Development of Selective Butyrylcholinesterase Inhibitors Using (R)-Lipoic Acid-Polyphenol Hybrid Molecules[†]

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A series of hybrid molecules between (R)-lipoic acid (ALA) and the acetylated or methylated polyphenol compounds were synthesized and their *in vitro* cholinesterase [acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE)] inhibition activities were checked. The IC_{50} values of all hybrid molecules for a BuChE inhibition were lower than those of the single parent compounds. Specifically, ALA-acetyl protected caffeic acid (**11**, ALA-AcCA) was shown as an effective inhibitor of BuChE (IC_{50} = 0.5 ± 0.2 μM) and also had a great selectivity for BuChE over AChE (more than 800 fold). Inhibition kinetic study indicated that **11** is a mixed inhibition type. Its binding affinity (K_i) value to BuChE is 1.52 ± 0.18 μM.

Key Words : Molecular hybridization, (R)-Lipoic acid, Polyphenols, Cholinesterase inhibitor

Introduction

Recently, the single-target-directed drug discovery method has been challenged because 1) many diseases such as diabetes, cancer, cardiovascular disease, neurodegenerative diseases, *etc.*,[1,2] have been identified as having multiple pathogenic factors and 2) the appearance of drug resistant organisms.

Even though many kinds of efficient drug discovery methods such as the construction of chemical libraries having high molecular diversity, computer-aided drug design (CADD), quantitative structure-activity relationship (QSAR), and High Throughput Screening (HTS) have been developed to solve these problems, it has been still difficult to develop new drugs. Therefore, there are demands to quickly develop the efficient drug development methods. Combinations of different drugs or drug cocktails are candidates, and they have been applied to special diseases. Another good candidate is the hybridization of molecules. Molecular hybridization concept is the combination of appropriate pharmacophores (parents) onto one compound (hybrid molecule).[3] Since parent molecules used in molecular hybridization were already applied to human as a drug or a dietary supplementary, hybrid molecules may show the same or less undesired side effects or toxicity compared to the individual parent molecules. Also they may show better activities compared to the parent and may have new biological activities which parents do not have.[4]

Scientists have been interested in the natural bioactive compounds and the secondary metabolites as lead compounds

for the development of new bioactive compounds. Our group has been carrying out research on the synthesis of novel hybrid molecules between natural bioactive compounds. Previously, we synthesized ALA-nitron hybrid compounds and showed their positive activity for cholinesterase inhibitor.[5] In this work, we selected the ALA and polyphenol (PP) compounds as parents for the synthesis of the hybrid molecules because they showed many interesting biological activities.

ALA and its reduced form, dihydrolipoic acid (DHLA), act as a multifunctional antioxidant against a variety of reactive oxygen species (ROS).[6,7] ALA is known as the antioxidant of antioxidants because it assists for regeneration and *de novo* syntheses of endogenous antioxidants such as glutathione, α-tocopherol, and vitamin C.[8] ALA is a cofactor of pyruvate dehydrogenase complex and results in producing an adequate amount of ATP from glucose in aerobic metabolism.[9] The other functions of ALA is a chelator for metal ions such as mercury or iron.[10,11] ALA is used as a dietary supplement and has been applied to medical treatments such as diabetes,[12-14] ischemia-reperfusion injury,[15] cataract formation,[16] neurodegeneration,[17-19] and hypertension.[20]

Many ALA derivatives have been synthesized to improve their biological activities and to give a synergic effect. ALA-*L*-dopa and ALA-dopamine,[21] ALA-Trolox (a water-soluble analogue of vitamin E),[22] ALA-amphiphilic hybrid of α-phenyl-*N-tert*-butyl nitrone (PBN) (PBNLP),[23] ALA-nitric oxide synthase inhibitors,[24] and ALA-*N*-alkyl-substituted morpholine,[25] ALA-chroman analogues,[26] ALA-quinazolinimines,[27] and ALA-quinazolinimines[28] have been synthesized.

Polyphenols (PPs) are known as a natural antioxidant due to reduce reactive oxygen species levels *in vivo*.[29] Therefore, they showed several beneficial results such as reducing the

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risk of cardiovascular disease,[30] reducing inflammatory effects on coronary artery disease,[31,32] preventing peripheral artery disease,[33,34] and anti-aging effect by slowing the process of skin wrinkling.[35]

In this paper, we report the synthesis of the hybrid molecules and their inhibition activity for cholinesterase.

Results and Discussions

Two types of cholinesterases (ChE) exist within the nervous system. One is acetylcholinesterase (AChE, EC 3.1.1.7) that is primarily associated with cholinergic neurons. The other is butyrylcholinesterase (BuChE, EC 3.1.1.8) that is associated with supporting glial cells in the human brain and specific cholinergic nerve tracts.[36] More than 10,000 molecules of acetylcholine (Ach) per second can be hydrolyzed by both cholinesterases at a rate that is limited more by the diffusion of ACh into the enzyme, rather than by catalytic capacity.[37] AChE and BuChE both play important roles in the regulation of ACh level and may also have an important role in the development and progression of Alzheimer's disease (AD).[38] Until recently, the relative contribution of BuChE in the regulation of ACh level had been largely ignored. However, there are growing evidences that BuChE may be one of the important enzymes involved for AD. AChE activity is decreased but BuChE activity is increased 40-90% in AD.[39,40] Also, BuChE activity predominates in cognition and behavior regions of the brain.[41,42] Selective BuChE inhibition by using cymserine analogs resulted in raising acetylcholine levels in the brains of rodents [43] and BuChE knockout mice and silent mutants in humans show no physiological disadvantage.[44,45] Therefore, development of BuChE-specific inhibitors may be the promising strategy for treating AD without any serious side effects.[46] In this work, we synthesized ALA-polyphenol derivatives and checked their cholinesterase inhibition activity by Ellman's coupled enzyme assay.[47] ALA and polyphenol compounds utilized in this work were listed at Figure 1.

ALA-acetyl protected-syringic acid (AcSA) was prepared by the activation/coupling reaction (Scheme 1). ALA was initially activated with EDC/NHS in dichloromethane (MC). NHS-activated ALA was reacted with 2-(2-aminoethoxy)
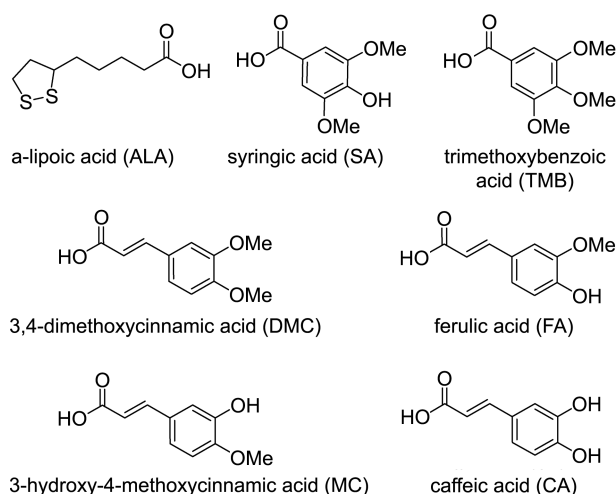

Figure 1. The structures of parent molecules utilized in this work.

ethanol linker to result in compound **3** (73% isolated yield). Acetyl protected syringic acid was converted to acid chloride **4** with $SOCl_2$ (89% isolated yield). Coupling reaction between **3** and **4** in the presence of DMAP gave rise to compound **5** (ALA-AcSA, 65% isolated yield). Acetyl protection group was removed by treatment of **5** with NH_2NH_2 in MeOH to form compound **6**.

3,4,5-Trimethoxybenzoic acid (TMB), 3,4-dimethoxycinnamic acid (DMC), acetyl protected ferulic acid (AcFA), 4-acetyl protected-3-methoxycinnamic acid (AcMC), and 3,4-diacetyl protected caffeic acid (AcCA) were activated to the corresponding acid chloride and then coupled with **3** to result in the ALA-TMB (**7**), ALA-DMC (**8**), ALA-AcFA (**9**), ALA-AcMC (**10**), and ALA-AcCA (**11**), respectively. The synthesized ALA-derivatives were listed in Figure 2.

The inhibitory results (IC_{50} value) for AChE and BuChE with ALA, PPs, acetated-PPs, and ALA-hybridized compounds were shown in Table 1.

The starting parent compounds didn't show any inhibition activity for cholinesterase. Also, all ALA-derivatives (**5-11**) showed less than 50% inhibition efficiency at 400 μM for AChE. But all ALA-derivatives improved inhibition activity
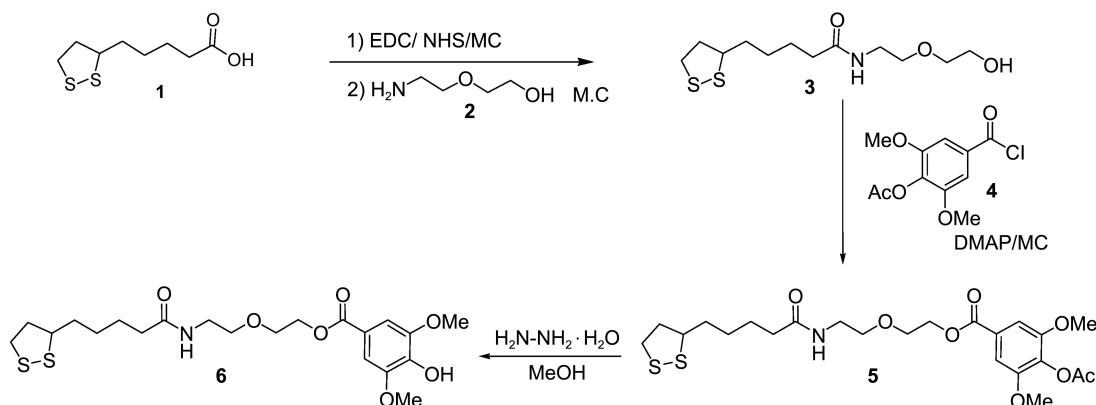
Scheme 1. Synthesis of ALA-AcSA (**5**) and ALA-SA (**6**).

for BuChE. Specially, the IC$_{50}$ values of ALA-AcMC (**10**) and ALA-AcCA (**11**) decreased to 1.9 ± 0.7 and 0.5 ± 0.2 μM for BuChE inhibition, respectively. They also showed a great
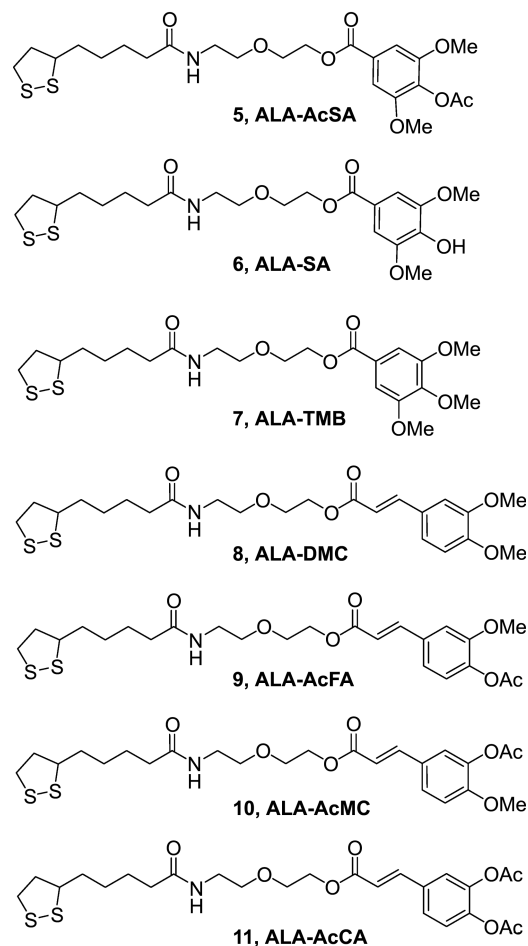

Figure 2. The structures of ALA-derivatives synthesized in this work.

Table 1. IC$_{50}$ values of ALA, PPs, AcPPs, and ALA-derivatives for cholinesterase inhibition

Samples	AChE inhibition IC$_{50}$ (μM)	BuChE inhibition IC$_{50}$ (μM)
Lipoic acid	>1000	>1000
Caffeic acid	>1100	>1100
Acetyl caffeic acid	>800	>800
Syringic acid	>1000	>1000
Acetyl syringic acid	>800	>800
Ferulic acid	>1000	>1000
Acetyl ferulic acid	>800	>800
3,4,5-Trimethoxy benzoic acid	>900	>900
5 (ALA-AcSA)	>400	124.0 ± 38.2
6 (ALA-SA)	>400	228.7 ± 57.2
7 (ALA-TMB)	>400	39.1 ± 0.9
8 (ALA-DMC)	>400	26.5 ± 6.4
9 (ALA-AcFA)	>400	60.9 ± 17.4
10 (ALA-AcMC)	>400	1.9 ± 0.7
11 (ALA-AcCA)	>400	**0.5 ± 0.2**

selectivity (more than 800 fold) for BuChE over AChE. Since free phenolic compound **6** obtained from removing acetyl group showed less inhibition effect than acetyl protected compound **5**, we didn't carry out deprotection procedure for compounds, **9**, **10**, & **11**.

From the comparison between **8** vs **9**, **8** vs **10**, **9** vs **11**, and **10** vs **11**, substitution at *meta* position with acetyl group would be the most important factor to increase the inhibition efficiency for compounds **8-11**. Compound **11**, having two acetyl groups at *meta* and *para* position, resulted in the best inhibition effect for BuChE. There are several factors for QSAR analysis; hydrophobicity parameter (π), Hammett electronic substituent constant (σ$_m$ & σ$_p$), molar refractivity (MR), *etc* (Table 2).[48] The QSAR parameter values between 3-acetyl and 3-methoxy functional group of aromatic compounds were analyzed. Hydrophilic group substituted at *meta* position is more important than hydrophobic group (π values : −0.66 for -OAc and −0.02 for -OMe). Since -OAc group is more electron withdrawing group (from Hammett electronic substituent constant value, σ$_m$) and bigger size (from molar refractivity, MR) than the -OMe group, electron withdrawing effect and bigger size effect might be another important factor to increase inhibition effect at the *meta* position. Once acetyl group was substituted at the *meta* position, more hydrophobic, more electron withdrawing, and bigger size functional groups substituted at the *para* position would increase the BuChE inhibition efficiency.

To explore the inhibition kinetics of **11**, inhibition kinetic studies at a different concentration of **11** were carried out. The Lineweaver-Burk plot showed that it was a mixed

Table 2. Some aromatic substituent constants for structure-activity correlations[48]

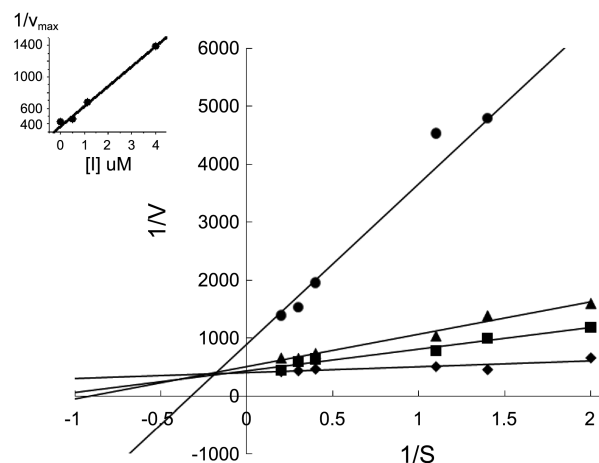| Substituent | Parameter | | | |
	π	σ$_m$	σ$_p$	MR
-OH	−0.67	0.12	−0.37	2.85
-OMe	−0.02	0.12	−0.27	7.87
-OAc	−0.64	0.39	0.31	12.47

Figure 3. Lineweaver-Burk plot using LA-AcCA (**11**) for the inhibition kinetic study against BuChE (concentration: (●) 4 μM, (▲) 1 μM, (■) 0.5 μM, (◆) = 0 μM).

inhibition type, which varied both V_{max} and K_m value (figure 3). The K_i value of **11** for BuChE was 1.52 ± 0.18 μM.

Conclusions

Seven hybrid compounds (**5-11**) were synthesized. Even though the hybrid compounds between ALA and PPs didn't show any big improvement on AChE inhibition efficiency, hybrid ALA-derivatives generally showed high inhibition effect on BuChE inhibition. Specially, the IC_{50} value of **10** and **11** was 1.9 ± 0.7 and 0.5 ± 0.2 μM for BuChE inhibition, respectively. The concentration of acetylcholine (ACh) in brain regions of patients suffering Alzheimer's disease (AD) is lower than that of a healthy brain. This cholinergic deficit can be partly corrected by inhibiting ChEs. In healthy brains, AChE predominates (80%) and BuChE is considered to play a minor role in regulating brain ACh levels. But in the AD brain, BuChE activity rises while AChE activity remains unchanged or declines. Recent research indicates that the selective inhibition of BuChE may provide more sustained efficacy over the course of AD and may help to slow disease progression.[49] Indeed, selective BuChE inhibition may provide all the cognitive benefits associated with classical AChE inhibition without the characteristic and dose-limiting adverse effect profile.[50] In general, the majority of potent cholinesterase inhibitors that are the focus of clinical and scientific interest are alkaloids or quaternary ammonium salts.[51] ALA-PP derivatives would become a new type among cholinesterase inhibitors. Since they showed high selective inhibition effect for BuChE rather than AChE, further investigations will be carried out to check the activity against AD. In this study, we reported one example of hybrid molecules that had a positive activity for BuChE inhibition which parents didn't have. Since hybrid molecules synthesized from this work showed new biological activity, molecular hybridization between bioactive natural compounds will be a good candidate to develop biological active compounds. More compounds are now under synthesized to increase inhibition effect and selectivity for BuChE.

Experimental

General Methods. ^{1}H-NMR, and ^{13}C-NMR spectra were recorded on a Varian Mercury 400 (400 MHz) and Bruker ARX-300 (300 MHz). Melting points were determined on SMP3. High-resolution mass spectra (HRMS) were recorded on a JMS-700 Mstation mass spectrometer under fast atom bombardment (FAB) conditions with nitro benzyl alcohol (NBA) as the matrix in the Korea Basic Science Institute (Seoul), Korea. Flash column chromatography was performed using E. Merck silica gel (60, particle size 0.040-0.063 mm). Analytical thin layer chromatography (TLC) was performed using pre-coated TLC plates with silica Gel 60 F254 (E. Merck). All of the synthetic reactions were carried out under argon atmosphere with dry solvent, unless otherwise noted. Tetrahydrofuran (THF) was distilled from sodium/benzophenone immediately prior to use and methylene chloride

(CH_2Cl_2) was dried from calcium hydride. All chemicals were reagent grade unless otherwise specified. The (R)-lipoic acid, NHS, and EDC were purchased from Sigma-Aldrich Chemical Co. and used without purification.

Cholinesterase Assay. ChE-catalyzed hydrolysis of the thiocholine esters was monitored by following production of the anion of thiocholine at 412 nm by the Ellman's coupled assay. Assays were conducted on HP8452A or HP8453A diode array UV-visible spectrophotometers and the cell compartments were thermostated by circulating water or Peltier temperature controller, respectively. Acetylthiocholine (ATCh) and butyrylthiocholine (BuTCh) were used as substrates for AChE and BuChE, respectively.

Synthesis.

2-(2-(5-(1,2-Dithiolan-3-yl)pentanamido)ethoxy)ethyl 4-acetoxy-3,5-dimethoxybenzoate (5): (R)-Lipoic acid-linker (30 mg, 0.10 mmol) was dissolved in 3 mL methylene chloride. DMAP (31 mg, 0.15 mmol) were added to the lipoic acid-linker solution. The mixture was stirred for 15 min and then acetyl syringic acid chloride (40 mg, 0.15 mmol) was added to the solution at ice-bath. The mixture was stirred for 3 h at ice-bath and then extracted with 1N NaOH, 1N HCl, and then washed with brine. The combined organic layer was dried over anhydrous $MgSO_4$. After the organic solvent was removed under vacuum, the crude product was purified by column chromatography (MC:MeOH = 9:1) to give **5** as an oil (34 mg, 65% yield).

^{1}H-NMR ($CDCl_3$, 400 MHz) 1.42 (m, 2H), 1.68 (m, 4H), 1.90 (m, 1H), 2.16 (t, J = 7.2, 2H), 2.35 (s, 3H), 2.45 (m, 1H), 3.18 (m, 2H), 3.49 (t, J = 4.8, 2H), 3.58 (m, 1H), 3.61 (t, J = 4.8, 2H), 3.80 (t, J = 4.8, 2H), 3.90 (s, 6H), 4.50 (t, J = 4.8, 2H), 5.87 (bs, 1H), 7.33 (s, 2H) ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 20.6, 25.4, 29.0, 34.7, 36.5, 38.6, 39.5, 40.4, 56.5 ($CH_3 \times 2$), 56.6, 64.2, 69.2, 69.9, 106.5 (CH×2), 128.0, 132.9, 152.3 (CH×2), 166.1, 168.3 173.2, HRMS-FAB[+] (m/z) clacd for $C_{23}H_{33}NO_8S_2Na$ (M[+] + Na) : 538.1545, found: 538.1714.

2-(2-(5-(1,2-Dithiolan-3-yl)pentanamido)ethoxy)ethyl 4-hydroxy-3,5-dimethoxybenzoate (6): Compound **5** (100 mg, 0.19 mmol) was dissolved in methanol. Hydrazine monohydrate (0.02 mL, 0.43 mmol) was added to the solution at room temperature. The mixture was stirred at room temperature for 30 min. The reaction mixture was extracted with ethylacetate. The organic layer was washed water and then dried over anhydrous $MgSO_4$. After the organic solvent was removed under vacuum, the crude product was purified by column chromatography to give **6** as a white salt (87 mg, 95% yield).

^{1}H-NMR ($CDCl_3$, 400 MHz) 1.42 (m, 2H), 1.68 (m, 4H), 1.90 (m, 1H), 2.25 (t, J = 7.2, 2H), 2.45 (m, 1H), 3.18 (m, 2H), 3.51 (q, J = 4.8, 2H), 3.59 (m, 1H), 3.61 (t, J = 4.8, 2H), 3.80 (t, J = 4.8, 2H), 3.90 (s, 6H), 4.49 (t, J = 4.8, 2H), 5.85 (bs, 1H), 7.34 (s, 2H) ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 25.5, 29.1, 34.8, 36.5, 38.7, 39.3, 40.4, 56.6, 56.7 ($CH_3 \times 2$), 63.9, 69.3, 70.0, 106.9 (CH×2), 120.9, 139.7, 146.9 (CH×2), 166.6, 173.0, HRMS-FAB[+] (m/z) clacd for $C_{21}H_{32}NO_7S_2$ (M[+] + H): 474.1620, found: 474.1616.

2-(2-(5-(1,2-Dithiolan-3-yl)pentanamido)ethoxy)ethyl-3,4,5-trimethoxybenzoate (7): (*R*)-Lipoic acid-linker (120 mg, 0.40 mmol) and TMB-acid chloride (150 mg, 0.50 mmol) were reacted by following the previous procedure. After the crude product was purified by column chromatography (MC:MeOH = 9:1), **7** was obtained as a white solid (190 mg, 79% yield).

^{1}H-NMR (CDCl$_3$, 400 MHz) 1.38 (m, 2H), 1.58 (m, 4H), 1.82 (m, 1H), 2.09 (t, *J* = 7.2, 2H), 2.38 (m, 1H), 3.04 (m, 2H), 3.40 (q, *J* = 4.8, 2H), 3.49 (m, 1H), 3.51 (t, *J* = 4.8, 2H), 3.75 (t, *J* = 4.8, 2H), 3.85 (s, 9H), 4.41 (t, *J* = 4.8, 2H), 5.93 (bs, 1H), 7.24 (s, 2H) ^{13}C-NMR (CDCl$_3$, 100 MHz) δ 24, 26 (CH$_2$×2), 28.8, 30.9, 34.1, 34.6, 38.7, 40.3, 40.4, 56.5 (CH$_3$ ×2), 63.2, 69.3, 104.6 (CH$_2$×2), 130.1, 153.3 (C×2), 167.3, 168.6, 173.7, HRMS-FAB[+] (*m/z*) clacd for C$_{22}$H$_{33}$NO$_7$S$_2$ Na (M[+] + Na): 510.1596, found: 510.1587

2-(2-(5-(1,2-Dithiolan-3-yl)pentanamido)ethoxy)ethyl 3-(3,4-dimethoxyphenyl) acrylate (8): Compound **8** was obtained as an oil (248 mg, 66% yield) from the following the previous procedure by using lipoic acid-linker (233 mg, 0.87 mmol), DMAP (160 mg, 1.31 mmol) and 3,4-dimethoxycinnamic acid-chloride (298 mg, 1.31 mmol).

^{1}H-NMR (CDCl$_3$, 400 MHz) 1.39 (m, 2H), 1.60 (m, 4H), 1.81 (m, 1H), 2.13 (t, *J* = 7.6, 2H), 2.98 (m, 1H), 3.05 (m, 2H), 3.41 (q, *J* = 5.2, 2H), 3.50 (m, 1H), 3.52 (t, *J* = 4.8, 2H), 3.69 (t, *J* = 4.2, 2H), 3.84 (s, 6H), 4.30 (t, *J* = 4.2, 2H), 5.89 (bs, 1H), 6.28 (d, *J* = 16, 1H), 6.80 (d, *J* = 8.4, 1H), 6.99 (s, 1H), 7.04 (d, *J* = 8.4, 1H) 7.58 (d, *J* = 16, 1H) ^{13}C-NMR (CDCl$_3$, 100 MHz) δ 24.3, 27.9, 33.6, 35.4, 37.4, 38.1, 39.2, 54.9, 55.0, 55.4, 62.2, 68.1, 68.8, 108.6, 110, 114.2, 121.8, 126.2, 144.3, 148.2, 150.3, 166.2, 171.7 MS (M+H)[+] 484.17.

2-(2-(5-(1,2-Dithiolan-3-yl)pentanamido)ethoxy)ethyl 3-(4-acetoxy-3-methoxyphenyl) acrylate (9): Compound **9** was obtained as an oil (240 mg, 59% yield) from the following the previous procedure by using lipoic acid-linker (200 mg, 0.68 mmol), DMAP (90 mg, 0.817 mmol) and acetyl ferulic acid-chloride (260 mg, 1.02 mmol).

^{1}H-NMR (CDCl$_3$, 400 MHz) 1.44 (m, 2H), 1.68 (m, 4H), 1.89 (m, 1H), 2.19 (t, *J* = 7.6, 2H) 2.34 (s, 3H), 2.44 (m, 1H), 3.14 (m, 2H), 3.48 (q, *J* = 5.2, 2H), 3.55 (m, 1H), 3.60 (t, *J* = 5.2, 2H), 3.73 (t, *J* = 4.8, 2H) 3.88 (s, 3H), 4.38 (t, *J* = 4.8, 2H), 5.88 (bs, 1H), 6.43 (d, *J* = 15.6, 2H) 7.06 (d, *J* = 8, 1H), 7.10 (s, 1H) 7.14 (d, *J* = 8, 1H), 7.67 (d, *J* = 15.6, 1H) ^{13}C-NMR (CDCl$_3$, 100 MHz) δ 20.8, 25.5, 29.0, 34.8, 36.5, 38.6, 39.3, 40.4, 56.1, 56.6, 63.6, 69, 77.2, 105.0, 111.4, 118.3, 121.5, 123.5, 133.3 144.8, 151.6, 166.9, 168.9, 172.9, HRMS-FAB[+] (*m/z*) clacd for C$_{24}$H$_{34}$NO$_7$S$_2$ (M[+] + H): 512.1777, found: 512.1777.

2-(2-(5-(1,2-Dithiolan-3-yl)pentanamido)ethoxy)ethyl 3-(3-acetoxy-4-methoxyphenyl) acrylate (10): Compound **10** was obtained as an oil (242 mg, 60% yield) from the following the previous procedure by using lipoic acid-linker (233 mg, 0.78 mmol), DMAP (105 mg, 0.86 mmol) and acetyl ferulic acid-chloride (239 mg, 0.94 mmol).

^{1}H-NMR (CDCl$_3$, 400 MHz) 1.44 (m, 2H), 1.68 (m, 4H), 1.89 (m, 1H), 2.19 (t, *J* = 7.6, 2H) 2.34 (s, 3H), 2.44 (m,

1H), 3.14 (m, 2H), 3.48 (q, *J* = 5.2, 2H), 3.55 (m, 1H), 3.60 (t, *J* = 5.2, 2H), 3.73 (t, *J* = 4.8, 2H) 3.88 (s, 3H), 4.37 (t, *J* = 4.8, 2H), 5.92 (bs, 1H), 6.34 (d, *J* = 16, 1H) 6.97 (d, *J* = 8.8, 1H), 7.26 (s, 1H) 7.38 (d, *J* = 8.8, 1H), 7.63 (d, *J* = 16, 1H) ^{13}C-NMR (CDCl$_3$, 100 MHz) δ 20.9, 25.6, 29.1, 34.8, 36.6, 38.7, 39.4, 40.4, 56.3, 56.6, 63.5, 69.3, 70.1, 112.5, 116.4, 122.3, 127.5, 127.9, 140.2, 144.4, 153.2, 167.2, 169.1, 172.9 MS (M+H)[+] 512.17.

4-(3-(2-(2-(5-(1,2-Dithiolan-3-yl)pentanamido)ethoxy)ethoxy)-3-oxoprop-1-enyl)-1,2-phenylene diacetate (11): Compound **11** was obtained as a pale yellow oil (220 mg, 60% yield) from the following the previous procedure by using lipoic acid-linker (200 mg, 0.68 mmol), DMAP (91 mg, 0.75 mmol) and acetyl caffeic acid-chloride (401 mg, 1.42 mmol).

^{1}H-NMR (CDCl$_3$, 400 MHz) 1.44 (m, 2H), 1.68 (m, 4H), 1.90 (m, 1H), 2.20 (t, *J* = 7.6, 2H) 2.32 (s, 3H), 2.33 (s, 3H), 2.46 (m, 1H), 3.14 (m, 2H), 3.48 (q, *J* = 5.2, 2H), 3.55 (m, 1H), 3.60 (t, *J* = 5.2, 2H), 3.73 (t, *J* = 4.8, 2H), 4.38 (t, *J* = 4.8, 2H), 5.88 (bs, 1H), 6.43 (d, *J* = 15.6, 2H) 7.23 (d, *J* = 8, 1H), 7.41 (s, 1H) 7.43 (d, *J* = 8, 1H), 7.65 (d, *J* = 15.6, 1H) ^{13}C-NMR (DMSO, 100 MHz) δ 20.9, 21.0, 25.7, 28.9, 34.7, 35.7, 39.0, 39.5, 56.8, 63.8, 68.6, 69.7, 119.6, 123.9, 124.8, 127.6, 133.5, 143.0, 143.6, 144.2, 166.6, 168.7, 168.8, 172.7, HRMS-FAB[+] (*m/z*) clacd for C$_{25}$H$_{33}$NO$_8$S$_2$ Na (M[+] + Na): 562.1545, found: 562.1541

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