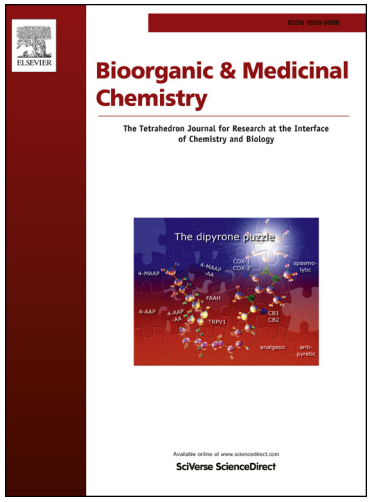

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Synthesis and Evaluation of 3-Hydroxy-3-phenylpropanoate Ester-AZT Conjugates as Potential Dual-action HIV-1 Integrase and Reverse Transcriptase Inhibitors

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Abstract. Novel 3-hydroxy-3-phenylpropanoate ester-azidothymidine (AZT) conjugates have been prepared using Baylis-Hillman methodology, and their potential as dual-action HIV-1 Integrase and Reverse Transcriptase inhibitors has been explored using enzyme inhibition and computer modelling techniques; their activity and HeLa cell toxicity have been compared with those of their cinnamate ester analogues.

Key Words: Dual-action HIV-1 Integrase/Reverse Transcriptase inhibitors, Baylis-Hillman reaction, 3-hydroxy-3-phenylpropanoate esters, cinnamate esters, azidothymidine (AZT).

1. Introduction

Different stages in the HIV replicative cycle have been identified as targets for chemotherapeutic intervention and, while an increasing number of target-specific drugs have been developed for clinical use, their toxicity, the emergence of drug resistance and problems of patient non-compliance present medicinal chemists with serious challenges.[1] HAART (Highly Active Anti-Retroviral Therapy), a combination therapy designed to minimise the development of drug resistance, involves the co-administration of an HIV-1 protease (PR) inhibitor together with a nucleoside and a non-nucleoside HIV-1 reverse transcriptase (RT) inhibitor.[2] Designed Multiple Ligands (DMLs)[3-5] or "portmanteau" drugs, as they are also known,[6] offer an alternative strategy in which different, target-specific, drug-like moieties are combined in the same molecule, and we have previously reported research on Baylis-Hillman-derived coumarin-AZT conjugates (*e.g.* **1**) as potential, dual-action HIV-1 PR/RT inhibitors,[7-9] Wang *et al.*[6] have reported compound **2** as a dual-action HIV-1 RT/IN inhibitor with nanomolar IC_{50} values for both enzymes.

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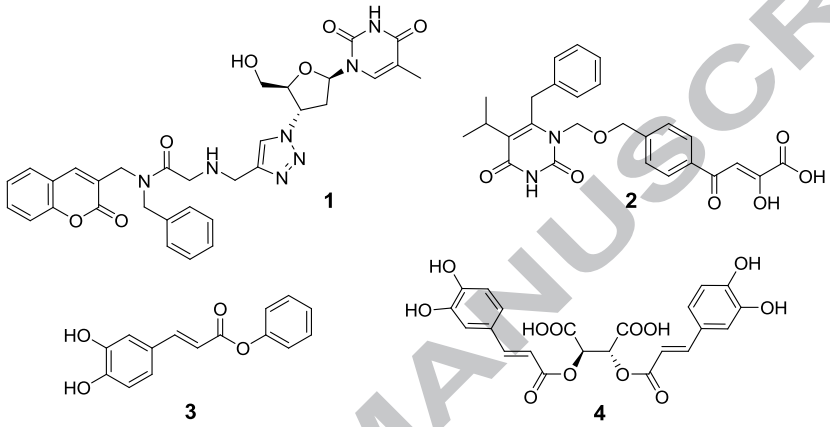
The apparent HIV-1 IN inhibition properties of caffeic acid phenethyl ester **3** and L-chicoric acid **4** have been attributed to the presence of cinnamate ester moieties,[10,11] while azidothymidine (AZT) is a known HIV-1 RT inhibitor.[12] We now report the preparation of series of novel 3-hydroxy-3-phenylpropanoate ester-AZT conjugates and the evaluation of their potential, and that of their cinnamate ester analogues, as dual-action HIV-1 IN/RT inhibitors.



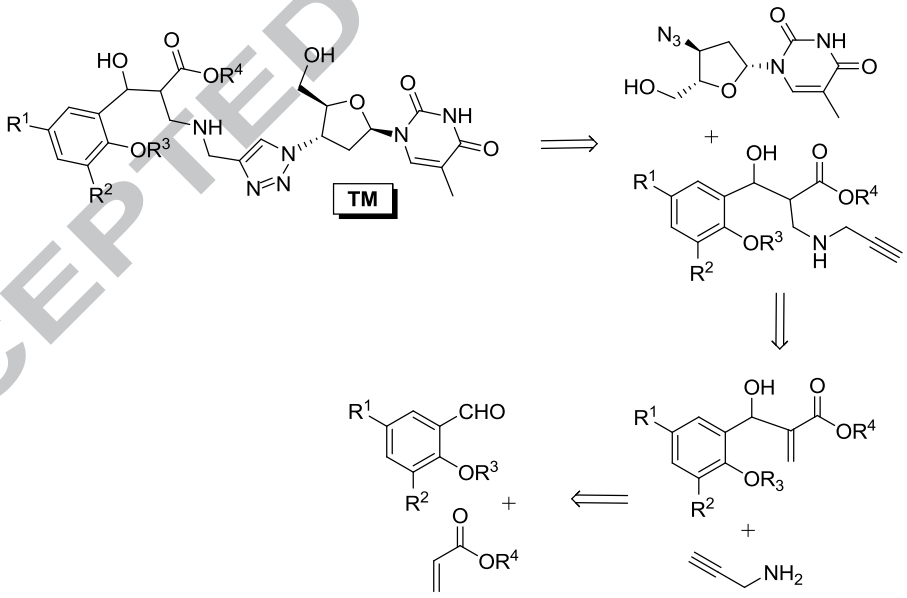
2. Results and Discussion

2.1. Chemistry

Access to the 3-hydroxy-3-phenylpropanoate ester-AZT conjugates **11a-e** and **15a-c** involved the application of Baylis-Hillman methodology, the general approach being summarised by the formal retrosynthetic analysis summarised in Scheme 1. Baylis-Hillman reactions between salicylaldehydes and methyl or ethyl acrylate are characterised by uncontrolled cyclisation to complex mixtures of 2*H*-chromene and coumarin derivatives,[13,14] and isolation of Baylis-Hillman adducts *per se* requires protection of the phenolic group through benzylation. The *tert*-butyl acrylate-derived Baylis-Hillman adducts, however, are stable and isolable and, in this paper, we report the use of both approaches.[15] The *O*-benzylated salicylaldehydes **12a-c** were obtained in yields of 65-87% by boiling mixtures of the salicylaldehydes **5a-c** and benzyl bromide in aqueous NaOH under reflux for 30 minutes. [An alternative approach involving the use of K_2CO_3 and KI for a period of 12 hours gave lower yields (≤ 54%).] Reaction of the *non*-benzylated salicylaldehyde derivatives **5b-e** with *tert*-butyl acrylate **6a**, and the *O*-benzylated salicylaldehyde derivatives **12a-c** with methyl acrylate **6b**, led to the *isolable* Baylis-Hillman adducts **7a-e** and **13a-c**, respectively. As α,β-unsaturated esters, the adducts **7b-e** and **13a-c** underwent conjugate addition by

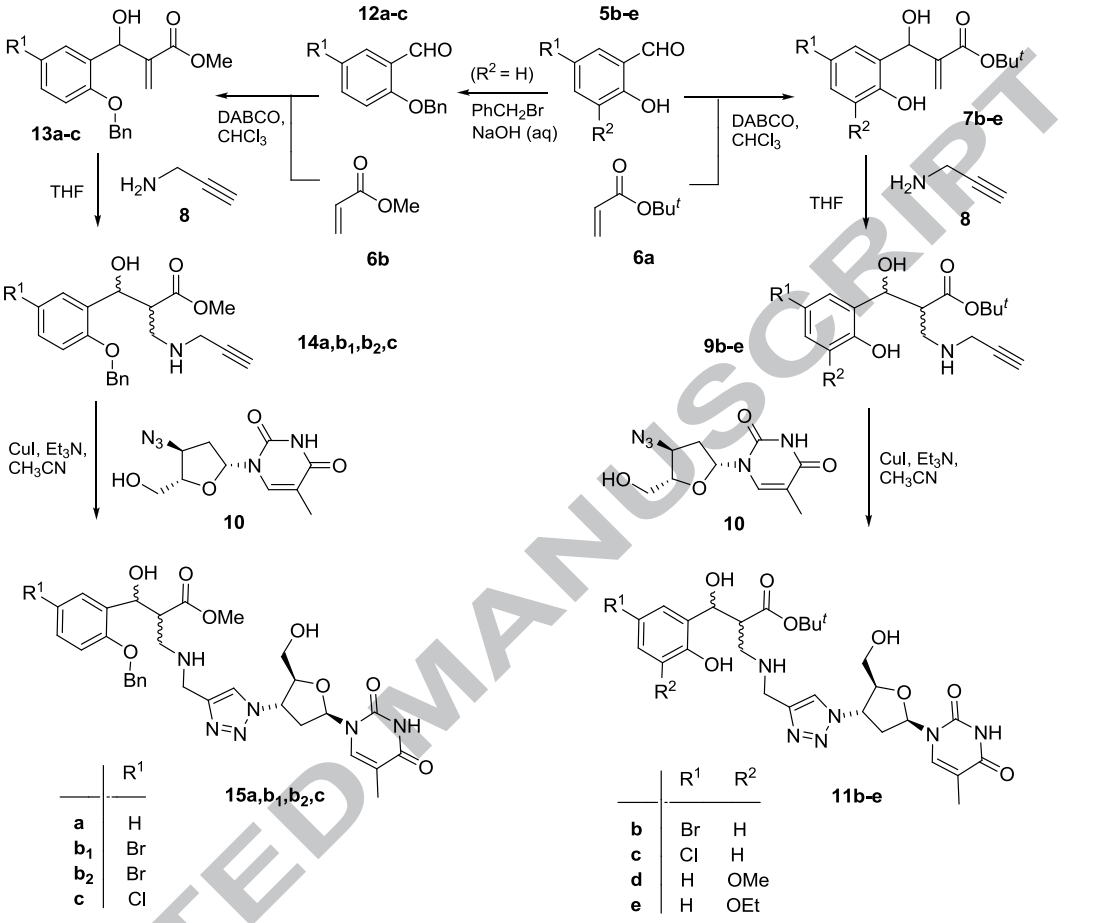
propargylamine **8** to afford the corresponding diastereomeric β-hydroxy products (**9b-e** and **14a-c)**. Generally, chromatography afforded a single diastereomer but, in two cases, both diastereomers (**14a$_1$**,**14a$_2$** and **14b$_1$**,**14b$_2$**) were isolated.

In the final steps, the target molecules **11b-e** and **15a,b$_1$,b$_2$,c** were obtained *via* "Click Chemistry" (CuAAC) reactions[16] involving AZT **10** and the corresponding alkynylated intermediates. Flash chromatography, following work-up, afforded the products **15a-c** in yields of up to 97%. Further purification using preparative layer chromatography (PLC) permitted the isolation of the 5-bromophenyl diastereomers (**15b$_1$** and **15b$_2$**) in a diastereomeric ratio (based on the isolated yields) of 72:36, respectively. In all other cases, NMR analysis of the chromatographed ester-AZT conjugates indicated the presence of a single diastereomer. Access to the cinnamate ester analogues **17a-e**, reported elsewhere,[17] involved addition-elimination (effectively, allylic substitution) steps which led to the unsaturated cinnamate ester intermediates **16a-e** (Scheme 3).



Scheme 1.

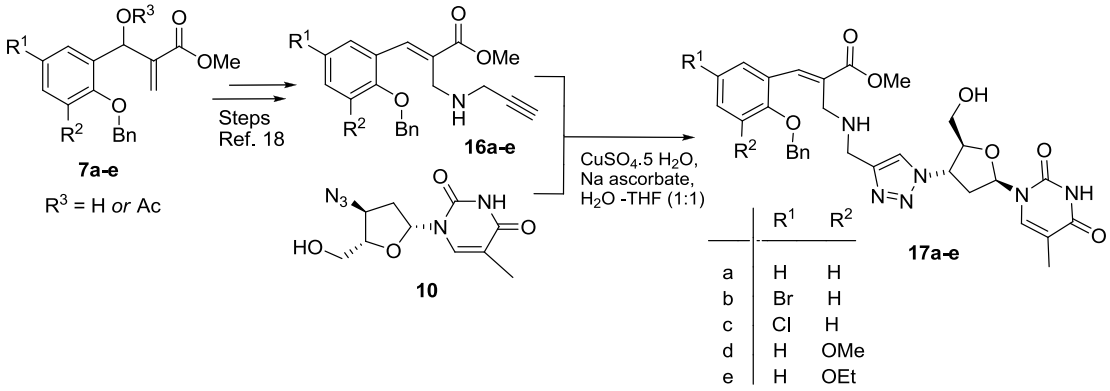
Scheme 2



	R^1
a	H
b_1	Br
b_2	Br
c	Cl

	R^1	R^2
b	Br	H
c	Cl	H
d	H	OMe
e	H	OEt

Scheme 3.

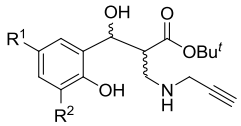


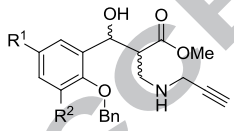
	R^1	R^2
a	H	H
b	Br	H
c	Cl	H
d	H	OMe
e	H	OEt

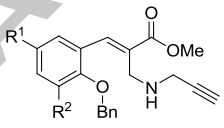
2.2. Enzyme Inhibition Assays

Having been designed as potential HIV-1 RT/IN dual-action inhibitors, the target compounds **11a-e**, **15a-c** and **17a-e** were evaluated for their inhibition of each enzyme using the established inhibitors, nevirapine and raltegravir, as standards for the RT and IN assays, respectively The propargylated precursors (**9a-e**, **14a-c** and **16a-e**) of all three series were also assayed, in their own right, for HIV-1 IN inhibition potential. The 3-hydroxypropanoate esters (**9)** and (**11**) contain a free phenolic hydroxyl group and the bulky, hydrophobic tert-butyl moiety, whereas their ester analogues (**14)** and (**16**) are methyl esters and, due to *O*-benzylation, lack a free, phenolic hydroxyl group. The results of these bioassays are summarised in Tables 1 and 2.

Table 1. HIV-1 IN enzyme activity data at inhibitor concentrations of 10 μM for compounds **9a-e**, **14a-c** and **16a-e** .



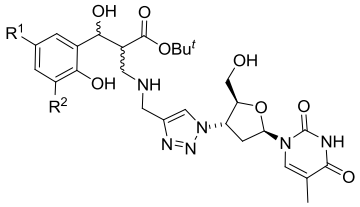
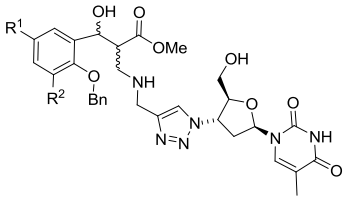
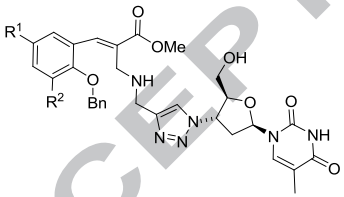




Compd.	R^1	R^2	IN activity[a] (%)[b]
9b	Br	H	83.9 (1.8)
9c	Cl	H	80.6 (2.2)
9d	H	OMe	48.3 (0.8)
9e	H	OEt	63.2 (9.8)
14a$_1$	H	H	84.5 (2.6)
14a$_2$	H	H	81.8 (5.1)
14b$_1$	Br	H	56.9 (4.0)
14b$_2$	Br	H	52.0 (2.1)
14c	Cl	H	48.3 (11.5)
16a	H	H	69.0 (0.1)
16b	Br	H	27.1 (10.0)
16c	Cl	H	90.9 (3.2)
16d	H	OMe	84.8 (6.2)
16e	H	OEt	48.7 (4.9)

[a] Raltegravir decreases IN activity to 0.76 ± 2.53% under comparable conditions.
[b] Percentage enzyme activity relative to untreated controls, followed, in parentheses, by the standard deviation.

Table 2. HIV-1 RT and IN enzyme activity and toxicity (HeLa cell activity) data for compounds **11a-e**, **15a-c** and **17a-e**.

Compd.	R^1	R^2	RT activity[a] (%)[c]	IN activity[b] (%)[c]	HeLa cell activity (%)[c]
					
11b	Br	H	73.7 (7.3)	42.2 (8.1)	85.0
11c	Cl	H	109.4 (5.1)	54.4 (4.9)	88.8
11d	H	OMe	68.6 (4.6)	78.4 (5.7)	79.9
11e	H	OEt	92.2 (13.2)	63.3 (1.9)	95.9
					
15a	H	H	80.6 (1.5)	96.7 (1.8)	90.9
15b$_1$	Br	H	73.7 (7.3)	72.1 (8.2)	92.3
15b$_2$	Br	H	94.2 (11.1)	73.7 (5.9)	84.7
15c	Cl	H	89.7 (6.7)	67.4 (9.9)	96.3
					
17a	H	H	118.4 (1.2)	64.0 (1.0)	104
17b	Br	H	108.3 (2.9)	70.2 (12.8)	56.4
17c	Cl	H	97.8 (12.8)	91.0 (4.8)	104.8
17d	H	OMe	95.7 (13.8)	56.6 (9.9)	57.7
17e	H	OEt	77.5 (16.1)	81.3 (8.0)	94.8

[a] At 20 µM. (Nevirapine: 9.45% RT activity under comparable conditions.)
[b] At 10 µM. (Raltegravir reduces IN activity to 0.76 ± 2.53% under comparable conditions.)
[c] Followed, in parentheses, by the standard deviation.

It is evident that all of the propargylated intermediates (Table 1), which contain either 3-hydroxy-3-phenylpropanoate or cinnamate ester moieties, exhibit some measure of HIV-1 IN inhibition activity at 10 μM. The % IN activity data for four of them, however, are less than 50% [**9d** (48.3%); **14c** (48.3%); **16b** (27.1%); and **16e** (48.7%)]. The results for these four compounds thus correspond to IC_{50} values of less than 10 μM, indicating significant HIV-1 IN inhibitory promise.

The 3-hydroxy-3-phenylpropanoate ester-AZT conjugates **11b-e** and **15a-c** (effectively hydrated cinnamate ester analogues), together with the cinnamate ester-AZT conjugates **17a-**e, all exhibit a measure of HIV-1 IN inhibitory activity (Table 2); however, only one of these ligands (**11b**) would have an IC_{50} value of less than 10 μM. In some cases, the % IN activity observed for the propargylated precursors remains *essentially unchanged* on conversion to the corresponding ester-AZT conjugates [**9e** and **11e** ≈ 63%; **16c** and **17c** ≈ 91%]. In other cases, the % IN activity *increases* [**9d** (48%) → **11d** (78%); **14c** (48%) → **15c** (67%); and **16b** (27%) → **17b** (70%)] yet, in others the % IN viability *decreases* [**9b** (84%) → **11b** (42%); **9c** (81%) → **11c** (54%); and **16a** (69%) → **17a** (64%)].

The HIV-1 RT bioassay data, summarised in Table 2, reflect % RT activity in the presence of the ligands **11b-e**, **15a-c** and **17a-e** – each at a concentration of 20 μM. Although most of the ligands show some RT inhibition activity, the levels are disappointing albeit better, in most cases, than AZT itself (ca. 100.% RT activity at a concentration of 20 μM). Of course, AZT serves as a nucleoside analogue (NRTI) pro-drug which requires *in vivo* triphosphorylation.[18] This will not occur during *in vitro* enzyme inhibition assays, and the HIV-1 RT inhibition data reflected in Table 2 is attributed to binding of the ligands to the allosteric *non-nucleoside* (NNRTI) binding pocket. Triphosphorylated derivatives of two of the ligands were subsequently obtained in low yield; while their ^{1}H NMR spectra were dominated by the ethyl signals corresponding to the triethylammonium internal salts, their ^{31}P NMR spectra revealed the expected three ^{31}P signals, as reported by Van Calenbergh and co-workers[19] for analogous systems. Bioassay of these derivatives, however, failed to reveal any significant inhibition of the HIV-1 enzyme.

Several patterns emerging from the foregoing analysis warrant comment.

i) In general, the inhibitory activities of the ligands against *both* HIV-1 RT *and* IN appear to follow the order: 3-hydroxy-3-phenylpropanoate ester-AZT conjugates **11b-e** > *O*-benzylated 3-hydroxy-3-phenylpropanoate ester-AZT conjugates **15a-c** > cinnamate ester-AZT conjugates **17a-**e.

ii) With few exceptions, incorporation of the AZT moiety appears to increase % IN activity, suggesting that lengthening the linker between the IN- and RT-active moieties might be advantageous.

iii) The 5'-bromo-3-hydroxy derivatives **11b** and **15b$_1$** show encouraging, simultaneous promise against both enzymes.

iv) Most of the ester-AZT conjugates exhibit little or no cell toxicity (as illustrated in Figure 1).

v) Four ester-AZT conjugates (**11b**, **11c, 11e** and **17a**), which exhibit greater or equivalent IN inhibition than their propargylated precursors and low cell toxicity levels (≥ 85% cell viability at 20 μM), will be considered as candidates for bioassay against the live virus.

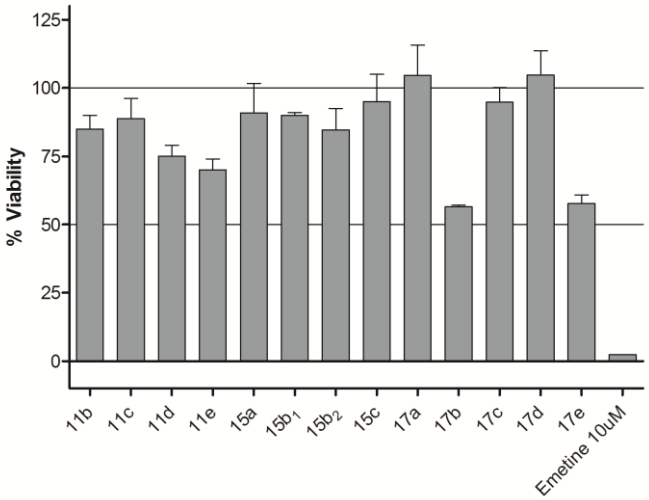


Figure 1. HeLa cell toxicity assay data for ligands **11b-e**, **15a-c** and **17a-e** at 20 μM.

2.3. Computer Modelling Studies

Docking of the parent cinnamate ester-AZT conjugate **17a** into both the HIV-1 IN and the HIV-1 NNRT receptor cavities was explored. Structures of the cinnamate ester-AZT conjugate **17a** and the respective proteins were prepared using Discovery Studio Visualizer.[20] The ligand occupying the receptor cavity and all water molecules were removed from the original PDB files; hydrogen atoms were added and each atom was assigned an Autodock

Type using AutoDock Tools (ADT). The Autodock 4.2 programme[21] was used to explore the binding mode of compound **17a** using a flexible dock approach. The protein active-site and surrounding residues were mapped using the AutoGrid 4.2 algorithm, and a generic algorithm was used to perform the conformation search. Atom maps were generated for all potential interactions between the ligand and the active site residues, while selected catalytic residues were kept flexible. For docking calculations, Gasteiger partial charges[22] were assigned to compound **17a** and non-polar hydrogen atoms were merged. All torsions were allowed to rotate during docking. Docked conformations were then viewed and explored using Discovery Studio Visualizer.[20]

In order to explore its binding mode, compound **17a** was docked into the HIV-1 NNRT (PDB 1IKW)[23] active-site with the Arg8 catalytic residues being kept flexible. As shown in Figure 2, the cinnamate ester-AZT conjugate **17a** appears to fit well in the active-site exhibiting potential hydrogen-bonding interactions between amino acid residues Lys101, Lys103, Lys172, Ile180, Tyr318, Thr1139 and Glu1138, and both the cinnamate ester and the AZT moieties, while the *O*-benzyl group occupies a hydrophobic pocket next to Leu234 and Phe227 in the HIV-1 NNRT active site. However, based on the disappointing bioassay data, it would seem that these binding features alone are not sufficient to facilitate RT inhibition *via* binding at the HIV-1 NNRT allosteric site.

Since the full crystal structure of HIV-1 IN is not yet known, the cinnamate ester-AZT conjugate **17a** was docked in the core domain structure of the HIV-1 IN enzyme (PDB 1QS4)[24] which contains the active-site receptor cavity. A charge of +2 was manually assigned to the Mg cation in the active site and residues Asp64 and Asp116 were defined as flexible residues for the simulated docking. The docked conformation of compound **17a** in the HIV-1 IN receptor cavity exhibits potential hydrogen-bonding interactions with amino acid residues Ser119, Lys156, Glu152 and Lys159 (Figure 3). The ligand adopts a conformation in which the OH group is close to the Mg co-factor (a distance of 3.09 Å) but does not displace the metal ion which remains complexed to the two aspartate residues. An overlay of the docked conformation of compound **17a** and the core domain crystal structure of the known inhibitor, 5CITEP,[25] in the active-site of HIV-1 IN (Figure 4) shows reasonable overlap between the two ligands; however, the fact that compound **17a** extends beyond the binding limits of 5CITEP, might decrease the binding affinity and account for comparatively low, observed levels of HIV-1 IN inhibition (64% enzyme viability at 10 μM) .

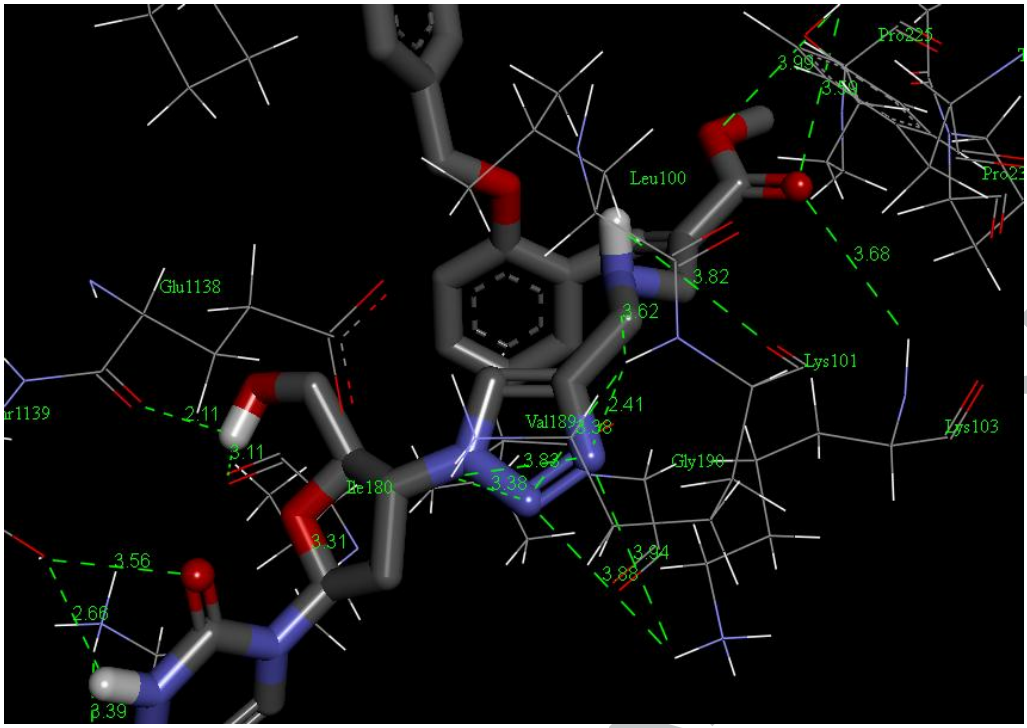


Figure 2. Docked conformation of cinnamate ester-AZT conjugate **17a** in the HIV-1 NNRT active-site (PDB 1IKW).[23] Protein active-site residues are shown in wire-frame and coloured by atom type, the ligand is shown as sticks coloured by atom type. Non-polar hydrogen atoms have been omitted for clarity and H-bonding interactions are shown as green dashed lines with distances in Å.

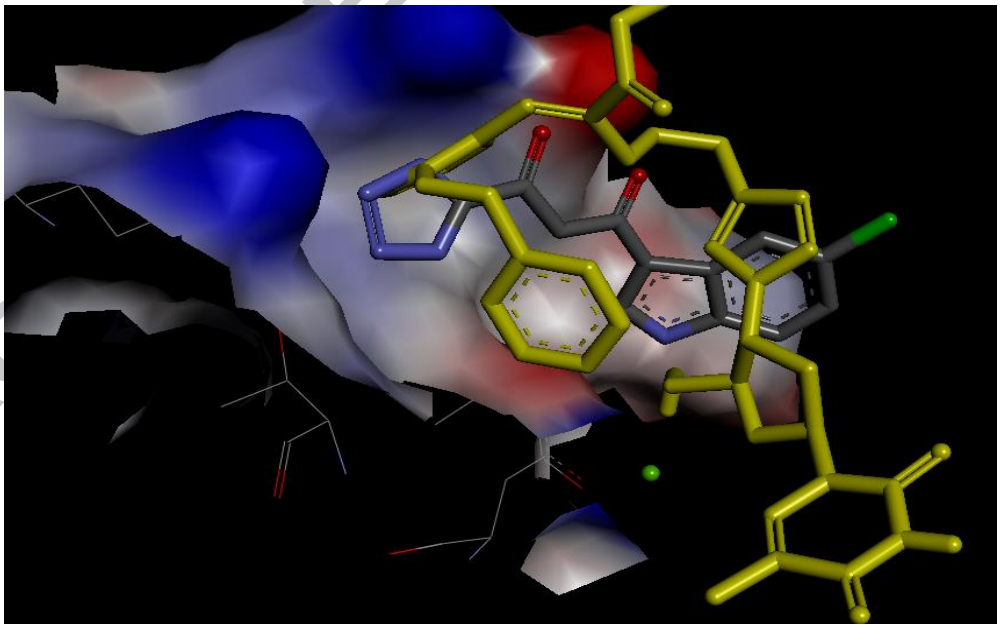


Figure 3. Overlay of the docked conformations of cinnamate ester-AZT conjugate **17a** (in yellow) and 5CITEP as found in the crystal structure PDB 1QS4[24] (in atom type colours) in the HIV-1 IN active-site (surface zone coloured by atom types). Mg^{2+} is shown as a green sphere and protein residues are shown in wire-frame, coloured by atom type.

3. Conclusions

Baylis-Hillman methodology has been successfully used to access two series of 3-hydroxy-3-phenylpropanoate ester-AZT conjugates **11a-e** and **15a-c**. Enzyme inhibition and computer-modelling studies of these compounds and their cinnamate ester-AZT analogues **17a-e**, as potential dual-action HIV-1 IN and RT inhibitors, have been undertaken. Some of the HIV-1 IN inhibition levels are encouraging, but structural modification is clearly required to improve the inhibitions levels.

4. Experimental

4.1. Synthesis

The synthesis of compounds **7b-e**, **9b-e**, **13a-c**, **14b$_1$**, **16a-e** and **17a-e** have been reported previously.[17] The intermediates **14a$_1$,a$_2$,b$_1$,c** and the 3-hydroxypropanoate ester-AZT conjugates **11b-e** and **15a-c** are all new and were obtained as follows.

4.1.1. The general procedure for the aza-Michael reaction of the Baylis-Hillman adducts 7a-e and 13a-c with propargylamine is illustrated by the following example**.** Propargylamine **8** (0.192 mL, 3 mmol) was added to a solution of methyl 3-(2-benzyloxyphenyl)-3-hydroxy-2-methylenepropanoate **13a** (0.33, 1.1 mmol) in dry THF (1.5 mL) and the mixture stirred at r.t. for 48 h. The reaction mixture was then concentrated *in vacuo* to afford the crude product (0.30 g, 76%), which was flash chromatographed [on silica gel; elution with hexane–EtOAc (1:1)] to afford two fractions comprising the diastereomeric *methyl 3-[2-(benzyloxyphenyl)-3-hydroxy-2-[(2-propynylamino)methyl]propanoate esters* **14a$_1$** and **14a$_2$**.

Diastereomer **14a$_1$** (60%) as a yellow oil [HMRS: *m/z* calculated for $C_{21}H_{24}NO_4$ (MH^+) 354.1705. Found 354.1695]; δ_H (400 MHz; $CDCl_3$) 2.16 (1H, s, C≡CH), 2.90 (1H, dd, *J* = 6.6 and 12.0 Hz, CHC*H$_a$*), 3.01 (1H, dd, *J* = 4.7 and 12.1 Hz, CHC*H$_b$*), 3.15 (1H, 2 x d, *J* = 4.0 Hz, CHCO), 3.32 (1H, dd, *J* = 2.6 and 6.2 Hz, C*H$_a$*C≡CH), 3.39 (1H, m, C*H$_b$*C≡CH) 3.55 (3H, s, OCH_3), 5.10 (2H, 2 x overlapping d, OCH_2), 5.32 (1H, d, *J* = 5.3 Hz, C*H*OH), 6.93 (1H, d, *J* = 8.2 Hz, ArH) 6.99 (1H, t, *J* = 7.5 Hz, ArH) and 7.20-7.50 (7H, overlapping m, ArH); δ_C (100 MHz; $CDCl_3$) 38.0 and 48.4 (2 × NCH_2), 50.4 (*C*HCO), 51.5 (CH_3), 70.0 (OCH_2), 70.2 (CHOH), 71.6 and 81.4 (C≡CH), 111.4, 120.9, 127.16, 127.22, 128.0, 128.5, 128.6, 130.0 and 136.7 (Ar-C), 155.0 [ArC(OBn)] and 174.1 (C=O).

Diastereomer **14a$_2$** (40%) as a yellow oil [HMRS: *m/z* calculated for $C_{21}H_{24}NO_4$ (MH^+) 354.1705. Found 354.1699]; ν_{max}/cm^{-1} (C=O); δ_H (400 MHz; $CDCl_3$) 2.19 (1H, s, C≡CH), 2.53 (1H, dd, *J* = 3.9 and 12.3 Hz, CHC*H$_a$*), 3.15 (1H, q, *J* = 3.5 Hz. CHCO), 3.19-3.29 (2H, m, CHC*H$_b$* and C*H$_a$*C≡CH), 3.41 (1H, m, C*H$_b$*C≡CH), 3.76 (3H, s, OCH_3), 5.12 (2H, d, *J* = 5.6 Hz, OCH_2), 5.73 (1H, d, *J* = 3.5 Hz, C*H*OH), 6.94 (1H, d, *J* = 8.2 Hz, ArH), 7.04 (1H, t, *J* = 7.5 Hz, ArH), 7.23-7.49 (6H, overlapping m, ArH) and 7.56 (1H, d, *J* = 8.0 Hz, ArH); δ_C (100 MHz; $CDCl_3$) 38.3 and 45.9 (NCH_2), 47.5 (*C*HCO), 52.0 (CH_3), 69.6 (OCH_2), 71.7 (CHOH), 72.1 and 80.8 (C≡CH), 111.4, 120.8, 126.7, 127.1, 127.7, 128.3, 128.4, 131.2 and 136.9 (ArC), 154.5 [ArC(OBn)] and 174.1 (C=O).

4.1.1.1. *The diastereomeric methyl 3-(2-benzyloxy-5-bromophenyl)-3-hydroxy-2-[(2-propynylamino)methyl]propanoate esters* **14b$_1$ and 14b$_2$** were obtained following flash chromatography of the crude product (0.39 g, 84%).

Diastereomer **14b$_1$** (56%) as a cream solid, m.p. 78-82 ^oC (Lit.[17] 97-99 °C).

Diastereomer **14b$_2$** (44%) as cream solid, m.p. 68-70 ^oC; [HMRS: *m/z* calculated for $C_{21}H_{23}BrNO_4$ (MH^+) 432.0810. Found 432.0816]; ν_{max}/cm^{-1} 3336 (OH) and 1719 (C=O); δ_H (400 MHz; $CDCl_3$) 2.29 (1H, m, C≡CH), 2.58 (1H, dd, *J* = 3.7 and 12.4 Hz, CHC*H*$_a$), 3.09 (1H, q, *J* = 3.4 Hz, CHCO), 3.20 (1H, dd, *J* = 3.2 and 12.5 Hz, CHC*H$_b$*), 3.37 (2H, qd, *J* = 17.0 and 2.6 Hz, C*H$_2$*C≡CH), 3.76 (3H, s, OCH_3), 5.08 (2H, 2 x overlapping d, *J* = 12.0 Hz, OCH_2), 5.71 (1H, d, *J* = 3.1 Hz, C*H*OH), 6.80 (1H, d, *J* = 8.6 Hz, ArH), 7.27-7.48 (6H, overlapping m, ArH) and 7.72 (1H, d, *J* = 2.7 Hz, ArH); δ_C (100 MHz; $CDCl_3$) 38.3 and 45.6 (NCH_2), 46.9 (*C*HCO), 52.1 (CH_3), 70.0 (OCH_2) 71.4 (CHOH), 72.4 and 80.6 (C≡CH), 113.1, 113.6, 126.7, 127.9, 128.5, 130.3, 130.9, 133.8, and 136.4 (ArC), 153.5 [ArC(OBn)] and 173.8 (C=O).

4.1.1.2. *Methyl 3-(2-benzyloxy-5-chlorophenyl)-3-hydroxy-2-[(2-propynylamino)methyl]-propanoate* **14c** as a cream solid (0.41 g, 97%), m.p. 88-92 ^oC; [HMRS: *m/z* calculated for $C_{21}H_{23}ClNO_4$ (MH^+) 388.1316. Found 388.1320]; ν_{max}/cm^{-1} 3460 (OH) and 1717 (C=O); δ_H (400 MHz; MeOD-*d*$_4$) 2.48 (1H, t, *J* = 2.6 Hz, C≡CH), 2.66 (1H, m, CHCO), 2.90-3.00 (2H, m, CHC*H$_2$*), 3.19 (2H, d, *J* = 2.6 Hz, C*H$_2$*C≡CH), 3.56 (3H, s, OCH_3), 5.09 (2H, d, *J* = 2.7 Hz, OCH_2), 5.27 (1H, d, *J* = 6.1 Hz, C*H*OH), 6.99 (1H, d, *J* = 8.8 Hz, ArH), 7.19 (1H, dd, *J* = 2.8 and 8.7 Hz, ArH) and 7.29-7.50 (6H, overlapping m, ArH); δ_C (100 MHz; MeOD-*d*$_4$) 38.2 and 48.4 (NCH_2), 52.1 (*C*HCO), 53.6 (CH_3), 68.2 (C*H*OH), 71.6 (OCH_2), 73.4 and 81.8 (C≡CH), 114.4, 127.0, 128.2, 128.7, 129.1, 129.2, 129.7, 134.5 and 138.1 (ArC), 155.3 [Ar(OBn)] and 175.1 (C=O).

4.1.2. General procedure for the preparation of the 3-hydroxypropanoate ester-AZT conjugates is illustrated by the following example.

tert-Butyl 3-(5-bromo-2-hydroxyphenyl)-3-hydroxy-2-[(2-propynylamino)methyl]propanoate **9b** (0.15 g, 0.4 mmol) was dissolved in CH_3CN (2 mL) and AZT (0.12 g, 0.44 mmol), Et_3N (67 µL) and CuI (0.008 g) were added to the solution. The mixture was stirred for 48 hours then diluted with DCM (10 mL), washed with saturated aq. NH_4Cl solution (5 mL), followed by brine (5 mL), and dried over anhydr. $MgSO_4$. The organic solution was concentrated *in vacuo* and the crude product purified by column chromatography [on silica gel; elution with hexane-EtOAc (2:1)] to afford the tert-*butyl 3-hydroxypropanoate ester-AZT conjugate* **11b** as a pale yellow oil (0.32 g, 13%); [HMRS: *m/z* calculated for $C_{27}H_{36}BrN_6O_8$ (MH^+) 651.1778. Found 651.1790]; ν_{max}/cm^{-1} 1683 (C=O); δ_H (400 MHz; CD_3OD) 1.30 [9H, s, $C(CH_3)_3$], 1.86 (3H, s, CH_3), 2.6 – 3.1 (5H, overlapping m, C*H*$_2$CHN, CHC*H*$_2$N and CHCO), 3.7 - 3.8 (4H, overlapping m, C*H*$_2$CN and CH_2OH), 4.30 (1H, s, OCHC*H*N), 5.15 (1H, s, C*H*OH), 5.36 (1H, s, OC*H*CH_2OH), 6.44 (1H, q, *J* = 5.6 Hz, OCHN), 6.64 (1H, m, ArH), 7.15 (1H, m, ArH) 7.34 (1H, d, *J* = 10.0 Hz, ArH) 7.89 (2H, m, ArH); δ_C (100 MHz; CD_3OD) 12.5 (CH_3Ar), 28.2 [C(*C*$H_3)_3$], 39.1 (*C*H_2CHN), 44.8 and 48.0 (CH_2N), 52.1 (CHCO), 60.9 (CHN), 62.1 (CH_2OH), 71.1 (CHOH), 82.2 [*C*$(CH_3)_3$], 86.4 (HOCH_2*C*HO), 86.7 (NCHO), 111.6, 112.0, 118.2, 123.9, 131.7, 131.8, 132.0, 132.1, 138.3, 152.3, 155.1, 166.4 and 173.5 (ArC, C=C and C=O).

4.1.2.1. *The* tert-*butyl 3-hydroxypropanoate ester-AZT conjugate* **11c** as a pale yellow solid (0.036 g, 14%), m.p. 100-102 ^oC; [HMRS: *m/z* calculated for $C_{27}H_{36}ClN_6O_8$ (MH^+) 607.0610. Found 607.1104]; ν_{max}/cm^{-1} 1683 (C=O); δ_H (400 MHz; CD_3OD) 1.29 [9H, s, $C(CH_3)_3$], 1.84 (3H, s, CH_3), 2.58-2.97 (4H, m, C*H*$_2$CHN, and CHC*H*$_2$N), 3.03 (1H, s, CHCO), 3.60-3.94 (4H, m, C*H*$_2$CN and CH_2OH), 4.29 (1H, s, OCHC*H*N), 5.15 (1H, d, *J* = 6.2 Hz, C*H*OH), 5.35 (1H, s, OC*H*CH_2OH), 6.42 (1H, s, OCHN), 6.63 (1H, d, *J* = 8.3 Hz, ArH), 7.17 (1H, m, ArH), 7.33 (1H, s, ArH), 7.67-8.05 (2H, m, ArH); δ_C (100 MHz; CD_3OD) 12.5 (CH_3Ar), 28.2 [C(*C*$H_3)_3$], 39.1 (*C*H_2CHN), 44.8 and 48.2 (CH_2N), 52.0 (CHCO), 60.9 (CHN), 62.1 (CH_2OH), 71.1 (CHOH), 82.2 [*C*$(CH_3)_3$], 86.4 (HOCH_2*C*HO), 86.6 (NCHO), 111.6, 118.3, 119.3, 124.0, 131.7, 132.1, 135.1, 138.2, 140.1, 152.2, 155.1, 166.4 and 173.5 (ArC, C=C and C=O).

4.1.2.2. *The* tert-*butyl 3-hydroxypropanoate ester-AZT conjugate* **11d** as a pale yellow oil (0.16 g, 66%); [HMRS: *m/z* calculated for $C_{28}H_{39}N_6O_9$ (MH^+) 603.2779. Found 603.2783]; ν_{max}/cm^{-1} 1683 (C=O); δ_H (400 MHz; CD_3OD) 1.30 [9H, s, $C(CH_3)_3$], 1.87 (3H, s, CH_3), 2.6

– 3.1 (5H, series of multiplets, C*H*$_2$CHN, CHC*H*$_2$N and CHCO), 3.31 (2H, s, C*H*$_2$CN), 3.76-3.84 (5H, overlapping s and m, OCH$_3$ and C*H*$_2$OH), 4.30 (1H, m, OCHC*H*N), 5.27 (1H, d, *J* = 6.1 Hz, C*H*OH), 5.36 (1H, m, OC*H*CH$_2$OH), 6.44 (1H, t, *J* = 6.4 Hz, OCHN), 6.7-6.9 (2H, m, ArH), 7.89 (2H, m, ArH); δ_C (100 MHz; CD$_3$OD) 12.5 (CH$_3$Ar), 28.2 [C(*C*H$_3$)$_3$], 39.1 (*C*H$_2$CHN), 44.7 and 48.1 (CH$_2$N), 51.9 (CHCO), 56.6 (OCH$_3$), 60.9 (CHN), 62.1 (CH$_2$OH), 71.4 (CHOH), 82.1 [*C*(CH$_3$)$_3$], 86.4 (HOCH$_2$*C*HO), 86.7 (NCHO), 111.5, 111.7, 119.9, 120.6, 124.1, 129.5, 138.3, 144.7, 146.7, 148.7, 152.3, 166.4 and 173.8 (ArC, C=C and C=O).

4.1.2.3. *The* tert-*butyl 3-hydroxypropanoate ester-AZT conjugate* **11e** as a pale yellow oil (0.30 g, 10%); [HMRS: *m/z* calculated for $C_{29}H_{41}N_6O_9$ (MH^+) 617.2935. Found 617.2956]; ν_{max}/cm^{-1} 1682 (C=O); δ_H (400 MHz; CD$_3$OD) 1.32 [9H, s, C(CH$_3$)$_3$], 1.35 (3H, t, *J* = 6.9 Hz, OCH$_2$C*H*$_3$), 1.86 (3H, s, CH$_3$), 2.68 (1H, ddd, *J* = 6.1, 8.6 and 14.3 Hz, C*H*$_a$CHN), 2.7-2.9 (3H, overlapping m, CHC*H*$_2$N and C*H*$_b$CHN), 3.07 (3H, td, *J* = 4.8 and 7.0 Hz, CHCO), 3.65-3.79 (2H, m, C*H*$_2$CN), 3.81-3.90 (2H, m, C*H*$_2$OH), 3.99-4.07 (2H, m, OC*H*$_2$CH$_3$), 4.30 (1H, dt, *J* = 3.0 and 5.7 Hz, OCHC*H*N), 5.25 (1H, d, *J* = 6.2 Hz, C*H*OH), 5.35 (1H, m, OC*H*CH$_2$OH), 6.43 (1H, t, *J* = 6.4 Hz, OCHN), 6.71 (1H, t, *J* = 7.9 Hz, ArH), 6.79 (1H, dd, *J* = 1.6 and 8.1 Hz, ArH), 6.85 (1H, dd, *J* = 1.6 and 7.7 Hz, ArH), 7.88 (2H, m, ArH); δ_C (100 MHz; CD$_3$OD) 12.5 (CH$_3$Ar), 15.1 (CH$_2$*C*H$_3$), 28.2 [C(*C*H$_3$)$_3$], 39.0 (*C*H$_2$CHN), 44.8 and 48.2 (CH$_2$N), 52.0 (CHCO), 60.9 (CHN), 62.1 (CH$_2$OH), 65.6 (O*C*H$_2$CH$_3$), 71.5 (CHOH), 82.0 [*C*(CH$_3$)$_3$], 86.4 (HOCH$_2$*C*HO), 86.7 (NCHO), 111.6, 112.7, 119.9, 120.6, 124.0, 129.6, 138.3, 144.9, 146.9, 147.8, 152.3, 166.4 and 173.8 (ArC, C=C and C=O).

4.1.2.4. *The methyl* O-*benzylated 3-hydroxypropanoate ester-AZT conjugate* **15a** as a pale yellow solid (0.069 g, 55%), m.p. 64-66 ^oC; [HMRS: *m/z* calculated for $C_{31}H_{37}N_6O_8$ (MH^+) 621.2673. Found 621.2683]; ν_{max}/cm^{-1} 1683 (C=O); δ_H (400 MHz; CD$_3$OD) 1.87 (3H, s, CH$_3$), 2.48 (1H, m, C*H*$_a$CHN), 2.63 (1H, m, CHC*H*$_a$N), 2.70-2.87 (2H, overlapping m, CHC*H*$_b$N and C*H*$_b$CHN), 3.04 (1H, m, CHCO), 3.58 (3H, s, OCH$_3$), 3.63-3.75 (3H, overlapping signals, CH$_2$OH and C*H*$_a$CN), 3.84 (1H, d, *J* = 6.0 Hz, C*H*$_b$CN), 4.22 (1H, br s, OCHC*H*N), 5.07 (2H, s, OCH$_2$Ph), 5.29 (2H, d, *J* = 7.6 Hz, C*H*OH and OC*H*CH$_2$OH), 6.42 (1H, t, *J* = 6.4 Hz, OCHN), 6.96 (2H, m, ArH), 7.18-7.44 (7H, overlapping m, ArH), 7.72 (1H, d, *J* = 7.6 Hz, ArH) and 7.87 (1H, s, ArH); δ_C (100 MHz; CD$_3$OD) 12.5 (CH$_3$Ar), 39.0 (*C*H$_2$CHN), 44.6 and 48.8 (CH$_2$N), 52.2 (OCH$_3$), 54.1 (CHCO), 60.8 (CHN), 62.1 (CH$_2$OH), 68.7 (CHOH), 71.1 (OCH$_2$Ph), 86.3 (HOCH$_2$*C*HO), 86.6 (NCHO), 111.7, 113.0, 122.0,

123.7, 123.8, 128.3, 128.5, 128.9, 129.6, 129.8, 132.0, 138.2, 138.6, 147.0, 147.1, 152.2, 156.8, 166.4 and 175.6 (ArC, C=C and C=O).

4.1.2.5. *The disatereomeric methyl* O*-benzylated 3-hydroxypropanoate ester-AZT conjugates* **15b$_1$ and 15b$_2$**.

Diastereomer **15b$_1$** as a pale yellow solid (0.1 g, 72%), m.p. 96-100 ^{o}C; [HMRS: *m/z* calculated for $C_{31}H_{36}BrN_6O_8$ (MH^+) 699.1778. Found 699.1805]; ν_{max}/cm^{-1} 1683 (C=O); δ_H (400 MHz; CD_3OD) 1.87 (3H, s, CH_3), 2.53 (1H, m, CH_aCHN), 2.64 (1H, m, CHCH_aN), 2.79 (1H, m, CHCH_bN), 2.87 (1H, t, *J* = 10.4 Hz, CH_bCHN), 2.99 (1H, m, CHCO), 3.55 (3H, s, OCH_3), 3.7 (3H, overlapping signals, CH_2OH and CH_aCN), 3.84 (1H, d, *J* = 12.0 Hz, CH_bCN), 4.24 (1H, br s, OCHC*H*N), 5.06 (2H, d, *J* = 3.9 Hz, OCH_2Ph), 5.23 (1H, d, *J* = 4.0 Hz, C*H*OH), 5.31 (1H, m, OC*H*CH_2OH), 6.42 (1H, t, *J* = 6.4 Hz, OCHN), 6.91 (1H, d, *J* = 8.8 Hz, ArH), 7.2-7.4 (6H, overlapping m, ArH), 7.50 (1H, s, ArH), 7.78 (1H, s, ArH) and 7.88 (1H, s, ArH); δ_C (100 MHz; CD_3OD) 12.5 (CH_3Ar), 39.1 (*C*H_2CHN), 44.6 and 48.8 (CH_2N), 52.1 (OCH_3), 53.7 (CHCO), 60.9 (CHN), 62.1 (CH_2OH), 68.2 (CHOH), 71.5 (OCH_2Ph), 86.4 ($HOCH_2$*C*HO), 86.6 (NCHO), 111.7, 114.2, 115.0, 123.76, 123.83, 128.6, 129.1, 129.7, 131.1, 132.3, 134.9, 138.1, 138.2, 147.08, 147.13, 152.3, 155.8, 166.4 and 175.1 (ArC, C=C and C=O).

Diastereomer **15b$_2$** as a pale yellow solid (0.05 g, 36%), m.p. 97-100 ^{o}C; [HMRS: *m/z* calculated for $C_{31}H_{36}BrN_6O_8$ (MH^+) 699.1778. Found 699.1786]; ν_{max}/cm^{-1} 1683 (C=O); δ_H (400 MHz; CD_3OD) 1.87 (3H, s, CH_3), 2.46 (1H, m, CH_aCHN), 2.63 (1H, m, CHCH_aN), 2.6.8-2.89 (2H, overlapping m, CHCH_bN and CH_bCHN), 3.03 (1H, m, CHCO), 3.59 (3H, s, OCH_3), 3.61-3.76 (3H, overlapping m, CH_2OH and CH_aCN), 3.83 (1H, d, *J* = 12.0 Hz, CH_bCN), 4.23 (1H, br s, OCHC*H*N), 5.07 (2H, m, OCH_2Ph), 5.27 (2H, d, m, C*H*OH and OC*H*CH_2OH), 6.42 (1H, t, *J* = 6.0 Hz, OCHN), 6.96 (2H, t, *J* = 10.0 Hz, ArH), 7.14-7.43 (6H, overlapping m, ArH), 7.71 (1H, d, *J* = 7.8 Hz, ArH) and 7.87 (1H, s, ArH); δ_C (100 MHz; CD_3OD) 12.5 (CH_3Ar), 39.0 (*C*H_2CHN), 44.5 and 48.8 (CH_2N), 52.2 (OCH_3), 54.2 (CHCO), 60.9 (CHN), 62.1 (CH_2OH), 68.8 (CHOH), 71.2 (OCH_2Ph), 86.4 ($HOCH_2$*C*HO), 86.7 (NCHO), 111.7, 113.0, 122.0, 123.7, 128.3, 128.5, 129.0, 129.4, 129.6, 129.80, 129.84, 132.0, 138.2, 138.6, 147.1, 152.3, 156.8, 166.4 and 175.7 (ArC, C=C and C=O).

4.1.2.6. *The methyl* O*-benzylated 3-hydroxypropanoate ester-AZT conjugate* **15c** as a pale yellow solid (0.24 g, 92%), m.p. 86-90 ^{o}C; [HMRS: *m/z* calculated for $C_{31}H_{36}ClN_6O_8$ (MH^+) 655.2283. Found 655.2297]; ν_{max}/cm^{-1} (C=O); δ_H (400 MHz; CD_3OD) 1.86 (3H, s, CH_3), 2.53 (1H, m, CH_aCHN), 2.63 (1H, m, CHCH_aN), 2.77 (1H, m, CHCH_bN), 2.87 (1H, t, *J* =

10.7 Hz, C*H*$_b$CHN), 2.99 (1H, m, CHCO), 3.54 (3H, s, OCH_3), 3.62-3.75 (3H, overlapping signals, C*H*$_2$OH and C*H*$_a$CN), 3.84 (1H, dd, *J* = 2.9 and 12.2 Hz, C*H*$_b$CN), 4.24 (1H, m, OCHC*H*N), 5.05 (2H, d, *J* = 4.0 Hz, OCH_2Ph), 5.23 (1H, d, *J* = 4.0 Hz, C*H*OH), 5.30 (1H, m, OC*H*CH_2OH), 6.42 (1H, t, *J* = 6.4 Hz, OCHN), 6.95 (1H, d, *J* = 8.7 Hz, ArH), 7.15 (1H, dd, *J* = 2.8 and 8.9 Hz, ArH), 7.24-7.42 (6H, overlapping m, ArH), 7.78 (1H, s, ArH) and 7.87 (1H, s, ArH); δ_C (100 MHz; CD_3OD) 12.5 (CH_3Ar), 39.0 (*C*H_2CHN), 44.6 and 48.8 (CH_2N), 52.1 (OCH_3), 53.7 (CHCO), 60.9 (CHN), 62.1 (CH_2OH), 68.2 (CHOH), 71.5 (OCH_2Ph), 86.4 ($HOCH_2$*C*HO), 86.6 (NCHO), 111.6, 114.5, 123.8, 123.9, 126.9, 128.1, 128.6, 129.1, 129.3, 129.7, 134.5, 138.1, 138.2, 147.0, 147.1, 152.2, 155.3, 166.4 and 175.1 (ArC, C=C and C=O).

4.2. Bioassay procedures.

4.2.1. HIV-1 RT assay. Quantification of the inhibitory effect of the ligands was performed in triplicate using a commercially available HIV-RT kit (Roche Applied Science, USA) as per the manufacturer's instructions. The inhibitory activity of the reverse transcriptase inhibitors was calculated as the percentage of the enzyme activity compared to a sample that does not contain any inhibitor.

4.2.2. HIV-1 IN assay. The HIV-1 IN strand transfer inhibition assay was adapted from previously described methods.[26] Briefly, 0.15 µM double-stranded biotinylated donor DNA (5'-biotin-GTGTGGAAAATCTCTAGCA-3' and 5'-ACTGCTAGAGATTTTCCACAC-3') was added to the wells of streptavidin-coated 96-well microtiter plates (R&D Systems, USA). Following incubation at room temperature for 60 minutes and a stringent wash step, 1 µM purified recombinant HIV-1 subtype B IN (in the presence of $MgCl_2$ and $MnCl_2$) was assembled onto the pre-processed donor DNA through incubation for 30 minutes at 22 °C. Following a wash step, the test compounds and raltegravir were titrated into individual wells at a final concentration of 10 µM. The microtiter plates were incubated for 30 minutes at 37 °C, washed and the strand transfer reaction was initiated through the addition of 0.25 µM double-stranded FITC-labelled target DNA (5'-TGACCAAGGGCTAATTCACT-FITC-3' and 5'-AGTGAATTAGCCCTTGGTCA-FITC-3') in Hepes buffer containing $MgCl_2$ and $MnCl_2$. After an incubation period of 60 minutes at 37 °C, the plates were washed as before and an alkaline phosphatase (AP) – conjugated anti-FITC secondary antibody (Sigma, USA) was added. Finally, the plates were washed and substrate (BluePhos, KPL, USA) was added to

allow for detection at 620 nm using a microplate reader (xMark^{TM}, Bio-Rad, USA). All inhibition values are the average of triplicate experiments.

4.2.3. Cell toxicity assay. HeLa cells were cultured in DMEM supplemented with 10% foetal bovine serum and penicillin/streptomycin/amphotericin B and plated at density of $2x10^4$ cells in 150µL medium per well in 96 well plates. The following day, compounds were added to duplicate wells at a final concentration of 20 µM and incubated with the cells for 24 h. Cell viability was assessed by adding 20 µL per well resazurin-based toxicology assay reagent (Sigma-Aldrich), incubating for 2-4 h and measuring fluorescence using 560 nm and 590 nm excitation and emission wavelengths, respectively, in a Molecular Devices Spectramax M3 plate reader. Fluorescence readings in compound-treated wells were used to calculate cell viability as a percentage of the average readings obtained from wells without the test compounds.

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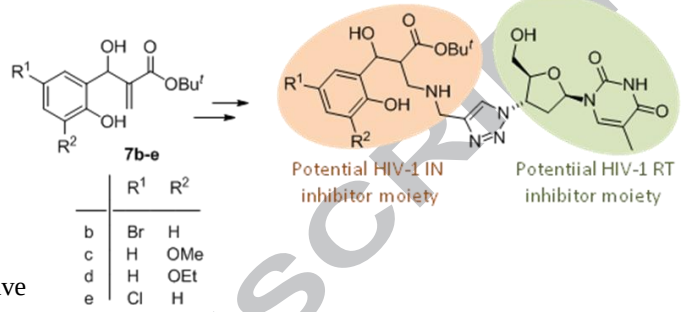
Graphical Abstract



	R^1	R^2
b	Br	H
c	H	OMe
d	H	OEt
e	Cl	H

3-Hydroxy-3-phenylpropanoate ester-AZT conjugates have been prepared and their potential as dual-action HIV-1 Integrase and Reverse Transcriptase inhibitors has been explored and compared with their cinnamate ester analogues.