SUPPORTING INFORMATION

Efficient Atom and Step Economic (EASE) Synthesis of smart drug Modafinil

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1. General information

All reagents and solvents were purchased from commercial sources and used as received. The progress of the reaction was monitored by analytical TLC on silica gel G/GF 254 plates. Reagent grade solvents were used for extraction and flash chromatography. The column chromatography was performed with silica gel 230-400 mesh. NMR (^{1}H and ^{13}C) spectra were recorded on a 300 & 400 MHz using TMS as an internal standard and chemical shifts (δ ppm) (multiplicity, coupling constant (Hz), integration). The abbreviations for multiplicity are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets. Melting points are uncorrected were determined in capillary tubes on a hot stage melting point apparatus containing silicon oil. High-resolution mass spectra (ESI-HRMS) were recorded on Agilent 6520 ESI-QTOP mass spectrometer.. IR spectra were recorded using a FTIR spectrophotometer.

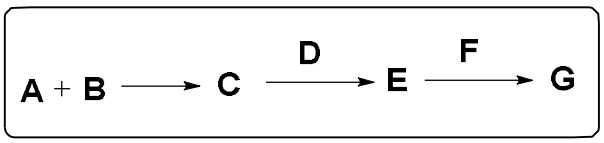
Background

Smart drug[1] Modafinil (2-(diphenylmethylsulfinyl)acetamide) is a wakefulness promoting agent approved by the Food and Drug Administration in the United States[2], used for treatment of disorders such as shift work sleep disorder, and excessive daytime sleepiness associated with obstructive sleep apnea[3]. It is a central nervous system stimulant reported to have little abuse potential. At pharmacologically relevant concentrations, modafinil does not bind to most potentially relevant receptors for sleep/wake regulation, including those for norepinephrine, serotonin, dopamine, adenosine, histamine-3, melatonin, or benzodiazepines. Modafinil is under investigation as a possible method to treat cocaine dependence[4]. It is also used in militaries where soldiers face sleep deprivation as an alternative to amphetamine[5] as well as by astronauts on long-term missions aboard the International Space Station[6]. We report an efficient atom and step economic (EASE) synthesis for Modafinil, a key

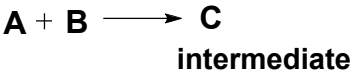
psychostimulant drug, utilised for treatment of narcolepsy[7,8]. The developed post-sulfoxidation protocol for the synthesis of Modafinil, exhibits improved green chemistry matrix, utilizing recyclable heterogeneous catalyst Nafion-H. Additionally a superior pre-sulfoxidation approach for Modafinil has been developed.

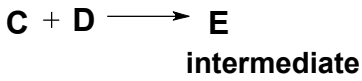
3. Green metrics calculations: Formulae used

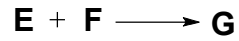
For a **linear synthetic process**[9,10]:



Steps involved in this process are:







The reactants and reagents efficiently participate in product formation excluding intermediates are:

1. No. of steps = No. of steps involved in the process

2. Atom economy =

[(M.W. of product G)/(M.W. of A+ M.W. of B+ M.W. of D+ M.W. ofF)]x100

3. % yield = (Observed yield/ Calculated yield) x100

4. Atom efficiency = % yield x Atom economy

5. Carbon efficiency =

[(no. of moles of product G x no. of carbons in product G)/{(no. of moles of A x no. of carbons in A)+ (no. of moles of B x no. of carbons in B)+ (no. of moles of D x no. of carbons in D)+ (no. of moles of F x no. of carbons in F)}]x100

6. Mass intensity = (Total mass used in the process / Mass of the product)

7. Mass productivity = (1/ Mass intensity) x100

8. E- factor = (Mass intensity – 1)

9. Effective Mass Yield = (1/ E- factor) x100

10. Reaction Mass Efficiency =

[(Mass of product G) / (Mass of A + Mass of B + Mass of D + Mass of F)] x 100

3. Green metrics calculations:

Post-Sulfoxidation approach:

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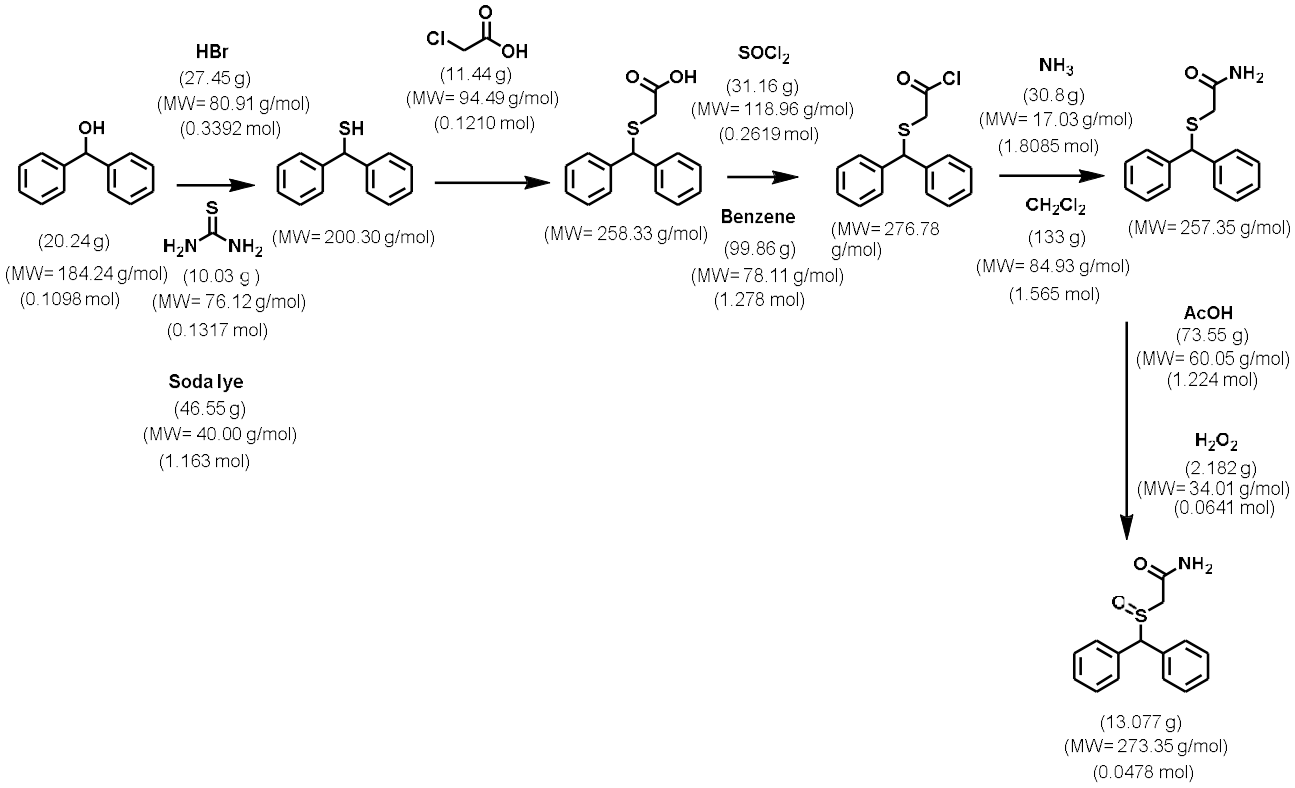
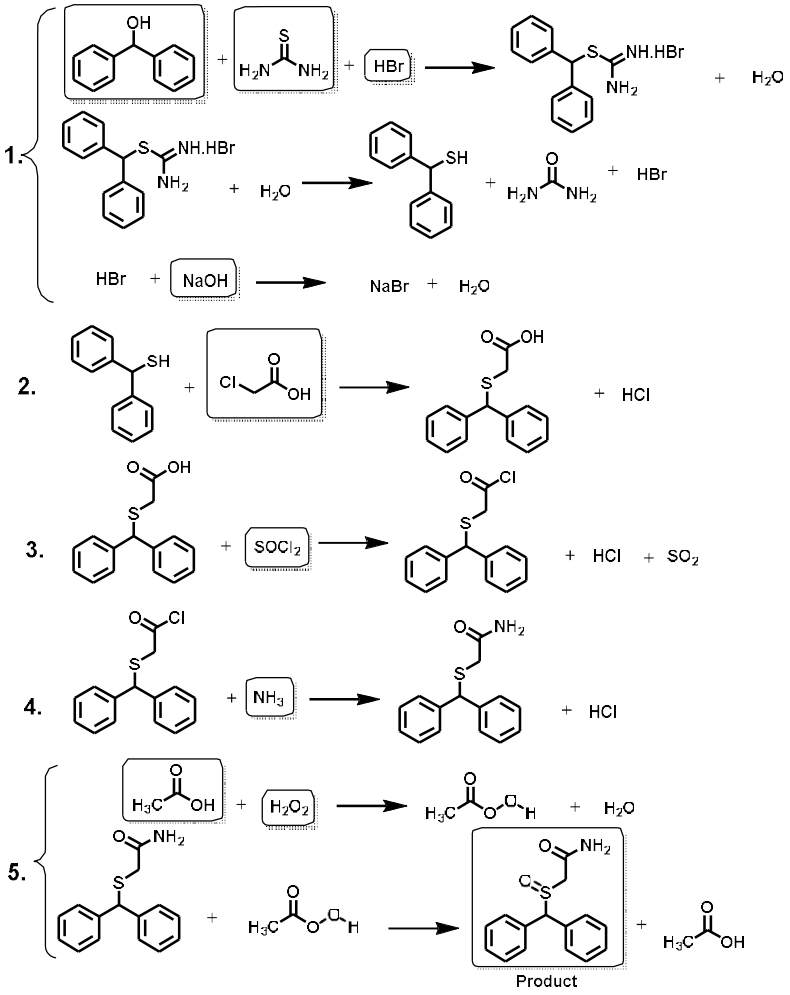


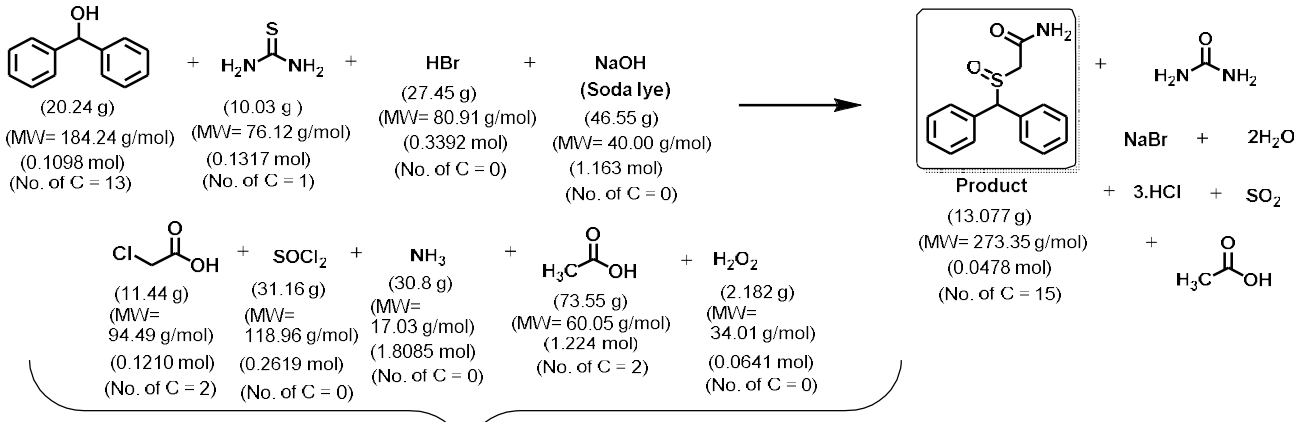
Scheme 1.1

These individual steps are involved in the reaction:



Note: Reactants and reagents present in circle efficiently participate in product formation excluding intermediates. Each step should be a balanced step for calculation purpose.

Scheme 1.2



Note:
These reactants and reagents efficiently participate in the product formation excluding intermediates.
Reaction stoichiometry should be balanced for calculation.

Scheme 1.3

1. No of steps = 5

2. Atom economy =
{(273.35)/(184.24+76.12+80.91+40.00+94.49+118.96+17.03+60.05+34.01)}x100 = 38.72%

3. % yield = (13.077/30.029)x100 = 43.54%

4. Atom efficiency = (43.54/100) x 38.72 = 16.85

5. Carbon efficiency =

[(0.0478x15)/{(0.1098x13)+(0.1317x1)+(0.3392x0)+(1.163x0)+(0.1210x2)+(0.2619x0)+(1.8085x0)+(1.224x2)+(0.0641x0)}]x100

= 16.87%

6. Mass intensity =
(20.24+10.03+27.45+46.55+11.44+31.16+99.86+30.8+133+73.55+2.182)/(13.077) = 37.184 kg/kg

7. Mass productivity = (1 / 37.184) x100 = 2.689 %

8. E-factor = (37.184 -1) = 36.184 kg/kg

9. Effective Mass Yield = (1/36.184) x100 = 2.763%

10. Reaction Mass Efficiency =
[(13.077)/(20.24+10.03+27.45+46.55+11.44+31.16+30.8+73.55+2.182)] x100 = 5.16%

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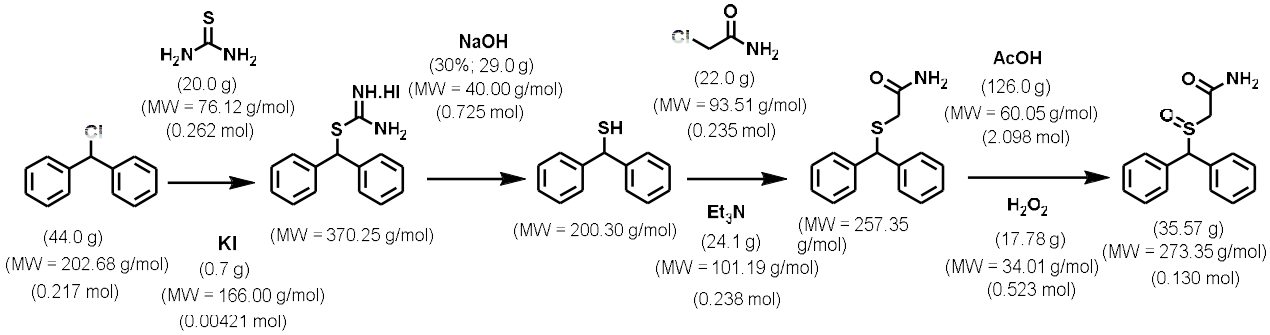
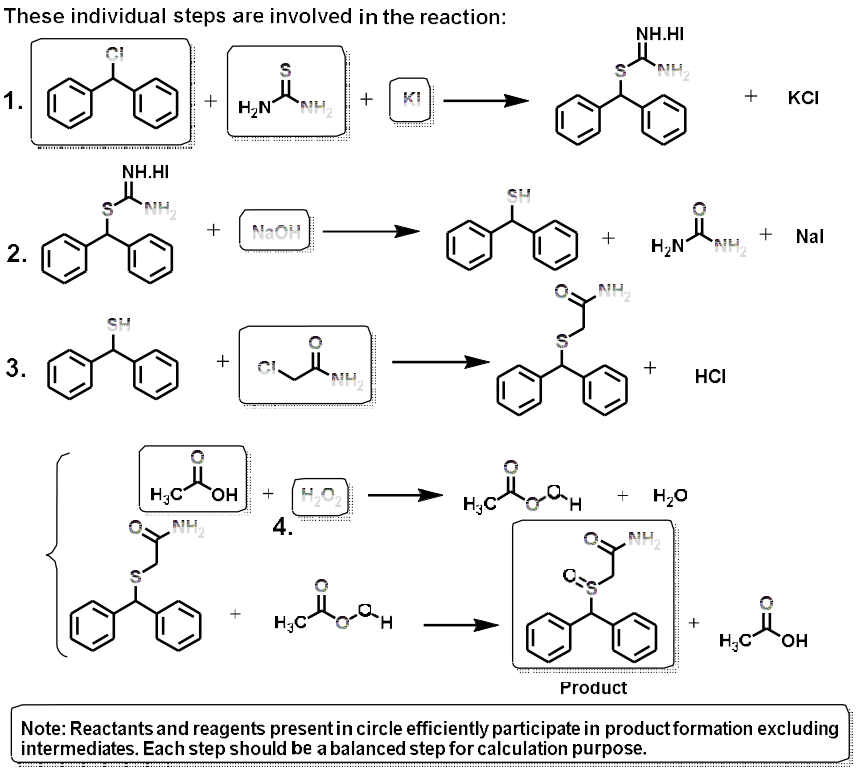
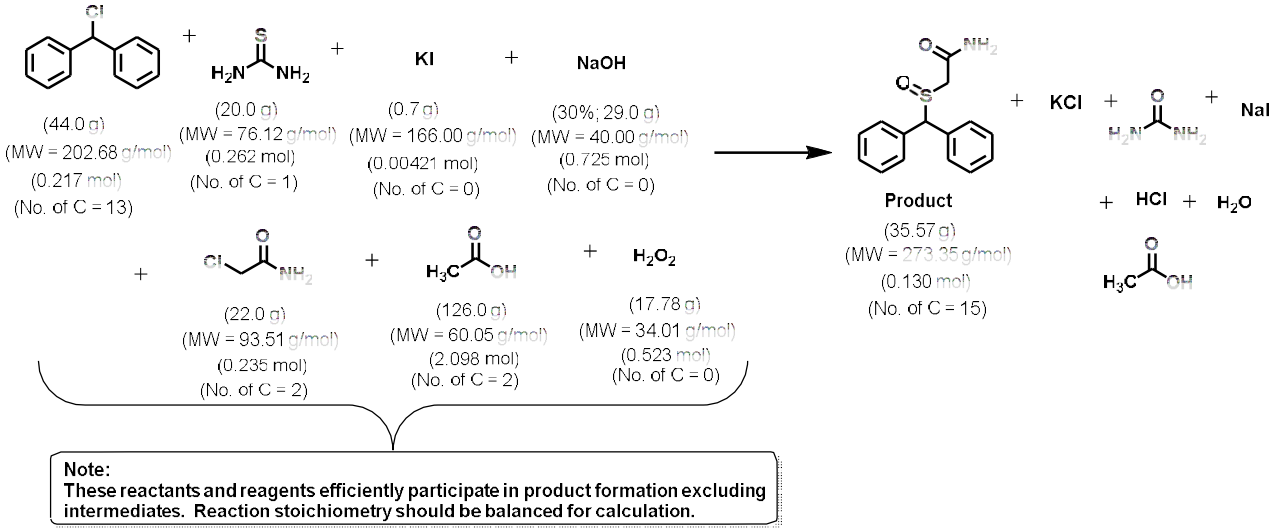


Scheme 2.1



Scheme 2.2



Scheme 2.3

1. No of steps = 4

2. Atom economy = {(273.35)/(202.68+76.12+166.00+40.00+93.51+60.05+34.01)}x100 = 40.65%

3. % yield = (35.57/59.34)x100 = 60%

4. Atom efficiency = (60/100) x 40.65% = 24.39

5. Carbon efficiency =

[(0.130x15)/{(0.217x13)+(0.262x1)+(0.00421x0)+(0.725x0)+(0.235x2)+(2.098x2)+(0.523x0)}]x100 = 25.164%

6. Mass intensity = (44.0+20.0+0.7+29.0+22.0+24.1+17.78+126.0)/(35.57) = 7.972kg/kg ≈8kg/kg

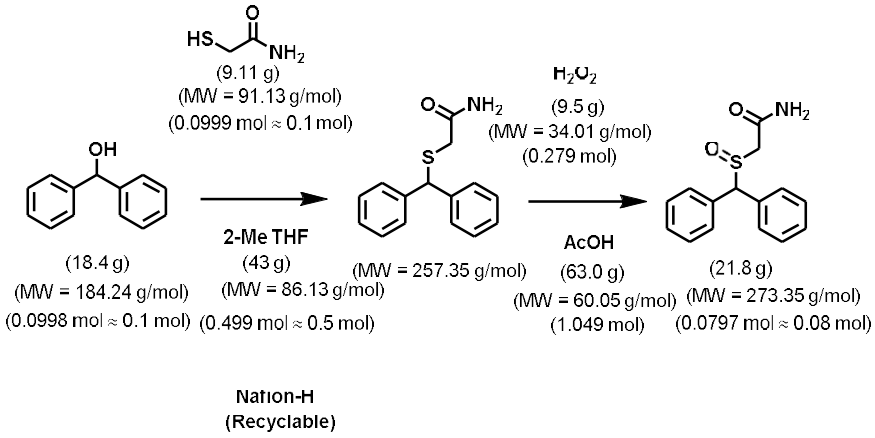
7. Mass productivity = (1 / 7.972) x100 = 12.54 %

8. E-factor = (7.972 -1) = 6.972kg/kg ≈ 7kg/kg

9. Effective Mass Yield = (1/6.972) x100 = 14.343%

10. Reaction Mass Efficiency = [(35.57)/(44.0+20.0+0.7+29.0+22.0+126.0+17.78)] x100 = 13.708%

Our work



Scheme 3.

1. No of steps = 2

2. Atom economy = {(273.35)/(184.24+91.13+34.01)}x100 = 88.35%

3. % yield = (21.8/27.29)x100 = 80%

4. Atom efficiency = (80/100) x 88.35 = 70.68

5. Carbon efficiency = [(0.08x15)/{(0.1x13)+(0.1x2)+(0.279x0)}]x100 = 80.0%

6. Mass intensity = (18.4+9.11+43.0+63.0+9.5)/(21.8) = 6.56 kg/kg

7. Mass productivity = (1 / 6.56) x100 = 15.24 %

8. E-factor = (6.56 -1) = 5.56 kg/kg

9. Effective Mass Yield = (1/5.56) x100 = 17.98% ≈ 18 %

10. Reaction Mass Efficiency = [(21.8)/(18.4+9.11+9.5)] x100 = 59.0%

Pre-Sulfoxidation approach:

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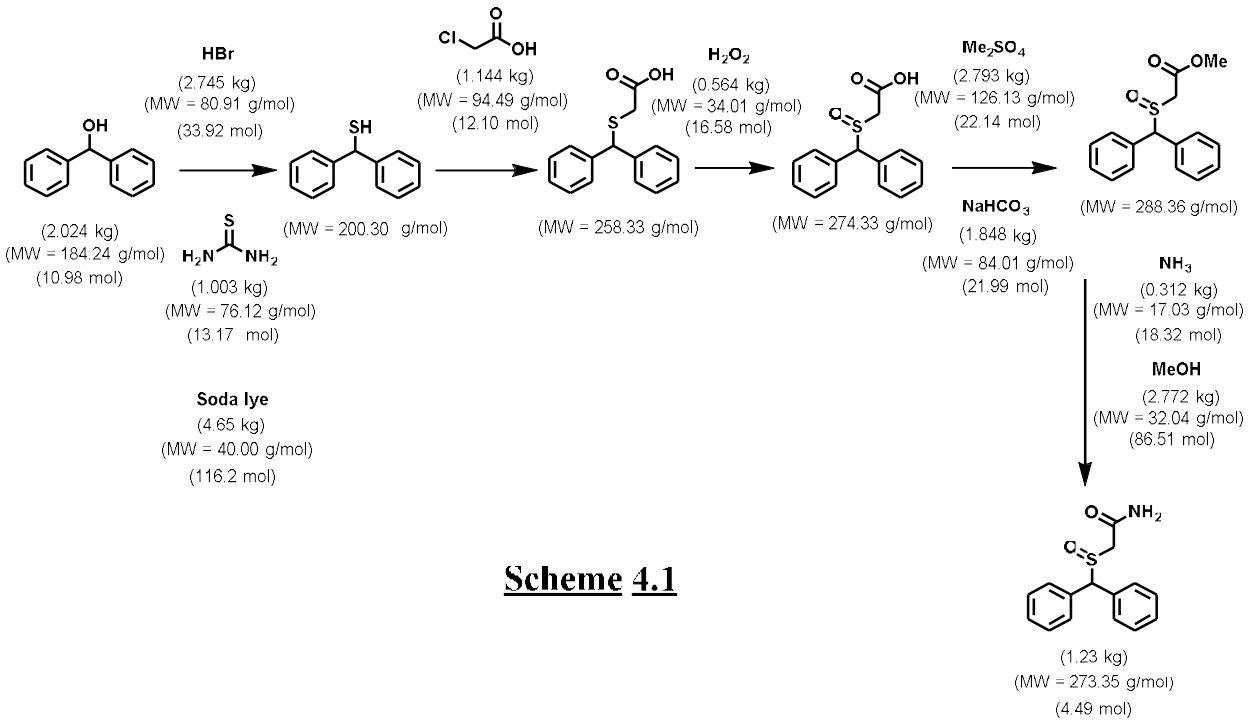
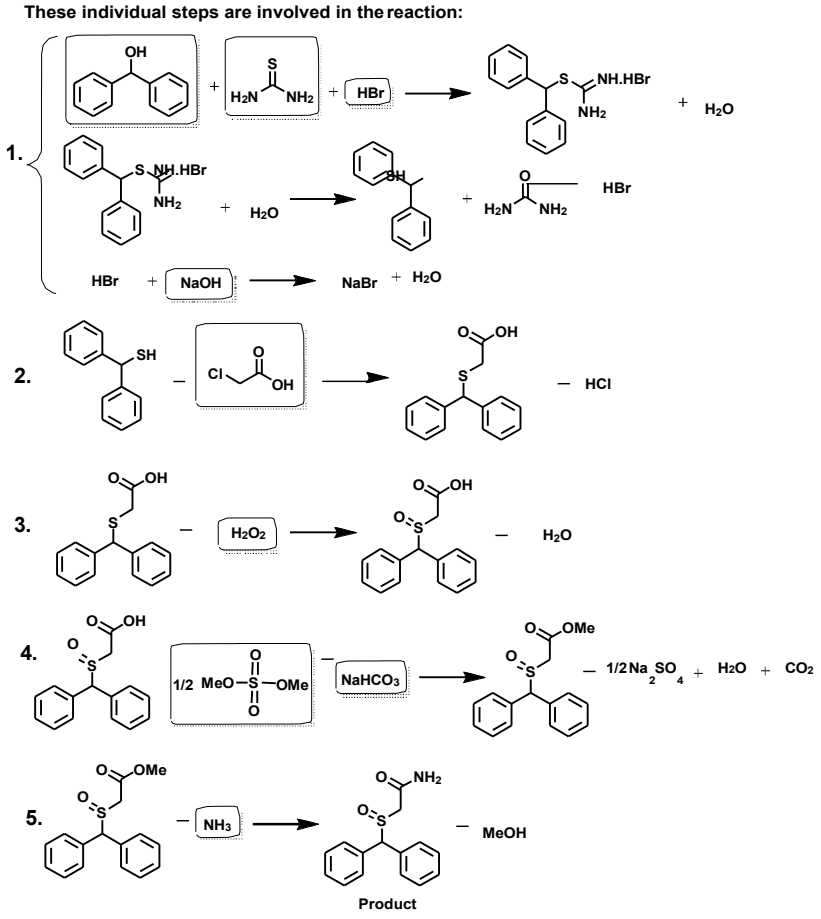


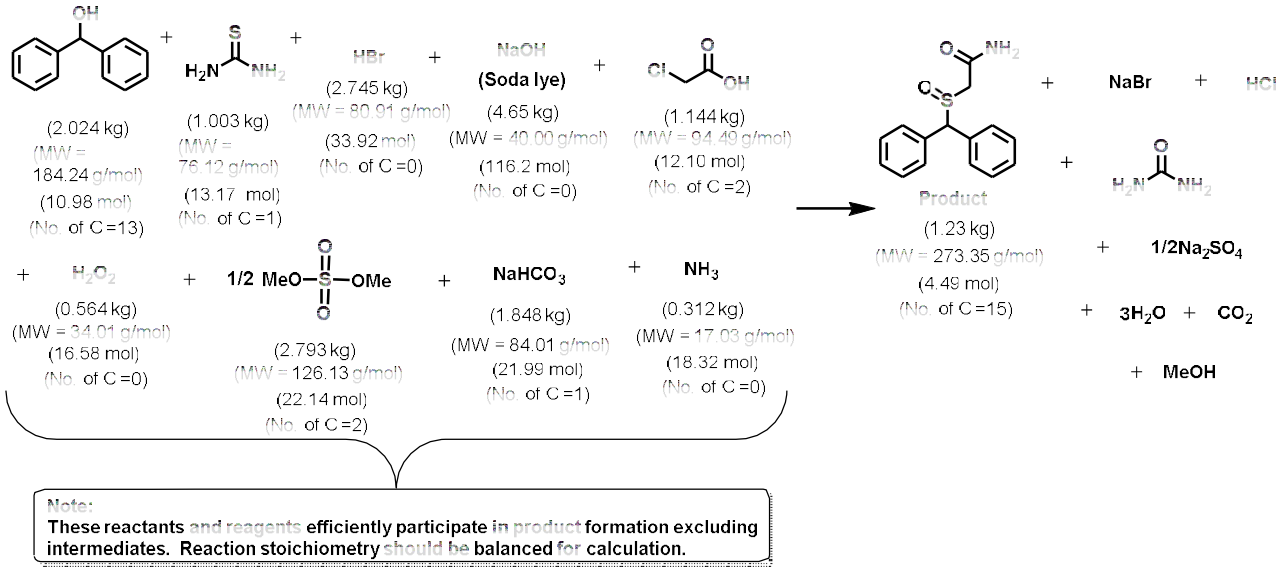
Scheme 4.1

These individual steps are involved in the reaction:



Note: Reactants and reagents present in circle efficiently participate in product formation excluding intermediates. Each step should be a balanced step for calculation purpose.

Scheme 4.2



Scheme 4.3

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1. No of steps = 5

2. Atom economy =

{(273.35)/(184.24+76.12+80.91+40.00+94.49+34.01+(0.5x126.13)+84.01+17.03)}x100 = 40.563%

3. % yield = (1.23/3.00)x100 = 41%

4. Atom efficiency = (41/100) x 40.563 = 16.63

5. Carbon efficiency =

[(4.49x15)/{(10.98x13)+(13.17x1)+(33.92x0)+(116.2x0)+(12.10x2)+(16.58x0)+(22.14x2)+(21.99x1)+(18.32x0)}]x100

= 27.335%

6. Mass intensity =

(2.024+1.003+2.745+4.655+1.144+0.564+2.793+1.848+1.463+0.312+2.772)/(1.23) = 17.335 kg/kg

7. Mass productivity = (1 / 17.335) x100 = 5.768 %

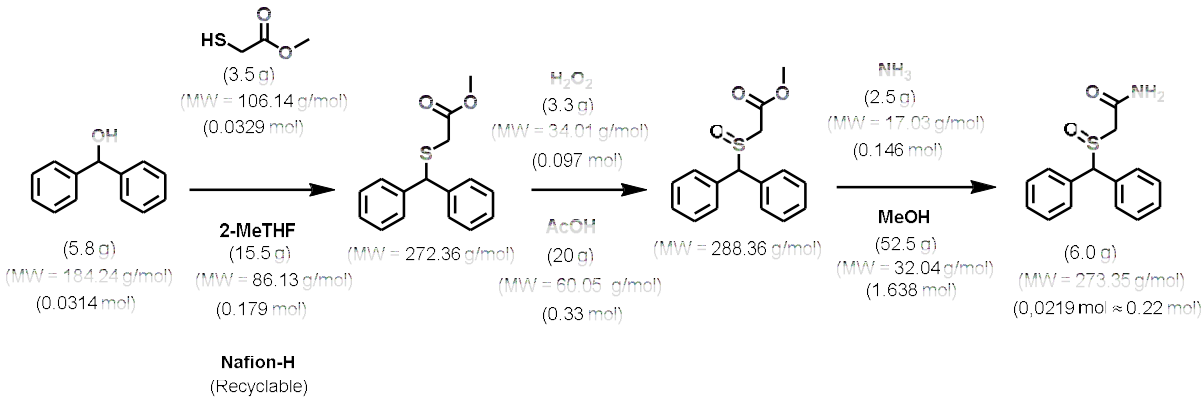
8. E-factor = (17.335 -1) = 16.335 kg/kg

9. Effective Mass Yield = (1/16.335) x100 = 6.121 %

10. Reaction Mass Efficiency =

[(1.23)/(2.024+1.003+2.745+4.65+1.144+0.564+2.793+1.848+0.312)] x100 = 7.20 %

Our work



Scheme 5.

1. No of steps = 3

2. Atom economy = {(273.35)/(184.24+106.14+34.01+17.03)}x100 = 80.0%

3. % yield = (6.0/8.6)x100 = 70%

4. Atom efficiency = (70/100) x 80.0 = 56

5. Carbon efficiency = [(0.0219x15)/{(0.0314x13)+(0.0329x3)}]x100 = 65.1%

6. Mass intensity = (5.8+3.5+15.5+20.0+3.3+2.5+52.5)/(6.0) = 17.183 kg/kg

7. Mass productivity = (1 / 17.183) x100 = 5.819 %

8. E-factor = (17.183 -1) = 16.183 kg/kg

9. Effective Mass Yield = (1/ 16.183) x100 = 6.17 %

10. Reaction Mass Efficiency = [(6.0)/(5.8+3.5+3.3+2.5)] x100 = 39.73%

4. Experimental procedure : Post-Sulfoxidation approach:

Synthesis of 2-(benzhydrylthio)acetamide: Mixture of 2-mercaptoacetamide (0.1 mol), diphenylmethanol (0.1 mol) and Nafion-H (0.02 gm) in 2-Me THF (50 ml) was stirred at r.t. overnight. The solvent was removed, the mixture was diluted with H_2O (20 mL), extracted and dried with Na_2SO_4. The solvent was removed and obtained white pure product (Yield 88%).

Synthesis of 2-(benzhydrylsulfinyl)acetamide (Modafinil): H_2O_2 (35% w/w aqueous solution; 0.28 mol) was slowly added in 2-(benzhydrylthio)acetamide (0.087 mol) in AcOH (60 ml; d = 1.05 g/cm^3). The reaction was stirred and heated in water bath at 50°C for 2 hrs and reaction progress was monitored by TLC. The mixture was cooled by adding ice

followed by vacuum filtration to obtain the crude solid which upon recrystallization in aqueous methanol yield white solid (Yield 91%).

Pre-Sulfoxidation approach:

Synthesis of Methyl 2-(benzhydrylthio)acetate: A mixture of Diphenylmethanol (0.034 mol) and methylthioglycolate (0.033 mol) and Nafion-H (0.05 mol) in 2-MeTHF (18 mL; d=0.86 g/ml) was stirred at r.t. overnight. The solvent was removed, the mixture was diluted with H_2O (20 mL), extracted and dried with Na_2SO_4. The solvent was removed and obtained light red (oily) pure product (Yield 92%).

Synthesis of Methyl 2-(benzhydrylsulfinyl)acetate : H_2O_2 (35% w/w aqueous solution; 0.097 mol) was slowly added in Methyl 2-(benzhydrylthio)acetate (0.029 mol) in AcOH (19 ml; d=1.05 g/cm^3). The reaction was stirred and heated in water bath at 50°C for 2 hrs and reaction progress was monitored by TLC. The mixture was cooled by adding ice followed by vacuum filtration to obtain pale yellow gummy liquid (Yield 96%).

Synthesis of 2-(benzhydrylsulfinyl)acetamide (Modafinil): A mixture of Methyl 2-(benzhydrylsulfinyl)acetate (0.0277 mol), NH_3 (2.5 g) solution in MeOH (50 ml) (ie. 50 ml, methanolic ammonia 3M) was stirred at 50°C for 4-5 hr. Reaction mixture was filtered, filtrate was collected and dried to get white solid pure product (Yield 79%).

Regeneration of catalyst: The catalyst was washed with acetone and deionized water then dried overnight at 100°**C** to reuse.

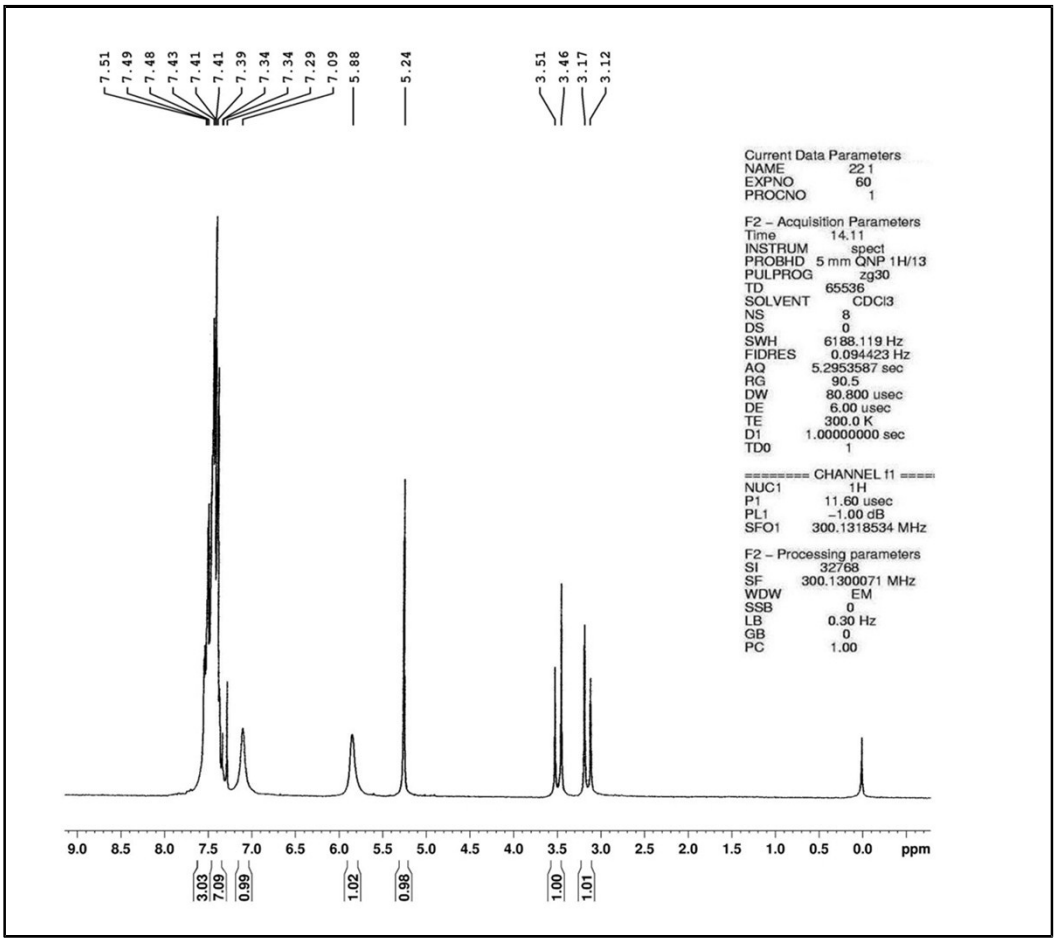
Table. Recyclability studies of Nafion-H in the synthesis of 2-(benzhydrylthio)acetamide (2)

Run	1st	2nd	3rd	4th	5th
Yield	88	88	87	85	84

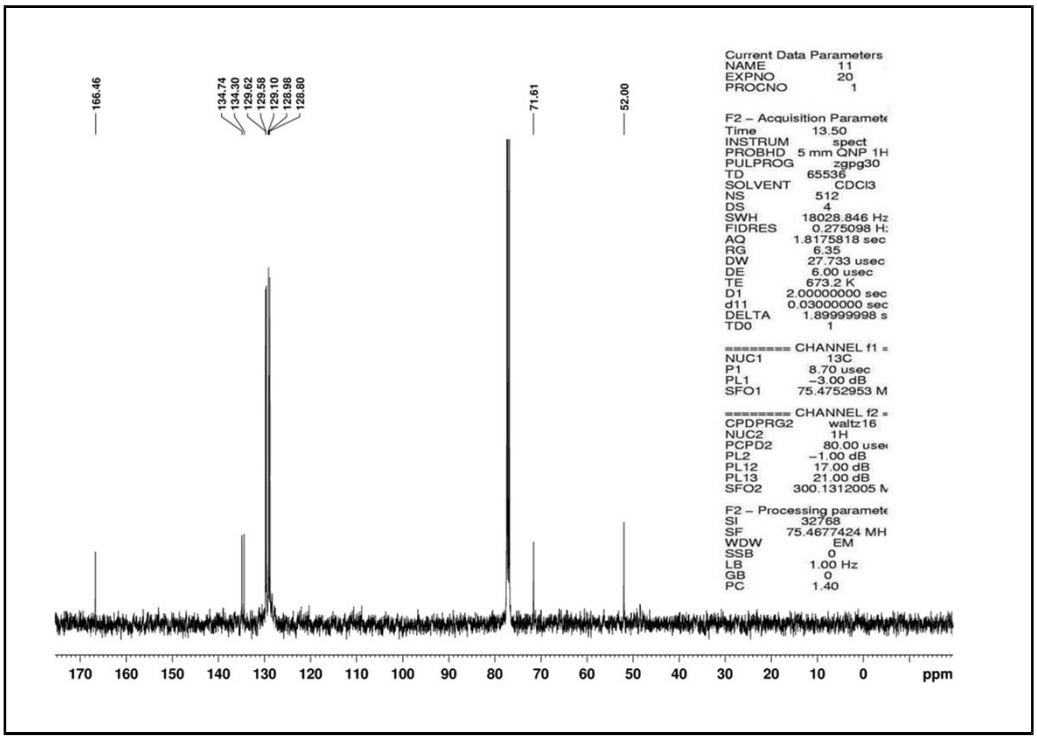
5. Spectral charts

Modafinil Physical State – White solid; M.p. 158-159ºC, IR (KBr): 3383, 3314, 3256, 1690, 1616, 1494, 1376, 1027, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ(ppm): 3.14(d, *J*=14.3 Hz, 1H); 3.48(d, *J*=14.3 Hz, 1H); 5.24(s, 1H); 5.88(br s, 1H); 7.09(br s, 1H); 7.29-7.43(m, 7H); 7.43-7.51(m, 3H); ^{13}C NMR ($CDCl_3$) δ(ppm): 52.00, 71.61, 128.80, 128.98, 129.10, 129.58, 129.62, 134.30, 134.74, 166.46; Molecular formula $C_{15}H_{15}NO_2S$; ESI-MS (m/z): 274.1 $(M+H)^+$.

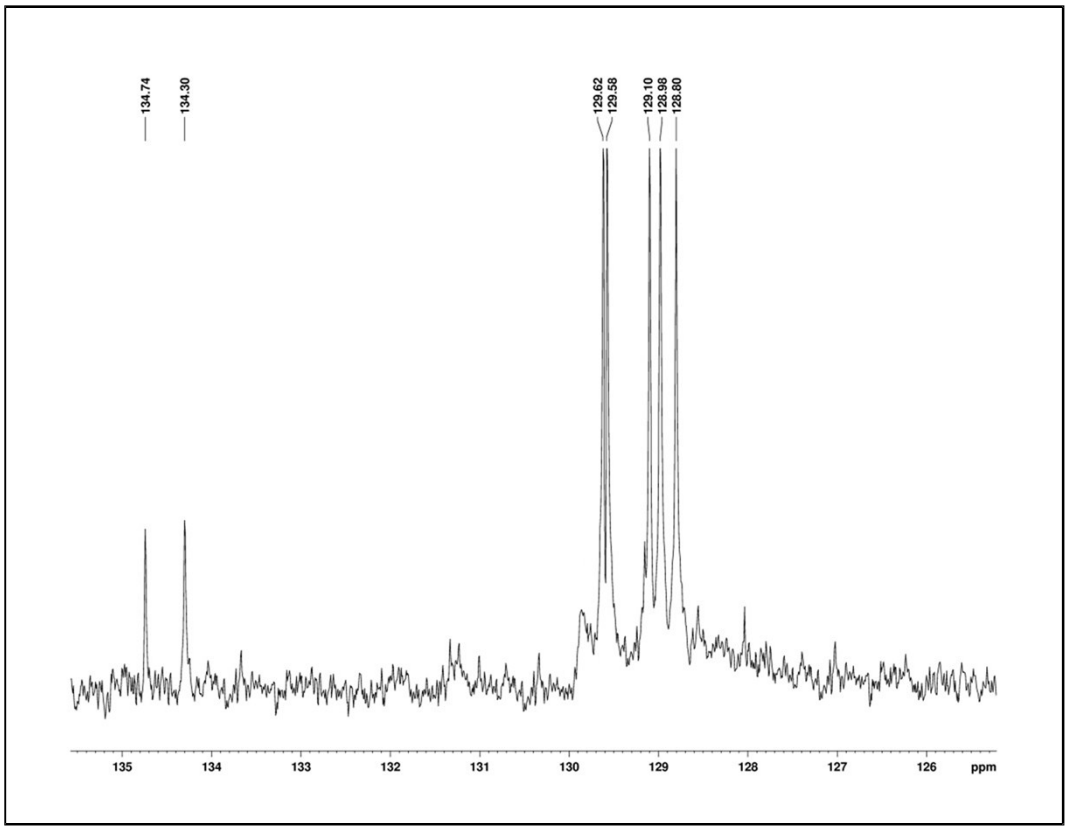
2-(Benzhydrylthio)acetamide Physical State – White solid; M.p. 108-110ºC, IR (KBr): 3383, 3026, 1643, 1490, 1449, 1409, 696cm^{-1}; ^{1}H NMR ($CDCl_3$) δ(ppm): 3.12(s, 2H); 5.20(s, 1H), 5.55(br s, 1H); 6.54(br s, 1H); 7.26-7.30(m, 2H); 7.30-7.37(m, 4H); 7.37-7.45(m, 4H). ^{13}C NMR ($CDCl_3$) δ(ppm): 35.60, 54.75, 127.65, 128.29, 128.78, 140.24, 171.48. Molecular formula $C_{15}H_{15}NOS$; ESI-MS (m/z): 258.3 $(M+H)^+$.



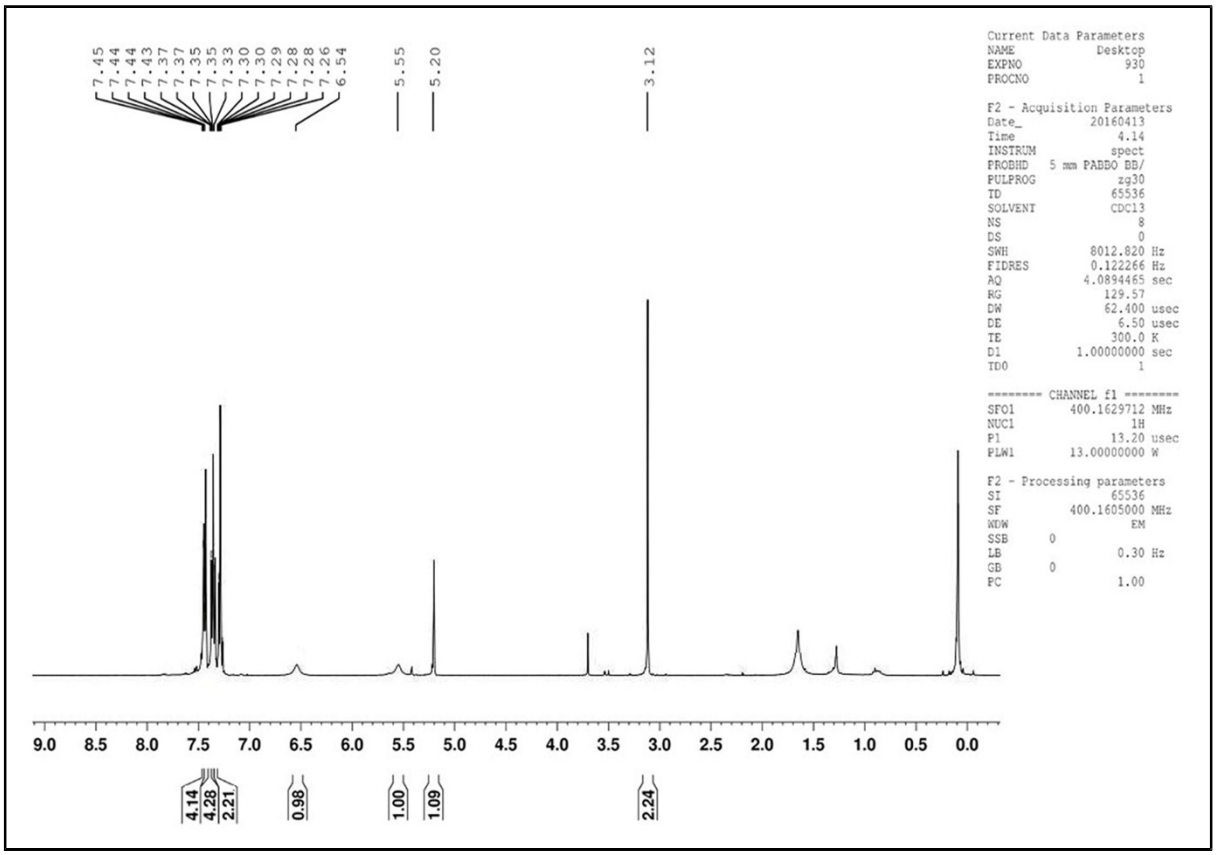
^{1}H Spectra of Modafinil



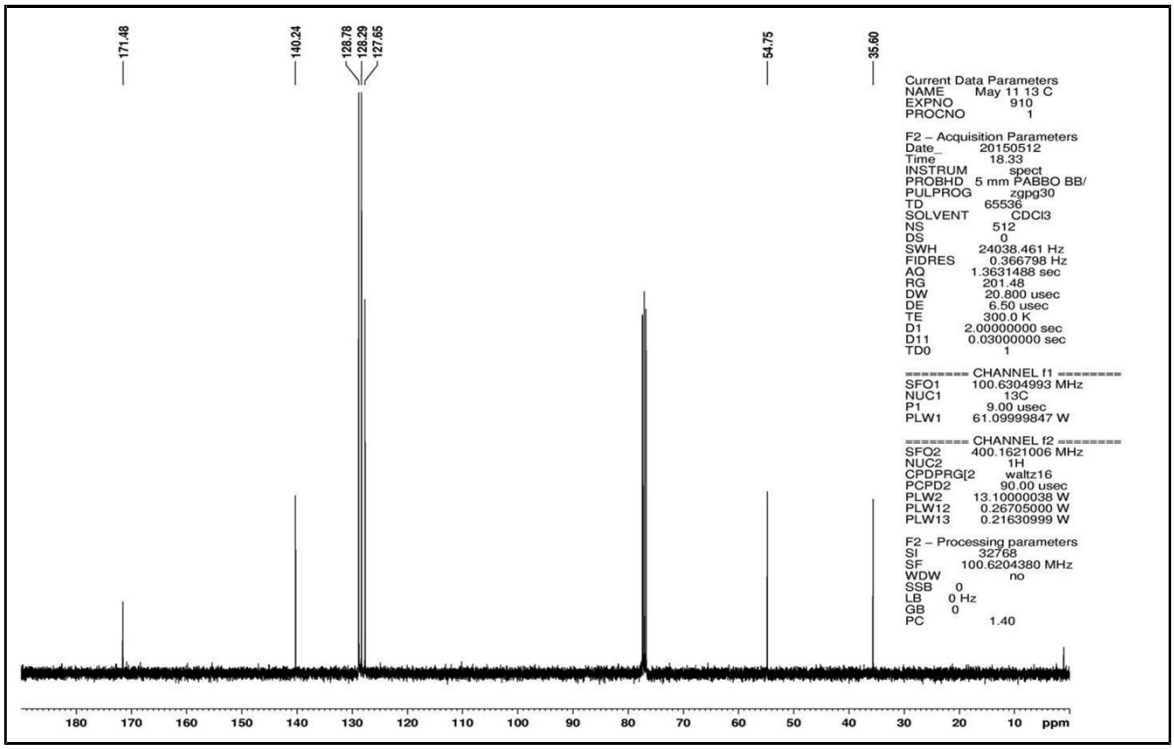
^{13}C Spectra of Modafinil



13C NMR spectrum of modafinil expanded in the aromatic region



[1]H Spectra of 2-(Benzhydrylthio)acetamide



^{13}C Spectra of 2-(Benzhydrylthio)acetamide

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