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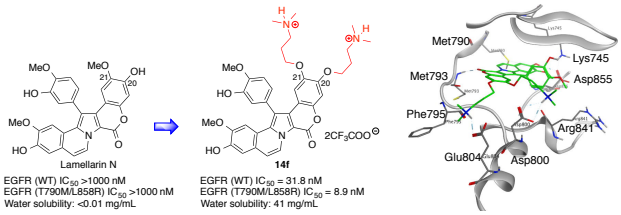

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Design, synthesis, and evaluation of A-ring-modified lamellarin N analogues as noncovalent inhibitors of the EGFR T790M/L858R mutant

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ABSTRACT

A series of A-ring-modified lamellarin N analogues were designed, synthesized, and evaluated as potential noncovalent inhibitors of the EGFR T790M/L858R mutant, a causal factor in the drug-resistant non-small cell lung cancer. Several water-soluble ammonium- or guanidinium-tethered analogues exhibited good kinase inhibitory activities. The most promising analogue, **14f**, displayed an excellent inhibitory profile against the T790M/L858R mutant [IC_{50} (WT) = 31.8 nM; IC_{50} (T790M/L858R) = 8.9 nM]. The effects of A-ring-substituents on activity were rationalized by docking studies.

1. Introduction

Epidermal growth factor receptor (EGFR) is a transmembrane protein involved in multiple signal transduction pathways associated with cell proliferation, survival, and migration.[1,2] Upon EGF binding to the extracellular receptor domain, EGFR monomers dimerize and activate their intracellular tyrosine kinase domains to initiate signaling.[3] Malignant mutations in the kinase domain of wild-type EGFR (EGFR WT) lead to constitutive activation, without ligand binding.[4,5] The most frequent mutations are the substitution of Leu858 in the activation loop with arginine (L858R) and an exon 19 deletion. These activating mutations cause a subset of non-small cell lung cancer (NSCLC). To treat this type of NSCLC, many small molecule tyrosine kinase inhibitors (TKIs) have been developed, two of which (gefitinib[6] and erlotinib[7]) were approved by the US Food and Drug Administration (FDA) in 2002 and 2004, respectively (Fig. 1). These drugs have a common 4-anilinoquinazoline motif and are highly effective for the treatment of NSCLC harboring activating EGFR mutations. Unfortunately, the efficacy of these drugs is limited by the emergence of resistance via the mutation of Thr790, referred to as the gatekeeper residue, to methionine (T790M),[8] which leads to an increased affinity to ATP and resistance to first-generation EGFR-TKIs.[9] To overcome this issue, 4-anilinoquinazoline-based irreversible (covalent) inhibitors, such as afatinib (BIBW2992),[10] have been developed. These second-generation inhibitors possess an appropriate Michael acceptor on the quinazoline ring to form a covalent bond with the SH group of Cys797. Although afatinib was approved in 2013, its use for the treatment of NSCLC harboring EGFR T790M/L858R is limited by its dose-limiting toxicity associated with the concurrent inhibition of EGFR WT.[11]

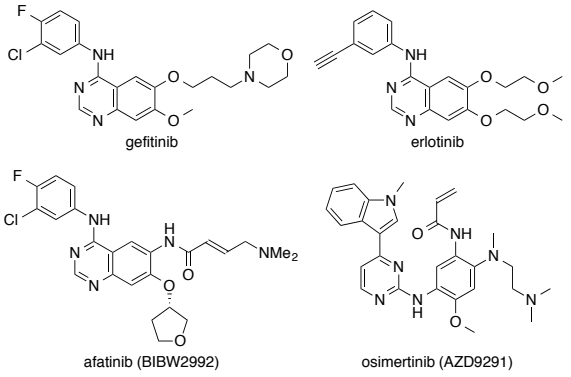

Fig. 1. Approved EGFR-TKIs for the treatment of NSCLC.

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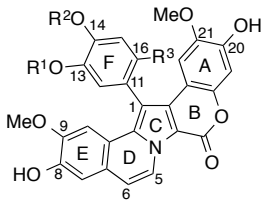
More recently, pyrimidine-based irreversible inhibitors, such as WZ4002,[12] rociletinib (CO-1686),[13] and osimertinib (AZD9291),[14] have been developed. These third-generation TKIs exhibit much a higher affinity to EGFR T790M/L858R than to EGFR WT and show promising responses to resistant NSCLC in clinical evaluations. The FDA approved osimertinib for the treatment of patients with EGFR T790M mutation-positive metastatic NSCLC in 2015. However, a new mutation at Cys797, the site of covalent binding, to serine (C797S) leads to resistance to osimertinib and related irreversible inhibitors.[15] It has been reported that the EGFR T790M/C797S/L858R triple mutation causes resistance to all currently available EGFR-TKIs, except for combined therapy with the anti-EGFR antibody cetuximab.[16–18] Thus, new EGFR-TKIs that do not rely on covalent bond formation with Cys797 for potency are needed.[19-21]

Lamellarins are DOPA-derived marine natural products with a unique polyaromatic structure (Fig. 2).[22,23] Some lamellarins exhibit potent cytotoxicity against cancer cell lines, including multi-drug resistant phenotype.[24–27] In 2003, Bailly reported that lamellarin D (**1**) is a potent inhibitor of DNA topoisomerase I.[28] There is a strong correlation between cytotoxicity and topoisomerase I inhibition, suggesting that topoisomerase I is a major molecular target of **1** in cancer cells.[29] In 2008, Meijer reported that lamellarin N (**2**) strongly inhibits several protein kinases related to cancer and neurodegenerative diseases, such as CDKs and GSK-3α/β,[30] but has low selectivity. Recently, we investigated the effects of the axial chirality of **2** on the selectivity of kinase inhibtion.[31] Although **2** could not be resolved at room temperature due to the relatively low energy barrier for rotation around the C1–C11 single bond (83–87 kJ/mol),[32] 16-methyllamellarin N (**3**) with hindered rotation was successfully resolved by HPLC over the chiral stationary phase to yield thermally stable atropisomers.[31] Interestingly, these isomers differed in selectivity to 8 protein kinases (CDK1/cyclin B, CDK2/cyclin A, CDK5/p25, GSK-3α/β, PIM1, DYRK1A, CLK3, and CK1). Although (a*R*)-**3** showed potent, but non-selective inhibition of all kinases, except for CK1, (a*S*)-**3** selectively inhibited GSK-3α/β, PIM1, and DYRK1A. In contrast to parental



	R¹	R²	R³
lamellarin D (**1**)	Me	H	H
lamellarin N (**2**)	H	Me	H
16-methyllamellarin N (**3**)	H	Me	Me

Fig. 2. Biologically active lamellarins.

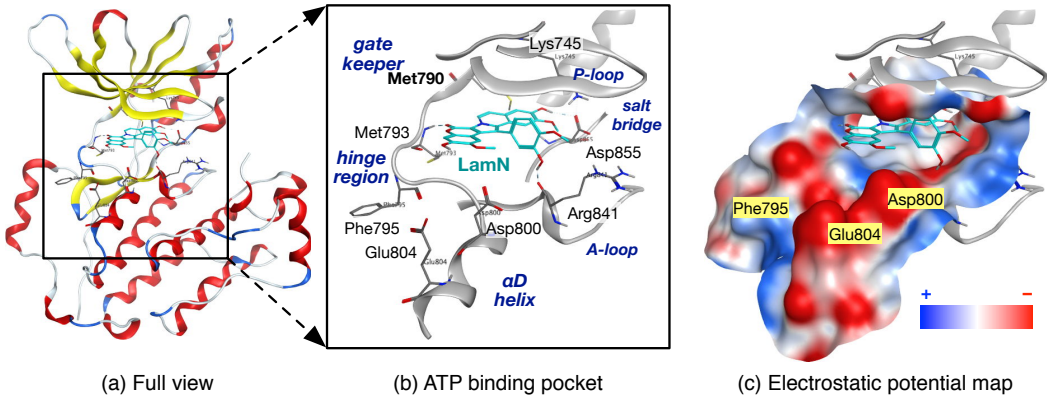
2, both (a*R*)- and (a*S*)-**3** showed no inhibition of topoisomerase I. These results suggested that the lamellarin scaffold is a unique structural motif that can be used to design selective inhibitors of protein kinases. In this study, we generated potent noncovalent inhibitors of the EGFR T790M/L858R mutant based on **2**.

2. Results and discussion

2.1. Structure-based drug design

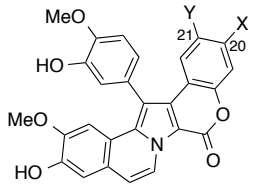
We initially investigated the binding mode of **2** in the EGFR T790M/L858R kinase domain by docking simulations using published X-ray crystallographic data for the T790M/L858R/V948R kinase–gefitinib complex[33] [PDB ID: 4I22]. An additional V948R mutation was introduced to prevent dimerization of the T790M/L858R kinase during crystallization. This mutation had essentially no influence on the structure or activity of the T790M/L858R kinase beyond the changes observed in a monomeric state in solution.[33] Gefitinib in the ATP-binding pocket of the kinase was replaced with **2** and the resulting complex was minimized using the MOE program.[34] The model with the highest docking score is depicted in Fig. 3. In this model, the planar pentacyclic core (ABCDE-ring) of **2** occupied the ATP-binding pocket in such a way that the A-ring was directed to the solvent channel (entrance region) and the E-ring was oriented to the specificity (back) pocket. The F-ring perpendicularly connected to the pentacyclic core was situated at the ribose-binding site. The lactone carbonyl (C=O) of the B-ring formed a hydrogen bond with the NH of Met793 located in the hinge region. The phenolic OH at C8 also formed a hydrogen bond with the side chain carboxylate of Asp855 in the conserved catalytic salt bridge (Lys745–Asp855). Another phenolic OH at C13 of the F-ring was directed downward and formed an additional hydrogen bond with C=O of Arg841 in the A-loop. Overall, the binding mode of **2** in the EGFR T790M/L858R kinase domain was similar to the previously reported binding modes of **2** in CDK2 or GSK-3β.[31]

Further inspection of this model revealed the presence of a negatively charged small pocket at the edge of the entrance region. This pocket was surrounded by stem chain C=O of Phe795 and side chain carboxylates of both Asp800 and Glu804 [Fig. 3 (c)]. Since the oxygen functionalities (20-OH and 21-OMe) at the A-ring of **2** were directed to this pocket, we thought that positively charged ammonium group(s) tethered to these oxygens may increase the activity of **2** by ionic and/or hydrogen bonding interactions. Examples of the designed inhibitors are illustrated in Fig. 4.



(a) Full view (b) ATP binding pocket (c) Electrostatic potential map

Fig. 3. A docking model of lamellarin N (**2**) in the ATP-binding pocket of the EGFR T790M/L858R/V948R kinase domain [Scoring (GBVI/WSA dG): –9.06 kcal/mol].



X	Y
$O(CH_2)_nN^+HR_2$	OMe
OMe	$O(CH_2)_nN^+HR_2$
$O(CH_2)_nN^+HR_2$	$O(CH_2)_nN^+HR_2$

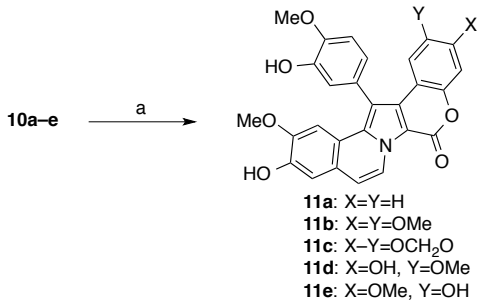
Fig. 4. A-ring-modified lamellarin N analogues designed to target EGFR-TKIs.

2.2. Synthesis

We recently developed a modular synthesis of lamellarins by the regioselective assembly of 3,4,5-differentially arylated pyrrole-2-carboxylates.[35,36] In the present study, we improved this method to produce diverse A-ring-modified lamellarin N analogues by preassembling the common tricyclic intermediate **7** (CDEF-ring of the lamellarin core), followed by Suzuki–Miyaura coupling with a variety of 2-(methoxymethoxy)arylboronic acids **8a**–**g** corresponding to the A-ring (Scheme 1).

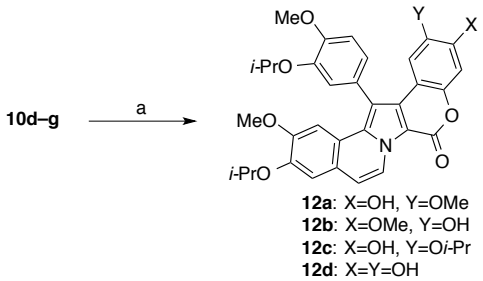
Readily available *N*-Boc-2,5-dibromopyrrole (**4**) was converted to a known tetra-substituted pyrrole **5** in 6 steps using procedures established in our laboratories.[35] Compound **5** was alkylated at the pyrrole-nitrogen with bromoacetaldehyde dimethyl acetal in the presence of Cs_2CO_3 to give **6** (91% yield). Subsequent trifluoromethanesulfonic acid (TfOH)-catalyzed cyclization[35] of **6** to produce a key tricyclic intermediate **7** was difficult due to the unexpected partial elimination of an *O*-isopropyl-protecting group in the highly acidic conditions. This unfavorable overreaction could be avoided by the slow addition of a catalytic amount (0.1 equiv) of TfOH as a diluted dichloromethane (DCM) solution (condition b in Scheme 1). Under carefully controlled conditions, intact **7** was isolated in 88% yield. We later found that this cyclization could be performed more conveniently using trimethylsilyl trifluoromethanesulfonate (TMSOTf) (0.5 equiv) as a Lewis acid catalyst[37] (condition c in Scheme 1). Subsequent Suzuki–Miyaura coupling of **7** with a range of 2-(methoxymethoxy)arylboronic acids **8a**–**g** gave **9a**–**g** in good yields using $Pd(dba)_2$–dppf[35] as a catalyst. The coupling products were lactonized directly to *O*-protected lamellarins **10a**–**g** by heating in methanol in the presence of *p*-TsOH·H_2O.

Next, deprotection of *O*-isopropyl and/or *O*-benzyl groups of **10a**–**e** was performed. Both protecting groups were simultaneously removed by treatment with BCl_3[38] in DCM to give fully deprotected lamellarins **11a**–**e** in good yields (Scheme 2). Compound **11d** was identical to lamellarin N based on a spectroscopic comparison with an authentic sample.[35,38] An attempted deprotection of **10g** (X=Y=OBn) with BCl_3 gave only an intractable material.

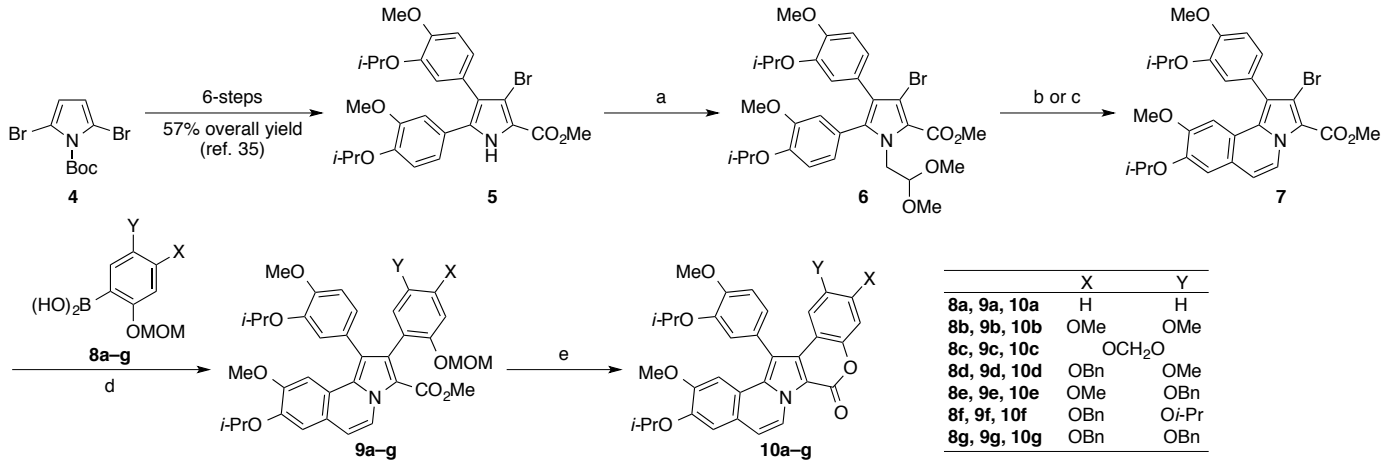


Scheme 2. Deprotection of *O*-*i*-Pr and *O*-Bn groups of **10a**–**e**. *Reagents and conditions:* (a) BCl_3, DCM, approximately –78 °C to room temperature or –78 °C to –40 °C (**11a**: 97%, **11b**: 96%, **11c**: 70%. **11d**: 71%, **11e**: 90%).

The *O*-benzyl groups of **10d**–**g** were selectively removed by hydrogenolysis[39] over Pd-C using HCO_2NH_4 as a hydrogen source to give **12a**–**d** in excellent yields (Scheme 3). When the solubility of the substrate was poor (e.g., **10g**) in the solvent (AcOEt/EtOH = 1:1), partial hydrogenation of the 5,6-unsaturated bond at the D-ring was observed. However, this unfavorable overreaction was avoided by carrying out the reaction in a sufficient amount of the solvent for a short period of time (<1 h). Acidolysis[40] could also be used for selective debenzylation. For example, treatment of **10g** (X=Y=OBn) with trifluoroacetic acid in the presence of pentamethylbenzene[41] gave **12d** (X=Y=OH) in 87% yield.



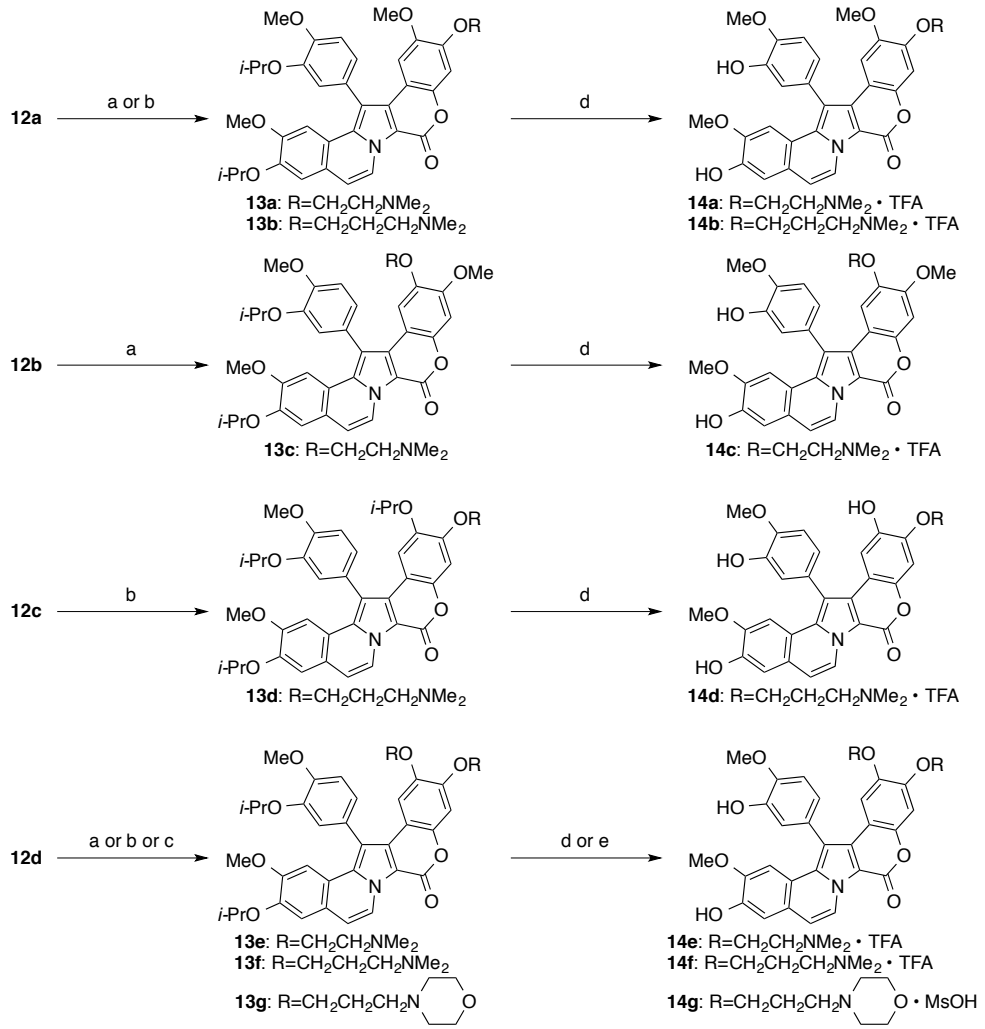
Scheme 3. Selective deprotection of the *O*-Bn group of **10d**–**g**. *Reagents and conditions:* (a) HCO_2NH_4, 10% Pd-C, AcOEt/EtOH = 1:1, reflux, 0.5–1 h (**12a**: 93%, **12b**: 95%, **12c**: 96%, **12d**: 93%).



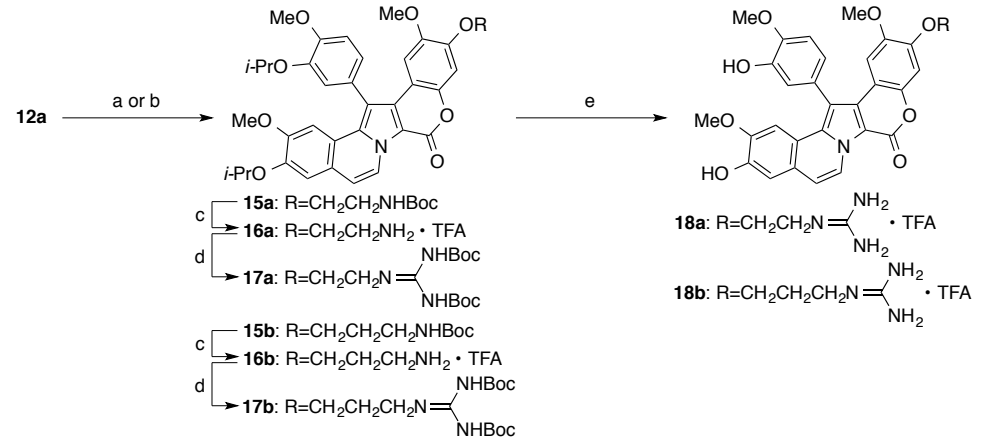
	X	Y
8a, 9a, 10a	H	H
8b, 9b, 10b	OMe	OMe
8c, 9c, 10c	OCH_2O	
8d, 9d, 10d	OBn	OMe
8e, 9e, 10e	OMe	OBn
8f, 9f, 10f	OBn	O*i*-Pr
8g, 9g, 10g	OBn	OBn

Scheme 1. Synthesis of *O*-protected lamellarins **10a**–**g**. *Reagents and conditions:* (a) $BrCH_2CH(OMe)_2$, Cs_2CO_3, DMF, 110 °C, 16 h (91%); (b) TfOH (0.1 equiv), DCM, 0 °C, 2 h (88%); (c) TMSOTf (0.5 equiv), DCM, rt, 1.5 h (91%); (d) $Pd(dba)_2$ (10 mol%), dppf (10 mol%), **8** (1.5 equiv), Na_2CO_3 (6.6 equiv), DME, water, 85 °C in a sealed tube or reflux, 24 h (**9a**: 94%, **9b**: 90%, **9c**: 94%, **9d**: 77%, **9e**: 97%, **9f**: 87%, **9g**: quant.); (e) *p*-TsOH·H_2O (4.0 equiv), MeOH, 65 °C in a sealed tube or reflux, 18 h (**10a**: 98%, **10b**: 96%, **10c**: 92%, **10d**: 93%, **10e**: 90%, **10f**: 88%, **10g**: 84%).

Next, selectively debenzylated lamellarins **12a**–**d** were converted to a series of ammonium-tethered analogues **14a**–**g** in two additional steps (Scheme 4). Thus, **12a**–**d** were reacted with an appropriate alkylating agent, such as 2-(dimethylamino)ethyl chloride, 3-(dimethylamino)propyl chloride, and 4-(3-chloropropyl)morpholine, in acetone in the presence of K_2CO_3 to give **13a**–**g** in good yields. The *O*-isopropyl protecting groups of **13a**–**g** were cleanly removed by treatment with $AlCl_3$[42] at room temperature, without affecting *O*-aminoalkyl groups. The deprotected lamellarins were purified using a Sephadex column and isolated as trifluoroacetates **14a**–**f** or methanesulfonate **14g**. The trifluoroacetate corresponding to **14g** was not obtained

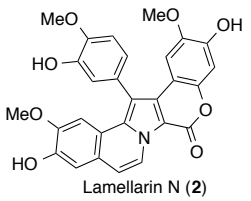


Scheme 4. Synthesis of ammonium-tethered lamellarin N analogues **14a–g**. *Reagents and conditions:* (a) $ClCH_2CH_2NMe_2 \cdot HCl$, K_2CO_3, acetone, reflux (**13a**: 88%, **13c**: 82%, **13e**: 54 %); (b) $ClCH_2CH_2CH_2NMe_2 \cdot HCl$, K_2CO_3, acetone, reflux (**13b**: 70%, **13d**: 34%, **13f**: 71%); (c) 4-(3-chloropropyl)morpholine, NaI, K_2CO_3, acetone, reflux (**13g**: 97%); (d) (1) $AlCl_3$, DCM, rt, (2) TFA (**14a**: 97%, **14b**: 82%, **14c**: 88%, **14d**: 98%, **14e**: 93%, **14f**: quant); (e) (1) $AlCl_3$, DCM, rt, (2) MsOH (**14g**: 86%).



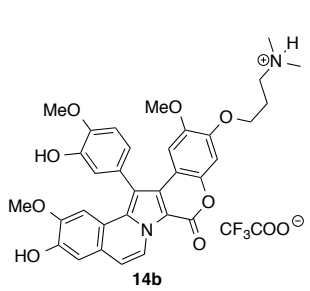
Scheme 5. Synthesis of guanidinium-tethered lamellarin N analogues **18a, b**. *Reagents and conditions:* (a) $BocNHCH_2CH_2OH$ (1.5 equiv), DIAD (1.5 equiv), PPh_3 (1.5 equiv), THF, rt (**15a**: 90%); (b) $BocNHCH_2CH_2CH_2OH$ (1.5 equiv), DIAD (1.5 equiv), PPh_3 (1.5 equiv), THF, rt (**15b**: 87%); (c) TFA (**16a**: quant, **16b**: 96%); (d) *N,N′*-bis(Boc)-1*H*-pyrazole-1-carboxamidine (2.0 equiv), Et_3N (2.0 equiv), THF, rt, (**17a**: 87%, **17b**: 75%); (e) (1) $AlCl_3$ (10 equiv), DCM, rt, 2 d (2) TFA (**18a**: 46%, **18b**: 81%).

owing to the lower basicity of morpholino nitrogen (ca. 1/1000 of common tertiary amines). In contrast to the highly lipophilic parental lamellarins,[40] these ammonium salts were highly soluble in water. For example, the estimated solubilities of **14b** and **14f** in water were 19 mg/mL and 41 mg/mL, respectively, as determined by a HPLC method (Fig. 5).[43]



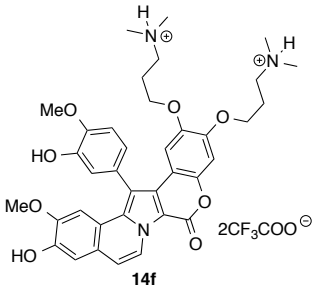
Lamellarin N (**2**)

Water solubility: <0.01 mg/mL



14b

Water solubility: 19 mg/mL



14f

Water solubility: 41 mg/mL

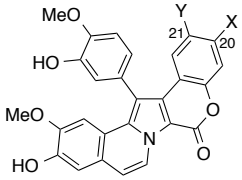
Fig. 5. Solubilities of lamellarin N (**2**) and its ammonium-tethered analogues **14b** and **14f**.

The guanidinium group can recognize carboxylate anions by exceptionally potent ionic and hydrogen bonding interactions.[44] We predicted that the guanidinium group at the A-ring side chain could interact with Asp800 or Glu804 more strongly than the simple ammonium groups. Thus, we synthesized guanidinium-tethered analogues **18a** and **18b** from **12a** (Scheme 5). The Mitsunobu reaction of **12a** with *tert*-butyl *N*-(2-hydroxyethyl)carbamate produced the *O*-alkylated compound **15a** in good yield. After deprotection of the Boc group by TFA, the resulting **16a** was reacted with *N,N′*-bis(*tert*-butoxycarbonyl)-1*H*-pyrazole-1-carboxamidine[45,46] to give **17a**. Treatment of this compound with $AlCl_3$ in DCM caused the simultaneous deprotection of both *i*-Pr and Boc groups. The resulting guanidinium compound was isolated as a TFA salt **18a** in good yield. Another guanidinium derivative **18b** with a propylene linker was prepared in a similar manner using *tert*-butyl *N*-(3-hydroxypropyl)carbamate as an alkylating agent. The guanidinium salts **18a** and **18b** were soluble in water, like the ammonium salts **14a–g**.

2.3. In vitro kinase assay and structure-activity relationships

Kinase inhibitory activities of the synthetic lamellarins **11b, d, e, 14a–g,** and **18a, b** were evaluated by enzyme-linked immunosorbent assays using the recombinant kinase domains of EGFR WT and the T790M/L858R mutant.[47] Approved EGFR-TKIs, gefitinib and afatinib, were used as positive controls. Half-maximal inhibitory concentrations (IC_{50}) of the tested compounds are shown in Table 1. Lamellarin N (**11d**) and its 20-*O*-methyl derivative **11b** were inactive at concentrations of lower than 1000 nM (entries 1, 2). Interestingly, compound **11e**, in which 20-OH and 21-OMe of **11d** is simply replaced, exhibited moderate activity (entry 3). These results indicate that 21-OH (not 20-OH) is an important structural unit to potentiate the kinase inhibitory activity. The inhibitor **14a** with a 2-(*N,N*-dimethylamino)ethoxy group at C20 showed modest activity (entry 4). Homologous **14b** bearing a 3-(*N,N*-dimethylamino)propoxy group at the same position exhibited higher activity (entry 5). Thus the 1,3-propylene linker seems to be better than the ethylene linker to connect the positively charged ammonium group to the lamellarin core. Transposition of the 20- and 21-substituents (X and Y) of **14a** decreased the activity (entry 6). Compound **14d** with 21-OH and 20-[3-(*N,N*-dimethylamino)propoxy] had greater

Table 1
Inhibitory activities of A-ring-modified lamellarin N analogues toward EGFR WT and T790M/L858R kinase domains.



Entry	Compound	X	Y	IC_{50} (nM)	
				WT	T790M/L858R
1	**11b**	OMe	OMe	>1000	>1000
2	**11d**	OH	OMe	>1000	>1000
3	**11e**	OMe	OH	249.1	396.7
4	**14a**	$OCH_2CH_2NMe_2 \cdot$ TFA	OMe	595.4	559.8
5	**14b**	$OCH_2CH_2CH_2NMe_2 \cdot$ TFA	OMe	215.4	188.3
6	**14c**	OMe	$OCH_2CH_2NMe_2 \cdot$ TFA	842.3	>1000
7	**14d**	$OCH_2CH_2CH_2NMe_2 \cdot$ TFA	OH	47.8	82.6
8	**14e**	$OCH_2CH_2NMe_2 \cdot$ TFA	$OCH_2CH_2NMe_2 \cdot$ TFA	190.6	232.9
9	**14f**	$OCH_2CH_2CH_2NMe_2 \cdot$ TFA	$OCH_2CH_2CH_2NMe_2 \cdot$ TFA	31.8	8.9
10	**14g**	$OCH_2CH_2CH_2N$(morpholine) $\cdot$ MsOH	$OCH_2CH_2CH_2N$(morpholine) $\cdot$ MsOH	>1000	>1000
11	**18a**	OCH_2CH_2N=C(NH$_2$)(NH$_2$) $\cdot$ TFA	OMe	>1000	>1000
12	**18b**	$OCH_2CH_2CH_2N$=C(NH$_2$)(NH$_2$) $\cdot$ TFA	OMe	47	39
13	gefitinib	–	–	4.0	>1000
14	afatinib	–	–	<1.0	3.8

activity than that of **14b** (entry 7), indicating again that 21-OH potentiates the activity of lamellarins. However, lamellarins with 21-OH selectively inhibited WT, rather than the T790M/L858R mutant (entries 3, 7). The activities of 20, 21-bis(*N,N*-dimethylamino)alkyloxy lamellarins **14e** and **14f** were higher than those of the corresponding monoalkyloxy lamellarins **14a** and **14b** (entries 8, 9). In particular, **14f** showed potent and selective activity toward the T790M/L858R mutant at a low nM concentration (entry 9). The activity was comparable to that of the covalent inhibitor afatinib (entry 14). Of interest, the less basic morpholino derivative **14g** was inactive at concentration of below 1000 nM (entry 10). The activities of the guanidinium derivatives were sensitive to the length of the linker. Compound **18a** with the ethylene linker was inactive, whereas compound **18b** bearing the 1,3-propylene linker was quite active (entries 11, 12).

2.4. Docking analysis

To rationalize the effects of A-ring-substituents X and Y on kinase inhibitory activity, docking simulations of the active compounds **14b**, **14d**, **14f**, and **18b** in the ATP-binding pocket of EGFR T790M/L858R/V948R were performed using the protocol described in section 2.1. Plausible binding modes are represented

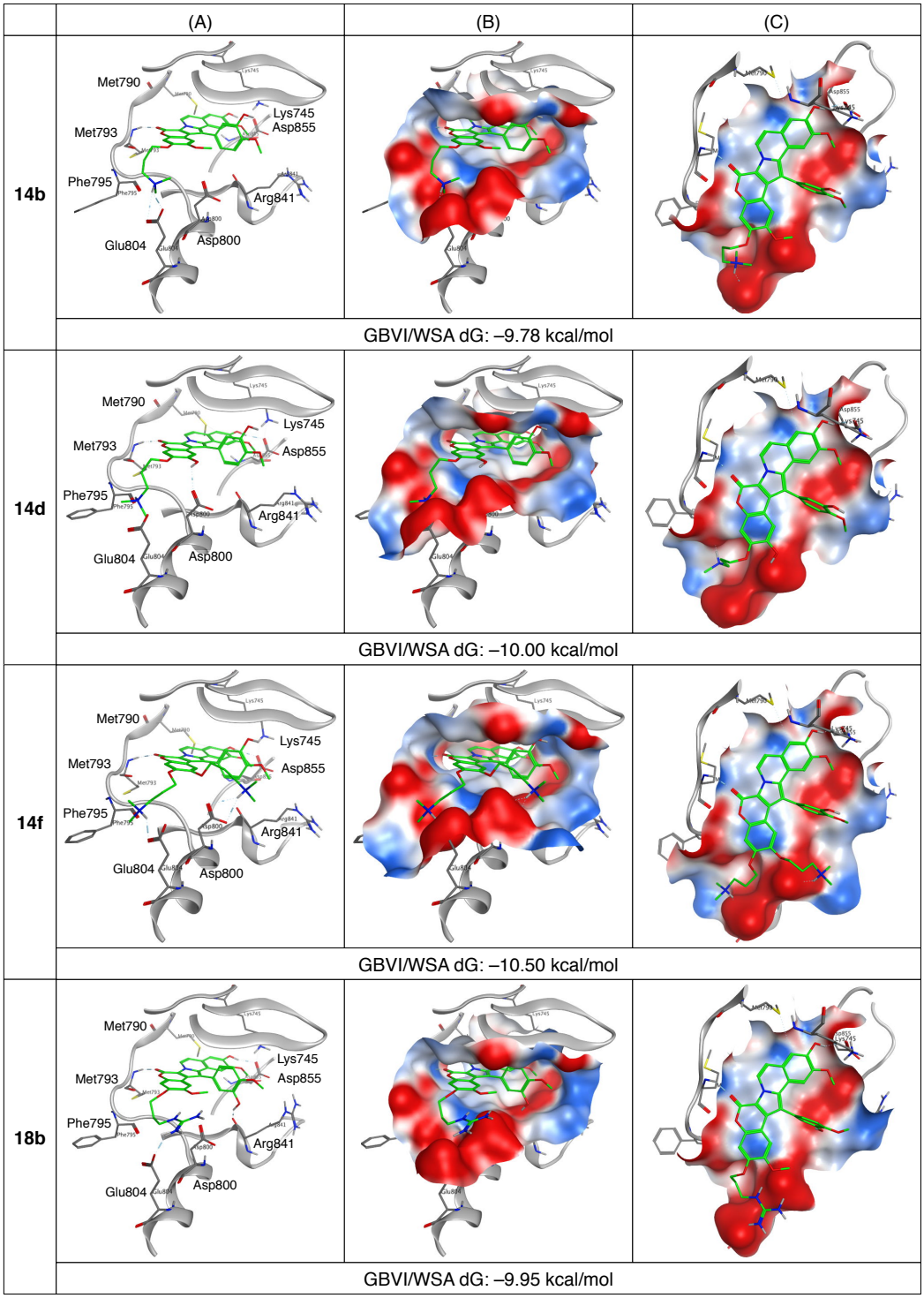


Fig. 6. Plausible binding modes of **14b**, **14d**, **14f**, and **18b** in the ATP-binding pocket of EGFR T790M/L858R/V948R. (**A**) Side view from the entrance region; (**B**) side-view from the entrance region (the region surrounding the ATP-binding pocket is shown by an electrostatic potential map); (**C**) top view from the *N*-terminal lobe (floor of the ATP-binding pocket is shown by an electrostatic potential map).

in Fig. 6. The orientation of the lamellarin core of each compound was quite similar to that of lamellarin N shown in Fig. 3. Each 3-(*N,N*-dimethylamino)propoxy group at the 20-position of **14b**, **14d**, and **14f** was nicely embedded in the negatively charged small pocket in the entrance region and the ammonium group makes hydrogen bonding and/or ionic interactions with the side chain carboxylate of Glu804 or stem chain carbonyl of Phe795. The 21-OH of **14d** and 21-[3-(*N,N*-dimethylamino)propoxy] group of **14f** can form additional hydrogen bonds with Asp800. This may explain the higher activities of **14d** and **14f** compared to **14b**. The high activity of **18b** may be rationalized by unique dual hydrogen bonding interactions of the guanidinium moiety with the carboxylates of Asp800 and Glu804.

3. Conclusion

Various A-ring-modified lamellarin N analogues were designed, synthesized, and evaluated as non-covalent inhibitors of the EGFR T790M/L858R mutant. Several water-soluble ammonium- and guanidinium-tethered analogues, such as **14b, d**, **e, f**, and **18b**, exhibited good inhibitory activity against the kinases. In particular, **14f** showed a low nM IC_{50} towards the T790M/L858R mutant. Docking studies suggested that hydrogen bonding and/or ionic interactions of A-ring-substituent(s) with Phe795, Asp800, and Asp804 are major determinants of the increased activities of these analogues. Further biological evaluations of the most promising analogue, **14f**, are in progress in our laboratories.

4. Experimental section

4.1. Synthesis–general

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were obtained with a Thermo Nicolet Nexus 670 NT FT-IR instrument and are reported in terms of absorption frequency (cm^{-1}). NMR spectra were recorded on a JEOL JNM-AL400 instrument (400 MHz for ^1H and 100 MHz for ^{13}C) or a Varian NMR System 500PS SN instrument (500 MHz for ^1H and 126 MHz for ^{13}C). Chemical shifts for ^1H NMR are expressed in parts per million (ppm) relative to the following internal standards: $CDCl_3$ (tetramethylsilane, δ 0.0 ppm); DMSO-d_6 (DMSO, δ 2.50 ppm). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, dd = double doublet, t = triplet, sext = sextet, sep = septet, m = multiplet, br s = broad singlet), coupling constant (Hz), and integration. Chemical shifts for ^{13}C NMR are expressed in ppm relative to the following internal standards: $CDCl_3$ (tetramethylsilane, δ 0.0 ppm); DMSO-d_6 (DMSO-d_6, δ 39.52 ppm). ^{13}C NMR data are reported in terms of chemical shift. High-resolution mass spectra (HRMS) were recorded on a JEOL JMS-T100TD (direct analysis in real-time mass spectrometry, DARTMS) instrument or a JEOL JMS-700N (fast atom bombardment mass spectrometry, FABMS or electron ionized mass spectrometry, EIMS) instrument. Column chromatography was conducted using silica gel 60N, 63–210 μm (Kanto Chemical Co., Inc.) or Chromatorex NH-DM1020 (Fuji Silysia Chemical Ltd.). Flash chromatography was conducted using silica gel 60N, 40–50 μm (Kanto Chemical Co., Inc.).

4.2. Synthesis of A-ring-modified lamellarin N analogues

*4.2.1. Synthesis of tricyclic intermediate **7***

*4.2.1.1. Methyl 3-bromo-1-(2,2-dimethoxyethyl)-4-(3-isopropoxy-4-methoxyphenyl)-5-(4-isopropoxy-3-methoxyphenyl)-1H-pyrrole-2-carboxylate (**6**)*

Under an argon atmosphere, a mixture of **5** (2.66 g, 5.00 mmol), 2-bromo-1,1-dimethoxyethane (3.72 mL, 31.5 mmol), and Cs_2CO_3 (11.7 g, 35.8 mmol) in DMF (60 mL) was stirred for 16 h at 110 °C. After cooling to room temperature, the mixture was diluted with water and and the products were extracted with a mixed solvent of hexane–EtOAc (1:1). The extract was washed with water and brine, dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography over silica gel 60N (hexane–ethyl acetate = 3:1) to give **6** as a colorless semisolid (2.83 g, 91%). IR (KBr): 1698, 1467, 1441, 1255, 1136, 1093 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.21 (d, J = 6.1 Hz, 6H), 1.35 (d, J = 6.1 Hz, 6H), 3.23 (s, 6H), 3.67 (s, 3H), 3.81 (s, 3H), 3.93 (s, 3H), 4.27 (sep, J = 6.1 Hz, 1H), 4.41–4.46 (m, 3H), 4.50 (sep, J = 6.1 Hz, 1H), 6.66 (s, 1H), 6.72–6.76 (m, 3H), 6.76 (d, J = 1.7 Hz, 1H), 6.79 (d, J = 8.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 22.0, 48.4, 51.4, 54.9, 55.8, 55.9, 71.0, 71.1, 104.2, 106.4, 111.1, 114.5, 115.3, 118.3, 120.3, 123.0, 123.3, 124.0, 125.0, 126.0, 138.8, 146.3, 147.5, 149.0, 149.7, 161.6. HRDARTMS *m/z*. Calcd for $C_{30}H_{38}BrNO_8$ (M^+): 619.17808. Found: 619.17815.

4.2.1.2. Methyl 2-bromo-8-isopropoxy-1-(3-isopropoxy-4-methoxyphenyl)-9-methoxy-pyrrolo[2,1-a]isoquinoline-3-carboxylate (7)

Method 1: Under an argon atmosphere, to a solution of **6** (255 mg, 0.411 mmol) in DCM (8.0 mL) was added a DCM solution of TfOH (74.5 mM, 550 μL, 41.1 μmol) at 0 °C. After stirring for 2 h at 0 °C, Na_2CO_3 (50 mg) and $MgSO_4$ (50 mg) was added to the mixture. The suspension was allowed to warm to room temperature and then stirred for an additional 0.5 h. The mixture was passed through a filter paper. The filtrate was evaporated and the residue was purified by column chromatography over silica gel 60N (hexane–ethyl acetate = 3:1) to give **7** as a colorless solid (202 mg, 88%).

Method 2: Under an argon atmosphere, to a solution of **6** (1.84 g, 2.97 mmol) in DCM (110 mL) was added TMSOTf (270 μL, 1.49 mmol) at 0 °C. After stirring for 1.5 h at 0 °C, a saturated aqueous $NaHCO_3$ was added to the mixture. The mixture was allowed to warm to room temperature and stirred for an additional 0.5 h. The products were extracted with DCM and the extract was washed with water and brine, dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography over silica gel 60N (hexane–ethyl acetate = 4:1) to give **7** as a colorless solid (1.50 g, 91%).

Recrystallization from Et_2O–hexane gave a colorless granules. Mp 165–166 °C. IR (KBr): 1675, 1449, 1352, 1213, 1111 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.35 (d, J = 6.1 Hz, 3H), 1.38 (d, J = 6.1 Hz, 3H), 1.42 (d, J = 6.1 Hz, 6H), 3.41 (s, 3H), 3.93 (s, 3H), 3.98 (s, 3H), 4.53 (sep, J = 6.1 Hz, 1H), 4.66 (sep, J = 6.1 Hz, 1H), 6.93 (d, J = 7.6 Hz, 1H), 6.95 (d, J = 1.9 Hz, 1H), 6.99 (dd, J = 1.9 and 8.2 Hz, 1H), 7.02 (s, 1H), 7.05 (d, J = 8.2 Hz, 1H), 7.07 (s, 1H), 9.28 (d, J = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 22.0, 22.1, 51.2, 55.2, 56.1, 71.1, 71.2, 105.4, 110.1, 112.1, 112.3, 112.4, 112.4, 118.6, 118.7, 119.3, 123.3, 123.5, 124.1, 127.8, 130.9, 147.5, 148.0, 150.0, 150.2, 161.6. HRDARTMS *m/z*. Calcd for $C_{28}H_{31}BrNO_6$ [$(M+H)^+$]: 556.13347. Found: 556.13474.

*4.2.2. Synthesis of O-protected lamellarins **10a–g***

*4.2.2.1. Methyl 8-isopropoxy-1-(3-isopropoxy-4-methoxyphenyl)-9-methoxy-2-[2-(methoxymethoxy)phenyl]pyrrolo[2,1-a]isoquinoline-3-carboxylate (**9a**)*

Under an argon atmosphere, a mixture of **7** (50.0 mg, 89.9 μmol), **8a** (24.6 mg, 0.135 mmol), $Pd(dba)_2$ (5.2 mg, 9.0 μmol), dppf (5.0 mg, 9.0 μmol), Na_2CO_3 (63.0 mg, 0.594 mmol), DME

(3.0 mL), and degassed water (0.2 mL) was heated in a sealed tube at 85 °C for 24 h. After cooling to room temperature, the mixture was evaporated and the products were extracted with DCM. The extract was washed with water and brine, dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography over silica gel 60N (hexane–ethyl acetate = 4:1) to give **9a** as a pale yellow solid (51.8 mg, 94%). Recrystallization from DCM–hexane gave a pale yellow needles. Mp 186–187 °C. IR (KBr): 1688, 1473, 1379, 1256, 1226, 1190, 1114 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.07 (d, J = 6.1 Hz, 1.5H), 1.20 (d, J = 6.1 Hz, 1.5H), 1.21 (d, J = 6.1 Hz, 1.5H), 1.27 (d, J = 6.1 Hz, 1.5H), 1.42 (d, J = 6.1 Hz, 6H), 3.30 (s, 3H), 3.42 (br s, 3H), 3.59 (s, 3H), 3.81 (s, 1.5H), 3.82 (s, 1.5H), 4.25 (sep, J = 6.1 Hz, 0.5H), 4.33 (sep, J = 6.1 Hz, 0.5H), 4.66 (sep, J = 6.1 Hz, 1H), 4.86 (d, J = 6.9 Hz, 0.5H), 4.96 (d, J = 6.9 Hz, 0.5H), 4.99 (d, J = 6.9 Hz, 0.5H), 5.04 (d, J = 6.9 Hz, 0.5H), 6.75–6.89 (m, 4H), 6.93 (d, J = 7.6 Hz, 1H), 6.95–7.01 (m, 1H), 7.04 (s, 1H), 7.08 (d, J = 8.3 Hz, 1H), 7.11–7.21 (m, 2H), 9.30 (d, J = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.7, 21.8, 21.9, 21.9, 22.0, 22.2, 50.7, 55.3, 55.7, 56.0, 71.1, 71.1, 71.2, 95.1, 105.6, 110.6, 111.4, 111.7, 112.0, 112.8, 114.6, 117.4, 118.1, 118.2, 118.6, 119.0, 119.4, 119.8, 121.0, 121.2, 123.5, 123.9, 124.1, 124.2, 124.4, 128.2, 128.3, 128.4, 130.4, 131.4, 131.8, 132.3, 132.4, 146.9, 147.5, 148.5, 149.3, 149.9, 150.4, 155.6, 162.6. HRDARTMS *m*/*z*. Calcd for $C_{36}H_{40}NO_8$ [$(M+H)^+$]: 614.27539. Found: 614.27399.

*4.2.2.2. Methyl 2-[4,5-dimethoxy-2-(methoxymethoxy)phenyl]-8-isopropoxy-1-(3-isopropoxy-4-methoxyphenyl)-9-methoxy-pyrrolo[2,1-a]isoquinoline-3-carboxylate (**9b**)*

According to the procedure described for the preparation of **9a**, **7** (50.0 mg, 89.9 μmol), **8b** (32.7 mg, 0.135 mmol), $Pd(dba)_2$ (5.2 mg, 9.0 μmol), and dppf (5.0 mg, 9.0 μmol) were reacted. After purification by column chromatography over silica gel 60N (hexane–ethyl acetate = 2:1), **9b** was obtained as a pale brown solid (54.4 mg, 90%). Recrystallization from DCM–hexane gave a pale brown powder. Mp 72–73 °C. IR (KBr): 1683, 1438, 1372, 1214, 1188, 1122, 1019 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.05–1.33 (m, 6H), 1.42 (d, J = 6.1 Hz, 6H), 3.28 (br s, 3H), 3.43 (s, 3H), 3.62 (br s, 3H), 3.66 (s, 3H), 3.84 (s, 3H), 3.85 (s, 3H), 4.31 (br s, 1H), 4.66 (sep, J = 6.1 Hz, 1H), 4.70–5.00 (m, 2H), 6.48–6.63 (m, 1H), 6.75 (br s, 1H), 6.77–7.03 (m, 5H), 7.22–7.30 (m, 1H), 9.28 (d, J = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6, 21.9, 22.0, 22.2, 50.8, 55.3, 55.7, 55.9, 56.1, 71.0, 71.1, 71.3, 96.6, 96.7, 101.5, 102.4, 105.6, 110.5, 111.5, 112.0, 112.9, 114.7, 118.6, 119.1, 119.7, 120.7, 123.4, 123.4, 124.2, 128.6, 130.3, 131.8, 143.4, 144.1, 147.5, 148.5, 148.5, 148.8, 149.0, 149.3, 149.7, 149.9, 162.6. HRDARTMS *m*/*z*. Calcd for $C_{38}H_{44}NO_{10}$ [$(M+H)^+$]: 674.29652. Found: 674.29513.

*4.2.2.3. Methyl 8-isopropoxy-1-(3-isopropoxy-4-methoxyphenyl)-9-methoxy-2-[6-(methoxymethoxy)-1,3-benzodioxol-5-yl]pyrrolo[2,1-a]isoquinoline-3-carboxylate (**9c**)*

According to the procedure described for the preparation of **9a**, **7** (50.0 mg, 89.9 μmol), **8c** (30.5 mg, 0.135 mmol), $Pd(dba)_2$ (5.2 mg, 9.0 μmol), and dppf (5.0 mg, 9.0 μmol) were reacted. After purification by column chromatography over silica gel 60N (hexane–ethyl acetate = 3:1), **9c** was obtained as a pale brown solid (55.3 mg, 94%). Recrystallization from DCM–hexane gave a pale brown powder. Mp 200–201 °C. IR (KBr): 1670, 1438, 1379, 1256, 1161, 1112 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.15 (d, J = 6.0 Hz, 1.5H), 1.24 (d, J = 6.0 Hz, 1.5H), 1.25 (d, J = 6.0 Hz, 1.5H), 1.29 (d, J = 6.0 Hz, 1.5H), 1.42 (d, J = 6.0 Hz, 6H), 3.26 (s, 1.5H), 3.28 (s, 1.5H), 3.42 (s, 1.5H), 3.43 (s, 1.5H), 3.66 (s, 3H), 3.83 (s, 1.5H), 3.85 (s, 1.5H), 4.32 (sep, J = 6.0 Hz, 0.5H), 4.38 (sep, J = 6.0 Hz, 0.5H), 4.66 (sep, J = 6.0 Hz, 1H), 4.69 (d, J = 6.6 Hz, 0.5H), 4.83 (d, J = 6.6 Hz, 0.5H), 4.84 (d, J = 6.6 Hz, 0.5H), 4.92 (d, J = 6.6 Hz, 0.5H), 5.86 (d, J = 5.9 Hz, 0.5H), 5.91 (d, J = 7.3 Hz, 0.5H), 6.45 (s, 0.5H), 6.58 (s, 0.5H), 6.72 (s, 1H), 6.81–6.99 (m, 4H), 7.04 (s, 1H), 7.18 (s, 0.5H), 7.24 (s, 0.5H), 9.27 (d, J = 7.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.7, 21.9, 22.0, 22.2, 50.8, 55.3, 55.6, 56.0, 71.0, 71.1, 71.2, 96.3, 98.9, 101.1, 105.6, 110.5, 110.7, 110.9, 111.5, 111.8, 112.0, 118.7, 118.9, 119.0, 119.2, 119.3, 119.7, 119.8, 123.5, 124.1, 124.4, 128.3, 128.4, 130.4, 132.0, 141.7, 141.7, 146.8, 147.0, 147.0, 147.5, 149.4, 149.9, 150.4, 162.5. HRDARTMS *m*/*z*. Calcd for $C_{37}H_{40}NO_{10}$ [$(M+H)^+$]: 658.26522. Found: 658.26263.

*4.2.2.4. Methyl 2-[4-benzyloxy-5-methoxy-2-(methoxymethoxy)phenyl]-8-isopropoxy-1-(3-isopropoxy-4-methoxyphenyl)-9-methoxy-pyrrolo[2,1-a]isoquinoline-3-carboxylate (**9d**)*

Under an argon atmosphere, a mixture of **7** (290 mg, 0.521 mmol), **8d** (497 mg, 1.56 mmol), $Pd(dba)_2$ (30.0 mg, 52.1 μmol), dppf (28.9 mg, 52.1 μmol), Na_2CO_3 (365 mg, 3.44 mmol), DME (12 mL), and degassed water (1.0 mL) was refluxed for 24 h. After cooling to rt, the mixture was evaporated and the products were extracted with DCM. The extract was washed with water and brine, dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography over silica gel 60N (hexane–ethyl acetate = 3:1) to give **9d** as a pale brown solid (302 mg, 77%). Recrystallization from DCM–hexane gave a pale brown granules. Mp 56–57 °C. IR (KBr): 1683, 1509, 1436, 1374, 1260, 1215, 1121, 1024 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.98–1.33 (m, 6H), 1.40–1.48 (m, 6H), 3.22 (br s, 3H), 3.43 (br s, 3H), 3.61 (br s, 6H), 3.84 (br s, 3H), 4.20–4.43 (m, 1H), 4.63–4.95 (m, 3H), 5.06–5.16 (m, 2H), 6.48–7.50 (m, 13H), 9.27 (d, J = 7.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6, 21.9, 22.0, 22.2, 50.8, 55.3, 55.5, 56.1, 56.4, 71.1, 71.2, 96.5, 102.8, 104.3, 104.4, 105.5, 105.6, 110.4, 110.5, 111.5, 111.9, 112.0, 112.4, 112.8, 112.9, 115.3, 118.6, 119.0, 119.7, 123.2, 123.4, 123.4, 124.2, 124.7, 127.3, 127.6, 127.8, 128.1, 128.2, 128.4, 128.7, 130.3, 131.7, 137.1, 144.2, 147.5, 149.3, 149.6, 149.9, 162.6. HRDARTMS *m*/*z*. Calcd for $C_{44}H_{48}NO_{10}$ [$(M+H)^+$]: 750.32782. Found: 750.32788.

*4.2.2.5. Methyl 2-[5-benzyloxy-4-methoxy-2-(methoxymethoxy)phenyl]-8-isopropoxy-1-(3-isopropoxy-4-methoxyphenyl)-9-methoxy-pyrrolo[2,1-a]isoquinoline-3-carboxylate (**9e**)*

According to the procedure described for the preparation of **9d**, **7** (421 mg, 0.756 mmol), **8e** (361 mg, 1.13 mmol), $Pd(dba)_2$ (41.9 mg, 72.9 μmol), dppf (45.0 mg, 81.2 μmol), Na_2CO_3 (529 mg, 4.99 mmol), DME (30 mL), and degassed water (2.0 mL) was reacted for 24 h. After purification by column chromatography over silica gel 60N (hexane–ethyl acetate = 2:1), **9e** was obtained as a pale brown solid (552 mg, 97%). Recrystallization from DCM–hexane gave a pale brown granules. Mp 53–54 °C. IR (KBr): 1683, 1437, 1374, 1259, 1217, 1122, 1065 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.10–1.22 (m, 3H), 1.25 (br d, J = 6.0 Hz, 3H), 1.42 (d, J = 6.0 Hz, 6H), 3.28 (s, 3H), 3.43 (s, 3H), 3.59 (br s, 3H), 3.82 (s, 3H), 3.84 (s, 3H), 4.31 (sep, J = 6.0 Hz, 1H), 4.66 (sep, J = 6.0 Hz, 1H), 4.67–4.98 (m, 4H), 6.59 (br s, 1H), 6.68–6.89 (m, 4H), 6.91 (d, J = 7.6 Hz, 1H), 7.04 (s, 1H), 7.24 (s, 1H), 7.25–7.40 (m, 5H), 9.27 (d, J = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.7, 21.9, 22.0, 22.2, 50.8, 55.3, 55.6, 56.0, 71.0, 71.1, 71.2, 71.9, 96.4, 101.7, 105.6, 110.5, 111.5, 111.8, 112.0, 112.8, 118.1, 118.7, 119.0, 119.7, 123.4, 124.2, 127.4, 127.7, 128.4, 128.5, 130.3, 131.8, 137.4, 142.6, 147.0, 147.5, 149.3, 149.4, 149.9, 150.2, 162.6. HRDARTMS *m*/*z*. Calcd for $C_{44}H_{48}NO_{10}$ [$(M+H)^+$]: 750.32782. Found: 750.32836.

4.2.2.6. Methyl 2-[4-benzyloxy-5-isopropoxy-2-(methoxymethoxy)phenyl]-8-isopropoxy-1-(3-isopropoxy-4-

*methoxyphenyl)-9-methoxy-pyrrolo[2,1-a]isoquinoline-3-carboxylate (**9f**)*

According to the procedure described for the preparation of **9a**, **7** (186 mg, 0.334 mmol), **8f** (173 mg, 0.500 mmol), $Pd(dba)_2$ (19.6 mg, 34.1 μmol), and dppf (18.3 mg, 33.0 μmol) were reacted. After purification by flash chromatography over silica gel 60N (hexane–ethyl acetate = 2:1), **9f** was obtained as a pale yellow solid (226.1 mg, 87%). Recrystallization from Et_2O–hexnae gave a pale yellow powder. Mp 61–64 °C. IR (KBr): 1683, 1437, 1373, 1245, 1191, 1121, 1063 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.02–1.31 (m, 12H), 1.42 (d, J = 6.1 Hz, 6H), 3.23 (br s, 3H), 3.42 (s, 3H), 3.60 (s, 3H), 3.82 (s, 3H), 4.14–4.42 (m, 2H), 4.66 (sep, J = 6.1 Hz, 1H), 4.69–4.93 (m, 2H), 5.02–5.13 (m, 2H), 6.57 (br s, 0.5H), 6.66 (br s, 0.5H), 6.75–6.90 (m, 3.5H), 6.91 (d, J = 7.6 Hz, 1H), 6.96–7.02 (m, 0.5H), 7.04 (s, 1H), 7.20–7.33 (m, 2H), 7.34–7.39 (m, 2H), 7.42–7.47 (m, 2H), 9.28 (d, J = 7.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.6, 21.8, 21.9, 22.0, 22.1, 22.2, 50.7, 55.3, 55.5, 56.1, 70.9, 71.1, 71.2, 72.7, 96.2, 104.7, 105.6, 110.5, 111.6, 111.9, 112.8, 118.6, 118.8, 119.2, 119.7, 122.4, 122.7, 123.4, 124.0, 124.3, 127.5, 127.7, 128.4, 128.6, 130.3, 131.7, 137.4, 142.0, 147.0, 147.5, 149.2, 149.7, 149.9, 150.7, 162.7. HRDARTMS *m/z*. Calcd for $C_{46}H_{52}NO_{10}$ $[(M+H)^+]$: 778.35912. Found: 778.35688.

*4.2.2.7. Methyl 2-[4,5-bis(benzyloxy)-2-(methoxymethoxy)phenyl]-8-isopropoxy-1-(3-isopropoxy-4-methoxyphenyl)-9-methoxy-pyrrolo[2,1-a]isoquinoline-3-carboxylate (**9g**)*

According to the procedure described for the preparation of **9d**, **7** (1.23 g, 2.21 mmol), **8g** (1.31 g, 3.32 mmol), $Pd(dba)_2$ (123 mg, 0.213 mmol), dppf (132 mg, 0.237 mmol), Na_2CO_3 (1.55 g, 14.6 mmol), DME (80 mL), and degassed water (6.0 mL) was reacted for 24 h. After purification by column chromatography over silica gel 60N (hexane–ethyl acetate = 5:1), **9g** was obtained as a pale yellow semisolid (1.83 g, quant.). IR (KBr): 1682, 1436, 1373, 1217, 1188, 1121, 1063 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.03–1.30 (m, 6H), 1.42 (d, J = 6.1 Hz, 6H), 3.23 (br s, 3H), 3.42 (s, 3H), 3.56 (br s, 3H), 3.82 (s, 3H), 4.23–4.40 (m, 1H), 4.66 (sep, J = 6.1 Hz, 1H), 4.79–4.93 (m, 4H), 5.04–5.14 (m, 2H), 6.63 (br s, 0.5H), 6.71–6.90 (m, 4.5H), 6.91 (d, J = 7.6 Hz, 1H), 7.03 (s, 1H), 7.20–7.38 (m, 9H), 7.40–7.45 (m, 2H), 9.27 (d, J = 7.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.6, 21.9, 22.0, 22.2, 50.7, 55.3, 55.5, 56.0, 70.9, 71.1, 71.4, 72.3, 96.2, 104.6, 105.6, 110.5, 111.5, 111.8, 112.0, 112.8, 118.6, 118.8, 119.0, 119.2, 119.4, 119.7, 123.4, 124.2, 127.5, 127.6, 127.7, 127.8, 128.3, 128.4, 128.5, 130.3, 131.7, 137.2, 137.6, 143.3, 147.0, 147.5, 148.6, 149.2, 149.9, 150.3, 162.6. HRDARTMS *m/z*. Calcd for $C_{50}H_{52}NO_{10}$ $[(M+H)^+]$: 826.35912. Found: 826.36040.

*4.2.2.8. 11-Isopropoxy-14-(3-isopropoxy-4-methoxyphenyl)-12-methoxy-6H-[1]benzopyrano[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one (**10a**)*

Under an argon atmosphere, a mixture of **9a** (50.0 mg, 81.5 μmol), *p*-TsOH·H_2O (62.0 mg, 0.326 mmol), and MeOH (2.0 mL) was heated in a sealed tube at 65 °C for 18 h. After cooling to room temperature, the mixture was evaporated and the products were extracted with DCM. The extract was washed with water and brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography over silica gel 60N (hexane–ethyl acetate = 2:1) to give **10a** as a pale yellow solid (42.9 mg, 98%). Recrystallization from DCM–hexane gave a colorless granules. Mp 208–209 °C. IR (KBr): 1716, 1476, 1263, 1221, 1178, 1111, 1043 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.34 (d, J = 6.1 Hz, 3H), 1.37 (d, J = 6.1 Hz, 3H), 1.44 (d, J = 6.1 Hz, 6H), 3.45 (s, 3H), 3.99 (s, 3H), 4.55 (sep, J = 6.1 Hz, 1H), 4.70 (sep, J = 6.1 Hz, 1H), 7.01–7.07 (m, 2H), 7.09 (s, 1H), 7.11–7.18 (m, 4H), 7.31–7.37 (m, 2H), 7.39–7.44 (m, 1H), 9.23 (d, J = 7.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 21.9, 22.0, 55.2, 56.2, 71.2, 71.3, 105.6, 108.4, 110.4, 112.2, 112.8, 117.3, 118.1, 119.1, 123.0, 123.8, 123.9, 124.2, 124.7, 128.0, 128.3, 128.7, 134.6, 148.2, 148.5, 150.2, 150.4, 151.8, 155.2. HRDARTMS *m/z*. Calcd for $C_{33}H_{32}NO_6$ $[(M+H)^+]$: 538.22296. Found: 538.22569.

*4.2.2.9. 11-Isopropoxy-14-(3-isopropoxy-4-methoxyphenyl)-2,3,12-trimethoxy-6H-[1]benzopyrano[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one (**10b**)*

According to the procedure described for the preparation of **10a**, **9b** (50.0 mg, 74.2 μmol), *p*-TsOH·H_2O (56.5 mg, 0.297 mmol), and MeOH (2.0 mL) were reacted. After purification by column chromatography over silica gel 60N (hexane–ethyl acetate = 2:1), **10b** was obtained as a pale yellow solid (42.6 mg, 96%). Recrystallization from DCM–hexane gave a pale gray needles. Mp 192–193 °C. IR (KBr): 1704, 1418, 1269, 1225, 1163, 1039 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.36 (d, J = 6.1 Hz, 3H), 1.37 (d, J = 6.1 Hz, 3H), 1.44 (d, J = 6.1 Hz, 6H), 3.46 (s, 3H), 3.49 (s, 3H), 3.84 (s, 3H), 3.97 (s, 3H), 4.58 (sep, J = 6.1 Hz, 1H), 4.70 (sep, J = 6.1 Hz, 1H), 6.74 (s, 1H), 6.86 (s, 1H), 6.99 (d, J = 7.4 Hz, 1H), 7.09 (s, 1H), 7.17 (d, J = 8.2 Hz, 1H), 7.17 (d, J = 1.8 Hz, 1H), 7.19 (s, 1H), 7.23 (dd, J = 1.8 and 8.2 Hz, 1H), 9.14 (d, J = 7.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 21.9, 22.0, 22.0, 55.2, 55.4, 56.0, 56.4, 71.2, 71.3, 100.5, 105.0, 105.6, 107.7, 109.9, 110.4, 111.0, 112.3, 112.7, 118.2, 119.0, 123.1, 124.2, 124.7, 128.2, 129.3, 134.5, 145.5, 146.6, 148.2, 148.5, 149.5, 150.2, 150.3, 155.5. HRDARTMS *m/z*. Calcd for $C_{35}H_{36}NO_8$ $[(M+H)^+]$: 598.24409. Found: 598.24289.

*4.2.2.10. 3-Isopropoxy-15-(3-isopropoxy-4-methoxyphenyl)-2-methoxy-8H-[1,3]dioxolo[6',7']-[1]benzopyrano[4',3':4,5]pyrrolo[2,1-a]isoquinolin-8-one (**10c**)*

According to the procedure described for the preparation of **10a**, **9c** (50.0 mg, 76.0 μmol), *p*-TsOH·H_2O (57.8 mg, 0.304 mmol), and MeOH (2.0 mL) were reacted. After purification by column chromatography over silica gel 60N (hexane–ethyl acetate = 2:1), **10c** was obtained as a pale yellow solid (40.6 mg, 92%). Recrystallization from DCM–hexane gave a pale yellow granules. Mp 235.5–236.5 °C. IR (KBr): 1703, 1475, 1434, 1262, 1153, 1033 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.34 (d, J = 6.1 Hz, 3H), 1.38 (d, J = 6.1 Hz, 3H), 1.43 (d, J = 6.1 Hz, 6H), 3.44 (s, 3H), 3.98 (s, 3H), 4.56 (sep, J = 6.1 Hz, 1H), 4.68 (sep, J = 6.1 Hz, 1H), 5.94 (d, J = 1.4 Hz, 1H), 5.95 (d, J = 1.4 Hz, 1H), 6.70 (s, 1H), 6.90 (s, 1H), 6.99 (d, J = 7.4 Hz, 1H), 7.06 (s, 1H), 7.07 (s, 1H), 7.10 (s, 1H), 7.13 (s, 1H), 7.13 (s, 1H), 9.18 (d, J = 7.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 21.9, 22.0, 55.2, 56.2, 71.1, 71.3, 98.9, 101.7, 102.3, 105.6, 107.5, 110.3, 111.3, 111.4, 112.5, 112.8, 118.2, 119.0, 123.0, 124.0, 124.7, 127.7, 129.2, 134.6, 144.2, 147.7, 148.0, 148.2, 148.4, 150.2, 150.5, 155.2. HRDARTMS *m/z*. Calcd for $C_{34}H_{32}NO_8$ $[(M+H)^+]$: 582.21279. Found: 582.21551.

*4.2.2.11. 3-Benzyloxy-11-isopropoxy-14-(3-isopropoxy-4-methoxyphenyl)-2,12-dimethoxy-6H-[1]benzopyrano[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one (**10d**)*

According to the procedure described for the preparation of **10a**, **9d** (30.0 mg, 40.0 μmol), *p*-TsOH·H_2O (30.4 mg, 0.160 mmol), and MeOH (1.5 mL) were reacted. After purification by column chromatography over silica gel 60N (hexane–ethyl acetate = 2:1), **10d** was obtained as a pale yellow solid (25.0 mg, 93%). Recrystallization from DCM–hexane gave a colorless powder. Mp 219.5–220.5 °C. IR (KBr): 1702, 1431, 1268, 1224, 1164, 1038 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.35 (d, J = 6.1 Hz, 3H), 1.37 (d, J = 6.1 Hz, 3H), 1.43 (d, J = 6.1 Hz, 6H), 3.45 (s, 3H), 3.49 (s, 3H), 3.96 (s, 3H), 4.55 (sep, J = 6.1 Hz, 1H),

4.69 (sep, J = 6.1 Hz, 1H), 5.17 (s, 2H), 6.76 (s, 1H), 6.93 (s, 1H), 7.01 (d, J = 7.4 Hz, 1H), 7.09 (s, 1H), 7.14 (d, J = 1.8 Hz, 1H), 7.15 (d, J = 8.2 Hz, 1H), 7.17 (s, 1H), 7.20 (dd, J = 1.8 and 8.2 Hz, 1H), 7.27–7.33 (m, 1H), 7.33–7.40 (m, 2H), 7.40–7.45 (m, 2H), 9.19 (d, J = 7.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 22.0, 22.0, 55.2, 55.5, 56.4, 70.9, 71.2, 71.3, 102.7, 105.5, 105.6, 107.8, 110.4, 111.1, 112.4, 112.8, 118.2, 119.0, 123.2, 124.1, 124.7, 127.2, 128.1, 128.2, 128.7, 129.3, 134.5, 136.2, 146.1, 146.5, 148.2, 148.5, 148.5, 150.2, 150.3, 155.5. HRDARTMS *m*/*z*. Calcd for $C_{41}H_{40}NO_8$ [$(M+H)^+$]: 674.27539. Found: 674.27820.

*4.2.2.12. 2-Benzyloxy-11-isopropoxy-14-(3-isopropoxy-4-methoxyphenyl)-3,12-dimethoxy-6H-[1]benzopyrano[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one (**10e**)*

According to the procedure described for the preparation of **10a**, **9e** (30.0 mg, 40.0 μmol), *p*-TsOH·H_2O (30.4 mg, 0.160 mmol), and MeOH (1.5 mL) were reacted. After purification by column chromatography over silica gel 60N (hexane–ethyl acetate = 2:1), **10e** was obtained as a pale yellow solid (24.3 mg, 90%). Recrystallization from DCM–hexane gave a pale yellow needles. Mp 208–209 °C. IR (KBr): 1702, 1418, 1268, 1220, 1162, 1028 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (d, J = 6.1 Hz, 3H), 1.37 (d, J = 6.1 Hz, 3H), 1.43 (d, J = 6.1 Hz, 6H), 3.45 (s, 3H), 3.89 (s, 3H), 3.95 (s, 3H), 4.54 (sep, J = 6.1 Hz, 1H), 4.69 (sep, J = 6.1 Hz, 1H), 4.74 (s, 2H), 6.89 (s, 1H), 6.94 (s, 1H), 6.99 (d, J = 7.4 Hz, 1H), 7.08 (s, 1H), 7.11 (d, J = 1.8 Hz, 1H), 7.12 (s, 1H), 7.12 (d, J = 8.1 Hz, 1H), 7.16 (dd, J = 1.8 and 8.1 Hz, 1H), 7.21–7.25 (m, 2H), 7.26–7.36 (m, 3H), 9.19 (d, J = 7.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 22.0, 22.1, 55.2, 56.1, 56.4, 70.6, 71.2, 71.2, 100.9, 105.6, 107.8, 107.8, 110.0, 110.4, 111.1, 112.4, 112.8, 118.1, 119.0, 123.1, 124.0, 124.7, 127.3, 127.8, 128.1, 128.4, 129.2, 134.5, 136.4, 144.5, 147.1, 148.3, 148.5, 150.2, 150.3, 150.3, 155.5. HRDARTMS *m*/*z*. Calcd for $C_{41}H_{40}NO_8$ [$(M+H)^+$]: 674.27539. Found: 674.27240.

*4.2.2.13. 3-Benzyloxy-2,11-diisopropoxy-14-(3-isopropoxy-4-methoxyphenyl)-12-methoxy-6H-[1]benzopyrano[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one (**10f**)*

Under an argon atmosphere, a mixture of **9f** (202 mg, 0.260 mmol), *p*-TsOH·H_2O (198 mg, 1.04 mmol), and MeOH (10 mL) was refluxed for 18 h. After cooling to room temperature, the mixture was evaporated and the products were extracted with DCM. The extract was washed with water and brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography over silica gel 60N (hexane–ethyl acetate = 2:1) to give **10f** as a pale yellow solid (161 mg, 88%). Recrystallization from DCM–hexane gave a colorless powder. Mp 231–232 °C. IR (KBr): 1701, 1433, 1267, 1212, 1162, 1033 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.19 (d, J = 6.1 Hz, 3H), 1.20 (d, J = 6.1 Hz, 3H), 1.35 (d, J = 6.1 Hz, 3H), 1.36 (d, J = 6.1 Hz, 3H), 1.43 (d, J = 6.1 Hz, 6H), 3.44 (s, 3H), 3.98 (s, 3H), 4.02 (sep, J = 6.1 Hz, 1H), 4.54 (sep, J = 6.1 Hz, 1H), 4.69 (sep, J = 6.1 Hz, 1H), 5.15 (s, 2H), 6.77 (s, 1H), 6.94 (s, 1H), 7.00 (d, J = 7.4 Hz, 1H), 7.08 (s, 1H), 7.11–7.16 (m, 3H), 7.17 (s, 1H), 7.27–7.33 (m, 1H), 7.33–7.39 (m, 2H), 7.40–7.45 (m, 2H), 9.18 (d, J = 7.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 21.9, 22.0, 22.0, 22.0, 55.2, 56.4, 71.0, 71.1, 71.2, 71.9, 103.5, 105.6, 107.8, 110.0, 110.3, 110.6, 111.1, 112.3, 112.8, 117.6, 119.0, 123.2, 123.8, 124.7, 127.1, 127.9, 128.2, 128.5, 129.4, 134.4, 136.6, 144.5, 146.6, 148.4, 148.4, 149.8, 150.2, 150.2, 155.5. HRDARTMS *m*/*z*. Calcd for $C_{43}H_{44}NO_8$ [$(M+H)^+$]: 702.30669. Found: 702.30518.

*4.2.2.14. 2,3-Bis(benzyloxy)-11-isopropoxy-14-(3-isopropoxy-4-methoxyphenyl)-12-methoxy-6H-[1]benzopyrano[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one (**10g**)*

Under an argon atmosphere, a mixture of **9g** (1.77 g, 2.14 mmol), *p*-TsOH·H_2O (1.63 g, 8.57 mmol), and MeOH (60 mL) was refluxed for 18 h. After cooling to room temperature, the mixture was evaporated and the products were extracted with DCM. The extract was washed with water and brine, dried over Na_2SO_4, and evaporated. The residue was purified by recrystallization from DCM–hexane to give **10g** as a pale yellow needles (1.35 g, 84%). Mp 232–233 °C. IR (KBr): 1711, 1421, 1261, 1222, 1165, 1039 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.34 (d, J = 6.1 Hz, 3H), 1.37 (d, J = 6.1 Hz, 3H), 1.43 (d, J = 6.1 Hz, 3H), 1.43 (d, J = 6.1 Hz, 3H), 3.44 (s, 3H), 3.97 (s, 3H), 4.54 (sep, J = 6.1 Hz, 1H), 4.69 (sep, J = 6.1 Hz, 1H), 4.76 (d, J = 12.4 Hz, 1H), 4.78 (d, J = 12.4 Hz, 1H), 5.19 (s, 2H), 6.91 (s, 1H), 6.98 (s, 1H), 7.00 (d, J = 7.4 Hz, 1H), 7.08 (s, 1H), 7.10 (s, 1H), 7.12 (s, 1H), 7.13–7.16 (m, 2H), 7.23–7.39 (m, 8H), 7.43–7.46 (m, 2H), 9.20 (d, J = 7.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.9, 22.0, 22.1, 55.2, 56.4, 70.8, 71.0, 71.2, 71.3, 103.4, 105.6, 107.8, 108.7, 110.4, 110.6, 111.2, 112.4, 112.8, 118.1, 119.0, 123.2, 124.0, 124.7, 127.2, 127.2, 127.8, 128.0, 128.1, 128.4, 128.6, 129.2, 134.5, 136.5, 136.7, 145.0, 147.0, 148.3, 148.5, 149.4, 150.2, 150.3, 155.5. HRDARTMS *m*/*z*. Calcd for $C_{47}H_{44}NO_8$ [$(M+H)^+$]: 750.30669. Found: 750.30535.

*4.2.3. Synthesis of lamellarins **11a–e***

*4.2.3.1. 11-Hydroxy-14-(3-hydroxy-4-methoxyphenyl)-12-methoxy-6H-[1]benzopyrano[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one (**11a**)*

Under an argon atmosphere, a heptane solution of BCl_3 (1.0 M, 1.41 mL, 1.41 mmol) was added dropwise to a solution of **10a** (101 mg, 0.188 mmol) in DCM (25 mL) at –78 °C. After stirring for 0.5 h at –78 °C, the mixture was allowed to warm to room temperature and stirred for an additional 3 h at room temperature. The mixture was quenched with saturated aqueous $NaHCO_3$ and the products were extracted with ethyl acetate. The extract was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography over silica gel 60N (hexane–ethyl acetate = 1:1) to give **11a** as a pale gray powder (82.9 mg, 97%). Mp 291.5–295 °C (sealed capillary). IR (KBr): 3531, 1678, 1409, 1277, 1217, 1049 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.38 (s, 3H), 3.90 (s, 3H), 6.97–7.01 (m, 3H), 7.14–7.19 (m, 1H), 7.19 (s, 1H), 7.21–7.24 (m, 1H), 7.25 (d, J = 7.4 Hz, 1H), 7.37 (dd, J = 1.4 and 8.0 Hz, 1H), 7.41–7.48 (m, 2H), 9.04 (d, J = 7.4 Hz, 1H), 9.39 (s, 1H), 9.96 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 54.5, 55.9, 105.2, 107.3, 111.6, 111.8, 113.1, 113.5, 117.1, 117.5, 117.6, 117.9, 121.8, 121.9, 123.7, 124.0, 124.6, 127.2, 127.4, 128.7, 134.2, 147.7, 148.0, 148.3, 148.6, 151.2, 153.9. HRFABMS *m*/*z*. Calcd for $C_{27}H_{20}NO_6$ [$(M+H)^+$]: 454.1291. Found: 454.1282.

*4.2.3.2. 11-Hydroxy-14-(3-hydroxy-4-methoxyphenyl)-2,3,12-trimethoxy-6H-[1]benzopyrano[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one (**11b**)*

Under an argon atmosphere, a heptane solution of BCl_3 (1.0 M, 0.500 mL, 0.500 mmol) was added dropwise to a solution of **10b** (50.0 mg, 83.7 μmol) in DCM (5.0 mL) at –78 °C and then the mixture was allowed to warm to room temperature. After stirring for 1 h at room temperature, the mixture was quenched with saturated aqueous $NaHCO_3$. The precipitate thus formed was collected by filtration, washed with water, and dried under reduced pressure to give **11b** as a pale brown powder (41.2 mg, 96%). Mp >300 °C (sealed capillary). IR (KBr): 3451, 1696, 1420, 1273, 1218, 1165, 1043 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.37 (s, 3H), 3.39 (s, 3H), 3.79 (s, 3H), 3.86 (s, 3H), 6.74 (s, 1H), 6.99 (dd, J = 2.1 and 8.1 Hz, 1H), 7.01 (d, J = 2.1 Hz, 1H), 7.06 (s, 1H), 7.16 (s, 1H), 7.18 (s, 1H), 7.19 (d, J = 7.4 Hz, 1H), 7.20 (d, J = 8.1 Hz, 1H), 8.95 (d, J = 7.4 Hz, 1H), 9.36 (br s, 1H),

9.93 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 54.5, 54.9, 55.8, 56.1, 100.9, 105.1, 105.3, 106.6, 109.1, 110.6, 111.5, 112.5, 113.6, 117.4, 118.3, 121.9, 122.1, 124.6, 127.3, 128.3, 133.8, 145.2, 146.2, 147.7, 148.0, 148.3, 148.5, 149.5, 154.2. HRFABMS *m*/*z*. Calcd for $C_{29}H_{24}NO_8$ [(M+H)$^+$]: 514.1502. Found: 514.1520.

*4.2.3.3. 3-Hydroxy-15-(3-hydroxy-4-methoxyphenyl)-2-methoxy-8H-[1,3]dioxolo[6',7'][1]benzopyrano[4',3':4,5]pyrrolo[2,1-a]isoquinolin-8-one (**11c**)*

Under an argon atmosphere, a heptane solution of BCl_3 (1.0 M, 1.41 mL, 1.41 mmol) was added dropwise to a solution of **10c** (20.0 mg, 34.4 μmol) in DCM (5.0 mL) at –78 °C. After stirring for 0.5 h at –78 °C, the mixture was allowed to warm to –40 °C and stirred for an additional 25.5 h at –40 °C. The mixture was quenched with saturated aqueous $NaHCO_3$ and the products were extracted with ethyl acetate. The extract was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography over silica gel 60N (hexane–ethyl acetate = 2:1) to give **11c** as a pale brown powder (11.9 mg, 70%). Mp >300 °C (sealed capillary). IR (KBr): 3426, 1685, 1425, 1260, 1152, 1126, 1037 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.37 (s, 3H), 3.90 (s, 3H), 6.05 (d, J = 0.8 Hz, 1H), 6.05 (d, J = 0.8 Hz, 1H), 6.62 (s, 1H), 6.96 (d, J = 2.1 Hz, 1H), 6.98 (dd, J = 2.1 and 8.1 Hz, 1H), 7.01 (s, 1H), 7.18 (s, 1H), 7.19 (s, 1H), 7.24 (d, J = 8.1 Hz, 1H), 7.24 (d, J = 7.3 Hz, 1H), 9.01 (d, J = 7.3 Hz, 1H), 9.42 (s, 1H), 9.97 (br s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 54.5, 55.9, 98.9, 101.3, 102.1, 105.2, 106.4, 110.4, 110.9, 111.6, 112.8, 113.5, 117.4, 117.9, 121.9, 121.9, 124.7, 127.0, 128.1, 134.2, 143.9, 147.2, 147.7, 148.0, 148.1, 148.4, 148.6, 154.0. HRFABMS *m*/*z*. Calcd for $C_{28}H_{20}NO_8$ [(M+H)$^+$]: 498.1189. Found: 498.1171.

*4.2.3.4. 3,11-Dihydroxy-14-(3-hydroxy-4-methoxyphenyl)-2,12-dimethoxy-6H-[1]benzopyrano[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one (lamellarin N, **11d**)*

Under an argon atmosphere, a heptane solution of BCl_3 (1.0 M, 0.401 mL, 0.401 mmol) was added dropwise to a solution of **10d** (30.0 mg, 44.5 μmol) in DCM (3.0 mL) at –78 °C. After stirring for 0.5 h at –78 °C, the mixture was allowed to warm to room temperature and stirred for an additional 3 h at room temperature. The mixture was quenched with saturated aqueous $NaHCO_3$ and the precipitate thus formed was collected by filtration, washed with water, and dried under reduced pressure. The crude product was purified by column chromatography over silica gel 60N (acetone) to give **11d** as a pale gray powder (15.7 mg, 71%). Mp 280–300 °C (dec) (sealed capillary) [lit.[38] Mp 280–300 °C (dec) (sealed capillary)]. ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.39 (s, 3H), 3.40 (s, 3H), 3.86 (s, 3H), 6.75 (s, 1H), 6.86 (s, 1H), 7.00 (dd, J = 2.0 and 8.6 Hz, 1H), 7.00 (d, J = 2.0 Hz, 1H), 7.16 (s, 1H), 7.18 (s, 1H), 7.20 (d, J = 7.4 Hz, 1H), 7.23 (d, J = 8.6 Hz, 1H), 8.99 (d, J = 7.4 Hz, 1H), 9.39 (s, 1H), 9.84 (br s, 1H), 9.94 (br s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 54.6, 55.1, 56.1, 103.8, 105.3, 105.7, 106.5, 108.2, 110.5, 111.6, 112.4, 113.6, 117.5, 118.3, 122.1, 122.1, 124.7, 127.4, 128.8, 133.9, 144.6, 146.3, 147.7, 147.8, 148.0, 148.3, 148.5, 154.4. These physical and spectroscopic data are in good agreement with those previously reported.[35,38]

*4.2.3.5. 2,11-Dihydroxy-14-(3-hydroxy-4-methoxyphenyl)-3,12-dimethoxy-6H-[1]benzopyrano[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one (**11e**)*

According to the procedure described for the preparation of **11b**, **10e** (37.3 mg, 55.4 μmol) and BCl_3 (1.0 M, 0.500 mL, 0.500 mmol) were reacted to give **11e** as a pale brown powder (8.8 mg, 90%). Mp >300 °C (sealed capillary). IR (KBr): 3543, 3427, 1691, 1421, 1278, 1206, 1160, 1043 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.37 (s, 3H), 3.84 (s, 3H), 3.90 (s, 3H), 6.77 (s, 1H), 6.94 (s, 1H), 6.94 (d, J = 2.0 Hz, 1H), 6.95 (dd, J = 2.0 and 8.6 Hz, 1H), 7.08 (s, 1H), 7.17 (s, 1H), 7.19 (d, J = 7.4 Hz, 1H), 7.21 (d, J = 8.6 Hz, 1H), 9.02 (d, J = 7.4 Hz, 1H), 9.08 (br s, 1H), 9.37 (br s, 1H), 9.92 (br s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 54.5, 55.8, 55.9, 100.8, 105.2, 106.7, 108.9, 109.7, 111.0, 111.5, 112.5, 113.5, 117.5, 118.0, 121.9, 122.0, 124.7, 127.2, 128.2, 134.1, 143.0, 145.3, 147.6, 148.0, 148.2, 148.5, 148.8, 154.4. HRDARTMS *m*/*z*. Calcd for $C_{28}H_{22}NO_8$ [(M+H)$^+$]: 500.13454. Found: 500.13512.

*4.2.4. Synthesis of debenzylated lamellarins **12a–d***

*4.2.4.1. 3-Hydroxy-11-isopropoxy-14-(3-isopropoxy-4-methoxyphenyl)-2,12-dimethoxy-6H-[1]benzopyrano[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one (**12a**)*

Under an argon atmosphere, ammonium formate (1.14 g, 18.0 mmol) was added portionwise to a mixture of **10d** (405 mg, 0.601 mmol), palladium carbon (Pd: 10%, 80.8 mg), ethyl acetate (15 mL), and EtOH (15 mL) at room temperature and the mixture was refluxed for 1 h. After cooling to room temperature, the mixture was passed through a pad of Celite. The filtrate was evaporated under reduced pressure. The residue was purified by column chromatography over silica gel 60N (hexane–ethyl acetate = 1:1) to give **12a** as a pale yellow powder (328 mg, 93%). Recrystallization from DCM–hexane gave a yellow powder. Mp 260–261 °C. IR (KBr): 3421, 1701, 1432, 1264, 1223, 1042 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 (d, J = 6.0 Hz, 3H), 1.37 (d, J = 6.0 Hz, 3H), 1.43 (d, J = 6.0 Hz, 6H), 3.45 (s, 3H), 3.51 (s, 3H), 3.97 (s, 3H), 4.57 (sep, J = 6.0 Hz, 1H), 4.70 (sep, J = 6.0 Hz, 1H), 5.95 (br s, 1H), 6.71 (s, 1H), 6.99 (s, 1H), 6.99 (d, J = 7.3 Hz, 1H), 7.08 (s, 1H), 7.15 (d, J = 8.1 Hz, 1H), 7.15 (d, J = 1.7 Hz, 1H), 7.16 (s, 1H), 7.19 (dd, J = 1.7 and 8.1 Hz, 1H), 9.18 (d, J = 7.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 21.9, 22.0, 22.0, 55.1, 55.5, 56.4, 71.2, 71.4, 103.6, 104.7, 105.6, 107.7, 109.9, 110.4, 110.9, 112.3, 112.8, 118.2, 119.0, 123.2, 124.2, 124.8, 128.3, 129.5, 134.4, 143.4, 146.3, 147.0, 148.2, 148.5, 150.2, 150.3, 155.6. HRDARTMS *m*/*z*. Calcd for $C_{34}H_{34}NO_8$ [(M+H)$^+$]: 584.22844. Found: 584.22588.

*4.2.4.2. 2-Hydroxy-11-isopropoxy-14-(3-isopropoxy-4-methoxyphenyl)-3,12-dimethoxy-6H-[1]benzopyrano[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one (**12b**)*

According to the procedure described for the preparation of **12a**, **10e** (292 mg, 0.434 mmol), palladium carbon (Pd: 10%, 58 mg), ethyl acetate (25 mL), and EtOH (15 mL) were reacted for 0.5 h. After purification by column chromatography over silica gel 60N (acetone), **12b** was obtained as a pale yellow powder (240 mg, 95%). Recrystallization from DCM–hexane gave a pale yellow powder. Mp 286–289 °C. IR (KBr): 3260, 1679, 1421, 1263, 1209, 1160, 1046 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.20 (d, J = 6.0 Hz, 3H), 1.24 (d, J = 6.0 Hz, 3H), 1.30 (d, J = 6.0 Hz, 6H), 3.32 (s, 3H), 3.83 (s, 3H), 3.88 (s, 3H), 4.57 (sep, J = 6.0 Hz, 1H), 4.73 (sep, J = 6.0 Hz, 1H), 6.73 (s, 1H), 6.91 (s, 1H), 7.07 (s, 1H), 7.10 (dd, J = 1.9 and 8.0 Hz, 1H), 7.11 (d, J = 1.9 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 7.27 (d, J = 7.3 Hz, 1H), 7.40 (s, 1H), 9.06 (d, J = 7.3 Hz, 1H), 9.06 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 21.7, 21.7, 21.7, 21.9, 54.3, 55.7, 55.9, 100.8, 104.9, 106.8, 108.8, 109.6, 110.4, 111.2, 112.8, 113.5, 117.8, 118.2, 122.1, 123.6, 124.4, 127.0, 128.4, 133.9, 143.1, 145.2, 147.6, 148.0, 148.8, 149.6, 150.1, 154.4. HRDARTMS *m*/*z*. Calcd for $C_{34}H_{34}NO_8$ [(M+H)$^+$]: 584.22844. Found: 584.22655.

*4.2.4.3. 3-Hydroxy-2,11-diisopropoxy-14-(3-isopropoxy-4-methoxyphenyl)-12-methoxy-6H-[1]benzopyrano[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one (**12c**)*

According to the procedure described for the preparation of **12a**, **10f** (84.9 mg, 0.121 mmol), palladium carbon (Pd: 10%, 17 mg), ethyl acetate (5 mL), and EtOH (5 mL) were reacted for 0.5 h. After purification by column chromatography over silica gel 60N (acetone), **12c** was obtained as a pale brown powder (71.2 mg, 96%). Recrystallization from DCM–hexane gave a pale brown powder. Mp 256.5–257.5 °C. IR (KBr): 3482, 1706, 1434, 1219, 1135, 1030 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.19 (d, J = 6.0 Hz, 6H), 1.35 (d, J = 6.0 Hz, 3H), 1.36 (d, J = 6.0 Hz, 3H), 1.44 (d, J = 6.0 Hz, 6H), 3.45 (s, 3H), 3.98 (s, 3H), 4.01 (sep, J = 6.0 Hz, 1H), 4.55 (sep, J = 6.0 Hz, 1H), 4.70 (sep, J = 6.0 Hz, 1H), 5.92 (s, 1H), 6.68 (s, 1H), 6.99 (d, J = 7.3 Hz, 1H), 6.99 (s, 1H), 7.09 (s, 1H), 7.12–7.17 (m, 3H), 7.17 (s, 1H), 9.18 (d, J = 7.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 21.9, 22.0, 22.0, 55.2, 56.4, 71.1, 71.2, 71.8, 103.5, 105.6, 106.7, 107.7, 109.8, 110.3, 110.8, 112.2, 112.7, 117.7, 119.0, 123.2, 123.8, 124.7, 128.4, 129.5, 134.4, 141.4, 146.8, 147.0, 148.4, 148.4, 150.1, 150.2, 155.5. HRDARTMS *m*/*z*. Calcd for $C_{36}H_{38}NO_8$ $[(M+H)^+]$: 612.25974. Found: 612.26035.

4.2.4.4. 2,3-Dihydroxy-11-isopropoxy-14-(3-isopropoxy-4-methoxyphenyl)-12-methoxy-6H-[1]benzopyrano[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one ***(12d)***

Method 1: According to the procedure described for the preparation of **12a**, **10g** (200 mg, 0.267 mmol), palladium carbon (Pd: 10%, 40 mg), ethyl acetate (10 mL), and EtOH (10 mL) were reacted for 1 h. After purification by column chromatography over silica gel 60N (acetone), **12d** was obtained as a pale yellow powder (71.2 mg, 93%).

Method 2: Pentamethylbenzene (59.3 mg, 0.400 mmol) and **10g** (15 mg, 20.0 μmol) was dissolved in TFA (2.0 mL). After stirring for 24 h at room temperature, the mixture was concentrated. The residue was purified by column chromatography over silica gel 60N (hexane–ethyl acetate = 1:1) to give **12d** as a pale yellow powder (9.5 mg, 83%).

Recrystallization from acetone–hexane gave a pale gray powder. Mp 270–290 °C (dec) (sealed capillary). IR (KBr): 3461, 1700, 1668, 1429, 1278, 1222, 1137, 1033 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 1.21 (d, J = 6.0 Hz, 3H), 1.25 (d, J = 6.0 Hz, 3H), 1.31 (d, J = 6.0 Hz, 6H), 3.33 (s, 3H), 3.89 (s, 3H), 4.58 (sep, J = 6.0 Hz, 1H), 4.74 (sep, J = 6.0 Hz, 1H), 6.74 (s, 1H), 6.84 (s, 1H), 6.90 (s, 1H), 7.08–7.12 (m, 2H), 7.26 (d, J = 7.3 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.41 (s, 1H), 9.04 (br s, 1H), 9.08 (d, J = 7.3 Hz, 1H), 9.76 (br s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 21.7, 21.7, 21.7, 21.9, 54.3, 55.7, 70.1, 70.1, 103.5, 104.9, 106.6, 108.6, 109.2, 110.4, 111.0, 112.6, 113.5, 117.8, 118.2, 122.1, 123.6, 124.4, 127.1, 128.7, 133.9, 142.4, 145.3, 147.0, 147.6, 147.9, 149.6, 150.1, 154.5. HRDARTMS *m*/*z*. Calcd for $C_{33}H_{32}NO_8$ $[(M+H)^+]$: 570.21279. Found: 570.21008.

4.2.5. Synthesis of ammonium-tethered lamellarin N analogues ***14a–e***

4.2.5.1. 3-[2-(Dimethylamino)ethoxy]-11-isopropoxy-14-(3-isopropoxy-4-methoxyphenyl)-2,12-dimethoxy-6H-[1]benzopyrano[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one ***(13a)***

Under an argon atmosphere, a mixture of **12a** (20.0 mg, 34.3 μmol), 2-(dimethylamino)ethyl chloride hydrochloride (5.9 mg, 41 μmol), K_2CO_3 (23.8 mg, 0.172 mmol), and acetone (4.0 mL) was refluxed for 7 h. After cooling to room temperature, saturated aqueous $NaHCO_3$ was added to the mixture. The mixture was evaporated and the products were extracted with DCM. The extract was washed with water and brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography over Chromatorex NH-DM1020 (DCM–ethyl acetate = 1:1) to give **13a** as a pale yellow solid (19.8 mg, 88%). Recrystallization from DCM–hexane gave a colorless needles. Mp 188–189 °C IR (KBr): 1704, 1431, 1267, 1224, 1167, 1039 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.36 (d, J = 6.1 Hz, 6H), 1.44 (d, J = 6.1 Hz, 6H), 2.34 (s, 6H), 2.80 (t, J = 6.0 Hz, 2H), 3.45 (s, 3H), 3.46 (s, 3H), 3.96 (s, 3H), 4.13 (t, J = 6.0 Hz, 2H), 4.55 (sep, J = 6.1 Hz, 1H), 4.70 (sep, J = 6.1 Hz, 1H), 6.74 (s, 1H), 6.96 (s, 1H), 7.02 (d, J = 7.4 Hz, 1H), 7.10 (s, 1H), 7.14 (d, J = 1.7 Hz, 1H), 7.15 (d, J = 8.2 Hz, 1H), 7.18 (s, 1H), 7.20 (dd, J = 1.7 and 8.2 Hz, 1H), 9.21 (d, J = 7.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 22.0, 22.0, 45.9, 55.2, 55.4, 56.4, 57.8, 67.1, 71.2, 71.3, 101.9, 105.4, 105.6, 107.8, 110.2, 110.4, 111.1, 112.4, 112.8, 118.2, 119.1, 123.2, 124.1, 124.7, 128.2, 129.4, 134.5, 145.9, 146.6, 148.2, 148.5, 148.8, 150.2, 150.3, 155.5. HRDARTMS *m*/*z*. Calcd for $C_{38}H_{43}N_2O_8$ $[(M+H)^+]$: 655.30194. Found: 655.29902.

4.2.5.2. 3-[3-(Dimethylamino)propoxy]-11-isopropoxy-14-(3-isopropoxy-4-methoxyphenyl)-2,12-dimethoxy-6H-[1]benzopyrano[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one ***(13b)***

According to the procedure described for the preparation of **13a**, **12a** (150 mg, 0.257 mmol), 3-(dimethylamino)propyl chloride hydrochloride (48.7 mg, 0.308 mmol), K_2CO_3 (178 mg, 1.29 mmol), and acetone (7.0 mL) were reacted for 24 h. After purification by column chromatography over Chromatorex NH-DM1020 (hexane–ethyl acetate = 3:2), **13b** was obtained as a colorless powder (120 mg, 70%). Recrystallization from DCM–hexane gave a colorless needles. Mp 192.5–193.5 °C. IR (KBr): 1706, 1432, 1267, 1225, 1166, 1040 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.36 (d, J = 6.1 Hz, 3H), 1.36 (d, J = 6.1 Hz, 3H), 1.43 (d, J = 6.1 Hz, 6H), 2.01 (quin, J = 7.0 Hz, 2H), 2.25 (s, 6H), 2.44 (t, J = 7.0 Hz, 2H), 3.45 (s, 3H), 3.47 (s, 3H), 3.97 (s, 3H), 4.07 (t, J = 7.0 Hz, 2H), 4.56 (sep, J = 6.1 Hz, 1H), 4.69 (sep, J = 6.1 Hz, 1H), 6.74 (s, 1H), 6.94 (s, 1H), 7.00 (d, J = 7.4 Hz, 1H), 7.09 (s, 1H), 7.16 (d, J = 1.8 Hz, 1H), 7.16 (d, J = 8.2 Hz, 1H), 7.18 (s, 1H), 7.21 (dd, J = 1.8 and 8.2 Hz, 1H), 9.18 (d, J = 7.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 21.9, 22.0, 27.2, 45.5, 55.1, 55.5, 56.2, 56.4, 67.4, 71.1, 71.3, 101.8, 105.4, 105.6, 107.8, 109.9, 110.4, 111.0, 112.3, 112.7, 118.2, 119.0, 123.1, 124.1, 124.7, 128.2, 129.4, 134.4, 145.8, 146.7, 148.2, 148.4, 149.0, 150.2, 150.2, 155.5. HRDARTMS *m*/*z*. Calcd for $C_{39}H_{45}N_2O_8$ $[(M+H)^+]$: 669.31759. Found: 669.31472.

4.2.5.3. 2-[2-(Dimethylamino)ethoxy]-11-isopropoxy-14-(3-isopropoxy-4-methoxyphenyl)-3,12-dimethoxy-6H-[1]benzopyrano[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one ***(13c)***

According to the procedure described for the preparation of **13a**, **12b** (47.1 mg, 80.7 μmol), 2-(dimethylamino)ethyl chloride hydrochloride (13.9 mg, 96.5 μmol), K_2CO_3 (55.8 mg, 0.404 mmol), and acetone (5.0 mL) were reacted for 24 h. After purification by column chromatography over Chromatorex NH-DM1020 (DCM–ethyl acetate = 1:1), **13c** was obtained as a colorless powder (43.2 mg, 82%). Mp 188–189 °C. IR (KBr): 1703, 1418, 1268, 1219, 1162, 1026 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.34 (d, J = 6.1 Hz, 3H), 1.35 (d, J = 6.1 Hz, 3H), 1.44 (d, J = 6.1 Hz, 6H), 2.27 (s, 6H), 2.56–2.66 (m, 2H), 3.45 (s, 3H), 3.69 (dt, J = 0.9 and 6.0 Hz, 2H), 3.87 (s, 3H), 3.97 (s, 3H), 4.54 (sep, J = 6.1 Hz, 1H), 4.70 (sep, J = 6.1 Hz, 1H), 6.78 (s, 1H), 6.93 (s, 1H), 7.01 (d, J = 7.4 Hz, 1H), 7.09 (s, 1H), 7.12 (d, J = 1.8 Hz, 1H), 7.15 (d, J = 8.1 Hz, 1H), 7.17 (s, 1H), 7.19 (dd, J = 1.8 and 8.1 Hz, 1H), 9.21 (d, J = 7.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.9, 22.0, 22.0, 45.8, 55.2, 56.0, 56.2, 57.9, 67.0, 71.2, 71.2, 100.8, 105.6, 107.2, 107.8, 110.0, 110.4, 111.1, 112.3, 112.7, 118.0, 119.1, 123.2, 123.9, 124.7, 128.1, 129.4, 134.5, 144.8, 146.9, 148.3, 148.5, 150.2, 150.2, 150.3, 155.5. HRDARTMS *m*/*z*. Calcd for $C_{38}H_{43}N_2O_8$ $[(M+H)^+]$: 655.30194. Found: 655.30250.

4.2.5.4. 3-[3-(Dimethylamino)propoxy]-2,11-diisopropoxy-14-(3-isopropoxy-4-methoxyphenyl)-12-methoxy-6H-[1]benzopyrano[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one ***(13d)***

According to the procedure described for the preparation of **13a**, **12c** (30.0 mg, 49.0 μmol), 3-(dimethylamino)propyl chloride hydrochloride (9.3 mg, 58.8 μmol), K_2CO_3 (40.6 mg, 0.294 mmol), and acetone (2.0 mL) were reacted for 21 h. After purification by column chromatography over silica gel 60N (hexane–ethyl acetate = 1:1 to DCM–MeOH = 1:1), **13d** was obtained as a pale yellow powder (11.6 mg, 34%). Recrystallization from DCM–hexane gave a pale yellow powder. Mp 191–192 °C. IR (KBr): 1702, 1434, 1259, 1221, 1136, 1031 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.17 (d, J = 6.1 Hz, 3H), 1.17 (d, J = 6.1 Hz, 3H), 1.34 (d, J = 6.1 Hz, 3H), 1.35 (d, J = 6.1 Hz, 3H), 1.43 (d, J = 6.1 Hz, 6H), 2.00 (quin, J = 6.8 Hz, 2H), 2.25 (s, 6H), 2.47 (t, J = 7.3 Hz, 2H), 3.44 (s, 3H), 3.97 (s, 3H), 3.97 (sep, J = 6.1 Hz, 1H), 4.07 (t, J = 6.4 Hz, 2H), 4.53 (sep, J = 6.1 Hz, 1H), 4.70 (sep, J = 6.1 Hz, 1H), 6.76 (s, 1H), 6.96 (s, 1H), 7.02 (d, J = 7.4 Hz, 1H), 7.10 (s, 1H), 7.11 (s, 1H), 7.14 (s, 2H), 7.17 (s, 1H), 9.22 (d, J = 7.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.9, 21.9, 22.0, 22.0, 22.0, 27.3, 45.5, 55.2, 56.3, 56.4, 67.4, 71.2, 71.3, 72.2, 102.5, 105.6, 107.8, 110.2, 110.4, 110.6, 111.1, 112.3, 112.8, 117.7, 119.1, 123.2, 123.8, 124.7, 128.3, 129.5, 134.5, 144.2, 147.1, 148.4, 148.4, 150.2, 150.2, 150.5, 155.6. HRDARTMS *m/z*. Calcd for $C_{41}H_{49}N_2O_8$ $[(M+H)^+]$: 697.34889. Found: 697.35000.

4.2.5.5. 2,3-Bis[2-(dimethylamino)ethoxy]-11-isopropoxy-14-(3-isopropoxy-4-methoxyphenyl)-12-methoxy-6H-[1]benzopyrano[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one ***(13e)***

Under an argon atmosphere, a mixture of **12d** (40.3 mg, 70.8 μmol), 2-(dimethylamino)ethyl chloride hydrochloride (51.0 mg, 0.354 mmol), sodium iodide (10.0 mg, 66.7 μmol), K_2CO_3 (147 mg, 1.06 mmol), and acetone (10.0 mL) was refluxed for 10 h. After cooling to room temperature, 2-(dimethylamino)ethyl chloride hydrochloride (51.0 mg, 0.354 mmol) and K_2CO_3 (147 mg, 1.06 mmol) was added to the mixture and then refluxed for 12 h. After cooling to room temperature, the mixture was diluted with DCM and passed through a pad of Celite. The filtrate was evaporated under reduced pressure. The residue was purified by column chromatography over Chromatorex NH-DM1020 (hexane–ethyl acetate = 1:2 to ethyl acetate) to give **13e** as a pale yellow solid (27.0 mg, 54%). Mp 142–145 °C. IR (KBr): 1704, 1434, 1260, 1221, 1163, 1032 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.34 (d, J = 6.1 Hz, 3H), 1.34 (d, J = 6.1 Hz, 3H), 1.43 (d, J = 6.1 Hz, 6H), 2.28 (s, 6H), 2.34 (s, 6H), 2.55–2.65 (m, 2H), 2.78 (t, J = 5.8 Hz, 2H), 3.44 (s, 3H), 3.67 (t, J = 5.8 Hz, 2H), 3.96 (s, 3H), 4.12 (t, J = 5.8 Hz, 2H), 4.53 (sep, J = 6.1 Hz, 1H), 4.70 (sep, J = 6.1 Hz, 1H), 6.76 (s, 1H), 6.96 (s, 1H), 7.02 (d, J = 7.4 Hz, 1H), 7.10 (s, 1H), 7.11 (d, J = 1.8 Hz, 1H), 7.15 (d, J = 8.1 Hz, 1H), 7.17 (s, 1H), 7.18 (dd, J = 1.8 and 8.1 Hz, 1H), 9.22 (d, J = 7.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.9, 22.0, 22.0, 45.8, 46.0, 55.2, 56.2, 57.8, 57.9, 67.1, 67.3, 71.2, 71.2, 102.2, 105.6, 107.4, 107.8, 110.3, 110.4, 111.1, 112.4, 112.7, 118.0, 119.1, 123.2, 124.0, 124.7, 128.1, 129.4, 134.5, 145.2, 146.9, 148.2, 148.5, 149.4, 150.2, 150.3, 155.5. HRDARTMS *m/z*. Calcd for $C_{41}H_{50}N_3O_8$ $[(M+H)^+]$: 712.35979. Found: 712.36040.

4.2.5.6. 2,3-Bis[3-(dimethylamino)propoxy]-11-isopropoxy-14-(3-isopropoxy-4-methoxyphenyl)-12-methoxy-6H-[1]benzopyrano[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one ***(13f)***

According to the procedure described for the preparation of **13a**, **12d** (146 mg, 0.256 mmol), 3-(dimethylamino)propyl chloride hydrochloride (194 mg, 1.23 mmol), K_2CO_3 (708 mg, 5.12 mmol), and acetone (25.0 mL) were reacted for 48 h. After purification by recrystallization from DCM–hexane, **13f** was obtained as a pale brown powder (134 mg, 71%). Mp 174–176 °C. IR (KBr): 1705, 1678, 1434, 1265, 1223, 1166, 1036 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.34 (d, J = 6.1 Hz, 3H), 1.35 (d, J = 6.1 Hz, 3H), 1.43 (d, J = 6.1 Hz, 6H), 1.81 (quin, J = 6.9 Hz, 2H), 2.00 (quin, J = 6.8 Hz, 2H), 2.23 (s, 6H), 2.25 (s, 6H), 2.31–2.41 (m, 2H), 2.47 (t, J = 7.3 Hz, 2H), 3.44 (s, 3H), 3.62 (t, J = 6.3 Hz, 2H), 3.97 (s, 3H), 4.08 (t, J = 6.5 Hz, 2H), 4.53 (sep, J = 6.1 Hz, 1H), 4.70 (sep, J = 6.1 Hz, 1H), 6.75 (s, 1H), 6.96 (s, 1H), 7.01 (d, J = 7.3 Hz, 1H), 7.09 (s, 1H), 7.11 (d, J = 1.8 Hz, 1H), 7.14 (d, J = 8.1 Hz, 1H), 7.16 (s, 1H), 7.18 (dd, J = 1.8 and 8.1 Hz, 1H), 9.22 (d, J = 7.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.9, 22.0, 22.0, 27.3, 27.4, 45.6, 45.6, 55.2, 56.3, 67.1, 67.4, 71.2, 71.3, 102.2, 105.6, 107.4, 107.8, 110.1, 110.4, 111.1, 112.3, 112.7, 118.2, 119.1, 123.2, 124.1, 124.7, 128.2, 129.5, 134.5, 145.2, 146.8, 148.3, 148.4, 149.6, 150.2, 150.3, 155.6. HRDARTMS *m/z*. Calcd for $C_{43}H_{54}N_3O_8$ $[(M+H)^+]$: 740.39109. Found: 740.39380.

4.2.5.7. 11-Isopropoxy-14-(3-isopropoxy-4-methoxyphenyl)-12-methoxy-2,3-bis(3-morpholinopropoxy)-6H-[1]benzopyrano[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one ***(13g)***

Under an argon atmosphere, a mixture of **12d** (73.5 mg, 0.129 mmol), 4-(3-chloropropyl)morpholine (98.0 μL, 0.647 mmol), sodium iodide (20.0 mg, 0.133 mmol), K_2CO_3 (178 mg, 1.29 mmol), and acetone (20.0 mL) was refluxed for 5 h. After cooling to room temperature, 4-(3-chloropropyl)morpholine (49.0 μL, 0.323 mmol) and K_2CO_3 (89.0 mg, 0.644 mmol) was added to the mixture and then refluxed for 18 h. After cooling to room temperature, the mixture was diluted with DCM and passed through a pad of Celite. The filtrate was evaporated under reduced pressure. The residue was purified by column chromatography over Chromatorex NH-DM1020 (hexane–ethyl acetate = 1:1 to 1:2) and subsequent trituration with ether to give **13g** as a pale brown solid (103 mg, 97%). Recrystallization from DCM–hexane gave a pale brown powder. Mp 186–187 °C. IR (KBr): 1699, 1435, 1266, 1223, 1170, 1114, 1032 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.34 (d, J = 6.1 Hz, 3H), 1.35 (d, J = 6.1 Hz, 3H), 1.44 (d, J = 6.1 Hz, 6H), 1.81 (quin, J = 6.9 Hz, 2H), 2.01 (quin, J = 6.8 Hz, 2H), 2.39–2.49 (m, 10H), 2.53 (t, J = 7.2 Hz, 2H), 3.44 (s, 3H), 3.64 (t, J = 6.3 Hz, 2H), 3.72 (t, J = 4.3 Hz, 8H), 3.96 (s, 3H), 4.09 (t, J = 6.4 Hz, 2H), 4.53 (sep, J = 6.1 Hz, 1H), 4.70 (sep, J = 6.1 Hz, 1H), 6.75 (s, 1H), 6.97 (s, 1H), 7.03 (d, J = 7.3 Hz, 1H), 7.10 (s, 1H), 7.11 (d, J = 1.8 Hz, 1H), 7.14 (d, J = 8.1 Hz, 1H), 7.15 (s, 1H), 7.18 (dd, J = 1.8 and 8.1 Hz, 1H), 9.22 (d, J = 7.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.9, 22.0, 22.1, 26.2, 26.3, 53.8, 53.8, 55.2, 55.4, 55.5, 56.4, 67.0, 67.3, 71.2, 71.3, 102.2, 105.6, 107.4, 107.8, 110.1, 110.4, 111.0, 112.4, 112.7, 118.2, 119.0, 123.2, 124.0, 124.7, 128.3, 129.4, 134.5, 145.1, 146.8, 148.3, 148.5, 149.5, 150.2, 150.3, 155.5. HRDARTMS *m/z*. Calcd for $C_{47}H_{58}N_3O_{10}$ $[(M+H)^+]$: 824.41222. Found: 824.40976.

4.2.5.8. Trifluoroacetic acid salt of 3-[2-(dimethylamino)ethoxy]-11-hydroxy-14-(3-hydroxy-4-methoxyphenyl)-2,12-dimethoxy-6H-[1]benzopyrano[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one ***(14a)***

Under an argon atmosphere, a nitrobenzene solution of $AlCl_3$ (1.0 M, 230 μL, 0.230 mmol) was added dropwise to a solution of **13a** (25.0 mg, 38.2 μmol) in DCM (2.0 mL) at room temperature. After stirring for 18 h at room temperature, a solution of $NaHCO_3$ (115 mg, 1.37 mmol) and Rochelle salt (194 mg, 0.687 mmol) in water (1.0 mL) was added. The mixture was stirred for an additional 1 h and then evaporated. The nitrobenzene was removed azeotropically with water under reduced pressure. To the residue was added water and the precipitate was collected by filtration, washed with water, and dried under reduced pressure to give 3-[2-(dimethylamino)ethoxy]-11-hydroxy-14-(3-hydroxy-4-

methoxyphenyl)-2,12-dimethoxy-6*H*-[1]benzopyrano[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (**14a′**) as a pale brown powder (21.2 mg, 97%). Mp 213–218 °C. IR (KBr): 3362, 1689, 1425, 1282, 1222, 1168, 1037 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 2.08 (s, 3H), 2.08 (s, 3H), 2.64 (t, J = 5.7 Hz, 2H), 3.38 (s, 3H), 3.39 (s, 3H), 3.87 (s, 3H), 4.10 (t, J = 5.7 Hz, 2H), 6.78 (s, 1H), 7.00–7.05 (m, 2H), 7.15 (s, 1H), 7.18 (s, 1H), 7.20 (s, 1H), 7.23 (d, J = 7.3 Hz, 1H), 7.24 (d, J = 7.6 Hz, 1H), 9.01 (d, J = 7.3 Hz, 1H), 9.40 (br s, 1H), 9.97 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 45.6, 54.6, 55.0, 56.2, 57.5, 66.8, 101.7, 105.3, 105.3, 106.7, 109.2, 110.7, 111.6, 112.5, 113.6, 117.5, 118.3, 122.0, 122.2, 124.7, 127.4, 128.4, 133.9, 145.3, 146.1, 147.7, 148.0, 148.4, 148.6, 148.7, 154.3. HRDARTMS *m*/*z*. Calcd for $C_{32}H_{31}N_2O_8$ [$(M+H)^+$]: 571.20804. Found: 571.20778.

To a suspension of **14a′** (20.0 mg, 35.1 μmol) in DCM (1.0 mL) was added trifluoroacetic acid (1.0 mL) at room temperature. After stirring for 0.5 min at room temperature, the mixture was evaporated. The crude product was purified by column chromatography over Sephadex LH-20 (MeOH containing 0.1% TFA) to give **14a** as a brown solid (23.9 mg, quant). Mp 166.5–167.5 °C. IR (KBr): 3419, 1681, 1424, 1277, 1205, 1132, 1041 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 2.89 (s, 6H), 3.40 (s, 3H), 3.40 (s, 3H), 3.55 (t, J = 4.8 Hz, 2H), 3.86 (s, 3H), 4.40 (t, J = 4.8 Hz, 2H), 6.82 (s, 1H), 6.99–7.03 (m, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.22 (d, J = 8.1 Hz, 1H), 7.24 (d, J = 7.3 Hz, 1H), 7.26 (s, 1H), 8.99 (d, J = 7.3 Hz, 1H), 9.44 (br s, 1H), 9.92 (br s, 1H), 10.03 (br s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 43.1, 54.5, 55.0, 55.2, 56.1, 63.9, 103.2, 105.3, 105.4, 106.8, 110.4, 110.9, 111.6, 112.8, 113.6, 117.4, 118.2, 122.0, 122.1, 124.7, 127.2, 128.1, 134.0, 145.5, 145.9, 147.4, 147.8, 148.0, 148.4, 148.6, 154.2. HRDARTMS *m*/*z*. Calcd for $C_{32}H_{31}N_2O_8$ [$(M–CF_3COO)^+$]: 571.20804. Found: 571.20854.

*4.2.5.9. Trifluoroacetic acid salt of 3-[3-(dimethylamino)propoxy]-11-hydroxy-14-(3-hydroxy-4-methoxyphenyl)-2,12-dimethoxy-6H-[1]benzopyrano[4′,3′:4,5]pyrrolo[2,1-a]isoquinolin-6-one (**14b**)*

Under an argon atmosphere, a nitrobenzene solution of $AlCl_3$ (1.0 M, 540 μL, 0.540 mmol) was added dropwise to a solution of **13b** (60.0 mg, 89.7 μmol) in DCM (4.0 mL) at room temperature. After stirring for 18 h at room temperature, a solution of $NaHCO_3$ (200 mg, 2.38 mmol) and Rochelle salt (440 mg, 1.56 mmol) in water (7.0 mL) was added. The mixture was stirred for an additional 1 h and then evaporated. The nitrobenzene was removed azeotropically with water under reduced pressure. To the residue was added water and the precipitate was collected by filtration, washed with water, and dried under reduced pressure to give 3-[3-(dimethylamino)propoxy]-11-hydroxy-14-(3-hydroxy-4-methoxyphenyl)-2,12-dimethoxy-6*H*-[1]benzopyrano[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (**14b′**) as a pale gray powder (47.5 mg, 91%). Mp 250–255 °C. IR (KBr): 3525, 3401, 1704, 1427, 1278, 1218, 1169, 1041 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 1.85 (quin, J = 6.8 Hz, 2H), 2.14 (s, 6H), 2.34 (t, J = 7.1 Hz, 2H), 3.39 (s, 3H), 3.40 (s, 3H), 3.87 (s, 3H), 4.04 (t, J = 6.5 Hz, 2H), 6.78 (s, 1H), 7.00–7.04 (m, 2H), 7.08 (s, 1H), 7.19 (s, 1H), 7.21 (s, 1H), 7.22 (d, J = 7.3 Hz, 1H), 7.24 (d, J = 8.7 Hz, 1H), 9.00 (d, J = 7.3 Hz, 1H), 9.39 (br s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 26.7, 45.2, 54.5, 55.0, 55.5, 56.1, 66.9, 101.8, 105.3, 105.3, 106.6, 109.1, 110.7, 111.5, 112.5, 113.6, 117.4, 118.2, 122.0, 122.1, 124.6, 127.2, 128.4, 133.9, 145.4, 146.1, 147.7, 148.0, 148.3, 148.5, 148.9, 154.2. HRDARTMS *m*/*z*. Calcd for $C_{33}H_{33}N_2O_8$ [$(M+H)^+$]: 585.22369. Found: 585.22183.

To a suspension of **14b′** (20.0 mg, 34.2 μmol) in DCM (1.0 mL) was added trifluoroacetic acid (1.0 mL) at room temperature. After stirring for 0.5 min at room temperature, the mixture was evaporated. The crude product was purified by column chromatography over Sephadex LH-20 (MeOH containing 0.1% TFA) to give **14b** as a brown solid (21.6 mg, 90%). Mp 203–206 °C. IR (KBr): 3409, 3132, 1682, 1424, 1277, 1205, 1169, 1041 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 2.13 (quin, J = 6.9 Hz, 2H), 2.82 (s, 3H), 2.83 (s, 3H), 3.21 (quin, J = 5.1 Hz, 2H), 3.40 (s, 3H), 3.40 (s, 3H), 3.88 (s, 3H), 4.13 (t, J = 6.1 Hz, 2H), 6.81 (s, 1H), 7.00–7.04 (m, 2H), 7.17 (s, 1H), 7.19 (s, 1H), 7.21 (s, 1H), 7.25 (d, J = 7.3 Hz, 1H), 7.25 (d, J = 9.2 Hz, 1H), 9.01 (d, J = 7.3 Hz, 1H), 9.43 (br s, 2H), 9.98 (br s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 23.8, 42.4, 54.4, 54.5, 55.0, 56.1, 66.1, 102.3, 105.3, 106.7, 109.6, 110.7, 111.5, 112.7, 113.6, 117.4, 118.2, 121.9, 122.0, 124.6, 127.2, 128.2, 133.9, 145.4, 146.0, 147.7, 148.0, 148.2, 148.4, 148.6, 154.2. HRDARTMS *m*/*z*. Calcd for $C_{33}H_{33}N_2O_8$ [$(M–CF_3COO)^+$]: 585.22369. Found: 585.22208.

*4.2.5.10. Trifluoroacetic acid salt of 2-[2-(dimethylamino)ethoxy]-11-hydroxy-14-(3-hydroxy-4-methoxyphenyl)-3,12-dimethoxy-6H-[1]benzopyrano[4′,3′:4,5]pyrrolo[2,1-a]isoquinolin-6-one (**14c**)*

Under an argon atmosphere, a nitrobenzene solution of $AlCl_3$ (1.0 M, 400 μL, 0.400 mmol) was added dropwise to a solution of **13c** (43.2 mg, 66.0 μmol) in DCM (3.0 mL) at room temperature. After stirring for 40 h at room temperature, a solution of $NaHCO_3$ (150 mg, 1.79 mmol) and Rochelle salt (325 mg, 1.15 mmol) in water (5.0 mL) was added. The mixture was stirred for an additional 1 h and then evaporated. The nitrobenzene was removed azeotropically with water under reduced pressure. To the residue was added water and the precipitate was collected by filtration, washed with water, and dried under reduced pressure to give 2-[2-(dimethylamino)ethoxy]-11-hydroxy-14-(3-hydroxy-4-methoxyphenyl)-3,12-dimethoxy-6*H*-[1]benzopyrano[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (**14c′**) as a pale brown powder (35.3 mg, 94%). Mp 189.5–192.5 °C. IR (KBr): 3435, 1677, 1417, 1272, 1217, 1163, 1027 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 2.16 (s, 6H), 2.47 (t, J = 6.0 Hz, 2H), 3.39 (s, 3H), 3.58 (t, J = 6.0 Hz, 2H), 3.82 (s, 3H), 3.87 (s, 3H), 6.78 (s, 1H), 6.99 (d, J = 1.8 Hz, 1H), 7.01 (dd, J = 1.8 and 8.2 Hz, 1H), 7.12 (s, 1H), 7.17 (s, 1H), 7.19 (s, 1H), 7.21–7.24 (m, 2H), 9.00 (d, J = 7.3 Hz, 1H), 9.38 (br s, 1H), 9.96 (br s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 45.3, 54.6, 55.9, 55.9, 57.2, 66.3, 101.1, 105.3, 106.5, 106.7, 109.1, 110.7, 111.6, 112.6, 113.4, 117.5, 118.1, 122.0, 122.0, 124.7, 127.2, 128.4, 134.0, 144.3, 146.3, 147.7, 148.0, 148.4, 148.6, 149.8, 154.3. HRDARTMS *m*/*z*. Calcd for $C_{32}H_{31}N_2O_8$ [$(M+H)^+$]: 571.20804. Found: 571.21021.

To a suspension of **14c′** (20.0 mg, 35.1 μmol) in DCM (1.0 mL) was added trifluoroacetic acid (1.0 mL) at room temperature. After stirring for 0.5 min at room temperature, the mixture was evaporated. The crude product was purified by column chromatography over Sephadex LH-20 (MeOH containing 0.1% TFA) to give **14c** as a brown solid (22.6 mg, 94%). Mp 134–135 °C. IR (KBr): 3395, 1685, 1418, 1277, 1205, 1131, 1024 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 2.83 (s, 6H), 3.38 (t, J = 6.1 Hz, 2H), 3.40 (s, 3H), 3.86 (s, 3H), 3.90 (s, 3H), 3.93 (q, J = 5.0 Hz, 2H), 6.86 (s, 1H), 7.01 (d, J = 2.1 Hz, 1H), 7.03 (dd, J = 2.1 and 8.0 Hz, 1H), 7.12 (s, 1H), 7.20 (s, 1H), 7.21 (s, 1H), 7.24 (d, J = 7.3 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 9.00 (d, J = 7.3 Hz, 1H), 9.45 (br s, 1H), 9.80 (br s, 1H), 10.02 (br s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 42.9, 54.5, 55.3, 56.1, 56.2, 64.3, 101.6, 105.3, 106.6, 109.4, 109.4, 110.8, 111.6, 112.8, 113.5, 117.4, 118.2, 122.0, 122.0, 124.7, 127.1, 127.9, 134.1, 143.1, 147.5,

147.7, 148.0, 148.4, 148.6, 150.5, 154.1. HRDARTMS *m*/*z*. Calcd for $C_{32}H_{31}N_2O_8$ [(M–CF_3COO)$^+$]: 571.20804. Found: 571.21068.

*4.2.5.11. Trifluoroacetic acid salt of 3-[3-(dimethylamino)propoxy]-2,11-dihydroxy-14-(3-hydroxy-4-methoxyphenyl)-12-methoxy-6H-[1]benzopyrano[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one (**14d**)*

Under an argon atmosphere, a nitrobenzene solution of $AlCl_3$ (1.0 M, 218 μL, 0.218 mmol) was added dropwise to a solution of **13d** (20.0 mg, 28.7 μmol) in DCM (5.0 mL) at room temperature. After stirring for 48 h at room temperature, a solution of $NaHCO_3$ (55.0 mg, 0.654 mmol) and Rochelle salt (185 mg, 0.654 mmol) in water (3.3 mL) was added and the mixture was evaporated. The nitrobenzene was removed azeotropically with water under reduced pressure. To the residue was added DCM (2.0 mL) and TFA (2.0 mL) and then the mixture was evaporated. The residue was purified by column chromatography over Sephadex LH-20 using following solvent systems (water containing 0.1% TFA, water–MeOH = 1:1 containing 0.1% TFA, and MeOH containing 0.1% TFA) to give **14d** as a brown solid (19.3 mg, 98%). Mp 170–190 °C (dec) (sealed capillary). IR (KBr): 3351, 1682, 1425, 1280, 1202, 1163, 1041 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.12 (quin, J = 5.5 Hz, 2H), 2.82 (s, 6H), 3.28 (t, J = 7.8 Hz, 2H), 3.37 (s, 3H), 3.90 (s, 3H), 4.12 (t, J = 5.9 Hz, 2H), 6.81 (s, 1H), 6.92 (s, 1H), 6.94 (d, J = 2.0 Hz, 1H), 6.95 (dd, J = 2.0 and 8.0 Hz, 1H), 7.11 (s, 1H), 7.18 (s, 1H), 7.21 (d, J = 7.4 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 9.03 (d, J = 7.4 Hz, 1H), 9.04 (br s, 1H), 9.41 (br s, 1H), 9.53 (br s, 1H), 9.98 (br s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 23.8, 42.4, 54.4, 54.5, 55.9, 65.9, 102.1, 105.2, 106.7, 109.1, 110.2, 111.1, 111.6, 112.7, 113.6, 117.5, 118.0, 122.0, 122.0, 124.7, 127.2, 128.1, 134.2, 143.1, 145.2, 147.5, 147.7, 148.0, 148.3, 148.5, 154.4. HRDARTMS *m*/*z*. Calcd for $C_{32}H_{31}N_2O_8$ [(M–CF_3COO)$^+$]: 571.20804. Found: 571.20608.

*4.2.5.12. Trifluoroacetic acid salt of 2,3-bis[2-(dimethylamino)ethoxy]-11-dihydroxy-14-(3-hydroxy-4-methoxyphenyl)-12-methoxy-6H-[1]benzopyrano[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one (**14e**)*

Under an argon atmosphere, a nitrobenzene solution of $AlCl_3$ (1.0 M, 120 μL, 0.120 mmol) was added dropwise to a solution of **13e** (13.4 mg, 18.8 μmol) in DCM (1.0 mL) at room temperature. After stirring for 48 h at room temperature, a solution of $NaHCO_3$ (30.3 mg, 0.361 mmol) and Rochelle salt (102 mg, 0.361 mmol) in water (0.7 mL) was added. The mixture was stirred for an additional 1 h and then evaporated. The nitrobenzene was removed azeotropically with water under reduced pressure. To the residue was added water and the precipitate was collected by filtration, washed with water, and dried under reduced pressure. To the product was added DCM (1.0 mL) and TFA (1.0 mL) and then the mixture was evaporated. The residue was purified by column chromatography over Sephadex LH-20 (MeOH containing 0.1% TFA) to give **14e** as a brown solid (15.0 mg, 93%). Mp 95–100 °C. IR (KBr): 3441, 1693, 1424, 1280, 1204, 1177, 1133 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.82 (s, 6H), 2.88 (s, 6H), 3.40 (s, 3H), 3.54 (t, J = 4.8 Hz, 2H), 3.90 (s, 3H), 3.90–3.98 (m, 2H), 4.44 (t, J = 5.0 Hz, 2H), 6.87 (s, 1H), 7.01 (d, J = 2.1 Hz, 1H), 7.03 (dd, J = 2.1 and 8.1 Hz, 1H), 7.14 (s, 1H), 7.21 (s, 1H), 7.25 (d, J = 8.1 Hz, 1H), 7.27 (d, J = 7.4 Hz, 1H), 7.35 (s, 1H), 9.02 (d, J = 7.4 Hz, 1H), 9.48 (br s, 1H), 10.04 (br s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 43.0, 43.1, 54.6, 55.2, 55.2, 56.1, 64.0, 64.2, 103.4, 105.3, 106.7, 108.9, 110.5, 110.9, 111.6, 113.0, 113.6, 117.4, 118.1, 122.0, 122.0, 124.7, 127.0, 127.7, 134.1, 143.4, 147.0, 147.7, 148.1, 148.3, 148.5, 148.7, 154.0. HRDARTMS *m*/*z*. Calcd for $C_{35}H_{38}N_3O_8$ [(M–2CF_3COO–H)$^+$]: 628.26589. Found: 628.26746.

*4.2.5.13. Trifluoroacetic acid salt of 2,3-bis[3-(dimethylamino)propoxy]-11-hydroxy-14-(3-hydroxy-4-methoxyphenyl)-12-methoxy-6H-[1]benzopyrano[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one (**14f**)*

Under an argon atmosphere, a nitrobenzene solution of $AlCl_3$ (1.0 M, 780 μL, 0.780 mmol) was added dropwise to a solution of **13f** (90.2 mg, 0.122 mmol) in DCM (19.5 mL) at room temperature. After stirring for 84.5 h at room temperature, a solution of $NaHCO_3$ (166 mg, 1.97 mmol) and Rochelle salt (557 mg, 1.97 mmol) in water (3.9 mL) was added. The mixture was stirred for an additional 1 h and then evaporated. The nitrobenzene was removed azeotropically with water under reduced pressure. To the residue was added water and the precipitate was collected by filtration, washed with water, and dried under reduced pressure to give 2,3-bis[3-(dimethylamino)propoxy]-11-hydroxy-14-(3-hydroxy-4-methoxyphenyl)-12-methoxy-6*H*-[1]benzopyrano[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (**14f′**) as a brown powder (80.0 mg, quant). Mp 180–210 °C (dec) (sealed capillary). IR (KBr): 3410, 1686, 1428, 1283, 1217, 1174 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.63–1.70 (m, 2H), 1.82–1.89 (m, 2H), 2.14 (s, 6H), 2.17 (s, 6H), 2.23–2.30 (m, 2H), 2.36–2.43 (m, 2H), 3.39 (s, 3H), 3.53–3.60 (m, 2H), 3.88 (s, 3H), 4.01–4.08 (m, 2H), 6.76 (s, 1H), 6.97–7.02 (m, 2H), 7.07 (s, 1H), 7.15 (s, 1H), 7.19 (s, 1H), 7.20–7.24 (m, 2H), 8.99 (d, J = 7.3 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 26.5, 26.6, 45.0, 45.1, 54.6, 55.3, 55.5, 56.0, 66.5, 66.8, 102.1, 105.3, 106.7, 107.0, 109.3, 110.7, 111.6, 111.6, 112.6, 113.4, 117.5, 118.2, 122.0, 124.7, 127.2, 128.4, 133.9, 144.6, 146.2, 147.7, 148.1, 148.4, 148.6, 149.3, 154.3. HRDARTMS *m*/*z*. Calcd for $C_{37}H_{42}N_3O_8$ [(M+H)$^+$]: 656.29719. Found: 656.30016.

To a suspension of **14f′** (78.3 mg, 0.106 mmol) in DCM (3.0 mL) was added trifluoroacetic acid (3.0 mL) at room temperature. After stirring for 0.5 min at room temperature, the mixture was evaporated. The crude product was purified by column chromatography over Sephadex LH-20 (MeOH containing 0.1% TFA) to give **14f** as a brown solid (94.2 mg, quant). Mp 110–130 °C (dec) (sealed capillary). IR (KBr): 3435, 1682, 1426, 1279, 1206, 1132 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.92–2.00 (m, 2H), 2.09–2.17 (m, 2H), 2.81 (s, 6H), 2.83 (s, 6H), 3.06–3.13 (m, 2H), 3.21 (t, J = 7.2 Hz, 2H), 3.40 (s, 3H), 3.59–3.70 (m, 2H), 3.90 (s, 3H), 4.13 (t, J = 6.2 Hz, 2H), 6.79 (s, 1H), 7.01 (d, J = 2.0 Hz, 1H), 7.02 (dd, J = 2.0 and 8.0 Hz, 1H), 7.17 (s, 1H), 7.19 (s, 1H), 7.21 (s, 1H), 7.25 (d, J = 7.4 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 9.00 (d, J = 7.4 Hz, 1H), 9.50 (br s, 1H), 9.84 (br s, 1H), 9.87 (br s, 1H), 10.05 (br s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 23.7, 23.7, 42.3, 42.4, 54.1, 54.2, 54.6, 56.1, 65.7, 66.1, 102.6, 105.3, 106.7, 107.3, 109.7, 110.8, 111.6, 112.8, 113.6, 117.4, 118.2, 122.0, 122.1, 124.7, 127.2, 128.1, 134.0, 144.1, 146.5, 147.7, 148.0, 148.5, 148.6, 148.7, 154.2. HRDARTMS *m*/*z*. Calcd for $C_{37}H_{42}N_3O_8$ [(M–2CF_3COO–H)$^+$]: 656.29719. Found: 656.29442.

*4.2.5.14. Methanesulfonic acid salt of 11-hydroxy-14-(3-hydroxy-4-methoxyphenyl)-12-methoxy-2,3-bis(3-morpholinopropoxy)-6H-[1]benzopyrano[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one (**14g**)*

Under an argon atmosphere, a nitrobenzene solution of $AlCl_3$ (1.0 M, 310 μL, 0.310 mmol) was added dropwise to a solution of **12g** (40.0 mg, 48.5 μmol) in DCM (3.0 mL) at room temperature. After stirring for 42 h at room temperature, a solution of $NaHCO_3$ (78.0 mg, 0.928 mmol) and Rochelle salt (262 mg, 0.928 mmol) in water (1.0 mL) was added. The mixture was stirred for an additional 2 h and then evaporated. The nitrobenzene was removed azeotropically with water under reduced pressure. The residue was diluted with water and the

precipitate was collected by filtration, washed with ether, and dried under reduced pressure to give 11-hydroxy-14-(3-hydroxy-4-methoxyphenyl)-12-methoxy-2,3-bis(3-morpholinopropoxy)-6*H*-[1]benzopyrano[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (**14g′**) as a pale brown powder (28.0 mg, 78%). The filtrate was extracted with ethyl acetate–THF (1:1). The extract was dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography over silica gel 60N (ethyl acetate to ethyl acetate–MeOH = 1:1) to give an additional **14g′** (4.8 mg, 13%). Mp >300 °C (sealed capillary). IR (KBr): 1697, 1423, 1276, 1205, 1165, 1115, 1032 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 1.67 (quin, J = 6.7 Hz, 2H), 1.87 (quin, J = 6.7 Hz, 2H), 2.28 (t, J = 7.2 Hz, 2H), 2.30–2.38 (m, 8H), 2.41 (t, J = 7.2 Hz, 2H), 3.39 (s, 3H), 3.53–3.61 (m, 10H), 3.87 (s, 3H), 4.06 (t, J = 6.2 Hz, 2H), 6.77 (s, 1H), 6.98–7.01 (m, 2H), 7.10 (s, 1H), 7.15 (s, 1H), 7.19 (s, 1H), 7.20–7.24 (m, 2H), 8.99 (d, J = 7.4 Hz, 1H), 9.41 (br s, 1H), 9.94 (br s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 25.6, 25.8, 53.3, 53.4, 54.6, 54.6, 54.8, 56.0, 66.2, 66.2, 66.6, 66.9, 102.2, 105.3, 106.7, 107.1, 109.3, 110.7, 111.6, 112.6, 113.4, 117.5, 118.2, 122.0, 122.0, 124.7, 127.2, 128.4, 133.9, 144.6, 146.2, 147.7, 148.0, 148.3, 148.6, 149.3, 154.3. HRDARTMS *m*/*z*. Calcd for $C_{41}H_{46}N_3O_{10}$ [$(M+H)^+$]: 740.31832. Found: 740.31675.

To a suspension of **14g′** (19.3 mg, 26.1 μmol) in MeOH (4.0 mL) was added a MeOH solution of MsOH (0.105 M, 498 μL, 52.2 μmol) at room temperature. The solution was passed through a pad of Sephadex LH-20 using MeOH as an eluent. The filtrate was evaporated and the residue was dried under reduced pressure to give **14g** as a brown powder (23.1 mg, 95%). Mp 225–228 °C. IR (KBr): 3400, 1698, 1423, 1278, 1193, 1059 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 1.99 (br s, 2H), 2.16 (br s, 2H), 2.36 (s, 6H), 3.00–3.55 (m, 12H), 3.40 (s, 3H), 3.60–4.10 (m, 10H), 3.91 (s, 3H), 4.15 (t, J = 6.1 Hz, 2H), 6.81 (s, 1H), 7.02 (d, J = 2.0 Hz, 1H), 7.03 (dd, J = 2.0 and 8.0 Hz, 1H), 7.17 (s, 1H), 7.21 (s, 2H), 7.25 (d, J = 7.4 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 9.00 (d, J = 7.4 Hz, 1H), 9.46 (br s, 1H), 9.71 (br s, 2H), 10.01 (br s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 23.1, 39.8, 51.4, 53.6, 53.7, 54.6, 56.2, 63.6, 65.9, 66.2, 102.8, 105.3, 106.7, 107.6, 109.8, 110.8, 111.6, 112.8, 113.7, 117.5, 118.2, 122.0, 122.2, 124.8, 127.2, 128.2, 134.1, 144.1, 146.5, 147.7, 148.0, 148.5, 148.7, 148.7, 154.2. HRDARTMS *m*/*z*. Calcd for $C_{41}H_{46}N_3O_{10}$ [$(M–2CH_3SO_3–H)^+$]: 740.31832. Found: 740.31617.

*4.2.6. Synthesis of guanidinium-tethered lamellarin N analogues **18a** and **18b***

*4.2.6.1. 3-[2-(tert-Butoxycarbonylamino)ethoxy]-11-isopropoxy-14-(3-isopropoxy-4-methoxyphenyl)-2,12-dimethoxy-6H-[1]benzopyrano[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one **(15a)***

Under an argon atmosphere, triphenylphosphine (59.0 mg, 0.227 mmol) and DIAD (45.0 μL, 0.229 mmol) were added in sequence to a mixed solution of **12a** (88.2 mg, 0.151 mmol) and 2-(*tert*-butoxycarbonylamino)-1-ethanol (36.7 mg, 0.228 mmol) in THF (5 mL). After stirring for 5 h at room temperature, one drop of water was added to the mixture and the product was evaporated. The residue was purified by column chromatography over silica gel 60N (hexane–ethyl acetate = 1:1) to give a mixture of **15a** and diisopropyl hydrazinedicarboxylate. The latter hydrazine derivative was easily removed by bulb-to-bulb distillation (120 °C, 0.1 mmHg) to leave **15a** as a pale yellow solid (99.0 mg, 90%). Mp 130–132 °C. IR (KBr): 1709, 1432, 1267, 1224, 1166, 1038 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.36 (d, J = 6.1 Hz, 3H), 1.36 (d, J = 6.1 Hz, 3H), 1.44 (d, J = 6.1 Hz, 6H), 1.44 (s, 9H), 3.45 (s, 3H), 3.46 (s, 3H), 3.57 (q, J = 4.9 Hz, 2H), 3.97 (s, 3H), 4.09 (t, J = 4.9 Hz, 2H), 4.55 (sep, J = 6.1 Hz, 1H), 4.70 (sep, J = 6.1 Hz, 1H), 5.11 (br s, 1H), 6.75 (s, 1H), 6.95 (s, 1H), 7.02 (d, J = 7.4 Hz, 1H), 7.10 (s, 1H), 7.14 (d, J = 1.8 Hz, 1H), 7.16 (d, J = 8.2 Hz, 1H), 7.18 (s, 1H), 7.20 (dd, J = 1.8 and 8.2 Hz, 1H), 9.21 (d, J = 7.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.9, 22.0, 22.0, 28.4, 39.9, 55.2, 55.4, 56.4, 68.9, 71.2, 71.3, 79.6, 102.8, 105.5, 105.6, 107.9, 110.4, 110.8, 111.1, 112.4, 112.7, 118.1, 119.0, 123.2, 124.1, 124.7, 128.2, 129.2, 134.5, 146.0, 146.6, 148.2, 148.5, 148.5, 150.2, 150.3, 155.4, 155.9. HRDARTMS *m*/*z*. Calcd for $C_{41}H_{47}N_2O_{10}$ [$(M+H)^+$]: 727.32307. Found: 727.32476.

*4.2.6.2. 3-[3-(tert-Butoxycarbonylamino)propoxy]-11-isopropoxy-14-(3-isopropoxy-4-methoxyphenyl)-2,12-dimethoxy-6H-[1]benzopyrano[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one **(15b)***

According to the procedure described for the preparation of **15a**, **12a** (50.0 mg, 85.7 μmol) and 3-(*tert*-butoxycarbonylamino)-1-propanol (22.6 mg, 0.129 mmol) were reacted. After purification by column chromatography over silica gel 60N (hexane–ethyl acetate = 2:1–1:1), a mixture of **15b** and diisopropyl hydrazinedicarboxylate was obtained. The latter hydrazine derivative was easily removed by bulb-to-bulb distillation (120 °C, 0.1 mmHg) to leave **15b** as a pale yellow solid (55.4 mg, 87%). Mp 108–115 °C. IR (KBr): 1705, 1432, 1268, 1223, 1165, 1038 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.36 (d, J = 6.0 Hz, 3H), 1.37 (d, J = 6.0 Hz, 3H), 1.44 (d, J = 6.0 Hz, 6H), 1.45 (s, 9H), 1.98–2.08 (m, 2H), 3.37 (q, J = 5.3 Hz, 2H), 3.45 (s, 3H), 3.48 (s, 3H), 3.97 (s, 3H), 4.10 (t, J = 5.6 Hz, 2H), 4.56 (sep, J = 6.0 Hz, 1H), 4.70 (sep, J = 6.0 Hz, 1H), 5.51 (br s, 1H), 6.74 (s, 1H), 6.90 (s, 1H), 7.02 (d, J = 7.3 Hz, 1H), 7.10 (s, 1H), 7.14–7.23 (m, 4H), 9.20 (d, J = 7.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 22.0, 22.0, 28.5, 29.1, 39.0, 55.1, 55.3, 56.4, 68.4, 71.2, 71.3, 78.9, 101.6, 105.1, 105.6, 107.8, 110.3, 110.4, 111.0, 112.4, 112.7, 118.1, 119.0, 123.1, 124.1, 124.7, 128.2, 129.3, 134.5, 145.8, 146.6, 148.2, 148.5, 148.6, 150.2, 150.2, 155.5, 156.1. HRDARTMS *m*/*z*. Calcd for $C_{42}H_{49}N_2O_{10}$ [$(M+H)^+$]: 741.33872. Found: 741.33968.

*4.2.6.3. Trifluoroacetic acid salt of 3-(2-aminoethoxy)-11-isopropoxy-14-(3-isopropoxy-4-methoxyphenyl)-2,12-dimethoxy-6H-[1]benzopyrano[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one **(16a)***

To a solution of **15a** (49.5 mg, 68.1 μmol) in DCM (1.0 mL) was added trifluoroacetic acid (1.0 mL) at room temperature. After stirring for 0.5 h, the mixture was concentrated to give **16a** as a brown solid (50.6 mg, quant). Mp 150–160 °C. IR (KBr): 1700, 1422, 1267, 1206, 1171, 1136, 1013 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 1.21 (d, J = 6.0 Hz, 3H), 1.22 (d, J = 6.0 Hz, 3H), 1.31 (d, J = 6.0 Hz, 3H), 1.31 (d, J = 6.0 Hz, 3H), 3.24 (br s, 2H), 3.34 (s, 3H), 3.38 (s, 3H), 3.85 (s, 3H), 4.24 (t, J = 5.2 Hz, 2H), 4.57 (sep, J = 6.0 Hz, 1H), 4.75 (sep, J = 6.0 Hz, 1H), 6.73 (s, 1H), 7.11 (s, 1H), 7.17 (dd, J = 1.8 and 8.1 Hz, 1H), 7.18 (d, J = 1.8 Hz, 1H), 7.24 (s, 1H), 7.29 (d, J = 8.1 Hz, 1H), 7.32 (d, J = 7.4 Hz, 1H), 7.45 (s, 1H), 8.02 (br s, 3H), 9.05 (d, J = 7.4 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 21.7, 21.7, 21.7, 21.8, 38.2, 54.4, 54.9, 56.0, 65.9, 70.3, 70.4, 103.1, 105.0, 105.4, 106.9, 110.3, 110.5, 111.1, 113.1, 113.6, 118.1, 118.2, 122.1, 123.7, 124.5, 127.0, 128.3, 133.8, 145.6, 146.0, 147.8, 147.9, 148.2, 149.8, 150.3, 154.2. HRDARTMS *m*/*z*. Calcd for $C_{36}H_{39}N_2O_8$ [$(M–CF_3COO)^+$]: 627.27064. Found: 627.27098.

*4.2.6.4. Trifluoroacetic acid salt of 3-(3-aminopropoxy)-11-isopropoxy-14-(3-isopropoxy-4-methoxyphenyl)-2,12-dimethoxy-6H-[1]benzopyrano[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one **(16b)***

According to the procedure described for the preparation of **16a**, **15b** (26.7 mg, 36.0 μmol) was reacted to give **16b** as a brown solid (26.2 mg, 96%). Mp 140–145 °C. IR (KBr): 1696,

1432, 1268, 1205, 1170, 1134 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 1.22 (d, J = 6.0 Hz, 6H), 1.30 (d, J = 6.0 Hz, 3H), 1.31 (d, J = 6.0 Hz, 3H), 2.02 (quin, J = 6.7 Hz, 2H), 2.96 (sext, J = 6.3 Hz, 2H), 3.33 (s, 3H), 3.36 (s, 3H), 3.85 (s, 3H), 4.09 (t, J = 6.1 Hz, 2H), 4.57 (sep, J = 6.0 Hz, 1H), 4.73 (sep, J = 6.0 Hz, 1H), 6.67 (s, 1H), 7.08 (s, 1H), 7.08 (s, 1H), 7.13 (dd, J = 2.0 and 8.2 Hz, 1H), 7.18 (d, J = 2.0 Hz, 1H), 7.25 (d, J = 8.2 Hz, 1H), 7.27 (d, J = 7.4 Hz, 1H), 7.40 (s, 1H), 7.86 (br s, 3H), 8.98 (d, J = 7.4 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 21.7, 21.7, 21.7, 21.8, 26.7, 36.4, 54.4, 54.9, 56.0, 65.7, 70.2, 70.5, 102.0, 105.0, 105.1, 106.8, 109.5, 110.4, 110.9, 112.9, 113.5, 118.1, 122.0, 123.8, 124.5, 127.1, 128.4, 133.8, 145.4, 146.1, 147.8, 148.1, 148.4, 149.7, 150.2, 154.2. HRDARTMS *m*/*z*. Calcd for $C_{37}H_{41}N_2O_8$ [$(M–CF_3COO)^+$]: 641.28629. Found: 641.28500.

4.2.6.5. 3-{2-[Bis(tert-butoxycarbonylamino)methylideneamino]ethoxy}-11-isopropoxy-14-(3-isopropoxy-4-methoxyphenyl)-2,12-dimethoxy-6H-[1]benzopyrano[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one ***(17a)***

Under an argon atmosphere, a mixture of **16a** (91.2 mg, 0.123 mmol), *N*,*N*′-bis(*tert*-butoxycarbonyl)-1*H*-pyrazole-1-carboxamidine (76.3 mg, 0.246 mmol) and triethylamine (34 μL, 0.243 mmol) in chloroform (15 mL) was stirred for 19 h at room temperature. The mixture was evaporated and the residue was purified by column chromatography over silica gel 60N (hexane–ethyl acetate = 2:1–1:1) to give **17a** as a colorless powder (93.0 mg, 87%). Mp 200–210 °C (dec) (sealed capillary). IR (KBr): 3326, 1716, 1643, 1420, 1268, 1159, 1139, 1041 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.35 (d, J = 6.1 Hz, 3H), 1.36 (d, J = 6.1 Hz, 3H), 1.44 (d, J = 6.1 Hz, 6H), 1.49 (s, 9H), 1.51 (s, 9H), 3.45 (s, 3H), 3.48 (s, 3H), 3.87 (dq, J = 1.6 and 5.2 Hz, 2H), 3.97 (s, 3H), 4.18 (dt, J = 1.6 and 5.2 Hz, 2H), 4.55 (sep, J = 6.1 Hz, 1H), 4.70 (sep, J = 6.1 Hz, 1H), 4.74 (br s, 1H), 6.77 (s, 1H), 7.00 (s, 1H), 7.03 (d, J = 7.4 Hz, 1H), 7.10 (s, 1H), 7.13 (d, J = 1.8 Hz, 1H), 7.16 (d, J = 8.1 Hz, 1H), 7.17 (s, 1H), 7.19 (dd, J = 1.8 and 8.1 Hz, 1H), 8.76 (t, J = 5.4 Hz, 1H), 9.23 (d, J = 7.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.9, 22.0, 22.0, 28.1, 28.3, 40.0, 55.2, 55.6, 56.4, 68.1, 71.2, 71.3, 79.4, 83.0, 103.5, 105.6, 106.0, 107.9, 110.4, 111.1, 111.1, 112.4, 112.8, 118.1, 119.1, 123.2, 124.1, 124.7, 127.3, 128.2, 128.4, 129.2, 134.5, 146.4, 146.6, 148.2, 148.5, 150.2, 150.2, 153.0, 155.5, 156.4, 163.5. HRFABMS *m*/*z*. Calcd for $C_{47}H_{57}N_4O_{12}$ [$(M+H)^+$]: 869.3973. Found: 869.3970.

4.2.6.6. 3-{3-[Bis(tert-butoxycarbonylamino)methylideneamino]propoxy}-11-isopropoxy-14-(3-isopropoxy-4-methoxyphenyl)-2,12-dimethoxy-6H-[1]benzopyrano[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one ***(17b)***

According to the procedure described for the preparation of **17a**, **16b** (26.2 mg, 34.7 μmol) was reacted. After purification by column chromatography over silica gel 60N (hexane–ethyl acetate = 2:1–1:1), **17b** was obtained as a colorless powder (23.1 mg, 75%). Mp 120–170 °C (dec) (sealed capillary). IR (KBr): 3334, 1725, 1642, 1421, 1267, 1165, 1135 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.35 (d, J = 6.1 Hz, 3H), 1.36 (d, J = 6.1 Hz, 3H), 1.44 (d, J = 6.1 Hz, 6H), 1.48 (s, 9H), 1.50 (s, 9H), 2.15 (quin, J = 6.6 Hz, 2H), 3.45 (s, 3H), 3.45 (s, 3H), 3.63 (q, J = 6.4 Hz, 2H), 3.96 (s, 3H), 4.10 (t, J = 6.2 Hz, 2H), 4.55 (sep, J = 6.1 Hz, 1H), 4.70 (sep, J = 6.1 Hz, 1H), 6.74 (s, 1H), 6.95 (s, 1H), 7.03 (d, J = 7.3 Hz, 1H), 7.10 (s, 1H), 7.14 (d, J = 1.8 Hz, 1H), 7.16 (d, J = 8.1 Hz, 1H), 7.17 (s, 1H), 7.20 (dd, J = 1.8 and 8.1 Hz, 1H), 8.45 (t, J = 5.3 Hz, 1H), 9.23 (d, J = 7.3 Hz, 1H), 11.49 (br s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.9, 22.0, 22.0, 28.1, 28.3, 28.7, 37.9, 55.2, 55.4, 56.4, 66.6, 71.2, 71.3, 79.3, 83.1, 102.1, 105.4, 105.6, 107.9, 110.3, 110.4, 111.1, 112.4, 112.7, 118.1, 119.1, 123.2, 124.1, 124.7, 128.2, 129.4, 134.5, 146.0, 146.6, 148.2, 148.5, 148.8, 150.2, 150.2, 153.3, 155.5, 156.3, 163.6. HRFABMS *m*/*z*. Calcd for $C_{48}H_{59}N_4O_{12}$ [$(M+H)^+$]: 883.4129. Found: 883.4133.

4.2.6.7. Trifluoroacetic acid salt of 3-(2-guanidinoethoxy)-11-isopropoxy-14-(3-isopropoxy-4-methoxyphenyl)-2,12-dimethoxy-6H-[1]benzopyrano[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one ***(18a)***

Under an argon atmosphere, a nitrobenzene solution of $AlCl_3$ (1.0 M, 461 μL, 0.461 mmol) was added dropwise to a solution of **17a** (40.0 mg, 46.0 μmol) in DCM (7.0 mL) at room temperature. After stirring for 48 h at room temperature, a solution of $NaHCO_3$ (116 mg, 1.38 mmol) and Rochelle salt (389 mg, 1.38 mmol) in water (2.7 mL) was added and the mixture was evaporated. The nitrobenzene was removed azeotropically with water under reduced pressure. To the residue was added DCM (2.0 mL) and TFA (2.0 mL) and then the mixture was evaporated. The residue was purified by column chromatography over Sephadex LH-20 using following solvent systems (water containing 0.1% TFA, water–MeOH = 1:1 containing 0.1% TFA, and MeOH containing 0.1% TFA) to give **18a** as a brown powder (14.7 mg, 46%). Mp 130–170 °C (dec) (sealed capillary). IR (KBr): 3166, 1685, 1422, 1275, 1205, 1170, 1131 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 3.40 (s, 6H), 3.55 (q, J = 5.2 Hz, 2H), 3.87 (s, 3H), 4.14 (t, J = 5.2 Hz, 2H), 6.81 (s, 1H), 7.01 (dd, J = 2.1 and 8.7 Hz, 1H), 7.01 (d, J = 2.1 Hz, 1H), 7.16 (s, 1H), 7.17 (s, 1H), 7.20 (s, 1H), 7.23 (d, J = 8.7 Hz, 1H), 7.23 (d, J = 7.3 Hz, 1H), 7.30 (br s, 4H), 7.75 (t, J = 5.7 Hz, 1H), 8.99 (d, J = 7.3 Hz, 1H), 9.42 (br s, 1H), 10.01 (br s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 29.6, 54.6, 55.0, 56.1, 67.1, 102.4, 105.3, 105.4, 106.7, 109.9, 110.8, 111.6, 112.7, 113.6, 117.4, 118.2, 122.0, 122.1, 124.7, 127.2, 128.2, 134.0, 145.3, 146.0, 147.7, 148.0, 148.1, 148.4, 148.6, 154.2, 157.2. HRFABMS *m*/*z*. Calcd for $C_{31}H_{29}N_4O_8$ [$(M–CF_3COO)^+$]: 585.1985. Found: 585.1989.

4.2.6.8. Trifluoroacetic acid salt of 3-(3-guanidinopropoxy)-11-isopropoxy-14-(3-isopropoxy-4-methoxyphenyl)-2,12-dimethoxy-6H-[1]benzopyrano[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one ***(18b)***

According to the procedure described for the preparation of **18a**, **17b** (13.0 mg, 14.7 μmol) was reacted. After purification by column chromatography over Sephadex LH-20 using following solvent systems (water containing 0.1% TFA, water–MeOH = 1:1 containing 0.1% TFA, and MeOH containing 0.1% TFA), **18b** was obtained as a brown powder (8.9 mg, 81%). Mp 150–170 °C (dec) (sealed capillary). IR (KBr): 3366, 1678, 1423, 1277, 1204, 1168, 1132 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 1.95 (quin, J = 6.5 Hz, 2H), 3.26 (q, J = 6.4 Hz, 2H), 3.39 (s, 3H), 3.40 (s, 3H), 3.87 (s, 3H), 4.08 (t, J = 6.1 Hz, 2H), 6.79 (s, 1H), 7.01 (d, J = 2.1 Hz, 1H), 7.01 (dd, J = 2.1 and 8.7 Hz, 1H), 7.14 (s, 1H), 7.18 (s, 1H), 7.20 (s, 1H), 7.20 (br s, 4H), 7.23 (d, J = 7.3 Hz, 1H), 7.24 (d, J = 8.7 Hz, 1H), 7.68 (t, J = 5.5 Hz, 1H), 9.00 (d, J = 7.3 Hz, 1H), 9.41 (br s, 1H), 10.00 (br s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 28.0, 37.8, 54.6, 55.0, 56.1, 65.8, 102.1, 105.3, 105.3, 106.7, 109.5, 110.7, 111.6, 112.7, 113.6, 117.4, 118.2, 122.0, 122.1, 124.7, 127.2, 128.3, 134.0, 145.4, 146.1, 147.7, 148.0, 148.4, 148.5, 148.6, 154.2, 156.8. HRFABMS *m*/*z*. Calcd for $C_{32}H_{31}N_4O_8$ [$(M–CF_3COO)^+$]: 599.2142. Found: 599.2145.

4.3. Determination of the water solubility of ***14b*** *and* ***14f***

Water solubility for **14b** and **14f** was determined by an HPLC method.[43] An excess amount of the solid sample was added to water and the resulting mixture was sonicated for 15 min at room temperature and then passed through a Minisart RC syringe filter (pore size, 0.2 μm; Sartorius). Aliquots (0.4 μL) of the filtrate were injected into the HPLC system equipped with an Inertsil

Diol column (particle size, 5 μm; 250 × 4.6 mm I.D.; GL Sciences), eluting with methanol (0.01% trifluoroacetic acid). One point calibration was done by injecting 0.4 μL aliquots of the corresponding water solutions of **14b** and **14f** with known concentrations.

4.4. In vitro kinase assay–general

Recombinant kinase domains (amino residues 696 to the C-terminus) of the EGFR WT and T790M/L858R (Cell Signaling Technology) (100 ng) were preincubated with 1–10,000 nM of lamellarins in 25 mL of kinase reaction buffer (120mM HEPES, pH 7.5; 10 mM $MnCl_2$; 6 mM Na_3VO_4; and 2.5 mM DTT) at 25 °C for 30 min. Then, 25 mL ATP/substrate solution containing 20 mM of ATP and 6 mM poly (Glu-Tyr) biotinylated peptide (Cell Signaling Technology) was added to the preincubation. The kinase reaction was performed at 25 °C for 30 min and terminated by adding 50 mL of 50 mM of EDTA, pH 8.0. Phosphorylation levels were quantified using ELISA with avidin-coated 96-well plates and an anti-phosphotyrosine antibody (PY20). Relative inhibitions were calculated from at least three independent experiments, and IC_{50} values were estimated using the mean relative inhibition.[47]

4.5. Docking simulation

Docking studies were performed using MOE 2014.0901.[34] Crystal structures of EGFR (T790M/L858R/V948R)–gefitinib complex (PDB ID: 4I22)[33] was obtained from the Protein Data Bank. The protein structures for the docking was prepared by the following sequence: (i) A EGFR (T790M/L858R/V948R)–gefitinib complex was loaded. (ii) To the complex was added hydrogen atoms and electric charge by Protonate 3D (default settings), (iii) The hydrogen atoms were optimized by MMFF94x force field (the heavy atoms were fixed during the optimization). (iv) The dummy atoms were disposed in the docking site by Site Finder (default settings). On the other hand, the conformers of **2**, **14b**, **14d**, **14f**, and **18b** were obtained by Conformational Search using the LowModeMD search method with default parameters except for the followings: the hydrogens check box was selected in order to include both hydrogen and heavy atoms in the RMSD calculation for duplication detection and the value of energy window was set to 10 kcal/mol. Finally, the ligands were docked into the binding site of the kinases by using the Dock docking program according to the following sequence: (i) Initial poses were obtained using the Triangle Matcher placement (timeout: 3000 s; No. of return poses: 10000), London dG rescoring 1 (the maximum number of poses: 500), GridMin refinement (default settings), and GBVI/WSA dG rescoring 2 (the maximum number of poses: 100). (ii) The poses obtained in (i) were refined by Forcefield refinement (default settings) and rescored by GBVI/WSA dG scoring function (the maximum number of poses: 100). (iii) The poses obtained in (ii) were refined by Forcefield refinement (sidechain: tether, the tether value was set to 10) and rescored by GBVI/WSA dG scoring function (the maximum number of poses: 100). (iv) The poses obtained in (iii) were refined by Forcefield refinement (sidechain: free) and rescored by GBVI/WSA dG scoring function (the maximum number of poses: 100). The obtained poses were evaluated using the GBVI/WSA dG scoring function and the plausible low energy binding modes of these lamellarins in the kinase are shown in Fig. 6.

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Supplementary data

Supplementary data (synthesis of **8a–g**; ^1H and ^{13}C NMR spectra of all compounds synthesized in this work) can be found, in the online version, at doi:10.1016/j.bmc.2017.00.000.

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