Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron 64 (2008) 3966–3974
Tetrahedron
www.elsevier.com/locate/tet

Solvent-free Ugi four-component condensation: application to synthesis of philanthotoxins-12 analogues

Nianjin Liu, Song Cao*, Jingjing Wu, Jinlong Yu, Li Shen, Xin Feng, Xuhong Qian*

Shanghai Key Laboratory of Chemical Biology, Center of Fluorine Chemical Technology, School of Pharmacy, East China University of Science and Technology, Shanghai 200237, China

Received 23 November 2007; received in revised form 1 February 2008; accepted 15 February 2008
Available online 20 February 2008

Abstract

Philanthotoxins-12 analogues was synthesized by a highly convergent approach, utilizing an efficient, simple, and convenient one-pot Ugi four-component solvent-free method as key step, followed by removal of the protecting groups in the presence of trifluoroacetic acid.
© 2008 Elsevier Ltd. All rights reserved.

Keywords: α-Acylamino amide; Philanthotoxins analogues; Solvent-free; Ugi 4CR

1. Introduction

Polyamine toxins have attracted considerable attention owing to their diverse biological activities.[1] Philanthotoxins-433 (PhTX-433), a low molecular weight natural polyamine toxin that originally isolated from the venom of wasp,[2] showed potential noncompetitive inhibitory effects on various types of ionotropic receptors in the central nervous system such as ionotropic glutamate receptors (iGluRs)[3] and nicotinic acetylcholine receptors (nAChRs) in mammalians and in insects (Fig. 1).[4] Many new more active and higher selective synthetic analogues of philanthotoxins-433 have been obtained by modification of the structure of this natural product.[5] For example, philanthotoxins-12 (PhTX-12), which was obtained via the change of the polyamine skeleton, has exhibited pronounced selectivity toward nAChR, whereas is inactive at various iGluRs.[6]

Due to their wide applications in medicinal chemistry, the search for general, efficient syntheses of philanthotoxins analogues under mild conditions is of growing interest for organic chemists.[7] The conventional method has been developed by Nakanishi et al., involving coupling of *p*-nitrophenyl esters of *N*-acylamino acids with appropriately protected polyamines.[8] Recently, a number of methods for solid-phase synthesis (SPS) of polyamine toxins have been reported. For example, Olsen described an efficient solid-phase synthesis of novel hybrid toxins using a backbone amide linker (BAL) resin.[9] However, these methodologies are associated with several shortcomings such as the limited variation of the amino acid moiety, the lengthy and repeated protection and deprotection of amido and carboxyl during the synthesis of α-acylamino amide backbone, activation of the carboxyl group, too many steps, and the use of organic solvents.

Among the protocols for the synthesis of peptides or amino acids, the important method is the Ugi four-component

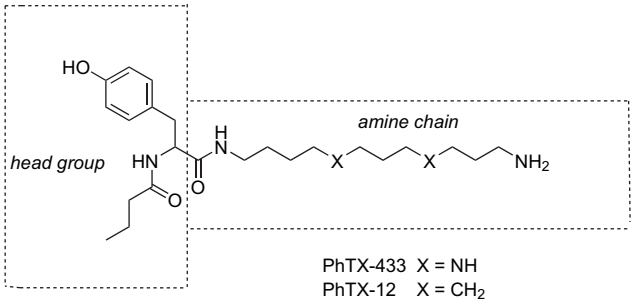


Figure 1. Structure of PhTX-433 and PhTX-12.

* Corresponding authors. Fax: +86 21 6425 2603.
E-mail addresses: scao@ecust.edu.cn (S. Cao), xhqian@ecust.edu.cn (X. Qian).

0040-4020/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.02.051

reaction (Ugi 4CR).[10] Ugi 4CR offers significant advantages over stepwise procedures, especially with respect to diversity, complexity, green chemistry, and atom economy.[11] To date, many efforts have been made to modify the Ugi 4CR condition in order to improve the synthetic efficiency.[12] Dai reported the use of microwave-assisted conditions to greatly accelerate the Ugi 4CR.[13] Fülöp focused on the application of a modified Ugi reaction in aqueous medium to construct β-lactam libraries.[14] Curran developed a new protocol for Ugi multi-component condensation by using fluorous technology.[15] Despite the latest development, there is still an urgent need for a highly efficient and mild method for Ugi 4CR.

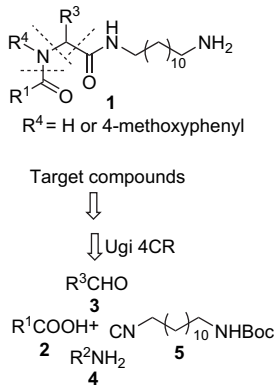
In this paper, we report an efficient, simple, and convenient protocol for the synthesis of α-acylamino amide backbone under one-pot Ugi four-component solvent-free conditions, followed by the simple removal of the protecting groups in the presence of trifluoroacetic acid (TFA) to obtain PhTX-12 derivatives.

2. Results and discussion

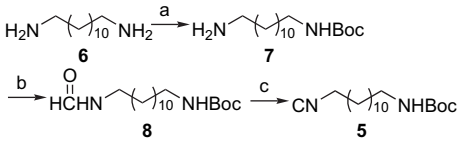
The results of structure–activity investigations emphasized the importance of the aromatic headgroup of philanthotoxins.[16] For example, PhTX(Cha)-343, an analogue of PhTX-343 (a kind of synthetic analogues of Philanthotoxins-433) in which the tyrosine moiety has been replaced by cyclohexylalanine (Cha), showed high selectivity toward human muscle-type nAChR and exhibited unprecedented activity at nanomolar concentrations.[17] Strømgaard et al. modified the aromatic headgroup of philanthotoxin-56 (another kind of synthetic analogues of philanthotoxins-433) by changing the butyramide moiety to adamantylacetamide. They also demonstrated that this modification led to a significant improvement in activity at AMPA receptors.[18]

However, little has been reported on the structure–activity relationships (SAR) of PhTX-12. In 2002, Strømgaard reported that it would lead to a dramatic decrease in activity when the number of methylene spacer between the primary amino group and the aromatic headgroup of PhTX-12 was less than eleven.[19] In addition, he also demonstrated the *S*- and *R*-enantiomers of PhTX-12 had nearly the same activity on nicotinic acetylcholine receptors.[20] Therefore, in this paper chemical transformations were conducted to modify the aromatic headgroup present in PhTX-12 and to synthesize 2 series of 15 PhTX-12 analogues for further SAR study. The first series of the target compounds **1a–i** are α-*N*-unsubstituted α-acylamino amides. The second series **1j–o** are α-*N*-substituted α-acylamino amides.

The retrosynthetic analysis of the target compounds is shown in Scheme 1. It was indicated that **1** could be resolved into a set of four easily available building blocks. Therefore, we proposed that this dipeptide could be made from the Ugi 4CR of carboxylic acid **2**, aldehyde **3**, amine **4**, and mono-*N*-Boc-protected 12-dodecylisocyanide **5**. Firstly, novel isocyanide **5** was synthesized, as illustrated in Scheme 2. Thus, beginning with 1,12-diaminododecane **6**, one of the amine was protected by Boc group using standard method. The mono(Boc)-protected



Scheme 1. Retrosynthesis of target compounds.



Scheme 2. Synthesis of 12-(*tert*-butoxycarbonylamino)dodecylisocyanide. (a) $(Boc)_2O$, CH_2Cl_2/CH_3OH (3:2), rt; (b) HCOOH, DCC, CH_2Cl_2, rt; (c) PPh_3, CCl_4, NEt_3, $ClCH_2CH_2Cl$, 60 °C.

1,12-diaminododecane **7** was *N*-formylated with formic acid in the presence of dicyclohexylcarbodiimide (DCC), and then *tert*-butyl 12-formamidododecylcarbamate **8** was dehydrated by treatment with equimolar amounts of carbon tetrachloride, triethylamine, and triphenylphosphine (20% excess) to give the desired product 12-(*tert*-butoxycarbonylamino)dodecylisocyanide **5**.[21] This novel isocyanide could be stored for several months in desiccator at room temperature without obvious decomposition.

Generally, the Ugi 4CR was performed in organic solvents such as methanol, tetrahydrofuran at room temperature for 1–2 days.[22] According to the classical procedure, methanol is the best solvent for the Ugi 4CR.[23] Therefore, we carried out this Ugi 4CR with carboxylic acid, aldehyde, amine, and isocyanide in the presence of 4 Å molecular sieves in methanol at room temperature, which afforded the key intermediate in moderate to good yield. To survey the generality and scope of this one-pot four-component protocol, and also to enlarge the SAR studies of parent compound, the methodology was applied to the synthesis of a variety of α-acylamino amide derivatives **9a–o**. For compounds **9a–i**, R^2 was kept as 2,4-dimethoxybenzyl (a readily cleavable protecting group) in order to make its cleavage possible. The reaction times and isolated yields are summarized in Table 1. In addition, it was reported that Ugi 4CR could be carried out in boiling methanol smoothly.[24] Hence we also tried to carry out this Ugi reaction under reflux conditions to synthesize several intermediates **9c**, **9j**, **9n**. Despite the shorter reaction time it needed (9–11 h), the yields were slightly lower at reflux temperature than those at room temperature. It seems that refluxing in methanol is unfavorable to Ugi 4CR.

Although this Ugi 4CR was carried out successfully in methanol at room temperature to afford the desired

Table 1
Synthesis of compounds **9a–o** in methanol or under solvent-free conditions

Compounds	R^1	R^2	R^3	Methanol		Solvent-free	
				Time[a] (h)	Yield[b] (%)	Time[a] (h)	Yield[b] (%)
9a	6-Chloropyridin-3-yl	2,4-Dimethoxybenzyl	6-Chloropyridin-3-yl	43	71	0.5	83
9b	6-Chloropyridin-3-yl	2,4-Dimethoxybenzyl	Benzo[*d*][1,3]dioxol-5-yl	38	61	0.6	71
9c	4-Trifluoromethylphenyl	2,4-Dimethoxybenzyl	6-Chloropyridin-3-yl	48	63	0.5	72
9d	4-Trifluoromethylphenyl	2,4-Dimethoxybenzyl	Benzo[*d*][1,3]dioxol-5-yl	39	63	0.6	70
9e	2,4,5-Trifluoro-3-methoxyphenyl	2,4-Dimethoxybenzyl	6-Chloropyridin-3-yl	41	61	0.5	81
9f	2,4,5-Trifluoro-3-methoxyphenyl	2,4-Dimethoxybenzyl	Benzo[*d*][1,3]dioxol-5-yl	45	65	0.6	74
9g	4-Trifluoromethylphenyl	2,4-Dimethoxybenzyl	3-Chloro-2-fluorophenyl	42	68	0.6	75
9h	4-Fluorophenyl	2,4-Dimethoxybenzyl	3-Chloro-2-fluorophenyl	39	64	0.6	71
9i	2-Fluorophenyl	2,4-Dimethoxybenzyl	3-Chloro-2-fluorophenyl	43	62	0.6	73
9j	6-Chloropyridin-3-yl	4-Methoxyphenyl	Benzo[*d*][1,3]dioxol-5-yl	42	57	0.8	60
9k	4-Trifluoromethylphenyl	4-Methoxyphenyl	Benzo[*d*][1,3]dioxol-5-yl	46	55	0.7	56
9l	2,4,5-Trifluoro-3-methoxyphenyl	4-Methoxyphenyl	Benzo[*d*][1,3]dioxol-5-yl	48	52	0.7	53
9m	6-Chloropyridin-3-yl	4-Methoxyphenyl	6-Chloropyridin-3-yl	37	64	0.7	68
9n	4-Trifluoromethylphenyl	4-Methoxyphenyl	6-Chloropyridin-3-yl	39	62	0.6	65
9o	2,4,5-Trifluoro-3-methoxyphenyl	4-Methoxyphenyl	6-Chloropyridin-3-yl	36	59	0.7	61

[a] Time after addition of acid and isocyanide into flask.
[b] Yields of pure isolated compound after silica gel chromatography.

compounds, there are some drawbacks in Ugi reaction such as too long reaction time and using methanol as solvent leading to side reaction. More recently, Shaabani studied the reaction of carboxylic acids and isocyanides in methanol at ambient temperature carefully. Aryl amides were obtained in high yield after 24 h. He also proved that methanol took part in this reaction and converted to methylformate.[25] Furthermore, it was also reported that methanol took part in the reaction to form unintended byproducts. For example, de Mello demonstrated that under the Ugi reaction conditions, the iminium cation underwent another competing reactions involving reaction solvent (methanol) to give undesired byproduct.[26] These studies have shown that the utility of methanol as solvent led inevitably the formation of some undesired side products.

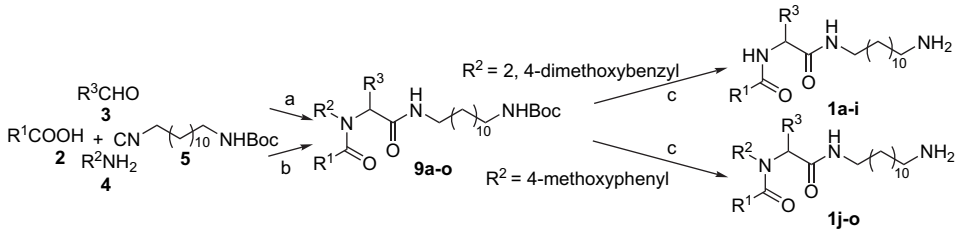
Organic synthesis involving multi-component reactions (MCRs) under solvent-free conditions has been receiving much attention.[27] As part of our continuing interest to develop more efficient and practical methods in organic synthesis, we explored the possibility of obtaining the key intermediate **9a–o** by the Ugi 4CR under solvent-free conditions (Scheme 3). To the best of our knowledge, no solvent-free Ugi 4CR has been documented.

The synthesis of **9c** was served as the basic reaction model. We were delighted to find that the reaction proceeded smoothly in a much shorter time at elevated temperature and resulted in the formation of products in higher yield. The reaction was significantly affected by the reaction temperature. It was observed that 60 °C was the optimum reaction temperature. At low reaction temperature, i.e., 50 °C, the longer reaction time was needed. When the reaction temperature was higher than 60 °C, low yield was observed. The optimum conditions were then applied to the condensation of several different acids, aldehyde, amine, and isocyanide. The yields and reaction times are listed in Table 1. As can be seen from Table 1, shorter reaction time was needed and higher yields have been achieved under solvent-free conditions compared to conventional method.

Finally, the target compounds **1a–o** were obtained via the deprotection of the Boc group and 2,4-dimethoxybenzyl in the presence of trifluoroacetic acid in dichloromethane at room temperature. The crude residue was purified by chromatography to give pure compounds **1a–o**.

3. Conclusion

In conclusion, we have developed a mild and efficient organic solvent-free Ugi four-component condensation for the synthesis of α-acylamino amides **9a–o**, the key intermediates in the synthesis of PhTX-12 derivatives. Reaction times were dramatically reduced and yields were generally improved by this new method. Further removal of protective groups, by treatment with trifluoroacetic acid, gave final products **1a–o**. This new class of compounds may be used as new lead compounds for biological activity evaluation, especially as noncompetitive antagonist of nAChRs.



Scheme 3. Synthesis of PhTX-12 derivatives via Ugi 4CR. (a) No solvent, 60 °C; (b) 4 Å molecular sieves, CH_3OH, rt; (c) TFA, CH_2Cl_2.

4. Experimental

4.1. General

All reactions were carried out under dry nitrogen except Ugi 4CR and the deprotection reaction. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 400 MHz spectrometer (400 and 100 MHz, respectively); chemical shifts (δ) are given in parts per million. High-resolution mass spectra were recorded under electron impact conditions using a MicroMass GCT CA055 instrument. Melting points were measured on a Büchi B-540 melting point apparatus and are uncorrected. All reagents were of analytic grade and obtained from commercial suppliers and used without further purification with the following exceptions. Dichloromethane and 1,2-dichloroethane were distilled from phosphorus pentoxide. Methanol was heated to reflux over magnesium methoxide for 12 h and then distilled.

4.2. Preparation of tert-butyl 12-formamidododecylcarbamate **8**

To a stirred suspension of mono(Boc)-protected 1,12-diaminododecane **7** (24.60 g, 82 mmol) and dried formic acid (3.2 mL, 82 mmol) in 150 mL CH_2Cl_2, solution of dicyclohexylcarbodiimide (17.72 g, 86 mmol) in 100 mL CH_2Cl_2 was added dropwise for about half an hour at room temperature. The reaction mixture was stirred for another 5 h (TLC) at room temperature. A white solid 1,3-dicyclohexylurea (DCU) was filtered and the filtrate was washed with 8 mL saturated solution of $NaHCO_3$. The organic layer was separated, washed with water, dried over anhydrous sodium sulfate, and concentrated in vacuo, and a white solid mixture was obtained. The resultant crude residue was purified by chromatography (AcOEt/heptane=2:1) to obtain the product. Yield: 73%; mp 43–45 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (s, 1H), 5.78 (s, 1H), 3.34–3.29 (m, 2H), 3.10 (t, J=7.2 Hz, 2H), 1.54 (t, J=6.8 Hz, 2H), 1.45 (s, 11H), 1.31–1.27 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.38, 156.28, 79.37, 42.05, 41.08, 38.51, 36.80, 34.32, 30.29, 29.66, 29.44, 28.66, 27.01; HRMS (ESI) *m/z*: 329.2805 $[M+H]^+$, calcd for $C_{18}H_{36}N_2O_3$+H: 329.2804.

4.3. 12-(tert-Butoxycarbonylamino)dodecylisocyanide **5**

tert-Butyl 12-formamidododecylcarbamate **8** (15.00 g, 46 mmol), carbon tetrachloride (4.50 mL, 46 mmol), triethylamine (6.50 mL, 46 mmol), and triphenylphosphane (14.50 g, 55.2 mmol) were dissolved in 50 mL 1,2-dichloroethane and the mixture was stirred at 60 °C for about 2.5 h (TLC). Then, the dark brown reaction mixture was cooled to room temperature. Subsequently, white triethylamine hydrochloride salt was removed by filtration and the solid was washed with CH_2Cl_2. The filtrate was concentrated under reduced pressure and the resultant crude residue was purified by chromatography (AcOEt/heptane=1:8), and white isocyanide **5** was obtained. Yield, 90%; mp 84–86 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.51 (s, 1H), 3.40–3.37 (m, 2H), 3.11 (d, J=6.0 Hz, 2H), 1.67 (d, J=6.4 Hz, 2H), 1.44 (s, 13H), 1.27 (s, 14H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.98, 155.54, 78.99, 41.62, 41.56, 41.50, 40.63, 30.06, 29.50, 29.47, 29.44, 29.33, 29.26, 29.10, 28.68, 28.43, 26.78, 26.30; HRMS (ESI) *m/z*: 333.2519 $[M+Na]^+$; calcd for $C_{18}H_{34}N_2O_2$+Na: 333.2518.

4.4. General procedure for the synthesis of compounds **9a–o** in methanol

The appropriate primary amino (1.65 mmol) and aldehyde (1.5 mmol) were dissolved in 2 mL of anhydrous methanol and the mixture was stirred at room temperature for 2 h after adding a small quantity of 4 Å molecular sieves. To this solution the carboxylic acid (1.5 mmol) and isocyanide **5** (1.5 mmol) were added successively. The reaction mixture was stirred at ambient temperature for 36–48 h. Subsequently, molecular sieves were removed by filtration and the solid was washed with adequate methanol. The filtrate was concentrated under reduced pressure and the resultant crude residue was purified by chromatography (AcOEt/heptane=1:5) to give the corresponding **9a–o** in yields of 52–71%.

4.5. General procedure for the synthesis of compounds **9a–i** under solvent-free conditions

To a stirred 2,4-dimethoxybenzyl amine (0.83 mmol), aldehyde (0.75 mmol) was added in portions for about 5 min. The mixture was stirred for 25 min again at room temperature. Then, the reaction mixture was heated to 60 °C. The isocyanide **5** (0.75 mmol) and carboxylic acid (0.75 mmol) were added in portions for 10 min. Stirring was continued at 60 °C for 25 min (TLC). The crude residue was purified by chromatography (AcOEt/heptane=1:5) to give the desired products.

4.5.1. tert-Butyl 12-(2-(N-(2,4-dimethoxybenzyl)-2-chloronicotinamido)-2-(6-chloropyridin-3-yl)acetamido)-dodecylcarbamate (**9a**)

White solid, mp 102–104 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57 (s, 1H), 8.19 (s, 1H), 7.82–7.78 (m, 2H), 7.37 (d, J=8.4 Hz, 1H), 7.22 (d, J=8.4 Hz, 1H), 7.09 (d, J=8.4 Hz, 1H), 6.40 (d, J=8.4 Hz, 1H), 6.25 (d, J=2.0 Hz, 1H), 5.95 (s, 1H), 5.15 (s, 1H), 4.54 (d, J=3.6 Hz, 2H), 3.77 (s, 3H), 3.64 (s, 3H), 3.21 (q, J=6.8 Hz, 2H), 3.09 (t, J=6.4 Hz, 2H), 1.44 (s, 13H), 1.27–1.23 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.44, 167.44, 161.39, 158.08, 155.99, 152.91, 151.29, 150.36, 148.15, 140.04, 137.50, 130.63, 130.38, 130.35, 124.03, 123.96, 115.32, 104.44, 98.51, 79.01, 62.30, 55.45, 55.09, 50.24, 40.06, 30.06, 29.49, 29.34, 29.26, 29.18, 28.43, 26.85, 26.78; HRMS (ESI) *m/z*: 780.3268 $[M+Na]^+$; calcd for $C_{39}H_{53}Cl_2N_5O_6$+Na: 780.3271.

4.5.2. tert-Butyl 12-(2-(N-(2,4-dimethoxybenzyl)-2-chloronicotinamido)-2-(benzo[d][1,3]dioxol-5-yl)-acetamido)dodecylcarbamate (**9b**)

Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 (d, J=2.0 Hz, 1H), 7.77 (q, J=2.0 Hz, 1H), 7.35 (d, J=8.4 Hz, 1H), 7.29 (d, J=8.4 Hz, 1H), 6.95 (s, 1H), 6.80 (d,

J=8.0 Hz, 1H), 6.72 (d, J=8.0 Hz, 1H), 6.44 (dd, J=2.0, 8.0 Hz, 1H), 6.25 (d, J=2.0 Hz, 1H), 5.96 (s, 2H), 5.76 (s, 1H), 5.10 (s, 1H), 4.46 (s, 2H), 3.78 (s, 3H), 3.62 (s, 3H), 3.30–3.19 (m, 2H), 3.10 (t, J=6.8 Hz, 2H), 1.93 (s, 1H), 1.45 (s, 13H), 1.28–1.23 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.33, 168.68, 160.66, 157.79, 156.00, 152.48, 148.02, 147.83, 141.24, 137.44, 131.06, 129.28, 128.75, 123.78, 123.54, 116.58, 109.77, 108.32, 104.09, 101.32, 98.24, 79.01, 65.45, 55.38, 54.97, 39.98, 30.06, 29.50, 29.48, 29.32, 29.27, 29.18, 28.43, 26.87, 26.78; HRMS (ESI) *m/z*: 767.3790 $[M+H]^+$; calcd for $C_{41}H_{55}ClN_4O_8$+H: 767.3787.

4.5.3. tert-Butyl 12-(2-(N-(2,4-dimethoxybenzyl)-4-(trifluoromethyl)benzamido)-2-(6-chloropyridin-3-yl)acetamido)dodecylcarbamate (**9c**)

Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, J=2.4 Hz, 1H), 7.77 (d, J=7.2 Hz, 1H), 7.62 (dd, J=8.0, 19.2 Hz, 4H), 7.17 (d, J=8.4 Hz, 1H), 7.03 (d, J=8.4 Hz, 1H), 6.37 (dd, J=2.0, 8.0 Hz, 1H), 6.22–6.18 (m, 1H), 5.21 (s, 1H), 4.51 (s, 2H), 3.74 (s, 3H), 3.61 (s, 3H), 3.18 (q, J=6.8 Hz, 2H), 3.07 (d, J=6.4 Hz, 2H), 1.42 (s, 13H), 1.25–1.22 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.47, 167.79, 161.27, 158.07, 156.02, 150.96, 150.14, 140.19, 139.36, 132.11, 131.79, 131.46, 130.64, 130.47, 127.38, 125.50, 125.46, 124.96, 123.88, 122.28, 115.61, 104.43, 98.44, 79.03, 62.12, 61.56, 55.42, 55.04, 50.14, 40.02, 30.05, 29.50, 29.34, 29.26, 29.20, 28.41, 26.87, 26.77; HRMS (ESI) *m/z*: 813.3553 $[M+Na]^+$; calcd for $C_{41}H_{54}ClF_3N_4O_6$+Na: 813.3582.

4.5.4. tert-Butyl 12-(2-(N-(2,4-dimethoxybenzyl)-4-(trifluoromethyl)benzamido)-2-(benzo[d][1,3]dioxol-5-yl)acetamido)dodecylcarbamate (**9d**)

Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (s, 4H), 7.32 (d, J=8.0 Hz, 1H), 6.95 (s, 1H), 6.80 (d, J=8.0 Hz, 1H), 6.71 (d, J=8.0 Hz, 1H), 6.43 (dd, J=2.4, 8.4 Hz, 1H), 6.24 (d, J=2.0 Hz, 1H), 5.95 (s, 2H), 5.84 (s, 1H), 5.14 (s, 1H), 4.46 (s, 2H), 3.77 (s, 3H), 3.61 (s, 3H), 3.29–3.18 (m, 2H), 3.10 (t, J=6.8 Hz, 2H), 2.00 (s, 1H), 1.45 (s, 13H), 1.28–1.24 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.46, 168.89, 160.51, 157.82, 155.99, 147.92, 147.69, 139.87, 131.70, 131.37, 129.42, 128.97, 127.23, 125.23, 125.11, 123.43, 122.40, 116.90, 109.77, 108.22, 104.03, 101.25, 98.14, 79.00, 65.28, 55.35, 54.90, 39.95, 30.06, 29.49, 29.33, 29.27, 29.19, 28.42, 26.89, 26.78; HRMS (ESI) *m/z*: 800.4096 $[M+H]^+$; calcd for $C_{43}H_{56}F_3N_3O_8$+H: 800.4098.

4.5.5. tert-Butyl 12-(2-(N-(2,4-dimethoxybenzyl)-2,4,5-trifluoro-3-methoxybenzamido)-2-(6-chloropyridin-3-yl)-acetamido)dodecylcarbamate (**9e**)

Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, J=1.6 Hz, 1H), 7.75 (d, J=6.8 Hz, 1H), 7.19 (d, J=8.0 Hz, 1H), 6.96 (d, J=8.0 Hz, 1H), 6.89 (dd, J=8.4, 6.8 Hz, 1H), 6.38 (dd, J=2.0, 6.4 Hz, 1H), 6.26 (d, J=2.0 Hz, 1H), 6.21 (s, 1H), 5.21 (s, 1H), 4.48 (s, 2H), 4.04 (s, 3H), 3.75 (s, 3H), 3.65 (s, 3H), 3.19 (q, J=6.4 Hz, 2H), 3.08 (d, J=5.6 Hz, 2H), 1.43 (s, 13H), 1.24 (s, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.28, 165.71, 161.56, 158.33, 155.96, 150.96, 150.14, 139.87, 131.04, 130.33, 123.63, 120.03, 119.99, 119.92, 119.86, 119.79, 119.75, 114.99, 108.81, 108.60, 104.65, 98.57, 78.90, 62.07, 61.82, 55.39, 55.08, 49.59, 39.96, 30.04, 29.46, 29.32, 29.23, 29.18, 28.39, 26.83, 26.74; HRMS (ESI) *m/z*: 807.3698 $[M+H]^+$; calcd for $C_{41}H_{54}ClF_3N_4O_7$+H: 807.3633.

4.5.6. tert-Butyl 12-(2-(N-(2,4-dimethoxybenzyl)-2,4,5-trifluoro-3-methoxybenzamido)-2-(benzo[d][1,3]dioxol-5-yl)acetamido)dodecylcarbamate (**9f**)

Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09 (d, J=8.4 Hz, 1H), 6.91–6.86 (m, 2H), 6.79 (d, J=7.2 Hz, 1H), 6.71 (d, J=8.0 Hz, 1H), 6.38 (dd, J=2.0, 8.0 Hz, 1H), 6.22 (s, 1H), 5.94 (s, 3H), 5.21 (s, 1H), 4.43 (s, 2H), 4.02 (s, 3H), 3.76 (s, 3H), 3.62 (s, 3H), 3.23 (q, J=6.8 Hz, 2H), 3.09 (s, 2H), 1.45 (s, 13H), 1.28–1.24 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.61, 165.80, 160.80, 158.04, 155.98, 147.82, 147.57, 146.17, 146.07, 143.71, 130.10, 128.78, 123.14, 120.59, 120.35, 116.18, 109.67, 108.79, 108.62, 108.14, 104.10, 101.20, 98.14, 78.98, 64.76, 62.07, 55.34, 54.94, 48.30, 40.70, 39.89, 30.06, 29.49, 29.31, 29.26, 29.19, 28.41, 26.87, 26.77; HRMS (ESI) *m/z*: 838.3923 $[M+Na]^+$; calcd for $C_{43}H_{56}F_3N_3O_9$+Na: 838.3866.

4.5.7. tert-Butyl 12-(2-(N-(2,4-dimethoxybenzyl)-4-(trifluoromethyl)benzamido)-2-(3-chloro-2-fluorophenyl)-acetamido)dodecylcarbamate (**9g**)

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64–7.59 (m, 4H), 7.50 (s, 1H), 7.22 (t, J=7.2 Hz, 1H), 7.07 (d, J=8.0 Hz, 1H), 6.95 (t, J=7.6 Hz, 1H), 6.35 (dd, J=2.0, 8.4 Hz, 2H), 6.14 (d, J=2.0 Hz, 1H), 5.62 (s, 1H), 4.58 (s, 1H), 4.53 (s, 2H), 3.72 (s, 3H), 3.58 (s, 3H), 3.16 (q, J=6.4 Hz, 2H), 3.06 (d, J=6.0 Hz, 2H), 1.41 (s, 13H), 1.24–1.21 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.55, 167.88, 160.71, 157.72, 157.60, 155.98, 155.13, 139.74, 103.82, 98.20, 78.86, 55.26, 54.86, 40.58, 39.85, 30.02, 29.47, 29.28, 29.24, 29.18, 28.37, 26.82, 26.75.

4.5.8. tert-Butyl 12-(2-(N-(2,4-dimethoxybenzyl)-4-fluorobenzamido)-2-(3-chloro-2-fluorophenyl)acetamido)-dodecylcarbamate (**9h**)

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52–7.49 (m, 2H), 7.44 (s, 1H), 7.20 (t, J=6.8 Hz, 1H), 7.09–7.01 (m, 3H), 6.94 (t, J=8.0 Hz, 1H), 6.46 (t, J=5.6 Hz, 1H), 6.34 (dd, J=2.4, 8.4 Hz, 1H), 6.16 (d, J=2.4 Hz, 1H), 5.53 (s, 1H), 4.60 (s, 2H), 3.71 (s, 3H), 3.58 (s, 3H), 3.15–3.10 (m, 2H), 3.05 (d, J=6.4 Hz, 2H), 1.40 (s, 13H), 1.24–1.21 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.00, 168.08, 164.79, 162.30, 160.65, 157.82, 157.63, 155.98, 155.15, 132.21, 132.18, 130.46, 129.99, 129.50, 129.44, 129.36, 124.93, 124.80, 124.16, 124.12, 120.70, 120.52, 116.58, 115.48, 115.27, 103.80, 98.24, 78.82, 55.26, 54.89, 40.58, 39.79, 30.02, 29.48, 29.28, 29.24, 29.19, 28.38, 26.83, 26.75.

*4.5.9. tert-Butyl 12-(2-(N-(2,4-dimethoxybenzyl)-2-fluorobenzamido)-2-(3-chloro-2-fluorophenyl)-acetamido)dodecylcarbamate (**9i**)*

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (t, J=6.8 Hz, 1H), 7.40–7.32 (m, 2H), 7.22 (t, J=7.2 Hz, 1H), 7.15 (t, J=7.6 Hz, 1H), 7.07 (t, J=8.8 Hz, 1H), 6.99–6.90 (m, 2H), 6.38–6.31 (m, 2H), 6.17 (d, J=1.6 Hz, 1H), 5.54 (s, 1H), 4.62 (s, 1H), 4.49 (dd, J=15.2 Hz, 2H), 3.70 (s, 3H), 3.60 (s, 3H), 3.17–3.12 (m, 2H), 3.05 (d, J=6.4 Hz, 2H), 1.40 (s, 13H), 1.22 (s, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.77, 167.58, 161.00, 159.85, 158.17, 157.60, 157.38, 155.99, 155.12, 131.48, 131.40, 130.76, 130.26, 130.08, 128.87, 124.92, 124.78, 124.45, 124.28, 124.07, 124.03, 120.52, 120.34, 116.01, 115.79, 115.72, 103.93, 98.34, 78.82, 60.31, 58.25, 55.26, 54.94, 54.85, 49.50, 40.59, 39.85, 30.02, 29.49, 29.25, 29.21, 29.15, 28.39, 26.80, 26.76.

*4.6. General procedure for the synthesis of compounds **9j–o** under solvent-free conditions*

At 60 °C, to a stirred 4-methoxybenzenamine (0.83 mmol), aldehyde (0.75 mmol) was added in portions for about 5 min. The mixture was stirred for 20 min again. The isocyanide **5** (0.75 mmol) and carboxylic acid (0.75 mmol) were added in portions for 10 min. Stirring was continued at 60 °C (TLC). The crude residue was purified by chromatography (AcOEt/heptane=1:5) to give the desired products.

*4.6.1. tert-Butyl 12-(2-(benzo[d][1,3]dioxol-5-yl)-2-(2-chloro-N-(4-methoxyphenyl)nicotinamido)-acetamido)dodecylcarbamate (**9j**)*

Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (d, J=2.4 Hz, 1H), 7.59 (dd, J=2.4, 8.4 Hz, 1H), 7.12 (d, J=8.4 Hz, 1H), 6.94 (s, 1H), 6.71–6.67 (m, 3H), 6.60 (d, J=8.8 Hz, 2H), 6.05 (s, 1H), 5.94 (d, J=0.8 Hz, 2H), 5.69 (t, J=5.6 Hz, 1H), 4.51 (s, 1H), 3.71 (s, 3H), 3.36–3.26 (m, 2H), 3.10 (t, J=6.8 Hz, 2H), 1.95 (s, 1H), 1.45 (s, 13H), 1.28–1.24 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.05, 167.69, 158.88, 156.00, 151.81, 149.52, 147.95, 147.81, 138.73, 132.57, 131.64, 131.07, 127.78, 124.47, 123.31, 113.98, 110.59, 108.25, 101.31, 79.00, 66.03, 60.37, 55.26, 40.70, 40.02, 30.06, 29.49, 29.47, 29.44, 29.26, 29.18, 28.43, 26.85, 26.78; HRMS (ESI) *m/z*: 745.3336 $[M+Na]^+$; calcd for $C_{39}H_{51}ClN_4O_7$+Na: 745.3344.

*4.6.2. tert-Butyl 12-(2-(benzo[d][1,3]dioxol-5-yl)-2-(N-(4-methoxyphenyl)-4-(trifluoromethyl)benzamido)acetamido)-dodecylcarbamate (**9k**)*

Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (s, 4H), 6.93 (s, 2H), 6.73–6.71 (m, 2H), 6.56 (d, J=9.2 Hz, 1H), 6.07 (s, 1H), 5.94 (d, J=0.8 Hz, 2H), 5.75 (s, 1H), 4.54 (s, 1H), 3.69 (s, 3H), 3.35–3.29 (m, 2H), 3.10 (t, J=7.2 Hz, 2H), 1.97 (s, 1H), 1.52–1.45 (m, 13H), 1.26–1.24 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.96, 169.21, 158.59, 155.98, 147.84, 147.76, 139.84, 133.00, 131.54, 131.06, 130.73, 128.63, 128.07, 124.65, 124.62, 124.36, 122.33, 113.68, 110.68, 108.20, 101.26, 79.00, 65.99, 55.23, 40.64, 39.99, 30.05, 29.67, 29.48, 29.26, 29.19, 28.42, 26.86, 26.77; HRMS (ESI) *m/z*: 778.3651 $[M+Na]^+$; calcd for $C_{41}H_{52}F_3N_3O_7$+Na: 778.3655.

*4.6.3. tert-Butyl 12-(2-(benzo[d][1,3]dioxol-5-yl)-2-(2,4,5-trifluoro-3-methoxy-N-(4-methoxyphenyl)benzamido)-acetamido)dodecylcarbamate (**9l**)*

Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.94 (s, 1H), 6.83–6.77 (m, 1H), 6.67 (d, J=7.6 Hz, 3H), 6.55 (d, J=8.8 Hz, 2H), 6.04 (s, 1H), 5.93 (s, 2H), 5.76 (d, J=5.2 Hz, 1H), 4.52 (s, 1H), 3.85 (s, 3H), 3.68 (s, 3H), 3.32–3.29 (m, 2H), 3.09 (t, J=7.2 Hz, 2H), 1.95 (s, 1H), 1.49–1.45 (m, 13H), 1.28–1.24 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.80, 165.43, 158.90, 156.07, 148.16, 147.88, 147.74, 145.74, 131.64, 131.34, 127.62, 124.40, 113.44, 110.57, 109.19, 109.02, 106.20, 101.27, 79.18, 65.45, 61.93, 60.37, 55.22, 40.82, 40.02, 30.04, 29.50, 29.48, 29.43, 29.26, 29.19, 28.42, 26.86, 26.77; HRMS (ESI) *m/z*: 772.3798 $[M+H]^+$; calcd for $C_{41}H_{52}F_3N_3O_8$+H: 772.3785.

*4.6.4. tert-Butyl 12-(2-(2-chloro-N-(4-methoxyphenyl)-nicotinamido)-2-(6-chloropyridin-3-yl)acetamido)-dodecylcarbamate (**9m**)*

Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, J=2.4 Hz, 1H), 8.27 (d, J=2.0 Hz, 1H), 7.57 (dd, J=2.4, 8.4 Hz, 1H), 7.49 (dd, J=2.4, 8.4 Hz, 1H), 7.16 (t, J=8.4 Hz, 2H), 6.87 (s, 1H), 6.63 (d, J=8.0 Hz, 2H), 6.21 (s, 1H), 6.01 (s, 1H), 4.50 (s, 1H), 3.72 (s, 3H), 3.36–3.31 (m, 2H), 3.10 (t, J=7.2 Hz, 2H), 1.90 (s, 1H), 1.46–1.45 (m, 13H), 1.28–1.25 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.02, 167.95, 159.34, 152.35, 151.97, 151.21, 149.50, 140.81, 138.67, 131.68, 131.38, 130.30, 129.09, 126.48, 123.97, 123.47, 121.01, 114.47, 79.09, 62.35, 56.76, 55.32, 40.14, 30.05, 29.44, 29.23, 29.15, 28.43, 26.83, 26.76; HRMS (ESI) *m/z*: 736.3005 $[M+Na]^+$; calcd for $C_{37}H_{49}Cl_2N_5O_5$+Na: 736.3008.

*4.6.5. tert-Butyl 12-(2-(6-chloropyridin-3-yl)-2-(N-(4-methoxyphenyl)-4-(trifluoromethyl)benzamido)-acetamido)dodecylcarbamate (**9n**)*

Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (d, J=2.4 Hz, 1H), 7.51 (dd, J=2.4, 8.4 Hz, 1H), 7.41 (dd, J=8.4, 15.2 Hz, 4H), 7.16 (d, J=8.4 Hz, 1H), 6.86 (s, 1H), 6.59 (d, J=8.8 Hz, 2H), 6.26 (s, 1H), 6.19 (s, 1H), 4.51 (s, 1H), 3.70 (s, 3H), 3.33 (q, J=6.4 Hz, 2H), 3.10 (t, J=7.2 Hz, 2H), 2.21 (s, 1H), 1.55–1.45 (m, 13H), 1.28–1.24 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.21, 168.20, 159.05, 156.05, 151.65, 151.08, 141.02, 138.99, 131.72, 131.59, 131.22, 129.38, 128.64, 124.84, 124.80, 123.93, 122.19, 114.18, 79.13, 62.17, 60.38, 55.29, 40.77, 40.10, 30.14, 29.47, 29.43, 29.18, 29.05, 28.42, 26.87, 26.76; HRMS (ESI) *m/z*: 769.3312 $[M+Na]^+$; calcd for $C_{39}H_{50}ClN_4O_7$+Na: 769.3320.

*4.6.6. tert-Butyl 12-(2-(6-chloropyridin-3-yl)-2-(2,4,5-trifluoro-3-methoxy-N-(4-methoxyphenyl)benzamido)-acetamido)dodecylcarbamate (**9o**)*

Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (d, J=2.0 Hz, 1H), 7.46 (dd, J=2.4, 8.4 Hz, 1H), 7.14 (d, J=8.4 Hz, 1H), 6.86 (s, 1H), 6.79–6.73 (m, 1H), 6.58 (d, J=8.8 Hz, 2H), 6.25 (s, 1H), 6.21 (s, 1H), 3.86 (s, 3H), 3.69 (s, 3H), 3.36–3.31 (m, 2H), 3.09 (t, J=7.2 Hz, 2H), 1.53–1.44 (m, 13H), 1.28–1.25 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.13, 167.76, 165.79, 159.36, 156.02, 151.78, 151.17, 148.12, 146.01, 145.90, 145.67, 140.92, 131.26, 130.41, 128.96, 123.86, 113.96, 108.93, 108.76, 108.72, 79.07, 61.95, 61.78, 60.38, 55.27, 40.13, 31.57, 30.05, 29.48, 29.40, 29.25, 29.19, 29.04, 28.41, 26.86, 26.76; HRMS (ESI) m/z: 785.3258 $[M+Na]^+$; calcd for $C_{39}H_{50}F_3ClN_4O_6$+Na: 785.3269.

*4.7. General procedure for the synthesis of compounds **1a–o***

To a solution of **9a–o** (0.50 mmol) in 2 mL CH_2Cl_2, TFA (**9a–i**, 30.00 mmol; **9j–o**, 15.00 mmol) was added and stirred for 5 h (TLC, CH_2Cl_2/CH_3OH/28%NH_4OH=100:10:1) at room temperature. The reaction mixture was basified to pH 14 with 10% aqueous sodium hydroxide solution. The organic layer was separated, washed with water, dried over anhydrous sodium sulfate, and concentrated in vacuo. The crude residue was purified by chromatography (CH_2Cl_2/CH_3OH/28%NH_4OH=500:10:1) to afford the final product.

*4.7.1. N-(2-(12-Aminododecylamino)-1-(6-chloropyridin-3-yl)-2-oxoethyl)-6-chloronicotinamide (**1a**)*

Colorless oil. Yield 91%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.81 (d, J=2.4 Hz, 1H), 8.49 (d, J=2.4 Hz, 1H), 8.06 (dd, J=2.4, 8.4 Hz, 1H), 7.77 (dd, J=2.4, 8.0 Hz, 1H), 7.35 (d, J=8.0 Hz, 1H), 7.25 (s, 1H), 5.86 (s, 1H), 3.20 (d, J=6.0 Hz, 2H), 2.68 (t, J=6.8 Hz, 2H), 2.44 (s, 2H), 1.42 (d, J=6.0 Hz, 4H), 1.25–1.19 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.58, 164.43, 154.78, 151.44, 148.95, 148.83, 137.85, 137.56, 137.44, 132.72, 127.85, 124.56, 124.17, 55.43, 55.06, 54.44, 41.86, 40.17, 40.05, 32.94, 29.58, 29.48, 29.38, 29.36, 29.32, 29.29, 29.15, 29.06, 26.82, 26.74; HRMS (ESI) m/z: 508.2235 $[M+H]^+$; calcd for $C_{25}H_{35}Cl_2N_5O_2$+H: 508.2246.

*4.7.2. N-(2-(12-Aminododecylamino)-1-(benzo[d][1,3]-dioxol-5-yl)-2-oxoethyl)-6-chloronicotinamide (**1b**)*

Colorless oil. Yield 90%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.84 (d, J=2.0 Hz, 1H), 8.08 (q, J=2.4 Hz, 1H), 8.03 (s, 1H), 7.36 (d, J=8.4 Hz, 1H), 6.96 (d, J=8.0 Hz, 1H), 6.93 (s, 1H), 6.76 (d, J=8.0 Hz, 1H), 6.28 (s, 1H), 5.94 (s, 2H), 5.59 (d, J=4.8 Hz, 1H), 3.22 (q, J=6.8 Hz, 2H), 3.10 (d, J=6.0 Hz, 2H), 1.53–1.45 (m, 4H), 1.21 (s, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.65, 163.89, 154.47, 148.83, 148.24, 147.82, 137.75, 131.65, 128.27, 124.08, 121.16, 108.59, 107.48, 101.35, 57.15, 41.53, 40.06, 31.86, 30.06, 29.32, 29.28, 29.20, 29.04, 28.89, 26.65; HRMS (ESI) m/z: 517.2581 $[M+H]^+$; calcd for $C_{27}H_{38}ClN_4O_4$+H: 517.2582.

*4.7.3. N-(2-(12-Aminododecylamino)-1-(6-chloropyridin-3-yl)-2-oxoethyl)-4-(trifluoromethyl)benzamide (**1c**)*

White solid, mp 92–94 °C. Yield 87%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (s, 1H), 7.89 (d, J=6.4 Hz, 2H), 7.79 (dd, J=2.0, 8.0 Hz, 1H), 7.65 (s, 2H), 7.25 (d, J=7.6 Hz, 1H), 5.93 (s, 1H), 3.20 (s, 2H), 2.68 (d, J=4.8 Hz, 2H), 2.46 (s, 2H), 1.42 (s, 4H), 1.24–1.17 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.66, 165.92, 151.38, 148.90, 137.40, 136.40, 134.29, 134.00, 133.65, 133.29, 132.95, 129.39, 128.37, 128.12, 127.77, 127.55, 125.62, 124.84, 124.51, 122.13, 119.43, 54.42, 41.92, 40.65, 40.12, 33.08, 29.96, 29.39, 29.32, 29.16, 29.08, 27.56, 27.29, 26.76; HRMS (ESI) m/z: 541.2555 $[M+H]^+$; calcd for $C_{27}H_{36}ClF_3N_4O_2$+H: 541.2557.

*4.7.4. N-(2-(12-Aminododecylamino)-1-(benzo[d][1,3]-dioxol-5-yl)-2-oxoethyl)-4-(trifluoromethyl)-benzamide (**1d**)*

Colorless oil. Yield 92%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (m, 3H), 7.67 (d, J=8.0 Hz, 2H), 6.99–6.95 (m, 2H), 6.75 (d, J=7.6 Hz, 1H), 6.43 (s, 1H), 5.92 (s, 2H), 5.64 (d, J=6.0 Hz, 1H), 3.23 (q, J=6.4 Hz, 2H), 2.82 (s, 2H), 2.71 (t, J=6.8 Hz, 2H), 1.46 (t, J=6.8 Hz, 4H), 1.21 (s, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.75, 165.37, 148.21, 147.74, 136.97, 133.60, 133.28, 131.88, 127.71, 125.55, 125.52, 124.97, 122.26, 121.08, 108.56, 107.46, 101.28, 57.12, 41.79, 40.02, 32.64, 29.42, 29.39, 29.35, 29.30, 29.24, 29.09, 26.74, 26.69; HRMS (ESI) m/z: 550.2883 $[M+H]^+$; calcd for $C_{29}H_{38}F_3N_3O_4$+H: 550.2893.

*4.7.5. N-(2-(12-Aminododecylamino)-1-(6-chloropyridin-3-yl)-2-oxoethyl)-2,4,5-trifluoro-3-methoxybenzamide (**1e**)*

Light yellow oil. Yield 89%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (s, 1H), 7.77 (dd, J=2.4, 8.4 Hz, 1H), 7.42–7.36 (m, 1H), 7.30 (s, 1H), 5.76 (s, 1H), 4.04 (s, 3H), 3.76–3.64 (m, 2H), 3.20 (t, J=6.4 Hz, 2H), 2.71 (s, 2H), 1.48–1.42 (m, 4H), 1.18 (s, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.17, 161.02, 151.81, 151.35, 149.34, 149.03, 148.70, 148.60, 137.40, 137.34, 133.09, 124.63, 124.44, 116.47, 111.36, 111.15, 62.28, 54.64, 41.48, 40.11, 40.01, 32.01, 29.51, 29.45, 29.37, 29.34, 29.31, 29.25, 29.16, 29.05, 29.02, 26.72; HRMS (ESI) m/z: 557.2510 $[M+H]^+$; calcd for $C_{27}H_{36}ClF_3N_4O_3$+H: 557.2506.

*4.7.6. N-(2-(12-Aminododecylamino)-1-(benzo[d][1,3]-dioxol-5-yl)-2-oxoethyl)-2,4,5-trifluoro-3-methoxybenzamide (**1f**)*

White solid, mp 86–89 °C. Yield 90%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.82 (d, J=7.6 Hz, 1H), 8.26 (d, J=4.8 Hz, 1H), 7.76 (s, 2H), 7.42–7.35 (m, 1H), 7.02 (s, 1H), 6.99–6.93 (m, 1H), 6.86 (d, J=8.0 Hz, 1H), 5.98 (s, 2H), 5.48 (d, J=7.6 Hz, 1H), 4.00 (s, 3H), 3.07–3.00 (m, 2H), 2.73 (t, J=7.6 Hz, 2H), 1.52–1.47 (m, 2H), 1.34 (d, J=6.0 Hz, 2H), 1.22–1.18 (m 16H); ^{13}C NMR (100 MHz,

DMSO-d_6): δ 169.85, 169.57, 161.59, 161.41, 151.06, 148.60, 147.98, 147.61, 147.16, 147.07, 137.83, 137.75, 137.66, 133.60, 133.41, 132.77, 129.39, 128.64, 128.55, 121.08, 120.76, 119.96, 111.01, 110.80, 108.43, 107.94, 107.77, 101.47, 62.72, 57.09, 30.76, 29.41, 29.36, 29.26, 29.22, 29.08, 29.01, 27.88, 27.15, 26.60, 26.31; HRMS (ESI) *m/z*: 566.2832 $[M+H]^+$; calcd for $C_{29}H_{39}F_3N_3O_5$+H: 566.2842.

*4.7.7. N-(2-(12-Aminododecylamino)-1-(3-chloro-2-fluorophenyl)-2-oxoethyl)-4-(trifluoromethyl)-benzamide (**1g**)*

White solid, mp 83–85 °C. Yield 85%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, *J*=8.0 Hz, 2H), 7.86 (d, *J*=5.6 Hz, 1H), 7.72 (d, *J*=8.0 Hz, 2H), 7.39–7.35 (m, 2H), 7.10 (t, *J*=8.0 Hz, 1H), 5.97 (s, 1H), 5.85 (d, *J*=6.0 Hz, 1H), 3.27 (q, *J*=6.4 Hz, 2H), 2.68 (t, *J*=7.2 Hz, 2H), 1.49–1.42 (m, 6H), 1.28–1.23 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.16, 165.14, 157.11, 154.65, 136.65, 133.83, 133.51, 130.79, 127.70, 127.06, 126.93, 126.75, 126.72, 125.69, 125.65, 125.27, 125.22, 124.94, 122.23, 121.80, 121.62, 51.76, 51.74, 42.21, 40.17, 33.72, 29.52, 29.48, 29.42, 29.38, 29.21, 29.09, 26.84, 26.61.

*4.7.8. N-(2-(12-Aminododecylamino)-1-(3-chloro-2-fluorophenyl)-2-oxoethyl)-4-fluorobenzamide (**1h**)*

White solid, mp 91–93 °C. Yield 88%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89–7.85 (m, 2H), 7.71 (d, *J*=6.0 Hz, 1H), 7.38–7.35 (m, 2H), 7.15–7.08 (m, 3H), 5.98 (s, 1H), 5.84 (d, *J*=6.0 Hz, 1H), 3.26 (q, *J*=6.8 Hz, 2H), 2.68 (t, *J*=7.2 Hz, 2H), 1.48–1.42 (m, 6H), 1.28–1.23 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.35, 166.30, 165.38, 163.79, 157.11, 154.65, 130.66, 129.63, 129.61, 129.56, 129.54, 127.31, 127.18, 126.80, 126.77, 125.22, 125.17, 121.72, 121.54, 115.80, 115.58, 51.75, 51.73, 42.24, 40.13, 33.80, 29.53, 29.49, 29.44, 29.43, 29.39, 29.22, 29.10, 26.85, 26.62.

*4.7.9. N-(2-(12-Aminododecylamino)-1-(3-chloro-2-fluorophenyl)-2-oxoethyl)-2-fluorobenzamide (**1i**)*

White solid, mp 88–91 °C. Yield 86%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28–8.24 (m, 1H), 8.03 (t, *J*=7.6 Hz, 1H), 7.51–7.47 (m, 1H), 7.39–7.35 (m, 2H), 7.24 (d, *J*=7.2 Hz, 1H), 7.18 (dd, *J*=8.0, 11.6 Hz, 1H), 7.10 (t, *J*=7.2 Hz, 1H), 5.94–5.89 (m, 2H), 3.30–3.24 (m, 2H), 2.69 (t, *J*=6.8 Hz, 2H), 1.55 (s, 2H), 1.49–1.42 (m, 4H), 1.29–1.23 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.10, 162.57, 162.54, 162.16, 159.70, 157.07, 154.61, 133.81, 133.71, 131.91, 131.89, 130.77, 130.57, 127.32, 127.18, 126.74, 126.71, 125.26, 125.22, 124.77, 124.74, 121.61, 121.43, 120.43, 120.32, 116.34, 116.10, 51.87, 51.85, 42.25, 40.08, 33.81, 29.54, 29.50, 29.45, 29.44, 29.40, 29.10, 26.86, 26.62, 26.51.

*4.7.10. N-(2-(12-Aminododecylamino)-1-(benzo[d][1,3]-dioxol-5-yl)-2-oxoethyl)-6-chloro-N-(4-methoxyphenyl)-nicotinamide (**1j**)*

White solid, mp 112–115 °C. Yield 91%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, *J*=2.4 Hz, 1H), 7.58–7.56 (m, 1H), 7.11 (d, *J*=8.4 Hz, 1H), 6.93 (s, 1H), 6.68 (d, *J*=2.0 Hz, 3H), 6.58 (d, *J*=8.4 Hz, 2H), 6.05 (s, 1H), 5.93 (t, *J*=1.2 Hz, 2H), 5.81 (d, *J*=5.6 Hz, 1H), 3.69 (s, 3H), 3.35–3.24 (m, 2H), 2.73–2.69 (m, 2H), 2.59–2.40 (m, 2H), 1.48 (s, 4H), 1.23 (s, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.08, 167.69, 158.85, 151.80, 149.52, 147.92, 147.78, 138.71, 132.53, 131.66, 131.07, 127.79, 124.46, 123.30, 113.94, 110.60, 108.24, 101.30, 65.96, 55.25, 41.93, 40.01, 32.99, 29.52, 29.50, 29.47, 29.44, 29.39, 29.17, 26.85, 26.81; HRMS (ESI) *m/z*: 623.3015 $[M+H]^+$; calcd for $C_{34}H_{43}ClN_4O_5$+H: 623.3000.

*4.7.11. N-(2-(12-Aminododecylamino)-1-(benzo[d][1,3]-dioxol-5-yl)-2-oxoethyl)-N-(4-methoxyphenyl)-4-(trifluoromethyl)benzamide (**1k**)*

White solid, mp 92–95 °C. Yield 93%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (s, 4H), 6.92 (s, 1H), 6.73–6.67 (m, 3H), 6.56 (d, *J*=8.8 Hz, 2H), 6.08 (s, 1H), 5.93 (s, 2H), 5.85 (s, 1H), 3.68 (s, 3H), 3.34–3.28 (m, 2H), 2.79 (t, *J*=6.8 Hz, 2H), 1.55–1.48 (m, 4H), 1.24 (s, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.98, 169.25, 158.58, 147.82, 147.74, 139.84, 132.95, 131.58, 130.73, 128.63, 128.07, 125.03, 124.67, 124.63, 124.38, 113.67, 110.60, 108.20, 101.26, 65.94, 55.23, 41.62, 39.99, 32.15, 29.47, 29.45, 29.37, 29.31, 29.17, 26.86, 26.74; HRMS (ESI) *m/z*: 656.3294 $[M+H]^+$; calcd for $C_{36}H_{44}F_3N_3O_5$+H: 656.3311.

*4.7.12. N-(2-(12-Aminododecylamino)-1-(benzo[d][1,3]-dioxol-5-yl)-2-oxoethyl)-2,4,5-trifluoro-3-methoxy-N-(4-methoxyphenyl)benzamide (**1l**)*

White solid, mp 95–97 °C. Yield 90%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.95 (s, 1H), 6.79 (d, *J*=5.6 Hz, 1H), 6.55 (d, *J*=8.4 Hz, 2H), 6.05 (s, 1H), 5.93 (s, 2H), 5.82 (s, 1H), 3.85 (s, 3H), 3.68 (s, 3H), 3.31 (t, *J*=5.6 Hz, 4H), 2.77 (s, 2H), 1.52 (d, *J*=8.4 Hz, 4H), 1.25 (s, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.81, 165.43, 158.92, 147.87, 147.73, 145.75, 131.65, 131.35, 127.66, 124.40, 113.44, 110.57, 109.22, 109.01, 108.19, 101.25, 65.44, 61.91, 55.21, 41.59, 40.02, 32.09, 31.56, 29.45, 29.42, 29.30, 29.17, 29.04, 26.85, 26.74; HRMS (ESI) *m/z*: 672.3265 $[M+H]^+$; calcd for $C_{36}H_{44}F_3N_3O_6$+H: 672.3260.

*4.7.13. N-(2-(12-Aminododecylamino)-1-(6-chloropyridin-3-yl)-2-oxoethyl)-6-chloro-N-(4-methoxyphenyl)-nicotinamide (**1m**)*

White solid, mp 93–96 °C. Yield 95%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40–8.28 (m, 2H), 7.57 (dd, *J*=2.0, 8.0 Hz, 1H), 7.48 (dd, *J*=2.4, 8.0 Hz, 1H), 7.14 (dd, *J*=2.0, 8.0 Hz, 2H), 6.62–6.57 (m, 3H), 6.31 (s, 1H), 3.71 (s, 3H), 3.33–3.28 (m, 2H), 3.01 (s, 2H), 2.42 (s, 2H), 1.78 (t, *J*=7.2 Hz, 2H), 1.51 (t, *J*=6.8 Hz, 2H), 1.39–1.23 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.25, 168.05, 159.28, 152.21, 151.10, 149.45, 138.67, 131.95, 131.68, 131.32, 130.50, 129.64, 124.08, 123.47, 114.47, 114.37, 62.07, 55.31, 40.08, 40.02, 31.27, 29.41, 29.23, 29.05, 28.91, 28.68, 27.51, 26.73, 26.29; HRMS (ESI) *m/z*: 614.2661 $[M+H]^+$; calcd for $C_{32}H_{42}Cl_2N_5O_3$+H: 614.2661.

*4.7.14. N-(2-(12-Aminododecylamino)-1-(6-chloropyridin-3-yl)-2-oxoethyl)-N-(4-methoxyphenyl)-4-(trifluoromethyl)-benzamide (**1n**)*

White solid, mp 113–115 °C. Yield 92%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (s, 1H), 7.47 (dd, J=2.4, 8.4 Hz, 1H), 7.40 (dd, J=8.4, 14.4 Hz, 4H), 7.14 (d, J=8.0 Hz, 1H), 6.88 (s, 1H), 6.57 (d, J=8.4 Hz, 2H), 6.52 (s, 1H), 6.30 (s, 1H), 3.69 (s, 3H), 3.31 (d, J=7.2 Hz, 2H), 2.95 (s, 2H), 1.72 (s, 2H), 1.50 (s, 2H), 1.26–1.23 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.28, 168.41, 168.33, 158.98, 151.71, 151.34, 151.29, 140.79, 139.06, 131.75, 131.65, 131.48, 131.15, 129.39, 128.61, 124.84, 124.81, 123.86, 122.19, 114.09, 62.11, 55.28, 40.69, 40.08, 36.74, 30.12, 29.32, 29.23, 29.09, 28.80, 27.96, 26.81, 26.50, 26.36; HRMS (ESI) *m/z*: 647.2956 $[M+H]^+$; calcd for $C_{34}H_{42}ClF_3N_4O_3$+H: 647.2976.

*4.7.15. N-(2-(12-Aminododecylamino)-1-(6-chloropyridin-3-yl)-2-oxoethyl)-2,4,5-trifluoro-3-methoxy-N-(4-methoxyphenyl)benzamide (**1o**)*

White solid, mp 101–103 °C. Yield 95%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (s, 1H), 7.45 (dd, J=2.4, 8.4 Hz, 1H), 7.14 (d, J=8.4 Hz, 1H), 6.87 (s, 1H), 6.80–6.75 (m, 1H), 6.58 (d, J=8.4 Hz, 2H), 6.37 (s, 1H), 6.24 (s, 1H), 3.87 (s, 3H), 3.70 (s, 3H), 3.33 (q, J=6.4 Hz, 2H), 2.88 (s, 2H), 1.65–1.52 (m, 4H), 1.29–1.25 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.81, 165.81, 159.34, 151.85, 151.26, 140.82, 131.28, 130.39, 128.92, 123.83, 113.94, 108.96, 108.92, 108.76, 108.71, 61.97, 61.78, 55.28, 41.78, 40.13, 30.14, 29.46, 29.38, 29.33, 29.17, 29.11, 26.85, 26.76; HRMS (ESI) *m/z*: 663.2914 $[M+H]^+$; calcd for $C_{34}H_{42}ClF_3N_4O_4$+H: 663.2914.

Acknowledgements

This work was financially supported by National Key Project for Basic Research (2003CB114405), the National High Technology Research and Development Program of China (863 Program, 2006AA10A201), the Shanghai Foundation of Science of Technology (073919107), and Shanghai Leading Academic Discipline Project (B507) for financial support.

References and notes

1. (a) Strømgaard, K.; Mellor, I. *Med. Res. Rev.* **2004**, *24*, 589–620; (b) Mellor, I. R.; Usherwood, P. N. R. *Toxicon* **2004**, *43*, 493–508; (c) Nilsen, A.; England, P. M. *J. Am. Chem. Soc.* **2007**, *129*, 4902–4903.
2. (a) Eldefrawi, A. T.; Eldefrawi, M. E.; Konno, K.; Mansour, N. A.; Nakanishi, K.; Oltz, E.; Usherwood, P. N. R. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 4910–4913; (b) Andersen, T. F.; Tikhonov, D. B.; Bølcho, U.; Bolshakov, K.; Nelson, J. K.; Pluteanu, F.; Mellor, I. R.; Egebjerg, J.; Strømgaard, K. *J. Med. Chem.* **2006**, *49*, 5414–5423.
3. (a) Choi, S. K.; Kalivretenos, A. G.; Usherwood, P. N. R.; Nakanishi, K. *Chem. Biol.* **1995**, *2*, 23–32; (b) Bixel, M. G.; Weise, C.; Bolognesi, M. L.; Rosini, M.; Brierley, M. J.; Mellor, I. R.; Usherwood, P. N. R.; Melchiorre, C.; Hucho, F. *J. Biol. Chem.* **2001**, *276*, 6151–6160.
4. (a) Blagbrough, I. S.; Brackley, P. T. H.; Bruce, M.; Bycroft, B. W.; Mather, A. J.; Millington, S.; Sudan, H. L.; Usherwood, P. N. R. *Toxicon* **1992**, *30*, 303–322; (b) Strømgaard, K.; Jensen, L. S.; Vogensen, S. B. *Toxicon* **2005**, *45*, 249–254.
5. Strømgaard, K.; Andersen, K.; Krogsgaard-Larsen, P.; Jaroszewski, J. W. *Mini Rev. Med. Chem.* **2001**, *1*, 317–338.
6. (a) Strømgaard, K.; Brierley, M. J.; Andersen, K.; Sløk, F. A.; Mellor, I. R.; Usherwood, P. N. R.; Krogsgaard-Larsen, P.; Jaroszewski, J. W. *J. Med. Chem.* **1999**, *42*, 5224–5234; (b) Brier, T. J.; Mellor, I. R.; Tikhonov, D. B.; Neagoe, I.; Shao, Z.; Brierley, M. J.; Strømgaard, K.; Jaroszewski, J. W.; Krogsgaard-Larsen, P.; Usherwood, P. N. R. *Mol. Pharmacol.* **2003**, *64*, 954–964; (c) Tikhonov, D. B.; Mellor, I. R.; Usherwood, P. N. R. *Biophys. J.* **2004**, *87*, 159–170.
7. (a) Wang, F.; Manku, S.; Hall, D. G. *Org. Lett.* **2000**, *2*, 1581–1583; (b) Usherwood, P. N. R.; Jaroszewski, J. W.; Franzyk, H. *Eur. J. Org. Chem.* **2003**, *23*, 3288–3299; (c) Olsen, C. A.; Witt, M.; Jaroszewski, J. W.; Franzyk, H. *J. Org. Chem.* **2004**, *69*, 6149–6152; (d) Olsen, C. A.; Jørgensen, M. R.; Hansen, S. H.; Witt, M.; Jaroszewski, J. W.; Franzyk, H. *Org. Lett.* **2005**, *7*, 1703–1706.
8. (a) Goodnow, R.; Konno, K.; Niwa, M., Jr.; Kallimopoulos, T.; Bukownik, R.; Lenares, D.; Nakanishi, K. *Tetrahedron* **1990**, *46*, 3267–3286; (b) Nakanishi, K.; Huang, X.; Jiang, H.; Liu, Y.; Fang, K.; Huang, D.; Choi, S.-K.; Katz, E.; Eldefrawi, M. *Bioorg. Med. Chem.* **1997**, *5*, 1969–1988.
9. Olsen, C. A.; Witt, M.; Franzyk, H.; Jaroszewski, J. W. *Tetrahedron Lett.* **2007**, *48*, 405–408.
10. (a) Park, W. K. C.; Auer, M.; Jaksche, H.; Wong, C. H. *J. Am. Chem. Soc.* **1996**, *118*, 10150–10155; (b) Bauer, S. M.; Armstrong, R. W. *J. Am. Chem. Soc.* **1999**, *121*, 6355–6366; (c) Hebach, C.; Kazmaier, U. *Chem. Commun.* **2003**, 596–597; (d) Wessjohann, L. A.; Voigt, B.; Rivera, D. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4785–4790; (e) El Kaïm, L.; Grimaud, L.; Oble, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 7961–7964; (f) Giovenzana, G. B.; Tron, G. C.; Di Paola, S.; Menegotto, I. G.; Pirali, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 1099–1102.
11. Dömling, A. *Curr. Opin. Chem. Biol.* **2002**, *6*, 306–313.
12. (a) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89; (b) Ngouansavanh, T.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 5775–5778.
13. Xing, X.; Wu, J.; Feng, G.; Dai, W. *Tetrahedron* **2006**, *62*, 6774–6781.
14. Kanizsai, I.; Gyónfalvi, S.; Szakonyi, Z.; Sillanpää, R.; Fülöp, F. *Green Chem.* **2007**, *9*, 357–360.
15. Studer, A.; Jeger, P.; Wipf, P.; Curran, D. P. *J. Org. Chem.* **1997**, *62*, 2917–2924.
16. Jørgensen, M. R.; Olsen, C. A.; Mellor, I. R.; Usherwood, P. N. R.; Witt, M.; Franzyk, H.; Jaroszewski, J. W. *J. Med. Chem.* **2005**, *48*, 56–70.
17. Olsen, C. A.; Mellor, I. R.; Wellendorph, P.; Usherwood, P. N. R.; Witt, M.; Franzyk, H.; Jaroszewski, J. W. *ChemMedChem* **2006**, *1*, 303–305.
18. Jensen, L. S.; Bølcho, U.; Egebjerg, J.; Strømgaard, K. *ChemMedChem* **2006**, *1*, 419–428.
19. Strømgaard, K.; Mellor, I. R.; Andersen, K.; Neagoe, I.; Pluteanu, F.; Usherwood, P. N. R.; Krogsgaard-Larsen, P.; Jaroszewski, J. W. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1159–1162.
20. Strømgaard, K.; Bjørnsdottir, I.; Andersen, K.; Brierley, M. J.; Rizoli, S.; Eldursi, N.; Mellor, I. R.; Usherwood, P. N. R.; Hansen, S. H.; Krogsgaard-Larsen, P.; Jaroszewski, J. W. *Chirality* **2000**, *12*, 93–102.
21. Appel, R.; Kleistück, R.; Ziehn, K. D. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 132.
22. (a) Lee, D.; Sello, J. K.; Schreiber, S. L. *Org. Lett.* **2000**, *2*, 709–712; (b) Murphy, P. V.; Bradley, H.; Tosin, M.; Pitt, N.; Fitzpatrick, G. M.; Glass, W. K. *J. Org. Chem.* **2003**, *68*, 5692–5704; (c) Basso, A.; Banfi, L.; Guanti, G.; Riva, R.; Riu, A. *Tetrahedron Lett.* **2004**, *45*, 6109–6111.
23. Xiang, Z.; Luo, T.; Lu, K.; Cui, J.; Shi, X.; Fathi, R.; Chen, J.; Yang, Z. *Org. Lett.* **2004**, *6*, 3155–3158.
24. (a) Hanusch-Kompa, C.; Ugi, I. *Tetrahedron Lett.* **1998**, *39*, 2725–2728; (b) Endo, A.; Yanagisawa, A.; Abe, M.; Tohma, S.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 6552–6554.
25. Shaabani, A.; Soleimani, E.; Rezayan, A. H. *Tetrahedron Lett.* **2007**, *48*, 6137–6141.
26. Mitchell, M. C.; Spikmans, V.; de Mello, A. J. *Analyst* **2001**, *126*, 24–27.
27. (a) Bhagat, S.; Chakraborti, A. K. *J. Org. Chem.* **2007**, *72*, 1263–1270; (b) Régnier, T.; Berrée, F.; Lavastre, O.; Carboni, B. *Green Chem.* **2007**, *9*, 125–126.