Supporting information for

Out-smarting smart drug modafinil through flow chemistry

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1. Continuous flow setups

1.1. Microfluidic setups and parts

All microfluidic setups were assembled with commercially available parts.

1.1.1. Pumps

Chemyx Fusion 6000 High Force syringe pumps equipped with stainless steel syringes (6 or 20 mL) with Dupont Kalrez Spectrum AS-568 O-rings (0.549 x 0.103") and HPLC pumps (ThalesNano, THS 09037) were utilized to handle the liquid feeds. For heated feed solutions, a Chemyx Heating sleeve was added to a 20 mL SS syringe.

1.1.2. Connectors, ferrules, and mixers

Capillaries were assembled with coned PEEK fittings or Super Flangeless PEEK nuts, ETFE ferrules and SS rings. Mixers consisted of PEEK T-mixers (0.02" through hole) or PEEK cross-junctions (0.02" trough hole). Connectors, ferrules, unions and mixers were purchased from IDEX/Upchurch (details in Table S1).

1.1.3. Check-valves

Check-valves (IDEX/Upchurch Scientific) inserted between the pumps and the reactor were purchased from IDEX/Upchurch Scientific (PEEK check-valve holder).

1.1.4. Back-pressure regulator

Spring loaded BPRs were purchased from IDEX/Upchurch Scientific (PEEK holder). Dome-type BPRs were purchased from Zaiput Flow Technologies (BPR-10). The dome-type BPR was connected to a compressed gas cylinder (nitrogen) to set the working pressure

1.1.5. Thermoregulatory devices

PFA coils reactors were thermoregulated in oil baths (Heidolph MR Hei-Tec equipped with Pt-1000 temperature sensors).

1.2. Mesofluidic scale setup (Corning® Advanced-Flow™ Lab reactor)

1.2.1. Pumps

Chemyx Fusion 6000 High Force syringe pumps equipped with stainless steel syringes (20 mL) with Dupont Kalrez Spectrum AS-568 O-rings (0.549 x 0.103"); HPLC pumps (ThalesNano, THS 09037); and Syrris Asia pumps equipped with Asia Red Syringes (2.5 mL / 5 mL) were utilized to handle the liquid feeds.

1.2.2. Mesofluidic reactor

The lab scale setup was manufactured by Corning SAS (Corning® Advanced-Flow™ Lab Reactor) and equipped with one or several fluidic modules connected in series (glass fluidic modules: 2.5 mL internal volume).

1.2.3. Thermoregulatory devices

For the individual (one plate) reactions, the reactor was maintained at reaction temperature using a Huber Ministat 230 thermostat.
For the telescoped reaction, the reactor was maintained at reaction temperature with a LAUDA Integral XT 280 thermostat (THERM 180 thermofluid).

1.2.4. Back-pressure regulators

Dome-type BPRs were purchased from Zaiput Flow Technologies (BPR-10). The dome-type BPR was connected to a compressed gas cylinder (nitrogen) to set the working pressure.

1.3. Table of part numbers & vendors

Standard fluidic elements and connectors were purchased from INACOM Instruments/IDEX and Zaiput Flow Technologies (**Table S1**).
Table S1. Parts list for fluidic elements and connectors

Item	Details	Vendor	Reference
Connectors	SuperFlangeless™ Male Nut 1/16in PEEK	INACOM Instruments/IDEX	P-255
	SuperFlangeless™ Ferrule Assembly 1/16in	INACOM Instruments/IDEX	P-259
	FingerTight I PEEK	INACOM Instruments/IDEX	F-120
Unions	Union body 1/4-28 - 1/16in PEEK	INACOM Instruments/IDEX	P702-01
Mixers	T-mixer, natural PEEK 1/4-28 thread for 1/16" o.d. tubing, 0.02" through hole	INACOM Instruments/IDEX	P-712
	PEEK Y Assembly 1/4-28	INACOM Instruments/IDEX	P-512
	High Pressure mixing Tee UHMWPE Frit	INACOM Instruments/IDEX	U-466
Check-valves	Check-valve inline cartridge 1.5 psi and cartridge holder, PEEK	INACOM Instruments/IDEX	CV-3000
Back pressure regulators	Dome-type back pressure regulator	Zaiput Flow Techn.	BPR-10
	Spring loaded BPR cartridge with gold coating (100 psi)	INACOM Instruments/IDEX	P-787
Tubing	Tubing PFA High Purity 1/16” OD, 0.030” ID (50ft)	INACOM Instruments/IDEX	1632L
	Tubing PFA High Purity 1/16” OD, .020” ID (50ft)	INACOM Instruments/IDEX	1622L

1.4. Detailed schemes for continuous flow setups

1.4.1. Continuous flow setup for the preparation of sodium carbamoylmethyl sulfate (SCS).

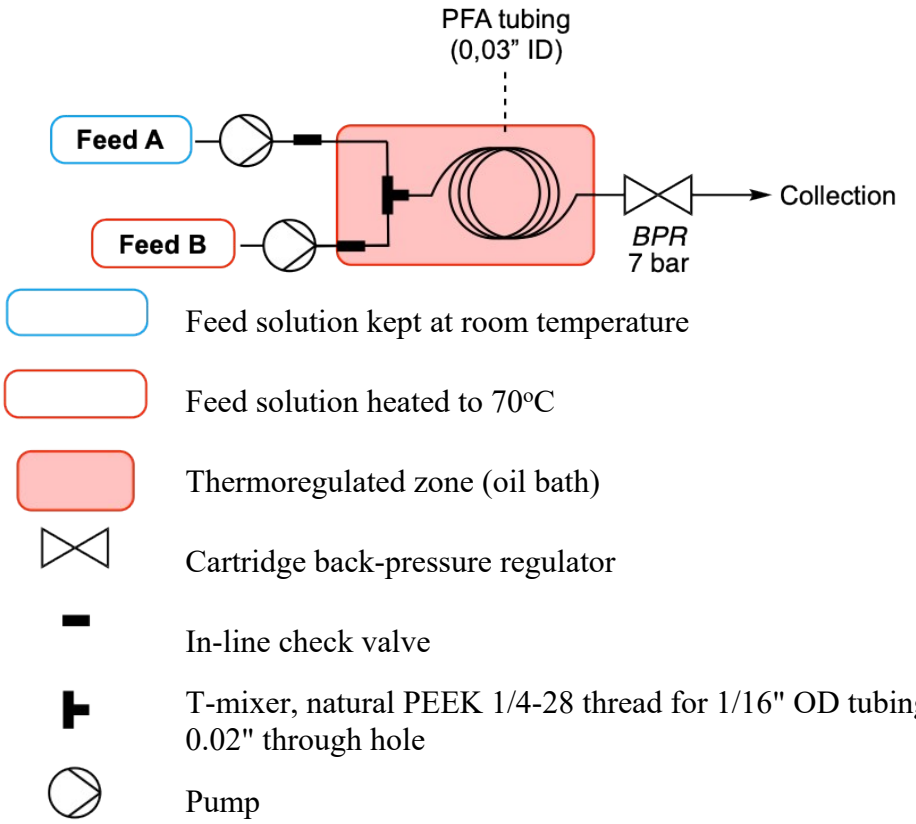


Figure S1. Detailed setup for the continuous flow preparation of sodium carbamoylmethyl sulfate (**SCS**).

1.4.2. Continuous flow setup for the preparation of 2-(benzhydrylthio)acetamide (6).

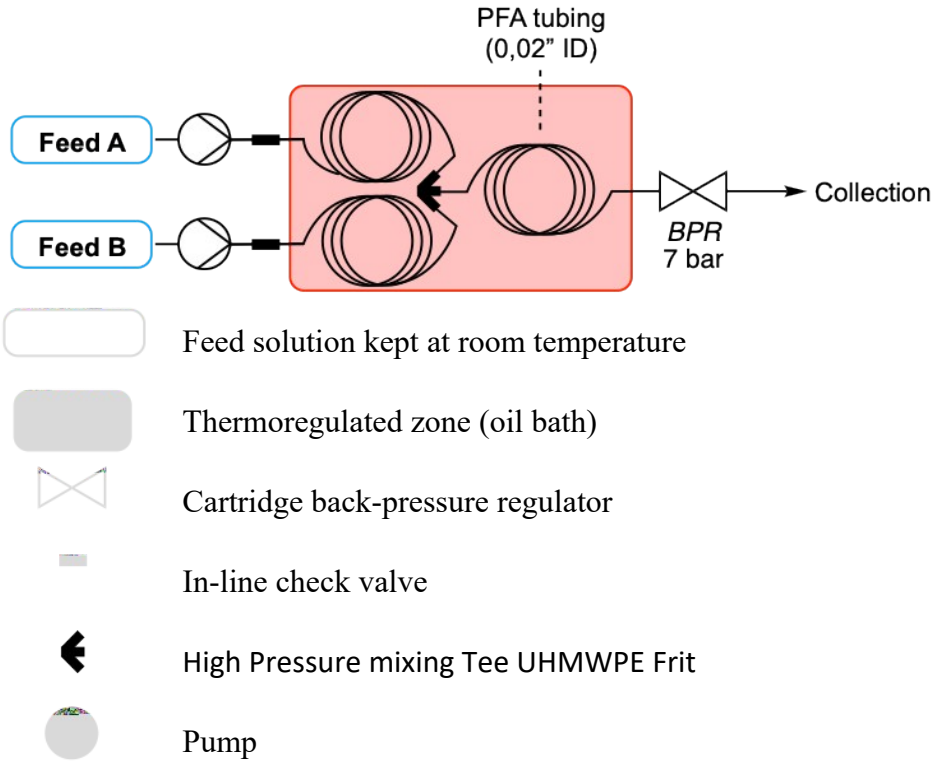


Figure S2. Detailed setup for the continuous flow preparation of 2-(benzhydrylthio)acetamide (**6**).

1.4.3. Continuous flow setup for the preparation of modafinil (**1**)

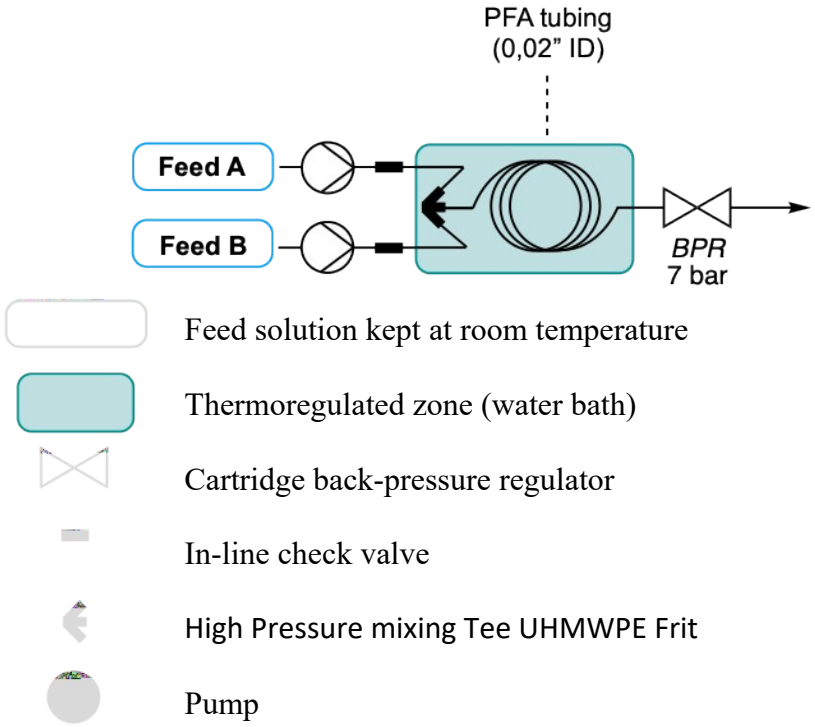
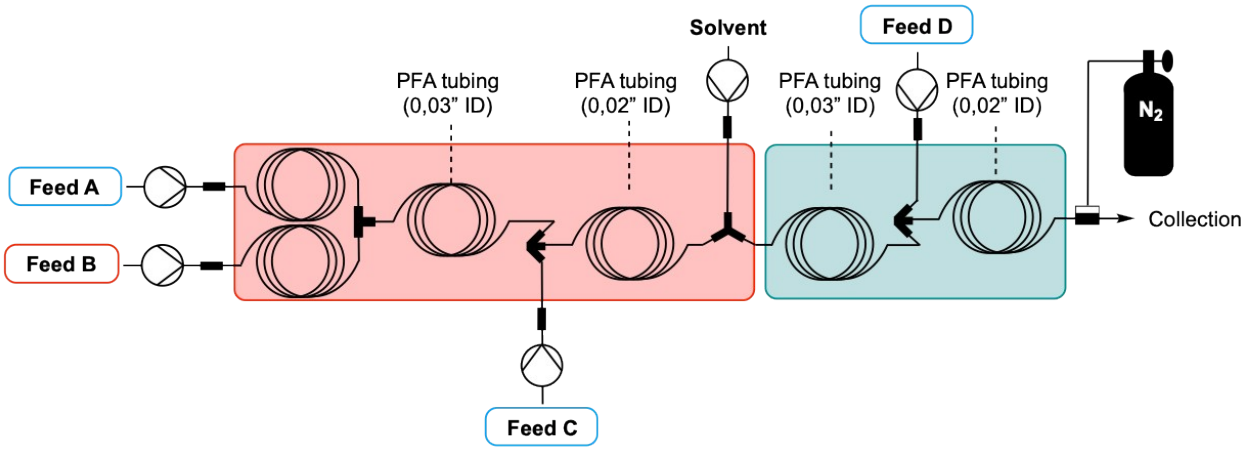


Figure S3. Detailed setup for the continuous flow preparation of modafinil.

1.4.4. Fully concatenated continuous flow setup for the preparation of modafinil (**1**).



Feed solution kept at room temperature

Feed solution heated to 70°C

Thermoregulated zones (water bath)

Thermoregulated zones (oil bath)

Dome-shaped back-pressure regulator

In-line check valve

High Pressure mixing Tee UHMWPE Frit

T-mixer, natural PEEK 1/4-28 thread for 1/16" OD tubing, 0.02" through hole

PEEK Y Assembly 1/4-28

Pump

Figure S4. Detailed setup for the fully concatenated continuous flow preparation of Modafinil.

1.4.5. Mesofluidic preparation of Sodium carbamoylmethyl sulfate (SCS) (lab scale)

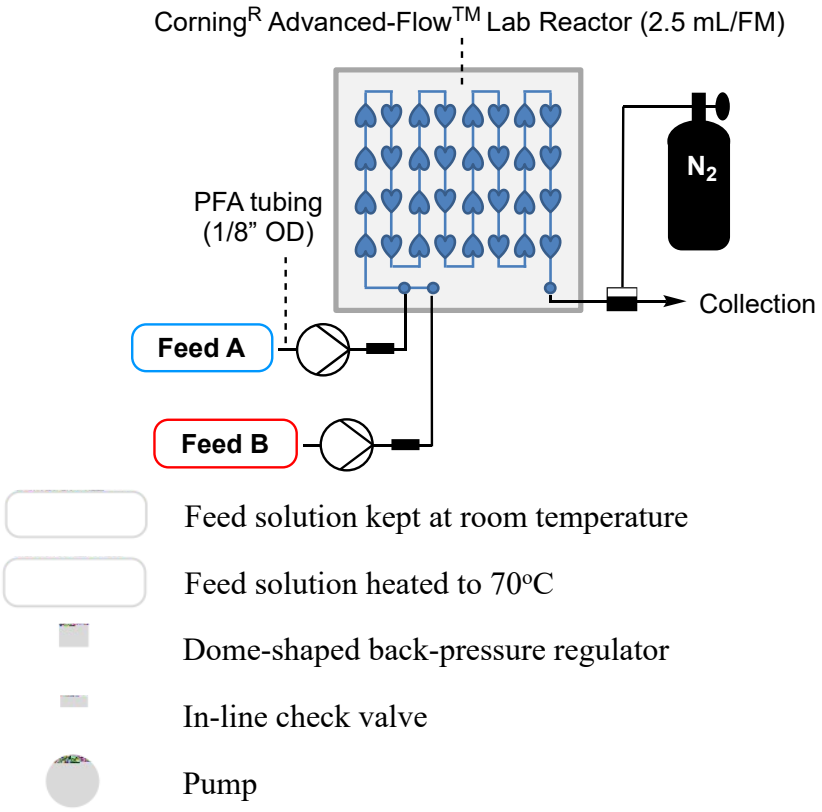


Figure S5. Detailed setup for the continuous flow preparation of Sodium carbamoylmethyl sulfate (**SCS**).

1.4.6. Mesofluidic preparation of 2-(benzhydrylthio)acetamide (6) (lab scale)

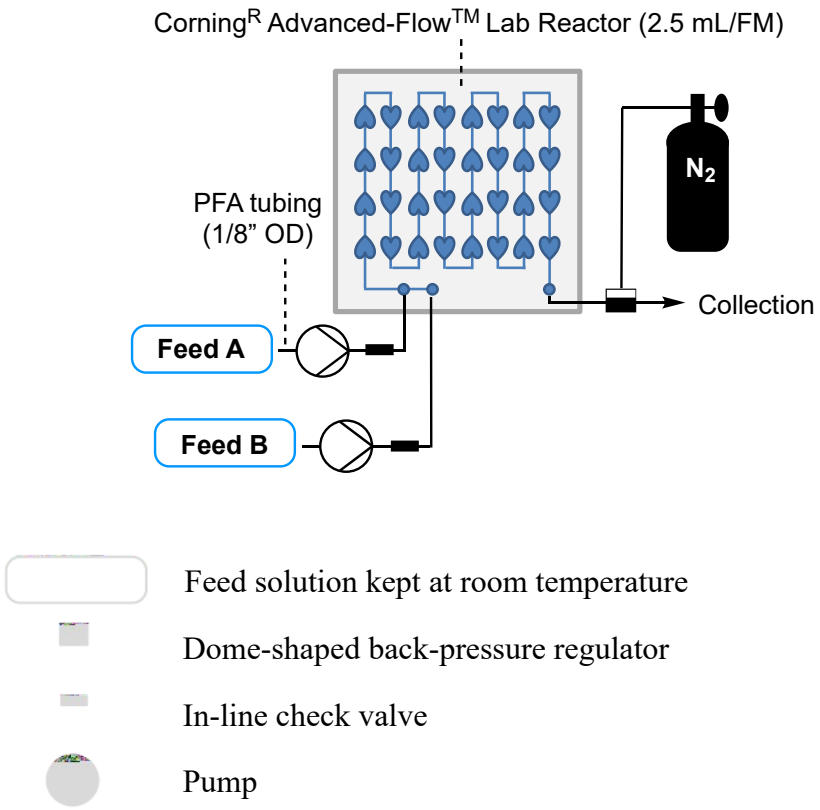


Figure S6. Detailed setup for the continuous flow preparation of 2-(benzhydrylthio)acetamide (**6**).

1.4.7. Mesofluidic preparation of modafinil (**1**) (lab scale)

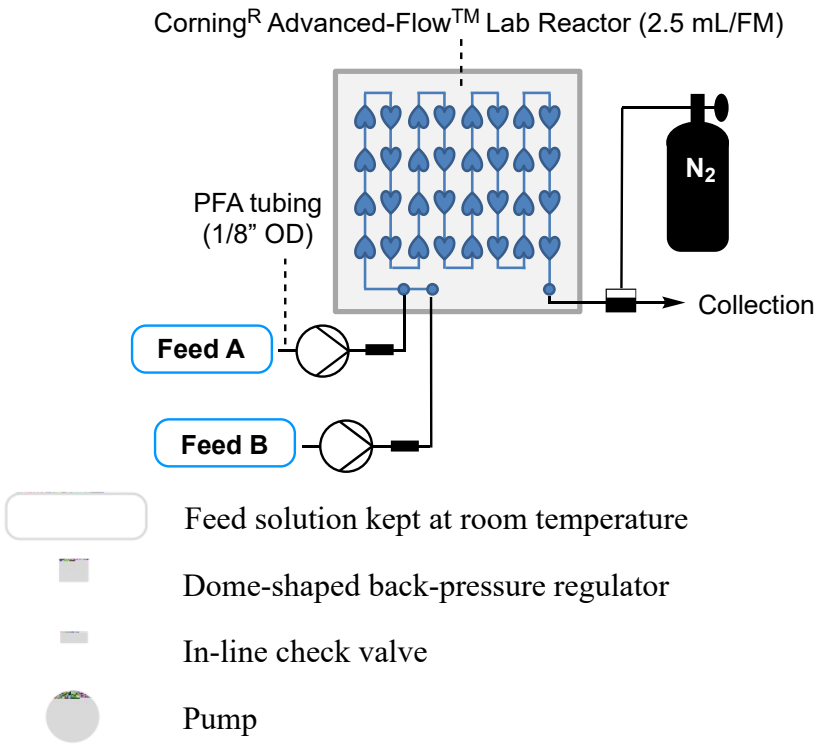


Figure S7. Detailed setup for the continuous flow preparation of Modafinil.

1.4.8. Concatenated mesofluidic preparation of 2-(benzhydrylthio)acetamide (**6**) (lab scale)

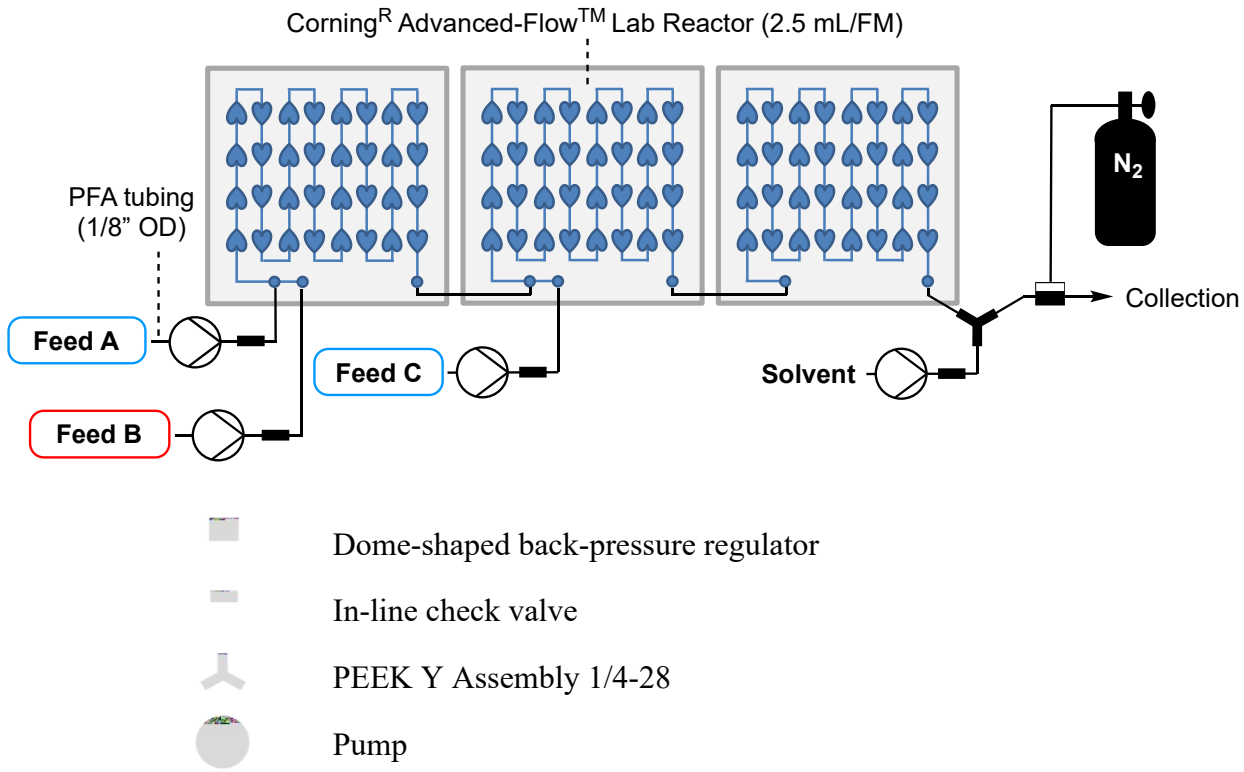


Figure S8. Detailed setup for the concatenated mesofluidic preparation of 2-(benzhydrylthio)acetamide (**6**) (lab scale).

2. Additional details on methods

2.1. Details on commercially purchased chemicals

Solvents	Purity (%)	CAS Number	Supplier
Methylethylketone (FDA class 3)	≥99.0%	78-93-3	J.T. Baker
tert-Butyl methyl ether (FDA class 3)	≥95%	1634-04-4	Acros Organic
Formic acid (FDA class 3)	98-100%	64-18-6	Merck
DI water			
Chemicals	Purity (%)	CAS Number	Supplier
Sodium thiosulfate	99%	7772-98-7	VWR Chemicals
2-chloroacetamide	98%	79-07-2	Janssen Chimica
Benzhydrol	>99.0%	91-01-0	TCI
2-[(diphenylmethyl)thioacetamide	N/A	68524-30-1	abcr
Hydrogen Peroxide	Meets USP testing specifications	7722-84-1	Sigma-Aldrich
Sodium tungstate	≥99%	10213-10-2	Sigma-Aldrich
Phenylphosphonic acid	>98.0%	1571-33-1	TCI
Sodium sulfite	N/A	7757-83-7	Federa

2.2. Addition instrumental details

HPLC method:

Eluent: A: Water + 0.1% CF_3COOH (v:v)
B: Acetonitrile

Gradient Table:

Time [min]	A [%]	B [%]
0	100	0
20	20	80
23	20	80
25	100	0
31	100	0

Flow: 1 mL min^{-1}
Injection Volume: 10 µL
Column: C18, 100 × 4.6 mm, 3 µm
Oven Temperature: 40 °C
Diode Array Detector: 180-800 nm

3. Details on flow synthesis procedures and results

3.1. Continuous flow procedure to produce sodium carbamoylmethyl sulfate (SCS).

For a typical experiment, 2-chloroacetamide (3.50 g, 0.0375 mols) was transferred to a 25 mL volumetric flask and volume was completed using deionized water. The solution was placed in a 60 ºC water bath for a few minutes to fully dissolve the compound. Sodium thiosulfate (11.86 g, 0.075 mols) was transferred to a 50 mL volumetric flask and volume was completed with deionized water.

Two Chemyx 6000 Fusion syringe pumps were used to deliver the feeds. A 20 mL SS syringe with an attached Chemyx Heating sleeve was preheated to 50 ºC and the 2-chloroacetamide solution was added without allowing the solution to cool. Immediately after the syringe was loaded, the temperature on the heating sleeve was set to 70ºC and the reaction was started promptly to avoid the compound from precipitating in the syringe tubing. Furthermore, the syringe was placed as close as possible to the oil bath to avoid precipitation of the compound. The flow rate for the pumps was set at 0.5 mL min^{-1}. Both streams were joined through a PEEK T-mixer and the resulting mixture was flowed through a PFA capillary coil (ID 0,03, 2.19 m length) with an 1 mL internal volume, 1 min residence time. Reaction temperature was set at 120 °C using an oil bath. A dome-shaped back pressure regulator (Zaiput) was used to maintain the pressure at 7 bar.

The output solution was collected and analyzed by 43 MHz ^{1}H NMR (>99% conv.). Samples were prepared by taking ~150 µL of the aqueous output solution and adding 500 µL of deuterium oxide. The concentration of the output solution was verified by taking a 100 µL aliquot, evaporating the solvent at 90 ºC overnight and weighing the solid. The mass obtained for all samples was always between 99-101% of the expected mass.

3.1.1. Representative ^{1}H-NMR (43 MHz) spectra used to monitor the production of SCS.

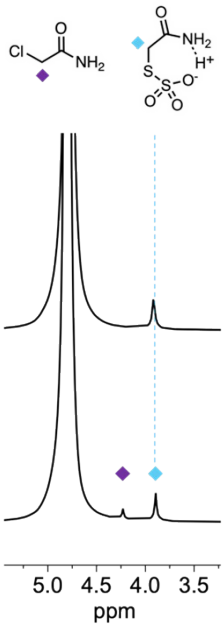


Figure S9. Representative ^{1}H-NMR (43 MHz) in D_2O/H_2O of (bottom) a spectrum showing incomplete conversion, and (top) a spectrum obtained after complete reaction to form **SCS**. The protons monitored are highlighted in purple for 2-chloroacetamide (starting material) and blue for **SCS** (product).

3.2. Initial experiments for continuous flow synthesis of 2-(benzhydrylthio)acetamide (6).

Our initial experiments used a 0.7 M solution of benzhydrol in formic acid, and a 0.75 M solution of **SCS** obtained through continuous flow synthesis as described in section 3.1. These solutions were delivered using two Chemyx 6000 Fusion syringe pumps at a flow rate of 0.400 mL min^{-1}. Feeds were joined through a T-mixer and flowed through a PFA coil with internal volume 1 mL (ID 0,03, 2.19 m length). This coil was placed in an oil bath at 137 °C. A 40 psi cartridge BPR was placed at the end to keep the system. The output solution was analyzed by HPLC-DAD.

3.2.1. Results obtained from initial experiments for the continuous flow synthesis of 2-(benzhydrylthio)acetamide (6).

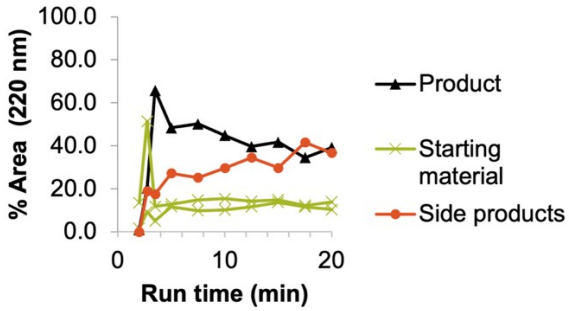


Figure S10. Percent area for the product (**6**), starting material (**2** & **10**) and side products as determined by HPLC (detection 220 nm). Samples were taken from the reactor effluent at intervals while the reactor was running.

Table S2. Relative conversion and selectivity obtained over time (corresponds to the experiment shown in **Figure S10**).

Run time (min)	Conversion (%)	Selectivity (%)
2	6	100
2.75	39	52
3.5	**83**	**79**
5.	76	64
7.5	75	67
10	75	60
12.5	74	53
15	71	58
17.5	76	45
20	**76**	**52**

3.3. Continuous flow procedure to produce 2-(benzhydrylthio)acetamide (6).

For a typical experiment, benzhydrol (2.76 g, 0.015 mols) was transferred to a 25 mL volumetric flask and volume was completed using formic acid. This solution was placed in a 40 °C water bath and left for ~30 min until all compound was dissolved. Analysis of this solution by HPLC-DAD and ^{1}H-NMR showed that the compound undergoes esterification to form the formate ester under these conditions (see characterization in section 4.5 and **Figure S21**). After full dissolution of the

compound, the solution can be removed from the heated water bath without re-precipitation of the compound.
A second 20 mL SS syringe was loaded with the **SCS** solution produced in the previous step.
Two Chemyx 6000 Fusion syringe pumps were used to deliver the feeds at a flow rate of 0.125 ml min^{-1}. Both streams were mixed through a High Pressure mixing Tee (arrow mixer) and the resulting mixture was flowed through a PFA capillary coil (ID 0,02, 4.93 m length) with an 1 mL internal volume, 4 min residence time. Reaction temperature was set at 115 °C using an oil bath. The output solution was analyzed by HPLC-DAD. A dome-shaped back pressure regulator (Zaiput) was used to maintain the pressure at 7 bar.
When the output solution was intended for use in the next step (oxidation to the sulfoxide) a ThalesNano HPLC pump was connected to add methylethylketone (MEK) in the stream before leaving the oil bath. MEK was added at a flow rate of 0.08 mL min^{-1}.

3.3.1. Representative results obtained for the synthesis of 2-(benzhydrylthio)acetamide (6) under optimized conditions

Flow reactor was run for over 30 min. Samples were analyzed at approximately 5-minute intervals after equilibration. The average and standard deviation of these samples were used to report the following:

Conversion: (98.4 ± 0.2)%
Selectivity: (88.7 ± 0.4)%

Table S3. Percent area of all the peaks in the HPLC chromatogram (detection at 220 nm) for samples analyzed during the continuous flow synthesis of 2-(benzhydrylthio)acetamide (**6**) under optimized conditions.

Compound	**%Area** (average ± standard deviation)
2-(benzhydrylthio)acetamide ***(6)***	88.6 ± 0.3
Benzhydrol ***(2)***	1.4 ± 0.3
M. Acid sulfide ***(4)***	7.98 ± 0.04
Bzh-FA ***(10)***	0.3 ± 0.1
Bzh ether ***(12)***	0.4 ± 0.1
Unidentified compounds	1.5 ± 0.2

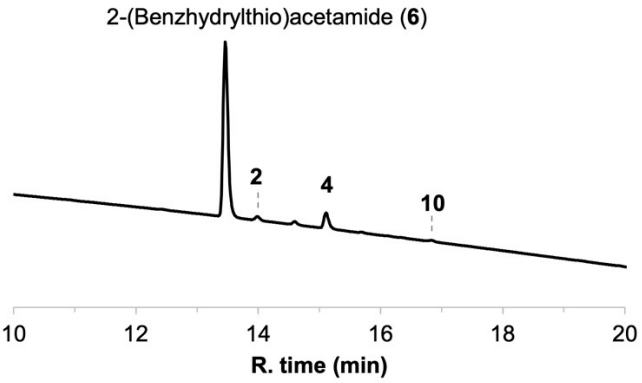


Figure S11. Representative HPLC chromatogram (detection at 220 nm) obtained from the continuous flow synthesis of 2-(benzhydrylthio)acetamide (**6**) under optimized conditions. Sample taken after 30 minutes of run time.

3.4. Continuous flow procedure to produce modafinil from the output solution of step 2

For a typical experiment, the output solution of step 2 containing 2-(benzhydrylthio)acetamide (**6**) in approximately 0.23 M was loaded into a 20 mL SS syringe and used as feed solution. The concentration of the solution was calculated based on the starting materials assuming total conversion. Although this is certainly not the case, it was done this way to keep consistency between batches and in views of future concatenation of the entire synthesis.

The second feed consisted of a 15% hydrogen peroxide solution containing sodium tungstate (4 mol%) and phenylphosphonic acid (4.5 mol%). Preparation of the solution was done as follows: hydrogen peroxide (30%) was diluted to half the concentration using deionized water. Sodium tungstate (415.5 mg, 1.26 mmol) and phenylphosphonic acid (221.8 mg, 1.40 mmol) were added to a 10 mL volumetric flask and the volume was completed using the 15% hydrogen peroxide solution. This solution was prepared fresh before each use.

Both feeds were delivered using a Chemyx Fusion 6000 syringe pump. The flow rates were set to 0.330 mL min^{-1} for the feed containing 2-(benzhydrylthio)acetamide (**6**) feed and 0.0241 mL min^{-1} for the feed containing hydrogen peroxide. Both streams were mixed through a High Pressure mixing Tee (arrow mixer) and the resulting mixture was flowed through a PFA capillary coil (ID 0,02, 2.47 m length) with an 0.5 mL internal volume, 1.4 min residence time. Reaction temperature was set at 20 °C using a water bath. A dome-shaped back pressure regulator (Zaiput) was used to maintain the pressure at 7 bar. The output solution was immediately quenched by collecting in a vial placed in an ice bath containing at least 100 mg of sodium sulfite per each 100 mL of output solution and under stirring. The output solution was analyzed by HPLC-DAD.

3.4.1. Results obtained for the continuous flow synthesis to produce modafinil from the output solution of step 2, using 2 equivalents of hydrogen peroxide

Flow reactor was run for over 20 min. Three samples were analyzed at different time intervals after equilibration. The average and standard deviation of these samples were used to report the following:

Conversion: (98 ± 1)%

Selectivity: (82 ± 3)%

Table S4. Precent area of all peaks in the HPLC chromatogram (detection at 220 nm) of for samples analyzed during continuous flow synthesis of modafinil (**1**) from the output solution of step 2, using 2 equivalents of hydrogen peroxide

Compound	**%Area** (average ± standard deviation)
*Modafinil (**1**)*	80.9 ± 2.8
*M.Acid sulfoxide (**7**)*	7.2 ± 0.3
*M.Sulfone (**11**)*	1.6 ± 0.6
*M.Acid sulfone (**13**)*	0.2 ± 0.1
*M.Sulfide (**6**)*	2.5 ± 1.7
*Benzhydrol (**2**)*	3.9 ± 0.1
*M.Acid sulfide (**4**)*	0.2 ± 0.1
*Bzh-FA (**10**)*	1.2 ± 0
*Bzh ether (**12**)*	0.6 ± 0.1
Unidentified compounds	3.3 ± 1.2

3.4.2. Results obtained for the continuous flow synthesis to produce modafinil from the output solution of step 2, using optimized conditions

Five samples were analyzed at different time intervals after equilibration. The average and standard deviation of these samples were used to report the following:

Conversion: (99 ± 1)%

Selectivity: (77 ± 3)%

Table S5. Percent area of all peak in the HPLC chromatogram (detection at 220 nm) for the samples analyzed during the continuous flow synthesis of modafinil (**1**) from the output solution of step 2, using optimized conditions

Compound	**%Area** (average ± standard deviation)
*Modafinil (**1**)*	76.2 ± 2.8
*M.Acid sulfoxide (**7**)*	11.1 ± 1.3
*M.Sulfone (**11**)*	0.5 ± 0.5
*M.Acid sulfone (**13**)*	1.1 ± 0.2
*M.Sulfide (**6**)*	0.9 ± 0.3
*Benzhydrol (**2**)*	4.9 ± 0.6
*M.Acid sulfide (**4**)*	0.1 ± 0

*Bzh-FA (**10**)*	1.7 ± 0.2
*Bzh ether (**12**)*	0.9 ± 0.1
Unidentified compounds	2.9 ± 0.8

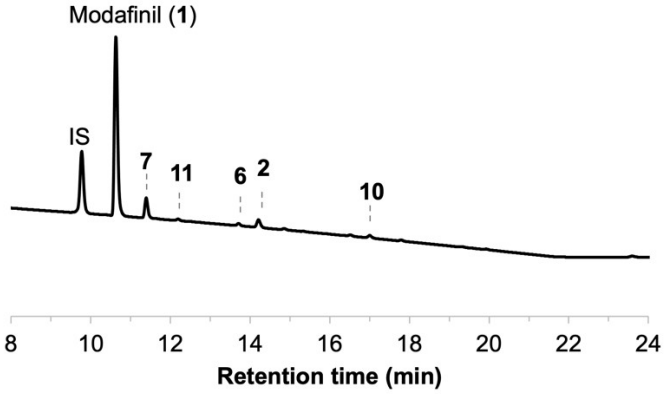


Figure S12. Representative HPLC chromatogram (detection at 220 nm) obtained during the synthesis of modafinil (**1**) from the output solution of step 2, under optimized conditions. **IS** stands for internal standard.

3.5. Continuous flow procedure to produce modafinil from commercially available 2-(benzhydrylthio)acetamide (6)

For a typical experiment, 2-(benzhydrylthio)acetamide (**6**) (450.4 mg, 1.75 mols) was added to a 10 mL volumetric flask and volume was completed using a mixture of water, formic acid and methylethylketone (37.9%, 37.9% and 24.2% respectively). This solvent mixture was used to mimic the solvent composition obtained after step 2 (section 3.3).

The second feed consisted in a hydrogen peroxide solution containing sodium tungstate (4.5 mol%) and phenylphosphonic acid (5 mol%). Preparation of the solution was done as follows: hydrogen peroxide (30%) was diluted to half the concentration using deionized water. Sodium tungstate (207.6 mg, 0.63 mmol) and phenylphosphonic acid (110.6 mg, 0.70 mmol) were added to a 5 mL volumetric flask and the volume was completed using the 15% hydrogen peroxide solution.

Both feeds were delivered using a Chemyx Fusion 6000 syringe pump. The flow rates were set to 0.315 mL min^{-1} for the feed containing 2-(benzhydrylthio)acetamide (**6**) feed and 0.0197 mL min^{-1} for the feed containing hydrogen peroxide. Both streams were mixed through a High Pressure mixing Tee (arrow mixer) and the resulting mixture was flowed through a PFA capillary coil (ID 0,02, 2.47 m length) with an 0.5 mL internal volume, 1.5 min residence time. Reaction temperature was set at 20 °C using a water bath. A dome-shaped back pressure regulator (Zaiput) was used to maintain the pressure at 7 bar. The output solution was immediately quenched by collecting in a vial placed in an ice bath containing at least 100 mg of sodium sulfite per each 100 mL of output solution and under stirring. The output solution was analyzed by HPLC-DAD.

3.5.1. Results obtained for the continuous flow synthesis to produce modafinil commercially available 2-(benzhydrylthio)acetamide (6)

The reactor was run for more than 15 min. Five samples were analyzed at different time intervals after equilibration. The average and standard deviation of these samples were used to report the following:

Conversion: (99.9 ± 0.3)%

Selectivity: (99.4 ± 0.4)%

Table S6. Percent area of all peaks in the HPLC chromatogram (detection at 220 nm) for samples analyzed during the continuous flow synthesis of modafinil (**1**) from the output solution of step 2, using optimized conditions

Compound	**%Area** (average ± standard deviation)
*Modafinil (**1**)*	99.4 ± 0.4
*M.Acid sulfoxide (**7**)*	0.2 ± 0.1
*M.Sulfone (**11**)*	0.2 ± 0.3
*M.Acid sulfone (**13**)*	0
*M.Sulfide (**6**)*	0.2 ± 0.3
*Benzhydrol (**2**)*	0
*M.Acid sulfide (**4**)*	0
*Bzh-FA (**10**)*	0
*Bzh ether (**12**)*	0
Unidentified compounds	0

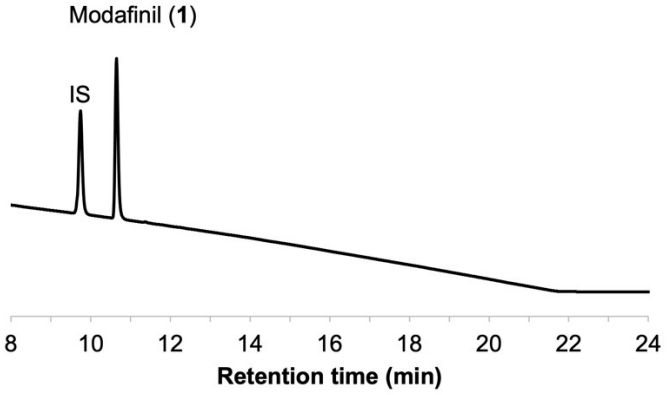


Figure S13. Representative HPLC chromatogram (detection at 220 nm) obtained during the continuous flow synthesis of modafinil (**1**) from commercial 2-(benzhydrylthio)acetamide (**6**). **IS** stands for internal standard.

3.6. Concatenated continuous flow procedure to produce modafinil (**1**)

Feed solutions of 2-chloroacetamide (1.51 M) and sodium thiosulfate (1.5 M) were injected at a flow rate of 0.0625 mL min^{-1} using two Chemyx 6000 Fusion syringe pumps equipped with 20 mL SS syringes. A Chemyx heating sleeve was attached to the syringe containing the 2-chloroacetamide solution (the loading procedure was analogous to the one described in section 3.1). Both streams were mixed through a PEEK T-mixer and the resulting mixture was flowed through a PFA capillary coil (ID 0,03, 0.55 m length) with an 0.25 mL internal volume (2 min residence time).

The output was directly connected to a High Pressure mixing Tee (arrow mixer), where it was mixed with a solution of benzhydrol in formic acid (0.6 M, solution prepared in as described in section 3.3). This solution was delivered at a flow rate of 1.25 mL min^{-1} using a Chemyx 6000 Fusion syringe pumps equipped with a 20 mL SS syringe. The resulting mixture was flowed through a PFA capillary coil (ID 0,02, 4.93 m length) with a 1 mL internal volume (4 min residence time). The coils for both steps one and two were placed in an oil bath at 115 °C.

The output solution was then connected to a Y-mixer, where it was mixed with a flow of methyl ethyl ketone (MEK). This solvent was delivered at a flow rate of 0.08 mL min^{-1} using a ThalesNano HPLC pump. This Y-mixer was also kept at 115 °C using the same oil bath as for steps 1 and 2. The output of this Y-mixer was connected to a PFA coil (0.88 m, 0.4 mL) that was placed in a water bath at 20 °C. This coil was used to allow the reaction to cool, before being connected to a High-Pressure mixing Tee (arrow mixer), where it was mixed with a solution of hydrogen peroxide solution containing sodium tungstate (4 mol%) and phenylphosphonic acid (4.5 mol%). Preparation of the solution was done performed as described in section 3.4.

This solution was delivered at a flow rate of 0.0241 mL min^{-1} using a Chemyx Fusion 6000 syringe pump equipped with a 6 mL SS syringe. The resulting mixture was flowed through a PFA capillary coil (ID 0,02, 2.47 m length) with an 0.5 mL internal volume (1.4 min residence time).

A dome-shaped back pressure regulator (Zaiput) was used at the end of the concatenated PFA reaction coils to maintain the pressure at 7 bar. The output solution was immediately quenched by collecting in a vial placed in an ice bath containing at least 100 mg of sodium sulfite per each 100 mL of output solution and under stirring. The output solution was analyzed by HPLC-DAD.

3.6.1. Results obtained for the concatenated continuous flow synthesis to produce modafinil (**1**).

Reactor was run for over 90 min. Three samples were analyzed at different time intervals after equilibration. The average and standard deviation of these samples were used to report the following:

Conversion: (92 ± 1)%

Selectivity: (81 ± 2)%

Table S7. Percent area of all peaks in the HPLC chromatogram (detection at 220 nm) for the samples analyzed during the concatenated continuous flow production of modafinil (**1**).

Compound	**%Area** (average ± standard deviation)
*Modafinil (**1**)*	80.7 ± 2.1
*M.Acid sulfoxide (**7**)*	7.5 ± 0.3

*M.Sulfone (**11**)*	0.66 ± 0.03
*M.Acid sulfone (**13**)*	0
*M.Sulfide (**6**)*	0.9 ± 0.7
*Benzhydrol (**2**)*	5.1 ± 0.9
*M.Acid sulfide (**4**)*	0.2 ± 0.1
*Bzh-FA (**10**)*	1.8 ± 0.4
*Bzh ether (**12**)*	0.4 ± 0.3
Unidentified compounds	2.7 ± 0.5

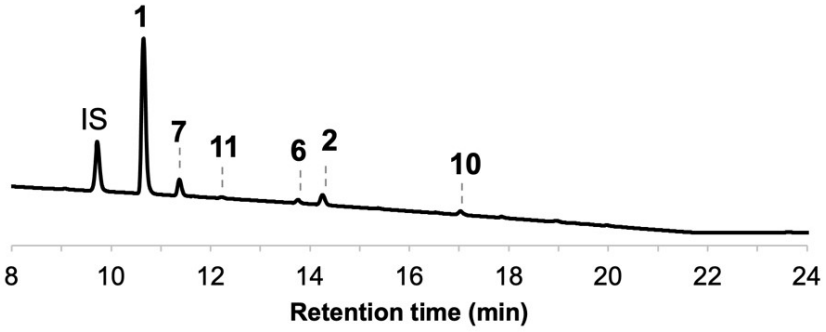


Figure S14. Representative HPLC chromatogram (detection at 220 nm) for the fully concatenated synthesis of modafinil (**1**). **IS** stands for internal standard.

3.7. Continuous flow procedure to produce sodium carbamoylmethyl sulfate (SCS); mesofluidic scale.

Feed solutions for 2-chloroacetamide (3.50 g, 0.0375 mols) and sodium thiosulfate were prepared and loaded as described in section 3.1.

Two Chemyx 6000 Fusion syringe pumps were used to deliver the feeds. The flow rate for the pumps was set at 1.25 mL min^{-1}. Both streams were connected to a Corning® Advanced Lab Reactor with a single glass module (2.5 mL internal volume), obtaining a 1 min residence time. Reaction temperature was set at 120 °C a Huber Ministat 230 thermostat. A dome-shaped back pressure regulator (Zaiput) was used to maintain the pressure at 7 bar.

The output solution was collected and analyzed by 43 MHz ^{1}H NMR (>99% conv.).

3.8. Continuous flow procedure to produce 2-(benzhydrylthio)acetamide (6); mesofluidic scale.

Feed solution for benzhydrol was prepared as described in section 3.3. The feed solution for **SCS** was taken from the output solution of the scale-up synthesis of **SCS** as described in section 3.7.

Two Chemyx 6000 Fusion syringe pumps were used to deliver the feeds at a flow rate of 1.25 ml min^{-1}. Both streams were connected to a Corning® Advanced Lab Reactor with a single glass module (2.5 mL internal volume), obtaining a 1 min residence time. Reaction temperature was set to 130 °C, 140 °C or 150 °C using a Huber Ministat 230 thermostat. A dome-shaped back pressure

regulator (Zaiput) was used to maintain the pressure at 7 bar. The output solution was analyzed by HPLC-DAD.

3.8.1. Results for the re-optimization of the production 2-(benzhydrylthio)acetamide (6) using a Corning AFR reactor; mesofluidic scale.

Table S8. Relative conversion and selectivity for the mesoscale continuous flow of 2-(benzhydrylthio)acetamide (**6**) at different temperatures as determined by HPLC-DAD (220 nm)

	130 °C	**140** °C	**150** °C
Conversion	78.1%	90.7%	97.3%
Selectivity	85.8%	87.9%	88.3%

Table S9. Percent area of all peaks in the HPLC chromatogram (detection at 220 nm) for the mesoscale continuous flow synthesis of 2-(benzhydrylthio)acetamide (**6**) at different temperature

	%Area		
Compound	**130 °C**	**140 °C**	**150 °C**
*M.Sulfide (**6**)*	67.0	79.8	85.9
*Benzhydrol (**2**)*	15.9	7.0	2.1
*M.Acid sulfide (**4**)*	3.8	6.2	7.8
*Bzh-FA (**10**)*	6.1	2.3	0.6
*Bzh ether (**12**)*	5.2	2.2	1.5
Unidentified compounds	2.1	2.6	2.2

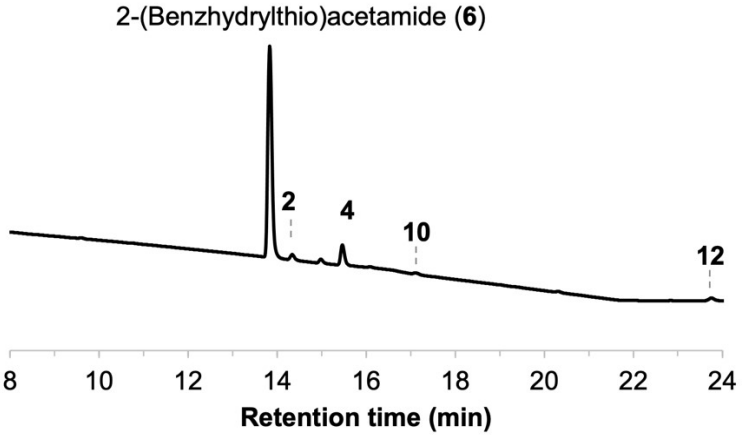


Figure S15. Representative HPLC chromatogram (detection at 220 nm) for the mesoscale continuous flow synthesis 2-(benzhydrylthio)acetamide (**6**). Reaction temperature of 150 °C.

3.9. Continuous flow procedure to produce modafinil (1) from commercially available 2-(benzhydrylthio)acetamide (6); mesofluidic scale.

Feed solution for 2-(benzhydrylthio)acetamide (**6**) and hydrogen peroxide (containing sodium tungstate and phenylphosphonic acid) were prepared as described in section 3.5.

Both feeds were delivered using a Chemyx Fusion 6000 syringe pump. The flow rates were set to 0.330 mL min^{-1} for the feed containing 2-(benzhydrylthio)acetamide (**6**) and 0.1066 mL min^{-1} for the feed containing hydrogen peroxide. Both feeds were connected to a Corning® Advanced Lab Reactor with a single glass module (2.5 mL internal volume), obtaining a 1.25 min residence time. Reaction temperature was set at 20 °C using a Huber Ministat 230 thermostat. A dome-shaped back pressure regulator (Zaiput) was used to maintain the pressure at 7 bar.

The output solution was immediately quenched by collecting in a vial placed in an ice bath containing at least 100 mg of sodium sulfite per each 100 mL of output solution and under stirring. The output solution was analyzed by HPLC-DAD.

3.9.1. Results for the production of modafinil (1) from commercially available 2-(benzhydrylthio)acetamide (6); mesofluidic scale

Conversion: 98.4%
Selectivity: 99.3%

Table S10. Percent area of all peaks in the HPLC chromatogram (detection at 220 nm) for the mesoscale continuous flow synthesis of modafinil (**1**) using a Corning AFR reactor.

Compound	%Area
*Modafinil (**1**)*	97.8
*M.Acid sulfoxide (**7**)*	0.1
*M.Sulfone (**11**)*	0.6
*M.Acid sulfone (**13**)*	0
*M.Sulfide (**6**)*	1.6
*Benzhydrol (**2**)*	0
*M.Acid sulfide (**4**)*	0
*Bzh-FA (**10**)*	0
*Bzh ether (**12**)*	0
Others	0

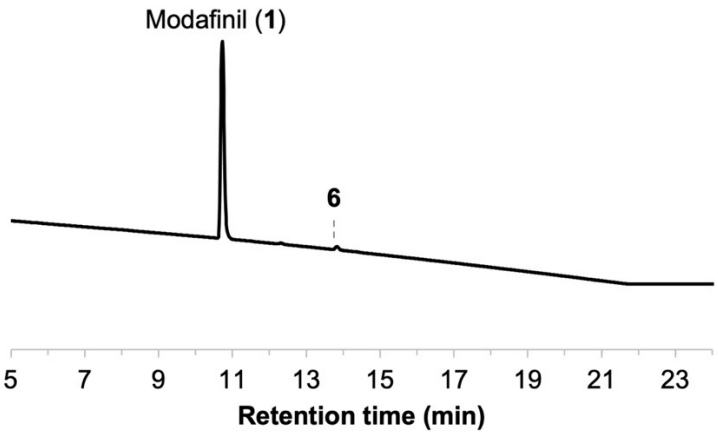


Figure S16. Representative HPLC chromatogram (detection at 220 nm) for the mesoscale continuous flow synthesis of modafinil (**1**) using a Corning Lab Reactor.

3.10. Concatenated continuous flow procedure to produce modafinil (**1**); mesofluidic scale.

Feed solutions of 2-chloroacetamide (1.51 M) and sodium thiosulfate (1.5 M) were injected at a flow rate of 1.25 mL min^{-1} using two Chemyx 6000 Fusion syringe pumps equipped with 20 mL SS syringes. A Chemyx heating sleeve was attached to the syringe containing the 2-chloroacetamide solution (the loading procedure was similar to the one described in section 3.1). Both streams were connected to a Corning® Advanced-Flow™ Lab Reactor (2.5 mL internal volume glass fluidic modules), for a residence time of 1 min. The output was directly coupled to subsequent Lab Reactor glass module, where it was mixed with a solution of benzhydrol in formic acid (0.6 M, solution prepared in as described in section 3.3). This solution was delivered at a flow rate of 2.5 mL min^{-1} using a Syrris Asia pump. The resulting mixture was flowed through two fluidic modules connected in series, 5 mL total internal volume (1 min residence time). Temperature for all three modules was maintained at 115 °C using a LAUDA Integral XT 280 thermostat.

The output solution of these reactors was connected to a Y-mixer where it was mixed with methyl ethyl ketone. This solvent (MEK) was injected at a flow rate of 1.6 mL min^{-1} using a ThalesNano HPLC pump. A dome-shaped back pressure regulator (Zaiput) was used at the end of the concatenated glass modules to maintain the pressure at 7 bar.

The output solution was collected, loaded into a 20 mL SS syringe and injected into a separate Lab Reactor glass module using a Chemyx Fusion 6000 syringe pump (flow rate 1.86 mL min^{-1}). Another Chemyx Fusion 6000 syringe pump equipped with a 6 mL SS syringe was used to inject a solution of hydrogen peroxide containing sodium tungstate (4 mol%) and phenylphosphonic acid (4.5 mol%). Preparation of the solution was done performed as described in section 3.4. This solution was delivered at a flow rate of 0.1356 mL min^{-1} and reacted through a single Lab reactor glass module (2.5 mL) to obtain a residence time of 1.4 min.

A dome-shaped back pressure regulator (Zaiput) was used to maintain the pressure at 7 bar. The output solution was immediately quenched by collecting in a vial placed in an ice bath containing at least 100 mg of sodium sulfite per each 100 mL of output solution and under stirring. The output solution was analyzed by HPLC-DAD.

3.10.1. Results for the mesoscale concatenated continuous flow synthesis of modafinil (**1**) using a Corning AFR reactor

Steps 1 & 2:

Conversion: (96.5 ± 0.9)%

Selectivity: (87 ± 3)%

Table S11. Percent area of all peaks in the HPLC chromatogram (detection at 220 nm) for the mesoscale concatenated synthesis of 2-(benzhydrylthio)acetamide (**6**) using a Corning AFR reactor.

Compound	**%Area** (average ± standard deviation)
*M.Sulfide (**6**)*	84.2 ± 0.5
*Benzhydrol (**2**)*	2.6 ± 0.3
*M.Acid sulfide (**4**)*	8.2 ± 0.2
*Bzh-FA (**10**)*	1.1 ± 0.1
*Bzh ether (**12**)*	1 ± 0.3
Unidentified compounds	4 ± 0.4

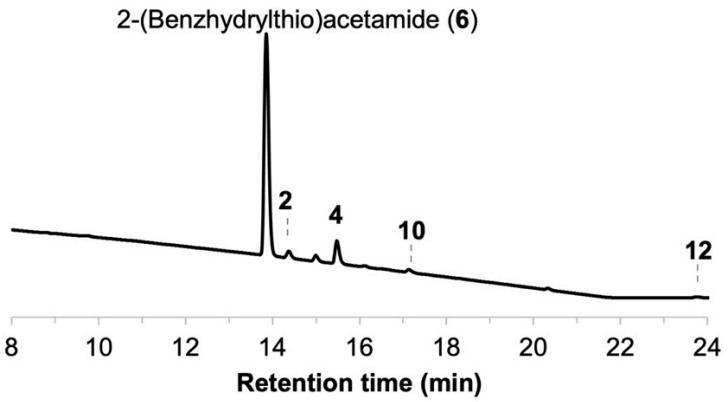


Figure S17. Representative HPLC chromatogram (detection at 220 nm) for the concatenated synthesis 2-(benzhydrylthio)acetamide (**6**) using Corning Lab Reactor. Reaction temperature of 150 °C.

Step 3

Conversion: 95.1.6%

Selectivity: 85.7%

Table S12. Percent area of all peaks in the HPLC chromatogram (detection at 220 nm) for the mesoscale concatenated synthesis of modafinil (**1**) using a Corning AFR reactor.

Compound	%Area
*Modafinil (**1**)*	81.5
*M.Acid sulfoxide (**7**)*	8.9
*M.Sulfone (**11**)*	1.1
*M.Acid sulfone (**13**)*	0.0
*M.Sulfide (**6**)*	0.6
*Benzhydrol (**2**)*	3.1
*M.Acid sulfide (**4**)*	0.1
*Bzh-FA (**10**)*	1.2
*Bzh ether (**12**)*	0.4
Unidentified compounds	3.5

3.10.2. On the isolation and purification of modafinil from the output solution

The effluent of the telescoped reactions is alkalinized using a saturated aqueous solution of sodium carbonate (Na_2CO_3). This is done by adding 2.5 times the volume of the effluent collected. A large amount of gas evolves, so care must be taken to add the solution slowly and/or in a large recipient to avoid spilling. Using more diluted solutions of sodium carbonate or solutions of sodium bicarbonate resulted in lower recovery.
After addition of sodium carbonate solution, a solid is formed that can be decanted. The solid is resuspended in fresh sodium carbonate solution, briefly sonicated (~20 min) and again decanted. This step may be repeated a third time if necessary so that all of 2-[(Diphenylmethyl)sulfinyl]acetic acid (**7**) has been eliminated (i.e. HPLC shows less than 0.5% of **7** at 220 nm detection).
The solid is then dried, resuspended in MTBE, and briefly sonicated (~20 min). The solid is decanted and this process is repeated a second time. This affords modafinil in 99% purity (HPLC detection at 220 nm). If 2-(benzhydrylthio)acetamide (**6**) is still present, an extra cycle of MTBE wash can be performed.

3.10.3. On the initiation and termination of the concatenated reactor

Initiation of the concatenated reactor
Note: before beginning, it is important to make sure to have check valves installed between each pump and the reactor to be able to change the feed solutions with the reaction pressure and temperature already set.
The concatenated reactor is first run with water, to verify for leakage and to bring the system to the adequate pressure (7 bar).
The feeds are then changed to the corresponding reagents and the feed solutions corresponding to step 1 (sodium thiosulfate and 2-chloroacetamide) are initialized. The reactor is left to equilibrate

for about 2x residence time of step 1 (i.e., typically 2 min, if the residence time of the first step is 1 min).
Afterwards, the feed with benzhydrol/formic acid and the MEK solvent are initialized. The system should be left running for about 1.5x the residence time of the second reaction (i.e., 6 min) and then the hydrogen peroxide feed can be initialized. The reaction is then left to equilibrate at least 3 more minutes before collection.

Termination of the concatenated reactor
Note: it is important to install check valves between each pump and the reactor to be able to change the feed solutions before reducing the pressure and temperature.
The first feeds to be stopped are those for benzhydrol in formic acid and hydrogen peroxide.
The benzhydrol/formic acid feed is then washed with a mixture of water: acetone (2:1) for 1x residence times (4 min). The feed with hydrogen peroxide is washed with water for about 1x residence times (i.e., 1 min). This can be run concomitantly with the water: acetone wash.
The MEK feed can be stopped and, if necessary, solvent can be changed to isopropanol.
Finally, the 2-chloroacetamide and the sodium thiosulfate feeds are washed with water.
Once all the system has been flushed the temperature can be brought back to ambient. Once the temperature is below 80 °C, the pressure can be released.

3.10.4. On the formation of solid sulfur

During some of our initial attempts at performing step 2 (synthesis of 2-(benzhydrylthio)acetamide (**6**), the reactor was severely clogged by the formation of a solid
Thiosulfate is known to react with acids to produce sulfur dioxide and sulfur:
$S_2O_3^{2-} + 2H^+ \longrightarrow SO_2 + H_2O + S$
The color (yellow) of the solid, poor solubility in most solvents, low polarity hinted that the sold being formed was sulfur. The reactor could be unclogged at high temperature (> 120 °C), as would be expected by the melting point of sulfur. Finally, recovery of the solid and analysis under HPLC-DAD revealed an un-polar compound with a UV absorption similar to that of sulfur.[1]

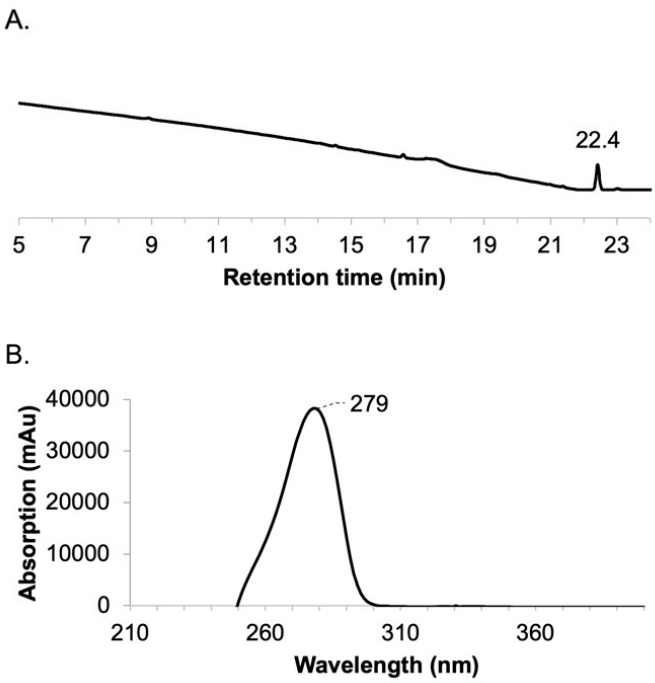


Figure S18. A. HPLC-DAD chromatogram of the solid recovered from a clogged reactor (detection at 220 nm). **B.** UV spectrum corresponding to the peak at 22.4 min.

3.11. Productivity of the concatenated syntheses

Specifications of the reactor	Microfluidic (telescoped)	Mesofluidic (steps 1 & 2)	Mesofluidic (step 3)	
Theor.l output concentration	0.212	0.227	0.212	mmol/mL
Isolated yield	77%	77%	77%	
MW Product	273.350	257.350	273.35	mg/mmol
Output volume/time	0.354	6.600	1.996	mL/min
Reactor volume	2.15	7.5	2.5	mL
Calculated productivity				
Conc. (Molarity x MW x yield)	44.6	45.0	44.6	mg/mL
Productivity (conc. x flow rate)	15.8	297.2	89.0	mg/min
	0.94	17.8	5.3	g/hr
	22.7	428.0	128.1	g/day
STY (productivity / vol reactor)	7.3	39.6	35.6	mg/ (min mL)
	440.5	2377.9	2135.4	g/ (h L)

4. Details for batch syntheses

4.1. Batch procedure for the synthesis of 2-[(Diphenylmethyl)sulfinyl]acetic acid (7)

In a 5 mL round bottom flask, 2-(diphenylmethyl)sulfanylacetic acid (100 g, 0.39 mmol) was dissolved in 2 mL of glacial acetic acid. A 30% hydrogen peroxide solution (42 µL, 1.1 equiv.) was added. Reaction was left stirring overnight. Afterwards, the reaction mixture was washed with brine and extracted three times with DCM. Organic phase was dried over anhydrous $MgSO_4$, filtered and solvent was evaporated under reduced pressure. The product was recovered as a white solid.

4.2. Batch procedure for the synthesis 2-[(Diphenylmethyl)sulfonyl]acetic acid (13)

In a 5 mL round bottom flask, 2-(diphenylmethyl)sulfanylacetic acid (100 g, 0.39 mmol) was dissolved in 2 mL of glacial acetic acid. A 30% hydrogen peroxide solution (112 µL, 3 equiv.) was added. Reaction was placed at 40 °C and left stirring overnight. Afterwards, solvent was evaporated under reduced pressure, and product recovered as a white solid.

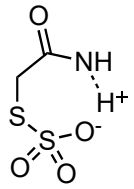
4.3. Batch procedure for the synthesis 2-(Benzhydrylsulfonyl)acetamide (11)

Procedure adapted from reference.[2] In a 5 mL round bottom flask, 2-[(Diphenylmethyl)thio]]acetamide (250 g, 0.97 mmol) was dissolved in 2 mL of glacial acetic acid. A 30% hydrogen peroxide solution (300 µL, 3 equiv.) was added. Reaction was placed at 35 °C and left stirring overnight. Afterwards, 10 mL of water were added, and the reaction was briefly placed on ice. The solid was filtered and washed with cold water. The product was recovered as a white solid.

4.4. Batch procedure for the synthesis Bis(diphenylmethyl) ether (12)

Procedure adapted from reference.[3] Dipheylmethanol (368.5 mg, 2 mmol) was dissolved in 10 mL of dichloroethane. Anhydrous zinc chloride (270 mg, 2 mmol) was added under stirring. Reaction mixture was left at room temperature for 2.5 hours. Afterwards, 20 mL of dichloroethane were added and the mixture was washed with brine. Organic phase was dried over anhydrous $MgSO_4$, filtered and solvent was evaporated under reduced pressure.

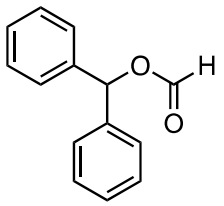
4.5. Characterization of compounds



$C_2H_4NO_4S_2$
MW = 170.18

Sodium carbamoylmethyl sulfate (**SCS**)

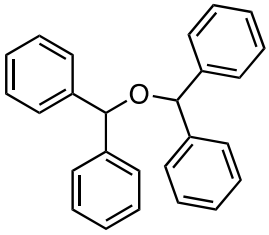
^{1}H NMR (400 MHz, DMSO): δ 7.49 (s, 1H), 7.05 (s, 1H), 3.47 (s, 2H). **^{13}C NMR (101 MHz, DMSO): δ** 171.23, 37.86. **IR** (cm^{-1}). 3456.2, 3316.3, 1693.9, 1666.7, 1571.1, 1377.1, 1248.6, 1198.7



$C_{14}H_{12}O_2$
MW = 212.25

Benzhydryl formate (**10**)

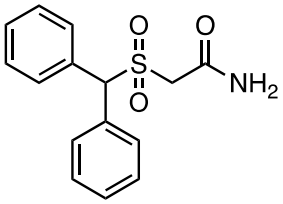
^{1}H NMR (400 MHz, DMSO): δ 8.43 (d, *J* = 1.1 Hz, 1H), 7.48 – 7.33 (m, 8H), 7.33 – 7.26 (m, 2H), 6.92 (s, 1H). **^{13}C NMR (101 MHz, DMSO):** δ 161.23, 140.06, 128.56, 127.91, 126.60, 75.87.



$C_{26}H_{22}O$
MW = 350.46

Bis(diphenylmethyl) ether (**12**)
Modafinil related compound D

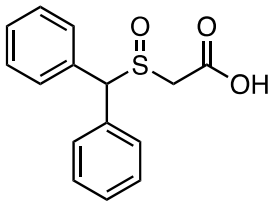
^{1}H NMR (700 MHz, $CDCl_3$): δ 7.36 (d, *J* = 6.8 Hz, 8H), 7.31 (t, *J* = 7.7 Hz, 8H), 7.25 (t, *J* = 7.3 Hz, 4H), 5.39 (s, 2H). **^{13}C NMR (176 MHz, $CDCl_3$):** δ 142.23, 128.40, 127.45, 127.28, 79.99. **IR** (cm^{-1}) 3058.1, 3026.7, 2846.9, 1599.7, 1494.1, 1445.6, 1337.1, 1261.5. **ESI HRMS** *m/z* $C_{26}H_{22}O$ [M+Na]+: calcd 373.1568; found 373.1603



$C_{15}H_{15}NO_3S$
MW = 289.35

2-(Benzhydrylsulfonyl)acetamide (**11**)
Modafinil related compound B

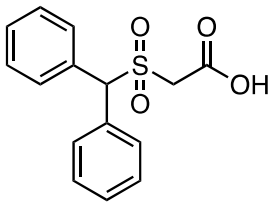
^{1}H NMR (400 MHz, DMSO): δ 7.72 (s, 1H), 7.65 (d, *J* = 6.7 Hz, 4H), 7.49 (s, 1H), 7.46 – 7.34 (m, 6H), 6.10 (s, 1H), 3.76 (s, 2H). **^{13}C NMR (101 MHz, DMSO):** δ 163.26, 133.22, 129.89, 128.82, 128.60, 71.35, 55.85. **IR** (cm^{-1}) 3434.8, 3272.1, 3189.3, 1675.3, 1494.1, 1452.7, 1308.6. **ESI HRMS** *m/z* $C_{15}H_{15}NO_3S$ [M+Na]+: calcd 312.0670; found 312.0656



$C_{15}H_{14}O_3S$
MW = 274.33

2-(benzhydrylsulfinyl)acetic acid (**7**)
Modafinil related compound A

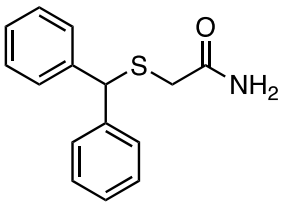
^{1}H NMR (400 MHz, DMSO): δ 7.51 (d, *J* = 6.9 Hz, 4H), 7.45 – 7.31 (m, 6H), 5.40 (s, 1H), 3.55 (d, *J* = 14.3 Hz, 1H). **^{13}C NMR (101 MHz, DMSO):** δ 167.32, 136.64, 134.87, 129.59, 129.10, 128.56, 128.50, 128.10, 128.04, 69.20, 55.43. **IR** (cm^{-1}) 3006.7, 2919.6, 2656.7, 2522.9, 1726.7, 1492.6, 1451.3, 1267.2. **ESI HRMS** *m/z* $C_{15}H_{14}O_3S$ [M+Na]+: calcd 297.0561; found 297.0605.



$C_{15}H_{14}O_4S$
MW = 290.33

2-(benzhydrylsulfonyl)acetic acid (**13**)

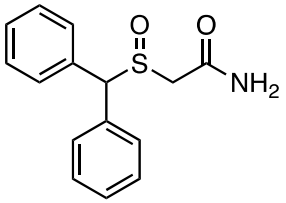
^{1}H NMR (400 MHz, DMSO): δ 9.89 (s, 1H), 7.71 – 7.59 (m, 4H), 7.39 (dd, *J* = 8.3, 6.2 Hz, 4H), 7.44 – 7.29 (m, 2H), 6.49 (s, 1H), 3.51 (s, 1H). **^{13}C NMR (101 MHz, DMSO):** δ 163.68, 134.19, 130.07, 128.75, 128.39, 69.73, 57.97. **IR** (cm^{-1}) 3252.1, 2999.6, 2936.8, 1731.0, 1495.5, 1452.68, 1310.0, 1220.1. **ESI HRMS** *m/z* $C_{15}H_{14}O_4S$ [M+H]+: calcd 291.0697; found 291.0411.



$C_{15}H_{15}NOS$
MW = 257.35

2-(Benzhydrylthio)acetamide (**6**)
Modafinil Related Compound C

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.43 (d, J = 7.0 Hz, 5H), 7.33 (t, J = 7.6 Hz, 4H), 7.24 (t, J = 7.3 Hz, 2H), 7.02 (s, 1H), 5.40 (s, 1H), 2.94 (s, 2H). **^{13}C NMR (101 MHz, DMSO-d_6)** δ 170.37, 141.24, 128.58, 128.01, 127.16, 52.95, 34.90. **IR** (cm^{-1}) 3454.8, 3025.2, 1641.1, 1489.8, 1448.4, 1369.9, 1237.2, 1201.53.



$C_{15}H_{15}NO_2S$
MW = 273.35

2-(benzhydrylsulfinyl)acetamide
Modafinil

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.67 (s, 1H), 7.55 – 7.48 (m, 4H), 7.46 – 7.38 (m, 4H), 7.38 – 7.33 (m, 2H), 7.31 (d, J = 4.9 Hz, 1H), 5.34 (s, 1H), 3.37 (d, J = 13.7 Hz, 1H), 3.22 (d, J = 13.6 Hz, 1H). **^{13}C NMR (101 MHz, DMSO-d_6)** δ 166.36, 137.21, 134.94, 129.72, 129.04, 128.50, 128.49, 127.96, 127.93, 68.78, 56.16. **IR** (cm^{-1}) 3304.9, 3165.1, 1683.9, 1494.1, 1450.0, 1400.0, 1368.5. **ESI HRMS** *m/z* $C_{15}H_{15}NO_2S$ [M+Na]+: calcd 296.0721; found 296.0743.

4.5.1. Copies of NMR spectra

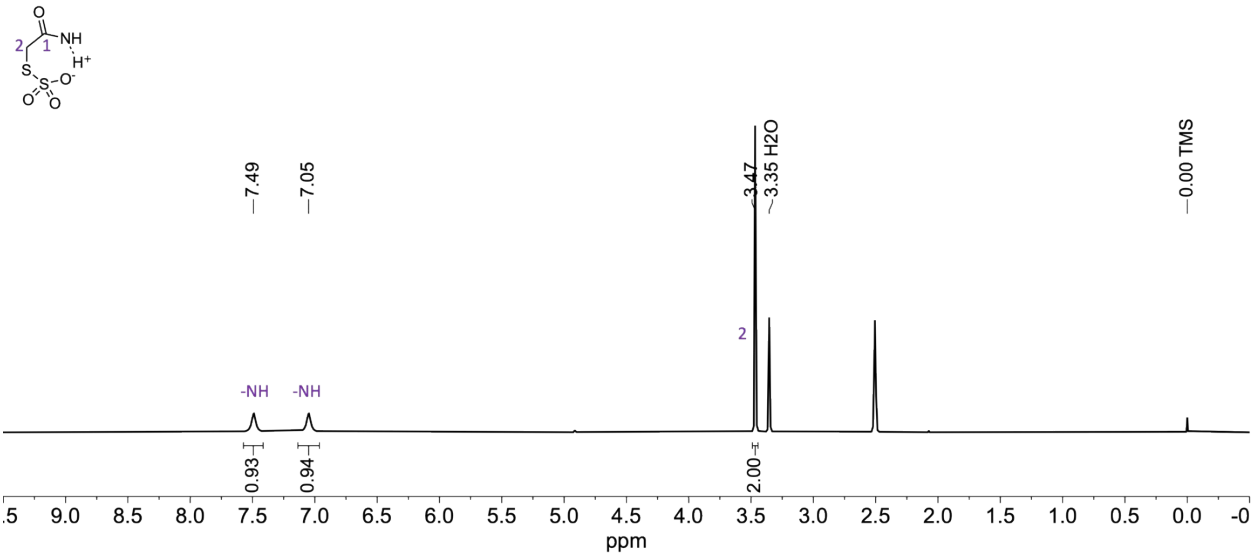


Figure S19. ^{1}H NMR spectrum (400 MHz) of sodium carbamoylmethyl sulfate (**SCS**) in DMSO-d_6.

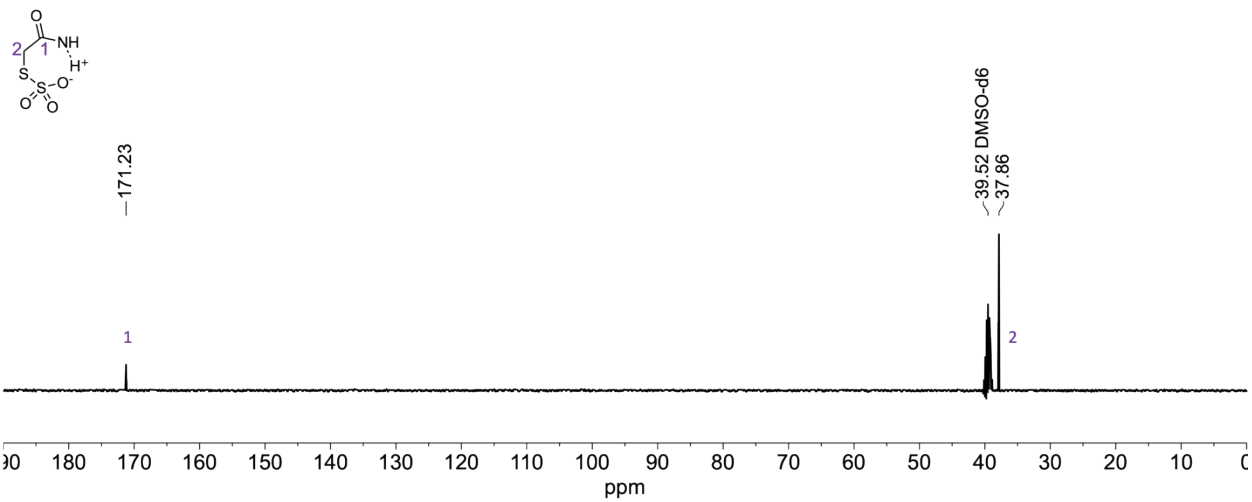


Figure S20. ^{13}C APT NMR spectrum (110.6 MHz) of sodium carbamoylmethyl sulfate (**SCS**) in DMSO-d_6.

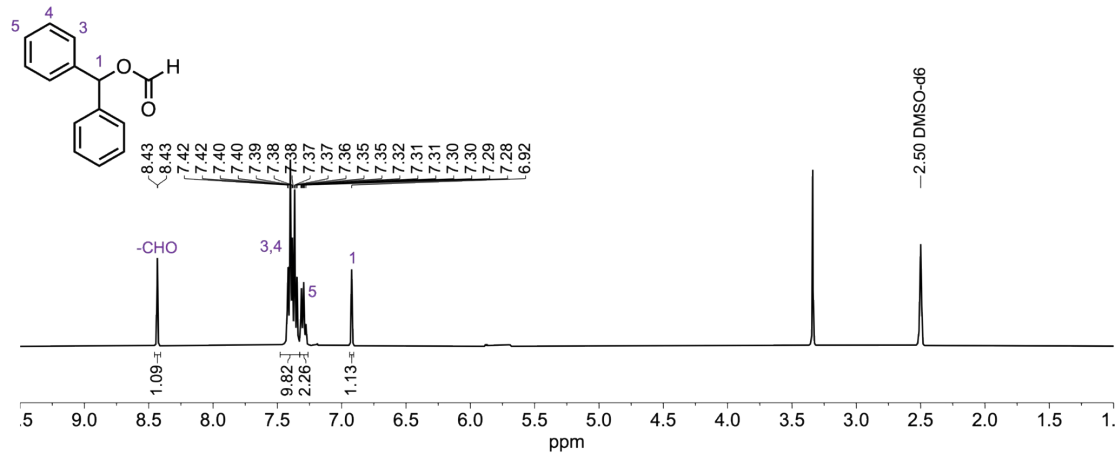


Figure S21. ^{1}H NMR spectrum (400 MHz) of benzhydryl formate (**10**) in DMSO-d_6.

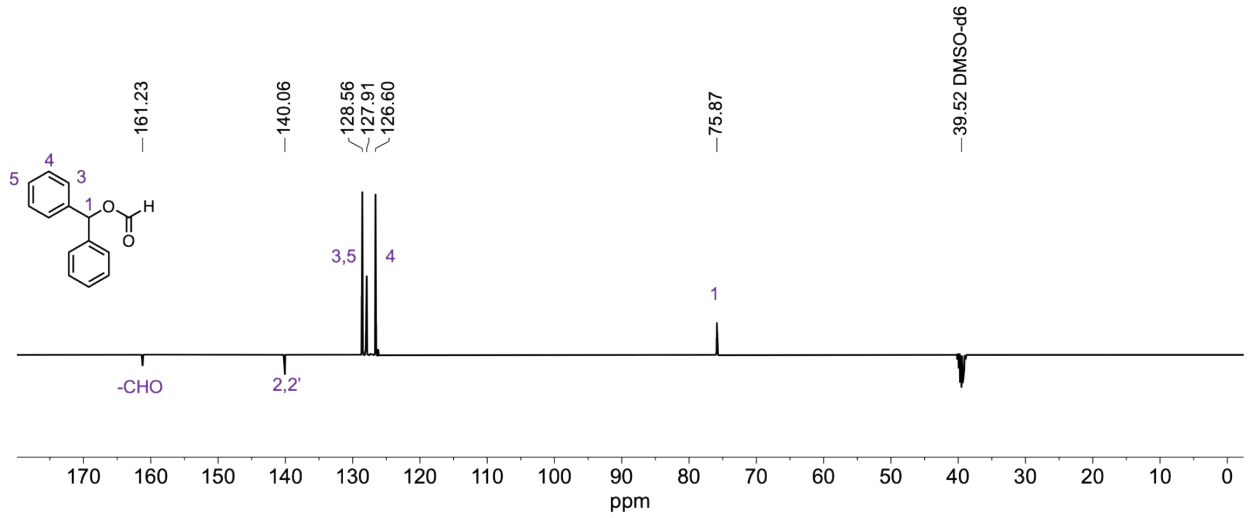


Figure S22. ^{13}C APT NMR spectrum (110.6 MHz) of benzhydryl formate (**10**) in DMSO-d_6.

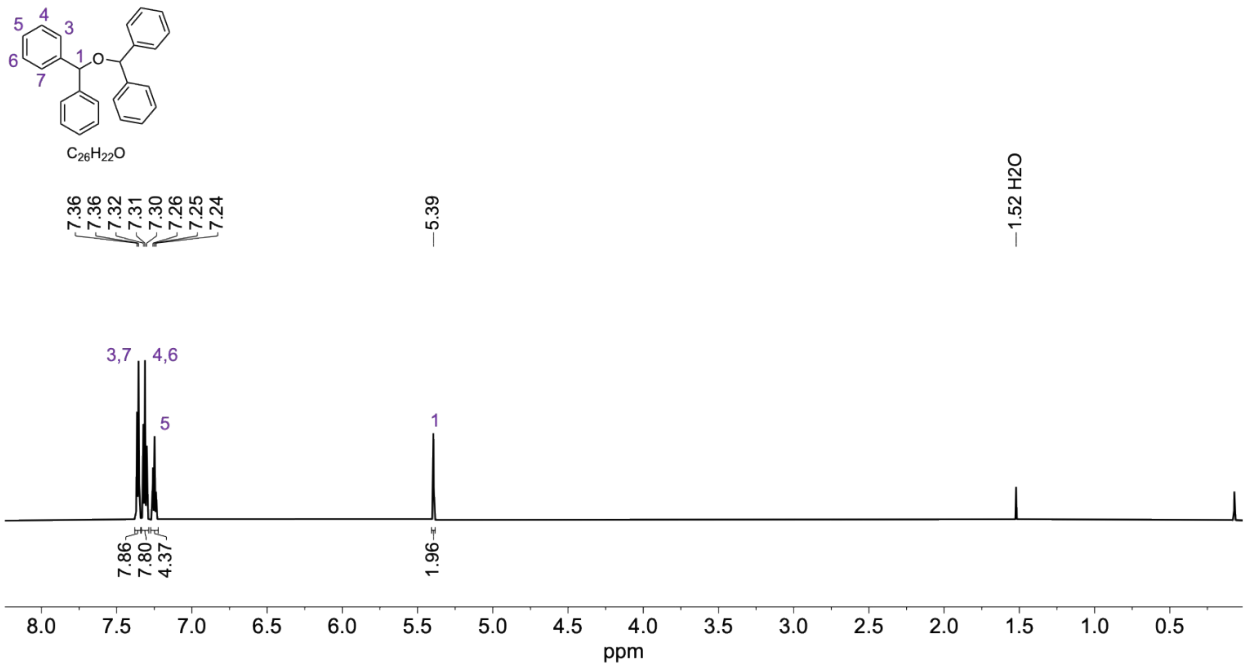


Figure S23. ^{1}H NMR spectrum (700 MHz) of bis(diphenylmethyl) ether (**12**) in $CDCl_3$.

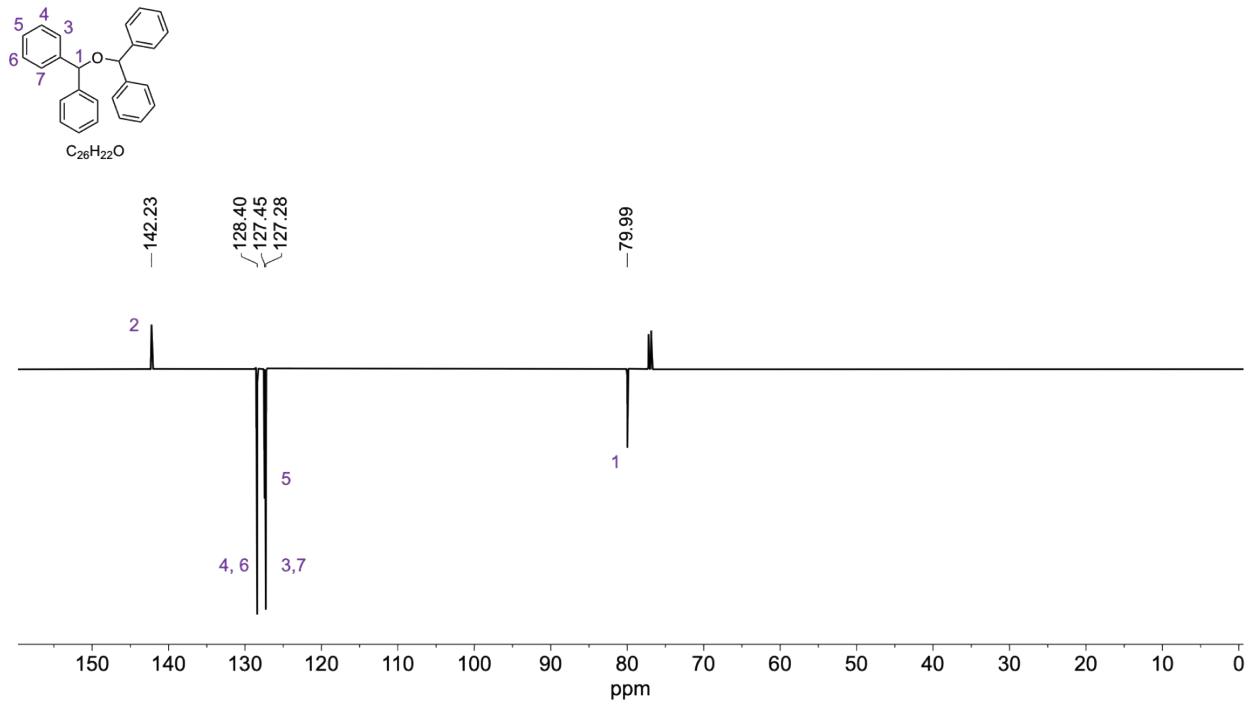


Figure S24. ^{13}C APT NMR spectrum (176 MHz) of bis(diphenylmethyl) ether (**12**) in $CDCl_3$.

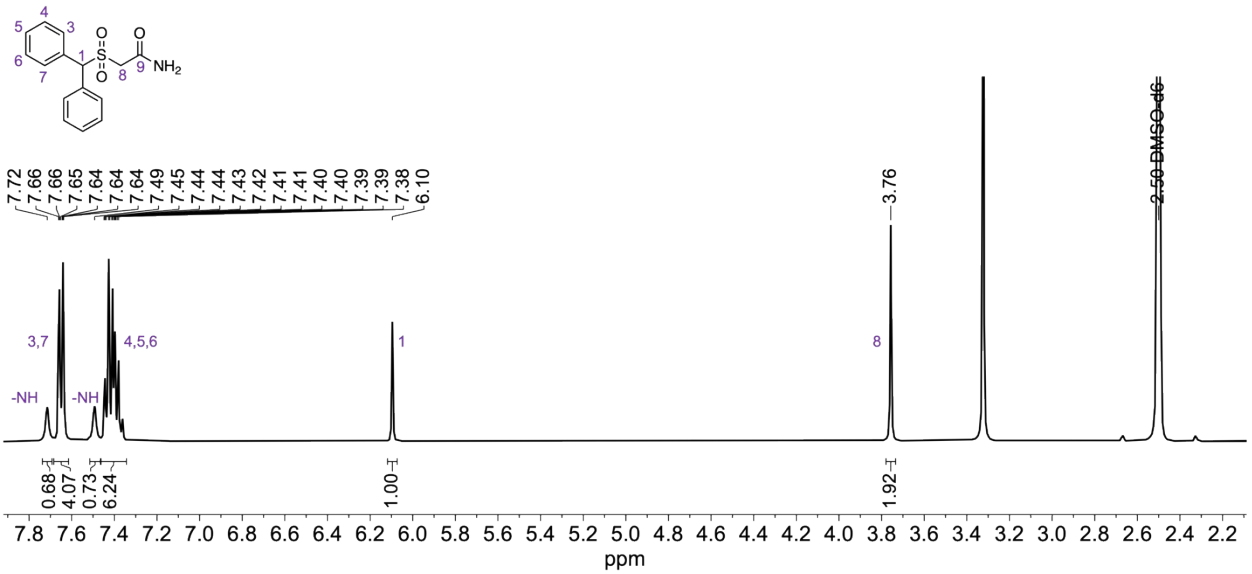


Figure S25. ^{1}H NMR spectrum (400 MHz) of 2-(benzhydrylsulfonyl)acetamide (**11**) in $CDCl_3$.

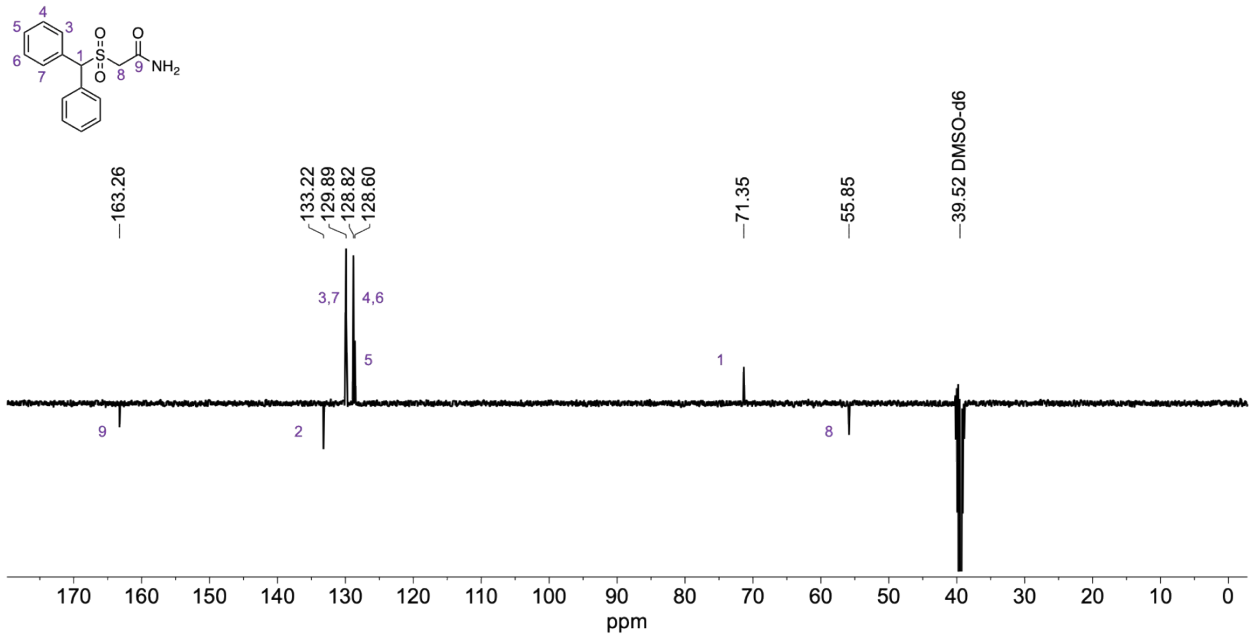


Figure S26. ^{13}C APT NMR spectrum (100.6 MHz) of 2-(benzhydrylsulfonyl)acetamide (**11**) in $CDCl_3$.

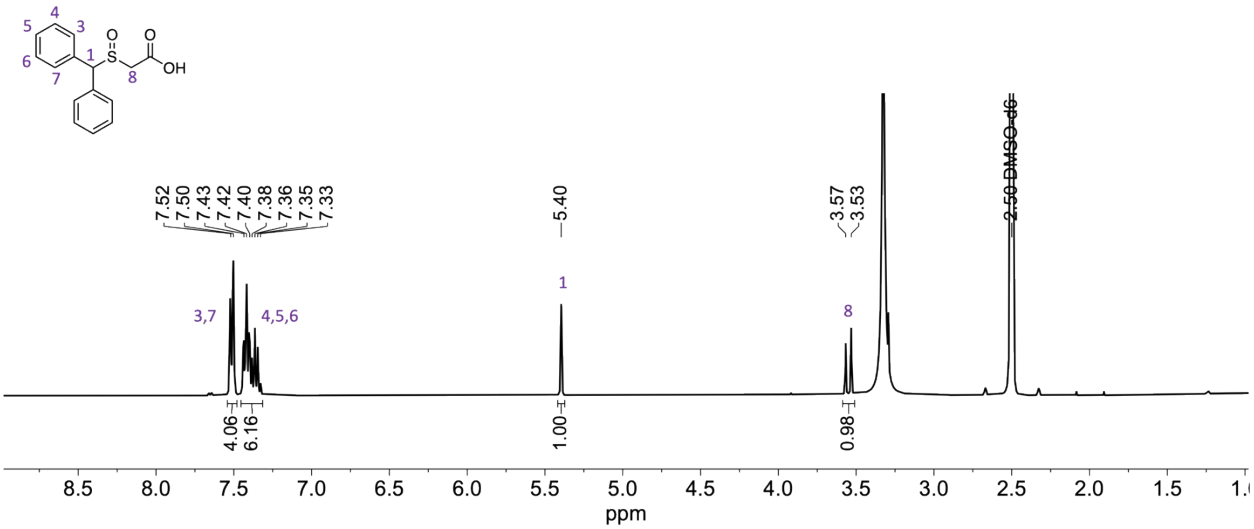


Figure S27. ^{1}H NMR spectrum (400 MHz) of 2-(benzhydrylsulfinyl)acetic acid (**7**) in $CDCl_3$.

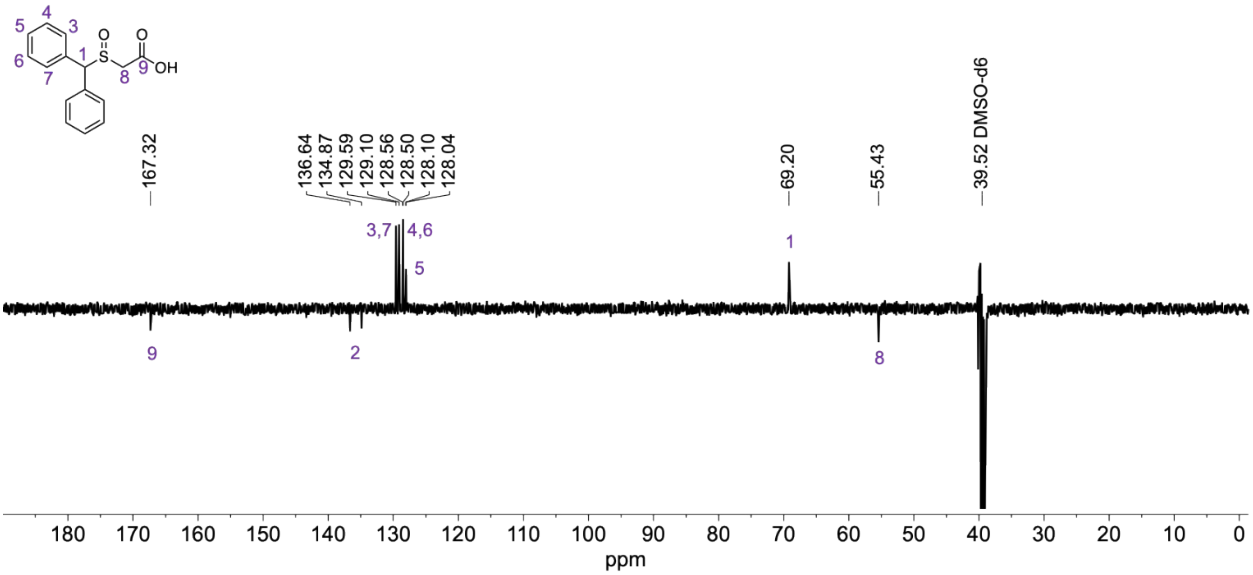


Figure S28. ^{13}C APT NMR spectrum (100.6 MHz) of 2-(benzhydrylsulfinyl)acetic acid (**7**) in $CDCl_3$.

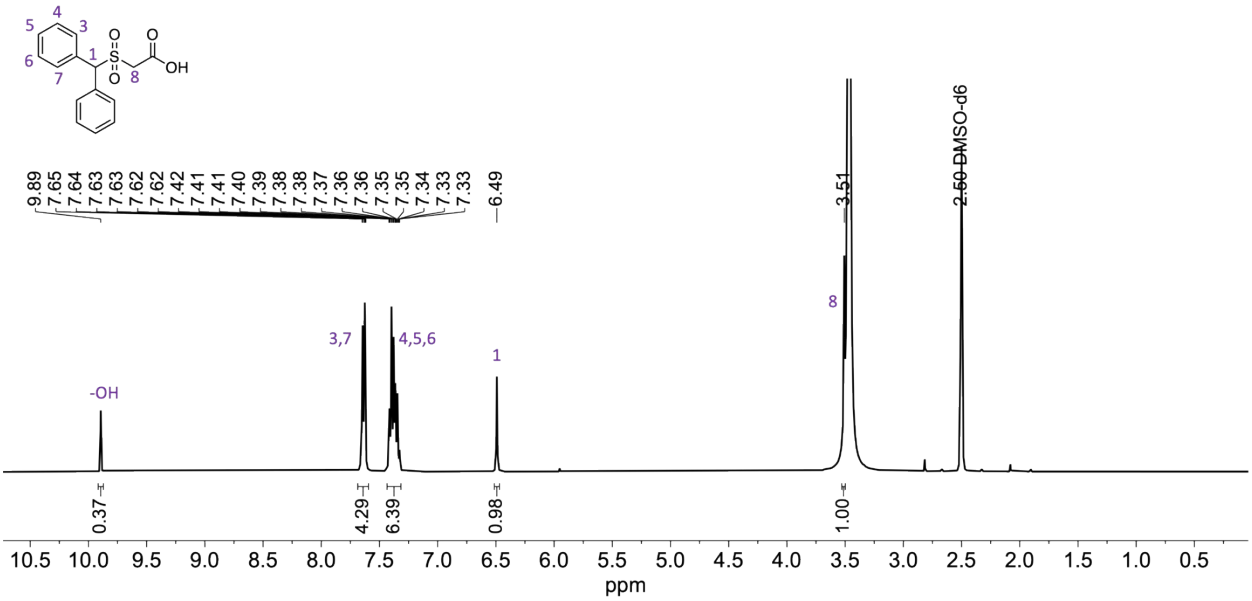


Figure S29. ^{1}H NMR spectrum (400 MHz) of 2-(benzhydrylsulfonyl)acetic acid (**13**) in $CDCl_3$.

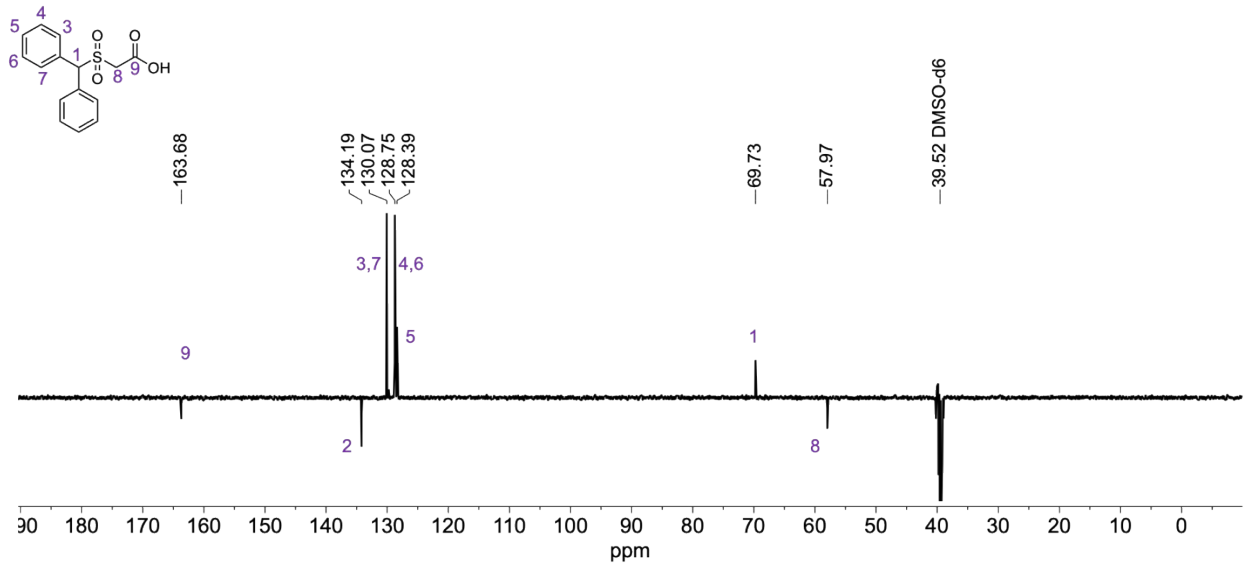


Figure S30. ^{13}C APT NMR spectrum (100.6 MHz) of 2-(benzhydrylsulfonyl)acetic acid (**13**) in $CDCl_3$.

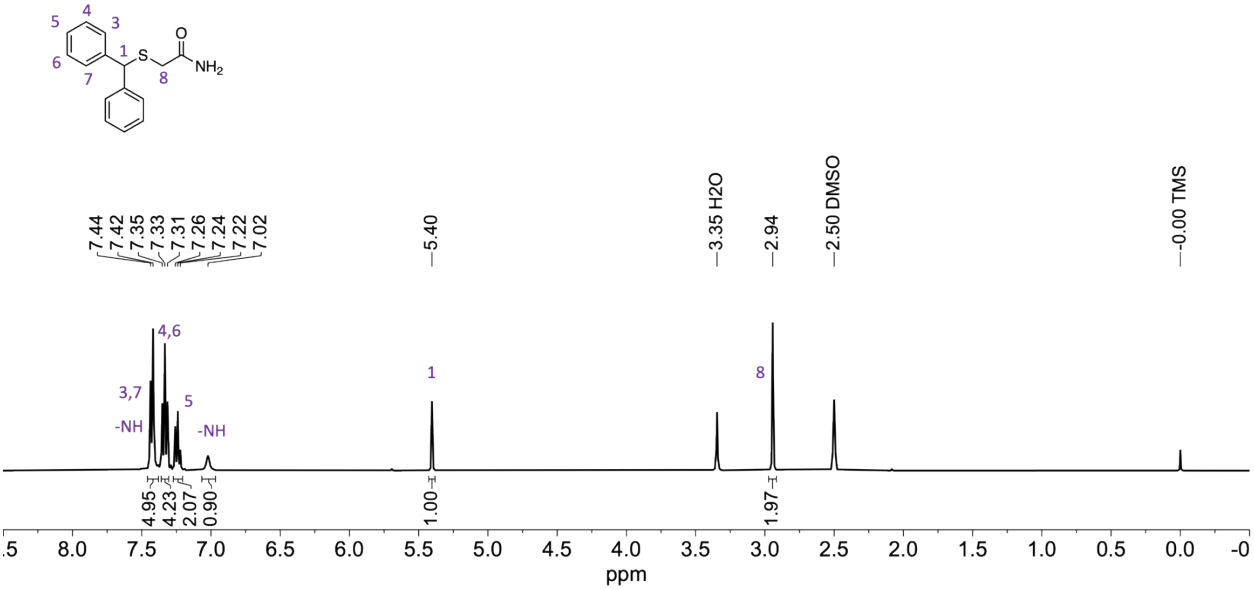


Figure S31. ^{1}H NMR spectrum (400 MHz) of 2-(benzhydrylthio)acetamide (**6**) produced by continuous flow synthesis in DMSO-d_6.

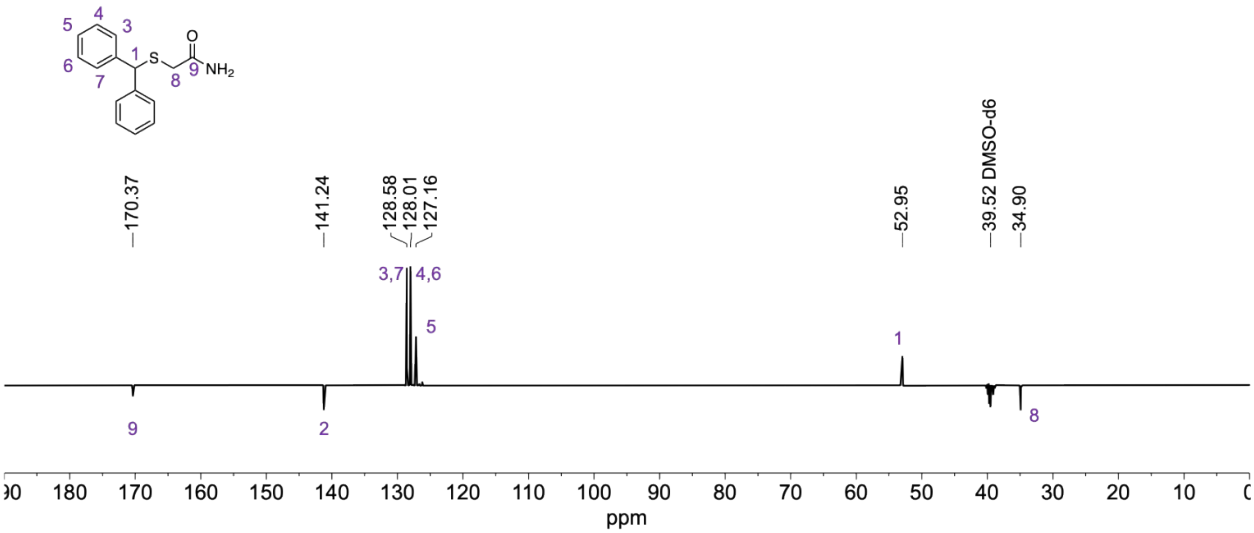


Figure S32. ^{13}C NMR spectrum (100.6 MHz) of 2-(benzhydrylthio)acetamide (**6**) produced by continuous flow synthesis in DMSO-d_6.

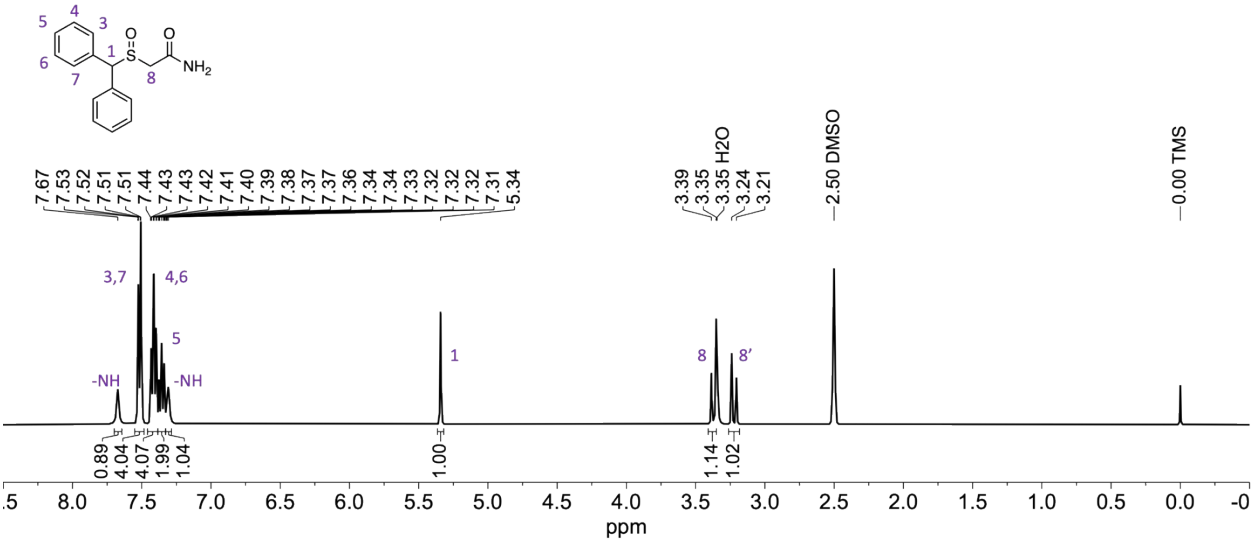


Figure S33. ^{1}H NMR spectrum (400 MHz) of modafinil (**1**, 2-(benzhydrylsulfinyl)acetamide) produced by continuous flow synthesis in DMSO-d_6.

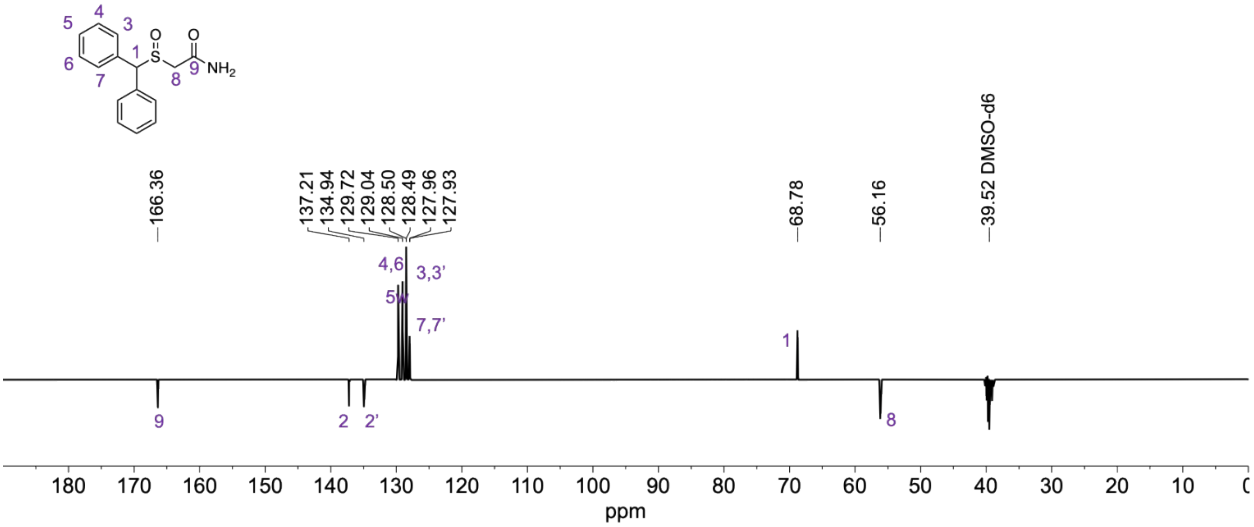


Figure S34. ^{13}C NMR spectrum (100.6 MHz) of modafinil (**1**, 2-(benzhydrylsulfinyl)acetamide) produced by continuous flow synthesis in DMSO-d_6.

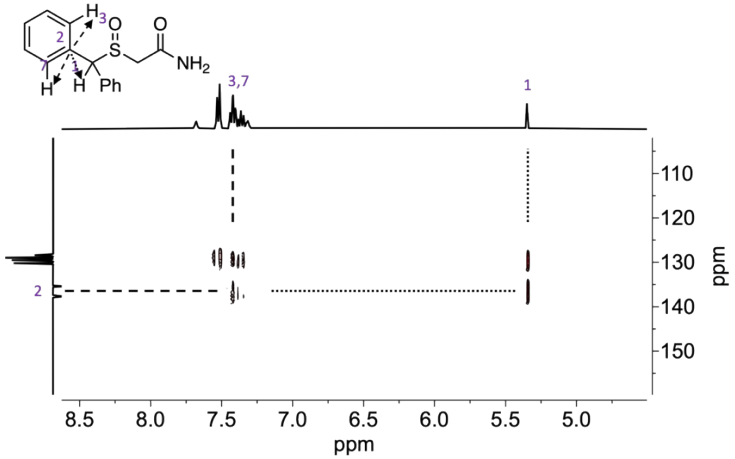


Figure S35. HMBC of modafinil (**1**, 2-(benzhydrylsulfinyl)acetamide) produced by continuous flow synthesis in DMSO-d_6 showing the cross-relations of the two signal for C2.

5. Sustainability metrics

5.1. Synthesis details for Lafon (1)

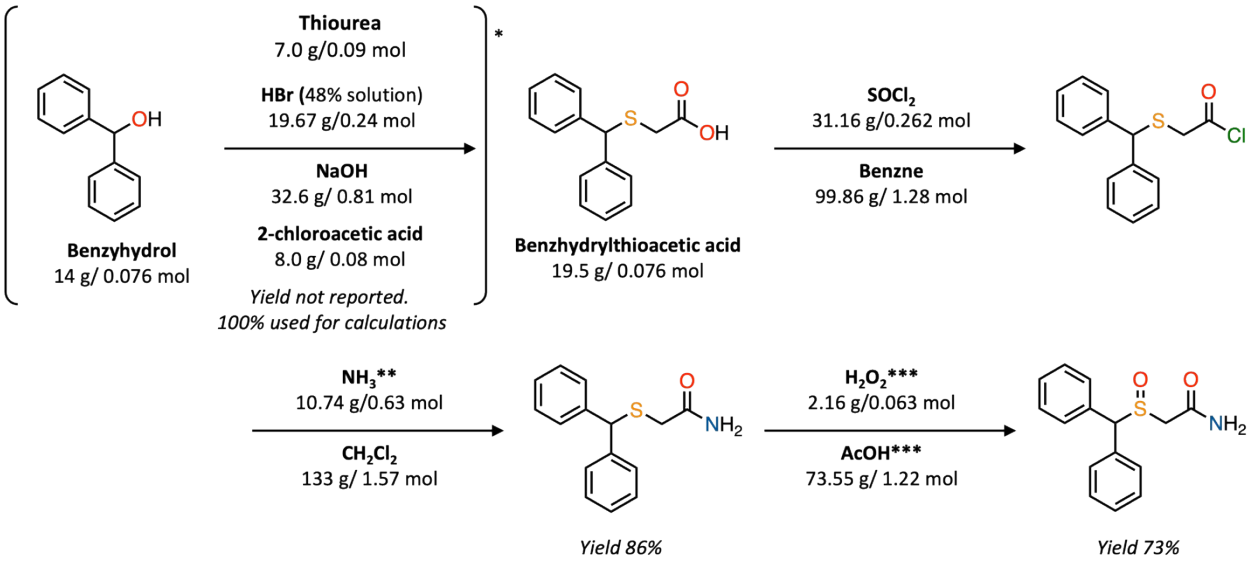


Figure S37. Synthetic scheme and detailed reactions conditions for the synthesis published by Lafon.[4]

5.2. Synthesis details for Lafon (2) (industrial)

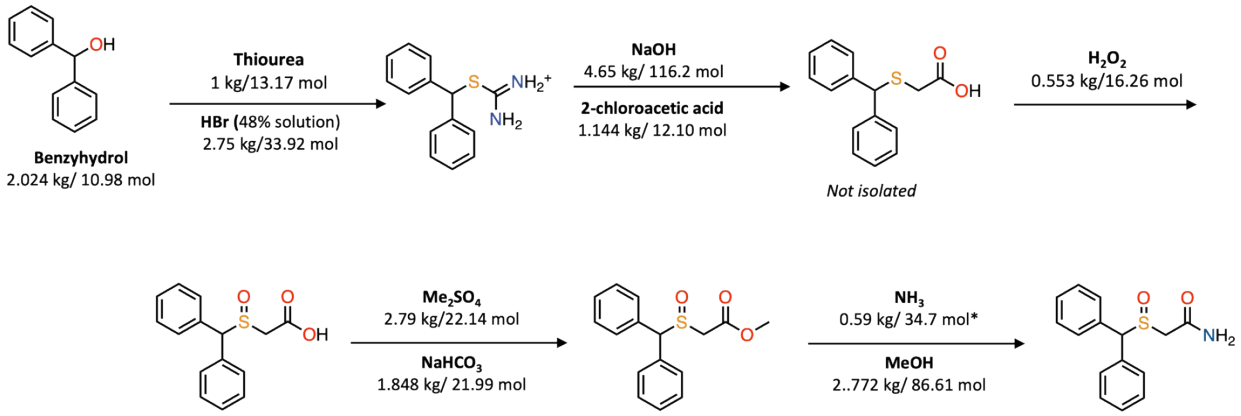


Figure S36. Synthetic scheme and detailed reactions conditions for the synthesis published by Lafon.[4]

5.3. Synthesis details for Castaldi

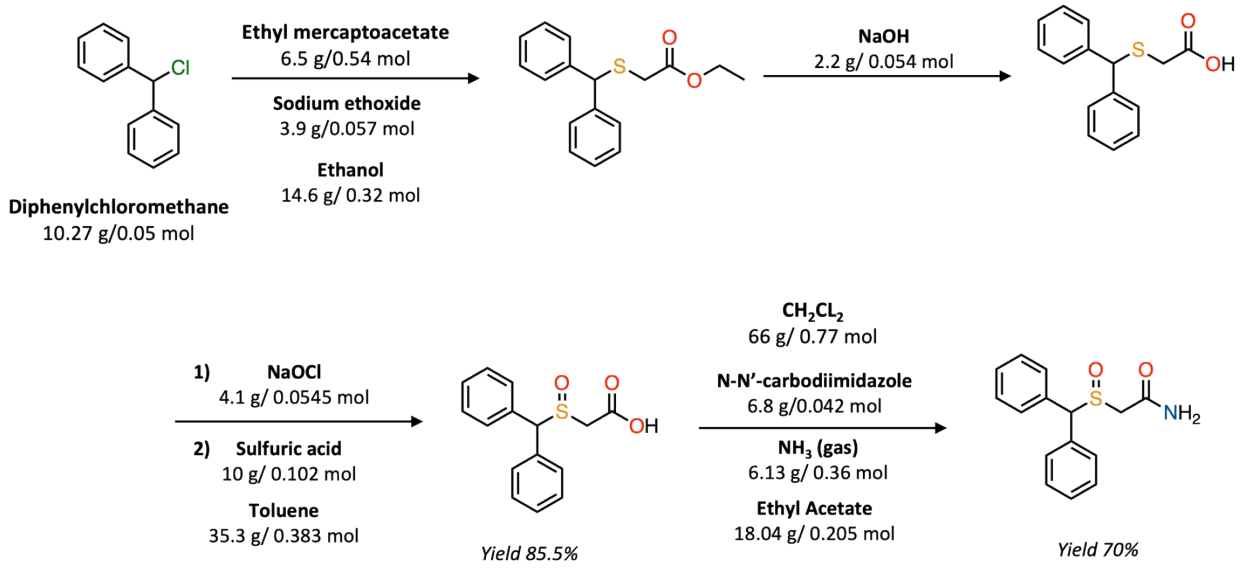


Figure S38. Synthetic scheme and detailed reactions conditions for the synthesis published by Castaldi.[5]

5.4. Synthesis details for Maurya

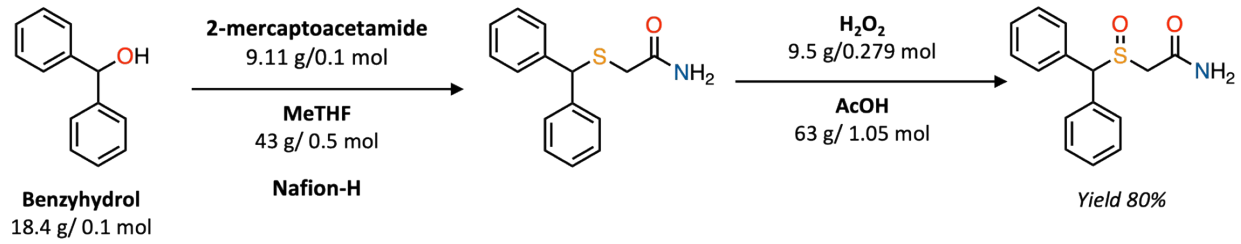


Figure S39. Synthetic scheme and detailed reactions conditions for the synthesis published by Maurya.[6]

5.5. Synthesis details for Bicherov

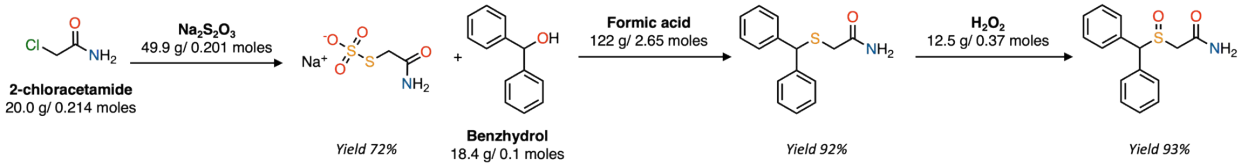


Figure S40. Synthetic scheme and detailed reactions conditions for the synthesis published by Bicherov.[7]

5.6. Synthesis details for this work

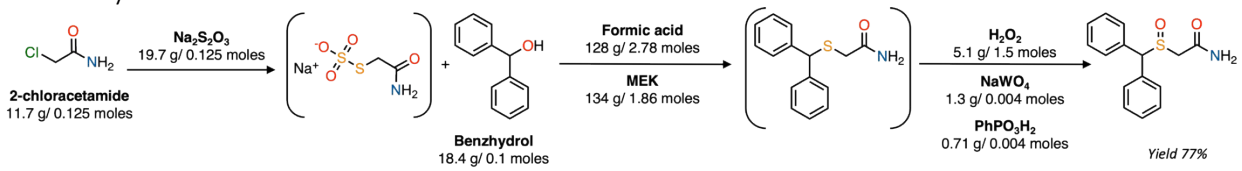


Figure S41. Synthetic scheme and detailed reactions conditions for the synthesis as reported here.

5.7. Estimations for the time to complete a full synthesis cycle

Author	Tiem for each step in the synthesis (min)					Total (min)	Total (hr)
	i	ii	iii	iv	v		
Lafon (1)	150	130	80	100	24	484	**8.1**
Lafon (2)	1500	1030	180	60	240	3010	**50.2**
Castaldi	290	95	215	155		755	**12.6**
Maurya	24	130				154	**2.6**
Bicherov	110	155				265	**4.4**
This work						9	**0.1**

Note: most procedures do not include enough details to accurately determine the time for each step. The following assumptions were made:

1. Heating and cooling procedures are arbitrarily estimated to take 1 min per 1 ºC in lab scale and 10 min per 1 ºC for the industrial scale.
2. Dropwise additions are estimated as 1 mL / min.

5.8. Summary of the calculations for E-factor and percent atom economy of each synthesis

Entry	Starting material (diphenymethane derivative)	SM (mol)	MW (g/mol)	Mass (g)	Reagents & solvents	Comments	Reagents & solvents n (mol)	Reagents & solvents equivalents	Reagents & solvents MW (g/mol)	Mass (g) Reagents & solvents	Product(s) yield (%)	Mol of product(s)	MW (g/mol) product(s)	Mass (g) product(s)	E-Factor	Atom economy	Ref.
2 Lafon 1 Comment 1		0.076	184.24	14.00	Thiourea	2	0.09	1.2	76.12	7.0	63	0.05	273.35	13.1	32	38.7%	1
					Hydrobromic acid (48%)	3	0.24	3.1	80.91	19.2							
					Sodium lye	4	0.81	10.7	40	32.6							
					2-chloroacetic acid	5	0.08	1.1	94.49	8.0							
					Thionylchloride	7	0.262	3.4	118.97	31.2							
					Benzene	8	1.28	16.8	78.11	99.9							
					Ammonia	9	0.63	8.3	17.03	10.7							
					Dichloromethane	10	1.57	20.7	84.93	133.3							
					Hydrogen peroxide	11	0.063	0.8	34.01	2.1							
					Acetic acid	12	1.22	16.1	60.052	73.5							
1 Lafon 2		11.0	184.24	2024.00	Thiourea		13.17	1.2	76.12	**1003**	41	4.50	273.35	1231	18	38.3%	1
					Hydrobromic acid (48%)	13	33.92	3.1	80.91	2744							
					Sodium lye	14	116.2	10.6	40	4648							
					2-chloroacetic acid		12.1	1.1	94.49	**1144**							
					Hydrogen peroxide	15	16.25	1.5	34.01	553							
					Dimethyl sulfate	16	22.14	2.0	126.13	2793							
					Sodium carbonate		21.99	2.0	84.01	1847							
					Sodium lye	17	36.6	3.3	40	1463							
					Ammonia	18	109.9	**10.0**	17.03	1871							
					Methanol	19	86.5	7.9	32.04	2772							
3 Maurya		0.100	184.24	18.42	2-mercaptoacetamide		0.1	1.0	91.13	9.11	80	0.08	273.35	22	6	88.4%	2
					methyl-THF		0.5	5.0	86.13	43.07							
					Hydrogen peroxide		0.279	2.8	34.01	9.49							
					Acetic acid		1.05	10.5	60.052	63.05							
4 Bicherov		0.10	184.24	18.42	2-chloroacetamide	20	0.21	2.1	93.51	20.01	62	0.06	273.35	17	12	58.2%	3
					Sodium thiosulfate	21	0.20	2.0	248.19	50.00							
					Formic acid	22	2.65	26.5	46.03	121.98							
					Hydrogen peroxide	23	0.37	3.7	34.01	12.49							
5 Castaldi		0.050	202.68	10.23	Ethyl mercaptoacetate	24	0.054	1.1	120.17	6.5	50	0.03	273.35	6.9	26.0	39.9%	4
					Sodium ethoxide	25	0.057	1.1	68.05	3.9							
					Ethanol	26	0.317	6.3	46.07	14.6							
					Sodium hydroxide	27	0.054	1.1	39.997	2.2							
					Sodium hypochlorite	28	0.055	1.1	74.42	4.1							
					Toluene	29	0.383	7.6	92.14	35.3							
					Sulfuric acid	30	0.102	2.0	98.1	10.0							
					Dichloromethane		0.777	15.4	84.93	**66.0**							
					N-N'-carbodiimidazole		**0.042**	0.8	162.15	6.8							
					Ammonia	31	0.505	10.0	17.03	8.6							
					Ethyl acetate	31	0.205	4.1	88.11	18.0							
6 Our work		1.00	184.24	184.24	2-chloroacetamide		1.25	1.25	93.51	116.9	76.5	0.77	273.35	209	14	58.2%	
					Sodium thiosulfate		1.25	1.25	158.11	197.6							
					Formic acid		28.30	28.30	46.03	1302.6							
					Hydrogen peroxide		1.50	1.50	34.01	51.0							
					Sodium tungstate		0.04	0.04	329.85	13.2							
					Phenylphosphonic acid		0.05	0.045	158.09	7.1							
					Methylethylketone		18.59	18.59	72.11	1340.5							

References	Scale	Sector
1 *United States Pat.*, US4177290, 1979.	<0.1	Oil refining
2 S. Maurya, D. Yadav, K. Pratap and A. Kumar, *Green Chemistry* , 2017, **19**, 629-633.	<1 - 5	Bulk chemicals
3 A. V. Bicherov, A. R. Akopova, V. I. Spiglazov and A. S. Morkovnik, *Russ. Chem. Bull.* , 2010, **59**, 91-101.	5 - 50	Fine chemicals
4 WO2003095423, 2007.	25 - 100	Pharmaceuticals

Comments for Lafon (1)			
	Scale: (step i and ii)	0.007x	
	Scale: (step v)	1.167x	
1	Lafon begins this report with benzhydrylthioacetic acid, which is not commercially available. The quantities to calculate the E-factor for the synthesis of this intermediate were taken from the report cited here as Lafon (2) adjusting the scale of the reactions. Because Lafon doesn't report the yield for this intermediate, 100% yield was used for this first step. The E-factor thus calculated is an underestimation.		
2	**Thiourea**		
	Qty reported	1003	g
	Grams (G x scale)	7.0	g
3	**HBr**		
	Qty reported	5720	mL
	Concentation (HBr)	48%	
	Grams (L x conc)	2745.6	g
	Grams (G x scale)	19.22	g
4	**Sodium lye**		
	Qty reported	3.55	g
	Density reported	1.33	g/ mL
	Grams (L x dens)	1463	g
	Grams (G x scale)	32.59	g
5	**2-chloroacetic acid**		
	Qty reported	1144	g
	Grams (G x scale)	8.01	g
7	**Thionylchloride**		
	Qty reported	19	mL
	Density (SOCl2)	1.64	g/ mL
	Grams (L x dens)	31.2	g
8	**Benzene**		
	Qty reported	114	mL
	Denstiy (benzene)	0.876	g/ mL
	Grams (L x dens)	99.9	g
9	**Ammonia**	35	mL

Comments for Lafon (2) (Industrial)			
13	**HBr**		
	Qty reported	5.72	L
	Concentation (HBr)	48%	
	Grams (L x conc)	2.7456	Kg
14	**Sodium lye**		
	Qty reported	3.5	L
	Density reported	1.33	g/ mL
	Grams (L x dens)	4.655	Kg
15	**H2O2**		
	Qty reported	1.43	L
	Concentration	130	vol
	Volumes to M)	11.44	vol/M
	Molarity (H2O2)	11.36	M
	Moles H2O2	16.25	
16	**Dimethyl sulfate**		
	Qty reported	2.1	L
	Density	1.33	
	Grams (L x dens)	2.793	g
17	**Sodium lye**		
	Qty reported	1.1	L
	Density reported	1.33	g/ mL
	Grams (L x dens)	1.463	Kg
18	**Ammonia**		
	Quantity not reported. Equivalents arbitrarily set to 10.		
19	**Methanol**		
	Qty reported	3.5	L
	Density	0.792	g/ mL
	Grams (L x dens)	2.772	Kg

Comments for Bicherov			
	Scale (to prepare 28 g of **SCS**)	0.1x	
20	**2-chloroacetamide**		
	Qty reported	200	g
	Grams (G x scale)	20.0	g
21	**Sodium thiosulfate**		
	Qty reported	500	g
	Grams (G x scale)	50.0	g
22	**Formic acid**		
	Qty reported	100	mL
	Density (FA)	1.22	g/mL
	Grams (L x dens)	122.0	g
23	**H2O2**		
	Qty reported	11	mL
	Density (FA)	1.135	g/ mL
	Grams (L x dens)	12.49	g

Comments for Castaldi			
	Scale (to prepare 10.23 g of benzyhydrylthioacetamide)	0.23x	
24	**Ethyl mercaptoacetate**		
	Qty reported	28.6	g
	Grams (G x scale)	6.5	g
25	**Sodium ethoxide**		
	Qty reported	81.5	g
	Grams (G x scale)	18.5	g
	Concentration	21%	
	Grams (G x conc)	3.9	g
26	**Ethanol**		
	Qty reported	81.5	g
	Grams (G x scale)	18.5	g
	Concentration	79%	
	Grams (G x conc)	14.6	g
27	**Sodium hydroxide**		
	Qty reported	0.239	mol
	mmol (mmol x scale)	0.054	mol
28	**Sodium hypochlorite**		
	Qty reported	360	mL
	mL (mL x scale)	81.8	mL
=	Concentration (NaOCl)	5%	
	Grams (mL x conc)	4.1	g
29	**Toluene**		
	Qty reported	180	mL
	mL (mL x scale)	40.9	mL
	Density	0.87	
	Grams (mL x conc)	35.5	g
28	**Sulfuric acid**		
	Qty reported	88	mL
	mL (mL x scale)	20.0	mL

	Assuming saturated concentration	18	M
	Moles (NH3)	0.63	moles
10	**DCM**		
	Qty reported	100	mL
	Density (DCM)	1.33	g/ mL
	Grams (L x dens)	133.0	g
	Scale (to prepare 13.07 g of product)		1.17
11	**H2O2**		
	Qty reported	5.6	mL
	mL (G x scale)	6.5	ml
	Concentration (H2O2)	110	vol
	Volumes to M (H2O2)	11.44	vol/M
	Molarity (H2O2)	9.62	M
	Moles H2O2	0.063	
12	**Acetic acid**		
	Qty reported	60	mL
	mL (G x scale)	70.0	ml
	Density (AcOH)	1.05	g/mL
	Grams (L x dens)	73.5	g

	Concentration (NaOCl)	50%	
	Grams (mL x conc)	10.0	g
31	**Ammonia**		
	Quantity not reported. Equivalents arbitrarily set to 10.		
32	**Ethyl acetate**		
	Qty reported	20	mL
	Density (EA)	0.902	g/mL
	Grams (L x dens)	18.04	g

5.9. EcoScale (EcoSynth)

Data was generated from the EcoScale web-based calculator (http://ecoscale.cheminfo.org/calculator)

The EcoScale 11/10/21, 3:09 PM

THE ECOSCALE
Fast and transparent evaluation of organic preparations

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Reagents

Link

	identifier*	name	MF*	MW	density	purity*	ml	g	mmoles	equiv.
1		Benzhydrol	C13H12O	184.23768		100%	0	18.4	99.870992	1
2		2-Chloroacetamide	C2H4ClNO	93.51286	0.84	100%	13.897652	11.674028	124.83874	1.25
3		Sodium thiosulfate	Na2O3S2	158.09774		100%	0	19.736723	124.83874	1.25
4		Formic acid	CH2O2	46.02568	1.22	100%	105.49643	128.70565	2796.3877	28
5		Hydrogen peroxide	H2O2	34.01468		100%	0	5.09562	149.80648	1.5
6		Sodium tungstate dihydrate	Na2O4W . 2H	329.8577	4.18	100%	0.315246	1.317729	3.9948397	.04
7		Phenylphosphonic acid	C6H7O3P	158.09354		100%	0	0.710503	4.4941946	.045
8		2-Butanone	C4H8O	72.10692	0.806	100%	160.82507	129.62501	1797.6778	18

Products

identifier*:	name:	MF*:	MW:	g:	mmoles:	g theor:	yield:
	2-[di(phenyl)methylsulfinyl]acetamide	C15H15NO2S	273.3496	21.1	77.190528	27.299696	77.2902

Conditions

Reagents

Name	mmoles	eq.	Bp	Hazard	Price
Benzhydrol	4.73	1	297		
2-Chloroacetamide	5.91	1.25	224.5		
Sodium thiosulfate	5.91	1.25			
Formic acid	132.53	28	101		
Hydrogen peroxide	7.09	1.5			
Sodium tungstate dihydrate	0.18	0.04			
Phenylphosphonic acid	0.21	0.04			
2-Butanone	85.19	18	80		

Yield 77 -11

Price / availability -13

Safety -15

Technical setup
Possible items: Common set-up; Instruments for controlled addition of chemicals; Unconventional activation technique; Pressure equipment, > 1 atm
Selected items: Pressure equipment, > 1 atm
-3

Temperature / time
Possible items: Heating, < 1h; Heating, > 1h; Cooling to 0°C; Cooling, < 0°C
Selected items: Heating, < 1h
-2

Workup and purification
Possible items: Distillation; Sublimation; Liquid - liquid extraction or washing; Classical chromatography
Selected items: Liquid - liquid extraction or washing
-3

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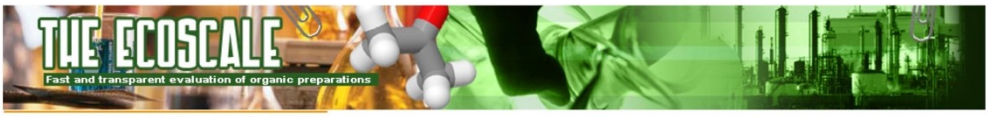
http://ecoscale.cheminfo.org/ Page 1 of 1

Figure S42. Ecoscale calculations for the synthesis according to our work.



Ecoscale calculator Manual Paper Contact

Reagents

Link

	identifier*	name	MF*	MW	density	purity*	ml	g	mmoles	equiv.
1		Nafion PFSA (10% aqueous dispersion)			1.06	100%	0	0	0	0
2		2-Mercaptoacetamide (in Methanolic Ammoni	C2H5NOS	91.1278		100%	0	9.101024	99.870992	1
3		Benzhydrol	C13H12O	184.23768		100%	0	18.4	99.870992	1
4		2-Methyltetrahydrofuran	C5H10O	86.1338	0.86	100%	50.013187	43.011341	499.35496	5
5		Hydrogen peroxide	H2O2	34.01468		100%	0	9.477853	278.64006	2.79
6		Acetic acid	C2H4O2	60.05256	1.048	100%	6.003232	6.291387	104.76467	1.049

Products

identifier*:	name:	MF*:	MW:	g:	mmoles:	g theor:	yield:
	2-[di(phenyl)methylsulfinyl]acetamide	C15H15NO2S	273.3496	21.8	79.751351	27.299696	79.8544

Conditions

Reagents

Name	mmoles	eq.	Bp	Hazard	Price
2-Mercaptoacetamide (in Methanolic Ammonia Solution 10g/100ml approx.)	4.58	1	110		
Benzhydrol	4.58	1	297		
2-Methyltetrahydrofuran	22.9	5	78		
Hydrogen peroxide	12.78	2.79			
Acetic acid	4.8	1.04	117		

Yield	80		-10
Price / availability			-15
Safety			-15
Technical setup	Possible items: Common set-up; Instruments for controlled addition of chemicals; Unconventional activation technique; Pressure equipment, > 1 atm	Selected items: Common set-up	0
Temperature / time	Possible items: Heating, < 1h; Heating, > 1h; Cooling to 0°C; Cooling, < 0°C	Selected items: Room temperature, < 24h; Heating, > 1h	-4
Workup and purification	Possible items: Removal of solvent with bp < 150°C; Crystallization and filtration; Removal of solvent with bp > 150°C; Solid phase extration	Selected items: Crystallization and filtration; Liquid - liquid extraction or washing; Removal of solvent with bp < 150°C	-4
EcoScale			52

Figure S43. Ecoscale calculations for the synthesis according to Maurya.

5.10. Cost estimation

Prices for reagents were searched on VWR.[8] Largest units (most economic options) were chosen for each reagent.

Table S13. Estimation of costs to produce one modafinil pill (100 mg) using the synthesis reported by Maurya.

Reagent	**g or L (size of reagent unit as reported on website)**	**Cost of reagent per unit (euro)**	**Qty used per batch***	**Qty used per 100 mg of product**	**Cost per 100 mg of product (euro)**
Nafion	50	608.00	0.02 g	0.00018 g	0.0011
2-Mercaptoacetamide[1]	10	168.00	94.5 g[2]	0.43332 g	7.2798
Benzhydrol	1000	125.00	18.4 g	0.08451 g	0.0106
2-MeTHF	4	124.80	0.05 L[3]	0.00023 L	0.0072
Acetic acid	25	71.68	0.06 L[4]	0.00028 L	0.0008
Peroxide (35%)	25	196.00	0.008 L[5]	0.00004 L	0.0003
Total					**7.30 euro**

Notes:

* Values taken from the table in section 5.4 and adjusted as necessary as described in the notes below.

[1] The reagent could only be found online for purchase as a 0.1 (w/v) solution in methanolic ammonia, even after searching through several major providers for chemical reagents. The authors do not mention where the compound was purchased nor of the form in which it was acquired.

[2] The reagent is sold in units of 10 grams. The value used for the reaction was calculated as follows:

Quantity for the reaction (g) / concentration of reagent (g/mL) * density of the reagent (g/mL) = quantity of the reagent needed (using the commercially available 0.1 (w/v) solution).

10.6 (g) / 0.1 (g/mL) x 0.89 (g/mL) = 94.5 g

[3] Quantity calculated as follows:

Quantity for the reaction (g) / density (g/mL) / 1000 = Quantity needed in L

42.7 (g) / 0.85 (g/mL) / 1000 = 0.05 (L)

[4] Quantity calculated as follows:

Quantity for the reaction (g) / density (g/mL) / 1000 = Quantity needed in L

63.0 (g) / 1.05 (g/mL) / 1000 = 0.06 (L)

[5] Quantity calculated as follows:

Quantity for the reaction (g) / density (g/mL) / 1000 = Quantity needed in L

9.5 (g) / 1.13 (g/mL) / 1000 = 0.008 (L)

Table S14. Estimation of costs to produce one modafinil pill (100 mg) using the synthesis in this report.

Reagent	**g or L**	**Cost of**	**Qty used**	**Qty used per**	**Cost per**

	(size of reagent unit as reported on website)	reagent per unit (euro)	per batch*	100 mg of product	100 mg of product (euro)
sodium thiosulfate	50000	896	197.6g	0.09455 g	0.0017
2-chloroacetamide	25000	531.2	116.9 g	0.05593 g	0.0012
benzhydrol	1000	125	184.2 g	0.08815 g	0.0110
formic acid	5	70.72	1.07 L[1]	0.00051 L	0.0072
MEK	190	1792	1.67 L[2]	0.00080 L	0.0075
Peroxide (35%)	25	196	0.05 L[3]	0.00002 L	0.0002
Sodium tungstate	25000	4272	13.2 g	0.00631 g	0.0011
Phosphonic acid	2500	443	7.1 g	0.00340 g	0.0006
Total					**0.03 euro**

Notes:

* Values taken from the table in section 5.4 and adjusted as necessary as described in the notes below.

[1] Quantity calculated as follows:

Quantity for the reaction (g) / density (g/mL) / 1000 = Quantity needed in L

1302.6 (g) / 1.22 (g/mL) / 1000 = 1.07 (L)

[2] Quantity calculated as follows:

Quantity for the reaction (g) / density (g/mL) / 1000 = Quantity needed in L

1340.5 (g) / 0.81 (g/mL) / 1000 = 1.67 (L)

[3] Quantity calculated as follows:

Quantity for the reaction (g) / density (g/mL) / 1000 = Quantity needed in L

51 (g) / 1.11 (g/mL) / 1000 = 0.05 (L)

6. References

1. R. Steudel, D. Jensen, P. Göbel and P. Hugo, *Berichte der Bunsengesellschaft für physikalische Chemie*, 1988, **92**, 118-122.
2. N. Chatterjie, J. P. Stables, H. Wang and G. J. Alexander, *Neurochemical Research*, 2004, **29**, 1481-1486.
3. G.-P. Yang, D. Dilixiati, T. Yang, D. Liu, B. Yu and C.-W. Hu, *Applied Organometallic Chemistry*, 2018, **32**.
4. *US Pat.,* US 4,177,290, 1979.
5. *EP Pat.,* WO 2003/095423, 2007.
6. S. Maurya, D. Yadav, K. Pratap and A. Kumar, *Green Chemistry*, 2017, **19**, 629-633.
7. A. V. Bicherov, A. R. Akopova, V. I. Spiglazov and A. S. Morkovnik, *Russ. Chem. Bull.*, 2010, **59**, 91-101.
8. VWR Online Store, https://be.vwr.com/store/, (accessed on December 2021).