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Annonaceous acetogenin mimics bearing a terminal lactam and their cytotoxicity against cancer cells

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Abstract—Annonaceous acetogenins are a large class of naturally occurring polyketides exhibiting potent anticancer activities. Based on our previous discovery of AA005, a multi-ether mimic of natural acetogenins having potent antitumor activities and significant selectivity between normal cells and cancer cells, a new series of mimics containing a terminal lactam were designed, synthesized and evaluated. Bioactivity study against cancer cells shows that the *N*-methylated lactam-containing compounds **3**, **4**, and **5** exhibit comparable potencies to that of AA005, as well as the similar selectivity to cancer cells. Hydrocarbon-length effects of *N*-alkyl were further explored through synthesizing derivatives **24**–**26**, and application of this derivation protocol to the fluorescent labeling was also investigated.

Annonaceous acetogenins are a large family of fatty acid-derived natural products with unique structures. Many diverse members in this family display a broad spectrum of biological activities, among which the most impressive is the antitumor activity.[1,2] It is believed that acetogenins directly act at the terminal electron transfer step in complex I of mitochondria. However, studies toward determining the accurate binding sites of acetogenins still remain unclear due to lack of detail structural information about complex I.[3,4] Previous studies in our group showed that a mimic of natural acetogenins (AA005, **1**) containing most potential functionalities of natural acetogenins exhibited potent antitumor activity in 50–100 nM range against a variety of human cancer cell lines. Furthermore, this compound presented general selectivity between human normal and cancer cells.[5] It would be of great significance to reveal the detailed action mechanism which is presented by AA005. In order to carry out such studies, a fluorescent derivative of AA005 that can be visualized in the living cells by microscopy is required in most priority. The second, more chemical space in the acetogenin mimicry is still urgent to be explored for understanding essential SAR knowledge through creative chemistry.[6] As part of our continuing efforts on AA005-initiated studies, we report herein the synthesis of a new series of actogenin mimics bearing a terminal lactam functionality instead of the original lactone unit, and the evaluation of their biological activities, as well as its application to the fluorescent labeling.

As mentioned as above, the acetogenin mimic AA005 (**1**) was found to inhibit complex I of the mitochondrial electron transport chain.[7] Considering the proposed model by McLaughlin's group[8] for the interaction between natural acetogenins with complex I, introduction of a labeling group into the hydrocarbon skeleton between terminal lactone unit and middle ethylene glycol moiety of AA005 might alter the configuration of the whole skeleton and weaken the binding of AA005 to the target. Based on our previous results,[6] we suppose that introduction of a fluorescent label at one terminal of the molecule (lactone moiety) may affect less on binding of AA005 to the target. It is known the α,β-unsaturated γ-butenolide is an essential functionality for the bioactivities of these acetogenins. If this lactone moiety could be replaced by an unsaturated lactam, the newly introduced nitrogen atom may offer us the opportunities

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to introduce a fluorescent label directly through a proper spacer. Also, such new AA005-like molecules with a terminal lactam are of value to be explored. Guided by the above idea, a series of new acetogenin mimics **2**–**5** with a terminal lactam moiety were designed (Fig. 1).

Retrosynthetically, the terminal α,β-unsaturated lactam could be constructed by a sequential aldol condensation, lactamization, and β-elimination (Fig. 2). Two directional successive *O*-alkylations of ethylene glycol could introduce both required long-hydrocarbon chains. This protocol allows us to rapidly assemble the lactam moiety in considerable diversity from a common intermediate **6** and a variety of easily prepared aminoaldehydes **7**–**10** from corresponding amino acids.

As shown in Scheme 1, the synthesis started from diol **13**.[5b] Selective protection of the secondary alcohol[9]

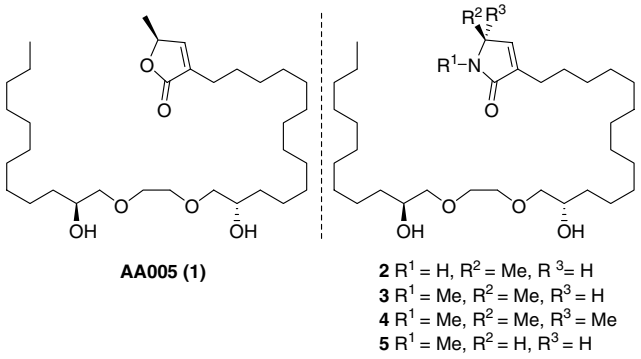


Figure 1. Annonaceous mimics AA005 (**1**) and lactam-containing derivatives **2**–**5**.

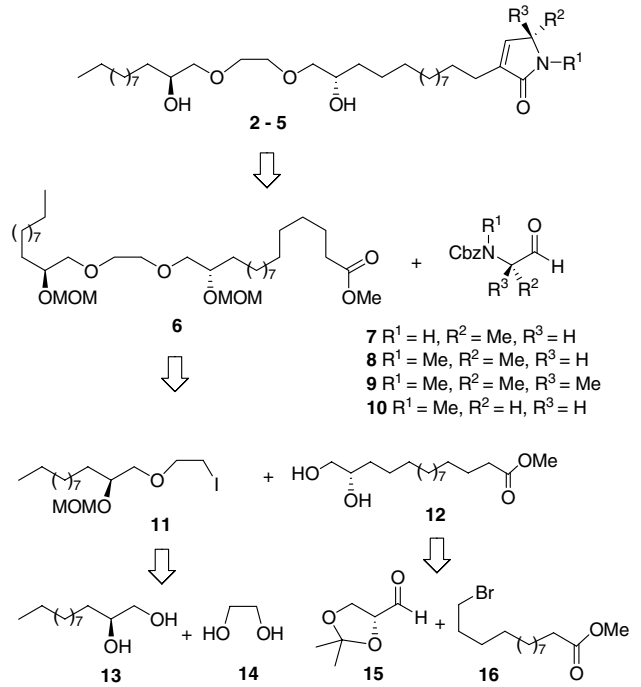
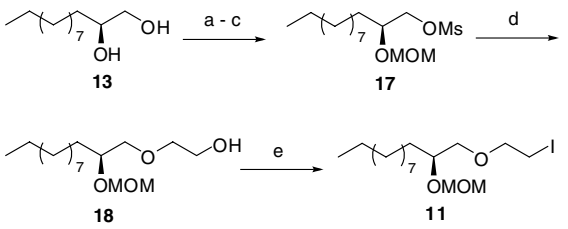


Figure 2. Retrosynthetic analysis of terminal lactam-containing mimics of acetogenin.



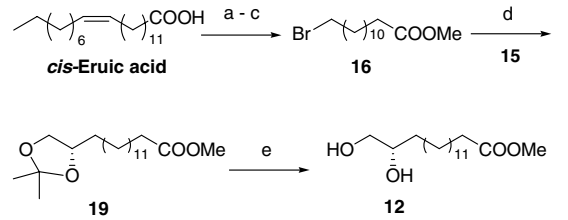
Scheme 1. Reagents and conditions: (a) $HC(OCH_3)_3$, *D*-10-CSA, CH_2Cl_2; (b) DIBAL-H (1.0 M in toluene), CH_2Cl_2, 0 °C, 90% (two steps); (c) MsCl, Et_3N, CH_2Cl_2, 100%; (d) ethylene glycol, NaH, DMF, 130 °C, 80%; (e) I_2, Ph_3P, imidazole, CH_2Cl_2, 90%.

and followed by the mesylation[10] of the primary hydroxyl group afforded mesylate **17** in 90% yield (2 steps). Mono *O*-alkylation of ethylene glycol with freshly prepared mesylate **17** gave alcohol **18**, which was further converted to the corresponding iodide **11** in 72% yield (2 steps).

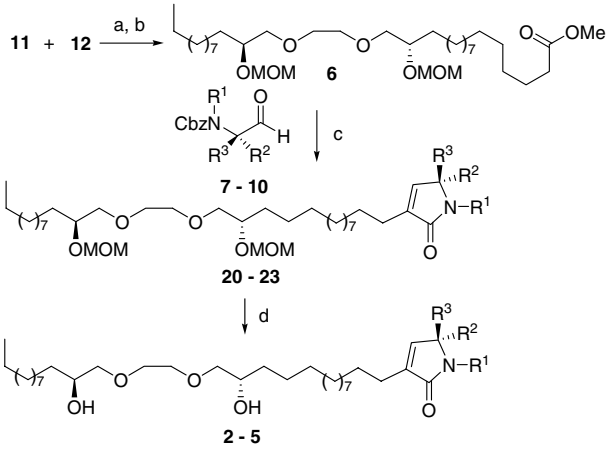
Right-hand part of the common skeleton **6** was prepared from the commercially available *cis*-eruic acid (Scheme 2). Ozonization of the double bond of *cis*-eruic acid gave the desired aldehyde, which was reduced immediately by KBH_4. Bromination of the resulting alcohol with HBr followed by esterification afforded the methyl ester **16** in a satisfactory overall yield. Subsequently, Wittig olefination, hydrogenation, and removal of the acetonide protecting group gave the expected diol **12**.

Cross-coupling of both fragments **11** and **12** was accomplished through an etherification in the presence of Bu_2SnO and CsF (Scheme 3). Protection of exposed secondary hydroxyl group with MOMCl gave the linear skeleton **6** in good yield. Final construction of the terminal lactam moiety was achieved by the following three-step sequential procedure. Aldol reactions of the enolate derived from ester **6** with various adehydes **7**–**10**,[11] removal of *N*-Cbz-protection by hydrogenation and in situ cyclization (to form the lactams), and β-elimination gave compounds **20**–**23** in reasonable yields, respectively. Finally, global deprotection of the MOM ethers by treatment with $BF_3{\cdot}Et_2O$ in Me_2S[12] afforded target mimics **2**–**5**.

The results of biological evaluation of compounds **2**–**5** are shown in Table 1. All five lactam-based mimics of



Scheme 2. Reagents and conditions: (a) i—O_3, 0–5 °C, EtOH-cyclohexane (1:5), ii—KBH_4; (b) HBr, HOAc; (c) MeOH, $SOCl_2$ 61% in 3 steps; (d) i—PPh_3, ii—*t*-BuOK, then (*R*)-glyceraldehyde acetonide **15**, iii—H_2 (1 atm), EtOH, 10% Pd-C, 80% over three steps; (e) 50% HOAc, THF, 94%.



Scheme 3. Reagents and conditions: (a) i—Bu_2SnO, $CHCl_3$/MeOH, reflux, ii—CsF, then **11**, DMF, 79%; (b) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 90%; (c) i—LDA, then **7**–**10** (see Fig. 2), THF, ii—H_2, cat. $Pd(OH)_2$, EtOH, 40 °C, ii—TFAA, Et_3N (R^1 = H), or MsCl, Et_3N, then DBU (R^1 = Me), 77% for **7**, 62% for **8**, 55% for **9**, and 58% for **10** over three steps; (d) $BF_3{\cdot}Et_2O$, Me_2S, 83% for **2**, 70% for **3**, 72% for **4** and 67% for **5**.

Table 1. Cytotoxicity screenings of acetogenin mimics **2**–**5**[a,b]

Compound	IC_{50}[c] (μM)			
	Chang	B16	BEL-7404	SK-Hep1
AA005 (1)	NA	0.035	0.041	0.065
2	NA	0.87	2.20	NA
3	NA	0.013	0.234	0.589
4	NA	0.478	0.845	0.583
5	NA	0.168	0.168	0.104

[a] AA005 was used as a positive control.
[b] Exponentially growing cells were treated with compounds **1**–**5** for 48 h, respectively. Cell viability was determined by MTT assay.
[c] NA, not active.

AA005 retain the selectivity between the human cells (Chang) and tumor cells (B16, BEL-7404, and SK-Hep1), while they are 5–10-fold less potent than AA005. Compound **2** (without an *N*-methyl in the lactam) exhibits weaker activities as compared to compound **3** (with an *N*-methyl in the lactam). Such kind of difference was often found in some known *N*-methylated peptides with unique physicochemical properties.[13] Compound **3** also shows some kind of selectivity among different tumor cells, which is a defection of AA005, and other three *N*-methylated compounds **3**–**5** only show slight difference. In addition, elimination of the stereogenic center on the lactam by replacement of the (*S*)-methyl with a hydrogen atom or replacement of the hydrogen there with a methyl (compounds **4** and **5**) does not decrease the bioactivity dramatically.

According to the above biological results, *N*-methylation on the terminal lactam increases the activity, and those mimics retain the cell selectivity. It mentions that the chemical space to introduce other longer alkyls carrying on more functional groups, including a fluorescent group, is possible. Therefore, compounds **24**–**26** with different lengths of alkyls at the nitrogen atom of terminal lactam were designed. Such a protocol extended to the fluorescent labeling is illustrated in Figure 3.

Derivatives **24**–**26** were prepared using a similar procedure as described above (Scheme 4). Reductive alkylation[14] of L-alanine methyl ester **28** with aldehyde **29** followed by *N*-Cbz protection of the secondary amine afforded ester **30**, which was further reduced by Dibal-H at −78 °C to give aldehyde **31**.[15] By a similar three-step procedure, lactam **32** was prepared in a satisfactory overall yield. After removal of two MOM ethers and the *N*-Boc protecting group, further branch extension was achieved by coupling(s) with the linear amino acid **33** under standard conditions (EDCI/HOBt), affording compounds **24** (a by-product), **25**, and **26**, respectively.

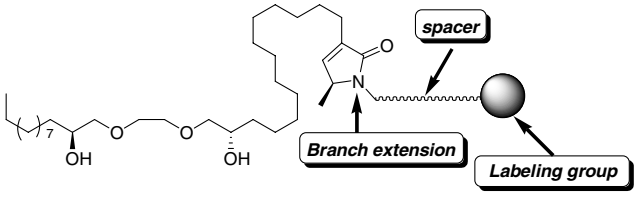
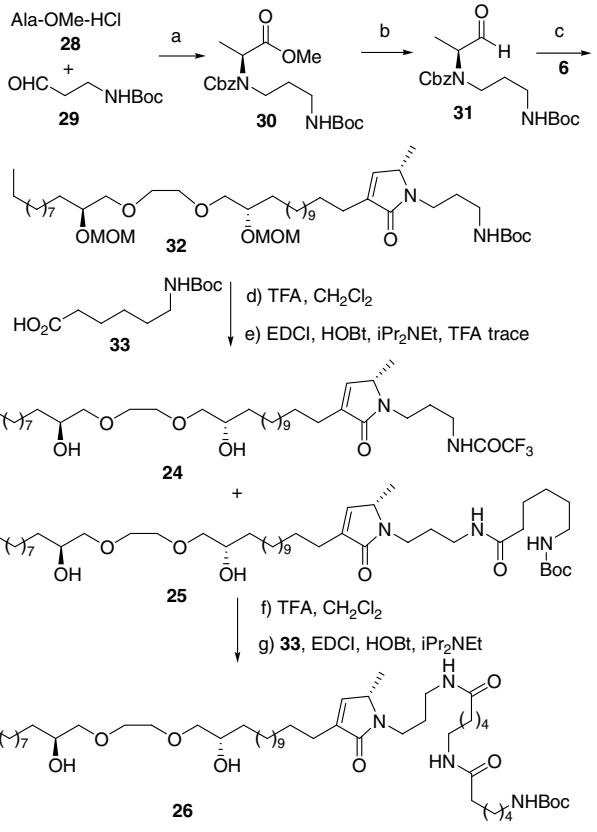


Figure 3. Fluorescent labeling protocol through the *N*-alkylation.

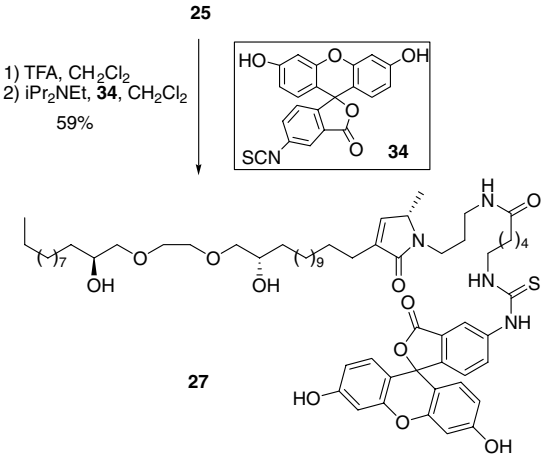


Scheme 4. Reagents and conditions: (a) $NaBH(OAc)_3$, then aq. $NaHCO_3$, CbzCl, 42%; (b) DIBAL-H, CH_2Cl_2, −78 °C, 90%; (c) i—LDA, THF, then **31**, ii—H_2, cat. $Pd(OH)_2$, EtOH, 40 °C, ii—MsCl, Et_3N, then DBU, 62% over three steps; (d) TFA, CH_2Cl_2; (e) EDCI, HOBt, **33**, *i*-Pr_2NEt, TFA trace CH_2Cl_2, 17% for **24** and 41% for **25**; (f) TFA, CH_2Cl_2; (g) **33**, EDCI, HOBt, *i*-Pr_2NEt, CH_2Cl_2, 60%.

A fluorescent probe **27** was synthesized from intermediate **25** (Scheme 5). Deprotection of the *N*-Boc group of **25** followed by coupling with a commonly used fluorescent labeling reagent **34** gave the designed fluorescein-labeled compound **27** in 59% yield.

Unfortunately, these compounds bearing the longer branches decrease the antitumor activity dramatically as compared to the *N*-methyl compound **3** (Table 2), and no activity was measured for the fluorescent labeling compound **27**. According to these data, it mentions that the longer the *N*-terminal alkyl chain is, the less active it is.

In summary, a new series of AA005-like acetogenin mimics bearing a terminal lactam moiety have been synthesized[16] for the first time and their cytotoxicities were measured and evaluated. Among these compounds, *N*-methyl compound **3** shows comparable activities to that of AA005 and retains similar cell selectivity. It was also revealed that the stereogenic center on the lactam is not an essential to the antitumoral activity. Utilizing the newly introduced nitrogen atom, new fluorescent labeling through *N*-branching was also studied, and all these efforts are negative. The compounds bearing longer chains through *N*-alkylation dramatically decrease the activities, and no activity was observed for the designed fluorescent probe **27**. However, the presented work opens an entrance to those new AA005-like acetogenin mimics containing nitrogen functionalities. Further optimization of the structures and selective labeling of the acetogenin mimics are currently underway in our laboratory.



Scheme 5. Synthesis of fluorescent labeling compound **27**.

Table 2. Biological evaluation of compounds **3** and **24**–**27**[a,b]

Compound	IC_{50}[c] (μM)			
	Chang	SK-hep1	B16	Bel-7404
3	NA	0.437	0.075	0.295
24	NA	NA	0.995	1.35
25	NA	NA	NA	3.20
26	NA	NA	NA	2.50
27	NA	NA	NA	NA

[a] Compound **3** was used as a positive control.
[b] Exponentially growing cells were treated with compounds **3**, **24**–**27** for 48 h, respectively. Cell viability was determined by MTT assay.
[c] NA, not active.

Acknowledgments

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16. Data for final compounds: *Compound* **2**. $[\alpha]_D^{25} = +34.4$ (*c* 0.13, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 0.88 (3H, t, *J* = 6.9 Hz), 1.20–1.60 (43H, m), 2.24 (2H, t, *J* = 8.0 Hz), 2.83 (2OH, br s), 3.32 (2H, dd, *J* = 8.2, 9.8 Hz), 3.53 (2H, dd, *J* = 2.8, 9.8 Hz), 3.67 (4H, m), 3.79 (2H, m), 4.13 (1H, q, *J* = 7.0 Hz), 6.51 (1H, s), 6.60 (1H, s) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): 174.0, 143.2, 139.0, 75.8, 70.5, 70.2, 52.7, 33.0, 31.8, 29.6, 29.59, 29.57, 29.55, 29.51, 29.3, 29.2, 27.5, 25.5, 25.2, 22.6, 19.0, 14.0 ppm; IR (KBr): 3443, 1689, 1637, 1471, 1465, 1159, 1143, 1093, 958 cm^{-1}; MS (ESI, *m*/*z*): 576 (M^++Na); HRMS (ESI) calcd for $C_{33}H_{63}NO_5Na$ 576.4598, Found 576.4599. *Compound* **3**. $[\alpha]_D^{25} = +8.4$ (*c* 0.25, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): 0.88 (3H, t, *J* = 7.1 Hz), 1.22–1.55 (43 H, m), 2.25 (2H, t, *J* = 8.0 Hz), 2.95 (3H, s), 3.32 (2H, dd, *J* = 8.3, 9.7 Hz), 3.54 (2H, dd, *J* = 2.8, 9.8 Hz), 3.64 (4H, m), 3.78 (2H, m), 3.88 (1H, dq, *J* = 1.4, 6.9 Hz), 6.53 (1H, dd, *J* = 1.6, 3.1 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): 171.2, 140.1, 139.3, 75.9, 70.5, 70.3, 57.7, 33.0, 31.9, 29.7, 29.6, 29.59, 29.57, 29.4, 29.3, 27.5, 26.6, 25.6, 25.5, 22.6, 16.7, 14.1 ppm; IR (KBr): 3441, 2977, 2850, 1683, 1641, 1464, 1431, 1398, 1328, 1159, 1141, 957 cm^{-1}; MS (ESI, *m*/*z*): 590 (M^++Na); HRMS (ESI) calcd for $C_{34}H_{65}NO_5Na$ 590.4754, found 590.4753. *Compound* **4**. $[\alpha]_D^{25} = 5.55$ (*c* 3.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): 0.88 (3H, t, *J* = 7.0 Hz), 1.22 (6H, s), 1.22–1.70 (40H, m), 2.24 (2H, t, *J* = 8.0 Hz), 2.85 (3H, s), 3.32 (2H, dd, *J* = 8.2 9.7 Hz), 3.53 (2H, dd, *J* = 2.9, 9.8 Hz), 3.66 (4H, m), 3.78 (2H, m), 6.54 (1H, t, *J* = 1.4 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 170.3, 145.8, 137.9, 75.9, 70.5, 70.2, 61.5, 33.0, 31.9, 29.68, 29.60, 29.5, 29.4, 29.3, 29.32, 29.30, 27.4, 25.5, 25.4, 23.5, 23.2, 22.6, 14.0 ppm; IR (KBr): 3443, 2918, 2850, 1683, 1647, 1467, 1336, 1160, 1092 cm^{-1}; MS (ESI, *m*/*z*): 604 (M^++Na); HRMS (ESI) calcd for $C_{35}H_{67}NO_5Na$ 604.4911, found 604.4911. *Compound* **5**. $[\alpha]_D^{25} = 5.77$ (*c* 0.40, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): 0.88 (3H, t, *J* = 6.9 Hz), 1.22–1.70 (40H, m), 2.27 (2H, t, *J* = 8.0 Hz), 3.04 (3H, s), 3.32 (2H, t, *J* = 9.7 Hz), 3.53 (2H, dd, *J* = 2.7, 9.8 Hz), 3.66 (4H, m), 3.78 (2 H, m), 3.82 (2H, s), 6.59 (1H, d, *J* = 1.6 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): 171.8, 140.7, 133.5, 75.9, 70.5, 70.3, 52.6, 33.0, 31.9, 29.69, 29.61, 29.5, 29.4, 29.34, 29.33, 29.2, 25.9, 25.5, 22.6, 14.1 ppm; IR (KBr): 3440, 2918, 2850, 1669, 1633, 1472, 1464, 1330, 1160, 1143, 957 cm^{-1}; MS (ESI, *m*/*z*): 576 (M^++Na); HRMS (ESI) calcd for $C_{33}H_{63}NO_5Na$ 576.4598, found 576.4596. *Compound* **27**. ^1H NMR (500 MHz, $CDCl_3$/MeOD): 0.88 (3H, t, *J* = 7.1 Hz), 1.22–1.75 (51H, m), 2.24 (4H, m), 3.07 (1H, m), 3.27 (3H, m), 3.49 (2H, m), 3.62–3.80 (10H, m), 4.08 (1H, q, *J* = 6.5 Hz), 6.57 (2H, d, *J* = 8.7 Hz), 6.68 (1H, s), 6.70 (2H, s), 6.80 (2H, d, *J* = 8.7 Hz), 7.14 (1H, d, *J* = 8.2 Hz), 7.90 (1H, d, *J* = 8.2 Hz), 8.07 (1H, s) ppm; ^{13}C NMR (125 MHz, $CDCl_3$/MeOD): 181.9, 176.9, 175.2, 173.2, 171.4, 155.0, 142.8, 141.4, 139.1, 130.6, 129.5, 126.7, 115.6, 112.5, 103.6, 76.4, 71.0, 70.9, 57.4, 50.5, 50.0, 36.9, 33.9, 32.6, 31.4, 30.4, 30.4, 30.3, 30.2, 30.0, 26.2, 23.3, 18.2, 14.6 ppm; IR (film): 3282, 3070, 2924, 2853, 1736, 1658, 1610, 1501, 1465, 1378, 1326, 1254, 1210, 1180, 1110, 993, 913, 851, 787, 730 cm^{-1}; MS (MALDI, *m*/*z*): 1135 (M^++Na); HRMS (MALDI) calcd for $C_{63}H_{92}N_4O_{11}SNa$ 1135.6375, found 1135.6360.