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Fused heterocyclic amido compounds as anti-hepatitis C virus agents

Hiroshi Aoyama [a,*], Kazuyuki Sugita [a], Masahiko Nakamura [a], Atsushi Aoyama [a], Mohammed T. A. Salim [b], Mika Okamoto [b], Masanori Baba [b,*], Yuichi Hashimoto [a]

[a] Institute of Molecular and Cellular Biosciences, The University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo 113-0032, Japan
[b] Division of Antiviral Chemotherapy, Center for Chronic Viral Diseases, Graduate School of Medical and Dental Sciences, Kagoshima University, 8-35-1 Sakuragaoka, Kagoshima 890-8544, Japan

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ABSTRACT

We identified a fused heteroaromatic amido structure based on the phenanthridine skeleton as a superior scaffold for candidate drugs with potent anti-HCV activity. Among the compounds synthesized, a phenanthridine analogue with a 1,3-dioxolyl group (**24**) possessed the most potent anti-HCV activity (EC_{50} value: 50 nM), with acceptable cytotoxicity. The structural development and structure–activity relationships of these compounds are described.

1. Introduction

Hepatitis C virus (HCV: a member of the *Flaviviridae* family) is thought to be a major cause of human hepatitis,[1,2] and it is estimated that at least 170 million people worldwide are chronically infected with this virus.[3] Most infections become persistent, and about 60% of cases progress to chronic liver disease, which in turn can lead to cirrhosis, hepatocellular carcinoma, and liver failure.[4,5] Currently, no vaccine is available to prevent HCV infection, and the standard treatment for chronic hepatitis C consists of pegylated interferon (IFN)-α in combination with the nucleoside analogue ribavirin (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide). However, the virus cannot be eliminated from approximately half of infected patients treated with these agents.[6] In addition, the side effects of these agents are sometimes serious and unacceptable to patients. A number of molecules are being studied in clinical trials,[7] but none of them has yet been approved. Therefore, alternative agents for the treatment and prevention of HCV infection are urgently needed.

Recently, we have succeeded in the development of antiviral agents with polyphyletic skeletons.[8–16] Among them, several fused-heterocyclic compounds, including 3,4,5-trimethyl-γ-carboline (**1**)[9] and 5-butyl-2-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenanthridin-6(5*H*)-one (**2**),[12] exhibited anti-flavivirus activity (Fig. 1). The γ-carboline analogue **1** showed powerful inhibitory activity for bovine viral diarrhea virus (BVDV) replication, with an EC_{50} value of 3.5 nM. Although BVDV belongs to the *Flaviviridae* family, as HCV does,[17] and is thought to be a surrogate model for HCV,[18–20] compound **1** showed only very weak activity against HCV. On the other hand, phenanthridine analogue **2**, which has a fused heterocyclic amido structure, exhibited moderate, dose-dependent HCV replication-inhibitory activity,[12] supporting the idea that phenanthridine analogues could be lead compounds in the development of anti-HCV drugs.

In this paper, we describe the synthesis of a series of fused heterocyclic amido compounds based on the structure of phenanthridine **2**, as well as the evaluation of their anti-HCV activity, and the creation of potent anti-HCV agents possessing one or more methoxy group(s) and/or a 1,3-dioxolyl group.

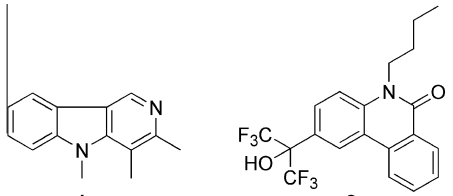

Figure 1. Antiviral activity of fused heterocyclic compounds.

* Corresponding authors. Tel.: +81 3 5841 7848; fax: +81 3 5841 8495 (H.A.); tel.: +81 99 275 5930; fax: +81 99 275 5932 (M.B.).
E-mail addresses: aoyama@iam.u-tokyo.ac.jp (H. Aoyama), m-baba@vanilla.ocn.ne.jp (M. Baba).

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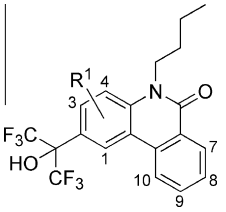
2. Results and discussion

2.1. Electronic effects of substituents

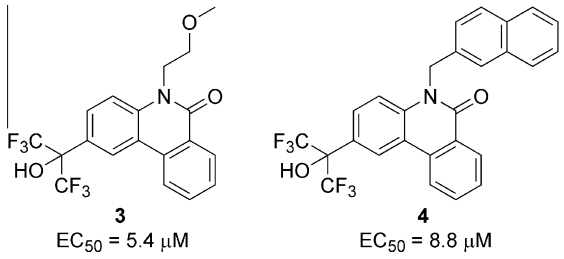
Our previous study[12] on the anti-HCV activity of phenanthridine analogues indicated that a 1,1,1,3,3,3-hexafluoro-2-hydroxypropyl group at the 2-position is essential for inhibition of HCV replication. As for the substituent on the amido nitrogen, a butyl group is appropriate in terms of size and electric charge. Indeed, introduction of a polar methoxyethyl (**3**) or bulky 2-naphthyl (**4**) group at this position did not result in improvement of anti-HCV activity in further investigations (Fig. 2). On the basis of these findings, we designed new phenanthridine analogues (derived from **2**) modified at the 3- or 4-position with three kinds of substituents (F, Me and OMe) possessing different properties, and examined their antiviral activity. These compounds were synthesized as shown in Scheme 1. Briefly, *N*-butylaniline derivatives **28a**–**f**, prepared from the corresponding anilines, were treated with hexafluoroacetone trihydrate to give 1,1,1,3,3,3-hexafluoro-2-hydroxypropyl derivatives **29a**–**f**, which were condensed with 2-iodobenzoyl chloride. The resulting anilides **30a**–**f** were cyclized in the presence of Pd catalyst to give compounds **5**–**10**.

As shown in Table 1, introduction of substituents at the 4-position enhanced the anti-HCV activity in the order of fluoro (**6**) < methyl (**8**) < methoxy (**10**), whereas introduction of substituents at the 3-position did not improve the anti-HCV activity, compared with unsubstituted **2**. The analogues with a non-polar methyl group, that is, compounds **7** and **8**, showed almost the same anti-HCV activity as the analogues substituted at the corresponding site (3- or 4-position) with an electron-withdrawing fluoro group, that is, compounds **5** and **6**, respectively. On the other hand, analogues with an electron-donating methoxy group (compounds **9** and **10**) exhibited higher anti-HCV activity than the corresponding methyl- and/or fluoro-substituted analogues. As regards cytotoxicity, electron-withdrawing character of the substituent seems to be unfavorable, that is, introduction of a fluoro group at the 4-position (**6**) resulted in an increase of the cytotoxicity compared to other 4-substituted compounds, **8** and **10**. These results suggest that the substituent effect is determined more by electronic character than by the steric factor, and an electron-donating group is favorable for anti-HCV activity. Therefore, we selected the methoxy group as a fixed substituent for further structural development studies.

Table 1
Effects of substituents of phenanthridine on anti-HCV activities and cytotoxicities



	R^1	EC_{50} (μM)	CC_{50} (μM)
2	H	3.2	15.8
5	3-F	5.3	25.5
6	4-F	2.4	12.1
7	3-CH_3	5.6	28.9
8	4-CH_3	2.1	31.9
9	3-OCH_3	3.4	>40
10	4-OCH_3	1.1	22.3



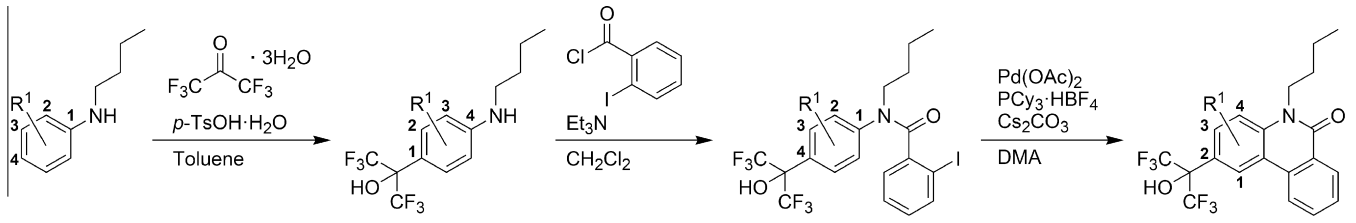
3 EC_{50} = 5.4 μM **4** EC_{50} = 8.8 μM

Figure 2. Antiviral efficacy of **3** and **4** against HCV proliferation.

2.2. Regioisomers of methoxyl-substituted analogues

Based on our previous structure–activity relationship studies of anti-BVDV γ-carboline analogues, which indicated that regioselective methyl substitution dramatically influenced the antiviral activity,[8,9] we next investigated the effect of methoxy substitution. For this purpose, we synthesized all regioisomers of methoxy-substituted phenanthridine analogues **9**–**15** by using the same method as in Scheme 1 (see Scheme 2).

The anti-HCV activity and cytotoxicity of prepared compounds **9**–**15** are summarized in Table 2. The effect of methoxylation on the anti-HCV activity seems to be dependent on the position at which the methoxy group is introduced. Introduction of a methoxy group at positions 1, 7, 9 and 10 decreased the anti-HCV activity compared to methoxy-unsubstituted analogue **2**, whereas introduction at positions 3, 4 and 8 increased the activity. The 8-methoxylated analogue (**13**) showed the most potent anti-HCV activity among this series of compounds, with the EC_{50} value of 0.98 μM. As for cytotoxicity, the introduction of the methoxy group at positions



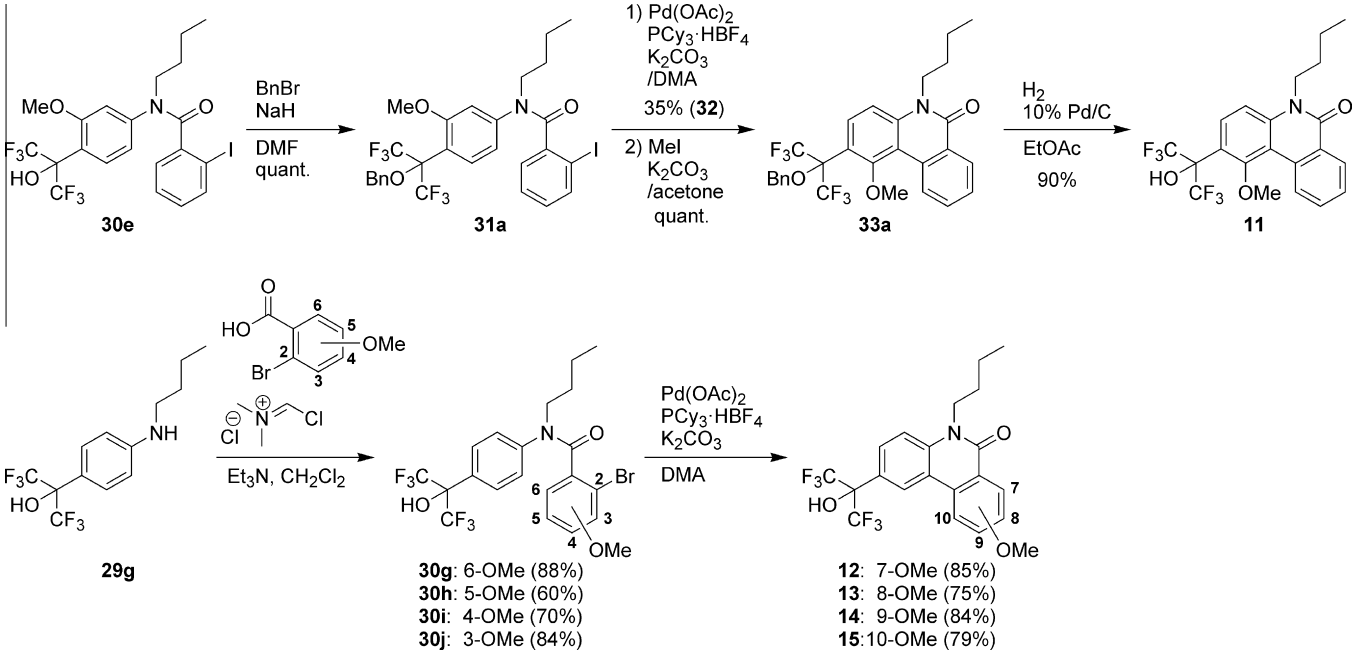
28a: R^1 = 3-F
28b: R^1 = 2-F
28c: R^1 = 3-Me
28d: R^1 = 2-Me
28e: R^1 = 3-OMe
28f: R^1 = 2-OMe

29a: R^1 = 2-F (37%)
29b: R^1 = 3-F (74%)
29c: R^1 = 2-Me (39%)
29d: R^1 = 3-Me (93%)
29e: R^1 = 2-OMe (35%)
29f: R^1 = 3-OMe (76%)

30a: R^1 = 3-F (85%)
30b: R^1 = 2-F (87%)
30c: R^1 = 3-Me (81%)
30d: R^1 = 2-Me (85%)
30e: R^1 = 3-OMe (quant.)
30f: R^1 = 2-OMe (82%)

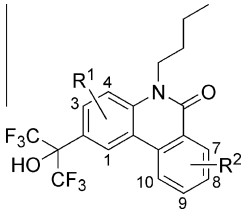
5: R^1 = 3-F (36%)
6: R^1 = 4-F (73%)
7: R^1 = 3-Me (37%)
8: R^1 = 4-Me (81%)
9: R^1 = 3-OMe (27%)
10: R^1 = 4-OMe (73%)

Scheme 1. Synthesis of **5**–**10**.



Scheme 2. Synthesis of **11**–**15**.

Table 2
Anti-HCV activities and cytotoxicities of regioisomers of methoxyphenanthridine **9**–**15**



	R^1	R^2	EC_{50} (μM)	CC_{50} (μM)
2	H	H	3.2	15.8
11	1-OCH_3	H	7.2	25.3
9	3-OCH_3	H	3.4	>40
10	4-OCH_3	H	1.1	22.3
12	H	7-OCH_3	9.96	12.6
13	H	8-OCH_3	0.98	9.6
14	H	9-OCH_3	16.6	28.9
15	H	10-OCH_3	5.0	6.9

7, 8 and 10 increased the cytotoxicity, while introduction at other positions decreased the cytotoxicity or had no effect.

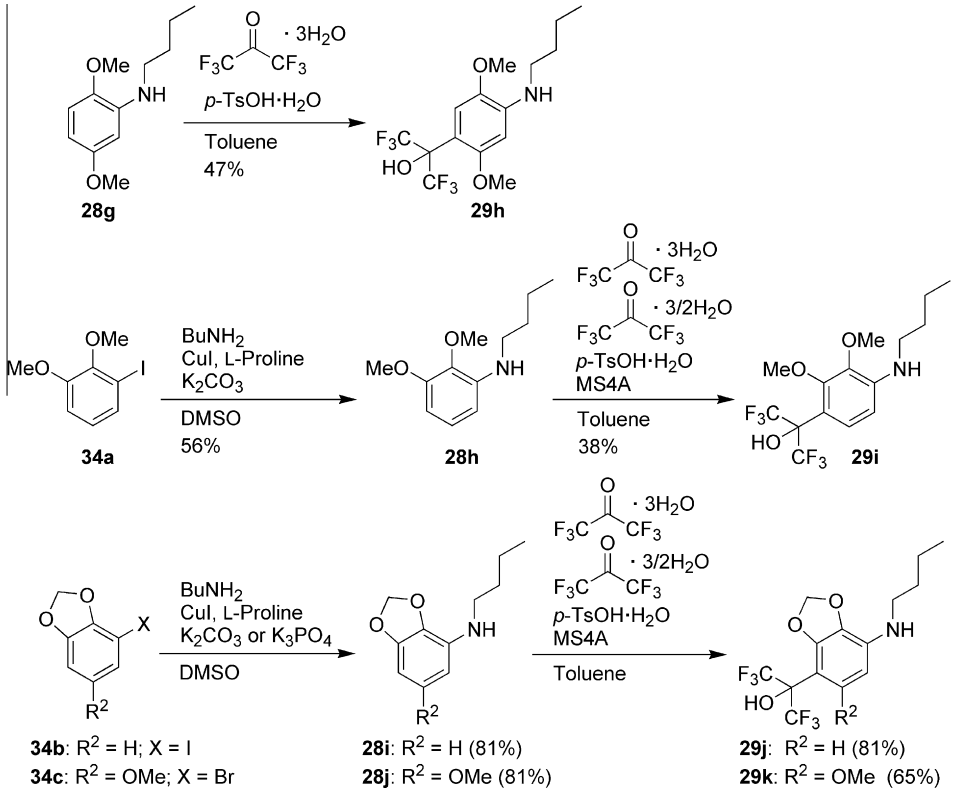
2.3. Dimethoxyl- and trimethoxyl-substituted analogues

The results for the regioisomers of the monomethoxy-substituted analogues indicate that the introduction of a methoxy group at the 3, 4, or 8 position of the phenanthridine skeleton enhanced the anti-HCV activity, compared to unsubstituted analogue **2**. In addition, introduction of a methoxy group at the 1-position seems to have potential for the reduction of cytotoxicity, without affecting the anti-HCV activity. On the basis of these results, we expected that dimethoxylation and/or trimethoxylation at a combination of the 1, 3, 4 and 8-positions might lead to more potent anti-HCV agents. Various compounds, except for analogues possessing methoxy groups at both the 1 and 3 positions, were prepared by means of a method similar to that used for the synthesis of **5**–**10**, as illustrated in Schemes 4 and 5. The commercially unavailable aniline **28h** was prepared by means of metal-catalyzed reaction, as shown in Scheme 3. Briefly, 1-iodo-2,3-dimethoxybenzene (**34a**), prepared from 1,2-dimethoxybenzene by the literature method,[21] was coupled with butylamine by amino acid-promoted CuI-catalyzed C–N bond formation reaction.[22]

As shown in Table 3, among the dimethoxylated compounds, 3,8-disubstituted (**18**) and 4,8-disubstituted analogues (**19**) exhibited anti-HCV activity several-fold higher than that of the monomethoxy compounds: the EC_{50} values of **18** and **19** were 0.18 and 0.51 μM, respectively. Two other dimethoxylated compounds, 1,4-disubstituted (**16**) and 3,4-disubstituted (**17**) analogues, showed anti-HCV potency similar to that of the monomethoxy compounds. On the other hand, trimethoxylated compounds **20** and **21** showed only a slight improvement in the anti-HCV activity compared to the monomethoxy compounds. As for cytotoxicity, analogues possessing a methoxy group at the 1-position, **16** and **20**, exhibited almost no cytotoxicity, while other polymethoxylated compounds were more cytotoxic than the monomethoxylated compounds. These results suggest that introduction of two methoxy groups on the same phenyl ring is unfavorable for anti-HCV activity: *n*,4-dimethoxy analogues (*n* = 1 or 3: **16** and **17**, respectively) show weaker anti-HCV activity than 4-methoxy analogue **10**, and *n*,4,8-trimethoxy analogues (*n* = 1 or 3: **20** and **21**, respectively) show weaker anti-HCV activity than 4-methoxy (**10**) or 8-methoxy (**13**) analogues. In addition, it was suggested that introduction of a methoxy group at the 1-position reduced the cytotoxicity.

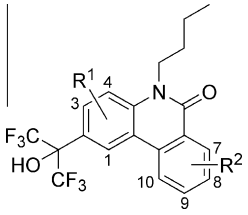
2.4. [1,3]Dioxolophenanthridine analogues

Although 3,8-(**18**) and 4,8-dimethoxyphenanthridine (**19**) analogues showed potent anti-HCV activity, which seems to arise from a synergistic effect of the methoxy groups, 3,4,8-trimethoxy-substituted phenanthridine analogue (**21**) showed enhancement of only the cytotoxicity, but not the anti-HCV activity. This result suggests that the unfavorable effect of steric hindrance between adjacent methoxy groups at the 3 and 4 positions is larger than the cumulative antiviral activity-enhancing effect of these methoxy groups. This hypothesis prompted us to examine the introduction of a 1,3-dioxolyl group (so-called methylenedioxy group)



Scheme 3. Synthesis of **29h–k**.

Table 3
Anti-HCV activities and cytotoxicities of dimethoxy and trimethoxyphenanthridine **16–21**



	R^1	R^2	EC_{50} (μM)	CC_{50} (μM)
16	1,4-$(OCH_3)_2$	H	5.7	>100
17	3,4-$(OCH_3)_2$	H	2.6	10.4
18	3-OCH_3	8-OCH_3	0.18	7.6
19	4-OCH_3	8-OCH_3	0.51	11.1
20	1,4-$(OCH_3)_2$	8-OCH_3	6.1	>100
21	3,4-$(OCH_3)_2$	8-OCH_3	1.8	6.8

instead of the adjacent methoxy structure of analogue (**21**), and we prepared various related analogues with a 1,3-dioxolyl group as illustrated in Schemes 3, 6 and 7.

As expected, the compounds with a 1,3-dioxolyl group at the 3/4-positions, that is, compounds **23** and **24**, exhibited potent anti-HCV activity, with EC_{50} values of 0.29 and 0.050 μM, respectively (Table 4). As with the dimethoxylated compounds, introduction of a methoxy group at the 8-position enhanced the anti-HCV activity. Although introduction of a methoxy group at the 1-position in this series of compounds, **26** and **27**, greatly decreased the cytotoxicity, it did not affect the anti-HCV activity. The compound possessing a 1,3-dioxolyl group at the 8/9-positions (**22**) showed moderate anti-HCV activity with almost no cytotoxicity, whereas introduction of an additional 1,3-dioxolyl group at the 3/4-positions (**25**) resulted in enhancement of the cytotoxicity.

3. Conclusion

We have developed a series of potent anti-HCV agents consisting of fused heterocyclic amido structure with good selectivity for virus replication-inhibitory activity over cytotoxicity. Among them, compound **24** showed the most potent anti-HCV activity, having an EC_{50} value of 50 nM, with a selectivity index (SI: CC_{50}/EC_{50}) value of 128.

4. Experimental

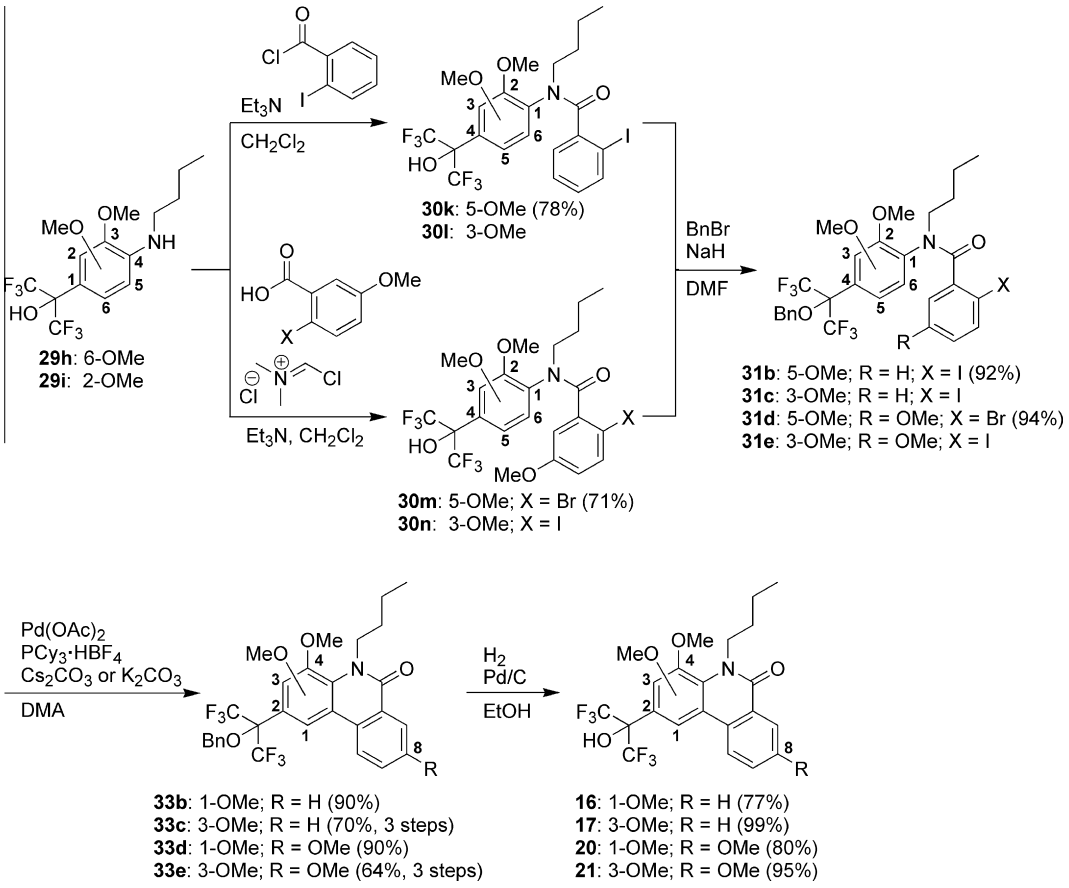
4.1. General comments

Melting points were determined by using a Yanagimoto hot-stage melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a JEOL JNM-GX500 (500 MHz) spectrometer. Chemical shifts are expressed in δ (ppm) values with tetramethylsilane (TMS) as an internal reference. Mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded on a JEOL JMS-DX303 spectrometer. Elemental analyses were carried out in the Microanalytical Laboratory, Faculty of Pharmaceutical Sciences, The University of Tokyo, and were within ±0.4% of the theoretical values.

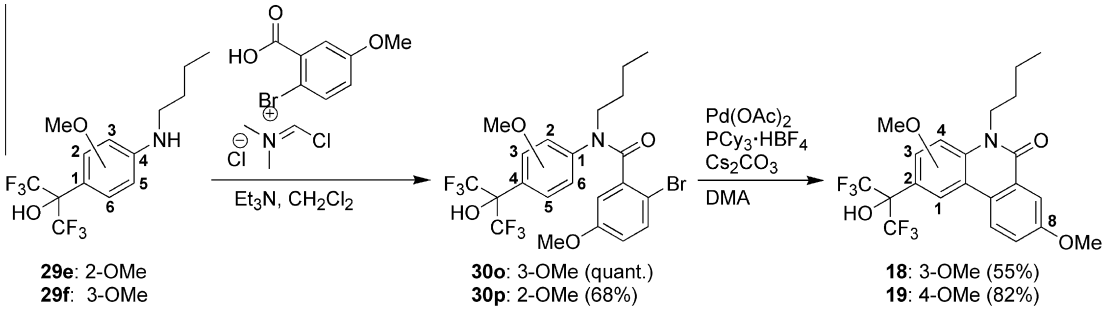
4.2. Chemistry

4.2.1. General procedure A: synthesis of phenylhexafluoropropanol analogues

4.2.1.1. 2-(4-Butylamino-2-fluorophenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (29a). To a mixture of hexafluoroacetone trihydrate (707 mg, 3.21 mmol) and toluene (5.0 ml) were added *N*-butyl-3-fluoroaniline (**28a**) (358 mg, 2.14 mmol) and *p*-TsOH·H_2O (81.5 mg, 428 μmol), then the mixture was stirred at 120 °C for 10 h. After cooling to room temperature, the mixture was diluted with ethyl acetate and then washed with satd $NaHCO_3$



Scheme 4. Synthesis of **16**, **17**, **20**, **21**.



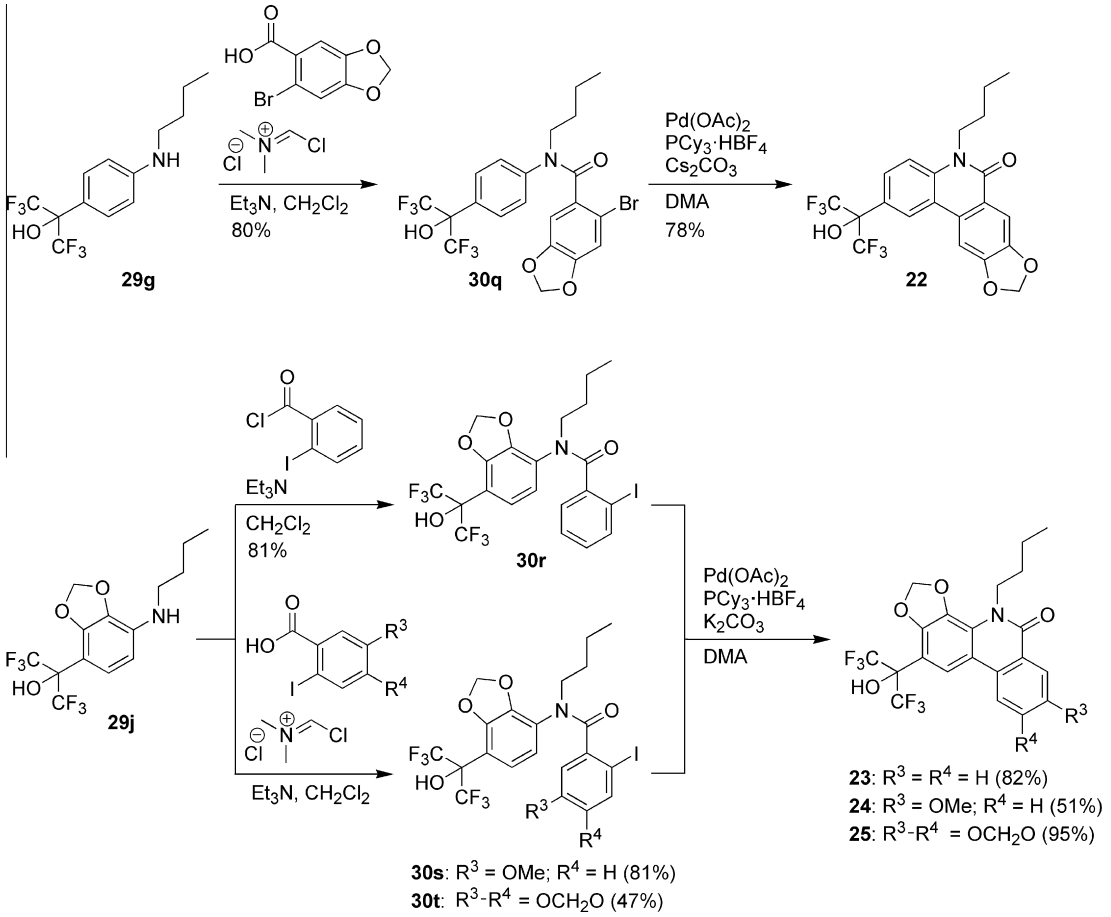
Scheme 5. Synthesis of **18**, **19**.

aqueous solution and brine, and dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (*n*-hexane/AcOEt = 1:0–2:1) to give **29a** (263 mg, 0.790 mmol, 37%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.24 (m, 1H), 6.41–6.38 (m, 1H), 6.31–6.27 (m, 1H), 4.30 (br s, 1H), 4.02 (br s, 1H), 3.11 (t, 2H, J = 6.1 Hz), 1.61 (quin, 2H, J = 7.3 Hz), 1.43 (sext, 2H, J = 7.3 Hz), 0.97 (t, 3H, J = 7.3 Hz); MS (FAB) m/z 334 $(M+H)^+$.

4.2.1.2. 2-(4-Butylamino-3-fluorophenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (29b). Prepared from *N*-butyl-2-fluoroaniline (**28b**) in accordance with the general procedure A. Colorless oil (74%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.29 (m, 2H), 6.71–6.67 (m, 1H), 4.06 (br s, 1H), 3.70 (br s, 1H), 3.19–3.12 (m, 2H), 1.65 (quin, 2H, J = 7.3 Hz), 1.44 (sext, 2H, J = 7.3 Hz), 0.97 (t, 3H, J = 7.3 Hz); MS (FAB) m/z 334 $(M+H)^+$.

4.2.1.3. 2-(4-Butylamino-2-methylphenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (29c). Prepared from *N*-butyl-3-methylaniline (**28c**) in accordance with the general procedure A. Colorless oil (39%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, 1H, J = 7.9 Hz), 7.09 (d, 1H, J = 7.9 Hz), 7.07 (s, 1H), 3.52 (br s, 1H), 3.03 (t, 2H, J = 7.3 Hz), 2.37 (s, 3H), 1.65 (quin, 2H, J = 7.3 Hz), 1.52 (s, 1H), 1.44 (sext, 2H, J = 7.3 Hz), 0.96 (t, 3H, J = 7.3 Hz); MS (FAB) m/z 330 $(M+H)^+$.

4.2.1.4. 2-(4-Butylamino-3-methylphenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (29d). Prepared from *N*-butyl-2-methylaniline (**28d**) in accordance with the general procedure A. Colorless oil (93%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, 1H, J = 8.5 Hz), 7.33 (s, 1H), 6.61 (d, 1H, J = 8.5 Hz), 3.65 (br s, 1H), 3.32 (br s, 1H), 3.17 (t, 2H, J = 7.3 Hz), 2.15 (s, 3H), 1.66 (quin, 2H, J = 7.3 Hz), 1.45 (sext, 2H, J = 7.3 Hz), 0.98 (t, 3H, J = 7.3 Hz); MS (FAB) m/z 330 $(M+H)^+$.



Scheme 6. Synthesis of **22**–**25**.

4.2.1.5. 2-(4-Butylamino-2-methoxyphenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (29e). Prepared from *N*-butyl-3-methoxyaniline (**28e**) in accordance with the general procedure A. Colorless oil (35%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (s, 1H), 7.27 (d, 1H, J = 8.5 Hz), 6.26 (dd, 1H, J = 8.5, 2.4 Hz), 6.18 (d, 1H, J = 2.4 Hz), 4.15 (br s, 1H), 3.91 (s, 1H), 3.12 (m, 2H), 1.61 (quin, 2H, J = 7.3 Hz), 1.43 (sext, 2H, J = 7.3 Hz), 0.97 (t, 3H, J = 7.3 Hz); MS (FAB) m/z 346 $(M+H)^+$.

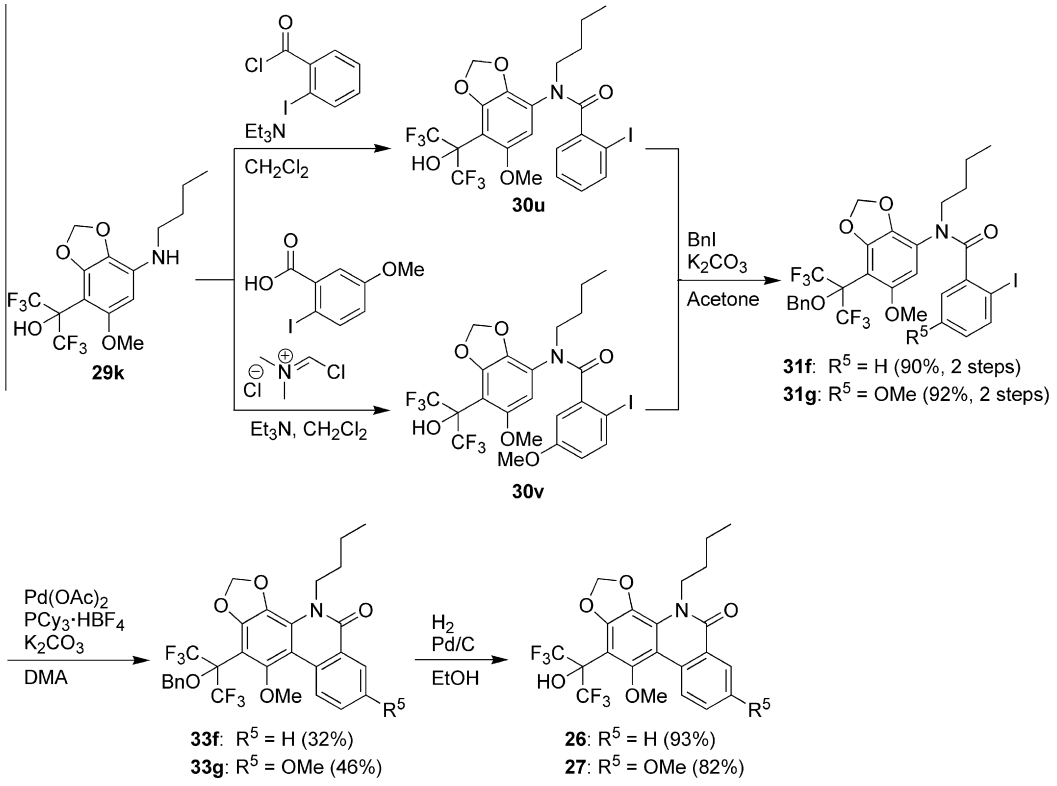
4.2.1.6. 2-(4-Butylamino-3-methoxyphenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (29f). Prepared from *N*-butyl-2-methoxyaniline (**28f**) in accordance with the general procedure A. Colorless oil (76%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (d, 1H, J = 8.5 Hz), 7.05 (s, 1H), 6.58 (d, 1H, J = 8.5 Hz), 4.36 (br s, 1H), 3.95 (br s, 1H), 3.85 (s, 3H), 3.14 (t, 2H, J = 7.3 Hz), 1.64 (quin, 2H, J = 7.3 Hz), 1.44 (sext, 2H, J = 7.3 Hz), 0.96 (t, 3H, J = 7.3 Hz); MS (FAB) m/z 346 $(M+H)^+$.

4.2.1.7. 2-(4-Butylamino-2,5-dimethoxyphenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (29h). Prepared from 2,5-dimethoxy-*N*-butylaniline (**28g**) in accordance with the general procedure A. Colorless oil (47%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (s, 1H), 6.80 (s, 1H), 6.21 (s, 1H), 4.46 (br s, 1H), 3.92 (s, 3H), 3.80 (s, 3H), 3.14 (m, 2H), 1.66 (quin, 2H, J = 7.3 Hz), 1.45 (sext, 2H, J = 7.3 Hz), 0.98 (t, 3H, J = 7.3 Hz); MS (FAB) m/z 376 $(M+H)^+$.

4.2.1.8. 2-(4-Butylamino-2,3-dimethoxyphenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (29i). Prepared from **28b** in accordance with a slight modification of the general procedure A. To a mixture of hexafluoroacetone sesquihydrate (309 mg, 1.60 mmol) and hexafluoroacetone trihydrate (352 mg, 1.60 mmol) were added a solution of **28h** (167 mg, 0.800 mmol) in toluene (1.6 mL), *p*-TsOH·H_2O (15.2 mg, 79.9 μmol), and MS4A (600 mg), and the mixture was stirred at 120 °C for 10 h. After cooling to room temperature, the mixture was diluted with ethyl acetate, and then filtered off under suction and washed with ethyl acetate. The filtrate was washed with water and brine, and dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (*n*-hexane/CH_2Cl_2 = 7:1) to give **29i** (115 mg, 0.306 mmol, 38%) as a colorless oil. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.00 (s, 1H), 7.18 (d, J = 9.2 Hz, 1H), 6.41 (d, J = 9.2 Hz, 1H), 5.52 (t, J = 6.1 Hz, 1H), 3.79 (s, 3H), 3.63 (s, 3H), 3.08 (td, J = 6.1, 6.7 Hz, 2H), 1.52 (tt, J = 6.7, 7.3 Hz, 2H), 1.34 (qt, J = 7.3, 7.3 Hz, 2H), 0.90 (t, J = 7.3 Hz, 3H); MS (FAB) m/z 375 $(M)^+$.

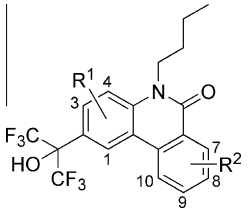
4.2.1.9. 4-(Butylamino)benzo[*d*][1,3]dioxole-2-(1,1,1,3,3,3-hexafluoro)propan-2-ol (29j). Prepared from **28i** in accordance with the synthesis of **29i**. White solid (81%); mp 60.5–62.0 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.19 (s, 1H), 6.93 (d, J = 9.2 Hz, 1H), 6.33 (d, J = 9.2 Hz, 1H), 5.91 (s, 2H), 5.47 (t, J = 6.7 Hz, 1H), 3.08 (td, J = 6.7, 7.3 Hz, 2H), 1.52 (tt, J = 7.3, 7.9 Hz, 2H), 1.34 (qt, J = 7.3, 7.9 Hz, 2H), 0.90 (t, J = 7.3 Hz, 3H); MS (FAB) m/z 359 $(M)^+$.

4.2.1.10. 4-(Butylamino)-6-methoxybenzo[*d*][1,3]dioxole-2-(1,1,1,3,3,3-hexafluoro)propan-2-ol (29k). Prepared from **28j** in accordance with the synthesis of **29i**. Yellow amorphous solid (65%); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.55–7.85 (br, 1H), 5.98 (br s, 1H), 5.84 (s, 2H), 5.40–5.80 (br, 1H), 3.72 (br s, 2H), 3.13 (td, J = 6.7, 6.7 Hz [with NH–CH_2 coupling], 2H), 1.50 (tt, J = 6.7, 7.3 Hz, 2H), 1.33 (qt, J = 6.7, 7.3 Hz, 2H), 0.89 (t, J = 7.3 Hz, 3H); MS (FAB) m/z 389 $(M)^+$.



Scheme 7. Synthesis of **26** and **27**.

Table 4
Anti-HCV activities and cytotoxicities of phenanthridine analogues with 1,3-dioxolyl group (**22–27**)



	R^1	R^2	EC_{50} (μM)	CC_{50} (μM)	SI[a]
23	3,4-(OCH_2O)	H	0.29	24.2	83.3
22	H	8,9-(OCH_2O)	2.3	>100	>43.1
26	1-OCH_3 3,4-(OCH_2O)	H	9.8	93.9	9.56
24	3,4-(OCH_2O)	8-OCH_3	0.050	6.4	128
27	1-OCH_3 3,4-(OCH_2O)	8-OCH_3	12.0	>100	>8.31
25	3,4-(OCH_2O)	8,9-(OCH_2O)	1.73	15.9	9.18

[a] Selectivity index (CC_{50}/EC_{50}).

4.2.2. 3-Iodo-1,2-dimethoxybenzene (34a)

To a solution of veratrol (1.80 g, 13.0 mmol) in THF (10.0 mL) was added *n*-butyllithium (1.65 M hexane solution, 8.70 mL, 14.4 mmol) at −10 °C, and the mixture was stirred at the room temperature for 2 h. After the reaction mixture was cooled to −45 °C, to this was added a solution of I_2 (3.63 g, 14.3 mmol) in THF (10.0 mL), and the mixture was stirred at the room temperature for 1.5 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution and then extracted with ethyl acetate. The combined organic extracts were washed with 10% aqueous $Na_2S_2O_3$ solution, brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (*n*-hexane to *n*-hexane/ethyl acetate = 29:1) to give **34a** (2.44 g, 9.25 mmol, 71%) as a white solid. Mp 35.0–35.5 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.33 (dd, J = 7.9, 1.2 Hz, 1H), 6.87 (dd, J = 7.9, 1.2 Hz, 1H), 6.78 (dd, J = 7.9, 7.9 Hz, 1H), 3.84 (s, 3H), 3.81 (s, 3H); MS (FAB) m/z 264 $(M)^+$.

4.2.3. *N*-Butyl-2,3-dimethoyxaniline (28h)

To a mixture of **34a** (396 mg, 1.50 mmol) and K_2CO_3 (415 mg, 3.00 mmol) were added a solution of CuI (85.7 mg, 0.450 mmol) and L-proline (104 mg, 0.900 mmol) in DMSO (2.0 mL) and *n*-butylamine (600 μl, 6.07 mmol), and the mixture was stirred at 90 °C for 15 h. After cooling to room temperature, the mixture was diluted with ethyl acetate, and then washed with water and brine. The organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (*n*-hexane/ethyl acetate/CH_2Cl_2 = 50:1:1 to 30:1:1) to give **28h** (174 mg, 0.833 mmol, 56%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.85–6.96 (m, 3H), 3.87 (s, 3H), 3.83 (s, 3H), 3.15 (t, J = 7.3 Hz, 2H), 1.65 (tt, J = 7.3, 7.3 Hz, 2H), 1.38 (qt, J = 7.3, 7.3 Hz, 2H), 0.90 (t, J = 7.3 Hz, 3H); MS (FAB) m/z 209 $(M)^+$, 210 $(M+H)^+$.

4.2.4. 4-Iodobenzo[*d*][1,3]dioxole (34b)

To a solution of **34a** (792 mg, 3.00 mmol) in CH_2Cl_2 (10.0 mL) was added BBr_3 (1.0 M CH_2Cl_2 solution, 14.0 mL, 14.0 mmol) at −78 °C under Ar atmosphere, and the mixture was stirred at the room temperature. After 42 h, the reaction mixture was poured into ice, and volatile materials were removed under reduced pressure. The residue was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in DMF (30 mL), and to this were added Cs_2CO_3 (1.00 g, 3.07 mmol) and CH_2I_2 (250 mL, 3.10 mmol) and the mixture was stirred at 120 °C for 1 h under Ar atmosphere. After the reaction mixture was cooled to room temperature, DMF was removed under reduced pressure. To the residue were added ethyl acetate and water, and the resulting insoluble material was removed by filtration and washed with ethyl acetate. The filtrate was extracted with ethyl

acetate, and the combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (*n*-hexane/ethyl acetate = 50:1) to give **34b** [563 mg, 2.27 mmol, 76% (2 steps)] as a white solid. Mp 35.5–37.0 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.11 (dd, J = 1.2, 8.6 Hz, 1H), 6.75 (dd, J = 1.2, 7.9 Hz, 1H), 6.78 (dd, J = 7.9, 8.6 Hz, 1H), 5.99 (s, 2H); MS (FAB) m/z 248 $(M)^+$.

4.2.5. 4-(Butylamino)benzo[*d*][1,3]dioxole (28i)

Prepared from **34b** in accordance with the synthesis of **28h**. Colorless oil (81%); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.73 (t, J = 7.9 Hz, 1H), 6.36–6.53 (m, 2H), 5.92 (s, 2H), 3.19 (t, J = 6.7 Hz, 2H), 1.64 (tt, J = 6.7, 8.0 Hz, 2H), 1.40 (qt, J = 7.3, 8.0 Hz, 2H), 0.92 (t, J = 7.3 Hz, 3H); MS (FAB) m/z 193 $(M+H)^+$.

4.2.6. 4-(Butylamino)-6-methoxybenzo[*d*][1,3]dioxole (28j)

Prepared from 3-bromo-5-methoxybenzo[*d*][1,3]dioxole (**34c**)[23] in accordance with the synthesis of **28h**. Pale yellow oil (81%); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 5.89 (d, J = 2.5 Hz, 1H), 5.81 (s, 2H), 5.77(d, J = 2.5 Hz, 1H), 5.14 (t, J = 6.1 Hz, 1H), 3.61 (s, 3H), 3.05 (dt, J = 6.1, 6.7 Hz, 2H), 1.47 (tt, J = 6.7, 7.3 Hz, 2H), 1.32 (qt, J = 7.3, 7.3 Hz, 2H), 0.88 (t, J = 7.3 Hz, 3H); MS (FAB) m/z 223 $(M)^+$.

4.2.7. General procedure B: synthesis of benzamide analogues (I)

4.2.7.1. *N*-Butyl-*N*-[3-fluoro-4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl]-2-iodobenzamide (30a). To a solution of **29a** (100 mg, 300 μmol) in CH_2Cl_2 (5.0 mL) were added dropwise 2-iodobenzoyl chloride (88.0 mg, 330 μmol) and Et_3N (82.5 μl, 750 μmol) at 0 °C, then the mixture was stirred for 3 h, and was allowed to warm to room temperature. After cooling to 0 °C, the mixture was diluted with ethyl acetate and then water was added. The organic layer was separated and washed with brine, and dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (*n*-hexane/AcOEt = 1:0–1:1) to give **30a** (144 mg, 256 μmol, 85%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90–6.80 (m, 7H), 4.05–3.80 (m, 2H), 3.50 (br s, 1H), 1.76–1.57 (m, 2H), 1.57–1.35 (m, 2H), 1.02–0.83 (m, 3H); MS (FAB) m/z 436 $(M+H)^+$.

4.2.7.2. *N*-Butyl-*N*-[2-fluoro-4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl]-2-iodobenzamide (30b). Prepared from **29b** in accordance with the general procedure B. White solid (87%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, 2H, J = 7.3 Hz), 7.52–7.25 (m, 3H), 7.02–6.93 (m, 2H), 6.89–6.81 (m, 1H), 4.20–4.00 (m, 1H), 3.73–3.50 (m, 1H), 3.50–3.37 (m, 1H), 1.72–1.53 (m, 2H), 1.53–1.37 (m, 2H), 0.96 (t, 3H, J = 7.3 Hz); MS (FAB) m/z 436 $(M+H)^+$.

4.2.7.3. *N*-Butyl-*N*-[4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-3-methylphenyl]-2-iodobenzamide (30c). Prepared from **29c** in accordance with the general procedure B. White solid (81%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, 2H, J = 7.9 Hz), 7.10–6.95 (m, 5H), 6.80–6.77 (m, 1H), 4.85 (br s, 1H), 3.93–3.82 (m, 2H), 2.23 (s, 3H), 1.70–1.55 (m, 2H), 1.49–1.30 (m, 2H), 0.93 (t, 3H, J = 7.3 Hz); MS (FAB) m/z 432 $(M+H)^+$.

4.2.7.4. *N*-Butyl-*N*-[4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2-methylphenyl]-2-iodobenzamide (30d). Prepared from **29d** in accordance with the general procedure B. White solid (85%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, 1H, J = 7.9 Hz), 7.48 (s, 1H), 7.28 (s, 2H), 6.96 (dd, 1H, J = 7.9, 7.3 Hz), 6.82–6.76 (m, 2H), 4.47–4.38 (m, 2H), 3.18–3.10 (m, 1H), 2.38 (s, 3H), 1.83–1.76 (m, 1H),1.67–1.52 (m, 1H), 1.52–1.30 (m, 2H), 0.95 (t, 3H, J = 7.3 Hz); MS (FAB) m/z 432 $(M+H)^+$.

4.2.7.5. *N*-Butyl-*N*-[4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-3-methoxyphenyl]-2-iodobenzamide (30e). Prepared from **29e** in accordance with the general procedure B. White solid (quant.); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, 2H, J = 7.9 Hz), 7.41 (d, 1H, J = 9.1 Hz), 7.21–6.97 (m, 2H), 6.95–6.83 (m, 3H), 6.80 (s, 1H), 4.85 (br s, 1H), 4.12–3.85 (m, 2H), 3.77 (s, 3H), 1.72–1.60 (m, 2H), 1.52–1.37 (m, 2H), 0.96 (t, 3H, J = 7.3 Hz); MS (FAB) m/z 448 $(M+H)^+$.

4.2.7.6. *N*-Butyl-*N*-[4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2-methoxyphenyl]-2-iodobenzamide (30f). Prepared from **29f** in accordance with the general procedure B. White solid (82%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, 2H, J = 7.9 Hz), 7.30 (d, 1H, J = 8.5 Hz), 7.14 (s, 1H), 7.06 (d, 1H, J = 8.5 Hz), 6.99–6.92 (m, 2H), 6.80–6.77 (m, 1H), 4.71 (br s, 1H), 4.22–4.07 (m, 1H), 3.85 (s, 1H), 3.48–3.34 (m, 1H), 1.72–1.51 (m, 2H), 1.51–1.32 (m, 2H), 0.94 (t, 3H, J = 7.3 Hz); MS (FAB) m/z 576 $(M+H)^+$.

4.2.7.7. *N*-Butyl-*N*-[4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2,5-dimethoxyphenyl]-2-iodobenzamide (30k). Prepared from **29h** in accordance with the general procedure B. White solid (78%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, 1H, J = 7.9 Hz), 7.34 (br s, 1H), 7.04 (dd, 1H, J = 7.3, 6.7 Hz), 7.01 (s, 1H), 6.93 (d, 1H, J = 7.3 Hz), 6.91 (s, 1H), 6.87 (dd, 1H, J = 7.9, 6.7 Hz), 4.30–4.20 (m, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 3.44–3.33 (m, 1H), 1.75–1.50 (m, 2H), 1.50–1.40 (m, 2H), 0.96 (t, 3H, J = 7.3 Hz); MS (FAB) m/z 606 $(M+H)^+$.

4.2.7.8. *N*-Butyl-*N*-[7-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)benzo[*d*][1,3]dioxol-4-yl]-2-iodobenzamide (30r). Prepared from **29j** in accordance with the general procedure B. White solid (81%); mp 113.0–115.0 °C; ^{1}H NMR (DMSO-d_6, 500 MHz, 50 °C) δ 8.52 (s, 1H), 7.70 (d, J = 7.9 Hz, 1H), 7.20 (dd, J = 7.3, 7.9 Hz, 1H), 7.12 (d, J = 7.9 Hz, 1H), 6.96 (dd, J = 7.3, 8.6 Hz, 1H), 6.86 (d, J = 8.6 Hz, 1H), 5.98 (s, 2H), 3.79 (t, J = 6.7 Hz, 2H), 1.54 (tt, J = 6.7, 8.0 Hz, 2H), 1.39 (dd, J = 7.3, 8.0 Hz, 2H), 6.86 (t, J = 7.3 Hz, 3H); MS (FAB) m/z 590 $(M+H)^+$.

4.2.8. General procedure C: synthesis of benzamide analogues (II)

4.2.8.1. *N*-Butyl-2-bromo-*N*-[4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl]-6-methoxybenzamide (30g). To a solution of 2-bromo-6-methoxybenzoic acid (104 mg, 397 μmol) in CH_2Cl_2 (3.0 mL) were added chloromethlenedimethyliminium chloride (50.8 mg, 397 μmol) at 0 °C under Ar atmosphere, then the mixture was stirred at room temperature for 1 h. At 0 °C, 2-(4-butylaminophenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (**29g**)[24] (50.0 mg, 159 μmol) and Et_3N (166 μl, 1.19 mmol) then the mixture was stirred for 3 h, and was allowed to warm to room temperature. At 0 °C, the mixture was diluted with ethyl acetate and then water was added. The organic layer was separated and washed with brine, and dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (*n*-hexane/AcOEt = 1:0–1:1) to give **30g** (73.5 mg, 139 μmol, 88%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, 1H, J = 8.5 Hz), 7.30 (d, 1H, J = 8.5 Hz), 6.96–6.93 (m, 2H), 6.51 (d, 1H, J = 7.3 Hz), 4.20–4.08 (m, 1H), 4.06 (br s, 1H), 4.75–4.67 (m, 1H), 3.65 (s, 3H), 1.81–1.54 (m, 2H), 1.52–1.34 (m, 2H), 0.94 (t, 3H, J = 7.3 Hz); MS (FAB) m/z 528 $(M+H)^+$.

4.2.8.2. *N*-Butyl-2-bromo-*N*-[4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl]-5-methoxybenzamide (30h). Prepared from **29g** and 2-bromo-5-methoxybenzoic acid in accordance with the general procedure C. White solid (60%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, 1H, J = 9.1 Hz), 7.21 (d, 1H, J = 8.5 Hz), 7.13 (s, 1H), 7.07 (d, 1H, J = 8.5 Hz), 6.56 (d, 1H, J = 3.1 Hz), 6.53

(dd, 1H, *J* = 9.1, 3.1 Hz), 4.25 (br s, 1H), 4.25–4.12 (m, 1H), 3.85 (s, 3H), 3.56 (s, 3H), 3.50–3.35 (m, 1H), 1.72–1.50 (m, 2H), 1.50–1.35 (m, 2H), 0.94 (t, 3H, *J* = 7.3 Hz); MS (FAB) *m*/*z* 558 $(M+H)^+$.

4.2.8.3. *N*-Butyl-2-bromo-*N*-[4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl]-4-methoxybenzamide (30i).

Prepared from **29g** and 2-bromo-4-methoxybenzoic acid in accordance with the general procedure C. White solid (70%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70–7.47 (m, 2H), 7.32–7.10 (m, 3H), 7.10–6.85 (m, 1H), 6.70–6.48 (m, 1H), 4.05–3.78(m, 3H), 3.70 (s, 3H), 1.70–1.50 (m, 2H), 1.50–1.33 (m, 2H), 0.99–0.78 (m, 3H); MS (FAB) *m*/*z* 528 $(M+H)^+$.

4.2.8.4. *N*-Butyl-2-bromo-*N*-[4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl]-3-methoxybenzamide (30j).

Prepared from **29g** and 2-bromo-3-methoxybenzoic acid in accordance with the general procedure C. White solid (84%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, 1H, *J* = 8.5 Hz), 7.00 (dd, 1H, *J* = 7.9, 7.9 Hz), 6.66 (d, 1H, *J* = 7.9 Hz), 6.59 (d, 1H, *J* = 7.9 Hz), 4.05–3.90 (m, 2H), 3.80 (s, 3H), 1.73–1.63 (m, 2H), 1.50–1.35 (m, 2H), 0.94 (t, 3H, *J* = 7.3 Hz); MS (FAB) *m*/*z* 528 $(M+H)^+$.

4.2.8.5. 2-Bromo-*N*-butyl-*N*-[4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2,5-dimethoxyphenyl]-5-methoxybenzamide (30m).

Prepared from **29h** and 2-bromo-5-methoxybenzoic acid in accordance with the general procedure C. White solid (71%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (br s, 1H), 7.26 (d, 1H, *J* = 9.2 Hz), 6.97 (s, 1H), 6.92 (s, 1H), 6.58 (dd, 1H, *J* = 9.2, 3.1 Hz), 6.55 (d, 1H, *J* = 3.1 Hz), 4.28–4.18 (m, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.59 (s, 3H), 3.48–3.35 (m, 1H), 1.72–1.50 (m, 2H), 1.50–1.37 (m, 2H), 0.96 (t, 3H, *J* = 7.3 Hz); MS (FAB) *m*/*z* 588 $(M+H)^+$.

4.2.8.6. 2-Bromo-*N*-butyl-*N*-[4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-3-methoxyphenyl]-5-methoxybenzamide (30o).

Prepared from **29e** and 2-bromo-5-methoxybenzoic acid in accordance with the general procedure C. White solid (quant.); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, 1H, *J* = 8.5 Hz), 7.30 (d, 2H, *J* = 9.2 Hz), 7.13 (br s, 1H), 6.92 (d, 1H, *J* = 8.5 Hz), 6.80 (s, 1H), 6.63 (d, 1H, *J* = 9.2 Hz), 6.50 (s, 1H), 4.10–3.85 (m, 1H), 3.77 (s, 3H), 3.61 (s, 3H), 1.70–1.59 (m, 2H), 1.50–1.38 (m, 2H), 0.96 (t, 3H, *J* = 7.3 Hz); MS (FAB) *m*/*z* 478 $(M+H)^+$.

4.2.8.7. 2-Bromo-*N*-butyl-*N*-[4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2-methoxyphenyl]-5-methoxybenzamide (30p).

Prepared from **29f** and 2-bromo-5-methoxybenzoic acid in accordance with the general procedure C. White solid (68%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, 1H, *J* = 9.1 Hz), 7.21 (d, 1H, *J* = 8.5 Hz), 7.13 (s, 1H), 7.07 (d, 1H, *J* = 8.5 Hz), 6.56 (d, 1H, *J* = 3.1 Hz), 6.53 (dd, 1H, *J* = 9.1, 3.1 Hz), 4.25 (br s, 1H), 4.25–4.12 (m, 1H), 3.85 (s, 3H), 3.56 (s, 3H), 3.50–3.35 (m, 1H), 1.72–1.50 (m, 2H), 1.50–1.35 (m, 2H), 0.94 (t, 3H, *J* = 7.3 Hz); MS (FAB) *m*/*z* 558 $(M+H)^+$.

4.2.8.8. 6-Bromo-*N*-butyl-*N*-[4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl]benzo[*d*][1,3]dioxole-5-carboxamide (30q).

Prepared from **29g** and 6-bromobenzo[*d*][1,3]dioxole-5-carboxylic acid[25] in accordance with the general procedure C. White solid (80%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70–7.50 (m, 2H), 7.25–7.13 (m, 2H), 6.83–6.77 (m, 1H), 6.50–6.45 (m, 1H), 5.85 (s, 1H), 4.50–4.30 (m, 1H), 4.00–3.80 (m, 2H), 1.70–1.50 (m, 2H), 1.50–1.25 (m, 2H), 1.05–0.80 (m, 3H); MS (FAB) *m*/*z* 542 $(M+H)^+$.

4.2.8.9. *N*-Butyl-*N*-[7-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)benzo[*d*][1,3]dioxol-4-yl]-2-iodo-5-methoxbenzamide (30s).

Prepared from **29j** and 2-iodo-5-methoxybenzoic acid[26] in accordance with the general procedure C. White solid (99%); mp 123.0–125.5 °C; ^{1}H NMR (DMSO-d_6, 500 MHz, 1:0.3 mixture of amide conformers) δ 8.74 (s, 0.3H), 8.66 (s, 1H), 7.78 (d, *J* = 9.2 Hz, 0.3H), 7.55 (d, *J* = 9.2 Hz, 1H), 7.22 (d, *J* = 9.2 Hz, 0.3H), 7.07 (d, *J* = 9.2 Hz, 0.3H), 6.97 (d, *J* = 9.2 Hz, 1H), 6.95 (d, *J* = 3.1 Hz, 0.3H), 6.85 (d, *J* = 9.2 Hz, 1H), 6.84 (dd, *J* = 3.1, 9.2 Hz, 0.3H), 6.63 (d, *J* = 3.1 Hz, 1H), 6.59 (dd, *J* = 3.1, 9.2 Hz, 1H), 6.13 (br s, 0.6H), 5.99 (br s, 2H), 3.72–3.82 (m, [2+0.6]H), 3.57 (s, [3+0.9]H), 1.52 (tt, *J* = 7.3, 8.0 Hz, [2+0.6]H), 1.38 (qd, *J* = 7.3, 8.0 Hz, [2+0.6]H), 0.90 (t, *J* = 7.3 Hz, [3+0.9]H); MS (FAB) *m*/*z* 620 $(M+H)^+$.

4.2.8.10. *N*-Butyl-*N*-[7-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)benzo[*d*][1,3]dioxol-4-yl]-6-iodobenzo[*d*][1,3]dioxole-5-carboxamide (30t).

Prepared from **29j** and 6-iodobenzo[*d*][1,3]dioxole-5-carboxylic acid[27] in accordance with the general procedure C. Pale yellow foam (47%); ^{1}H NMR (DMSO-d_6, 500 MHz, 1:0.3 mixture of amide conformers) δ 8.75 (s, 0.3H), 8.68 (s, 1H), 7.45 (s, 0.3H), 7.24 (s, 1H), 7.21 (d, *J* = 9.2 Hz, 0.3H), 7.05 (d, *J* = 9.2 Hz, 0.3H), 7.01 (s, 0.3H), 6.99 (d, *J* = 9.2 Hz, 1H), 6.85 (d, *J* = 9.2 Hz, 1H), 6.69 (s, 1H), 6.12 (br s, 1.2H), 6.01 (s, 2H), 5.93 (s, 2H), 3.65–3.85 (br, 2H), 3.35–3.55 (br, 0.6H), 1.50 (tt, *J* = 7.3, 7.3 Hz, [2+0.6]H), 1.35 (qd, *J* = 7.3, 7.3 Hz, [2+0.6]H), 0.87 (t, *J* = 7.3 Hz, [3+0.9]H); MS (FAB) *m*/*z* 634 $(M+H)^+$.

4.2.9. General procedure D: synthesis of benzyloxyhexafluoropropane analogues

4.2.9.1. *N*-[4-(2-Benzyloxy-1,1,1,3,3,3-hexafluoropropan-2-yl)-*N*-butyl-3-methoxyphenyl]-2-iodobenzamide (31a).

To a solution of **30e** (41.0 mg, 71.3 μmol) in DMF (3.0 mL) was added 55% NaH (3.73 mg, 85.5 μmol) at 0 °C under Ar atmosphere, then the mixture was stirred for 0.5 h at room temperature. At 0 °C, benzyl bromide (12.7 μl, 107 μmol) was added, then the mixture was stirred for 3 h, and allow to warm to room temperature. At 0 °C, the mixture was diluted with ethyl acetate and then water was added. The organic layer was separated and washed with brine, and dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (*n*-hexane/ethyl acetate = 1:0–2:1) to give **31a** (48.5 mg, 71.3 μmol, quant.) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75–7.70 (m, 1H), 7.40–7.28 (m, 6H), 7.15–7.05 (m, 1H), 6.95–6.80 (m, 3H), 6.76 (s, 1H), 4.70 (s, 2H), 4.10–3.75 (m, 2H), 3.61 (s, 3H), 1.77–1.70 (m, 2H), 1.55–1.38 (m, 2H), 1.03–0.90 (m, 3H); MS (FAB) *m*/*z* 666 $(M+H)^+$.

4.2.9.2. *N*-[4-(2-Benzyloxy-1,1,1,3,3,3-hexafluoropropan-2-yl)-2,5-dimethoxyphenyl]-*N*-butyl-2-iodobenzamide (31b).

Prepared from **30k** in accordance with the general procedure D. White solid (92%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, 1H, *J* = 7.9 Hz), 7.45–7.25 (m, 5H), 7.01 (dd, 1H, *J* = 7.3, 6.7 Hz), 6.96 (s, 1H), 6.92 (d, 1H, *J* = 7.3 Hz), 6.90–6.80 (m, 2H), 4.56 (d, 1H, *J* = 12.1 Hz), 4.39 (d, 1H, *J* = 12.1 Hz), 4.25–4.15 (m, 1H), 3.65 (s, 3H), 3.45–3.32 (m, 1H), 3.41 (s, 3H), 1.75–1.50 (m, 2H), 1.50–1.37 (m, 2H), 0.96 (t, 3H, *J* = 7.3 Hz); MS (FAB) *m*/*z* 696 $(M+H)^+$.

4.2.9.3. *N*-[4-(2-Benzyloxy-1,1,1,3,3,3-hexafluoropropan-2-yl)-2,5-dimethoxyphenyl]-2-bromo-*N*-butyl-5-methoxybenzamide (31d).

Prepared from **30m** in accordance with the general procedure D. White solid (94%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.28 (m, 5H), 7.24 (d, 1H, *J* = 8.5 Hz), 6.93 (s, 1H), 6.84 (s, 1H), 6.57 (dd, 1H, *J* = 8.5, 3.0 Hz), 6.54 (d, 1H, *J* = 3.0 Hz), 4.58 (d, 1H, *J* = 11.6 Hz), 4.36 (d, 1H, *J* = 11.6 Hz), 4.25–4.18 (m, 1H), 3.35 (s, 3H), 3.55 (s, 3H), 3.48–3.35 (m, 1H), 3.41 (s, 3H), 1.75–1.50 (m, 2H), 1.50–1.40 (m, 2H), 0.96 (t, 3H, *J* = 7.3 Hz); MS (FAB) *m*/*z* 598 $(M+H)^+$.

4.2.9.4. *N*-[7-(2-Benzyloxy-1,1,1,3,3,3-hexafluoropropan-2-yl)-6-methoxybenzo[*d*][1,3]dioxol-4-yl]-*N*-butyl-2-iodobenzamide (31f).

Prepared from **29k** in accordance with the general pro-

cedure B and subsequent the general procedure D. Yellow oil [90% (2 steps)]; ^{1}H NMR (DMSO-d_6, 500 MHz, 1:0.15 mixture of amide conformers) δ 7.74 (d, J = 8.0 Hz, 1H), 7.26–7.46 (m, [5+1.2]H), 7.18–7.26 (m, [1+0.15]H), 7.15 (dd, J = 1.2, 7.3 Hz, 1H), 7.00 (ddd, J = 1.8, 7.3, 8.0 Hz, 1H), 6.73 (s, 0.15H), 6.44 (s, 1H), 6.07 (s, 0.3H), 5.90 (s, 2H), 4.65 (s, 0.3H), 4.37 (s, 2H), 3.75–3.95 (br, 2H), 3.76 (s, 0.3H), 3.55 (s, [3+0.45]H), 1.59 (tt, J = 7.3, 8.0 Hz, [2+0.3]H), 1.40 (qd, J = 7.3, 8.0 Hz, [2+0.3]H), 0.92 (t, J = 7.3 Hz, [3+0.45]H); MS (FAB) m/z 709 (M)$^+$, 710 (M+H)$^+$.

4.2.9.5. *N*-[7-(2-Benzyloxy-1,1,1,3,3,3-hexafluoropropan-2-yl)-6-methoxybenzo[*d*][1,3]dioxol-4-yl]-*N*-butyl-2-iodo-5-methoxybenzamide (31g). Prepared from **29k** and 2-iodo-5-methoxybenzoic acid in accordance with the synthesis of **30s** and subsequent the general procedure D. Yellow solid [92% (2 steps)]; mp 123.0–125.5 °C; ^{1}H NMR (DMSO-d_6, 500 MHz, 1:0.135 mixture of amide conformers) δ 7.90 (d, J = 8.6 Hz, 0.135H), 7.59 (d, J = 8.6 Hz, 1H), 7.25–7.43 (m, [5+0.675]H), 7.01 (d, J = 3.1 Hz, 0.135H), 6.97 (dd, J = 3.1, 8.6 Hz, 0.135H), 6.75 (s, 0.135H), 6.68 (d, J = 3.1 Hz, 1H), 6.61 (dd, J = 3.1, 8.6 Hz, 1H), 6.47 (s, 1H), 6.07 (br s, 0.27H), 5.89 (br s, 2H), 4.64 (s, 0.27H), 4.37 (s, 1H), 3.75–3.90 (br, 2H), 3.80 (s, 0.405H), 3.79 (s, 0.405H), 3.76 (s, 0.27H), 3.56 (s, 3H), 3.55 (s, 3H), 1.60 (tt, J = 7.3, 8.0 Hz, [2+0.27]H), 1.41 (qd, J = 7.3, 8.0 Hz, [2+0.27]H), 0.92 (t, J = 7.3 Hz, [3+0.405]H); MS (FAB) m/z 739 (M)$^+$.

4.2.10. General procedure E: synthesis of phenanthridine analogues by Pd-catalyzed cyclization

4.2.10.1. 2-(2-Benzyloxy-1,1,1,3,3,3-hexafluoropropan-2-yl)-5-butyl-1,4-dimethoxyphenanthridin-6(5*H*)-one (33b). To a solution of **31b** (50.0 mg, 71.9 μmol) in DMA (3.0 mL) were added $PCy_3{\cdot}HBF_4$ (13.2 mg, 35.9 μmol), Cs_2CO_3 (141 mg, 431 μmol) and $Pd(OAc)_2$ (4.04 mg, 18.0 μmol) under Ar atmosphere, then the mixture was stirred for 3 h at 120 °C. At 0 °C, the mixture was diluted with ethyl acetate and then water was added. The organic layer was separated and washed with brine, and dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (*n*-hexane/AcOEt = 1:0–2:1) to give **33b** (36.7 mg, 41.0 μmol, 90%) as a white solid. Mp 98.0–100.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.90 (d, J = 8.5 Hz, 1H), 8.50 (d, J = 7.9 Hz, 1H), 7.72 (dd, J = 8.5, 7.3 Hz, 1H), 7.59 (dd, J = 7.9, 7.3 Hz, 1H), 7.47–7.25 (m, 5H), 7.12 (s, 1H), 4.85–4.80 (m, 1H), 4.60–4.52 (m, 1H), 4.52–4.40 (m, 1H), 4.40–4.25 (m, 1H), 3.61 (s, 3H), 3.51 (s, 3H), 1.95–1.75 (m, 2H), 1.42 (sext, J = 7.3 Hz, 2H), 0.97 (t, J = 7.3 Hz, 3H); MS (FAB) m/z 568 (M+H)$^+$; HRMS (FAB) calcd for $C_{29}H_{28}F_6NO_4$ 568.1923; found: 568.1891 (M+H)$^+$.

4.2.10.2. 2-(2-Benzyloxy-1,1,1,3,3,3-hexafluoropropan-2-yl)-5-butyl-3,4-dimethoxyphenanthridin-6(5*H*)-one (33c). Prepared from **29i** in accordance with the general procedure B and subsequent the general procedures D and E. Pale yellow oil (70%, 3 steps). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.26–8.31 (m, 1H), 8.06 (s, 1H), 7.56–7.61 (m, 2H), 7.43–7.50 (m, 5H), 7.34–7.40 (m, 1H), 4.77 (s, 2H), 4.47 (t, J = 7.3 Hz, 2H), 3.94 (s, 3H), 3.77 (s, 3H), 1.68 (tt, J = 7.3, 7.9 Hz, 2H), 1.31 (qt, J = 7.3, 7.9 Hz, 2H), 0.91 (t, J = 7.3 Hz, 3H); MS (FAB) m/z 568 (M+H)$^+$.

4.2.10.3. 2-(2-Benzyloxy-1,1,1,3,3,3-hexafluoropropan-2-yl)-5-butyl-1,4,8-trimethoxyphenanthridin-6(5*H*)-one (33d). Prepared from **31d** in accordance with the general procedure E. White solid (90%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.84 (d, J = 9.2 Hz, 1H), 7.93 (d, J = 3.1 Hz, 1H), 7.46–7.26 (m, 6H), 7.07 (s, 1H), 4.85–4.80 (m, 1H), 4.60–4.52 (m, 1H), 4.52–4.40 (m, 1H), 4.40–4.30 (m, 1H), 3.96 (s, 3H), 3.60 (s, 3H), 3.52 (s, 3H), 1.95–1.75 (m, 2H), 1.43 (sext, J = 7.3 Hz, 2H), 0.98 (t, J = 7.3 Hz, 3H); MS (FAB) m/z 598 (M+H)$^+$; HRMS (FAB) calcd for $C_{30}H_{30}F_6NO_5$ 598.2028; found: 598.2045 (M+H)$^+$.

4.2.10.4. 2-(2-Benzyloxy-1,1,1,3,3,3-hexafluoropropan-2-yl)-5-butyl-3,4,8-trimethoxyphenanthridin-6(5*H*)-one (33e). Prepared from **29i** and 2-iodo-5-methoxybenzoic acid in accordance with the synthesis of **30s** and subsequent the general procedures D and E. Pale yellow oil (64%, 3 steps). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.97 (s, 1H), 7.71 (d, J = 2.5 Hz, 1H), 7.41–7.51 (m, 5H), 7.32 (d, J = 9.2 Hz, 1H), 7.19 (dd, J = 2.5, 9.2 Hz, 1H), 4.75 (s, 2H), 4.48 (t, J = 8.0 Hz, 2H), 3.92 (s, 3H), 3.88 (s, 3H), 3.77 (s, 3H), 1.68 (tt, J = 7.3, 8.0 Hz, 2H), 1.32 (qt, J = 7.3, 7.3 Hz, 2H), 0.91 (t, J = 7.3 Hz, 3H); MS (FAB) m/z 598 (M+H)$^+$.

4.2.10.5. 11-(2-Benzyloxy-1,1,1,3,3,3-hexafluoropropan-2-yl)-4-butyl-10-methoxy-[1,3]dioxolo[4,5-*c*]phenanthridin-5(4*H*)-one (33f). Prepared from **31f** in accordance with the general procedure E. White solid (32%); mp 165.0–167.0 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.68 (d, J = 8.6 Hz, 1H), 8.33 (dd, J = 1.2, 7.9 Hz, 1H), 7.84 (ddd, J = 1.2, 7.4, 8.6 Hz, 1H), 7.61 (dd, J = 7.4, 7.9 Hz, 1H), 7.31–7.44 (m, 5H), 6.15 (s, 1H), 6.05 (s, 1H), 4.64 (d, J = 9.8 Hz, 1H), 4.59 (d, J = 9.8 Hz, 1H), 4.42–4.52 (m, 1H), 4.29–4.40 (m, 1H), 3.55 (s, 3H), 1.62–1.79 (m, 2H), 1.36 (qt, J = 7.3, 7.3 Hz, 2H), 0.93 (t, J = 7.3 Hz, 3H); HRMS (FAB) calcd for $C_{29}H_{26}F_6NO_5$ 582.1715; found: 582.1704 (M+H)$^+$.

4.2.10.6. 11-(2-Benzyloxy-1,1,1,3,3,3-hexafluoropropan-2-yl)-4-butyl-7,10-dimethoxy-[1,3]dioxolo[4,5-*c*]phenanthridin-5(4*H*)-one (33g). Prepared from **31g** in accordance with the general procedure E. White solid (46%); mp 134.5–136.0 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.63 (d, J = 9.2 Hz, 1H), 7.77 (d, J = 3.1 Hz, 1H), 7.45 (dd, J = 3.1, 9.2 Hz, 1H), 7.31–7.43 (m, 5H), 6.14 (s, 1H), 6.03 (s, 1H), 4.63 (d, J = 9.8 Hz, 1H), 4.57 (d, J = 9.8 Hz, 1H), 4.43–4.52 (m, 1H), 4.31–4.41 (m, 1H), 3.90 (s, 3H), 3.54 (s, 3H), 1.70 (ttd, J = 6.7, 7.3, 7.3 Hz, 2H), 1.36 (qt, J = 7.3, 7.3 Hz, 2H), 0.93 (t, J = 7.3 Hz, 3H); MS (FAB) m/z 611 (M)$^+$, 612 (M+H)$^+$.

4.2.10.7. 5-Butyl-2-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-3-fluorophenanthridin-6(5*H*)-one (5). Prepared from **30a** in accordance with the general procedure E. White solid (36%); mp 182.0–184.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (d, J = 9.7 Hz, 1H), 8.58 (d, J = 7.9 Hz, 1H), 7.94 (dd, J = 9.1, 8.5 Hz, 1H), 7.77 (dd, J = 9.7, 7.9 Hz, 1H), 7.63 (dd, J = 7.9, 7.9 Hz, 1H), 7.29 (d, J = 9.1 Hz, 1H), 4.66 (s, 1H), 4.37 (t, J = 7.3 Hz, 2H), 1.77 (quin, J = 7.3 Hz, 2H), 1.51 (sext, J = 7.3 Hz, 2H), 1.02 (t, J = 7.3 Hz, 3H); MS (FAB) m/z 436 (M+H)$^+$; Anal. Calcd for $C_{20}H_{16}F_7NO_2$: C, 55.18; H, 3.70; N, 3.22. Found: C, 55.18; H, 3.78; N, 3.37.

4.2.10.8. 5-Butyl-2-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-4-fluorophenanthridin-6(5*H*)-one (6). Prepared from **30b** in accordance with the general procedure E. White solid (73%); mp 188.5–190.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (d, J = 9.8 Hz, 1H), 8.46 (s, 1H), 8.21 (d, J = 7.9 Hz, 1H), 7.75 (dd, J = 8.5, 7.9 Hz, 1H), 7.60 (dd, J = 9.8, 8.5 Hz, 1H), 7.60 (s, 1H), 4.98 (s, 1H), 4.46 (s, 2H), 1.82 (quin, J = 7.3 Hz, 2H), 1.47 (sext, J = 7.3 Hz, 2H), 0.99 (t, J = 7.3 Hz, 3H); MS (FAB) m/z 436 (M+H)$^+$; Anal. Calcd for $C_{20}H_{16}F_7NO_2$: C, 55.18; H, 3.70; N, 3.22. Found: C, 54.80; H, 3.75; N, 3.40.

4.2.10.9. 5-Butyl-2-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-3-methylphenanthridin-6(5*H*)-one (7). Prepared from **30c** in accordance with the general procedure E. White solid (37%); mp 64.0–67.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8,56 (d, J = 7.9 Hz, 1H), 8.29 (d, J = 7.9 Hz, 1H), 7.77 (dd, J = 7.9, 7.9 Hz, 1H), 7.64 (dd, J = 7.9, 7.9 Hz, 1H), 7.58 (d, J = 7.9 Hz, 1H), 7.19 (d,

J = 7.9 Hz, 1H), 4.03 (t, J = 7.3 Hz, 2H), 2.98 (s, 3H), 1.56 (s, 1H), 1.56 (quin, J = 7.3 Hz, 2H), 1.13 (sext, J = 7.3 Hz, 2H), 0.82 (t, J = 7.3 Hz, 3H); HRMS (FAB) calcd for $C_{21}H_{20}F_6NO_2$ 432.1398; found: 432.1350 $(M+H)^+$.

4.2.10.10. 5-Butyl-2-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-4-methylphenanthridin-6(5*H*)-one (8). Prepared from **30d** in accordance with the general procedure E. White solid (81%); mp 133.0–135.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (s, 1H), 8.47 (d, J = 7.9 Hz, 1H), 8.21 (d, J = 7.9 Hz, 1H), 7.73 (dd, J = 7.9, 7.9 Hz, 1H), 7.61 (s, 1H), 7.57 (dd, J = 7.9, 7.9 Hz, 1H), 4.45 (t, J = 7.3 Hz, 2H), 4.43 (s, 1H), 2.69 (s, 3H), 1.65 (quin, J = 7.3 Hz, 2H), 1.26 (sext, J = 7.3 Hz, 2H), 0.87 (t, J = 7.3 Hz, 3H); MS (FAB) m/z 432 $(M+H)^+$; Anal. Calcd for $C_{21}H_{19}F_6NO_2$: C, 58.47; H, 4.44; N, 3.25. Found: C, 58.37; H, 4.50; N, 3.24.

4.2.10.11. 5-Butyl-2-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-3-methoxyphenanthridin-6(5*H*)-one (9). Prepared from **30e** in accordance with the general procedure E. White solid (27%); mp 101.0–104.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (d, J = 7.9 Hz, 1H), 8.47 (s, 1H), 8.12 (d, J = 8.6 Hz, 1H), 7.79 (dd, J = 8.6, 6.7 Hz, 1H), 7.59 (dd, J = 7.9, 6.7 Hz, 1H), 6.98 (s, 1H), 4.38 (t, J = 7.3 Hz, 2H), 4.12 (s, 3H), 1.82 (quin, J = 7.3 Hz, 2H), 1.54 (sext, J = 7.3 Hz, 2H), 1.05 (t, J = 7.3 Hz, 3H); HRMS (FAB) calcd for $C_{21}H_{20}F_6NO_3$ 448.1347; found: 448.1350 $(M+H)^+$.

4.2.10.12. 5-Butyl-2-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-4-methoxyphenanthridin-6(5*H*)-one (10). Prepared from **30f** in accordance with the general procedure E. White solid (73%); mp 91.0–95.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (d, J = 7.9 Hz, 1H), 8.26 (s, 1H), 8.22 (d, J = 7.9 Hz, 1H), 7.75 (dd, J = 7.9, 7.3 Hz, 1H), 7.59 (dd, J = 7.9, 7.3 Hz, 1H), 7.36 (s, 1H), 4.54 (t, J = 7.3 Hz, 1H), 4.03 (s, 1H), 3.97 (s, 3H), 1.84 (quin, J = 7.3 Hz, 2H), 1.44 (sext, J = 7.3 Hz, 2H), 0.99 (t, J = 7.3 Hz, 3H); MS (FAB) m/z 448 $(M+H)^+$; Anal. Calcd for $C_{21}H_{19}F_6NO_3 \cdot 1/2H_2O$: C, 55.30; H, 4.42; N, 3.07. Found: C, 55.27; H, 4.46; N, 3.09.

4.2.10.13. 5-Butyl-2-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-7-methoxyphenanthridin-6(5*H*)-one (12). Prepared from **30g** in accordance with the general procedure E. White solid (85%); mp 226.0–230.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.37 (d, J = 9.1 Hz, 1H), 7.82 (d, J = 8.5 Hz, 1H), 7.48 (d, J = 2.4 Hz, 1H), 7.37 (d, J = 8.5 Hz, 1H), 7.10 (dd, J = 9.1, 2.4 Hz, 1H), 5.09 (br s, 1H), 4.26 (t, J = 7.3 Hz, 2H), 3.94 (s, 3H), 1.72 (quin, J = 7.3 Hz, 2H), 1.44 (sext, J = 7.3 Hz, 2H), 0.95 (t, J = 7.3 Hz, 3H); MS (FAB) m/z 448 $(M+H)^+$; Anal. Calcd for $C_{21}H_{19}F_6NO_3 \cdot 3/4H_2O$: C, 54.73; H, 4.48; N, 3.04. Found: C, 54.71; H, 4.51; N, 2.91.

4.2.10.14. 5-Butyl-2-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-8-methoxyphenanthridin-6(5*H*)-one (13). Prepared from **30h** in accordance with the general procedure E. White solid (75%); mp 195.0–197.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (s, 1H), 8.18 (d, J = 9.2 Hz, 1H), 7.94 (d, J = 3.0 Hz, 1H), 7.79 (d, J = 9.2 Hz, 1H), 7.44 (d, J = 9.2 Hz, 1H), 7.34 (dd, J = 9.2, 3.0 Hz, 1H), 4.59 (s, 1H), 4.38 (t, J = 7.3 Hz, 2H), 1.77 (quin, J = 7.3 Hz, 2H), 1.52 (sext, J = 7.3 Hz, 2H), 1.02 (t, J = 7.3 Hz, 3H); MS (FAB) m/z 448 $(M+H)^+$; Anal. Calcd for $C_{21}H_{19}F_6NO_3 \cdot H_2O$: C, 54.20; H, 4.55; N, 3.01. Found: C, 53.89; H, 4.12; N, 2.96.

4.2.10.15. 5-Butyl-2-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-9-methoxyphenanthridin-6(5*H*)-one (14). Prepared from **30i** in accordance with the general procedure E. White solid (84%); mp 85.5–87.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.83 (d, J = 9.1 Hz, 1H), 7.81 (d, J = 7.9 Hz, 1H), 7.60 (dd, J = 7.9, 7.9 Hz, 1H), 7.33 (d, J = 9.1 Hz, 1H), 7.06 (d, J = 7.9 Hz, 1H), 5.22 (br s, 1H), 4.20 (t, J = 7.3 Hz, 2H), 4.04 (s, 3H), 1.68 (quin, J = 7.3 Hz, 2H), 1.48 (sext, J = 7.3 Hz, 2H), 0.99 (t, J = 7.3 Hz, 3H); MS (FAB) m/z 448 $(M+H)^+$; Anal. Calcd for $C_{21}H_{19}F_6NO_3 \cdot H_2O$: C, 54.20; H, 4.55; N, 3.01. Found: C, 54.32; H, 4.54; N, 3.13.

4.2.10.16. 5-Butyl-2-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-10-methoxyphenanthridin-6(5*H*)-one (15). Prepared from **30j** in accordance with the general procedure E. White solid (79%); mp 175.5–177.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.75 (s, 1H), 8.16 (d, J = 7.9 Hz, 1H), 7.84 (d, J = 9.2 Hz, 1H), 7.50 (dd, J = 7.9, 7.9 Hz, 1H), 7.38 (d, J = 9.2 Hz, 1H), 7.22 (d, J = 7.9 Hz, 1H), 4.68 (br s, 1H), 4.30 (t, J = 7.3 Hz, 2H), 4.01 (s, 3H), 1.74 (quin, J = 7.3 Hz, 2H), 1.49 (sext, J = 7.3 Hz, 2H), 1.00 (t, J = 7.3 Hz, 3H); MS (FAB) m/z 448 $(M+H)^+$; Anal. Calcd for $C_{21}H_{19}F_6NO_3$: C, 56.38; H, 4.28; N, 3.13. Found: C, 56.15; H, 4.41; N, 3.14.

4.2.10.17. 5-Butyl-2-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-3,8-dimethoxyphenanthridin-6(5*H*)-one (18). Prepared from **30o** in accordance with the general procedure E. White solid (55%); mp 184.5–186.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (s, 1H), 8.04 (d, J = 8.5 Hz, 1H), 7.93 (d, J = 3.1 Hz, 1H), 7.33 (dd, J = 8.5, 3.1 Hz, 1H), 7.32 (s, 1H), 4.56 (t, J = 7.3 Hz, 2H), 4.34 (s, 1H), 3.97 (s, 3H), 3.95 (s, 3H), 1.85 (quin, J = 7.3 Hz, 2H), 1.45 (sext, J = 7.3 Hz, 2H), 0.99 (t, J = 7.3 Hz, 3H); MS (FAB) m/z 478 $(M+H)^+$; Anal. Calcd for $C_{22}H_{21}F_6NO_4$: C, 55.35; H, 4.43; N, 2.93. Found: C, 55.17; H, 4.39; N, 2.93.

4.2.10.18. 5-Butyl-2-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-4,8-dimethoxyphenanthridin-6(5*H*)-one (19). Prepared from **30p** in accordance with the general procedure E. White solid (82%); mp 177.0–181.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (s, 1H), 8.14 (d, J = 9.1 Hz, 1H), 7.92 (d, J = 3.1 Hz, 1H), 7.38 (dd, J = 8.5, 3.1 Hz, 1H), 7.23 (br s, 1H), 6.98 (s, 1H), 4.39 (t, J = 7.3 Hz, 2H), 4.11 (s, 3H), 3.96 (s, 3H), 1.82 (quin, J = 7.3 Hz, 2H), 1.55 (sext, J = 7.3 Hz, 2H), 1.05 (t, J = 7.3 Hz, 3H); MS (FAB) m/z 478 $(M+H)^+$; HRMS (FAB) calcd for $C_{22}H_{22}F_6NO_4$ 478.1453; found: 478.1412 $(M+H)^+$.

4.2.10.19. 5-Butyl-2-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-[1,3]dioxolo[4,5-*j*]phenanthridin-6(5*H*)-one (22). Prepared from **30q** in accordance with the general procedure E. White solid (78%); mp 214.5–215.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.84 (s, 1H), 7.79 (d, J = 9.1 Hz, 1H), 7.55 (s, 1H), 7.41 (d, J = 9.1 Hz, 1H), 6.13 (s, 2H), 4.45 (s, 1H), 4.31 (t, J = 7.3 Hz, 2H), 1.75 (quin, J = 7.3 Hz, 2H), 1.50 (sext, J = 7.3 Hz, 2H), 1.01 (t, J = 7.3 Hz, 3H); MS (FAB) m/z 462 $(M+H)^+$; Anal. Calcd for $C_{21}H_{17}F_6NO_4$: C, 54.67; H, 3.71; N, 3.04. Found: C, 54.45; H, 3.72; N, 3.12.

4.2.10.20. 4-Butyl-11-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-[1,3]dioxolo[4,5-*c*]phenanthridin-5(4*H*)-one (23). Prepared from **30r** in accordance with the general procedure E. White solid. Mp 186.5–188.5 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.98 (s, 1H), 8.32 (dd, J = 7.9, 1.2 Hz, 1H), 8.27 (s, 1H), 8.26 (d, J = 7.9 Hz, 1H), 7.85 (td, J = 7.3, 1.2 Hz, 1H), 7.62 (t, J = 7.3 Hz, 1H), 6.19 (s, 2H), 4.43 (t, J = 7.9 Hz, 2H), 1.68 (tt, J = 7.3, 7.9 Hz, 2H), 1.37 (qt, J = 7.3, 7.3 Hz, 2H), 0.93 (t, J = 7.3 Hz, 3H); HRMS (FAB) calcd for $C_{21}H_{18}F_6NO_4$ 462.1140; found: 462.1169 $(M+H)^+$.

4.2.10.21. 4-Butyl-11-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-7-methoxy-[1,3]dioxolo[4,5-*c*]phenanthridin-5(4*H*)-one (24). Prepared from **30s** in accordance with the general procedure E. White solid (51%); mp 196.0–197.5 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.94 (s, 1H), 8.20 (d, J = 9.2 Hz, 1H), 8.16 (s, 1H), 7.74 (d, J = 3.1 Hz, 1H), 7.46 (dd, J = 9.2, 3.1 Hz, 1H), 6.16 (s, 2H), 4.44 (t, J = 7.9 Hz, 2H), 3.89 (s, 3H), 1.68 (tt, J = 7.3, 7.9 Hz, 2H), 1.36 (qt,

J = 7.3, 7.9 Hz, 2H), 0.92 (t, J = 7.9 Hz, 3H); HRMS (FAB) calcd for $C_{22}H_{20}F_6NO_5$ 492.1246; found: 492.1257 $(M+H)^+$.

4.2.10.22. 4-Butyl-12-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-bis[1,3]dioxolo[4,5-*c*:4',5'-*j*]phenanthridin-5(4*H*)-one (25). Prepared from **30t** in accordance with the general procedure E. White solid (95%); mp 236.0–237.0 °C; ^1H NMR (DMSO-d_6, 500 MHz) δ 8.89 (s, 1H), 8.10 (s, 1H), 7.70 (s, 1H), 7.63 (s, 1H), 6.22 (s, 2H), 6.16 (s, 2H), 4.40 (t, J = 7.9 Hz, 2H), 1.66 (tt, J = 7.3, 7.9 Hz, 2H), 1.35 (qt, J = 7.3, 7.3 Hz, 2H), 0.92 (t, J = 7.3 Hz, 3H); HRMS (FAB) calcd for $C_{22}H_{18}F_6NO_6$ 506.1038; found: 506.1010 $(M+H)^+$.

4.2.11. General procedure F: synthesis of phenanthridine analogues via debenzylation by hydrogenation

4.2.11.1. 5-Butyl-2-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-3,4,8-trimethoxyphenanthridin-6(5*H*)-one (21). To a solution of **33e** (19.2 mg, 32.1 μmol) in ethanol (0.5 mL) was added 10% Pd/C (2.2 mg), and the mixture was stirred for 3 h at room temperature under an H_2 atmosphere. The reaction mixture was filtered through a pad of Celite®, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (*n*-hexane/ethyl acetate = 9:1) to give **21** (95%) as a white solid. Mp 108.0–110.0 °C; ^1H NMR (DMSO-d_6, 500 MHz) δ 8.72 (s, 1H), 8.40 (s, 1H), 8.21 (d, J = 9.2 Hz, 1H), 7.75 (d, J = 3.1 Hz, 1H), 7.48 (dd, J = 9.2, 3.1 Hz, 1H), 4.50 (t, J = 7.3 Hz, 2H), 3.90 (s, 3H), 3.89 (s, 3H), 3.73 (s, 3H), 1.67 (tt, J = 7.3, 7.3 Hz, 2H), 1.28 (qt, J = 7.3, 7.3 Hz, 2H), 0.89 (t, J = 7.3 Hz, 3H); HRMS (FAB) calcd for $C_{23}H_{24}F_6NO_5$ 508.1559; found: 508.1549 $(M+H)^+$.

4.2.11.2. 5-Butyl-2-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-1-methoxyphenanthridin-6(5*H*)-one (11). Prepared from **33a** in accordance with the general procedure F. White solid (90%); mp 123.0–123.5 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.88 (d, J = 8.5 Hz, 1H), 8.59 (d, J = 6.7 Hz, 1H), 8.27 (br s, 1H), 7.79 (dd, J = 8.5, 6.7 Hz, 1H), 7.73 (d, J = 9.8 Hz, 1H), 7.65 (dd, J = 8.5, 6.7 Hz, 1H), 7.29 (d, J = 9.8 Hz, 1H), 4.48–4.40 (m, 1H), 4.35–4.4.22 (m, 1H), 3.86 (s, 3H), 1.90–1.73 (m, 2H), 1.60–0.97 (m, 2H), 1.03 (t, J = 7.3 Hz, 3H); MS (FAB) m/z 448 $(M+H)^+$; HRMS (FAB) calcd for $C_{21}H_{20}F_6NO_3$ 448.1347; found: 448.1394 $(M+H)^+$.

4.2.11.3. 5-Butyl-2-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-1,4-dimethoxyphenanthridin-6(5*H*)-one (16). Prepared from **33b** in accordance with the general procedure F. White solid (77%); mp 134.0–134.5 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.80 (d, J = 7.9 Hz, 1H), 8.53 (d, J = 7.9 Hz, 1H), 8.39 (br s, 1H), 7.74 (dd, J = 7.9, 6.7 Hz, 1H), 7.63 (dd, J = 7.9, 6.7 Hz, 1H), 7.18 (s, 1H), 4.55–4.45 (m, 1H), 4.40–4.30 (m, 1H), 3.92 (s, 3H), 3.78 (s, 3H), 1.92–1.80 (m, 1H), 1.44 (sext, J = 7.3 Hz, 2H), 1.00 (t, J = 7.3 Hz, 3H); MS (FAB) m/z 478 $(M+H)^+$; HRMS (FAB) calcd for $C_{22}H_{22}F_6NO_4$ 478.1453; Found: 478.1420 $(M+H)^+$.

4.2.11.4. 5-Butyl-2-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-3,4-dimethoxyphenanthridin-6(5*H*)-one (17). Prepared from **33c** in accordance with the general procedure F. White solid (99%); mp 106.0–107.0 °C; ^1H NMR (DMSO-d_6, 500 MHz) δ 8.76 (s, 1H), 8.50 (s, 1H), 8.33 (d, J = 8.6 Hz, 1H), 8.28 (d, J = 7.3 Hz, 1H), 7.87 (t, J = 8.6 Hz, 1H), 7.64 (t, J = 7.3 Hz, 2H), 4.49 (t, J = 7.3 Hz, 2H), 3.91 (s, 3H), 3.73 (s, 3H), 1.67 (tt, J = 7.3, 7.3 Hz, 2H), 1.28 (qt, J = 7.3, 7.3 Hz, 2H), 0.89 (t, J = 7.3 Hz, 3H); HRMS (FAB) calcd for $C_{22}H_{22}F_6NO_4$ 478.1453; found: 478.1445 $(M+H)^+$.

4.2.11.5. 5-Butyl-2-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-1,4,8-trimethoxyphenanthridin-6(5*H*)-one (20). Prepared from **33d** in accordance with the general procedure F. White solid (80%); mp 156.0–157.0 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.73 (d, J = 9.2 Hz, 1H), 8.42 (br s, 1H), 7.96 (d, J = 3.0 Hz, 1H), 7.31 (dd, J = 9.2, 3.0 Hz, 1H), 7.13 (s, 1H), 4.55–4.45 (m, 1H), 4.40–4.30 (m, 1H), 3.97 (s, 3H), 3.92 (s, 3H), 3.76 (s, 3H), 1.92–1.80 (m, 1H), 1.45 (sext, J = 7.3 Hz, 2H), 1.00 (t, J = 7.3 Hz, 3H); MS (FAB) m/z 508 $(M+H)^+$; HRMS (FAB) calcd for $C_{23}H_{24}F_6NO_5$ 508.1559; found: 508.1605 $(M+H)^+$.

4.2.11.6. 4-Butyl-11-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-10-methoxy-[1,3]dioxolo[4,5-*c*]phenanthridin-5(4*H*)-one (26). Prepared from **33f** in accordance with the general procedure F. White solid (93%); mp 160.0–161.5 °C; ^1H NMR (DMSO-d_6, 500 MHz) δ 8.67 (d, J = 8.6 Hz, 1H), 8.35 (s, 1H), 8.31 (d, J = 8.0 Hz, 1H), 7.81 (dd, J = 7.3, 8.6 Hz, 1H), 7.59 (dd, J = 7.3, 8.0 Hz, 1H), 6.10 (s, 2H), 4.22–4.55 (br, 2H), 3.54 (s, 3H), 1.66 (tt, J = 7.3, 7.9 Hz, 2H), 1.35 (qt, J = 7.3, 7.9 Hz, 2H), 0.92 (t, J = 7.3 Hz, 3H); HRMS (FAB) calcd for $C_{22}H_{20}F_6NO_5$ 492.1246; found: 492.1261 $(M+H)^+$.

4.2.11.7. 4-Butyl-11-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-7,10-dimethoxy-[1,3]dioxolo[4,5-*c*]phenanthridin-5(4*H*)-one (27). Prepared from **33c** in accordance with the general procedure F. White solid (82%); mp 138.5–140.0 °C; ^1H NMR (DMSO-d_6, 500 MHz) δ 8.62 (d, J = 9.2 Hz, 1H), 8.34 (s, 1H), 7.76 (d, J = 3.1 Hz, 1H), 7.43 (dd, J = 3.1, 9.2 Hz, 1H), 6.08 (s, 2H), 4.28–4.53 (br, 2H), 3.89 (s, 3H), 3.53 (s, 3H), 1.66 (tt, J = 7.3, 7.3 Hz, 2H), 1.35 (qt, J = 7.3, 7.3 Hz, 2H), 0.92 (t, J = 7.3 Hz, 3H); HRMS (FAB) calcd for $C_{23}H_{22}F_6NO_6$ 522.1351; found: 522.1361 $(M+H)^+$.

4.2.12. *N*-[4-(2-Benzyloxy-1,1,1,3,3,3-hexafluoropropan-2-yl)-*N*-butyl-3-hydroxyphenyl]-2-iodobenzamide (32)

To a solution of **31a** (40.0 mg, 60.1 μmol) in DMA (3.0 mL) were added dropwise $PCy_3{\cdot}HBF_4$ (5.53 mg, 15.0 μmol), Cs_2CO_3 (68.6 mg, 210 μmol) and $Pd(OAc)_2$ (1.75 mg, 7.81 μmol) under Ar atmosphere, then the mixture was stirred for 2 h at 165 °C. At 0 °C, the mixture was diluted with ethyl acetate and then water was added. The organic layer was separated and washed with brine, and dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (*n*-hexane/AcOEt = 1:0–2:1) to give **32** (11.0 mg, 21.0 μmol, 35%) as a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 9.26 (d, J = 8.5 Hz, 1H), 8.92 (s, 1H), 8.63 (d, J = 7.9 Hz, 1H), 7.74 (dd, J = 8.5, 7.3 Hz, 1H), 7.60 (dd, J = 7.9, 7.3 Hz, 1H), 7.53 (d, 1H, J = 9.2 Hz), 7.46 (s, 5H), 7.11 (d, 1H, J = 9.2 Hz), 4.83 (s, 2H), 4.45–4.35 (m, 2H), 1.82 (quin, 2H, J = 7.3 Hz), 1.54 (sext, J = 7.3 Hz, 2H), 1.04 (t, J = 7.3 Hz, 3H); MS (FAB) m/z 524 $(M+H)^+$.

4.2.13. 2-(2-Benzyloxy-1,1,1,3,3,3-hexafluoropropan-2-yl)-5-butyl-1-methoxyphenanthridin-6(5*H*)-one (33a)

To a solution of **32** (10.0 mg, 19.1 μmol) in CH_2Cl_2 (0.5 mL) were added dropwise methyl iodide (1.78 μl, 28.7 μmol) and K_2CO_3 (3.96 mg, 28.7 μmol) at 0 °C, then the mixture was stirred for 3 h and was allowed to warm to room temperature. At 0 °C, the mixture was diluted with ethyl acetate and then water was added. The organic layer was separated and washed with brine, and dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (n-hexane/AcOEt = 1:0–2:1) to give **33a** (13.5 mg, 19.1 μmol, quant.) as a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 8.91 (d, J = 7.9 Hz, 1H), 8.56 (d, J = 6.7 Hz, 1H), 7.78 (dd, J = 7.9, 7.3 Hz, 1H), 7.71 (d, J = 9.2 Hz, 1H), 7.62 (dd, 1H, J = 7.3, 6.7 Hz), 7.41 (s, 5H), 7.21 (d, 1H, J = 9.2 Hz), 4.76–4.25 (m, 2H), 3.69 (s, 3H), 1.82–1.74 (m, 2H), 1.52 (sext, J = 7.3 Hz, 2H), 1.02 (t, J = 7.3 Hz, 3H); MS (FAB) m/z 538 $(M+H)^+$.

4.2.14. 2-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-5-(2-methoxyethyl)phenanthridin-6(5*H*)-one (3)

Prepared from *N*-[4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl]-2-iodobenzamide and 2-chloroethyl methyl ether in

accordance with the literature method.[28] White solid (84%); mp 174.0–178.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.52 (d, J = 7.9 Hz, 1H), 8.29 (d, J = 8.5 Hz, 1H), 7.83 (d, J = 9.2 Hz, 1H), 7.76 (dd, J = 8.5, 8.5 Hz, 1H), 7.67 (d, J = 9.2 Hz, 1H), 7.61 (dd, J = 8.5, 7.9 Hz, 1H), 4.60 (t, J = 5.5 Hz, 2H), 3.38 (s, 3H); MS (FAB) m/z 420 $(M+H)^+$; HRMS (FAB) calcd for $C_{19}H_{16}F_6NO_3$ 420.1034; found: 420.0997 $(M+H)^+$.

4.2.15. 2-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-5-(2-naphthylmethyl)phenanthridin-6(5*H*)-one (4)

Prepared from *N*-[4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl]-2-iodobenzamide and 2-(bromomethyl)naphthalene in accordance with the literature method.[28] White solid (48%); mp 128.0–129.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.64 (d, J = 7.9 Hz, 1H), 8.34 (d, J = 8.5 Hz, 1H), 7.85–7.77 (m, 3H), 7.73–57 (m, 4H), 7.49–7.33 (m, 4H), 5.76 (br s, 2H), 4.39 (s, 1H); MS (FAB) m/z 502 $(M+H)^+$; Anal. Calcd for $C_{27}H_{17}F_6NO_2 \cdot 2/3H_2O$: C, 63.16; H, 3.60; N, 2.73. Found: C, 63.16; H, 3.66; N, 2.79.

4.3. Bioassay

Subgenome HCV RNA replicon cells containing the luciferase gene (LucNeo#2)[29] were cultured and maintained in Dulbecco's Modified Eagle Medium supplemented with 10% fetal bovine serum, antibiotics, and 1 mg/ml geneticin (Wako, Osaka, Japan). For anti-HCV assays, the cells were suspended (50,000 cells/ml) in the culture medium without geneticin and inoculated into a mictotiter plate. After incubation for 24 h, the cells were further incubated with fresh culture medium containing various concentrations of test compounds. After 3 days, the cells were washed with phosphate-buffered saline and treated with a cell-lysis solution for 10 min by intermittent shaking. The cell lysate (25 μl) was transferred to a white microtiter plate. One hundred microlitre of a luciferase assay reagent (Promega, Madison, WI) was added into each well, and its luciferase activity was measured by a luminometer. For cell viability assay, 10 μl of a tetrazolium dye solution (TetraColor One®, Seikagaku Biobusiness Corp., Tokyo, Japan) was added into each well. After incubation for 1 h, specific absorbance (450 nm) was measured by a microplate reader.

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References and notes

1. Liang, T. J.; Rehermann, B.; Seeff, L. B.; Hoofnagle, J. H. *Ann. Intern. Med.* **2000**, *132*, 296.
2. Hayashi, P. H.; Di Bisceglie, A. M. *Med. Clin. North Am.* **2005**, *89*, 371.
3. Memon, M. I.; Memon, M. A. *J. Viral Hepat.* **2002**, *9*, 84.
4. Echevarria-Mayo, J. M. *Enferm. Infecc. Microbiol. Clin.* **2006**, *24*, 45.
5. Bosch, F. X.; Ribes, J.; Cleries, R.; Diaz, M. *Clin. Liver Dis.* **2005**, *9*, 191.
6. McHutchison, J. G.; Gordon, S. C.; Schiff, E. R.; Shiffman, M. L.; Lee, W. M.; Rustgi, V. K.; Goodman, Z. D.; Ling, M. H.; Cort, S.; Albrecht, J. K. *N. Eng. J. Med.* **1998**, *339*, 1485.
7. <http://www.hcvadvocate.org/hepatitis/hepC/HCVDrugs.html>.
8. Sako, K.; Aoyama, H.; Sato, S.; Hashimoto, Y.; Baba, M. *Bioorg. Med. Chem.* **2008**, *16*, 3780.
9. Aoyama, H.; Sako, K.; Sato, S.; Nakamura, M.; Miyachi, H.; Baba, M.; Hashimoto, Y. *Heterocycles* **2009**, *77*, 779.
10. Hosoda, S.; Aoyama, H.; Goto, Y.; Salim, M. T. A.; Okamoto, M.; Hashimoto, M.; Baba, M.; Hashimoto, Y. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3157.
11. Nakamura, M.; Hamasaki, T.; Tokitou, M.; Baba, M.; Hashimoto, Y.; Aoyama, H. *Bioorg. Med. Chem.* **2009**, *17*, 4740.
12. Nakamura, M.; Aoyama, A.; Salim, M. T. A.; Okamoto, M.; Baba, M.; Miyachi, H.; Hashimoto, Y.; Aoyama, H. *Bioorg. Med. Chem.* **2010**, *18*, 2402.
13. Salim, M. T. A.; Okamoto, M.; Hosoda, S.; Aoyama, H.; Hashimoto, Y.; Baba, M. *Antiviral Chem. Chemother.* **2010**, *20*, 193.
14. Aoyama, H.; Baba, M.; Hashimoto, Y. *Curr. Bioactive Comp.* **2010**, *6*, 118.
15. Misawa, T.; Salim, M. T. A.; Okamoto, M.; Baba, M.; Aoyama, H.; Hashimoto, Y.; Sugita, K. *Heterocycles* **2010**, *81*, 1419.
16. Salim, M. T. A.; Goto, Y.; Hamasaki, T.; Okamoto, M.; Aoyama, H.; Hashimoto, Y.; Musiu, S.; Paeshuyse, J.; Neyts, J.; Froeyen, M.; Herdewijn, P.; Baba, M. *Antiviral Res.* **2010**, *88*, 263.
17. Tan, S. L.; Pause, A.; Shi, Y.; Sonenberg, N. *Nat. Rev. Drug. Disc.* **2002**, *1*, 867.
18. Buckwold, V. E.; Beer, B. E.; Donis, R. O. *Antiviral Res.* **2003**, *60*, 1.
19. Buckwold, V. E.; Wei, J.; Wenzel-Mathers, M.; Russell, J. *Antimicrob. Agents Chemother.* **2003**, *47*, 2293.
20. Yanagida, K.; Baba, C.; Baba, M. *Antiviral Res.* **2004**, *64*, 195.
21. Kiehne, U.; Lützen, A. *Eur. J. Org. Chem.* **2007**, 5703.
22. Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164.
23. Shánchez, I. H.; Mendoza, S.; Calderón, M.; Larraza, M. I.; Flores, H. J. *J. Org. Chem.* **1985**, *50*, 5077.
24. Chao, E. Y.; Caravella, J. A.; Watson, M. A.; Campobasso, N.; Ghisletti, S.; Billin, A. N.; Galardi, C.; Wang, P.; Laffitte, B. A.; Iannone, M. A.; Goodwin, B. J.; Nichols, J. A.; Parks, D. J.; Stewart, E.; Wiethe, R. W.; Williams, S. P.; Smallwood, A.; Pearce, K. H.; Glass, C. K.; Willson, T. M.; Zuercher, W. J.; Collins, J. L. *J. Med. Chem.* **2008**, *51*, 5758.
25. Padwa, A.; Dimitroff, M.; Waterson, A. G.; Wu, T. *J. Org. Chem.* **1998**, *63*, 3986.
26. Uyanik, M.; Akakura, M.; Ishihara, K. *J. Am. Chem. Soc.* **2009**, *131*, 251.
27. Takeda, S.; Abe, H.; Takeuchi, Y.; Harayama, T. *Tetrahedron* **2007**, *63*, 396.
28. Aoyama, A.; Aoyama, H.; Dodo, K.; Makishima, M.; Hashimoto, Y.; Miyachi, H. *Heterocycles* **2008**, *76*, 137.
29. Goto, M.; Watashi, K.; Murata, T.; Hishiki, T.; Hijikata, M.; Shimotohno, K. *Biochem. Bipphys. Res. Commun.* **2006**, *343*, 879.