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COMMUNICATION

Design, synthesis and biological evaluation of optically pure functionalized spiro[5,5]undecane-1,5,9-triones as HIV-1 inhibitors†

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A single-step amino acid-catalyzed diastereoselective three-component synthesis of optically pure highly functionalized spiro[5,5]undecane-1,5,9-triones preferentially over the four stereoisomers was accomplished in very good yields with >99% ee/de. Preliminary cell culture-based *in vivo* screening on these molecules revealed that *cis*-1aca and *cis*-1jca are better lead compounds for HIV-1 treatment than the known antiretroviral drug azidothymidine (AZT).

One of the ultimate goals in organic/medicinal chemistry is the high-yielding synthesis of optically pure drugs/natural products through catalytic asymmetric assembly of simple and readily available precursor molecules in one pot. In this regard, currently developing organocatalytic cascades and sequential one-pot combinations of multi-component reactions (MCR's)/multi-catalysis cascade (MCC) reactions will be victorious towards this fundamental goal.[1] To simultaneously address the modernization of organic synthesis through high-yielding asymmetric synthesis of optically pure drug-like molecules in one pot and show them to be better molecular therapeutics, herein we are proposing the design, synthesis and biological evaluation of optically pure functionalized spiro[5,5]undecane-1,5,9-triones **1** as HIV-1 inhibitors (see Fig. 1). The art of designing, synthesizing and characterizing good quality chemical probes for AIDS is an exciting challenge for medicinal chemistry. Recent studies on simple racemic mixture of spiro-ketones revealed that they can inhibit both 3′-processing and strand transfer reactions catalyzed by HIV-1 integrase.[2] As our group is working on the development of asymmetric synthesis of drug-like spirocyclic compounds,[3a–h] herein we propose to develop better inhibitors for HIV-1 compared to the known antiretroviral drug azidothymidine (AZT) through highly functionalized optically pure designed spiroundecanes **1**, as shown in Fig. 1.

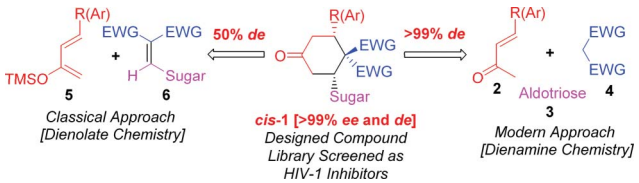

Fig. 1 Design and synthesis of chiral products **1** for HIV-1 inhibitors.

In a continuation of our interest in the development of high-yielding asymmetric syntheses of drug-like molecules in one pot,[3] herein we report amino acid-catalyzed diastereoselective three-component Diels–Alder (DTCDA) reactions that produce highly functionalized chiral spiro[5,5]undecane-1,5,9-triones **1** from commercially available 4-substituted-3-buten-2-ones **2**, protected glyceraldehydes **3** and CH-acids **4** through modern dienamine chemistry (Fig. 1). Functionalized chiral spiro[5,5]undecane-1,5,9-triones **1** are biologically active compounds and also attractive intermediates in the total synthesis of natural products.[4]

In our reaction we designed and proved that diastereoselective synthesis of product *cis*-**1** preferentially over four possible stereoisomers is possible through modern Diels–Alder reaction of *in situ* generated 2-amino-1,3-butadiene (Barbas dienamine) with chiral alkylidenes **6** instead of classical Diels–Alder reaction of 1-aryl-3-trimethylsiloxy-butadiene **5** with **6** as shown in Fig. 1.[5]

We were pleased to find that the cascade reaction of *trans*-4-phenyl-3-buten-2-one **2a**, the butane-2,3-diacetal of (*R*)-glyceraldehyde **3a** (>99% ee) and Meldrum's acid **4a** with a catalytic amount of L-proline **7a** in MeOH at 25 °C for 48 h furnished the Diels–Alder product *cis*-**1aaa** in 60% yield with >99% ee/de out of four stereoisomers (Table 1, entry 1). In the DTCDA reaction of **2a**, (*R*)-**3a** and **4a** catalyzed by L-proline **7a**, we found that the solvent and catalyst had a significant effect on yields and de's (Table 1). Interestingly, cascade reaction of **2a**, (*R*)-**3a** and **4a** under L-proline **7a**-catalysis in EtOH at 25 °C for 48 h furnished the product *cis*-**1aaa** in 67% yield with >99% ee and 85% de (Table 1, entry 2). Surprisingly, the same reaction in DMSO furnished the *cis*-**1′aaa** in only 40% yield with >99% ee and 15% de (Table 1, entry 3). But the same reaction in THF, CH_3CN and 20% aqueous CH_3CN solvents furnished the expected product *cis*-**1aaa** in 55/70/60% yield, respectively, with >99% ee/de (Table 1, entries 4–6).

Next we screened the effect of the structure/reactivity of other amino acids/amines **7b–7g** as catalysts by monitoring the reaction

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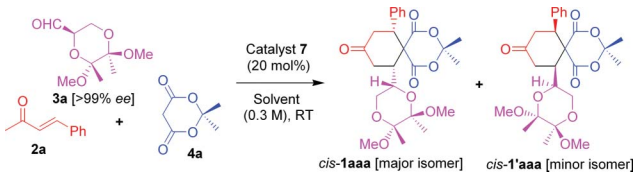
† Electronic supplementary information (ESI) available: Experimental procedures, compound characterization data (^{1}H NMR, ^{13}C NMR, HRMS and HPLC), X-ray crystallographic data (CIF) for **1gab** and **1gcb**, and biological studies data. CCDC reference numbers 828199 and 828200. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob06133j

Table 1 Preliminary optimization of DTCDA reaction[a]



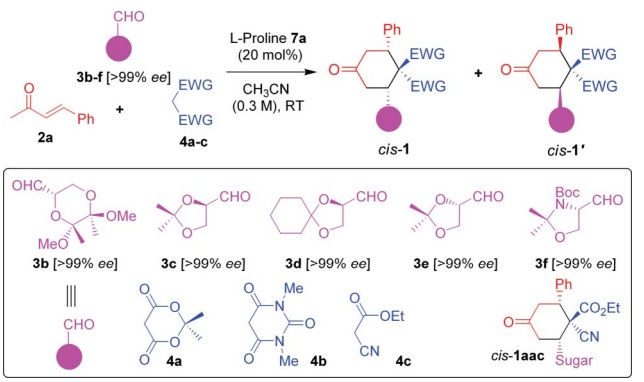
Entry	Catalyst (20 mol%)	Solvent (0.3 M)	Time (h)	Products	Yield[b] (%)	de[c] (%)
1	L-proline **7a**	MeOH	48	*cis*-**1aaa**	60	>99
2	L-proline **7a**	EtOH	48	*cis*-**1aaa**/*cis*-**1′aaa**	67	85
3	L-proline **7a**	DMSO	48	*cis*-**1aaa**/*cis*-**1′aaa**	40	−15
4	L-proline **7a**	THF	48	*cis*-**1aaa**	55	>99
5	***L-proline 7a***	***CH_3CN***	***48***	***cis-1aaa***	***70***	***>99***
6	L-proline **7a**	$CH_3CN + H_2O$	76	*cis*-**1aaa**	60	>99
7	***D-proline 7b***	***CH_3CN***	***48***	***cis-1aaa***	***75***	***>99***
8	L-thioproline **7c**	CH_3CN	48	*cis*-**1aaa**	51	>99
9	4-hydroxy-L-proline **7d**	CH_3CN	72	—	—	—
10	glycine **7e**	CH_3CN	48	*cis*-**1aaa**	50	>99
11[d]	Q-NH_2/$PhCO_2H$ **7f**	CH_3CN	72	*cis*-**1aaa**/*cis*-**1′aaa**	65	60
12[e]	L-diamine **7g**	CH_3CN	48	*cis*-**1aaa**	40	>99

[a] Amino acid **7** (0.06 mmol), benzylidene acetone **2a** (0.6 mmol), chiral triose sugar **3a** (0.3 mmol) and Meldrum's acid **4a** (0.3 mmol) in solvent (1 mL) were stirred at 25 °C for 48 to 76 h. [b] Yield refers to the column-purified product. [c] Diastereomeric excesses (de) determined by ^1H and ^{13}C NMR analysis on isolated products. [d] 9-Amino-9-deoxyepiquinine **7f**. [e] (*S*)-1-(2-Pyrrolidinylmethyl)pyrrolidine **7g**.

yield and de of the DTCDA reaction of enone **2a**, (*R*)-**3a** and **4a** in CH_3CN (Table 1, entries 7–12). Among the catalysts screened, D-proline **7b** proved to be the best catalyst with respect to yield, providing *cis*-**1aaa** in 75% yield with >99% ee/de (Table 1, entry 7). Not much improvement in the yield and de of the reaction beyond L-proline **7a**-catalysis was found with L-thioproline **7c**, *trans*-4-hydroxy-L-proline **7d**, glycine **7e**, Q-NH_2/$PhCO_2H$ **7f**, and L-diamine **7g**-catalyzed DTCDA reactions (Table 1, entries 8–12). Catalyst studies revealed that L/D-proline-catalysis furnished the same isomer (*cis*-**1aaa**) as the major compound without effect of the catalyst stereochemistry in the transition state, and there was no reaction observed under **7d**-catalysis. Interestingly, cascade reaction under 9-amino-9-deoxyepiquinine/$PhCO_2H$ **7f**-catalysis furnished the product *cis*-**1aaa** in 65% yield with only 60% de as shown in Table 1, entry 11. *Observation of these results revealed that the selective* endo*-transition state of the bimolecular Diels–Alder reaction is affected by protic/polar solvents and catalyst topology through changes in the strength of the electrostatic interactions between the diene* (*2-amino-1,3-butadiene*) *and chiral dienophile*.

We further investigated the proline-catalyzed DTCDA reaction of **2a** with various protected glyceraldehydes **3a–3e**/Garner aldehyde **3f** and CH-acids **4a–4c** to study the effect of electronic factors/electrostatic interactions on the outcome of product formation and selectivity (Table 2). Surprisingly, reaction of the butane-2,3-diacetal of (*S*)-glyceraldehyde **3b** (>99% ee) with Meldrum's acid **4a** and enone **2a** through **7a**-catalysis furnished the chiral spirotrione *cis*-**1′aba** in 60% yield with only 50% de (Table 2, entry 1). Interestingly, reaction of (*R*)-glyceraldehyde acetonide **3c** and (*R*)-1,4-dioxaspiro[4.5]decane-2-carbaldehyde **3d** with Meldrum's acid **4a** and enone **2a** through **7a**-catalysis furnished the chiral spirotriones *cis*-**1aca** and *cis*-**1ada** in 75% and 50% yields, respectively, with >99% ee/de (Table 2, entries 2 and 3). Reaction of (*S*)-glyceraldehyde acetonide **3e** with Meldrum's acid **4a** and enone **2a** through **7a**- and **7b**-catalysis furnished the same chiral spirotrione *cis*-**1′aea** in 55% and 45% yields, respectively,

Table 2 General optimization of DTCDA reaction[a]

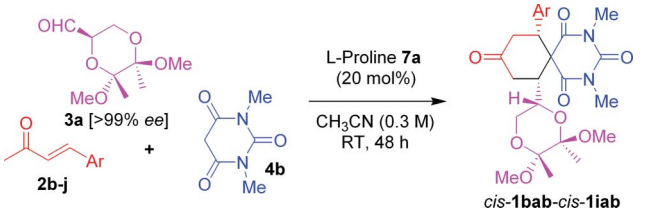


Entry	Triose sugar **3**	CH-acid **4**	Time (h)	Products	Yield[b] (%)	de[c] (%)
1	**3b**	**4a**	48	*cis*-**1′aba**	60	50
2	***3c***	***4a***	***72***	***cis-1aca***	***75***	***>99***
3	**3d**	**4a**	72	*cis*-**lada**	50	>99
4	**3e**	**4a**	72	*cis*-**1′aea**	55	>99
5[d]	**3e**	**4a**	72	*cis*-**1′aea**	45	>99
6	**3f**	**4b**	48	*cis*-**1′afb**	76	60
7	***3a***	***4b***	***36***	***cis-1aab***	***81***	***>99***
8	**3a**	**4c**	48	*cis*-**1aac**	52	>99
9	***3c***	***4b***	***48***	***cis-1acb***	***86***	***>99***

[a] See the ESI for experimental conditions.† [b] Yield refers to the column-purified product. [c] Diastereomeric excesses (de) determined by using ^1H and ^{13}C NMR analysis on isolated products. [d] D-Proline **7b** used as catalyst.

with >99% ee/de (Table 2, entries 4 and 5). Reaction of (*S*)-Garner aldehyde **3f** (>99% ee) with 1,3-dimethylbarbituric acid **4b** and enone **2a** through **7a**-catalysis furnished the chiral spirotrione *cis*-**1′afb** in 76% yield with only 60% de (Table 2, entry 6). Interestingly, reaction of (*R*)-**3a** with ethyl cyanoacetate **4c** and enone **2a** through **7a**-catalysis furnished the chiral product *cis*-**1aac** in 52% yield

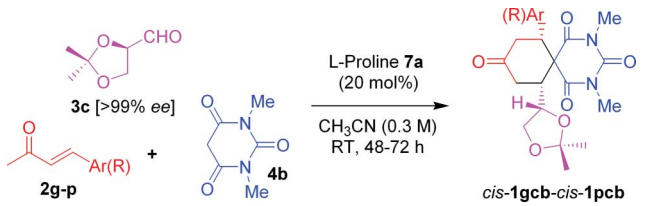
Table 3 Diversity-oriented synthesis of chiral products *cis*-**1** from **2b–j**, (*R*)-**3a** and **4b**[a]



Entry	Ar	Products	Yield[b] (%)	de[c] (%)
1	1-Naphthalenyl **2b**	*cis*-**1bab**	75	>99
2	Piperonyl **2c**	*cis*-**1cab**	65	>99
3	4-OHC_6H_4 **2d**	*cis*-**1dab**	78	>99
4	4-$OBnC_6H_4$ **2e**	*cis*-**1eab**	83	>99
5	2-$NO_2C_6H_4$ **2f**	*cis*-**1fab**	60	>99
6	3-BrC_6H_4 **2g**	*cis*-**1gab**	85	>99
7	2,6-$Cl_2C_6H_3$ **2h**	*cis*-**1hab**	80	>99
8	2-Thiophenyl **2i**	*cis*-**1iab**	85	>99
9[d]	2-Furanyl **2j**	*cis*-**1jaa**	76	>99

[a] See the ESI for experimental conditions.† [b] Yield refers to the column-purified product. [c] Diastereomeric excesses (de) determined by ^1H and ^{13}C NMR analysis on isolated products. [d] Meldrum's acid **4a** used as active methylene.

Table 4 Diversity-oriented synthesis of chiral products *cis*-**1** from **2g–p**, (*R*)-**3c** and **4b**[a]



Entry	Ar	Products	Yield[b] (%)	de[c] (%)
1	3-BrC_6H_4 **2g**	*cis*-**1gcb**	93	>99
2	2-Furanyl **2j**	*cis*-**1jcb**	80	>99
3[d]	***2-Furanyl 2j***	***cis*-1jca**	***78***	***>99***
4	*trans*-PhCH=CH **2k**	*cis*-**1kcb**	80	>99
5	Methyl **2l**	*cis*-**1lcb**	72	>99
6	*n*-Propyl **2m**	*cis*-**1mcb**	55	>99
7	*n*-Butyl **2n**	*cis*-**1ncb**	61	>99
8	*n*-Pentyl **2o**	*cis*-**1ocb**	70	>99
9	*n*-Hexyl **2p**	*cis*-**1pcb**	60	>99

[a] See the ESI for experimental conditions.† [b] Yield refers to the column-purified product. [c] Diastereomeric excesses (de) determined by ^1H and ^{13}C NMR analysis on isolated products. [d] Meldrum's acid **4a** used as active methylene.

with >99% ee/de out of eight possible stereoisomers (Table 2, entry 8). In a final optimization, cascade reaction of protected glyceraldehydes (*R*)-**3a** and (*R*)-**3c** with **4b** and **2a** through **7a**-catalysis furnished the chiral spirotriones *cis*-**1aab** and *cis*-**1acb** in 81% and 86% yields, respectively, with >99% ee/de (Table 2, entries 7/9). *Observation of the results in Table 2 reveals that the outcome of product selectivity is strongly affected by the chiral dienophile's structure as well as the solvent and catalyst topology*.

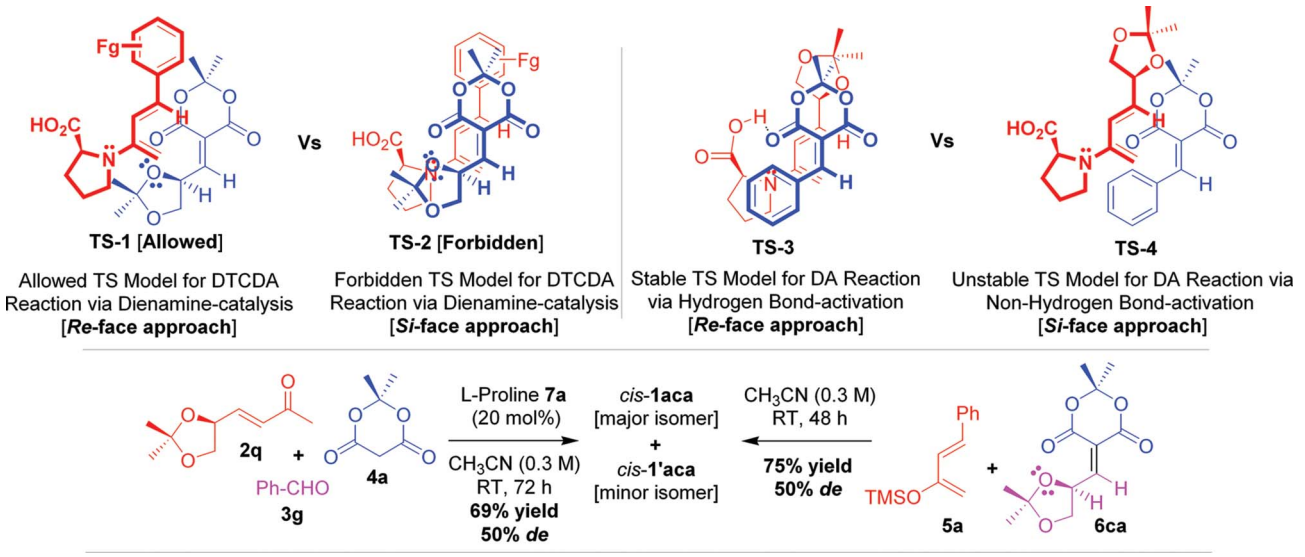
We further explored the scope of the proline-catalyzed DTCDA reaction by developing the diversity-oriented synthesis of optically pure products *cis*-**1** through cascade reaction of **4a**/**4b** with protected (*R*)-glyceraldehydes **3a**/**3c** and enones **2b–2p** (Tables 3 and 4). The chiral spirotriones *cis*-**1** were obtained from DTCDA reaction as single diastereomers in good to excellent yields and excellent ee/de's with a variety of neutral, electron-donating, electron-withdrawing, halogenated and heteroatom-substituted *trans*-4-aryl-3-buten-2-ones **2a–2j** and also aliphatic *trans*-4-alkyl-3-buten-2-ones **2k–2p**, as shown in Tables 3 and 4. Interestingly, for the first time in organocatalysis, aliphatic *trans*-4-alkyl-3-buten-2-ones **2k–2p** are used as the Barbas dienamine source in the DTCDA reaction to furnish the spirotriones *cis*-**1kcb**–*cis*-**1pcb** with >99% ee/de's in good to excellent yields as shown in Table 4.[5] The structure and absolute stereochemistry of cascade DTCDA products **1** was confirmed by NMR analysis and also finally confirmed by X-ray structure analysis on (–)-**1gab** and (–)-**1gcb** as shown in Fig. S1 and S2 (see the ESI†).[6]

Although further mechanistic studies are needed to firmly elucidate the mechanism of DTCDA reactions through **7a**- or **7b**-catalysis, the reaction proceeds by concerted *endo*-[4 + 2]-cycloaddition between *in situ* generated Barbas dienamine and chiral alkylidenes (Scheme 1).[5] In the case of the treatment of *in situ* chiral alkylidene **6ca** with 2-amino-1,3-butadienes generated from **2**, (*R*)-**3c** and **4a** *via* **7a**/**7b**-catalysis, we can rationalize the observed high diastereoselectivity through an allowed transition state where the *re*-face of **6ca** approaches the dienamine due to the strong electrostatic interactions as shown in **TS-1**. Lack of formation of other isomers may be explained by model **TS-2**, in which there are very poor electrostatic interactions between the partially positive nitrogen of the dienamine and the lone pair electrons of the oxygen of the sugar in the transition state (Scheme 1).

Based on the internal correlation of DTCDA results and X-ray structural analysis, we proposed transition states where electrostatic interactions are the main controlling factor rather than hydrogen bonding interactions, CH–π interactions or steric hindrance in biomimetic cascade DTCDA reactions, because L-**7a** or D-**7a** didn't show much impact on the outcome of product selectivity (see Tables 1 and 2).[7] The importance of electrostatic interactions between the partially positive nitrogen of the dienamine and the lone pair electrons of oxygen of the sugar can be easily understood through controlled Diels–Alder experiments performed on **2q**, **3g** and **4a** under **7a**-catalysis, and also between **5a** and **6ca** at 25 °C as shown in Scheme 1. The observed poor selectivity of the above reactions can be explained through **TS-3** and **TS-4**, in which only hydrogen bonding interactions are possible to control the moderate selectivity.

Biological studies on chiral products 1 as HIV-1 inhibitors

After the successful high-yielding synthesis of the optically pure single enantiomer functionalized spiroundecane library **1**, we had further interest in screening a few preliminary chiral compounds, ***cis*-1aaa**, ***cis*-1aca** and ***cis*-1jca**, for antiretroviral properties. A cell culture-based HIV infection model was used for this purpose and differences in HIV turnover in the presence and absence of these compounds were monitored. For all the assays, azidothymidine (AZT), a known anti-HIV compound, was used as a positive control.[8] Before checking for anti-HIV activities, compounds were checked for cytotoxicity in Sup-T1 cells by MTT assay. The assay is based on the reduction of the yellow colored tetrazolium salt



Scheme 1 Proposed transition states for the DTCDA reaction.

MTT by a mitochondrial dehydrogenase of viable or live cells, that converts this compound to a purple coloured formazan product that is measured spectrometrically at a wavelength of 570 nm. The amount of formazan formed is proportional to the number of living cells. It was interesting to observe that AZT, the molecule that is used for retroviral treatment, was more cytotoxic than *cis*-**1aca** and *cis*-**1jca**, and less cytotoxic than *cis*-**1aaa** (Fig. S3, see the ESI†). Compound *cis*-**1jca** had the least cytotoxicity under our conditions, with almost 90% of cells alive even after 16 h of treatment.

With the cytotoxicity results in hand, the anti-HIV-1 activities of these compounds were tested for 100 pM, 100 nM and 10 μM concentrations (Fig. 2). Cells without any compound treatment, but infected with NL4-3 viruses were taken as background control. As virus infection was expected to increase cell death, the cells were treated with different compounds along with infection only for 5 h, which was sufficient for viral entry and drug adsorption/absorption. The percentage inhibition (decrease in HIV-1 [here, NL4-3] turnover) as a function of concentration was plotted (Fig. 2). Higher percentage inhibition indicates enhanced decrease in HIV-1 turnover and therefore is indicative of a more effective antiretroviral molecule. We observed that all the three test compounds reduced the NL4-3 turnover on average by 45%, which was comparable with AZT, the drug in use for HIV-1 treatment. Even though compound *cis*-**1aaa** decreased NL4-3 turnover by 50%, the cells at the end of the experiments were only 69% ± 5% viable. The chiral compound *cis*-**1aca** could reduce NL4-3 turnover rate by as much as 58% at a concentration of 10 μM, which was marginally more than the antiretroviral effect of AZT at that concentration. In both the cases, a cell viability of about 77% ± 8% was maintained. The compound *cis*-**1jca** at a concentration of 100 nM showed comparatively improved antiretroviral activity over AZT. The percentage inhibition of *cis*-**1jca** was 56% ± 0.4% with cell viability of 82% ± 5.6%, while that of AZT at 100 nM is 51.7% ± 3% with almost equal cell viability. The % inhibition of NL4-3 turnover by *cis*-**1jca** increased to 59% ± 1% at 10 μM, which was the highest amongst all the four compounds used. From these preliminary experiments, it could be concluded that the newly synthesized chiral compounds, especially *cis*-**1aca** and *cis*-**1jca**, are bioactive molecules that bear the property of decreasing HIV-1 turnover upon 5 h of treatment, while maintaining more than 75% cell viability.

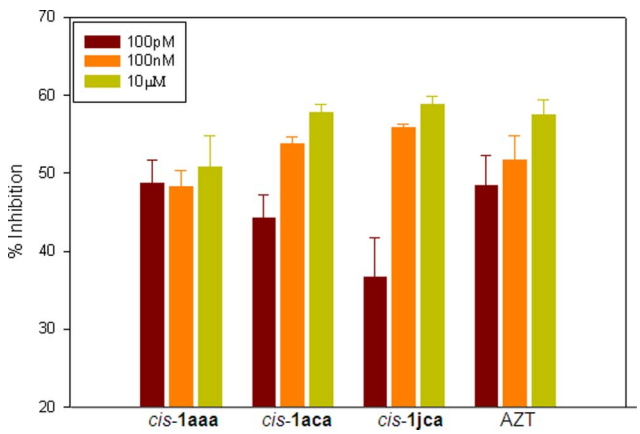


Fig. 2 Screening of products **1** as HIV-1 inhibitors [percentage inhibition, measured in terms of decrease in NL4-3 virus, upon treatment with 100 pM, 100 nM and 10 μM of compounds ***cis*-1aaa**, ***cis*-1aca** and ***cis*-1jca** for 5 h. AZT was used as a reference compound].

In summary, we have designed and developed the proline-catalyzed direct DTCDA reaction for diversity-oriented synthesis of optically pure products of spirotriones *cis*-**1**. For the first time in organocatalysis, we have shown electrostatic interactions as a major controlling factor rather than hydrogen bonding interactions, CH–π interactions or steric hindrance in amino acid-catalyzed Diels–Alder reactions.[7] Biological cell-culture based *in vivo* screening on chiral *cis*-spirotrione **1** molecules showed that *cis*-**1aca** and *cis*-**1jca** are better lead compounds for HIV-1 inhibition than the known antiretroviral drug azidothymidine (AZT). Further optimization and screening of biological/pharmacological studies on these molecules may lead to better drugs for HIV. Herein for the first time we have shown an experimentally simple and environmentally friendly DTCDA

approach as a novel metal-free tool for the synthesis of molecular therapeutics.[9]

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