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Synthesis and structure–activity relationship of histone deacetylase (HDAC) inhibitors with triazole-linked cap group

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Abstract—Histone deacetylase (HDAC) inhibition is a recent, clinically validated therapeutic strategy for cancer treatment. Small molecule HDAC inhibitors identified so far fall in to three distinct structural motifs: the zinc-binding group (ZBG), a hydrophobic linker, and a recognition cap group. Here we report the suitability of a 1,2,3-triazole ring as a surface recognition cap group-linking moiety in suberoylanilide hydroxamic acid-like (SAHA-like) HDAC inhibitors. Using ''click'' chemistry (Huisgen cycloaddition reaction), several triazole-linked SAHA-like hydroxamates were synthesized. Structure–activity relationship revealed that the position of the triazole moiety as well as the identity of the cap group markedly affected the in vitro HDAC inhibition and cell growth inhibitory activities of this class of compounds.
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1. Introduction

Histone deacetylase (HDAC) inhibitors have become promising anticancer agents in recent years. They have shown ability to block angiogenesis and cell cycling, as well as initiate differentiation and apoptosis.[1,2] HDAC inhibition has recently been clinically validated as a new therapeutic strategy for cancer treatment with the FDA approval of suberoylanilide hydroxamic acid (SAHA) for the treatment of cutaneous T cell lymphoma.[3] Intense research activities are ongoing in pharmaceutical and academic laboratories toward improving the pharmacokinetic and therapeutic indices of current HDAC inhibitors. The classic pharmacophore for HDAC inhibitors consists of three distinct structural motifs: the zinc-binding group (ZBG), a hydrophobic linker, and a recognition cap group (Fig. 1).[4] The X-ray structures of a bacterial HDAC homolog, histone deacetylase-like protein (HDLP), bound to SAHA or Trichostatin A (TSA) and, more recently, human HDAC8, confirmed that the ZBG interacts with a Zn^{2+} ion at the base of a channel-like active site.[4–6] The hydrophobic linker efficiently presents the ZBG to the active site by filling the channel while the cap group at the other end of the linker makes contacts with amino acid residues at the rim of the channel.

The common ZBG of HDAC inhibitors is the hydroxamate moiety. The structural modifications of the hydroxamate ZBG have been modestly successful; yielding isosteres such as benzamide, α-ketoesters, electrophilic ketones, mercaptoamide and phosphonates.[4,7] Hence, the cap group presents an alternative opportunity to discover potent and more selective HDAC inhibitors. In this regard, recent work by Schreiber and coworkers has led to the identification of cap group-modified agents that display differential inhibition against specific HDAC sub-types.[8,9]

In a prototypical HDAC inhibitor, the cap group could be linked to the aliphatic linker group through either hydrogen-bond accepting or donating groups such as keto- and amide-groups (Fig. 1). The apparent lack of preference for H-bond donor or acceptor in the linking-moiety presents an opportunity to incorporate other more synthetically accessible and pharmacokinetically desirable moieties that may help simplify the molecular design and synthesis of novel HDAC inhibitors. We proposed that a 1,2,3-triazole ring could act as a linking-moiety which joins the cap group to the linker group

Keywords: Histone deacetylase (HDAC); Histone deacetylase-like protein (HDLP); Suberoylanilide hydroxamic acid (SAHA); Trichostatin A (TSA); Zinc-binding group (ZBG); SAHA-like hydroxamates, 1,2,3-triazole; Click chemistry; Molecular docking; AutoDock.
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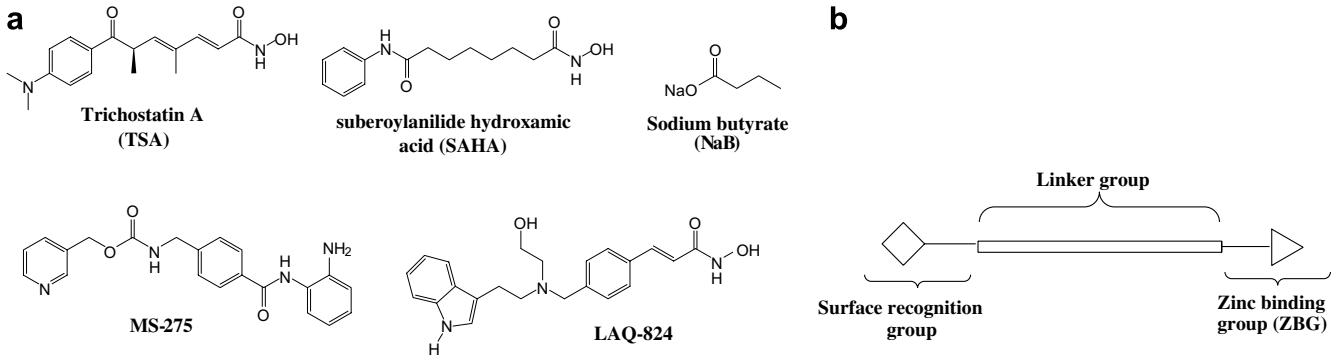


Figure 1. Small molecule HDAC inhibitors. (a) Selected examples of acyclic HDAC inhibitors; (b) pharmacophoric model of HDAC inhibitors.

in a HDAC inhibitor. The triazole ring will serve two purposes: (1) it could facilitate stronger cap group interactions with the amino acid side chains at the entrance of the HDAC active site; (2) it could serve as an isostere to the pharmacokinetically and toxicologically disadvantageous groups such as amide and ketone. We report here the synthesis and structure–activity relationship for HDAC inhibitors incorporating 1,2,3-triazole as the cap group-linking moiety.

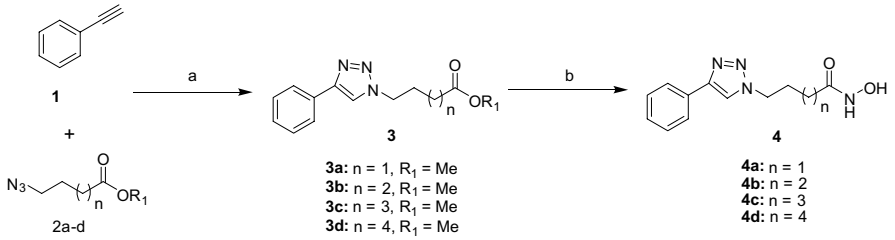
2. Chemistry

The key reaction in the synthesis of the proposed HDAC inhibitors is the Cu(I)-catalyzed Huisgen cycloaddition between azides and terminal alkynes (click chemistry). Click chemistry was popularized by elegant works from Sharpless and Meldal's laboratories,[10,11] and has become a tool for the construction of various complex macromolecules and for rapid identification of small molecules with interesting biological activities.[11] To directly assess the effect of triazole ring as a cap group-linking moiety in simple linear aliphatic-hydroxamate HDAC inhibitors, we first synthesized a series of SAHA-like hydroxamates **4a**–**d**. These compounds link the aromatic surface recognition cap group to the aliphatic zinc-binding hydroxamate moiety via a 1,2,3-triazole ring. Cu(I)-catalyzed Huisgen cycloaddition between phenylacetylene **1** and known azido esters **2a**–**d**,[12–14] followed by treatment of the intermediate esters **3a**–**d** with 50% aqueous hydroxylamine[15] furnished the desired hydroxamic acids **4a**–**d** in good to excellent yields (Scheme 1). Similarly, the synthesis of analogs with other aromatic surface recognition cap groups is achieved starting from the corresponding aryl alkynes and azido esters (Scheme 2). Aryl alkynes, **5g**, **5i**, **5j**, **5l**, **5p**, and **5q**, that were not commercially available were synthesized from the corresponding aldehydes and carboxylic acids (through the intermediacy of aldehyde) using the Bestmann-Ohira reagent.[16–18]

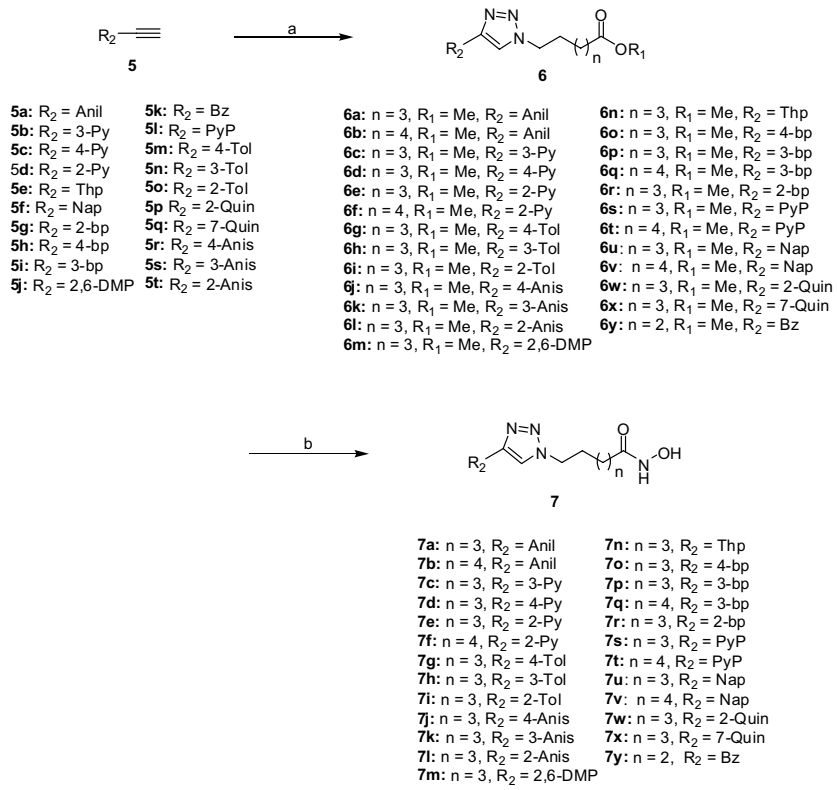
3. Results and discussion

3.1. In vitro enzyme inhibition

To establish whether a 1,2,3-triazole ring is a suitable moiety for connecting the surface recognition cap group to the aliphatic zinc-binding hydroxamate in a prototypical HDAC inhibitor, we initially synthesized simple SAHA-like linear aliphatic-hydroxamates **4a**–**d**. Subsequent in vitro evaluation using the *Fluor de Lys* assay[19] revealed some interesting features about the anti-HDAC activity of these compounds. Compound **4a**, an analog with three methylene spacers separating the triazole ring and the hydroxamate moiety, had no detectable anti-HDAC activity. Conversely, compounds **4b**–**d** displayed spacer length-dependent HDAC inhibition activities with **4c** and **4d**, analogs with five- and six-methylene spacers, respectively, being the most potent (Table 1). This preliminary result showed that the anti-HDAC activities of these compounds tracked with, and thus confirmed the early observation about the optimal spacer length for TSA- and SAHA-like anti-HDAC hydroxamates.[4,20] More importantly, a head-to-head comparison revealed that incorporation of triazole ring enhanced HDAC inhibition. For example, compound **4c**, the closest analog of SAHA, was about fourfold more active than SAHA.

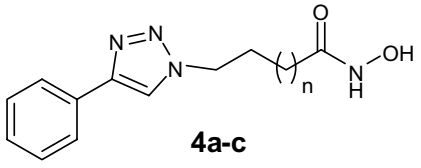


Scheme 1. Synthesis of aryltriazolylhydroxamate **4a**–**d**. Reagents and conditions: (a) CuI, Hunig's base, THF, rt; (b) $NH_2OH_{(aq)}$, KCN, 1:1 THF/MeOH, rt.



Scheme 2. Synthesis of aryltriazolylhydroxamates **7** for SAR studies. Reagents and conditions: (a) **2b–d**, CuI, Hunig's base, THF, rt; (b) $NH_2OH_{(aq)}$, KCN, 1:1 THF/MeOH, rt. *Abbreviation:* Anil, *p*-anilyl; 4-Py, 4-pyridyl; 3-Py, 3-pyridyl; 2-Py, 2-pyridyl; Thp, thiopyl; Nap, 6-methoxynapthyl; 4-bp, 4-biphenyl; 3-bp, 3-biphenyl; 2-bp, 2-biphenyl; 2,6-DMP, 2,6-dimethoxyphenyl; PyP, 4-pyridylphenyl; 4-Tol, 4-tolyl; 3-Tol, 3-tolyl; 2-Tol, 2-tolyl; 2-Quin, 2-quinolyl; 7-Quin, 7-quinolyl; 4-Anis, 4-anisolyl; 3-Anis, 3-anisolyl; 2-Anis, 2-anisolyl.

Table 1. In vitro inhibition data for aryltriazolylhydroxamates **4**



Compound	*N*	IC_{50}[a] (nM)
4a	1	N.D.[b]
4b	2	110.0
4c	3	14.2
4d	4	9.6

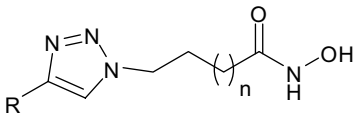
TSA and SAHA with IC_{50} values of 5 nM and 65 nM, respectively, were used as controls.

[a] Data represent mean values of at least three-independent experiments in *Fluor de Lys* assay.

[b] N.D., not determinable.

Interestingly, there was no clear trend in activity between the five- or six-methylene group spacer groups. For the simple phenyl-substituted compounds, the six-methylene-linked compound **4d** was slightly more active than the five-methylene compound **4c** (Table 1). However, the introduction of a *N*,*N*-dimethylamino moiety to the *para* position of the cap group, similar to the substitution pattern on TSA (Fig. 1a), led to a five-methylene-linked compound that is about 25-fold more active than the corresponding six-methylene compound in the *Fluor de Lys* assay (Table 2, comparing **7a** and **7b**). Because of this cap group-dependent potency of the five- and six-methylene spacer group, we prepared a series of aromatic and heteroaromatic derivatives consisting of either spacer group in order to further explore the SAR of these compounds. This exercise resulted in compounds that display potent HDAC inhibition, which trends with both the hydrophobicity and the substitution pattern of the aromatic ring. Relative to compounds **4c** and **4d**, nitrogen substitution into the phenyl ring did not improve the potency of the simple phenyl-substituted compounds (Table 2, compounds **7c–f**). However, the HDAC inhibitory activity of these pyridine derivatives was dependent on the ring location of the nitrogen atom with the 2-pyridyl derivative **7e** being more active than the corresponding 3-pyridyl and 4-pyridyl analogs, **7c** and **7d**, respectively. Additionally, homologous analogs **7e** and **7f**, differing by a methylene group, showed a chain length dependency similar to that observed with **4c** and **4d**. Similarly, methyl-substituted compounds **7g–i** had ring *ortho*-position substitution preference. However, *para*-substitution was preferred when the substitutent was a methoxy group (Table 2, comparing compounds **7j–l** with **7g–i**). In fact, the activity of *para*-methoxylated compound **7j** was enhanced compared to the reference compound **4c**. A similar *para*-substitution preference has been observed with methoxy-substituted SAHA-like HDAC inhibitors in which the surface recognition cap group is linked to the aliphatic zinc-binding hydroxamate

Table 2. In vitro inhibition data for aryltriazolylhydroxamates **7**



7a-y

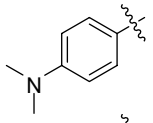
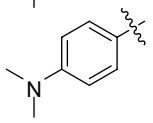
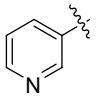
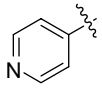
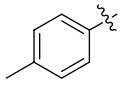
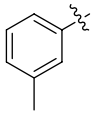
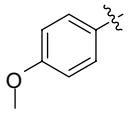
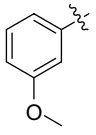
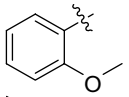
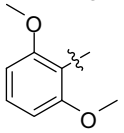
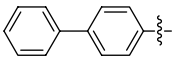
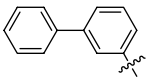
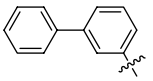
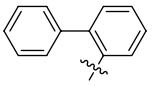
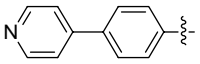
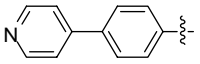
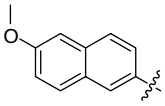
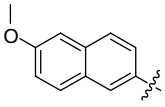
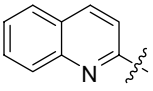
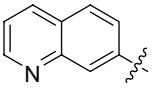
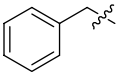
Compound	R	*n*	IC_{50}[a] (nM)
7a		3	4.3
7b		4	106.1
7c		3	287.2
7d		3	112.5
7e		3	67.6
7f		4	23.9
7h		3	43.4
7h		3	31.9
7i		3	17.4
7j		3	2.09
7k		3	13.9
7l		3	76.0
7m		3	315.9
7n		3	31.7

Table 2. (*continued*)

Compound	R	*n*	IC_{50}[a] (nM)
7o		3	52.4
7p		3	1.9
7q		4	5.4
7r		3	162.6
7s		3	2.3
7t		4	16.6
7u		3	1.8
7v		4	15.3
7w		3	2.1
7x		3	151.5
7y		2	N.D.[b]
	SAHA		65

In addition to SAHA, TSA with IC_{50} value of 5 nM was used as control.

[a] Data represent mean values of at least three-independent experiments in *Fluor de Lys* assay.

[b] N.D., not determinable.

through a ketone moiety.[21] The *para*-position preference may be due to the increased steric bulk of the methoxy group. To further investigate this possibility, we synthesized a bisortho methoxy-substituted compound **7m**. We observed an attenuation of the anti-HDAC activity of compound **7m** relative to **7l**. This observation confirmed the influence of steric constraints at the ortho position on the potency of SAHA-like compounds.

Cap groups consisting of fused six-six ring systems such as naphthalenes and quinolines also furnished com-

pounds with potent HDAC inhibitory activities. Parallel to the activity of pyridine derivatives **7c**–**e**, the 2-quinoline analog **7w** was more active than the 7-quinoline analog **7x**. The enhanced potency of the five-methylene linked, 6-methoxynaphthalene capped compound **7u**, relative to the corresponding six-methylene analog **7v**, further underscored the preference of the larger cap groups for a five-methylene spacer. Furthermore, biphenyl compounds **7o**–**t** displayed varying anti-HDAC activity that is dependent on the relative position of the triazole ring and the ring heteroatomic substitution pattern. In general, unsubstituted biphenyl compounds showed preference for the *meta*-placement of the triazole ring and a five-methylene spacer (Table 2, comparing compounds **7o**–**r**).

Finally, the location of the triazole ring was found to influence anti-HDAC activity. Compounds **4c** and **7y** are two isomeric compounds with the same number of carbon atoms separating the cap group and the hydroxamate moiety. Compound **4c**, which has the triazole ring directly attached to the phenyl cap group, was several orders of magnitude more potent than **7y**, whose triazole ring is separated from the cap group by a methylene group. This result is an indirect evidence that the triazole ring is indeed an active participant in the interaction of this class of compound with the HDAC active site.

3.2. Molecular docking

To obtain information on the structural basis of the observed disparity in the HDAC inhibitory activity of these compounds, we performed molecular docking using a validated molecular dock program (AutoDock)[22–24] Docking analysis was performed on histone deacetylase-like protein (HDLP).[5] We chose HDLP because it shares conserved active site residues with the rest of the HDAC family of proteins. In addition, the crystal structures of HDLP alone, as well as those bound to two known HDAC inhibitors, SAHA and TSA, are currently available in the public domain.[5] We performed docking studies with AutoDock 3.05 as described by Lu et al.[24] Independent docking of SAHA (IC_{50} = 65 nM), **4c** (IC_{50} = 14 nM), **7o** (IC_{50} = 52 nM), **7p** (IC_{50} = 1.9 nM), and **7u** (IC_{50} = 1.8 nM) into HDLP revealed that these compounds have preferences for two different binding pockets at the protein surface (Fig. 2). Previous investigations have shown that there are four possible binding pockets on the HDLP surface whose interactions with the aromatic cap groups could enhance the inhibitor-binding ability.[23] Compounds **7o** and **7u** bound within the binding pocket designated pocket 1 while SAHA, **4c** and **7p** bound within pocket 2. The 1,4-biphenyl ring of **7o** adopted a co-planar geometry in order to fit within pocket 1. Presumably, the stacking interactions in pocket 1 favored a co-planar geometry of the cap group, an inference that may be supported by the binding of **7u**, an analog with a flat fused six-six ring, within pocket 1. To adopt the observed conformation, a sharp kink was introduced into the methylene spacer group portion of **7o**. The consequence of this kinked structure was a twist in the orientation of the critical

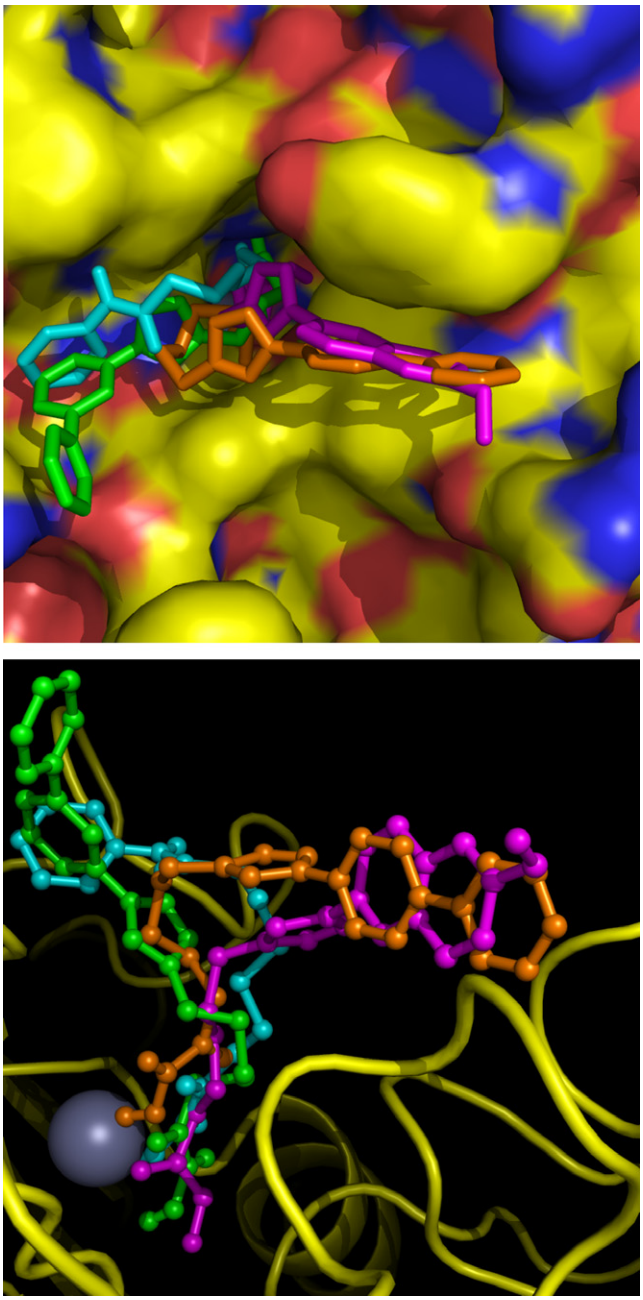


Figure 2. Molecular docking of aryltriazolylhydroxamates **7o** (orange), **7p** (green), **7u** (magenta), and **SAHA** (cyan) to HDLP using AutoDock 3.05[19–21] and viewed in PYMOL. Upper picture: surface of HDLP near the active site; lower picture: side view of the triazolylhydroxamates **7o**, **7p**, **7u**, and **SAHA** coordinating to zinc with amino acid residues in and near the active sites.[19–21]

hydroxamate moiety of **7o**, pulling its hydroxamate-group farther from the active site Zn^{2+} ion, compared to that of **7p** and SAHA. This potentially nullified any positive effects derived from the cap group interaction with pocket 1 and may proffer explanation about the reduced potency of **7o** compared to the structurally related **7p**. Unlike **7o**, the 1,3-biphenyl ring of **7p** preferred a non-planar geometry with the biphenyl ring protruding deeper into binding pocket 2 where it hydrophobically interacted further with the pocket residues. This extra

interaction could explain the higher potency of **7p** compared to **4c** and SAHA.

3.3. Cell growth inhibitory assay

To preliminarily screen for the whole cell activity of compounds described in this study, we tested the effect of the exposure of selected compounds on the viability of DU-145, a human prostate cancer cell line known to respond to HDAC inhibitors.[25] We evaluated compounds **7s**, **7u**, **7v** and **7w** with SAHA as a reference, using both the MTS test (a colorimetric method) and trypan blue exclusion, to qualitatively and quantitatively measure the effect of compound exposure to cell viability.[26,27] We obtained an EC_{50} value of 2.12 μM for SAHA, a value in close agreement with the reported EC_{50} in DU-145 under similar experimental conditions.[28] Compounds **7s**, **7u**, **7v** and **7w** also inhibited the proliferation of DU-145 in a dose-dependent manner, with EC_{50} values ranging from 2.2 to 8.0 μM (Table 3). These results validated the suitability of the triazole ring as a linking moiety in the design of SAHA-like HDAC inhibitors.

4. Conclusion

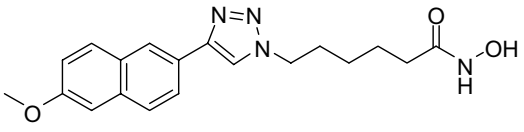
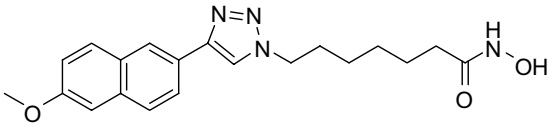
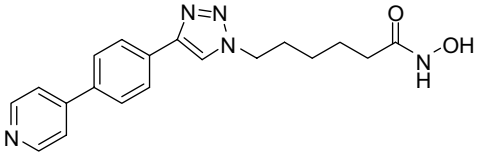
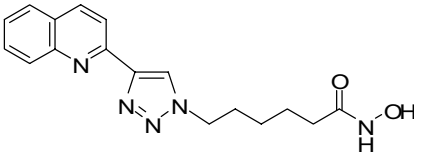
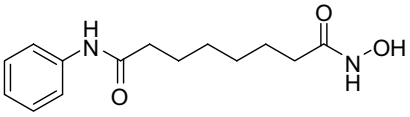
We have established that a 1,2,3-triazole ring is suitable as a surface recognition cap group-linking moiety in SAHA-like HDAC inhibitors. The structure–activity relationship of the resulting triazole-linked hydroxamates displayed a cap group dependent preference for either five- or six-methylene spacer groups. We identified compounds that are several folds more potent than SAHA. A subset of these compounds also inhibited the proliferation of DU-145 cells. Due to their anticipated resistance to intracellular peptidases, these triazole-linked HDAC inhibitors may display improved in vivo activity relative to the common amide based inhibitors.

5. Experimental

5.1. Analogue synthesis

5.1.1. General. 4-Bromobutyric acid, 5-bromovaleric acid, 6-bromohexanoic acid, and 7-bromoheptane nitrile were purchased from Sigma–Aldrich. Anhydrous sol-

Table 3. Cell growth inhibitory data for lead compounds

Aryltriazolylhydroxamates **7**	IC_{50} (nM)	EC_{50}[a] (μM)	EC_{50}[b] (μM)
 **7u**	1.8	3.95	2.6
 **7v**	15.3	7.76	3.99
 **7s**	2.3	4.72	3.07
 **7w**	2.1	2.25	2.46
 **SAHA**	65.0	2.12	2.11

SAHA was used as a control for these experiments.

[a] EC_{50} values were determined from trypan blue exclusion data in DU-145 prostate cancer cell line.

[b] EC_{50} values were determined from MTS assay (Promega), in DU-145 prostate cancer cell line.

vents and other reagents were purchased and used without further purification. Analtech silica gel plates (60 F_{254}) were used for analytical TLC, and Analtech preparative TLC plates (UV 254, 2000 μm) were used for purification. UV light was used to examine the spots. Silica gel (200–400 Mesh) was used in column chromatography. NMR spectra were recorded on a Varian-Gemini 400 magnetic resonance spectrometer. ^{1}H NMR spectra were recorded in parts per million (ppm) relative to the peak of $CDCl_3$, (7.24 ppm), CD_3OD (3.31 ppm), or DMSO-d_6 (2.49 ppm). ^{13}C spectra were recorded relative to the central peak of the $CDCl_3$ triplet (77.0 ppm), CD_3OD (49.0 ppm), or the DMSO-d_6 septet (39.7 ppm), and were recorded with complete heterodecoupling. Multiplicities are described using the abbreviation s, singlet; d, doublet, t, triplet; q, quartet; m, multiplet; and app, apparent. High-resolution mass spectra were recorded at the Georgia Institute of Technology mass spectrometry facility in Atlanta. Melting points (uncorrected) were recorded on a Mel-Temp II apparatus. Methyl bromoalkanoates **1a**–**d** and azido alkylesters **2a**–**d** were synthesized by adapting literature protocol.[12–14] The Bestmann-Ohira reagent was prepared as described by Ghosh et al.[17] Alkynes that we could not obtain from commercial sources were synthesized using the Bestmann-Ohira reagent as described before (see Supporting information for details).[29]

5.1.2. Representative procedure for Cu(I)-catalyzed cycloaddition reaction

5.1.2.1. Methyl 4-(phenyl)triazolylbutanoate (3a). Methyl 4-azidobutanoate **2a** (0.125 g, 0.87 mmol) and phenylacetylene (0.21 mL, 1.92 mmol) were dissolved in anhydrous THF (10 mL) and stirred under argon at room temperature. Copper(I) iodide (0.011 g, 0.07 mmol) and Hunig's base (0.1 mL) were then added to the reaction mixture, and stirring continued for 24 h.[30] The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with 1:4 NH_4OH/saturated NH_4Cl (3× 30 mL) and saturated NH_4Cl (30 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography (silica, gradient 2:1; 3:2 hexanes/EtOAc) to give 117 mg (55%) of **3a** as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.24 (2H, m), 2.36 (2H, t, J = 6.4 Hz), 3.65 (3H, s), 4.45 (2H, t, J = 6.8 Hz), 7.28–7.33 (1H, m), 7.37–7.41 (2H, m), 7.75 (1H, s), 7.78–7.81 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.5, 30.4, 49.2, 51.8, 119.5, 125.5, 127.9, 128.6, 130.3, 147.6, 172.5; HMRS (FAB, thioglycerol) calcd for $[C_{13}H_{15}N_3O_2+H]^+$ 246.1242, found 246.1245.

5.1.2.2. Methyl 5-(phenyl)triazolylpentanoate (3b). Reaction of methyl 5-azidopentanoate **2b** (0.211 g, 1.34 mmol) and phenylacetylene (0.3 mL, 2.79 mmol) within 24 h as described for the synthesis of **3a**, followed by flash chromatography (silica, 1:1 hexanes/EtOAc) gave 180 mg (52%) of **3b** as a white solid.^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.66–1.70 (2H, m), 1.97–2.01 (2H, m), 2.36 (2H, t, J = 7.2 Hz), 3.65 (3H, s), 4.40 (2H, t, J = 6.8 Hz), 7.31 (1H, t, J = 8.0 Hz), 7.40 (2H, t, J = 8.4 Hz) 7.74 (1H, s), 7.81 (2H, d, J = 8.4 Hz); HRMS (FAB, thioglycerol) calcd for $[C_{14}H_{17}N_3O_2+H]^+$ 260.1399, found 260.1386.

5.1.2.3. Methyl 6-(phenyl)triazolylhexanoate (3c). Reaction of methyl 6-azidohexanoate **2c** (0.075 g, 0.43 mmol) and phenylacetylene (1.0 mL, 0.87 mmol) within 24 h as described for the synthesis of **3a**, followed by prep TLC (silica, 1:1 hexanes/EtOAc) gave 94 mg (79%) of **3c** as a white solid.^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26–1.33 (2H, m), 1.56–1.64 (2H, m), 1.84–1.91 (2H, m), 2.24 (2H, t, J = 7.2 Hz), 3.58 (3H, s), 4.30 (2H, t, J = 7.2 Hz), 7.26 (1H, t, J = 7.2 Hz), 7.35 (2H, t, 7.6 Hz), 7.74 (1H, s), 7.77 (2H, d, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.9, 25.6, 29.7, 33.3, 49.7, 51.3, 117.4, 125.3, 127.8, 128.5, 130.4, 147.3, 173.5.

5.1.2.4. Methyl 7-(phenyl)triazolylheptanoate (3d). Reaction of methyl 7-azidoheptanoate **2d** (0.15 g, 0.81 mmol) and phenylacetylene (182 mg, 1.78 mmol) within 24 h as described for the synthesis of **3a**, followed by flash chromatography (silica, 3:2 hexanes/EtOAc) gave 151 mg (65%) of **3d** as colorless oil.^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.35 (4H, p, J = 7.3, 3.5 Hz), 1.57–1.64 (2H, m), 1.89–1.96 (2H, m), 2.28 (2H, t, J = 7.3 Hz), 3.63 (3H, s), 4.36 (2H, t, J = 7.1 Hz), 7.30 (1H, t, J = 7.2 Hz), 7.39 (2H, t, J = 7.3 Hz), 7.72 (1H, s), 7.80 (2H, d, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.7, 26.2, 28.5, 30.2, 33.9, 50.2, 51.5, 119.2, 125.5, 127.9, 128.6, 130.5, 147.5, 173.7; HRMS (FAB, thioglycerol) calcd for $[C_{16}H_{21}N_3O_2+H]^+$ 288.1712, found 288.1711.

5.1.2.5. Methyl 6-(4-anilyl)triazolylhexanoate (6a). Reaction of methyl 6-azidohexanoate **2c** (0.075 g, 0.44 mmol) and 4-ethynyl-*N*,*N*-dimethylaniline **5a** (131 mg, 0.90 mmol) within 24 h as described for the synthesis of **3a**, followed by prep TLC (silica, 1:1 hexanes/EtOAc) gave 114 mg (83%) of **6a** as a pale yellowish solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.30–1.36 (2H, m), 1.60–1.66 (2H, m), 1.87–1.93 (2H, m), 2.26 (2H, t, J = 7.2 Hz), 2.93 (6H, s), 3.61 (3H, s), 4.30 (2H, t, J = 7.2 Hz), 6.72 (2H, d, J = 8.8 Hz), 7.58 (1H, s), 7.66 (2H, d, J = 9.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.0, 25.8, 29.8, 33.5, 40.3, 49.8, 51.4, 112.3, 117.9, 118.7, 126.4, 148.0, 150.2, 173.7.

5.1.2.6. Methyl 7-(4-anilyl)triazolylheptanoate (6b). Reaction of methyl 7-azidoheptanoate **2d** (0.15 g, 0.81 mmol) and 4-ethynyl-*N*,*N*-dimethylaniline **5a** (127 mg, 0.87 mmol) within 24 h as described for the synthesis of **3a**, followed by flash chromatography (silica, 3:2 hexanes/EtOAc) gave 165 mg (62%) of **6b** as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.34–1.37 (4H, m), 1.58–1.64 (2H, m), 1.92 (2H, m), 2.28 (2H, t, J = 7.3 Hz), 2.97 (6H, s), 3.64 (3H, s), 4.34 (2H, t, J = 7.1 Hz), 6.75 (2H, d, J = 8.9 Hz), 7.58 (1H, s), 7.65–7.69 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.0, 26.5, 28.8, 30.5, 34.1, 40.8, 50.4, 51.7, 112.6, 118.1, 119.1, 126.7, 148.2, 150.4, 174.0; HRMS (FAB, thioglycerol) calcd for $[C_{18}H_{26}N_4O_2+H]^+$ 331.2134, found 331.2150.

5.1.2.7. Methyl 6-(3-pyridyl)triazolylhexanoate (6c). Reaction of methyl 6-azidohexanoate **2c** (0.2 g, 1.17 mmol) and 3-ethynylpyridine **5b** (180 mg, 1.74 mmol) within 24 h as described for the synthesis of **3a**, followed

by flash chromatography (silica, 3:2 hexanes/EtOAc) gave 294 mg (92%) of **6c** as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.34–1.41 (2H, m), 1.67 (2H, m), 1.93–2.01 (2H, m), 2.30 (2H, t, J = 7.2 Hz), 3.63 (3H, s), 4.41 (2H, t, J = 7.1 Hz), 7.34 (1H, q, J = 7.9, 4.8 Hz), 7.85 (1H, s), 8.18 (1H, d, J = 7.9 Hz), 8.54 (1H, d, J = 4.3 Hz), 8.97 (1H, d, J = 2.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.1, 25.9, 30.0, 33.6, 50.2, 51.5, 119.7, 123.5, 126.6, 132.7, 144.4, 146.8, 148.9, 173.4; HRMS (FAB, thioglycerol) calcd for $[C_{14}H_{18}N_4O_2+H]^+$ 275.1508, found 275.1491.

5.1.2.8. Methyl 6-(4-pyridyl)triazolylhexanoate (6d). Reaction of methyl 6-azidohexanoate **2c** (0.2 g, 1.17 mmol) and 4-ethynylpyridine **5c** (180 mg, 1.74 mmol) within 24 h as described for the synthesis of **3a**, followed by flash chromatography (silica, 3:2 hexanes/EtOAc) gave 288 mg (90%) of **6d** as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.30–1.38 (2H, m), 1.64 (2H, m), 1.90–1.99 (2H, m), 2.28 (2H, t, J = 7.2 Hz), 3.6 (3H, s), 7.39 (2H, t, J = 7.1 Hz), 7.67 (2H, dd, J = 4.5, 1.5 Hz), 7.90 (1H, s), 8.6 (2H, dd, J = 4.5, 1.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.1, 25.8, 29.9, 33.5, 50.2, 51.5, 119.7, 120.9, 137.7, 145.1, 150.1, 173.4; HRMS (FAB, thioglycerol) calcd for $[C_{14}H_{18}N_4O_2+H]^+$ 275.1508, found 275.1512.

5.1.2.9. Methyl 6-(2-pyridyl)triazolylhexanoate (6e). Reaction of methyl 6-azidohexanoate **2c** (0.2 g, 1.17 mmol) and 2-ethynylpyridine **5d** (180 mg, 1.74 mmol) within 24 h as described for the synthesis of **3a**, followed by flash chromatography (silica, 3:2 hexanes/EtOAc) gave 269 mg (84%) of **6e** as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31–1.39 (2H, m), 1.65 (2H, m), 1.94 (2H, m), 2.27 (2H, t, J = 7.3 Hz), 3.62 (3H, s), 4.39 (2H, t, J = 7.1 Hz), 7.17–7.20 (1H, m), 7.71 (1H, m), 8.09 (1H, s), 8.13 (1H, d, J = 7.9 Hz), 8.52–8.54 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.6, 26.3, 30.3, 34.0, 50.5, 51.8, 120.3, 121.9, 122.9, 137.0, 148.4, 149.4, 150.4, 173.7; HRMS (FAB, thioglycerol) calcd for $[C_{14}H_{18}N_4O_2+H]^+$ 275.1508, found 275.1518.

5.1.2.10. Methyl 7-(2-pyridyl)triazolylheptanoate (6f). Reaction of methyl 7-azidoheptanoate **2d** (0.225 g, 1.21 mmol) and 2-ethynylpyridine **5d** (134 mg, 1.30 mmol) within 24 h as described for the synthesis of **3a**, followed by flash chromatography (silica, 3:2 hexanes/EtOAc) gave 271 mg (78%) of **6f** as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.35–1.39 (4H, m), 1.58–1.68 (2H, m), 1.92–1.99 (2H, m), 2.29 (2H, t, J = 7.4 Hz), 3.65 (3H, s), 4.42 (2H, t, J = 7.1 Hz), 7.21–7.24 (1H, m), 7.75–7.79 (1H, m), 8.14 (1H, s), 8.17 (1H, d, J = 7.9 Hz), 8.56–8.58 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.5, 26.0, 28.3, 29.9, 33.7, 50.2, 51.3, 119.8, 121.5, 122.5, 136.6, 147.9, 148.9, 149.9, 173.5; HRMS (EI) calcd for $[C_{15}H_{20}N_4O_2+H]^+$ 289.1664, found 289.1665.

5.1.2.11. Methyl 6-(4-tolyl)triazolylhexanoate (6g). Reaction of methyl 6-azidohexanoate **2c** (0.2 g, 1.17 mmol) and 4-ethynyltoluene **5m** (204 mg, 1.76 mmol) within 24 h as described for the synthesis of **3a**, followed by flash chromatography (silica, 3:2 hexanes/EtOAc) gave 287 mg (85%) of **6g** as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.18–1.26 (2H, m), 1.53 (2H, m), 1.79 (2H, m), 2.17 (2H, t, J = 7.3 Hz), 2.24 (3H, s), 3.52 (3H, s), 4.21 (2H, t, J = 7.1 Hz), 7.09 (2H, t, J = 7.9 Hz), 7.60 (2H, t, J = 8.0 Hz), 7.67 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.9, 23.9, 25.6, 29.6, 33.3, 49.6, 51.1, 118.9, 125.0, 127.4, 128.9, 137.2, 147.0, 173.1; HRMS (EI) calcd for $[C_{16}H_{21}N_3O_2+H]^+$ 288.1712, found 288.1732.

5.1.2.12. Methyl 6-(3-tolyl)triazolylhexanoate (6h). Reaction of methyl 6-azidohexanoate **2c** (0.2 g, 1.17 mmol) and 3-ethynyltoluene **5n** (204 mg, 1.76 mmol) within 24 h as described for the synthesis of **3a**, followed by flash chromatography (silica, 3:2 hexanes/EtOAc) gave 287 mg (84%) of **6h** as colorless oil. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.33–1.40 (2H, m), 1.63–1.70 (2H, m), 1.95 (2H, m), 2.30 (2H, t, J = 7.3 Hz), 2.38 (3H, s), 4.38 (2H, s, J = 7.1 Hz), 7.11–7.13 (1H, m), 7.28 (1H, t, J = 7.6 Hz), 7.55–7.59 (1H, m), 7.67 (1H, d, J = 0.5 Hz), 7.72 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.9, 24.5, 26.2, 30.3, 33.9, 50.3, 51.8, 119.8, 122.8, 126.4, 128.8, 128.9, 130.6, 138.5, 147.8, 147.8; HRMS (EI) calcd for $[C_{16}H_{21}N_3O_2+H]^+$ 288.1752, found 288.1744.

5.1.2.13. Methyl 6-(2-tolyl)triazolylhexanoate (6i). Reaction of methyl 6-azidohexanoate **2c** (0.2 g, 1.17 mmol) and 2-ethynyltoluene **5o** (204 mg, 1.76 mmol) within 24 h as described for the synthesis of **3a**, followed by flash chromatography (silica, 3:2 hexanes/EtOAc) gave 287 mg (60%) of **6i** as colorless oil. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.25–1.33 (2H, m), 1.58 (2H, m), 1.87 (2H, m), 2.22 (2H, t, J = 7.3 Hz), 2.37 (3H, s), 3.56 (3H, s), 4.30 (2H, t, J = 7.1 Hz), 7.16 (2H, d, J = 3.1 Hz), 7.62 (1H, s), 7.66–7.70 (1H, s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 21.1, 23.9, 25.7, 29.7, 33.3, 49.6, 51.1, 121.4, 125.5, 127.5, 128.2, 129.5, 130.3, 134.9, 146.3, 173.1; HRMS (EI) calcd for $[C_{16}H_{21}N_3O_2+H]^+$ 288.1712, found 288.1709.

5.1.2.14. Methyl 6-(4-anisolyl)triazolylhexanoate (6j). Reaction of methyl 6-azidohexanoate **2c** (0.2 g, 1.17 mmol) and 4-ethynylanisole **5r** (0.232 mg, 1.75 mmol) within 24 h as described for the synthesis of **3a**, followed by flash chromatography (silica, 3:2 hexanes/EtOAc) gave 347 mg (98%) of **6j** as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.29–1.37 (2H, m), 1.63 (2H, p, J = 15.0, 7.3 Hz), 1.91 (2H, p, J = 15.0, 7.3 Hz), 2.27 (2H, t, J = 7.3 Hz), 3.61 (3H, s), 3.79 (3H, s), 4.33 (2H, t, J = 7.1 Hz), 6.88–6.92 (2H, m), 7.64 (1H, s), 7.69–7.72 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.2, 25.9, 30.1, 33.6, 44.9, 51.5, 55.2, 114.0, 118.5, 123.2, 126.7, 147.3, 159.2, 173.4; HRMS (EI) calcd for $[C_{16}H_{21}N_3O_3+H]^+$ 304.1661, found 304.1685.

5.1.2.15. Methyl 6-(3-anisolyl)triazolylhexanoate (6k). Reaction of methyl 6-azidohexanoate **2c** (0.2 g, 1.17 mmol) and 3-ethynylanisole **5s** (0.232 g, 1.75 mmol) within 24 h as described for the synthesis of **3a**, followed by flash chromatography (silica, 3:2 hexanes/EtOAc) gave 301 mg (85%) of **6k** as colorless oil. ^{1}H NMR

(DMSO-d_6, 400 MHz) δ 1.18–1.26 (2H, m), 1.52 (2H, p, J = 14.9, 7.4 Hz), 1.84 (2H, p, J = 7.0, 14.3 Hz), 1.93 (2H, t, J = 7.2 Hz), 3.79 (3H, s), 4.36 (2H, t, J = 6.9 Hz), 6.86–6.89 (1H, m), 7.33 (1H, app. t), 7.39–7.41 (2H, m), 8.58 (1H, s), 8.67 (1H, s), 10.33 (1H, s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 24.5, 25.4, 29.3, 32.0, 49.3, 55.0, 110.1, 113.3, 117.2, 121.2, 129.8, 131.9, 145.9, 159.3, 168.6; HRMS (EI) calcd for $[C_{16}H_{20}N_3O_3+H]^+$ 304.1661, found 304.1688.

5.1.2.16. Methyl 6-(2-anisolyl)triazolylhexanoate (6l). Reaction of methyl 6-azidohexanoate **2c** (0.2 g, 1.17 mmol) and 2-ethynylanisole **5t** (0.232 mg, 1.75 mmol) within 24 h as described for the synthesis of **3a**, followed by flash chromatography (silica, 3:2 hexanes/EtOAc) gave 336 mg (95%) of **6l** as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.41–1.21 (2H, m), 1.47 (2H, p, J = 15.1, 7.4 Hz), 1.75 (2H, p, J = 14.8, 7.2 Hz), 2.11 (2H, t, J = 7.42 Hz), 3.47 (3H, s), 3.73 (3H, s), 4.18 (2H, t, J = 7.1 Hz), 6.79 (1H, d, J = 8.3 Hz), 6.89 (1H, t, J = 7.4 Hz), 7.09–7.13 (1H, m), 8.21 (1H, dd, J = 7.6, 1.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.8, 25.4, 29.5, 33.1, 49.3, 50.9, 54.8, 110.2, 118.8, 120.1, 122.4, 126.6, 128.1, 142.1, 154.8, 172.8; HRMS (FAB, thioglycerol) calcd for $[C_{16}H_{21}N_3O_3+H]^+$ 304.1661, found 304.1676.

5.1.2.17. Methyl 6-(2,6-dimethoxyphenyl)triazolylhexanoate (6m). Reaction of methyl 6-azidohexnoate **2c** (0.15 g, 0.88 mmol) and 2-ethynyl-1,3-dimethoxybenzene **5j** (0.16 g, 0.99 mmol) within 24 h as described for the synthesis of **3a**, followed by flash chromatography (silica, gradient 2:1; 1:1; 1:2; hexanes/EtOAc) gave 114 mg (39%) of **6m** as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.38–1.46 (2H, m), 1.66–1.73 (2H, m), 1.95–2.02 (2H, m), 2.33 (2H, t, J = 7.2 Hz), 3.66 (3H, s), 3.80 (6H, s), 4.40 (2H, t, J = 7.2 Hz), 6.65 (2H, d, J = 8.4 Hz), 7.29 (1H, t, J = 9.2 Hz), 7.68 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.1, 25.8, 29.8, 33.5, 49.6, 51.2, 55.7, 103.8, 108.4, 123.7, 129.2, 139.3, 157.8, 173.2; HRMS (FAB, thioglycerol) calcd for $[C_{17}H_{23}N_3O_4+H]^+$ 334.1766, found 334.1776.

5.1.2.18. Methyl 6-(2-thiopyl)triazolylhexnoate (6n). Reaction of methyl 6-azidohexnoate **2c** (0.2 g, 1.16 mmol) and 2-ethynylthiophene **5e** (0.1 mL, 1.02 mmol) within 24 h as described for the synthesis of **3a**, followed by flash chromatography (silica, gradient 2:1; 1:1 hexanes/EtOAc) gave 209 mg (74%) of **6n** as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.24–1.31 (2H, m), 1.54–1.62 (2H, m), 1.81–1.89 (2H, m), 2.22 (2H, t, J = 7.2 Hz), 3.57 (3H, s), 4.28 (3H, t, J = 5.4 Hz), 7.29 (1H, dd, J = 4.8, 2.8 Hz), 7.38 (1H, dd, J = 4.8, 1.2 Hz), 7.59 (1H, dd, J = 3.2, 1.2 Hz), 7.63 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.0, 25.7, 29.8, 33.5, 49.8, 51.3, 119.1, 120.5, 125.4, 125.9, 131.6, 143.4, 173.2; HRMS (FAB, thioglycerol) calcd for $[C_{13}H_{17}N_3O_2S+H]^+$ 280.1244, found 280.1223.

5.1.2.19. Methyl 6-(4-biphenyl)triazolylhexnoate (6o). Reaction of methyl 6-azidohexanoate **2c** (0.2 g, 1.17 mmol) and 4-ethynylbiphenyl **5h** (0.317 g, 1.75 mmol) within 24 h as described for the synthesis of **3a**, followed by flash chromatography (silica, gradient 2:1; 1:1 hexanes/EtOAc) to give 90 mg (22%) of **6o** as a pale yellowish solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31–1.39 (2H, m), 1.61–1.69 (2H, m), 1.89–1.95 (2H, m), 2.28 (2H, t, J = 7.2 Hz), 3.62 (3H, s), 4.35 (2H, t, J = 7.2 Hz), 7.32 (1H, t, J = 8.0 Hz), 7.41 (2H, t, J = 8.0 Hz), 7.58–7.63 (4H, m), 7.76 (1H, s), 7.87 (2H, d, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.1, 25.9, 29.9, 33.6, 49.9, 51.4, 119.4, 125.7, 126.6, 127.1, 128.5, 129.4, 140.1, 140.4, 147.0, 173.3; HRMS (FAB, thioglycerol) calcd for $[C_{21}H_{23}N_3O_2+H]^+$ 350.1868, found 350.1885.

5.1.2.20. Methyl 6-(3-biphenyl)triazolylhexnaoate (6p). Reaction of methyl 6-azidohexnoate **2c** (0.2 g, 1.16 mmol) and 3-ethynylbiphenyl **5i** (0.32 g, 1.79 mmol) within 24 h as described for the synthesis of **3a**, followed by flash chromatography (silica, gradient 2:1; 1:1 hexanes/EtOAc) gave 300 mg (74%) of **6p** as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27–1.35 (2H, m), 1.58–1.65 (2H, m), 1.85–1.93 (2H, m), 2.25 (2H, t, J = 7.6 Hz), 3.60 (3H, s), 4.31 (2H, t, J = 7.2 Hz), 7.32 (1H, t, J = 7.2 Hz), 7.39–7.46 (3H, m), 7.52 (1H, d, J = 8.0 Hz), 7.62 (2H, d, J = 7.6 Hz), 7.77 (1H, d, J = 7.6 Hz), 7.82 (1H, s), 8.08 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.9, 25.7, 29.7, 33.4, 49.7, 51.2, 119.5, 123.9, 124.1, 126.3, 126.7, 127.0, 128.3, 128.8, 130.8, 140.2, 141.2, 147.0, 173.2; HRMS (FAB, thioglycerol) calcd for $[C_{21}H_{23}N_3O_2+H]^+$ 350.1868, found 350.1870.

5.1.2.21. Methyl 7-(3-biphenyl)triazolylheptanaoate (6q). Reaction of methyl 7-azidoheptanoate **2d** (0.184 g, 1.03 mmol) and 3-ethynylbiphenyl **5i** (185 mg, 1.03 mmol) within 24 h as described for the synthesis of **3a**, followed by flash chromatography (silica, 3:2 hexanes/EtOAc) gave 201 mg (54%) of **6q** as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.32–1.35 (4H, m), 1.59 (2H, p, J = 14.72, 7.36), 1.91 (2H, m), 2.26 (2H, t, J = 7.4 Hz), 3.62 (3H, s), 4.35 (2H, t, J = 7.1 Hz), 7.31–7.35 (1H, m), 7.39–7.44 (2H, m), 7.46 (1H, dd, J = 7.6, 0.4 Hz), 7.51–7.54 (1H, m), 7.60–7.63 (2H, m), 7.73–7.78 (1H, m), 7.79 (1H, s), 8.05–8.06 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.6, 26.1, 28.4, 30.1, 33.8, 50.2, 51.4, 119.4, 124.2, 124.3, 126.9, 127.2, 128.5, 129.0, 129.3, 130.9, 140.5, 141.5, 147.3, 173.6; HRMS (EI) calcd for $[C_{22}H_{25}N_3O_2+H]^+$ 364.2025, found 364.2045.

5.1.2.22. Methyl 6-(2-biphenyl)triazolylhexanoate (6r). Reaction of methyl 6-azidohexnoate **2c** (0.16 g, 0.93 mmol) and 2-ethynylbiphenyl **5g** (0.11 g, 0.62 mmol) within 24 h as described for the synthesis of **3a**, followed by flash chromatography (silica, gradient 2:1; 1:1 hexanes/EtOAc) gave 161 mg (75%) of **6r** as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.09–1.17 (2H, m), 1.49–1.57 (2H, m), 1.61–1.69 (2H, m), 2.21 (2H, t, J = 7.6 Hz), 3.59 (3H, s), 4.09 (2H, t, J = 6.8 Hz), 6.35 (1H, s), 7.16–7.18 (2H, m), 7.24–7.34 (5H, m), 7.39 (2H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.0, 25.6, 29.6, 33.4, 49.5, 51.3, 121.8, 126.9, 127.4, 127.5, 128.0, 128.2, 128.8, 128.9, 129.7, 139.8, 141.3, 145.8, 173.2; HRMS (FAB, thioglycerol) calc for $[C_{21}H_{23}N_3O_2+H]^+$ 350.1868, found 350.1877.

5.1.2.23. Methyl 6-(4-pyridylphenyl)triazolylhexanoate (6s). Reaction of methyl 6-azidohexanoate **2c** (0.2 g, 1.17 mmol) and 4-(4-ethynylphenyl)-pyridine **5l** (0.232 g, 1.76 mmol) within 24 h as described for the synthesis of **3a**, followed by flash chromatography (silica,1:3 hexanes/EtOAc) gave 274 mg (67%) of **6s** as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.32–1.40 (2H, m), 1.62–1.70 (2H, m), 1.91–2.00 (2H, m), 2.29 (2H, t, J = 7.42), 3.62 (3H, s), 4.38 (2H, t, J = 7.1 Hz), 7.49–7.50 (2H, m), 7.67 (2H, d, J = 8.3 Hz), 7.82 (1H, s), 7.91–7.93 (2H, m), 8.61–8.63 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.0, 25.7, 29.8, 33.4, 50.0, 51.4, 119.8, 121.2, 126.1, 127.2, 127.8, 128.5, 128.9, 131.3, 137.4, 146.8, 147.5, 150.1, 173.6. HRMS (FAB) calcd for $[C_{20}H_{22}N_4O_2+H]^+$ 351.1821, found 351.1844.

5.1.2.24. Methyl 7-(4-pyridylphenyl)triazolylheptanoate (6t). Reaction of methyl 7-azidoheptanoate **2d** (0.17 g, 0.91 mmol) and 4-(4-ethynylphenyl)-pyridine **5l** (163 mg, 0.91 mmol) within 24 h as described for the synthesis of **3a**, followed by flash chromatography (silica, 3:2 hexanes/EtOAc) gave 231 mg (70%) of **6t** as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28–1.32 (4H, m), 1.51–1.58 (2H, m), 1.85–1.92 (2H, m), 2.21 (2H, app. q), 3.58 (3H, s), 4.33 (2H, t, J = 7.2 Hz), 7.42–7.46 (2H, m), 7.62 (2H, d, J = 8.3 Hz), 7.78 (1H, s), 7.84–7.90 (2H, m), 8.58 (2H, d, J = 5.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.8, 26.4, 28.6, 30.3, 34.0, 50.5, 51.7, 119.9, 121.3, 126.3, 127.4, 131.5, 137.4, 146.8, 147.5, 150.2, 173.8; HRMS (FAB, MNBA) calcd for $[C_{21}H_{24}N_4O_2+H]^+$ 365.1977, found 365.1982.

5.1.2.25. Methyl 6-(6-methoxynapthalyl)triazolylhexanoate (6u). Reaction of methyl 6-azidohexnoate **2c** (0.2 g, 1.16 mmol) and 2-ethynyl-6-methoxy-napthalene **5f** (0.32 g, 1.76 mmol) within 24 h as described for the synthesis of **3a**, followed by flash chromatography (silica, gradient 2:1; 1:1; 1:2; 0:1 hexanes/EtOAc) gave 284 mg (70%) of **6u** as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.32–1.39 (2H, m), 1.61–1.69 (2H, m), 1.87–1.99 (2H, m), 2.28, (2H, t, J = 7.2 Hz), 3.62 (3H, s), 3.89 (3H, s), 4.36 (2H, t, J = 6.8 Hz), 7.10–7.14 (2H, m), 7.74 (2H, d, J = 10.8 Hz), 7.78 (1H, s), 7.85 (2H, d, J = 8.4 Hz), 8.22 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.2, 25.9, 30.0, 33.6, 50.0, 51.5, 55.2, 105.6, 119.0, 119.2, 124.0, 124.1, 125.7, 127.1, 128.7, 129.4, 134.0, 147.6, 157.5, 173.4; HRMS (FAB, thioglycerol) calcd for $[C_{20}H_{23}N_3O_3+H]^+$ 354.1817, found 354.1819.

5.1.2.26. Methyl 7-(6-methoxynapthalyl)triazolylheptanoate (6v). Reaction of methyl 7-azidoheptanoate **2d** (0.15 g, 0.81 mmol), and 2-ethynyl-6-methoxy-napthalene **5f** (162 mg, 0.89 mmol) within 24 h as described for the synthesis of **3a**, followed by flash chromatography (silica, 6:1:1 hexanes/acetone/dichloromethane) gave 202 mg (68%) of **6v** as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.45–1.49 (4H, m), 1.72 (2H, m), 2.02–2.07 (2H, m), 2.39 (2H, t, J = 7.3 Hz), 3.75 (3H, s), 4.01 (3H, s), 4.42 (2H, t, J = 7.1 Hz), 7.20–7.27 (2H, m), 7.87 (2H, app. t), 4.48 (2H, t, J = 7.1 Hz), 7.23–7.26 (2H, m), 7.86 (2H, dd, J = 8.5, 1.9 Hz), 7.90 (1H, s), 7.98 (1H, dd, J = 8.4, 1.5 Hz), 8.34 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.6, 26.2, 28.5, 30.1, 33.8, 50.2, 51.5, 55.3, 105.6, 119.11, 119.17, 124.0, 124.2, 125.7, 127.1, 128.8, 129.4, 134.1, 147.7, 157.6, 173.7; HRMS (FAB, MNBA) calcd for $[C_{21}H_{25}N_3O_3+H]^+$ 368.1974, found 368.1977.

5.1.2.27. Methyl 6-(2-quinolyl)triazolylhexanoate (6w). Reaction of methyl 6-azidohexanoate **2c** (0.13 g, 0.76 mmol) and 2-ethynylquinoline **5p** (0.09 g, 0.58 mmol) within 24 h as described for the synthesis of **3a**, followed by flash chromatography (silica, 3:2 hexanes/EtOAc) gave 167 mg (68%) of **6w** as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25–1.33 (2H, m), 1.58 (2H, p, J = 15.0, 7.3 Hz), 1.89 (2H, p, J = 14.9, 7.3 Hz), 2.22 (2H, t, J = 7.3 Hz), 3.57 (3H, s), 4.34 (2H, t, J = 7.1 Hz), 7.39–7.43 (1H, m), 7.59–7.63 (1H, m), 7.71 (1H, d, J = 8.0 Hz), 7.98 (1H, d, J = 8.4 Hz), 8.13 (1H, d, J = 8.6 Hz), 8.24–8.28 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.0, 25.7, 29.7, 33.4, 50.0, 51.3, 118.2, 122.3, 125.9, 127.3, 127.4, 128.5, 129.3, 136.4, 147.5, 148.1, 150.1, 173.5; HRMS (FAB, thioglycerol) calcd for $[C_{18}H_{20}N_4O_2+H]^+$ 325.1624, found 325.1621.

5.1.2.28. Methyl 6-(7-quinolyl)triazolylhexanoate (6x). Reaction of methyl 6-azidohexanoate **2c** (0.184 g, 1.07 mmol) and 7-ethynylquinoline **5q** (0.15 g, 0.98 mmol) within 24 h as described for the synthesis of **3a**, followed by flash chromatography (silica, 1:4 hexanes/EtOAc) gave 209 mg (60%) of **6x** as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.20–1.28 (2H, m), 1.53 (2H, p, J = 15.0, 7.3 Hz), 1.79–1.88 (2H, m), 2.16 (2H, t, J = 7.2 Hz), 3.49 (3H, s), 4.27 (2H, t, J = 7.0 Hz), 7.19–7.23 (1H, m), 7.70 (1H, d, J = 8.4 Hz), 7.81 (1H, s), 7.97 (1H, d, J = 8.0 Hz), 8.02 (1H, d, J = 8.4 Hz), 8.26 (1H, s), 8.75 (1H, d, J = 4.1 Hz);^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.1, 25.8, 29.9, 33.5, 50.0, 51.4, 120.2, 120.8, 124.2, 125.1, 127.6, 128.1, 131.5, 135.5, 146.7, 148.0, 150.6, 173.3; HRMS (FAB, thioglycerol) calcd for $[C_{18}H_{20}N_4O_2+H]^+$ 325.1704, found 325.1697.

5.1.2.29. Methyl 5-(benzyl)triazolylpentanoate (6y). Reaction of methyl 5-azidopentanoate **2b** (0.2 g, 1.27 mmol) and 3-phenyl-1-propyne **5k** (221 mg, 1.91 mmol) within 24 h as described for the synthesis of **3a**, followed by flash chromatography (silica, 3:2 hexanes/EtOAc) gave 287 mg (87%) of **6y** as colorless oil.^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.56–1.63 (2H, m), 1.84–1.91 (2H, m), 2.30 (2H, t, J = 7.2 Hz), 3.62 (3H, s), 4.05 (2H, s), 4.26 (2H, t, J = 7.1 Hz), 7.14 (1H, s), 7.17–7.29 (5H, m); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 21.7, 29.5, 32.2, 33.1, 49.7, 51.5, 121.0, 126.2, 128.4, 138.8, 147.3, 172.9; HRMS (FAB, thioglycerol) calcd for $[C_{15}H_{19}N_3O_2+H]^+$ 274.1555, found 274.1558.

5.1.3. Representative procedure for conversion of methyl ester to hydroxamic acid

5.1.3.1. 4-(Phenyl)triazolylbutahydroxamic acid (4a). To a solution of methyl 4-(phenyl)triazolylbutanoate **3a** (0.05 g, 0.204 mmol) in 1:1 THF (1.5 mL) and methanol (1.5 mL) was added aqueous hydroxylamine (0.13 mL, 2.11 mmol) and KCN (0.004 g, 0.062 mmol), and the stirring continued for 24 h. The reaction was diluted with EtOAc (30 mL) and washed with saturated $NaHCO_3$ (2× 30 mL) and saturated brine (30 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo

to give 40 mg (80%) of **4a** as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.98 (2H, t, J = 7.2 Hz), 2.04–2.11 (2H, m), 4.39 (2H, t, J = 6.8 Hz), 7.31 (1H, t, J = 6.8 Hz), 7.43 (2H, t, J = 8.0 Hz), 7.82 (2H, d, J = 8.4 Hz), 8.55 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.9, 29.1, 49.2, 93.8, 121.1, 124.9, 127.6, 128.7, 130.6, 146.1; HRMS (FAB, thioglycerol) calcd for $[C_{12}H_{14}N_4O_2+H]^+$ 247.1195, found 247.1195.

5.1.3.2. 5-(Phenyl)triazolylpentahydroxamic acid (4b). Reaction of methyl 5-(phenyl)triazolylpentanoate **3b** (0.06 g, 0.231 mmol) and aqueous hydroxylamine (0.15 mL, 2.44 mmol) within 24 h, as described for the synthesis of **4a**, gave 30 mg (50%) of **4b** as a white solid; mp 151.0–152.0 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.45–1.49 (2H, m), 1.80–1.84 (2H, m), 1.98 (2H, t, J = 6.8 Hz), 4.38 (2H, t, J = 6.8 Hz), 7.30 (1H, t, J = 8.0 Hz), 7.42 (2H, t, J = 7.2 Hz), 7.81 (2H, d, J = 7.6 Hz), 8.54 (1H, s), 8.67 (1H, s), 10.3 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.1, 29.2, 31.5, 49.1, 121.0, 124.8, 127.5, 128.6, 130.6, 146.0, 168.3; HRMS (FAB, thioglycerol) calcd for $[C_{13}H_{16}N_4O_2+H]^+$ 261.1351, found 261.1354.

5.1.3.3. 6-(Phenyl)triazolylhexahydroxamic acid (4c). Reaction of methyl 6-(phenyl)triazolylhexanoate **3c** (0.15 g, 0.522 mmol) and aqueous hydroxylamine (0.37 mL, 6.03 mmol) within 24 h, as described for the synthesis of **4a**, gave 79 mg (55%) of **4c** as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.18–1.26 (2H, m), 1.48–1.55 (2H, m), 1.81–1.88 (2H, m), 1.93 (2H, t, J = 7.2 Hz), 4.36 (2H, t, J = 7.2 Hz), 7.31 (1H, t, J = 7.2 Hz), 7.42 (2H, t, J = 6.8 Hz), 7.82 (2H, d, J = 8.0 Hz), 8.56 (1H, s), 8.68 (1H, s), 10.3 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.5, 25.4, 29.3, 32.0, 49.3, 121.0, 124.8, 127.5, 128.6, 130.6, 146.0, 168.6; HMS (FAB, thioglycerol) calcd for $[C_{14}H_{18}N_4O_2+H]^+$ 275.1508, found 275.1513.

5.1.3.4. 7-(Phenyl)triazolylheptahydroxamic acid (4d). Reaction of methyl 7-(phenyl)triazolylheptanoate **3d** (0.1 g, 0.35 mmol) and aqueous hydroxylamine (0.23 mL, 3.74 mmol) within 32 h, as described for the synthesis of **4a**, gave 73 mg (73%) of **4d** as a white solid; mp 145.0–146.0 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.22–1.27 (4H, m), 1.43–1.51 (2H, m), 1.84 (2H, m), 1.92 (2H, t, J = 7.2 Hz), 4.36 (2H, t, J = 7.0 Hz), 7.31 (1H, t, J = 7.2 Hz), 7.43 (2H, t, J = 7.5 Hz), 7.82 (2H, d, J = 7.1 Hz), 8.56 (1H, s), 8.63 (1H, s), 10.31 (1H, s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 24.9, 25.5, 27.9, 29.5, 32.1, 49.4, 120.9, 124.8, 127.5, 128.6, 130.6, 145.9, 168.6; HRMS (FAB, thioglycerol) calcd for $[C_{15}H_{20}N_4O_2+H]^+$ 289.1664, found 289.1612.

5.1.3.5. 6-(4-Anilyl)triazolylhexahydroxamic acid (7a). Reaction of methyl 6-(4-anilyl)triazolylhexanoate **6a** (0.1 g, 0.303 mmol) and aqueous hydroxylamine (0.6 mL, 9.78 mmol) within 24 h, as described for the synthesis of **4a**, gave 50 mg (53%) of **7a** as a white solid; mp 165.0–166.0 °C.^{1}H NMR (CD_3OD, 400 MHz) δ 1.20–1.26 (2H, m), 1.48–1.56 (2H, m), 1.79–1.86 (2H, m), 1.93 (2H, t, J = 6.8 Hz), 2.917 (6H, s), 4.32 (2H, t, J = 6.8 Hz), 6.76 (2H, d, J = 8.8 Hz), 7.63 (2H, d, J = 8.8 Hz), 8.32 (1H, s), 8.66 (1H, s), 10.3 (1H, s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 25.3, 26.3, 30.2, 32.8, 50.0, 112.9, 119.4, 119.9, 126.6, 147.4, 150.5, 169.4; HRMS (FAB, thioglycerol) calcd for $[C_{16}H_{23}N_4O_2+H]^+$ 318.1930, found 318.1929.

5.1.3.6. 7-(4-Anilyl)triazolylheptahydroxamic acid (7b). Reaction of methyl 7-(4-anilyl)-triazolylheptanoate **6b** (0.128 g, 0.38 mmol) and aqueous hydroxylamine (0.25 mL, 4.07 mmol) within 32 h, as described for the synthesis of **4a**, gave 95 mg (76%) of **7b** as a white solid; mp 121.0–125.0 °C. ^{1}H NMR (CD_3OD, 400 MHz) δ 1.23–1.36 (4H, m), 1.52–1.59 (2H, m), 1.84–1.91 (2H, m), 2.02 (2H, t, J = 7.2 Hz), 2.91 (6H, s) 4.33 (2H, t, J = 6.9 Hz), 6.75 (2H, d, J = 8.5 Hz), 7.58 (2H, d, J = 8.5 Hz), 8.05 (1H, s); ^{13}C NMR (CD_3OD, 100 MHz) δ 26.5, 27.1, 29.4, 31.1, 33.6, 40.7, 51.2, 113.6, 119.6, 120.4, 127.3, 149.2, 151.8, 172.5; HRMS (FAB, thioglycerol) calcd for $[C_{17}H_{25}N_5O_2+H]^+$ 332.2086, found 332.2071.

5.1.3.7. 6-(3-Pyridyl)triazolylhexahydoxamic acid (7c). Reaction of methyl 6-(3-pyridyl)triazolylhexanoate **6c** (0.14 g, 0.51 mmol) and aqueous hydroxylamine (0.33 mL, 5.37 mmol) within 32 h, as described for the synthesis of **4a**, gave 103 mg (74%) of **7c** as a white solid; mp 126.0–128.0 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.19–1.30 (2H, m), 1.54 (2H, m), 1.85 (2H, m), 1.96 (2H, t, J = 7.2 Hz), 4.34 (2H, t, J = 7.0 Hz), 7.28 (1H, q, J = 7.6, 4.9 Hz), 8.13 (1H, d, J = 7.9 Hz), 8.36–8.38 (2H, m), 8.86 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.0, 26.9, 30.8, 33.4, 51.3, 122.9, 125.4, 128.5, 134.7, 146.9, 149.2, 173.2; HRMS (FAB, thioglycerol) calcd for $[C_{13}H_{17}N_5O_2+H]^+$ 276.1460, found 276.1478.

5.1.3.8. 6-(4-Pyridyl)triazolylhexahydroxamic acid (7d). Reaction of methyl 6-(4-pyridyl)triazolylhexanoate **6d** (0.14 g, 0.51 mmol) and aqueous hydroxylamine (0.33 mL, 5.37 mmol) within 32 h, as described for the synthesis of **4a**, gave 96 mg (69%) of **7d** as a white solid; mp 150.0–153.0 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.18–1.25 (2H, m), 1.51 (2H, m), 1.85 (2H, m), 1.92 (2H, t, J = 7.2 Hz), 4.40 (2H, t, J = 6.9 Hz), 7.78 (2H, d, J = 5.6 Hz), 8.60 (2H, d, J = 5.5 Hz), 8.78 (1H, s), 10.35 (1H, s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 24.5, 25.4, 29.3, 32.1, 49.6, 54.9, 119.3, 123.1, 137.8, 143.7, 150.1, 168.9, 184.0; HRMS (FAB, thioglycerol) calcd for $[C_{13}H_{17}N_5O_2+H]^+$ 276.1460, found 276.1469.

5.1.3.9. 6-(2-Pyridyl)triazolylhexahydroxamic acid (7e). Reaction of methyl 6-(2-pyridyl)triazolylhexanoate **6e** (0.14 g, 0.51 mmol) and aqueous hydroxylamine (0.33 mL, 5.37 mmol) within 32 h, as described for the synthesis of **4a**, gave 89 mg (64%) of **7e** as a white solid; mp 127.0–130.0 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.17–1.25 (2H, m), 1.51 (2H, m), 1.82–1.89 (2H, m), 1.92 (2H, t, J = 7.2 Hz), 4.40 (2H, t, J = 6.9 Hz), 7.30–7.34 (1H, m), 7.85–7.89 (1H, m), 7.99–8.02 (1H, m), 8.56–8.58 (1H, m), 8.60 (1H, s), 10.32 (1H, s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 24.5, 25.4, 29.3, 32.0, 49.4, 119.1, 122.6, 122.9, 136.9, 146.9, 149.3, 149.8, 168.5; HRMS (FAB, thioglycerol) calcd for $[C_{13}H_{17}N_5O_2+H]^+$ 276.1460, found 276.1457.

5.1.3.10. 7-(2-Pyridyl)triazolylheptahydroxamic acid (7f). Reaction of methyl 7-(2-pyridyl)-triazolylheptanoate **6f** (0.1 g, 0.35 mmol) and aqueous hydroxylamine (0.2 mL, 3.26 mmol) within 32 h, as described for the synthesis of **4a**, gave 57 mg (57%) of **7f** as a white solid; mp 120.0–123.0 °C. ^{1}H NMR (CD_3OD, 400 MHz) δ 1.36–1.40 (4H, m), 1.61 (2H, m), 1.96 (2H, m), 2.07 (2H, t, J = 7.5 Hz), 4.47 (2H, t, J = 7.0 Hz), 7.34–7.37 (1H, m), 7.88–7.92 (1H, m), 8.05 (1H, d, J = 7.9 Hz), 8.40 (1H, s), 8.56 (1H, d, J = 4.4 Hz); ^{13}C NMR (CD_3OD, 100 MHz) δ 26.5, 27.1, 29.4, 31.1, 33.6, 51.4, 121.3, 123.9, 124.3, 138.6, 148.3, 150.8, 150.9, 172.5; HRMS (EI) calcd for $[C_{14}H_{19}N_5O_2+H]^+$ 290.1617, found 290.1590.

5.1.3.11. 6-(4-Tolyl)triazolylhexahydroxamic acid (7g). Reaction of methyl 6-(4-tolyl)triazolylhexanoate **6g** (0.15 g, 0.52 mmol) and aqueous hydroxylamine (0.34 mL, 5.54 mmol) within 32 h, as described for the synthesis of **4a**, gave 94 mg (63%) of **7g** as a white solid; mp 141.0–143.0 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.18–1.26 (2H, m), 1.48–1.55 (2H, m), 1.80–1.89 (2H, m), 1.92 (2H, app. t), 2.31 (3H, s), 4.35 (2H, t, J = 7.4 Hz), 7.23 (2H, d, J = 7.5 Hz), 7.71 (2H, d, J = 7.8 Hz), 8.50 (1H, s), 10.31 (1H, s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 20.8, 24.5, 25.4, 29.3, 32.0, 49.3, 120.6, 124.8, 127.8, 29.2, 136.8, 146.0, 168.5; HRMS (FAB, MNBA) calcd for $[C_{15}H_{20}N_4O_2+H]^+$ 289.1664, found 289.1636.

5.1.3.12. 6-(3-Tolyl)triazolylhexahydroxamic acid (7h). Reaction of methyl 6-(3-tolyl)triazolylhexanoate **6h** (0.15 g, 0.52 mmol) and aqueous hydroxylamine (0.34 mL, 5.54 mmol) within 32 h, as described for the synthesis of **4a**, gave 115 mg (77%) of **7h** as a white solid; mp 99.0–102.0 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.17–1.24 (2H, m), 1.44–1.57 (2H, m), 1.83 (2H, p, J = 14.4, 7.1 Hz), 1.92 (2H, t, J = 7.2 Hz), 2.33 (3H, s), 4.35 (2H, t, J = 6.9 Hz), 7.11 (1H, d, J = 7.5 Hz), 7.29 (1H, t, J = 7.6 Hz), 7.60 (1H, d, J = 7.2 Hz), 7.65 (1H, s), 8.52 (1H, s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 21.1, 24.5, 25.5, 29.3, 32.0, 49.3, 120.9, 122.0, 125.4, 128.2, 128.5, 130.5, 137.5, 146.1, 168.6; HRMS (EI) calcd for $[C_{15}H_{20}N_4O_2+H]^+$ 289.1664, found 289.1684.

5.1.3.13. 6-(3-Tolyl)triazolylhexahydroxamic acid (7i). Reaction of methyl 6-(3-tolyl)triazolylhexanoate **6i** (0.15 g, 0.52 mmol) and aqueous hydroxylamine (0.34 mL, 5.54 mmol) within 32 h, as described for the synthesis of **4a**, gave 116 mg (78%) of **7i** as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.21–1.29 (2H, m), 1.52 (2H, m), 1.82–1.89 (2H, m), 1.93 (2H, t, J = 7.9 Hz), 2.41 (3H, s), 4.38 (2H, t, J = 6.9 Hz), 7.23–7.28 (3H, m), 7.70–7.73 (1H, m), 8.36 (1H, s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 21.2, 24.5, 25.5, 29.4, 32.0, 49.2, 122.9, 125.7, 127.4, 127.9, 129.9, 130.6, 134.6, 145.2, 168.5; HRMS (EI) calcd for $[C_{15}H_{20}N_4O_2+H]^+$ 289.1664, found 289.1681.

5.1.3.14. 6-(4-Anisolyl)triazolylhexahydroxamic acid (7j). Reaction of methyl 6-(4-anisolyl)triazolylhexanoate **6j** (0.15 g, 0.52 mmol) and aqueous hydroxylamine (0.34 mL, 5.2 mmol) within 32 h, as described for the synthesis of **4a**, gave 99 mg (60%) of **7j** as a white solid, mp 152.0–154.0 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.18–1.26 (2H, m), 1.52 (2H, p, J = 14.5, 6.9 Hz), 1.83 (2H, p, J = 14.5, 7.1 Hz), 1.93 (2H, t, J = 7.3 Hz), 4.34 (2H, t, J = 7.0 Hz), 6.99 (2H, d, J = 7.9 Hz), 7.74 (2H, d, J = 7.9 Hz), 8.44 (1H, s), 10.31 (1H, s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 24.5, 25.4, 29.3, 32.0, 49.2, 55.0, 114.0, 120.0, 123.2, 126.2, 145.4, 158.6, 168.5; HRMS (FAB, thioglycerol) calcd for $[C_{15}H_{20}N_4O_3+H]^+$ 305.1613, found 305.1629.

5.1.3.15. 6-(3-Anisolyl)triazolylhexahydroxamic acid (7k). Reaction of methyl 6-(3-anisolyl)triazolylhexanoate **6k** (0.15 mg, 0.52 mmol) and aqueous hydroxylamine (0.34 mL, 5.2 mmol) within 32 h, as described for the synthesis of **4a**, gave 75 mg (50%) of **7k** as a white solid; mp 95.0–98.0 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.18–1.26 (2H, m), 1.52 (2H, p, J = 15.0, 7.4 Hz), 1.84 (2H, p, J = 14.4, 7.0 Hz), 1.93 (2H, t, J = 7.2 Hz), 3.79 (3H, s), 4.36 (2H, t, J = 6.9 Hz), 6.86–6.89 (1H, m), 7.33 (1H, app. t), 7.39–7.41 (2H, m), 8.59 (1H, s), 10.3 (1H, s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 24.5, 25.4, 29.3, 32.0, 49.3, 55.0, 110.1, 113.3, 117.2, 121.2, 129.8, 131.9, 145.9, 159.3, 168.5; HRMS (FAB, thioglycerol) calcd for $[C_{15}H_{20}N_4O_3+H]^+$ 305.1613, found 305.1633.

5.1.3.16. 6-(2-Anisolyl)triazolylhexahydroxamic acid (7l). Reaction of methyl 6-(2-anisolyl)triazolylhexanoate **6l** (0.15 mg, 0.52 mmol) and aqueous hydroxylamine (0.34 mL, 5.2 mmol) within 32 h, as described for the synthesis of **4a**, gave 82 mg (55%) of **7l** as a white solid; mp 78.0–80.0 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.41–1.21 (2H, m), 1.19–1.26 (2H, m), 1.52 (2H, p, J = 15.0, 7.5 Hz), 1.80–1.88 (2H, m), 1.93 (2H, t, J = 7.3 Hz), 3.90 (3H, s), 4.38 (2H, t, J = 7.0 Hz), 7.03 (1H, app. t), 7.11 (1H, d, J = 8.2 Hz), 7.28–7.33 (1H, m), 8.12 (1H, dd, J = 7.6, 1.7 Hz), 8.36 (1H, s), 10.23 (1H, s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 24.5, 25.5, 29.5, 32.0, 49.1, 55.3, 111.4, 120.3, 123.7, 126.2, 128.5, 141.4, 155.0, 168.5; HRMS (FAB, MNBA) calcd for $[C_{15}H_{20}N_4O_3+H]^+$ 305.1673, found 305.1576.

5.1.3.17. 6-(2,6-Dimethoxyphenyl)triazolylhexahydroxamic acid (7m). Reaction of methyl 6-(2,6-dimethoxyphenyl)triazolylhexanoate **6m** (0.1 g, 0.30 mmol) and aqueous hydroxylamine (0.4 mL, 6.52 mmol) within 24 h, as described for the synthesis of **4a**, gave 90 mg (90%) of **7m** as a white solid; mp 98.0–100.0 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.33–1.41 (2H, m), 1.63–1.71 (2H, m), 1.92–1.99 (2H, m), 2.10 (2H, t, J = 7.2 Hz), 3.76 (6H, s), 4.42 (2H, t, J = 6.8 Hz), 6.71 (2H, d, J = 8.4 Hz), 7.32 (1H, t, J = 8.4 Hz), 7.96 (1H, s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 26.1, 27.0, 31.0, 33.5, 51.0, 55.2, 104.9, 108.9, 126.1, 131.1, 140.7, 148.9, 159.4, 172.3; HRMS (FAB, thioglycerol) calcd for $[C_{16}H_{22}N_4O_4+H]^+$ 335.1719, found 335.1724.

5.1.3.18. 6-(2-Thiopyl)triazolylhexahydroxamic acid (7n). Reaction of methyl 6-thiopyl-triazolylhexanoate **6n** (0.1 g, 0.35 mmol) and aqueous hydroxylamine (0.2 mL, 3.26 mmol) within 24 h, as described for the synthesis of **4a**, gave 54 mg (55%) of **7n** as a white solid;

mp 148.0–149.0 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.17–1.24 (2H, m), 1.47–1.55 (2H, m), 1.79–1.86 (2H, m), 1.92 (2H, t, J = 7.2 Hz), 4.35 (3H, t, J = 6.8 Hz), 7.48 (1H, d, J = 5.2 Hz), 7.62 (1H, dd, J = 5.2, 3.2 Hz), 7.80 (1H, d, J = 2.8 Hz), 8.42 (1H, s), 8.68 (1H, s), 10.36 (1H, s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 24.4, 25.3, 29.3, 31.9, 49.1, 120.3, 120.7, 125.4, 126.8, 131.8, 142.4; HRMS (FAB, thioglycerol) calcd for $[C_{12}H_{16}N_4O_2S+H]^+$ 281.1072, found 281.1087.

5.1.3.19. 6-(4-Biphenyl)triazolylhexahydroxamic acid (7o). Reaction of methyl 6-(4-biphenyl)triazolylhexanoate **6o** (0.09 g, 0.258 mmol) and aqueous hydroxylamine (0.2 mL, 3.26 mmol) within 24 h, as described for the synthesis of **4a**, gave 35 mg (39%) of **7o** as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.50–1.60 (2H, m), 1.87 (2H, t, J = 7.2 Hz), 1.94 (2H, t, J = 7.6 Hz), 2.30 (2H, t, J = 7.6 Hz), 4.39 (2H, t, J = 6.8 Hz), 7.36 (1H, t, J = 7.2 Hz), 7.46 (2H, t, J = 7.6 Hz), 7.72 (4H, q, J = 17.6, 8.0 Hz), 7.921 (2H, t, J = 8.0 Hz), 8.61 (1H, s), 10.3 (1H, s); HRMS (FAB, thioglycerol) calcd for $[C_{20}H_{22}N_4O_2+H]^+$ 351.1828, found 351.1864. [*Note:* Strong aggregation prevent collection of ^{13}C NMR.]

5.1.3.20. 6-(3-Biphenyl)triazolylhexahydroxamic acid (7p). Reaction of methyl 6-(3-biphenyl)triazolylhexanoate **6p** (0.12 g, 0.34 mmol) and aqueous hydroxylamine (0.4 mL, 6.52 mmol) within 24 h, as described for the synthesis of **4a**, gave 73 mg (61%) of **7p** as a white solid; mp 101.0–102.0 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.18–1.21 (2H, m), 1.48–1.51 (2H, m), 1.81–1.85 (2H, m), 1.92 (2H, t, J = 6.4 Hz), 4.36 (2H, t, J = 6.8 Hz), 7.36 (1H, t, J = 6.0 Hz), 7.44–7.54 (3H, m), 7.59 (1H, d, J = 8.0 Hz), 7.68 (2H, d, J = 7.2 Hz), 8.06 (1H, s), 8.59 (1H, s), 8.85 (1H, br s), 10.48 (1H, s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 24.9, 25.8, 29.7, 32.5, 50.0, 121.9, 123.6, 124.5, 126.6, 127.0, 128.0, 129.3, 130.0, 131.4, 140.0, 141.1, 146.5, 169.7; HRMS (FAB, thioglycerol) calcd for $[C_{20}H_{22}N_4O_2+H]^+$ 351.1821, found 351.1832.

5.1.3.21. 7-(3-Biphenyl)triazolylheptahydroxamic acid (7q). Reaction of methyl 7-(3-biphenyl)-triazolylheptanoate **6q** (0.1 g, 0.27 mmol) and aqueous hydroxylamine (0.2 mL, 3.26 mmol) within 32 h, as described for the synthesis of **4a**, gave 47 mg (48%) of **7q** as a white solid. ^{1}H NMR (CD_3OD, 400 MHz) δ 1.18–1.21 (4H, m), 1.39–1.49 (2H, m), 1.72–1.80 (2H, m), 1.90 (2H, t, J = 7.5 Hz), 2.02 (2H, t, J = 7.5 Hz), 4.21–4.25 (2H, m), 7.14–7.18 (1H, m), 7.24–7.28 (2H, m), 7.31 (1H, d, J = 7.6 Hz), 7.39–7.41 (1H, m), 7.47–7.50 (2H, m), 7.58–7.61 (1H, m), 7.91 (1H, d, J = 1.6 Hz), 8.19 (1H, d, J = 6.1 Hz). ^{13}C NMR (CD_3OD, 100 MHz) δ 26.5, 27.1, 29.4, 31.0, 33.6, 51.3, 122.2, 124.9, 125.3, 127.6, 127.8, 128.4, 129.7, 130.3, 132.0, 141.7, 142.9, 148.5, 172.8. HRMS (EI) calcd for $[C_{21}H_{24}N_4O_2+H]^+$ 365.1977, found 365.1954.

5.1.3.22. 6-(2-Biphenyl)triazolylhexahydroxamic acid (7r). Reaction of methyl 6-(2-biphenyl)triazolylhexanoate **6r** (0.1 g, 0.28 mmol) and aqueous hydroxylamine (0.4 mL, 6.52 mmol) within 24 h, as described for the synthesis of **4a**, gave 42 mg (43%) of **7r** as a white solid; mp 115.0–117.0 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.85–1.01 (2H, m), 1.37–1.43 (2H, m), 1.56–1.59 (2H, m), 1.88 (2H, t, J = 7.2 Hz), 4.15 (2H, t, J = 6.4 Hz), 7.00 (1H, s), 7.12 (2H, d, J = 6.8 Hz), 7.32 (4H, d, J = 5.2 Hz), 7.40–7.46 (2H, m), 7.76 (1H, d, J = 8.0 Hz), 8.79 (1H, br s), 10.44 (1H, s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 24.9, 25.6, 29.7, 32.5, 49.5, 123.2, 127.5, 128.0, 128.5, 128.6, 129.1, 129.2, 129.4, 130.4, 140.4, 141.1, 145.6, 169.5; HRMS (FAB, thioglycerol) calcd for $[C_{20}H_{22}N_4O_2+H]^+$ 351.1821, found 351.1842.

5.1.3.23. 6-(4-Pyridylphenyl)triazolylhexahydroxamic acid (7s). Reaction of methyl 6-(4-pyridylphenyl)triazolylhexanoate **6s** (0.1 g, 0.28 mmol) and aqueous hydroxylamine (0.2 mL, 2.7 mmol) within 32 h, as described for the synthesis of **4a**, gave 54 mg (54%) of **7s** as a white solid; mp 192.0–193.0 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.24–1.33 (2H, m), 1.50–1.58 (2H, m), 1.83–1.98 (4H, m), 4.39 (2H, t, J = 7.3 Hz), 7.75–7.76 (2H, m), 7.90 (2H, d, J = 8.3 Hz), 7.98 (2H, d, J = 8.3 Hz), 8.64 (1H, s), 8.66–8.68 (2H, m), 10.34 (1H, s). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 24.5, 25.4, 29.3, 32.0, 49.4, 120.8, 121.5, 125.5, 127.1, 131.5, 135.9, 145.3, 146.0, 149.9, 168.5. HRMS (FAB, thioglycerol) calcd for $[C_{19}H_{21}N_5O_2+H]^+$ 352.1773, found 352.1756.

5.1.3.24. 7-(4-Pyridylphenyl)triazolylheptahydroxamic acid (7t). Reaction of methyl 7-(4-pyridylphenyl)triazolylheptanoate **6t** (0.1 g, 0.27 mmol) and aqueous hydroxylamine (0.2 mL, 3.26 mmol) within 32 h, as described for the synthesis of **4a**, followed by prep TLC (silica, 91:9 dichloromethane/MeOH) gave 54 mg (55%) of **7t** as a white solid; mp 255.0–258.0 °C (with charring). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.24–1.33 (4H, m), 1.44–1.50 (2H, m), 1.83–1.87 (2H, m), 2.18 (2H, t, J = 7.3 Hz), 4.39 (2H, t, J = 7.3 Hz), 7.74–7.76 (2H, m), 7.90 (2H, d, J = 8.3 Hz), 7.98 (2H, d, J = 8.3 Hz), 8.63 (2H, d, J = 4.4 Hz), 8.69 (1H, s), 10.34 (1H, s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 24.3, 25.6, 27.9, 29.4, 33.5, 49.5, 120.7, 121.5, 125.5, 127.1, 131.5, 135.9, 145.3, 146.0, 149.9, 174.0; HRMS (FAB, thioglycerol) calcd for $[C_{20}H_{23}N_5O_2+H]^+$ 366.1930, found 365.1942.

5.1.3.25. 6-(6-Methoxynapthalyl)triazolylhexahydroxamic acid (7u). Reaction of methyl 6-(6-methoxynapthalenyl)triazolylhexanoate **6u** (0.095 g, 0.27 mmol) and aqueous hydroxylamine (0.2 mL, 3.26 mmol) within 24 h, as described for the synthesis of **4a**, gave 31 mg (33%) of **7u** as a white solid; mp 166.0–167.0 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.23–1.27 (2H, m), 1.51–1.57 (2H, m), 1.85–1.97 (4H, m), 2.28, 3.88 (3H, s), 4.40 (2H, t, J = 6.4 Hz), 7.19 (1H, d, J = 10.4 Hz), 7.33 (1H, s), 7.90 (3H, dd, J = 22.4, 9.2 Hz), 8.30 (1H, s), 8.63 (2H, d, J = 12.0 Hz), 10.32 (1H, s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 24.5, 25.4, 29.3, 32.0, 49.3, 55.1, 105.8, 118.9, 120.9, 123.1, 123.9, 125.7, 127.1, 128.3, 129.2, 133.6,146.2,157.1; HRMS (FAB, thioglycerol) calcd for $[C_{19}H_{22}N_4O_3+H]^+$ 355.1809, found 355.1806.

5.1.3.26. 7-(6-Methoxynapthalyl)triazolylheptahydroxamic acid (7v). Reaction of methyl 7-(6-methoxynapthalyl)triazolylheptanoate **6v** (0.217 g, 0.59 mmol) and aqueous hydroxylamine (0.4 mL, 6.52 mmol) within

32 h, as described for the synthesis of **4a**, gave 110 mg (51%) of **7v** as a white solid; mp 240.0–242.0 °C (with charring). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.26–1.28 (4H, m), 1.43–1.53 (2H, m), 1.82–1.89 (2H, m), 1.92 (2H, t, J = 7.2 Hz), 3.87 (3H, s), 4.39 (2H, t, J = 7.0 Hz), 7.17 (1H, dd, J = 8.9, 2.5 Hz), 7.33 (1H, d, J = 2.3 Hz), 7.85–7.93 (3H, m), 8.30 (1H, s), 8.63 (1H, s), 8.66 (1H, s), 10.35 (1H, s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 24.9, 25.6, 28.0, 29.5, 32.1, 49.4, 55.1, 105.8, 118.9, 120.9, 123.1, 123.9, 125.8, 127.1, 128.3, 129.2, 133.6, 146.2, 157.1, 168.7; HRMS (EI) calcd for $[C_{20}H_{24}N_4O_3+H]^+$ 369.1926, found 369.1900.

5.1.3.27. 6-(2-Quinolyl)triazolylhexahydroxamic acid (7w). Reaction of methyl 6-(2-quinolyl)triazolylhexanoate **6w** (0.129 g, 0.39 mmol) and aqueous hydroxylamine (0.26 mL, 3.9 mmol) within 32 h, as described for the synthesis of **4a**, gave 77 mg (60%) of **7w** as a white solid; mp 155.0–156.0 °C.^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.24 (2H, app. p), 1.53 (2H, p, J = 14.7, 7.1 Hz), 1.86–1.95 (4H, m), 4.45 (2H, t, J = 7.0 Hz), 7.56–7.60 (1H, m), 7.75–7.79 (1H, m), 7.98 (2H, d, J = 8.4 Hz), 8.21 (1H, d, J = 8.5 Hz), 8.45 (1H, d, J = 8.5 Hz), 8.65 (1H, s), 8.81 (1H, s), 10.32 (1H, s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 24.5, 25.4, 29.3, 32.0, 49.5, 117.9, 123.7, 126.1, 127.0, 127.8, 128.2, 129.8, 136.9, 146.9, 147.2, 150.0, 168.6; HRMS (FAB, thioglycerol) calcd for $[C_{17}H_{19}N_5O_2+H]^+$ 326.1576, found 326.1572.

5.1.3.28. 6-(7-Quinolyl)triazolylhexahydroxamic acid (7x). Reaction of methyl 6-(7-quinolyl)triazolylhexanoate **6x** (0.1 g, 0.31 mmol) and aqueous hydroxylamine (0.2 mL, 3.1 mmol) within 32 h, as described for the synthesis of **4a**, followed by prep TLC (9% MeOH in Dichloromethane) gave 66 mg (66%) of **7x** as a white solid; mp 105.0–108.0 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.21–1.29 (2H, m), 1.50–1.57 (2H, m), 1.84–1.95 (4H, m), 4.41 (2H, t, J = 7.3 Hz), 7.50 (1H, q, J = 8.4, 4.3 Hz), 8.04 (1H, d, J = 8.5 Hz), 8.10 (1H, dd, J = 8.5, 1.6 Hz), 8.33–8.36 (1H, m), 8.44 (1H, s), 8.61–8.64 (1H, m), 8.82 (1H, s), 8.90 (1H, q, J = 4.2, 4.1 Hz), 10.31 (1H, s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 26.0, 26.9, 30.9, 33.4, 51.3, 122.4, 123.1, 124.8, 125.6, 129.8, 129.3, 133.3, 137.9, 147.6, 148.7, 151.6, 172.3; HRMS (EI) calcd for $[C_{17}H_{19}N_5O_2+H]^+$ 326.1617, found 326.1646.

5.1.3.29. 5-(Benzyl)triazolylpentahydroxamic acid (7y). Reaction of methyl 5-(benzyl)triazolylpentanoate **6y** (0.15 g, 0.52 mmol) and aqueous hydroxylamine (0.5 mL, 8.15 mmol) within 32 h, as described for the synthesis of **4a**, gave 111 mg (78%) of **7y** as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.38–1.45 (2H, m), 1.71–1.77 (2H, m), 1.95 (2H, t, J = 7.28), 3.96 (2H, s), 4.27 (2H, t, J = 7.10), 7.16–7.29 (5H, m), 7.81 (1H, s), 8.67 (1H, s), 10.34 (1H, s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 22.1, 29.3, 31.3, 31.5, 48.8, 122.1, 125.8, 128.1, 128.2, 139.4, 145.6, 168.3; HRMS (FAB, thioglycerol) calcd for $[C_{14}H_{18}N_4O_2+H]^+$ 275.1508, found 275.1506.

5.2. HDAC activity assay

Inhibitor screening was performed using the HDAC Fluorescent Activity assay/Drug Discovery (*Fluor de Lys*) kit AK-500 (Biomol). Briefly, 15 μl HeLa nuclear extract was diluted with 5 μl 10× compound and 5 μl Assay Buffer. After addition of fluorogenic HDAC substrate, reaction mixtures were incubated at room temperature for 15 minutes and stopped by addition of Developer/TSA. Fluorescence was monitored after 20 min at excitation and emission wavelengths of 360 and 460 nm, respectively. In vitro IC_{50} values were determined using a graph of log(concentration) vs. logit(fluorescence).

5.3. Cell culture and viability

Human prostate carcinoma cells (DU-145) were obtained from American Type Culture Collection (Manassas, VA). Cultures were grown in EMEM containing L-glutamine (5 mM), sodium pyruvate (1 mM), sodium bicarbonate (1500 mg/L) and 10% fetal bovine serum, and maintained at 37 °C in an atmosphere of 5% CO_2. SAHA, and all other potential HDAC inhibitors, were dissolved in DMSO at a stock concentration of 10 mM and stored at −80 °C. Cultures were passaged and allowed to grow for 24 h prior to addition of compounds. Compounds were diluted to the appropriate concentration in new medium and incubated with cultures for 72 h. Viability was assessed by Trypan Blue staining and a colorimetric mitochondrial activity using MTS.

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Supplementary data

Detailed experimental procedures including proton and carbon NMR spectra for all compounds are described in Section 5. This material is available free of charge via the Internet at http://pubs.acs.org. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2008.03.050.

References and notes

1. (a) Marson, C. M.; Mahadevan, T.; Dines, J.; Segmany, S.; Morrell, J. M.; Alao, J. P.; Joel, S. P.; Vigushin, D. M.; Coombes, R. C. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 136–141; (b) Hassig, C. A.; Schreiber, S. L. *Curr. Opin. Chem. Biol.* **1997**, *1*, 300.
2. (a) Moradei, O.; Maroun, C. R.; Paquin, I.; Vaisburg, A. *Curr. Med. Chem. Anti-Cancer Agents* **2005**, *5*, 529–560;

(b) Bolden, J. E.; Part, M. J.; Johnstone, R. W. *Nat. Rev. Drug Disc.* **2006**, *5*, 769–784.
3. FDA approves vorinostat (Zolinza) for the treatment of cutaneous manifestations of cutaneous T-cell lymphoma (CTCL) http://www.fda.gov/cder/Offices/OODP/whats-new/vorinostat.htm.
4. Miller, T. A.; Witter, D. J.; Belvedere, S. *J. Med. Chem.* **2003**, *46*, 5097–5116.
5. Finnin, M. S.; Donigian, J. R.; Cohen, A.; Richon, V. M.; Rifkind, R. A., et al. *Nature* **1999**, *401*, 188–193.
6. Vannini, A.; Volpari, C.; Filocamo, G.; Casavola, E. C.; Brunetti, M.; Renzoni, D.; Chakravarty, P.; Paolini, C.; De Francesco, R.; Gallinari, P.; Steinkuhler, C.; Di Marco, S. *Proc. Natl. Acad Sci. U.S.A.* **2004**, *101*, 15064–15069.
7. Monneret, C. *Eur. J. Med. Chem.* **2005**, *40*, 1–13.
8. Wong, J.; Hong, R.; Schreiber, S. *J. Am. Chem. Soc.* **2003**, *125*, 5586–5587.
9. Haggarty, S. J.; Koeller, K. M.; Wong, J. C.; Grozinger, C. M.; Schreiber, S. L. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 4389–4394.
10. Numerous examples of Cu(I) catalyzed Huigsen cycloaddition reaction have appeared in the literature (A comprehensive list is available at http://www.scripps.edu/chem/sharpless/click.html). Cited here are two pioneering examples: (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599; (b) Tornoe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057–3064.
11. For reviews on application of click chemistry see: (a) Kolb, H. C.; Sharpless, K. B. *DDT* **2003**, *8*, 1128–1137; (b) Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2006**, 51–68.
12. Savariar, E. N.; Aathimanikandan, S. V.; Thayumanavan, S. *J. Am. Chem. Soc.* **2006**, *128*, 16224–16230.
13. Heine, H. W.; Becker, E. B.; Lane, J. F. *J. Am. Chem. Soc.* **1953**, *75*, 4514–4515.
14. (a) Collman, J. P.; Devaraj, N. K.; Chidsey, C. E. D. *Langmuir* **2004**, *20*, 1051–1053; (b) Shon, Y.; Kelly, K. F.; Halas, N. J.; Lee, T. R. *Langmuir* **1999**, *15*, 5329–5332.
15. Ho, C. Y.; Strobel, E.; Ralbovsky, J.; Galemmo, R. A., Jr. *J. Org. Chem.* **2005**, *70*, 4873–4875.
16. Quesada, E.; Taylor, R. J. K. *Tetrahedron Lett.* **2005**, *6*, 6473–6476.
17. Ghosh, A. K.; Bischoff, A.; Cappiello, J. *J. Eur. Org. Chem.* **2003**, 821–832.
18. (a) Anhoury, M. L.; Arickx, M.; Crooy, P.; De Neys, R.; Eliaers, J. *J. Chem. Soc., Perkin 1* **1974**, 191–192; (b) Callant, P.; D'Haenens, L.; Vandewalle, M. *Synth. Commun.* **1984**, *14*, 155–161.
19. HDAC Fluorimetric Assay/Drug Discovery Kit—AK-500 Manual. Fluorescent Assay System (BIOMOL® International, Plymouth Meeting, PA), 2005.
20. Breslow, R.; Belvedere, S.; Gershell, L. *Helv. Chim. Acta* **2000**, *83*, 1685–1692.
21. Woo, S. H.; Frechette, S.; Abou Khalil, E.; Bouchain, G.; Vaisburg, A., et al. *J. Med. Chem.* **2002**, *45*, 2877–2885.
22. Morris, G. M.; Goodsell, D. S., Halliday, R. S., Huey, R., Hart, W. E., Belew, R. K.; Olson, A. J. *J. Comput. Chem.* **1998**, *19*, 1639–1662. http://www.scripps.edu/pub/olson-web/doc/autodock/.
23. Wang, D.-F.; Wiest, O.; Helquist, P.; Lan-Hargest, H.-Y.; Wiech, N. L. *J. Med. Chem.* **2004**, *47*, 3409–3417.
24. Lu, Q.; Wang, D.-S.; Chen, C.-S.; Hu, Y.-D.; Chen, C.-S. *J. Med. Chem.* **2005**, *48*, 5530–5535.
25. Butler, L. M.; Agus, D. B.; Scher, H. I.; Higgins, B.; Rose, A.; Cordon-Cardo, C.; Thaler, H. T.; Rifkind, R. A.; Marks, P. A.; Richon, V. M. *In Vivo Cancer Res.* **2000**, *60*, 5165–5170.
26. Mosmann, T. *J. Immunol. Methods* **1983**, *65*, 55–63.
27. Freshney, R. *Culture of Animal Cells: A Manual of Basic Technique*; Alan R. Liss, Inc.: New York, 1987, p. 117.
28. Suzuki, T.; Nagano, Y.; Kouketsu, A.; Matsuura, A.; Maruyama, S.; Kurotaki, M.; Nakagawa, H.; Miyata, N. *J. Med. Chem.* **2005**, *48*, 1019–1032.
29. Chen, P. C.; Emrich, R. E.; Patel, P. A.; Oyelere, A. K. *Bioorg. Med. Chem.* **2007**, *15*, 7288–7300.
30. The reaction could also be catalyzed by the addition of Cu-chelating ligand called tris-(benzyltriazolylmethyl)amine (TBTA).