Synthesis and Anti-Hepatitis B Virus Activity of Novel Benzimidazole Derivatives

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A series of novel benzimidazole derivatives was synthesized and evaluated for their anti-hepatitis B virus (HBV) activity and cytotoxicity in vitro. Strong activity against HBV replication and low cytotoxicity were generally observed in these benzimidazoles. The most promising compounds were **12a** and **12b**, with similar high antiviral potency (IC_{50} = 0.9 and 0.7 μM, respectively) and remarkable selectivity indices (>1111 and 714, respectively). They were selected for further evaluation as novel HBV inhibitors.

Introduction

Hepatitis B virus (HBV) can cause both acute and chronic infections, and constitutes the ninth leading cause of death in the world.[1] Of the approximately two billion people who have been infected with HBV worldwide, an estimated 350−400 million are chronically infected, with 0.5−1.2 million deaths annually from the resulting cirrhosis, liver failure, and hepatocellular carcinoma.[2] Although new HBV infections can be prevented by vaccination, the present vaccine is not effective for chronic carriers. There remain millions of chronically infected patients, who will eventually succumb to the sequela of the infection unless treated with currently available therapies. The major therapeutic options for HBV carriers are α-interferon (IFN-α), lamivudine (3-TC), and adefovir dipivoxil (Figure 1). However, they have limited efficacy in a significant proportion of patients and often have severe adverse effects.[3] Entecavir was approved by the US Food and Drug Administration in 2005 for the treatment of chronic hepatitis B infection. However, because its chemical structure is similar to that of lamivudine and adefovir dipivoxil, it may exert its effects via the same biological mechanism and encounter the same problems as lamivudine and adefovir dipivoxil. Although the combination therapy of lamivudine with adefovir dipivoxil, or antiviral drugs together with immunomodulators such as α-interferon might be more effective and safer in the therapeutic context, much more study is required.[4] Therefore, there is a tremendous clinical need to develop novel classes of antiviral agents for the treatment of HBV infection.

When we screened an in-house collection of compounds for anti-HBV activity, 2-{2-[1-(4-nitro-benzenesulfonyl)-1*H*-benzoimidazol-2-yl]-ethyl}-isoindole-1,3-dione (**1**, Figure 1) was identified as a modest inhibitor of HBV, with an IC_{50} of 14.2 μM in inhibiting HBV DNA replication and low cytotoxicity (CC_{50} = 200 μM) in vitro. In view of its novel structural template, which differs from those of all reported anti-HBV agents, we were interested to study further the structure−activity relationships of the related class of compounds. Thus, with compound **1** as the starting point, we developed a novel series of benzimidazole derivatives and investigated their biological activities as potential HBV inhibitors.

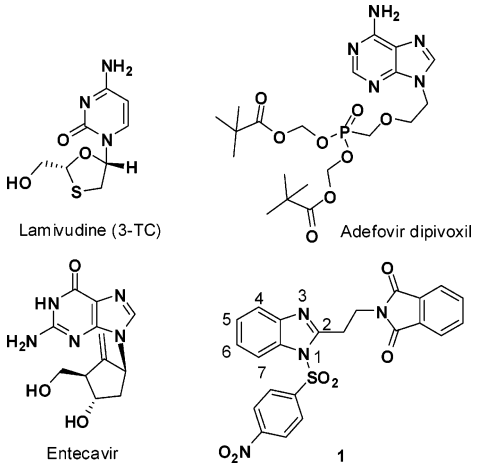

Figure 1. Structures of known HBV agents and compound **1**.

Chemistry. The benzimidazole scaffolds **4a**,[5] **4b**, and **4c** were prepared by condensation of *o*-phenylenediamine (**2a**), 4,5-difluoro-*o*-phenylenediamine (**2b**),[6] and 4,5-dichloro-*o*-phenylenediamine (**2c**),[7] respectively, with 3-phthalimidopropionic acid (**3**) in polyphosphoric acid (PPA). The first subseries of derivatives **5a**−**l**, together with **1**, were prepared with good yields via the reaction of the appropriate sulfonyl chloride with benzimidazole scaffolds **4a**−**c** in CH_2Cl_2 using 4-(dimethylamino)pyridine (DMAP) as the catalyst (Scheme 1). Clemmensen reduction[8] of the phthalimide group of **4c** with amalgamated zinc in hydrochloric acid yielded the corresponding lactam **6**, which was then converted to the *N*-Ts product **7**. The amine **8**, resulting from the hydrazinolysis of phthalimide **4c**, was treated with maleic anhydride in dry acetic acid[9] to yield the maleimide **9**, which was also sulfonylated with tosyl chloride to produce the *N*-Ts derivative **10**.

Treatment of **4c** with 4-methylbenzoyl chloride in the presence of DMAP in CH_2Cl_2 formed the *N*-benzoyl derivative **11**. N-Methylation of the benzimidazole of compound **4c** with iodomethane in the presence of potassium carbonate in DMF produced the *N*-methyl product **12a**. Compound **12b** was obtained through the reaction of compound **4c** with 4-methylbenzyl chloride in the presence of sodium hydroxide in acetonitrile, at the reflux temperature. Hydrazinolysis of the phthalimide functionality of the *N*-benzyl compound **12b** with hydrazine hydrate in refluxing ethanol produced the corresponding primary amine **13**.

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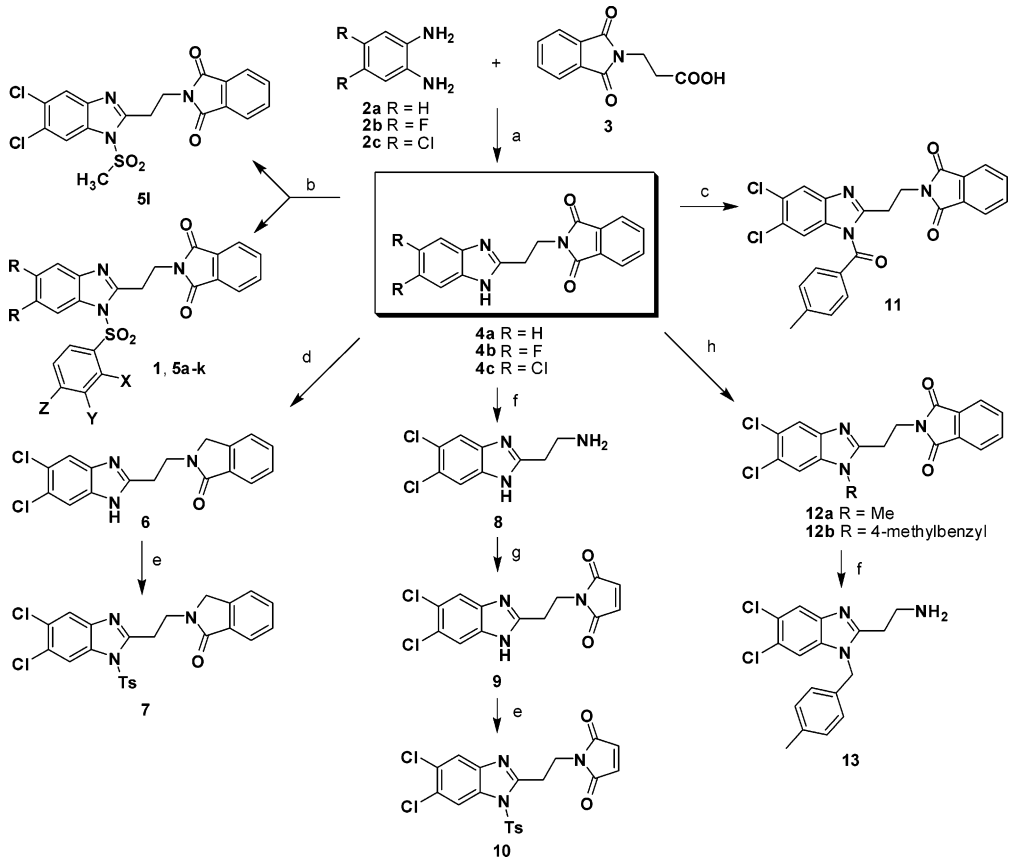
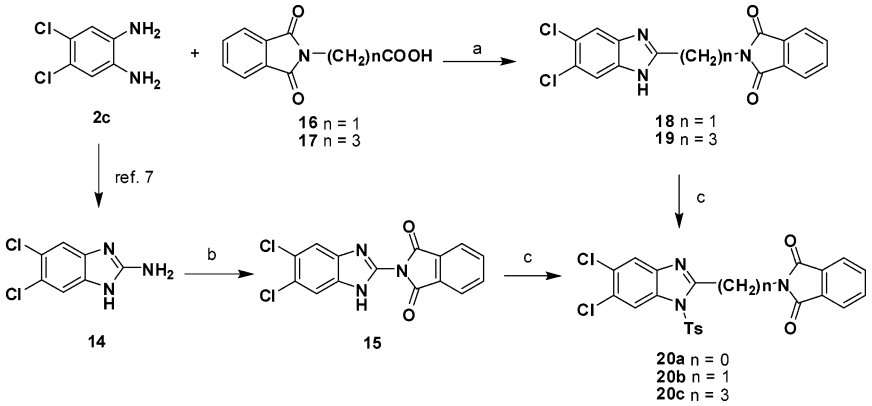
Scheme 1[a]



[a] Reagents and conditions: (a) PPA, 170−180 °C; (b) substituted benzenesulfonyl chloride (for **1** and **5a**−**k**) or MsCl (for **5l**), DMAP, CH_2Cl_2, 50 °C; (c) *p*-toluoyl chloride, DMAP, CH_2Cl_2, 50 °C; (d) Zn, $HgCl_2$, HCl, reflux; (e) TsCl, DMAP, CH_2Cl_2, 50 °C; (f) hydrazine hydrate, EtOH, reflux; (g) maleic anhydride, AcOH, reflux; (h) MeI, K_2CO_3, DMF, rt (for **12a**), or 4-methylbenzyl chloride, NaOH, CH_3CN, reflux (for **12b**).

Scheme 2[a]

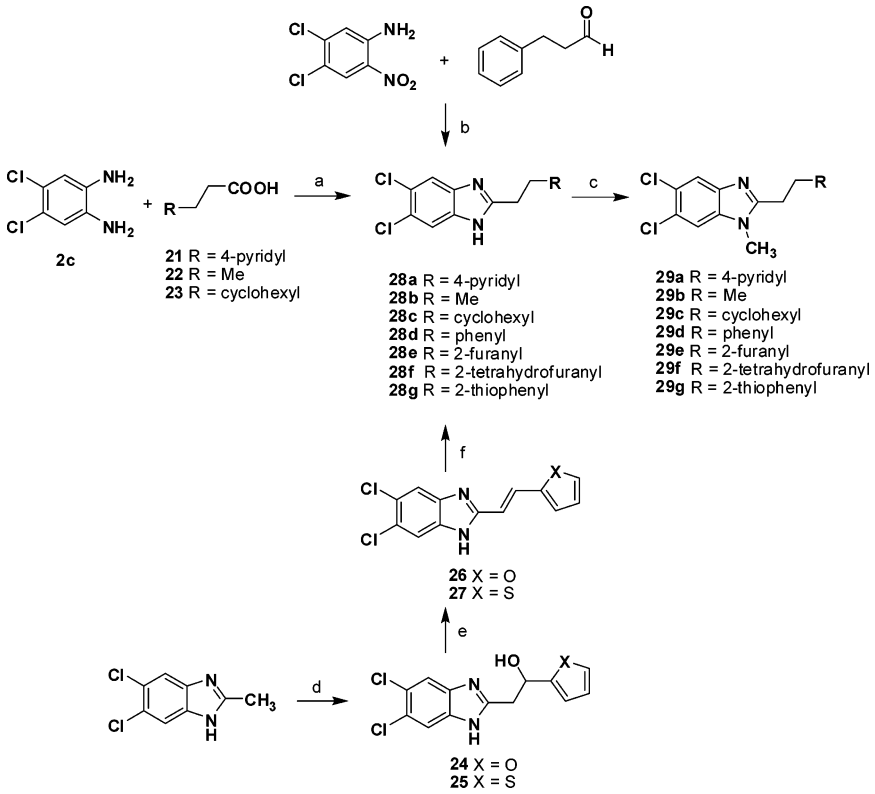


[a] Reagents and conditions: (a) PPA, 170−180 °C; (b) *o*-phthaloyl dichloride, dry pyridine, reflux; (c) TsCl, DMAP, CH_2Cl_2, 50 °C.

The benzimidazole scaffold **18** was synthesized by condensation of *N*-phthaloylglycine (**16**) with **2c** in PPA. Similarly, the reaction of 4-phthalimidobutyric acid (**17**) with **2c** produced compound **19**. Compound **14**[7] was treated with *o*-phthaloyl dichloride in dry pyridine[10] to afford compound **15**. N-Sulfonylation of the benzimidazole scaffolds **15**, **18**, and **19** with tosyl chloride in the presence of DMAP in CH_2Cl_2 produced the derivatives **20a**−**c** (Scheme 2).

Compounds **28a**−**c** were obtained by condensation in PPA of **2c** with 3-(4-pyridinyl)propionic acid (**21**), butyric acid (**22**), and cyclohexanepropionic acid (**23**), respectively (Scheme 3). Applying the method of Yang et al.,[11] the benzimidazole **28d** was prepared with a good yield. Condensation of 2-methyl-5,6-dichlorobenzimidazole with 2-furaldehyde at 170−180 °C afforded compound **24**, which was dehydrated in a mixed solution of acetic acid and acetic anhydride to provide **26**. Hydrogenation of compound **26** with Raney nickel in ethanol under a hydrogen atmosphere produced a mixture of **28e** and **28f**. Similarly, compound **27** was derived from **25**, which was prepared by the condensation of 2-methyl-5,6-dichlorobenzimidazole with 2-thiophenecarboxaldehyde. Reduction of the unsaturated alkyl linker in compound **27**, following the method of Fry et al.,[12] produced benzimidazole **28g** as the sole product. N-Methylation of the free benzimidazole nitrogen of **28a**−**g** with iodomethane in the presence of potassium carbonate in DMF at room temperature afforded **29a**−**g**.

Scheme 3[a]



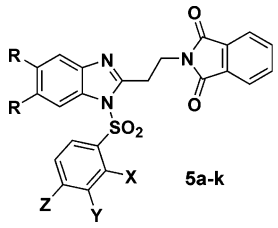
[a] Reagents and conditions: (a) PPA, 170−180 °C; (b) 1N $Na_2S_2O_4$, EtOH, 70 °C; (c) MeI, K_2CO_3, DMF, rt; (d) 2-furaldehyde (for **24**) or 2-thiophenecarboxaldehyde (for **25**), 170−180 °C; (e) AcOH, Ac_2O, reflux; (f) H_2, Ra−Ni, EtOH, rt (for **28e** and **28f**), or I_2, H_3PO_2, AcOH, reflux (for **28g**).

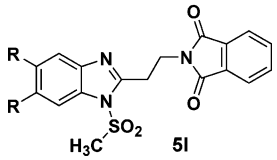
Results and Discussion

The potential anti-HBV activity and cytotoxicity of the synthesized benzimidazoles, together with those of the reference antiviral drugs lamivudine (3-TC) and adefovir, were evaluated in HepG2.2.15 cells. The results are summarized in Tables 1−4. The anti-HBV activity of each compound was expressed as the concentration of compound that achieved 50% inhibition (IC_{50}) of HBV DNA synthesis. The cytotoxicity of each compound was expressed as the concentration of compound required to kill 50% (CC_{50}) of the HepG 2.2.15 cells. The selectivity index (SI), a major pharmaceutical parameter that estimates possible future clinical development, was determined as the ratio of CC_{50} to IC_{50}. The bioactivity of each compound was evaluated by the combination of its IC_{50} and SI.

The subseries of compounds **5a**−**k** has different patterns of substitution on the fused phenyl ring of the benzimidazole pharmacophore. As shown in Table 1, these compounds generally exhibited good antiviral potency, with IC_{50}s of less than 4 μM, except compounds **5c** and **5k**, which had only moderate activities (IC_{50} = 30 and 50 μM, respectively). This result indicates that a range of substituents with different lipophilic, electronic, and steric characters is tolerated at the benzenesulfonyl group at the N-1 position of the benzimidazole core. The three tosylates **5b**, **5g**, and **5h** showed similar antiviral activities (IC_{50} = 1.2−2.9 μM), but the Cl analogue **5h** appeared to be less toxic than the corresponding H (**5b**) and F (**5g**) analogues. The most potent compound in this subseries was compound **5d** (IC_{50} = 0.14 μM), which was nearly three times more potent than the reference drug lamivudine (IC_{50} = 0.38 μM) and nine times more potent than adefovir (IC_{50} = 1.3 μM). However, it had pronounced cytotoxicity (CC_{50} = 10 μM), resulting in a relatively small selectivity index (SI = 71). Compounds **5e** and **5j** demonstrated similar antiviral potency, with IC_{50}s of less than 0.75 μM. Of these, **5e** had higher selectivity (SI = 120) compared to that of adefovir (SI = 156). The introduction of a methanesulfonyl moiety to the N-1 position of the benzimidazole core of **4c** produced an inactive compound (**5l**). It is noteworthy that compound **5h** showed potent antiviral activity (IC_{50} = 2.9 μM) and the highest SI (299). Thus, compound **5h** was selected as the benchmark compound for subsequent optimization.

Table 1. Anti-HBV Activity and Cytotoxicity of Analogues **5a**−**l** in Vitro

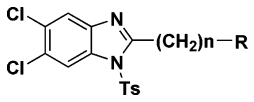




compd	R	X	Y	Z	IC_{50}[a] (μM)	CC_{50}[b] (μM)	SI[c]
5a	H	H	H	H	2.2	28	13
5b	H	H	H	CH_3	2.2	164	75
5c	H	H	CF_3	H	30.4	10	0.3
5d	F	H	NO_2	H	0.14	10	71
5e	F	NO_2	H	H	0.64	77	120
5f	F	H	H	CF_3	3.2	11	3
5g	F	H	H	CH_3	1.2	31	26
5h	Cl	H	H	CH_3	2.9	867	299
5i	Cl	H	H	OCH_3	7.2	189	26
5j	Cl	H	H	*i*-Pr	0.7	17	24
5k	Cl	H	H	NO_2	50.2	181	4
5l	Cl	-	-	-	NA[d]	175	-
lamivudine	-	-	-	-	0.38	>1000	>2632
adefovir	-	-	-	-	1.3	203	156

[a] Concentrations of compounds achieving 50% inhibition of cytoplasmic HBV-DNA synthesis. [b] Concentrations of compounds required for 50% extinction of HepG 2.2.15 cells. [c] Selectivity index (SI) was determined as the CC_{50}/IC_{50} value. [d] Not active.

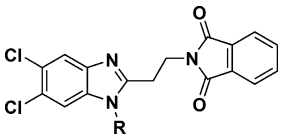
Table 2. Anti-HBV Activity and Cytotoxicity of Analogues (**7**, **10**, and **20a**−**c**) in Vitro



compd	*n*	R	IC_{50}[a] (μM)	CC_{50}[b] (μM)	SI[c]
7	2	*N*-phthalimidino	3.4	23	7
10	2	*N*-maleimide	0.68	33	49
20a	0	*N*-phthalimido	19.4	122	6
20b	1	*N*-phthalimido	0.5	90	180
20c	3	*N*-phthalimido	0.34	13	38

[a] Concentrations of compounds achieving 50% inhibition of cytoplasmic HBV-DNA synthesis. [b] Concentrations of compounds required for 50% extinction of HepG 2.2.15 cells. [c] Selectivity index (SI) was determined as the CC_{50}/IC_{50} value.

Table 3. Anti-HBV Activity and Cytotoxicity of Analogues (**4c**, **11**, and **12a**,**b**) in Vitro



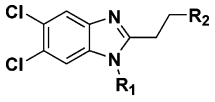
compd	R	IC_{50}[a] (μM)	CC_{50}[b] (μM)	SI[c]
4c	H	300	330	1
11	4-methylbenzoyl	53.2	>1000	>19
12a	CH_3	0.9	>1000	>1111
12b	4-methylbenzyl	0.7	>500	>714

[a] Concentrations of compounds achieving 50% inhibition of cytoplasmic HBV-DNA synthesis. [b] Concentrations of compounds required for 50% extinction of HepG 2.2.15 cells. [c] Selectivity index (SI) was determined as the CC_{50}/IC_{50} value.

Little change in antiviral potency was observed with the reduction of the phthalimide **5h** to the corresponding lactam **7** (Scheme 1, Table 2), whereas compound **7** had a small SI (7), suggesting that the carbonyl group of the phthalimide **5h** is an important feature in conferring relatively low cytotoxicity. Replacement of the phthalimide group of **5h** with maleimide (**10**) yielded a 4-fold improvement in antiviral potency. The SI of compound **10** was below 50, because of its significantly greater cytotoxicity (CC_{50} = 33 μM) compared with that of **5h** (CC_{50} = 867 μM). This result suggests that the phenyl moiety in the phthalimide group of compound **5h** plays less important role in its potent inhibitory activity, although conferring an advantageous SI on **5h**. To identify the optimal chain length between the benzimidazole and phthalimide moieties, different alkyl linkers of variable length were introduced between the benzimidazole and the phthalimide, producing the three derivatives **20a**−**c** (Scheme 2). Compound **20a**, with no linker between the benzimidazole and phthalimide moieties, showed moderate activity (IC_{50} = 19.4 μM), suggesting that the alkyl linker is important for potent antiviral activity. The methylene analogue **20b** was nearly six times more potent than the corresponding ethylene analogue **5h**, whereas an increase in cytotoxicity was also noted, resulting in a relatively small selectivity index (SI = 180). The propylene analogue **20c**, with similar antiviral potency to that of the methylene analogue **20b**, displayed an increase in cytotoxicity of about 7-fold relative to that of **20b**.

The effects of introducing different kinds of substituents to the N-1 position of the benzimidazole core were then studied. Replacement of the benzenesulfonyl moiety of **5h** with a simple benzoyl, alkyl, or benzyl group produced the derivatives **11** and **12a**,**b** (Scheme 1). As shown in Table 3, removal of the N-1 substituent (**4c**) resulted in a tremendous loss of activity (IC_{50} = 300 μM), suggesting that the N-1 substituent is an important determinant of antiviral activity. Introducing 4-methylbenzoyl to the N-1 position of the benzimidazole core resulted in the noncytotoxic derivative **11** (CC_{50} > 1000 μM), which had only moderate activity (IC_{50} = 53.2 μM). An important advance was made when the N-1 position of the benzimidazole core was substituted with methyl or 4-methylbenzyl. The *N*-methyl analogue **12a** (IC_{50} = 0.9 μM, SI > 1111) and the 4-methylbenzyl derivative **12b** (IC_{50} = 0.7 μM, SI > 714) exhibited more highly potent anti-HBV activities and much higher SI values than those of **5h** (IC_{50} = 2.9 μM, SI = 299) or adefovir (IC_{50} = 1.3 μM, SI = 156).

Table 4. Anti-HBV Activity and Cytotoxicity of Analogues (**13** and **29a**−**g**) in Vitro



13, **29a-g**

compd	R_1	R_2	IC_{50}[a] (μM)	CC_{50}[b] (μM)	SI[c]
13	4-methylbenzyl	NH_2	1.4	4	3
29a	CH_3	4-pyridyl	4.6	35.8	8
29b	CH_3	CH_3	3.9	24.6	6
29c	CH_3	cyclohexyl	18.5	>500	>27
29d	CH_3	phenyl	NA[d]	15.3	-
29e	CH_3	2-furanyl	NA	5.9	-
29f	CH_3	2-tetrahydrofuranyl	10.3	56	5
29g	CH_3	2-thiophenyl	NA	16	-

[a] Concentrations of compounds achieving 50% inhibition of cytoplasmic HBV-DNA synthesis. [b] Concentrations of compounds required for 50% extinction of HepG 2.2.15 cells. [c] Selectivity index (SI) was determined as the CC_{50}/IC_{50} value. [d] Not active.

It is worth noting that analogues of the phthalimide (**5h**), lactam (**7**), and maleimide (**10**) all exhibited potent activity against HBV (IC_{50} = 0.68−3.4 μM). The presence of amides at the end of the alkyl linker seems to be important for anti-HBV activity. To extend this result, we prepared another group of new benzimidazole derivatives that differ at the right-hand side of the structure (Scheme 3). A methyl group, which characterized one of the optimal analogues **12a**, was used as the N-1 substituent. The free amine **13** was derived from another optimal derivative **12b** (Scheme 1). The anti-HBV activity and cytotoxicity of analogues **13** and **29a**−**g** are summarized in Table 4.

The free amine **13** (IC_{50} = 1.4 μM) displayed a slight decrease in antiviral potency compared with that of compound **12b** (IC_{50} = 0.7 μM), whereas its antiviral activity was poorly separated from its cytotoxicity (CC_{50} = 4 μM). Replacement of the phthalimide group of **12a** with different types of functional groups led to significant decreases in antiviral potency and SI relative to those of **12a**. In particular, replacing the phthalimide group of **12a** with phenyl, 2-furanyl, or 2-thiophenyl resulted in a complete loss of inhibitory activity, as seen in compounds **29d**, **29e**, and **29g**. These findings suggest that the presence of amides at the end of the alkyl linker plays an important role in potent anti-HBV activity.

In summary, a series of novel benzimidazole analogues based on **1** was synthesized and assessed for their anti-HBV activity in vitro, using lamivudine and adefovir as reference controls. Most proved to be potential HBV inhibitors (IC_{50} < 4 μM) with high selectivity indices. Compounds **5b**, **5d**, **5e**, **5h**, **10**, **12a**, **12b**, **20b**, and **20c** displayed optimal profiles, with IC_{50}s of 0.14−2.9 μM and SIs of 38−1111. The most promising results were observed for compounds **12a** and **12b**, with potent antiviral activities (IC_{50} = 0.9 and 0.7 μM, respectively) and extraordinarily high selectivity (SI > 1111 and 714, respectively). Such activity and cytotoxicity profiles and their ease of preparation make them attractive candidate compounds for further assessment in vivo as anti-HBV agents.

Experimental Section

General Procedure A: Synthesis of Benzimidazole Scaffolds. The appropriately substituted *o*-phenylenediamine (1 equiv) and the appropriate carboxylic acid (1 equiv) were suspended in PPA (1 g/mmol) under nitrogen. The suspension was heated in an oil bath at 170−180 °C for 6 h. The reaction mixture was cooled and poured into ice water (10 mL/mmol). The resulting mixture was neutralized to pH 8 with 25% NH_4OH. The formed precipitate was filtered, washed with water, and dried to give the crude product.

General Procedure B: N-Sulfonylation of Benzimidazole Scaffolds. To a suspension of the appropriate benzimidazole scaffold (1 equiv) and the appropriate sulfonyl chloride (1 equiv) in dry CH_2Cl_2 (20 mL/mmol) was added DMAP (1 equiv), and a clear solution was obtained at once. The resulting solution was stirred at 50 °C for 10 h, cooled to room temperature, and partitioned between chloroform and water. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was subjected to silica gel chromatography or crystallization to give the target compound.

General Procedure C: N-Methylation of Benzimidazole Scaffolds. To a solution of the appropriate benzimidazole scaffold (1 equiv) in DMF (15 mL/mmol) were added K_2CO_3 (1 equiv) and iodomethane (1.1 equiv). The reaction mixture was stirred overnight at room temperature and poured into water (100 mL/mmol). The resulting precipitate was filtered and dried to obtain the product.

2-[2-(5,6-Dichloro-1*H*-benzoimidazol-2-yl)-ethyl]-isoindole-1,3-dione (4c). Compound **4c** was synthesized from 4,5-dichloro-*o*-phenylenediamine (**2c**) and 3-phthalimidopropionic acid (**3**) using general procedure A. The crude product was recrystallized from methanol to give pale yellow crystals. Yield = 72%; ^{1}H NMR (DMSO-d_6) δ 12.6 (br s, 1H), 7.83 (br s, 4H), 7.71 (s, 2H), 4.01 (t, 2H, J = 7.2), 3.16 (t, 2H, J = 7.0); ^{13}C NMR (DMSO-d_6) δ 167.63 (2C), 154.81, 142.99, 134.39 (2C), 133.69, 131.64 (2C), 124.05, 123.57, 123.06 (2C), 119.38, 112.45, 36.07, 27.59; MS (EI) *m*/*z* 359 (M^+), 212, 200, 160. Anal. ($C_{17}H_{11}Cl_2N_3O_2$) C, H, N.

2-{2-[5,6-Dichloro-1-(toluene-4-sulfonyl)-1*H*-benzoimidazol-2-yl]-ethyl}-isoindole-1,3-dione (5h). Compound **5h** was prepared from **4c** and tosyl chloride using general procedure B as a white crystalline solid. Yield = 75%; ^{1}H NMR ($CDCl_3$) δ 8.13 (s, 1H), 7.80−7.86 (m, 4H), 7.71−7.74 (m, 2H), 7.67 (s, 1H), 7.34 (d, 2H, J = 8.1), 4.24 (t, 2H, J = 7.2), 3.52 (t, 2H, J = 7.2), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 167.97 (2C), 153.21, 146.67, 141.22, 134.68, 134.01 (2C), 132.00 (2C), 131.96, 130.56 (2C), 129.16, 128.92, 126.86 (2C), 123.32 (2C), 121.07, 114.97, 35.51, 28.62, 21.69; MS (EI) *m*/*z* 513 (M^+), 449, 358, 324, 160, 91; HRMS (EI): cal. for $C_{24}H_{17}Cl_2N_3O_4S$ 513.0317, found 513.0307. Purity: HPLC analysis.

2-[2-(5,6-Dichloro-1-methyl-1*H*-benzoimidazol-2-yl)-ethyl]-isoindole-1,3-dione (12a). Compound **12a** was prepared from **4c** using general procedure C as a white solid. Yield = 96%; ^{1}H NMR ($CDCl_3$) δ 7.71−7.85 (m, 5H), 7.42 (s, 1H), 4.21 (t, 2H, J = 7.2), 3.77 (s, 3H), 3.26 (t, 2H, J = 7.2); ^{13}C NMR (C_5D_5N) δ 168.21 (2C), 154.75, 142.81, 134.27 (2C), 132.55 (2C), 125.71, 125.31, 123.25 (2C), 120.62, 111.73, 35.56, 29.85, 26.50; MS (EI) *m*/*z* 373 (M^+), 227, 160; HRMS (EI): cal. for $C_{18}H_{13}Cl_2N_3O_2$ 373.0385, found 373.0396. Purity: HPLC analysis.

2-{2-[5,6-Dichloro-1-(4-methyl-benzyl)-1*H*-benzoimidazol-2-yl]-ethyl}-isoindole-1,3-dione (12b). A mixture of compound **4c** (315 mg, 0.87 mmol) and NaOH (40 mg, 1.0 mmol) in CH_3CN (100 mL) was heated until a nearly clear solution was obtained. 4-Methylbenzyl chloride (167 mg, 1.19 mmol) was added in one portion, and the resulting mixture was refluxed for 10 h. The reaction mixture was filtered while hot and washed with CH_3CN (30 mL). The combined filtration was concentrated under reduced pressure until the product crystallized from the mother liquid as a white crystalline solid (270 mg, 67% yield). ^{1}H NMR ($CDCl_3$) δ 7.80−7.82 (m, 2H), 7.78 (s, 1H), 7.70−7.72 (m, 2H), 7.32 (s, 1H), 7.09 (d, 2H, J = 8.0), 6.92 (d, 2H, J = 8.0), 5.31 (s, 2H), 4.17 (t, 2H, J = 7.2), 3.21 (t, 2H, J = 7.2), 2.29 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 167.60 (2C), 153.26, 141.64, 137.73, 134.32, 133.70 (2C), 131.60 (2C), 131.44, 129.49 (2C), 126.29, 125.86, 125.68 (2C), 123.00 (2C), 120.33, 110.77, 46.76, 35.20, 26.14, 20.71; MS (EI) *m*/*z* 463 (M^+), 358, 303, 105. HRMS (EI): cal. for $C_{25}H_{19}Cl_2N_3O_2$ 463.0854, found 463.0855. Purity: HPLC analysis.

2-[5,6-Dichloro-1-(toluene-4-sulfonyl)-1*H*-benzoimidazol-2-yl]-isoindole-1,3-dione (20a). Compound **20a** was prepared from **15** and tosyl chloride using general procedure B as a pale yellow solid. Yield = 69%; ^{1}H NMR ($CDCl_3$) δ 8.03−8.06 (m, 2H), 8.00 (s, 1H), 7.88−7.91 (m, 3H), 7.78 (d, 2H, J = 8.4), 7.31 (d, 2H, J = 8.4), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.60 (2C), 147.12, 139.63, 138.68, 135.25 (2C), 133.70, 131.59 (2C), 131.51, 130.74, 130.39 (2C), 129.78, 127.68 (2C), 124.69 (2C), 122.44, 115.15, 21.77; MS (EI) *m*/*z* 485 (M^+), 421, 330, 155, 104, 91, 76; HRMS (EI): cal. for $C_{22}H_{13}Cl_2N_3O_4S$ 485.0004, found 485.0008. Purity: HPLC analysis.

5,6-Dichloro-1-methyl-2-(2-pyridin-4-yl-ethyl)-1*H*-benzoimidazole (29a). Compound **29a** was prepared from **28a** using general procedure C as an orange solid. Yield = 76%; ^{1}H NMR ($CDCl_3$) δ 8.51 (d, 2H, J = 6.0), 7.80 (s, 1H), 7.38 (s, 1H), 7.16 (d, 2H, J = 6.0), 3.57 (s, 3H), 3.13−3.28 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 157.15, 149.84, 149.53 (2C), 141.63, 135.49, 124.16, 124.05 (2C), 123.82, 119.50, 111.76, 31.32, 29.94, 26.96; MS (EI) *m*/*z* 305 (M^+), 276, 227, 213, 149; HRMS (EI): cal. for $C_{15}H_{13}Cl_2N_3$ 305.0487, found 305.0473. Purity: HPLC analysis.

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Supporting Information Available: Experimental details for intermediates (**4a**, **4b**, **6**, **8**, **9**, **15**, **18**, **19**, **24**−**27**, and **28a**−**g**) and target compounds (**1**, **5a**−**g**, **5i**−**l**, **7**, **10**, **11**, **13**, **20b**−**c**, and **29b**−**g**). HPLC purity data for target compounds: **1**, **5a**−**l**, **7**, **10**, **12a**,**b**, **13**, **20a**−**c**, and **29a**−**g**. This material is available free of charge via Internet at http://pubs.acs.org.

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