Benzimidazole Derivatives Bearing Substituted Biphenyls as Hepatitis C Virus NS5B RNA-Dependent RNA Polymerase Inhibitors: Structure−Activity Relationship Studies and Identification of a Potent and Highly Selective Inhibitor JTK-109

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Following the discovery of a new series of benzimidazole derivatives bearing a diarylmethyl group as inhibitors of hepatitis C virus NS5B RNA-dependent RNA polymerase (HCV NS5B RdRp),[1,2] we extended the structure−activity relationship (SAR) study to analogues bearing a substituted biphenyl group and succeeded in a significant advancement of activity. Starting from compound **1**, optimization of the A, B, and C rings afforded potent inhibitors with low nanomolar potency against genotype 1b NS5B. The compounds, which have a substituent with a carbonyl function at the 4-position of the B-ring, efficiently blocked subgenomic viral RNA replication in the replicon cell assay at low submicromolar concentrations. Among the new compounds, compound **10n** (JTK-109) exhibited favorable pharmacokinetic profiles, high selectivity for NS5B, and good safety profiles, suggesting the potential for a clinical candidate in the treatment of hepatitis C.

Introduction

In 1989, a main causative virus of non-A, non-B posttransfusion hepatitis was first identified and named hepatitis C virus (HCV),[3] which is a positive single-stranded RNA virus of the *Flaviviridae* family.[4] According to a press release from the World Health Organization, HCV has infected an estimated 170 million people worldwide.[5] Of those infected, over 85% will develop chronic hepatitis and 20% of the chronic infections progress to liver cirrhosis.[6]

Presently, there is no vaccine for HCV and there is no broadly effective therapy for all genotypes of HCV. The current therapy for chronic HCV infection is based on interferon-α (IFN-α) and ribavirin, but sustained virological response (SVR) rates are limited particularly in the patients infected with the most prevalent HCV genotype 1 virus. The SVR rates in the recent standard treatment, a combination therapy of pegylated IFN-α with ribavirin, are below 50%.[7] In addition, considerable side effects are often associated with these treatments, thereby resulting in limited patient compliance. Therefore, development of an improved therapeutic agent for hepatitis C, especially for genotype 1 hepatitis C, is an urgent medical need.

To inhibit HCV growth, a viral protein such as NS3 serine protease, NS3 RNA helicase, or NS5B RNA-dependent RNA polymerase (RdRp) can be targeted and has been drawing attention.[8] One of the specific proteins, NS5B RdRp, is considered to play a central role in the HCV gene replication from several reports including a finding by Kolykhalov et al.[9] that NS5B RdRp's activity is essential for HCV viral replication and infectivity in a chimpanzee model. Several classes of potent NS5B inhibitors have been reported in the past several years,[8,10−12] and several compounds have entered clinical trials. Recently, antiviral activity in HCV infected patients was demonstrated by two inhibitors, a nucleoside NS5B inhibitor NM283[13] and a nonnucleoside inhibitor HCV-796.[14]

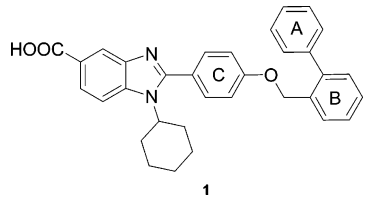

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Figure 1.

In our earlier paper, we reported a new series of benzimidazole derivatives bearing substituted diarylmethyl groups as NS5B inhibitors.[1] However, improvement of the activity was the next major challenge in the development of new anti-HCV drugs. We also found in the report that compound **1** (Figure 1) bearing a biphenyl group inhibits genotype 1b NS5B RdRp with an IC_{50} of 0.30 μM. To address the challenge, we selected compound **1** as a new lead compound and advanced the SAR study. Compared to the diarylmethyl series, the substituents on the phenyl rings showed more distinct SARs and generated significant improvement in potency. Here, we report the benzimidazole derivatives bearing substituted biphenyl groups and related compounds as potent NS5B inhibitors with efficient viral RNA reduction activity (low submicromolar EC_{50}) in replicon cells. Our work led to the identification of the potent and highly selective inhibitor **10n** (JTK-109) with favorable pharmacokinetic and safety profiles in rat.

Chemistry

The compounds prepared for this study are shown in Tables 1−5. Syntheses were accomplished as schematized in Schemes 1−7. The general synthetic route for compounds **2a**−**i**, **3a**−**d**,**i**, and **7** is described in Scheme 1. The phenol **11a**[1] was alkylated with the benzyl halide **16** to give 2-[4-(2-bromobenzyloxy)phenyl]-1-cyclohexyl-*1H*-benzimidazole-5-carboxylic acid methyl/ethyl ester derivatives **12**. The benzyl bromides **16** were prepared from the corresponding toluene/picoline **14** by bro-

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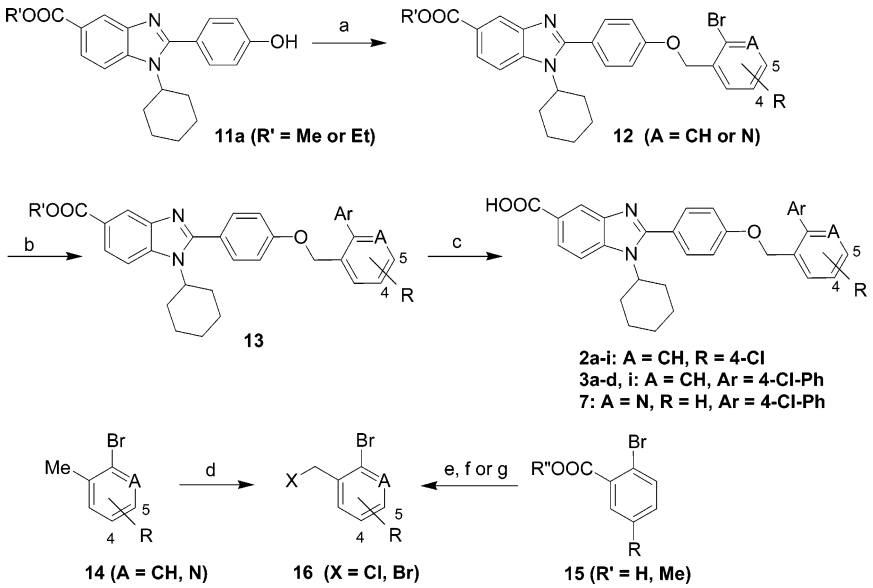
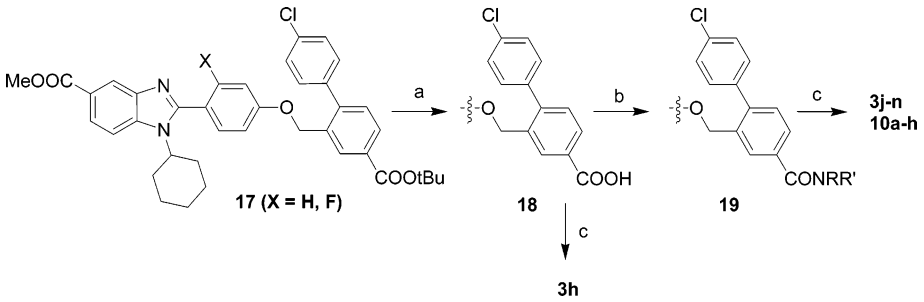
Scheme 1[a]



[a] Reagents and conditions: (a) **16**, K_2CO_3, DMF, 80 °C; (b) $ArB(OR)_2$, $Pd(PPh_3)_4$, $NaHCO_3$, DME−H_2O, reflux; (c) 2 N aqueous NaOH, EtOH−THF, reflux; (d) NBS, AIBN, CCl_4, reflux; (e) $LiAlH_4$, THF; (f) $SOCl_2$, pyridine, $CHCl_3$, room temp; (g) CBr_4, PPh_3, THF, 0 °C.

Scheme 2[a]



[a] Reagents and conditions: (a) CF_3COOH, CH_2Cl_2, room temp; (b) $(COCl)_2$, DMF, CH_2Cl_2, room temp, then HNRR′, THF−CH_2Cl_2, 0 °C; (c) 2 N aqueous NaOH, EtOH−THF, reflux.

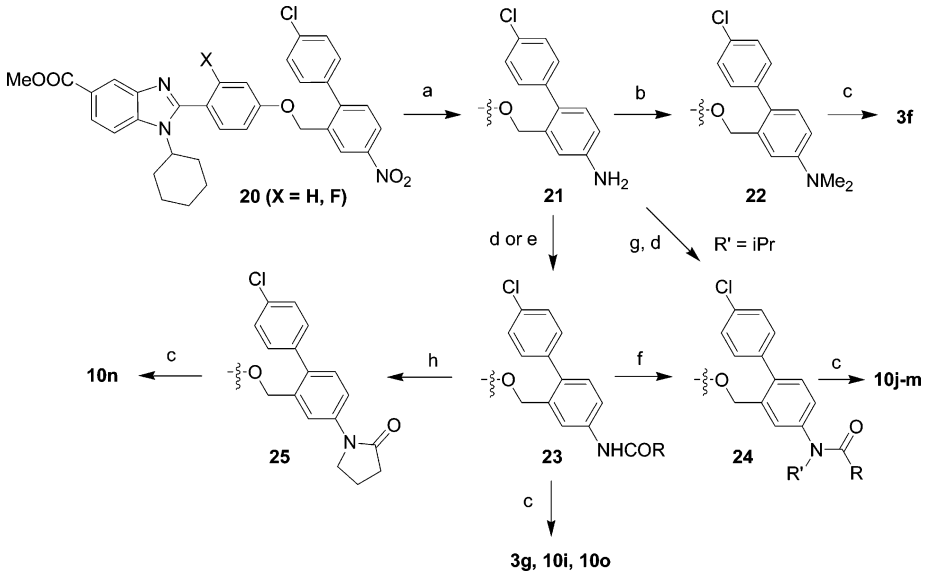
mination with *N*-bromosuccinimide. Alternatively, the benzoic acid or ester **15** was converted to the benzyl halide **16** with a two-step sequence: hydride reduction of the carboxylic acid or ester and subsequent halogenation of the resulting alcohol. Suzuki coupling[15] of **12** with the corresponding aryl boronic acids provided the biphenyl derivatives **13**, after which hydrolysis of the ester group under alkaline conditions gave the desired compounds **2a**−**i**, **3a**−**d**,**i**, and **7**.

Dibenzoic acid **3h** and benzamides **3j**−**n** and **10a**−**h** were synthesized from the esters **17** (prepared by the route in Scheme 1), as shown in Scheme 2. The *tert*-butyl group of **17** was removed by treating with trifluoroacetic acid to give benzoic acid **18**, which was subjected to hydrolysis to yield **3h**. Benzamides **3j**−**m** and **10a**−**h** were prepared from the benzoic acid **18** in two steps. Coupling between **18** and the corresponding amines using the acid chloride of **18** and subsequent hydrolysis of the methyl esters **19** yielded compounds **3j**−**m** and **10a**−**h**. Compound **3n**, a regioisomer of **3l**, was synthesized from 3-bromo-4-methylbenzoic acid *tert*-butyl ester (compound **14**, A = CH, R = 5-COOt-Bu) by the same procedure employed for **3l**.

Compounds **3f**,**g** and **10i**−**o** were synthesized from **20** (prepared by the route in Scheme 1), as shown in Scheme 3. The nitro group of **20** was reduced with stannous chloride to give an aniline **21**. Eschweiler−Clarke amine methylation[16] and subsequent hydrolysis of the methyl ester afforded compound **3f** via the *N*,*N*-dimethylaniline **22**. The *N*-acyl derivatives **3g** and **10i** were derived from **21** in two steps: acylation with an appropriate acid chloride to acylanilide **23** and subsequent hydrolysis of the ester. Compounds **10j**−**l** were derived from **23** via compound **24** by alkylation with the corresponding alkyl iodide in the presence of sodium hydride followed by hydrolysis of the methyl ester. Compound **10m** was prepared from the aniline **21** in three steps: reductive amino alkylation with acetone in the presence of sodium triacetoxyborohydride, acetylation with acetyl chloride, and hydrolysis of the methyl ester. Lactam **10n** was synthesized from the aniline **21** in three steps. Aniline **21** was acylated with 4-chlorobutyryl chloride and then cyclized in the presence of K_2CO_3 in DMF at 80 °C to give the lactam **25**. Hydrolysis of the methyl ester afforded compound **10n**. The aniline **21** was converted to the urea **10o** by reaction with dimethylcarbamoyl chloride and subsequent hydrolysis of the methyl ester.

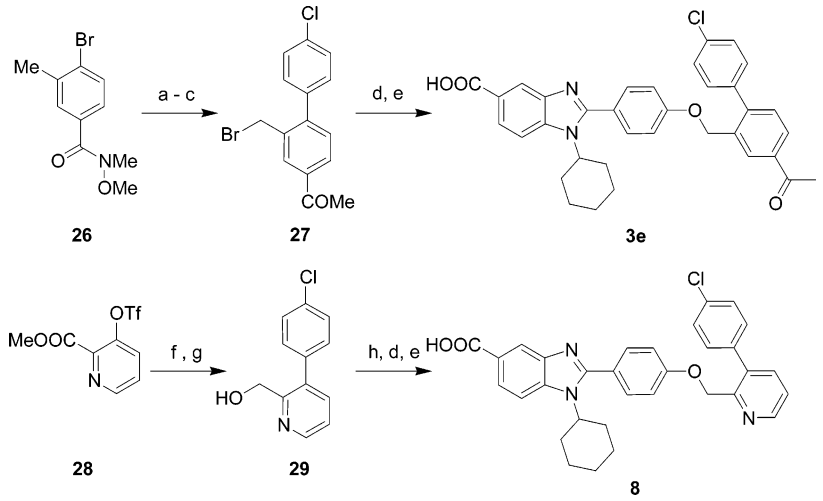
Compounds **3e** and **8** were prepared by an alternative way shown in Scheme 4. Ketone **3e** was synthesized from Weinreb amide[17] **26** (prepared from 4-bromo-3-methylbenzoic acid; see Experimental Section). Conversion of the Weinreb amide **26** with the following three-step sequence gave a biphenylmethyl bromide **27**: Grignard reaction with methylmagnesium bromide, Suzuki coupling with 4-chlorophenylboronic acid, and bromination of the 2-methyl group with *N*-bromosuccinimide. Coupling between **27** and phenol **11a** with subsequent hydrolysis of the ester gave the methyl ketone **3e**. Compound **8** was synthesized from a trifluoromethanesulfonate **28** (prepared from

Scheme 3[a]



[a] Reagents and conditions: (a) $SnCl_2$, EtOH−THF, reflux; (b) HCHO (37% aqueous), HCOOH, reflux; (c) 2 N aqueous NaOH, EtOH−THF, reflux; (d) RCOCl, Et_3N, $CHCl_3$, 0 °C, then room temp; (e) Me_2NCOCl, pyridine, $CHCl_3$, reflux; (f) NaH, MeI/EtI, DMF, 0 °C, then room temp; (g) acetone, $NaBH(OAc)_3$, AcOH−THF, room temp; (h) K_2CO_3, DMF, 80 °C.

Scheme 4[a]



[a] Reagents and conditions: (a) 4-Cl−$PhB(OH)_2$, $Pd(PPh_3)_4$, $NaHCO_3$, DME-H_2O, reflux; (b) MeMgBr, THF, 0 °C to room temperature; (c) NBS, AIBN, CCl_4, reflux; (d) **11a**, K_2CO_3, DMF, 80 °C; (e) 2 N aqueous NaOH, EtOH−THF, reflux; (f) 4-Cl−$PhB(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, toluene, 90 °C; (g) $LiAlH_4$, THF, 0 °C; (h) $SOCl_2$, pyridine, $CHCl_3$, room temp.

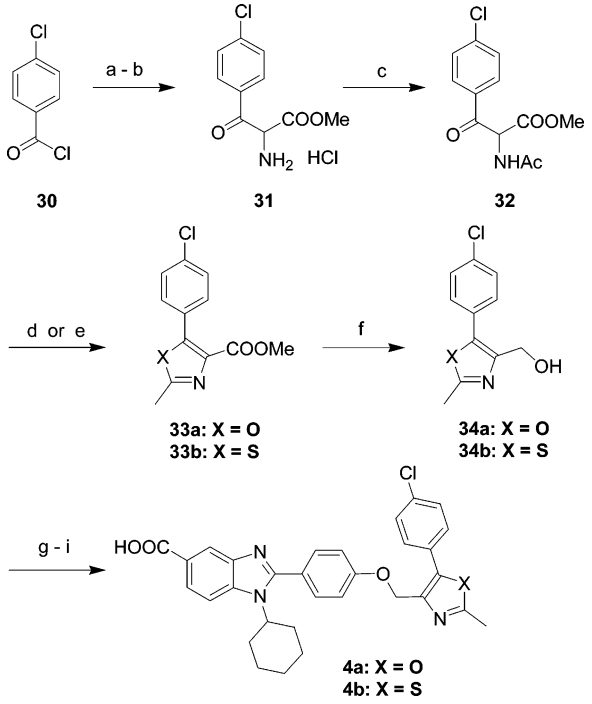
3-hydroxypicolinic acid; see Experimental Section). Compound **28** was converted to the benzyl alcohol **29** in two steps: Suzuki coupling with 4-chlorophenylboronic acid, followed by lithium aluminum hydride reduction of the methyl ester. Chlorination of the alcohol **29**, coupling with the phenol **11a**, and subsequent hydrolysis of the methyl ester gave the pyridine **8**.

Preparation of oxazole **4a** and thiazole **4b** was achieved via the key intermediate **32** (Scheme 5). 4-Chlorobenzoyl chloride **30** was converted to α-*C*-4-chlorobenzoylamino acid methyl ester **31** by the reaction with methyl isocyanoacetate in the presence of triethylamine and the subsequent acidic methanolysis of the oxazole intermediate.[18] Compound **31** was allowed to react with acetic anhydride in the presence of sodium acetate to give an acetylamide **32**. A facile ring closure of compound **32** to the oxazole 2-carboxylic acid methyl ester **33a** was effected in concentrated H_2SO_4 at room temperature. Compound **33a** was converted to oxazole **4a** in four steps by the same procedure as described for compound **8**. Cyclization to provide thiazole **33b** from compound **32** was achieved with Lawesson's reagent[19] in refluxing THF. Compound **33b** was converted to thiazole **4b** in four steps by the procedure described above.

The reversed thiazole **5** and pyrimidine **6** were synthesized from a common starting material **35**[20] as shown in Scheme 6. The *β*-keto ester **35** was reacted with Br_2 in 1,4-dioxane and then with thioacetamide in EtOH at reflux to give a thiazole **36**. Compound **36** was converted to the reversed thiazole **5** in four steps by using the procedure described in Scheme 5. Pyrimidine **37** was obtained by the condensation of compound **35** with *N*,*N*-dimethylformamide dimethylacetal and subsequent reaction with acetamidine hydrochloride in the presence of sodium ethoxide in refluxing EtOH.[21] Compound **37** was converted to the pyrimidine **6** by using the procedure described above.

The biphenylmethyl derivatives **9a**−**e** were synthesized from the corresponding phenol **11** in two steps (Scheme 7). The phenols **11c**−**f** were prepared by the previously described procedure for **11a**,**b**.[1,2] The phenols **11b**−**f** were alkylated with

Scheme 5[a]



[a] Reagents and conditions: (a) methyl isocyanoacetate, Et_3N, THF, reflux; (b) AcCl, MeOH, reflux; (c) Ac_2O, NaOAc, H_2O, 0 °C; (d) concentrated H_2SO_4, room temp; (e) Lawesson's reagent, THF, reflux; (f) $LiAlH_4$, THF, 0 °C; (g) $SOCl_2$, pyridine, $CHCl_3$, room temp; (h) **11a**, K_2CO_3, DMF, 80 °C; (i) 2 N aqueous NaOH, EtOH−THF, reflux.

2-phenylbenzyl bromide and subjected to hydrolysis of the methyl ester to give compounds **9a**−**e**.

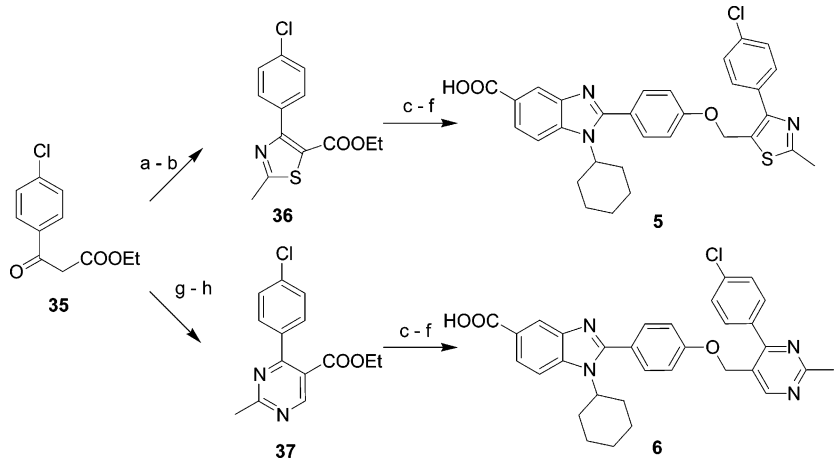
Results and Discussion

The compounds synthesized in this study were tested in the in vitro HCV genotype 1b NS5B RdRp assay. Our assay employed a genotype 1b enzyme (BK strain) lacking the 47 C-terminal residues with an additional hexahistidine tag (1b $NS5B_{544}$).[22] The results are summarized in Tables 1−5 as IC_{50} values. The compounds in Tables 1−3 and 5 were evaluated for their ability to inhibit the replication of subgenomic HCV RNA in a replicon cell system using a Huh-5-2 cells (a Huh-7 derived cell line that possesses a 1b HCV replicon containing the luciferase reporter gene).[23,24] The results were described as replicon EC_{50} values in the tables. Although the replicon system does not generate infectious particles, monitoring a reduction of HCV RNA is a facile method for quantifying anti-HCV activity of NS5B inhibitors.

We started our SAR study around the A-ring of compound **1** (Table 1). We chose 4-chloro group as a substituent on the B-ring of compound **1** because we had already discovered in an earlier report that meta-chloro substitution of the benzyl group proved to be favorable over the H atom.[1] Indeed, compound **2a** showed a slightly increased potency for NS5B inhibition compared to the lead compound **1**. Various substituents were introduced at the 4-position of the A-ring as shown in Table 1. These analogues **2b**−**g** generally exhibited potencies for NS5B greater than the potency of compound **2a**. Specifically, small electron-withdrawing groups such as the chloro (**2b**), carboxylic acid (**2e**), carboxamide (**2f**), or cyano (**2g**) group tend to be preferred. These compounds exhibit 3- to 4-fold increased potency compared to **2a**. The position of the substituent seems to be important. Introduction of the Cl atom at the 3-position (compound **2h**) reduced the potency about 2-fold. Changing the phenyl ring to 3-pyridine (**2i**) retained the activity.

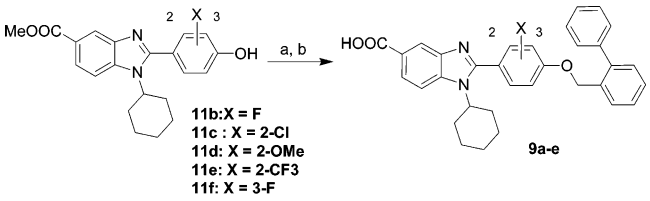
The ability of the compounds in Table 1 to inhibit cellular replication of HCV RNA was evaluated, and they effectively inhibited replication at low micromolar concentrations except for compound **2e**. The compounds were not toxic at the concentration required for the cell activity. The shift in potency between NS5B IC_{50} and replicon EC_{50} seems large (more than 20-fold) except for compound **2i**, although the biochemical potency varies depending on the enzyme or assay conditions employed. Cellular activity is influenced by a number of factors such as membrane permeability, metabolism, and affinity for proteins such as albumin. The lack of the cellular activity in compound **2e**, despite potent NS5B inhibition (IC_{50} = 0.058 μM), is not considered coming from its permeability problem because it has a log *D* value of 3.26 at pH 7.2 and showed a good membrane permeability in the Caco-2 cell monolayer assay (P_{app} = 23.4 cm/s × 10^{-6} when propranolol showed a value of 16.5) despite the existence of negatively charged carboxylate functions. The compound might have a high affinity to albumin in the assay media because of the existence of two acidic functions (COOH). Pyridine **2i** showed the smallest shift in potency between the biochemical assay and cell assay, indicating that introduction of a polar fragment, such as pyridine, could improve the cellular activity by reducing protein affinity.[25] In

Scheme 6[a]



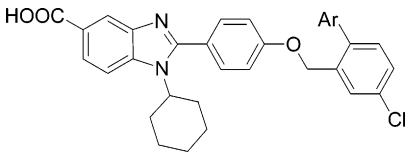
[a] Reagents and conditions: (a) Br_2, 1,4-dioxane, room temp; (b) thioacetamide, EtOH, reflux; (c) $LiAlH_4$, THF, 0 °C; (d) $SOCl_2$, pyridine, $CHCl_3$, room temp; (e) **11a**, K_2CO_3, DMF, 80 °C; (f) 2 N aqueous NaOH, EtOH−THF, reflux; (g) *N*,*N*-dimethylformamide dimethylacetal, reflux; (h) acetamidine·HCl, NaOEt, EtOH, reflux.

Scheme 7[a]



[a] Reagents and conditions: (a) 2-phenylbenzyl bromide, K_2CO_3, DMF, 80 °C; (b) 2 N aqueous NaOH, EtOH−THF, reflux.

Table 1. NS5B Enzyme Assay IC_{50} Values, Replicon Cell-Based Assay EC_{50} Values, and Cell Viability CC_{50} Values for Compounds **2** (A-Ring Variation)



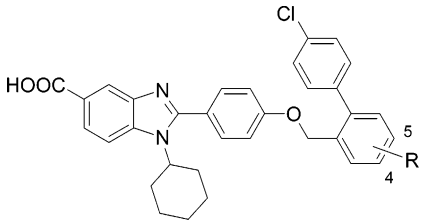
compd	Ar	NS5B[a] IC_{50} (μM)[d]	replicon[b] EC_{50} (μM)[d]	cell viability[c] CC_{50} (μM)[d]
1		0.30[e]		
2a	Ph	0.20	3.7	25
2b	4-Cl−Ph	0.050	3.0	26
2c	4-Me-Ph	0.098	3.4	25
2d	4-OMe-Ph	0.10	2.4	25
2e	4-COOH−Ph	0.058	>10	>50
2f	4-$CONH_2$−Ph	0.069	2.5	>50
2g	4-CN−Ph	0.055	1.3	26
2h	3-Cl−Ph	0.48	6.5	32
2i	3-pyridine	0.29	2.6	>50

[a] Six His-tagged C-terminally truncated 544-amino acid genotype 1b NS5B. [b] Compounds were incubated in Huh-5-2 cell culture for 48 h. [c] MTT assay on parallel samples at the same time. [d] Values are the mean of three independent experiments. Standard deviations are within 30% of the mean. [e] Reference 1.

addition, the cytotoxicity was reduced in compounds **2f** and **2i**, giving an improved therapeutic index (TI, the ratio CC_{50}/EC_{50}) compared with other compounds in Table 1.

Having investigated the requirements for the A-ring substituents, we next turned our attention to the B-ring (Tables 2 and 3). We employed the 4-Cl−Ph group as the A-ring and examined the effect of a substituent at the 4- or 5-position of the B-ring (Table 2). To reexamine the effect of the Cl group on the B-ring in **2b**, compound **3a** (R = H) was synthesized. As seen in Table 2, there is no change in the biochemical activity and the cellular potency. To test the idea that reduction of protein binding may be necessary to improve the cellular potency in this series from the results in Table 1, polar substituents were intentionally introduced. By comparison of the inhibitory activity of compounds **3b**−**n** to that of **3a**, it clearly appears that both biochemical and cellular potencies can be improved by addition of a substituent. Especially, carbonyl/sulfonyl functional groups are preferred, suggesting that these carbonyl/sulfonyl oxygen atoms might have some interactions with the enzyme as a hydrogen-bond acceptor. For example, 4-SO_2NH_2 (**3c**, IC_{50} = 0.016 μM), 4-acetyl (**3e**, IC_{50} = 0.018 μM), and 4-$CONH_2$ (**3j**, IC_{50} = 0.013 μM) are particularly notable with a 4- to 6-fold improvement in potency compared to **3a**. The increase in cellular potency was 2- to 3-fold in compounds **3c** and **3j** and ∼10-fold in **3e** compared with **3a**. The therapeutic indexes were also improved. Adding an alkyl group onto the nitrogen atom of the sulfonamide **3c** or carboxamide **3j** retained biochemical activity: 4-SO_2NMe_2 (**3d**), 4-CONHMe (**3k**), 4-$CONMe_2$ (**3l**), and 4-CONHBn (**3m**). However, these compounds, except **3m**, showed better cellular activity than **3c** or **3j**. These compounds

Table 2. NS5B Enzyme Assay IC_{50} Values, Replicon Cell-Based Assay EC_{50} Values, and Cell viability CC_{50} Values for Compounds **3** (B-Ring Variation)



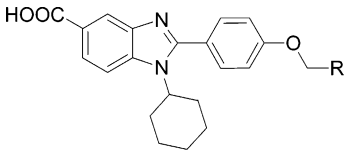
compd	R	NS5B[a] IC_{50} (μM)[e]	replicon[b] EC_{50} (μM)[e]	cell viability[c] CC_{50} (μM)[e]	TI[d] CC_{50}/EC_{50}
2b	4-Cl	0.050	3.0	25	13
3a	H	0.078	3.2	35	11
3b	4-OMe	0.037	1.6	24	15
3c	4-SO_2NH_2	0.016	1.5	27	18
3d	4-SO_2NMe_2	0.023	0.66	26	39
3e	4-Ac	0.018	0.34	24	71
3f	4-NMe_2	0.063	2.6	30	12
3g	4-NHAc	0.022	1.3	23	18
3h	4-COOH	0.024	>10	>50	
3i	4-CN	0.041	0.82	23	28
3j	4-$CONH_2$	0.013	0.79	26	33
3k	4-CONHMe	0.018	0.53	25	47
3l	4-$CONMe_2$	0.015	0.37	28	76
3m	4-CONHBn	0.029	1.1	22	20
3n	5-$CONMe_2$	0.032	0.84	25	30

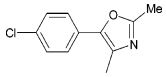
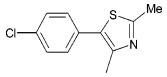
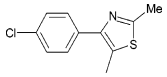
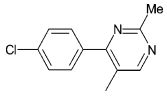
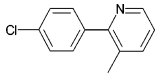
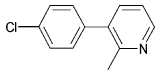
[a] Six His-tagged C-terminal deleted 544-amino acid genotype 1b NS5B. [b] Compounds were incubated in Huh-5-2 cell culture for 48 h. [c] MTT assay on parallel samples at the same time. [d] Therapeutic index: the ratio CC_{50}/EC_{50}. [e] Values are the mean of three independent experiments. Standard deviations are within 30% of the mean.

are obviously more lipophilic compared to **3c** or **3j**. Therefore, improvement of cellular potency cannot be achieved by just lowering the lipophilicity. *N*,*N*-Dimethylamide **3l** showed one of the best cellular potencies (EC_{50} = 0.37 μM) in Table 2 with an improved TI of over 70 and was ∼10-fold more potent than **3a**. The amide substituent was also effective in the regioisomer (**3n**, R = 5-$CONMe_2$) but less active than at the 4-position. The reversed amide **3g** showed biochemical and cellular activities similar to the activities of sulfonamide and amide. The lack of the activity in cells was again observed in compound **3h** bearing the COOH substituent, as was the case for **2e**. As a result, an NS5B inhibitory potency of <20 nM was achieved and the cellular potency was increased ∼10-fold. Moreover, the TI improved in accordance with the increase in cellular potency.

Next, we examined the effect of replacing the B-ring with heteroaryl rings (Table 3). As a first attempt, the oxazole compound **4a** was synthesized and examined. It inhibited NS5B at an IC_{50} of 0.58 μM, which is 7-fold less potent than compound **3a**, and showed weak activity in the replicon assay (30−36% inhibition at 10 μM). Changing the oxazole ring to a thiazole ring (**4b**) and to the reversed thiazole ring (**5**) afforded 3- to 6-fold better biochemical activities than **4a**, although they are not better than the phenyl ring (**3a**). Then, the five-membered ring was changed to six-membered rings such as pyrimidine (**6**) and pyridines (**7** and **8**). The pyrimidine **6** and the 6-pyridine **7** exhibited biochemical activities similar to that of the phenyl ring **3a**, whereas the 3-pyridine **8** was slightly less potent. The cellular activity of **7** (EC_{50} = 1.2 μM) was ∼3-fold better than **3a**, which is probably a result of the lowered protein binding by the basic or polar pyridine ring. In addition, the TI improved to >42. However, the introduction of heteroaryl rings in place of the B-phenyl ring did not improve the potency against NS5B, although the cellular potency was improved slightly in compound **7**.

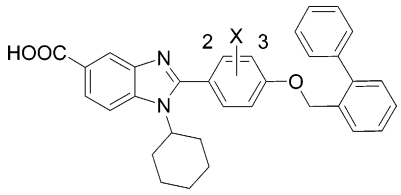
Table 3. NS5B Enzyme Assay IC_{50} Values, Replicon Cell-Based Assay EC_{50} Values, and Cell Viability CC_{50} Values for Compounds **4**−**8** (Heterocycles)



compd	R	NS5B[a] IC_{50} (μM)[e]	replicon[b] EC_{50} (μM)[e]	cell viability[c] CC_{50} (μM)[e]	TI[d] CC_{50}/EC_{50}
4a		0.58	>10[f]	39	
4b		0.17	6.3	31	4.9
5		0.090	2.9	39	13
6		0.088	1.5	24	16
7		0.053	1.2	>50	>41
8		0.15	3.9	25	6

[a] Six His-tagged C-terminal deleted 544-amino acid genotype 1b NS5B. [b] Compounds were incubated in Huh-5-2 cell culture for 48 h. [c] MTT assay on parallel samples at the same time. [d] Therapeutic index: the ratio CC_{50}/EC_{50}. [e] Values are the mean of three independent experiments. Standard deviations are within 30% of the mean. [f] 30−36% inhibition at 10 μM.

Table 4. NS5B Inhibitory Activity of Compounds **9** (C-Ring Variation)



compd	X	NS5B IC_{50} (μM)[a]
1	H	0.30[b]
9a	2-F	0.10
9b	2-Cl	0.35
9c	2-OMe	1.1
9d	2-CF_3	0.93
9e	3-F	0.38

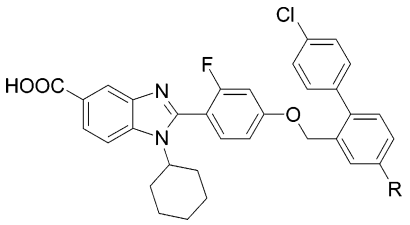
[a] Six His-tagged C-terminal deleted 544-amino acid genotype 1b NS5B. Values are the mean of three independent experiments. Standard deviations are within 20% of the mean. [b] Reference 1.

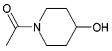
Since we had found in the earlier report[1] that introduction of a fluorine atom at a position ortho to the benzimidazole ring on the C-ring modestly improved the potency against NS5B, we looked at the effects of substituents on the C-ring. Compounds **9a**−**e** were synthesized and tested in the NS5B RdRp assay (Table 4). Introduction of a fluorine atom at a position ortho to the benzimidazole (2-position on the C-ring, compound **9a**) increased potency as expected. On the other hand, another halogen, chloro, did not change the potency (**9b**). Then an electron-donating group OMe (**9c**) and an electron-withdrawing group CF_3 (**9d**) were examined and gave 3- to 4-fold reduction in potency. To examine the effect of a fluorine atom at the other position, a regioisomer **9e** was tested. No increase in potency was observed in compound **9e** compared with **1**. It seems that the potency is influenced by the size of the substituent at the 2-position of the C-ring. The dihedral angle between the benzimidazole ring and the C-ring might be an important factor.[26] A fluorine atom at the ortho position seems to make the torsional angle optimal for gaining NS5B affinity.

Encouraged by these findings and to find more potent inhibitors, we prepared compounds bearing a substituent at the 4-position of the B-ring with a focus on carboxamides and the reversed amides and with 2-fluoro on the C-ring. As shown in Table 5, most of the compounds showed significant inhibitory activity against NS5B RNA polymerization (IC_{50} < 20 nM) and effectively blocked cellular replication of HCV RNA at low submicromolar concentrations (EC_{50} < 0.5 μM). The therapeutic index (TI) was further improved and reached to over 100 in several compounds. Unlike the result observed in compound **9a**, the increase in biochemical potency was not apparent by introduction of a fluorine atom (**10a** vs **3k**, **10e** vs **3l**, and **10i** vs **3g**), whereas the cellular potency tends to increase. In the carboxamides, enlarging the size of the amide *N*-alkyl group from methyl (**10a**) to propyl (**10b**,**c**) or from *N*,*N*-dimethyl (**10e**) to piperidine (**10f**) was well tolerated. Replacement of the amide hydrogen with a methyl group increased cellular potency (**10a** vs **10e**), as was the case in Table 3. Compound **10e** is one of the most potent replicon inhibitors in this series with an EC_{50} of 0.16 μM. Introduction of additional polarity by a hydroxyl group tends to decrease cellular potency (**10d**,**h**). In the reversed amide, N-alkylation of acetylanilide **10i** increased cellular potency (**10j**,**k**,**m**) as in the carboxamide series. Compounds **10j**,**k**,**m** showed the best EC_{50} values (0.14−0.16 μM) in this series with TI over 100. The lactam **10n** showed a slightly reduced cellular potency but gave a biochemical activity similar to that of the ring-opened compound **10k**. Last, urea **10o** has a similar biochemical potency but a reduced cellular activity compared to the amide and the reversed amide.

In a summary of the SAR of the benzimidazole derivatives bearing substituted biphenyl groups, some general comments

Table 5. NS5B Enzyme Assay IC_{50} Values, Replicon Cell-Based Assay EC_{50} Values, Cell Viability CC_{50} Values, and Oral Absorption Data for Compounds **10** (A-Ring Variation)



compd	R	NS5B[a] IC_{50} (μM)[f]	replicon[b] EC_{50} (μM)[f]	cell viability[c] CC_{50} (μM)[f]	TI[d] CC_{50}/EC_{50}	C_{1h}/C_{2h} [e] (μM)
10a	CONHMe	0.012	0.36	25	69	0.7/0.5
10b	CONHnPr	0.021	0.38	24	63	1.3/0.6
10c	CONH*i*-Pr	0.013	0.20	22	110	1.1/0.3
10d		0.021	0.94	26	28	
10e	$CONMe_2$	0.012	0.16	26	163	1.6/1.8
10f		0.018[g]	0.27	24	89	2.2/0.7
10g		0.014	0.28	25	89	1.1/0.5
10h		0.014	0.38	26	68	0.1/ND
10i	NHAc	0.014	0.46	24	52	1.0/0.3
10j	NMeAc	0.016	0.15	26	173	0.9/1.1
10k	NEtAc	0.019	0.14	25	179	1.5/0.8
10l	NMeCO*i*-Pr	0.032	0.35	22	63	1.9/1.1
10m	N*i*-PrAc	0.021	0.16	20	125	1.1/0.7
10n		0.017	0.32	25	78	4.0/4.5
10o	$NHCONMe_2$	0.022	0.62	25	40	

[a] Six His-tagged C-terminal deleted 544-amino acid genotype 1b NS5B. [b] Compounds were incubated in Huh-5-2 cell culture for 48 h. [c] MTT assay on parallel samples at the same time. [d] Therapeutic index: the ratio CC_{50}/EC_{50}. [e] Plasma concentration at 1 and 2 h after oral dosing in rats (30 mg/kg, $n = 2$ or 3). [f] Values are the mean of three independent experiments. Standard deviations are within 30% of the mean. [g] $n = 2$.

can be made on the basis of available data. (a) Small electron-withdrawing groups at the 4-position of the A-ring are preferred for NS5B RdRp. (b) Substituents with a carbonyl function such as amide, reversed amide, and ketone at position 4 of the B-ring afford potent biochemical and cellular activity. (c) Introduction of a polar fragment such as pyridine and alkylated amide tends to reduce the shift in potency between biochemical and cellular assays. (d) A fluorine atom ortho to the benzimidazole ring on the C-ring is generally preferred.

The oral absorptions of the compounds in Table 5 were tested to evaluate the possibility of development of an oral anti-HCV drug from this series. Plasma concentrations at 1 and 2 h after oral dosing (30 mg/kg) in rats were compared. As shown in Table 5, this series of compounds is orally available; compound **10n** exhibited the highest plasma concentration. A pharmacokinetic study of **10n** in rats (10 mg/kg) showed an acceptable oral bioavailability ($F = 36\%$) with a plasma half-life ($T_{1/2}$) of 2.1 h. Since liver is a site of infection and viral replication for HCV, the drug concentration in liver is considered to be very important. Therefore, we investigated the relationship between liver and plasma concentrations of compound **10n** and found that the mean drug liver concentration is more than 10 times higher than in plasma after oral dosing (10 mg/kg): 78.5 μM in liver at 2 h, which is approximately 250-fold higher than its EC_{50}.

With these favorable pharmacokinetic profiles, compound **10n** was further investigated. Inhibitory activity against other HCV genotypes is summarized in Table 6, showing a high potency for genotypes 1a, 1b, and 3a but a 100- to 300-fold reduced activity for genotypes 2a and 2b compared to genotype 1b.

Table 6. Inhibitory Activity of Compound **10n** against Other HCV Genotypes

NS5B genotype	IC_{50} (μM)[a]
1a	0.062
2a	6.4
2b	2.0
3a	0.061

[a] Values are the mean of four independent experiments. Standard deviations are within 30% of the mean.

Compound **10n** was highly selective against other polymerases such as DNA polymerases (α, β, γ), mammalian DNA-dependent RNA polymerase, and HIV reverse transcriptase (all $IC_{50} > 10$ μM). No inhibition or induction of CYP450s such as 2C9, 3A4, or 2D6 was observed. Furthermore, no controversial adverse event was seen in a rat 4-week toxicity test at doses up to 300 mg/kg per day.

When the replicon assay was performed under high serum conditions (50% human serum), the EC_{50} for compound **10n** was increased about 20-fold. At this point, it is unclear how much this potency shift affects efficacy in vivo. The lack of a facile animal model for HCV infection is making it difficult to understand the relation between replicon potency and efficacy in vivo and also to estimate the clinically effective drug trough level in plasma. However, high affinity for plasma proteins is known to influence significantly the effective trough level in plasma for anti-HIV agents. Although this correlation is not yet known for HCV, it might be a crucial factor for developing effective anti-HCV drugs.[11,12] This is the next subject for this series of compounds, and the results will be reported in due course.

Conclusion

We designed and prepared a series of benzimidazole derivatives bearing substituted biphenyl groups and evaluated their abilities to inhibit HCV NS5B RdRp and cellular HCV RNA replication in replicon cells. We showed that small electron-withdrawing groups at the 4-position of the A-ring are preferred for biochemical activity, whereas substituents bearing a carbonyl function such as amide, reversed amide, or ketone at position 4 of the B-ring are favored for both biochemical and cellular activities. It was also learned that the introduction of a fluorine atom at a position ortho to the benzimidazole ring on the C-ring is generally preferred. The biochemical potency was increased ~30-fold compared to that of compound **1**. Cellular potency of low submicromolar concentrations (EC_{50} as low as 0.14 μM) was achieved. Among the compounds studied, compound **10n** (JTK-109) showed the highest plasma concentration and favorable pharmacokinetic profiles with high liver distribution in rats. This compound exhibits high selectivity for NS5B and good safety profiles. Thus, the favorable absorption, distribution, metabolism, and excretion (ADME) and safety profiles of compound **10n** as a clinical candidate demonstrate the potential of this series for the development of an anti-HCV drug.

Experimental Section

Chemistry. Solvents and reagents were obtained from commercial suppliers and used as received. Flash column chromatography was performed with Merck 230−400 mesh silica gel 60. Melting points were determined using a Yanagimoto micro melting point apparatus or a Büchi 535 melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a JEOL JNM-A300W, JEOL ALPHA300W, or Bruker AMX-300 spectrometer in the indicated solvent. Chemical shifts (δ) are reported in parts per million relative to internal standard tetramethylsilane. Combustion analyses were performed with a Perkin-Elmer 2402 series II CHNS/O analyzer. Low-resolution mass spectra (MS) analyses were performed on either a Finnigan TSQ-700 mass spectrometer in FAB ionization mode or an Agilent 1100 series LC/MSD mass spectrometer in ESI ionization mode. High-resolution mass spectra (HRMS) analyses were performed on a JEOL SX-102 mass spectrometer. HPLC analyses were performed using either (A) a Shimazu LC10A, using a Shiseido CAPCELL PAK C18 VG120 column (4.6 mm × 150 mm, solvent system CH_3CN−0.1% TFA/ water−0.1% TFA, gradient 30−90% over 15 min, 1 mL/min, 40 °C), or (B) a Waters micromass ZQ apparatus, using an Xterra column (3.0 mm × 50 mm, solvent system CH_3CN−0.1% formic acid/water−0.1% formic acid, gradient 10−100% over 12 min, 0.1 mL/min).

1-Cyclohexyl-2-[4-(4,4′-dichlorobiphenyl-2-ylmethoxy)phenyl]-1*H*-benzimidazole-5-carboxylic Acid (2b). Steps 1 and 2: Preparation of 2-[4-(2-Bromo-5-chlorobenzyloxy)phenyl]-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid Ethyl Ester (12a). To a solution of 2-bromo-5-chlorotoluene (**14a**, 50.00 g, 243.3 mmol) in CCl_4 (250 mL) were added *N*-bromosuccinimide (43.00 g, 241.6 mmol) and 2,2′-azobisisobutyronitrile (AIBN, 4.00 g, 24.4 mmol). The solution was heated overnight at reflux temperature. After the mixture was cooled, the insoluble material was removed by filtration and the filtrate was concentrated in vacuo. The residue was diluted with *n*-hexane, washed with water and brine, and was dried over $MgSO_4$. Filtration and concentration in vacuo gave 68.50 g (99%) of 2-bromo-5-chlorobenzyl bromide **16a** as a crude oil.

To a solution of the benzyl bromide **16a** (47.00 g, 165.3 mmol) obtained above in DMF (300 mL) were added phenol **11a**[1] (50.00 g, 137.2 mmol) and K_2CO_3 (38.00 g, 274.9 mmol). The reaction mixture was heated at 80 °C for 2.5 h. The reaction mixture was poured into ice-cold water and extracted with $CHCl_3$. The $CHCl_3$ layer was separated, washed with water and brine, and dried over $MgSO_4$. Filtration and evaporation of the solvent in vacuo gave a solid, which was recrystallized from EtOH and collected by filtration to give 54.80 g (70%) of **12a** as a white solid: ^{1}H NMR ($CDCl_3$) δ 1.21−1.46 (m, 3H), 1.42 (t, J = 7.8 Hz, 3H), 1.69−1.84 (m, 1H), 1.85−2.02 (m, 4H), 2.20−2.40 (m, 2H), 4.38 (m, 1H), 4.41 (q, J = 7.1 Hz, 2H), 5.17 (s, 2H), 7.14 (d, J = 8.7 Hz, 2H), 7.20 (dd, J = 2.5, 8.4 Hz, 1H), 7.54 (d, J = 8.5 Hz, 1H), 7.60−7.63 (m, 3H), 7.65 (d, J = 8.6 Hz, 1H), 7.97 (dd, J = 1.5, 8.6 Hz, 1H), 8.50 (d, J = 1.4 Hz, 1H).

Step 3: Preparation of 1-Cyclohexyl-2-[4-(4,4′-dichlorobiphenyl-2-ylmethoxy)phenyl]-1*H*-benzimidazole-5-carboxylic Acid Ethyl Ester (13b). To a suspension of **12a** (49.00 g, 86.28 mmol) obtained above in 1,2-dimethoxyethane (DME, 600 mL) were added 4-chlorophenylboronic acid (18.70 g, 117.3 mmol), tetrakis-(triphenylphosphine)palladium(0) (10.00 g, 8.65 mmol), and saturated aqueous $NaHCO_3$ (300 mL). The mixture was heated at reflux temperature for 1 h. The solvent was removed by evaporation in vacuo. The residue was diluted with $CHCl_3$ and washed with saturated aqueous $NaHCO_3$, water, and brine, and dried over $MgSO_4$. Filtration and concentration in vacuo and purification by silica gel flash chromatography ($CHCl_3$/AcOEt = 97/3) gave a solid, which was triturated in AcOEt and diisopropyl ether to give 44.00 g (85%) of **13b** as a white solid: ^{1}H NMR ($CDCl_3$) δ 1.20−1.47 (m, 3H), 1.41 (t, J = 7.1 Hz, 3H), 1.70−1.85 (m, 1H), 1.86−2.02 (m, 4H), 2.20−2.40 (m, 2H), 4.35 (m, 1H), 4.40 (q, J = 7.1 Hz, 2H), 4.95 (s, 2H), 6.99 (d, J = 8.7 Hz, 2H), 7.26 (d, J = 8.2 Hz, 1H), 7.31 (d, J = 8.8 Hz, 2H), 7.39−7.42 (m, 3H), 7.55 (d, J = 8.7 Hz, 2H), 7.65 (d, J = 8.7 Hz, 1H), 7.67 (s, 1H), 7.97 (dd, J = 1.6, 8.6 Hz, 1H), 8.49 (d, J = 1.4 Hz, 1H).

Step 4: Preparation of 1-Cyclohexyl-2-[4-(4,4′-dichlorobiphenyl-2-ylmethoxy)phenyl]-1*H*-benzimidazole-5-carboxylic Acid (2b). To a suspension of **13b** (43.00 g, 71.72 mmol) obtained above in EtOH (150 mL) and THF (150 mL) was added 2 N aqueous NaOH (75.00 mL, 150.0 mmol). The mixture was heated at reflux temperature for 1 h. The solvent was removed by evaporation in vacuo, and water was added to the residue. The mixture was acidified with 2 N aqueous HCl with cooling by an ice−water bath, and the precipitated crystals were collected by filtration to give a solid (38.00 g). The solid was recrystallized from EtOH−THF and collected by filtration to give 33.80 g (82%) of **2b** as a white solid: mp 160−161 °C; ^{1}H NMR (DMSO-d_6) δ 1.15−1.45 (m, 3H), 1.55−1.70 (m, 1H), 1.75−1.95 (m, 4H), 2.15−2.40 (m, 2H), 4.25 (m, 1H), 5.05 (s, 2H), 7.09 (d, J = 8.7 Hz, 2H), 7.37 (d, J = 8.3 Hz, 1H), 7.45 (d, J = 8.6 Hz, 2H), 7.49 (d, J = 8.6 Hz, 2H), 7.51−7.58 (m, 3H), 7.73 (d, J = 1.7 Hz, 1H), 7.85 (d, J = 8.6 Hz, 1H), 7.90 (d, J = 8.6 Hz, 1H), 8.20 (d, J = 1.4 Hz, 1H), 12.70 (brs, 1H); MS (FAB) m/z 571 $(M + H)^+$. Anal. ($C_{33}H_{28}Cl_2N_2O_3 \cdot C_2H_5OH$) C, H, N.

Compounds 2a,c−j were prepared by using the general procedure described above. In these cases, appropriate boronic acids were used instead of 4-chlorophenylboronic acid in step 3.

2-[4-(4-Chlorobiphenyl-2-ylmethoxy)phenyl]-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (2a). Mp 275−276 °C; ^{1}H NMR (DMSO-d_6) δ 1.20−1.55 (m, 3H), 1.55−1.75 (m, 1H), 1.75−1.95 (m, 2H), 1.95−2.15 (m, 2H), 2.15−2.40 (m, 2H), 4.36 (m, 1H), 5.11 (s, 2H), 7.22 (d, J = 8.7 Hz, 2H), 7.35−7.55 (m, 6H), 7.56 (d, J = 8.4 Hz, 1H), 7.70−7.75 (m, 3H), 8.05 (d, J = 8.7 Hz, 1H), 8.27 (d, J = 9 Hz, 1H), 8.32 (s, 1H); MS (FAB) m/z 537 $(M + H)^+$. Anal. ($C_{33}H_{29}ClN_2O_3 \cdot HCl \cdot H_2O$) C, H, N.

2-[4-(4-Chloro-4′-methylbiphenyl-2-ylmethoxy)phenyl]-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (2c). Mp 279−280 °C; ^{1}H NMR (DMSO-d_6) δ 1.15−1.55 (m, 3H), 1.55−1.75 (m, 1H), 1.75−1.95 (m, 2H), 1.95−2.15 (m, 2H), 2.15−2.35 (m, 2H), 2.35 (s, 3H), 4.36 (m, 1H), 5.11 (s, 2H), 7.22−7.39 (m, 7H), 7.54 (d, J = 8.4 Hz, 1H), 7.72−7.76 (m, 3H), 8.05 (d, J = 9 Hz, 1H), 8.27 (d, J = 8.7 Hz, 1H), 8.32 (s, 1H); MS (FAB) m/z 551 $(M + H)^+$. Anal. ($C_{34}H_{31}ClN_2O_3 \cdot HCl$) C, H, N.

2-[4-(4-Chloro-4′-methoxybiphenyl-2-ylmethoxy)phenyl]-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (2d). Mp 161−164 °C; ^{1}H NMR (DMSO-d_6) δ 1.15−1.55 (m, 3H), 1.55−1.75 (m, 1H), 1.75−1.95 (m, 2H), 1.95−2.15 (m, 2H), 2.15−2.45 (m, 2H), 3.79 (s, 3H), 4.35 (m, 1H), 5.11 (s, 2H), 7.01 (d, J = 8.7 Hz, 2H), 7.23 (d, J = 8.8 Hz, 2H), 7.36−7.40 (m, 3H), 7.52 (d, J =

8.3 Hz, 1H), 7.71−7.74 (m, 3H), 8.03 (d, J = 8.7 Hz, 1H), 8.24 (d, J = 8.8 Hz, 1H), 8.30 (s, 1H), 13.10 (brs, 1H); MS (FAB) *m*/*z* 567 $(M + H)^+$. Anal. ($C_{34}H_{31}ClN_2O_4 \cdot H_2O$) C, H, N.

2-[4-(4′-Carboxy-4-chlorobiphenyl-2-ylmethoxy)phenyl]-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (2e). Mp 274−275 °C; ^{1}H NMR (DMSO-d_6) δ 1.15−1.75 (m, 3H), 1.75−1.95 (m, 1H), 1.95−2.15 (m, 2H), 2.15−2.45 (m, 2H), 4.35 (m, 1H), 5.13 (s, 2H), 7.23 (d, J = 8.8 Hz, 2H), 7.44 (d, J = 8.3 Hz, 1H), 7.56−7.61 (m, 3H), 7.73 (d, J = 8.7 Hz, 2H), 7.79 (s, 1H), 8.00 (d, J = 8.2 Hz, 2H), 8.04 (d, J = 8.8 Hz, 1H), 8.26 (d, J = 8.8 Hz, 1H), 8.30 (s, 1H), 13.20 (brs, 2H); MS (FAB) *m*/*z* 581 $(M + H)^+$. Anal. ($C_{34}H_{29}ClN_2O_5 \cdot HCl$) C, H, N.

2-[4-(4′-Carbamoyl-4-chlorobiphenyl-2-ylmethoxy)phenyl]-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (2f). Mp 228−230 °C; ^{1}H NMR (DMSO-d_6) δ 1.10−1.55 (m, 3H), 1.55−1.75 (m, 1H), 1.75−2.10 (m, 4H), 2.15−2.40 (m, 2H), 4.30 (m, 1H), 5.10 (s, 2H), 7.17 (d, J = 8.7 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.51−7.59 (m, 3H), 7.65 (d, J = 8.4 Hz, 2H), 7.77 (s, 1H), 7.92−8.09 (m, 5H), 8.25 (s, 1H); MS (FAB) *m*/*z* 580 $(M + H)^+$. Anal. ($C_{34}H_{30}ClN_3O_4 \cdot C_2H_5OH$) C, H, N.

2-[4-(4-Chloro-4′-cyanobiphenyl-2-ylmethoxy)phenyl]-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (2g). Mp 270−271 °C; ^{1}H NMR (DMSO-d_6) δ 1.21−1.50 (m, 3H), 1.60−1.72 (m, 1H), 1.80−2.09 (m, 4H), 2.19−2.37 (m, 2H), 4.34 (m, 1H), 5.13 (s, 2H), 7.20 (d, J = 9 Hz, 2H), 7.44 (d, J = 8.1 Hz, 1H), 7.60 (dd, J = 2.2, 8.1 Hz, 1H), 7.67 (d, J = 8.1 Hz, 2H), 7.72 (d, J = 8.6 Hz, 2H), 7.80 (d, J = 2.2 Hz, 1H), 7.93 (d, J = 8.1 Hz, 2H), 8.04 (dd, J = 1.5, 8.6 Hz, 1H), 8.25 (d, J = 8.6 Hz, 1H), 8.30 (d, J = 1.5 Hz, 1H); MS (FAB) *m*/*z* 561 $(M + H)^+$. Anal. ($C_{34}H_{28}ClN_3O_3 \cdot HCl \cdot 0.2H_2O$) C, H, N.

1-Cyclohexyl-2-[4-(4,3′-dichlorobiphenyl-2-ylmethoxy)phenyl]-1*H*-benzimidazole-5-carboxylic Acid (2h). Mp 259−260 °C; ^{1}H NMR (DMSO-d_6) δ 1.15−1.55 (m, 3H), 1.55−1.75 (m, 1H), 1.75−1.95 (m, 2H), 1.95−2.15 (m, 2H), 2.15−2.40 (m, 2H), 4.35 (m, 1H), 5.11 (s, 2H), 7.23 (d, J = 9 Hz, 2H), 7.41−7.59 (m, 6H), 7.71−7.78 (m, 3H), 8.05 (d, J = 8.7 Hz, 1H), 8.26 (d, J = 8.7 Hz, 1H), 8.31 (s, 1H); MS (FAB) *m*/*z* 571 $(M + H)^+$. Anal. ($C_{33}H_{28}Cl_2N_2O_3 \cdot HCl \cdot 0.5H_2O$) C, H, N.

2-[4-(5-Chloro-2-pyridin-3-yl-benzyloxy)phenyl]-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (2i). Mp 167−168 °C; ^{1}H NMR (DMSO-d_6) δ 1.15−1.50 (m, 3H), 1.55−1.75 (m, 1H), 1.75−2.05 (m, 4H), 2.15−2.40 (m, 2H), 4.26 (m, 1H), 5.09 (s, 2H), 7.10 (d, J = 8.7 Hz, 2H), 7.43−7.50 (m, 2H), 7.56−7.61 (m, 3H), 7.79−7.92 (m, 4H), 8.21 (s, 1H), 8.61 (m, 1H), 8.66 (s, 1H), 12.70 (brs, 1H); MS (FAB) *m*/*z* 538 $(M + H)^+$. Anal. ($C_{32}H_{28}ClN_3O_3 \cdot H_2O$) C, H, N.

2-[4-(4′-Chlorobiphenyl-2-ylmethoxy)phenyl]-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (3a). Compound **3a** was prepared from 2-bromobenzyl bromide **16b** using the procedure described above for **2b** (steps 2−4) in 56% yield: mp 150−151 °C; ^{1}H NMR (DMSO-d_6) δ 1.10−1.43 (m, 3H), 1.59−1.72 (m, 1H), 1.75−1.95 (m, 4H), 2.15−2.35 (m, 2H), 4.27 (m, 1H), 5.05 (s, 2H), 7.10 (d, J = 8 Hz, 2H), 7.34−7.38 (m, 1H), 7.45−7.53 (m, 6H), 7.57 (d, J = 8 Hz, 2H), 7.65−7.69 (m, 1H), 7.85 (d, J = 8 Hz, 1H), 7.93 (d, J = 8 Hz, 1H), 8.22 (s, 1H), 12.73 (brs, 1H); MS (FAB) *m*/*z* 537 $(M + H)^+$. Anal. ($C_{33}H_{29}ClN_2O_3$) C, H, N.

2-[4-(4′-Chloro-4-cyanobiphenyl-2-ylmethoxy)phenyl]-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (3i). Compound **3i** was prepared from 2-bromo-5-cyanotoluene **14b** using the procedure described above for **2b**: mp 280−281 °C; ^{1}H NMR (DMSO-d_6) δ 1.19−1.49 (m, 3H), 1.58−1.71 (m, 1H), 1.80−1.93 (m, 2H), 1.96−2.10 (m, 2H), 2.20−2.39 (m, 2H), 4.34 (m, 1H), 5.16 (s, 2H), 7.23 (d, J = 8.6 Hz, 2H), 7.52 (d, J = 8.9 Hz, 2H), 7.55 (d, J = 8.9 Hz, 2H), 7.59 (d, J = 8 Hz, 1H), 7.72 (d, J = 8.6 Hz, 2H), 7.98 (dd, J = 1.7, 8 Hz, 1H), 8.04 (d, J = 8.7 Hz, 1H), 8.18 (s, 1H), 8.26 (d, J = 8.8 Hz, 1H), 8.30 (s, 1H); MS (FAB) *m*/*z* 562$(M + H)^+$. Anal. ($C_{34}H_{28}ClN_3O_3 \cdot HCl$) C, H, N.

2-{4-[2-(4-Chlorophenyl)pyridin-3-ylmethoxy]phenyl}-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (7). Compound **7** was prepared from 2-bromo-3-methylpyridine **14c** using the procedure described above for **2b**: mp 256−257 °C; ^{1}H NMR (DMSO-d_6) δ 1.15−1.55 (m, 3H), 1.55−1.75 (m, 1H), 1.75−1.95 (m, 2H), 1.95−2.15 (m, 2H), 2.15−2.50 (m, 2H), 4.38 (m, 1H), 5.26 (s, 2H), 7.30 (d, J = 8.7 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H), 7.64−7.72 (m, 3H), 7.79 (d, J = 8.7 Hz, 2H), 8.08 (d, J = 8.8 Hz, 1H), 8.26−8.36 (m, 3H), 8.77 (d, J = 3.6 Hz, 1H); MS (FAB) *m*/*z* 538 $(M + H)^+$. Anal. ($C_{32}H_{28}ClN_3O_3 \cdot 2HCl \cdot 2H_2O$) C, H, N.

2-[4-(4′-Chloro-4-methoxybiphenyl-2-ylmethoxy)phenyl]-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (3b). Steps 1 and 2: Preparation of 2-Bromo-5-methoxybenzyl Bromide (16c). To a suspension of lithium alminum hydride (600 mg, 15.8 mmol) in THF (5 mL) was added a solution of 2-bromo-5-methoxybenzoic acid **15a** (5.00 g, 21.6 mmol) in THF (10 mL) dropwise with cooling by an ice−water bath. The reaction mixture was stirred at 0 °C for 30 min. To the mixture were added water (0.6 mL), 4 N aqueous NaOH (1.2 mL), and water (1.8 mL) in sequential order, and the slurry was filtered. After the solid was washed with THF (10 mL), the combined filtrates were concentrated in vacuo. The residue was purified by silica gel flash chromatography (*n*-hexane/AcOEt = 11/5) to give 2.29 g (48%) of the benzyl alcohol as a white solid: ^{1}H NMR ($CDCl_3$) δ 2.07 (brs, 1H), 3.80 (s, 3H), 4.70 (s, 2H), 6.71 (dd, J = 2.7, 8.4 Hz, 1H), 7.06 (d, J = 2.7 Hz, 1H), 7.41 (d, J = 8.7 Hz, 1H).

To a solution of the benzyl alcohol (1.00 g, 4.61 mmol) obtained above and carbon tetrabromide (2.29 g, 6.91 mmol) in THF (25 mL) was added triphenylphosphine (1.81 g, 6.90 mmol) with cooling by an ice−water bath. The solution was stirred at room temperature for 1 h and concentrated in vacuo. To the residue was added *n*-hexane (30 mL), and the slurry was filtered. After the solid was washed with *n*-hexane (10 mL), the combined filtrates were concentrated in vacuo. The residue was purified by silica gel flash chromatography (*n*-hexane/AcOEt = 1/1) to give a solid, which was triturated in *n*-hexane and collected by filtration to give 0.71 g (55%) of **16c** as a white solid: ^{1}H NMR (CDCl3) δ 3.80 (s, 3H), 4.56 (s, 2H), 6.74 (dd, J = 3, 8.8 Hz, 1H), 6.99 (d, J = 3 Hz, 1H), 7.45 (d, J = 8.8 Hz, 1H).

Steps 3−5: Preparation of 2-[4-(4′-Chloro-4-methoxybiphenyl-2-ylmethoxy)phenyl]-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (3b). Compound **3b** was prepared from **16c** obtained above using the procedure described for **2b** (steps 2−4) in 57% yield: mp 254−255 °C; ^{1}H NMR (DMSO-d_6) δ 1.17−1.48 (m, 3H), 1.57−1.70 (m, 1H), 1.77−1.98 (m, 4H), 2.15−2.38 (m, 2H), 3.83 (s, 3H), 4.27 (m, 1H), 5.04 (s, 2H), 7.05 (dd, J = 3, 8.4 Hz, 1H), 7.11 (d, J = 8.7 Hz, 2H), 7.23 (d, J = 3 Hz, 1H), 7.29 (d, J = 8.4 Hz, 1H), 7.43 (d, J = 8.7 Hz, 2H), 7.46 (d, J = 8.7 Hz, 2H), 7.57 (d, J = 8.7 Hz, 2H), 7.85 (dd, J = 1.2, 8.7 Hz, 1H), 7.93 (d, J = 8.7 Hz, 1H), 8.21 (d, J = 1.2 Hz, 1H), 12.73 (brs, 1H); MS (FAB) *m*/*z* 538 $(M + H)^+$. Anal. ($C_{34}H_{31}ClN_2O_4 \cdot CH_3CH_2OH$) C, H, N.

2-[4-(4′-Chloro-4-dimethylsulfamoylbiphenyl-2-ylmethoxy)-phenyl]-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (3d). Step 1: Preparation of 2-Bromo-5-dimethylsulfamoylbenzoic Acid Methyl Ester (15b). A solution of 2-bromobenzoic acid (10.00 g, 49.75 mmol) in chlorosulfonic acid (23.0 mL, 346 mmol) was heated at 140 °C for 3 h. After cooling, the solution was poured into ice and extracted with $CHCl_3$. The $CHCl_3$ layer was separated, washed with brine, and dried over $MgSO_4$. Filtration and evaporation of the solvent in vacuo gave 13.80 g (92%) of 2-bromo-5-chlorosulfonylbenzoic acid as a crude solid.

To a suspension of 2-bromo-5-chlorosulfonylbenzoic acid (3.00 g, 10.0 mmol) as prepared above in CH_2Cl_2 (30 mL) were added oxalyl chloride (1.30 mL, 14.9 mmol) and a catalytic amount of DMF. The mixture was stirred at room temperature for 2 h. The solvent was removed by evaporation in vacuo. To a solution of the residue in THF (10 mL) was added MeOH (30 mL) with cooling by an ice−water bath. The mixture was stirred at room temperature for 1 h. The solvent was removed by evaporation in vacuo. To a solution of the residue in THF (10 mL) was added 40% aqueous dimethylamine (10 mL) dropwise with cooling by an ice−water bath. The mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with AcOEt, washed with water, saturated aqueous $NaHCO_3$, and brine, and dried over $MgSO_4$.

Filtration and concentration in vacuo and separation by silica gel flash chromatography (*n*-hexane/AcOEt = 1/1) gave 3.10 g (96%) of **15b** as a white solid: ^{1}H NMR ($CDCl_3$) δ 2.69 (s, 6H), 3.98 (s, 3H), 7.71 (dd, J = 2.3, 8.4 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 8.17 (d, J = 2.3 Hz, 1H).

Steps 2−6: Preparation of 2-[4-(4′-Chloro-4-dimethylsulfamoylbiphenyl-2-ylmethoxy)phenyl]-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (3d). Compound **3d** was prepared from **15b** obtained above using the general procedure described for **3b** (steps 1−5) in 36% yield: mp 250−251 °C; ^{1}H NMR (DMSO-d_6) δ 1.15−1.50 (m, 3H), 1.55−1.75 (m, 1H), 1.78−2.10 (m, 4H), 2.15−2.40 (m, 2H), 2.67 (s, 6H), 4.33 (m, 1H), 5.25 (s, 2H), 7.23 (d, J = 8.7 Hz, 2H), 7.56 (s, 4H), 7.65 (d, J = 8.1 Hz, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.84 (d, J = 8.1 Hz, 1H), 8.00−8.04 (m, 2H), 8.24 (d, J = 8.7 Hz, 1H), 8.30 (s, 1H); MS (FAB) m/z 644 $(M + H)^+$. Anal. ($C_{35}H_{34}ClN_3O_5S$·HCl) C, H, N.

2-[4-(4′-Chloro-4-sulfamoylbiphenyl-2-ylmethoxy)phenyl]-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (3c). A solution of 2-[4-(4-*tert*-butylsulfamoyl-4′-chlorobiphenyl-2-ylmethoxy)phenyl]-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic acid (300 mg, 0.446 mmol) (prepared from 2-bromo-5-chlorosulfonylbenzoic acid using the procedure described for **3d**; in this case, *tert*-butylamine was used instead of dimethylamine in step 1) in CF_3COOH (5 mL) was heated at 50 °C for 4 h. The solution was concentrated in vacuo, and the residue was dissolved in AcOEt. The solution was washed with water and brine and was dried over $MgSO_4$. Filtration and concentration in vacuo gave a solid, which was recrystallized from *n*-hexane/AcOEt and collected by filtration to give 185 mg (67%) of **3c** as a white solid: mp >300 °C; ^{1}H NMR (DMSO-d_6) δ 1.17−1.51 (m, 3H), 1.55−1.71 (m, 1H), 1.75−2.10 (m, 4H), 2.15−2.40 (m, 2H), 4.31 (m, 1H), 5.17 (s, 2H), 7.19 (d, J = 8.8 Hz, 2H), 7.48−7.60 (m, 5H), 7.66 (d, J = 8.6 Hz, 2H), 7.88−7.99 (m, 2H), 8.08−8.16 (m, 2H), 8.25 (d, J = 1.5 Hz, 1H); MS (FAB) m/z 616 $(M + H)^+$. Anal. ($C_{33}H_{30}ClN_3O_5S$) C, H, N.

2-[4-(4-Carboxy-4′-chlorobiphenyl-2-ylmethoxy)phenyl]-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (3h). Step 1: Preparation of 4-Bromo-3-methylbenzoic Acid *tert*-Butyl Ester (14d). To a suspension of 4-bromo-3-methylbenzoic acid (10.00 g, 46.50 mmol) in CH_2Cl_2 (100 mL) were added oxalyl chloride (4.80 mL, 55.0 mmol) and a catalytic amount of DMF. The mixture was stirred at room temperature for 2 h. The solvent was removed by evaporation in vacuo. To a solution of the residue in THF (100 mL) was added a solution of potassium *tert*-butoxide (7.80 g, 69.5 mmol) in THF (60 mL) dropwise with cooling by an ice−water bath. The mixture was stirred at room temperature for 30 min. The reaction mixture was poured into ice-cold water and extracted with AcOEt. The AcOEt layer was separated, washed with water and brine, and dried over $MgSO_4$. Filtration and concentration in vacuo gave 12.61 g (100%) of *tert*-butyl benzoate **14d** as a crude oil: ^{1}H NMR ($CDCl_3$) δ 1.59 (s, 9H), 2.43 (s, 3H), 7.56 (d, J = 8.3 Hz, 1H), 7.64 (dd, J = 1.9, 8.3 Hz, 1H), 7.83 (d, J = 1.9 Hz, 1H).

Steps 2−4: Preparation of 2-[4-(4-*tert*-Butoxycarbonyl-4′-chlorobiphenyl-2-ylmethoxy)phenyl]-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid Methyl Ester (17a). Compound **17a** was prepared from **14d** obtained above using the procedure described for **2b** (steps 1−3) in 36% yield: ^{1}H NMR ($CDCl_3$) δ 1.27−1.45 (m, 3H), 1.63 (s, 9H), 1.72−1.82 (m, 1H), 1.88−2.02 (m, 4H), 2.17−2.40 (m, 2H), 3.95 (s, 3H), 4.36 (m, 1H), 5.00 (s, 2H), 7.02 (d, J = 8.8 Hz, 2H), 7.33−7.43 (m, 5H), 7.56 (d, J = 8.8 Hz, 2H), 7.65 (d, J = 8.7 Hz, 1H), 7.97 (dd, J = 1.7, 8.6 Hz, 1H), 8.04 (dd, J = 1.7, 8.0 Hz, 1H), 8.27 (d, J = 1.7 Hz, 1H), 8.48 (d, J = 1.4 Hz, 1H).

Step 5: Preparation of 2-[4-(4-Carboxy-4′-chlorobiphenyl-2-ylmethoxy)phenyl]-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid Methyl Ester Hydrochloride (18a). To a solution of **17a** (3.50 g, 5.37 mmol) in CH_2Cl_2 (35 mL) was added CF_3COOH (35 mL). The mixture was stirred at room temperature for 1 h. The solvent was removed by evaporation in vacuo, and the residue was dissolved in AcOEt. To the solution was added 4 N HCl in AcOEt (2.70 mL, 10.8 mmol) and the precipitated crystals were collected by filtration to give 3.30 g (97%) of **18a** as a white solid: ^{1}H NMR (DMSO-d_6) δ 1.17−1.50 (m, 3H), 1.57−1.71 (m, 1H), 1.75−1.92 (m, 2H), 1.94−2.12 (m, 2H), 2.14−2.39 (m, 2H), 4.00 (s, 3H), 4.37 (m, 1H), 5.19 (s, 2H), 7.25 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 8.7 Hz, 2H), 7.55 (d, J = 8.7 Hz, 2H), 7.75 (d, J = 8.7 Hz, 2H), 8.04 (dd, J = 1.8, 8.1 Hz, 1H), 8.06 (dd, J = 1.5, 8.6 Hz, 1H), 8.25 (d, J = 1.6 Hz, 1H), 8.31 (d, J = 8.6 Hz, 1H), 8.34 (d, J = 1.4 Hz, 1H).

Step 6: Preparation of 2-[4-(4-Carboxy-4′-chlorobiphenyl-2-ylmethoxy)phenyl]-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (3h). Compound **3h** was prepared from **18a** as obtained above using the procedure described for **2b** (step 4) in 95% yield: mp 230 °C decomposition; ^{1}H NMR (DMSO-d_6) δ 1.10−1.55 (m, 3H), 1.55−1.75 (m, 1H), 1.75−2.10 (m, 4H), 2.15−2.40 (m, 2H), 4.36 (m, 1H), 5.19 (s, 2H), 7.24 (d, J = 9 Hz, 2H), 7.46−7.60 (m, 5H), 7.74 (d, J = 9 Hz, 2H), 7.98−8.10 (m, 2H), 8.20−8.30 (m, 2H), 8.32 (s, 1H); HRMS calcd for $C_{34}H_{30}ClN_2O_5$ $(M + H)^+$ 581.184, found 581.185; HPLC method A, >99% (11.3 min); HPLC method B, >99% (6.50 min).

2-[4-(4′-Chloro-4-methylcarbamoylbiphenyl-2-ylmethoxy)-2-fluorophenyl]-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (10a). Steps 1−5: Preparation of 2-[4-(4-Carboxy-4′-chlorobiphenyl-2-ylmethoxy)-2-fluorophenyl]-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid Methyl Ester Hydrochloride (18b). Compound **18b** was prepared from **11b** using the procedure described for **3h** (steps 1−5) in 57% yield: ^{1}H NMR (DMSO-d_6) δ 1.20−1.49 (m, 3H), 1.56−1.71 (m, 1H), 1.75−2.02 (m, 4H), 2.10−2.35 (m, 2H), 3.92 (s, 3H), 4.10 (m, 1H), 5.19 (s, 2H), 7.06 (dd, J = 2.1, 8.4 Hz, 1H), 7.19 (dd, J = 2.1, 12 Hz, 1H), 7.48−7.56 (m, 5H), 7.66 (t, J = 8.4 Hz, 1H), 8.00 (d, J = 8.7 Hz, 1H), 8.04 (dd, J = 1.5, 7.8 Hz, 1H), 8.19 (d, J = 8.7 Hz, 1H), 8.25 (s, 1H), 8.33 (s, 1H).

Step 6: Preparation of 2-[4-(4-Methylcarbamoyl-4′-chlorobiphenyl-2-ylmethoxy)-2-fluorophenyl]-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid Methyl Ester (19f). To a suspension of **18b** (1.20 g, 1.85 mmol) in CH_2Cl_2 (15 mL) were added oxalyl chloride (0.50 mL, 5.7 mmol) and a catalytic amount of DMF. The mixture was stirred at room temperature for 2 h. The solvent was removed by evaporation in vacuo to give 1.20 g (100%) of the acid chloride of **18b**.

To a solution of 40% aqueous methylamine (5 mL) in THF (5 mL) was added a solution of the acid chloride (560 mg, 0.887 mmol) obtained above in CH_2Cl_2 (10 mL) dropwise with cooling by an ice−water bath. The mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with AcOEt, washed with aqueous saturated $NaHCO_3$, water, and brine, and dried over $MgSO_4$. Filtration and concentration in vacuo and purification by silica gel flash chromatography ($CHCl_3$/MeOH = 50/1) gave 334 mg (60%) of **19f** as a white solid: ^{1}H NMR ($CDCl_3$) δ 1.21−1.42 (m, 3H), 1.68−1.81 (m, 1H), 1.86−2.03 (m, 4H), 2.11−2.33 (m, 2H), 3.06 (d, J = 4.9 Hz, 3H), 3.95 (s, 3H), 4.03 (m, 1H), 5.00 (s, 2H), 6.34 (m, 1H), 6.71 (dd, J = 2.4, 11.6 Hz, 1H), 6.80 (dd, J = 2.4, 8.6 Hz, 1H), 7.32 (d, J = 8.5 Hz, 2H), 7.40 (d, J = 8.1 Hz, 1H), 7.43 (d, J = 8.6 Hz, 2H), 7.50 (t, J = 8.4 Hz, 1H), 7.67 (d, J = 8.7 Hz, 1H), 7.83 (dd, J = 1.9, 8.0 Hz, 1H), 7.98 (dd, J = 1.6, 8.6 Hz, 1H), 8.05 (d, J = 1.8 Hz, 1H), 8.49 (d, J = 1.4 Hz, 1H).

Step 7: Preparation of 2-[4-(4′-Chloro-4-methylcarbamoylbiphenyl-2-ylmethoxy)-2-fluorophenyl]-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (10a). Compound **10a** was prepared from the amide **19f** obtained above using the procedure described for **2b** (step 4) in 76% yield: mp 266−267 °C; ^{1}H NMR (DMSO-d_6) δ 1.15−1.50 (m, 3H), 1.55−1.72 (m, 1H), 1.75−2.00 (m, 4H), 2.10−2.35 (m, 2H), 2.83 (d, J = 4.4 Hz, 3H), 4.10 (m, 1H), 5.15 (s, 2H), 7.06 (d, J = 8.7 Hz, 1H), 7.19 (d, J = 12.1 Hz, 1H), 7.47 (d, J = 8 Hz, 1H), 7.49 (d, J = 8.9 Hz, 2H), 7.53 (d, J = 8.8 Hz, 2H), 7.66 (t, J = 8.6 Hz, 1H), 7.96 (d, J = 8.4 Hz, 1H), 7.99 (d, J = 8.4 Hz, 1H), 8.15 (s, 1H), 8.17 (d, J = 8 Hz, 1H), 8.31 (s, 1H), 8.63 (q, J = 4.4 Hz, 1H); MS (FAB) m/z 612 $(M + H)^+$. Anal. ($C_{35}H_{31}ClFN_3O_4$·HCl·2H_2O) C, H, N.

Compounds 3j−n and 10b−h were prepared from **18a** or **18b** by using the procedure described for **10a** (steps 6 and 7). In these cases, appropriate amines were used instead of methylamine.

2-[4-(4-Carbamoyl-4′-chlorobiphenyl-2-ylmethoxy)phenyl]-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (3j). Mp 280−281 °C; ^{1}H NMR (DMSO-d_6) δ 1.20−1.52 (m, 3H), 1.58−1.73 (m, 1H), 1.80−1.93 (m, 2H), 1.97−2.12 (m, 2H), 2.18−2.38 (m, 2H), 4.36 (m, 1H), 5.14 (s, 2H), 7.24 (d, J = 9 Hz, 2H), 7.43−7.57 (m, 6H), 7.73 (d, J = 9 Hz, 2H), 7.99 (dd, J = 1.7, 8 Hz, 1H), 8.04 (d, J = 9 Hz, 1H), 8.13 (brs, 1H), 8.19 (d, J = 1.8 Hz, 1H), 8.26 (d, J = 9 Hz, 1H), 8.30 (d, J = 1.5 Hz, 1H); MS (FAB) m/z 580 (M + H)$^+$. Anal. ($C_{34}H_{30}ClN_3O_4$·HCl·0.5H_2O) C, H, N.

2-[4-(4′-Chloro-4-methylcarbamoylbiphenyl-2-ylmethoxy)-phenyl]-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (3k). Mp 268−269 °C; ^{1}H NMR (DMSO-d_6) δ 1.18−1.50 (m, 3H), 1.55−1.72 (m, 1H), 1.75−2.10 (m, 4H), 2.18−2.40 (m, 2H), 2.82 (d, J = 4.4 Hz, 3H), 4.34 (m, 1H), 5.14 (s, 2H), 7.22 (d, J = 8.7 Hz, 2H), 7.47 (d, J = 8.1 Hz, 1H), 7.52 (s, 4H), 7.71 (d, J = 8.7 Hz, 2H), 7.95 (d, J = 8.1 Hz, 1H), 8.01 (d, J = 8.7 Hz, 1H), 8.15 (s, 1H), 8.22 (d, J = 8.7 Hz, 1H), 8.28 (s, 1H), 8.61 (q, J = 4.4 Hz, 1H); MS (FAB) m/z 594 (M + H)$^+$. Anal. ($C_{35}H_{32}ClN_3O_4$·HCl·0.8H_2O) C, H, N.

2-[4-(4′-Chloro-4-dimethylcarbamoylbiphenyl-2-ylmethoxy)-phenyl]-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (3l). Mp 266−267 °C; ^{1}H NMR (DMSO-d_6) δ 1.21−1.50 (m, 3H), 1.60−1.72 (m, 1H), 1.81−1.94 (m, 2H), 1.97−2.09 (m, 2H), 2.20−2.37 (m, 2H), 2.97 (brs, 3H), 3.01 (brs, 3H), 4.35 (m, 1H), 5.15 (s, 2H), 7.23 (d, J = 8.7 Hz, 2H), 7.42 (d, J = 7.6 Hz, 1H), 7.49−7.55 (m, 5H), 7.71 (s, 1H), 7.72 (d, J = 8.7 Hz, 2H), 8.03 (dd, J = 1.5, 8.7 Hz, 1H), 8.25 (d, J = 9.1 Hz, 1H), 8.30 (d, J = 1.5 Hz, 1H); MS (FAB) m/z 608 (M + H)$^+$. Anal. ($C_{36}H_{34}ClN_3O_4$·HCl) C, H, N.

2-[4-(4-Benzylcarbamoyl-4′-chlorobiphenyl-2-ylmethoxy)phenyl]-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (3m). Mp 231−233 °C; ^{1}H NMR (DMSO-d_6) δ 1.19−1.47 (m, 3H), 1.59−1.72 (m, 1H), 1.79−1.91 (m, 2H), 1.95−2.08 (m, 2H), 2.18−2.37 (m, 2H), 4.35 (m, 1H), 4.52 (d, J = 5.9 Hz, 2H), 5.15 (s, 2H), 7.22−7.28 (m, 3H), 7.34 (d, J = 4.4 Hz, 4H), 7.48−7.55 (m, 5H), 7.72 (d, J = 8.6 Hz, 2H), 8.03 (d, J = 7.9 Hz, 2H), 8.22 (s, 1H), 8.24 (d, J = 8.9 Hz, 1H), 8.29 (s, 1H), 9.23 (t, J = 6.2 Hz, 1H); MS (FAB) m/z 670 (M + H)$^+$. Anal. ($C_{41}H_{36}ClN_3O_4$·HCl·CH_3-CH_2OH) C, H, N.

2-[4-(4′-Chloro-5-dimethylcarbamoylbiphenyl-2-ylmethoxy)-phenyl]-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (3n). Compound **3n** was prepared from 3-bromo-4-methylbenzoic acid using the procedure described for **3h** (steps 1−5) and **10a** (steps 1−3) in 39% yield. In this case, dimethylamine was used instead of methylamine: mp 261−262 °C; ^{1}H NMR (DMSO-d_6) δ 1.21−1.50 (m, 3H), 1.60−1.70 (m, 1H), 1.81−2.08 (m, 4H), 2.20−2.37 (m, 2H), 2.98 (brs, 6H), 4.36 (m, 1H), 5.14 (s, 2H), 7.23 (d, J = 9 Hz, 2H), 7.37 (d, J = 1.8 Hz, 1H), 7.51−7.54 (m, 5H), 7.73 (d, J = 9 Hz, 2H), 7.74 (d, J = 8.1 Hz, 1H), 8.03 (dd, J = 1.5, 8.4 Hz, 1H), 8.43 (d, J = 8.4 Hz, 1H), 8.31 (d, J = 1.5 Hz, 1H); MS (FAB) m/z 608 (M + H)$^+$. Anal. ($C_{36}H_{34}ClN_3O_4$·HCl·H_2O) C, H, N.

2-[4-(4′-Chloro-4-propylcarbamoylbiphenyl-2-ylmethoxy)-2-fluorophenyl]-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (10b). Mp 263−264 °C; ^{1}H NMR (DMSO-d_6) δ 0.91 (t, J = 7.5 Hz, 3H), 1.05−1.45 (m, 3H), 1.47−1.70 (m, 3H), 1.75−2.00 (m, 4H), 2.05−2.30 (m, 2H), 3.26 (m, 2H), 4.08 (m, 1H), 5.13 (s, 2H), 7.04 (d, J = 8.7 Hz, 1H), 7.17 (d, J = 12 Hz, 1H), 7.47 (d, J = 7.2 Hz, 1H), 7.48 (d, J = 9 Hz, 2H), 7.53 (d, J = 9 Hz, 2H), 7.64 (t, J = 9 Hz, 1H), 7.95−8.00 (m, 2H), 8.14 (d, J = 8.4 Hz, 1H), 8.16 (s, 1H), 8.29 (s, 1H), 8.60 (t, J = 6.3 Hz, 1H); MS (FAB) m/z 640 (M + H)$^+$. Anal. ($C_{37}H_{35}ClFN_3O_4$·HCl·0.5H_2O) C, H, N.

2-[4-(4′-Chloro-4-isopropylcarbamoylbiphenyl-2-ylmethoxy)-2-fluorophenyl]-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (10c). Mp 272−273 °C; ^{1}H NMR (DMSO-d_6) δ 1.19 (d, J = 6.3 Hz, 6H), 1.14−1.44 (m, 3H), 1.57−1.72 (m, 1H), 1.78−1.99 (m, 4H), 2.13−2.34 (m, 2H), 4.03−4.22 (m, 2H), 5.13 (s, 2H), 7.06 (dd, J = 2.1, 8.4 Hz, 1H), 7.18 (dd, J = 1.8, 12 Hz, 1H), 7.46 (d, J = 7.8 Hz, 1H), 7.48 (d, J = 8.7 Hz, 2H), 7.53 (d, J = 8.4 Hz, 2H), 7.65 (t, J = 8.4 Hz, 1H), 7.95−8.02 (m, 2H), 8.15 (d, J = 7.8 Hz, 1H), 8.16 (s, 1H), 8.30 (s, 1H), 8.37 (d, J = 7.3 Hz, 1H); MS (FAB) m/z 640 (M + H)$^+$. Anal. ($C_{37}H_{35}ClFN_3O_4$·HCl) C, H, N.

2-{4-[4′-Chloro-4-(2-hydroxyethylcarbamoyl)biphenyl-2-ylmethoxy]-2-fluorophenyl}-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (10d). Mp 270−271 °C; ^{1}H NMR (DMSO-d_6) δ 1.17−1.48 (m, 3H), 1.58−1.70 (m, 1H), 1.76−2.00 (m, 4H), 2.12−2.37 (m, 2H), 3.37 (m, 2H), 3.55 (t, J = 6.3 Hz, 2H), 3.60 (s, 1H), 4.11 (m, 1H), 5.14 (s, 2H), 7.07 (d, J = 8.7 Hz, 1H), 7.19 (d, J = 12.6 Hz, 1H), 7.47 (d, J = 7.5 Hz, 1H), 7.49 (d, J = 8.7 Hz, 2H), 7.53 (d, J = 8.7 Hz, 2H), 7.66 (t, J = 7.7 Hz, 1H), 7.98−8.02 (m, 2H), 8.17 (d, J = 9 Hz, 1H), 8.19 (s, 1H), 8.31 (s, 1H), 8.62 (t, J = 6 Hz, 1H); HRMS calcd for $C_{36}H_{34}ClFN_3O_5$ (M + H)$^+$ 642.2171, found 642.2159; HPLC method A, 99% (10.36 min); HPLC method B, 99% (6.50 min).

2-[4-(4′-Chloro-4-dimethylcarbamoylbiphenyl-2-ylmethoxy)-2-fluorophenyl]-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (10e). Mp 240−241 °C; ^{1}H NMR (DMSO-d_6) δ 1.21−1.45 (m, 3H), 1.59−1.72 (m, 1H), 1.79−1.95 (m, 4H), 2.13−2.32 (m, 2H), 2.98 (s, 3H), 3.01 (s, 3H), 4.06 (m, 1H), 5.14 (s, 2H), 7.03 (dd, J = 1.8, 8.2 Hz, 1H), 7.17 (dd, J = 2.2, 12 Hz, 1H), 7.43 (d, J = 7.9 Hz, 1H), 7.44−7.56 (m, 5H), 7.63 (t, J = 8.2 Hz, 1H), 7.71 (d, J = 1.8 Hz, 1H), 7.97 (dd, J = 1.5, 8.6 Hz, 1H), 8.13 (d, J = 9 Hz, 1H), 8.29 (s, 1H); MS (FAB) m/z 626 (M + H)$^+$. Anal. ($C_{36}H_{33}$-$ClFN_3O_4$·HCl) C, H, N.

2-{4-[4′-Chloro-4-(piperidine-1-carbonyl)biphenyl-2-ylmethoxy]-2-fluorophenyl}-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (10f). Mp 223−224 °C; ^{1}H NMR (DMSO-d_6) δ 1.18−1.71 (m, 10H), 1.71−1.98 (m, 4H), 2.10−2.35 (m, 2H), 3.23−3.71 (m, 2H), 4.07 (m, 1H), 5.15 (s, 2H), 7.02 (dd, J = 2.2, 8.4 Hz, 1H), 7.16 (dd, J = 2.2, 12 Hz, 1H), 7.43 (d, J = 7.5 Hz, 1H), 7.47−7.51 (m, 5H), 7.63 (t, J = 8.4 Hz, 1H), 7.67 (s, 1H), 7.97 (dd, J = 1.4, 8.7 Hz, 1H), 8.13 (d, J = 8.7 Hz, 1H), 8.29 (s, 1H); MS (FAB) m/z 666 (M + H)$^+$. Anal. ($C_{39}H_{37}ClFN_3O_4$·HCl) C, H, N.

2-{4-[4′-Chloro-4-(morpholine-4-carbonyl)biphenyl-2-ylmethoxy]-2-fluorophenyl}-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (10g). Mp 248−249 °C; ^{1}H NMR (DMSO-d_6) δ 1.21−1.47 (m, 3H), 1.58−1.70 (m, 1H), 1.78−1.96 (m, 4H), 2.14−2.31 (m, 2H), 3.33−3.75 (m, 6H), 4.05 (m, 1H), 4.00−4.40 (m, 2H), 5.12 (s, 2H), 7.03 (d, J = 8.4 Hz, 1H), 7.18 (dd, J = 2.1, 12.1 Hz, 1H), 7.43−7.57 (m, 6H), 7.64 (t, J = 8.8 Hz, 1H), 7.72 (s, 1H), 7.98 (d, J = 8.8 Hz, 1H), 8.15 (d, J = 8.6 Hz, 1H), 8.29 (s, 1H); MS (FAB) m/z 668 (M + H)$^+$. Anal. ($C_{38}H_{35}ClFN_3O_5$·0.3H_2O) C, H, N.

2-{4-[4′-Chloro-4-(4-hydroxypiperidine-1-carbonyl)biphenyl-2-ylmethoxy]-2-fluorophenyl}-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (10h). Mp 182−185 °C; ^{1}H NMR (DMSO-d_6) δ 1.19−1.55 (m, 5H), 1.60−1.95 (m, 7H), 2.10−2.30 (m, 2H), 3.10−3.35 (m, 2H), 3.45−4.40 (m, 5H), 5.14 (s, 2H), 7.02 (d, J = 8.4 Hz, 1H), 7.15 (d, J = 11.7 Hz, 1H), 7.43 (d, J = 7.5 Hz, 1H), 7.45−7.55 (m, 5H), 7.62 (t, J = 8.2 Hz, 1H), 7.68 (s, 1H), 7.96 (d, J = 8.9 Hz, 1H), 8.11 (d, J = 8.9 Hz, 1H), 8.28 (s, 1H); MS (FAB) m/z 682 (M + H)$^+$. Anal. ($C_{39}H_{37}ClFN_3O_5$·HCl·0.5H_2O) C, H, N.

2-[4-(4′-Chloro-4-dimethylaminobiphenyl-2-ylmethoxy)phenyl]-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (3f). Steps 1−3: Preparation of 2-[4-(4′-Chloro-4-nitrobiphenyl-2-ylmethoxy)-phenyl]-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid Methyl Ester (20a). Compound **20a** was prepared from 2-bromo-5-nitrotoluene **14e** and the phenol **11a** using the procedure described above for **2b** (steps 1−3) in 51% yield: ^{1}H NMR ($CDCl_3$) δ 1.15−1.39 (m, 3H), 1.60−1.77 (m, 1H), 1.78−1.95 (m, 4H), 2.10−2.32 (m, 2H), 3.87 (s, 3H), 4.26 (m, 1H), 4.97 (s, 2H), 6.94 (d, J = 8.5 Hz, 2H), 7.27 (d, J = 8.3 Hz, 2H), 7.39 (d, J = 8.6 Hz, 2H), 7.42 (d, J = 8.6 Hz, 1H), 7.49 (d, J = 8.5 Hz, 2H), 7.57 (d, J = 8.7 Hz, 1H), 7.88 (d, J = 8.6 Hz, 1H), 8.26 (d, J = 8.4 Hz, 1H), 8.39 (s, 1H), 8.49 (s, 1H).

Step 4: Preparation of 2-[4-(4-Amino-4′-chlorobiphenyl-2-ylmethoxy)phenyl]-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid Methyl Ester (21a). To a solution of **20a** (1.70 g, 2.85 mmol) obtained above in EtOH (20 mL) and THF (15 mL) was added tin(II) chloride dihydrate (3.20 g, 14.2 mmol). The mixture

was heated at reflux temperature for 1 h. The solvent was removed by evaporation in vacuo. The residue was diluted with $CHCl_3$, washed with 4 N aqueous NaOH, water, and brine, and dried over Na_2SO_4. Filtration and concentration in vacuo gave 1.44 g (90%) of aniline **21a** as a crude solid.

Steps 5 and 6: Preparation of 2-[4-(4′-Chloro-4-dimethylaminobiphenyl-2-ylmethoxy)phenyl]-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (3f). To a solution of **21a** (500 mg, 0.883 mmol) obtained above in formic acid (15 mL) was added 37% formaldehyde (10 mL). The mixture was heated at reflux temperature for 1 h. The solvent was removed by evaporation in vacuo. The residue was diluted with $CHCl_3$, washed with saturated aqueous $NaHCO_3$, water, and brine, and dried over Na_2SO_4. Filtration and concentration in vacuo and purification by silica gel flash chromatography (*n*-hexane/AcOEt = 1/1) gave 178 mg (34%) of the dimethylamino compound **22** as a white solid. Compound **22** was converted to **3f** by using the procedure described above for **2b** (step 4) in 81% yield: mp 245−246 °C; ^{1}H NMR (DMSO-d_6) δ 1.20−1.50 (m, 3H), 1.55−1.70 (m, 1H), 1.75−1.90 (m, 2H), 1.95−2.10 (m, 2H), 2.15−2.40 (m, 2H), 3.04 (s, 6H), 4.39 (m, 1H), 5.09 (s, 2H), 7.25−7.48 (m, 9H), 7.78 (d, J = 8.7 Hz, 2H), 8.09 (d, J = 9.3 Hz, 1H), 8.35 (d, J = 9.3 Hz, 1H), 8.36 (s, 1H); MS (FAB) m/z 580 (M + H)$^+$. Anal. ($C_{35}H_{34}ClN_3O_3$·2HCl) C, H, N.

2-[4-(4-Acetylamino-4′-chlorobiphenyl-2-ylmethoxy)phenyl]-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (3g). To a solution of **21a** (130 mg, 0.224 mmol) and triethylamine (38 μL, 0.27 mmol) in $CHCl_3$ (3 mL) was added a solution of acetyl chloride (17 μL, 0.24 mmol) in $CHCl_3$ (2 mL) dropwise with cooling by an ice−water bath. The mixture was stirred overnight at room temperature. The reaction mixture was diluted with $CHCl_3$, washed with water and brine, and dried over Na_2SO_4. Filtration and evaporation of the solvent in vacuo gave 138 mg (99%) of the acetylamino compound **23a** as a crude solid. Compound **23a** was converted to **3g** by using the procedure described above for **2b** (step 4) in 81% yield: mp 274−275 °C; ^{1}H NMR (DMSO-d_6) δ 1.15−1.50 (m, 3H), 1.55−1.70 (m, 1H), 1.75−2.07 (m, 4H), 2.08 (s, 3H), 2.15−2.40 (m, 2H), 4.31 (m, 1H), 5.06 (s, 2H), 7.14 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 1H), 7.44 (d, J = 8.7 Hz, 2H), 7.48 (d, J = 8.1 Hz, 2H), 7.64 (d, J = 8.4 Hz, 2H), 7.69 (d, J = 8.4 Hz, 1H), 7.88 (s, 1H), 7.93 (d, J = 8.7 Hz, 1H), 8.07 (d, J = 8.7 Hz, 1H), 8.25 (s, 1H), 10.16 (s, 1H); MS (FAB) m/z 594 (M + H)$^+$. Anal. ($C_{35}H_{32}ClN_3O_4$·HCl·0.5H_2O) C, H, N.

Compounds **10i** and **10o** were synthesized from **20b** (prepared from 2-bromo-5-nitrotoluene **14e** and the phenol **11b**) by using the procedure described for **3g**, except dimethylcarbamoyl chloride was used instead of acetyl chloride for **10o**.

2-[4-(4-Acetylamino-4′-chlorobiphenyl-2-ylmethoxy)-2-fluorophenyl]-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid Methyl Ester (23b). ^{1}H NMR ($CDCl_3$) δ 1.20−1.44 (m, 3H), 1.69−1.80 (m, 1H), 1.82−2.02 (m, 4H), 2.10−2.33 (m, 2H), 2.21 (s, 3H), 3.95 (s, 3H), 4.02 (m, 1H), 4.98 (s, 2H), 6.69 (d, J = 11.4 Hz, 1H), 6.79 (d, J = 8.7 Hz, 1H), 7.20−7.34 (m, 3H), 7.38−7.43 (m, 3H), 7.49 (t, J = 8.4 Hz, 1H), 7.61−7.72 (m, 3H), 7.98 (d, J = 8.7 Hz, 1H), 8.49 (s, 1H).

2-[4-(4-Acetylamino-4′-chlorobiphenyl-2-ylmethoxy)-2-fluorophenyl]-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (10i). Compound **23b** was converted to **10i** by using the procedure described for **3g**: mp 268−269 °C; ^{1}H NMR (DMSO-d_6) δ 1.23−1.53 (m, 3H), 1.59−1.68 (m, 1H), 1.79−1.87 (m, 4H), 2.08 (s, 3H), 2.18−2.30 (m, 2H), 4.09 (m, 1H), 5.08 (s, 2H), 7.02 (dd, J = 2.4, 8.6 Hz, 1H), 7.14 (dd, J = 2.5, 12.1 Hz, 1H), 7.32 (d, J = 8.4 Hz, 1H), 7.43 (d, J = 9 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 7.63 (t, J = 8.5 Hz, 1H), 7.69 (dd, J = 2.2, 8.4 Hz, 1H), 7.90 (d, J = 2.2 Hz, 1H), 7.98 (dd, J = 1.7, 8.7 Hz, 1H), 8.14 (d, J = 8.8 Hz, 1H), 8.29 (d, J = 1.5 Hz, 1H), 10.19 (s, 1H); MS (FAB) m/z 598 (M + H)$^+$. Anal. ($C_{35}H_{31}ClFN_3O_4$·HCl) C, H, N.

2-{4-[4′-Chloro-4-(3,3-dimethylureido)biphenyl-2-ylmethoxy]-2-fluorophenyl}-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (10o). Mp 243−244 °C; ^{1}H NMR (DMSO-d_6) δ 1.20−1.50 (m, 3H), 1.55−1.70 (m, 1H), 1.75−2.00 (m, 4H), 2.10−2.40 (m, 2H), 2.96 (s, 6H), 4.12 (m, 1H), 5.05 (s, 2H), 7.05 (dd, J = 2.3, 8.6 Hz, 1H), 7.17 (dd, J = 2.3, 12.1 Hz, 1H), 7.25 (d, J = 8.4 Hz, 1H), 7.43 (d, J = 8.8 Hz, 2H), 7.47 (d, J = 8.6 Hz, 2H), 7.61 (dd, J = 2.3, 8.4 Hz, 1H), 7.64 (t, J = 8.4 Hz, 1H), 7.81 (d, J = 2.1 Hz, 1H), 8.01 (d, J = 8.6 Hz, 1H), 8.19 (d, J = 8.6 Hz, 1H), 8.31 (s, 1H), 8.54 (s, 1H); MS (FAB) m/z 641 (M + H)$^+$. Anal. ($C_{36}H_{34}ClFN_4O_4$·HCl) C, H, N.

2-{4-[4-(Acetylmethylamino)-4′-chlorobiphenyl-2-ylmethoxy]-2-fluorophenyl}-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (10j). To a suspension of sodium hydride (41.3 mg, 60%, 1.03 mmol) in DMF (5 mL) was added a solution of **23b** (534 mg, 0.853 mmol) in DMF (5 mL) dropwise with cooling by an ice−water bath. The solution was stirred for 15 min, followed by the addition of methyl iodide (183 mg, 1.29 mmol) in DMF (5 mL). The solution was stirred overnight at room temperature. The reaction mixture was poured into water and extracted with AcOEt. The AcOEt layer was separated, washed with water and brine, and dried over $MgSO_4$. Filtration and concentration in vacuo and purification by silica gel flash chromatography ($CHCl_3$/MeOH = 60/1) gave 286 mg (52%) of the acetylmethylamino compound **24a** as a white solid: ^{1}H NMR ($CDCl_3$) δ 1.20−1.42 (m, 3H), 1.70−1.80 (m, 1H), 1.85−2.05 (m, 7H), 2.11−2.21 (m, 2H), 2.34 (s, 3H), 3.95 (s, 3H), 4.02 (m, 1H), 4.99 (s, 2H), 6.71 (dd, J = 2.3, 11.5 Hz, 1H), 6.82 (dd, J = 2.3, 8.6 Hz, 1H), 7.28 (d, J = 8.1 Hz, 1H), 7.33 (d, J = 8.5 Hz, 2H), 7.38 (d, J = 8.1 Hz, 1H), 7.44 (d, J = 8.4 Hz, 2H), 7.49 (s, 1H), 7.53 (t, J = 8.4 Hz, 1H), 7.66 (d, J = 8.6 Hz, 1H), 7.99 (dd, J = 1.6, 8.7 Hz, 1H), 8.49 (d, J = 1.4 Hz, 1H).

Compound **10j** was prepared from **24a** obtained above by using the procedure described for **2b** (step 4) in 58% yield: mp 183−185 °C; ^{1}H NMR (DMSO-d_6) δ 1.28−1.41 (m, 3H), 1.59−1.68 (m, 1H), 1.79−1.87 (m, 4H), 2.18−2.30 (m, 2H), 2.50 (s, 3H), 3.24 (s, 3H), 4.04 (m, 1H), 5.12 (s, 2H), 7.03 (dd, J = 2, 9 Hz, 1H), 7.16 (dd, J = 2.2, 12.1 Hz, 1H), 7.42−7.53 (m, 6H), 7.61 (d, J = 8.4 Hz, 1H), 7.65 (s, 1H), 7.97 (d, J = 8.5 Hz, 1H), 8.11 (d, J = 8.5 Hz, 1H), 8.29 (s, 1H); MS (FAB) m/z 626 (M + H)$^+$. Anal. ($C_{36}H_{33}ClFN_3O_4$·H_2O) C, H, N.

2-{4-[4-(Acetylethylamino)-4′-chlorobiphenyl-2-ylmethoxy]-2-fluorophenyl}-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (10k). Compound **10k** was prepared by using the procedure described for **10j**. In this case, ethyl iodide was used instead of methyl iodide: mp 212−213 °C; ^{1}H NMR (DMSO-d_6) δ 1.05 (t, J = 7.1 Hz, 3H), 1.16−1.43 (m, 3H), 1.57−1.69 (m, 1H), 1.82−1.92 (m, 4H), 2.12−2.31 (m, 2H), 2.50 (s, 3H), 3.70 (q, J = 7.1 Hz, 2H), 4.04 (m, 1H), 5.14 (s, 2H), 7.02 (d, J = 8.5 Hz, 1H), 7.15 (d, J = 12.2 Hz, 1H), 7.44 (s, 2H), 7.51 (s, 4H), 7.58−7.64 (m, 2H), 7.96 (d, J = 8.6 Hz, 1H), 8.11 (d, J = 8.8 Hz, 1H), 8.29 (s, 1H); HRMS calcd for $C_{37}H_{36}ClFN_3O_4$ (M + H)$^+$ 640.238, found 640.236; HPLC method A, >99% (12.4 min); HPLC method B, >99% (7.58 min).

2-{4-[4′-Chloro-4-(isobutyrylmethylamino)biphenyl-2-ylmethoxy]-2-fluorophenyl}-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (10l). Compound **10l** was prepared by using the procedure described for **10j**. In this case, isobutyryl chloride was used instead of acetyl chloride: mp 234−235 °C; ^{1}H NMR (DMSO-d_6) δ 0.96 (d, J = 6.5 Hz, 6H), 1.17−1.45 (m, 3H), 1.59−1.69 (m, 1H), 1.77−1.95 (m, 4H), 2.15−2.30 (m, 2H), 2.42−2.56 (m, 1H), 3.21 (s, 3H), 4.06 (m, 1H), 5.15 (s, 2H), 7.01 (d, J = 8.6 Hz, 1H), 7.15 (d, J = 12.2 Hz, 1H), 7.46 (s, 2H), 7.51 (s, 4H), 7.59−7.65 (m, 2H), 7.97 (d, J = 8.8 Hz, 1H), 8.12 (d, J = 8.8 Hz, 1H), 8.29 (s, 1H); MS (FAB) m/z 654 (M + H)$^+$. Anal. ($C_{38}H_{37}ClFN_3O_4$·HCl) C, H, N.

2-{4-[4-(Acetylisopropylamino)-4′-chlorobiphenyl-2-ylmethoxy]-2-fluorophenyl}-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (10m). To a solution of **21b** (300 mg, 0.502 mmol) in THF (5 mL) and AcOH (0.5 mL) was added acetone (100 μL, 1.36 mmol) at room temperature. The solution was stirred for 15 min, followed by the addition of sodium triacetoxyborohydride (212 mg, 1.00 mmol). The solution was stirred overnight at room temperature. The reaction mixture was poured into water and extracted with AcOEt. The AcOEt layer was separated, washed with saturated aqueous $NaHCO_3$, water, and brine, and dried over $MgSO_4$. Filtration and concentration in vacuo and purification by silica gel

flash chromatography (*n*-hexane/AcOEt = 2/1) gave 169 mg (52%) of the *N*-isoproyl compound 2-{4-[4-(acetylisopropylamino)-4′-chlorobiphenyl-2-ylmethoxy]-2-fluorophenyl}-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic acid methyl ester as a white solid: ^{1}H NMR ($CDCl_3$) δ 1.25 (d, J = 6.3 Hz, 6H), 1.26−1.41 (m, 3H), 1.67−1.80 (m, 1H), 1.81−2.05 (m, 4H), 2.15−2.32 (m, 2H), 3.69 (sept, J = 6.3 Hz, 1H), 3.95 (s, 3H), 4.05 (m, 1H), 4.94 (s, 2H), 6.64 (dd, J = 2.6, 8.3 Hz, 1H), 6.71 (d, J = 11.7 Hz, 1H), 6.79 (s, 1H), 6.81 (d, J = 8 Hz, 1H), 7.14 (d, J = 8.3 Hz, 1H), 7.29 (d, J = 8.6 Hz, 2H), 7.35 (d, J = 8.6 Hz, 2H), 7.50 (t, J = 8.4 Hz, 1H), 7.66 (d, J = 8.6 Hz, 1H), 7.98 (d, J = 8.7 Hz, 1H), 8.51 (s, 1H).

Compound **10m** was prepared from the *N*-isopropyl compound obtained above using the hydrolysis procedure described for **3g** in 87% yield: mp 210−211 °C; ^{1}H NMR (DMSO-d_6) δ 1.02 (d, J = 6.6 Hz, 6H), 1.20−1.50 (m, 3H), 1.55−1.75 (m, 4H), 1.80−2.00 (m, 4H), 2.10−2.40 (m, 2H), 3.98 (m, 1H), 4.09 (m, 1H), 4.85 (sept, J = 6.6 Hz, 1H), 5.18 (s, 2H), 6.97 (dd, J = 2.2, 8.7 Hz, 1H), 7.08 (dd, J = 2.3, 12 Hz, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.45 (d, J = 8.7 Hz, 1H), 7.48−7.54 (m, 5H), 7.56 (t, J = 8.4 Hz, 1H), 7.93 (d, J = 8.8 Hz, 1H), 8.02 (d, J = 8.8 Hz, 1H), 8.26 (s, 1H); MS (FAB) m/z 654 $(M + H)^+$. Anal. ($C_{38}H_{37}ClFN_3O_4 \cdot HCl \cdot 0.5H_2O$) C, H, N.

2-{4-[4′-Chloro-4-(2-oxopyrrolidin-1-yl)biphenyl-2-ylmethoxy]-2-fluorophenyl}-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (10n). To a solution of **21b** (500 mg, 0.856 mmol) and triethylamine (140 μL, 1.00 mmol) in $CHCl_3$ (3 mL) was added a solution of 4-chlorobutyryl chloride (100 μL, 0.892 mmol) in $CHCl_3$ (2 mL) dropwise with cooling by an ice−water bath. The mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with $CHCl_3$, washed with water and brine, and dried over Na_2SO_4. Filtration and evaporation of the solvent in vacuo gave 589 mg (100%) of the acylamino compound as a crude solid: ^{1}H NMR ($CDCl_3$) δ 1.24−1.47 (m, 3H), 1.70−1.81 (m, 1H), 1.84−2.05 (m, 4H), 2.10−2.34 (m, 4H), 2.59 (t, J = 7 Hz, 2H), 3.67 (t, J = 6.1 Hz, 2H), 3.95 (s, 3H), 4.04 (m, 1H), 4.96 (s, 2H), 6.68 (dd, J = 2.3, 11.6 Hz, 1H), 6.79 (dd, J = 2.3, 8.6 Hz, 1H), 7.28 (d, J = 8.1 Hz, 1H), 7.29 (d, J = 8.5 Hz, 2H), 7.39 (d, J = 8.5 Hz, 2H), 7.48 (t, J = 8.4 Hz, 1H), 7.61 (s, 1H), 7.67 (d, J = 8.7 Hz, 1H), 7.75 (d, J = 8.7 Hz, 1H), 7.76 (s, 1H), 7.99 (dd, J = 1.6, 8.7 Hz, 1H), 8.49 (d, J = 1.4 Hz, 1H).

To a solution of the acylamino compound (589 mg, 0.855 mmol) obtained above in DMF (6 mL) was added K_2CO_3 (244 mg, 1.77 mmol). The reaction mixture was heated at 80 °C for 1 h. The reaction mixture was poured into water, and the precipitated crystals were collected by filtration to give 502 mg (90%) of the lactam **25** as a crude solid: ^{1}H NMR ($CDCl_3$) δ 1.20−1.45 (m, 3H), 1.70−1.80 (m, 1H), 1.85−2.01 (m, 4H), 2.12−2.32 (m, 4H), 2.66 (t, J = 7.8 Hz, 2H), 3.94 (t, J = 7.1 Hz, 2H), 3.95 (s, 3H), 4.04 (m, 1H), 5.00 (s, 2H), 6.71 (d, J = 11.6 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 7.31 (d, J = 8.6 Hz, 2H), 7.37 (d, J = 8.2 Hz, 1H), 7.40 (d, J = 8.5 Hz, 2H), 7.50 (t, J = 8.4 Hz, 1H), 7.67 (d, J = 8.5 Hz, 1H), 7.70 (dd, J = 2.3, 8.5 Hz, 1H), 7.90 (d, J = 2.3 Hz, 1H), 7.98 (dd, J = 1.7, 8.6 Hz, 1H), 8.49 (d, J = 1.4 Hz, 1H).

Compound **10n** was prepared from the lactam **25** obtained above using the procedure described for **2b** (step 4) in 87% yield: mp 243−246 °C; ^{1}H NMR (DMSO-d_6) δ 1.20−1.50 (m, 3H), 1.55−1.70 (m, 1H), 1.75−2.00 (m, 4H), 2.05−2.40 (m, 4H), 2.54 (t, J = 8.1 Hz, 2H), 3.91 (t, J = 7 Hz, 2H), 4.13 (m, 1H), 5.11 (s, 2H), 7.06 (dd, J = 2.2, 8.8 Hz, 1H), 7.20 (dd, J = 2.2, 12.1 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.45 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 7.68 (t, J = 8.4 Hz, 1H), 7.77 (dd, J = 2.2, 8.4 Hz, 1H), 8.00 (d, J = 2.2 Hz, 1H), 8.02 (d, J = 8.8 Hz, 1H), 8.21 (d, J = 8.8 Hz, 1H), 8.33 (d, J = 1.1 Hz, 1H); MS (FAB) m/z 638 $(M + H)^+$. Anal. ($C_{37}H_{33}ClFN_3O_4 \cdot HCl$) C, H, N.

2-[4-(4-Acetyl-4′-chlorobiphenyl-2-ylmethoxy)phenyl]-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (3e). Step 1: Preparation of 4-Bromo-*N*-methoxy-3,*N*-dimethylbenzamide (26). To a solution of 4-bromo-3-methylbenzoic acid (10.00 g, 46.50 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (4.99 g, 51.2 mmol) in DMF (150 mL) were added 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (9.82 g, 51.2 mmol) and 1-hydroxy-1*H*-benzotriazole monohydrate (7.84 g, 51.2 mmol), and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water and extracted with AcOEt. The AcOEt layer was separated, washed with water, 2 N aqueous HCl, saturated aqueous $NaHCO_3$, and brine, and dried over $MgSO_4$. Filtration and evaporation of the solvent in vacuo gave 9.47 g (79%) of **26** as a crude oil: ^{1}H NMR (DMSO-d_6) δ 2.38 (s, 3H), 3.25 (s, 3H), 3.54 (s, 3H), 7.34 (dd, J = 2.1, 8.3 Hz, 1H), 7.56 (d, J = 1.8 Hz, 1H), 7.66 (d, J = 8.2 Hz, 1H).

Steps 2−4: Preparation of 1-(2-Bromomethyl-4′-chlorobiphenyl-4-yl)ethanone (27). Compound **26** obtained above was converted to 4′-chloro-2-methylbiphenyl-4-carboxylic acid methoxymethylamide by Suzuki coupling using the procedure described for **2b** (step 3) in 90% yield: ^{1}H NMR (DMSO-d_6) δ 2.26 (s, 3H), 3.27 (s, 3H), 3.59 (s, 3H), 7.27 (d, J = 7.8 Hz, 1H), 7.41 (d, J = 8.5 Hz, 2H), 7.47 (s, 1H), 7.49−7.54 (m, 3H).

To a solution of 4′-chloro-2-methylbiphenyl-4-carboxylic acid methoxymethylamide (2.18 g, 7.52 mmol) obtained above in THF (15 mL) was added 0.93 M methylmagnesium bromide in THF (16.1 mL, 15.0 mmol) dropwise with cooling by an ice−water bath, and the mixture was stirred at room temperature for 2.5 h. The reaction mixture was poured into 2 N aqueous HCl and extracted with AcOEt. The AcOEt layer was separated, washed with saturated aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. Filtration and concentration in vacuo and separation by silica gel flash chromatography (*n*-hexane/AcOEt = 6/1) gave 1.56 g (85%) of the methyl ketone as a pale-yellow solid: ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 3H), 2.63 (s, 3H), 7.25 (dd, J = 1.8, 8.4 Hz, 2H), 7.29 (d, J = 8.1 Hz, 1H), 7.42 (dd, J = 2.1, 8.7 Hz, 2H), 7.59 (dd, J = 2.1, 8.1 Hz, 1H), 7.87 (s, 1H).

Bromination of the ketone obtained above by NBS using the procedure described for **2b** (step 1) gave compound **27** in 72% yield: ^{1}H NMR ($CDCl_3$) δ 2.65 (s, 3H), 4.44 (s, 2H), 7.34 (d, J = 8.1 Hz, 1H), 7.39 (dd, J = 2.1, 8.4 Hz, 2H), 7.46 (dd, J = 2.1, 8.4 Hz, 2H), 7.93 (dd, J = 1.8, 8.1 Hz, 1H), 8.11 (d, J = 1.8 Hz, 1H).

Steps 5 and 6: Preparation of 2-[4-(4-Acetyl-4′-chlorobiphenyl-2-ylmethoxy)phenyl]-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (3e). Compound **3e** was prepared from **27** obtained above using the procedure described for **2b** (steps 2 and 4) in 60% yield: mp 269−270 °C; ^{1}H NMR (DMSO-d_6) δ 1.20−1.50 (m, 3H), 1.60−1.71 (m, 1H), 1.80−2.06 (m, 4H), 2.20−2.37 (m, 2H), 2.65 (s, 3H), 4.33 (m, 1H), 5.17 (s, 2H), 7.22 (d, J = 8.8 Hz, 2H), 7.53 (s, 4H), 7.54−7.56 (m, 1H), 7.70 (d, J = 8.8 Hz, 2H), 8.00 (dd, J = 1.5, 8.8 Hz, 1H), 8.07 (dd, J = 1.8, 7.7 Hz, 1H), 8.19 (d, J = 8.8 Hz, 1H), 8.26 (d, J = 1.8 Hz, 1H), 8.28 (d, J = 1.5 Hz, 1H); MS (FAB) m/z 579 $(M + H)^+$. Anal. ($C_{35}H_{31}ClN_2O_4 \cdot HCl$) C, H, N.

2-{4-[3-(4-Chlorophenyl)pyridin-2-ylmethoxy]phenyl}-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (8). Steps 1 and 2: Preparation of 3-Trifluoromethanesulfonyloxypicolinic Acid Methyl Ester (28). To a solution of 3-hydroxypicolinic acid (1.00 g, 7.19 mmol) in MeOH (10 mL) was added concentrated sulfuric acid (1.0 mL) dropwise with cooling by an ice−water bath. The solution was heated at reflux temperature for 5 h. After cooling to the ambient temperature, the solution was poured into saturated aqueous $NaHCO_3$ with cooling by an ice−water bath and extracted with $CHCl_3$. The $CHCl_3$ layer was separated, washed with saturated aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. Filtration and evaporation of the solvent in vacuo gave 711 mg (64%) of the methyl ester as a crude solid: ^{1}H NMR ($CDCl_3$) δ 4.07 (s, 3H), 7.38 (dd, J = 1.7, 8.5 Hz, 1H), 7.44 (dd, J = 4.1, 8.6 Hz, 1H), 8.29 (dd, J = 1.6, 4.1 Hz, 1H), 10.64 (s, 1H).

To a solution of the methyl ester (710 mg, 4.64 mmol) obtained above and triethylamine (770 μL, 5.52 mmol) in CH_2Cl_2 (7 mL) was added trifluoromethanesulfonic anhydride (860 μL, 5.08 mmol) dropwise with cooling by an ice−water bath. The mixture was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with AcOEt. The AcOEt layer was separated, washed with brine, and dried over $MgSO_4$. Filtration and concentration in vacuo gave 1.20 g (90%) of **28** as a crude oil:

^{1}H NMR ($CDCl_3$) δ 4.06 (s, 3H), 7.63 (dd, J = 4.5, 8.4 Hz, 1H), 7.74 (dd, J = 1.1, 8.4 Hz, 1H), 8.78 (dd, J = 1.3, 4.5 Hz, 1H).

Steps 3 and 4: Preparation of 3-(4-Chlorophenyl)-2-hydroxymethylpyridine (29). To a solution of **28** (1.20 g, 4.21 mmol) obtained above in toluene (40 mL) were added 4-chlorophenylboronic acid (1.30 g, 8.31 mmol), tetrakis(triphenylphosphine)-palladium(0) (1.40 g, 1.21 mmol), and K_2CO_3 (872 mg, 6.31 mmol). The mixture was heated at 90 °C for 3 h. The reaction mixture was poured into water and extracted with AcOEt. The AcOEt layer was separated, washed with saturated aqueous $NaHCO_3$, water, and brine, and dried over $MgSO_4$. Filtration and concentration in vacuo and purification by silica gel flash chromatography (*n*-hexane/AcOEt = 3/2) gave 728 mg (70%) of the biphenyl compound as a white solid: ^{1}H NMR ($CDCl_3$) δ 3.81 (s, 3H), 7.28 (dd, J = 2.4, 8.4 Hz, 2H), 7.41 (dd, J = 2, 8.5 Hz, 2H), 7.49 (dd, J = 4.7, 7.9 Hz, 1H), 7.73 (dd, J = 1.7, 7.9 Hz, 1H), 8.69 (dd, J = 1.6, 4.7 Hz, 1H).

To a suspension of lithium alminum hydride (160 mg, 4.22 mmol) in THF (5 mL) was added a solution of the biphenyl compound (720 mg, 2.91 mmol) obtained above in THF (5 mL) dropwise with cooling by an ice−water bath. The reaction mixture was stirred at 0 °C for 1 h. To the mixture were added water (1.6 mL), 15% aqueous NaOH (1.6 mL), and water (4.8 mL) in sequential order, and the slurry was filtered. After the solid was washed with THF (10 mL), the combined filtrates were concentrated in vacuo to give a solid, which was purified with silica gel flash chromatography (*n*-hexane/AcOEt = 1/1) to give 208 mg (32%) of the benzyl alcohol as a white solid: ^{1}H NMR ($CDCl_3$) δ 4.61 (s, 2H), 7.24 (dd, J = 2.6, 8.9 Hz, 2H), 7.32 (dd, J = 6.5, 10.2 Hz, 1H), 7.44 (dd, J = 2.6, 7.9 Hz, 2H), 7.58 (dd, J = 2.1, 10.2 Hz, 1H), 8.60 (dd, J = 2.1, 6.5 Hz, 1H).

Steps 5−7: Preparation of 2-{4-[3-(4-Chlorophenyl)pyridin-2-ylmethoxy]phenyl}-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (8). To a solution of the benzyl alcohol **29** (960 mg, 3.64 mmol) obtained above in $CHCl_3$ (15 mL) were added thionyl chloride (0.40 mL, 5.5 mmol) and a catalytic amount of pyridine. The mixture was stirred at room temperature for 2 h. The solvent was removed by evaporation in vacuo. The residue was diluted with $CHCl_3$, washed with water and brine, and dried over $MgSO_4$. Filtration and concentration in vacuo gave the benzyl chloride **29** as a crude oil. Compound **8** was prepared from compound **29** obtained above using the procedure described for **3e** (steps 5 and 6) in 18% yield: mp >300 °C; ^{1}H NMR (DMSO-d_6) δ 1.15−1.55 (m, 3H), 1.55−1.75 (m, 1H), 1.80−2.05 (m, 4H), 2.15−2.40 (m, 2H), 4.26 (m, 1H), 5.16 (s, 2H), 7.10 (d, J = 8.8 Hz, 2H), 7.50−7.58 (m, 7H), 7.80−7.87 (m, 2H), 7.94 (d, J = 8.6 Hz, 1H), 8.21 (d, J = 1.4 Hz, 1H), 8.68 (dd, J = 1.7, 4.8 Hz, 1H), 12.75 (brs, 1H); MS (FAB) m/z 538 $(M + H)^+$. Anal. ($C_{32}H_{28}ClN_3O_3 \cdot 0.5H_2O$) C, H, N.

2-{4-[5-(4-Chlorophenyl)-2-methyloxazol-4-ylmethoxy]phenyl}-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (4a). Steps 1−3: Preparation of 2-Acetylamino-3-(4-chlorophenyl)-3-oxopropionic Acid Methyl Ester (32). To a solution of methyl isocyanoacetate (30.00 g, 302.7 mmol) and 4-chlorobenzoyl chloride (40.0 mL, 315 mmol) in THF (300 mL) were added triethylamine (93.0 mL, 667 mmol) and a catalytic amount of 4-(dimethylamino)-pyridine. The mixture was heated overnight at reflux temperature, and the slurry was filtered. After the solid was washed with AcOEt (100 mL), the combined filtrates were concentrated in vacuo. The residue was dissolved in AcOEt, and the solution was washed with water and brine and was dried over $MgSO_4$. Filtration and concentration in vacuo gave a solid, which was triturated in ether and collected by filtration to give 48.79 g (68%) of 5-(4-chlorophenyl)oxazole-4-carboxylic acid methyl ester as a crude solid.

To a solution of 5-(4-chlorophenyl)oxazole-4-carboxylic acid methyl ester (48.79 g, 205.5 mmol) obtained above in MeOH (600 mL) was added acetyl chloride (128.0 mL, 1.80 mol) dropwise with cooling by an ice−water bath. The mixture was heated at reflux temperature for 7 h. After the solution was concentrated in vacuo, the residue was triturated in acetone and collected by filtration to give 42.88 g (79%) of 2-amino-3-(4-chlorophenyl)-3-oxopropionic acid methyl ester hydrochloride **31** as a crude solid.

To a solution of **31** (2.34 g, 8.86 mmol) obtained above and sodium acetate (730 mg, 8.90 mmol) in water (60 mL) was added acetic anhydride (1.76 mL, 18.7 mmol) with cooling by an ice−water bath. After the mixture was stirred at 0 °C for 30 min, the precipitated crystals were collected by filtration to give 2.20 g (92%) of **32** as a crude solid: ^{1}H NMR ($CDCl_3$) δ 2.10 (s, 3H), 3.73 (s, 3H), 6.18 (d, J = 7.2 Hz, 1H), 6.82 (d, J = 7.2 Hz, 1H), 7.49 (d, J = 8.7 Hz, 2H), 8.07 (d, J = 8.7 Hz, 2H).

Steps 4 and 5: Preparation of [5-(4-Chlorophenyl)-2-methyloxazol-4-yl]methanol (34a). A solution of **32** (1.00 g, 3.71 mmol) in concentrated sulfuric acid (10 mL) was stirred at room temperature for 4 h. The solution was poured into ice, and the precipitated crystals were collected by filtration to give 925 mg (99%) of the oxazole-4-carboxylic acid methyl ester **33a** as a crude solid. Compound **33a** was converted to the alcohol **34a** by using the procedure described for **8** (step 4) in 88% yield: ^{1}H NMR ($CDCl_3$) δ 2.50 (s, 3H), 4.70 (s, 2H), 7.41 (d, J = 8.6 Hz, 2H), 7.57 (d, J = 8.6 Hz, 2H).

Steps 6−8: Preparation of 2-{4-[5-(4-Chlorophenyl)-2-methyloxazol-4-ylmethoxy]phenyl}-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (4a). Compound **4a** was prepared from **34a** obtained above by using the procedure described for **8** (steps 5−7) in 16% yield: mp 262−263 °C; ^{1}H NMR (DMSO-d_6) δ 1.15−1.55 (m, 3H), 1.55−1.75 (m, 1H), 1.75−1.95 (m, 2H), 1.95−2.15 (m, 2H), 2.15−2.50 (m, 2H), 2.51 (s, 3H), 4.39 (m, 1H), 5.28 (s, 2H), 7.39 (d, J = 8.8 Hz, 2H), 7.61 (d, J = 8.7 Hz, 2H), 7.70 (d, J = 8.7 Hz, 2H), 7.79 (d, J = 8.7 Hz, 2H), 8.06 (d, J = 8.7 Hz, 1H), 8.30 (d, J = 8.9 Hz, 1H), 8.33 (s, 1H); MS (FAB) m/z 542 $(M + H)^+$. Anal. ($C_{31}H_{28}ClN_3O_4 \cdot HCl$) C, H, N.

2-{4-[5-(4-Chlorophenyl)-2-methylthiazol-4-ylmethoxy]phenyl}-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (4b). To a solution of **32** (1.00 g, 3.71 mmol) in THF (10 mL) was added 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent, 1.50 g, 3.71 mmol). The mixture was heated at reflux temperature for 1 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with AcOEt. The AcOEt layer was separated, washed with 1.0% aqueous NaClO and brine, and dried over Na_2SO_4. Filtration and concentration in vacuo gave a solid, which was triturated in *n*-hexane and collected by filtration to give 807 mg (81%) of the thiazole-4-carboxylic acid methyl ester **33b** as a crude solid. Compound **33a** was converted to compound **4b** by using the procedure described for **8** (steps 4−7) in 73% yield: mp 274−275 °C; ^{1}H NMR (DMSO-d_6) δ 1.15−1.55 (m, 3H), 1.55−1.75 (m, 1H), 1.75−1.95 (m, 2H), 1.95−2.20 (m, 2H), 2.20−2.45 (m, 2H), 2.71 (s, 3H), 4.39 (m, 1H), 5.19 (s, 2H), 7.35 (d, J = 8.8 Hz, 2H), 7.54 (d, J = 8.9 Hz, 2H), 7.58 (d, J = 8.9 Hz, 2H), 7.77 (d, J = 8.7 Hz, 2H), 8.06 (d, J = 8.7 Hz, 1H), 8.29 (d, J = 8.8 Hz, 1H), 8.33 (s, 1H), 13.10 (brs, 1H); MS (FAB) m/z 558 $(M + H)^+$. Anal. ($C_{31}H_{28}ClN_3O_3S \cdot HCl$) C, H, N.

2-{4-[4-(4-Chlorophenyl)-2-methylthiazol-5-ylmethoxy]phenyl}-1-cyclohexyl-1*H*-benzoimidazole-5-carboxylic Acid (5). To a solution of 3-(4-chlorophenyl)-3-oxopropionic acid ethyl ester **35** (3.00 g, 13.2 mmol) in 1,4-dioxane (25 mL) was added Br_2 (700 μL, 13.6 mmol) dropwise at room temperature. The mixture was stirred for 1 h and poured into ice−water, and AcOEt was added to the solution. The AcOEt layer was separated, washed with water and brine, and dried over Na_2SO_4. Filtration and concentration in vacuo gave 2-bromo-3-(4-chlorophenyl)-3-oxopropionic acid ethyl ester as a crude oil.

To a solution of 2-bromo-3-(4-chlorophenyl)-3-oxopropionic acid ethyl ester obtained above in EtOH (25 mL) was added thioacetamide (1.00 g, 13.3 mmol). The mixture was heated at reflux temperature for 3 h. After the mixture was cooled, the precipitated crystals were collected by filtration to give 1.69 g (46%) of the thiazole **36** as a crude solid: ^{1}H NMR ($CDCl_3$) δ 1.29 (t, J = 6.9 Hz, 3H), 2.74 (s, 3H), 4.27 (q, J = 6.9 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 7.70 (d, J = 8.7 Hz, 2H).

Compound **5** was prepared from the thiazole **36** obtained above by using the procedure described for **8** (steps 4−7) in 26% yield:

mp 250−251 °C; ^{1}H NMR (DMSO-d_6) δ 1.15−1.55 (m, 3H), 1.55−1.75 (m, 1H), 1.80−2.05 (m, 4H), 2.15−2.40 (m, 2H), 2.71 (s, 3H), 4.31 (m, 1H), 5.45 (s, 2H), 7.26 (d, J = 8.7 Hz, 2H), 7.56 (d, J = 8.5 Hz, 2H), 7.67 (d, J = 8.7 Hz, 2H), 7.72 (d, J = 8.5 Hz, 2H), 7.91 (d, J = 8.6 Hz, 1H), 8.04 (d, J = 8.7 Hz, 1H), 8.25 (s, 1H), 12.90 (brs, 1H); MS (FAB) m/z 558 (M + H)$^+$. Anal. ($C_{31}H_{28}ClN_3O_3S\cdot H_2O$) C, H, N.

2-{4-[4-(4-Chlorophenyl)-2-methylpyrimidin-5-ylmethoxy]-phenyl}-1-cyclohexyl-1*H*-benzimidazole-5-carboxylic Acid (6). A solution of 3-(4-chlorophenyl)-3-oxopropionic acid ethyl ester **35** (3.60 g, 15.9 mmol) in *N*,*N*-dimethylformamide dimethylacetal (10 mL) was heated at reflux temperature for 2 h. The solution was concentrated in vacuo, and the residue was dissolved in AcOEt. The solution was washed with water and brine and was dried over $MgSO_4$. Filtration and concentration in vacuo gave 4.86 g of 2-(4-chlorobenzoyl)-3-(dimethylamino)acrylic acid ethyl ester as a crude solid: ^{1}H NMR ($CDCl_3$) δ 0.94 (t, J = 7.1 Hz, 3H), 2.97 (brs, 6H), 3.97 (q, J = 7.1 Hz, 2H), 7.36 (d, J = 8.5 Hz, 2H), 7.56−7.86 (m, 3H).

To a suspension of 2-(4-chlorobenzoyl)-3-(dimethylamino)-acrylic acid ethyl ester (2.50 g, 8.87 mmol) obtained above and sodium ethoxide (1.30 g, 19.1 mmol) in EtOH (40 mL) was added acetamidine hydrochloride (1.70 g, 18.0 mmol). The mixture was heated overnight at reflux temperature. The solution was concentrated in vacuo, and the residue was dissolved in AcOEt. The solution was washed with water and brine and was dried over Na_2SO_4. Filtration and concentration in vacuo gave 1.94 g (79%) of the pyrimidine **37** as a crude solid: ^{1}H NMR ($CDCl_3$) δ 1.18 (t, J = 7.1 Hz, 3H), 2.83 (s, 3H), 4.25 (q, J = 7.1 Hz, 2H), 7.44 (d, J = 8.5 Hz, 2H), 7.54 (d, J = 8.5 Hz, 2H), 9.03 (s, 1H).

Compound **6** was prepared from the pyrimidine **37** obtained above by using the procedure described for **8** (steps 4−7) in 11% yield: mp 255−256 °C; ^{1}H NMR (DMSO-d_6) δ 1.15−1.55 (m, 3H), 1.55−1.75 (m, 1H), 1.75−1.95 (m, 2H), 1.95−2.15 (m, 2H), 2.15−2.50 (m, 2H), 2.72 (s, 3H), 4.36 (m, 1H), 5.26 (s, 2H), 7.30 (d, J = 8.7 Hz, 2H), 7.60 (d, J = 8.5 Hz, 2H), 7.74−7.79 (m, 4H), 8.04 (d, J = 8.6 Hz, 1H), 8.25 (d, J = 8.8 Hz, 1H), 8.32 (s, 1H), 8.99 (s, 1H), 13.20 (brs, 1H); MS (FAB) m/z 553 (M + H)$^+$. Anal. ($C_{32}H_{29}ClN_4O_3\cdot H_2O$) C, H, N.

2-[4-(Biphenyl-2-ylmethoxy)-2-fluorophenyl]-1-cyclohexyl-1*H*-benzoimidazole-5-carboxylic Acid (9a). To a suspension of **11b** (250 mg, 0.679 mmol) and K_2CO_3 (122 mg, 0.882 mmol) in DMF (3.75 mL) was added 2-phenylbenzyl bromide (0.161 mL, 0.882 mmol). The reaction mixture was heated at 80 °C for 2.5 h. The reaction mixture was poured into water and extracted with AcOEt. The AcOEt layer was washed with water and brine and was dried over $MgSO_4$. Filtration and evaporation of the solvent in vacuo and purification by silica gel flash chromatography (*n*-hexane/AcOEt = 2/1) gave a solid, which was triturated in AcOEt and *n*-hexane to give 318 mg (88%) of 2-[4-(biphenyl-2-ylmethoxy)-2-fluorophenyl]-1-cyclohexyl-1*H*-benzoimidazole-5-carboxylic acid methyl ester as white solid: ^{1}H NMR (DMSO-d_6) δ 1.20−1.45 (brm, 3H), 1.60−1.71 (brm, 1H), 1.79−1.91 (brm, 4H), 2.13−2.27 (brm, 2H), 3.90 (s, 3H), 3.95−4.04 (brm, 1H), 5.08 (s, 2H), 6.96 (dd, J = 8.6, 2.3 Hz, 1H), 7.08 (dd, J = 12.1, 2.3 Hz, 1H), 7.38−7.57 (m, 9H), 7.67−7.69 (m, 1H), 7.90 (dd, J = 8.8, 1.6 Hz, 1H), 8.01 (d, J = 8.8 Hz, 1H), 8.27 (d, J = 1.4 Hz, 1H).

To a solution of the ester (318 mg, 0.595 mmol) obtained above in MeOH (3.6 mL) and THF (1.8 mL) was added 4 N aqueous NaOH (1.09 mL, 4.38 mmol). The reaction mixture was heated at reflux temperature for 2 h. The mixture was acidified to pH 3 with 2 N hydrochloric acid with cooling by an ice−water bath, and the precipitated solid was collected by filtration to give a solid (303 mg). The solid was recrystallized from acetone (3 mL) and collected by filtration to give 179 mg (58%) of **9a** as white solid: mp 223−224 °C; ^{1}H NMR (DMSO-d_6) δ 1.20−1.44 (brm, 3H), 1.61−1.70 (brm, 1H), 1.80−1.91 (brm, 4H), 2.15−2.29 (brm, 2H), 3.93−4.04 (brm, 1H), 5.08 (s, 2H), 6.96 (dd, J = 8.6, 2.3 Hz, 1H), 7.08 (dd, J = 12.1, 2.3 Hz, 1H), 7.38−7.56 (m, 9H), 7.67−7.69 (m, 1H), 7.89 (dd, J = 8.8, 1.6 Hz, 1H), 7.97 (d, J = 8.8 Hz, 1H), 8.25 (d, J = 1.6 Hz, 1H), 12.80 (s, 1H); MS (ESI) m/z 521(M + H)$^+$. Anal. ($C_{33}H_{29}FN_2O_3$) C, H, N.

Compounds 9b−e were prepared from the corresponding phenols **11c−f** (synthesized according to the procedure previously described[1]) by using the procedure described for **9a**.

2-[4-(Biphenyl-2-ylmethoxy)-2-chlorophenyl]-1-cyclohexyl-1*H*-benzoimidazole-5-carboxylic Acid (9b). Mp 227−228 °C; ^{1}H NMR (DMSO-d_6) δ 1.10−1.42 (brm, 3H), 1.58−1.68 (brm, 1H), 1.71−2.33 (brm, 6H), 3.77−3.89 (brm, 1H), 5.09 (s, 2H), 7.07 (dd, J = 8.6, 2.6 Hz, 1H), 7.24 (d, J = 2.6 Hz, 1H), 7.37−7.53 (m, 8H), 7.67−7.69 (m, 1H), 7.89 (dd, J = 8.6, 1.6 Hz, 1H), 7.96 (d, J = 8.6 Hz, 1H), 8.25 (s, 1H), 12.80 (s, 1H); MS (ESI) m/z 537(M + H)$^+$. Anal. ($C_{33}H_{29}ClN_2O_3$) C, H, N.

2-[4-(Biphenyl-2-ylmethoxy)-2-methoxyphenyl]-1-cyclohexyl-1*H*-benzoimidazole-5-carboxylic Acid (9c). Mp 239−240 °C; ^{1}H NMR (DMSO-d_6) δ 1.27−1.36 (brm, 3H), 1.63−1.66 (brm, 1H), 1.84−1.86 (brm, 4H), 2.20 (brs, 2H), 3.76 (s, 3H), 3.84−3.87 (m, 1H), 5.08 (s, 2H), 6.64 (dd, J = 8.4, 2.3 Hz, 1H), 6.75 (d, J = 2.3 Hz, 1H), 7.33 (d, J = 8.4 Hz, 1H), 7.38−7.52 (m, 8H), 7.67−7.70 (m, 1H), 7.85 (dd, J = 8.6, 1.6 Hz, 1H), 7.90 (d, J = 8.6 Hz, 1H), 8.20 (d, J = 1.6 Hz, 1H), 12.74 (brs, 1H), MS (ESI) m/z 533(M + H)$^+$. Anal. ($C_{34}H_{32}N_2O_4$) C, H, N.

2-[4-(Biphenyl-2-ylmethoxy)-2-trifluoromethylphenyl]-1-cyclohexyl-1*H*-benzoimidazole-5-carboxylic Acid (9d). Mp 229−230 °C; ^{1}H NMR (DMSO-d_6) δ 1.09−1.27 (brm, 2H), 1.28−1.43 (brm, 1H), 1.57−1.74 (brm, 2H), 1.76−1.87 (brm, 2H), 1.89−1.99 (brm, 1H), 2.06−2.32 (brm, 2H), 3.71−3.83 (brm, 1H), 5.17 (s, 2H), 7.34−7.53 (m, 10H), 7.61 (d, J = 8.6 Hz, 1H), 7.68−7.71 (m, 1H), 7.89 (dd, J = 8.6, 1.6 Hz, 1H), 7.96 (d, J = 8.6 Hz, 1H), 8.24 (d, J = 1.6 Hz, 1H), 12.73 (brs, 1H); MS (ESI) m/z 571(M + H)$^+$. Anal. ($C_{34}H_{29}F_3N_2O_3$) C, H, N.

2-[4-(Biphenyl-2-ylmethoxy)-3-fluorophenyl]-1-cyclohexyl-1*H*-benzoimidazole-5-carboxylic Acid (9e). Mp 233−237 °C; ^{1}H NMR (DMSO-d_6) δ 1.33 (brm, 3H), 1.65−1.67 (m, 1H), 1.85−1.93 (brm, 4H), 2.22−2.34 (m, 2H), 4.24−4.27 (m, 1H), 5.14 (s, 2H), 7.28 (t, J = 8.7 Hz, 1H), 7.39−7.41 (m, 3H), 7.44−7.47 (m, 4H), 7.49−7.52 (m, 2H), 7.56 (dd, J = 11.8, 5.9 Hz, 1H), 7.68−7.70 (m, 1H), 7.87 (dd, J = 8.6, 1.6 Hz, 1H), 7.96 (d, J = 8.6 Hz, 1H), 8.23 (d, J = 1.6 Hz, 1H), 12.81 (brs, 1H); MS (ESI) m/z 521-(M + H)$^+$. Anal. ($C_{33}H_{29}FN_2O_3$) C, H, N.

Biochemical RdRp Assays. HCV genotype 1 NS5B polymerases lacking C-terminal 47 residues (1b NS5B$_{544}$) was expressed in *E. coli* and purified as described previously.[22] The RdRp assays were carried out in 96-well plates by using 5 μg of HCV 3′X RNA as template-primer in a 30 μL of reaction mixture containing 7 nM HCV genotype 1b NS5B$_{544}$, 1 μCi [5,6-^{3}H]-UTP, 50 μM ATP, 50 μM GTP, 50 μM CTP, 2 μM UTP, 20 mM Tris-HCl (pH 7.5), 5 mM $MgCl_2$, 50 mM NaCl, 1 mM EDTA, 1 mM DTT, and 0.01% BSA. After incubation for 60 min at 25 °C, the reactions were terminated by addition of 150 μL of a solution containing 10% trichloroacetic acid and 1% sodium diphosphate. The RdRp activity was evaluated from the radioactivity present in the acid-insoluble material. Compounds were dissolved in DMSO and added to the reaction mixtures at a final DMSO concentration of 5%. Assays were performed in triplicate, and the results were expressed as the mean of three experiments.

HCV Replicon Assay and Cell Viability Studies. Inhibitory activity of compounds on HCV replication was evaluated by measuring the luciferase activity in Huh-5-2 cells,[23,24] which harbor HCV genotype 1b subgenomic replicon encoding chimeric reporter luciferase, and expressed as EC_{50} (concentration to reduce 50% of the replication). Huh-5-2 cells were seeded in a 96-well plate at 5 × 10^3 cells and cultured in Dulbecco's modified essential medium (Nikken Bio Medical Laboratory) supplemented with 100 U/mL penicillin, 100 μg/mL streptomycin, 2 mM l-glutamine, and 10% fetal bovine serum at 37 °C under 5% CO_2. On the following day, compounds were added and cultures were continued for 48 h in the presence of compounds. Luciferase assay was carried out using Steady-Glo reagent (Promega) according to the manufacture's instruction. Cell viability of compounds was also evaluated in Huh-5-2 cells using CellTiter 96 Aqueous One Solution reagent

(Promega) according to the manufacturer's instructions (MTT method[27]) and expressed as CC_{50} (concentration to reduce 50% of cell viability). Assays were performed in triplicate, and the results were expressed as the mean of three experiments.

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Supporting Information Available: Results from elemental analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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