

Drug Testing and Analysis



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

Journal:	<i>Drug Testing and Analysis</i>
Manuscript ID	DTA-16-0306.R1
Wiley - Manuscript type:	Research Article
Date Submitted by the Author:	26-Nov-2016
Complete List of Authors:	Dowling, Geraldine; Dublin Institute of Technology, School of Chemistry and Pharmaceutical Sciences; Trinity College Dublin, Pharmacology and Therapeutics Kavanagh, Pierce; Trinity College, Pharmacology and Therapeutics Talbot, Brian; Trinity College, School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin, Dublin 2, Ireland O'Brien, John; School of Chemistry, Trinity College Dublin, Dublin 2, Ireland Hessman, Gary; School of Chemistry, Trinity College Dublin, Dublin 2, Ireland McLaughlin, Gavin; University of Dublin Trinity College, Pharmacology & Therapeutics; Athlone Institute of Technology, Life & Physical Sciences Twamley, Brendan; School of Chemistry, Trinity College Dublin, Dublin 2, Ireland Brandt, Simon; School of Pharmacy & Biomolecular Sciences, Liverpool John Moores University
Keywords:	Modafinil, Adrafinil, Modafinic Acid, GC-MS Degradation
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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

	and characterization by x-ray crystallography. The investigated compounds were also characterized by ¹ H and ¹³ 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.
--	--

SCHOLARONE™
Manuscripts

1
2
3
4 **Outsmarted by nootropics? An investigation into the thermal**
5 **degradation of modafinil, modafinic acid, adrafinil, CRL-40,940 and**
6 **CRL-40,941 in the GC injector: formation of 1,1,2,2-**
7 **tetraphenylethane and its tetra fluoro analog**
8
9

10
11 Geraldine Dowling^{a,b} *, Pierce V. Kavanagh^b, Brian Talbot^c, John O'
12 Brien^d, Gary Hessman^d, Gavin McLaughlin^b, Brendan Twamley^d, and
13 Simon D. Brandt^e
14

15
16 ^a *School of Chemical and Pharmaceutical Sciences, Dublin Institute of Technology, Dublin 2,*
17 *Ireland*
18

19 ^b *Department of Pharmacology and Therapeutics, School of Medicine, Trinity Centre for*
20 *Health Sciences, St. James Hospital, Dublin 8, Ireland*
21

22 ^c *School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin, Dublin 2, Ireland*
23

24 ^d *School of Chemistry, Trinity College Dublin, Dublin 2, Ireland*
25

26 ^e *School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Byrom*
27 *Street, Liverpool L3 3AF, UK*
28
29

30
31 *Correspondence: School of Chemical and Pharmaceutical Sciences, Dublin Institute
32 of Technology, Kevin Street, Dublin 2. E-Mail: Geraldine.Dowling@dit.ie
33

34
35 **Keywords:** Modafinil, adrafinil, modafinic acid, CRL-40,940, CRL-40,941,
36 modafiendz, smart drugs, nootropic, forensic
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 ^1H and ^{13}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

1
2
3 Modafinil (Figure 1) has been used for treating excessive daytime sleepiness or
4 narcolepsy without interfering with nocturnal sleep^[1,2] and it is well tolerated with little
5 or no side effects.^[3] It was also reported in a case of doping violation in 2003 at the
6 World Track and Field Championship for the first time^[4] followed by inclusion in the
7 stimulant-drug list prohibited by the World Anti-Doping Agency (WADA) in 2004.^[5]
8 The pharmacokinetics of modafinil has been well studied and it is primarily
9 hydrolyzed by esterases and amidases to modafinic acid, which is its major
10 metabolite.^[3,6,7]
11
12

13 Studies have also identified that modafinil might be useful to treat cocaine
14 dependence as it was found to reduce cocaine self-administration and cocaine
15 reduced euphoria in human studies.^[8-10] However, a 2012 randomized study,
16 involving cocaine dependent subjects using cocaine (0 mg/day, 200 mg/day or 400
17 mg/day), with a once per week cognitive behavioral therapy session, indicated that
18 modafinil had no effect.^[11] Investigations have shown^[12-13] that modafinil is ineffective
19 for the treatment of cocaine dependence in cocaine-dependent subjects without
20 comorbid alcohol dependence. In separate trials,^[14,15] there was evidence that
21 cocaine-dependent individuals, without co-morbid alcohol dependence, treated with
22 modafinil had showed usefulness as a treatment for these patients.
23
24
25

26 Modafinil can be considered an interesting alternative to current amphetamine based
27 medications that show high abuse liability and dependence producing properties. As
28 a result of its presumed lower potential for abuse and lack of peripheral
29 sympathomimetic effects that are associated with amphetamine stimulants, it has
30 also been researched for off-label use to treat sedation associated with other
31 disorders such as parkinsonism, fatigue in human immunodeficiency virus (HIV)
32 infection, multiple sclerosis, cancer and attention deficit hyperactivity disorder
33 (ADHD).^[16-20] The mechanism of action of modafinil is complex and poorly
34 understood. Studies regarding its effects on dopaminergic pathways and evidence
35 regarding effects on serotonergic and GABAergic pathways are reviewed elsewhere.
36^[21] The standard therapeutic dose of modafinil in adult patients is 200-400 mg
37 daily.^[22]
38
39
40

41 Although originally prescribed to help narcoleptic patients stay awake and alert there
42 are studies reporting improved performance that came alongside its wakefulness
43 properties.^[23] Due to its off-label use for improved performance, modafinil has been
44 sought by healthy individuals to improve user performance in specific tasks^[24] In
45 addition modafinil use has been noted regarding enhancing task ability versus
46 cheating in other fields.^[25] Studies showed that neuropsychological performance was
47 improved by increasing short-term memory and boosting an individual's ability to plan
48 and process information.^[24,26] Use of cognitive enhancers is gaining ground. In 2008,
49 the journal Nature presented the results of an informal survey polling readers
50 regarding the use of three specific cognition enhancement agents. The results
51 showed that 20% of the respondents reported the use of such agents for
52 nontherapeutic enhancement purposes. In addition, 69% of the respondents agreed
53 that healthy adults should have the choice to use cognitive enhancement agents.^[27]
54 In 2016, an online survey was carried out to evaluate pharmacological enhancement
55 of professional workers in the field of economics. A total of 1021 participants
56
57
58
59
60

1
2
3 completed the anonymous survey and results showed that lifetime use of any drug
4 for neuroenhancement was 88% and for the use of illicit or prescription drugs was
5 19%.^[28] Poll participants stated reasons such as “curiosity”, “to enhance mood”, “for a
6 confident appearance”, “stress/pressure to perform” and “deadline pressure” for use
7 of such substances.
8

9
10 Modafinil has rapidly gained a positive reputation for improving attention, executive
11 function and memory.^[29] The interest in the off-label use of modafinil in the media has
12 directed the general public and scientific community towards brain-boosting nootropic
13 supplements. Nootropic supplements are substances claimed to improve cognitive
14 function, particularly attention, executive function and memory in healthy patients.
15 Such supplements are easy to purchase through online vendors. A popular modafinil
16 alternative is the *N*-hydroxy derivative of modafinil called adrafinil (2-
17 ((diphenylmethyl)sulfinyl-*N*-hydroxyacetamide) (Figure 1). Adrafinil is also a pro-drug
18 and it is metabolized, mainly in the liver, to its bioactive amide, modafinil.^[30] CRL-
19 40,940 (Figure 1) is also advertised as a wakefulness promoting agent that
20 represents the bisfluoro analog of modafinil but it has also been reported as a so-
21 called designer drug.^[31-34] CRL-40,941 and modafiendz are also wakefulness
22 promoting agents and related to modafinil and adrafinil (Figure 1).
23
24

25
26 Customs and forensic laboratories are increasingly encountering these substances in
27 both tablet and powdered forms. The first detection of modafinil has been reported to
28 the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) *via* the
29 European Union early warning system (EWS) in 2015.^[35] Both adrafinil and
30 modafiendz detections were first reported in 2014.^[36] In Ireland, a recent media
31 report (April 2016) indicated that there has been a surge in the purchasing of smart-
32 drugs illegally on the dark web.^[37] The three most popular smart-drugs detected
33 smuggled into Ireland were amphetamine, dextroamphetamine, methylphenidate and
34 modafinil.
35
36

37
38 Gas chromatography mass spectrometry (GC-MS) is widely utilized in forensic
39 chemistry laboratories and is regarded as a robust methodology but, in the case of
40 thermally labile compounds, analytical challenges arise when attempting to
41 investigate the analytical profile. This study reports on the thermal degradation of
42 modafinil, adrafinil, modafinic acid, CRL-40,940 and CRL-40,941 in the GC injector
43 and the formation of common degradation products, i.e. 1,1,2,2-tetraphenylethane,
44 and its fluoro analog. This study confirmed the presence of the degradants by
45 comparison with authenticated synthesized standards. As the popularity and
46 abundance of neuroenhancement drugs appears to be increasing, it is expected that
47 challenges faced by customs and forensic laboratories might arise when employing
48 GC-MS as the standard tool of analysis, similar to what has been reported for other
49 drugs.^[38]
50
51

52 53 **Experimental**

54
55 All reagents and dry solvents used in the syntheses were obtained from Sigma
56 Aldrich Ltd (Arklow, Co. Wicklow, Ireland). LC-MS grade solvents were obtained from
57 Fisher Scientific (Dublin, Ireland).
58
59
60

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); ¹H NMR (CDCl₃) δ 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; ¹³C NMR (CDCl₃) δ 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; ¹H NMR (d₆ DMSO) δ 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 CH₂) and 3.35 (d; *J* = 14.3 Hz; 1H, one H from CH₂) ppm; ¹³C NMR (d₆ DMSO) δ 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 (CH₂) ppm; ESI HRMS: Found *m/z* 273.0569 (calc. for [M-H]⁻, C₁₅H₁₃O₃S, *m/z* 273.0580, Δ = -4.03 ppm).

Modafinil

Purchased from Sigma Aldrich (EPCRS grade): m.pt. 164-166 °C ¹H NMR (d₆ DMSO) δ 7.70 (s; 1H; one H from NH₂), 7.50-7.56 (m; 4H; Ar-H), 7.31-7.45 (m; 7H; Ar-H and one H from NH₂), 5.36 (s; 1H; CH), 3.38 (d; *J* = 13.6 Hz; 1H, one H from CH₂) and 3.23 (d; *J* = 13.6 Hz; 1H, one H from CH₂) ppm; ¹³C NMR (d₆ DMSO) δ 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 (CH₂) ppm; ESI HRMS: Found *m/z* 296.0706 (calc. for [M+Na]⁺, C₁₅H₁₅NO₂NaS, *m/z* 296.0716, Δ = -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; ¹H NMR (d₆ DMSO) δ 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 CH₂) and 3.08

(d; $J = 13.4$ Hz; 1H, one H from CH_2) ppm; ^{13}C NMR (d_6 -DMSO) δ 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 (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; ^1H NMR (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; CH_2); ^{13}C NMR (d_6 DMSO) δ 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 (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; ^1H NMR (d_6 -DMSO) δ 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 CH_2), 3.17 (d; $J = 13.4$ Hz; 1H; 1H from CH_2) and 2.57 (d, $J = 4.6$ Hz; 3H; CH_3); ^{13}C NMR (d_6 DMSO) δ 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 (CH_2) and 25.70 (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; ^1H NMR (d_6 DMSO) δ 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 CH_2) and 3.17 (d; $J = 13.7$ Hz; 1H; 1H from CH_2); ^{13}C NMR (d_6 DMSO) δ 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 (CH_2); ^{19}F NMR (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; ^1H NMR (d_6 DMSO) δ 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 CH_2) and 3.02 (d; $J = 13.3$ Hz; 1H; 1H from CH_2); ^{13}C NMR (d_6 DMSO) δ 160.99 (C=O), 161.95 (d; $J_{C,F} = 245$ Hz; Ar-C), 161.69 (d; $J_{C,F} = 245$ Hz; Ar-C), 133.16 (d; $J_{C,F} = 3$ Hz; Ar-C), 131.67 (d; $J_{C,F} = 8$ Hz; Ar-CH), 130.66 (d; $J_{C,F} = 3$ Hz; Ar-C), 130.57 (d; $J_{C,F} = 8$ Hz; Ar-CH), 115.93 (d; $J_{C,F} = 21$ Hz; Ar-CH), 115.39 (d; $J_{C,F} = 21$ Hz; Ar-CH), 66.64 (CH) and 53.83 (CH_2); ^{19}F NMR (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; ^1H NMR (CDCl_3) δ 7.03-7.10 (m; 8H; Ar-H), 6.81-6.90 (m; 8H; Ar-H) and 4.65 (s; 2H; CH); ^{13}C NMR (CDCl_3) δ 161.14 (d; $J_{C,F} = 245$ Hz; Ar-C), 138.56 (d; $J_{C,F} = 3$ Hz; Ar-C), 129.70 (d; $J_{C,F} = 8$ Hz; Ar-CH), 115.23 (d; $J_{C,F} = 21$ Hz; Ar-CH), 115.39 (d; $J_{C,F} = 21$ Hz; Ar-CH) and 55.11 (CH); ^{19}F NMR (d_6 DMSO) δ -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 μm) 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

1
2
3 respectively. The initial oven temperature was 60°C, held for 2 minutes and then
4 ramped at 25 °C/min to 295 °C with a final hold time of 3 min (run time 14.4 min).
5 The ionization energy was set at 70 eV, the quadrupole at 150°C, the ion source at
6 230 °C and the mass range was m/z 40-550.
7

8 9 *Gas chromatography ion trap mass spectrometry*

10
11 Electron ionization mass spectra were recorded under standard conditions. Chemical
12 ionization mass spectra were recorded using HPLC grade methanol as the liquid CI
13 reagent. A Varian 450-GC gas chromatograph coupled to a Varian 220-MS ion trap
14 mass spectrometer and a Varian 8400 autosampler was employed with a Varian CP-
15 1177 injector (275 °C) in split mode (1:50) (Walnut Creek, CA, USA). The Varian MS
16 Data Review function of the Workstation software, version 6.91, was used for data
17 acquisition. The carrier gas was helium at a flow rate of 1 mL/min using the EFC
18 constant flow mode. The default settings for CI ionization parameters (0.4 s/scan)
19 were used: CI storage level m/z 19.0; ejection amplitude m/z 15.0; background mass
20 m/z 55; maximum ionization time 2000 μ s; maximum reaction time 40 ms; target TIC
21 5000 counts. Temperatures for ion trap, manifold, and transfer line were set at 170
22 °C, 120 °C, and 280 °C, respectively. An Agilent J&W VF-5ms GC column (30 m \times
23 0.25 mm, 0.25 μ m) was employed for separation. The starting temperature was set
24 at 80 °C and held for 1 min. The temperature then increased at 20 °C/min to 280 °C
25 and held constant for 9 min to give a total run time of 20.00 min.
26
27
28
29

30 31 *High-resolution electrospray ionization mass spectrometry (HR-ESI-MS)*

32
33 *Instrument 1:* HR-ESI mass spectra were recorded by direct injection into a LTQ
34 Orbitrap Discovery (Thermo Fisher Scientific, Bremen, Germany). Samples were
35 dissolved in acetonitrile/water (1:1, containing 0.1% formic acid) and infused at a rate
36 of 5 μ L/min. Full accurate high-resolution (30 000) mass scans were performed in
37 positive electrospray mode. Measured accurate masses were within \pm 5 ppm of the
38 theoretical masses. The following conditions were used: drying gas (N_2) 10 L/min,
39 capillary temperature 310 °C, spray voltage 4 V, capillary voltage 22 V and tube lens
40 77 V. Mass calibrations were performed in both positive and negative mode using
41 solutions of caffeine, *L*-methionyl-arginyl-phenylalanylalanine acetate \times H_2O (MRFA),
42 Ultramark 1621[®], sodium docecyl sulfate and sodium taurocholate.
43
44

45
46 *Instrument 2:* ESI mass spectra were also acquired using a Micromass LCT Classic
47 ToF mass spectrometer interfaced to a Waters 2690 HPLC. Leucine Enkephalin was
48 used as an internal lock mass. Operating conditions were as follows: ESI capillary
49 voltage 2500 V, cone voltage 25 V, desolvation temperature 300°C, source
50 temperature 100°C. MassLynx[™] 4.0 software was used to carry out the analysis.
51

52 53 *Liquid chromatography-mass spectrometry (LC-MS)*

54
55 LC-MS analyses were performed on an Agilent 1100 HPLC system equipped with a
56 G13795 degasser, G1312A BinPump, a G1313A ALS and G1316A column oven
57 (COLCOM) (Agilent, Little Island, Cork, Ireland). Separation was obtained on a
58
59
60

Kinetex phenyl-hexyl column (2.6 μm , 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 (N_2) 12 L/min at 350 $^\circ\text{C}$, and nebulizer gas (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 μL , 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. ^1H (600 MHz) and ^{13}C (150 MHz, referenced to the NMR solvent peak) spectra were recorded on a Bruker AV600 NMR spectrometer using a 5 mm TCI cryoprobe. ^1H NMR spectra were referenced to an external TMS reference at $\delta = 0$ ppm. ^{19}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 $K\alpha$ radiation ($\lambda = 0.71073$ \AA) using a MiTeGen micromount and at 100(2) K (Oxford Cryosystem). Bruker APEX3^[39] software was used to collect and reduce data, determine the space group, solve and refine the structure. Absorption corrections were applied using SADABS.^[40] All final refinements were performed with OLEX/SHELXL.^[41,42] 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, $C2/c$, $a = 17.5758(9)$, $b = 5.8709(3)$, $c = 17.5462(10)$ \AA , $\beta = 91.110(3)^\circ$, $V = 1810.18(17)$ \AA^3 , $Z = 4$, μ (Mo $K\alpha$) = 0.069 mm^{-1} , $\rho = 1.227$ Mg/cm^3 , 14094 reflections collected, 1915 independent ($R_{\text{int}} = 0.0857$), $^aR_1 = 0.0566$, $wR_2 = 0.1063$ ($I > 2\sigma(I)$), $S = 1.032$. CCDC 1483400 $^aR_1 = \sum ||F_o| - |F_c|| / \sum |F_o|$, $wR_2 = [\sum w(F_o^2 - F_c^2)^2 / \sum w(F_o^2)^2]^{1/2}$.

Results and discussion

Previously, a GC-MS method was reported for the detection of modafinil in human urine.^[43] 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

1
2
3 merited further investigation although it was not identified. It has been reported that
4 modafinil, adrafinil and modafinic acid are significantly degraded under EI-GC-MS
5 conditions,^[44] therefore resulting in an artifact peak for modafinil, adrafinil and
6 modafinic acid that eluted as a single peak at the same retention time. In that study,
7 the artifact peak was used as a marker for screening purposes. A possible site of
8 ionization in the modafinil structure is the diphenylmethyl sulfinyl linkage and, as
9 expected, the main fragment derives from this at m/z of 167 (base peak).
10 Subsequently, demethylation occurs, yielding m/z 152 as the second major fragment.
11 The authors showed that the operation of the GC at high temperature gave rise to
12 the single artifact peak at the same retention time in each chromatogram albeit the
13 authors did not identify this compound.^[44] Other authors have reported modafinil as
14 being thermally labile and unsuitable for GC-MS analysis.^[44-46]
15
16

17
18 In the work presented in this study, modafinil, adrafinil and modafinic acid were found
19 to produce similar GC chromatograms when acetonitrile, dichloromethane or ethanol
20 were used as solvents (Figure 2a, Supporting Information 2). Two major peaks were
21 present and identified as diphenylmethanol (6.75 min) and 1,1,2,2-tetraphenylethane
22 (10.22 min). However, diphenylmethane (5.81 min) and thiobenzophenone (7.05 min,
23 Supplemental 2) were also identified in some instances. Possible mechanisms for
24 the formation of diphenylmethane and diphenylmethanol are presented in Figure 2a
25 and the EI mass spectrum of 1,1,2,2-tetraphenylethane is shown in Figure 2b (with a
26 magnification in Figure 2c). It displays a very weak molecular ion, m/z 334, and a
27 number of fragments that potentially arise from ion/hydrogen scrambling. It has
28 previously been reported that the benzhydrylium ion, m/z 167, which is in rapid
29 equilibration with the phenyl tropylium ion, transitions to m/z 152 by loss of a methyl
30 radical, formed from the bridging CH unit and two *ortho* hydrogens.^[47-50] As the
31 formation of ions, such as m/z 239 and m/z 252, are not readily rationalized, it is
32 suggested that these might also arise from ion scrambling mechanisms.
33
34
35

36
37 Conventionally, dimerization of two diphenylmethyl radicals ($\text{Ph}_2\text{CH}^\bullet$), formed by the
38 thermolysis of modafinil or a related compound, may lead to the formation of 1,1,2,2-
39 tetraphenylethane.^[51,52] However, an alternative mechanism (Figure 3) involves the
40 initial formation of the well-known and characterized benzhydrylium
41 (diphenylcarbonium) ion.^[53-55] It is suggested that thermal degradation of modafinil,
42 adrafinil or modafinic acid could result in the formation of a benzhydrylium ion (Figure
43 3a). The benzhydrylium ion may then form an oxysulfonium intermediate with the
44 sulfoxide oxygen on modafinil, adrafinil or modafinic acid. This oxysulfonium salt may
45 then degrade to 1,1,2,2-tetraphenylethane *via* a benzhydryl oxy sulfide species
46 (Figure 3b). Interestingly, the analogous dibenzhydryl disulfide has been shown to
47 decompose on heating to yield 1,1,2,2-tetraphenylethane^[56,57] and oxysulfonium
48 salts have also been reported previously.^[58-60] When equimolar (30-970 μM)
49 acetonitrile solutions of modafinil or modafinil sulfide (Figure 3c) were injected
50 separately on to the GC, the relative amount of 1,1,2,2-tetraphenylethane formed,
51 based upon peak areas, was on average approximately 90 % lower for the sulfide
52 (Supporting Information 3), indicating the sulfoxide oxygen may promote thermal
53 degradation by the facile formation of the oxysulfonium intermediate. The sulfur lone
54 pairs in modafinil sulfide may less readily form a sulfonium salt intermediate with the
55 benzhydrylium ion (Figure 3c), thus resulting in relatively lower yields of 1,1,2,2-
56
57
58
59
60

1
2
3 tetraphenylethane. It may be also the case that the postulated intermediate,
4 dibenzhydryl sulfide, is more thermally stable than the corresponding oxysulfide.
5 Varying the split ratio in the GC injector was evaluated but degradant formation was
6 still observed (Supporting Information 4).
7

8
9 Interestingly, in the electrospray ionization mass spectra of modafinil and adrafinil,
10 oxysulfonium ($M + \text{benzhydrylium ion}$)⁺ adducts were observed (Supporting
11 Information 5), which were consistent with triphenylcyclopropenylum cations that
12 undergo adduct formation in the presence of nucleophiles such as thiols.^[61]
13

14
15 CRL-40,490 is the fluoro analog of modafinil, CRL-40,491 is the fluoro analog of
16 adrafinil and modafiendz (for analytical data see Supporting Information 6) is the *N*-
17 methyl analog of modafinil, respectively. The corresponding fluoro-analogs of
18 modafinil and adrafinil, namely CRL-40,490 and CRL-40,491, yielded analogous
19 fluorinated degradants indicating that a similar mechanism was implicated. When a
20 mixture of a non-fluorinated and fluorinated derivatives was injected, a mixture of
21 three tetraphenylethanes are observed that represented one *hetero* and two *homo*
22 coupling products. For example, this was observed when a mixture of modafinil and
23 modafiendz (Figure 1) was subjected to GC analysis. The formation of a cross-
24 reaction product was detected at 11.76 min (Figure 4a) along with the two expected
25 diphenylmethane dimers. The cross-reaction product represented the fact that
26 modafinil did not contain the two fluorine atoms attached to modafiendz.
27
28
29

30
31 The CI mass spectra for the three tetraphenylethane products are shown in Figure
32 4b. In each case, it was not possible to obtain the protonated molecule due to loss of
33 either benzene or fluorobenzene from the molecule. With 1,1,2,2-tetrakis(4-
34 fluorophenyl)ethane (the modafiendz degradation product), CI did not provide any
35 more information other than m/z 311 obtained by loss of fluorobenzene, and for 4,4'-
36 (2,2-diphenylethane-1,1-diyl)bis(fluorobenzene) (the modafinil-modafiendz cross-
37 reaction product), m/z 293 was obtained following loss of benzene and m/z 275 was
38 obtained by loss of benzene, respectively. With the modafinil product (1,1,2,2-
39 tetraphenylethane), the protonated ion also lost benzene from m/z 257. The
40 formation of diphenylmethanol and its fluoro analog (bis(4-fluorophenyl)methane)
41 was also observed (Supporting Information 7). Interestingly, both 1,1,2,2-
42 tetraphenylethane and 1,1,2,2-tetrakis(4-fluorophenyl)ethane also failed to produce
43 molecular ions using atmospheric-pressure chemical ionization. This further
44 highlighted the complexities expected when customs/forensic seized samples
45 contain mixtures of these compounds.
46
47
48

49 Both 1,1,2,2-tetraphenylmethane and 1,1,2,2-tetrakis(4-fluorophenyl)ethane were
50 synthesized, and characterized. X-ray crystallographic analysis of 1,1,2,2-
51 tetraphenylmethane was also performed. Clear colorless plates were isolated from a
52 hexane solution and the structure determined at 100K. The data were solved and
53 refined in the monoclinic space group C2/c. The asymmetric unit consists of one half
54 occupied molecule and symmetry generates the complete disordered molecule
55 (symmetry operation = $1-x, y, 1.5-z$, Figures 5a and 5b). Hydrogen atoms H7 and
56 H7a, which are fully occupied, are shared between each disordered molecule. These
57
58
59
60

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.^[62] 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 (fladrafinitil) (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, adrafinitil and modafinilic acid and a mechanism for its formation was proposed. Caution should be exercised in the analysis of modafinil and adrafinitil 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, adrafinitil, 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

1
2
3 capabilities. However, special attention should be paid to the potential for ambiguity
4 when using this technique.
5
6

7 8 References

- 9
10
11 [1] P. Burnat, F. Robles, B. Do. High performance liquid chromatographic
12 determination of modafinil and its two metabolites in human plasma using
13 solid phase extraction. *J. Chromatogr. B* **1998**, 706, 295.
14
15 [2] D.B. Biovin, J. Montplaisir, D. Petit, C. Lambert, S. Lubin. Effects of modafinil
16 on symptomatology of human narcolepsy. *Clin. Neuropharmacol.* **1993**, 16,
17 46.□
18
19 [3] P. Robertson Jr, E.T. Hellriegel. Clinical pharmacokinetic profile of modafinil.
20 *Clin. Pharmacokinet.* **2003**, 42, 123.
21
22 [4] S. Hart. Drug shame for US sprint star, Sport Telegraph, August 31, 2003.
23 Available at:
24 [http://www.telegraph.co.uk/sport/othersports/athletics/2410643/Drug-shame-](http://www.telegraph.co.uk/sport/othersports/athletics/2410643/Drug-shame-for-US-sprint-star.html)
25 [for-US-sprint-star.html](http://www.telegraph.co.uk/sport/othersports/athletics/2410643/Drug-shame-for-US-sprint-star.html) [20th September 2016].
26
27 [5] The World Anti-Doping Code. The 2015 Prohibited List International
28 Standard, World Anti-Doping Agency. Available at: [https://wada-main-](https://wada-main-prod.s3.amazonaws.com/resources/files/wada-2015-prohibited-list-en.pdf)
29 [prod.s3.amazonaws.com/resources/files/wada-2015-prohibited-list-en.pdf](https://wada-main-prod.s3.amazonaws.com/resources/files/wada-2015-prohibited-list-en.pdf)
30 [20th September 2016].
31
32 [6] M.J. Minzenberg, C.S. Carter. Modafinil: a review of neurochemical actions
33 and effects on cognition. *Neuropsychopharmacology* **2008**, 33,1477.
34
35 [7] K. Wu, T. Guo, C. Deng, Z. Guan, L. Li, T. Zhou, W. Lu. Population
36 pharmacokinetics of modafinil and estimation of the metabolic conversion of
37 modafinil into modafinil acid in 5 major ethnic groups of China. *Acta*
38 *Pharmacol. Sin.* **2012**, 33, 1401.
39
40 [8] C.A. Dackis, K.G. Lynch, E. Yu, F.F. Samaha, K.M. Kampman, J.W. Cornish,
41 A. Rowan, S. Poole, L. White, C.P. O'Brien. Modafinil and cocaine: a double-
42 blind, placebo-controlled drug interaction study. *Drug Alcohol Depend.* **2003**,
43 70, 29.
44
45 [9] C.L. Hart, M. Haney, S.K. Vosburg, E. Rubin, R.W. Foltin. Smoked cocaine
46 self-administration is decreased by modafinil. *Neuropsychopharmacology*
47 **2008**, 33. 761.
48
49 [10] R. Malcolm, K. Swayngim, J.L. Donovan, C.L. DeVane, A. Elkashef, N.
50 Chiang, R. Khan, J. Mojsiak, D.L. Myrick, S. Hedden, K. Cochran, R.F.
51 Woolson. Modafinil and cocaine interactions. *Am. J. Drug Alcohol Abuse*,
52
53
54
55
56
57
58
59
60

- 1
2
3 **2006**, 32, 577.
4
5 [11] C.A. Dackis, K.M. Kampman, K.G. Lynch, J.G. Plebani, H.M. Pettinati, T.
6 Sparkman, C.P. O'Brien, C.P. A double-blind, placebo-controlled trial of
7 modafinil for cocaine dependence. *J. Subst. Abuse Treat.* **2012**, 43, 303.
8
9 [12] J.M. Schmitz, C.E. Green, A.L. Stotts, J.A. Lindsay, N.S. Rathnayaka, J.
10 Grabowski, F.G. Moeller. A two-phased screening paradigm for evaluating
11 candidate medications for cocaine cessation or relapse prevention: modafinil,
12 levodopa-carbidopa, naltrexone. *Drug Alcohol Depend.* **2014**, 136, 100.
13
14 [13] J.M. Schmitz, N. Rathnayaka, C.E. Green, F.G. Moeller, A.E. Dougherty, J.
15 Grabowski. Combination of modafinil and d-amphetamine for the treatment of
16 cocaine dependence: a preliminary investigation. *Front. Psychiatry* **2012**, 3,
17 77.
18
19 [14] K.M. Kampman, K.G. Lynch, H.M. Pettinati, K. Spratt, M.R. Wierzbicki, C.
20 Dackis, C.P. O'Brien. A double blind placebo controlled trial of modafinil for
21 the treatment of cocaine dependence without co-morbid alcohol dependence.
22 *Drug Alcohol Depend.* **2015**, 155, 105.
23
24 [15] C.A. Dackis, K.M. Kampman, K.G. Lynch, H.M. Pettinati, C.P. O'Brien. A
25 double-blind, placebo-controlled trial of modafinil for cocaine dependence.
26 *Neuropsychopharmacology* **2005**, 30, 205.
27
28 [16] W.G. Ondo, R. Fayle, F. Atassi, J. Jankovic. Modafinil for daytime
29 somnolence in Parkinson's disease: double blind, placebo controlled
30 parallel trial. *J Neurol Neurosurg Psychiatry* **2005**, 76,1636.
31
32 [17] J.G. Rabkin, M.C. McElhiney, R. Rabkin, P.J. McGrath. Modafinil treatment
33 for fatigue in HIV/AIDS: a randomized placebo-controlled study. *J. Clin.*
34 *Psychiatry* **2010**, 71, 707.
35
36 [18] R. Lange, M. Volkmer, C. Heesen, J. Liepert. Modafinil effects in multiple
37 sclerosis patients with fatigue. *J. Neurol.* **2009**, 256, 645.
38
39 [19] P. Jean-Pierre, G.R. Morrow, J.A. Roscoe, C. Heckler, S. Mohile, M.
40 Janelsins, L. Peppone, A. Hemstad, B.T. Esparaz, J.O. Hopkins. A Phase 3
41 randomized, placebo-controlled, double-blind, clinical trial of the effect of
42 modafinil on cancer-related fatigue among 631 patients receiving
43 chemotherapy. *Cancer* **2010**, 116, 3513.
44
45 [20] M. Kahbazi, A. Ghoteishi, F. Rahiminejad, M.R. Mohammadi, A. Kamalipour,
46 S. Akhondzadeh. A randomized, double-blind and placebo-controlled trial of
47 modafinil in children and adolescents with attention deficit and hyperactivity
48 disorder. *Psychiatry Res.* **2009**, 168, 234.
49
50 [21] R. Kumar. Approved and investigational uses of modafinil: an evidence-
51
52
53
54
55
56
57
58
59
60

- 1
2
3 based review. *Drugs* **2008**, *68*, 1803. □
- 4
5 [22] K.A. Bohnenberger, E.P. Krenzelok. Retrospective review of trend in
6 modafinil overexposures reported to American poison information centers.
7 *Asia Pacific J. Med. Toxicol.* **2014**, *3*, 50.
- 8
9 [23] D.C. Randall, J.M. Shneerson, S.E. File. Cognitive effect of modafinil in
10 student volunteers may depend on IQ. *Pharmacol. Biochem. Behav.* **2005**,
11 *82*, 133.
- 12
13 [24] D.C. Turner, T.W. Robbins, L. Clark, A.R. Aron, J. Dowson, B.J. Sahakian.
14 Cognitive enhancing effects of modafinil in healthy □volunteers.
15 *Psychopharmacology* **2003**, *165*, 260. □
- 16
17 [25] Anonymous. Enhancing not cheating. *Nature*, **2007**, *450*, 320.
- 18
19
20
21
22 [26] A.M. Kelley, C.M. Webb, J.R. Athy, S. Ley, S. Gaydos. Cognitive
23 □enhancement by modafinil: a meta-analysis. *Aviat. Space □Environ. Med.*
24 **2012**, *83*, 685. □
- 25
26 [27] B. Maher. Poll results: look who's doping. *Nature* **2008**, *452*, 674.
- 27
28 [28] P. Dietz, M. Soyka, A.G. Franke, Pharmacological neuroenhancement in the
29 field of economics - poll results from an online survey. *Front. Psychology*
30 **2016**, *7*, article 520.
- 31
32 [29] R.M. Battledaya, A.K. Brema. Modafinil for cognitive neuroenhancement in
33 healthy non-sleep deprived subjects: a systematic review. *Eur.*
34 *Neuropsychopharmacol.* **2015**, *25*, 1865.
- 35
36 [30] N.W. Milgram, H. Callahan, C. Siwak. Adrafinil: a novel vigilance promoting
37 agent. *CNS Drug Rev.* **1999**, *5*, 193.
- 38
39 [31] L. Lafon (Laboratoire L. Lafon, 28 January 1986). Patent CA 1199916.
40 Benzhydrylsulfinylacetamide derivatives and their therapeutic use.
- 41
42 □□□□ J. Cao, T.E. Prisinzano, O.M. Okunola, T. Kopajtic, M. Shook, J. L. Katz, A.
43 Hauck Newman. SARs at the Monoamine Transporters for a Novel Series of
44 Modafinil Analogues. *Med.Chem. Letters.* **2011**, *5*, 48.
- 45
46 [33] E. Konofal (Assistance Publique, 7 November 2013). Patent US
47 20130295196. Lauflumide and the enantiomers thereof, method for preparing
48 same and therapeutic uses thereof.
- 49
50 [34] L. Lafon (Laboratoire L. Lafon, 18 December 1984). Patent US 4489095.
51 Halogenobenzhydrylsulfinylacetohydroxamic acids.
52
53
54
55
56
57
58
59
60

- 1
2
3 [35] EMCDDA-Europol. EMCDDA-Europol 2015 Annual Report on the
4 implementation of Council Decision 2005/387/JHA. EMCDDA-Europol,
5 Lisbon, **2016**. Available at:
6 <http://www.emcdda.europa.eu/system/files/publications/2880/TDAS16001EN>
7 [N.pdf](#) [20th September 2016]
8
9
10 [36] EMCDDA-Europol. EMCDDA-Europol 2014 Annual Report on the
11 implementation of Council Decision 2005/387/JHA. EMCDDA-Europol,
12 Lisbon, **2015**. Available at:
13 <http://www.emcdda.europa.eu/system/files/publications/1018/TDAN15001EN>
14 [N.pdf](#) [20th September 2016]
15
16
17 [37] Irish Independent newspaper. Students warned over 'brain viagra' (April 24,
18 2016). Available at [http://www.independent.ie/irish-](http://www.independent.ie/irish-news/health/students-warned-over-brain-viagra-34654177.html)
19 [news/health/students-warned-over-brain-viagra-34654177.html](http://www.independent.ie/irish-news/health/students-warned-over-brain-viagra-34654177.html) [20th
20 September 2016]
21
22
23 [38] K. Tsujikawa, K. Kuwayama, T. Kanamori, YT Iwata, H Inoue. Thermal
24 degradation of α -pyrrolidinopentiophenone during injection in gas
25 chromatography/mass spectrometry. *Forensic Sci. Int.* **2013**, 231, 296.
26
27
28 [39] APEX3 (2015) Bruker AXS Inc., Madison, Wisconsin, USA. Available
29 at [https://www.bruker.com/products/x-ray-diffraction-and-elemental-](https://www.bruker.com/products/x-ray-diffraction-and-elemental-analysis/single-crystal-x-ray-diffraction/sc-xrd-software/overview/sc-xrd-software/apex3.html)
30 [analysis/single-crystal-x-ray-diffraction/sc-xrd-software/overview/sc-](https://www.bruker.com/products/x-ray-diffraction-and-elemental-analysis/single-crystal-x-ray-diffraction/sc-xrd-software/overview/sc-xrd-software/apex3.html)
31 [xrd-software/overview/sc-](https://www.bruker.com/products/x-ray-diffraction-and-elemental-analysis/single-crystal-x-ray-diffraction/sc-xrd-software/overview/sc-xrd-software/apex3.html)
32 [xrd-software/apex3.html](https://www.bruker.com/products/x-ray-diffraction-and-elemental-analysis/single-crystal-x-ray-diffraction/sc-xrd-software/overview/sc-xrd-software/apex3.html) [20th September 2016]
33
34 [40] SADABS (2014/5) Bruker AXS Inc., Madison, Wisconsin, USA. Available at
35 [https://www.bruker.com/products/x-ray-diffraction-and-elemental-](https://www.bruker.com/products/x-ray-diffraction-and-elemental-analysis/single-crystal-x-ray-diffraction/sc-xrd-software/overview/sc-xrd-software/proteum2/proteum2-software/data-scaling-and-absorption-correction.html)
36 [analysis/single-crystal-x-ray-diffraction/sc-xrd-software/overview/sc-](https://www.bruker.com/products/x-ray-diffraction-and-elemental-analysis/single-crystal-x-ray-diffraction/sc-xrd-software/overview/sc-xrd-software/proteum2/proteum2-software/data-scaling-and-absorption-correction.html)
37 [xrd-software/overview/sc-](https://www.bruker.com/products/x-ray-diffraction-and-elemental-analysis/single-crystal-x-ray-diffraction/sc-xrd-software/overview/sc-xrd-software/proteum2/proteum2-software/data-scaling-and-absorption-correction.html)
38 [xrd-software/proteum2/proteum2-software/data-scaling-and-](https://www.bruker.com/products/x-ray-diffraction-and-elemental-analysis/single-crystal-x-ray-diffraction/sc-xrd-software/overview/sc-xrd-software/proteum2/proteum2-software/data-scaling-and-absorption-correction.html)
39 [absorption-correction.html](https://www.bruker.com/products/x-ray-diffraction-and-elemental-analysis/single-crystal-x-ray-diffraction/sc-xrd-software/overview/sc-xrd-software/proteum2/proteum2-software/data-scaling-and-absorption-correction.html) [20 september 2016]
40
41
42 [41] G.M Sheldrick. A short history of SHELX. *Acta Cryst.*, **2008**, A64, 112.
43
44 [42] O.V. Dolomanov, L.J. Bourhis, R.J. Gildea, J.A.K Howard, H. Puschmann,
45 H. *J. Appl. Cryst.* **2009**, 42, 339.
46
47 [43] Y.L. Tseng, V. Uralets, C.T. Lin. Detection of modafinil in human urine by
48 gas chromatography mass spectrometry. *J. Pharm. Biomed. Anal.* **2005**, 39,
49 1042.□
50
51
52 [44] S. Dubey, S. Ahi, I.M. Reddy, T. Kaur, A. Beotra, S. Jain. A novel study of
53 screening and confirmation of modafinil, adrafinil and their metabolite
54 modafinic acid under EI-GC-MS and ESI-LC-MS-MS ionization. *Indian*
55 *Journal of Pharmacology.* **2008**, 41, 278.
56
57
58
59
60

- 1
2
3 [45] A.R. McKinney, C.J. Suann, A.M. Stenhouse. The detection of modafinil and
4 its major metabolite in equine urine by liquid chromatography/mass
5 spectrometry *Rapid Comm. Mass Spectrometry*. **2006**, *19*, 1217.
6
7
8 [46] T. Becue. Confirmation of the structure of by-products in the synthesis of
9 modafinil by liquid chromatography mass spectrometry *J. Chrom.*, **1991**, *557*
10 489,
11
12 [47] R.A.W. Johnstone. B.J. Millard. Some novel eliminations of neutral fragments
13 from ions in mass spectrometry. *Z. Naturforsch.* **1966**, *21a*, 604.
14
15 [48] D.H. Williams, R.S. Ward, R.G. Cooks. Role of frequency factors in
16 determining difference between low and high voltage mass spectra. *J. Chem.*
17 *Soc., (B)*. **1968**, *90*.
18
19 [49] J.H. Bowie, R.G. Cooks, G.E. Gream, M.H. Laffer. Mass spectra of alpha-
20 diketones. I. Non-enolized alpha-diketones. *Aust. J. Chem.* **1968**, *21*, 1247.
21
22 [50] D.H. Williams, R.S. Ward, R. G. Cooks. Studies in mass spectrometry. Part
23 XXVII. Hydrogen scrambling between phenyl rings of diphenylmethanol and
24 diphenylmethyl chloride. *J. Chem. Soc.* **1968**, 522.
25
26 [51] S. Jockusch, T. Hirano, Z. Liu, N.J Turro. A spectroscopic study of
27 diphenylmethyl radicals and diphenylmethyl carbocations stabilized by
28 zeolites. *J. Phys. Chem. B*. **2000**, *104*, 1212.
29
30 [52] C. Bohne, J.C Scalano. Thermochemical parameters for molecules and
31 reaction intermediates containing the diphenylmethyl moiety. *Quimica Nova*
32 **1993**, *16*, 288.
33
34 [53] M. Ma, K.E Johnson. Carbocation formation by selected hydrocarbons in
35 trimethylsulfonium bromide-AlCl₃/AlBr₃-HBr ambient temperature molten salts.
36 *J. Am. Chem. Soc.* **1995**, *117*, 1508.
37
38 [54] S.Jurie, B. Denegri O. Kronja. Leaving group property of dimethyl sulfide. *J.*
39 *Org. Chem.* **2010**, *75*, 3851.
40
41 [55] X. Duan, B. Maji, H. Mayr. Characterisation of the nucleophilic reactivities of
42 thiocarboxylate, dithiocarbonate and dithiocarbamate anions. *Org. Biomol.*
43 *Chem.* **2011**, *9*, 8046.
44
45 [56] J. Tsurugi, T. Nakabayashi, T. Yamanaka. Reaction of diphenylmethane with
46 sulfur. VI. Pyrolysis of dibenzhydryl disulfide. *Nippon kagaku zasshi.* **1956**, *77*,
47 578.
48
49 [57] R.C. Moreau. Thermal decomposition of dibenzhydryl disulfide. *Bull. Soc.*
50 *Chim. France.* **1955**, 969.
51
52
53
54
55
56
57
58
59
60

- 1
2
3 [58] M.A. Khuddus, D. Swern. Preparations and reactions of sulfonium salts from
4 epoxides and DMSO. A stereospecific synthesis of 1,2-Glycols *Tet. Letters*
5 **1971**, 5, 411.
6
7 [59] R. Minkwitz, W. Molsbeck. Preparation and spectroscopic characterization of
8 methoxysulfonium salts. *Z. Naturforsch.* **1992**, 47b, 22.
9
10 [60] J. Forrester, R.V.H. Jones, P.N. Preston, E. S.C. Simpson, Generation of
11 trimethylsulfonium cation from dimethyl sulfoxide and dimethyl sulfate:
12 implications for the synthesis of epoxides from aldehydes and ketones. *J.*
13 *Chem. Soc., Perkin Trans. 1* **1995**, 2289.
14
15 [61] A.P. Topolyan, D.A. Strizhevskaya, M.A. Belyaeva, V.A. Brylev, A.V. Ustinov,
16 A.A. Formanovsky, V.A. Korshun. A triphenylcyclopropenylum mass tag:
17 synthesis and application to ultrasensitive LC-MS analysis of amines.
18 *Analyst.* **2016**, 141, 3289.
19
20 [62] D.A. Dougherty, K. Mislow, J.F. Blount, J.B. Wooten, J.B. Jacobus. *J. Am.*
21 *Chem. Soc.*, **1977**, 99, 6149.
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

Figure captions

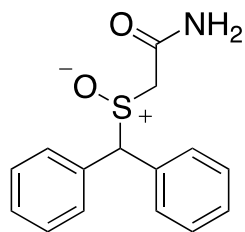
47
48
49 **Figure 1.** Molecular structures of compounds discussed in manuscript
50

51 **Figure 2.** (a). Typical GC chromatogram for modafinil, adrafinil or modafinic acid
52 (chromatogram for modafinil shown) along with mechanisms for the formation of
53 dipheylmethane and dipheylmethanol, (b). EI mass spectrum and potential fragments
54 for 1,1,2,2-tetraphenylethane and (c). magnification of 1,1,2,2-tetraphenylethane
55 mass spectrum.
56
57
58
59
60

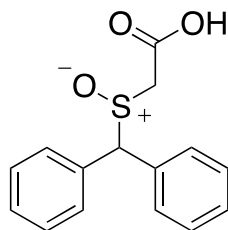
1
2
3 **Figure 3.** Potential mechanism for the formation of 1,1,2,2-tetraphenylethane: (a)
4 formation of the benzhydrylium ion, (b). reaction of modafinil with the benzhydrylium
5 ion to form 1,1,2,2-tetraphenylethane and (c). formation of 1,1,2,2-tetraphenylethane
6 from modafinil sulfide.
7

8
9 **Figure 4.** (a). Chromatograms depicting the formation of 1,1,2,2-tetraphenylethane, its
10 di-fluoro and tetra-fluoro analogs, following the injection of modafinil, modafinil
11 or co-injection of modafinil and modafinil and (b). ion trap CI and EI mass spectra for
12 1,1,2,2-tetraphenylethane, its di-fluoro and tetra-fluoro analogs
13

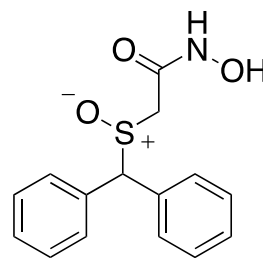
14
15 **Figure 5.** (a). Structure 1,1,2,2-tetraphenylethane showing one symmetry unique
16 complete conformation at 50% occupancy (excluding H7, H7a). Atomic displacement
17 shown at 50% probability, (b). Partially labelled symmetry generated (1-x, y, 1.5-z)
18 complete molecule of 1. One disordered molecule is labeled completely and only H7
19 and H7a shown for clarity and (c). Newman projection down the C7-C7a ethane axis
20 showing the anti-conformation of the molecule with the dihedral angles shown.
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



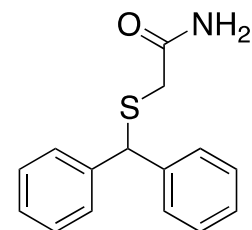
Modafinil



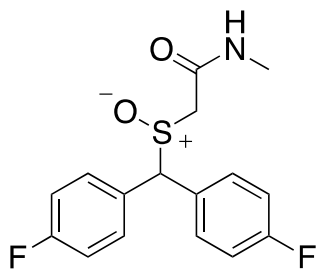
Modafinic acid



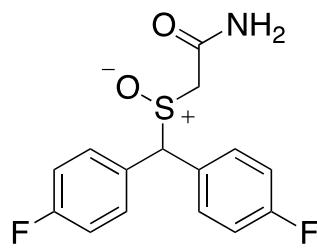
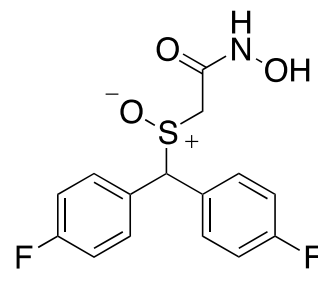
Adrafinil



Modafinil sulfide



Modafiendz

CRL 40,490
(Flmodafinil)CRL 40,491
(Fladrafinil)

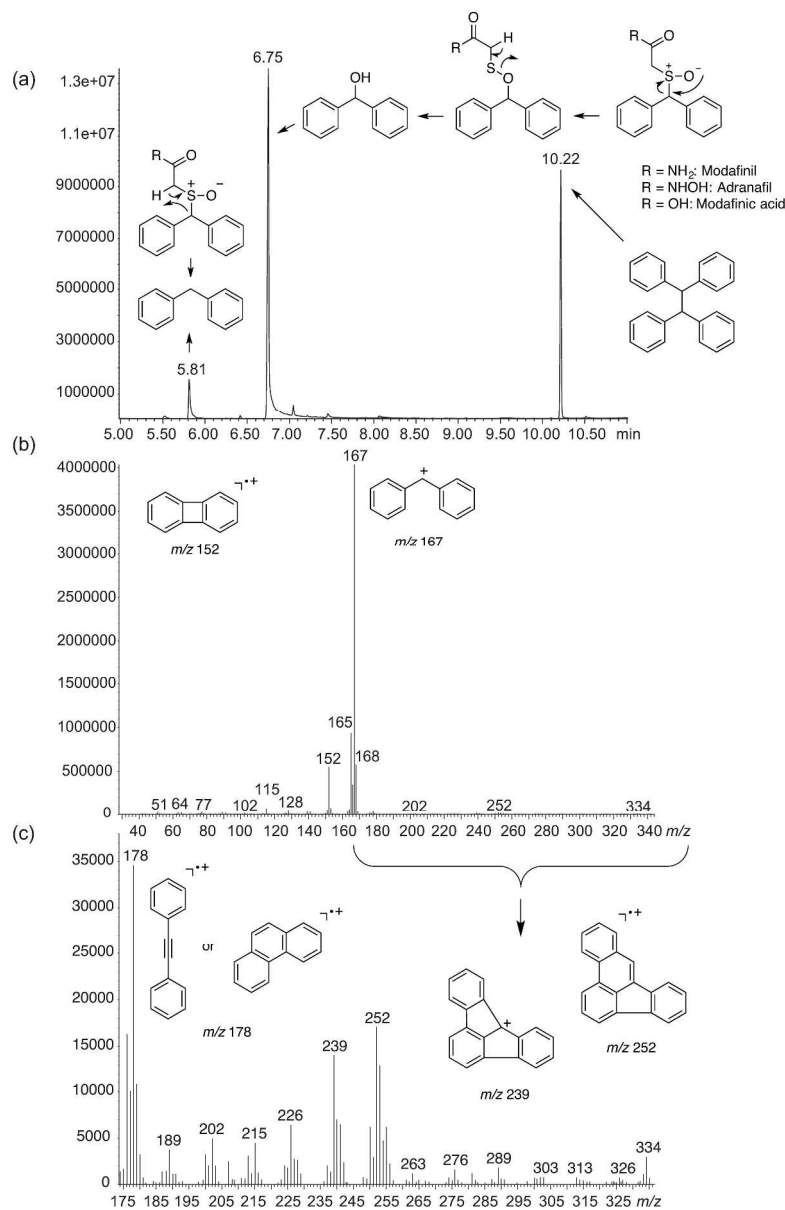
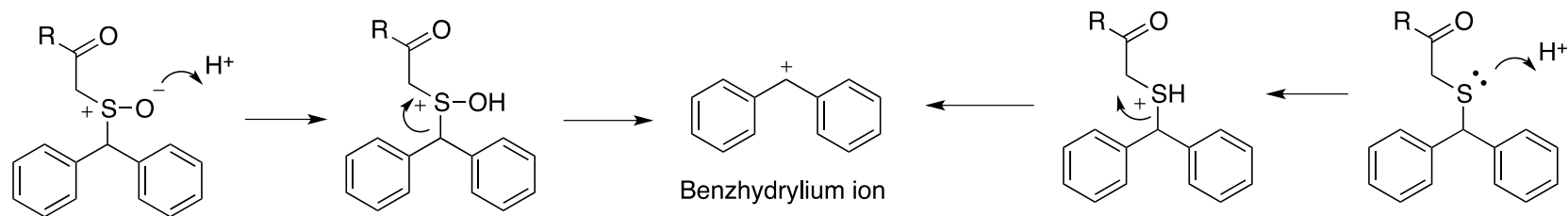
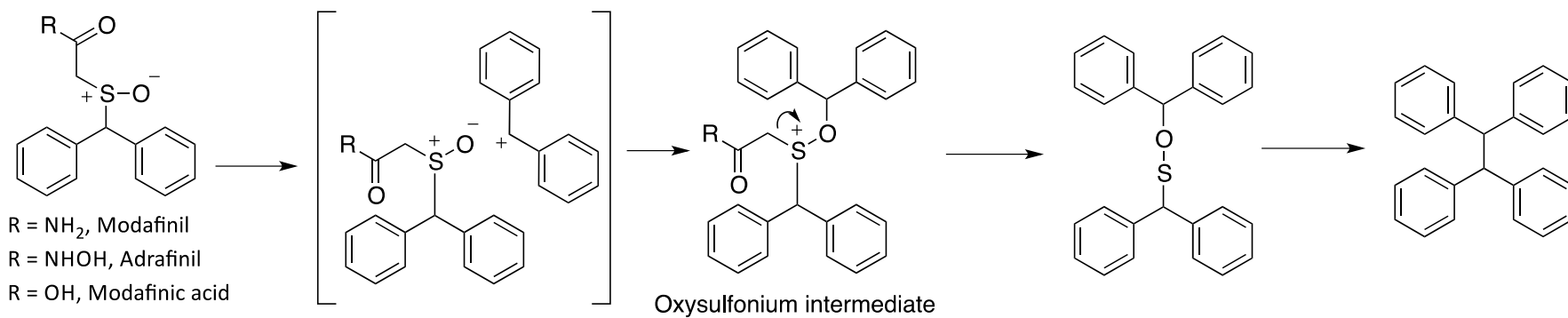


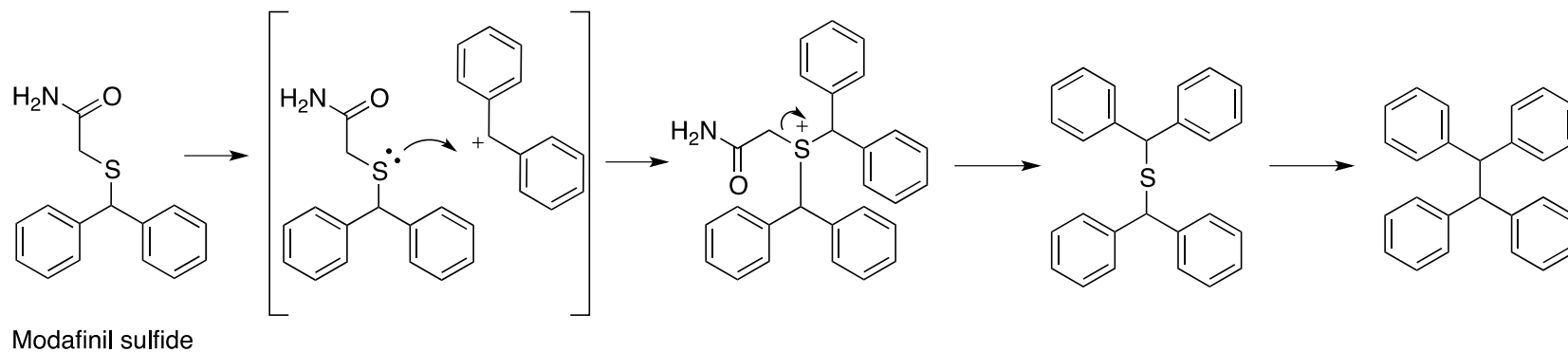
Figure 2. (a). Typical GC chromatogram for modafinil, adrafinil or modafinic acid (chromatogram for modafinil shown) along with mechanisms for the formation of dipheylmethane and dipheylmethanol, (b). EI mass spectrum and potential fragments for 1,1,2,2-tetraphenylethane and (c). magnification of 1,1,2,2-tetraphenylethane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

289x448mm (300 x 300 DPI)

1 (a).

10
11 (b).

25(c).



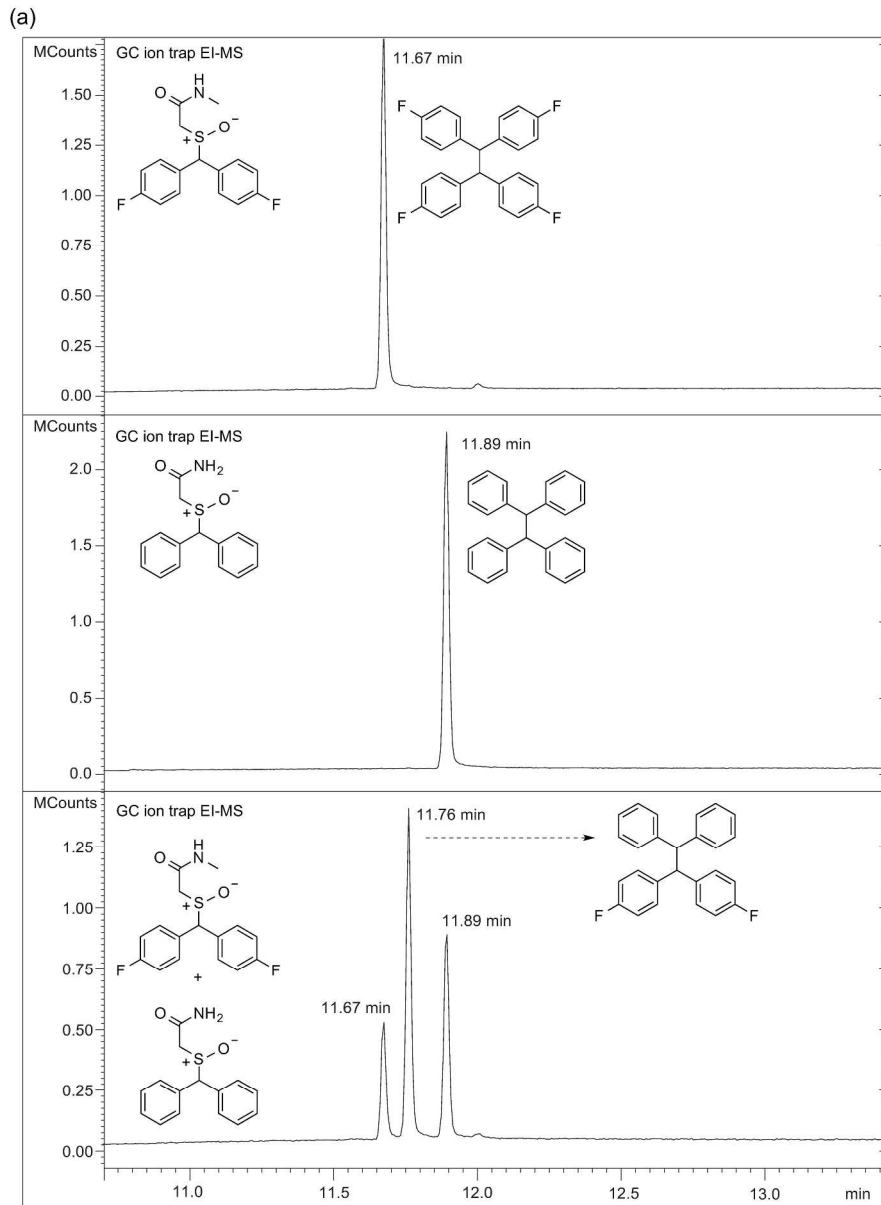


Figure 4. (a). Chromatograms depicting the formation of 1,1,2,2-tetraphenylethane, its di-fluoro and tetra-fluoro analogs, following the injection of modafinil, modafinidz or co-injection of modafinil and modafinidz

271x371mm (300 x 300 DPI)

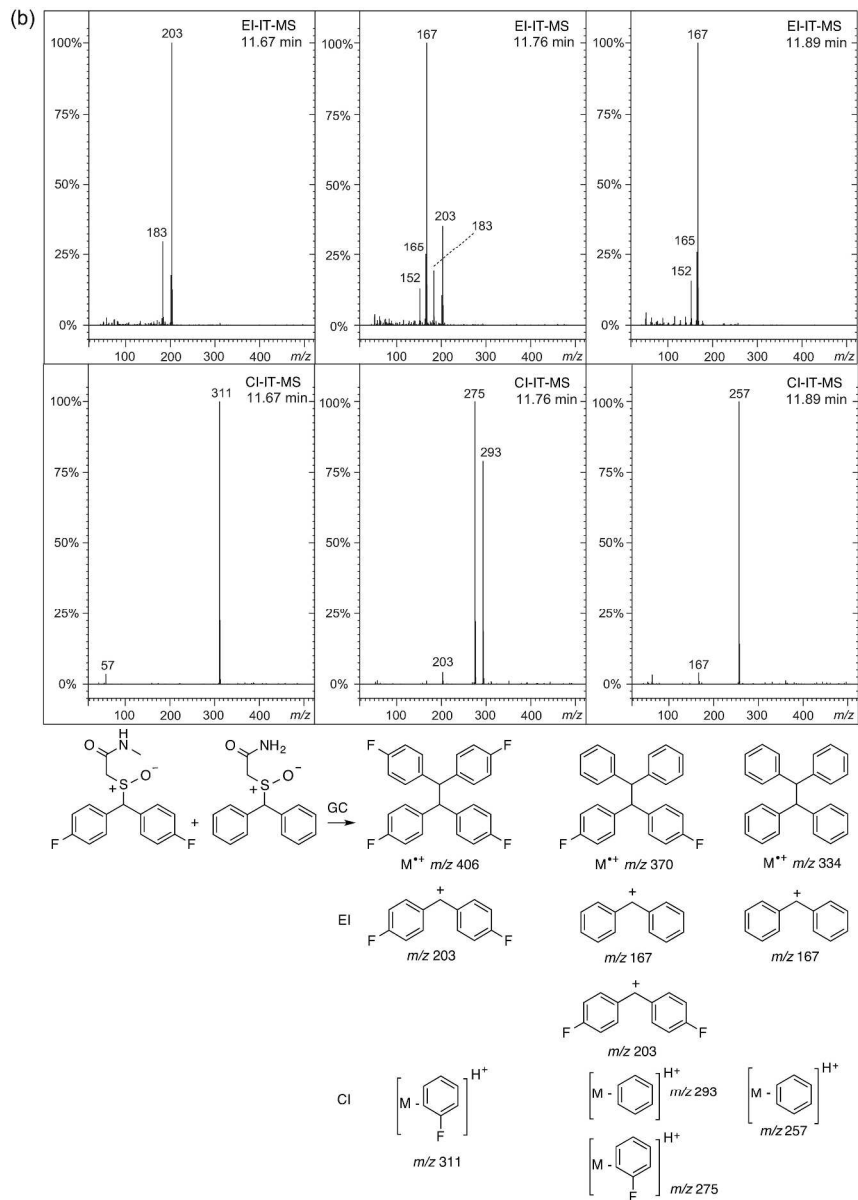
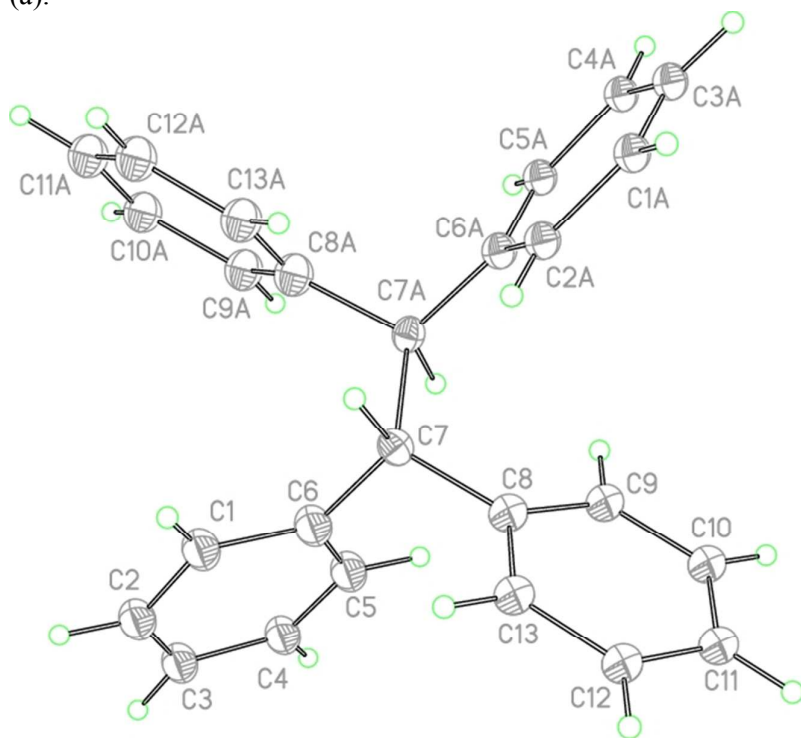


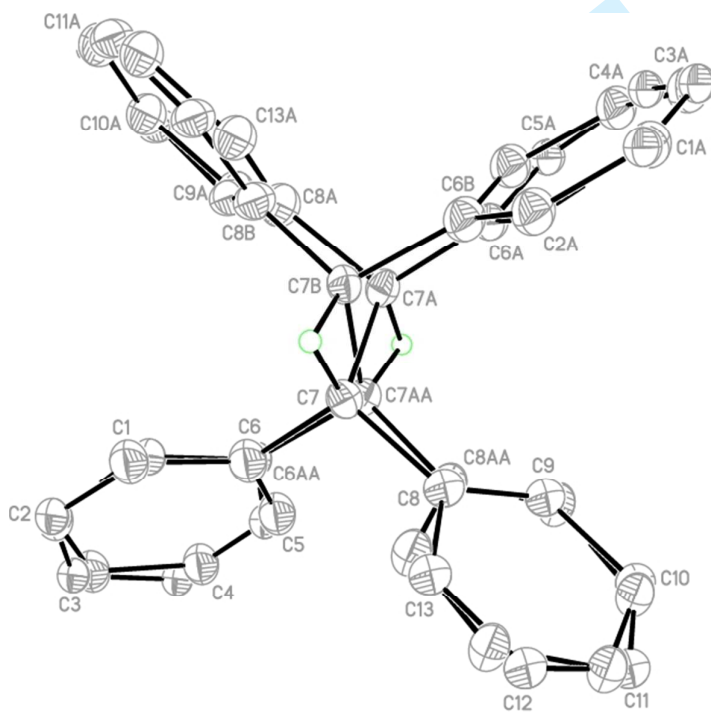
Figure 4. (b). Ion trap CI and EI mass spectra for 1,2,2-tetraphenylethane, its di-fluoro and tetra-fluoro analogs

292x413mm (300 x 300 DPI)

(a).

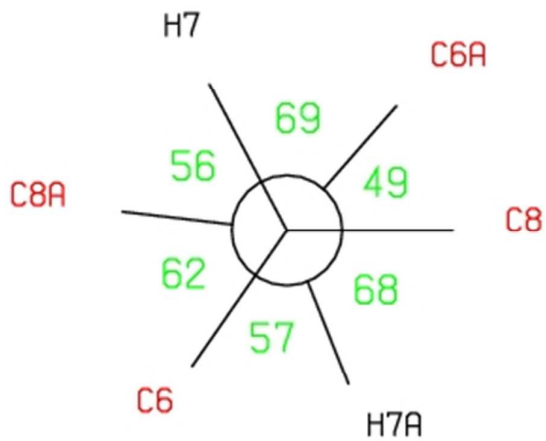


(b).



1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

(c).



Peer Review