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COVALENT AND IONIC CONJUGATES OF TROLOX AND α-TOCOPHEROL WITH 1-AMINOADAMANTANE

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Covalent, ionic, and ionic-covalent conjugates of trolox and α-tocopherol with 1-aminoadamantane were synthesized. Their structures were elucidated using mass spectrometry and IR, PMR, and ^{13}C NMR spectroscopy. The water solubility of the ionic trolox conjugates with 1-aminoadamantane increased by 2–24 times as compared with that of trolox whereas that of the α-tocopherol succinate conjugates remained the same as that of α-tocopherol.

Keywords: trolox, α-tocopherol, 1-aminoadamantane, adamantane dimers, ionic conjugates, covalent conjugates, water solubility.

Targeted modification of lead molecules with pronounced biological activity is one of the most promising thrusts of synthetic organic and pharmaceutical chemistry for new drug development [1, 2]. Conjugation of two or more pharmacologically active molecules with considerably different properties can be utilized to synthesize new biologically active compounds [3, 4]. Molecular hybridization of natural and synthetic medicinal and inactive compounds has been demonstrated in the last 20 years to be effective for developing anticancer, antiviral, antifungal, antimalarial, antituberculosis, anti-inflammatory, and other agents. In most instances, the hybrid molecules are less toxic than the individual starting compounds and exhibit synergism, indicating that conjugates have greater pharmacological potential [5].

The platform molecules α-tocopherol and trolox were considered promising for synthesizing hybrid compounds because they contain the chromane moiety, an important chemical synthon for constructing drugs to treat diseases associated with oxidative stress. Several examples showed that compounds with chromane moieties exhibit broad spectra of biological activity, e.g., antioxidant, neuroprotective, anticancer, etc. [6, 7].

The second pharmacophore consisted of adamantane derivatives, which exhibit broad spectra of biological activity and can enhance the lipophilicity and stability of pharmacologically active compounds by improving their pharmacokinetics and ability to penetrate the blood–brain barrier as compared with the unmodified analogs [8, 9]. Amine-derivatives of adamantane such as amantadine, rimantadine, and trimantadine became famous for their activity against flu virus. However, amantadine is a CNS-active compound, i.e., an NMDA-receptor antagonist, and is used for complex therapy of mid-stage Parkinson's and Alzheimer's diseases. Currently, memantine is under scrutiny as a moderate non-competitive NMDA-receptor antagonist.

α-Tocopherol and trolox acted as platforms for preparing many hybrid compounds with various biological activities. In most instances, trolox was modified at the chromane 2-carboxylic acid; α-tocopherol, at the phenolic 6-OH. α-Tocopherol and trolox were chemically modified at three positions, i.e., the aromatic 5-Me, the phenolic 6-OH, and the trolox chromane 2-COOH, by selecting 1-aminoadamantane as the modifier and using both covalent and ionic bonding. The ionic hybridization allowed the water solubility of the obtained conjugates to be increased, thereby expanding their possible applications [10].

The amide of trolox (**3**) was prepared by reacting 1-aminoadamantane with succinimide **2**, which was synthesized from **1** and *N*-hydroxysuccinimide in THF in the presence of carbonyldiimidazole (CDI). Ammonium salt **4** was prepared by adding a solution of 1-aminoadamantane to a solution of trolox in THF in a 1:1 mole ratio at 20–25°C (Scheme 1).

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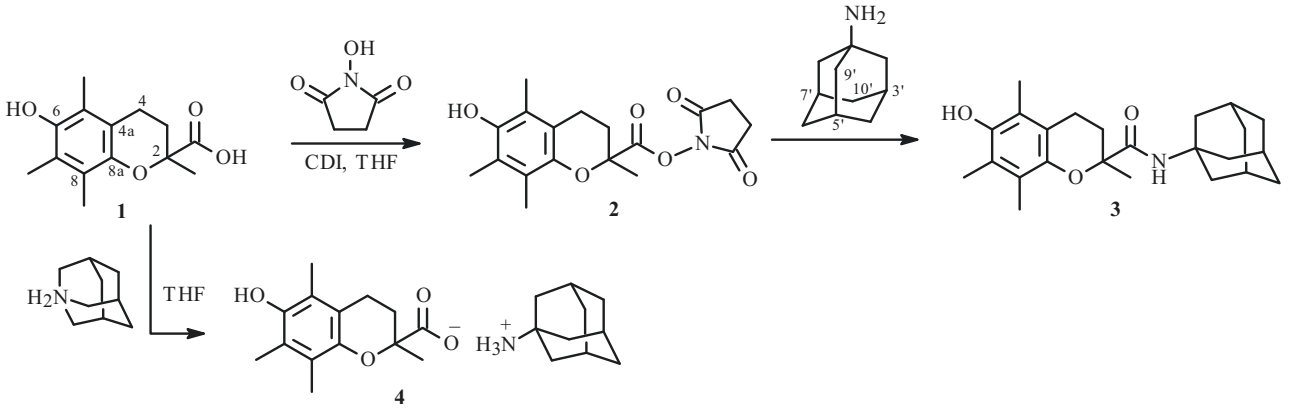
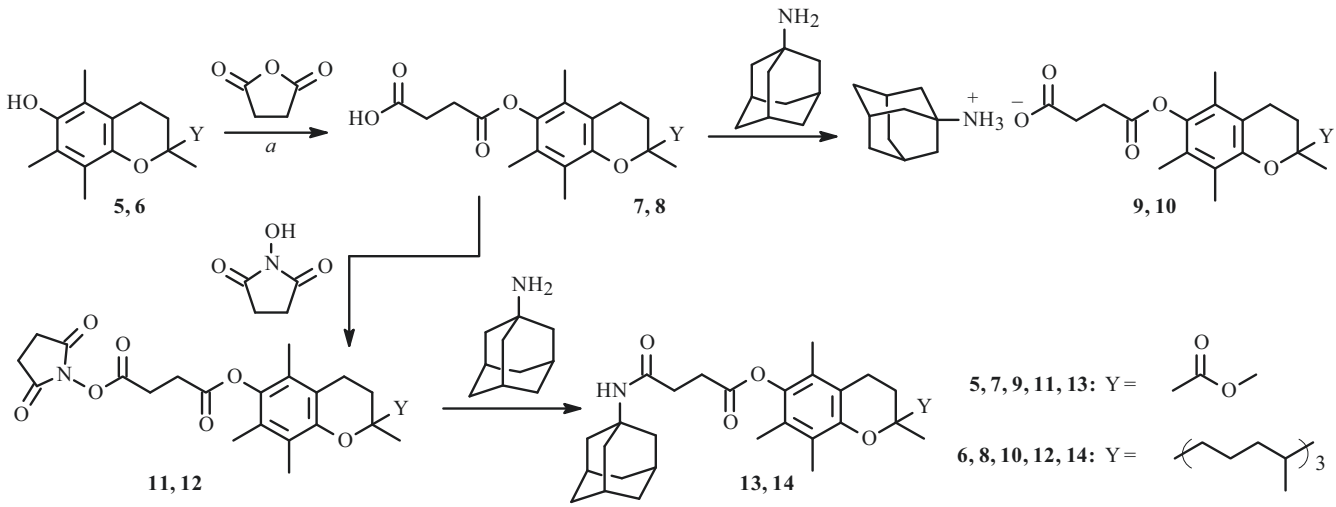


Scheme 1

Trolox and α-tocopherol derivatives modified at the phenolic 6-OH were prepared from trolox methyl ester **5** and α-tocopherol **6** by reacting their succinyl derivatives **7** and **8** with a solution of 1-aminoadamantane in THF in a 1:1 mole ratio to give the corresponding ammonium salts **9** and **10**. Treatment of trolox and α-tocopherol succinyl derivatives **7** and **8** with *N*-hydroxysuccinimide and 1-aminoadamantane gave their amide derivatives **13** and **14** (Scheme 2).



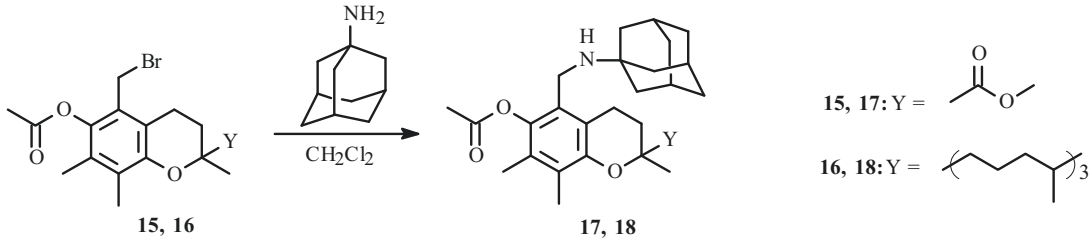
a. DMAP, Et_3N, CH_2Cl_2

Scheme 2

IR spectra of covalent conjugates **3**, **13**, and **14** exhibited characteristic bands for amide stretching vibrations at 1660–1678 cm^{-1}; ionic conjugates **4**, **9**, and **10**, bands for asymmetric and symmetric carboxylate-anion stretching vibrations at 1606–1637 and 1398–1408 cm^{-1}, respectively; and bands for quaternary N bending vibrations (δN–H) at 1552–1556 cm^{-1} [11, 12]. This argued in favor of ionic structures for **4**, **9**, and **10**. Furthermore, IR spectra of **9**, **10**, **13**, and **14** showed characteristic bands for ester C=O stretching vibrations at 1737–1755 cm^{-1}.

PMR and ^{13}C NMR spectra of **3**, **4**, **9**, **10**, **13**, and **14** exhibited all characteristic resonances of trolox, α-tocopherol, and 1-aminoadamantane moieties. The resonance of the carboxylate C atom of **4** (181.74 ppm) underwent a weak-field shift of 5.44 ppm relative to that of the carboxylic C atom of trolox (176.30 ppm), which was characteristic for carboxylic C atoms after forming salts [13].

Trolox and α-tocopherol conjugates with 1-aminoadamantane in the aromatic 5-position were prepared by synthesizing their 5-bromomethyl derivatives **15** and **16** via bromination of trolox methyl ester **5** and α-tocopherol **6** followed by acylation with acetic anhydride in CH_2Cl_2 in the presence of AcOH and H_2SO_4 [14, 15]. The reactions of **15** and **16** with 1-aminoadamantane in CH_2Cl_2 followed by neutralization of the reaction mixture with KOH solution produced 5-aminomethyl derivatives **17** and **18** (Scheme 3).



Scheme 3

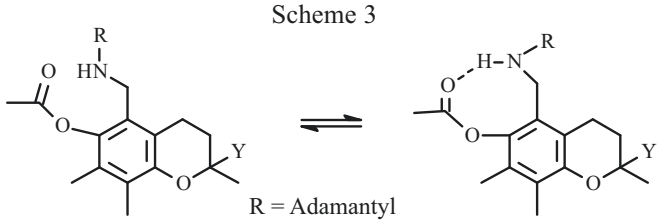
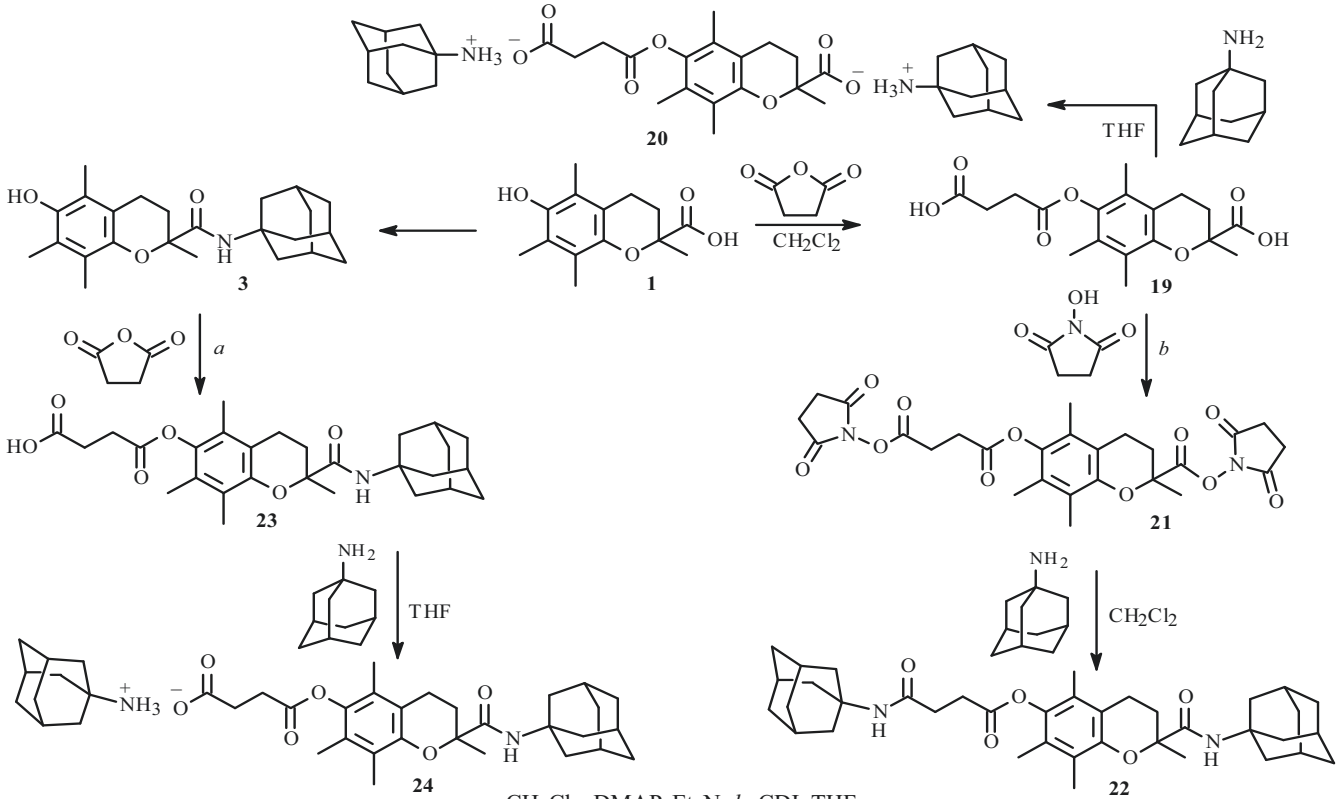


Fig. 1. Formation of intramolecular H-bond in **17** and **18**.

IR spectra of amines **17** and **18** contained characteristic bands for 6-C=O ester stretching vibrations as 1755–1759 cm^{-1} and bands at 1620 cm^{-1}. The shift of characteristic bands at 1760–1730 to 1620 cm^{-1} could have been due to the formation of an intramolecular H-bond of the C=O O atom and the NH H atom (Fig. 1). Trolox amine **17** showed ester 2-C=O stretching bands at 1738 cm^{-1}. PMR and ^{13}C NMR spectra of **17** and **18** had all characteristic resonances for the 1-aminoadamantane, α-tocopherol, and trolox moieties.

Furthermore, dimers of 1-aminoadamantane in which its molecules were joined by covalent, ionic, and ionic-covalent bonds using trolox succinate as a linker were also synthesized.

Ionic dimer **20** was synthesized by reacting trolox succinate **19** with 1-aminoadamantane in a 1:2 mole ratio in THF. Compound **19** was produced via acylation of trolox by succinic anhydride in CH_2Cl_2 in the presence of DMAP and Et_3N. Reaction of **19** with *N*-hydroxysuccinimide in a 1:2 ratio in THF in the presence of CDI gave trolox succinate succinimide **21**, which reacted with 1-aminoadamantane in a 1:2 ratio in CH_2Cl_2 to synthesize covalent dimer **22**. Acylation of amide **3** by succinic anhydride in CH_2Cl_2 in the presence of DMAP and Et_3N synthesized succinate **23** that reacted further with 1-aminoadamantane in THF to afford ionic-covalent dimer **24** (Scheme 4).



a. CH_2Cl_2, DMAP, Et_3N; *b*. CDI, THF

Scheme 4

IR spectra of **20** and **22**–**24** exhibited characteristic bands for ester C=O stretching vibrations at 1743–1757 cm^{-1} and for amides at 1645–1679 cm^{-1}. Compound **23** also showed a carboxylic C=O stretching band at 1715 cm^{-1}. IR spectra of **20** and **24** contained bands for asymmetric and symmetric carboxylate-anion stretching vibrations at 1626, 1627 and 1389,1392 cm^{-1}, respectively, and bands for quaternary N bending vibrations (δN–H) at 1560 cm^{-1} [10, 11], indicating that these conjugates had ionic bonds.

PMR and ^{13}C NMR spectra of **20** and **22**–**24** exhibited all characteristic resonances for succinyl, trolox, and 1-aminoadamantane moieties. The ^{13}C NMR spectrum of **20** showed characteristic weak-field shifts of 3.92 and 4.13 ppm for the carboxylate C atoms relative to those of carboxylic C atoms of trolox succinate **19** [13]. PMR and ^{13}C NMR spectra of ionic-covalent conjugate **24** contained two sets of resonances in a 2:1 ratio. This may have been due to the presence of the asymmetric C atom and hindered rotation around the C–N amide bond.

Thus, spectral results confirmed the structures of the ionic, covalent, and ionic-covalent conjugates of trolox and α-tocopherol.

Water solubilities of ionic conjugates **4**, **9**, **10**, **20**, and **24** were determined by the literature method [16]. The results are given below:

Compound	*Water solubility, g/L*	*Compound*	*Water solubility, g/L*
1	0.1	**10**	< 0.1
6	< 0.1	**20**	2.4
4	1	**24**	0.2
9	0.3		

The water solubility of trolox conjugates with 1-adamantane **4**, **9**, **20**, and **24** increased by 2–24 times as compared with trolox (**1**). This allowed these conjugates to be given the pharmacopoeial classifications [17] very slightly (VSS) and slightly soluble (SS), respectively. However, the solubility of ionic conjugate **10** turned out to be the same as that of α-tocopherol **6**. This may have been due to the high lipophilicity of the 2-alkyl group of α-tocopherol. Ionic conjugate **10**, like **6**, had the pharmacopoeial classification insoluble in water (PI).

Thus, covalent, ionic, and ionic-covalent conjugates were synthesized from trolox and α-tocopherol and 1-adamantane. Their compositions and structures were confirmed by elemental analyses, mass spectrometry, and IR, PMR, and ^{13}C NMR spectroscopy. The obtained conjugates were variously soluble in water and, obviously, had different lipophilicities and bioavailabilities. This provided an opportunity to construct new drug prototypes from them.

EXPERIMENTAL

NMR spectra of compounds in CD_3OD and $CDCl_3$ solutions were recorded on Bruker AV-300, AV-400, and DRX-500 spectrometers. IR spectra were recorded from KBr pellets on a Vector-22 instrument. Elemental analyses used a Euro EA3000 CHN Elemental Analyzer and agreed with those calculated for **4**, **10**, **18**, and **20**. Melting points were measured on a Mettler Toledo FP 90 Central Processor apparatus at heating rate 5°C/min in the range 50–300°C with an uncertainty of ±0.3°C. Mass spectrometry was performed on an Agilent 1200 liquid chromatograph with a micrOTOF-Q hybrid quadrupole–time-of-flight mass spectrometer (Bruker) using direct sample introduction, mass detection with electrospray at atmospheric pressure (API-ES), scanning of positive and negative ions in the range *m*/*z* 80–3000, capillary potential (V_{cap}) 4500 V, sprayer pressure 1.6 bar, drying-gas (N_2) temperature 230°C at flow rate 8 L/min.

Trolox, CDI, and 1-aminoadamantane hydrochloride (Acros Organics); D,L-α-tocopherol (Alfa Aesar), and *N*-hydroxysuccinimide (Aldrich) were purchased.

Trolox succinimide (**2**) was prepared by reacting trolox (**1**) with *N*-hydroxysuccinimide in THF in the presence of CDI [18]. Trolox methyl ester (**5**) was prepared by methylating **1** with diazomethane in MeOH–CH_2Cl_2 in a 1:1 ratio and was recrystallized from this mixture [19]. Succinyl derivatives **7** and **8** were synthesized from **5** and **6** according to the literature [20]. 5-Bromomethyl derivatives of trolox and α-tocopherol (**15** and **16**) were synthesized as before [14, 15] via bromination of **5** and **6** followed by acylation by acetic anhydride in CH_2Cl_2 in the presence of AcOH and H_2SO_4. Trolox succinate **19** was prepared by reacting trolox with succinic anhydride in CH_2Cl_2 in the presence of Et_3N and DMAP [20]. Trolox succinate succinimide **21** was obtained from the reaction of **19** with *N*-hydroxysuccinimide in a 1:2 ratio in THF in the presence of CDI [18]. 1-Aminoadamantane was obtained by extraction with Et_2O from an alkaline aqueous solution of 1-aminoadamantane hydrochloride.

6-Hydroxy-*N*-(1-adamantanamine)-2,5,7,8-tetramethylchromane-2-carboxamide (3). A solution of trolox succinimide (**2**, 36 mg, 0.1 mmol) in CH_2Cl_2 (0.5 mL) at 20–25°C was stirred, treated with 1-aminoadamantane (17.3 mg, 0.11 mmol) in CH_2Cl_2 (1 mL), stirred for 16–20 h at 20–25°C, washed with H_2O, dried over Na_2SO_4, and evaporated. Yield 83%, viscous light-yellow liquid. IR spectrum (KBr, ν, cm^{-1}): 1661 (CONH). Mass spectrum: found *m/z* 384.255 $[M + H]^+$, calcd for $C_{24}H_{34}NO_3$, 384.253. ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.45, 2.08, 2.14, 2.17 (each 3H, s, CH_3), 2.18–2.27 (1H, m, Ha-3), 2.50–2.63 (2H, m, CH_2-4), 1.62 (6H, t, J = 3.0, H-4′, 6′, 10′), 1.86–1.88 (6H, m, H-2′, 8′, 9′), 1.98–2.05 (4H, m, H-3′, 5′, 7′, Hb-3). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 11.36, 11.91, 12.29 (CH_3-5, 7, 8), 20.47, 24.05, 29.39 (C-3, 4, CH_3-2), 29.36, 36.29, 41.34 (CH_2-4′, 6′, 10′, 2′, 8′, 9′, CH-3′, 5′, 7′), 51.23 (C-1′), 78.12 (C-2), 118.08, 118.96, 121.33, 121.74 (C-5, 7, 8, 4a), 144.27, 145.46 (C-6, 8a), 173.40 (C=O).

1-Adamantylammonium 6-Hydroxy-2,5,7,8-tetramethylchromane-2-carboxylate (4). Trolox (21 mg, ~0.08 mmol) in THF (0.5 mL) was treated with 1-aminoadamantane (12.6 mg, 0.08 mmol) in THF (0.3 mL), held for 16–20 h at 20–25°C, and evaporated. The viscous residue was triturated with Et_2O until the formation of a powder that was filtered off, rinsed with EtOAc, and dried to constant weight. Yield 72%, white powder, mp 247.9–249.4°C. $C_{24}H_{35}NO_4$. IR spectrum (KBr, ν, cm^{-1}): 1398 and 1606 (COO^-), 1554 (δN-H). ^1H NMR spectrum (400 MHz, CD_3OD, δ, ppm): 1.52, 2.07, 2.15, 2.17 (each 3H, s, CH_3), 1.66–1.85 (13H, m, H-2′, 4′, 6′, 8′, 9′, 10′, Hb-3), 2.13–2.18 (3H, m, H-3′, 5′, 7′), 2.39–2.45 (1H, m, Ha-3), 2.55–2.69 (2H, m, H-4). ^{13}C NMR spectrum (125 MHz, $CDCl_3$, δ, ppm) 11.84, 12.34, 12.80 (C-5, 7, 8), 22.60, 25.73, 32.35 (C-3, 4, 2), 30.41, 36.46, 41.50 (C-2′, 4′, 6′, 8′, 9′, 10′, 3′, 5′, 7′), 52.58 (C-1′), 79.55 (C-2), 118.65, 121.69, 123.02, 124.05 (C-5, 7, 8, 4a), 145.89, 147.96 (C-6, 8a), 181.74 (C=O).

1-Adamantanylammonium 4-[2-(Methoxycarbonyl)-2,5,7,8-tetramethylchroman-6-yloxy]-4-oxobutanoate (9). Succinate **7** (16.2 mg, ~0.04 mmol) in THF (0.5 mL) was treated with 1-aminoadamantane (6.7 mg, 0.04 mmol) in THF (0.3 mL), held for 16–20 h at 20–25°C, and evaporated. The viscous residue was triturated with Et_2O until the formation of a powder that was filtered off, rinsed with EtOAc, and dried to constant weight. Yield 85%, white powder, mp 141.5–142.4°C. IR spectrum (KBr, ν, cm^{-1}): 1408 and 1625 (COO^-), 1556 (δN-H), 1737, 1753 (ester COO). Mass spectrum: found *m/z* 516.292 $[M + H]^+$, calcd for $C_{29}H_{42}NO_7$, 516.296. ^1H NMR spectrum (400 MHz, CD_3OD, δ, ppm, J/Hz): 1.60, 1.95, 2.03, 2.14 (each 3H, s, CH_3), 1.66–1.90 (14H, m, H-3, 2′, 4′, 6′, 8′, 9′, 10′), 2.15–2.19 (3H, m, H-3′, 5′, 7′), 2.40–2.50 (2H, m, H-4), 2.56 (2H, t, J = 7.0), 2.88 (2H, t, J = 7.0) – succinyl CH_2; 3.67 (3H, s, $COOCH_3$).

1-Adamantanylammonium 4-Oxo-4-[2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)chroman-6-yloxy]butanoate (10). Succinate **7** (13.3 mg, ~0.025 mmol) in THF (0.5 mL) was treated with 1-aminoadamantane (3.8 mg, 0.025 mmol) in THF (0.3 mL), held for 16–20 h at 20–25°C, and evaporated. The residue was triturated with Et_2O until the formation of a viscous precipitate that was filtered off, rinsed with EtOAc, and dried to constant weight. Yield 96%, white viscous liquid. $C_{43}H_{71}NO_5$. IR spectrum (KBr, ν, cm^{-1}): 1408 and 1637 (νCOO$^-$), 1552 (δN-H), 1755 (ester νCOO). ^1H NMR spectrum (400 MHz, CD_3OD, δ, ppm, J/Hz): 0.87–0.93 (12H, m, alkyl side-chain CH_3), 1.07–1.64 (21H, m, alkyl side-chain CH_2 and CH), 1.27, 2.00, 2.03, 2.10 (each 3H, s, CH_3), 2.60–2.67 (4H, m) and 2.91 (2H, t, J = 7.0) succinyl CH_2-4 and CH_2; 1.69–1.91 (14H, m, H-3, 2′, 4′, 6′, 8′, 9′, 10′), 2.15–2.22 (3H, m, H-3′, 5′, 7′).

Methyl-6-[4-(1-aminoadamantane)-4-oxobutanoyloxy]-2,5,7,8-tetramethylchromane-2-carboxylate (13). Succinimide **11** was prepared by reacting succinate **7** with *N*-hydroxysuccinimide in a 1:1 ratio [17] and used without further purification. Succinimide **11** (22.4 mg, 0.048 mmol) in CH_2Cl_2 (0.2 mL) was treated with 1-aminoadamantane (7.4 mg, 0.048 mmol) in CH_2Cl_2 (0.4 mL), held for 16–20 h at 20–25°C, washed with H_2O, dried over $MgSO_4$, and evaporated. Yield 70%, viscous light-yellow liquid. IR spectrum (ν, cm^{-1}): 1660 (CONH), 1737, 1751 (ester COO). Mass spectrum: found *m/z* 498.283 $[M + H]^+$, calcd for $C_{29}H_{40}NO_6$, 498.285. ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm): 1.57 (s) and 1.58 (s) (3H, CH_3), 1.95 (s) and 1.96 (s) (3H, CH_3), 1.99 (3H, s, CH_3), 2.12 (s) and 2.13 (s) (3H, CH_3), 1.66–1.90 (14H, m, H-3, 2′, 4′, 6′, 8′, 9′, 10′), 2.15–2.19 (3H, m, H-3′, 5′, 7′), 2.34–2.66 (4H, m) and 2.81–2.96 (2H, m) succinyl CH_2-4 and CH_2; 3.65 (s) and 3.66 (s) (3H, COO-$\underline{CH_3}$).

2,5,7,8-Tetramethyl-2-(4,8,12-trimethyltridecyl)chroman-6-yl 1-Aminoadamantane-4-oxobutanoate (14). 1-Aminoadamantane (5.7 mg, 0.04 mmol) in CH_2Cl_2 (0.7 mL) was treated dropwise with a solution of succinimide **12** (21.6 mg, 0.03 mmol) in CH_2Cl_2 (0.4 mL), held for 16–20 h at 20–25°C, washed with H_2O, dried over $MgSO_4$, and evaporated. Succinimide **12** was prepared by reacting succinate **8** with *N*-hydroxysuccinimide in a 1:1 ratio [17] and used without further purification. Yield 86%, viscous light-yellow liquid. IR spectrum (KBr, ν, cm^{-1}): 1678 (CONH), 1747 (ester COO). Mass spectrum: found *m/z* 664.527 $[M + H]^+$, calcd for $C_{43}H_{70}NO_4$, 664.530. ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.80–0.86 (12H, m, alkyl side-chain CH_3; 0.96–1.56 (21H, m, alkyl side-chain CH_2 and CH), 1.93, 1.98, 2.06 (each 3H, s,

CH_3), 2.49 (2H, t, J = 6.7), 2.52–2.59 (2H, m), 2.93 (2H, t, J = 6.7) succinyl CH_2-4 and CH_2; 1.70–1.81 (2H, m, H-3), 1.62–1.66 (6H, m) and 1.94–1.97 (6H, m) adamantane CH_2 CH_2-2′, 4′, 6′, 8′, 9′, 10′, 2.01–2.05 (3H, m, H-3′, 5′, 7′).

Methyl-6-acetoxy-5-[(1-adamantaneamino)methyl]-2,7,8-trimethylchromane-2-carboxylate (17). A solution of 1-adamantane (11.8 mg, 0.08 mmol) in CH_2Cl_2 (0.1 mL) at 20–25°C was stirred, treated with a solution of trolox methyl ester 5-bromomethyl derivative **15** (12 mg, 0.03 mmol), stirred for 16–20 h at 20–25°C, treated with aqueous KOH solution (10%), stirred for 30 min, washed with H_2O, dried over $MgSO_4$, and purified by column chromatography over silica gel using $CHCl_3$–MeOH (10:0.5). Yield 81%, viscous light-orange liquid. IR spectrum (KBr, ν, cm^{-1}): 1738, 1755 (ester COO). Mass spectrum: found *m/z* 456.274 $[M + H]^+$, calcd for $C_{27}H_{38}NO_5$, 456.274. ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm): 1.64, 2.05, 2.20 (each 3H, s, CH_3), 1.60–1.76 (12H, m, H-2′, 4′, 6′, 8′, 9′, 10′), 1.85–1.97 (2H, m, H-3), 2.07–2.14 (3H, m, H-3′, 5′, 7′), 2.37 (3H, s, acetate CH_3), 2.39–2.48 (1H, m, Ha-4), 2.59–2.76 (1H, m, Hb-4), 3.40–3.64 (2H, m, H-5), 3.72 (3H, s, COO-$\underline{CH}_3$). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 12.09, 13.01 phenol CH_3; 19.50 (CH_3-2), 20.78, 52.47 (acetate CH_3, COO-$\underline{CH}_3$); 30.13, 36.27 (C-3, 4), 41.83 (CH_2-5), 77.49 (C-2), 117.98, 124.95, 127.49 (C-5, 7, 8, 4a), 141.61, 149.60 (C-6, 8a), 170.39, 174.44 – carbonyl C atoms; 29.61, 36.76, 42.40 (C-2′, 4′, 6′, 8′, 9′, 10′, 3′, 5′, 7′), 50.75 (C-1′).

5-[(1-Adamantanamino)methyl]-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)chroman-6-yl Acetate (18). A solution of 1-aminoadamantane (26.4 mg, 0.17 mmol) in CH_2Cl_2 (0.1 mL) at 20–25°C was stirred, treated with a solution of α-tocopherol 5-bromomethyl derivative **16** (48 mg, 0.09 mmol), stirred for 16–20 h at 20–25°C, treated with aqueous KOH (10%), stirred for 30 min, washed with H_2O, dried over $MgSO_4$, and purified by column chromatography over silica gel using EtOAc. Yield 45%, viscous yellow liquid. $C_{41}H_{67}NO_3$. IR spectrum (KBr, ν, cm^{-1}): 1620, 1759 (ester COO). ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm): 0.79–0.86 (12H, m, alkyl side-chain CH_3); 0.98–1.79 (23H, m, CH_2-3, alkyl side-chain CH_2 and CH), 1.20, 2.06, 2.07 (each 3H, s, CH_3), 2.12 (3H, s, acetate CH_3), 1.56–1.75 (12H, m, H-2′, 4′, 6′, 8′, 9′, 10′), 2.04–2.10 (3H, m, H-3′, 5′, 7′), 2.57–2.66 (2H, m, H-4), 3.89 (2H, s, H-5a).

1-Adamantaneammonium 6-(3-Carboxylatopropanoyloxy)-2,5,7,8-tetramethylchromane-2-carboxylate (20). Trolox succinate **19** (14.1 mg, ~0.04 mmol) in THF (0.5 mL) was treated with 1-aminoadamantane (12.2 mg, 0.08 mmol) in THF (0.3 mL), held for 16–20 h at 20–25°C, and evaporated. The viscous precipitate was triturated with Et_2O until the formation of a powder that was filtered off, washed with EtOAc, and dried to constant weight. Yield 85%, white powder, mp 179.6°C (dec.). $C_{38}H_{56}N_2O_7$. IR spectrum (KBr, ν, cm^{-1}): 1389 and 1626 (COO^-), 1560 (δN-H), 1757 (ester COO). ^1H NMR spectrum (300 MHz, CD_3OD, δ, ppm, J/Hz): 1.56, 1.96, 2.03, 2.19 (each 3H, s, CH_3), 2.41–2.49 (1H, m, Ha-3), 2.56–2.66 (4H, m) and 2.89 (2H, t, J = 7.1) succinyl CH_2-4 and CH_2; 1.70–1.88 (25H, m, H-2′, 4′, 6′, 8′, 9′, 10′, 2″, 4″, 6″, 8″, 9″, 10″, Hb-3), 2.14–2.19 (6H, m, H-3′, 5′, 7′, 3″, 5″, 7″). ^{13}C NMR spectrum (75 MHz, CD_3OD, δ, ppm): 12.27, 13.19 (CH_3-5, 7, 8), 22.50, 25.89, 31.51, 32.03, 33.28 (C-3, 4, succinyl CH_3-2 and CH_2), 30.41, 36.45, 41.52 (C-4′, 6′, 10′, 2′, 8′, 9′, 3′, 5′, 7′), 52.66 (C-1′), 80.16 (C-2), 119.30, 123.76, 126.02, 127.63 (C-5, 7, 8, 4a), 141.93, 151.67 (C-6, 8a), 174.17 – carbonyl C atom; 179.64, 181.15 – carboxylate C atoms.

2,5,7,8-Tetramethyl-2-(1-adamantanecarbamoyl)chroman-6-yl 4-Oxo-4-(1-adamantaneamino)butanoate (22). A solution of trolox succinate succinimide **21** (20 mg, 0.036 mmol) in CH_2Cl_2 (0.4 mL) at 20–25°C was stirred, treated with 1-aminoadamantane (11.1 mg, 0.07 mmol) in CH_2Cl_2 (0.8 mL), stirred for 48 h at 20–25°C, washed with H_2O, dried over Na_2SO_4, and evaporated. Yield 54%, viscous light-yellow liquid. IR spectrum (KBr, ν, cm^{-1}): 1662 (CONH), 1743 (ester COO). Mass spectrum: found *m/z* 617.386 $[M + H]^+$, calcd for $C_{38}H_{53}N_2O_5$, 617.395. ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm): 1.42–1.48 (3H, s, CH_3-2), 1.94, 2.01, 2.12 (each 3H, s, CH_3), 2.45–2.51 (2H, m), 2.52–2.62 (2H, m) and 2.86–2.95 (2H, m) succinyl CH_2-4 and CH_2; 1.56–1.67 (13H, m), 1.86–1.98 (4H, m), 1.92–1.97 (12H, m), 2.02–2.06 (3H, m) H-2′, 4′, 6′, 8′, 9′, 10′, 2″, 4″, 6″, 8″, 9″, 10″, Ha-3′, 5′, 7′, 3″, 5″, 7″, 3.

4-[2-(1-Adamantanecarbamoyl)-2,5,7,8-tetramethylchroman-6-yloxy]-4-oxobutanoic Acid (23). A solution of trolox amide **3** (27.3 mg, 0.07 mmol) in CH_2Cl_2 (0.3 mL) at 20–25°C was stirred; treated with succinic anhydride (21.3 mg, 0.21 mmol), DMAP (4 mg), and Et_3N (11 μL); stirred for 48 h at 20–25°C; washed with HCl solution (5%); dried over Na_2SO_4; and evaporated. Yield 79%, viscous light-yellow liquid. IR spectrum (KBr, ν, cm^{-1}): 1645 (CONH), 1714 (COOH), 1747 (ester COO). Mass spectrum: found *m/z* 482.265 $[M + H]^+$, calcd for $C_{28}H_{36}NO_6$, 482.255. ^1H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm): 1.45, 1.94, 2.02, 2.12 (each 3H, s, CH_3), 2.50–2.62 (2H, m, H-4), 2.77–2.83 (2H, m) and 2.88–2.94 (2H, m) succinyl CH_2; 1.58–1.66 (7H, m), 1.83–1.93 (7H, m) – H-4′, 6′, 10′, 2′, 8′, 9′ and 3; 2.00–2.05 (3H, m, H-3′, 5′, 7′). ^{13}C NMR spectrum (75 MHz, $CDCl_3$, δ, ppm): 11.81, 11.95, 12.82 (CH_3-5, 7, 8), 20.14, 24.18, 28.23, 28.45, 28.72 (C-3, 4, CH_3-2, succinyl CH_2); 29.22, 36.11, 41.21 (CH_2-2′, 4′, 6′, 8′, 9′, 10′, CH-3′, 5′, 7′), 51.20 (C-1′), 78.35 (C-2), 118.16, 122.11, 125.53, 127.10 (C-5, 7, 8, 4a), 141.24, 147.95 (C-6, 8a), 170.62, 173.12, 177.11 – carbonyl, carboxylic, and carboxamide C atoms.

1-Adamantaneammonium 4-[2-(1-Adamantanecarbamoyl)-2,5,7,8-tetramethylchroman-6-yloxy]-4-oxobutanoate (24). A solution of succinate **23** (19.1 mg, 0.04 mmol) in THF (0.3 mL) at 20–25°C was treated with 1-aminoadamantane (5.99 mg, 0.04 mmol) in THF (0.3 mL), held for 16–20 h at 20–25°C, and evaporated. The residue was triturated with Et_2O until the formation of a viscous precipitate that was filtered off, washed with EtOAc, and dried to constant weight. Yield 71%, light-yellow liquid. IR spectrum (KBr, ν, cm^{-1}): 1392 и 1628 (COO^-), 1560 (δN-H), 1657 (CONH), 1757 (ester COO). Mass spectrum: found *m/z* 635.405 $[M + H]^+$, calcd for $C_{38}H_{55}N_2O_6$, 635.406. ^1H NMR spectrum (400 MHz, CD_3OD, δ, ppm): 1.49 (1H, s) and 1.52 (2H, s) CH_3; 2.08 (2H, s) and 2.10 (1H, s) CH_3; 2.16–2.22 (6H, m, CH_3), 1.67–1.93 (28H, m) and 1.98–2.07 (4H, m) CH_2-3, adamantane CH_2 and CH; 2.44–2.68 (5H, m) and 2.91 (1H, t, J = 6.9) succinyl CH_2-4 and CH_2. ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 10.45, 10.58, 10.64, 10.90, 11.39, 11.80 (CH_3-5, 7, 8), 19.95, 20.18, 23.47, 23.69, 29.32, 29.40, 29.42, 29.52, 31.28, 31.75 (C-3, 4, succinyl CH_3-2 and CH_2); 29.00, 29.82, 35.06, 36.13, 40.13, 40.79 (CH_2-4′, 6′, 10′, 2′, 8′, 9′, CH-3′, 5′, 7′), 50.61, 51.30 (C-1′); 77.87, 78.34 (C-2), 117.49, 118.10, 120.96, 121.07, 121.81, 123.40, 125.80, 127.43 (C-5, 7, 8, 4a), 141.76, 144.04, 145.93, 147.74 (C-6, 8a); 173.81, 174.09, 174.27, 177.74, 178.03, 178.14 – carbonyl, carboxylic, and carboxamide C atoms.

Determination of the Solubility of 1, 4, 6, 9, 10, 20, and 24 [16]. Weighed portions of **1**, **4**, **6**, **9**, **10**, **20**, and **24** (0.5–1 mg) were treated with distilled H_2O (0.1–0.5 mL) and shaken for 10 min. The addition of H_2O was repeated until the compounds were completely dissolved or a solubility of <0.1 g/L was reached. The transparency was determined visually by comparing the test solution with the solvent.

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