http://dx.doi.org/10.5012/bkcs.2013.34.4.1025

Articles

Synthesis of Selective Butyrylcholinesterase Inhibitors Coupled between α-Lipoic Acid and Polyphenols by Using 2-(Piperazin-1-yl)ethanol Linker

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Received December 17, 2012, Accepted January 3, 2013

In the previous paper (*Bull. Korean Chem. Soc.*, **2011**, *32*, 2997), the hybrid molecules between α-lipoic acid (ALA) and polyphenols (PPs) connected with neutral 2-(2-aminoethoxy)ethanol linker (linker-1) showed new biological activity such as butyrylcholinesterase (BuChE) inhibition. In order to increase the binding affinity of the hybrid compounds to cholinesterase (ChE), the neutral 2-(2-aminoethoxy)ethanol (linker 1) was switched to the cationic 2-(piperazin-1-yl)ethanol linker (linker 2). The IC_{50} values of the linker-2 hybrid molecules for BuChE inhibition were lower than those of linker-1 hybrid molecules (except **9-2**) and they also had the same great selectivity for BuChE over AChE (> 800 fold) as linker-1 hybrid molecules. ALA-acetyl caffeic acid (**10-2**, ALA-AcCA) was shown as an effective inhibitor of BuChE (IC_{50} = 0.44 ± 0.24 μM). A kinetic study using **7-2** showed that it is the same mixed type inhibition as **7-1**. Its inhibition constant (*Ki*) to BuChE is 4.3 ± 0.09 μM.

Key Words : Molecular hybridization, α-Lipoic acid (ALA), Polyphenols (PPs), Butyrylcholinesterase inhibitor, 2-(Piperazin-1-yl)ethanol linker

Introduction

Two types of cholinesterase (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 BuChE (EC 3.1.1.8) that is associated with supporting glial cells in the human brain and specific cholinergic nerve tracts.[1,2] AChE and BuChE both play important roles in the regulation of acetylcholine (Ach) level and may also have an important role in the development and progression of Alzheimer's disease (AD).[3] Until nowadays, 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. Some of the evidences are as follows. AChE activity is decreased but BuChE activity is increased by 40-90% in AD.[4,5] Also, BuChE activity predominates in cognition and behavior regions of the brain.[6,7] Selective BuChE inhibition by cymserine analogs resulted in increased ACh levels in the brains of rodents.[8] BuChE knockout mice and silent mutants in humans do not show any physiological disadvantage.[9,10] Therefore, development of BuChE-specific inhibitors may be a promising strategy for treating AD without any serious side effects.[11]

Recently, the molecular hybridization, the combination of appropriate pharmacophores onto one compound,[12] has been developed to quickly find out promising drug candidates. It may overcome the recent problems in the pharmaceutical field such as appearing diseases having multiple pathogenic factors and drug resistant organisms.[13,14] Hybrid compounds may have advantages over their parent molecules in having new biological activities.[15]

Previously, we synthesized hybrid compounds by coupling between two parents either by direct connection or indirect coupling by using 2-(2-aminoethoxy)ethanol linker (linker 1). The directly coupled ALA-nitron hybrid compounds showed moderate cholinesterase inhibitory activity.[16] ALA-linker 1-polyphenol[17] and polyphenol- linker 1-polyphenol hybrid compounds[18] selectively inhibited BuChE over AChE.

The substrate of ChEs, ACh or butyrylcholine (BuCh), contains the cationic choline moiety which improves binding affinity of the substrate to the enzyme active site. Since linker 1 exists as a neutral form inside hybrid molecules, we proposed a linker containing cationic moiety at pH7.4 that might improve the inhibitory activity due to the improved binding affinity to cholinesterase compared to the neutral linker. Therefore, we switched neutral 2-(2-aminoethoxy)-ethanol (linker-1) to cationic 2-(piperazin-1-yl)ethanol linker (linker 2). In this study, we report the synthesis of hybrid compounds connected with linker-2 and their *in vitro* inhibitory activities against ChEs.

Results and Discussion

The structures of compounds involved in this work such as ALA, 2-(2-aminoethoxy)ethanol (linker 1), 2-(piperazin-1-

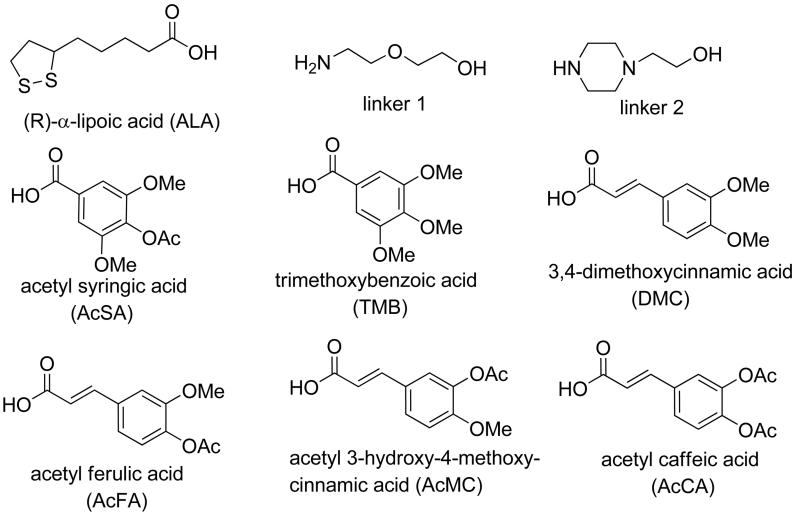
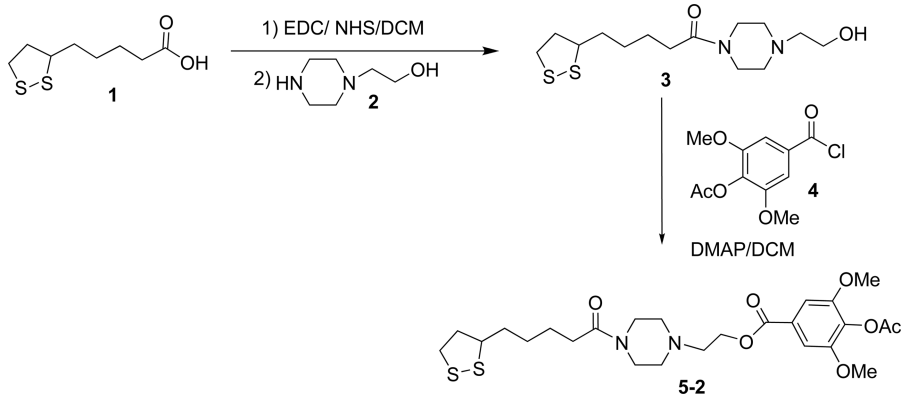


Figure 1. The structures of ALA, linker 1, linker 2, and PPs involved in this work.



Scheme 1. Synthesis of ALA-linker 2-AcSA (**5-2**).

yl)ethanol (linker 2), and polyphenols (PPs) are shown in Figure 1.

ALA-linker 2-PPs were prepared by the activation/coupling reaction. For example, synthesis of ALA-linker 2-acetyl syringic acid (ALA-AcSA, **5-2**) was shown at Scheme 1. NHS-activated ALA was reacted with 2-(piperazin-1-yl)-ethanol (linker 2) to result in compound **3** (73% isolated yield). Acetyl 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).

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 (**6-2**), ALA-DMC (**7-2**), ALA-AcFA (**8-2**), ALA-AcMC (**9-2**), and ALA-AcCA (**10-2**), respectively. The synthesized ALA-derivatives connected with linker 1[17] and 2 are listed in Table 1.

At the physiological pH 7.4, **5-2**~**10-2** can be majorly existed as a protonated ammonium form (Fig. 2).

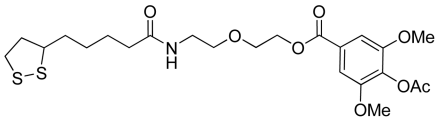
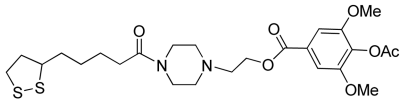
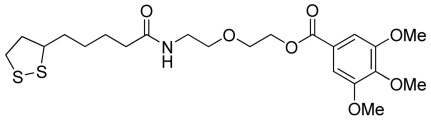
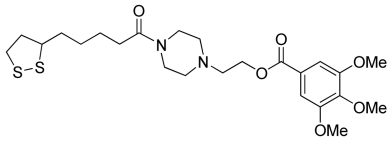
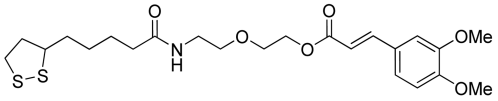
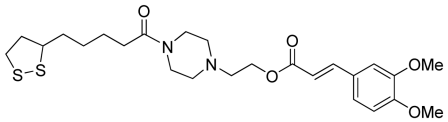
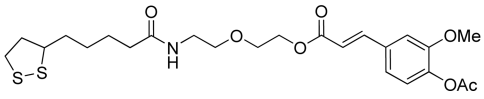
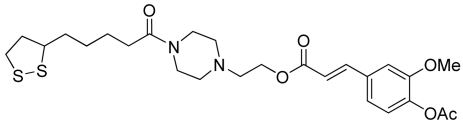
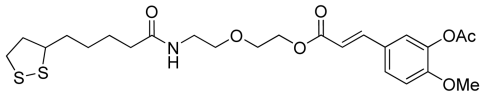
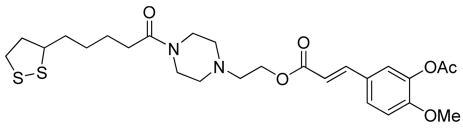
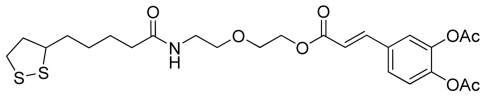
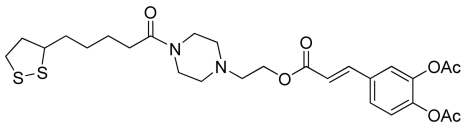
The inhibitory results (IC_{50} value) for AChE and BuChE with ALA, PPs, acetated-PPs, and ALA-hybridized compounds are shown in Table 2.

The parent compounds did not show any inhibitory activity for ChEs. Also, all ALA-derivatives (**5-10**) showed less than 50% inhibition activity at 180 μM for AChE. But all ALA-derivatives showed inhibitory activity for BuChE. Especially, the IC_{50} values of ALA-AcSA (**5-2**) and ALA-AcCA (**10-2**) are decreased to 3.79 ± 1.18 and 0.44 ± 0.24 μM for BuChE inhibition, respectively. They showed a great selectivity for BuChE over AChE.

As we expected, all ALA-linker-2-derivatives improved inhibitory activity for BuChE compared to ALA-linker 1-derivatives except **9-2**. It means the cationic linker moiety of the hybrid compounds may influence to increase their binding affinity to BuChE.

From the activity comparison of 3,4,5-trisubstituted compounds (**5-2** *vs* **6-2**), substitution of acetyl group at *para* position showed slightly better inhibition activity rather than methoxy group substitution. The π value of -OAc group is −0.66 and that of -OMe is −0.02. The Hammett electronic substituent constant value (σ_p) of -OAc group is 0.31 and that of -OMe is −0.27. Molar refractivity (MR) of -OAc group is 12.47 and that of -OMe is 7.87. Since -OAc is more hydrophilic (π values), more electron withdrawing (σ_p value), and bigger MR value[18] than -OMe, hydrophilicity, electron

Table 1. The structures of ALA-derivatives synthesized at the previous[16] and present work

Compounds	Structures with linker 1[16]	Structures with linker 2
ALA-AcSA (**5**)	 (**5-1**)	 (**5-2**)
ALA-TMB (**6**)	 (**6-1**)	 (**6-2**)
ALA-DMC (**7**)	 (**7-1**)	 (**7-2**)
ALA-AcFA (**8**)	 (**8-1**)	 (**8-2**)
ALA-AcMC (**9**)	 (**9-1**)	 (**9-2**)
ALA-AcCA (**10**)	 (**10-1**)	 (**10-2**)

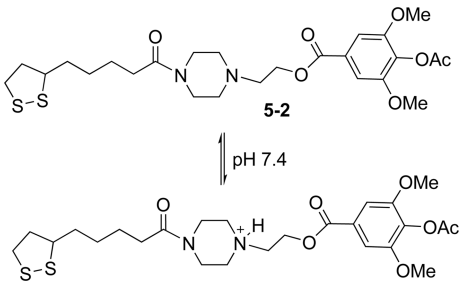


Figure 2. The possible protonated structure of **5-2** at pH 7.4.

withdrawing effect, and size effect might be important factors to increase inhibition potency at 3,4,5-trisubstituted benzoic acid derivatives. At 3,4-disubstituted cinnamic acid derivatives, 3,4-diacetyl group turned out to be better substitution group than mono or dimethoxy group.

To explore the inhibition mechanism, kinetic studies at different concentrations of **7-2** were carried out. The Lineweaver-Burk plot showed that it is the same mixed type inhibition as compound **7-1**, which varied both V_{max} and K_m value (Fig. 3). The K_i value of **7-2** for BuChE is 1.52±0.18 μM.

Conclusions

Seven hybrid compounds (**5-2** ~ **10-2**) were synthesized by using linker 2 to improve binding affinity to ChE. Since ALA-linker 2-PP derivatives majorly exist as quaternary ammonium compounds at pH 7.4, they showed slightly improved inhibitory activity against BuChE compared to ALA-linker 1-PP derivatives. The ammonium moiety of hybrid compounds might affect to enhance binding affinity for BuChE. Especially, the IC_{50} values of **5-2** and **10-2** are 3.79 ± 1.18 and 0.44 ± 0.24 μM, respectively. The selective BuChE inhibitors may have beneficial effect compared to only AChE inhibitors.[8] Further investigations will be carried out to evaluate the activity against AD.

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 record-

Table 2. IC_{50} values of ALA, PPs, AcPPs, and ALA-derivatives for ChE inhibition[a]

Compound	AChE inhibition IC_{50} (μM)	BuChE inhibition IC_{50} (μM)
ALA	>1000	>1000
AcCA	>800	>800
AcSA	>800	>800
AcFA	>800	>800
TMB	>900	>900
DMC	>1000	>400
Galantamine-HBr	1.7 ± 0.9	9.4 ± 2.5

Compound	Compounds **5-1** ~ **10-1** (Linker 1)[16]		Compounds **5-2** ~ **10-2** (Linker 2)	
	AChE inhibition IC_{50} (μM)	BuChE inhibition IC_{50} (μM)	AChE inhibition IC_{50} (μM)	BuChE inhibition IC_{50} (μM)
5 (ALA-AcSA)	>400	124.0 ± 38.2	>400	**3.8 ± 1.2**
6 (ALA-TMB)	>400	39.1 ± 0.9	>190	**10.6 ± 0.2**
7 (ALA-DMC)	>400	26.5 ± 6.4	>180	**11.0 ± 4.6**
8 (ALA-AcFA)	>400	60.9 ± 17.4	>400	**27.7 ± 12.5**
9 (ALA-AcMC)	>400	1.9 ± 0.7	>400	**14.3 ± 0.4**
10 (ALA-AcCA)	>400	**0.5 ± 0.2**	>400	**0.4 ± 0.2**

[a]AChE (from electric eel) and BChE (from horse serum) were used. IC_{50} values represent the concentration of inhibitor required to decrease enzyme activity by 50% and are calculated by using the mean of measurements performed in triplicate.

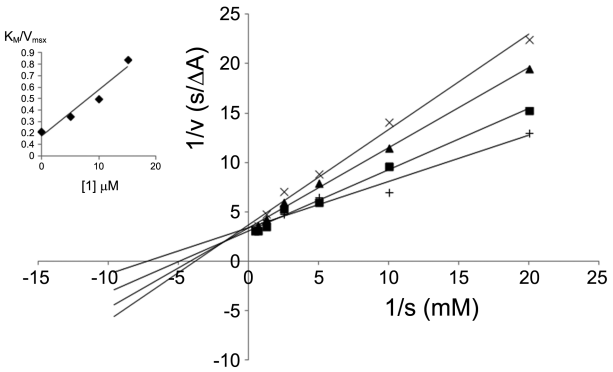


Figure 3. Lineweaver-Burk plot using ALA-DMC (**7-2**) for the inhibitory kinetic study against BuChE (x = 15 μM, ▲ = 10 μM, ■ = 5 μM, = 0 μM). The inset is a plot of [I] *vs*. K_M/V_{max}.

ed 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 dichloromethane (DCM) was dried from calcium hydride. All chemicals were reagent grade unless otherwise specified. The (α)-lipoic acid, NHS, EDC, and cholinesterases [acetylcholinesterase (electric eel, cat. C2888) and butyrylcholinesterase (from horse serum, cat. C-7512)] 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.[19] 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. Acetylthiocholine (ATCh) and butyrylthiocholine (BuTCh) were used as substrates for AChE and BuChE, respectively.

Synthesis.

(α)-2-(4-(5-(1,2-Dithiolan-3-yl)pentanoyl)piperazin-1-yl)ethyl 4-acetoxy-3,5-dimethoxybenzoate (5-2): (α)-Lipoic acid-linker-2 (30 mg, 0.10 mmol) was dissolved in 3 mL DCM. DMAP (31 mg, 0.15 mmol) was 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 quenched by adding 1 N NaOH. The aqueous layer was extracted with 10 mL ether three times. The combined organic layer was washed with 1 N HCl solution and brine. The organic layer was dried over anhydrous $MgSO_4$. After the organic solvent was removed under vacuum, the crude product was purified by column chromatography (DCM:MeOH = 9:1) to give **5-2** as oil (34 mg, 65% yield).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.50 (m, 2H), 1.69 (m, 4H), 1.92 (m, 1H), 2.31 (t, J = 7.6, 2H), 2.34 (s, 3H), 2.42 (m, 1H), 2.56 (m, 4H), 3.11 (m, 2H), 3.47 (t, J = 7.6 2H), 3.60 (m, 4H), 3.87 (s, 6H), 4.46 (t, J = 7.6, 2H), 7.277 (s, 2H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22, 26 (CH_2 × 2), 30, 32, 34, 38, 40, 42, 46 (CH_2 × 2), 51, 54.6, 54.2, 56, 62, 108 (CH × 2), 128, 152 (C × 2), 166, 168, 172, ESI-HRMS: [M]+540.80 (calcd 540.1964).

(α)-2-(4-(5-(1,2-Dithiolan-3-yl)pentanoyl)piperazin-1-yl)ethyl 3,4,5-trimethoxybenzoate (6-2): (α)-Lipoic acid-linker-2 (120 mg, 0.40 mmol) and TMB-acid chloride (150 mg, 0.50 mmol) were reacted by the previous procedure. After the crude product was purified by column chromatography (DCM: MeOH = 9:1), 190 mg **6-2** was obtained (79% yield).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.46 (m, 2H), 1.68 (m, 4H), 1.90 (m, 1H), 2.33 (t, J = 7.6, 2H), 2.47 (m, 1H), 2.56 (q, J = 4.8, 4H), 2.80 (t, J = 6, 2H), 3.15 (m, 6H), 3.475 (t, J = 4.8, 2H), 3.59 (m, 1H), 3.633 (t, J = 5.2, 2H), 3.913 (s, 9H), 4.456 (t, J = 5.6, 2H), 7.275 (s, 1H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.2, 29.3, 31.2, 33.2, 38.7, 40.5, 41.7, 45.7, 53.4, 53.7, 56.4 (CH_2 × 2), 56.6, 56.7, 61.1, 62.6, 106.9 (CH_2 × 2) 125.2, 142.4, 153.1, 166.2, 171.3.

(*R*,*E*)-2-(4-(5-(1,2-Dithiolan-3-yl)pentanoyl)piperazin-1-yl)ethyl 3-(3,4-dimethoxyphenyl)acrylate (7-2): Compound **7-2** (248 mg, 66% yield) was obtained from the previous procedure by using lipoic acid-linker-2 (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) δ 1.49 (m, 2H), 1.67 (m, 4H), 1.92 (m, 1H), 2.33 (s, 3H), 2.48 (m, 6H), 2.73 (t, J = 5.6, 2H), 3.16 (m, 2H), 3.48 (m, 2H), 3.61 (m, 1H), 3.65 (m, 2H), 3.8 (s, 3H), 4.34 (m, 2H), 6.04 (d, J = 16, 1H), 6.92 (d, J = 8, 1H), 7.09 (d, J = 8.4, 2H), 7.63 (t, J = 13.2, 1H), ^{13}C NMR ($CDCl_3$, 100 MHz) 25.2, 29.3, 31.2, 33.1, 35.0, 38.7 40.4, 41.6, 45.6, 53.3, 53.7, 56.1, 56.2, 56.6, 56.9, 61.7, 109.6, 111.1, 115.6, 123.0, 127.4, 145.3, 149.4, 151.4, 167.3, 171.3, ESI-HRMS: [M]+508.90 (calcd 508.2066).

(*R*,*E*)-2-(4-(5-(1,2-Dithiolan-3-yl)pentanoyl)piperazin-1-yl)ethyl 3-(4-acetoxy-3-methoxyphenyl)acrylate (8-2): Compound **8-2** (240 mg, 59% yield) was obtained from 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) δ 1.46 (m, 2H), 1.68 (m, 4H), 1.90 (m, 1H), 2.33 (t, J = 7.6, 2H), 2.47 (m, 1H), 2.56 (q, J = 4.8, 4H), 2.80 (t, J = 6, 2H), 3.15 (m, 6H), 3.475 (t, J = 4.8, 2H), 3.59 (m, 1H), 3.633 (t, J = 5.2, 2H), 3.913 (s, 9H), 4.456 (t, J = 5.6, 2H), 7.275 (s, 1H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.2, 29.3, 31.2, 33.2, 38.7, 40.5, 41.7, 45.7, 53.4, 53.7, 56.4 (CH_2 × 2), 56.6, 56.7, 61.1, 62.6, 106.9 (CH_2 × 2) 125.2, 142.4, 153.1, 166.2, 171.3, ESI-HRMS: [M]+536.80 (calcd 536.2015).

(*R*,*E*)-2-(4-(5-(1,2-Dithiolan-3-yl)pentanoyl)piperazin-1-yl)ethyl 3-(3-acetoxy-4-methoxyphenyl)acrylate (9-2): Compound **9-2** (242 mg, 60% yield) was obtained from 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) δ 1.49 (m, 2H), 1.68 (m, 4H), 1.92 (m, 1H), 2.35 (t, J = 5.6, 2H), 2.44 (m, 1H), 2.53 (m, 4H), 2.72 (t, J = 5.6, 2H), 3.13 (m, 2H), 3.48 (t, J = 4.4, 2H), 3.58 (m, 1H), 3.64 (t, J = 4.8, 2H), 3.87 (s, 3H), 4.33 (t, J = 5.6, 2H), 6.31 (d, J = 16, 1H), 6.97 (d, J = 8.8, 1H), 7.25 (d, J = 2, 1H), 7.37 (d, J = 6.4, 1H), 7.60 (d, J = 2, 1H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.9, 25.2, 29.4, 33.2, 35.0, 38.7, 40.5, 41.7, 45.7, 53.7, 56.2, 56.7, 56.9, 61.9, 112.5, 116.6, 122.2, 128.0, 137.0, 144.2, 171.4 ESI-HRMS: [M]+536.7 (calcd 536.2015).

(*R*,*E*)-4-(3-(2-(4-(5-(1,2-Dithiolan-3-yl)pentanoyl)piperazin-1-yl)ethoxy)-3-oxoprop-1-enyl)-1,2-phenylene diacetate (10-2): Compound **10-2** (220 mg, 60% yield) was obtained from 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) δ 7.23 (d, J = 18.2, 2H), 7.09 (d, 2H), 6.88 (d, 1H), 3.92 (s, 3H), 3.661 (t, 2H), 3.554 (t, 2H), 3.59 (m, 1H), 3.22 (m, 2H), 3.08 (m, 2H), 2.62 (m, 2H), 2.50 (m, 2H), 2.484 (t, 2H), 2.33 (s, 3H), 1.994 (m, 4H), 1.68 (m, 4H), 1.42 (m, 2H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.8 (C × 2), 166.6, 143.7 (C), 142.6 (CH), 133.3 (C × 2), 131.1, 128.0, 124.9, 122.9 (C), 119.2 (CH), 62.0 (CH_2), 56.8 (CH_2 × 2), 56.6 (CH_2 × 2), 53.6 (CH_2), 53.3 (CH), 45.6 (CH_2), 41.6 (CH_2 × 2), 38.6 (CH_2 × 2), 23.1 (CH_3 × 2), ESI-HRMS: [M]+564.70 (calcd 564.1964).

Acknowledgments. This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2012R1A1A2006937).

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