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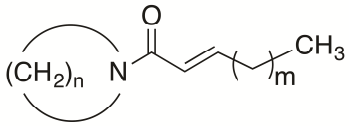

Inhibition of AChE
best: n = 5, m = 12

n = 3, 4, 5, 6, 7; m = 10, 12, 14

Piperlongumine B and analogs are promising and selective inhibitors for acetylcholinesterase

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Abstract

Piperlongumine B (**19**), an alkaloid previously isolated from long pepper (*Piper longum*) has been synthesized for the first time in a short sequence and in good yield together with 19 analogs. Screening of these compounds in Ellman's assays showed several of them to be good inhibitors of acetylcholinesterase while being less active for butyrylcholinesterase. Activity of the compounds increased with the ring size of the heterocycle, and a maximum of activity was observed for an analog holding 12 methylene groups in the aliphatic side chain. These compounds may be regarded as promising candidates for the development of efficient inhibitors of acetylcholinesterase being useful for the treatment of Alzheimer's disease.

1. Introduction

Piper Longum, also known as long pepper or Indian pepper is a small plant native to the tropical rain forests of the Indo-Malaya region. Its fruits have been used for many centuries not only in the traditional Indian medicine Ayurveda but also as a spice. Most important secondary metabolites of this plant are the alkaloids piperine, and piperlongumine A (Fig. 1).

While piperine adds to the hot/spicy taste of the fruits, piperlongumine A (= piplartine) moved into the focus of scientific interest [1-11] due to its anticancer activity [12-17] and as a senolytic agent [18].

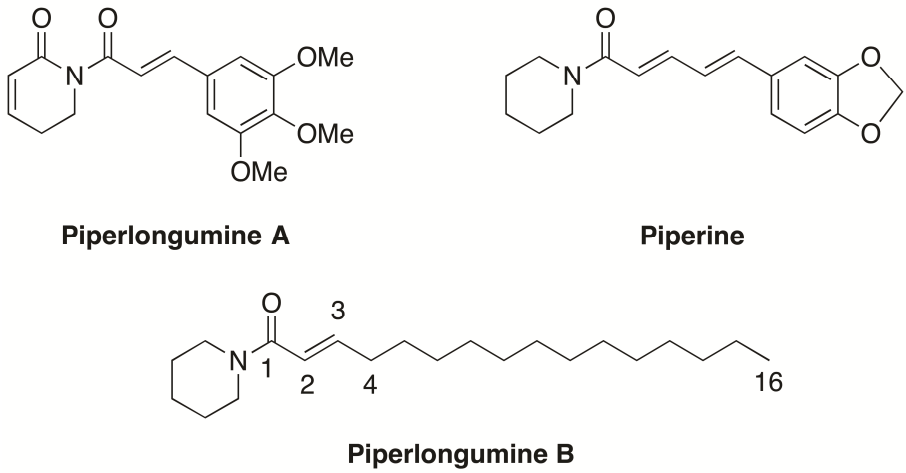


Fig. 1. Structures of most important alkaloids from *Piper longum*.

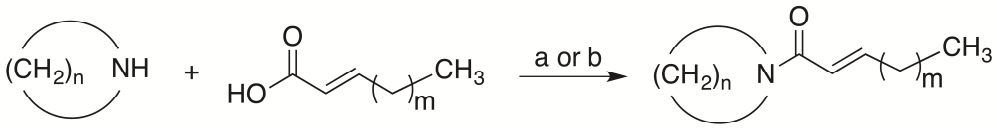
Parallel to the discovery of these compounds, extraction of the fruits yielded another compound, piperlongumine B, and preliminary studies showed some anti-leishmanial activity [19, 20] combined with a weak cytotoxicity [7] for HL-60 human leukemia cells. Piperlongumine B has been accessed by extraction of the fruits only. Generally, extraction processes are convenient, but not so for the isolation of piperlongumine B. Thus, extraction [21-23] of 2.5 kg of air-dried fruits finally gave 6 mg of piperlongumine B. To allow extended biological screening the preparation of larger amounts of this compound (and of analogs thereof) was called for.

The cholinergic system plays an important role in the regulation of learning and memory processes. As a consequence, it has been a target for the design and development of anti-Alzheimer's drugs. Alzheimer's disease (AD) is characterized by deficits in the cholinergic system. Inhibitors of cholinesterases are regarded as enhancers of cholinergic transmission, and several of them (for example, galantamine, donezepil, and rivastigmine) are already on the market to help Ad patients do deal with her progressive neurodegenerative disorder and to increase their quality of life.[24]

Recent investigations showed two enzymes being involved in AD: acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), the latter of which seems to serve as a co-regulator of the cholinergic transmission. BChE, however, is mainly localized in the peripheral tissues, and only a very small amount is present in the brain region. As a consequence, the selective inhibition of AChE over BChE may result in drugs showing a lesser degree of side effects while being equally effective.[24-26] Thus, we became interested in the investigation of piperlongumine B and analogs as potential inhibitors of cholinesterases.

2. Results and Discussion

α,β-Unsaturated acids **1**-**4** are ideal starting materials for these syntheses (Scheme 1); they were either bought or easily prepared from aldehydes by Wittig reaction using (*tert*-butoxycarbonylmethylene)triphenylphosphorane [27, 28] followed by a hydrolysis of intermediary *tert*-butyl esters with TFA. Reaction of the acids **1**-**4** with cyclic amines **5**-**9** in the presence of EDC/HOBt [29] for several hours, or by the reaction of the acids with oxalyl chloride [30] followed by the addition of the amines in the presence of DMAP and NEt_3 in DCM furnished the target compounds **10**-**29** in good yields. The latter method failed to give fair yields of azetidine derived **10**-**13**. Modification of the conditions following a procedure previously reported by Liu [31], however, gave better results and higher yields of **10**-**13** were obtained.



5 n = 3
6 n = 4
7 n = 5
8 n = 6
9 n = 7

1 m = 10
2 m = 12
3 m = 14
4 m = 16

10 n = 3, m = 10
11 n = 3, m = 12
12 n = 3, m = 14
13 n = 3, m = 16
14 n = 4, m = 10
15 n = 4, m = 12
16 n = 4, m = 14
17 n = 4, m = 16
18 n = 5, m = 10
19 n = 5, m = 12
20 n = 5, m = 14
21 n = 5, m = 16
22 n = 6, m = 10
23 n = 6, m = 12
24 n = 6, m = 14
25 n = 6, m = 16
26 n = 7, m = 10
27 n = 7, m = 12
28 n = 7, m = 14
29 n = 7, m = 16

Scheme 1. Synthesis of piperlogumine B (**19**) and analogs **13**-**18** and **20**-**29**: a) EDC, HOBt, DCM, r.t., 12 h, 67-99%; b) oxalyl chloride, DCM, 2 h, then K_2CO_3, Et_2O, H_2O, 71-79%.

Furthermore, compounds **15** and **16** have previously been extracted from *Piper nigrum* and *Piper amalgo* [32, 33] , **17** also from *Piper reticulatum* [34]; compound **18** from *Piper longum* and muntok pepper [22, 35]. Compound **20** [36-40] is an inhibitor of cytochrome P450 2D6 but has also been discussed as an antibacterial and antiinsectal compound; it has also been extracted from the underground parts of *Achillea lyaaconica* and *A. chamaemelifora*. There have been no syntheses for compounds **10**-**26** so far.

Compounds **10**-**29** were subjected to Ellman's assays [41] using acetylcholinesterase (from *Electrophorus electricus*, electric eel) and butyrylcholinesterase (from equine serum) to

evaluate their potential as inhibitors. The results of these investigations are summarized in Table 1 and in Fig. 2.

Table 1. Inhibition of acetylcholinesterase (AChE from *Electrophorus electricus*) and butyrylcholinesterase (BChE from equine serum) from Ellman's assays in % (final substrate concentration 50 µM); single experiments were each repeated ten times; standard: GH galantamine hydrobromide. Compounds **12**, **13**, **16**, **17**, **20**, **21**, **25** and **29** were not soluble.

	Inhibition [%][a]	
	AChE	**BChE**
GH	97.77 ± 0.38	85.97 ± 0.81
10	1.28 ± 0.29	38.91 ± 0.96
11	12.09 ± 1.81	9.82 ± 1.51
14	10.14 ± 0.64	32.63 ± 0.45
15	23.16 ± 1.99	10.95 ± 0.95
18	44.20 ± 0.95	18.79 ± 0.21
19	51.86 ± 1.86	17.76 ± 0.54
22	61.21 ± 0.36	28.56 ± 3.27
23	62.25 ± 0.75	18.54 ± 0.48
24	61.28 ± 1.00	22.16 ± 2.23
26	71.00 ± 0.64	28.72 ± 2.31
27	74.28 ± 0.42	16.76 ± 0.60
28	73.12 ± 0.07	18.72 ± 1.80

[a] Mean ± SEM (standard mean error)

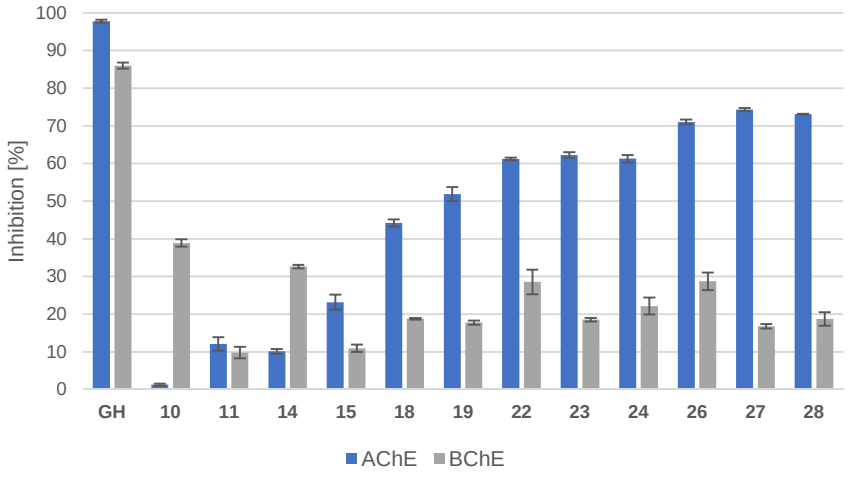


Fig. 2. Graphical representation: Inhibition of acetylcholinesterase (AChE from Electrophorus electricus) and butyrylcholinesterase (BChE, equine serum) from Ellman's assays in %; experiments were performed ten times; standard: GH galantamine hydrobromide. Compounds **12**, **13**, **16**, **17**, **20**, **21**, **25** and **29** were not soluble.

For the most active compounds of this series kinetic data were measured, and the inhibition constants Ki were determined (Table 2). This data showed compounds **19**, **22-24**, and **26-28** as competitive inhibitors of AChE.

Table 2. Inhibition of AChE (*Electrophorus electricus*); data from Ellman's assays; individual experiments were repeated ten times; standard galantamine hydrobromide (GH); K_i in μM.

Compound	Inhibition constant K_i, K_i' [in μM]
GH	$K_i = 0.37 \pm 0.14$
19	$K_i = 7.45 \pm 0.64$; $K_i' > 50$
22	$K_i = 9.99 \pm 0.52$; $K_i' = 45.41 \pm 0.42$
23	$K_i = 3.41 \pm 0.42$; $K_i' = 81.85 \pm 1.11$
24	$K_i = 3.16 \pm 0.15$; $K_i' = 41.48 \pm 0.75$
26	$K_i = 6.83 \pm 0.07$; $K_i' = 22.99 \pm 0.04$
27	$K_i = 2.04 \pm 0.03$; $K_i' = 23.32 \pm 4.30$
28	$K_i = 5.09 \pm 0.54$; $K_i' > 50$

As a result, compounds holding larger rings are stronger inhibitors for AChE. For smaller rings, chain extension, too, led to analogs of higher activity for this enzyme. These compounds are – by and large – only weak inhibitors for BChE. Interestingly enough, while all compounds of this study are stronger inhibitors for AChE than for BChE, compounds **10** and **14** are an exception.

Molecular modeling studies were performed, and the results help at least partially to understand the results ofvthe biological screening. These calculations showed the interaction energy of the compounds being much higher for AChE than for BChE. This is mainly caused by the narrower and even more hydrophobic gorge of the entrance to the active site in AChE as compared to BChE. Thus, the hydrophobic interactions of the lipophilic aliphatic moiety are much more favored to interact with AChE than with BChE. For example, the docking arrangements of compound **27** are displayed in Fig. 3 and Fig. 4.

Compound **27** exhibited hydrophobic interactions with the side chains of the amino acids Y72, Y124, W286, F295, F297, F338, and Y341. Furthermore, the hydrophobic ring of this compound interacts with the side chains of W86 and Y337. Obviously, these hydrophobic interactions increase with the ring size getting larger. This corresponds well with the results from the biological screening.

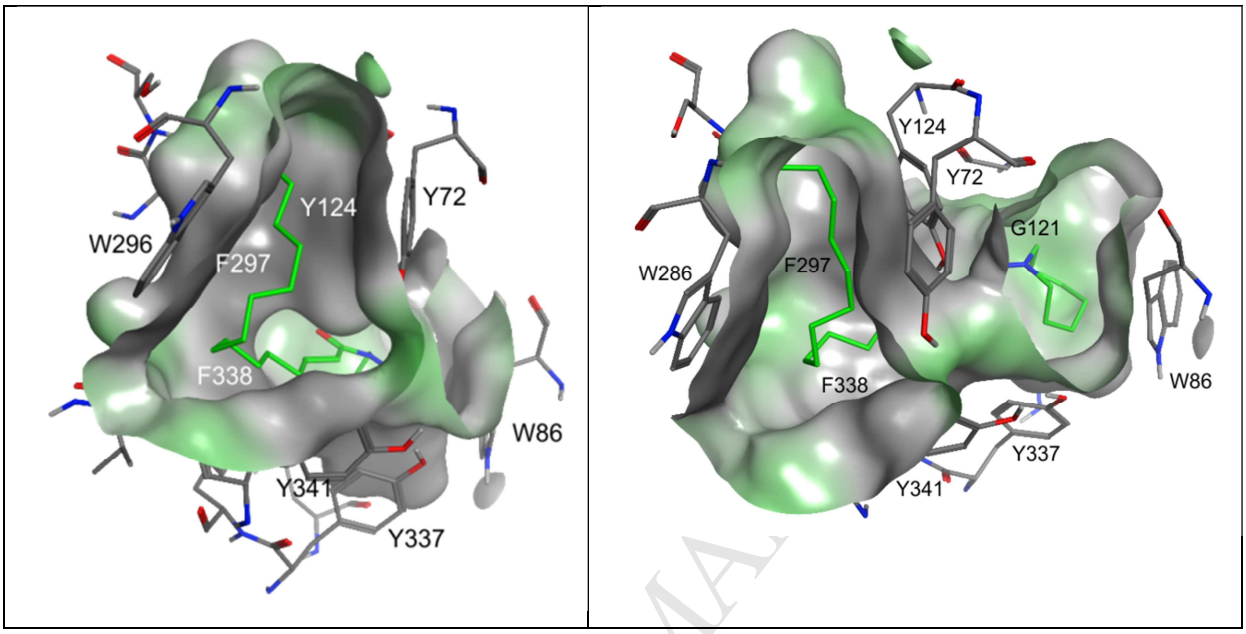


Fig. 3. Docking arrangement of **27** to AChE. Grey shaded surfaces represent lipophilic and green shaded surfaces hydrophilic areas. Left: View from to top the gorge of the ligand binding site. Right: Side view for better visualization of the hydrophobic interaction between the side chain of W286 and the hydrophobic ring system of the ligand.

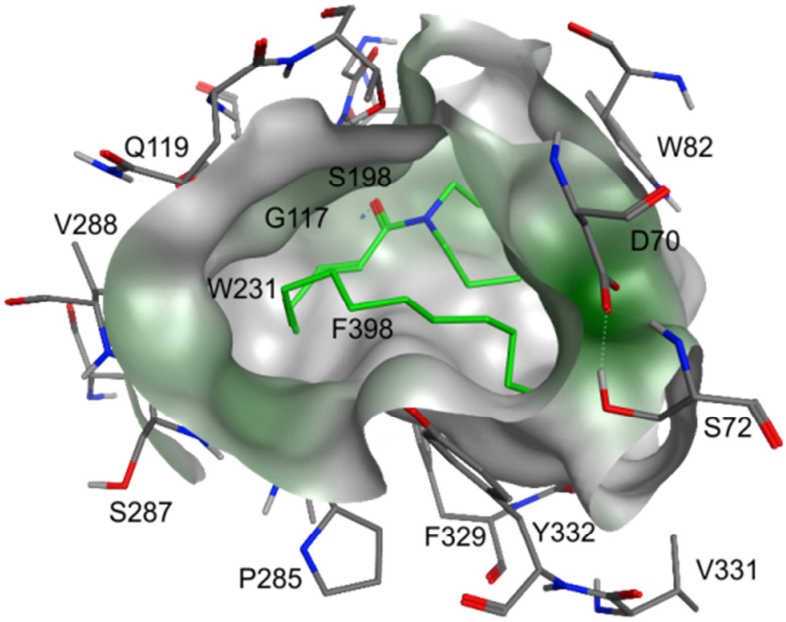


Fig. 4. Docking arrangement of **27** to BChE. Grey shaded surfaces represent lipohilic and green shaded surfaces hydrophilic areas.

A length of the side chain m = 12 seems to be optimal for the hydrophobic interactions in the gorge. As a consequence, the very end of longer aliphatic residues is located at the water accessible surface, and residues of diminished chain length (m < 12) exhibit reduced hydrophobic interactions. These results from the docking, however, must be critically review since these compounds are very flexible.

Penetration of the blood brain barrier (BBB) is crucial for AChE inhibitors intended to be of any help in fighting AD. Hence, some calculations were performed to predict BBB penetration using molecular dynamics simulations.[42] Thus, for the most active compound **27** of this series a log BBB = 1.4 was calculated; compounds with log BBB > 0.3 are usually regarded to readily cross the BBB.[43]

In addition, the compounds were subjected to a cytotoxicity screening using sulforhodamine B assays. As a result, highest cytotoxicity (*cf.* Supplementary data) was observed for **27** and the human malignant cell line HT29 (colorectal adenocarcinoma). The cytotoxicity of this compound was significant lower for the non-malignant cell line NIH 3T3 (mouse fibroblasts), Piperlongumine B (**19**) showed only weak cytotoxicity for human breast adenocarcinoma cell line MCF-7 even at a concentration of 60 μM.

3. Conclusion

Piperlongumine B and 19 analogs were synthesized and screened in Ellman's assays. Several of them were good inhibitors of acetylcholinesterase while being less active for butyrylcholinesterase. Activity of the compounds for acetylcholinesterase increased with the ring size of the heterocycle, and a maximum of activity was observed for an analog holding 12 methylene groups in the aliphatic side chain.

4. Experimental

General

Detailed procedures for the screening and modelling as well as a description of the equipment is given in the Supplementary material; ^{1}H and ^{13}C NMR spectra are depicted.

*4.1. (2E) Tetradecenoic acid (**1**)*

A solution of dodecanal (700 mg, 3.797 mmol) and (*tert*-butoxycarbonylmethylene)-triphenylphosphorane (1400 mg, 3.72 mmol) in dry DCM (2.5 mL) was stirred for 12 h at room temperature. The solvent was removed under diminished pressure, and the residue was suspended in Et_2O/*n*-hexane (1:1, 20 mL). The filtrate was evaporated, and the residue subjected to chromatography (SiO_2, *n*-hexane/ethyl acetate, 95:5) to yield *tert*-butyl-tetradecenoate (861 mg, 80.3%) as a colorless oil. An analytical sample showed: R_F = 0.29 (SiO_2, *n*-hexane/ethyl acetate, 95:5); IR (KBr): ν□= 3456*m*, 2926*vs*, 2854*s*, 1718*vs*, 1654*m*, 1466*m*, 1458*m*, 1392*w*, 1368*m*, 1290*m*, 1256*m*, 1156*s*, 1126*m*, 980*m* cm^{-1}; UV-Vis ($CHCl_3$): λ_{max} (log ε) = 238 (2.86) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.85 (*ddd*, *J* = 15.5, 6.9, 6.9 Hz, 1H, C*H* (3)), 5.73 (*ddd*, *J* = 15.5, 1.6, 1.6 Hz, 1H, C*H* (2)), 2.16 (*dddd*, *J* = 7.2, 7.2, 7.0, 1.5 Hz, 2H, CH_2 (4)), 1.48 (*s*, 9H, CH_3 (16)), 1.46 – 1.39 (*m*, 2H, CH_2 (5)), 1.34 – 1.23 (*m*, 16H, CH_2 (6) + CH_2 (7) + CH_2 (8) + CH_2 (9) + CH_2 (10) + CH_2 (11) + CH_2 (12) + CH_2 (13)), 0.88 (*t*, *J* = 6.8 Hz, 3H, CH_3 (14)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.0 (*C*=O, C1), 148.0 (*C*H, C3), 122.7 (*C*H, C2), 79.8 (C_{quart}, C15), 31.9 (*C*H_2, C4), 31.8 (*C*H_2, C12), 29.5 (*C*H_2), 29.5 (*C*H_2), 29.4 (*C*H_2), 29.3 (*C*H_2), 29.2 (*C*H_2), 29.0 (*C*H_2), 28.0 (*C*H_3, C16), 27.9 (*C*H_2, C5), 22.5 (*C*H_2, C13), 13.9 (*C*H_3, C14) ppm; MS (ESI, MeOH): *m/z* = 227.1 (34%, [M+H−*iso*-butene]$^+$), 305.1 (100%, [M+Na]$^+$), 337.1 (36%, [M+Na+MeOH]$^+$), 587.1 (50%, [2M+Na]$^+$). A solution of this ester (486 mg, 1.72 mmol) in TFA (1.5 mL) was stirred at room temperature for 12 h, the solvent was removed under diminished pressure, and **1** (386 mg, 99.0%) was obtained as a colorless solid; an analytical sample showed: m.p.: 33 °C; R_F = 0.31 (SiO_2, *n*-hexane/ethyl acetate/HCOOH, 7:3:0.05); IR (KBr): ν□= 3450*vs*, 2960*m*,

2920*s*, 2850*s*, 1718*m*, 1694*m*, 1656*m*, 1468*w*, 1420*w*, 1312*w*, 1304*w*, 1286*w* cm^{-1}; UV-Vis (acetone): λ_{max} (log ε) = 209 (4.11) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.09 (*ddd*, *J* = 15.6, 7.0, 7.0 Hz, 1H, C*H* (3)), 5.82 (*ddd*, *J* = 15.6, 1.6, 1.6 Hz, 1H, C*H* (2)), 2.23 (*dddd*, *J* = 7.1, 7.1, 7.1, 1.6 Hz, 2H, CH_2 (4)), 1.47 (*quint*, *J* = 7.2 Hz, 2H, CH_2 (5)), 1.36 – 1.22 (*m*, 16H, CH_2 (6) + CH_2 (7) + CH_2 (8) + CH_2 (9) + CH_2 (10) + CH_2 (11) + CH_2 (12) + CH_2 (13)), 0.88 (*t*, *J* = 7.0 Hz, 3H, CH_3 (14)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.8 (*C*=O, C1), 152.5 (*C*H, C3), 120.5 (*C*H, C2), 32.3 (*C*H_2, C4), 31.9 (*C*H_2, C12), 29.6 (*C*H_2), 29.6 (*C*H_2), 29.5 (*C*H_2), 29.3 (*C*H_2), 29.3 (*C*H_2), 29.1 (*C*H_2, C6), 27.9 (*C*H_2, C5), 22.7 (*C*H_2, C13), 14.1 (*C*H_3, C14) ppm; MS (ESI, MeOH): *m/z* = 225.3 (34%, $[M-H]^-$), 271.0 (6%, $[M+HCO_2]^-$), 467.1 (20%, $[2M-H]^-$), 473.5 (100%, $[2M-2H+Na]^-$); analysis calcd for $C_{14}H_{26}O_2$ (226.36): C 74.29, H 11.58; found: C 74.02, H 11.83.

*4.2. (2E) Hexadecenoic acid (**2**)*

Commercially obtained.

*4.3. (2E) Octadecenoic acid (**3**)*

Following the procedure given for the synthesis of **1**, from hexadecanal (510 mg, 2.121 mmol) and (*tert*-butoxycarbonylmethylene)triphenylphosphorane (974 mg, 2.587 mmol) in dry DCM (5 mL) followed by chromatography (SiO_2, *n*-hexane/ethyl acetate, 95:5) *tert*-butyl octadecenoate (710 mg, 98.8%) was obtained as a colorless oil; an analytical sample showed: R_F = 0.27 (SiO_2, *n*-hexane/ethyl acetate, 95:5); IR (KBr): ν□= 3438*m*, 2924*vs*, 2852*s*, 1716*s*, 1654*m*, 1470*m*, 1390*w*, 1366*m*, 1322*m*, 1292*m*, 1158*s*, 1128*m* cm^{-1}; UV-Vis (acetone): λ_{max} (log ε) = 213 (2.58) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.86 (*ddd*, *J* = 15.5, 6.9, 6.9 Hz, 1H, C*H* (3)), 5.73 (*ddd*, *J* = 15.6, 1.5, 1.5 Hz, 1H, C*H* (2)), 2.15 (*dddd*, *J* = 7.1, 7.1, 7.1, 1.6 Hz, 2H, CH_2 (4)), 1.48 (*s*, 9H, CH_3 (20)), 1.46 – 1.39 (*m*, 2H, CH_2 (5)), 1.35 – 1.21 (*m*, 24H, CH_2 (6) + CH_2 (7) + CH_2 (8) + CH_2 (9) + CH_2 (10) + CH_2 (11) + CH_2 (12) + CH_2 (13) + CH_2 (14) + CH_2 (15) + CH_2 (16) + CH_2 (17)), 0.88 (*t*, *J* = 6.9 Hz, 3H, CH_3 (18)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.4 (*C*=O, C1), 148.3 (*C*H, C3), 123.0 (*C*H, C2), 80.1 (C_{quart}, C19), 32.2 (*C*H_2, C4), 32.1 (*C*H_2, C16), 29.9 (*C*H_2), 29.8 (*C*H_2), 29.8 (*C*H_2), 29.8 (*C*H_2), 29.8 (*C*H_2), 29.7 (*C*H_2), 29.6 (*C*H_2), 29.5 (*C*H_2), 29.4 (*C*H_2, C6), 28.3 (*C*H_3, C20), 28.3 (*C*H_2, C5), 22.9 (*C*H_2, C17), 14.3 (*C*H_3, C18) ppm; MS (ESI, MeOH): *m/z* = 283.2 (16%, $[M+H-$*iso*-butene$]^+$), 361.2 (98%, $[M+Na]^+$), 677.1 (42%, $[2M+H]^+$), 696.4 (36%, $[4M+K+H]^{2+}$), 699.1 (100%, $[2M+Na]^+$). From the reaction of this ester (205 mg, 0.605 mmol) in dry DCM (6 mL) with TFA (1.8 mL) for 1 h at room temperature **3** (169 mg,

98.8%) was obtained as a colorless solid. An analytical sample showed: m.p.: 56 °C (lit.: 58 °C [44]) R_F = 0.80 (SiO_2, *n*-hexane/ethyl acetate, 1:1); IR (KBr): ν□= 3448*m*, 2960*m*, 2920*vs*, 2848*s*, 1720*m*, 1692*m*, 1656*m*, 1468*m*, 1420*w*, 1312*w*, 1288*w* cm^{-1}; UV-Vis (acetone): λ_{max} (log ε) = 209 (4.10) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.09 (*ddd*, *J* = 15.6, 7.0, 7.0 Hz, 1H, C*H* (3)), 5.82 (*ddd*, *J* = 15.6, 1.6, 1.6 Hz, 1H, C*H* (2)), 2.23 (*dddd*, *J* = 7.1, 7.1, 7.1, 1.6 Hz, 2H, CH_2 (4)), 1.53 – 1.41 (*m*, 2H, CH_2 (5)), 1.35 – 1.22 (*m*, 24H, CH_2 (6) + CH_2 (7) + CH_2 (8) + CH_2 (9) + CH_2 (10) + CH_2 (11) + CH_2 (12) + CH_2 (13) + CH_2 (14) + CH_2 (15) + CH_2 (16) + CH_2 (17)), 0.88 (*t*, *J* = 6.5 Hz, 3H, CH_3 (18)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0 (*C*=O, C1), 152.8 (*C*H, C3), 120.6 (*C*H, C2), 32.5 (*C*H_2, C4), 32.1 (*C*H_2, C16), 29.9 (*C*H_2), 29.9 (*C*H_2), 29.8 (*C*H_2), 29.8 (*C*H_2), 29.8 (*C*H_2), 29.7 (*C*H_2), 29.5 (*C*H_2), 29.5 (*C*H_2), 29.3 (*C*H_2, C6), 28.0 (*C*H_2, C5), 22.9 (*C*H_2, C17), 14.3 (*C*H_3, C18) ppm; MS (ESI, MeOH): *m/z* = 281.3 (12%, $[M-H]^-$), 327.0 (12%, $[M+HCO_2]^-$), 563.1 (100%, $[2M-H]^-$); analysis calcd for $C_{18}H_{34}O_2$ (282.47): C 76.54, H 12.13; found: C 76.37, H 12.30.

*4.4. (2E) Eicosenoic acid (**4**)*

Following the precedure given for the synthesis of **1**, from octadecanal (500 mg, 1.862 mmol) and (*tert*-butoxycarbonylmethylen)triphenylphosphorane (873 mg, 2.319 mmol) followed by chromatography (SiO_2, *n*-nexan/ethyl acetate, 95:5) *tert*-butyl eicosenoate (558 mg, 81.7%) was obtained as a colorless solid; analytical data: m.p.: 34 °C; R_F = 0.32 (SiO_2, *n*-hexane/ethyl acetate, 95:5); IR (KBr): ν□= 3444*s*, 2920*vs*, 2850*s*, 1710*s*, 1652*m*, 1472*m*, 1366*m*, 1284*w*, 1250*m*, 1166*m*, 1128*w*, 1060*w* cm^{-1}; UV-Vis (acetone): λ_{max} (log ε) = 213 (2.96) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.86 (*ddd*, *J* = 15.6, 6.9, 6.9 Hz, 1H, C*H* (3)), 5.73 (*ddd*, *J* = 15.6, 1.6, 1.6 Hz, 1H, C*H* (2)), 2.16 (*dddd*, *J* = 7.1, 7.1, 7.1, 1.6 Hz, 2H, CH_2 (4)), 1.48 (*s*, 9H, CH_3 (22)), 1.46 – 1.39 (*m*, 2H, CH_2 (5)), 1.34 – 1.23 (*m*, 28H, CH_2 (6) + CH_2 (7) + CH_2 (8) + CH_2 (9) + CH_2 (10) + CH_2 (11) + CH_2 (12) + CH_2 (13) + CH_2 (14) + CH_2 (15) + CH_2 (16) + CH_2 (17) + CH_2 (18) + CH_2 (19)), 0.87 (*t*, *J* = 7.0 Hz, 3H, CH_3 (20)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.4 (*C*=O, C1), 148.4 (*C*H, C3), 123.0 (*C*H, C2), 80.1 (C_{quart}, C21), 32.2 (*C*H_2, C4), 32.1 (*C*H_2, C18), 29.9 (*C*H_2), 29.8 (*C*H_2), 29.8 (*C*H_2), 29.8 (*C*H_2), 29.7 (*C*H_2), 29.6 (*C*H_2), 29.5 (*C*H_2), 29.4 (*C*H_2, C6), 28.3 (*C*H_3, C22), 28.3 (*C*H_2, C5), 22.9 (*C*H_2, C19), 14.3 (*C*H_3, C20) ppm; MS (ESI, MeOH): *m/z* = 311.2 (26%, $[M+H-iso\text{-butene}]^+$), 332.6 (4%, $[M+Na-iso\text{-butene}]^+$), 342.9 (40%, $[M+H-iso\text{-butene+MeOH}]^+$), 267.2 (8%, $[M+H]^+$), 389.2 (100%, $[M+Na]^+$); analysis calcd for $C_{24}H_{48}O_2$ (366.63): C 78.63, H 12.65; found: C 78.49, H

12.75. To a solution of this ester (330 mg, 0.90 mmol) in dry DCM (8 mL) at 0 °C TFA (2.7 mL) was added; stirring at room temperature was continued for another 45 min, and the solvents were removed under reduced pressure to yield **4** (259 mg, 92.7%) as a colorless solid; an analytical sample showed: m.p.: 63 °C; R_F = 0.32 (SiO_2, *n*-hexane/ethyl acetate, 9:1); IR (KBr): ν□= 3452*s*, 2960*m*, 2920*vs*, 2848*s*, 1718*m*, 1654*m*, 1470*m*, 1420*w*, 1284*w* cm^{-1}; UV-Vis (acetone): λ_{max} (log ε) = 211 (4.09) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.09 (*ddd*, *J* = 15.5, 6.9, 6.9 Hz, 1H, C*H* (3)), 5.82 (*ddd*, *J* = 15.6, 1.6, 1.6 Hz, 1H, C*H* (2)), 2.23 (*dddd*, *J* = 7.1, 7.1, 7.1, 1.5 Hz, 2H, CH_2 (4)), 1.47 (*quint*, *J* = 7.1 Hz, 2H, CH_2 (5)), 1.34 – 1.23 (*m*, 28H, CH_2 (6) + CH_2 (7) + CH_2 (8) + CH_2 (9) + CH_2 (10) + CH_2 (11) + CH_2 (12) + CH_2 (13) + CH_2 (14) + CH_2 (15) + CH_2 (16) + CH_2 (17) + CH_2 (18) + CH_2 (19)), 0.88 (*t*, *J* = 6.7 Hz, 3H, CH_3 (20)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.9 (*C*=O, C1), 152.7 (*C*H, C3), 120.6 (*C*H, C2), 32.5 (*C*H_2, C4), 32.1 (*C*H_2, C18), 29.9 (*C*H_2), 29.8 (*C*H_2), 29.8 (*C*H_2), 29.8 (*C*H_2), 29.8 (*C*H_2), 29.7 (*C*H_2), 29.5 (*C*H_2), 29.5 (CH_2), 29.3 (*C*H_2, C6), 28.0 (*C*H_2, C5), 22.9 (*C*H_2, C19), 14.3 (*C*H_3, C20) ppm; MS (ESI, MeOH): *m/z* = 309.3 (100%, $[M-H]^-$), 354.9 (36%, $[M+HCO_2]^-$); analysis calcd for $C_{20}H_{38}O_2$ (310.52): C 77.36, H 12.34; found: C 77.26, H 12.51.

*4.5. (2E) 1-(Azetidin-1-yl)-tetradec-2-en-1-one (**10**)*

To a solution of **1** (150 mg, 0.663 mmol) in dry DCM (5 mL) at 0 °C oxalyl chloride (0.14 mL, 1.657 mmol) was slowly added, and stirring was continued for another 2 h. The volatiles were removed under reduced pressure, and the residue was added slowly to a mixture of potassium carbonate (106 mg, 0.763 mmol) and azetidine hydrochloride (**5**.HCl, 71 mg, 0.763 mmol) in Et_2O (1 mL) and water (1 mL). Stirring at 0 °C was continued overnight, and the mixture was diluted with ether (100 mL). Usual aq. workup followed by chromatography (SiO_2, ethyl acetate) yielded **10** (137 mg, 77.8%) as a colorless solid; m.p.: 57 °C; R_F = 0.31 (SiO_2, ethyl acetate); IR (KBr): ν□= 3448*m*, 2950*m*, 2916*vs*, 2872*m*, 2848*s*, 1668*s*, 1618*vs*, 1490*w*, 1470*s*, 1442*s*, 1382*w*, 1324*w*, 1298*w*, 1242*w*, 1158*w*, 1022*w*, 990*m* cm^{-1}; UV-Vis (acetone): λ_{max} (log ε) = 213 (4.14) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.85 (*ddd*, *J* = 15.4, 7.0, 7.0 Hz, 1H, C*H* (3)), 5.81 (*ddd*, *J* = 15.3, 1.6, 1.6 Hz, 1H, C*H* (2)), 4.13 (*t*, *J* = 7.7 Hz, 4H, CH_2 (1') + CH_2 (3')), 2.32 – 2.23 (*m*, 2H, CH_2 (2')), 2.17 (*dddd*, *J* = 7.2, 7.2, 7.2, 1.5 Hz, 2H, CH_2 (4)), 1.42 (*quint*, *J* = 7.2 Hz, 2H, CH_2 (5)), 1.33 – 1.21 (*m*, 16H, CH_2 (6) + CH_2 (7) + CH_2 (8) + CH_2 (9)+ CH_2 (10) + CH_2 (11) + CH_2 (12) + CH_2 (13)), 0.87 (*t*, *J* = 6.9 Hz, 3H, CH_3 (14)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.4 (*C*=O, C1), 145.8 (*C*H, C3), 118.5 (*C*H, C2), 49.0 (*C*H_2, C1' + C3'), 32.5 (*C*H_2, C4), 32.1 (*C*H_2, C12), 29.8 (*C*H_2), 29.8

(CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2, C6), 28.5 (CH_2, C5), 22.8 (CH_2, C13), 15.5 (CH_2, C2'), 14.2 (CH_3, C14) ppm; MS (ESI, MeOH): *m/z* = 266.3 (44%, $[M+H]^+$), 288.2 (8%, $[M+Na]^+$), 531.13 (20%, $[2M+H]^+$), 553.2 (100%, $[2M+Na]^+$); analysis calcd for $C_{17}H_{31}NO$ (265.44): C 76.92, H 11.77, N 5.28; found: C 76.73, H 11.97, N 5.04.

*4.6. (2E) 1-(Azetidin-1-yl)-hexadec-2-en-1-one (**11**)*

Following the procedure given for the synthesis of **10**, from **2** (200 mg, 0.786 mmol) oxalyl chloride (0.17 mL, 1.965 mmol) azetidine hydrochlorid (**5**.HCl, 88 mg, 0.943 mmol) and K_2CO_3 (130 mg, 0.943 mmol) followed by chromatography (SiO_2, *n*-hexane/ethyl acetate, 1:1) **11** (173 mg, 75.0%) was obtained as a colorless solid; m.p.: 66 °C; R_F = 0.23 (SiO_2, *n*-hexane/ethyl acetate, 1:1); IR (KBr): ν□= 3448*vs*, 2950*m*, 2916*vs*, 2848*s*, 1668*m*, 1618*s*, 1470*m*, 1442*m*, 1384*w*, 1298*w*, 1242*w*, 1160*w* cm^{-1}; UV-Vis (acetone): λ_{max} (log ε) = 212 (4.34) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.85 (*ddd*, *J* = 15.1, 7.1, 7.1 Hz, 1H, C*H* (3)) 5.81 (*ddd*, *J* = 15.3, 1.5, 1.5 Hz, 1H, C*H* (2)), 4.13 (*t*, *J* = 7.7 Hz, 4H, CH_2 (1') + CH_2 (3')), 2.32 – 2.23 (*m*, 2H, CH_2 (2')), 2.17 (*dddd*, *J* = 7.2, 7.2, 7.2, 1.5 Hz, 2H, CH_2 (4)), 1.43 (*quint*, *J* = 7.2 Hz, 2H, CH_2 (5)), 1.34 – 1.21 (*m*, 20H, CH_2 (6) + CH_2 (7) + CH_2 (8) + CH_2 (9) + CH_2 (10) + CH_2 (11) + CH_2 (12) + CH_2 (13) + CH_2 (14) + CH_2 (15)), 0.87 (*t*, *J* = 6.9 Hz, 3H, CH_3 (16)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.4 (*C*=O, C1), 145.8 (*C*H, C3), 118.5 (*C*H, C2), 48.9 (*br*, *C*H_2, C1' + C3'), 32.5 (*C*H_2, C4), 32.1 (*C*H_2, C14), 29.8 (*C*H_2), 29.8 (*C*H_2), 29.8 (*C*H_2), 29.7 (*C*H_2), 29.6 (*C*H_2), 29.5 (*C*H_2), 29.3 (*C*H_2, C6), 28.5 (*C*H_2, C5), 22.8 (*C*H_2, C15), 15.5 (*C*H_2, C2'), 14.3 (*C*H_3, C16) ppm; MS (ESI, MeOH): *m/z* = 294.4 (100%, $[M+H]^+$), 316.2 (16%, $[M+Na]^+$); analysis calcd for $C_{19}H_{35}NO$ (293.50): C 77.76, H 12.07, N 4.77; found: C 77.46, H 12.18, N 4.46.

*4.7. (2E) 1-(Azetidin-1-yl)-octadec-2-en-1-one (**12**)*

Following the procedure given for the synthesis of **10**, from **3** (150 mg, 0.531 mmol), oxalyl chloride (0.12 mL, 1.33 mmol), potassium carbonate (88 mg, 0.637 mmol) and **5**.HCl (60 mg, 0.637 mmol) followed by chromatography (SiO_2, ethyl acetate) **12** (134 mg, 78.5%) was obtained as a colorless solid; m.p.: 72 °C; R_F = 0.31 (SiO_2, ethyl acetate); IR (KBr): ν□= 3448*s*, 2916*vs*, 2848*s*, 1668*m*, 1618*s*, 1470*m*, 1442*m*, 1384*w* cm^{-1}; UV-Vis (acetone): λ_{max} (log ε) = 214 (4.18) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.86 (*ddd*, *J* = 15.2, 7.0, 7.0 Hz, 1H, C*H* (3)), 5.81 (*ddd*, *J* = 15.3, 1.6, 1.6 Hz, 1H, C*H* (2)), 4.13 (*t*, *J* = 7.3 Hz, 4H, CH_2 (1') + CH_2 (3')), 2.32 – 2.23 (*m*, 2H, CH_2 (2')), 2.17 (*dddd*, *J* = 7.2, 7.2, 7.2, 1.5 Hz, 2H, CH_2 (4)), 1.43 (*quint*, *J* = 7.1 Hz, 2H, CH_2 (5)), 1.34 – 1.21 (*m*, 24H, CH_2 (6) + CH_2 (7) + CH_2 (8) +

C*H*$_2$ (9) + C*H*$_2$ (10) + C*H*$_2$ (11) + C*H*$_2$ (12) + C*H*$_2$ (13) + C*H*$_2$ (14) + C*H*$_2$ (15) + C*H*$_2$ (16) + C*H*$_2$ (17)), 0.87 (*t*, *J* = 6.8 Hz, 3H, C*H*$_3$ (18)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.4 (*C*=O, C1), 145.8 (*C*H, C3), 118.5 (*C*H, C2), 49.1 (*br*, *C*H$_2$, C1' + C3'), 32.5 (*C*H$_2$, C4), 32.1 (*C*H$_2$, C16), 29.8 (*C*H$_2$), 29.8 (*C*H$_2$), 29.8 (*C*H$_2$), 29.8 (*C*H$_2$), 29.7 (*C*H$_2$), 29.6 (*C*H$_2$), 29.5 (*C*H$_2$), 29.3 (*C*H$_2$, C6), 28.5 (*C*H$_2$, C5), 22.8 (*C*H$_2$, C17), 15.5 (*C*H$_2$, C2'), 14.3 (*C*H$_3$, C18) ppm; MS (ESI, MeOH): *m/z* = 322.4 (36%, $[M+H]^+$), 344.2 (4%, $[M+Na]^+$), 643.3 (54%, $[2M+H]^+$), 665.3 (100%, $[2M+Na]^+$); analysis calcd for $C_{21}H_{39}NO$ (321.55): C 78.44, H 12.23, N 4.36; found: C 78.19, H 12.41, N 4.25.

*4.8. (2E) 1-(Azetidin-1-yl)-eicos-2-en-1-one (**13**)*

Following the procedure given for the synthesis of **10**, from **4** (150 mg, 0.483 mmol), oxalyl chloride (153 mg, 1.208 mmol) and **5**.HCl (54 mg, 0.579 mmol) followed by chromatography (SiO_2, ethyl acetate) **13** (120 mg, 71.1%) was obtained as a colorless solid; m.p.: 74 °C; R_F = 0.36 (SiO_2, ethyl acetate); IR (KBr): ν□= 3450*s*, 2916*vs*, 2848*s*, 1668*m*, 1618*s*, 1470*m*, 1442*m*, 1384*w*, 1298*w*, 1240*vw*, 1160*w* cm^{-1}; UV-Vis (acetone): λ_{max} (log ε) = 212 (4.15) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.85 (*ddd*, *J* = 14.6, 7.0, 7.0 Hz, 1H, C*H* (3)), 5.82 (*ddd*, *J* = 15.3, 1.7, 1.7 Hz, 1H, C*H* (2)), 4.13 (*br*, 4H, C*H*$_2$ (1') + C*H*$_2$ (3')), 2.28 (*quint*, *J* = 7.7 Hz, 2H, C*H*$_2$ (2')), 2.17 (*dddd*, *J* = 7.2, 7.2, 7.2, 1.4 Hz, 2H, C*H*$_2$ (4)), 1.43 (*quint*, *J* = 7.2 Hz, 2H, C*H*$_2$ (5)), 1.33 – 1.21 (*m*, 28H, C*H*$_2$ (6) + C*H*$_2$ (7) + C*H*$_2$ (8) + C*H*$_2$ (9) + C*H*$_2$ (10) + C*H*$_2$ (11) + C*H*$_2$ (12) + C*H*$_2$ (13) + C*H*$_2$ (14) + C*H*$_2$ (15) + C*H*$_2$ (16) + C*H*$_2$ (17) + C*H*$_2$ (18) + C*H*$_2$ (19)), 0.87 (*t*, *J* = 6.7 Hz, 3H, C*H*$_3$ (20)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.4 (*C*=O, C1), 145.8 (*C*H, C3), 118.5 (*C*H, C2), 49.9 (*C*H$_2$, C3'), 48.1 (*C*H$_2$, C1'), 32.5 (*C*H$_2$, C4), 32.1 (*C*H$_2$, C18), 29.8 (*C*H$_2$), 29.8 (*C*H$_2$), 29.8 (*C*H$_2$), 29.8 (*C*H$_2$), 29.7 (*C*H$_2$), 29.6 (*C*H$_2$), 29.5 (*C*H$_2$), 29.3 (*C*H$_2$, C6), 28.5 (*C*H$_2$, C5), 22.8 (*C*H$_2$, C19), 15.5 (*C*H$_2$, C2'), 14.3 (*C*H$_3$, C20) ppm; MS (ESI, MeOH): *m/z* = 350.5 (34%, $[M+H]^+$), 372.3 (4%, $[M+Na]^+$), 699.3 (52%, $[2M+H]^+$), 721.3 (100%, $[2M+Na]^+$); analysis calcd for $C_{23}H_{43}NO$ (349.60): C 79.02, H 12.40, N 4.01; found: C 78.87, H 12.53, N 3.81.

*4.9. (2E) 1-(Pyrrolidin-1-yl)-tetradec-2-en-1-one (**14**)*

To an ice-cold solution of **1** (144 mg, 0.636 mmol) in dry DCM (5 mL) EDC (134 mg, 0.699 mmol) and HOBt (127 mg, 0.827 mmol) were added, and stirring was continued for 15 min. Freshly distilled pyrrolidine (**6**, 0.06 mL, 0.763 mmol) was added, the reaction allowed to warm to room temperature, and stirring was continued overnight. The solvent was removed under reduced pressure, and the residue subjected to chromatography (SiO_2, *n*-hexane/ethyl

acetate, 1:1) to yield **14** (135 mg, 75.9%) as a colorless solid; m.p.: 45 °C; R_F = 0.29 (SiO_2, *n*-hexane/ethyl acetate, 1:1); IR (KBr): ν□= 3452*s*, 2956*s*, 2918*vs*, 2852*s*, 1670*m*, 1614*s*, 1472*m*, 1448*m*, 1318*w*, 1276*vw*, 986*w* cm^{-1}; UV-Vis (acetone): λ_{max} (log ε) = 213 (4.11) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.91 (*ddd*, *J* = 15.0, 7.0, 7.0 Hz, 1H, C*H* (3)), 6.08 (*ddd*, *J* = 15.1, 1.6, 1.6 Hz, 1H, C*H* (2)), 3.51 (*t*, *J* = 6.7 Hz, 3H, CH_2 (1') + CH_2 (4')), 2.19 (*dddd*, *J* = 7.2, 7.2, 7.2, 1.5 Hz, 2H, CH_2 (4)), 1.90 (*br*, 4H, CH_2 (2') + CH_2 (3')), 1.44 (*quint*, *J* = 7.2 Hz, 2H, CH_2 (5)), 1.34 – 1.21 (*m*, 16H, CH_2 (6) + CH_2 (7) + CH_2 (8) + CH_2 (9) + CH_2 (10) + CH_2 (11) + CH_2 (12) + CH_2 (13)), 0.87 (*t*, *J* = 6.7 Hz, 3H, CH_3 (14)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.1 (*C*=O, C1), 146.2 (*C*H, C3), 121.6 (*C*H, C2), 46.3 (*br*, *C*H_2, C1' + C4'), 32.6 (*C*H_2, C4), 32.1 (*C*H_2, C12), 29.8 (*C*H_2), 29.8 (*C*H_2), 29.7 (*C*H_2), 29.6 (*C*H_2), 29.5 (*C*H_2), 29.4 (*C*H_2, C6), 28.6 (*C*H_2, C5), 26.2 (*br*, *C*H_2, C3'), 24.5 (*br*, *C*H_2, C2'), 22.8 (*C*H_2, C13), 14.3 (*C*H_3, C14) ppm; MS (ESI, MeOH): *m/z* = 280.3 (30%, $[M+H]^+$), 302.3 (6%, $[M+Na]^+$), 559.1 (36%, $[2M+H]^+$), 581.2 (100%, $[2M+Na]^+$); analysis calcd for $C_{18}H_{33}NO$ (279.47): C 77.36, H 11.90, N 5.01; found: C 77.15, H 12.04, N 4.86.

*4.10. (2E) 1-(Pyrrolidin-1-yl)-hexadec-2-en-1-one (**15**)*

To a solution of **2** (300 mg, 1.179 mmol) in dry DCM (10 mL) at 0 °C EDC (249 mg, 1.299 mmol) and DMAP (144 mg, 1.179 mmol) were added. After 5 min of stirring, pyrrolidine (**6**, 0.10 mL, 1.299 mmol) was slowly added. The mixture was allowed to warm to room tempetrature, and stirring was continued overnight. The solvent was removed under reduced pressure, and the residue subjected to chromatography (SiO_2, *n*-hexane/ethyl acetate, 6:4) to yield **15** (243 mg, 66.9%) as a colorless solid; m.p.: 53 °C; R_F = 0.23 (SiO_2, *n*-hexane/ethyl acetate, 6:4); IR (KBr): ν□= 3447*vs*, 2920*s*, 2852*m*, 1668*m*, 1616*m*, 1472*w*, 1448*w* cm^{-1}; UV-Vis ($CHCl_3$): λ_{max} (log ε) = 232 (3.93) nm; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.91 (*ddd*, *J* = 15.1, 7.0, 7.0 Hz, 1H, C*H* (3)), 6.08 (*ddd*, *J* = 15.1, 1.6, 1.6 Hz, 1H, C*H* (2)), 3.51 (*t*, *J* = 6.7, Hz, 4H, CH_2 (1') + CH_2 (4')), 2.19 (*dddd*, *J* = 7.2, 7.2, 7.2, 1.5 Hz, 2H, CH_2 (4)), 1.93 (*br*, 2H, CH_2 (3')), 1.87 (*br*, 2H, CH_2 (2')), 1.44 (*quint*, *J* = 7.3 Hz, 2H, CH_2 (5)), 1.34 – 1.21 (*m*, 20H, CH_2 (6) + CH_2 (7) + CH_2 (8) + CH_2 (9) + CH_2 (10) + CH_2 (11) + CH_2 (12) + CH_2 (13) + CH_2 (14) + CH_2 (15)), 0.87 (*t*, *J* = 6.9 Hz, 3H, CH_3 (16)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.1 (*C*=O, C1), 146.1 (*C*H, C3), 121.7 (*C*H, C2), 46.6 (*br*, *C*H_2, C4'), 46.0 (*br*, *C*H_2, C1'), 32.6 (*C*H_2, C4), 32.1 (*C*H_2, C14), 29.8 (*C*H_2), 29.8 (*C*H_2), 29.8 (*C*H_2), 29.7 (*C*H_2), 29.6 (*C*H_2), 29.5 (*C*H_2), 29.4 (*C*H_2, C6), 28.6 (*C*H_2, C5), 26.3 (*br*, *C*H_2,

C3'), 24.5 (*br*, *C*H_2, C2'), 22.8 (*C*H_2, C15), 14.3 (*C*H_2, C16) ppm; MS (ESI, MeOH): *m/z* = 308.4 (80%, $[M+H]^+$), 315.2 (18%, $[2M+H]^+$), 330.3 (12%, $[M+Na]^+$), 480.9 (5%, $[3M+K+H]^{2+}$), 637.3 (100%, $[2M+Na]^+$); analysis calcd for $C_{20}H_{37}NO$ (307.52): C 78.11, H 12.13 N 4.55; found: C 77.90, H 12.32, N 4.21.

*4.11. (2E) 1-(Pyrrolidin-1-yl)-octadec-2-en-1-one (**16**)*

To an ice-cold solution of **3** (158 mg, 0.559 mmol) in dry DCM (5 mL) EDC (118 mg, 0.615 mmol) and HOBt (111 mg, 0.727 mmol) were added, and stirring was continued for another 15 min; pyrrolidine (**6**, 0.06 mL, 0.671 mmol) was slowly added, the mixture was allowed to warm to room temperature, and stirring was continued for 12 h. The solvent was removed under reduced pressure, and the residue was subjected to chromatography (SiO_2, *n*-hexane/ethyl acetate, 1:1) to yield **16** (159 mg, 0.474 mmol, 84.8%) as a colorless solid; m.p.: 63 °C; R_F = 0.41 (SiO_2, *n*-hexane/ethyl acetate, 1:1); IR (KBr): ν□= 3448*s*, 2956*m*, 2918*vs*, 2850*s*, 1670*m*, 1614*m*, 1472*m*, 1448*m*, 1384*w*, 1338*vw* cm^{-1}; UV-Vis (acetone): λ_{max} (log ε) = 212 (4.19) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.92 (*ddd*, *J* = 15.2, 7.0, 7.0 Hz, 1H, C*H* (3)), 6.08 (*ddd*, *J* = 15.1, 1.5, 1.5 Hz, 1H, C*H* (2)), 3.56 – 3.47 (*m*, 4H, CH_2 (1') + CH_2 (4')), 2.19 (*dddd*, *J* = 7.2, 7.2, 7.2, 1.5 Hz, 2H, CH_2 (4)), 1.90 (*br*, 4H, CH_2 (2') + CH_2 (3')), 1.44 (*quint*, *J* = 7.1 Hz, 2H, CH_2 (5)), 1.34 – 1.22 (*m*, 24H, CH_2 (6) + CH_2 (7) + CH_2 (8) + CH_2 (9)+ CH_2 (10) + CH_2 (11) + CH_2 (12) + CH_2 (13) + CH_2 (14) + CH_2 (15) + CH_2 (16) + CH_2 (17)), 0.87 (*t*, *J* = 6.9 Hz, 3H, CH_3 (18)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.1 (*C*=O, C1), 146.2 (*C*H, C3), 121.6 (*C*H, C2), 46.3 (*br*, *C*H_2, C1' + C4'), 32.6 (*C*H_2, C4), 32.1 (*C*H_2, C16), 29.8 (*C*H_2), 29.8 (*C*H_2), 29.8 (*C*H_2), 29.8 (*C*H_2), 29.7 (*C*H_2), 29.6 (*C*H_2), 29.5 (*C*H_2), 29.4 (*C*H_2, C6), 28.6 (*C*H_2, C5), 26.0 (*br*, *C*H_2, C3'), 24.7 (*br*, *C*H_2, C2'), 22.8 (*C*H_2, C17), 14.3 (*C*H_3, C18) ppm; MS (ESI, MeOH): *m/z* = 366.4 (82%, $[M+H]^+$), 358.3 (4%, $[M+Na]^+$), 671.3 (80%, $[2M+H]^+$), 693.3 (100%, $[2M+Na]^+$); analysis calcd for $C_{22}H_{41}NO$ (335.58): C 78.74, H 12.32, N 4.17; found; C 78.51, H 12.33, N 4.02.

*4.12. (2E) 1-(Pyrrolidin-1-yl)-eicos-2-en-1-one (**17**)*

To an ice-cold solution of **4** (150 mg, 0.483 mmol) in dry DCM (5 mL) EDC (101 mg, 0.528 mmol) and HOBt (96 mg, 0.624 mmol) werde added, and stirring was continued for 15 min. Pyrrolidine (**6**, 0.05 mL, 0.624 mmol) was slowly added, the mixture was allowed to warm to room temperature, and stirred for another 12 h. The solvent was removed, and the residue was subjected to chromatography (SiO_2, *n*-hexane/ethyl acetate, 1:1) to yield **17** (161 mg, 91.7%) as a colorless solid; m.p.: 70 °C; R_F = 0.38 (SiO_2, *n*-hexane/ethyl acetate,

1:1); IR (KBr): ν□= 3448*m*, 2954*m*, 2916*vs*, 2870*m*, 2850*s*, 1670*m*, 1614*s*, 1472*m*, 1448*m* cm^{-1}; UV-Vis (acetone): λ_{max} (log ε) = 212 (4.21) nm; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.91 (*ddd*, *J* = 15.1, 7.0, 7.0 Hz, 1H, C*H* (3)), 6.08 (*ddd*, *J* = 15.1, 1.6, 1.6 Hz, 1H, C*H* (2)), 3.51 (*t*, *J* = 6.7 Hz, 4H, CH_2 (1') + CH_2 (4')), 2.19 (*dddd*, *J* = 7.2, 7.2, 7.2, 1.5 Hz, 2H, CH_2 (4)), 1.90 (*br*, 4H, CH_2 (2') + CH_2 (3')), 1.44 (*quint*, *J* = 7.3 Hz, 2H, CH_2 (5)), 1.33 – 1.22 (*m*, 28H, CH_2 (6) + CH_2 (7) + CH_2 (8) + CH_2 (9) + CH_2 (10) + CH_2 (11) + CH_2 (12) + CH_2 (13) + CH_2 (14) + CH_2 (15) + CH_2 (16) + CH_2 (17) + CH_2 (18) + CH_2 (19)), 0.87 (*t*, *J* = 6.9 Hz, 3H, CH_3 (20)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.1 (*C*=O, C1), 146.2 (*C*H, C3), 121.6 (*C*H, C2), 46.3 (*br*, *C*H_2, C1' + C4'), 32.6 (*C*H_2, C4), 32.1 (*C*H_2, C18), 29.8 (*C*H_2), 29.8 (*C*H_2), 29.8 (*C*H_2), 29.8 (*C*H_2), 29.7 (*C*H_2), 29.6 (*C*H_2), 29.5 (*C*H_2), 29.4 (*C*H_2, C6), 28.6 (*C*H_2, C5), 26.2 (*br*, *C*H_2, C3'), 24.7 (*br*, *C*H_2, C2'), 22.8 (*C*H_2, C19), 14.3 (*C*H_3, C20) ppm; MS (ESI, MeOH): *m/z* = 364.5 (68%, $[M+H]^+$), 386.3 (4%, $[M+Na]^+$), 727.3 (64%, $[2M+H]^+$), 749.4 (100%, $[2M+Na]^+$); analysis calcd for $C_{24}H_{45}NO$ (363.63): C 79.27, H 12.47, N 3.85; found: C 79.02, H 12.60, N 3.58.

*4.13. (2E) 1-(Piperidin-1-yl)-tetradec-2-en-1-one (**18**)*

To an ice-cold solution of **1** (270 mg, 1.193 mmol) in dry DCM (10 mL) EDC (247 mg, 1.299 mmol) and HOBt (235 mg, 1.534 mmol) were added, and stirring was continued for 15 min. zugegeben. Piperidine (**7**, 0.14 mL, 1.416 mmol) was added, the mixture was allowed to warm to room temperature, and stirring was continued overnight. The solvent was removed under reduced pressure, and the residue was subjected to chromatography (SiO_2, *n*-hexane/ethyl acetate, 7:3) to yield **18** (331 mg, 99.2%) as a colorless solid; m.p.: 34 °C; R_F = 0.37 (SiO_2, *n*-hexane/ethyl acetate, 7:3); IR (KBr): ν□= 3448*s*, 2918*vs*, 2850*s*, 1660*m*, 1612*s*, 1466*m*, 1442*m*, 1300*vw*, 1278*w*, 1258*w*, 1230*w*, 1220*w*, 1136*w*, 1122*w* cm^{-1}; UV-Vis (acetone): λ_{max} (log ε) = 212 (4.53) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.82 (*ddd*, *J* = 15.0, 7.0, 7.0 Hz, 1H, C*H* (3)), 6.22 (*ddd*, *J* = 15.0, 1.5, 1.5 Hz, 1H, C*H* (2)), 3.53 (*br*, 4H, CH_2 (1') + CH_2 (5')), 2.18 (*dddd*, *J* = 7.1, 7.1, 7.1, 1.5 Hz, 2H, CH_2 (4)), 1.68 – 1.60 (*m*, 2H, CH_2 (3')), 1.59 – 1.51 (*m*, 4H, CH_2 (2') + CH_2 (4')), 1.44 (*quin*t, *J* = 7.2 Hz, 2H, CH_2 (5)), 1.34 – 1.21 (*m*, 16H, CH_2 (6) + CH_2 (7) + CH_2 (8) + CH_2 (9) + CH_2 (10) + CH_2 (11) + CH_2 (12) + CH_2 (13)), 0.87 (*t*, *J* = 6.8 Hz, 3H, CH_3 (14)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.8 (*C*=O, C1), 146.2 (*C*H, C3), 120.4 (*C*H, C2), 45.7 (*br*, *C*H_2, C5'), 43.9 (*br*, *C*H_2, C1'), 32.7 (*C*H_2, C4), 32.1 (*C*H_2, C12), 29.8 (*C*H_2), 29.8 (*C*H_2), 29.7 (*C*H_2), 29.6 (*C*H_2), 29.5 (*C*H_2), 29.4 (*C*H_2, C6), 28.6 (*C*H_2, C5), 26.2 (*br*, *C*H_2, C2' + C4'), 24.8 (*C*H_2, C3'), 22.8 (*C*H_2, C13), 14.2 (*C*H_3, C14) ppm; MS (ESI, MeOH): *m/z* = 294.4 (100%, $[M+H]^+$), 316.3 (16%, $[M+Na]^+$);

analysis calcd for $C_{19}H_{35}NO$ (293.50): C 77.76, H 12.02, N 4.77; found: C 77.49, H 12.31, N 4.56.

*4.14. (2E) 1-(Pyrrolidin-1-yl)-hexadec-2-en-1-one (**19**), Piperlongumine B*

To an ice-cold solution of **2** (100 mg, 0.393 mmol) in dry DCM (3 mL), oxalyl chloride (0.18 mL, 0.983 mmol) and one drop of DMF were added; stirring at 0 °C was continued for 2 h, and the volatiles were removed under diminished pressure. The residue was dissolved in dry DCM (5 mL) containing catalytic amounts of DMAP and TEA. Slow addition of piperidine (**7**, 0.43 mL, 0.589 mmol) followed by stirring at room temperature overnight and chromatography (SiO_2, *n*-hexane/ethyl acetate, 7:3) gave **19** (74 mg, 58.5%) as a colorless solid; m.p.: 42 °C; R_F = 0.45 (SiO_2, *n*-hexane/ethyl acetate, 7:3); IR (KBr): ν□= 3448*vs*, 2920*s*, 2850*s*, 1660*m*, 1636*m*, 1614*m*, 1470*w*, 1454*w*, 1442*w*, 1254*w*, 1226*w*, 1136*w*, 1120*w* cm^{-1}; UV-Vis ($CHCl_3$): λmax (log ε) = 232 (3.78) nm; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.82 (*ddd*, *J* = 15.1, 7.0, 7.0 Hz, 1H, C*H* (3)), 6.22 (*ddd*, *J* = 15.1, 1.6, 1.6 Hz, 1H, C*H* (2)), 3.53 (*br*, 4H, CH_2 (1‘) + CH_2 (5‘)), 2.18 (*dddd*, *J* = 7.1, 7.1, 7.1, 1.5 Hz, 2H, CH_2 (4)), 1.69 – 1.59 (*m*, 2H, CH_2 (3‘)), 1.60 – 1.51 (*m*, 4H, CH_2 (2‘) + CH_2 (4‘)), 1.48 – 1.37 (*m*, 2H, CH_2 (C5)), 1.33 – 1.23 (*m*, 20H, CH_2 (6) + CH_2 (7) + CH_2 (8) + CH_2 (9) + CH_2 (10) + CH_2 (11) + CH_2 (12) + CH_2 (13) + CH_2 (14) + CH_2 (15)), 0.87 (*t*, *J* = 6.8 Hz, 3H, CH_3 (16)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.8 (*C*=O, C1), 146.1 (*C*H, C3), 120.4 (*C*H, C2), 47.0 (*br*, *C*H_2, C5‘), 43.3 (*br*, *C*H_2, C1‘), 32.7 (*C*H_2, C4), 32.1 (*C*H_2, C14), 29.8 (*C*H_2), 29.8 (*C*H_2), 29.8 (*C*H_2), 29.7 (*C*H_2), 29.6 (*C*H_2), 29.5 (*C*H_2), 29.4 (*C*H_2, C6), 28.6 (*C*H_2, C5), 26.6 (*br*, *C*H_2, C4‘), 26.1 (*br*, *C*H_2, C2‘), 24.8 (*C*H_2, C3‘), 22.8 (*C*H_2, C15), 14.2 (*C*H_3, C16) ppm; MS (ESI, MeOH): *m/z* = 322.4 (97%, $[M+H]^+$), 344.3 (28%, $[M+Na]^+$), 643.3 (8%, $[2M+H]^+$), 665.3 (100%, $[2M+Na]^+$); analysis calcd for $C_{21}H_{39}NO$ (321.55): C 78.44, H 12.23, N 4.36; found: C 74.21, H 12.42, N 4.17.

*4.15. (2E) 1-(Pyrrolidin-1-yl)-octadec-2-en-1-one (**20**)*

To an ice-cold solution of **3** (150 mg, 0.531 mmol) in dry DCM (5 mL) EDC (112 mg, 0.584 mmol) and HOBt (106 mg, 0.690 mmol) were added, and stirring was continued for another 5 min. Piperidine (**7**, 0.07 mL, 0.690 mmol) was slowly added, the mixture was allowed to warm to room temperature, and stirring was continued overnight. The solvent was removed, and the residue was subjected to chromatography (SiO_2, *n*-hexane/ethyl acetate, 7:3) to yield **20** (174 mg, 93.7%) as a colorless solid; m.p.: 48 °C; R_F = 0.38 (SiO_2, *n*-hexane/ethyl

acetate, 7:3); IR (KBr): ν□= 3446*s*, 2920*vs*, 2850*s*, 2362*w*, 2344*w*, 1660*m*, 1614*s*, 1472*m*, 1454*m*, 1442*m*, 1384*w*, 1274*w*, 1222*w*, 1120*w*, 1020*w* cm^{-1}; UV-Vis (acetone): λ_{max} (log ε) = 211 (4.24) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.83 (*ddd*, *J* = 15.0, 7.0, 7.0 Hz, 1H, C*H* (3)), 6.22 (*ddd*, *J* = 15.0, 1.5, 1.5 Hz, 1H, C*H* (2)), 3.54 (*t*, *J* = 5.4 Hz, 4H, CH_2 (1‘) + CH_2 (5‘)), 2.18 (*dddd*, *J* = 7.1, 7.1, 7.1, 1.5 Hz, 2H, CH_2 (4)), 1.68 – 1.61 (*m*, 2H, CH_2 (3')), 1.60 – 1.52 (*m*, 4H, CH_2 (2') + CH_2 (4')), 1.48 – 1.38 (*m*, 2H, CH_2 (5)), 1.34 – 1.19 (*m*, 24H, CH_2 (6) + CH_2 (7) + CH_2 (8) + CH_2 (9) + CH_2 (10) + CH_2 (11) + CH_2 (12) + CH_2 (13) + CH_2 (14) + CH_2 (15) + CH_2 (16) + CH_2 (17)), 0.87 (*t*, *J* = 6.6 Hz, 3H, CH_3 (18)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.8 (*C*=O, C1), 146.2 (*C*H, C3), 120.4 (*C*H, C2), 45.6 (*br*, *C*H_2, C5'), 44.3 (*br*, *C*H_2, C1'), 32.7 (*C*H_2, C4), 32.1 (*C*H_2, C16), 29.8 (*C*H_2), 29.8 (*C*H_2), 29.8 (*C*H_2), 29.8 (*C*H_2), 29.8 (*C*H_2), 29.7 (*C*H_2), 29.6 (*C*H_2), 29.5 (*C*H_2), 29.4 (*C*H_2, C6), 28.6 (*C*H_2, C5), 26.3 (*br*, *C*H_2, C2' + C4'), 24.8 (*C*H_2, C3'), 22.8 (*C*H_2, C17), 14.3 (*C*H_3, C18) ppm; MS (ESI, MeOH): *m/z* = 350.5 (46%, $[M+H]^+$), 372.3 (2%, $[M+Na]^+$), 699.3 (100%, $[2M+H]^+$), 721.3 (98%, $[2M+Na]^+$); analysis calc dor C23H43NO (349.60): C 79.02, H 12.40, N 4.01; found: C 78.82, H 12.51, N 3.86.

*4.16. (2E) 1-(Pyrrolidin-1-yl)-eicos-2-en-1-one (**21**)*

Reaction of **4** (150 mg, 0.483 mmol) in dry DCM (5 mL) with EDC (102 mg, 0.531 mmol), HOBt (96 mg, 0.628 mmol) and piperidine (**7**, 0.06 mL, 0.628 mmol) for 12 h as described above, followed by chromatography (SiO_2, *n*-hexane/ethyl acetate, 7:3) gave **21** (160 mg, 87.7%) as a colorless solid; m.p.: 57 °C; R_F = 0.36 (SiO_2, *n*-hexane/ethyl acetate, 7:3); IR (KBr): ν□= 3450*m*, 2918*vs*, 2850*s*, 1660*m*, 1612*s*, 1472*m*, 1454*m*, 1442*m*, 1278*w*, 1252*w*, 1218*w*, 1020*w* cm^{-1}; UV-Vis (acetone): λ_{max} (log ε) = 212 (4.26) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.82 (*ddd*, *J* = 15.1, 7.0, 7.0 Hz, 1H, C*H* (3)), 6.22 (*ddd*, *J* = 15.1, 1.6, 1.6 Hz, 1H, C*H* (2)), 3.53 (*br*, 4H, CH_2 (1') + CH_2 (5')), 2.18 (*dddd*, *J* = 7.1, 7.1, 7.1, 1.5 Hz, 2H, CH_2 (4)), 1.68 – 1.61 (*m*, 2H, CH_2 (3')), 1.60 – 1.51 (*m*, 4H, CH_2 (2') + CH_2 (4')), 1.44 (*quint*, *J* = 7.3 Hz, 2H, CH_2 (5)), 1.34 – 1.20 (*m*, 28H, CH_2 (6) + CH_2 (7) + CH_2 (8) + CH_2 (9) + CH_2 (10) + CH_2 (11) + CH_2 (12) + CH_2 (13) + CH_2 (14) + CH_2 (15) + CH_2 (16) + CH_2 (17) + CH_2 (18) + CH_2 (19)), 0.87 (*t*, *J* = 6.7 Hz, 3H, CH_3 (20)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.8 (*C*=O, C1), 146.2 (*C*H, C3), 120.4 (*C*H, C2), 45.8 (*br*, *C*H_2, C5'), 44.6 (*br*, *C*H_2, C1'), 32.7 (*C*H_2, C4), 32.1 (*C*H_2, C18), 29.8 (*C*H_2), 29.8 (*C*H_2), 29.8 (*C*H_2), 29.8 (*C*H_2), 29.8 (*C*H_2), 29.7 (*C*H_2), 29.6 (*C*H_2), 29.5 (*C*H_2), 29.4 (*C*H_2, C6), 28.6 (*C*H_2, C5), 26.3 (*br*, *C*H_2, C2' + C4'), 24.8 (*C*H_2, C3'), 22.8 (*C*H_2, C19), 14.3 (*C*H_3, C20) ppm; MS (ESI, MeOH): *m/z* = 378.5 (64%, $[M+H]^+$), 400.3 (4%, $[M+Na]^+$), 755.3 (56%, $[2M+H]^+$), 777.4 (100%, $[2M+Na]^+$);

analysis calcd for $C_{25}H_{47}NO$ (377.66): C 79.51, H 12.54, N 3.71; found C 79.39, H 12.72, N 3.51.

*4.17. (2E) 1-(Azepan-1-yl)-tetradec-2-en-1-one (**22**)*

Reaction of **1** (126 mg, 0.557 mmol) in dry DCM (5 mL) with EDC (117 mg, 0.613 mmol), HOBt (111 mg, 0.724 mmol) and hexamethylenimine (**8**, 0.08 mL, 0.668 mmol) for 12 h as described above, followed by chromatography (SiO_2, *n*-hexane/ethyl acetate, 7:3) yielded **22** (156 mg, 91.1%) as a colorless oil; R_F = 0.36 (SiO_2, *n*-hexane/ethyl acetate, 7:3); IR (KBr): ν□= 3448*vs*, 2926*s*, 2854*m*, 1660*m*, 1618*m*, 1458*w*, 1448*w*, 1426*w*, 1374*w*, 1356*vw*, 1290*w*, 1128*vw*, 1102*vw* cm^{-1}; UV-Vis (acetone): λ_{max} (log ε) = 212 (3.81) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.89 (*ddd*, *J* = 15.0, 7.0, 7.0 Hz, 1H, C*H* (3)), 6.21 (*ddd*, *J* = 15.0, 1.5, 1.5 Hz, 1H, C*H* (2)), 3.57 (*br*, 2H, CH_2 (1')), 3.50 (*br*, 2H, CH_2 (6')), 2.19 (*dddd*, *J* = 7.1, 7.1, 7.1, 1.5 Hz, 2H, CH_2 (4)), 1.72 (*br*, 4H, CH_2 (3') + CH_2 (4')), 1.56 (*br*, 4H, CH_2 (2') + CH_2 (5')), 1.44 (*quint*, *J* = 7.3 Hz, 2H, CH_2 (5)), 1.36 – 1.22 (*m*, 16H, CH_2 (6) + CH_2 (7) + CH_2 (8) + CH_2 (9) + CH_2 (10) + CH_2 (11) + CH_2 (12) + CH_2 (13)), 0.87 (*t*, *J* = 7.0 Hz, 3H, CH_3 (14)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.7 (*C*=O, C1), 146.5 (*C*H, C3), 120.5 (*C*H, C2), 48.0 (*C*H_2, C6'), 46.4 (*C*H_2, C1'), 32.7 (*C*H_2, C4), 32.1 (*C*H_2, C12), 29.8 (*C*H_2), 29.8 (*C*H_2), 29.7 (*C*H_2), 29.6 (*C*H_2), 29.5 (*C*H_2), 29.4 (*br*, *C*H_2, C3'/C4'), 29.4 (*C*H_2, C6), 28.6 (*C*H_2, C5), 27.8 (*br*, *C*H_2, C3' or C4'), 27.1 (*br*, *C*H_2, C2' or C5'), 26.8 (*br*, *C*H_2, C2' or C5'), 22.8 (*C*H_2, C13), 14.3 (*C*H_3, C14) ppm; MS (ESI, MeOH): *m/z* = 308.4 (44%, $[M+H]^+$), 330.3 (8%, $[M+Na]^+$), 615.1 (30%, $[2M+H]^+$), 637.3 (100%, $[2M+Na]^+$); analysis calc for $C_{20}H_{37}NO$ (307.52): C 78.11, H 12.13, N 4.55; found: C 78.01, H 12.34, N 4.39.

*4.18. (2E) 1-(Azepan-1-yl)-hexadec-2-en-1-one (**23**)*

Reaction of **2** (300 mg, 1.179 mmol) in dry DCM (10 mL) with EDC (247 mg, 1.299 mmol), HOBt (235 mg, 1.534 mmol) and hexamethylenimine (**8**, 0.16 mL, 1.416 mmol) for 12 h as described above followed by chromatography (SiO_2, *n*-hexane/ethyl acetate, 7:3) gave **23** (370 mg, 93.4%) as a colorless oil; R_F = 0.46 (SiO_2, n-hexane/ethyl acetate, 7:3); IR (KBr): ν□= 3450*m*, 2924*vs*, 2854*s*, 1660*m*, 1618*m*, 1450*m*, 1426*m*, 1374*w*, 1354*w*, 1286*w*, 1192*w*, 1170*w* cm^{-1}; UV-Vis (acetone): λ_{max} (log ε) = 212 (4.04) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.89 (*ddd*, *J* = 15.2, 7.0, 7.0 Hz, 1H, C*H* (3)), 6.20 (*ddd*, *J* = 15.0, 1.6, 1.6 Hz, 1H, C*H* (2)), 3.56 (*br*, 2H, CH_2 (1')), 3.50 (*br*, 2H, CH_2 (6')), 2.19 (*dddd*, *J* = 7.2, 7.2, 7.2, 1.5 Hz, 2H, CH_2 (4)), 1.72 (*br*, 4H, CH_2 (3') + CH_2 (4')), 1.56 (*br*, 4H, CH_2 (2') + CH_2 (5')), 1.49 – 1.38 (*m*, 2H, CH_2 (5)), 1.35 – 1.20 (*m*, 20H, CH_2 (6) + CH_2 (7) + CH_2 (8) + CH_2 (9) + CH_2 (10) + CH_2 (11)

+ C*H*$_2$ (12) + C*H*$_2$ (13) + C*H*$_2$ (14) + C*H*$_2$ (15)), 0.87 (*t*, *J* = 7.2 Hz, 3H, C*H*$_3$ (16)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.7 (*C*=O, C1), 146.4 (*C*H, C3), 120.5 (*C*H, C2), 48.0 (*C*H$_2$, C6'), 46.4 (*C*H$_2$, C1'), 32.7 (*C*H$_2$, C4), 32.1 (*C*H$_2$, C14), 29.8 (*C*H$_2$), 29.8 (*C*H$_2$), 29.8 (*C*H$_2$), 29.7 (*C*H$_2$), 29.6 (*C*H$_2$), 29.5 (*C*H$_2$), 29.4 (*br*, *C*H$_2$, C3' or C4'), 29.4 (*C*H$_2$, C6), 28.6 (*C*H$_2$, C5), 27.8 (*br*, *C*H$_2$, C3' or C4'), 27.1 (*br*, *C*H$_2$, C2' or C5'), 26.8 (*br*, *C*H$_2$, C2' or C5'), 22.8 (*C*H$_2$, C15), 14.3 (*C*H$_3$, C16) ppm; MS (ESI, MeOH): *m/z* = 336.4 (58%, $[M+H]^+$), 358.3 (6%, $[M+Na]^+$), 523.1 (4%, $[3M+K+H]^{2+}$), 671.3 (8%, $[2M+H]^+$), 693.3 (100%, $[2M+Na]^+$); analysis calcd for $C_{22}H_{41}NO$ (335.58): C 78.74, H 12.32, N 4.17; found: C 78.58, H 12.51, N 4.03.

*4.19. (2E) 1-(Azepan-1-yl)-octadec-2-en-1-one (**24**)*

Reaction of **3** (130 mg, 0.460 mmol) in dry DCM (5 mL) with EDC (97 mg, 0.506 mmol), HOBt (92 mg, 0.598 mmol) and hexamethylenimine (**8**, 0.07 mL, 0.598 mmol) for 12 h as described above followed by chromatography (SiO_2, *n*-hexane/ethyl acetate, 7:3) gave **25** (141 mg, 84.2%) as a colorless solid; m.p.: 32 °C; R_F = 0.38 (SiO_2, *n*-hexane/ethyl acetate, 7:3); IR (KBr): ν□= 3346*s*, 2916*vs*, 2850*s*, 1660*m*, 1612*m*, 1472*m*, 1456*w*, 1428*m*, 1370*w*, 1196*w*, 1170*w*, 1126*vw* cm^{-1}; UV-Vis (acetone): λ_{max} (log ε) = 212 (4.12) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.90 (*ddd*, *J* = 15.0, 7.0, 7.0 Hz, 1H, C*H* (3)), 6.21 (*ddd*, *J* = 15.0, 1.6, 1.6 Hz, 1H, C*H* (2)), 3.58 (*br*, 2H, C*H*$_2$ (1')), 3.50 (*br*, 2H, C*H*$_2$ (6')), 2.19 (*dddd*, *J* = 7.2, 7.2, 7.2, 1.5 Hz, 2H, C*H*$_2$ (4)), 1.73 (*br*, 4H, C*H*$_2$ (3') + C*H*$_2$ (4')), 1.57 (*br*, 4H, C*H*$_2$ (2') + C*H*$_2$ (5')), 1.44 (*quint*, *J* = 7.2 Hz, 2H, C*H*$_2$ (5)), 1.35 – 1.21 (*m*, 24H, C*H*$_2$ (6) + C*H*$_2$ (7) + C*H*$_2$ (8) + C*H*$_2$ (9) + C*H*$_2$ (10) + C*H*$_2$ (11) + C*H*$_2$ (12) + C*H*$_2$ (13) + C*H*$_2$ (14) + C*H*$_2$ (15) + C*H*$_2$ (16) + C*H*$_2$ (17)), 0.87 (*t*, *J* = 7.0 Hz, 3H, C*H*$_3$ (18)) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.7 (*C*=O, C1), 146.5 (*C*H, C3), 120.5 (*C*H, C2), 48.0 (*C*H$_2$, C6'), 46.5 (*C*H$_2$, C1'), 32.7 (*C*H$_2$, C4), 32.1 (*C*H$_2$, C16), 29.8 (*C*H$_2$), 29.8 (*C*H$_2$), 29.8 (*C*H$_2$), 29.8 (*C*H$_2$), 29.8 (*C*H$_2$), 29.7 (*C*H$_2$), 29.6 (*C*H$_2$), 29.5 (*C*H$_2$), 29.4 (*br*, *C*H$_2$, C3' or C4'), 29.4 (*C*H$_2$, C6), 28.6 (*C*H$_2$, C5), 27.8 (*br*, *C*H$_2$, C3' or C4'), 27.1 (*br*, *C*H$_2$, C2' or C5'), 26.8 (*br*, *C*H$_2$, C2' or C5'), 22.8 (*C*H$_2$, C17), 14.3 (*C*H$_3$, C18) ppm; MS (ESI, MeOH): *m/z* = 364.5 (54%, $[M+H]^+$), 386.33 (4%, $[M+Na]^+$), 727.3 (42%, $[2M+H]^+$), 749.4 (100%, $[2M+Na]^+$); analysis calc for $C_{24}H_{45}NO$ (363,63): C 79.27, H 12.47, N 3.85; found: C 79.03, H 12.57, N 3.70.

*4.20. (2E) 1-(Azepan-1-yl)-eicos-2-en-1-one (**25**)*

Reaction of **4** (150 mg, 0.483 mmol) in dry DCM (5 mL) with EDC (102 mg, 0.531 mmol), HOBt (96 mg, 0.628 mmol) and hexamethylenimine (**8**, 0.07 mL, 0.628 mmol) for 12 h as

described above followed by chromatography (SiO_2, *n*-hexane/ethyl acetate, 7:3) gave **25** (174 mg, 92.0%) as a colorless solid; m.p.: 40 °C; R_F = 0.34 (SiO_2, *n*-Hexan/Ethylacetat 7:3); IR (KBr): ν = 3448*m*, 2916*vs*, 2850*s*, 1660*m*, 1612*s*, 1472*m*, 1428*m*, 1370*w*, *1252w*, 1194*w*, 1170*w* cm^{-1}; UV-Vis (Aceton): λ_{max} (log ε) = 212 (4.21) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.89 (*ddd*, *J* = 14.7, 7.0, 7.0 Hz, 1H, C*H* (3)), 6.21 (*ddd*, *J* = 15.1, 1.5, 1.5 Hz, 1H, C*H* (2)), 3.57 (*t*, *J* = 6.2 Hz, 2H, CH_2 (1')), 3.49 (*t*, *J* = 6.0 Hz, 2H, CH_2 (6')), 2.19 (*dddd*, *J* = 7.2, 7.2, 7.2, 1.5 Hz, 2H, CH_2 (4)), 1.79 – 1.66 *(m*, 4H, CH_2 (3') + CH_2 (4')), 1.61 – 1.52 (*m*, 4H, CH_2 (2') + CH_2 (5')), 1.44 (*quint*, *J* = 7.1 Hz, 2H, CH_2 (5)), 1.34 – 1.21 *(m*, 28H, CH_2 (6) + CH_2 (7) + CH_2 (8) + CH_2 (9) + CH_2 (10) + CH_2 (11) + CH_2 (12) + CH_2 (13) + CH_2 (14) + CH_2 (15) + CH_2 (16) + CH_2 (17) + CH_2 (18) + CH_2 (19)), 0.88 (*t*, *J* = 6.7 Hz, 3H, CH_3 (20)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.7 (*C*=O, C1), 146.4 (*C*H, C3), 120.6 (*C*H, C2), 48.0 (*C*H_2, C6'), 46.4 (*C*H_2, C1'), 32.7 (*C*H_2, C4), 32.1 (*C*H_2, C18), 29.8 (*C*H_2), 29.8 (*C*H_2), 29.8 (*C*H_2), 29.8 (*C*H_2), 29.7 (*C*H_2), 29.6 (*C*H_2), 29.5 (*C*H_2), 29.5 (*br*, *C*H_2, C4'), 29.4 (*C*H_2, C6), 28.6 (*C*H_2, C5), 27.8 (*C*H_2, C3'), 27.2 (*C*H_2, C5'), 26.8 (*C*H_2, C2'), 22.8 (*C*H_2, C19), 14.3 (*C*H_3, C20) ppm; MS (ESI, MeOH): *m/z* = 392.5 (36%, $[M+H]^+$), 414.3 (2%, $[M+Na]^+$), 783.4 (50%, $[2M+H]^+$), 805.5 (100%, $[2M+Na]^+$); analysis calcd for $C_{26}H_{49}NO$ (391.68): C 79.73, H 12.61, N 3.58; found: C 79.54, H 12.89, N 3.32.

*4.21. (2E) 1-(Azocan-1-yl)-tetradec-2-en-1-one (**26**)*

Reaction of **1** (158 mg, 0.698 mmol) in dry DCM (5 mL) with EDC (147 mg, 0.768 mmol), HOBt (139 mg, 0.907 mmol) and heptamethylenimine (**9**, 0.11 mL, 0.838 mmol) for 12 h as described above followed by chromatography (SiO_2, *n*-hexane/ethyl acetate, 7:3) gave **26** (188 mg, 83.8%) as a colorless oil; R_F = 0.42 (SiO_2, *n*-hexane/ethyl acetate, 7:3); IR (KBr): ν = 3348*vs*, 2926*s*, 2854*m*, 2360*m*, 2342*w*, 1658*m*, 1618*m*, 1466*w*, 1424*w*, 1376*w* cm^{-1}; UV-Vis (acetone): λ_{max} (log ε) = 210 (4.49) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.90 (*ddd*, *J* = 14.4, 7.0, 7.0 Hz, 1H, C*H* (3)), 6.20 (*ddd*, *J* = 15.0, 1.5, 1.5 Hz, 1H, C*H* (2)), 3.53 (*t*, *J* = 6.0 Hz, 2H, CH_2 (1')), 3.47 (*t*, *J* = 5.7 Hz, 2H, CH_2 (7')), 2.19 (*dddd*, *J* = 7.2, 7.2, 7.2, 1.5 Hz, 2H, CH_2 (4)), 1.81 – 1.66 (*m*, 4H, CH_2 (2') + CH_2 (6')), 1.62 – 1.49 (*m*, 6H, CH_2 (3') + CH_2 (4') + CH_2 (5')), 1.44 (*quint*, *J* = 7.1 Hz, 2H, CH_2 (5)), 1.35 – 1.21 (*m*, 16H, CH_2 (6) + CH_2 (7) + CH_2 (8) + CH_2 (9)+ CH_2 (10) + CH_2 (11) + CH_2 (12) + CH_2 (13)), 0.87 (*t*, *J* = 6.4 Hz, 3H, CH_3 (14)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.7 (*C*=O, C1), 146.3 (*C*H, C3), 120.9 (*C*H, C2), 48.9 (*C*H_2, C7'), 48.1 (*C*H_2, C1'), 32.7 (*C*H_2, C4), 32.1 (*C*H_2, C12), 29.8 (*C*H_2), 29.8 (*C*H_2), 29.7 (*C*H_2), 29.6 (*C*H_2), 29.5 (*C*H_2), 29.4 (*C*H_2, C6), 28.8 (*C*H_2, C6'), 28.6 (*C*H_2, C5), 27.1 (*C*H_2, C4'), 26.1 (*C*H_2, C2' + C3'), 25.4 (*C*H_2, C5'), 22.8 (*C*H_2, C13), 14.3 (*C*H_3,

C14) ppm; MS (ESI, MeOH): *m/z* = 322.4 (54%, $[M+H]^+$), 344.2 (6%, $[M+Na]^+$), 643.3 (28%, $[2M+H]^+$), 665.3 (100%, $[2M+Na]^+$); analysis calcd for $C_{21}H_{39}NO$ (321.55): C 78.44, H 12.23, N 4.36; found: C 78.21, H 12.50, N 4.17.

*4.22. (2E) 1-(Azocan-1-yl)-hexadec-2-en-1-one (**27**)*

Reaction of **2** (300 mg, 1.179 mmol) in dry DCM (10 mL) with EDC (247 mg, 1.299 mmol), HOBt (235 mg, 1.534 mmol) and heptamethylenimine (**9**, 0.19 mL, 1.416 mmol) for 12 h as described above followed by chromatography (SiO_2, *n*-hexane/ethyl acetate, 6:4) gave **27** (335 mg, 81.2%) as a colorless solid; m.p.: 26 °C; R_F = 0.48 (SiO_2, *n*-hexane/ethyl acetate, 7:3); IR (KBr): ν□= 3448*s*, 2924*vs*, 2854*s*, 1660*m*, 1620*m*, 1446*w*, 1422*w*, 1374*w*, 1356*w*, 1202*w*, 1120*w* cm^{-1}; UV-Vis ($CHCl_3$): λ_{max} (log ε) = 230 (4.37) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.91 (*ddd*, *J* = 15.0, 7.0, 7.0 Hz, 1H, C*H* (3)), 6.20 (*ddd*, *J* = 15.0, 1.5, 1.5 Hz, 1H, C*H* (2)), 3.53 (*t*, *J* = 5.9 Hz, 2H, CH_2 (1')), 3.47 (*t*, *J* = 5.9 Hz, 2H, CH_2 (7')), 2.19 (*dddd*, *J* = 7.2, 7.2, 7.2, 1.5 Hz, 2H, CH_2 (4)), 1.81 – 1.67 (*m*, 4H, CH_2 (2') + CH_2 (6')), 1.62 – 1.50 (*m*, 6H, CH_2 (3') + CH_2 (4') + CH_2 (5')), 1.44 (*quint*, *J* = 7.0 Hz, 2H, CH_2 (5)), 1.34 – 1.21 (*m*, 20H, CH_2 (6) + CH_2 (7) + CH_2 (8) + CH_2 (9) + CH_2 (10) + CH_2 (11) + CH_2 (12) + CH_2 (13) + CH_2 (14) + CH_2 (15)), 0.87 (*t*, *J* = 6.9 Hz, 3H, CH_3 (16)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.7 (*C*=O, C1), 146.3 (*C*H, C3), 120.8 (*C*H, C2), 48.9 (*C*H_2, C7'), 48.1 (*C*H_2, C1'), 32.7 (*C*H_2, C4), 32.1 (*C*H_2, C14), 29.8 (*C*H_2), 29.8 (*C*H_2), 29.8 (*C*H_2), 29.7 (*C*H_2), 29.6 (*C*H_2), 29.5 (*C*H_2), 29.4 (*C*H_2, C6), 28.8 (*C*H_2, C6'), 28.6 (*C*H_2, C5), 27.1 (*C*H_2, C4'), 26.1 (*C*H_2, C2' + C3'), 25.4 (*C*H_2, C5'), 22.8 (*C*H_2, C15), 14.3 (*C*H_3, C16) ppm; MS (ESI, MeOH): *m/z* = 350.5 (82%, $[M+H]^+$), 372.3 (8%, $[M+Na]^+$), 544.5 (4%, $[3M+K+H]^{2+}$), 699.1 (5%, $[2M+H]^+$), 721.3 (100%, $[2M+Na]^+$); analysis calc for $C_{23}H_{43}NO$ (349.60): C 79.02, H 12.40, N 4.01; found: C 78.88, H 12.57, N 3.79.

*4.23. (2E) 1-(Azocan-1-yl)-octadec-2-en-1-one (**28**)*

Reaction of **3** (143 mg, 0.506 mmol) in dry DCM (5 mL) with EDC (107 mg, 0.557 mmol), HOBt (101 mg, 0.658 mmol) and heptamethylenimine (**9**, 0.09 mL, 0.658 mmol) for 12 h as described above followed by chromatography (SiO_2, *n*-hexane/ethyl acetate, 7:3) gave **28** (161 mg, 84.3%) as a colorless solid; m.p.: 29 °C; R_F = 0.42 (SiO_2, *n*-hexane/ethyl acetate, 7:3); IR (KBr): ν□= 3448*s*, 2922*vs*, 2850*s*, 1658*m*, 1608*s*, 1490*w*, 1466*m*, 1452*m*, 1426*m*, 1378*w*, 1290*w*, 1212*w*, 1148*w* cm^{-1}; UV-Vis (acetone): λ_{max} (log ε) = 214 (4.27) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.91 (*ddd*, *J* = 14.9, 7.0, 7.0 Hz, 1H, C*H* (3)), 6.20 (*ddd*, *J* = 15.0, 1.5, 1.5 Hz, 1H, C*H* (2)), 3.53 (*t*, *J* = 6.1, 2H, CH_2 (1')), 3.48 (*t*, *J* = 6.2, Hz, 2H, CH_2 (7')), 2.19

(*dddd*, *J* = 7.2, 7.2, 7.2, 1.5 Hz, 2H, C*H*$_2$ (4)), 1.81 – 1.65 (*m*, 4H, C*H*$_2$ (2') + C*H*$_2$ (6')), 1.62 – 1.50 (*m*, 6H, C*H*$_2$ (3') + C*H*$_2$ (4') + C*H*$_2$ (5')), 1.54 – 1.37 (*m*, 2H, C*H*$_2$ (5)), 1.36 – 1.20 (*m*, 24H, C*H*$_2$ (6) + C*H*$_2$ (7) + C*H*$_2$ (8) + C*H*$_2$ (9) + C*H*$_2$ (10) + C*H*$_2$ (11) + C*H*$_2$ (12) + C*H*$_2$ (13) + C*H*$_2$ (14) + C*H*$_2$ (15) + C*H*$_2$ (16) + C*H*$_2$ (17)), 0.88 (*t*, *J* = 6.5 Hz, 3H, C*H*$_3$ (18)) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.7 (*C*=O, C1), 146.4 (*C*H, C3), 120.8 (*C*H, C2), 48.9 (*C*H$_2$, C7'), 48.1 (*C*H$_2$, C1'), 32.7 (*C*H$_2$, C4), 32.1 (*C*H$_2$, C16), 29.8 (*C*H$_2$), 29.8 (*C*H$_2$), 29.8 (*C*H$_2$), 29.8 (*C*H$_2$), 29.8 (*C*H$_2$), 29.7 (*C*H$_2$), 29.6 (*C*H$_2$), 29.5 (*C*H$_2$), 29.4 (*C*H$_2$, C6), 28.8 (*C*H$_2$, C6'), 28.6 (*C*H$_2$, C5), 27.1 (*C*H$_2$, C4'), 26.1 (*C*H$_2$, C2' + C3'), 25.4 (*C*H$_2$, C5'), 22.8 (*C*H$_2$, C17), 14.3 (*C*H$_3$, C18) ppm; MS (ESI, MeOH): *m/z* = 378.5 (58%, $[M+H]^+$), 400.3 (4%, $[M+Na]^+$), 755.3 (78%, $[2M+H]^+$), 777.4 (100%, $[2M+Na]^+$); analysis calcd for $C_{25}H_{47}NO$ (377.66): C 79.51, H 12.54, N 3.71; found: C 79.38, H 12.74, N 3.50

*4.24. (2E) 1-(Azocan-1-yl)-eicos-2-en-1-one (**29**)*

Reaction of **4** (150 mg, 0.483 mmol) in dry DCM (5 mL) with EDC (102 mg, 0.531 mmol), HOBt (96 mg, 0.628 mmol) and heptamethylenimine (**9**, 0.08 mL, 0.628 mmol) for 12 h as described above followed by chromatography (SiO_2, *n*-hexane/ethyl acetate, 7:3) gave **29** (181 mg, 92.3%) as a colorless solid; m.p.: 38 °C; R_F = 0.40 (SiO_2, *n*-hexane/ethyl acetate, 7:3); IR (KBr): ν□= 3448*vs*, 2920*s*, 2850*m*, 1658*m*, 1610*m*, 1466*w*, 1424*w*, 1380*w* cm^{-1}; UV-Vis (acetone): λ_{max} (log ε) = 212 (4.24) nm; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.90 (*ddd*, *J* = 14.8, 7.0, 7.0 Hz, 1H, C*H* (3)), 6.20 (*ddd*, *J* = 15.0, 1.5, 1.5 Hz, 1H, C*H* (2)), 3.53 (*t*, *J* = 5.9 Hz, 2H, C*H*$_2$ (1')), 3.48 (*t*, *J* = 5.7 Hz, 2H, C*H*$_2$ (7')), 2.19 (*dddd*, *J* = 7.2, 7.2, 7.2, 1.5 Hz, 2H, C*H*$_2$ (4)), 1.81 – 1.67 (*m*, 4H, C*H*$_2$ (2') + C*H*$_2$ (6')), 1.62 − 1.50 (*m*, 6H, C*H*$_2$ (3') + C*H*$_2$ (4') + C*H*$_2$ (5')), 1.48 – 1.40 (*m*, 2H, C*H*$_2$ (5)), 1.36 – 1.20 (*m*, 28H, C*H*$_2$ (6) + C*H*$_2$ (7) + C*H*$_2$ (8) + C*H*$_2$ (9) + C*H*$_2$ (10) + C*H*$_2$ (11) + C*H*$_2$ (12) + C*H*$_2$ (13) + C*H*$_2$ (14) + C*H*$_2$ (15) + C*H*$_2$ (16) + C*H*$_2$ (17) + C*H*$_2$ (18) + C*H*$_2$ (19)), 0.88 (*t*, *J* = 6.9 Hz, 3H, C*H*$_3$ (20)) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 166.7 (*C*=O, C1), 146.3 (*C*H, C3), 120.9 (*C*H, C2), 48.9 (*C*H$_2$, C7'), 48.1 (*C*H$_2$, C1'), 32.7 (*C*H$_2$, C4), 32.1 (*C*H$_2$, C18), 29.9 (*C*H$_2$), 29.8 (*C*H$_2$), 29.8 (*C*H$_2$), 29.8 (*C*H$_2$), 29.7 (*C*H$_2$), 29.6 (*C*H$_2$), 29.5 (*C*H$_2$), 29.4 (*C*H$_2$, C6), 28.8 (*C*H$_2$, C6'), 28.6 (*C*H$_2$, C5), 27.1 (*C*H$_2$, C4'), 26.1 (*C*H$_2$, C2' + C3'), 25.4 (*C*H$_2$, C5'), 22.8 (*C*H$_2$, C19), 14.3 (*C*H$_3$, C20) ppm; MS (ESI, MeOH): *m/z* = 406.5 (50%, $[M+H]^+$), 428.4 (4%, $[M+Na]^+$), 811.4 (70%, $[2M+H]^+$), 833.4 (100%, $[2M+Na]^+$); analysis calcd for $C_{27}H_{51}NO$ (405.71): C 79.93, H 12.67, N 3.45; found: C 79.86, H 12.76, N 3.16.

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Appendix A. Supplementary data

Supplemenatry data related to this article can be found at

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Highlights

* Piperlongumine B is an alkaloid previously only isolated from long pepper in tiny amounts.
* A facile synthesis for Piperlongumine B and analogs has been developed.
* These compounds were screend for their potential as inhibitors for cholinesterases.
* Screening showed several of them as good inhibitors of acetylcholinesterase.