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, cataract formation, etc. Destruction of cartilage tissue and bone atrophy is the result of over expressed cathepsins, which are also involved in carcinoma progression and metastasis. Other cysteine proteases play an essential role in life cycles of some viruses (e.g., coronavirus) and parasites (e.g., malaria). 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, acyloxymethyl ketones, and a three-membered ring heterocycles (e.g., epoxide, aziridine), the latter generally having greater potency. 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. Surprisingly, among carbocyclic unsaturated three-membered ring compounds, only cyclopropenone derivatives have been used as cysteine protease inhibitors, and their binding appears to be reversible. 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. 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.

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. Destruction of cartilage tissue and bone atrophy is the result of over expressed cathepsins, which are also involved in carcinoma progression and metastasis. Other cysteine proteases play an essential role in life cycles of some viruses (e.g., coronavirus) and parasites (e.g., malaria). 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, acyloxymethyl ketones, and a three-membered ring heterocycles (e.g., epoxide, aziridine), the latter generally having greater potency. 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. Surprisingly, among carbocyclic unsaturated three-membered ring compounds, only cyclopropenone derivatives have been used as cysteine protease inhibitors, and their binding appears to be reversible. 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. 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.
2. Results and Discussion

There are three main routes 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; metalloccarbenoids also readily undergo reaction with alkynes, with dirhodium(II) catalyst being the most efficient for cyclopropenation of terminal alkynes using the corresponding diazo compounds to form the cyclopropene with the desired C3-substitution pattern. This method, however, does not work well for halo carbenes, as their metallocarbenoids react differently with terminal alkynes, so 3,3-difluorocyclopropenes were synthesized by addition of the difluorocarbene, generated in situ, to the alkynes (Scheme 1). Furthermore, 1-(trimethylsilyl)cyclopropene can be easily converted into 1,2-non-substituted cyclopropenes by hydrolysis in mild basic conditions.

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-acetyl cysteine methyl ester using $^1$H NMR spectroscopy in CD$_3$CN 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 °C. The reaction progress was monitored by disappearance of the cyclopropene hydrogen signal in $^1$H 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| $1.1 \times 10^2$ |
| H     | $4.3 \times 10^2$ |
| TMS   | $4.2 \times 10^2$ |
| CH$_3$OMe | $9 \times 10^4$ |
| CH$_2$OAc | $5 \times 10^4$ |
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Figure 2. $^1$H 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 $N$-acetyl cysteinate
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 diasteromeric 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 carbamion 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. 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. 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. 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.  
\[\text{Yield: 81\%} \]  
\[\text{\textit{^1}H NMR (CDCl}_3, 400 MHz): \delta 7.64 (m, 2 H), 7.45 (m, 3 H), 6.90 (s, 1 H), 3.72 (s, 6 H)\]

1-trimethylsilyl-3,3-dicarboxymethylcyclopropene.  
\[\text{Yield: 92\%} \]  
\[\text{\textit{^1}H NMR (CDCl}_3, 400 MHz): \delta 7.04 (s, 1 H), 3.69 (s, 6 H), 0.24 (s, 9 H)\]

1-(acetoxy)methyl-3,3-dicarboxymethylcyclopropene.  
\[\text{Yield: 47\%} \]  
\[\text{\textit{^1}H NMR (CDCl}_3, 400 MHz): \delta 6.71 (s, 1 H), 5.08 (s, 2 H), 3.73 (s, 6 H), 2.11 (s, 3 H)\]

1-(methoxy)methyl-3,3-dicarboxymethylcyclopropene.  
\[\text{Yield: 10\%} \]  
\[\text{\textit{^1}H NMR (CDCl}_3, 400 MHz): \delta 6.64 (t, J = 1.6 Hz, 1 H), 4.43 (d, J = 1.6 Hz, 2 H), 3.66 (s, 6 H), 3.36 (s, 3 H)\]

General procedure for TMS deprotection.  
1-(trimethyl)silyl-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.  
\[\text{Yield: 95\%} \]  
\[\text{\textit{^1}H NMR (CDCl}_3, 400 MHz): \delta 6.89 (s, 2 H), 3.70 (s, 6 H)\]

General procedure for difluorocarbene addition to a carbon-carbon triple bond.  
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.  
This compound was not stable enough for subsequent studies.

1-phenyl-2-(1-acetoxy-2-methyl)propyl-3,3-difluorocyclopropene.  
\[\text{Yield: 43\%} \]  
\[\text{\textit{^1}H NMR (CDCl}_3, 400 MHz): \delta 7.63 (m, 2 H), 7.48 (m, 3 H), 5.76 (m, 1 H), 2.20 (s, 3 H), 2.22 (m, 1 H), 1.08 (d, 3 H, J = 6.9 Hz), 1.04 (d, 3 H, J = 6.8Hz). \text{\textit{^13}C NMR (CDCl}_3, 400 MHz): \delta 169.97 (s), 131.23 (s), 130.34 (s), 129.10 (s), 128.57 (t, J = 10.8 Hz), 124.33 (t, J = 11.9 Hz), 123.36 (s), 102.09 (t, J = 273 Hz), 73.19 (s), 31.62 (s), 20.93 (s), 17.83 (s), 17.48 (s)\]

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\%).  
\[\text{\textit{^1}H NMR (CDCl}_3, 400 MHz): \text{for major diastereomer } \delta 7.28 (m, 3 H), 7.20 (m, 2 H), 6.53 (d, J = 6.9 Hz), 4.93 (m, 1 H), 4.43 (d, J = 1.6 Hz, 2 H), 3.66 (s, 6 H), 3.36 (s, 3 H)\]

Supporting Information Available

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

Supporting Information: Spectra (1H, 13C, DEPT 13C, HRMS), HPLC profiling
Solvent: CDCl₃
Solvent: CDCl₃

1-phenyl-3,3-dicarboxymethylcyclopropene

Solvent: CDCl₃

1-trimethylsilyl-3,3-dicarboxymethylcyclopropene
Solvent: CDCl$_3$

3,3-dicarboxymethylcyclopropane

Solvent: CDCl$_3$

1-phenyl-2-(1-acetoxy-2-methyl)butyl-3,3-difluorocyclopropane
Solvent: CDCl₃

![NMR Spectrum 1](image1)

1-phenyl-2-(1-acetoxy-2-methylbutyl)-3,3-difluorocyclopropane

Solvent: CDCl₃

![NMR Spectrum 2](image2)

MeOOC

Ph

S

NH₂Ac

COOMe

COOMe

4.03

1.78

1.90

2.00

2.39

2.39

2.39

2.39

2.39
Solvent: CDCl₃
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