

Cyclopropenes as Potential Warheads for Inhibitors of Cysteine Proteases

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Abstract Over expression of cysteine proteases in human body causes neurodegenerative diseases, destruction of cartilage tissue, and bone atrophy, and some of them are implicated in destructive role of malignant tumors and cancer metastasis. Several non-human cysteine proteases play a key role in life cycles of certain foreign invasive organisms. Therefore, inhibition of cysteine proteases represents an important venue for finding potential therapeutic agents against Alzheimer's disease, multiple sclerosis, ischemic stroke, myocardial infarcts, carcinoma progression, as well as some parasitic and viral infections. Affinity labeling agents used as inhibitors of cysteine proteases normally bear an electrophilic "warhead", a reactive group that covalently binds the active site cysteine residue thereby inactivating the enzyme, but achieving *both* high activity and selectivity remains challenging. We are developing cyclopropene derivatives that show selective binding of thiol residues of cysteine. Several derivatives of cyclopropenes have been synthesized and evaluated as potential cysteine-binding "warheads". Their stability in aqueous media and reactivity toward cysteine and other amino acid chemical probes was examined. We have found that 1,2-cyclopropene moiety irreversibly binds the thiol group of cysteine, leaving other amino acid residues unaffected, which has the advantage for targeting enzymes expressed in foreign organisms or promoting carcinoma progression.

Keywords Cyclopropene, Cysteine, Thiol, Affinity Labeling

1. Introduction

Cysteine proteases are protein processing and protein degrading enzymes whose overexpression in human body may result in serious pathological changes. For instance, calpains, one type of cysteine proteases, are involved in Alzheimer disease, multiple sclerosis, stroke, myocardial

infarcts, cataract formation, *etc.*¹ Destruction of cartilage tissue and bone atrophy is the result of over expressed cathepsins,² which are also involved in carcinoma progression and metastasis.³ Other cysteine proteases play an essential role in life cycles of some viruses (*e.g.*, coronavirus⁴) and parasites (*e.g.*, malaria⁵). Therefore, developing inhibitors of cysteine proteases is an important target for organic and medicinal chemists.

The most efficient inhibitors of cysteine proteases bear an electrophilic "warhead" capable of covalently binding active site cysteine residues. Examples include species containing activated carbon-carbon double bonds,⁶ acyloxymethyl ketones,⁷ and a three-membered ring heterocycles (*e.g.*, epoxide,⁸ aziridine⁹), the latter generally having greater potency.⁹⁻¹⁰ Their activity, however, is strongly pH dependent, and the inhibition is not always restricted to cysteine proteases, often affecting aspartate and serine proteases as well.^{10a} Surprisingly, among carbocyclic unsaturated three-membered ring compounds, only cyclopropenone derivatives have been used as cysteine protease inhibitors,¹¹ and their binding appears to be reversible (**Figure 1**).^{11b} This suggests the addition of the cysteine thiol group to the 3-carbonyl, rather than to the cyclopropene double bond. To the contrary, 1,2-cyclopropene moiety irreversibly inhibits acyl desaturases, other enzymes where cysteine residue plays the catalytic role, by reaction with the cysteine residue of the active site, leaving other amino acid chemical probes unaffected.¹² It can, therefore, be hypothesized that inhibitors bearing a cyclopropene "warhead" will provide excellent drug candidates that will inhibit cysteine proteases selectively and irreversibly, which is particularly advantageous for targeting enzymes expressed in foreign organisms (*e.g.* falcipains in malaria parasite or C3-like protease in coronavirus) or those that are over expressed in neoplastic tissues (*e.g.* cathepsins L, B, H, and S).

In this paper, we report the synthesis of model cyclopropenes and their evaluation as potential warheads that could be incorporated into the existing cysteine protease inhibitors in order to increase their selectivity and potency.

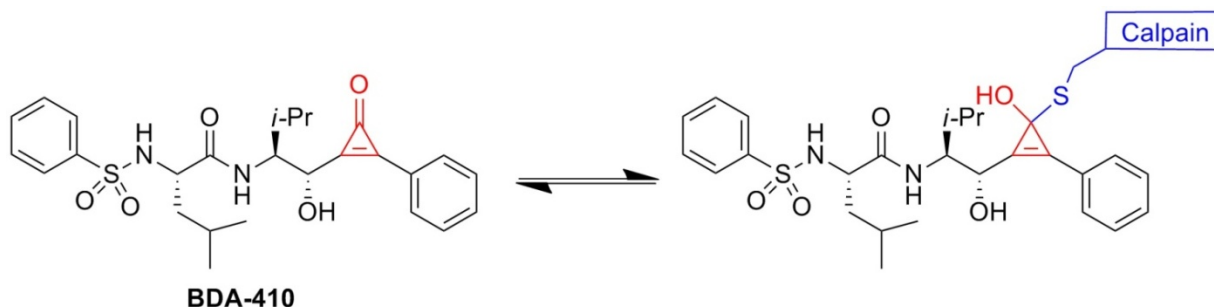
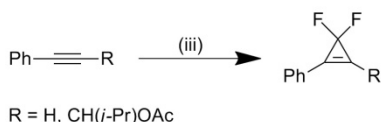
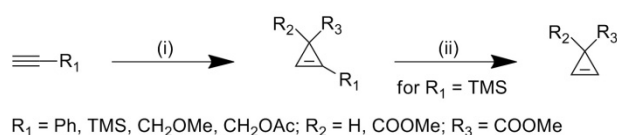


Figure 1. Cysteine protease inhibitor containing a cyclopropenone warhead and its mechanism of action.

2. Results and Discussion

There are three main routes¹³ to access cyclopropenes by synthesis: 1,2-elimination of cyclopropanes, cyclization of vinylcarbenes, and addition of carbenes to carbon-carbon triple bonds. The latter method represents, perhaps, the most plausible way to synthesize cyclopropenes, as it constructs the three membered ring by simultaneous formation of the two sigma bonds. Most importantly, it is not limited to free carbenes; metallocarbenoids also readily undergo reaction with alkynes, with dirhodium(II) catalyst being the most efficient for cyclopropanation of terminal alkynes using the corresponding diazo compounds¹⁴ to form the cyclopropene with the desired C3-substitution pattern. This method, however, does not work well for halocarbenes, as their metallocarbenoids react differently with terminal alkynes,¹⁵ so 3,3-difluorocyclopropenes were synthesized by addition of the difluorocarbene, generated in situ,¹⁶ to the alkynes (**Scheme 1**). Furthermore, 1-(trimethylsilyl)cyclopropene¹⁷ can be easily converted into 1,2-non-substituted cyclopropenes by hydrolysis in mild basic conditions.



Scheme 1. Synthesis of cyclopropenes by carbene addition to a triple bond. (i) $R_2R_3C=N_2$, $Rh_2(OAc)_4$, CH_2Cl_2 , r.t.; (ii) K_2CO_3 , THF/H_2O , r.t.; (iii) $TMSCF_3$, NaI , $110^\circ C$, 2h.

Our initial stability studies revealed that 3-monosubstituted cyclopropenes ($R_2=H$) and 1-phenyl-3,3-difluorocyclopropene were not stable for an extended

period of time, even in $CDCl_3$. The other halogenated analog, 1-phenyl-2-(1-acetoxy-2-methyl)propyl-3,3-difluorocyclopropene, albeit stable at room temperature in an aprotic solvent, rapidly decomposed upon the contact with a phosphate aqueous buffer (pH 7.4). Other cyclopropene derivatives turned out to be sufficiently stable toward hydrolysis, so we proceeded with studies of their reactivity toward N-acetyl cysteine methyl ester.

We, therefore, measured the pseudo-first-order reaction rates for each of the 3, 3-dicarboxymethylcyclopropenes with N-acetylcysteine methyl ester using 1H NMR spectroscopy in CD_3CN in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) needed to ionize the SH (without any base no reaction is observed) at $37^\circ C$. The reaction progress was monitored by disappearance of the cyclopropene hydrogen signal in 1H NMR (**Figure 2**). We found that the fastest reacting cyclopropene was the 1-phenyl derivative, while 1-alkyl substituted cyclopropenes reacted the slowest, displaying more than 459-826 fold difference (**Table 1**). This is consistent with the stabilization effect of 1-aryl group on the intermediate carbanion whose formation is commonly proposed (**Scheme 2**). Surprisingly, however, the reactivity of 1-trimethylsilyl-3,3-dicarboxymethylcyclopropene was somewhat lower, matching closely that of the parent 3, 3-dicarboxymethylcyclopropene, but still substantially higher than that of the 3-alkyl derivatives.

Table 1. Pseudo first order reaction rates

R	k (s^{-1})
Phenyl	1.1×10^{-2}
H	4.3×10^{-2}
TMS	4.2×10^{-2}
CH_2OMe	9×10^{-4}
CH_2OAc	5×10^{-4}

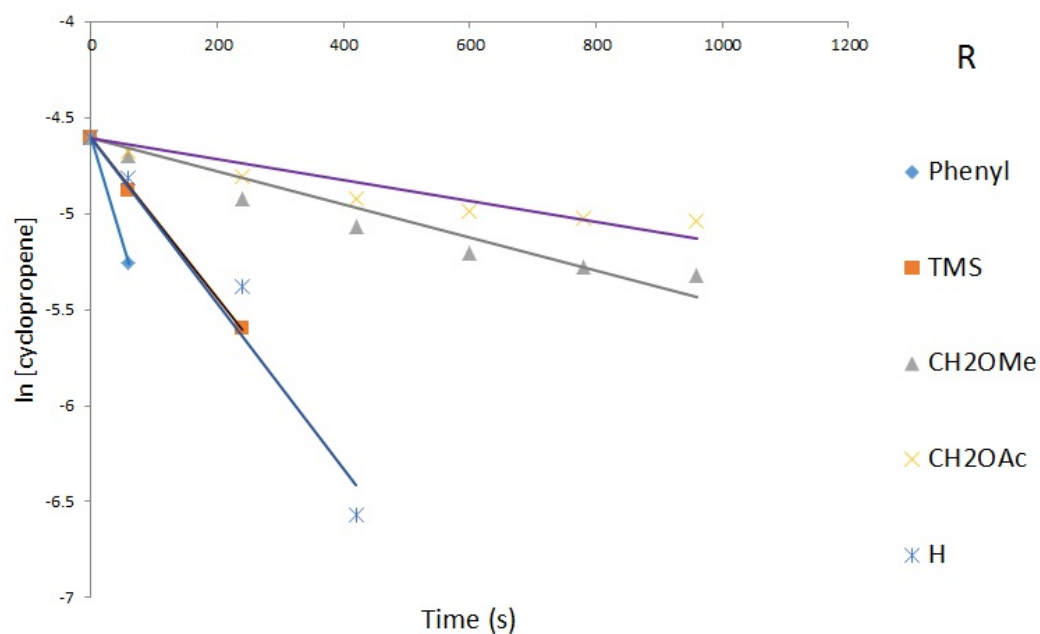
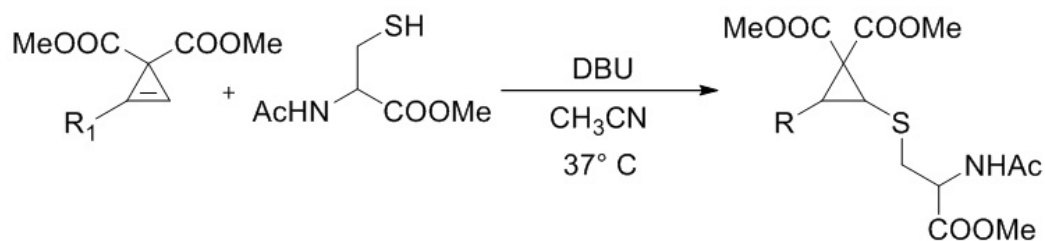
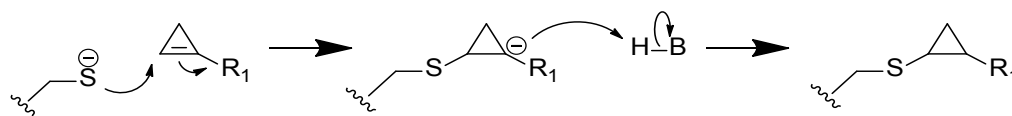


Figure 2. ^1H NMR studies to determine reaction rate for addition of cyclopropene derivatives to methyl *N*-acetylcysteinate



Scheme 2. Proposed mechanism of the thiol addition to cyclopropene

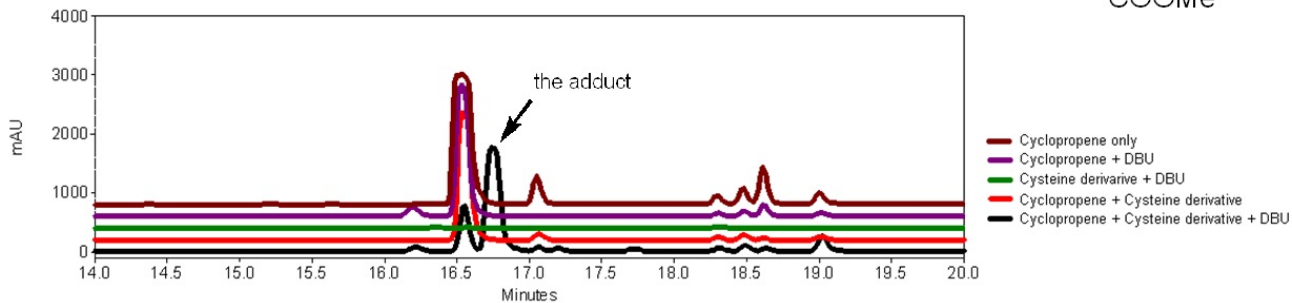
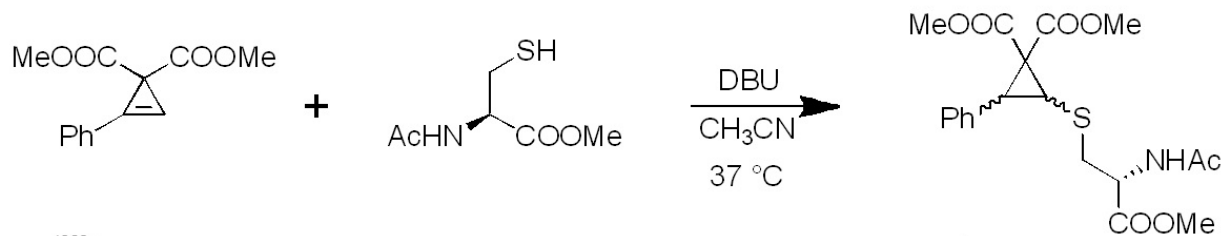


Figure 3. HPLC profile of the reaction of 1-phenyl-3,3-dicarboxymethylcyclopropene with methyl *N*-acetylcysteinate

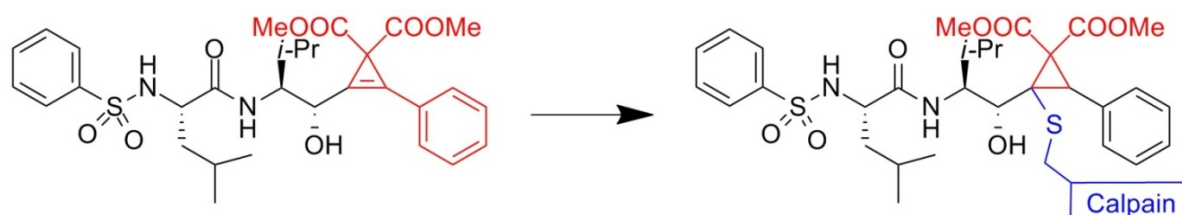


Figure 4. Proposed novel irreversible cysteine protease inhibitor with a cyclopropene warhead

The reaction of 1-phenyl-3,3-dicarboxy-methylcyclopropene with methyl *N*-acetylcysteinate, was profiled using HPLC with UV detection (**Figure 3**). The addition product was isolated as a diastomeric mixture and identified by NMR and HRMS spectroscopy. There was no reaction between either cyclopropene derivative in **Table 1** with similarly derivatized serine and aspartic acid.

Thus, 1-phenyl-3,3-dicarboxymethyl-cyclopropene appears to be the warhead of choice for the contemplated synthesis of the proposed irreversible inhibitor analogous to BDA-410 (**Figure 4**), as it is most reactive toward cysteine among all the reasonably stable cyclopropene derivatives identified in these studies.

3. Conclusions

We have determined that 1,3,3-trisubstituted cyclopropenes are sufficiently stable, reactive, and selective toward cysteine residues. Attachment of a phenyl substituent at C-1 capable of stabilizing an intermediate carbanion enhances the reactivity of the cyclopropene moiety toward cysteine residue, thereby making 1-phenylcyclopropenes promising warheads for potential cysteine protease inhibitors. The substitution at C3, however, has to be limited to carbon atoms, as 3,3-dihalo derivatives appear to be too reactive to be stable in aqueous media.

Acknowledgements

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Experimental

All chemicals, reagents, and solvents were purchased from Sigma-Aldrich Inc., TCI, and Fisher Scientific, Inc., and used as received. Unless stated otherwise, all reactions were carried out under an atmosphere of dry argon in oven-dried glassware. Indicated reaction temperatures refer to those of the reaction bath, while room temperature (rt) is noted as 25°C. Analytical thin layer chromatography (TLC) was performed with glass backed silica plates (5 x 20 cm, 60 Å, 250 µm). Visualization was accomplished using a 254 nm UV lamp. ¹H and ¹³C NMR spectra were recorded on either a Bruker Avance 400 MHz spectrometer or Bruker DPX 500

MHz spectrophotometer using solutions of samples in either of the deturated solvents: chloroform or acetonitrile. Chemical shifts are reported in ppm with tetramethylsilane as standard. Data are reported as follows: chemical shift, number of protons, multiplicity (s = singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, b = broad, m = multiplet), and coupling constants. High resolution mass spectral data were collected on a Shimadzu Q-TOF 6500. All novel compounds were characterized by ¹H, ¹³C NMR spectroscopy and high resolution mass spectrometry. Previously synthesized compounds were identified by comparison of their ¹H NMR to the published data (reference provided). Preparative high performance liquid chromatography (HPLC) was performed on an Agilent 1200 HPLC with UV detection.

Tosyl azide.¹⁸ To a solution of sodium azide (11.9 g, 62.5 mmol) in the mixture of water (15 mL) and 95% ethanol (25 mL) a solution of p-toluenesulfonyl chloride (4.475 g, 70 mmol) in 95% ethanol (125 mL) was added. After stirring at 40 °C for 3 hours, the solvent was removed *in vacuo*. The oily crude product was dissolved in diethyl ether, washed with water, dried using sodium sulfate and purified with hexane/ethyl acetate (6:1) to yield 11.6 g (84%) of product. ¹H NMR (CDCl₃, 400 MHz): δ 7.83 (d, *J* = 8.0 Hz, 2 H), 7.40 (d, *J* = 8.0 Hz, 2 H), 2.47 (s, 3 H).

Dimethyl diazomalonate.¹⁹ Dimethylmalonate (1.05 mL, 1.0 eq), triethylamine (1.4 mL, 1.1 eq) and tosyl azide (2 g, 1.0 eq) were dissolved in acetonitrile (20 mL). The solution was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure and partitioned between CH₂Cl₂ and water. The resulting solution was stirred for 1 hour at room temperature. The organic layer was collected, dried over anhydrous MgSO₄ and concentrated. Crude mixture was first filtered over a plug of silica gel (Pet ether/diethyl ether 1:1) to remove most of the tosylamide. The purification by silica gel chromatography with Pet ether/diethyl ether 1:1 afforded product as a yellow oil. ¹H NMR (CDCl₃, 400 MHz): δ 3.84 (s, 6 H).

General procedure for rhodium acetate mediated cyclopropenation.²⁰ To a solution of an appropriate alkyne (3.0 eq) and Rh₂(OAc)₄ (0.01 eq) in anhydrous CH₂Cl₂ solution of dimethyl diazomalonate (1.0 eq) in anhydrous CH₂Cl₂ was added dropwise using an automated syringe pump with the rate of 0.7 mL/hour at room temperature. After the completion of addition, reaction was stirred for additional 3 hours followed by filtration through a plug of

celite and purification using silica gel chromatography with hexane-ethyl acetate eluent system.

1-phenyl-3,3-dicarboxymethylcyclopropene.²⁰ (Yield: 81%) ¹H NMR (CDCl₃, 400 MHz): δ 7.64 (m, 2 H), 7.45 (m, 3 H), 6.90 (s, 1 H), 3.72 (s, 6 H)

1-trimethylsilyl-3,3-dicarboxymethylcyclopropene.¹⁷ (Yield: 92%) ¹H NMR (CDCl₃, 400 MHz): δ 7.04 (s, 1 H), 3.69 (s, 6 H), 0.24 (s, 9 H)

1-(acetoxy)methyl-3,3-dicarboxymethylcyclopropene.² (Yield: 47%) ¹H NMR (CDCl₃, 400 MHz): δ 6.71 (s, 1 H), 5.08 (s, 2 H), 3.73 (s, 6 H), 2.11 (s, 3 H)

1-(methoxy)methyl-3,3-dicarboxymethylcyclopropene.²¹ (Yield: 10%) ¹H NMR (CDCl₃, 400 MHz): δ 6.64 (t, *J* = 1.6 Hz, 1 H), 4.43 (d, *J* = 1.6 Hz, 2 H), 3.66 (s, 6 H), 3.36 (s, 3 H)

General procedure for TMS deprotection. 1-(trimethylsilyl)-3,3-disubstituted cyclopropene (1 g) was dissolved in 20 mL of regular THF. The resulting solution was cooled at 0 °C and 10% aq. K₂CO₃ was added dropwise. Upon completion of the addition, the reaction mixture was stirred for another 10 min at 0 °C, then for 24 hours while gradually warming up to room temperature. The solvent was removed under reduced pressure and crude mixture was purified using silica gel chromatography with hexane-ethyl acetate system.

3,3-dicarboxymethylcyclopropene.²² (Yield: 95%) ¹H NMR (CDCl₃, 400 MHz): δ 6.89 (s, 2 H), 3.70 (s, 6 H).

General procedure for difluorocarbene addition to a carbon-carbon triple bond.¹⁶ Appropriate alkyne (1 eq), anhydrous NaI (2.2 eq), TMSCF₃ (2 eq) were dissolved in anhydrous THF. The reaction mixture was heated overnight at 110 °C in a high pressure sealed tube. Upon cooling down, the mixture was quenched with saturated Na₂CO₃ solution, followed by extraction with diethyl ether. The organic phase was dried over anhydrous K₂CO₃. The solvent was removed under reduced pressure, and the residue was purified using silica gel chromatography with petroleum ether / triethylamine (40:1, v/v) as eluent.

1-phenyl-3,3-difluorocyclopropene.¹⁵ This compound

was not stable enough for subsequent studies.

1-phenyl-2-(1-acetoxy-2-methyl)propyl-3,3-difluorocyclopropene. (Yield: 43%) ¹H NMR (CDCl₃, 400 MHz): δ 7.63 (m, 2 H), 7.48 (m, 3 H), 5.76 (m, 1 H), 2.20 (s, 3 H), 2.22 (m, 1 H), 1.08 (d, 3 H, *J* = 6.9 Hz), 1.04 (d, 3 H, *J* = 6.8 Hz). ¹³C NMR (CDCl₃, 400 MHz): δ 169.97 (s), 131.23 (s), 130.34 (s), 129.10 (s), 128.57 (t, *J* = 10.8 Hz), 124.33 (t, *J* = 11.9 Hz), 123.36 (s), 102.09 (t, *J* = 273 Hz), 73.19 (s), 31.62 (s), 20.93 (s), 17.83 (s), 17.48 (s).

General procedure for reaction of modified cysteine with cyclopropenes. A solution of cyclopropene (1 eq.) and methyl *N*-acetylcysteinate (10 eq.) in 500 μL acetonitrile-D₃ was placed into the NMR tube, and DBU (2 mol%) was added. The mixture was stirred using a vortex and NMR was taken at regular time intervals. The rate of the reaction was calculated using disappearance of the characteristic cyclopropene peak.

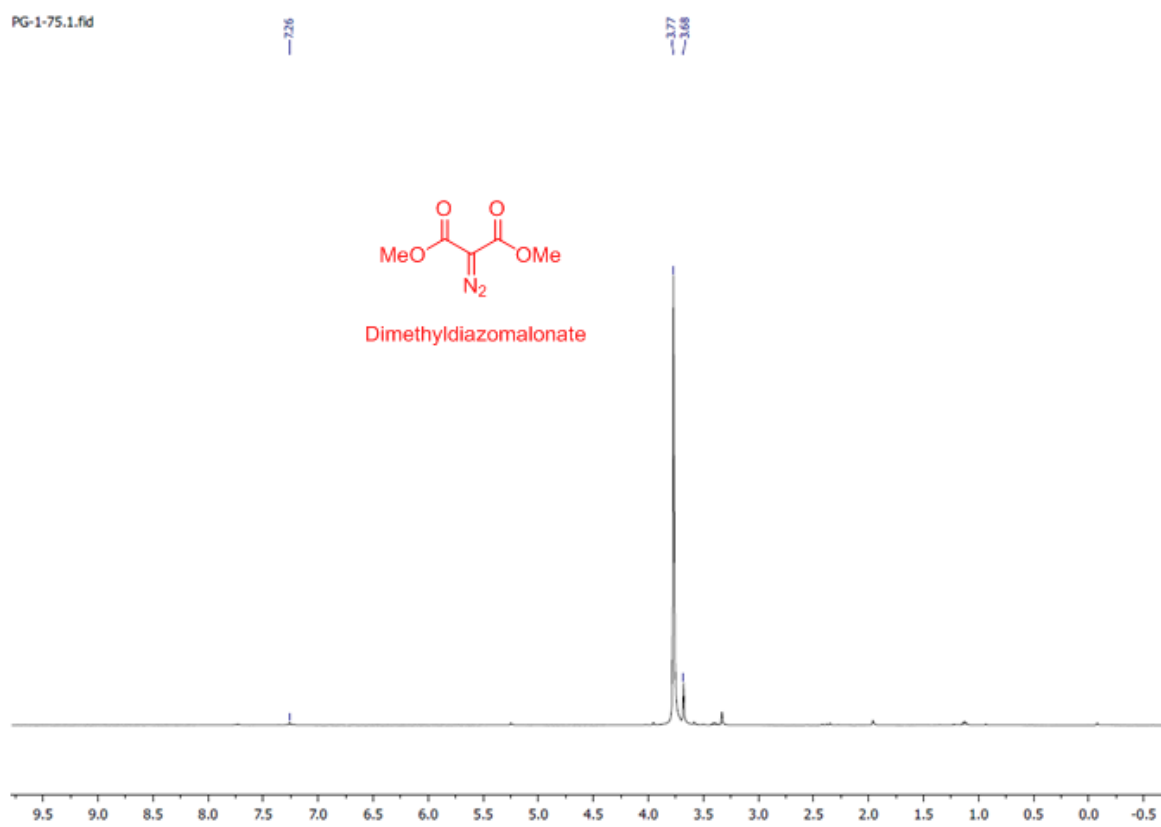
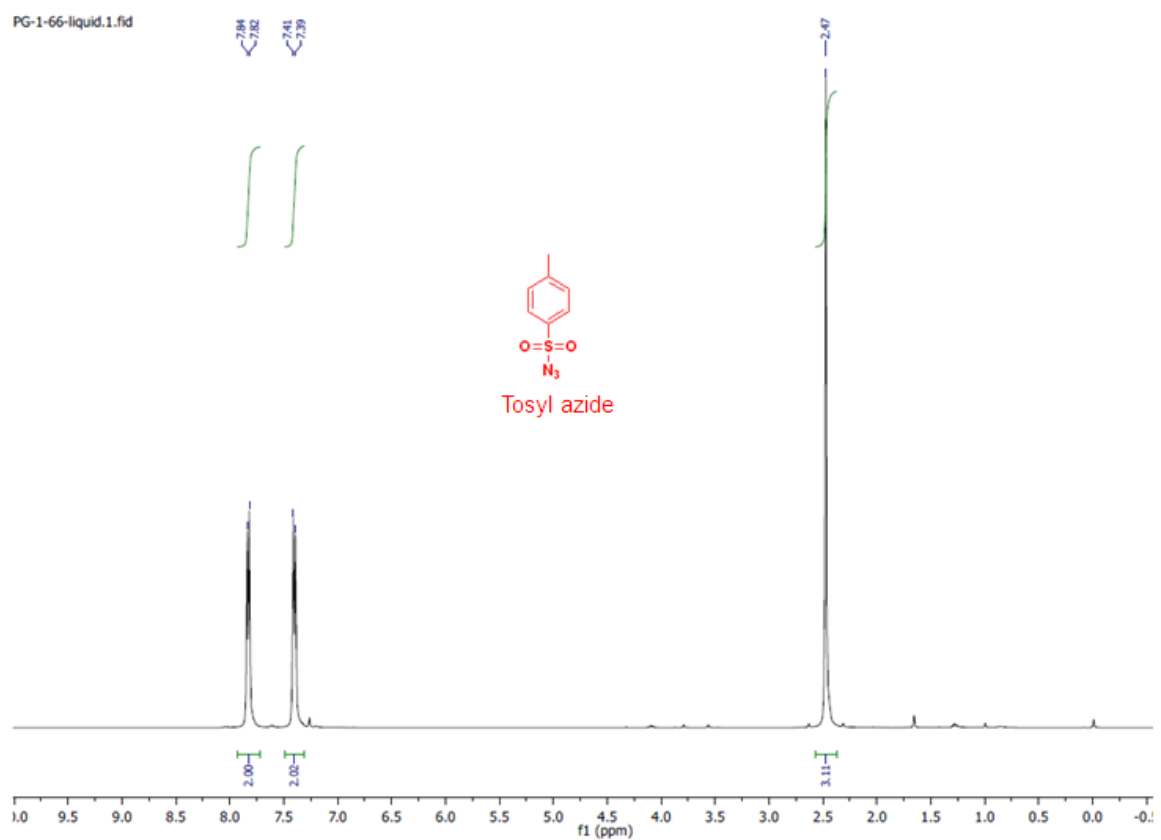
Methyl *N*-acetyl-S-(2-phenyl-3,3-dicarboxymethylcyclopropan-1-yl)cysteinate. The adduct between *N*-acetyl-cysteine methyl ester and 1-phenyl-3,3-dicarboxymethylcyclopropene was isolated by preparative HPLC using reverse-phase C18 column and acetonitrile/water = 5:95 to 50:50 as a mixture of stereoisomers (Yield: ca 15%). ¹H NMR (CDCl₃, 400 MHz): for major diastereomer δ 7.28 (m, 3 H), 7.20 (m, 2 H), 6.53 (d, 1 H, *J* = 6.9 Hz), 4.93 (m, 1 H), 3.85 (d, 3 H, *J* = 11.5 Hz), 3.78 (s, 3 H), 3.45 (d, 3 H, *J* = 5.6 Hz), 3.32 (t, 1 H, *J* = 8.3 Hz), 3.20 (m, 1 H), 3.07 (m, 1 H), 2.03 (d, 3 H, *J* = 8.2 Hz). ¹³C NMR (CDCl₃, 400 MHz): for major diastereomer δ 170.85, 169.95, 166.17, 166.17, 133.22, 128.69, 128.40, 127.77, 53.16, 52.81, 52.36, 46.13, 37.02, 35.78, 32.37, 31.20, 22.99. HRMS (ESI): *m/z* calculated for [M+Na]⁺ 432.1021, observed 432.1087

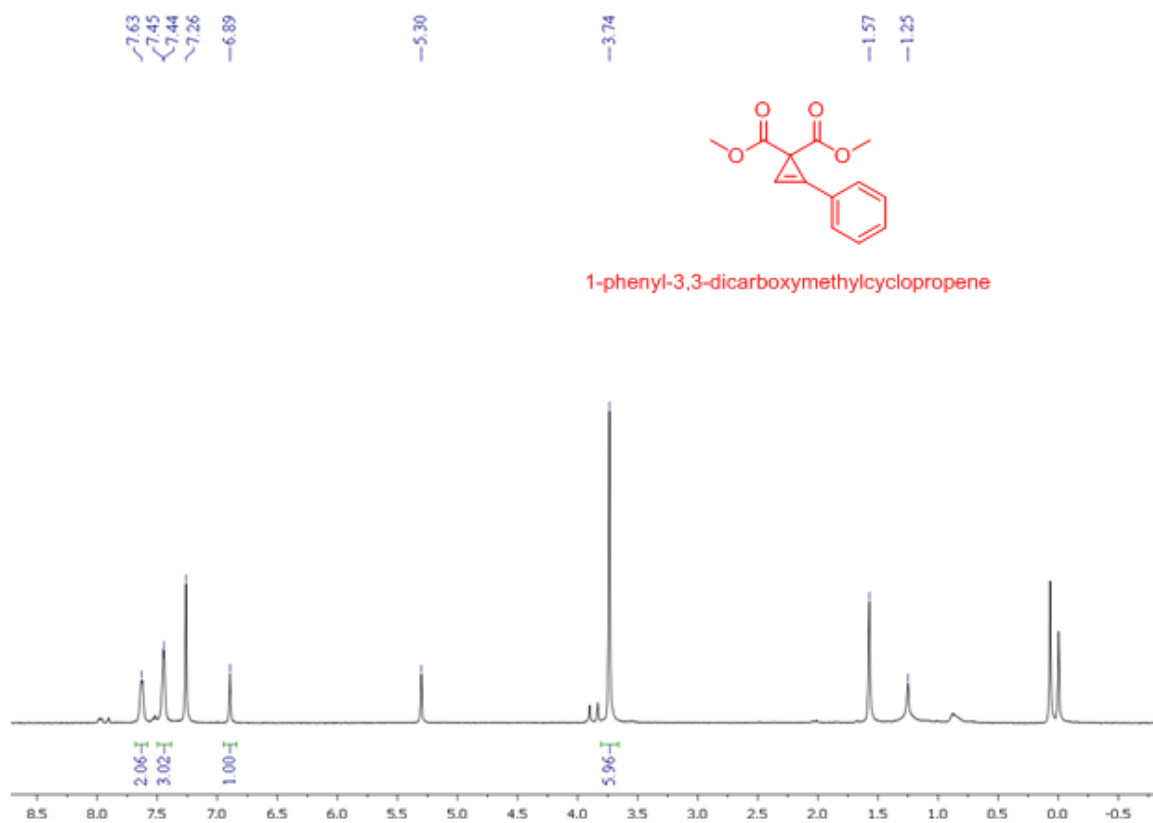
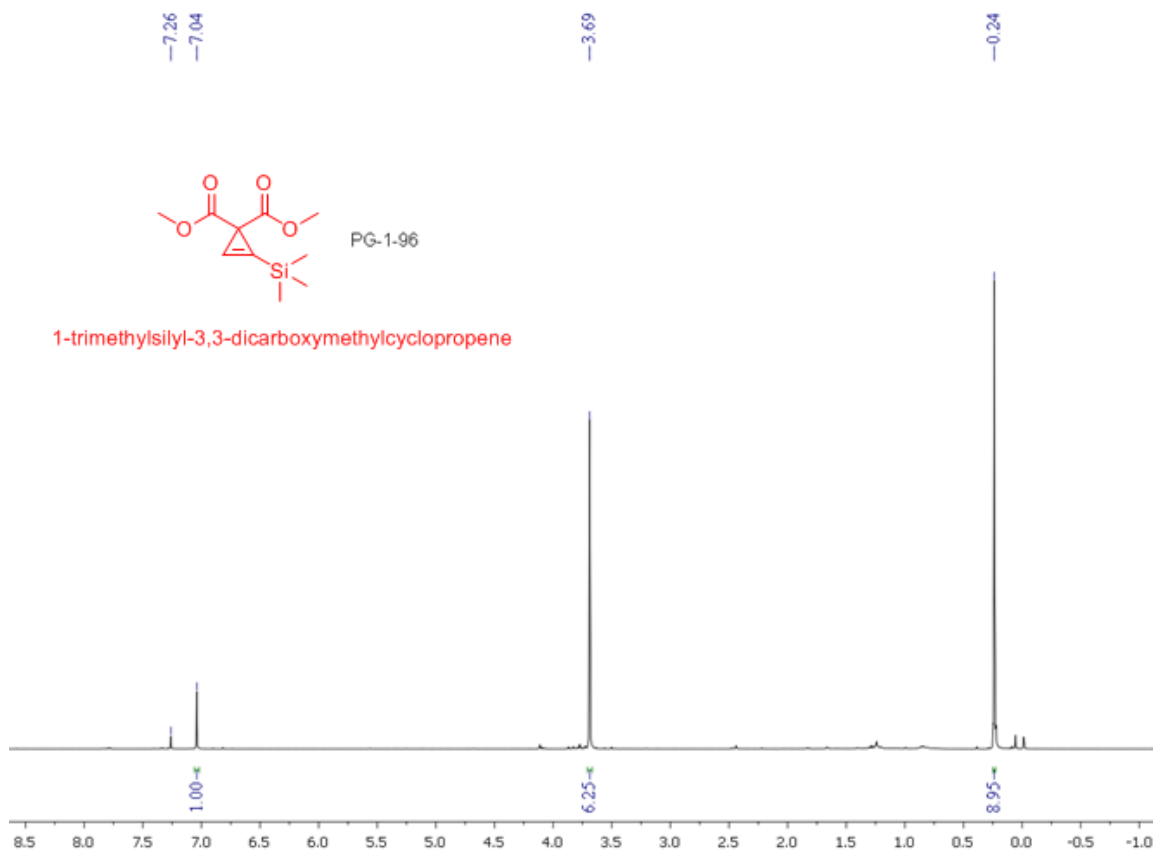
Supporting Information Available

¹H, ¹³C NMR and HRMS spectra of synthesized compounds.

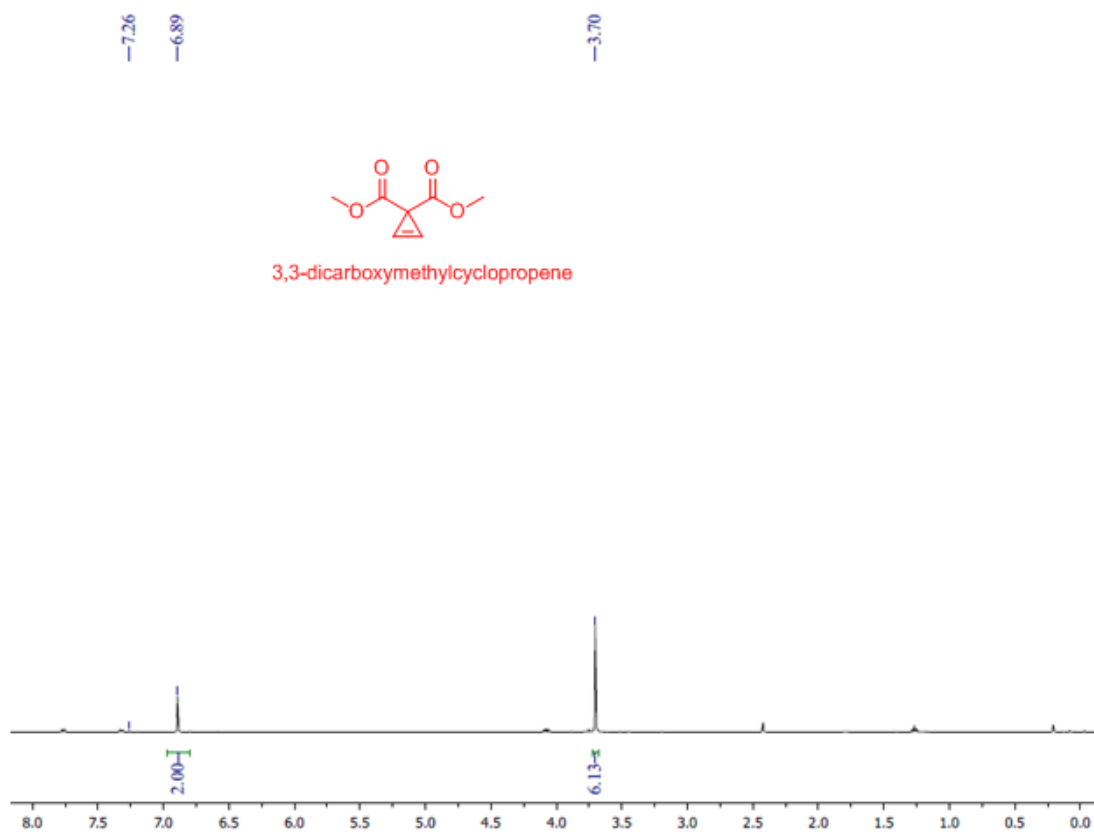
Supporting Information: Spectra (¹H, ¹³C, DEPT ¹³C, HRMS), HPLC profiling

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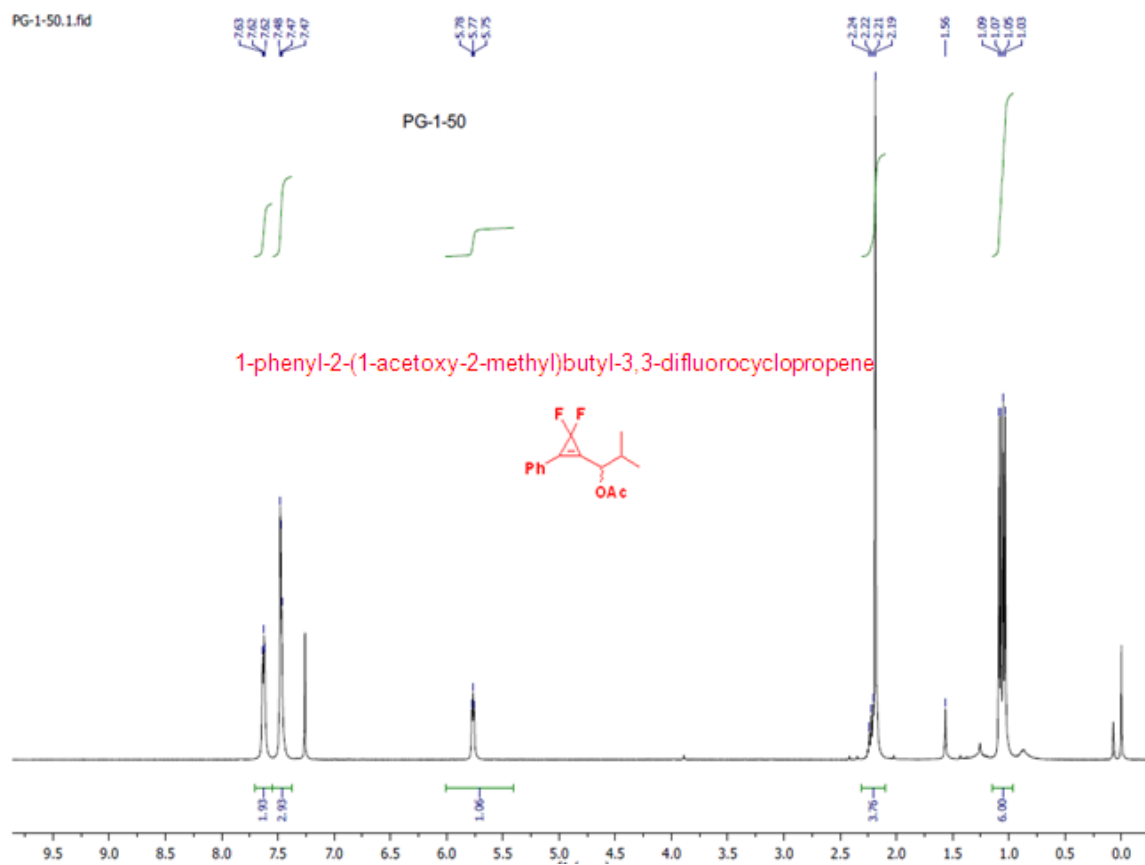


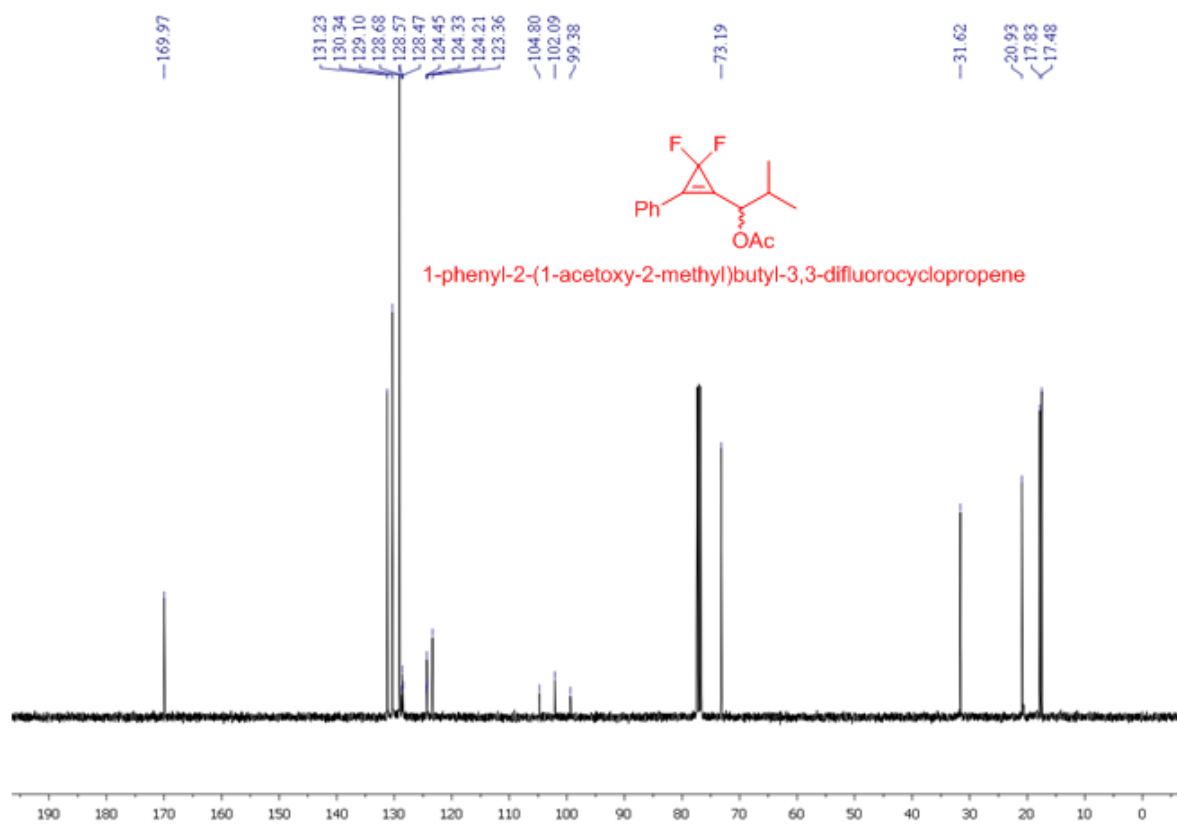
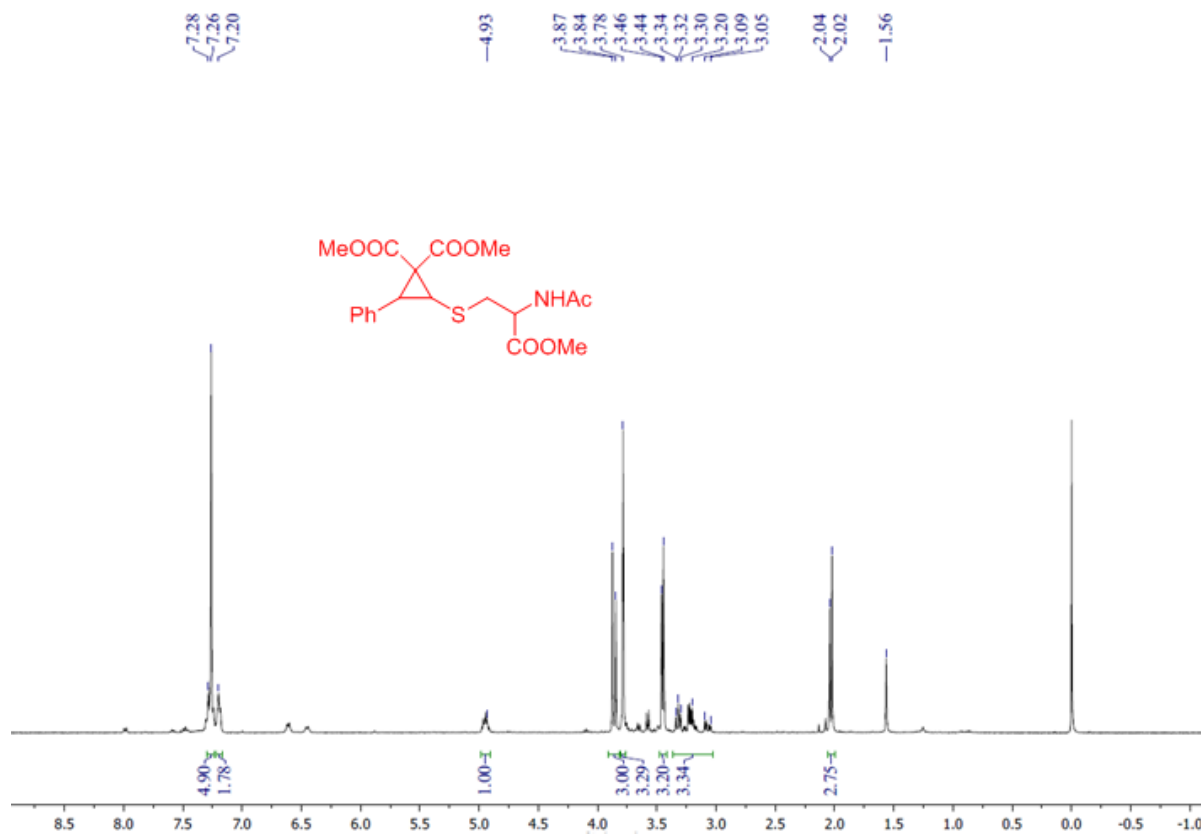
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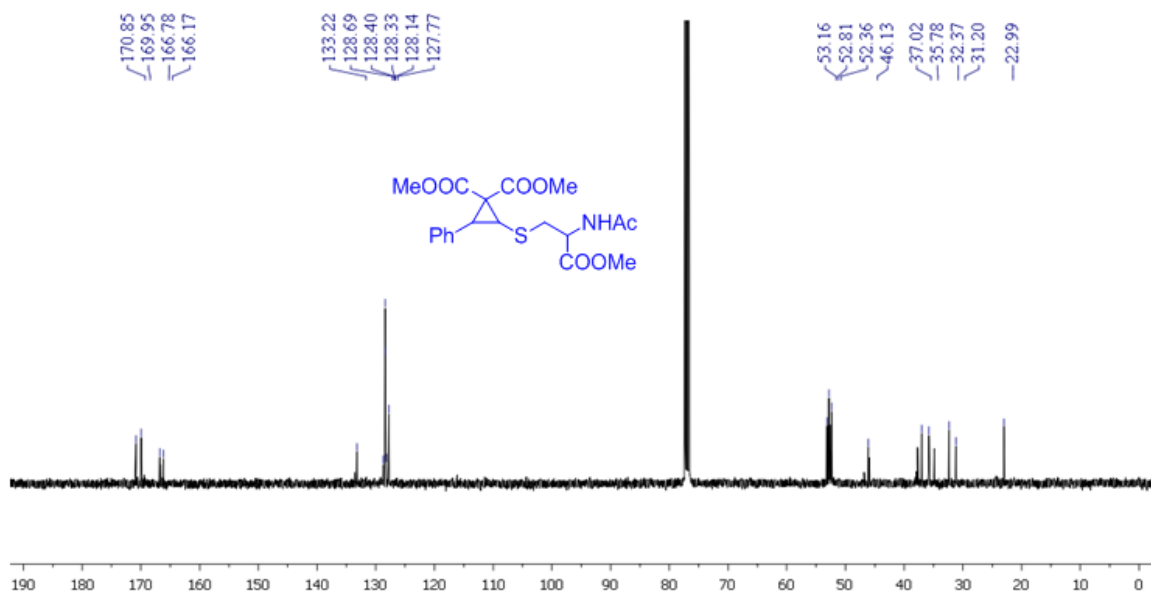


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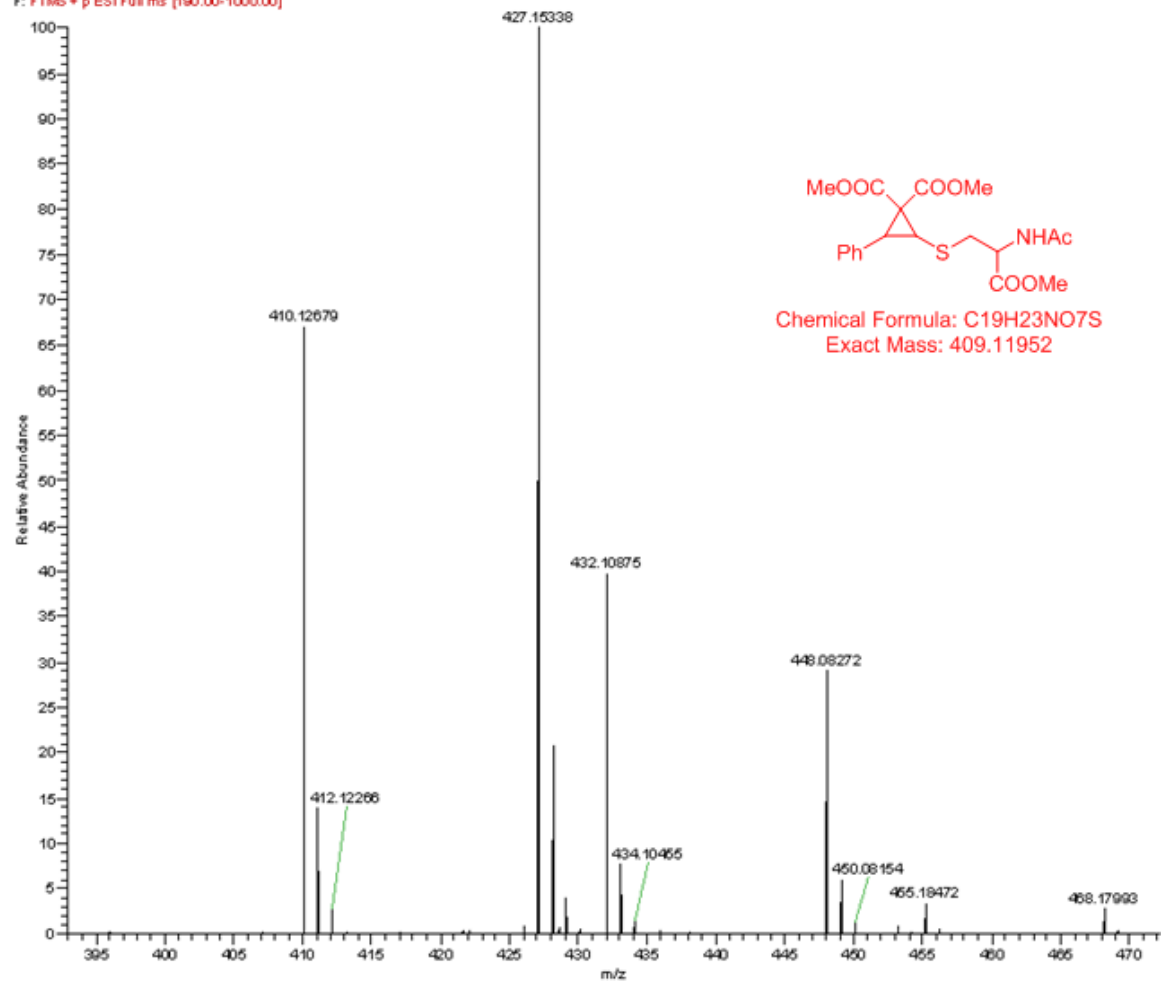


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