



**Outsmarted by nootropics? An investigation into the thermal degradation of modafinil, modafinic acid, adrafinil, CRL-40,940 and CRL-40,941 in the GC injector: formation of 1,1,2,2-tetraphenylethane and its tetra fluoro analog**

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Keywords:	Modafinil, Adrafinil, Modafinic Acid, GC-MS Degradation
Abstract:	<p>2-[(Diphenylmethyl)sulfinyl]acetamide (modafinil) is commonly prescribed for the treatment of narcolepsy and increasing popularity and off-label use as a cognitive enhancer resulted in a reputation as an intelligence boosting 'wonder drug'. Common alternatives available from online shops and other retail outlets include 2-[(diphenylmethyl)sulfinyl]-N-hydroxyacetamide (adrafinil), 2-[[bis(4-fluorophenyl)methyl]sulfinyl]acetamide (CRL-40,940), 2-[[bis(4-fluorophenyl)methyl]sulfinyl]-N-hydroxyacetamide (CRL-40,941) and N-methyl-4,4-difluoro-modafinil (modafiendz), respectively. Gas chromatography mass spectrometry (GC-MS) is a common tool used in forensic and clinical analysis but there is a potential for inducing analysis-related ambiguities. This study reports on the thermal degradation of modafinil, modafinic acid, adrafinil, CRL-40,940 and CRL-40,941 due to exposure to the heated GC injection port dissolved in a variety of solvents. Key degradation products common to modafinil, modafinic acid, adrafinil analysis included diphenylmethanol and 1,1,2,2-tetraphenylethane (TPE), the latter of which was verified by its synthesis</p>

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	<p>and characterization by x-ray crystallography. The investigated compounds were also characterized by <sup>1</sup>H and <sup>13</sup>C NMR. Diphenylmethane and thiobenzophenone were also identified in some instances. TPE formation was suggested to involve the generation of a benzhydrylium ion and its reaction with the sulfoxide oxygen of the parent compound to give an oxysulfonium intermediate. Correspondingly, the fluorinated TPE analog was formed during heat-induced degradation of modafinil, CRL-40,940 and CRL-40,941, respectively. When a mixture of modafinil (non-fluorinated) and modafinil (fluorinated) were subjected to GC analysis, 4,4'-(2,2-diphenylethane-1,1-diyl)bis(fluorobenzene) was detected as a third cross reaction product in addition to the two expected TPE analogs. These observations served as a reminder that the seemingly straightforward implementation of GC-MS analysis can lead to challenges during routine analysis.</p>

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**Keywords:** Modafinil, adrafinil, modafinic acid, CRL-40,940, CRL-40,941, modafiendz, smart drugs, nootropic, forensic

**Abstract**

2-[(Diphenylmethyl)sulfinyl]acetamide (modafinil) is commonly prescribed for the treatment of narcolepsy and increasing popularity and off-label use as a cognitive enhancer resulted in a reputation as an intelligence boosting ‘wonder drug’. Common alternatives available from online shops and other retail outlets include 2-[(diphenylmethyl)sulfinyl]-*N*-hydroxyacetamide (adrafinil), 2-[[bis(4-fluorophenyl)methyl]sulfinyl]acetamide (CRL-40,940), 2-[[bis(4-fluorophenyl)methyl]sulfinyl]-*N*-hydroxyacetamide (CRL-40,941) and *N*-methyl-4,4-difluoro-modafinil (modafiendz), respectively. Gas chromatography mass spectrometry (GC-MS) is a common tool used in forensic and clinical analysis but there is a potential for inducing analysis-related ambiguities. This study reports on the thermal degradation of modafinil, modafinic acid, adrafinil, CRL-40,940 and CRL-40,941 due to exposure to the heated GC injection port dissolved in a variety of solvents. Key degradation products common to modafinil, modafinic acid, adrafinil analysis included diphenylmethanol and 1,1,2,2-tetraphenylethane (TPE), the latter of which was verified by its synthesis and characterization by x-ray crystallography. The investigated compounds were also characterized by <sup>1</sup>H and <sup>13</sup>C NMR. Diphenylmethane and thiobenzophenone were also identified in some instances. TPE formation was suggested to involve the generation of a benzhydrylium ion and its reaction with the sulfoxide oxygen of the parent compound to give an oxysulfonium intermediate. Correspondingly, the fluorinated TPE analog was formed during heat-induced degradation of modafiendz, CRL-40,940 and CRL-40,941, respectively. When a mixture of modafinil (non-fluorinated) and modafiendz (fluorinated) were subjected to GC analysis, 4,4'-(2,2-diphenylethane-1,1-diyl)bis(fluorobenzene) was detected as a third cross reaction product in addition to the two expected TPE analogs. These observations served as a reminder that the seemingly straightforward implementation of GC-MS analysis can lead to challenges during routine analysis.

**Introduction**

Modafinil (Figure 1) has been used for treating excessive daytime sleepiness or narcolepsy without interfering with nocturnal sleep<sup>[1,2]</sup> and it is well tolerated with little or no side effects.<sup>[3]</sup> It was also reported in a case of doping violation in 2003 at the World Track and Field Championship for the first time<sup>[4]</sup> followed by inclusion in the stimulant-drug list prohibited by the World Anti-Doping Agency (WADA) in 2004.<sup>[5]</sup> The pharmacokinetics of modafinil has been well studied and it is primarily hydrolyzed by esterases and amidases to modafinic acid, which is its major metabolite.<sup>[3,6,7]</sup>

Studies have also identified that modafinil might be useful to treat cocaine dependence as it was found to reduce cocaine self-administration and cocaine reduced euphoria in human studies.<sup>[8-10]</sup> However, a 2012 randomized study, involving cocaine dependent subjects using cocaine (0 mg/day, 200 mg/day or 400 mg/day), with a once per week cognitive behavioral therapy session, indicated that modafinil had no effect.<sup>[11]</sup> Investigations have shown<sup>[12-13]</sup> that modafinil is ineffective for the treatment of cocaine dependence in cocaine-dependent subjects without comorbid alcohol dependence. In separate trials,<sup>[14,15]</sup> there was evidence that cocaine-dependent individuals, without co-morbid alcohol dependence, treated with modafinil had showed usefulness as a treatment for these patients.

Modafinil can be considered an interesting alternative to current amphetamine based medications that show high abuse liability and dependence producing properties. As a result of its presumed lower potential for abuse and lack of peripheral sympathomimetic effects that are associated with amphetamine stimulants, it has also been researched for off-label use to treat sedation associated with other disorders such as parkinsonism, fatigue in human immunodeficiency virus (HIV) infection, multiple sclerosis, cancer and attention deficit hyperactivity disorder (ADHD).<sup>[16-20]</sup> The mechanism of action of modafinil is complex and poorly understood. Studies regarding its effects on dopaminergic pathways and evidence regarding effects on serotonergic and GABAergic pathways are reviewed elsewhere.<sup>[21]</sup> The standard therapeutic dose of modafinil in adult patients is 200-400 mg daily.<sup>[22]</sup>

Although originally prescribed to help narcoleptic patients stay awake and alert there are studies reporting improved performance that came alongside its wakefulness properties.<sup>[23]</sup> Due to its off-label use for improved performance, modafinil has been sought by healthy individuals to improve user performance in specific tasks.<sup>[24]</sup> In addition modafinil use has been noted regarding enhancing task ability versus cheating in other fields.<sup>[25]</sup> Studies showed that neuropsychological performance was improved by increasing short-term memory and boosting an individual's ability to plan and process information.<sup>[24,26]</sup> Use of cognitive enhancers is gaining ground. In 2008, the journal Nature presented the results of an informal survey polling readers regarding the use of three specific cognition enhancement agents. The results showed that 20% of the respondents reported the use of such agents for nontherapeutic enhancement purposes. In addition, 69% of the respondents agreed that healthy adults should have the choice to use cognitive enhancement agents.<sup>[27]</sup> In 2016, an online survey was carried out to evaluate pharmacological enhancement of professional workers in the field of economics. A total of 1021 participants

completed the anonymous survey and results showed that lifetime use of any drug for neuroenhancement was 88% and for the use of illicit or prescription drugs was 19%.<sup>[28]</sup> Poll participants stated reasons such as “curiosity”, “to enhance mood”, “for a confident appearance”, “stress/pressure to perform” and “deadline pressure” for use of such substances.

Modafinil has rapidly gained a positive reputation for improving attention, executive function and memory.<sup>[29]</sup> The interest in the off-label use of modafinil in the media has directed the general public and scientific community towards brain-boosting nootropic supplements. Nootropic supplements are substances claimed to improve cognitive function, particularly attention, executive function and memory in healthy patients. Such supplements are easy to purchase through online vendors. A popular modafinil alternative is the *N*-hydroxy derivative of modafinil called adrafinil (2-((diphenylmethyl)sulfinyl)-*N*-hydroxyacetamide) (Figure 1). Adrafinil is also a pro-drug and it is metabolized, mainly in the liver, to its bioactive amide, modafinil.<sup>[30]</sup> CRL-40,940 (Figure 1) is also advertised as a wakefulness promoting agent that represents the bisfluoro analog of modafinil but it has also been reported as a so-called designer drug.<sup>[31-34]</sup> CRL-40,941 and modafiendz are also wakefulness promoting agents and related to modafinil and adrafinil (Figure 1).

Customs and forensic laboratories are increasingly encountering these substances in both tablet and powdered forms. The first detection of modafinil has been reported to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) via the European Union early warning system (EWS) in 2015.<sup>[35]</sup> Both adrafinil and modafiendz detections were first reported in 2014.<sup>[36]</sup> In Ireland, a recent media report (April 2016) indicated that there has been a surge in the purchasing of smart-drugs illegally on the dark web.<sup>[37]</sup> The three most popular smart-drugs detected smuggled into Ireland were amphetamine, dextroamphetamine, methylphenidate and modafinil.

Gas chromatography mass spectrometry (GC-MS) is widely utilized in forensic chemistry laboratories and is regarded as a robust methodology but, in the case of thermally labile compounds, analytical challenges arise when attempting to investigate the analytical profile. This study reports on the thermal degradation of modafinil, adrafinil, modafinic acid, CRL-40,940 and CRL-40,941 in the GC injector and the formation of common degradation products, i.e. 1,1,2,2-tetraphenylethane, and its fluoro analog. This study confirmed the presence of the degradants by comparison with authenticated synthesized standards. As the popularity and abundance of neuroenhancement drugs appears to be increasing, it is expected that challenges faced by customs and forensic laboratories might arise when employing GC-MS as the standard tool of analysis, similar to what has been reported for other drugs.<sup>[38]</sup>

**Experimental**

All reagents and dry solvents used in the syntheses were obtained from Sigma Aldrich Ltd (Arklow, Co. Wicklow, Ireland). LC-MS grade solvents were obtained from Fisher Scientific (Dublin, Ireland).

### 1,1,2,2-Tetraphenylethane

A solution of 1,1,2,2-tetraphenylethylene (250 mg, 0.75 mmol) in ethyl acetate (40 mL), containing palladium on charcoal (10%, 150 mg) was stirred under an atmosphere of hydrogen for 96 h. The catalyst was removed by filtration and the solvent was then removed to afford a colorless solid (161 mg, 0.50 mmol, 67%): m.pt. 198-200 °C (recrystallized from ethyl acetate/acetonitrile);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.18-7.23 (m; 8 H; Ar-H), 7.11-7.17 (m; 8 H; Ar-H), 7.03-7.08 (m; 4H; Ar-H) and 4.81 (s; 2H, CH) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  143.46 (Ar-C), 128.52 (Ar-CH), 128.15 (Ar-CH), 125.86 (Ar-CH) and 56.33 (CH) ppm. The compound did not produce a suitable quasimolecular ion for accurate mass determination.

### 2-(Benzhydrylsulfinyl)acetic acid (modafinic acid)

Aqueous hydrogen peroxide solution (35 % wt., 0.43 mL, 5.0 mmol) was added to a solution of 2-(benzhydrylthio)acetic acid (1.28 g, 5 mmol) in glacial acetic acid (8 mL) and the mixture was allowed to stand at room temperature for 2 h. The solvent was allowed to evaporate overnight and the residue was recrystallized from acetonitrile to afford colorless crystals (814 mg, 3.0 mmol, 60%): m.pt. 144-146 °C;  $^1\text{H}$  NMR ( $d_6$  DMSO)  $\delta$  13.23 (s; 1H; OH), 7.52-7.56 (m; 4H; Ar-H), 7.33-7.47 (m; 6H; Ar-H), 5.43 (s; 1H; CH), 3.58 (d;  $J$  = 14.3 Hz; 1H, one H from  $\text{CH}_2$ ) and 3.35 (d;  $J$  = 14.3 Hz; 1H, one H from  $\text{CH}_2$ ) ppm;  $^{13}\text{C}$  NMR ( $d_6$  DMSO)  $\delta$  167.84 (C=O), 137.07 (Ar-C), 135.34 (Ar-C), 130.06 (Ar-CH), 129.58 (Ar-CH), 129.04 (Ar-CH), 128.96 (Ar-CH), 128.57 (Ar-CH), 128.51 (Ar-CH), 69.69 (CH) and 55.88 ( $\text{CH}_2$ ) ppm; ESI HRMS: Found  $m/z$  273.0569 (calc. for  $[\text{M-H}]^-$ ,  $\text{C}_{15}\text{H}_{13}\text{O}_3\text{S}$ ,  $m/z$  273.0580,  $\Delta$  = -4.03 ppm).

### Modafinil

Purchased from Sigma Aldrich (EPCRS grade): m.pt. 164-166 °C  $^1\text{H}$  NMR ( $d_6$  DMSO)  $\delta$  7.70 (s; 1H; one H from  $\text{NH}_2$ ), 7.50-7.56 (m; 4H; Ar-H), 7.31-7.45 (m; 7H; Ar-H and one H from  $\text{NH}_2$ ), 5.36 (s; 1H; CH), 3.38 (d;  $J$  = 13.6 Hz; 1H, one H from  $\text{CH}_2$ ) and 3.23 (d;  $J$  = 13.6 Hz; 1H, one H from  $\text{CH}_2$ ) ppm;  $^{13}\text{C}$  NMR ( $d_6$  DMSO)  $\delta$  166.35 (C=O), 137.20 (Ar-C), 134.92 (Ar-C), 129.70 (Ar-CH), 129.03 (Ar-CH), 128.48 (2 x Ar-CH), 127.95 (Ar-CH), 127.92 (Ar-CH), 68.71 (CH) and 56.15 ( $\text{CH}_2$ ) ppm; ESI HRMS: Found  $m/z$  296.0706 (calc. for  $[\text{M}+\text{Na}]^+$ ,  $\text{C}_{15}\text{H}_{15}\text{NO}_2\text{NaS}$ ,  $m/z$  296.0716,  $\Delta$  = -3.37 ppm).

### Adrafinil

Purchased from Scientific Supplies Ltd (London, UK) in 2015 and recrystallized from acetonitrile/ethanol to afford almost colorless crystals: m.pt. 140-142 °C;  $^1\text{H}$  NMR ( $d_6$  DMSO)  $\delta$  10.81 (s; 1H; NOH), 9.17 (s; 1H; NH), 7.51-7.57 (m; 4H; Ar-H), 7.31-7.48 (m; 6H; Ar-H), 5.41 (s; 1H; CH), 3.35 (d;  $J$  = 13.4 Hz; 1H, one H from  $\text{CH}_2$ ) and 3.08



(d;  $J = 13.4$  Hz; 1H, one H from  $\text{CH}_2$ ) ppm;  $^{13}\text{C}$  NMR ( $\text{d}_6$ -DMSO)  $\delta$  161.14 (C=O), 137.01 (Ar-C), 134.85 (Ar-C), 129.68 (Ar-CH), 129.07 (Ar-CH), 128.53 (Ar-CH), 128.51 (Ar-CH), 128.02 (Ar-CH), 127.97 (Ar-CH), 68.93 (CH) and 43.83 ( $\text{CH}_2$ ) ppm; ESI HRMS: Found  $m/z$  312.0653 (calc. for  $[\text{M}+\text{Na}]^+$ ,  $\text{C}_{15}\text{H}_{15}\text{NO}_3\text{NaS}$ ,  $m/z$  312.0665,  $\Delta = -3.84$  ppm).

#### 2-(Benzhydrylthio)acetamide

A mixture of 2-(benzhydrylthio)acetic acid (1.034 g, 4 mmol), thionyl chloride (595 mg, 5 mmol) and toluene (10 mL) was refluxed for 1 hr. The mixture was allowed to cool to room temperature and the volatiles were removed under vacuum. The residue was dissolved in dichloromethane (20 mL) and a solution of methanolic ammonia (7 M, 4 mL) in dichloromethane (40 mL) was added slowly. The mixture was stirred at room temperature for 30 minutes and then centrifuged (3,000 rpm for 5 min.). The supernatant was collected, evaporated to dryness to afford a colorless solid (941 mg). A portion (533 mg) was purified by preparative TLC (silica gel, 2 mm; ethyl acetate/hexane, 8/2) to afford a colorless solid (253 mg, 35 %): m.pt. 108-110 °C;  $^1\text{H}$  NMR ( $\text{d}_6$  DMSO) 7.47-7.40 (m; Ar-H and one NH; 5H), 7.37-7.31 (m; 4H; Ar-H), 7.27-7.22 (m; 2H; Ar-H), 7.03 (s; 1H; NH), 5.41 (s; 1H; CH) and 2.95 (s; 2H;  $\text{CH}_2$ );  $^{13}\text{C}$  NMR ( $\text{d}_6$  DMSO)  $\delta$  170.81 (C=O), 141.70 (Ar-C), 129.03 (Ar-CH), 128.47 (Ar-CH), 127.62 (Ar-CH), 53.42 (CH) and 35.38 ( $\text{CH}_2$ ); ESI HRMS Found:  $m/z$  280.0773 (calc. for  $[\text{M}+\text{Na}]^+$ ,  $\text{C}_{15}\text{H}_{15}\text{NOSNa}$ ,  $m/z$  280.0772,  $\Delta = 0.4$  ppm).

#### 2-((Bis(4-fluorophenyl)methyl)sulfinyl)-N-methylacetamide (Modafinidz)

Purchased from Scientific Supplies Ltd (London, UK). M.pt. 86-88 °C;  $^1\text{H}$  NMR ( $\text{d}_6$ -DMSO)  $\delta$  8.17 (q;  $J = 4.6$  Hz, 1H; NH), 7.50-7.59 (m; 4H; Ar-H), 7.23-7.30 (m; 4H; Ar-H), 5.43 (s; 1 H; CH), 3.44 (d;  $J = 13.4$  Hz; 1H; 1 H from  $\text{CH}_2$ ), 3.17 (d;  $J = 13.4$  Hz; 1H; 1H from  $\text{CH}_2$ ) and 2.57 (d,  $J = 4.6$  Hz; 3H;  $\text{CH}_3$ );  $^{13}\text{C}$  NMR ( $\text{d}_6$  DMSO)  $\delta$  164.44 (C=O), 161.91 (d;  $J_{\text{C,F}} = 245$  Hz; Ar-C), 161.64 (d;  $J_{\text{C,F}} = 245$  Hz; Ar-C), 133.24 (d;  $J_{\text{C,F}} = 3$  Hz; Ar-C), 131.65 (d;  $J_{\text{C,F}} = 8$  Hz; Ar-CH), 130.73 (d;  $J_{\text{C,F}} = 3$  Hz; Ar-C), 130.56 (d;  $J_{\text{C,F}} = 8$  Hz; Ar-CH), 115.86 (d;  $J_{\text{C,F}} = 21$  Hz; Ar-CH), 115.34 (d;  $J_{\text{C,F}} = 21$  Hz; Ar-CH), 66.53 (CH), 56.22 ( $\text{CH}_2$ ) and 25.70 ( $\text{CH}_3$ ); ESI HRMS: Found  $m/z$  324.0869 (calc. for  $[\text{M}+\text{H}]^+$ ,  $\text{C}_{16}\text{H}_{16}\text{F}_2\text{NO}_2\text{S}$ ,  $m/z$  324.0864,  $\Delta = 1.54$  ppm).

#### 2-((Bis(4-fluorophenyl)methyl)sulfinyl)acetamide (CRL-40,940)

Purchased from NewMind (Chicago, USA). M.pt. 130-132 °C;  $^1\text{H}$  NMR ( $\text{d}_6$  DMSO)  $\delta$  7.68 (s; 2H; NH), 7.50-7.61 (m; 4H; Ar-H), 7.33 (s; 1H, NH), 7.22-7.31 (m; 4H; Ar-H), 5.41 (s; 1H; CH), 3.41 (d;  $J = 13.7$  Hz; 1H; 1H from  $\text{CH}_2$ ) and 3.17 (d;  $J = 13.7$  Hz; 1H; 1H from  $\text{CH}_2$ );  $^{13}\text{C}$  NMR ( $\text{d}_6$  DMSO)  $\delta$  166.17 (C=O), 161.89 (d;  $J_{\text{C,F}} = 245$  Hz; Ar-C), 161.63 (d;  $J_{\text{C,F}} = 245$  Hz; Ar-C), 133.35 (d;  $J_{\text{C,F}} = 3$  Hz; Ar-C), 131.65 (d;  $J_{\text{C,F}} = 8$  Hz; Ar-CH), 130.75 (d;  $J_{\text{C,F}} = 3$  Hz; Ar-C), 130.51 (d;  $J_{\text{C,F}} = 8$  Hz; Ar-CH), 115.86 (d;  $J_{\text{C,F}} = 21$  Hz; Ar-CH), 115.32 (d;  $J_{\text{C,F}} = 21$  Hz; Ar-CH), 66.37 (CH) and 56.17 ( $\text{CH}_2$ );  $^{19}\text{F}$  NMR ( $\text{d}_6$  DMSO) -114.04 and -114.18 ppm; ESI HRMS Found 332.0533 (calc. for  $[\text{M}+\text{H}]^+$ ,  $\text{C}_{15}\text{H}_{13}\text{F}_2\text{NO}_2\text{SNa}$ , 332.0533,  $\Delta = 0.0$  ppm).

#### 2-((Bis(4-fluorophenyl)methyl)sulfinyl)-N-hydroxyacetamide (CRL- 40,941)



Purchased from NewMind (Chicago, USA). M.pt. 110-112 °C;  $^1\text{H}$  NMR ( $\text{d}_6$  DMSO)  $\delta$  10.78 (s; 1 H, OH), 9.17 (s; 1H; NH), 7.50 – 7.63 (m; 4H; Ar-H), 7.21-7.32 (m; 4H; Ar-H), 5.46 (s; 1H; CH), 3.39 (d;  $J$  = 13.3 Hz; 1H; 1H from  $\text{CH}_2$ ) and 3.02 (d;  $J$  = 13.3 Hz; 1H; 1H from  $\text{CH}_2$ );  $^{13}\text{C}$  NMR ( $\text{d}_6$  DMSO)  $\delta$  160.99 (C=O), 161.95 (d;  $J_{\text{C,F}}$  = 245 Hz; Ar-C), 161.69 (d;  $J_{\text{C,F}}$  = 245 Hz; Ar-C), 133.16 (d;  $J_{\text{C,F}}$  = 3 Hz; Ar-C), 131.67 (d;  $J_{\text{C,F}}$  = 8 Hz; Ar-CH), 130.66 (d;  $J_{\text{C,F}}$  = 3 Hz; Ar-C), 130.57 (d;  $J_{\text{C,F}}$  = 8 Hz; Ar-CH), 115.93 (d;  $J_{\text{C,F}}$  = 21 Hz; Ar-CH), 115.39 (d;  $J_{\text{C,F}}$  = 21 Hz; Ar-CH), 66.64 (CH) and 53.83 ( $\text{CH}_2$ );  $^{19}\text{F}$  NMR ( $\text{d}_6$  DMSO) -113.90 and -114.08 ppm; ESI HRMS: Found  $m/z$  324.0491 (calc. for  $[\text{M-H}]^-$ ,  $\text{C}_{15}\text{H}_{12}\text{F}_2\text{NO}_3\text{S}$ ,  $m/z$  324.0506,  $\Delta$  = -4.6 ppm).

### *1,1,2,2-Tetrakis(4-fluorophenyl)ethane*

A mixture of 4,4'-difluorobenzophenone (2.18 g, 10 mmol), thionyl chloride (1.81 mL, 25 mmol) and DMF (0.75 mL) was heated at 75 °C for 20 h. After cooling to room temperature, the reaction mixture was poured into ice-cold water (with thorough mixing) and extracted with toluene. The organic extract was dried (anhydrous magnesium sulfate) and the volatiles were removed under vacuum to afford a colorless oil (2.34 g, 8.8 mmol). Toluene (10 mL) and copper-tin alloy (2.0 g) were added and the mixture was refluxed for 3 h. After cooling to room temperature, the mixture was washed with aqueous hydrochloric acid (2 M), centrifuged (3,000 rpm for 5 min) and the organic layer was collected. Removal of the volatiles under vacuum afforded a light brown semi-solid (1.70 g). A portion of this (600 mg) was purified by preparative TLC (silica gel, 2 mm; hexane) to afford a colorless powder (124 mg). This was dissolved in ethyl acetate (10 mL), palladium on charcoal (10 %, 200 mg) was then added and the mixture was stirred under an atmosphere of hydrogen for 48 h. Analysis by GC-MS revealed about 40% conversion (peak areas). More ethyl acetate (10 mL) and palladium on charcoal (10%, 200 mg) were then added and hydrogen was bubbled through the mixture for 30 min. The mixture was then stirred under an atmosphere of hydrogen for 24 h. The catalyst was removed by filtration and the filtrate was evaporated to dryness to afford an almost colorless solid. This was recrystallized (ethyl acetate/hexane) to give colorless crystals (29 mg, 4%): m.pt. 258-262 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.03-7.10 (m; 8H; Ar-H), 6.81-6.90 (m; 8H; Ar-H) and 4.65 (s; 2H; CH);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  161.14 (d;  $J_{\text{C,F}}$  = 245 Hz; Ar-C), 138.56 (d;  $J_{\text{C,F}}$  = 3 Hz; Ar-C), 129.70 (d;  $J_{\text{C,F}}$  = 8 Hz; Ar-CH), 115.23 (d;  $J_{\text{C,F}}$  = 21 Hz; Ar-CH), 115.39 (d;  $J_{\text{C,F}}$  = 21 Hz; Ar-CH) and 55.11 (CH);  $^{19}\text{F}$  NMR ( $\text{d}_6$  DMSO)  $\delta$  -116.51 ppm. The compound did not produce a suitable quasimolecular ion for accurate mass determination.

## **Instrumentation**

### *Gas chromatography-mass spectrometry (GC-MS)*

Samples were analyzed on an Agilent 6890N gas chromatograph coupled to a 5975 insert MSD. A HP ULTRA 1 column (12 m  $\times$  0.2 mm  $\times$  0.33  $\mu\text{m}$ ) was used in split mode (1:1 or as stated) with helium carrier gas at a constant flow of 0.8 mL/min. The injection port and transfer line temperatures were set at 250°C and 280°C

respectively. The initial oven temperature was 60°C, held for 2 minutes and then ramped at 25 °C/min to 295 °C with a final hold time of 3 min (run time 14.4 min). The ionization energy was set at 70 eV, the quadrupole at 150°C, the ion source at 230 °C and the mass range was  $m/z$  40-550.

*Gas chromatography ion trap mass spectrometry*

Electron ionization mass spectra were recorded under standard conditions. Chemical ionization mass spectra were recorded using HPLC grade methanol as the liquid CI reagent. A Varian 450-GC gas chromatograph coupled to a Varian 220-MS ion trap mass spectrometer and a Varian 8400 autosampler was employed with a Varian CP-1177 injector (275 °C) in split mode (1:50) (Walnut Creek, CA, USA). The Varian MS Data Review function of the Workstation software, version 6.91, was used for data acquisition. The carrier gas was helium at a flow rate of 1 mL/min using the EFC constant flow mode. The default settings for CI ionization parameters (0.4 s/scan) were used: CI storage level  $m/z$  19.0; ejection amplitude  $m/z$  15.0; background mass  $m/z$  55; maximum ionization time 2000  $\mu$ s; maximum reaction time 40 ms; target TIC 5000 counts. Temperatures for ion trap, manifold, and transfer line were set at 170 °C, 120 °C, and 280 °C, respectively. An Agilent J&W VF-5ms GC column (30 m  $\times$  0.25 mm, 0.25  $\mu$ m) was employed for separation. The starting temperature was set at 80 °C and held for 1 min. The temperature then increased at 20 °C/min to 280 °C and held constant for 9 min to give a total run time of 20.00 min.

*High-resolution electrospray ionization mass spectrometry (HR-ESI-MS)*

*Instrument 1:* HR-ESI mass spectra were recorded by direct injection into a LTQ Orbitrap Discovery (Thermo Fisher Scientific, Bremen, Germany). Samples were dissolved in acetonitrile/water (1:1, containing 0.1% formic acid) and infused at a rate of 5  $\mu$ L/min. Full accurate high-resolution (30 000) mass scans were performed in positive electrospray mode. Measured accurate masses were within  $\pm$  5 ppm of the theoretical masses. The following conditions were used: drying gas ( $N_2$ ) 10 L/min, capillary temperature 310 °C, spray voltage 4 V, capillary voltage 22 V and tube lens 77 V. Mass calibrations were performed in both positive and negative mode using solutions of caffeine, L-methionyl-arginyl-phenylalanylalanine acetate  $\times$   $H_2O$  (MRFA), Ultramark 1621<sup>®</sup>, sodium docetyl sulfate and sodium taurocholate.

*Instrument 2:* ESI mass spectra were also acquired using a Micromass LCT Classic ToF mass spectrometer interfaced to a Waters 2690 HPLC. Leucine Enkephalin was used as an internal lock mass. Operating conditions were as follows: ESI capillary voltage 2500 V, cone voltage 25 V, desolvation temperature 300°C, source temperature 100°C. MassLynx<sup>™</sup> 4.0 software was used to carry out the analysis.

*Liquid chromatography-mass spectrometry (LC-MS)*

LC-MS analyses were performed on an Agilent 1100 HPLC system equipped with a G13795 degasser, G1312A BinPump, a G1313A ALS and G1316A column oven (COLCOM) (Agilent, Little Island, Cork, Ireland). Separation was obtained on a

Kinetex phenyl-hexyl column (2.6  $\mu\text{m}$ , 100 x 2.10 mm) Phenomenex (Macclesfield, Cheshire, United Kingdom). The analytes were eluted under isocratic conditions using a mobile phase of 97% water and 3% acetonitrile (both containing 0.1% formic acid). The Agilent single quadrupole MSD settings were as follows: positive electrospray mode, capillary voltage 3500 V, drying gas ( $\text{N}_2$ ) 12 L/min at 350  $^\circ\text{C}$ , and nebulizer gas ( $\text{N}_2$ ) pressure 50 psi. In-source collision-induced dissociation experiments were carried out with an increased fragmentor voltage of 110 V. Samples were dissolved in acetonitrile/water (1:1, containing 0.1% formic acid) at a concentration of 10  $\mu\text{g/mL}$ . The injection volume was 0.5  $\mu\text{L}$ , flow rate was 0.4 mL/min and the column temperature was set at 30  $^\circ\text{C}$ . Total run time was 25 min.

#### *Nuclear magnetic resonance spectroscopy (NMR)*

All samples were prepared in the stated deuterated solvent at a concentration of 20 mg/mL.  $^1\text{H}$  (600 MHz) and  $^{13}\text{C}$  (150 MHz, referenced to the NMR solvent peak) spectra were recorded on a Bruker AV600 NMR spectrometer using a 5 mm TCI cryoprobe.  $^1\text{H}$  NMR spectra were referenced to an external TMS reference at  $\delta = 0$  ppm.  $^{19}\text{F}$  (376 MHz) spectra were recorded on a Bruker DPX400 NMR spectrometer and the external reference was trifluorotoluene set at  $\delta = -64$  ppm.

#### *X-Ray crystallography for 1,1,2,2-tetraphenylethane*

Data was collected on a Bruker D8 Quest ECO with Mo  $\text{K}\alpha$  radiation ( $\lambda = 0.71073$  Å) using a MiTeGen micromount and at 100(2) K (Oxford Cryosystem). Bruker APEX3<sup>[39]</sup> software was used to collect and reduce data, determine the space group, solve and refine the structure. Absorption corrections were applied using SADABS.<sup>[40]</sup> All final refinements were performed with OLEX/SHELXL.<sup>[41,42]</sup> The molecule exhibits complete molecular disorder with each moiety at 50% occupancy, except for H7 and H7a which are shared at 100% occupancy between each disordered moiety. H7 and H7a were located and refined. All non-hydrogen atoms were refined anisotropically using constraints (EADP). Hydrogen atoms (with the exception of H7, H7a) were assigned to calculated positions using a riding model. See below for crystal data and structure refinement parameters. CCDC 1483400 contains the supplementary crystallographic data (see Supporting Information 1):  $\text{C}_{26}\text{H}_{22}$ ,  $M = 334.43$ ,  $T = 100(2)$  K, Monoclinic,  $\text{C}2/c$ ,  $a = 17.5758(9)$ ,  $b = 5.8709(3)$ ,  $c = 17.5462(10)$  Å,  $\beta = 91.110(3)^\circ$ ,  $V = 1810.18(17)$  Å<sup>3</sup>,  $Z = 4$ ,  $\mu$  (Mo  $\text{K}\alpha$ ) = 0.069  $\text{mm}^{-1}$ ,  $\rho = 1.227$   $\text{Mg/cm}^3$ , 14094 reflections collected, 1915 independent ( $R_{\text{int}} = 0.0857$ ),  $R_1 = 0.0566$ ,  $wR_2 = 0.1063$  ( $I > 2\sigma(I)$ ),  $S = 1.032$ . CCDC 1483400  $R_1 = \sum ||F_o| - |F_c|| / \sum |F_o|$ ,  $wR_2 = [\sum w(F_o^2 - F_c^2)^2 / \sum w(F_o^2)^2]^{1/2}$ .

#### **Results and discussion**

Previously, a GC-MS method was reported for the detection of modafinil in human urine.<sup>[43]</sup> The authors extracted modafinil from drug-spiked urine samples and analyzed directly by GC-MS. Two other characteristic ions, related to the diphenylmethyl fragment ( $m/z$  167), namely  $m/z$  165 and  $m/z$  152, were identified in the mass spectrum. It was stated that the reason for obtaining the single artifact peak

merited further investigation although it was not identified. It has been reported that modafinil, adrafinil and modafinic acid are significantly degraded under EI-GC-MS conditions,<sup>[44]</sup> therefore resulting in an artifact peak for modafinil, adrafinil and modafinic acid that eluted as a single peak at the same retention time. In that study, the artifact peak was used as a marker for screening purposes. A possible site of ionization in the modafinil structure is the diphenylmethyl sulfinyl linkage and, as expected, the main fragment derives from this at  $m/z$  of 167 (base peak). Subsequently, demethylation occurs, yielding  $m/z$  152 as the second major fragment. The authors showed that the operation of the GC at high temperature gave rise to the single artifact peak at the same retention time in each chromatogram albeit the authors did not identify this compound.<sup>[44]</sup> Other authors have reported modafinil as being thermally labile and unsuitable for GC-MS analysis.<sup>[44-46]</sup>

In the work presented in this study, modafinil, adrafinil and modafinic acid were found to produce similar GC chromatograms when acetonitrile, dichloromethane or ethanol were used as solvents (Figure 2a, Supporting Information 2). Two major peaks were present and identified as diphenylmethanol (6.75 min) and 1,1,2,2-tetraphenylethane (10.22 min). However, diphenylmethane (5.81 min) and thiobenzophenone (7.05 min, Supplemental 2) were also identified in some instances. Possible mechanisms for the formation of diphenylmethane and diphenylmethanol are presented in Figure 2a and the EI mass spectrum of 1,1,2,2-tetraphenylethane is shown in Figure 2b (with a magnification in Figure 2c). It displays a very weak molecular ion,  $m/z$  334, and a number of fragments that potentially arise from ion/hydrogen scrambling. It has previously been reported that the benzhydrylium ion,  $m/z$  167, which is in rapid equilibration with the phenyl tropylium ion, transitions to  $m/z$  152 by loss of a methyl radical, formed from the bridging CH unit and two *ortho* hydrogens.<sup>[47-50]</sup> As the formation of ions, such as  $m/z$  239 and  $m/z$  252, are not readily rationalized, it is suggested that these might also arise from ion scrambling mechanisms.

Conventionally, dimerization of two diphenylmethyl radicals ( $\text{Ph}_2\text{CH}^\bullet$ ), formed by the thermolysis of modafinil or a related compound, may lead to the formation of 1,1,2,2-tetraphenylethane.<sup>[51,52]</sup> However, an alternative mechanism (Figure 3) involves the initial formation of the well-known and characterized benzhydrylium (diphenylcarbonium) ion.<sup>[53-55]</sup> It is suggested that thermal degradation of modafinil, adrafinil or modafinic acid could result in the formation of a benzhydrylium ion (Figure 3a). The benzhydrylium ion may then form an oxysulfonium intermediate with the sulfoxide oxygen on modafinil, adrafinil or modafinic acid. This oxysulfonium salt may then degrade to 1,1,2,2-tetraphenylethane via a benzhydryl oxy sulfide species (Figure 3b). Interestingly, the analogous dibenzhydryl disulfide has been shown to decompose on heating to yield 1,1,2,2-tetraphenylethane<sup>[56,57]</sup> and oxysulfonium salts have also been reported previously.<sup>[58-60]</sup> When equimolar (30-970  $\mu\text{M}$ ) acetonitrile solutions of modafinil or modafinil sulfide (Figure 3c) were injected separately on to the GC, the relative amount of 1,1,2,2-tetraphenylethane formed, based upon peak areas, was on average approximately 90 % lower for the sulfide (Supporting Information 3), indicating the sulfoxide oxygen may promote thermal degradation by the facile formation of the oxysulfonium intermediate. The sulfur lone pairs in modafinil sulfide may less readily form a sulfonium salt intermediate with the benzhydrylium ion (Figure 3c), thus resulting in relatively lower yields of 1,1,2,2-

tetraphenylethane. It may be also the case that the postulated intermediate, dibenzhydryl sulfide, is more thermally stable than the corresponding oxysulfide. Varying the split ratio in the GC injector was evaluated but degradant formation was still observed (Supporting Information 4).

Interestingly, in the electrospray ionization mass spectra of modafinil and adrafinil, oxysulfonium ( $M + \text{benzhydrylium ion}$ )<sup>+</sup> adducts were observed (Supporting Information 5), which were consistent with triphenylcyclopropenylum cations that undergo adduct formation in the presence of nucleophiles such as thiols.<sup>[61]</sup>

CRL-40,490 is the fluoro analog of modafinil, CRL-40,491 is the fluoro analog of adrafinil and modafiendz (for analytical data see Supporting Information 6) is the *N*-methyl analog of modafinil, respectively. The corresponding fluoro-analogs of modafinil and adrafinil, namely CRL-40,490 and CRL-40,491, yielded analogous fluorinated degradants indicating that a similar mechanism was implicated. When a mixture of a non-fluorinated and fluorinated derivatives was injected, a mixture of three tetraphenylethanes are observed that represented one *hetero* and two *homo* coupling products. For example, this was observed when a mixture of modafinil and modafiendz (Figure 1) was subjected to GC analysis. The formation of a cross-reaction product was detected at 11.76 min (Figure 4a) along with the two expected diphenylmethane dimers. The cross-reaction product represented the fact that modafinil did not contain the two fluorine atoms attached to modafiendz.

The CI mass spectra for the three tetraphenylethane products are shown in Figure 4b. In each case, it was not possible to obtain the protonated molecule due to loss of either benzene or fluorobenzene from the molecule. With 1,1,2,2-tetrakis(4-fluorophenyl)ethane (the modafiendz degradation product), CI did not provide any more information other than  $m/z$  311 obtained by loss of fluorobenzene, and for 4,4'-(2,2-diphenylethane-1,1-diyl)bis(fluorobenzene) (the modafinil-modafiendz cross-reaction product),  $m/z$  293 was obtained following loss of benzene and  $m/z$  275 was obtained by loss of benzene, respectively. With the modafinil product (1,1,2,2-tetraphenylethane), the protonated ion also lost benzene from  $m/z$  257. The formation of diphenylmethanol and its fluoro analog (bis(4-fluorophenyl)methane) was also observed (Supporting Information 7). Interestingly, both 1,1,2,2-tetraphenylethane and 1,1,2,2-tetrakis(4-fluorophenyl)ethane also failed to produce molecular ions using atmospheric-pressure chemical ionization. This further highlighted the complexities expected when customs/forensic seized samples contain mixtures of these compounds.

Both 1,1,2,2-tetraphenylmethane and 1,1,2,2-tetrakis(4-fluorophenyl)ethane were synthesized, and characterized. X-ray crystallographic analysis of 1,1,2,2-tetraphenylmethane was also performed. Clear colorless plates were isolated from a hexane solution and the structure determined at 100K. The data were solved and refined in the monoclinic space group C2/c. The asymmetric unit consists of one half occupied molecule and symmetry generates the complete disordered molecule (symmetry operation =  $1-x, y, 1.5-z$ , Figures 5a and 5b). Hydrogen atoms H7 and H7a, which are fully occupied, are shared between each disordered molecule. These



hydrogen atoms lie on the two-fold rotation axis. The molecule is in the anti-conformation with a C7-C7a bond length of 1.548(5) Å and C7-ring of 1.530(6) and 1.507(6)Å. The torsion angles between the ring/ethane/ring carbons are ca. -173.6(4) and -173.4(4)° (C6-C7-C7a-C6a and C8-C7-C7a-C8a respectively). The dihedral angles between the substituents in the Newman projection are given in Figure 5c where 60° is the ideal. The anti-conformation dihedral is ca. 5-6° off the ideal of 180°. The structure has been reported previously and is similar to that shown here. In the literature model, reported at room temperature in the Space Group A2/a with comprehensive disorder modeling, the ethane C-C distance is recorded as 1.540 and 1.556Å for each disordered moiety.<sup>[62]</sup> In this structure, the ring atoms were not completely modeled as disordered. Overall, the x-ray structure data were fully consistent with the structure.

Analysis of CRL-40,940 (flmodafinil) and CRL-40,941 (fladrafinil) (LCMS data for both compounds shown in Supporting Information 8) by GC-MS revealed the formation 1,1,2,2-tetrakis(4-fluorophenyl)ethane (Supporting Information 9), in a similar manner to modafinil. The *para*-fluoro analogs of diphenylmethane, benzophenone and diphenylmethanol (major product) were also observed in both cases. Interestingly, CRL-40,940 also produced a small amount of the thiobenzophenone derivative but it was not possible to distinguish between the two compounds. These observations might have significant implications for forensic drug analysis given that CRL-40,940, CRL-40,941 and modafinil produced similar degradant profiles. The GC-MS method used in this study is typical of routine forensic screening protocols. Essentially our group replicated conditions using methodologies widely utilised in most laboratories on a routine basis and therefore other laboratories might encounter similar issues regarding degradation for these compounds.

## Conclusion

The nootropics phenomenon is an area of investigation that attracts attention from multi-disciplinary stakeholders who face the challenge of keeping up-to-date with older substances used in newly emerging off-label ways where few data are available that aid their identification. This study identified a common GC injector port thermolysis product in the analysis of modafinil, adrafinil and modafinilic acid and a mechanism for its formation was proposed. Caution should be exercised in the analysis of modafinil and adrafinil and potentially other nootropic agents containing a similar molecular skeleton. CRL-40,940, CRL-40,941 and modafinil produced the same degradant profile which could lead to ambiguity during forensic analysis. The characterization of modafinil, adrafinil, modafinilic acid, CRL-40,940, CRL-40,941 and modafinil yielded a set of analytical data that were collected to serve research communities involved with the study of these substances in both customs/forensic laboratories and clinical applications. The monitoring of these compounds is important and analytical data presented in this study allows the scientific community to support this endeavor.

GC-MS is frequently implemented in a customs or forensic laboratory setting due to its high sensitivity, fast analysis time, low cost, excellent separation and identification

capabilities. However, special attention should be paid to the potential for ambiguity when using this technique.

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## Figure captions

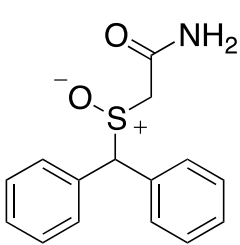
**Figure 1.** Molecular structures of compounds discussed in manuscript

**Figure 2.** (a). Typical GC chromatogram for modafinil, adrafinil or modafinilic acid (chromatogram for modafinil shown) along with mechanisms for the formation of dipheylmethane and dipheylmethanol, (b). EI mass spectrum and potential fragments for 1,1,2,2-tetraphenylethane and (c). magnification of 1,1,2,2-tetraphenylethane mass spectrum.

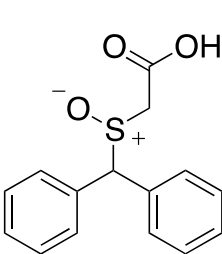
**Figure 3.** Potential mechanism for the formation of 1,1,2,2-tetraphenylethane: (a) formation of the benzhydrylium ion, (b). reaction of modafinil with the benzhydrylium ion to form 1,1,2,2-tetraphenylethane and (c). formation of 1,1,2,2-tetraphenylethane from modafinil sulfide.

**Figure 4.** (a). Chromatograms depicting the formation of 1,1,2,2-tetraphenylethane, its di-fluoro and tetra-fluoro analogs, following the injection of modafinil, modafinil-d<sub>2</sub> or co-injection of modafinil and modafinil-d<sub>2</sub> and (b). ion trap CI and EI mass spectra for 1,1,2,2-tetraphenylethane, its di-fluoro and tetra-fluoro analogs

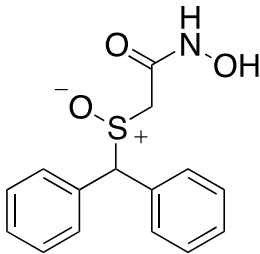
**Figure 5.** (a). Structure 1,1,2,2-tetraphenylethane showing one symmetry unique complete conformation at 50% occupancy (excluding H7, H7a). Atomic displacement shown at 50% probability, (b). Partially labelled symmetry generated (1-x, y, 1.5-z) complete molecule of 1. One disordered molecule is labeled completely and only H7 and H7a shown for clarity and (c). Newman projection down the C7-C7a ethane axis showing the anti-conformation of the molecule with the dihedral angles shown.



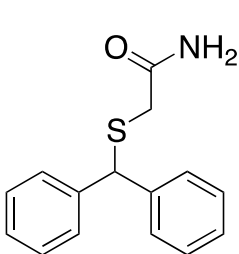
Modafinil



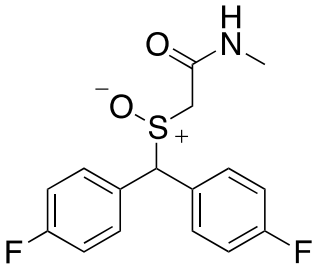
Modafinic acid



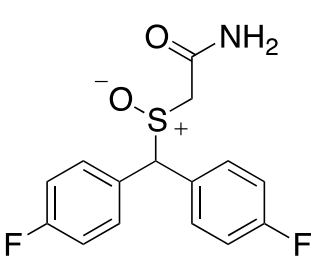
Adrafinil



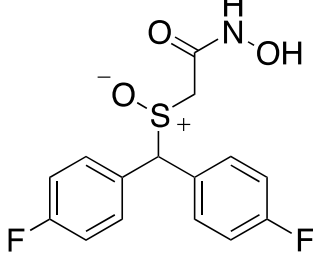
Modafinil sulfide



Modafiendz



CRL 40,490  
(Flmodafinil)



CRL 40,491  
(Fladrafinil)



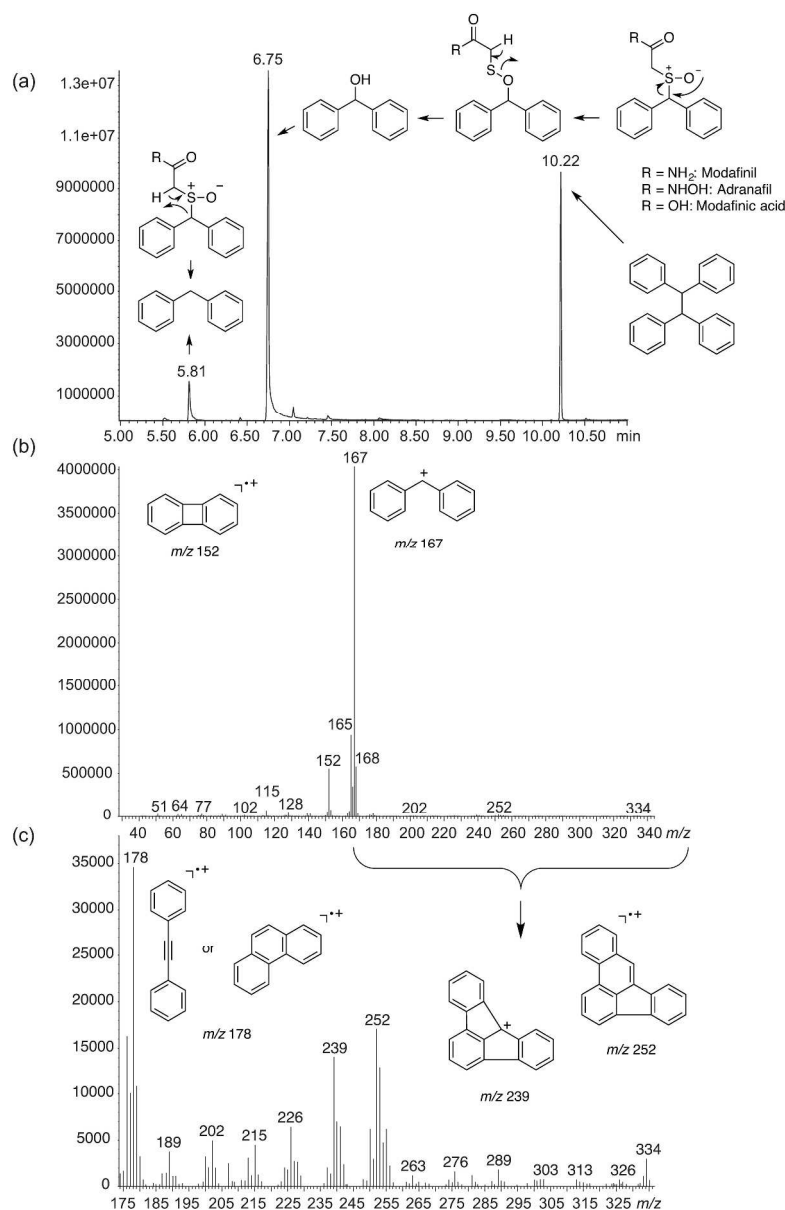
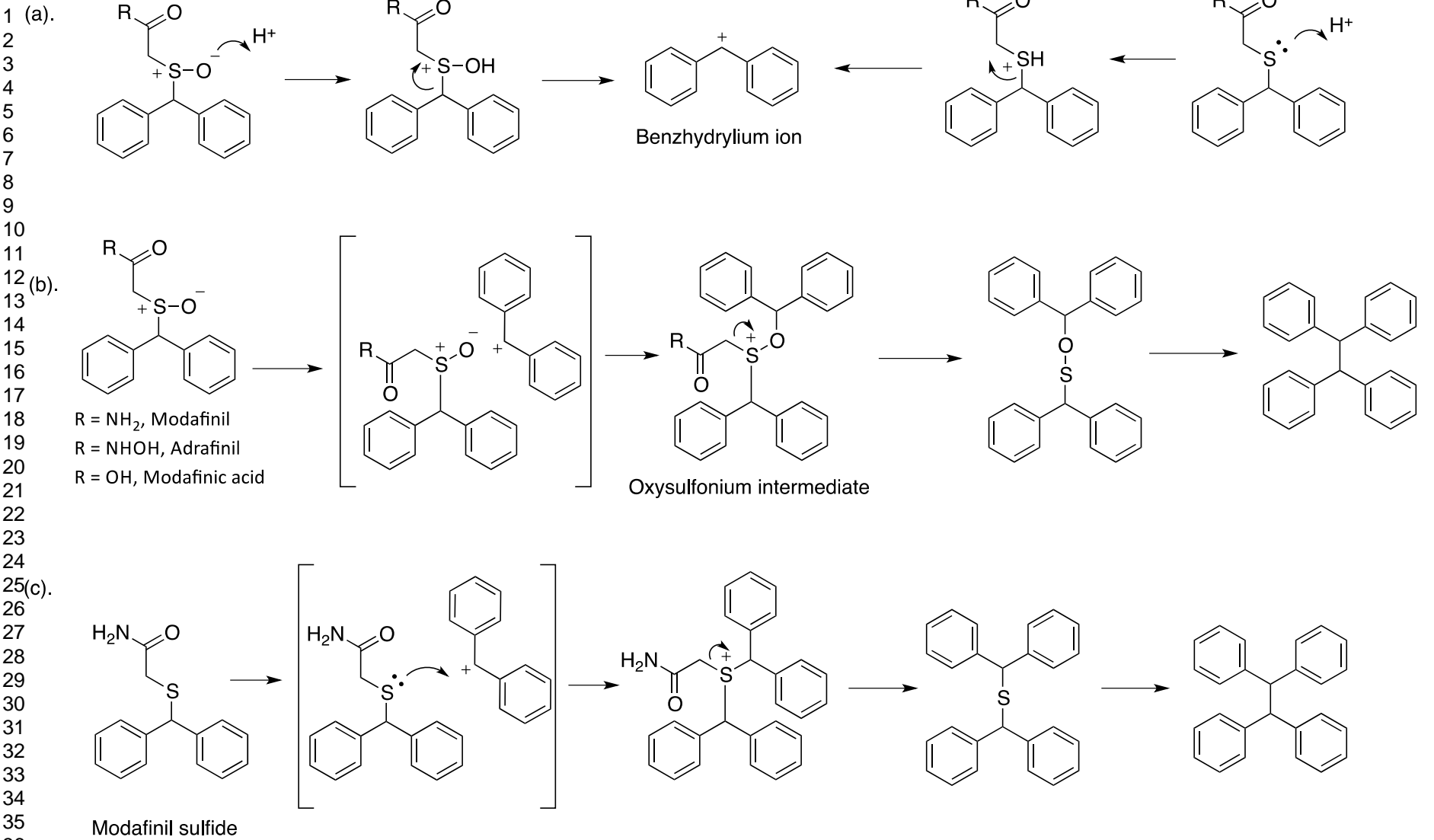


Figure 2. (a). Typical GC chromatogram for modafinil, adrafinil or modafinic acid (chromatogram for modafinil shown) along with mechanisms for the formation of diphenylmethane and diphenylmethanol, (b). EI mass spectrum and potential fragments for 1,1,2,2-tetraphenylethane and (c). magnification of 1,1,2,2-tetraphenylethane mass spectrum.

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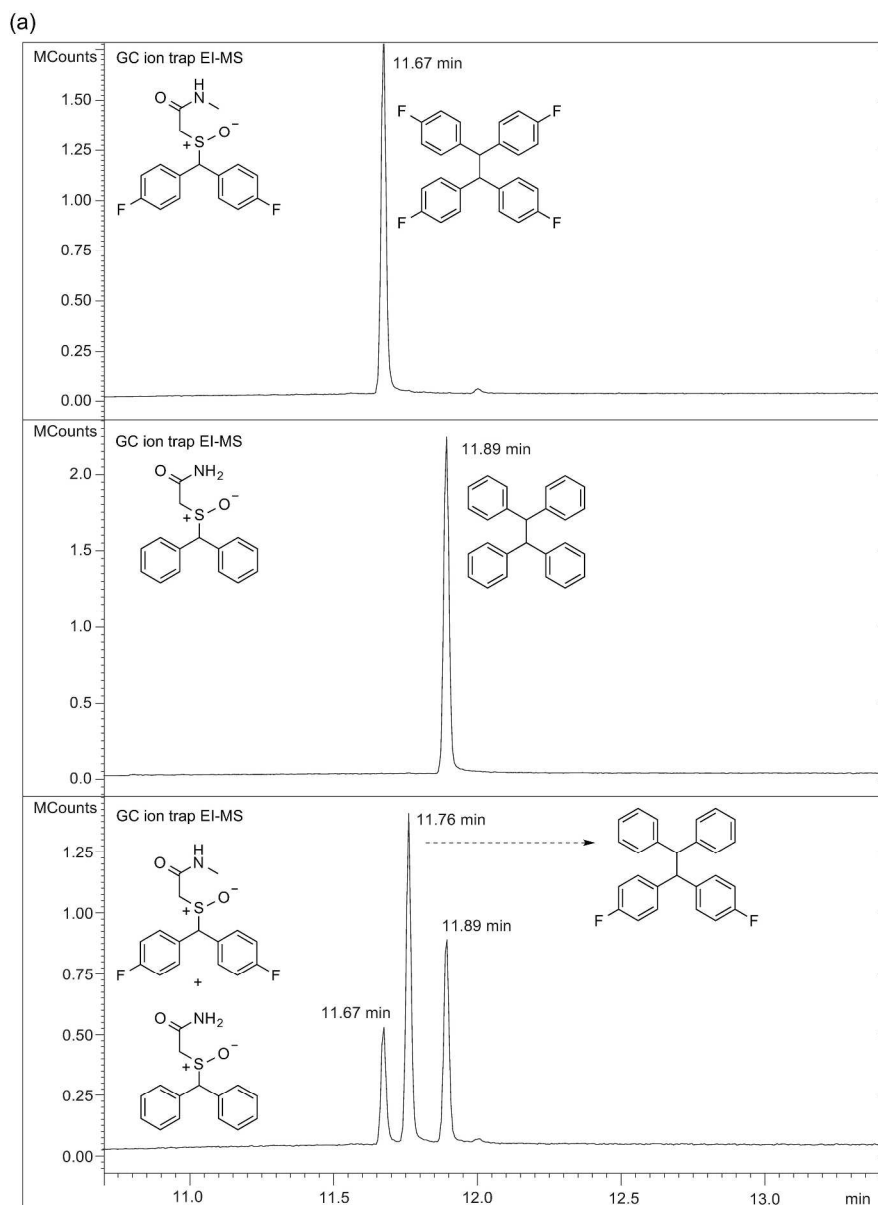


Figure 4. (a). Chromatograms depicting the formation of 1,1,2,2-tetraphenylethane, its di-fluoro and tetra-fluoro analogs, following the injection of modafinil, modafiendz or co-injection of modafinil and modafiendz

271x371mm (300 x 300 DPI)

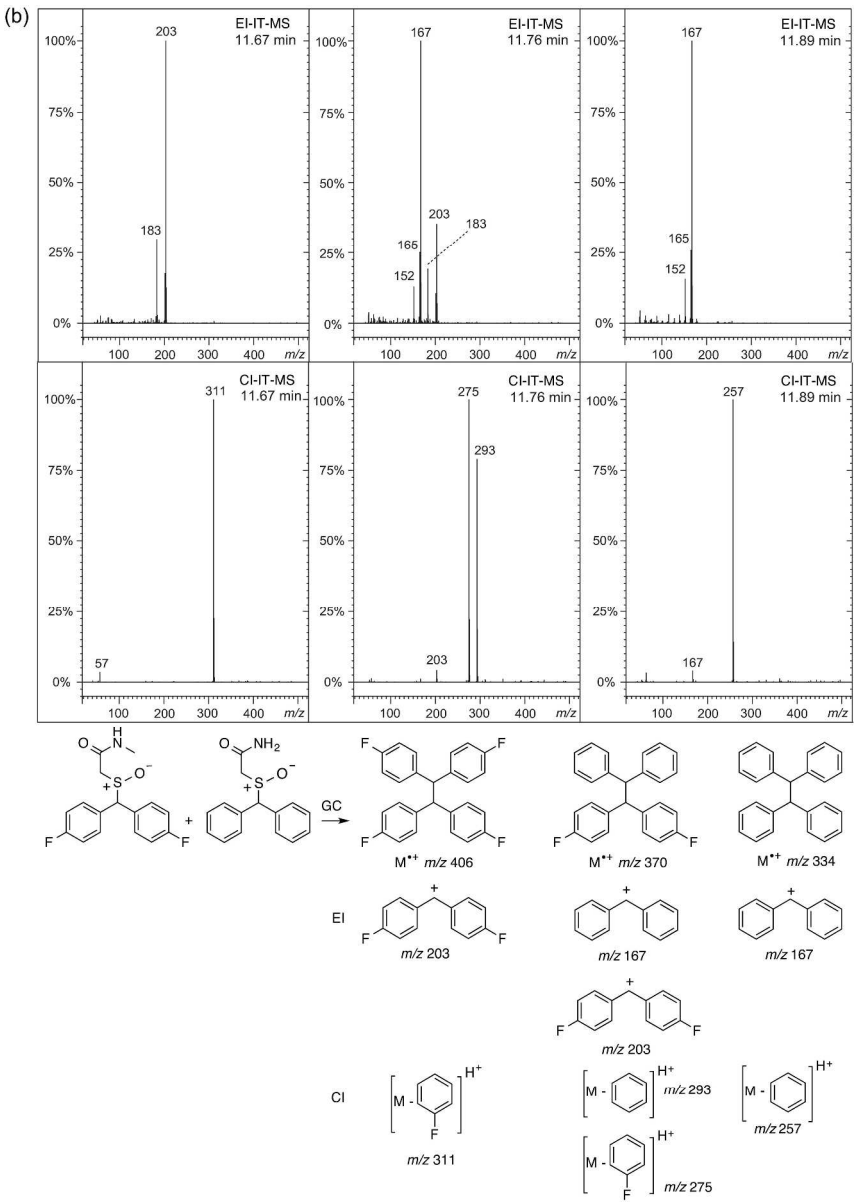
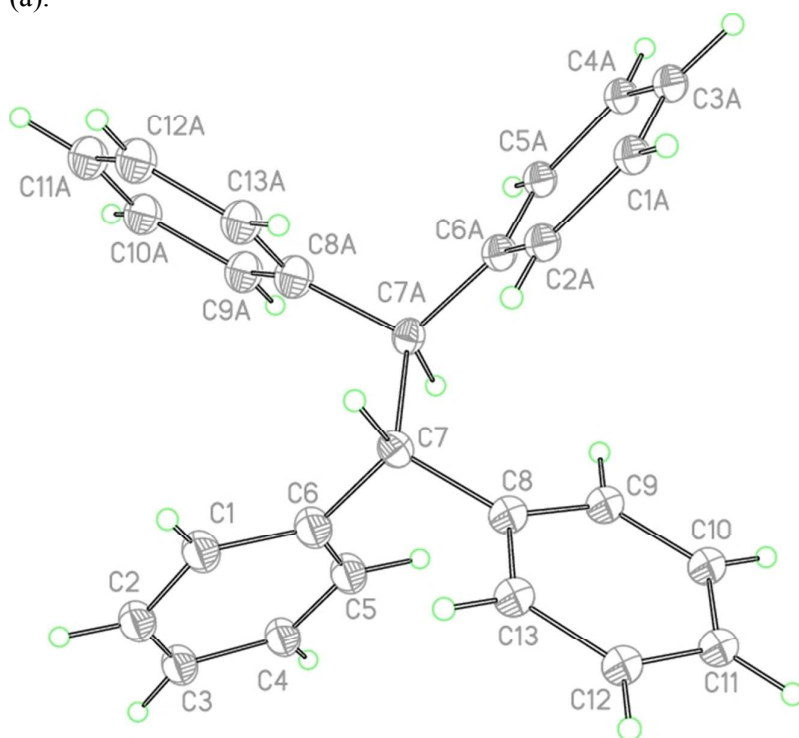


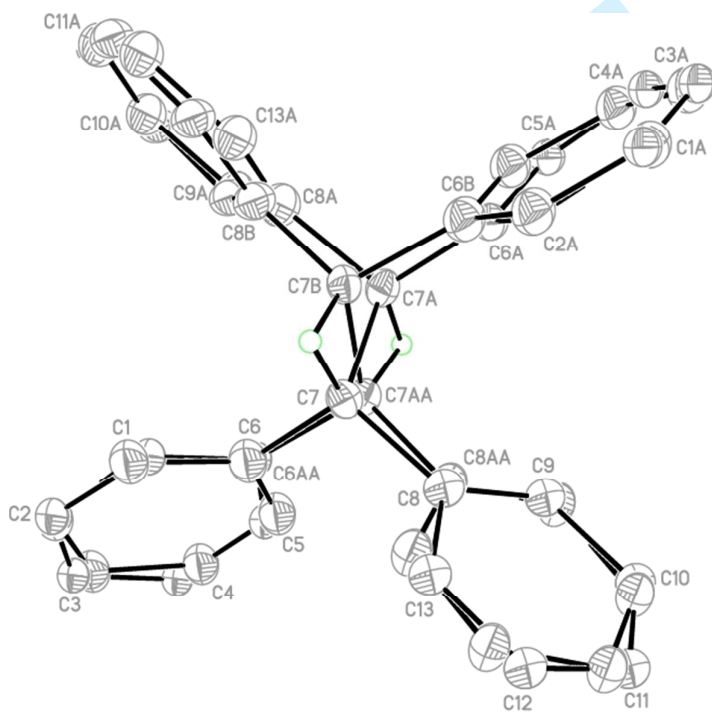
Figure 4. (b). Ion trap CI and EI mass spectra for 1,2,2-tetraphenylethane, its di-fluoro and tetra-fluoro analogs

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(a).

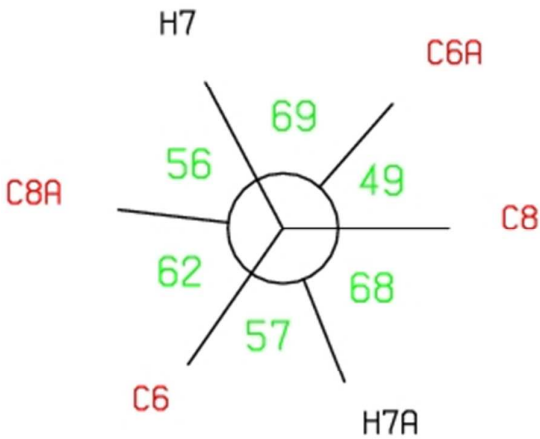


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