2,3-Dihydro-6,7-dihydroxy-1H-isoindol-1-one-Based HIV-1 Integrase Inhibitors

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The bis-salicylhydrazides class of HIV-1 integrase (IN) inhibitors has been postulated to function by metal chelation. However, members of this series exhibit potent inhibition only when Mn^{2+} is used as cofactor. The current study found that bis-aroylhydrazides could acquire inhibitory potency in Mg^{2+} using dihydroxybenzoyl substituents as both the right and left components of the hydrazide moiety. Employing a 2,3-dihydro-6,7-dihydroxy-1*H*-isoindol-1-one ring system as a conformationally constrained 2,3-dihydroxybenzoyl equivalent provided good selectivity for IN-catalyzed strand transfer versus the 3′-processing reactions as well as antiviral efficacy in cells using HIV-1 based vectors.

Introduction

Inhibitors of HIV-1 integrase (IN) have emerged as a promising new class of therapeutics for the treatment of AIDS.[1] Although IN has long been regarded as a potentially attractive target for anti-HIV drug development, discovery of clinically relevant inhibitors has been challenging.[2−4] Many potent inhibitors against the IN-catalyzed 3′-processing (3′-P) and strand transfer (ST) reactions were initially developed using in vitro IN assays[5] that employ Mn^{2+} as a metal cofactor.[6] However, under physiological conditions, Mg^{2+} serves as the IN cofactor, and frequently, these inhibitors either failed to show good antiviral potencies in HIV-1 infected cells or they were inhibited by non-IN-dependent mechanisms.[7] The identification of metal chelating inhibitors bearing the general structure **1** (Figure 1) was a significant advance in the field of IN inhibitor design.[2] Members of this class include diketoacid-containing analogues typified by L-731,988 (**1**)[8] and later-generation analogues, such as the 7-carboxamido-8-hydroxy-1,6-naphthyridine L-870,812 (**2**)[9,10] and the 5-hydroxy-6-oxo-4-pyrimidinecarboxamide clinical candidate from Merck, Raltegravir (MK0518, **3**).[11−14] The 3,4-dihydroxy-2-pyridinecarboxamide **4**[15,16] may be seen as a simplified variant of this latter structural class that retains key features needed for metal chelation.

Compound **4** bears similarity to the bis-salicylhydrazide **5a**, which had previously been reported to inhibit IN through metal chelation but was effective only in assays using Mn^{2+} but not Mg^{2+} and lacked antiviral efficacy in HIV-1 infected cells.[17−20] Compound **5a** differs from **4** both by being a hydrazide rather than a carboxamide and by containing a methylene at the 6-position of the aryl ring rather than a pyridyl nitrogen. Of greater significance in relation to potential metal chelating ability of **5a** is the absence of a second hydroxyl group at the salicyl 3-position, which would correspond to the pyridyl 4-hydroxyl in **4** or the 6-oxo group in the 4-pyrimidinecarboxamide **3**. This report describes structural modifications of the original hydrazide **5a** that could potentially affect metal chelating ability and the preparation of new analogues generally represented by structure **6** (Figure 1). Selected compounds were tested in cell-based infectivity assays to gauge potential antiviral activities.

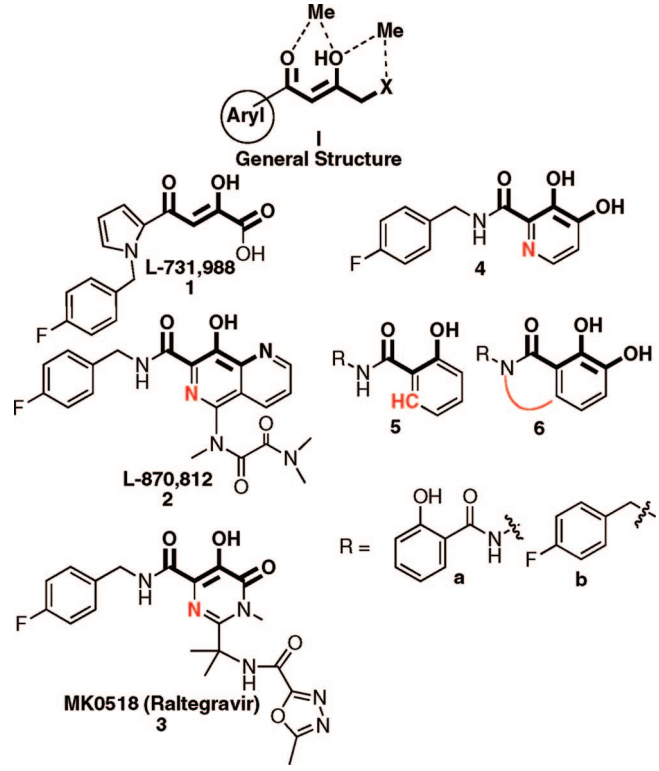

Figure 1. Structural features of a general IN inhibitor (I) common to diketo acid (**1**) and later generation inhibitors.

Synthesis. Starting from Corey's 2,3-dioxosulfinylbenzoylchloride (**7**),[21,22] the 2,3-dihydroxybenzoic acid hydrazides **8a−e** and the dihydroxybenzamides **9a−c** were prepared by reaction with the appropriate hydrazides or amines, respectively in dichloromethane at room temperature (Scheme 1).

The 2-hydroxy-3-methoxybenzoic acid hydrazides **12a−c** were prepared by reaction of the pentafluorophenyl ester **10** with commercially available hydrazides in DMF at room temperature (Scheme 2).[23] The benzoic acid hydrazides **13a** and **13b**, prepared by treating **7** and **10** with hydrazine, respectively, were

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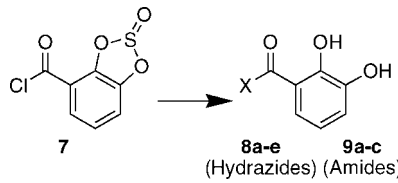
Scheme 1. Synthesis of Hydrazides and Amides with X, as Indicated in Table 1



converted to the hydrazones **14a**−**c** by reaction with the corresponding aldehydes (Scheme 3).

Methylation of commercially available 3,4-dimethoxybenzyl alcohol (**16**) (iodomethane/NaH in THF at 0 °C) provided **17** (93% yield), which was metalated (*n*-butyllithium) and quenched with methyl chloroformate to provide the methyl ester **18** (79% yield, Scheme 4).[24] Brief treatment with excess acetyl chloride in the presence of a catalytic amount of anhydrous zinc chloride directly produced the benzyl chloride **19** (86% yield).[24,25] Refluxing with hydrazine in anhydrous acetonitrile afforded the key hydrazide **20** (38% yield), which was acylated to afford the 2,3-dimethoxy-containing series **21a**−**p**. For the benzisothiazol hydrazide **21i**, the acylating species required separate preparation. This consisted of metalating methyl ether **17** (*n*-butyl lithium) followed by reaction with sulfuric chloride to give 5,6-dimethoxy-2-(methoxymethyl)benzene sulfonyl chloride. Treatment with anhydrous zinc chloride, as described above for the preparation of **19**, gave the corresponding benzyl chloride, which was reacted with hydrazide **19** to yield **21i**. Demethylation of the series **21a**−**p** (BBr_3 in dichloromethane) provided the final products **22a**−**p**. Hydrazones **20o** and **20p** were prepared by the reaction of hydrazide **20** with aldehydes followed by demethylation as above.

Amides **23a**−**g** were synthesized from benzyl chloride **19** by refluxing with the appropriate amines in anhydrous acetonitrile[26] and then demethylating, as described above, to yield the final products **24a**−**g** (Scheme 5).

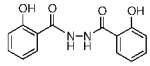
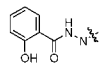
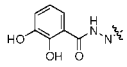
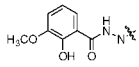
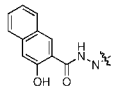
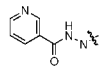
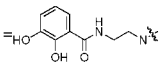
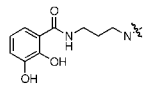
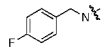
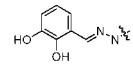
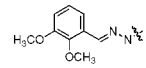
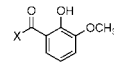
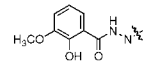
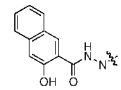
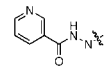
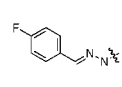
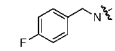
Results and Discussion

Introduction of Oxygen Functionality onto the Aryl Rings of Salicylhydrazide HIV-1 Integrase Inhibitors. In confirmation of our previous results,[19] the bis-salicylhydrazide (**5a**) exhibited potent but nonselective inhibition of both 3′-P and ST reactions in assays using purified recombinant IN with Mn^{2+} as cofactor. A striking loss of inhibitory potency was observed when the assays were performed using Mg^{2+} (entry 1, Table 1). A series of hydrazides was prepared in which a "right side" (2,3-dihydroxybenzoyl) group was combined with variety of "left side" components (**8a**–**e**, entries 2–6). Maintaining the left side salicyl group found in **5a** gave inhibitor **8a** (entry 2), whose inhibitory profile was unchanged from the parent **5a**. In contrast, adding a 3-OH to the left side salicyl ring to provide the bis-(3,4-dihdroxybenzoyl)hydrazide (**8b**, entry 3) conferred good but nonselective 3′-P and ST inhibitory potencies with both Mg^{2+} as well as Mn^{2+} cofactors. Converting the left side 3-OH to a 3-OMe (**8c**, entry 4) had little effect on inhibitory potency in Mn^{2+}, but reduced inhibitory potency in Mg^{2+} by slightly more than 20-fold. Extending the left side benzoyl ring system of **8a** to a naphthoyl system (**8d**, entry 5) reduced inhibitory potency in Mn^{2+} and gave low but measurable inhibition in Mg^{2+}. Removal of the hydroxyl in the left side aryl ring and introduction of a nitrogen to form a picalinoyl group (**8e**, entry 6) resulted in the loss of all inhibitory potency, except for very weak ST inhibition in Mn^{2+}. This was very similar to the effects of completely removing the left side (**13a**, entry 10). Replacement of the left side hydrazide carbonyl in **8b** with a hydrazone moiety (**14a**, entry 11) had little effect on inhibitory potency in Mn^{2+} but significantly reduced inhibitory potency in Mg^{2+}. The corresponding 2,3-dimethoxybenzyl hydrazone (**14b**, entry 12) had reduced inhibitory potency. Introducing into the hydrazide N-N bond in **8b** a 2-methylene spacer (**9a**, entry 7) or a 3-methylene spacer (**9b**, entry 8) reduced inhibitory potency in Mg^{2+}. The 4-fluorobenzylamide analogue **9c** (entry 9) showed ST inhibition only at the upper limits of the assay detection. Replacing the 2,3-dihydroxybenzoyl "right side" with a 2-hydroxy-3-methoxybenzoyl group and examining a similar series of left side-modified hydrazides (entries 13–18) generally resulted in little or no measurable inhibitory potency, except for **12a** and **12b**, which had good potency in assays using Mn^{2+} but not Mg^{2+} cofactor.

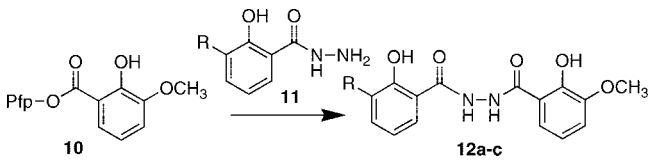
Introduction of Carboxamide Conformational Constraint in the Hydrazide Series: *N*-(1,3-Dihydro-6,7-dihydroxy-1-oxo-2*H*-isoindol-2-yl)-benzamides. For inhibitors **2**–**4** to optimally undergo metal interactions, as shown in the general structure I (Figure 1), the heteroatoms forming the metal chelating triads should be coplanar. The potency enhancement of ring nitrogens adjacent to the carboxamide groups (shown in red, Figure 1) have been thought to be derived from facilitating such coplanarity.[2] For bicyclic inhibitors typified by the naphthyridine nucleus in **2**, a coplanar alignment of the carboxamide carbonyl was maintained by removing the adjacent nitrogen and linking the carboxamide nitrogen to the parent bicycle through a methylene bridge to form conformationally constrained tricyclic inhibitors.[27,28] A similar rationale was used for the bicyclic compounds of type **6** (Figure 1), which can be viewed as conformationally constrained variants of the 2,3-dihdroxybenzoylhydrazides and amides presented in Table 1. Synthesis of the series of *N*-(1,3-dihydro-6,7-dihydroxy-1-oxo-2*H*-isoindol-2-yl)-benzamides (**22a**–**p**, Table 2) was readily achieved through a common methoxy-protected bicyclic hydrazide **20** by acylation and final demethylation. The series **22** is characterized by a common bicyclic "right side" consisting of a 2,3-dihydroxy-substituted benzoylhydrazide, conformationally restricted, in which planarity was achieved by means of a ring-closing *N*-methylene bridge.

Examination of "left side" effects is the focus of compounds listed in Table 2 where poor inhibitory potencies resulted from unsubstituted (**22a**, entry 1) or 2-hydroxy monosubstituted (**22b**, entry 2) benzoylhydrazides. Addition of a second hydroxyl group provided a 50-fold enhancement in potency with greater than 50-fold selectivity for ST versus 3′-P (**22c**, entry 3). This contrasts with the absence of ST selectivity in the corresponding nonconstrained analogue **8b** (entry 3, Table 1). The 4-fluorobenzoylhydrazide (**22d**, entry 4) showed low inhibitor potency, with ST inhibition falling between the values shown by **22a** and **22b**. Constraining the 2,3-dihdroxybenzoyl left side in a fashion identical to the "right side" reduced ST inhibitory potency and decreased selectivity over 3′-P (**22h**, entry 8). Interestingly, the sulfonamide variant of this latter compound showed high inhibitory potency against both 3′-P and ST (**22i**, entry 9). The nonconstrained bis-(3,4-dihydroxybenzenesulfonamide)-containing compound **22g** (entry 7) showed good inhibitory potency against both 3′-P and ST reactions. Using a left side phthalimide motif to induce conformational constraint resulted in no measurable inhibition for the unsubstituted analogue **22j** (entry 10) and moderate inhibitory potency for the 4-hydroxy derivative (**22k**). However, high inhibitory potency and greater than 100-fold ST selectivity resulted for the 4,5-dihydroxyphthalimide derivative **22l** (entry 12). Equally

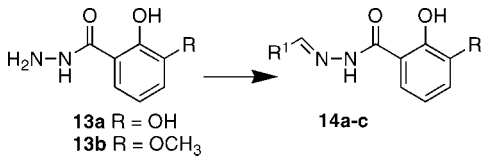
Table 1. In Vitro Inhibition of Integrase 3′-P and ST Reactions in the Presence of Mn^{2+} or Mg^{2+} Cofactor

Entry	No.	Structure	Metal Cofactor	IC_{50} (μM) 3′-P	IC_{50} (μM) ST
1	**5a**		Mg^{2+}	>333	>333
			Mn^{2+}	3.6	1.8 ± 0.3
					
2	**8a** X =		Mg^{2+}	>333	>333
			Mn^{2+}	2.8	0.5 ± 0.1
3	**8b** X =		Mg^{2+}	6.9 ± 3.0	1.6 ± 0.5
			Mn^{2+}	8.9 ± 3.2	5.0 ± 1.5
4	**8c** X =		Mg^{2+}	138 ± 30	44 ± 23
			Mn^{2+}	11 ± 3	9 ± 4
5	**8d** X =		Mg^{2+}	72 ± 10	32 ± 5
			Mn^{2+}	19 ± 3	16 ± 4
6	**8e** X =		Mg^{2+}	>333	>333
			Mn^{2+}	>333	112 ± 13
7	**9a** X =		Mg^{2+}	85 ± 9	50 ± 13
8	**9b** X =		Mg^{2+}	33 ± 4	31 ± 8
9	**9c** X =		Mg^{2+}	>333	108 ± 12
10	**13a** X =		Mg^{2+}	>333	>333
			Mn^{2+}	>333	111 ± 27
11	**14a** X =		Mg^{2+}	61 ± 26	54 ± 13
			Mn^{2+}	11 ± 5	1.3 ± 0.5
12	**14b** X =		Mg^{2+}	112 ± 28	68 ± 38
			Mn^{2+}	>333	18 ± 5
					
13	**12a** X =		Mg^{2+}	245 ± 87	123 ± 16
			Mn^{2+}	26 ± 5	22 ± 7
14	**12b** X =		Mg^{2+}	>333	>333
			Mn^{2+}	12 ± 5	8 ± 4
15	**12c** X =		Mg^{2+}	>333	>333
			Mn^{2+}	>333	>333
16	**13b** X =		Mg^{2+}	>333	>333
			Mn^{2+}	>333	>333
17	**14c** X =		Mg^{2+}	>333	>333
18	**15** X =		Mg^{2+}	>333	>333

Scheme 2. Synthesis of Bis-aroylhydrazines with R, as Indicated in Table 1



Scheme 3. R and R^1 are as Indicated in Table *1*

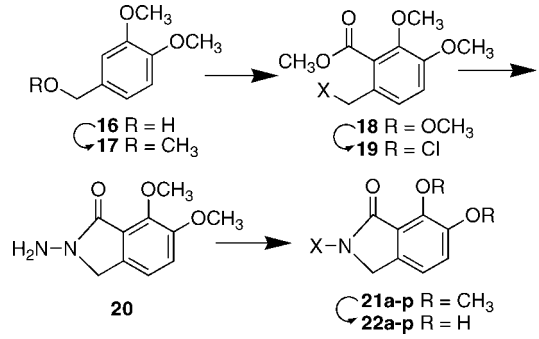


high ST inhibitory potency but 10-fold less selectivity over 3′-P was observed for the isomeric 5,6-dihydroxyphthalimide (**22m**, entry 13).

Introduction of Carboxamide Conformational Constraint in the Benzamide Series. The compounds **22** (Table 2) are all hydrazides intended to examine aspects of the previously reported inhibitor **5a**. We prepared a parallel series of bicyclic analogues that would represent conformationally constrained variants of the 2,3-dihydroxybenzamide nucleus (**6**, Figure 1). These bicycles consisted of the 2,3-dihydro-6,7-dihydroxy-1*H*-isoindol-1-ones (**24a**–**g**, Table 3). As stated above, this approach has recently been applied to bicyclic nuclei, such as the hydroxynaphthyridines, to yield tricyclic analogues.[27–29]

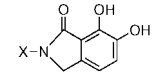
2,3-Dihydro-6,7-dihydroxy-1*H*-isoindol-1-ones. In the 1*H*-isoindol-1-one series an unsubstituted benzyl group provided

Scheme 4. X is as Indicated in Table *2*

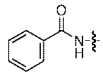
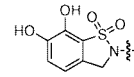
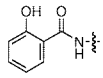
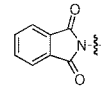
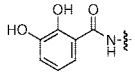
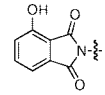
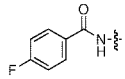
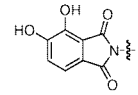
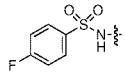
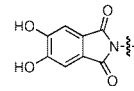
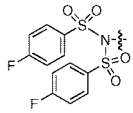
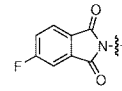
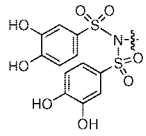
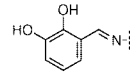
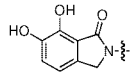
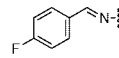


good ST inhibitory potency and high selectivity over 3′-P (**24a**, entry 1, Table 3). Adding a methylene had little effect on ST inhibitory potency (**24b**, entry 2), however, replacing the benzyl group with a 1-naphthyl system (**24c**, entry 3) increased 3′-P and ST inhibitory potencies by more than 5-fold and 10-fold, respectively. It has been reported in a related series of compounds that adding a 4-fluoro substituent to the benzyl ring enhances inhibitory potency (for example, see refs 10 and 28). This has been attributed to the binding of the 4-flourophenyl group in a hydrophobic pocket present in the integrase·DNA complex.[27] However, in the present series, adding a 4-fluoro substituent had little effect (**24d**, entry 4). This contrasts sharply with the 3-chloro-4-fluoro substituted analogue (**24e**, entry 5), which exhibits significant enhancement of both 3′-P and ST inhibitory potencies relative to the 4-fluoro compound. This agrees with the previously reported beneficial effects of 3-chloro-4-fluoro substitution.[28]

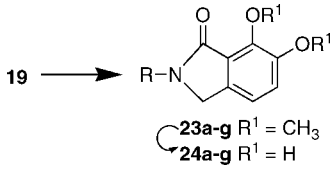
Table 2. In Vitro Inhibition of Integrase 3′-P and ST Reactions in the Presence of Mg^{2+} Cofactor



General Structure

Entry	No.	X =	IC_{50} (μM) 3′-P	IC_{50} (μM) ST	Entry	No.	X =	IC_{50} (μM) 3′-P	IC_{50} (μM) ST
1	**22a**		>333	129 ± 38	9	**22i**		7.0 ± 1.3	1.2 ± 0.4
2	**22b**		>333	293 ± 47	10	**22j**		>333	>333
3	**22c**		>333	6 ± 2	11	**22k**		42	11
4	**22d**		>333	170 ± 105	12	**22l**		78 ± 18	0.6 ± 0.2
5	**22e**		69 ± 23	21± 20	13	**22m**		6.7 ± 1.9	0.81 ± 0.35
6	**22f**		>333	33 ± 12	14	**22n**		186 ± 47	53 ± 18
7	**22g**		1.6 ± 0.8	0.21 ± 0.10	15	**22o**		87 ± 29	54 ± 12
8	**22h**		124 ± 32	41 ± 5	15	**22p**		>333	>333

Scheme 5. R is as Indicated in Table 3



During the early stages of DKA-based analogue development, the 3-(phenylmethyl)phenyl group had shown utility in the design of high affinity inhibitors.[8,30] However, in the present series, this motif proved to be deleterious (**24g**, entry 7). Finally, the importance of the three oxygen atoms in the 2,3-dihydro-6,7-dihydroxy-1*H*-isoindol-1-ones is shown by the significant reduction in ST inhibitory potency of **24d** incurred by either transposing the position of the oxo-group (**27**, entry 8) or by removing the 6-hydroxyl substituent (**28**, entry 9).

Effects in Cellular Assays Using HIV-1 Based Vectors. The antiviral effects of a select set of inhibitors was tested using HIV-1 based vectors in cultured cells (Table 4). These studies showed that the bicyclic conformationally constrained analogues **24a** and **24d** exhibited submicromolar antiviral potencies. Elimination of the conformational constraint from **24d** (compound **9c**) or removal of the 4-fluoro-substituent (compound **24a**) resulted in significant loss of antiviral potency. Hydrazides **5a**, **8a**, and **8b** all exhibited low micromolar antiviral effects. While the data for **8b** was consistent with its potent inhibition of IN in extracellular assays employing the Mg^{2+} cofactor, the antiviral effects observed for **5a** and **5b** potentially indicate cellular mechanisms of action independent of IN.

Conclusions

Chelation of divalent Mg^{2+} is thought to be central to IN inhibition by several classes of agents, including diketoacids (**1**), 8-hydroxynaphthyridines (**2**), and 5-hydroxy-6-oxopyrimidinecarboxamides, such as **3**. The bis-salicylhydrazide **5a** is typical of an alternate family of IN inhibitors that have also been postulated to function by metal chelation. However, the hydrazide inhibitors exhibit high inhibitory potency only when Mn^{2+} is used as cofactor and they have little potency in the presence of Mg^{2+}. The current study was undertaken to understand the mechanistic disparity between the bis-salicylhydrazides and other classes of metal chelators. For nonconstrained hydrazides, potent inhibition in the presence of Mg^{2+} was found to require dihydroxybenzoyl substituents on both the right and left sides (for example, **8b**). Elimination of a phenolic hydroxyl from one side by removal (**8a**) or by conversion to a methyl ether (**8c**) or by removing a benzoyl carbonyl (**14a**) significantly reduced inhibitory potency in Mg^{2+}, although good potency in Mn^{2+} could be retained. High selectivity of ST versus 3′-P found for many DKA inhibitors, was not observed in Mg^{2+} for the nonconstrained hydrazides. However, good ST selectivity

Table 3. In Vitro Inhibition of Integrase 3′-P and ST Reactions in the Presence of Mg^{2+} Cofactor

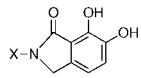
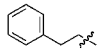
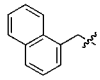
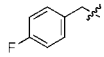
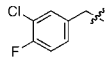
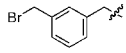
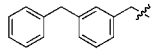
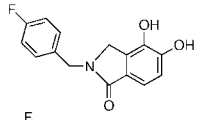
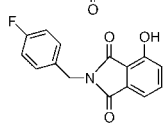
Entry	No.	Structure	IC_{50} (μM) 3′-P	IC_{50} (μM) ST
				
1	**24a**	X = 	>333	12.3 ± 5.6
2	**24b**	X = 	>333	28 ± 10
3	**24c**	X = 	61 ± 29	0.74 ± 0.16
4	**24d**	X = 	282 ± 41	10 ± 4
5	**24e**	X = 	13 ± 3	0.16 ± 0.08
6	**24f**	X = 	37 ± 12	13 ± 7
7	**24g**	X = 	>333	172 ± 63
8	**27**		>333	>333
9	**28**		>333	>333

Table 4. Antiviral Potencies of Select Inhibitors in HIV-1 Infected Cells

cmpd	EC_{50} ± sd (μM)	cmpd	EC_{50} ± sd (μM)
5a	2.2 ± 0.23	**9c**	>30
8a	4.8 ± 1.0	**24a**	0.68 ± 0.28
8b	1.67 ± 0.62	**24d**	0.77 ± 0.13

in Mg^{2+} could be achieved by conformational constraint of at least one benzoyl carbonyl using an isoindole ring structure (for example, **22c** and **22l**).

Conversion of the constrained dihydroxylated isoindole hydrazide series **22** to the corresponding amide series (**24**) generally resulted in good inhibitory potency in Mg^{2+} and ST selectivity without the need for metal-chelating functionality on the "left side" amide group. The arrangement of oxygen functionality on the "right side" dihydroxylated isoindole portion was critical because all activity was lost on rearrangement of the carbonyl (**27**) or removal of a hydroxyl group (**28**). Carbonyl conformational constraint was important, as the constrained benzylamides **24a** and **24d** exhibited 10-fold higher potency than the nonconstrained amide **9c**. The 2,3-dihydro-6,7-dihydroxy-1*H*-isoindol-1-one nucleus offers a structurally simple starting point for the further development of IN inhibitors.

Experimental Section

Cell-Based Assays. Human embryonyl kidney cell culture line 293 was obtained from the American type Culture Collection (ATCC). The human osteosarcoma cell line, HOS, was obtained from Dr. Richard Schwartz (Michigan State University, East Lansing, MI). Cell lines were maintained in Dulbecco's modified Eagle's medium (Invitrogen, Carlbad, CA) supplemented with 5% (v/v) fetal bovine serum, 5% newborn calf serum, and penicillin (50 units/mL) plus streptomycin (50 μg/mL; Quality Biological, Gaithersburg, MD). The transfection vector, pNLNgoMIVR$^-$ΔEnv.LUC, was prepared from pNLNgoMIVR$^-$ΔEnv.HSA[31] by replacing the HSA reporter gene (between NotI and XhoI) with a luciferase reporter gene between NotI and XhoI.

VSV-g-pseudotyped HIV was produced by transfection of 293 cells.[32] On the day prior to transfection, 293 cells were plated in 100 mm dishes at a density of 9×10^5 cells per plate. A total of 293 cells were transfected with 10 μg of pNLNgoMIVR$^-$ΔEnv.LUC and 3 μg of pHCMV-g (obtained from Dr. Jane Burns, University of California, San Diego) using calcium phosphate precipitation. After 48 h, virus-containing supernatants were harvested, clarified by low-speed centrifugation and filtration, and diluted 1-to-5 in preparation for infection assays. HOS cells were plated in 96-well luminescence cell culture plates at a density of 4000 cells in 100 μL per well the day prior to infection. On the day of infection, cells were pretreated with the target compounds for 3 h. Infections were carried out by adding 100 μL of virus-containing supernatants to each well and incubating for 48 h. Infectivity was measured via the luciferase reporter assay.[33] Cells were lysed with 100 μL of Glo-Lysis Buffer (Promega, Madison, WI). Luciferase activity was measured by adding 100 μL of Steady-Glo reagent (Promega) directly to the lysed cells and measuring luminescence using a microplate reader. Activity was normalized to infections in the absence of target compounds. NFit (University of Texas, Galveston, Texas) was used to perform regression analysis on the data. EC_{50} values (Table 4) were determined from the fit model.

Integrase Catalytic Assay. Expression of the recombinant IN in *Escherichia coli* and subsequent purification of the protein were performed as previously reported[34,35] with addition of 10% glycerol to all buffers. Preparation of oligonucleotide substrates has been described.[36] Integrase reactions were performed in 10 μL with 400 nM of recombinant IN, 20 nM of 5′-end [^{32}P]-labeled oligonucleotide substrate, and inhibitors at various concentrations. Solutions of 10% DMSO without inhibitors were used as controls. Reactions were incubated at 37 °C (30 min) in buffer containing at a final concentration of 50 mM MOPS, pH 7.2 and 7.5 mM of divalent cations ($MgCl_2$ unless $MnCl_2$ is otherwise indicated). Reactions were stopped by addition of 20 μL of loading dye (10 mM EDTA, 98% deionized formamide, 0.025% xylene cyanol, and 0.025% bromophenol blue). Reactions were heated at 95 °C (1 min) then subjected to electrophoresis in 20% polyacrylamide−7 M urea gels. Gels were dried and reaction products were visualized and quantitated with a PhosphorImager (GE Healthcare, Little Chalfont, Buckinghamshire, U.K.). Densitometric analyses were performed using ImageQuant from Molecular Dynamics, Inc. The concentrations at which enzyme activity was reduced by 50% (IC_{50}) were determined using "Prism" software (GraphPad Software, San Diego, CA) for nonlinear regression to fit dose–response data to logistic curve models.

General Synthetic. ^{1}H and ^{13}C NMR data were obtained on a Varian 400 MHz spectrometer and are reported in ppm relative to TMS and referenced to the solvent in which the spectra were collected. Solvent was removed by rotary evaporation under reduced pressure and anhydrous solvents were obtained commercially and used without further drying. Purification by silica gel chromatography was performed using EtOAc−hexanes sovent systems. Preparative high pressure liquid chromatography (HPLC) was conducted using a Waters Prep LC4000 system having photodiode array detection and using a YMC J'sphere ODS-H80 column [YMC] (250 mm × 20 mm; 4 μm particle size, 80 Å pore) or a Phenomenex C_{18} column [Phe] (250 mm × 21.2 mm; 5 μm particle size, 110 Å pore) at a flow rate of 10 mL/min, with binary solvent systems consisting of A = 0.1% aqueous TFA and B = 0.1% TFA in acetonitrile as indicated. Products were obtained as amorphous

solids following lyophilization. High-resolution mass spectra (HRMS) were obtained from UCR Mass Spectrometry Facility, University of California at Riverside and fast-atom bombardment mass spectra (FABMS) were acquired with a VG Analytical 7070E mass spectrometer under the control of a VG 2035 data system.

2-Hydroxybenzoic Acid 2-(2-Hydroxybenzoyl)hydrazide (5a). Compound **5a** was prepared as indicated in ref 18.

General Procedure A for the Synthesis of 2,3-Dihydroxybenzoic Acid Hydrazides 8a–e and 13. To a suspension of hydrazide in dichloromethane was added 2,3-dioxosulfinylbenzoylchloride (**7**;[21,22] 1 equiv) followed by triethylamine (1 equiv), and the mixture was stirred at room temperature overnight. The reaction was quenched by the addition of H_2O, and the mixture was filtered to yield a solid product, which was purified by HPLC using a [YMC] column to give 2,3-dihydroxybenzoic acid 2-(2-hydroxybenzoyl)hydrazide (**8a**), 2,3-dihydroxybenzoic acid 2-(2,3-dihydroxybenzoyl)hydrazide (**8b**), 2,3-dihydroxybenzoic acid 2-(2-hydroxy-3-methoxybenzoyl)hydrazide (**8c**), 2,3-dihydroxybenzoic acid 2-(3-hydroxy-2-naphthoyl)hydrazide (**8d**), and 2,3-dihydroxybenzoic acid 2-picalinoylhydrazide (**8e**).

General Procedure B for the Synthesis of *N*-Alkyl-2,3-dihydroxybenzamides 9a–c. To a solution of amine in dichloromethane was added 2,3-dioxosulfinylbenzoylchloride (**7**; 2 equiv) followed by triethylamine (2 equivalents) and the mixture stirred at room temperature (overnight). The reaction was quenched by the addition of H_2O and the crude product was purified by HPLC using a [YMC] column to give *N*,*N*′-1,3-ethanediylbis[2,3-dihydroxybenzamide] (**9a**), *N*,*N*′-1,3-propanediylbis[2,3-dihydroxybenzamide] (**9b**), and *N*-(4-fluorobenzyl)-2,3-dihydroxybenzamide (**9c**).

General Procedure C for the Synthesis of 2-Hydroxy-3-methoxybenzoic Acid Hydrazides 12a–c and 13b. A solution of the appropriate 2-aroylhydrazide (for products **12a–c**) or hydrazine (for product **13b**; 1 equiv) and 3-methoxysalylic acid pentafluorophenyl ester (**10**, 1 equiv), prepared in a fashion similar to that reported for salicylic acid pentafluorophenyl ester,[23] in DMF was stirred at room temperature overnight. Crude product was collected by filtration and purified by preparative [YMC] HPLC to give 2-hydroxy-3-methoxybenzoic acid 2-(2-hydroxy-3-methoxybenzoyl)hydrazide (**12a**), 2-hydroxy-3-methoxybenzoic acid 2-(3-hydroxy-2-naphthoyl)hydrazide (**12b**), 2-hydroxy-3-methoxybenzoic acid 2-picalinoylhydrazide (**12c**), 2,3-dihydroxybenzoic acid hydrazide (**13a**), and 2-hydroxy-3-methoxybenzoic acid hydrazide (**13b**).

General Procedure D for the Synthesis of Hydrazones 14a–c. Hydrazide **13a** (for products **14a** and **14b**) or **13b** (for product **14c**; 1 mmol) was suspended together with the appropriate aldehyde (1 mmol) in THF (2 mL), and the mixture was stirred at room temperature overnight. The crude product was collected by filtration and purified directly by HPLC using a [YMC] column to give 2,3-dihydroxybenzoic acid [(2,3-dihydroxyphenyl)methylene] hydrazide (**14a**), 2,3-dihydroxybenzoic acid [(2,3-dimethoxyphenyl)methylene]hydrazide (**14b**), and 2-hydroxy-3-methoxybenzoic acid [(4-fluorophenyl)methylene]hydrazide (**14c**).

***N*-(4-Fluorobenzyl)-2-hydroxy-3-methoxybenzamide (15).** To a solution of 3-methoxysalicylic acid pentfluorophenyl ester (**10**; 479 mg, 1.43 mmol) in anhydrous dichloromethane (10 mL) was added 4-fluorobenzylamine (0.25 mL, 2.20 mmol), and the solution was stirred at room temperature overnight. The mixture was concentrated and purified by silica gel column chromatography to provide the crude product as a solid (361 mg, 92% crude yield). Further purification was achieved by preparative HPLC [YMC] with a linear gradient from 40% B to 55% B over 30 min; retention time = 25.6 min and yielded **15** as a white solid following lyophilization.^{1}H NMR ($CDCl_3$): δ 7.26–7.21 (m, 3H), 7.12 (dd, 1H, J = 1.6 Hz, 8.0 Hz), 6.97–6.91 (m, 2H), 6.74 (dd, 1H, J = 6.4 Hz, 8.0 Hz), 4.53 (d, 2H, J = 6.0 Hz), 3.82 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 169.2, 160.7 (d, 1C, J = 244.1 Hz), 150.5, 148.7, 133.5 (d, 1C, J = 3.1 Hz), 129.4 (d, 2C, J = 8.4 Hz), 118.4, 118.0, 115.5 (d, 2C, J = 21.3 Hz), 115.0, 114.7, 56.1, 42.9. FAB-MS *m*/*z* 274.1 (M − H). HRMS calcd for $C_{15}H_{15}FNO_3$ [MH^+], 276.1036; found, 276.1037.

1,2-Dimethoxy-3-(methoxymethyl)benzene (17). Sodium hydride (95% in oil, 5.22 g, 0.207 mol) was added portionwise to a solution of 3,4-dimethoxybenzyl alcohol (**16**; 23 mL, 0.158 mol) in anhydrous THF (150 mL) at 0 °C, and the resulting mixture was stirred at 0 °C (10 min). To this was added iodomethane (12.86 mL, 0.207 mol) dropwise, and the mixture was allowed to come to ambient temperature and stirred (3 h). The reaction was quenched by the addition of ice and EtOAc, extracted with EtOAc, and the combined organic phase was washed with brine and dried (Na_2SO_4). Evaporation of solvent provided **17** as a colorless residue (27.8 g, 93% yield). ^{1}H NMR ($CDCl_3$): δ 6.83–6.77 (m, 2H), 4.32 (s, 2H), 3.82 (s, 3H), 3.80 (s, 3H), 3.30 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 149.0, 148.5, 130.7, 120.2, 110.9, 110.8, 74.5, 57.8, 55.8, 55.7. FAB-MS *m*/*z* 182.1 (M^+).

2,3-Dimethoxy-6-(methoxymethyl)benzoic Acid Methyl Ester (18). To a solution of methyl ether **17** (1.0g, 5.49 mmol) in anhydrous ether (15 mL) was added *n*-butyl lithium (1.6 M in hexanes, 6.4 mmol) dropwise with stirring at 0 °C (1 h). The resulting precipitate suspension was cooled to −80 °C, methyl chloroformate (2.0 mL, 26.0 mmol) was added, and then the reaction mixture was allowed to return to room temperature. The mixture was partitioned between H_2O and ether, and the organic phase was dried (Na_2SO_4) and concentrated to provide a residue, which was purified by silica gel column chromatography to yield **18**[24] as a colorless oil (1.04 g, 79% yield). ^{1}H NMR ($CDCl_3$): δ 6.96–6.93 (m, 1H), 6.83–6.81 (m, 1H), 4.31 (s, 2H), 3.82 (s, 3H), 3.77 (s, 3H), 3.23 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 167.7, 152.2, 146.4, 128.2 (2C), 124.2, 113.1, 72.0, 61.4, 58.0, 55.8, 52.0. FAB-MS *m*/*z* 240.1 (M^+).

6-(Chloromethyl)-2,3-dimethoxybenzoic Acid Methyl Ester (19). Acetyl chloride (0.36 mL, 5.07 mmol) was added dropwise with stirring to a solution of methyl ether **18** (362 mg, 1.51 mmol) and anhydrous zinc chloride (10 mg, 0.07 mmol) in anhydrous ether (3 mL) at 0 °C. After 30 min, aluminum oxide (360 mg) was added and the mixture was filtered through a short pad of aluminum oxide. The eluent was evaporated and the residue was purified by silica gel column chromatography to yield **19**[24,37] as a colorless oil (317 mg, 85.9% yield). ^{1}H NMR ($CDCl_3$): δ 7.01 (d, 1H, J = 8.4 Hz), 6.82 (d, 1H, J = 8.4 Hz), 4.51 (s, 2H), 3.86 (s, 3H), 3.79 (s, 3H), 3.77 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 167.1, 153.0, 146.7, 128.6, 127.3, 125.7, 113.4, 61.4, 55.8, 52.4, 43.6. FAB-MS *m*/*z* 245 (MH^+).

2-Amino-2,3-dihydro-7,8-dimethoxy-1*H*-isoindol-1-one (20). Anhydrous hydrazine (0.44 mL, 14.1 mmol) was added to a solution of benzyl chloride **19** (3.45 g, 14.1 mmol) in anhydrous acetonitrile (10 mL), and the solution was stirred at reflux (3 h). Solvent was removed under reduced pressure, the residue was partitioned between H_2O and methylene chloride, and the organic phase was dried (Na_2SO_4) and evaporated to dryness to provide a residue, which was crystallized from EtOAc−hexanes (20:1) to provide **20** as a white solid (1.11 g, 38% yield). ^{1}H NMR ($CDCl_3$): δ 7.02 (dd, 2H, J = 8.0 Hz, 14.4 Hz), 4.36 (s, 2H), 4.28 (bs, 2H), 4.02 (s, 3H), 3.84 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 166.1, 152.2, 147.0, 132.6, 123.5, 117.8, 116.3, 62.5, 56.6, 52.0. FAB-MS *m*/*z* 209.1 (MH^+).

General Procedure E for the Synthesis of Hydrazides 21a−h. Triethylamine (1.0 mmol) was added dropwise to a solution of hydrazide **20** (1.0 mmol) and the appropriate acid chloride (1.0 mmol) or pentafluorophenyl ester (1.0 mmol) or anhydride (0.5 mmol) in anhydrous dichloromethane (2.0 mL), and the reaction mixture was stirred at room temperature overnight. The mixture was partitioned between brine and EtOAc, and the combined organic phase was dried (Na_2SO_4) and evaporated to dryness and the residue was purified by silica gel column chromatography to give *N*-(1,3-dihydro-6,7-dimethoxy-1-oxo-2*H*-isoindol-2-yl)-benzamide (**21a**), *N*-(1,3-dihydro-6,7-dimethoxy-1-oxo-2*H*-isoindol-2-yl)-(2-hydroxy)benzamide (**21b**), *N*-(1,3-dihydro-6,7-dimethoxy-1-oxo-2*H*-isoindol-2-yl)-(2,3-dimethoxy)benzamide (**21c**), *N*-(1,3-dihydro-6,7-dimethoxy-1-oxo-2*H*-isoindol-2-yl)-*N*-(4-fluorobenzoyl)-4-fluorobenzamide (**21d**), *N*-(1,3-dihydro-6,7-dimethoxy-1-oxo-2*H*-isoindol-2-yl)-*N*-(4-fluorobenzenesulfonyl)-4-fluorobenzesulfonamide (**21f**), *N*-(1,3-dihydro-6,7-dimethoxy-1-oxo-2*H*-isoindol-2-yl)-*N*-

(3,4-dimethoxybenzenesulfonyl)-3,4-dimethoxybenzesulfonamide (**21g**), and 6,6′,7,7′-tetramethoxy-[2,2′-bi-2*H*-isoindole]-1,1′(3*H*,3′*H*)-dione (**21h**).

***N*-[(1,3-Dihydro-6,7-dimethoxy-1-oxo-2*H*-isoindol-2-yl)-*N*′-[(6,7-dimethoxy-1,1-dioxido-1,2-benzisothiazol-2(3*H*)-yl)] Hydrazide (21i).** To a solution of methyl ether **17** (857 mg, 4.71 mmol) was added dropwise *n*-butyl lithium (1.6 M in hexane, 3.24 mL, 5.18 mmol) at 0 °C. The resulting white suspension was stirred at 0 °C (1 h), then cooled (−78 °C), and sulfuric chloride (1.2 mL, 14.8 mmol) was added, then the mixture was allowed to come to room temperature and stirred overnight. The reaction was quenched by the addition of MeOH (1.0 mL) while stirring (2 h). Solvent was removed by evaporation and the residue was purified by silica gel column chromatography to afford intermediate 5,6-dimethoxy-2-(methoxymethyl)benzenesulfonyl chloride as a colorless oil (737 mg, 55.7% yield). ^{1}H NMR ($CDCl_3$): δ 7.35 (d, 1H, J = 8.8 Hz), 6.18 (d, 1H, J = 8.8 Hz), 4.71 (s, 2H), 3.99 (s, 3H), 3.88 (s, 3H), 3.40 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 153.0, 148.9, 135.8, 129.9, 123.5, 118.4, 71.1, 61.8, 58.7, 56.3. FAB-MS *m*/*z* 280 (M^+). Acetyl chloride (0.43 mL, 16.7 mmol) under argon at 0 °C (1 h) was added to an aliquot of this material (494 mg, 1.76 mmol) and anhydrous zinc chloride (9 mg, 0.066 mmol) in anhydrous ether (5.0 mL). Aluminum oxide was added, then the mixture was filtered through a short pad of aluminum oxide, the eluent was evaporated, and the residue was purified by silica gel column chromatography to yield 2-(chloromethyl)-5,6-dimethoxybenzenesulfonyl chloride (407 mg, 81.2% yield) as colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.23 (d, 1H, J = 8.8 Hz), 7.17 (d, 1H, J = 8.8 Hz), 4.93 (s, 2H), 4.01 (s, 3H), 3.90 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 154.3, 149.5, 136.3, 128.0, 127.3, 118.2, 61.9, 56.4, 43.6. FAB-MS *m*/*z* 283.9 (M^+). Triethylamine (86 μL, 0.62 mmol) was added to a solution of this material (88 mg, 0.31 mmol) and hydrazide **19** (64 mg, 0.31 mmol) in anhydrous acetonitrile (2.0 mL), and the resulting mixture was stirred at reflux overnight. The solvent was evaporated and the residue was extracted using dichloromethane. The organic phase was dried (Na_2SO_4) and evaporated, and the residue was recrystallized from MeOH to afford **20i** as a solid (62 mg, 47.8% yield). ^{1}H NMR ($CDCl_3$): δ 7.11 (t, 2H, J = 8.4 Hz), 7.02 (d, 1H, J = 8.4 Hz), 6.97 (d, 1H, J = 8.4 Hz), 4.77 (s, 2H), 4.64 (s, 2H), 4.02 (s, 3H), 3.98 (s, 3H), 3.85 (s, 3H), 3.83 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 165.3, 152.2, 152.1, 147.6, 144.3, 133.1, 127.1, 125.6, 122.2, 119.4, 118.8, 118.1, 117.6, 62.4, 61.8, 56.7 (2C), 50.5, 49.2. FAB-MS *m*/*z* 421.1 (MH^+).

General Procedure F for the Synthesis of Hydrazides 21j–n. Triethylamine (1.0 mmol) was added dropwise to a mixture of appropriately substituted phthalic anhydride (1.0 mmol) and hydrazide **20** (1.0 mmol) in toluene (5.0 mL), and the resulting mixture was stirred at reflux overnight. The solvent was evaporated, and the residue was extracted with dichloromethane. The organic phase was dried (Na_2SO_4) and taken to dryness. Purification of the resulting residue by silica gel column chromatography afforded the desired products **21j–n**: 2-[1,3-dihydro-6,7-dimethoxy-3-oxo-2H-isoindol-2-yl]-1*H*-isoindole-1,3(2*H*)-dione (**21j**), 2-[1,3-dihydro-6,7-dimethoxy-3-oxo-2*H*-isoindol-2-yl]-1*H*-3-hydroxyisoindole-1,3(2*H*)-dione (**21k**), 2-[1,3-dihydro-6,7-dimethoxy-3-oxo-2*H*-isoindol-2-yl]-1*H*-3,4-dimethoxyisoindole-1,3(2*H*)-dione (**21l**), 2-[1,3-dihydro-6,7-dimethoxy-3-oxo-2*H*-isoindol-2-yl]-1*H*-4,5-dimethoxyisoindole-1,3(2*H*)-dione (21m), and 2-[1,3-dihydro-6,7-dimethoxy-3-oxo-2*H*-isoindol-2-yl]-1*H*-4-fluoroisoindole-1,3(2*H*)-dione (**21n**).

2,3-Dihydro-6,7-dimethoxy-2-[(2,3-dihydroxyphenylmethylene)amino]-1*H*-isoindol-1-one (21o). A suspension of hydrazide **20** (248 mg, 1.19 mmol) and 2,3-dihydroxybenzylaldehyde (165 mg, 1.20 mmol) in anhydrous toluene (3 mL) was stirred at reflux overnight. The product hydrazone **21o** was collected by filtration (350 mg, 90% yield). ^{1}H NMR (DMSO): δ 8.26 (s, 1H), 7.27 (dd, 2H, J = 8.0 Hz, 25.2 Hz), 6.98 (dd, 1H, J = 1.6 Hz, 8.0 Hz), 6.81 (dd, 1H, J = 1.6 Hz, 8.0 Hz), 6.71 (t, 1H, J = 8.0 Hz), 4.74 (s, 2H), 3.86 (s, 3H), 3.79 (s, 3H). ^{13}C NMR (DMSO): δ 162.1, 152.4, 147.1, 146.2, 146.0, 145.4, 132.3, 123.2, 120.6, 119.6, 119.4, 119.3, 118.4, 117.7, 62.1, 56.8, 46.5. FAB-MS *m*/*z* 329.1 (M − H).

2,3-Dihydro-6,7-dimethoxy-2-[(4-fluorophenylmethylene)amino]-1*H*-isoindol-1-one (21p). A suspension of hydrazide **20** (297 mg, 1.43 mmol) and 4-fluorobenzylaldehyde (0.15 mL, 1.44 mmol) in anhydrous toluene (2.5 mL) was stirred at reflux (4 h). The reaction mixture was cooled to room temperature and extracted with dichloromethane, and the organic phase was dried (Na_2SO_4) and taken to dryness. Crystallization from EtOAc provided product hydrazone **21p** as a white solid (203 mg, 45% yield). ^{1}H NMR (DMSO): δ 8.13 (s, 1H), 7.79 (dd, 2H, J = 5.6 Hz, 8.8 Hz), 7.31–7.22 (m, 4H), 4.72 (s, 2H), 3.84 (s, 3H), 3.79 (s, 3H). ^{13}C NMR (DMSO): δ 163.4 (d, 1C, J = 246.4 Hz), 162.5, 152.4, 147.1, 143.1, 132.3, 131.7 (d, 1C, J = 3.0 Hz), 129.7 (t, 2C, J = 9.1 Hz), 123.6, 119.3 (d, 1C, J = 16.7 Hz), 118.4 (d, 1C, J = 16.8 Hz), 116.4 (d, 1C, J = 21.4 Hz), 116.2 (d, 1C, J = 22.2 Hz), 62.1 (d, 1C, J = 16.7 Hz), 56.8 (d, 1C, J = 16.8 Hz), 47.2; FAB-MS *m*/*z* 315.1 (MH^+).

General Procedure F for the Demethylation of Methyl Ethers. Boron tribromide (1.0 M in dichloromethane, 8.5 mmol) was added carefully to a solution of appropriate methyl ether (1.0 mmol in 1.0 mL anhydrous dichloromethane) and the mixture was stirred at room temperature (overnight). The reaction was quenced by the addition of ice–water (1.0 mL) then the mixture was stirred at room temperature (overnight). The resulting suspension was filtered and the collected solid was purified by preparative HPLC.

The following were prepared by demethylation of intermediates **21** using general procedure F: *N*-(1,3-dihydro-6,7-dihydroxy-1-oxo-2*H*-isoindol-2-yl)-benzamide (**22a**), *N*-(1,3-dihydro-6,7-dihydroxy-1-oxo-2*H*-isoindol-2-yl)-(2-hydroxy)benzamide (**22b**), *N*-(1,3-dihydro-6,7-dihydroxy-1-oxo-2*H*-isoindol-2-yl)-(2,3-dihydroxy)benzamide (**22c**), *N*-(1,3-dihydro-6,7-dihydroxy-1-oxo-2*H*-isoindol-2-yl)-4-fluorobenzamide (**22d**), *N*-(1,3-dihydro-6,7-dihydroxy-1-oxo-2*H*-isoindol-2-yl)-*N*-(4-fluorobenzenesulfonyl)-4-fluorobenzesulfonamide (**22e**), *N*-(1,3-dihydro-6,7-dihydroxy-1-oxo-2*H*-isoindol-2-yl)-4-fluorobenzesulfonamide (**22f**), *N*-(1,3-dihydro-6,7-dihydroxy-1-oxo-2*H*-isoindol-2-yl)-*N*-(3,4-dihydroxybenzenesulfonyl)-3,4-dihydroxybenzesulfonamide (**22g**), 6,6′,7,7′-tetrahydroxy-[2,2′-bi-2*H*-isoindole]-1,1′(3*H*,3′*H*)-dione (**22h**), *N*-[(1,3-dihydro-6,7-dihydroxy-1-oxo-2*H*-isoindol-2-yl)-*N*′-[(6,7-dihydroxy-1,1-dioxido-1,2-benzisothiazol-2(3*H*)-yl)] hydrazide (**22i**), 2-[1,3-dihydro-6,7-dihydroxy-3-oxo-2*H*-isoindol-2-yl]-1*H*-isoindole-1,3(2*H*)-dione (**22j**), 2-[1,3-dihydro-6,7-dihydroxy-3-oxo-2*H*-isoindol-2-yl]-1*H*-4-hydroxyisoindole-1,3(2*H*)-dione (**22k**), 2-[1,3-dihydro-6,7-dihydroxy-3-oxo-2*H*-isoindol-2-yl]-1*H*-4,5-dihydroxyisoindole-1,3(2*H*)-dione (**22l**), 2-[1,3-dihydro-6,7-dihydoxy-3-oxo-2*H*-isoindol-2-yl]-1*H*-4,5-dihydroxyisoindole-1,3(2*H*)-dione (**22m**), 2-[1,3-dihydro-6,7-dihydroxy-3-oxo-2*H*-isoindol-2-yl]-1*H*-4-fluoroisoindole-1,3(2*H*)-dione (**22n**), 2,3-dihydro-6,7-dihydroxy-2-[(2,3-dihydroxyphenylmethylene)amino]-1*H*-isoindol-1-one (**22o**), and 2,3-dihydro-6,7-dihydroxy-2-[(4-fluorophenylmethylene)amino]-1*H*-isoindol-1-one (**22p**).

General Procedure G for the Synthesis of Amides 23a–e. Triethylamine (2.0 mmol) was added to a solution of methyl 2-chloromethyl-3,4-dimethoxybenzoate (**19**; 1.0 mmol), and appropriate amine (1.0 mmol) in anhydrous acetonitrile (3.0 mL) was added. The mixture was stirred at reflux until the starting material was consumed, as indicated by silica gel TLC. The solvent was evaporated and the residue was partitioned between chloroform and brine. The combined organic phase was dried (Na_2SO_4) and evaporated, and the residue was purified by silica gel column chromatography to give 2,3-dihydro-6,7-dimethoxy-2-phenylmethyl-1*H*-isoindol-1-one (23a), 2,3-dihydro-6,7-dimethoxy-2-(2-phenylethyl)-1*H*-isoindol-1-one (**23b**), 2,3-dihydro-6,7-dimethoxy-2-(1-naphthylmethyl)-1*H*-isoindol-1-one (**23c**), 2,3-dihydro-6,7-dimethoxy-2-(4-fluorophenylmethyl)-1*H*-isoindol-1-one (**23d**), and 2,3-dihydro-6,7-dimethoxy-2-[(3-chloro-4-fluorophenyl)methyl]-1*H*-isoindol-1-one (**23e**).

2,3-Dihydro-6,7-dimethoxy-2-[3-((hydroxymethyl)phenyl)methyl]-1*H*-isoindol-1-one (23f). Lithium aluminum hydride (1.0 M in THF, 29.9 mL, 29.9 mmol) was added slowly to a solution of 3-cyanobenzaldehyde (1.12 g, 9.25 mmol) in anhydrous THF (25.0 mL) at room temperature under argon, and the mixture was stirred at reflux overnight. The reaction mixture was cooled to room

temperature and quenched by the addition of ice and NaOH (aq, 3.0 N, 10.0 mL). The mixture was extracted with chloroform (3 × 80 mL), and the combined organic phase was washed with brine (2 × 20 mL) and dried (Na_2SO_4). The solvent was evaporated and the residue was purified by silica gel column chromatography to yield [3-(hydroxymethyl)phenyl]amine as colorless oil (70% yield). ^{1}H NMR ($CDCl_3$): δ 7.26–7.22 (m, 1H), 7.21–7.19 (m, 1H), 7.16–7.14 (m, 1H), 7.12–7.09 (m, 1H), 4.55 (d, 2H, J = 6.0 Hz), 3.71 (d, 2H, J = 8.0 Hz). ^{13}C NMR ($CDCl_3$): δ 142.7, 142.0, 128.6, 126.0, 125.5, 125.4, 64.4, 46.1. FAB-MS *m/z* 138.1 (MH^+). Reaction of this material according to general procedure G provided **23f** in 38% yield. ^{1}H NMR ($CDCl_3$): δ 7.22 (s, 1H), 7.20–7.18 (m, 2H), 7.11–7.09 (m, 1H), 6.98 (d, 1H, J = 8.4 Hz), 6.91 (d, 1H, J = 8.4 Hz), 4.60 (s, 2H), 4.57 (s, 2H), 4.06 (s, 2H), 4.01 (d, 3H, J = 1.2 Hz), 3.80 (d, 3H, J = 1.2 Hz). ^{13}C NMR ($CDCl_3$): δ 166.8, 152.2, 147.2, 141.9, 137.1, 134.5, 128.8, 127.0, 126.6, 126.1, 124.7, 117.8, 116.5, 64.6, 62.4, 56.7, 48.5, 46.2. FAB-MS *m/z* 314.1 (MH^+).

2,3-Dihydro-6,7-dimethoxy-2-[3-((phenylmethyl)phenyl)methyl]-1*H*-isoindol-1-one (23g). Tetrakis(triphenylphosphine)palladium(0) (354 mg, 0.306 mmol) was added under argon to a mixture of (3-benzyl)phenyl bromide[8] (688 mg, 2.49 mmol) and zinc cyanide (1.96 g, 16.7 mmol) in dimethylformamide (5.0 mL), and the resulting mixture was stirred under argon at 95 °C (2 d). The mixture was diluted with ethyl acetate and washed successively with H_2O, dilute aqueous HCl acid, and brine. The organic phase was dried (Na_2SO_4), and the solvent was removed under vacuum. The residue was purified by silica column chromatography (ethyl acetate–hexanes) to yield 2-cyano-4-methylbiphenyl as a colorless oil (369 mg, 69% yield). ^{1}H NMR ($CDCl_3$): δ 7.48–7.45 (m, 2H), 7.43–7.41 (m, 1H), 7.38–7.30 (m, 3H), 7.26–7.22 (m, 1H), 7.17–7.12 (m, 2H), 3.99 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 142.6, 139.5, 133.4, 132.3, 129.9, 129.3, 128.9 (2C), 128.8 (2C), 126.7, 118.9, 112.5, 41.4. FAB-MS *m/z* 193 (M^+). Lithium aluminum hydride (1.0 M in THF, 5.35 mL, 5.35 mmol) was added to a solution of this material (344 mg, 1.78 mmol) in anhydrous THF (5.0 mL) at room temperature under argon, and the mixture was stirred at reflux (4 h). The mixture was cooled to room temperature and quenched by the addition of aqueous NaOH (3.0 N, 10.0 mL). The mixture was extracted with ethyl acetate (3 × 80 mL), and the combined organic phase was washed with brine (2 × 20 mL) and dried (Na_2SO_4). The solvent was evaporated, and the residue was purified by silica gel column chromatography to provide [3-((phenylmethyl)phenyl)methyl]amine as a colorless oil (94 mg, 27% yield). ^{1}H NMR ($CDCl_3$): δ 7.31–7.25 (m, 3H), 7.24–7.19 (m, 3H), 7.15–7.14 (m, 2H), 7.09–7.07 (m, 1H), 3.98 (s, 2H), 3.81 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 143.2, 141.4, 141.1, 128.9 (2C), 128.7, 128.5 (2C), 127.7, 127.5, 126.1, 124.9, 46.3, 41.9. FAB-MS *m/z* 198.1 (MH^+). Treatment of this material according to general procedure G provided **23 g** in 76% yield. ^{1}H NMR ($CDCl_3$): δ 7.25–7.20 (m, 3H), 7.18–7.16 (m, 1H), 7.15–7.13 (m, 2H), 7.12–7.09 (m, 2H) 7.06–7.04 (m, 1H), 7.03 (d, 1H, J = 8.4 Hz), 6.96 (d, 1H, J = 8.4 Hz), 4.68 (s, 2H), 4.10 (s, 2H), 4.09 (s, 3H), 3.92 (s, 2H), 3.86 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 166.6, 152.3, 147.4, 141.7, 140.8, 137.2, 134.5, 128.8 (3C), 128.4 (2C), 128.2, 126.1, 126.0, 124.9, 117.7, 116.5, 62.6, 56.8, 48.5, 46.3, 41.7.

The following were prepared by demethylation of intermediates **23** using general procedure F: 2,3-dihydro-6,7-dihydroxy-2-phenylmethyl-1*H*-isoindol-1-one (**24a**), 2,3-dihydro-6,7-dihydroxy-2-(2-phenylethyl)-1*H*-isoindol-1-one (**24b**), 2,3-dihydro-6,7-dihydroxy-2-(1-naphthylmethyl)-1*H*-isoindol-1-one (**24c**), 2,3-dihydro-6,7-dihydroxy-2-(4-fluorophenylmethyl)-1*H*-isoindol-1-one (**24d**), 2,3-dihydro-6,7-dihydroxy-2-[(3-chloro-4-fluorophenyl)methyl]-1*H*-isoindol-1-one (**24e**), 2,3-dihydro-6,7-dihydroxy-2-[3-((bromomethyl)phenyl)methyl]-1*H*-isoindol-1-one (**24f**), and 2,3-dihydro-6,7-dihydroxy-2-[3-((phenylmethyl)phenyl)methyl]-1*H*-isoindol-1-one (**24g**).

4,5-Dimethoxy-2-[(4-fluorophenyl)methyl]-1*H*-isoindole-1,3(2*H*)-dione (25). Triethylamine (2.0 mmol) was added dropwise to a solution of 3,4-dimethoxyphthalic anhydride[38] (1.0 mmol) and [(4-fluorophenyl)methyl]amine (1.0 mmol) in toluene (5.0 mL), and the mixture was stirred at reflux (overnight). The solvent was evaporated, and the residue was taken up in dichloromethane, dried (Na_2SO_4), and evaporated. The product was obtained following purification by silica gel column chromatography to provide **25** in 52% yield. ^{1}H NMR ($CDCl_3$): δ 7.48 (d, 1H, J = 8.0 Hz), 7.37 (dd, 2H, J = 5.2 Hz, 8.4 Hz), 7.05 (d, 1H, J = 8.0 Hz), 6.94 (t, 2H, J = 8.4 Hz), 4.71 (s, 2H), 4.09 (s, 3H), 3.89 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 167.3, 166.0, 162.2 (d, 1C, J = 244.8 Hz), 157.8, 147.2, 132.4 (d, 1C, J = 3.1 Hz), 130.5 (d, 1C, J = 8.4 Hz), 124.4, 121.9, 119.4, 115.8, 115.4 (d, 2C, J = 21.4 Hz), 62.5, 56.5, 40.8; APCI-MS *m/z* 315.3 (MH^+).

4,5-Dihydroxy-2-[(4-fluorophenyl)methyl]-1*H*-isoindole-1,3(2*H*)-dione (26). Treatment of **25** with boron tribromide, as described in general method F, followed by preparative HPLC [YMC] (linear gradient of 30% B to 50% B over 30 min; retention time = 24.0 min) afforded product **26** as a white solid following lyophilization. ^{1}H NMR (DMSO): δ 7.26 (dd, 2H, J = 6.0 Hz, 8.4 Hz), 7.13 (dd, 1H, J = 1.6 Hz, 8.0 Hz), 7.08 (t, 2H, J = 8.4 Hz), 7.01 (dd, 1H, J = 1.6 Hz, 8.0 Hz), 4.60 (s, 2H). ^{13}C NMR (DMSO): δ 167.6, 166.8, 161.8 (d, 1C, J = 241.8 Hz), 152.9, 144.7, 133.8 (d, 1C, J = 3.0 Hz), 129.9 (d, 2C, J = 8.4 Hz), 122.6, 119.2, 116.2, 116.1, 115.7 (d, 2C, J = 21.4 Hz), 40.1; FAB-MS *m/z* 288.1 (MH^+) HRMS calcd for $C_{15}H_{11}FNO_4$ [MH^+]: 288.0672. Found: 274.0666.

2,3-Dihydro-4,5-dihydroxy-2-(4-fluorophenylmethyl)-*H*-isoindol-1-one (27). Zinc dust (80 mg, 1.23 mmol) was added to a solution of **26** (59 mg, 0.21 mmol) in acetic acid (1.0 mL) at room temperature, and the mixture was stirred overnight. The resulting mixture was filtered, the filtrate was concentrated, and the residue was purified by preparative HPLC [YMC] (linear gradient of 30% B to 50% B over 30 min; retention time = 16.4 min) to provide **26** as a white solid following lyophilization. ^{1}H NMR (CD_3OD): δ 7.29 (dd, 2H, J = 5.6 Hz, 8.8 Hz), 7.15 (d, 1H, J = 8.0 Hz), 7.04 (t, 2H, J = 8.8 Hz), 6.87 (d, 2H, J = 8.0 Hz), 4.71 (s, 2H), 4.21 (s, 2H). FAB-MS *m/z* 274.1 (MH^+). HRMS calcd for $C_{15}H_{13}FNO_3$ [MH^+], 274.0879; found, 274.0888.

4-Hydroxy-2-[(4-fluorophenyl)methyl]-1*H*-isoindole-1,3(2*H*)-dione (28). To a suspension of 3-hydroxyphthalic anhydride (704 mg, 4.29 mmol) in anhydrous toluene (15.0 mL) was added dropwise [(4-fluorophenyl)methyl]amine (0.49 mL, 4.32 mmol) followed by triethylamine (1.20 mL, 8.63 mmol), and the mixture was stirred at reflux overnight. The solvent was evaporated, and the residue was crystallized from EtOAc to provide **28** as a yellow solid (133 mg, 11% yield). The solid was further purified by preparative HPLC [YMD] (linear gradient of 30% B to 65% B over 30 min; retention time = 24.6 min) to yield **29** as a white solid following lyophilization. ^{1}H NMR (DMSO): δ 7.56 (dd, 1H, J = 7.2 Hz, 8.4 Hz), 7.30–7.23 (m, 3H), 7.16 (d, 1H, J = 8.4 Hz), 7.10 (t, 2H, J = 8.8 Hz), 4.64 (s, 2H). FAB-MS *m/z* 269.9 (M − H). HRMS calcd for $C_{15}H_{11}FNO_3$ [MH^+], 272.0723; found, 272.0728.

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Supporting Information Available: Physical data for **8a**−**e**, **9a**−**c**, **12a**−**c**, **13a**,**b**, **14a**−**c**, **21a**−**d**, **21f**−**h**, **21j**−**o**, **22a**−**p**, **23a**−**e**, and **24a**−**g**.This material is available free of charge via the Internet at http://pubs.acs.org.

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