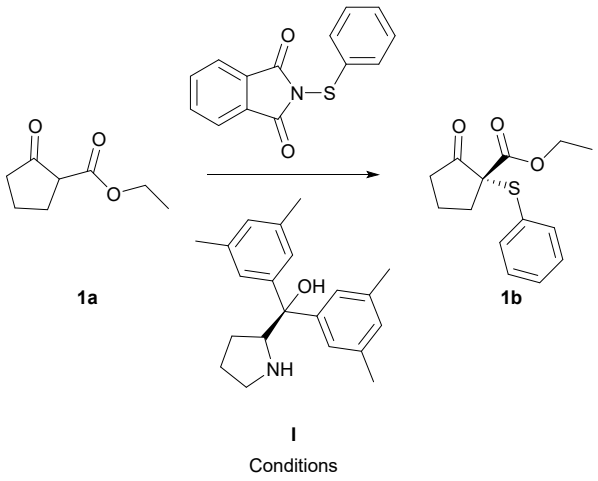
Contents

Supporting Information

General experimental methods

Reagents and solvents were purchased from Sigma Aldrich, DLD scientific, and Merck and unless otherwise noted used without further purification. All solvents were reagent grade or better. Deuterated solvents were used as received. Dry ice was made from with tech grade-wet CO_2 (90%). Thin layer chromatography (TLC) was performed using Merck Kieselgel 60 F254 plates. Synthetic steps were characterised using LC-MS (Shimadzu 2020 UFLC-MS, Japan) or GC-MS-QP2010 Ultra (Shimadzu, Japan). Chiral HPLC (Agilent technologies) was used for the determination of enantiomeric excess. NMR data were recorded using a Bruker AVANCE III 600 MHz at room temperature. The NMR chemical shifts (δ) are reported in parts per million (ppm) relative to the residual solvent peak (^{1}H-NMR δ 7.26 for $CDCl_3$, δ 3.31 for CD_3OD; ^{13}C-NMR δ 77.0 for $CDCl_3$, δ 49.00 for CD_3OD). ^{13}C NMR is the APT experiment. The APT experiment yields methine (CH) and methyl (CH_3) signals positive and quaternary (C) and methylene (CH_2) signals negative.

Procedure for the sulfenylation of ethyl 2-oxocyclopentane-1-carboxylate



Scheme 1: Synthesis of Ethyl 2-oxo-1-(phenylthio)cyclopentanecarboxylate (**1b**).

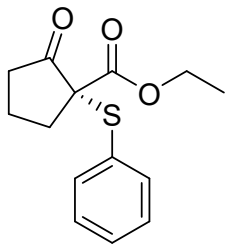
Procedure A: Green solvent

A mixture of ethyl 2-oxocyclopentane-1-carboxylate (**1a**, 0.19 mmol), N-(Phenylthio)phthalimide (1.2 equiv.), (S)-α,α-Bis(3,5-dimethylphenyl)-2-pyrrolidinemethanol (**I**, 5 mol%), and green solvent (0.1 M) were added into a 10 mL microwave reaction tube. The reaction was stirred for 3 hours at RT. Thereafter, the solvent was evaporated under reduced pressure. The crude mixture was purified by flash column chromatography using a mixture of ethyl acetate (0-5%) in hexane (100-95%).

Procedure B: Liquid CO_2

A mixture of ethyl 2-oxocyclopentane-1-carboxylate (**1a**, 0.19 mmol), N-(Phenylthio)phthalimide (1.2 equiv.), (S)-α,α-Bis(3,5-dimethylphenyl)-2-pyrrolidinemethanol (**I**, 5 mol%), and dry ice (CO_2, 2g) were added into a 10 mL microwave reaction tube and placed into a high-pressure reaction vessel (Parr instrument company, USA). The reaction vessel was then placed in water bath at 25 °C to warm up. The vessel was left to stir at RT for 3 hours. Thereafter, the reaction vessel was placed in an ice bath to cool, and the pressure was released. Hexane was added to the microwave reaction tube and the crude mixture was purified by flash column chromatography using a mixture of ethyl acetate (0-5%) in hexane (100-95%).

Ethyl 2-oxo-1-(phenylthio)cyclopentanecarboxylate (1b)[1]



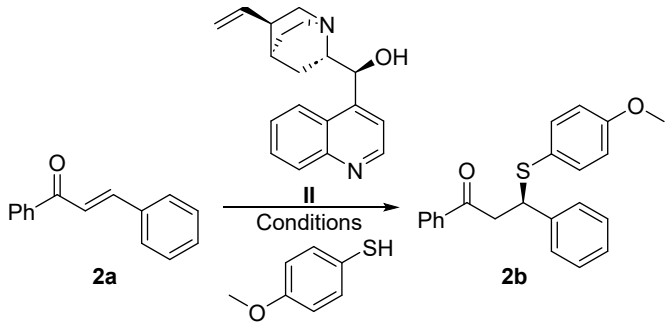
Compound **1b** was prepared according to the preceding general procedure. White solid. Yield: 99%.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.25 (t, 3H), 1.94-2.15 (m, 3H), 2.34-2.60 (m, 3H), 4.2 (m, 2H), 7.3-7.38 (m, 3H), 7.54-7.55 (m, 2H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.1, 19.1, 35.0, 37.0, 62.5, 64.8, 129.0, 129.7, 130.3, 136.4, 169.4, 207.3

Enantiomeric excess: 84%, determined by HPLC (CHIRALART Cellulose-SC, hexane/ isopropanol = 99:1, flow rate 1 mL/min): tR = 19.63 min (minor), tR = 21.52 min (minor)

Procedure for the Michael addition of 4-methoxybenzenethiol to chalcone



Scheme 2: Synthesis of 3-((4-methoxyphenyl)thio)-1,3-diphenylpropan-1-one (**2b**).

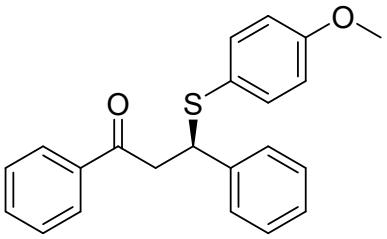
Procedure A: Green solvent

A mixture of *trans*-chalcone (**2a**, 0.24 mmol), 4-Methoxythiophenol (1.1 equiv.), cinchonine (**II**,1.5 mol%), and green solvent (0.33 M) were added into a 10 mL microwave reaction tube. The reaction was stirred for 4 hours at -20 °C. Thereafter, the solvent was evaporated under reduced pressure. The crude mixture was purified by flash column chromatography using a mixture of ethyl acetate (0-10%) in hexane (100-90%).

Procedure B: Liquid CO_2

A mixture of *trans*-chalcone (**2a**, 0.24 mmol), 4-Methoxythiophenol (1.1 equiv.), cinchonine (**II**, 1.5 mol%), and dry ice (CO_2, 2g) were added into a 10 mL microwave reaction tube and placed into a high-pressure reaction vessel. The vessel was left to stir at -20 °C for 4 hours. Thereafter, the reaction vessel was placed in an ice bath to cool, and the pressure was released. Hexane was added to the microwave reaction tube and the crude mixture was purified by flash column chromatography using a mixture of ethyl acetate (0-10%) in hexane (100-90%).

3-((4-methoxyphenyl)thio)-1,3-diphenylpropan-1-one (2b)[2]



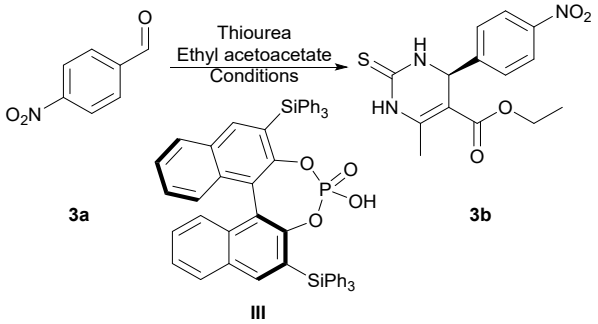
Compound **2b** was prepared according to the preceding general procedure. White solid. Yield: 85%.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.54-3.63 (m, 2H), 3.76 (s, 3H), 4.76-4.78 (t, 1H), 6.75 (d, 2H), 7.16-7.26 (m, 7H), 7.43 (t, 2H), 7.54 (t, 1H), 7.87 (d, 2H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 44.4, 49.5, 55.4, 114.5, 124.4, 127.4, 128.0, 128.2, 128.5, 128.7, 133.3, 136.4, 137.0, 141.5, 160.0, 197.3.

Enantiomeric excess: 40%, determined by HPLC (CHIRALART Cellulose-SB, hexane/ isopropanol = 90:10, flow rate 0.5 mL/min): tR = 21.53 min (minor), tR = 22.76 min (minor)

Procedure for the asymmetric Biginelli reaction of 4-nitrobenzaldehyde, thiourea, and ethyl acetoacetate



Scheme 3: Synthesis of Ethyl-6-methyl-4-(4-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3b**).

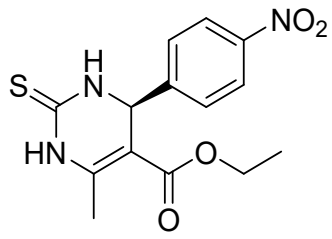
Procedure A: Green solvent

A mixture of 4-nitrobenzaldehyde (**3a**, 0.03 mmol), thiourea (1.2 equiv.), (S)-3,3′-Bis(triphenylsilyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate (**III,** 10 mol%), and green solvent (0.1 M), were added into a 10 mL microwave reaction tube. The reaction was stirred for 1 hour at RT. Thereafter, ethyl acetoacetate (3 equiv.) was added to the reaction and the reaction was stirred for 60 hour at 50 °C. Thereafter, the solvent was evaporated under reduced pressure. The crude mixture was purified by flash column chromatography using a mixture of ethyl acetate (0-30%) in hexane (100-70%).

Procedure B: scCO$_2$

A mixture of 4-nitrobenzaldehyde (**3a**, 0.03 mmol), thiourea (1.2 equiv.), ethyl acetoacetate (3 equiv.), (S)-3,3′-Bis(triphenylsilyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate (**III,** 10 mol%), and dry ice (CO_2, 2g) were added into a 10 mL microwave reaction tube and placed into a high-pressure reaction vessel. The vessel was then placed in a preheated oil bath left to stir at 50 °C for 60 hours. Thereafter, the reaction vessel was placed in an ice bath to cool, and the pressure was released. Acetonitrile was added to the microwave reaction tube and the crude mixture was submitted for LC-MS analysis.

Ethyl-6-methyl-4-(4-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (3b)[3]



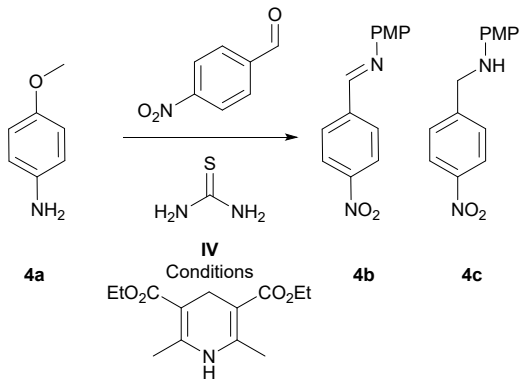
Compound **3b** was prepared according to the preceding general procedure. white solid. Yield: 98%.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.20 (t, 3H), 2.38 (s, 3H), 4.11-4.13 (m, 2H), 5.51 (d, 1H), 7.48 (d, 2H), 7.74 (brs, 1H), 8.13 (brs, 1H), 8.19 (d, 2H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.3, 18.7, 55.6, 61.0, 102.3, 124.4, 127.9, 143.7, 147.9, 149.1, 165.0, 175.1.

Enantiomeric excess: 92%, determined by HPLC (CHIRALART Cellulose-SC, hexane/ isopropanol = 70:30, flow rate 0.5 mL/min): tR = 13.90 min (major), tR = 15.66 min (minor)

Procedure for the direct reductive amination of 4-nitrobenzaldehyde and p-anisidine



Scheme 4: Synthesis of 4-methoxy-N-(4-nitrobenzyl)aniline (**4c**).

Procedure A: Green solvent

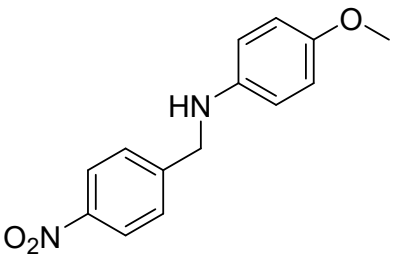
A mixture of p-Anisidine (**4a**, 0.24 mmol), 4-nitrobenzaldehyde (1.2 equiv.), Hantzsch ester (1.2 equiv.), thiourea (**IV,** 10 mol%), and green solvent (0.4 M) were added into a 10 mL microwave reaction tube. The reaction was stirred for 16 hours at 70 °C. Thereafter, water was

added to the reaction mixture to precipitate the product. The crude mixture was purified by flash column chromatography using a mixture of ethyl acetate (0-10%) in hexane (100-90%).

Procedure B: Liquid CO_2

A mixture of p-Anisidine (**4a**, 0.24 mmol), 4-nitrobenzaldehyde (1.2 equiv.), Hantzsch ester (1.2 equiv.), thiourea (**IV,** 10 mol%), and dry ice (CO_2, 2g) were added into a 10 mL microwave reaction tube and placed into a high-pressure reaction vessel. The vessel was then placed in a preheated oil bath left to stir at 70 °C for 16 hours. Thereafter, the reaction vessel was placed in an ice bath to cool, and the pressure was released. Acetonitrile was added to the microwave reaction tube and the crude mixture was submitted for GC-MS analysis.

4-methoxy-N-(4-nitrobenzyl)aniline (4c)[4]

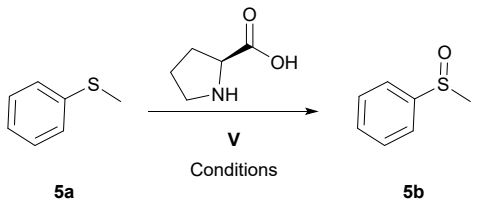


Compound **4c** was prepared according to the preceding general procedure. yellow solid. Yield: 90%.

^{1}H NMR (600 MHz, CD_3OD): δ = 3.67 (s, 3H), 4.39 (s, 2H), 6.56 (m, 2H), 6.70 (m, 2H), 7.58 (d, 2H), 8.16 (d, 2H).

^{13}C NMR (150 MHz, CD_3OD): δ = 48.7, 56.2, 115.4, 115.9, 124.5, 129.2, 143.6, 148.3, 150.2, 153.6.

Procedure for the oxidation of thioanisole



Scheme 5: Synthesis of methyl phenyl sulfoxide (**5b**).

Procedure A: Green solvent

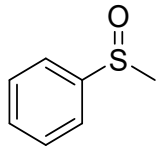
A mixture of thioanisole (**5a**, 0.24 mmol), L-proline (**V**, 0.01 equiv.), H_2O_2 (2.5 equiv.), and green solvent (3.8 M) were added into a 10 mL microwave reaction tube and placed into a

preheated oil bath. The reaction was stirred for 2 hours at 40 °C. Thereafter, the mixture was extracted with ethyl acetate. The resultant organic layer was dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure.

Procedure B: scCO_2

A mixture of thioanisole (**5a**, 0.24 mmol), L-proline (**V**, 0.01 equiv.), H_2O_2 (2.5 equiv.), and dry ice (CO_2, 2g) were added into a 10 mL microwave reaction tube and placed into a high-pressure reaction vessel. The reaction vessel was then placed in an oil bath preheated to 40 °C. The temperature was maintained by an external temperature probe connected to a digital hot plate. The pressure was monitored by a pressure gauge attached to the reaction vessel. After 2 hours, the high-pressure reaction vessel was placed in an ice bath to cool, and the pressure was released. Thereafter, acetonitrile was added to the microwave vessel, and the mixture was submitted for LC-MS analysis.

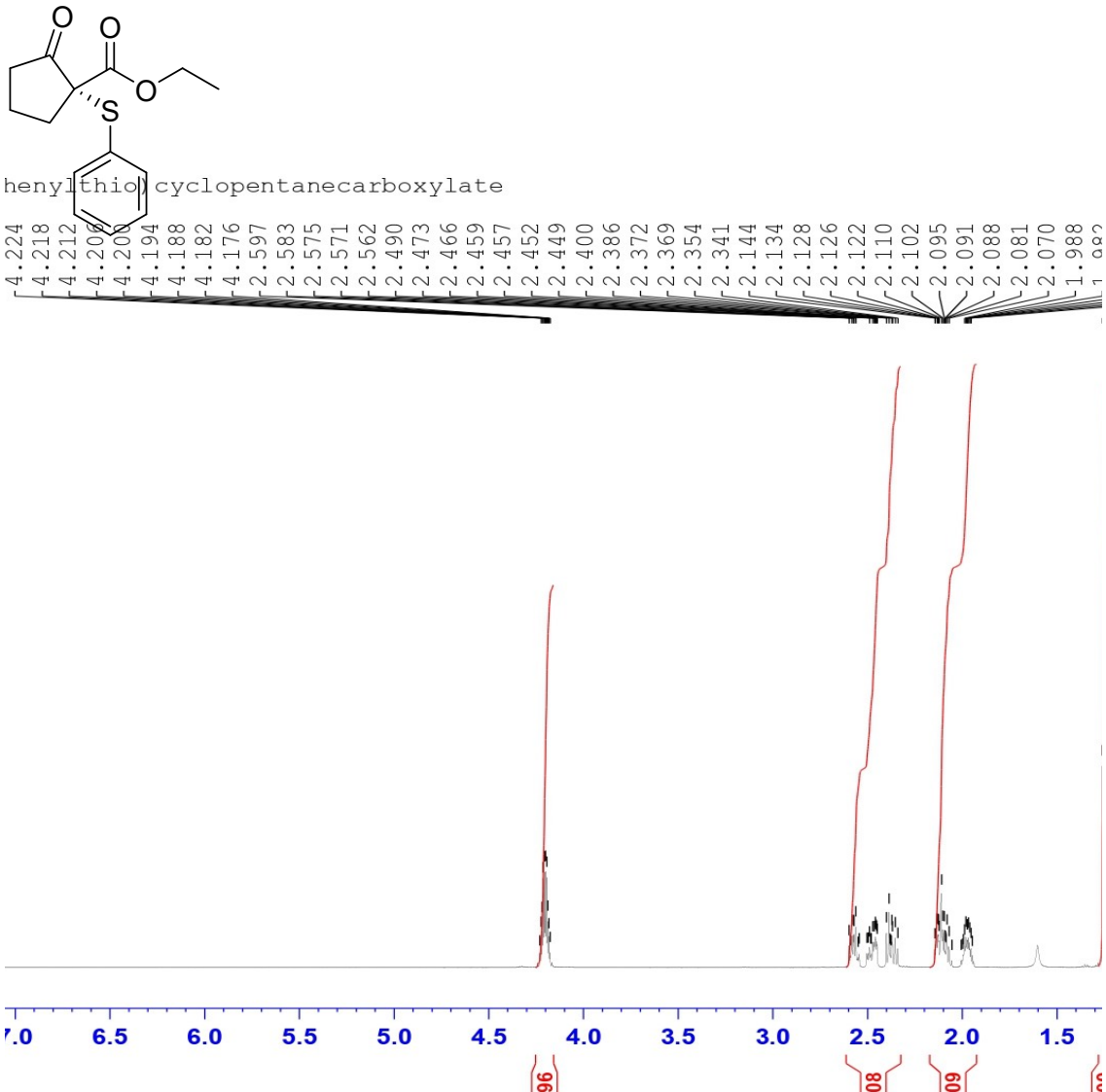
Methyl phenyl sulfoxide (5b)[5]



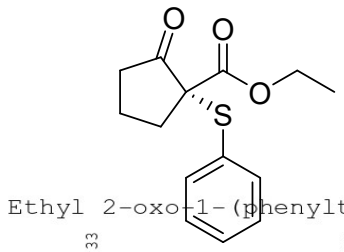
Compound **5b** was prepared according to the preceding general procedure. White solid. Yield: 99%.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.71 (s, 3H), 7.49-7.53 (m, 3H), 7.63 (d, 2H).

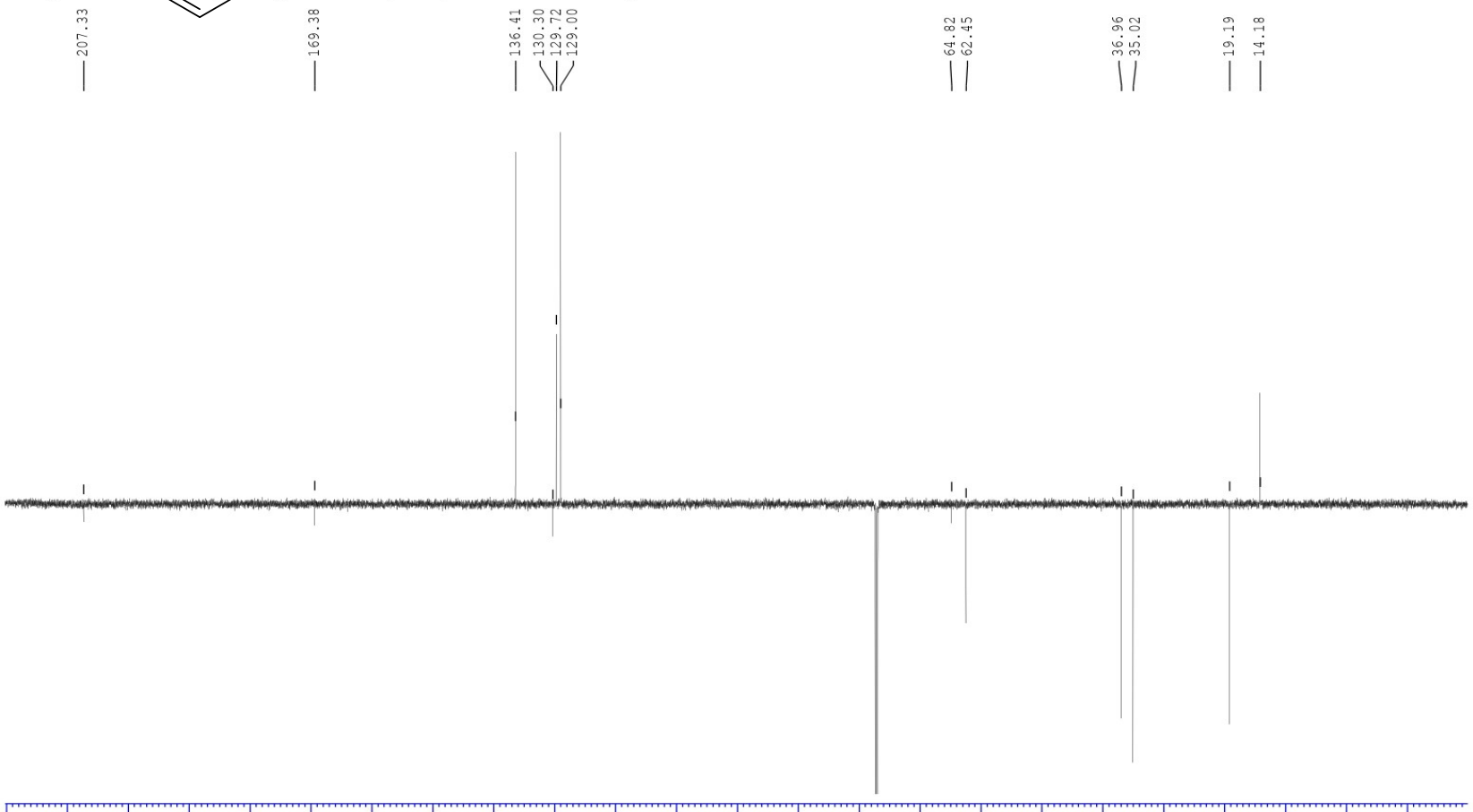
^{13}C NMR (150 MHz, $CDCl_3$): δ = 44.0, 123.6, 129.5, 131.1, 145.8.


henylthio)cyclopentanecarboxylate
4.224
4.218
4.212
4.206
4.200
4.194
4.188
4.182
4.176
2.597
2.583
2.575
2.571
2.562
2.490
2.473
2.466
2.459
2.457
2.452
2.449
2.400
2.386
2.372
2.369
2.354
2.341
2.144
2.134
2.128
2.126
2.122
2.110
2.102
2.095
2.091
2.088
2.081
2.070
1.988
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5

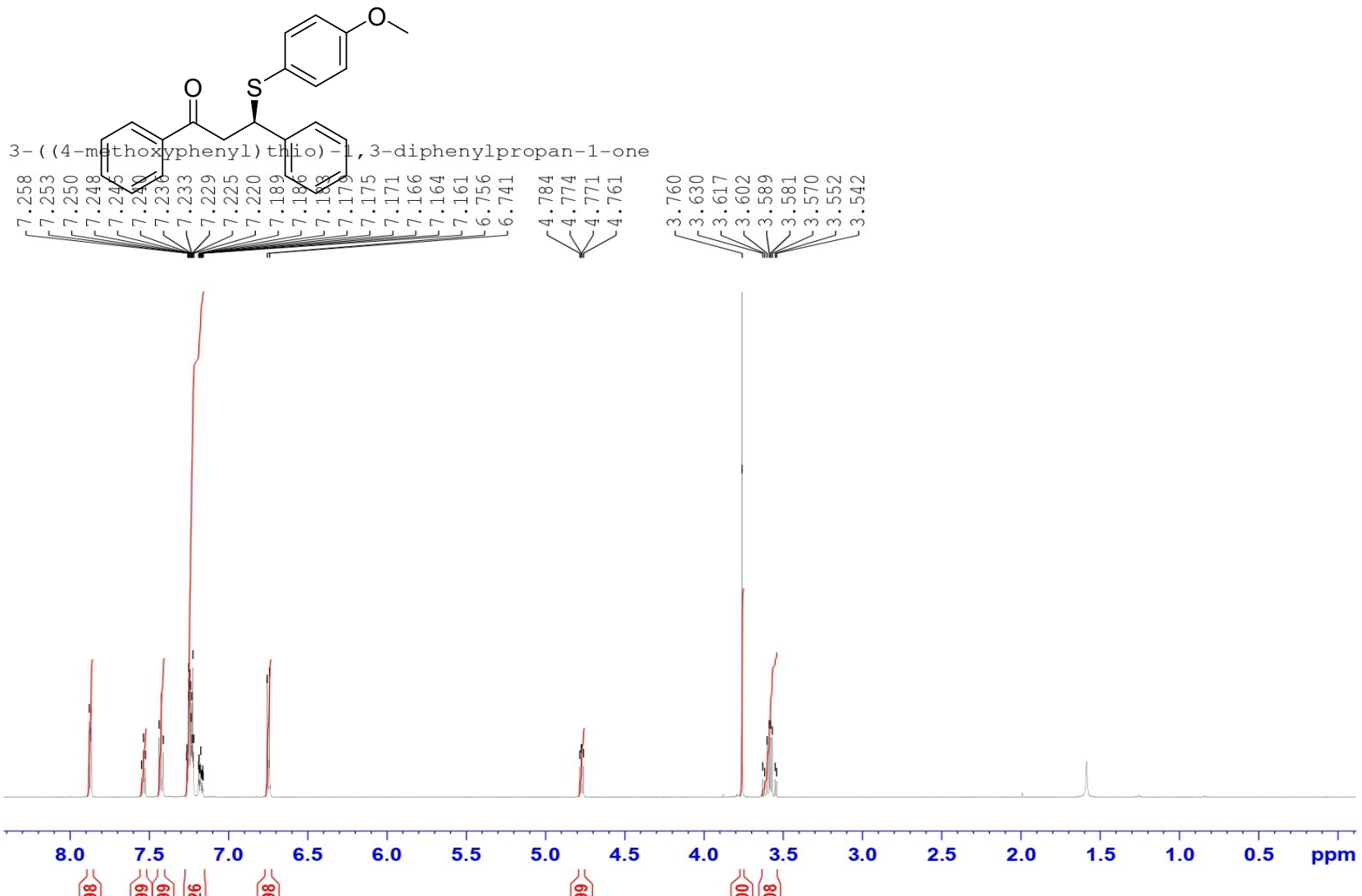
^{1}H NMR of Ethyl 2-oxo-1-(phenylthio)cyclopentanecarboxylate in $CDCl_3$ (1b)



Ethyl 2-oxo-1-(phenylthio)cyclopentanecarboxylate



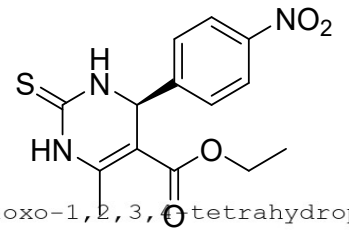
^{13}C NMR of Ethyl 2-oxo-1-(phenylthio)cyclopentanecarboxylate in $CDCl_3$ (1b)


3-((4-methoxyphenyl)thio)-1,3-diphenylpropan-1-one
7.258
7.253
7.250
7.248
7.245
7.240
7.230
7.233
7.229
7.225
7.220
7.189
7.186
7.183
7.179
7.175
7.171
7.166
7.164
7.161
6.756
6.741
4.784
4.774
4.771
4.761
3.760
3.630
3.617
3.602
3.589
3.581
3.570
3.552
3.542
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

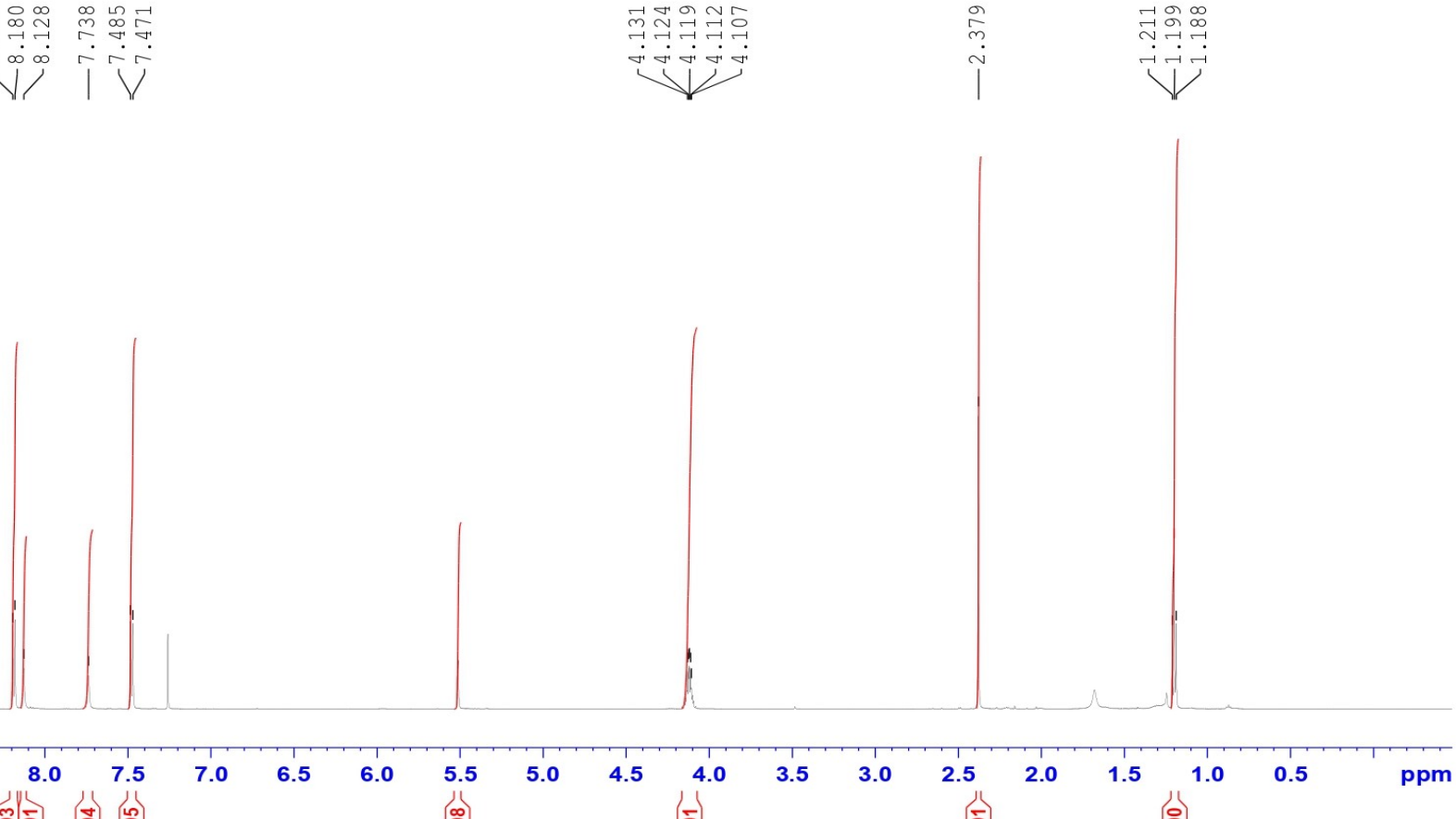
^{1}H NMR of 3-((4-methoxyphenyl)thio)-1,3-diphenylpropan-1-one in $CDCl_3$ (2b)


O
S
O
3-((4-methoxyphenyl)thio)-1,3-diphenylpropan-1-one
197.25
160.00
141.53
136.99
136.36
133.32
128.73
128.49
128.20
127.97
127.37
124.40
114.51
55.41
49.54
44.44

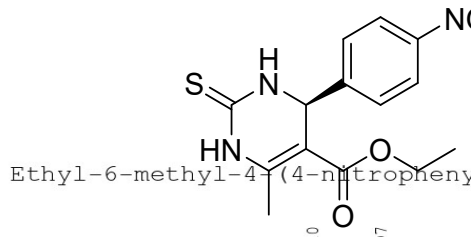
^{13}C NMR of 3-((4-methoxyphenyl)thio)-1,3-diphenylpropan-1-one in $CDCl_3$ (2b)



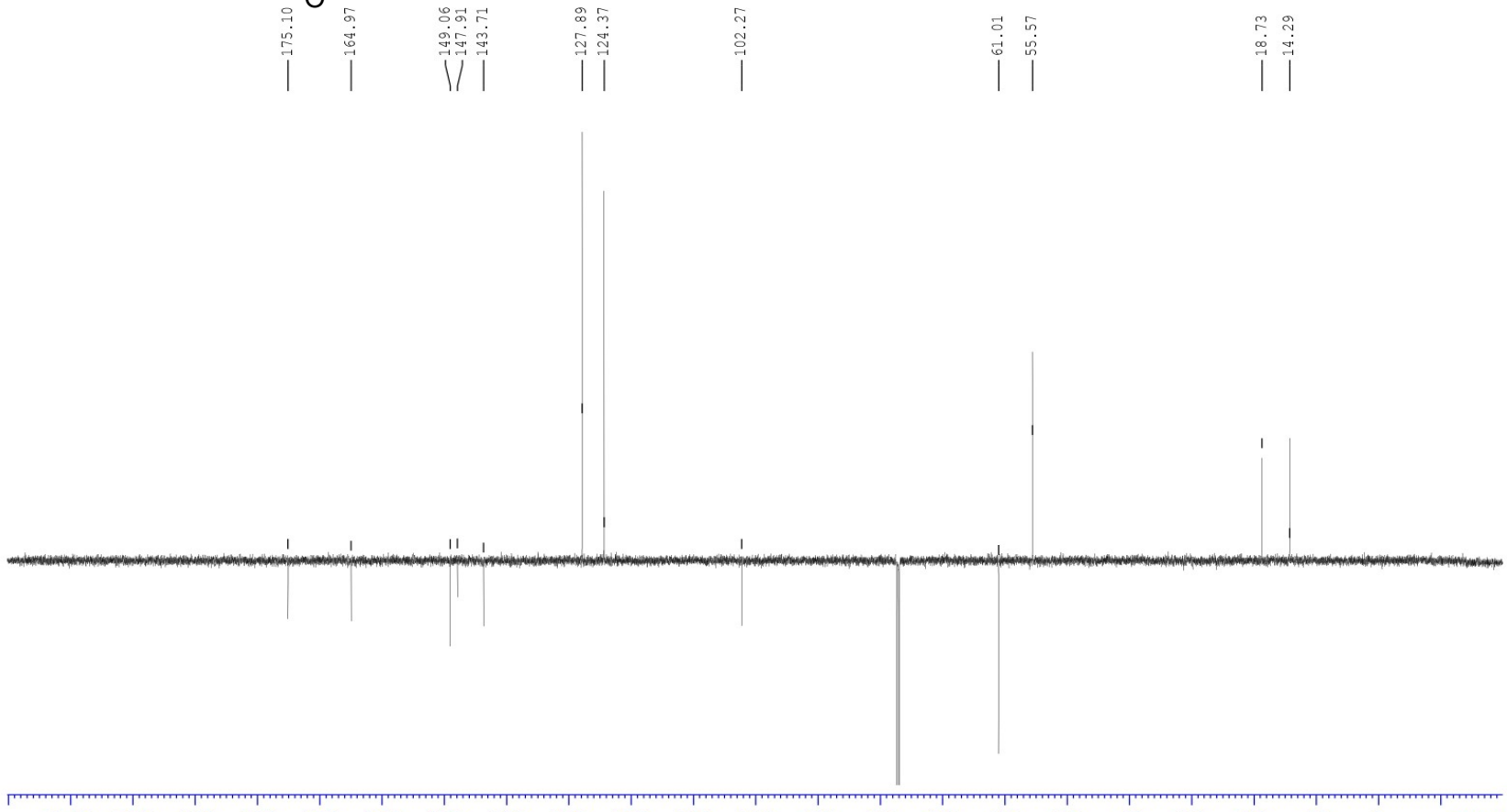
1-6-methyl-4-(4-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbox



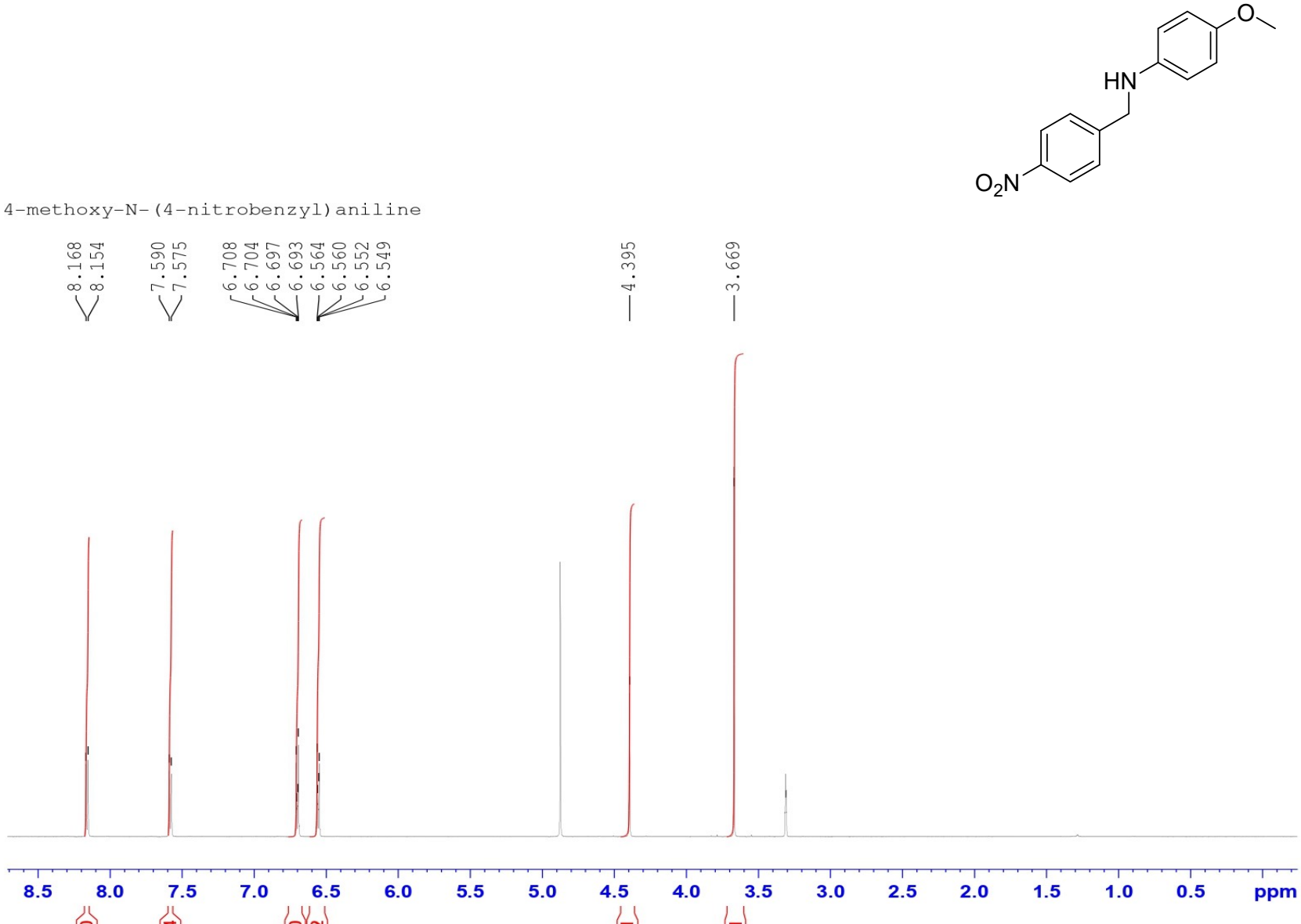
1,2,3,4-tetrahydropyrimidine-5-carboxylate in $CDCl_3$ (3b)



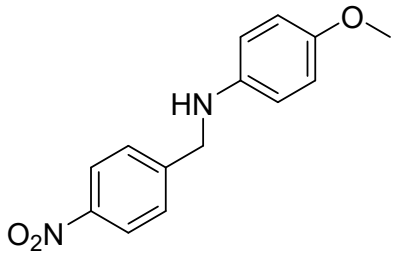
Ethyl-6-methyl-4-(4-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbox



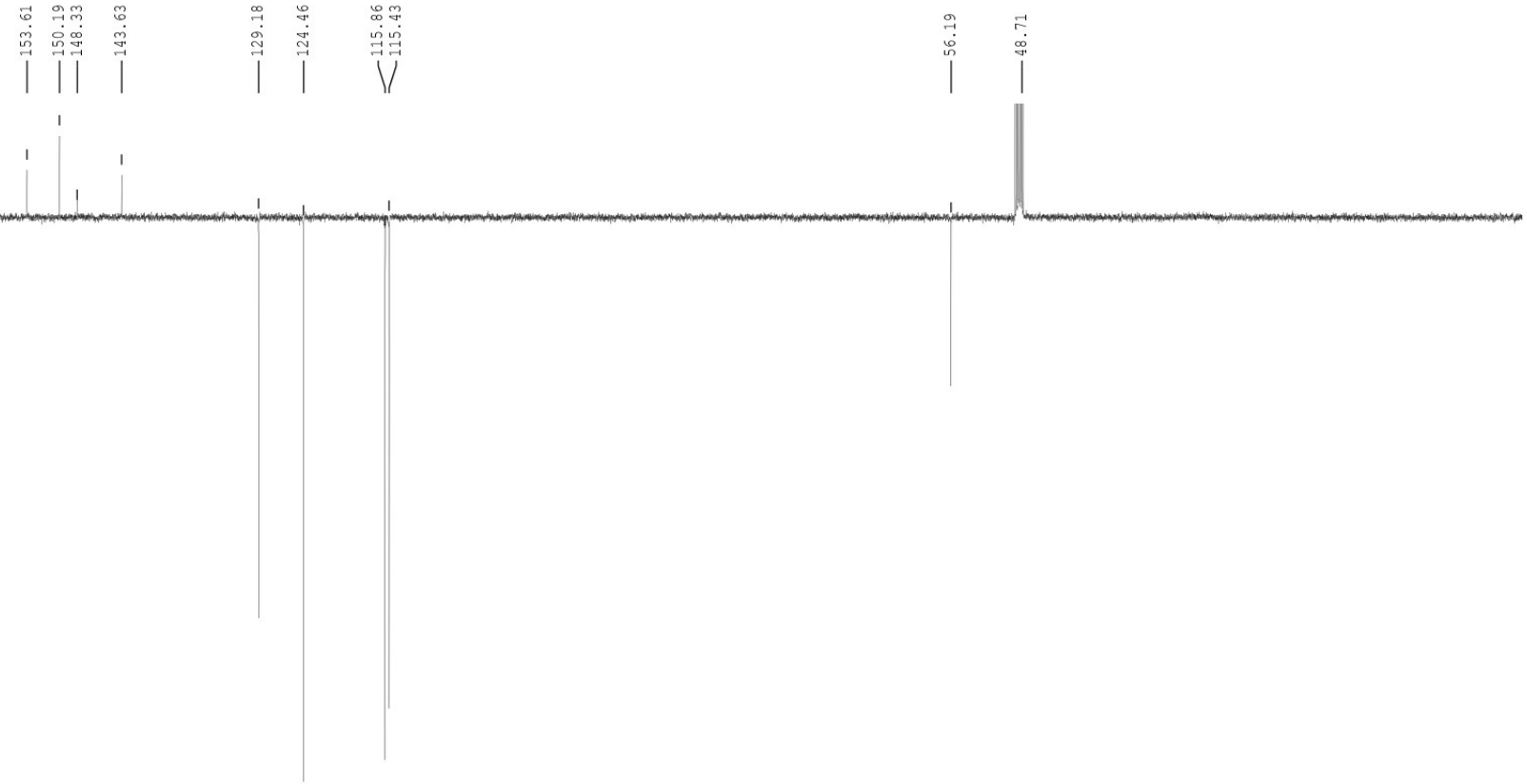
^{13}C NMR of Ethyl-6-methyl-4-(4-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate in $CDCl_3$ (3b)


4-methoxy-N-(4-nitrobenzyl)aniline
8.168
8.154
7.590
7.575
6.708
6.704
6.697
6.693
6.564
6.560
6.552
6.549
4.395
3.669
HN
O
O2N
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

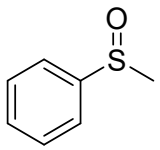
^{1}H NMR of 4-methoxy-N-(1-phenylethyl)aniline in CD_3OD (4b)



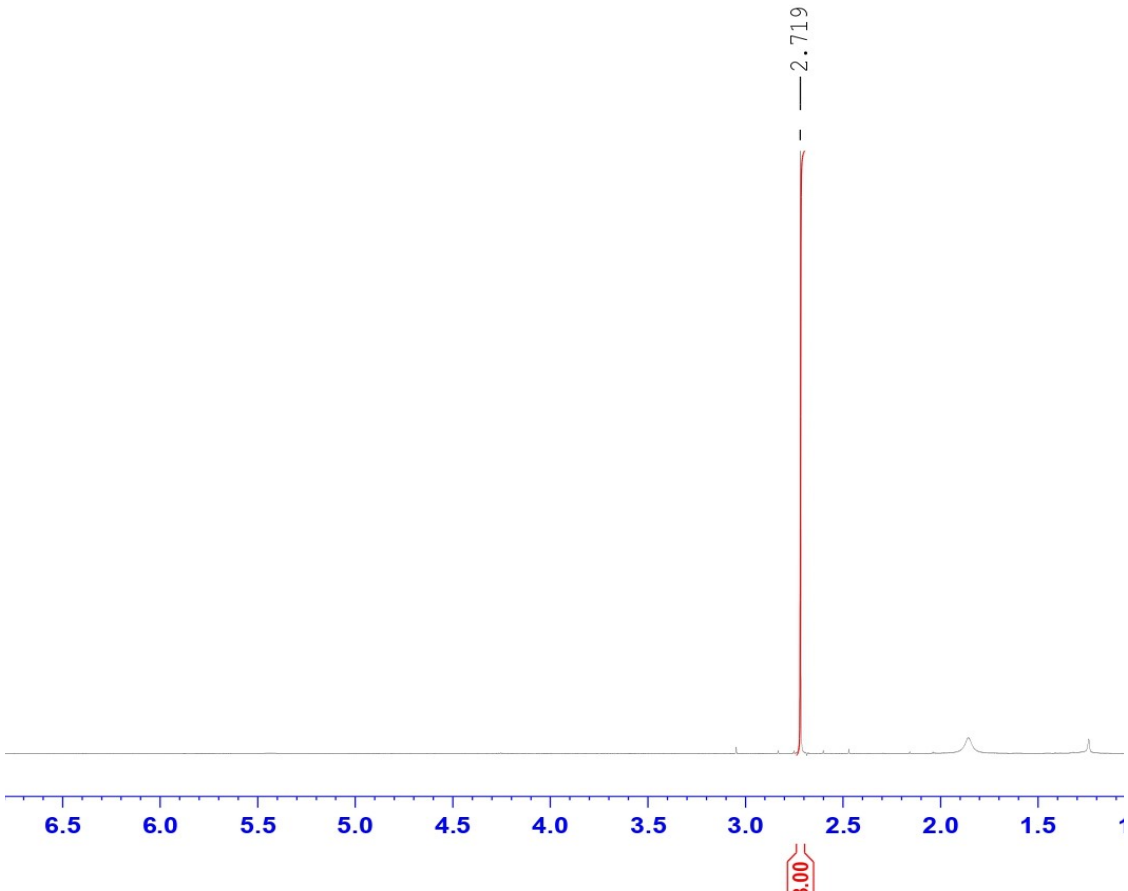
ethoxy-N-(1-phenylethyl)aniline



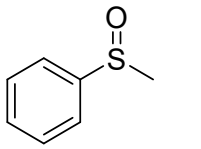
CD_3OD(4b)



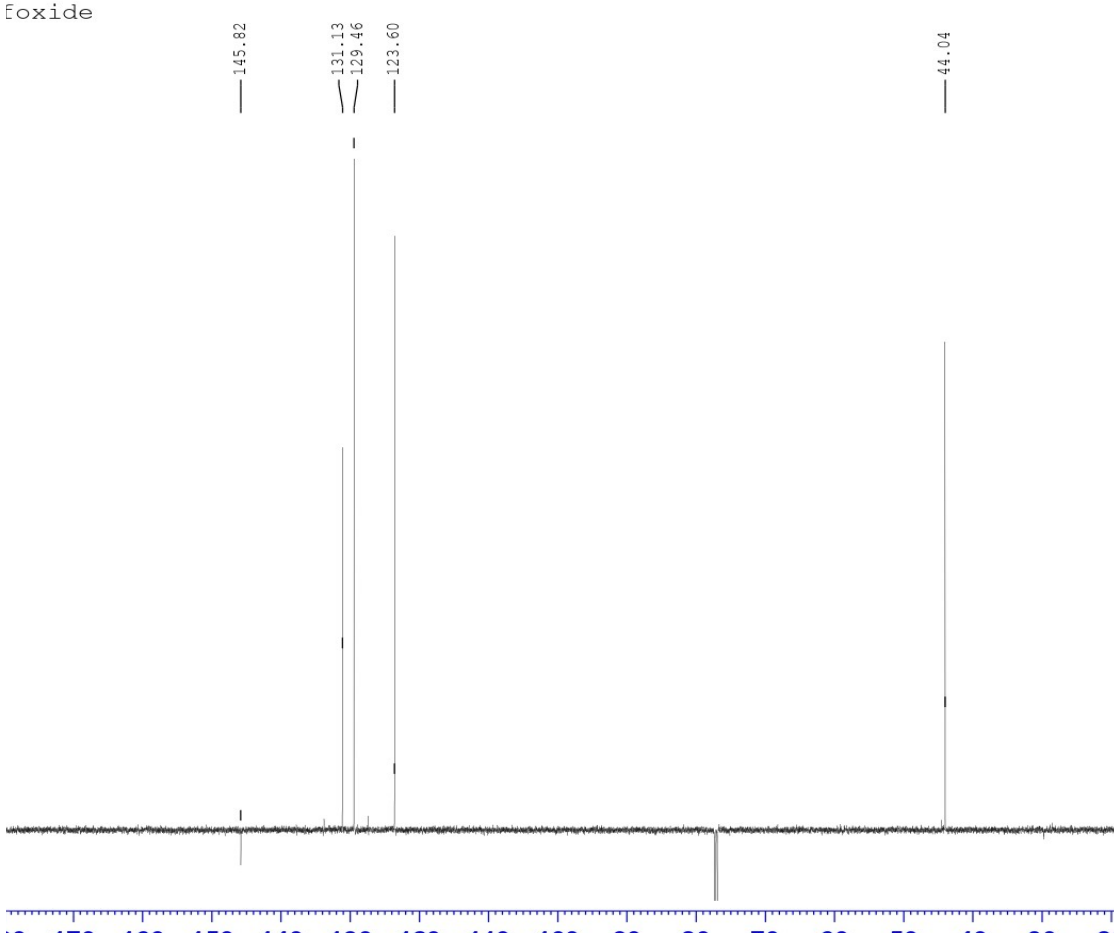
benzene



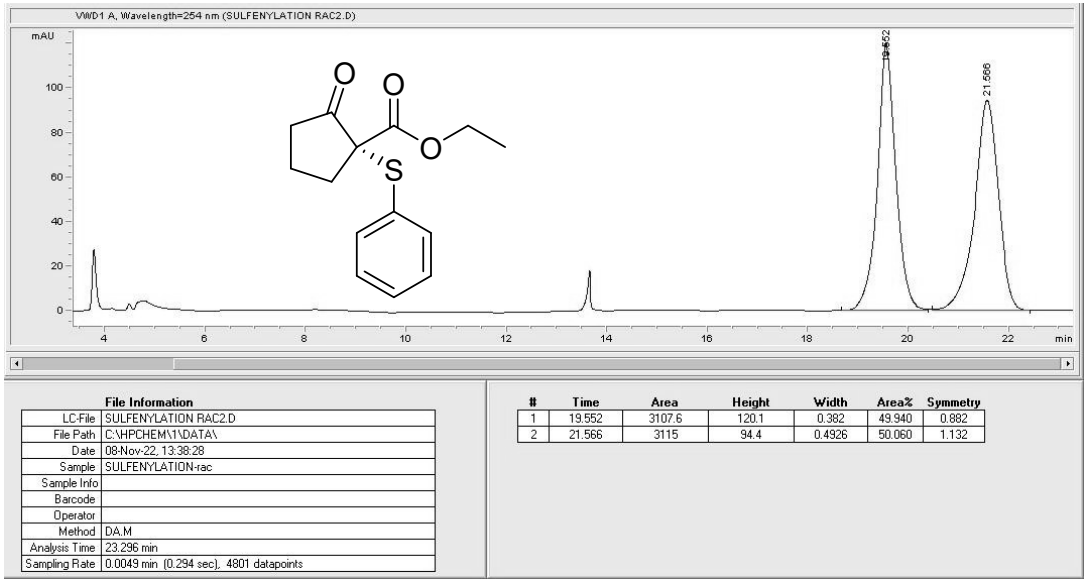
^{1}H NMR of methyl phenyl sulfoxide in $CDCl_3$ (5b)



foxide



^{13}C NMR of methyl phenyl sulfoxide in $CDCl_3$ (5b)



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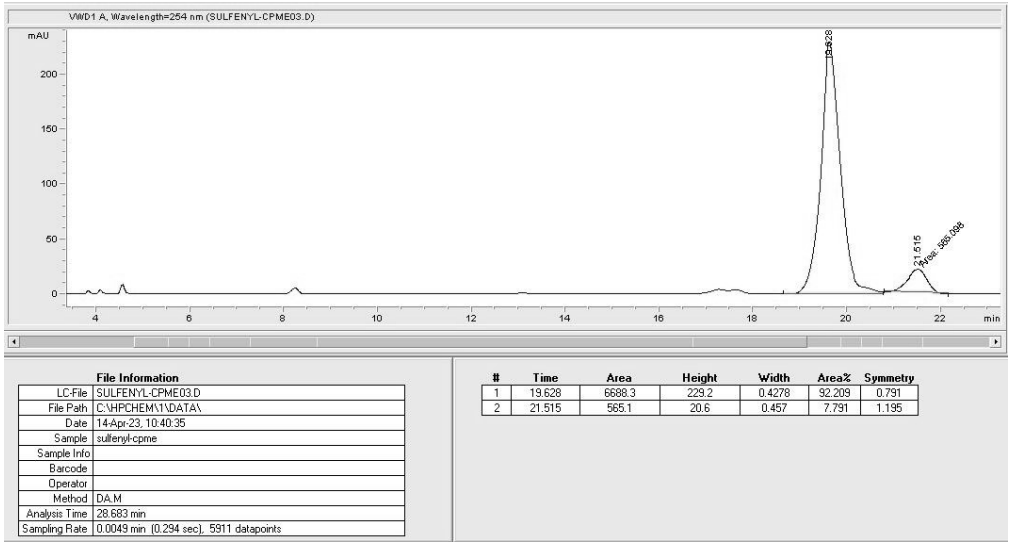
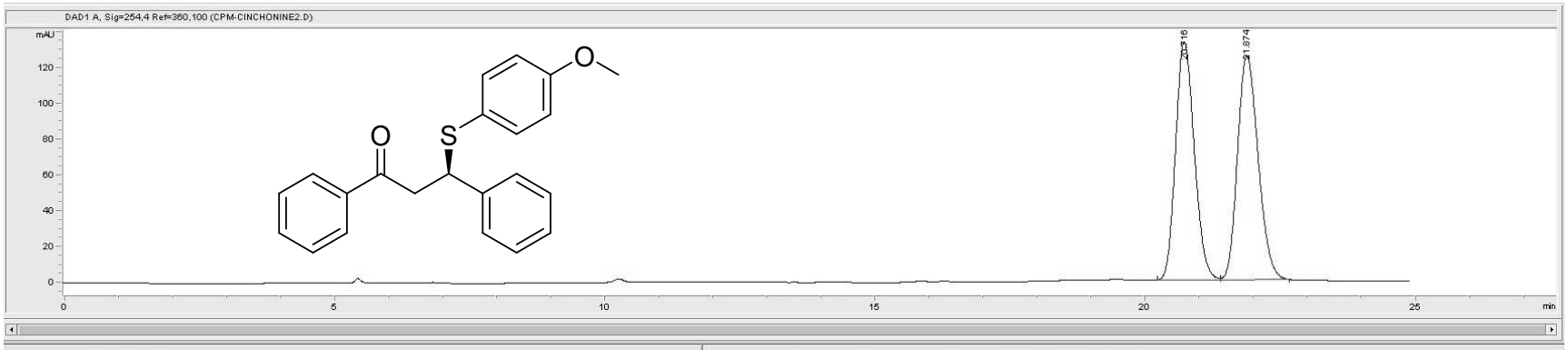
Sample Info	
Barcode	
Operator	
Method	DA.M
Analysis Time	23.296 min
Sampling Rate	0.0049 min (0.294 sec), 4801 datapoints

#	Time	Area	Height	Width	Area%	Symmetry
1	19.552	3107.6	120.1	0.382	49.940	0.882
2	21.566	3115	94.4	0.4926	50.060	1.132



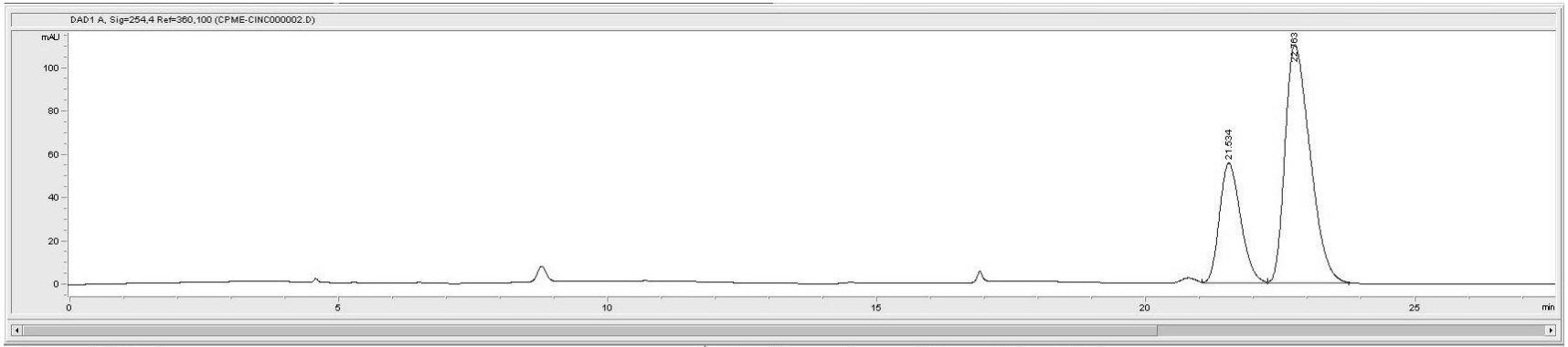
File Information	
LC-File	SULFENYL-CPME03.D
File Path	C:\HPCHEM\1\DATA\
Date	14-Apr-23, 10:40:35
Sample	sulfenyl-cpme
Sample Info	
Barcode	
Operator	
Method	DA.M
Analysis Time	28.683 min
Sampling Rate	0.0049 min (0.294 sec), 5911 datapoints

#	Time	Area	Height	Width	Area%	Symmetry
1	19.628	6688.3	229.2	0.4278	92.209	0.791
2	21.515	565.1	20.6	0.457	7.791	1.195



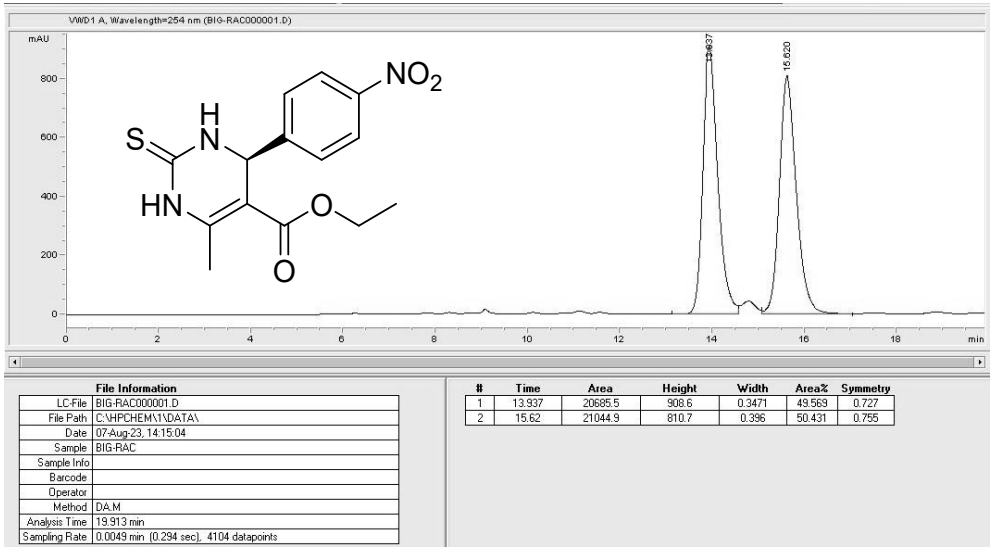
File Information	
LC-File	CPM-CINCHONINE2.D
File Path	C:\CHEM32\1\DATA\
Date	08-Mar-23, 16:52:57
Sample	cpme-cinchonine
Sample Info	cpme-cinchonine
Barcode	
Operator	
Method	DEF_LC2.M
Analysis Time	24.933 min
Sampling Rate	0.0067 min (0.402 sec), 3741 datapoints

#	Time	Area	Height	Width	Area%	Symmetry
1	20.716	3216.9	133.1	0.376	49.100	0.813
2	21.874	3334.9	125.3	0.4164	50.900	0.773



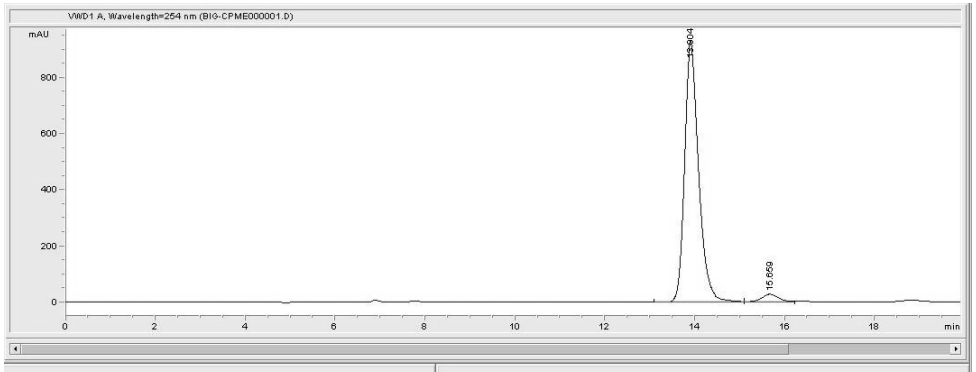
File Information	
LC-File	CPME-CINC000002.D
File Path	C:\CHEM32\1\DATA\
Date	05-Apr-23, 09:55:26
Sample	cpme-CINC
Sample Info	cpme-CINC
Barcode	
Operator	
Method	DEF_LC2.M
Analysis Time	37.08 min
Sampling Rate	0.0067 min (0.402 sec), 5563 datapoints

#	Time	Area	Height	Width	Area%	Symmetry
1	21.534	1525.8	55.5	0.4266	29.932	0.747
2	22.763	3571.7	110.3	0.4858	70.068	0.616



File Information	
LC-File	BIG-RAC000001.D
File Path	C:\HPCHEM\1\DATA\
Date	07-Aug-23, 14:15:04
Sample	BIG-RAC
Sample Info	
Barcode	
Operator	
Method	DA.M
Analysis Time	19.913 min
Sampling Rate	0.0049 min (0.294 sec), 4104 datapoints

#	Time	Area	Height	Width	Area%	Symmetry
1	13.937	20685.5	908.6	0.3471	49.569	0.727
2	15.62	21044.9	810.7	0.396	50.431	0.755



File Information	
LC-File	BIG-CPME000001.D
File Path	C:\HPCHEM\1\DATA\
Date	07-Aug-23, 15:32:21
Sample	BIG-CPME
Sample Info	
Barcode	
Operator	
Method	DA.M
Analysis Time	24.082 min
Sampling Rate	0.0049 min (0.294 sec), 4963 datapoints

#	Time	Area	Height	Width	Area%	Symmetry
1	13.904	20467.6	926.8	0.3392	96.179	0.734
2	15.659	813.2	28.8	0.4222	3.821	0.902

References

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