FULL PAPER

Synthesis and Evaluation of Pancreatic Lipase Inhibitory Effects Halogenated Polyunsaturated Lipids from Marine Natural Products: Methyl Xestospongoate and Analogs

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Methyl xestospongoate (MXS), a brominated polyunsaturalted lipid recently isolated from the Chinese marine sponge *Xestospongia testudinaria*, showed strong *in vitro* pancreatic lipase (PL) inhibitory activity. Inspired by its promising activity and potential clinical application, a series of shorter or longer-chain and chlorinated analogs of MXS was prepared and evaluated for PL inhibitory activity. The result of a bioassay indicated that the terminal brominated ones are better than the chlorinated ones on their bioactivity, and 16 – 20 C-atoms in the structures of MXS analogs might be optimal for their PL inhibitory activity. The results obtained in the present work are useful for the design of novel pancreatic lipase inhibitors.

1. Introduction. – Obesity, caused by an imbalance between energy intake and expenditure, is widely recognized as a major public health problem in developed countries, since it is associated with several pathological disorders, including hypertension, hyperlipidemia, arteriosclerosis, and type II diabetes [1]. Lipases, a highly ubiquitous family of hydrolyzing enzymes present in various human organ systems including pre-duodenal (lingual and gastric) and extra-duodenal (pancreatic, hepatic, lipoprotein, and the endothelial), have served as important therapeutic targets [2]. Among these enzymes, the pancreatic lipase (PL) plays an important role in nutrition absorption processes and is responsible for 50 – 70% hydrolysis of dietary triacylglycerols into diacylglycerols, monoacylglycerol, glycerol, and fatty acid anions [3][4]. The inhibition of PL can reduce unwanted lipid intake; therefore, PL inhibitors (as those of recently reported lipid lowering agents [5] or inhibitors of fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) [6]) are considered to be valuable therapeutic agents to treat diet-induced obesity since they can prevent the absorption of fats. For example, orlistat (**1**, *Xenical*®, *Alli*®), a tetrahydrogenated derivative of lipstatin (a natural product obtained from *Streptomyces toxytricini*), is an approved anti-obesity drug, which acts through inhibition of PL and consequently reducing fat digestion [7][8]. Although orlistat is one of the best-selling anti-obesity drugs worldwide, it has certain unpleasant gastrointestinal adverse effects, such as oily stools, oily spotting, and flatulence. Over the last decade, continuous efforts in the identification of novel PL inhibitors without some of these unpleasant side effects were made, and many new kinds of PL inhibitors as drug candidates from natural sources and reports on about 100 active compounds can be estimated. The structures of these compounds range from saponins to terpenes and phenolics [9]. However, in the majority of the cases, the reported activity was only marginal or poorly characterized, and the toxicity issues were not properly considered.

Marine natural brominated polyunsaturated lipids have received considerable attentions in the last few decades because of their unique chemical structures and their potential biological activities [10][11]. In the course of our investigation on the ether extract of the marine sponge *Xestospongia testudinaria* collected off Weizhou Island, Guangxi, P. R. China, a series of brominated unsaturated lipids with promising PL inhibitory activity were isolated [12]. Of all the tested compounds, methyl xestospongoate (MXS, **2**; *Fig.*), a known brominated lipid isolated from Mayotte *X. testudinaria* for the first time [13], was found to

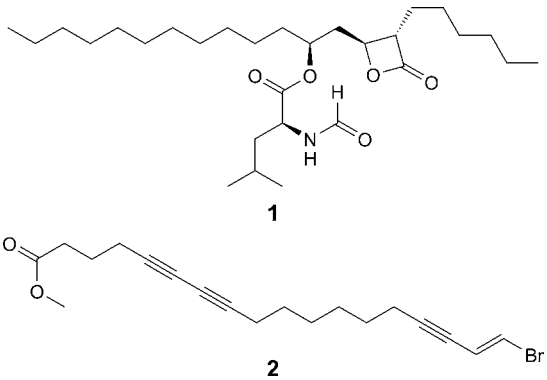

Figure. *Structure of orlistat* (**1**) *and methyl xestospongoate* (**2**)

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exhibit strongest activity ($IC_{50} = 3.1$ μM), similar to that of the positive control orlistat ($IC_{50} = 0.78$ μM). Later, the first total synthesis of **2** was reported by our group [14]. Further *in vivo* biological investigation on **2** revealed a significant decrease in the plasma triglyceride level following an oral lipid challenge in C57BLKS/J male mice. In addition, an acute toxicology study demonstrated that compound **2** was non-toxic up to 1600 mg/kg p.o. in mice [12]. All these results allowed **2** to be a potent and bioavailable drug candidate for the treatment of obesity.

The *PL* inhibitory activity of **2** sparked our great interest in marine anti-obesity drug research, however the chemical structural modification of **2** related to its PL inhibitory activity has not been studied yet in detail. Although our previous preliminary structure–activity relationships (SARs) of this series of compounds had demonstrated that the terminal (*E*)-enyne functionality, diyne within the chain, and methyl ester groups are all key functional group for the activity of this class of PL inhibitors [14], the effects of the different carbon chain lengths and the terminal Br-atom have not been studied very well. To find detailed SARs information about molecular length and terminal halogen atoms, a series of MXE analogs possessing terminal chlorine/bromine and different chain length were prepared and evaluated for their PL inhibitory activity. Herein, we present our periodical research results on the structural modification of compound **2**, with an aim to increase its PL inhibitory activity and study the SARs.

2. Results and Discussion. – 2.1. *Chemistry.* As outlined in the *Scheme*, the synthesis of analogs of compound **2** was started from the alkynes **3**, which were first brominated with NBS in the presence of $AgNO_3$ to yield bromo-alkynes **4** [14][15]. The copper-catalyzed cross-coupling reaction of **4** with diynes **5** afforded the desired triynes **6**. Bromoalkynes **4** were added to three equivalents of diynes **5** in MeOH to reduce the likeliness of the coupling of **6** to both termini of diynes **5**. Finally, the coupling reaction between **6** and (*E*/*Z*)-1,2-dibromoethylene or (*Z*)-1,2-dichloroethylene in the presence of $Pd(PPh_3)_4$ and CuI in piperidine or Et_3N afforded the desired triynes **7**. The alkynes **6** react preferentially with (*E*)-1,2-dibromoethylene, which is consistent with a previous report where it was found that (*E*)-1,2-dibromoethylene is more reactive than the corresponding (*Z*)-isomer in the Pd-catalyzed cross-coupling reactions [16]. The structures and yields of compounds **6** and **7** are shown in *Table 1*.

2.2. *PL Inhibitory Activity.* The PL assay was performed as *Gilham et al.* [17]. reported with some modifications. Briefly, porcine pancreatic lipase (*Sigma*, St. Louis, MO) was dissolved in 0.1M phosphate buffered solution (PBS, pH = 7.4) at a concentration of 0.25 mg/ml. The tested compounds or pancreatic lipase inhibitor orlistat in different concentration were then mixed with enzyme buffer, and incubated for 10 min at 37°. After pre-incubation, 0.54 mM *p*-NPA (*p*-nitrophenyl acetate) was added to start the enzyme reaction at 37°. PL Activity was determined by measuring the hydrolysis of *p*-NPA to *p*-nitrophenol at 405 nm every 5 min for 30 min by *Flexstation III* instrument (*Molecular Devices CA*).

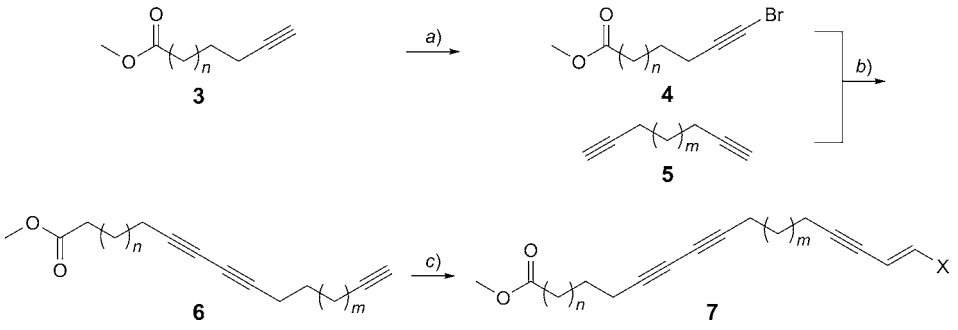
Based on our previous research results, a series of target compounds **6** and **7** with different chain length and halogen substitution were synthesized (*Table 1*), and then evaluated for their inhibitory activity against PL. The results of PL inhibitory activity are shown in *Table 2*.

Among all the tested compounds, three compounds including **6c**, **7o**, and **7p** showed obvious PL inhibitory activity (33.91 ± 0.88, 24.45 ± 1.88, and $44.53 \pm 1.00\%$, resp.) at the concentration of 50 μM, but their activity was indeed decreased compared with the MXS ($68.84 \pm 0.23\%$) at the same concentration.

3. Conclusions. – In the present work, a series of novel MXS analogs has been synthesized and evaluated for their PL inhibitory activity. To the best of our knowledge, this is the first report for the synthesis of MXS analogs and their bioactive evaluation for PL inhibitory activity.

We next performed a qualitative analysis of the structure–activity relationships of compounds **6** and **7**. In the series of compounds **6**, interestingly only methyl heptadecanoate **6c** showed inhibitory activity against PL, indicating the number of C-atoms in the alkye chain significantly affect the PL inhibitory activity. In fact, the

Scheme. *Synthesis of a Series of Methyl Xestospongoate Analogs* **6** *and* **7**



a) NBS, $AgNO_3$, acetone, r.t. *b*) $NH_2OH \cdot HCl$, CuCl, $EtNH_2$, MeOH, r.t. *c*) *Method A*: (*E*)-1,2-dichloroethylene, $Pd(Ph_3P)_4$, CuI, piperidine, Et_2O, r.t.; *Method B*: (*E*/*Z*)-1,2-dibromoethylene, $Pd(Ph_3P)_4$, CuI, Et_3N, r.t.

Table 1. *Prepation of Compounds* **6** *and* **7**

Compound	*n*	*m*	X	Yield [%]	Compound	*n*	*m*	X	Yield [%]
6a	1	1		59	**7g**	5	1	Cl	48
6b	1	2		57	**7h**	5	2	Cl	42
6c	1	4		51	**7i**	5	4	Cl	45
6d	2	1		61	**7j**	8	1	Cl	45
6e	2	2		52	**7k**	8	2	Cl	40
6f	2	4		54	**7l**	8	4	Cl	43
6g	5	1		55	**7m**	1	1	Br	44
6h	5	2		57	**7n**	1	2	Br	41
6i	5	4		50	**7o**	2	1	Br	39
6j	8	1		49	**7p**	2	2	Br	30
6k	8	2		52	**7q**	2	4	Br	47
6l	8	4		48	**7r**	5	1	Br	51
7a	1	1	Cl	62	**7s**	5	2	Br	46
7b	1	2	Cl	56	**7t**	5	4	Br	35
7c	1	4	Cl	54	**7u**	8	1	Br	41
7d	2	1	Cl	45	**7v**	8	2	Br	37
7e	2	2	Cl	43	**7w**	8	4	Br	35
7f	2	4	Cl	47					

Table 2. *The Inhibition Percentages against PL for Compounds* **6c**, **7o**, *and* **7p**, *together with Methyl Xestospongoate* (**2**) *and the Positive Control Orlistat at 50* μM

Compounds	Inhibition at 50 μM [%]
6c	33.91 ± 0.88
7o	24.45 ± 1.88
7p	44.53 ± 1.00
2	68.84 ± 0.23
Orlistat	74.26 ± 0.88

structure of **6c** is almost identical with that of lead compound **2** except for without terminal (1*E*)-2-bromoeth-en-1-yl moiety, which revealed that the terminal Br-atom also played a crucial role in the bioactivity. In the series of analogs **7** with terminal halogen, only two of the compounds with terminal bromine (**7o** and **7p**) showed PL inhibitory activity, while all the compounds with terminal chlorine (**7a** – **7l**) were completely inactive indicating that the terminal bromine is superior to the chlorine on their bioactivity. Compared with **2**, **7o**, and **7p**, the other compounds with terminal bromide all show no activity, including the shorter chain length compounds **7m** and **7n** and longer chain length compounds **7q** – **7w**. This result further demonstrated that the chain length with 16 – 20 C-atoms plays an important role for the activity.

The pharmacological data obtained here may be useful for the design of novel PL inhibitors with the skeleton of brominated polyunsaturated lipids. Further studies to improve the PL inhibitory activity and *in vivo* bioassay of this class of compounds are in progress.

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Experimental Part

General. The starting materials and reagents, purchased from commercial suppliers, were used without further purification. All solvents used for the reactions were dried prior to use according to standard procedures. All primary reagents were commercially available. Anal. TLC: pre-coated *G60 F-254* silica gel plates (SiO_2; *Yan Tai Zi Fu Chemical Group Co.*). Column chromatography (CC): silica gel (SiO_2, 200 – 300 mesh; *Qing Dao Hai Yang Chemical Group Co.*), solvents were of analytical grade. NMR Spectra: *Bruker Avance* spectrometer (300 MHz for ^1H and 100 MHz for ^{13}C), using the residual $CHCl_3$ signal (δ(H) 7.26) as an internal standard for ^1H-NMR and $CDCl_3$ signal (δ(C) 77.0 ppm) for ^{13}C-NMR; δ in ppm, *J* in Hz. ESI-MS: *Q-TOF Micro* LC/MS-MS mass spectrometer; in *m*/*z*. EI-MS: *Finnigan-MAT-95* mass spectrometer; in *m*/*z*.

General Procedure for the Synthesis of Compounds **6**. To a round-bottom flask equipped with a stirring bar under N_2 was added 10 ml of MeOH, $NH_2OH \cdot HCl$ (31 mg, 0.45 mmol), 10 ml 70% aq. soln. of $EtNH_2$, CuCl (45 mg, 0.45 mmol), and diyne **5** (9 mmol) in that order. The bromoalkyne **4** (3 mmol) in 5 ml MeOH was added over a period of 1.5 h to the mixture *via* a syringe pump keeping the temp. between 30 – 35°, the mixture was the stirred for additional 1 h. The product was isolated by extraction with Et_2O, and the combined org. layers were washed with sat. NH_4Cl soln. and dried ($MgSO_4$). The solvents were removed under reduced pressure, and the residue was purified over SiO_2 to yield the title compounds **6**.

Methyl Trideca-5,7,12-triynoate (**6a**). Yield 59%. Yellowish oil. ^1H-NMR (400 MHz): 3.70 (*s*, 3 H); 2.47 (*t*, *J* = 7.4, 2 H); 2.41 (*t*, *J* = 7.4, 2 H); 2.37 – 2.31 (*m*, 4 H); 1.99 (*t*, *J* = 2.6, 1 H); 1.90 – 1.83 (*m*, 2 H); 1.80 – 1.73 (*m*, 2 H). ^{13}C-NMR: 172.9; 82.7; 76.1; 75.8; 68.6; 65.6; 65.3; 51.2; 32.2; 26.7; 23.0; 18.1; 17.1; 17.0. HR-MS: 216.1123 (M^+, $C_{14}H_{16}O_2^+$; calc. 216.1150).

Methyl Tetradeca-5,7,13-triynoate (**6b**). Yield 57%. Colorless oil. ^1H-NMR (400 MHz): 3.67 (*s*, 3 H); 2.44 (*t*, *J* = 7.4, 2 H); 2.35 – 2.28 (*m*, 4 H); 2.24 – 2.18 (*m*, 2 H); 1.94 (*t*, *J* = 2.6, 1 H); 1.89 – 1.80 (*m*, 2 H); 1.64 – 1.58 (*m*, 4 H). ^{13}C-NMR: 172.9; 83.4; 76.7; 75.7; 68.2; 65.6; 65.0; 51.2; 32.2; 26.9; 26.7; 23.0; 18.2; 18.1; 17.4. HR-MS: HR-MS: 230.1306 (M^+, $C_{15}H_{18}O_2^+$; calc. 230.1307).

Methyl Hexadeca-5,7,15-triynoate (**6c**). Yield 51%. Colorless oil. The spectra similar to the reference [13].

Methyl Tetradeca-6,8,13-triynoate (**6d**). Yield 61%. Colorless oil. ^1H-NMR: 3.69 (*s*, 3 H); 2.41 (*t*, *J* = 7.0, 2 H); 2.35 – 2.28 (*m*, 6 H); 1.98 (*t*, *J* = 2.5, 1 H); 1.79 – 1.72 (*m*, 4 H); 1.63 – 1.54 (*m*, 2 H). ^{13}C-NMR:

174.5; 83.9; 77.0; 69.7; 66.6; 66.3; 52.2; 34.2; 28.4; 27.9; 24.8; 19.6; 18.9; 18.2. HR-MS: 253.1211 ($[M+Na]^+$, $C_{15}H_{18}NaO_2^+$; calc. 253.1204).

Methyl Pentadeca-6,8,14-triynoate (**6e**). Yield 52%. Colorless oil. ^{1}H-NMR: 3.69 (*s*, 3 H); 2.34 (*t*, *J* = 7.3, 2 H); 2.32 – 2.28 (*m*, 4 H); 2.25 – 2.21 (*m*, 2 H); 1.97 (*t*, *J* = 2.6, 1 H); 1.67 – 1.64 (*m*, 4 H); 1.61 – 1.55 (*m*, 2 H). ^{13}C-NMR: 174.5; 84.6; 77.5; 69.3; 66.3; 66.2; 52.2; 34.2; 28.4; 28.1; 27.9; 24.7; 19.6; 19.4; 18.6. HR-MS: 267.1367 ($[M+Na]^+$, $C_{15}H_{18}NaO_2^+$; calc. 267.1361).

Methyl Heptadeca-6,8,16-triynoate (**6f**). Yield 54%. Colorless oil. ^{1}H-NMR: 3.69 (*s*, 3 H); 2.34 (*t*, *J* = 7.4, 2 H); 2.31 – 2.25 (*m*, 4 H); 2.20 (*td*, *J* = 7.0, 2.6, 2 H); 1.96 (*t*, *J* = 2.6, 1 H); 1.79 – 1.71 (*m*, 2 H); 1.63 – 1.53 (*m*, 6 H); 1.43 – 1.40 (*m*, 4 H). ^{13}C-NMR: 174.5; 85.2; 78.3; 77.4; 68.9; 66.4; 66.0; 52.2; 34.3; 29.0; 28.9; 28.8; 28.4; 24.8; 19.8; 19.6; 19.0. HR-MS: 295.1669 ($[M+Na]^+$, $C_{18}H_{24}NaO_2^+$; calc. 295.1674).

Methyl Heptadeca-9,11,16-triynoate (**6g**). Yield 55%. Colorless oil. ^{1}H-NMR: 3.68 (*s*, 3 H); 2.41 (*t*, *J* = 7.0, 2 H); 2.35 – 2.30 (*m*, 4 H); 2.26 (*d*, *J* = 7.0, 2 H); 1.98 (*t*, *J* = 2.6, 1 H); 1.79 – 1.72 (*m*, 2 H); 1.67 – 1.60 (*m*, 2 H); 1.56 – 1.49 (*m*, 2 H); 1.43 – 1.36 (*m*, 2 H); 1.36 – 1.26 (*m*, 4 H). ^{13}C-NMR: 174.3; 83.2; 77.8; 76.1; 69.1; 66.0; 65.2; 51.5; 34.1; 29.0; 28.7; 28.6; 28.2; 24.9; 19.2; 18.2; 17.6. HR-MS: 272.1779 (M^+, $C_{18}H_{24}O_2^+$; calc. 272.1776).

Methyl Octadeca-9,11,17-triynoate (**6h**). Yield 57%. Colorless oil. ^{1}H-NMR: 3.68 (*s*, 3 H); 2.33 – 2.29 (*m*, 4 H); 2.27 – 2.20 (*m*, 4 H); 1.96 (*t*, *J* = 2.7, 1 H); 1.68 – 1.59 (*m*, 6 H); 1.56 – 1.49 (*m*, 2 H); 1.43 – 1.36 (*m*, 2 H); 1.34 – 1.29 (*m*, 4 H). ^{13}C-NMR: 174.2; 83.9; 77.6; 68.6; 65.6; 65.2; 51.5; 34.0; 29.0; 28.7; 28.6; 28.2; 24.9; 19.2; 18.7; 17.9. HR-MS: 286.1943 (M^+, $C_{19}H_{26}O_2^+$; calc. 286.1933).

Methyl Icosa-9,11,19-triynoate (**6i**). Yield 50%. Colorless oil. ^{1}H-NMR: 3.68 (*s*, 3 H); 2.32 (*t*, *J* = 7.5, 2 H); 2.29 – 2.24 (*m*, 4 H); 2.20 (*td*, *J* = 7.0, 2.7, 2 H); 1.95 (*t*, *J* = 2.7, 1 H); 1.67 – 1.60 (*m*, 2 H); 1.58 – 1.49 (*m*, 6 H); 1.44 – 1.37 (*m*, 6 H); 1.35 – 1.30 (*m*, 4 H). ^{13}C-NMR: 173.7; 84.1; 77.0; 76.9; 67.7; 64.8; 64.7; 51.0; 33.6; 28.5; 28.2; 28.1; 27.8; 27.7; 27.7; 27.6; 24.4; 18.7; 17.8. HR-MS: 314.2255 (M^+, $C_{21}H_{30}O_2^+$; calc. 314.2246).

Methyl Icosa-12,14,19-triynoate (**6j**). Yield 49%. Colorless oil. ^{1}H-NMR: 3.68 (*s*, 3 H); 2.41 (*t*, *J* = 7.0, 2 H); 2.35 – 2.30 (*m*, 4 H); 2.26 (*t*, *J* = 7.0, 2 H); 1.98 (*t*, *J* = 2.7, 1 H); 1.79 – 1.72 (*m*, 2 H); 1.64 – 1.59 (*m*, 2 H); 1.56 – 1.49 (*m*, 2 H); 1.41 – 1.34 (*m*, 2 H); 1.30 – 1.27 (*m*, 10 H). ^{13}C-NMR: 174.3; 83.2; 77.9; 76.0; 69.0; 66.0; 65.1; 51.4; 34.1; 29.4; 29.2; 29.1; 29.0; 28.8; 28.2; 27.2; 24.9; 19.2; 18.2; 17.5. HR-MS: 337.2147 ($[M+Na]^+$, $C_{21}H_{30}NaO_2^+$; calc. 337.2143).

Methyl Henicosa-12,14,20-triynoate (**6k**). Yield 52%. Colorless oil. ^{1}H-NMR: 3.68 (*s*, 3 H); 2.34 – 2.30 (*m*, 4 H); 2.27 – 2.21 (*m*, 4 H); 1.97 (*t*, *J* = 2.6, 1 H); 1.67 – 159 (*m*, 6 H); 1.56 – 1.48 (*m*, 2 H); 1.40 – 1.35 (*m*, 2 H); 1.28 – 1.26 (*m*, 10 H). ^{13}C-NMR : 174.3; 83.9; 77.8; 76.7; 68.6; 65.7; 65.1; 51.4; 34.1; 29.4; 29.2; 29.1; 29.0; 28.8; 28.3; 27.4; 27.2; 24.9; 19.2; 18.7; 17.9. HR-MS: 351.2292 ($[M+Na]^+$, $C_{22}H_{32}NaO_2^+$; calc. 351.2300).

Methyl Tricosa-12,14,22-triynoate (**6l**). Yield 48%. Colorless oil. ^{1}H-NMR: 3.66 (*s*, 3 H); 2.32 – 2.15 (*m*, 8 H); 1.93 (*t*, *J* = 2.6, 1 H); 1.63 – 1.58 (*m*, 2 H); 1.54 – 1.45 (*m*, 6 H); 1.42 – 1.36 (*m*, 6 H); 1.28 – 1.26 (*m*, 10 H). ^{13}C-NMR: 174.3; 84.5; 77.6; 68.2; 65.4; 65.2; 51.4; 34.1; 29.4; 29.1; 29.0; 28.8; 28.3; 28.2; 28.1; 24.9; 19.2; 19.1; 18.3. HR-MS: 379.2618 ($[M+Na]^+$, $C_{24}H_{36}NaO_2^+$; calc. 379.2613).

Method A. General Procedure for the Synthesis of Compounds **7a** – **7l**. To a round bottom flask equipped with a stirring bar under N_2 was added compound **6** (2 mmol), (*E*)-1,2-dichloroethylene (4 mmol), dry Et_2O (20 ml), $Pd(PPh_3)_4$ (0.12 g, 0.10 mmol), CuI (40 mg, 0.21 mmol), and piperidine (0.2 ml). The mixture was stirred at r.t. for 16 h and then diluted with $CHCl_3$ (20 ml) and filtered through a pad of *Florisil* using $CHCl_3$. The solvents were removed under reduced pressure and the residue was purified over SiO_2 to yield the title compounds **7a** – **7l**.

*Methyl (14*E*)-15-Chloropentadec-14-ene-5,7,12-triynoate* (**7a**). Yield 62%. Colorless oil. ^{1}H-NMR: 6.45 (*d*, *J* = 13.6, 1 H); 5.91 (*dt*, *J* = 13.6, 2.3, 1 H); 3.69 (*s*, 3 H); 2.46 (*t*, *J* = 7.4, 2 H); 2.37 – 2.30 (*m*, 6 H); 1.89 – 1.82 (*m*, 2 H); 1.67 – 1.63 (*m*, 2 H). ^{13}C-NMR: 172.9; 128.8; 113.6; 91.3; 76.8; 76.0; 76.0; 75.9; 65.6; 65.5; 51.6; 32.3; 26.7; 23.0; 18.2; 18.1; 17.9. HR-MS: 276.0925 (M^+, $C_{16}H_{17}ClO_2^+$; calc. 276.0917).

*Methyl (15*E*)-16-Chlorohexadec-15-ene-5,7,13-triynoate* (**7b**). Yield 56%. Colorless oil. ^{1}H-NMR: 6.45 (*d*, *J* = 13.6, 1 H); 5.91 (*dt*, *J* = 13.6, 2.3, 1 H); 3.69 (*s*, 3 H); 2.46 (*t*, *J* = 7.4, 2 H); 2.37 – 2.30 (*m*, 6 H); 1.89 – 1.84 (*m*, 2 H); 1.67 – 1.63 (*m*, 6 H). ^{13}C-NMR: 173.4; 128.9; 114.1; 92.5; 77.1; 76.1; 76.0; 66.0; 65.5; 51.6; 32.6; 27.3; 27.2; 18.8; 18.7; 18.6. HR-MS: 290.1082 (M^+, $C_{17}H_{19}ClO_2^+$; calc. 290.1074).

*Methyl (17*E*)-18-Chlorooctadec-17-ene-5,7,15-triynoate* (**7c**). Yield 54%. Colorless oil. ^{1}H-NMR: 6.45 (*d*, *J* = 13.6, 1 H); 5.92 (*dt*, *J* = 13.6, 2.4, 1 H); 3.70 (*s*, 3 H); 2.47 (*t*, *J* = 7.4, 2 H); 2.36 (*t*, *J* = 6.9, 2 H); 2.31 (*dt*, *J* = 7.0, 2.3, 2 H); 2.27 (*t*, *J* = 6.9, 2 H); 1.90 – 1.85 (*m*, 2 H); 1.58 – 1.51 (*m*, 4 H); 1.42 – 1.40 (*m*, 4 H). ^{13}C-NMR: 173.0; 128.4; 113.8; 92.8; 77.3; 76.8; 75.6; 75.3; 65.7; 64.8; 51.2; 32.3; 27.8; 27.6; 23.1; 18.9; 18.7; 18.2. HR-MS: 318.1401 (M^+, $C_{19}H_{23}ClO_2^+$; calc. 318.1387).

*Methyl (15*E*)-16-Chlorohexadec-15-ene-6,8,13-triynoate* (**7d**). Yield 45%. Colorless oil. ^{1}H-NMR: 6.46 (*d*, *J* = 13.6, 1 H); 5.91 (*dt*, *J* = 13.6, 2.3, 1 H); 3.69 (*s*, 3 H); 2.44 (*dt*, *J* = 7.0, 2.3, 2 H); 2.39 (*t*, *J* = 6.9, 2 H); 2.35 (*t*, *J* = 7.5, 2 H); 2.30 (*t*, *J* = 7.0, 2 H); 1.79 – 1.71 (*m*, 4 H); 1.61 – 1.54 (*m*, 2 H). ^{13}C-NMR: 174.5; 129.9; 114.7; 92.5; 77.8; 77.2; 76.9; 66.7; 66.3; 52.3; 34.2; 28.4; 27.9; 24.8; 19.6; 19.2; 19.1. HR-MS: 313.0969 ($[M+Na]^+$, $C_{17}H_{19}ClNaO_2^+$; calc. 313.0971).

*Methyl (16*E*)-17-Chloroheptadec-16-ene-6,8,14-triynoate* (**7e**). Yield 43%. Colorless oil. ^{1}H-NMR: 6.43 (*d*, *J* = 13.6, 1 H); 5.99 (*dt*, *J* = 13.6, 2.2, 1 H); 3.66 (*s*, 3 H); 2.34 – 2.27 (*m*, 8 H); 1.78 – 1.67 (*m*, 2 H); 1.62 – 1.52 (*m*, 6 H). ^{13}C-NMR: 173.8; 129.0; 114.1; 92.6; 77.0; 76.9; 76.1; 51.6; 33.5; 27.7; 27.4; 27.3; 19.0; 18.9; 18.7. HR-MS: 304.1223 (M^+, $C_{18}H_{21}ClO_2^+$; calc. 304.1230).

*Methyl (18*E*)-19-Chlorononadec-18-ene-6,8,16-triynoate* (**7f**). Yield 47%. Colorless oil. ^{1}H-NMR: 6.43 (*d*, *J* = 13.6, 1 H); 5.91 (*dt*, *J* = 13.6, 2.4, 1 H); 3.67 (*s*, 3 H); 2.35 – 2.22 (*m*, 8 H); 1.78 – 1.68 (*m*, 2 H); 1.60 – 1.48 (*m*, 6 H); 1.40 – 1.37 (*m*, 4 H). ^{13}C-NMR: 173.7; 128.7; 114.2; 93.2; 77.5; 77.2; 75.7; 65.6; 65.3; 51.6; 33.5; 28.2; 28.0; 27.7; 24.0; 19.3; 19.1; 18.9. HR-MS: 332.1535 (M^+, $C_{20}H_{25}ClO_2^+$; calc. 332.1543).

*Methyl (18*E*)-19-Chlorononadec-18-ene-9,11,16-triynoate* (**7g**). Yield 48%. Colorless oil. ^{1}H-NMR: 6.46 (*d*, *J* = 13.6, 1 H); 5.91 (*d*, *J* = 13.6, 1 H); 3.69 (*s*, 3 H); 2.44 (*d*, *J* = 7.0, 2 H); 2.39 (*t*, *J* = 7.0, 2 H); 2.32 (*t*, *J* = 7.5, 2 H); 2.26 (*t*, *J* = 7.0, 2 H); 1.79 – 1.72 (*m*, 2 H); 1.67 – 1.59 (*m*, 2 H); 1.57 – 1.50 (*m*, 2 H); 1.44 – 1.40 (*m*, 2 H). ^{13}C-NMR: 173.7; 128.7; 114.2; 93.2; 77.5; 77.2; 75.7; 65.6; 65.3; 51.6; 33.5; 28.2; 28.0; 27.7; 24.0; 19.3; 19.1; 18.9. HR-MS: 332.1544 (M^+, $C_{20}H_{25}ClO_2^+$; calc. 332.1543).

*Methyl (19*E*)-20-Chloroicos-19-ene-9,11,17-triynoate* (**7h**). Yield 42%. Colorless oil. ^{1}H-NMR: 6.58 (*d*, *J* = 14.0, 1 H); 6.16 (*dt*, *J* = 14.0, 2.3, 1 H); 3.66 (*s*, 3 H); 2.32 – 2.22 (*m*, 6 H); 1.53 – 1.46 (*m*, 2 H); 1.40 – 1.31 (*m*, 6 H). ^{13}C-NMR: 173.7; 117.4; 116.7; 91.8; 77.2; 77.1; 65.2; 64.7; 50.9; 33.5; 28.5; 28.2; 28.1; 27.7; 26.9; 26.8; 24.4; 18.6; 18.4; 18.3. HR-MS: 369.1596 ($[M+Na]^+$, $C_{21}H_{27}ClNaO_2^+$; calc. 369.1597).

*Methyl (21*E*)-22-Chlorodocos-21-ene-9,11,19-triynoate* (**7i**). Yield 45%. Colorless oil. ^{1}H-NMR: 6.42 (*d*, *J* = 13.6, 1 H); 6.16 (*dt*, *J* = 13.6, 2.3, 1 H); 3.66 (*s*, 3 H); 2.32 – 2.21 (*m*, 8 H); 1.63 – 1.48 (*m*, 6 H); 1.32 – 1.28 (*m*, 4 H). ^{13}C-NMR: 174.2; 128.7; 114.2; 93.2; 77.5; 75.7; 65.4; 65.3; 51.5; 34.0; 28.9; 28.7; 28.6; 28.3; 28.2; 28.1; 24.8; 19.3; 19.2; 19.1. HR-MS: 397.1916 ($[M+Na]^+$, $C_{23}H_{31}ClNaO_2^+$; calc. 397.1910).

*Methyl (21*E*)-22-Chlorodocos-21-ene-12,14,19-triynoate* (**7j**). Yield 45%. Colorless oil. ^{1}H-NMR: 6.44 (*d*, *J* = 13.6, 1 H); 5.89 (*dt*, *J* = 13.6, 2.3, 1 H); 3.66 (*s*, 3 H); 2.42 (*dt*, *J* = 6.8, 1.8, 2 H); 2.37 (*t*, *J* = 6.9, 2 H); 2.23 (*t*, *J* = 7.0, 2 H); 1.77 – 1.68 (*m*, 2 H); 1.77 – 1.68 (*m*, 2 H); 1.63 – 1.50 (*m*, 2 H); 1.52 – 1.45 (*m*, 2 H); 1.38 – 1.26 (*m*, 12 H). ^{13}C-NMR: 173.8; 117.4; 116.7; 91.9; 77.3; 77.1; 76.1; 65.2; 64.6; 50.9; 33.6; 29.2; 28.8; 28.7; 28.6; 28.5; 28.3; 27.8; 26.9; 26.8; 26.5; 24.4; 18.7; 18.4; 18.2. HR-MS: 397.1911 ($[M+Na]^+$, $C_{23}H_{31}ClNaO_2^+$; calc. 397.1910).

*Methyl (22*E*)-23-Chlorotricos-22-ene-12,14,20-triynoate* (**7k**). Yield 40%. Colorless oil. ^{1}H-NMR: 6.44 (*d*, *J* = 13.6, 1 H); 5.89 (*dt*, *J* = 13.6, 2.3, 1 H); 3.66 (*s*, 3 H); 2.42 (*dt*, *J* = 6.8, 1.8, 2 H); 2.37 (*t*, *J* = 6.9, 2 H); 2.23 (*t*, *J* = 7.0, 2 H); 1.77 – 1.68 (*m*, 2 H); 1.77 – 1.68 (*m*, 2 H); 1.63 – 1.50 (*m*, 2 H); 1.52 – 1.45 (*m*, 2 H); 1.38 – 1.26 (*m*, 12 H). ^{13}C-NMR: 173.8; 128.5; 113.6; 92.1; 77.3; 77.1; 76.2; 75.6; 65.2; 64.6;

50.9; 33.6; 29.2; 28.9; 28.7; 28.6; 28.5; 28.3; 27.8; 26.9; 26.8; 24.4; 18.7; 18.4; 18.2. HR-MS: 411.2059 ($[M+Na]^+$, $C_{24}H_{33}ClNaO_2^+$; calc. 411.2067).

*Methyl (24*E*)-25-Chloropentacos-24-ene-12,14,22-triynoate* (**7l**). Yield 43%. Colorless oil. ^{1}H-NMR: 6.45 (*d*, *J* = 13.6, 1 H); 5.93 (*dt*, *J* = 13.6, 2.3, 1 H); 3.69 (*s*, 3 H); 2.34 – 2.24 (*m*, 8 H); 1.66 – 1.61 (*m*, 2 H); 1.56 – 1.49 (*m*, 6 H); 1.44 – 1.37 (*m*, 6 H); 1.33 – 1.26 (*m*, 10 H). ^{13}C-NMR: 173.8; 128.3; 113.7; 92.7; 77.1; 75.3; 64.9; 64.7; 50.9; 33.6; 29.2; 29.0; 28.8; 28.7; 28.6; 28.5; 28.3; 27.8; 28.7; 28.8; 28.6; 24.4; 18.8; 18.7; 18.6. HR-MS: 416.2486 (M^+, $C_{26}H_{37}ClO_2^+$; calc. 416.2486).

Method B. General Procedure for the Synthesis Compounds **7m** – **7w**. To a round bottom flask equipped with a stirring bar under N_2 was added Et_3N (50 ml), $Pd(PPh_3)_4$ (0.21 g, 0.18 mmol), CuI (70 mg, 0.36 mmol), a mixture of (*E*/*Z*)-**1**, 2-dibromoethylene (12 mmol), and compound **7** (3 mmol). The mixture was stirred at r.t. for 16 h. The mixture was then diluted with $CHCl_3$ (20 ml) and filtered through a pad of *Florisil* using $CHCl_3$. The solvents were removed under reduced pressure and the residue was purified over silica gel to yield the title compounds **7m** – **7w**.

*Methyl (14*E*)-15-Bromopentadec-14-ene-5,7,12-triynoate* (**7m**). Yield 44%. Colorless oil. ^{1}H-NMR: 6.61 (*d*, *J* = 14.0, 1 H); 6.18 (*d*, *J* = 14.0, 2.3, 1 H); 3.69 (*s*, 3 H); 2.46 (*t*, *J* = 7.4, 2 H); 2.43 – 2.34 (*m*, 6 H); 1.90 – 1.83 (*m*, 2 H); 1.79 – 1.74 (*m*, 2 H). ^{13}C-NMR: 173.3; 117.7; 117.5; 78.0; 77.2; 77.4; 77.3; 66.0; 65.8; 51.6; 32.6; 27.0; 23.4; 18.6; 18.5; 18.3. HR-MS: 320.0411 (M^+, $C_{16}H_{17}BrO_2^+$; calc. 320.0412).

*Methyl (15*E*)-16-Bromohexadec-15-ene-5,7,13-triynoate* (**7n**). Yield 41%. Colorless oil. ^{1}H-NMR: 6.60 (*d*, *J* = 14.0, 1 H); 6.19 (*dt*, *J* = 14.0, 2.3, 1 H); 3.70 (*s*, 3 H); 2.47 (*t*, *J* = 7.4, 2 H); 2.36 (*t*, *J* = 6.9, 2 H); 2.33 – 2.30 (*m*, 4 H); 1.90 – 1.83 (*m*, 2 H); 1.68 – 1.64 (*m*, 6 H). ^{13}C-NMR: 173.4; 117.8; 117.2; 92.3; 77.7; 77.1; 76.2; 66.1; 65.6; 51.6; 32.7; 27.3; 27.3; 23.5; 18.9; 18.7; 18.6. HR-MS: 334.0549 (M^+, $C_{17}H_{19}BrO_2^+$; calc. 334.0568).

*Methyl (15*E*)-16-Bromohexadec-15-ene-6,8,13-triynoate* (**7o**). Yield 39%. Colorless oil. ^{1}H-NMR: 6.62 (*d*, *J* = 14.0, 1 H); 6.18 (*dt*, *J* = 14.0, 2.2, 1 H); 3.69 (*s*, 3 H); 2.43 – 2.37 (*m*, 4 H); 2.35 (*t*, *J* = 7.5, 2 H); 2.30 (*t*, *J* = 6.9, 2 H); 1.79 – 1.71 (*m*, 4 H); 1.63 – 1.54 (*m*, 2 H). ^{13}C-NMR: 174.4; 118.5; 118.2; 92.3; 78.7; 77.7; 76.9; 66.7; 66.3; 52.3; 34.2; 28.4; 27.8; 24.7; 19.6; 19.3; 19.1. HR-MS: 357.0460 ($[M+Na]^+$, $C_{17}H_{19}BrNaO_2^+$; calc. 357.0466).

*Methyl (16*E*)-17-Bromoheptadec-16-ene-6,8,14-triynoate* (**7p**). Yield 30%. Colorless oil. ^{1}H-NMR: 6.60 (*d*, *J* = 14.0, 1 H); 6.18 (*dt*, *J* = 14.0, 2.3, 1 H); 3.69 (*s*, 3 H); 2.35 (*t*, *J* = 7.4, 2 H); 2.31 – 2.28 (*m*, 6 H); 1.79 – 1.71 (*m*, 2 H); 1.68 – 1.61 (*m*, 4 H); 1.61 – 1.54 (*m*, 2 H). ^{13}C-NMR: 174.5; 118.6; 117.9; 93.0; 78.3; 77.6; 77.6; 66.3; 52.3; 34.2; 30.4; 28.4; 28.0; 24.7; 19.6; 19.4. HR-MS: 348.0752 (M^+, $C_{18}H_{21}BrO_2^+$; calc. 348.0725).

*Methyl (18*E*)-19-Bromononadec-18-ene-6,8,16-triynoate* (**7q**). Yield 47%. Colorless oil. ^{1}H-NMR: 6.57 (*d*, *J* = 14.0, 1 H); 6.17 (*dt*, *J* = 14.0, 2.4, 1 H); 3.67 (*s*, 3 H); 2.35 – 2.25 (*m*, 8 H); 1.78 – 1.68 (*m*, 2 H); 1.60 – 1.48 (*m*, 6 H); 1.41 – 1.31 (*m*, 4 H). ^{13}C-NMR: 173.8; 118.0; 117.0; 93.0; 77.6; 65.7; 65.3; 51.5; 33.5; 28.3; 28.2; 28.2; 27.7; 24.0; 19.4; 19.1; 18.9. HR-MS: 376.1035 (M^+, $C_{20}H_{25}BrO_2^+$; calc. 376.1038).

*Methyl (18*E*)-19-Bromononadec-18-ene-9,11,16-triynoate* (**7r**). Yield 51%. Colorless oil. ^{1}H-NMR: 6.62 (*d*, *J* = 13.6, 1 H); 6.19 (*dt*, *J* = 13.6, 2.4, 1 H); 3.69 (*s*, 3 H); 2.44 – 2.40 (*m*, 4 H); 2.32 (*t*, *J* = 7.3, 2 H); 2.27 (*t*, *J* = 7.4, 2 H); 1.80 – 1.73 (*m*, 2 H); 1.67 – 1.60 (*m*, 4 H); 1.57 – 1.50 (*m*, 2 H); 1.45 – 1.33 (*m*, 2 H). ^{13}C-NMR: 173.7; 128.7; 114.2; 93.2; 77.5; 77.2; 75.7; 65.6; 65.3; 51.6; 33.5; 28.2; 28.0; 27.7; 24.0; 19.3; 19.1; 18.9. HR-MS: 376.1054 (M^+, $C_{20}H_{25}BrO_2^+$; calc. 376.1038).

*Methyl (19*E*)-20-Bromoicos-19-ene-9,11,17-triynoate* (**7s**). Yield 46%. Colorless oil. ^{1}H-NMR: 6.58 (*d*, *J* = 14.0, 1 H); 6.16 (*dt*, *J* = 14.0, 2.3, 1 H); 3.66 (*s*, 3 H); 2.32 – 2.22 (*m*, 6 H); 1.53 – 1.46 (*m*, 2 H); 1.40 – 1.31 (*m*, 6 H). ^{13}C-NMR: 173.7; 117.4; 116.7; 91.8; 77.2; 77.1; 65.2; 64.7; 50.9; 33.5; 28.5; 28.2; 28.1; 27.7; 26.9; 26.8; 24.4; 18.6; 18.4; 18.3. HR-MS: 413.1102 ($[M+Na]^+$, $C_{21}H_{27}BrNaO_2^+$; calc. 413.1092).

*Methyl (21*E*)-22-Bromodocos-21-ene-9,11,19-triynoate* (**7t**). Yield 35%. Colorless oil. ^{1}H-NMR: 6.56 (*d*, *J* = 14.0, 1 H); 6.16 (*dt*, *J* = 14.0, 1.8, 1 H); 3.66 (*s*, 3 H); 2.31 – 2.23 (*m*, 8 H); 1.63 – 1.58 (*m*, 2 H); 1.56 – 1.48 (*m*, 6 H); 1.38 – 1.24 (*m*, 10 H). ^{13}C-NMR: 174.3; 118.0; 117.0; 93.0; 77.3; 65.4; 65.3; 51.5; 34.0; 28.9; 28.7; 28.6; 28.3; 28.2; 28.2; 28.2; 28.1; 24.9; 19.4; 19.2; 19.1. HR-MS: 418.1507 (M^+, $C_{23}H_{31}BrO_2^+$; calc. 418.1057).

*Methyl (21*E*)-22-Bromodocos-21-ene-12,14,19-triynoate* (**7u**). Yield 41%. Colorless oil. ^{1}H-NMR: 6.44 (*d*, *J* = 13.6, 1 H); 5.89 (*dt*, *J* = 13.6, 2.3, 1 H); 3.66 (*s*, 3 H); 2.42 (*dt*, *J* = 6.8, 1.8, 2 H); 2.37 (*t*, *J* = 6.9, 2 H); 2.23 (*t*, *J* = 7.0, 2 H); 1.77 – 1.68 (*m*, 2 H); 1.77 – 1.68 (*m*, 2 H); 1.63 – 1.50 (*m*, 2 H); 1.52 – 1.45 (*m*, 2 H); 1.38 – 1.26 (*m*, 12 H). ^{13}C-NMR: 174.4; 117.7; 117.5; 91.6; 78.1; 78.0; 76.0; 66.1; 65.1; 51.5; 34.1; 29.4; 29.2; 29.1; 29.0; 28.8; 28.3; 27.1; 24.9; 19.2; 18.6; 18.4. HR-MS: 441.1400 ($[M+Na]^+$, $C_{23}H_{31}BrNaO_2^+$; calc. 441.1405).

*Methyl (22*E*)-23-Bromotricos-22-ene-12,14,20-triynoate* (**7v**). Yield 37%. Colorless oil. ^{1}H-NMR: 6.58 (*d*, *J* = 13.9, 1 H); 5.89 (*dt*, *J* = 13.9, 2.3, 1 H); 3.66 (*s*, 3 H); 2.32 – 2.42 (*m*, 8 H); 1.63 – 1.50 (*m*, 8 H); 1.36 – 1.27 (*m*, 12 H). ^{13}C-NMR: 173.8; 117.4; 116.7; 91.9; 77.3; 77.1; 76.1; 65.2; 64.6; 50.9; 33.6; 29.2; 28.8; 28.7; 28.6; 28.5; 28.3; 27.8; 26.9; 26.8; 24.4; 18.7; 18.4; 18.2. HR-MS: 432.1665 (M^+, $C_{24}H_{33}BrO_2^+$; calc. 432.1664).

*Methyl (24*E*)-25-Bromopentacos-24-ene-12,14,22-triynoate* (**7w**). Yield 35%. Colorless oil. ^{1}H-NMR: 6.56 (*d*, *J* = 13.9, 1 H); 6.16 (*d*, *J* = 13.9, 1 H); 3.66 (*s*, 3 H); 2.32 – 2.23 (*m*, 8 H); 1.62 – 1.58 (*m*, 2 H); 1.53 – 1.45 (*m*, 6 H); 1.43 – 1.38 (*m*, 6 H); 1.32 – 1.26 (*m*, 10 H). ^{13}C-NMR: 173.8; 117.5; 116.5; 92.5; 77.1; 76.8; 76.7; 64.9; 64.7; 50.9; 33.6; 29.2; 28.8; 28.7; 28.6; 28.5; 28.3; 27.9; 27.8; 27.7; 27.7; 27.6; 24.4; 18.8; 18.7; 18.6. HR-MS: 460.1977 (M^+, $C_{26}H_{37}BrO_2^+$; calc. 460.1977).

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