Solid Phase Synthesis of Novel Pyrrolidinedione Analogs as Potent HIV-1 Integrase Inhibitors

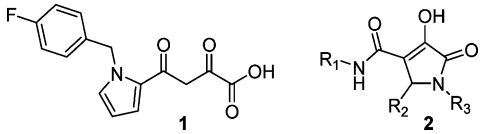
Annapurna Pendri,* Timothy L. Troyer, Michael J. Sofia, Michael A. Walker, B. Narasimhulu Naidu, Jacques Banville, Nicholas A. Meanwell, Ira Dicker, Zeyu Lin, Mark Krystal, and Samuel W. Gerritz

Bristol-Myers Squibb Research and Development, 5 Research Parkway, Wallingford, Connecticut 06492

Received July 15, 2009

A novel series of HIV-1 integrase inhibitors were identified from a 100 member ($4R_1 \times 5R_2 \times 5R_3$) library of pyrrolidinedione amides. A solid-phase route was developed which facilitates the simultaneous variation at R_1, R_2, and R_3 of the pyrrolidinedione scaffold. The resulting library samples were assayed for HIV-1 integrase activity and analyzed to determine the R_1, R_2, and R_3 reagent contributions towards the activity.

The human immunodeficiency virus-1 (HIV-1) remains a highly infectious and incurable disease, but the discovery of chemotherapeutic agents which inhibit HIV-1 replication has provided dramatic improvements in both the quality and duration of life for patients infected with HIV-1. The targets of approved antiretroviral agents are viral enzymes and proteins that are indispensable for the virus to complete its replication cycle, namely, virus entry, fusion, reverse transcription, integration, and proteolytic maturation.[1] The administration of a combination of these medications routinely suppresses the HIV-1 titer to undetectable levels. While the clinical benefit of these combination therapies is considerable, the emergence of multiple drug-resistant viral strains necessitates the discovery of new and improved anti-HIV-1 drugs. HIV integrase is an enzyme involved in the integration of reverse-transcribed viral DNA into host cell DNA. HIV-1 integrase is essential for viral replication, but is absent in host cells, making it a very attractive target for therapeutic intervention. An inhibitor of HIV-1 integrase has proved to be an effective addition to antiretroviral therapy.[2] As part of an effort to prepare heterocyclic variants of the diketoacid inhibitor **1**,[3] the pyrrolidinedione scaffold **2** was identified as a promising HIV-1 integrase inhibitor chemotype.



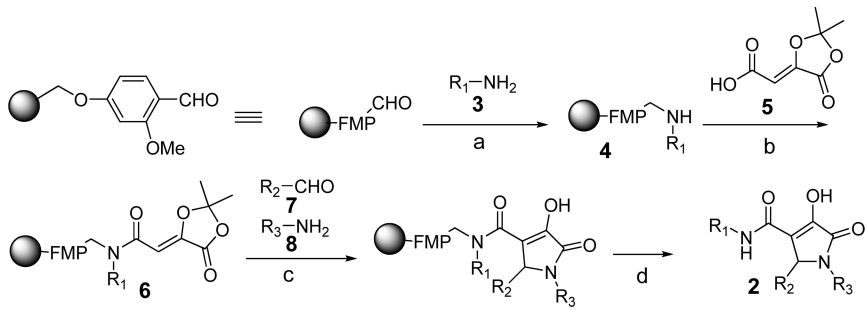
From a library perspective, **2** represents an attractive chemotype because it contains three points of diversity (denoted R_1, R_2, and R_3) which can be accessed using readily available starting materials (vide infra). As outlined in Scheme 1, we have developed a solid-phase synthesis of **2** that facilitates the simultaneous variation of R_1, R_2, and R_3 under mild conditions. The first diversity element (R_1) in **2** was introduced by loading primary amine **3** onto 4-formyl-3-methoxyphenoxy (FMP) resin[4] via standard reductive amination[5] conditions to provide resin-bound amine **4**. The coupling of **4** with 2,2-dimethyl-5-(carboxymethylene)-1,3-dioxolan-4-one **5** using PyBOP afforded resin-bound amide **6**. Amide **6** can also be prepared by the coupling of the acid chloride generated from dioxolanone **5** with **4**. Dioxolanone **5** was readily synthesized from malic acid in five steps via a procedure developed in-house.[6] Amide **6** was then transformed into pyrrolidinedione **9** via a two-step, one-pot Mannich cyclization procedure which efficiently installs the second (R_2) and third (R_3) points of diversity via aldehyde **7** and amine **8**, respectively. This unusual transformation merits additional discussion. In general, the Mannich reaction[7] utilizes three components: an aldehyde, a primary or secondary amine, and a reactant bearing an active hydrogen. In our protocol, dioxolanone amide **6** serves as the active hydrogen component. The R_2 aldehyde component and R_3 amine component for the Mannich reaction constitute the other two diversity elements in the pyrrolidinedione scaffold. Preforming the Schiff base at 75 °C from **7** and **8** using *N*-methylpyrrolidine (NMP) with 20% methanol as the solvent followed by the addition of **6** generated the final compound **2** in 10−30% overall yield, after cleavage from the solid support. Final products were obtained as racemic mixtures and no attempt was made to separate the enantiomers in the present work.

We have observed that a small amount of methanol is required for dioxolanone **6** to undergo the Mannich reaction. We hypothesize that dioxolanone **6** itself is unreactive and methanol converts it to the reactive enol methyl ester in situ. Although we have never isolated the enol ester from the reaction mixture, we have made the following observations with the analogous solution phase reaction: (1) in the absence of methanol the benzamide derivative of dioxolanone **5** does not undergo the Mannich reaction; (2) the corresponding benzamide enol methyl ester (synthesized independently) affords the desired Mannich product; and (3) in methanolic solutions the benzamide derivative of dioxolonone ester **5**

* Corresponding author. Fax: 203-677-7702. E-mail: annapurna.pendri@bms.com.

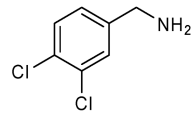
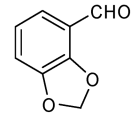
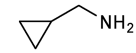
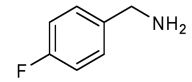
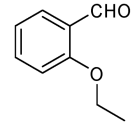
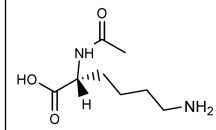
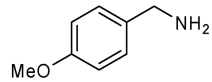
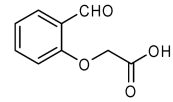
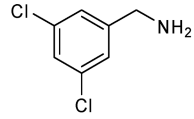
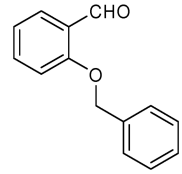
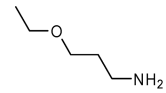
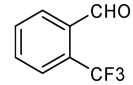
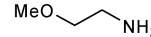
10.1021/cc9001026 CCC: $40.75
Published on Web 11/10/2009

Scheme 1[a]



[a] Reagents and conditions: (a) **3**, 2% HOAc in DMF/$(CH_3O)_3CH$ (7:3), 0.25 M $NaBH(OAc)_3$, 25 °C, 72 h; (b) **5**, PyBOP, DIEA, CH_2Cl_2, 25 °C, 24 h; (c) 0.25 M R_2CHO, 0.2 M R_3NH_2, NMP/CH_3OH (4:1), 75 °C, 2 h, then add **6**, 75 °C, 72 h; (d) 50% TFA/DCM, RT, 1 h.

Table 1. R_1, R_2, and R_3 Reagent Chemsets Utilized for the Synthesis of 100 Analogs of **2**

Chemset Identifier	Reagent **3** (R_1)	Reagent **7** (R_2)	Reagent **8** (R_3)
1			
2			
3			
4			
5			

is readily converted into the corresponding methyl ester. These observations are consistent with our hypothesis.

The application of Mannich chemistry to resin bound substrates has been reported recently.[8] However, the solid-phase synthesis of 4-carboxamido-2,3-pyrrolidinediones via the Mannich reaction is not precedented.[9]

Having developed a general solid-phase route to **2**, we synthesized a 100-member library as a 4 R_1 × 5 R_2 × 5 R_3 array using the reagent chemsets listed in Table 1. Each compound was analyzed by HPLC[10] with UV ($\lambda = 220$ nm) and evaporative light scattering (ELS) detection.[11] The molecular masses of the compounds were determined by MS using a Waters LCT time-of-flight mass analyzer, with a multiplexed electrospray (MUX) four-way source. Of 100 compounds prepared, 75 compounds (75%) passed our criteria of correct mass and ≥80% purity. The crude yields were determined gravimetrically. The overall yield based on initial FMP resin loading for the four step sequence ranged between 10−30%. The yields of representative products were also determined by ^1H NMR, using 2,5-dimethylfuran (DMFu) as an internal standard,[12] and were found to be in close agreement with the gravimetric method.

All 75 library members were tested using a previously described HIV-1 integrase strand transfer inhibition assay,[13] to assess the potency of compounds. In general, this library was quite active; the dose−response HIV integrase inhibition data for all 75 analogs of **2** is provided in the Supporting Information. A summary of the data is illustrated in Table 2-15% of the library members exhibited an $IC_{50} \leq 100$ nM,

Table 2. Sample Counts by Activity Cutoff

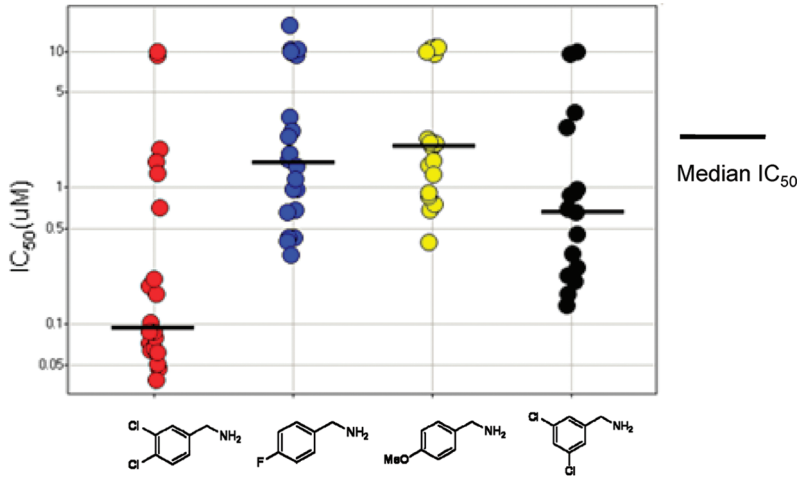
activity cutoff	number of samples (percentage)
≤50 nM	3 (4%)
≤100 nM	11 (15%)
≤250 nM	19 (25%)
≤500 nM	26 (35%)
≤1000 nM	40 (53%)

and more than half of the library members provided submicromolar activity in the integrase assay.

Rather than simply identifying the most potent analogs from the library, we were interested in obtaining a deeper understanding of the underlying structure activity relationships (SARs) by leveraging the statistical analysis opportunities inherent to a library approach. Specifically, each diversity reagent appears in ~15−20 analogs, and this allows the use of traditional statistical techniques to address two key parameters: (1) the overall contribution of each point of diversity (i.e., R_1, R_2, or R_3) to integrase inhibition and (2) the contribution of each reagent within a given point of diversity to integrase inhibition. Our approach to conducting this type of library data analysis is shown in Figures 1−3, where each figure corresponds to a single point of diversity and comprises a "bubble diagram" (constructed using Spotfire™) and a statistical summary table. In our experience, these bubble diagrams display qualitative and quantitative comparisons better than tables alone for large multivariate data sets. For example, two common ways to estimate the center of a set of data are the sample mean and the sample median. As shown in Figure 1, if one compares the mean IC_{50} values, it appears that $R_1\{4\}$ (mean IC_{50} = 2.47 μM) demonstrated a comparable inhibitory profile to that of $R_1\{1\}$ (mean IC_{50} = 1.34 μM). However, comparison of the median IC_{50} values of these two reagents reveals that samples containing $R_1\{4\}$ (median IC_{50} = 0.74 μM) afford substantially weaker integrase activity than samples containing $R_1\{1\}$ (median IC_{50} = 0.09 μM). Visual inspection of the bubble diagram in Figure 1 suggests that the median is more representative of the activity distribution for the R_1 substituents—there are clearly more samples with $IC_{50} < 0.1$ μM for $R_1\{1\}$ than $R_1\{4\}$. The situation is similar for Figures 2 and 3, and thus, a line representing the median is included on each bubble diagram and the median will be used exclusively for all further activity comparisons between substituents.

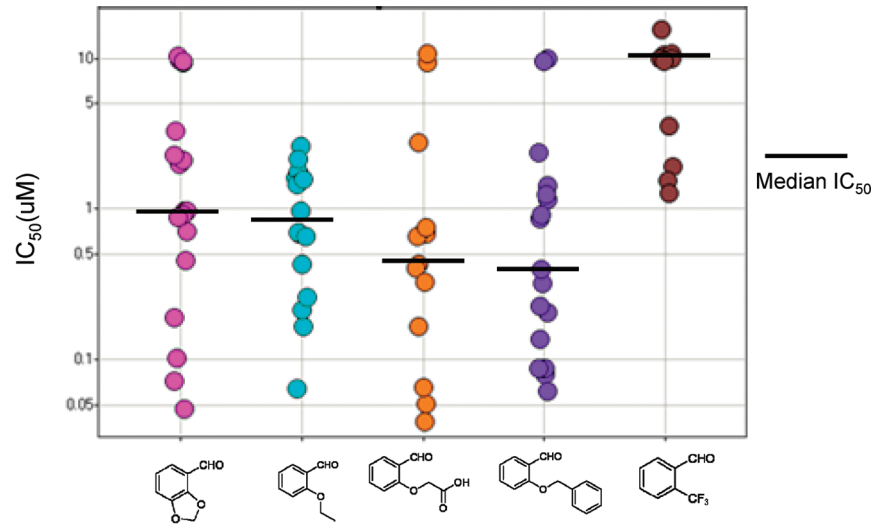
A comparison of Figures 1−3 offers some insight into the relative sensitivity of each point of diversity to structural variation. For example, Figure 1 (R_1) shows a wide range of median IC_{50} values across the four substituents included in the library, whereas the five R_3 substituents in Figure 3 afford similar median IC_{50} values. One interpretation of this data is that the R_3 position is more tolerant to substitution than R_1, and thus, the R_3 position offers an opportunity to modulate other properties (i.e., lipophilicity, metabolic stability) with minimal effect on integrase inhibitory potency.

Further inspection of Figure 1 suggests that the contribution of the R_1 reagent toward integrase inhibitory activity follows the trend $R_1\{1\} > R_1\{4\} > R_1\{2\} = R_1\{3\}$, with the 3,4-dichlorobenzyl group for R_1 ($R_1\{1\}$) conferring optimal potency for HIV-1 integrase inhibition. In fact, this group is incorporated in every sample affording an $IC_{50} < 0.1$ μM. Figure 2 suggests that ortho *O*-alkyl-substituted phenyl groups ($R_2\{1-4\}$) confer equivalent potency, even when one of the groups ($R_2\{3\}$) bears a carboxylic acid and another bears a phenyl ring ($R_2\{4\}$); in contrast, replacement of the O-alkyl group with a CF_3 substituent ($R_2\{5\}$) results in a significant loss of activity. As previously described, variation in the R_3 reagent (Figure 3; $R_3\{1-5\}$) did not significantly affect the activity, but it should be noted that $R_3\{5\}$ did not appear in a single sample with an $IC_{50} < 0.1$ μM. This is particularly interesting in light of the strong structural similarity between $R_3\{4\}$ and $R_3\{5\}$.



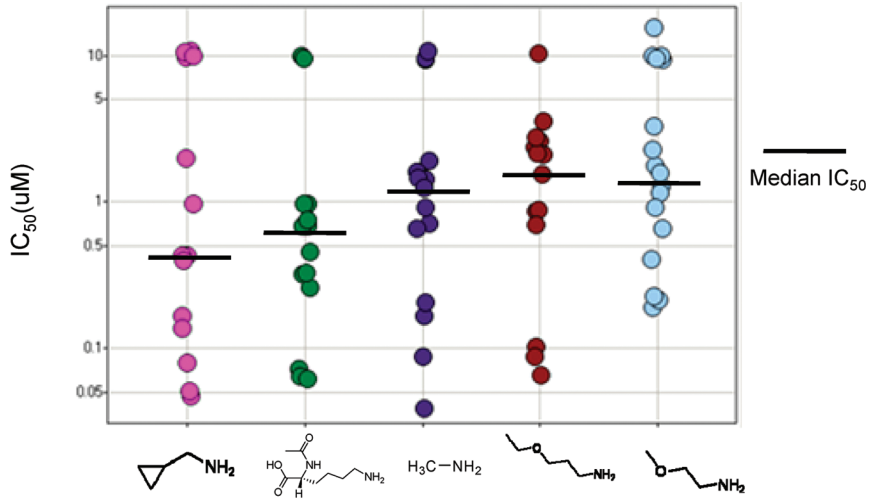
IC_{50}(uM)	$R_1\{1\}$	$R_1\{2\}$	$R_1\{3\}$	$R_1\{4\}$
Mean	1.34	4.05	3.92	2.47
SD	3.01	4.76	4.08	3.70
Median	0.09	1.57	2.03	0.74
N	20	21	17	17

Figure 1. Library analysis of R_1 reagents vs integrase IC_{50} (IC_{50} values are represented in log scale on the *y* axis).



IC_{50}(uM)	R_2{*1*}	R_2{*2*}	R_2{*3*}	R_2{*4*}	R_2{*5*}
Mean	3.05	1.02	2.03	1.75	7.86
SD	3.91	0.77	3.60	3.17	4.67
Median	0.96	0.74	0.42	0.39	10
N	18	15	13	17	12

Figure 2. Library analysis of R_2 reagents vs integrase IC_{50} (IC_{50} values are represented in log scale on the *y* axis).



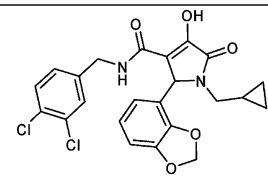
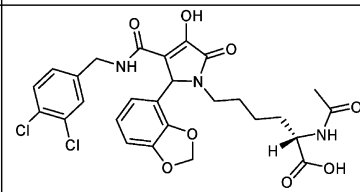
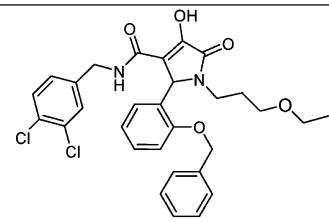
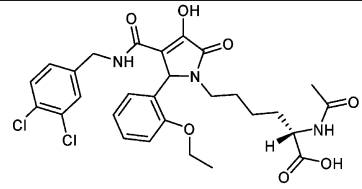
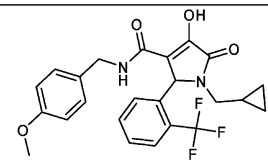
IC_{50}(uM)	R_3{*1*}	R_3{*2*}	R_3{*3*}	R_3{*4*}	R_3{*5*}
Mean	3.64	1.84	2.70	2.11	4.13
SD	4.73	3.57	3.82	2.50	4.99
Median	0.42	0.56	1.28	1.8	1.66
N	15	14	15	14	17

Figure 3. Library analysis of R_3 reagents vs integrase IC_{50} (IC_{50} values are represented in log scale on the *y* axis).

A significant outcome of this study is the observation that the previously unexplored R_2 position afforded a number of potent compounds and thus provided a novel vector on the pyrrolidinedione scaffold. Additionally, this study revealed that variation in the R_3 position has minimal effect on potency, suggesting that this group can be varied to impart better pharmaceutical properties to the molecule. Several active samples from the library were resynthesized and purified by preparative HPLC and the IC_{50} values were determined (Table 3). The close correlation observed for the IC_{50} values of crude and purified samples suggests that reliable biological data can be obtained from the crude library samples of established purity.

In conclusion, a novel series of HIV-1 integrase inhibitors were identified from a 100 member (4 × 5 × 5) library of pyrrolidinedione amides synthesized on solid support. Even though the original library comprised crude samples (>80% pure by HPLC), the activity of crude and resynthesized samples showed a good correlation. This solid phase synthesis route facilitated the rapid assembly of compounds for SAR exploration at three diversity points on the pyrrolidinedione scaffold and provided access to a relatively

Table 3. IC_{50} Values for Crude and Resynthesized Library Samples

Entry	Sample	Structure	IC_{50} (μM) of Crude Sample	IC_{50} (μM) of Purified Sample
1	**2** {*1,1,1*}		0.050	0.039
2	**2** {*1,1,2*}		0.067	0.029
3	**2** {*1,4,4*}		0.09	0.08
4	**2** {*1,2,2*}		0.057	0.026
5	**2** {*3,5,1*}		11.98	10.33

unexplored vector at R_2. Statistical analysis of library sample biological data using bubble diagrams provides an effective visualizing tool as to the contribution of each point of diversity as well as the contribution of each reagent within a given point of diversity to biological activity.

Experimental Section

Each compound was analyzed by HPLC with UV and ELS detection to determine the purity of the compounds (conditions: Xterra MS-C18 (2.1 × 50 mm); eluted with 0−100% B, 2.75 min gradient (A = 100% water−0.1% TFA and B = acetonitrile with 0.1% TFA); flow rate at 1 mL/min; UV detection at 220 nm and with evaporative light scattering (ELS) detection. The molecular mass of the compounds were determined by MS (ES) by the formula *m/z* using Waters LCT time-of-flight mass analyzer, with a multiplexed electrospray (MUX) 4-way source.

General Reaction Conditions with MicroKans. IRORI MicroKan technology was used for execution of the 100 member library. Approximately 30 mg (36 μmol) of 4-formyl-3-methoxyphenoxy (FMP) resin, (Polymer Laboratories, 1.2 mmol/g, 75−150 uM mesh) and an Rf tag were loaded into each MicroKan using the IRORI dry-resin loader and Rf tag dispenser. All MicroKans were sorted into bins for each diversity step using the IRORI AutoSort 10K. After every reaction, the solvent was drained from the reaction vessel, and each reaction batch was rinsed with DMF (2×). The MicroKans were combined and then washed in the IRORI Wash Station for thorough washing. Each wash included two degas cycles where a vacuum was applied to remove air pockets from the MicroKans and two cycles of stirring for 10 min. Finally MicroKans were washed with DMF (2×), 1:1 DMF-MeOH (2×), and DCM (3×). MicroKans were dried under vacuum for 12 h in a vacuum oven at 30 °C before each reaction. Cleavage of the final products from the resin was performed in Bohdan Mini Blocks.

General Procedure for Reductive Amination (step 1). Twenty-five MicroKans in a 100 mL glass bottle were suspended in 2% HOAc in DMF/TMOF (50 mL), and the appropriate R_1 amine (13.5 mmol, 15 X) and $NaBH(OAc)_3$

(13.5 mmol, 15 X) added to make a 0.25 M solution and shaken for 72 h. The solvent was drained into a solvent waste, followed by initial wash with DMF (40 mL) in the reaction vessel. After the initial wash, all the MicroKans were pooled in the IRORI auto washer washed as described above.

General Procedure for Acylation. The MicroKans after the step 1 reaction and washing were pooled into a 500 mL glass bottle and were suspended in anhydrous DCM (250 mL). To this suspension was added 2,2-dimethyl-5- (carboxymethylene)-1,3-dioxalan-4-one (**3**) (2X, 1.548 g, 9 mmol), PYBOP (2X, 4.68 g, 9 mmol), and iPr_2NEt (2.3 g, 18 mmol). The MicroKans were shaken for 48 h at room temperature. The solvent was drained and the MicroKans were washed in the IRORI Wash Station as described.

General Procedure for Cyclization. Imines were preformed in 20 mL reaction vials by heating a 0.25 M solution of R_2 aldehyde (40 μmol) and R_3 amine (36 μmol) in a 1.1:1 ratio in NMP (1 mL) containing 20% methanol at 70−80 °C for 2 h using a turbo coil. The MicroKans from step 2 were sorted into 5 separate bins using the IRORI Autosorter. These were added to the reagent vials containing preformed imine and the reaction vessels were heated with agitation at 80 °C for 72 h. The MicroKans were pooled in the IRORI Wash Station and washed successively with DMF, DMF/MeOH (1:1), THF, DCM, and dried in a vacuum oven.

General Procedure for Final Cleavage. The MicroKans from step 3 were sorted into 48 well Red and Blue Bohdan Mini Blocks fitted with polypropylene tubes. The cleavage solution (1.5 mL, trifluoroacetic acid, DCM 1:1) was added, and the MicroKans were shaken for 60 min. Products in the cleavage solution in both Red and Blue Mini Blocks were drained into a 96 deep-well block. MicroKans were rinsed with methanol for 20 min, and the combined solutions were dried under reduced pressure. The residues were dissolved in MeOH and analyzed by HPLC (conditions: Xterra MS-C18 (2.1−50 mm); eluted with 0−100% B, 2.75 min gradient (A = 100% water−0.1% TFA and B = acetonitrile with 0.1% TFA); flow rate at 1 mL/min. UV detection at 220 nm. The molecular mass of the compounds were determined by MS (ES) by the formula *m/z* using Waters LCT time-of-flight mass analyzer, with a multiplexed electrospray (MUX) 4-way source.

General Procedure for the Purification of Resynthesized Compounds. Five samples from Table 3 entries 1−5 were resynthesized on solid support using loose resin. The resulting product was purified by chromatography (YMC Combiprep ODS-A, 30 mm × 50 mm, MeOH/H_2O/0.1% TFA) to yield the title compounds: entry 1 (36 mg, 21% yield), entry 2 (34 mg, 10% yield), entry 3 (56 mg, 27% yield), entry 4 (65 mg, 10% yield), entry 5 (56 mg, 18% yield).

Analytical Data for Selected Compounds. Entry 1: 2{*1,1,1*}. ^{1}H NMR 500 MHz (MeOD) δ (ppm): 0.25−0.5 (4H, m, cyclopropyl), 0.9 (1H, m, cyclopropyl), 2.5 (2H, m, CH_2), 4.29−4.38 (2H, m, CH_2), 5.463 (1H, s, CH), 5.845−5.863 (2H, m, OCH_2), 6.732−6.758 (3H, m, aromatic), 7.266−7.341 (3H, m, aromatic), LCMS, RT 2.587 min, [M + H] 475.23 and 477.22.

Entry 2: 2{*1,1,2*}. ^{1}H NMR 500 MHz (MeOD) δ (ppm): 1.3−1.9 (6H, m, CH_2), 1.992 (3H, s, CH_3), 2.68 (2H, m, CH_2), 3.71 (m, 1H), 4.29−4.5 (2H, m, CH_2), 5.463 (1H, s, CH), 5.943−5.962 (2H, m, OCH_2), 6.6−6.829 (3H, m, aromatic), 6.829−7.412 (3H, m, aromatic), LCMS, RT 2.277 min, [M + H] 592.09 and 594.07.

Entry 3: 2{*1,4,1*}. ^{1}H NMR 500 MHz (MeOD) δ (ppm): 0.95 (3H, bS, CH_3), 1.564−1.68 (2H, m, CH_2), 2.6−2.89 (2H, m, CH_2), 3.4−3.42, (2H, m, CH_2), 3.54−3.58, (2H, m, CH_2), 4.19−4.337 (2H, q, CH_2), 5.0−5.07 (m, 2H, OCH_2), 5.883 (1H, s, CH), 6.5−7.2 (12H, m, aromatic), LCMS, RT 2.207 min, [M + H] 569.12 and 571.12.

Entry 4: 2{*1,2,2*}. ^{1}H NMR 500 MHz (MeOD) δ (ppm): 1.1−1.657 (9H, m, CH_2, CH_3), 1.895 (3H, s, CH_3), 2.68 (2H, m, CH_2), 3.71 (m, 1H), 3.9−4.1(2H, m, OCH_2) 4.2−4.4 (2H, m, CH_2), 5.83 (1H, s, CH), 6.8−7.082 (3H, m, aromatic), 7.311−7.415 (4H, m, aromatic), LCMS, RT 2.420 min, [M + H] 592.32.

Entry 5: 2{*3,5,1*}. ^{1}H NMR 500 MHz (MeOD) δ (ppm): 0.2−0.4 (4H, m, cyclopropyl), 0.6 (1H, m, cyclopropyl), 2.8−3.0 (2H, m, CH_2), 3.58 (3H, s, OCH_3), 4.2−4.4 (2H, m, CH_2), 5.549 (1H, s, CH), 6.646−6.663 (2H, m, aromatic),6.937−6.954 (3H, m, aromatic) 7.3−7.4 (2H, m, aromatic), 7.6 (1H, m, aromatic), LCMS, RT 2.505 min, [M + H] 461.31.

Acknowledgment. The authors would like to thank Peter Tidswell, Thomas Swann, Marianne Vath, and Scott Lapaglia for the analysis of the library.

Supporting Information Available. ^{1}H NMR data of purified compounds followed by LCMS data (UV absorbance, TIC, and mass spectrum). This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Greene, W. C.; Debyser, Z.; Ikeda, Y.; Freed, E. O.; Stephens, E.; Yonemoto, W.; Buckheit, R. W.; Este, J. A.; Cihlar, T. *Antiviral Res.* **2008**, *80*, 251–265. (b) Young, S. D. *Annu. Rep. Med. Chem.* **2003**, *38*, 173–182. (c) De Clercq, E. *Int. J. Biochem. Cell Biol.* **2004**, *36*, 1800–1822. (d) Este, J. A. *Curr. Med. Chem.* **2003**, *10*, 1617–1632.

(2) (a) Nair, V.; Chi, G. *Rev. Med. Virol.* **2007**, *17*, 277–295. (b) Evering, T. H.; Markowitz, M. *Expert Opin. Invest. Drugs* **2008**, *17*, 413–422. (c) Pais, G. C. G.; Burke, T. R., Jr. *Drugs Future* **2002**, *27*, 1101–1111. (d) Chiu, T. K.; Davies, D. R. *Curr. Top. Med. Chem.* **2004**, *4*, 965–979.

(3) Wai, J. S.; Egbertson, M. S.; Payne, L. S.; Fisher, T. E.; Embrey, M. W.; Tran, L. O.; Melamed, J. Y.; Langford, H. M.; Guare, J. P., Jr.; Zhuang, L.; Grey, V. E.; Vacca, J. P.; Holloway, M. K.; Naylor-Olsen, A. l. M.; Hazed, D. J.; Felock, P. J.; Wolfe, A. L.; Stillmock, K. A.; Schleif, W. A.; Gabryelski, L. J.; Young, S. D. *J. Med. Chem.* **2000**, *43*, 4923–4926.

(4) Boojamra, C. G.; Burow, K. M.; Thompson, L. A.; Ellman, J. A. *J. Org. Chem.* **1997**, *62*, 1240–1256.

(5) Bilodeau, M. T.; Cunningham, A. M. *J. Org. Chem.* **1998**, *63*, 2800–2801.

(6) (a) Walker, M. A.; Ma, Z.; Naidu, B. N.; Sorenson, M. E.; Pendri, A.; Banville, J.; Plamondon, S.; Remillard, R. HIV Integrase Inhibitors. WO 2004004657. (b) Walker, M. A.; Banville, J.; Plamondon, S.; Remillard, R. HIV Integrase Inhibitors. WO 2004004657. For previous methods for the synthesis of pyrrolidinones. (a) Pace, P.; Spieser, S. A. H.; Summa, V. *Bioorg. Med. Chem. Lett.* **2008**, *8*, 3865–3869. (b) Kawasuji, T.; Fuji, M.; Yoshinaga, T.; Sato, A.; Fujiwara, T.; Kiyama, R. *Bioorg. Med. Chem. Lett.* **2007**, *15*, 5487–

5492. (c) Davam, R.; Al-Mawsawi, L. Q.; Neamati, N. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6155–6159. (d) Madhav, R.; Snyder, Carroll, A.; Southwick, P. L. *J. Heterocycl. Chem.* **1980**, *17*, 1231–1235. (e) Campbell, J. B.; Firor, J. W. *J. Org. Chem.* **1995**, *60*, 7687–7689. (f) Larsen, S. D.; Spilman, C. H.; Bell, F. P.; Dinh, D. M.; Martinborough, E.; Wilson, G. J. *J. Med. Chem.* **1991**, *34*, 1721–1727. (g) Mylari, B. L.; Beyer, T. A.; Siegel, T. W. *J. Med. Chem.* **1991**, *34*, 1011–1018. (h) Baldwin, J. E.; Chan, M.; Fai; Gallacher, G.; Otsuka, M. *Tetrahedron* **1984**, *40*, 4513–4526. (i) Southwick, S. *J. Am. Chem. Soc.* **1949**, *71*, 2532–2537.

(7) (a) Ma, D.; Ma, J.; Ding, W.; Dai, L. *Tetrahedron: Asymm.* **1996**, *7*, 2365–2370. (b) Besbes, R.; Villieras, M.; Amri, H. *Ind. J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1997**, *36*, 5–8. (c) Campbell, S. E.; Comer, M. C.; Derbyshire, P. A.; Despinoy, X. L. M.; Mcnab, H.; Morrisson, R.; Sommerville, C. C.; Thornley, C. *J. Chem. Soc., Perkin Trans. 1* **1997**, *15*, 2195–2202. (d) Manabe, K.; Mori, Y.; Kobayashi, S. *Synlett* **1999**, *9*, 1401–1402.

(8) (a) Kobayashi, S.; Moriwaki, M.; Akiyama, R.; Suzuki, S.; Hachiya, I. *Tetrahedron Lett.* **1996**, 7783–7786. (b) Youngman, M. A.; Dax, S. L. *Tetrahedron Lett.* **1997**, *38*, 6347–6350. (c) Jonsson, D.; Molin, H.; Unden, A. *Tetrahedron Lett.* **1998**, *39*, 1059–1062. (d) Zhang, H. C.; Brumfield, K. K.; Jaroslova, I. *Tetrahedron Lett.* **1998**, *39*, 4449–4452.

(9) Solid phase synthesis of 3-acyl-2,4-pyrrolidinediones was reported using amino acid ester loaded Merrifield resin, an aldehyde and Meldrum's acid. Romoff, T. T.; Ma, L.; Wang, Y.; Campbell, D. A. *Synlett.* **1998**, *12*, 1341–1342.

(10) HPLC conditions: Xterra MS-C18 (2.1 × 50 mm); eluted with 0−100% B, 2.75 min gradient (A = 100% water−0.1% TFA and B = acetonitrile with 0.1% TFA); flow rate at 1 mL/min.

(11) Kyranos, J. N.; Lee, H.; Goetzinger, W. K.; Li, L. Y. T. *J. Comb. Chem.* **2004**, *6*, 796–804.

(12) Gerritz, S. W.; Sefler, A. M. *J. Comb. Chem.* **2000**, *2*, 39–41.

(13) (a) Walker, M. A.; Johnson, T.; Ma, Z.; Banville, J.; Remillard, R.; Kim, O.; Zhang, Y.; Staab, A.; Wong, H.; Torri, A.; Samanta, H.; Lin, Z.; Deminie, C.; Terry, B.; Krystal, M.; Meanwell, N. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2920–2924. (b) Engelman, A.; Craigie, R. *J. Virol.* **1995**, *69*, 5908–5911.

CC9001026