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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Design and synthesis of *N*-hydroxytriazole-4-carboxamides as HIV integrase inhibitors

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Abstract A series of *N*-hydroxytriazole-4-carboxamide derivatives were synthesized, and their potential HIV integrase inhibitory activities were evaluated.

Keywords *N*-hydroxytriazole-4-carboxamides · HIV integrase inhibitors · Diketo acids · Metal binding

Introduction

Design and synthesis of HIV-1 integrase (IN) inhibitors have emerged as the main interest for the treatment of AIDS (Malet *et al*., 2012; Wainberg *et al*., 2012). During the past decades, extensive efforts have been made, which lead to the finding of a type of HIV IN inhibitors bearing an aryl *β*-diketo acid scaffold (See Fig. 1 for its structure and some typical inhibitors) (Hazuda *et al*., 2000, 2004; Grobler *et al*., 2002; Johnson *et al*., 2004), and to the recent approval of raltegravir (MK-0518) (Summa *et al*., 2008; Anker and Corales, 2008) and phase II clinical trial of elvitegravir (GS-9137) (Shimura *et al*., 2008) (Fig. 1). The general structure of the aryl *β*-diketo acid type of HIV IN inhibitors comprises a pharmacophore (such as diketo acid scaffold) and a hydrophobic subunit (the aryl ring side chain) with or without a linking unit (Fig. 1). Since the two aspartate (Asp64, Asp116) and one glutamate (Glu152) residues, situating at the catalytic core domain of HIV IN, are believed to bind Mg^{2+} and Mn^{2+} ions, which is essential for the catalytic activity of IN (Engelman and Craigie, 1992; Hazuda *et al*., 1997), it is commonly anticipated that the pharmacophore of aryl *β*-diketo acid type of HIV IN inhibitors binds competitively the two Mg^{2+} metal ions in the IN active site and thus to block the access of a host DNA to the IN enzyme. On the other hand, the hydrophobic subunit is identified to participate in a specific interaction with an adjacent hydrophobic pocket or surface (Bacchi *et al*., 2008; Sechui *et al*., 2006).

Given the above mentioned structural characteristics of diketo acid type of HIV inhibitors, we have recently carried out a project with an basic assumption that the development of a new HIV inhibitor can be logically conducted by an assembly of appropriate pharmacophore(s) and a hydrophobic subunit(s) linked by an 1,2,3-triazole ring through "click reaction" (Bock *et al*., 2006; Hou *et al*., 2012). We speculate that, in this way, HIV IN inhibitors library can be easily created, and thus the finding and modification of a lead compound can be dramatically accelerated, due to the fact that click reaction can be furnished under benign reaction conditions, and thus most of the functional groups may tolerate. In addition, click reaction requires only fairly simple workup and purification process. To this end, we have synthesized 1,4-dihydro-4-oxo-1,5-napthyridine-3-carboxylic acids as HIV IN inhibitors (Zeng *et al*., 2009). As a continuation of our project, in this paper, we design and synthesize *N*-hydroxy-triazole-4-carboxamides and evaluate their potential HIV IN inhibitory activity.

Results and discussion

Our inspiration comes from Plewe's discovery. Recently, Plewe *et al*. have found that azaindole carboxylic acid

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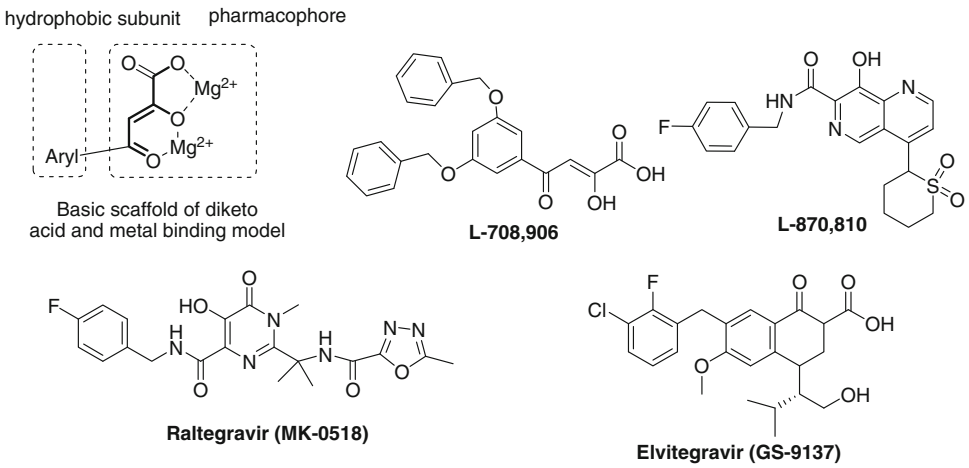


Fig. 1 The metal-binding model of aryl diketo acid and some typical HIV IN inhibitors

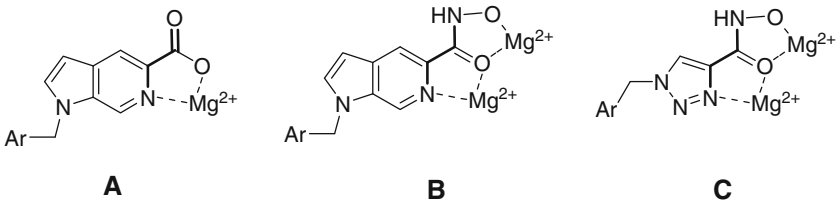


Fig. 2 Metal binding of picolinic acid (**a**), picoline hydroxamic acid (**b**), and *N*-hydroxy triazole-4-carboxamide (**c**)

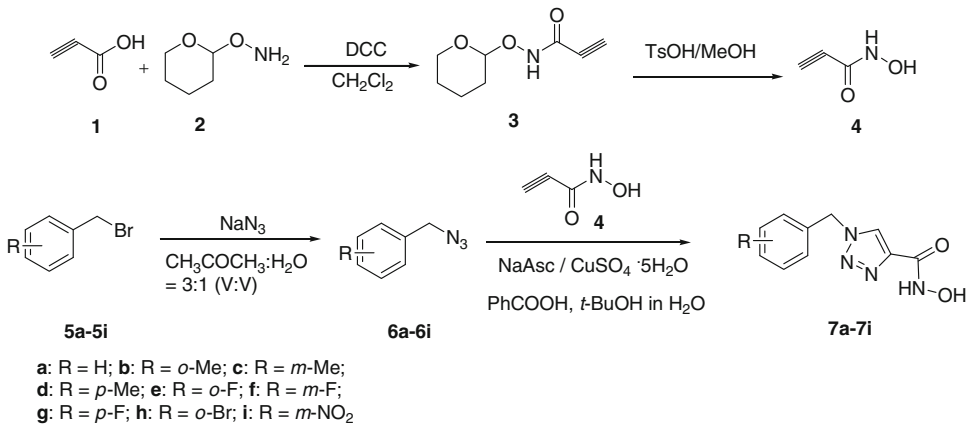
derivatives exhibit modest HIV IN inhibitory activity (IC_{50}: 0.95–7.35 μM) (Plewe *et al*., 2009) and good ligand efficiencies (LE) ($\Delta g > 0.35$ kcal/mol) (Hopkins *et al*., 2004; Kuntz *et al*., 1999). However, improved inhibitory activity was achieved when the carboxylic acid moiety was replaced by a hydroxamic acid moiety. The authors proposed that this results were stemmed from the one Mg^{2+} ion binding of the bidentate picolinic acid subunit (A, Fig. 2), whereas a picoline hydroxamic acid moiety would greatly facilitate binding of two Mg^{2+} ions (B, Fig. 2) (Plewe *et al*., 2009). Based on this observation, we believe that the *N*-hydroxy carboxamide subunit appended by an azo-heteroaromatic may be a suitable pharmocophore for the design of HIV IN inhibitor. Moreover, if the azo-heteroaromatic is a triazole ring generated from a click reaction, alike our previous report on design of HIV IN inhibitors using click reaction (Zeng *et al*., 2009), the desired *N*-hydroxy-triazole-4-carboxamide is thus supposed to bind two metal ions in a pattern analogous to the picoline hydroxamic acid (C, Fig. 2). It is worthy noting that in the *N*-hydroxy-triazole-4-carboxamide structural scaffold, the triazole cycle functions not only as one of the component of the pharmacophore, but also as a linker for efficient assembly of the pharmacophore and a hydrophobic unit through "click reaction". As a result, a library of *N*-hydroxy-triazole-4-carboxamide derivatives may be easily accessible.

As expected, the synthesis of *N*-hydroxytriazole-4-carboxamide is fairly straightforward, and the synthetic routes are showed in Schemes 1 and 2. At the beginning, followed a known procedure (Suzuki *et al*., 2010), the condensation of propynoic acid (**1**) and NH_2OTHP gives tetrahydropyran-2-yloxy propynoic acid amide **3**. After treatment using TsOH, the key intermediate propynoic acid hydroxyamide **4** was produced. On the other hand, nucleophilic substitution of benzyl bromides **5** with sodium azide afforded benzyl azides **6**. Finally, the click reaction of **6** and **4** generated the desired benzyl-substituted *N*-hydroxy-triazole-4-carboxamide **7** in good to excellent yields.

To investigate the influence of the rigidity of the linker on the inhibitory activity, we also designed phenyl-substituted *N*-hydroxytriazole-4-carboxamides. As shown in Scheme 2, aniline derivatives **8** were initially converted into corresponding aromatic azides **9** (Barral *et al*., 2007), which underwent click reaction with **4** to give the desired *N*-hydroxytriazole-4-carboxamides **10** in good yield. It is worthy noting that compounds **10** could also be accessible by a one pot, two-step procedure.

During the synthetic processes, the click reaction between propynoic acid hydroxyamide **4** and various azides was the key step. It was reported that the presence of carbonylic acid could promote the fragmentation of triazole-Cu adduct, an essential intermediate, to form the final click reaction product (Shao *et al*., 2010). Then following a modified procedure (Shao *et al*., 2010), we initially optimized the click reaction conditions taking azidobenzene **9a** as a model compound. As shown in Table 1, when the reaction of azidobenzene and propynoic acid hydroxyamide **4** was conducted in the presence of a ratio of 0.01:0.02:0.1 for $CuSO_4 5H_2O$, NaAsc, and $PhCO_2H$, the

Scheme 1 Synthesis of benzyl-substituted *N*-hydroxy-triazole-4-carboxamide **7**



Scheme 2 Synthesis of phenyl-substituted *N*-hydroxy-triazole-4-carboxamide **10**

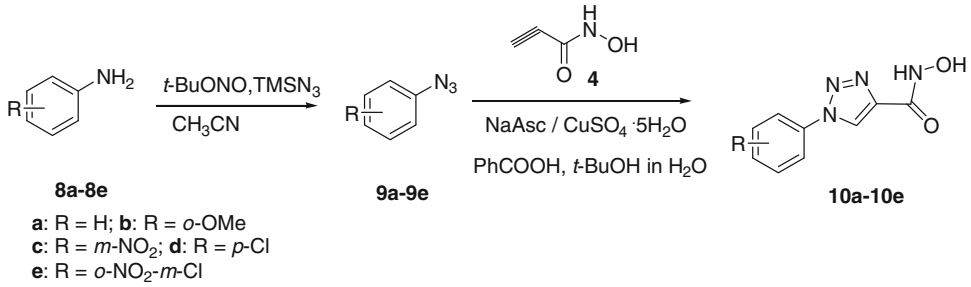


Table 1 Condition optimization of click reaction using **9a** as model starting material

Entry 1	$CuSO_4 \cdot 5H_2O$, NaAsc and $PhCO_2H$ (eq)	Time (h)	Temperature (°C)	Yield (%)
1	0.01, 0.02, 0.1	2	rt	–
2	0.01, 0.02, 0.1	5	rt	–
3	0.01, 0.02, 0.1	5	45	–
4	0.02, 0.04, 0.2	5	rt	65
5	0.02, 0.04, 0.2	5	45	68

Conditions: propynoic acid hydroxyamide **4** (1 mmol) and azido-benzene (1.1 mmol) in 2 mL of *t*-butanol/water (*V*:*V* = 1:2) mixed solvent

Table 2 Inhibitory rate of synthesized *N*-hydroxytriazole-4-carboxamides

Compound	Inhabitory rate % (0.39 μg/mL)	Compound	Inhabitory rate % (0.39 μg/mL)
Raltegravir	94.09 (0.1 μg/mL)[a]	Raltegravir	70.99 (0.01 μg/mL)[a]
7a	37.77	**7h**	5.49
7b	21.93	**7i**	0.00
7c	0.00	**10a**	31.57
7d	0.00	**10b**	16.88
7e	13.11	**10c**	19.17
7f	0.00	**10d**	4.25
7g	15.94	**10e**	35.25

[a] IC_{50} of Raltegravir is 0.00427 μg/mL under the same antiviral assays conditions

desired **10a** did not generate (Table 1, entry 1). Prolonging to 5 h or raising temperature to 45 °C did not improve the reaction (Table 1, entries 2 and 3). Delightly, the desired **10a** was afforded in 65 % yield when the loading amount of catalysts and benzoic acid was doubled while maintaining same ratio of catalysts to benzoic acid. A slightly increasing of yield could also achieve when the reaction was conducted at 45 °C. With the optimized conditions in hand, all products **7** and **10** were afforded in good to excellent yields (see experimental section for the yields).

The possible HIV inhibitory activity of the title compounds **7** and **10** was preliminarily tested using multinuclear activation of a galactosidase indicator (MAGI) method (Vodicka *et al*., 1997; Hu *et al*., 2012). The inhibitory rates of all samples at a concentration of 0.39 μg/mL are listed in Table 2. For comparison, the known IN inhibitor, Raltegravir, was used as a positive drug control, whose inhibitory rates were measured to be 94.09 % (at 0.1 μg/mL) and 70.99 % (0.01 μg/mL) under the same biological testing conditions. Very lower inhibitory efficiency was observed for most of the compounds **7,** wherein the triazole cycles are appended with benzyl group, although **7a** exhibited 37.77 % inhibitory rate. When the benzyl group was replaced by a phenyl group, as in the cases of compounds **10**, a little higher inhibitory activity was afforded, and **10e** gave 35.24 % of inhibitory

rate. These results indicate that a rigid hydrophobic side chain may improve the inhibitory activity of the *N*-hydroxytriazole-4-carboxamides.

Conclusion

In conclusion, based on the possible metal-binding mode of picoline hydroxamic acid, we assumed that an *N*-hydroxytriazole-4-carboxamide scaffold may serve as a pharmacophore for the design of HIV IN inhibitor. Therefore, a series of *N*-hydroxy-triazole-4-carboxamide derivatives appended by hydrophobic benzyl and phenyl side chain were synthesized. The two subunits were efficiently assembled by a click reaction between a terminal alkyne and an azide compound. Their HIV inhibitory activity was evaluated, and no satisfactory activities were observed.

Experimental

All melting points (mp) were measured with an XT4A electrothermal apparatus equipped with a microscope and are uncorrected. Infrared spectra (IR) were recorded as thin films on KBr plates on a Bruker IR spectrophotometer and are expressed in v (cm^{-1}). ^1H and ^{13}C NMR spectra were recorded on an AV 400 M Bruker spectrometer (400 MHz for ^1H frequency, 100 MHz for ^{13}C frequency) in solvent ($CDCl_3$ or DMSO-d_6) with TMS as an internal reference. MS data (ESI) were recorded on a Bruker esquire 6000 mass spectrometer. All solvents were of commercial quality and were dried and purified by standard procedures. Propynoic acid hydroxyamide **4** (Suzuki *et al*., 2010), benzyl azides **5** (Sá and Ramos, 2006), and aromatics azides **9** (Barral *et al*., 2007) were synthesized following known procedures and used directly.

General procedure for the synthesis of benzyl-substituted *N*-hydroxy-triazole-4-carboxamides (**7**)

A 25-mL round flask was charged with $CuSO_4{\cdot}5H_2O$ (5.0 mg, 0.02 mmol), sodium ascorbate (7.9 mg, 0.04 mmol), benzoic acid (24.4 mg, 0.2 mmol), and 2 mL of *t*-butanol/water ($V{:}V = 1{:}2$) mixed solvent. To the solution was added azides **6** (1.1 mmol) and propynoic acid hydroxyamide **4** (1 mmol), and the reaction was stirred at room temperature. After stirring for about 50 min, TLC monitoring showed that starting materials were consumed. Dichloromethane (30 mL) was added, the organic layer was washed with brine and then water, and finally dried by anhydrous $MgSO_4$. After filtration, most of the solvents were evaporated under reduced pressure, and the product was then precipitated to give gray solid. Pure products *N*-hydroxy-triazole-4-carboxamides **7** could be obtained after recrystallization with ethyl acetate/petroleum ether or flash chromatograph ($V_{ethyl\ acetate}/V_{petroleum\ ether} = 1{:}10$).

*1-Benzyl-N-hydroxy-1H-1,2,3-triazole-4-carboxamide (**7a**)*

Yield: 90 %; m.p.: 197–198 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 5.64 (s, 2H), 7.33–7.41 (m, 5*H*, Ar–H), 8.59 (s, 1H, triazole-H), 9.03 (s, 1H, OH), 11.25 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 53.5, 126.7, 128.5, 128.8, 129.3, 136.1, 141.9, 158.0; IR (KBr): v 3,290, 3,129, 2,894, 1,643, 1,577, 1,458, 1,432, 1,256, 1,051, 1,005, 881, 716, 696, 575 cm^{-1}; ESI–MS: *ESI–MS* m/z 219.0 (M^++1); 241.0 $(M + Na)^+$.

*1-(2-Methylbenzyl)-N-hydroxy-1H-1,2,3-triazole-4-carboxamide (**7b**)*

Yield: 88 %; m.p.: 191–193 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 2.32 (s, 3H, CH_3), 5.65 (s, 2*H*, CH_2), 7.11 (d, 1H, $J = 7.2$ Hz, Ar–H), 7.18–7.28 (m, 3H, Ar–H), 8.47 (s, 1H, triazole-H), 9.04 (s, 1H, OH), 11.25 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 19.1, 51.6, 126.7, 126.8, 128.9, 129.2, 130.9, 134.2, 136.8, 141.8, 158.0; IR (KBr): v 3,429, 3,316, 3,120, 2,921, 2,853, 1,644, 1,625, 1,578, 1,381, 1,239, 1,045, 880, 690 cm^{-1}; ESI–MS m/z 233.0 (M^++1); 254.9 $(M + Na)^+$.

*1-(3-Methylbenzyl)-N-hydroxy-1H-1,2,3-triazole-4-carboxamide (**7c**)*

Yield: 85 %; m.p.: 174.2–179 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 2.29 (s, 3H, CH_3), 5.58 (s, 2H, CH_2), 7.12–7.29 (m, 4H, Ar–H), 8.58 (s, H, triazole-H), 9.03 (s, 1H, OH), 11.24 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.4, 53.5, 125.6, 126.7, 129.1, 129.2, 129.4, 136.0, 138.6, 142.0, 158.1; IR (KBr): v 3,435, 3,348, 3,116, 2,856, 1,635, 1,574, 1,096, 880, 754 cm^{-1}; ESI–MS m/z 233.0 (M^++1); 254.9 $(M + Na)^+$.

*1-(4-Methylbenzyl)-N-hydroxy-1H-1,2,3-triazole-4-carboxamide (**7d**)*

Yield: 86 %; m.p.: 192–194 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 2.28 (s, 3H, CH_3), 5.58 (s, 2H, CH_2), 7.19 (d, 2H, $J = 7.6$ Hz, Ar–H), 7.25 (d, 2H, $J = 7.6$ Hz, Ar–H), 8.55 (s, 1H, triazole-H), 9.03 (s, 1H, OH), 11.24 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.2, 53.3, 126.6, 128.6, 129.8, 133.1, 138.1, 142.3, 158.0; IR (KBr): v 3,316, 3,114, 2,922, 2,854, 1,625, 1,578, 1,449, 1,252, 1,045, 882, 761 cm^{-1}; ESI–MS m/z 232.9 (M^++1); 254.9 $(M + Na)^+$.

*1-(2-Fluorobenzyl)-N-hydroxy-1H-1,2,3-triazole-4-carboxamide (**7e**)*

Yield: 85 %; m.p.: 189–192 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.71 (s, 2H, CH_2), 7.25–7.29 (m, 2H, Ar–H), 7.36–7.46 (m, 2*H*, Ar–H), 8.55 (s, 1H, triazole-H), 9.04 (s, 1*H*, OH), 11.25 (s, 1*H*, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 47.63 (d), 116.1 (d), 123.0 (d), 125.3 (d), 126.8, 131.2 (d), 131.3 (d), 141.8, 158.0, 161.8 (d); IR (KBr): *v* 3,291, 3,125, 2,919, 1,641, 1,577, 1,493, 1,239, 1,049, 881, 756 cm^{-1}; ESI–MS *m/z* 237.0 (M^++1); 259.1 $(M + Na)^+$.

*1-(3-Fluorobenzyl)-N-hydroxy-1H-1,2,3-triazole-4-carboxamide (**7f**)*

Yield: 87 %; m.p.: 193–194 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.67 (s, 2H, CH_2), 7.16–7.22 (m, 3H, Ar–H), 7.41–7. 47 (m, 1H, Ar–H), 8.63 (s, 1H, triazole-H), 9.04 (s, 1H, OH), 11.25 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 52.8, 115.3 (d), 115.5 (d), 124.6 (d), 126.9, 131.3 (d), 138.7 (d), 142.0, 158.0, 162.6 (d); IR (KBr): *v* 3,289, 3,132, 2,893, 1,642, 1,580, 1,488, 1,454, 1,006, 881, 742, 593 cm^{-1}; ESI–MS *m/z* 237.0 (M^++1); 258.9 $(M + Na)^+$.

*1-(4-Fluorobenzyl)-N-hydroxy-1H-1,2,3-triazole-4-carboxamide (**7g**)*

Yield: 80 %; m.p.: 178–189 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.63 (s, 2H, CH_2), 7.22 (t, 2H, J = 8.8 Hz, Ar–H), 7.41–7.45 (m, 2H, Ar–H), 8.60 (s, 1H, triazole-H), 9.04 (s, 1H, OH), 11.25 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 52.7, 116.1 (d), 126.7, 130.9 (d), 132.3 (d), 142.0, 158.0, 162.4 (d); IR (KBr): *v* 3,322, 3,126, 2,993, 2,919, 1,902, 1,640, 1,514, 1,235, 1,015, 880, 858 cm^{-1}; ESI–MS *m/z* 237.0 (M^++1); 259.0 $(M + Na)^+$.

*1-(2-Bromobenzyl)-N-hydroxy-1H-1,2,3-triazole-4-carboxamide (**7h**)*

Yield: 79 %; m.p.: 200–205 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.73 (s, 2H, CH_2), 7.21 (d, 1H, J = 7.2 Hz, Ar–H), 7.33 (t, 1H, J = 7.6 Hz, Ar–H), 7.42 (t, 1H, J = 7.6 Hz, Ar–H), 7.70 (d, 1H, J = 8.0 Hz, Ar–H), 8.53 (s, 1H, triazole-H), 9.06 (s, 1H, OH), 11.28 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 53.7, 123.4, 127.1, 128.8, 131.0, 131.1, 133.4, 134.9, 141.7, 157.9; IR (KBr): *v* 3,425, 3329, 3,131, 2,920, 2,851, 1,623, 1,579, 1,445, 1,046, 746 cm^{-1}; ESI–MS: *m/z* 296.9 (M^++1); 318.9 $(M + Na)^+$.

*1-(3-Nitrobenzyl)-N-hydroxy-1H-1,2,3-triazole-4-carboxamide (**7i**)*

Yield: 82 %; m.p.: 178–181 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.82 (s, 2H, CH_2), 7.70 (t, 1H, J = 8.0 Hz, Ar–H), 7.80 (d, 1H, J = 7.6 Hz, Ar–H), 8.21 (t, 2H, J = 8.4 Hz, Ar–H), 8.26 (s, 1H, Ar–H), 8.69 (s, 1H, triazole-H), 9.06 (s, 1H, OH), 11.29 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 52.5, 123.4, 123.7, 127.1, 130.9, 135.3, 138.1, 142.1, 148.4, 157.9; IR (KBr): *v* 3,427, 3,313, 3,131, 3,070, 1,630, 1,581, 1,538, 1,350, 1,048, 880, 810 cm^{-1}; ESI–MS *m/z* 264.0 (M^++1).

General procedure for the synthesis of phenyl-substituted *N*-hydroxy-triazole-4-carboxamides (**10**)

Similar to the synthesis of benzyl-substituted *N*-hydroxy-triazole-4-carboxamides **7**, but the reaction mixture was stirred at 45 °C for about 4 h.

*N-Hydroxy-1-phenyl-1H-1,2,3-triazole-4-carboxamide (**10a**)*

Yield: 68 %; m.p.: 195–196 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.53 (t, 1H, J = 7.2 Hz, Ar–H), 7.62 (t, 2H, J = 7.6 Hz, Ar–H), 7.96 (d, 2H, J = 8.0 Hz, Ar–H), 9.16 (s, 1H, OH), 9.26 (s, 1H, triazole-H), 11.42 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 120.9, 124.9, 129.6, 130.4, 136.7, 142.7, 157.8; IR (KBr): *v* 3,427, 3,328, 3,141, 1,632, 1,570, 1,498, 878, 762, 685 cm^{-1}; ESI–MS: *m/z* 203.1 (M^+–1); 205.1 (M^++1); 227.1 $(M + Na)^+$.

*N-Hydroxy-1-(2-methoxyphenyl)-1H-1,2,3-triazole-4-carboxamide (**10b**)*

Yield: 71 %; m.p.: 194–195 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.87 (s, 3H, OCH_3), 7.16 (t, 1H, J = 7.6 Hz, Ar–H), 7.11 (d, 1H, J = 8.4 Hz, Ar–H). 7.57 (t, 1H, J = 7.6 Hz, Ar–H), 7.66 (d, 1H, J = 7.6 Hz, Ar–H), 8.82 (s, 1H, triazole-H), 9.12 (s, 1H, OH), 11.36 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 56.7, 113.5, 121.3, 125.7, 126.4, 128.3, 131.6, 141.5, 152.2, 158.0; IR (KBr): *v* 3,231, 3,172, 2,919, 2,849, 1,658, 1,603, 1,513 cm^{-1}; ESI–MS *m/z* 235.1 (M^++1); 257.0 $(M + Na)^+$.

*N-Hydroxy-1-(3-nitrophenyl)-1H-1,2,3-triazole-4-carboxamide (**10c**)*

Yield: 70 %; m.p.: 199-201 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.93 (t, 1H, J = 8.0 Hz, Ar–H), 8.36–8.47 (m, 2H, Ar–H), 8.80 (s, 1H, Ar–H), 9.22 (s, 1H, OH), 9.51 (s, 1H, triazole-H), 11.52 (s, 1H, NH); ^{13}C NMR

(100 MHz, DMSO-d_6): δ 115.8, 124.0, 125.7, 127.0, 132.0, 137.3, 143.1, 149.0, 157.5; IR (KBr): v 3,449, 3,249, 3,113, 2,920, 2,851, 1,671, 1,630, 1,535, 1,351, 1,017, 778 cm^{-1}; ESI–MS: m/z 250.0 $(M^+ + 1)$, 272.0 $(M + Na)^+$.

*1-(4-Chlorophenyl)-N-hydroxy-1H-1,2,3-triazole-4-carboxamide (**10d**)*

Yield: 75 %; m.p.: 206–208 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.69 (d, 2H, $J = 8.8$ Hz, Ar–H), 8.00 (d, 2H, $J = 8.8$ Hz, Ar–H), 9.17 (s, 1H, OH), 9.29 (s, 1H, triazole-H), 11.43 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 122.7, 125.2, 130.3, 134.0, 135.5, 142.9, 157.7; IR (KBr): v 3,319, 3,142, 2,889, 1,632, 1,598, 1,040, 994, 880, 836, 650 cm^{-1}; ESI–MS: *ESI–MS* m/z 239.0 $(M^+ + 1)$, 261.0 $(M + Na)^+$.

*1-(5-Chloro-2-nitrophenyl)-N-hydroxy-1H-1,2,3-triazole-4-carboxamide (**10e**)*

Yield: 82 %; m.p.: 206–209 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.99 (dd, 1H, $J = 8.8$ Hz, $J = 2.0$ Hz, Ar–H), 8.22 (d, 1H, $J = 1.6$ Hz, Ar–H), 8.31 (d, 1H, $J = 8.4$ Hz, Ar–H), 9.16 (s, 1H, triazole-H), 9.21 (s, 1H, OH), 11.51 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 127.8,128.5,130.4,131.9,139.1,142.4,143.1,157.3; IR (KBr): v 3,295, 3,134, 1,629, 1,606, 1,531, 1,036, 882, 858 cm^{-1}; ESI–MS: *ESI–MS* m/z 283.9 $(M^+ + 1)$, 305.9 $(M + Na)^+$.

Antiviral assays

The HeLa-CD4-LTR-β-gal indicator cells were plated in 96-well plates at 6,000 cells per well. The highest concentration of the test compounds was 200 μg/mL and then diluted by four-fold serially. There were five dilutions and four duplicates for each dilution. The wells added only with virus-infected cells and without compounds were used as viral control, and the wells added only with mock-infected cells and without virus or compounds were used as cell control. The supernatant in the test wells and the viral control wells was discarded and then infected with 100 μL 2000 TCID50 HIV-1 pseudoviruses. Then, 100 μL diluted test compounds described above were added to the wells, making the final concentration of the test compounds decreased by half. The cell cultures were incubated at 37 °C in 5 % CO_2 humidified atmosphere for 40–48 h and then fixed and stained. Blue plaques were counted and analyzed with software Imagpro 7.0 of Olympus IX71 inverted fluorescence Microscope (Japan, Olympus). Viral control and cell control were set, and Raltegravir was chose as positive drug control.

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