Gold-catalyzed cyclization in the synthesis of antimitotic 2,3-dihydrobenzo[*b*]oxepine derivatives of colchicine*

S. Yu. Bukhvalova,[a,b] A. A. Maleev,[b] Yu. A. Gracheva,[b] Yu. V. Voitovich,[b] S. K. Ignatov,[b] E. V. Svirshchevskaya,[c] and A. Yu. Fedorov[b]★

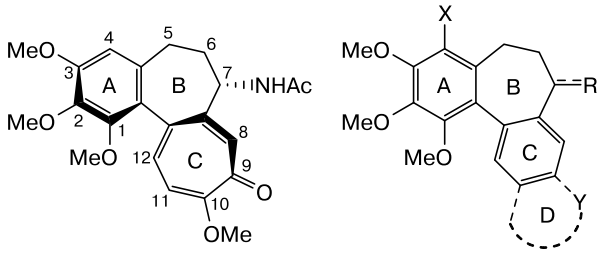
[a]*G. A. Razuvaev Institute of Organometallic Chemistry, Russian Academy of Sciences, 49 ul. Tropinina, 603137 Nizhny Novgorod, Russian Federation. Fax: +7 (831) 462 7497. E-mail: sv-4.4.1991@rambler.ru*
[b]*N. I. Lobachevsky State University of Nizhny Novgorod, 23 prosp. Gagarina, 603950 Nizhny Novgorod, Russian Federation. Fax: +7 (831) 462 3085. E-mail: afedorovnn@yandex.ru*
[c]*M. M. Shemyakin—Yu. A. Ovchinnikov Institute of Bioorganic Chemistry, Russian Academy of Sciences, 16/10 ul. Miklukho-Maklaya, 117997 Moscow, Russian Federation. Fax: +7 (495) 330 4011. E-mail: esvir@yandex.ru*

New allocolchicine derivatives bearing 2,3-dihydrobenzo[*b*]oxepine moiety were synthesized *via* gold-catalyzed cyclization as a key synthetic step. The obtained 2,3-dihydrobenzo[*b*]oxepine-containing allocolchicinoids possess cytotoxic activity against HEK293, PANC-1, COLO357, HeLa, and Colon26 cancer cell lines at low micromolar range of concentrations.

Key words: antitumor agents, colchicine, tubulin, benzo[*b*]oxepines, gold-catalyzed cyclization.

Scaffolds of natural compounds are the most promising in the design of new efficient therapeutic molecules.[1—3] Thus, colchicine, an alkaloid isolated from plants of *Colchicaceae* family, is widely used as an anti-inflammatory drug for the treatment of acute gouty arthritis, Behcet's disease, and familial Mediterranean fever.[4—7] Its positive effect has been reported in the cases of amyloidosis, scleroderma, and Sweet's disease.[8] It can potentially be administered for the treatment of cardiovascular diseases caused by inflammatory processes[9—12] and also chronic infectious, autoimmune, allergic, and neurodegenerative diseases.[13,14] Despite the pronounced antimitotic effect, colchicine has never been applied in the antitumor clinical practice due to the high and poorly controlled systemic toxicity at therapeutic doses.[15,16]

Nevertheless, the structure of colchicine (**1**) has been recognized as one of the keys in the development of new potentially less toxic cytostatic chemotherapeutic drugs.[17—24] Currently, the only successful approach of solving the toxicity problem is the synthesis of heterocyclic allocolchicinoids *via* the conversion of seven-membered cycle C into the six-membered ring and the formation of heterocyclic moiety D.[25—28] Compounds of general structure **2** obtained in our group exhibit cytotoxic activity at nano- and picomolar concentrations,[29—36] demonstrate a significant decrease in tumor growth rate *in vivo* without any pronounced side effects in test animals.[30]



(−)-(a*R*,7*S*)-Colchicine (**1**) **2**

X = H, Br;
Y = O (substituted furan), NH(Me) (substituted pyrrole);
R = O, OH, NHAc

The present work was aimed to search for the new colchicine analogs possessing improved antitumor properties. We have examined a series of derivatives **3a—f** bearing a 2,3-dihydrobenzo[*b*]oxepine moiety that replaces cycle C in the colchicine structure. Benzo[*b*]oxepine is a frequently found motif in natural products such as pterulone,[37,38] ptaeroxylin, radulanins, heliannuols, and their natural and synthetic analogs.[39—46] These compounds demonstrate a wide range of biological effects, including anti-inflammatory, anti-diabetic, antiviral, antiproliferative, antituberculosis, antispermetogenic, and antipsychotic activities.[47]

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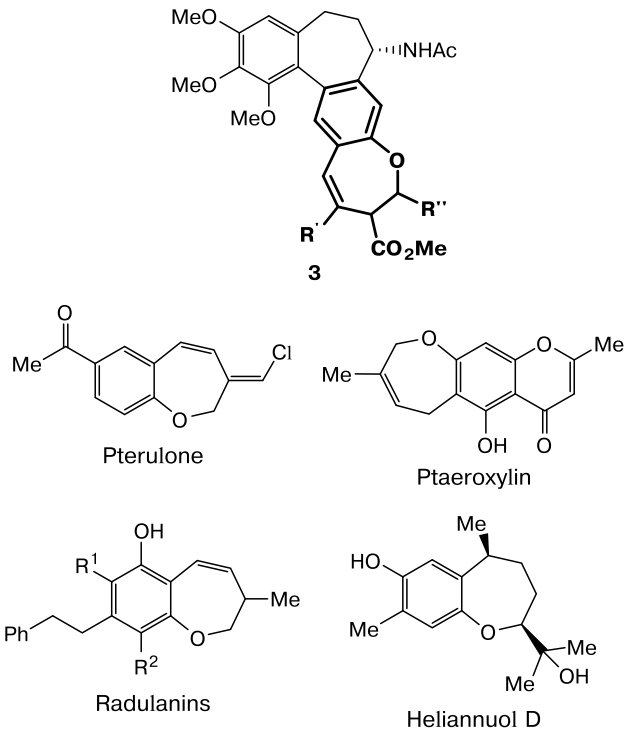


The performed molecular docking demonstrated that 2,3-dihydrobenzo[*b*]oxepinoallocolchicines **3** fit well in the colchicine site of tubulin, while the geometry of binding to the colchicine site is fundamentally different for compounds **1** and **3a** (X = CO_2Me, R^1 = Ph, R^2 = Bu^n). Thus, the molecule containing 2,3-dihydrobenzo[*b*]oxepine moiety turned out to be rotated 90° compared to colchicine, which provides a new hydrogen bond with Asn101, Van-der-Waals contacts with Met259, and hydrophobic interactions with Tyr224 and Lys254 (Fig. 1). The number of established interactions allowed us to expect effective binding of new derivatives to tubulin.

An efficient approach to the formation of 2,3-dihydrobenzo[*b*]oxepine rings with high stereoselectivity has been recently proposed by J. Liu *et al.*[48] The application of gold-catalyzed cyclization of (*o*-alkynyl)phenoxyacrylates with nucleophiles allowed the formation of benzoxepines under mild conditions. Herein we report a series of new colchicine derivatives bearing a 2,3-dihydrobenzo[*b*]oxepine moiety and synthesized exploiting the gold-catalyzed cyclization as a key step of the synthesis.

Results and Discussion

The synthesis of the series of 2,3-dihydrobenzo[*b*]-oxepine derivatives of colchicine was started from the preparation of iodocolchinol according to the known procedure.[28,30,33] At the first step, colchiceine **4** was obtained from colchicine (**1**) in 98% yield by the treatment with 0.1 *M* hydrochloric acid (Scheme 1). In this case, the methyl group was removed from the tropolone cycle of

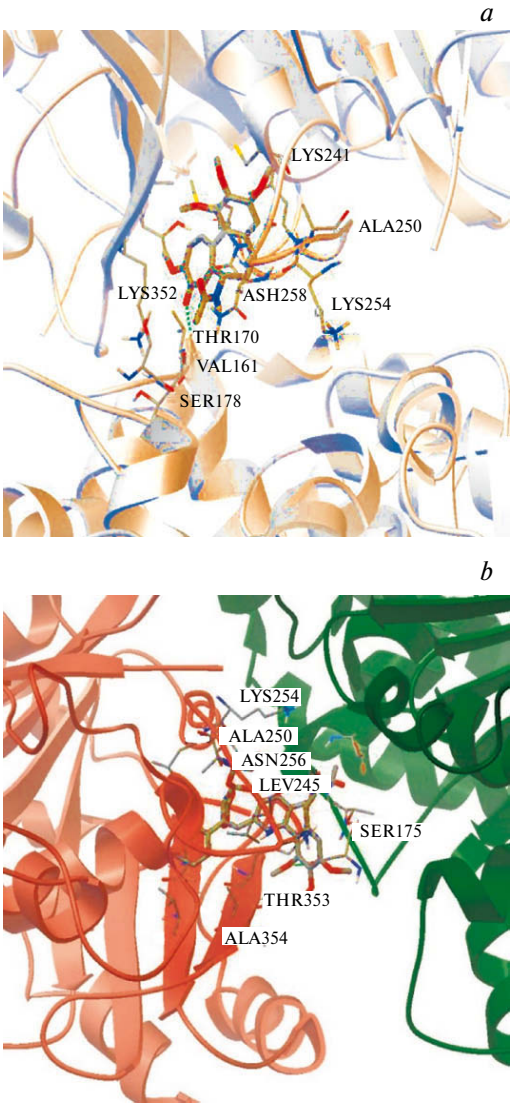
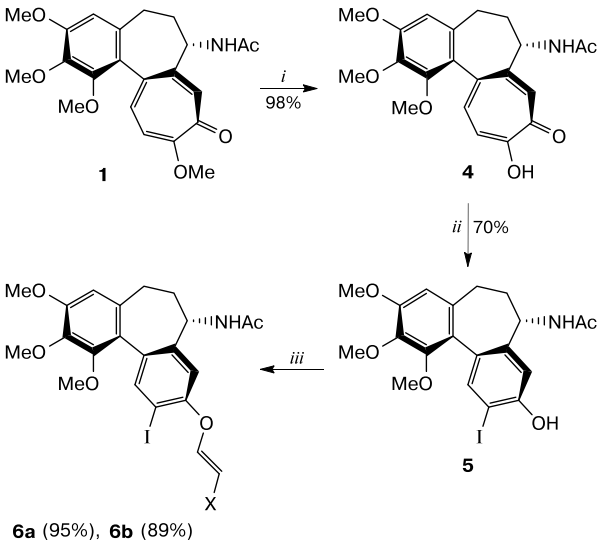


Fig. 1. Calculated structures of colchicine (*a*) and compound **3a** (*b*) at the tubulin binding site.

colchicine. Colchiceine **4** was then introduced into a NaOH—I_2—NaI system, which led to the oxidative constriction of seven-membered cycle caused by alkali and its iodination.

Iodocolchinol **5** isolated in 70% yield was further introduced into the Michael reaction with terminal alkynes in the presence of base to give vinyl esters **6a,b**. To optimize reaction conditions in the case of methyl propiolate, various bases (1,4-diazabicyclo[2.2.2]octane (DABCO), diisopropylethylamine (DIPEA), a mixture of diazabicycloundecene (DBU)—DABCO, and 4-dimethylaminopyridine (DMAP)) and solvents (CH_2Cl_2, THF, toluene, and DMF) were used (Table 1). A positive result was achieved only in the case of DABCO taken in the amount of three equivalents and reaction time increased to three days. In this case, the target vinyl ether **6a** was obtained

Scheme 1



Reagents and conditions: *i*. 0.1 *M* HCl, AcOH, 3 h, 100 °C; *ii*. I_2, KI, NaOH, 2 h, 0 °C; *iii*. Alkyne, DABCO, CH_2Cl_2, 72 h, 25 °C.

in the yield close to quantitative (see Table 1, experiment *4*), and product **6b** was isolated in 89% yield (see Scheme 1).

It should be noted that compounds **6a,b** were obtained in the form of their (*E*)-isomers, which was confirmed by NMR spectroscopy: *J* values of the protons of the double bond correspond to the (*E*)-configuration of vinyl ethers (see Experimental part).[49]

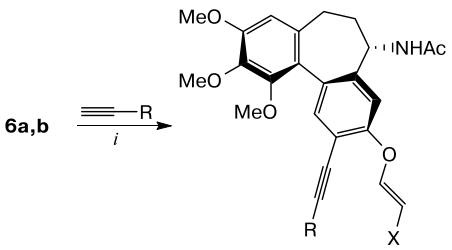
At the next step, compounds **6a,b** were used in the Sonogashira cross-coupling reaction with a set of functionalized terminal alkynes (Scheme 2). The reactions were carried out at 45 °C using a $Pd(OAc)_2$—CuI—PPh_3 catalytic system (5 : 10 : 15 mol.%).[30] Target *o*-alkynylvinyl ethers **7** and **8** were obtained in 54—90% yields.

The intramolecular cyclization of compounds **7** and **8** with various alcohols catalyzed by gold complexes was carried out at the last step to afford desired functionalized 2,3-dihydrobenzo[*b*]oxepines **3a—f**. Scheme 3 shows a proposed mechanism of the cyclization (according to the literature[49]). Obviously, at the first step the Au^+ com-

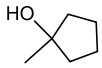
Table 1. Optimization of the Michael reaction conditions

Exp.	DABCO /equiv.	Solvent	Time /days	Yield of **6a** (%)
1	0.1	THF	1	—
2	0.3	Toluene	1	—
3	1	CH_2Cl_2	2	~10
4	3	CH_2Cl_2	3	95

Scheme 2



Compound **7**	X	R	Yield (%)
a	CO_2Me	Ph	90
b	CO_2Me	Pr	72
c	CO_2Me	CH_2OAc	54
d	CO_2Me	$(CH_2)_4Cl$	65

Compound **8**	X	R	Yield (%)
a	C(O)Me	Ph	63
b	C(O)Me	Pr	78
c	C(O)Me	CH_2OAc	65
d	C(O)Me		78
e	C(O)Me		76
f	C(O)Me		80

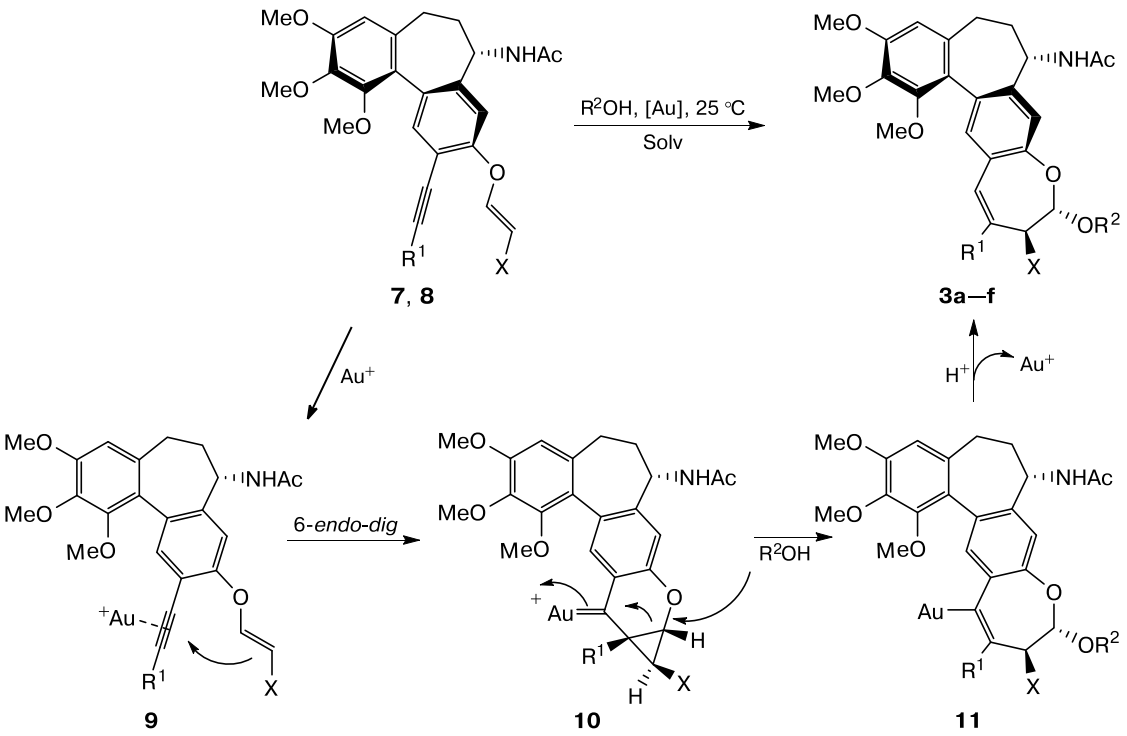
Reagents and conditions: *i*. $Pd(OAc)_2$, CuI, Ph_3P, AcOK, MeCN, 16 h, 45 °C.

plex is coordinated by the triple bond of substrate **7** (**8**). The electron-deficient triple bond in complex **9** undergoes 6-*endo*-*dig* cyclization to form pentacyclic organometallic intermediate **10** bearing a substituted cyclopropane moiety. A subsequent nucleophilic attack leads to the expansion of cyclopropyl-containing bicyclic moiety to yield intermediate **11**. The further protonolysis leads to the formation of target benzoxepine and catalyst regeneration.

We have explored the cyclization of compound **7a** in the presence of freshly prepared gold complexes ($Ph_3PAuNTf_2$, $(C_6F_5)_3PAuNTf_2$, and $Ph_3PAuSbF_6$) in various solvents (1,2-dichloroethane, CH_2Cl_2, toluene, and THF) with Bu^nOH as a nucleophile to find optimal conditions for this reaction. However, neither of attempts resulted in obtaining the desired benzoxepine structure, which was obviously due to the instability of gold complexes. An *in situ* preparation of the catalytic system led to **3a** in 25% yield (Table 2, experiment *1*). A subsequent increase in the product yield was achieved by carrying out the reaction in the dark (see Table 2, experiments *2—4*). The best yield was observed using SbF_6 as an anion, which could be explained by its lower nucleophilicity.[50,51]

With found optimal conditions in hand, a set of novel allocolchicinoids **3a—f** possessing a 2,3-dihydrobenzo[*b*]-oxepine ring has been prepared with good and moderate

Scheme 3

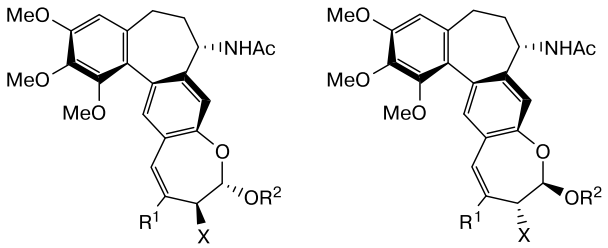


X = CO_2Me

Compound **3**	R^1	R^2	Yield (%)	Compound **3**	R^1	R^2	Yield (%)
a	Ph	Bu	60	**d**	Ph	Me	30
b	Ph	Pr^i	53	**e**	Pr	Bu	40
c	Ph	Et	40	**f**	$Cl(CH_2)_4$	Bu	22

yields from compounds **7** in the presence of various alcohols. In the case of compounds **8** as starting materials in this reaction, the desired products could not be obtained.

It should be noted that 2,3-dihydrobenzo[*b*]oxepinoallocolchicines **3a—f** were formed as mixtures of diastereomers **A** and **B** in the ratios of 2 : 1 or 3 : 2, which differ in the configurations of carboxymethyl and alkoxyl moieties of the oxepine ring. Separation of these diastereomers by column chromatography failed. Since compounds of such type can exist in the solution as *Z*/*E* isomers about the amide group and as atropisomers (colchicinoids possess an axial chirality),[29] it was impossible to determine a configuration of the major isomer in the mixture using a two-dimensional NMR spectroscopy. According to the proposed mechanism, the major diastereomer should possess the configuration shown in Scheme 3.



Diastereomers of **3** (**A** and **B**)

Table 2. Optimization of conditions for the gold-catalyzed cyclization of **7a**[a] in 1,2-dichloroethane

Exp.	Catalyst (equiv.)	Yield of **3a** (%)
1	$Ph_3PAuCl + AgSbF_6$ (0.05)	25
2[b]	$Ph_3PAuCl + AgSbF_6$ (0.05)	60
3[b]	$Ph_3PAuCl + AgNTf_2$ (0.05)	42
4[b]	$(C_6F_5)_3PAuCl + AgSbF_6$ (0.05)	52

[a] 2 equiv. of Bu^nOH were used for the reaction.
[b] The reactions were carried out in the dark.

Cytotoxicity of the synthesized compounds against human (HEK293, PANC-1, COLO357, and HeLa) and mice (Colon26) cancer cell lines was investigated *in vitro* using the standard MTT assay (Table 3).[52] The lower overall activity of all the obtained target compounds as compared to the starting colchicine is presumably related to a position of the compounds at the tubulin binding site.

Table 3. Cytotoxic activity (IC_{50}/μmol L^{-1}) of compounds **3a—f**

Compound	Cells				
	HEK293	PANC-1	COLO-357	HeLa	Colon26
3a	2.76	2.86	2.16	1.97	2.00
3b	0.50	—*	0.52	0.53	0.47
3c	0.52	0.65	0.62	0.59	0.45
3d	0.54	—	0.58	0.50	0.14
3e	2.53	3.27	3.67	2.82	2.46
3f	0.36	0.80	—	2.48	2.67
Colchicine	0.005	0.031	0.004	0.021	0.006

* Not tested.

As was demonstrated by the study of binding geometry, the bulky benzoxepine moiety does not allow the molecule to occupy a position similar to that shown for colchicine. A loss of several hydrogen bonds and hydrophobic interactions may lead to a decrease in the activity of compounds.

In conclusion, we have developed a simple synthetic approach to new allocolchicine derivatives containing the 2,3-dihydrobenzo[*b*]oxepine ring, starting from commercially available natural colchicine. The key step of synthesis, formation of 2,3-dihydrobenzo[*b*]oxepine moiety, was performed using the gold-catalyzed intramolecular cyclization. The synthesized compounds demonstrated moderate *in vitro* cytotoxicity towards the human (HEK293, PANC-1, COLO357, and HeLa) and mouse (Colon26) cancer cell lines. Research efforts are currently underway to improve the antimitotic properties of allocolchicinoids of such type.

Experimental

^1H and ^{13}C NMR spectra were recorded in DMSO-d_6 at 25 °C on Agilent DD2 400 spectrometer at the operating frequencies of 400 and 101 MHz for ^1H and ^{13}C, respectively. Chemical shifts (δ) are reported in parts per million (ppm) from Me_4Si. Signals in the proton spectra were assigned using the data reported previously.[26—31] The reaction progress was monitored by analytical HPLC using Agilent Infinity chromatograph (Zorbax SB-C18 column of 1.8 μm (2.1×50 mm); mobile phase A aqueous 0.1% solution of formic acid, and B 0.1% solution of formic acid in MeCN; flow rate 0.3 mL min^{-1}) equipped with a diode array UV detector (DAAD) operating at 230 nm. Mass spectra were recorded on Agilent SQ G6120B mass spectrometer operating in positive electrospray mode. Combustion analysis was performed using an Elementar (Vario Micro Cube) apparatus. Silica gel 60 (70—230 mesh, Alfa Aesar) was used for the column chromatography. Commercially available reagents (Aldrich, Alfa Aesar, Acros) were used as received without any further purification. The solvents were purified according to standard procedures. The petroleum ether (PE) refers to the fraction with distillation range 40—70 °C.

Colchiceine 4 was synthesized according to the previously proposed procedure.[28,30,33] The product was isolated as a greenish foam, yield: 98%, m.p. 149—151 °C. ^1H NMR (400 MHz, DMSO-d_6), δ: 8.63 (d, 1 H, NH, J = 7.3 Hz); 7.32 (d, 1 H, H(12), J = 11.8 Hz); 7.31 (s, 1 H, H(8)); 7.15 (d, 1 H, H(11), J = 11.8 Hz); 6.80 (s, 1 H, H(4)); 4.43—4.27 (m, 1 H, H(7)); 3.84 (s, 3 H, OMe(1)); 3.78 (s, 3 H, OMe(3)); 3.56 (s, 3 H, OMe(2)); 2.35—1.89 (m, 4 H, H(5) and H(6)); 1.87 (s, 3 H, NHC(O)C$\underline{H}_3$). ^{13}C NMR (101 MHz, DMSO-d_6), δ: 168.7, 153.1, 150.2, 149.9, 140.7, 140.1, 134.7, 128.9, 128.2, 125.7, 125.3, 124.2, 118.2, 107.8, 60.7, 60.7, 55.9, 51.6, 36.9, 29.2, 22.5.

Iodocolchinol 5 was synthesized according to the previously proposed procedure.[28,30,33] The product was isolated as light beige crystals, yield: 70%, m.p. 237—239 °C. ^1H NMR (400 MHz, DMSO-d_6), δ: 10.28 (s, 1 H, OH); 8.38 (d, 1 H, NH, J = 8.0 Hz); 7.56 (s, 1 H, H(11)); 6.86 (s, 1 H, H(4)); 6.76 (s, 1 H, H(8)); 4.40—4.33 (m, 1 H, H(7)); 3.82 (s, 3 H, OMe(1)); 3.77 (s, 3 H, OMe(3)); 3.48 (s, 3 H, OMe(2)); 2.23—1.87 (m, 4 H, H(5) and H(6)); 1.87 (s, 3 H, NHC(O)C$\underline{H}_3$). ^{13}C NMR (101 MHz, DMSO-d_6), δ: 168.3, 155.6, 152.2, 150.2, 142.4, 140.5, 139.2, 134.8, 126.6, 123.2, 110.1, 108.1, 81.4, 60.6, 60.5, 55.8, 48.2, 37.9, 29.9, 22.6.

Synthesis of compounds 6a,b (general procedure). A mixture of iodocolchinol **5** and DABCO was dissolved in CH_2Cl_2 under an argon atmosphere; the corresponding alkyne was then added dropwise to the resulting solution. The reaction mixture was stirred at 40 °C for 72 h after that the product was isolated using silica gel column chromatography, eluent PE—AcOEt—EtOH (8 : 1 : 1).

***N*-{3-[(*E*)-2-Carboxymethylethenyloxy]-2-iodo-6,7-dihydro-5*H*-9,10,11-trimethoxydibenzo[*a*,*c*]cyclohepten-5-yl}acetamide (6a).** Iodocolchinol **5** (500 mg, 1.04 mmol), DABCO (348 mg, 3.12 mmol), and methyl propiolate (102 μL, 1.14 mmol) were used. Product **6a** (500 mg, 84%) was isolated as yellow crystals, m.p. 147—149 °C. Found (%): C, 50.99; H, 4.68. $C_{24}H_{26}INO_7$. Calculated (%): C, 50.81; H, 4.62. ^1H NMR (400 MHz, DMSO-d_6), δ: 8.44 (d, 1 H, NH, J = 8.4 Hz); 7.81 (d, 1 H, OC$\underline{H}$=CH, J = 12.2 Hz); 7.78 (s, 1 H, H(11)); 7.16 (s, 1 H, H(8)); 6.81 (s, 1 H, H(4)); 5.53 (d, 1 H, OCH=C$\underline{H}$, J = 12.2 Hz); 4.55—4.44 (m, 1 H, H(7)); 3.84 (s, 3 H, OC$\underline{H}_3$(3)); 3.79 (s, 3 H, OC$\underline{H}_3$(2)); 3.67 (s, 3 H, C(O)OC$\underline{H}_3$); 3.54 (s, 3 H, OC$\underline{H}_3$(1)), 2.20—1.95 (m, 4 H, H(5) and H(6)); 1.86 (s, 3 H, NHC(O)C$\underline{H}_3$). ^{13}C NMR (101 MHz, DMSO-d_6), δ: 168.6, 166.4, 159.4, 153.6, 153.0, 150.2, 143.4, 140.5, 140.1, 134.9, 133.1, 122.1, 114.2, 108.3, 101.6, 85.0, 60.8, 60.6, 55.9, 51.2, 48.1, 38.2, 29.8, 22.6. MS (GC/MS), m/z: 568.1 $[M + H]^+$. R_t = 9.939 min.

***N*-{3-[(*E*)-3-Oxobuten-1-yloxy]-2-iodo-6,7-dihydro-5*H*-9,10,11-trimethoxydibenzo[*a*,*c*]cyclohepten-5-yl}acetamide (6b).** Iodocolchinol **5** (200 mg, 0.41 mmol), DABCO (138 mg, 1.23 mmol), and but-3-yne-2-one (24 μL, 0.41 mmol) were used. Product **6b** (220 mg, 95%) was isolated as yellow crystals, m.p. 185—187 °C. Found (%): C, 52.17; H, 4.80. $C_{24}H_{26}INO_6$. Calculated (%): C, 52.28; H, 4.75. ^1H NMR (400 MHz, DMSO-d_6), δ: 8.45 (d, 1 H, NH, J = 8.5 Hz); 7.96 (d, 1 H, OC$\underline{H}$=CH, J = 12.5 Hz); 7.79 (s, 1 H, H(11)); 7.20 (s, 1 H, H(8)); 6.81 (s, 1 H, H(4)); 5.77 (d, 1 H, OCH=C$\underline{H}$, J = 12.5 Hz); 4.51 (dt, 1 H, H(7), J = 12.3 and 7.8 Hz); 3.84 (s, 3 H, OC$\underline{H}_3$(3)); 3.79 (s, 3 H, OC$\underline{H}_3$(2)); 3.55 (s, 3 H, OC$\underline{H}_3$(1)); 2.24 (s, 3 H, C(O)C$\underline{H}_3$); 2.19—1.92 (m, 4 H, H(5) and H(6)); 1.87 (s, 3 H, NHC(O)C$\underline{H}_3$). ^{13}C NMR (101 MHz, DMSO-d_6), δ: 196.6, 168.6, 160.0, 153.7, 153.0, 150.2, 143.3, 140.5, 140.0, 134.9, 132.9, 122.1, 114.3, 112.4, 108.3, 85.0, 60.8, 60.6, 55.9, 48.1, 36.5, 29.9, 27.5, 22.6. MS (GC/MS), m/z: 552.2 $[M + H]^+$, R_t = 6.649 min.

Synthesis of compounds 7a—d and 8a—f (general procedure). Anhydrous MeCN was poured under an argon atmosphere into a Schlenk flask containing starting aryl iodide **6a,b**, $Pd(OAc)_2$, CuI, Ph_3P, and AcOK; and the corresponding alkyne was then added to the resulting solution. The reaction mixture was kept at 45 °C for 12 h. The product was isolated using silica gel column chromatography, eluent PE—AcOEt—EtOH (7 : 1 : 1).

***N*-{3-[(*E*)-2-Carboxymethylethenyloxy]-6,7-dihydro-5*H*-2-phenylethynyl-9,10,11-trimethoxydibenzo[*a*,*c*]cyclohepten-5-yl}-acetamide (7a).** Aryl iodide **6a** (150 mg, 0.26 mmol), $Pd(OAc)_2$ (3 mg, 0.013 mmol), CuI (5 mg, 0.026 mmol), Ph_3P (11 mg, 0.039 mmol), AcOK (76 mg, 0.78 mmol), and phenylacetylene (28 μL, 0.26 mmol) were used. Product **7a** (105 mg, 75%) was isolated as beige crystals, m.p. 178—180 °C. Found (%): C, 70.88; H, 5.69. $C_{32}H_{31}NO_7$. Calculated (%): C, 70.97; H, 5.77. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 8.44 (d, 1 H, NH, J = 8.6 Hz); 7.81 (d, 1 H, OC<u>H</u>=CH, J = 12.2 Hz); 7.58 (s, 1 H, H(11)); 7.51 (d, 2 H, Ph, J = 7.6 Hz); 7.38 (t, 3 H, Ph, J = 6.7 Hz); 7.19 (s, 1 H, H(8)); 6.79 (s, 1 H, H(4)); 5.54 (d, 1 H, OCH=C<u>H</u>, J = 12.2 Hz); 4.65—4.47 (m, 1 H, H(7)); 3.84 (s, 3 H, OC<u>H</u>$_3$(3)); 3.79 (s, 3 H, OC<u>H</u>$_3$(2)); 3.67 (s, 3 H, C(O)OC<u>H</u>$_3$); 3.55 (s, 3 H, OC<u>H</u>$_3$(1)); 2.27—2.02 (m, 4 H, H(5) and H(6)); 1.89 (s, 3 H, NHC(O)C<u>H</u>$_3$). ^{13}C NMR (101 MHz, DMSO-d_6), δ: 168.6, 166.4, 159.4, 154.4, 153.6, 153.0, 150.2, 143.4, 140.5, 140.1, 135.0, 133.8, 132.9 (2 C), 128.9 (2 C), 122.1, 120.9, 114.1, 111.4, 108.2, 101.6, 93.0, 84.9, 60.8, 60.6, 55.8, 51.2, 48.2, 38.3, 29.9, 22.6. MS (GC/MS), m/z: 542.3 $[M + H]^+$, R_t = 7.399 min.

***N*-{3-[(*E*)-2-Carboxymethylethenyloxy]-2-propylethynyl-6,7-dihydro-5*H*-9,10,11-trimethoxydibenzo[*a*,*c*]cyclohepten-5-yl}acetamide (7b).** Aryl iodide **6a** (150 mg, 0.26 mmol), $Pd(OAc)_2$ (3 mg, 0.013 mmol), CuI (5 mg, 0.026 mmol), Ph_3P (11 mg, 0.039 mmol), AcOK (76 mg, 0.78 mmol), and pent-1-yne (26 μL, 0.26 mmol) were used. Product **7b** (124 mg, 65%) was isolated as light beige crystals, m.p. 158—160 °C. Found (%): C, 68.68; H, 6.58. $C_{29}H_{33}NO_7$. Calculated (%): C, 68.62; H, 6.55. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 8.43 (d, 1 H, NH, J = 8.5 Hz); 7.84 (d, 1 H, OC<u>H</u>=CH, J = 12.2 Hz); 7.37 (s, 1 H, H(11)); 7.15 (s, 1 H, H(8)); 6.81 (s, 1 H, H(4)); 5.52 (d, 1 H, OCH=C<u>H</u>, J = 12.2 Hz); 4.56—4.49 (m, 1 H, H(7)); 3.84 (s, 3 H, OC<u>H</u>$_3$(3)); 3.79 (s, 3 H, OC<u>H</u>$_3$(2)); 3.65 (s, 3 H, C(O)OC<u>H</u>$_3$); 3.51 (s, 3 H, OC<u>H</u>$_3$(1)); 2.41 (t, 2 H, C<u>H</u>$_2$CH$_2$CH$_3$, J = 6.8 Hz); 2.25—2.01 (m, 4 H, H(5) and H(6)); 1.87 (s, 3 H, NHC(O)C<u>H</u>$_3$); 1.53 (dd, 2 H, CH$_2$C<u>H</u>$_2$CH$_3$, J = 14.3 and 7.1 Hz); 0.97 (t, 3 H, CH$_2$CH$_2$C<u>H</u>$_3$, J = 7.3 Hz). ^{13}C NMR (101 MHz, DMSO-d_6), δ: 168.6, 166.5, 160.0, 154.3, 152.8, 150.2, 142.7, 140.5, 134.9, 134.2, 131.2, 122.6, 114.1, 112.6, 108.3, 100.8, 95.8, 75.4, 60.7, 60.6, 55.8, 51.2, 48.1, 38.3, 29.8, 22.6, 21.4, 20.8, 13.2. MS (GC/MS), m/z: 508.3 $[M + H]^+$, R_t = 7.764 min.

***N*-{3-[(*E*)-2-Carboxymethylethenyloxy]-2-acetoxyethynyl-6,7-dihydro-5*H*-9,10,11-trimethoxydibenzo[*a*,*c*]cyclohepten-5-yl}acetamide (7c).** Aryl iodide **6a** (100 mg, 0.17 mmol), $Pd(OAc)_2$ (2 mg, 0.009 mmol), CuI (3 mg, 0.017 mmol), Ph_3P (7 mg, 0.026 mmol), AcOK (51 mg, 0.52 mmol), and propargyl acetate (17 μL, 0.17 mmol) were used. Product **7c** (50 mg, 54%) was isolated as light beige crystals, m.p. 167—169 °C. Found (%): C, 64.89; H, 6.73. $C_{29}H_{31}NO_9$. Calculated (%): C, 64.80; H, 5.81. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 8.46 (d, 1 H, NH, J = 8.3 Hz); 7.84 (d, 1 H, OC<u>H</u>=CH, J = 11.5 Hz); 7.43 (s, 1 H, H(11)); 7.19 (s, 1 H, H(8)); 6.82 (s, 1 H, H(4)); 5.58 (d, 1 H, OCH=C<u>H</u>, J = 12.2 Hz); 4.93 (s, 2 H, C<u>H</u>$_2$OC(O)CH$_3$); 4.57—4.50 (m, 1 H, H(7)), 3.84 (s, 3 H, OC<u>H</u>$_3$(3)), 3.79 (s, 3 H, OC<u>H</u>$_3$(2)), 3.67 (s, 3 H, C(O)OC<u>H</u>$_3$); 3.48 (s, 3 H, OC<u>H</u>$_3$(1)); 2.26—2.07 (m, 4 H, H(5) and H(6)); 2.06 (s, 3 H, CH$_2$OC(O)C<u>H</u>$_3$); 1.89 (s, 3 H, NHC(O)C<u>H</u>$_3$). ^{13}C NMR (101 MHz, DMSO-d_6), δ: 169.7, 168.6, 166.4, 159.4, 154.5, 152.9, 150.2, 144.2, 140.5, 134.9, 134.5, 131.2, 122.3, 113.8, 110.8, 108.3, 101.5, 89.0, 80.5, 60.7, 60.6, 55.8, 52.2, 51.2, 48.3, 38.3, 29.8, 22.6, 20.4. MS (GC/MS), m/z: 538.9 $[M + H]^+$, R_t = 7.762 min.

***N*-{3-[(*E*)-2-Carboxymethylethenyloxy]-2-(4-chlorobutyl)-ethynyl-6,7-dihydro-5*H*-9,10,11-trimethoxydibenzo[*a*,*c*]cyclohepten-5-yl}acetamide (7d).** Aryl iodide **6a** (682 mg, 1.18 mmol), $Pd(OAc)_2$ (13 mg, 0.06 mmol), CuI (23 mg, 0.118 mmol), Ph_3P (46 mg, 0.177 mmol), AcOK (693 mg, 7.08 mmol), and 6-chlorhex-1-yne (150 μL, 1.30 mmol) were used. Product **7d** (430 mg, 65%) was isolated as light beige crystals, m.p. 138—140 °C. Found (%): C, 67.29; H, 6.50. $C_{31}H_{36}ClNO_6$. Calculated (%): C, 67.20; H, 6.55. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 8.46 (d, 1 H, NH, J = 8.4 Hz); 7.87 (d, 1 H, OC<u>H</u>=CH, J = 12.2 Hz); 7.41 (s, 1 H, H(11)); 7.19 (s, 1 H, H(8)); 6.82 (s, 1 H, H(4)); 5.56 (d, 1 H, OCH=C<u>H</u>, J = 12.2 Hz); 4.61—4.51 (m, 1 H, H(7)); 3.86 (s, 3 H, OC<u>H</u>$_3$(3)); 3.81 (s, 3 H, OC<u>H</u>$_3$(2)); 3.68 (s, 3 H, C(O)OC<u>H</u>$_3$); 3.68—3.56 (m, 2 H, CH$_2$CH$_2$CH$_2$C<u>H</u>$_2$Cl); 3.54 (s, 3 H, OC<u>H</u>$_3$(1)); 2.44—2.01 (m, 4 H, H(5) and H(6)); 1.90 (s, 3 H, NHC(O)C<u>H</u>$_3$); 1.88—1.84 (m, 4 H, C<u>H</u>$_2$CH$_2$C<u>H</u>$_2$CH$_2$Cl); 1.66 (dd, 2 H, CH$_2$C<u>H</u>$_2$CH$_2$CH$_2$Cl, J = 14.6 and 7.1 Hz). ^{13}C NMR (101 MHz, DMSO-d_6), δ: 168.6, 166.5, 160.0, 154.4, 152.9, 150.2, 142.8, 140.5, 134.9, 134.2, 131.3, 122.6, 114.0, 112.5, 108.2, 100.8, 95.4, 75.6, 60.7, 60.6, 55.8, 51.1, 48.2, 44.8, 38.4, 31.2, 25.3, 25.2, 22.6, 18.2. MS (GC/MS), m/z: 556.3 $[M]^+$, R_t = 7.761 min.

***N*-{3-[(*E*)-3-Oxobuten-1-yloxy]-6,7-dihydro-5*H*-2-phenylethynyl-9,10,11-trimethoxydibenzo[*a*,*c*]cyclohepten-5-yl}acetamide (8a).** Aryl iodide **6b** (200 mg, 0.36 mmol), $Pd(OAc)_2$ (4 mg, 0.018 mmol), CuI (7 mg, 0.036 mmol), Ph_3P (14 mg, 0.054 mmol), AcOK (106 mg, 1.08 mmol), and phenylacetylene (24 μL, 0.41 mmol) were used. Product **8a** (155 mg, 81%) was isolated as light beige crystals, m.p. 208—210 °C. Found (%): C, 73.09; H, 5.90. $C_{32}H_{31}NO_6$. Calculated (%): C, 73.13; H, 5.94. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 8.48 (d, 1 H, NH, J = 8.5 Hz); 8.10 (d, 1 H, OC<u>H</u>=CH, J = 12.5 Hz); 7.54 (s, 1 H, H(11)); 7.53—7.48 (m, 2 H, Ph); 7.45—7.40 (m, 3 H, Ph); 7.27 (s, 1 H, H(8)); 6.83 (s, 1 H, H(4)); 5.87 (d, 1 H, OCH=C<u>H</u>, J = 12.5 Hz); 4.60 (dd, 1 H, H(7), J = 9.3 Hz, J = 5.9 Hz); 3.85 (s, 3 H, OC<u>H</u>$_3$(3)); 3.80 (s, 3 H, OC<u>H</u>$_3$(2)); 3.54 (s, 3 H, OC<u>H</u>$_3$(1)); 2.21 (s, 3 H, C(O)C<u>H</u>$_3$); 2.17—1.92 (m, 4 H, H(5) and H(6)); 1.90 (s, 3 H, NHC(O)C<u>H</u>$_3$). ^{13}C NMR (101 MHz, DMSO-d_6), δ: 196.7, 168.7, 160.7, 154.5, 152.9, 150.3, 143.8, 140.6, 134.9, 134.2, 131.3, 131.2 (2 C), 129.1, 128.8 (2 C), 122.5, 122.1, 114.3, 112.1, 111.8, 108.3, 94.2, 84.4, 60.8, 60.6, 55.9, 48.3, 38.4, 29.9, 27.3, 22.7. MS (GC/MS), m/z: 526.3 $[M + H]^+$, R_t = 7.167 min.

***N*-{3-[(*E*)-3-Oxobuten-1-yloxy]-6,7-dihydro-5*H*-2-propylethynyl-9,10,11-trimethoxydibenzo[*a*,*c*]cyclohepten-5-yl}acetamide (8b).** Aryl iodide **6b** (200 mg, 0.36 mmol), $Pd(OAc)_2$ (4 mg, 0.018 mmol), CuI (7 mg, 0.036 mmol), Ph_3P (14 mg, 0.054 mmol), AcOK (106 mg, 1.08 mmol), and pent-1-yne (24 μL, 0.41 mmol) were used. Product **8b** (140 mg, 78%) was isolated as light beige crystals, m.p. 135—137 °C. Found (%): C, 70.79; H, 6.70. $C_{29}H_{33}NO_6$. Calculated (%): C, 70.86; H, 6.77. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 8.42 (d, 1 H, NH, J = 8.4 Hz); 7.99 (d, 1 H, OC<u>H</u>=CH, J = 12.5 Hz); 7.37 (s, 1 H, H(11)); 7.17 (s, 1 H, H(8)); 6.81 (s, 1 H, H(4)); 5.74 (d, 1 H, OCH=C<u>H</u>, J = 12.5 Hz); 4.54 (dd, 1 H, H(7), J = 12.2 and 5.1 Hz); 3.84

(s, 3 H, OC$\underline{H}_3$(3)); 3.79 (s, 3 H, OC$\underline{H}_3$(2)); 3.51 (s, 3 H, OC$\underline{H}_3$(1)); 2.41 (t, 2 H, C$\underline{H}_2$CH$_2$CH$_3$, J = 6.9 Hz); 2.21 (s, 3 H, C(O)C$\underline{H}_3$); 2.20—1.93 (m, 4 H, H(5) and H(6)); 1.87 (s, 3 H, NHC(O)C$\underline{H}_3$); 1.53 (dd, 2 H, CH$_2$C$\underline{H}_2$CH$_3$, J = 14.3 Hz, J = 7.1 Hz); 0.97 (t, 3 H, CH$_2$CH$_2$C$\underline{H}_3$, J = 7.4 Hz). ^{13}C NMR (101 MHz, DMSO-d$_6$), δ: 196.5, 168.6, 160.9, 154.4, 152.8, 150.2, 142.7, 140.5, 134.9, 134.2, 131.2, 122.6, 114.3, 112.7, 111.8, 108.3, 95.8, 75.5, 60.7, 60.6, 55.8, 48.1, 38.4, 29.9, 27.2, 22.6, 21.5, 20.8, 13.2. MS (GC/MS), m/z: 492.3 [M + H]$^+$, R_t = 6.929 min.

***N*-{3-[(*E*)-3-Oxobuten-1-yloxy]-2-[(1-acetoxy)ethynyl]-6,7-dihydro-5*H*-9,10,11-trimethoxydibenzo[*a*,*c*]cyclohepten-5-yl}acetamide (8c).** Aryl iodide **6b** (200 mg, 0.36 mmol), Pd(OAc)$_2$ (4 mg, 0.018 mmol), CuI (7 mg, 0.036 mmol), Ph$_3$P (14 mg, 0.054 mmol), AcOK (106 mg, 1.08 mmol), and propargyl acetate (36 μL, 0.41 mmol) were used. Product **8c** (124 mg, 65%) was isolated as light beige crystals, m.p. 168—170 °C. Found (%): C, 66.89; H, 6.08. $C_{29}H_{31}NO_8$. Calculated (%): C, 66.78; H, 5.99. ^{1}H NMR (400 MHz, DMSO-d$_6$), δ: 8.46 (d, 1 H, NH, J = 8.2 Hz); 8.00 (d, 1 H, OC$\underline{H}$=CH, J = 12.5 Hz); 7.43 (s, 1 H, H(11)); 7.22 (s, 1 H, H(8)); 6.82 (s, 1 H, H(4)); 5.79 (d, 1 H, OCH=C$\underline{H}$, J = 12.5 Hz); 4.93 (s, 2 H, C$\underline{H}_2$OC(O)CH$_3$); 4.60—4.51 (m, 1 H, H(7)); 3.84 (s, 3 H, OC$\underline{H}_3$(3)); 3.79 (s, 3 H, OC$\underline{H}_3$(2)); 3.51 (s, 3 H, OC$\underline{H}_3$(1)); 2.22 (s, 3 H, C(O)C$\underline{H}_3$); 2.21—2.09 (m, 4 H, H(5) and H(6)); 2.05 (s, 3 H, CH$_2$OC(O)C$\underline{H}_3$); 1.88 (c, 3 H, NHC(O)C$\underline{H}_3$). ^{13}C NMR (101 MHz, DMSO-d$_6$), δ: 196.7, 169.7, 168.6, 160.4, 154.6, 152.9, 150.2, 144.1, 140.5, 134.9, 134.5, 131.2, 122.4, 114.1, 112.4, 110.9, 108.3, 89.1, 80.6, 60.8, 60.6, 55.9, 52.2, 48.2, 38.3, 29.8, 27.3, 22.7, 20.4. MS (GC/MS), m/z: 521.5 [M]$^+$, R_t = 7.689 min.

***N*-{3-[(*E*)-3-Oxobuten-1-yloxy]-2-[(1-hydroxycyclopentyl)-ethynyl]-6,7-dihydro-5*H*-9,10,11-trimethoxydibenzo[*a*,*c*]cyclohepten-5-yl}acetamide (8d).** Aryl iodide **6b** (200 mg, 0.36 mmol), Pd(OAc)$_2$ (4 mg, 0.018 mmol), CuI (7 mg, 0.036 mmol), Ph$_3$P (14 mg, 0.054 mmol), AcOK (106 mg, 1.08 mmol), and 1-ethynylcyclopentanol (40 mg, 0.41 mmol) were used. Product **8d** (108 mg, 57%) was isolated as light beige crystals, m.p. 151—153 °C. Found (%): C, 69.70; H, 6.70. $C_{31}H_{35}NO_7$. Calculated (%): C, 69.78; H, 6.61. ^{1}H NMR (400 MHz, DMSO-d$_6$), δ: 8.42 (d, 1 H, NH, J = 8.5 Hz); 7.98 (d, 1 H, OC$\underline{H}$=CH, J = 12.5 Hz); 7.38 (s, 1 H, H(11)); 7.19 (s, 1 H, H(8)); 6.82 (s, 1 H, H(4)); 5.74 (d, 1 H, OCH=C$\underline{H}$, J = 12.5 Hz); 5.36 (s, 1 H, OH); 4.60—4.51 (m, 1 H, H(7)); 3.84 (s, 3 H, OC$\underline{H}_3$(3)); 3.79 (s, 3 H, OC$\underline{H}_3$(2)); 3.50 (s, 3 H, OC$\underline{H}_3$(1)); 2.20 (s, 3 H, C(O)C$\underline{H}_3$); 2.18—1.89 (m, 4 H, H(5) and H(6)); 1.88 (s, 3 H, NHC(O)C$\underline{H}_3$); 1.86—1.60 (m, 8 H, CyP). ^{13}C NMR (101 MHz, DMSO-d$_6$), δ: 196.6, 168.6, 161.1, 154.3, 152.8, 150.2, 143.1, 140.5, 134.9, 134.1, 131.3, 122.5, 114.5, 112.3, 111.8, 108.3, 100.3, 76.2, 72.9, 60.8, 60.6, 55.8, 48.1, 41.9, 41.8, 38.4, 29.8, 27.2, 23.0 (2 C), 22.7. MS (GC/MS), m/z: 534.5 [M + H]$^+$, R_t = 6.987 min.

***N*-{3-[(*E*)-3-Oxobuten-1-yloxy]-2-[(1-hydroxycyclohexyl)-ethynyl]-6,7-dihydro-5*H*-9,10,11-trimethoxydibenzo[*a*,*c*]cyclohepten-5-yl}acetamide (8e).** Aryl iodide **6b** (200 mg, 0.36 mmol), Pd(OAc)$_2$ (4 mg, 0.018 mmol), CuI (7 mg, 0.036 mmol), Ph$_3$P (14 mg, 0.054 mmol), AcOK (106 mg, 1.08 mmol), and 1-ethynylcyclohexanol (45 mg, 0.41 mmol) were used. Product **8e** (124 mg, 65%) was isolated as light beige crystals, m.p. 153—155 °C. Found (%): C, 70.28; H, 6.89. $C_{32}H_{37}NO_7$. Calculated (%): C, 70.18; H, 6.81. ^{1}H NMR (400 MHz, DMSO-d$_6$), δ: 8.43 (d, 1 H, NH, J = 8.4 Hz); 8.00 (d, 1 H, OC$\underline{H}$=CH, J = 12.5 Hz); 7.38 (s, 1 H, H(11)); 7.20 (s, 1 H, H(8)); 6.82 (s, 1 H, H(4)); 5.70 (d, 1 H, OCH=C$\underline{H}$, J = 12.5 Hz); 5.47 (s, 1 H, OH); 4.62—4.50 (m, 1 H, H(7)); 3.84 (s, 3 H, OC$\underline{H}_3$(3)); 3.79 (s, 3 H, OC$\underline{H}_3$(2)); 3.50 (s, 3 H, OC$\underline{H}_3$(1)); 2.21 (s, 3 H, C(O)C$\underline{H}_3$); 2.19—1.92 (m, 4 H, H(5) and H(6)); 1.88 (s, 3 H, NHC(O)C$\underline{H}_3$); 1.82 (d, 2 H, CyH, J = 7.2 Hz); 1.60 (d, 2 H, CyH, J = 2.0 Hz); 1.48 (dd, 6 H, CyH, J = 18.2 and 9.6 Hz). ^{13}C NMR (101 MHz, DMSO-d$_6$), δ: 196.5, 168.6, 161.0, 154.2, 152.9, 150.2, 143.1, 140.5, 134.9, 134.1, 131.3, 122.5, 114.5, 112.4, 111.8, 108.3, 99.9, 77.6, 67.3, 60.8, 60.6, 55.8, 48.1, 38.4, 30.9, 29.8, 27.1 (2 C), 24.9, 22.8 (2 C), 22.7. MS (GC/MS), m/z: 547.7 [M]$^+$, R_t = 7.133 min.

***N*-{3-[(*E*)-3-Oxobuten-1-yloxy]-6,7-dihydro-5*H*-2-[α-pyridin-2-ylethynyl]-9,10,11-trimethoxydibenzo[*a*,*c*]cyclohepten-5-yl}acetamide (8f).** Aryl iodide **6b** (200 mg, 0.36 mmol), Pd(OAc)$_2$ (4 mg, 0.018 mmol), CuI (7 mg, 0.036 mmol), Ph$_3$P (14 mg, 0.054 mmol), AcOK (106 mg, 1.08 mmol), and 1-ethynylpyridine (36 μL, 0.41 mmol) were used. Product **8f** (124 mg, 65%) was isolated as light beige crystals, m.p. 169—171 °C. Found (%): C, 70.83; H, 5.81. $C_{31}H_{30}N_2O_6$. Calculated (%): C, 70.71; H, 5.74. ^{1}H NMR (400 MHz, DMSO-d$_6$), δ: 8.61 (d, 1 H, Py, J = 4.6 Hz); 8.48 (d, 1 H, NH, J = 8.3 Hz); 8.11 (d, 1 H, OC$\underline{H}$=CH, J = 12.5 Hz); 7.85 (dd, 1 H, Py, J = 8.7 Hz, J = 7.7 Hz); 7.64—7.55 (m, 1 H, Py); 7.59 (s, 1 H, H(11)); 7.42 (dd, 1 H, Py, J = 6.7 Hz, J = 5.7 Hz); 7.28 (s, 1 H, H(8)); 6.84 (s, 1 H, H(4)); 5.88 (d, 1 H, OCH=C$\underline{H}$, J = 12.5 Hz); 4.64—4.53 (m, 1 H, H(7)); 3.85 (s, 3 H, OC$\underline{H}_3$(3)); 3.80 (s, 3 H, OC$\underline{H}_3$(2)); 3.55 (s, 3 H, OC$\underline{H}_3$(1)); 2.23 (s, 3 H, C(O)C$\underline{H}_3$); 2.20—1.93 (m, 4 H, H(5) and H(6)); 1.90 (s, 3 H, NHC(O)C$\underline{H}_3$). ^{13}C NMR (101 MHz, DMSO-d$_6$), δ: 196.7, 168.7, 160.3, 154.7, 153.0, 150.3, 144.6, 142.0, 140.6, 136.9 (2 C), 134.9, 134.6, 131.3, 127.3, 123.7, 122.4, 114.1, 112.5, 110.8, 108.3, 93.5, 83.4, 60.8, 60.6, 55.9, 48.3, 38.3, 29.8, 27.4, 22.7. MS (GC/MS), m/z: 526.8 [M]$^+$, R_t = 7.532 min.

Synthesis of compounds 3a—f (general procedure). Starting compound **7** (or **8**) was placed in a Schlenk flask equipped with a stirrer and dissolved in 1,2-dichloroethane (1.5 mL) under an inert atmosphere. The resulting system was isolated from the daylight by a foil. A solution of corresponding alcohol in 1,2-dichloroethane (0.5 mL) and a mixture of Ph$_3$PAuCl and Ag[SbF$_6$] in 1,2-dichloroethane (1 mL) were then added. The reaction mixture was stirred at ~20 °C in the dark for 24 h. The product was isolated using column chromatography on silica gel, eluent PE—AcOEt—EtOH (9 : 1 : 1).

Methyl (7*S*,10*S*,11*R*,14a*R*)-7-acetamido-10-butoxy-6,7,10,11-tetrahydro-5*H*-1,2,3-trimethoxy-12-phenylbenzo[6′,7′]cyclohepta[1′,2′:4,5]benzo[1,2-*b*]oxepine-11-carboxylate (3a). Compound **7a** (40 mg, 0.074 mmol), *n*-butanol (11 mg, 0.148 mmol), Ph$_3$PAuCl (2 mg, 0.004 mmol), and Ag[SbF$_6$] (2 mg, 0.004 mmol) were used. Product **3a** (27 mg, 60%) was isolated as a mixture of two diastereomers **A** and **B** in the ratio of 2 : 1, light yellow crystals, m.p. 169—171 °C. Found (%): C, 70.37; H, 6.62. $C_{36}H_{41}NO_8$. Calculated (%): C, 70.23; H, 6.71. Diastereomer **A**. ^{1}H NMR (400 MHz, DMSO-d$_6$), δ: 8.40 (d, 1 H, NH, J = 8.5 Hz); 7.48 (d, 2 H, Ph, J = 7.6 Hz); 7.36 (t, 3 H, Ph, J = 6.7 Hz); 7.28 (s, 1 H, H(11)); 7.01 (s, 1 H, H(8)); 6.92 (s, 1 H, —C$\underline{H}$=C<); 6.78 (s, 1 H, H(4)); 5.66 (d, 1 H, C$\underline{H}$–OBu, J = 4.6 Hz); 4.57—4.51 (m, 1 H, H(7)); 4.47 (d, 1 H, C$\underline{H}$C(O)OCH$_3$, J = 4.3 Hz); 3.84 (s, 3 H, OC$\underline{H}_3$(3)); 3.79 (s, 3 H, OC$\underline{H}_3$(2)); 3.71—3.64 (m, 2 H, OC$\underline{H}_2$CH$_2$CH$_2$CH$_3$); 3.59 (s, 3 H, C(O)OC$\underline{H}_3$); 3.56 (s, 3 H, OC$\underline{H}_3$(1)); 2.20—2.00 (m, 4 H, H(5) and

H(6)); 1.88 (s, 3 H, NHC(O)C$\underline{H}_3$); 1.39—1.30 (m, 2 H, $OCH_2C\underline{H}_2CH_2CH_3$); 1.06—0.96 (m, 2 H, $OCH_2CH_2C\underline{H}_2CH_3$); 0.67 (t, 3 H, $OCH_2CH_2CH_2C\underline{H}_3$, J = 7.4 Hz). ^{13}C NMR (101 MHz, DMSO-d_6), δ: 169.4, 168.4, 152.4, 151.0, 150.3, 142.1, 140.6, 134.7, 134.4, 132.4, 129.6, 128.4 (2 C), 127.2, 126.2 (2 C), 124.5, 124.4, 123.7, 115.3, 108.1, 97.9, 68.1, 60.8, 60.5 (2 C), 55.8, 52.2, 47.8, 38.4, 30.8, 29.9, 22.6, 18.5, 13.4. Diastereomer **B**. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 8.36 (d, 1 H, NH, J = 8.9 Hz); 7.48 (d, 2 H, Ph, J = 7.6 Hz); 7.36 (t, 3 H, Ph, J = 6.7 Hz); 7.29 (s, 1 H, H(11)); 7.01 (s, 1 H, H(8)); 6.86 (s, 1 H, —C$\underline{H}$=C<); 6.80 (s, 1 H, H(4)); 5.61 (d, 1 H, C$\underline{H}$—OBu, J = 5.2 Hz); 4.57—4.51 (m, 1 H, H(7)); 4.47 (d, 1 H, C$\underline{H}$C(O)OCH_3, J = 4.3 Hz); 3.84 (s, 3 H, OC$\underline{H}_3$(3)); 3.78 (s, 3 H, OC$\underline{H}_3$(2)); 3.71—3.64 (m, 2 H, $OC\underline{H}_2CH_2CH_2CH_3$); 3.51 (s, 3 H, C(O)OC$\underline{H}_3$); 3.46 (s, 3 H, OC$\underline{H}_3$(1)); 2.20—2.00 (m, 4 H, H(5) and H(6)); 1.88 (s, 3 H, NHC(O)C$\underline{H}_3$); 1.39—1.30 (m, 2 H, $OCH_2C\underline{H}_2CH_2CH_3$); 1.06—0.96 (m, 2 H, $OCH_2CH_2C\underline{H}_2CH_3$); 0.71 (t, 3 H, $OCH_2CH_2CH_2C\underline{H}_3$, J = 7.4 Hz). ^{13}C NMR (101 MHz, DMSO-d_6), δ: 169.3, 168.2, 152.3, 151.2, 150.4, 142.0, 140.5, 134.8, 134.1, 132.8, 129.6, 128.5, 128.3 (2 C), 127.2, 126.2 (2 C), 124.6, 124.2, 123.7, 115.2, 108.1, 98.9, 68.3, 60.8, 60.6, 60.5, 55.8, 52.0, 47.9, 38.4, 30.8, 30.1, 22.6, 18.5, 13.4. MS (GC/MS), m/z: 638.7 $[M + Na]^+$, R_t = 7.663 min.

Methyl (7*S*,10*S*,11*R*,14a*R*)-7-acetamido-10-isopropyloxy-6,7,10,11-tetrahydro-5*H*-1,2,3-trimethoxy-12-phenylbenzo-[6′,7′]cyclohepta[1′,2′:4,5]benzo[1,2-*b*]oxepine-11-carboxylate (3b). Compound **7a** (100 mg, 0.184 mmol), propan-2-ol (22 mg, 0.37 mmol), Ph_3PAuCl (5 mg, 0.009 mmol), and Ag[SbF_6] (3 mg, 0.009 mmol) were used. Product **3b** (60 mg, 53%) was isolated as a mixture of two diastereomers **A** and **B** in the ratio of 2 : 1, light yellow crystals, m.p. 173—175 °C. Found (%): C, 69.99; H, 6.42. $C_{35}H_{39}NO_8$. Calculated (%): C, 69.87; H, 6.53. Diastereomer **A**. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 8.42 (d, 1 H, NH, J = 8.8 Hz); 7.48 (d, 2 H, Ph, J = 8.0 Hz); 7.36 (t, 3 H, Ph, J = 7.6 Hz); 7.27 (s, 1 H, H(11)); 7.01 (s, 1 H, H(8)); 6.88 (s, 1 H, —C$\underline{H}$=C<); 6.78 (s, 1 H, H(4)); 5.67 (d, 1 H, C$\underline{H}$—OPr^i, J = 5.0 Hz); 4.55—4.50 (m, 1 H, H(7)); 4.42 (d, 1 H, C$\underline{H}$C(O)-OCH_3, J = 5.1 Hz); 4.04—3.96 (m, 1 H, C$\underline{H}(CH_3)_2$); 3.83 (s, 3 H, OC$\underline{H}_3$(3)); 3.80 (s, 3 H, OC$\underline{H}_3$(2)); 3.60 (s, 3 H, C(O)OC$\underline{H}_3$); 3.53 (s, 3 H, OC$\underline{H}_3$(1)); 2.23—1.98 (m, 4 H, H(5) and H(6)); 1.88 (s, 3 H, NHC(O)C$\underline{H}_3$); 1.09 (t, 3 H, $CH(C\underline{H}_3)_2$, J = 6.0 Hz); 0.96 (t, 3 H, $CH(C\underline{H}_3)_2$, J = 6.0 Hz). ^{13}C NMR (101 MHz, DMSO-d_6), δ: 169.4, 168.4, 152.4, 151.5, 150.3, 142.0, 141.8, 140.6, 134.7, 134.3, 132.7, 129.4, 128.6, 128.3 (2 C), 127.2, 126.2 (2 C), 124.5, 123.7, 115.2, 108.1, 97.4, 70.8, 60.8, 60.5, 55.8, 52.1, 47.9, 38.5, 30.1, 22.6 (2 C), 21.4. Diastereomer **B**. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 8.39 (d, 1 H, NH, J = 8.8 Hz); 7.48 (d, 2 H, Ph, J = 8.0 Hz); 7.36 (t, 3 H, Ph, J = 7.6 Hz); 7.29 (s, 1 H, H(11)); 7.99 (s, 1 H, H(8)); 6.84 (s, 1 H, —C$\underline{H}$=C<); 6.80 (s, 1 H, H(4)); 5.66 (d, 1 H, C$\underline{H}$—OPr^i, J = 5.0 Hz); 4.55—4.50 (m, 1 H, H(7)); 4.41 (d, 1 H, C$\underline{H}$C(O)OCH_3, J = 5.1 Hz); 4.04—3.96 (m, 1 H, C$\underline{H}(CH_3)_2$); 3.84 (s, 3 H, OC$\underline{H}_3$(3)); 3.78 (s, 3 H, OC$\underline{H}_3$(2)); 3.67 (s, 3 H, C(O)OC$\underline{H}_3$); 3.54 (s, 3 H, OC$\underline{H}_3$(1)); 2.23—1.98 (m, 4 H, H(5) and H(6)); 1.88 (s, 3 H, NHC(O)C$\underline{H}_3$); 1.09 (t, 3 H, $CH(C\underline{H}_3)_2$, J = 6.0 Hz); 0.97 (t, 3 H, $CH(C\underline{H}_3)_2$, J = 6.0 Hz). ^{13}C NMR (101 MHz, DMSO-d_6), δ: 169.3, 168.3, 152.3, 151.6, 150.4, 141.9, 141.6, 140.5, 134.8, 133.9, 133.0, 129.5, 128.6, 128.3 (2 C), 127.2, 126.3 (2 C), 124.4, 123.7, 115.2, 108.1, 98.1, 70.5, 60.8, 60.5, 55.9, 51.9, 48.0, 38.3, 29.8, 22.7, 22.6, 21.3. MS (GC/MS), m/z: 624.3 $[M + Na]^+$, R_t = 7.207 min.

Methyl (7*S*,10*S*,11*R*,14a*R*)-7-acetamido-10-ethoxy-6,7,10,11-tetrahydro-5*H*-1,2,3-trimethoxy-12-phenyl-benzo[6′,7′]cyclohepta[1′,2′:4,5]benzo[1,2-*b*]oxepine-11-carboxylate (3c). Compound **7a** (40 mg, 0.074 mmol), ethanol (11 mg, 0.148 mmol), Ph_3PAuCl (2 mg, 0.004 mmol), and Ag[SbF_6] (2 mg, 0.004 mmol) were used. Product **3c** (17 mg, 40%) was isolated as a mixture of two diastereomers **A** and **B** in the ratio of 2 : 1, light yellow crystals, m.p. 175—177 °C. Found (%): C, 69.64; H, 6.29. $C_{34}H_{37}NO_8$. Calculated (%): C, 69.49; H, 6.35. Diastereomer **A**. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 8.45 (d, 1 H, NH, J = 8.4 Hz); 7.48 (d, 2 H, Ph, J = 7.6 Hz); 7.36 (t, 3 H, Ph, J = 6.7 Hz); 7.27 (s, 1 H, H(11)); 7.03 (s, 1 H, H(8)); 6.90 (s, 1 H, —C$\underline{H}$=C<); 6.78 (s, 1 H, H(4)); 5.65 (d, 1 H, C$\underline{H}$—OEt, J = 4.6 Hz); 4.58—4.50 (m, 1 H, H(7)); 4.46 (d, 1 H, C$\underline{H}$C(O)OCH_3, J = 5.0 Hz); 3.83 (s, 3 H, OC$\underline{H}_3$(3)); 3.79 (s, 3 H, OC$\underline{H}_3$(2)); 3.70—3.61 (m, 2 H, $OC\underline{H}_2CH_3$); 3.59 (s, 3 H, C(O)OC$\underline{H}_3$); 3.54 (s, 3 H, OC$\underline{H}_3$(1)); 2.20—2.01 (m, 4 H, H(5) and H(6)); 1.89 (s, 3 H, NHC(O)C$\underline{H}_3$); 1.01 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7.0 Hz). ^{13}C NMR (101 MHz, DMSO-d_6), δ: 169.4, 168.4, 152.4, 151.3, 150.3, 142.0, 141.8, 140.6, 134.7, 134.4, 132.6, 129.5, 128.5, 128.4 (2 C), 127.2, 126.2 (2 C), 124.2, 123.7, 115.2, 108.1, 98.4, 64.2, 60.8, 60.5, 55.8, 52.2, 47.9, 38.5, 30.1, 22.7, 14.7. Diastereomer **B**. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 8.43 (d, 1 H, NH, J = 8.4 Hz); 7.48 (d, 2 H, Ph, J = 7.6 Hz); 7.36 (t, 3 H, Ph, J = 6.7 Hz); 7.26 (s, 1 H, H(11)); 7.03 (s, 1 H, H(8)); 6.86 (s, 1 H, —C$\underline{H}$=C<); 6.80 (s, 1 H, H(4)), 5.61 (d, 1 H, C$\underline{H}$—OEt, J = 5.3 Hz); 4.58—4.50 (m, 1 H, H(7)); 4.47 (d, 1 H, C$\underline{H}$C(O)OCH_3, J = 5.0 Hz); 3.83 (s, 3 H, OC$\underline{H}_3$(3)); 3.78 (s, 3 H, OC$\underline{H}_3$(2)); 3.70—3.61 (m, 2 H, $OC\underline{H}_2CH_3$); 3.59 (s, 3 H, C(O)OC$\underline{H}_3$); 3.50 (s, 3 H, OC$\underline{H}_3$(1)); 2.20—2.01 (m, 4 H, H(5) and H(6)); 1.89 (s, 3 H, NHC(O)C$\underline{H}_3$); 1.03 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7.0 Hz). ^{13}C NMR (101 MHz, DMSO-d_6), δ: 169.3, 168.4, 152.4, 151.4, 150.4, 141.9, 141.6, 140.5, 134.8, 134.1, 132.9, 129.5, 128.5, 128.3 (2 C), 127.3, 126.3 (2 C), 124.2, 123.6, 115.2, 108.1, 99.2, 69.8, 60.6, 60.3, 56.0, 52.0, 47.9, 38.4, 30.2, 22.7, 15.1. MS (GC/MS), m/z: 610.8 $[M + Na]^+$, R_t = 7. 291 min.

Methyl (7*S*,10*S*,11*R*,14a*R*)-7-acetamido-6,7,10,11-tetrahydro-5*H*-10-methoxy-1,2,3-trimethoxy-12-phenylbenzo[6′,7′]-cyclohepta[1′,2′:4,5]benzo[1,2-*b*]oxepine-11-carboxylate (3d). Compound 7a (40 mg, 0.074 mmol), methanol (11 mg, 0.148 mmol), Ph_3PAuCl (2 mg, 0.004 mmol), and Ag[SbF_6] (2 mg, 0.004 mmol) were used. Product **3d** (32 mg, 30%) was isolated as a mixture of two diastereomers **A** and **B** in the ratio of 2 : 1, light yellow crystals, m.p. 189—191 °C. Found (%): C, 69.24; H, 6.21. $C_{33}H_{35}NO_8$. Calculated (%): C, 69.10; H, 6.15. Diastereomer **A**. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 8.42 (d, 1 H, NH, J = 8.6 Hz); 7.47 (d, 2 H, Ph, J = 7.3 Hz); 7.38—7.34 (m, 3 H, Ph); 7.28 (s, 1 H, H(11)); 7.05 (s, 1 H, H(8)); 6.91 (s, 1 H, —C$\underline{H}$=C<); 6.79 (s, 1 H, H(4)); 5.60 (d, 1 H, C$\underline{H}$—OMe, J = 4.7 Hz); 4.58—4.52 (m, 1 H, H(7)); 4.47 (d, 1 H, C$\underline{H}$C(O)-OCH_3, J = 4.7 Hz); 3.84 (s, 3 H, OC$\underline{H}_3$(3)); 3.79 (s, 3 H, OC$\underline{H}_3$(2)); 3.57 (s, 3 H, C(O)OC$\underline{H}_3$); 3.56 (s, 3 H, OC$\underline{H}_3$(1)); 3.40 (s, 3 H, CH—O$\underline{Me}$); 2.22—2.02 (m, 4 H, H(5) and H(6)); 1.89 (s, 3 H, NHC(O)C$\underline{H}_3$). ^{13}C NMR (101 MHz, DMSO-d_6), δ: 169.4, 168.4, 152.4, 151.0, 150.3, 142.1, 141.7, 140.6, 134.7, 134.4, 132.4, 129.6, 128.5, 128.4 (2 C), 127.2, 126.2 (2 C), 124.6, 124.2, 115.3, 108.1, 97.9, 60.8, 60.5, 55.8, 55.7, 52.2, 51.2, 47.8, 38.6, 30.8, 22.6. Diastereomer **B**. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 8.39 (d, 1 H, NH, J = 8.4 Hz); 7.47 (d, 2 H, Ph, J = 7.3 Hz); 7.38—7.34 (m, 3 H, Ph); 7.30 (s, 1 H, H(11)); 7.05 (s, 1 H, H(8)); 6.87 (s, 1 H, —C$\underline{H}$=C<); 6.76 (s, 1 H, H(4));

5.57 (d, 1 H, CH—OMe, J = 4.9 Hz); 4.58—4.52 (m, 1 H, H(7)); 4.50 (d, 1 H, $CHC(O)OCH_3$, J = 4.9 Hz); 3.82 (s, 3 H, OCH_3(3)); 3.78 (s, 3 H, OCH_3(2)); 3.53 (s, 3 H, $C(O)OCH_3$); 3.48 (s, 3 H, OCH_3(1)); 3.40 (s, 3 H, CH—OMe); 2.22—2.02 (m, 4 H, H(5) and H(6)); 1.87 (s, 3 H, $NHC(O)CH_3$). ^{13}C NMR (101 MHz, DMSO-d_6), δ: 169.3, 168.2, 152.3, 151.2, 150.4, 142.0, 141.6, 140.5, 134.8, 134.1, 132.8, 129.1, 128.4, 128.3 (2 C), 127.2, 126.3 (2 C), 124.4, 123.7, 115.2, 108.1, 98.9, 60.6, 60.5, 55.8, 55.7, 52.0, 51.3, 47.8, 38.6, 30.8, 22.6. MS (GC/MS), m/z: 596.3 $[M + Na]^+$, R_t = 7.454 min.

Methyl (7*S*,10*S*,11*R*,14a*R*)-7-acetamido-10-butoxy-6,7,10,11-tetrahydro-5*H*-1,2,3-trimethoxy-12-propyl-benzo[6′,7′]cyclohepta[1′,2′:4,5]benzo[1,2-*b*]oxepine-11-carboxylate (3e). Compound **7b** (100 mg, 0.197 mmol), *n*-butanol (29 mg, 0.394 mmol), Ph_3PAuCl (5 mg, 0.010 mmol), and $Ag[SbF_6]$ (4 mg, 0.010 mmol) were used. Product **3e** (46 mg, 40%) was isolated as a mixture of two diastereomers **A** and **B** in the ratio of 2 : 1, light yellow crystals, m.p. 181—183 °C. Found (%): C, 68.25; H, 7.52. $C_{33}H_{43}NO_8$. Calculated (%): C, 68.14; H, 7.45. Diastereomer **A**. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 8.36 (d, 1 H, NH, J = 8.5 Hz); 7.14 (s, 1 H, H(8)); 6.96 (s, 1 H, H(11)); 6.77 (s, 1 H, H(4)); 6.36 (s, 1 H, —CH=C<); 5.39 (d, 1 H, CH—OBu, J = 5.2 Hz); 4.52—4.48 (m, 1 H, H(7)); 3.83 (s, 3 H, OCH_3(3)); 3.78 (s, 3 H, OCH_3(2)); 3.71—3.69 (m, 1 H, $CHC(O)OCH_3$); 3.65 (s, 3 H, $C(O)OCH_3$); 3.55 (s, 3 H, OCH_3(1)); 3.20—3.14 (m, 2 H, $OCH_2CH_2CH_2CH_3$); 2.17—2.10 (m, 4 H, H(5) and H(6)); 2.08—2.00 (m, 2 H, CH=C—$CH_2CH_2CH_3$); 1.86 (s, 3 H, $NHC(O)CH_3$); 1.55—1.48 (m, 2 H, $OCH_2CH_2CH_2CH_3$); 1.47—1.42 (m, 2 H, CH=C—$CH_2CH_2CH_3$); 1.41—1.32 (m, 2 H, $OCH_2CH_2CH_2CH_3$); 0.86 (t, 3 H, CH=C—$CH_2CH_2CH_3$, J = 7.7 Hz); 0.74 (t, 3 H, $OCH_2CH_2CH_2CH_3$, J = 7.4 Hz). ^{13}C NMR (101 MHz, DMSO-d_6), δ: 169.7, 168.5, 159.0, 152.4, 151.3, 150.3, 140.8, 140.6, 136.7, 134.8, 133.5, 128.6, 126.7, 124.8, 123.8, 115.2, 108.1, 99.6, 68.0, 60.8, 60.5, 56.2, 55.9, 52.1, 47.8, 40.3, 38.5, 30.8, 30.0, 22.6, 20.8, 18.5, 13.5 (2 C). Diastereomer **B**. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 8.43 (d, 1 H, NH, J = 8.5 Hz); 7.15 (s, 1 H, H(8)); 6.97 (s, 1 H, H(11)); 6.78 (s, 1 H, H(4)); 6.36 (s, 1 H, —CH=C<); 5.36 (d, 1 H, CH—OBu, J = 6.1 Hz); 4.52—4.48 (m, 1 H, H(7)); 3.83 (s, 3 H, OCH_3(3)); 3.79 (s, 3 H, OCH_3(2)); 3.78—3.73 (m, 1 H, $CHC(O)OCH_3$); 3.64 (s, 3 H, $C(O)OCH_3$); 3.55 (s, 3 H, OCH_3(1)); 3.28—3.22 (m, 2 H, $OCH_2CH_2CH_2CH_3$); 2.17—2.10 (m, 4 H, H(5) and H(6)); 2.08—2.00 (m, 2 H, CH=C—$CH_2CH_2CH_3$); 1.86 (s, 3 H, $NHC(O)CH_3$); 1.55—1.48 (m, 2 H, $OCH_2CH_2CH_2CH_3$); 1.47—1.42 (m, 2 H, CH=C—$CH_2CH_2CH_3$); 1.41—1.32 (m, 2 H, $OCH_2CH_2CH_2CH_3$); 0.89 (t, 3 H, CH=C—$CH_2CH_2CH_3$, J = 7.7 Hz); 0.76 (t, 3 H, $OCH_2CH_2CH_2CH_3$, J = 7.3 Hz). ^{13}C NMR (101 MHz, DMSO-d_6), δ: 169.7, 168.5, 159.0, 152.4, 151.5, 150.4, 140.8, 140.6, 136.7, 134.8, 133.8, 128.8, 126.7, 125.0, 123.8, 115.2, 108.2, 99.6, 68.1, 60.8, 60.6, 56.2, 55.9, 52.0, 47.9, 40.3, 38.5, 30.8, 30.1, 22.7, 21.0, 18.6, 13.4 (2 C). MS (GC/MS), m/z: 604.5 $[M + Na]^+$, R_t = 7.120 min.

Methyl (7*S*,10*S*,11*R*,14a*R*)-7-acetamido-10-butoxy-12-(4-chlorobutyl)-6,7,10,11-tetrahydro-5*H*-1,2,3-trimethoxybenzo[6′,7′]cyclohepta[1′,2′:4,5]benzo[1,2-*b*]oxepine-11-carboxylate (3f). Compound **7d** (96 mg, 0.184 mmol), *n*-butanol (22 mg, 0.370 mmol), Ph_3PAuCl (5 mg, 0.009 mmol), and $Ag[SbF_6]$ (3 mg, 0.009 mmol) were used. Product **3f** (30 mg, 22%) was isolated as a mixture of two diastereomers **A** and **B** in the ratio of 3 : 2, light yellow crystals, m.p. 168—170 °C. Found (%): C, 64.97; H, 7.14. $C_{34}H_{44}ClNO_8$. Calculated (%): C, 64.80; H, 7.04. Diastereomer **A**. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 8.37 (d, 1 H, NH, J = 8.3 Hz); 7.15 (s, 1 H, H(8)); 6.96 (s, 1 H, H(11)); 6.77 (s, 1 H, H(4)); 6.40 (s, 1 H, —CH=C<); 5.39 (d, 1 H, CH—OBu, J = 5.7 Hz); 4.54—4.47 (m, 1 H, H(7)); 3.83 (s, 3 H, OCH_3(3)); 3.78 (s, 3 H, OCH_3(2)); 3.72—3.69 (m, 1 H, $CHC(O)OCH_3$); 3.66 (s, 3 H, $C(O)OCH_3$); 3.62—3.57 (m, 2 H, $CH_2CH_2CH_2CH_2Cl$); 3.55 (s, 3 H, OCH_3(1)); 3.54—3.47 (m, 2 H, $OCH_2CH_2CH_2CH_3$); 2.20—2.12 (m, 4 H, H(5) and H(6)); 2.08—1.98 (m, 2 H, CH=C—$CH_2CH_2CH_2CH_2Cl$); 1.86 (s, 3 H, $NHC(O)CH_3$); 1.76—1.69 (m, 2 H, $CH_2CH_2CH_2CH_2Cl$); 1.61—1.52 (m, 2 H, $CH_2CH_2CH_2CH_2Cl$); 1.19—1.09 (m, 2 H, $OCH_2CH_2CH_2CH_3$); 1.08—0.98 (m, 2 H, $OCH_2CH_2CH_2CH_3$); 0.72 (t, 3 H, $OCH_2CH_2CH_2CH_3$, J = 7.4 Hz). ^{13}C NMR (101 MHz, DMSO-d_6), δ: 169.5, 168.4, 158.6, 152.3, 151.2, 150.3, 140.8, 140.5, 136.7, 134.7, 133.1, 128.5, 126.7, 124.7, 123.7, 115.2, 108.1, 99.0, 68.0, 60.7, 60.5, 55.8, 52.1 (2 C), 47.8, 45.1, 38.4, 31.4, 31.3, 30.8, 30.0, 24.6, 22.6, 18.5, 13.4. Diastereomer **B**. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 8.43 (d, 1 H, NH, J = 8.1 Hz); 7.14 (s, 1 H, H(8)); 6.97 (s, 1 H, H(11)); 6.78 (s, 1 H, H(4)); 6.36 (s, 1 H, —CH=C<); 5.43 (d, 1 H, CH—OBu, J = 5.1 Hz); 4.54—4.47 (m, 1 H, H(7)); 3.83 (s, 3 H, OCH_3(3)); 3.78 (s, 3 H, OCH_3(2)); 3.72—3.69 (m, 1 H, $CHC(O)OCH_3$); 3.65 (s, 3 H, $C(O)OCH_3$); 3.62—3.57 (m, 2 H, $CH_2CH_2CH_2CH_2Cl$); 3.55 (s, 3 H, OCH_3(1)); 3.54—3.47 (m, 2 H, $OCH_2CH_2CH_2CH_3$); 2.20—2.12 (m, 4 H, H(5) and H(6)); 2.08—1.98 (m, 2 H, CH=C—$CH_2CH_2CH_2CH_2Cl$); 1.86 (s, 3 H, $NHC(O)CH_3$); 1.76—1.69 (m, 2 H, $CH_2CH_2CH_2CH_2Cl$); 1.61—1.52 (m, 2 H, $CH_2CH_2CH_2CH_2Cl$); 1.19—1.09 (m, 2 H, $OCH_2CH_2CH_2CH_3$); 1.08—0.98 (m, 2 H, $OCH_2CH_2CH_2CH_3$); 0.75 (t, 3 H, $OCH_2CH_2CH_2CH_3$, J = 7.4 Hz). ^{13}C NMR (101 MHz, DMSO-d_6), δ: 169.6, 168.4, 158.6, 152.3, 151.3, 150.4, 140.9, 140.5, 136.7, 134.8, 133.1, 128.7, 126.8, 124.8, 123.8, 115.2, 108.2, 99.0, 68.1, 60.6, 60.5, 55.8, 52.1, 52.0, 47.8, 45.2, 38.5, 31.5, 31.3, 30.8, 30.1, 24.7, 22.6, 18.5, 13.5. MS (GC/MS), m/z: 653.1 $[M + Na]^+$, R_t = 7.347 min.

Analysis of cytotoxicity *in vitro*. Cytotoxic effect of the allocolchicinoids was estimated by a standard 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT, Sigma) test. Human cell lines of pancreatic carcinoma (metastases) COLO-357, pancreatic duct carcinomas PANC-1, embryonic kidney cells HEK293, cervical cancer cells HeLa, and cells of mouse colon adenocarcinoma Colon26 were used. The cells were cultivated in RPMI-1640 (PANC-1, COLO-357, HeLa, and Colon26) or DMEM (HEK293) medium. Fetal bovine serum (FBS) (8%), L-glutamine (300 μg mL^{-1}), ampicillin/streptomycin (50 μg mL^{-1}), and 2-mercaptoethanol ($5 \cdot 10^{-5}$ mol L^{-1}) were added to the media. The cells were cultivated in a CO_2-filled incubator at 37 °C. To this end, the cells were introduced into a flat-bottomed 96-well plate (50 thousands per well), wherein the preparations were titrated in advance. The plates were incubated in a CO_2-filled incubator for 72 h, and before the last 4 h, MTT (250 μg mL^{-1}) was added. The supernatants were removed at the end of incubation, and DMSO (100 μL) was added into the wells in order to dissolve formazan. The plates were analyzed on a Titertek plate reader at the wavelength of 540 nm. The inhibition index (II) was calculated according to the formula

$$II = 1 - OD_{exp}/OD_{contr},$$

wherein OD_{exp} and OD_{contr} are the optical density of experimental and control solution, respectively. IC_{50} values were determined as a half of the inhibition index.

Docking was performed using Autodock 4.2[53] and AutoGrid programs. A MGLTools 1.5.6 shell was used during the work with the program. Each the docking experiment was performed using a LGA genetic algorithm (200 conformations, 25 000 000 calculations per each). The α- and β-subunits of stathmin-like domain 1SA0.pdb[54] were taken as the starting protein. The geometry of colchicinoid molecules was optimized using the Gaussian 03[55] program according to the density functional method B3LYP/6-31G(d,p).

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