Arylamide Inhibitors of HIV-1 Integrase

He Zhao,[†] Nouri Neamati,[‡] Abhijit Mazumder,[‡] Sanjay Sunder,[‡] Yves Pommier,[‡] and Terrence R. Burke, Jr.*[,†]

Laboratories of Medicinal Chemistry and Molecular Pharmacology, Division of Basic Sciences, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892

Received June 21, 1996[⊗]

Based on data derived from a large number of HIV-1 integrase inhibitors, similar structural features can be observed, which consist of two aryl units separated by a central linker. For many inhibitors fitting this pattern, at least one aryl ring also requires *ortho* bis-hydroxylation for significant inhibitory potency. The ability of such catechol species to undergo in situ oxidation to reactive quinones presents one potential limitation to their utility. In an effort to address this problem, a series of inhibitors were prepared which did not contain *ortho* bis-hydroxyls. None of these analogues exhibited significant inhibition. Therefore an alternate approach was taken, whose aim was to increase potency rather than eliminate catechol substructures. In this latter study, naphthyl nuclei were utilized as aryl components, since a previous report had indicated that fused bicyclic rings may afford higher affinity relative to monocyclic phenyl-based systems. In preliminary work with monomeric units, it was found that the 6,7-dihydroxy-2-naphthoic acid (**17**) ($IC_{50} = 4.7\ \mu M$) was approximately 10-fold more potent than its 5,6-dihydroxy isomer **19** ($IC_{50} = 62.4\ \mu M$). Of particular note was the dramatic difference in potency between free acid **17** and its methyl ester **21** ($IC_{50} > 200\ \mu M$). The nearly total loss of activity induced by esterification strongly indicates that the free carboxylic −OH is important for high potency of this compound. This contrasts with the isomeric 5,6-dihydroxy species **19**, where esterification had no effect on inhibitory potency (**23**, $IC_{50} = 52.7\ \mu M$). These data provide evidence that the monomeric 6,7- and 5,6-dihydroxynaphthalenes may be interacting with the enzyme in markedly different fashions. However, when these naphthyl nuclei were incorporated into dimeric structures, significant enhancements in potencies each relative to the monomeric acids were observed, with bis-6,7-dihydroxy analogue **49** and bis-5,6-dihydroxy analogue **51** both exhibiting approximately equal potencies (IC_{50} values of 0.81 and 0.11 μM, respectively).

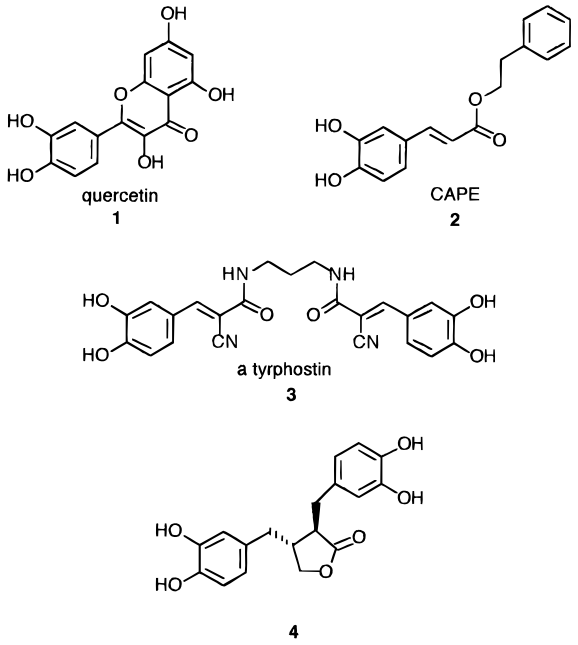
AIDS is a pandemic which portends an increasing toll in human suffering and a draining of national resources. Current approaches for the treatment of AIDS using single agents are plagued by the development of tolerance. Combination therapies employing multiple components, each directed against different viral enzymes, may potentially provide an effective means of countering such tolerance. The HIV reverse transcriptase and protease enzymes are two targets which currently provide the basis for most AIDS therapies. To augment these approaches, inhibitors directed at new enzyme targets are needed, with the HIV integrase enzyme being one such important target.[1] Its attractiveness is attributed to the absolute requirement for its participation in HIV replication [2−5] and to the fact that it is not indigenous in humans. The enzyme functions in a two-step manner by initially removing a dinucleotide unit from the 3′-ends of the viral DNA (termed "3′-processing"). The 3′-processed strands are then transferred from the cytoplasm to the nucleus where they are introduced into the host DNA following 5-base pair offset cleavages of opposing host strands (termed "strand transfer"). Radiolabeled oligonucleotide-based assays have been devised which allow the in vitro determination of IC_{50} values for inhibition of both 3′-processing and strand transfer by prospective inhibitors.[6,7] Several reports have utilized these or similar assays to examine a wide range of potential structures. A consistent theme in many active compounds is the presence of multiple aromatic rings, with polyaryl hydroxylation, frequently in the 1,2-catechol arrangement. Examples of this are the flavones, including quercetin (**1**),[8] caffeic acid phenethyl ester (CAPE, **2**),[8] and analogues,[9] and the structurally related "tyrphostins" (**3**), which contain α-cyanocaffeic acid-like moieties.[10] Additionally, arctigenin-based compounds such as **4**[11] and bis-catechols such as β-conidendrol[12] have recently been reported which also fall within this category. These inhibitors may be described in general as consisting of two aryl units, one of which contains the 1,2-dihydroxy pattern, separated by an appropriate linker segment (Figure 1).

Figure 1. General structural features common to many HIV integrase inhibitors.

It should be carefully pointed out that Figure 1 is a very general summary of observed structural features which are common to many integrase inhibitors. It is entirely possible that inhibitors fitting the general criteria depicted by Figure 1 interact with the integrase enzyme at different binding sites or in varied orientations within a given binding site. For these reasons, Figure 1 does not imply a three-dimensional overlap of

* To whom correspondence should be addressed at Bldg 37, Rm 5C06, National Institutes of Health, Bethesda, MD 20892. Fax: (301) 402-2275. E-mail: tburke@helix.nih.gov.
[†] Laboratory of Medicinal Chemistry.
[‡] Laboratory of Molecular Pharmacology.
[⊗] Abstract published in *Advance ACS Abstracts,* March 15, 1997.

S0022-2623(96)00449-9



either aryl or linker components and, as such, is not a "pharmacophore model" in the traditional sense. It also does not imply that all structural features of Figure 1 are absolutely required for potent integrase inhibition. It does, however, summarize graphically general features which empirically are common to many integrase inhibitors.

One limitation of these catechol-based inhibitors is collateral cytotoxicity, envisioned to arise by oxidation of the catechols to reactive quinone species. Once formed, such quinones can undergo attack by cellular nucleophiles, resulting in a variety of adverse effects. An example of this is the recent report that CAPE-like analogues can induce cell protein cross-linking at low micromolar concentrations in a nonspecific manner, presumably through such quinone intermediates.[13] This type of chemical reactivity may contribute to the observation that although some CAPE-like analogues effectively inhibit HIV integrase in isolated enzyme systems and additionally show protective effects in HIV-infected CEM cell preparations, innate cytotoxicity limits the overall effectiveness of the compounds.

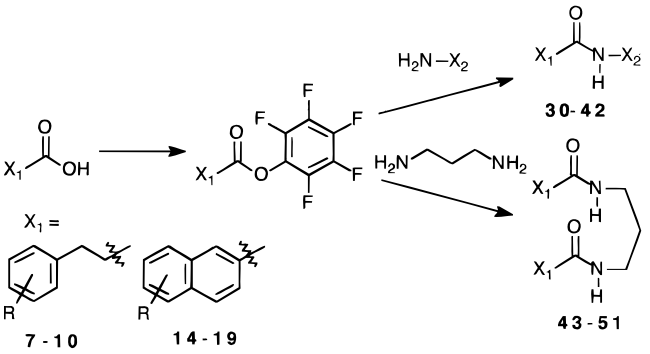
In order to address this problem, one could either (1) reduce the ability of the compounds to form quinone species or (2) increase inhibitory potency relative to parent compounds, thereby reducing the amount of compound required for effective inhibition. In the present study we extend our previous structure−activity study on the HIV integrase inhibition of CAPE analogues,[9] by examining these questions.

Synthesis

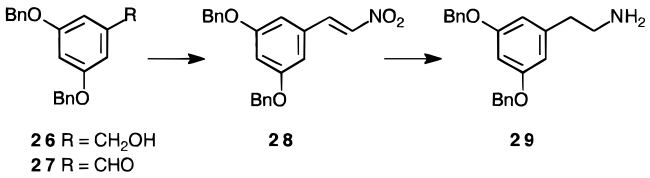
All final products examined in this study were either monomeric aryl-containing acids or esters or bis-arylamides. The bis-arylamides were uniformly prepared by conversion of the acid precursors to their pentafluorophenyl (Pfp) esters followed by reaction with appropriate amines (Scheme 1). Activation as the Pfp ester allowed coupling of acids containing free hydroxyl groups without prior protection of the hydroxyls.

Unsymmetrical Bis-Arylamides. For unsymmetrical bis-arylamides **30**−**42** (Scheme 1), the necessary

Scheme 1



Scheme 2



amines were either obtained commercially or prepared in straightforward fashions. Of note was the synthesis of 2-[3,5-bis(benzyloxy)phenyl]ethylamine (**29**; Scheme 2). Benzylation of 3,5-dihydroxybenzyl alcohol (benzyl bromide, K_2CO_3 in DMF) gave the 3,5-bis-benzyloxy derivative **26**, which was oxidized to the aldehyde **27** using MnO_2. The nitrostyrene **28**, which was then obtained by reaction with nitromethane in the presence of ammonium acetate catalyst, was reduced with $LiAlH_4$ to provide the final phenylethylamine **29**. Amine **29** was coupled to Pfp esters in its bis-benzyloxy form to provide amide **37**, which was subsequently subjected to hydrogenolytic removal of the benzyl groups. Attempted removal of benzyl protection resulted in a mixture of monodebenzylated and didebenzylated amides (**39** and **38**, respectively). Additionally, hydrogenolysis of 3-(3,4-dihydroxyphenyl)propanoic acid [β-[3,5-bis(benzyloxy)-phenyl]ethyl]amide (**40**) provided a similar result (**42** and **41**, respectively).

Symmetrical Bis-Arylamides. Symmetrical 1,3-diamidopropanes were prepared by reaction of Pfp esters with 1,3-diaminopropane (Scheme 1). The resulting bis-amidopropanes were of two families according to the nature of their aryl components. The first class of dimers (**43**−**45**) was derived from phenylpropionates, while the second class (**46**−**51**) was derived from naphthoates. In the naphthalene series, it was anticipated that demethylation of methoxy-containing naphthalene dimers (**46**, **48**, and **50**) would provide the corresponding phenoxy analogues (**47**, **49**, and **51**). While this approach proved successful for the pyridine·HCl-mediated demethylation of **46** to give the desired product **47**, when demethylation of tetramethoxy derivatives **48** and **50** was attempted, it was not possible to isolate usable quantities of fully demethylated products **49** and **51**, respectively. An alternate approach was therefore taken which utilized monomer naphthoyl Pfp esters bearing free hydroxyl groups (**22** and **25**). Upon reaction with diaminopropane, these gave the desired phenolic products directly.

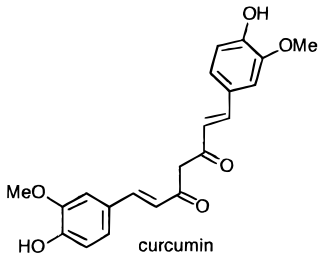
Monomeric Acids and Esters. Monomeric aryl carboxylic acids consisted of either phenylpropanoic acids (**7**−**10**) or 2-naphthoic acids (**14**−**19**). Except for

3-(4-hydroxyphenyl)propanoic acid (**7**), which was obtained commercially directly, all phenylpropanoic acids were prepared by hydrogenation of the corresponding commercially available cinnamic acids. The 3,5-dihydroxy acid **10** was prepared by demethylation (pyridine·HCl) of the 3,5-dimethoxy precursor, which itself was obtained from the corresponding cinnamic acid.

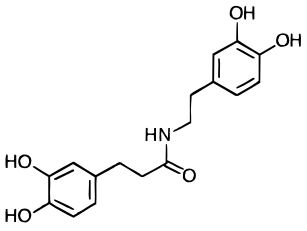
Several of the 2-naphthoic acids (**14**−**19**) and the methyl esters (**20**−**23**) have been previously reported. Methyl 6,7-dihydroxy-2-naphthoate (**21**) was obtained by esterification (methanolic HCl) of the known acid **17**. Methyl 6-hydroxy-2-naphthoate[14] (**20**) was obtained by treatment of commercially available 2-bromo-6-methoxynaphthalene with *n*-butyllithium followed by reaction with solid CO_2 to provide 6-methoxy-2-naphthoic acid, which was then demethylated by treatment with pyridine·HCl at 180 °C. The resulting 6-hydroxy-2-naphthoic acid was converted to **20** by refluxing in methanolic HCl. Similarly, demethylation of 6,7-dimethoxy-2-naphthoic acid[15] with pyridine·HCl gave 6,7-dihydroxy-2-naphthoic acid **17**, which upon treatment with methanolic HCl gave the corresponding methyl ester **21**. In the naphthoyl series, acids and esters were examined both in their monomeric forms as well as components of dimeric amides.

Results and Discussion

Elimination of Quinone-Forming Potential for Arylamide 6. One means of diminishing quinone-forming potential is to eliminate 1,2- or 1,4-dihydroxyl substitution patterns. Curcumin (**5**), which bears strong structural similarity to CAPE, affords an example of a moderately potent inhibitor which does not contain the catechol pattern.[16] The evidence provided by curcumin, that bis-aryl analogues containing a single free hydroxyl on each ring can achieve effective inhibition of HIV integrase, renews speculation that other CAPE-like compounds, which do not contain the catechol arrangement, may also have good potency. With this objective in mind, we directed our attention to a series of CAPE-like bis-arylamides.[9] Arylamide **6** is interesting, in that



5



6

as indicated in our previous report[9] inhibitory potency requires hydroxylation on both rings, in contrast to other CAPE analogues, which require *ortho* bis-hydroxylation on a single ring. In light of the precedence set by curcumin, where a single free hydroxyl on each aryl ring can achieve moderate inhibitory potency, it was of interest whether **6** could also tolerate monohydroxylation on each ring, since such bis-monohydroxylated arylamides would no longer be readily liable to quinone formation.

In order to explore this possibility, a series of new compounds (**30**, **31**, **33**, and **35**) were designed, which represented all possible isomeric bis-monohydroxylated

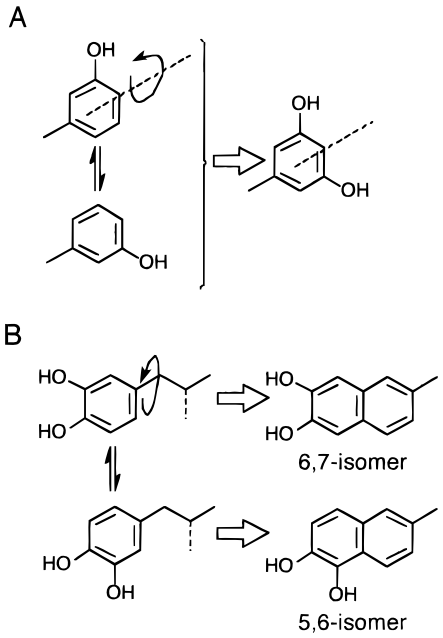


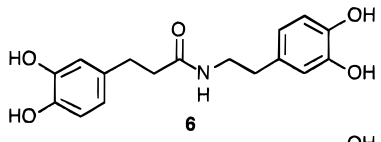
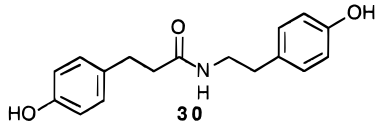
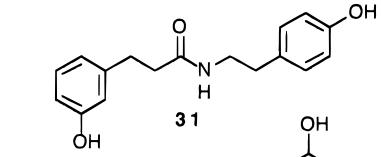
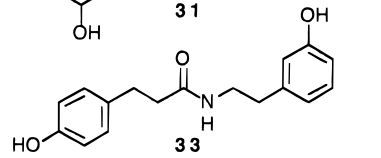
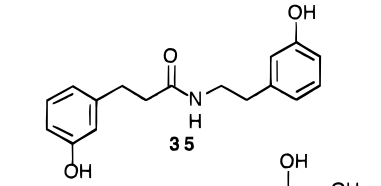
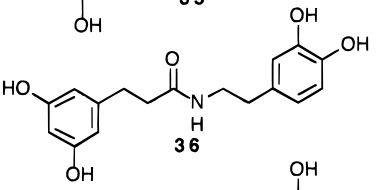
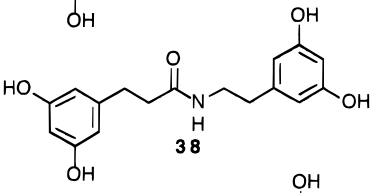
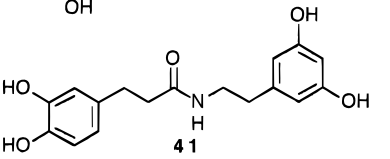
Figure 2. Rotational isomer mimetics of hydroxylated phenyl species: (A) *meta* hydroxy analogue mimicked by 3,5-dihydroxy species and (B) 3,4-dihydroxy analogue mimicked by 6,7- and 5,6-dihydroxynaphth-2-yl species.

arylamides derived from parent amide **6**. Since an aryl ring bearing a single *meta* hydroxyl can exist in two rotational conformers symmetric about the axis of rotation (Figure 2), the study was extended and additional analogues (**36**, **38**, and **41**) were also designed which contained the 3,5-dihyroxy pattern. This ring pattern simultaneously represents both conformers found in a *meta*-substituted monohydroxy analogue, yet the 3,5-dihydroxy pattern is not properly situated for undesired quinone formation. All members of this series retain the fundamental inhibitory structure shown in Figure 1. It should be noted that the intent here is not necessarily to increase the potency of **6** but rather to examine whether the *ortho* bis-hydroxy pattern is a *required* component of inhibitory action for these CAPE amides.

To measure integrase inhibitory potency, the effects of these compounds on the catalytic activities of both HIV-1 integrase 3′-processing and strand transfer were measured. During 3′-processing, the enzyme initially processes linear viral DNA by removing a two-nucleotide unit from each 3′-end. In the second, strand transfer step, the resulting free 3′-OH termini is transesterified as a phosphodiester to host DNA. The receptor host DNA is first cut and its 5′-end then joined to the recessed 3′-end of the processed viral DNA. These two steps, which are known as 3′-processing and DNA strand transfer, can be readily measured in an in vitro assay employing purified recombinant integrase and a 21-mer duplex oligonucleotide substrate corresponding to the U5 region of the HIV LTR (long terminal repeat) sequence. The assay employed in our studies allows simultaneous measurement of inhibition constants for both 3′-processing and strand transfer. The IC_{50} values presented in the following discussion will refer to strand transfer.

The results of this first study are shown in Table 1. It had previously been observed for a series of 1,2-dihydroxy-containing analogues of **6** that good inhibitory

Table 1. Inhibition of HIV-1 Integrase-Mediated 3′-Processing as Described in the Experimental Section

Compound	IC_{50} (μM)
 **6**	33
 **30**	>350
 **31**	>350
 **33**	>350
 **35**	>350
 **36**	>350
 **38**	>350
 **41**	>350

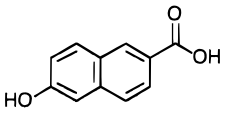
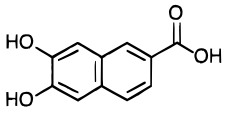
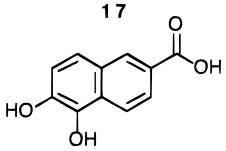
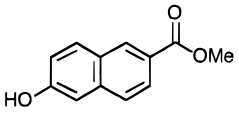
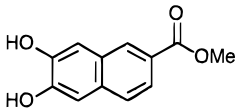
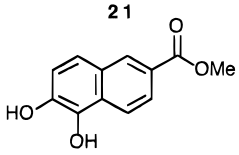
potency was achieved only when 3,4-dihydroxylation was present on *both* rings.[9] In that former study, **6** exhibited an IC_{50} value of 3 μM. However in the current work, an IC_{50} value of 30 μM was observed for this same compound. The reason for this difference is not known as IC_{50} values for other compounds presented in that study can be reproduced quite closely. Compounds **30**, **31**, **33**, and **35**, which represent possible bis-monohydroxy isomers derived from **6** and which were designed to assess whether all hydroxyls of bis-catechol **6** are required for inhibitory potency, were not active. Additional analogues **36**, **38**, and **41**, which contained the 3,5-dihydroxy pattern as a rotationally symmetrical non-quinone-forming mimic of a 3-hydroxy-substituted ring (Figure 2), also did not shown demonstrable inhibitory potency. These results strongly suggest that all bis-hydroxyls in the parent amide **6** are required for inhibitory potency. It should be pointed out that these results pertain to the parent amide **6**, which was the focus of the study. The requirement for *ortho* bis-hydroxylation is consistent with previous results in which *ortho* bis-hydroxylation has been shown to be important for inhibitory potency for a variety of other integrase inhibitors.

Increasing Inhibitory Potency. A second approach toward reducing cytotoxicity could be to increase potency, although it is understood that an increase in potency also potentially may be accompanied by an increase in toxicity. As shown in Figure 1, many HIV integrase inhibitors contain two isolated aromatic rings. This may indicate interaction of the inhibitor with the enzyme at two distinct aryl-binding sites. In contrast, 5,6-dihydroxy-2-naphthoic acid methyl ester (**23**) contains a single fused aromatic system yet has been reported to exhibit inhibitory potency equivalent to the parent CAPE.[9] The good inhibitory potency previously reported for **23** is surprising since it does not fit the model shown in Figure 1 and cannot bridge two putative aryl-binding sites. The possibility therefore exists that the naphthalene-based **23** interacts at a single binding site but with very high affinity. Naphthalene-based structures may therefore represent high-affinity motifs for incorporation into inhibitors of the type shown in Figure 1. Coupling of two naphthyl monomers via a spacer could potentially facilitate interaction at two separate sites, thereby enhancing potency relative to the isolated monomeric units. To examine this possibility, a series of dimeric naphthalene compounds were designed (**46**−**51**) based on the 6-, 6,7-, and 5,6-substituted naphthalene substructures. The isomeric 6,7- and 5,6-patterns were originally designed to mimic the constrained rotational conformers of the caffeic acid nucleus found in CAPE (Figure 2),[9] while the choice of the 1,3-diaminopropane linker was predicated on the high potency of dimeric tyrphostin inhibitors such as **3**.[10]

The results for this second study are shown in Tables 2 and 3. The rationale for the study was based on the previous finding that the 5,6-dihydroxynaphth-2-yl compound **23** exhibited good inhibitory potency. In the current assay, **23** exhibited decreased potency (IC_{50} = 52.7 μM) relative to the previously reported value (IC_{50} = 8 μM).[9] The discrepancy in IC_{50} values obtained for both **6** and **23** relative to values we previously reported may be attributable to several factors. The current HIV-1 integrase assay system has been slightly modified. These modifications include retention of the histidine tag used to purify the enzyme and addition of fresh 2-mercaptoethanol to the assay mixtures. Additionally, quantitation of results was performed using a different curve-fitting program. Retesting of several compounds under current assay conditions (unpublished data) provided IC_{50} values in close agreement with results obtained under these earlier conditions, indicating that a general upward drift in inhibitory potency is not at work. Additionally, multiple independent analysis of compounds under the current assay conditions provides reproducible IC_{50} values, arguing against inherent variability in the enzyme assay. Since compounds **6** and **23** would be expected to be easily oxidized, sample preparation could potentially contribute to observed differences in potency. Finally, it should be noted that, in spite of their elevated IC_{50} values, both **6** and **23** remain classified as "active" compounds and are therefore valuable leads.

The inhibitory data for monomeric hydroxylated 2-naphthoyl analogues, both as their free acids and as

Table 2. Inhibition of HIV-1 Integrase-Mediated 3′-Processing and Strand Transfer as Described in the Experimental Section

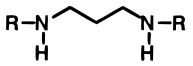
R	IC_{50} (μM) 3′-Processing	Integration
 **15**	172.3	172.3
 **17**	5.4 ± 0.8	4.7 ± 0.6
 **19**	53.3 ± 11.9	62.4 ± 1.1
 **20**	>200	>200
 **21**	>200	>200
 **23**	58.4 ± 0.8	52.7 ± 8.9

their methyl esters (Table 2), show that the *ortho* bis-hydroxy pattern is required for significant inhibitory potency and that the 6,7-dihydroxy-2-naphthoic acid (**17**) is approximately 10-fold more potent than its 5,6-dihydroxy isomer **19**. Of particular note is the dramatic difference in potency between free acid **17** (IC_{50} = 4.7 μM) and its methyl ester **21** (IC_{50} > 200 μM). The nearly total loss of activity induced by esterification strongly indicates that the free carboxylic −OH is important for inhibitory potency of this compound. This contrasts with the isomeric 5,6-dihydroxy species **19** (IC_{50} = 62.4 μM), where esterification has no effect on inhibitory potency (**23**, IC_{50} = 52.7 μM). These data provide evidence that the 6,7- and 5,6-dihydroxynaphthalenes may be interacting with the enzyme in markedly different fashions.

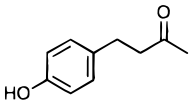
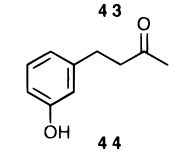
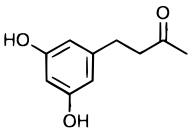
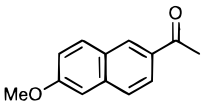
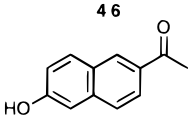
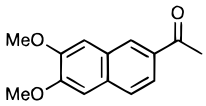
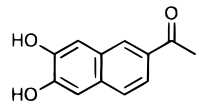
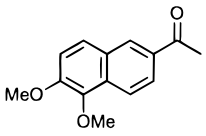
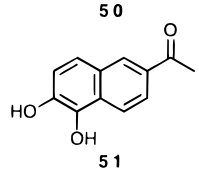
The inhibitory data for symmetrical 1,3-bis-amidopropanes is shown in Table 3. The initial entries (**43**−**45**) represent an extension of the amides presented in Table 1 and examine whether non-quinone-forming phenylpropanoylamides can be employed successfully for inhibitory design. Similar to the results in Table 1, none of these analogues showed measurable inhibitory potency.

The remaining entries in Table 3 deal with bis-2-naphthoamides. Similar to what was observed with the phenyl-containing compounds, derivatives lacking the *ortho* bis-hydroxy pattern (including monohydroxy ana-

Table 3. Inhibition of HIV-1 Integrase-Mediated 3′-Processing and Strand Transfer as Described in the Experimental Section



General Structure

R	IC_{50} (μM) 3′-Processing	Integration
 **43**	>200	>200
 **44**	>200	>200
 **45**	>200	>200
 **46**	>200	>200
 **47**	>200	>200
 **48**	>200	>200
 **49**	0.98 ± 0.5	0.81 ± 0.1
 **50**	>200	>200
 **51**	0.23 ± 0.05	0.11 ± 0.07

logue **47** and all methoxy-containing compounds) were not active. Dimerization of 6,7- or 5,6-dihydroxy-containing compounds (**17** and **19**, respectively) resulted in a significant enhancement in potency each relative to the monomeric acids, with both analogues bordering on submicromolar potency (IC_{50} values of 0.81 ± 0.1 and 0.11 ± 0.07 μM for **49** and **51**, respectively).

A representative gel and dose−response curves illustrating the inhibition of integrase-catalyzed reactions by **3**, **6**, **47**, and **49** are shown in Figure 3, which graphically illustrates the important findings of this study. First, in the 2-naphthoyl series, the 6,7-dihy-

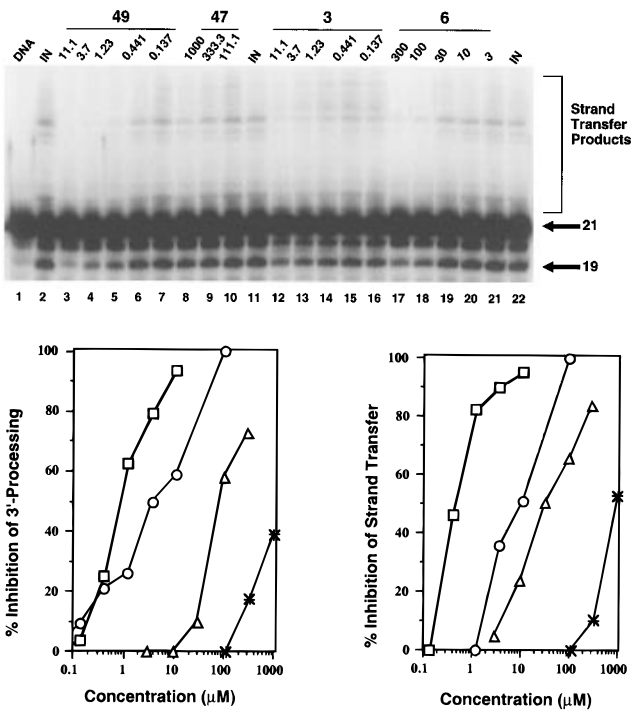


Figure 3. (Top) Inhibition by amides of HIV-1 integrase-catalyzed 3′-processing and strand transfer using blunt-ended DNA substrate: lane 1, DNA alone; lanes 2, 11, and 22, with integrase; lanes 3−7, 8−10, 12−16, and 17−21, with integrase in the presence of the indicated concentrations (μM) of compounds **49**, **47**, **3**, and **6**, respectively. (Bottom) Graphical quantitation of results presented in the top panel: □, **49**; ○, **3**; △, **6**; *, **47**. Percent inhibition was calculated from a phosphorimager as described in the Experimental Section.

droxy analogue **49** exhibited more than a 1200-fold increase in potency as compared with monohydroxy-containing **47**, clearly showing the critical nature of the *ortho* bis-hydroxy pattern. Figure 3 also presents data which support the importance of extended planarity. Compound **3**, which contains α-cyanocinnamoyl units, exhibits much higher potency ($IC_{50} = 3.7$ μM) than the phenylpropanoyl-derived **6**. The phenyl rings of α-cyanocinnamoyl structures exist in conformational minima at angles close to coplanar with their vinyl side chains,[17] and 5,6- and 6,7-dihydroxynaphth-2-yl nuclei have been utilized previously as planar, conformationally constrained mimics of α-cyanocinnamoyl-like structures (see Figure 2).[18] The increased inhibitory potency of naphthyl-derived analogues versus phenyl-containing derivatives, along with the significant enhancement in potency observed when monomeric naphthyl nuclei were incorporated into dimeric structures (compare monomeric **17** and **19** versus dimeric **49** and **51**, respectively), supports the use of hydroxylated polycyclic aryls in the general inhibitor structure of Figure 1.

In conclusion, despite efforts to examine hydroxylation patterns which are not quinone-forming, a consistent finding throughout the present study was the importance of *ortho* bis-hydroxylation for high inhibitory potency. Further, not only the presence of *ortho* bis-hydroxylation but also the positioning of these hydroxyls can have a significant effect on inhibitory potency.

Experimental Section

Preparation of Oligonucleotide Substrates. The HPLC-purified oligonucleotides AE117 (5′-ACTGCTAGAGATTTTC-CACAC-3′) and AE118 (5′-GTGTGGAAAATCTCTAGCAGT-3′) were purchased from Midland Certified Reagent Co. (Midland, TX). Purified recombinant wild-type HIV-1 was prepared as described.[19] The extent of 3′-processing and strand transfer was determined using 5′-end-labeled substrate, with 5′-labeled AE118 having been prepared using T4 polynucleotide kinase (Gibco BRL) and [γ-^{32}P]ATP (DuPont NEN). The kinase was heat inactivated prior to adding AE117 to the same final concentration. The resulting mixture was heated to 95 °C, allowed to cool slowly to room temperature, and run on a G-25 Sephadex quick spin column (Boehringer Mannheim, Indianapolis, IN) to separate double-stranded oligonucleotide from unincorporated label.

Integrase Assay. Integrase was preincubated with inhibitor at 30 °C for 30 min at a final concentration of 200 nM in reaction buffer [50 mM NaCl, 1 mM HEPES, pH 7.5, 50 μM EDTA, 50 μM dithiothreitol, 10% glycerol (w/v), 7.5 mM $MnCl_2$, 0.1 mg/mL bovine serum albumin, 10 mM 2-mercaptoethanol, 10% dimethyl sulfoxide, and 25 mM MOPS, pH 7.2]. Following preincubation, 5′-end ^{32}P-labeled linear oligonucleotide substrate was added and incubation was continued for an additional 1 h. Reactions were quenched by addition of an equal volume (16 μL) of loading dye (98% deionized formamide, 10 mM EDTA, 0.025% xylene cyanol, and 0.025% bromophenol blue), and an aliquot (5 μL) was electrophoresed on a denaturing 20% polyacrylamide gel (0.09 M Tris-borate, pH 8.3, 2 mM EDTA, 20% acrylamide, and 8 M urea). Gels were dried, exposed in a Molecular Dynamics phosphorimager cassette, and analyzed using a Molecular Dynamics phosphorimager (Sunnyvale, CA). Percent inhibition was calculated using the equation: $100 \times [1 - (D - C)/(N - C)]$, where C, N, and D are the fractions of 21-mer substrate converted to 19-mer (3′-processed product) or strand transfer product for DNA alone, DNA plus integrase, and integrase plus drug, respectively. Determination of IC_{50} values was achieved by plotting drug concentration versus percent inhibition and measuring the concentration at which 50% inhibition occurred. Results are expressed as the average of three independent experiments ±SE, except for compound **15**, Table 2, which is the result of a single experiment.

Synthesis. Melting points were determined on a Mel Temp II melting point apparatus and are uncorrected. Elemental analyses were obtained from Atlantic Microlab Inc., Norcross, GA, and are within 0.4% of theoretical values unless otherwise indicated. Fast atom bombardment mass spectra (FABMS) were acquired with a VG Analytical 7070E mass spectrometer under the control of a VG 2035 data system. ^{1}H NMR data were obtained on a Bruker AC250 spectrometer (250 MHz) and are reported in ppm relative to TMS and referenced to the solvent in which they were run. Anhydrous solvents were obtained commercially and used without further drying.

3-(4-Hydroxyphenyl)propanoic Acid (7). This compound was obtained commercially.

3-(3-Hydroxyphenyl)propanoic Acid (8). A solution of 3-hydroxycinnamic acid (6.57 g, 40 mmol) in EtOH (50 mL) was hydrogenated over 10% Pd·C (330 mg) under 40 psi of hydrogen in a Parr apparatus (room temperature, 1 h). The reaction mixture was filtered through silica gel, concentrated, and crystallized from benzene:petroleum ether to provide **8** in 96% yield, mp 110.5−112 °C (lit.[20] mp 99−100 °C): ^{1}H NMR ($CDCl_3$) δ 7.16 (m, 1H), 6.77 (m, 1H), 6.68 (m, 1H), 6.66 (m, 1H), 2.91 (t, 2H, $J = 7.8$ Hz), 2.66 (t, 2H, $J = 7.8$ Hz); IR (KBr) 3494, 2934, 1684, 1283, 1225 cm^{-1}.

3-(3,5-Dimethoxyphenyl)propanoic Acid (9). Hydrogenation of 3,5-dimethoxycinnamic acid as outlined above for the preparation of compound **8** [EtOH:EtOAc (1:1), 1 h] provided **9** in 86% yield, mp 60.5−61.5 °C: ^{1}H NMR ($CDCl_3$) δ 6.35 (d, 2H, $J = 2.2$ Hz), 6.31 (t, 1H, $J = 2.2$ Hz), 3.76 (s, 6H), 2.89 (t, 2H, $J = 8.2$ Hz), 2.66 (t, 2H, $J = 8.2$ Hz); IR (KBr) 3450, 2958, 1715, 1598, 1207 cm^{-1}.

3-(3,5-Dihydroxyphenyl)propanoic Acid (10). A mixture of 3-(3,5-dimethoxyphenyl)propanoic acid (**9**) (1.05 g, 5 mmol) and pyridine·HCl (11.56 g, 100 mmol) was heated under argon (180−200 °C, 90 min). Excess pyridine·HCl was distilled off under high vacuum; the residue was mixed with 1 N HCl, extracted (EtOAc), washed with brine, and dried (Na_2SO_4). Concentration and crystallization (EtOAc:hexane) pro-

vided product **10** (510 mg, 56%), mp 145−146 °C: ^{1}H NMR (DMSO-d_6) δ 12.08 (s, 1H), 9.07 (s, 2H), 6.03 (m, 3H), 2.61 (t, 2H, J = 7.3 Hz), 2.66 (t, 2H, J = 7.3 Hz); IR (KBr) 3380, 3299, 2701, 1719, 1676, 1602, 1407, 1306, 1161 cm^{-1}.

3-(4-Hydroxyphenyl)propanoic Acid Pentafluorophenyl Ester (11). A mixture of 3-(4-hydroxyphenyl)propanoic acid (1.66 g, 10 mmol), pentafluorophenol (2.21 g, 12 mmol), and dicyclohexylcarbodiimide (DCC) (2.1 g, 1 mmol) in dioxane (40 mL) was stirred (room temperature, overnight). The mixture was cooled, dicyclohexylurea was removed by filtration, and the filtrate was taken to dryness. Residue was dissolved in a small amount of Et_2O (10 mL) and diluted with petroleum ether (40 mL) to provide crystalline product **11** (3.06 g, 92%), mp 71−73 °C: ^{1}H NMR ($CDCl_3$) δ 7.10 (d, 2H, J = 8.3 Hz), 6.77 (d, 2H, J = 8.3 Hz), 2.95 (m, 4H); IR (KBr) 3444, 2934, 1792, 1524, 1095, 988 cm^{-1}.

3-(3-Hydroxyphenyl)propanoic Acid Pentafluorophenyl Ester (12). Treatment of 3-(3-hydroxyphenyl)propanoic acid (**8**) as described above for the preparation of **11** provided **12** in 96% yield, mp 56−57 °C (Et_2O:petroleum ether): ^{1}H NMR ($CDCl_3$) δ 7.21 (m, 1H), 6.80 (m, 1H), 6.71 (m, 2H), 5.00 (s, 1H), 2.98 (m, 4H); IR (KBr) 3507, 2930, 1774, 1513, 1113, 987 cm^{-1}.

3-(3,5-Dihydroxyphenyl)propanoic Acid Pentafluorophenyl Ester (13). Treatment of 3-(3,5-dihydroxyphenyl)-propanoic acid (**10**) as described above for the preparation of **11** provided **13** in 95% yield, mp 95−97 °C (ether:petroleum ether): ^{1}H NMR ($CDCl_3$) δ 6.29 (d, 2H, J = 2.1 Hz), 6.22 (t, 1H, J = 2.1 Hz), 2.95 (m, 4H).

6-Methoxy-2-naphthoic Acid (14). This compound has been previously prepared.[21]

6-Hydroxy-2-naphthoic Acid (15). This compound has been previously prepared.[21]

6,7-Dimethoxy-2-naphthoic Acid (16). This compound has been previously prepared.[15]

6,7-Dihydroxy-2-naphthoic Acid (17). Treatment of **16** (232 mg, 1.0 mmol) with pyridine·HCl as described above for the preparation of **10** and purification by silica gel flash column chromatography (EtOAc:hexane, 2:1) provided **17** (178 mg, 87%), mp 237−238.5 °C (EtOAc:hexane): ^{1}H NMR (DMSO-d_6) δ 13.48 (s, 1H), 10.77 (s, 1H), 10.58 (s, 1H), 9.08 (s, 1H), 8.48 (m, 2H), 8.08 (s, 1H), 7.99 (s, 1H).

5,6-Dimethoxy-2-naphthoic Acid (18). This compound has been previously prepared.[18]

5,6-Dihydroxy-2-naphthoic Acid (19). Treatment of **18** as described above for the preparation of **17** provided **19** in 85% yield, mp 216−218 °C (EtOAc:hexane): ^{1}H NMR (DMSO-d_6) δ 10.11 (s, 1H), 9.69 (s, 1H), 9.02 (s, 1H), 8.40 (s, 1H), 8.04 (d, 1H, J = 8.9 Hz), 7.85 (d, 1H, J = 8.7 Hz), 7.46 (d, 1H, J = 8.8 Hz), 7.36 (d, 1H, J = 8.7 Hz).

Methyl 6-Hydroxy-2-naphthoate (20). To a solution of **15** (188 mg, 1.0 mmol) in anhydrous MeOH (20 mL) was passed HCl gas until saturated. The solution was refluxed overnight, then concentrated, and diluted (EtOAc) and water separated. The resulting solution was dried (Na_2SO_4) and purified by silica gel chromatography [EtOAc:$CHCl_3$ (1:3)] to provide **20** (152 mg, 75%), mp 158−159 °C (EtOAc:hexane): ^{1}H NMR ($CDCl_3$) δ 8.53 (s, 1H), 8.00 (dd, 1H, J = 8.6, 1.7 Hz), 7.84 (d, 1H, J = 8.5 Hz), 7.69 (d, 1H, J = 8.6 Hz), 7.17 (m, 2H), 3.96 (s, 3H).[14]

Methyl 6,7-Dihydroxy-2-naphthoate (21). Treatment of **17** as described above for the preparation of **20** provided **21** in 78% yield, mp 193−195 °C (EtOAc:hexane): ^{1}H NMR ($CDCl_3$) δ 8.39 (s, 1H), 7.88 (dd, 1H, J = 8.7, 2.1 Hz), 7.65 (d, 1H, J = 8.7 Hz), 7.32 (s, 1H), 7.24 (s, 1H), 3.94 (s, 3H); IR (KBr) 3448, 3338, 1687, 1638, 1488 cm^{-1}; FABMS m/z 218 (MH^+). Anal. ($C_{12}H_{10}O_4$) C, H.

6,7-Dihydroxy-2-naphthoic Acid Pentafluorophenyl Ester (22). A solution of **17** (700 mg, 3.4 mmol), pentafluorophenol (692 mg, 4.1 mmol), and DCC (680 mg, 3.4 mmol) in THF (15 mL) was stirred at room temperature overnight, then diluted with petroleum ether (50 mL), and filtered and the filtrate taken to dryness. The resulting syrup was triturated with petroleum ether (30 mL) and cooled and crude product collected by filtration as a tan-colored solid (1.20 g). Purification by silica gel chromatography (10% EtOAc in $CHCl_3$) gave a syrup, which on setting provided **22** as white crystals (691 mg, 55%), mp 171−182 °C: ^{1}H NMR (DMSO-d_6) δ 8 (s, 1H), 7.82 (brs, 2H), 7.41 (s, 1H), 7.27 (s, 1H).

Methyl 5,6-Dihydroxy-2-naphthoic Acid (23). This compound has been previously prepared.[18]

5,6-Dimethoxy-2-naphthoic Acid Pentafluorophenyl Ester (24). Treatment of 5,6-dimethoxy-2-naphthoic acid (**18**) as described above for the preparation of **11** provided **24** in 80% yield, mp 140.5−142 °C (acetone:hexane): ^{1}H NMR ($CDCl_3$) δ 8.72 (d, 1H, J = 1.5 Hz), 8.23 (d, 1H, J = 8.9 Hz), 8.10 (dd, 1H, J = 9.0, 1.6 Hz), 7.78 (d, 1H, J = 9.0 Hz), 7.39 (d, 1H, J = 9.0 Hz), 4.04 (s, 3H), 4.00 (s, 3H).

5,6-Dihydroxy-2-naphthoic Acid Pentafluorophenyl Ester (25). Treatment of 5,6-dihydroxy-2-naphthoic acid (**19**) as described above for the preparation of **11** provided **25** in 77% yield, mp 154−157 °C (acetone:hexane): ^{1}H NMR ($CDCl_3$) δ 8.73 (s, 1H), 8.18 (d, 1H, J = 8.9 Hz), 7.94 (dd, 1H, J = 9.0, 1.6 Hz), 7.62 (d, 1H, J = 8.9 Hz), 7.30 (d, 1H, J = 8.9 Hz).

3,5-Bis(benzyloxy)benzyl Alcohol (26). A mixture of 3,5-dihydroxybenzyl alcohol (14.0 g, 100 mmol), benzyl bromide (30 mL, 250 mmol), and anhydrous K_2CO_3 (48 g, 350 mmol) in DMF was stirred at refluxed (3 h). After cooling, solids were removed by filtration, the filtrate was concentrated, and the residue taken up in EtOAc, washed well successively with H_2O, 10% HCl, saturated $NaHCO_3$, and brine, and then dried (Na_2SO_4). Purification by silica gel flash column chromatography (EtOAc:hexane, 1:3) provided **26** (28.7 g, 90%), mp 72−74 °C (Et_2O:hexane): ^{1}H NMR ($CDCl_3$) δ 7.39 (m, 10H), 6.62 (d, 2H, J = 2.2 Hz), 6.54 (t, 1H, J = 2.2 Hz), 5.03 (s, 4H), 4.69 (s, 1H, -OH), 4.62 (s, 2H); IR ($CHCl_3$) 3368, 2904, 1595, 1450, 1159 cm^{-1}.

3,5-Bis(benzyloxy)benzaldehyde (27). A mixture of **26** (9.6 g, 30 mmol) and activated MnO_2 (18 g, 200 mmol) in CH_2Cl_2 (200 mL) was stirred (room temperature, overnight), filtered, concentrated, and purified by silica gel flash column chromatography (EtOAc:hexane, 1:5) to provide **27** as an oil (8.1 g, 84%): ^{1}H NMR ($CDCl_3$) δ 9.89 (s, 1H), 7.41 (m, 10H), 7.10 (d, 2H, J = 2.3 Hz), 6.85 (t, 1H, J = 2.3 Hz), 5.08 (s, 4H); IR (neat) 1688, 1594, 1351, 1297, 1174 cm^{-1}.

3,5-Bis(benzyloxy)-β-nitrostyrene (28). A solution of **27** (9.6 g, 30 mmol), ammonium acetate (2.6 g, 33 mmol), and nitromethane (3.66 g, 60 mmol) in glacial acetic acid (50 mL) was refluxed (5 h). The solution was cooled to room temperature, diluted with Et_2O (500 mL), and washed with ice-cold H_2O, 10% NaOH, and brine. The organic phase was dried (Na_2SO_4), concentrated, and purified by silica gel flash column chromatography (EtOAc:hexane, 1:3) to provide **28** as an oil (6.5 g, 60%): ^{1}H NMR ($CDCl_3$) δ 7.49 (d, 1H, J = 13.6 Hz), 7.39 (m, 14H), 5.02 (s, 4H); IR (neat) 1738, 1595, 1351, 1341 cm^{-1}.

[2-[3,5-Bis(benzyloxy)phenyl]ethyl]amine (29). A solution of **28** (6.4 g, 17.5 mmol) in CH_2Cl_2 (30 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (1.6 g, 40 mmol) in anhydrous Et_2O (60 mL) at room temperature. The mixture was stirred (2 h); then the reaction was cautiously quenched by dropwise addition of H_2O (2 mL), 15% NaOH (4 mL), and then H_2O (6 mL). The resulting mixture was filtered (silica gel in a sintered glass funnel) and the filter pad eluted with a mixture of EtOAc:MeOH. The filtrate was dried (Na_2SO_4), concentrated in vacuo, and purified by silica gel flash column chromatography ($CHCl_3$:EtOAc, gradient from 1:1 to 0:1; Et_3N was added to final eluent) to provide **29** as a colorless solid (1.67 g, 28%), mp 78−81 °C: ^{1}H NMR ($CDCl_3$) δ 7.39 (m, 10H), 6.48 (t, 1H, J = 2.1 Hz), 6.44 (d, 2H, J = 2.1 Hz), 5.01 (s, 4H), 2.94 (t, 2H, J = 6.7 Hz), 2.68 (t, 2H, J = 6.7 Hz), 1.65 (s, 2H).

3-(4-Hydroxyphenyl)propanoic Acid [β-(4-Hydroxyphenyl)ethyl]amide (30). To a solution of **11** (664 mg, 2.0 mmol) in $CHCl_3$ (8 mL) and DMF (3 mL) were added triethylamine (200 μL, 1.5 mmol) and tyramine (329 mg, 2.4 mmol), and the mixture was stirred (room temperature, 2 h). Solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography [EtOAc:$CHCl_3$ (1:3)] to provide **30** (478 mg, 84%), mp 172−173 °C (EtOAc:hexane): ^{1}H NMR (DMSO-d_6) δ 9.16 (s, 1H), 9.13 (s, 1H), 7.82 (t, 1H, J = 5.5 Hz), 6.96 (d, 2H, J = 8.2 Hz), 6.93 (d, 2H, J = 8.2 Hz), 6.65 (d, 2H, J = 8.2 Hz), 6.64 (d, 2H, J = 8.2 Hz), 3.16 (m,

2H), 2.66 (t, 2H, J = 7.2 Hz), 2.53 (t, 2H, J = 7.6 Hz), 2.26 (t, 2H, J = 7.2 Hz); IR (KBr) 3228, 2940, 1612, 1558, 1515, 1219 cm^{-1}; FABMS m/z 286 (MH^+). Anal. ($C_{17}H_{19}NO_3$) C, H, N.

3-(3-Hydroxyphenyl)propanoic Acid [β-(4-Hydroxyphenyl)ethyl]amide (31). Reaction of **12** and tyramine as described above for the preparation of **30** provided **31** in 91% yield, mp 98−100 °C: ^{1}H NMR (DMSO-d_6) δ 9.24 (s, 1H), 9.16 (s, 1H), 7.85 (t, 1H, J = 5.5 Hz), 7.04 (m, 1H), 6.94 (d, 2H, J = 8.2 Hz), 6.65 (d, 2H, J = 8.2 Hz), 6.57 (m, 3H), 3.16 (m, 2H), 2.71 (t, 2H, J = 7.4 Hz), 2.53 (t, 2H, J = 7.6 Hz), 2.28 (t, 2H, J = 7.4 Hz); IR (KBr) 3332, 2936, 1615, 1545, 1515, 1242 cm^{-1}; FABMS m/z 286 (MH^+). Anal. ($C_{17}H_{19}NO_3 \cdot {}^3/_4H_2O$) C, H, N.

3-(4-Hydroxyphenyl)propanoic Acid [β-[3-(Benzyloxy)phenyl]ethyl]amide (32). Reaction of **11** and 2-[3-(benzyloxy)phenyl]ethylamine[22] as described above for the preparation of **30** provided **32** as a syrup in 95% yield: ^{1}H NMR ($CDCl_3$) δ 7.99 (s, 1H), 7.39 (m, 6H), 6.98 (d, 2H, J = 8.3 Hz), 6.74 (m, 5H), 5.02 (s, 2H), 3.44 (m, 2H), 2.87 (m, 2H), 2.67 (t, 2H, J = 7.2 Hz), 2.35 (t, 2H, J = 7.4 Hz); IR (neat) 3286, 2931, 1664, 1516, 1258 cm^{-1}; FABMS m/z 376 (MH^+).

3-(4-Hydroxyphenyl)propanoic Acid [β-(3-Hydroxyphenyl)ethyl]amide (33). A solution of **32** (182 mg, 0.5 mmol) in 20 mL of EtOH:EtOAc (1:1) was hydrogenated over 10% Pd·C (30 mg) under 40 psi of hydrogen in a Parr apparatus (4 h, room temperature). The reaction mixture was filtered through silica gel, concentrated, and purified by silica gel chromatography [EtOAc:$CHCl_3$ (1:3)] to provide **33** as a syrup (120 mg, 94%): ^{1}H NMR (DMSO-d_6) δ 9.25 (s, 1H), 9.12 (s, 1H), 7.87 (t, 1H, J = 5.5 Hz), 7.05 (m, 1H), 6.96 (d, 2H, J = 8.4 Hz), 6.64 (d, 2H, J = 8.4 Hz), 6.58 (m, 3H), 3.19 (m, 2H), 2.66 (t, 2H, J = 7.1 Hz), 2.56 (t, 2H, J = 7.7 Hz), 2.26 (t, 2H, J = 7.1 Hz); IR (neat) 3333, 2936, 1614, 1590, 1515, 1246 cm^{-1}; FABMS m/z 286 (MH^+).

3-(3-Hydroxyphenyl)propanoic Acid [β-[3-(Benzyloxy)phenyl]ethyl]amide (34). Reaction of **12** and 2-[3-(benzyloxy)phenyl]ethylamine[22] as outlined above for the preparation of **30** provided **34** as a syrup in 96% yield: ^{1}H NMR ($CDCl_3$) δ 7.99 (s, 1H), 7.39 (m, 4H), 7.19 (m, 3H), 6.69 (m, 6H), 5.01 (s, 2H), 3.44 (m, 2H), 2.85 (t, 2H, J = 7.4 Hz), 2.67 (t, 2H, J = 7.8 Hz), 2.38 (t, 2H, J = 7.4 Hz); IR (neat) 3287, 2932, 1664, 1516, 1257 cm^{-1}; FABMS m/z 376 (MH^+).

3-(3-Hydroxyphenyl)propanoic Acid [β-(3-Hydroxyphenyl)ethyl]amide (35). Hydrogenation of **34** (5 h) as outlined above for the preparation of **33** provided **35** as a syrup in 84% yield: ^{1}H NMR (DMSO-d_6) δ 9.24 (s, 2H), 7.89 (t, 1H, J = 5.5 Hz), 7.04 (m, 2H), 6.57 (m, 6H), 3.19 (m, 2H), 2.69 (t, 2H, J = 7.4 Hz), 2.56 (t, 2H, J = 7.8 Hz), 2.29 (t, 2H, J = 7.4 Hz); IR (neat) 3332, 2940, 1620, 1588, 1272 cm^{-1}; FABMS m/z 286 (MH^+). Anal. ($C_{17}H_{19}NO_3 \cdot {}^3/_4H_2O$) C, H, N.

3-(3,5-Dihydroxyphenyl)propanoic Acid [β-(3,4-Dihydroxyphenyl)ethyl]amide (36). Reaction of **13** and 3-hydroxytyramine·HCl as described above for the preparation of **30** provided **36** as a foam in 97% yield: ^{1}H NMR (DMSO-d_6) δ 9.05 (s, 2H), 8.75 (s, 1H), 8.63 (s, 1H), 7.85 (t, 1H, J = 5.4 Hz), 6.59 (m, 1H), 6.40 (d, 2H, J = 7.8 Hz), 6.02 (m, 3H), 3.14 (m, 2H), 2.57 (t, 2H, J = 7.9 Hz), 2.49 (m, 2H), 2.28 (t, 2H, J = 7.9 Hz); IR (KBr) 3318, 2972, 1650, 1602, 1521, 1284 cm^{-1}; FABMS m/z 318 (MH^+). Anal. ($C_{17}H_{19}NO_5 \cdot H_2O \cdot {}^1/_4C_3H_7NO$) C, H, N.

3-(3,5-Dihydroxyphenyl)propanoic Acid [β-[3,5-Bis(benzyloxy)phenyl]ethyl]amide (37). Reaction of **13** and **29** as described above for the preparation of **30** provided **37** as a syrup in 85% yield: ^{1}H NMR (DMSO-d_6) δ 9.06 (s, 2H), 7.89 (t, 1H, J = 5.5 Hz), 7.41 (m, 3H), 7.19 (t, 1H, J = 8.2 Hz), 6.47 (d, 2H, J = 8.2 Hz), 5.05 (s, 4H), 3.24 (m, 2H), 2.58 (m, 4H), 2.24 (t, 2H, J = 7.6 Hz); IR (KBr) 3386, 2932, 1666, 1651, 1538, 1302 cm^{-1}; FABMS m/z 498 (MH^+).

3-(3,5-Dihydroxyphenyl)propanoic Acid [β-(3,5-Dihydroxyphenyl)ethyl]amide (38) and 3-(3,5-Dihydroxyphenyl)propanoic Acid [β-[3-Hydroxy-5-(benzyloxy)phenyl]ethyl]amide (39). Hydrogenation (5 h) of **37** as outlined in the preparation of **33** gave two products as syrups, which were separated by silica gel chromatography (acetone:hexane, 1:1).

38 (69%): ^{1}H NMR (DMSO-d_6) δ 9.09 (s, 2H), 9.07 (s, 2H), 7.89 (t, 1H, J = 5.4 Hz), 6.04 (m, 6H), 3.17 (m, 2H), 2.59 (t, 2H, J = 8.6 Hz), 2.47 (t, 2H, J = 7.5 Hz), 2.25 (t, 2H, J = 8.6 Hz); IR (neat) 3332, 1633, 1566, 1218 cm^{-1}; FABMS m/z 318 (MH^+). Anal. ($C_{17}H_{19}NO_3 \cdot 2{}^1/_2H_2O \cdot {}^1/_2C_3H_6O$) C, H, N.

39 (13%): ^{1}H NMR (DMSO-d_6) δ 9.34 (s, 1H), 9.07 (s, 2H), 7.90 (t, 1H, J = 5.5 Hz), 7.37 (m, 5H), 6.23 (m, 3H), 6.03 (m, 3H), 3.18 (m, 2H), 2.55 (m, 4H), 2.25 (t, 2H, J = 8.5 Hz); IR (neat) 3332, 1633, 1566, 1218 cm^{-1}; FABMS m/z 408 (MH^+).

3-(3,4-Dihydroxyphenyl)propanoic Acid [β-[3,5-Bis(benzyloxy)phenyl]ethyl]amide (40). Reaction of 3-(3,4-dihydroxyphenyl)propanoic acid pentafluorophenyl ester[9] and **29** as described in the preparation of **30** gave **40** as a syrup (97%): ^{1}H NMR (DMSO-d_6) δ 8.71 (s, 1H), 8.61 (s, 1H), 7.87 (t, 1H, J = 5.5 Hz), 7.34 (m, 3H), 6.49 (m, 3H), 5.04 (s, 4H), 3.31 (m, 2H), 2.60 (t, 2H, J = 7.9 Hz), 2.49 (m, 2H), 2.24 (t, 2H, J = 8.5 Hz); IR (KBr) 3294, 2931, 1650, 1594, 1284 cm^{-1}; FABMS m/z 498 (MH^+). Anal. ($C_{31}H_{31}NO_5 \cdot H_2O$) C, H, N.

3-(3,4-Dihydroxyphenyl)propanoic Acid [β-(3,5-Dihydroxyphenyl)ethyl]amide (41) and 3-(3,4-Dihydroxyphenyl)propanoic Acid [β-[3-Hydroxy-5-(benzyloxy)phenyl]ethyl]amide (42). Hydrogenation (5 h) of **40** as outlined above for the preparation of **33** gave two products as syrups, which were separated by silica gel chromatography (acetone:hexane, 1:1).

41 (69%): ^{1}H NMR (DMSO-d_6) δ 9.08 (s, 2H), 8.71 (s, 1H), 8.60 (s, 1H), 7.86 (t, 1H, J = 5.4 Hz), 6.58 (m, 2H), 6.40 (m, 1H), 6.03 (m, 3H), 3.13 (m, 2H), 2.60 (t, 2H, J = 8.5 Hz), 2.47 (m, 2H), 2.23 (t, 2H, J = 8.6 Hz); IR (neat) 3332, 1650, 1566, 1212 cm^{-1}; FABMS m/z 318 (MH^+).

42 (19%): ^{1}H NMR (DMSO-d_6) δ 9.33 (s, 1H), 8.72 (s, 1H), 8.62 (s, 1H), 7.87 (t, 1H, J = 5.4 Hz), 7.40 (m, 6H), 6.58 (m, 2H), 6.43 (m, 1H), 6.23 (m, 2H), 3.18 (m, 2H), 2.45 (m, 4H), 2.24 (t, 2H, J = 8.5 Hz); IR (neat) 3356, 2933, 1701, 1597, 1284 cm^{-1}; FABMS m/z 408 (MH^+). Anal. ($C_{24}H_{25}NO_5 \cdot {}^3/_4H_2O$) C, H, N.

1,3-Bis[3-(4-hydroxyphenyl)propanamido]propane (43). A solution of **11** (332 mg, 1.0 mmol) and 1,3-diaminopropane (37 μL, 0.5 mmol) in anhydrous DMF (4 mL) was stirred (room temperature, overnight), then solvent was removed, and the residue was purified by silica gel flash column chromatography (EtOAc) to provide **43** in 48% yield, mp 225−226 °C (EtOAc:$CHCl_3$): ^{1}H NMR (DMSO-d_6) δ 9.12 (s, 2H), 7.73 (t, 2H, J = 5.5 Hz), 6.96 (d, 4H, J = 8.4 Hz), 6.64 (d, 4H, J = 8.4 Hz), 2.97 (m, 4H), 2.67 (t, 4H, J = 7.2 Hz), 2.27 (t, 4H, J = 7.2 Hz), 1.44 (quintuplet, 2H, J = 6.9 Hz). Anal. ($C_{21}H_{26}N_2O_4 \cdot {}^1/_4H_2O$) C, H, N.

1,3-Bis[3-(3-hydroxyphenyl)propanamido]propane (44). Reaction of **12** and 1,3-diaminopropane as described above for the preparation of **43** provided **44** as a syrup in 56% yield: ^{1}H NMR (DMSO-d_6) δ 9.23 (s, 2H), 7.77 (t, 2H, J = 5.6 Hz), 7.03 (m, 4H), 6.57 (m, 12H), 3.02 (m, 4H), 2.70 (t, 4H, J = 7.1 Hz), 2.19 (t, 4H, J = 7.1 Hz), 1.46 (quintuplet, 2H, J = 6.9 Hz). Anal. ($C_{21}H_{26}N_2O_4 \cdot {}^1/_2H_2O \cdot C_4H_8O_2$) C, H, N.

1,3-Bis[3-(3,5-dihydroxyphenyl)propanamido]propane (45). Reaction of **13** and 1,3-diaminopropane as described above for the preparation of **43** provided **45** as a foam in 58% yield: ^{1}H NMR (DMSO-d_6) δ 9.05 (s, 2H), 7.77 (t, 2H, J = 5.5 Hz), 6.02 (m, 6H), 3.01 (m, 4H), 2.59 (t, 4H, J = 7.1 Hz), 2.25 (t, 4H, J = 7.1 Hz), 1.48 (quintuplet, 2H, J = 6.9 Hz). Anal. ($C_{21}H_{26}N_2O_4 \cdot H_2O$) C, H, N.

1,3-Bis(6-methoxy-2-naphthalenecarboxamido)propane (46). To a solution of 6-methoxy-2-naphthoic acid (**14**) (1.01 g, 5.0 mmol) and pentafluorophenol (1.00 g, 6.0 mmol) in anhydrous Et_2O (100 mL) and dioxane (20 mL) was added DCC (1.03 g, 5.0 mmol). The reaction mixture was stirred (room temperature, overnight), then filtered, and taken to dryness. Trituration with petroleum ether provided the Pfp ester as white crystals contaminated with a small amount of dicyclohexylurea (1.51 g). To a 1.06 g (3 mmol) portion of this compound in $CHCl_3$ was added 1,3-diaminopropane (74 μL, 1.0 mmol). The reaction mixture was stirred (room temperature, 1 h), then anhydrous DMF (10 mL) was added, and the reaction was continued overnight, first at room temperature and then for a second 24 h at 55 °C. Removal of $CHCl_3$ was achieved by rotary evaporation; then DMF was distilled off under high vacuum to provide a snow-white solid, which was triturated with Et_2O and collected by filtration. The resulting

solid (505 mg) was heated in boiling MeOH and filtered while warm to provide **46** as a white solid (383 mg, 87%), mp 259−260 °C: ^{1}H NMR (DMSO-d_6, DCl) δ 8.42 (s, 2H), 7.96−7.84 (m, 6H), 7.37 (d, 2H, J = 2 Hz), 7.21 (dd, 2H, J = 2, 9 Hz), 3.89 (s, 6H), 3.40 (brt, 4H, J = 7 Hz), 1.84 (brt, 2H, J = 7 Hz); FABMS m/z 443 (MH^+). Anal. ($C_{27}H_{26}N_2O_4 \cdot {}^1/_2H_2O$) C, H, N.

1,3-Bis(6-hydroxy-2-naphthalenecarboxamido)propane (47). A mixture of pyridine·HCl (5.0 g) and **46** (133 mg, 0.3 mmol) was heated under argon at 240−250 °C (20 min); then pyridine·HCl was removed by sublimation under high vacuum. The resulting syrup was mixed with H_2O (10 mL) to provide an off-white solid, which was collected by filtration (74 mg). Silica gel chromatography (EtOAc) first eluted 6-hydroxy-2-naphthoic acid side product (30 mg) followed by the product fraction (47 mg). Trituration with petroleum ether provided **47** as a cream-colored amorphous solid (35 mg, 28%). Further purification was achieved by preparative HPLC (Vydac C_{18} peptide and protein preparative column; 10 mL/min; A = H_2O, B = acetonitrile; isocratic, 25% B; retention time 16 min) to yield analytically pure **47** as a white solid (15 mg): ^{1}H NMR (DMSO-d_6, DCl) δ 8.35 (s, 2H), 7.86 (dd, 2H, J = 2, 8 Hz), 7.74 (d, 2H, J = 9 Hz), 7.18−7.14 (m, 4H), 3.44−3.36 (m, 4H), 1.90−1.78 (m, 2H); FABMS m/z 415 (MH^+). Anal. ($C_{25}H_{22}N_2O_4 \cdot 1{}^1/_4H_2O$) C, H, N.

1,3-Bis(6,7-dimethoxy-2-naphthalenecarboxamido)propane (48). To a solution of 6,7-dimethoxy-2-naphthoic acid[15] (**16**) (1.16 g, 5.0 mmol) and pentafluorophenol (1.00 g, 6.0 mmol) in anhydrous THF (40 mL) was added a solution of DCC (1.03 g, 5.0 mmol) in THF (10 mL). The reaction mixture was stirred (room temperature, overnight), then diluted with petroleum ether (100 mL), and filtered. The filtrate was taken to dryness and the residue triturated with petroleum ether to provide the Pfp ester as a cream-colored solid (1.25 g, 63%). To a solution of this ester (995 mg, 2.5 mmol) in anhydrous DMF (6 mL) was added 1,3-diaminopropane (71 μL, 0.83 mmol). The reaction mixture was stirred at 70 °C overnight, and then DMF was distilled off under high vacuum. The residue was suspended in MeOH (15 mL), collected by filtration, and dried, providing **48** in quantitative yield as a white solid (442 mg), mp 248−249 °C: ^{1}H NMR (DMSO-d_6) δ 8.58 (brt, 2H, J = 7 Hz), 8.30 (s, 2H), 7.82 (d, 2H, J = 9 Hz), 7.77 (dd, 2H, J = 2, 9 Hz), 7.38 (s, 2H), 7.37 (s, 2H), 3.92 (s, 6H), 3.90 (s, 6H), 3.45−3.37 (m, 4H), 1.92−1.79 (m, 2H). Anal. ($C_{29}H_{30}N_2O_6$) C, H, N.

1,3-Bis(6,7-hydroxy-2-naphthalenecarboxamido)propane (49). A solution of **22** and 1,3-diaminopropane (28 μL, 0.33 μmol) in anhydrous DMF (2 mL) was stirred at 65 °C overnight. Solvent was removed by vacuum distillation to provide a syrup, which was triturated with Et_2O:petroleum ether and then placed under high vacuum to yield **49** as a foam (128 mg, 82%): ^{1}H NMR (DMSO-d_6) δ 9.90 (brs, 2H), 8.50 (brt, 2H, J = 6 Hz), 8.14 (s, 2H), 7.68−7.60 (m, 4H), 7.21 (s, 2H), 7.16 (s, 2H), 3.50−3.55 (m, 4H), 1.90−1.78 (m, 2H). Anal. ($C_{25}H_{22}N_2O_6 \cdot 1{}^1/_4H_2O$) C, H, N.

Further purification was achieved by preparative HPLC (Vydac C_{18} peptide and protein preparative column; 10 mL/min; A = H_2O, B = acetonitrile; isocratic, 20% B; retention time 5.9 min) to provide a sample of **49** for biological testing.

1,3-Bis(5,6-dimethoxy-2-naphthalenecarboxamido)propane (50). Reaction of 5,6-dimethoxy-2-naphthoic acid pentafluorophenyl ester (**23**) and 1,3-diaminopropane as described above for the preparation of **43** provided **50** in 73% yield, mp 140.5−142 °C (acetonitrile:water): ^{1}H NMR (DMSO-d_6) δ 8.63 (t, 2H, J = 5.5 Hz), 8.39 (s, 2H), 8.02 (d, 2H, J = 8.9 Hz), 7.90 (dd, 1H, J = 9.0, 1.5 Hz), 7.79 (d, 2H, J = 9.1 Hz), 7.53 (d, 2H, J = 9.1 Hz), 3.96 (s, 6H), 3.88 (s, 6H), 3.39 (m, 4H), 1.88 (quintuplet, 2H, J = 6.8 Hz). Anal. ($C_{29}H_{30}N_2O_6 \cdot 1{}^1/_2H_2O$) C, H, N.

1,3-Bis(5,6-dihydroxy-2-naphthalenecarboxamido)propane (51). Reaction of 5,6-dihydroxy-2-naphthoic acid pentafluorophenyl ester (**24**) and 1,3-diaminopropane as described above for the preparation of **43** provided **51** as a foam in 15% yield: ^{1}H NMR (DMSO-d_6) δ 9.57 (s, 2H), 8.99 (s, 2H), 8.55 (t, 2H, J = 5.5 Hz), 8.64 (s, 2H), 8.02 (d, 2H, J = 8.9 Hz), 7.81 (dd, 2H, J = 8.9, 1.5 Hz), 7.38 (d, 2H, J = 8.8 Hz), 7.15 (d, 2H, J = 8.7 Hz), 3.37 (m, 4H), 1.83 (quintuplet, 2H, J = 6.7 Hz). Anal. ($C_{25}H_{22}N_2O_6 \cdot 1{}^1/_2H_2O \cdot {}^1/_4C_3H_7NO$) C, H, N.

References

(1) De Clercq, E. Toward improved anti-HIV chemotherapy: Therapeutic strategies for intervention with HIV infections. *J. Med. Chem.* **1995**, *38*, 2491−2517.

(2) LaFemina, R. L.; Schneider, C. L.; Robbins, H. L.; Callahan, P. L.; LeGrow, K.; Roth, E.; Schleif, W. A.; Emini, E. A. Requirement of active human immunodeficiency virus type 1 integrase for productive infection of human T-lymphoid cells. *J. Virol.* **1992**, *66*.

(3) Sakai, H.; Kawamura, M.; Sakuragi, J.; Sakuragi, S.; Shibata, R.; Ishimoto, A.; Ono, H.; Ueda, S.; Adachi, A. Integration is essential for efficient gene expression of human immunodeficiency virus type 1. *J. Virol.* **1993**, *7*, 1169−1174.

(4) Taddeo, B.; Haseltine, W. A.; Farnet, C. M. Integrase mutants of human immunodeficiency virus type 1 with a specific defect in integration. *J. Virol.* **1994**, *68*, 8401−8405.

(5) Engelman, A.; Englund, G.; Orenstein, J. M.; Martin, M. A.; Craigie, R. Multiple effects of mutations in human immunodeficiency virus type 1 integrase on viral replication. *J. Virol.* **1995**, *69*, 2729−2736.

(6) Katz, R. A.; Merkel, G.; Kulkosky, J.; Leis, J.; Skalka, A. M. The avian retroviral IN protein is both necessary and sufficient for integrative recombination in vitro. *Cell* **1990**, *63*, 87−95.

(7) Craigie, R.; Mizuuchi, K.; Bushman, F. D.; Engleman, S. A. A rapid in vitro assay for HIV DNA integration. *Nucleic Acid Res.* **1991**, *19*, 2729−2734.

(8) Fesen, M. R.; Pommier, Y.; Leteurtre, F.; Hiroguchi, S.; Yung, J.; Kohn, K. Inhibition of HIV-1 integrase by flavones, caffeic acid phenethlyl ester (CAPE) and related compounds. *Biochem. Pharmacol.* **1994**, *48*, 595−608.

(9) Burke, T. R.; Fesen, M. R.; Mazumder, A.; Wang, J.; Carothers, A. M.; Grunberger, D.; Driscoll, J.; Kohn, K.; Pommier, Y. Hydroxylated aromatic inhibitors of HIV-1 integrase. *J. Med. Chem.* **1995**, *38*, 4171−4178.

(10) Mazumder, A.; Gazit, A.; Levitzki, A.; Nicklaus, M.; Yung, J.; Kohlhagen, G.; Pommier, Y. Effects of tyrphostins, protein kinase inhibitors, on human immunodeficiency virus type 1 integrase. *Biochemistry* **1995**, *34*, 15111−15122.

(11) Eich, E.; Pertz, H.; Kaloga, M.; Schulz, J.; Fesen, M. R.; Mazumder, A.; Pommier, Y. (-)-Arctigenin as a lead structure for inhibitors of human immunodeficiency virus type-1 integrase. *J. Med. Chem.* **1996**, *39*, 86−95.

(12) LaFemina, R. L.; Graham, P. L.; LeGrow, K.; Hastings, J. C.; Wolfe, A.; Young, S. D.; Emini, E. A.; Hazuda, D. Inhibition of human immunodeficiency virus integrase by bis-catechols. *Antimicrob. Agents Chemother.* **1995**, *39*, 320−324.

(13) Stanwell, C.; Ye, B.; Yuspa, S. H.; Burke, T. R., Jr. Cell protein cross-linking by erbstatin and related compounds. *Biochem. Pharmacol.* **1996**, *52*, 475−480.

(14) Khorana, M. L.; Pandit, S. Y.; Pishawikar, A. D. Antibacterial and antifungal properties of β-naphthol derivatives VI. *J. Pharm. Sci.* **1967**, *56*, 993−997.

(15) Zee, C. K. Y.; Nyberg, W. H.; Cheng, C. C. Synthesis of 8,9-dialkoxy-substituted tetrahydrobenz[h]isoquinolines. *J. Heterocycl. Chem.* **1972**, *9*, 805−811.

(16) Mazumder, A.; Raghavan, K.; Weinstein, J.; Kohn, K. W.; Pommier, Y. Inhibition of human immunodeficiency virus type-1 integrase by curcumin. *Biochem. Pharmacol.* **1995**, *49*, 1165−1170.

(17) Nicklaus, M. C.; Milne, G.; Burke, T. R. QSAR of Conformationally Flexible Molecules - Comparative Molecular Field Analysis of Protein-Tyrosine Kinase Inhibitors. *J. Comput.-Aided Mol. Des.* **1992**, *6*, 487−504.

(18) Burke, T. R., Jr.; Lim, B.; Marquez, V. E.; Li, Z.-H.; Bolen, J. B.; Stefanova, I.; Horak, I. Bicyclic compounds as ring-constrained inhibitors of protein-tyrosine kinase p56lck. *J. Med. Chem.* **1993**, *36*, 425−432.

(19) Jenkins, T. M.; Engleman, A.; Ghirlando, R.; Craigie, R. A soluble active mutant of HIV-1 integrase. *J. Biol. Chem.* **1996**, *271*, 7712−7718.

(20) Schwenk, E.; Papa, D. *J. Org. Chem.* **1945**, *10*, 232.

(21) Gray, G. W.; Jones, B. The preparation of 4- and 5-n-alkoxy-1-naphthoic and 6- and 7-n-alkoxy-2-naphthoic acids. *J. Chem. Soc.* **1954**, 678−683.

(22) Anderson, W. K.; McPherson, J.; Rick, A. C. *J. Med. Chem.* **1984**, *27*, 1321.

JM960449W