

Synthesis and evaluation of novel 7- and 8-aminophenoxazinones for the detection of β -alanine aminopeptidase activity and the reliable identification of *Pseudomonas aeruginosa* in clinical samples

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1.1 Chemicals, materials and methods

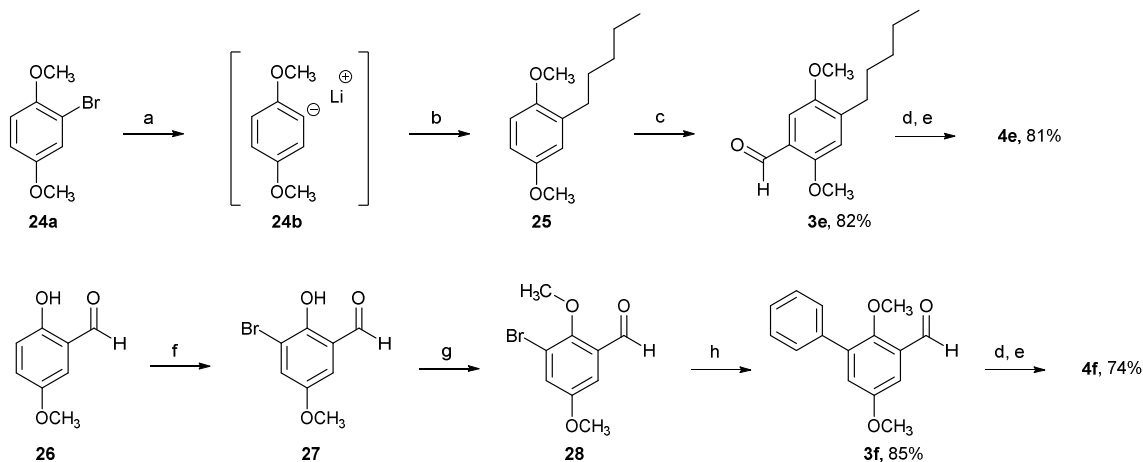
All commercially available reagents and solvents were obtained from Sigma-Aldrich, Fluka or Riedel-de-Haan and were used without further purification. All synthesized compounds were pure to $\geq 95\%$ by at least one analytical method, except **23a**, which had approx. 90% purity. Melting points were recorded on a Reichart-Kofler hot-stage microscope apparatus and are uncorrected. Infrared spectra were recorded in the range $4000 - 600\text{ cm}^{-1}$ using a Perkin Elmer Spectrum BX FT-IR spectrophotometer. NMR spectra were obtained using a Bruker Ultrashield 300 spectrometer at 300 MHz for ^1H spectra or at 75 MHz for ^{13}C spectra. Low-resolution mass spectra were recorded on a Bruker Esquire 3000plus analyser using an electrospray source in either positive or negative ion mode. High resolution accurate mass measurements were collected by the EPSRC National Mass Spectrometry Facility at Swansea University. Elemental analyses were performed using an Exeter Analytical CE-440 Elemental Analyzer. Thin layer chromatography was performed on Merck silica gel 60F₂₅₄. Fisons silica gel, 60 (35-70 micron) was used for flash chromatography; the samples were pre-absorbed onto silica 60 (35-70 micron).

1.2 Synthesis of dimethoxyphenols **4e** and **4f**

2,5-Dimethoxybenzaldehydes **3a-d** and 2,5-dimethoxyphenols **4a-d** were prepared according to procedures previously described¹, while phenols **4e** and **4f** were accessed by introduction of alkyl or aryl substituents (**Scheme S1**) in order to increase the lipophilic properties of the final chromogen. 2,5-Dimethoxy-4-pentylphenol **4e** was prepared from commercially available 1-bromo-2,5-dimethoxybenzene **24a**(**Scheme S1**). Lithium-halogen exchange, in dry THF at -78°C under a protective N_2 atmosphere, gave 2,5-dimethoxyphenyl lithium **24b**, and the addition of 1-bromopentane followed by refluxing of the resulting mixture yielded 1,4-dimethoxy-2-pentylbenzene **25**. Formylation of ether **25** using the Duff conditions² gave 2,5-dimethoxy-4-pentylbenzaldehyde **3e** in good yield. 2,5-Dimethoxy-4-pentylphenol **4e** was finally obtained *via* the Baeyer-Villiger oxidation of **3e** and hydrolysis of the resulting formate ester (**Scheme S1**).

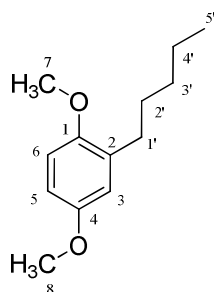
2,5-Dimethoxy-3-phenylphenol **4f** was prepared from the commercially available 2-hydroxy-5-methoxybenzaldehyde **26**. Regioselective bromination, to give the tri-substituted benzaldehyde **27**, followed by methylation gave 3-bromo-2,5-dimethoxybenzaldehyde **28**³. Suzuki coupling of benzaldehyde **28** with phenylboronic acid, using the conditions described

by Yonezawa *et al.*⁴, gave 2,5-dimethoxy-3-phenylbenzaldehyde **3f**, the Baeyer-Villiger oxidation of which provided 2,5-dimethoxy-3-phenylphenol **4f** in good yield (**Scheme S1**).



Scheme S1. Synthesis of substituted dimethoxyphenols **4e** and **4f**. *Reagents and conditions:* [a] 2.5M *n*-BuLi, dry THF, TMEDA, N₂ atm., -78°C, 1h; [b] 1-bromopentane, -78°C to reflux, 15h; [c] TFA, urotropine, reflux, 12h; [d] *m*-CPBA, DCM, R.T., 24h; [e] 10% aq. NaOH, MeOH; [f] Br₂, AcOH, AcONa, R.T.; [g] DMF, K₂CO₃, (MeO)₂SO₂; [h] 2M Na₂CO₃, Pd(PPh₃)₄, phenyl boronic acid, DME, EtOH, 100°C, 18h.

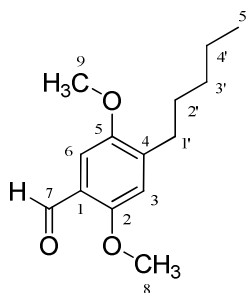
1.2.1 1,4-Dimethoxy-2-pentylbenzene **25**



A flame dried round bottomed flask, flushed with N₂, was charged with 1-bromo-2,5-dimethoxybenzene **24a** (4.0mL, 5.78g, 26.63mmol), TMEDA (8.03mL, 6.18g, 53.20mmol) and dry THF (150mL). The resulting solution was cooled to -75°C, then a 2.5M hexane solution of *n*-BuLi (24mL, 60.00mmol) was added dropwise and the reaction mixture stirred a further 1h at -75°C. Neat 1-bromopentane (18.65mL, 150.0mmol) was added dropwise and the resulting solution left with stirring at -75°C under N₂ flow for 1h, allowed to warm to rt, and then refluxed for a period of 15h. The formation of a white precipitate was noted after the reflux. The resulting mixture was allowed to cool to rt, quenched with water (200mL) and extracted with Et₂O (2 × 200mL). The combined organic layers were successively washed with water (200mL) and brine (200mL), and dried (MgSO₄). The solvent was removed *in*

vacuo and the residue purified by column chromatography eluting with petroleum ether (60-80°C) : Et₂O (95:5). 1,4-Dimethoxy-2-pentylbenzene **25** was isolated as a pale yellow oil (4.75g, 22.80mmol, 85.7%), bp 81-82°C/ 0.2mbar [lit. bp 114°C/6.7mbar⁵]; *m/z* 209.0 (*MH*)⁺; (found: C, 74.65; H, 9.5%. C₁₃H₂₀O₂ requires C, 75.0; H, 9.7%); $\nu_{\max}/\text{cm}^{-1}$ 2832-2928 (C-H), 1498 (C=C), 1219 (C-O), 1048 (C-O); δ_H (300 MHz, CDCl₃) 0.81 (3H, t, *J* = 6.9Hz, 5'-H), 1.24-1.28 (4H, m, 3'-H and 4'-H), 1.45-1.52 (2H, m, 2'-H), 2.49 (2H, t, *J* = 7.5Hz, 1'-H), 3.67 (3H, s, 1-OCH₃ or 4-OCH₃), 3.68 (3H, s, 1-OCH₃ or 4-OCH₃), 6.59 (1H, dd, *J* = 8.7, 3.0Hz, 5-H), 6.65 (1H, d, *J* = 3.0Hz, 3-H), 6.67 (1H, d, *J* = 8.7Hz, 6-H); δ_C (75 MHz, CDCl₃) 14.1 (CH₃, 5'-C), 22.6 (CH₂, 3'-C or 4'-C), 29.6 (CH₂, 2'-C), 30.3 (CH₂, 1'-C), 31.8 (CH₂, 3'-C or 4'-C), 55.7 (OCH₃, 8-C), 56.0 (OCH₃, 7-C), 110.6 (CH, 5-C), 111.3 (CH, 6-C), 116.3 (CH, 3-C), 132.8 (quat., 2-C), 151.9 (quat., 1-C), 153.55 (quat., 4-C).

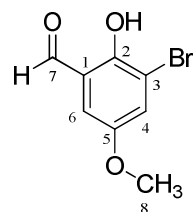
1.2.2 2,5-Dimethoxy-4-pentylbenzaldehyde **3e**



In a 250mL round bottomed flask equipped with a reflux condenser, 2,5-dimethoxy-1-pentylbenzene **25** (4.49g, 21.56mmol) was dissolved in TFA (120mL) and hexamethylene tetramine (6.04g, 43.12mmol) was added to the resulting solution, which was gently refluxed (*t*_{ext} = 95°C) for 48h. The solution was allowed to cool to rt; most of the TFA was removed *in vacuo* and the residue diluted with water (50mL) and neutralised by the portion-wise addition of solid Na₂CO₃. When no more evolution of CO₂ was observed, the resulting mixture was diluted with another 50mL of water and then extracted with Et₂O (3 x 200mL), washed with brine (200mL) and dried (MgSO₄). The solvent was removed *in vacuo* and the residue purified by column chromatography, eluting with a mixture of petroleum ether (60-80°C) : Et₂O (80:20). 2,5-Dimethoxy-4-pentylbenzaldehyde **3e** was isolated as a pale yellow oil (4.19g, 17.73mmol, 82.4%); bp 119-120°C/0.2mbar [lit. bp 201-205°C/27mbar⁶]; (found C, 71.0; H, 8.5. C₁₄H₂₀O₃ requires C, 71.2; H, 8.5%); *m/z* 237.0 (*MH*)⁺, 259.0 (*MNa*)⁺; $\nu_{\max}/\text{cm}^{-1}$ 1675 (C=O), 1610 (C=C), 1210 and 1040 (C-O); δ_H (300 MHz, CDCl₃) 0.94 (3H, t, *J* = 6.9Hz, 5'-H), 1.35-1.42 (4H, m, 3'-H and 4'-H), 1.60-1.65 (2H, m, 2'-H), 2.67 (2H, t, *J* =

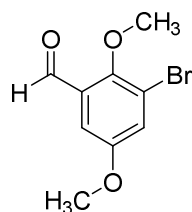
7.5Hz, 1'-H), 3.85 (3H, s, 2-OCH₃), 3.92 (3H, s, 5-OCH₃), 6.82 (1H, s, 3-H), 7.29 (1H, s, 6-H), 10.43 (1H, s, CHO, 7-H); δ_C (75 MHz, CDCl₃) 14.0 (CH₃, 5'-C), 22.5 (CH₂, 3'-C or 4'-C), 29.2 (CH₂, 2'-C), 31.0 (CH₂, 1'-C), 31.8 (CH₂, 3'-C or 4'-C), 55.8 (OCH₃, 2-OCH₃), 56.2 (OCH₃, 5-OCH₃), 108.1 (CH, 6-C), 113.8 (CH, 3-C), 122.9 (quat., 1-C), 141.2 (quat., 4-C), 151.8 (quat., 2-C), 156.7 (quat., 5-C), 189.15 (CHO, 7-C).

1.2.3 3-Bromo-2-hydroxy-5-methoxybenzaldehyde **27**



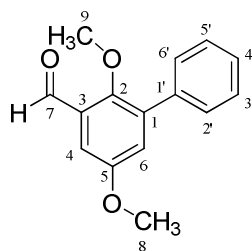
In a 3 necked round bottomed flask equipped with a thermometer and a pressure equalizing dropping funnel, 2-hydroxy-5-methoxybenzaldehyde **26** (11.51g, 75.65mmol) was dissolved in glacial AcOH (300mL). To this solution was added AcONa (10.34g, 126.05mmol) and the resulting solution was cooled with a water/ice bath. A solution of Br₂ (4.91mL, 95.33mmol) in AcOH (50mL) was then introduced into the pressure equalizing dropping funnel and added dropwise to the 2-hydroxy-4-methoxybenzaldehyde solution. Upon completion of the addition (1h), the ice/water bath was removed and the resulting orange solution left with stirring overnight. The reaction was quenched with sodium thiosulfate (10%, Na₂S₂O₃), resulting in the instantaneous formation of a yellow precipitate, which was recovered by filtration, washed several times with water and dried. The filtrate was extracted with DCM (4 × 200mL) and the yellow precipitate dissolved in the combined organic layers, which were washed with water (2 × 150mL) and brine (150mL), and dried (MgSO₄). The solvent was evaporated *in vacuo* yielding 3-bromo-2-hydroxy-5-methoxybenzaldehyde **27** as a yellow crystalline solid (12.86g, 55.66mmol, 75.1%). Small crescent-like yellow plates were obtained from aq. EtOH; mp 108-109°C [lit.: 108°C (from EtOH)³]; (found C, 41.6; H, 2.95%. C₈H₇BrO₃ requires C, 41.6; H, 3.05%); $\nu_{\max}/\text{cm}^{-1}$ 3071 (O-H), 3006, 2944, 2901 and 2840 (C-H), 1644 (C=O), 1609 and 1582 (C=C), 1315, 1237, 1129 and 1036 (C-O); δ_H (300 MHz, d₆-DMSO) 3.78 (3H, s, OCH₃), 7.31 (1H, d, *J* = 3.0Hz, 6-H), 7.51 (1H, d, *J* = 3.0Hz, 4-H), 10.08 (1H, s, CHO), 10.65 (1H, s, OH); δ_C (75 MHz, d₆-DMSO) 56.5 (OCH₃, 8-C), 112.4 (quat., 3-C), 114.7 (CH, 6-C), 123.3 (quat., 1-C), 126.6 (CH, 4-C), 151.4 (quat., 2-C), 153.1 (quat., 5-C), 194.5 (CHO, 7-C).

1.2.4 3-Bromo-2,5-dimethoxybenzaldehyde **28**



An oven dried round bottomed flask was charged with 3-bromo-2-hydroxy-5-methoxybenzaldehyde **27** (12.86g, 55.70mmol), K_2CO_3 (10.78g, 77.98mmol) and dry DMF (300mL). The resulting mixture was stirred for 5 min and DMS (7.38mL, 77.98mmol) was then added dropwise. The reaction was left stirring overnight at ambient temperature. The resulting olive green coloured mixture was quenched with water resulting in the formation of a white precipitate. This mixture was extracted with Et_2O (4×300 mL) and the combined organic layers were washed with brine (3×250 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* yielding 3-bromo-2,5-dimethoxybenzaldehyde **28** as a white crystalline solid (13.61g, 55.54mmol, 99.7%). White crystals were obtained from petroleum ether (60-80°C); mp 62.5-63.5°C [lit. mp 68°C³]; (found: C, 41.1; H, 3.6%. $C_9H_9BrO_3$ requires C, 41.1; H, 3.7%); ν_{max}/cm^{-1} 2935, 2854 and 2832 (C-H), 1685 (C=O), 1600 (C=C), 1225, 1205 and 1042 (C-O); δ_H (300 MHz, $CDCl_3$) 3.85 (3H, s, OCH_3 , 8-H), 3.97 (3H, s, OCH_3 , 9-H), 7.30 (1H, d, $J = 3.0$ Hz, 6-H), 7.41 (1H, d, $J = 3.0$ Hz, 4-H), 10.34 (1H, s, CHO); δ_C (75 MHz, $CDCl_3$) 56.0 (OCH_3 , 8-C), 63.8 (OCH_3 , 9-C), 110.3 (CH, 6-C), 118.6 (quat., 3-C), 126.5 (CH, 4-C), 130.6 (quat., 1-C), 154.4 (quat., 5-C), 156.5 (quat., 2-C), 189.0 (CHO , 7-C).

1.2.5 2,5-Dimethoxybiphenyl-3-carbaldehyde **3f**



A two necked round bottomed flask equipped with a reflux condenser was charged with 3-bromo-2,5-dimethoxybenzaldehyde **28** (2.72g, 11.10mmol), phenylboronic acid (1.62g, 13.29mmol) and DME (75mL). The resulting solution was degassed with N_2 , with stirring, over 15min. A separate round bottomed flask was charged with Na_2CO_3 (2M, 20mL) and EtOH (20mL); the resulting mixture was also degassed with N_2 over 15min. It was then transferred, along with $Pd(Ph_3)_4$ (0.64g, 0.56mmol), into the two necked round bottomed flask

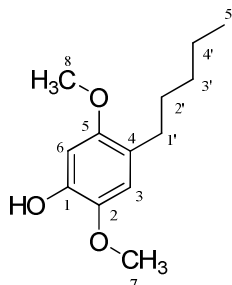
containing the 3-bromo-2,5-dimethoxybenzaldehyde **28** solution. The resulting mixture was brought to reflux ($T_{\text{oil bath}} = 100^{\circ}\text{C}$), while keeping a constant N_2 flow over the reaction. The reflux was stopped after 23h and the reaction cooled to rt, then the reaction was cooled with an ice bath and acidified (to pH 1-2) with HCl (10%). The resulting mixture was diluted with EtOAc and filtered through Celite, which was washed several times with small portions of EtOAc. The filtrate was decanted into a separating funnel and the aqueous layer was further extracted with EtOAc ($3 \times 50\text{mL}$). The combined organic layers were washed with water (100mL) and brine (100mL), and dried (MgSO_4). The solvent was evaporated *in vacuo* and the residue subjected to column chromatography, eluting with petroleum ether ($60\text{-}80^{\circ}\text{C}$) : Et_2O (80:20). 2,5-Dimethoxybiphenyl-3-carbaldehyde **3f** was isolated as clear cubic white plates (2.29g, 9.43mmol, 85.0%); mp (Et_2O : petroleum ether $60\text{-}80^{\circ}\text{C}$) $64.5\text{-}65.5^{\circ}\text{C}$; (found: C, 74.3; H, 5.9%. $\text{C}_{15}\text{H}_{14}\text{O}_3$ requires C, 74.4; H, 5.8%); m/z 243.0 ($M\text{H}^+$), 265.0 ($M\text{Na}^+$); $\nu_{\text{max}}/\text{cm}^{-1}$ 2877 and 2754 (C-H), 1680 (C=O), 1596 (C=C), 1229 and 1041 (C-O); δ_{H} (300 MHz, CDCl_3) 3.51 (3H, s, OCH_3 , 9-H), 3.89 (3H, s, OCH_3 , 8-H), 7.22 (1H, d, $J = 3.3\text{Hz}$, 6-H), 7.36 (1H, d, $J = 3.3\text{Hz}$, 4-H), 7.41-7.53 (3H, m, 3'-H, 4'-H and 5'-H), 7.60-7.64 (2H, m, 2'-H and 6'-H), 10.48 (1H, CHO, 7-H); δ_{C} (75 MHz, CDCl_3) 55.8 (OCH_3 , 8-C), 62.9 (OCH_3 , 9-C), 109.1 (CH, 4-C), 124.75 (CH, 6-C), 127.9 (CH, 4'-C), 128.6 (CH, 3'-C and 5'-C), 128.9 (CH, 2'-C and 6'-C), 130.1 (quat., 3-C), 136.9 (quat., 1-C), 137.3 (quat., 1'-C), 155.4 (quat., 2-C), 156.0 (quat., 5-C), 190.05 (CHO, 7-C).

1.2.6 General procedure for the Baeyer-Villiger oxidation of benzaldehydes **3e** and **3f**

In a two necked round bottomed flask equipped with a reflux condenser, the correctly substituted benzaldehyde (1 mol equivalent) was dissolved in DCM (70 mL). The resulting solution was cooled in an ice bath and *meta*-chloroperbenzoic acid (1.7 mol equivalent) was added portion-wise. The ice bath was removed 1h after the end of the addition and the resulting solution left with stirring overnight at rt. The reaction progress was monitored by TLC and the reaction was refluxed for 5-6h to drive it to completion, when necessary. The reaction, after cooling to rt if heated, was washed with NaHCO_3 (5%, $3 \times 100\text{mL}$). The DCM layer was then dried (MgSO_4) and the solvent removed *in vacuo*. The residual oil was dissolved in methanol (20mL) and NaOH (10%, excess) was added; the resulting dark solution was stirred for 2-3 hours and then acidified (to pH 1-2) with HCl (10%). The resulting mixture was extracted with DCM ($3 \times 80\text{mL}$) and the combined organic extracts were successively washed with NaHCO_3 (5%, 100mL), water (100mL) and brine (100mL),

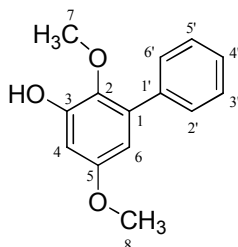
and dried (MgSO₄). The solvent was removed *in vacuo* and the residue subjected to column chromatography on silica gel. The product was recrystallized from petroleum ether (60-80°C).

1.2.7 2,5-Dimethoxy-4-pentylphenol **4e**



Prepared from 2,5-dimethoxy-4-pentylbenzaldehyde **3e** (3.44g, 14.58mmol); elution with petroleum ether (60-80°C) : Et₂O (70:30) yielded 2,5-dimethoxy-4-pentylphenol **4e** as a white crystalline solid (2.66g, 11.87mmol, 81.4%). Recrystallization from Et₂O : petroleum ether (60-80°C) produced white needles, mp 33-35°C; (found: C, 69.55; H, 9.0%. C₁₃H₂₀O₃ requires C, 69.6; H, 9.0%); m/z 225.0 (MH)⁺; $\nu_{\max}/\text{cm}^{-1}$ 3354 (O-H), 2953 and 2930 (C-H), 1598 and 1515 (C=C), 1192 and 1038 (C-O); δ_H (300 MHz, CDCl₃) 0.96 (3H, t, J = 6.9Hz, 5'-H), 1.38-1.415 (4H, m, 3'-H and 4'-H), 1.58-1.63 (2H, m, 2'-H), 2.59 (2H, t, J = 7.5Hz, 1'-H), 3.81 (3H, s, OCH₃, 8-H), 3.89 (3H, s, OCH₃, 7-H), 5.61 (1H, s, OH), 6.60 (1H, s, 6-H), 6.73 (1H, s, 3-H); δ_C (75 MHz, CDCl₃) 14.1 (CH₃, 5'-C), 22.6 (CH₂, 3'-C or 4'-C), 29.8 (CH₂, 1'-C), 30.1 (CH₂, 2'-C), 31.8 (CH₂, 3'-C or 4'-C), 56.1 (OCH₃, 8-C), 56.8 (OCH₃, 7-C), 99.5 (CH, 6-C), 113.3 (CH, 3-C), 122.3 (quat., 4-C), 140.1 (quat., 2-C), 144.1 (quat., 1-C), 152.0 (quat., 5-C).

1.2.8 2,5-Dimethoxybiphenyl-3-ol **4f**



The title compound was prepared as described from 2,5-dimethoxybiphenyl-3-carbaldehyde **3f** (2.02g, 8.34mmol); elution with petroleum ether (60-80°C) : Et₂O (70:30) yielded 2,5-dimethoxybiphenyl-3-ol **4f** as a white crystalline solid (1.43g, 6.19mmol, 74.2%). White needles were obtained from petroleum ether (60-80°C); mp 67-69°C; (found: C, 73.1; H,

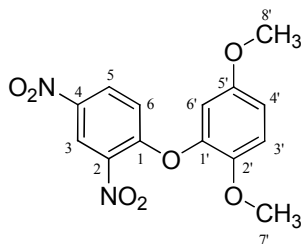
6.2%. $C_{14}H_{14}O_3$ requires C, 73.0; H, 6.1%); m/z 231.0 (MH)⁺; ν_{max}/cm^{-1} 3396 (O-H), 1619, 1591 and 1573 (C=C), 1206 and 1049 (C-O); δ_H (300 MHz, $CDCl_3$) 3.44 (3H, s, OCH_3 , 7-H), 3.85 (3H, s, OCH_3 , 8-H), 6.10 (1H, s, OH), 6.51 (1H, d, $J = 3.0$ Hz, 6-H), 6.64 (1H, d, $J = 3.0$ Hz, 4-H), 7.39-7.52 (3H, m, 3'-H, 5'-H and 4'-H), 7.64-7.67 (2H, m, 2'-H and 6'-H); δ_C (75 MHz, $CDCl_3$) 55.6 (OCH_3 , 8-C), 60.9 (OCH_3 , 7-C), 100.6 (CH, 4-C), 107.2 (CH, 6-C), 127.6 (CH, 4'-C), 128.5 (CH, 3'-C and 5'-C), 128.8 (CH, 2'-C and 6'-C), 134.7 (quat., 1-C), 138.0 (quat., 1'-C), 138.5 (quat., 2-C), 149.9 (quat., 3-C), 156.45 (quat., 5-C).

1.3 Synthesis of diphenylethers 6a-f

1.3.1 General procedure

The appropriately substituted phenol (1mol equivalent) was dissolved in DMSO (5mL/mmol of substituted phenol) and Et_3N (1mol equivalent) was added immediately. The resulting solution was stirred for 5min, before 2,4-dinitro-1-fluorobenzene (1mol equivalent) was added; the solution became an orange-red colour. The reaction was left stirring for 5 hours, then quenched with water (5mL/mL of DMSO) and the resulting mixture extracted with DCM (3×0.5 mL/mL of suspension). The combined DCM extracts were successively washed with NaOH (10%, 3×0.5 mL/mL of DCM extract), water (0.5mL/mL of DCM extract), brine (0.5mL/mL of DCM extract), and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was either subjected to column chromatography or directly recrystallised from ethanol.

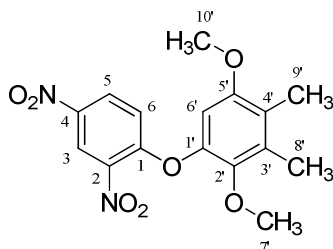
1.3.2 2,4-Dinitro-2',5'-dimethoxydiphenylether 6a



Prepared from 2,5-dimethoxyphenol **4a** (6.38g, 41.37mmol) and 2,4-dinitrofluorobenzene **5** (7.70g, 41.37mmol). 2,4-Dinitro-2,5-dimethoxydiphenylether **6a** (11.68g, 36.47mmol, 88.2%) was isolated as crescent shaped yellow crystals from EtOH; mp 95-96°C; m/z 343.1 (MNa)⁺; (found C, 52.4; H, 3.7; N, 8.7%. $C_{14}H_{12}N_2O_6$ requires C, 52.5; H, 3.8; N, 8.75%); ν_{max}/cm^{-1} 1604 (C=C), 1506 and 1340 (NO_2), 1274, 1035 and 1014 (C-O); δ_H (300 MHz, d_6 -DMSO) 3.69 (3H, s, OCH_3 , 7'-H), 3.74 (3H, s, OCH_3 , 8'-H), 6.92 (1H, dd, $J = 9.0, 3.0$ Hz, 4'-

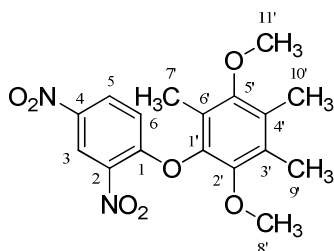
H), 6.98 (1H, d, $J = 2.7\text{Hz}$, 6'-H), 6.99 (1H, d, $J = 9.3\text{Hz}$, 6-H), 7.20 (1H, d, $J = 9.0\text{Hz}$, 3'-H), 8.39 (1H, dd, $J = 9.3, 3.0\text{Hz}$, 5-H), 8.86 (1H, d, $J = 3.0\text{Hz}$, 3-H); δ_C (75 MHz, d_6 -DMSO) 56.2 (OCH₃, 7'-C), 56.8 (OCH₃, 8'-C), 109.1 (CH, 6'-C), 113.1 (CH, 4'-C), 115.3 (CH, 3'-C), 117.9 (CH, 6-C), 122.2 (CH, 3-C), 129.9 (CH, 5-C), 138.6 (quat., 2-C), 141.4 (quat., 4-C), 141.7 (quat., 1'-C), 145.1 (quat., 2'-C), 154.3 (quat., 5'-C), 155.6 (quat., 1-C).

1.3.3 2,4-Dinitro-2',5'-dimethoxy-3',4'-dimethyldiphenylether **6b**



Prepared from 2,5-dimethoxy-3,4-dimethylphenol **4b** (0.65g, 3.56mmol). Elution with petroleum ether (60-80°C) : EtOAc (70:30) yielded 2,4-dinitro-2',5'-dimethoxy-3',4'-dimethyldiphenylether **6b** as an orange solid (0.76g, 2.19mmol, 61.6%). Orange crystals were obtained from aqueous ethanol, mp 100°C; (found C, 55.4; H, 4.6; N, 8.0%. C₁₆H₁₆N₂O₇ requires C, 55.2; H, 4.6; N, 8.0%); m/z 371.0 (MNa)⁺; $\nu_{\max}/\text{cm}^{-1}$ 1606 (C=C), 1529 and 1345 (NO₂), 1263, 1233 and 1026 (C-O); δ_H (300 MHz, d_6 -DMSO) 2.13 (3H, s, CH₃, 9'-H), 2.19 (3H, s, CH₃, 8'-H), 3.60 (3H, s, OCH₃, 7'-H), 3.77 (3H, s, OCH₃, 10'-H), 6.89 (1H, s, 6'-H), 7.01 (1H, d, $J = 9.0\text{Hz}$, 6-H), 8.38 (1H, dd, $J = 9.3, 3.0\text{Hz}$, 5-H), 8.88 (1H, d, $J = 3.0\text{Hz}$, 3-H); δ_C (75 MHz, d_6 -DMSO) 12.3 (CH₃, 9'-C), 12.8 (CH₃, 8'-C), 56.5 (OCH₃, 10'-C), 61.4 (OCH₃, 7'-C), 103.4 (CH, 6'-C), 118.0 (CH, 6-C), 122.1 (CH, 3-C), 124.4 (quat., 4'-C), 129.9 (CH, 5-C), 132.9 (quat., 3'-C), 138.7 (quat., 2-C), 141.3 (quat., 4-C), 143.2 (quat., 1'-C), 143.7 (quat., 2'-C), 154.4 (quat., 5'-C), 155.7 (quat., 1-C).

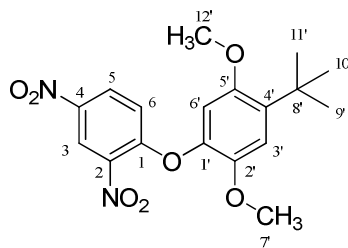
1.3.4 2,4-Dinitro-2',5'-dimethoxy-3',4',6'-trimethyldiphenylether **6c**



Prepared from 2,5-dimethoxy-3,4,6-trimethylphenol **4c** (0.37g, 1.89mmol), using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.30mL, 2.00mmol) instead of Et₃N. Elution with

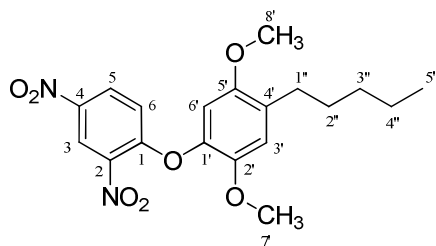
petroleum ether (60-80°C) : EtOAc (30:70) yielded 2,4-dinitro-2',5'-dimethoxy-3',4',6'-trimethyldiphenylether **6c** as an off-white solid (0.59g, 1.63mmol, 85.7%). Long off-white needles were obtained from ethanol; mp 142°C; (found C, 56.4; H, 5.05; N, 7.7%. $C_{17}H_{18}N_2O_7$ requires C, 56.35; H, 5.0; N, 7.7%); m/z 385.1 (MNa)⁺; ν_{max}/cm^{-1} 1609 (C=C), 1540 and 1345 (NO₂), 1260, 1250 and 1072 (C-O); δ_H (300 MHz, CDCl₃) 2.04 (3H, s, CH₃, 7'-H), 2.12 (3H, s, CH₃, 10'-H), 2.16 (3H, s, CH₃, 9'-H), 3.59 (3H, s, OCH₃, 8'-H), 3.63 (3H, s, OCH₃, 11'-H), 6.69 (1H, d, J = 9.3Hz, 6-H), 8.15 (1H, dd, J = 9.3, 2.7Hz, 5-H), 8.76 (1H, d, J = 2.7Hz, 3-H); δ_C (75 MHz, CDCl₃) 9.6 (CH₃, 7'-C), 12.4 (CH₃, 9'-C or 10'-C), 12.8 (CH₃, 9'-C or 10'-C), 60.5 (OCH₃, 8'-C), 61.2 (OCH₃, 11'-C), 116.6 (CH, 6-C), 122.0 (CH, 3-C), 122.1 (quat., 6'-C), 128.9 (CH, 5-C), 129.6 (quat., 3'-C or 4'-C), 130.0 (quat., 3'-C or 4'-C), 138.15 (quat., 2-C), 141.0 (quat., 4-C), 142.2 (quat., 1'-C), 146.1 (quat., 2'-C), 153.5 (quat., 5'-C), 155.8 (quat., 1-C).

1.3.5 2,4-Dinitro-2',5'-dimethoxy-4'-*t*-butyldiphenylether **6d**



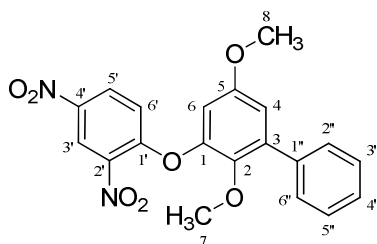
Prepared from 2,5-dimethoxy-4'-*t*-butylphenol **4d** (3.55g, 16.88mmol). Elution with petroleum ether (60-80°C) : Et₂O (70:30) yielded 2,4-dinitro-2',5'-dimethoxy-4'-*t*-butyldiphenylether **6d** as a yellow crystalline solid (6.06g, 16.09mmol, 95.8%). Recrystallization from EtOH produced small bright yellow needles; mp 131-132°C; (found C, 57.45; H, 5.4; N, 7.4%. $C_{18}H_{20}N_2O_7$ requires C, 57.4; H, 5.4; N, 7.4%); m/z 399.1 (MNa)⁺; ν_{max}/cm^{-1} 1608 (C=C), 1535 and 1342 (NO₂), 1209 and 1031 (C-O); δ_H (300 MHz, CDCl₃) 1.32 (9H, s, C(CH₃)₃), 3.64 (3H, s, OCH₃, 7'-H), 3.72 (3H, s, OCH₃, 12'-H), 6.66 (1H, s, 6'-H), 6.84 (1H, d, J = 9.3Hz, 6-H), 6.94 (1H, s, 3'-H), 8.17 (1H, dd, J = 9.3, 3.0Hz, 5-H), 8.74 (1H, d, J = 2.7Hz, 3-H); δ_C (75 MHz, CDCl₃) 29.7 (3 × CH₃, 9'/10'/11'-C(CH₃)₃), 35.2 (quat., 8'-C(CH₃)₃), 55.8 (OCH₃, 7'-C), 57.1 (OCH₃, 12'-C), 106.5 (CH, 6'-C), 113.8 (CH, 3'-C), 117.5 (CH, 6-C), 122.0 (CH, 3-C), 128.6 (CH, 5-C), 138.1 (quat., 4'-C), 138.3 (quat., 2-C), 139.5 (quat., 1'-C), 141.0 (quat., 4-C), 143.8 (quat., 2'-C), 153.4 (quat., 5'-C), 156.5 (quat., 1-C).

1.3.6 2,4-Dinitro-2',5'-dimethoxy-4'-pentyldiphenylether **6e**



Prepared from 2,5-dimethoxy-4-pentylphenol **4e** (2.71g, 12.09mmol). 2,4-Dinitro-2',5'-dimethoxy-4'-pentyldiphenylether **6e** was isolated as a yellow crystalline solid (4.36g, 11.17mmol, 92.4%). Recrystallization from EtOH yielded small yellow needles; mp (EtOH): 85-87°C; (found: C, 58.3; H, 5.7; N, 7.2%. $C_{19}H_{22}N_2O_7$ requires C, 58.5; H, 5.7; N, 7.2%); m/z 390.1 (MH)⁺, 413.1 (MNa)⁺; ν_{max}/cm^{-1} 2855-2957 (C-H), 1608, 1508 (C=C), 1536 and 1342 (NO₂), 1212 and 1037 (C-O); δ_H (300 MHz, CDCl₃) 0.96 (3H, t, J = 6.9Hz, 5''-H), 1.39-1.43 (4H, m, 3''-H and 4''-H), 1.62-1.67 (2H, m, 2''-H), 2.66 (2H, t, J = 7.5Hz, 1''-H), 3.755 (3H, s, OCH₃, 7'-H), 3.82 (3H, s, OCH₃, 8'-H), 6.76 (1H, s, 6'-H), 6.91 (1H, s, 3'-H), 6.96 (1H, d, J = 9.3Hz, 6-H), 8.31 (1H, dd, J = 9.3, 2.7Hz, 5-H), 8.87 (1H, d, J = 3.0Hz, 3-H); δ_C (75 MHz, CDCl₃) 14.1 (CH₃, 5''-C), 22.6 (CH₂, 3''-C or 4''-C), 29.6 (CH₂, 2''-C), 30.1 (CH₂, 1''-C), 31.75 (CH₂, 3''-C or 4''-C), 56.1 (OCH₃, 8'-C), 56.9 (OCH₃, 7'-C), 105.6 (CH, 6'-C), 115.85 (CH, 3'-C), 117.4 (CH, 6-C), 122.0 (CH, 3-C), 128.65 (CH, 5-C), 131.0 (quat., 4'-C), 138.3 (quat., 2-C), 139.3 (quat., 1'-C), 141.0 (quat., 4-C), 144.3 (quat., 2'-C), 152.2 (quat., 5'-C), 156.6 (quat., 1-C)

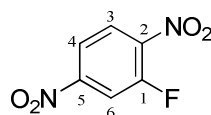
1.3.7 3-(2',4'-Dinitrophenoxy)-2,5-dimethoxybiphenyl **6f**



Prepared from 2,5-dimethoxybiphenyl-3-ol **4f** (0.98g, 4.25mmol). 3-(2',4'-Dinitrophenoxy)-2,5-dimethoxybiphenyl **6f** was isolated as a cream solid (1.55g, 3.96mmol, 91.8%). Recrystallization from EtOH yielded cream coloured plates; mp 146-148°C; (found: C, 60.6; H, 4.1; N, 7.0%. $C_{20}H_{16}N_2O_7$ requires C, 60.6; H, 4.1; N, 7.1%); m/z 397.1 (MH)⁺, 419.1 (MNa)⁺; ν_{max}/cm^{-1} 1610 (C=C), 1529 and 1337 (NO₂), 1271 and 1048 (C-O); δ_H (300 MHz, CDCl₃) 3.32 (3H, s, OCH₃, 7-H), 3.75 (3H, s, OCH₃, 8-H), 6.68 (1H, d, J = 3.0Hz, 6-H), 6.81

(1H, d, $J = 3.0\text{Hz}$, 4-H), 7.01 (1H, d, $J = 9.3\text{Hz}$, 6'-H), 7.26-7.37 (3H, m, 3''-H, 5''-H and 4''-H), 7.42 (2H, m, 2''-H and 6''-H), 8.25 (1H, dd, $J = 9.3, 2.7\text{Hz}$, 5'-H), 8.76 (1H, d, $J = 2.7\text{Hz}$, 3'-H); δ_C (75 MHz, CDCl_3) 55.95 (OCH_3 , 8-C), 61.4 (OCH_3 , 7-C), 107.2 (CH, 6-C), 114.3 (CH, 4-C), 117.7 (CH, 6'-C), 121.95 (CH, 3'-C), 128.0 (CH, 4''-C), 128.5 (CH, 3''-C and 5''-C), 128.9 (CH, 5'-C), 129.0 (CH, 2''-C and 6''-C), 136.9 (quat., 3-C), 138.1 (quat., 1''-C), 138.6 (quat., 4'-C), 141.4 (quat., 2'-C), 142.7 (quat., 2-C), 146.7 (quat., 1-C), 156.1 (quat., 1'-C), 156.4 (quat., 5-C).

1.4 Preparation of 2,5-dinitro-1-fluorobenzene 13



1.4.1 Nitration of 2-fluoroacetanilide

A 500mL 3 necked flask equipped with a dropping funnel and a thermometer was charged with 2-fluoroacetanilide (16.87g, 0.110mol) and glacial acetic acid (90mL). The resulting solution was cooled to 10°C ($T_{\text{int.}}$). The dropping funnel was charged with a solution of fuming HNO_3 (55mL) and conc. H_2SO_4 (55mL), which was added dropwise to the 2-fluoroacetanilide solution. The temperature was maintained at 10°C during the addition (1h). The ice-bath was then removed and the resulting solution was stirred for a further 1h 30min. The reaction mixture was poured into ice, resulting in the formation of a cream coloured precipitate. The precipitate was recovered by filtration, washed several times with water until the filtrate was of a clear colour, and dried under vacuum. The resulting solid was partially redissolved in EtOH (250mL) and NaOH (10%, 150mL) added. The resulting orange solution was stirred for 5h or until the acetyl product was fully hydrolysed. The reaction was then quenched with HCl (10%, 200mL) resulting in the formation of a yellow precipitate. The precipitate was recovered by filtration, washed several times with water and dried. It was then redissolved into EtOAc, dried (MgSO_4) and purified by column chromatography, eluting with petroleum ether ($60\text{-}80^\circ\text{C}$) : EtOAc (70:30). The more mobile band yielded 6-nitro-2-fluoroaniline (2.64g, 16.91mmol, 15.3%) as a yellow solid. Recrystallisation from EtOH produced yellow plates; mp $71.5\text{-}72.5^\circ\text{C}$ [lit. mp $75.5\text{-}76.5^\circ\text{C}$]⁷; (found: C, 46.0; H, 3.2; N, 17.9%. $\text{C}_6\text{H}_5\text{FN}_2\text{O}_2$ requires C, 46.2; H, 3.2; N, 17.9%); $\nu_{\text{max}}/\text{cm}^{-1}$ 3487 and 3366 (NH_2), 1583 ($\text{C}=\text{C}$), 1525 and 1329 (NO_2), 1068 (C-F); δ_H (300 MHz, $\text{d}_6\text{-DMSO}$) 6.62 (1H, td, $J = 8.7, 5.4\text{Hz}$, 4-H), 7.22 (2H, br. s, NH_2), 7.42 (1H, dd, $J = 10.2, 7.8\text{Hz}$, 3-H), 7.82 (1H, d, $J = 8.7\text{Hz}$, 5-H); δ_C (75 MHz, $\text{d}_6\text{-DMSO}$) 113.95 (CH, d, $J = 7.9\text{Hz}$, 4-C), 120.2 (CH, d, $J =$

18.3Hz, 3-C), 121.5 (CH, d, $J = 3.3\text{Hz}$, 5-C), 132.4 (quat., d, $J = 5.1\text{Hz}$, 6-C), 136.45 (quat., d, $J = 16.6\text{Hz}$, 1-C), 152.2 (quat., d, $J = 242.7\text{Hz}$, 2-C). Further elution gave 4-nitro-2-fluoroaniline (11.61g, 74.37mmol, 67.5%) as a bright yellow crystalline solid. Recrystallization from ethanol gave small yellow needles; mp 130-131°C [lit. mp 135-136°C]⁵; $\nu_{\text{max}}/\text{cm}^{-1}$ 3493 and 3395 (NH₂), 1626 (C=C), 1523 and 1314 (NO₂), 1079 (C-F); δ_{H} (300 MHz, d₆-DMSO) 6.77 (2H, br. s, NH₂), 6.85 (1H, t, $J = 8.7\text{Hz}$, 6-H), 7.87-7.93 (2H, m, 3-H and 5-H); δ_{C} (75 MHz, d₆-DMSO) 111.8 (CH, d, $J = 22.3\text{Hz}$, 3-C), 114.3 (CH, d, $J = 5.4\text{Hz}$, 6-C), 122.7 (CH, d, $J = 1.8\text{Hz}$, 5-C), 135.3 (quat., d, $J = 7.8\text{Hz}$, 4-C), 144.8 (quat., d, $J = 13.1\text{Hz}$, 1-C), 148.4 (quat., d, $J = 241.2\text{Hz}$, 2-C).

1.4.2 Oxidation of 2-fluoro-4-nitroaniline

In a 2L 3 necked flask equipped with a pressure equalizing dropping funnel and a thermometer, urea hydrogen peroxide adduct (45.93g, 0.488mol) was suspended in acetonitrile (400mL) and the resulting suspension was cooled with an ice and salt slurry to -10°C (T_{int.}). The pressure equalizing dropping funnel was charged with a solution of trifluoroacetic anhydride (61.7mL, 0.444mol) in acetonitrile (100mL), which was added dropwise to the urea hydrogen peroxide adduct suspension; the addition rate was adjusted to keep the temperature below 5°C. The resulting clear solution was stirred at -5°C for 45 min. A solution of 2-fluoro-4-nitroaniline (9.90g, 63.40mmol) in acetonitrile (400mL) was added dropwise *via* the pressure equalizing dropping funnel to the trifluoroacetic acid solution. The addition rate was adjusted to keep the temperature close to -5°C; the solution colour ranged from emerald green to blue during the addition of 2-fluoro-4-nitroaniline. Upon completion of the addition, the cooling bath was removed and the resulting solution left with stirring at ambient temperature overnight. Most of the acetonitrile was then removed under reduced pressure and the acidic residue was neutralised by addition of Na₂CO₃ (10%), until no more evolution of CO₂ was observed. The resulting mixture was extracted with Et₂O (3 x 300mL) and the combined organic layers washed with NaHCO₃ (5%, 2 x 250mL), water (200mL), brine (200mL), and dried (MgSO₄). The solvent was removed under reduced pressure and the residue recrystallised from petroleum ether (60-80°C) using decolourising charcoal, yielding 2,5-dinitro-1-fluorobenzene **13** as large pale yellow plates (6.97g, 37.45mmol, 59.1%); mp 72-74°C [lit. mp 74-75°C (from hexane)]⁸; (found: C, 38.5; H, 1.6; N, 14.7%. C₆H₃FN₂O₄ requires C, 38.7; H, 1.6; N, 15.05%); $\nu_{\text{max}}/\text{cm}^{-1}$ 3118 (C-H), 1549 and 1343 (NO₂); δ_{H} (300 MHz, d₆-DMSO) 8.26 (1H, ddd, $J = 9.0, 2.4, 1.5\text{Hz}$, 4-H), 8.42 (1H, dd, $J = 9.0, 7.5\text{Hz}$, 3-H), 8.53 (1H, dd, $J = 10.5, 2.4\text{Hz}$, 6-H); δ_{C} (75

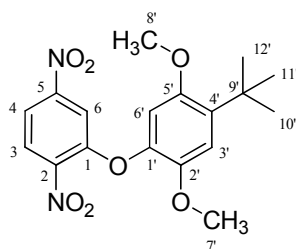
MHz, d₆-DMSO) 115.05 (CH, d, $J = 26.0$ Hz, 6-C), 120.75 (CH, d, $J = 4.45$ Hz, 4-C), 128.2 (CH, d, $J = 2.5$ Hz, 3-C), 141.2 (quat., d, $J = 7.9$ Hz, 5-C), 151.2 (quat., d, $J = 8.5$ Hz, 2-C), 154.8 (quat., d, $J = 264.9$ Hz, 1-C).

1.5 Synthesis of diphenylethers **14a-b**

1.5.1 General procedure

The appropriately substituted phenol (1mol equivalent) was dissolved in dry DMF (3mL/mmol of substituted phenol) in an oven dried two necked flask equipped with reflux condenser and CaCl₂ drying tube. NaH in an oil dispersion 60% w/w (2.2mol equivalent) was then added portion-wise and, once evolution of H₂ had stopped, a solution of 2,5-dinitrofluorobenzene **13** (1mol equivalent) was added in DMF (3mL/mmol of 2,5-dinitrofluorobenzene). The resulting deep red solution was left with stirring for 1h at rt and then heated at 50°C for another 5h. The reaction was then allowed to cool to rt and quenched with brine (2mL/mL of DMF). The resulting mixture was extracted with DCM (3 × 0.5mL/mL of suspension), the combined DCM layers washed with water (0.5mL/mL of DCM extract), brine (2 × 0.5mL/mL of DCM extract) and then dried (MgSO₄). The solvent was removed *in vacuo* and the residue subjected to column chromatography, eluting with a solvent mixture of petroleum ether (60:80°C) : EtOAc. The product was recrystallized from EtOH.

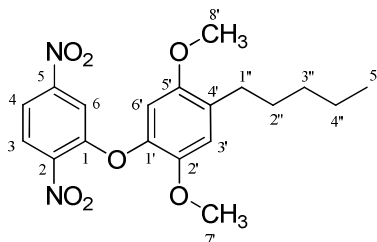
1.5.2 2,5-Dinitro-4'-*t*-butyl-2',5'-dimethoxydiphenylether **14a**



Prepared from 2,5-dimethoxy-4'-*t*-butylphenol **4d** (1.88g, 8.92mmol). 2,5-Dinitro-4'-*t*-butyl-2',5'-dimethoxydiphenylether **14a** was isolated as an orange solid (1.59g, 4.23mmol, 47.4%). Recrystallization from EtOH produced bright orange plates; mp (EtOH) 138°C; (found: C, 57.4; H, 5.35; N, 7.25%. C₁₈H₂₀N₂O₇ requires C, 57.4; H, 5.4; N, 7.4%); m/z 399.1 (MNa)⁺; $\nu_{\max}/\text{cm}^{-1}$ 1586 (C=C), 1537 and 1348 (NO₂), 1206 and 1038 (C-O); δ_H (300 MHz, CDCl₃) 1.33 (9H, s, C(CH₃)₃), 3.64 (3H, s, OCH₃, 7'-H), 3.72 (3H, s, OCH₃, 8'-H), 6.66 (1H, s, 6'-H), 6.94 (1H, s, 3'-H), 7.56 (1H, d, $J = 3.0$ Hz, 6-H), 7.82 (1H, dd, $J = 8.7, 2.1$ Hz, 4-H), 7.92 (1H, d, $J = 8.7$ Hz, 3-H); δ_C (75 MHz, CDCl₃) 29.7 (CH₃, 10'/11'/12'-C(CH₃)₃), 35.2 (quat., 9'-

C(CH₃)₃), 55.8 (OCH₃, 8'-C), 57.0 (OCH₃, 7'-C), 106.5 (CH, 6'-C), 112.8 (CH, 6-C), 113.8 (CH, 3'-C), 116.3 (CH, 4-C), 126.1 (CH, 3-C), 137.9 (quat., 4'-C), 139.7 (quat., 1'-C), 142.8 (quat., 5-C), 143.9 (quat., 2'-C), 150.4 (quat., 2-C), 152.3 (quat., 1-C), 153.4 (quat., 5'-C).

1.5.3 2,5-Dinitro-2',5'-dimethoxy-4'-pentyldiphenylether **14b**



Prepared from 2,5-dimethoxy-4-pentylphenol **4e** (2.07g, 9.25mmol). The product was purified by column chromatography, eluting with petroleum ether (60-80°C) : Et₂O (75:25). 2,5-Dinitro-2',5'-dimethoxy-4'-pentyldiphenylether **14b** was isolated as a bright orange solid (1.69g, 4.33mmol, 46.8%). Recrystallization from EtOH produced small yellow needles; mp 77-79°C; (found: C, 58.3; H, 5.65; N, 7.2%. C₁₉H₂₂N₂O₇ requires C, 58.5; H, 5.7; N, 7.2%); *m/z* 391.2 (*MH*)⁺, 413.2 (*MNa*)⁺; *v*_{max}/cm⁻¹ 2853-2952 (C-H), 1629 (C=C), 1531 and 1347 (NO₂), 1209 and 1038 (C-O); *δ*_H (300 MHz, CDCl₃) 0.84 (3H, t, *J* = 6.9Hz, 5''-H), 1.25-1.30 (4H, m, 3''-H and 4''-H), 1.48-1.55 (2H, m, 2''-H), 2.54 (2H, t, *J* = 8.1Hz, 1''-H), 3.63 (3H, s, OCH₃, 7'-H), 3.70 (3H, s, OCH₃, 8'-H), 6.63 (1H, s, 6'-H), 6.785 (1H, s, 3'-H), 7.53 (1H, d, *J* = 2.4Hz, 6-H), 7.83 (1H, dd, *J* = 9.0, 2.4Hz, 4-H), 7.93 (1H, d, *J* = 8.7Hz, 3-H); *δ*_C (75 MHz, CDCl₃) 14.0 (CH₃, 5''-C), 22.6 (CH₂, 3''-C or 4''-C), 29.6 (CH₂, 2''-C), 30.1 (CH₂, 1''-C), 31.8 (CH₂, 3''-C or 4''-C), 56.1 (OCH₃, 8'-C), 56.9 (OCH₃, 7'-C), 105.6 (CH, 6'-C), 112.6 (CH, 6-C), 115.9 (CH, 3'-C), 116.25 (CH, 4-C), 126.1 (CH, 3-C), 130.8 (quat., 4'-C), 139.5 (quat., 1'-C), 142.8 (quat., 5-C), 144.4 (quat., 2'-C), 150.4 (quat., 2-C), 152.2 (quat., 5'-C), 152.4 (quat., 1-C).

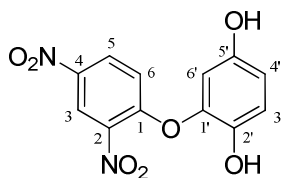
1.6 Synthesis of dihydroxydiphenylethers **7a-b**

1.6.1 General procedure for the demethylation of 2,4-dinitro-2',5'-dimethoxydiphenyl ethers **6a-b**

In a flame dried 2 necked flask equipped with a thermometer and flushed with N₂, the substituted biarylether (1mol equivalent) was dissolved in dry DCM (10mL/mmol of biarylether). The resulting solution was cooled to -78°C in a dry ice/acetone bath and a 1M DCM solution of BBr₃ (6mol equivalents) was slowly added to the biarylether solution. The addition rate was adjusted in order to keep the temperature below -55°C. The resulting

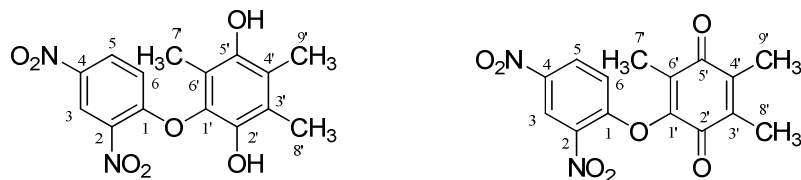
solution was maintained at -78°C for 40 min, then was allowed to warm up to rt and left with stirring overnight under a nitrogen atmosphere. After 18-20 hours, the solution was cooled again to -78°C and further 1M DCM solution of BBr₃ (3 mol equivalents) was added. The resulting solution was allowed to warm to rt and stirred for a further 5 hours, then quenched with ice to neutralise the excess BBr₃, and the DCM was removed under reduced pressure. The resulting mixture was extracted with diethyl ether (3x10mL/mmol of biarylether) and the combined organic extracts were washed once with brine (0.5mL/mL of diethyl ether extract) and dried (MgSO₄). The solvent was removed *in vacuo* and the residue subjected to column chromatography.

1.6.2 2,4-Dinitro-2',5'-dihydroxydiphenylether **7a**



The title compound was prepared as described from 2,4-dinitro-2',5'-dimethoxydiphenylether **6a** (4.01g, 12.50mmol). The product was purified by column chromatography, eluting with petroleum ether (60-80°C) : EtOAc (30:70). 2,4-Dinitro-2',5'-dihydroxydiphenylether **7a** was isolated as an amorphous hygroscopic yellow solid (3.53g, 12.10mmol, 96.7%) and further purified by hot trituration with DCM; mp 113-115°C; (found: C, 49.0; H, 2.8; N, 9.55%. C₁₂H₈N₂O₆ requires C, 49.3; H, 2.8; N, 9.6%); *m/z* 243.9 (*M*-H₂NO₂)⁻, 290.9 (*M*-H)⁻; *v*_{max}/ cm⁻¹ 3401 and 3347 (OH), 1600 (C=C), 1506 and 1340 (NO₂); *δ*_H (300 MHz, d₆-DMSO) 6.29 (1H, dd, *J* = 8.7, 2.7Hz, 4'-H), 6.49 (1H, d, *J* = 2.7Hz, 6'-H), 6.97 (1H, d, *J* = 3.3Hz, 6-H), 7.00 (1H, d, *J* = 2.7Hz, 3'-H), 8.39 (1H, dd, *J* = 9.3, 3.0Hz, 5-H), 8.82 (1H, d, *J* = 3.0Hz, 3-H), 9.49 (1H, s, 5'-OH), 9.84 (1H, s, 2'-OH); *δ*_C (75 MHz, d₆-DMSO) 104.8 (CH, 6'-C), 107.2 (CH, 4'-C), 117.6 (CH, 6-C), 122.1 (CH, 3-C), 123.2 (CH, 3'-C), 129.8 (CH, 5-C), 133.0 (quat., 2'-C), 138.5 (quat., 2-C), 140.85 (quat., 4-C), 149.8 (quat., 1'-C), 156.7 (quat., 5'-C), 157.1 (quat., 1-C).

1.6.3 2,4-Dinitro-2',5'-dihydroxy-3',4',6'-trimethyldiphenylether **7b** and 2,4-dinitrophenoxy-3',4',6'-trimethyl-2',5'-benzoquinone **8a**



The title compounds were prepared as described from 2,4-dinitro-2',5'-dimethoxy-3',4',6'-trimethyldiphenylether **6b** (3.38g, 9.32mmol); elution used petroleum ether (60-80°C) : Et₂O (70:30). Ambient evaporation of the solvent until crystals of 2,4-dinitro-2',5'-dihydroxy-3',4',6'-trimethyldiphenylether **7b** formed, and collection by filtration, yielded 2,4-dinitro-2',5'-dihydroxy-3',4',6'-trimethyldiphenylether **7b** (1.67g, 4.99mmol, 53.5%) as cream coloured prisms; mp 131-139°C; (found: C, 53.8; H, 4.2; N, 8.3%. C₁₅H₁₄N₂O₇ requires C, 53.9; H, 4.2; N, 8.4%); *m/z* 285.9 (*M*-H₂NO₂)⁻, 332.9 (*M*-H)⁻; *v*_{max}/cm⁻¹ 3431 (O-H), 1602 and 1517 (C=C), 1537 and 1348 (NO₂), 1244 (C-O); *δ*_H (300 MHz, d₆-DMSO) 1.99 (3H, s, CH₃, 7'-H), 2.09 (6H, s, 2 × CH₃, 8'-H and 9'-H), 6.83 (1H, d, *J* = 9.6Hz, 6-H), 7.965 (1H, s, 5'-OH), 8.40 (1H, dd, *J* = 9.6, 3.0Hz, 5-H), 8.79 (1H, s, 2'-OH), 8.84 (1H, d, *J* = 3.0Hz, 3-H); *δ*_C (75 MHz, d₆-DMSO) 10.2 (CH₃, 7'-C), 12.7 (CH₃, 8'-C or 9'-C), 12.8 (CH₃, 8'-C or 9'-C), 111.9 (quat., 3'-C), 115.8 (quat., 4'-C), 116.85 (CH, 6-C), 122.2 (CH, 3-C), 126.1 (quat., 6'-C), 130.0 (CH, 5-C), 132.7 (quat., 1'-C), 138.6 (quat., 4-C), 140.8 (quat., 2-C), 145.1 (quat., 2'-C), 152.0 (quat., 5'-C), 156.6 (quat., 1-C).

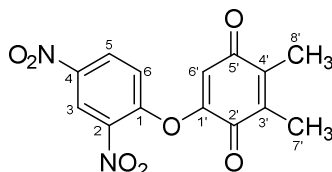
Evaporation of the filtrate and recrystallization of the residue from MeOH provided 2,4-dinitrophenoxy-3',4',6'-trimethyl-2',5'-benzoquinone **8a** as fluffy orange crystals (0.40g, 1.22 mmol, 13.0%); mp 142-145°C; (found: C, 54.2; H, 3.6; N, 8.4%. C₁₂H₈N₂O₆ requires C, 54.2; H, 3.6; N, 8.4%); *m/z* 355.1 (*MNa*)⁺; *v*_{max}/cm⁻¹ 1666 and 1648 (C=O), 1602 (C=C), 1526 and 1343 (NO₂), 1249 (C-O); *δ*_H (300 MHz, d₆-DMSO) 1.95 (3H, d, *J* = 1.2Hz, CH₃, 7'-H), 1.97 (3H, s, CH₃, 9'-H), 2.04 (3H, d, *J* = 0.9Hz, CH₃, 8'-H), 7.54 (1H, d, *J* = 9.3Hz, 6-H), 8.38 (1H, dd, *J* = 9.3, 2.7Hz, 5-H), 8.89 (1H, d, *J* = 2.7Hz, 3-H); *δ*_C (75 MHz, d₆-DMSO) 9.85 (CH₃, 9'-C), 12.2 (CH₃, 7'-C), 12.9 (CH₃, 8'-C), 119.2 (CH, 6-C), 122.3 (CH, 5-C), 129.7 (CH, 3-C), 134.3 (quat., 6'-C), 138.6 (quat., 2-C), 139.1 (quat., 4'-C), 141.7 (quat., 3'-C), 142.3 (quat., 4-C), 149.0 (quat., 1'-C), 154.1 (quat., 1-C), 180.5 (quat., 2'-C), 186.9 (quat., 5'-C).

1.7 Synthesis of dinitrobenzophenones 8b-8e and 15a-b

1.7.1 General procedure for the oxidative-demethylation of 2,4-dinitro-2',5'-dimethoxydiphenylethers 6b, d-f and 2,5-dinitro-2',5'-dimethoxydiphenylethers 14a-b

The correctly substituted dinitro-2',5'-dimethoxydiphenylether (1mol equivalent) was dissolved in CH₃CN (20mL/mmol of diphenylether) in a 2 necked flask equipped with a thermometer and a dropping funnel. Cerium (IV) ammonium nitrate (3mol equivalent) was dissolved in water (3mL/mmol of cerium (IV) ammonium nitrate) and the resulting solution added slowly to the biaryl ether solution via the dropping funnel. The yellow solution usually darkened upon addition of the cerium (IV) ammonium nitrate solution, followed by the formation of a yellow precipitate soon after the addition was finished. The resulting mixture was stirred for a further 1h to ensure completion of the reaction. CH₃CN was removed under reduced pressure and, whenever possible, the precipitate formed was collected by filtration and washed with water. It was then redissolved in DCM, the resulting solution dried (MgSO₄) and the solvent was removed *in vacuo*. The residue was recrystallized from ethanol. When no precipitate, but a yellow oil/syrup, was observed, the reaction mixture was extracted twice with DCM and the combined organic layers washed once with brine and dried (MgSO₄). The solvent was then removed under reduced pressure and the residue either subjected to column chromatography or recrystallized from EtOH.

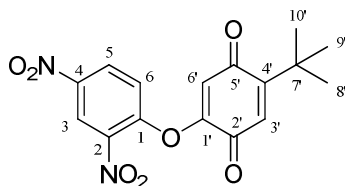
1.7.2 2,4-Dinitrophenoxy-3',4'-dimethyl-2',5'-benzoquinone 8b



Prepared from 2,4-dinitro-2',5'-dimethoxy-3',4'-dimethyldiphenylether **6b** (0.57g, 1.63mmol). Elution with petroleum ether (60:80°C) : EtOAc (30:70) yielded 2,4-dinitrophenoxy-3',4'-dimethyl-2',5'-benzoquinone **8b** as a yellow solid (0.47g, 1.48mmol, 90.9%). Recrystallization from EtOH produced yellow prisms; mp 110-111°C; (found: C, 52.8; H, 3.2; N, 8.7%. C₁₄H₁₀N₂O₇ requires C, 52.8; H, 3.2; N, 8.8%); *m/z* 341.1 (*MNa*)⁺; $\nu_{\max}/\text{cm}^{-1}$ 1666 and 1648 (C=O, quinone), 1600 (C=C), 1537 and 1347 (NO₂), 1190 (C-O); δ_H (300 MHz, d₆-DMSO) 2.01 (6H, s, 2 x CH₃, 7'-H and 8'-H), 6.46 (1H, s, 6'-H), 7.77 (1H, d, *J* = 9.0 Hz, 6-H), 8.55 (1H, dd, *J* = 9.0, 2.7 Hz, 5-H), 8.91 (1H, d, *J* = 2.7 Hz, 3-H); δ_C (75 MHz, d₆-DMSO) 12.3 (CH₃, 7'-C or 8'-C), 12.6 (CH₃, 7'-C or 8'-C), 117.9 (CH, 6'-C), 122.5 (CH, 3-C), 123.5 (CH,

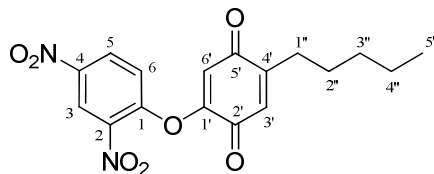
6-C), 130.3 (CH, 5-C), 139.5 (quat., 3'-C), 140.5 (quat., 2-C), 141.4 (quat., 4'-C), 144.1 (quat., 4-C), 152.1 (quat., 1-C), 155.2 (quat., 1'-C), 180.8 (quat., 2'-C), 187.1 (quat., 5'-C).

1.7.3 2,4-Dinitrophenoxy-4'-*t*-butyl-2',5'-benzoquinone **8c**



Prepared from 2,4-dinitro-4'-*t*-butyl-2',5'-dimethoxydiphenylether **6d** (2.87g, 7.69mmol). The crude product was recrystallized from MeOH yielding 2,4-dinitrophenoxy-4'-*t*-butyl-2',5'-benzoquinone **8c** as a fluffy yellow solid (1.68g, 4.85mmol, 63.0%); mp 179.5-182.5°C; (found: C, 55.5; H, 4.1; N, 8.1%. C₁₆H₁₄N₂O₇ requires C, 55.5; H, 4.1; N, 8.1%); *m/z* 369.1 (*MNa*)⁺; $\nu_{\max}/\text{cm}^{-1}$ 2870-2957 (C-H), 1665 and 1647 (C=O, quinone), 1611 and 1591 (C=C), 1533 and 1341 (NO₂), 1145 (C-O); δ_H (300 MHz, d₆-DMSO) 1.27 (9H, s, C(CH₃)₃), 6.40 (1H, s, 6'-H), 6.67 (1H, s, 3'-H), 7.82 (1H, d, *J* = 9.3Hz, 6-H), 8.56 (1H, dd, *J* = 9.0, 2.7Hz, 5-H), 8.92 (1H, d, *J* = 2.7Hz, 3-H); δ_C (75 MHz, d₆-DMSO) 29.5 (CH₃, 8'/9'/10'-C(CH₃)₃), 35.5 (quat., 7'-C(CH₃)₃), 119.6 (CH, 6'-C), 122.5 (CH, 3'-C), 123.9 (CH, 6-C), 130.3 (CH, 3'-C or 5-C), 130.5 (CH, 3'-C or 5-C), 140.6 (quat., 2-C), 144.3 (quat., 4-C), 151.8 (quat., 1-C), 154.5 (quat., 1'-C), 156.3 (quat., 4'-C), 181.4 (quat., 2'-C), 187.6 (quat., 5'-C).

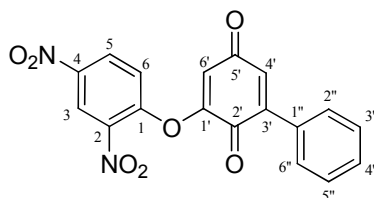
1.7.4 2,4-Dinitrophenoxy-4'-pentyl-2',5'-benzoquinone **8d**



Prepared from 2,4-dinitro-2',5'-dimethoxy-4'-pentyldiphenylether **6e** (2.65g, 6.79mmol). Elution with petroleum ether (60-80°C) : EtOAc (70:30) yielded 2,4-dinitrophenoxy-2',5'-dimethoxy-4'-pentylbenzoquinone **8d** as a yellow solid (2.36g, 6.56mmol, 96.7%). Recrystallization from EtOH produced shiny yellow plates; mp 110-114°C; (found: C, 56.5; H, 4.4; N, 7.7%. C₁₇H₁₆N₂O₇ requires C, 56.7; H, 4.5; N, 7.8%); *m/z* 383.1 (*MNa*)⁺; $\nu_{\max}/\text{cm}^{-1}$ 2927 (C-H), 1673 and 1649 (C=O, quinone), 1610 (C=C), 1530 and 1342 (NO₂), 1224 (C-O); δ_H (300 MHz, CDCl₃) 0.83 (3H, t, *J* = 6.9Hz, 5''-H), 1.26-1.29 (4H, m, 3''-H and 4''-H), 1.43-1.48 (2H, m, 2''-H), 2.38 (2H, td, *J* = 7.8, 1.2Hz, 1''-H), 6.03 (1H, s, 6'-H), 6.53 (1H, t, *J* =

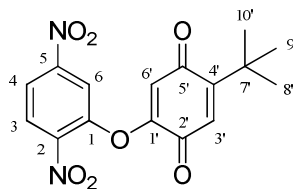
1.5Hz, 3'-H), 7.31 (1H, d, J = 9.0Hz, 6-H), 8.43 (1H, dd, J = 9.0, 2.7Hz, 5-H), 8.88 (1H, d, J = 2.7Hz, 3-H); δ_C (75 MHz, CDCl₃) 13.9 (CH₃, 5"-C), 22.4 (CH₂, 3"-C or 4"-C), 27.6 (CH₂, 1"-C), 28.9 (CH₂, 2"-C), 31.45 (CH₂, 3"-C or 4"-C), 116.3 (CH, 6'-C), 122.5 (CH, 3-C), 123.6 (CH, 6-C), 129.4 (CH, 5-C), 130.6 (CH, 3'-C), 140.7 (quat., 2-C), 144.5 (quat., 4-C), 151.2 (quat., 4'-C), 151.8 (quat., 1-C), 155.3 (quat., 1'-C), 180.3 (quat., 2'-C), 186.6 (quat., 5'-C).

1.7.5 2,4-Dinitrophenoxy-3'-phenyl-2',5'-benzoquinone **8e**



Prepared from 3-(2',4'-dinitrophenoxy)-2,5-dimethoxybiphenyl **6f** (1.48g, 3.97mmol). Elution with petroleum ether (60-80°C) : EtOAc (20:80) yielded 2,4-dinitrophenoxy-3'-phenyl-2',5'-benzoquinone **8e** as a yellow crystalline solid (1.23g, 3.36mmol, 84.6%). Recrystallization from EtOH/EtOAc produced golden orange plates; mp 158.5-160°C; (found: C, 58.8; H, 2.8; N, 7.6%. C₁₈H₁₀N₂O₇ requires C, 59.0; H, 2.75; N, 7.65%); m/z 389.1 (MNa)⁺; ν_{max}/cm^{-1} 1676 and 1649 (C=O, quinone), 1590 and 1523 (C=C), 1543 and 1347 (NO₂), 1226 and 1082 (C-O); δ_H (300 MHz, d₆-DMSO) 6.59 (1H, d, J = 2.4Hz, 6'-H), 7.00 (1H, d, J = 2.4Hz, 4'-H), 7.48-7.51 (3H, m, 3"-H, 5"-H and 4"-H), 7.54-7.58 (2H, m, 2"-H and 6"-H), 7.90 (1H, d, J = 9.3Hz, 6-H), 8.60 (1H, dd, J = 9.3, 2.7Hz, 5-H), 8.94 (1H, d, J = 2.7Hz, 3-H); δ_C (75 MHz, d₆-DMSO) 117.95 (CH, 6'-C), 122.5 (CH, 3-C), 123.6 (CH, 6-C), 128.8 (CH, 3"-C and 5"-C), 129.8 (CH, 2"-C and 6"-C), 130.4 (CH, 5-C and 4"-C), 132.7 (quat., 1"-C), 133.15 (CH, 4'-C), 140.6 (quat., 2-C), 144.1 (quat., 4-C), 144.7 (quat., 3'-C), 152.2 (quat., 1-C), 155.9 (quat., 1'-C), 179.9 (quat., 2'-C), 187.3 (quat., 5'-C).

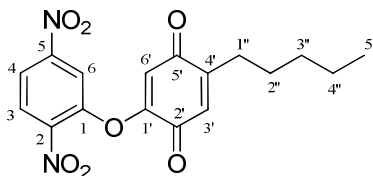
1.7.6 2,5-Dinitrophenoxy-4'-*t*-butyl-2',5'-benzoquinone **15a**



Prepared from 2,5-dinitro-4'-*t*-butyl-2',5'-dimethoxydiphenylether **14a** (1.57g, 4.18mmol). 2,5-Dinitrophenoxy-4'-*t*-butyl-2',5'-benzoquinone **15a** was isolated as a pale yellow solid (1.35g,

3.89mmol, 93.2%). Recrystallization from EtOH produced a pale yellow microcrystalline solid; mp 165-168°C; (found: C, 55.1; H, 4.0; N, 8.0%. $C_{16}H_{14}N_2O_7$ requires C, 55.5; H, 4.1; N, 8.1%); m/z 369.1 (MNa)⁺; ν_{max}/cm^{-1} 2952 (C-H), 1672 and 1650 (C=O, quinone), 1594 (C=C), 1540 and 1347 (NO₂), 1237 (C-O); δ_H (300 MHz, d₆-DMSO) 1.26 (9H, s, C(CH₃)₃), 6.19 (1H, s, 6'-H), 6.66 (1H, s, 3'-H), 8.33 (1H, dd, J = 9.0, 2.4Hz, 4-H), 8.41 (1H, d, J = 9.0Hz, 3-H), 8.51 (1H, d, J = 2.4Hz, 6-H); δ_C (75 MHz, d₆-DMSO) 29.5 (3 × CH₃, 8'/9'/10'-C(CH₃)₃), 35.4 (quat., 7'-C(CH₃)₃), 116.5 (CH, 6'-C), 119.9 (CH, 6-C), 122.3 (CH, 4-C), 127.9 (CH, 3-C), 130.4 (CH, 3'-C), 145.3 (quat., 2-C), 146.65 (quat., 5-C), 151.1 (quat., 1-C), 155.8 (quat., 1'-C), 156.1 (quat., 4'-C), 181.4 (quat., 2'-C), 187.8 (quat., 5'-C).

1.7.7 2,5-Dinitrophenoxy-4'-pentyl-2',5'-benzoquinone **15b**



Prepared from 2,4-dinitro-2',5'-dimethoxy-4'-pentyldiphenylether **14b** (1.41g, 3.62mmol). Elution with petroleum ether (60-80°C) : EtOAc (75:25) yielded 2,5-dinitrophenoxy-4'-pentyl-2',5'-benzoquinone **15b** as a yellow solid (1.19g, 3.31mmol, 91.4%). Recrystallization from EtOH produced golden prisms; mp 91-94°C; (found: C, 56.4; H, 4.5; N, 7.8%. $C_{17}H_{16}N_2O_7$ requires C, 56.7; H, 4.5; N, 7.8%); m/z 383.2 (MNa)⁺; ν_{max}/cm^{-1} 2870-2957 (C-H), 1676 and 1651 (C=O, quinone), 1603 (C=C), 1544 and 1343 (NO₂), 1230 (C-O); δ_H (300 MHz, d₆-DMSO) 0.79 (3H, t, J = 6.9Hz, 5''-H), 1.24-1.19 (4H, m, 3''-H and 4''-H), 1.42-1.35 (2H, m, 2''-H), 2.29 (2H, t, J = 6.9Hz, 1''-H), 6.18 (1H, s, 6'-H), 6.675 (1H, s, 3'-H), 8.23 (1H, dd, J = 9.0, 2.4Hz, 4-H), 8.32 (1H, d, J = 9.0Hz, 3-H), 8.41 (1H, d, J = 2.4Hz, 6-H); δ_C (75 MHz, d₆-DMSO) 14.3 (CH₃, 5''-H), 22.3 (CH₂, 3''-C or 4''-C), 27.75 (CH₂, 2''-C), 28.6 (CH₂, 1''-C), 31.4 (CH₂, 3''-C or 4''-C), 115.1 (CH, 6'-C), 119.8 (CH, 6-C), 122.2 (CH, 4-C), 127.9 (CH, 3-C), 131.2 (CH, 3'-C), 145.25 (quat., 2-C), 146.7 (quat., 5-C), 150.2 (quat., 4'-C), 151.1 (quat., 1-C), 156.6 (quat., 1'-C), 181.0 (quat., 2'-C), 187.65 (quat., 5'-C).

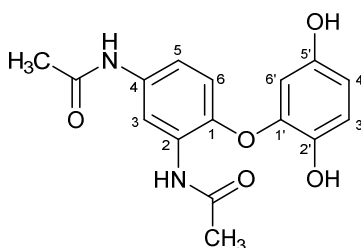
1.8 Trapping of diamino-dihydroxydiphenyl ether intermediates **9a**, **11b-d** and **16a**

1.8.1 General procedure

Either 2,4-dinitro-2',5'-dihydroxydiphenylether **9a** (1mol equivalent) or the correctly substituted dinitrophenoxy-2',5'-benzoquinone **11b-d** and **16a** (1mol equivalent) was dissolved in MeOH (10mL/mmol of 2,4-dinitro-2',5'-dihydroxydiphenylether) or an

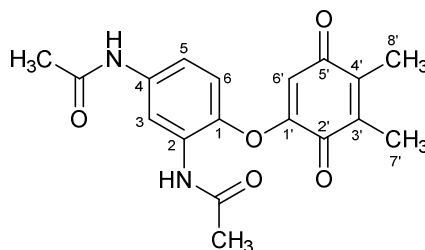
EtOAc:MeOH (1:1) solvent mixture (20mL/mmol of dinitrophenoxy-2',5'-benzoquinone) and Pd/C 5% (10% w/w of starting material) was added to the resulting solution. The resulting mixture was hydrogenated in a Berghof apparatus for 4h at a H₂ pressure of 2.4bar. Acetic anhydride (10mol equivalent) was added as soon as the hydrogenation was stopped and the resulting mixture was stirred at ambient atmosphere overnight. The reaction mixture was filtered through a pad of Celite, which was washed several times with MeOH and the filtrate evaporated *in vacuo*. NaHCO₃ (5%) was added to the residue and the resulting mixture extracted with EtOAc (2 × 60 mL). The combined organic layers were washed with NaHCO₃ (5%, 70mL) and brine (100mL), and dried (MgSO₄). The solvent was removed *in vacuo* and the crude product was purified by column chromatography.

1.8.2 2,4-Diacetamido-2',5'-dihydroxydiphenylether **10a**



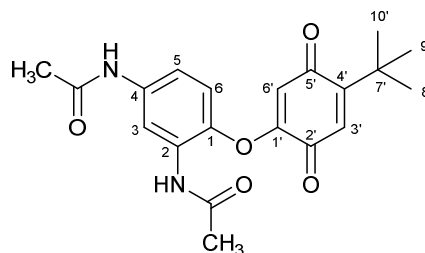
Prepared from 2,4-dinitro-2',5'-dihydroxydiphenylether **7a** (0.57g, 1.955mmol). Elution with EtOAc (100%) yielded 2,4-diacetamido-2',5'-dihydroxydiphenylether **10a** (0.49g, 1.555mmol, 79.5%) as a white solid. Recrystallization was achieved from petroleum ether (60-80°C) : EtOAc; mp 194.5-196°C; (found: C, 60.5; H, 5.1; N, 8.65%. C₁₆H₁₆N₂O₅ requires C, 60.75; H, 5.1; N, 8.9%); *m/z* 314.9 (*M-H*⁻); *v*_{max}/cm⁻¹ 3416 (N-H), 3317 (N-H), (br., O-H), 1698 (C=O), 1665 (C=O), 1616 (C=C), 1240 and 1205 (C-O); *δ*_H (300 MHz, d₆-DMSO) 2.025 (3H, s, COCH₃, 4-Ac), 2.11 (3H, s, COCH₃, 2-Ac), 6.28 (1H, d, *J* = 2.7Hz, 6'-H), 6.45 (1H, dd, *J* = 8.7, 2.7Hz, 4'-H), 6.70 (1H, d, *J* = 8.7Hz, 6-H), 6.78 (1H, d, *J* = 8.7Hz, 3'-H), 7.35 (1H, dd, *J* = 9.0, 2.4Hz, 5-H), 8.12 (1H, d, *J* = 2.1Hz, 3-H), 8.67 (1H, s, 2'-OH), 8.88 (1H, s, 5'-OH), 9.44 (1H, s, 2-NH), 9.89 (1H, s, 4-NH); *δ*_C (75 MHz, d₆-DMSO) 24.2 (CH₃, 2-Ac or 4-Ac), 24.3 (CH₃, 2-Ac or 4-Ac), 108.3 (CH, 6'-C), 111.85 (CH, 4'-C), 114.9 (CH, 3-C), 116.1 (CH, 5-C), 117.0 (CH, 6-C), 118.0 (CH, 3'-C), 128.85 (quat., 4-C), 134.6 (quat., 2-C), 141.3 (quat., 2'-C), 144.0 (quat., 1-C and 1'-C), 150.8 (quat., 5'-C), 168.5 (quat., 4-Ac, C=O), 169.1 (quat., 2-Ac, C=O).

1.8.3 2,4-Diacetamido-3',4'-dimethyl-2',5'-benzoquinone **12a**



Prepared from 2,4-dinitrophenoxy-3',4'-dimethyl-2',5'-benzoquinone **8b** (0.26g, 0.88mmol) and acetic anhydride (2.5mL). Elution with a gradient mixture of petroleum ether (60-80°C) : EtOAc (10:90 to 0:100) yielded 2,4-diacetamido-3',4'-dimethyl-2',5'-benzoquinone **12a** as a bright orange crystalline solid (0.26g, 0.77mmol, 95.8%). Recrystallization from EtOAc : hexane produced small orange prisms, mp 161°C (dec.); (found: C, 63.4; H, 5.4; N, 8.1%. $C_{18}H_{18}N_2O_5$ requires C, 63.15; H, 5.3; N, 8.2%); m/z 298.9 ($M-CH_3CO$), 340.9 ($M-H$); ν_{max}/cm^{-1} 3403 and 3277 (N-H), 1711 (C=O), 1655 and 1648 (C=O, quinone), 1606 (C=C), 1207 (C-O); δ_H (300 MHz, d_8 -THF) 2.00 (3H, d, $J = 1.2$ Hz, 7'-H), 2.05-2.06 (6H, m, $2 \times CH_3$, 8'-H and 2-Ac or 4-Ac), 2.08 (3H, s, 2-Ac or 4-Ac), 5.655 (1H, s, 6'-H), 6.98 (1H, d, $J = 9.0$ Hz, 6-H), 7.915 (1H, dd, $J = 8.7, 2.1$ Hz, 5-H), 8.30 (1H, d, $J = 2.4$ Hz, 3-H), 8.63 (1H, s, 2-NH), 9.31 (1H, s, 4-NH); δ_C (75 MHz, d_8 -THF) 9.1 (CH_3 , 7'-C or 8'-C), 9.3 (CH_3 , 7'-C or 8'-C), 21.1 (CH_3 , 2-Ac or 4-Ac), 21.25 (CH_3 , 2-Ac or 4-Ac), 108.5 (CH, 6'-C), 110.45 (CH, 3-C), 113.0 (CH, 5-C), 118.8 (CH, 6-C), 129.5 (quat., 2-C), 135.35 (quat., 4-C), 136.2 (quat., 1-C), 136.6 (quat., 3'-C), 138.8 (quat., 4'-C), 156.1 (quat., 1'-C), 165.8 (quat., 2-Ac or 4-Ac, C=O), 166.3 (quat., 2-Ac or 4-Ac, C=O), 179.0 (quat., 2'-C), 184.3 (quat., 5'-C).

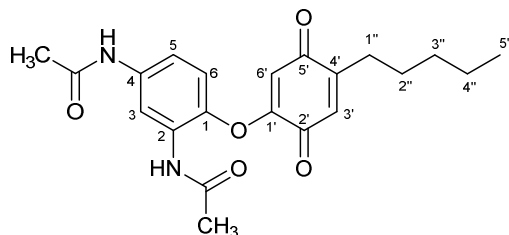
1.8.4 2,4-Diacetamido-4'-*t*-butyl-2',5'-benzoquinone **12b**



Prepared from 2,4-dinitrophenoxy-4'-*t*-butyl-2',5'-benzoquinone **8c** (0.18g, 0.51mmol). Elution with petroleum ether (60-80°C) : EtOAc (20 : 80) yielded 2,4-diacetamido-4'-*t*-butyl-2',5'-benzoquinone **12b** as a yellow-brown solid (0.19g, 0.51mmol, 99.0%). Recrystallization from petroleum ether (60-80°C) : EtOAc produced light brown micro-crystalline solid; mp 174-178°C; (found: C, 64.9; H, 6.1; N, 7.5%. $C_{20}H_{22}N_2O_5$ requires C, 64.85; H, 6.0; N, 7.6%); m/z

371.2 (MH^+); $\nu_{\max}/\text{cm}^{-1}$ 3330 (N-H), 2997-2868 (C-H), 1697 (C=O), 1665 and 1639 (C=O, quinone), 1594 and 1534 (C=C), 1168 (C-O); δ_H (300 MHz, d_6 -DMSO) 1.25 (9H, s, $C(CH_3)_3$), 2.03 (3H, s, 2-Ac or 4-Ac), 2.055 (3H, s, 2-Ac or 4-Ac), 5.42 (1H, s, 6'-H), 6.63 (1H, s, 3'-H), 7.13 (1H, d, $J = 9.0\text{Hz}$, 6-H), 7.55 (1H, dd, $J = 9.0, 2.4\text{Hz}$, 5-H), 8.18 (1H, d, $J = 2.4\text{Hz}$, 3-H), 9.33 (1H, s, 2-NH), 10.07 (1H, s, 4-NH); δ_C (75 MHz, d_6 -DMSO) 24.1 (CH_3 , 2-Ac or 4-Ac), 24.4 (CH_3 , 2-Ac or 4-Ac), 29.5 (CH_3 , 8'/9'/10'- $C(CH_3)_3$), 35.3 (quat., 7'- $C(CH_3)_3$), 112.2 (CH, 6'-C), 115.2 (CH, 3-C), 116.2 (CH, 5-C), 121.9 (CH, 6-C), 130.4 (CH, 3'-C), 130.9 (quat., 2-C), 137.9 (quat., 1-C), 138.5 (quat., 4-C), 155.7 (quat., 4'-C), 157.6 (quat., 1'-C), 168.8 (quat., 2-Ac or 4-Ac, C=O), 169.2 (quat., 2-Ac or 4-Ac, C=O), 182.1 (quat., 2'-C), 187.8 (quat., 5'-C).

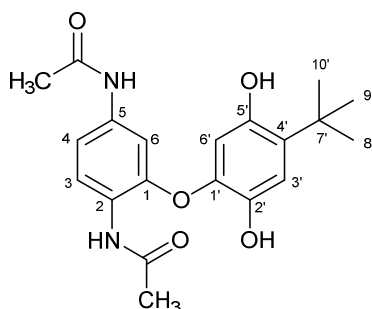
1.8.5 2,4-Diacetamido-4'-pentyl-2',5'-benzoquinone **12c**



Prepared from 2,4-dinitrophenoxy-4'-pentyl-2',5'-benzoquinone **8d** (0.46g, 1.26mmol). The crude product was purified by column chromatography on silica eluting with petroleum ether (60-80°C) : EtOAc (90:10). 2,4-Diacetamido-4'-pentyl-2',5'-benzoquinone **12c** was isolated as a dark orange crystalline solid (0.48g, 1.24mmol, 98.3%). Recrystallization from EtOAc : hexane produced red prisms; mp 90-93°C; (found: C, 65.6; H, 6.4; N, 7.2%. $C_{21}H_{24}N_2O_5$ requires C, 65.6; H, 6.3; N, 7.3%); m/z 341.0 ($M-CH_3CO$), 383.0 ($M-H$); $\nu_{\max}/\text{cm}^{-1}$ 3357 (N-H), 3269 (N-H), 2955 (C-H), 2929 (C-H), 1726 (C=O), 1663 and 1647 (C=O, quinone), 1599 (C=C), 1206 (C-O); δ_H (300 MHz, d_8 -THF) 0.93 (3H, t, $J = 6.9\text{Hz}$, 5''-H), 1.34-1.39 (4H, m, 3''-H and 4''-H), 1.48-1.55 (2H, m, 2''-H), 2.04 (3H, s, 2-Ac or 4-Ac), 2.07 (3H, s, 2-Ac or 4-Ac), 2.40 (2H, dt, $J = 7.5, 1.2\text{Hz}$, 1''-H), 5.67 (1H, s, 6'-H), 6.59 (1H, br. s, 3'-H), 6.98 (1H, d, $J = 8.7\text{Hz}$, 6-H), 7.91 (1H, dd, $J = 9.0, 2.1\text{Hz}$, 5-H), 8.28 (1H, d, $J = 2.1\text{Hz}$, 3-H), 8.63 (1H, s, 2-NH), 9.31 (1H, s, 4-NH); δ_C (75 MHz, d_8 -THF) 13.3 (CH_3 , 5''-C), 22.3 (CH_2 , 3''-C or 4''-C), 23.0 (CH_3 , 2-Ac or 4-Ac), 23.1 (CH_3 , 2-Ac or 4-Ac), 27.85 (CH_2 , 2''-C), 28.6 (CH_2 , 1''-C), 31.5 (CH_2 , 3''-C or 4''-C), 110.8 (CH, 6'-C), 112.5 (CH, 3-C), 114.9 (CH, 5-C), 120.7 (CH, 6-C), 130.45 (CH, 3'-C), 131.3 (quat., 2-C), 137.15 (quat., 1-C), 138.2 (quat., 4-C), 149.8 (quat.,

4'-C), 158.2 (quat., 1'-C), 167.7 (quat., 2-Ac or 4-Ac, C=O), 168.1 (quat., 2-Ac or 4-Ac, C=O), 181.0 (quat., 2'-C), 186.6 (quat., 5'-C).

1.8.6 2,5-Diacetamido-2',5'-dihydroxy-4'-*t*-butyldiphenylether **18a**



Prepared from 2,5-dinitrophenoxy-4'-*t*-butyl-2',5'-benzoquinone **15a** (0.11g, 0.32mmol). Elution with petroleum ether (60-80°C) : EtOAc (20:80) yielded 2,5-diacetamido-2',5'-dihydroxy-4'-*t*-butyldiphenylether **18a** (0.12g, 0.31mmol, 97.5%) was isolated as a white solid. Recrystallization from petroleum ether (60-80°C) : EtOAc produced a white crystalline solid; mp 148-152°C; (found: C, 64.7; H, 6.55; N, 7.6%. C₂₀H₂₄N₂O₅ requires C, 64.5; H, 6.5; N, 7.5%); *m/z* 371.0 (*M-H*)⁻; *v*_{max}/cm⁻¹ 3345 (N-H), 3259 (N-H), (br., O-H), 2957 (C-H), 1701 (C=O), 1667 (C=O), 1605 (C=C); *δ*_H (300 MHz, d₆-DMSO) 1.25 (9H, s, C(CH₃)₃), 1.87 (3H, s, 2-Ac or 5-Ac), 1.99 (3H, s, 2-Ac or 5-Ac), 6.36 (1H, s, 3'-H), 6.69 (1H, s, 6'-H), 6.85 (1H, d, *J* = 1.8Hz, 6-H), 7.25 (1H, dd, *J* = 8.4, 1.5Hz, 4-H), 7.60 (1H, d, *J* = 8.7Hz, 3-H), 8.44 (1H, s, 2'-OH), 8.76 (1H, s, 5'-OH), 9.33 (1H, s, 2-NH), 9.77 (1H, s, 5-NH); *δ*_C (75 MHz, d₆-DMSO) 24.0 (CH₃, 2-Ac or 5-Ac), 24.3 (CH₃, 2-Ac or 5-Ac), 29.9 (CH₃, 8'/9'/10'-C(CH₃)₃), 34.5 (quat., 7'- C(CH₃)₃), 107.1 (CH, 6-C), 109.7 (CH, 3'-C), 113.1 (CH, 4-C), 115.9 (CH, 6'-C), 123.55 (quat., 2-C), 124.2 (CH, 3-C), 132.8 (quat., 4'-C), 136.9 (quat., 5-C), 140.4 (quat., 1'-C), 140.7 (quat., 2'-C), 148.8 (quat., 5'-C), 149.7 (quat., 1-C), 168.5 (quat., 2-Ac or 5-Ac, C=O), 169.0 (quat., 2-Ac or 5-Ac, C=O).

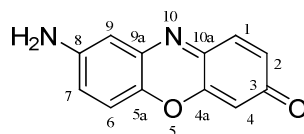
1.9 Synthesis of 8-amino-alkyl-3*H*-phenoxazin-3-ones **2a-f** and 7-amino-2-alkyl-3*H*-phenoxazin-3-ones **17a-b**

1.9.1 General procedure

The appropriately substituted 2,4-dinitro-2',5'-dihydroxydiphenyl ether **7a-b** was dissolved in MeOH (10mL/mmol of 2,4-dinitro-2',5'-dihydroxydiphenyl ether), or the appropriately substituted dinitrophenoxy-2',5'-benzoquinone **8a-e** or **15a-b** was dissolved in an EtOAc : MeOH (1:1) solvent mixture (20mL/mmol of dinitrophenoxy-2',5'-benzoquinone). Pd/C 5%

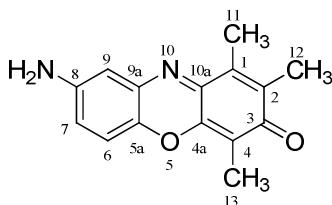
(10% w/w of starting material) was added to the solution and the resulting mixture was hydrogenated in a Berghof apparatus. The H₂ pressure was set to 2.4bar and reset to this pressure when necessary. When the H₂ pressure was steady, the catalyst was removed by filtration through Celite, which was washed several times with small portions of MeOH. Either AgO, Ag₂O or MnO₂ (3mol equivalent) was then added quickly to the filtrate; when reducing 2',5'-dihydroxydiphenyl ether **7a-b**, Et₃N (1mL) was also added. A purple suspension was rapidly produced for 8-amino-alkyl-3*H*-phenoxazin-3-ones **2a-f** and a red-pink fluorescent suspension for 7-amino-alkyl-3*H*-phenoxazin-3-ones **17a-b**. The filtrate was then stirred at rt and completion of the reaction was monitored by TLC. The metal oxide was then removed by filtration through Celite, which was washed several times with MeOH. The combined filtrates were evaporated *in vacuo* and the residue subjected to column chromatography on silica.

1.9.2 8-Amino-3*H*-phenoxazin-3-one **2a**



Prepared from 2,4-dinitro-2'-5'-dihydroxydiphenylether **7a** (0.56g, 1.91mmol). Elution with a gradient mixture of petroleum ether (60-80°C) : EtOAc (70:30 to 100:0), yielded 8-amino-3*H*-phenoxazin-3-one **2a** as a dark purple solid (0.37g, 1.75mmol, 91.3%); mp >290°C; (found: C, 68.2; H, 3.9; N, 13.4%. C₁₂H₈N₂O₂ requires C, 67.9; H, 3.8; N, 13.2%); *m/z* 213.0 (*MH*)⁺ and 234.9 (*MNa*)⁺; $\nu_{\max}/\text{cm}^{-1}$ 3387, 3320, 3200 (NH₂), 1640 (C=O), 1591 (C=C); δ_{H} (300 MHz, d₆-DMSO) 5.45 (2H, br. s, NH₂), 6.21 (1H, d, *J* = 2.1Hz, 4-H), 6.82 (1H, dd, *J* = 9.6, 2.1Hz, 2-H), 6.97 (2H, m, 7-H and 9-H), 7.24 (1H, d, *J* = 9.6Hz, 6-H), 7.49 (1H, d, *J* = 9.9Hz, 1-H); δ_{C} (75 MHz, d₆-DMSO) 105.3 (CH, 4-C), 111.6 (CH, 9-C), 116.7 (CH, 6-C), 121.0 (CH, 7-C), 134.3 (quat., 8-C), 135.0 (CH, 1-C and 2-C), 135.5 (quat., 9a-C), 147.4 (quat., 5a-C), 148.2 (quat., 10a-C), 150.4 (quat., 4a-C), 185.6 (quat., 3-C).

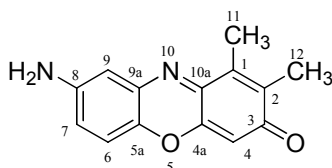
1.9.3 8-Amino-1,2,4-trimethyl-3*H*-phenoxazin-3-one **2b**



Prepared from 2,4-dinitrophenoxy-3',4',6'-trimethylbenzoquinone **8a** (0.27g, 0.81mmol). Elution using petroleum ether (60-80°C) : EtOAc (30:70) yielded 8-amino-1,2,4-trimethyl-3*H*-phenoxazin-3-one **2b** as a dark violet solid (0.19g, 0.77mmol, 94.0%). Analytical data were identical to the product obtained from 2,4-dinitro-2',5'-dihydroxy-3',4',6'-trimethyldiphenylether **7b** below.

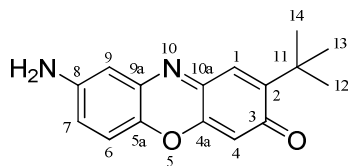
Also prepared from 2,4-dinitro-2',5'-dihydroxy-3',4',6'-trimethyldiphenylether **7b** (0.33g, 0.98mmol). Elution using petroleum ether (60-80°C) : EtOAc (30:70) yielded 8-amino-1,2,4-trimethyl-3*H*-phenoxazin-3-one **2b** as a dark violet solid (0.22g, 0.85mmol, 86.7%); mp 235-246°C; m/z 255.0 (MH)⁺; $\nu_{\max}/\text{cm}^{-1}$ 3355, 3332 and 3219 (NH₂), 2850-2920 (C-H), 1649 (C=O), 1595, 1577 and 1505 (C=C); δ_{H} (300 MHz, d₆-DMSO) 1.95 (3H, s, 13-H), 2.06 (3H, d, J = 0.9Hz, 12-H), 2.32 (3H, d, J = 0.9Hz, 11-H), 5.32 (2H, br. s, NH₂), 6.86 (1H, dd, J = 8.7, 2.7Hz, 7-H), 6.93 (1H, d, J = 2.7Hz, 9-H), 7.19 (1H, d, J = 8.7Hz, 6-H); δ_{C} (75 MHz, d₆-DMSO) 8.08 (CH₃, 13-C), 13.0 (CH₃, 11-C), 13.4 (CH₃, 12-C), 111.75 (quat., 4-C), 112.1 (CH, 9-C), 116.3 (CH, 6-C), 119.6 (CH, 7-C), 133.3 (quat., 8-C), 135.8 (quat., 9a-C), 136.6 (quat., 1-C or 2-C), 138.4 (quat., 1-C or 2-C), 145.9 (quat., 4a-C), 146.8 (quat., 5a-C), 148.1 (quat., 10a-C), 184.1 (quat., 3-C). HPLC-MS spectra: Figure S1.

1.9.4 8-Amino-1,2-dimethyl-3*H*-phenoxazin-3-one **2c**



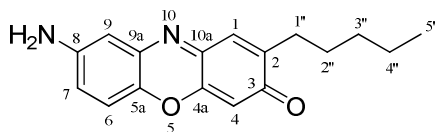
Prepared from 2,4-dinitrophenoxy-3',4'-dimethyl-2',5'-benzoquinone **8b** (0.41g, 1.28mmol). Elution with petroleum ether (60-80°C) : EtOAc yielded 8-amino-1,2-dimethyl-3*H*-phenoxazin-3-one **2c** (0.28g, 1.18mmol, 92.0%) as a dark violet solid; mp 260-265°C; m/z 241.0 (MH)⁺; $\nu_{\max}/\text{cm}^{-1}$ 3414, 3332 and 3225 (NH₂), 2851-2920 (C-H), 1638 (C=O), 1570 (C=C); δ_{H} (300 MHz, d₆-DMSO) 2.05 (3H, d, J = 0.9 Hz, 12-H), 2.35 (3H, d, J = 0.9Hz, 11-H), 5.38 (2H, br. s, NH₂), 6.12 (1H, s, 4-H), 6.90 (1H, dd, J = 9.0, 2.7Hz, 7-H), 6.96 (1H, d, J = 2.7Hz, 9-H), 7.20 (1H, d, J = 8.7Hz, 6-H); δ_{C} (75 MHz, d₆-DMSO) 13.1 (CH₃, 11-C or 12-C), 13.2 (CH₃, 11-C or 12-C), 104.0 (CH, 4-C), 112.0 (CH, 9-C), 116.3 (CH, 6-C), 120.1 (CH, 7-C), 133.7 (quat., 8-C), 135.3 (quat., 9a-C), 137.5 (quat., 1-C), 139.1 (quat., 2-C), 147.1 (quat., 5a-C), 148.2 (quat., 10a-C), 149.8 (quat., 4a-C), 184.5 (quat., 3-C). HPLC-MS spectra: Figure S2.

1.9.5 8-Amino-2-*t*-butyl-3*H*-phenoxazin-3-one **2d**



Prepared from 2,4-dinitrophenoxy-4'-*t*-butyl-2',5'-benzoquinone **8c** (0.62g, 1.78mmol). Elution with petroleum ether (60-80°C) : EtOAc (40:60) yielded 8-amino-2-*t*-butyl-3*H*-phenoxazin-3-one **2d** (0.41g, 1.55mmol, 86.8%) as a dark violet solid; mp 217-226°C; (found: C, 71.6; H, 6.3; N, 10.1%. C₁₆H₁₆N₂O₂ requires C, 71.6; H, 6.0; N, 10.4%); m/z 269.0 (MH)⁺; $\nu_{\max}/\text{cm}^{-1}$ 3420 and 3337 (NH₂), 2952 (C-H), 1649 (C=O), 1601 and 1575 (C=C); δ_{H} (300 MHz, CDCl₃) 1.31 (9H, s, C(CH₃)₃), 3.74 (2H, br. s, NH₂), 6.12 (1H, s, 4-H), 6.78 (1H, dd, J = 8.7, 2.7Hz, 7-H), 6.94 (1H, d, J = 2.7Hz, 9-H), 7.05 (1H, d, J = 8.7Hz, 6-H), 7.20 (1H, s, 1-H); δ_{C} (75 MHz, CDCl₃) 29.3 (CH₃, 12/13/14-C(CH₃)₃), 35.8 (quat., 11-C(CH₃)₃), 107.6 (CH, 4-C), 113.6 (CH, 9-C), 116.5 (CH, 6-C), 119.9 (CH, 7-C), 129.4 (CH, 1-C), 134.25 (quat., 8-C), 137.0 (quat., 9a-C), 143.9 (quat., 5a-C), 148.7 (quat., 4a-C or 10a-C), 149.8 (quat., 4a-C or 10a-C), 154.9 (quat., 2-C), 185.9 (quat., 3-C).

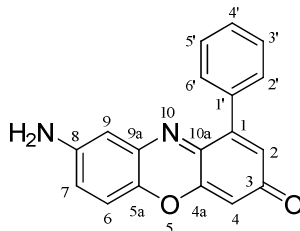
1.9.6 8-Amino-2-pentyl-3*H*-phenoxazin-3-one **2e**



Prepared from 2,4-dinitrophenoxy-4'-pentyl-2',5'-benzoquinone **8d** (0.38g, 1.07mmol). Elution with a gradient mixture of petroleum ether (60-80°C) : EtOAc (50 : 50 to 35 : 65) yielded 8-amino-2-pentyl-3*H*-phenoxazin-3-one **2e** as a dark violet solid (0.29g, 1.01mmol, 94.7%); mp 141-144°C; (found: C, 71.9; H, 6.6; N, 9.7%. C₁₇H₁₈N₂O₂ requires C, 72.2; H, 6.4; N, 9.9%); m/z 283.1 (MH)⁺; $\nu_{\max}/\text{cm}^{-1}$ 3400, 3337 and 3222 (N-H), 2853 and 2928 (C-H), 1639 (C=O), 1585, 1566 and 1508 (C=C); δ_{H} (300 MHz, d₆-DMSO) 0.87 (3H, t, J = 6.9Hz, 5'-H), 1.28-1.32 (4H, m, 3'-H and 4'-H), 1.46-1.56 (2H, m, 2'-H), 2.45 (2H, t, J = 6.9Hz, 1'-H), 5.41 (2H, br. s, NH₂), 6.17 (1H, s, 4-H), 6.90-6.93 (2H, m, 7-H and 9-H), 7.21 (1H, d, J = 9.3Hz, 6-H), 7.25 (1H, s, 1-H); δ_{C} (75 MHz, d₆-DMSO) 14.3 (CH₃, 5'-C), 22.4 (CH₂, 3'-C or 4'-C), 28.1 (CH₂, 2'-C), 29.5 (CH₂, 1'-C), 31.5 (CH₂, 3'-C or 4'-C), 105.0 (CH, 4-C), 111.55 (CH, 9-C), 116.55 (CH, 6-C), 120.3 (CH, 7-C), 130.6 (CH, 1-C), 134.3 (quat., 8-C), 135.3

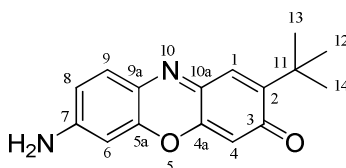
(quat., 9a-C), 147.25 (quat., 2-C or 5a-C), 147.3 (quat., 2-C or 5a-C), 148.4 (quat., 4a-C), 149.7 (quat., 10a-C), 184.8 (quat., 3-C).

1.9.7 8-Amino-1-phenyl-3*H*-phenoxazin-3-one **2f**



Prepared from 2,4-dinitrophenoxy-3'-phenyl-2',5'-benzoquinone **8e** (0.065g, 0.18mmol) using THF as solvent. Hydrogenation time of 48h was required; cyclisation occurred in the presence of Ag₂O (0.16g, 0.71mmol) and Et₃N (1mL). Elution with petroleum ether (60-80°C) : EtOAc (30:70) yielded 8-amino-1-phenyl-3*H*-phenoxazin-3-one **2f** as a dark violet solid (0.04g, 0.13mmol, 73.4%); mp 205°C (dec.); (found: C, 75.1; H, 4.4; N, 9.65%. C₁₈H₁₂N₂O₂ requires C, 75.0; H, 4.2; N, 9.7%); *m/z* 289.0 (*MH*)⁺, *v*_{max}/cm⁻¹ 3421, 3308 and 3198 (N-H), 1634 (C=O), 1586, 1560 and 1502 (C=C); *δ*_H (300 MHz, d₆-DMSO) 5.31 (2H, br. s, *NH*₂), 6.18 (1H, d, *J* = 2.1Hz, 4-H), 6.68 (1H, d, *J* = 2.1Hz, 2-H), 6.77 (1H, d, *J* = 2.7Hz, 9-H), 6.87 (1H, dd, *J* = 8.7, 2.7Hz, 7-H), 7.17 (1H, d, *J* = 8.7Hz, 6-H), 7.38-7.40 (3H, m, 3'-H, 4'-H and 5'-H), 7.48-7.53 (2H, m, 2'-H and 6'-H); *δ*_C (75 MHz, d₆-DMSO) 105.15 (CH, 4-C), 112.0 (CH, 9-C), 116.5 (CH, 6-C), 121.15 (CH, 7-C), 128.3 (CH, 3'-C and 5'-C), 129.1 (CH, 4'-C), 130.6 (CH, 2'-C and 6'-C), 133.0 (CH, 2-C), 133.9 (quat., 8-C), 135.3 (quat., 9a-C), 135.5 (quat., 1-C), 144.9 (quat., 1'-C), 147.2 (quat., 5a-C or 10a-C), 147.3 (quat., 5a-C or 10a-C), 150.6 (quat., 4a-C), 184.5 (quat., 3-C).

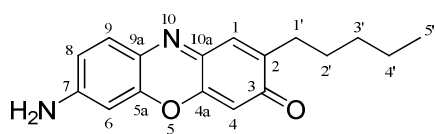
1.9.8 7-Amino-2-*t*-butyl-3*H*-phenoxazin-3-one **17a**



Prepared from 2,5-dinitrophenoxy-4'-*t*-butyl-2',5'-benzoquinone **15a** (1.01g, 2.91mmol). Elution with petroleum ether (60-80°C) : EtOAc (40:60), yielded 7-amino-2-*t*-butyl-3*H*-phenoxazin-3-one **17a** as a dark solid with a metallic shine (0.76g, 2.84mmol, 97.5%); mp 255-260°C; (found: C, 71.5; H, 6.1; N, 10.4%. C₁₆H₁₆N₂O₂ requires C, 71.6; H, 6.0; N,

10.4%); m/z 269.1 (MH)⁺; $\nu_{\max}/\text{cm}^{-1}$ 3408, 3317 and 3205 (NH₂), 2944 (C-H), 1643 (C=O), 1589, 1568 and 1547 (C=C); δ_{H} (300 MHz, d₆-DMSO) 1.31 (9H, s, C(CH₃)₃), 6.04 (1H, s, 4-H), 6.475 (1H, d, J = 2.4Hz, 6-H), 6.69 (1H, dd, J = 9.0, 2.4Hz, 8-H), 6.81 (2H, br. s, NH₂), 7.14 (1H, s, 1-H), 7.43 (1H, d, J = 8.7Hz, 9-H); δ_{C} (75 MHz, d₆-DMSO) 29.4 (CH₃, 12/13/14-C(CH₃)₃), 35.4 (quat., 11-C(CH₃)₃), 97.9 (CH, 6-C), 106.5 (CH, 4-C), 113.6 (CH, 8-C), 126.4 (quat., 7-C), 129.45 (CH, 1-C), 132.0 (CH, 9-C), 140.7 (quat., 10a-C), 146.6 (quat., 9a-C), 149.0 (quat., 4a-C), 150.4 (quat., 2-C), 155.1 (quat., 5a-C), 184.6 (quat., 3-C).

1.9.9 7-Amino-2-pentyl-3*H*-phenoxazin-3-one **17b**



Prepared from 2,5-dinitrophenoxy-4'-pentyl-2',5'-benzoquinone **15b** (0.80g, 2.23mmol). Elution with a gradient mixture of petroleum ether (60-80°C) : EtOAc (40:60 to 0:100) yielded 7-amino-2-pentyl-3*H*-phenoxazin-3-one **17b** as a dark violet solid (0.62g, 2.18mmol, 97.6%); mp 250-254°C; (found: C, 72.15; H, 6.6; N, 9.8%. C₁₇H₁₈N₂O₂ requires C, 72.2; H, 6.4; N, 9.9%); m/z 283.2 (MH)⁺; $\nu_{\max}/\text{cm}^{-1}$ 3420, 3329 and 3226 (NH₂), 2923 (C-H), 1654 (C=O), 1599 and 1565 (C=C); δ_{H} (300 MHz, d₆-DMSO) 0.88 (3H, t, J = 6.9Hz, 5'-H), 1.29-1.33 (4H, m, 3'-H and 4'-H), 1.47-1.54 (2'-H), 2.45 (2H, t, J = 7.5Hz, 1'-H), 6.17 (1H, s, 4-H), 6.51 (1H, d, J = 2.4Hz, 6-H), 6.71 (1H, dd, J = 8.7, 2.4Hz, 8-H), 6.83 (2H, br. s, NH₂), 7.24 (1H, s, 1-H), 7.48 (1H, d, J = 8.7Hz, 9-H); δ_{C} (75 MHz, d₆-DMSO) 14.4 (CH₃, 5'-C), 22.4 (CH₂, 3'-C or 4'-C), 28.3 (CH₂, 2'-C), 29.5 (CH₂, 1'-C), 31.55 (CH₂, 3'-C or 4'-C), 97.8 (CH, 6-C), 105.1 (CH, 4-C), 113.8 (CH, 8-C), 126.4 (quat., 7-C), 130.8 (CH, 1-C), 132.1 (CH, 9-C), 140.6 (quat., 9a-C), 144.0 (quat., 4a-C), 146.7 (quat., 10a-C), 149.8 (quat., 2-C), 155.1 (quat., 5a-C), 184.3 (quat., 3-C).

1.10 Synthesis of 7-*N* and 8-*N*-(*N'*-*t*-butoxycarbonyl-β-alanyl)amino-3*H*-phenoxazin-3-ones **20a-b** and **21a-f**

1.10.1 General procedure

In a 100mL flame dried flask flushed with nitrogen, *N'*-*t*-boc-β-alanine (3 mol equivalent) was dissolved in dry THF (10mL/mmol of *N'*-*t*-boc-β-alanine) and the solution was cooled with an ice bath to 2-3°C (T_{int.}). *N*-Methylpiperidine (3.5mol equivalent) was then added dropwise, the resulting solution stirred for 5min and *isobutylchloroformate* (3mol equivalent) was added

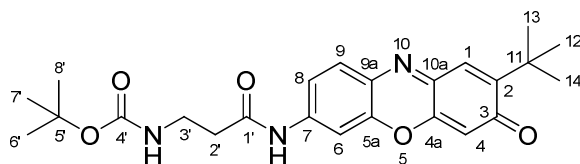
dropwise (temperature rose to 5°C). The resulting cloudy solution was stirred at 3°C for 1h to allow the mixed anhydride to form.

Method A. In the meantime, the correctly substituted 7-amino-3*H*-phenoxazin-3-one (1mol equivalent) was dissolved in dry DMF (5mL/mmol of 7-amino-3*H*-phenoxazin-3-one) in a 10mL round-bottomed flask, and Pd/C 5% (10% w/w of the starting material) was added to the resulting solution. The resulting mixture was hydrogenated in a Berghof apparatus for 1h with the H₂ pressure initially set at 2 bar. The flask was immediately sealed after hydrogenation and protected with an N₂ atmosphere. The resulting 7-amino-3-hydroxy-phenoxazine was added *via* canula to anhydride mixture.

Method B. The correctly substituted 8-amino-3*H*-phenoxazin-3-one (1mol equivalent) was directly added as a solid to the anhydride mixture.

The resulting mixture (**method A** or **method B**) was stirred under nitrogen for 48-72h. The reaction mixture was quenched with NaHCO₃ (5%) and extracted with EtOAc (3 x 70 mL). The combined organic extracts were washed successively with NaHCO₃ (5%, 100mL), water (100mL), brine (100mL), and dried (MgSO₄). The solvent was evaporated *in vacuo* and the residue was subjected to column chromatography on silica gel.

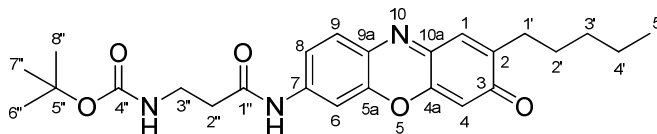
1.10.2 7-*N*-(*N'*-*t*Butoxycarbonyl-β-alanyl)amino-2-*t*butyl-3*H*-phenoxazin-3-one 20a



Prepared (**method A**) from 7-amino-2-*t*butyl-3*H*-phenoxazin-3-one **17a** (0.52g, 1.92mmol). Elution with a gradient mixture of petroleum ether (60-80°C) : EtOAc (50:50 to 30:70) yielded 7-*N*-(*N'*-*t*butoxycarbonyl-β-alanyl)amino-2-*t*butyl-3*H*-phenoxazin-3-one **20a** as an orange solid (0.38g, 0.87mmol, 45.3%); mp 194.5-197.5°C; (found: C, 65.3; H, 6.7; N, 9.4%. C₂₄H₂₉N₃O₅ requires C, 65.6; H, 6.65; N, 9.6%); *m/z* 438.1 (*M-H*)⁻; 440.2 (*MH*)⁺; ν_{max}/cm⁻¹ 3373 and 3311 (N-H), 3001-2883 (C-H), 1712, 1685 and 1644 (C=O), 1165 (C-O); δ_H (300 MHz, d₆-DMSO) 1.32 (9H, s, 12/13/14-C(CH₃)₃), 1.39 (9H, s, 6'/7'/8'-C(CH₃)₃), 2.56 (2H, t, *J* = 6.9Hz, 2'-H), 3.26 (2H, q, *J* = 6.9Hz, 3'-H), 6.16 (1H, s, 4-H), 6.88 (1H, br. s, *NH*^{*t*}Boc), 7.20 (1H, s, 1-H), 7.47 (1H, dd, *J* = 8.7, 2.1Hz, 8-H), 7.69 (1H, d, *J* = 8.7Hz, 9-H), 7.87 (1H, d, *J* = 2.1Hz, 6-H), 10.485 (1H, s, *NH*-Ar); δ_C (75 MHz, d₆-DMSO) 28.7 (CH₃, 12/13/14-C(CH₃)₃), 29.4 (CH₃, 6'/7'/8'-C(CH₃)₃), 35.6 (quat., 11-C(CH₃)₃), 36.8 (CH₂, 3'-C), 37.5 (CH₂, 2'-C), 78.2 (quat., 5'-C(CH₃)₃), 105.35 (CH, 6-C), 107.5 (CH, 4-C), 116.7 (CH, 8-C), 129.7

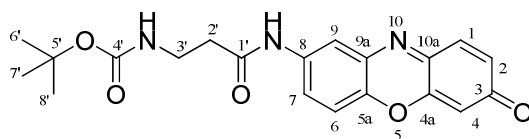
(quat., 7-C), 129.8 (CH, 1-C), 130.7 (CH, 9-C), 143.5 (quat., 9a-C), 144.4 (quat., 5a-C), 146.9 (quat., 4a-C), 148.75 (quat., 10a-C), 153.1 (quat., 2-C), 156.05 (quat., 1'-C), 170.8 (quat., 4'-C), 185.3 (quat., 3-C).

1.10.3 7-*N*-(*N'*-*t*Butoxycarbonyl- β -alanyl)amino-2-pentyl-3*H*-phenoxazin-3-one **20b**



Prepared (**method A**) from 7-amino-2-pentyl-3*H*-phenoxazin-3-one **17b** (0.48g, 1.69mmol). Elution with petroleum ether (60-80°C) : EtOAc (40:60) yielded 7-*N*-(*N'*-*t*butoxycarbonyl- β -alanyl)amino-2-pentyl-3*H*-phenoxazin-3-one **20b** as an orange solid (0.36g, 0.78mmol, 46.0%). Recrystallization from EtOAc produced a microcrystalline orange solid with a green metallic shine; mp 205-209°C; (found: C, 66.35; H, 6.9; N, 9.25%. C₂₅H₂₁N₃O₅ requires C, 66.2; H, 6.9; N, 9.3%); *m/z* 453.2 (*M-H*)⁻; 454.3 (*MH*)⁺; $\nu_{\max}/\text{cm}^{-1}$ 3263 and 3190 (N-H), 2951 and 2922 (C-H), 1710 and 1651 (C=O); δ_{H} (300 MHz, d₆-DMSO) 0.79 (3H, t, *J* = 6.9Hz, 5'-H), 1.20-1.245 (4H, m, 3'-H and 4'-H), 1.30 (9H, s, C(CH₃)₃), 1.39-1.46 (2H, m, 2'-H), 2.39 (2H, t, *J* = 7.5Hz, 1'-H), 2.47 (2H, t, *J* = 7.2Hz, 2''-H), 3.17 (2H, q, *J* = 7.2Hz, 3''-H), 6.20 (1H, s, 4-H), 6.80 (1H, br. s, NH^{*t*}Boc), 7.22 (1H, s, 1-H), 7.40 (1H, dd, *J* = 8.7, 2.1Hz, 7-H), 7.66 (1H, d, *J* = 8.7Hz, 9-H), 7.82 (1H, d, *J* = 2.1Hz, 6-H), 10.41 (1H, s, NH-Ar); δ_{C} (75 MHz, d₆-DMSO) 14.3 (CH₃, 5'-C), 22.4 (CH₂, 3'-C or 4'-C), 28.1 (CH₂, 2'-C), 28.7 (CH₂, 1'-C), 29.4 (CH₃, 6''/7''/8''-C(CH₃)₃), 31.5 (CH₂, 3'-C or 4'-C), 36.8 (CH₂, 3''-C), 37.5 (CH₂, 2''-C), 78.2 (quat., 5''-C(CH₃)₃), 105.3 (CH, 6-C), 106.05 (CH, 4-C), 116.8 (CH, 8-C), 129.6 (quat., 7-C), 130.7 (CH, 9-C), 130.9 (CH, 1-C), 143.4 (quat., 9a-C), 144.5 (quat., 5a-C), 146.7 (quat., 10a-C and 2-C), 149.5 (quat., 4a-C), 156.0 (quat., 4''-C), 170.8 (quat., 1''-C), 185.1 (quat., 3-C).

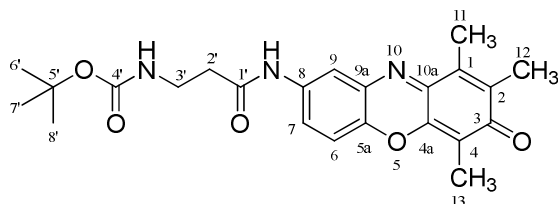
1.10.4 8-*N*-(*N'*-*t*Butoxycarbonyl- β -alanyl)amino-3*H*-phenoxazin-3-one **21a**



Prepared (**method B**) from 8-amino-3*H*-phenoxazin-3-one **2a** (0.37g, 1.75mmol). Elution with a gradient mixture of petroleum ether (60-80°C) : EtOAc (20:80 to 0:100) yielded 8-*N*-(*N'*-*t*butoxycarbonyl- β -alanyl)amino-3*H*-phenoxazin-3-one **21a** as a dark orange solid (0.36g,

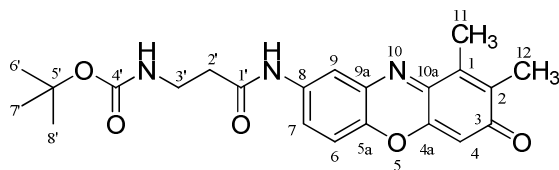
0.95mmol, 54.3%); mp 213-215°C; (found: C, 62.3; H, 5.6; N, 10.7%. C₂₀H₂₁N₃O₅ requires C, 62.65; H, 5.5; N, 11.0%); m/z 384.1 (MH)⁺, 406.1 (MNa)⁺; $\nu_{\max}/\text{cm}^{-1}$ 3385 and 3304 (N-H), 1683 and 1644 (C=O), 1172 and 1136 (C-O); δ_{H} (300 MHz, d₆-DMSO) 1.38 (9H, s, C(CH₃)₃), 2.51 (2H, t, J = 7.8Hz, 2'-H), 3.25 (2H, q, J = 6.9Hz, 3'-H), 6.24 (1H, d, J = 2.1Hz, 4-H), 6.81 (1H, dd, J = 9.9, 2.1Hz, 2-H), 6.86 (1H, br. s, NH^{*t*}Boc), 7.42 (1H, d, J = 8.7Hz, 6-H), 7.52 (1H, d, J = 9.9Hz, 1-H), 7.73 (1H, dd, J = 9.0, 2.7Hz, 7-H), 8.14 (1H, d, J = 2.7Hz, 9-H), 10.20 (1H, s, NH-Ar); δ_{C} (75 MHz, d₆-DMSO) 28.75 (CH₃, 6'/7'/8'-C(CH₃)₃), 37.0 (CH₂, 3'-C), 37.35 (CH₂, 2'-C), 78.2 (quat., 5'-C(CH₃)₃), 106.1 (CH, 4-C), 116.6 (CH, 6-C), 119.3 (CH, 9-C), 124.7 (CH, 7-C), 133.3 (quat., 9a-C), 135.3 (2 × CH, 1-C and 2-C), 137.1 (quat., 8-C), 139.65 (quat., 5a-C), 149.2 (quat., 10a-C), 150.1 (quat., 4a-C), 156.1 (quat., 4'-C), 170.2 (quat., 1'-C), 185.9 (quat., 3-C).

1.10.5 8-*N*-(*N'*-^{*t*}Butoxycarbonyl-β-alanyl)amino-1,2,4-trimethyl-3*H*-phenoxazin-3-one **21b**



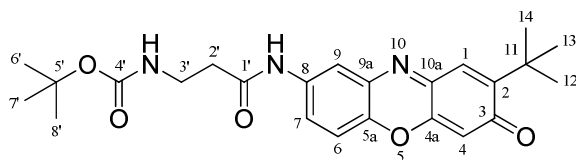
Prepared (**method B**) from 8-amino-1,2,4-trimethyl-3*H*-phenoxazin-3-one **2b** (0.67g, 2.65mmol). Elution with petroleum ether (60-80°C) : EtOAc (30:70) yielded 8-*N*-(*N'*-^{*t*}butoxycarbonyl-β-alanyl)amino-1,2,4-trimethyl-3*H*-phenoxazin-3-one **21b** (0.38g, 0.98mmol, 37.0%) as a dark orange solid. Recrystallization from EtOAc produced a microcrystalline orange solid; mp 195-198°C; (found: C, 64.75; H, 6.65; N, 9.7%. C₂₃H₂₇N₃O₅ requires C, 64.9; H, 6.4; N, 9.9%); m/z 426.2 (MH)⁺, 448.2 (MNa)⁺; $\nu_{\max}/\text{cm}^{-1}$ 3333 (N-H), 1713, 1690 and 1650 (C=O), 1167 (C-O); δ_{H} (300 MHz, d₆-DMSO) 1.42 (9H, s, C(CH₃)₃), 1.98 (3H, s, 13-H), 2.07 (3H, s, 12-H), 2.33 (3H, s, 11-H), 2.545 (2H, t, J = 6.9Hz, 2'-H), 3.32 (2H, q, J = 6.6Hz, 3'-H), 6.49 (1H, br. s, NH^{*t*}Boc), 7.32 (1H, d, J = 8.7Hz, 6-H), 7.64 (1H, dd, J = 8.7, 2.1Hz, 7-H), 8.09 (1H, d, J = 1.8Hz, 9-H), 9.90 (1H, s, Ar-NHCO); δ_{C} (75 MHz, d₆-DMSO) 7.9 (CH₃, 13-C), 12.8 (CH₃, 11-C), 13.2 (CH₃, 12-C), 28.8 (CH₃, 6'/7'/8'-C(CH₃)₃), 37.3 (CH₂, 3'-C), 37.5 (CH₂, 2'-C), 78.3 (quat., 5'-C(CH₃)₃), 113.0 (quat., 4-C), 116.0 (CH, 6-C), 119.8 (CH, 9-C), 123.7 (CH, 7-C), 132.55 (quat., 9a-C), 136.55 (quat., 1-C or 2-C), 136.9 (quat., 8-C), 138.9 (quat., 1-C or 2-C), 140.1 (quat., 5a-C), 145.6 (quat., 4a-C), 149.1 (quat., 10a-C), 156.0 (quat., 4'-C), 170.1 (quat., 1'-C), 184.4 (quat., 3-C).

1.10.6 8-*N*-(*N'*-*t*Butoxycarbonyl- β -alanyl)amino-1,2-dimethyl-3*H*-phenoxazin-3-one **21c**



Prepared (**method B**) from 8-amino-1,2-dimethyl-3*H*-phenoxazin-3-one **2c** (0.27g, 1.14mmol). Elution with petroleum ether (60-80°C) : EtOAc : (30:70) yielded 8-*N*-(*N'*-*t*butoxycarbonyl- β -alanyl)amino-1,2-dimethyl-3*H*-phenoxazin-3-one **21c** as a bright orange solid (0.46g, 1.12mmol, 98.3%). Recrystallization from EtOAc produced a microcrystalline orange solid; mp 216-217°C; (found: C, 64.2; H, 6.2; N, 10.2%. C₂₂H₂₅N₃O₅ requires C, 64.2; H, 6.1; N, 10.2%); *m/z* 412.1 (*MH*)⁺, 434.1 (*MNa*)⁺; $\nu_{\max}/\text{cm}^{-1}$ 3337 (N-H), 2973 and 2927 (C-H), 1700, 1679 and 1647 (C=O), 1166 (C-O); δ_{H} (300 MHz, d₆-DMSO) 1.31 (9H, s, C(CH₃)₃), 1.95 (3H, s, CH₃, 12-H), 2.24 (3H, s, CH₃, 11-H), 2.425 (2H, t, *J* = 7.2 Hz, CH₂, 2'-H), 3.175 (2H, q, *J* = 7.2 Hz, 3'-H), 6.06 (1H, s, 4-H), 6.78 (1H, br. s, NH^{*t*}Boc), 7.28 (1H, d, *J* = 8.7Hz, 6-H), 7.53 (1H, dd, *J* = 9.0, 2.4Hz, 7-H), 8.08 (1H, d, *J* = 2.4Hz, 9-H), 10.06 (1H, s, NH-Ar); δ_{C} (75 MHz, d₆-DMSO) 13.0 (CH₃, 11-C or 12-C), 13.15 (CH₃, 11-C or 12-C), 28.7 (CH₃, 6'/7'/8'-C(CH₃)₃), 37.0 (CH₂, 3'-C), 37.3 (CH₂, 2'-C), 78.15 (quat., 5'-C(CH₃)₃), 104.9 (CH, 4-C), 116.2 (CH, 6-C), 119.3 (CH, 9-C), 123.8 (CH, 7-C), 132.7 (quat., 9a-C), 136.8 (quat., 8-C), 137.8 (quat., 1-C), 139.4 (quat., 2-C or 5a-C), 139.5 (quat., 2-C or 5a-C), 149.0 (quat., 10a-C), 149.4 (quat., 4a-C), 156.05 (quat., 4'-C), 170.1 (quat., 1'-C), 184.8 (quat., 3-C).

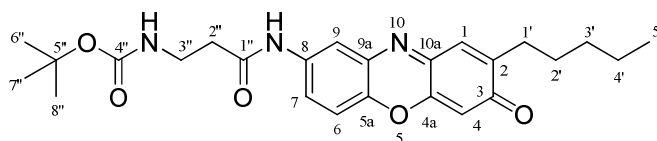
1.10.7 8-*N*-(*N'*-*t*Butoxycarbonyl- β -alanyl)amino-2-*t*butyl-3*H*-phenoxazin-3-one **21d**



Prepared (**method B**) from 8-amino-2-*t*butyl-3*H*-phenoxazin-3-one **2d** (0.53g, 1.96mmol). Elution with petroleum ether (60-80°C) : EtOAc (30:70) yielded 8-*N*-(*N'*-*t*butoxycarbonyl- β -alanyl)amino-2-*t*butyl-3*H*-phenoxazin-3-one **21d** (0.53g, 1.21mmol, 61.7%) as a dark orange solid; mp 191.5-193.5°C; (found: C, 65.5; H, 6.8; N, 9.5%. C₂₄H₂₉N₃O₅ requires C, 65.6; H, 6.65; N, 9.6%); *m/z* 438.1 (*M-H*)⁻; $\nu_{\max}/\text{cm}^{-1}$ 3340 and 3304 (N-H), 2962 (C-H), 1682 and 1648 (C=O), 1167 (C-O); δ_{H} (300 MHz, d₆-DMSO) 1.375 (9H, s, 12/13/14-C(CH₃)₃), 1.44 (9H, s, 6'/7'/8'-C(CH₃)₃), 2.57 (2H, t, *J* = 7.2Hz, 2'-H), 3.31 (2H, q, *J* = 7.2Hz, 3'-H), 6.21 (1H, s, 4-H), 6.90 (1H, br. s, NH^{*t*}Boc), 7.29 (1H, s, 1-H), 7.78 (1H, dd, *J* = 9.0, 2.4Hz, 7-H), 8.17

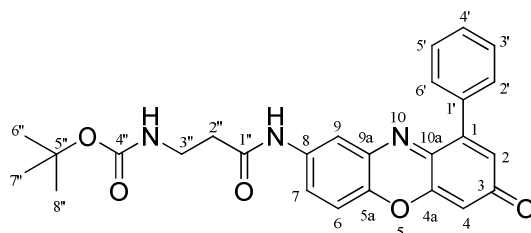
(1H, d, $J = 2.4$ Hz, 9-H), 10.24 (1H, s, NH -Ar); δ_C (75 MHz, d_6 -DMSO) 28.7 (CH_3 , 6'/7'/8'-C(CH_3)₃), 29.4 (CH_3 , 12/13/14-C(CH_3)₃), 35.7 (quat., 11-C(CH_3)₃), 37.0 (CH_2 , 3'-C), 37.3 (CH_2 , 2'-C), 78.1 (quat., 5'-C(CH_3)₃), 107.4 (CH , 4-C), 116.5 (CH , 6-C), 119.1 (CH , 9-C), 124.1 (CH , 7-C), 129.8 (CH , 1-C), 133.5 (quat., 9a-C), 137.0 (quat., 8-C), 139.4 (quat., 5a-C), 148.0 (quat., 4a-C or 10a-C), 149.6 (quat., 4a-C or 10a-C), 154.05 (quat., 2-C), 156.05 (quat., 4'-C), 170.1 (quat., 1'-C), 185.5 (quat., 3-C).

1.10.8 8-*N*-(*N'*-*t*Butoxycarbonyl- β -alanyl)amino-2-pentyl-3*H*-phenoxazin-3-one **21e**



Prepared (**method B**) from 8-amino-2-pentyl-3*H*-phenoxazin-3-one **2e** (0.50g, 1.78mmol). Elution with a gradient mixture of petroleum ether (60-80°C) : EtOAc (35:65 to 20:80) yielded 8-*N*-(*N'*-*t*butoxycarbonyl- β -alanyl)amino-2-pentyl-3*H*-phenoxazin-3-one **21e** as an orange solid (0.73g, 1.60mmol, 90.1%); mp 176-179°C; (found: C, 66.2; H, 6.8; N, 9.1%. $C_{25}H_{31}N_3O_5$ requires C, 66.2; H, 6.9; N, 9.3%); m/z 454.3 (MH)⁺, 476.3 (MNa)⁺; ν_{max}/cm^{-1} 3322 (N-H), 2954 and 2930 (C-H), 1684, 1658 and 1648 (C=O), 1171 (C-O); δ_H (300 MHz, d_6 -DMSO) 0.78 (3H, t, $J = 6.6$ Hz, 5'-H), 1.21-1.23 (4H, m, 3'-H and 4'-H), 1.30 (9H, s, C(CH_3)₃), 1.38-1.40 (2H, m, 2'-H), 2.34 (2H, t, $J = 7.2$ Hz, 1'-H), 2.42 (2H, t, $J = 6.6$ Hz, 2''-H), 3.19 (2H, q, $J = 6.6$ Hz, 3''-H), 6.095 (1H, s, 4-H), 6.77 (1H, br. s, NH^t Boc), 7.15 (1H, s, 1-H), 7.28 (1H, d, $J = 8.7$ Hz, 6-H), 7.60 (1H, dd, $J = 8.7, 2.4$ Hz, 7-H), 8.00 (1H, d, $J = 2.1$ Hz, 9-H), 10.08 (1H, s, NH -Ar); δ_C (75 MHz, d_6 -DMSO) 14.3 (CH_3 , 5'-C), 22.4 (CH_2 , 3'-C or 4'-C), 28.0 (CH_2 , 2'-C), 28.7 (CH_3 , 6''/7''/8''-C(CH_3)₃), 29.4 (CH_2 , 1'-C), 31.5 (CH_2 , 3'-C or 4'-C), 36.95 (CH_2 , 3''-C), 37.3 (CH_2 , 2''-C), 78.1 (quat., 5''-C(CH_3)₃), 105.8 (CH , 4-C), 116.5 (CH , 6-C), 119.0 (CH , 9-C), 124.0 (CH , 7-C), 130.7 (CH , 1-C), 133.3 (quat., 9a-C), 137.0 (quat., 8-C), 139.3 (quat., 5a-C), 147.6 (quat., 2-C), 149.2 (quat., 4a-C or 10a-C), 149.3 (quat., 4a-C or 10a-C), 156.0 (quat., 4''-C), 170.05 (quat., 1''-C), 185.1 (quat., 3-C).

1.10.9 8-*N*-(*N'*-*t*Butoxycarbonyl- β -alanyl)amino-1-phenyl-3*H*-phenoxazin-3-one **21f**



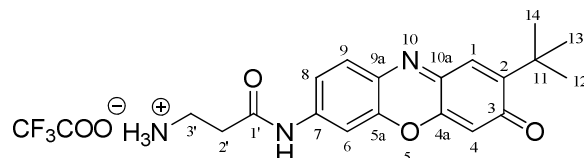
Prepared (**method B**) from 8-amino-1-phenyl-3*H*-phenoxazin-3-one **2f** (0.12g, 0.39mmol). Elution used a gradient mixture of petroleum ether (60-80°C) : EtOAc (50:50 to 40:60) yielding 8-*N*-(*N*'-*t*-butoxycarbonyl-β-alanyl)amino-1-phenyl-3*H*-phenoxazin-3-one **21f** as an orange-red solid (0.12g, 0.27mmol, 69.6%); mp 241-243°C; (found: C, 67.7; H, 5.6; N, 8.9%. C₂₆H₂₅N₃O₅ requires C, 68.0; H, 5.5; N, 9.1%); *m/z* 460.2 (*MH*)⁺; *v*_{max}/cm⁻¹ 3422 and 3263 (N-H), 1679 and 1639 (C=O), 1167 (C-O); δ_H (300 MHz, d₆-DMSO) 1.385 (9H, s, C(CH₃)₃), 2.50 (2H, t, *J* = 7.2Hz, 2''-H), 3.24 (2H, q, *J* = 6.9Hz, 3''-H), 6.32 (1H, d, *J* = 2.1Hz, 4-H), 6.80 (1H, d, *J* = 2.1Hz, 2-H), 6.86 (1H, br. s, NH'Boc), 7.45 (1H, d, *J* = 9.0Hz, 6-H), 7.49-7.51 (3H, m, 3'-H, 4'-H and 5'-H), 7.59-7.63 (2H, m, 2'-H and 6'-H), 7.68 (1H, dd, *J* = 9.0, 2.4Hz, 7-H), 8.12 (1H, d, *J* = 2.4Hz, 9-H), 10.17 (1H, s, NH-Ar); δ_C (75 MHz, d₆-DMSO) 28.7 (CH₃, 6''/7''/8''-C(CH₃)₃), 37.0 (CH₂, 3''-C), 37.3 (CH₂, 2''-C), 78.1 (quat., 5''-C(CH₃)₃), 106.0 (CH, 4-C), 116.5 (CH, 6-C), 119.6 (CH, 9-C), 124.8 (CH, 7-C), 128.4 (CH, 3'-C and 5'-C), 129.3 (CH, 4'-C), 130.55 (CH, 2'-C and 6'-C), 133.0 (quat., 9a-C), 133.2 (CH, 2-C), 135.2 (quat., 1-C), 136.95 (quat., 8-C), 139.5 (quat., 5a-C), 145.2 (quat., 1'-C), 148.25 (quat., 10a-C), 150.4 (quat., 4a-C), 156.0 (quat., 4''-C), 170.1 (quat., 1''-C), 184.9 (quat., 3-C).

1.11 Synthesis of 7-*N*- and 8-*N*-(β-alanyl)amino-3*H*-phenoxazin-3-one TFA salts **22a-b** and **23a-f**

1.11.1 General procedure

To the appropriately substituted 7-*N*- or 8-*N*-(*N*'-*t*-butoxycarbonyl-β-alanyl)amino-alkyl-3*H*-phenoxazin-3-one **20a-b** or **21a-f** in a round bottomed flask, an excess of neat TFA was added and the resulting solution was swirled for one minute. The TFA was evaporated *in vacuo*, then sequential portions of MeOH were added to the residue and evaporated. The residue was redissolved in minimal MeOH and diluted with Et₂O. After overnight standing, the microcrystalline solid that formed was collected and washed with Et₂O.

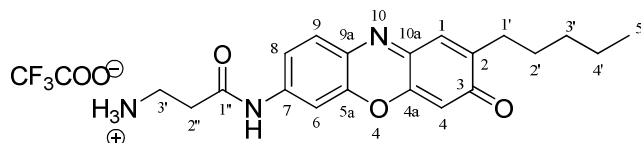
1.11.2 7-*N*-(β-Alanyl)amino-2-*t*-butyl-3*H*-phenoxazin-3-one TFA salt **22a**



Prepared from 7-*N*-(*N*'-*t*-butoxycarbonyl-β-alanyl)amino-2-*t*-butyl-3*H*-phenoxazin-3-one **20a** (0.11g, 0.25mmol). 7-*N*-(β-Alanyl)amino-2-*t*-butyl-3*H*-phenoxazin-3-one TFA salt **22a** was isolated as dark-red solid (0.105g, 0.23mmol, 92.0%); mp 192-195°C; HRMS (Found (*M*)⁺,

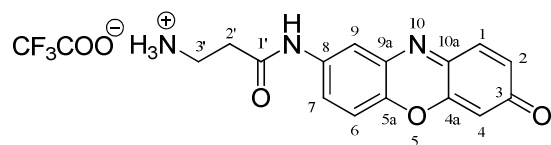
340.1657. Calc. for $C_{19}H_{22}N_3O_3$: (M)⁺, 340.1656); m/z 340.2 (M)⁺; $\nu_{\max}/\text{cm}^{-1}$ 3180 (N-H), 3028 (N⁺-H), 2961 (C-H), 1672 (C=O); δ_H (300 MHz, d_6 -DMSO) 1.235 (9H, s, $C(CH_3)_3$), 2.73 (2H, t, $J = 6.6\text{Hz}$, 2'-H), 3.07 (2H, t, $J = 6.6\text{Hz}$, 3'-H), 6.07 (1H, s, 4-H), 7.12 (1H, s, 1-H), 7.42 (1H, dd, $J = 8.7, 1.8\text{Hz}$, 8-H), 7.62 (1H, d, $J = 8.7\text{Hz}$, 9-H), 7.77 (1H, d, $J = 2.1\text{Hz}$, 6-H), 7.84 (3H, br. s, NH_3^+), 10.69 (1H, s, $NH\text{-Ar}$); δ_C (75 MHz, d_6 -DMSO) 29.4 (CH_3 , 12/13/14- $C(CH_3)_3$), 34.1 (CH_2 , 2'-C), 35.3 (CH_2 , 3'-C), 35.6 (quat., 11- $C(CH_3)_3$), 105.7 (CH, 6-C), 107.6 (CH, 4-C), 116.9 (CH, 8-C), 129.8 (CH, 1-C), 129.89 (quat., 7-C), 130.7 (CH, 9-C), 143.1 (quat., 7-C), 144.4 (quat., 5a-C), 147.2 (quat., 10a-C), 148.7 (quat., 4a-C), 153.3 (quat., 2-C), 169.7 (quat., 1'-C), 185.35 (quat., 3-C). HPLC-MS spectra: Figure S2; 1H NMR spectrum: Figure S9.

1.11.3 7-*N*-(β -Alanyl)amino-2-pentyl-3*H*-phenoxazin-3-one TFA salt **22b**



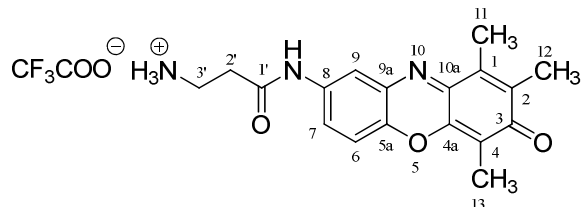
Prepared from 7-*N*-(N' -*t*-butoxycarbonyl- β -alanyl)amino-2-pentyl-3*H*-phenoxazin-3-one **20b** (0.14g, 0.30mmol). 7-*N*-(β -Alanyl)amino-2-pentyl-3*H*-phenoxazin-3-one TFA salt **22b** was isolated as a brown-red solid with a green metallic shine (0.12g, 0.27mmol, 88.5%); mp 213-223°C; HRMS (Found (M)⁺, 354.1815. Calc. for $C_{20}H_{24}N_3O_3$: (M)⁺, 354.1812); m/z 354.2 (M)⁺ $\nu_{\max}/\text{cm}^{-1}$ 3263 (N-H), 3188-3060 (N⁺-H), 2928 (C-H), 1674 (C=O), 1651 (C=O); δ_H (300 MHz, d_6 -DMSO) 0.88 (3H, t, $J = 6.9\text{Hz}$, 5'-H), 1.30-1.33 (4H, m, 3'-H and 4'-H), 1.485-1.53 (2H, m, 2'-H), 2.45 (2H, t, $J = 7.5\text{Hz}$, 1'-H), 2.82 (2H, t, $J = 6.3\text{Hz}$, 2''-H), 3.15 (2H, t, $J = 6.3\text{Hz}$, 3''-H), 6.25 (1H, s, 4-H), 7.26 (1H, s, 1-H), 7.50 (1H, dd, $J = 8.7, 1.8\text{Hz}$, 8-H), 7.73 (1H, d, $J = 8.7\text{Hz}$, 9-H), 7.89 (1H, d, $J = 1.8\text{Hz}$, 6-H), 7.97 (3H, br. s, NH_3^+), 10.83 (1H, s, $NH\text{-Ar}$); δ_C (75 MHz, d_6 -DMSO) 14.4 (CH_3 , 5'-C), 22.4 (CH_2 , 3'-C or 4'-C), 28.1 (CH_2 , 2'-C), 29.4 (CH_2 , 1'-C), 31.5 (CH_2 , 3'-H or 4'-H), 34.1 (CH_2 , 2''-C), 35.2 (CH_2 , 3''-C), 105.5 (CH, 6-C), 106.1 (CH, 4-C), 116.8 (CH, 8-C), 129.8 (quat., 7-C), 130.8 (quat., 9-C or 1-C), 130.9 (quat., 9-C or 1-C), 143.1 (quat., 9a-C), 144.4 (quat. 5a-C), 146.7 (quat., 2-C or 10a-C), 146.8 (quat., 2-C or 10a-C), 149.4 (quat., 4a-C), 169.7 (quat., 1''-C), 185.1 (quat., 3-C).

1.11.4 8-*N*-(β-Alanyl)amino-3*H*-phenoxazin-3-one TFA salt **23a**



The title compound was prepared as described from 8-*N*-(*N*'-*t*-butoxycarbonyl-β-alanyl)amino-3*H*-phenoxazin-3-one **21a** (0.16g, 0.43mmol). 8-*N*-(β-Alanyl)amino-3*H*-phenoxazin-3-one TFA salt **23a** was isolated as a dark red solid (0.14g, 0.35mmol, 80.7%); mp 167-170°C; HRMS (Found (M)⁺, 284.1031. Calc. for C₁₅H₁₄N₃O₃: (M)⁺, 284.1030); m/z 284.0 (M)⁺; $\nu_{\max}/\text{cm}^{-1}$ 3408-2907 (N⁺-H), 3053 (N-H), 1671 and 1643 (C=O); δ_{H} (300 MHz, d₆-DMSO) 2.77 (2H, t, J = 6.6Hz, 2'-H), 3.14 (2H, br. s, 3'-H), 6.245 (1H, d, J = 1.8Hz, 4-H), 6.835 (1H, dd, J = 9.9, 1.5Hz, 2-H), 7.44 (1H, d, J = 9.0Hz, 6-H), 7.52 (1H, d, J = 9.9Hz, 1-H), 7.77 (1H, dd, J = 9.0, 2.1Hz, 7-H), 7.98 (3H, br. s, NH₃⁺), 8.15 (1H, d, J = 2.4Hz, 9-H), 10.56 (1H, s, NH-Ar); δ_{C} (75 MHz, d₆-DMSO) 33.8 (CH₂, 2'-C), 35.4 (CH₂, 3'-C), 106.1 (CH, 4-C), 116.7 (CH, 6-C), 119.4 (CH, 9-C), 124.7 (CH, 7-C), 133.3 (quat., 9a-C), 135.3 (CH, 1-C and 2-C), 136.8 (quat., 8-C), 139.8 (quat., 5a-C), 149.2 (quat., 10a-C), 150.1 (quat., 4a-C), 169.05 (quat., 1'-C), 185.95 (quat., 3-C). ¹H NMR spectrum: Figure S11.

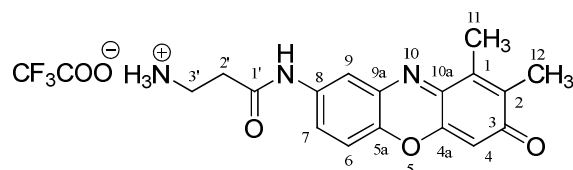
1.11.5 8-*N*-(β-Alanyl)amino-1,2,4-trimethyl-3*H*-phenoxazin-3-one TFA salt **23b**



Prepared from 8-*N*-(*N*'-*t*-butoxycarbonyl-β-alanyl)amino-1,2,4-trimethyl-3*H*-phenoxazin-3-one **21b** (0.06g, 0.16mmol). 8-*N*-(β-Alanyl)amino-1,2,4-trimethyl-3*H*-phenoxazin-3-one TFA salt **23b** was isolated as a red solid (0.06g, 0.14mmol, 91.2%); mp 231-235°C; HRMS (Found (M)⁺, 326.1501. Calc. for C₁₈H₂₀N₃O₃: (M)⁺, 326.1499); m/z 326.2 (M)⁺; $\nu_{\max}/\text{cm}^{-1}$ 3322 (N-H), 3054 (N⁺-H), 1670 and 1649 (C=O); δ_{H} (300 MHz, d₆-DMSO) 1.97 (3H, s, 13-H), 2.07 (3H, s, 12-H), 2.33 (3H, s, 11-H), 2.76 (2H, t, J = 6.6Hz, 2'-H), 3.15 (2H, t, J = 6.3Hz, 3'-H), 7.41 (1H, d, J = 8.7Hz, 6-H), 7.64 (1H, dd, J = 8.7, 2.1Hz, 7-H), 7.855 (3H, br. s, NH₃⁺), 8.15 (1H, d, J = 2.1Hz, 9-H), 10.40 (1H, s, NH-Ar); δ_{C} (75 MHz, d₆-DMSO) 7.9 (CH₃, 13-C), 12.8 (CH₃, 12-C), 13.2 (CH₃, 11-C), 33.9 (CH₂, 2'-C), 35.8 (CH₂, 3'-C), 113.2 (quat., 4-C), 116.1 (CH, 6-C), 120.0 (CH, 9-C), 123.8 (CH, 7-C), 132.6 (quat., 9a-C), 136.2 (quat., 8-C), 136.9

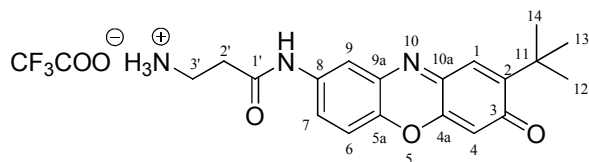
(quat., 1-C or 2-C), 139.0 (quat., 1-C or 2-C), 140.2 (quat., 5a-C), 145.5 (quat., 4a-C), 149.15 (quat., 10a-C), 169.0 (quat., 1'-C), 184.4 (quat., 3-C). HPLC-MS spectra: Figure S4; ^1H NMR spectrum: Figure S12.

1.11.6 8-*N*-(β -Alanyl)amino-1,2-dimethyl-3*H*-phenoxazin-3-one TFA salt **23c**



The title compound was prepared as described from 8-*N*-(*N*'-*t*-butoxycarbonyl- β -alanyl)amino-1,2-dimethyl-3*H*-phenoxazin-3-one **21c** (0.20g, 0.49mmol). 8-*N*-(β -Alanyl)amino-1,2-dimethyl-3*H*-phenoxazin-3-one TFA salt **23c** was isolated as an orange-red solid (0.20g, 0.47mmol, 96.1%); mp 202-207°C; HRMS (Found (M)⁺, 312.1344. Calc. for C₁₇H₁₈N₃O₃: (M)⁺, 312.1343); m/z 312.2 (M ⁺); $\nu_{\text{max}}/\text{cm}^{-1}$ 3282 (N-H), 3082 (N⁺-H), 1671 and 1645 (C=O); δ_{H} (300 MHz, d₆-DMSO) 2.00 (3H, s, 12-H), 2.26 (3H, s, 11-H), 2.77 (2H, t, J = 6.6 Hz, 2'-H), 3.16 (2H, t, J = 6.6 Hz, 3'-H), 6.08 (1H, s, 4-H), 7.32 (1H, d, J = 8.7 Hz, 6-H), 7.60 (1H, dd, J = 8.7, 1.8 Hz, 7-H), 7.99 (3H, br. s, NH₃⁺), 8.11 (1H, d, J = 1.8 Hz, 9-H), 10.46 (1H, s, NH-Ar); δ_{C} (75 MHz, d₆-DMSO) 13.0 (CH₃, 11-C or 12-C), 13.05 (CH₃, 11-C or 12-C), 33.75 (CH₂, 2'-C), 35.4 (CH₂, 3'-C), 104.9 (CH, 4-C), 116.25 (CH, 6-C), 119.3 (CH, 9-C), 123.7 (CH, 7-C), 132.6 (quat., 9a-C), 136.5 (quat., 8-C), 137.7 (quat., 1-C or 2-C), 139.4 (quat., 5a-C or 1-C or 2-C), 139.45 (quat., 5a-C or 1-C or 2-C), 148.9 (quat., 4a-C or 10a-C), 149.2 (quat., 4a-C or 10a-C), 168.9 (quat., 1'-C), 184.7 (quat., 3-C). HPLC-MS spectra: Figure S5; ^1H NMR spectrum: Figure S13.

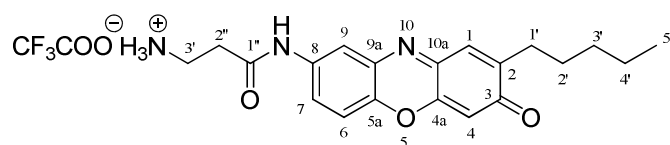
1.11.7 8-*N*-(β -Alanyl)amino-2-*t*-butyl-3*H*-phenoxazin-3-one TFA salt **23d**



Prepared from 8-*N*-(*N*'-*t*-butoxycarbonyl- β -alanyl)amino-4-*t*-butyl-3*H*-phenoxazin-3-one **21d** (0.16g, 0.37mmol). 8-*N*-(β -Alanyl)amino-4-*t*-butyl-3*H*-phenoxazin-3-one TFA salt **23d** was obtained as an orange-brown solid (0.16g, 0.35mmol, 93.5%); mp 119-126°C; HRMS (Found (M)⁺, 340.1657. Calc. for C₁₉H₂₂N₃O₃: (M)⁺, 340.1656); m/z 340.2 (M ⁺); $\nu_{\text{max}}/\text{cm}^{-1}$ 3462 (N-H), 3308-2965 (N⁺-H) and (C-H), 1678 (C=O), 1649 (C=O); δ_{H} (300 MHz, d₆-DMSO) 1.32

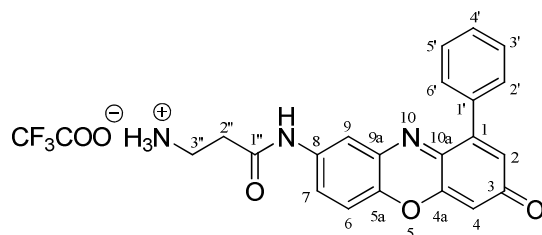
(9H, s, C(CH₃)₃), 2.78 (2H, t, *J* = 6.6Hz, 2'-H), 3.30 (2H, br. s, 3'-H), 6.15 (1H, s, 4-H), 7.225 (1H, s, 1-H), 7.42 (1H, d, *J* = 9.0Hz, 6-H), 7.74 (1H, dd, *J* = 9.0, 1.8Hz, 7-H), 7.97 (3H, br. s, NH₃⁺), 8.13 (1H, d, *J* = 1.8Hz, 9-H); δ_C (75 MHz, d₆-DMSO) 29.4 (CH₃, 12/13/14-C(CH₃)₃), 33.8 (CH₂, 2'-C), 35.4 (quat., 11-C(CH₃)₃), 35.7 (CH₂, 3'-C), 107.4 (CH, 4-C), 116.6 (CH, 6-C), 119.3 (CH, 9-C), 124.2 (CH, 1-C), 129.8 (CH, 7-C), 133.5 (quat., 9a-C), 136.6 (quat., 8-C), 139.5 (quat., 5a-C), 148.65 (quat., 4a-C or 10a-C), 149.6 (quat., 4a-C or 10a-C), 154.1 (quat., 2-C), 169.0 (quat., 1'-C), 183.2 (quat., 3-C). HPLC-MS spectra: Figure S6; ¹H NMR spectrum: Figure S14.

1.11.8 8-*N*-(β-alanyl)amino-2-pentyl-3*H*-phenoxazin-3-one TFA salt **23e**



Prepared from 8-*N*-(*N*'-t-butoxycarbonyl-β-alanyl)amino-2-pentyl-3*H*-phenoxazin-3-one **21e** (0.08g, 0.18mmol). 8-*N*-(β-Alanyl)amino-2-pentyl-3*H*-phenoxazin-3-one TFA salt **23e** was isolated as a dark red solid (0.07g, 0.15mmol, 87.0%); mp 132-139°C; HRMS (Found (*M*)⁺, 354.1813. Calc. for C₂₀H₂₄N₃O₃: (*M*)⁺, 354.1812); *m/z* 354.2 (*M*⁺); ν_{max}/cm⁻¹ 3312 (N-H), 3077 (N⁺-H), 2932-2861 (C-H), 1672 (C=O), 1649 (C=O); δ_H (300 MHz, d₆-DMSO) 0.80 (3H, t, *J* = 6.6Hz, 5'-H), 1.22-1.25 (4H, m, 3'-H and 4'-H), 1.425-1.47 (2H, m, 2'-H), 2.41 (2H, t, *J* = 8.1Hz, 1'-H), 2.67 (2H, t, *J* = 6.6Hz, 2''-H), 3.05 (2H, br. s, 3''-H), 6.21 (1H, s, 4-H), 7.27 (1H, s, 1-H), 7.40 (1H, d, *J* = 9.0Hz, 6-H), 7.65 (1H, dd, *J* = 9.0, 2.4Hz, 7-H), 7.75 (3H, br. s, NH₃⁺), 8.08 (1H, d, *J* = 2.4Hz, 9-H), 10.39 (1H, s, NH-Ar); δ_C (75 MHz, d₆-DMSO) 14.3 (CH₃, 5'-C), 22.4 (CH₂, 3'-C or 4'-C), 28.1 (CH₂, 2'-C), 29.4 (CH₂, 1'-C), 31.5 (CH₂, 3'-C or 4'-C), 33.9 (CH₂, 2''-C), 35.4 (CH₂, 3''-C), 105.9 (CH, 4-C), 116.7 (CH, 6-C), 119.2 (CH, 9-C), 124.1 (CH, 7-C), 130.9 (CH, 1-C), 133.4 (quat., 9a-C), 136.7 (quat., 8-C), 139.6 (quat., 5a-C), 147.75 (quat., 2-C), 149.4 (quat., 4a-C or 10a-C), 149.5 (quat., 4a-C or 10a-C), 169.0 (quat., 1''-C), 185.2 (quat., 3-C).

1.11.9 8-*N*-(β-Alanyl)amino-1-phenyl-3*H*-phenoxazin-3-one TFA salt **23f**



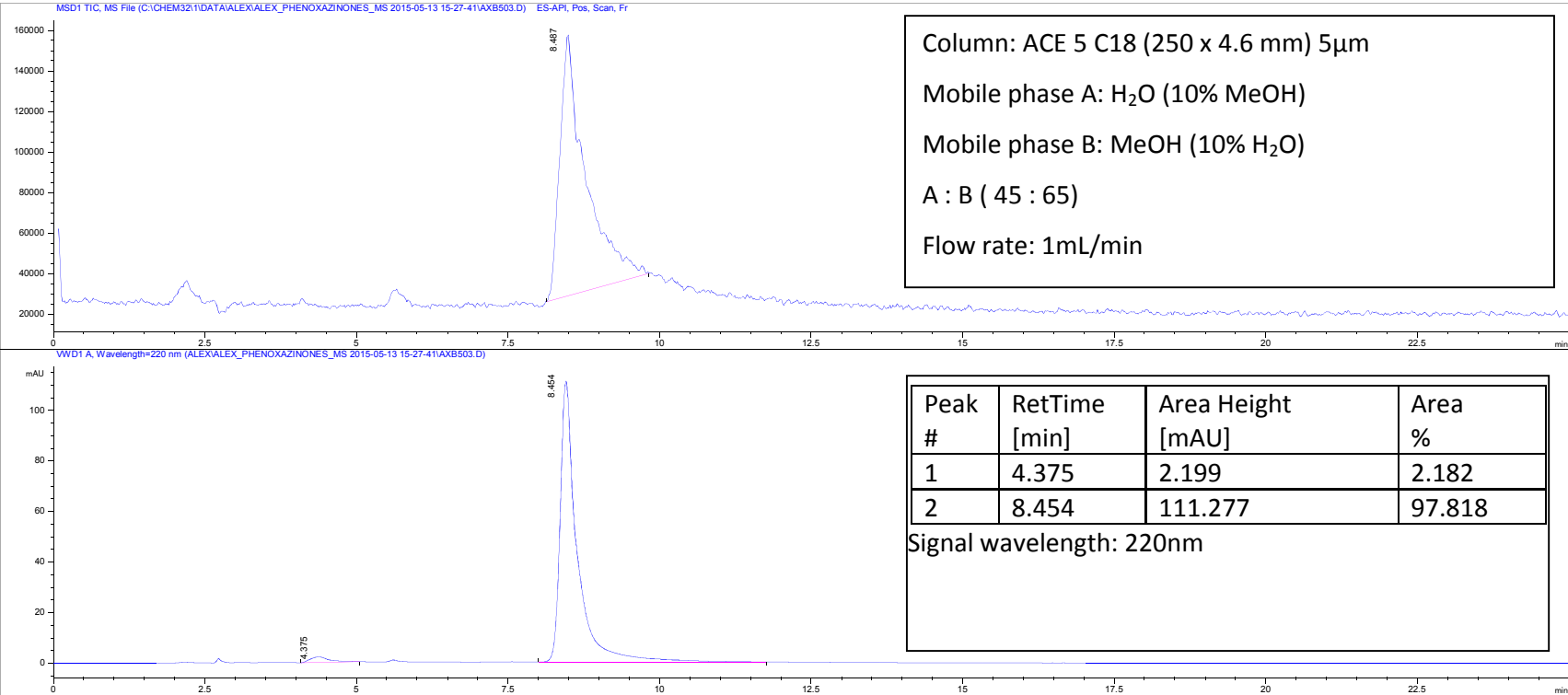
Prepared from 8-*N*-(*N'*-*t*butoxycarbonyl- β -alanyl)amino-1-phenyl-3*H*-phenoxazin-3-one **21f** (0.05g, 0.12mmol). 8-*N*-(β -Alanyl)amino-1-phenyl-3*H*-phenoxazin-3-one TFA salt **23f** was isolated as a dark red solid (0.05g, 0.10mmol, 82.2%); mp 236-243°C; HRMS (Found (*M*)⁺, 360.1345. Calc. for C₂₁H₁₈N₃O₃: (*M*)⁺, 360.1343); *m/z* 360.2 (*M*)⁺; $\nu_{\max}/\text{cm}^{-1}$ 3262 (N-H), 3068 (N⁺-H), 2903 (C-H), 1670 (C=O), 1640 (C=O); δ_{H} (300 MHz, d₆-DMSO) 2.67 (2H, t, *J* = 6.3Hz, 2''-H), 3.05 (2H, t, *J* = 6.3Hz, 3''-H), 6.23 (1H, d, *J* = 1.5Hz, 4-H), 6.72 (1H, d, *J* = 1.5Hz, 2-H), 7.37-7.42 (4H, m, 3'-H, 4'-H, 5'-H and 6-H), 7.52-7.53 (2H, m, 2'-H and 6'-H), 7.62 (1H, dd, *J* = 8.7, 1.8Hz, 7-H), 7.80 (3H, s, NH₃⁺), 8.03 (1H, d, *J* = 1.2Hz, 9-H), 10.33 (1H, s, NH-Ar); δ_{C} (75 MHz, d₆-DMSO) 33.8 (CH₂, 2''-C), 35.5 (CH₂, 3''-C), 106.1 (CH, 4-C), 116.5 (CH, 6-C), 120.0 (CH, 9-C), 125.0 (CH, 7-C), 128.35 (CH, 3'-C and 5'-C), 129.2 (CH, 4'-C), 130.5 (CH, 2'-C and 6'-C), 133.0 (quat., 9a-C), 135.2 (quat., 2-C), 136.6 (quat., 1-C), 139.7 (quat., 8-C), 145.3 (quat., 5a-C), 148.4 (quat., 10a-C), 150.35 (quat., 4a-C), 169.1 (quat., 1''-C), 184.9 (quat., 3-C). HPLC-MS spectra: Figure S8; ¹H NMR spectrum: Figure S16.

1.12 References

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1.14 Figures: Selected LC-MS and NMR spectra of key intermediates and products

Figure S1. HPLC-MS Spectra of 2b.



*MSD1 SPC, time=8.509 of C:\CHEM32\1\DATA\ALEX_ALEX_PHENOXAZINONES_MS 2015-05-13 15-27-41\AXB503.D ES-API, Pos, Scan

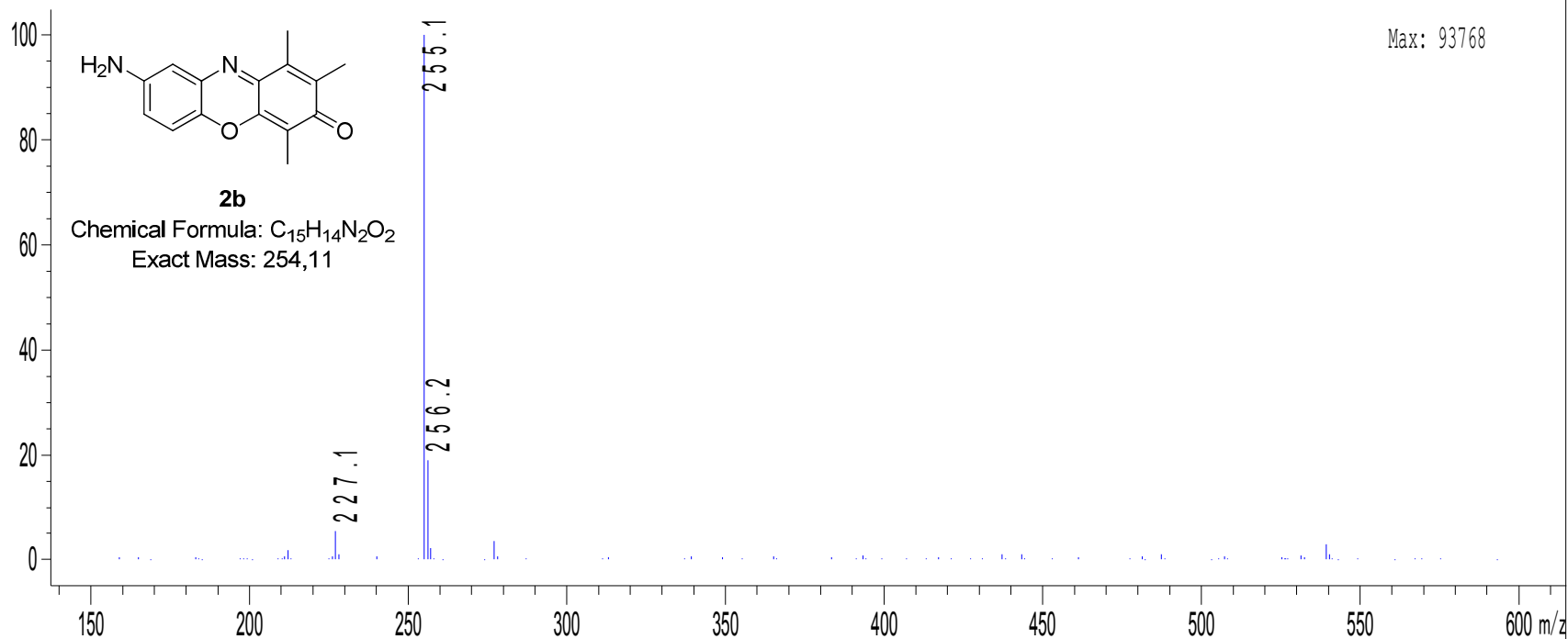
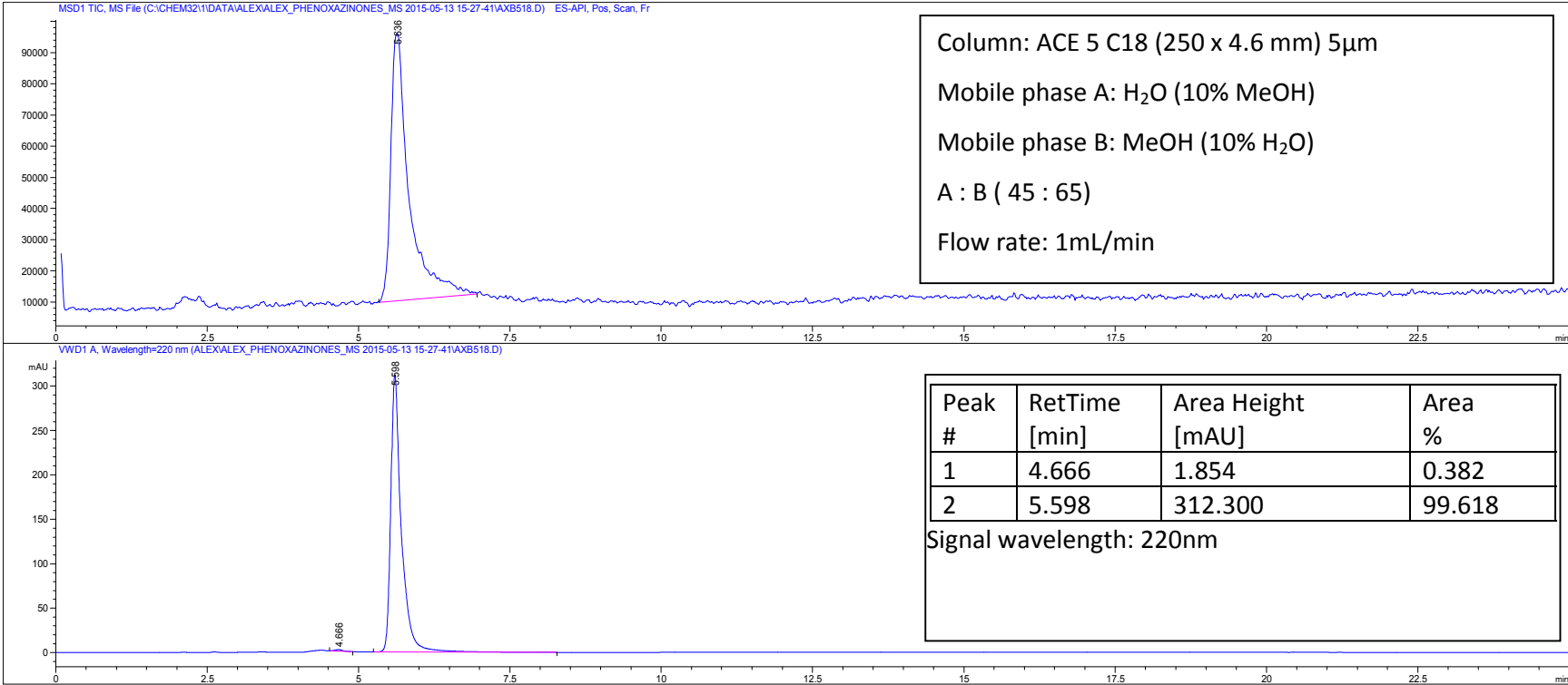


Figure S2. HPLC-MS Spectra of **2c**.



*MSD1 SPC, time=5.661 of C:\CHEM32\1\DATA\ALEX\ALEX_PHENOXAZINONES_MS 2015-05-13 15-27-41\XB518.D ES-API, Pos, Scan

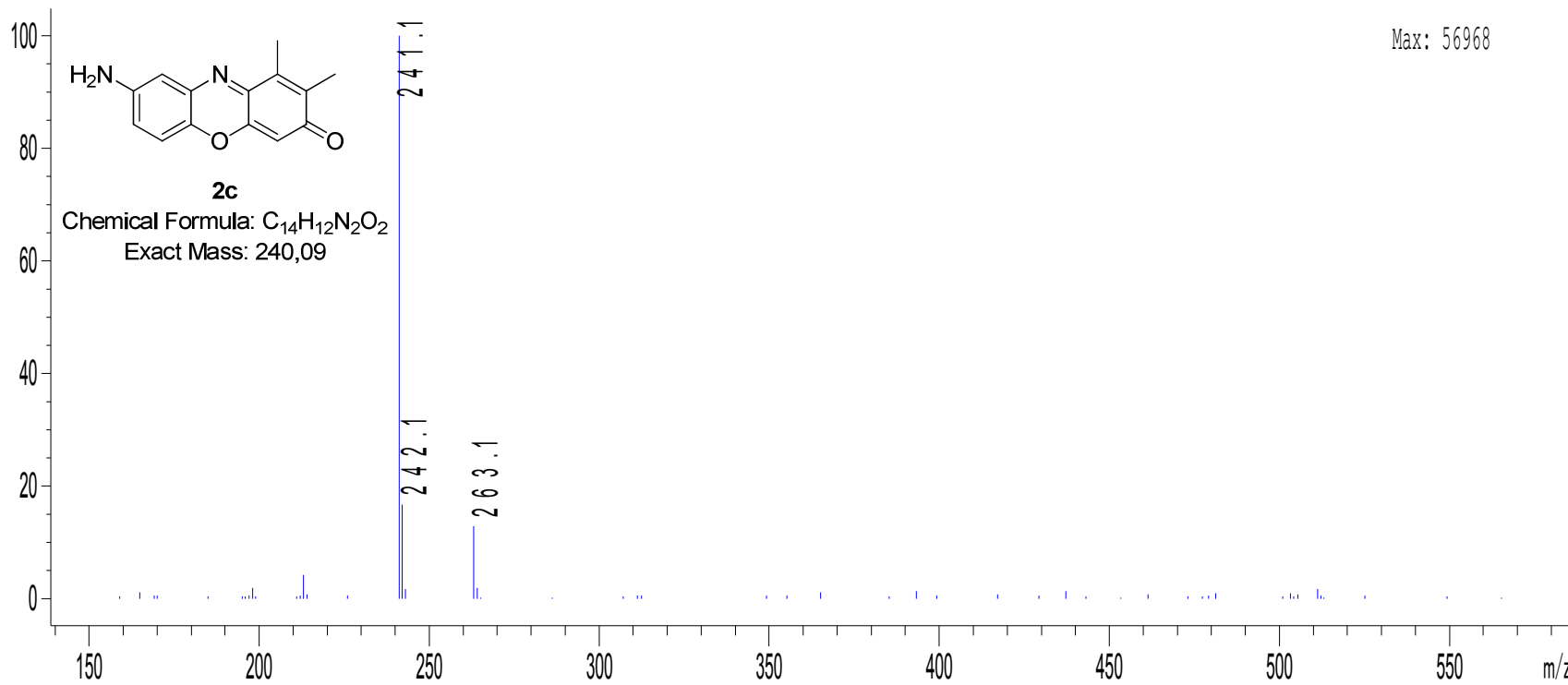
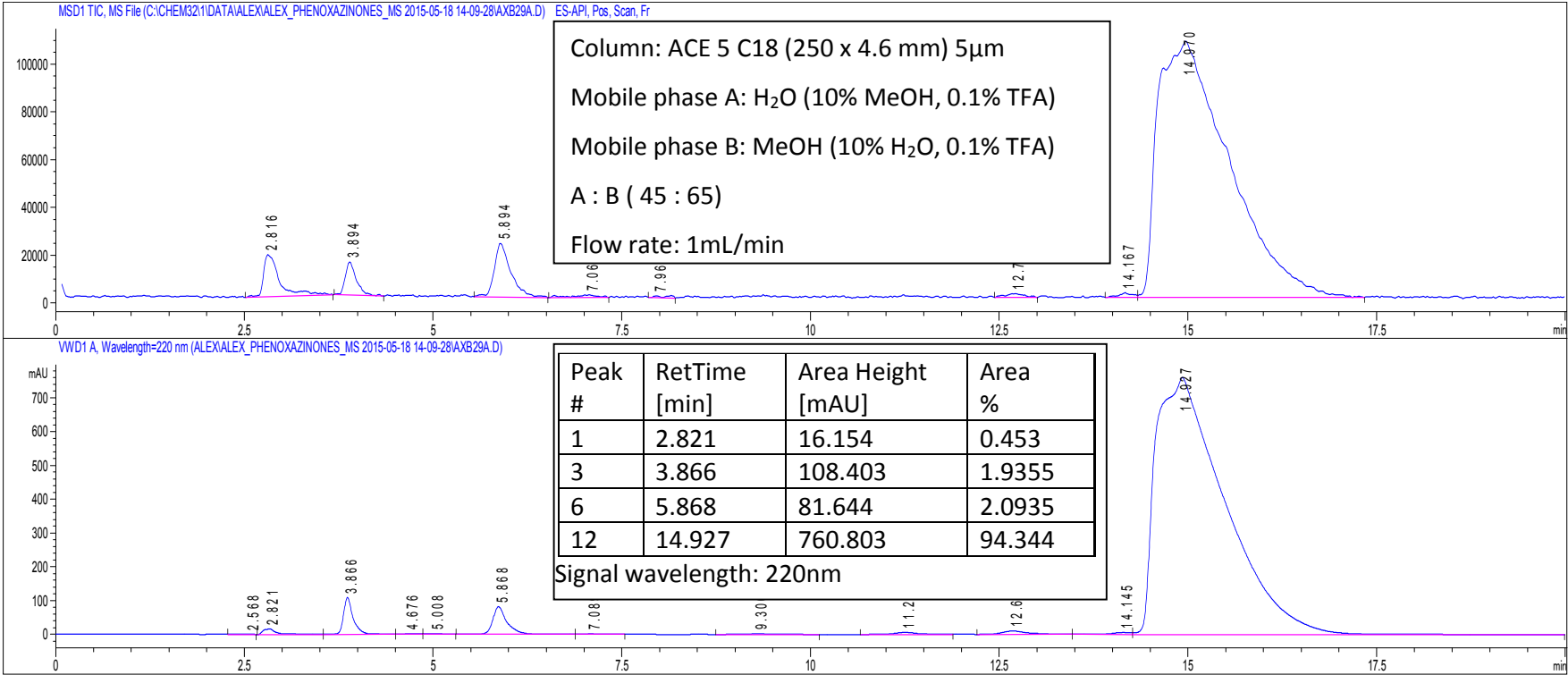


Figure S3. HPLC-MS Spectra of **22a**.



*MSD1 SPC, time=14.846 of C:\CHEM32\1\DATA\ALEX\ALEX_PHENOXAZINONES_MS 2015-05-18 14-09-28\AXB29A.D ES-API, Pos, Sca

Max: 61024

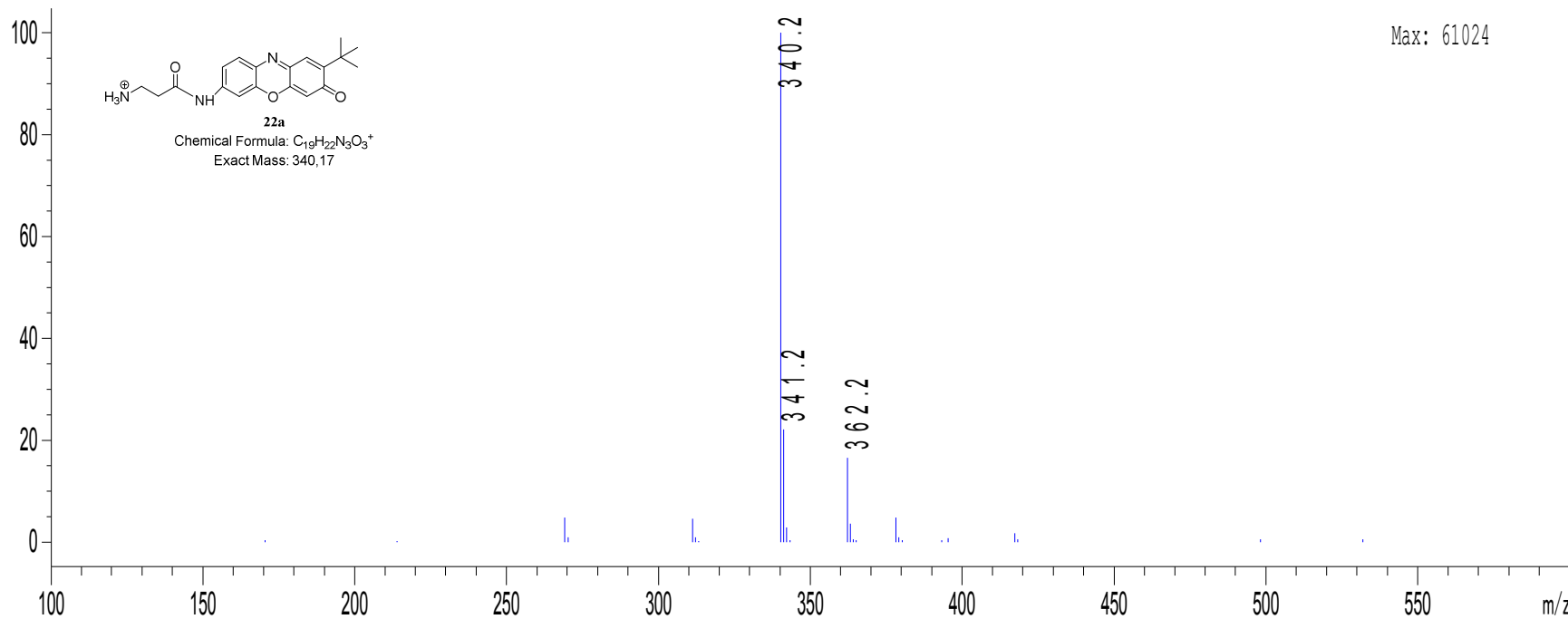
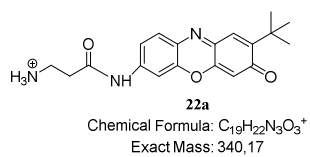
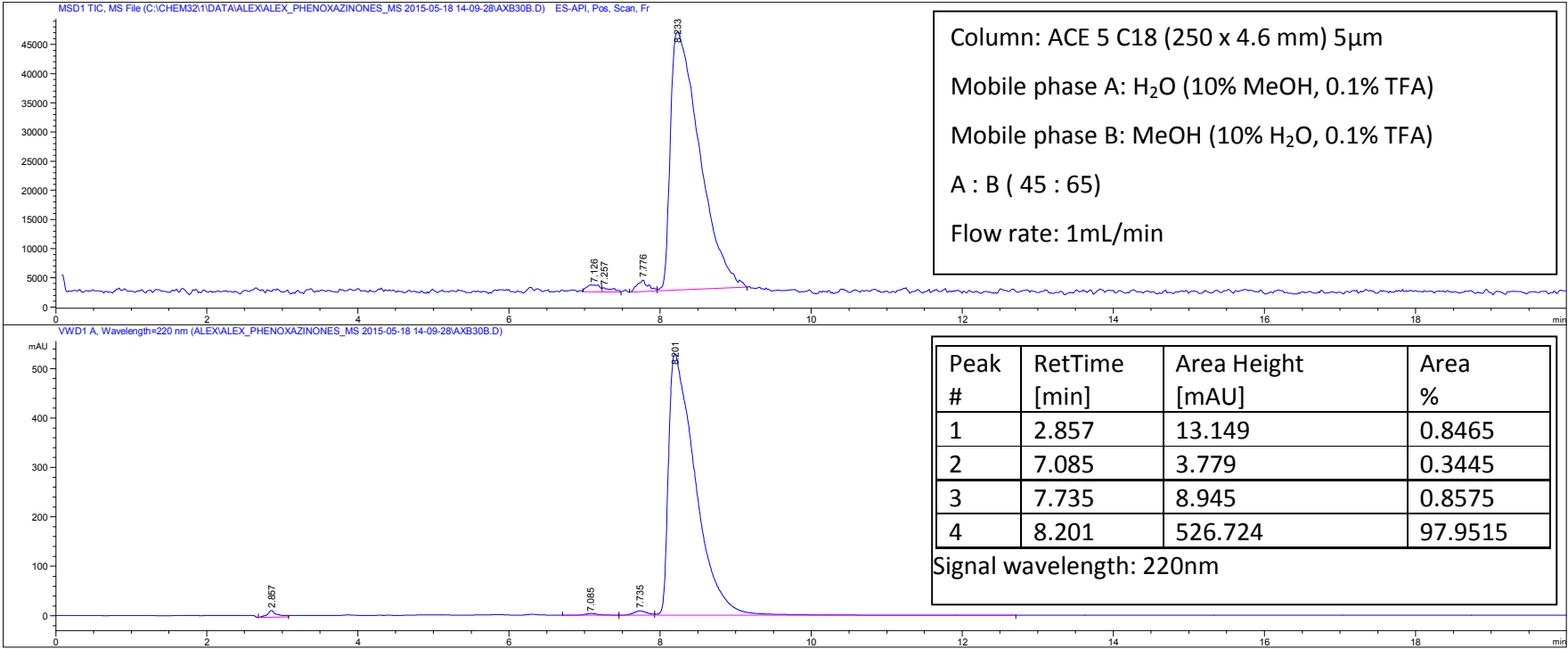


Figure S4. HPLC-MS Spectra of 23b.



*MSD1 SPC, time=8.256 of C:\CHEM32\1\DATA\ALEX_ALEX_PHENOXAZINONES_MS 2015-05-18 14-09-28\AXB30B.D+BSB ES-API, Pos,

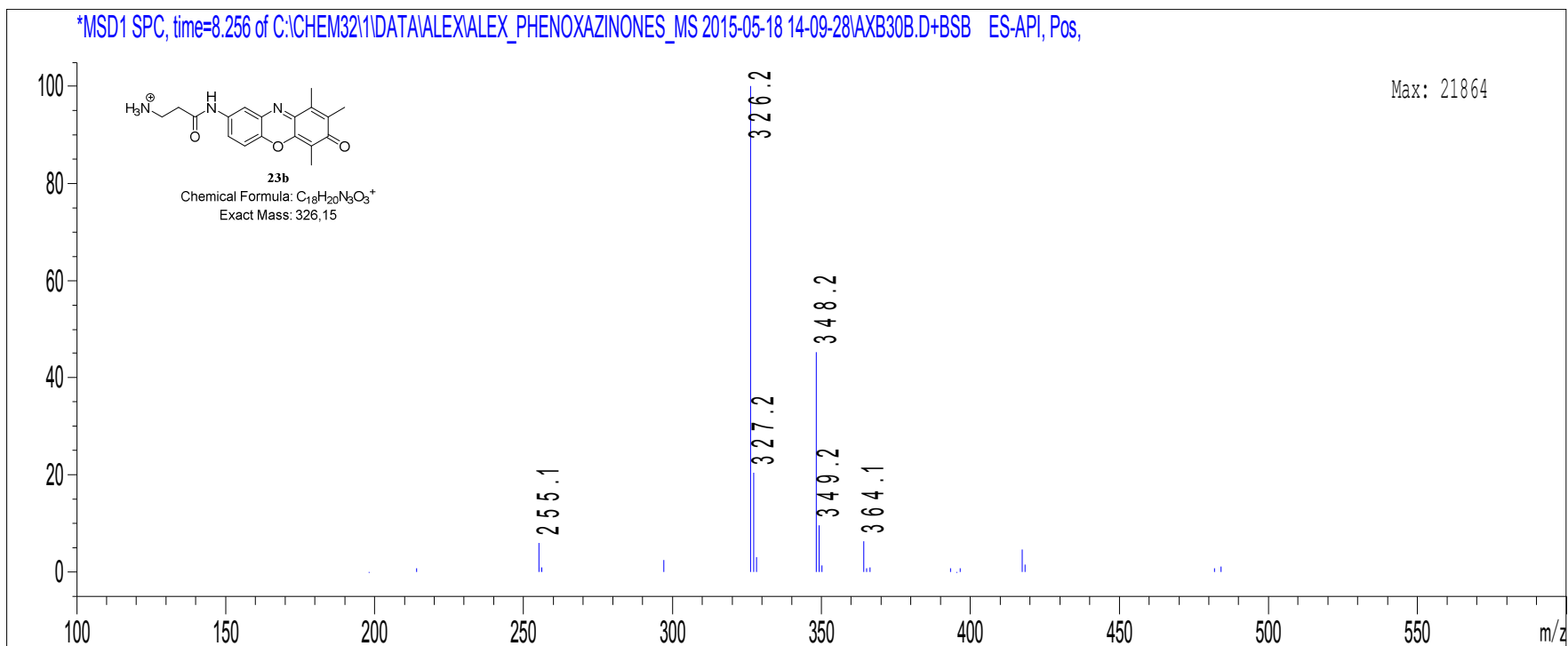
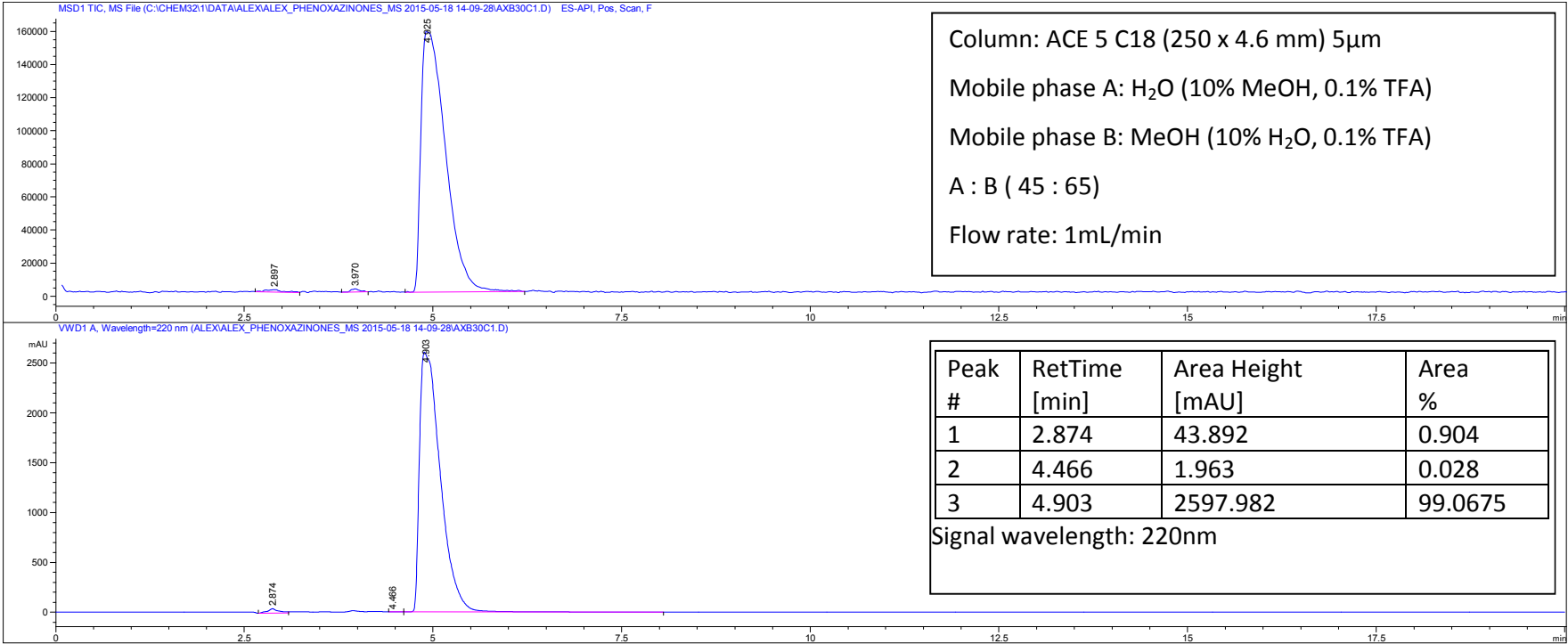


Figure S5. HPLC-MS Spectra of **23c**.



*MSD1 SPC, time=4.953 of C:\CHEM32\1\DATA\ALEXALEX_PHENOXAZINONES_MS 2015-05-18 14-09-28\AXB30C1.D ES-API, Pos, Sca

Max: 80562

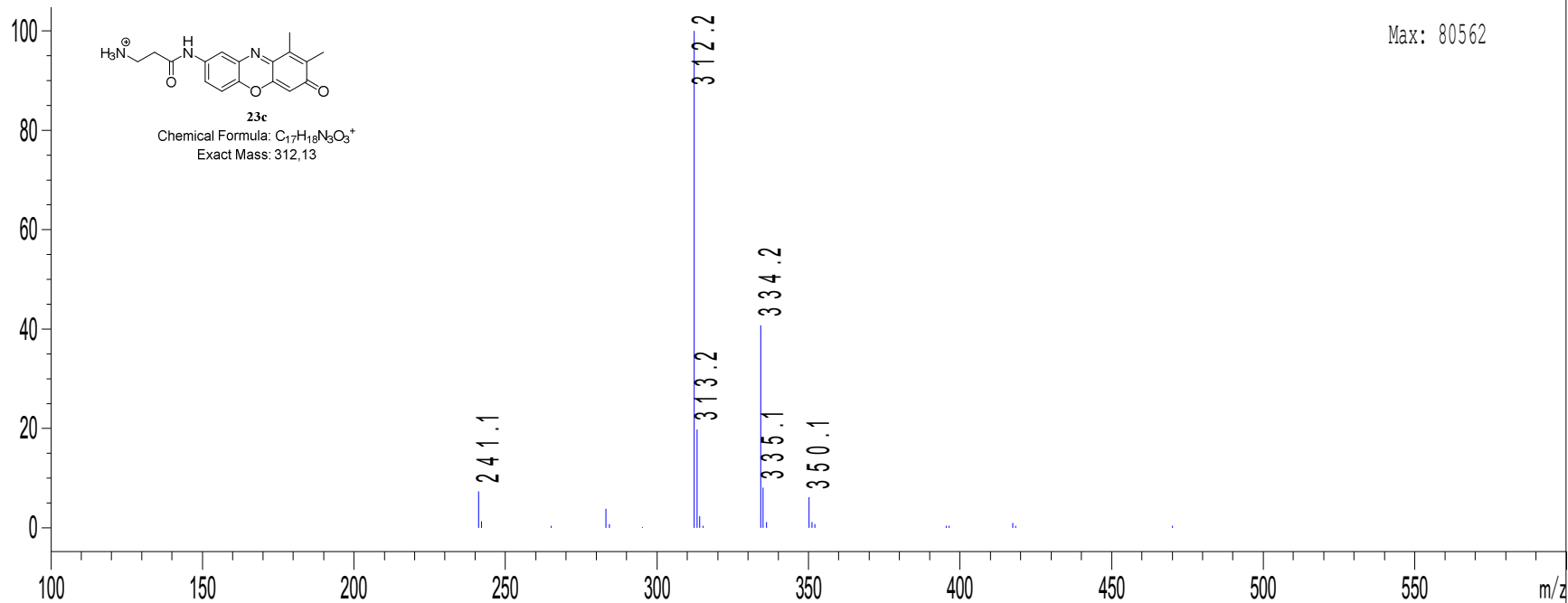
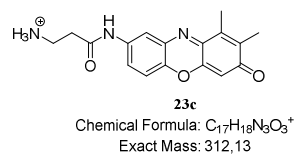
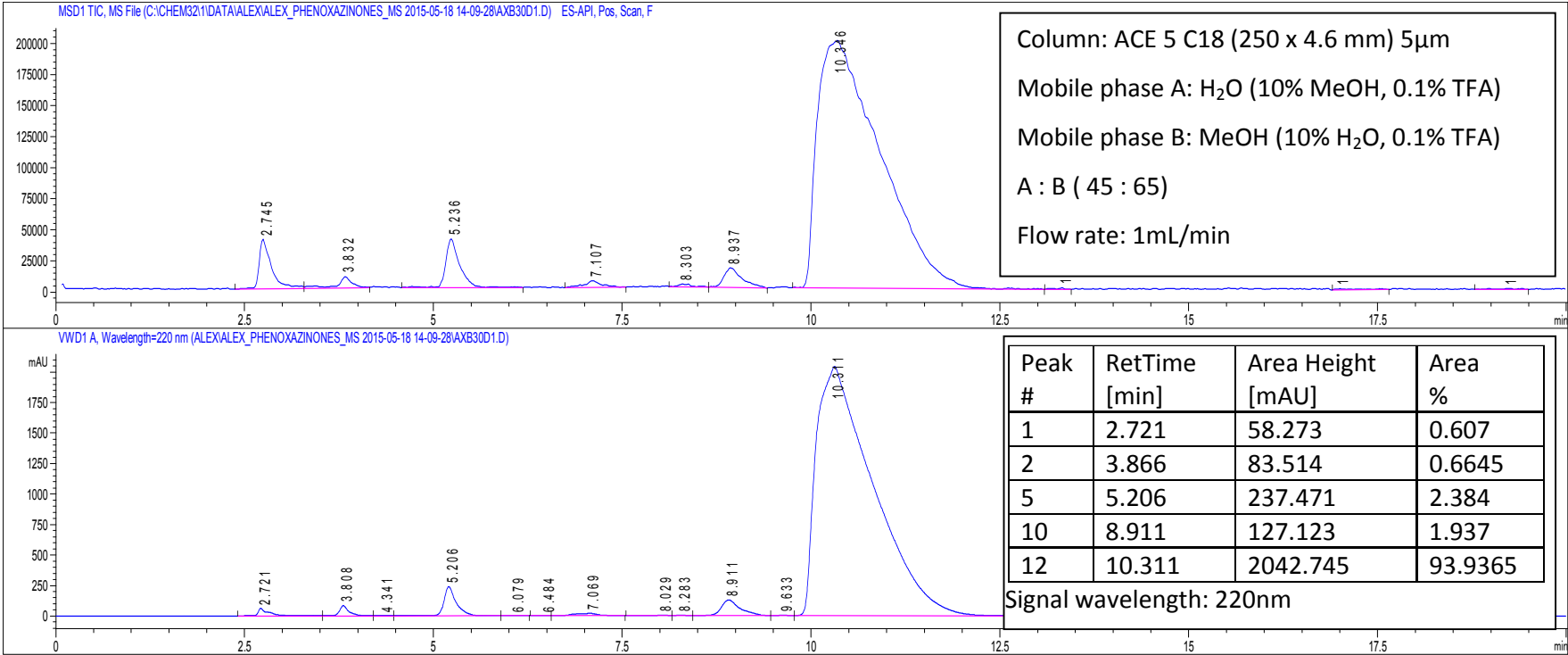


Figure S6. HPLC-MS Spectra of **23d**.



*MSD1 SPC, time=14.846 of C:\CHEM32\1\DATA\ALEX\ALEX_PHENOXAZINONES_MS 2015-05-18 14-09-28\AXB29A.D ES-API, Pos, Sca

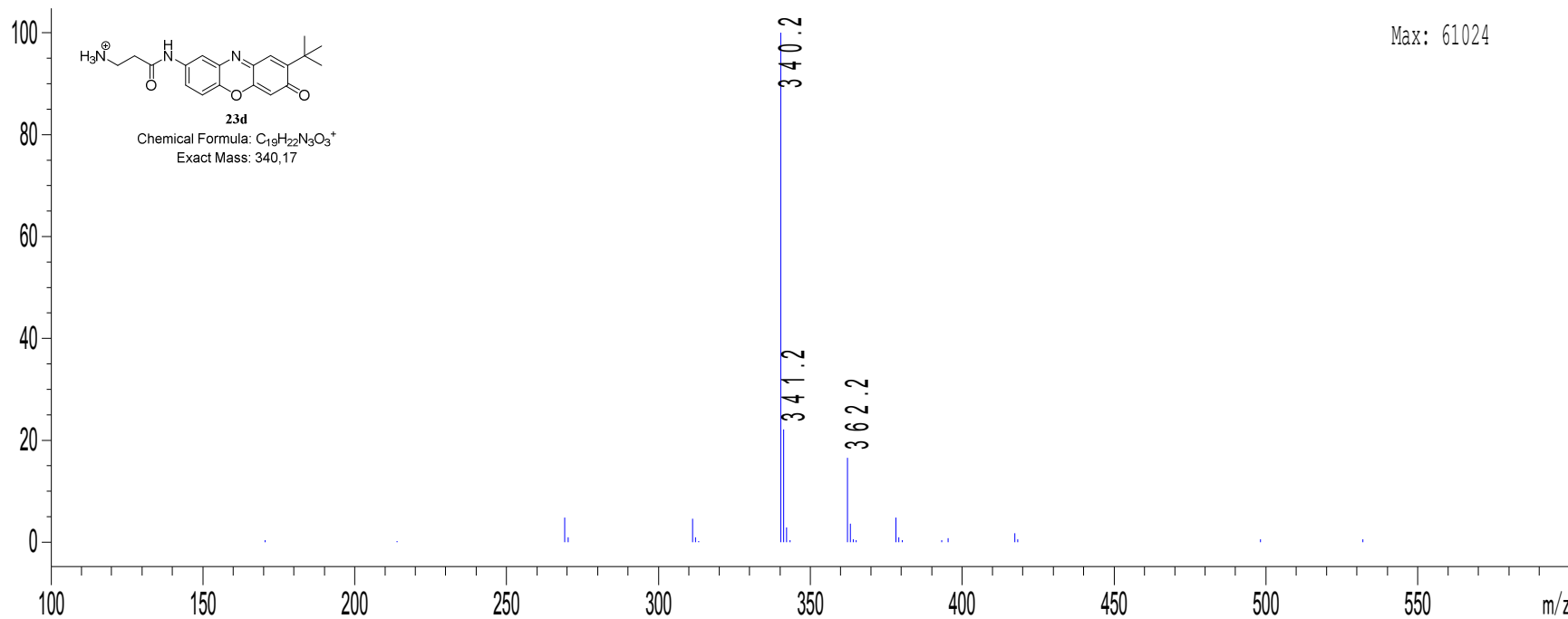
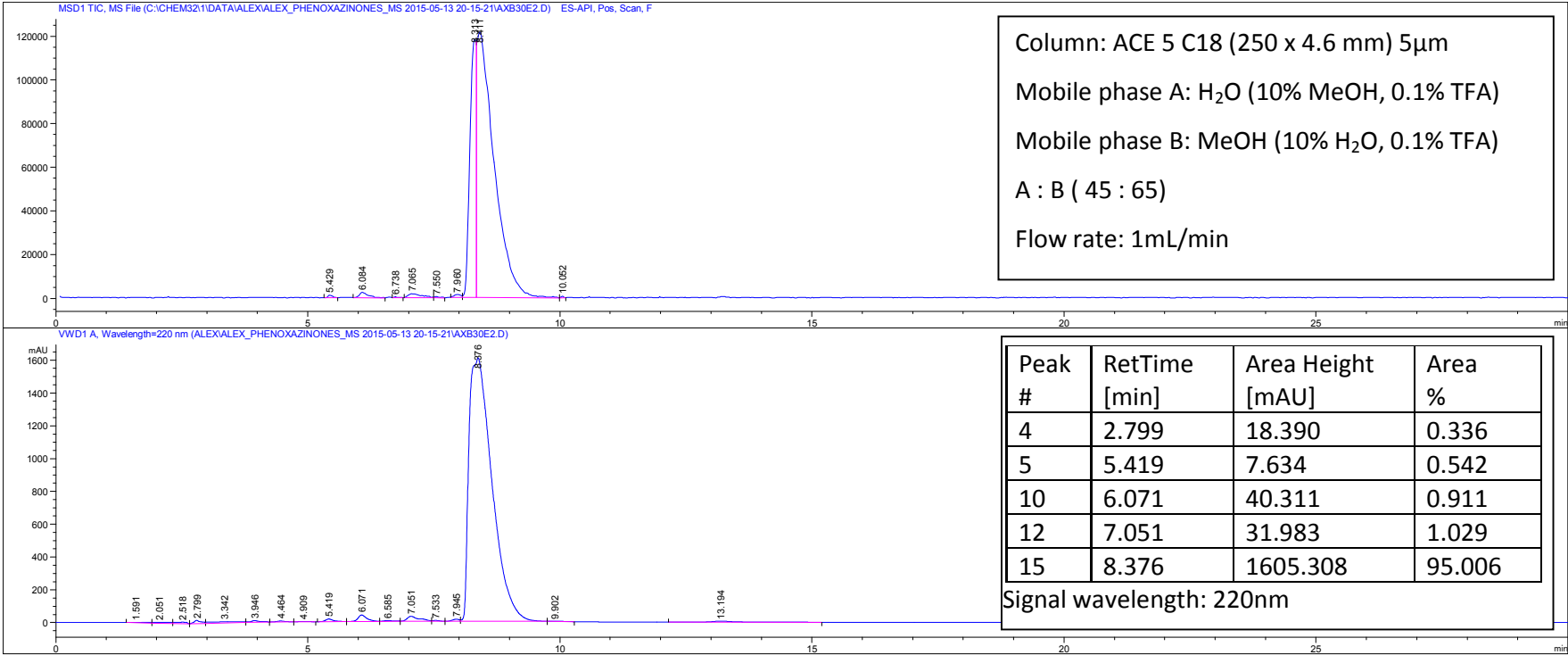


Figure S7. HPLC-MS Spectra of **23e**.



*MSD1 SPC, time=8.357 of C:\CHEM32\1\DATA\ALEX_ALEX_PHENOXAZINONES_MS 2015-05-13 20-15-21\AXB30E2.D ES-API, Pos, Sca

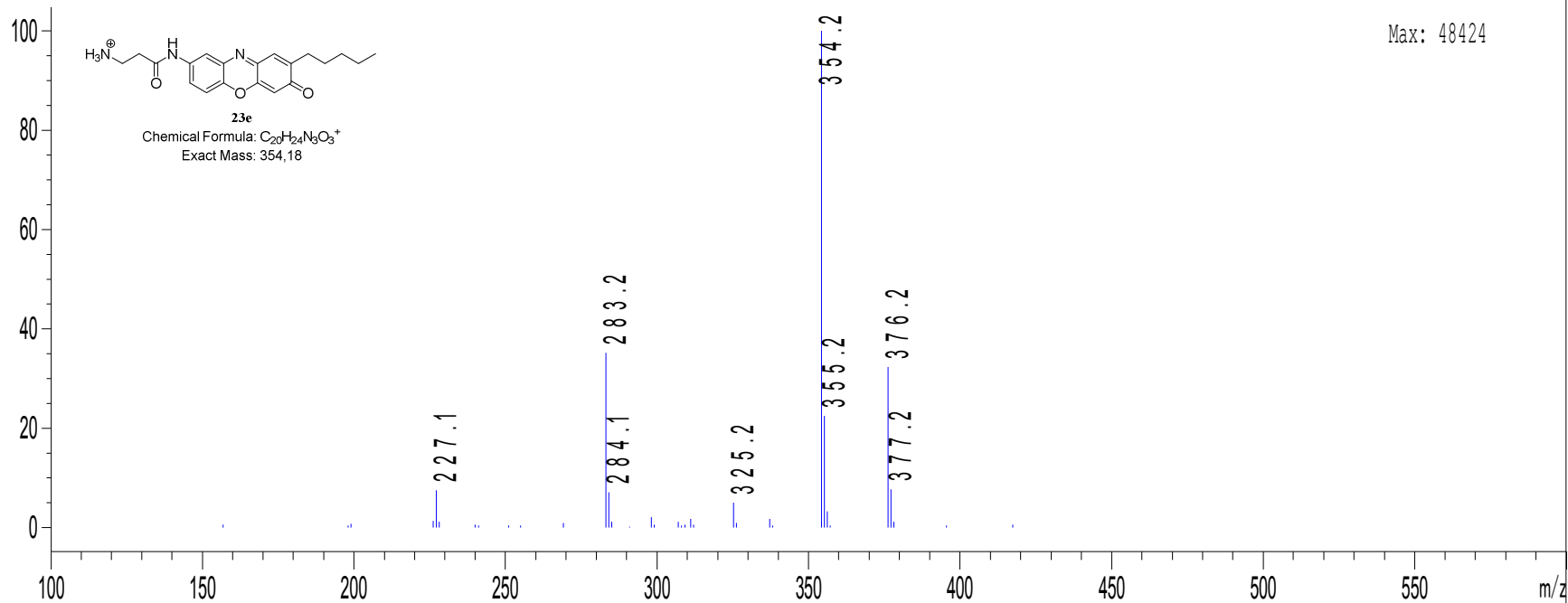
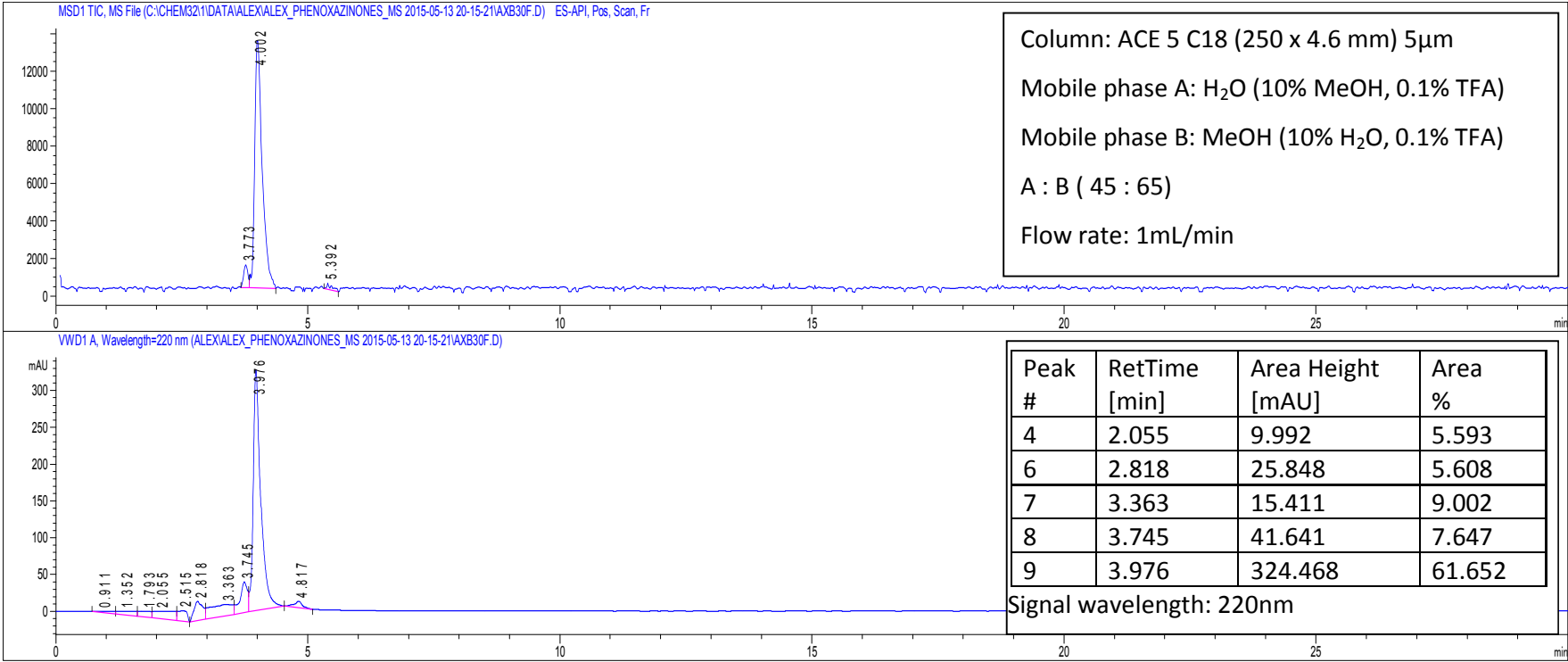


Figure S8. HPLC-MS Spectra of **23f**.



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Max: 4127

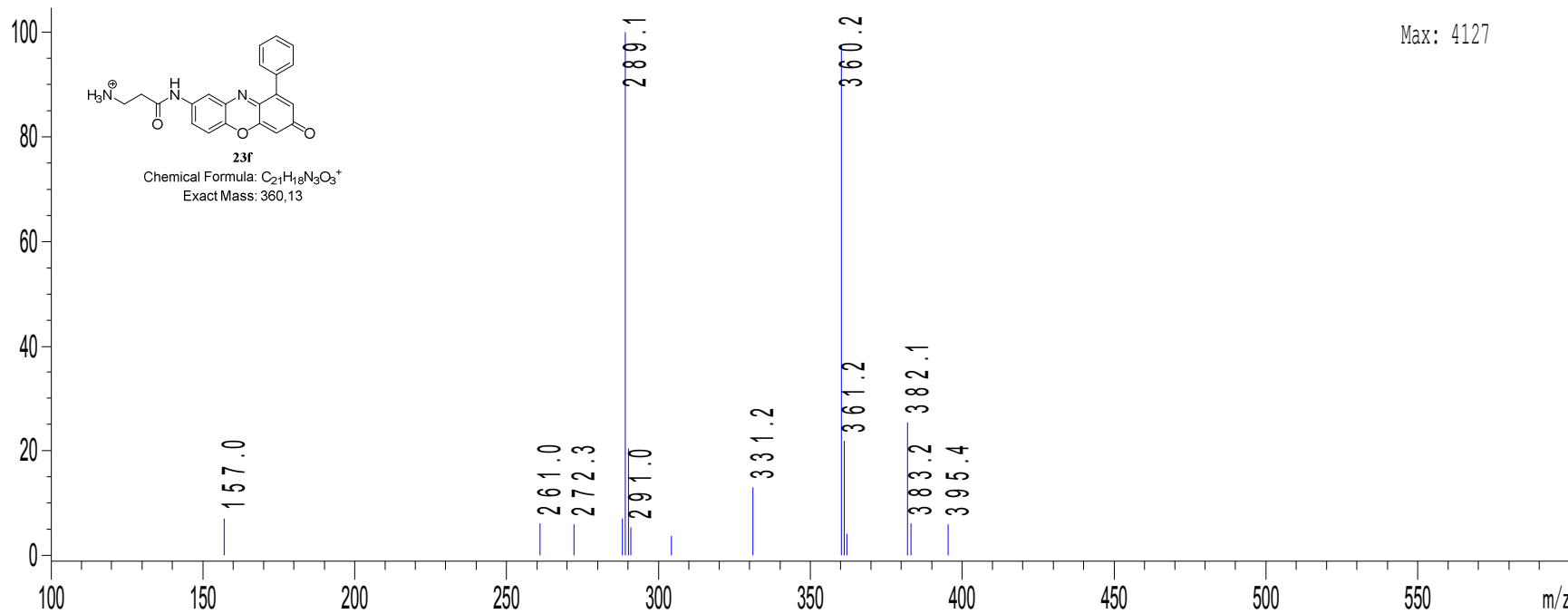
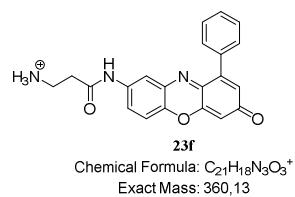
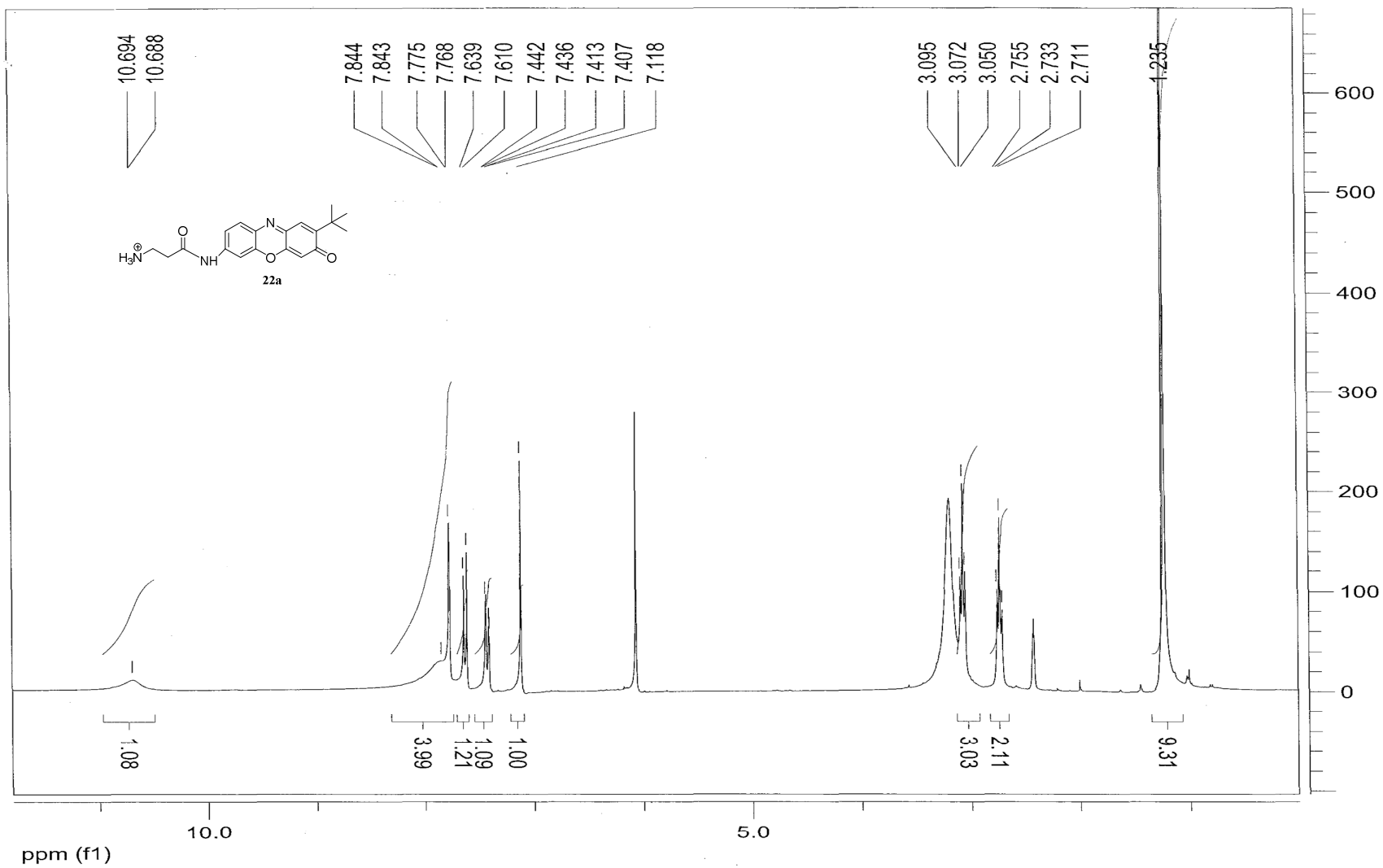
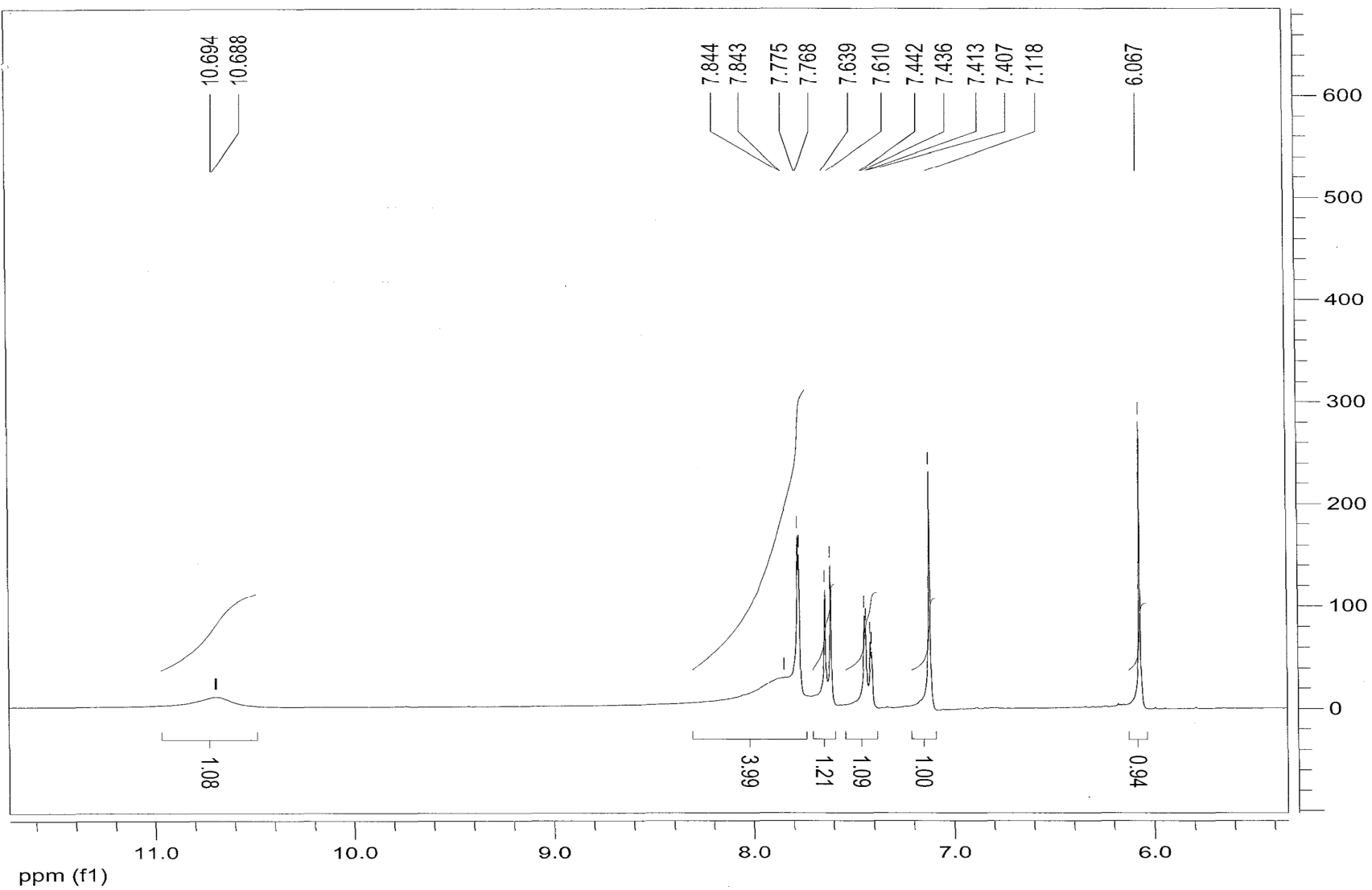


Figure S9. ^1H NMR spectrum of **22a** in d_6 -DMSO at 50°C .





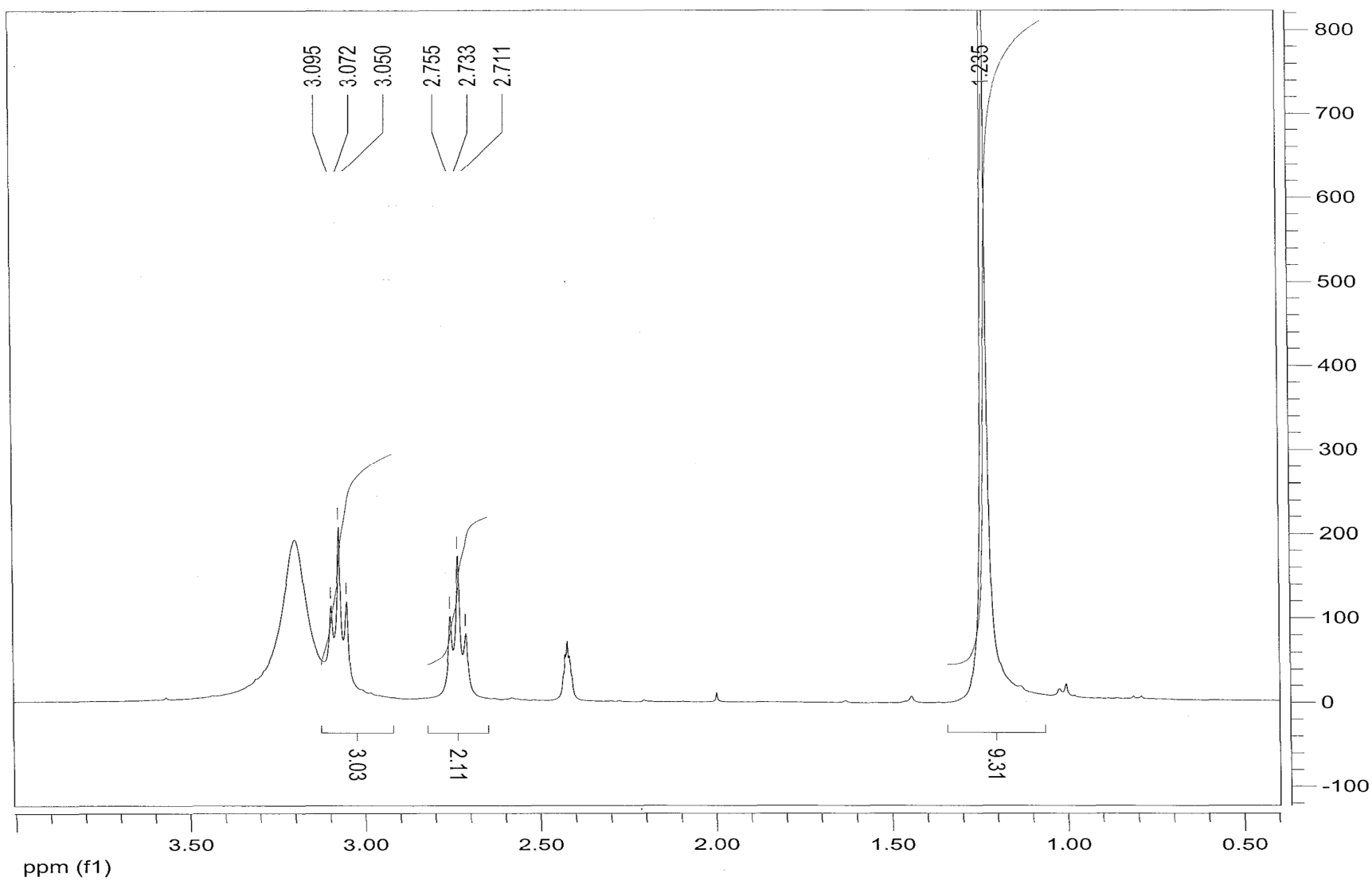
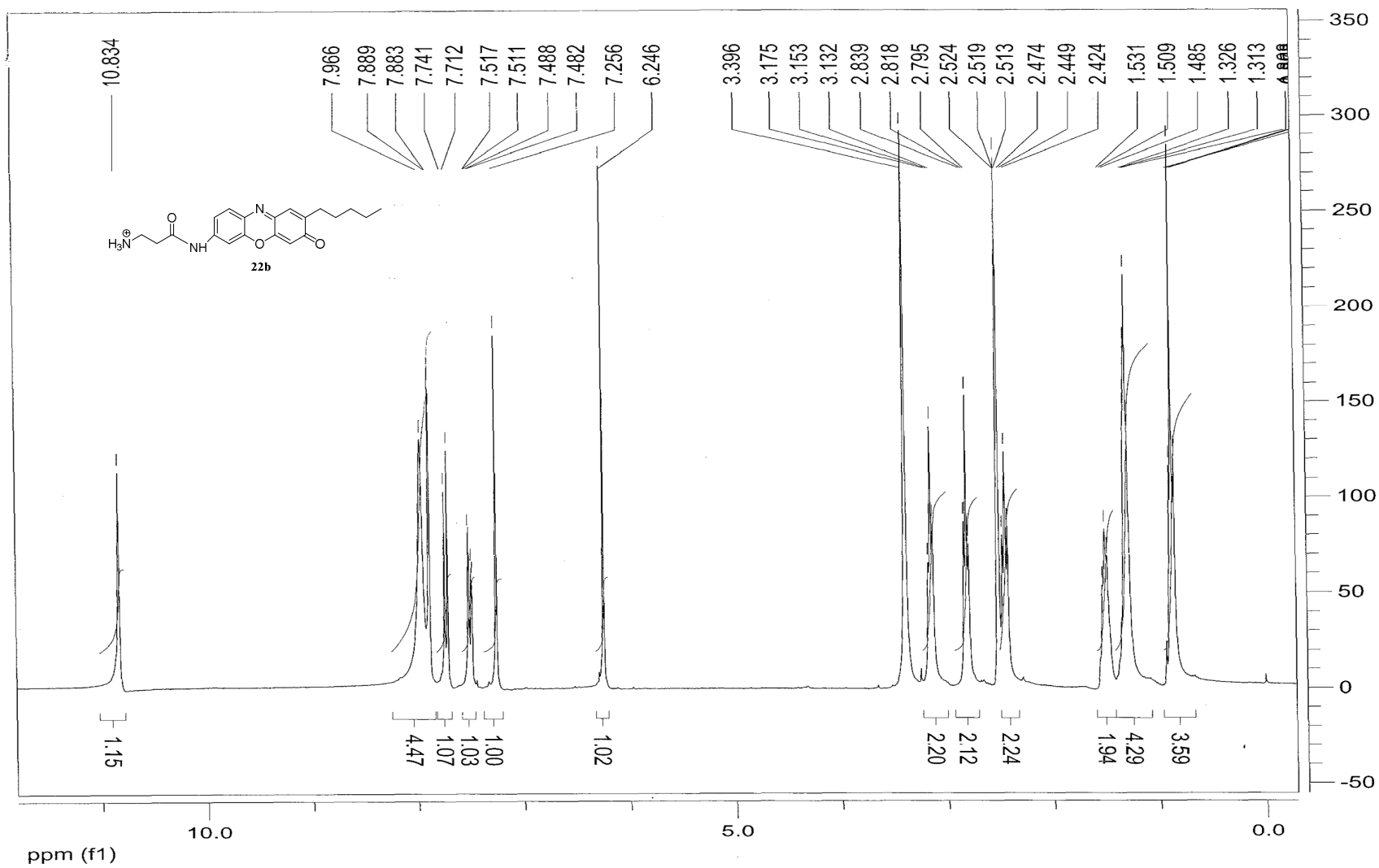
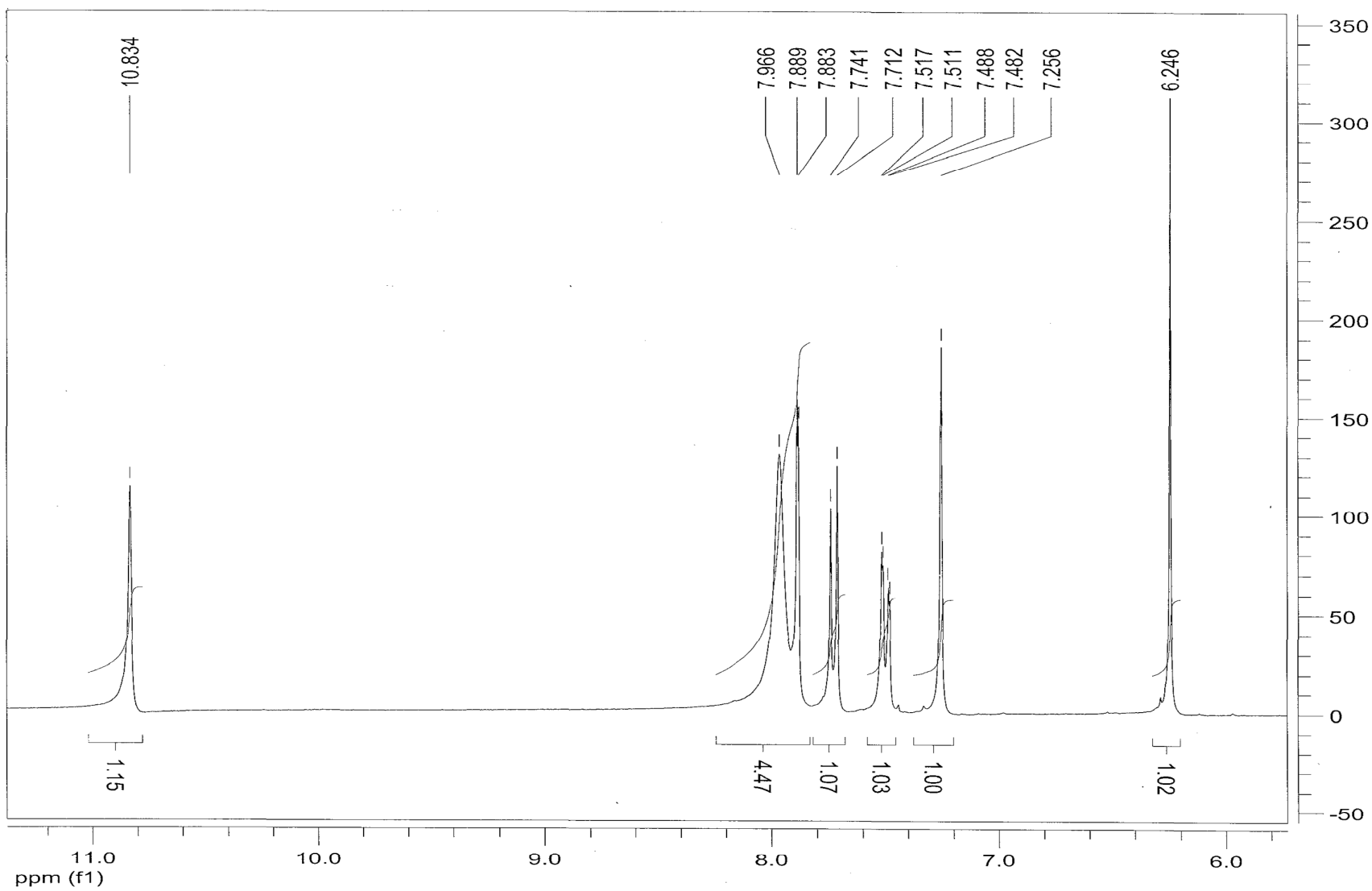


Figure S10. ^1H NMR spectrum of **22b** in d_6 -DMSO at 50°C .





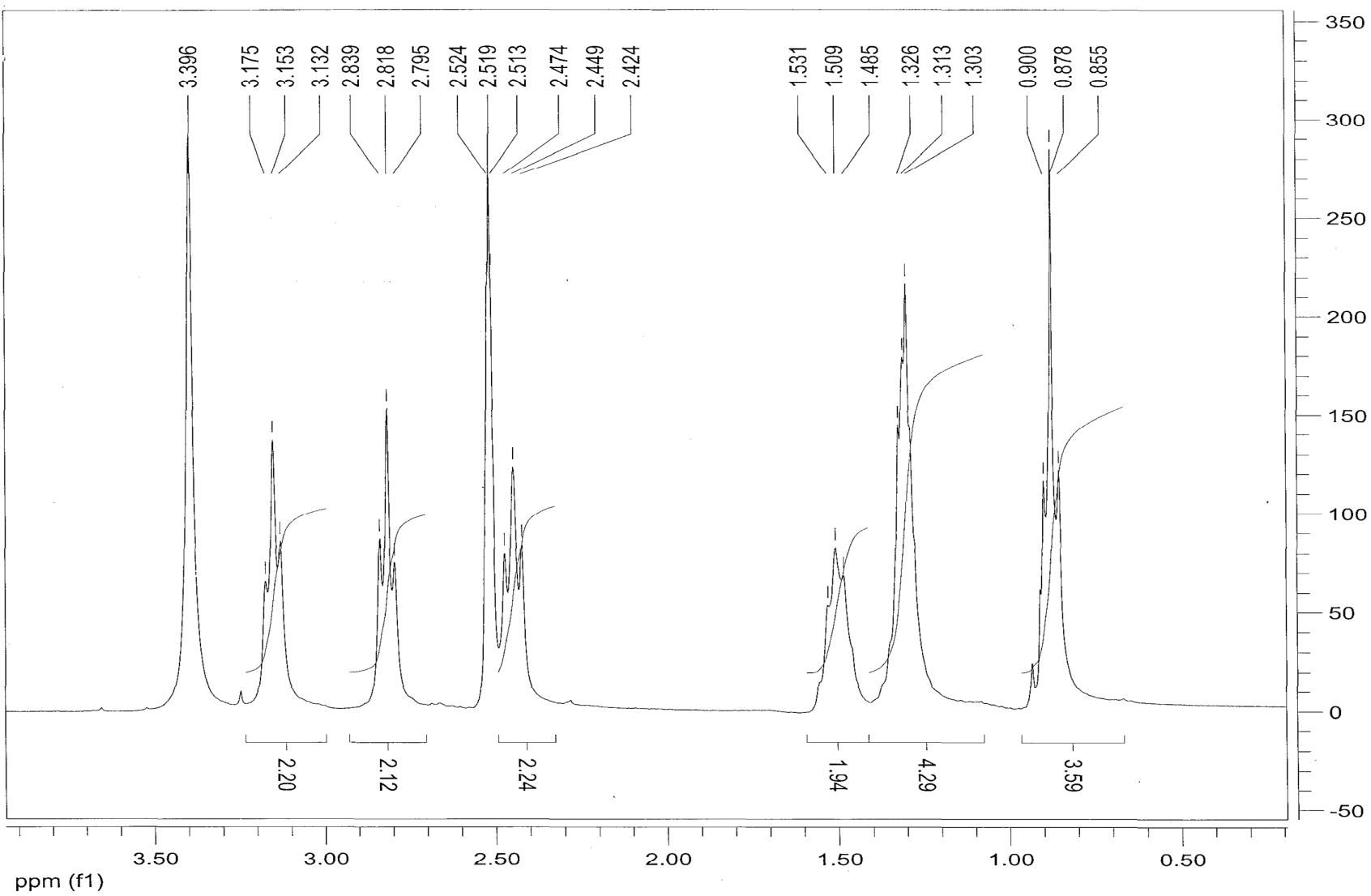
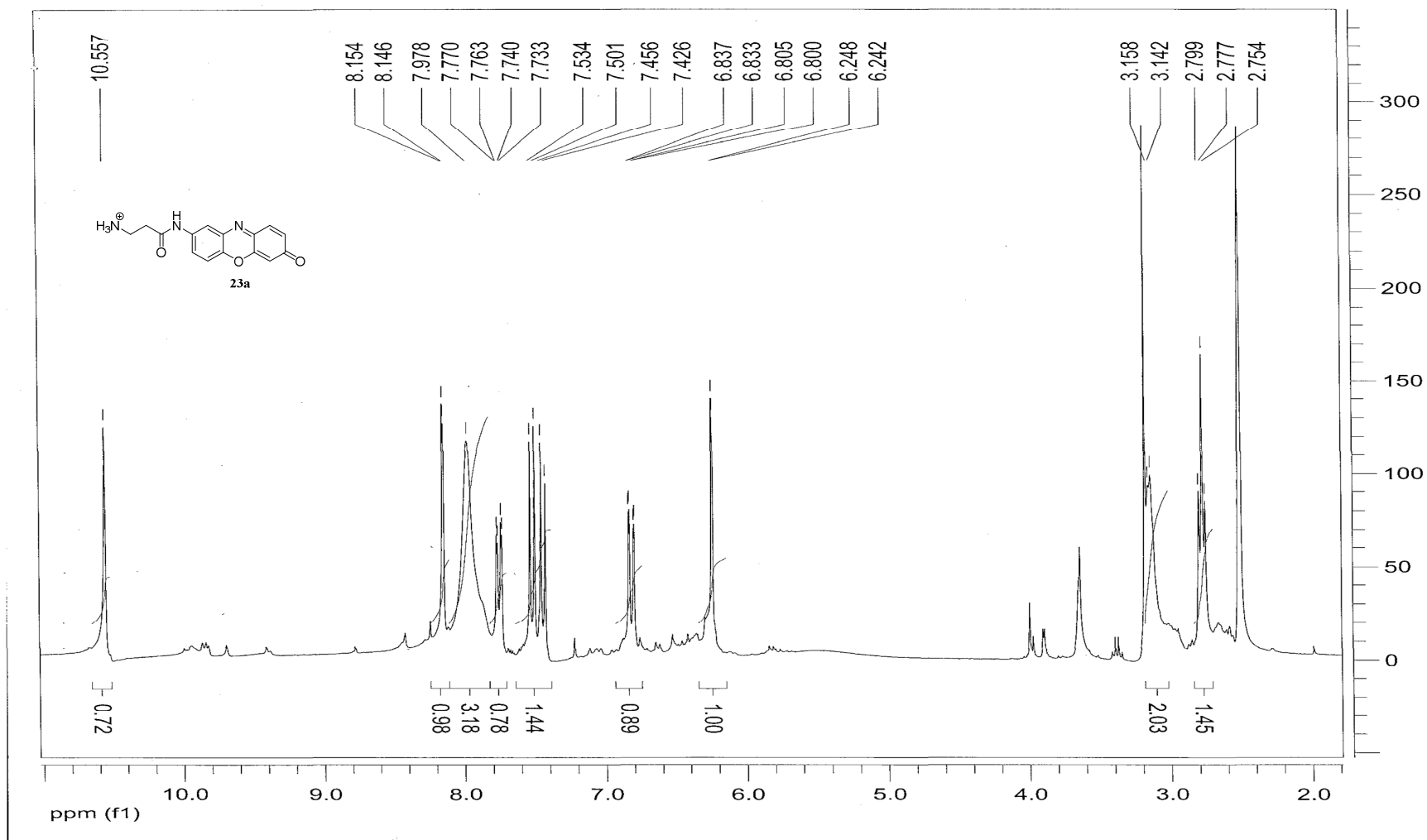
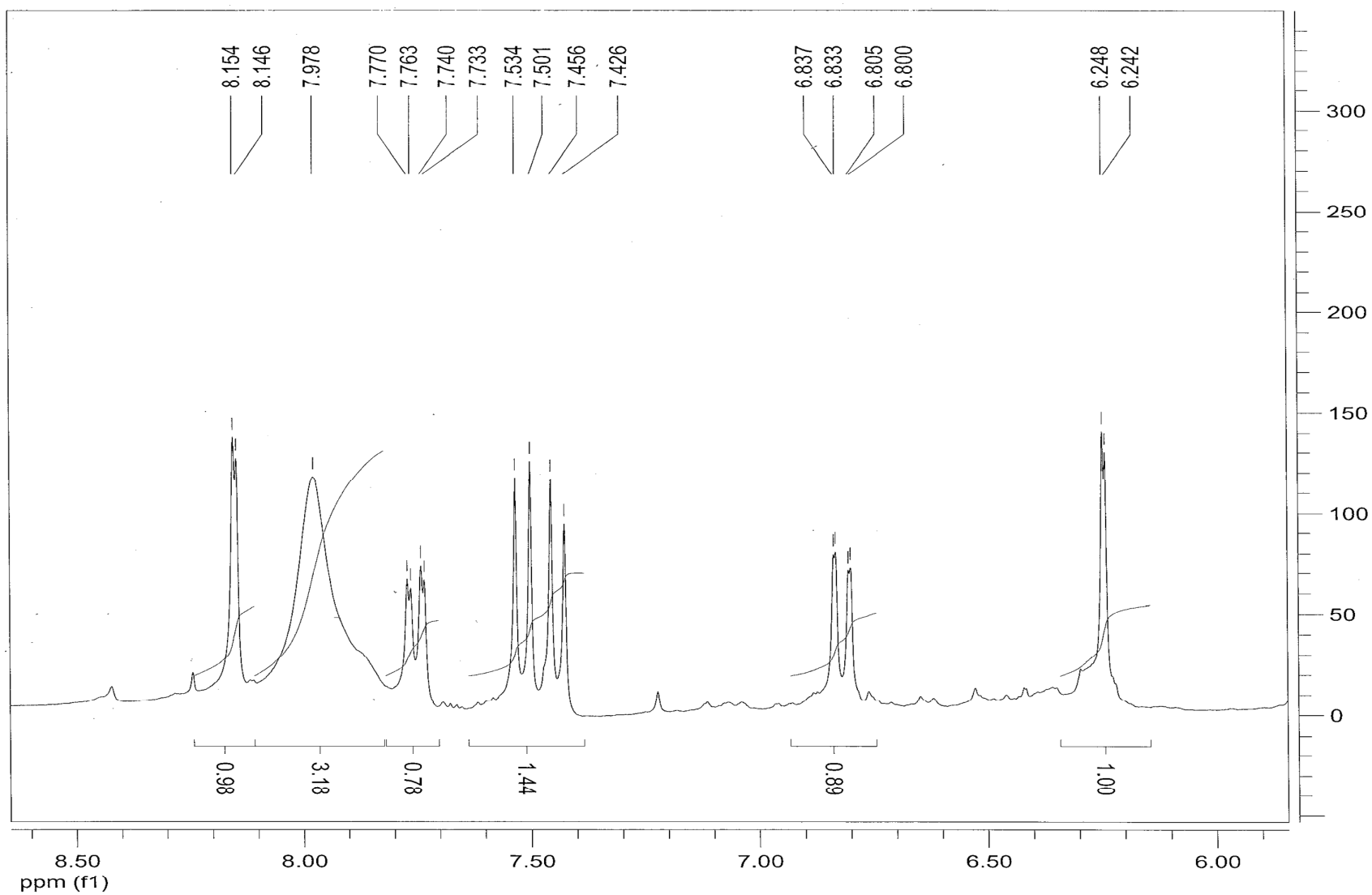


Figure S11. ^1H NMR spectrum of **23a** in d_6 -DMSO at 30°C .





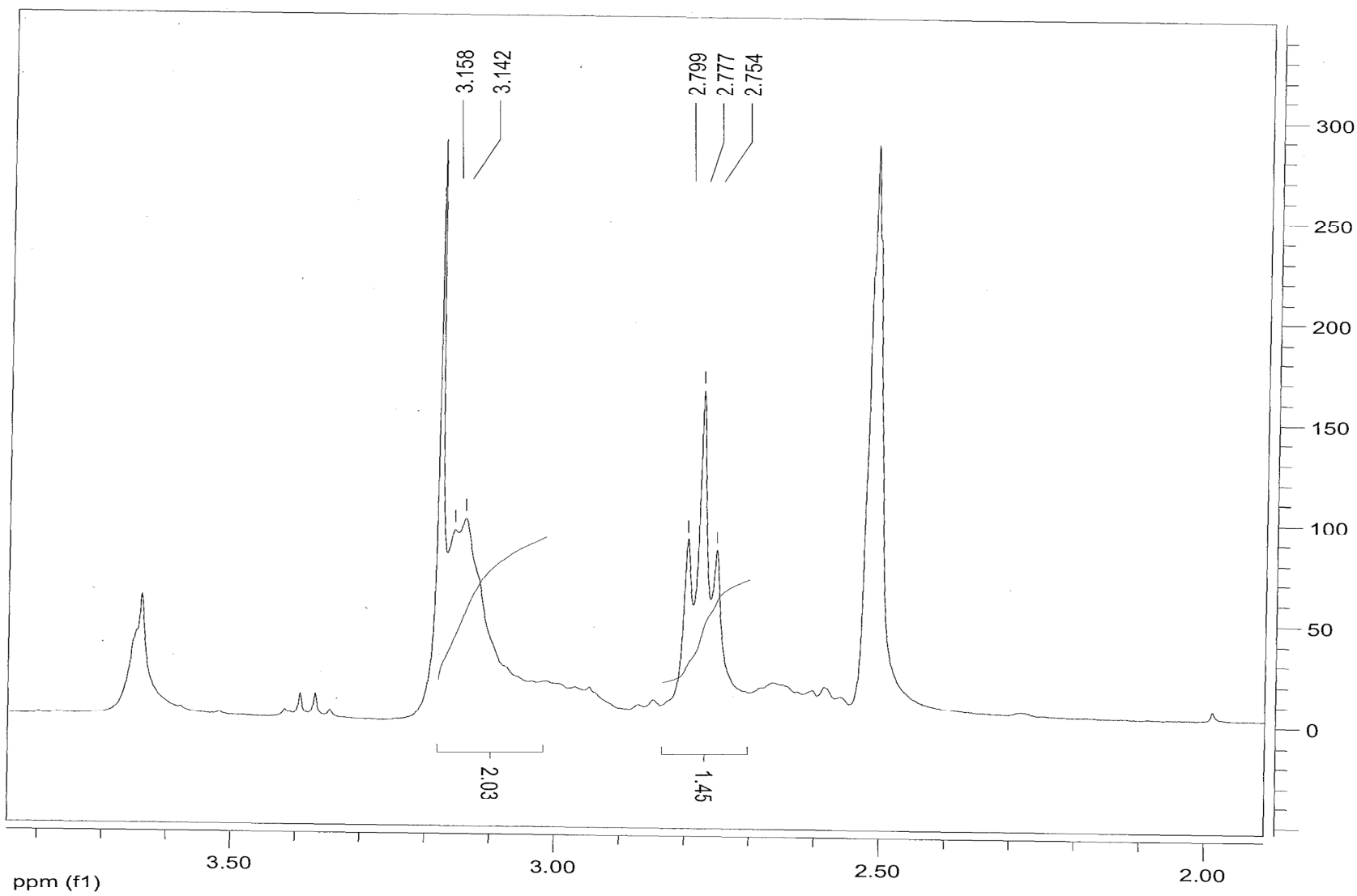
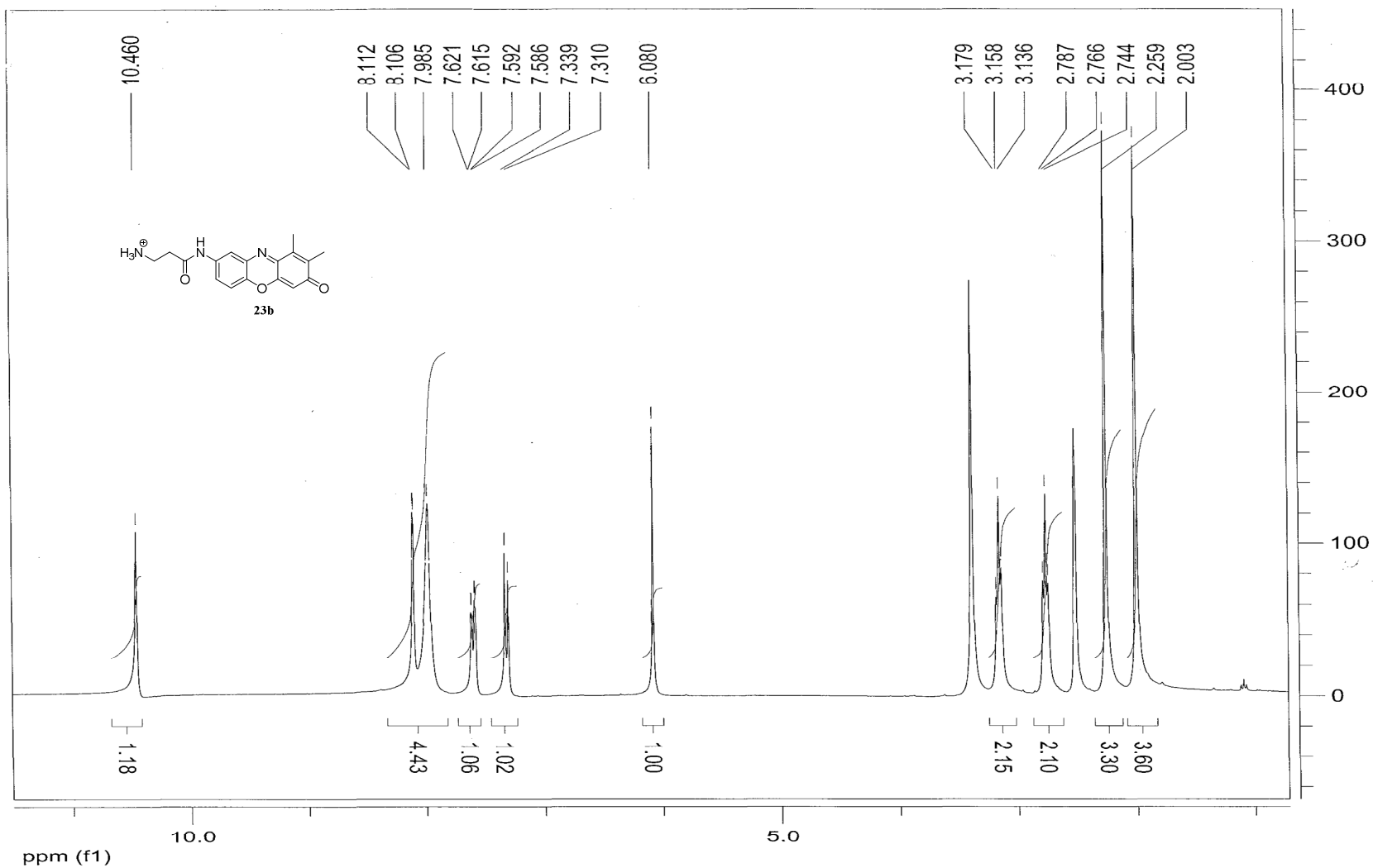
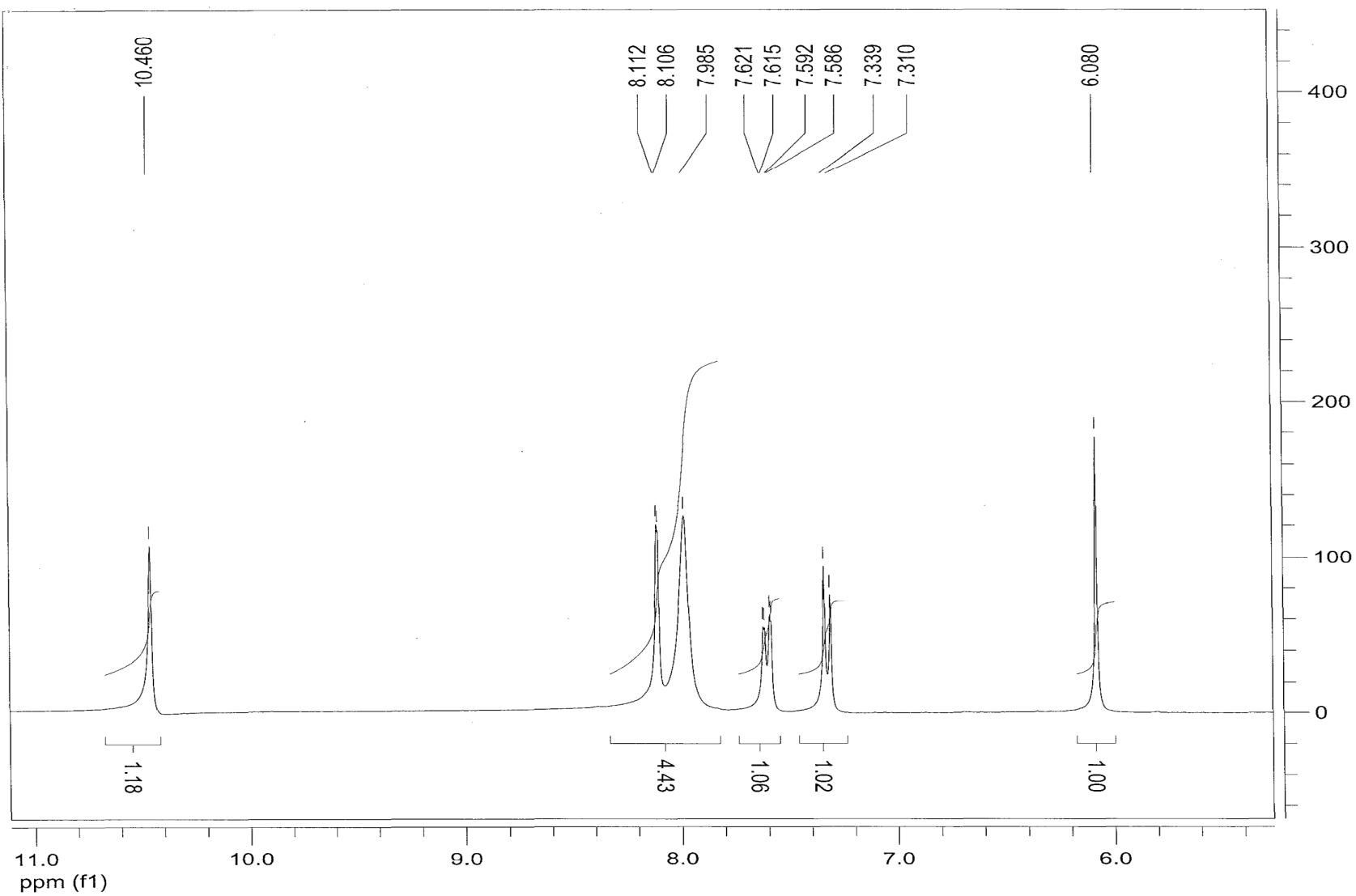


Figure S12. ^1H NMR spectrum of **23b** in d_6 -DMSO at 30°C .





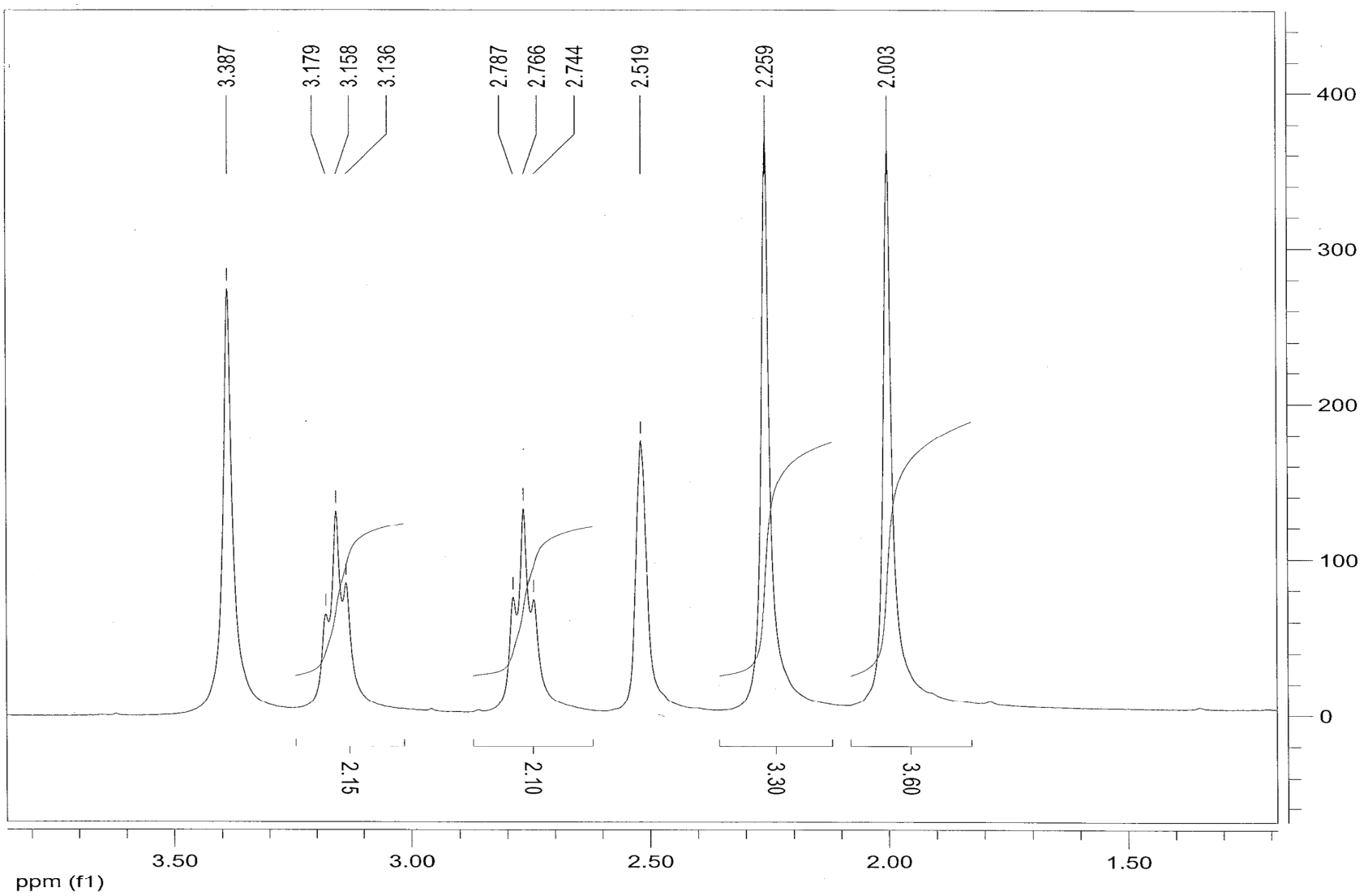
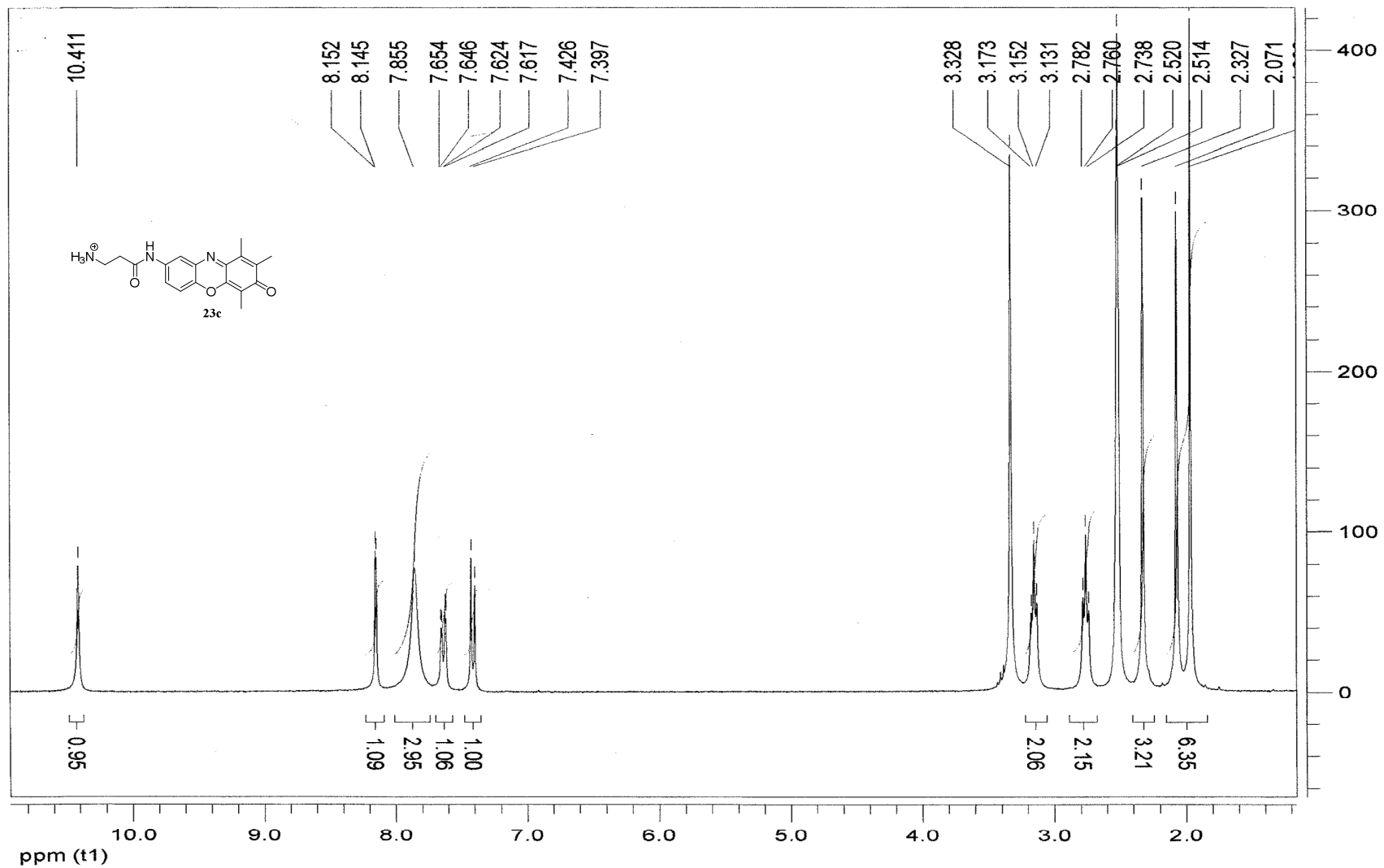


Figure S13. ^1H NMR spectrum of **23c** in d_6 -DMSO at 30°C .



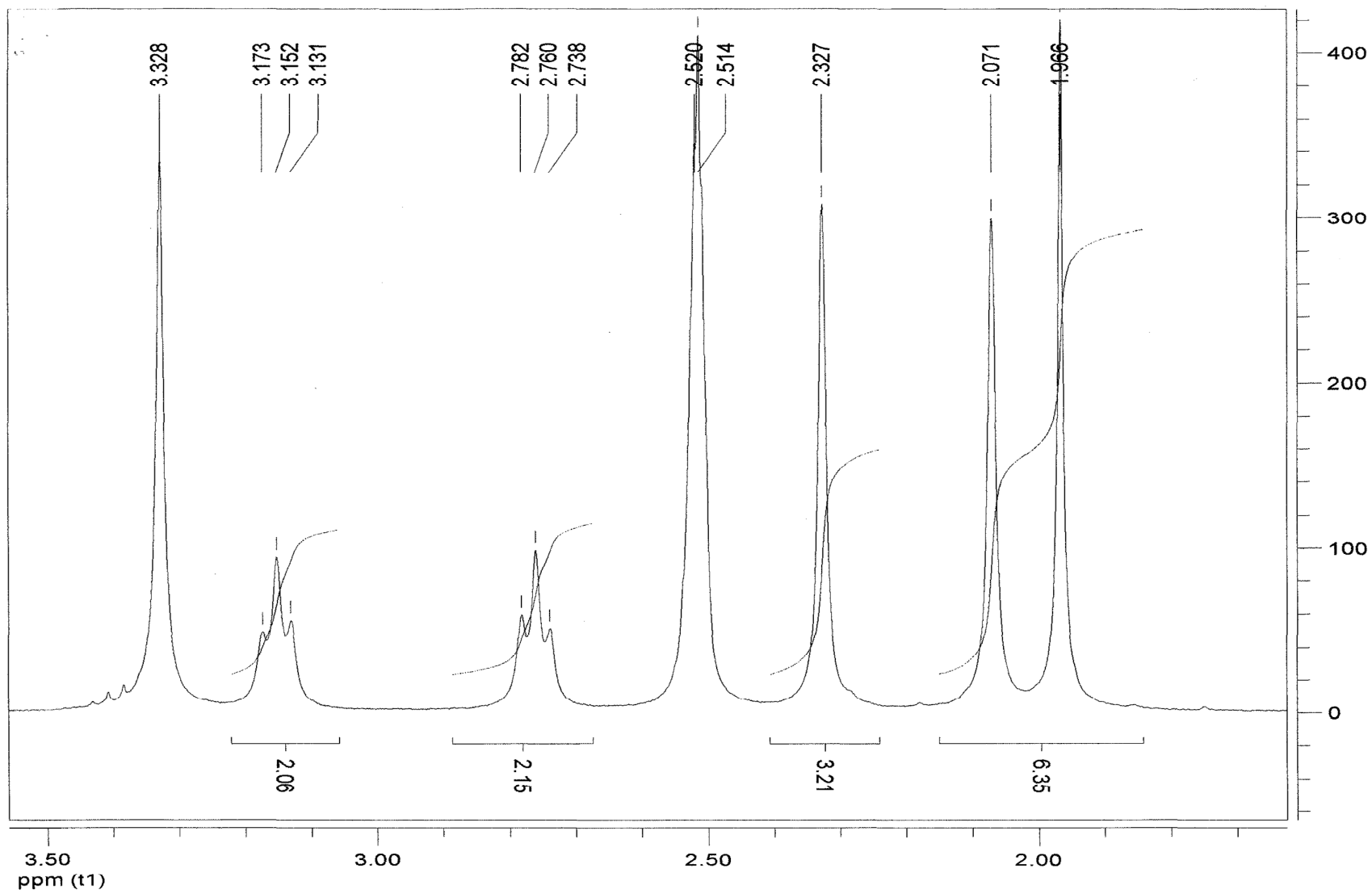
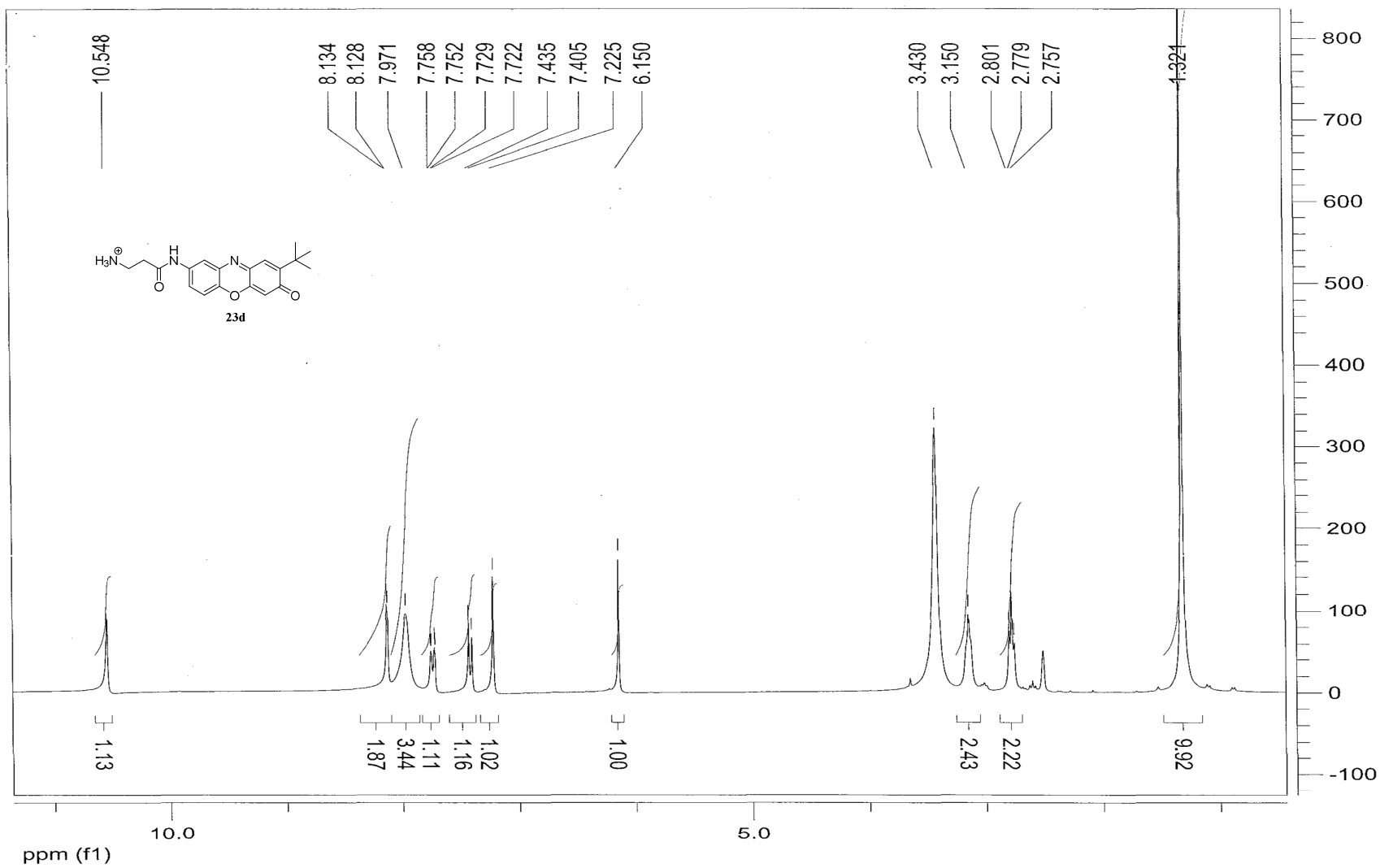
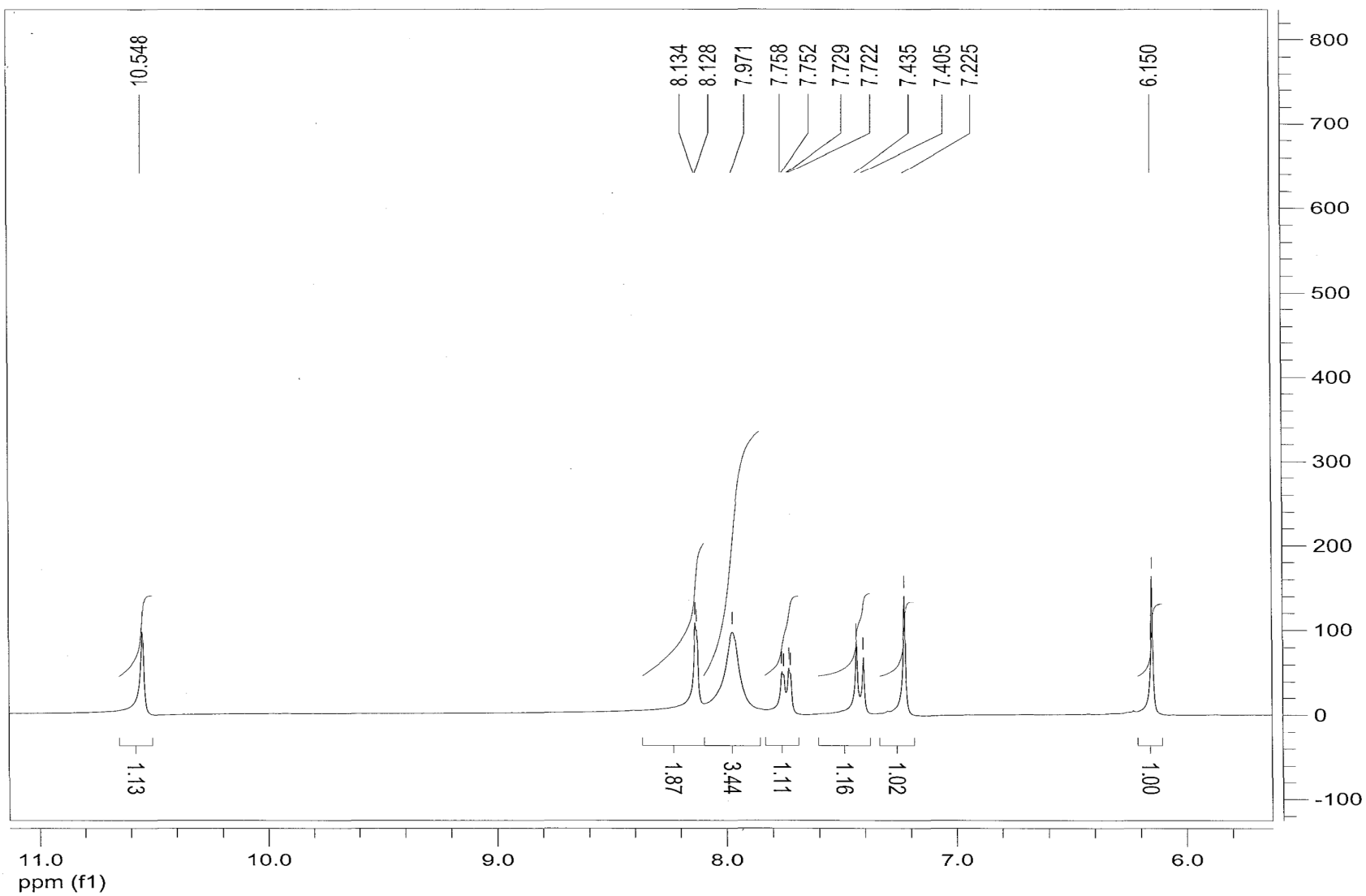


Figure S14. ^1H NMR spectrum of **23d** in d_6 -DMSO at 30°C .





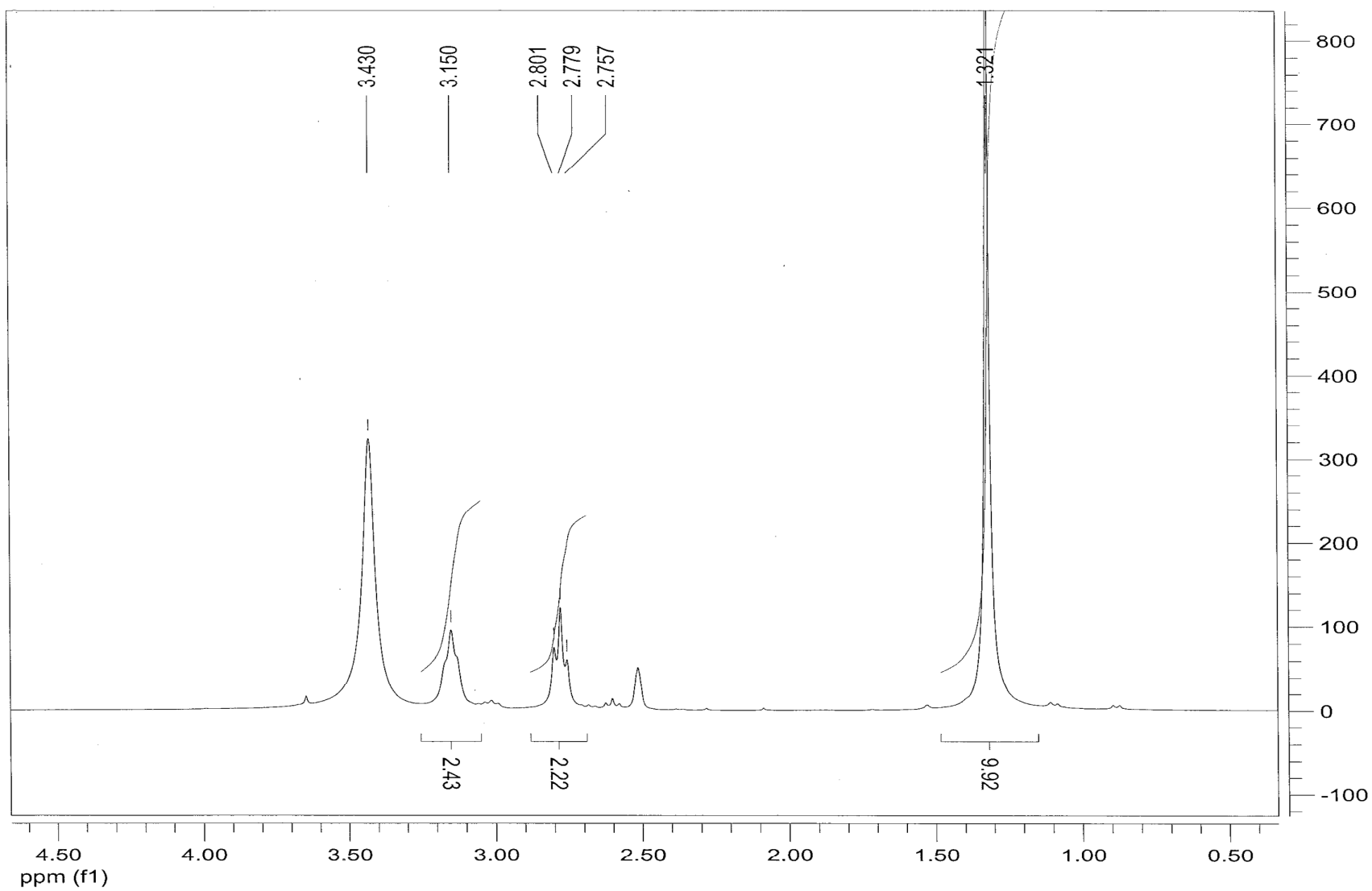
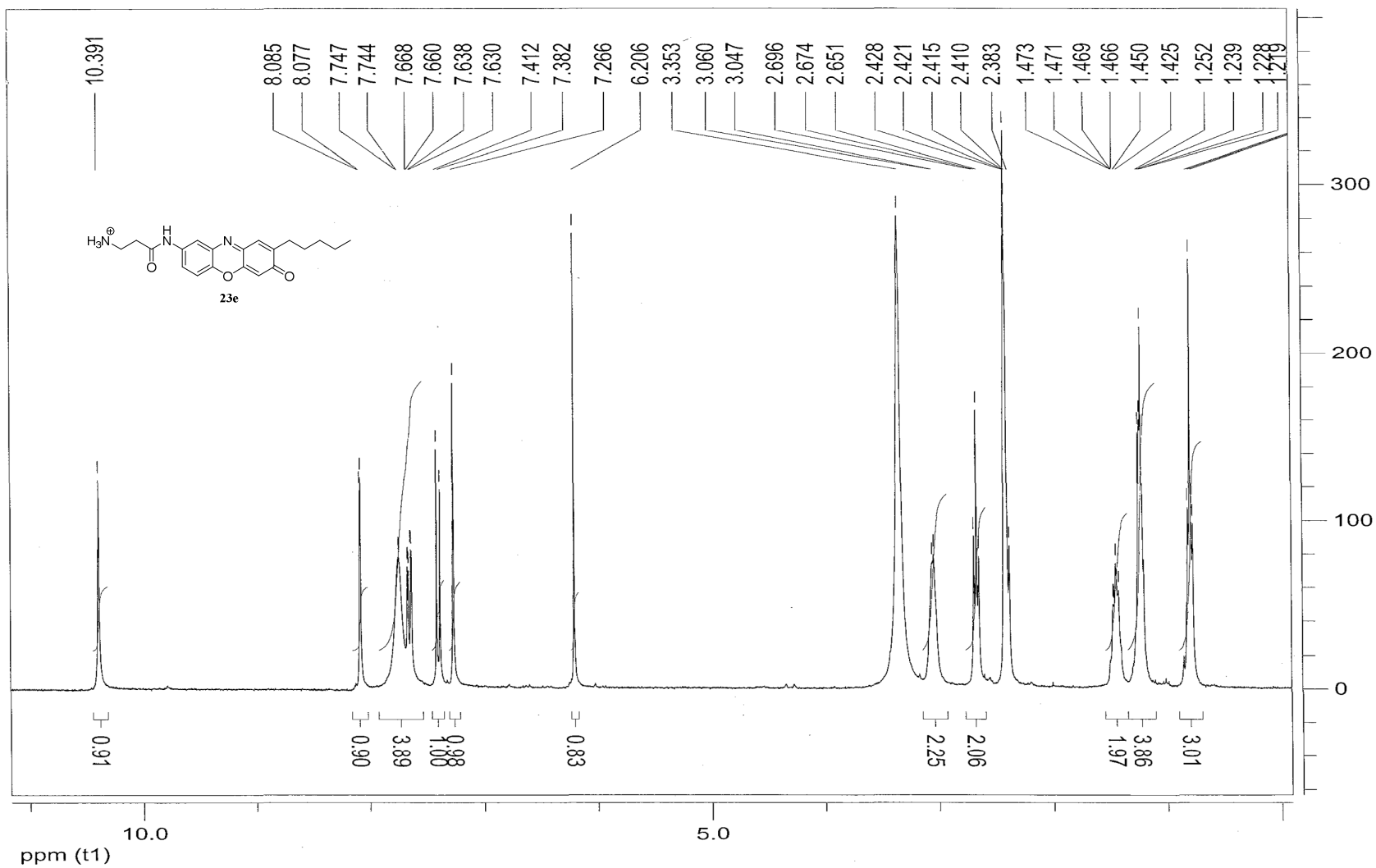
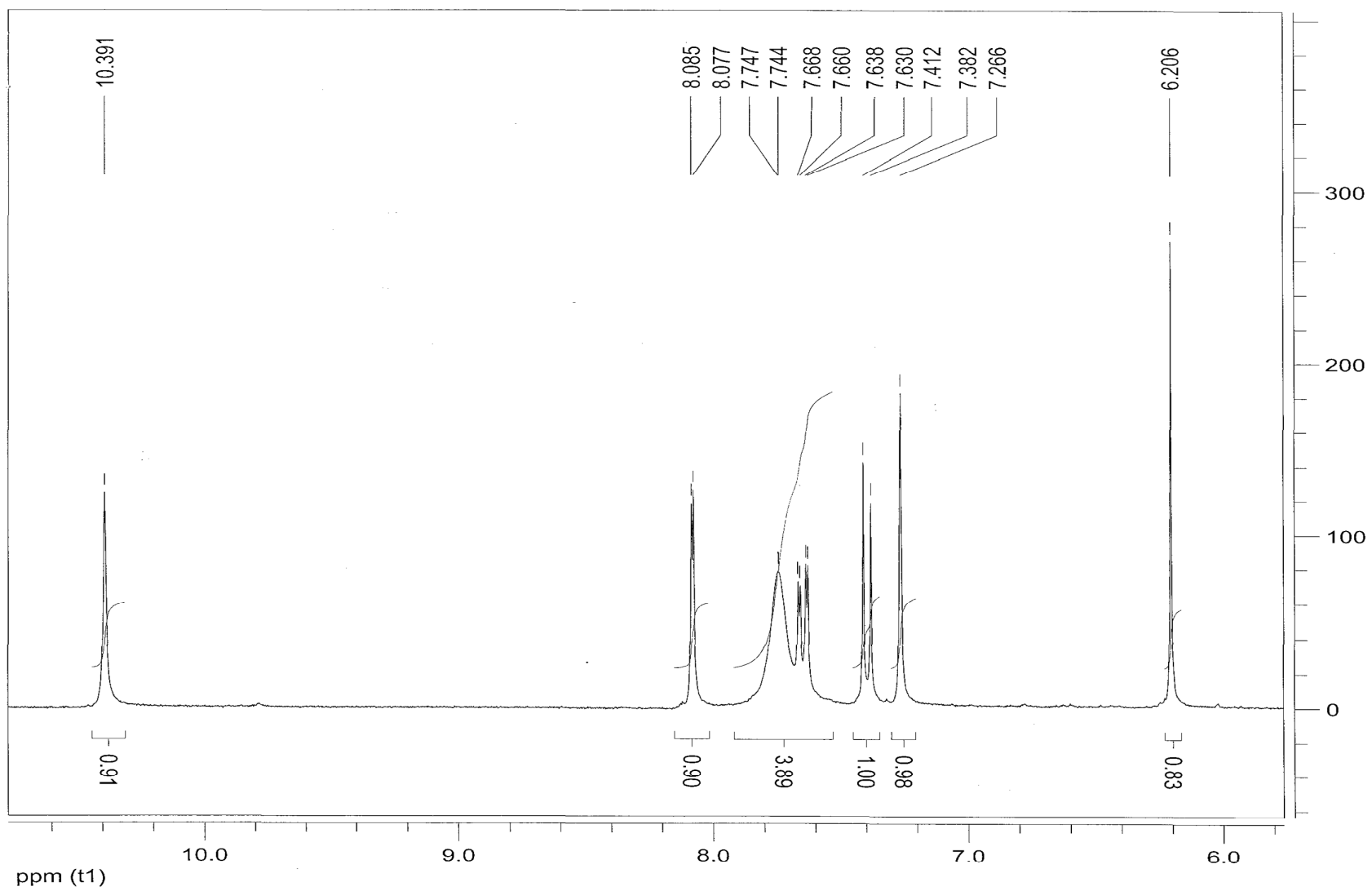
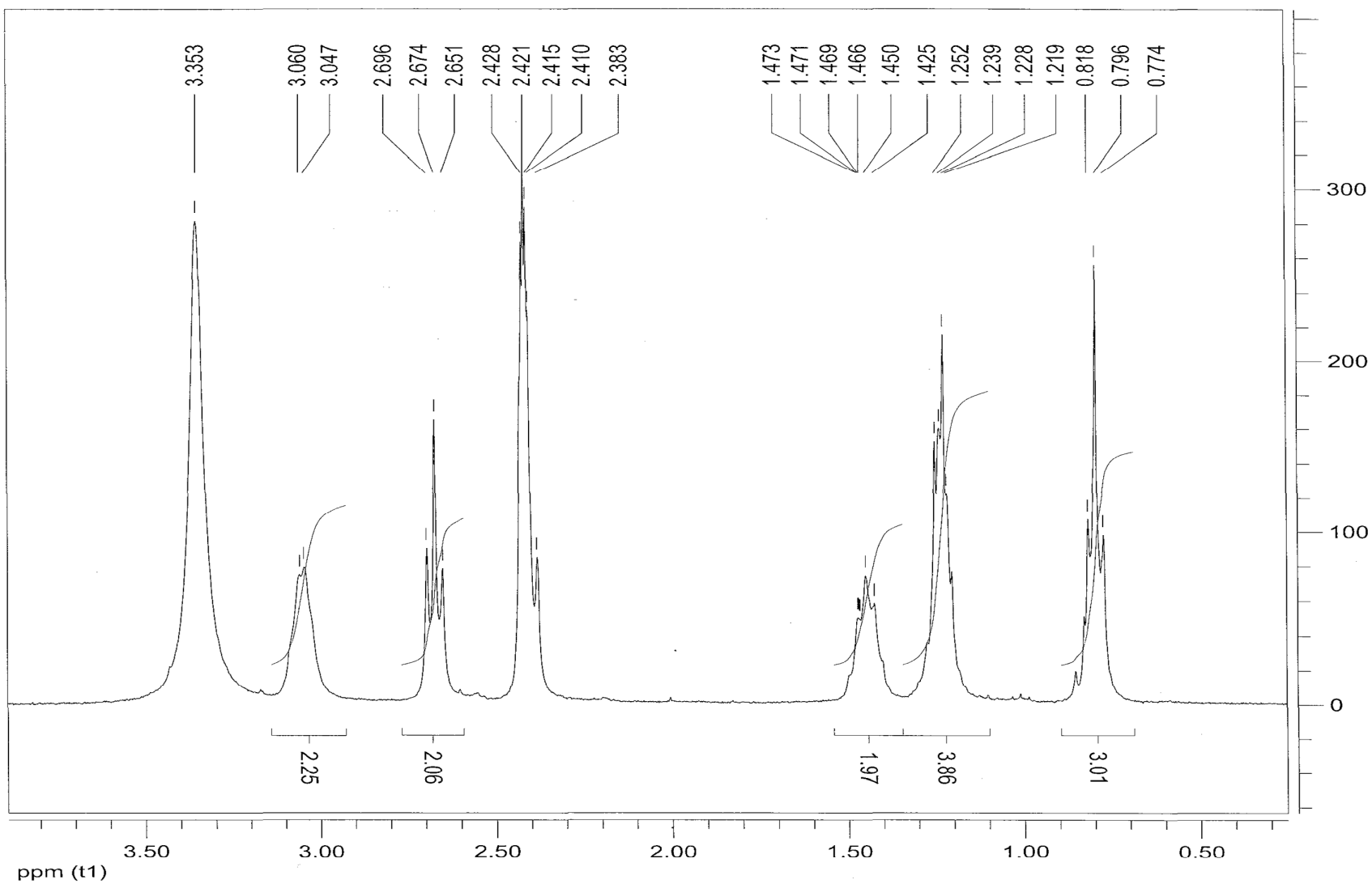


Figure S15. ^1H NMR spectrum of **23e** in d_6 -DMSO at 50°C .







S80

