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Structure–activity relationship study of non-steroidal NPC1L1 ligands identified through cell-based assay using pharmacological chaperone effect as a readout

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ABSTRACT

Niemann-Pick type C1-like 1 (NPC1L1) is an intestinal cholesterol transporter that is known to be the target of the cholesterol absorption inhibitor ezetimibe. We previously discovered steroidal NPC1L1 ligands by using a novel cell-based assay that employs pharmacological chaperone effect as a readout. Those steroid derivatives bound to a site different from both the sterol-binding domain and the ezetimibe-binding site, implying that they may be a novel class of NPC1L1 inhibitors with a distinct mode of action. As an extension of that work, we aimed here to find non-steroidal NPC1L1 ligands, which may be better candidates for clinical application than steroidal ligands, by using the same assay to screen our focused library of ligands for liver X receptor (LXR), a nuclear receptor that recognizes oxysterols as endogenous ligands. Here we describe identification of a novel class of NPC1L1 ligands with a ring-fused quinolinone scaffold, and an analysis of the structure–activity relationships of their derivatives as NPC1L1 ligands.

1. Introduction

Hypercholesterolemia is one of the key risk factors for coronary heart disease, a major cause of death in developed countries. Plasma cholesterol is derived from a combination of *de novo* biosynthesis and dietary intake. Statins, a class of HMG-CoA reductase inhibitors that reduce plasma LDL cholesterol level by inhibiting the rate-limiting step of the *de novo* cholesterol synthetic pathway, and ezetimibe (Zetia, Fig. 1), a cholesterol absorption inhibitor that inhibits intestinal cholesterol transporter NPC1L1 (Niemann-Pick type C1-like 1), have been shown to reduce plasma LDL cholesterol level.[1–6]

NPC1L1 is a 13-pass transmembrane protein expressed on the apical membrane of enterocytes and hepatocytes, and plays a critical role in the intestinal uptake of dietary cholesterol.[7–9] NPC1L1 has three large extracellular loops. The first N-terminal loop (N-terminal domain, NTD) is a cholesterol-binding domain and is required for cholesterol absorption.[10,11] The second loop connecting transmembrane domains 2 and 3 has been proposed to be important for binding of ezetimibe.[12] Recent efforts directed toward discovery of novel cholesterol absorption inhibitors have provided NPC1L1 inhibitors of several structural classes (Fig. 1, compound **2**).[13–15] However, these inhibitors were found by means of competitive binding assay with fluorescence- or radioisotope-labeled ezetimibe analogs, and they are considered to bind at the same site as ezetimibe.

We previously reported the identification of steroidal NPC1L1 ligands by means of a cell-based assay that employs the pharmacological chaperone effect as a readout.[16] Pharmacological chaperones are small-molecular ligands that correct trafficking defects of target proteins with reduced folding efficiency, such as point mutants or proteins with small deletions.[17–22] The mechanism of the pharmacological chaperone effect is thought to involve direct binding of the ligands to the destabilized folding intermediate of the mutant protein.[17] While folding-defective proteins are usually retained in the endoplasmic reticulum (ER) by the cellular quality control system, pharmacological chaperones added to the cells stabilize the mutant proteins and promote their escape from the ER to the proper locations. Thus, the trafficking defects of mutant proteins can be reversed by small-molecular ligands, and this can be visualized as a change in the localization pattern of the mutant proteins. We considered that this phenomenon could be applied for ligand screening. Thus, we generated folding-defective ER-retained NPC1L1 mutants and used them to screen for NPC1L1 ligands by monitoring correction of localization. This enabled us

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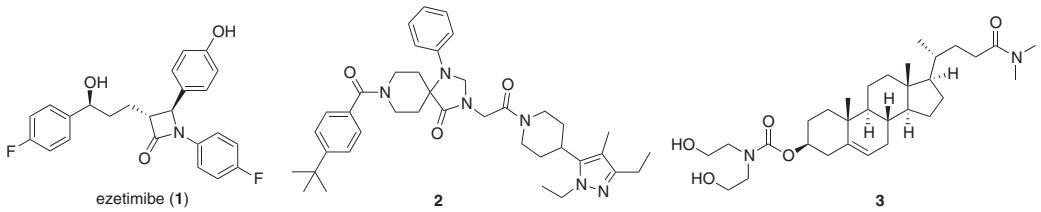


Figure 1. Chemical structures of reported NPC1L1 ligands [compound **2**: Ref. 13, compound **3**: Ref. 16].

to identify a new class of steroidal NPC1L1 ligands (Fig. 1).[16] We further established that the binding sites of these steroidal ligands are likely to be different from both the NTD and the ezetimibe-binding site.[16,23] This implies that these steroidal ligands might inhibit NPC1L1 via a different mode of action from that of ezetimibe. However, the metabolic instability and rather low selectivity of steroids might make them ineligible as antihyperlipidemic agents. Thus, we decided to search for non-steroidal counterparts of these ligands using our pharmacological chaperone effect-based assay.

In order to identify non-steroidal NPC1L1 ligands, we focused on our library of liver X receptor (LXR) ligands. Liver X receptor (LXR) is a member of the nuclear receptor family, and its endogenous ligands include oxysterols. As a subset of oxysterols was active toward NPC1L1 in our pharmacological chaperone-based assay,[16] we hypothesized that non-steroidal compounds that bind to NPC1L1 protein might be present in our library of non-steroidal LXR ligands and their analogs.

Here, we report the identification of ring-fused quinolinone derivatives as pharmacological chaperone effect-based assay hits from our LXR-related library, together with the results of structure–activity relationship studies of these compounds as NPC1L1 ligands.

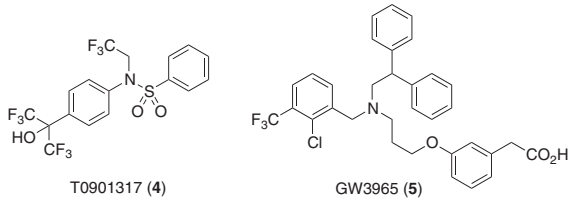
2. Results and discussion

2.1. Identification of phenanthridin-6-one derivatives that correct the cellular localization of mutant NPC1L1

Using pharmacological chaperone effect-based assay, we screened our LXR-related library, which includes well-known LXR agonists such as T0901317 (**4**) and GW3965 (**5**) (Fig. 2) and conformationally restricted T0901317 analogs with a phenanthridin-6-one scaffold.[24–27] We found that some 2-amide derivatives of phenanthridin-6-ones with no LXR activity could correct the localization of mutant NPC1L1. Other derivatives with alkyl, hydroxyl, carbonyl and other groups were ineffective (data not shown). As amide at the 2-position was necessary for the activity, we first performed structure–activity relationship studies focused on this position.

2.2. Structure–activity relationship for the 2-amide moiety of phenanthridin-6-one

Several 2-amide derivatives of phenanthridin-6-one were synthesized according to Scheme 1. Schotten–Baumann reaction between methyl 4-aminobenzoate (**63**) and 2-bromobenzoyl chloride gave the amide (**64**). *n*-Butylation on the amide nitrogen and subsequent intramolecular Heck reaction gave the phenanthridin-6-one (**65**). Hydrolysis of the 2-ester and condensation with various amines afforded the desired compounds.



Figue 2. Chemical structures of LXR agonists T0901317 and GW3965.

HEK293 cells stably expressing NPC1L1$^{L1072T/L1168I}$ were treated with test compounds and the % plasma membrane localization values at 30 μM and 10 μM were determined as previously reported.[16] As shown in Table 1, an alkyl chain on the nitrogen atom, either linear or cyclic, was required for the activity. Among amides with linear alkyl groups, the activity increased as the chain was elongated (**8**, **9**, **10**, **11**), which may indicate that hydrophobicity of this moiety is important for interaction with NPC1L1. This idea is consistent with the fact that compounds with free hydroxyl groups (**12**) and an ether moiety (**19**) were inactive. Nevertheless, amide NH proton did not diminish the activity (**7** vs **8**). Of the seven secondary amides, cyclopropyl amide (**15**) was the most potent. Isopropyl amide (**16**) and *tert*-butyl amide (**17**) were slightly less potent than the cyclopropyl derivative (**15**), and cyclopentyl amide (**13**), cyclohexyl amide (**14**) and benzyl amide (**20**) were almost inactive. This may indicate that the hydrophobic pocket cannot accommodate a group larger than a cyclopropyl moiety.

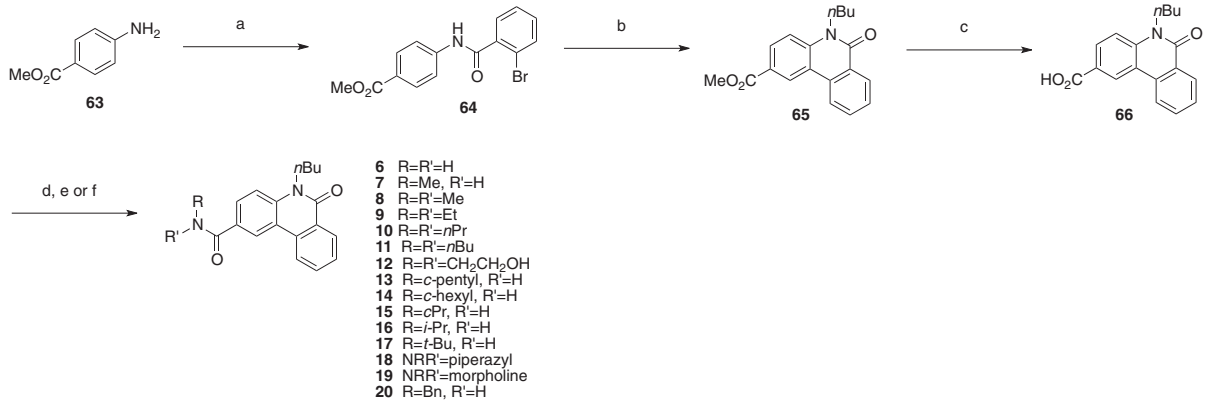
2.3. Structure–activity relationship for the 5-alkyl moiety of phenanthridin-6-one

We next investigated the effect of the 5-alkyl moiety of phenanthridin-6-one, after fixing the 2-substituent as diethylamide. The synthetic route to the 5-alkylated phenanthridin-6-ones is illustrated in Scheme 2. 4-Aminobenzoic acid (**67**) was converted to diethylamide and then condensed with 2-bromobenzoyl chloride. The amide nitrogen of **68** was protected with a *p*-methoxybenzyl (PMB) group, and the phenanthridinon-6-one scaffold was constructed by intramolecular Heck reaction. Then the PMB group of (**25**) was deprotected under acidic conditions, and various 5-alkylated phenanthridin-6-ones were obtained by means of alkylation reaction. The ester moieties of **70** and **71** were hydrolyzed to give **26** and **27**, and then condensation with dimethyamine afforded **28** and **29**, respectively.

As shown in Table 2, a sufficiently long alkyl chain at the 5-position is essential for activity (**21**, **22**, **23**, **9**). Considering that polar substituents (acids and amides) on the alkyl chain diminished the activity (**26**, **27**, **28**, **29**), it appears that the hydrophobicity of the alkyl group is important. The potency of the compound with a benzyl group (**24**), which is also hydrophobic, could not be determined precisely due to its low solubility. Since we considered that the poor solubility might be attributable to high planarity of the phenanthridin-6-one scaffold, we set out to evaluate less planar scaffolds.[28]

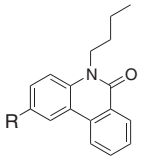
2.4. Structure development to obtain less planar scaffolds

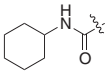
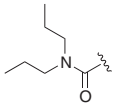
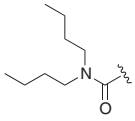
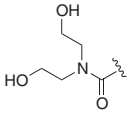
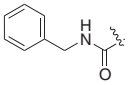
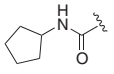
To design less planar scaffolds than phenanthridin-6-ones, we adopted three strategies: (1) replace the C-ring of phenanthridin-6-ones with saturated rings, (2) replace the pyridone moiety of phenanthridin-6-ones with a seven-membered oxazepinone ring



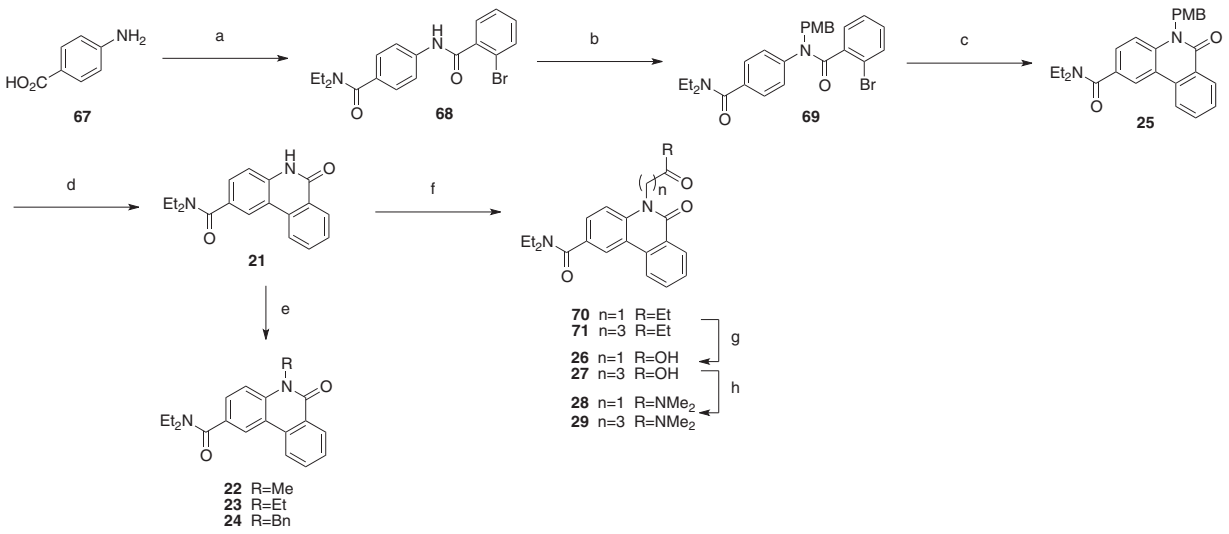
Scheme 1. Synthetic route to 2-amide derivatives of phenanthridin-6-one. Reagents and conditions: (a) 2-bromobenzoyl chloride, saturated aqueous $NaHCO_3$, CH_2Cl_2, rt; (b) NaH, *n*-butyl iodide, DMF, rt then $Pd(OAc)_2$, $PCy_3{\cdot}HBF_4$, Cs_2CO_3, DMA, 130 °C; (c) $LiOH{\cdot}H_2O$, THF, H_2O, rt; (d) $(COCl)_2$, DMF, CH_2Cl_2, RR′NH (for **6** 28% aqueous ammonia solution), Et_3N, rt; (e) $(COCl)_2$, DMF, CH_2Cl_2, diethanolamine, saturated aqueous $NaHCO_3$, rt; (f) isobutyl chloroformate, RR′NH (**9**, **19**) or 40% aqueous RR′NH solution (**7**, **8**), Et_3N, THF, rt.

Table 1
Pharmacological chaperone effect of 2-amide derivatives of phenanthridin-6-one



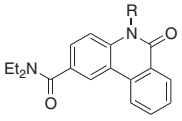
No.	R	% PM localization		No.	R	% PM localization	
		30 μM	10 μM			30 μM	10 μM
6		0	N.D.	**14**		11	3
7		24	1	**15**		55	14
8		4	N.D.	**16**		49	0
9		45	1	**17**		41*	11
10		50	14	**18**		47	0
11		Toxic	18	**19**		0	N.D.
12		0	N.D.	**20**		0	N.D.
13		0*	N.D.				

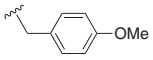
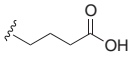
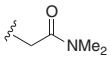
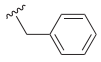
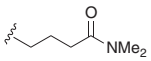
N.D.: not determined.
* Precipitation was observed.



Scheme 2. Synthetic route to 5-alkylated derivatives of phenanthridin-6-one. Reagents and conditions: (a) $SOCl_2$, DMF, CH_2Cl_2, rt then 2-bromobenzoyl chloride, saturated aqueous $NaHCO_3$, CH_2Cl_2 rt; (b) NaH, 4-methoxybenzyl chloride, DMF, rt; (c) $Pd(OAc)_2$, $PCy_3{\cdot}HBF_4$, Cs_2CO_3, DMA, 130 °C; (d) TFA (neat), reflux; (e) R-I (R = Me, Et) or R-Br (R = Bn), Cs_2CO_3, DMF, 90 °C; (f) $Br(CH_2)_nCO_2Et$, Cs_2CO_3, TBAI, DMF, 90 °C; (g) 10 M aqueous NaOH, MeOH, H_2O, rt; (h) isobutyl chloroformate, 40% aqueous dimethylamine solution, Et_3N, THF, CH_2Cl_2, rt.

Table 2
Pharmacological chaperone effect of 5-alkyl derivatives of phenanthridin-6-one



No.	R	% PM localization		No.	R	% PM localization	
		30 μM	10 μM			30 μM	10 μM
21		0	N.D.	**25**		18	0
22		0	N.D.	**26**		0*	N.D.
23		4	N.D.	**27**		0*	N.D.
9		45	1	**28**		0	N.D.
24		0*	N.D.	**29**		0	N.D.

N.D.: not determined.
* Precipitation was observed.

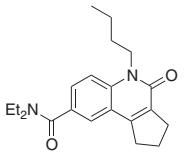
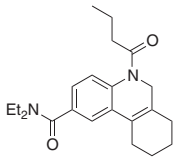
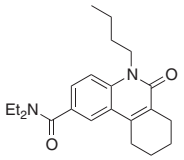
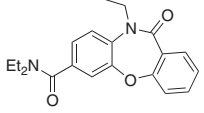
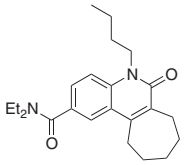
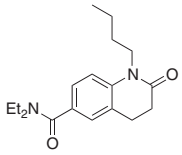
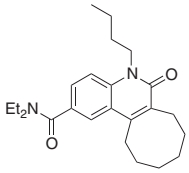
and (3) remove the C-ring of phenanthridin-6-ones. The designed compounds are shown in Table 3.

The synthetic route to the cycloalkaquinolinones (**30**, **31**, **32**, **33**) is illustrated in Scheme 3. 2-Bromocycloalkene-1-carboxylic acids (**74a**–**d**) to serve as C-ring units were synthesized from corresponding cycloalkanones according to the literature procedure.[29] Methyl 4-(butylamino)benzoate (**76**), which corresponds to the A-ring, was synthesized in two steps from methyl 4-aminobenzoate (**63**). **C**ondensation between methyl 4-(butylamino) benzoate (**76**) and 2-bromocycloalkene-1-carboxylic acids (**74a**–**d**), followed by intramolecular Heck cyclization afforded cycloalkaquinolinones (**78a**–**d**). Hydrolysis of the methyl esters under basic conditions and condensation with diethylamine gave the desired compounds.

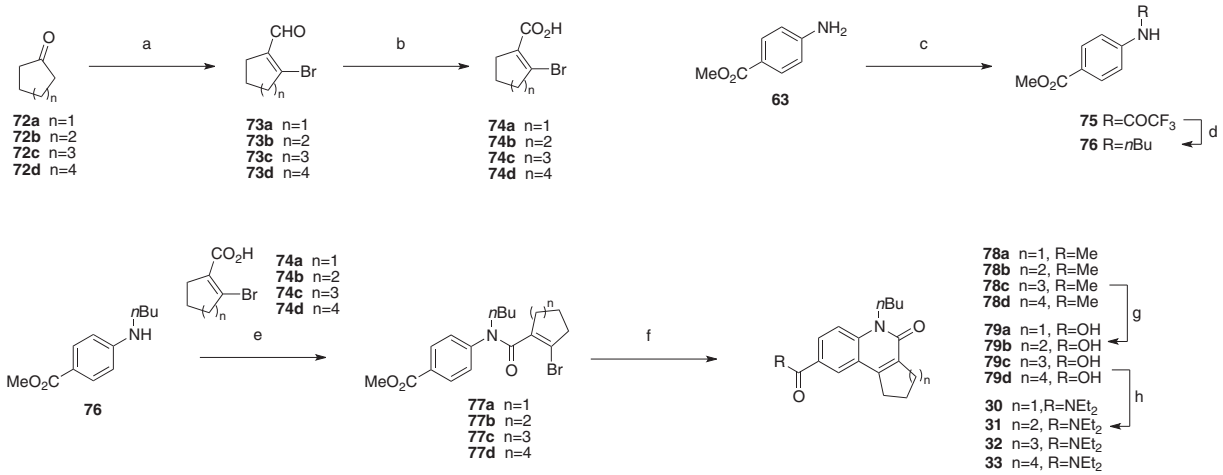
The synthetic route to the 5,6,7,8,9,10-hexahydrophenanthridine scaffold (**34**) is illustrated in Scheme 4. Methyl 4-butyrylamidobenzoate (**80**) was synthesized by Schotten–Baumann reaction between methyl 4-aminobenzoate (**63**) and butyryl chloride. (2-Bromocyclohex-1-en-1-yl)methanol (**81**) was obtained by Luche reduction of the aldehyde (**73b**). *O*-Mesylation of **81** and subsequent S_N2 reaction gave **82**. Intramolecular Heck reaction followed by hydrolysis of the ester and condensation with diethylamine afforded the desired compound.

The synthetic route to dibenzoxazepinone (**35**) is illustrated in Scheme 5. Schotten–Baumann reaction between methyl 4-amino-3-hydroxybenzoate and 2-fluorobenzoyl chloride and subsequent S_NAr reaction gave **86**. *N*-*n*-Butylation, hydrolysis of the ester, and condensation with diethylamine gave the desired compound.

Table 3
Pharmacological chaperone effect of compounds with various scaffolds

Compound		% PM localization		Compound		% PM localization	
		30 μM	10 μM			30 μM	10 μM
30		15	1	**34**		1	N.D.
31		42	2	**35**		3	N.D.
32		42	14	**36**		1	N.D.
33		44	5				

N.D.: not determined.



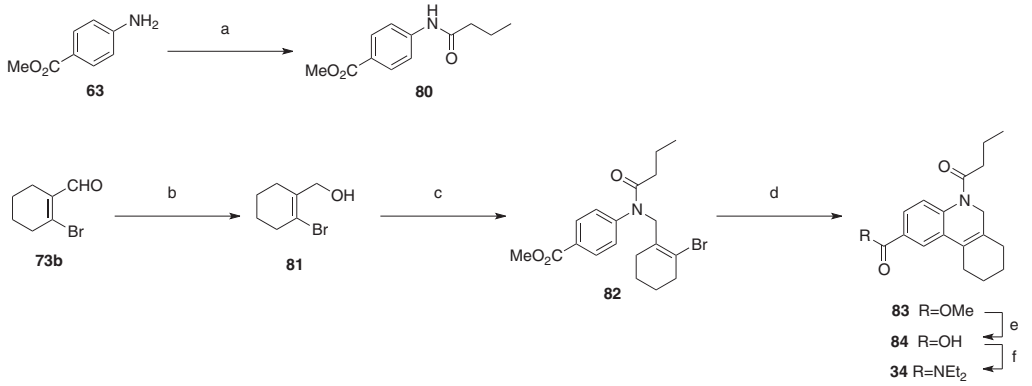
Scheme 3. Synthetic route to the cycloalkaquinolinones. Reagents and conditions: (a) DMF, PBr_3, $CHCl_3$, reflux or rt; (b) NaH_2PO_4, NaOClO, H_2O_2, CH_3CN, H_2O, rt; (c) $(CF_3CO)_2O$, Et_3N, CH_2Cl_2, rt; (d) *n*-butyl iodide, Cs_2CO_3, DMF, 90 °C then K_2CO_3, MeOH, 70 °C; (e) $(COCl)_2$, DMF, DMAP, CH_2Cl_2, 60 °C; (f) $Pd(OAc)_2$, $PCy_3{\cdot}HBF_4$, Cs_2CO_3, DMA, 130 °C; (g) NaOH, THF, MeOH, H_2O, rt; (i) $(COCl)_2$, DMF, Et_2NH, Et_3N, CH_2Cl_2, rt.

The synthetic route to 2-oxo-1,2,3,4-tetrahydroquinoline (**36**) is illustrated in Scheme 6. Bromination at the 6-position of 3,4-dihydro-2(1*H*)-quinolinone (**88**)[30] and subsequent coupling with phenyl formate[31] were conducted by employing reported reaction conditions. *N*-Alkylation, hydrolysis using hydrogen peroxide[32,33] and condensation gave the desired compound.

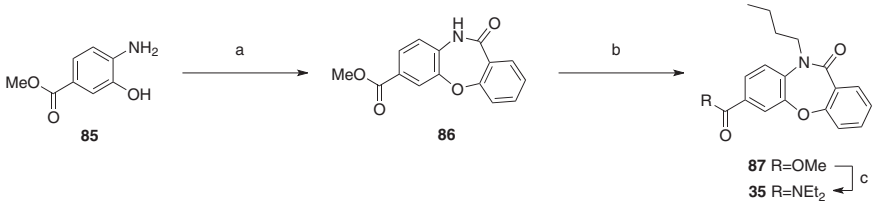
Although cycloalkaquinolinones corrected the localization of mutant NPC1L1, bicyclic compound (**36**) was inactive (Table 3). This may imply that a tricyclic scaffold is needed to serve as a steroid mimic for interaction with NPC1L1. However, tricyclic compounds **34** and **35** were almost inactive. One of the differences between cycloalkaquinolinones and the other tricyclic compounds is the planarity or aromaticity of the B-rings. Thus, the properties of the B-ring may be important for the activity. Among the cycloalkaquinolinones, cycloheptaquinolinone (**32**) was the most potent. Thus, the protein appears to contain a hydrophobic pocket large enough to interact with a cycloheptane ring.

2.5. Structure–activity relationship for the 2-amide moiety of cycloheptaquinolinone

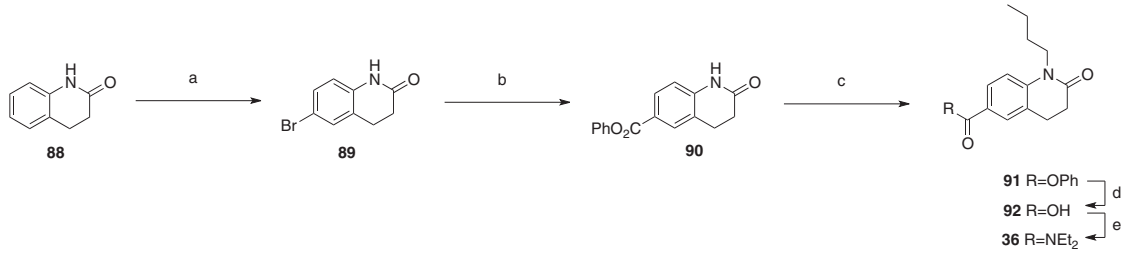
We next optimized the amide substituent at the 2-position of cycloheptaquinolinone. Various amides were synthesized from acid **79c** as illustrated in Scheme 7. Again, an alkyl group on amide



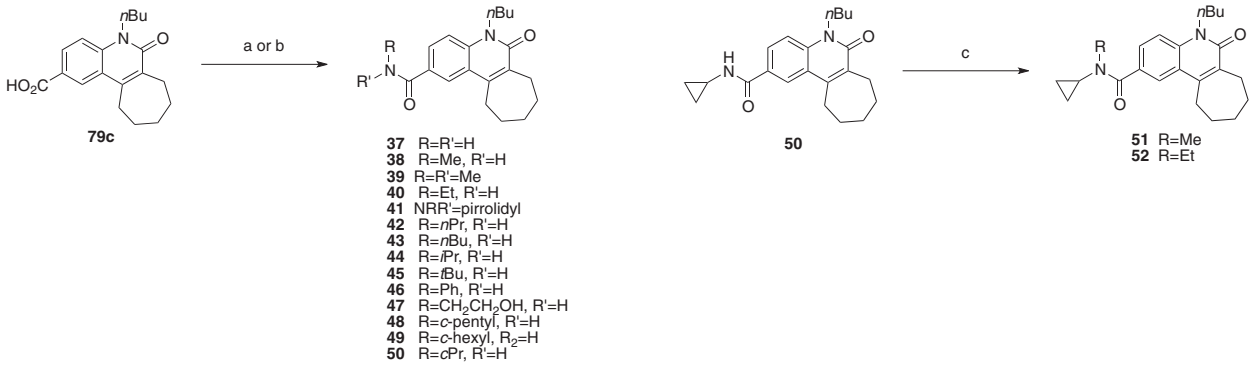
Scheme 4. Synthetic route to 5,6,7,8,9,10-hexahydrophenanthridine derivative. Reagents and conditions: (a) butyryl chloride, saturated aqueous $NaHCO_3$, CH_2Cl_2, rt; (b) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, THF, MeOH, rt; (c) methanesulfonyl chloride, Et_3N, CH_2Cl_2, 0 °C then NaH, **80**, TBAI, DMF, 90 °C; (d) $Pd(OAc)_2$, $PCy_3{\cdot}HBF_4$, Cs_2CO_3, DMA, 150 °C; (e) NaOH, THF, MeOH, H_2O, rt; (f) EDCI, DMAP, Et_2NH, CH_2Cl_2, rt.



Scheme 5. Synthetic route to the dibenzoxazepinone. Reagents and conditions: (a) 2-fluorobenzoyl chloride, saturated aqueous $NaHCO_3$, CH_2Cl_2, rt then K_2CO_3, DMF, 150 °C; (b) *n*-butyl iodide, Cs_2CO_3, DMF, 90 °C; (c) NaOH, MeOH, H_2O, 70 °C then EDCI, HOBt, Et_2NH, DMF, rt.



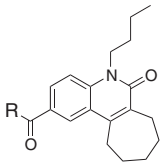
Scheme 6. Synthetic route to 2-oxo-1,2,3,4-tetrahydroquinoline derivative. Reagents and conditions: (a) NBS, DMF, 0 °C to rt; (b) phenyl formate, nBu_3N, $Pd(OAc)_2$, $P(tBu_3){\cdot}HBF_4$, NMP, 150 °C; (c) *n*-butyl iodide, Cs_2CO_3, DMF, rt; (d) NaOH, H_2O_2, 1,4-dioxane, H_2O, rt; (e) $(COCl)_2$, DMF, Et_2NH, Et_3N, CH_2Cl_2, rt.

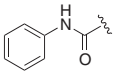
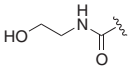
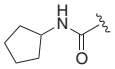
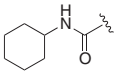
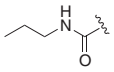
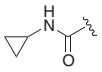
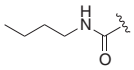
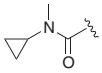
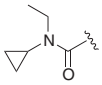


Scheme 7. Synthetic route to the amide derivatives of cycloheptaquinolinones. Reagents and conditions: (a) $(COCl)_2$, DMF, RR′NH, Et_3N, CH_2Cl_2, rt; (b) $(COCl)_2$, DMF, aqueous amine solution, CH_2Cl_2, rt; (c) NaH, R-I, DMF, rt.

nitrogen is required for activity (compare **37** with alkylated amides) and cyclopropyl amide (**50**) is relatively potent (Table 4). Cycloheptaquinolinones with isopropyl and *tert*-butyl groups (**44** and **45**, respectively) were less potent, even though phenanthridin-6-ones with these alkyl groups are quite potent. This may be attributable to the difference in the size of the C rings between the phenanthridin-6-ones and the cycloheptaquinolinones. As the C ring of the cycloheptaquinolinones is larger,

Table 4
Pharmacological chaperone effect of amide derivatives of cycloheptaquinolinone



No.	R	% PM localization		No.	R	% PM localization	
		30 μM	10 μM			30 μM	10 μM
37		0	N.D.	**44**		25	0
38		23	0	**45**		1	N.D.
39		2	N.D.	**46**		0	N.D.
40		28	0	**47**		0	N.D.
32		42	14	**48**		16	6
41		33	1	**49**		5	2
42		36	0	**50**		49	3
43		18	0	**51**		21	1
				52		45	8

N.D.: not determined.

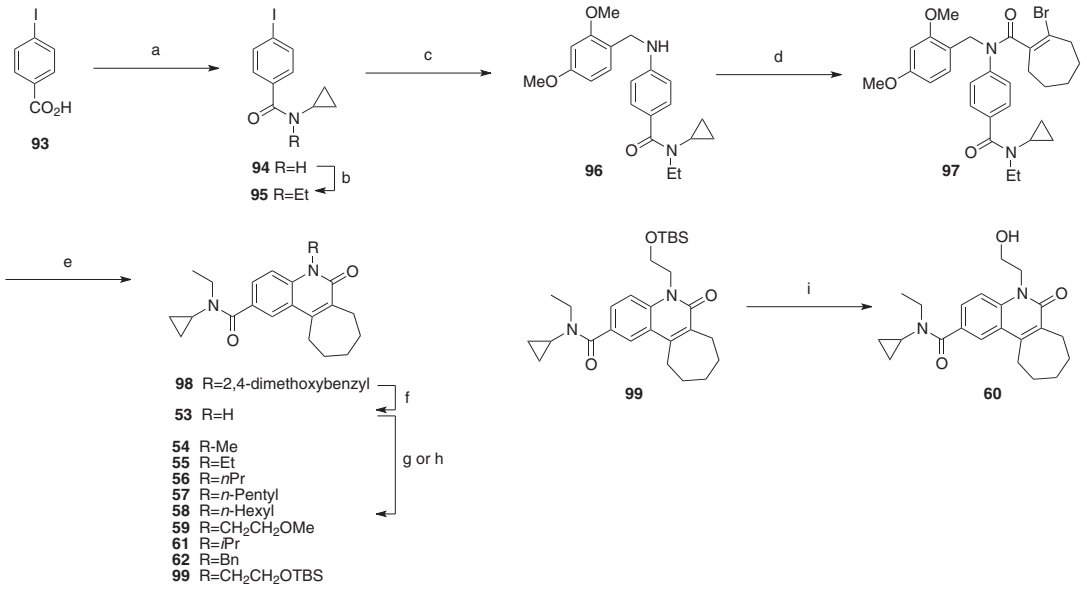
the position of the scaffold might be shifted slightly so that the amide group interacts less effectively with the binding pocket. Longer or more bulky substituents (**43**, **46**, **48** and **49**) and a hydrophilic group (**47**) diminished the activity. Amide NH proton did not diminish the activity, as was the case in the phenanthridin-6-ones. A methyl group diminished the activity (**38** vs **39** and **50** vs **51**), but an ethyl group did not (**40** vs **32** and **50** vs **52**). From these results it can be assumed that the pocket can accommodate both hydrogen bond-mediated interaction with NH proton and hydrophobic interaction with an ethyl group. The lower potency of **39** and **51** might be due to the absence of these two interactions.

2.6. Structure–activity relationship for the 5-alkyl moiety of cycloheptaquinolinone

Finally, we investigated the effect of 5-alkyl groups of cycloheptaquinolinones, with the 2-substituent fixed as cyclopropylethylamide. The synthetic route to the 5-alkylated derivatives is illustrated in Scheme 8. 4-Iodobenzoic acid (**93**) was condensed with cyclopropylamine and then alkylated with ethyl iodide to afford **95**. Then copper-catalyzed coupling of **95** and 2,4-dimethoxybenzylamine was performed according to the literature procedure.[34] The amine (**96**) was condensed with **74c**, and the resultant amide (**97**) was cyclized by intramolecular Heck reaction to afford **98** with a cycloalkaquinolinone scaffold. The 2,4-dimethoxybenzyl group of **98** was deprotected under acidic conditions to give **53**, and **53** was alkylated with various alkyl halides. The compound with a free hydroxyl group (**60**) was obtained by deprotecting the TBS group of **99** with TBAF.

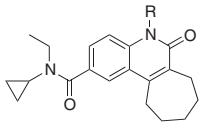
In the case of cycloheptaquinolinones, no precipitation was observed under our assay conditions, indicating improved solubility of these compounds compared to the phenanthridin-6-ones (Table 5). The effects of the 5-alkyl group were nearly the same as in phenanthridin-6-ones (Table 2). An alkyl chain at the 5-position was necessary for the activity and the optimum length was *n*-butyl; shorter or longer derivatives showed diminished activity (**53**–**56**, **52**, **57**). As the compounds with *n*-hexyl (**58**) and isopropyl (**61**) groups were cytotoxic, we could not evaluate their activity. In contrast to the *N*-benzyl derivative of phenanthridin-6-one (**24**), the *N*-benzyl counterpart of cycloheptaquinolinone (**62**) was sufficiently soluble to evaluate, but was only weakly active. Hydrophilic hydroxyl and ether groups (**59**, **60**) diminished the activity, as in the case of phenanthridin-6-ones.

So far, we could obtain potent non-steroidal NPC1L1 ligand **52** via structure–activity relationship study, starting from a hit compound in our library of LXR ligands, which mainly contains ring-fused derivatives of a LXR agonist T0901317. To examine selectivity of the ring-fused quinolinone **52** over LXR, we tested whether the ring-fused quinolinone **52** activate LXR by using reporter gene assay.[27] While T0901317 activate a LXR even at as low as 100 nM,



Scheme 8. Synthetic route to 5-alkyl derivatives of cycloheptaquinolinones. Reagents and conditions: (a) $(COCl)_2$, DMF, cyclopropylamine, CH_2Cl_2, rt; (b) NaH, ethyl iodide, DMF, 90 °C; (c) 2,4-dimethoxybenzylamine, CuI, K_3PO_4, ethylene glycol, *n*BuOH, 100 °C; (d) **74c**, $(COCl)_2$, DMAP, DMF, CH_2Cl_2, 50 °C; (e) $Pd(OAc)_2$, $PCy_3{\cdot}HBF_4$, Cs_2CO_3, DMA, 130 °C; (f) TFA (neat), 80 °C; (g) R-I, Cs_2CO_3, DMF, 90 °C; (h) R-Br, TBAI, Cs_2CO_3, DMF, 90 °C; (i) TBAF, THF, 50 °C.

Table 5
Pharmacological chaperone effect of 5-alkylated derivatives of cycloheptaquinolinone



No.	R	% PM localization		No.	R	% PM localization	
		30 μM	10 μM			30 μM	10 μM
53	—H	0	N.D.	**57**		35	3
54	—	0	N.D.	**58**		Toxic	1
55		7	N.D.	**59**	OMe	0	N.D.
56		39	0	**60**	OH	0	N.D.
52		45	8	**61**		Toxic	0
				62		14	0

N.D.: not determined.

the ring-fused quinolinone **52** was totally inactive at 30 μM (data not shown). Thus, the NPC1L1 ligand **52** was found to be selective over LXR by at least two orders of magnitude.

It has been reported that chemical perturbation of cellular folding machineries can also correct mislocalization of folding-defective proteins, and small molecules with such activity are called proteostasis regulators.[35–37] In order to exclude the possibility that the ring-fused quinolinone derivatives act as proteostasis regulators, we examined their effect on folding-defective $NPC1^{I1061T}$ mutant,[38] a close homologue of NPC1L1. While **mo56AZK**, a sterol-derived pharmacological chaperone for NPC1,[23] corrected the localization of $NPC1^{I1061T}$, the ring-fused quinolinone **52**, one of the most potent compounds towards $NPC1L1^{L1072T/L1168I}$ mutant, had no effect on $NPC1^{I1061T}$ (Fig. 3a). This specificity supports the idea that the ring-fused quinolinones indeed act as pharmacological chaperones and not as proteostasis regulators.

2.7. Cycloheptaquinolinone derivatives act independently of the N-terminal sterol-binding site

We previously proposed the existence of a non-NTD sterol-binding site on NPC1L1, and suggested that our steroidal NPC1L1 ligands were bound at this second sterol-binding site.[16] Accordingly, we tested whether or not the ligand-mediated rescue of mutant NPC1L1 by our newly discovered non-steroidal ligands requires the NTD. As shown in Figure 3b, cycloheptaquinolinone compound (**52**) corrected the localization defect of NTD-deleted $NPC1L1^{L1072T/L1168I}$ (ΔNTD-$NPC1L1^{L1072T/L1168I}$). Further, cycloheptaquinolinone

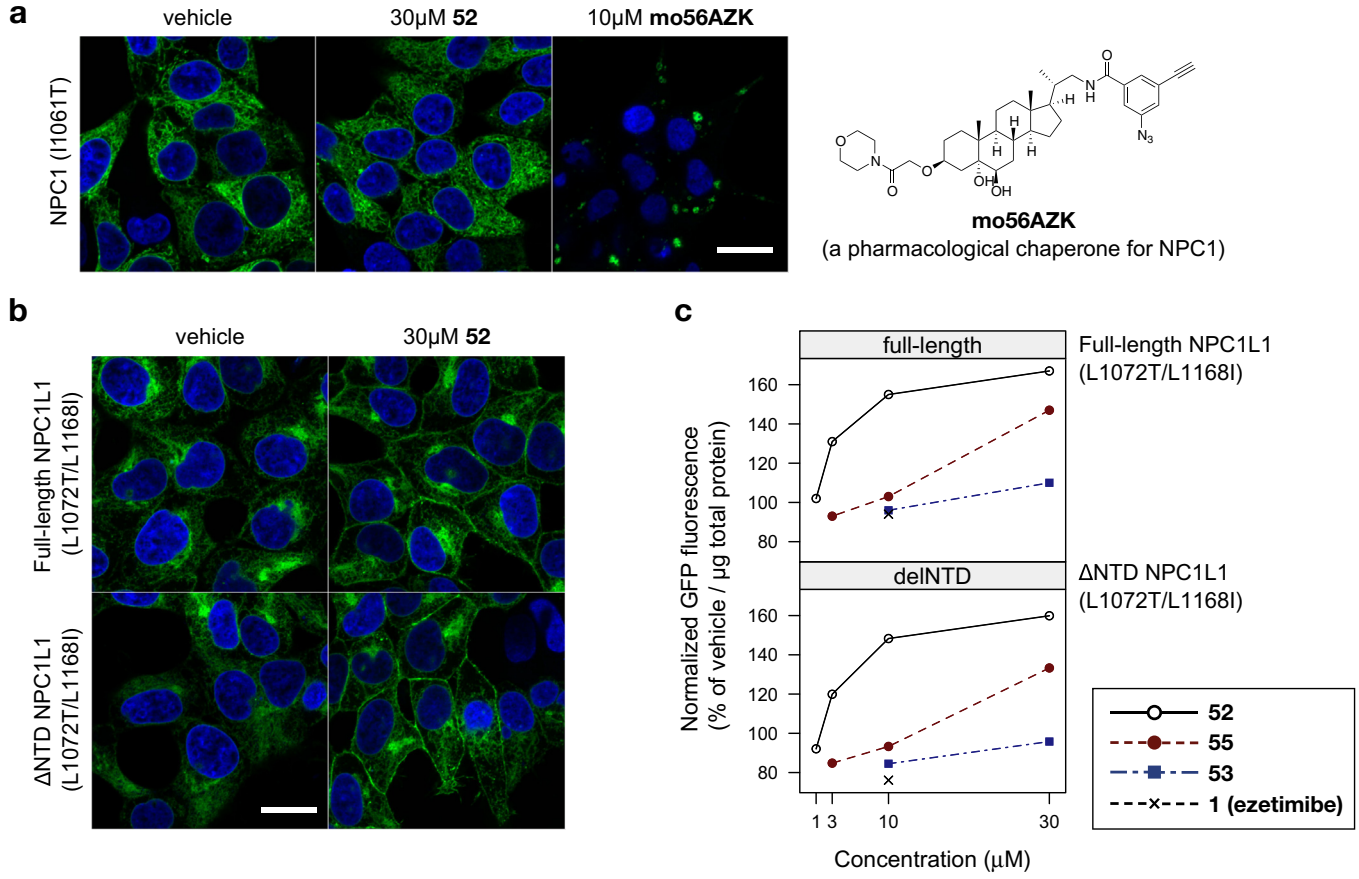


Figure 3. Characterization of cycloheptaquinolinones as pharmacological chaperones, dispensability of NTD for their activity, and selectivity for NPC1L1$^{L1072T/L1168I}$ over another folding-defective protein, NPC1^{I1061T} mutant. (a) HEK293 cells stably expressing folding-defective NPC1^{I1061T}-tGFP were treated as indicated for 20 h, and the localization of the NPC1 proteins was examined. The compound mo56AZK is a pharmacological chaperone for NPC1 proteins. (b) The N-terminal domain is dispensable for the pharmacological chaperone effect of the cycloheptaquinolinones. HEK293 cells stably expressing full-length NPC1L1$^{L1072T/L1168I}$-EGFP or ΔNTD-NPC1L1$^{L1072T/L1168I}$-EGFP were treated as indicated for 20 h and the localization of NPC1L1 was examined. Green, NPC1L1-GFPs. Blue, Hoechst-33342. Scale bar, 20 μm. (c) Ligand-mediated stabilization of NPC1L1 mutant proteins is independent of the presence of NTD. Upper, dose-dependent up-regulation of full-length NPC1L1 mutant. Lower, up-regulation of ΔNTD-NPC1L1 mutant. The steady-state expression levels of full-length or NTD-deleted NPC1L1$^{L1072T/L1168I}$-GFP were quantified by measuring GFP fluorescence in the lysate of cells treated with or without the indicated compounds. The GFP fluorescence was normalized with respect to total protein concentration determined by bicinchonic acid assay, and is presented as% of that of vehicle-treated cells.

derivatives stabilized both full-length and NTD-deleted NPC1L1$^{L1072T/L1168I}$ mutant proteins, and increased steady-state levels of the proteins in a similar manner to that observed with steroidal ligands[16,39] (Fig. 3c). Moreover, the order of the potency among the representative derivatives (**52** > **55** > **53** and ezetimibe, which had no effect) was also conserved between full-length and NTD-deleted NPC1L1 mutant proteins. These results strongly suggest that our non-steroidal ligands act independently of the NTD.

3. Conclusion

In the present work, we used our previously developed pharmacological chaperone effect screening assay to identify novel non-steroidal ligands targeting the non-NTD sterol-binding site of NPC1L1. Although the identified non-steroidal compounds, even after structure development based on structure–activity relationship studies, were not as potent as our steroidal ligands, our results confirm the effectiveness of the pharmacological chaperone-based assay as a screening tool. Screening of larger libraries may yield more potent compounds that would serve as better starting points for optimization. We are planning to examine the inhibitory activity of the compounds identified here on NPC1L1-mediated cholesterol absorption.

4. Experimental

4.1. Biology

4.1.1. General

Cell culture, NPC1L1$^{L1072T/L1168I}$ localization assay and quantification of GFP fluorescence in lysates were performed according to our previous report.[16]

4.1.2. Localization of NPC1L1-EGFP mutants and NPC1-tGFP in stably transfected cells[16,23]

HEK293 cells stably expressing NPC1L1 or NPC1 constructs were grown in EzView 96-well glass-bottomed plates coated with poly-D-lysine (20 μg/mL in PBS). After incubation for 24 h, cells were treated with test compounds (solutions contained 0.1% final concentration of DMSO) and further incubated for the indicated times. Cells were fixed with 3.7% formaldehyde-PBS containing Hoechst 33342 (1 μg/mL), and images were obtained on a Zeiss LSM710 (63× oil-immersion objective lens with NA 1.40). Image processing (noise reduction with median filter, contrast enhancement, and merging channels) was performed using ImageJ software with the Bio-Formats plugin.

4.2. Chemistry

4.2.1. General

Proton and carbon nuclear magnetic resonance spectra (^{1}H and ^{13}C NMR) were recorded on a JEOL JMM-ECA 500 (500 MHz) spectrometer in the indicated solvent. '$CD_3OD/CDCl_3$' indicates that 10% $CDCl_3$ in CD_3OD. '$CDCl_3/CD_3OD$' indicates that 10% CD_3OD in $CDCl_3$. Chemical shifts (δ) are reported in parts per million relative to the internal standard tetramethylsilane. Fast atom bombardment (FAB) mass spectra were recorded on a JEOL JMA-HX110 mass spectrometer. Reagents were purchased from Aldrich, Tokyo Kasei Kogyo, Wako Pure Chemical Industry, and Kanto Kagaku and used without purification. Open and flash column chromatographies were performed using silica gel 60 (particle size 0.060–0.210 mm) supplied by Kanto Kagaku.

4.2.2. Synthesis of 2-amide derivatives of phenanthridin-6-ones

4.2.2.1. Methyl 4-[(2-bromobenzoyl) butylamino] benzoate (64). To a vigorously stirred mixture of methyl 4-aminobenzoate (1581 mg, 10.46 mmol) in CH_2Cl_2 (50 mL) and saturated aqueous $NaHCO_3$ (50 mL) at 0 °C was added 2-bromobenzoyl chloride (1800 μL, 13.78 mmol). Stirring was continued for 9 h at ambient temperature. The biphasic mixture was separated and the organic phase was washed with saturated aqueous $NaHCO_3$, saturated aqueous NH_4Cl and brine, then dried over Na_2SO_4 and concentrated. The residue was recrystallized from CH_2Cl_2/*n*-hexane to afford the title compound (3060 mg, 9.157 mmol, 88% yield) as colorless needles. ^{1}H NMR ($CDCl_3$) δ: 8.05 (2H, d, J = 8.6 Hz), 7.93 (1H, br s), 7.73 (2H, d, J = 8.6 Hz), 7.66–7.64 (2H, m), 7.42 (1H, ddd, J = 6.9, 6.9, 1.2 Hz), 7.34 (1H, ddd, J = 8.0, 8.0, 1.7 Hz), 3.91 (3H, s). ^{13}C NMR ($CDCl_3$) δ: 166.52, 165.58, 141.60, 137.28, 133.64, 132.01, 130.93 (2C), 129.93, 127.86, 126.18, 119.19, 119.11 (2C), 52.11. FAB-MS *m*/*z*: 336, 334 (MH^+).

4.2.2.2. Methyl 5,6-dihydro-5-*n*-butyl-6-oxo-phenanthridine-2-carboxylate (65). To a solution of **64** (1026 mg, 3.072 mmol) in DMF (6 mL) was added NaH (210.1 mg, 5.253 mmol, ca. 60%) at 0 °C. The mixture was stirred for 1 h at ambient temperature, then 1-iodobutane (750 μL, 6.60 mmol) was added and stirring was continued at ambient temperature overnight. Water was added and the whole was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated. The resultant oil was subjected to the next reaction without further purification. A de-aerated mixture of the oil, $Pd(OAc)_2$ (81.8 mg, 0.364 mmol), $PCy_3{\cdot}HBF_4$ (143.6 mg, 0.3718 mmol) and Cs_2CO_3 (821.6 mg, 2.523 mmol) in DMA (10 mL) was stirred at 130 °C for 4 h, then cooled to ambient temperature and filtered through a Celite pad. The pad was washed with ethyl acetate. The filtrate and washing were combined, washed with water and brine, dried over Na_2SO_4 and concentrated. Open column chromatography (*n*-hexane/ethyl acetate = 8/1 to 4/1) gave the title compound (639.1 mg, 2.066 mmol, 67% yield for 2 steps) as a colorless solid. ^{1}H NMR ($CDCl_3$) δ: 8.97 (1H, d, J = 2.3 Hz), 8.53 (1H, dd, J = 8.1, 1.2 Hz), 8.35 (1H, d, J = 8.0 Hz), 8.16 (1H, dd, J = 9.2, 2.3 Hz), 7.79 (1H, ddd, J = 6.9, 6.9, 1.1 Hz), 7.62 (1H, ddd, J = 8.1, 8.1, 1.2 Hz), 7.42 (1H, d, J = 9.2 Hz), 4.39 (2H, t, J = 8.0 Hz), 3.99 (3H, s), 1.81–1.75 (2H, m), 1.57–1.49 (2H, m), 1.02 (3H, t, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 166.55, 161.44, 140.40, 133.10, 132.75, 130.33, 128.86, 128.49, 125.53, 125.49, 123.79, 121.85, 119.19, 114.99, 52.28, 42.84, 29.48, 20.33, 13.87. FAB-MS *m*/*z*: 310 (MH^+).

4.2.2.3. 5,6-Dihydro-5-*n*-butyl-6-oxo-phenanthridine-2-carboxylic acid (66). A solution of **65** (616.3 mg, 1.992 mmol) and $LiOH{\cdot}H_2O$ (278.4 mg, 6.635 mmol) in THF (12 mL) and water (8 mL) was stirred at ambient temperature for 4 h, then adjusted to pH 2 with 2 N aqueous HCl and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated to afford the title compound (609.3 mg, 2.063 mmol, quant.) as a colorless solid. ^{1}H NMR (DMSO-d_6) δ: 8.91 (1H, d, J = 2.3 Hz), 8.50 (1H, d, J = 8.6 Hz), 8.34 (1H, dd, J = 8.0, 1.7 Hz), 8.10 (1H, dd, J = 9.2, 2.3 Hz), 7.86 (1H, ddd, J = 8.0, 8.0, 1.2 Hz), 7.68–7.65 (2H, m), 4.33 (2H, t, J = 7.5 Hz), 1.65–1.62 (2H, m), 1.43–1.39 (2H, m), 0.93 (3H, t, J = 7.5 Hz). ^{13}C NMR (DMSO-d_6) δ: 166.85, 160.30, 139.75, 133.19, 132.61, 130.52, 128.67, 128.09, 124.99, 124.75, 124.53, 122.39, 118.25, 115.81, 41.96, 29.11, 19.64, 13.75. FAB-MS *m*/*z*: 296 (MH^+).

4.2.2.3.1. General procedure for the synthesis of 2-amide derivatives of phenanthridin-6-one (A). To a solution of **66** (40 mg, 0.15 mmol) and DMF (100 μL) in CH_2Cl_2 (1 mL) was added oxalyl chloride (30 μL, 0.35 mmol) at 0 °C. The mixture was stirred at this temperature for 10 min, then triethylamine (100 μL, 0.721 mmol) and amine (100 μL) were added at 0 °C. Stirring was continued at ambient temperature for 20 min, and then the mixture was diluted with ethyl acetate. The organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated. The product was purified as indicated below.

4.2.2.3.2. General procedure for the synthesis of 2-amide derivatives of phenanthridin-6-one (B). A solution of **66** (54 mg, 0.18 mmol) and Et_3N (65 μL, 0.50 mmol) in THF (6 mL) was treated with isobutyl chloroformate (35 μL, 0.27 mmol) at 0 °C, and stirred at the same temperature for 10 min. To the resulting mixture was added a suitable amine or 40% aqueous amine solution (100 μL) in one portion. The reaction mixture was stirred for 3 h at ambient temperature, then partitioned between water and AcOEt. The organic phase was washed with water and brine, dried, and concentrated. The product was purified as indicated below.

*4.2.2.3.3. 5-Butyl-6-oxo-5,6-dihydrophenanthridine-2-carboxamide (**6**).* This compound was prepared according to the general procedure A on 0.9 mmol scale. Column chromatography (CH_2Cl_2/MeOH = 20/1) gave the title compound (186 mg, 0.632 mmol, 72%) as a colorless solid. ^{1}H NMR ($CDCl_3$) δ 8.86 (d, 1H, J = 1.8 Hz), 8.56 (dd, 1H, J = 8.5, 1.5 Hz), 8.39 (d, 1H, J = 7.9 Hz), 7.91 (dd, 1H, J = 8.5, 1.8 Hz), 7.81 (ddd, 1H, J = 7.9, 6.4, 1.5 Hz), 7.64 (td, 1H, J = 7.9, 1.5 Hz), 7.45 (d, 1H, J = 8.5 Hz), 4.42 (t, 2H, J = 7.6 Hz), 1.83–1.76 (m, 2H), 1.56–1.51 (m, 2H), 1.03 (t, 3H, J = 7.3 Hz). MS (FAB, $[M+H]^+$) *m*/*z* 295. Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.22; H, 6.31; N, 9.52.

*4.2.2.3.4. N-Methyl-5,6-dihydro-5-n-butyl-6-oxo-phenanthridine-2-carboxamide (**7**).* This compound was prepared according to the general procedure B. Flash column chromatography (*n*-hexane/AcOEt/CH_2Cl_2 = 1/1/1 to 0/1/1) afforded the title compound (39.7 mg, 0.129 mmol, 70%) as colorless needles (recrystallized from CH_2Cl_2/*n*-hexane, mp 196.2–198.3 °C). ^{1}H NMR (CD_3OD) δ: 8.91 (1H, d, J = 1.7 Hz), 8.52 (1H, d, J = 8.0 Hz), 8.43 (1H, dd, J = 8.0, 1.7 Hz), 8.05 (1H, dd, J = 8.6, 2.3 Hz), 7.87 (1H, ddd J = 8.6, 8.6, 1.2 Hz), 7.66 (1H, ddd, J = 8.0, 8.0, 1.2 Hz), 7.64 (1H, d J = 9.2 Hz), 4.43 (2H, t, J = 7.5 Hz), 2.99 (3H, s), 1.81–1.73 (2H, m), 1.56–1.47 (2H, m), 1.02 (3H, t, J = 7.5 Hz). ^{13}C NMR (CD_3OD) δ: 169.64, 163.10, 140.19, 134.84, 134.32, 129.68, 129.65, 129.61, 129.44, 126.38, 124.05, 123.34, 120.53, 116.87, 43.78, 30.72, 27.02, 21.18, 14.19. FAB-MS *m*/*z*: 309 (MH^+). Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 74.22; H, 6.67; N, 8.98.

*4.2.2.3.5. N,N′-Dimethyl-5,6-dihydro-5-n-butyl-6-oxo-phenanthridine-2-carboxamide (**8**).* This compound was prepared according to the general procedure B. Flash column chromatography (*n*-hexane/AcOEt/CH_2Cl_2 = 1:1:1 to 0:1:1) afforded the title compound (22.3 mg, 0.0692 mmol, 44%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 8.55 (1H, dd, J = 8.0, 1.0 Hz), 8.41 (1H, d, J = 2.0 Hz), 8.27 (1H, d, J = 8.0 Hz), 7.76 (1H, td, J = 8.0, 1.0 Hz), 7.62–7.59 (2H, m), 7.41 (1H, d, J = 8.5 Hz), 4.40 (2H, t, J = 8.0 Hz), 3.13 (6H, s), 1.82–1.76

(2H, m), 1.55–1.50 (2H, m), 1.02 (3H, t, J = 7.5 Hz). ^{13}C NMR (CD_3OD) δ: 173.07, 163.02, 138.96, 134.65, 134.31, 131.58, 129.71, 129.69, 129.42, 126.41, 124.11, 123.39, 120.67, 116.87, 43.73, 40.27, 35.90, 30.72, 21.19, 14.20. FAB-MS m/z: 323 (MH^+). HRMS (FAB, $[M+H]^+$) calcd for $C_{20}H_{23}N_2O_2$ 323.1760, found 323.1739.

*4.2.2.3.6. N,N′-Diethyl-5,6-dihydro-5-n-butyl-6-oxo-phenanthridine-2-carboxamide (**9**).* This compound was prepared according to the general procedure B. Flash column chromatography (*n*-hexane/AcOEt/CH_2Cl_2 = 1:1:1) afforded the title compound (13.3 mg, 0.038 mmol, 24%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 8.55 (1H, dd, J = 8.0, 1.0 Hz), 8.34 (1H, d, J = 2.0 Hz), 8.26 (1H, d, J = 8.0 Hz), 7.77 (1H, td, J = 7.0, 1.0 Hz), 7.61 (1H, t, J = 7.5 Hz), 7.56 (1H, dd, J = 8.5, 1.5 Hz), 7.41 (1H, d, J = 9.0 Hz), 4.40 (2H, t, J = 7.5 Hz), 3.60–3.35 (4H, br m), 1.82–1.75 (2H, m), 1.56–1.48 (2H, m), 1.31–1.20 (6H, br m), 1.02 (3H, t, J = 7.5 Hz). ^{13}C NMR (CD_3OD/$CDCl_3$) δ: 172.83, 162.93, 138.68, 134.54, 134.24, 132.33, 129.67, 129.41, 128.85, 126.38, 123.28, 123.16, 120.74, 116.92, 45.14, 43.73, 41.08, 30.68, 21.17, 14.52, 14.21, 13.12. HRMS (FAB, $[M+H]^+$) calcd for $C_{22}H_{27}N_2O_2$ 351.2073, found 351.2073.

*4.2.2.3.7. N,N′-(Di-n-propyl)-5,6-dihydro-5-n-butyl-6-oxo-phenanthridine-2-carboxamide (**10**).* This compound was prepared according to the general procedure A. Open column chromatography (*n*-hexane/ethyl acetate = 2/1) gave the title compound (45.0 mg, 0.119 mmol, 83% yield) as colorless cubes (recrystallized from CH_2Cl_2/*n*-hexane, mp 80.1–80.7 °C). ^{1}H NMR ($CDCl_3$) δ: 8.56 (1H, dd, J = 8.0, 1.1 Hz), 8.32 (1H, d, J = 1.7 Hz), 8.26 (1H, d, J = 8.0 Hz), 7.77 (1H, ddd, J = 7.7, 7.7, 1.8 Hz), 7.61 (1H, dd, J = 7.0 Hz), 7.56 (1H, dd, J = 8.6, 1.8 Hz), 7.42 (1H, d, J = 8.6 Hz), 4.40 (2H, t, J = 8.0 Hz), 3.51 (2H, br s), 3.28 (2H, br s), 1.83–1.76 (2H, m), 1.75 (2H, br s), 1.62 (2H, br s), 1.57–1.49 (2H, m), 1.02 (3H, t, J = 7.5 Hz), 1.02 (3H, br s), 0.79 (3H, br s). ^{13}C NMR ($CDCl_3$) δ: 171.10, 161.28, 137.62, 133.12, 132.59, 131.11, 128.90, 128.35, 127.80, 125.68, 122.28, 121.65, 119.37, 114.99, 50.97, 46.62, 42.67, 29.49, 22.08, 20.80, 20.34, 13.89, 11.52, 11.18. FAB-MS m/z: 379 (MH^+). HRMS (FAB, $[M+H]^+$) calcd for $C_{24}H_{31}N_2O_2$ 379.2386, found 379.2426.

*4.2.2.3.8. N,N′-(Di-n-butyl)-5,6-dihydro-5-n-butyl-6-oxo-phenanthridine-2-carboxamide (**11**).* This compound was prepared according to the general procedure A. Open column chromatography (*n*-hexane/ethyl acetate = 3/1) gave the title compound (54.3 mg, 0.134 mmol, 95% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 8.55 (1H, dd, J = 8.0, 1.7 Hz), 8.33 (1H, d, J = 2.3 Hz), 8.26 (1H, d, J = 8.1 Hz), 7.77 (1H, ddd, J = 7.5, 7.5, 1.8 Hz), 7.61 (1H, ddd, J = 7.5, 7.5, 1.2 Hz), 7.56 (1H, dd, J = 8.6, 1.8 Hz), 7.42 (1H, d, J = 8.6 Hz), 4.41 (2H, t, J = 8.1 Hz), 3.55 (2H, br s), 3.30 (2H, br s), 1.82–1.76 (2H, m), 1.70 (2H, br s), 1.57 (2H, br s), 1.57–1.49 (2H, m), 1.45 (2H, br s), 1.18 (2H, br s), 1.02 (3H, t, J = 7.5 Hz), 1.02 (3H, br s), 0.81 (3H, br s). ^{13}C NMR ($CDCl_3$) δ: 170.96, 161.29, 137.63, 133.12, 132.58, 131.09, 128.90, 128.35, 127.83, 125.69, 122.29, 121.65, 119.33, 114.98, 49.09, 44.84, 42.67, 31.02, 29.70, 29.49, 20.34, 20.17, 19.85, 13.90, 13.82, 13.75. FAB-MS m/z: 407 (MH^+). HRMS (FAB, $[M+H]^+$) calcd for $C_{26}H_{35}N_2O_2$ 407.2699, found 407.2701.

*4.2.2.3.9. N-c-Pentyl-5,6-dihydro-5-n-butyl-6-oxo-phenanthridine-2-carboxamide (**13**).* This compound was prepared according to the general procedure A. Open column chromatography (*n*-hexane/ethyl acetate = 2/1) gave the title compound (35.7 mg, 0.0985 mmol, 70% yield) as a colorless powder (recrystallized from CH_2Cl_2/*n*-hexane, mp 179.8–180.8 °C). ^{1}H NMR ($CDCl_3$) δ: 8.65 (1H, d, J = 1.7 Hz), 8.45 (1H, d, J = 8.0 Hz), 8.21 (1H, d, J = 8.1 Hz), 7.82 (1H, dd, J = 9.2, 2.3 Hz), 7.67 (1H, ddd, J = 6.9, 6.9, 1.1 Hz), 7.54 (1H, dd, J = 8.0, 8.0 Hz), 7.27 (1H, d, J = 8.6 Hz), 6.66 (1H, d, J = 7.5 Hz), 4.51–4.42 (1H, m), 4.28 (2H, t, J = 7.5 Hz), 2.18–2.11 (2H, m), 1.84–1.73 (2H, m), 1.73–1.66 (4H, m), 1.66–1.57 (2H, m), 1.52–1.42 (2H, m), 0.98 (3H, t, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 166.65, 161.29, 138.88, 133.02, 132.54, 128.72, 128.70, 128.33, 127.58, 125.40, 122.95, 121.78, 119.13, 114.80, 51.92, 42.65, 33.21 (2C), 29.44, 23.91 (2C), 20.28, 13.85. FAB-MS m/z: 363 (MH^+). Anal. Calcd for $C_{23}H_{26}N_2O_2$: C, 76.21; H, 7.23; N, 7.73. Found: C, 76.19; H, 7.27; N, 7.70.

*4.2.2.3.10. N-c-Hexyl-5,6-dihydro-5-n-butyl-6-oxo-phenanthridine-2-carboxamide (**14**).* This compound was prepared according to the general procedure A. Open column chromatography (*n*-hexane/ethyl acetate = 12/5 to 2/1) gave the title compound (39.3 mg, 0.104 mmol, 70% yield) as colorless needles (recrystallized from CH_2Cl_2/*n*-hexane, mp 173.5–174.1 °C). ^{1}H NMR ($CDCl_3$) δ: 8.66 (1H, d, J = 2.3 Hz), 8.46 (1H, dd, J = 6.9, 1.2 Hz), 8.22 (1H, d, J = 8.6 Hz), 7.83 (1H, dd, J = 8.6, 1.8 Hz), 7.68 (1H, ddd, J = 8.1, 8.1, 1.2 Hz), 7.55 (1H, ddd, J = 8.0, 8.0, 1.2 Hz), 7.29 (1H, d, J = 9.2 Hz), 6.54 (1H, d, J = 8.0 Hz), 4.29 (2H, t, J = 8.1 Hz), 4.07–4.02 (1H, m), 2.11–2.08 (2H, m), 1.83–1.77 (2H, m), 1.74–1.36 (3H, m), 1.50–1.41 (4H, m), 1.40–1.33 (2H, m), 1.26–1.21 (1H, m), 0.98 (3H, t, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 166.05, 161.28, 138.88, 133.01, 132.54, 128.82, 128.73, 128.32, 127.56, 125.41, 122.95, 121.78, 119.14, 114.81, 48.98, 42.64, 33.27 (2C), 29.44, 25.57, 25.04 (2C), 20.27, 13.84. FAB-MS m/z: 377 (MH^+). Anal. Calcd for $C_{24}H_{28}N_2O_2{\cdot}2/3H_2O$: C, 74.20; H, 7.61; N, 7.21. Found: C, 74.21; H, 7.32; N, 7.26.

*4.2.2.3.11. N-c-Propyl-5,6-dihydro-5-n-butyl-6-oxo-phenanthridine-2-carboxamide (**15**).* This compound was prepared according to the general procedure A. Open column chromatography (*n*-hexane/ethyl acetate = 1/1) gave the title compound (44.7 mg, 0.134 mmol, 92% yield) as a colorless powder (recrystallized from CH_2Cl_2/MeOH/*n*-hexane, mp 203.3–204.9 °C). ^{1}H NMR ($CDCl_3$/CD_3OD) δ: 8.67 (1H, d, J = 2.3 Hz), 8.39 (1H, d, J = 8.0 Hz), 8.23 (1H, d, J = 8.6 Hz), 7.89 (1H, dd, J = 8.6, 1.8 Hz), 7.66 (1H, ddd, J = 7.8, 7.8, 1.2 Hz), 7.61 (1H, br s), 7.52 (1H, dd, J = 7.5, 7.5 Hz), 7.28 (1H, d, J = 9.2 Hz), 4.25 (2H, t, J = 8.0 Hz), 2.98–2.95 (1H, m), 1.72–1.66 (2H, m), 1.49–1.46 (2H, m), 0.98 (3H, t, J = 7.5 Hz), 0.89 (2H, dd, J = 12.6, 6.9 Hz), 0.75–0.73 (2H, m). ^{13}C NMR ($CDCl_3$/CD_3OD) δ: 168.81, 161.55, 138.89, 133.13, 132.72, 128.58, 128.40, 128.11, 128.03, 125.19, 122.95, 121.83, 119.15, 114.99, 42.78, 29.46, 23.25, 20.28, 13.83, 6.50 (2C). FAB-MS m/z: 335 (MH^+). Anal. Calcd for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.38. Found: C, 75.14; H, 6.66; N, 8.25.

*4.2.2.3.12. N-i-Propyl-5,6-dihydro-5-n-butyl-6-oxo-phenanthridine-2-carboxamide (**16**).* Open column chromatography (*n*-hexane/ethyl acetate = 2/1) gave the title compound (39.8 mg, 0.118 mmol, 85% yield) as colorless cubes (recrystallized from CH_2Cl_2/*n*-hexane, mp 181.1–183.9 °C). ^{1}H NMR ($CDCl_3$) δ: 8.62 (1H, d, J = 2.3 Hz), 8.41 (1H, dd, J = 8.1, 1.2 Hz), 8.17 (1H, d, J = 8.0 Hz), 7.80 (1H, dd, J = 8.6, 1.7 Hz), 7.62 (1H, ddd, J = 7.4, 7.4, 1.2 Hz), 7.50 (1H, ddd, J = 8.0, 8.0, 1.2 Hz), 7.23 (1H, d, J = 9.7 Hz), 6.59 (1H, br d, J = 6.9 Hz), 4.37–4.30 (1H, m), 4.24 (2H, t, J = 7.5 Hz), 1.66 (2H, tt, J = 7.5, 7.5 Hz), 1.44 (2H, tt, J = 7.5, 7.5 Hz), 1.31 (6H, d, J = 6.9 Hz), 0.94 (3H, t, J = 7.4 Hz). ^{13}C NMR ($CDCl_3$) δ: 166.15, 161.21, 138.85, 132.95, 132.47, 128.64, 128.54, 128.26, 127.55, 125.33, 122.89, 121.71, 119.06, 114.74, 42.59, 42.12, 29.38, 22.78 (2C), 20.20, 13.76. FAB-MS m/z: 337 (MH^+). HRMS (FAB, $[M+H]^+$) calcd for $C_{21}H_{25}N_2O_2$ 337.1916, found 337.1909.

*4.2.2.3.13. N-t-Butyl-5,6-dihydro-5-n-butyl-6-oxo-phenanthridine-2-carboxamide (**17**).* Open column chromatography (*n*-hexane/ethyl acetate = 3/1) gave the title compound (40.3 mg, 0.115 mmol, 82% yield) as a colorless amorphous solid. ^{1}H NMR ($CDCl_3$) δ: 8.59 (1H, d, J = 1.7 Hz), 8.43 (1H, dd, J = 8.0, 1.2 Hz), 8.21 (1H, d, J = 8.1 Hz), 7.72 (1H, dd, J = 8.6, 1.7 Hz), 7.67 (1H, ddd, J = 8.0, 8.0, 1.2 Hz), 7.53 (1H, ddd, J = 7.5, 7.5, 1.2 Hz), 7.23 (1H, d, J = 8.6 Hz), 6.31 (1H, br s), 4.25 (2H, t, J = 7.5 Hz), 1.68 (2H, ttt, J = 7.4, 7.4 Hz), 1.52 (9H, s), 1.48–1.41 (2H, m), 0.96 (3H, t, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 166.36, 161.23, 138.76, 132.99, 132.51, 129.44, 128.68, 128.28, 127.29, 125.40, 122.82, 121.73, 119.09, 114.68, 51.85, 42.59, 29.39, 28.89 (3C), 20.23, 13.79.

FAB-MS *m*/*z*: 351 (MH^+). HRMS (FAB, $[M+H]^+$) calcd for $C_{22}H_{27}N_2O_2$ 351.2073, found 351.2040.

*4.2.2.3.14. 5,6-Dihydro-5-n-butyl-6-oxo-phenanthridine-2-carboxylic acid piperazine amide (**18**).* Open column chromatography (*n*-hexane/ethyl acetate = 2/1 to 1/1) gave the title compound (44.1 mg, 0.122 mmol, 86% yield) as colorless needles (recrystallized from CH_2Cl_2/*n*-hexane, mp 100.5–102.3 °C). ^1H NMR ($CDCl_3$) δ: 8.50 (1H, dd, *J* = 8.0, 1.7 Hz), 8.34 (1H, d, *J* = 1.7 Hz), 8.22 (1H, d, *J* = 8.0 Hz), 7.72 (1H, ddd, *J* = 6.9, 6.9, 1.2 Hz), 7.58–7.53 (2H, m), 7.38 (1H, d, *J* = 8.6 Hz), 4.36 (2H, t, *J* = 7.5 Hz), 3.58 (4H, br s), 1.78–1.72 (2H, m), 1.71–1.66 (2H, m), 1.61 (4H, br s), 1.52–1.45 (2H, m), 0.98 (3H, t, *J* = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 50 °C) δ: 169.73, 161.24, 138.04, 133.14, 132.48, 130.05, 128.91, 128.28, 128.14, 125.78, 122.88, 121.65, 119.41, 114.86, 46.29 (2C), 42.64, 29.55, 26.15 (2C), 24.59, 20.27, 13.73. FAB-MS *m*/*z*: 363 (MH^+). Anal. Calcd for $C_{23}H_{26}N_2O_2$: C, 76.21; H, 7.23; N, 7.73. Found: C, 76.38; H, 7.31; N, 7.71.

*4.2.2.3.15. 5,6-Dihydro-5-n-butyl-6-oxo-phenanthridine-2-carboxylic acid morpholine amide (**19**).* This compound was prepared according to the general procedure B. Flash column chromatography (*n*-hexane/AcOEt = 1:1 to 1:3) afforded the title compound (22.2 mg, 0.061 mmol, 32%) as colorless cubes (recrystallized from CH_2Cl_2/*n*-hexane, mp 165.9–166.9 °C). ^1H NMR (CD_3OD) δ: 8.55 (1H, d, *J* = 1.2 Hz), 8.49 (1H, d, *J* = 8.6 Hz), 8.44 (1H, dd, *J* = 8.6, 1.2 Hz), 7.86 (1H, ddd, *J* = 6.9, 6.9, 1.2 Hz), 7.69–7.65 (3H, m), 4.44 (2H, t, *J* = 8.0 Hz), 3.99–3.45 (8H, m), 1.81–1.74 (2H, m), 1.56–1.48 (2H, m), 1.02 (3H, t, *J* = 7.5 Hz). FAB- MS *m*/*z*: 365 (MH+). Anal. Calcd for $C_{22}H_{24}N_2O_3$: C, 72.51; H, 6.64; N, 7.69. Found: C, 72.31; H, 6.77; N, 7.48.

*4.2.2.3.16. N-Benzyl-5,6-dihydro-5-n-butyl-6-oxo-phenanthridine-2-carboxamide (**20**).* Open column chromatography (*n*-hexane/ethyl acetate = 3/1) gave the title compound (42.0 mg, 0.109 mmol, 78% yield) as colorless needles (recrystallized from CH_2Cl_2/*n*-hexane, mp 152.0–154.2 °C). ^1H NMR ($CDCl_3$) δ: 8.73 (1H, d, *J* = 1.7 Hz), 8.41 (1H, dd, *J* = 8.0, 1.1 Hz), 8.18 (1H, d, *J* = 8.0 Hz), 7.87 (1H, dd, *J* = 9.2, 2.3 Hz), 7.61 (1H, ddd, *J* = 7.8, 7.8, 1.2 Hz), 7.50 (1H, ddd, *J* = 7.5, 7.5, 1.2 Hz), 7.36–7.22 (7H, m), 4.66 (1H, d, *J* = 4.6 Hz), 4.24 (2H, t, *J* = 8.0 Hz), 1.66 (2H, tt, *J* = 7.5, 7.5 Hz), 1.43 (2H, tt, *J* = 7.5, 7.5 Hz), 0.94 (3H, t, *J* = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 166.82, 161.25, 139.09, 138.20, 132.92, 132.53, 128.65 (4C), 128.32, 127.86 (2C), 127.70, 127.48, 125.33, 123.12, 121.74, 119.18, 114.85, 44.18, 42.62, 29.38, 20.19, 13.77. FAB-MS *m*/*z*: 385 (MH^+). Anal. Calcd for $C_{25}H_{24}N_2O_2$: C, 78.10; H, 6.29; N, 7.29. Found: C, 78.25; H, 6.31; N, 7.20.

4.2.2.4. *N,N′*-Bis(2-hydroxyethyl)-5,6-dihydro-5-*n*-butyl-6-oxo-phenanthridine-2-carboxamide (12). To a solution of **66** (43.8 mg, 0.148 mmol) and DMF (100 μL) in CH_2Cl_2 (1 mL) was added oxalyl chloride (30 μL, 0.35 mmol) at 0 °C. The mixture was stirred at this temperature for 10 min, then added to a vigorously stirred solution of diethanolamine (30 μL, 0.31 mmol) in saturated aqueous $NaHCO_3$ (1 mL). Stirring was continued for 5 h at ambient temperature, then the biphasic mixture was separated. The organic phase was washed with saturated aqueous NH_4Cl and brine, dried over Na_2SO_4 and concentrated. Open column chromatography (ethyl acetate then $CHCl_3$/MeOH = 9/1) gave the title compound (15.8 mg, 0.0413 mmol, 28% yield) as colorless cubes (recrystallized from CH_2Cl_2/*n*-hexane, mp 80.8–82.1 °C). ^1H NMR ($CDCl_3$) δ: 8.60 (1H, d, *J* = 1.2 Hz), 8.40 (1H, dd, *J* = 8.0, 1.2 Hz), 8.17 (1H, d, *J* = 8.0 Hz), 7.72 (1H, d, *J* = 8.6 Hz), 7.63 (1H, ddd, *J* = 7.5, 7.5, 1.2 Hz), 7.50 (1H, dd, *J* = 8.0, 8.0 Hz), 7.31 (1H, d, *J* = 8.6 Hz), 4.25 (2H, t, *J* = 8.0 Hz), 4.02 (2H, br s), 3.81 (2H, br s), 3.74 (2H, br s), 3.55 (2H, br s), 1.72–1.66 (2H, m), 1.47–1.42 (2H, m), 0.96 (3H, t, *J* = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 173.15, 161.22, 137.90, 133.04, 132.62, 129.12, 129.07, 128.59, 128.29, 125.32, 123.94, 121.87, 119.03, 115.05, 60.46, 59.49, 53.49, 49.29, 42.62, 29.40, 20.25, 13.82. FAB-MS *m*/*z*: 383 (MH^+). Anal. Calcd for $C_{22}H_{26}N_2O_4{\cdot}4/5H_2O$: C, 66.58; H, 7.01; N, 7.06. Found: C, 66.48; H, 6.99; N, 6.67.

4.2.3. Synthesis of 5-alkyl derivatives of phenanthridin-6-ones

4.2.3.1. *N,N′*-(Diethyl)-4-(2-bromobenzoyl)aminobenzoic amide (68). To a suspension of 4-aminobenzoic acid (1379 mg, 10.05 mmol) and DMF (2 drops) in CH_2Cl_2 (10 mL) was added thionyl chloride (3 mL, 40 mmol) at 0 °C. The mixture was stirred at 40 °C for 1 h and 60 °C for 1 h, and then cooled to ambient temperature. Diethylamine (10 mL) was added and stirring was continued overnight at ambient temperature, then the mixture was poured into water and extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated. The residue was subjected to the next reaction without further purification. To a vigorously stirred mixture of the crude amide in CH_2Cl_2 (50 mL) and saturated aqueous $NaHCO_3$ (50 mL) was added 2-bromobenzoyl chloride (1.8 mL, 13.78 mmol) at 0 °C. Stirring was continued for 15 h at ambient temperature. The biphasic mixture was separated and the organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated. Open column chromatography (*n*-hexane/ethyl acetate = 1/1 to 1/2) gave the title compound (1621 mg, 4.320 mmol, 43% yield for 2 steps) as a brown solid. ^1H NMR ($CDCl_3$/CD_3OD) δ: 7.68 (2H, d, *J* = 8.6 Hz), 7.64 (1H, d, *J* = 8.0 Hz), 7.61 (1H, br s), 7.60 (1H, dd, *J* = 7.5, 1.2 Hz), 7.43–7.40 (1H, m), 7.36 (1H, d, *J* = 8.0 Hz), 7.39–7.31 (2H, m), 3.52 (2H, br s), 3.31 (2H, br s), 1.23 (3H, br s), 1.14 (3H, br s). ^{13}C NMR ($CDCl_3$/CD_3OD) δ: 171.23, 166.20, 138.72, 137.91, 133.44, 132.95, 131.60, 129.47, 127.67, 127.36 (2C), 119.86 (2C), 119.42, 43.51, 38.54, 14.26, 12.82. FAB-MS *m*/*z*: 377, 375 (MH^+).

4.2.3.2. *N,N′*-(Diethyl)-4-[(2-bromobenzoyl)-*p*-methoxybenzyl]aminobenzoic amide (69). To a solution of **68** (1621 mg, 4.320 mmol) in DMF (15 mL) was added NaH (237.5 mg, 5.938 mmol, ca. 60%) at 0 °C. The mixture was stirred for 1 h at ambient temperature, then 4-methoxybenzyl chloride (750 μL, 5.56 mmol) was added and stirring was continued at ambient temperature overnight. Water was added and the whole was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated. Open column chromatography (*n*-hexane/ethyl acetate = 1/1) gave the title compound (2137 mg, 4.314 mmol, 100%) as a yellow amorphous solid. ^1H NMR (DMSO-d_6) δ: 7.45 (1H, d, *J* = 8.0 Hz), 7.28–7.21 (3H, m), 7.17 (1H, dd, *J* = 8.1 Hz), 7.13–7.04 (5H, m), 6.85 (2H, d, *J* = 8.6 Hz), 3.70 (3H, s), 3.36–3.26 (2H, m), 2.88–2.78 (2H, m), 1.04 (3H, br s), 0.81 (3H, br s). ^{13}C NMR (DMSO-d_6) δ: 169.03, 167.48, 158.49, 141.35, 138.14, 135.93, 132.17, 130.17, 129.60 (2C), 129.15, 128.68, 128.03 (2C), 126.94, 126.39 (2C), 119.05, 113.76 (2C), 54.95, 50.85, 40.00, 39.00, 13.80, 12.73. FAB-MS *m*/*z*: 497, 495 (MH^+).

4.2.3.3. *N,N′*-(Diethyl)-5,6-dihydro-5-*p*-methoxybenzyl-6-oxo-phenanthridine-2-carboxamide (25). A de-aerated mixture of **69** (1974 mg, 3.984 mmol), $Pd(OAc)_2$ (97.5 mg, 0.434 mmol), $PCy_3{\cdot}HBF_4$ (192.2 mg, 0.4976 mmol) and Cs_2CO_3 (1005 mg, 3.085 mmol) in DMA (15 mL) was stirred at 130 °C for 4 h, then cooled to ambient temperature and filtered through a Celite pad. The pad was washed with ethyl acetate. The filtrate and washing were combined, washed with water and brine, dried over Na_2SO_4 and concentrated. Open column chromatography (*n*-hexane/ethyl acetate = 1/1) gave the title compound (1565 mg, 3.774 mmol, 95% yield) as a pale yellow amorphous solid. ^1H NMR ($CDCl_3$) δ: 8.62 (1H, dd, *J* = 8.0, 1.2 Hz), 8.34 (1H, d, *J* = 2.3 Hz), 8.30 (1H, d, *J* = 8.0 Hz), 7.81 (1H, ddd, *J* = 7.5, 7.5, 1.7 Hz), 7.65 (1H, ddd, *J* = 7.5, 7.5, 1.2 Hz), 7.43 (1H, dd, *J* = 8.6, 2.3 Hz), 7.36 (1H, d,

J = 8.6 Hz), 7.20 (2H, d, J = 9.2 Hz), 6.83 (2H, dt, J = 8.6, 2.9 Hz), 5.61 (2H, br s), 3.76 (3H, s), 3.58 (2H, br s), 3.33 (2H, br s), 1.34–1.23 (3H, m), 1.23–1.11 (3H, m). ^{13}C NMR ($CDCl_3$) δ: 170.52, 161.80, 158.79, 137.88, 133.31, 132.86, 131.24, 129.21, 128.45, 128.23, 127.83 (2C), 127.52, 125.57, 122.01, 121.77, 119.45, 115.90, 114.22 (2C), 55.24, 46.00, 43.41, 39.51, 14.34, 12.88. FAB-MS m/z: 415 (MH^+). HRMS (FAB, $[M+H]^+$) calcd for $C_{26}H_{27}N_2O_3$ 415.2022, found 415.2004.

4.2.3.4. *N,N′*-(Diethyl)-5,6-dihydro-6-oxo-phenanthridine-2-carboxamide (21). A solution of **25** (1531 mg, 3.694 mmol) in TFA (4 mL) was refluxed for 8 h, then cooled to ambient temperature and diluted with ethyl acetate. The organic layer was washed with water, saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated. Open column chromatography (n-hexane/ethyl acetate = 1/2 to 1/3) gave the title compound (681.4 mg, 2.314 mmol, 63%) as colorless cubes (recrystallized from CH_2Cl_2/MeOH/n-hexane, mp 233.2–236.0 °C). ^{1}H NMR ($CDCl_3$) δ: 10.82 (1H, br s), 8.59 (1H, dd, J = 8.0, 1.2 Hz), 8.33–8.29 (2H, m), 7.84 (1H, ddd, J = 8.0, 8.0, 1.2 Hz), 7.66 (1H, ddd, J = 7.4, 7.4, 1.2 Hz), 7.53 (1H, dd, J = 8.6, 1.8 Hz), 7.40 (1H, d, J = 8.0 Hz), 3.60 (2H, br s), 3.36 (2H, br s), 1.28 (3H, br s), 1.21 (3H, br s). ^{13}C NMR ($CDCl_3$/CD_3OD) δ: 175.53, 166.70, 140.77, 138.22, 137.23, 135.06, 132.44, 132.09, 131.40, 129.64, 126.54, 125.38, 122.51, 120.57, 47.88, 43.90, 18.12, 16.63. FAB-MS m/z: 295 (MH^+). HRMS (FAB, $[M+H]^+$) calcd for $C_{18}H_{19}N_2O_2$ 295.1447, found 295.1418.

4.2.3.5. General procedure for synthesis of 5-alkyl derivatives of *N,N′*-(diethyl)-5,6-dihydro-6-oxo-phenanthridine-2-carboxamide. A solution of **21** (30 mg, 0.1 mmol), Cs_2CO_3 (70 mg, 0.2 mmol) and alkyl iodide or alkyl bromide (0.5 mmol) in DMF (500 μL) was stirred at 90 °C for 1 h, then diluted with ethyl acetate. The organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated. The product was purified as indicated below.

*4.2.3.5.1. N,N′-(Diethyl)-5,6-dihydro-5-methyl-6-oxo-phenanthridine-2-carboxamide (**22**).* Methyl iodide was used for the reaction. Open column chromatography (n-hexane/ethyl acetate = 1/2) gave the title compound (20.9 mg, 0.0678 mmol, 73% yield) as colorless cubes (recrystallized from CH_2Cl_2/n-hexane, mp 122.1–123.4 °C). ^{1}H NMR ($CDCl_3$) δ: 8.55 (1H, dd, J = 8.0, 1.1 Hz), 8.34 (1H, d, J = 1.7 Hz), 8.27 (1H, d, J = 8.0 Hz), 7.77 (1H, ddd, J = 6.9, 6.9, 1.2 Hz), 7.61 (1H, ddd, J = 7.4, 7.4, 1.2 Hz), 7.58 (1H, dd, J = 8.6, 1.8 Hz), 7.43 (1H, d, J = 8.6 Hz), 3.83 (3H, s), 3.60 (2H, br s), 3.36 (2H, br s), 1.29 (3H, br s), 1.22 (3H, br s). ^{13}C NMR ($CDCl_3$) δ: 170.65, 161.58, 138.54, 133.07, 132.65, 131.23, 128.97, 128.41, 127.62, 125.71, 121.99, 121.76, 119.21, 114.93, 43.52, 39.60, 30.11, 14.43, 13.02. FAB-MS m/z: 309 (MH^+). Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 74.14; H, 6.64; N, 8.99.

*4.2.3.5.2. N,N′-(Diethyl)-5,6-dihydro-5-ethyl-6-oxo-phenanthridine-2-carboxamide (**23**).* Ethyl iodide was used for the reaction. Open column chromatography (n-hexane/ethyl acetate = 1/2) gave the title compound (27.2 mg, 0.0844 mmol, 86% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 8.56 (1H, dd, J = 8.0, 1.1 Hz), 8.36 (1H, d, J = 1.8 Hz), 8.28 (1H, d, J = 8.0 Hz), 7.78 (1H, ddd, J = 6.9, 6.9, 1.2 Hz), 7.62 (1H, ddd, J = 8.1, 8.1, 1.2 Hz), 7.58 (1H, dd, J = 8.6, 1.7 Hz), 7.45 (1H, d, J = 8.6 Hz), 4.48 (2H, q, J = 7.5 Hz), 3.60 (2H, br s), 3.38 (2H, br s), 1.42 (3H, t, J = 6.9 Hz), 1.37–1.13 (6H, m). ^{13}C NMR ($CDCl_3$) δ: 170.66, 161.09, 137.47, 133.12, 132.61, 131.02, 128.86, 128.38, 127.67, 125.73, 122.22, 121.70, 119.44, 114.86, 43.49, 39.57, 37.85, 14.42, 13.03, 12.71. FAB-MS m/z: 323 (MH^+). HRMS (FAB, $[M+H]^+$) calcd for $C_{20}H_{23}N_2O_2$ 323.1760, found 323.1796.

*4.2.3.5.3. N,N′-(Diethyl)-5,6-dihydro-5-benzyl-6-oxo-phenanthridine-2-carboxamide (**24**).* Benzyl bromide was used for the reaction. Open column chromatography (n-hexane/ethyl acetate = 1/1) gave the title compound (11.0 mg, 0.0286 mmol, 27% yield) as colorless cubes (recrystallized from CH_2Cl_2/n-hexane, mp 221.5–223.0 °C). ^{1}H NMR ($CDCl_3$) δ: 8.63 (1H, dd, J = 8.0, 1.2 Hz), 8.35 (1H, d, J = 1.7 Hz), 8.31 (1H, d, J = 8.0 Hz), 7.82 (1H, ddd, J = 7.4, 7.4, 1.2 Hz), 7.65 (1H, ddd, J = 7.7, 7.7, 1.2 Hz), 7.41 (1H, dd, J = 8.6, 2.3 Hz), 7.32–7.23 (6H, m), 5.68 (2H, br s), 3.58 (2H, br s), 3.33 (2H, br s), 1.26 (3H, br s), 1.19 (3H, br s). ^{13}C NMR ($CDCl_3$) δ: 170.53, 161.85, 137.90, 136.22, 133.37, 132.95, 131.33, 129.27, 128.86 (2C), 128.52, 127.58, 127.33, 126.49 (2C), 125.55, 122.06, 121.83, 119.50, 115.95, 46.57, 43.48, 39.52, 14.40, 12.87. FAB-MS m/z: 385 (MH^+). Anal. Calcd for $C_{25}H_{24}N_2O_2$: C, 78.10; H, 6.29; N, 7.29. Found: C, 77.99; H, 6.37; N, 7.20.

4.2.3.6. General procedure for synthesis of 5-(ethoxycarbonyl)alkyl derivatives of *N,N′*-(diethyl)-5,6-dihydro-6-oxo-phenanthridine-2-carboxamide. A solution of **21** (120 mg, 0.39 mmol), Cs_2CO_3 (240 mg, 0.74 mmol), TBAI (20 mg, 0.05 mmol) and alkyl bromide (1.9 mmol) in DMF (2 mL) was stirred at 90 °C for 1 h, then diluted with ethyl acetate. The organic layer was washed with water and brine, dried (Na_2SO_4) and concentrated. The product was purified as indicated below.

*4.2.3.6.1. N,N′-(Diethyl)-5,6-dihydro-5-(ethoxycarbonyl)methyl-6-oxo-phenanthridine-2-carboxamide (**70**).* Open column chromatography (n-hexane/ethyl acetate = 1/1 to 1/2) gave the title compound (114.0 mg, 0.2996 mmol, 77% yield) as a colorless solid. ^{1}H NMR ($CDCl_3$) δ: 8.55 (1H, dd, J = 8.0, 1.7 Hz), 8.36 (1H, d, J = 1.7 Hz), 8.29 (1H, d, J = 8.6 Hz), 7.81 (1H, ddd, J = 7.5, 7.5, 1.7 Hz), 7.63 (1H, ddd, J = 7.5, 7.5, 1.2 Hz), 7.53 (1H, dd, J = 8.6, 2.3 Hz), 7.16 (1H, d, J = 8.6 Hz), 5.21 (2H, s), 4.26 (2H, q, J = 7.2 Hz), 3.60 (2H, br s), 3.35 (2H, br s), 1.28 (3H, br s), 1.27 (3H, t, J = 7.2 Hz), 1.21 (3H, br s). ^{13}C NMR ($CDCl_3$) δ: 170.47, 168.23, 131.49, 137.73, 133.39, 133.13, 131.65, 129.19, 128.57, 127.73, 125.28, 122.33, 121.90, 119.46, 114.43, 61.86, 44.44, 43.49, 39.56, 14.33, 14.16, 12.95. FAB-MS m/z: 381 (MH^+).

*4.2.3.6.2. N,N′-(Diethyl)-5,6-dihydro-5-(3-ethoxycarbonyl)propyl-6-oxo-phenanthridine-2-carboxamide (**71**).* Open column chromatography (n-hexane/ethyl acetate = 2/1 to 1/2) gave the title compound (103.6 mg, 0.2538 mmol, 66% yield) as a colorless solid. ^{1}H NMR ($CDCl_3$) δ: 8.55 (1H, dd, J = 8.1, 1.2 Hz), 8.36 (1H, d, J = 1.8 Hz), 8.28 (1H, d, J = 8.1 Hz), 7.78 (1H, ddd, J = 6.9, 6.9, 1.1 Hz), 7.67–7.58 (3H, m), 4.47 (2H, t, J = 6.9 Hz), 4.18 (2H, q, J = 7.5 Hz), 3.60 (2H, br s), 3.38 (2H, br s), 2.55 (2H, t, J = 6.9 Hz), 2.13 (2H, tt, J = 6.9 Hz), 1.29 (3H, t, J = 7.5 Hz), 1.34–1.16 (6H, m). ^{13}C NMR ($CDCl_3$) δ: 173.18, 170.64, 161.39, 137.65, 133.21, 132.72, 131.21, 128.90, 128.39, 127.78, 125.55, 122.24, 121.77, 119.41, 115.17, 60.64, 43.52, 42.12, 39.62, 31.34, 22.40, 14.40, 14.25, 12.97. FAB-MS m/z: 409 (MH^+).

4.2.3.7. General procedure for synthesis of 5-(carboxy)alkyl derivatives of *N,N′*-(diethyl)-5,6-dihydro-6-oxo-phenanthridine-2-carboxamide. To a solution of ethyl ester (0.15 mmol) in MeOH (15 mL) and water (10 mL) was added a 10 N aqueous solution of NaOH (200 μL). The mixture was stirred at ambient temperature for 16 h, then adjusted to pH 2 with 2 N aqueous HCl and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to give the desired compound.

*4.2.3.7.1. N,N′-(Diethyl)-5,6-dihydro-5-(carboxy)methyl-6-oxo-phenanthridine-2-carboxamide (**26**).* Colorless powder (recrystallized from CH_2Cl_2/MeOH/n-hexane, mp 283.5–285.1 °C). 60.3 mg, 0.171 mmol, 94%. ^{1}H NMR ($CDCl_3$/CD_3OD) δ: 8.53 (1H, d, J = 8.0 Hz), 8.36 (1H, d, J = 1.7 Hz), 8.32 (1H, d, J = 8.0 Hz), 7.83 (1H, ddd, J = 7.7, 7.7, 1.8 Hz), 7.65 (1H, dd, J = 8.0, 8.0 Hz), 7.54 (1H, dd, J = 8.0, 1.8 Hz), 7.28 (1H, d, J = 8.6 Hz), 5.19 (2H, s), 3.60 (2H, br s), 3.36 (2H, br s), 1.31 (3H, br s), 1.21 (3H, br s). ^{13}C

NMR ($CDCl_3/CD_3OD$) δ: 171.49, 170.32, 162.26, 138.04, 133.70 (2C), 131.53, 129.13, 129.04, 127.91, 125.32, 122.35, 122.28, 119.85, 115.34, 44.67, 44.16, 40.21, 14.43, 12.91. FAB-MS *m*/*z*: 353 (MH^+). HRMS (FAB, $[M+H]^+$) calcd for $C_{20}H_{21}N_2O_4$ 353.1501, found 353.1541.

*4.2.3.7.2. N,N′-(Diethyl)-5,6-dihydro-5-(3-carboxy)propyl-6-oxophenanthridine-2-carboxamide (**27**).* Colorless cubes (recrystallized from CH_2Cl_2/*n*-hexane, mp 181.1–184.7 °C). 51.3 mg, 0.135 mmol, quant. ^1H NMR ($CDCl_3$) δ: 8.54 (1H, dd, *J* = 8.0, 1.1 Hz), 8.36 (1H, br s), 8.29 (1H, d, *J* = 8.0 Hz), 7.99 (1H, ddd, *J* = 8.3, 8.3, 1.1 Hz), 7.64–7.63 (3H, m), 4.37 (2H, t, *J* = 7.5 Hz), 3.62 (2H, br s), 3.38 (2H, br s), 2.52 (2H, t, *J* = 6.9 Hz), 2.10 (2H, tt, *J* = 7.5, 7.5 Hz), 1.31 (3H, br s), 1.22 (3H, br s). ^{13}C NMR ($CDCl_3$) δ: 176.38, 171.21, 161.46, 137.62, 133.16, 132.83, 130.73, 128.94, 128.49, 127.92, 125.41, 122.18, 121.75, 119.40, 115.39, 43.68, 42.08, 39.81, 30.94, 22.20, 14.37, 12.94. FAB-MS *m*/*z*: 381 (MH^+). Anal. Calcd for $C_{22}H_{24}N_2O_2 \cdot 1/3H_2O$: C, 68.38; H, 6.43; N, 7.25. Found: C, 68.18; H, 6.26; N, 7.13.

4.2.3.8. General procedure for synthesis of 5-(*N,N′*,-dimethylcarbamoyl)alkyl derivatives of *N,N′*-(diethyl)-5,6-dihydro-6-oxo-phenanthridine-2-carboxamide. To a solution of the acid (0.1 mmol) and triethylamine (20 μL, 0.14 mmol) in THF (10 mL) and CH_2Cl_2 (4 mL) was added isobutyl chloroformate (18 μL, 0.14 mmol) at 0 °C. The mixture was stirred at this temperature for 20 min, then dimethylamine (40% in water, 0.5 mL) was added and stirring was continued at ambient temperature for 30 min. The whole was diluted with ethyl acetate. The organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated. The product was purified as indicated below.

*4.2.3.8.1. N,N′-(Diethyl)-5,6-dihydro-5-(N,N′,-dimethylcarbamoyl)methyl-6-oxo-phenanthridine-2-carboxamide (**28**).* Open column chromatography (ethyl acetate then $CHCl_3$/MeOH = 40/1) gave the title compound (22.0 mg, 0.0580 mmol, 53% yield) as colorless plates (recrystallized from CH_2Cl_2/*n*-hexane, mp 227.4–230.0 °C). ^1H NMR ($CDCl_3$) δ: 8.52 (1H, dd, *J* = 8.0, 1.2 Hz), 8.33 (1H, d, *J* = 1.7 Hz), 8.27 (1H, d, *J* = 8.0 Hz), 7.78 (1H, ddd, *J* = 7.7, 7.7, 1.7 Hz), 7.60 (1H, ddd, *J* = 8.0, 8.0, 1.1 Hz), 7.50 (1H, dd, *J* = 8.6, 1.7 Hz), 7.19 (1H, d, *J* = 8.6 Hz), 5.24 (2H, s), 3.59 (2H, br s), 3.36 (2H, br s), 3.36 (3H, s), 3.04 (3H, s), 1.28 (3H, br s), 1.20 (3H, br s). ^{13}C NMR ($CDCl_3$) δ: 170.65, 166.41, 161.64, 138.24, 133.48, 132.93, 131.34, 129.04, 128.35, 127.55, 125.32, 122.09, 121.81, 119.38, 115.15, 44.52, 43.42, 39.55, 36.61, 35.97, 14.30, 12.96. FAB-MS *m*/*z*: 380 (MH^+). Anal. Calcd for $C_{22}H_{25}N_3O_3 \cdot 1/5H_2O$: C, 68.98; H, 6.68; N, 10.97. Found: C, 69.16; H, 6.67; N, 10.80.

*4.2.3.8.2. N,N′-(Diethyl)-5,6-dihydro-5-(N,N′-dimethylcarbamoyl)propyl-6-oxo-phenanthridine-2-carboxamide (**29**).* Open column chromatography (ethyl acetate then $CHCl_3$/MeOH = 40/1) gave the title compound (26.9 mg, 0.0660 mmol, 74% yield) as colorless plates (recrystallized from CH_2Cl_2/*n*-hexane, mp 112.9–115.5 °C). ^1H NMR ($CDCl_3$) δ: 8.54 (1H, dd, *J* = 8.0, 1.2 Hz), 8.36 (1H, d, *J* = 2.3 Hz), 8.29 (1H, d, *J* = 8.0 Hz), 7.93 (1H, d, *J* = 8.6 Hz), 7.77 (1H, ddd, *J* = 7.7, 7.7, 1.2 Hz), 7.63–7.59 (2H, m), 4.48 (2H, t, *J* = 7.5 Hz), 3.60 (2H, br s), 3.37 (2H, br s), 3.03 (3H, s), 3.00 (3H, s), 2.55 (2H, t, *J* = 6.3 Hz), 2.14 (2H, tt, *J* = 7.5, 6.3 Hz), 1.29 (3H, br s), 1.22 (3H, br s). ^{13}C NMR ($CDCl_3$) δ: 172.16, 170.76, 161.42, 137.85, 133.34, 132.61, 131.13, 128.79, 128.24, 127.86, 125.59, 122.19, 121.80, 119.32, 115.80, 43.51, 42.74, 39.55, 37.23, 35.53, 30.35, 22.54, 14.39, 13.04. FAB-MS *m*/*z*: 408 (MH^+). HRMS (FAB, $[M+H]^+$) calcd for $C_{24}H_{30}N_3O_3$ 408.2287, found 408.2238.

4.2.4. Synthesis of cycloalkaquinolinones

4.2.4.1. General procedure for synthesis of 2-bromocycloalkene-1-carbaldehydes. Formylation was conducted as reported [Ohe 2000]. To a mixture of DMF (9 mL) and $CHCl_3$ (18 mL) was added dropwise PBr_3 (2.2 mL, 23 mmol) at 0 °C. The mixture was stirred at ambient temperature for 2 h until a pale-yellow precipitate was observed. Then cycloalkanone (20 mmol) in $CHCl_3$ (1.6 mL) was added and the whole was refluxed for 2 h. *n*-Hexane (20 mL) and 1 N aqueous NaOH (20 mL) were added and the whole was extracted with AcOEt/*n*-hexane = 1/1. The organic layer was washed with water and brine, dried and concentrated. The product was purified as indicated below.

*4.2.4.1.1. 2-Bromo-1-cyclopentene-1-carbaldehyde (**73a**).* Column chromatography (*n*-hexane/AcOEt = 99/1 to 91/9) gave the title compound (894.4 mg, 5.110 mmol, 26% yield) as a brown oil. ^1H NMR ($CDCl_3$) δ: 9.88 (1H, s), 2.88 (2H, tt, *J* = 7.5, 2.3 Hz), 2.51 (2H, tt, *J* = 7.5, 2.3 Hz), 2.00 (2H, tt, *J* = 7.5, 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 189.23, 141.41, 139.97, 42.52, 29.23, 21.34.

*4.2.4.1.2. 2-Bromo-1-cyclohexene-1-carbaldehyde (**73b**).* Column chromatography (*n*-hexane/AcOEt = 99/1 to 92/8) gave the title compound (1233 mg, 6.522 mmol, 33% yield) as a pale-yellow oil. ^1H NMR ($CDCl_3$) δ: 10.03 (1H, s), 2.76–2.73 (2H, m), 2.29–2.27 (2H, m), 1.78–1.76 (2H, m), 1.70–1.68 (2H, m).

*4.2.4.1.3. 2-Bromo-1-cycloheptene-1-carbaldehyde (**73c**).* Column chromatography (*n*-hexane/AcOEt = 99/1 to 91/9) gave the title compound (1738 mg, 8.557 mmol, 43% yield) as a pale-yellow oil. ^1H NMR ($CDCl_3$) δ: 9.90 (1H, s), 3.03–2.97 (2H, m), 2.49–2.45 (2H, m), 1.81–1.75 (2H, m), 1.67–1.61 (2H, m), 1.46–1.40 (2H, m). ^{13}C NMR ($CDCl_3$) δ: 193.28, 148.35, 140.51, 44.23, 31.38, 25.64, 25.15, 24.79.

*4.2.4.1.4. 2-Bromo-1-cyclooctene-1-carbaldehyde (**73d**).* To a mixture of DMF (2.4 mL) and $CHCl_3$ (8 mL) was added PBr_3 (2.4 mL, 25 mmol) dropwise at 0 °C. Then cyclooctanone (1258 mg, 9.968 mmol) in $CHCl_3$ (3 mL) was added at 0 °C, and the mixture was stirred at ambient temperature for 6 h. *n*-Hexane (10 mL) and water (20 mL) were added and the whole was extracted with AcOEt. The organic layer was washed with water and brine, dried and concentrated. Column chromatography (*n*-hexane/AcOEt = 99/1 to 91/9) gave the title compound (127.4 mg, 0.5868 mmol, 6% yield) as a colorless oil. ^1H NMR ($CDCl_3$) δ: 9.96 (1H, s), 2.92 (2H, t, J = 6.3 Hz), 2.45 (2H, t, J = 5.7 Hz), 1.81–1.73 (2H, m), 1.54–1.40 (6H, m). ^{13}C NMR ($CDCl_3$) δ: 193.46, 146.61, 138.20, 39.67, 29.83, 28.24, 26.52, 26.16, 25.51.

4.2.4.2. General procedure for synthesis of 2-bromocycloalkene-1-carboxylic acid. The oxidation was conducted under reported reaction conditions [Ohe 2000]. To a mixture of the aldehyde (0.59–8.5 mmol), NaH_2PO_4 (19.6–318 mg, 0.16–2.6 mmol, 0.3 equiv) and 30% aqueous H_2O_2 (0.06–1.1 mL) in CH_3CN (0.5–9 mL) and water (0.25–9 mL) was added $NaClO_2$ (92–1500 mg, 0.81–13 mmol, 1.4 equiv ca. 80%) in water (0.7–14 mL) at ambient temperature. The mixture was stirred at this temperature for 6–16 h, alkalified by the addition of 10 N aqueous NaOH, and then washed with AcOEt. The whole was acidified with 2 N aqueous HCl and extracted with $CHCl_3$/*i*PrOH = 3/1. The organic layer was washed with water and brine, dried and concentrated to give the desired compound.

*4.2.4.2.1. 2-Bromo-1-cyclopentene-1-carboxylic acid (**74a**).* Off-white solid. 828.0 mg, 4.335 mmol, 85% yield. ^1H NMR ($CDCl_3$) δ: 7.99 (1H, br s), 2.84 (2H, tt, *J* = 8.0, 2.3 Hz), 2.66 (2H, tt, *J* = 8.0, 2.3 Hz), 1.97 (2H, tt, *J* = 8.0, 8.0 Hz). ^{13}C NMR ($CDCl_3$) δ: 168.96, 135.60, 131.37, 43.53, 32.86, 21.56. FAB-MS *m*/*z*: 193, 191 (MH^+).

*4.2.4.2.2. 2-Bromo-1-cyclohexene-1-carboxylic acid (**74b**).* Colorless solid. 1567 mg, 7.642 mmol, 95% yield. ^1H NMR ($CDCl_3$) δ: 2.68–2.61 (2H, m), 2.46–2.39 (2H, m), 1.76–1.65 (4H, m).

*4.2.4.2.3. 2-Bromo-1-cycloheptene-1-carboxylic acid (**74c**).* Colorless solid. 1681 mg, 7.671 mmol, 90% yield. ^1H NMR ($CDCl_3$) δ: 2.90–2.84 (2H, m), 2.53–2.47 (2H, m), 1.81–1.74 (2H, m), 1.65–1.56 (4H, m). ^{13}C NMR ($CDCl_3$) δ: 173.37, 135.17, 132.10, 42.92, 31.19, 31.05, 25.56, 24.58. FAB-MS *m*/*z*: 221, 219 (MH^+).

*4.2.4.2.4. 2-Bromo-1-cyclooctene-1-carboxylic acid (**74d**).* Colorless solid. 121.6 mg, 0.5217 mmol, 89% yield. ^{1}H NMR ($CDCl_3$) δ: 2.81–2.75 (2H, m), 2.51–2.44 (2H, m), 1.76–1.67 (4H, m), 1.55–1.48 (4H, m). ^{13}C NMR ($CDCl_3$) δ: 172.35, 132.47, 131.01, 38.64, 30.72, 30.00, 28.09, 26.32, 25.66. FAB-MS *m*/*z*: 233, 235 (MH^+).

4.2.4.3. Methyl 4-(2,2,2-trifluoroacetamido)benzoate (75). To a solution of methyl 4-aminobenzoate (616.7 mg, 4.080 mmol) and triethylamine (2.0 mL, 14 mmol) in CH_2Cl_2 (30 mL) was added trifluoroacetic anhydride (1.0 mL, 7.1 mmol) at 0 °C. The mixture was stirred at ambient temperature for 14 h, then saturated aqueous $NaHCO_3$ was added dropwise to it. The whole was extracted with CH_2Cl_2 and the organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried and concentrated. Column chromatography (n-hexane/AcOEt = 96/4 to 68/32) gave the title compound (974.0 mg, 3.941 mmol, 97% yield) as an off-white solid. ^{1}H NMR ($CDCl_3$) δ: 8.74 (1H, br s), 8.05 (2H, d, *J* = 8.6 Hz), 7.72 (2H, d, *J* = 8.6 Hz), 3.92 (3H, s). ^{13}C NMR ($CDCl_3$) δ: 166.45, 155.16 (q, *J* = 38.4 Hz), 139.45, 130.89 (2C), 127.52, 119.98 (2C), 115.52 (q, *J* = 287.9 Hz), 52.28. FAB-MS *m*/*z*: 248 (MH^+).

4.2.4.4. Methyl 4-(butylamino)benzoate (76). To a suspension of **75** (1497 mg, 6.057 mmol) and Cs_2CO_3 (2792 mg, 7.914 mmol) in dry DMF (2 mL) was added *n*-butyl iodide (1350 μL, 12.0 mmol). The mixture was stirred at 90 °C for 2 h and diluted with AcOEt. The organic layer was washed with water and brine, dried and concentrated. To a solution of the crude trifluoroacetylamide in MeOH (8 mL) was added K_2CO_3 (2500 mg, 18.09 mmol). The whole was stirred at 70 °C for 1 h and diluted with AcOEt. The organic layer was washed with water and brine, dried and concentrated. Column chromatography (*n*-hexane/AcOEt = 98/2 to 84/16) gave the title compound (702.6 mg, 3.390 mmol, 56% for 2 steps) as a colorless solid. ^{1}H NMR ($CDCl_3$) δ: 7.85 (2H, d, *J* = 8.6 Hz), 6.54 (2H, d, *J* = 8.6 Hz), 4.08 (1H, br s), 3.85 (3H, s), 3.19–3.14 (2H, m), 1.65–1.58 (2H, m), 1.47–1.39 (2H, m), 0.96 (3H, t, *J* = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 167.35, 152.11, 131.53 (2C), 117.98, 111.27 (2C), 51.49, 43.04, 31.39, 20.19, 13.84. FAB-MS *m*/*z*: 208 (MH^+).

4.2.4.5. General procedure for synthesis of methyl 4-(2-bromo-*N*-butylcycloalk-1-ene-1-carboxamido)benzoate. To a solution of acid **74a–d** (0.50–1.0 mmol, 2 equiv) and DMF (2 drop) in dry CH_2Cl_2 (500 μL) was added oxalyl chloride (45–85 μL, 0.52–0.99 mmol, 2 equiv) at ambient temperature. The mixture was stirred at this temperature for 10 min, then FK273 (56–98 mg, 0.27–0.47 mmol) and DMAP (68–130 mg, 0.55–1.0 mmol, 2 equiv) were added and stirring was continued at 60 °C for 2 h. The whole was diluted with CH_2Cl_2. The organic layer was washed with water, 2 N HCl aq, 2 N NaOH aq, and brine, dried over Na_2SO_4 and concentrated. The product was purified as indicated below.

*4.2.4.5.1. Methyl 4-(2-bromo-N-butylcyclopent-1-ene-1-carboxamido)benzoate (**77a**).* Column chromatography (*n*-hexane/AcOEt = 96/4 to 68/32) gave the title compound (165.0 mg, 0.4339 mmol, 92% yield) as a pale-yellow oil. ^{1}H NMR (DMSO-d_6, 100 °C) δ: 7.95 (2H, d, *J* = 8.6 Hz), 7.38 (2H, d, *J* = 8.6 Hz), 3.87 (3H, s), 3.77 (2H, d, *J* = 6.9 Hz), 2.44 (2H, tt, *J* = 7.5, 2.3 Hz), 2.36 (2H, tt, *J* = 7.5, 2.3 Hz), 1.76 (2H, tt, *J* = 7.5, 7.5 Hz), 1.51–1.44 (2H, m), 1.34–1.26 (2H, m), 0.86 (3H, t, *J* = 7.5 Hz). FAB-MS *m*/*z*: 382, 380 (MH^+).

*4.2.4.5.2. Methyl 4-(2-bromo-N-butylcyclohex-1-ene-1-carboxamido)benzoate (**77b**).* Column chromatography (*n*-hexane/AcOEt = 97/3 to 76/24) gave the title compound (122.2 mg, 0.3099 mmol, 84% yield) as a colorless oil. ^{1}H NMR (DMSO-d_6, 100 °C) δ: 7.97 (2H, d, *J* = 8.6 Hz), 7.45 (2H, d, *J* = 8.6 Hz), 3.87 (3H,s), 3.74 (2H, t, *J* = 7.5 Hz), 2.28 (2H, br s), 2.12 (2H, br s), 1.54–1.35 (6H, brm), 1.34–1.25 (2H, m), 0.85 (3H, t, *J* = 7.5 Hz). FAB-MS *m*/*z*: 396, 394 (MH^+).

*4.2.4.5.3. Methyl 4-(2-bromo-N-butylcyclohept-1-ene-1-carboxamido)benzoate (**77c**).* Column chromatography (*n*-hexane/AcOEt = 94/6 to 52/48) gave the title compound (184.0 mg, 0.4506 mmol, 97% yield) as a colorless oil. ^{1}H NMR (DMSO-d_6, 100 °C) δ: 7.98 (2H, d, *J* = 8.6 Hz), 7.45 (2H, d, *J* = 8.6 Hz), 3.88 (3H, s), 3.72 (2H, t, *J* = 7.5 Hz), 2.55 (2H, br s), 2.18 (2H, br s), 1.54 (2H, br s), 1.49–1.42 (2H, m), 1.39 (2H, br s), 1.34–1.25 (4H, m), 0.85 (3H, t, *J* = 7.5 Hz). FAB-MS *m*/*z*: 410, 408 (MH^+).

*4.2.4.5.4. Methyl 4-(2-bromo-N-butylcyclooct-1-ene-1-carboxamido)benzoate (**77d**).* Column chromatography (*n*-hexane/AcOEt = 98/2 to 84/16) gave the title compound (63.6 mg, 0.151 mmol, 56% yield) as a colorless oil. ^{1}H NMR (DMSO-d_6, 100 °C) δ: 7.95 (2H, d, *J* = 8.0 Hz), 7.45 (2H, d, *J* = 8.0 Hz), 3.87 (3H, s), 3.74 (2H, t, *J* = 7.2 Hz), 2.46 (2H, br s), 2.21 (2H, br s), 1.62 (2H, br s), 1.56 (2H, br s), 1.51–1.40 (6H, m), 1.34–1.25 (2H, m), 0.85 (3H, t, *J* = 7.2 Hz). FAB-MS *m*/*z*: 424, 422 (MH^+).

4.2.4.6. General procedure for intramolecular Heck cyclization. A de-aerated mixture of the amide **77a–d** (0.14–0.44 mmol), $Pd(OAc)_2$ (3.4–11 mg, 0.015–0.049 mmol, 10 mol%), PCy_3-HBF_4 (5.6–19 mg, 0.015–0.049 mmol, 10 mol%) and Cs_2CO_3 (51–160 mg, 0.16–0.48 mmol, 1.1 equiv) in DMA (0.5–1.5 mL) was stirred at 130 °C for 4 h, then cooled to ambient temperature and diluted with AcOEt. The organic layer was washed with water and brine, dried and concentrated. The product was purified as indicated below.

*4.2.4.6.1. Methyl 5-butyl-4-oxo-2,3,4,5-tetrahydro-1H-cyclopenta[c]quinoline-8-carboxylate (**78a**).* Column chromatography (*n*-hexane/AcOEt = 94/6 to 52/48) gave the title compound (91.0 mg, 0.304 mmol, 72% yield) as a colorless solid. ^{1}H NMR ($CDCl_3$) δ: 8.12 (1H, d, *J* = 1.7 Hz), 8.07 (1H, dd, *J* = 8.6, 1.7 Hz), 7.30 (1H, d, *J* = 8.6 Hz), 4.24 (2H, t, *J* = 7.4 Hz), 3.89 (3H, s), 3.11 (2H, t, *J* = 6.9 Hz), 2.92 (2H, t, *J* = 6.9 Hz), 2.14 (2H, tt, *J* = 6.9, 6.9 Hz), 1.69–1.61 (2H, m), 1.47–1.39 (2H, m), 0.94 (3H, t, *J* = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 166.36, 160.61, 150.16, 141.99, 133.81, 129.96, 127.52, 123.04, 119.23, 114.23, 52.08, 42.01, 32.19, 31.23, 29.66, 22.43, 20.15, 13.72. FAB-MS *m*/*z*: 300 (MH^+).

*4.2.4.6.2. Methyl 5-butyl-6-oxo-5,6,7,8,9,10-hexahydrophenanthridine-2-carboxylate (**78b**).* Column chromatography (*n*-hexane/AcOEt = 97/3 to 68/32) gave the title compound (74.5 mg, 0.238 mmol, 83% yield) as a colorless solid. ^{1}H NMR ($CDCl_3$) δ: 8.43 (1H, d, *J* = 1.7 Hz), 8.13 (1H, dd, *J* = 9.2, 1.7 Hz), 7.37 (1H, d, *J* = 9.2 Hz), 4.32 (2H, t, *J* = 8.0 Hz), 3.95 (3H, s), 2.92 (2H, tt, *J* = 6.3, 1.7 Hz), 2.67 (2H, tt, *J* = 5.7, 1.7 Hz), 1.92–1.86 (2H, m), 1.85–1.79 (2H, m), 1.75–1.69 (2H, m), 1.53–1.46 (2H, m), 1.00 (3H, t, *J* = 6.9 Hz). ^{13}C NMR ($CDCl_3$) δ: 166.73, 162.00, 142.04, 140.49, 129.75, 129.38, 126.08, 123.08, 121.03, 114.03, 52.19, 42.53, 29.66, 25.56, 24.54, 21.88, 21.86, 20.33, 13.85. FAB-MS *m*/*z*: 314 (MH^+).

*4.2.4.6.3. Methyl 5-butyl-6-oxo-6,7,8,9,10,11-hexahydro-5H-cyclohepta[c]quinoline-2-carboxylate (**78c**).* Column chromatography (*n*-hexane/AcOEt = 97/3 to 76/24) gave the title compound (91.8 mg, 0.280 mmol, 64% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 8.49 (1H, d, *J* = 1.7 Hz), 8.08 (1H, dd, *J* = 8.6, 1.7 Hz), 7.32 (1H, d, *J* = 8.6 Hz), 4.27 (2H, t, *J* = 8.0 Hz), 3.92 (3H, s), 3.07–2.98 (4H, m), 1.90–1.84 (2H, m), 1.72–1.62 (4H, m), 1.59–1.53 (2H, m), 1.50–1.42 (2H, m), 0.96 (3H, t, *J* = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 166.64, 161.73, 148.64, 141.06, 134.31, 129.85, 126.82, 123.05, 120.19, 114.22, 52.11, 43.08, 32.07, 29.48, 28.02, 26.53, 25.76, 25.31, 20.25, 13.75. FAB-MS *m*/*z*: 328 (MH^+).

*4.2.4.6.4. Methyl 5-butyl-6-oxo-5,6,7,8,9,10,11,12-octahydrocycloocta[c]quinoline-2-carboxylate (**78d**).* Column chromatography (*n*-hexane/AcOEt = 97/3 to 76/24) gave the title compound (27.4 mg, 0.0803 mmol, 56% yield) as a colorless oil. ^{1}H NMR

($CDCl_3$) δ: 8.44 (1H, d, J = 1.7 Hz), 8.09 (1H, dd, J = 8.6, 1.7 Hz), 7.33 (1H, d, J = 8.6 Hz), 4.29 (2H, t, J = 8.0 Hz), 3.92 (3H, s), 3.10 (2H, t, J = 6.3 Hz), 2.91 (2H, t, J = 5.7 Hz), 1.85–1.78 (2H, m), 1.74–1.66 (4H, m), 1.51–1.41 (6H, m), 1.38–1.22 (2H, m), 0.97 (3H, t, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 166.67, 161.40, 145.22, 141.25, 132.56, 129.77, 127.18, 123.14, 119.93, 114.26, 52.15, 42.82, 29.88, 29.61, 29.57, 27.24, 26.58, 26.54, 25.91, 20.26, 13.78. FAB-MS m/z: 342 (MH^+).

4.2.4.7. General procedure for the ester hydrolysis of cycloalkaquinolinones. A solution of ester **78a–d** (0.080–0.30 mmol) in THF (2 or 4 mL) and MeOH (1 or 2 mL) was treated with 0.5 M aqueous NaOH (0.5 or 1 mL). The mixture was stirred at ambient temperature overnight, acidified by the addition of hydrochloric acid, and then extracted with $CHCl_3$/*i*PrOH = 3/1. The organic layer was washed with water and brine, dried, and concentrated. The product was purified as indicated below.

*4.2.4.7.1. 5-Butyl-4-oxo-2,3,4,5-tetrahydro-1H-cyclopenta[c]quinoline-8-carboxylic acid (**79a**).* Recrystallization (CH_2Cl_2/MeOH) gave the title compound (69.0 mg, 0.248 mmol, 80% yield) as a colorless solid. ^{1}H NMR ($CDCl_3$/CD_3OD) δ: 8.26 (1H, d, J = 1.7 Hz), 8.19 (1H, dd, J = 9.2, 1.7 Hz), 7.42 (1H, d, J = 9.2 Hz), 4.34 (2H, t, J = 8.0 Hz), 3.20 (2H, t, J = 7.5 Hz), 3.00 (2H, t, J = 7.5 Hz), 2.22 (2H, tt, J = 7.5, 7.5 Hz), 1.77–1.69 (2H, m), 1.54–1.46 (2H, m), 1.01 (3H, t, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$/CD_3OD) δ: 168.30, 161.06, 150.80, 141.99, 133.65, 130.48, 128.06, 123.42, 119.37, 114.45, 42.24, 32.23, 31.17, 29.71, 22.50, 20.16, 13.72. FAB-MS m/z: 286 (MH^+).

*4.2.4.7.2. 5-Butyl-6-oxo-5,6,7,8,9,10-hexahydrophenanthridine-2-carboxylic acid (**79b**).* The acid, obtained as a colorless solid (71.7 mg, 0.240 mmol, 100% yield), was subjected to the next reaction without further purification. ^{1}H NMR ($CDCl_3$) δ: 8.51 (1H, d, J = 1.7 Hz), 8.20 (1H, dd, J = 8.6, 1.7 Hz), 7.41 (1H, d, J = 8.6 Hz), 4.34 (2H, t, J = 7.5 Hz), 2.94 (2H, t, J = 6.3 Hz), 2.68 (2H, t, J = 6.3 Hz), 1.93–1.87 (2H, m), 1.87–1.79 (2H, m), 1.77–1.70 (2H, m), 1.55–1.47 (2H, m), 1.01 (3H, t, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 170.21, 162.03, 142.05, 141.06, 130.26, 129.54, 126.85, 121.98, 121.11, 114.18, 42.60 29.65, 25.52, 24.53, 21.85, 21.82, 20.31, 13.84. FAB-MS m/z: 300 (MH^+).

*4.2.4.7.3. 5-Butyl-6-oxo-6,7,8,9,10,11-hexahydro-5H-cyclohepta[c]quinoline-2-carboxylic acid (**79c**).* Reprecipitation ($CHCl_3$/MeOH) gave the title compound (78.2 mg, 0.250 mmol, 90% yield) as a colorless solid. ^{1}H NMR (DMSO-d_6) δ: 8.44 (1H, d, J = 1.7 Hz), 8.07 (1H, dd, J = 9.2, 1.7 Hz), 7.62 (1H, d, J = 9.2 Hz), 4.27 (2H, t, J = 7.5 Hz), 3.31 (3H, s), 3.08–3.02 (2H, m), 2.97–2.92 (2H, m), 1.88–1.81 (2H, m), 1.65–1.54 (4H, m), 1.51–1.44 (2H, m), 1.43–1.35 (2H, m), 0.93 (3H, t, J = 6.9 Hz). ^{13}C NMR (DMSO-d_6) δ: 171.01, 160.70, 148.26, 140.54, 133.43, 130.12, 126.12, 123.78, 119.31, 115.07, 42.22, 31.52, 29.22, 27.31, 25.90, 25.48, 24.92, 19.62, 13.72. FAB-MS m/z: 314 (MH^+).

*4.2.4.7.4. 5-Butyl-6-oxo-5,6,7,8,9,10,11,12-octahydrocycloocta[c]quinoline-2-carboxylic acid (**79d**).* Recrystallization (CH_2Cl_2/*n*-hexane) gave the title compound (21.1 mg, 0.0644 mmol, 80% yield) as a colorless solid. ^{1}H NMR ($CDCl_3$/CD_3OD) δ: 8.53 (1H, br s), 8.17 (1H, d, J = 9.2 Hz), 7.40 (1H, d, J = 9.2 Hz), 4.34 (2H, t, J = 7.5 Hz), 3.15 (2H, t, J = 6.3 Hz), 2.95 (2H, t, J = 5.2 Hz), 1.89–1.81 (2H, m), 1.78–1.70 (4H, m), 1.55–1.44 (4H, m), 1.42–1.36 (2H, m), 1.01 (3H, t, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$/CD_3OD) δ: 168.72, 161.60, 145.63, 141.23, 132.36, 130.19, 127.65, 123.24, 119.96, 114.36, 42.91, 29.80, 29.58, 29.53, 27.17, 26.55, 26.50, 25.87, 20.19, 13.72. FAB-MS m/z: 328 (MH^+).

4.2.4.8. General procedure for the synthesis of cycloalkaquinoline carboxamide derivatives. To a solution of acid **79a–d** (0.064–0.12 mmol) and DMF (50–100 μL) in CH_2Cl_2 (1 mL) was added oxalyl chloride (16–33 μL, 0.19–0.38 mmol, 3 equiv) at ambient temperature. The whole was stirred at this temperature for 10 min, then diethylamine (33–67 μL, 0.32–0.65 mmol, 5 equiv) and triethylamine (44–90 μL, 0.32–0.65 mmol, 5 equiv) were added. The mixture was stirred at ambient temperature for 30 min, then diluted with ethyl acetate. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The product was purified as indicated below.

*4.2.4.8.1. 5-Butyl-N,N-diethyl-4-oxo-2,3,4,5-tetrahydro-1H-cyclopenta[c]quinoline-8-carboxamide (**30**).* Column chromatography (*n*-hexane/AcOEt = 88/12 to 4/96) gave the title compound (32.9 mg, 0.0966 mmol, 89% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 7.55 (1H, d, J = 2.3 Hz), 7.50 (1H, dd, J = 8.6, 2.3 Hz), 7.33 (1H, d, J = 8.6 Hz), 4.27 (2H, t, J = 8.0 Hz), 3.42 (4H, br s), 3.09 (2H, t, J = 7.5 Hz), 2.95 (2H, t, J = 7.5 Hz), 2.16 (2H, tt, J = 7.5, 7.5 Hz), 1.71–1.64 (2H, m), 1.49–1.40 (2H, m), 1.19 (6H, br s), 0.96 (3H, t, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 170.55, 160.64, 149.82, 139.50, 133.96, 130.23, 127.50, 123.99, 119.50, 114.37, 43.26, 41.96, 39.47, 32.15, 31.29, 29.75, 22.56, 20.22, 14.01, 13.79, 13.21. FAB-MS m/z: 341 (MH^+). HRMS (FAB, $[M+H]^+$) calcd for $C_{21}H_{29}N_2O_2$ 341.2229, found 341.2258.

*4.2.4.8.2. 5-Butyl-N,N-diethyl-6-oxo-5,6,7,8,9,10-hexahydrophenanthridine-2-carboxamide (**31**).* Column chromatography (n-hexane/AcOEt = 88/12 to 4/96) gave the title compound (31.4 mg, 0.0886 mmol, 91% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 7.77 (1H, d, J = 1.7 Hz), 7.53 (1H, dd, J = 8.6, 1.7 Hz), 7.36 (1H, d, J = 8.6 Hz), 4.31 (2H, t, J = 8.0 Hz), 3.57 (2H, br s), 3.34 (2H, br s), 2.86 (2H, t, J = 6.3 Hz), 2.67 (2H, t, J = 6.3 Hz), 1.90–1.85 (2H, m), 1.82–1.80 (2H, m), 1.75–1.69 (2H, m), 1.53–1.47 (2H, m), 1.40–1.07 (6H, brm), 1.00 (3H, t, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 170.96, 161.91, 141.63, 137.89, 130.30, 129.50, 127.25, 122.42, 121.23, 114.15, 43.65, 42.43, 39.61, 29.75, 25.61, 24.66, 22.01, 21.96, 20.41, 14.50, 13.94, 12.98. FAB-MS m/z: 355 (MH^+). FAB-MS m/z: 341 (MH^+). HRMS (FAB, $[M+H]^+$) calcd for $C_{22}H_{31}N_2O_2$ 355.2386, found 355.2383.

*4.2.4.8.3. 5-Butyl-N,N-diethyl-6-oxo-6,7,8,9,10,11-hexahydro-5H-cyclohepta[c]quinoline-2-carboxamide (**32**).* Column chromatography (*n*-hexane/AcOEt = 88/12 to 4/96) gave the title compound (39.3 mg, 0.107 mmol, 91% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 7.85 (1H, d, J = 1.7 Hz), 7.48 (1H, dd, J = 8.6, 1.7 Hz), 7.31 (1H, d, J = 8.6 Hz), 4.27 (2H, t, J = 7.5 Hz), 3.41 (4H, br s), 3.04–2.97 (4H, m), 1.89–1.83 (2H, m), 1.73–1.60 (4H, m), 1.59–1.53 (2H, m), 1.50–1.41 (2H, m), 1.19 (6H, br s), 0.96 (3H, t, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 170.85, 161.60, 148.21, 138.47, 134.36, 130.10, 127.25, 123.26, 120.42, 114.18, 43.11, 42.92, 39.94, 32.04, 29.50, 28.01, 26.50, 25.81, 25.24, 20.27, 13.78, 13.61 (2C). FAB-MS m/z: 369 (MH^+). FAB-MS m/z: 341 (MH^+). HRMS (FAB, $[M+H]^+$) calcd for $C_{23}H_{33}N_2O_2$ 369.2542, found 369.2532.

*4.2.4.8.4. 5-Butyl-N,N-diethyl-6-oxo-5,6,7,8,9,10,11,12-octahydrocyclooctacycloocta[c]quinoline-2-carboxamide (**33**).* Column chromatography (*n*-hexane/AcOEt = 92/8 to 36/64) gave the title compound (23.4 mg, 0.0612 mmol, 95% yield) as colorless cubes (recrystallized from CH_2Cl_2/*n*-hexane, mp 91.1–92.0 °C). ^{1}H NMR ($CDCl_3$) δ: 7.82 (1H, d, J = 1.7 Hz), 7.53 (1H, dd, J = 8.6, 1.7 Hz), 7.36 (1H, d, J = 8.6 Hz), 4.32 (2H, t, J = 7.5 Hz), 3.56 (2H, br s), 3.36 (2H, br s), 3.08 (2H, t, J = 6.3 Hz), 2.95 (2H, t, J = 6.3 Hz), 1.84–1.78 (2H, m), 1.77–1.49 (4H, m), 1.53–1.46 (4H, m), 1.42–1.35 (2H, m), 1.24 (6H, br s), 1.01 (3H, t, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$) δ: 170.81, 161.28, 144.76, 138.66, 132.60, 130.21, 127.33, 123.48, 120.08, 114.31, 43.40, 42.67, 39.58, 29.88, 29.59, 29.52, 27.20, 26.58 (2C), 26.00, 20.29, 14.29, 13.81, 12.89. FAB-MS m/z: 383 (MH^+). Anal. Calcd for $C_{24}H_{34}N_2O_2$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.30; H, 8.89; N, 7.26.

4.2.5. Synthesis of the 5,6,7,8,9,10-hexahydrophenanthridine derivative

4.2.5.1. Methyl 4-butyramidobenzoate (80). To a vigorously stirred mixture of methyl 4-aminobenzoate (3037 mg, 20.09 mmol) in

CH_2Cl_2 (50 mL) and saturated aqueous $NaHCO_3$ (50 mL) at 0 °C was added butyryl chloride (2700 μL, 25.85 mmol). Stirring was continued for 11 h at ambient temperature. The biphasic mixture was separated and the organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated. The residue was recrystallized from CH_2Cl_2/*n*-hexane to afford the title compound (3190 mg, 14.42 mmol, 72% yield) as colorless needles. ^{1}H NMR ($CDCl_3$) δ: 7.96 (2H, d, J = 8.9 Hz), 7.65 (1H, br s), 7.59 (2H, d, J = 8.9 Hz), 3.87 (3H, s), 2.34 (2H, t, J = 7.5 Hz), 1.73 (2H, tq, J = 7.5, 7.5 Hz), 0.97 (3H, t, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 171.66, 166.65, 142.20, 130.77 (2C), 125.36, 118.75 (2C), 52.00, 39.67, 18.88, 13.68. FAB-MS *m*/*z*: 222 (MH^+).

4.2.5.2. (2-Bromocyclohex-1-en-1-yl)methanol (81). To a solution of **73b** (1148 mg, 6.074 mmol) in THF (20 mL) and MeOH (10 mL) was added $CeCl_3{\cdot}7H_2O$ (3409 mg, 9.151 mmol) and $NaBH_4$ (711.4 mg, 18.81 mmol). The whole was stirred at ambient temperature for 1 h, then partitioned between ethyl acetate and water, and the water layer was extracted with ethyl acetate. The combined organic layer was washed with water and brine, dried and concentrated. Column chromatography (*n*-hexane/AcOEt = 98/2 to 84/16) of the residue gave the title compound (1097 mg, 5.740 mmol, 95% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 4.21 (2H, s), 2.52–2.46 (2H, m), 2.27–2.21 (2H, m), 1.72–1.64 (4H, m).^{13}C NMR ($CDCl_3$) δ: 135.30, 121.49, 66.31, 36.62, 29.13, 24.62, 22.24. FAB-MS *m*/*z*: 192 (MH^+).

4.2.5.3. Methyl 4-(*N*-((2-bromocyclohex-1-en-1-yl)methyl)butyramido)benzoate (82). To a solution of **81** (189.6 mg, 0.9923 mmol) and triethylamine (210 μL, 1.52 mmol) in CH_2Cl_2 (1 mL) was added methanesulfonyl chloride (120 μL, 1.55 mmol) at 0 °C. The mixture was stirred at this temperature for 6 h, then water was added and the whole was extracted with ethyl acetate. The organic layer was washed with water and brine, dried and concentrated. The mixture of the mesylate and the chloride was subjected to the next reaction without further purification. To a solution of the crude product in dry DMF (300 μL) was added NaH (42.3 mg, 1.06 mmol, ca. 60%) and the whole was stirred at ambient temperature for 1 h. Then TBAI (39.2 mg, 0.106 mmol) and the mixture of the mesylate and the chloride in dry DMF (600 μL) were added and stirring was continued at 90 °C for 2 h. The whole was diluted with ethyl acetate. The organic layer was washed with water and brine, dried and concentrated. Column chromatography (*n*-hexane/AcOEt = 96/4 to 68/32) of the residue gave the title compound (196.7 mg, 0.4988 mmol, 50% for 2 steps) as a pale-yellow oil. ^{1}H NMR ($CDCl_3$) δ: 8.08 (2H, d, J = 8.0 Hz), 7.21 (2H, d, J = 8.0 Hz), 4.63 (2H, s), 3.94 (3H, s), 2.37 (2H, br s), 2.14 (2H, br s), 2.06 (2H, t, J = 7.5 Hz), 1.66–1.56 (6H, m), 0.83 (3H, t, J = 6.9 Hz).^{13}C NMR ($CDCl_3$) δ: 172.69, 166.25, 145.88, 131.14, 130.71 (2C), 129.43, 128.23 (2C), 123.41, 52.61, 52.27, 36.65, 36.26, 29.05, 24.55, 22.17, 18.84, 13.74. FAB-MS *m*/*z*: 396, 394 (MH^+).

4.2.5.4. Methyl 5-butyryl-5,6,7,8,9,10-hexahydrophenanthridine-2-carboxylate (83). A de-aerated mixture of **82** (104.8 mg, 0.2658 mmol), $Pd(OAc)_2$ (6.4 mg, 0.029 mmol), $PCy_3{\cdot}HBF_4$ (11.0 mg, 0.0285 mmol) and Cs_2CO_3 (91.7 mg, 0.281 mmol) in DMA (1 mL) was stirred at 150 °C for 7 h, then cooled to ambient temperature and diluted with AcOEt. The organic layer was washed with water and brine, dried and concentrated. Column chromatography (*n*-hexane/AcOEt = 96/4 to 68/32) of the residue gave the title compound (52.6 mg, 0.168 mmol, 63% yield) as a colorless solid. ^{1}H NMR ($CDCl_3$) δ: 7.88 (1H, d, J = 1.7 Hz), 7.83 (1H, dd, J = 8.6, 1.7 Hz), 7.21 (1H, br s), 4.21 (2H, s), 3.90 (3H, s), 2.44 (2H, t, J = 7.5 Hz), 2.42–2.38 (2H, m), 2.18–2.13 (2H, m), 1.81–1.72 (2H, m), 1.71–1.63 (4H, m), 0.89 (3H, t, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 172.72, 166.79, 139.99, 135.00, 131.59, 127.22, 126.70, 125.87, 123.49, 123.16, 52.12, 45.92, 36.09, 28.12, 24.27, 22.41, 22.08, 19.34, 13.79. FAB-MS *m*/*z*: 314 (MH^+).

4.2.5.5. 5-Butyryl-5,6,7,8,9,10-hexahydrophenanthridine-2-carboxylic acid (84). A solution of **83** (51.1 mg, 0.163 mmol) in THF (2 mL) and MeOH (1 mL) was treated with 0.5 M aqueous NaOH (0.5 mL). The mixture was stirred at ambient temperature for 6 h and diluted with water and 0.5 M aqueous NaOH. The whole was washed with CH_2Cl_2, acidified with hydrochloric acid, and extracted with $CHCl_3$/*i*PrOH = 3/1. The organic layer was washed with water and brine, dried, and concentrated. Recrystallization (CH_2Cl_2/*n*-hexane) gave the title compound (28.3 mg, 0.0945 mmol, 58%) as a pale-yellow solid. ^{1}H NMR ($CDCl_3$) δ: 7.94 (1H, d, J = 2.0 Hz), 7.90 (1H, dd, J = 8.6, 2.0 Hz), 7.31–7.19 (1H, m), 4.23 (2H, s), 2.46 (2H, t, J = 7.5 Hz), 2.44–2.39 (2H, m), 2.19–2.15 (2H, m), 1.82–1.76 (2H, m), 1.73–1.65 (4H, m), 0.90 (3H, t, J = 6.9 Hz). FAB-MS *m*/*z*: 300 (MH^+).

4.2.5.6. 5-Butyryl-*N*,*N*-diethyl-5,6,7,8,9,10-hexahydrophenanthridine-2-carboxamide (34). A mixture of **84** (26.1 mg, 0.0872 mmol), diethylamine (28 μL, 0.27 mmol) DMAP (11.9 mg, 0.0974 mmol) and EDC (40.5 mg, 0.211 mmol) in CH_2Cl_2 (1.5 mL) was stirred at ambient temperature for 14 h, then diluted with ethyl acetate. The organic layer was washed with water, 2 M aqueous HCl, saturated aqueous $NaHCO_3$, and brine, then dried, and concentrated. Column chromatography (*n*-hexane/AcOEt = 92/8 to 36/64) of the residue gave the title compound (18.4 mg, 0.0519 mmol, 60% yield) as a colorless oil. ^{1}H NMR (CD_3OD) δ: 7.42 (1H, br s), 7.27 (1H, d, J = 1.7 Hz), 7.23 (1H, dd, J = 8.0, 1.7 Hz), 4.21 (2H, br s), 3.54 (2H, br s), 3.33 (2H, br s), 2.51 (2H, t, J = 7.5 Hz), 2.42–2.37 (2H, m), 2.25–2.19 (2H, m), 1.84–1.78 (2H, m), 1.75–1.69 (2H, m), 1.66–1.57 (2H, m), 1.25 (3H, br s), 1.16 (3H, br s), 0.88 (3H, t, J = 6.6 Hz). ^{13}C NMR (CD_3OD) δ: 174.79, 173.23, 138.00, 135.30, 133.44, 128.60, 127.23, 125.21, 125.03, 121.33, 45.02 (2C), 40.97, 36.71, 29.06, 25.31, 23.62, 23.27, 20.20, 14.48, 13.95, 13.04. FAB-MS *m*/*z*: 355 (MH^+). HRMS (FAB, $[M+H]^+$) calcd for $C_{22}H_{31}N_2O_2$ 355.2386, found 355.2376.

4.2.6. Synthesis of dibenzoxazepinone derivatives

4.2.6.1. Methyl 11-oxo-10,11-dihydrodibenzo[*b*,*f*][1,4]oxazepine-7-carboxylate (86). 2-Fluorobenzoyl chloride (533 μL, 4.50 mmol) was added to a solution of methyl 4-amino-3-hydroxybenzoate (502 mg, 3.00 mmol) in CH_2Cl_2 (15 mL) and saturated aqueous $NaHCO_3$ at 0 °C. The reaction mixture was stirred for 20 h at rt, then acidified with hydrochloric acid, and extracted with $CHCl_3$ + MeOH. The organic phase was washed with brine, dried over $MgSO_4$ and concentrated. The crude amide was used for the next reaction without further purification. In the next step, DMF (15 mL) was added to the crude amide (1.07 g), K_2CO_3 (1.24 g, 9.00 mmol). The reaction mixture was stirred for 2 h at 150 °C, then cooled to rt, washed with H_2O and brine, dried over $MgSO_4$ and concentrated. The resulting residue was purified by silica gel chromatography (AcOEt/hexane = 1/13) and recrystallization ($CHCl_3$ + MeOH) to afford **13** (287 mg, 269 μmol, 36%) as colorless needles. ^{1}H NMR ($CDCl_3$) δ: 8.03 (1H, s), 7.96–7.94 (2H, m), 7.83 (1H, dd, J = 8.3, 2.0 Hz), 7.58–7.54 (1H, m), 7.29–7.27 (2H, m), 7.05 (1H, d, J = 7.4 Hz), 3.92 (3H, s). FAB-MS *m*/*z*: 270 $(M+H)^+$.

4.2.6.2. Methyl 10-butyl-11-oxo-10,11-dihydrodibenzo[*b*,*f*]-[1,4]oxazepine-7-carboxylate (87). Butyl iodide (66.0 μL, 585 μmol) was added to a suspension of **86** (105 mg, 390 μmol), Cs_2CO_3 (389 mg, 1.19 mmol) in DMF (4.0 mL) at ambient temperature. The reaction mixture was stirred for 1.5 h at 90 °C. The reaction was quenched with H_2O diluted with AcOEt. The organic phase was separated, washed with H_2O and brine, dried over Mg_2SO_4, and concentrated. The resulting residue was purified by silica gel

chromatography (AcOEt/hexane = 1/10 to 1/5) to afford the title compound (111 mg, 341 μmol, 87%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.92 (1H, d, J = 1.7 Hz), 7.86 (1H, dd, J = 8.6, 2.3 Hz), 7.84 (1H, dd, J = 7.4, 1.1 Hz), 7.47–7.44 (1H, m), 7.34 (1H, d, J = 8.6 Hz), 7.24–7.21 (2H, m), 4.15 (2H, br s), 3.92 (3H, s), 1.73–1.67 (2H, m), 1.42–1.33 (2H, m), 0.91 (3H, t, J = 7.4 Hz). FAB-MS m/z: 325 $(M)^+$, 326 $(M+H)^+$.

4.2.6.3. 10-Butyl-*N*,*N*-diethyl-11-oxo-10,11-dihydrodibenzo[*b*,*f*]-[1,4]oxazepine-7-carboxamide (35). Aqueous 5 N NaOH (320 μL, 1.60 mmol) was added to a solution of **87** (63.5 mg, 195 μmol) in MeOH (0.8 mL) at ambient temperature. The reaction mixture was stirred for 3 h at 70 °C, then acidified with hydrochloric acid, extracted with $CHCl_3$, dried over Na_2SO_4 and concentrated. The crude acid was used for the next reaction without further purification. In the next step, $HNEt_2$ (51 μL, 492 μmol) was added to a solution of the crude acid, EDC (47.0 mg, 246 μmol) and HOBt (33.0 mg, 246 μmol) in DMF (1.0 mL) at ambient temperature. The reaction mixture was stirred for 19 h at this temperature, then quenched with H_2O and diluted with ethyl acetate. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated. The resulting residue was purified by column chromatography (AcOEt/hexane = 1/1) to afford **35** (70.0 mg, 191 μmol, 98%) as a white oil. ^{1}H NMR ($CDCl_3$) δ: 7.86 (1H, dd, J = 7.4, 1.7 Hz), 7.45–7.42 (1H, m), 7.32–7.30 (2H, m), 7.24–7.20 (2H, m), 7.17 (1H, d, J = 7.4 Hz), 4.14 (2H, t, J = 7.2 Hz), 3.41 (4H, hrs), 1.76–1.70 (2H, m), 1.44–1.37 (2H, m), 1.20 (6H, s), 0.94 (3H, t, J = 7.4 Hz). FAB-MS m/z: 367 $(MH)^+$. HRMS (FAB, $[M+H]^+$) calcd for $C_{22}H_{27}N_2O_3$ 367.2022, found 367.2028.

4.2.7. Synthesis of 2-oxo-1,2,3,4-tetrahydroquinoline derivatives

4.2.7.1. 6-Bromo-3,4-dihydroquinolin-2(1*H*)-one (89). To a solution of 3,4-dihydro-2(1*H*)-quinolinone (454.8 mg, 3.090 mmol) in DMF (5 mL) was added *N*-bromosuccinimide (587.1 mg, 3.299 mmol) in DMF (5 mL) at 0 °C. The mixture was then allowed to warm to ambient temperature, stirred for 9 h, and diluted with ethyl acetate. The organic layer was washed with water and brine, dried, and concentrated. The residue was recrystallized from ethanol/water to yield the title compound (385.5 mg, 1.705 mmol) as an off-white solid. ^{1}H NMR ($CDCl_3$) δ: 8.56 (1H, br s), 7.30–7.26 (2H, m), 6.68 (1H, d, J = 8.0 Hz), 2.96 (2H, t, J = 7.5 Hz), 2.63 (2H, t, J = 8.0 Hz). ^{13}C NMR ($CDCl_3$) δ: 171.37, 136.34, 130.85, 130.39, 125.71, 116.84, 115.45, 30.32, 25.14.

4.2.7.2. Phenyl 2-oxo-1,2,3,4-tetrahydroquinoline-6-carboxylate (90). A de-aerated mixture of **89** (49.2 mg, 0.218 mmol), phenyl formate (51.3 mg, 0.420 mmol), tributylamine (95 μL, 0.40 mmol), $Pd(OAc)_2$ (5.2 mg, 0.023 mmol) and $P(tBu)_3{\cdot}HBF_4$ (26.6 mg, 0.0917 mmol) in NMP (600 μL) was stirred at 150 °C for 4 h, then cooled to ambient temperature and diluted with AcOEt. The organic layer was washed with water, 2 N aqueous HCl and brine, then dried and concentrated. Column chromatography (*n*-hexane/AcOEt = 94/6 to 52/48) of the residue gave the title compound (28.0 mg, 0.105 mmol, 48% yield) as a colorless solid. ^{1}H NMR ($CD_3OD/CDCl_3$) δ: 8.01 (1H, d, J = 1.7 Hz), 7.99 (1H, dd, J = 8.6, 1.7 Hz), 7.43 (2H, dd, J = 8.0, 7.5 Hz), 7.27 (1H, t, J = 7.5 Hz), 7.19 (2H, d, J = 8.0 Hz), 6.99 (1H, d, J = 8.6 Hz), 3.05 (2H, t, J = 6.9 Hz), 2.63 (2H, t, J = 6.9 Hz). ^{13}C NMR ($CD_3OD/CDCl_3$) δ: 173.79, 166.30, 152.46, 144.11, 130.97 (2C), 130.51 (2C), 126.91, 125.39, 124.88, 122.84 (2C), 116.43, 31.26, 25.96. FAB-MS m/z: 268 (MH^+).

4.2.7.3. Phenyl 1-butyl-2-oxo-1,2,3,4-tetrahydroquinoline-6-carboxylate (91). To a suspension of **90** (28.3 mg, 0.106 mmol) and Cs_2CO_3 (54.8 mg, 0.155 mmol) in DMF (500 μL) was added butyl iodide (23 μL, 0.20 mmol). The whole was stirred at ambient temperature for 3 h and diluted with AcOEt. The organic layer was washed with water and brine, dried and concentrated. Column chromatography (*n*-hexane/AcOEt = 95/5 to 60/40) of the residue gave the title compound (30.6 mg, 0.0946 mmol, 89% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 8.10 (1H, dd, J = 8.0, 2.3 Hz), 8.01 (1H, d, J = 2.3 Hz), 7.44 (2H, dd, J = 7.5, 7.5 Hz), 7.31–7.26 (1H, m), 7.21 (2H, d, J = 7.5 Hz), 7.09 (1H, d, J = 8.0 Hz), 3.99 (2H, t, J = 7.5 Hz), 2.99 (2H, t, J = 7.5 Hz), 2.70 (2H, t, J = 7.5 Hz), 1.69–1.61 (2H, m), 1.46–1.37 (2H, m), 0.98 (3H, t, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 170.05, 164.65, 150.92, 144.20, 130.05, 129.88, 129.50 (2C), 126.48, 125.87, 123.42, 121.71 (2C), 114.64, 42.09, 31.60, 29.19, 25.38, 20.11, 13.81. FAB-MS m/z: 324 (MH^+).

4.2.7.4. 1-Butyl-2-oxo-1,2,3,4-tetrahydroquinoline-6-carboxylic acid (92). A solution of **91** (47.8 mg, 0.148 mmol) in dioxane (1.5 mL) was treated with 30% aqueous H_2O_2 (400 μL) and 2 M aqueous NaOH (400 μL). The mixture was stirred at ambient temperature for 1 h, then 2 M aqueous $Na_2S_2O_3$ was added. The whole was acidified with hydrochloric acid, and extracted with $CHCl_3$/*i*PrOH = 4/1. The organic layer was washed with water and brine, dried, and concentrated. Recrystallization (CH_2Cl_2/*n*-hexane) gave the title compound (36.3 mg, 0.147 mmol, 99% yield) as a colorless solid. ^{1}H NMR ($CDCl_3$) δ: 7.98 (1H, d, J = 8.6 Hz), 7.89 (1H, s), 7.04 (1H, d, J = 8.6 Hz), 3.95 (2H, t, J = 8.0 Hz), 2.94 (2H, t, J = 6.9 Hz), 2.67 (2H, t, J = 6.9 Hz), 1.65–1.57 (2H, m), 1.42–1.35 (2H, m), 0.94 (3H, t, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 170.18, 144.33, 130.11, 129.91, 129.63, 126.39, 115.26, 114.60, 42.16, 31.54, 29.19, 25.32, 20.10, 13.80. FAB-MS m/z: 248 (MH^+).

4.2.7.5. 1-Butyl-*N*,*N*-diethyl-2-oxo-1,2,3,4-tetrahydroquinoline-6-carboxamide (36). To a solution of **92** (33.0 mg, 0.133 mmol) and DMF (2 drops) in CH_2Cl_2 (1.5 mL) was added oxalyl chloride (40 μL, 0.47 mmol) at ambient temperature. The mixture was stirred at this temperature for 10 min, then diethylamine (80 μL, 0.78 mmol) and triethylamine (100 μL, 0.721 mmol) were added. The whole was stirred at ambient temperature for 30 min, then diluted with CH_2Cl_2. The organic layer was washed with water and brine, dried and concentrated. Column chromatography (*n*-hexane/AcOEt = 88/12 to 0/100) of the residue gave the title compound (30.8 mg, 0.102 mmol, 76% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 7.24 (1H, dd, J = 8.6, 1.7 Hz), 7.20 (1H, d, J = 1.7 Hz), 6.96 (1H, d, J = 8.6 Hz), 3.90 (2H, t, J = 8.0 Hz), 3.42 (4H, br s), 2.87 (2H, t, J = 7.5 Hz), 2.62 (2H, t, J = 7.5 Hz), 1.62–1.55 (2H, m), 1.40–1.32 (2H, m), 1.78 (6H, t. J = 6.9 Hz), 0.93 (3H, t, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$, 60 °C) δ: 170.78, 169.79, 140.68, 131.40, 126.69, 126.62, 125.81, 114.45, 41.95, 41.52 (2C), 31.75, 29.36, 25.62, 20.09, 13.67, 13.54 (2C). FAB-MS m/z: 303 (MH^+). HRMS (FAB, $[M+H]^+$) calcd for $C_{18}H_{27}N_2O_2$ 303.2073, found 303.2058.

4.2.8. Synthesis of amide derivatives of 5-butyl-6-oxo-6,7,8,9,10,11-hexahydro-5*H*-cyclohepta[*c*]quinoline-2-carboxylic acid

4.2.8.1. General procedure for synthesis of amide derivatives of 5-butyl-6-oxo-6,7,8,9,10,11-hexahydro-5*H*-cyclohepta[*c*]quinoline-2-carboxylic acid (A). To a solution of **79c** (30 mg, 0.10 mmol) and DMF (100 μL) in CH_2Cl_2 (1 mL) was added oxalyl chloride (20 μL, 0.23 mmol) at ambient temperature. The mixture was stirred at this temperature for 10 min, then triethylamine (70 μL, 0.51 mmol) and amine (0.50 mmol) were added. The whole was stirred at ambient temperature for 30 min, then diluted with ethyl acetate. The organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated. The product was purified as indicated below.

4.2.8.2. General procedure for synthesis of amide derivatives of 5-butyl-6-oxo-6,7,8,9,10,11-hexahydro-5*H*-cyclohepta[*c*]quinoline-2-carboxylic acid (B). To a solution of **79c** (30 mg,

0.10 mmol) and DMF (100 μL) in CH_2Cl_2 (1 mL) was added oxalyl chloride (20 μL, 0.23 mmol) at ambient temperature. The mixture was stirred at this temperature for 10 min, then aqueous amine solution (1 mL) was added. The whole was stirred at ambient temperature for 60 min, then diluted with ethyl acetate. The organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated. The product was purified as indicated below.

*4.2.8.2.1. 5-Butyl-6-oxo-6,7,8,9,10,11-hexahydro-5H-cyclohepta[c]quinoline-2-carboxamide (**37**).* This compound was synthesized according to the general procedure B using 28% aqueous ammonia solution. Column chromatography (*n*-hexane/AcOEt = 83/17 to 0/100) gave the title compound (39.3 mg, 0.126 mmol, 99% yield) as colorless cubes (recrystallized from CH_2Cl_2/MeOH/*n*-hexane, mp 222.9–224.0 °C). ^{1}H NMR (DMSO-d_6) δ: 8.42 (1H, d, J = 1.7 Hz), 8.16 (1H, br s), 8.06 (1H, dd, J = 9.2, 1.7 Hz), 7.57 (1H, d, J = 9.2 Hz), 7.40 (1H, br s), 4.27 (2H, t, J = 8.0 Hz), 3.13–3.08 (2H, m), 2.97–2.91 (2H, m), 1.89–1.81 (2H, m), 1.64–1.54 (4H, m), 1.51–1.44 (2H, m), 1.43–1.35 (2H, m), 0.92 (3H, t, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$/CD_3OD) δ: 169.54, 161.83, 149.27, 139.95, 133.94, 127.93, 126.24, 124.87, 120.27, 114.34, 43.02, 31.84, 29.35, 27.77, 26.35, 25.51, 25.13, 20.03, 13.50. FAB-MS m/z: 313 (MH^+). Anal. Calcd for $C_{19}H_{24}N_2O_2 \cdot 1/4H_2O$: C, 72.01; H, 7.79; N, 8.84. Found: C, 72.29; H, 7.63; N, 8.82.

*4.2.8.2.2. N-Methyl-5-butyl-6-oxo-6,7,8,9,10,11-hexahydro-5H-cyclohepta[c]quinoline-2-carboxamide (**38**).* This compound was synthesized according to the general procedure B using 40% aqueous methylamine solution. Column chromatography (*n*-hexane/AcOEt = 83/17 to 0/100) gave the title compound (32.7 mg, 0.100 mmol, quant.) as colorless needles (recrystallized from CH_2Cl_2/*n*-hexane, mp 147.1–148.8 °C). ^{1}H NMR ($CDCl_3$) δ: 8.31 (1H, d, J = 2.3 Hz), 7.79 (1H, dd, J = 9.2, 2.3 Hz), 7.33 (1H, d, J = 9.2 Hz), 6.19 (1H, br s), 4.29 (2H, t, J = 7.5 Hz), 3.04 (3H, d, J = 4.6 Hz), 3.08–3.01 (4H, m), 1.92–1.86 (2H, m), 1.74–1.63 (4H, m), 1.61–1.55 (2H, m), 1.51–1.43 (2H, m), 0.98 (3H, t, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 167.57, 161.73, 148.59, 140.05, 134.60, 127.51, 126.90, 124.32, 120.51, 114.33, 43.10, 32.14, 29.58, 28.08, 26.96, 26.64, 25.85, 25.42, 20.33, 13.84. FAB-MS m/z: 327 (MH^+). Anal. Calcd for $C_{20}H_{26}N_2O_2$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.34; H, 7.89; N, 8.58.

*4.2.8.2.3. N,N′-Dimethyl-5-butyl-6-oxo-6,7,8,9,10,11-hexahydro-5H-cyclohepta[c]quinoline-2-carboxamide (**39**).* This compound was synthesized according to the general procedure B using 40% aqueous dimethylamine solution. Column chromatography (*n*-hexane/AcOEt = 83/17 to 0/100) gave the title compound (31.7 mg, 0.0931 mmol, quant.) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 7.94 (1H, d, J = 1.7 Hz), 7.54 (1H, dd, J = 8.6, 1.7 Hz), 7.33 (1H, d, J = 8.6 Hz), 4.30 (2H, t, J = 7.5 Hz), 3.12 (3H, br s), 3.19–2.99 (7H, br m), 1.91–1.85 (2H, m), 1.75–1.62 (4H, m), 1.61–1.55 (2H, m), 1.52–1.44 (2H, m), 0.99 (3H, t, J = 7.5 Hz). ^{13}C NMR (DMSO-d_6) δ: 169.64, 160.55, 148.21, 138.03, 133.34, 129.60, 128.44, 123.75, 119.29, 114.53, 42.01, 34.95 (2C), 31.55, 29.26, 27.21, 25.87, 25.56, 25.00, 19.65, 13.74. FAB-MS m/z: 341 (MH^+). HRMS (FAB, $[M+H]^+$) calcd for $C_{21}H_{29}N_2O_2$ 341.2229, found 341.2210.

*4.2.8.2.4. N-Ethyl-5-butyl-6-oxo-6,7,8,9,10,11-hexahydro-5H-cyclohepta[c]quinoline-2-carboxamide (**40**).* This compound was synthesized according to the general procedure B using 70% aqueous ethylamine solution. Column chromatography (*n*-hexane/AcOEt = 88/12 to 0/100) gave the title compound (31.8 mg, 0.0934 mmol, 100%) as colorless needles (recrystallized from CH_2Cl_2/*n*-hexane, mp 127.2–129.3 °C). ^{1}H NMR ($CDCl_3$) δ: 8.33 (1H, d, J = 2.3 Hz), 7.79 (1H, dd, J = 8.6, 2.3 Hz), 7.33 (1H, d, J = 8.6 Hz), 6.15 (1H, br s), 4.29 (2H, t, J = 8.0 Hz), 3.56–3.49 (2H, m), 3.09–3.05 (2H, m), 3.04–3.02 (2H, m), 1.92–1.86 (2H, m), 1.74–1.63 (4H, m), 1.61–1.55 (2H, m), 1.51–1.44 (2H, m), 1.27 (3H, t, J = 7.5 Hz), 0.98 (3H, t, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 166.77, 161.73, 148.62, 140.02, 134.58, 127.62, 126.81, 124.42, 120.54, 114.28, 43.09, 35.08, 32.15, 29.58, 28.08, 26.65, 25.85, 25.45, 20.33, 14.99, 13.84. FAB-MS m/z: 341 (MH^+). HRMS (FAB, $[M+H]^+$) calcd for $C_{21}H_{29}N_2O_2$ 341.2229, found 341.2180.

*4.2.8.2.5. 5-Butyl-6-oxo-6,7,8,9,10,11-hexahydro-5H-cyclohepta[c]quinoline-2-carboxylic acid pyrrolidine amide (**41**).* This compound was synthesized according to the general procedure A. Column chromatography (*n*-hexane/AcOEt = 83/17 to 0/100) gave the title compound (29.5 mg, 0.0806 mmol, 90%) as a colorless amorphous solid. ^{1}H NMR ($CDCl_3$) δ: 8.05 (1H, d, J = 1.7 Hz), 7.65 (1H, dd, J = 8.6, 1.7 Hz), 7.32 (1H, d, J = 8.6 Hz), 4.29 (2H, t, J = 7.5 Hz), 3.67 (2H, t, J = 6.9 Hz), 3.49 (2H, t, J = 6.3 Hz), 3.05–3.00 (4H, m), 2.01–1.93 (2H, m), 1.92–1.84 (4H, m), 1.75–1.55 (6H, m), 1.52–1.44 (2H, m), 0.98 (3H, t, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 169.17, 161.72, 148.40, 138.94, 134.37, 130.16, 127.96, 124.45, 120.36, 113.94, 49.86, 46.46, 43.01, 32.11, 29.58, 28.10, 26.58, 26.54, 25.88, 25.36, 24.46, 20.34, 13.84. FAB-MS m/z: 367 (MH^+). HRMS (FAB, $[M+H]^+$) calcd for $C_{23}H_{31}N_2O_2$ 367.2386, found 367.2381.

*4.2.8.2.6. N-n-Propyl-5-butyl-6-oxo-6,7,8,9,10,11-hexahydro-5H-cyclohepta[c]quinoline-2-carboxamide (**42**).* This compound was synthesized according to the general procedure A. Column chromatography (*n*-hexane/AcOEt = 92/8 to 36/64) gave the title compound (27.7 mg, 0.0781 mmol, 83%) as colorless needles (recrystallized from CH_2Cl_2/*n*-hexane, mp 223.6–224.8 °C).^{1}H NMR ($CDCl_3$) δ: 8.33 (1H, d, J = 2.3 Hz), 7.78 (1H, dd, J = 9.2, 2.3 Hz), 7.33 (1H, d, J = 9.2 Hz), 6.16 (1H, br s), 4.29 (2H, t, J = 8.0 Hz), 3.48–3.42 (2H, m), 3.10–3.05 (2H, m), 3.05–3.01 (2H, m), 1.92–1.86 (2H, m), 1.74–1.55 (8H, m), 1.51–1.43 (2H, m), 0.99 (3H, t, J = 7.5 Hz), 0.98 (3H, t, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 166.87, 161.73, 148.62, 140.02, 134.59, 127.68, 126.74, 124.49, 120.56, 114.27, 43.08, 41.89, 32.15, 29.58, 28.09, 26.65, 25.85, 25.44, 23.01, 20.33, 13.84, 11.47. FAB-MS m/z: 355 (MH^+). Anal. Calcd for $C_{22}H_{30}N_2O_2$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.25; H, 8.26; N, 7.78.

*4.2.8.2.7. N-n-Butyl-5-butyl-6-oxo-6,7,8,9,10,11-hexahydro-5H-cyclohepta[c]quinoline-2-carboxamide (**43**).* This compound was synthesized according to the general procedure A. Column chromatography (*n*-hexane/AcOEt = 92/8 to 36/64) gave the title compound (30.0 mg, 0.0815 mmol, 94%) as colorless needles (recrystallized from CH_2Cl_2/*n*-hexane, mp 129.3–131.0 °C).^{1}H NMR ($CDCl_3$) δ: 8.33 (1H, d, J = 1.7 Hz), 7.77 (1H, dd, J = 8.6, 1.7 Hz), 7.33 (1H, d, J = 8.6 Hz), 6.13 (1H, br s), 4.29 (2H, t, J = 8.0 Hz), 3.51–3.46 (2H, m), 3.09–3.05 (2H, m), 3.05–3.01 (2H, m), 1.92–1.86 (2H, m), 1.74–1.55 (8H, m), 1.51–1.38 (4H, m), 0.98 (3H, t, J = 7.5 Hz), 0.96 (3H, t, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$) δ: 166.82, 161.73, 148.61, 140.02, 134.59, 127.67, 126.71, 124.50, 120.57, 114.26, 43.08, 39.94, 32.15, 31.84, 29.58, 28.09, 26.65, 25.86, 25.45, 20.33, 20.19, 13.84, 13.81. FAB-MS m/z: 369 (MH^+). Anal. Calcd for $C_{23}H_{32}N_2O_2$: C, 74.96; H, 8.75; N, 7.60. Found: C, 74.61; H, 8.54; N, 7.51.

*4.2.8.2.8. N-i-Propyl-5-butyl-6-oxo-6,7,8,9,10,11-hexahydro-5H-cyclohepta[c]quinoline-2-carboxamide (**44**).* This compound was synthesized according to the general procedure A. Column chromatography (*n*-hexane/AcOEt = 92/8 to 36/64) gave the title compound (22.1 mg, 0.0623 mmol, 74%) as a colorless powder (recrystallized from CH_2Cl_2/*n*-hexane, mp 121.1–124.1 °C). ^{1}H NMR ($CDCl_3$) δ: 8.33 (1H, d, J = 1.7 Hz), 7.76 (1H, dd, J = 9.2, 1.7 Hz), 7.32 (1H, d, J = 9.2 Hz), 5.92 (1H, d, J = 7.5 Hz), 4.35–4.26 (3H, m), 3.10–3.05 (2H, m), 3.05–3.01 (2H, m), 1.92–1.86 (2H, m), 1.74–1.64 (4H, m), 1.62–1.55 (2H, m), 1.51–1.43 (2H, m), 1.29 (6H, d, J = 6.3 Hz), 0.98 (3H, t, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 166.01, 161.73, 148.64, 139.99, 134.57, 127.75, 126.66, 124.54, 120.57, 114.20, 43.07, 42.08, 32.15, 29.57, 28.09, 26.66, 25.85, 25.46, 22.93 (2C), 20.33, 13.84. FAB-MS m/z: 355 (MH^+). HRMS (FAB, $[M+H]^+$) calcd for $C_{22}H_{31}N_2O_2$ 355.2386, found 355.2397.

*4.2.8.2.9. N-t-Butyl-5-butyl-6-oxo-6,7,8,9,10,11-hexahydro-5H-cyclohepta[c]quinoline-2-carboxamide (**45**).* This compound was

synthesized according to the general procedure A. Column chromatography (*n*-hexane/AcOEt = 95/5 to 60/40) gave the title compound (31.8 mg, 0.0863 mmol, 93%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 8.34 (1H, d, J = 1.7 Hz), 7.71 (1H, dd, J = 8.6, 1.7 Hz), 7.31 (1H, d, J = 8.6 Hz), 5.96 (1H, br s), 4.29 (2H, t, J = 8.0 Hz), 3.09–3.05 (2H, m), 3.05–3.01 (2H, m), 1.91–1.85 (2H, m), 1.73–1.63 (4H, m), 1.61–1.55 (2H, m), 1.49 (9H, s), 1.50–1.44 (2H, m), 0.98 (3H, t, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 166.16, 161.73, 148.70, 139.87, 134.54, 128.55, 126.46, 124.57, 120.59, 114.08, 51.78, 43.05, 32.16, 29.57, 28.95 (3C), 28.06, 26.65, 25.87, 25.45, 20.33, 13.84. FAB-MS *m*/*z*: 369 (MH^+). HRMS (FAB, $[M+H]^+$) calcd for $C_{23}H_{33}N_2O_2$ 369.2542, found 369.2549.

*4.2.8.2.10. N-Phenyl-5-butyl-6-oxo-6,7,8,9,10,11-hexahydro-5H-cyclohepta[c]quinoline-2-carboxamide (**46**).* This compound was synthesized according to the general procedure A. Column chromatography (*n*-hexane/AcOEt = 95/5 to 60/40) gave the title compound (37.5 mg, 0.0965 mmol, 100%) as colorless cubes (recrystallized from CH_2Cl_2/MeOH, mp 199.5–200.6 °C). ^{1}H NMR ($CDCl_3$) δ: 8.41 (1H, d, J = 2.3 Hz), 7.91 (1H, dd, J = 8.6, 2.3 Hz), 7.66 (2H, d, J = 7.5 Hz), 7.40–7.36 (3H, m), 7.16 (1H, d, J = 7.5 Hz), 4.31 (2H, t, J = 8.0 Hz), 3.11–3.07 (2H, m), 3.06–3.02 (2H, m), 1.93–1.87 (2H, m), 1.76–1.65 (4H, m), 1.63–1.56 (2H, m), 1.52–1.45 (2H, m), 0.99 (3H, t, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 165.11, 161.73, 148.52, 140.36, 137.90, 134.86, 129.17 (3C), 127.77, 126.89, 124.75, 124.66, 120.22 (2C), 114.50, 43.14, 32.12, 29.59, 28.13, 26.68, 25.82, 25.41, 20.34, 13.85. FAB-MS *m*/*z*: 389 (MH^+). HRMS (FAB, $[M+H]^+$) calcd for $C_{25}H_{29}N_2O_2$ 389.2229, found 389.2209.

*4.2.8.2.11. N-(2-Hydroxy)ethyl-5-butyl-6-oxo-6,7,8,9,10,11-hexahydro-5H-cyclohepta[c]quinoline-2-carboxamide (**47**).* This compound was synthesized according to the general procedure A. Column chromatography (*n*-hexane/AcOEt = 50/50 to 0/100) gave the title compound (26.2 mg, 0.0735 mmol, 76%) as a colorless powder (recrystallized from CH_2Cl_2/*n*-hexane, mp 182.5–184.0 °C). ^{1}H NMR ($CDCl_3$) δ: 8.33 (1H, d, J = 1.7 Hz), 7.82 (1H, dd, J = 8.6, 1.7 Hz), 7.33 (1H, d, J = 8.6 Hz), 6.65 (1H, t, J = 5.7 Hz), 4.29 (2H, t, J = 8.0 Hz), 3.87 (2H, dt, J = 5.7, 5.7 Hz), 3.67 (2H, dt, J = 4.6, 5.7 Hz), 3.08–3.04 (2H, m), 3.04–3.01 (2H, m), 2.54 (1H, t, J = 4.6 Hz), 1.92–1.86 (2H, m), 1.74–1.63 (4H, m), 1.61–1.55 (2H, m), 1.51–1.44 (2H, m), 0.98 (3H, t, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 167.88, 161.73, 148.59, 140.23, 134.67, 126.98 (2C), 124.57, 120.54, 114.34, 62.56, 43.11, 42.96, 32.13, 29.58, 28.08, 26.66, 25.82, 25.44, 20.33, 13.84. FAB-MS *m*/*z*: 357 (MH^+). Anal. Calcd for $C_{21}H_{28}N_2O_3 \cdot 1/5H_2O$: C, 70.05; H, 7.95; N, 7.78. Found: C, 70.25; H, 7.81; N, 7.73.

*4.2.8.2.12. N-c-Pentyl-5-butyl-6-oxo-6,7,8,9,10,11-hexahydro-5H-cyclohepta[c]quinoline-2-carboxamide (**48**).* This compound was synthesized according to the general procedure A. Column chromatography (*n*-hexane/AcOEt = 92/8 to 36/64) gave the title compound (27.6 mg, 0.0725 mmol, 81%) as a colorless powder (recrystallized from CH_2Cl_2/*n*-hexane, mp 164.1–166.2 °C). ^{1}H NMR ($CDCl_3$) δ: 8.33 (1H, d, J = 1.7 Hz), 7.45 (1H, dd, J = 9.2, 1.7 Hz), 7.32 (1H, d, J = 9.2 Hz), 6.04 (1H, d, J = 7.5 Hz), 4.42 (1H, dt, J = 7.5, 6.9 Hz), 4.29 (2H, t, J = 8.0 Hz), 3.09–3.05 (2H, m), 3.05–3.01 (2H, m), 2.16–2.08 (2H, m), 1.92–1.86 (2H, m), 1.78–1.63 (8H, m), 1.61–1.55 (2H, m), 1.53–1.43 (4H, m), 0.98 (3H, t, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$) δ: 166.49, 161.72, 148.65, 139.98, 134.57, 127.72, 126.65, 124.59, 120.58, 114.19, 51.88, 43.07, 33.31 (2C), 32.15, 29.57, 28.09, 26.65, 25.85, 25.46, 23.86 (2C), 20.33, 13.84. FAB-MS *m*/*z*: 381 (MH^+). Anal. Calcd for $C_{24}H_{32}N_2O_2$: C, 75.75; H, 8.48; N, 7.36. Found: C, 75.47; H, 8.28; N, 7.28.

*4.2.8.2.13. N-c-Hexyl-5-butyl-6-oxo-6,7,8,9,10,11-hexahydro-5H-cyclohepta[c]quinoline-2-carboxamide (**49**).* This compound was synthesized according to the general procedure A. Column chromatography (*n*-hexane/AcOEt = 92/8 to 36/64) gave the title compound (27.1 mg, 0.0687 mmol, 78%) as a colorless powder (recrystallized from CH_2Cl_2/*n*-hexane, mp 184.1–187.8 °C). ^{1}H NMR ($CDCl_3$) δ: 8.32 (1H, d, J = 1.7 Hz), 7.76 (1H, dd, J = 8.6, 1.7 Hz), 7.32 (1H, d, J = 8.6 Hz), 5.96 (1H, d, J = 7.5 Hz), 4.29 (2H, t, J = 8.0 Hz), 4.04–3.94 (1H, m), 3.09–3.05 (2H, m), 3.05–3.01 (2H, m), 2.08–2.01 (2H, m), 1.92–1.85 (2H, m), 1.79–1.63 (8H, m), 1.62–1.55 (2H, m), 1.51–1.39 (4H, m), 1.30–1.19 (2H, m), 0.98 (3H, t, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 165.95, 161.72, 148.64, 139.96, 134.55, 127.90, 126.69, 124.52, 120.56, 114.20, 48.87, 43.06, 33.31 (2C), 32.15, 29.57, 28.10, 26.65, 25.85, 25.58, 25.46, 24.94 (2C), 20.33, 13.84. FAB-MS *m*/*z*: 395 (MH^+). HRMS (FAB, $[M+H]^+$) calcd for $C_{25}H_{35}N_2O_2$ 395.2699, found 395.2735.

*4.2.8.2.14. N-c-Propyl-5-butyl-6-oxo-6,7,8,9,10,11-hexahydro-5H-cyclohepta[c]quinoline-2-carboxamide (**50**).* This compound was synthesized according to the general procedure A. Column chromatography (*n*-hexane/AcOEt = 88/12 to 4/96) gave the title compound (20.5 mg, 0.0582 mmol, 69%) as a colorless powder (recrystallized from CH_2Cl_2/*n*-hexane, mp 177.4–180.5 °C). ^{1}H NMR ($CDCl_3$) δ: 8.30 (1H, d, J = 1.7 Hz), 7.75 (1H, dd, J = 8.6, 1.7 Hz), 7.32 (1H, d, J = 8.6 Hz), 6.26 (1H, br s), 4.29 (2H, t, J = 8.0 Hz), 3.09–3.05 (2H, m), 3.04–3.00 (2H, m), 2.95–2.89 (1H, m), 1.92–1.86 (2H, m), 1.73–1.64 (4H, m), 1.61–1.55 (2H, m), 1.51–1.43 (2H, m), 0.98 (3H, t, J = 7.5 Hz), 0.91–0.86 (2H, m), 0.66–0.62 (2H, m). ^{13}C NMR ($CDCl_3$) δ: 168.20, 161.71, 148.58, 140.12, 134.62, 127.25, 126.83, 124.39, 120.51, 114.27, 43.08, 32.14, 29.57, 28.08, 26.65, 25.84, 25.44, 23.26, 20.32, 13.83, 6.86 (2C). FAB-MS *m*/*z*: 353 (MH^+). Anal. Calcd for $C_{22}H_{28}N_2O_2 \cdot 2/3\ H_2O$: C, 72.50; H, 8.11; N, 7.69. Found: C, 72.29; H, 7.75; N, 7.50.

4.2.8.3. *N*-Alkylation of 50. *4.2.8.3.1. **N**-Methyl-**N′**-**c**-propyl-5-butyl-6-oxo-6,7,8,9,10,11-hexahydro-5**H**-cyclohepta[c]quinoline-2-carboxamide (**51**).* To a solution of **50** (32.0 mg, 0.0908 mmol) in DMF (0.5 mL) was added sodium hydride (8.9 mg, 0.22 mmol, ca. 60%) at ambient temperature. The mixture was stirred at this temperature for 1 h, then methyl iodide (13 μL, 0.21 mmol) was added. The whole was stirred at ambient temperature for 3 h, then diluted with ethyl acetate. The organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated. Column chromatography (*n*-hexane/AcOEt = 83/17 to 0/100) gave the title compound (32.0 mg, 0.0873 mmol, 96%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 8.05 (1H, d, J = 1.7 Hz), 7.67 (1H, d, J = 8.6 Hz), 7.31 (1H, d, J = 8.6 Hz), 4.30 (2H, t, J = 8.0 Hz), 3.11 (3H, s), 3.06–3.00 (4H, m), 2.90–2.85 (1H, m), 1.91–1.85 (2H, m), 1.75–1.56 (6H, m), 1.52–1.44 (2H, m), 0.99 (3H, t, J = 7.5 Hz), 0.63 (2H, br s), 0.49 (2H, br s). ^{13}C NMR (CD_3OD, 60 °C) δ: 174.20, 163.44, 150.89, 140.01, 134.88, 131.99, 129.93, 125.65, 121.51, 115.73, 44.09, 35.98, 34.15, 32.82, 30.82, 28.93, 27.41, 26.89, 26.52, 21.12, 14.05, 9.76 (2C). FAB-MS *m*/*z*: 367 (MH^+). HRMS (FAB, $[M+H]^+$) calcd for $C_{23}H_{31}N_2O_2$ 367.2386, found 367.2407.

*4.2.8.3.2. N-Ethyl-N′-c-propyl-5-butyl-6-oxo-6,7,8,9,10,11-hexahydro-5H-cyclohepta[c]quinoline-2-carboxamide (**52**).* To a solution of **50** (33.6 mg, 0.0953 mmol) in DMF (0.5 mL) was added sodium hydride (8.5 mg, 0.21 mmol, ca. 60%) at ambient temperature. The mixture was stirred at this temperature for 1 h, then ethyl iodide (16 μL, 0.20 mmol) was added. The whole was stirred at ambient temperature for 3 h, then diluted with ethyl acetate. The organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated. Column chromatography (*n*-hexane/AcOEt = 88/12 to 4/96) gave the title compound (21.3 mg, 0.0560 mmol, 59%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 8.01 (1H, d, J = 1.8 Hz), 7.64 (1H, d, J = 8.3 Hz), 7.30 (1H, d, J = 8.3 Hz), 4.30 (2H, t, J = 7.5 Hz), 3.58 (2H, q, J = 6.6 Hz), 3.06–2.99 (4H, m), 2.84–2.79 (1H, m), 1.91–1.85 (2H, m), 1.75–1.55 (6H, m), 1.51–1.44 (2H, m), 1.28 (3H, t, J = 6.6 Hz), 0.99 (3H, t, J = 7.5 Hz), 0.65 (2H, br s), 0.50 (2H, br s). ^{13}C NMR (CD_3OD, 60 °C) δ: 174.10, 163.45, 150.87, 139.89, 134.89, 132.42, 129.71, 125.32, 121.54, 115.74, 44.09, 44.00,

32.83, 32.14, 30.82, 28.93, 27.41, 26.89, 26.53, 21.12, 14.04, 13.57, 10.01 (2C). FAB-MS *m*/*z*: 381 (MH^+). HRMS (FAB, $[M+H]^+$) calcd for $C_{24}H_{33}N_2O_2$ 381.2542, found 381.2506.

4.2.9. Synthesis of the 5-alkyl derivatives of cycloheptaquinolinones

4.2.9.1. *N*-Cyclopropyl-4-iodobenzamide (94). To a suspension of 4-iodobenzoic acid (996.6 mg, 4.018 mmol) and DMF (3 drops) in CH_2Cl_2 (30 mL) was added oxalyl chloride (550 μL, 6.41 mmol) at ambient temperature. The mixture was stirred at this temperature for 40 min, and then cyclopropylamine (1390 μL, 19.96 mmol) was added. Stirring was continued at ambient temperature for 40 min, then water was added. Extraction with ethyl acetate provided an organic layer, which was washed with water and brine, dried over Na_2SO_4 and concentrated. Recrystallization of the residue from CH_2Cl_2/*n*-hexane gave the title compound (1058 mg, 3.686 mmol, 92%) as a colorless solid. ^1H NMR (CD_3OD) δ: 7.81 (2H, d, J = 8.6 Hz), 7.53 (2H, d, J = 8.6 Hz), 2.85–2.79 (1H, m), 0.82–0.75 (2H, m), 0.63–0.60 (2H, m). ^{13}C NMR (CD_3OD) δ: 170.94, 138.85 (2C), 135.06, 130.00 (2C), 99.13, 24.02, 6.51 (2C). FAB-MS *m*/*z*: 288 (MH^+).

4.2.9.2. *N*-Cyclopropyl-*N′*-ethyl-4-iodobenzamide (95). To a solution of **94** (315.3 mg, 1.098 mmol) and DMF (2 mL) was added sodium hydride (93.7 mg, 2.34 mmol, ca. 60%) at ambient temperature. The mixture was stirred at this temperature for 1 h, then ethyl iodide was added. The whole was stirred at 90 °C for 2 h, then diluted with ethyl acetate. The organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated. Column chromatography (*n*-hexane/AcOEt = 94/6 to 52/48) of the residue gave the title compound (299.5 mg, 0.9503 mmol, 87%) as a colorless oil.^1H NMR (CD_3OD) δ: 7.80 (2H, d, J = 8.0 Hz), 7.25 (2H, d, J = 8.0 Hz), 3.57 (2H, br s), 2.86 (1H, br s), 1.25 (3H, br s), 0.63 (2H, br s), 0.48 (2H, br s). ^{13}C NMR (CD_3OD, 60 °C) δ: 174.01, 138.58 (2C), 138.41, 129.89 (2C), 96.21, 43.72, 31.91, 13.42, 9.91 (2C). FAB-MS *m*/*z*: 316 (MH^+).

4.2.9.3. *N*-Cyclopropyl-*N′*-ethyl-4-((2,4-dimethoxybenzyl)-amino)benzamide (96). A suspension of **95** (278.5 mg, 0.8837 mmol), 2,4-dimethoxybenzylamine (290 μL, 1.93 mmol), copper(I) iodide (19.2 mg, 0.101 mmol), tripotassium phosphate 420.7 mg, 1.936 mmol) and ethylene glycol (220 μL, 3.93 mmol) in *n*-butanol (1 mL) was stirred under argon at 100 °C for 12 h, and then diluted with ethyl acetate. The organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated. Column chromatography (*n*-hexane/AcOEt = 88/12 to 4/96) of the residue gave the title compound (268.4 mg, 0.7572 mmol, 86%) as a colorless oil. ^1H NMR (CD_3OD, 60 °C) δ: 7.28 (2H, d, J = 8.8 Hz), 7.15 (1H, d, J = 8.0 Hz), 6.61 (2H, d, J = 8.8 Hz), 6.53 (1H, d, J = 2.3 Hz), 6.43 (1H, dd, J = 8.0, 2.3 Hz), 4.25 (2H, s), 3.83 (3H, s), 3.76 (3H, s), 3.52 (2H, q, J = 6.9 Hz), 2.87–2.82 (1H, m), 1.21 (3H, t, J = 6.9 Hz), 0.71–0.66 (2H, m), 0.51–0.46 (2H, m). FAB-MS *m*/*z*: 355 (MH^+).

4.2.9.4. 2-Bromo-*N*-(4-(cyclopropyl(ethyl)carbamoyl)phenyl)-*N′*-(2,4-dimethoxybenzyl)cyclohept-1-ene-1-carboxamide (97). To a solution of **96** (562.7 mg, 2.568 mmol) and DMF (3 drops) in CH_2Cl_2 (3 mL) was added oxalyl chloride (220 μL, 2.57 mmol) at ambient temperature. The mixture was stirred at this temperature for 10 min, then **74c** (605.9 mg, 1.709 mmol) in CH_2Cl_2 (4.5 mL) and DMAP (315.5 mg, 2.582 mmol) were added. The whole was stirred at 60 °C for 2 h, then diluted with ethyl acetate. The organic layer was washed with water, 2 N aqueous HCl, 2 N aqueous NaOH and brine, dried over Na_2SO_4 and concentrated. Column chromatography (*n*-hexane/AcOEt = 88/12 to 4/96) of the residue gave the title compound (857.9 mg, 1.544 mmol, 90%) as a colorless amorphous solid. ^1H NMR (DMSO-d_6, 100 °C) δ: 7.34 (2H,d, J = 8.0 Hz), 7.20 (2H, d, J = 8.0 Hz), 7.12 (1H, br s), 6.44 (1H, d, J = 2.3 Hz), 6.41 (1H, dd, J = 8.6, 2.3 Hz), 4.84 (2H, br s), 3.71 (3H, s), 3.63 (3H, br s), 3.40 (2H, q, J = 6.9 Hz), 2.77–2.72 (1H, m), 2.51 (2H, br s), 2.17 (2H, br s), 1.59–1.21 (6H, br m), 1.46 (3H, t, J = 6.9 Hz), 0.55–0.50 (2H, m), 0.41–0.37 (2H, m). FAB-MS *m*/*z*: 557, 555 (MH^+).

4.2.9.5. *N*-Cyclopropyl-*N′*-ethyl-5-(2,4-dimethoxybenzyl)-6-oxo-6,7,8,9,10,11-hexahydro-5*H*-cyclohepta[*c*]quinoline-2-carboxamide (98). A suspension of **97** (120.0 mg, 0.2160 mmol), $Pd(OAc)_2$ (5.4 mg, 0.024 mmol), $PCy_3{\cdot}HBF_4$ (9.3 mg, 0.024 mmol) and Cs_2CO_3 (77.2 mg, 0.237 mmol) in DMA (1 mL) was stirred under argon at 130 °C for 4 h, and then diluted with ethyl acetate. The organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated. Column chromatography (*n*-hexane/AcOEt = 88/12 to 4/96) of the residue gave the title compound (72.1 mg, 0.152 mmol, 70%) as a colorless amorphous solid. ^1H NMR (CD_3OD, 60 °C) δ: 8.05 (1H, d, J = 1.2 Hz), 7.54 (1H, dd, J = 8.9, 1.2 Hz), 7.32 (1H, d, J = 8.9 Hz), 6.58–6.55 (2H, m), 6.30 (1H, dd, J = 8.6, 2.3 Hz), 5.49 (2H, s), 3.91 (3H, s), 3.70 (3H, s), 3.54 (2H, q, J = 7.5 Hz), 3.16–3.12 (2H, m), 3.09–3.05 (2H, m), 2.89–2.84 (1H, m), 1.95–1.89 (2H, m), 1.74–1.68 (2H, m), 1.65–1.59 (2H, m), 1.24 (3H, t, J = 7.5 Hz), 0.64–0.58 (2H, m), 0.51–0.45 (2H, m). ^{13}C NMR (CD_3OD, 60 °C) δ: 173.99, 163.97, 161.91, 159.23, 151.26, 140.12, 134.94, 132.58, 129.54, 128.43, 125.11, 121.54, 117.69, 116.50, 106.20, 99.67, 56.24, 55.90, 43.94, 42.41, 32.84, 32.06, 29.00, 27.57, 26.94, 26.54, 13.57, 9.98 (2C). FAB-MS *m*/*z*: 475 (MH^+).

4.2.9.6. *N*-Cyclopropyl-*N′*-ethyl-6-oxo-6,7,8,9,10,11-hexahydro-5*H*-cyclohepta[*c*]quinoline-2-carboxamide (53). A solution of **98** (431.4 mg, 0.9090 mmol) in TFA (3 mL) was stirred at 80 °C for 90 min, and then diluted with ethyl acetate. The organic layer was washed with water, saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated. Column chromatography (*n*-hexane/AcOEt = 1/2 then AcOEt) of the residue gave the title compound (259.1 mg, 0.7987 mmol, 88%) as a brown solid. ^1H NMR (DMSO-d_6) δ: 11.79 (1H, s), 7.91 (1H, s), 7.57 (1H, d, J = 8.3 Hz), 7.27 (1H, d, J = 8.3 Hz), 3.44 (2H, q, J = 6.9 Hz), 3.04–2.99 (2H, m), 2.91 (1H, br s), 2.94–2.85 (2H, m), 1.87–1.81 (2H, m), 1.60–1.54 (2H, m), 1.49–1.43 (2H, m), 1.18 (3H, t, J = 6.9 Hz), 0.58–0.50 (2H, m), 0.39 (2H, br s). ^{13}C NMR (DMSO-d_6) δ: 170.58, 161.43, 149.63, 138.04, 133.89, 130.95, 128.33, 123.24, 118.12, 114.63, 41.83, 31.75 (2C), 27.27, 25.61, 25.16, 24.95, 13.30, 9.41 (2C). FAB-MS *m*/*z*: 325 (MH^+). HRMS (FAB, $[M+H]^+$) calcd for $C_{20}H_{25}N_2O_2$ 325.1916, found 325.1899.

4.2.9.7. *N*-Alkylation of a cycloheptaquinolinone 53. *4.2.9.7.1. General procedure for the synthesis of **N**-cyclopropyl-**N′**-ethyl-6-oxo-5-alkyl-6,7,8,9,10,11-hexahydro-5**H**-cyclohepta[**c**]quinoline-2-carboxamide (A).* To a suspension of **53** (30 mg, 0.1 mmol) and Cs_2CO_3 (65 mg, 0.2 mmol) in DMF (0.5 mL) was added alkyl iodide (0.5 mmol) at ambient temperature. The mixture was stirred at 90 °C for 1 h, then diluted with ethyl acetate. The organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated. The product was purified as indicated below.

4.2.9.7.2. General procedure for the synthesis of N-cyclopropyl-N′-ethyl-6-oxo-5-alkyl-6,7,8,9,10,11-hexahydro-5H-cyclohepta[c]quinoline-2-carboxamide (B). To a suspension of **53** (30 mg, 0.1 mmol), Cs_2CO_3 (65 mg, 0.2 mmol) and TBAI (10 mg, 0.03 mmol) in DMF (0.5 mL) was added alkyl bromide (0.5 mmol) at ambient temperature. The mixture was stirred at 90 °C for 1 h, and then diluted with ethyl acetate. The organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated. The product was purified as indicated below.

*4.2.9.7.3. N-Cyclopropyl-N′-ethyl-6-oxo-5-methyl-6,7,8,9,10,11-hexahydro-5H-cyclohepta[c]quinoline-2-carboxamide (**54**).* This compound was synthesized according to the general procedure A. Column chromatography (*n*-hexane/AcOEt = 83/17 to 0/100) gave the title compound (26.4 mg, 0.0780 mmol, 88%) as a pale-yellow oil. ^{1}H NMR (DMSO-d_6) δ: 8.01 (1H, br s), 7.69 (1H, d, J = 8.3 Hz), 7.50 (1H, d, J = 8.3 Hz), 3.66 (3H, s), 3.52–3.41 (2H, m), 3.08–3.02 (2H, m), 2.99–2.91 (3H, m), 1.88–1.80 (2H, m), 1.61–1.55 (2H, m), 1.50–1.44 (2H, m), 1.28–1.14 (3H, m), 0.54 (2H, br s), 0.41 (2H, br s). ^{13}C NMR (DMSO-d_6) δ: 175.76, 160.89, 148.37, 138.86, 133.20, 131.13, 128.64, 123.60, 118.80, 114.30, 41.82, 30.97, 30.31, 30.01, 27.19, 25.97, 25.56, 25.13, 13.30, 9.41 (2C). FAB-MS m/z: 339 (MH^+). HRMS (FAB, $[M+H]^+$) calcd for $C_{21}H_{27}N_2O_2$ 339.2073, found 339.2076.

*4.2.9.7.4. N-Cyclopropyl-N′-ethyl-6-oxo-5-ethyl-6,7,8,9,10,11-hexahydro-5H-cyclohepta[c]quinoline-2-carboxamide (**55**).* This compound was synthesized according to the general procedure A. Column chromatography (*n*-hexane/AcOEt = 80/20 to 0/100) gave the title compound (23.0 mg, 0.0653 mmol, 70%) as a colorless oil. ^{1}H NMR (DMSO-d_6) δ: 8.02 (1H, s), 7.48 (1H, d, J = 8.9 Hz), 7.55 (1H, d, J = 8.9 Hz), 4.31 (2H, q, J = 6.9 Hz), 3.46 (2H, q, J = 6.3 Hz), 3.07–3.01 (2H, m), 2.98–2.90 (3H, m), 1.87–1.80 (2H, m), 1.62–1.55 (2H, m), 1.51–1.44 (2H, m), 1.25–1.16 (6H, m), 0.56 (2H, br s), 0.42 (2H, br s). ^{13}C NMR (DMSO-d_6) δ: 174.77, 160.37, 148.38, 137.74, 133.17, 130.94, 128.70, 123.85, 119.03, 113.98, 54.92, 41.67, 37.43, 31.60, 27.24, 25.83, 25.56, 25.06, 13.31, 12.71, 9.24 (2C). FAB-MS m/z: 353 (MH^+). HRMS (FAB, $[M+H]^+$) calcd for $C_{22}H_{29}N_2O_2$ 353.2229, found 353.2211.

*4.2.9.7.5. N-Cyclopropyl-N′-ethyl-6-oxo-5-n-propyl-6,7,8,9,10,11-hexahydro-5H-cyclohepta[c]quinoline-2-carboxamide (**56**).* This compound was synthesized according to the general procedure A. Column chromatography (*n*-hexane/AcOEt = 92/8 to 36/64) gave the title compound (14.6 mg, 0.0398 mmol, 51%) as a pale-yellow oil. ^{1}H NMR (CD_3OD, 60 °C) δ: 8.06 (1H, d, J = 1.7 Hz), 7.71 (1H, dd, J = 9.2, 1.7 Hz), 7.56 (1H, d, J = 9.2 Hz), 4.33 (2H, t, J = 7.5 Hz), 3.59 (2H, q, J = 7.2 Hz), 3.15–3.10 (2H, m), 3.06–3.01 (2H, m), 2.95–2.90 (1H, m), 1.94–1.88 (2H, m), 1.82–1.73 (2H, m), 1.72–1.66 (2H, m), 1.62–1.56 (2H, m), 1.28 (3H, t, J = 7.2 Hz), 1.03 (3H, t, J = 7.5 Hz), 0.70–0.64 (2H, m), 0.56–0.50 (2H, m). ^{13}C NMR (CD_3OD, 60 °C) δ: 174.11, 163.51, 150.90, 139.93, 134.90, 132.44, 129.72, 125.31, 121.53, 115.79, 45.77, 43.99, 32.83, 32.12, 28.94, 27.41, 26.89, 26.53, 21.94, 13.56, 11.35, 10.00 (2C). FAB-MS m/z: 367 (MH^+). HRMS (FAB, $[M+H]^+$) calcd for $C_{23}H_{31}N_2O_2$ 367.2386, found 367.2345.

*4.2.9.7.6. N-Cyclopropyl-N′-ethyl-6-oxo-5-n-pentyl-6,7,8,9,10,11-hexahydro-5H-cyclohepta[c]quinoline-2-carboxamide (**57**).* This compound was synthesized according to the general procedure B. Column chromatography (*n*-hexane/AcOEt = 92/8 to 36/64) gave the title compound (17.2 mg, 0.0436 mmol, 48%) as a pale-yellow oil. ^{1}H NMR (CD_3OD, 60 °C) δ: 8.06 (1H, d, J = 1.7 Hz), 7.72 (1H, dd, J = 8.6, 1.7 Hz), 7.55 (1H, d, J = 8.6 Hz), 4.35 (2H, t, J = 8.0 Hz), 3.59 (2H, q, J = 6.9 Hz), 3.14–3.10 (2H, m), 3.05–3.01 (2H, m), 2.95–2.90 (1H, m), 1.94–1.88 (2H, m), 1.78–1.66 (4H, m), 1.62–1.56 (2H, m), 1.48–1.37 (4H, m), 1.28 (3H, t, J = 7.5 Hz), 0.92 (3H, t, J = 6.9 Hz), 0.70–0.63 (2H, m), 0.55–0.50 (2H, m). ^{13}C NMR (CD_3OD, 60 °C) δ: 174.11, 163.45, 150.88, 139.90, 134.90, 132.43, 129.72, 125.33, 121.55, 115.75, 44.30, 44.01, 32.83, 32.14, 30.12, 28.94, 28.35, 27.42, 26.90, 26.54, 23.38, 14.19, 13.57, 10.01 (2C). FAB-MS m/z: 395 (MH^+). HRMS (FAB, $[M+H]^+$) calcd for $C_{25}H_{35}N_2O_2$ 395.2699, found 395.2744.

*4.2.9.7.7. N-Cyclopropyl-N′-ethyl-6-oxo-5-n-hexyl-6,7,8,9,10,11-hexahydro-5H-cyclohepta[c]quinoline-2-carboxamide (**58**).* This compound was synthesized according to the general procedure A. Column chromatography (*n*-hexane/AcOEt = 92/8 to 36/64) gave the title compound (19.4 mg, 0.0475 mmol, 59%) as a pale-yellow oil. ^{1}H NMR (CD_3OD, 60 °C) δ: 8.06 (1H, d, J = 1.7 Hz), 7.72 (1H, dd, J = 8.6, 1.7 Hz), 7.55 (1H, d, J = 8.6 Hz), 4.36 (2H, t, J = 8.0 Hz), 3.59 (2H, q, J = 6.9 Hz), 3.14–3.10 (2H, m), 3.05–3.01 (2H, m), 2.96–2.90 (1H, m), 1.94–1.88 (2H, m), 1.77–1.66 (4H, m), 1.62–1.56 (2H, m), 1.49–1.42 (2H, m), 1.40–1.31 (4H, m), 1.28 (3H, t, J = 7.5 Hz), 0.90 (3H, t, J = 6.9 Hz), 0.70–0.63 (2H, m), 0.56–0.50 (2H, m). ^{13}C NMR (CD_3OD, 60 °C) δ: 174.11, 163.46, 150.88, 139.90, 134.90, 132.43, 129.71, 125.33, 121.55, 115.76, 44.31, 43.97, 32.83, 32.60, 32.10, 28.93, 28.62, 27.57, 27.42, 26.90, 26.54, 23.51, 14.16, 13.57, 10.01 (2C). FAB-MS m/z: 409 (MH^+). HRMS (FAB, $[M+H]^+$) calcd for $C_{26}H_{37}N_2O_2$ 409.2855, found 409.2837.

*4.2.9.7.8. N-Cyclopropyl-N′-ethyl-6-oxo-5-(2-methoxy)ethyl-6,7,8,9,10,11-hexahydro-5H-cyclohepta[c]quinoline-2-carboxamide (**59**).* This compound was synthesized according to the general procedure B. Column chromatography (*n*-hexane/AcOEt = 81/19 to 0/100) gave the title compound (21.3 mg, 0.0557 mmol, 65%) as a pale-yellow oil. ^{1}H NMR (CD_3OD, 60 °C) δ: 8.05 (1H, s), 7.69 (1H, s), 7.69 (1H, s), 4.57 (2H, t, J = 5.7 Hz), 3.73 (2H, t, J = 5.7 Hz), 3.59 (2H, q, J = 6.9 Hz), 3.32 (3H, s), 3.14–3.10 (2H, m), 3.05–3.01 (2H, m), 2.95–2.90 (1H, m), 1.94–1.88 (2H, m), 1.72–1.66 (2H, m), 1.62–1.57 (2H, m), 1.28 (3H, t, J = 6.9 Hz), 0.69–0.64 (2H, m), 0.55–0.51 (2H, m). ^{13}C NMR (CD_3OD, 60 °C) δ: 172.78, 162.36, 149.87, 139.21, 133.47, 131.22, 128.21, 123.80, 120.14, 115.00, 69.73, 57.96, 42.76, 42.66, 31.49, 30.77, 27.64, 26.05, 25.52, 25.15, 12.23, 8.67 (2C). FAB-MS m/z: 383 (MH^+). HRMS (FAB, $[M+H]^+$) calcd for $C_{23}H_{31}N_2O_3$ 383.2335, found 383.2306.

*4.2.9.7.9. N-Cyclopropyl-N′-ethyl-6-oxo-5-i-propyl-6,7,8,9,10,11-hexahydro-5H-cyclohepta[c]quinoline-2-carboxamide (**61**).* This compound was synthesized according to the general procedure A. Column chromatography (*n*-hexane/AcOEt = 94/6 to 52/48) gave the title compound (16.5 mg, 0.0450 mmol, 63%) as a pale-yellow oil. ^{1}H NMR (CD_3OD, 60 °C) δ: 8.11 (1H, d, J = 1.7 Hz), 7.75 (1H, d, J = 8.0 Hz), 7.62 (1H, dd, J = 8.0, 1.7 Hz), 5.55 (1H, sep, J = 6.3 Hz), 3.59 (2H, q, J = 6.9 Hz), 3.24–3.20 (2H, m), 3.06–3.03 (2H, m), 2.94–2.89 (1H, m), 1.94–1.89 (2H, m), 1.71–1.65 (2H, m), 1.63–1.57 (2H, m), 1.38 (6H, d, J = 6.3 Hz), 1.28 (3H, t, J = 6.9 Hz), 0.67–0.59 (2H, m), 0.56–0.49 (2H, m). ^{13}C NMR (CD_3OD, 60 °C) δ: 175.14, 161.59, 152.10, 147.39, 133.67, 129.13, 128.32, 127.76, 124.64, 123.73, 69.44, 43.98, 33.10, 32.10, 28.73, 27.24, 27.17, 26.64, 22.43 (2C), 13.58, 9.88 (2C). FAB-MS m/z: 367 (MH^+). HRMS (FAB, $[M+H]^+$) calcd for $C_{23}H_{31}N_2O_2$ 367.2386, found 367.2402.

*4.2.9.7.10. N-Cyclopropyl-N′-ethyl-6-oxo-5-benzyl-6,7,8,9,10,11-hexahydro-5H-cyclohepta[c]quinoline-2-carboxamide (**62**).* This compound was synthesized according to the general procedure B. Column chromatography (*n*-hexane/AcOEt = 88/12 to 4/96) gave the title compound (27.3 mg, 0.0656 mmol, 84%) as a colorless amorphous solid. ^{1}H NMR (CD_3OD, 60 °C) δ: 8.06 (1H, d, J = 1.7 Hz), 7.56 (1H, dd, J = 8.6, 1.7 Hz), 7.41 (1H, d, J = 8.6 H), 7.28–7.23 (2H, m), 7.21–7.14 (3H, m), 5.63 (2H, s), 3.55 (2H, q, J = 7.5 Hz), 3.18–3.14 (2H, m), 3.11–3.07 (2H, m), 2.89–2.84 (1H, m), 1.96–1.91 (2H, m), 1.75–1.69 (2H, m), 1.66–1.60 (2H, m), 1.25 (3H, t, J = 7.5 Hz), 0.64–0.58 (2H, m), 0.51–0.46 (2H, m). ^{13}C NMR (CD_3OD, 60 °C) δ: 173.98, 163.86, 151.48, 140.11, 137.89, 134.95, 132.71, 129.77 (2C), 129.57, 128.26, 127.53 (2C), 125.19, 121.62, 116.53, 47.68, 43.94, 32.82, 32.06, 29.03, 27.58, 26.92, 26.51, 13.54, 9.95 (2C). FAB-MS m/z: 415 (MH^+). HRMS (FAB, $[M+H]^+$) calcd for $C_{27}H_{31}N_2O_2$ 415.2386, found 415.2402.

*4.2.9.7.11. N-Cyclopropyl-N′-ethyl-6-oxo-5-(2-(tert-butyldimethylsilyl)oxy)ethyl-6,7,8,9,10,11-hexahydro-5H-cyclohepta[c]quinoline-2-carboxamide (**99**).* This compound was synthesized according to the general procedure B. Column chromatography (*n*-hexane/AcOEt = 92/8 to 36/64) gave the title compound (31.1 mg, 0.0664 mmol, 54%) as a pale-yellow oil. ^{1}H NMR (CD_3OD, 60 °C) δ: 8.05 (1H, d, J = 1.7 Hz), 7.75 (1H, d, J = 8.6 Hz), 7.67 (1H, d, J = 8.6, 1.7 Hz), 4.54 (2H, t, J = 5.7 Hz), 4.03 (2H, t, J = 5.7 Hz), 3.58 (2H, q, J = 7.5 Hz), 3.14–3.10 (2H, m), 3.05–3.01 (2H, m),

2.95–2.90 (1H, m), 1.94–1.88 (2H, m), 1.71–1.65 (2H, m), 1.62–1.56 (2H, m), 1.28 (3H, t, J = 7.5 Hz), 0.74 (9H, s), 0.70–0.63 (2H, m), 0.56–0.51 (2H, m), −0.14 (6H, s). ^{13}C NMR (CD_3OD, 60 °C) δ: 174.07, 163.71, 151.12, 141.01, 134.80, 132.40, 129.35, 125.05, 121.35, 116.97, 61.91, 48.66, 46.41, 32.82, 32.05, 28.94, 27.36, 26.85, 26.54, 26.27 (3C), 18.94, 13.59, 10.04 (2C), −5.44 (2C). FAB-MS m/z: 483 (MH^+).

4.2.9.8. *N*-Cyclopropyl-*N*′-ethyl-6-oxo-5-(2-hydroxy)ethyl-6,7,8,9,10,11-hexahydro-5*H*-cyclohepta[*c*]quinoline-2-carboxamide (60). To a solution of **99** (25.7 mg, 0.0532 mmol) in THF (2 mL) was added TBAF (1 M in THF, 200 μL, 0.200 mmol) at ambient temperature. The solution was stirred at 50 °C for 3 h, and then diluted with ethyl acetate. The organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated. Column chromatography ($CHCl_3$/MeOH = 50/1) of the residue gave the title compound (21.1 mg, 0.0573 mmol, quant.) as a pale-yellow amorphous solid. ^{1}H NMR (CD_3OD, 60 °C) δ: 8.05 (1H, br s), 7.81 (1H, br s), 7.70 (1H, br s), 4.51 (2H, t, J = 6.3 Hz), 3.87 (2H, t, J = 6.3 Hz), 3.59 (2H, q, J = 7.5 Hz), 3.14–3.09 (2H, m), 3.05–3.00 (2H, m), 2.95–2.90 (1H, m), 1.94–1.88 (2H, m), 1.72–1.65 (2H, m), 1.62–1.56 (2H, m), 1.28 (3H, t, J = 7.5 Hz), 0.70–0.64 (2H, m), 0.55–0.50 (2H, m). ^{13}C NMR (CD_3OD, 60 °C) δ: 174.05, 163.83, 151.14, 140.60, 134.82, 132.50, 129.58, 125.16, 121.48, 116.19, 60.42, 48.66, 46.50, 32.80, 32.07, 28.96, 27.38, 26.83, 26.47, 13.57, 10.01 (2C). FAB-MS m/z: 369 (MH^+). HRMS (FAB, $[M+H]^+$) calcd for $C_{22}H_{29}N_2O_3$ 369.2178, found 369.2223.

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