Novel macrocyclic molecules based on 12a-N substituted 16-membered azalides and azalactams as potential antifungal agents

ARTICLE *in* EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY · DECEMBER 2013

Impact Factor: 3.45 · DOI: 10.1016/j.ejmech.2013.11.032 · Source: PubMed

9 AUTHORS, INCLUDING:

Yanhong Dong

China Agricultural University

5 PUBLICATIONS **8** CITATIONS

SEE PROFILE

European Journal of Medicinal Chemistry 73 (2014) 286–294

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Novel macrocyclic molecules based on 12a-*N* substituted 16-membered azalides and azalactams as potential antifungal agents

Xiaolei Wang, Shun Zhang, Yanlong Pang, Huihui Yuan, Xiaomei Liang, Jianjun Zhang, Daoquan Wang, Mingan Wang, Yanhong Dong*

Department of Applied Chemistry, College of Science, China Agricultural University, Beijing 100193, China

ARTICLE INFO

Article history:
Received 2 August 2013
Received in revised form
19 November 2013
Accepted 24 November 2013
Available online 11 December 2013

Keywords:
Macrocyclic molecules
Azalides
Azalactams
Synthesis
Antifungal activity

ABSTRACT

Novel macrocyclic molecules comprising sulfonyl and acyl moiety at the position *N*-12a of 16-membered azalides (**6a**–**n**) and azalactams (**10a**–**r**) scaffold were synthesized from cyclododecanone **1** as starting material *via* 5 steps and 4 steps, respectively. The antifungal activity of these compounds against *Sclerotinia sclerotiorum*, *Pyricularia oryzae*, *Botrytis cinerea*, *Rhizoctonia solani* and *Phytophthora capsici* were evaluated and found that compounds possessing α-exomethylene (**6c**, **6d**, **6e** and **6g**) showed antifungal activity comparable to commercial fungicide Chlorothalonil against *P. oryzae* and compounds possessing *p*-chlorobenzoyl exhibited enhanced antifungal activity than those with other substituents against *S. sclerotiorum*, *P. oryzae*, and *B. cinerea*. These findings suggested that the α-exomethylene and *p*-chlorobenzoyl may be two potential pharmacological active groups with antifungal activities.

1. Introduction

Macrolide antibiotics are a class of safe and effective drugs widely used in the treatment of infectious diseases in clinical subjects. Azithromycin (AZ) [1–3] is a semisynthetic azalide antibiotic with 15-membered macrolide ring having an *N*-methyl inserted into the erythromycin aglycone. It has become a "heavy bomb" drug owing to its wide spectrum of activity and superior pharmacokinetic and safety properties. These properties prompt the exploration of synthesis of new antibacterial compounds with outstanding pharmacokinetics by using azalide scaffold in recent years [4,5]. Thus, azithromycin derivatives, 48 and 55 [6], were reported to exhibit excellent antibacterial activity against a wide range of clinically relevant macrolide-resistant organisms. The thiourea derivative **7a** and urea **9b** [7] have shown substantially improved activity compared to AZ when tested against efflux-mediated resistant *Streptococcus pneumoniae*. The novel aminoquinoline derivative 12 [8] exhibits high *in vitro* activity and selectivity against *Plasmodium falciparum* parasites.

Many natural macrolides bearing double bonds in the ring have multiple physiological activities and wide range of applications in the pharmaceuticals and pesticides. Pikromycin [9,10] is one of the 14-membered lactone antibiotics with double bonds. Avermectins [11], currently the most widely used insecticide in agriculture, have three double bonds in its lactone ring. Cladospolide B [12] with 12-membered unsaturated lactone was found to have a role in regulating plant growth. The unsaturated sex attractant lactones [13] have been isolated from secretions of the stored-grain pests *Cryptolestes pusillus*. Six pheromones containing unsaturated macrolide structure [14] have also been identified from the secretions of *Cryptolestes ferrugineus*.

The exocyclic double bond, mainly referred to as α-exomethylene, is present in many natural products with biological activities. The simplest lactone containing α-exomethylene is Tulipalin A, which could control *Fusarium oxysporum* [15] and *Botrytis cinerea* [16] efficiently. Alantolactone [17] shows bactericidal activity [18] and antifeedant activity against *Tribolium confusum* with potential application in pest control. Some studies suggest that Alantolactone also inhibits the proliferation of tumor cells [19,20]. Cedarmycin A [21,22] exhibits potent activity against *Candida glabrata* IFO 0622 with the MIC of 0.40 μg/mL.

It has been our goal to simplify structures and develop new potential pesticides *via* biomimetic synthesis of natural macrolides. We have synthesized cyclododecanone derivatives [23–25] and macrolactam/macrolactone derivatives [26–29], and all of them have shown moderate antifungal activities. For example, the saturated azalide (Fig. 1), 12a-aza-pentadecanelactone tetrafluoroborate, possesses excellent antifungal activity against

* Corresponding author. Tel.: +86 10 62732944; fax: +86 10 62732507.
E-mail address: dongyh@cau.edu.cn (Y. Dong).

0223-5234/$ – see front matter © 2013 Elsevier Masson SAS. All rights reserved.
http://dx.doi.org/10.1016/j.ejmech.2013.11.032

Rhizoctonia solani [30]. To further promote the research program aiming to discover novel bioactive wide-spectrum macrocyclic compounds, the novel azalactams and azalides containing the endocyclic or exocyclic double bond were designed and synthesized from cyclododecanone and their biological activities were reported here.

2. Results and discussion

2.1. Chemistry

Scheme 1 shows the synthetic route of novel 12a-*N* substituted 16-membered azalides and azalactams. Compound **2** [30] was obtained in high yield from cyclododecanone **1** and 2-azidoethanol in the presence of Lewis acid boron trifluoride etherate ($BF_3 \cdot OEt_2$). This fluoroborate was hydrolyzed with saturated sodium carbonate (Na_2CO_3) solution, and the free amino group was protected with di-*tert*-butyl pyrocarbonate ($(Boc)_2O$) to give intermediate **3** [31]. *tert*-Butyloxycarbonyl-2-methylene-12a-aza-pentadecanelactone (**4a**) [32] was synthesized *via* the condensation reaction of formaldehyde and lactone **3** mediated with lithium diisopropylamide (LDA) in anhydrous tetrahydrofuran (THF) at −78 °C for 2 h. This is the first time to use such a method to introduce 2-methylene into macrolide.

The lactone carbanion firstly reacted with bromoselenobenzene (PhSeBr) to form *tert*-butyloxycarbonyl-2-phenylselanyl-12a-aza-pentadecanelactone, which was then oxidized with hydrogen peroxide (H_2O_2) to yield *tert*-butyloxycarbonyl-12a-aza-2*E*-pentadecenelactone (**4b**) [33]. To separate *tert*-butyloxycarbonyl-2-phenylselanyl-12a-aza-pentadecanelactone from the reaction mixture by flash column, toluene/ethyl acetate were used as the eluent instead of petroleum ether/ethyl acetate to yield better separation resolution and high recovery yield of **4b**. Then, the Boc group of **4a** and **4b** was removed using trifluoroacetic acid (CF_3COOH) to yield **5a** and **5b** [34] in quantitative yield, which reacted with corresponding aryl chlorides to give compound **6a**–**g** and **6h**–**n**.

To prepare 12a-*N* substituted 16-membered azalactams, cyclododecanone **1** reacted with 2-azidoethanol in the presence of Lewis acid $BF_3 \cdot OEt_2$ *via* Boyer reaction [35,36] to give iminium ether, which reacted with sodium azide (NaN_3) in *N*,*N*-dimethylformamide (DMF) to yield compound **7**. Then, compound **7** reacted with triphenylphosphine (PPh_3) followed by hydrolysis to give compound **8** [37,38]. Compound **8** was treated with 4-toluene sulfonic acid (TsOH) at reflux under Argon condition to give bicyclic amidine, which was then hydrolyzed with potassium hydroxide (KOH) to generate compound **9** [39]. Compound **9** reacted with alkyl chlorides in dry methylene chloride (DCM) in the presence of potassium carbonate (K_2CO_3) to afford compounds **10a**–**r** in moderate to high yields.

2.2. Biological activity

Using mycelium growth assay [29], we evaluated antifungal activities of compounds azalides (**6a**–**n**) and azalactams (**10a**–**r**) against a panel of agriculturally important pathogens in China including *Sclerotinia sclerotiorum*, *Pyricularia oryzae*, *B. cinerea*, *R. solani* and *Phytophthora capsici*. Commercial fungicide Chlorothalonil was used as a positive control. As shown in Table 1, 32 compounds showed fair to high levels of antifungal activity against the five fungi. Notably, compound **6g** has shown excellent activity for *S. sclerotiorum* and *P. oryzae* and compound **10o** for *B. cinerea* and *R. solani*. Importantly, comparison of the inhibitory activity of azalides and azalactams demonstrated that azalide compounds had better activity than that of azalactams bearing the same *N*-substituted groups (e.g., **6a** and **6h** *vs* **10b**) against *S. sclerotiorum*, *P. oryzae*, *R. solani* and *P. capsici*. For *S. sclerotiorum* and *P. oryzae*, the inhibition rates of the azalides **6g** were 75.39% and 67.28%, respectively, whereas that of **6n** was 84.68% and 64.26%, respectively. These activities were higher than the azalactams **10o** having the same *p*-chlorobenzoyl with the rates of 61.35% and 42.17%, respectively. Among all test compounds, the compounds containing *p*-chlorobenzoyl (**6g**, **6n** and **10o**) exhibited the best antifungal activities against the most of the tested fungi. The inhibition rates of the compounds with α-exomethylene (**6c**, **6d**, **6e** and **6g**) were comparable to that of commercial fungicide Chlorothalonil against *P. oryzae*, whereas endocyclic compounds (**6j**, **6k**, **6l** and **6n**) were less active than Chlorothalonil. In addition, the compounds **6c**–**g** showed higher inhibition activity than **6j**–**n** against *S. sclerotiorum*, *P. oryzae*, and *B. cinerea*. The results indicated that *p*-chlorobenzoyl and α-exomethylene may be two active groups conferring potential antifungal activities.

To understand whether the electric charge distribution of these compounds may contribute their biological activities, the 3D structure of each compound was constructed using the Sketch Molecule module in SYBYL 7.3 software [40] and their energy minimizations were performed using Tripos force field with a distance dependent dielectric function and a Powell method with a convergence criterion of 0.001 kcal/mol. Also, partial atomic charges were calculated by the Merck molecular force field 94 (MMFF94) [41], which made significant approximations in the treatment of some important physical interactions and calculated the potential energy more accurately. Based on the atomic charges labeled by SYBYL 7.3, two important conclusions were given as follows: Firstly, α-exomethylene compound **6g** (75.39%), **6e** (55.76%) and **6f** (67.80%) have much better antifungal activity against *S. sclerotiorum* than the corresponding unsaturated compound **6n** (67.28%), **6l** (38.22%) and **6m** (36.39%) with the same *O*-substituted group, respectively. As shown in Table 1, this difference was because of the higher electropositivity (0.168) of $CH_2{=}C{-}CH_2$ group compared to CH=CH group (0.084). Secondly, the electrical property of benzene was analyzed and it indicated that higher electropositivity in benzene might be unfavorable to the compounds activity. For example, compound **10o** (0.187, 61.35% of inhibition rate) and **10f** (0.239, 28.29% of inhibition rate) are better than **10r** (0.238, 53.78% of inhibition rate) and **10i** (0.286, 5.58% of inhibition rate) against *S. sclerotiorum* respectively.

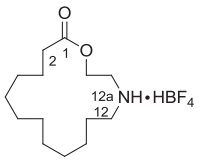
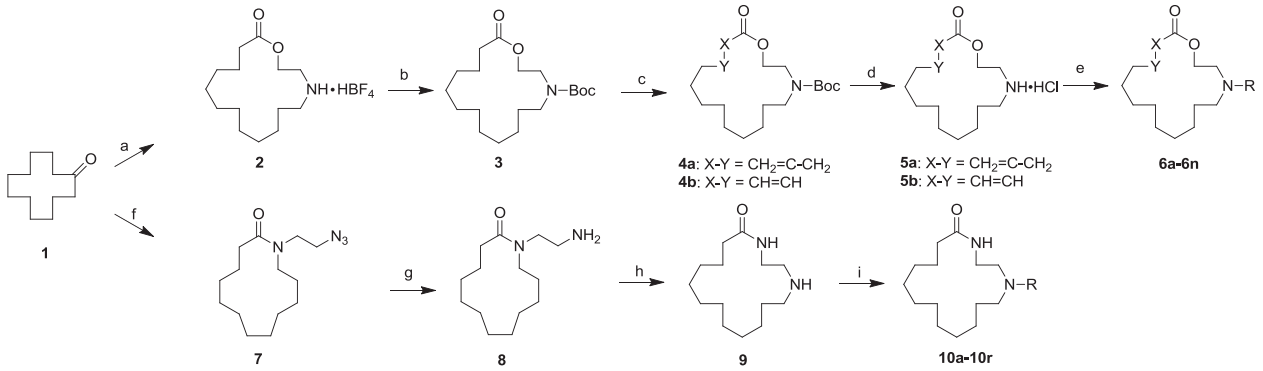


Fig. 1. The saturated azalide 12a-aza-pentadecanelactone tetrafluoroborate.

3. Conclusions

We have, for the first time designed and synthesized a novel double bond-containing azalides, 12a-*N*-substituted-2-methylene-12a-aza-pentadecane-lactones (**6a**–**f**) and 12a-*N*-substituted-12a-aza-2*E*-pentadecenelactones (**6g**–**l**), as well as new azalactams, 12a-*N*-substituted-12a-aza-pentadecanelactam (**10a**–**r**). All of them showed promising antifungal activities against several agricultural pathogens. Among them, the remarkable inhibitory activity of compounds possessing *p*-chlorobenzoyl or α-exomethylene (**6c**, **6d**, **6e**, **6n**, **6g** and **10o**) warrant further structural optimization to identify more potent antifungal agents.



Scheme 1. Synthesis of novel 12a-*N* substituted 16-membered azalides and azalactams. Reagents and conditions: (a) i) 2-Azidoethanol, $BF_3{\cdot}OEt_2$, reflux, 12h, 85%; ii) $NaHCO_3$; (b) i) Na_2CO_3; ii) $(Boc)_2O$, H_2O, 98%; (c) **4a**: i) LDA, THF, −78 °C for 3 h; ii) $(CH_2O)_n$, 40%; **4b**: i) LDA, THF, −78 °C for 2 h; ii) PhSeBr, 63%; iii) H_2O_2, Py, 84%; (d) i) CF_3COOH, r.t. for 3 h; ii) $NaHCO_3$; iii) $HCl{\cdot}OEt_2$, **5a**, 87%; **5b**, 77%; (e) RCl, K_2CO_3, Dry DCM; (f) i) 2-Azidoethanol, $BF_3{\cdot}OEt_2$, reflux, 12h, 94%; ii) NaN_3, DMF, 16h, 85%; (g) i) PPh_3; ii) H_2O, 86%; (h) i) TsOH, Xylene, reflux, 50h; ii) Acetone, KOH, 69%; (i) RCl, K_2CO_3, Dry DCM.

4. Experimental section

4.1. General

Infrared spectra were recorded in potassium bromide disks on a PerkinElmer Spectrum 100 Ft-IR spectrophotometer; the ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 300 MHz NMR spectrometer, chemical shift values were given in δ relative to TMS in $CDCl_3$; TLC was performed on precoated silica gel GF_{254}; column chromatography was performed on silica gel (Merck, 200–300 mesh); mass spectra (MS) was performed on a Agilent 1100 LC–MS instrument with the electrospray ionization (ESI) mode; high-resolution mass spectra (HRMS) were obtained on an Agilent TOF (G1969A) mass spectrometer; elemental analysis was performed on Elementar Vario EL (Germany); melting points were measured on a Cole–Parmer melting-point apparatus and were uncorrected. Unless otherwise indicated, all the materials were obtained from commercially available sources and were used without further purification.

4.2. 12a-Aza-pentadecanelactone tetrafluoroborate (**2**)

Compound **2** was synthesized in 85% yield according to the procedure reported in Ref. [30].

4.3. tert-Butyloxycarbonyl-12a-aza-pentadecanelactone (**3**)

$(Boc)_2O$ (1.20 g, 5.5 mmol) was added dropwise into a solution of 1-oxa-4-azacyclo-hexadecan-16-one (1.20 g, 5 mmol) in water (H_2O, 10 mL), which was obtained from compound **2** by hydrolyzing with saturated Na_2CO_3 solution. The mixture was stirred at room temperature until the reaction was complete, and then extracted with DCM (10 mL × 3). The organic layers were combined and dried over anhydrous sodium sulfate (Na_2SO_4). After the solution was removed by rotary evaporation, the crude mixture was purified by flash column chromatography (200–300 mesh of silica gel, petroleum ether/ethyl acetate, 10:1) to afford the desired compound **3** (1.68 g, 98%) as a colorless liquid. IR ν (KBr, cm^{-1}): 2931, 2860, 1739, 1696, 1459, 1409, 1366, 1158, 774; ^1H NMR (300 MHz, $CDCl_3$): δ 1.30–1.39 (m, 14H), 1.46 (s, 9H), 1.53–1.58 (m, 2H), 1.64–1.71 (m, 2H), 2.34 (t, J = 7.1 Hz, 2H), 3.23–3.24 (m, 2H), 3.45 (s, 2H), 4.22 (t, J = 4.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.95, 25.02, 26.11, 26.14, 26.21, 26.55, 27.28, 28.44, 33.91, 47.05, 48.64, 64.13, 79.59, 173.69; Anal. Calcd. for $C_{19}H_{35}NO_4$: C 66.83, H 10.33, N 4.10. Found: C 66.73, H 10.28, N 4.14.

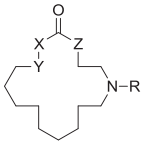
4.4. tert-Butyloxycarbonyl-2-methylene-12a-aza-pentadecanelactone (**4a**)

A solution of compound **3** (13.6 g, 40 mmol) in THF (100 mL) was added dropwise slowly into a solution of LDA (20 mL, 40 mmol) in THF (100 mL) at −78 °C under Ar in 2 h. Another 200 mL of anhydrous THF was added to the mixture under low temperature in 1 h. The formaldehyde gas, depolymerized from 6.00 g (200 mmol) of paraformaldehyde at 180 °C, was bubbled into the reaction mixture at −10 °C by Ar. The mixture was stirred at −10 °C for 1 h and then kept at room temperature overnight. After quenching the reaction by aqueous solution of saturated ammonium chloride (NH_4Cl) (100 mL) at −5 °C, the reaction mixture was poured into separatory funnel and separated. The aqueous layer was extracted with DCM (150 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4 and then evaporated under reduced pressure, the crude product was purified by flash column chromatography (200–300 mesh of silica gel, petroleum ether/ethyl acetate, 30:1) to afford the compound **4a** (5.81 g, 40%) as a colorless liquid. IR ν (KBr, cm^{-1}): 2930, 2860, 1718, 1700, 1629, 1156; ^1H NMR (300 MHz, $CDCl_3$): δ 1.28–1.32 (br, 12H), 1.46–1.55 (m, 13H), 2.36 (t, J = 6.8 Hz, 2H), 3.22 (s, 2H), 3.49 (s, 2H), 4.30 (s, 2H), 5.56 (d, J = 1.2 Hz, 1H), 6.21 (d, J = 1.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.97, 25.61, 25.71, 25.90, 26.07, 26.23, 27.05, 27.42, 27.64, 27.78, 28.04, 28.31, 28.57, 31.09, 47.07, 48.57, 64.49, 79.39, 79.44, 125.65, 140.45, 155.14, 155.52, 167.11; MS (ESI, m/z): 376.2 $[M + Na]^+$.

4.5. tert-Butyloxycarbonyl-12a-aza-2E-pentadecenelactone (**4b**)

A solution of compound **3** (6.8 g, 20 mmol) in THF (20 mL) was added dropwise slowly into a solution of LDA (10 mL, 20 mmol) in THF (20 mL) at −78 °C under Ar in 1 h. A solution of PhSeBr (4.7 g, 20 mmol) in THF (20 mL) was added dropwise into the mixture in 1 h after the mixture was stirred at −78 °C for 1 h. The mixture was stirred at −10 °C for 0.5 h and then kept at room temperature overnight. After quenching the reaction by aqueous solution of saturated NH_4Cl (100 mL) at −5 °C, the reaction mixture was poured into separatory funnel and separated. The aqueous layer was extracted with DCM (50 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4 and then evaporated under reduced pressure, the crude product was purified by flash column chromatography (200–300 mesh of silica gel, toluene/ethyl acetate, 60:1) to afford the compound *tert*-butyl 16-oxo-15-(phenylselanyl)-1-oxa-4-azacyclohexadecane-4-carboxylate (6.30 g, 63%) as a colorless liquid. IR ν (KBr, cm^{-1}): 2929, 2858, 1731, 1696, 1578, 1159; ^1H NMR (300 MHz, $CDCl_3$): δ 1.28–1.31 (br, 12H), 1.37–1.51

Table 1
Structures, inhibition rate and log *P* values of the compounds **6a**–**n** and **10a**–**r** against *S. sclerotiorum*, *P. oryzae*, *B. cinerea*, *R. solani* and *P. capsici* (50 μg/mL).



Comp.	X–Y	A	R	Inhibit. rate (%)					Log *P*[a]
				S. sclerotiorum	*P. oryzae*	*B. cinerea*	*R. solani*	*P. capsici*	
6a	CH_2=C–CH_2	O	$C_6H_5SO_2$	39.01	42.13	22.55	22.32	32.13	5.63
6b	CH_2=C–CH_2	O	*p*-$CH_3C_6H_4SO_2$	32.46	37.88	15.17	18.08	27.66	6.04
6c	CH_2=C–CH_2	O	*p*-$CH_3OC_6H_4SO_2$	65.45	84.68	39.35	4.47	42.74	5.69
6d	CH_2=C–CH_2	O	*p*-$CH_3COC_6H_4SO_2$	55.24	82.55	45.91	5.81	41.62	5.53
6e	CH_2=C–CH_2	O	*m*-$NO_2C_6H_4SO_2$	55.76	81.28	36.48	8.49	45.53	5.57
6f	CH_2=C–CH_2	O	*p*-$NO_2C_6H_4SO_2$	67.80	78.30	34.84	11.61	46.37	5.59
6g	CH_2=C–CH_2	O	*p*-ClC_6H_4CO	75.39	84.68	44.27	35.49	37.43	5.97
6h	CH=CH	O	$C_6H_5SO_2$	45.81	54.90	17.63	33.71	44.70	5.30
6i	CH=CH	O	*p*-$CH_3C_6H_4SO_2$	46.86	44.26	15.17	36.39	27.10	5.75
6j	CH=CH	O	*p*-$CH_3OC_6H_4SO_2$	44.24	47.24	17.63	23.22	42.46	5.36
6k	CH=CH	O	*p*-$CH_3COC_6H_4SO_2$	26.71	41.28	16.81	22.77	32.13	5.20
6l	CH=CH	O	*m*-$NO_2C_6H_4SO_2$	38.22	40.43	12.71	16.97	37.99	5.24
6m	CH=CH	O	*p*-$NO_2C_6H_4SO_2$	36.39	37.88	30.33	26.79	24.31	5.26
6n	CH=CH	O	*p*-ClC_6H_4CO	67.28	64.26	31.15	46.65	52.80	5.64
10a	CH_2–CH_2	N	CH_3SO_2	26.29	2.61	31.58	15.18	5.47	3.27
10b	CH_2–CH_2	N	$C_6H_5SO_2$	14.74	5.22	30.41	15.95	7.03	4.80
10c	CH_2–CH_2	N	*p*-$CH_3C_6H_4SO_2$	21.12	16.09	32.16	37.74	3.52	5.25
10d	CH_2–CH_2	N	*o*-$ClC_6H_4SO_2$	43.03	29.13	20.47	38.52	14.84	5.43
10e	CH_2–CH_2	N	*m*-$ClC_6H_4SO_2$	22.71	3.91	29.82	8.95	3.13	5.46
10f	CH_2–CH_2	N	*p*-$ClC_6H_4SO_2$	28.29	13.48	43.27	35.80	4.30	5.48
10g	CH_2–CH_2	N	*p*-$BrC_6H_4SO_2$	20.72	3.04	39.77	1.56	0.78	5.61
10h	CH_2–CH_2	N	*m*-$NO_2C_6H_4SO_2$	11.16	3.91	35.09	4.67	3.91	4.74
10i	CH_2–CH_2	N	*p*-$NO_2C_6H_4SO_2$	5.58	5.22	34.50	3.89	0.39	4.76
10j	CH_2–CH_2	N	CH_3CO	35.46	9.57	54.39	24.12	2.34	3.25
10k	CH_2–CH_2	N	C_6H_5CO	23.90	21.30	45.61	61.09	9.38	4.46
10l	CH_2–CH_2	N	*p*-$CH_3C_6H_4CO$	39.04	14.35	44.44	51.36	10.16	4.90
10m	CH_2–CH_2	N	*o*-ClC_6H_4CO	38.65	24.35	56.14	3.50	38.28	5.09
10n	CH_2–CH_2	N	*m*-ClC_6H_4CO	54.98	31.30	63.16	66.93	41.02	5.11
10o	CH_2–CH_2	N	*p*-ClC_6H_4CO	61.35	42.17	64.33	78.21	41.80	5.13
10p	CH_2–CH_2	N	*p*-BrC_6H_4CO	48.61	24.35	56.14	65.37	32.03	5.26
10q	CH_2–CH_2	N	*m*-$NO_2C_6H_4CO$	51.39	42.17	53.80	35.02	17.58	4.39
10r	CH_2–CH_2	N	*p*-$NO_2C_6H_4CO$	53.78	56.09	47.37	46.69	22.66	4.41
Chlorothalonil				96.07	84.68	87.81	85.71	85.48	

[a] Log *P*, calculated on http://www.molinspiration.com.

(m, 13H), 1.77–1.81 (m, 1H), 1.96–2.04 (m, 1H), 3.04 (br, 1H), 3.33 (br, 3H), 3.45 (s, 2H), 4.22 (s, 2H), 3.66 (m, 1H), 3.96 (t, J = 5.4 Hz, 2H), 4.29 (s, 2H), 7.27–7.37 (m, 3H), 7.58–7.61 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.89, 26.07, 26.36, 26.61, 28.31, 28.88, 29.36, 31.00, 31.74, 33.98, 38.83, 46.85, 48.22, 64.55, 79.43, 127.71, 128.44, 128.86, 135.67, 155.02, 172.82; MS (ESI, *m*/*z*): 496.2 $[M - H]^-$.

A solution of H_2O_2 (2.4 g, 21 mmol, 30%) was added dropwise into a solution of *tert*-butyl 16-oxo-15-(phenylselanyl)-1-oxa-4-azacyclohexadecane-4-carboxylate (2.09 g, 4.2 mmol) and pyridine (0.66 g, 8.4 mmol) in DCM (15 mL) at 0 °C. The mixture was stirred at room temperature for 3 h. After quenching the reaction by H_2O (10 mL), the reaction mixture was poured into separatory funnel and separated. The aqueous layer was extracted with DCM (10 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4 and then evaporated under reduced pressure, the crude product was purified by flash column chromatography (200–300 mesh of silica gel, petroleum ether/ethyl acetate, 20:1) to afford the compound **4b** (1.20 g, 84%) as a colorless solid. M.p. 38–40 °C; IR ν (KBr, cm^{-1}): 2931, 2858, 1724, 1697, 1655, 1159; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30 (br, 10H), 1.44–1.56 (m, 13H), 2.24–2.31 (m, 2H), 3.20 (s, 2H), 3.47–3.53 (m, 2H), 4.30 (s, 2H), 5.84–5.90 (m, 1H), 6.89–6.99 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.08, 25.29, 25.46, 26.40, 26.48, 27.80, 28.24, 30.70, 47.17, 49.49, 64.71, 79.27, 122.04, 149.45, 155.19, 155.41, 165.77; MS (ESI, *m*/*z*): 362.2 $[M + Na]^+$, HRMS (*m*/*z*) calcd for $C_{19}H_{34}NO_4$ $[M + H]^+$ 340.24824, found 340.24774.

4.6. 2-Methylene-12a-aza-pentadecanelactone hydrochloride (*5a*)

CF_3COOH (8.80 g, 77 mmol) was added dropwise into a solution of compound **4a** (5.40 g, 15 mmol) in DCM (30 mL) at room temperature. After the mixture was stirred for 3 h, a solution of saturated sodium bicarbonate ($NaHCO_3$) was added into the reaction mixture to make the solution to be basic after evaporating of CF_3COOH in vacuum. The aqueous layer was extracted with DCM (50 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4 and then evaporated under reduced pressure to give 15-methylene-1-oxa-4-azacyclohexadecan-16-one (3.70 g, 95%) as a light yellow solid. The ethereal hydrogen chloride (3 mL) was added into a solution of 15-methylene-1-oxa-4-azacyclohexadecan-16-one (0.40 g, 1.7 mmol) in anhydrous diethyl ether (Et_2O, 10 mL) at room temperature. The precipitate was dried to give compound **5a** (0.41 g, 89%) as a white solid. M.p. 135–136 °C. IR ν (KBr, cm^{-1}): 2932, 2858, 1701, 1626, 1146; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30–1.33 (m, 10H), 1.46–1.52 (m, 4H), 1.86–1.91 (m, 2H), 2.38 (t, J = 7.0 Hz, 2H), 3.05 (s, 2H), 3.39 (s, 2H), 4.58 (t,

J = 4.2 Hz, 2H), 5.62 (d, J = 1.0 Hz, 1H), 6.35 (br, s, 1H), 9.80 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.51, 24.72, 25.52, 25.58, 25.74, 25.82, 25.87, 26.42, 31.05, 44.89, 46.17, 59.81, 126.93, 139.49, 166.59; MS (ESI, m/z): 254.1 [M − Cl]$^+$; HRMS (m/z) calcd for $C_{15}H_{28}NO_2$ [M − Cl]$^+$ 254.21146, found 254.21133.

4.7. 12a-Aza-2E-pentadecenelactone hydrochloride (**5b**)

CF_3COOH (2.00 g, 18 mmol) was added dropwise into a solution of compound **4b** (1.20 g, 3.5 mmol) in DCM (5 mL) at room temperature. After the mixture was stirred for 3 h, a saturated aqueous solution of $NaHCO_3$ was added into the reaction mixture to make the solution to be basic. The aqueous layer was extracted with DCM (15 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4 and then evaporated under reduced pressure to give 12a-aza-2*E*-pentadecenelactone (0.75 g, 90%) as a light yellow viscous liquid. The ethereal hydrogen chloride (3 mL) was added into a solution of 12a-aza-2*E*-pentadecenelactone (0.40 g, 1.7 mmol) in anhydrous Et_2O (10 mL) at room temperature. The precipitate was dried to give compound **5b** (0.39 g, 89%) as a white solid. M.p. 168–169 °C. IR ν (KBr, cm^{-1}): 2936, 2858, 1719, 1642, 1250; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25–1.44 (m, 10H), 1.51–1.59 (m, 2H), 1.79–1.89 (m, 2H), 2.26–2.32 (m, 2H), 3.11–3.13 (m, 2H), 3.37 (s, 2H), 4.61 (t, J = 4.3 Hz, 2H), 5.86 (d, J = 15.7 Hz, 1H), 7.02–7.12 (m, 1H), 9.80 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.64, 24.74, 24.89, 25.18, 25.40, 25.99, 30.98, 44.39, 46.53, 59.58, 121.21, 151.36, 164.74; MS (ESI, m/z): 240.1 [M − Cl]$^+$; HRMS (m/z) calcd for $C_{14}H_{27}NO_2$ [M − Cl]$^+$ 240.19581, found 240.19574.

4.8. General procedure for the preparation of title compounds **6a**–**n**

Substituted sulfonyl chlorides/acyl chlorides (0.8 mmol) were added dropwise into a suspension of compound **5a** or **5b** (0.4 mmol), K_2CO_3 (0.12 g, 0.8 mmol) and DCM (10 mL) at room temperature. The mixture was stirred and monitored by TLC till TLC (petroleum ether/ethyl acetate, 5:1) showed the reaction was complete. After removal of the insoluble solid by filter, the solvent was purified by flash column chromatography (200–300 mesh of silica gel, petroleum ether/ethyl acetate, 5:1) to yield the title compounds **6a**–**n**.

4.8.1. 12a-N-(Phenylsulfonyl)-2-methylene-12a-aza-pentadecanelactone (**6a**)

Light yellow liquid (80% yield); IR ν (KBr, cm^{-1}): 2930, 2859, 1716, 1628, 1600, 1343, 1170; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28–1.32 (br, 12H), 1.47–1.64 (m, 4H), 2.32–2.36 (m, 2H), 3.15 (t, J = 7.6 Hz, 2H), 3.43 (t, J = 5.1 Hz, 2H), 4.35 (t, J = 4.9 Hz, 2H), 5.56 (d, J = 1.4 Hz, 1H), 6.19 (d, J = 1.4 Hz, 1H), 7.49–7.62 (m, 3H), 7.81–7.84 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.87, 25.70, 25.79, 26.06, 26.68, 26.70, 27.94, 31.18, 47.93, 49.96, 64.06, 126.13, 127.09, 129.09, 132.53, 139.27, 140.30, 167.17; MS (ESI, m/z): 392.2 [M − H]$^-$; HRMS (m/z) calcd for $C_{21}H_{32}NO_4S$ [M + H]$^+$ 394.20466, found 394.20395.

4.8.2. 12a-N-((4-Methylphenyl)sulfonyl)-2-methylene-12a-aza-pentadecanelactone (**6b**)

Light yellow liquid (79% yield); IR ν (KBr, cm^{-1}): 2930, 2859, 1718, 1628, 1598, 1341, 1170; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26–1.30 (br, 12H), 1.4–1.54 (m, 4H), 2.32 (t, J = 6.7 Hz, 2H), 2.41 (s, 3H), 3.11 (t, J = 7.5 Hz, 2H), 3.38 (t, J = 5.1 Hz, 2H), 4.33 (t, J = 4.9 Hz, 2H), 5.54 (d, J = 1.4 Hz, 1H), 6.17 (d, J = 1.4 Hz, 1H), 7.29 (d, J = 8.0 Hz, 2H), 7.67–7.70 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.36, 24.81, 25.63, 25.65, 25.73, 25.99, 26.61, 26.64, 27.89, 31.11, 47.86, 49.87, 64.02, 125.97, 127.07, 129.61, 136.17, 140.27, 143.21, 167.06; MS (ESI, m/z): 408.2 [M + H]$^+$; HRMS (m/z) calcd for $C_{22}H_{34}NO_4S$ [M + H]$^+$ 408.22031, found 408.21970.

4.8.3. 12a-N-((4-Methoxyphenyl)sulfonyl)-2-methylene-12a-aza-pentadecanelactone (**6c**)

White solid (67% yield); m.p.: 73–74 °C; IR ν (KBr, cm^{-1}): 2928, 2859, 1715, 1636, 1598, 1338, 1160; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27–1.31 (br, 12H), 1.46–1.57 (m, 4H), 2.31–2.36 (m, 2H), 3.11 (t, J = 7.5 Hz, 2H), 3.39 (t, J = 5.1 Hz, 2H), 3.87 (s, 3H), 4.34 (t, J = 4.9 Hz, 2H), 5.56 (d, J = 1.4 Hz, 1H), 6.19 (d, J = 1.4 Hz, 1H), 6.95–7.00 (m, 2H), 7.72–7.77 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.75, 25.57, 25.60, 25.68, 25.93, 26.54, 26.58, 27.81, 29.46, 31.03, 47.76, 49.75, 55.40, 63.95, 114.07, 125.83, 129.03, 130.66, 140.22, 162.64, 166.92; MS (ESI, m/z): 424.2 [M + H]$^+$; HRMS (m/z) calcd for $C_{22}H_{34}NO_5S$ [M + H]$^+$ 424.21522, found 424.21457.

4.8.4. 12a-N-((4-Acetylphenyl)sulfonyl)-2-methylene-12a-aza-pentadecanelactone (**6d**)

Light yellow liquid (59% yield); IR ν (KBr, cm^{-1}): 2930, 2859, 1716, 1693, 1629, 1596, 1345, 1163; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27–1.31 (br, 12H), 1.46–1.58 (m, 4H), 2.33 (t, J = 6.7 Hz, 2H), 2.66 (s, 3H), 3.17 (t, J = 7.5 Hz, 2H), 3.45 (t, J = 5.0 Hz, 2H), 4.35 (t, J = 4.8 Hz, 2H), 5.57 (d, J = 1.4 Hz, 1H), 6.18 (d, J = 1.4 Hz, 1H), 7.90–7.93 (m, 2H), 8.06–8.10 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.67, 25.50, 25.55, 25.62, 25.83, 26.45, 26.49, 26.63, 27.79, 30.95, 47.80, 49.82, 63.70, 125.98, 127.15, 128.79, 139.69, 140.08, 143.03, 166.84, 196.48; MS (ESI, m/z): 436.2 [M + H]$^+$; HRMS (m/z) calcd for $C_{23}H_{34}NO_5S$ [M + H]$^+$ 436.21522, found 436.21457.

4.8.5. 12a-N-((3-Nitrophenyl)sulfonyl)-2-methylene-12a-aza-pentadecanelactone (**6e**)

White solid (69% yield); m.p.: 67–68 °C; IR ν (KBr, cm^{-1}): 2928, 2858, 1717, 1630, 1536, 1349, 1168; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28–1.33 (br, 12H), 1.46–1.60 (m, 4H), 2.34 (t, J = 6.2 Hz, 2H), 3.22 (t, J = 7.6 Hz, 2H), 3.49 (t, J = 5.1 Hz, 2H), 4.37 (t, J = 4.9 Hz, 2H), 5.57 (d, J = 1.4 Hz, 1H), 6.19 (d, J = 1.4 Hz, 1H), 7.74 (t, J = 8.0 Hz, 1H), 8.14–8.17 (m, 1H), 8.42–8.46 (m, 1H), 8.64–8.66 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.90, 24.99, 25.16, 25.24, 26.60, 26.83, 29.00, 30.60, 47.77, 50.45, 64.71, 121.51, 122.10, 126.97, 130.54, 132.48, 141.83, 148.32, 150.40, 165.66; MS (ESI, m/z): 439.2 [M + H]$^+$; HRMS (m/z) calcd for $C_{21}H_{31}N_2O_6S$ [M + H]$^+$ 439.18973, found 439.18900.

4.8.6. 12a-N-((4-Nitrophenyl)sulfonyl)-2-methylene-12a-aza-pentadecanelactone (**6f**)

White solid (80% yield); m.p.: 62–63 °C; IR ν (KBr, cm^{-1}): 2928, 2860, 1707, 1623, 1530, 1348, 1168; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29–1.31 (br, 12H), 1.46–1.62 (m, 4H), 2.31–2.36 (m, 2H), 3.20 (t, J = 7.5 Hz, 2H), 3.48 (t, J = 5.1 Hz, 2H), 4.36 (t, J = 4.9 Hz, 2H), 5.58 (d, J = 1.4 Hz, 1H), 6.19 (d, J = 1.4 Hz, 1H), 8.00–8.03 (m, 2H), 8.35–8.38 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.78, 25.62, 25.67, 25.75, 25.93, 26.53, 26.64, 27.89, 31.06, 47.97, 50.01, 63.67, 124.34, 126.23, 128.22, 140.16, 145.26, 149.90, 166.95; MS (ESI, m/z): 437.1 [M − H]$^-$; HRMS (m/z) calcd for $C_{21}H_{31}N_2O_6S$ [M + H]$^+$ 439.18973, found 439.18918.

4.8.7. 12a-N-(4-Chlorobenzoyl)-2-methylene-12a-aza-pentadecanelactone (**6g**)

Light yellow liquid (78% yield); IR ν (KBr, cm^{-1}): 2930, 2859, 1718, 1638, 1597, 1165; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26–1.32 (br, 14H), 1.46–1.56 (m, 4H), 2.38 (t, J = 6.7 Hz, 2H), 3.22–3.75 (m, 4H), 4.20–4.51 (m, 2H), 5.58 (d, J = 1.1 Hz, 1H), 6.20 (s, 1H), 7.30–7.40 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.82, 25.43, 25.66, 25.69, 25.88, 26.06, 26.26, 26.92, 27.25, 31.10, 45.56, 50.54, 63.53, 125.71, 127.88, 128.34, 134.88, 135.27, 140.28, 166.91, 170.73; MS (ESI, m/z): 392.2 [M + H]$^+$; HRMS (m/z) calcd for $C_{22}H_{31}ClNO_3$ [M + H]$^+$ 392.19870, found 392.19855.

4.8.8. 12a-N-(Phenylsulfonyl)-12a-aza-2E-pentadecenelactone (**6h**)

White solid (86% yield); m.p.: 64–65 °C; IR ν (KBr, cm^{-1}): 2936, 2861, 1725, 1657, 1600, 1338, 1162; ^1H NMR (300 MHz, $CDCl_3$): δ 1.18–1.26 (br, 10H), 1.46–1.60 (m, 4H), 2.24–2.30 (m, 2H), 3.15–3.20 (m, 2H), 3.44–3.46 (m, 2H), 4.33–4.36 (m, 2H), 5.80–5.87 (m, 1H), 6.87–6.95 (m, 1H), 7.49–7.59 (m, 3H), 7.80–7.83 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.93, 25.06, 25.19, 25.25, 26.61, 26.93, 29.05, 30.56, 47.66, 50.27, 64.97, 121.68, 126.97, 129.03, 132.46, 139.33, 149.97, 165.74; MS (ESI, *m*/*z*): 378.1 $[M - H]^-$; HRMS (*m*/*z*) calcd for $C_{20}H_{30}NO_4S$ $[M + H]^+$ 380.18901, found 380.18884.

4.8.9. 12a-N-((4-Methylphenyl)sulfonyl)-12a-aza-2E-pentadecenelactone (**6i**)

White solid (82% yield); m.p.: 91–92 °C; IR ν (KBr, cm^{-1}): 2931, 2855, 1721, 1654, 1600, 1336, 1157; ^1H NMR (300 MHz, $CDCl_3$): δ 1.17–1.26 (br, 10H), 1.45–1.59 (m, 4H), 2.24–2.30 (m, 2H), 2.43 (s, 3H), 3.15 (t, J = 8.0 Hz, 2H), 3.42 (t, J = 4.4 Hz, 2H), 4.34 (t, J = 4.3 Hz, 2H), 5.84 (d, J = 15.7 Hz, 1H), 6.88–6.98 (m, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.69 (d, J = 8.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.43, 24.98, 25.13, 25.26, 25.30, 26.66, 26.99, 29.12, 30.63, 47.69, 50.31, 65.07, 121.76, 127.09, 129.68, 136.41, 143.25, 150.01, 165.85; MS (ESI, *m*/*z*): 394.2 $[M + H]^+$; HRMS (*m*/*z*) calcd for $C_{21}H_{32}NO_4S$ $[M + H]^+$ 394.20466, found 394.20407.

4.8.10. 12a-N-4-((4-Methoxyphenyl)sulfonyl)-12a-aza-2E-pentadecenelactone (**6j**)

White solid (45% yield); m.p.: 79–80 °C; IR ν (KBr, cm^{-1}): 2927, 2863, 1717, 1651, 1597, 1336, 1150; ^1H NMR (300 MHz, $CDCl_3$): δ 1.18–1.26 (br, 10H), 1.45–1.57 (m, 4H), 2.24–2.30 (m, 2H), 2.66 (s, 3H), 3.20 (t, J = 8.0 Hz, 2H), 3.47 (t, J = 4.4 Hz, 2H), 4.34–4.36 (m, 2H), 5.81–5.87 (m, 1H), 6.88–6.98 (m, 1H), 7.88–7.92 (m, 2H), 8.07–8.10 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.92, 25.07, 25.22, 25.24, 26.61, 26.96, 29.09, 30.58, 47.62, 50.25, 55.51, 65.01, 114.17, 121.70, 129.11, 130.92, 149.97, 162.72, 165.82; MS (ESI, *m*/*z*): 410.1 $[M + H]^+$; HRMS (*m*/*z*) calcd for $C_{21}H_{32}NO_5S$ $[M + H]^+$ 410.19957, found 410.19928.

4.8.11. 12a-N-4-((4-Acetylphenyl)sulfonyl)-12a-aza-2E-pentadecenelactone (**6k**)

White solid (57% yield); m.p.: 95–96 °C; IR ν (KBr, cm^{-1}): 2932, 2858, 1710, 1691, 1653, 1596, 1346, 1159; ^1H NMR (300 MHz, $CDCl_3$): δ 1.18–1.26 (br, 10H), 1.45–1.57 (m, 4H), 2.24–2.30 (m, 2H), 2.66 (s, 3H), 3.20 (t, J = 8.0 Hz, 2H), 3.47 (t, J = 4.4 Hz, 2H), 4.34–4.37 (m, 2H), 5.82–5.87 (m, 1H), 6.88–6.98 (m, 1H), 7.88–7.92 (m, 2H), 8.07–8.10 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.94, 25.06, 25.19, 25.28, 26.63, 26.75, 26.89, 28.97, 30.59, 47.67, 50.30, 64.90, 121.63, 127.27, 128.92, 139.87, 143.41, 150.19, 165.71, 196.59; MS (ESI, *m*/*z*): 422.2 $[M + H]^+$; HRMS (*m*/*z*) calcd for $C_{22}H_{32}NO_5S$ $[M + H]^+$ 422.19957, found 422.19919.

4.8.12. 12a-N-4-((3-Nitrophenyl)sulfonyl)-12a-aza-2E-pentadecenelactone (**6l**)

White solid (84% yield); m.p.: 88–89 °C; IR ν (KBr, cm^{-1}): 2934, 2859, 1718, 1656, 1608, 1536, 1354, 1166; ^1H NMR (300 MHz, $CDCl_3$): δ 1.22–1.26 (br, 10H), 1.53–1.59 (m, 4H), 2.27–2.29 (m, 2H), 3.21–3.27 (m, 2H), 3.49–3.52 (m, 2H), 4.36–4.39 (m, 2H), 5.82–5.87 (m, 1H), 6.92–6.97 (m, 1H), 7.76 (t, J = 7.9 Hz, 1H), 8.13–8.16 (m, 1H), 8.42–8.46 (m, 1H), 8.64–8.66 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.90, 24.99, 25.16, 25.24, 26.60, 26.83, 29.00, 30.60, 47.77, 50.45, 64.71, 121.51, 122.09, 126.97, 130.54, 132.48, 141.83, 148.32, 150.39, 165.66; MS (ESI, *m*/*z*): 425.1 $[M + H]^+$; HRMS (*m*/*z*) calcd for $C_{20}H_{29}N_2O_6S$ $[M + H]^+$ 425.17408, found 425.17346.

4.8.13. 12a-N-4-((4-Nitrophenyl)sulfonyl)-12a-aza-2E-pentadecenelactone (**6m**)

White solid (83% yield); m.p.: 120–122 °C; IR ν (KBr, cm^{-1}): 2938, 2859, 1703, 1653, 1605, 1531, 1347, 1162; ^1H NMR (300 MHz, $CDCl_3$): δ 1.18–1.26 (br, 10H), 1.46–1.60 (m, 4H), 2.25–2.31 (m, 2H), 3.23 (t, J = 8.1 Hz, 2H), 3.50 (t, J = 4.4 Hz, 2H), 4.36 (t, J = 4.3 Hz, 2H), 5.84 (d, J = 15.7 Hz, 1H), 6.89–6.99 (m, 1H), 7.98–8.02 (m, 2H), 8.36–8.39 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.91, 25.01, 25.15, 25.25, 26.61, 26.83, 28.92, 30.58, 47.70, 50.35, 64.76, 121.53, 124.37, 128.19, 145.41, 149.93, 150.37, 165.63; MS (ESI, *m*/*z*): 425.1 $[M + H]^+$; HRMS (*m*/*z*) calcd for $C_{20}H_{29}N_2O_6S$ $[M + H]^+$ 425.17408, found 425.17399.

4.8.14. 12a-N-4-(4-Chlorobenzoyl)-12a-aza-2E-pentadecenelactone (**6n**)

White solid (39% yield); m.p.: 67–68 °C; IR ν (KBr, cm^{-1}): 2934, 2857, 1726, 1660, 1630, 1600; ^1H NMR (300 MHz, $CDCl_3$): δ 1.09–1.27 (br, 10H), 1.54 (br, 4H), 2.28 (br, 2H), 3.25–3.79 (br, 4H), 4.22–4.52 (br, 2H), 5.88 (d, J = 15.6 Hz, 1H), 6.91–7.01 (m, 1H), 7.32–7.40 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.97, 20.78, 24.56, 25.10, 25.28, 26.42, 28.15, 30.48, 44.78, 44.81, 50.55, 63.81, 121.84, 127.76, 128.50, 134.92, 135.16, 149.94, 165.57, 170.64, 170.77; MS (ESI, *m*/*z*): 378.1 $[M + H]^+$; HRMS (*m*/*z*) calcd for $C_{21}H_{29}ClNO_3$ $[M + H]^+$ 378.18305, found 378.18289.

4.9. N-(2-Azidoethyl)laurolactam (**7**)

2-Azidoethanol (10.4 g, 120 mmol) was added dropwise to a solution of $BF_3 \cdot Et_2O$ (31.8 g, 220 mmol, 47%) and cyclododecanone (18.2 g, 100 mmol) in 250 mL three-necked flask under stirring at 35 °C for 1 h. The solution was then heated up to 65 °C in 1 h and stirred for 12 h. After cooling to room temperature, the reaction mixture was washed with anhydrous Et_2O (50 mL × 3) and the lower light yellow viscous liquid was separated. After DCM (50 mL) was added, the mixture was washed with distilled H_2O (30 mL × 3). The organic layer was dried over anhydrous Na_2SO_4 and then separated and evaporated to dryness to give the intermediate, iminium ether fluoroborate (29.1 g, 94%) as a yellow viscous liquid. ^1H NMR (300 MHz, $CDCl_3$): δ 1.34–1.39 (br, 14H), 1.83–1.85 (br, 4H), 2.81 (t, J = 7.0 Hz, 2H), 3.79 (t, J = 6.5 Hz, 2H), 4.24 (t, J = 10.0 Hz, 2H), 5.02 (t, J = 10.2 Hz, 2H).

NaN_3 (12.1 g, 190 mmol) was added in portion to a solution of iminium ether fluoroborate (51.8 g, 170 mmol) in anhydrous DMF (200 mL). The reaction mixture was stirred at room temperature for 0.5 h and then kept at 70 °C for 16 h. After cooling to room temperature, the reaction solution was diluted with H_2O (150 mL), then extracted with Et_2O (100 mL × 4). The combined organic layers were dried over anhydrous Na_2SO_4. After the solution was removed by rotary evaporation, the crude mixture was purified by flash column chromatography (200–300 mesh of silica gel, petroleum ether/ethyl acetate, 2:1) to afford the desired compound **7** (37.8 g, 85%) as a light yellow liquid. ^1H NMR (300 MHz, $CDCl_3$): δ 1.32–1.43 (br, 16H), 1.65–1.80 (m, 4H), 2.31–2.36 (m, 2H), 3.32–3.38 (m, 2H), 3.43–3.51 (m, 4H).

4.10. N-(2-Aminoethyl)laurolactam (**8**)

PPh_3 (8.0 g, 31 mmol) was added in portions to a solution of the compound **7** (7.9 g, 30 mmol) in anhydrous THF (20 mL). The reaction mixture was stirred at room temperature for 5 h. H_2O (10 mL) was added into the reaction mixture, then stirred at room temperature for 5 h. Et_2O (10 mL) was added and the insoluble solid was filtered. The filter was dried over anhydrous Na_2CO_3. The solution was removed by rotary evaporation to afford the desired compound **8** (6.5 g, 90%) as a light yellow liquid. ^1H NMR (300 MHz,

$CDCl_3$): δ 1.22–1.44 (br, 14H), 1.64–1.80 (m, 4H), 2.31–2.36 (m, 2H), 2.83–2.89 (m, 2H), 3.35–3.42 (m, 2H), 3.63–3.73 (m, 2H).

4.11. 12a-Aza-pentadecanelactam (**9**)

TsOH (0.09 g, 0.5 mmol) was added into a solution of the compound **8** (6.5 g, 27 mmol) in xylene (30 mL), and the mixture was stirred for 50 h under refluxing and Argon conditions. After removal of xylene by evaporation, a brown liquid was obtained and then dissolved in acetone (15 mL). After KOH solution (20 mL, 2 mol/L) was added, the mixture was stirred at room temperature for 7 h. The acetone was stripped by rotary evaporation, and the aqueous layer was extracted with DCM (20 mL). The organic layers were dried over anhydrous Na_2SO_4. After the solution was removed by rotary evaporation, the crude mixture was purified by flash column chromatography (200–300 mesh of silica gel, $CHCl_3$/CH_3OH/NH_4OH, 9:1:1) to afford the desired compound **9** (4.1 g, 69%) as a light yellow solid. M.p.: 78–81 °C; IR ν (KBr, cm^{-1}): 3327, 3288, 2926, 2858, 1631, 1553, 1461; ^1H NMR (300 MHz, $CDCl_3$): δ 1.24–1.50 (br, 16H), 1.62–1.69 (m, 2H), 2.22 (t, $J = 6.6$ Hz, 2H), 2.62 (t, $J = 5.5$ Hz, 2H), 2.76 (t, $J = 5.6$ Hz, 2H), 3.32–3.38 (m, 2H), 6.33 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.10, 25.18, 25.96, 26.12, 26.39, 26.63, 26.71, 27.32, 28.74, 36.17, 38.57, 47.58, 48.01, 173.24. MS (ESI, *m*/*z*): 241.0 $[M + H]^+$, HRMS (*m*/*z*) calcd for $C_{14}H_{28}N_2O$ $[M + H]^+$ 241.22744, found 241.22723.

4.12. General procedure for the preparation of title compounds **10a–r**

The sulfonyl chlorides/acyl chlorides (1.2 mmol) was added dropwise into a suspension of compound **9** (0.9 mmol) and K_2CO_3 (0.27 g, 2.0 mmol) in DCM (10 mL) at room temperature. The mixture was stirred until TLC ($CHCl_3$/CH_3OH, 9:1) showed the reaction was complete. After removal of the insoluble solid through filtering, the residue was purified by flash column chromatography (200–300 mesh of silica gel, petroleum ether/ethyl acetate, 1:2) to yield the title compounds **10a–r**.

4.12.1. 12a-N-(Methylsulfonyl)-12a-aza-pentadecanelactam (**10a**)

White solid (86% yield); m.p.: 127–128 °C; IR ν (KBr, cm^{-1}): 3337, 2928, 2859, 1645, 1532, 1459, 1367, 1329, 1140; ^1H NMR (300 MHz, $CDCl_3$): δ 1.26–1.38 (br, 16H), 1.59–1.69 (m, 4H), 2.23 (t, $J = 6.4$ Hz, 2H), 2.84 (s, 3H), 3.19 (t, $J = 7.0$ Hz, 2H), 3.28–3.34 (m, 2H), 3.46–3.52 (m, 2H), 6.22 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.52, 24.90, 25.89, 26.10, 26.29, 26.46, 26.73, 27.10, 28.79, 35.81, 39.53, 48.70, 50.80, 173.96; Anal. Calcd. for $C_{15}H_{30}N_2O_3S$: C 56.57, H 9.49, N 8.80. Found: C 56.55, H 9.49, N 8.86.

4.12.2. 12a-N-(Phenylsulfonyl)-12a-aza-pentadecanelactam (**10b**)

White solid (63% yield); m.p.: 117–118 °C; IR ν (KBr, cm^{-1}): 3375, 2933, 2855, 1640, 1530, 1463, 1331, 1156, 730, 694; ^1H NMR (300 MHz, $CDCl_3$): δ 1.34–1.38 (br, 14H), 1.56–1.61 (m, 2H), 1.66–1.71 (m, 2H), 2.26 (t, $J = 6.3$ Hz, 2H), 3.08–3.16 (m, 4H), 3.46–3.51 (m, 2H), 6.33 (s, 1H), 7.52–7.62 (m, 3H), 7.78–7.81 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.31, 24.85, 25.63, 25.74, 26.08, 26.15, 26.58, 26.82, 28.69, 35.69, 38.95, 48.63, 51.05, 127.02, 129.05, 132.68, 137.55, 173.43; Anal. Calcd. for $C_{20}H_{32}N_2O_3S$: C 63.12, H 8.48, N 7.36. Found: C 63.14, H 8.47, N 7.40.

4.12.3. 12a-N-((4-Methylphenyl)sulfonyl)-12a-aza-pentadecanelactam (**10c**)

White solid (61% yield); m.p.: 118–119 °C; IR ν (KBr, cm^{-1}): 3341, 2927, 2862, 1641, 1533, 1458, 1342, 1160, 807; ^1H NMR (300 MHz, $CDCl_3$): δ 1.34–1.38 (br, 14H), 1.56–1.58 (m, 2H), 1.64–1.70 (m, 2H), 2.25 (t, $J = 7.5$ Hz, 2H), 2.44 (s, 3H), 3.06–3.13 (m, 4H), 3.45–3.49 (m, 2H), 6.32 (s, 1H), 7.33 (d, $J = 8.0$ Hz, 2H), 7.66–7.69 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.49, 24.54, 25.12, 25.90, 26.00, 26.36, 26.41, 26.82, 27.08, 28.98, 35.93, 39.16, 48.90, 51.30, 127.29, 129.84, 134.83, 143.71, 173.59; Anal. Calcd. for $C_{21}H_{34}N_2O_3S$: C 63.92, H 8.69, N 7.10. Found: C 63.84, H 8.69, N 7.14.

4.12.4. 12a-N-((2-Chlorophenyl)sulfonyl)-12a-aza-pentadecanelactam (**10d**)

Light yellow liquid (71% yield); IR ν (KBr, cm^{-1}): 3300, 2931, 2858, 1650, 1538, 1455, 1336, 1158, 760; ^1H NMR (300 MHz, $CDCl_3$): δ 1.26–1.34 (br, 15H), 1.55–1.71 (m, 4H), 2.22–2.27 (m, 2H), 3.33–3.38 (m, 4H), 3.43–3.48 (m, 2H), 6.38 (s, 1H), 7.39–7.45 (m, 1H), 7.48–7.56 (m, 2H), 8.05–8.09 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.32, 24.66, 25.74, 25.89, 26.12, 26.33, 26.69, 26.89, 28.25, 35.59, 38.69, 47.71, 49.99, 126.95, 131.71, 131.87, 132.00, 133.57, 136.81,173.44; HRMS (*m*/*z*) calcd for $C_{20}H_{31}ClN_2O_3S$ $[M + H]^+$ 415.18167, found 415.18207.

4.12.5. 12a-N-((3-Chlorophenyl)sulfonyl)-12a-aza-pentadecanelactam (**10e**)

White solid (87% yield); m.p.: 126–127 °C; IR ν (KBr, cm^{-1}): 3332, 2931, 2858, 1644, 1543, 1464, 1340, 1165, 875, 689; ^1H NMR (300 MHz, $CDCl_3$): δ 1.34 (br, 14H), 1.58–1.71 (m, 4H), 2.26 (t, $J = 6.3$ Hz, 2H), 3.10–3.19 (m, 4H), 3.47–3.52 (m, 2H), 6.23 (br, 1H), 7.26–7.49 (m, 1H), 7.51–7.61 (m, 1H), 7.66–7.70 (m, 1H), 7.78–7.79 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.48, 25.08, 25.95, 26.07, 26.31, 26.41, 26.84, 27.10, 28.86, 35.87, 39.18, 48.94, 51.28, 125.31, 127.29, 130.53, 132.99, 135.58, 139.82, 173.63; Anal. Calcd. for $C_{20}H_{31}ClN_2O_3S$: C 57.88, H 7.53, N 6.75. Found: C 57.89, H 7.55, N 6.77.

4.12.6. 12a-N-((4-Chlorophenyl)sulfonyl)-12a-aza-pentadecanelactam (**10f**)

White solid (42% yield); m.p.: 162–163 °C; IR ν (KBr, cm^{-1}): 3320, 2933, 2859, 1620, 1551, 1473, 1341, 1156, 1090, 828; ^1H NMR (300 MHz, $CDCl_3$): δ 1.34 (br, 14H), 1.56–1.63 (m, 2H) 1.66–1.70 (m, 2H), 2.26 (t, $J = 6.2$ Hz, 2H), 3.07–3.16 (m, 4H), 3.46–3.52 (m, 2H), 6.25 (s, 1H), 7.50–7.55 (m, 2H), 7.71–7.76 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.48, 25.09, 25.94, 26.04, 26.30, 26.40, 26.83, 27.10, 28.86, 35.89, 39.16, 48.93, 51.28, 128.66, 129.57, 136.46, 139.50, 173.58; Anal. Calcd. for $C_{20}H_{31}ClN_2O_3S$: C 57.88, H 7.53, N 6.75. Found: C 57.70, H 7.56, N 6.76.

4.12.7. 12a-N-((4-Bromophenyl)sulfonyl)-12a-aza-pentadecanelactam (**10g**)

White solid (77% yield); m.p.: 165–165 °C; IR ν (KBr, cm^{-1}): 3318, 2933, 2858, 1650, 1573, 1551, 1467, 1341, 1150, 1087, 824; ^1H NMR (300 MHz, $CDCl_3$): δ 1.34 (br, 14H), 1.57–1.60 (m, 2H), 1.64–1.70 (m, 2H), 2.25 (t, $J = 6.4$ Hz, 2H), 3.07–3.16 (m, 4H), 3.46–3.52 (m, 2H), 6.21 (s, 1H), 7.64–7.71 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.48, 25.09, 25.94, 26.04, 26.30, 26.40, 26.83, 27.10, 28.85, 35.89, 39.16, 48.93, 51.27, 127.94, 128.75. 132.56, 136.99, 173.58; Anal. Calcd. for $C_{20}H_{31}BrN_2O_3S$: C 52.28, H 6.80, N 6.10. Found: C 52.23, H 6.80, N 6.11.

4.12.8. 12a-N-((3-Nitrophenyl)sulfonyl)-12a-aza-pentadecanelactam (**10h**)

White solid (81% yield); m.p.: 140–141 °C; IR ν (KBr, cm^{-1}): 3297, 2931, 2862, 1636, 1563, 1537, 1467, 1340, 1173, 1071, 738; ^1H NMR (300 MHz, $CDCl_3$): δ 1.35 (br, 14H), 1.59–1.71 (m, 4H), 2.27 (t, $J = 6.2$ Hz, 2H), 3.15–3.24 (m, 4H), 3.50–3.55 (m, 2H), 6.21 (s, 1H), 7.79 (t, $J = 8.0$ Hz, 1H), 8.13 (d, $J = 7.8$ Hz, 1H), 8.48 (d, $J = 8.2$ Hz, 1H), 8.64 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.35, 24.95, 25.92, 26.03, 26.16, 26.34, 26.80, 27.05, 28.57, 35.79, 39.13, 48.87, 51.12, 122.30,

127.27, 130.66, 132.65, 140.47, 148.46, 173.62; Anal. Calcd. for $C_{20}H_{31}N_3O_5S$: C 56.45, H 7.34, N 9.87. Found: C 56.43, H 7.32, N 9.96.

4.12.9. 12a-N-((4-Nitrophenyl)sulfonyl)-12a-aza-pentadecanelactam (**10i**)

White solid (81% yield); m.p.: 176–177 °C; IR ν (KBr, cm^{-1}): 3315, 2935, 2860, 1639, 1560, 1457, 1346, 1157, 1087, 856; ^1H NMR (300 MHz, $CDCl_3$): δ 1.22 (br, 14H), 1.47–1.51 (m, 4H), 2.06–2.10 (m, 2H), 3.13–3.22 (m, 6H), 8.00 (s, 1H), 8.10 (d, J = 8.8 Hz, 2H), 8.41 (d, J = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.85, 24.16, 25.54, 25.72, 26.00, 26.16, 26.52, 26.63, 26.73, 34.60, 38.44, 47.66, 48.70, 124.84, 128.69, 144.53, 149.94, 172.69; Anal. Calcd. for $C_{20}H_{31}N_3O_5S$: C 56.45, H 7.34, N 9.87. Found: C 56.01, H 7.34, N 9.73.

4.12.10. 12a-N-Acetyl-12a-aza-pentadecanelactam (**10j**)

Light yellow liquid (78% yield); IR ν (KBr, cm^{-1}): 3296, 2930, 2858, 1633, 1545, 1443, 1371, 1264; ^1H NMR (300 MHz, $CDCl_3$): δ 1.25–1.35 (br, 15H), 1.56–1.67 (m, 4H), 2.14 (s, 3H), 2.17–2.21 (m, 2H), 3.34–3.39 (m, 2H), 3.45–3.51 (m, 4H), 6.63 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.26, 24.33, 24.54. 25.92, 26.06, 26.36, 26.46, 27.04, 27.77, 35.58, 38.81, 46.42, 49.87, 171.45, 173.51; HRMS (m/z) calcd for $C_{16}H_{31}N_2O_2$ $[M + H]^+$ 283.23800, found 283.23801.

4.12.11. 12a-N-Benzoyl-12a-aza-pentadecanelactam (**10k**)

White solid (48% yield); m.p.: 100–101 °C; IR ν (KBr, cm^{-1}): 3279, 2933, 2857, 1620, 1543, 1448, 698; ^1H NMR (300 MHz, $CDCl_3$): δ 1.24–1.33 (br, 14H), 1.51 (br, 2H), 1.68 (br, 2H), 2.20–2.21 (br, 2H), 3.35–3.67 (br, 6H), 6.80 (br, 1H), 7.37–7.44 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.59, 24.73, 25.93, 26.06, 26.58, 26.70, 27.15, 28.05, 36.07, 39.38, 46.38, 50.95, 126.62, 128.44, 129.56, 136.43, 173.68; Anal. Calcd. for $C_{21}H_{32}N_2O_2$: C 73.22, H 9.36, N 8.13. Found: C 72.94, H 9.31, N 8.12.

4.12.12. 12a-N-(4-Methylbenzoyl)-12a-aza-pentadecanelactam (**10l**)

White solid (35% yield); m.p.: 115–116 °C; IR ν (KBr, cm^{-1}): 3284, 2936, 2857, 1645, 1615, 1555, 1440, 833; ^1H NMR (300 MHz, $CDCl_3$): δ 1.24–1.33 (br, 14H), 1.52 (br, 2H), 1.68 (br, 2H), 2.17–2.24 (m, 2H), 2.38 (s, 3H), 3.39–3.63 (br, 6H), 6.83 (br, 1H), 7.19–7.22 (m, 2H), 7.27–7.29 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.29, 24.60, 24.70, 25.98, 26.11, 26.58, 26.72, 27.00, 27.15, 27.89, 35.97, 39.30, 46.56, 50.86, 126.68, 128.99, 133.53, 139.63, 173.36, 173.66; Anal. Calcd. for $C_{22}H_{34}N_2O_2$: C 73.70, H 9.56, N 7.81. Found: C 73.58, H 9.53, N 7.84.

4.12.13. 12a-N-(2-Chlorobenzoyl)-12a-aza-pentadecanelactam (**10m**)

Light yellow liquid (82% yield); IR ν (KBr, cm^{-1}): 3307, 2930, 2858, 1633, 1540, 1434, 730; ^1H NMR (300 MHz, $CDCl_3$): δ 1.23–1.48 (br, 18H), 1.68 (br, 2H), 2.18–2.23 (m, 2H), 3.14–3.27 (br, 2H), 3.60–3.61 (br, 2H), 6.49 (br, 1H), 7.27–7.40 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.21, 24.41, 25.67, 25.96, 26.06, 26.17, 26.41, 26.53, 27.23, 35.71, 38.56, 45.42, 49.79, 126.90, 127.57, 129.50, 130.00, 130.05, 135.90, 169.24, 173.63; HRMS (m/z) calcd for $C_{21}H_{32}ClN_2O_2$ $[M + H]^+$ 379.21468, found 379.21466.

4.12.14. 12a-N-(3-Chlorobenzoyl)-12a-aza-pentadecanelactam (**10n**)

Light yellow liquid (75% yield); IR ν (KBr, cm^{-1}): 3309, 2930, 2858, 1726, 1634, 1541, 1459, 1276, 800, 733; ^1H NMR (300 MHz, $CDCl_3$): δ 1.25–1.34 (br, 14H), 1.53 (br, 2H), 1.66–1.75 (br, 4H), 2.21 (t, J = 5.8 Hz, 2H), 3.33 (br, 2H), 3.58–3.64 (br, 4H), 6.60 (br, 1H), 7.24–7.27 (m, 1H), 7.31–7.43 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.46, 24.51, 25.91, 26.47, 26.59, 26.60, 27.11, 27.71, 28.77, 35.79, 38.70, 46.17, 51.28, 124.53, 126.74, 129.76, 130.76, 134.42, 138, 12, 167.59, 173.62; HRMS (m/z) calcd for $C_{21}H_{32}ClN_2O_2$ $[M + H]^+$ 379.21468, found 379.21436.

4.12.15. 12a-N-(4-Chlorobenzoyl)-12a-aza-pentadecanelactam (**10o**)

White solid (48% yield); m.p.: 144–145 °C; IR ν (KBr, cm^{-1}): 3279, 2933, 2857, 1620, 1543, 1448, 698; ^1H NMR (300 MHz, $CDCl_3$): δ 1.25–1.33 (br, 14H), 1.53 (br, 2H), 1.68 (br, 2H), 2.17–2.21 (m, 2H), 3.34–3.63 (br, 6H), 6.69 (br, 1H), 7.27–7.42 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.60, 24.68, 26.01, 26.11, 26.60, 26.73, 27.20, 27.98, 36.05, 39.21, 46.60, 50.94, 128.19, 128.76, 134.83, 135.69, 172.15, 173.68; Anal. Calcd. for $C_{21}H_{31}ClN_2O_2$: C 66.56, H 8.25, N 7.39. Found: C 66.44, H 8.23, N 7.40.

4.12.16. 12a-N-(4-Bromobenzoyl)-12a-aza-pentadecanelactam (**10p**)

White solid (85% yield); m.p.: 146–147 °C; IR ν (KBr, cm^{-1}): 3284, 2936, 2857, 1645, 1615, 1555, 1440, 833; ^1H NMR (300 MHz, $CDCl_3$): δ 1.25–1.32 (br, 14H), 1.52 (br, 2H), 1.67 (br, 2H), 2.17–2.20 (br, 2H), 3.33 (br, 2H), 3.56–3.62 (br, 4H), 6.72 (br, 1H), 7.26 (d, J = 7.2 Hz, 2H), 7.56 (d, J = 8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.23, 24.34, 25.73, 25.77, 26.28, 26.40, 26.42, 26.89, 27.49, 35.60, 38.60, 46.12, 50.48, 123.54, 128.04, 131.39, 135.03, 171.71, 173.45; Anal. Calcd. for $C_{21}H_{31}BrN_2O_2$: C 59.57, H 7.38, N 6.62. Found: C 59.40, H 7.35, N 6.64.

4.12.17. 12a-N-(3-Nitrobenzoyl)-12a-aza-pentadecanelactam (**10q**)

White solid (69% yield); m.p.: 109–110 °C; IR ν (KBr, cm^{-1}): 3351, 2934, 2860, 1640, 1533, 1429, 1348, 810, 730; ^1H NMR (300 MHz, $CDCl_3$): δ 1.25–1.34 (br, 14H), 1.56 (br, 2H), 1.69 (br, 2H), 2.21–2.25 (br, 2H), 3.32 (br, 2H), 3.61–3.66 (br, 4H), 6.54 (br, 1H), 7.61–7.67 (m, 2H), 7.73–7.76 (m, 1H), 8.28–8.31 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.22, 24.25, 24.40, 25.08, 25.72, 26.21, 26.32, 26.38, 26.93, 27.46, 30.52, 33.09, 35.56, 38.35, 46.27, 50.60, 121.52, 123.98, 129.51, 132.33, 137.83, 147.68, 169.88, 173.42; Anal. Calcd. for $C_{21}H_{31}N_3O_4$: C 64.76, H 8.02, N 10.79. Found: C 64.70, H 8.05, N 10.57.

4.12.18. 12a-N-(4-Nitrobenzoyl)-12a-aza-pentadecanelactam (**10r**)

White solid (56% yield); m.p.: 158–159 °C; IR ν (KBr, cm^{-1}): 3270, 2933, 2858, 1626, 1601, 1522, 1443, 1352, 871; ^1H NMR (300 MHz, $CDCl_3$): δ 1.16–1.34 (br, 14H), 1.51–1.56 (br, 2H), 1.65–1.69 (br, 4H), 2.21–2.23 (br, 2H), 3.26–3.31 (br, 2H), 3.61–3.67 (br, 4H), 6.33 (br, 1H), 7.56 (d, J = 8.4 Hz, 2H), 8.30 (d, J = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.14, 24.23, 24.29, 25.74, 26.30, 26.40, 26.93, 27.44, 27.49, 35.70, 38.51, 46.06, 46.09, 46.10, 46.16, 50.41, 123.55, 127.30, 127.40, 142.33, 147.97, 170.39, 173.38; Anal. Calcd. for $C_{21}H_{31}N_3O_4$: C 64.76, H 8.02, N 10.79. Found: C 64.67, H 7.99, N 10.82.

4.13. Evaluation of biological activity

Antifungal activity of compounds **6a**–**n** and **10a**–**r** against *S. sclerotiorum*, *P. oryzae*, *B. cinerea*, *R. solani* and *P. capsici* was evaluated using the mycelium growth rate assay. Commercial fungicide Chlorothalonil was used as a positive control. The culture media with various concentrations of test compounds were prepared by mixing DMSO or DMSO solutions of compounds **6a**–**n** and **10a**–**r** with potato dextrose agar (PDA). Then, fungus cakes were placed in the media. The inoculated plates were kept at 25 °C. Each experiment was performed in triplicates. When the mycelia grew completely in DMSO treatment, the diameter of the mycelia was measured and the inhibition rate was calculated by the following formula and averaged.

$$I = \frac{\overline{D}_1 - \overline{D}_0}{\overline{D}_1} \times 100\%$$

In which I is the inhibition rate, $\overline{D}_1$ is the average diameter of mycelia in the blank test, and $\overline{D}_0$ is the average diameter of mycelia in the presence of compounds **6a**–**n** and **10a**–**r**. The inhibition rates of compounds **6a**–**n** and **10a**–**r** are given in Table 1.

Acknowledgments

We acknowledge financial support of this investigation by the National Natural Science Foundation of China (31272075) and the Science Foundation of China Agricultural University (No. 2007035).

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2013.11.032. These data include MOL files and InChiKeys of the most important compounds described in this article.

References

[1] G. Kobrehel, G. Radobolja, Z. Tamburasev, DE3012533-A, 16 Oct, 1980.
[2] G. Kobrehel, S. Djokic, S. Dokic, FR2501212-A1; BE892357-A, 01 July, 1982, 198228.
[3] S. Djokic, G. Kobrehel, G. Lazarevski, N. Lopotar, Z. Tamburasev, B. Kamenar, A. Nagl, I. Vickovic, J. Chem. Soc., Perkin Trans. 1 (1986) 1881–1890.
[4] M. Peric, A. Fajdetic, R. Rupcic, S. Alihodzic, D. Ziher, M.B. Krajacic, K.S. Smith, Z. Ivezic-Schoenfeld, J. Padovan, G. Landek, D. Jelic, A. Hutinec, M. Mesic, A. Ager, W.Y. Ellis, W.K. Milhous, C. Ohrt, R. Spaventi, J. Med. Chem. 55 (2012) 1389–1401.
[5] S. Mutak, J. Antibiot. 60 (2007) 85–122.
[6] A. Fajdetic, H.C. Paljetak, G. Lazarevski, A. Hutinec, S. Alihodzic, M. Derek, V. Stimac, D. Andreotti, V. Sunjic, J.M. Berge, S. Mutak, M. Dumic, S. Lociuro, D.J. Holmes, N. Marsic, V.E. Haber, R. Spaventi, Bioorg. Med. Chem. 18 (2010) 6559–6568.
[7] M.B. Krajacic, M. Dumic, P. Novak, M. Cindric, S. Kostrun, A. Fajdetic, S. Alihodzic, K. Brajsa, N. Kujundzic, Bioorg. Med. Chem. Lett. 21 (2011) 853–856.
[8] K. Starcevic, D. Pesic, A. Toplak, G. Landek, S. Alihodzic, E. Herreros, S. Ferrer, R. Spaventi, M. Peric, Eur. J. Med. Chem. 49 (2012) 365–378.
[9] H. Brockmann, W. Henkel, Naturwissenschaften 37 (1950) 138–139.
[10] L. Venkatraman, C.E. Salomon, D.H. Sherman, R.A. Fecik, J. Org. Chem. 71 (2006) 9853–9856.
[11] T. Pitterna, J. Cassayre, O.F. Hüter, P.M. Jung, P. Maienfisch, F.M. Kessabi, L. Quaranta, H. Tobler, Bioorg. Med. Chem. 17 (2009) 4085–4095.
[12] Y. Fujii, A. Fukuda, T. Hamasaki, I. Ichimoto, H. Nakajima, Phytochemistry 40 (1995) 1443–1446.
[13] J. Millar, H. Pierce, A. Pierce, A. Oehlschlager, J. Borden, A. Barak, J. Chem. Ecol. 11 (1985) 1053–1070.
[14] J. Wong, V. Verigin, A. Oehlschlager, J. Borden, H. Pierce, A. Pierce, L. Chong, J. Chem. Ecol. 9 (1983) 451–474.
[15] B. Bergman, Eur. J. Plant Pathol. 72 (1966) 222–230.
[16] F. Schönbeck, C. Schroeder, Physiol. Plant Pathol. 2 (1972) 91–99.
[17] A.K. Picman, R.H. Elliott, G.H.N. Towers, Biochem. Syst. Ecol. 6 (1978) 333–335.
[18] A.K. Pickman, Biochem. Syst. Ecol. 12 (1984) 13–18.
[19] T. Konishi, Y. Shimada, T. Nagao, H. Okabe, T. Konoshima, Biol. Pharm. Bull. 25 (2002) 1370–1372.
[20] M.-R. Zong, Y.-H. Zhao, K. Zhang, L.-F. Yang, Y.-C. Zheng, C.-Y. He, Chem. Res. Chin. Univ. 27 (2011) 241–244.
[21] T. Sasaki, Y. Igarashi, N. Saito, T. Furumai, J. Antibiot. 54 (2001) 567–572.
[22] Q. Cui, J. Wang, H. Yang, L. Xie, X. Xu, Chin. J. Org. Chem. 30 (2010) 1705–1710.
[23] M. Li, X. Liang, Z. Qin, D. Wang, Chin. J. Pest. Sci. 8 (2006) 209–213.
[24] S. Chen, C. Zhang, J. Liu, D. Wang, M. Wang, Chin. J. Org. Chem. 30 (2010) 1768–1773.
[25] X.P. Wang, D.Q. Wang, Chem. J. Chin. Univ. 18 (1997) 889–893.
[26] W.-J. Zhu, P. Wu, X.-M. Liang, Y.-H. Dong, J.-J. Zhang, H.-Z. Yuan, S.-H. Qi, X.-Q. Meng, J.-P. Wu, F.-H. Chen, D.-Q. Wang, J. Agric. Food Chem. 56 (2008) 6547–6553.
[27] X. Li, X. Yang, X. Liang, Z. Kai, H. Yuan, D. Yuan, J. Zhang, R. Wang, F. Ran, S. Qi, Y. Ling, F. Chen, D. Wang, Bioorg. Med. Chem. 16 (2008) 4538–4544.
[28] J.-X. Huang, Y.-M. Jia, X.-M. Liang, W.-J. Zhu, J.-J. Zhang, Y.-H. Dong, H.-Z. Yuan, S.-H. Qi, J.-P. Wu, F.-H. Chen, D.-Q. Wang, J. Agric. Food Chem. 55 (2007) 10857–10863.
[29] X.-H. Li, X.-L. Yang, Y. Ling, Z.-J. Fan, X.-M. Liang, D.-Q. Wang, F.-H. Chen, Z.-M. Li, J. Agric. Food Chem. 53 (2005) 2202–2206.
[30] Y. Dong, X. Liang, H. Yuan, S. Qi, F. Chen, D. Wang, Green Chem. 10 (2008) 990–994.
[31] S.V. Chankeshwara, A.K. Chakraborti, Org. Lett. 8 (2006) 3259–3262.
[32] M. Dai, I.J. Krauss, S.J. Danishefsky, J. Org. Chem. 73 (2008) 9576–9583.
[33] L.A. Paquette, G.D. Parker, T. Tei, S. Dong, J. Org. Chem. 72 (2007) 7125–7134.
[34] J.J. Farmer, A.B. Attygalle, S.R. Smedley, T. Eisner, J. Meinwald, Tetrahedron Lett. 38 (1997) 2787–2790.
[35] V. Gracias, K.E. Frank, G.L. Milligan, J. Aube, Tetrahedron 53 (1997) 16241–16252.
[36] J.E. Forsee, J. Aube, J. Org. Chem. 64 (1999) 4381–4385.
[37] O. Delgado, G. Heckmann, H.M. Mueller, T. Bach, J. Org. Chem. 71 (2006) 4599–4608.
[38] Y. Boland, P. Hertsens, J. Marchand-Brynaert, Y. Garcia, Synthesis (2006) 1504–1512.
[39] C. Heidelberger, A. Guggisberg, E. Stephanou, M. Hesse, Helv. Chim. Acta 64 (1981) 399–406.
[40] SYBYL, Tripos Inc., 1699 South Hanley Road, St. Louis, Missouri 63144, USA, 2007.
[41] T.A. Halgren, J. Comput. Chem. 17 (1996) 490–519.