Transition Metal-Free Amine Oxidation: a Chemoselective Strategy for the Late-Stage Formation of Lactams

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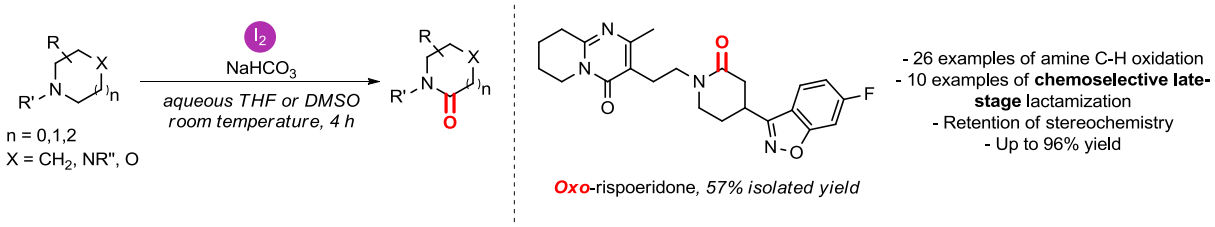
Supporting Information Placeholder



ABSTRACT: This manuscript describes a metal-free strategy for the formation of lactams via selective oxidation of cyclic secondary and tertiary amines. Molecular iodine facilitates both chemoselective and regioselective oxidation of C-H bonds directly adjacent to a cyclic amine. The mild conditions, functional group tolerance and substrate scope are demonstrated using a suite of diverse small molecule cyclic amines, including clinically approved drug scaffolds.

Late-stage C-H oxidation is a step- and atom-efficient strategy to tune the efficacy and physicochemical properties of biologically-active small molecule scaffolds.[1] The underlying driver of this powerful approach is the facile and chemoselective oxidation of C-H bonds in complex molecular architectures by exploiting the subtle differences in C-H bond reactivity. This in turn enables the formation or diversification of molecular frameworks that would otherwise require the development of a dedicated synthetic route at an early stage in the process. Of the myriad of privileged heterocycles found in clinically-approved medicinal agents and natural products,[2] the lactam motif is ubiquitous.[3] From a medicinal chemistry perspective, lactams reduce the hydrophilicity of secondary and tertiary ammonium species, and provide additional hydrogen bond acceptor sites that could enhance drug efficacy and potentially reduce toxicity. Current preparative methods of lactams typically involve condensation of amines with a tethered carboxylic acid,[4] Beckmann rearrangement,[5] or dehydrogenative coupling of amines with alcohols.[6] Each of these strategies involve lactam formation early in the synthetic sequence, which in turn limits the downstream diversification of complex molecular scaffolds.

A comparative process that involves the formation of the lactam moiety by chemoselective oxidation of cyclic amines is less well refined, and typically requires the use of expensive and toxic transition metal catalysts such as osmium[7a] or mercury[7b] complexes and harsh oxidative conditions such as organic peroxides[7c-e] or ruthenium oxides.[7f-h] Recent work by Milstein et al. shows that catalytic oxidation of cyclic amines to the corresponding lactam is indeed possible, although the efficiency of this process is limited by the need to heat an air-sensitive ruthenium catalyst **1**, to 150 °C for more than two days to effect this transformation (Figure 1a).[8]

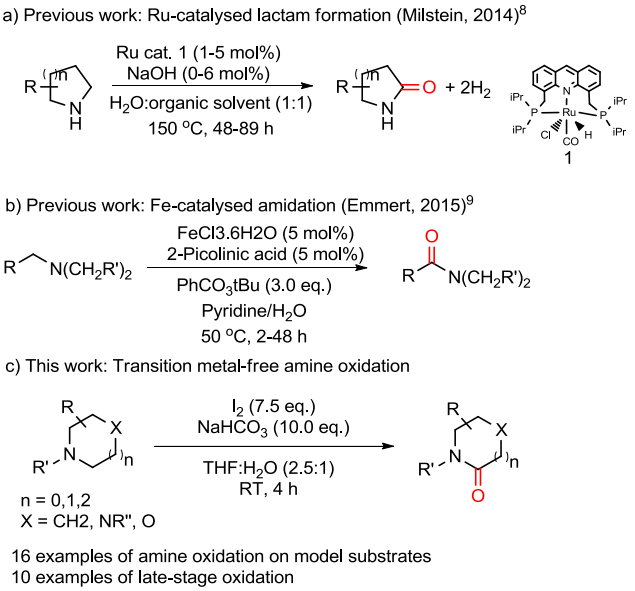


Figure 1. Lactam formation via C-H oxidation of cyclic amines. a) Ruthenium-catalyzed lactam formation;[8] b) Iron(III)-catalyzed oxidation of acyclic amines;[9] c) Late-stage lactam formation mediated by iodine oxidation of cyclic amines.

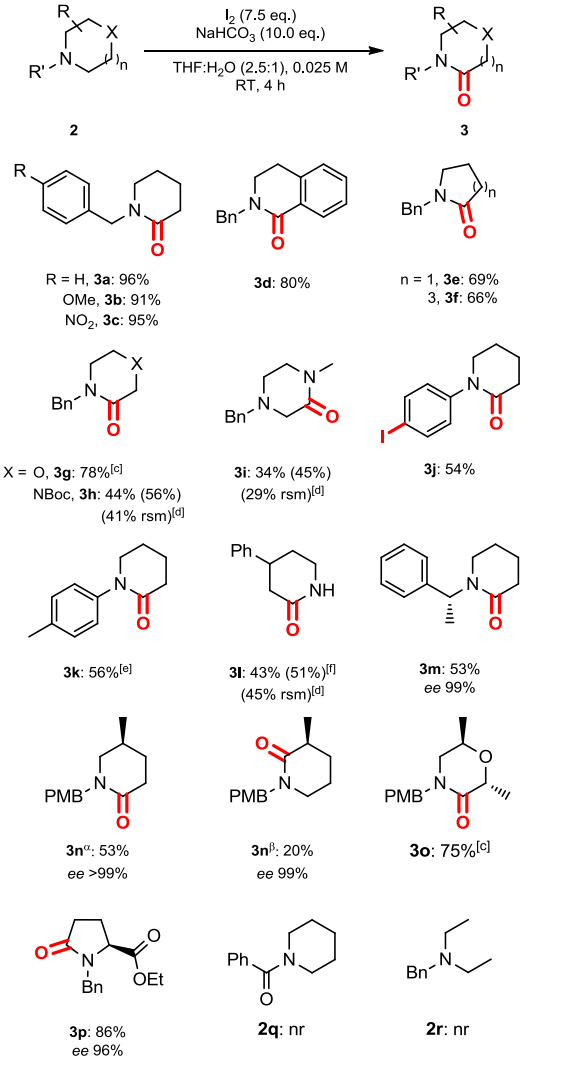
Ferric chloride offers a cheap alternative to ruthenium catalysts (Figure 1b), however substrate scope is currently limited

by the requirement of a strong peroxide oxidant.[9] Gold nanoparticles supported on alumina do offer a mild and chemoselective route to amide and lactam formation. However, large amounts of this expensive catalyst are required, which is further complicated by the multi-step process to prepare the colloid.[10] In contrast to the use of transition-metal catalysts, molecular iodine is a mild, cheap and metal-free oxidant[11] that has been used to chemoselectively oxidize a piperidine ring found in natural products to the corresponding lactam in the presence of aldehyde, alkene, alcohol, and heteroaromatic functionalities.[12] Although there are a number of reports that describe the use of electrophilic halogen sources to carry out α-oxidation of cyclic amines,[13] these procedures to date have limited functional group tolerance,[13a] and require harsh reaction conditions.[13b-e] Herein, we report a general strategy for the chemoselective oxidation of a range of secondary and tertiary saturated N-heterocycles to form γ-, δ- and ε-lactams. To explore the selectivity of our approach, a reaction screen was undertaken using the model substrate **2a**. The parameters of solvent, concentration, stoichiometry of iodine and iodine source were surveyed (SI, Table S1). Aqueous THF and aqueous DMSO were both found to be optimal solvents, resulting in 91% and 90% conversion of **2a** into **3a**, respectively. The stoichiometry of iodine and concentration of the substrate proved critical for high conversion to **3a**, with 7.5 equivalents of iodine and substrate concentration at 0.025 M required to produce 96% of **3a**.

With optimized conditions in hand, the substrate scope of this reaction was explored using a range of cyclic amines **2a-r** (Scheme 1). Our optimized conditions tolerated both electron-rich and electron-poor benzyl-protected piperidines (**2b-c**) and tetrahydroisoquinoline **2d**, with no oxidation of the exocyclic benzylic methylenes observed in **3a-d**. Chemoselective oxidation of the cyclic α-C-H bond was observed in both five-membered and seven-membered cyclic amines **2e-f**, morpholine **2g**, and piperazines **2h-i**. Interestingly, stalling of the reaction was seen for substrate **2g**, which was alleviated by using a DMSO/H_2O solvent system instead. In contrast to benzylic substrates **3a-i**, concomitant lactamization and para-iodination resulted in the formation of **3j** from **2j**. Blocking the para-position of the phenyl ring with a methyl group produced lactam **3k** exclusively. Formation of the secondary lactam **3l** and sterically-hindered **3m** was also tolerated. Oxidation of the asymmetric piperidine **2n** formed **3nα** and **3nβ**, isolated in a ratio of 2.7:1, demonstrating bias towards the sterically less-hindered product. Notably, no racemization of the stereogenic centers in **3m** and **3n** was observed. Retention of stereochemistry at positions β-to the nitrogen in morpholine **2o** was also observed, with the trans-orientation of the methyl groups conserved. The stereogenic centre in the proline-derived substrate **2p** was also conserved, which could potentially enable access to non-natural proline derivatives and proline-tagging experiments. However, no reaction was observed with benzoyl-protected **2q** or acyclic substrate **2r**. This suggests the availability of the amine lone pair and the conformationally-restricted ring structure is essential for chemoselective oxidation.

With the substrate scope and robustness of this methodology established, the chemoselectivity profile was further explored on a suite of drug molecules (Figure 2). Lactams **5a-e** were isolated in moderate to excellent yields (15-92%), demonstrating chemoselective oxidation in the presence of alkenes, electron-rich aromatic rings, pyridines, carboxylic acids and

Scheme 1. Substrate scope of iodine-mediated oxidation of cyclic amines.



a) *Conditions:* 2 (1.0 eq.), $NaHCO_3$ (10.0 eq.), I_2 (7.5 eq.) in THF/H_2O (2.5:1, 0.025 M), RT, 4 h. b) Isolated yields shown – values in parentheses show conversion to product determined by ^{1}H NMR analysis of the crude material against an internal standard. c) Reaction ran in 2.5:1 DMSO/H_2O solvent system. d) % rsm = percentage of remaining starting material observed by crude ^{1}H NMR. e) Iodine was added in three portions of 2.5 eq. each hour. f) Reaction stirred for 20 h.

sulfonamides. Products **5d** and **5e** were isolated in low isolated? yields (15% and 26%, respectively), and were formed in moderate conversions (56% and 57%, respectively). This is attributed to formation of other oxidative by-products that were not isolable, in addition to their challenging purification, which required the use of HPLC (see SI), all of which resulted in low recovery of product. The morpholino-lactam **5f** was also produced in 55% yield with retention of the cis-orientation of the ring-methyl groups. Of particular note was the regioselective oxidation of the asymmetrical azepane ring in **4g**, forming lactams **5gα** and **5gβ** in a ratio of 4.3:1. These results demonstrate the general chemoselectivity of this methodology for oxidation of cyclic amines in complex small molecules.

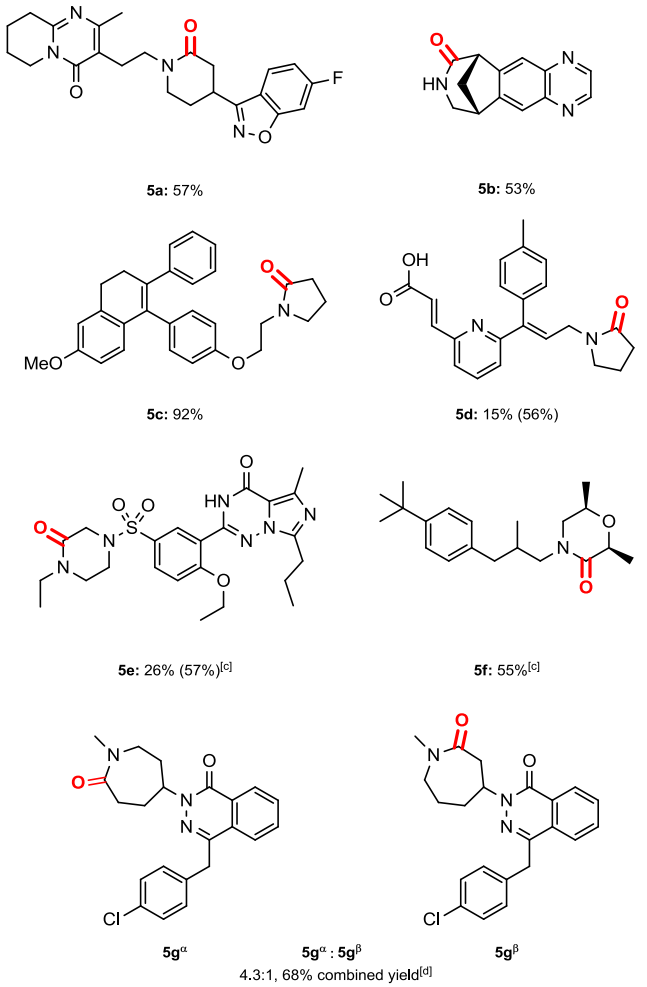


Figure 2. Substrate scope of late-stage C-H oxidation of industrially relevant drug scaffolds. [a]Conditions: 4 (1.0 eq.), $NaHCO_3$ (10.0 eq.), I_2 (7.5 eq.) in THF/H_2O (2.5:1, 0.025 M), RT, 4 h. [b]Isolated yields shown – values in parentheses show conversion to product determined by ^{1}H NMR analysis of the crude material against an internal standard. [c]Reaction run in 2.5:1 DMSO/H_2O solvent system. [d]Ratio of products determined by NMR analysis.

When compared to other conditions reported for oxidation of amines directly to amides/lactams,[7h,8,9,13c] (Figure 3) the conditions developed here offer substantially better chemoselective oxidation when applied to drugs **4h** and **4i** (Condition A), with **5h** isolated in high yield (83%) and **5i** formed in high conversion (81%). Product **5i** could only be isolated in low yield (30%) because further purification was required due to co-elution with an iodinated by-product during the first purification (see SI). ^{18}O-labelling studies were then undertaken using $Na^{18}OAc$ as the base and $H_2{}^{18}O$ (See SI). Full ^{18}O-incorporation was observed in the conversion of **2a** into ^{18}O-**3a** when $H_2{}^{18}O/Na^{18}OAc$ was used. In contrast, only **3a** was formed using $H_2O/Na^{18}OAc$. This confirmed that the source of the lactam oxygen in the product is derived from water and not from the base. Additionally, ^{1}H NMR experiments were carried out to further probe the mechanism of this reaction (See SI, Table S2). These revealed the formation of an N-iodoammonium intermediate upon addition of iodine (7.5 eq.) to **2**a. Dilution of the reaction mixture to 0.025 M with d_8-THF and D_2O, followed by the stepwise addition of sodium bicarbonate resulted in full conversion after 2 hours and 5.0 equivalents of base.

Taken collectively, we propose that this reaction proceeds via the initial formation of the charge-transfer complex **6** (Scheme 2a).[14]

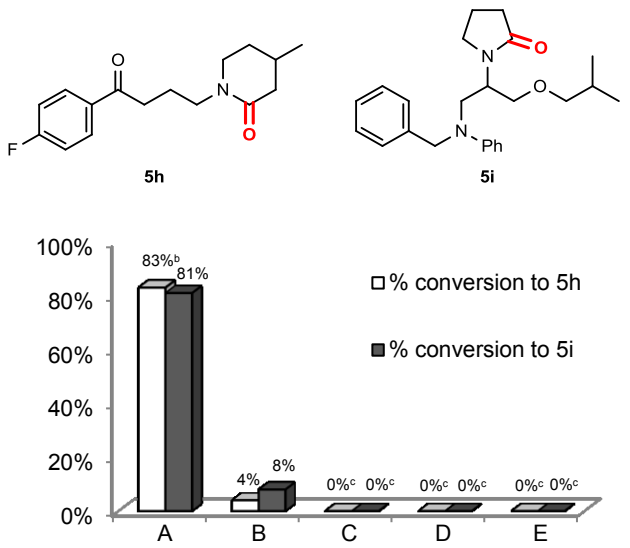
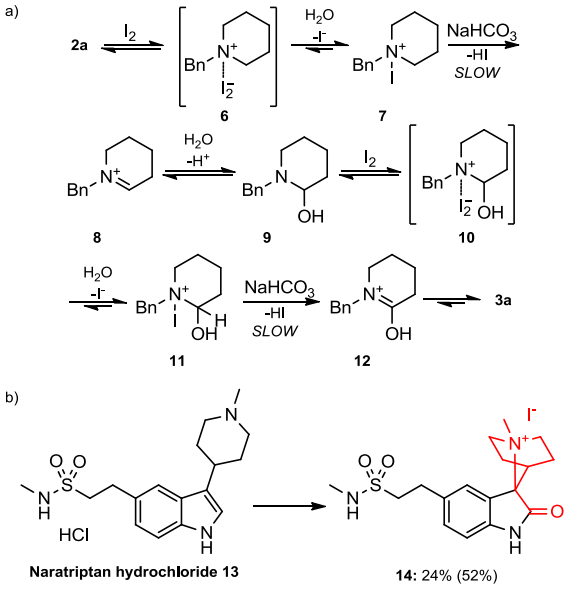


Figure 3. Comparative analysis of amine oxidation conditions using drug compounds 5h and 5i as exemplars. [a]General conditions: A = I_2, $NaHCO_3$, RT, 4 h; B[8] = 1 (1 mol%), NaOH, 150 °C, 48 h; C[9] = $FeCl_3$ (5 mol%), picolinic acid (5.0 mol%), $PhCO_3{}^tBu$ (3.0 eq.), H_2O, 50 °C, 24 h; D[7h] = RuO_2 (10 mol%), $NaIO_4$ (6.3 eq.), RT, 64 h; E[13c] = $PhI(OAc)_2$ (2.2 eq.), H_2O, RT, 16 h. For detailed conditions see SI. [b]Isolated yield. [c]Complex mixture of oxidative by-products observed.

Scheme 2. a) Proposed reaction mechanism, and b) the unexpected cyclization of Naratriptan.



a) *Conditions:* **13** (1.0 eq.), $NaHCO_3$ (10.0 eq.), I_2 (7.5 eq.) in THF/H_2O (2.5:1, 0.025 M), RT, 20 h. b) Isolated yield shown – value in parentheses shows conversion to product determined by ^{1}H NMR analysis of the reaction mixture run in deuterated solvents against an internal standard.

With moisture present, this would form **7**, followed by slow formation of iminium ion **8**. The observed endocyclic oxidation

is most likely due to a more effective anti-periplanar E2-elimination of the N-I and C-Hα bonds relative to the conformationally flexible exocyclic site. The low basicity of sodium bicarbonate may also be responsible for the selectivity of deprotonation seen for **2p**, with the less sterically hindered hydrogen being deprotonated over the more acidic one. Nucleophilic attack by water at the iminium carbon in **8** and subsequent deprotonation forms **9**. A second iodination step to form **11** via **10**, enables the formation of **12** via loss of hydrogen iodide, and tautomerization results in the formation of **3a**. The unexpected formation of product **14** in 52% conversion from the indole **13** (Scheme 2b) further underpins the formation of the N-iodoammonium intermediate such as **7** on the piperidine ring, which can be sequestered by the proximal indole in this instance.

In summary, we have developed a mild, late-stage strategy for the chemoselective oxidation of cyclic amines to the corresponding lactams under mild conditions. We envisage that this approach could be generalized by medicinal chemists to create a diverse range of compounds from a small subset of molecular scaffolds, as well as providing synthetic access to drug metabolites,[1e,15] potentially accelerating the hit-to-lead process of drug discovery compared to more traditional linear routes.

ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data is available free of charge on the ACS Publications website.

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Supporting Information for

Transition Metal-Free Amine Oxidation: a Chemoselective Strategy for the Late-Stage Formation of Lactams

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Table of Contents

General experimental

Solvents and reagents

Unless otherwise stated:

- Reactions were carried out under a standard atmosphere of air at room temperature, and glassware was not dried beforehand. Solvents used were non-anhydrous.
- Solvents and reagents were purchased from commercial suppliers or obtained from GlaxoSmithKline's internal compound storage and used as received without further purification. All drug compounds used in transformations are commercially available.
- Reactions were monitored by liquid chromatography-mass spectroscopy (LCMS) and Nuclear Magnetic Resonance (NMR).

Where substrates were synthesized in-house, literature references are given for spectral data of these compounds.

Chromatography

Thin layer chromatography (TLC) was carried out using plastic-backed 50 precoated silica plates (particle size 0.2 mm). Spots were visualized by ultraviolet (UV) light (λ_{max} = 254 nm or 365 nm) and then stained with potassium permanganate solution followed by gentle heating. Silica gel chromatography was carried out using the Teledyne ISCO CombiFlash® Rf+ apparatus with RediSep® silica cartridges. Reverse phase preparative HPLC was carried out using the Grace Reveleris® Prep apparatus with an XTerra® Prep RP_{18} OBD™ column.

Liquid chromatography mass spectrometry (LCMS)

LCMS analysis was carried out on an H_2Os Acquity UPLC instrument equipped with a BEH column (50 mm x 2.1 mm, 1.7 μm packing diameter) and H_2Os micromass ZQ MS using alternate-scan positive and negative electrospray. Analytes were detected as a summed UV wavelength of 210 – 350 nm. Two liquid phase methods were used: was a high pH method:

> **Method A – High pH** – 40 °C, 1 mL/min flow rate. Gradient elution with the mobile phases as (A) 10 mM aqueous ammonium bicarbonate solution, adjusted to pH 10 with 0.88 M aqueous ammonia and (B) acetonitrile. Gradient conditions were initially 1% B, increasing linearly to 97% B over 1.5 min, remaining at 97% B for 0.4 min then increasing to 100% B over 0.1 min.
>
> **Method B – Low pH** – 40 °C, 1 mL/min flow rate. Gradient elution with the mobile phases as (A) H_2O containing 0.1% volume/volume (v/v) formic acid and (B) acetonitrile containing 0.1% (v/v) formic acid. Gradient conditions were initially 1% B, increasing linearly to 97% B over 1.5 min, remaining at 97% B for 0.4 min then increasing to 100% B over 0.1 min.

Nuclear magnetic resonance (NMR) spectroscopy

Proton (^1H) and carbon (^{13}C) spectra were recorded in deuterated solvents at ambient temperature using standard pulse methods on any of the following spectrometers and signal frequencies: Bruker AV-400 (^1H = 400 MHz, ^{13}C = 101 MHz), Bruker AV-500 (^1H = 500 MHz, ^{13}C = 126 MHz) and Bruker AV-600 (^1H = 600 MHz, ^{13}C = 151 MHz). Chemical shifts are reported in ppm and are referenced to the following solvent peaks: $CDCl_3$ (^1H =

7.27 ppm, ^{13}C = 77.0 ppm), d_6-DMSO (^{1}H = 2.50 ppm, ^{13}C = 39.5 ppm), and D_2O (^{1}H = 4.79 ppm). Where D_2O was used as the solvent, the default referencing was used based on the D_2O lock frequency for ^{13}C NMR. Peak assignments were made on the basis of chemical shifts, integrations, and coupling constants using COSY, DEPT, HSQC, HMBC, NOESY and ROESY where appropriate. Coupling constants are quoted to the nearest 0.01 Hz and multiplicities are described as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin), sextet (sxt), br. (broad) and multiplet (m).

Infrared (IR) spectroscopy

IR spectra were recorded using a Perkin Elmer Spectrum 1 machine. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}).

Mass directed automated preparation (MDAP)

MDAP was carried out using an H_2Os ZQ MS using alternate-scan positive and negative electrospray and a summed UV wavelength of 210–350 nm. liquid phase method used was a high pH method:

> Xbridge C18 column (100 mm x 19 mm, 5 µm packing diameter, 20 mL/min flow rate) or Xbridge C18 column (150 mm x 30 mm, 5 µm packing diameter, 40 mL/min flow rate). Gradient elution at ambient temperature with the mobile phases as (A) 10 mM aqueous ammonium bicarbonate solution, adjusted to pH 10 with 0.88 M aqueous ammonia and (B) acetonitrile.

The elution gradients used were at a flow rate of 40 mL/min over 20 or 30 min depending on separation:

Gradient A	5-30% B
Gradient B	15-55% B
Gradient C	30-85% B
Gradient D	50-99% B
Gradient E	80-99% B

Optimization of conditions

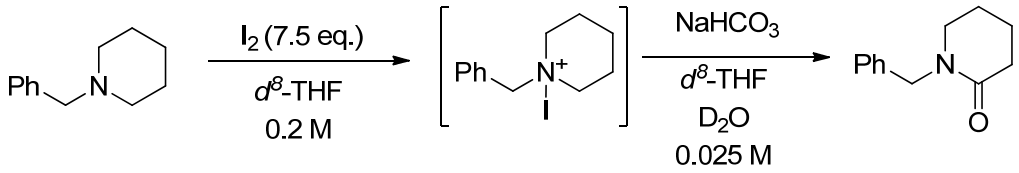
Table S1: Optimization of iodine-mediated oxidation with *N*-benzylpiperidine 2a[a]

Entry	Eq. of I_2	Solvent system	Concentration of 2a / M	Conversion[b] to 3a (%)
1	10	Toluene/H_2O (2.5:1)	0.025	nr
2	10	DCM/H_2O (2.5:1)	0.025	nr
3	10	MeOH/H_2O (2.5:1)	0.025	5
4	10	HFIP[c]/H_2O (2.5:1)	0.025	2
5	10	H_2O	0.025	6
6	10	MeCN/H_2O (2.5:1)	0.025	6
7	10	THF/H_2O (2.5:1)	0.025	91
8	10	DMSO/H_2O (2.5:1)	0.025	90
9	10	THF/H_2O (2.5:1)	0.1[d]	59
10	10	THF/H_2O (2.5:1)	0.05[d]	57
11	1.1	THF/H_2O (2.5:1)	0.025	15
12	2.5	THF/H_2O (2.5:1)	0.025	31
13	5.0	THF/H_2O (2.5:1)	0.025	68
14	**7.5**	**THF/H_2O (2.5:1)**	**0.025**	**96[~~d~~c]**
15	7.5[~~e~~f]	THF/H_2O (2.5:1)	0.025	62
16[~~f~~g]	7.5	THF/H_2O (2.5:1)	0.025	nr
17	7.5	THF	0.025	nr
18[~~g~~h]	7.5	THF/H_2O (2.5:1)	0.025	*No change in reaction profile by LCMS – no yield gathered*

[a]Reaction conditions: **2a** (1.0 eq.), $NaHCO_3$ (10.0 eq.), I_2 (1.1 – 10.0 eq.) in solvent stirred at room temperature for 4 h; [b]Conversion determined by ^1H NMR analysis of crude material against an internal standard; [c]HFIP = 1,1,1,3,3,3-hexafluoroisopropanol; [d]At higher concentrations of **2a**, formation of alpha -iodolactam by-products was observed; [~~d~~c]Isolated yield; [~~e~~f]*N*-iodosuccinimide used as the iodine source instead of I_2; [~~f~~g]No $NaHCO_3$ present; [~~g~~h]Reaction carried out under a nitrogen atmosphere.

Mechanistic studies

Table S2: NMR studies into mechanism of oxidation[a]



2a **7** **3a**

Entry	Eq. $NaHCO_3$	Time / min	Ratio of 2a:8:3a
1	0.0	0	0:1:0
2	1.0	30	0:1:0
3	2.0	60	0:1.53:1
4	3.0	90	0:0.56:1
5	5.0	120	0:0:1
6	8.0	240	0:0:1
7	10.0	360	0:0:1

[a] Reaction conditions: **2a** (0.57 mmol) was added to a solution of iodine (4.28 mmol) in d^8-THF (2.9 mL). This reaction mixture was stirred at RT for 1.5 h, and ^{1}H NMR analysis showed conversion of **2a** to **7**. A 1 mL aliquot of this 0.2 M solution of **7** in d^8-THF (0.2 mmol) was diluted to 0.025 M with d^8-THF (4.7 mL) and D_2O (2.3 mL). Solid $NaHCO_3$ was added portionwise, as described in Table S2, and the reaction mixture was monitored by ^{1}H NMR, analyzing conversion of intermediate **7** to product **3a**.

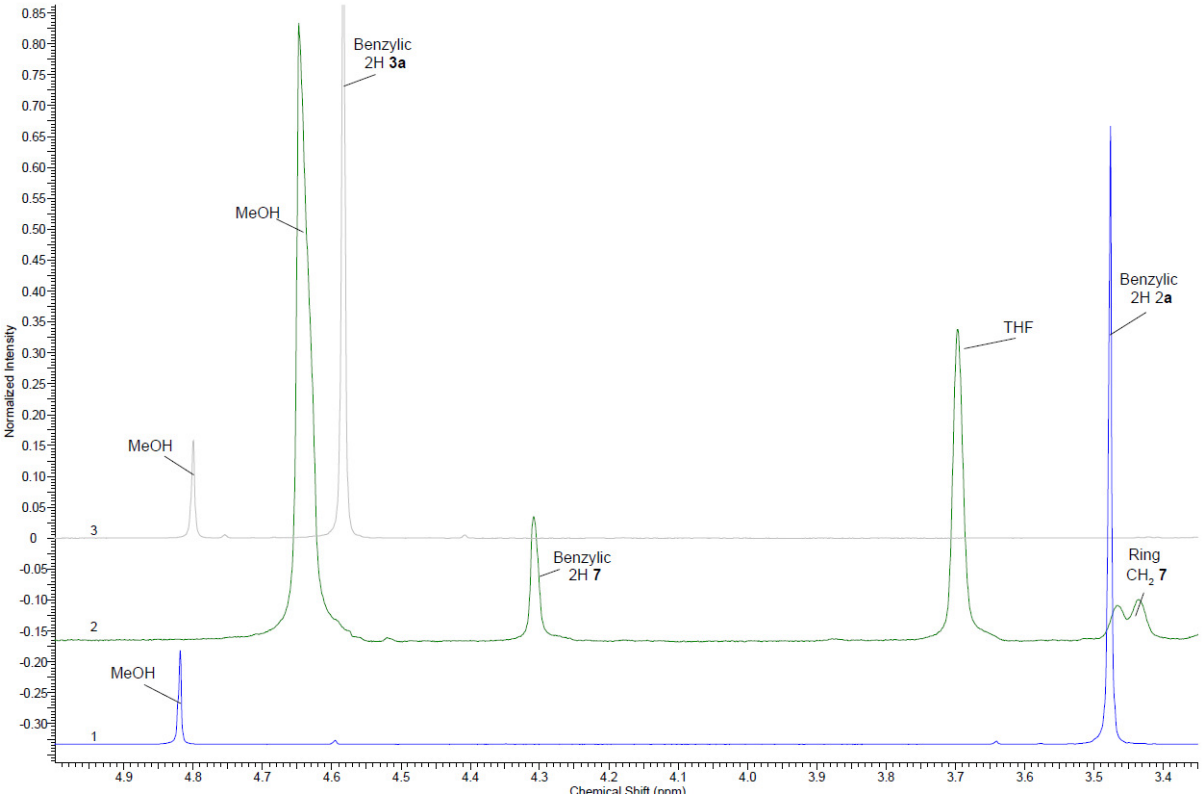


Figure S1: Identification of the proposed intermediate **7**. A change in the chemical shift of the benzylic protons of **2a** was observed that was typical in difference between an amine and an ammonium species.[1] Also no signal attributable to an iminium ion species was observed.[2]

Spectrum 1 (blue): **2a**

Spectrum 2 (green): **7**

Spectrum 3 (grey): **3a**

Experimental

General procedure A

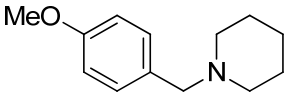
Iodine (7.5 eq.) was added to a mixture of cyclic amine (1.0 eq.) and sodium bicarbonate (10.0 eq.) in THF/H_2O (2.5:1, 0.025 M). The reaction mixture was stirred gently at room temperature for 4 h and monitored by LCMS. The reaction mixture was then pipetted into a solution of saturated aqueous sodium thiosulfate (10 mL) and saturated aqueous sodium bicarbonate (10 mL). The crude material was extracted in DCM (2 x 10 mL), and the combined organic layers were washed with saturated aqueous sodium bicarbonate (10 mL), passed through a hydrophobic frit, concentrated *in vacuo* and then purified as described.

General procedure B

Iodine (7.5 eq.) was added to a mixture of cyclic amine (1.0 eq.) and sodium bicarbonate (10.0 eq.) in DMSO/H_2O (2.5:1, 0.025 M). The reaction mixture was stirred gently at room temperature for 4 h and monitored by LCMS. The reaction mixture was then pipetted into a solution of saturated aqueous sodium thiosulfate (10 mL) and saturated aqueous sodium bicarbonate (10 mL). The crude material was extracted in DCM (2 x 10 mL), and the combined organic layers were washed with saturated aqueous sodium bicarbonate (10 mL), passed through a hydrophobic frit, concentrated *in vacuo* and then purified as described.

General procedure C

Iodine (7.5 eq.) was added to a mixture of cyclic amine (1.0 eq.) and sodium bicarbonate (10.0 eq.) in THF/H_2O (2.5:1, 0.025 M). The reaction mixture was stirred gently at room temperature for 20 h and monitored by LCMS. The reaction mixture was then pipetted into a solution of saturated aqueous sodium thiosulfate (10 mL) and saturated aqueous sodium bicarbonate (10 mL). The crude material was extracted in DCM (2 x 10 mL), and the combined organic layers were washed with saturated aqueous sodium bicarbonate (10 mL), passed through a hydrophobic frit, concentrated *in vacuo* and then purified as described.

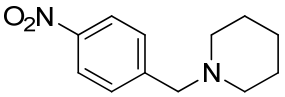


1-(4-Methoxybenzyl)piperidine 2b[3]

Piperidine (0.54 mL, 5.5 mmol), 4-methoxybenzyl chloride (0.68 mL, 5.0 mmol) and potassium carbonate (0.83 g, 6.0 mmol) were heated to 55 °C in MeCN (20 mL) for 42 h. The reaction mixture was cooled to RT, and then passed through a sintered funnel and the filtrate was concentrated *in vacuo*. The crude material was purified by silica gel chromatography, with 25-80% TBME (5% methanol, 2% triethylamine modifier)/cyclohexane, to afford **2b** (0.64 g, 63%) as a colorless oil.

LCMS (High pH, UV, ESI) R_t = 1.11 min, $[M+H]^+$ 206.1

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.23 (d, *J*=8.6 Hz, 2H), 6.86 (d, *J*=8.8 Hz, 2H), 3.81 (s, 3H), 3.42 (s, 2H), 2.37 (br. s., 4H), 1.58 (quin, *J*=5.6 Hz, 4H), 1.44 (br. s, 2H).

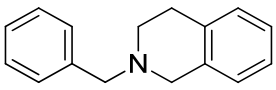


1-(4-Nitrobenzyl)piperidine 2c[4]

4-nitrobenzyl bromide (1.19 g, 5.5 mmol) was slowly added to a solution of piperidine (0.49 mL, 5.0 mmol) and DIPEA (1.31 mL, 7.5 mmol) in DCM (25 mL) at 0 °C. After the addition was complete, the solution was left to stir at RT for 18 h. The reaction mixture was then washed with distilled water (20 mL) and brine (20 mL), and the organic layer was passed through a hydrophobic frit and concentrated *in vacuo*. The crude material was purified by silica gel chromatography with 10-45% EtOAc/cyclohexane as the eluent, to afford **2c** (0.98 g, 89%) as a yellow oil.

LCMS (High pH, UV, ESI) R_t = 1.22 min, $[M+H]^+$ 221.1

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.13 (d, *J*=8.6 Hz, 2H), 7.48 (d, *J*=8.6 Hz, 2H), 3.52 (s, 2H), 2.36 (t, *J*=5.3 Hz, 4H), 1.56 (quin, *J*=5.6 Hz, 4H), 1.41-1.46 (m, *J*=5.6 Hz, 2H).

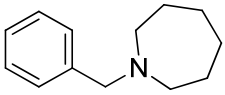


2-Benzyl-1,2,3,4-tetrahydroisoquinoline 2d[5]

2-picoline borane (1.05 g, 9.8 mmol) was added over 5 min to a mixture of benzaldehyde (1.0 mL, 9.8 mmol), 1,2,3,4-tetrahydroquinoline (1.2 mL, 9.8 mmol) and acetic acid (0.3 mL) and the reaction mixture stirred at RT for 72 h. The reaction was quenched with 10% aqueous HCl (10 mL) was added and the aqueous solution was stirred for 30 min at RT. The solution was then made alkaline to pH 9 with saturated aqueous sodium bicarbonate. The aqueous layer was extracted with EtOAc (2 x 30 mL), and the combined organic layers were washed with brine (15 mL), passed through a hydrophobic frit and concentrated *in vacuo*. The crude product was purified by silica gel chromatography with 0-50% EtOAc (1% 4M ammonia/methanol modifier)/cyclohexane as the eluent, to afford **2d** (2.08 g, 94%) as a colorless oil.

LCMS (High pH, UV, ESI) R_t = 1.32 min, $[M+H]^+$ 224.1

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.50 (d, *J*=7.1 Hz, 2H), 7.40-7.46 (m, 2H), 7.36 (tt, *J*=7.1, 2.3 Hz, 1H), 7.16-7.22 (m, 3H), 7.07 (s, 1H), 3.78 (s, 2H), 3.74 (s, 2H), 3.00 (t, *J*=5.8 Hz, 2H), 2.84 (t, *J*=6.1 Hz, 2H).

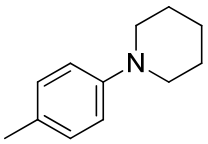


1-Benzylazepane 2f[6]

2-picoline borane (0.83 g, 8.3 mmol) was added over 5 min to a mixture of benzaldehyde (0.85 mL, 8.3 mmol), azepane (0.94 mL, 8.3 mmol) and acetic acid (0.3 mL) and the reaction mixture stirred at RT for 72 h. The reaction was quenched with 10% aqueous HCl (10 mL) was added and the aqueous solution was stirred for 30 min at RT. The solution was then made alkaline to pH 9 with saturated aqueous sodium bicarbonate. The aqueous layer was extracted with EtOAc (2 x 30 mL), and the combined organic layers were washed with brine (15 mL), passed through a hydrophobic frit and concentrated *in vacuo*. The crude product was purified by reverse phase prep HPLC, with 30-85% HpH MeCN/aq. $NaHCO_3$ as the eluent, to afford **2f** (0.91 g, 58%) as an amber oil.

LCMS (High pH, UV, ESI) R_t = 1.33 min, $[M+H]^+$ 190.2

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41 (d, *J*=7.3 Hz, 2H), 7.36 (t, *J*=7.4 Hz, 2H), 7.28 (tt, *J*=7.1, 2.5 Hz, 1H), 3.70 (s, 2H), 2.69 (br. t, *J*=5.2 Hz, 4H), 1.69 (br. s, 8H).

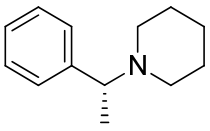


1-(*p*-Tolyl)piperidine 2k[7]

Under a nitrogen atmosphere, 4-chlorotoluene (0.59 mL, 5.0 mmol) was added to a solution of piperidine (0.59 mL, 6.0 mmol), 1,3-bis(2,6-diisopropylphenyl)-1H-imidazol-3-ium chloride (85 mg, 0.2 mmol), potassium *tert*-butoxide (842 mg, 7.5 mmol) and $Pd_2(dba)_3$ (46 mg, 0.05 mmol) in 1,4-dioxane (15 mL), and the reaction mixture was stirred at 100 °C for 24 h. The reaction mixture was allowed to cool to RT, before addition of water (20 mL) and extraction into diethyl ether (2 x 30 mL). The combined organic layers were washed with brine (25 mL), passed through a hydrophobic frit and concentrated *in vacuo.* The crude material was purified by silica gel chromatography using 0-40% (3:1 EtOAc:EtOH)/cyclohexane as the eluent, affording **2k** (363 mg, 41%) as a yellow oil.

LCMS (High pH, UV, ESI) R_t = 1.34 min, $[M+H]^+$ 176.2

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.07 (d, *J*=8.3 Hz, 2H), 6.87 (d, *J*=8.6 Hz, 2H), 3.11 (t, *J*=5.4 Hz, 4H), 2.28 (s, 3H), 1.73 (quin, *J*=5.6 Hz, 4H), 1.57 (quin, *J*=5.8 Hz, 2H).

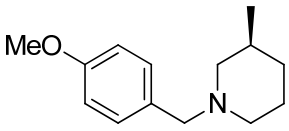


(*R*)- 1-(1-Phenylethyl)piperidine 2m[8]

A solution of (*R*)-1-phenylethanamine (0.80 mL, 6.2 mmol) in MeCN (8.8 mL) was added to a mixture of 1,5-dibromopentane (1.05 mL, 7.4 mmol) and potassium carbonate (3.4 g, 24.8 mmol) in Acetonitrile (16.0 mL). The reaction mixture was stirred at 50 °C for 42 h. The reaction mixture was allowed to cool to RT, and then filtered through a sintered funnel and the filtrate was concentrated *in vacuo*. The crude material was purified by silica gel chromatography, with 35-80% TBME (5% methanol, 2% triethylamine modifier)/cyclohexane to afford **2m** (0.95 g, 81%) as a colorless oil.

LCMS (High pH, UV, ESI) R_t = 1.23 min, $[M+H]^+$ 190.1

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31 (d, *J*=4.5 Hz, 4H), 7.21-7.26 (m, 1H), 3.41 (q, *J*=6.8 Hz, 1H), 2.31-2.46 (m, 4H), 1.56 (quin, *J*=5.6 Hz, 4H), 1.41 (t, *J*=5.8 Hz, 2H), 1.38 (d, *J*=6.8 Hz, 3H).



(*S*)-1-(4-Methoxybenzyl)-3-methylpiperidine 2n

(*S*)-3-Methylpiperidine (0.65 mL, 5.5 mmol), 4-methoxybenzyl chloride (0.68 mL, 5.0 mmol) and potassium carbonate (0.83 g, 6.0 mmol) were heated to 55 °C in MeCN (20 mL) for 42 h. The reaction mixture was cooled to RT, and then passed through a sintered funnel and the filtrate was concentrated *in vacuo*. The crude material was purified by silica gel chromatography, with 25-80% TBME (5% methanol, 2% triethylamine modifier)/cyclohexane, to afford **2n** (0.78 g, 71%) as a colorless oil.

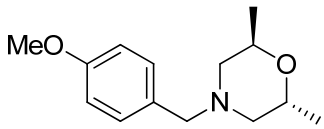
LCMS (High pH, UV, ESI) R_t = 1.23 min, $[M+H]^+$ 220.2

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.24 (d, *J*=8.8 Hz, 2H), 6.86 (d, *J*=8.6 Hz, 2H), 3.81 (s, 3H), 3.43 (s, 2H), 2.73-2.84 (m, 2H), 1.85 (td, *J*=11.1, 3.5 Hz, 1H), 1.51-1.74 (m, 5H), 0.86-0.92 (m, 1H), 0.85 (d, *J*=6.3 Hz, 3H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 158.6, 130.7, 130.3, 113.5, 63.0, 61.9, 55.2, 53.9, 33.1, 31.1, 25.6, 19.8

ν_{max} (cm^{-1}) (thin film): 2927, 1612, 1510

HRMS: Calculated for $C_{14}H_{22}NO$ 220.1696, found $[M+H]^+$: 220.1689 (-3.4 ppm).



(2*R*,6*R*)-4-(4-Methoxybenzyl)-2,6-dimethylmorpholine 2o

(2*R*,6*R*)-2,6-Dimethylmorpholine (0.70 mL, 5.5 mmol), 4-methoxybenzyl chloride (0.68 mL, 5.0 mmol) and potassium carbonate (0.83 g, 6.0 mmol) were heated to 50 °C in MeCN (20 mL) for 42 h. The reaction mixture was cooled to RT, and then passed through a sintered funnel and the filtrate was concentrated in vacuo. The crude material was purified by silica gel chromatography, with 0-20% (3:1 EtOAc:EtOH)/cyclohexane, to afford **2o** (1.03 g, 87%) as a colorless oil.

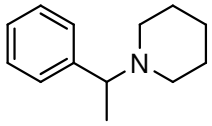
LCMS (High pH, UV, ESI) R_t = 1.11 min, $[M+H]^+$ 236.2

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.25 (d, *J*=8.6 Hz, 2H), 6.86 (d, *J*=8.6 Hz, 2H), 4.01 (quind, *J*=6.3, 3.5 Hz, 2H), 3.80 (s, 3H), 3.42 (d, *J*=12.6 Hz, 1H), 3.33 (d, *J*=12.9 Hz, 1H), 2.45 (dd, *J*=11.0, 3.2 Hz, 2H), 2.13 (dd, *J*=11.0, 5.7 Hz, 2H), 1.24 (d, *J*=6.3 Hz, 6H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 158.7, 130.4, 129.9, 113.6, 66.7, 62.5, 58.6, 55.2, 18.2

ν_{max} (cm^{-1}) (thin film): 2970, 2803, 1612, 1510

HRMS: Calculated for $C_{14}H_{22}NO_2$ 236.1645, found $[M+H]^+$: 236.1638 (-2.9 ppm).

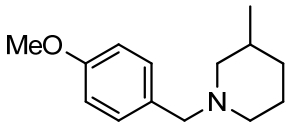


1-(1-Phenylethyl)piperidine 2s

A solution of 1-phenylethanamine (0.80 mL, 6.2 mmol) in MeCN (8.8 mL) was added to a mixture of 1,5-dibromopentane (1.05 mL, 7.4 mmol) and potassium carbonate (3.4 g, 24.8 mmol) in Acetonitrile (16.0 mL). The reaction mixture was stirred at 50 °C for 42 h. The reaction mixture was allowed to cool to RT, and then filtered through a sintered funnel and the filtrate was concentrated *in vacuo*. The crude material was purified by silica gel chromatography, with 35-80% TBME (5% methanol, 2% triethylamine modifier)/cyclohexane to afford **2m** (1.02 g, 87%) as a colorless oil.

LCMS (High pH, UV, ESI) R_t = 1.24 min, $[M+H]^+$ 190.2

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33 (d, J=4.3 Hz, 4H), 7.22-7.28 (m, 1H), 3.42 (q, J=6.8 Hz, 1H), 2.31-2.48 (m, 4H), 1.58 (quin, J=6.3 Hz, 4H), 1.41-1.45 (m, 2H), 1.40 ppm (d, J=6.8 Hz, 3H)



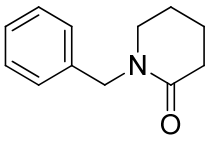
1-(4-Methoxybenzyl)-3-methylpiperidine 2t

3-methylpiperidine (0.65 mL, 5.5 mmol), 4-methoxybenzyl chloride (0.68 mL, 5.0 mmol) and potassium carbonate (0.83 g, 6.0 mmol) were heated to 55 °C in MeCN (20 mL) for 21 h.

The reaction mixture was cooled to RT, and then passed through a sintered funnel and the filtrate was concentrated *in vacuo*. The crude material was purified by silica gel chromatography, with 0-20% (3:1 EtOAc/EtOH)/cyclohexane, to afford **2p** (0.87 g, 79%) as a colorless oil.

LCMS (High pH, UV, ESI) R_t = 1.25 min, $[M+H]^+$ 220.3

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.25 (d, J=8.8 Hz, 2H), 6.87 (d, J=8.8 Hz, 2H), 3.80 (s, 3H), 3.44 (s, 2H), 2.81 (t, J=10.7 Hz, 2H), 1.86 (td, J=11.0, 3.8 Hz, 1H), 1.53-1.75 (m, 5H), 0.88-0.94 (m, 1H), 0.87 (d, J=6.3 Hz, 3H)



1-Benzylpiperidin-2-one 3a

Example synthetic procedure

Iodine (381 mg, 1.50 mmol) was added to a mixture of 1-benzylpiperidine (36.9 µL, 0.20 mmol) and sodium bicarbonate (168 mg, 2.00 mmol) in THF/H_2O (5.7/2.3 mL). The reaction mixture was stirred gently at room temperature for 4 h and monitored by LCMS. The reaction mixture was then pipetted into a solution of saturated aqueous sodium thiosulfate (10 mL) and saturated aqueous sodium bicarbonate (10 mL). The crude material was extracted in DCM (2 x 10 mL), and the combined organic layers were washed with saturated aqueous sodium bicarbonate (10 mL), passed through a hydrophobic frit, concentrated *in vacuo*. The crude material was purified by silica gel chromatography using 35-60% TBME (with 1% triethylamine, 5% methanol modifier)/cyclohexane as the eluent, to afford **3a** (36.3 mg, 96%) as a yellow oil.*

~~General procedure A was followed. Iodine (381 mg, 1.50 mmol) was added to a mixture of 1-benzylpiperidine (36.9 µL, 0.20 mmol) and sodium bicarbonate (168 mg, 2.00 mmol) in THF/H_2O (5.7/2.3 mL). Purification was carried out by silica gel chromatography using 35-60% TBME (with 1% triethylamine, 5% methanol modifier)/cyclohexane as the eluent, to afford **3a** (36.3 mg, 96%) as a yellow oil.*~~

LCMS (High pH, UV, ESI) R_t = 0.85 min, $[M+H]^+$ 190.1

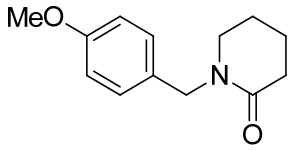
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.23-7.36 (m, 5H), 4.61 (s, 2H), 3.21 (t, *J*=5.7 Hz, 2H), 2.48 (t, *J*=6.5 Hz, 2H), 1.73-1.86 (m, 4H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 169.8, 137.3, 128.5, 128.0, 127.3, 50.1, 47.3, 32.5, 23.2, 21.4

ν_{max} (cm^{-1}) (thin film): 2944, 1632

HRMS: Calculated for $C_{12}H_{16}NO$ 190.1226, found $[M+H]^+$: 190.1227 (0.5 ppm).

**3.2 wt% iodinated lactam co-eluted with product*



1-(4-Methoxybenzyl)piperidin-2-one 3b

General procedure A was followed. Iodine (381 mg, 1.50 mmol) was added to a mixture of **2b** (41 mg, 0.20 mmol) and sodium bicarbonate (168 mg, 2.00 mmol) in THF/H_2O (5.7/2.3 mL). Purification was carried out by silica gel chromatography using 50-100% TBME (with 1% triethylamine & 5% methanol modifier)/cyclohexane as the eluent, to afford **3b** (39.8 mg, 91%) as a colorless oil.

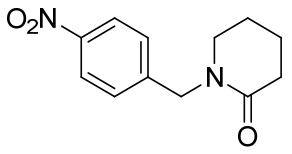
LCMS (High pH, UV, ESI) R_t = 0.85 min, $[M+H]^+$ 220.1

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.19 (d, *J*=8.6 Hz, 2H), 6.84 (d, *J*=8.6 Hz, 2H), 4.52 (s, 2H), 3.79 (s, 3H), 3.17 (t, *J*=5.5 Hz, 2H), 2.44 (t, *J*=6.5 Hz, 2H), 1.68-1.84 (m, 4H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 169.7, 158.9, 129.5, 129.5, 113.9, 55.2, 49.5, 47.0, 32.5, 23.2, 21.4

ν_{max} (cm^{-1}) (thin film): 2936, 1633

HRMS: Calculated for $C_{13}H_{18}NO_2$ 220.1332, found $[M+H]^+$: 220.1337 (2.4 ppm).



1-(4-Nitrobenzyl)piperidin-2-one 3c

General procedure A was followed. Iodine (432 mg, 1.70 mmol) was added to a mixture of **2c** (50 mg, 0.23 mmol) and sodium bicarbonate (191 mg, 2.27 mmol) in THF/H_2O (6.5/2.6 mL). Purification was carried out by silica gel chromatography using 40-60% (3:1 EtOAc/EtOH) (with 1% ammonia modifier)/cyclohexane as the eluent, to afford **3c** (50.4 mg, 95%) as a white solid.

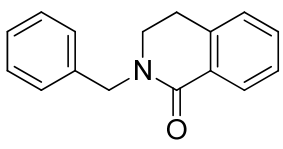
LCMS (High pH, UV, ESI) R_t = 0.84 min, $[M+H]^+$ 235.1

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.19 (d, *J*=8.8 Hz, 2H), 7.43 (d, *J*=8.6 Hz, 2H), 4.69 (s, 2H), 3.25 (t, *J*=5.4 Hz, 2H), 2.51 (t, *J*=6.2 Hz, 2H), 1.79-1.88 (m, 4H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.1, 147.4, 145.0, 128.6, 123.9, 49.9, 47.9, 32.3, 23.2, 21.3

ν_{max} (cm^{-1}) (thin film): 2953, 2879, 1628

HRMS: Calculated for $C_{12}H_{15}N_2O_3$ 235.1077, found $[M+H]^+$: 235.1079 (0.6 ppm).



2-Benzyl-3,4-dihydroisoquinolin-1(2H)-one 3d

General procedure A was followed. Iodine (426 mg, 1.68 mmol) was added to a mixture of **2d** (50 mg, 0.22 mmol) and sodium bicarbonate (188 mg, 2.24 mmol) in THF/H_2O (6.4/2.6 mL). Purification was carried out by silica gel chromatography using 10-30% TBME (with 1% 4M ammonia in methanol modifier)/cyclohexane as the eluent, to afford **3d** (42.6 mg, 80%) as a colorless oil.

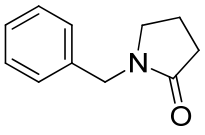
LCMS (High pH, UV, ESI) R_t = 1.09 min, $[M+H]^+$ 238.1

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.18 (dd, *J*=7.6, 1.8 Hz, 1H), 7.41-7.47 (m, 1H), 7.32-7.40 (m, 5H), 7.27-7.32 (m, 1H), 7.18 (d, *J*=7.3 Hz, 1H), 4.82 (s, 2H), 3.51 (t, *J*=6.7 Hz, 2H), 2.96 (t, *J*=6.7 Hz, 2H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 164.6, 138.1, 137.5, 131.7, 129.4, 128.7, 128.5, 128.1, 127.5, 127.1, 126.9, 50.5, 45.4, 28.1

ν_{max} (cm^{-1}) (thin film): 3030, 2935, 1644

HRMS: Calculated for $C_{16}H_{16}NO$ 238.1226, found $[M+H]^+$: 238.1226 (0.0 ppm).



1-Benzylpyrrolidin-2-one 3e[9]

General procedure A was followed. Iodine (295 mg, 1.16 mmol) was added to a mixture of 1-benzylpyrrolidine (25 mg, 0.16 mmol) and sodium bicarbonate (130 mg, 1.55 mmol) in THF/H_2O (4.4/1.8 mL). Purification was carried out by silica gel chromatography using 30-85% TBME (with 1% 4M ammonia in methanol modifier)/cyclohexane as the eluent, to afford **3e** (18.7 mg, 69%) as an orange oil.*

LCMS (High pH, UV, ESI) R_t = 0.79 min, $[M+H]^+$ 176.1

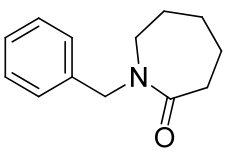
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.22-7.37 (m, 5H), 4.46 (s, 2H), 3.27 (t, *J*=7.1 Hz, 2H), 2.45 (t, *J*=8.1 Hz, 2H), 2.00 (quin, *J*=7.6 Hz, 2H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 174.9, 136.6, 128.6, 128.1, 127.5, 46.6, 30.9, 17.7

ν_{max} (cm^{-1}) (thin film): 2918, 1675

HRMS: Calculated for $C_{11}H_{14}NO$ 176.1070, found $[M+H]^+$: 176.1069 (-0.5 ppm).

**LCMS shows 9% area of an unknown artifact at 0.66 min, but no impurity was observed by NMR, so the peak was attributed to some small amount of a highly UV active impurity.*



1-Benzylazepan-2-one 3f

General procedure A was followed. Iodine (503 mg, 1.98 mmol) was added to a mixture of **2f** (50 mg, 0.26 mmol) and sodium bicarbonate (222 mg, 2.64 mmol) in THF/H_2O (7.6/3.0 mL). Purification was carried out by silica gel chromatography using 30-65% TBME (with 1% 4M ammonia in methanol modifier)/cyclohexane as the eluent, to afford **3f** (35.5 mg, 66%) as a brown oil.

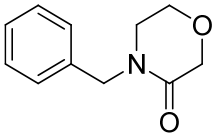
LCMS (High pH, UV, ESI) R_t = 0.95 min, $[M+H]^+$ 204.1

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.22-7.35 (m, 5H), 4.59 (s, 2H), 3.24-3.35 (m, 2H), 2.57-2.64 (m, 2H), 1.64-1.75 (m, 4H), 1.45-1.54 (m, 2H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 176.0, 137.9, 128.5, 128.1, 127.3, 51.1, 48.9, 37.2, 29.9, 28.1, 23.4

ν_{max} (cm^{-1}) (thin film): 2928, 2856, 1635

HRMS: Calculated for $C_{13}H_{18}NO$ 204.1383, found $[M+H]^+$: 204.1379 (-1.9 ppm).



4-Benzylmorpholin-3-one 3g

General procedure B was followed. Iodine (537 mg, 2.12 mmol) was added to a mixture of 4-benzylmorpholine (48.4 µL, 0.28 mmol) and sodium bicarbonate (237 mg, 2.82 mmol) in DMSO/H_2O (8.1/3.2 mL). Purification was carried out by silica gel chromatography using 30-80% TBME (with 2% triethylamine & 5% methanol modifier)/cyclohexane as the eluent, to afford **3g** (42.0 mg, 78%) as a colorless oil.*

LCMS (High pH, UV, ESI) R_t = 0.71 min, $[M+H]^+$ 192.0

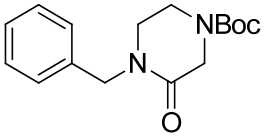
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.26-7.38 (m, 5H), 4.64 (s, 2H), 4.26 (s, 2H), 3.85 (t, *J*=5.3 Hz, 2H), 3.28 (t, *J*=5.0 Hz, 2H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 166.8, 136.1, 128.7, 128.3, 127.7, 68.2, 63.9, 49.5, 45.5

ν_{max} (cm^{-1}) (thin film): 2924, 2866, 1646

HRMS: Calculated for $C_{11}H_{14}NO_2$ 192.1019, found $[M+H]^+$: 192.1019 (-0.2 ppm).

**LCMS shows 8% area of an unknown artifact at 0.65 min, but no impurity was observed by NMR, so the peak was attributed to some small amount of a highly UV active impurity.*



***t*-Butyl 4-benzyl-3-oxopiperazine-1-carboxylate 3h**

General procedure A was followed. Iodine (381 mg, 1.50 mmol) was added to a mixture of *t*-butyl-4-benzylpiperazine-1-carboxylate (55 mg, 0.20 mmol) and sodium bicarbonate (168

mg, 2.00 mmol) in THF/H_2O (5.7/2.3 mL). ^{1}H NMR analysis of the crude material showed 56% conversion to **3h** based on the peak at 4.62 ppm, and 41% remaining starting material. Purification was carried out by silica gel chromatography using 0-35% TBME (with 1% triethylamine & 5% methanol modifier)/cyclohexane as the eluent, to afford **3h** (25.6 mg, 44%) as a white solid.

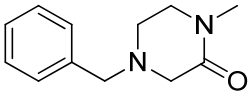
LCMS (High pH, UV, ESI) R_t = 1.04 min, $[M+H]^+$ 291.1

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.24-7.38 (m, 5H), 4.63 (s, 2H), 4.17 (s, 2H), 3.59 (t, *J*=5.4 Hz, 2H), 3.23-3.29 (m, 2H), 1.46 (s, 9H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 165.7, 153.8, 136.2, 128.8, 128.2, 127.8, 80.8, 50.0, 48.0, 45.6, 40.0, 28.3

ν_{max} (cm^{-1}) (thin film): 2979, 2928, 1684, 1637

HRMS: Calculated for $C_{16}H_{23}N_2O_3$ 291.1703, found $[M+H]^+$: 291.1709 (2.1 ppm).



4-Benzyl-1-methylpiperazin-2-one 3i

General procedure A was followed. Iodine (381 mg, 1.50 mmol) was added to a mixture of 1-benzyl-4-methylpiperazine (38 mg, 0.20 mmol) and sodium bicarbonate (168 mg, 2.00 mmol) in THF/H_2O (5.7/2.3 mL). ^{1}H NMR analysis of the crude material showed 45% conversion to **3i** based on the peak at 3.54 ppm, and 29% remaining starting material against 3,4,5-trichloropyridine (0.12 mmol) as a standard. Purification was carried out by silica gel chromatography using 30-100% TBME (with 1% triethylamine & 5% methanol modifier)/cyclohexane as the eluent, to afford **3i** (13.8 mg, 34%) as a colorless oil.*

LCMS (High pH, UV, ESI) R_t = 0.73 min, $[M+H]^+$ 205.2

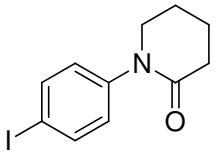
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.24-7.36 (m, 5H), 3.55 (s, 2H), 3.30 (t, *J*=5.3 Hz, 2H), 3.16 (s, 2H), 2.95 (s, 3H), 2.67 (t, *J*=5.6 Hz, 2H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 167.1, 136.9, 129.0, 128.4, 127.5, 61.9, 57.4, 49.2, 48.7, 33.8

ν_{max} (cm^{-1}) (thin film): 2924, 2807, 1645

HRMS: Calculated for $C_{12}H_{17}N_2O$ 205.1335, found $[M+H]^+$: 205.1326 (-4.7 ppm).

**LCMS shows 11% area of an unknown artifact at 0.64 min, but no impurity was observed by NMR, so the peak was attributed to some small amount of a highly UV active impurity.*



1-(4-Iodophenyl)piperidin-2-one 3j

General procedure A was followed. Iodine (381 mg, 1.50 mmol) was added to a mixture of 1-phenylpiperidine (32.0 μL, 0.20 mmol) and sodium bicarbonate (168 mg, 2.00 mmol) in THF/H_2O (5.7/2.3 mL). Purification was carried out by silica gel chromatography using 40-85% TBME (with 1% triethylamine & 5% methanol modifier)/cyclohexane as the eluent, to afford **3j** (32.3 mg, 54%) as white crystals.

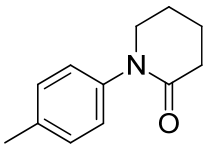
LCMS (High pH, UV, ESI) R_t = 0.97 min, $[M+H]^+$ 302.0

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.70 (d, *J*=8.6 Hz, 2H), 7.03 (d, *J*=8.6 Hz, 2H), 3.62 (t, *J*=5.9 Hz, 2H), 2.55 (t, *J*=6.0 Hz, 2H), 1.88-2.00 (m, 4H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 169.9, 143.1, 138.2, 128.1, 91.3, 51.4, 32.9, 23.5, 21.4

ν_{max} (cm^{-1}) (thin film): 2940, 2863, 1630

HRMS: Calculated for $C_{11}H_{13}INO$ 302.0036, found $[M+H]^+$: 302.0032 (-1.4 ppm).



1-(*p*-Tolyl)piperidin-2-one 3k

General procedure A was followed, except with the amendment that iodine was added to the reaction mixture in three portions of 2.5 equivalents after 0, 1 and 2 h. Iodine (381 mg, 1.50 mmol) was added in three portions to a mixture of 1-*p*-tolylpiperidine (35 mg, 0.20 mmol) and sodium bicarbonate (168 mg, 2.00 mmol) in THF/H_2O (5.7/2.3 mL). Purification was carried out by silica gel chromatography using 35-80% TBME (with 1% triethylamine, 5% methanol modifier)/cyclohexane as the eluent, to afford **3k** (21.2 mg, 56%) as a white solid.

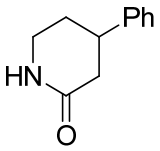
LCMS (High pH, UV, ESI) R_t = 0.85 min, $[M+H]^+$ 190.1

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.20 (d, *J*=8.3 Hz, 2H), 7.13 (d, *J*=8.3 Hz, 2H), 3.59-3.65 (m, 2H), 2.56 (t, *J*=5.6 Hz, 2H), 2.35 (s, 3H), 1.90-1.99 (m, 4H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.0, 140.9, 136.5, 129.8, 126.0, 51.8, 32.9, 23.6, 21.5, 21.0

ν_{max} (cm^{-1}) (thin film): 2954, 2856, 1636

HRMS: Calculated for $C_{12}H_{16}NO$ 190.1226, found $[M+H]^+$: 190.1229 (1.4 ppm).



4-Phenylpiperidin-2-one 3l

General procedure C was followed. Iodine (590 mg, 2.33 mmol) was added to a mixture of 4-phenylpiperidine (50 mg, 0.31 mmol) and sodium bicarbonate (260 mg, 3.10 mmol) in THF/H_2O (8.9/3.5 mL). ^{1}H NMR analysis of the crude material showed 51% conversion to **3l** based on the peak at 3.40 ppm, and 45% remaining starting material against 3,4,5-

trichloropyridine (0.07 mmol) as a standard. Purification was carried out by reverse phase chromatography with 0-60% Acetonitrile/10mM aqueous ammonium bicarbonate as the eluent, to afford **3l** (23.6 mg, 43%) as a white solid.*

LCMS (High pH, UV, ESI) R_t = 0.75 min, $[M+H]^+$ 176.1

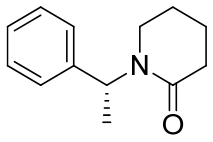
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36 (t, *J*=7.6 Hz, 2H), 7.20-7.31 (m, 3H), 6.64 (br. s., 1H), 3.37-3.47 (m, 2H), 3.12 (tdd, *J*=11.1, 5.4, 2.9 Hz, 1H), 2.71 (ddd, *J*=17.6, 5.4, 2.0 Hz, 1H), 2.51 (dd, *J*=17.9, 11.2 Hz, 1H), 2.06-2.15 (m, 1H), 1.89-2.02 (m, 1H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 172.1, 143.5, 128.8, 126.8, 126.6, 41.4, 38.7, 38.4, 29.6

ν_{max} (cm^{-1}) (thin film): 3286, 3193, 3029, 2872, 1651

HRMS: Calculated for $C_{11}H_{14}NO$ 176.1070, found $[M+H]^+$: 176.1074 (2.5 ppm).

**LCMS shows 6% area of an unknown artifact at 0.64 min, but no impurity was observed by NMR, so the peak was attributed to some small amount of a highly UV active impurity.*



(*R*)-1-(1-Phenylethyl)piperidin-2-one 3m

General procedure A was followed. Iodine (381 mg, 1.50 mmol) was added to a mixture of **2m** (38 mg, 0.20 mmol) and sodium bicarbonate (168 mg, 2.00 mmol) in THF/H_2O (5.7/2.3 mL). Purification was carried out by silica gel chromatography using 0-20% TBME (with 1% triethylamine & 5% methanol modifier)/cyclohexane as the eluent, to afford **3m** (21.6 mg, 53%) as an amber oil.*

LCMS (High pH, UV, ESI) R_t = 0.93 min, $[M+H]^+$ 204.2

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.22-7.40 (m, 5H), 6.16 (q, *J*=7.1 Hz, 1H), 3.11 (ddd, *J*=12.3, 7.9, 4.6 Hz, 1H), 2.76-2.83 (m, 1H), 2.49 (t, *J*=6.7 Hz, 2H), 1.70-1.81 (m, 3H), 1.57-1.68 (m, 1H), 1.51 (d, *J*=7.3 Hz, 3H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 169.6, 140.5, 128.4, 127.3, 127.2, 49.7, 41.4, 32.5, 23.2, 21.2, 15.3

ν_{max} (cm^{-1}) (thin film): 2940, 2867, 1616

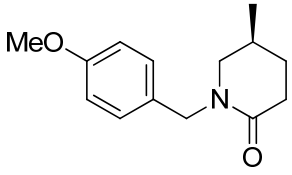
HRMS: Calculated for $C_{13}H_{18}NO$ 204.1383, found $[M+H]^+$: 204.1382 (-0.3 ppm)

Chiral HPLC (25 cm Chiralpak AS, 40% EtOH/*n*-heptane, 1.0 mL/min, detection at 215 nm) R_t = 3.9 min (major) and 8.0 min (minor), *ee* = 98.8%.

**LCMS shows 7% area of an unknown artifact at 1.09 min, but no impurity was observed by NMR, so the peak was attributed to some small amount of a highly UV active impurity.*

(*S*)-1-(4-Methoxybenzyl)-5-methylpiperidin-2-one 3n$^{\alpha}$ and (*S*)-1-(4-methoxybenzyl)-3-methylpiperidin-2-one 3n$^{\beta}$

General procedure A was followed. Iodine (381 mg, 1.50 mmol) was added to a mixture of **2n** (44 mg, 0.20 mmol) and sodium bicarbonate (168 mg, 2.00 mmol) in THF/H_2O (5.7/2.3 mL). Purification was carried out by silica gel chromatography using 0-50% TBME (with 1% triethylamine & 5% methanol modifier)/cyclohexane as the eluent, with 15 min isochratically at 40% TBME (with 1% triethylamine & 5% methanol modifier)/cyclohexane to afford **3n$^{\alpha}$** (24.9 mg, 53%) as a colorless oil, and **3n$^{\beta}$** (9.5 mg, 20%) as a colorless oil.



(*S*)-1-(4-Methoxybenzyl)-5-methylpiperidin-2-one 3n$^{\alpha}$

LCMS (High pH, UV, ESI) R_t = 0.95 min, $[M+H]^+$ 234.2

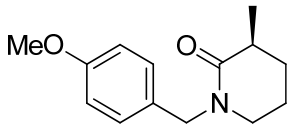
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.19 (d, *J*=8.6 Hz, 2H), 6.85 (d, *J*=8.6 Hz, 2H), 4.59 (d, *J*=14.9 Hz, 1H), 4.44 (d, *J*=14.1 Hz, 1H), 3.79 (s, 3H), 3.15 (ddd, *J*=11.9, 5.1, 1.8 Hz, 1H), 2.80 (dd, *J*=11.6, 10.4 Hz, 1H), 2.52 (ddd, *J*=17.7, 6.1, 3.3 Hz, 1H), 2.36-2.47 (m, 1H), 1.87-1.96 (m, 1H), 1.78-1.86 (m, 1H), 1.45 (dtd, *J*=13.1, 11.3, 5.9 Hz, 1H), 0.94 (d, *J*=6.6 Hz, 3H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 169.6, 158.9, 129.4, 119.6, 113.9, 55.2, 53.9, 49.5, 31.7, 29.5, 29.0, 18.5

ν_{max} (cm^{-1}) (thin film): 2928, 2837, 1634

HRMS: Calculated for $C_{14}H_{20}NO_2$ 234.1489, found $[M+H]^+$: 234.1492 (1.6 ppm)

Chiral HPLC (25 cm Whelk-o 1, 10% EtOH/*n*-heptane, 1.0 mL/min, detection at 215 nm) R_t = 39.6 min, *ee* = 100.0%.



(*S*)-1-(4-Methoxybenzyl)-3-methylpiperidin-2-one 3n$^{\beta}$

LCMS (High pH, UV, ESI) R_t = 0.97 min, $[M+H]^+$ 234.2

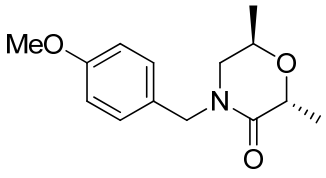
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.19 (d, *J*=8.6 Hz, 2H), 6.85 (d, *J*=8.6 Hz, 2H), 4.60 (d, *J*=14.4 Hz, 1H), 4.44 (d, *J*=14.4 Hz, 1H), 3.80 (s, 3H), 3.19 (dd, *J*=7.3, 5.1 Hz, 2H), 2.41-2.52 (m, 1H), 1.91-2.00 (m, 1H), 1.78-1.89 (m, 1H), 1.65-1.78 (m, 1H), 1.52 (dtd, *J*=12.9, 9.9, 3.3 Hz, 1H), 1.29 (d, *J*=7.1 Hz, 3H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 173.2, 158.9, 129.7, 129.4, 113.9, 55.3, 49.6, 47.4, 36.7, 29.6, 21.7, 18.1

ν_{max} (cm^{-1}) (thin film): 2931, 2867, 1631

HRMS: Calculated for $C_{14}H_{20}NO_2$ 234.1489, found $[M+H]^+$: 234.1495 (2.6 ppm)

Chiral HPLC (25 cm Chiralpak AS-H, 25% EtOH/*n*-heptane, 1.0 mL/min, detection at 215 nm) R_t = 5.3 min (minor) and 6.4 min (major), *ee* = 99.2%.



(2*R*,6*R*)-4-(4-Methoxybenzyl)-2,6-dimethylmorpholin-3-one 3o

General procedure B was followed. Iodine (381 mg, 1.50 mmol) was added to a mixture of **2o** (47 mg, 0.20 mmol) and sodium bicarbonate (168 mg, 2.00 mmol) in THF/H_2O (5.7/2.3 mL). Purification was carried out by silica gel chromatography using 0-30% (3:1 EtOAc/EtOH)/cyclohexane as the eluent, to afford **3o** (37.5 mg, 75%) as a colorless oil.

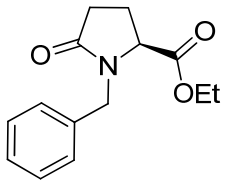
LCMS (High pH, UV, ESI) R_t = 0.87 min, $[M+H]^+$ 250.2

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.19 (d, *J*=8.8 Hz, 2H), 6.87 (d, *J*=8.6 Hz, 2H), 4.61 (d, *J*=14.4 Hz, 1H), 4.44 (d, *J*=14.2 Hz, 1H), 4.44 (q, *J*=6.9 Hz, 1H), 4.05 (sxt, *J*=6.3 Hz, 1H), 3.81 (s, 3H), 3.05-3.11 (m, 2H), 1.52 (d, *J*=7.1 Hz, 3H), 1.18 (d, *J*=6.4 Hz, 3H)

^{13}C NMR ($CDCl_3$, 151 MHz): δ 169.8, 159.2, 129.6, 128.5, 114.1, 71.9, 63.7, 55.3, 51.9, 49.1, 18.2, 17.7

ν_{max} (cm^{-1}) (thin film): 2977, 2934, 1645

HRMS: Calculated for $C_{14}H_{20}NO_3$ 250.1438, found $[M+H]^+$: 250.1429 (-3.6 ppm).



(*S*)-Ethyl 1-benzyl-5-oxopyrrolidine-2-carboxylate 3p[10]

General procedure A was followed. Iodine (381 mg, 1.50 mmol) was added to a mixture of *N*-benzyl-L-proline ethyl ester (44.5 µL, 0.20 mmol) and sodium bicarbonate (168 mg, 2.00 mmol) in THF/H_2O (5.7/2.3 mL). Purification was carried out by silica gel chromatography using 0-50% (3:1 EtOAc/EtOH) (with 1% triethylamine modifier)/cyclohexane as the eluent, to afford **3p** (42.4 mg, 86%) as a colorless oil.

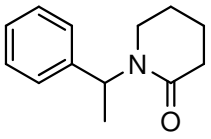
LCMS (Low pH, UV, ESI) R_t = 0.92 min, $[M+H]^+$ 248.2

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.25-7.34 (m, 3H), 7.19-7.23 (m, 2H), 5.02 (d, *J*=14.7 Hz, 1H), 4.06-4.19 (m, 2H), 4.00 (d, *J*=14.9 Hz, 1H), 3.96 (dd, *J*=9.0, 3.2 Hz, 1H), 2.51-2.62 (m, 1H), 2.41 (ddd, *J*=16.9, 9.5, 3.9 Hz, 1H), 2.18-2.30 (m, 1H), 2.07 (ddt, *J*=13.1, 9.6, 3.5 Hz, 1H), 1.24 (t, *J*=7.2 Hz, 3H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 175.0, 171.7, 135.9, 128.7, 128.5, 127.8, 61.4, 58.9, 45.6, 29.6, 22.8, 14.1

ν_{max} (cm^{-1}) (thin film): 2983, 1737, 1690

Chiral HPLC (25 cm Chiralcel OD-H, 5% EtOH/*n*-heptane, 1.0 mL/min, detection at 215 nm) R_t = 11.0 min (minor) and 12.4 (major), *ee* = 96.2%.



1-(1-Phenylethyl)piperidin-2-one 3s

General procedure A was followed. Iodine (381 mg, 1.50 mmol) was added to a mixture of **2s** (38 mg, 0.20 mmol) and sodium bicarbonate (168 mg, 2.00 mmol) in THF/H_2O (7.5/3.0 mL). Purification was carried out by silica gel chromatography using 10-60% TBME (with 5% MeOH, 1% triethylamine modifier)/cyclohexane as the eluant, but the resultant product was impure, so this material was re-purified by HpH MDAP (method C) to afford **3s** (11.1 mg, 27%) as an amber oil.*

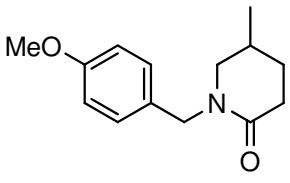
LCMS (High pH, UV, ESI) R_t = 0.94 min, $[M+H]^+$ 204.1

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.23-7.39 (m, 5H), 6.18 (q, *J*=7.1 Hz, 1H), 3.12 (ddd, *J*=12.3, 8.0, 4.4 Hz, 1H), 2.76-2.86 (m, 1H), 2.50 (t, *J*=6.7 Hz, 2H), 1.71-1.82 (m, 3H), 1.58-1.69 (m, 1H), 1.53 (d, *J*=7.1 Hz, 3H)

**LCMS shows 13% area of an unknown artifact at 0.66 min, but no impurity was observed by NMR, so the peak was attributed to some small amount of a highly UV active impurity.*

1-(4-Methoxybenzyl)-5-methylpiperidin-2-one 3t$^{\alpha}$ and 1-(4-methoxybenzyl)-3-methylpiperidin-2-one 3t$^{\beta}$

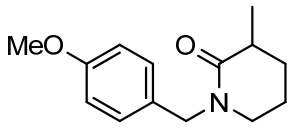
General procedure A was followed. Iodine (952 mg, 3.75 mmol) was added to a mixture of **2t** (110 mg, 0.50 mmol) and sodium bicarbonate (420 mg, 5.00 mmol) in THF/H_2O (14.3/5.7 mL). Purification was carried out by silica gel chromatography using 0-50% TBME (with 1% Et_3N & 5% MeOH modifier)/cyclohexane as the eluant, with 15 min isochratically at 40% TBME (with 1% triethylamine & 5% methanol modifier)/cyclohexane to afford **3t$^{\alpha}$** (21.6 mg, 19%) as a colorless oil, and **3t$^{\beta}$** (22.7 mg, 19%) as a colorless oil.*



1-(4-Methoxybenzyl)-5-methylpiperidin-2-one 3t$^{\alpha}$

LCMS (High pH, UV, ESI) R_t = 0.96 min, $[M+H]^+$ 234.1

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.19 (d, *J*=8.6 Hz, 2H), 6.86 (d, *J*=8.6 Hz, 2H), 4.59 (d, *J*=14.4 Hz, 1H), 4.44 (d, *J*=14.4 Hz, 1H), 3.80 (s, 3H), 3.16 (ddd, *J*=12.0, 5.1, 1.9 Hz, 1H), 2.81 (dd, *J*=11.9, 10.4 Hz, 1H), 2.53 (ddd, *J*=17.9, 5.8, 3.0 Hz, 1H), 2.42 (ddd, *J*=17.9, 11.4, 6.6 Hz, 1H), 1.79-1.98 (m, 2H), 1.45 (dtd, *J*=13.1, 11.3, 5.9 Hz, 1H), 0.95 (d, *J*=6.6 Hz, 3H).

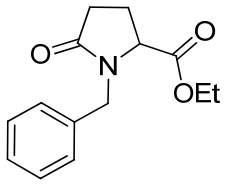


1-(4-methoxybenzyl)-3-methylpiperidin-2-one 3t$^{\beta}$

LCMS (High pH, UV, ESI) R_t = 0.97 min, $[M+H]^+$ 234.1

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.19 (d, *J*=8.6 Hz, 2H), 6.86 (d, *J*=8.8 Hz, 2H), 4.60 (d, *J*=14.4 Hz, 1H), 4.44 (d, *J*=14.4 Hz, 1H), 3.80 (s, 3H), 3.20 (dd, *J*=7.3, 5.1 Hz, 2H), 2.40-2.53 (m, 1H), 1.96 (dtd, *J*=12.9, 6.3, 3.3 Hz, 1H), 1.79-1.88 (m, 1H), 1.71 (dddt, *J*=17.2, 10.4, 6.9, 3.4 Hz, 1H), 1.47-1.57 (m, 1H), 1.29 (d, *J*=7.3 Hz, 3H).

**LCMS shows 13% area of an unknown artifact at 1.12 min, but no impurity was observed by NMR, so the peak was attributed to some small amount of a highly UV active impurity.*

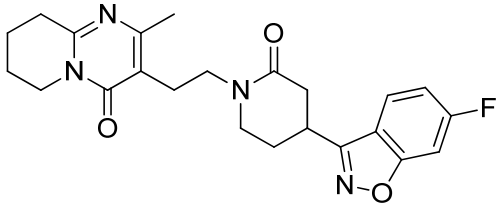


Ethyl 1-benzyl-5-oxopyrrolidine-2-carboxylate 3u

General procedure A was followed. Iodine (761 mg, 3.00 mmol) was added to a mixture of *N*-benzyl-L-proline ethyl ester (44.5 µL, 0.20 mmol), *N*-benzyl-D-proline ethyl ester (44.5 µL, 0.20 mmol) and sodium bicarbonate (336 mg, 4.00 mmol) in THF/H_2O (11.4/4.6 mL). Purification was carried out by silica gel chromatography using 0-50% (3:1 EtOAc/EtOH) (with 1% triethylamine modifier)/cyclohexane as the eluent, to afford **3u** (54.7 mg, 55%) as a colorless oil.

LCMS (Low pH, UV, ESI) R_t = 0.92 min, $[M+H]^+$ 248.2

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.27-7.36 (m, 3H), 7.20-7.24 (m, 2H), 5.03 (d, *J*=14.7 Hz, 1H), 4.08-4.21 (m, 2H), 4.01 (d, *J*=14.9 Hz, 1H), 3.97 (dd, *J*=9.0, 3.2 Hz, 1H), 2.53-2.63 (m, 1H), 2.42 (ddd, *J*=16.9, 9.5, 3.7 Hz, 1H), 2.19-2.31 (m, 1H), 2.08 (ddt, *J*=13.1, 9.6, 3.5 Hz, 1H), 1.25 (t, *J*=7.1 Hz, 3H).



Oxo-risperidone 5a

General procedure B was followed. Iodine (190 mg, 0.75 mmol) was added to a mixture of rispoeridone (41 mg, 0.10 mmol) and sodium bicarbonate (84 mg, 1.00 mmol) in THF/H_2O (2.9/1.1 mL). Purification was carried out by high pH MDAP (Method B), to afford **5a** (24.1 mg, 57%) as a pale brown solid.

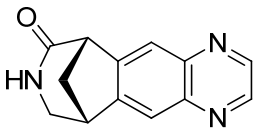
LCMS (High pH, UV, ESI) R_t = 0.88 min, $[M+H]^+$ 425.3

^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.06 (dd, *J*=8.7, 5.3 Hz, 1H), 7.70 (dd, *J*=9.3, 2.2 Hz, 1H), 7.30 (td, *J*=9.0, 2.2 Hz, 1H), 3.76-3.81 (m, 2H), 3.69-3.76 (m, 1H), 3.46-3.55 (m, 1H), 3.33-3.42 (m, 3H), 2.76 (t, *J*=6.6 Hz, 2H), 2.70 (dd, *J*=5.7, 1.3 Hz, 1H), 2.62-2.68 (m, 2H), 2.55-2.62 (m, 1H), 2.26-2.34 (m, 1H), 2.23 (s, 3H), 2.02-2.13 (m, 1H), 1.81-1.89 (m, 2H), 1.72-1.80 (m, 2H)

^{13}C NMR (DMSO-d_6, 126 MHz): δ 167.2, 163.6 (d, *J*=13.9 Hz), 163.2, 163.0, 161.2 (d, *J*=231.2 Hz), 158.8, 158.8, 156.9, 124.3 (d, *J*=12.0 Hz), 117.4 (d, *J*=3.7 Hz), 113.1 (d, *J*=25.0 Hz), 97.9 (d, *J*=27.7 Hz), 46.6, 45.4, 42.6, 36.1, 31.2, 30.8, 27.5, 24.0, 21.8, 21.3, 19.0

ν_{max} (cm^{-1}) (thin film): 3060, 2959, 1658, 1635

HRMS: Calculated for $C_{23}H_{26}F\ N_4O_3$ 425.1983, found $[M+H]^+$: 425.1977 (-1.6 ppm).



Oxo-varenicline 5b

General procedure A was followed. Iodine (190 mg, 0.75 mmol) was added to a mixture of varenicline hydrochloride (25 mg, 0.10 mmol) and sodium bicarbonate (84 mg, 1.00 mmol) in THF/H_2O (2.9/1.1 mL). Purification was carried out by reverse phase flash chromatography using 0-30% Acetonitrile/10 mM aqueous ammonium bicarbonate to afford **5b** (11.9 mg, 53%) as a white solid.

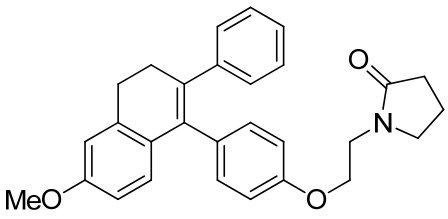
LCMS (High pH, UV, ESI) R_t = 0.56 min, $[M+H]^+$ 226.2

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.81 (dd, *J*=9.3, 2.0 Hz, 2H), 8.04 (d, *J*=13.0 Hz, 2H), 5.14 (br. s., 1H), 3.91 (d, *J*=3.9 Hz, 1H), 3.84 (ddd, *J*=11.1, 4.3, 1.2 Hz, 1H), 3.72 (t, *J*=4.3 Hz, 1H), 3.37 (ddt, *J*=11.1, 2.4, 1.0 Hz, 1H), 2.59-2.66 (m, 1H), 2.51 (d, *J*=11.5 Hz, 1H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 171.9, 147.8, 146.8, 144.5, 144.3, 143.5, 143.3, 123.1, 122.6, 49.2, 48.2, 38.9, 37.7

ν_{max} (cm^{-1}) (thin film): 3196, 2969, 1657

HRMS: Calculated for $C_{13}H_{12}N_3O$ 226.0975, found $[M+H]^+$: 226.0977 (0.8 ppm).



Oxo-nafoxidine 5c

General procedure A was followed. Iodine (95 mg, 0.38 mmol) was added to a mixture of nafoxidine hydrochloride (23 mg, 0.05 mmol) and sodium bicarbonate (42 mg, 0.50 mmol) in THF/H_2O (1.4/0.6 mL). Purification was carried out by silica gel chromatography using 10-45% EtOAc/cyclohexane as the eluent, to afford **5c** (20.2 mg, 92%) as a white solid.*

LCMS (High pH, UV, ESI) R_t = 1.42 min, $[M+H]^+$ 440.2

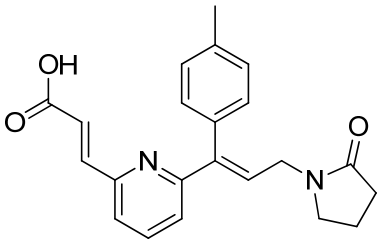
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.09-7.14 (m, 2H), 7.00-7.07 (m, 3H), 6.97 (d, *J*=8.8 Hz, 2H), 6.70-6.80 (m, 4H), 6.60 (dd, *J*=8.6, 2.8 Hz, 1H), 4.09 (t, *J*=5.2 Hz, 2H), 3.81 (s, 3H), 3.67 (t, *J*=5.2 Hz, 2H), 3.59 (t, *J*=7.1 Hz, 2H), 2.95 (dd, *J*=8.6, 7.1 Hz, 2H), 2.78 (dd, *J*=8.6, 6.3 Hz, 2H), 2.40 (t, *J*=8.1 Hz, 2H), 2.03 (quin, *J*=7.6 Hz, 2H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 175.3, 158.5, 157.0, 143.3, 137.7, 134.6, 134.5, 132.6, 132.2, 130.4, 128.3, 127.6, 127.4, 125.7, 113.9, 113.2, 110.8, 66.5, 55.3, 49.0, 42.5, 30.8, 30.8, 29.0, 18.2

ν_{max} (cm^{-1}) (thin film): 2930, 2833, 1681

HRMS: Calculated for $C_{29}H_{30}NO_3$ 440.2220, found $[M+H]^+$: 440.2219 (-0.4 ppm).

**^{1}H NMR analysis showed presence of 4wt% of an oxidized product – likely to arise from aromatization of the fused cyclohexene ring*



Oxo-acrivastine 5d

General procedure A was followed. Iodine (190 mg, 0.75 mmol) was added to a mixture of acrivastine (35 mg, 0.10 mmol) and sodium bicarbonate (84 mg, 1.00 mmol) in THF/H_2O (2.9/1.1 mL). ^{1}H NMR analysis of the crude material showed 56% conversion to **5d** based on the peak at 2.21 ppm against hexamethyldisiloxane (24.0 μmol) as a standard. Purification was carried out by reverse phase preparative HPLC using 15-55% MeCN (with 0.1% ammonia modifier)/10 mM aqueous ammonium bicarbonate as the eluent, to afford **5d** (5.6 mg, 15%) as a brown solid.*

LCMS (High pH, UV, ESI) R_t = 0.74 min, $[M+H]^+$ 363.2

^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.74 (t, *J*=7.6 Hz, 1H), 7.57 (d, *J*=8.1 Hz, 1H), 7.57 (d, *J*=15.7 Hz, 1H), 7.29 (d, *J*=8.1 Hz, 2H), 7.14 (d, *J*=8.1 Hz, 2H), 6.91 (d, *J*=7.6 Hz, 1H), 6.83

(d, *J*=15.7 Hz, 1H), 6.78 (t, *J*=6.9 Hz, 1H), 3.85 (d, *J*=7.1 Hz, 2H), 3.30 (t, *J*=7.1 Hz, 3H), 2.38 (s, 3H), 2.21 (t, *J*=8.1 Hz, 2H), 1.91 (quin, *J*=7.5 Hz, 2H)

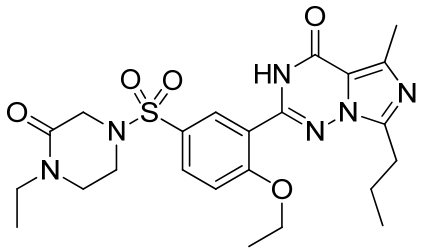
^{13}C NMR (DMSO-d_6, 126 MHz): δ 174.1, 167.6[a] 157.4, 152.3, 143.3, 142.7, 138.3, 137.3, 134.5, 129.8, 129.7, 127.9, 123.3, 122.9, 55.4, 46.8, 41.5, 30.7, 21.3, 17.8

[a]Peak not seen in 1D ^{13}C spectrum, coupling seen to this chemical shift in HMBC.

ν_{max} (cm^{-1}) (thin film): 3380 (br), 2923, 1678, 1643

HRMS: Calculated for $C_{22}H_{23}N_2O_3$ 363.1703, found $[M+H]^+$: 363.1703 (-0.1 ppm).

**LCMS shows 7% area of an unknown artifact at 0.73 min, but no impurity was observed by NMR, so the peak was attributed to some small amount of a highly UV active impurity.*



Oxo-vardenafil 5e

General procedure B was followed. Iodine (190 mg, 0.75 mmol) was added to a mixture of vardenafil hydrochloride trihydrate (58 mg, 0.10 mmol) and sodium bicarbonate (84 mg, 1.00 mmol) in THF/H_2O (2.9/1.1 mL). ^{1}H NMR analysis of the crude material showed 57% conversion to **5e** based on the peak at 3.66 ppm against hexamethyldisiloxane (24.0 μmol) as a standard. Purification was carried out by high pH MDAP (Method C), to afford **5e** (13.2 mg, 26%) as a white solid.

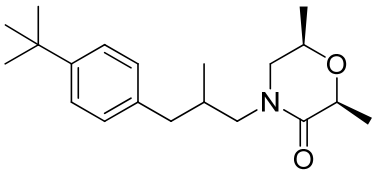
LCMS (High pH, UV, ESI) R_t = 0.93 min, $[M+H]^+$ 503.3

^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.70 (br. s., 1H), 8.48 (d, *J*=2.4 Hz, 1H), 7.92 (dd, *J*=8.8, 2.4 Hz, 1H), 7.19 (d, *J*=8.8 Hz, 1H), 4.35 (q, *J*=6.9 Hz, 2H), 3.72 (s, 2H), 3.34-3.47 (m, 6H), 3.01 (t, *J*=7.6 Hz, 2H), 2.64 (s, 3H), 1.89 (dq, *J*=14.9, 7.5 Hz, 2H), 1.60 (t, *J*=7.0 Hz, 3H), 1.09 (t, *J*=7.2 Hz, 3H), 1.04 (t, *J*=7.3 Hz, 3H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 163.1, 160.3, 154.5, 146.5, 144.3, 140.4, 132.5, 130.3, 128.4, 119.1, 113.6, 113.4, 66.2, 48.8, 45.5, 43.1, 41.7, 27.9, 20.9, 14.5, 14.4, 14.0, 12.0

ν_{max} (cm^{-1}) (thin film): 3533 (br), 3325, 2968, 1697, 1641

HRMS: Calculated for $C_{23}H_{31}N_6O_5S$ 503.2071, found $[M+H]^+$: 503.2073 (0.3 ppm).



Oxo-fenpropimorph (diastereomeric mixture) 5f

General procedure B was followed. Iodine (190 mg, 0.75 mmol) was added to a mixture of fenpropimorph (30 mg, 0.10 mmol) and sodium bicarbonate (84 mg, 1.00 mmol) in THF/H_2O (2.9/1.1 mL). Purification was carried out by silica gel chromatography using 0-25% TBME (with 1% triethylamine & 5% methanol modifier)/cyclohexane as the eluent, to afford **5f** (17.6 mg, 55%) (dr 1.2:1) as a colorless oil.

LCMS (High pH, UV, ESI) R_t = 1.38 min, $[M+H]^+$ 318.3

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.30 (dd, *J*=8.4, 2.3 Hz, 4H), 7.09 (d, *J*=8.3 Hz, 4H), 4.20 (q, *J*=6.8 Hz, 1H), 4.13 (q, *J*=6.8 Hz, 1H), 3.76-3.85 (m, 1H), 3.58-3.67 (m, 1H), 3.14-3.41 (m, 6H), 3.07 (dd, *J*=12.0, 2.7 Hz, 1H), 2.99 (dd, *J*=11.7, 2.7 Hz, 1H), 2.56-2.66 (m, 2H), 2.44-2.52 (m, *J*=7.3 Hz, 1H), 2.39 (dd, *J*=13.7, 8.6 Hz, 1H), 2.18 (dq, *J*=14.9, 7.6 Hz, 2H), 1.45 (dd, *J*=6.8, 2.4 Hz, 6H), 1.32 (s, 18H), 1.23 (dd, *J*=15.4, 6.1 Hz, 6H), 0.89 (t, *J*=7.0 Hz, 6H)

^{13}C NMR ($CDCl_3$, 151 MHz): δ 170.0, 169.9, 148.8, 148.7, 137.3, 137.2, 128.6, 128.5, 125.1, 125.1, 74.2, 74.2, 68.9, 68.6, 53.8, 53.4, 52.7, 52.3, 40.8, 40.3, 34.3, 32.9, 32.6, 31.4, 18.5, 18.4, 18.4, 18.3, 17.6, 17.5

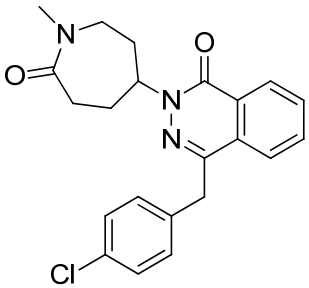
ν_{max} (cm^{-1}) (thin film): 2962, 2870, 1652

HRMS: Calculated for $C_{20}H_{32}NO_2$ 318.2428, found $[M+H]^+$: 318.2429 (0.5 ppm).

7-Oxo-azelastine 5g$^{\alpha}$ and 2-oxo-azelastine 5g$^{\beta}$

General procedure A was followed. Iodine (190 mg, 0.75 mmol) was added to a mixture of azelastine hydrochloride (42 mg, 0.10 mmol) and sodium bicarbonate (84 mg, 1.00 mmol) in THF/H_2O (2.9/1.1 mL). Purification was carried out by silica gel chromatography using 0-25% (3:1 EtOAc/EtOH, with 1% triethylamine modifier)/cyclohexane as the eluent, to afford a co-eluting mixture of **5g$^{\alpha}$** and **5g$^{\beta}$** (26.9 mg, 68%*), in 4.3:1 ratio of **5g$^{\alpha}$: 5g$^{\beta}$**, determined by ^{1}H NMR. The isomers were only separable by high pH MDAP (Method C) to afford **5g$^{\alpha}$** (14.8 mg, 37%) as a white solid and **5g$^{\beta}$** (2.2 mg, 6%) as a white solid.

**Based on 30.6 mg isolated yield, with 12.1 wt% cyclohexane impurity by ^{1}H NMR.*



7-Oxo-azelastine 5g$^{\alpha}$

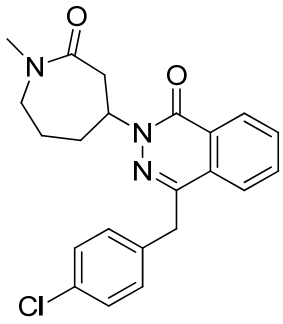
LCMS (High pH, UV, ESI) R_t = 1.10 min, $[M+H]^+$ 396.2

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.44-8.52 (m, 1H), 7.66-7.77 (m, 3H), 7.26-7.30 (m, 2H), 7.19 (d, *J*=8.3 Hz, 2H), 5.27 (tt, *J*=11.4, 4.4 Hz, 1H), 4.27 (s, 2H), 3.76 (dd, *J*=15.7, 10.3 Hz, 1H), 3.33 (ddd, *J*=15.5, 6.2, 1.3 Hz, 1H), 3.08 (s, 3H), 2.64-2.78 (m, 2H), 2.11-2.25 (m, 2H), 2.02-2.11 ppm (m, 2H)

^{13}C NMR ($CDCl_3$, 151 MHz): δ 174.7, 158.5, 144.8, 136.2, 133.0, 132.7, 131.3, 129.8, 128.9, 128.6, 128.1, 127.6, 124.7, 57.3, 48.5, 38.3, 35.8, 33.8, 32.4, 28.1

ν_{max} (cm^{-1}) (thin film): 2939, 1635

HRMS: Calculated for $C_{22}H_{23}ClN_3O_2$ 396.1473, found $[M+H]^+$: 396.1485 (3.0 ppm).



2-Oxo-azelastine 5g$^{\beta}$

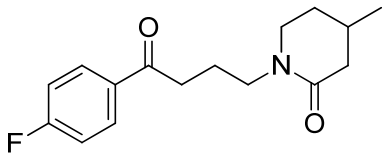
LCMS (High pH, UV, ESI) R_t = 1.16 min, $[M+H]^+$ 396.2

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.43-8.49 (m, 1H), 7.69-7.74 (m, 2H), 7.64-7.69 (m, 1H), 7.28 (d, *J*=8.6 Hz, 2H), 7.19 (d, *J*=8.6 Hz, 2H), 5.22-5.31 (m, 1H), 4.26 (s, 2H), 3.66 (dd, *J*=14.9, 10.3 Hz, 1H), 3.26-3.37 (m, 2H), 3.05 (s, 3H), 2.76 (dt, *J*=13.8, 1.9 Hz, 1H), 2.15-2.23 (m, 1H), 1.95-2.11 (m, 2H), 1.74-1.87 (m, 1H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 172.4, 158.2, 144.6, 136.2, 132.9, 132.6, 131.3, 129.8, 128.8, 128.6, 128.2, 127.6, 124.7, 52.3, 50.7, 42.6, 38.4, 36.0, 34.9, 26.2

ν_{max} (cm^{-1}) (thin film): 2926, 1646

HRMS: Calculated for $C_{22}H_{23}ClN_3O_2$ 39.1473, found $[M+H]^+$: 396.1475 (0.3 ppm).



Oxo-melperone 5h

General procedure A was followed. Iodine (190 mg, 0.75 mmol) was added to a mixture of melperone hydrochloride (30 mg, 0.10 mmol) and sodium bicarbonate (84 mg, 1.00 mmol) in THF/H_2O (2.9/1.1 mL). Purification was carried out by silica gel chromatography using 0-60% TBME (with 1% triethylamine, 5% methanol modifier)/cyclohexane as the eluent, to afford **5h** (23.0 mg, 83%) as a white solid.

LCMS (High pH, UV, ESI) R_t = 1.00 min, $[M+H]^+$ 278.2

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.97 (dd, *J*=9.0, 5.4 Hz, 2H), 7.11 (t, *J*=8.6 Hz, 2H), 3.47-3.55 (m, 1H), 3.36-3.44 (m, 1H), 3.32 (d, *J*=4.0 Hz, 1H), 3.29-3.31 (m, 1H), 2.97 (t, *J*=7.1 Hz, 2H), 2.40 (dtd, *J*=11.9, 10.1, 1.8 Hz, 1H), 1.99 (quind, *J*=7.1, 1.8 Hz, 2H), 1.81-1.93 (m, 3H), 1.36-1.48 (m, 1H), 0.97 (d, *J*=6.3 Hz, 3H)

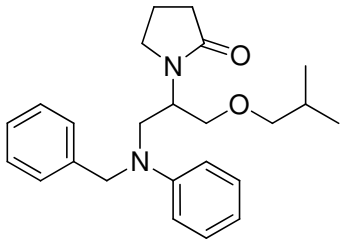
^{13}C NMR ($CDCl_3$, 101 MHz): δ 198.0, 169.7, 165.7 (d, *J*=258.0 Hz), 133.3 (d, *J*=3.2 Hz), 130.7 (d, *J*=9.6 Hz), 115.6 (d, *J*=22.4 Hz), 46.8, 46.0, 40.5, 35.6, 31.0, 27.9, 21.5, 21.0

ν_{max} (cm^{-1}) (thin film): 2950, 2869, 1684, 1627

HRMS: Calculated for $C_{16}H_{21}FNO_2$ 278.1551, found $[M+H]^+$: 278.1553 (0.7 ppm).

Oxo-bepridil 5i and oxo-iodo-bepridil 15

General procedure A was followed. Iodine (190 mg, 0.75 mmol) was added to a mixture of bepridil hydrochloride hydrate (42 mg, 0.10 mmol) and sodium bicarbonate (84 mg, 1.00 mmol) in THF/H_2O (2.9/1.1 mL). ^{1}H NMR analysis of the crude material showed 81% conversion to **5i** and 17% conversion to **15** based on peaks at 6.85 and 6.63 ppm, respectively, against hexamethyldisiloxane (24.0 μmol) as a standard. Purification was attempted initially by silica gel chromatography using 0-50% EtOAc (with 1% 4M ammonia in methanol modifier)/cyclohexane, but the products **5i** and **15** co-eluted. Separation could only be achieved by high pH MDAP (Method E), to afford **5i** (11.5 mg, 30%) as a yellow oil, and **15** (2.6 mg, 5%) as a yellow oil.



Oxo-bepridil 5i

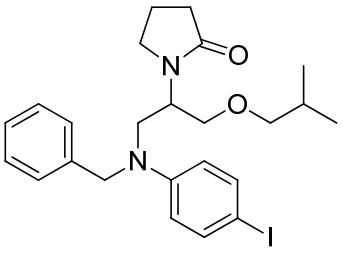
LCMS (High pH, UV, ESI) R_t = 1.40 min, $[M+H]^+$ 381.3

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.29 (t, *J*=6.8 Hz, 2H), 7.15-7.24 (m, 5H), 6.84 (d, *J*=8.3 Hz, 2H), 6.71 (t, *J*=7.2 Hz, 1H), 4.66 (d, *J*=16.7 Hz, 1H), 4.49-4.58 (m, 2H), 3.66 (dd, *J*=7.2, 2.9 Hz, 2H), 3.61 (q, *J*=5.1 Hz, 1H), 3.52 (dd, *J*=10.1, 4.0 Hz, 1H), 3.40-3.47 (m, 1H), 3.34 (td, *J*=9.0, 5.2 Hz, 1H), 3.11-3.20 (m, 2H), 2.15-2.34 (m, 2H), 1.80-1.93 (m, 2H), 1.66-1.77 (m, 1H), 0.91 (dd, *J*=6.7, 0.9 Hz, 6H)

^{13}C NMR ($CDCl_3$, 101 MHz): δ 175.4, 148.6, 138.5, 129.2, 128.5, 126.8, 126.7, 117.1, 113.4, 78.0, 69.8, 54.1, 49.9, 49.6, 45.6, 31.1, 28.6, 19.4, 18.4

ν_{max} (cm^{-1}) (thin film): 2957, 2872, 1679

HRMS: Calculated for $C_{24}H_{33}N_2O_2$ 381.2537, found $[M+H]^+$: 381.2538 (0.4 ppm).



Oxo-iodo-bepridil 15

LCMS (High pH, UV, ESI) R_t = 1.53 min, $[M+H]^+$ 507.1*

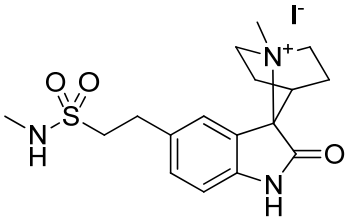
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.43 (d, *J*=9.1 Hz, 2H), 7.29 (t, *J*=7.6 Hz, 2H), 7.23 (t, *J*=7.1 Hz, 1H), 7.16 (d, *J*=7.1 Hz, 2H), 6.63 (d, *J*=9.1 Hz, 2H), 4.62 (d, *J*=17.2 Hz, 1H), 4.51 (d, *J*=16.9 Hz, 1H), 4.44-4.49 (m, 1H), 3.64 (d, *J*=7.1 Hz, 2H), 3.59 (dd, *J*=10.1, 5.3 Hz, 1H), 3.51 (dd, *J*=10.1, 4.0 Hz, 1H), 3.31-3.47 (m, 2H), 3.12-3.20 (m, 2H), 2.16-2.34 (m, 2H), 1.81-1.94 (m, 2H), 1.70-1.80 (m, 1H), 0.91 (d, *J*=6.8 Hz, 6H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 175.4, 147.9, 137.9, 137.8, 128.6, 127.0, 126.7, 115.6, 110.0, 78.0, 69.6, 54.1, 49.8, 49.7, 45.7, 31.0, 28.6, 19.4, 18.4

ν_{max} (cm^{-1}) (thin film): 2956, 2870, 1677

HRMS: Calculated for $C_{24}H_{32}IN_2O_2$ 507.1503, found $[M+H]^+$: 507.1518 (3.0 ppm).

LCMS analysis shows 12% area of an unknown impurity with a mass loss of 90 relative to **15 – possibly resulting from some debenzylation of **15** formed in LCMS. No impurity observed in NMR, so likely instability in LCMS.*



1-Methyl-5'-(2-(*N*-methylsulfamoyl)ethyl)-2'-oxo-1-azaspiro [bicyclo[2.2.1]heptane-7,3'-indolin]-1-ium iodide 14

General procedure C was followed. Iodine (190 mg, 0.75 mmol) was added to a mixture of naratriptan hydrochloride (37 mg, 0.10 mmol) and sodium bicarbonate (84 mg, 1.00 mmol) in THF/H_2O (2.9/1.1 mL). ^{1}H NMR analysis of a 0.6 mL aliquot from a reaction mixture using d^8-THF/D_2O as the solvent system showed 52% conversion to **14** based on the peak at 2.64 ppm against hexamethyldisiloxane (9.4 μmol) as a standard. Purification was carried out by reverse phase preparative HPLC using 0-25% MeCN (with 0.1% ammonia modifier)/10 mM aqueous ammonium bicarbonate as the eluent, to afford **14** (11.5 mg, 24%) as a white solid.

LCMS (High pH, UV, ESI) R_t = 0.52 min, $[M]^+$ 350.1

^{1}H NMR (D_2O, 500 MHz): δ 7.34 (d, *J*=8.0 Hz, 2H), 6.98 (d, *J*=8.2 Hz, 1H), 4.38 (tt, *J*=11.3, 4.4 Hz, 1H), 3.91 (tt, *J*=11.5, 4.7 Hz, 1H), 3.72-3.80 (m, 1H), 3.66 (ddd, *J*=10.8, 9.1, 5.1 Hz, 1H), 3.46 (td, *J*=7.6, 1.8 Hz, 2H), 3.07 (t, *J*=7.7 Hz, 2H), 3.01 (ddt, *J*=11.8, 8.0, 3.8 Hz, 1H), 2.89-2.94 (m, 1H), 2.82-2.89 (m, 1H), 2.76 (s, 3H), 2.69 (s, 3H), 2.12 (ddd, *J*=13.4, 8.4, 5.1 Hz, 1H), 1.91 (ddd, *J*=12.9, 8.0, 4.3 Hz, 1H)*

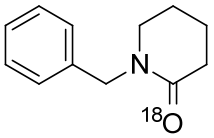
^{13}C NMR (D_2O, 101 MHz): δ 188.5, 136.1, 135.5, 131.4, 121.4, 115.3, 85.5, 66.0, 65.9, 53.9, 45.1, 43.0, 41.6, 31.6, 31.3, 31.1, 29.7

ν_{max} (cm^{-1}) (thin film): 3500-3000 (br), 2973, 1718, 1641

HRMS: Calculated for $C_{17}H_{24}N_3O_3S$ 350.1533, found $[M]^+$: 350.1537 (1.3 ppm).

**N-H signals not observed in D_2O*

Isotopic-labeling experiments



***^{18}O*-1-Benzylpiperidin-2-one ^{18}O-3a**

General procedure A was followed. Iodine (190 mg, 0.75 mmol) was added to a mixture of 1-benzylpiperidine (18.5 μL, 0.10 mmol) and sodium bicarbonate (84 mg, 1.00 mmol) in THF/$H_2{}^{18}O$ (2.9/1.1 mL). Purification was carried out by silica gel chromatography using 30-85% TBME (with 1% 4M ammonia in methanol modifier)/cyclohexane as the eluent, to afford ^{18}O-**3a** (19.2 mg, 100%) as a yellow oil.*

LCMS (High pH, UV, ESI) R_t = 0.86 min, $[M+H]^+$ 192.2 (100%), 190.2 (3%)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.30-7.36 (m, 2H), 7.24-7.30 (m, 3H), 4.61 (s, 2H), 3.21 (t, *J*=6.0 Hz, 2H), 2.48 (t, *J*=6.5 Hz, 2H), 1.73-1.85 (m, 4H)

HRMS: Calculated for $C_{12}H_{16}N^{18}O$ 192.1269, found $[M+H]^+$: 192.1266 (-1.6 ppm).

**LCMS and ^{1}H NMR analysis showed presence of 7% of an iodinated lactam by-product, which could not be separated*

Studies with sodium acetate: general procedure A was followed for all cases, although the reaction mixtures were not purified.

- with NaOAc/H_2O

  Iodine (381 mg, 1.50 mmol) was added to a mixture of 1-benzylpiperidine (36.9 μL, 0.20 mmol) and sodium acetate (164 mg, 2.00 mmol) in THF/H_2O (5.7/2.3 mL).

  LCMS (High pH, UV, ESI) R_t = 0.86 min (**3a**), $[M+H]^+$ 190.1 (100%).

- with $Na^{18}OAc$/H_2O

  Iodine (381 mg, 1.50 mmol) was added to a mixture of 1-benzylpiperidine (36.9 μL, 0.20 mmol) and sodium acetate (164 mg, 2.00 mmol) in THF/H_2O (5.7/2.3 mL).

LCMS (High pH, UV, ESI) R_t = 0.85 min (**3a**), $[M+H]^+$ 190.1 (100%).

- with $Na^{18}OAc/H_2{}^{18}O$

  Iodine (381 mg, 1.50 mmol) was added to a mixture of 1-benzylpiperidine (36.9 μL, 0.20 mmol) and sodium acetate (164 mg, 2.00 mmol) in THF/H_2O (5.7/2.3 mL).

  LCMS (High pH, UV, ESI) R_t = 0.86 min (**3a**), $[M+H]^+$ 192.1 (100%).

Investigating late-stage oxidation under Milstein conditions[11]

Stock solutions of Acridine Ru complex **1** (6 mg, 0.01 mmol) in 1,4-dioxane (1.5 mL) and NaOH (40 mg, 1.01 mmol) in water (1.5 mL) were prepared. 1.0 extra equivalent of NaOH was added compared to the literature conditions in order to neutralize the HCl salt of the drug substrates. A 0.15 mL aliquot of the catalyst solution and a 0.15 mL aliquot of the NaOH solution were added to either melperone hydrochloride (30 mg, 0.10 mmol) or bepridil hydrochloride hydrate (42 mg, 0.10 mmol). The reaction mixture was heated to 150 °C for 48 h. The reaction mixture was then allowed to cool to room temperature, before diluting in water (1 mL) and extracting into DCM (2 x 1.5 mL). The crude solution was concentrated under flow of nitrogen, and the crude material was redissolved in $CDCl_3$ and analyzed by ^1H NMR.

^1H NMR analysis of the crude materials showed:

- 4% conversion to **5h** and 93% remaining starting material based on peaks at 3.40 ppm and 7.10 ppm, respectively, against 3,4,5-trichloropyridine (0.086 mmol) as a standard;
- 8% conversion to **5i** and 91% remaining starting material based on peaks at 2.24 ppm and 6.79 ppm, respectively, against 3,4,5-trichloropyridine (0.119 mmol) as a standard.

Investigating late-stage oxidation under Emmert conditions[12]

A stock solution of $FeCl_3.6H_2O$ (14 mg, 0.05 mmol) in pyridine (3.60 mL) was prepared. A 0.36 mL aliquot of this solution was added to a mixture of 2-picolinic acid (0.6 mg, 5.0 μmol), *tert*-butyl benzoperoxoate (57.0 μL, 0.30 mmol), water (16.2 μL, 0.90 mmol), and either melperone hydrochloride (30 mg, 0.10 mmol) or bepridil hydrochloride hydrate (42 mg, 0.10 mmol), and the reaction mixture was stirred at 50 °C for 24 h. The solvent was removed and the crude residue was redissolved in $CDCl_3$ and analyzed by ^1H NMR.

^1H NMR analysis of the crude materials showed:

- 0% conversion to **5h** against 3,4,5-trichloropyridine (0.056 mmol) as a standard;
- 0% conversion to **5i** against 3,4,5-trichloropyridine (0.094 mmol) as a standard.

Investigating late-stage oxidation under classical RuIVO2/NaIO4 conditions[13]

Either melperone hydrochloride (30 mg, 0.10 mmol) or bepridil hydrochloride hydrate (42 mg, 0.10 mmol) was added to a mixture of ruthenium(IV) oxide (1.3 mg, 10.0 μmol) and sodium periodate (135.0 mg, 0.63 mmol) in ethyl acetate (0.24 mL) and water (0.94 mL), and the reaction mixture was stirred at RT for 64 h. The reaction mixture was diluted with water (10 mL) and extracted into EtOAc (3 x 10 mL). The combined organic layers were passed through a hydrophobic frit, and concentrated *in vacuo*. The crude residue was redissolved in $CDCl_3$ and analyzed by ^1H NMR.

^{1}H NMR analysis of the crude materials showed:

- 0% conversion to **5h** against 3,4,5-trichloropyridine (0.094 mmol) as a standard;
- 0% conversion to **5i** against 3,4,5-trichloropyridine (0.066 mmol) as a standard.

Investigating late-stage oxidation under hypervalent iodine conditions[14]

Either melperone hydrochloride (30 mg, 0.10 mmol) or bepridil hydrochloride hydrate (42 mg, 0.10 mmol) was added to a solution of iodobenzene diacetate (71 mg, 0.22 mmol) in THF (0.36 mL). Water (0.14 mL) was added, and the reaction mixture stirred at RT for 16 h. The solvent was evaporated under flow of nitrogen and the crude residue was redissolved in $CDCl_3$ and analyzed by 1H NMR.

^{1}H NMR analysis of the crude materials showed:

- 0% conversion to **5h** against 3,4,5-trichloropyridine (0.067 mmol) as a standard;
- 0% conversion to **5i** against 3,4,5-trichloropyridine (0.080 mmol) as a standard.

Water was used as a co-solvent in order to try to form phenyliodosobenzene[15] as the oxidant *in situ*. Comparitive reactions were also carried out using DCM as the solvent, as was used in the route described by Waghmode,[14] and also in anhydrous THF to ascertain if the presence of water was inhibiting the oxidation, but the reaction profiles were same as with the THF/H_2O system.

NMR Spectra of synthesized compounds

Crude ^{1}H NMR spectra of selected entries during optimization and mechanistic studies

Table S1, entry 7

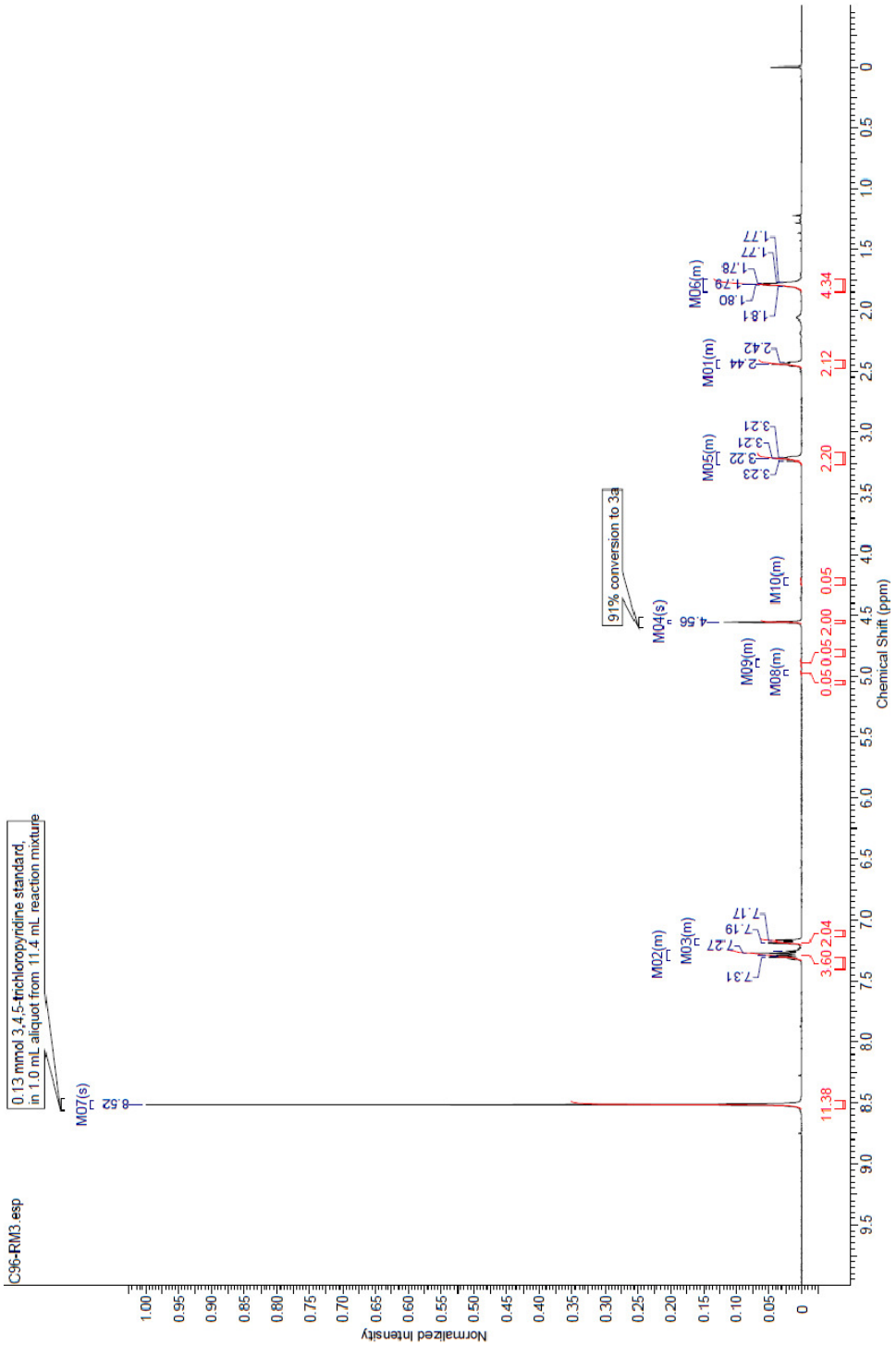


Table S1, entry 8

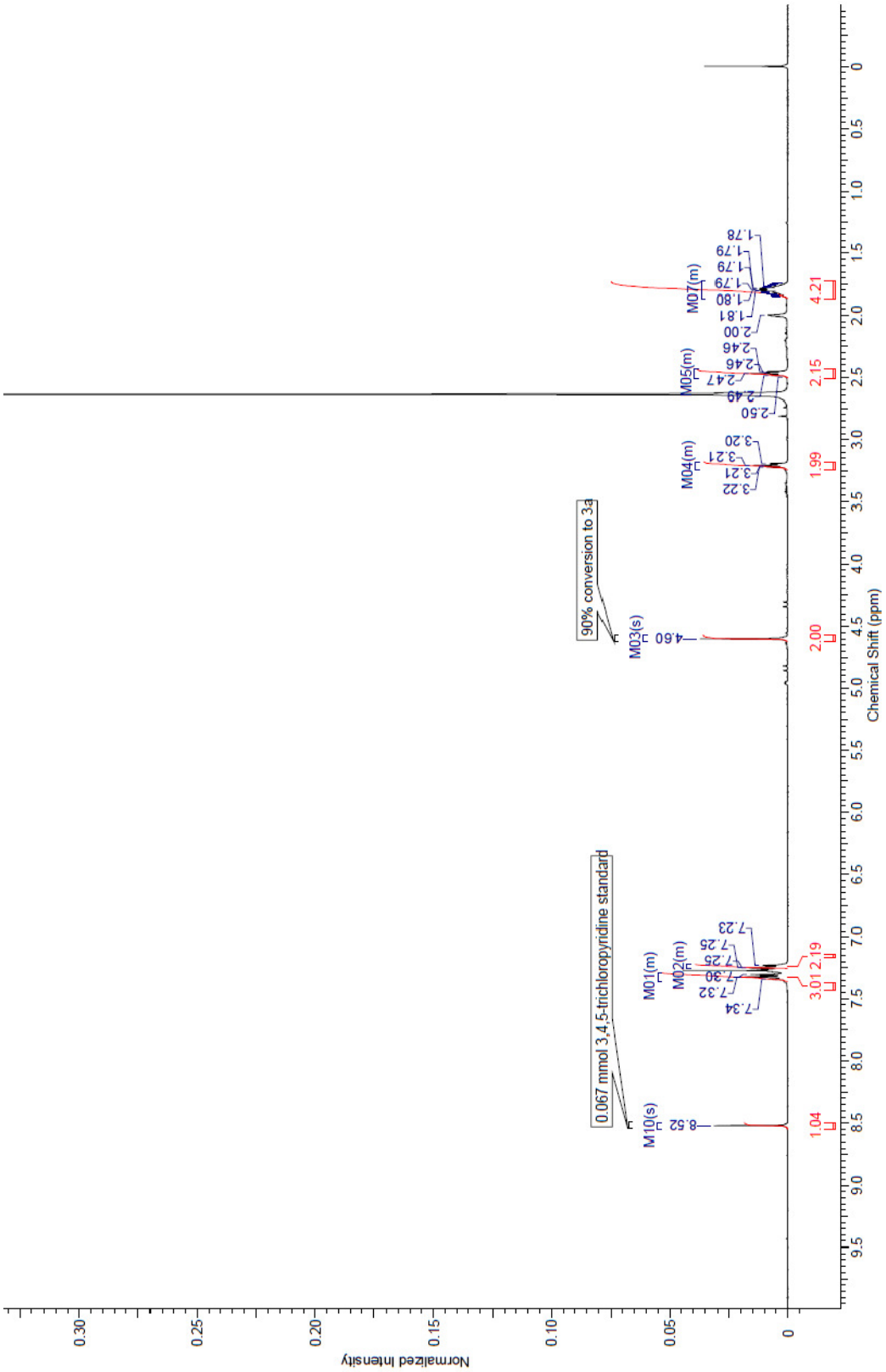
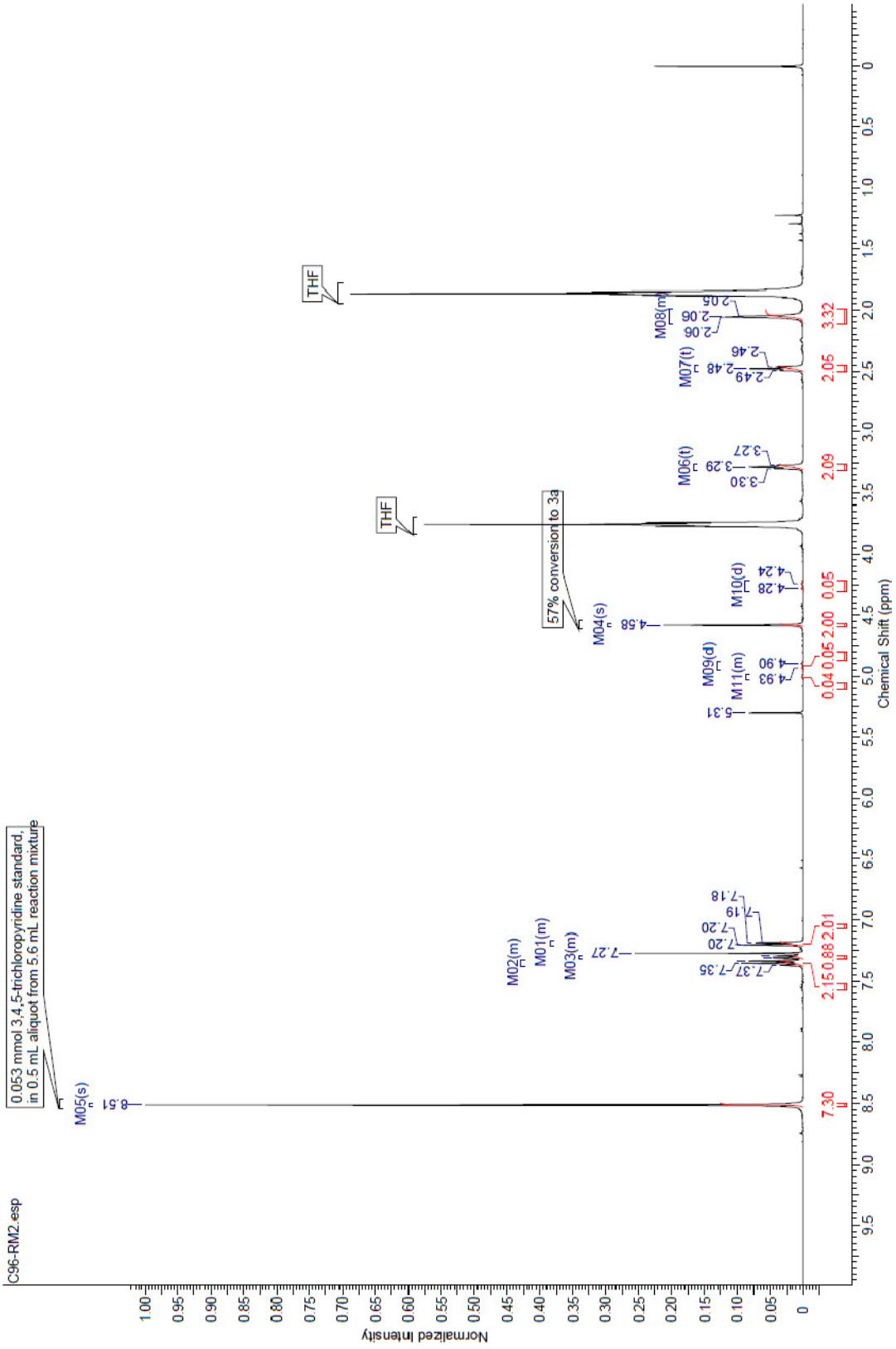


Table S1, entry 10



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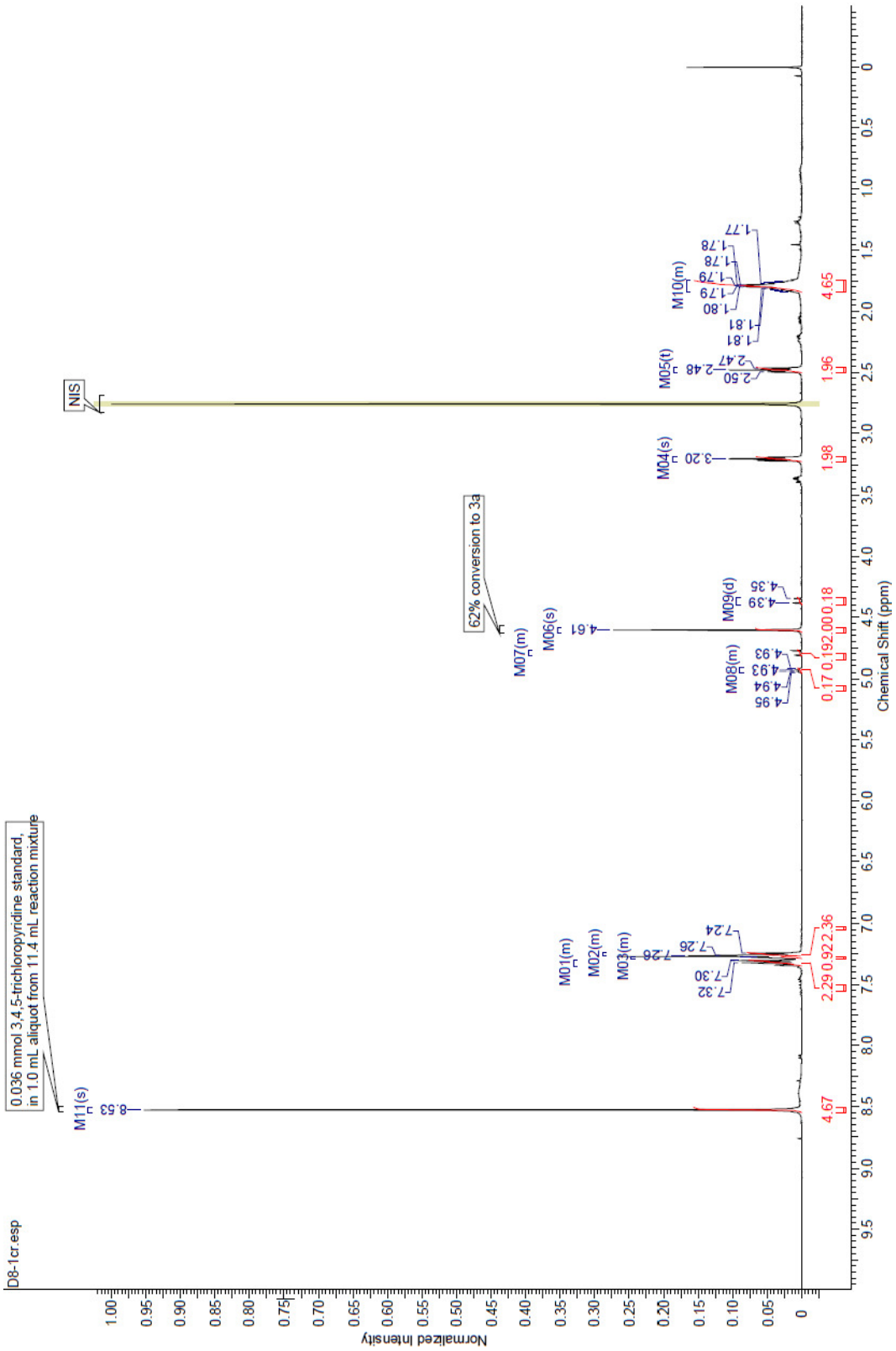


Table S2, entry 1

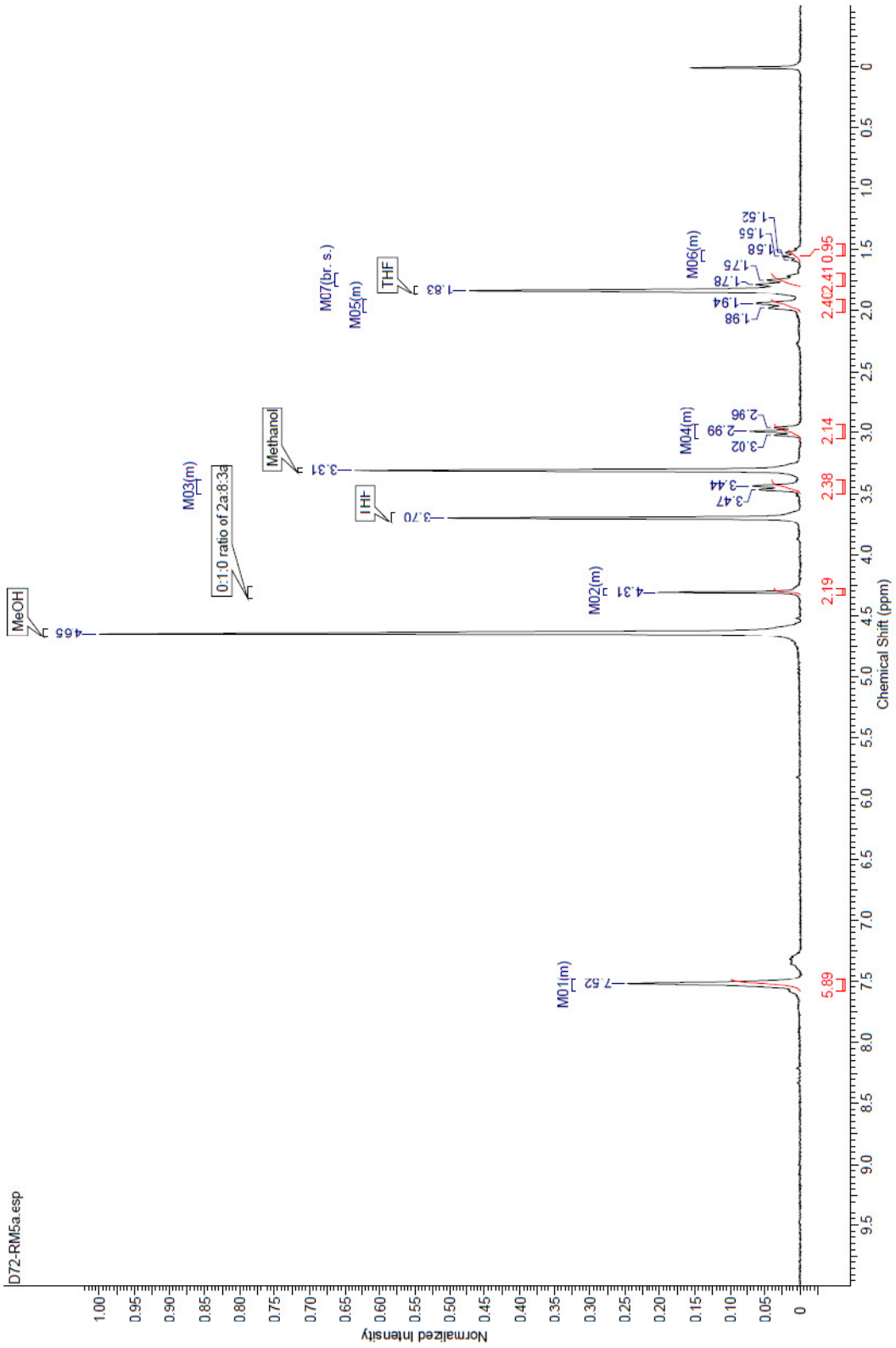


Table S2, entry 2

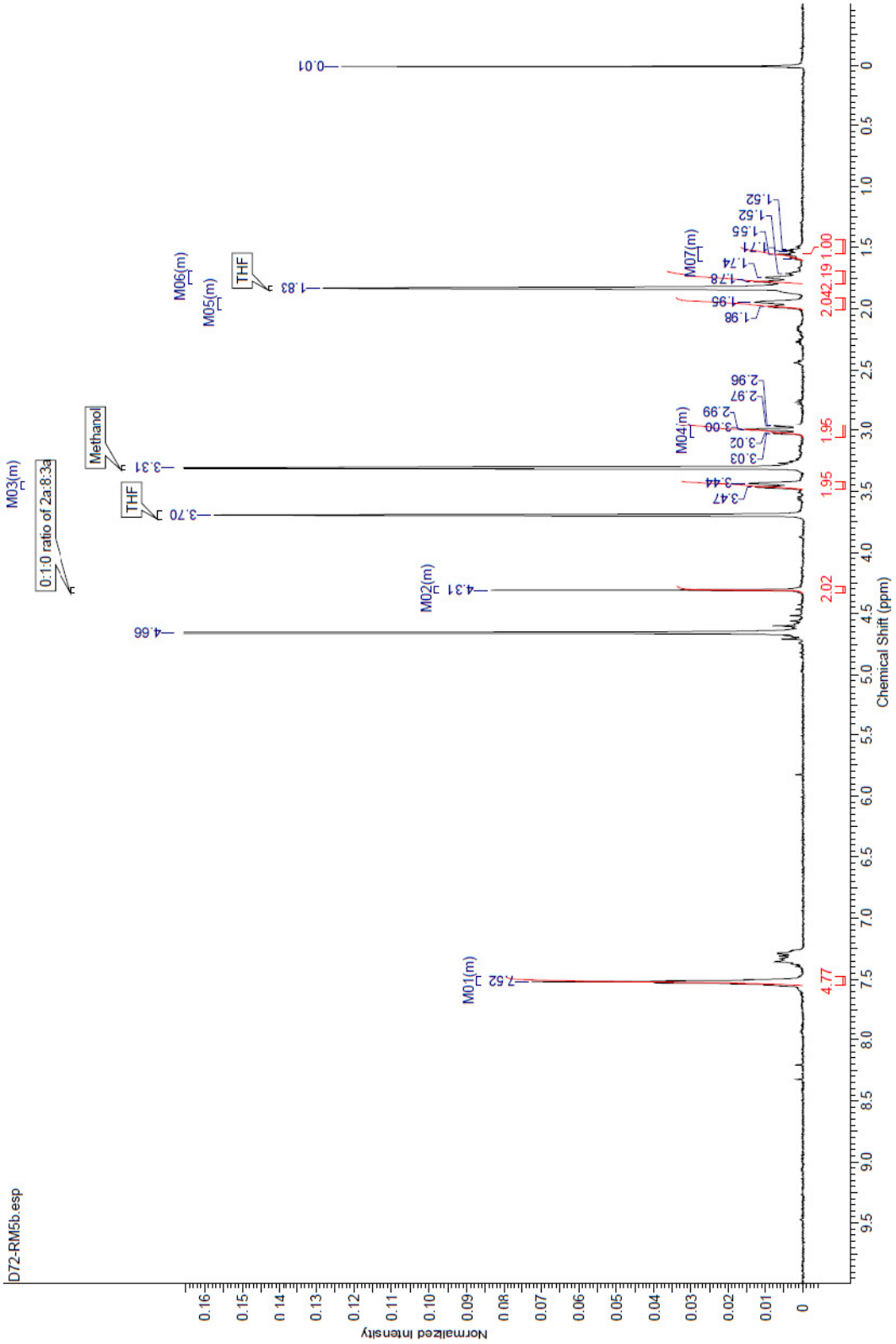


Table S2, entry 3

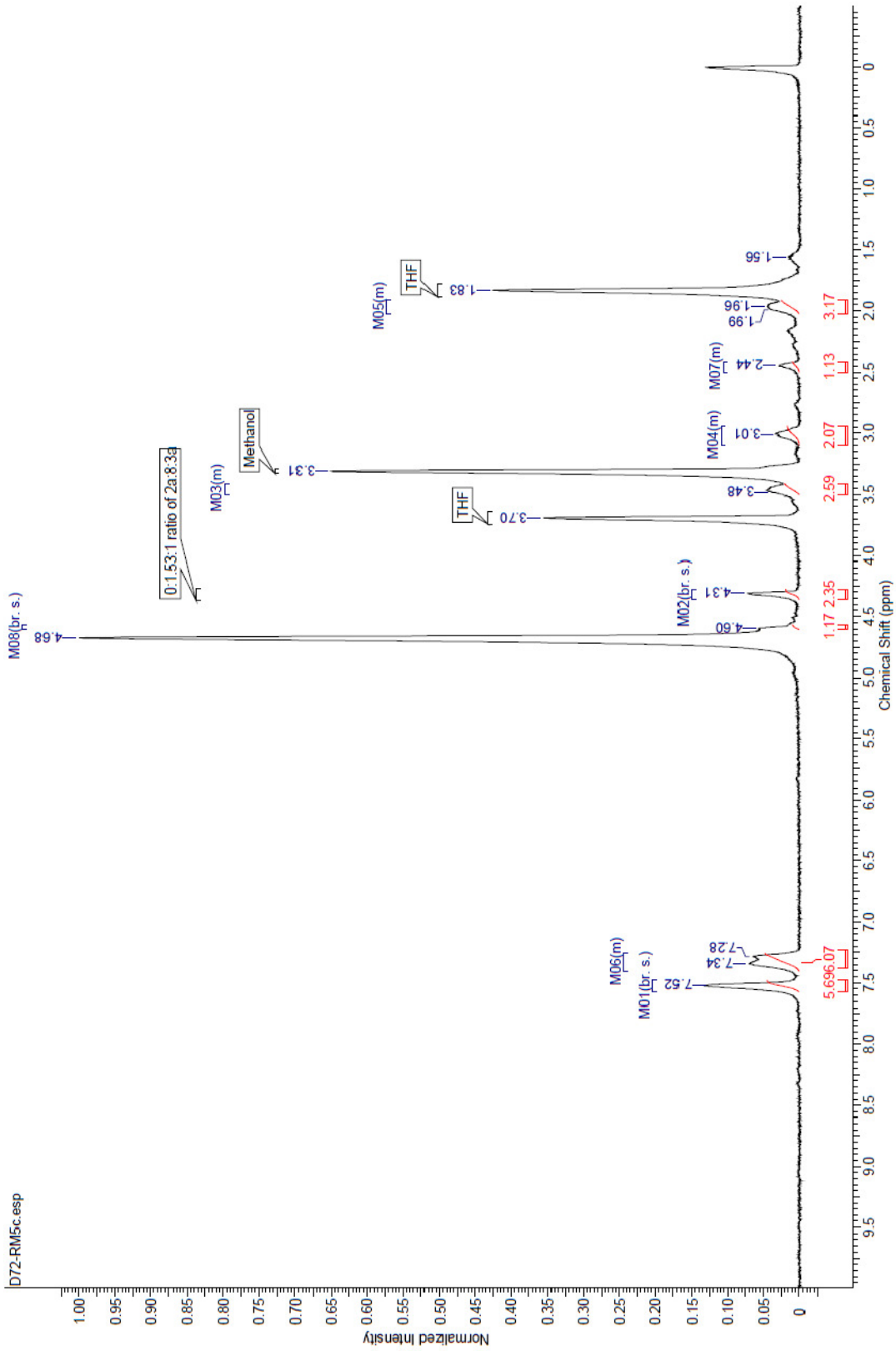


Table S2, entry 4

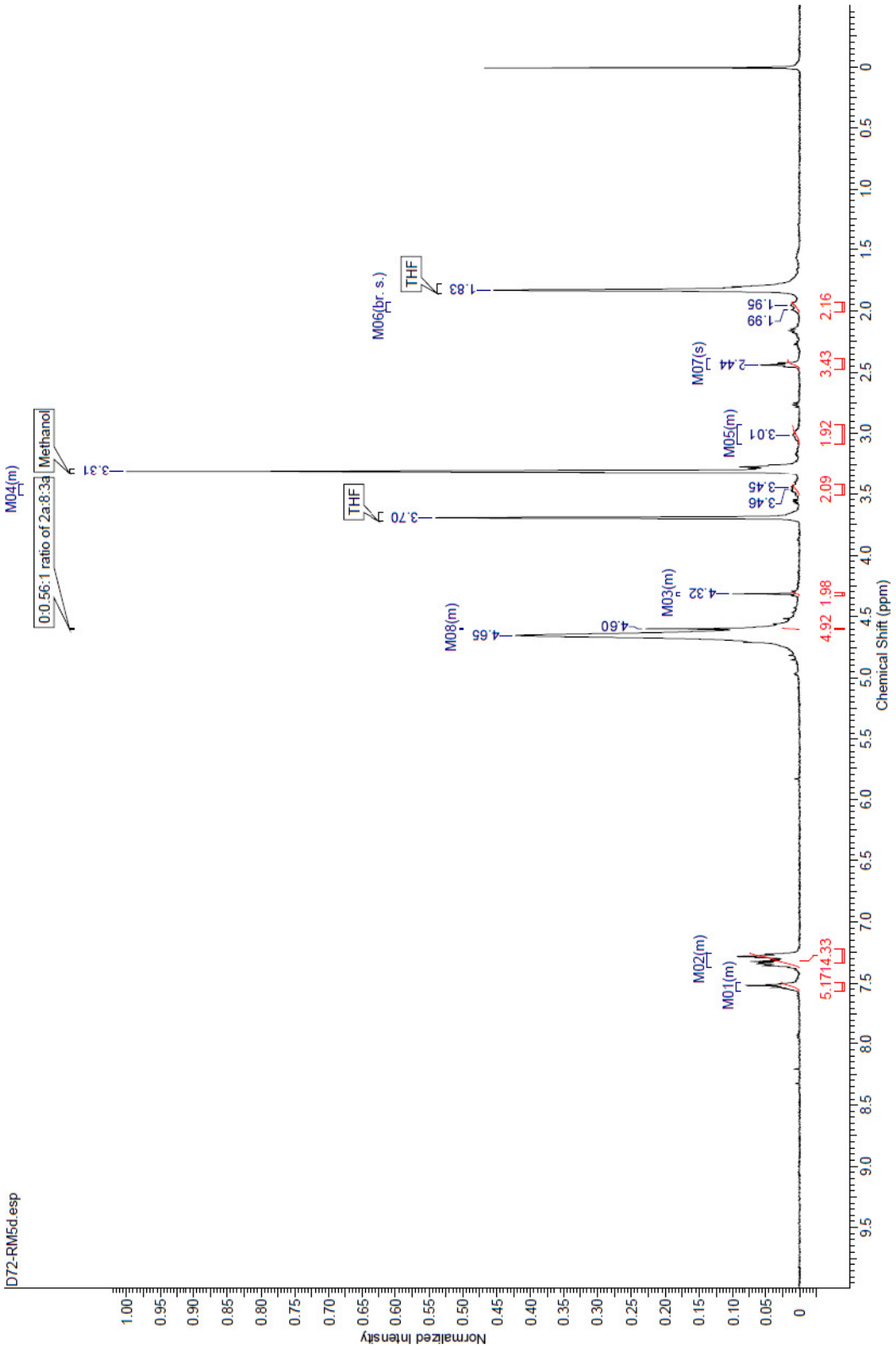


Table S2, entry 5

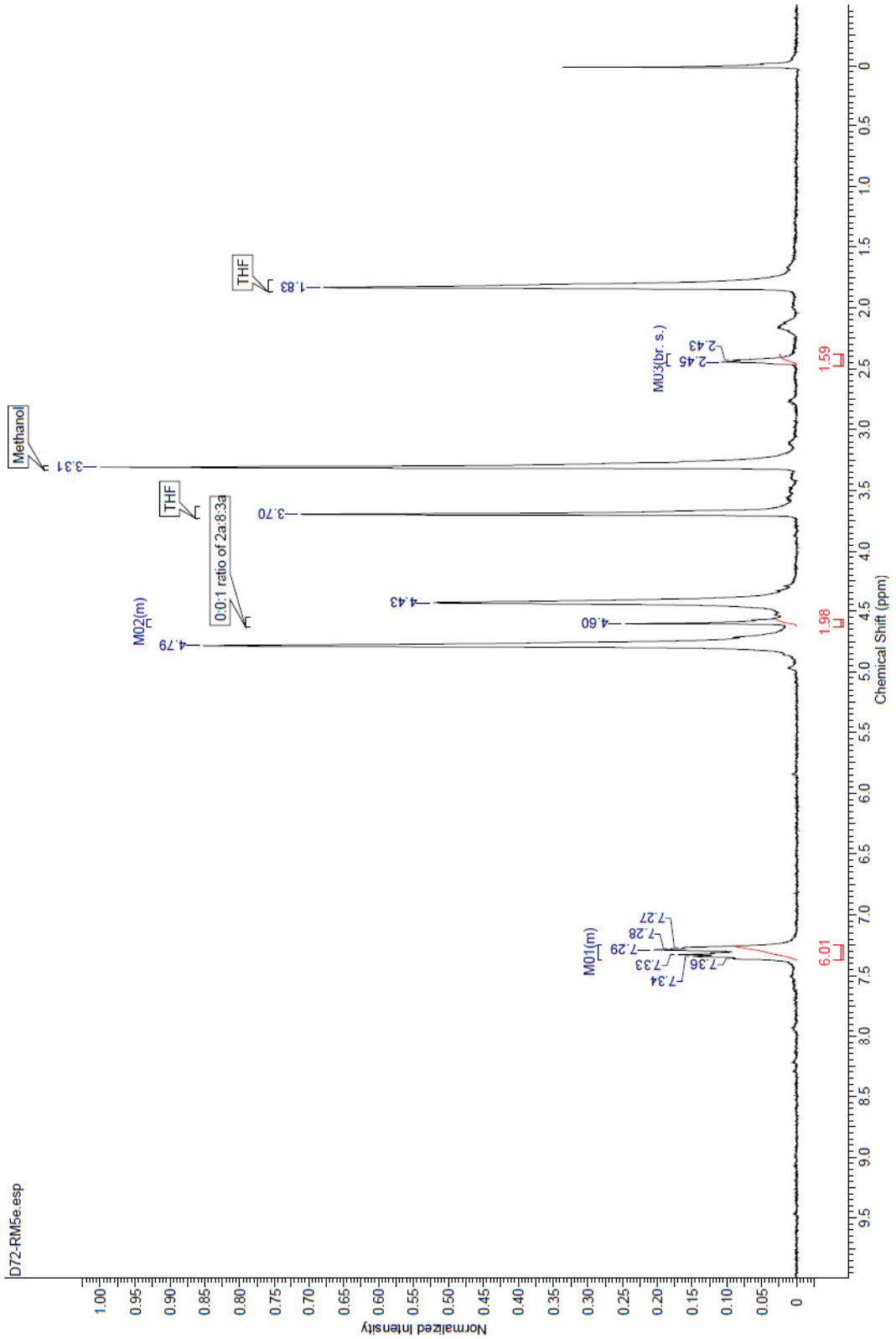


Table S2, entry 6

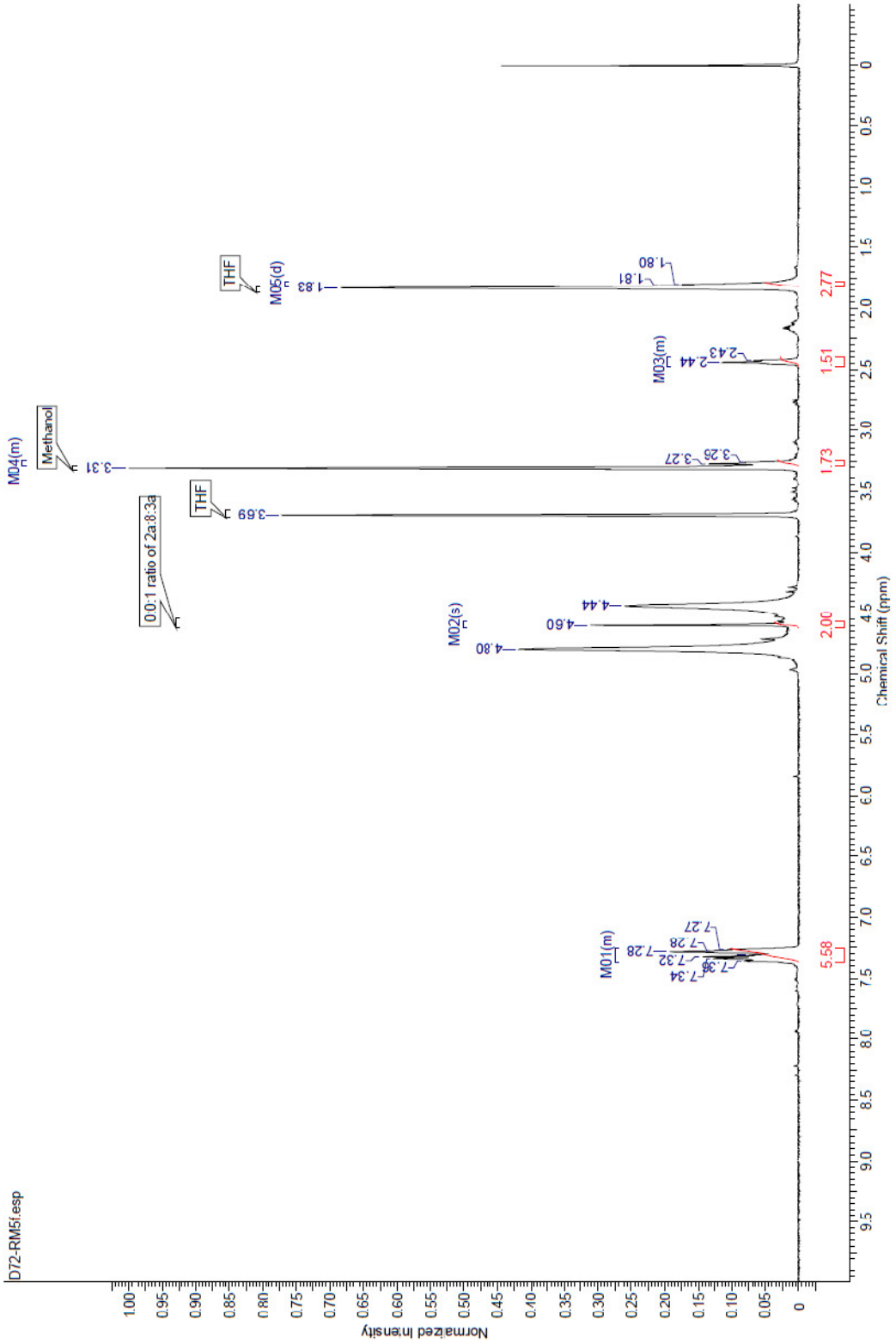
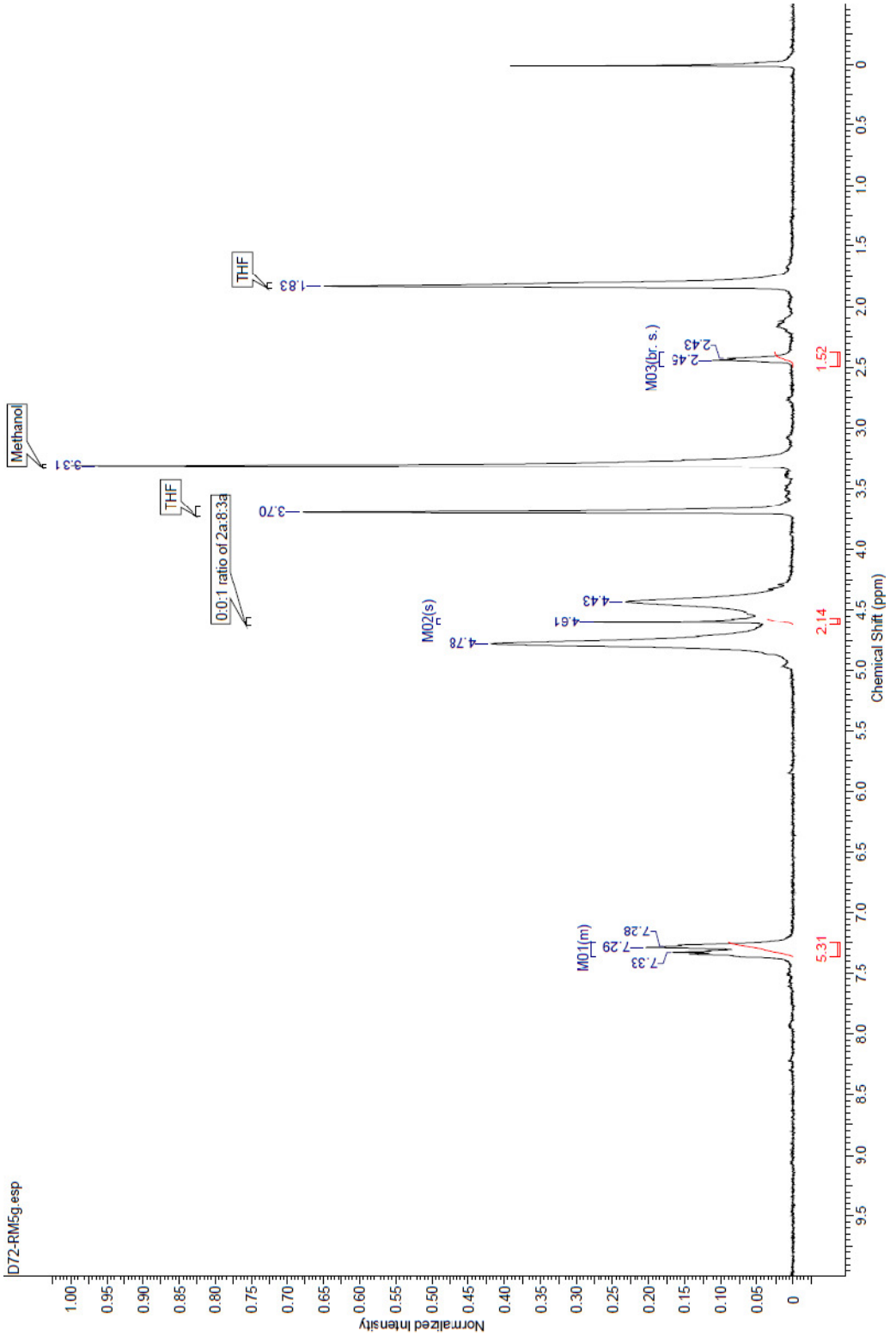
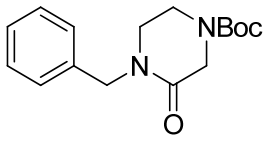


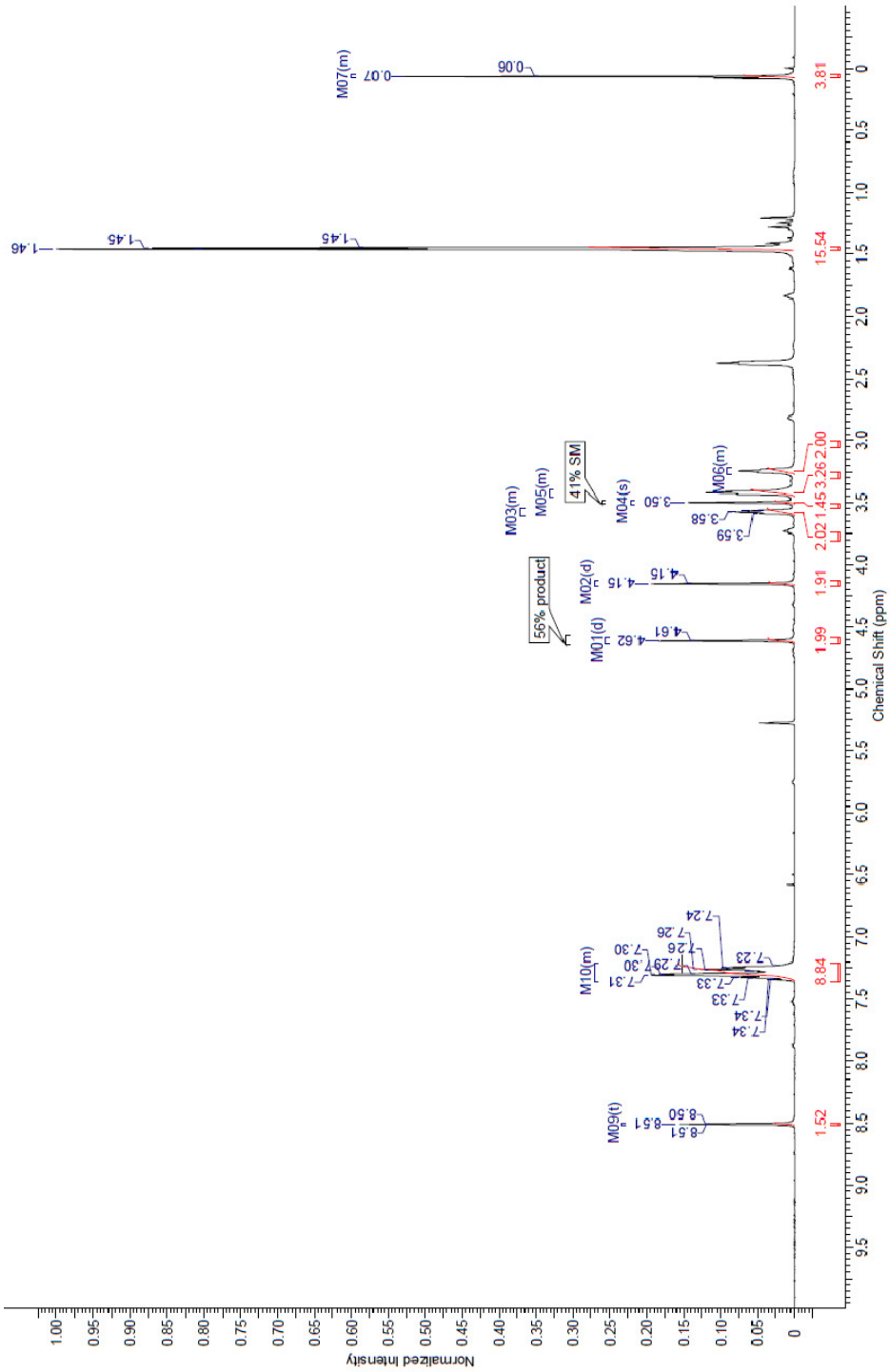
Table S2, entry 7

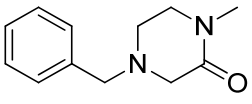


^{1}H NMR spectra of selected crude substrates determining NMR conversions

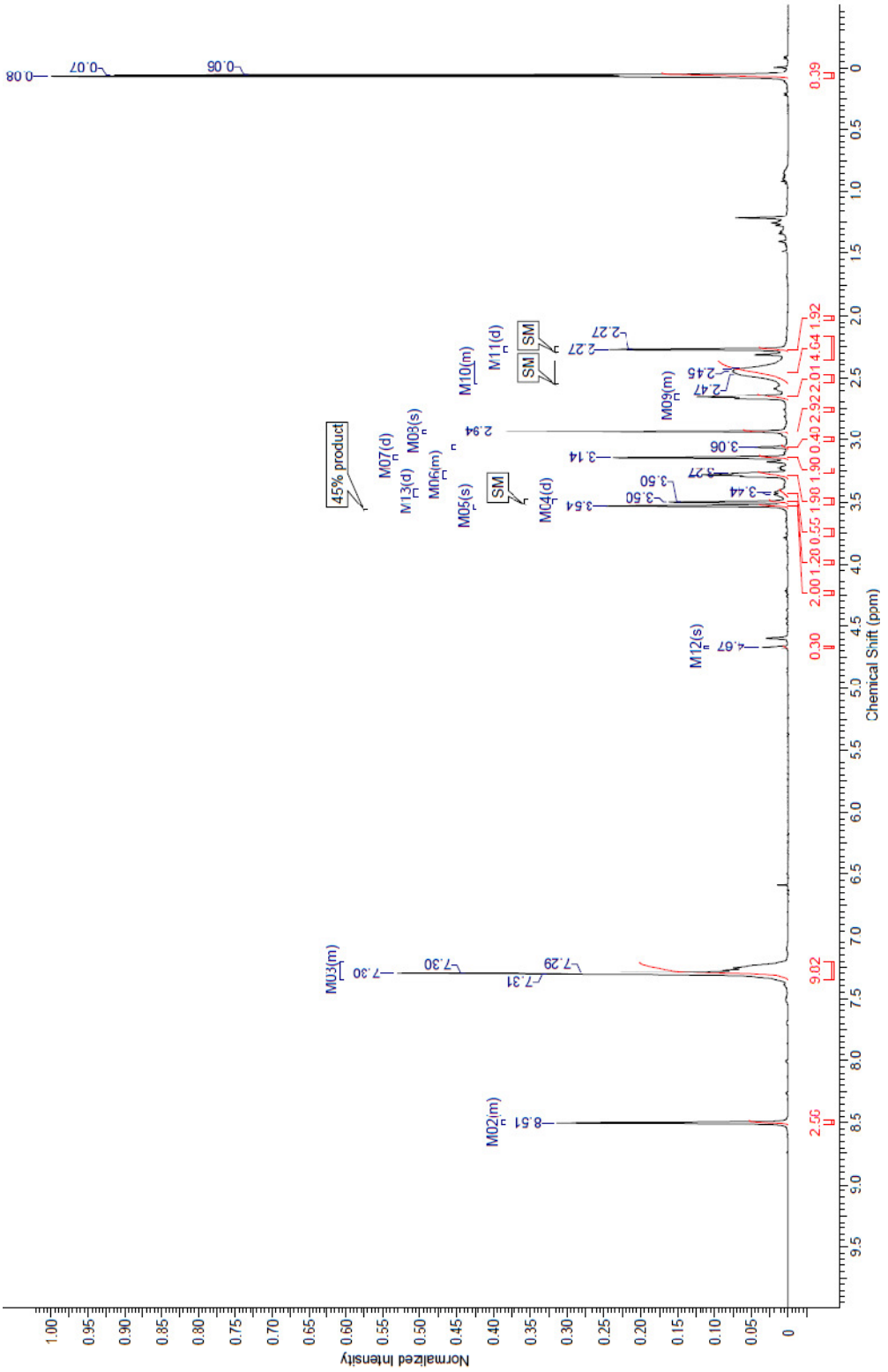


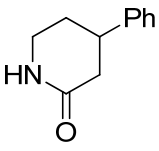
Tert-butyl 4-benzyl-3-oxopiperazine-1-carboxylate 3h



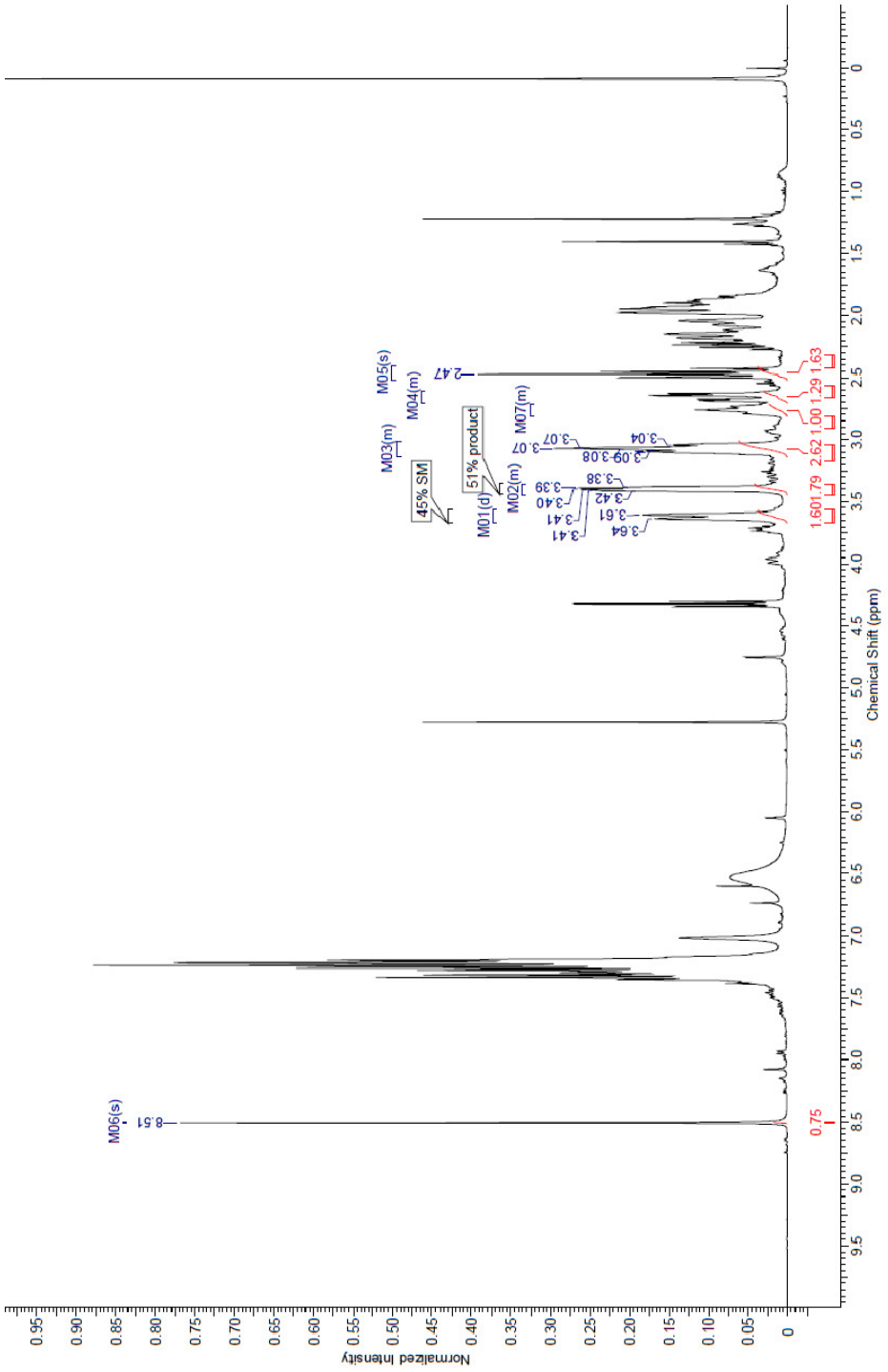


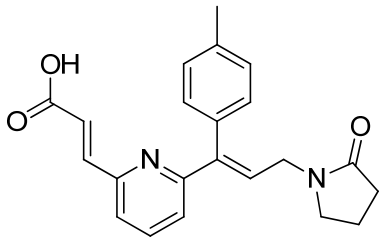
4-Benzyl-1-methylpiperazin-2-one 3i



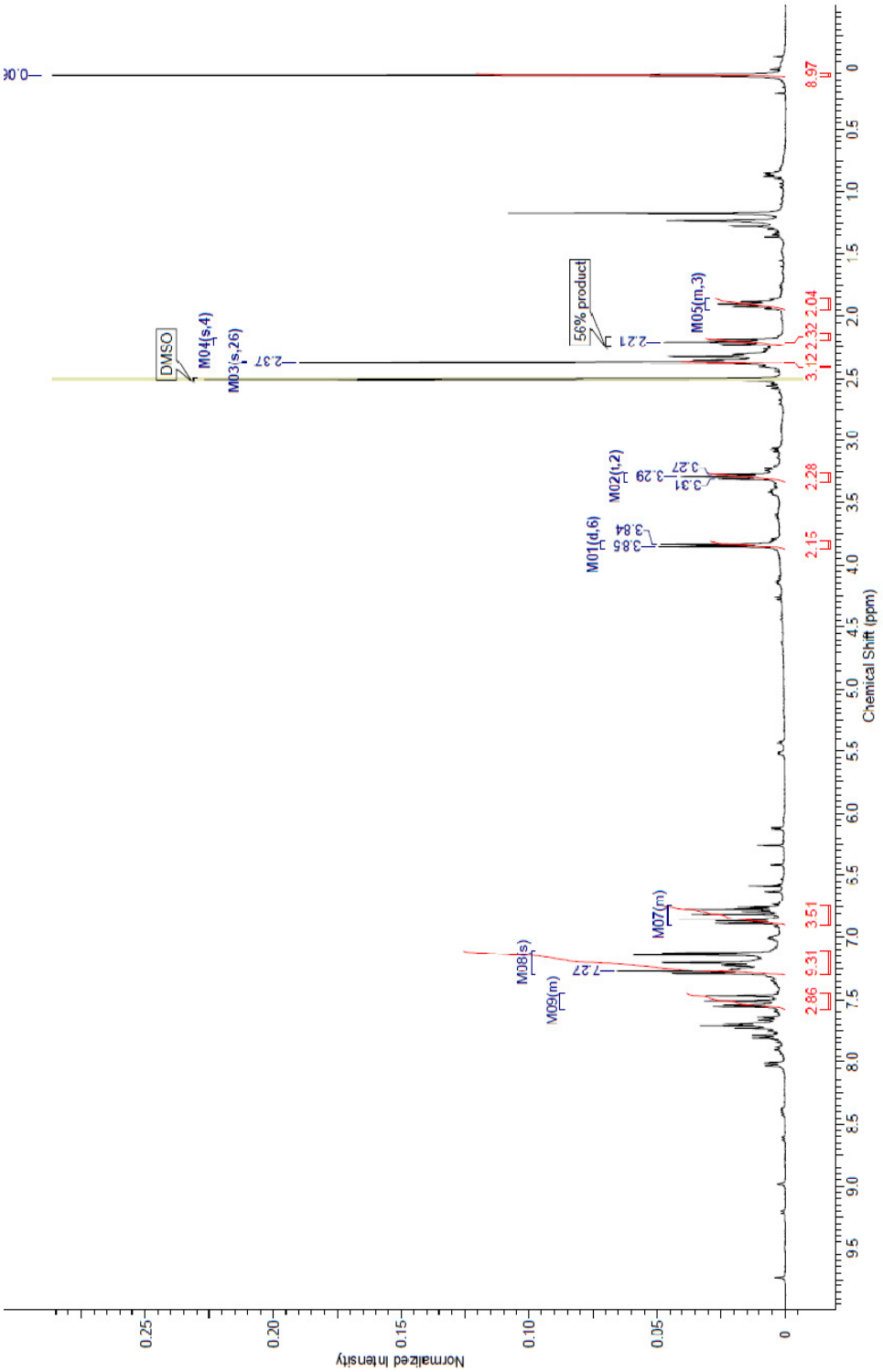


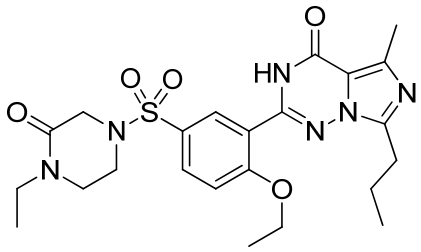
4-Phenylpiperidin-2-one 3l



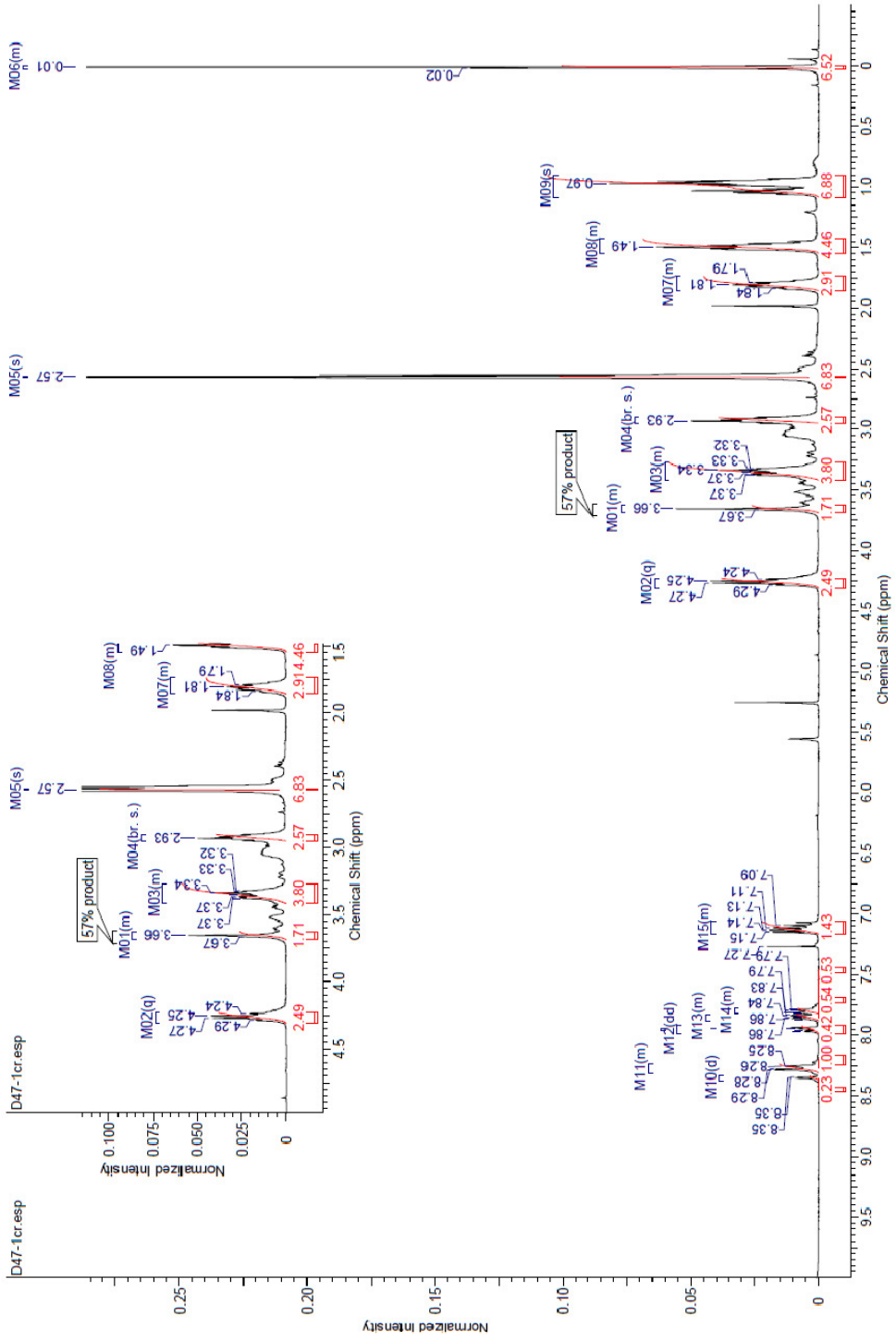


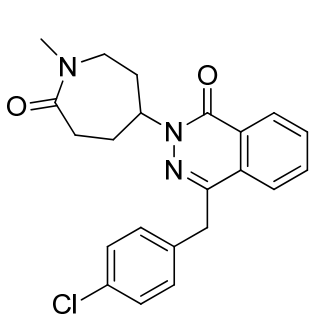
Oxo-acrivastine 5d

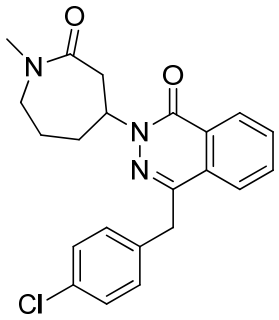




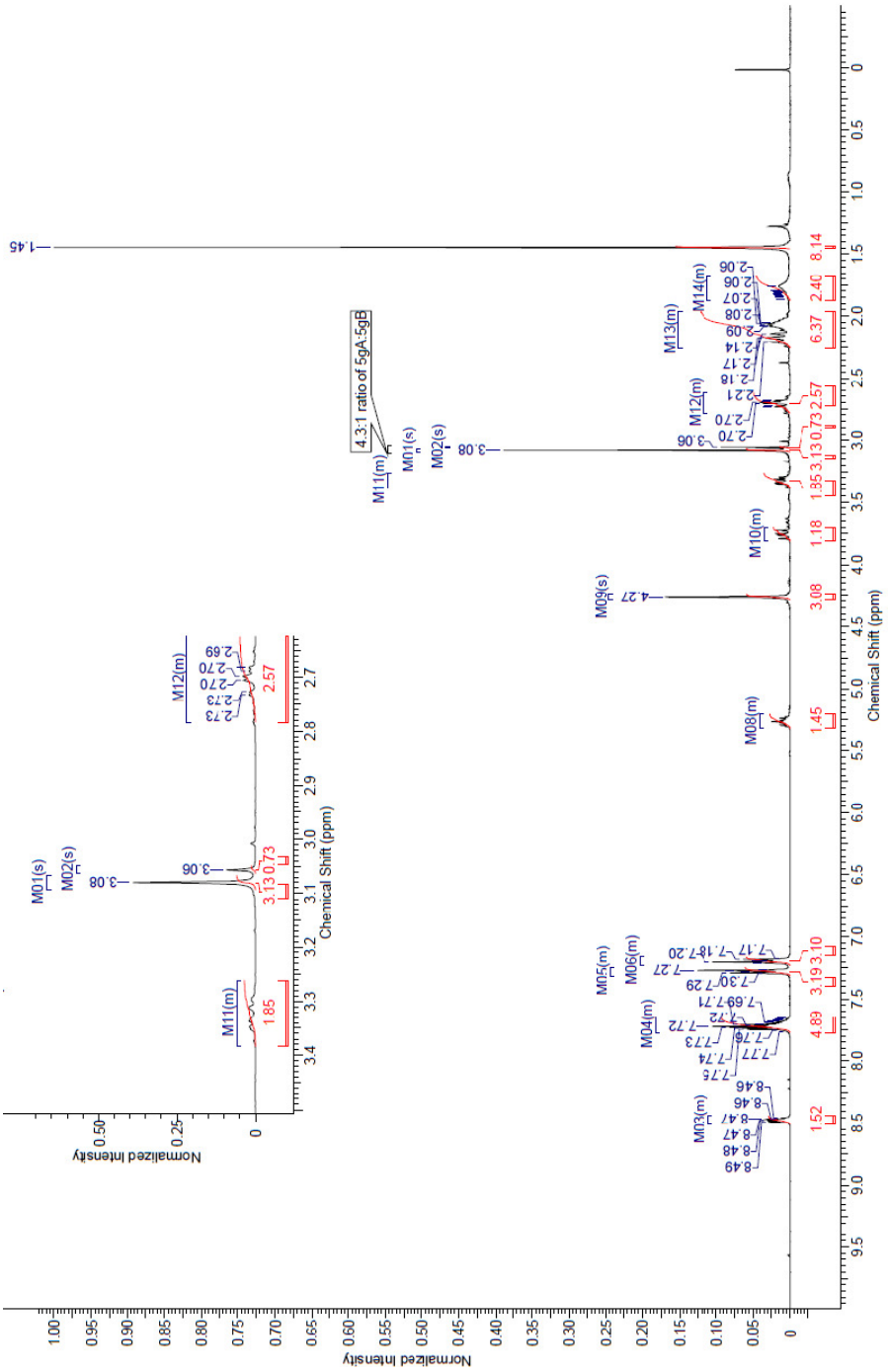
Oxo-vardenafil 5e

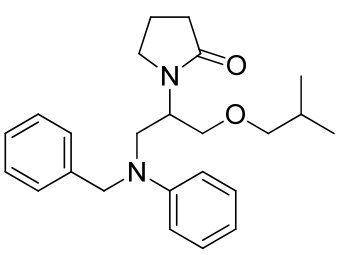




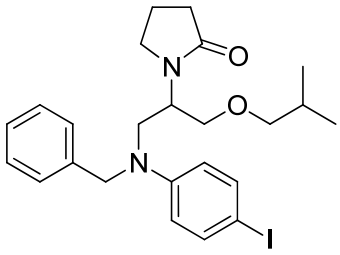


4.3:1 ratio of a mixture of co-eluting 7-Oxo-azelastine 5g$^{\alpha}$ and 2-oxo-azelastine 5g$^{\beta}$

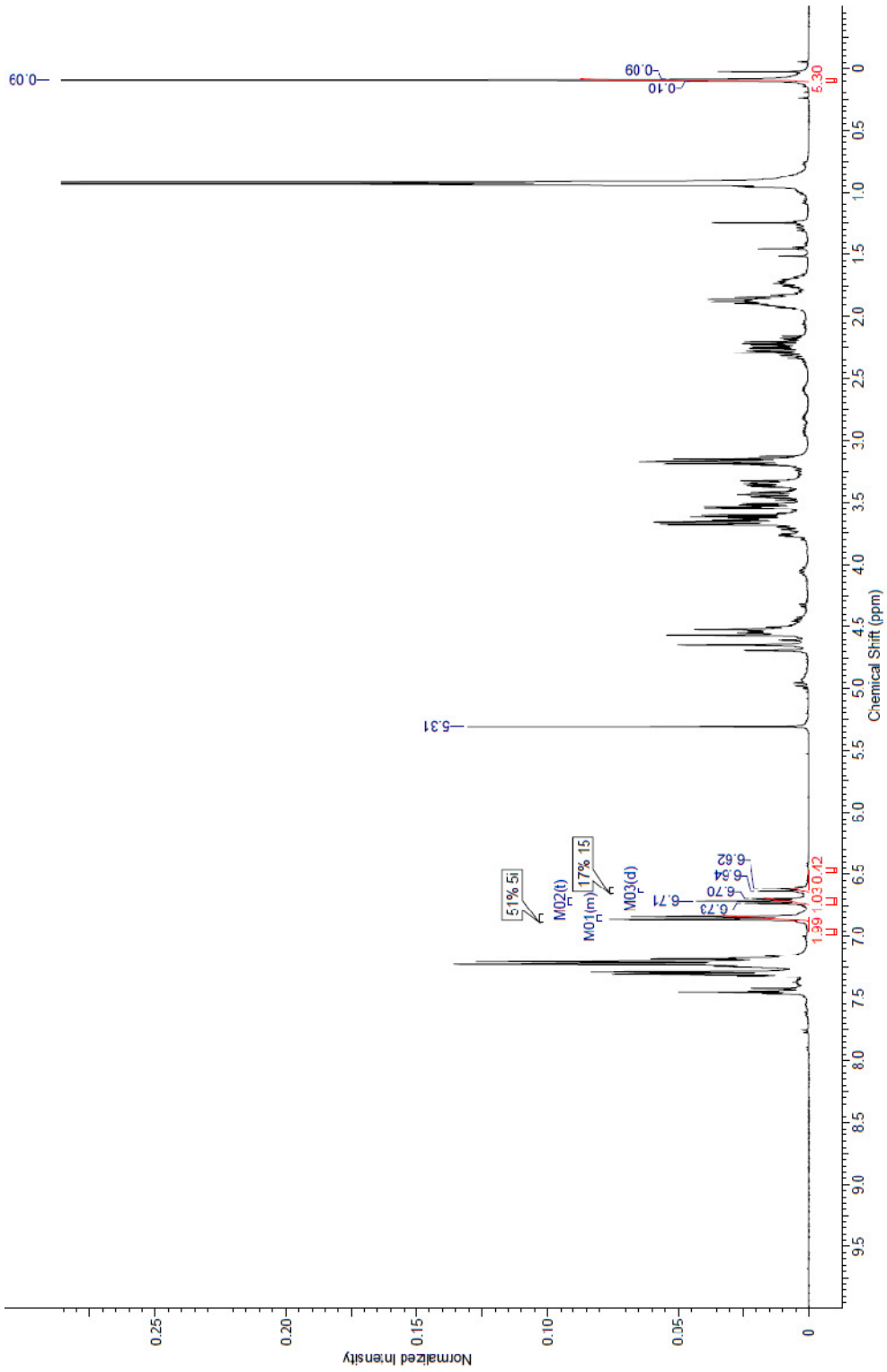


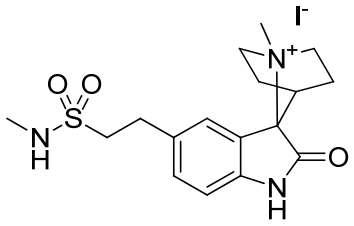


Oxo-bepridil 5j

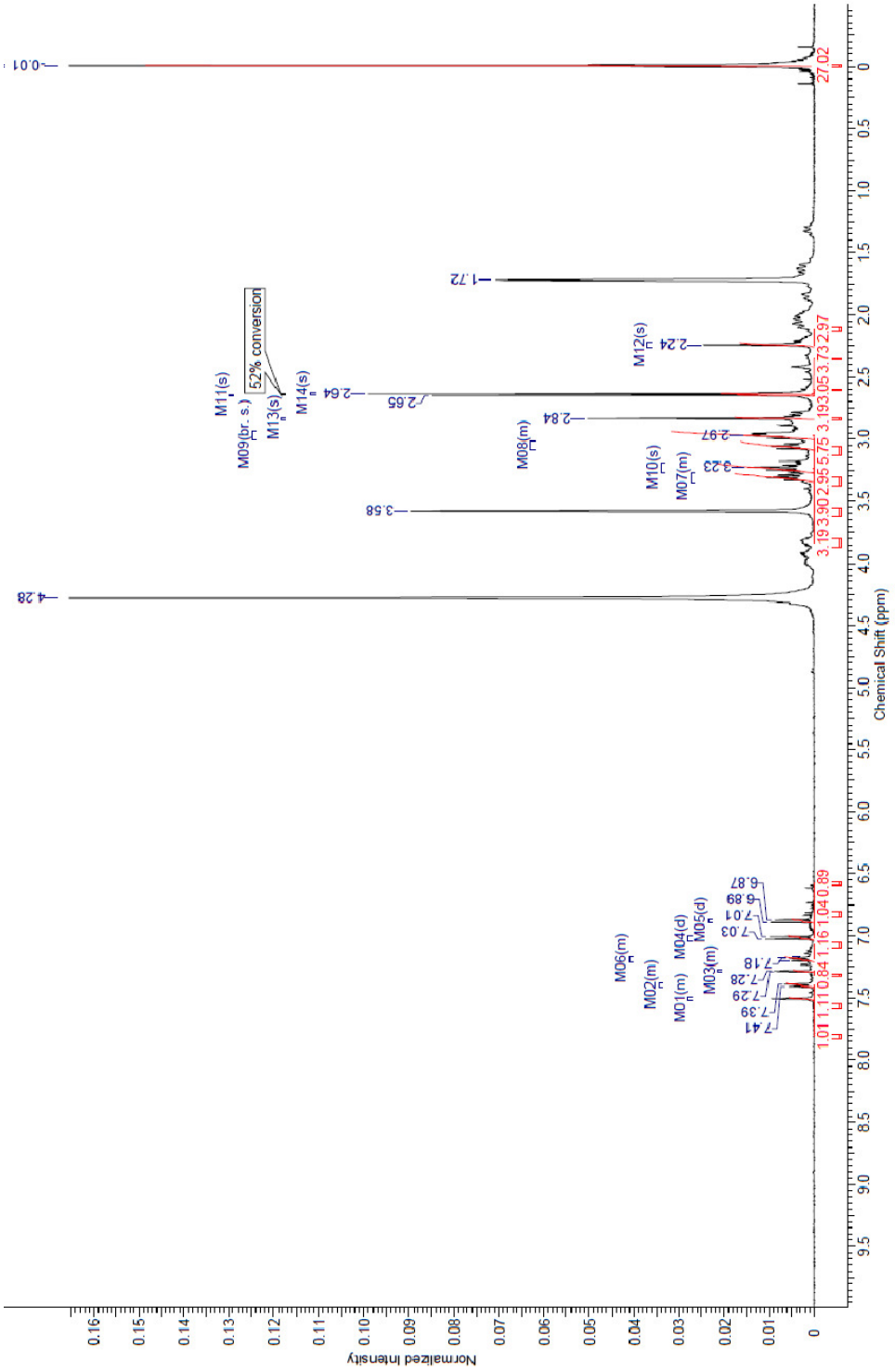


Oxo-iodo-bepridil 15

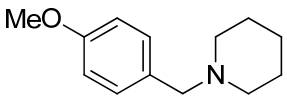




1-Methyl-5'-(2-(*N*-methylsulfamoyl)ethyl)-2'-oxo-1-azaspiro [bicyclo[2.2.1]heptane-7,3'-indolin]-1-ium iodide 14

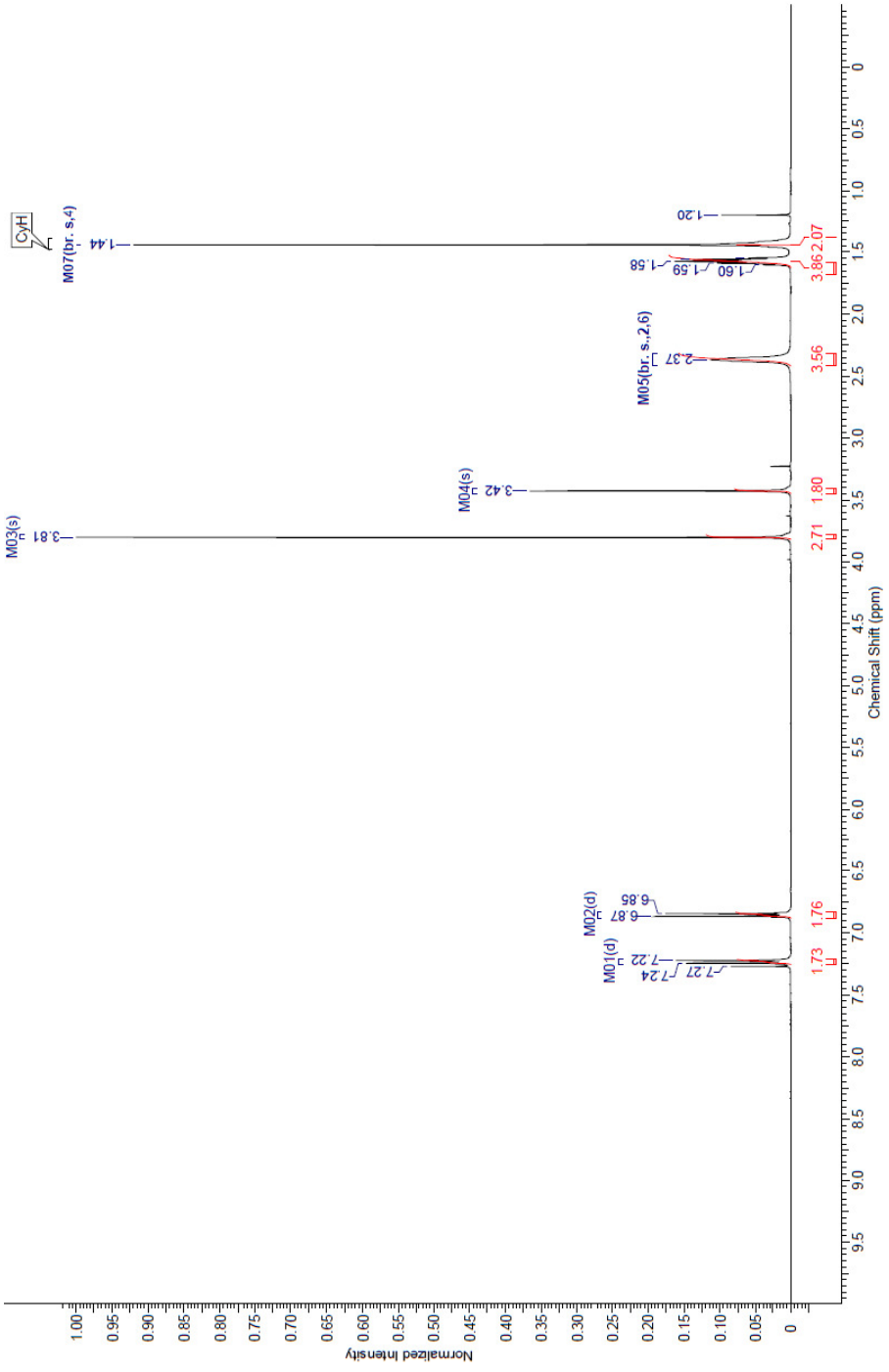


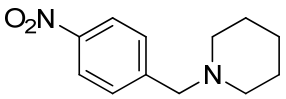
Isolated compounds



1-(4-Methoxybenzyl)piperidine 2b

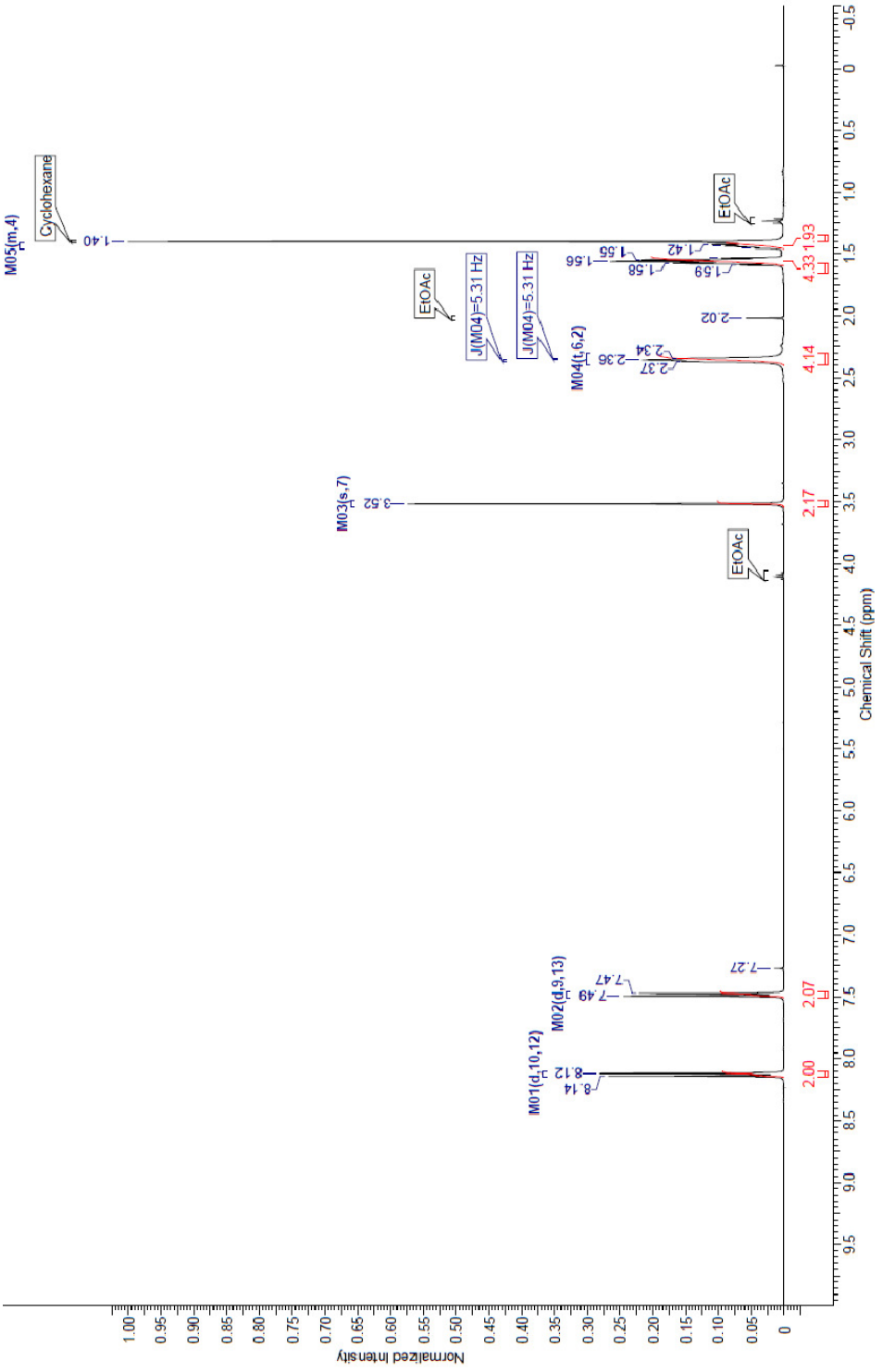
^{1}H NMR

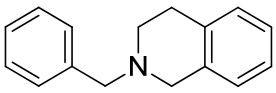




1-(4-Nitrobenzyl)piperidine 2c

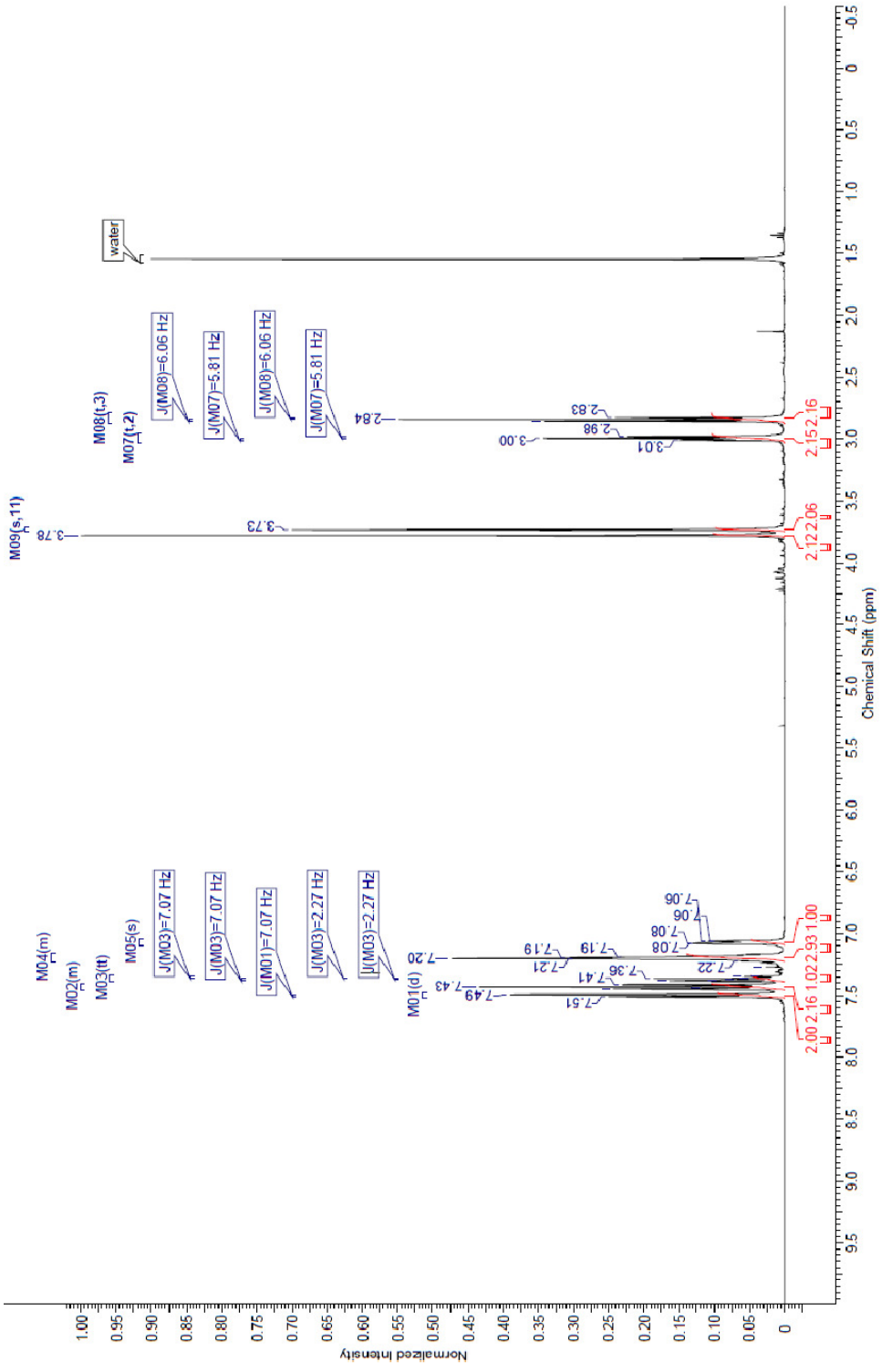
^{1}H NMR

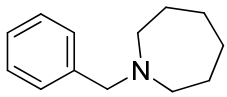




2-Benzyl-1,2,3,4-tetrahydroisoquinoline 2d

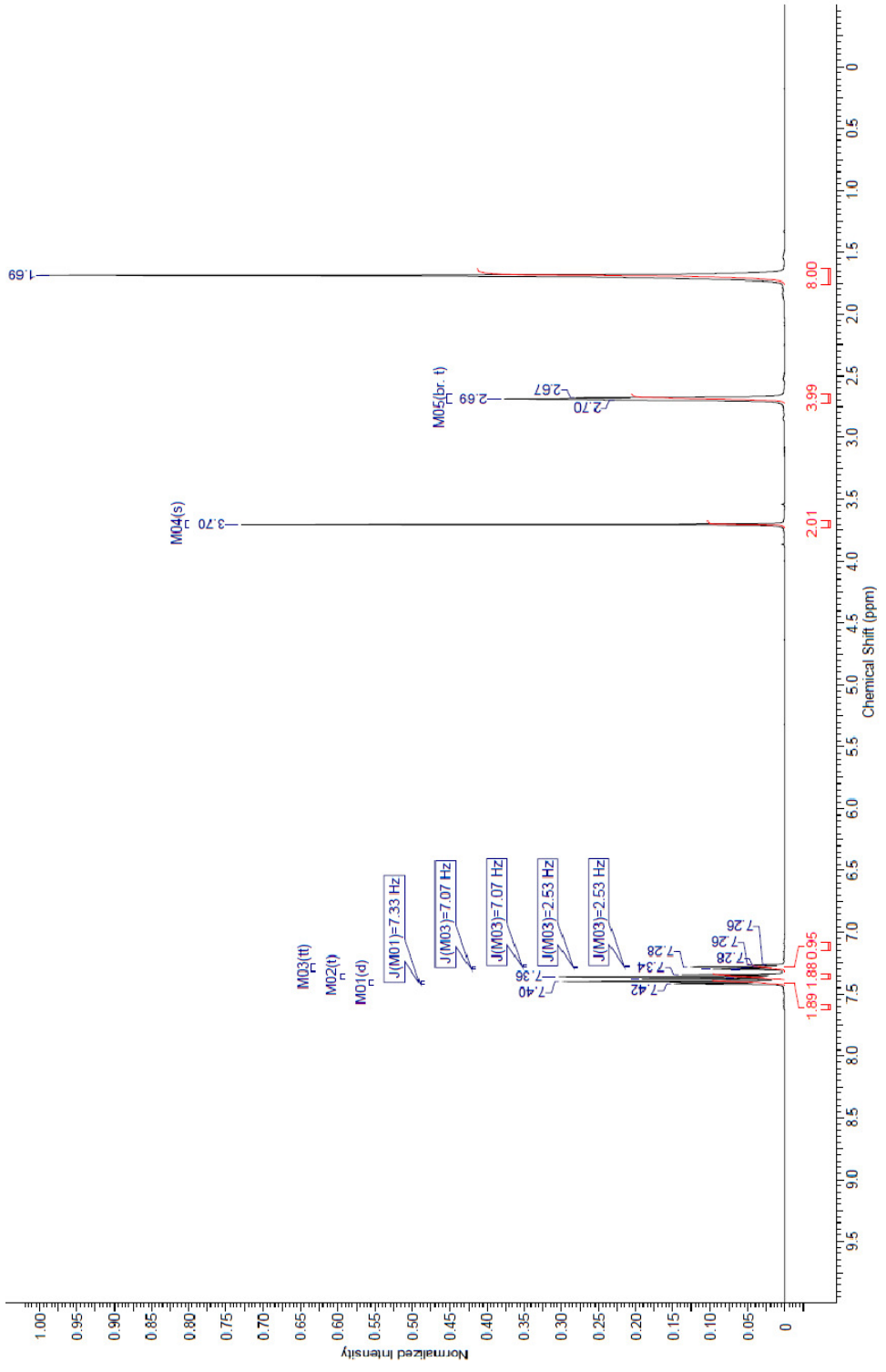
^{1}H NMR

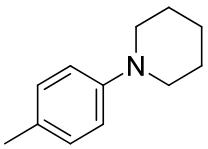




1-Benzylazepane 2f

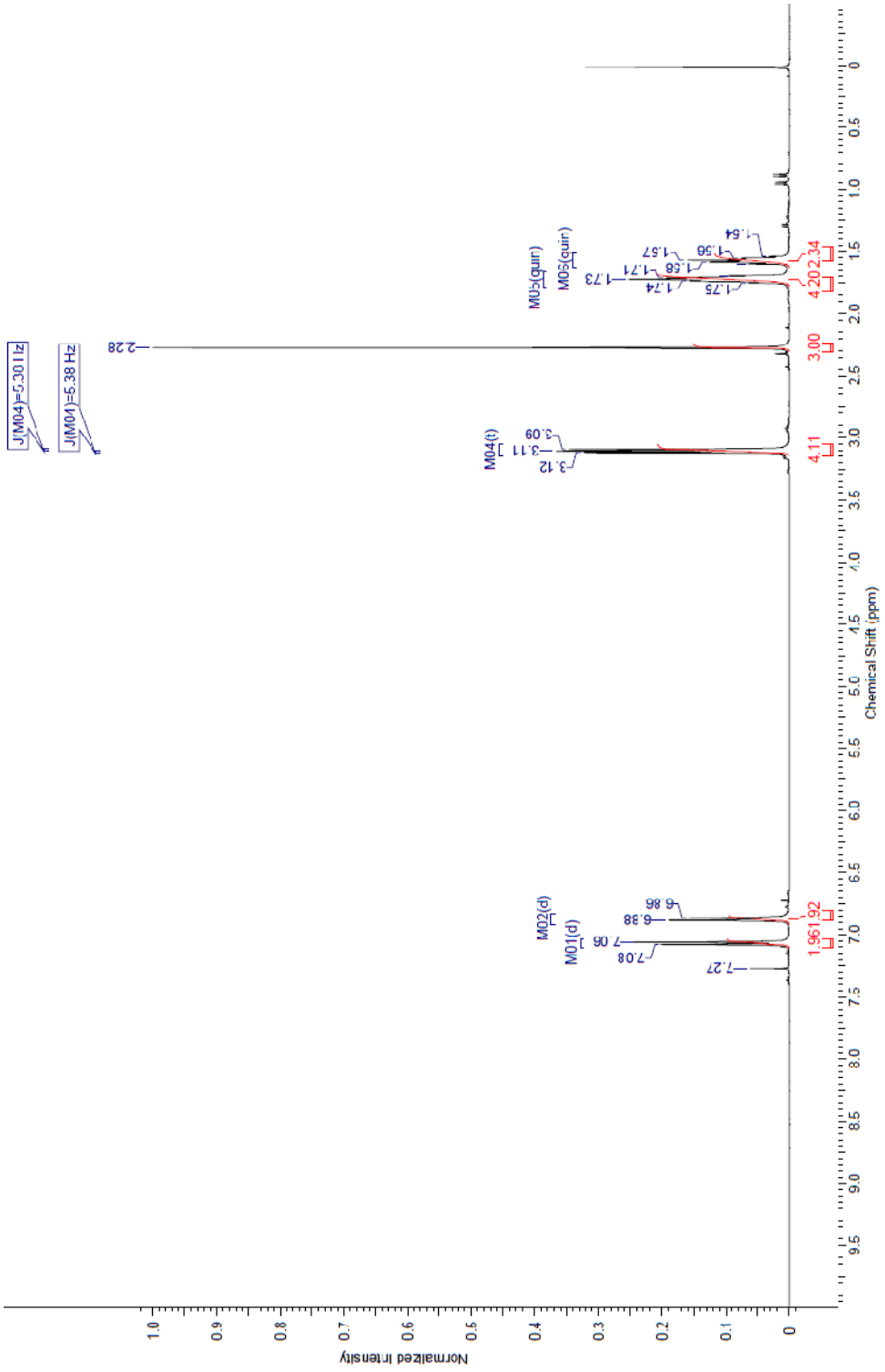
^{1}H NMR

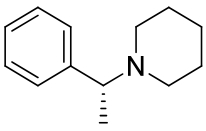




1-(*p*-Tolyl)piperidine 2k

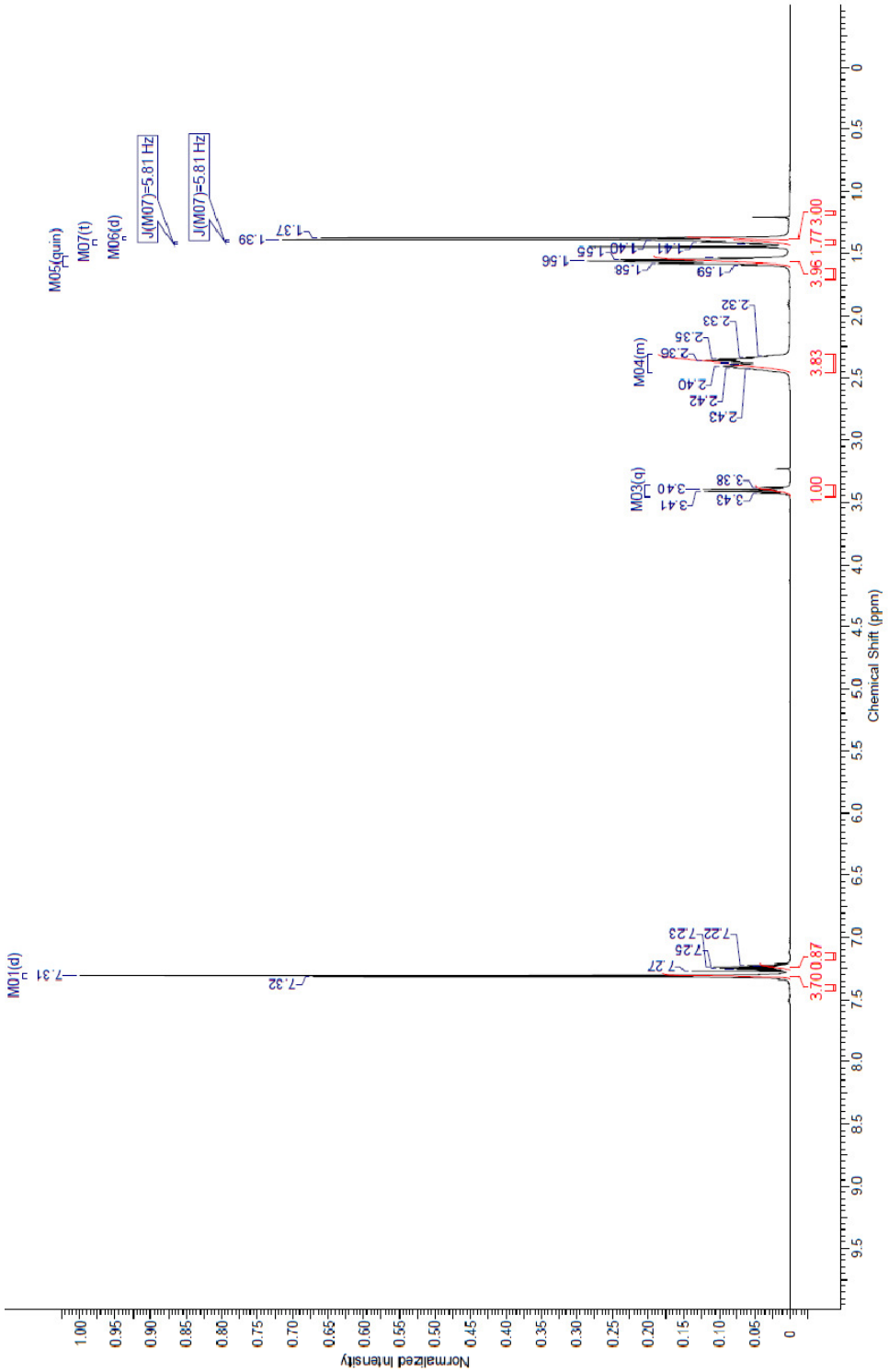
^{1}H NMR

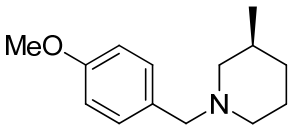




(*R*)-1-(1-Phenylethyl)piperidine 2m

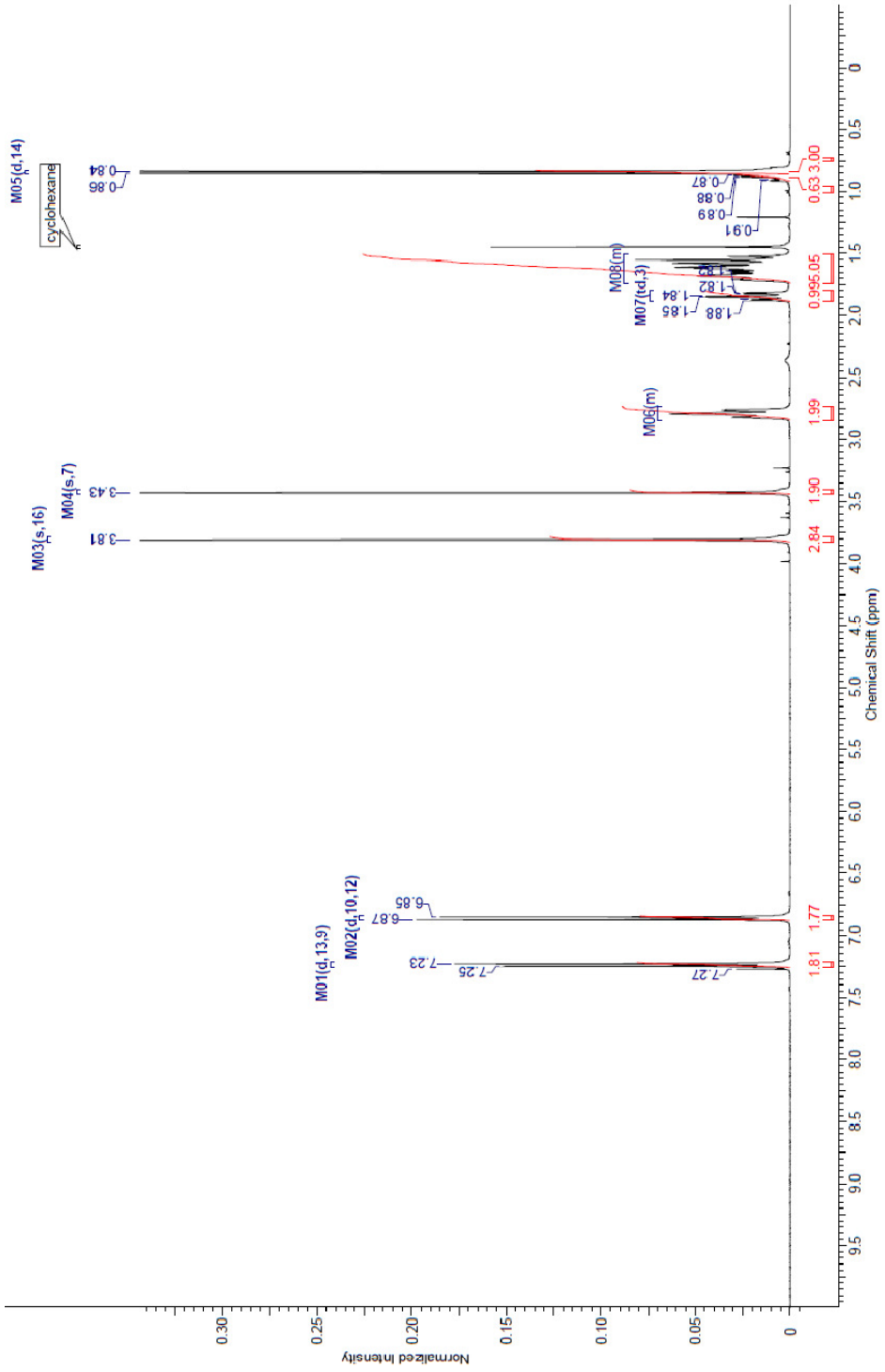
^{1}H NMR



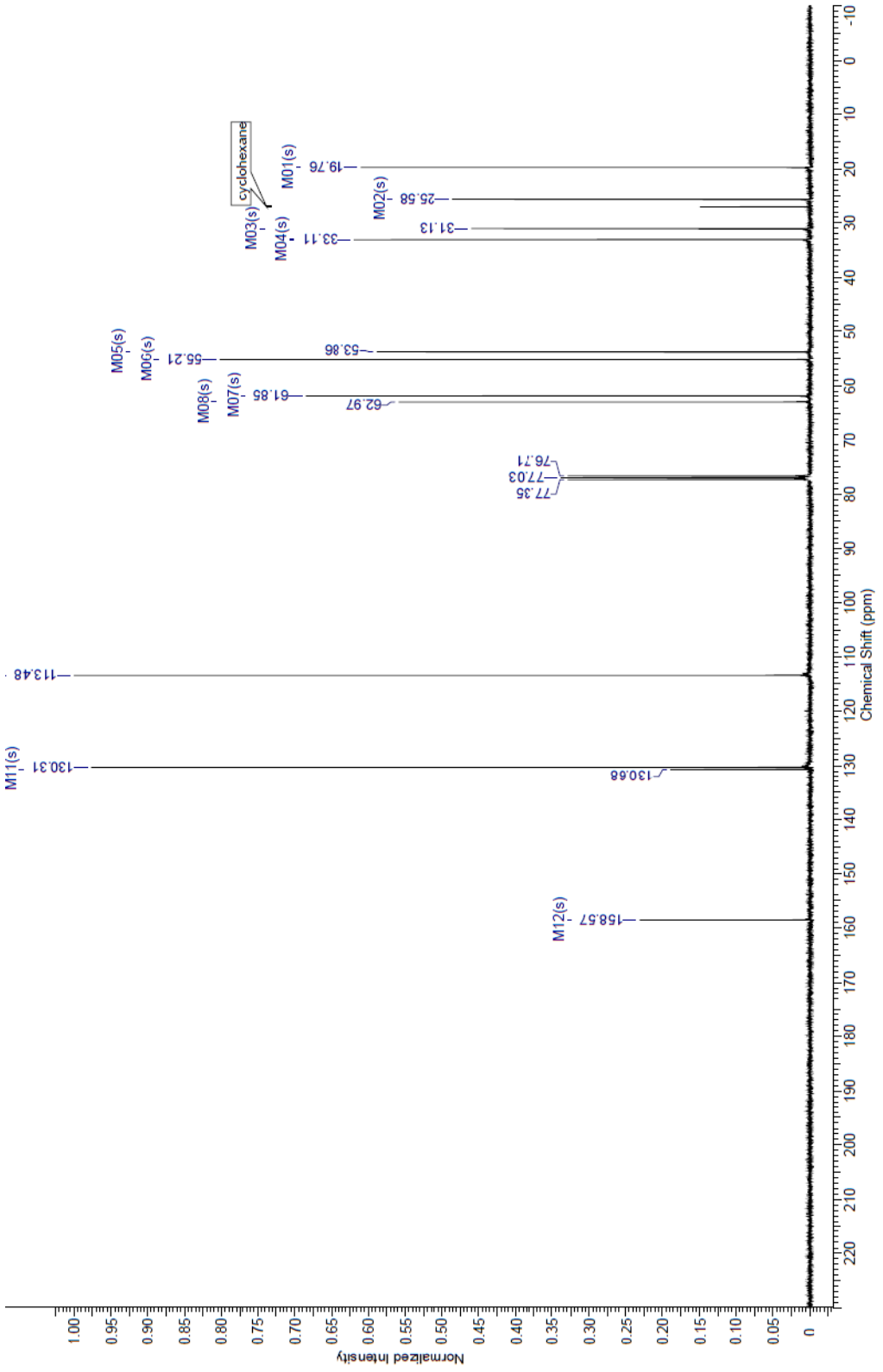


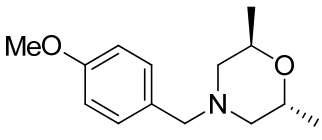
(*S*)-1-(4-Methoxybenzyl)-3-methylpiperidine 2n

^{1}H NMR



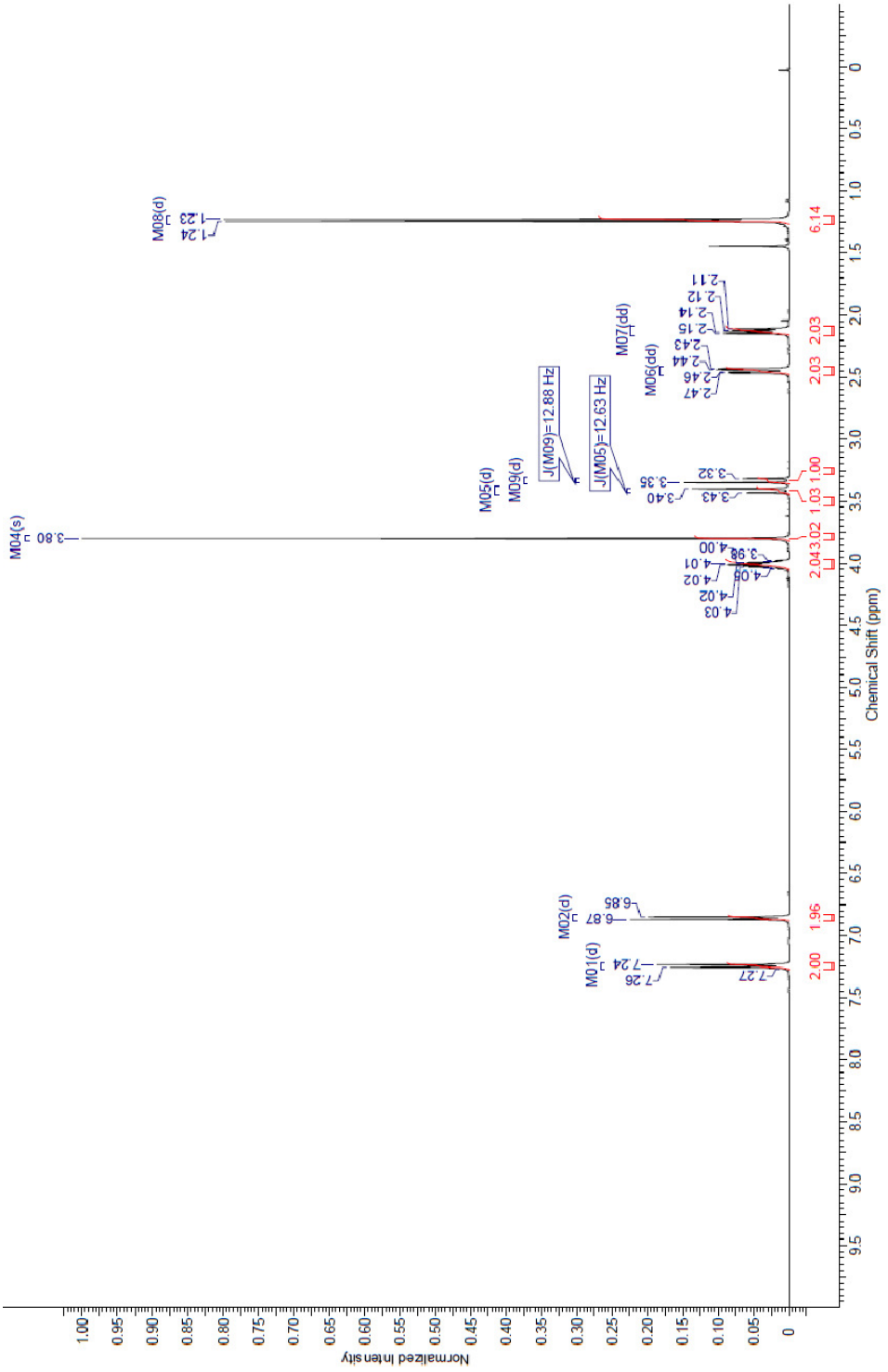
^{13}C NMR


cyclohexane
M01(s)
M02(s)
M03(s)
M04(s)
M05(s)
M06(s)
M07(s)
M08(s)
M11(s)
M12(s)
19.76
25.58
31.13
33.11
53.86
55.21
61.85
62.97
76.71
77.03
77.35
113.48
130.31
130.66
158.57
Chemical Shift (ppm)
Normalized Intensity

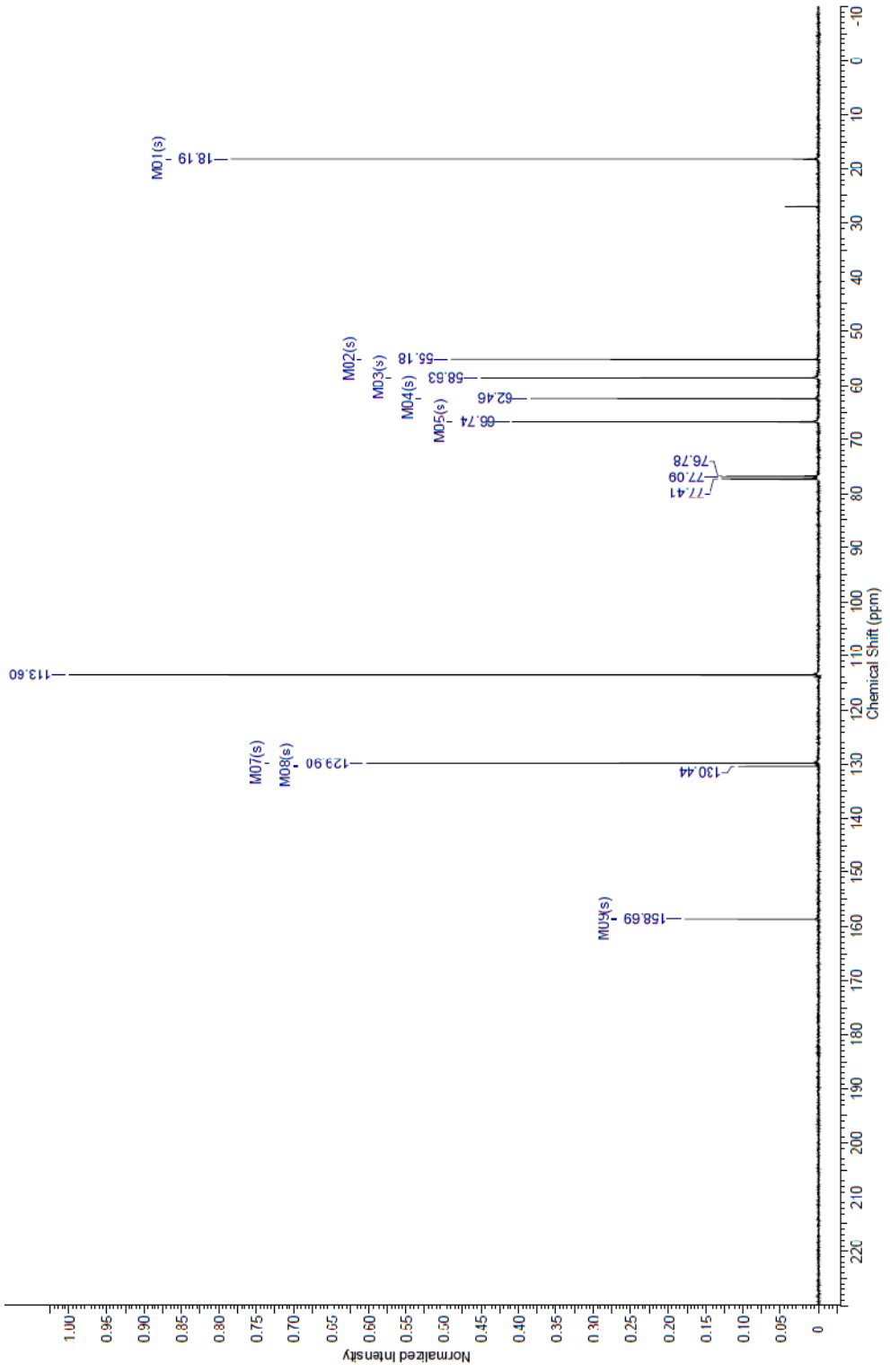


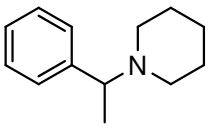
(2*R*,6*R*)-4-(4-Methoxybenzyl)-2,6-dimethylmorpholine 2o

^{1}H NMR



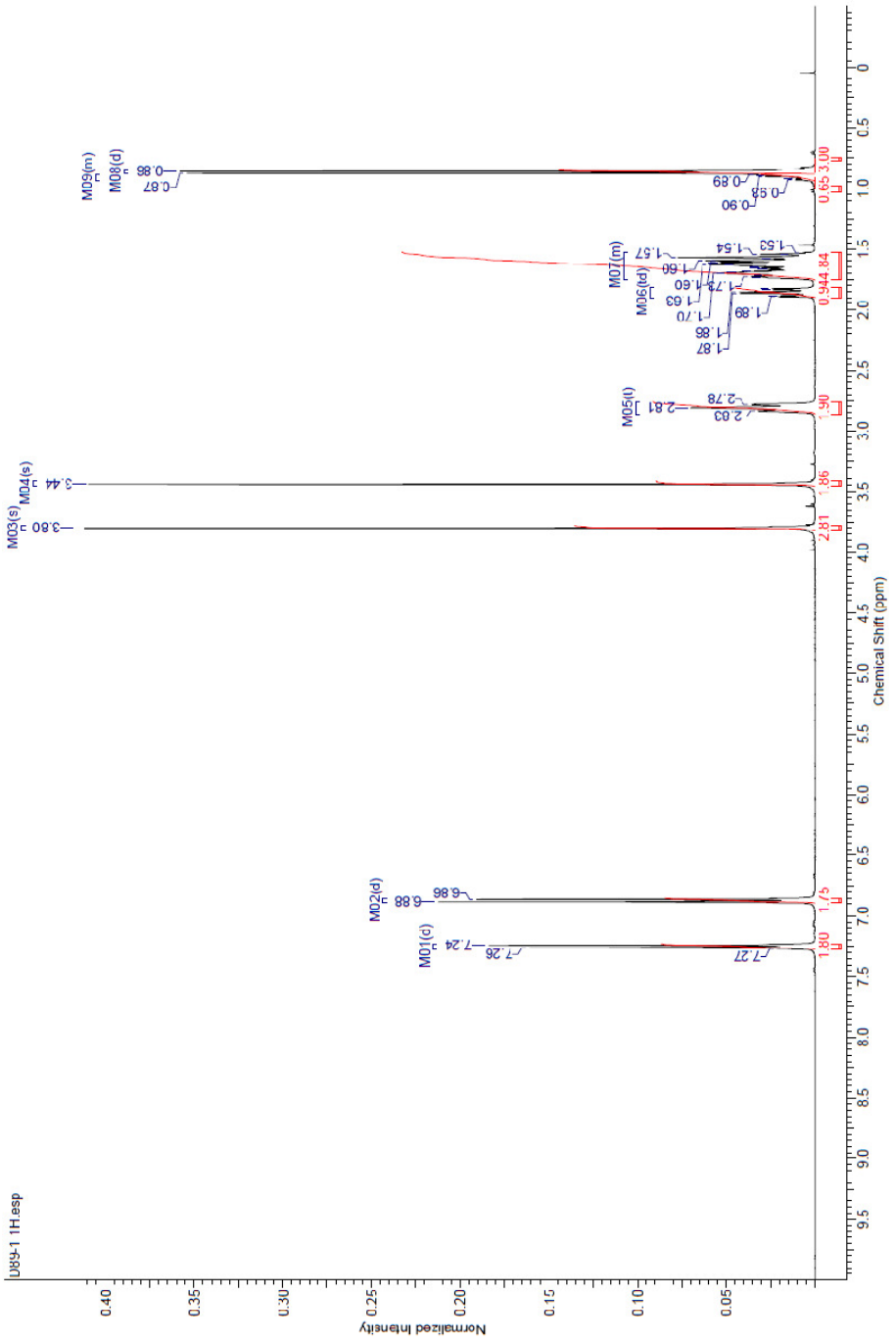
^{13}C NMR

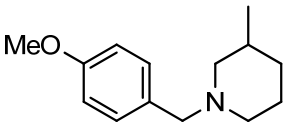

M01(s)
18.19
M02(s)
55.18
M03(s)
58.53
M04(s)
62.46
M05(s)
66.74
76.78
77.09
77.41
113.60
M07(s)
M08(s)
129.90
130.44
M09(s)
158.69
Chemical Shift (ppm)
Normalized Intensity



1-(1-Phenylethyl)piperidine 2s

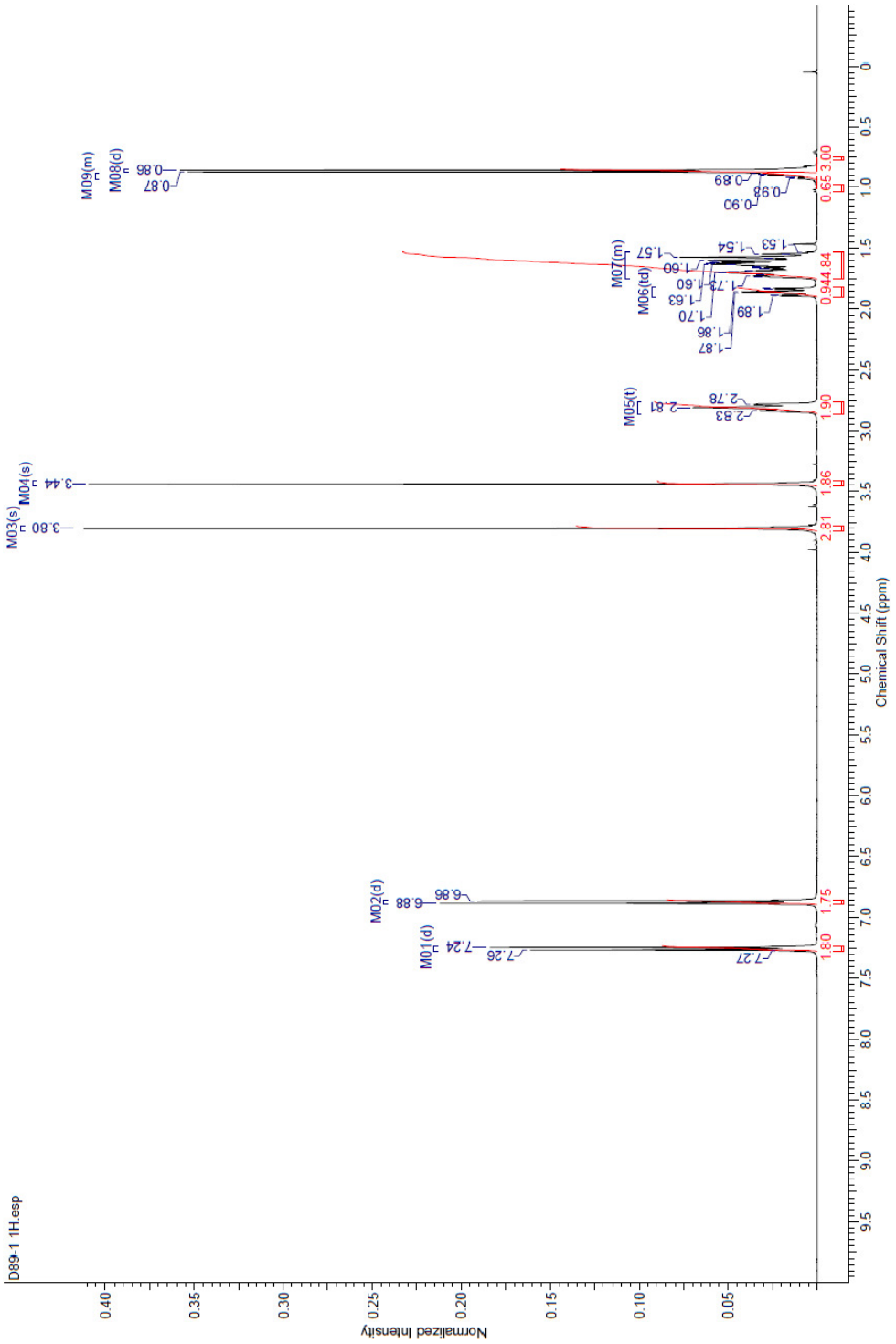
^{1}H NMR

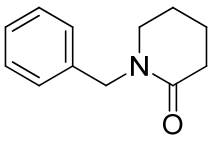




1-(4-Methoxybenzyl)-3-methylpiperidine 2t

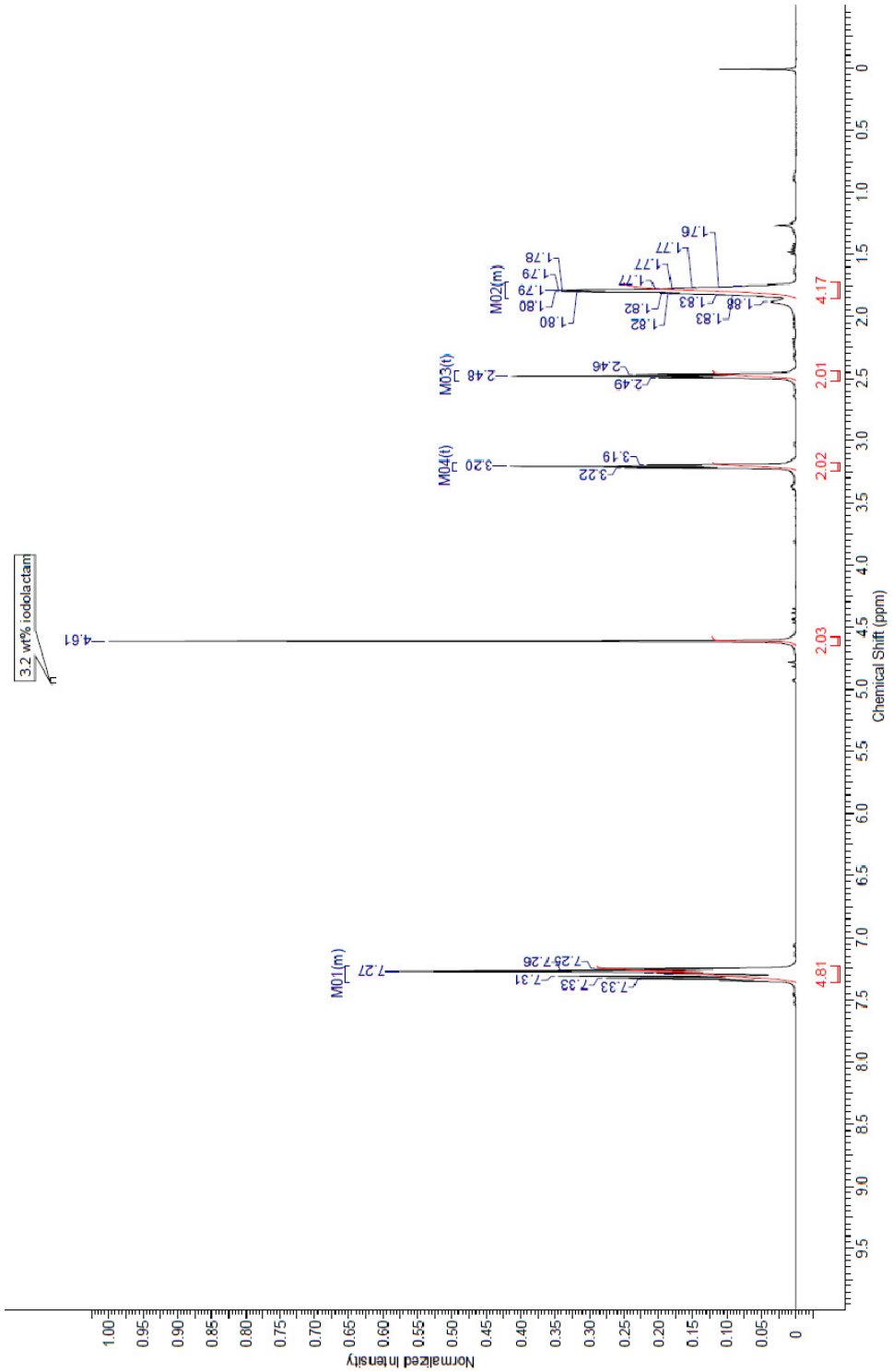
^{1}H NMR



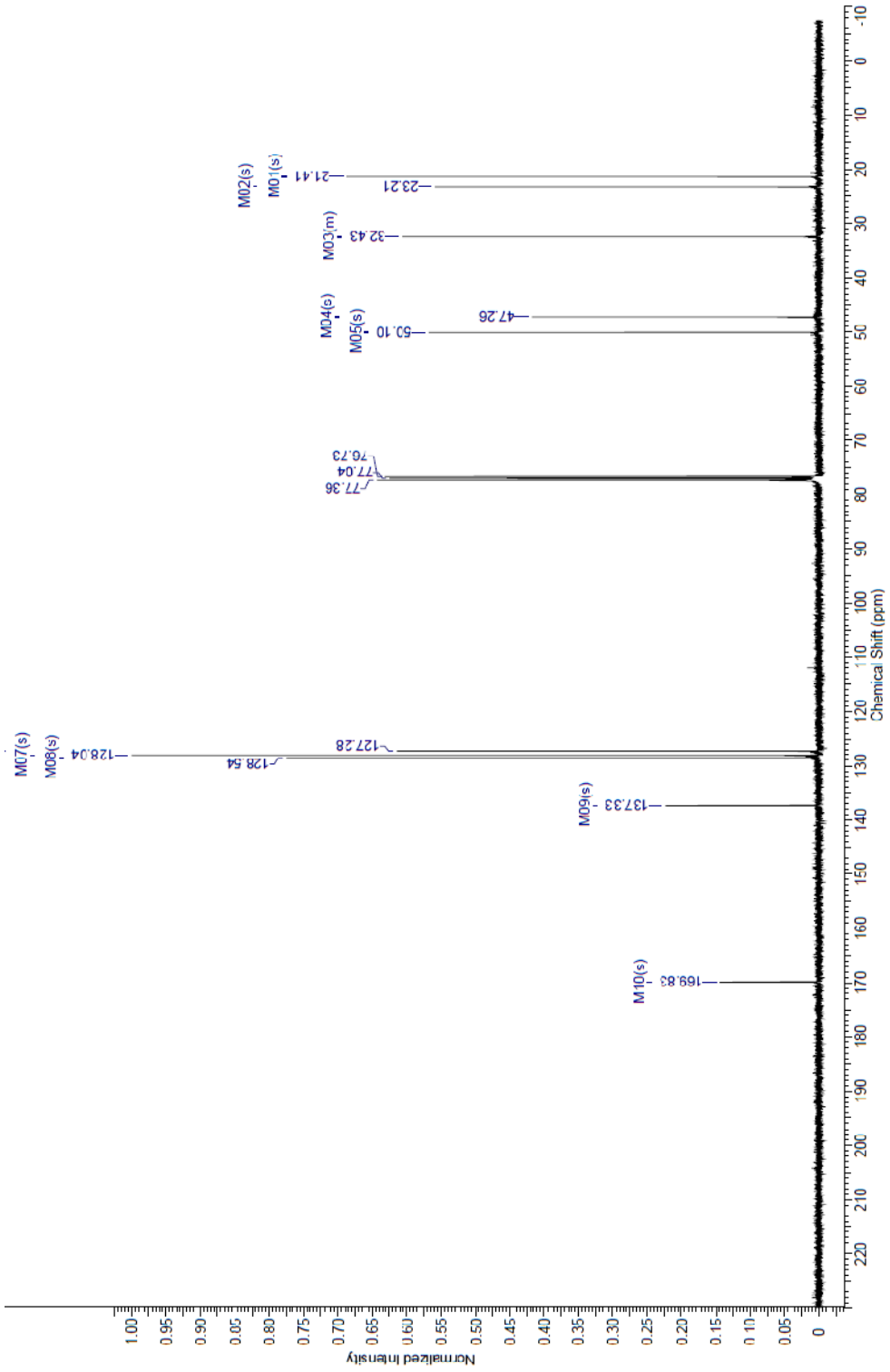


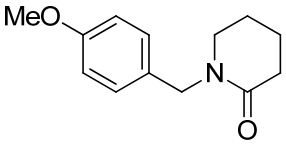
1-Benzylpiperidin-2-one 3a

^{1}H NMR



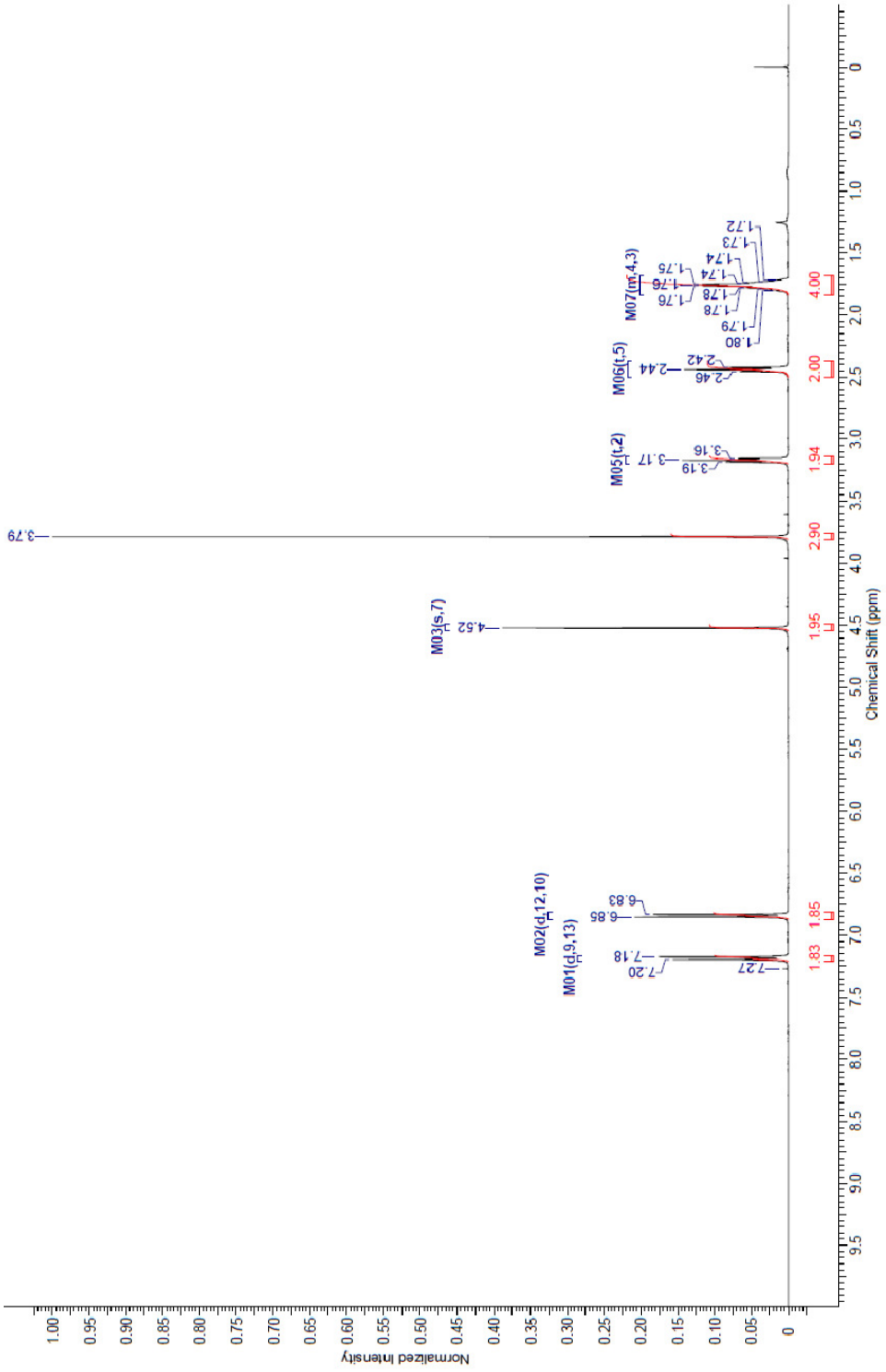
^{13}C NMR


M01(s)
M02(s)
M03(m)
M04(s)
M05(s)
M07(s)
M08(s)
M09(s)
M10(s)
21.41
23.21
32.43
47.26
53.10
76.73
77.04
77.36
127.28
128.54
128.04
137.33
169.83
Chemical Shift (ppm)
Normalized Intensity

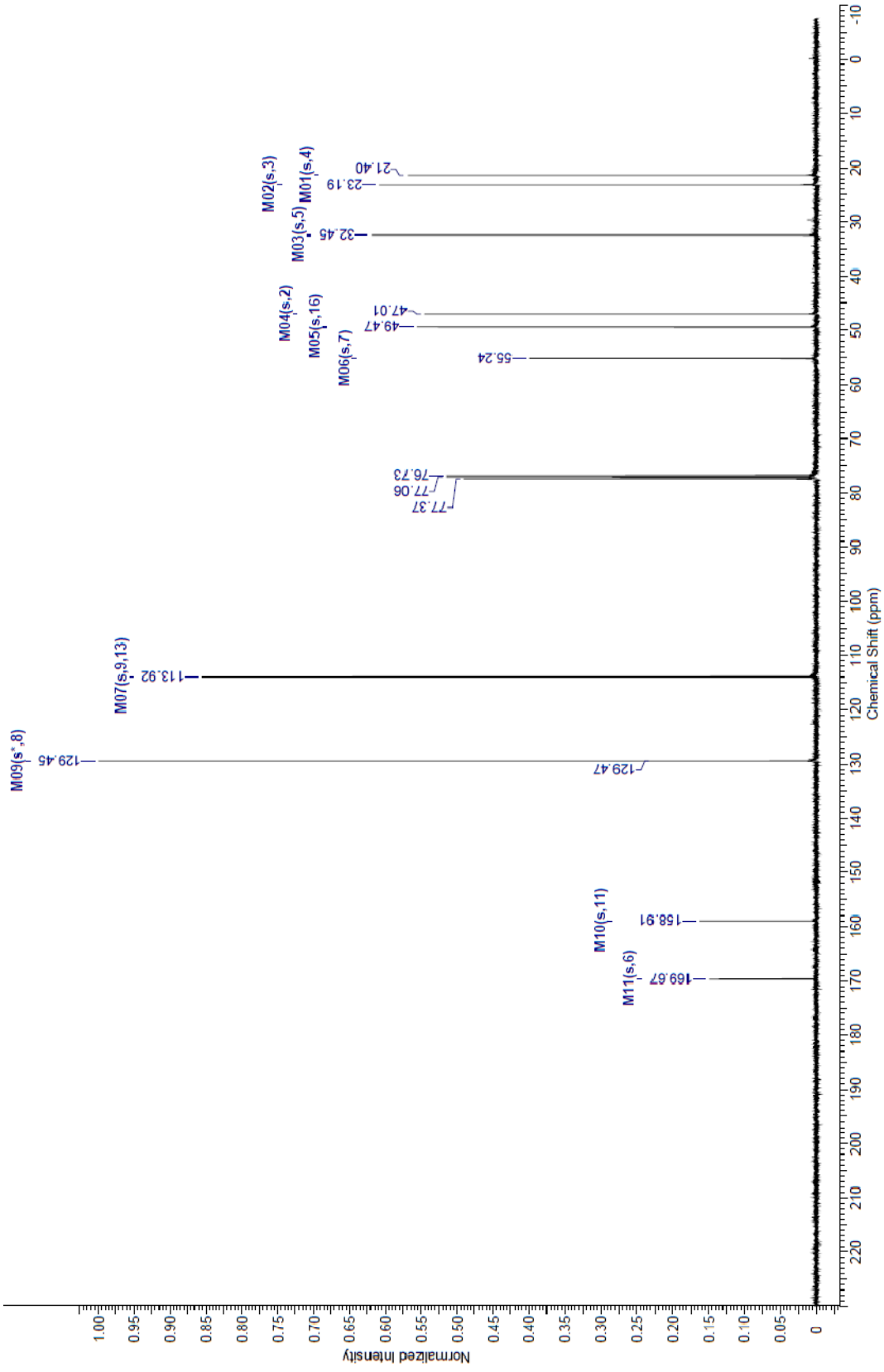


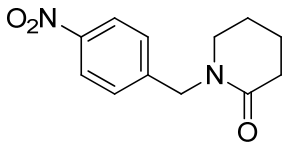
1-(4-Methoxybenzyl)piperidin-2-one 3b

^{1}H NMR



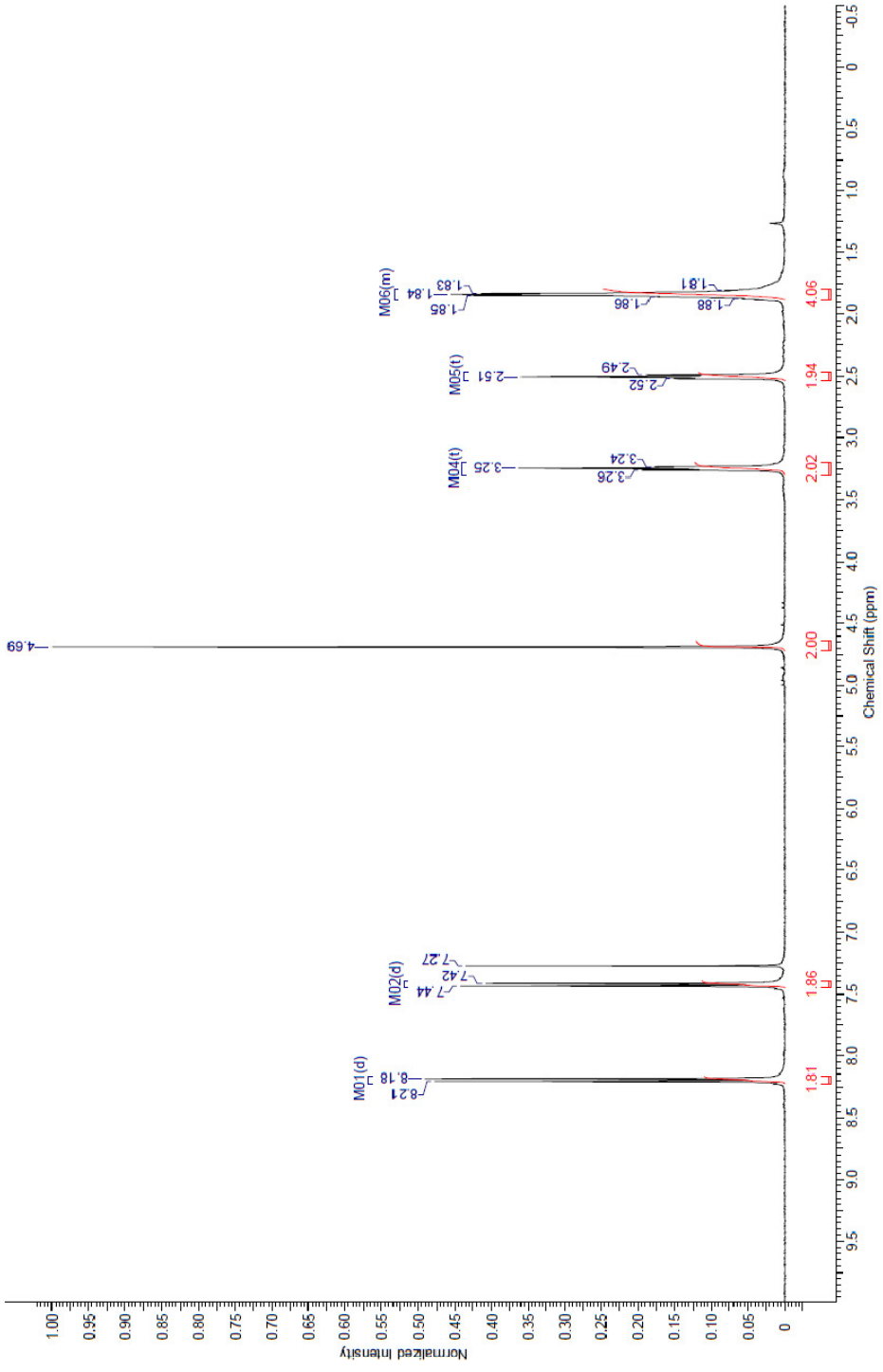
^{13}C NMR


M09(s,8)
129.45
129.47
M07(s,9,13)
113.92
M10(s,11)
158.91
M11(s,6)
169.67
M02(s,3)
M01(s,4)
21.40
23.19
M03(s,5)
32.45
M04(s,2)
M05(s,16)
47.01
49.47
M06(s,7)
55.24
77.37
77.06
76.73
Normalized Intensity
Chemical Shift (ppm)

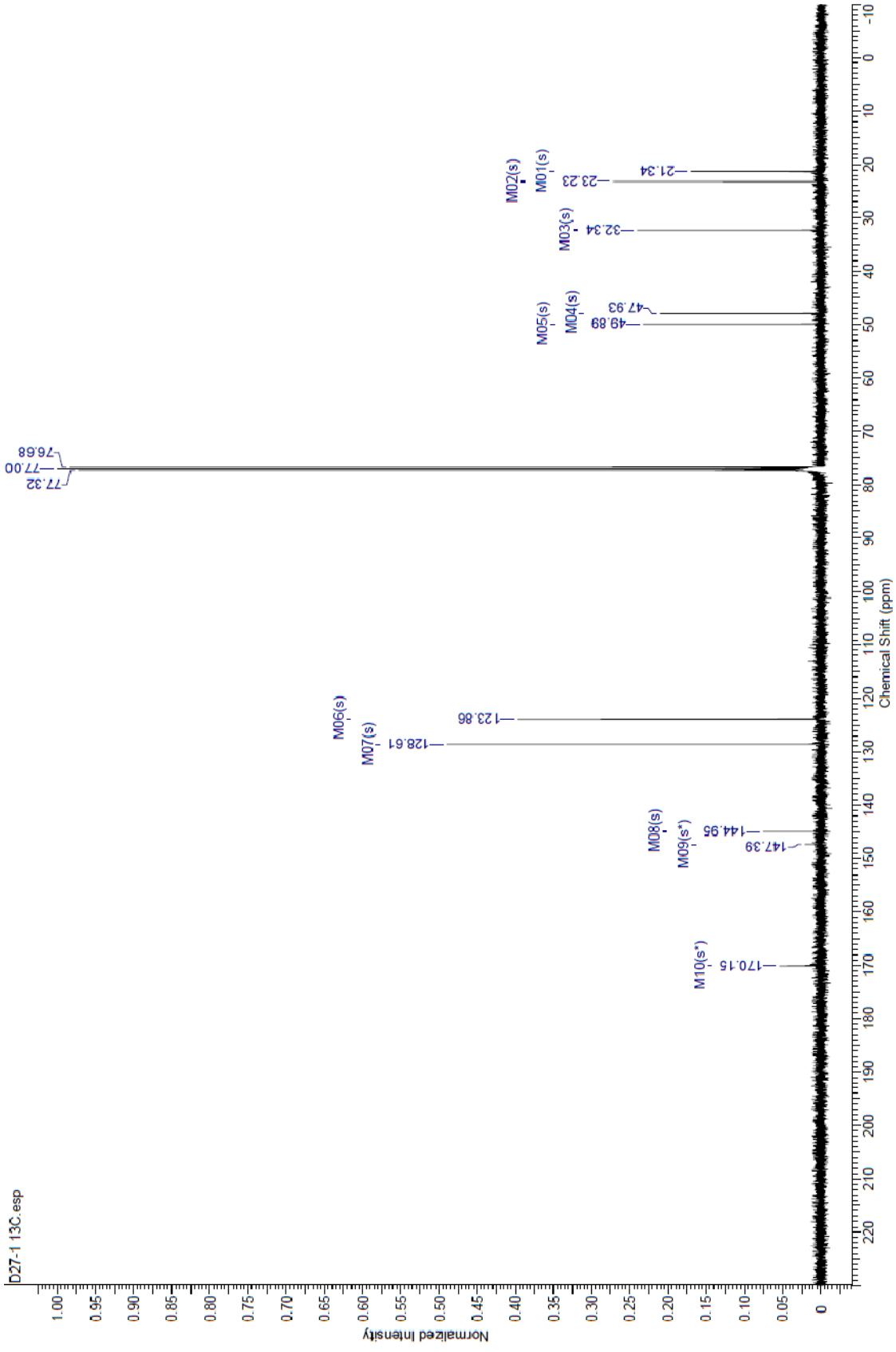


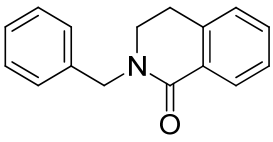
1-(4-Nitrobenzyl)piperidin-2-one 3c

^{1}H NMR



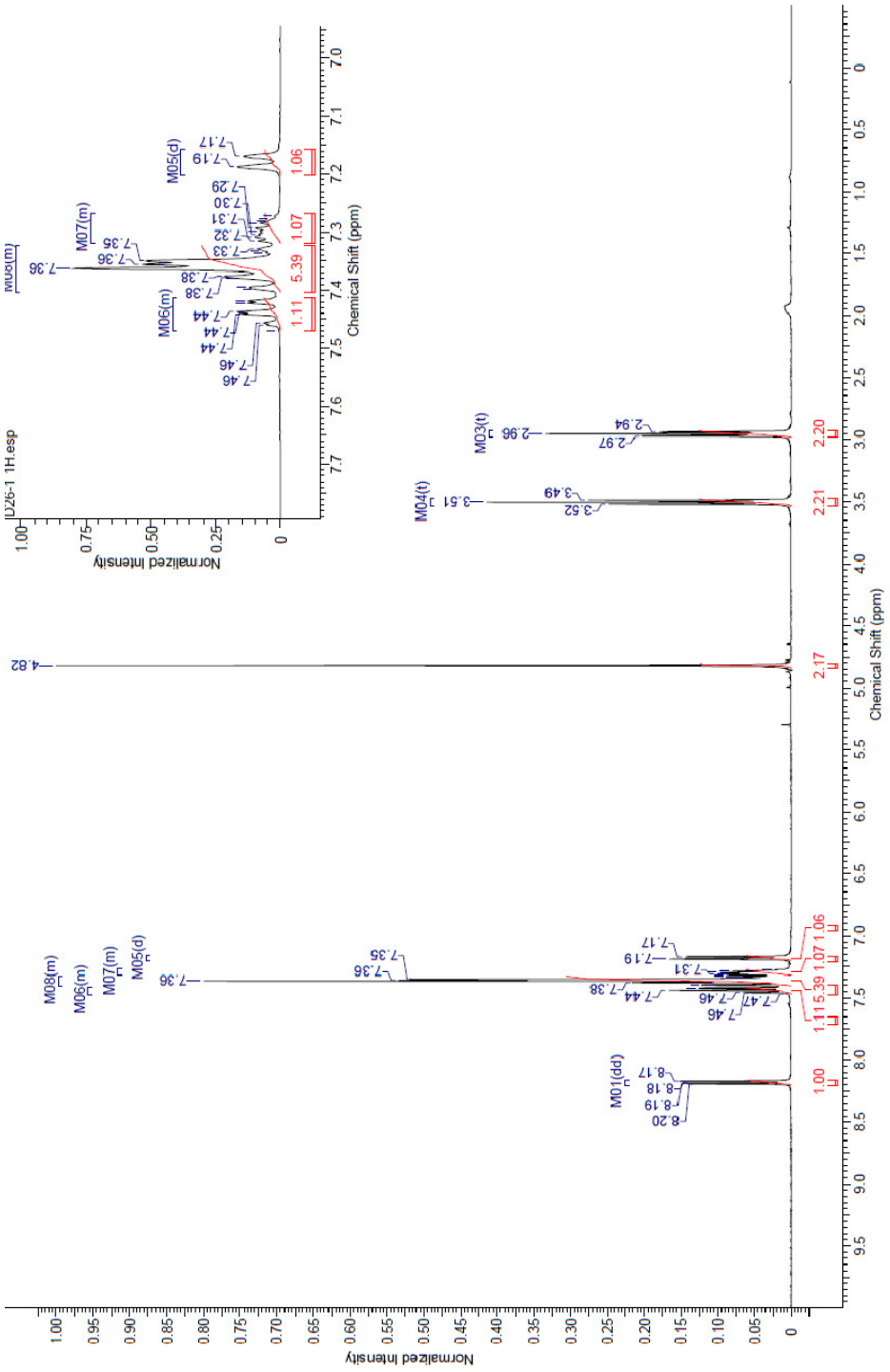
^{13}C NMR


D27-1 13C.esp
Normalized Intensity
Chemical Shift (ppm)
M01(s)
M02(s)
M03(s)
M04(s)
M05(s)
M06(s)
M07(s)
M08(s)
M09(s*)
M10(s*)
21.34
23.23
32.34
47.93
49.89
76.68
77.00
77.32
123.86
128.61
144.95
147.39
170.15

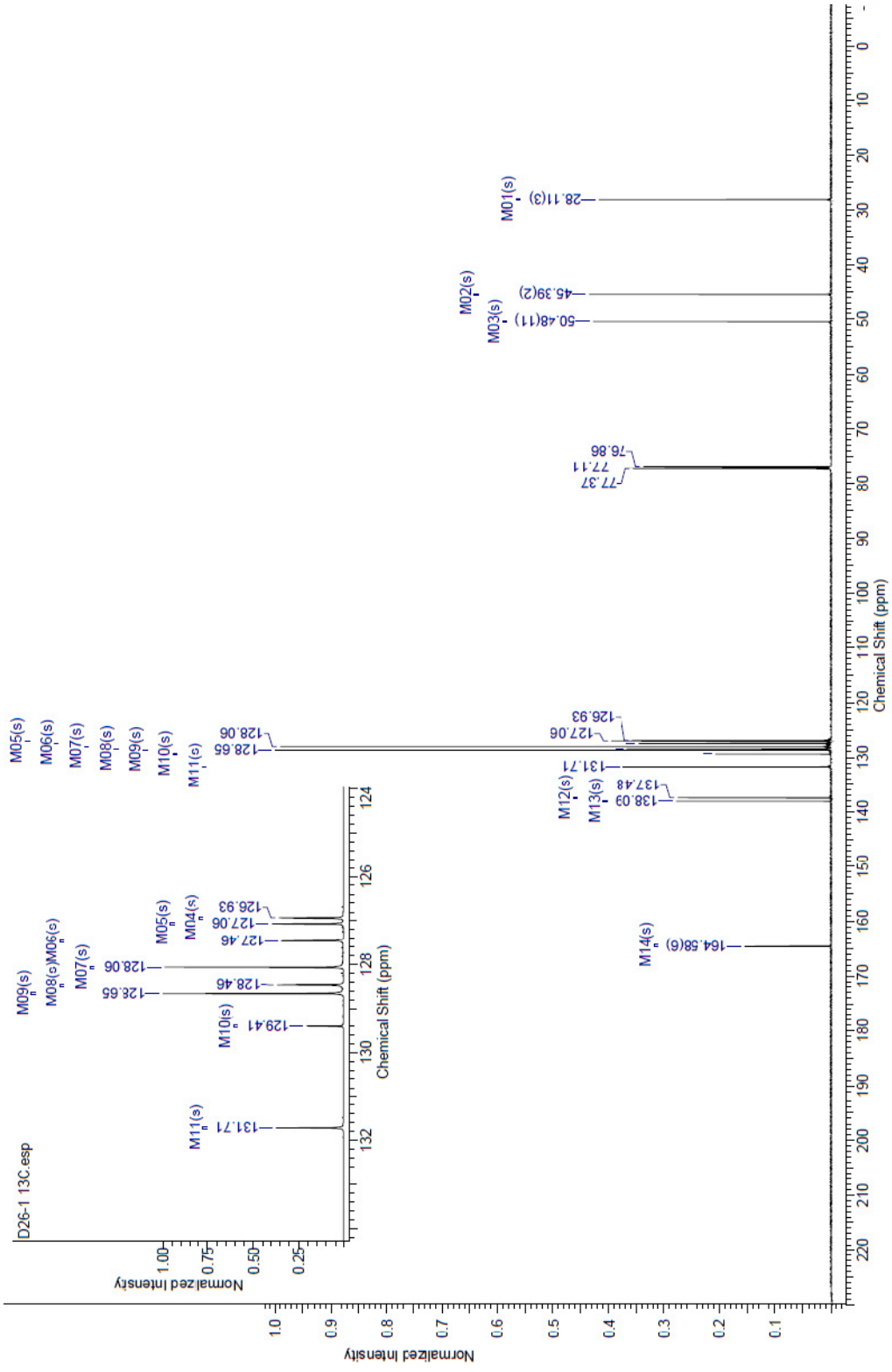


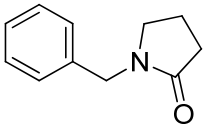
2-Benzyl-3,4-dihydroisoquinolin-1(2H)-one 3d

^{1}H NMR



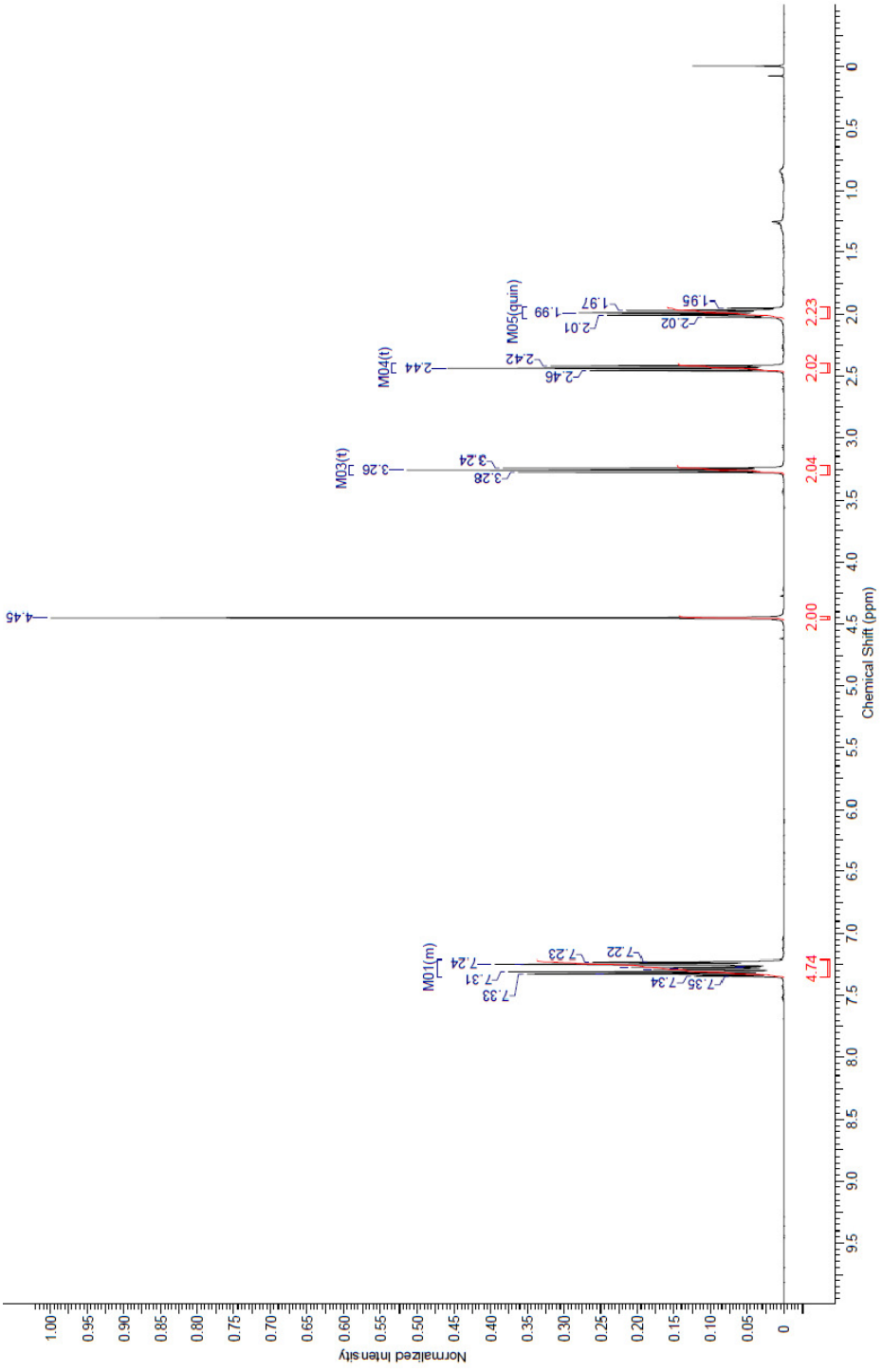
^{13}C NMR


Chemical Shift (ppm)
Normalized Intensity
M01(s)
28.11(3)
M02(s)
45.39(2)
M03(s)
50.48(11)
77.37
77.11
76.86
M14(s)
164.58(6)
M12(s)
M13(s)
138.09
137.48
131.71
127.06
126.93
M05(s)
M06(s)
M07(s)
M08(s)
M09(s)
M10(s)
M11(s)
128.65
128.06
D26-1 13C.esp
M09(s)
M08(s)M06(s)
M07(s)
128.06
126.65
M10(s)
129.41
M11(s)
131.71
M05(s)
M04(s)
126.93
127.06
127.46
128.46
Chemical Shift (ppm)
Normalized Intensity

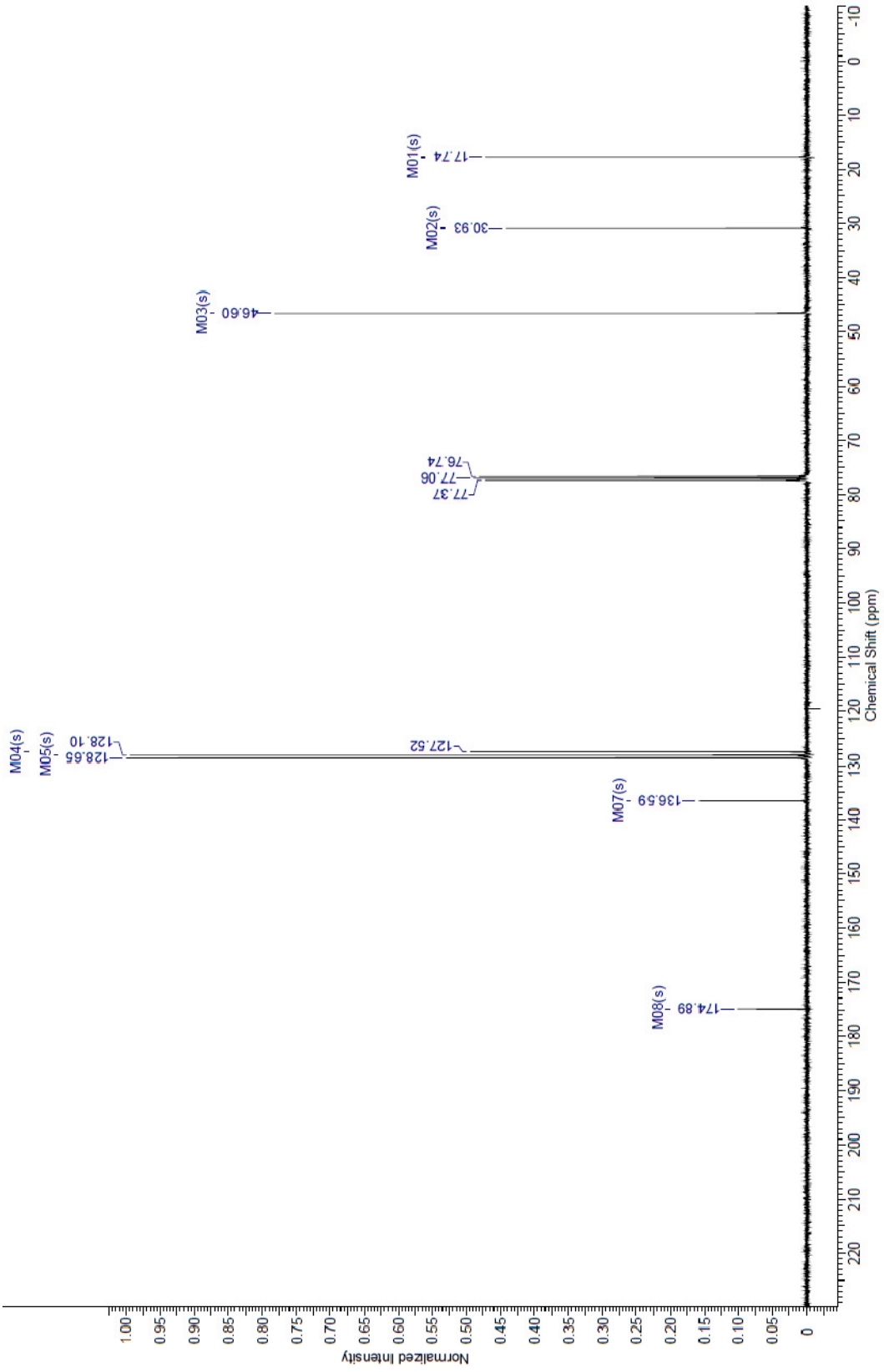


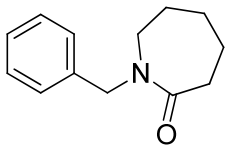
1-Benzylpyrrolidin-2-one 3e

^{1}H NMR



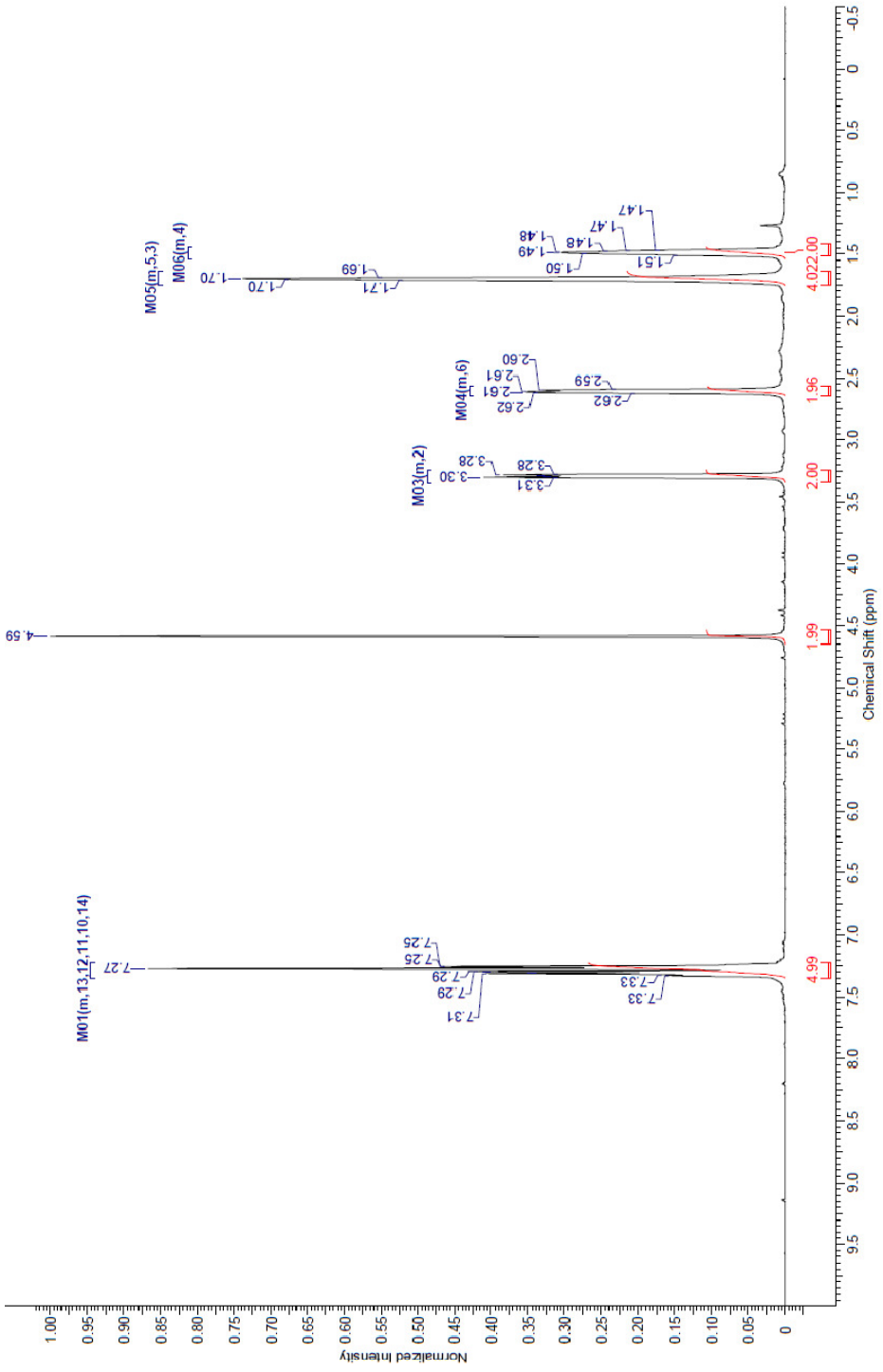
^{13}C NMR


M01(s)
17.74
M02(s)
30.93
M03(s)
46.60
77.37
77.06
76.74
M04(s)
M05(s)
128.65
128.10
127.52
M07(s)
136.59
M08(s)
174.89
Chemical Shift (ppm)
Normalized Intensity

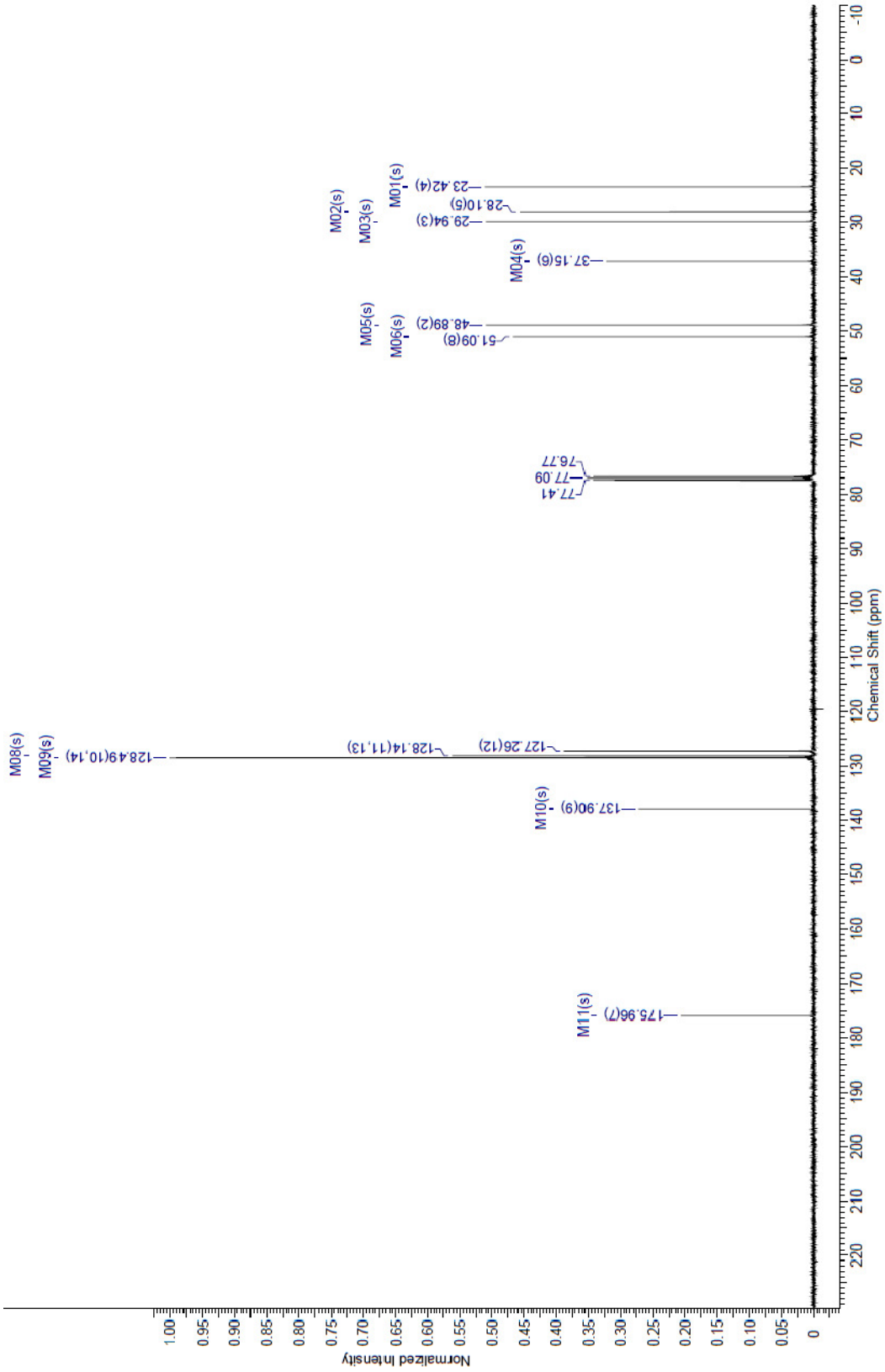


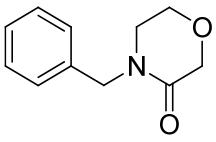
1-Benzylazepan-2-one 3f

^{1}H NMR



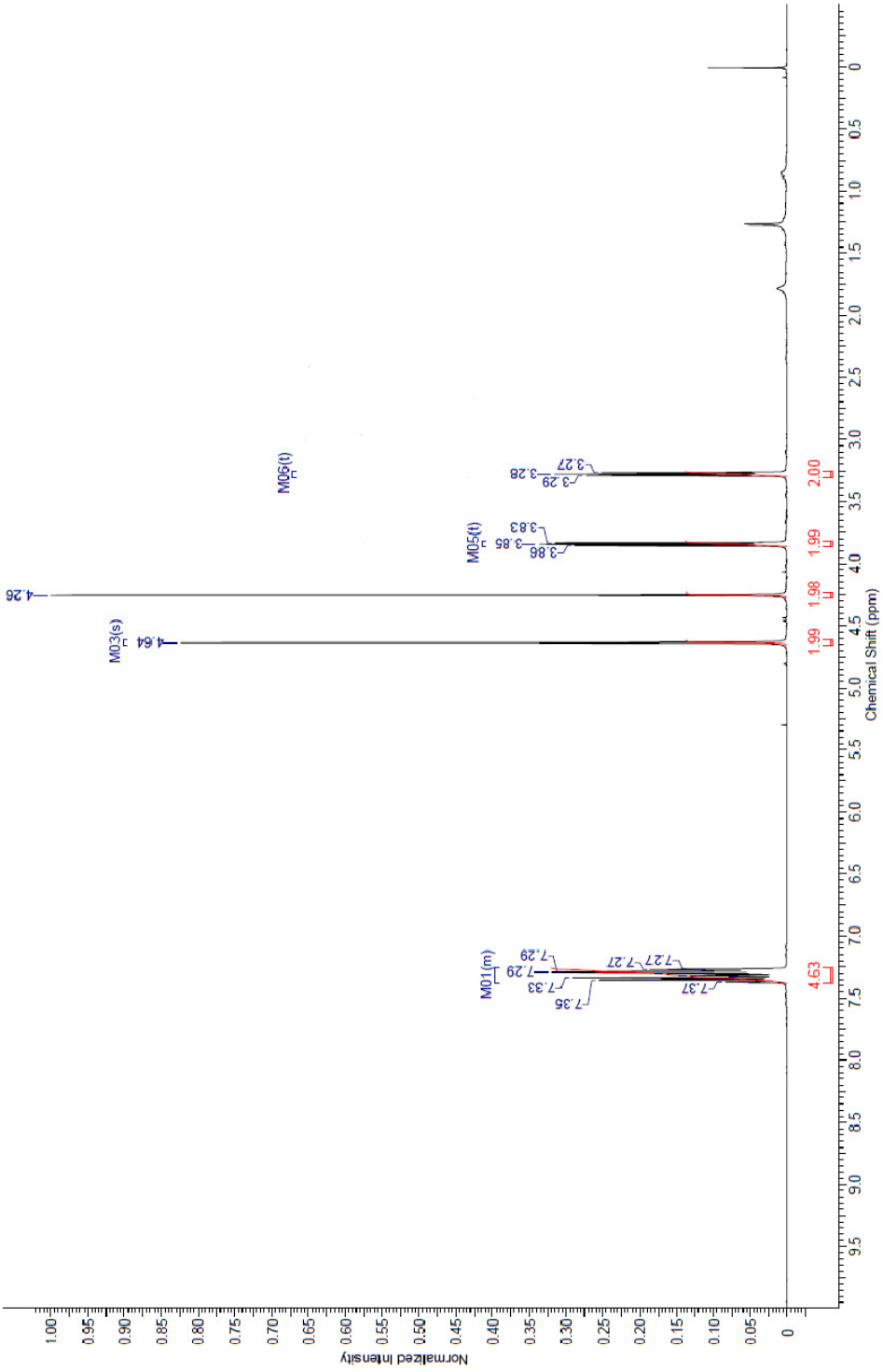
^{13}C NMR


M01(s)
23.42(4)
28.10(5)
29.94(3)
M02(s)
M03(s)
M04(s)
37.15(6)
M05(s)
48.89(2)
M06(s)
51.09(8)
77.41
77.09
76.77
M08(s)
M09(s)
128.49(10,14)
128.14(11,13)
127.26(12)
M10(s)
137.90(9)
M11(s)
175.96(7)
Chemical Shift (ppm)
Normalized Intensity

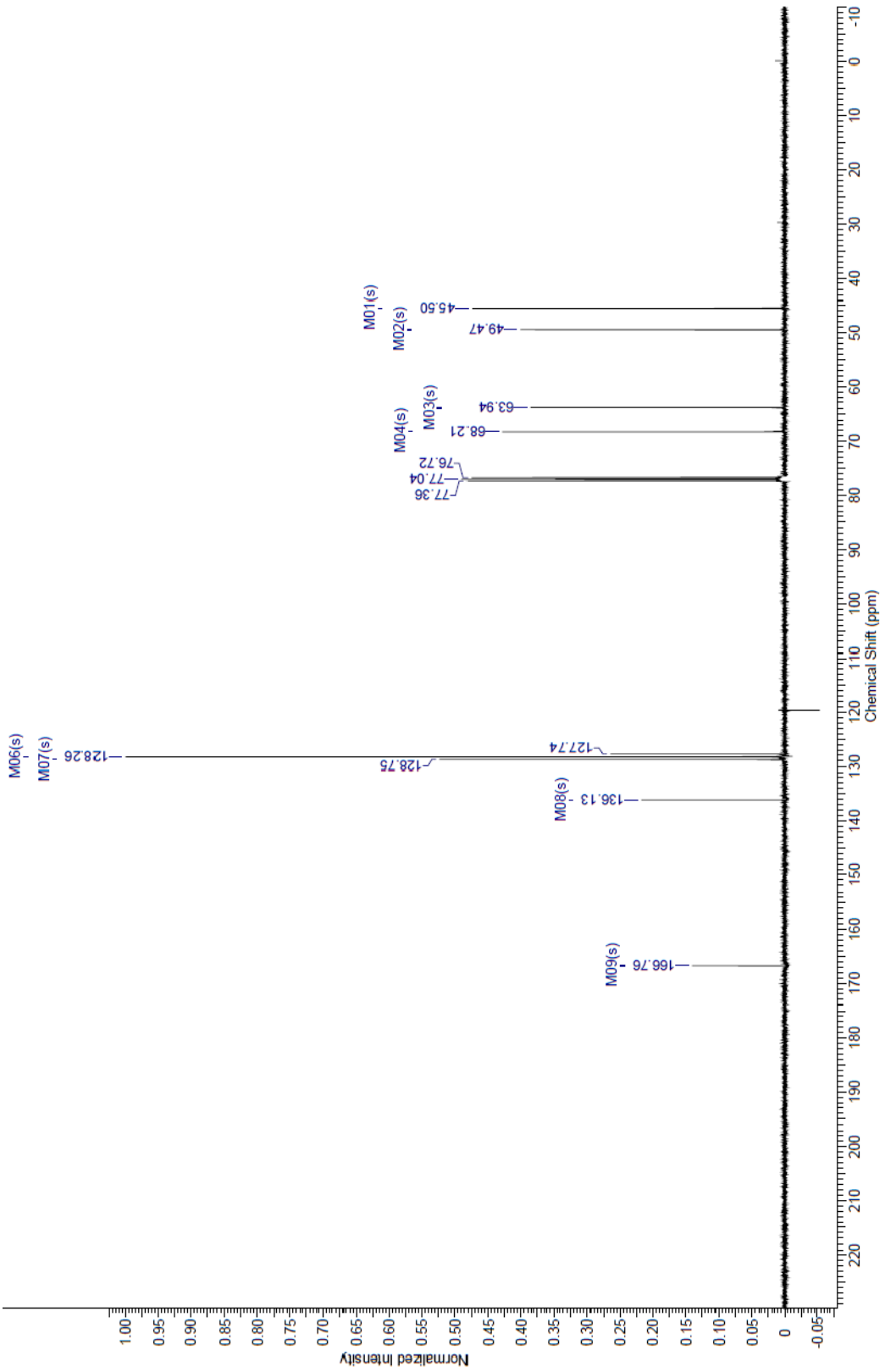


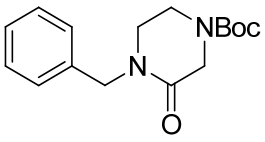
4-Benzylmorpholin-3-one 3g

^{1}H NMR



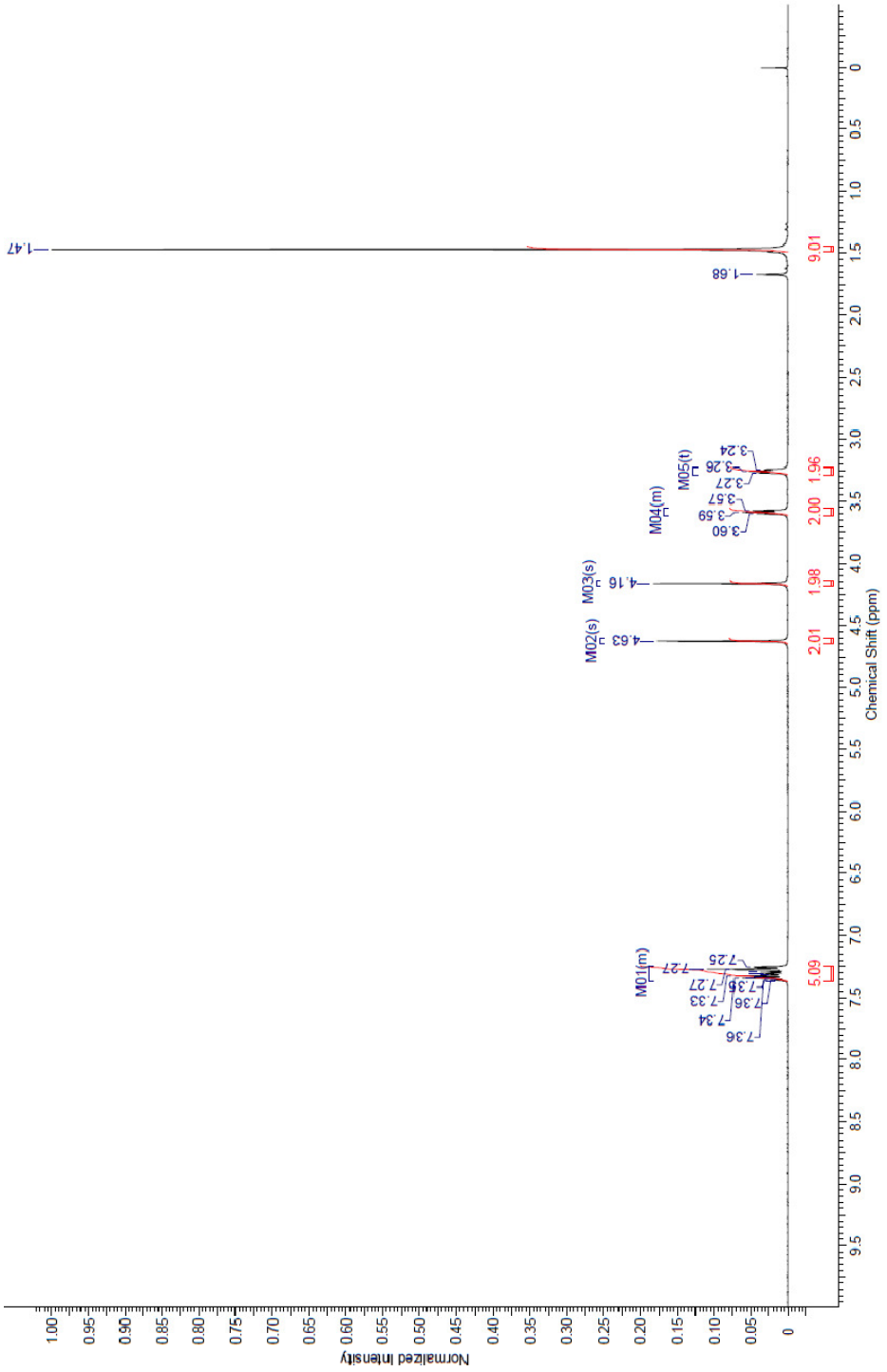
^{13}C NMR


M01(s)
M02(s)
M03(s)
M04(s)
M06(s)
M07(s)
M08(s)
M09(s)
45.50
49.47
63.94
68.21
76.72
77.04
77.36
127.74
128.26
128.75
136.13
166.76
Normalized Intensity
Chemical Shift (ppm)

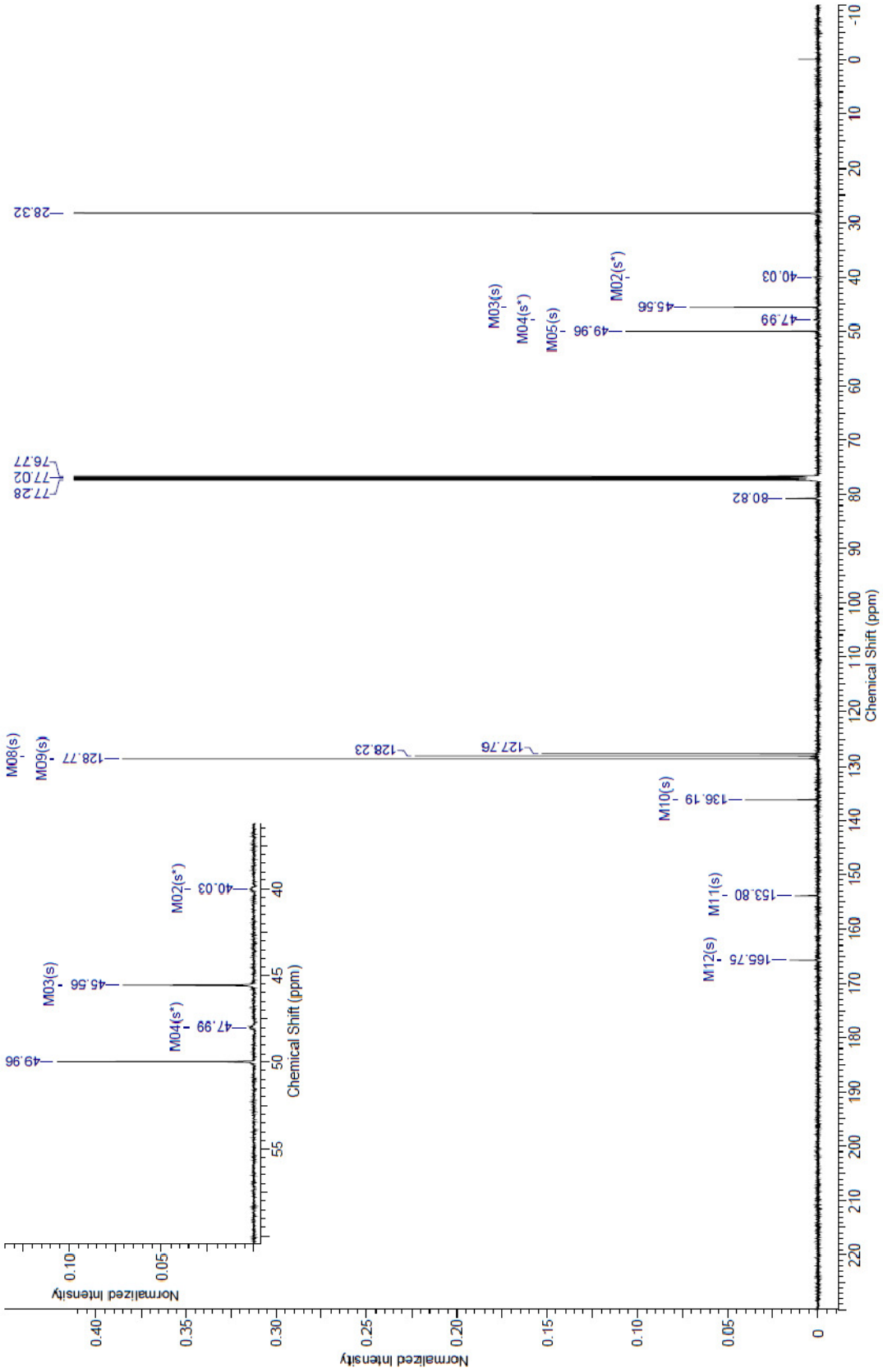


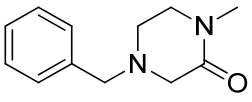
Tert-butyl 4-benzyl-3-oxopiperazine-1-carboxylate 3h

^{1}H NMR



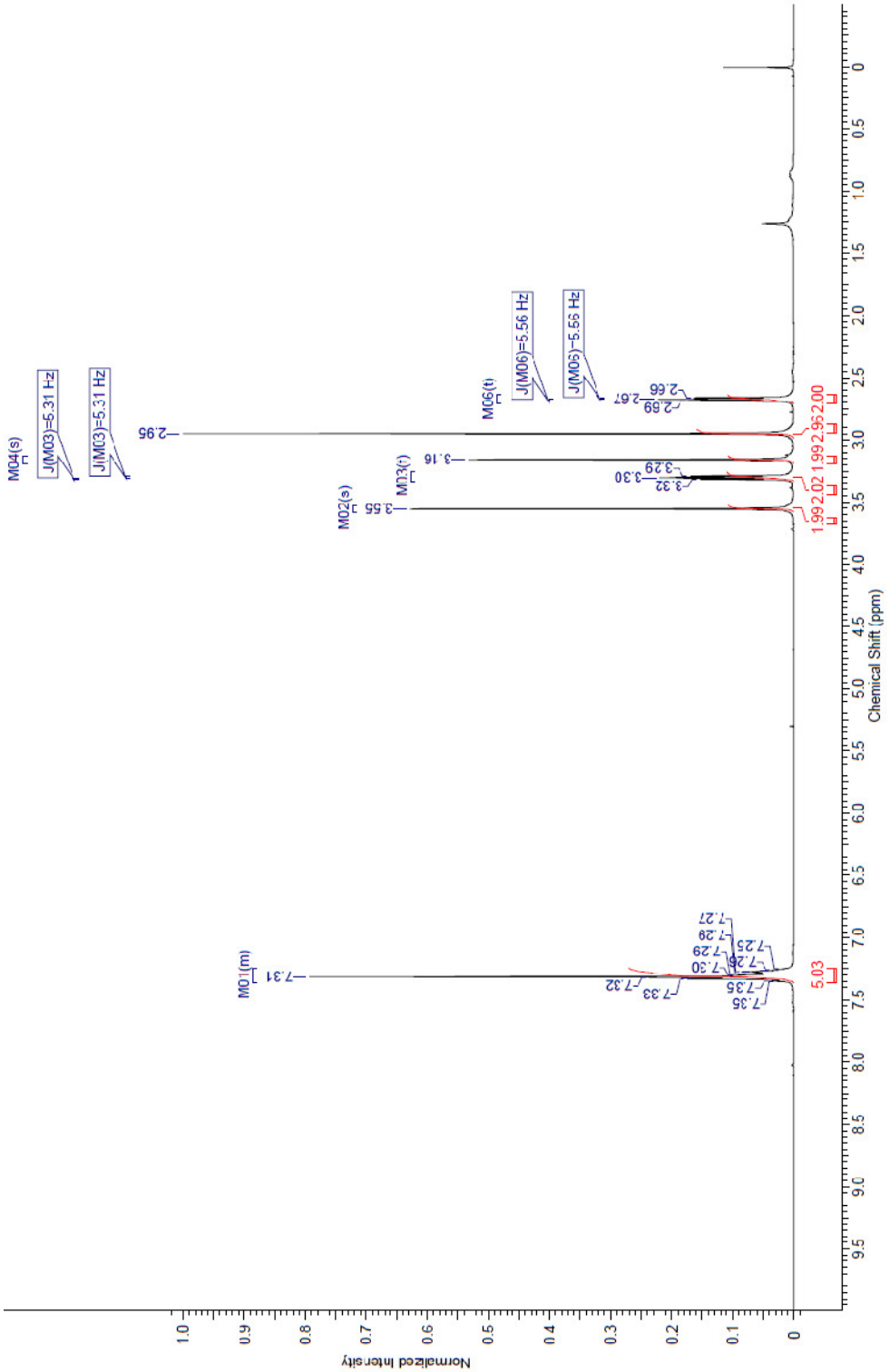
^{13}C NMR


28.32
40.03
45.56
47.99
49.96
80.82
128.77
128.23
127.76
136.19
153.80
165.75
Chemical Shift (ppm)
Normalized Intensity

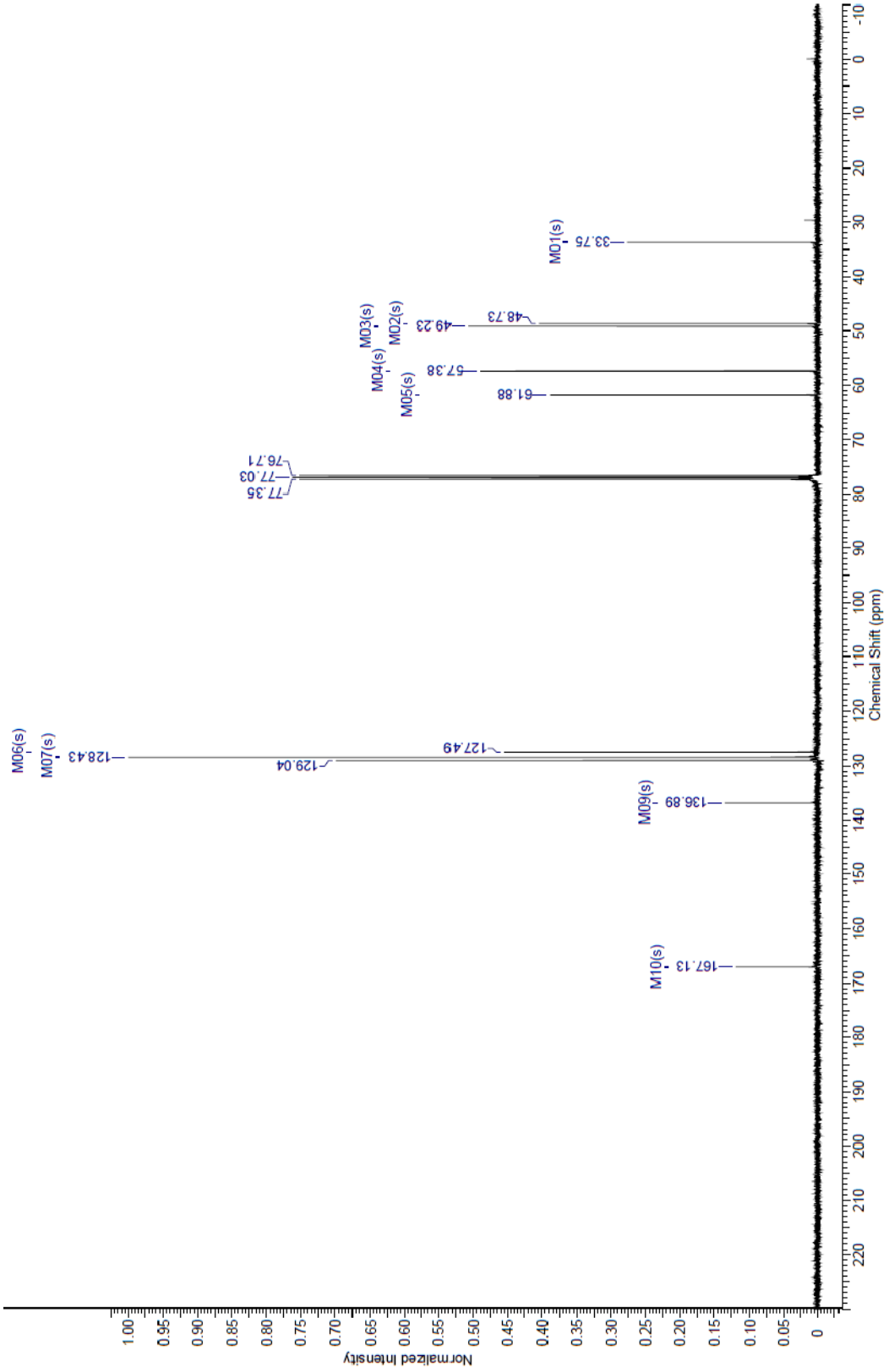


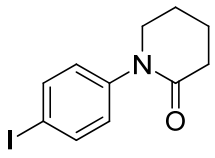
4-Benzyl-1-methylpiperazin-2-one 3i

^{1}H NMR



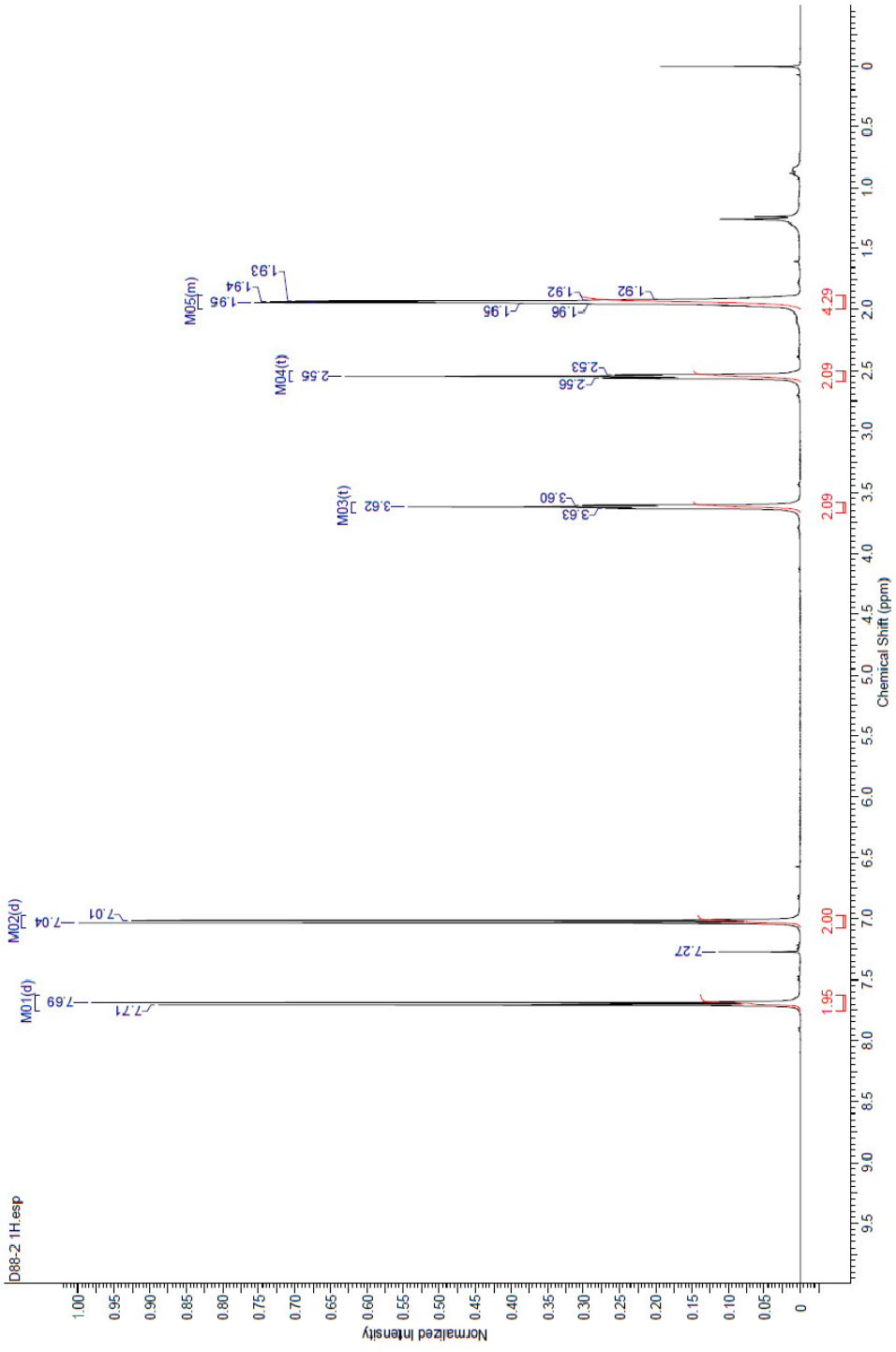
^{13}C NMR


M01(s)
33.75
M02(s)
M03(s)
49.23
48.73
M04(s)
M05(s)
57.38
61.88
77.35
77.03
76.71
M06(s)
M07(s)
128.43
129.04
127.49
M09(s)
136.89
M10(s)
167.13
Chemical Shift (ppm)
Normalized Intensity

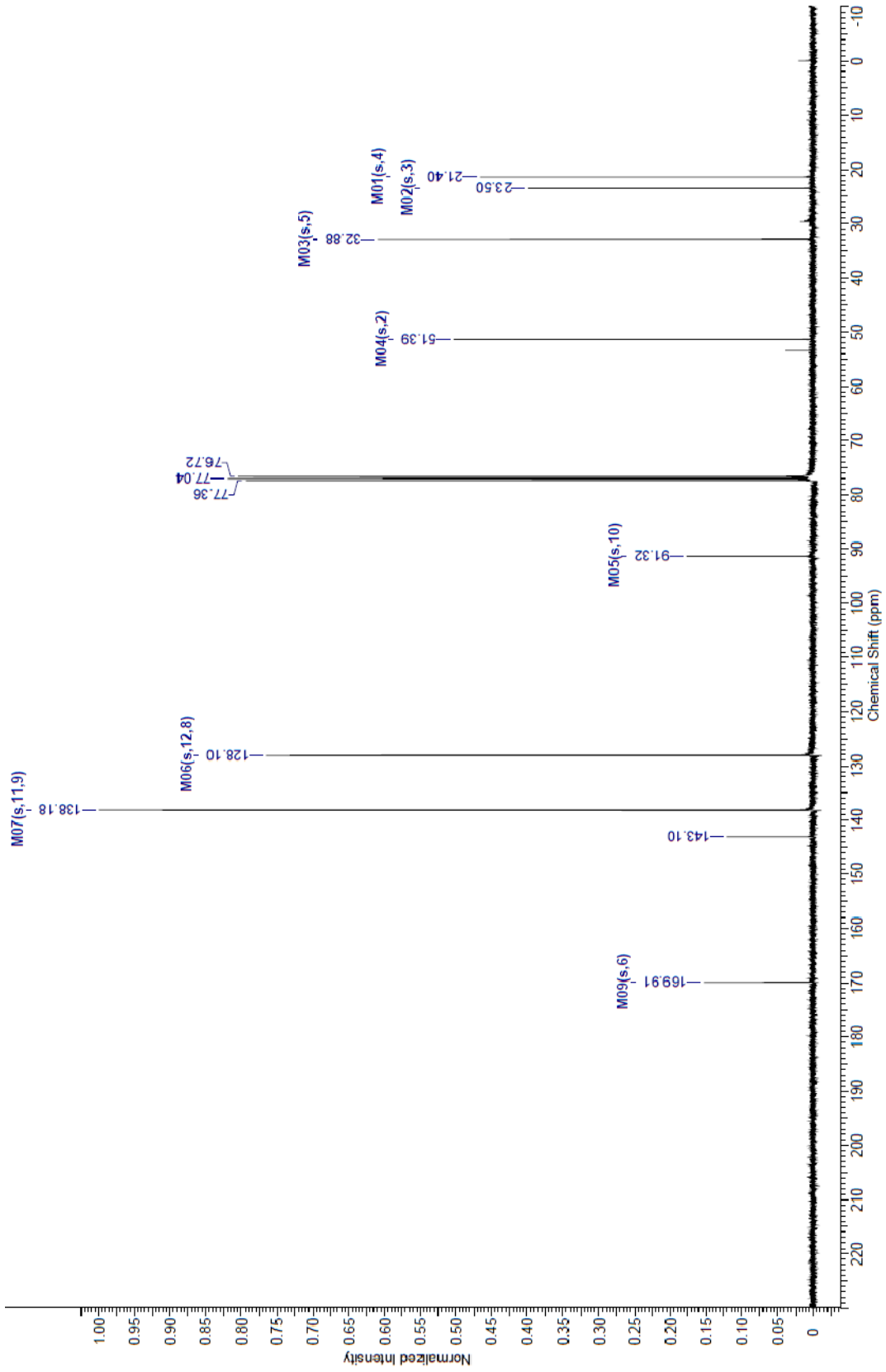


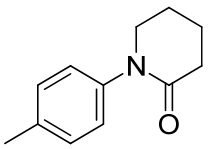
1-(4-Iodophenyl)piperidin-2-one 3j

^{1}H NMR



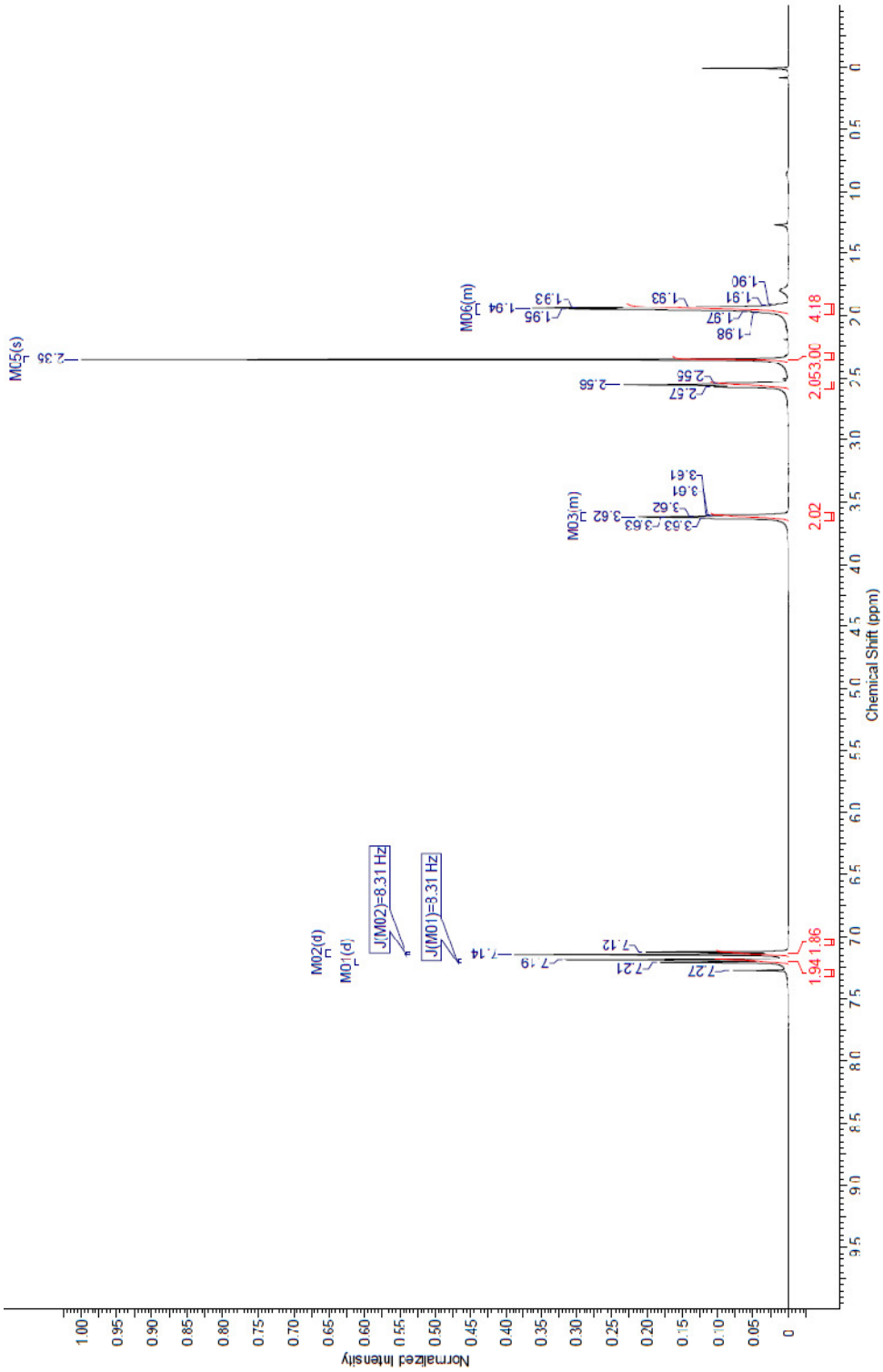
^{13}C NMR


M01(s,4)
M02(s,3)
M03(s,5)
M04(s,2)
M05(s,10)
M06(s,12,8)
M07(s,11,9)
M09(s,6)
21.40
23.50
32.88
51.39
76.72
77.04
77.36
91.32
128.10
138.18
143.10
169.91
Chemical Shift (ppm)
Normalized Intensity

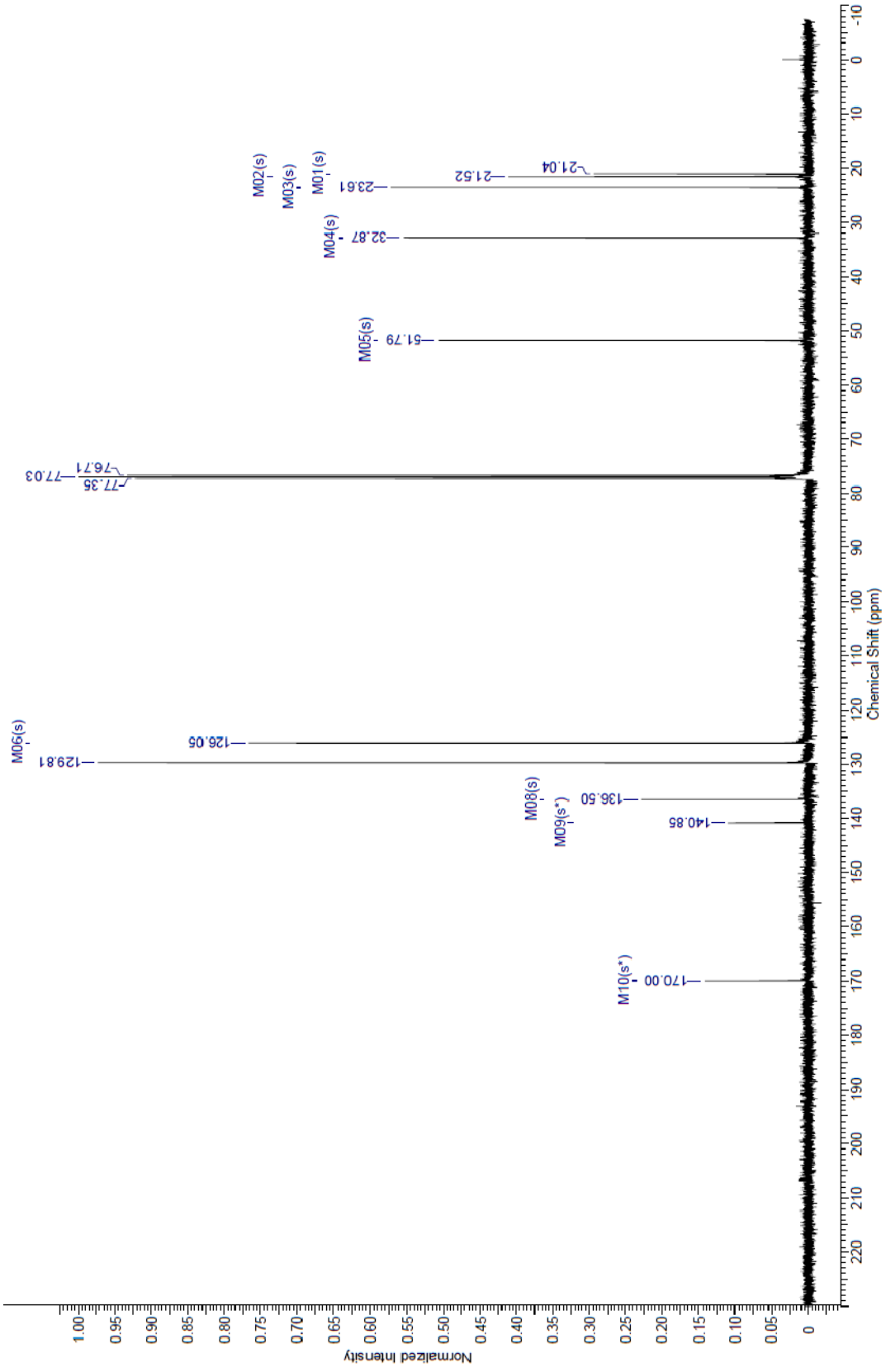


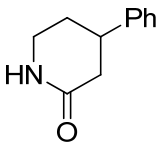
1-(*p*-Tolyl)piperidin-2-one 3k

^{1}H NMR



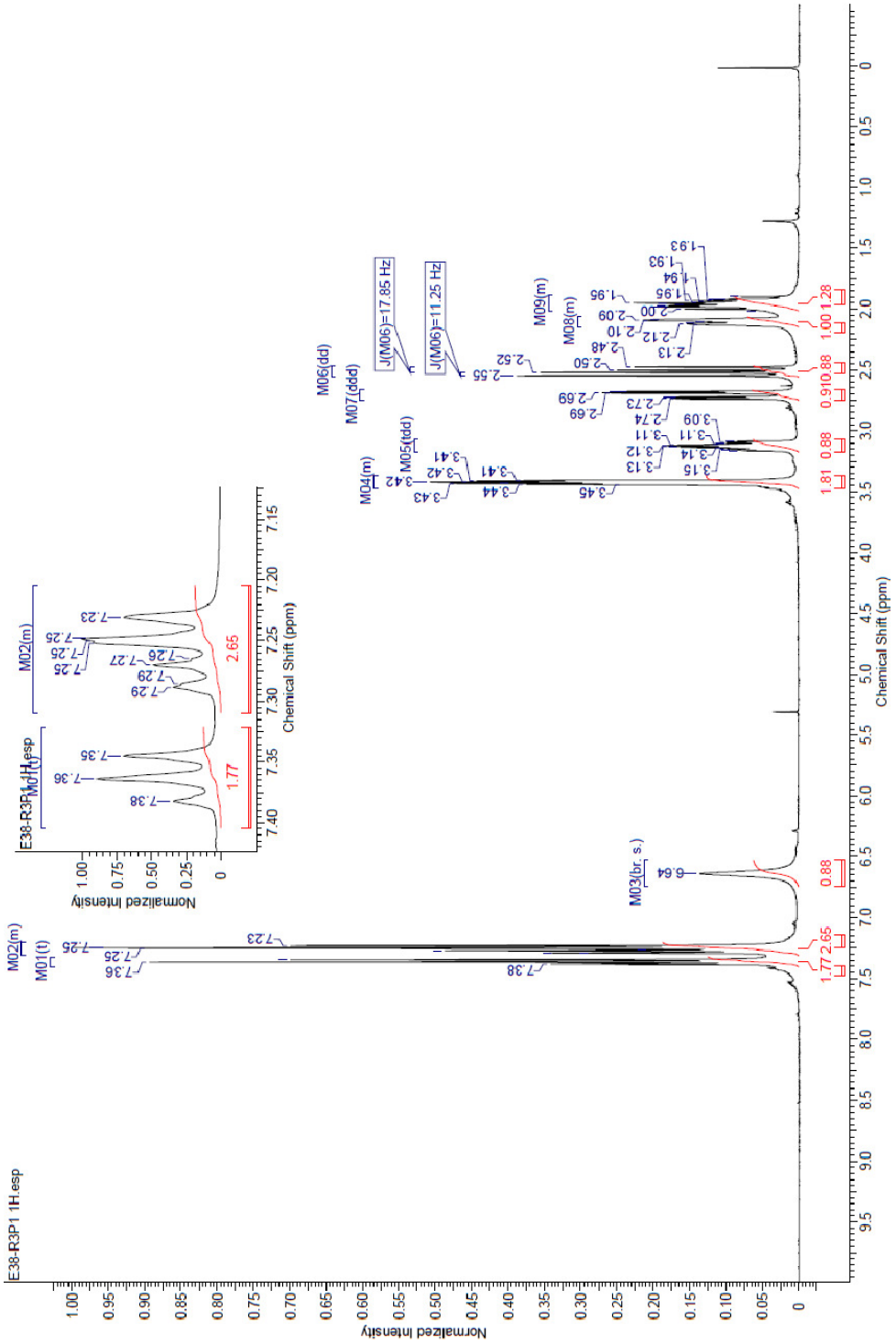
^{13}C NMR


M01(s)
M02(s)
M03(s)
M04(s)
M05(s)
M06(s)
M08(s)
M09(s*)
M10(s*)
21.04
21.52
23.61
32.87
51.79
76.71
77.03
77.35
126.05
129.81
136.50
140.85
170.00
Chemical Shift (ppm)
Normalized Intensity

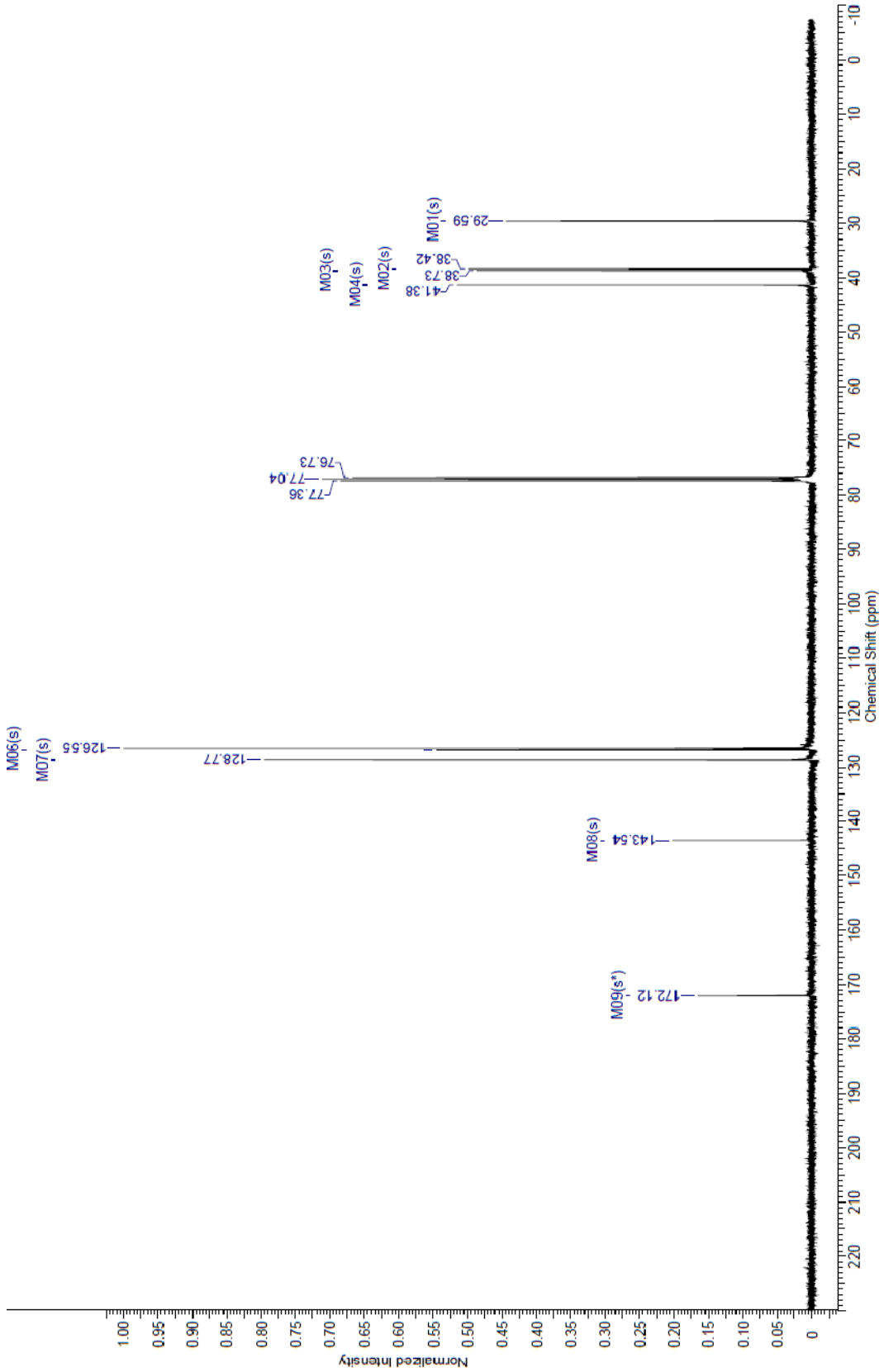


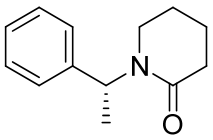
4-Phenylpiperidin-2-one 3l

^{1}H NMR



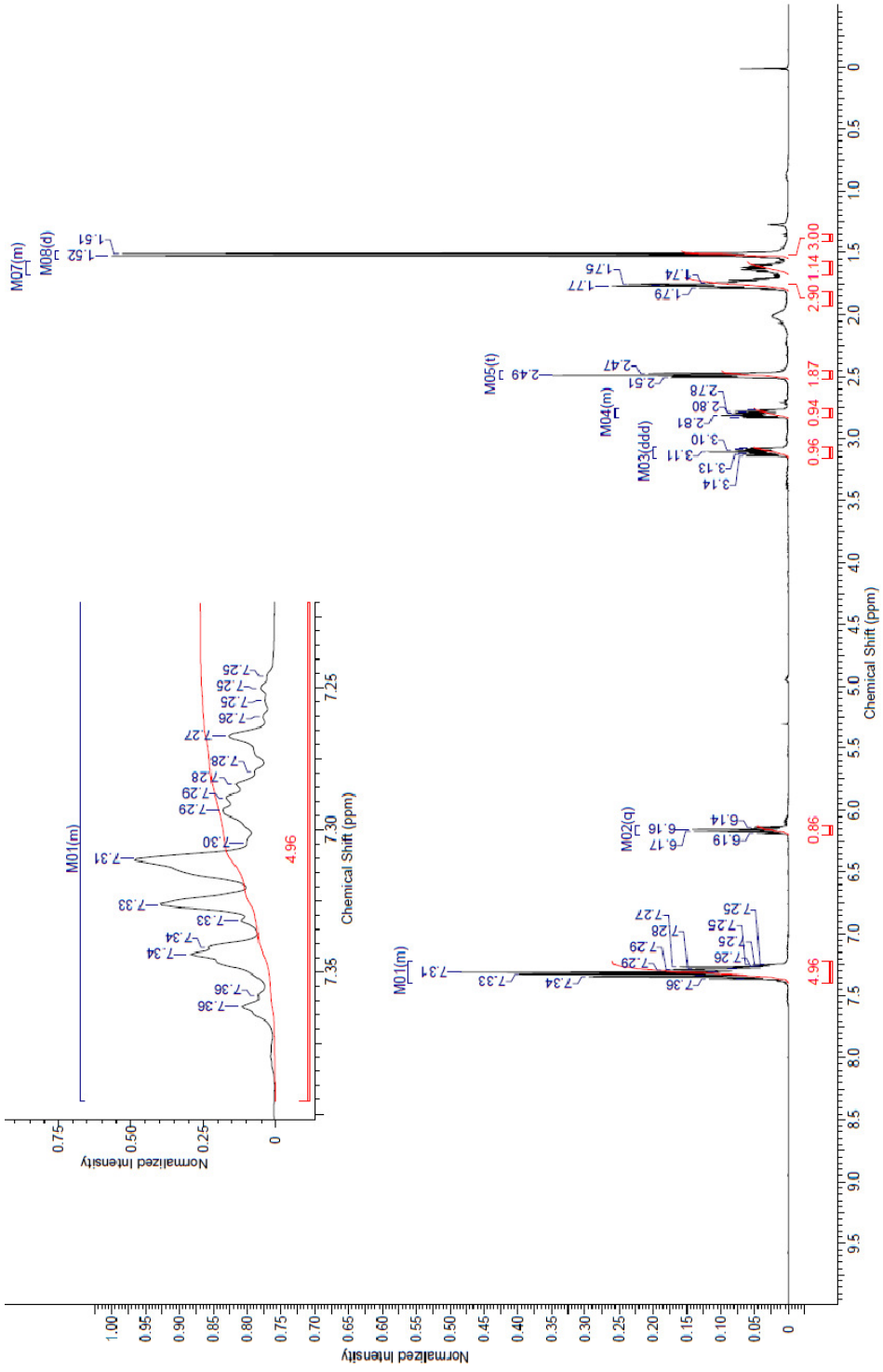
^{13}C NMR


M01(s)
29.59
M02(s)
38.42
38.73
41.38
M03(s)
M04(s)
76.73
77.04
77.36
M06(s)
M07(s)
126.55
128.77
M08(s)
143.54
M09(s*)
172.12
Chemical Shift (ppm)
Normalized Intensity

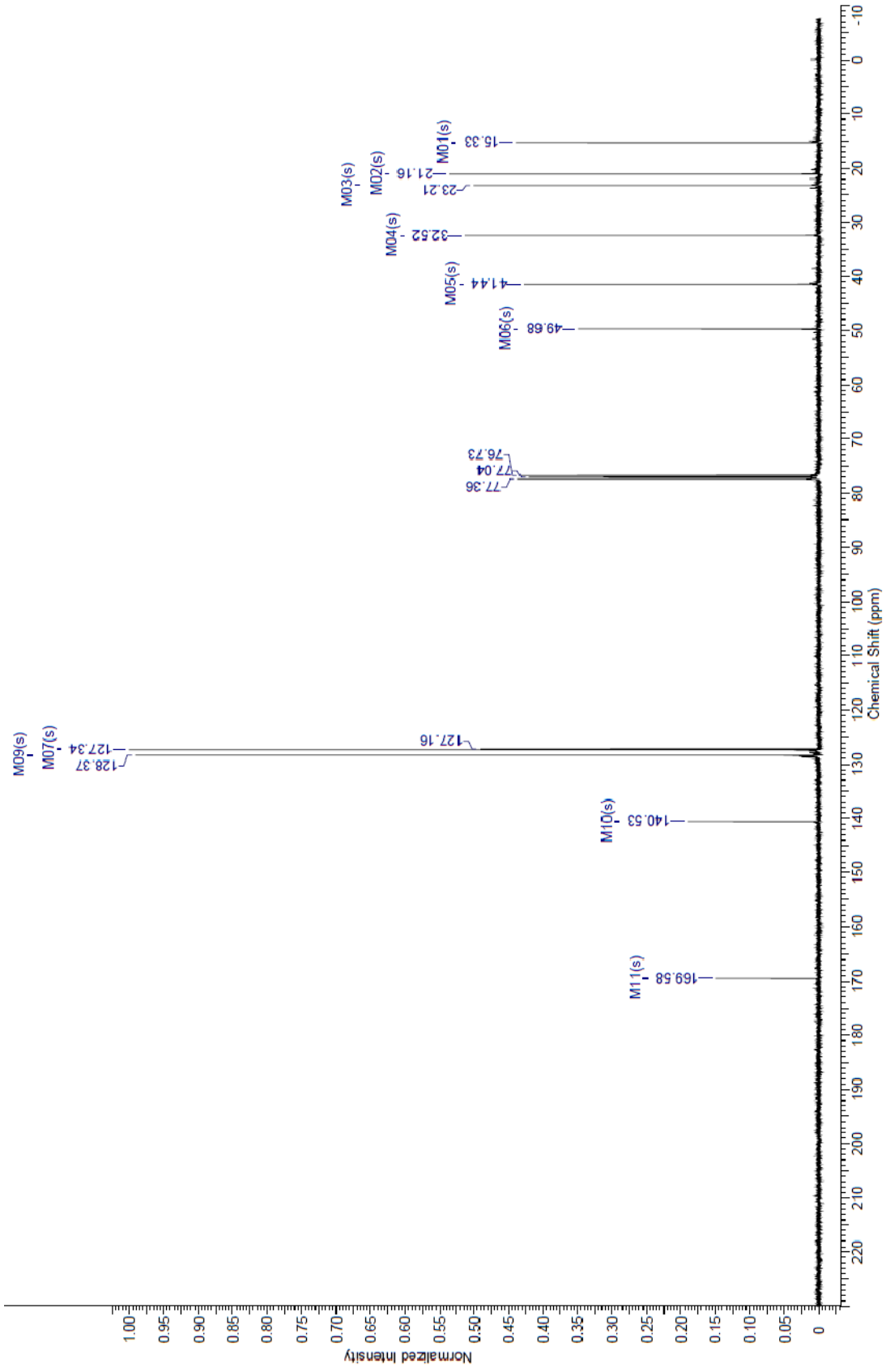


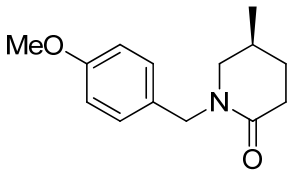
(*R*)-1-(1-Phenylethyl)piperidin-2-one 3m

^{1}H NMR



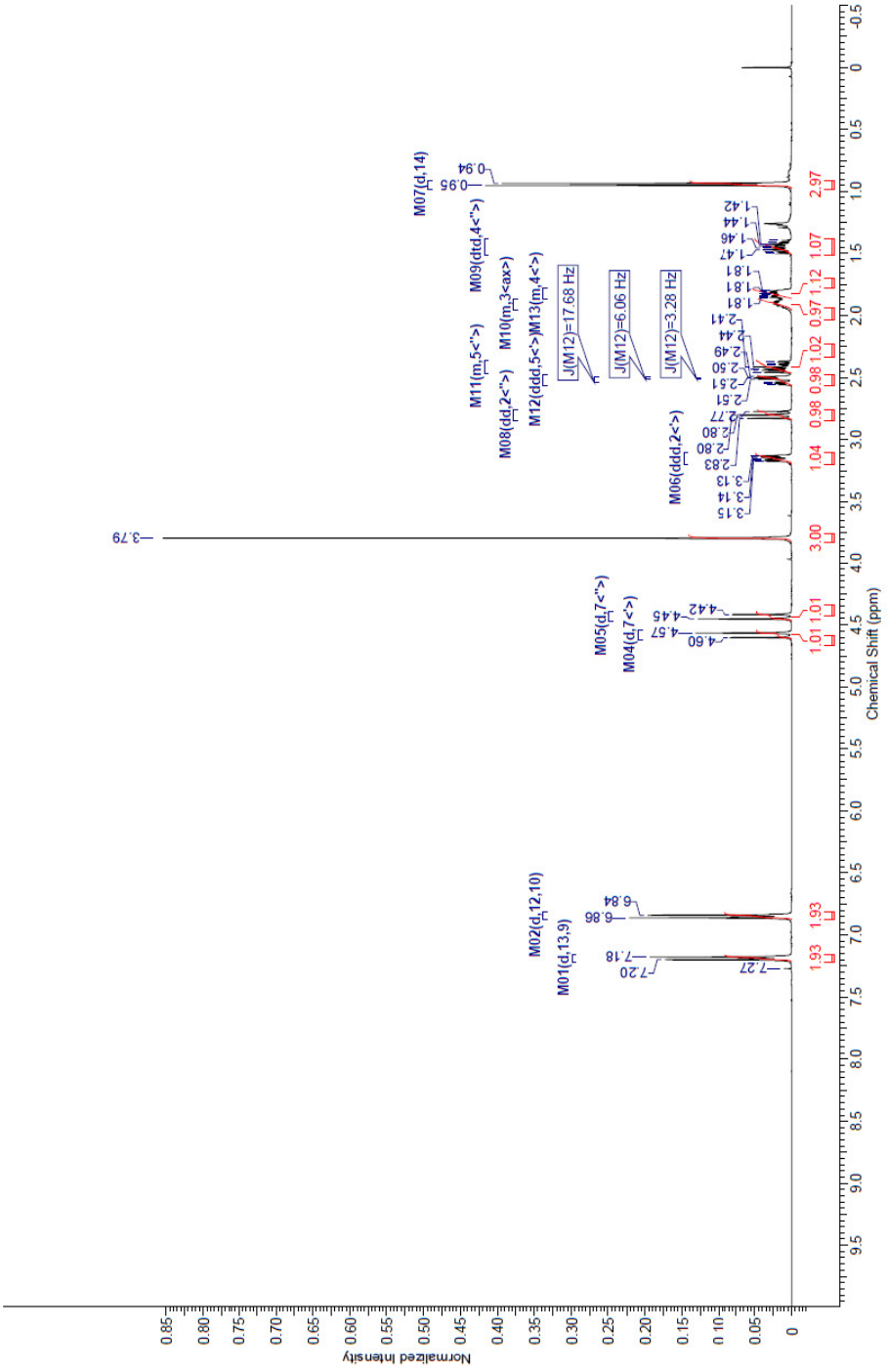
^{13}C NMR


M01(s)
15.33
M02(s)
21.16
23.21
M03(s)
M04(s)
32.52
M05(s)
41.44
M06(s)
49.68
76.73
77.04
77.36
M07(s)
127.16
M09(s)
127.34
128.37
M10(s)
140.53
M11(s)
159.58
Normalized Intensity
Chemical Shift (ppm)

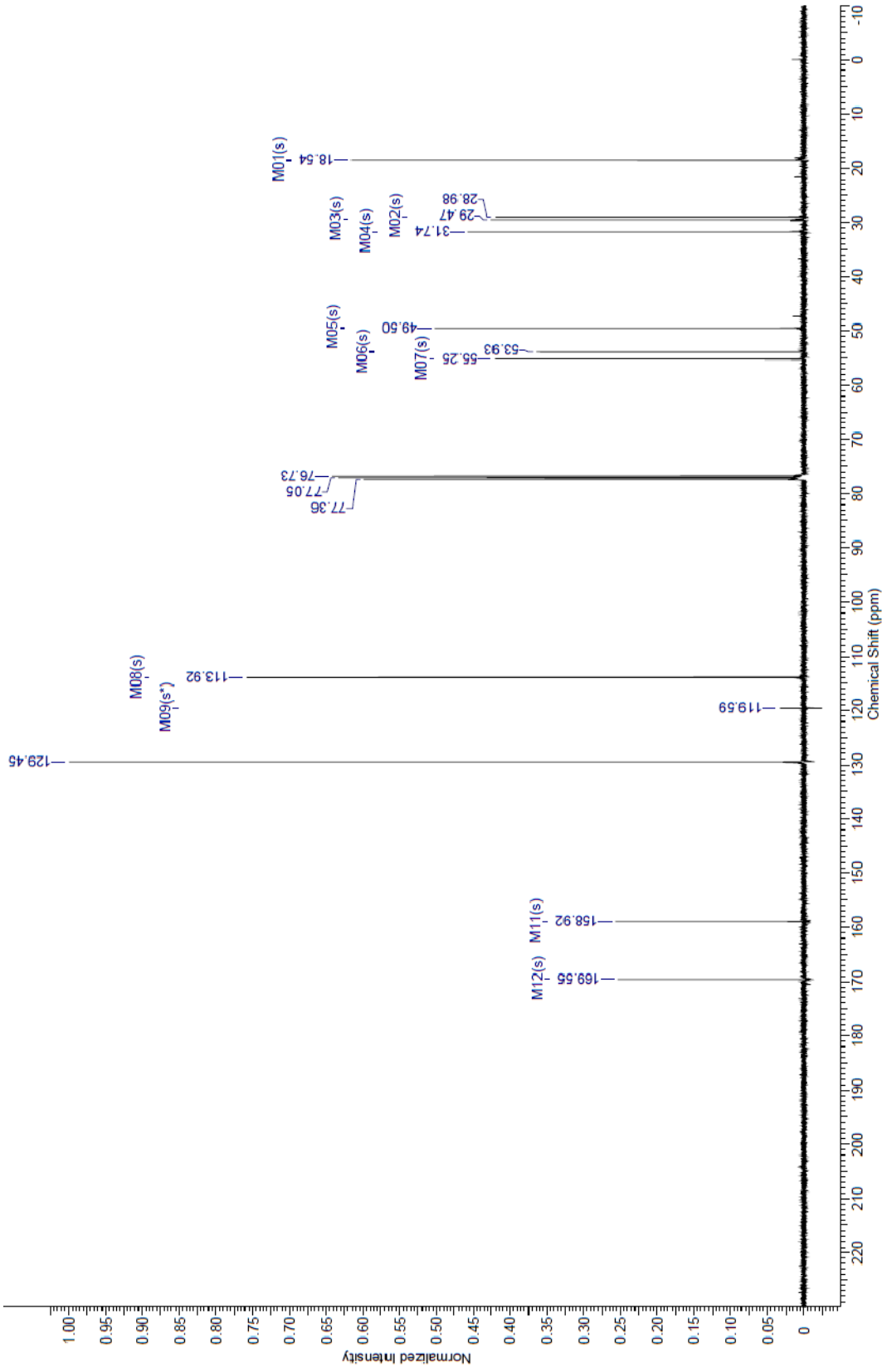


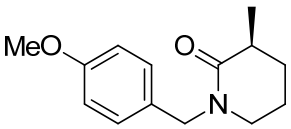
(*S*)-1-(4-Methoxybenzyl)-5-methylpiperidin-2-one 3n[α]

^{1}H NMR



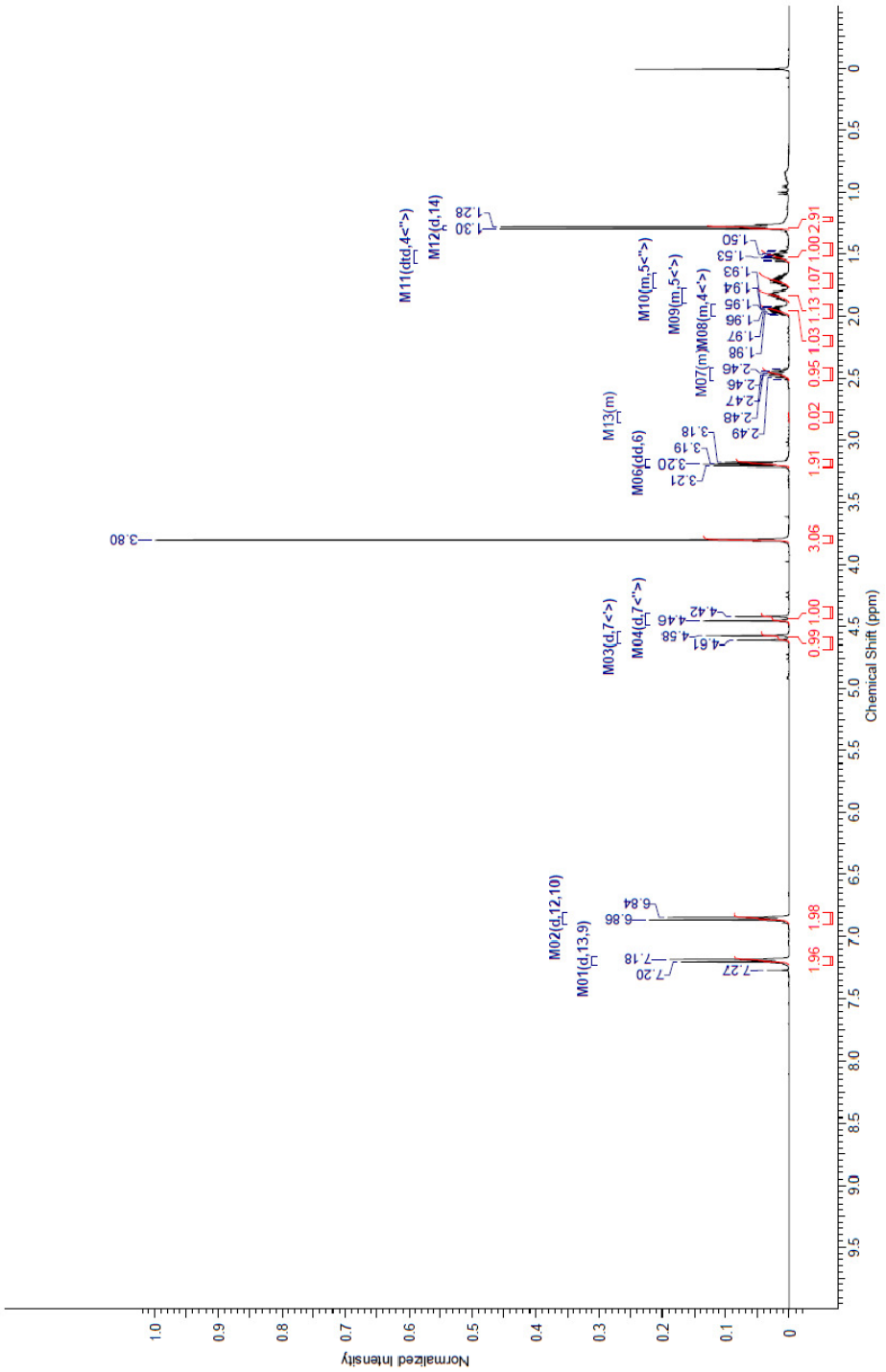
^{13}C NMR


M01(s)
18.54
M03(s)
M04(s)
M02(s)
28.98
29.47
31.74
M05(s)
M06(s)
M07(s)
49.50
53.93
55.25
77.36
77.05
76.73
M08(s)
M09(s*)
113.92
119.59
129.45
M12(s)
M11(s)
158.92
169.55
Normalized Intensity
Chemical Shift (ppm)

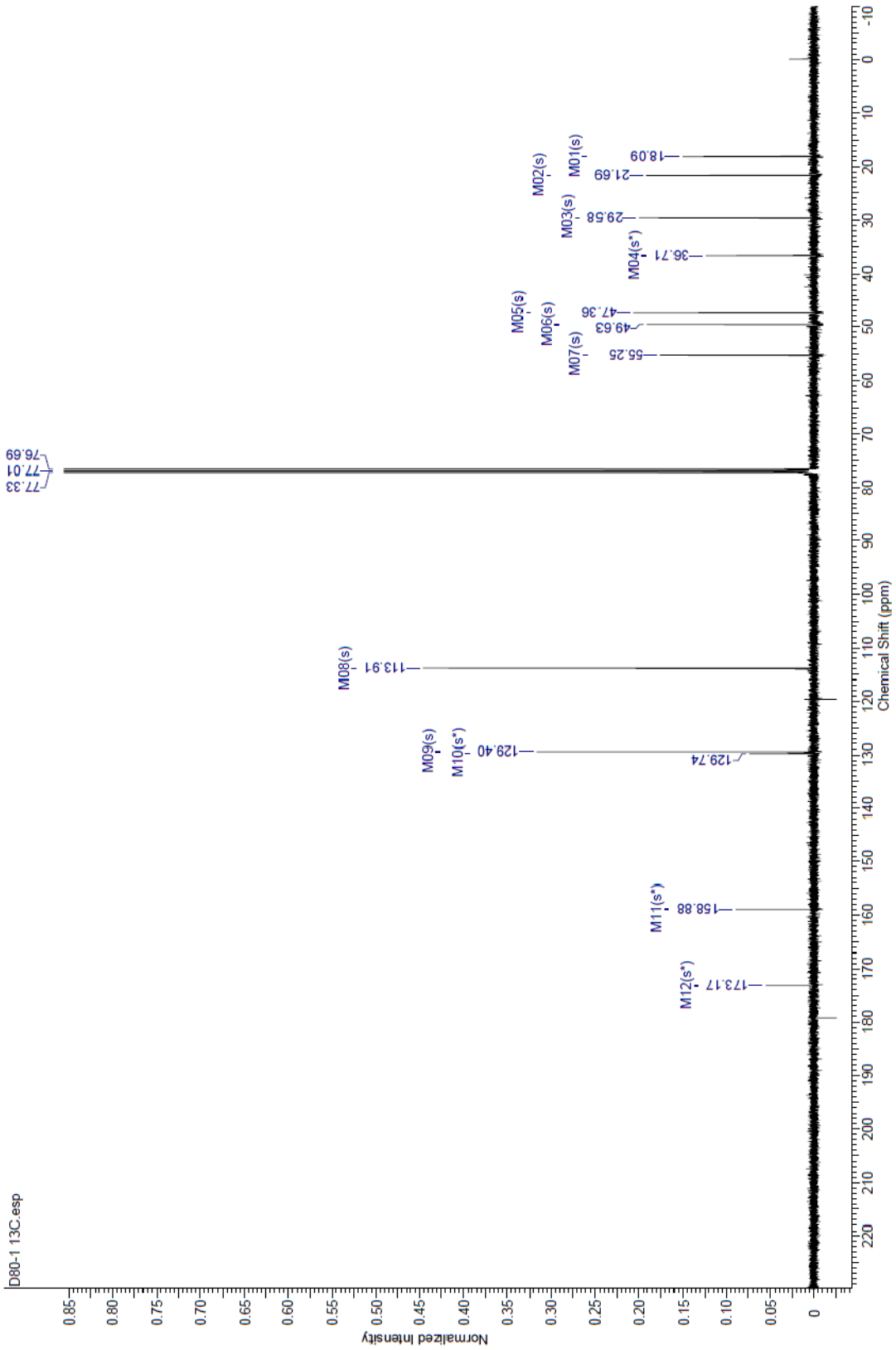


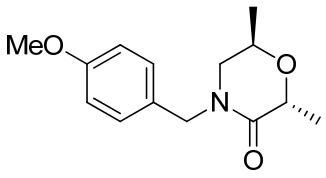
(*S*)-1-(4-Methoxybenzyl)-3-methylpiperidin-2-one 3n$^{\beta}$

^{1}H NMR



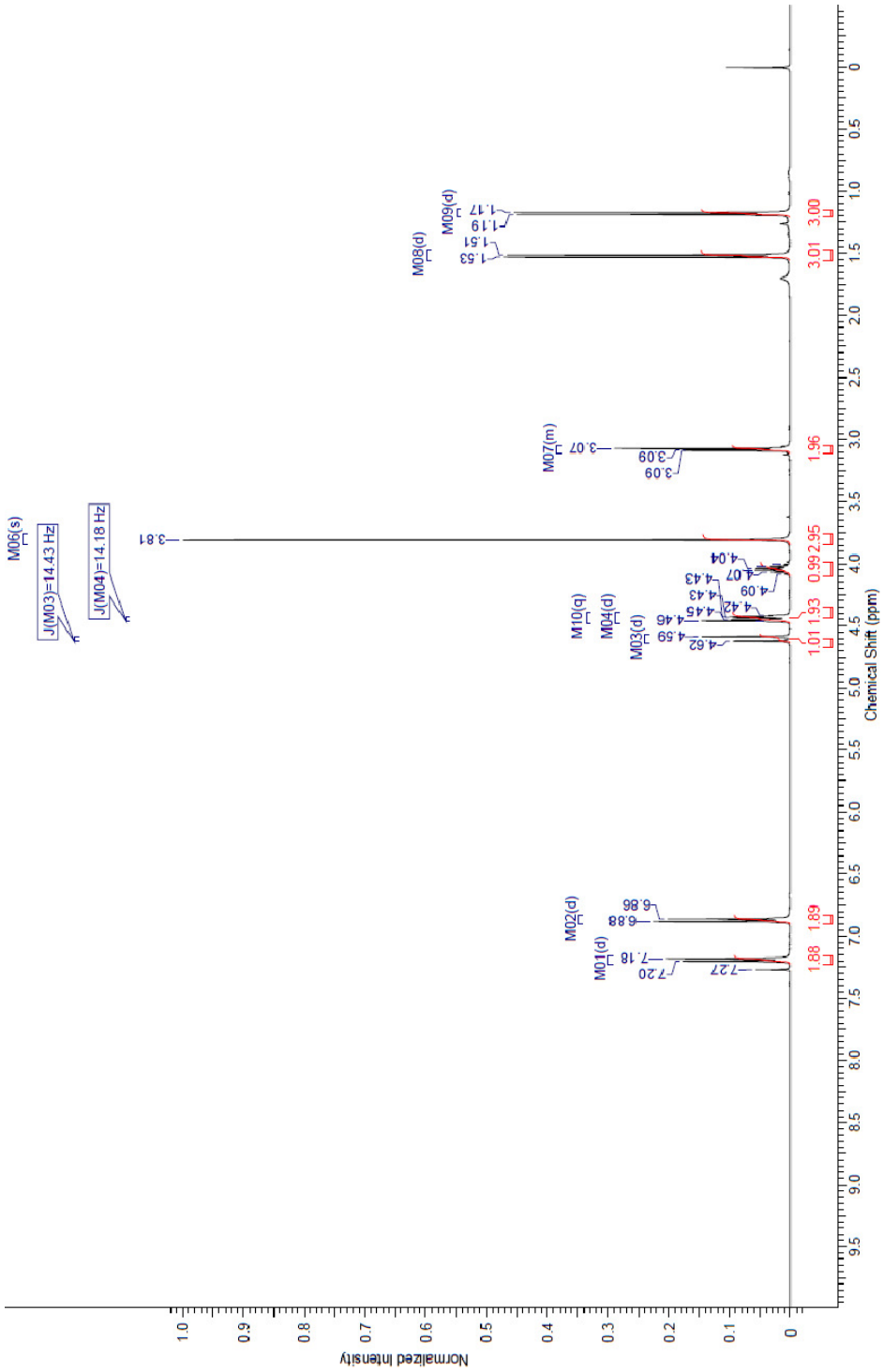
^{13}C NMR


D80-1 13C.esp
Normalized Intensity
Chemical Shift (ppm)
77.33
77.01
76.69
M08(s)
113.91
M09(s)
M10(s*)
129.40
129.74
M11(s*)
158.88
M12(s*)
173.17
M05(s)
M06(s)
M07(s)
55.26
49.63
47.36
M04(s*)
36.71
M03(s)
29.58
M02(s)
M01(s)
21.69
18.09

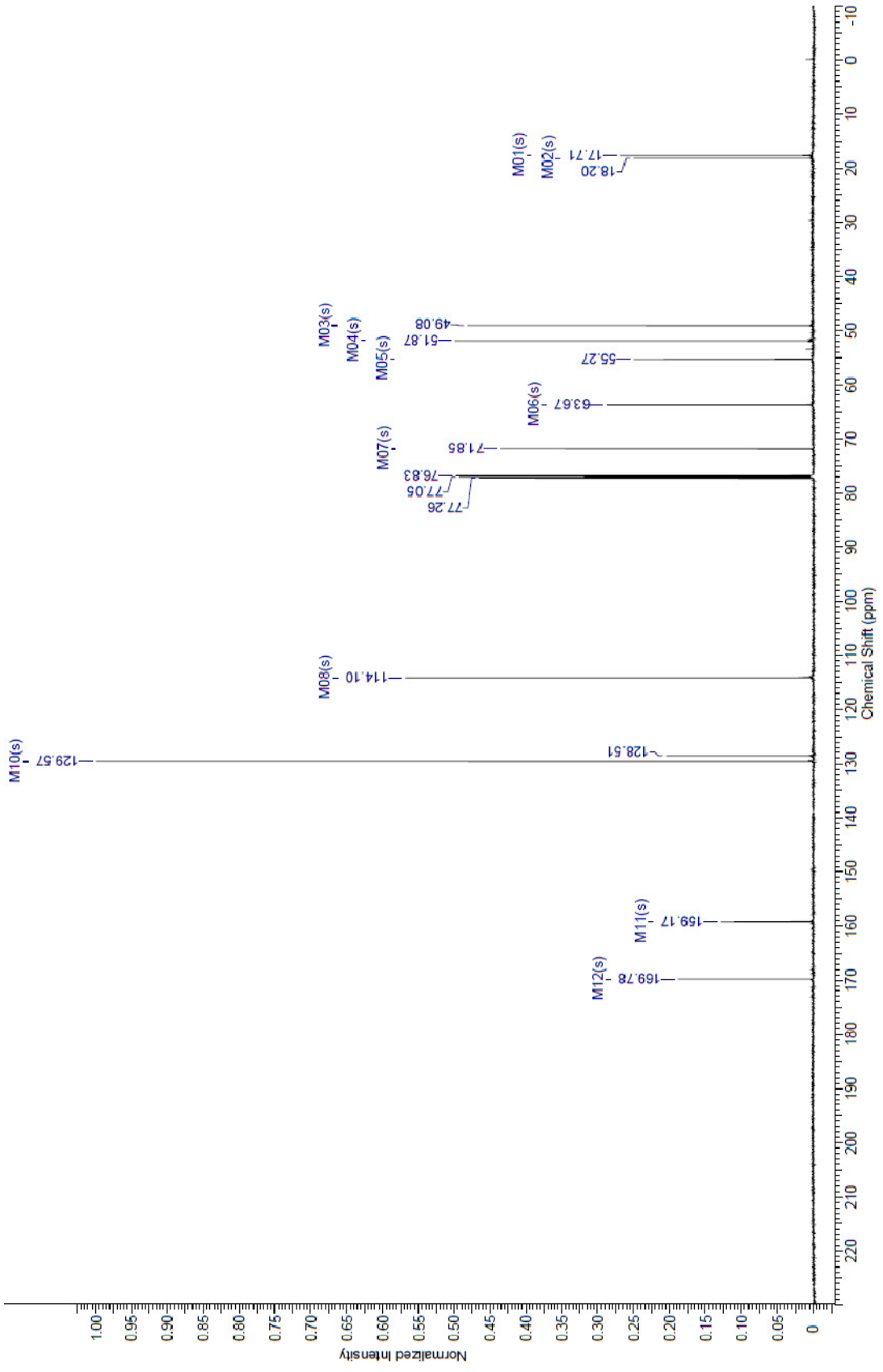


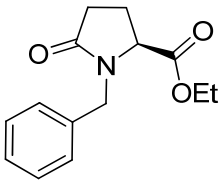
(2*R*,6*R*)-4-(4-Methoxybenzyl)-2,6-dimethylmorpholin-3-one 3o

^{1}H NMR



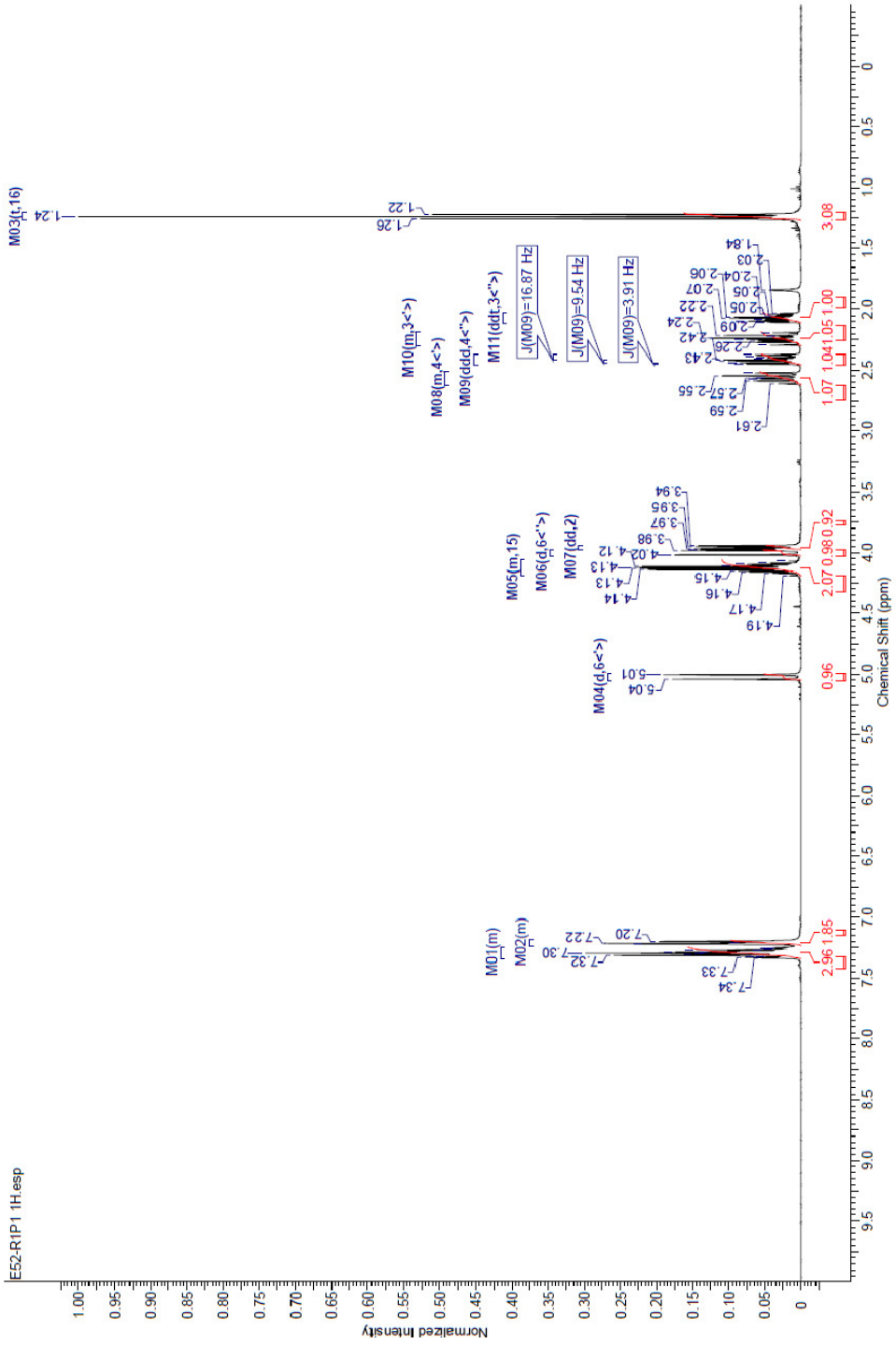
^{13}C NMR


M01(s)
M02(s)
17.71
18.20
M03(s)
M04(s)
M05(s)
49.08
51.87
55.27
M06(s)
63.67
M07(s)
71.85
76.83
77.05
77.26
M08(s)
114.10
128.51
M10(s)
129.57
M11(s)
159.17
M12(s)
169.78
Normalized Intensity
Chemical Shift (ppm)

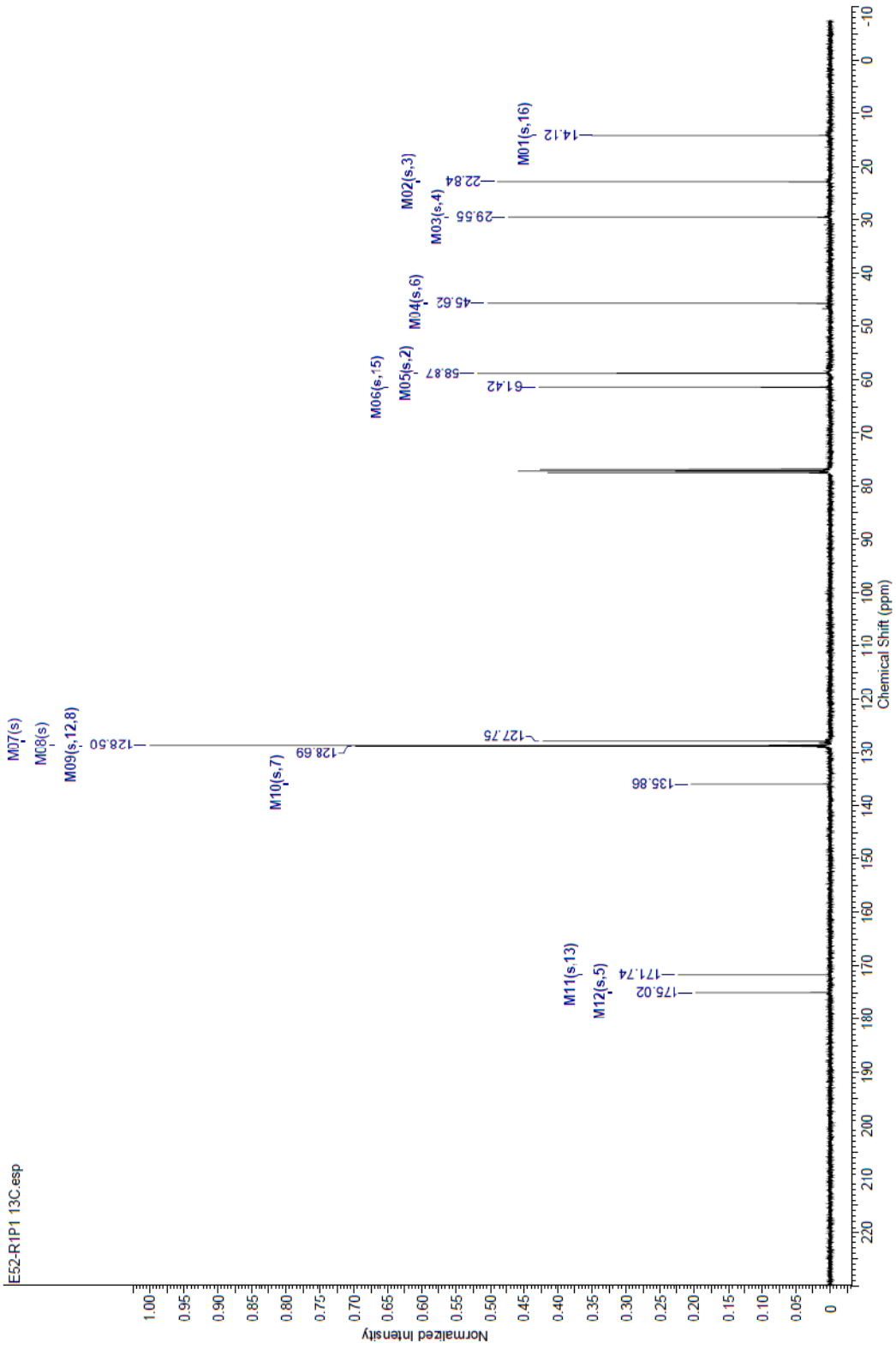


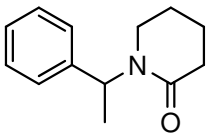
(*S*)-Ethyl 1-benzyl-5-oxopyrrolidine-2-carboxylate 3p

^{1}H NMR



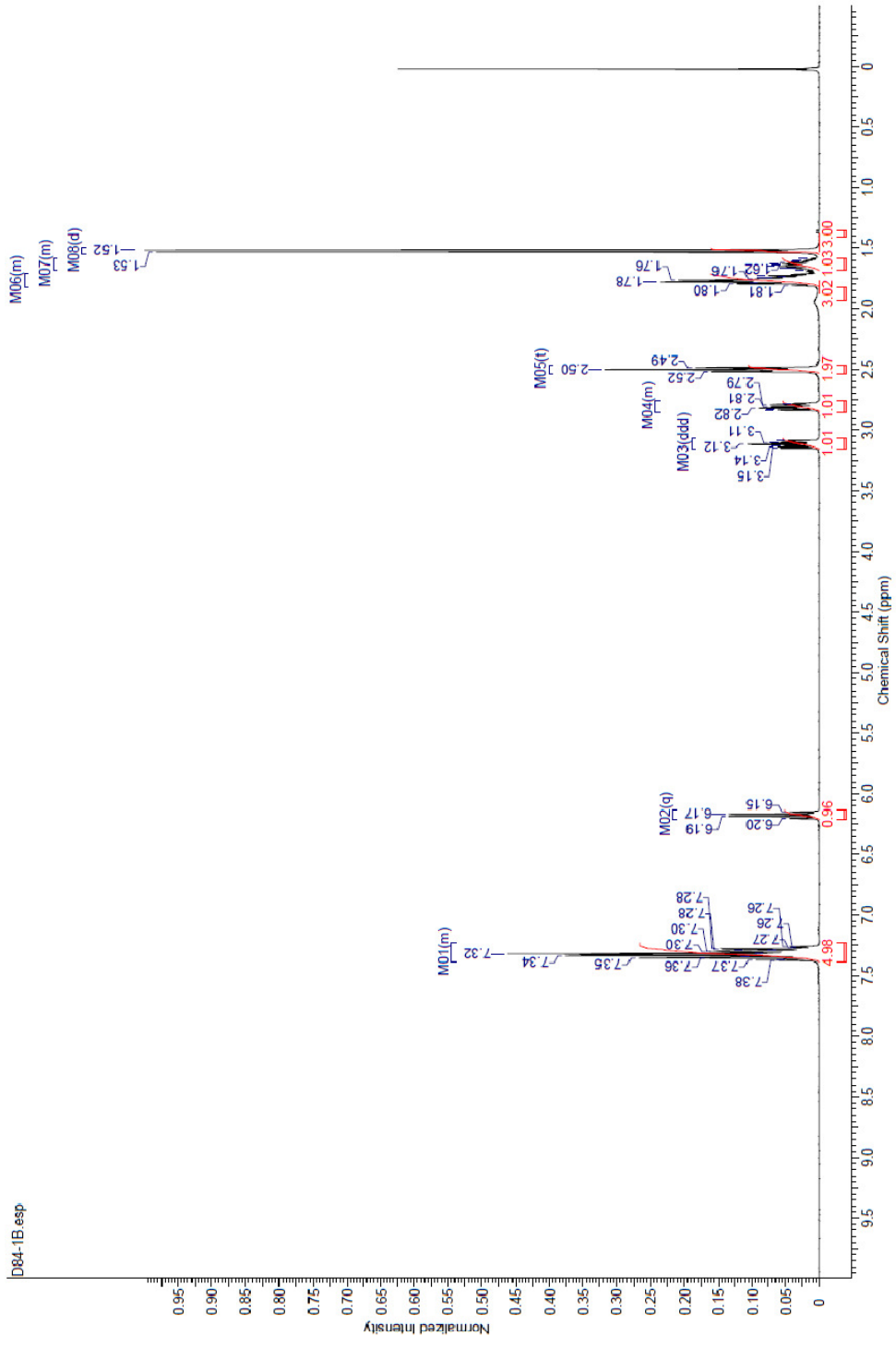
^{13}C NMR

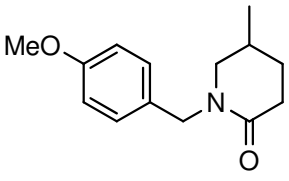

E52-R1P1 13C.esp
Normalized Intensity
Chemical Shift (ppm)
M01(s,16)
14.12
M02(s,3)
22.84
M03(s,4)
29.55
M04(s,6)
45.62
M05(s,2)
58.87
M06(s,15)
61.42
M07(s)
M08(s)
M09(s,12,8)
128.50
M10(s,7)
128.69
127.75
135.86
M11(s,13)
M12(s,5)
171.74
175.02



1-(1-Phenylethyl)piperidin-2-one 3s

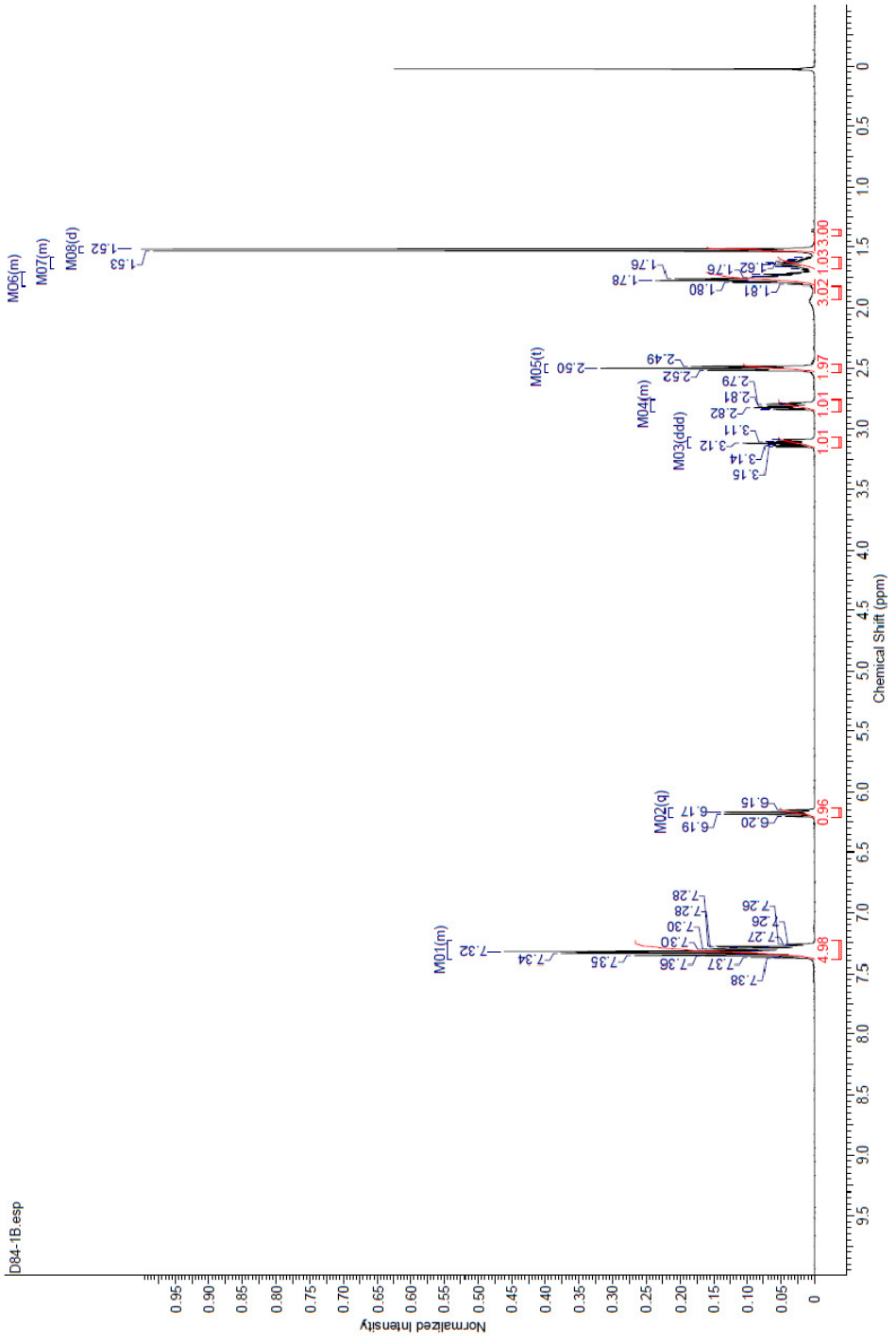
^{1}H NMR

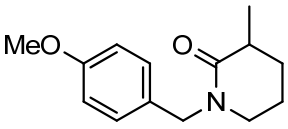




1-(4-Methoxybenzyl)-5-methylpiperidin-2-one 3t[α]

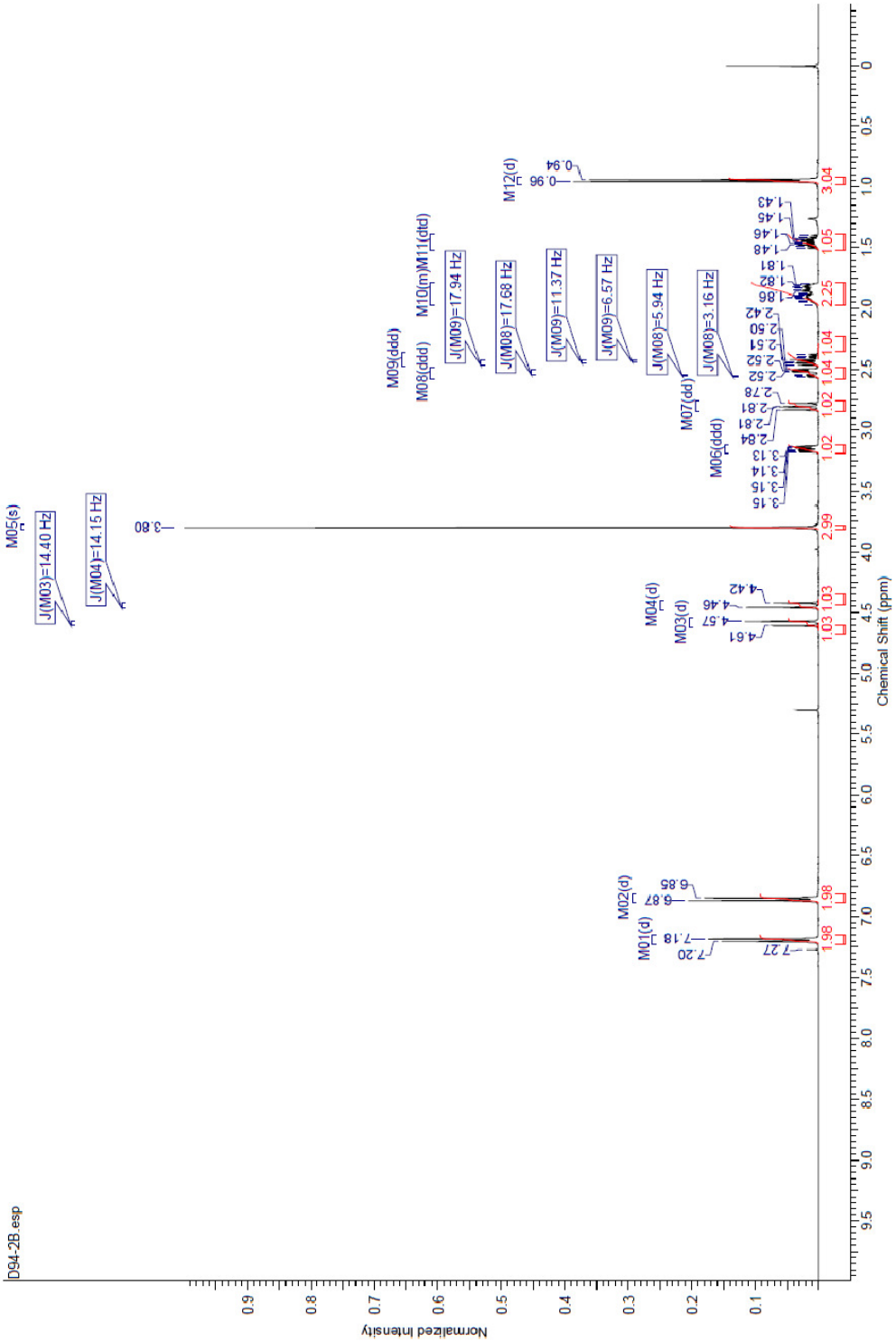
^{1}H NMR

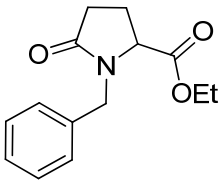




1-(4-methoxybenzyl)-3-methylpiperidin-2-one 3t[β]

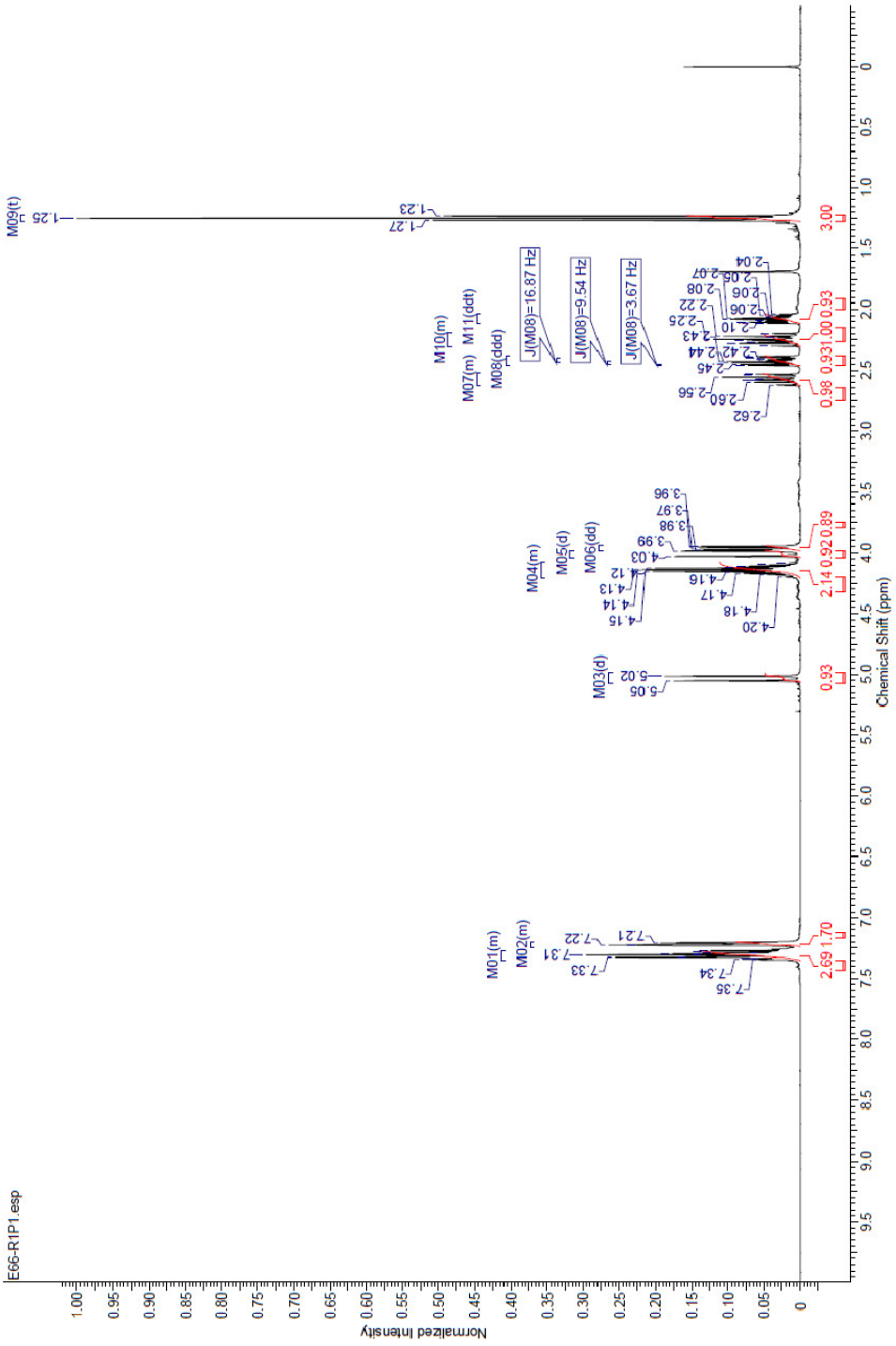
^{1}H NMR

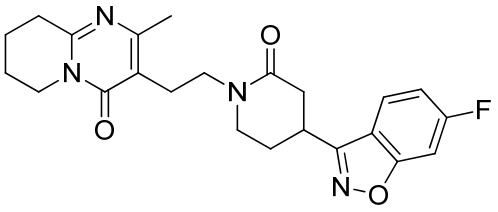




Ethyl 1-benzyl-5-oxopyrrolidine-2-carboxylate 3u

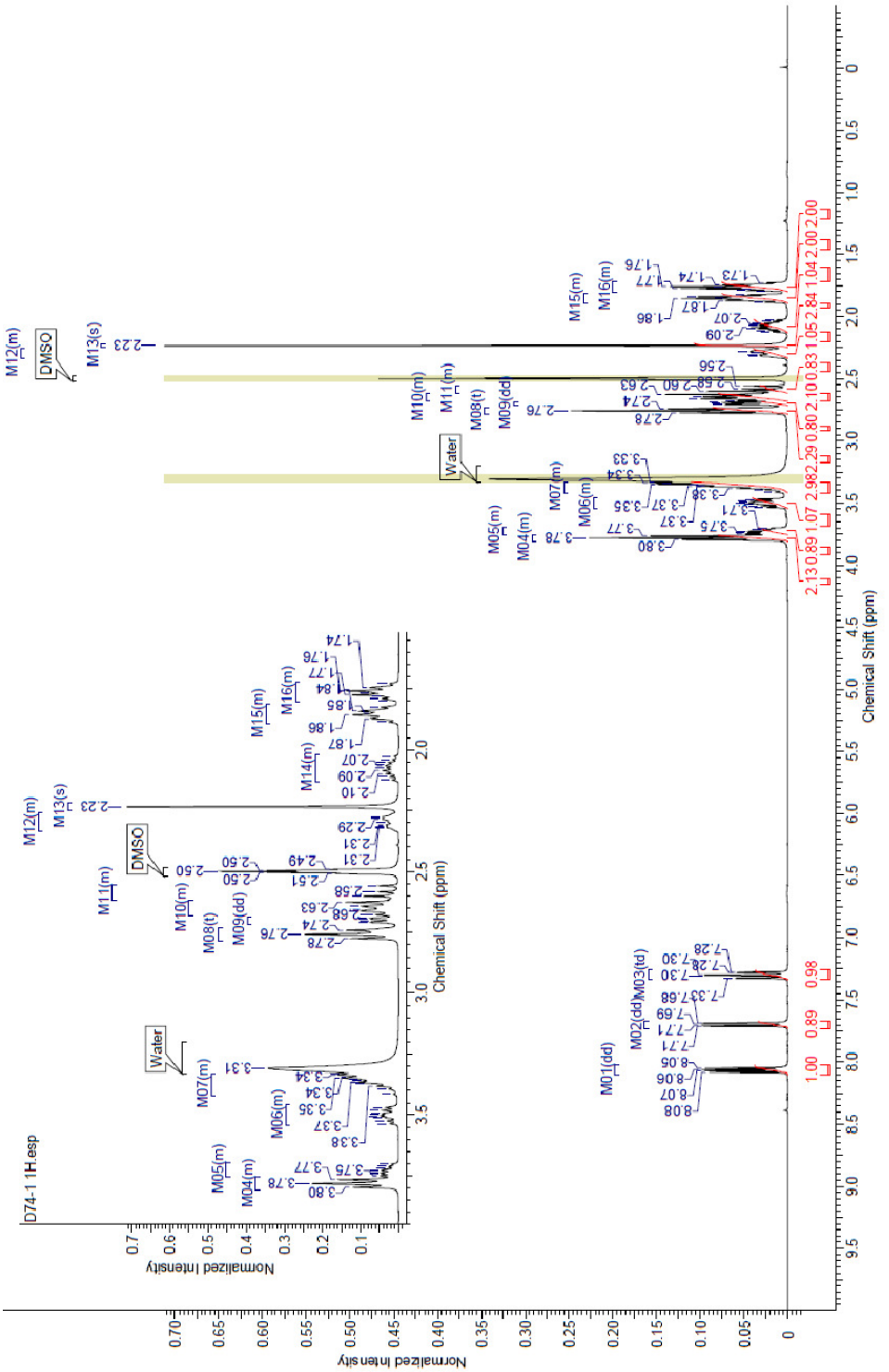
^{1}H NMR



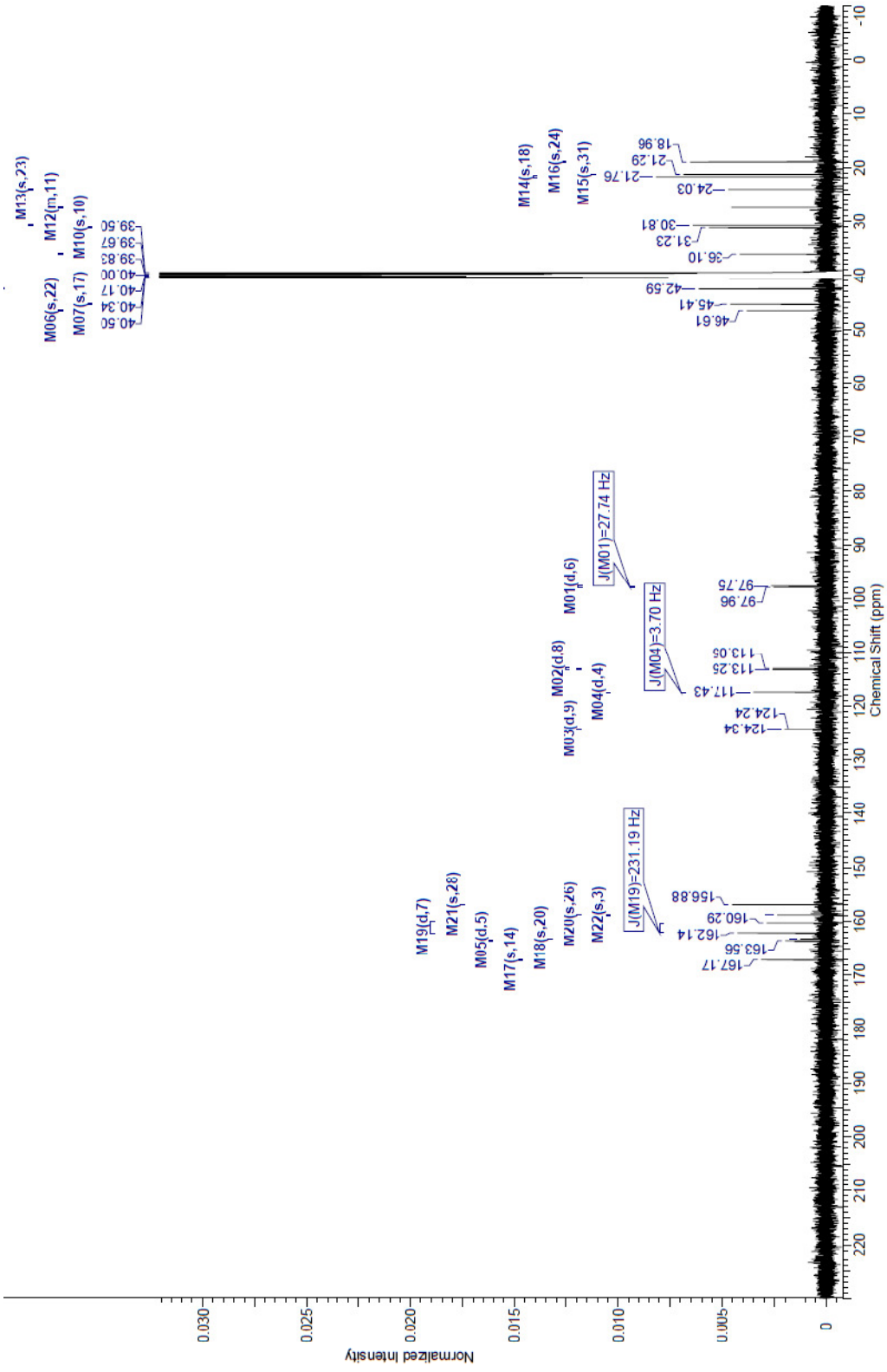


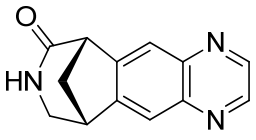
Oxo-rispoeridone 5a

^{1}H NMR



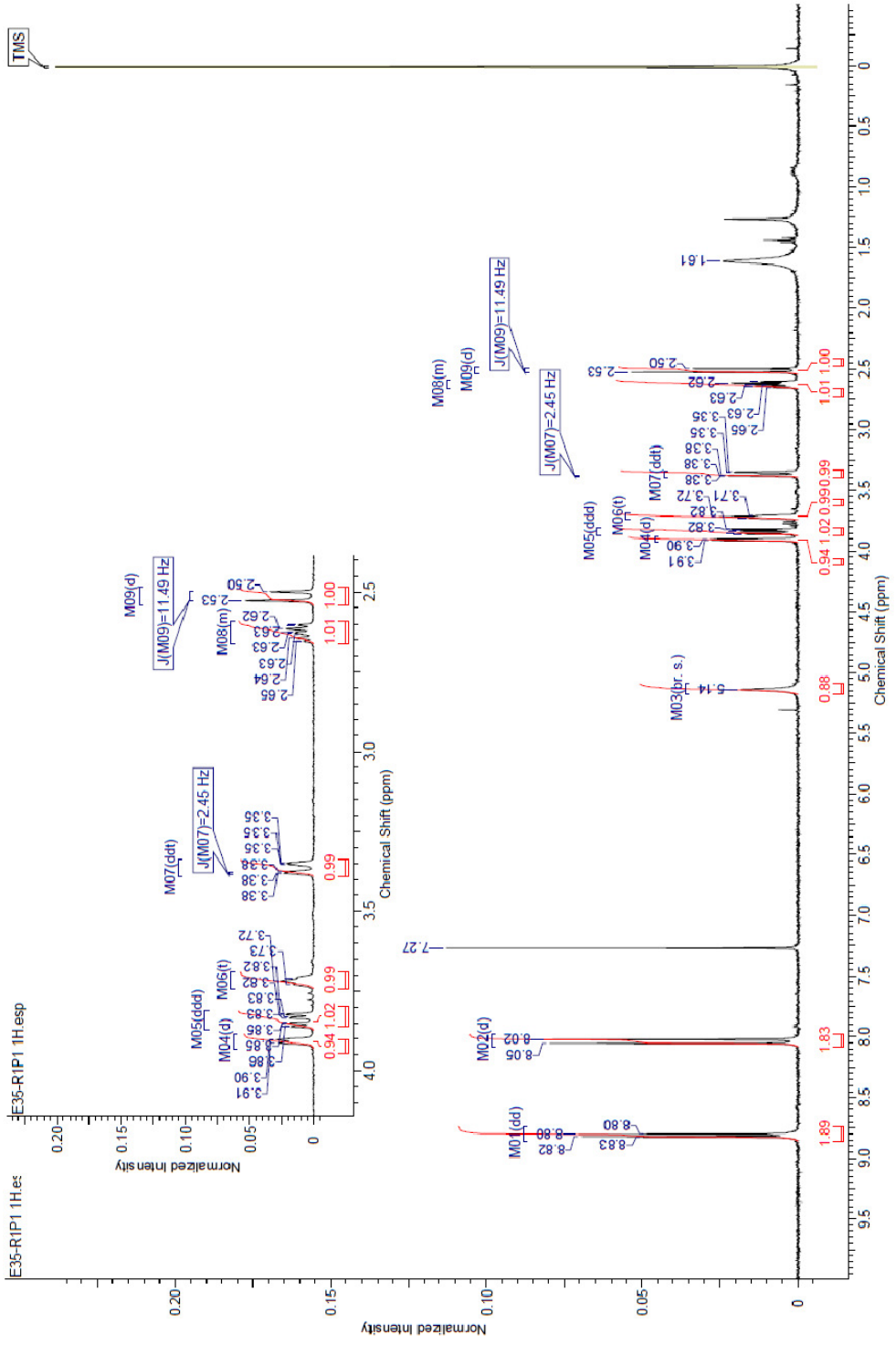
^{13}C NMR


M13(s,23)
M12(m,11)
M10(s,10)
M06(s,22)
M07(s,17)
39.50
39.67
39.83
40.00
40.17
40.34
40.50
M14(s,18)
M16(s,24)
M15(s,31)
18.96
21.29
21.76
24.03
30.81
31.23
36.10
42.59
45.41
46.61
M01(d,6)
J(M01)=27.74 Hz
J(M04)=3.70 Hz
M02(d,8)
M03(d,9)
M04(d,4)
97.75
97.96
113.25
113.05
117.43
124.24
124.34
M19(d,7)
M21(s,28)
M05(d,5)
M17(s,14)
M18(s,20)
M20(s,26)
M22(s,3)
J(M19)=231.19 Hz
156.88
160.29
162.14
163.56
167.17
Chemical Shift (ppm)
Normalized Intensity

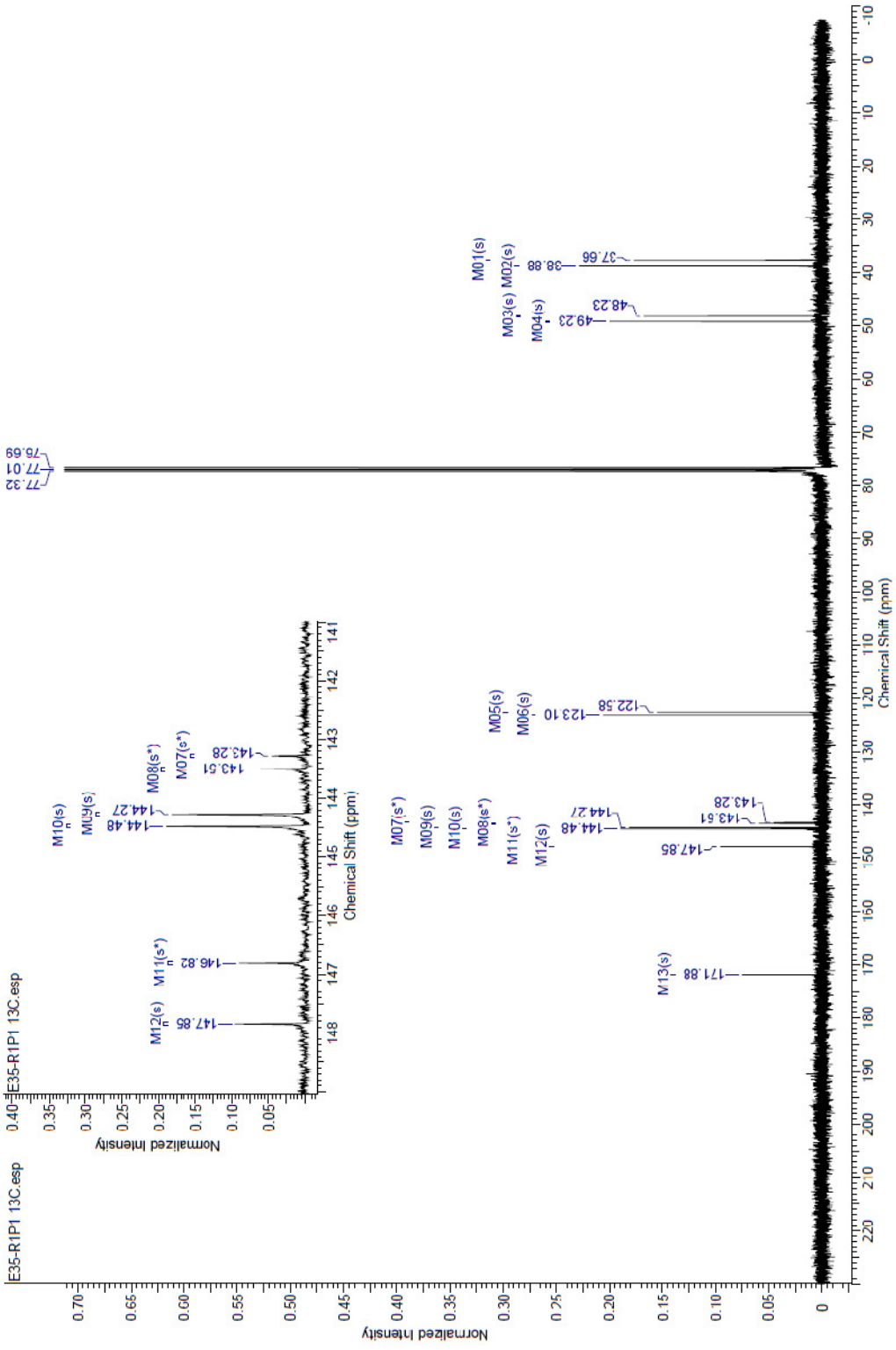


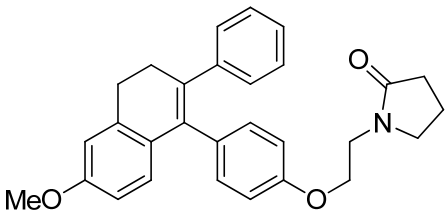
Oxo-varenicline 5b

^{1}H NMR



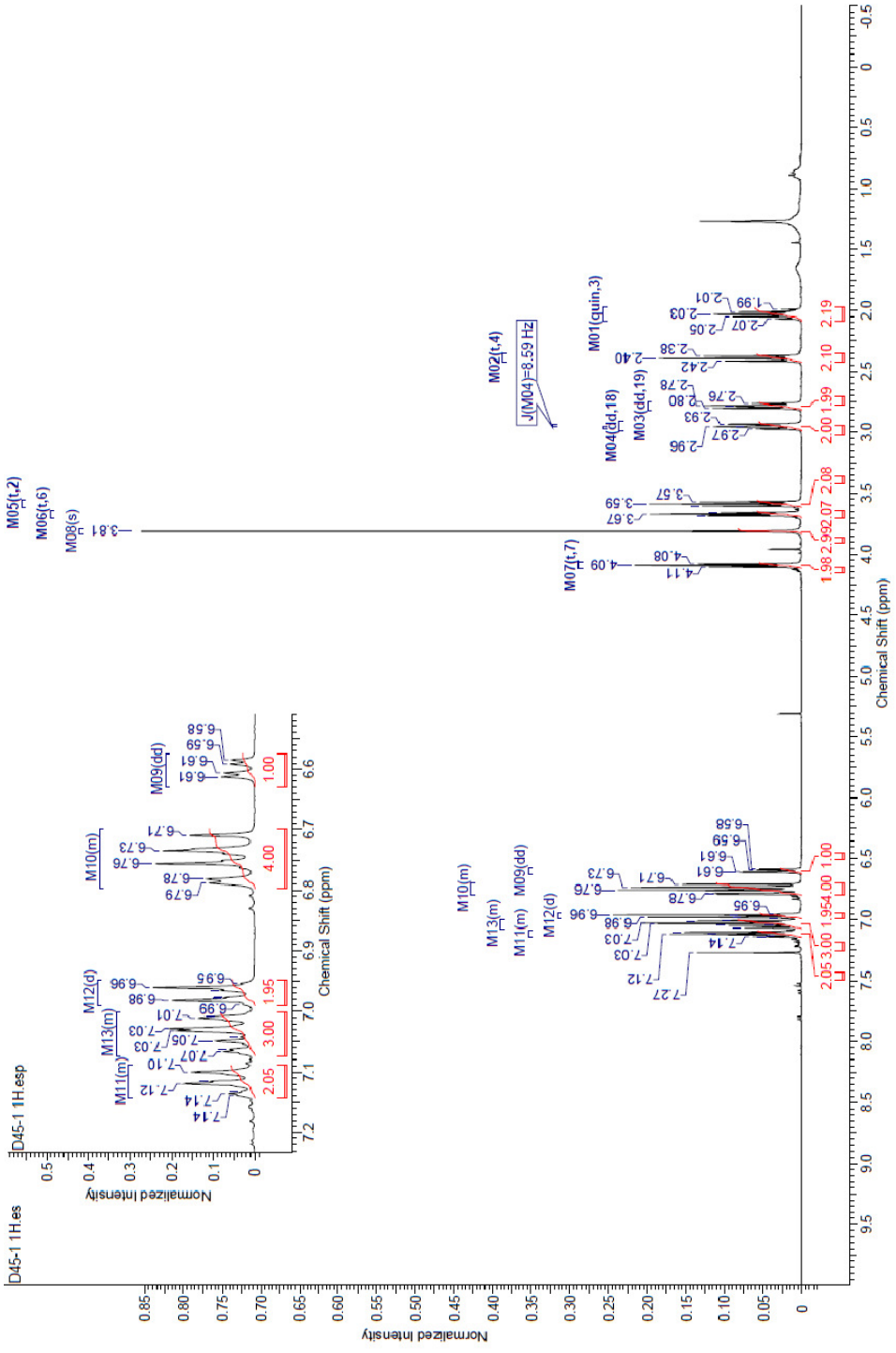
^{13}C NMR


E35-R1P1 13C.esp
Normalized Intensity
Chemical Shift (ppm)
77.32
77.01
76.69
M01(s)
M02(s)
M03(s)
M04(s)
37.66
38.88
48.23
49.23
M05(s)
M06(s)
122.58
123.10
M07(s*)
M08(s*)
M09(s)
M10(s)
M11(s*)
M12(s)
143.28
143.61
144.27
144.48
147.85
M13(s)
171.88
M10(s)
M09(s)
144.27
144.48
M08(s*)
M07(s*)
143.51
143.28
M11(s*)
M12(s)
146.82
147.85

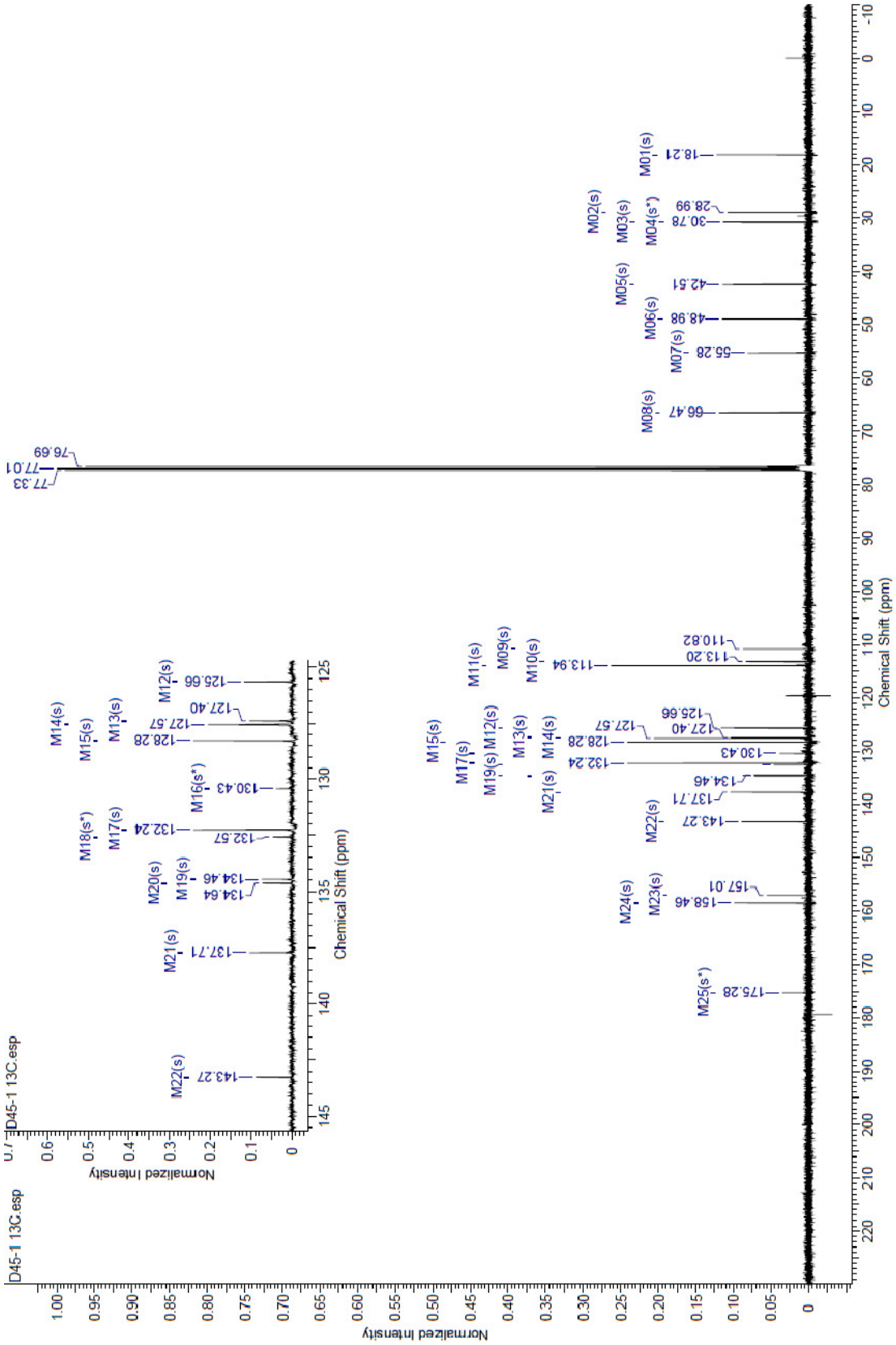


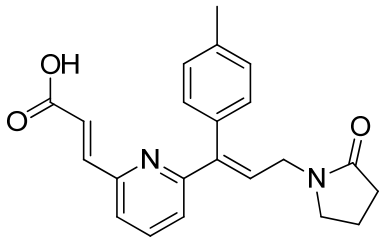
Oxo-nafoxidine 5c

^{1}H NMR



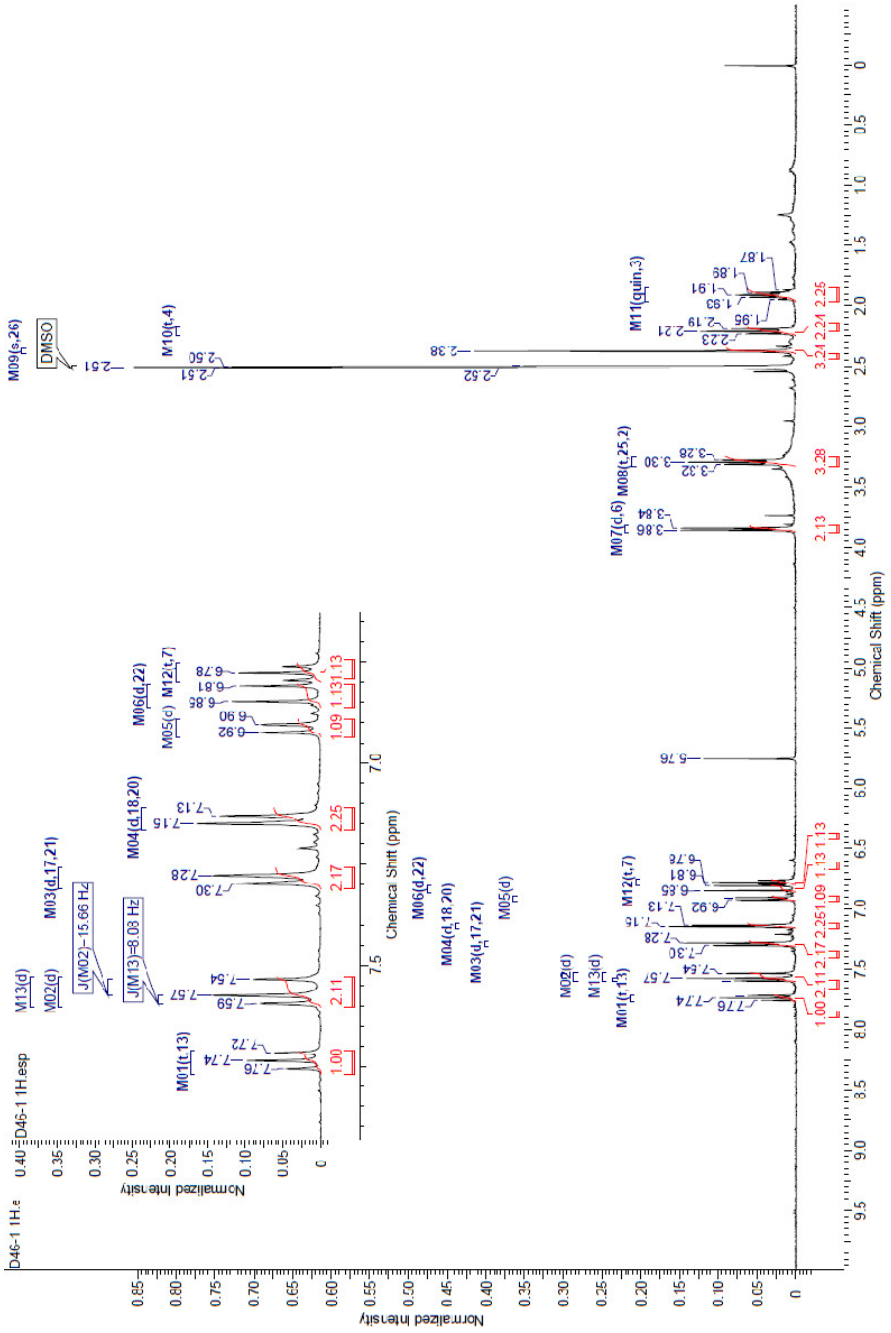
^{13}C NMR


D45-1 13C.esp
Normalized Intensity
Chemical Shift (ppm)
M01(s)
M02(s)
M03(s)
M04(s*)
M05(s)
M06(s)
M07(s)
M08(s)
M09(s)
M10(s)
M11(s)
M12(s)
M13(s)
M14(s)
M15(s)
M16(s*)
M17(s)
M18(s*)
M19(s)
M20(s)
M21(s)
M22(s)
M23(s)
M24(s)
M25(s*)
18.21
28.99
30.78
42.61
48.98
55.28
66.47
76.69
77.01
77.33
110.82
113.20
113.94
125.66
127.40
127.57
128.28
130.43
132.24
132.57
134.46
134.64
137.71
143.27
157.01
158.46
175.28

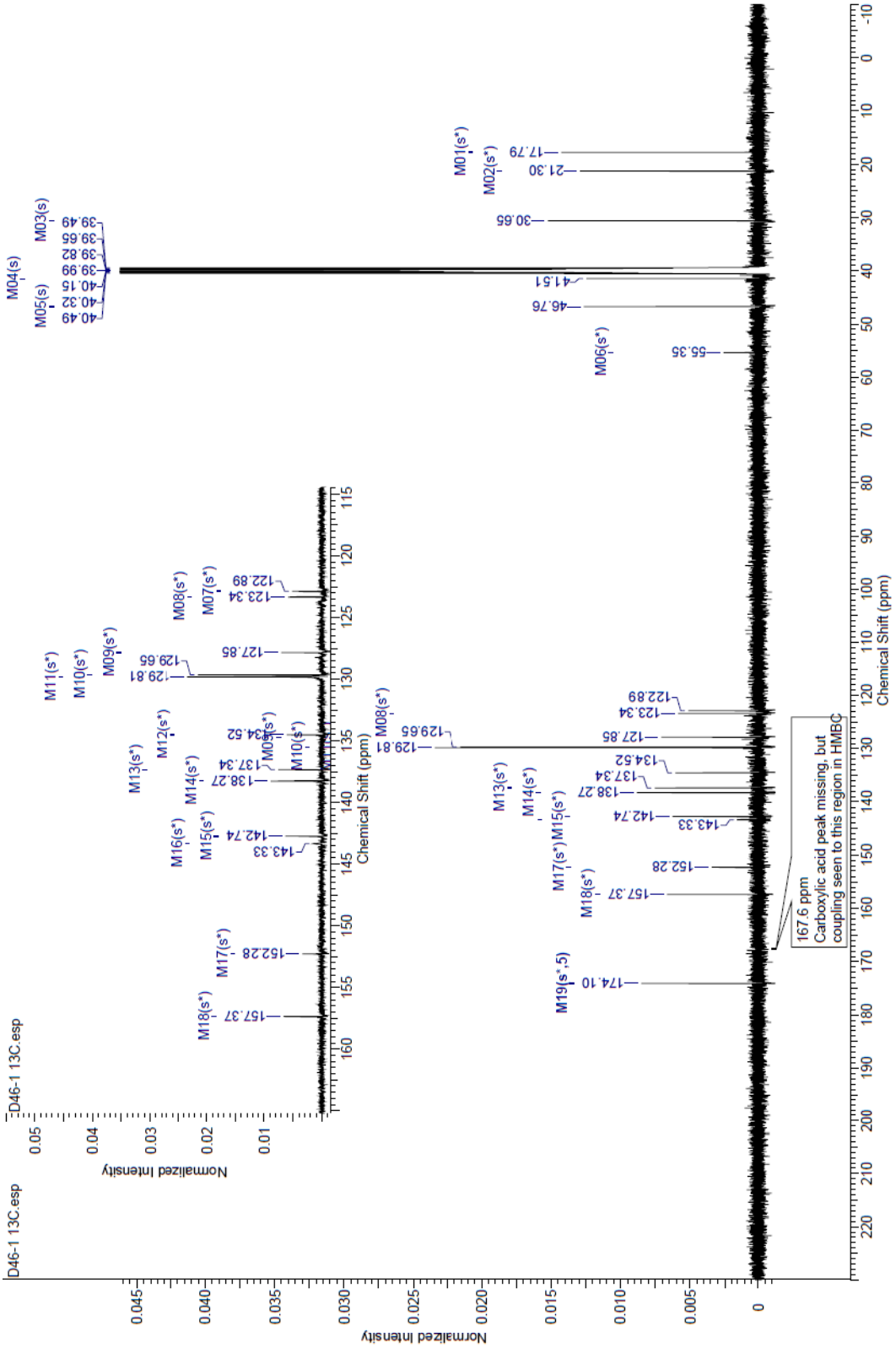


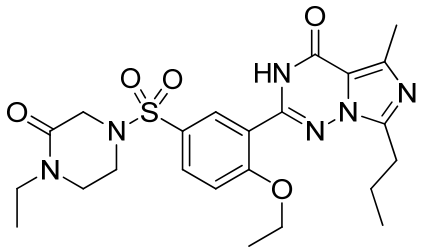
Oxo-acrivastine 5d

^{1}H NMR



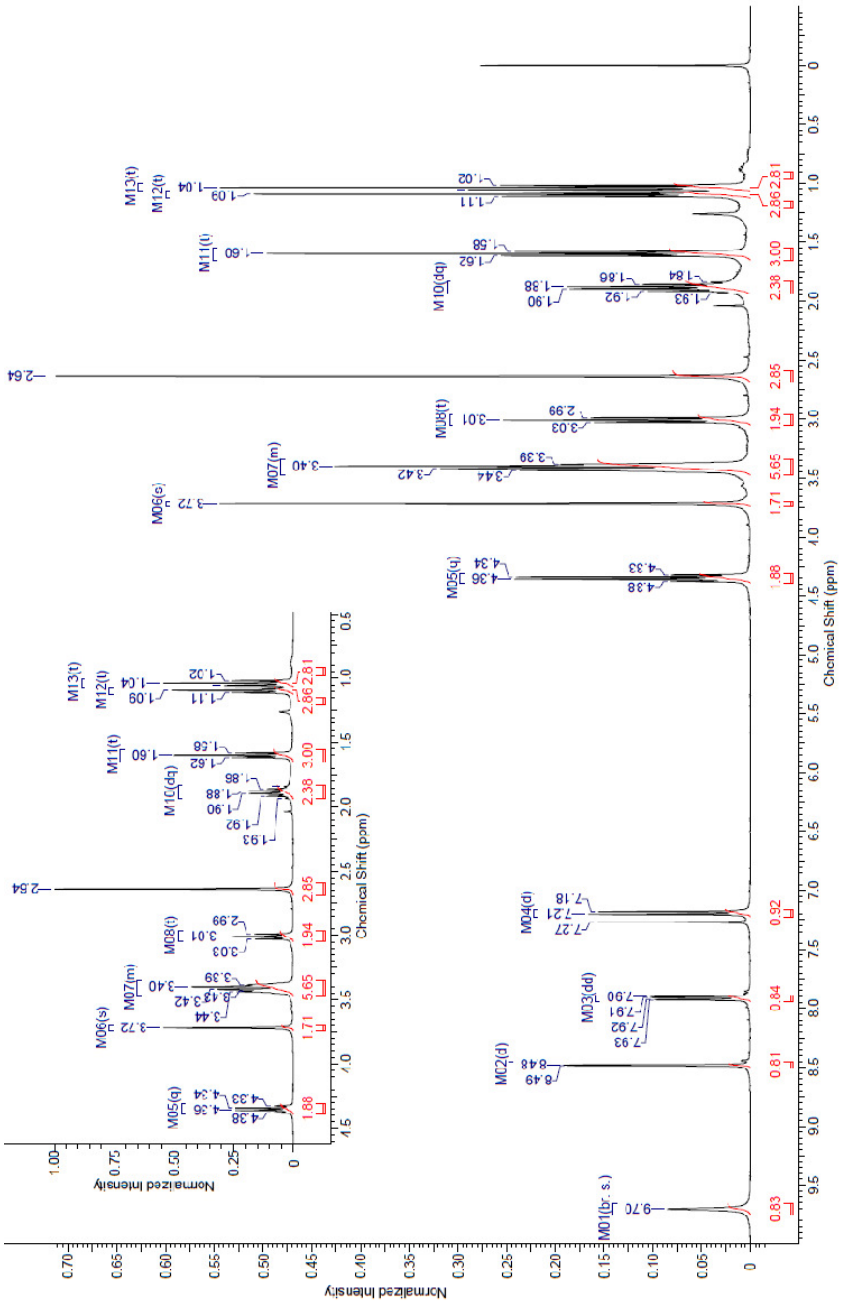
^{13}C NMR


D46-1 13C.esp
Normalized Intensity
Chemical Shift (ppm)
M01(s*)
M02(s*)
M03(s)
M04(s)
M05(s)
M06(s*)
M07(s*)
M08(s*)
M09(s*)
M10(s*)
M11(s*)
M12(s*)
M13(s*)
M14(s*)
M15(s*)
M16(s*)
M17(s*)
M18(s*)
M19(s*,5)
17.79
21.30
30.65
39.49
39.66
39.82
39.99
40.15
40.32
40.49
41.51
46.76
55.35
122.89
123.34
127.85
129.65
129.81
134.52
137.34
138.27
142.74
143.33
152.28
157.37
174.10
167.6 ppm
Carboxylic acid peak missing, but coupling seen to this region in HMBC

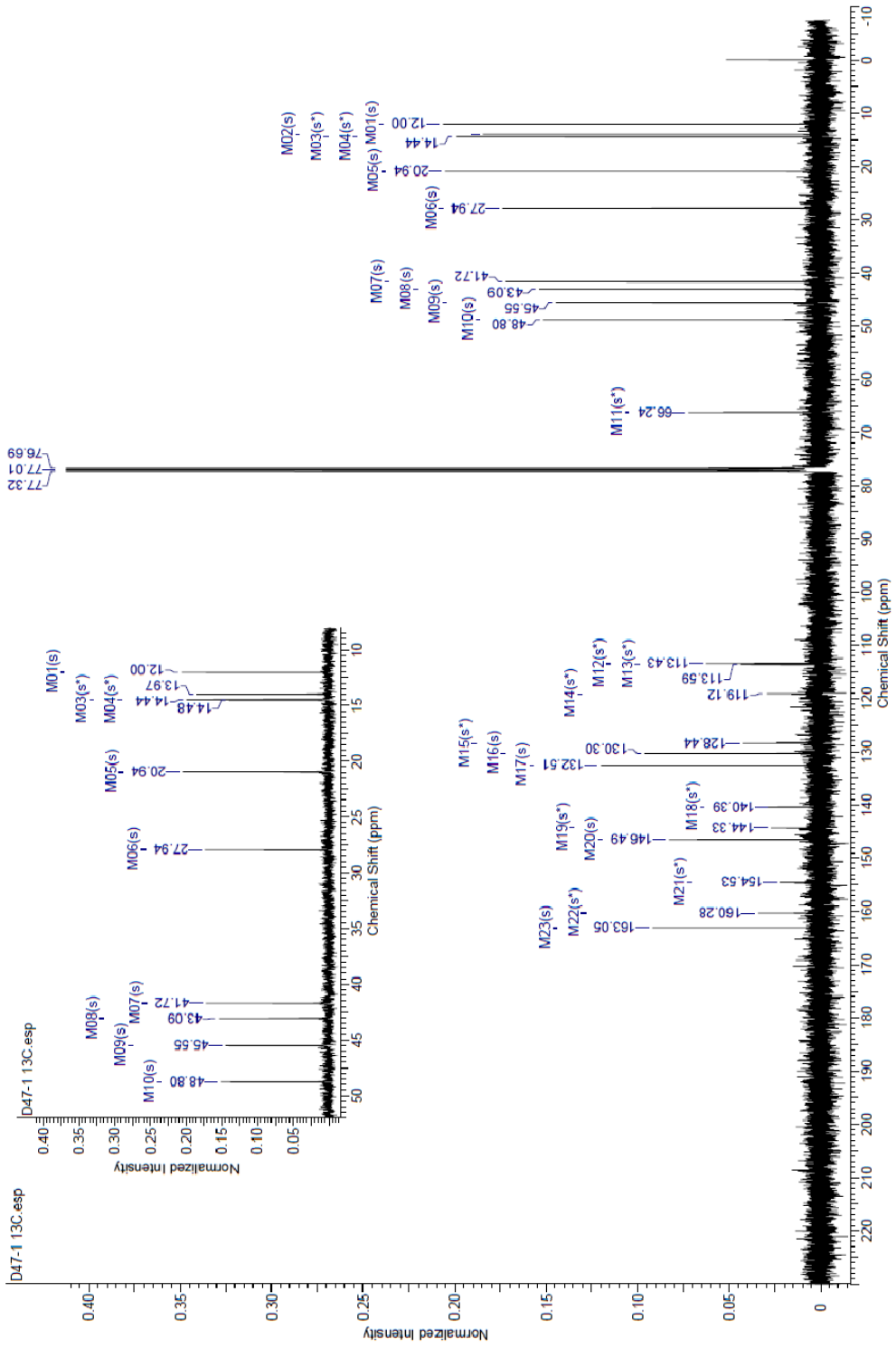


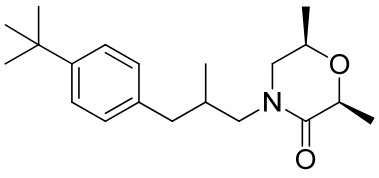
Oxo-vardenafil 5e

^{1}H NMR



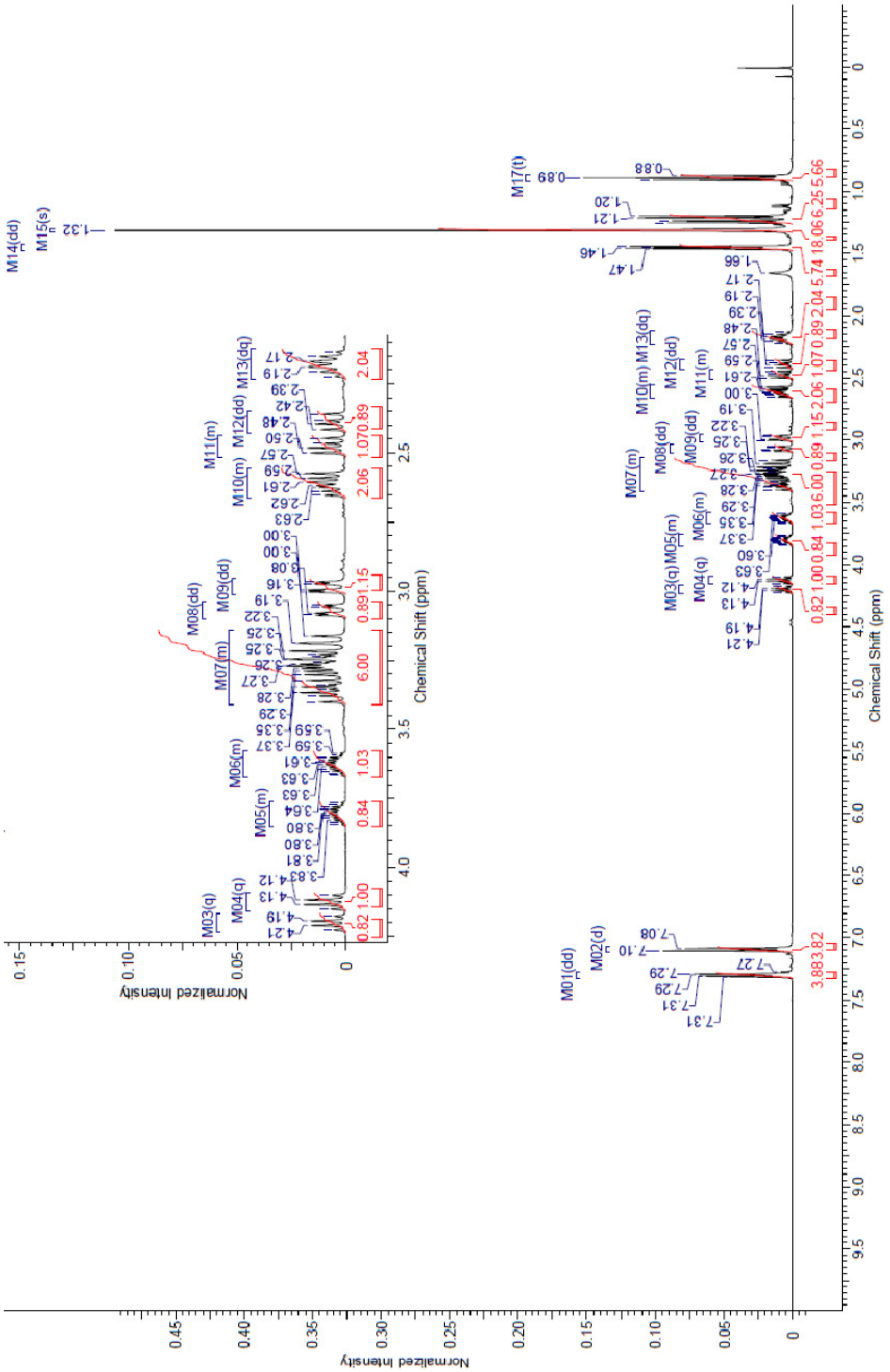
^{13}C NMR


D47-1 13C.esp
Normalized Intensity
Chemical Shift (ppm)
M01(s)
M02(s)
M03(s*)
M04(s*)
M05(s)
M06(s)
M07(s)
M08(s)
M09(s)
M10(s)
M11(s*)
M12(s*)
M13(s*)
M14(s*)
M15(s*)
M16(s)
M17(s)
M18(s*)
M19(s*)
M20(s)
M21(s*)
M22(s*)
M23(s)
12.00
13.97
14.44
14.48
20.94
27.94
41.72
43.09
45.55
48.80
66.24
76.69
77.01
77.32
113.43
113.59
119.12
128.44
130.30
132.51
140.39
144.33
146.49
154.53
160.28
163.05

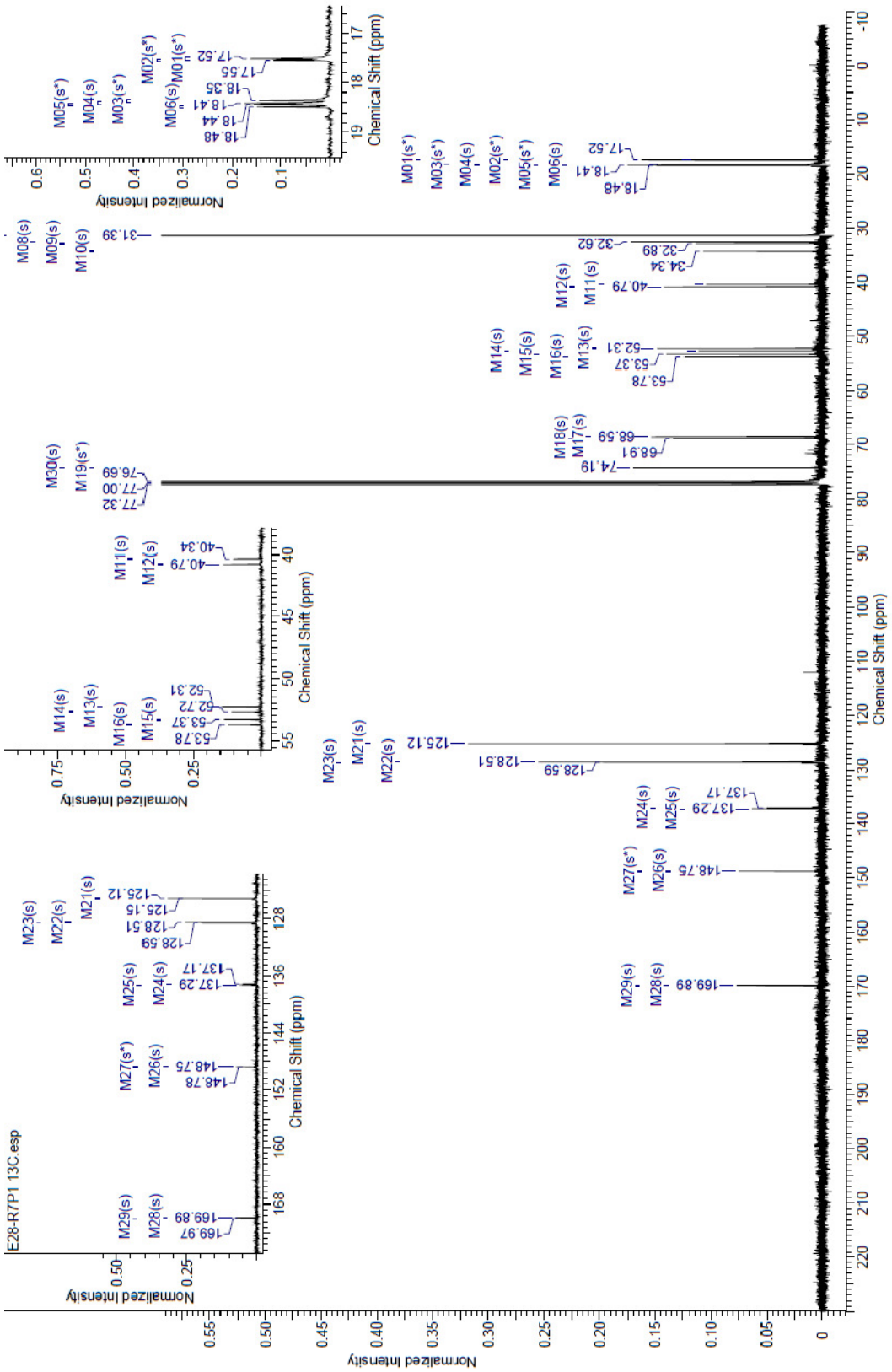


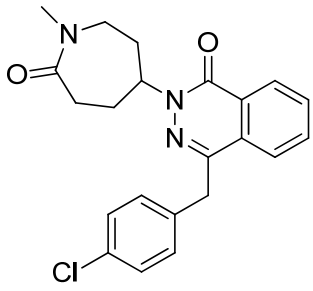
Oxo-fenpropimorph (diastereomeric mixture) 5f

^{1}H NMR



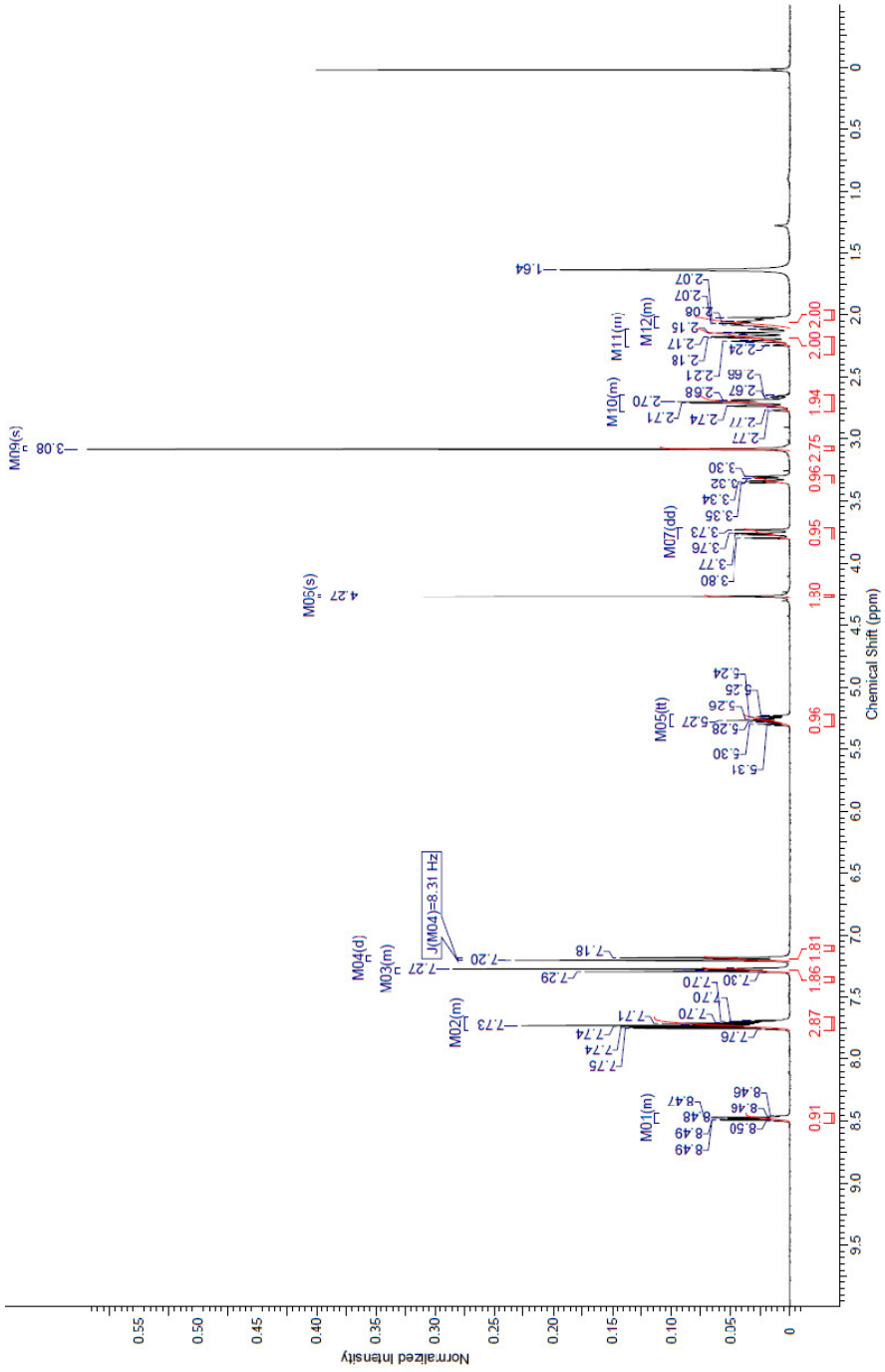
^{13}C NMR



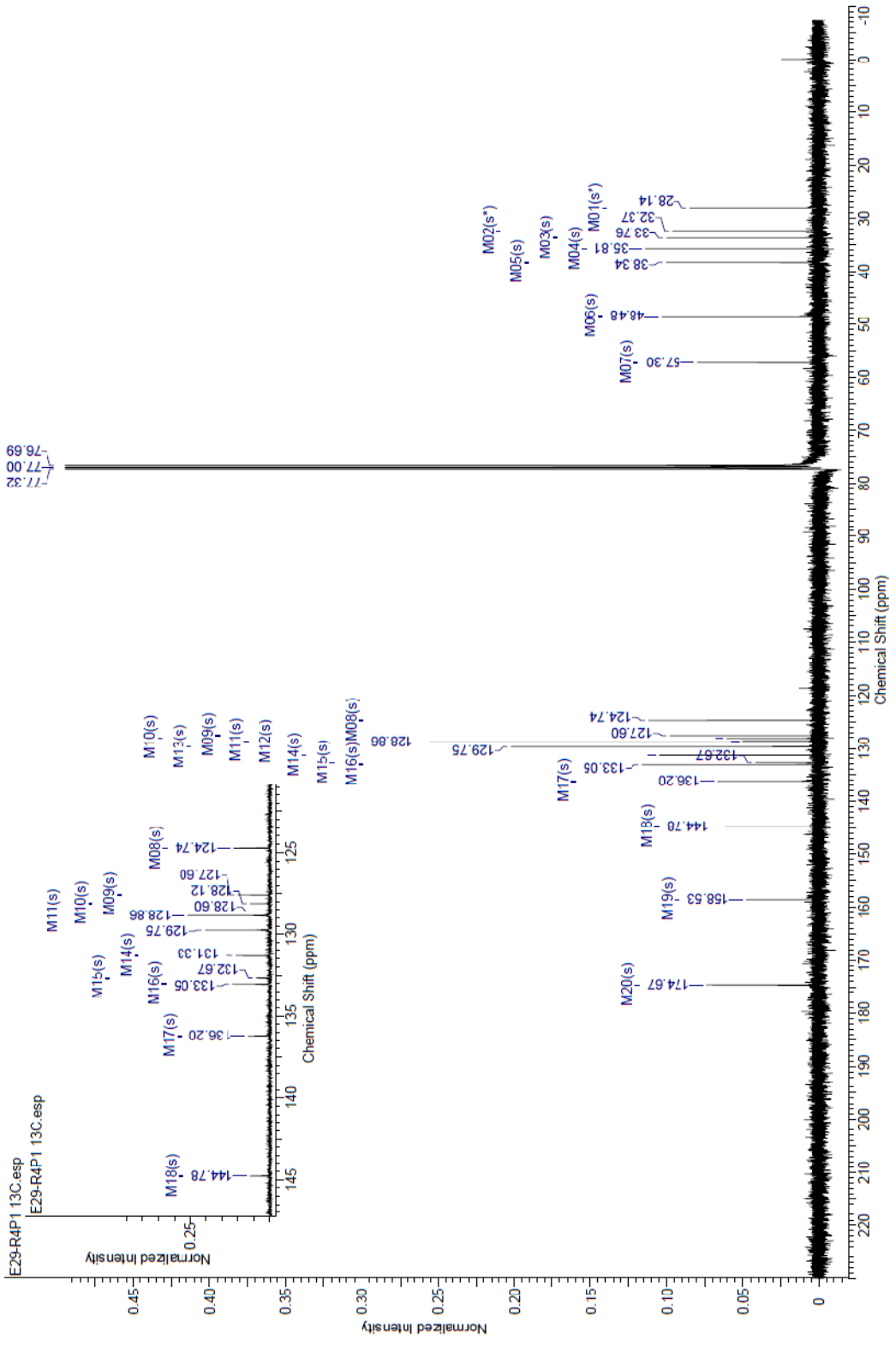


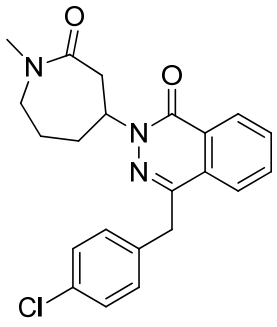
7-Oxo-azelastine 5g[α]

^{1}H NMR



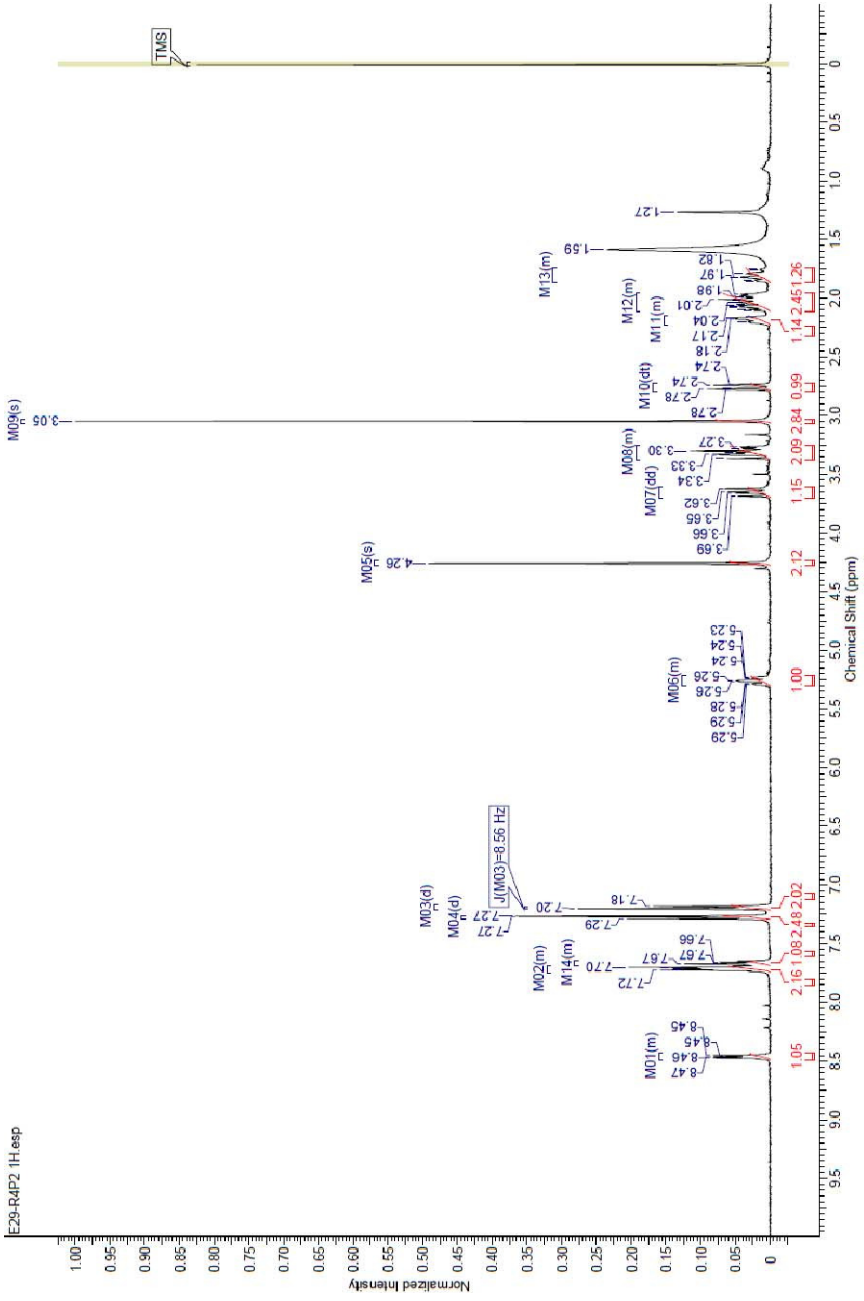
^{13}C NMR


Chemical Shift (ppm)
Normalized Intensity
E29-R4P1 13C.esp
E29-R4P1 13C.esp
M01(s*)
M02(s*)
M03(s)
M04(s)
M05(s)
M06(s)
M07(s)
M08(s)
M09(s)
M10(s)
M11(s)
M12(s)
M13(s)
M14(s)
M15(s)
M16(s)
M17(s)
M18(s)
M19(s)
M20(s)
28.14
32.37
33.76
35.81
38.34
48.48
57.30
76.69
77.00
77.32
124.74
127.60
128.12
128.60
128.86
129.75
131.33
132.67
133.05
136.20
144.78
158.53
174.67

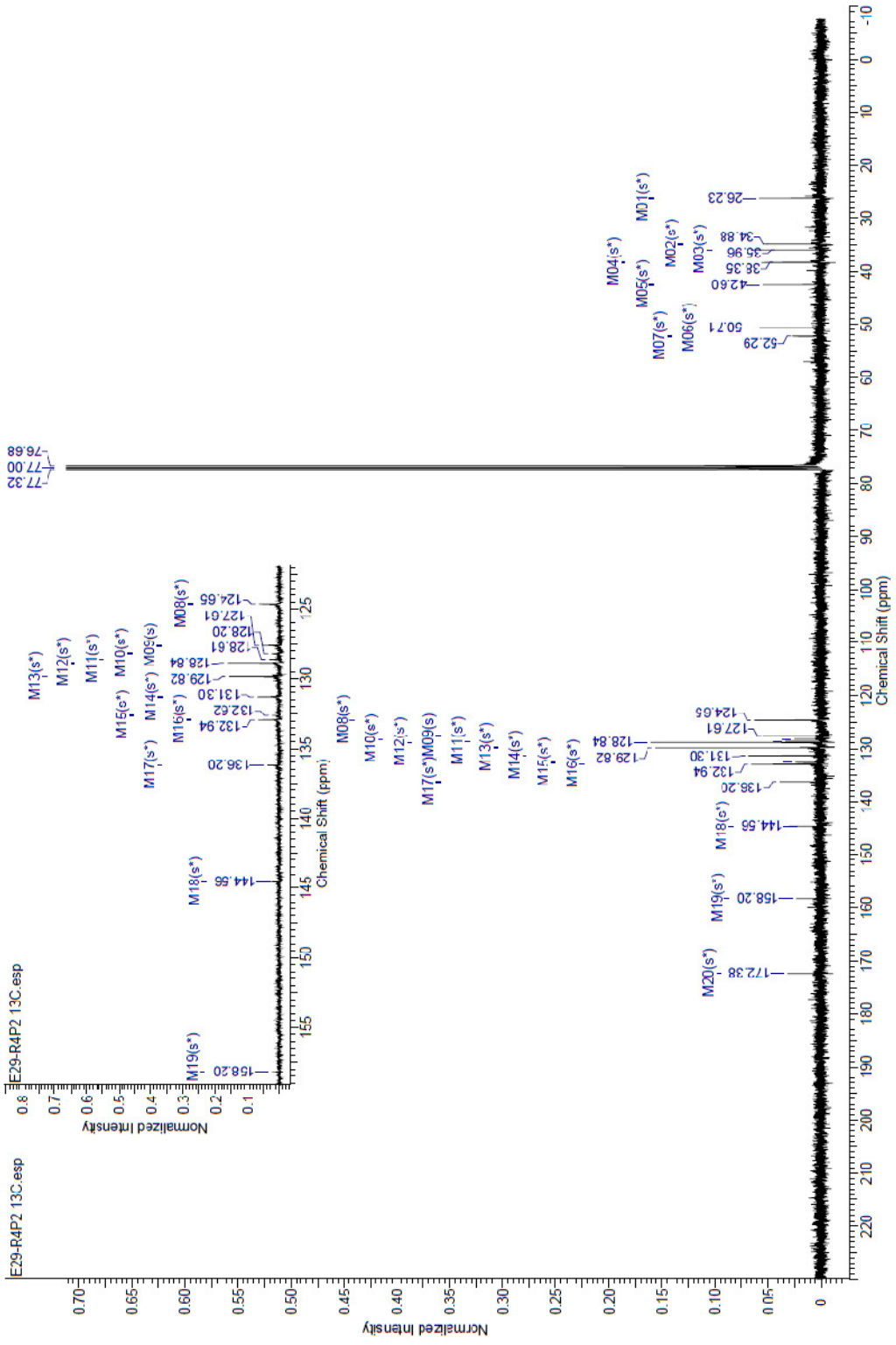


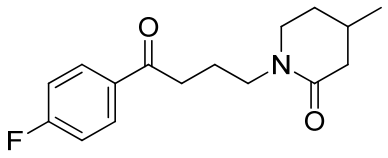
2-Oxo-azelastine 5g[β]

[1]H NMR



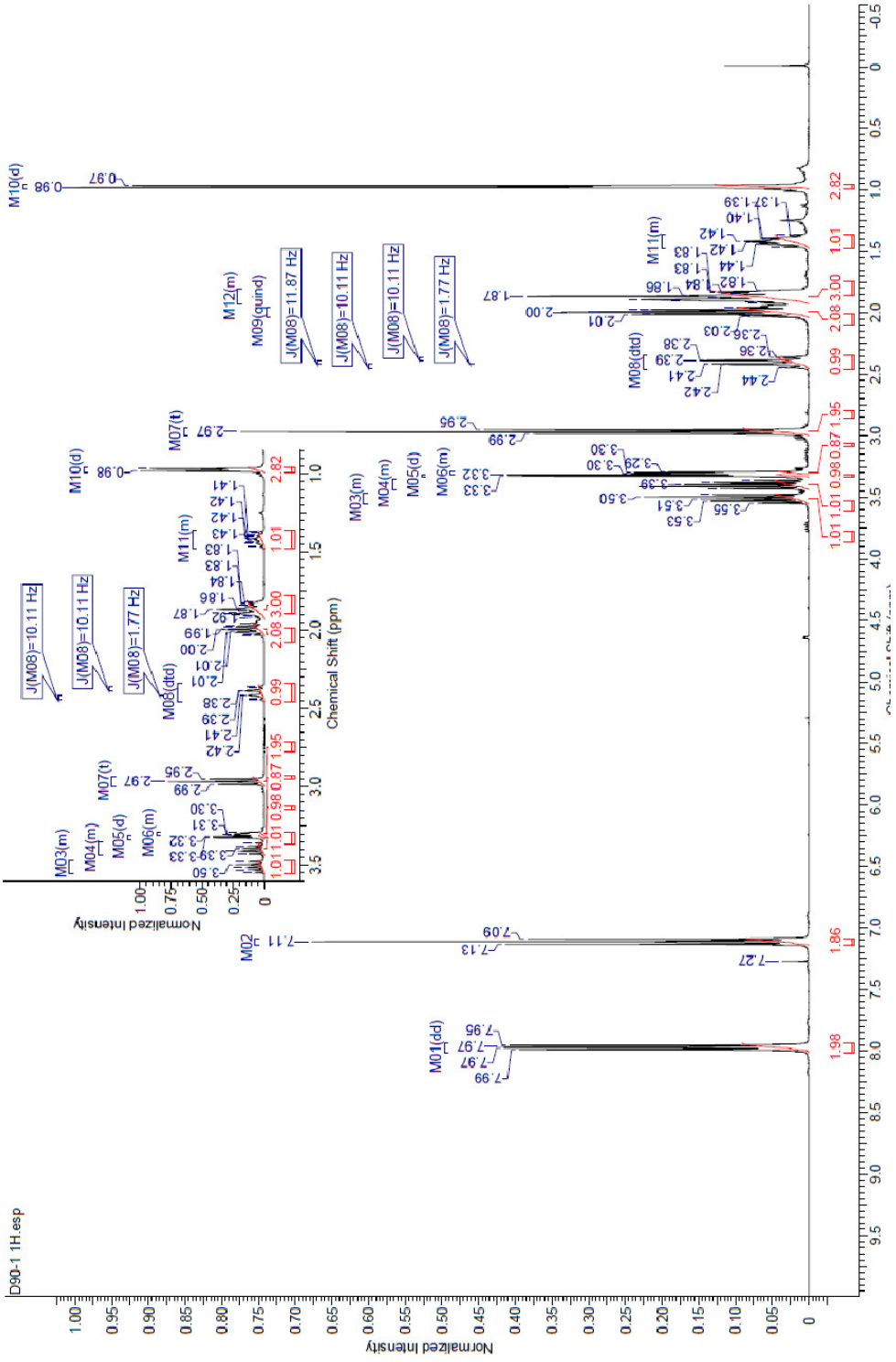
^{13}C NMR


E29-R4P2 13C.esp
Normalized Intensity
Chemical Shift (ppm)
77.32
77.00
76.68
26.23
34.88
35.96
36.35
42.60
50.71
52.29
124.65
127.61
128.20
128.61
128.84
129.82
131.30
132.62
132.94
136.20
144.55
158.20
172.38
M01(s*)
M02(s*)
M03(s*)
M04(s*)
M05(s*)
M06(s*)
M07(s*)
M08(s*)
M09(s)
M10(s*)
M11(s*)
M12(s*)
M13(s*)
M14(s*)
M15(s*)
M16(s*)
M17(s*)
M18(s*)
M19(s*)
M20(s*)

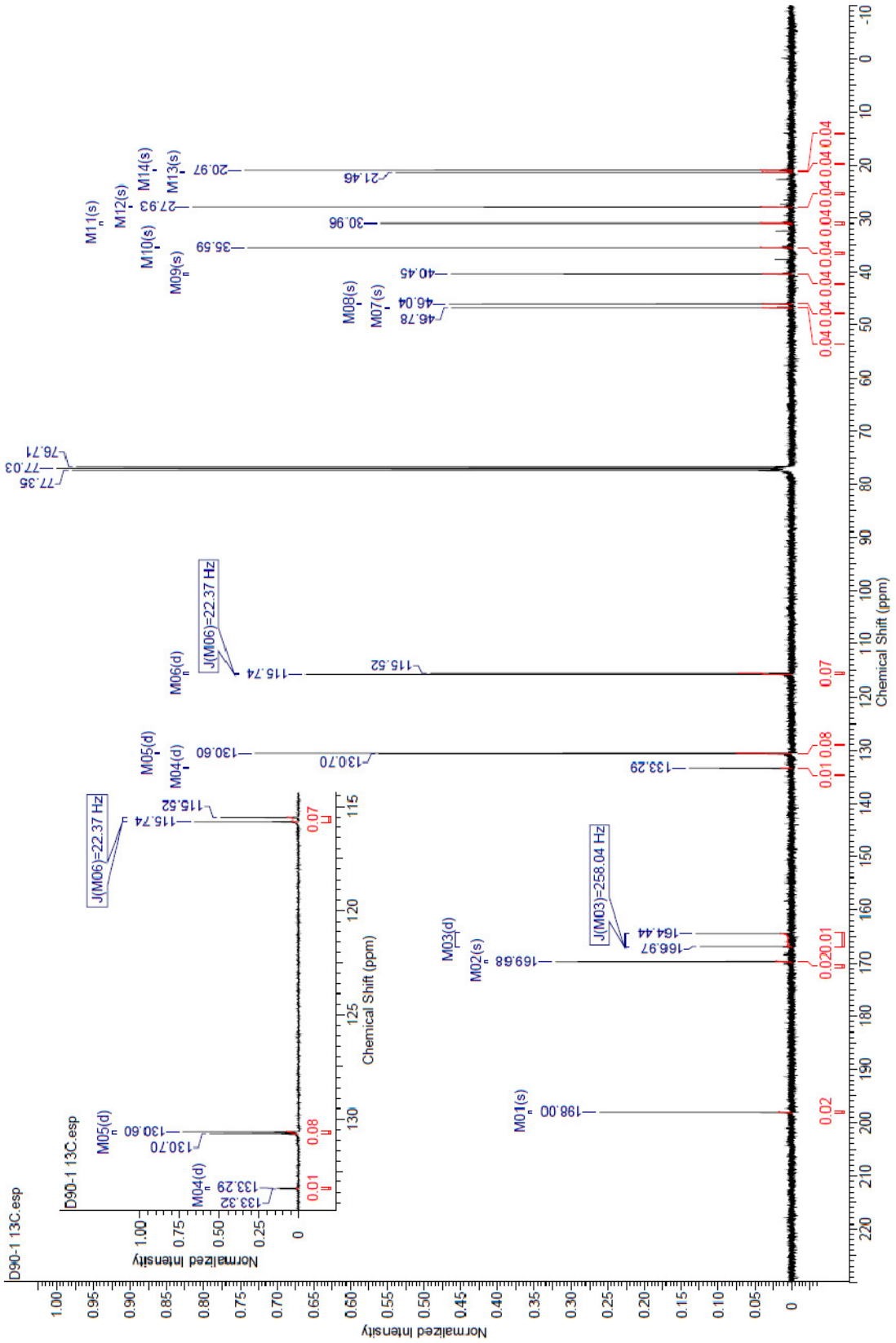


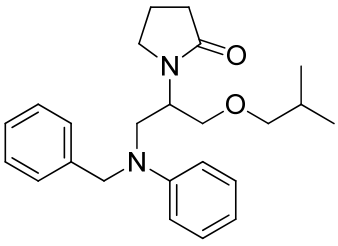
Oxo-Melperone 5h

^{1}H NMR



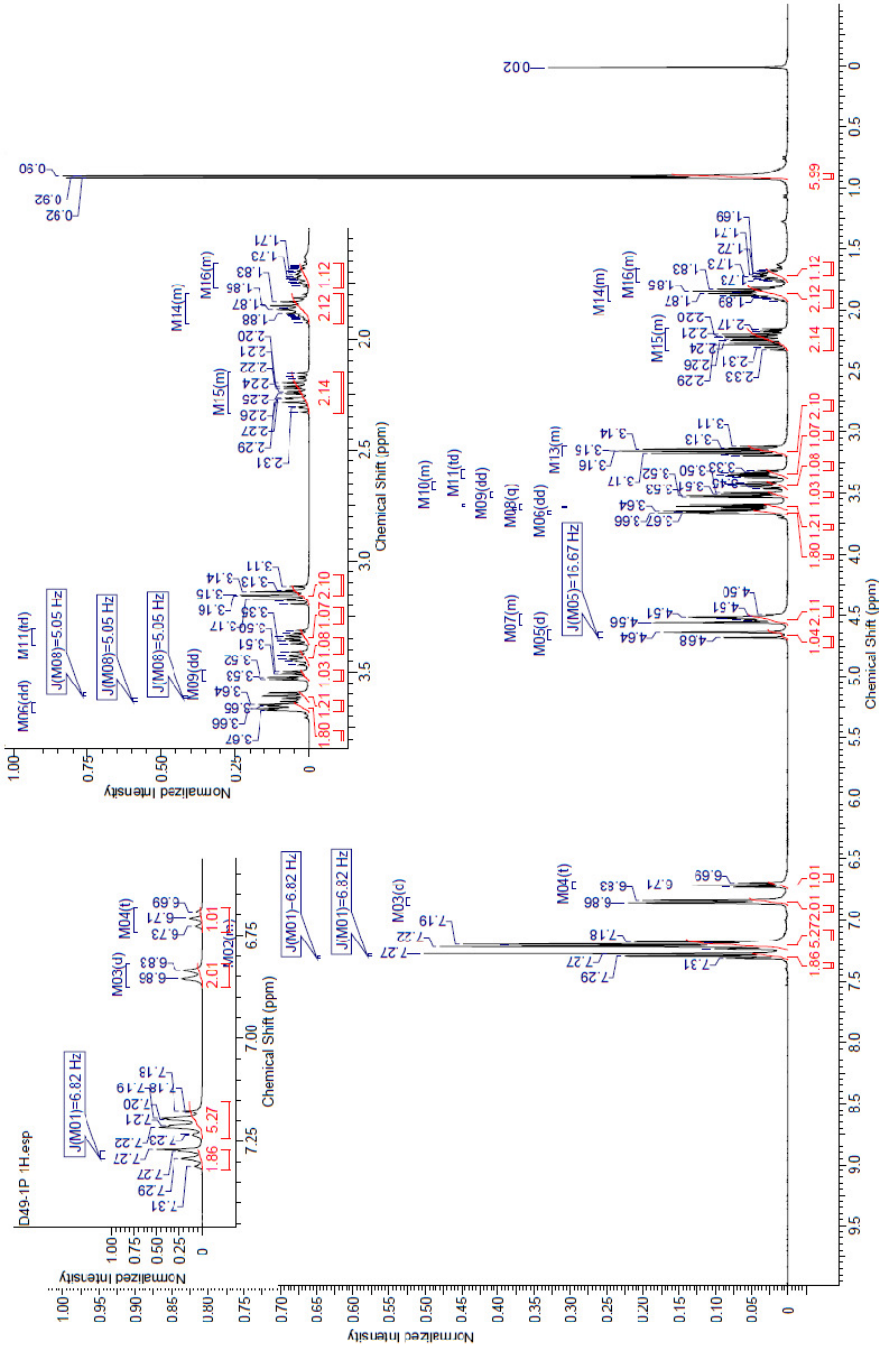
^{13}C NMR


D90-1 13C.esp
Normalized Intensity
Chemical Shift (ppm)
M01(s)
M02(s)
M03(d)
M04(d)
M05(d)
M06(d)
M07(s)
M08(s)
M09(s)
M10(s)
M11(s)
M12(s)
M13(s)
M14(s)
198.00
169.68
166.97
164.44
133.29
130.70
130.60
115.74
115.52
77.35
77.03
76.71
46.78
46.04
40.45
35.59
30.96
27.93
21.46
20.97
J(M06)=22.37 Hz
J(M03)=258.04 Hz

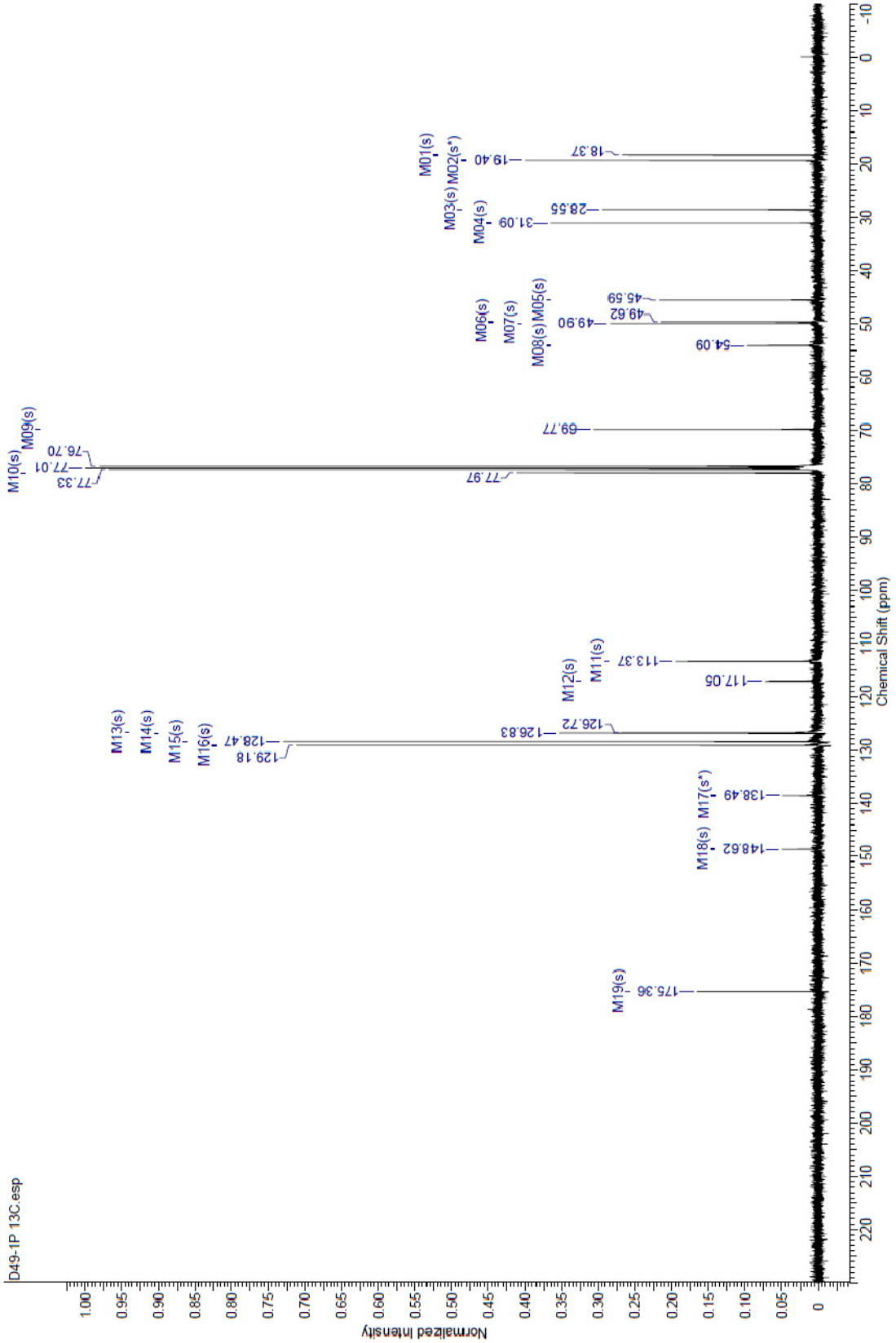


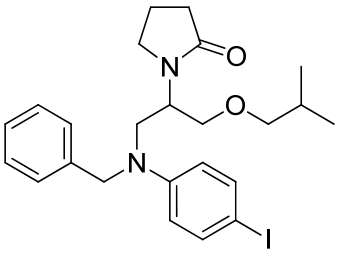
Oxo-Bepridil 5i

^{1}H NMR



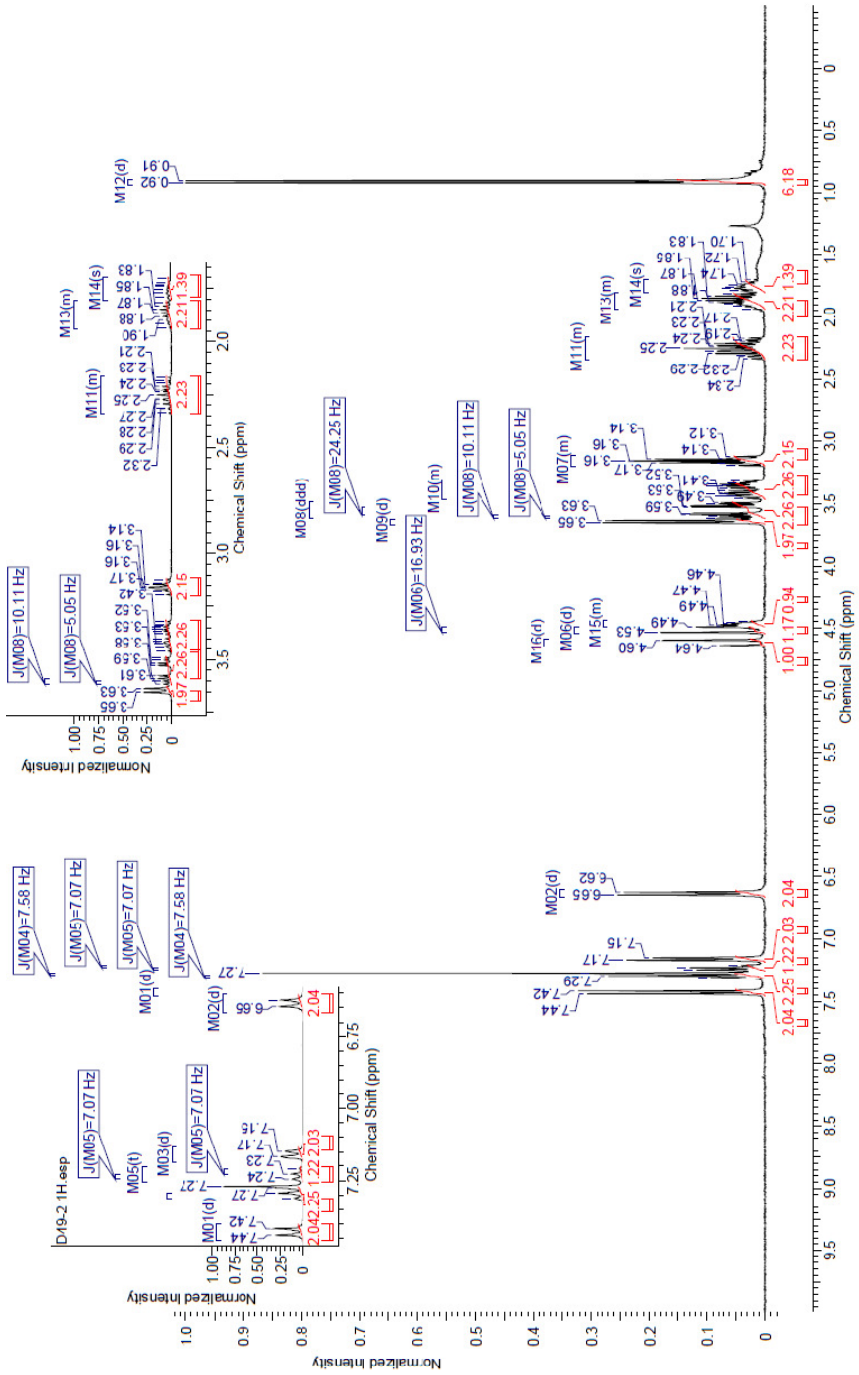
^{13}C NMR


D49-1P 13C.esp
Normalized Intensity
Chemical Shift (ppm)
M01(s)
M02(s*)
M03(s)
M04(s)
M05(s)
M06(s)
M07(s)
M08(s)
M09(s)
M10(s)
M11(s)
M12(s)
M13(s)
M14(s)
M15(s)
M16(s)
M17(s*)
M18(s)
M19(s)
18.37
19.40
28.55
31.09
45.59
49.62
49.90
54.09
69.77
76.70
77.01
77.33
77.97
113.37
117.05
126.72
126.83
128.47
129.18
138.49
148.62
175.36

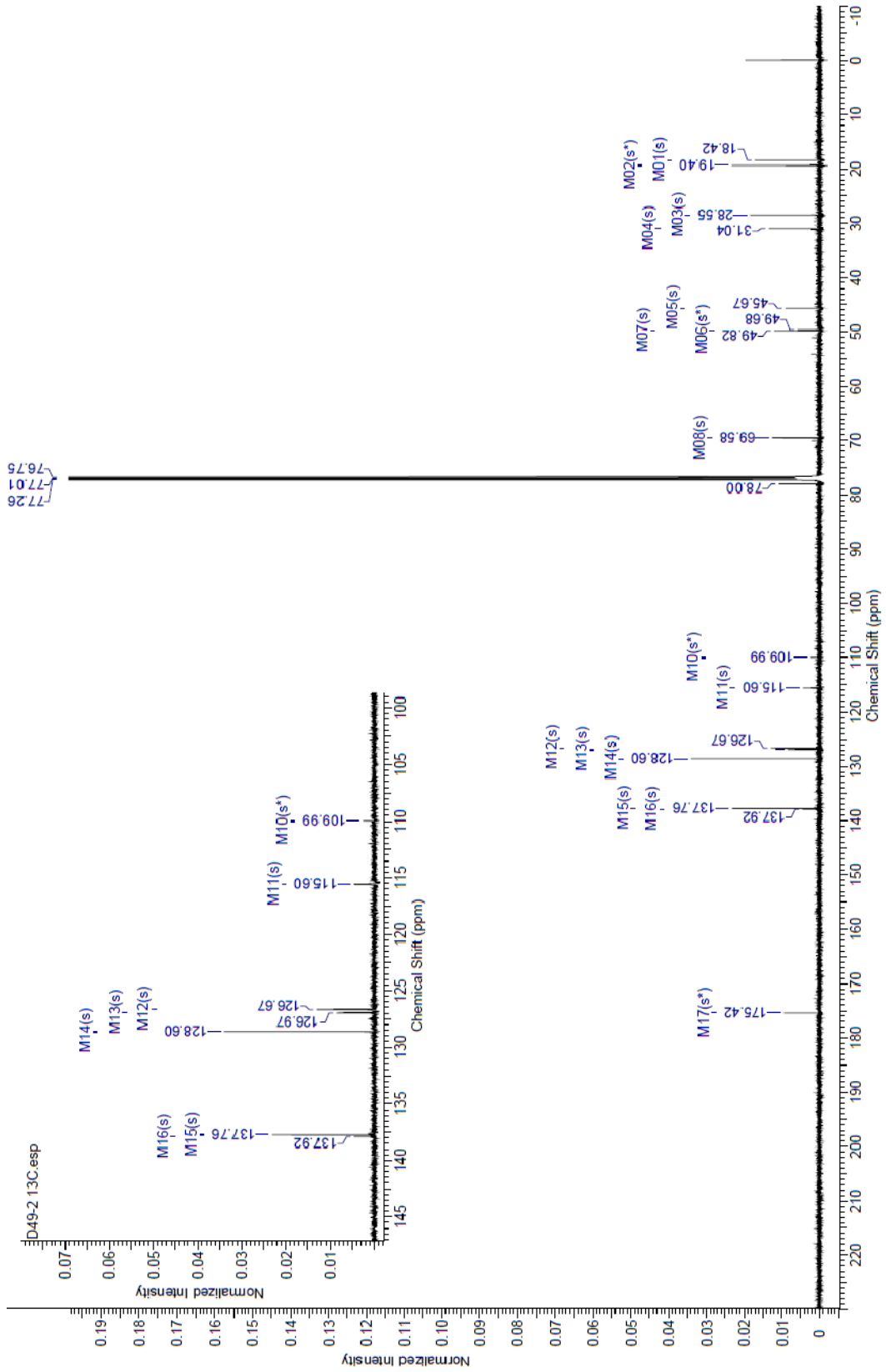


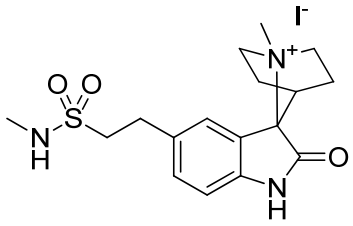
Oxo-iodo-Bepridil 15

^{1}H NMR



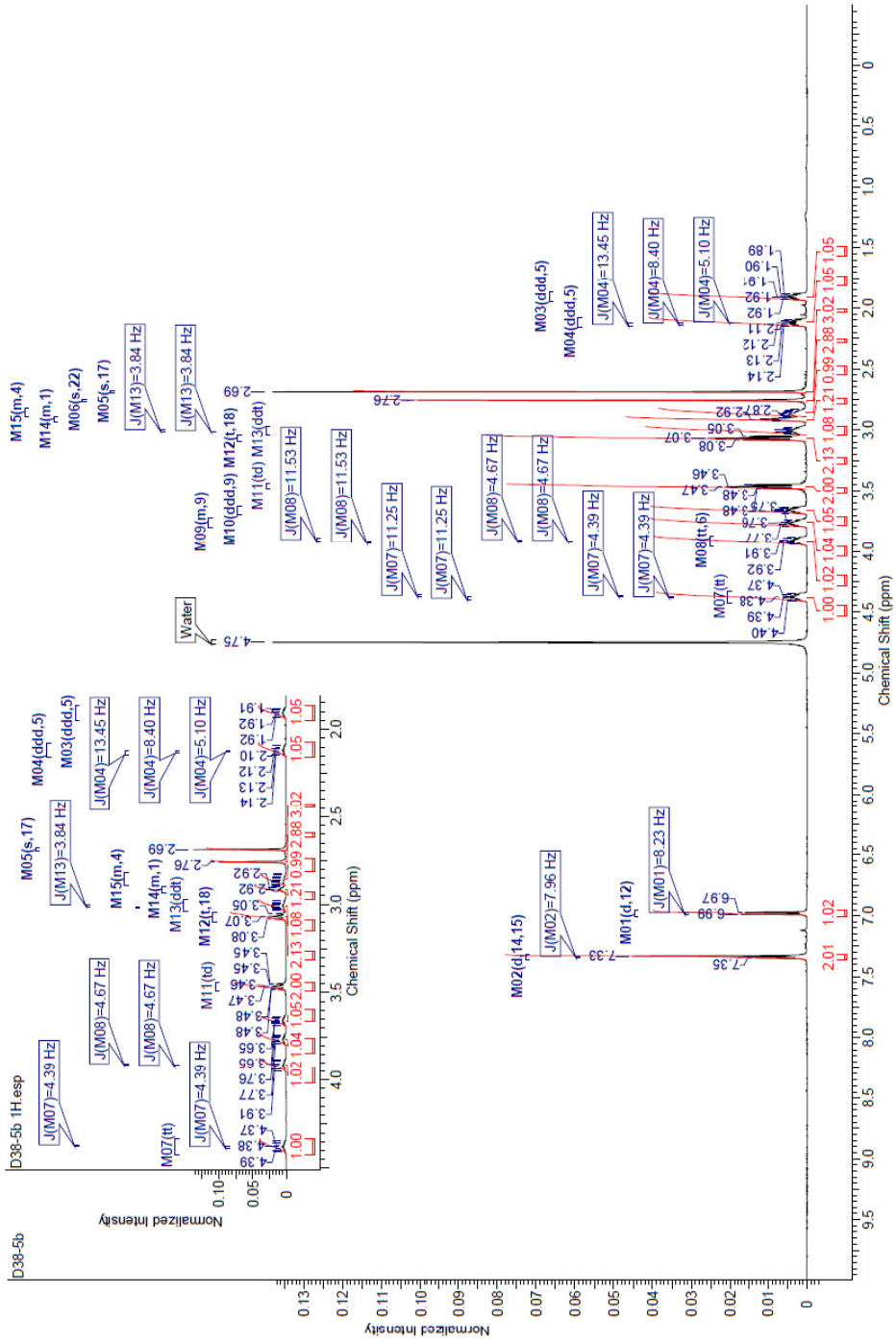
^{13}C NMR


Chemical Shift (ppm)
Normalized Intensity
D49-2 13C.esp
M01(s)
M02(s*)
M03(s)
M04(s)
M05(s)
M06(s*)
M07(s)
M08(s)
M09(s*)
M10(s*)
M11(s)
M12(s)
M13(s)
M14(s)
M15(s)
M16(s)
M17(s*)
18.42
19.40
28.55
31.04
45.67
49.68
49.82
69.58
76.75
77.01
77.26
78.00
109.99
115.60
126.67
126.97
128.60
137.76
137.92
175.42

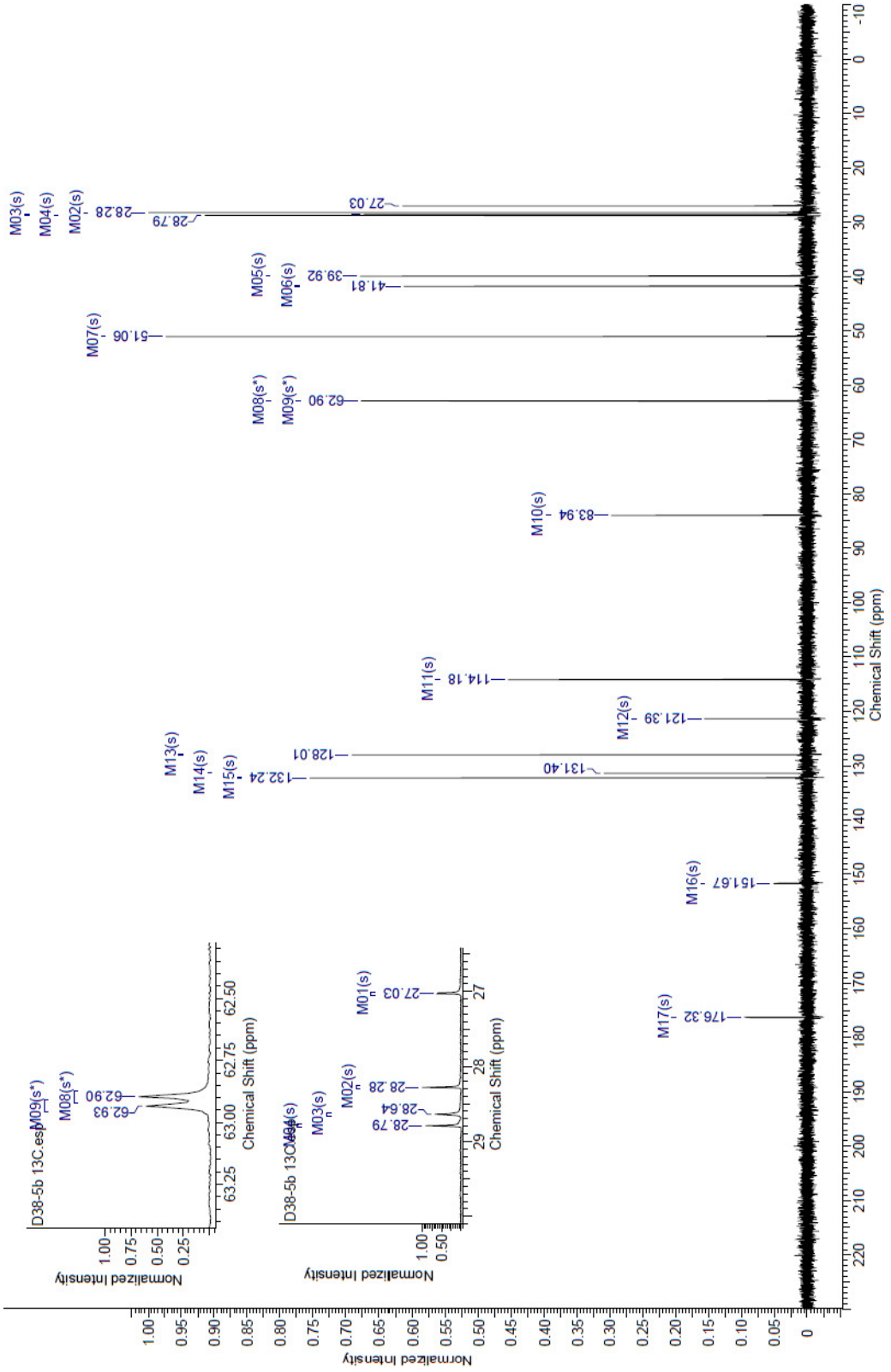


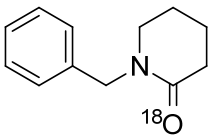
1-Methyl-5'-(2-(*N*-methylsulfamoyl)ethyl)-2'-oxo-1-azaspiro [bicyclo[2.2.1]heptane-7,3'-indolin]-1-ium iodide 14

^{1}H NMR



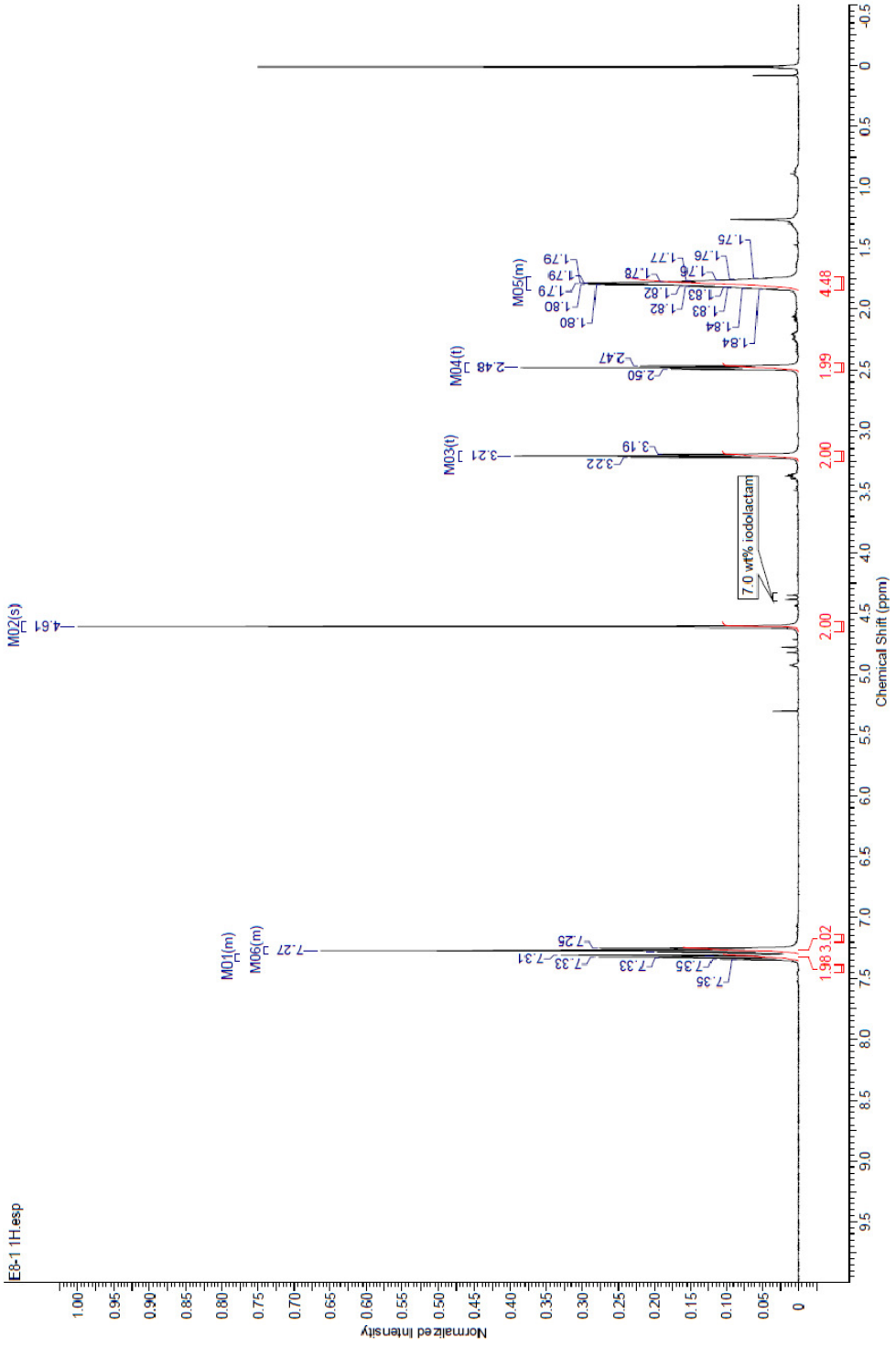
^{13}C NMR


M03(s)
M04(s)
M02(s)
28.79
28.28
27.03
M05(s)
M06(s)
39.92
41.81
M07(s)
51.06
M08(s*)
M09(s*)
62.90
M10(s)
83.94
M11(s)
114.18
M12(s)
121.39
M13(s)
M14(s)
M15(s)
128.01
131.40
132.24
M16(s)
151.67
M17(s)
176.32
Chemical Shift (ppm)
Normalized Intensity
D38-5b 13C.esp
M09(s*)
M08(s*)
62.93
62.90
63.25
63.00
62.75
62.50
Chemical Shift (ppm)
Normalized Intensity
D38-5b 13C.esp
M01(s)
M03(s)
M02(s)
27.03
28.28
28.64
28.79
29
28
27
Chemical Shift (ppm)
Normalized Intensity

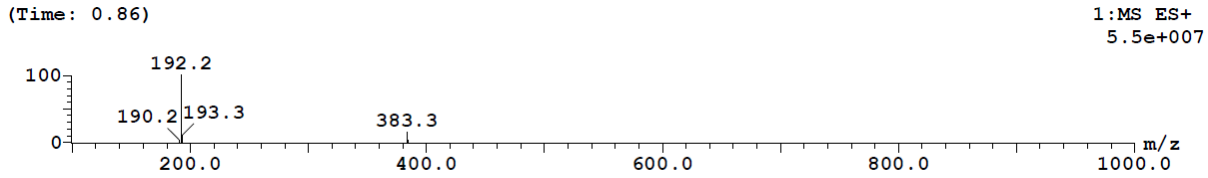


^{18}O-1-benzylpiperidin-2-one ^{18}O-3a

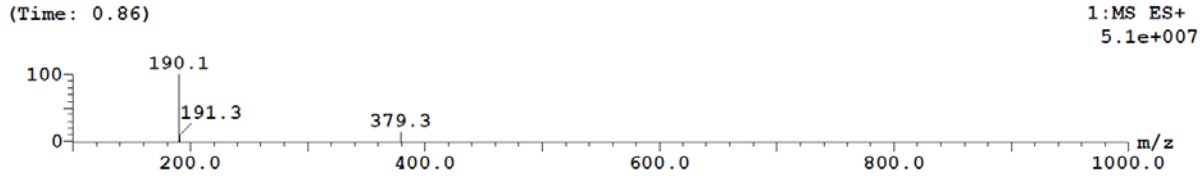
^{1}H NMR



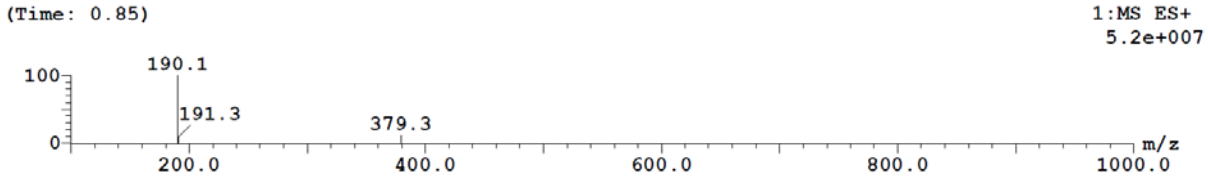
$NaHCO_3/H_2{}^{18}O$ reaction LCMS



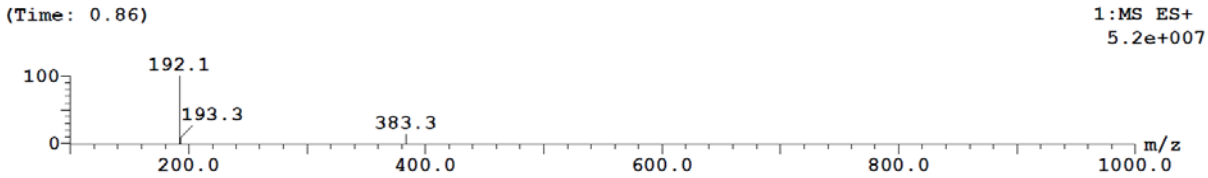
$NaOAc/H_2O$ reaction LCMS



$Na^{18}OAc/H_2O$ reaction LCMS



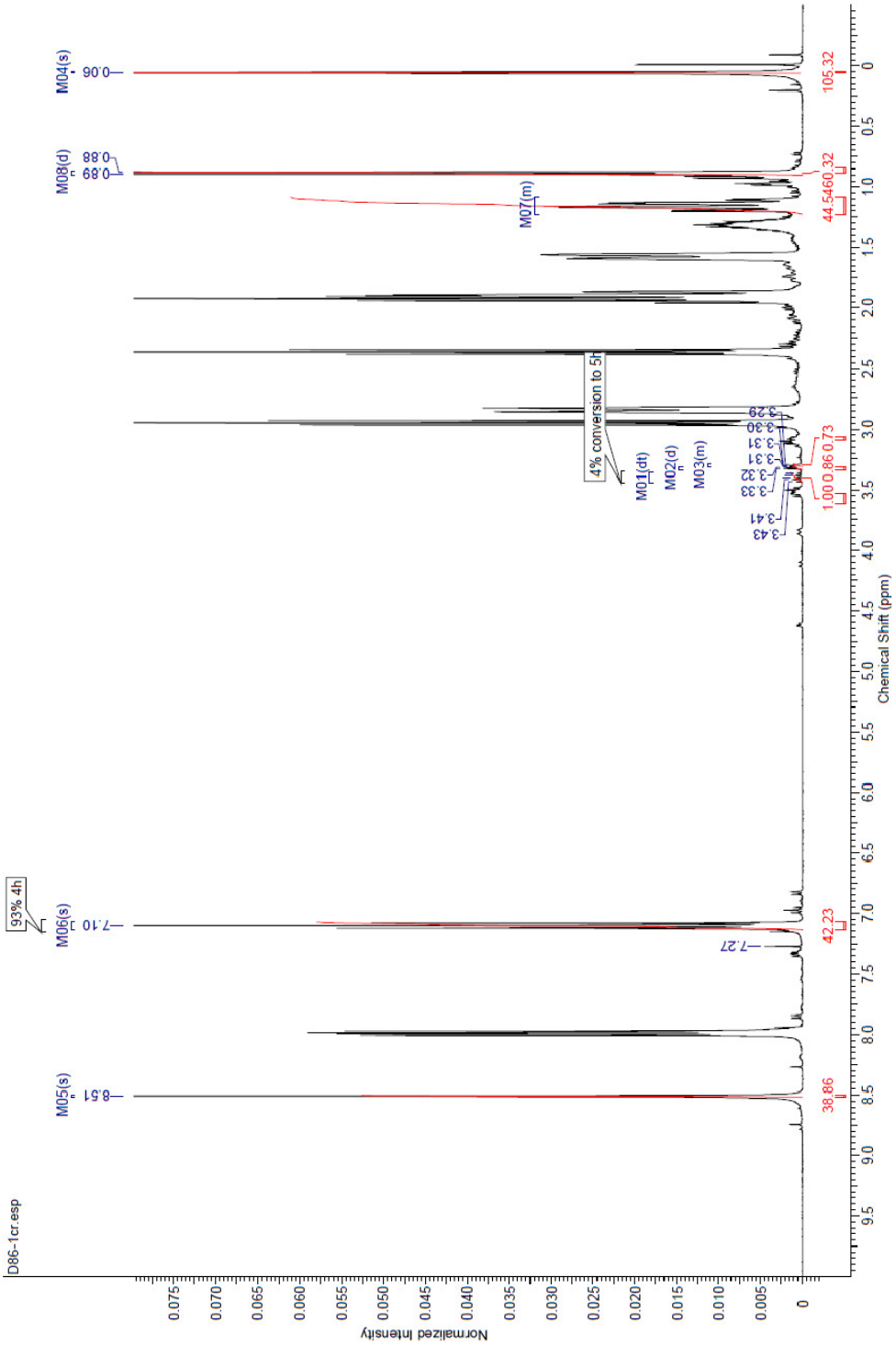
$Na^{18}OAc/H_2{}^{18}O$ reaction LCMS



Investigating late-stage oxidation under Milstein conditions

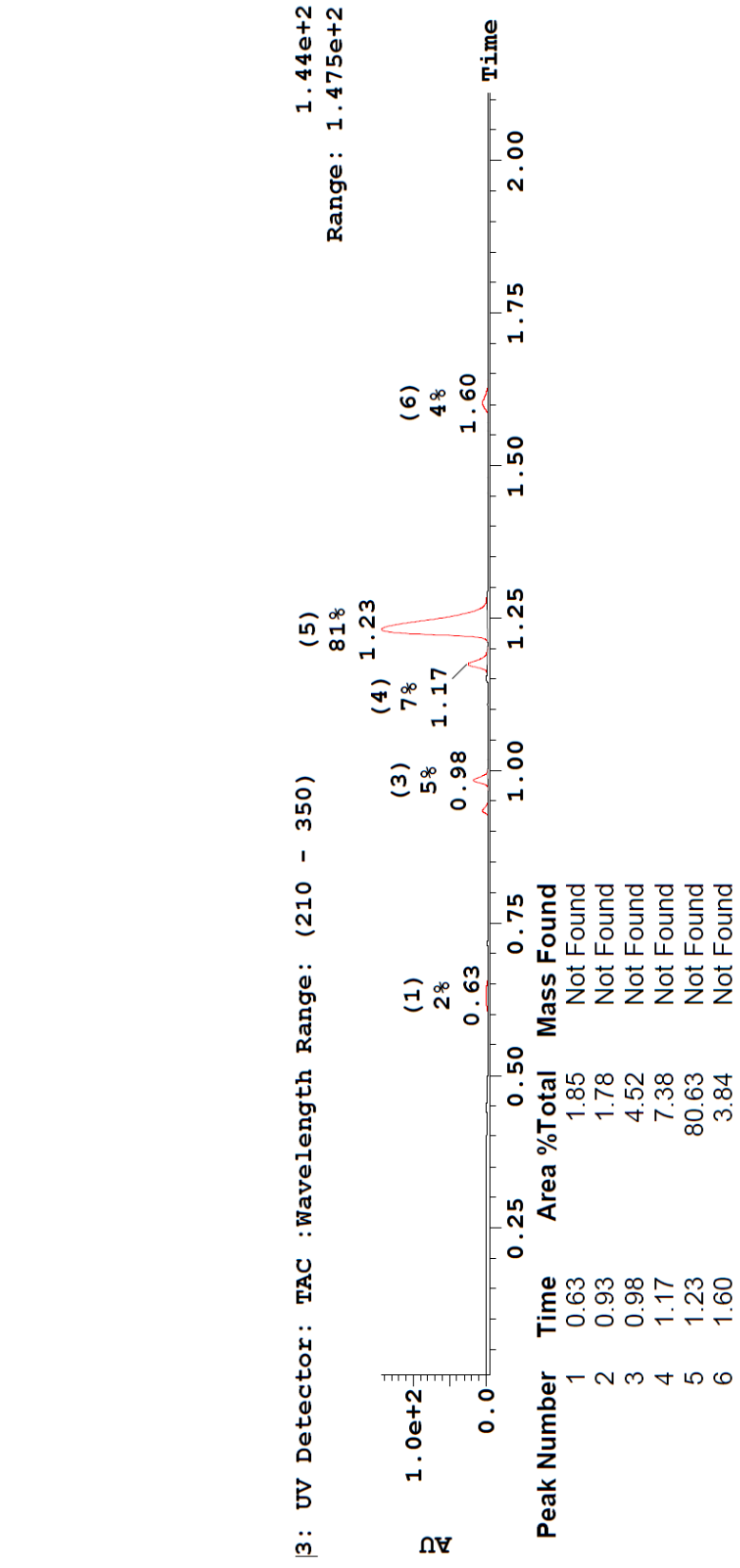
Applied to substrate 4h

^{1}H NMR of crude product



High pH LCMS spectrum of reaction mixture

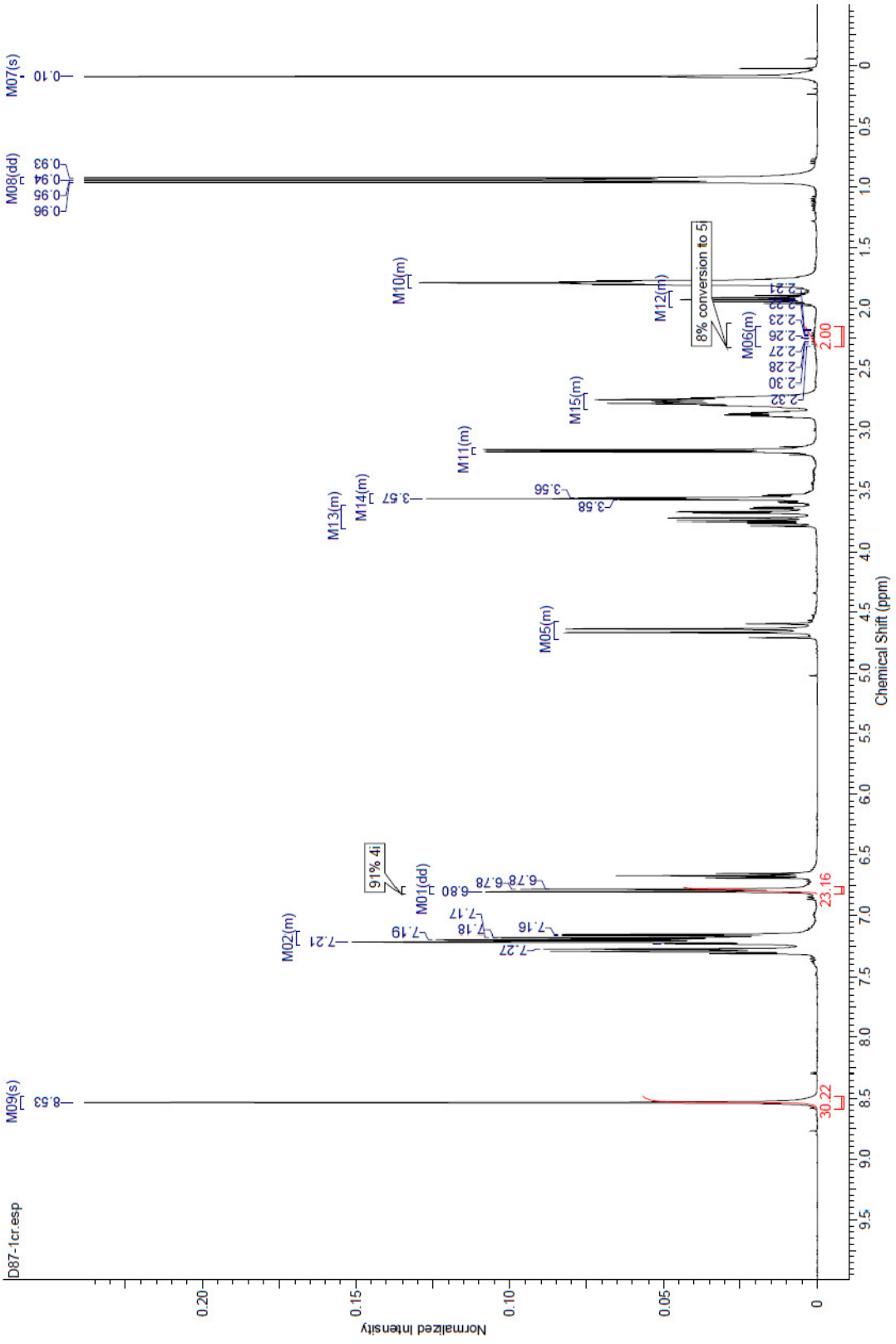
(Starting material R_t = 1.23 min)



Peak Number	Time	Area %Total	Mass Found
1	0.63	1.85	Not Found
2	0.93	1.78	Not Found
3	0.98	4.52	Not Found
4	1.17	7.38	Not Found
5	1.23	80.63	Not Found
6	1.60	3.84	Not Found

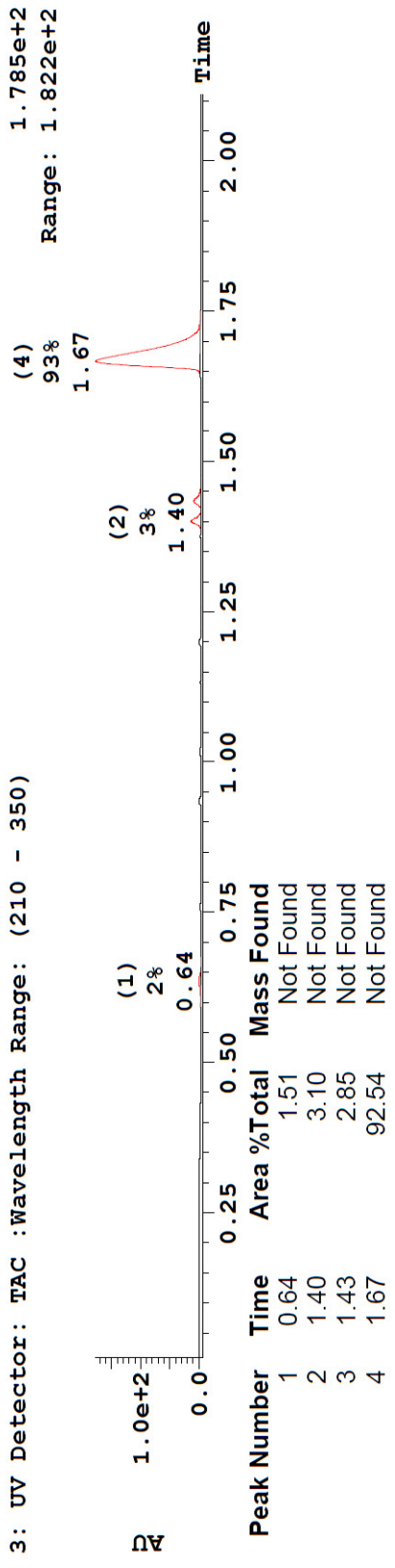
Applied to substrate 4i

^{1}H NMR of crude product



High pH LCMS spectrum of reaction mixture

(Starting material R_t = 1.67 min)

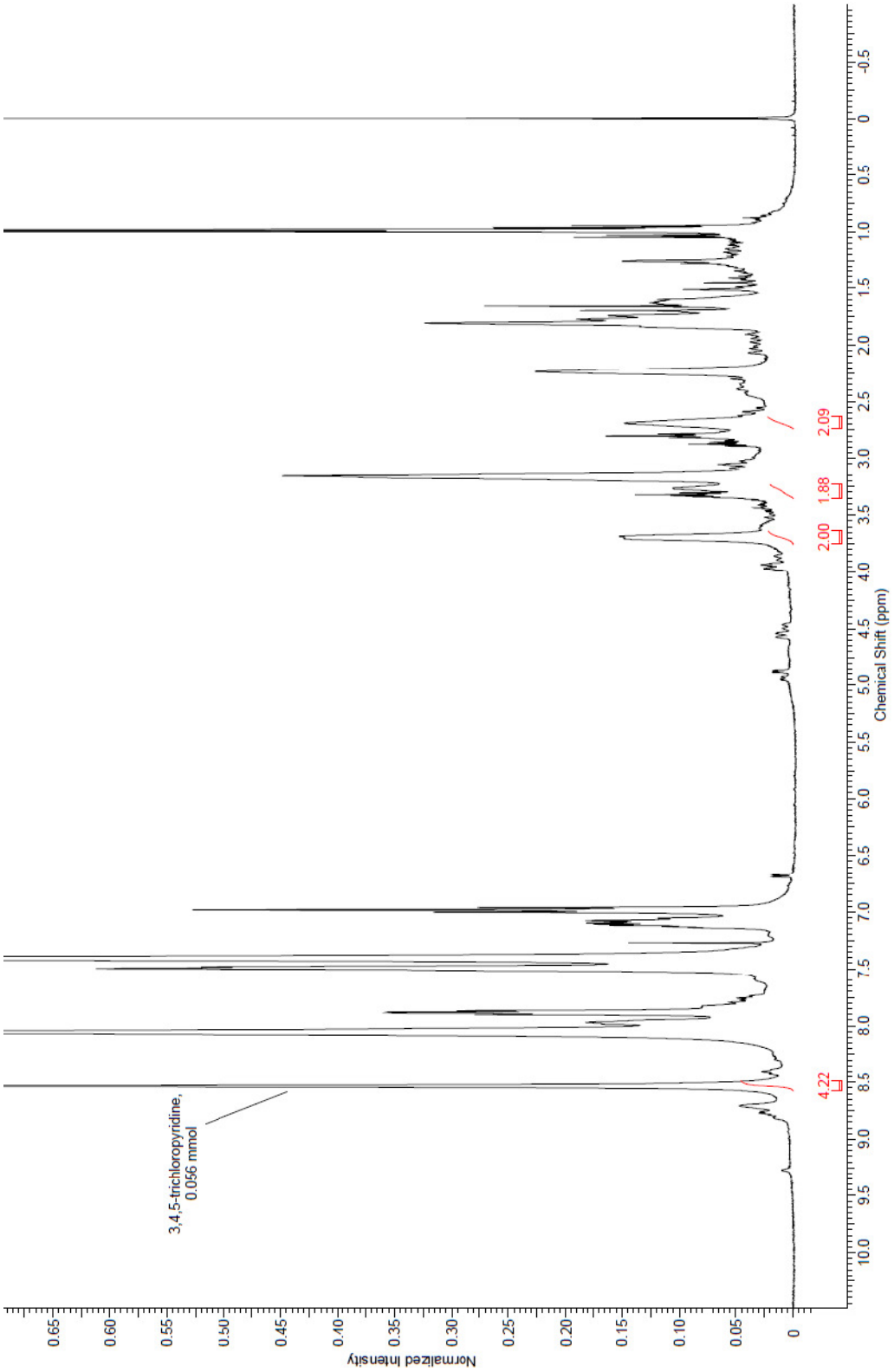


Peak Number	Time	Area %Total	Mass Found
1	0.64	1.51	Not Found
2	1.40	3.10	Not Found
3	1.43	2.85	Not Found
4	1.67	92.54	Not Found

Investigating late-stage oxidation under Emmert conditions

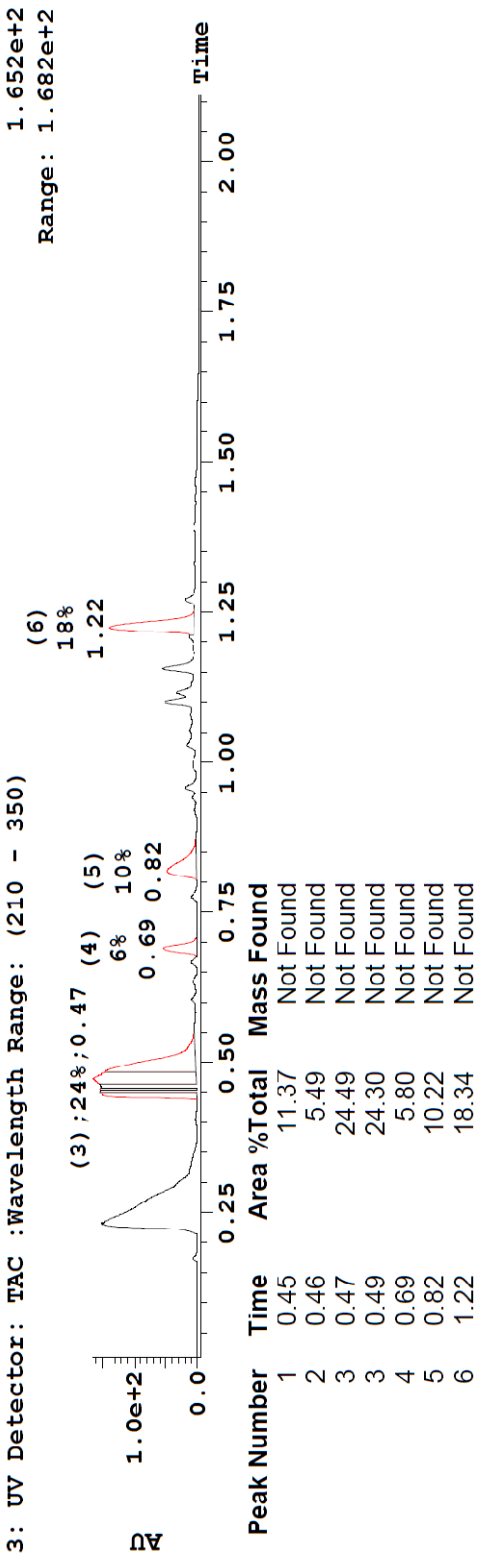
Applied to substrate 4h

^{1}H NMR of crude product



High pH LCMS spectrum of reaction mixture

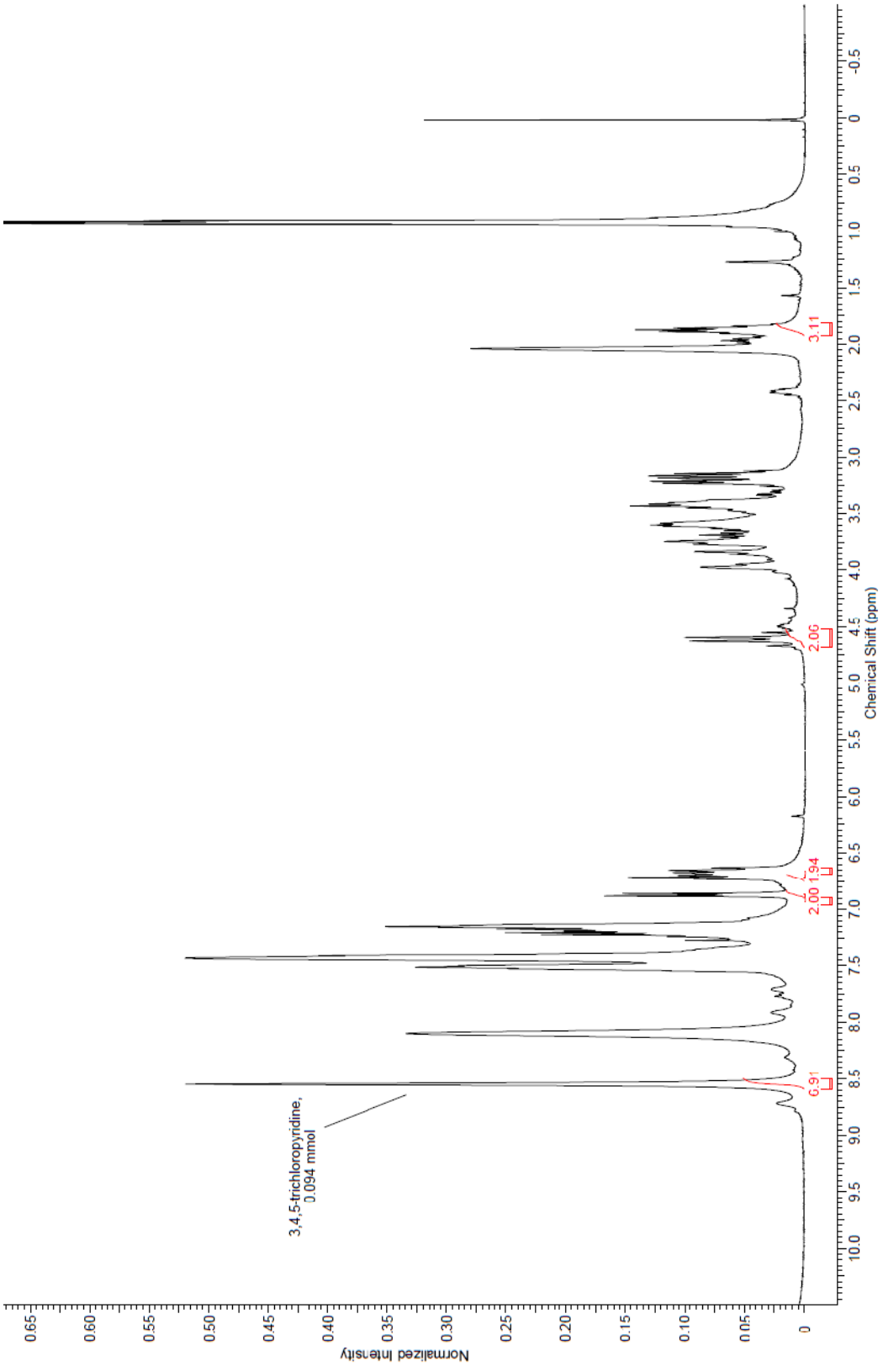
(Starting material R_t = 1.22 min)



Peak Number	Time	Area %Total	Mass Found
1	0.45	11.37	Not Found
2	0.46	5.49	Not Found
3	0.47	24.49	Not Found
3	0.49	24.30	Not Found
4	0.69	5.80	Not Found
5	0.82	10.22	Not Found
6	1.22	18.34	Not Found

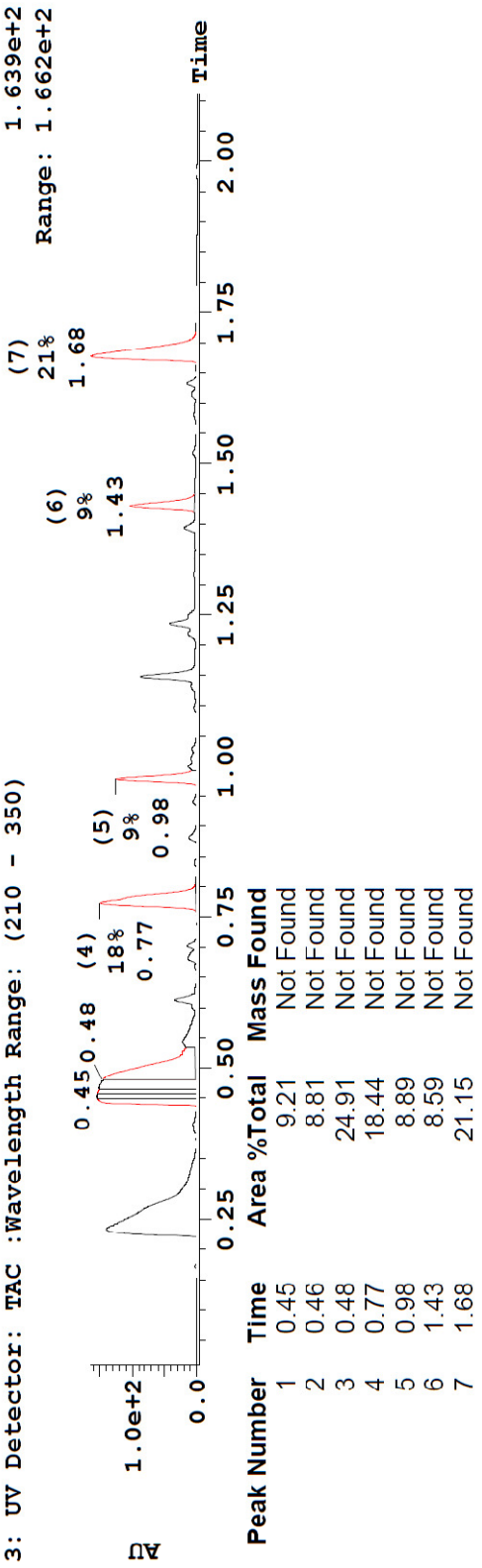
Applied to substrate 4i

^{1}H NMR of crude product



High pH LCMS spectrum of reaction mixture

(Starting material R_t = 1.68 min)

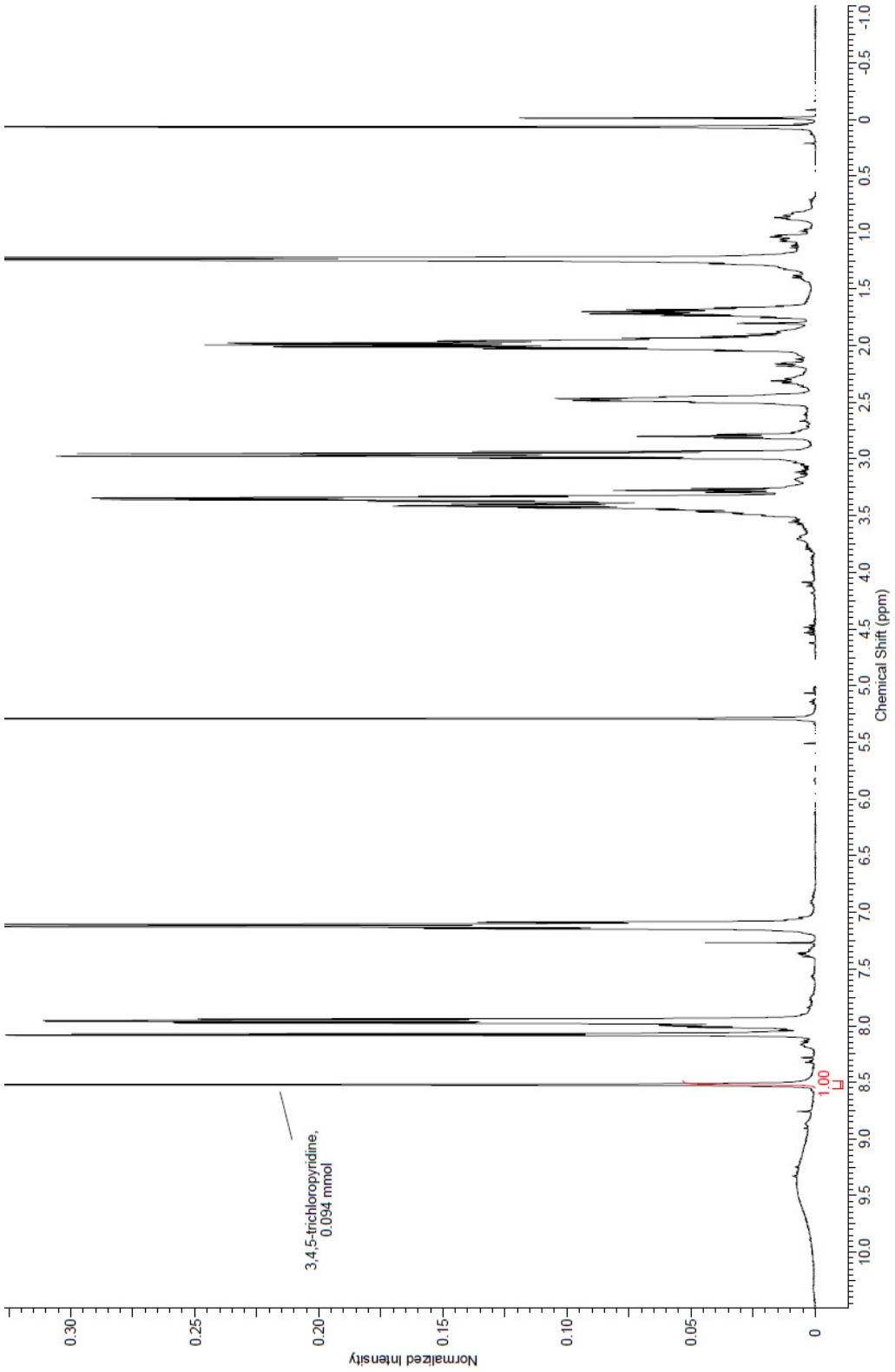


Peak Number	Time	Area %Total	Mass Found
1	0.45	9.21	Not Found
2	0.46	8.81	Not Found
3	0.48	24.91	Not Found
4	0.77	18.44	Not Found
5	0.98	8.89	Not Found
6	1.43	8.59	Not Found
7	1.68	21.15	Not Found

Investigating late-stage oxidation under classical $Ru^{IV}O_2/NaIO_4$ conditions

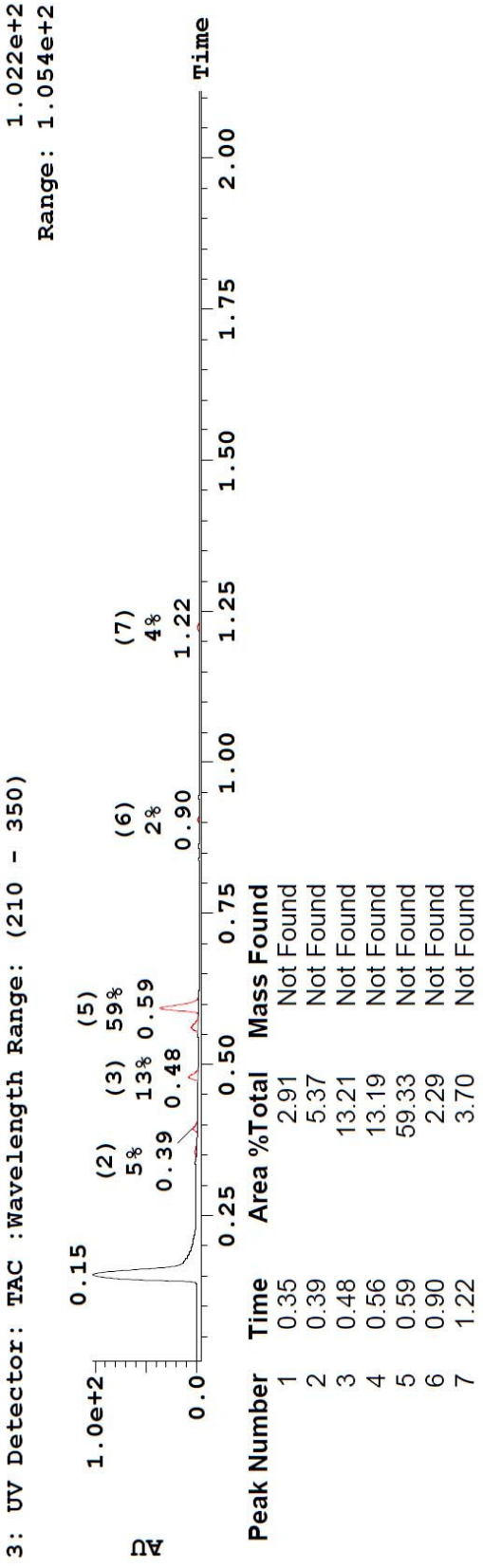
Applied to substrate 4h

^{1}H NMR of crude product



High pH LCMS spectrum of reaction mixture

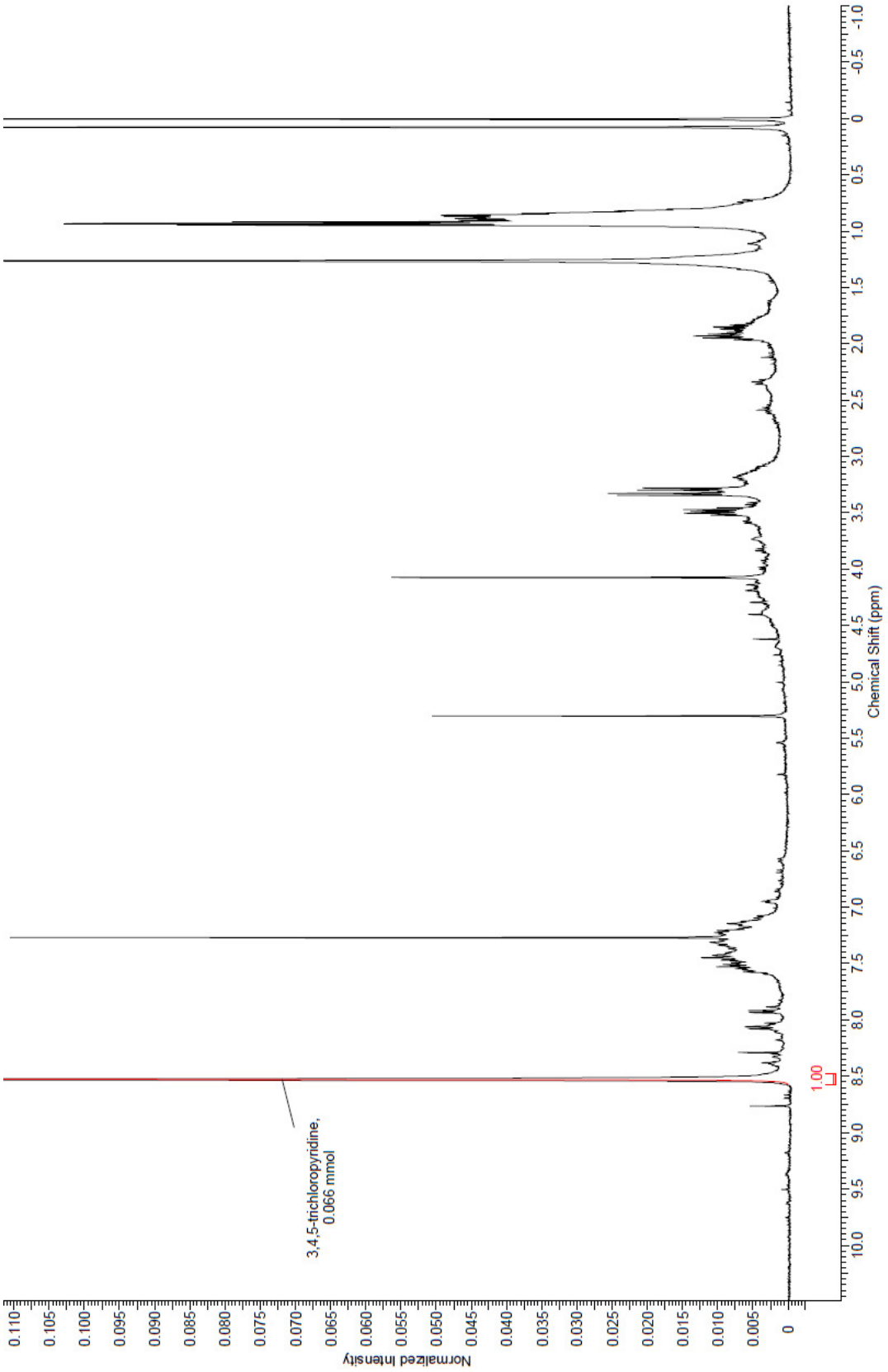
(Starting material R_t = 1.22 min)



Peak Number	Time	Area %Total	Mass Found
1	0.35	2.91	Not Found
2	0.39	5.37	Not Found
3	0.48	13.21	Not Found
4	0.56	13.19	Not Found
5	0.59	59.33	Not Found
6	0.90	2.29	Not Found
7	1.22	3.70	Not Found

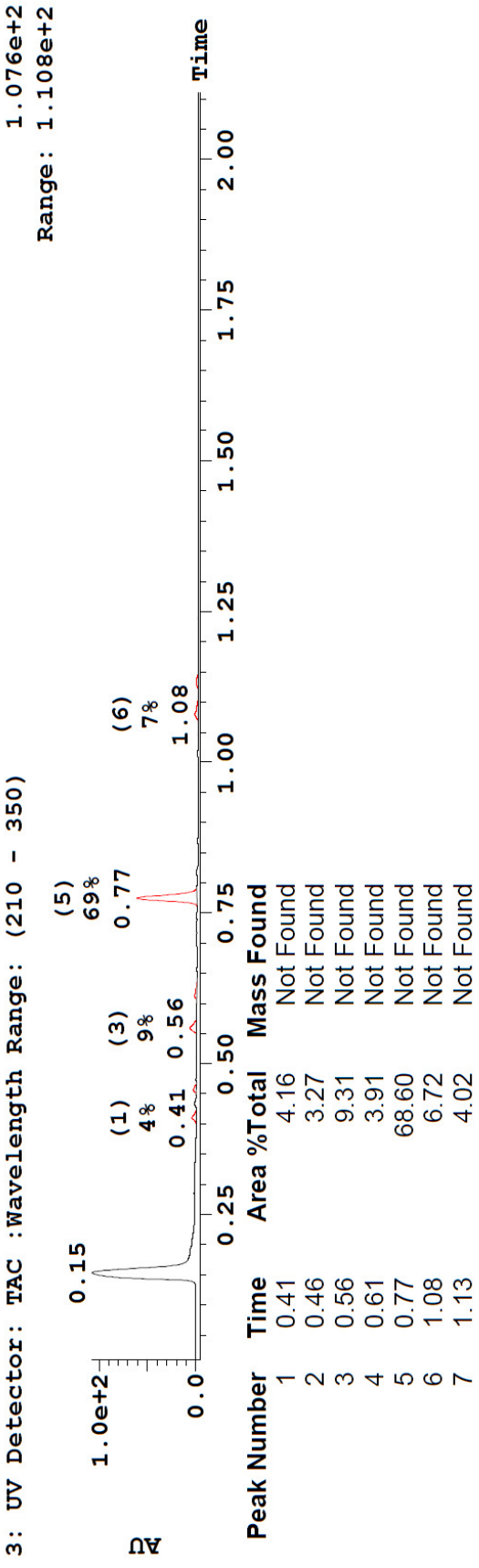
Applied to substrate 4i

^{1}H NMR of crude product



High pH LCMS spectrum of reaction mixture

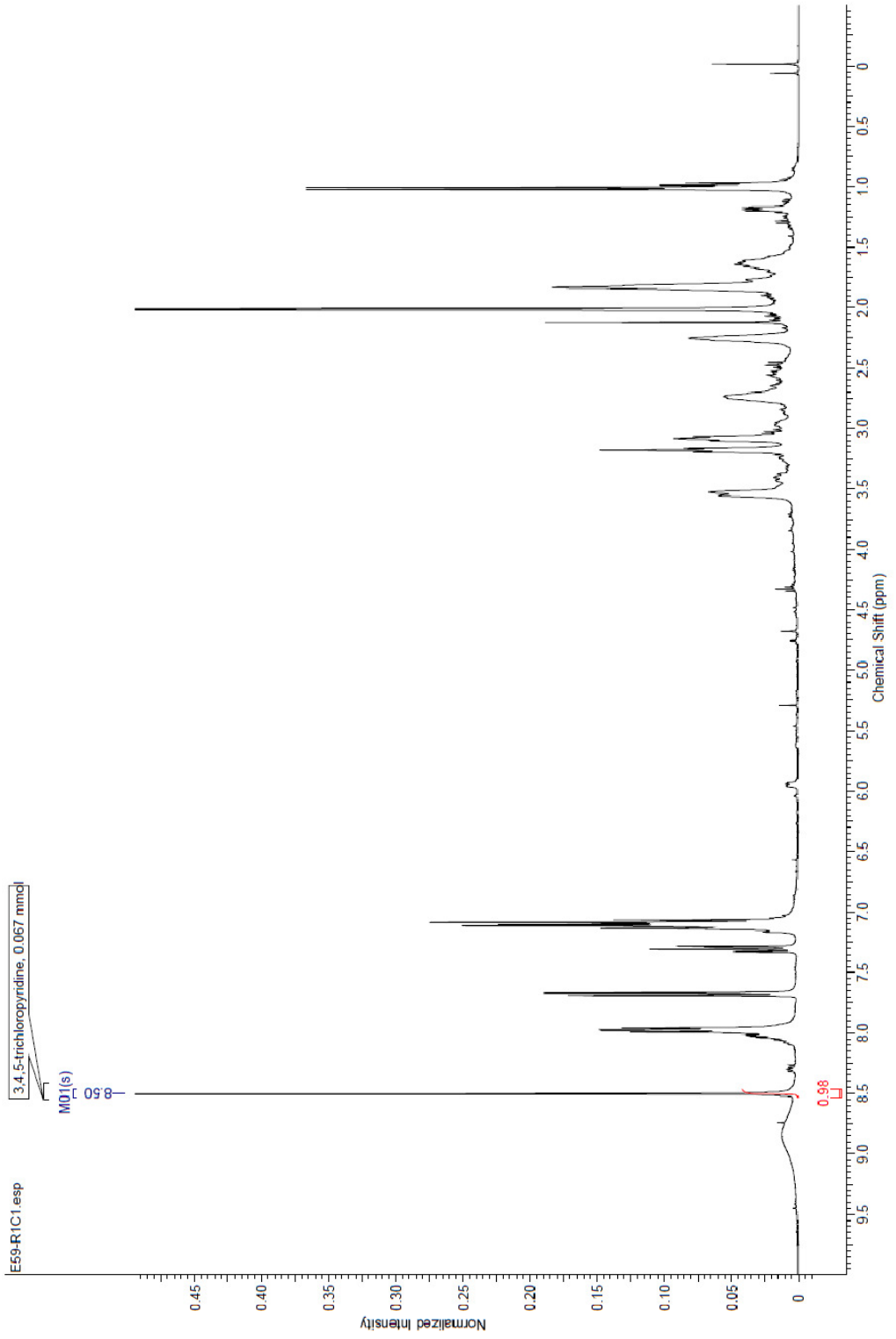
(Starting material R_t = 1.67 min)



Investigating late-stage oxidation under hypervalent iodine conditions

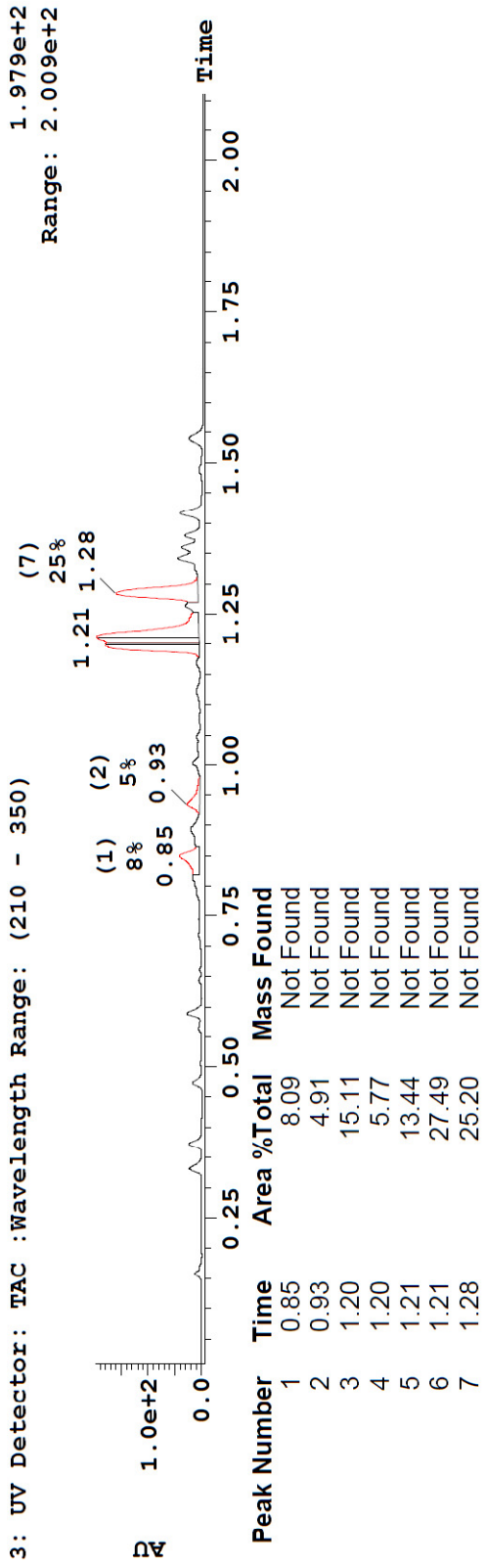
Applied to substrate 4h

^{1}H NMR of crude product



High pH LCMS spectrum of reaction mixture

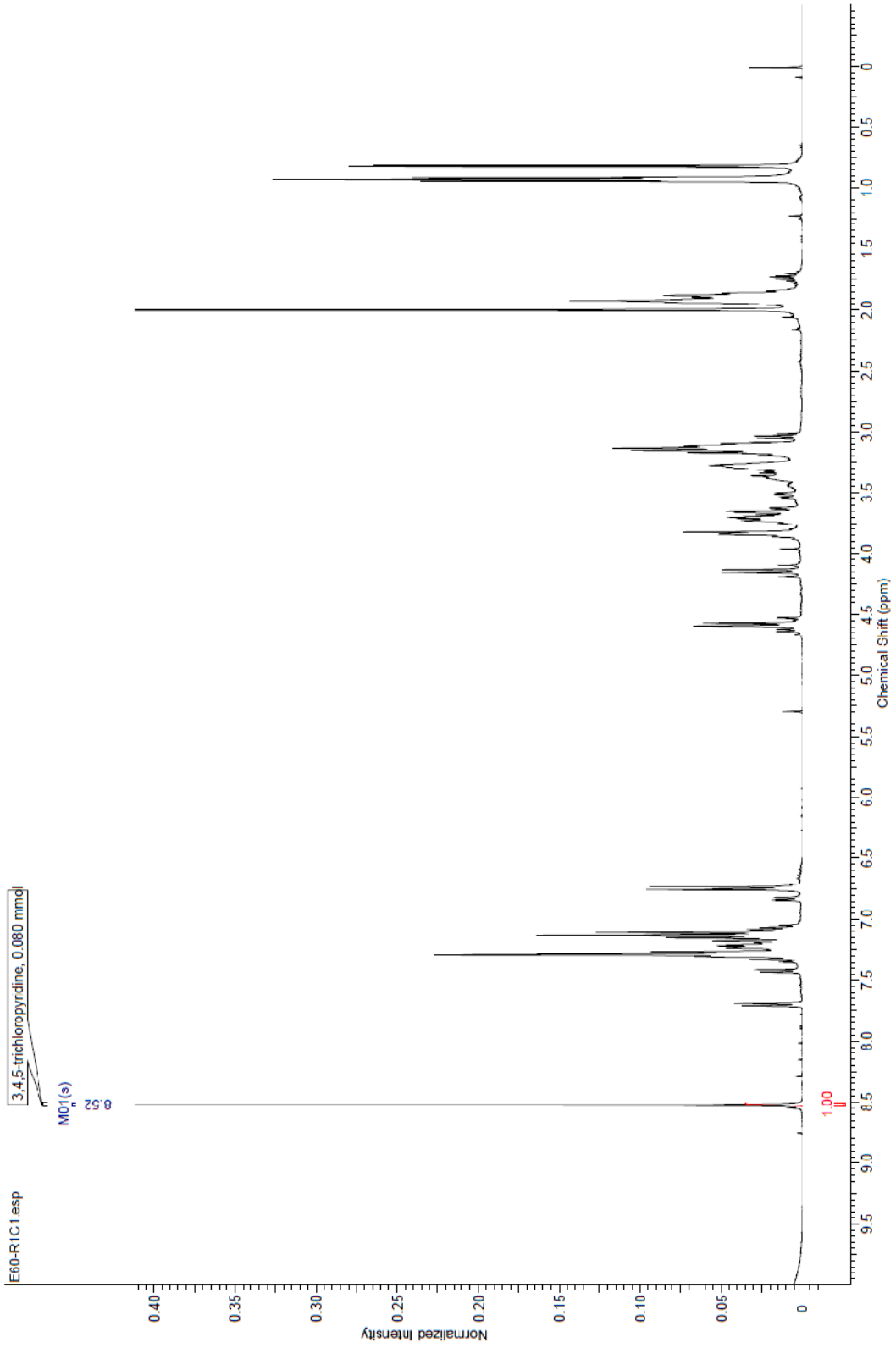
(Starting material R_t = 1.21 min)



Peak Number	Time	Area %Total	Mass Found
1	0.85	8.09	Not Found
2	0.93	4.91	Not Found
3	1.20	15.11	Not Found
4	1.20	5.77	Not Found
5	1.21	13.44	Not Found
6	1.21	27.49	Not Found
7	1.28	25.20	Not Found

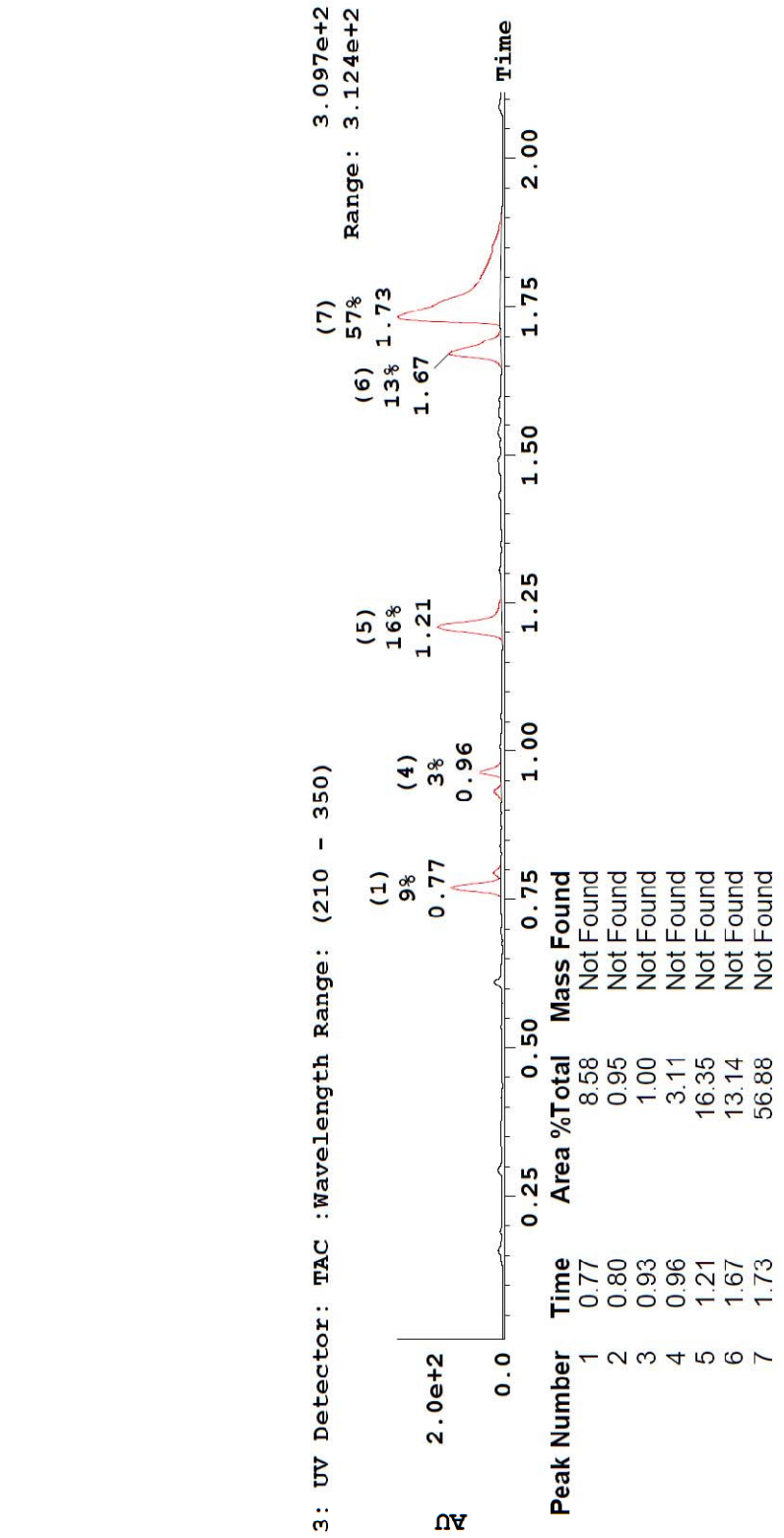
Applied to substrate 4i

^{1}H NMR of crude product



High pH LCMS spectrum of reaction mixture

(Starting material R_t = 1.67 min)



Peak Number	Time	Area %Total	Mass Found
1	0.77	8.58	Not Found
2	0.80	0.95	Not Found
3	0.93	1.00	Not Found
4	0.96	3.11	Not Found
5	1.21	16.35	Not Found
6	1.67	13.14	Not Found
7	1.73	56.88	Not Found

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