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Synthesis of Allocolchicine Conjugates with a Cetirizine Analog

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Abstract—Conjugates of allocolchicine and a cetirizine analog have been synthesized as potential anti-inflammatory and anti-allergic drugs.

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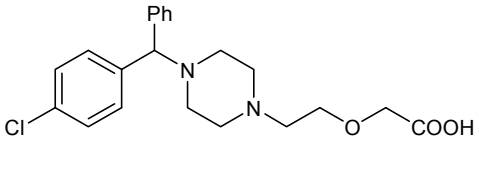
Allergy is one of the six most frequent pathologies [1]. Anti-allergic medications include mainly antihistamine drugs, in particular inverse agonists and neutral antagonists of histamine H1 receptors [2–9]. Inverse agonists bind to receptors and stabilize their inactive conformation [10]. Neutral antagonists do not affect the activity of basal receptors but hamper agonist binding thereto [11]. Cetirizine (**1**) [12–16] is one of the most known second-generation antihistamine drugs and is included into the list of vitally important drugs. One more known anti-inflammatory drug colchicine (**2**) is an alkaloid isolated from *Colchicum autumnale* [17], which is used for the treatment of gout and brucellosis [18]; it is also capable of exhibiting multiple anti-inflammatory effect, e.g., through neutrophil migration inhibition [19], and direct anti-inflammatory effect [20] via inhibition of key inflammatory signaling networks known as inflammatory and pro-inflammatory cytokines [21].

We anticipated that colchicine–cetirizine conjugates would exhibit enhanced anti-inflammatory activity since these compounds affect the nidus of inflammation according to different mechanisms, so that a combination of colchicine and cetirizine fragments in a single molecule could give rise to synergistic effect [22, 23]. Taking into account that colchicine itself possesses a significant systemic toxicity [24], we selected less toxic allocolchicine derivatives [25–35] as components of heterodimers **3a** and **3b**.



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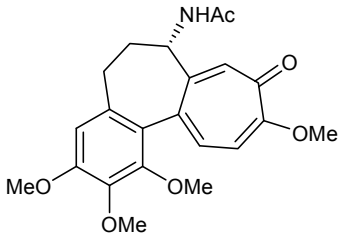

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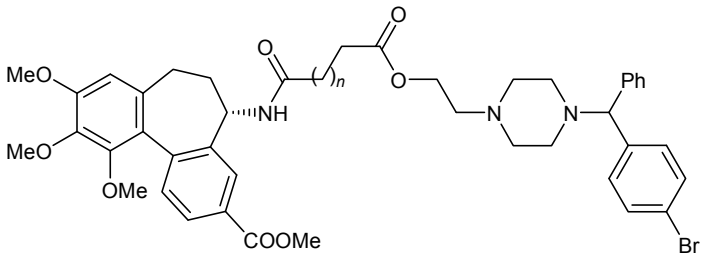
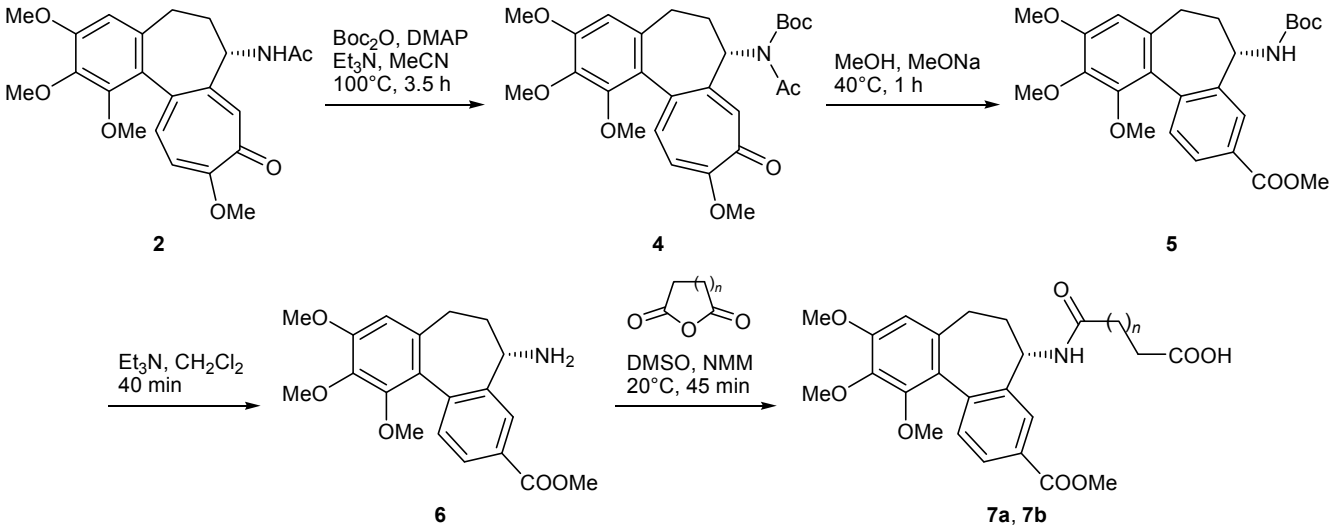


3a, **3b**

n = 1 (**a**), 2 (**b**).

Scheme 1.



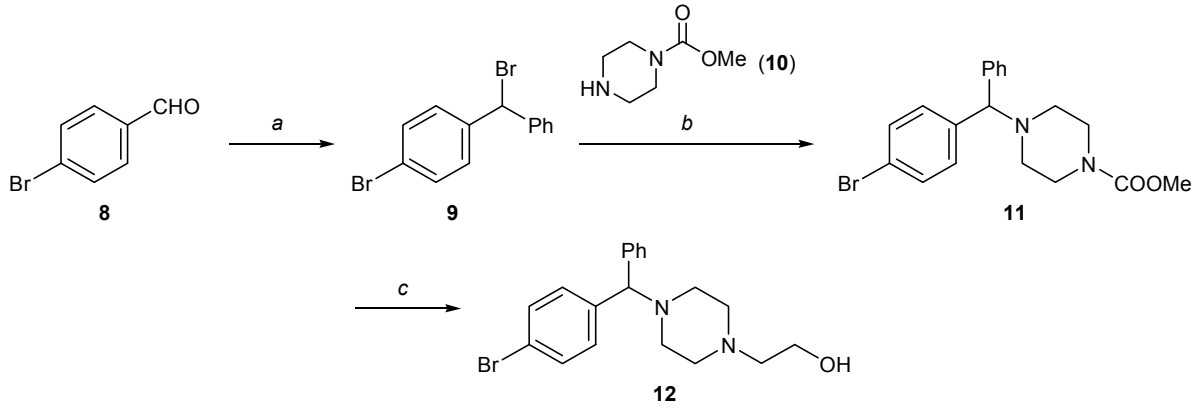
n = 1 (**a**), 2 (**b**); NMM is *N*-methylmorpholine.

The colchicine fragment of conjugates **3a** and **3b** was obtained from deacetylallocolcicine **6** which was prepared in three steps starting from colchicine (**2**) (Scheme 1). For this purpose, the NH group of **2** was protected by treatment with di-*tert*-butyl dicarbonate (Boc_2O) [36]. Deacetylation of compound **4** thus formed under basic conditions was accompanied by contraction of the seven-membered tropolone ring [37] to produce *N*-Boc-substituted colchicinoid **5** in 99% yield. Removal of the Boc protection gave amine **6** which was acylated with succinic and glutaric anhydrides in the presence of *N*-methylmorpholine (NMM). Amides **7a** and **7b** were isolated in 40 and 68% yield, respectively.

The cetirizine fragment [38] was synthesized in six steps starting from 4-bromobenzaldehyde (**8**) (Scheme 2). In the first step, the addition of phenylmagnesium bromide to aldehyde **8** gave the corresponding diphenylmethanol which was converted to dibromide **9** by treatment with carbon tetrabromide and triphenylphosphine (Appel reaction); the overall yield of **9** starting from **8** was 72%. Compound **9** reacted with substituted piperazine **10** [39] to afford 60% of ester **11**, and subsequent removal of the methoxycarbonyl group from **11** and N-alkylation led to cetirizine derivative **12** in 57% yield.

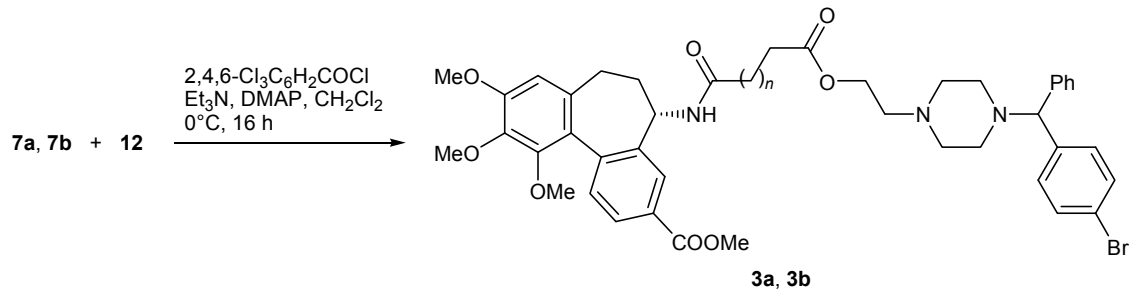
The colchicine (**7a**, **7b**) and cetirizine fragments (**12**) were combined by esterification according to Yamaguchi (Scheme 3). Conjugates **3a** and **3b** were obtained in 61 and 48% yield, respectively (15 and 12% over 10 steps). Study of their anti-inflammatory and anti-allergic activity is now in progress.

Scheme 2.



Reagents and conditions: *i*: (1) PhMgBr, THF, 2 h, –30°C; (2) HCl, H_2O; (3) PPh_3, CBr_4, CH_2Cl_2, 1.5 h; *ii*: toluene, reflux, 24 h; *iii*: (1) $(CH_2OH)_2$, $N_2H_2 \cdot H_2O$, KOH, 150°C, 1.5 h; (2) $BrCH_2CH_2OH$, toluene, Et_3N, 100°C, 24 h.

Scheme 3.



n = 1 (**a**), 2 (**b**).

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on an Agilent DD2 400 spectrometer at 400 and 101 MHz, respectively; the ^{1}H chemical shifts were measured relative to the residual proton signals of the deuterated solvents: (DMSO-d_5, δ 2.50 ppm; $CHCl_3$, δ 7.26 ppm). Column chromatography was performed on Silicagel 60 (70–230 mesh, Alfa Aesar). Commercially available reagents (Aldrich, Alfa Aesar, Acros) were used without additional purification. The solvents used were purified by standard methods. Petroleum ether was a fraction boiling at 40–65°C.

1-Bromo-4-[bromo(phenyl)methyl]benzene (9). 4-Bromobenzaldehyde (**8**), 1.0 g (5.4 mmol), was dissolved in 30 mL of THF at –20°C in an inert atmosphere, and 7.5 mL of a 1.1 M solution of phenylmagnesium bromide in THF was added dropwise. The mixture was stirred for 1.5 h at –20°C, acidified with 5% aqueous HCl to pH 4, and extracted with ethyl acetate (3×100 mL). The combined extracts were dried over anhydrous Na_2SO_4, the solvent was removed under reduced pressure, and the residue was subjected to column chromatography using petroleum ether–ethyl acetate (10:1) as eluent. We thus isolated 1.33 g (94%) of 4-bromophenyl(phenyl)methanol as colorless oily material. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.18 s (1H), 5.65 s (1H), 7.49–7.16 m (9H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 60.60, 122.14, 127.49, 127.91, 128.07, 129.46, 133.19, 142.27, 143.43.

Triphenylphosphine, 5.7 g (21.7 mmol), was dissolved in 30 mL of methylene chloride in an inert atmosphere, the solution was stirred for 15 min at room temperature, and 2.9 g (8.7 mmol) of carbon tetrabromide was added. The mixture was stirred for 5 min, and a solution of 1.9 g (7.24 mmol) of 4-bromophenyl(phenyl)methanol in 5 mL of methylene chloride was added dropwise. The mixture was stirred for 1.5 h, the precipitate of triphenylphosphine oxide was filtered off on a Schott filter, and the solvent was removed under reduced pressure. The residue was purified by column chromatography using petroleum ether–ethyl acetate (12:1) as eluent. Yield of **9** 1.82 g (77%), colorless oily material. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 6.25 s (1H), 7.51–7.27 m (9H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 63.42, 123.74, 129.15, 133.09, 133.83, 139.63, 140.50, 142.26, 143.41. Found, %: C 47.71; H 3.26. $C_{13}H_{10}Br_2$. Calculated, %: C 47.89; H 3.09.

Methyl 4-[(4-bromophenyl)(phenyl)methyl]-piperazine-1-carboxylate (11). Methyl piperazine-1-carboxylate [39], 1.11 g (6.24 mmol), and compound **9**, 2.03 g (6.24 mmol), were dissolved in toluene in an inert atmosphere, 5.35 g (18.7 mmol) of sodium carbonate decahydrate was added, and the mixture was stirred for 24 h at 110°C. The solvent was removed under reduced pressure, and the residue was purified by column chromatography using petroleum ether–ethyl acetate (10:1) as eluent. Yield 1.46 g (60%), colorless oily material. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.30 s (4H), 3.44 s (4H), 3.64 s (3H), 4.19 s (1H), 7.41–7.19 m (9H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 43.50, 51.08, 52.08, 74.83, 120.44, 124.67, 126.20, 126.95, 128.03, 130.87, 141.07, 141.18, 155.30. Found, %: C 58.33; H 5.54; N 7.09. $C_{19}H_{21}BrN_2O_2$. Calculated, %: C 58.62; H 5.44; N 7.20.

2-{4-[4-Bromophenyl(phenyl)methyl]piperazin-1-yl}ethanol (12). Compound **11**, 0.96 g (2.47 mmol), potassium hydroxide, 3.73 g (66.7 mmol), and hydrazine hydrate, 0.6 mL (12.35 mmol), were dissolved in 25 mL of ethylene glycol, and the solution was stirred for 1.5 h at 150°C. When the reaction was complete, the mixture was poured into 25 mL of distilled water, excess solid boric acid was added, sodium hydroxide was then added to pH 8, the mixture was extracted with *tert*-butyl methyl ether (3×100 mL), and the combined extracts were evaporated under reduced pressure to obtain 0.61 g (75%) of 1-[4-bromophenyl(phenyl)-

methyl]piperazine as colorless oily material. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.37 s (4H), 2.90 t (4H, *J* = 4.6 Hz), 4.18 s (1H), 7.18 t (1H, *J* = 7.2 Hz), 7.41–7.22 m (9H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 46.10, 53.08, 83.39, 120.51, 127.03, 127.79, 128.47, 129.53, 131.47, 141.73, 141.86. Found, %: C 61.91; H 6.12; N 8.13. $C_{17}H_{19}BrN_2$. Calculated, %: C 61.64; H 5.78; N 8.46.

1-[4-Bromophenyl(phenyl)methyl]piperazine, 0.5 g (1.5 mmol), was dissolved in 20 mL of toluene in an inert atmosphere, 0.13 mL (1.8 mmol) of 2-bromoethanol and 0.53 mL (3.75 mmol) of triethylamine were added, and the mixture was stirred for 24 h at 100°C. When the reaction was complete, the solvent was removed under reduced pressure, and the residue was purified by column chromatography using petroleum ether–ethyl acetate–acetone (5:1:1) as eluent. Yield of **12** 0.43 g (76%), colorless oily material. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.00 s (4H), 2.57–2.52 m (4H), 3.59 t (2H, *J* = 5.4 Hz), 3.66–3.61 m (2H), 3.79–3.76 m (1H), 4.19 s (1H), 7.41–7.24 m (9H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 53.21, 57.75, 59.43, 59.65, 83.87, 120.74, 127.27, 127.79, 128.66, 129.54, 131.66, 141.74, 141.87. Found, %: C 61.03; H 6.25; N 7.65. $C_{19}H_{23}BrN_2O$. Calculated, %: C 60.81; H 6.18; N 7.46.

***tert*-Butyl acetyl(1,2,3,10-tetramethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[*a*]heptalen-7-yl)carbamate (4).** Di-*tert*-butyl dicarbonate, 1.64 g (7.5 mmol), *N*,*N*-dimethylpyridin-4-amine, 1.83 g (15 mmol), and colchicine (**2**), 3.0 g (7.5 mmol), were dissolved in 30 mL of acetonitrile in an inert atmosphere, 1.1 mL (7.5 mmol) of triethylamine was added, and the mixture was stirred for 1 h at 100°C. An additional portion of di-*tert*-butyl dicarbonate, 3.27 g (15 mmol), was then added, and the mixture was stirred for 2.5 h. When the reaction was complete, the solvent was removed under reduced pressure, and the residue was purified by column chromatography using ethyl acetate–acetone (4:1) as eluent. Yield 2.63 g (70%), yellow crystals, mp 105°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.50 d (9H, *J* = 6.3 Hz), 1.91 d.d.d (1H, *J* = 15.8, 12.4, 6.5 Hz), 2.22 s (3H), 2.34–2.25 m (1H), 2.56–2.46 m (1H), 2.69 d.d (1H, *J* = 13.5, 6.4 Hz), 3.54 s (3H), 3.77 s (3H), 3.83 s (3H), 3.87 s (3H), 4.90 d.d (1H, *J* = 12.4, 6.0 Hz), 6.77 s (1H), 7.02 d (1H, *J* = 10.9 Hz), 7.11 d (1H, *J* = 10.7 Hz), 7.27 s (1H). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 27.31, 29.27, 31.83, 33.30, 55.86, 56.08, 60.68, 60.87, 84.40, 107.75, 112.19, 125.63, 131.75, 133.87, 134.55, 134.79, 140.85, 148.28, 150.50, 153.02, 153.14, 163.54, 170.48, 177.90.

Methyl (5*S*)-5-(*tert*-butoxycarbonylamino)-6,7-dihydro-9,10,11-trimethoxy-5*H*-dibenzo[*a*,*c*][7]-annulene-3-carboxylate (5). Solid sodium methoxide, 0.818 g (15.15 mmol), and compound **4**, 1.89 g (3.78 mmol), were dissolved in 25 mL of methanol in an inert atmosphere, and the solution was stirred for 1 h at 40°C. When the reaction was complete, excess sodium methoxide was neutralized with a 1 M solution of ammonium chloride, and the mixture was extracted with ethyl acetate (3×100 mL). The combined extracts were dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure, and the residue was purified by column chromatography using ethyl acetate as eluent. Yield 1.71 g (99%), dark yellow crystals, mp 152°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.31 s (9H), 1.86–1.77 m (1H), 2.03–1.94 m (1H), 2.21–2.11 m (1H), 2.55 d.d (1H, *J* = 13.2, 5.9 Hz), 3.54 s (3H), 3.78 s (3H), 3.83 s (3H), 3.87 s (3H), 4.11–4.03 m (1H), 6.76 s (1H), 7.02 d (1H, *J* = 10.9 Hz), 7.10 d (1H, *J* = 10.6 Hz), 7.21 s (1H), 7.69 d (1H, *J* = 7.8 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 28.18, 29.25, 37.84, 56.05, 58.37, 60.69, 60.88, 78.21, 107.69, 112.18, 125.34, 130.53, 134.31, 134.46, 135.15, 140.72, 150.39, 151.11, 152.99, 154.55, 163.54, 178.05.

Methyl (5*S*)-5-amino-6,7-dihydro-9,10,11-trimethoxy-5*H*-dibenzo[*a*,*c*][7]annulene-3-carboxylate (6). Trifluoroacetic acid, 8 mL, was added dropwise to a solution of 0.5 g (1.06 mmol) of compound **5** in 20 mL of methylene chloride, and the mixture was stirred for 40 min at room temperature. Excess trifluoroacetic acid was neutralized with $NaHCO_3$ to pH 8, the mixture was extracted with methylene chloride (3×100 mL), the combined extracts were dried over anhydrous Na_2SO_4, the solvent was removed under reduced pressure, and the residue was purified by column chromatography using methylene chloride–methanol (10:1) as eluent. Yield 0.31 g (83%), grayish yellow powder, mp 136°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.88–0.80 m (1H), 1.49 t.d (1H, *J* = 9.8, 4.7 Hz), 2.14 d.d.d.d (4H, *J* = 24.9, 18.9, 12.6, 6.3 Hz), 3.45 d.d (1H, *J* = 10.5, 5.9 Hz), 3.55 s (3H), 3.76 s (3H), 3.83 s (3H), 3.86 s (3H), 6.74 s (1H), 6.99 d (1H, *J* = 10.8 Hz), 7.05 d (1H, *J* = 10.6 Hz), 7.64 s (1H). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 24.89, 40.27, 53.11, 55.84, 55.90, 60.53, 60.66, 107.34, 111.84, 125.40, 131.83, 133.76, 134.88, 135.68, 140.47, 150.15, 152.73, 153.82, 163.26, 178.20.

Amides 7a and 7b (*general procedure*). Compound **6**, 1 equiv, was dissolved in DMSO in an inert atmosphere, 4 equiv of 4-methylmorpholine (NMM) and 1.1 equiv of succinic or glutaric anhydride were added, and the mixture was stirred for 45 min at room temperature. When the reaction was complete, the mixture was extracted with ethyl acetate. The combined extracts were dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure, and the residue was purified by column chromatography using methylene chloride–methanol (9:1) as eluent.

4-Oxo-4-{[(5*S*)-9,10,11-trimethoxy-3-(methoxycarbonyl)-6,7-dihydro-5*H*-dibenzo[*a*,*c*][7]annulen-5-yl]amino}butanoic acid (7a) was synthesized from 0.30 g (0.84 mmol) of compound **6** and 0.09 g (0.92 mmol) of succinic anhydride in 2 mL of DMSO in the presence of 0.37 mL (3.37 mmol) of NMM. Yield 0.15 g (40%), gray powder, mp 81°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.88–1.80 m (1H), 2.05–1.96 m (1H), 2.19 d.d (1H, J = 13.1, 7.2 Hz), 2.31–2.25 m (2H), 2.38–2.33 m (2H), 2.58 d.d (1H, J = 13.2, 6.1 Hz), 3.51 s (3H), 3.78 s (3H), 3.83 s (3H), 3.87 s (3H), 4.34–4.27 m (1H), 6.76 s (1H), 7.03 d (1H, J = 10.9 Hz), 7.11 d (1H, J = 10.6 Hz), 7.16 s (1H), 8.63 d (1H, J = 7.3 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 24.52, 24.64, 25.07, 35.80, 51.31, 55.90, 56.09, 60.73, 60.90, 107.76, 112.27, 125.46, 130.48, 134.27, 134.48, 135.30, 140.75, 140.97, 150.45, 150.94, 152.96, 163.53, 170.97, 178.06. Found, %: C 62.75; H 6.12; N 3.21. $C_{24}H_{27}NO_8$. Calculated, %: C 63.01; H 5.95; N 3.06.

4-Oxo-4-{[(5*S*)-9,10,11-trimethoxy-3-(methoxycarbonyl)-6,7-dihydro-5*H*-dibenzo[*a*,*c*][7]annulen-5-yl]amino}pentanoic acid (7b) was synthesized from 0.15 g (0.42 mmol) of **6** and 0.05 g (0.46 mmol) of glutaric anhydride in 1 mL of DMSO in the presence of 0.19 mL (1.73 mmol) of NMM. Yield 0.13 g (68%), gray powder, mp 76°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.66 d.d (2H, J = 14.6, 7.2 Hz), 1.82 d.d (1H, J = 12.0, 5.3 Hz), 2.04–1.97 m (1H), 2.16 t (4H, J = 7.5 Hz), 2.26–2.20 m (2H), 3.53 s (3H), 3.78 s (3H), 3.83 s (3H), 3.86 s (3H), 4.31 d.d (1H, J = 12.7, 5.9 Hz), 6.76 s (1H), 7.02 d (1H, J = 11.0 Hz), 7.10 d (1H, J = 8.9 Hz), 7.12 s (1H), 8.55 d (1H, J = 7.4 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 21.15, 29.25, 33.09, 34.18, 34.29, 55.90, 56.09, 60.74, 60.91, 107.78, 112.19, 125.47, 130.34, 134.27, 134.47, 135.24, 140.76, 140.92, 150.48, 150.89, 152.97, 163.55, 171.11, 178.01. Found, %: C 63.41; H 6.39; N 2.71. $C_{25}H_{29}NO_8$. Calculated, %: C 63.68; H 6.20; N 2.97.

Esters 3a and 3b (*general procedure*). Colchicine derivative **7a** or **7b**, 1 equiv, was dissolved in methylene chloride in an inert atmosphere, 3 equiv of triethylamine and 2 equiv of 2,4,6-trichlorobenzoyl chloride (Yamaguchi reagent) were added, and the mixture was stirred for 5 h at room temperature. A solution of 2 equiv of compound **12** and 2 equiv of DMAP in methylene chloride was then added, and the mixture was stirred for 16 h at room temperature in an inert atmosphere. The solvent was removed under reduced pressure, and the product was isolated by column chromatography.

Methyl (5*S*)-5-[4-(2-{4-[4-bromophenyl(phenyl)-methyl]piperazin-1-yl}ethoxy)-4-oxobutanamido]-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*][7]-annulene-3-carboxylate (3a) was synthesized using 0.04 g (0.09 mmol) of **7a**, 0.04 mL (0.26 mmol) of triethylamine, 0.03 mL (0.17 mmol) of Yamaguchi reagent, 0.065 g (0.17 mmol) of **12**, and 0.021 g (0.17 mmol) of DMAP. The product was purified by column chromatography using petroleum ether–ethyl acetate–ethanol (3.5:1:1) as eluent. Yield 0.045 g (61%), viscous oily material. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.57 d.d (1H, J = 7.3, 4.8 Hz), 1.83 d.d (1H, J = 12.7, 7.3 Hz), 2.03–1.95 m (1H), 2.28 d.d (4H, J = 19.0, 13.4 Hz), 2.41 s (4H), 2.45 d.d (4H, J = 7.4, 3.3 Hz), 2.72 d.d (1H, J = 7.8, 2.2 Hz), 3.50 s (3H), 3.78 s (3H), 3.82 s (3H), 3.85 s (3H), 4.04–3.99 m (2H), 4.08 t (2H, J = 5.8 Hz), 4.27 s (1H), 6.75 s (1H), 7.00 d (1H, J = 11.0 Hz), 7.09 d (1H, J = 10.7 Hz), 7.12 s (1H), 7.18 t (1H, J = 7.3 Hz), 7.29 t (2H, J = 7.6 Hz), 7.38 d (2H, J = 2.4 Hz), 7.47 s (2H), 7.49 s (2H), 8.61 d (1H, J = 7.4 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 23.75, 28.84, 40.43, 46.52, 51.36, 52.97, 55.85, 56.02, 60.24, 60.68, 61.55, 62.80, 72.28, 74.16, 85.97, 125.42, 127.09, 127.53, 128.60, 129.87, 130.01, 131.40, 134.19, 135.11, 135.74, 140.71, 142.40, 150.41, 152.91, 163.48, 164.84, 170.07, 172.11, 177.97, 184.17, 188.20, 193.01. Found, %: C 63.07; H 6.21; N 4.92. $C_{43}H_{48}BrN_3O_8$. Calculated, %: C 63.39; H 5.94; N 5.16.

Methyl (5*S*)-5-[4-(2-{4-[4-bromophenyl(phenyl)-methyl]piperazin-1-yl}ethoxy)-4-oxopentanamido]-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*][7]-annulene-3-carboxylate (3b) was synthesized using 0.03 g (0.07 mmol) of **7b**, 0.03 mL (0.20 mmol) of triethylamine, 0.02 mL (0.13 mmol) of Yamaguchi reagent, 0.05 g (0.13 mmol) of **12**, and 0.016 g (0.13 mmol) of DMAP. The product was purified by column chromatography using petroleum ether–ethyl acetate–ethanol (4:1:1) as eluent. Yield 0.028 g

(48%), viscous oily material. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.75–1.70 m (1H), 1.86–1.77 m (1H), 2.04–1.95 m (1H), 2.16 t (2H, J = 7.4 Hz), 2.24 d.d (4H, J = 7.1, 4.9 Hz), 2.33–2.27 m (4H), 2.45–2.39 m (4H), 2.61–2.55 m (1H), 3.52 s (3H), 3.78 s (3H), 3.82 s (3H), 3.86 s (3H), 4.11–4.03 m (2H), 4.26 s (1H), 4.37–4.28 m (2H), 5.75 s (1H), 6.76 s (1H), 7.01 d (1H, J = 10.7 Hz), 7.10 d (2H, J = 7.8 Hz), 7.18 t (1H, J = 7.1 Hz), 7.28 t (2H, J = 7.5 Hz), 7.38–7.36 m (2H), 7.46 d (2H, J = 2.4 Hz), 7.48 d (2H, J = 2.4 Hz), 8.54 d (1H, J = 7.4 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 32.71, 38.43, 40.19, 43.98, 51.34, 53.12, 52.92, 54.92, 55.86, 56.03, 60.25, 60.70, 60.86, 72.28, 74.16, 87.24, 112.09, 119.77, 125.44, 127.09, 127.53, 128.60, 129.72, 129.85, 130.02, 134.21, 135.16, 140.72, 142.27, 142.41, 150.44, 150.74, 152.91, 163.50, 164.70, 170.90, 172.45, 177.94. Found, %: C 63.46; H 6.34; N 4.78. $C_{44}H_{50}BrN_3O_8$. Calculated, %: C 63.76; H 6.08; N 5.07.

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