ derivatives.

The 5 benzyloxyindole **1b** used for the synthesis of **5** produces a $[M + H]^+$ at *m/z* 224. This ion subsequently fragments to yield discernible ions at *m/z* 196 and *m/z* 146 (loss of phenyl). The acid chloride **2b** shows similar behaviour compared with **2a** and is found to be hydrolysed to the corresponding acid. $[M + H]^+$ is at *m/z* 296 which fragments mainly into the $[5\ benzyloxy\ indole\ CO]^+$ counterpart of **2a** represented by the species at *m/z* 250. Exact mass measurement of the *m/z* 296 species gave an unacceptably large mass error of 23 ppm (Table 2). This large mass error has been attributed to the difficulty encountered in mass measuring this unstable species. Apart from the chemical reactivity of the acid chlorides, thermal instability is also observed. As expected, an attempt to obtain suitable GC MS data failed due to decomposition in the hot injector (data not shown), whereas other researchers did obtain EI MS data for compound **2a**.[28,30]

Analysis of synthetic step 2: Indole-3-yl-*N*,*N*-diisopropyl-glyoxalylamides. Reaction of the *N*,*N* diisopropylamine with

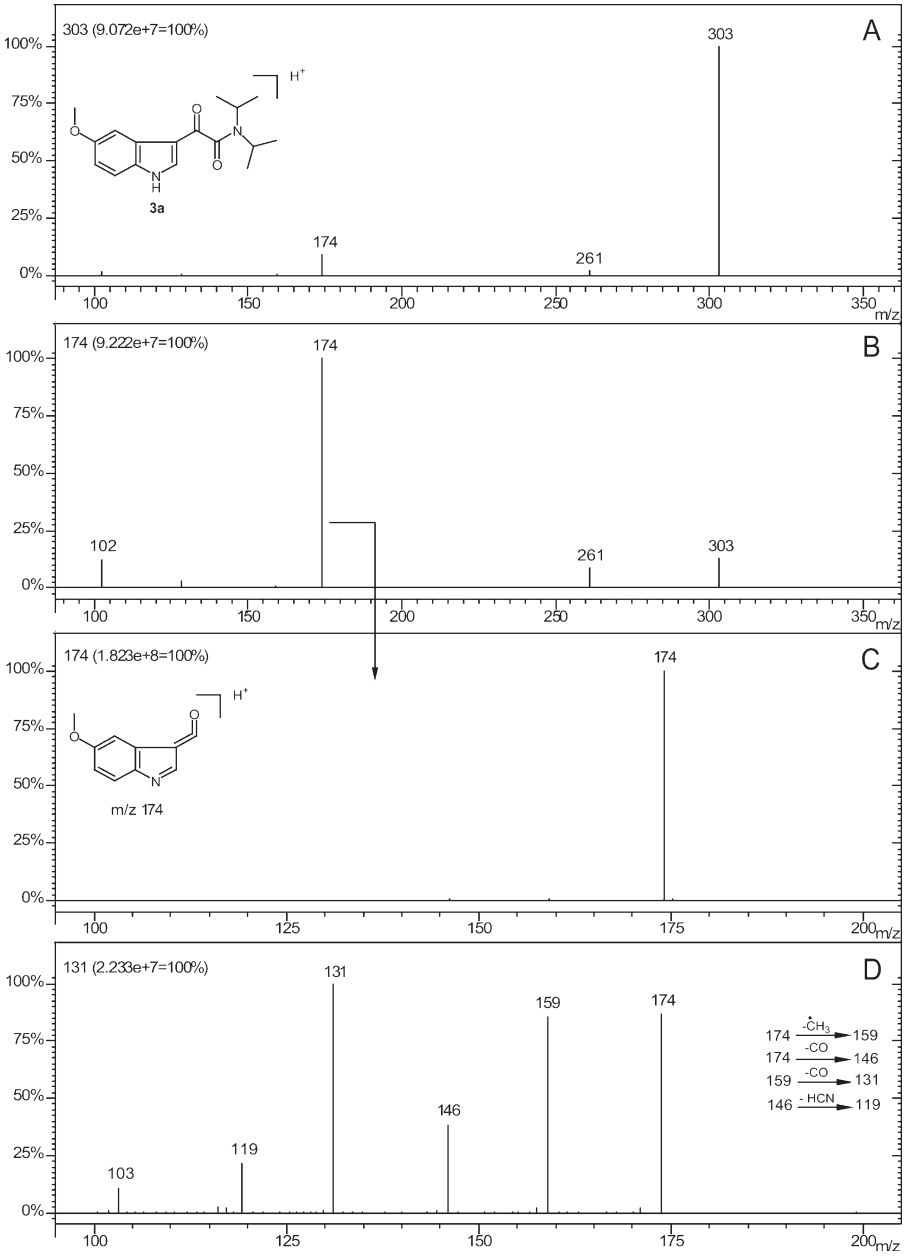

Fig. 1 ESI TQ MS MS spectra and proposed fragmentation pathway for compound **3a** using flow injection analysis. A: $[M + H]^+$. B: MS MS fragmentation of **3a**; collision energy: −10 eV. C: The major fragment at *m/z* 174 is mass selected in Q1 *via* in source CID (capillary voltage: 100 V instead of 35 V). D: Product ions are scanned with Q3 after dissociation of *m/z* 174 with a collision energy of −25 eV, thus mimicking MS^3 measurements. The exact mass of *m/z* 174 has been determined as shown in Table 2.

glyoxalylchlorides **2a** and **2b** lead to the amides **3a** and **3b**. ESI MS MS data for **3a** are shown in Fig. 1. The $[M + H]^+$ at *m/z* 303 dominates the spectrum as expected, however just filling the collision cell with the CID gas at 0 V applied, induces a certain degree of fragmentation (Fig. 1A). Increased collision energy enhances the formation of these fragments (Fig. 1B), namely *m/z* 261, *m/z* 174 and *m/z* 102. The ease of fragmenta tion allowed exact mass analysis with the TOF MS as shown in Table 2. The ion at *m/z* 261, having a mass difference of 42 Da, represents the expulsion of propene from one of the mono isopropyl groups of the parent molecule. Fig. 3A gives an overview of the proposed fragmentation pathway of compound **3a**. The base peak ion in this spectrum has a mass of 174 Da and the exact mass was determined (Table 2) using TOF MS. It is formed by two fragmentations: a) *via* the cleavage of neutral *N*,*N* diisopropyl formamide from $[M + H]^+$ and b) *via* the cleavage of neutral *N* isopropyl formamide derived from the monoisopropyl glyoxalylamide at *m/z* 261. Based on these fragmentations and the exact masses of *m/z* 261 and 174, the structure of *m/z* 174 was assigned to protonated (5 methoxy indole 3 ylidene) methanone, $[5\ MeO\ indole\ CO]^+$ (Fig. 3A). As shown below the ESI MS MS of the final tryptamine 5 MeO DIPT produces an ion at *m/z* 174 as well. Figs. 1D and 2D show an example of the application of in source CID in order to gain additional structural information about the fate of the species *m/z* 174. These experiments were performed by increasing the capillary voltage to 100 V. This procedure applied to both *m/z* 174 ions from **3a** and **4a** experiments, leads to dissociation of these species before entering into the first quadrupole. Q_1 is set to scan for *m/z* 174 which is then subjected to CID in q_2. This approach enables the performance of MS^3 studies. The *m/z* 174 ion derived from the amide **3a** dissociates into fragments at *m/z* 159, *m/z* 146, *m/z* 131, *m/z* 119 and *m/z* 103. As illustrated in Fig. 3A, two fragmentation

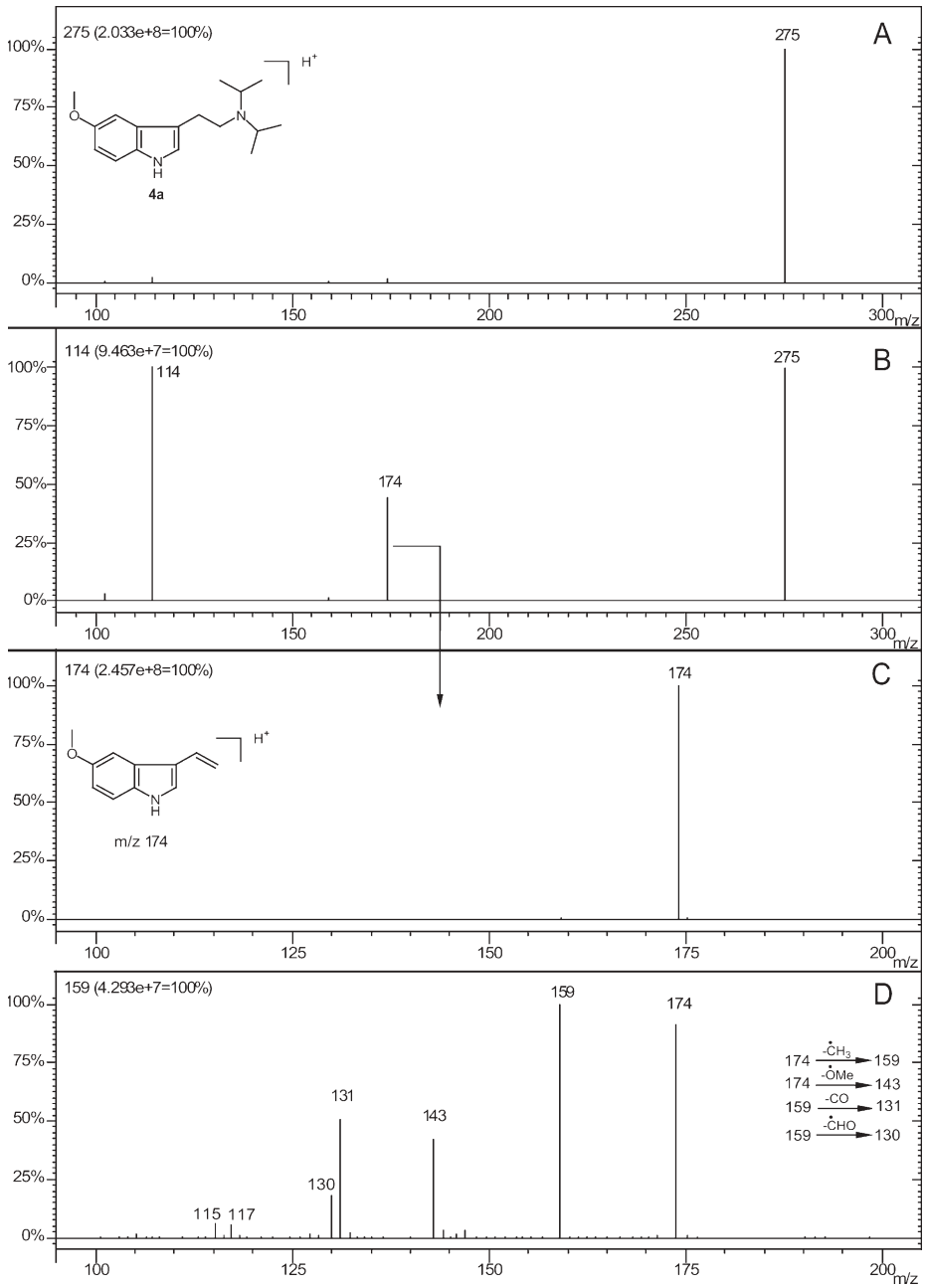

Fig. 2 ESI TQ MS MS spectra and proposed fragmentation pathway for compound **4a** using flow injection analysis. A: $[M + H]^+$. B: MS MS fragmentation of **4a**; collision energy: −10 eV. C: The major fragment at *m/z* 174 is mass selected in Q1 *via* in source CID (capillary voltage: 100 V instead of 35 V). D: Product ions are scanned with Q3 after dissociation of *m/z* 174 with a collision energy of −20 eV, thus mimicking MS^3 measurements. The exact mass of *m/z* 174 has been determined as shown in Table 2.

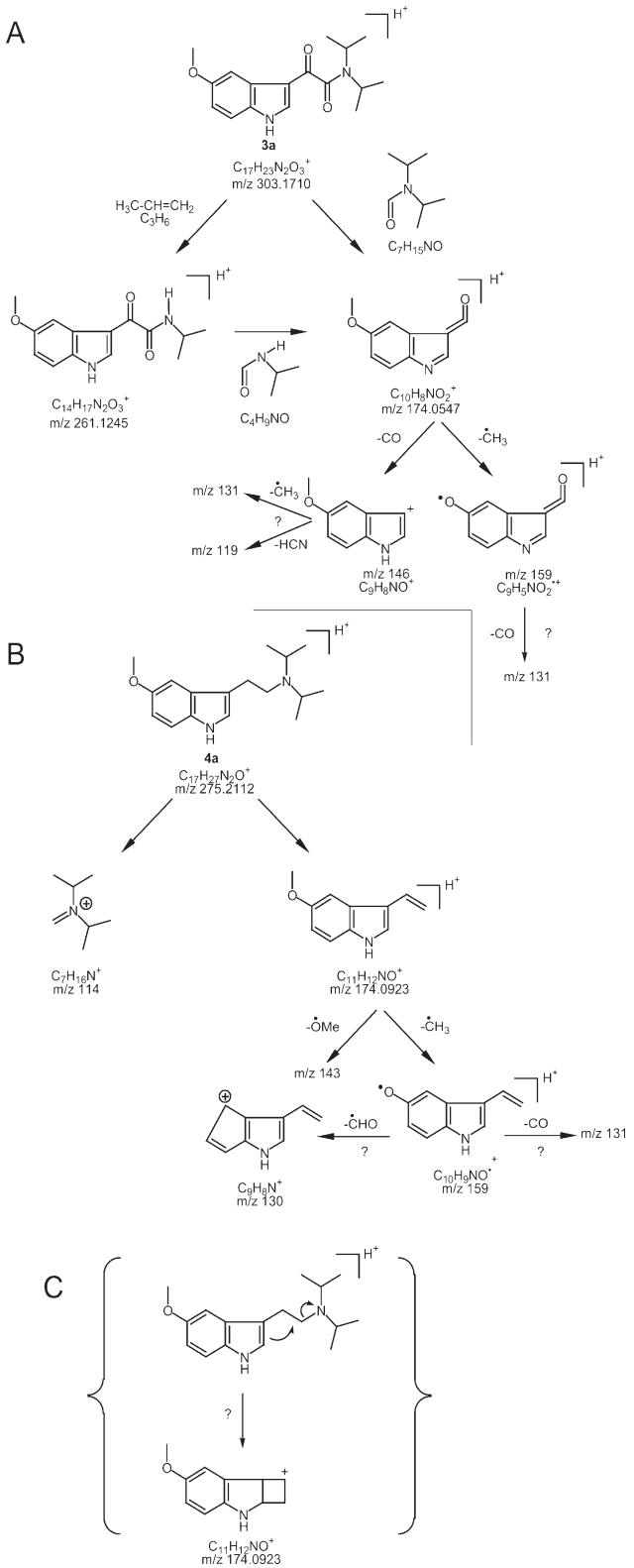

Fig. 3 Summary of the proposed fragmentation pathways for compounds **3a** and **4a** using ESI TQ MS MS. Both compounds dissociate into a fragment at *m/z* 174 that can be distinguished by its exact mass and by two different fragmentation pathways following in source CID (see text). A: Fragmentation of the glyoxalylamide and the acquired exact masses of the protonated molecular ion, *m/z* 261 and *m/z* 174. B: Fragmentation of the tryptamine derivative and the acquired exact masses of $[M + H]^+$ and *m/z* 174. Theoretical and observed masses are shown in Table 2. C: Formation of *m/z* 174 after cyclisation has also been suggested for the dissociation of melatonin (see text).

pathways are conceivable: 1) It is proposed that *m/z* 159 is derived from the loss of a methyl group. The formation of ion *m/z* 131 can be rationalized through a loss of one CO from *m/z* 159 ion. A second loss of CO gives rise to *m/z* 103 *via* a five membered ring contraction. 2) The species at *m/z* 146 may also be attributed to the cleavage of CO from *m/z* 174 ion, yielding the 5 methoxyindole carbocation. This species may lose a methyl group and subsequently generate an ion at *m/z* 131. The *m/z* 131 in turn undergoes loss of CO to yield *m/z* 103. Addi tionally, *m/z* 119 ion can be rationalised by the loss of HCN from the species at *m/z* 146.

The proposed benzyloxy fragmentation pathway **3b** appears to behave in a similar manner to its counterpart **3a**. $[M + H]^+$ is at *m/z* 379 and its exact mass measurement is shown in Table 2. The *m/z* 379 ion appears to be more stable than its 5 methoxy counterpart since little fragmentation is observed. A similar fragmentation pathway is proposed, leading to the mono isopropyl derivative at *m/z* 337 and the [5 benzyloxyindole $CO]^+$ derivative at *m/z* 250. Fragment ions at *m/z* 128 and *m/z* 102 are also observed. The higher stability of the protonated molecular ion, *m/z* 379, has limited the use of TOF MS to assign an exact mass to the *m/z* 250 species. Attempts to mass measure this ion, *m/z* 250, yielded a low signal intensity pro ducing an unsatisfactory experimental error of 14.0 ppm (see Table 2). The dissociation of the *m/z* 250 ion yields a fragment at *m/z* 159. It is proposed that this species be identical to the ion *m/z* 159 that was formed during the fragmentation of **3a**. This *m/z* 159 species, derived from *m/z* 250, is presumably formed *via* a loss of C_7H_7 (*m/z* 91). Subsequent loss of CO, from the *m/z* 159 ion, yields *m/z* 131. The fragmentation of *m/z* 250 however, shows several differences when compared to the fragmentation pathway of **3a**. No equivalent ions at *m/z* 146, *m/z* 119 and *m/z* 103 are observed. For instance, the loss of CO from the [5 methoxyindole $CO]^+$ of **3a** yields the corresponding *m/z* 146 ion. A similar loss for the [5 benzyloxyindole $CO]^+$ fragment would be expected to produce a 5 benzyloxyindole carbocation at *m/z* 222 which is not observed. Furthermore, the species at *m/z* 232, *m/z* 204 and *m/z* 194 are observed in this mass spectrum. ESI MS spectra of glyoxalylamides show that adduct formation can be expected to arise because of the two carbonyl functions. The ESI TQ MS spectrum of com pound **3a** yields the sodiated adduct at *m/z* 325, [M + acetonitrile + $Na]^+$ (*m/z* 366) and a dimeric $[2M + Na]^+$ at *m/z* 627 (data not shown). The intensities varied between 30% and 60% in relation to the $[M + H]^+$. TOF MS spectra present similar adducts and two additional ions at *m/z* 605 and *m/z* 929, which have been attributed to $[2M + H]^+$ and $[3M+Na]^+$, respectively.

Analysis of synthetic step 3: *N*,*N*-diisopropyltryptamines. The reduction of glyoxalylamides **3a** and **3b** with $LiAlH_4$ leads to the required tryptamine compounds **4a** and **4b**. Fig. 2 shows the ESI TQ MS MS spectra of 5 MeO DIPT. As expected for a tertiary amine the base peak is represented by the formation of $[CH_2{=}NiPr_2]^+$ at *m/z* 114. Fig. 2B also shows a second fragment at *m/z* 174 that is formed after a cleavage of neutral diisopropylamine to $[M + H\ NHiPr_2]^+$. A common cleavage process involving a hydrogen rearrangement is proposed to account for the formation of the [5 methoxy 3 vinyl indole]$^+$ at *m/z* 174. TOF MS data support this proposal Table 2. This proposed fragmentation pathway is shown in Fig. 3B. As shown above both compounds, 5 MeO DIPT **4a** and its precursor **3a**, produce a fragment at *m/z* 174. Using the same in source CID approach both *m/z* 174 ions yield unique fragmentation behaviour. The *m/z* 174 ion that derives from 5 MeO DIPT (**4a**) dissociates into fragments at *m/z* 159, *m/z* 143, *m/z* 131 and *m/z* 130. Two additional ions at *m/z* 115 and *m/z* 117 are also observed. As suggested in Fig. 3B, losses of a

methyl radical and CO appear to be consistent with the proposed fragmentation pathway: thus rationalising the ions at *m/z* 159 and *m/z* 131. One of the differences in fragmentation behaviour is the presence of *m/z* 143 compared to *m/z* 146 (Figs. 3A and 3B). The vinyl indole fragment *m/z* 174 may loose its methoxyl group to give *m/z* 143. Under the conditions used the mass spectrum displays a *m/z* 131:*m/z* 130 ratio of ~2:1 (Fig. 2D). Interestingly, increasing the collision energy to 45 eV reverses the ratio to ~1:2. A more facile cleavage of CO (from the fragment *m/z* 159) in a lower collision energy environment compared with the cleavage of CHO (*m/z* 29) that produces the ion at *m/z* 130 is proposed. An increase in collision energy is also found to give rise to a more intense signal at *m/z* 103, indicating a loss of HCN from *m/z* 130 which is not seen under lower energy conditions.

As expected, the benzyloxy derivative **4b** appears to show similar fragmentation dynamics including the appearance of a base peak at *m/z* 114. The existence of ions *m/z* 117, *m/z* 131 and *m/z* 159 are common to both spectra. Certain differences between these spectra are observed. In source fragmentation and tandem MS of [5 benzyloxy 3 vinylindole]$^+$ at *m/z* 250 produces a fragment at *m/z* 222. This indicates a cleavage of CH_2=CH_2 which is not observed during the dissociation of *m/z* 174 of **4a** (Fig. 3B). The ion transition *m/z* 250 → *m/z* 222 may represent an additional distinctive feature compared to its amide precursor **3b** where this transition is not observed. Neither tryptamine spectrum shows any adduct formation. It is thought that ESI MS of tryptamine derivatives usually involves α cleavage and a hydrogen rearrangment resulting in the vinylindole intermediate.[38] Interestingly, it should be noted that Xie and coworkers[39] proposed a cyclised structure (Fig. 3C), using APCI MS MS in the study of melatonin (5 methoxy N acetyltryptamine) in commercially available tablets. In this case α cleavage would not be followed by a

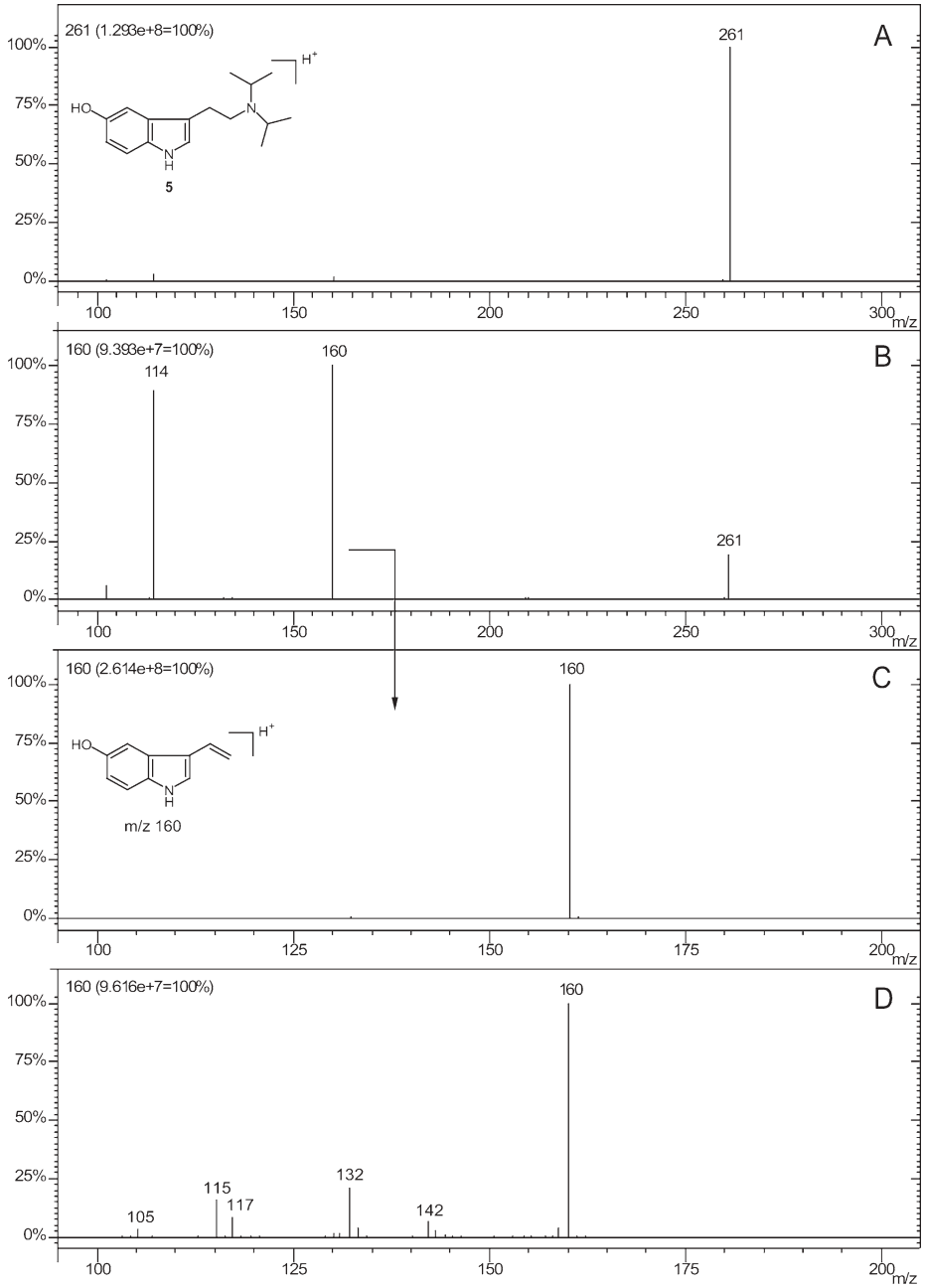

Fig. 4 ESI TQ MS MS spectra of compound **5** using flow injection analysis. A: $[M + H]^+$. B: MS MS fragmentation of **5**; collision energy: −15 eV. C: The major fragment at *m/z* 160 is mass selected in Q1 *via* in source CID (capillary voltage: 100 V instead of 35 V). D: Product ions are scanned with Q3 after dissociation of *m/z* 160 with a collision energy of −15 eV, thus mimicking MS^3 measurements. The exact masses of *m/z* 261 and *m/z* 160 have been determined as shown in Table 2.

hydrogen rearrangement and subsequently the pyrrole moiety would lose its aromatic character, followed by cyclisation.

Analysis of synthetic step 4: 5-hydroxy-*N*,*N*-diisopropyltryptamine (Impurity 5). Figs. 4A and 4B show the ESI TQ MS MS spectra of compound **5**. Its fragmentation pathway appears to be comparable with those of both tryptamines discussed above. Exact masses of the protonated molecular ion and the 5 hydroxyvinyl indole fragment at *m*/*z* 160 have been deter mined Table 2. Further fragmentation of *m*/*z* 160 produces a spectrum that consists of ions at *m*/*z* 132, *m*/*z* 117, *m*/*z* 115, *m*/*z* 142 and *m*/*z* 105 Fig. 4D. The loss of 28 Da may represent the cleavage of CO to give the ring contracted species at *m*/*z* 132 as suggested by McClean and coworkers.[38] Further loss of HCN may result in the formation of ion *m*/*z* 105. As described above however, 5 benzyloxyvinylindole generates an ion at *m*/*z* 222 that can be rationalised as a loss of ethene. If this occurred with *m*/*z* 160, the fragment at *m*/*z* 132 would be assigned as a 5 hydroxyindole carbocation. This carbocation undergoes a further consecutive loss of CO. Distinction between these two pathways is not possible without exact measurement data. It is proposed that the weak signal at *m*/*z* 142 results from the cleavage of the hydroxyl group as water, although that is somewhat speculative. In contrast, a facile loss of water is observed for aliphatic OH groups as shown for compound **6** below.

5-MeO-β-hydroxy-DIPT (Impurity 6). Compound **6** pro duces a protonated molecular ion at *m*/*z* 291 that shows a minor fragment, *m*/*z* 273, without applying any collision energy (Fig. 5A). As expected for an aliphatic hydroxyl group, its facile cleavage as water is seen to take place and manifested in the ion at *m*/*z* 273 Fig. 5B. This instance enables the use of TOF MS and its exact mass has been determined for $[M + H]^+$ and $[M + H\ H_2O]^+$ (Table 2). Further fragments are observed at *m*/*z* 231, *m*/*z* 189, *m*/*z* 188, *m*/*z* 174 and *m*/*z* 162.

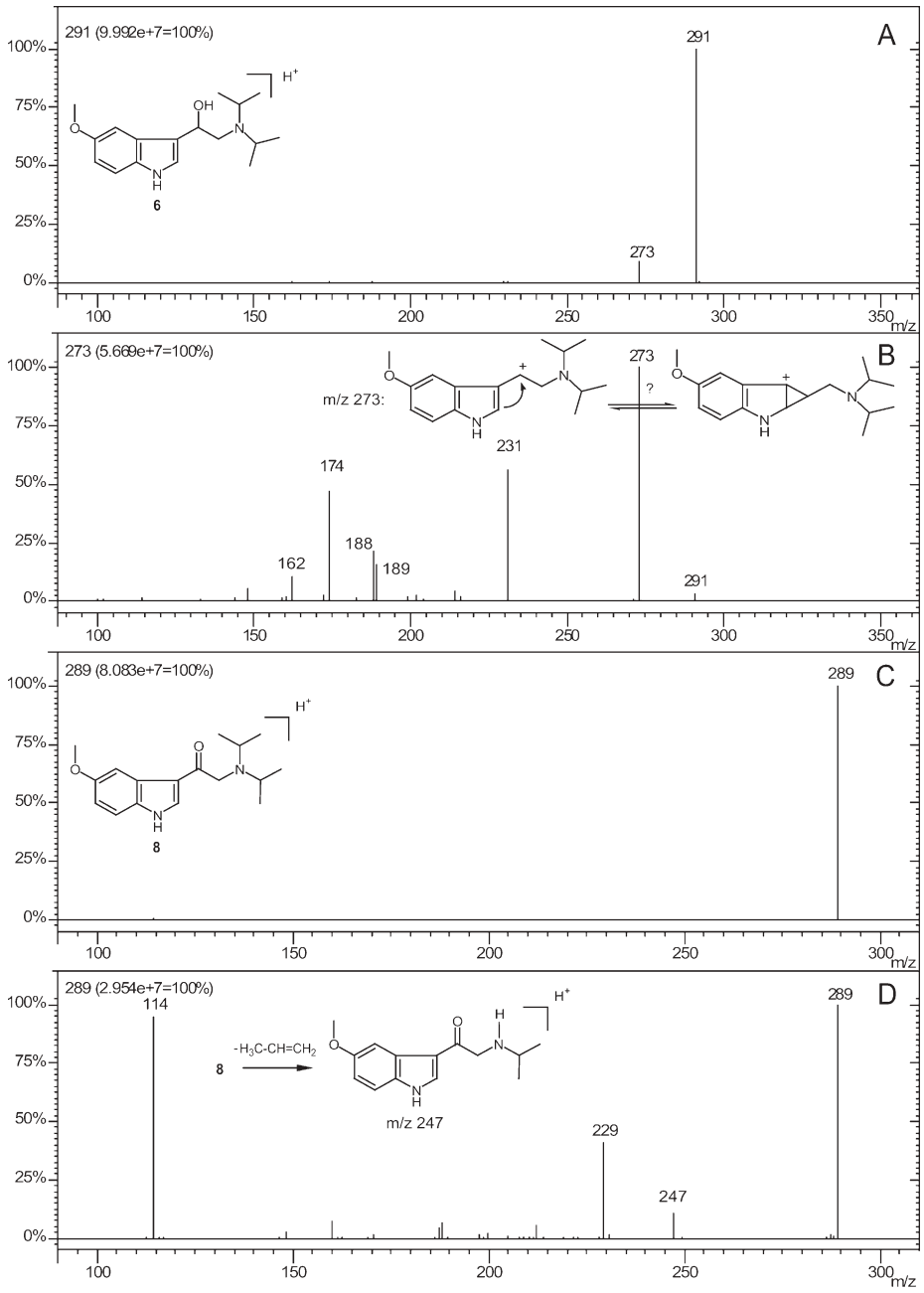

Fig. 5 ESI TQ MS MS spectra and some proposed fragmentations for compounds **6** and **8** using flow injection analysis. A: [M + H]+ of compound **6**. B: MS MS fragmentation of **6**; collision energy: −20 eV. In case of fragment *m*/*z* 273: Two structural arrangements are conceivable. C: $[M + H]^+$ of compound **8**. D: MS MS fragmentation of **8**; collision energy: −17.5 eV. Both exact masses are shown in Table 2.

5-Methoxytryptophol (Impurity 7). The fragmentation path way of compound **7**, as shown above for the tryptamine 5 MeO DIPT (**4a**), is also characterised by the formation of the vinylindole derivative at *m*/*z* 174 resulting from loss of water (exact masses: Table 2) and subsequent loss of a methyl radical to form fragment *m*/*z* 159 (Fig. 6A, 6B). Compound **7** was not isolated, however its presence in the free base product **4a** was confirmed by LC MS MS in comparison with an authentic standard.

5-MeO-β-keto-DIPT (Impurity 8). Fig. 5C and 5D show the ESI TQ MS MS of compound **8** that was isolated from the mother liquor after recrystallisation of 5 MeO DIPT HCl (**4a**). Its exact mass (Table 2) confirms the presence of 5 MeO β keto DIPT. The $[M + H]^+$ occurs at *m*/*z* 289. Further fragmentation produces a base peak of *m*/*z* 114 and two major fragments at *m*/*z* 247 (monoisopropyl derivative) and *m*/*z* 229 (Fig. 5D). The presence of the fragment at *m*/*z* 114, corresponding to $[CH_2{=}NiPr_2]^+$, indicates that the keto func tion may reside on the β carbon. This is supported by NMR data as explained below.

Implications of the NMR data

As far as the ^1H NMR chemical shifts of the indolic protons are concerned, all compounds that possess the 1,2 di carbonyl function, namely the keto acid chlorides (**2a**, **2b**) and their corresponding amides (**3a**, **3b**), show a downfield to upfield sequence in the order: H 2, H 4, H 7, H 6 (Table 3) in d_6 DMSO. The proximity of H 2 to the β carbonyl function causes resonance to occur at relatively low field around 8 ppm compared to the corresponding tryptamines. This sequence can be distinguished from the amine counterparts (**4a**, **4b**, **5**, **6**) as this sequence appears in the order: H 7, H 2, H 4, H 6. Without the presence of the keto function, H 2 is found to shift further upfield around 7 ppm. This circumstance gives an additional indication for the carbonyl function of the incompletely reduced compound **8** being on the β carbon of the side chain. The sequence observed is H 2, H 4, H 7, H 6, again pointing to the proximity of the keto function. This is also reflected in the ^{13}C NMR spectrum where compound **8** shows a carbonyl (ketone) shift at 182.2 ppm, and the α methylene carbon signal at 52.8 ppm.

The ^1H and ^{13}C NMR spectra of both *N*,*N* diisopropyl glyoxalylamides **3a** and **3b** show the phenomenon of restricted rotation.[40] Due to the planarity of the amide bond, the isopropyl groups are not equivalent and therefore there are two sets of peaks. For instance, in the case of **3a** the otherwise equivalent N CH proton of the isopropyl groups resonate at different frequencies so two septets are observed at 3.76 and 3.59 ppm respectively. The corresponding carbon signals are found at 49.8 and 44.7 ppm. A similar phenomenon has been reported during the synthesis of psilocin analogues[41,42] and for *N*,*N* (disubstituted) 5,6 methylenedioxyindole 3 yl glyoxalyl amides.[43] For several glyoxalylamides Spaeth and coworkers[44] found a coalescence temperature of 80 150 °C and calculated that the rotation barriers in these amides were 10 15 kJ mol $^{-1}$ higher than in simple acid amides like *N*,*N* indole 3 acetamide that do not possess a β carbonyl group.

The incompletely reduced compound **6** shows a chemical shift of the methine proton at 4.74 ppm in the ^1H NMR spectrum. The presence of the hydroxyl group on the β carbon creates a chiral center and the two adjacent methylene protons are non equivalent. The methine proton signal at 4.74 ppm therefore appears as a doublet of doublets ($^3J_{H\beta,\ H\alpha} = 8$ Hz, 5.5 Hz) due to two vicinal couplings. The hydroxyl group is detected as a broad singlet at 4.36 ppm in d_6 DMSO that disappears after a "D_2O shake". The non equivalency of the methylene protons is consistent with two doublets of doublets at 3.10 and 2.69 ppm for the methylene protons. Each of them shows vicinal coupling with the methine proton and geminal coupling with each other. Accordingly, the ^{13}C NMR spectrum indicates the presence of the methine carbon at 65.3 ppm and the methylene carbon at 51.8 ppm, respectively. Interestingly, both NMR spectra of compound **6** show the presence of two separate isopropyl signals even without the presence of an amide bond, which is attributed to the presence of a chiral centre.

Using preparative TLC, Cowie and coworkers isolated the incompletely reduced hydroxy derivatives of tetramethylene tryptamine (3 [2 pyrrolidinylethyl]indole) and diethyltrypta mine (DET). The position of the hydroxyl groups was concluded to be on the α carbon[45] which seems unlikely based on the NMR results discussed above for compound **6**. It is also known that β hydroxy tryptamines are characterised by

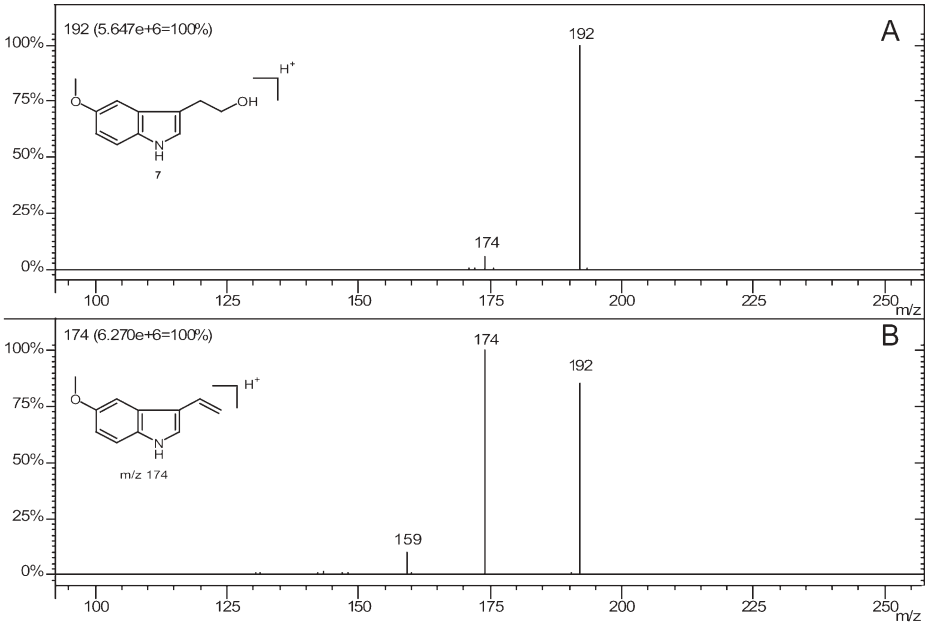

Fig. 6 ESI TQ MS MS spectra and proposed fragmentation for compound **7** using flow injection analysis. A: $[M + H]^+$. B: MS MS fragmentation of **7**; collision energy: −10 eV. Exact masses for *m*/*z* 192 and *m*/*z* 174 are shown in Table 2.

their instability in the presence of acids to give deep red solutions, probably due to polymerisation.[46] This phenomenon was observed for compound **6** as well. In fact, Crookes and coworkers[47] investigated the $LiAlH_4$ reduction of indole 3 yl *N*,*N* dimethylglyoxalylamide and identified a dimeric product that was formed only during the acidic workup.[47]

Conclusion

The implementation of LC ESI MS MS, LC TOF MS and NMR enabled the characterisation of 5 MeO DIPT, its pre cursors, and importantly its side products that were formed during the classical synthetic route of Speeter and Anthony. The identification of key impurities and their mass spectral behaviour made it possible to determine compound specific ion transitions that may be used for screening purposes. For instance, the use of multiple reaction monitoring studies would allow the unambiguous identification of a synthetic route and the exact quantification of impurities. Evidently this is of particular importance in connection with clinical and forensic investigations.

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