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Discovery of a 1,5-dihydrobenzo[*b*][1,4]diazepine-2,4-dione series of inhibitors of HIV-1 capsid assembly

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ABSTRACT

The discovery of a 1,5-dihydrobenzo[*b*][1,4]diazepine-2,4-dione series of inhibitors of HIV-1 capsid assembly is described. Synthesis of analogs of the 1,5-dihydrobenzo[*b*][1,4]diazepine-2,4-dione hit established structure–activity relationships. Replacement of the enamine functionality of the hit series with either an imidazole or a pyrazole ring led to compounds that inhibited both capsid assembly and reverse transcriptase. Optimization of the bicyclic benzodiazepine scaffold to include a 3-phenyl substituent led to lead compound **48**, a pure capsid assembly inhibitor with improved antiviral activity.

The status of the HIV/AIDS epidemic has evolved with time and by many estimates the global adult prevalence of HIV has stabilized at slightly less than one percent of the world population.[1] Highly active antiretroviral therapy (HAART) has improved the prognosis and quality of life for individuals living with HIV such that the disease is now thought of as a manageable, chronic disorder with life expectancy estimated as great as twenty years from the start of HAART. Currently, there are twenty five approved direct-acting antiretrovirals for the treatment of HIV and the majority of them fall into either the nucleoside reverse transcriptase inhibitor (NRTI), non-nucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitor (PI) mechanistic class. In spite of this impressive arsenal of treatment options for HIV infected individuals, the development of resistance, patient compliance and drug tolerability are major factors that challenge the management of HIV. In response to emerging cross-resistance within mechanistic classes and multi-drug resistance in general, discovery efforts have gradually shifted away from these major drug classes, giving rise to marketed drugs with new mechanisms of action, such as the CCR5 antagonist maraviroc[2] and the integrase (IN) inhibitor raltegravir.[3]

As part of our own interest in this area, we recently disclosed the identification of two structurally distinct chemical series that inhibit the assembly of the viral capsid protein p24 (CA).[4] The assembly of CA is an essential step in HIV life cycle and thus presents an opportunity for small molecules to disrupt viral replication.[5] After budding of immature HIV virions, proteolytic cleavage of the Gag polyprotein yields matrix (MA), CA, nucleocapsid (NC) and p6, which allows for assembly of CA into a conical core that encapsulates the viral RNA complexed with NC, RT and IN. Assembly of CA is driven by three distinct intermolecular protein–protein interactions: (a) interaction between CA *C*-terminal domain (CTD) and CA *N*-terminal domain (NTD); (b) CTD dimerization; and (c) interaction between NTD of adjacent CA molecules.[6] The finding that CA assembly can be recapitulated in vitro has led to the development of a high throughput capsid assembly assay (CAA) that, based on the prior work of Sundquist et al.,[7] employed a recombinant CA-NC protein construct and oligonucleotide template, as previously described.[4,8] Using this assay, we screened a cluster collection of ~13,000 compounds and identified a 1,5-dihydrobenzo[*b*][1,4]diazepine-2,4-dione hit series exemplified by compound **1**. Herein, we describe our efforts toward optimization of this hit and the discovery of potent inhibitors of capsid assembly and viral replication.

The benzodiazepine hit **1** had an IC_{50} value in the CAA of 1.4 μM, but was inactive in a counter screen involving assembly of Rous

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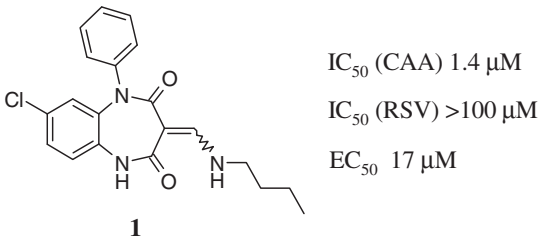


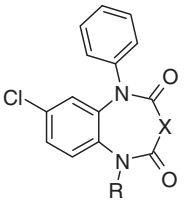
Figure 1. Profile of hit compound **1** identified by screening compound collection using the capsid assembly assay.

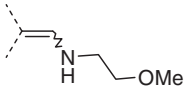
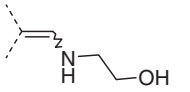
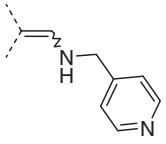
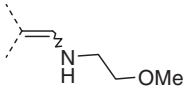
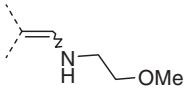
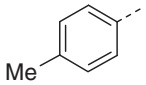
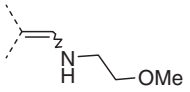
sarcoma virus capsid, consistent with selective inhibition of assembly of only the HIV-1 CA (Fig. 1). Furthermore, compound **1** displayed modest antiviral activity in a viral replication assay, having an EC_{50} value of 17 μM.[9] With these promising results in hand, we prepared analogs of compound **1** in hopes of establishing structure–activity relationships. In doing so, we were particularly concerned with the inherent electrophilicity of the enamine moiety, which could lead to problems of chemical instability and even to conjugation to biomolecules in vivo.

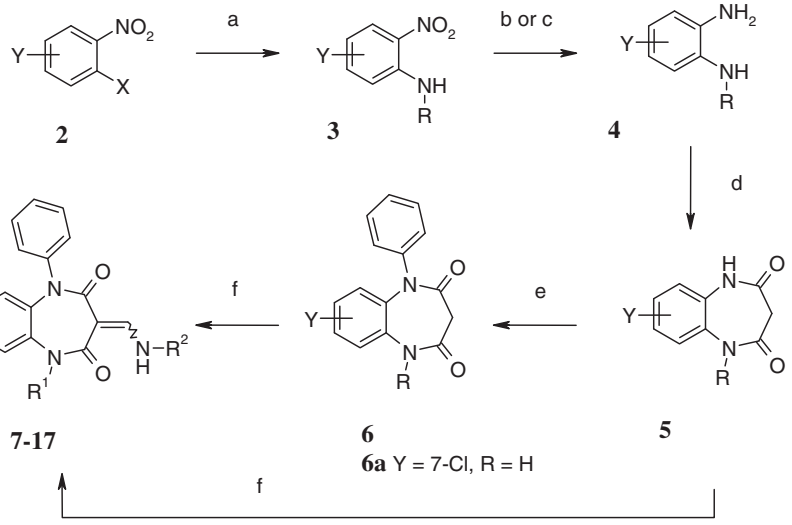
The synthesis of analogs of benzodiazepine **1** is outlined in Scheme 1. The route began with SN_{Ar} of appropriately substituted 2-chloro- or 2-fluoronitrobenzene derivatives **2** with a primary amine, which gave nitroanilines **3**. The nitro group of compounds **3** was then reduced to give substituted phenylenediamines **4**, which then participate in a cyclization reaction to give benzodiazepines **5**. If R^1 was a hydrogen (i.e., compounds **6a**–**9**), then aniline was used in the SN_{Ar} reaction to give compounds **3** (i.e., R = Ph) and compounds **5** were directly converted to the final inhibitors (i.e., compounds **7**–**9**). If R^1 was a small alkyl group, the N1 phenyl group was installed using copper mediated arylation of the anilide as originally described by Barton,[10] where the phenyl group was transferred from triphenylbismuth. Finally, the enamine substituent at the 3-position was introduced via a three-component condensation between compounds **6**, Bredereck's reagent and a primary amine to give inhibitors **10**–**17**.

We began developing SAR in this series with modification of the enamine substituent at the 3-position of the benzodiazepine core (Table 1). It was noteworthy that the enamine functionality was important for potency since the C3 unsubstituted analog **6a** suffered a complete loss of potency in the CAA. In general, we observed flexibility in the size and polarity of the substituent on the nitrogen atom of the enamine. For example, the polarity of the group had little effect on inhibition of capsid assembly, as is illustrated by the fact that the butyl side chain of compound **1** could be replaced with the more polar 2-methoxyethyl or 2-hydroxyethyl chains without any loss in potency (cf. compound

Table 1
Effect of modification at the 3- and 5-positions of the benzodiazepine core



	R	X	IC_{50} (μM)
6a	H		>46
7	H		1.4
8	H		0.85
9	H		0.67
10	Me		0.59
11	Et		0.47
12			>9



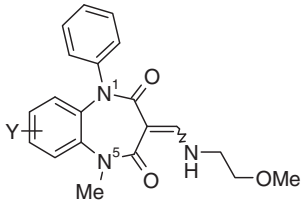
Scheme 1. Synthesis of analogs **7**–**20**. Reagents and conditions: (a) RNH_2, TEA, THF; (b) Fe/AcOH, 100 °C; (c) Sn/aq HCl; (d) simultaneous co-addition of **4**/THF and $CH_2(COCl)_2$/THF into THF; (e) Ph_3Bi, $Cu(OAc)_2$, TEA or pyr, DCM; (f) Bredereck's reagent, 140 °C then R^2NH_2, rt.

1 to compounds **7** or **8**, respectively). We also found that this position tolerated large or small substituents very well, as was illustrated by comparison of compound **7** or **8** to compound **9**. For this study, we also varied the N5 group and the general finding was that small alkyl groups were well tolerated, even leading to moderate improvements in IC_{50} value of 2- to 3-fold (cf. compound **7** to compounds **10** and **11**). However, aromatic groups, such as the *p*-tolyl, led to a dramatic loss in potency (cf. compounds **10** and **12**).

We then conducted several positional scans around the benzene ring of the benzodiazepine core. The case of a chlorine atom was illustrative of the general trends we observed (cf. compounds **10**, **13–15**, Table 2). It was generally found that lipophilic substituents were well tolerated at all positions of the phenyl ring, but the 7-position was convincingly preferred. Having this information, we also conducted a broad screen at the 7-position and found that cyclopropyl and CF_3 might be tolerated as chlorine atom replacements.[11] However, over the course of subsequent investigations, it was found that only the 7-CF_3 and 7-Cl substituents were broadly tolerated and so development of new SAR was narrowed to include just these modifications.

Extensive effort was made to modify the N1–Ph group. Almost all substitutions that were attempted at this position led to a dramatic loss in potency. The only substitutions tolerated on the phenyl ring were the *m*- and *p*-Cl groups, although at a significant loss in potency (Table 3, compounds **18** and **19**, respectively).

Table 2
Effect of 5-, 6-, 7- and 8-substitution on the benzodiazepine core



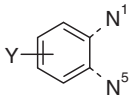
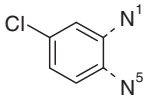
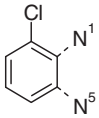
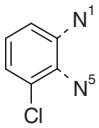
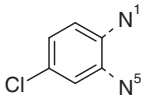
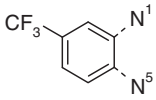
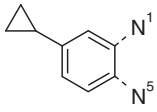
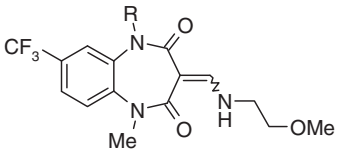
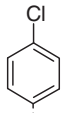
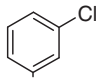
		IC_{50} (μM)
10		0.59
13		0.93
14		2.6
15		1.6
16		0.89
17		1.4

Table 3
Tolerated modifications of the N1 phenyl group



	R	IC_{50} (μM)
18		4.0
19		7.8
20		0.50

However, it was found that substitution of the phenyl group with a 2-thiophenyl group led to an equipotent analog (cf. compound **20** to **10**).

Concurrent with our early hit to lead activity, we conducted detailed NMR and X-ray crystallographic experiments to elucidate the binding mode of this series on the CA-NC protein. These studies revealed that the 1,5-dihydro-benzo[*b*][1,4]diazepine-2,4-diones bind to the NTD of CA.[12] A full account of these studies will be disclosed in due course but two key findings were used to guide the next phase of our lead optimization. First, both of the carbonyl oxygen atoms on the benzodiazepine scaffold participated in hydrogen bonding interactions within the binding pocket. Second, the enamine side chain protruded from the binding pocket, which accounted for broad flexibility encountered during our SAR study. Based on these observations and due to our concern about the enamine functionality (vide supra), we began to search for a modification capable of replacing this functional group. Our solution involved incorporation of a heterocycle that mimicked both the hydrogen bonding interaction and sp^2-character of the C3 atom. A key design consideration was the knowledge that all the enamine inhibitors described above were prepared and tested as mixtures of enamine stereoisomers. This fact prompted us to evaluate the pyrazole isomer exemplified by compound **21** as a N/Ph *trans*-isomer mimic and the imidazole analog **22** as a N/Ph *cis*-isomer mimic (Fig. 2).

The general synthetic strategy used to prepare analogs of both the imidazole and pyrazole scaffold is illustrated in Scheme 2. From heterocyclic amino ester **23**,[13,14] we introduced the N5-alkyl group in the three-step acylation, alkylation and deprotection sequence leading to compound **26**. A nucleophilic aromatic substitution then allowed for the installation of the appropriately substituted benzene ring destined to be part of the benzodiazepine core. The seven-membered ring was then formed through a nitro reduction and concomitant cyclization sequence to provide compound **28**. For the imidazole and pyrazole series, we relied on Barton's Cu/Bi-based chemistry for introduction of the N1-phenyl group. At this stage, the deprotection of the PMB group was done under acidic conditions to give building block **30** and the point of diversity was introduced by mild, regioselective alkylation to give compound **31**.

We first examined structure–activity relationships in the pyrazole series in an effort to mimic the N/Ph *trans*-isomer of the enamine series. The unsubstituted compound **30a** had an IC_{50} value of 0.30 μM in the capsid assembly assay and an EC_{50} of 7.8 μM in

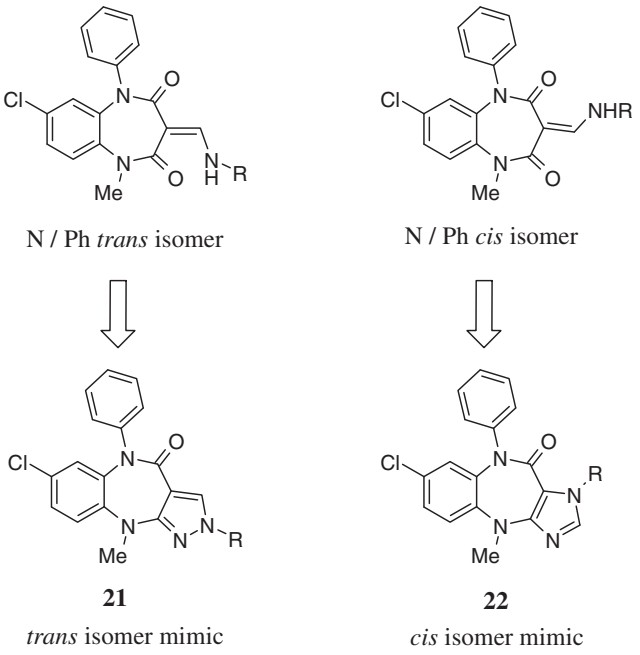
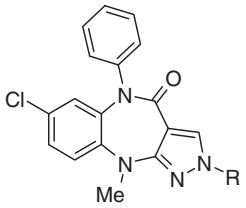


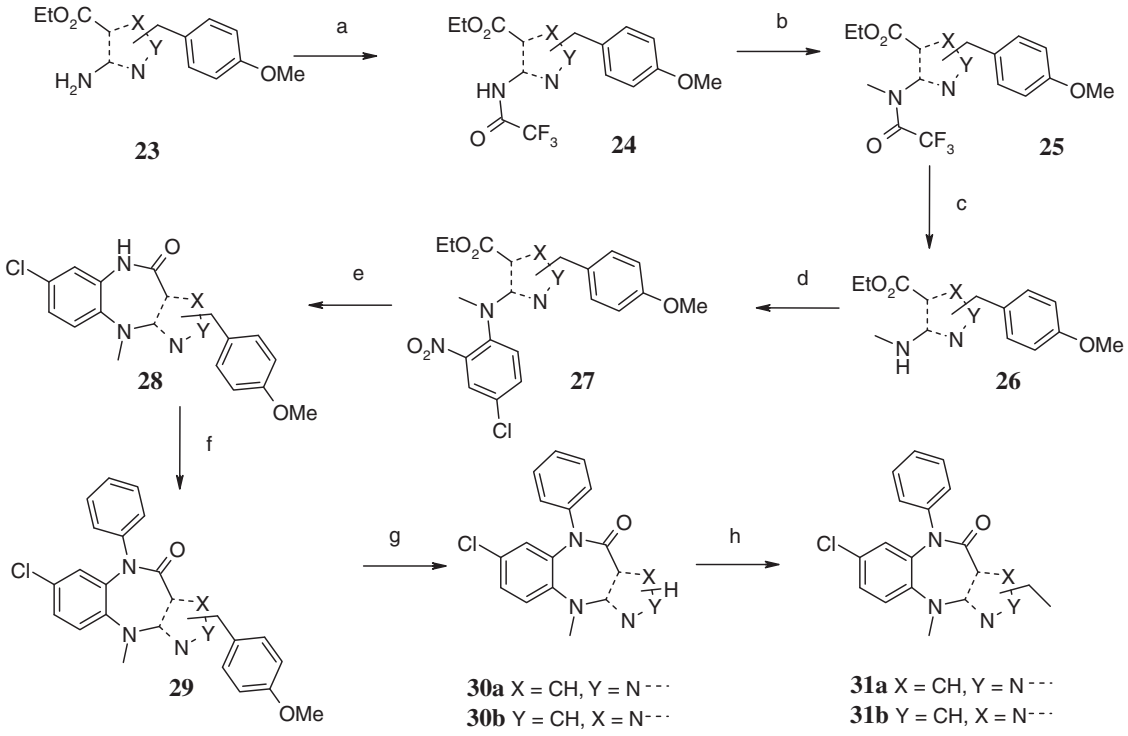
Figure 2. Design of enamine stereoisomer mimics.

Table 4
Effect of pyrazole substitution



	R	IC_{50} (μM)	EC_{50} (μM)
30a	H	0.30	7.8
32	Me	0.7	7.0
31a		2.2	–
33	OMe	1.5	16
34	N	6.8	16
35	N O	1.0	0.90
36	CO_2H	0.60	2.0
37	OH	0.60	4.7

the viral replication assay (Table 4).[15] Addition of a methyl group to give analog **32** led to a 2-fold loss in potency in the CAA, but had no effect on the antiviral activity. However, installation of the slightly larger ethyl group led to a 3-fold increase in the IC_{50} value compared to compound **32**. Similar results were obtained with polar groups that were reminiscent of those used in our investigation of the enamine hit series. For example, incorporation of an ether or dimethylamino group (compounds **33** and **34**) both lead to 5- to 10-fold loss in the CAA, accompanied by similar losses in antiviral potency. However, potency was restored with the larger, aromatic benzyl groups, such as those found in compounds **35**–**37**. Not only were IC_{50} values in the sub-micromolar range for these compounds, but antiviral potency reached the sub-micromolar level for the first time in the case of the basic analog **35**. Although these results were encouraging, it was difficult to account for the

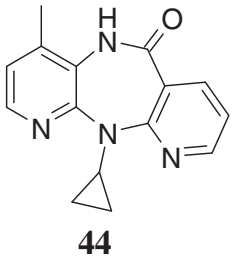


Scheme 2. General synthetic pathway for heterocyclic analogs in Tables 4 and 5. Reagents and conditions: imidazole series X = N, Y = CH; pyrazole series X = CH, Y = N; (a) TFAA, TEA, DCM; (b) MeI, NaHMDS, DMF; (c) NaOEt/EtOH; (d) NaHMDS, 2-fluoro-5-chloronitrobenzene, THF; (e) Fe/AcOH; (f) Ph_3Bi, $Cu(OAc)_2$, Pyr, DCM; (g) TFMSA/TFA; (h) EtI, K_2CO_3, DMF.

relatively steep SAR observed in the pyrazole series without recalling that the N/Ph *cis*-isomer was preferred in our X-ray studies involving the enamine series. With this in mind, we turned our attention to the imidazole series designed to mimic the N/Ph *cis*-enamine isomer.

We began our investigation of the imidazole series by making modifications common to the pyrazole series in order to allow a direct comparison. The unsubstituted analog **30b** was among the most potent analogs tested, having an IC_{50} value similar to that of unsubstituted pyrazole **30a**, but an EC_{50} value about 2-fold lower (Table 5). The SAR began to diverge upon substitution of the imidazole nitrogen, where small alkyl groups were well tolerated, giving lower IC_{50} values compared to similar substitutions explored in the pyrazole series (cf. compounds **38** and **31b** to compound **30b**). Polar substituents were also well tolerated in this series and benzyl groups also improved potency in both the CA assembly and antiviral assays. As with the pyrazole series, the benzylic amine **43** led to analogs that reached sub-micromolar activity in the antiviral assay. Taken together, the results supported the hypothesis that the *cis*-enamine stereoisomer was the more potent of the two.

Over the course of our investigation of the pyrazole and imidazole series, trends in antiviral potency often did not correlate to SAR observed in the CAA. Cognizant of the structural similarity of the pyrazole and imidazole series to that of the NNRTI nevirapine (**44**, Fig. 3), several analogs were profiled in an antiviral assay that used engineered HIV virus having the clinically relevant K103N/Y181C double mutation in reverse transcriptase associated with resistance to NNRTIs. If compounds showed no shift in this assay relative to the one using wild type virus, that would help us rule out a mixed mechanism of action composed of both NNRTI and capsid assembly inhibition. However, if a shift was observed, suggesting some level of inhibition of RT, this might account for the unusual SAR that was emerging in these series. A number of analogs tested did show a shift between the two antiviral assays, and so a full evaluation of the collection of capsid assembly inhibitors was undertaken. The results are presented in Figure 4 as a plot of EC_{50} for the wild type (WT) virus versus EC_{50} for the double mutant (DM) virus. The ideal situation for a series of capsid assembly



44

Figure 3. Structure of the NNRTI nevirapine.

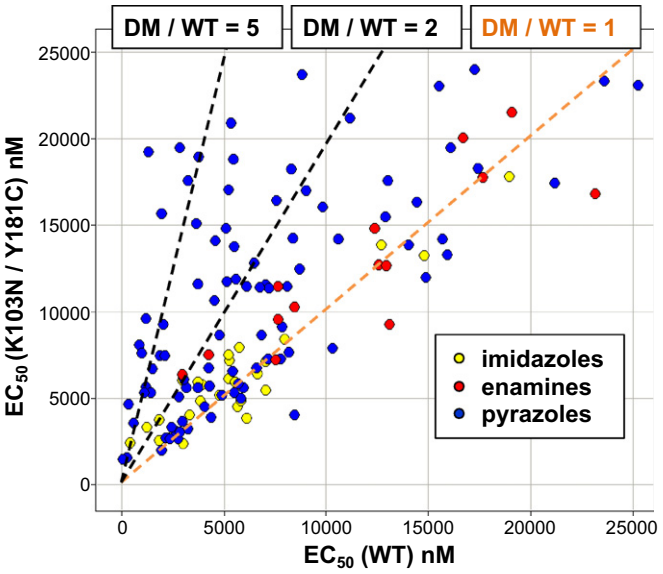
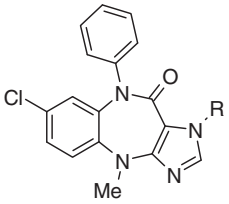


Figure 4. Plot of EC_{50} (K103N/Y181C) versus EC_{50} (WT) for different subseries of capsid assembly inhibitors.

inhibitors is to trend along the orange line in Figure 4 where the shift between the assays is essentially 1. For the pyrazole series (blue circles), the shift was as high as 15-fold between the two assays and Figure 4 shows that this was generally found across the whole series. In the case of the imidazole series (yellow circles), the shift was not as dramatic as with the pyrazole series, but for the most potent compounds, a shift was apparent and could be as high as fivefold. It should be noted that when the results shown in Figure 4 indicated that the NNRTI mechanism may be contributing to antiviral potency, we performed enzymatic assays with WT RT and DM RT and were able to show similar, often more dramatic shifts between the two assays (data not shown). In these cases, this confirmed some contribution of the NNRTI mechanism to antiviral potency and explained the unusual SAR we had observed.

The primary objective of our research program was to discover a new antiretroviral belonging to a novel mechanistic class that could be administered to HIV-infected individuals with no limitation with respect to past treatment history and potential resistance profile. Therefore, we concentrated our effort on the search for a pure capsid assembly inhibitor devoid of inhibition of reverse transcriptase. To move forward, we took a step back from the imidazole and pyrazole series in order to implement a different strategy toward structural replacement of the enamine group. Examination of the data presented in Figure 4 revealed that the original enamine series remained clustered along the orange dotted line, indicating little or no contribution from inhibition of RT to the antiviral activity of these compounds. Furthermore, a remaining avenue that we had not yet investigated was substitution of the C3 atom of the benzodiazepine core that was sp^3-hybridized. In hopes that main-

Table 5
Effect of substitution of the imidazole ring



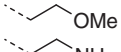
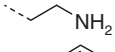
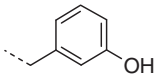
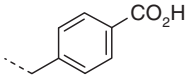
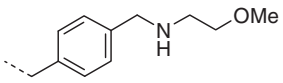
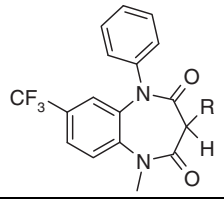
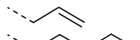
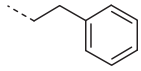
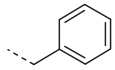
	R	IC_{50} (μM)	EC_{50} (μM)
30b	H	0.21	3.8
38	Me	0.3	2.9
31b		0.22	5.2
39		0.36	5.8
40		0.37	4.8
41		0.56	7.3
42		0.43	6.1
43		0.17	0.90

Table 6
Effect of substituted sp3-C3 on potency

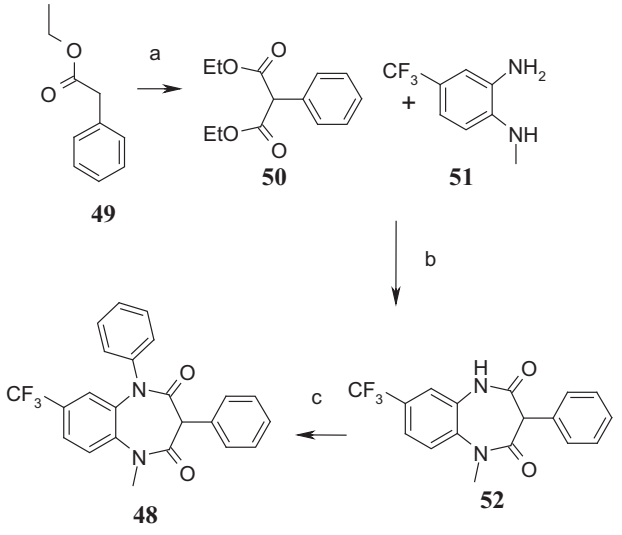


	R	IC_{50} (μM)	EC_{50} WT/DM (μM)	CC_{50} (μM)
45		16	–/–	–
46		10% inhibition @ 1.4	–/–	–
47		40% inhibition @ 3.8	>20/–	–
48		1.2	3.0/2.7	>20

taining a bicyclic scaffold was the key to minimizing the NNRTI mechanism of action, we initiated prospecting efforts that revealed that addition of both simple and more complex alkyl substitutions did not improve potency (Table 6, cf. compounds **45**–**47** to compound **6a**). To our surprise, the directly attached phenyl analog **48** regained the potency lost in the CAA caused by excising the enamine functionality. Furthermore, compound **48** showed good potency in the antiviral assay with an acceptable window versus cytotoxicity and, importantly, showed no shift when the wild type and double mutant assay results were compared.

The synthetic scheme we used to prepare analog **48** is shown in Scheme 3.[16,17] A salient feature of the route included the relatively short sequence from commercially available ethyl ester **49**. Importantly, there are a plethora of commercially available phenyl acetic acid building blocks, which will allow for the rapid introduction of diversity at the 3-position.

In conclusion, we have used our capsid assembly assay to screen a focused collection of compounds and identified a hit series based on a 1,5-dihydrobenzo[*b*][1,4]diazepine-2,4-dione scaffold. Hit-to-lead activity based on hit compound **1** established structure–activity relationships at several positions on the molecular framework. Furthermore, rationally designed replacements of the potentially reactive enamine functional group led to the potent imidazole and pyrazole series of capsid assembly inhibitors. Unfortunately, these two new series displayed a mixed mechanism of action in viral replication assays that involved inhibition of HIV reverse transcriptase.[18] Finally, reinvestigation of the bicyclic benzodiazepine scaffold identified the 3-phenylbenzodiazepine lead candidate showing similar potency to the original hit compound in the capsid assembly assay, a >5-fold improvement in antiviral potency and no inhibition of reverse transcriptase. Importantly, this series is devoid of the enamine functional group, a potential liability from the perspective of in vivo toxicity due to its electrophilic nature. Efforts to optimize this new lead with the objective of identifying a direct-acting antiretroviral that operates through a novel mechanism of action and with a unique resistance profile will be reported in due course.



Scheme 3. Synthesis of 3-phenylbenzodiazepine analog **48**. Reagents and conditions: (a) NC–CO_2Et, NaHMDS; (b) **50** + **51**, μW @ 160 °C, 25 min; (c) Ph_3Bi, $Cu(OAc)_2$, Pyr, DCM.

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References and notes

1. UNAIDS/WHO 'AIDS epidemic update 2009', November, 2009, Geneva, Available online at http://data.unaids.org/pub/Report/2009/JC1700_Epi_Update_2009_en.pdf (Accessed July 16, 2010).
2. For a recent review of this target, including a discussion on maraviroc see: Tilton, J. C.; Doms, R. W. *Antiviral Res.* **2010**, *85*, 91.
3. For a recent review of this target, including a discussion on raltegravir see: McColl, D. J.; Chen, X. *Antiviral Res.* **2010**, *85*, 101.
4. Titolo, S., Mercier, J.-F.; Wardrop, E.; von Schwedler, U.; Goudreau, N.; Lemke, C.; Faucher, A.-M.; Yoakim, C.; Simoneau, .B.; Sundquist, W. I.; Mason, S. 'Discovery of potent HIV-1 capsid assembly inhibitors.' 17th Conference on Retroviruses and Opportunistic Infections 2010. Oral abstract 50.
5. For a comprehensive review of emerging HIV targets, including a detailed discussion of the structure and function of CA, see: Adamson, C. S.; Freed, E. O. *Antiviral Res.* **2010**, 119.
6. (a) Ganser-Pornillos, B. K.; Yeager, M.; Sundquist, W. I. *Curr. Opin. Struct. Biol.* **2008**, *18*, 203; (b) Pornillos, O.; Ganser-Pornillos, B. K.; Kelly, B. N.; Hua, Y.; Whitby, F. G.; Stout, C. D.; Sundquist, W. I.; Hill, C. P.; Yeager, M. *Cell* **2009**, *137*, 1282.
7. Sundquist, W. I.; Wang, H.; Hill, C. P.; Stemmler, T. L.; Davis, D. R.; Alam, S. PCT Int. Appl. WO 2003013425, 2003, p 127.
8. Our modification to the assay described by Sundquist et al. in Ref. 7, and its adaptation to a plate format suitable for high-throughput screening is the subject of a manuscript in preparation.
9. All EC_{50} determinations were made as previously described: see: Yoakim, C.; Deroy, P.; Duplessis, M.; Gagnon, A.; Goulet, S.; Hucke, O.; Lemke, C.; Surprenant, S. PCT Int. Appl. WO 2008067644, 2008, p 90.
10. Barton, D. H. R.; Finet, J. P.; Khamsi, J. *Tetrahedron Lett.* **1986**, *2731*, 3615.
11. Examples of substitutions that lead to dramatic loss in potency included: C-linked amides, N-linked amides, ureas, N-linked sulfonamides, C-linked acylsulfonamides, N-linked imides, amines, carboxylate acid and esters, cyano, methoxy, hydroxyl, methanolyl,benzyl ethers, C2–C4 alkyl, sulfones, heterocycles.
12. Other small molecules that bind to CA_{NTD} and disrupt capsid assembly have been discovered. See the pioneering work of Michael Summers and coworkers: (a) Tang, C.; Loeliger, E.; Kinde, I.; Kyere, S.; Mayo, K.; Barklis, E.; Sun, Y.; Huang, M.; Summers, M. F. *J. Mol. Biol.* **2003**, *327*, 1013; (b) Kelly, B. N.; Kyere, S.; Kinde, I.; Tang, C.; Howard, B. R.; Robinson, H.; Sundquist, W. I.; Summers, M. F.; Hill, C. P. *J. Mol. Biol.* **2007**, *373*, 355; See also: (c) Li, J.; Tan, Z.; Tang, S.; Hewlett, I.; Pang, R.; He, M.; He, S.; Tian, B.; Chen, K.; Yang, M. *Bioorg. Med. Chem.* **2009**, *17*, 3177.
13. (a) For the prior disclosures of the pyrazole derivative see: Bolea, C. PCT Int. Appl. WO 2010079239 2010, p 107.; (b) Macor, J. E.; Bi, Y. U.S. Pat. Appl. Publ. US 2002133008 2002, p 14.; (c) Bi, Y.; Stoy, P.; Adam, L.; He, B.; Krupinski, J.; Normandin, D.; Pongrac, R.; Seliger, L.; Watson, A.; Macor, J. E. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2461.
14. For the prior disclosures of the imidazole derivative see: (a) Zavialov, I. A.; Dahanukar, V. H.; Nguyen, H.; Orr, C.; Zhang, F.; Andrews, D. R. *Org. Lett.* **2004**,

6, 3017; (b) Zavialov, I. A.; Dahanukar, V. H.; Nguyen, H.; Orr, C.; Andrews, D. R. *Org. Lett.* **2004**, *6*, 2237.

15. The CC_{50}/EC_{50} window (CI) was determined for selected capsid assembly inhibitors presented in this study: CI was 5.2, 7.0, 8.3, 5.1 and >6.7 for compounds **37**, **30b**, **41**, **43** and **48**, respectively.
16. All inhibitors synthesized in this manuscript gave satisfactory ^{1}H NMR, HPLC and MS data, allowing us to confirm their identity and purity. Representative data for compound **48** is included: Compound **48** exists as a mixture of diastereomeric conformations that are separable by HPLC, but are not stable enough to be isolated and characterized as individual atropisomers. The following NMR data is given for the major set of resonances: ^{1}H NMR (400 MHz) δ: 3.52, (s, 3H), 4.93 (s, 1H), 7.18 (d, 1H, J = 2.0 Hz), 7.27–7.32 (m, 5H), 7.36–7.40 (m, 1H), 7.44–7.50 (m, 5H), 7.77 (dd, 1H, J = 1.9, 8.6 Hz), 7.88 (d, 1H, J = 8.3 Hz). UPLC-MS (column: HSST3, gradient of 5–100% MeCN/H_2O with 0.06% TFA over 3.8 min, UV detection at 220 nm): rt = 1.54 (14.9%)/1.58 min (85.1%), m/z (ES, +ve mode): 411.0 [M+H]+.
17. All evidence to date is consistent with the assigned tautomer that is sp^3-hybridized at C-3 for compound **48**. For example, the resonance at 4.93, which is assigned to the H-3 atom of compound **48**, was unaffected by addition of 50 μL of D_2O to a solution of 0.62 mg of compound **48** in 500 μL DMSO-d_6, even after prolonged incubation over several hours at room temperature.
18. A related pyrazole based tricyclic compound that lacks the N1-Ph substitution has been reported to be inactive in HIV viral replication and recombinant reverse transcriptase assays. See: Di Braccioa, M.; Grossia, G.; Romaa, G.; Vargiub, L.; Murab, M.; Marongiu, M. E. *Eur. J. Med. Chem.* **2001**, *36*, 935.