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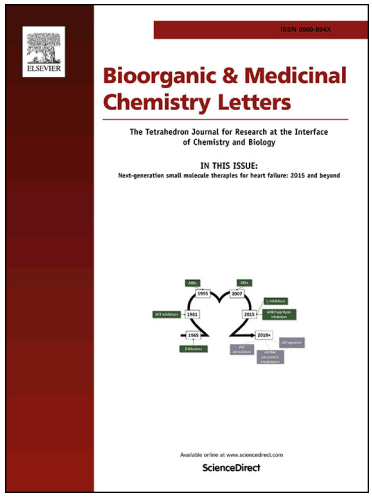

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The mimics of N$^{\varepsilon}$-acyl-lysine derived from cysteine as sirtuin inhibitors

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ABSTRACT

Sirtuin inhibitors as physiological research tools and therapeutic potentials have caught many attentions in last decades. The mimics of acyl lysine have been approved to be a very efficient strategy for development of mechanism-based sirtuin inhibitors. In current study, a novel scaffold of *L*-S-(3-carboxamidopropyl) cysteine (*L*-CAPC) has been exploited for design and synthesis of sirtuin inhibitors. As a result, the mimics of N ε -acyl-lysine derived from cysteine including small molecules (**5a-m**) and peptides (**9a-m**) have been synthesized. Among these, the peptides **9g** and **9h** were found to be the most inhibitory potency and selectivity against SIRT2.

Sirtuins are a class of enzymes recently re-recognized as nicotinamide adenine dinucleotide (NAD^+)-dependent deacylases[1-6]. By deacylating lysine residues of proteins, they regulate the activity of many proteins and have been shown to be involved in several important biological processes, including life span, transcription, genome stability, metabolism and protein secretion[4-6]. Sirtuin inhibitors are important pharmacological research tools that can be used to further study the biology of sirtuins[4]. Furthermore, it has been reported that sirtuin inhibitors have potential in treating several human diseases, including diabetes, inflammation, cancer, Parkinson's disease and other metabolic and neurodegenerative diseases[7-9]. Therefore, there is continued interest in developing better sirtuin inhibitors with various and variable scaffolds.

Since the catalytic mechanism of the sirtuin-catalyzed deacylation reaction has been well established[10-14], mechanism-based inhibitors for sirtuins have been extensively studied[4, 15]. One type of these mechanism-based sirtuin inhibitors are thioacetyl lysine analogs developed by Zheng group[16] and Denu group[13], respectively. It was shown that thio-acetyl lysine-containing peptide can undergo a sirtuin-catalyzed reaction with NAD^+ to form a covalent and installed intermediate (e.g., α-1'-*S*-alkylamidate or α-1'-*S*-bicyclic intermediate)[17-20], similar to the enzymatic reaction with acetyl lysine peptides[13, 14]. However, the covalent intermediate formed with thioacetyl lysine peptide is more stable and it occupies the sirtuin active site, blocking its normal enzymatic activity[13]. Therefore, thioacetyl amide as one of acetyl amide isosteres was also called as one kind of sirtuin inhibitory warhead (Fig. 1)[15, 21]. To improve the inhibitory potency, some sirtuin inhibitors have been developed with modified acetyl amide moieties as inhibitory warheads[15, 21], such as α-fluoroacetyl amide[13, 22-24], seleno- amide[25-27], hydrazide-containing amide[28], and ethyl malonyl amide (Fig. 1) [29].

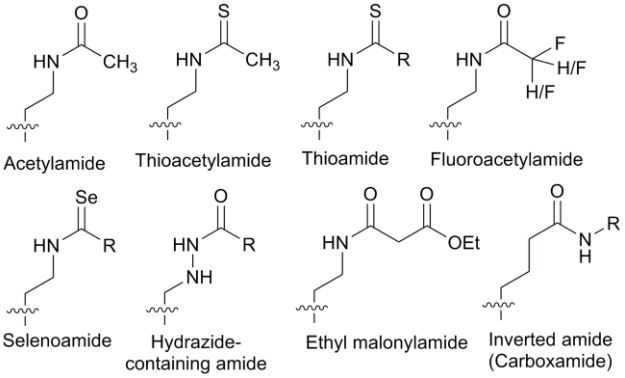


Figure 1. Mechanism-based sirtuin inhibitors with various acetylamide isosteres as inhibitory warheads (R stands for different substitute groups).

Although the thioamide lysine peptides or non-peptide analogs have been shown to demonstrate potent sirtuin inhibition, many concerns have been raised about the potential metabolic toxicity, especially hepatotoxicity, associated with the scaffold of the thioamide[30-34]. Thiourea group as another amide isostere have been successfully introduced to design and synthesis of sirtuin inhibitors to avoid such possible toxicity. Thiourea lysine analogs have been approved to be potent sirtuin inhibition in a similar manner to that thioamides-based sirtuin inhibitors[35-38]. Another attempt to maintain the inhibitory potency and selectivity and simultaneously avoid the possible toxicity along with thioamide

is to utilized the scaffold of *L*-α-aminosuberic acid (*L*-Asu) to construct sirtuin inhibitors, which resulting in L-2-amino-7-carboxamidoheptanoic acid (*L*-ACAH) containing acetyl lysine analogs with an "inverted amide" by isosteric swapping of the NH and the CH_3 groups of the acetyl amide of acetyl lysine (Fig. 1 and Fig. 2). These analogs with a minor change of the swapping are similar to their native amide substrates and thus show more potent sirtuin inhibition[39, 40]. Additionally, the carboxamide group of *L*-ACAH as a novel inhibitory warhead is a common functional group in drug molecules[15]and the side chain of *L*-ACAH may have better potential for binding the tunnel toward the catalytic pocket of sirtuin[39, 40].

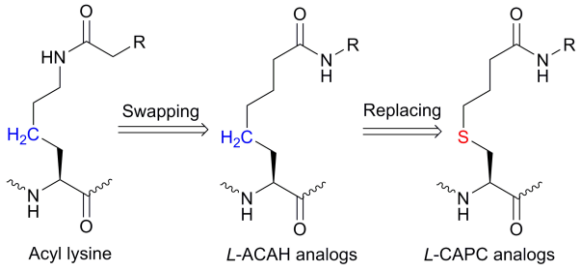
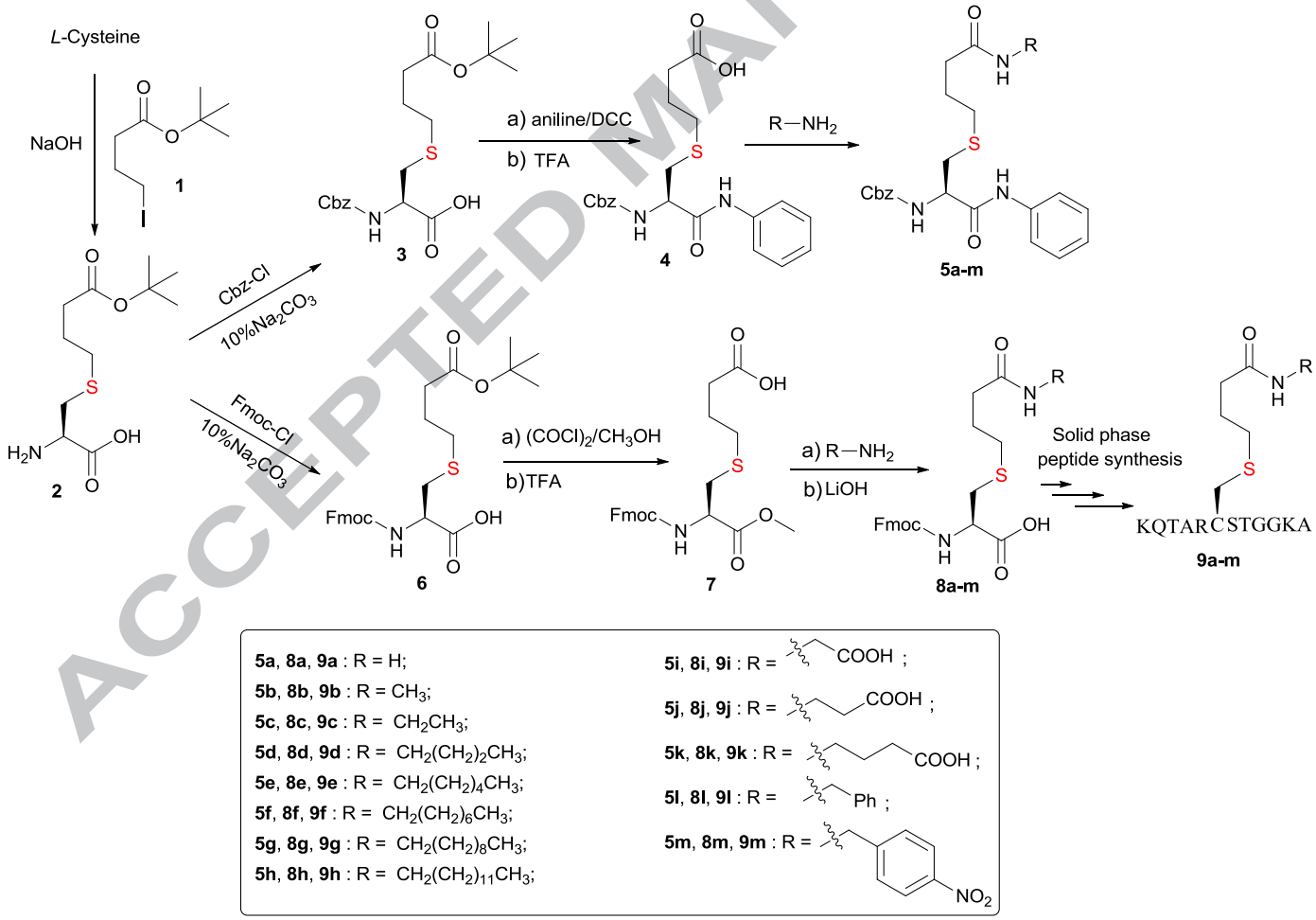


Figure 2. The mimics (*L*-CAPC analogs) of N^{ε}-acyl-lysine derived from cysteine (R stands for different substitute groups).

starting material of *L*-α-aminosuberic acid (*L*-Asu) is not readily available since it's not a nature amino acid. To solve this issue and further develop novel sirtuin mechanism-based inhibitors, we could simply replace the methylene at 4-position of *L*-ACAH with the atom of sulphur to give a novel scaffold of *L*-S-(3-carboxamidopropyl) cysteine (*L*-CAPC), which could be easily synthesized by starting from *L*-cysteine, a nature amino acid (Fig. 2)[41, 42]. Because there is not much attempts to use this strategy[5, 43] and sirtuins recently have been found to preferentially remove some novel acyl groups other than the typical group of acetyl, like malonyl[44], succinyl[44], glutaryl[45], crotonyl[46], myristoyl[47] and so on[5, 48], we would like to report herein the design and synthesis of novel *L*-CAPC analogs with different acyl groups (small molecules **5a-m** and peptides **9a-m**, Fig.3) and the following investigation of their sirtuin inhibitory potency.

As shown in Fig. 3, unprotected cysteine as a starting material was alkylated at the atom of sulfur with 4-iodobutyric acid tert-butyl ester (**1**) to give the key intermediate of amino acid **2** with a side chain containing an atom of sulfur as the same length of *L*-α-aminosuberic acid's[49]. For the synthesis of *L*-CAPC small molecules **5a-m**, the amino group of amino acid **2** was first protected with carbobenzoxy (Cbz) group to give the compound **3**, which was condensed with aniline and then followed by removal of tert-butyl group with trifluoroaceticacid (TFA) to give



5a, **8a**, **9a** : R = H;
5b, **8b**, **9b** : R = CH_3;
5c, **8c**, **9c** : R = CH_2CH_3;
5d, **8d**, **9d** : R = $CH_2(CH_2)_2CH_3$;
5e, **8e**, **9e** : R = $CH_2(CH_2)_4CH_3$;
5f, **8f**, **9f** : R = $CH_2(CH_2)_6CH_3$;
5g, **8g**, **9g** : R = $CH_2(CH_2)_8CH_3$;
5h, **8h**, **9h** : R = $CH_2(CH_2)_{11}CH_3$;

5i, **8i**, **9i** : R = COOH ;
5j, **8j**, **9j** : R = COOH ;
5k, **8k**, **9k** : R = COOH ;
5l, **8l**, **9l** : R = Ph ;
5m, **8m**, **9m** : R = NO_2

Figure 3. Synthesis of novel *L*-CAPC analogs including small molecules **5a-m** and peptides **9a-m.**

Therefore, further developments of *L*-Asu-based inhibitors have been extensively studied for discovering more safe and potent mechanism-based sirtuin inhibitors[15, 21]. However, the compound **4**. Finally, compound **4** was activated by isobutyl chloroformate and then coupled with different amines to give the *L*-CAPC analogs **5a-m** (Fig. 3 and Table 1). For the synthesis of

peptides of *L*-CAPC analogs **9a-m**, the amino group of amino acid **2** was first protected with 9-fluorenylmethoxycarbonyl (Fmoc) group to give the compound **6**, which was esterified with methanol and then followed by removal of tert-butyl group with TFA to give compound **7**. And compound **7** was coupled with different amines and then hydrolysis of the methyl ester to give the modified cysteines **8a-m** as building blocks. In order to mimick sirtuin substrate, the sequence we choose for the following peptide synthesis is derived from histone H3K9 peptide, which is used as one common substrate sequence for sirtuin.[44,47] Therefore, the synthesis of *L*-CAPC peptides **9a-m** with the sequence of KQTARC*STGGK (C* stand for modified cysteine) was finally completed by using standard Fmoc-chemistry solid phase peptide synthesis (SPSS) along with several *L*-Fmoc-amino acids and building blocks **8a-m** on Wang resin, followed by cleavage from the resin with a trifluoroacetic acid (TFA) solution containing phenol (5%), thioanisole (5%), ethanedithiol (2.5%) and water (5%), and purification by preparative Reversed-phase high performance liquid chromatography (RP-HPLC) (Fig. 3 and Table 2). The details for the synthesis and identification of *L*-CAPC small molecules **5a-m** and *L*-CAPC peptides **9a-m** are shown in the Electronic Supplementary Information (ESI).

Table 1 High resolution mass spectrometer (HRMS) analysis of *L*-CAPC small molecules **5a-m**.

Compound	Ionic formula	Calculated m/z	Observed m/z
5a	$[C_{21}H_{26}N_3O_4S]^+$	416.1639	416.1604
5b	$[C_{22}H_{28}N_3O_4S]^+$	430.1795	430.1763
5c	$[C_{23}H_{30}N_3O_4S]^+$	444.1952	444.1916
5d	$[C_{25}H_{34}N_3O_4S]^+$	472.2265	472.2251
5e	$[C_{27}H_{38}N_3O_4S]^+$	500.2578	500.2559
5f	$[C_{29}H_{42}N_3O_4S]^+$	528.2891	528.2883
5g	$[C_{31}H_{45}N_3NaO_4S]^+$	578.3023	578.3038
5h	$[C_{34}H_{52}N_3O_4S]^+$	598.3473	598.3495
5i	$[C_{23}H_{28}N_3O_6S]^+$	474.1693	474.1672
5j	$[C_{24}H_{29}N_3NaO_6S]^+$	510.1669	510.1672
5k	$[C_{25}H_{31}N_3NaO_6S]^+$	524.1826	524.1815
5l	$[C_{27}H_{30}N_3O_4S]^+$	492.1952	492.1934
5m	$[C_{27}H_{29}N_4O_6S]^+$	537.1802	537.1794

Table 2 High resolution mass spectrometer (HRMS) analysis of *L*-CAPC peptides **9a-m**.

Compound	Ionic formula	Calculated m/z	Observed m/z
9a	$[M+3H]^{3+}$	407.8838	407.8831
9b	$[M+3H]^{3+}$	412.5557	412.5524
9c	$[M+3H]^{3+}$	417.2276	417.2257
9d	$[M+3H]^{3+}$	426.5713	426.5689
9e	$[M+3H]^{3+}$	435.9151	435.9132
9f	$[M+3H]^{3+}$	445.2589	445.2719
9g	$[M+3H]^{3+}$	454.6026	454.6010
9h	$[M+3H]^{3+}$	468.6183	468.6348
9i	$[M+3H]^{3+}$	427.2190	427.2193
9j	$[M+3H]^{3+}$	431.8908	431.8892
9k	$[M+3H]^{3+}$	436.5627	436.5620
9l	$[M+3H]^{3+}$	433.2276	433.2263
9m	$[M-2H]^{2-}$	669.8157	669.8161

Considering sirtuin's novel acyl groups preference, we have synthesized a series of different length alkyl chains containing *L*-CAPC small molecules or *L*-CAPC peptides (from **5a** or **9a** to **5h** or **9h**), and different carboxyl groups or nitro group (carboxyl isostere) containing *L*-CAPC small molecules or *L*-CAPC peptides (from **5i** or **9i** to **5m** or **9m**). With these small molecules (**5a-m**) and peptides (**9a-m**) in hand, we then did the pilot screening for the inhibition of SIRT1, 2, 3, 5 and 6 at a compound's concentration of 250μM or 333μM. All tested compounds were subjected to several inhibition assays against the deacetylation reaction for SIRT1/2/3, the desuccinylation reaction for SIRT5 and the demyristoylation reaction for SIRT6, respectively. As shown in Table 3, peptides (**9a-m**) show better sirtuin inhibition than that of small molecules (**5a-m**). Unexpectedly, small molecule **5a** showed no inhibition unlike that of *L*-ACAH and its thioacetyl or thiourear counterparts[35]. And small molecules **5i-k** with negative charged acyl groups also did not show inhibition against the SIRT5-catalyzed desuccinylation reaction. Among small molecules (**5a-m**), **5f** and **5g** gave the best inhibitory potency against SIRT2 with the inhibitions of 60±1% and 61±5% at 333 μM, respectively. Small molecule **5h** with longer acyl chain gave a decrease of SIRT2 inhibition to 20±3% at 333 μM. However, they demonstrated general inhibition against SIRT1 and SIRT2 when small molecules (**5a-m**) were transformed to peptides (**9a-m**) (Fig. 3 and Table 3). Among these, peptides **9g** and **9h** displayed the best inhibitory potency against SIRT2 with the inhibitions of 95±1% and 87±1%, respectively. They were the only two *L*-CAPC analogs in this study shown better inhibitions than that of nicotiamide (NAM), a pan sirtuin inhibitor.

Table 3 Pilot screening of sirtuin inhibiton for *L*-CAPC small molecules **5a-m** and peptides **9a-m**.

	Inhibition-%				
Compound	SIRT1	SIRT2	SIRT3	SIRT5	SIRT6
***5a**	N.I.	N.I.	N.I.	N.I.	11±3
***5b**	N.I.	N.I.	N.I.	N.I.	N.I.
***5c**	N.I.	12±5	N.I.	N.I.	15±4
***5d**	N.I.	25±4	N.I.	N.I.	26±1
***5e**	N.I.	25±7	N.I.	N.I.	N.I.
***5f**	N.I.	60±1	N.I.	14±8	N.I.
***5g**	N.I.	61±5	14±5	24±11	28±4
***5h**	N.I.	20±3	N.I.	N.I.	31±3
***5i**	26±4	N.I.	N.I.	N.I.	53±6
***5j**	N.I.	N.I.	N.I.	N.I.	43±4
***5k**	N.I.	N.I.	N.I.	N.I.	35±5
***5l**	N.I.	47±5	11±4	34±5	30±2
***5m**	N.I.	N.I.	15±1	N.I.	N.I.
****9a**	40±1	27±7	N.I.	18±2	N.I.
****9b**	34±3	N.I.	N.I.	10±6	N.I.
****9c**	35±7	13±9	N.I.	N.I.	N.I.
****9d**	30±1	12±7	N.I.	N.I.	N.I.
****9e**	36±3	20±1	N.I.	N.I.	N.I.
****9f**	23±4	66±1	N.I.	N.I.	N.I.
****9g**	60±1	95±1	15±1	N.I.	41±2
****9h**	67±3	87±1	17±2	N.I.	54±4
****9i**	60±2	28±3	22±2	20±8	25±5
****9j**	66±2	45±3	20±5	15±9	54±1
****9k**	23±1	33±6	N.I.	16±6	43±1
****9l**	30±1	N.I.	N.I.	N.I.	28±3
****9m**	38±1	26±8	N.I.	N.I.	26±2
**NAM	73±1	83±2	74±2	69±1	76±2

*333μM; **250μM; N.I.: No inhibition at indicated concentration.

Table 4 IC_{50} values of peptides **9f-h**.

	IC_{50} (μM)				
Inhibitor	SIRT1	SIRT2	SIRT3	SIRT5	SIRT6
9f	>300	237	>500	>500	>500
9g	>200	20	>500	>500	>250
9h	>200	35	>500	>500	>200
TM[50]	98	0.028	>200	>200	>200
***L*-ACAH(7)**[40]	-	-	-	-	20.9
BHJH-TM1[51]	5.3	2.3	4.5	-	2.8

To further evaluate the inhibitory potency and selectivity of peptides **9f-h**, we measured their IC_{50} values using an HPLC assay (Table 4). Interestingly, the IC_{50} values of peptides **9f-h** were all higher against SIRT1/3 catalyzed-deacetylation reaction, SIRT5 catalyzed-desucinylation reaction and SIRT6 catalyzed-demyristoylation reaction. Exceptionally, an IC_{50} value of 20 μM was obtained when **9g** was subjected to an inhibition assay against the SIRT2-catalyzed deacetylation reaction while an IC_{50} value of 35 μM was obtained when **9h** was used under the same conditions. Considering that *L*-ACAH is a known weaker SIRT1/2/3 inhibitory warhead than thioacetyl group, it's reasonable that peptides **9f-h** with the warhead of *L*-CAPC like *L*-ACAH demonstrated lower SIRT2 inhibitory potency than that of **TM** with thioacetyl as a warhead (Table 4)[40, 50]. Notably, *L*-CAPC (**9g** or **9h**) show better selectivity toward SIRT2 compared with our previously reported sirtuin inhibitor of **BHJH-TM1**, a thiomyristoyl lysine peptide (Table 4)[51]. On the other hand, the *L*-ACAH (**7**) with "inverted amide", which contains the carboxamide NH_2-dodecylated analog with the similar sequence as peptides **9** all derived from histone H3K9, has shown an inhibitory potency against SIRT6 with IC_{50} of 20.9 μM[40] while *L*-CAPC (**9g** or **9h**) containing the carboxamide NH_2- decylated or tridecylated or analogs only show the inhibitions against SIRT2 (Table 4). The replacing the methylene at 4-position of *L*-ACAH with the atom of sulphur may increase the flexibility of the carboxamide NH_2-long chain fatty acylated side chain and thus more readily orientate and target SIRT2 (Fig. 3). However, too long or short for the length of hydrophobic acyl group is not quite appropriate for SIRT2 inhibition in *L*-CAPC (**9g** vs **9f** or **9h**, Table 4). Therefore, peptide **9g** was come from the coupling of decyl amine (Fig. 3), which showed the best inhibitory potency with an IC_{50} value of 20 μM against SIRT2 and the best inhibitory selectivity with over 10-fold higher than that of other tested sirtuins (SIRT1, SIRT3, SIRT5 and SIRT6). Additionally, we have performed the mechanism analysis by doing the kinetics study to find out whether *L*-CAPC peptides **9** are mechanism-based inhibitors. As shown in Figure S4 in supporting information, the apparent Km value for H3K9AcWW (SIRT2 substrate) increased with increasing concentrations of **9g** (0μM, 5μM and 10μM). Furthermore, plots of 1/ V versus 1/[S] revealed a series of lines that intersected at the 1/V axis at each inhibitor concentration (V stands for initial velocities, [S] stands for substrate concentration, Figure S5 in supporting information). The features of kinetics and the double reciprocal plot indeed demonstrated that **9g** is a competitive inhibitor for SIRT2 (Figures S4 and S5).

Due to the concern about the possible toxicity associated with thioamide-based sirtuin inhibitors[30-34]. *L*-2-amino-7-carboxamidoheptanoic acid (*L*-ACAH) as sirtuin inhibitors have been developed for several years[39, 40]. However, the starting material of *L*-α-aminosuberic acid (*L*-Asu) as an unnatural amino acid is not readily available. An alternative strategy here has been proposed and employed to develop novel sirtuin mechanism-based inhibitors, which involves in simply replacing the methylene at 4-position of *L*-ACAH with an atom of sulphur to give a novel scaffold of *L*-S-(3-carboxamidopropyl) cysteine (*L*-CAPC) constructed by starting from *L*-cysteine, a nature amino acid (Fig. 2). According to recent discoveries of sirtuin novel enzymatic activities for preferentially removing some acyl groups, like malonyl[44], succinyl[44], glutaryl[45], crotonyl[46], myristoyl[47] and so on[5, 48], we have designed and synthesised *L*-CAPC small molecules **5a-m** and *L*-CAPC peptides **9a-m**. Similar to the results from the strategies of thioamide or *L*-ACAH[15, 21], peptides show better inhibition compared to that of small molecules in this study (**9a-m** vs **5a-m**, Table 3). In the current study, we found that **9g** and **9h** were the best two inhibitors against SIRT2 with IC_{50} values of 20 μM and 35 μM, respectively. Notably, both of them (**9g** and **9h**) show 10-fold higher SIRT2 inhibition than that of other sirtuins. Therefore, this novel scaffold of *L*-S-(3-carboxamidopropyl) cysteine (*L*-CAPC) could be exploited for developing more potent and highly selective sirtuin inhibitors. Due to the limited cell permeability of peptide-based sirtuin inhibitors, *L*-CAPC small molecules as sirtuin inhibitors are under further investigation in our laboratory.

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Supplementary Material

Supplementary data associated with this article can be found, in the online version, at http://

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Highlights

- *L*-S-(3-carboxamidopropyl) cysteine (*L*-CAPC) was used to design sirtuin inhibitors
- Small molecules **5** and peptides **9** derived from *L*-CAPC have been synthesized
- Among them, peptide **9g** is the most inhibitory potency and selectivity against SIRT2

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The mimics of N ε -acyl-lysine derived from cysteine as sirtuin inhibitors

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Chun Wang, Fang Wang, Xiaoxue Chen, Yefang Zou, Hong Zhu, Qingjie Zhao, Jingshan Shen, Yan Li, Yongjun Li, Bin He

A novel scaffold of L-S-(3-carboxamidopropyl) cysteine (L-CAPC) has been exploited for design and synthesis of sirtuin inhibitors