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Hydroxamates: Relationships between Structure and Plasma Stability

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Hydroxamates are valuable tools for chemical biology as well as interesting leads for medicinal chemistry. Although many hydroxamates display nanomolar activities against metalloproteases, only three hydroxamates have reached the market, among which is the HDAC inhibitor vorinostat. Failures in development are generally attributed to lack of selectivity, toxicity, or poor stability. To help medicinal chemists with respect to plasma stability, we have performed the first and preliminary study on structure−plasma stability for hydroxamates. We define some structural rules to predict or improve the plasma stability in the preclinical stage.

Introduction

Hydroxamic acids are often potent bioactive molecules.[1,2] Because of their chelating group, they target metalloproteases and can serve as both biological probes[3] and leads. They can also be used as bioisosters of carboxylic acid, being weak acids.[4] Recently reported biological activities of these compounds include: inhibition of peptide deformylase (PDF) or of botulinum neurotoxin A protease.[5,6] Also, inhibition of the protease responsible for the shedding of the extracelullar domain of HER-2 by hydroxamates has been described.[7] Furthermore, inhibition of aggrecanases by hydroxamates has been reported in the literature, following the initial work on matrix metalloproteases (MMP).[8] The related tumor necrosis factor converting enzyme (TACE, ADAM17) is also inhibited by hydroxamates.[9] Other hydroxamates are active on *Plasmodium falciparum*, either by inhibiting metalloproteases or zinc hydrolases like histone deacetylases (HDAC).[10,11] Finally, the field of human histone deacetylase hydroxamate inhibitors has been extensively studied and led to the successful development of vorinostat (SAHA).[12]

Although hydroxamates are often very potent enzyme inhibitors, several challenges need to be addressed in the context of drug discovery. First, a relatively low selectivity (due to a significant contribution of Zn binding to their affinity to the target) may lead to several adverse effects. For example, broad MMP inhibition in patients gives rise to "stiffening" of the joints referred to as musculoskeletal syndrome (MSS).[13] Although this lack of selectivity hampered clinical development of the first generation of inhibitors, the discovery of more selective hydroxamates has been possible thanks to chemical modulation.[14] Second, pharmacokinetics and toxicological issues are not easily solved. These challenges have forced medicinal chemists to search for surrogates for this highly efficient zinc binding group (ZBG).[15] For example, some teams have shifted back to carboxylic acids or tetrazoles.[16,17] Other series include *o*-aminobenzamides or retrohydroxamates.[18,19] Nevertheless, after 25 years, the first hydroxamate was approved in 2006 for marketing: vorinostat (SAHA, Merck & Co.), a histone deacetylase (HDAC) inhibitor for the treatment of cancer.[20]

Hydroxamic acids may be hydrolyzed to the corresponding carboxylic acid under physiological conditions (Scheme 1).[21] Although involvement of the liver aldehyde oxidase was proposed, the hydrolytic activity of the plasma is the most widely accepted explanation.[22−24] Some hydroxamates are prone to hydrolysis in plasma. This is deleterious to their distribution and efficiency because the carboxylic acid is generally much less active. Hydrolysis may also contribute to toxicity because of the mutagenicity of the byproduct hydroxylamine.[25] Other metabolites of the hydroxamic function include glucuronides and sulfonates.[26,27] Recently, glycosylhydroxamates have been proposed as pro-drugs.[28]

Although many hydroxamates are disclosed in the literature, as well as their pharmacokinetics, no consistent information is yet available on structure−plasma stability relationships (SPSR). We and other groups have tried to improve the pharmacokinetics properties of hydroxamates by chemical modulation.[10,29] Unstable molecules exhibit a rapid clearance and short half-life, resulting in poor in vivo exposure of the organism and thus poor bioactivity. Determining plasma stability is critical for prioritizing compounds before in vivo experiments. This is therefore an important driver for the medicinal chemist. We report here the first and preliminary in vitro structure−plasma stability relationships (SPSR) of hydroxamates in rat plasma that could be useful for drug design. We discuss the structural features that potentially affect in vitro stability and relate our findings to those reported in the literature on hydroxamates.

Chemistry

Compounds **1**−**3** (Figure 1) were synthesized as previously described.[10] Compound **1** and (*Z*)-**2** were respectively a hit

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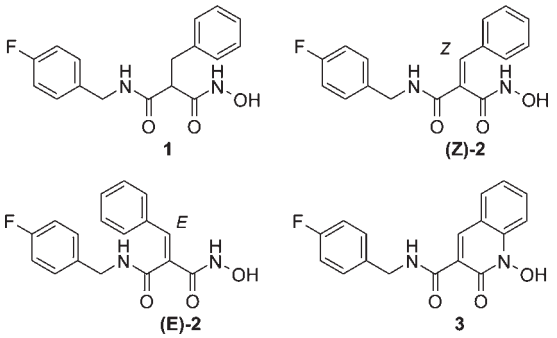
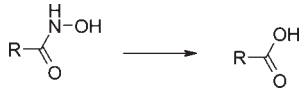
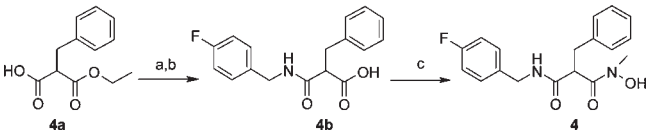


Figure 1. Structures of compounds **1**−**3**.

Scheme 1. Metabolic Hydrolysis of Hydroxamic Acids in Plasma

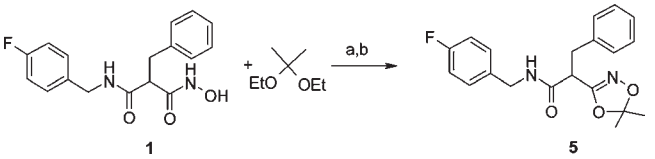


Scheme 2. Synthesis of Compound **4**[a]



[a] Reagents and conditions: (a) (1) CDI, THF, DIEA, DMF, 1.5 h, room temp; (2) *p*-F-C_6H_4-CH_2-NH_2, room temp, 3 h, 81%. (b) KOH, abs EtOH, 12 h, room temp, 80%. (c) PyBrop, CH_3-NH-OH, CH_2Cl_2, DIEA/DMF, 12 h, room temp, 40%.

Scheme 3. Synthesis of Prodrug **5**[a]

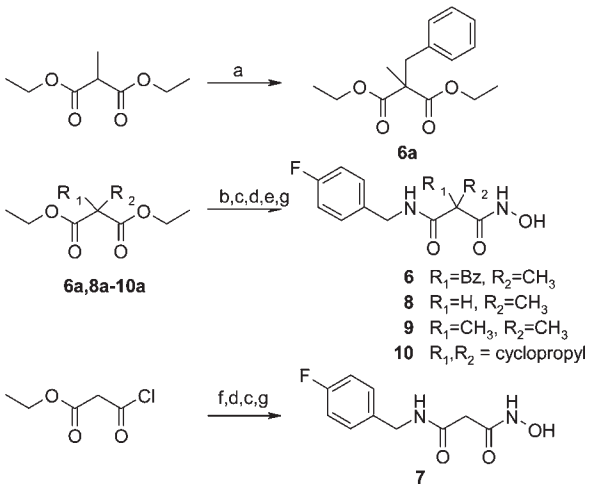


[a] Reagents and conditions: (a) camphor sulfonic acid, CH_2Cl_2, 2 h, room temp, (b) NaOH 0.1 M, dioxane, 3.5 h, room temp, 50%.

and a lead, which were identified in our optimization program aiming at the development of inhibitors of the plasmodial zinc metalloprotease *Pf*AM1.[10] In the course of this program, several analogues were developed for SAR purposes and also for structure−plasma stability relationships (SPSR). Syntheses of compounds **4**−**11** are described in Schemes 2−5. Compound **4** was obtained in three steps from 2-benzylmalonic acid monoethyl ester (Scheme 2). Coupling of *N*-methylhydroxylamine required some optimization because the classical protocol used for unsubstituted hydroxylamine (e.g., activation by oxalyl chloride) was unsuccessful (Table 1). The best activator was PyBrop[a] (Table 1). Compound **5** was designed as a prodrug of **1**.[30] Its synthesis proceeds as described in Scheme 3, giving **5** with an overall yield of 50%. Indeed, the ethyl ester derivative is a major

[a] Abbreviations: AcOEt, ethyl acetate; AcOH, acetic acid; CDI: *N*,*N*′-carbonyldiimidazole; CH_3CN, acetonitrile; DCM, dichloromethane; DIEA, diisopropylethylamine; DMF, dimethylformamide; DMSO, dimethylsulfoxide; EDCI, *N*-ethyl-3-(3-dimethyaminopropyl)-carbodiimide; Et_2O, diethyl ether; EtOH, ethanol; EWG, electron-withdrawing group; HOBT, *N*-hydroxybenzotriazole; MeOH, methanol; PyBrop, bromo-tris-pyrrolidinophosphonium hexafluorophosphate; TEA, triethylamine; TFA, trifluoroacetic acid; THF, tetrahydrofuran; Trt, trityl.

Scheme 4. Synthesis of Compounds **6**−**10**[a]



[a] Reagents and conditions: (a) (1) EtONa/EtOH, 1 h, 50 °C; (2) $C_6H_5CH_2Br$, 2 h, 50 °C, 83%. (b) KOH, abs EtOH, 4 h, room temp, 80%. (c) *p*-fluoro-benzylamine, EDCI/HOBt, DMF, DIEA, room temp, 12 h. (d) KOH, abs EtOH, 12 h, room temp. (e) (1) Ethyl chloroformate, TEA, CH_2Cl_2, 40 min, 0 °C; (2) H_2NO-Trt, 1 h, room temp; (3) TFA 2%/CH_2Cl_2, triisopropylsilane, 5 min room temp. (f) H_2NOTrt, DIEA, CH_2Cl_2, 3 h, room temp, 79%. (g) TFA 2%/CH_2Cl_2, triisopropylsilane, 5 min room temp.

byproduct.[31] Compounds **6** and **8**−**10** were obtained from the corresponding substituted diethylmalonate, using *N*-tritylhydroxylamine (Scheme 4). Compound **6** required the synthesis of the 2-benzyl-2-methylmalonic acid diethyl ester precursor. Hydroxamate **7** was obtained from the chlorocarbonylacetic acid ethyl ester (Scheme 4). Compound **11** differs from **1** by the inversion of amide function and was obtained from phenylalanine using a solid support strategy that allowed both anchoring and protection of the hydroxamate moiety (Scheme 5).

A second series of compounds was investigated with the aim of varying the structure and length of the chain between the terminal hydroxamic moiety and an aryl group (compounds **12**−**22**).

These compounds were obtained from the corresponding carboxylic acid and *O*-trityl-hydroxylamine by activation using either oxalylchloride or EDCI/HOBt (Scheme 6). For compound **19**, the acid precursor was synthesized by a Sonogashira reaction from the corresponding acetylenic derivative and 4-iodobenzoic ethyl ester (Scheme 6). Compound **22** derived from *N*-Boc-L-phenylalanine (Scheme 6). Finally, SAHA and compounds **20**−**21** were synthesized as reported in the literature (Scheme 7).[32,33]

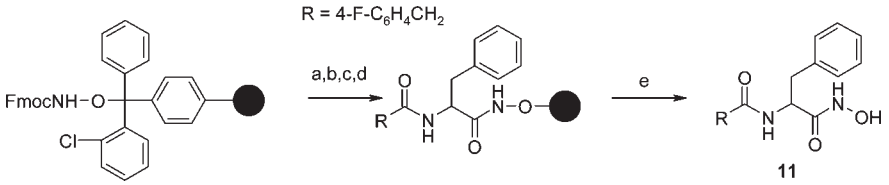
Plasma Stabilities

Rat plasma stabilities were evaluated for hydroxamates **1**−**22** and expressed as their corresponding half-lives. The stability of **1** was also measured in the presence of phenylmethylsulfonyl fluoride (PMSF), an esterase inhibitor. Stability of compounds **1**, (*Z*)-**2**, (*E*)-**2**, **14**, and **15** was further evaluated in human plasma. In all cases, quantification was performed in duplicate using LC-MSMS (MRM or SIM detection modes) in the presence of an internal standard.

Results and Discussion

Evidencing Esterase Implication. All compounds are stable when incubated in potassium phosphate buffer (pH 7.4),

Scheme 5. Solid-Phase Synthesis of **11**[a]



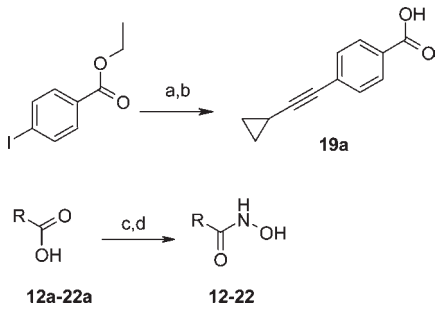
[a] Reagents and conditions: (a) piperidine 20%/DMF 80%, 30 min; (b) D,L-Fmoc-Phe-OH, HATU, DIEA, DMF, 12 h (twice); (c) piperidine 20%/DMF 80%, 30 min; (d) RCOOH, HOBt, TBTU, DIEA, DMF 3 h; (e) TFA 2%/CH_2Cl_2, triisopropylsilane, 2 min.

Table 1. Reaction Conditions for the Coupling of *N*-Methyl Hydroxylamine with **4b**

reagent	solvent	temp (°C)	time (h)	conversion[a] (%)	comments
oxalyl chloride[44]	DCM	0 then rt	4	27	complex mixture
ethyl chloroformate	DCM	0 then rt	1.5		obtention of diethyl ester
TBTU/HOBt	DMF	rt	overnight	60	complex mixture
EDCI/HOBt[45]	DMF	rt	overnight	25	complex mixture
PyBrop	DCM	rt	overnight	70	

[a] **4b** conversion to final product determined by HPLC (215 nm).

Scheme 6. Synthesis of Compounds **19a**, **12**−**22**[a]



[a] Reagents and conditions: (a) cyclopropylacetylene, $PdCl_2(PPh_3)_2$, CuI, NEt_3, DMF, 70 °C, 90%; (b) NaOH, EtOH, H_2O, room temp, 98%; (c) (i) oxalylchloride (1.2 equiv), DCM, cat. DMF, 45 min, 0 °C; (ii) DIEA (3 equiv), *O*-tritylhydroxylamine (0.85 equiv), DCM, 0 °C then room temp, 3 h; or carboxylic acid 0.1 M/DMF (1 equiv), DIEA (2.4 equiv), EDCI (1.1 equiv), HOBt (1.1 equiv), room temp, 5 min then *O*-tritylhydroxylamine (0.85 equiv) 0.1 M/DMF, DIEA (2 equiv), room temp, 5 h; (d) TFA 2%/DCM, triisopropylsilane, 5 min, room temp.

suggesting that degradation occurring in rat plasma was most likely enzymatic.[34] To demonstrate the esterasic activity of plasma, we preincubated rat plasma with 2 mM PMSF (phenylmethylsulfonyl fluoride), a known broad spectrum serine-hydrolase inhibitor, in experiments aiming at the measurement of the half-life of **1** (Table 2). The increase in half-life in the presence of PMSF is similar to that of enalapril, an ester prodrug known to be hydrolyzed by plasma esterases, showing that hydrolysis is enzyme-dependent.

Rat Plasma Stabilities. In vitro half-lives of compounds in rat plasma are presented in Tables 3−6. The following paragraphs are based largely on pairwise comparisons of plasma stabilities. These results are consolidated and put into perspective in the Summary.

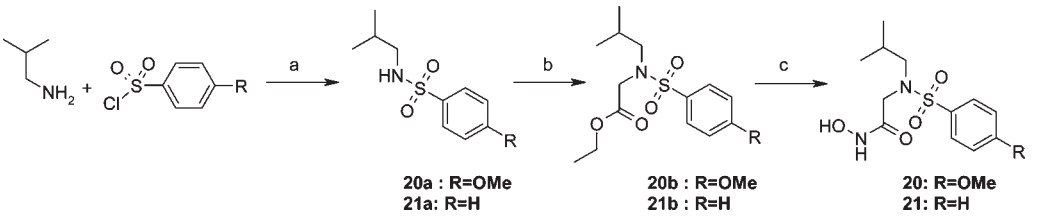
Influence of Substituent and Spacer in Arylalkanoic Hydroxamate Derivatives. In the series designed to explore the influence of the length and nature of the chain between the aryl ring and the hydroxamate function, large variations of half-lives are observed (**11**−**22**, Table 4). While benzohydroxamic and phenylacetohydroxamic acids **12** and **13** are very stable, the homologous compound **14** is much less stable. Summers et al. showed for hydroxamate derivatives of ibuprofen that an important structural feature for resistance to metabolism is the spacer unit between the hydroxamate group and the phenyl ring.[35] They concluded that introduction of a larger spacer enhances metabolism to the corresponding carboxylic acid. However, we believe that the dramatic drop in stability observed in our series between **13** and **14** cannot be explained solely by the increase of accessibility of the carbonyl center. In fact, SAHA which has the longest alkylidene spacer has an intermediate half-life of 9.7 h (Table 4). Rather, recognition of the phenyl group by esterases is likely to be a key component of hydrolysis.

Interestingly, replacing a methylene moiety by an oxygen atom does not alter the half-life (**15** vs **18**) or increases the half-life by 100% (**14** vs **17**). Decreasing flexibility (due to the introduction of a trans double bond) better protects from hydrolysis (**16** vs **14**). Interestingly, hydroxamate **19** is less stable than its analogue **12**. An explanation could be that **19** has a greater lipophilicity (AlogP = 2.2 and 0.8 for **19** and **12**, respectively)[36] and that this longer substituent enhances the hydrophobic contact with the esterases.[37] Along with the possible hydrogen bond with NH in **22**, this explanation could also be valid for the difference between **14** and **22**, the latter bearing an additional hydrophobic tBoc-amino group (AlogP = 1.3 and 1.8 for **14** and **22**, respectively).

Phenylalanine derivatives **11** and **22** that bear a benzyl group in alpha to the hydroxamate are rapidly hydrolyzed. In contrast, compounds **20** and **21** are more stable because they lack a benzyl substituent on the Cα.

Influence of the Nature of the Substituent in Malonic Hydroxamic series. Plasma stabilities for malonic compound **1** and analogues **2**−**4** and **6**−**10** are presented in Table 3. In the malonic series, again, the nature of the substituant on the malonic carbon (e.g., alpha to the hydroxamate function) has a great impact on stability. Indeed, the half-lives range from 0.8 to 33 h. For example, **7**, which bears no substituent, displays an intermediate stability of 10.5 h, comparable to that of the glycine derivatives **20** and **21** in the previous series. The shortest half-lives were observed for hydroxamic acids **1**, **4**, and **6**. Again, as for the previous series, the benzyl substituent appears to be deleterious for the stability as it can be seen when comparing **1** and **7**, as well as **6** and **8**. In contrast, introduction of a methyl group on the same malonic carbon decreases the susceptibility to hydrolysis (**6** vs **1** and **8**−**10** vs **7**). Interestingly, in the benzyl series,

Scheme 7. Synthesis of Derivatives **20**−**21**[a]



[a] Reagents and conditions: (a) DIEA, DMF, THF, room temp, 1 h; (b) NaH, ethylbromoacetate, THF, room temp, 12 h; (c) $NH_2OH \cdot HCl$, NaOMe, MeOH, room temp, 12 h.

Table 2. Influence of PMSF on Plasma Stability of **1** and Enalapril ($t_{1/2}$ in h)

compd	w/o PMSF	2 mM PMSF
1	0.8	15
enalapril	0.05	> 24

methylation on the nitrogen of the hydroxamate did not increase stability (**4** vs **1** and **6**).

Electronic and Geometric Effects. Three α,β-unsaturated derivatives were prepared and tested ((***E***)-**2**, (***Z***)-**2**, and **3**). The three compounds are more stable than the saturated analogue **1**. This improved stability could be attributed to the dispersion of the electrophilic character on two centers. Another explanation could be the influence of steric constraints caused by the insaturation. Indeed, for **2**, the *Z* configuration is much more stable than the *E* configuration. This could be due to a better recognition by hydrolases of the extended configuration of (***E***)-**2** or a steric protection of the electrophilic carbonyl by the aromatic ring in (***Z***)-**2**. The high stability of **3** is probably mainly due to its cyclic nature.

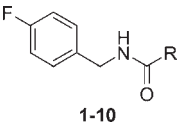
Summary

Comparison of half-lives of all direct analogues of phenylpropionohydroxamic acid **14** provides useful information (Table 5). Conformationnally flexible analogues **14**, **22**, **1**, and **11** are globally highly unstable. Compounds (***E***)-**2** and **16** that unveil the hydroxamate moiety are more stable than the previous flexible compounds, probably due to the less electrophilic carbonyl group vicinal to a double bond. (***Z***)-**2** presents two stabilizing features that are the steric hindrance of the hydroxamate and the less electrophilic carbonyl group. Finally, it is possible that an extended conformation ((***E***)-**2**, **1**, and **14**) of the arylated chain is favorable to the recognition by esterases. A phenylbutanoic ester chain is also found in enalapril which is very rapidly hydrolyzed.

We have shown that methylation of the α position to the electophilic carbonyl increases in each case the stability. This effect is consistent with the frequent occurrence of neopentyl centers in α position to hydroxamic acids developed as lead compounds. However, a highly substituted center is not always required to obtain stable compounds, as we have demonstrated here (**SAHA**, **7** vs **1**). Gilmore et al. were surprised that a compound lacking a substituent at the α position is as stable as its neopentyl analogue.[38] In our opinion, this stability reflects more the fact that both compounds are devoid of a correctly placed aryl substituent favoring the hydrolysis.

In conclusion, plasma stability of hydroxamates seems to be the result of two opposing factors (Figure 3). Stabilizing factors are the steric hindrance around the hydroxamate

Table 3. Rat Plasma Stabilities of Analogues of Malonyl Hydroxamic Acid **1**



1-10

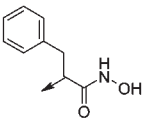
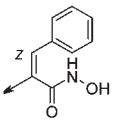
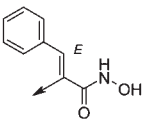
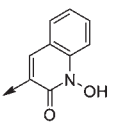
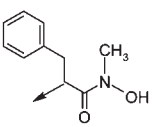
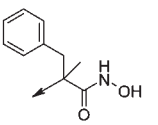
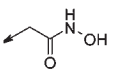
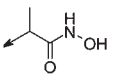
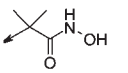
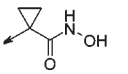
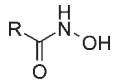
Cpd	-R	$t_{1/2}$ (h)
1		0.8
(Z)-2		22.0
(E)-2		4.1
3		>48.0
4		0.5
6		3.0
7		10.5
8		33.0
9		19.9
10		22.3

Table 4. Rat Plasma Stabilities of Hydroxamic Acids **11**−**22**



11-23

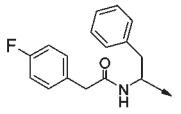
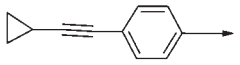
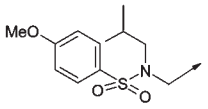
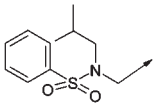
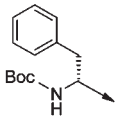
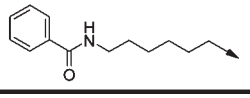
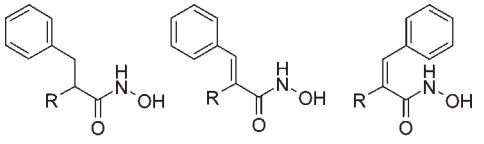
Cpd	-R	$t_{1/2}$ (h)
11		1.3
12	Ph-	>24.0
13	Ph-CH_2-	>24.0
14	Ph-$(CH_2)_2$-	1.5
15	Ph-$(CH_2)_3$-	2.0
16	Ph-CH=CH-	6.2
17	Ph-O-CH_2-	3.0
18	Ph-O-$(CH_2)_2$-	1.4
19		4.0
20		10.5
21		9.6
22		<1
SAHA		9.7

Table 5. Comparing Stabilities of Analogues of **14**



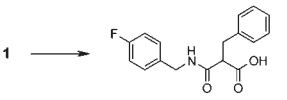
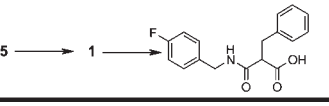
1,11,14,22-23 **(E)-2,16** **(Z)-2**

compd	R−	$t_{1/2}$ (h)
14	H−	1.5
22[a]	Boc-NH−	< 1
1	F-C_6H_4-CH_2-NHCO−	0.8
11	F-C_6H_4-CH_2-CONH−	1.0
16	H−	6.2
(***E***)-**2**	F-C_6H_4-CH_2-NHCO−	4.1
(***Z***)-**2**	F-C_6H_4-CH_2-NHCO−	22.0

[a] Derived from D-Phe.

group and the mesomeric effects that reduce the electrophilic nature of the carbonyl. Among potential hydrolysis-promoting factors, we have identified hydrophobicity and the presence of an extended phenylpropiono- or phenylbutyro-hydroxamic motif. These results allow us to hypothesize a preliminary pharmacophore for plasma hydrolysis or stability of hydroxamic acids (Figure 3).

Table 6. Enhancement of Apparent Half-Life of **1** Using Prodrug **5**

Hydrolysis	$t_{1/2}$ (h)
	0.8
	1.0

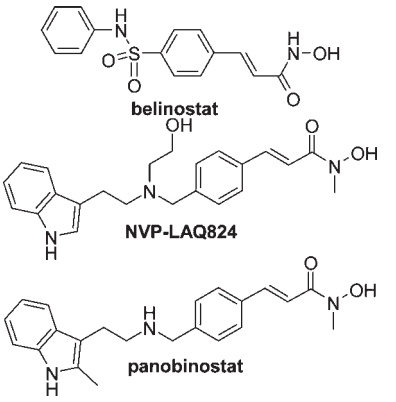


Figure 2. Structures of NVP-LAQ824, panobinostat (NVP-LBH589), and belinostat (PXD101).

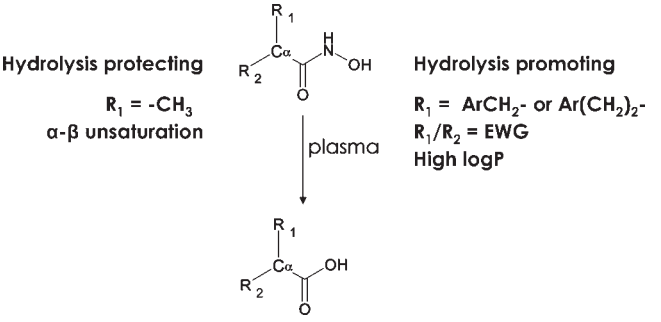


Figure 3. Hydrolysis promoting or protecting factors. EWG: electron-withdrawing group.

In case of significant hydrolysis, it may be interesting to design a prodrug. Only a few prodrugs of hydroxamates are described.[28,30] Our attempts to protect **1** as prodrug **5** did not significantly improve the half-life (Table 6).[39] Prodrug **5** is hydrolyzed into **1** with a half-life of 0.3 h, and then compound **1** is hydrolyzed into the corresponding carboxylic acid in 0.8 h, resulting in an almost unchanged half-life of **1**.

The result obtained with *trans*-cinnamic compound (***Z***)-**2** is of high interest in the light of the current development of cinnamic inhibitors of botulinum neurotoxin A or histone deacetylases (Figure 2).[40,41] For example, the direct analogue of cinnamic acid, belinostat PXD101, is currently evaluated in 18 clinical trials in cancer therapy.[42]

Several papers report species differences for the plasma stability of amides or hydroxamates.[43−45] It is known that generally speaking, rat plasma is "more aggressive" than

Table 7. Comparison of Stability ($t_{1/2}$ in h) in Various Media

compd	rat plasma	human plasma	buffer (PBS, pH = 7.4)
1	0.8	> 24	> 24
(*E*)-**2**	4.1	> 24	> 24
(*Z*)-**2**	22	> 24	> 24
14	1.5	> 24	> 24
15	2.0	> 24	> 24

human plasma.[23] Not surprisingly, independently of their half-lives in rat plasma, all our compounds are very stable in human plasma ($t_{1/2}$ > 24 h) (Table 7). The difference in stability in human and rodent plasma remains a specific hurdle in the development of hydroxamates. In fact, hydroxamates must be stable in preclinical in vivo models (often rodents) for proof of concept. In this context, our results help to rationalize structure−stability relationships. These should help medicinal chemists to reconcile the pharmacophore of their target and the structural requirements for rodent plasma stability.

Experimental Section

Chemistry. General Information. 2-Chlorotrityl *N*-Fmoc-hydroxylamine, polymer-bound, 100−200 mesh, was purchased from Sigma-Aldrich Inc. NMR spectra were recorded on a Bruker DRX-300 spectrometer. Chemical shifts are in parts per million (ppm). The assignments were made using one-dimensional (1D) ^{1}H and ^{13}C spectra and two-dimensional (2D) HSQC and COSY spectra. Mass spectra were recorded on a MALDI-TOF Voyager-DE-STR spectrometer or with a LCMS-MS triple-quadrupole system (Varian 1200ws). The purities of the desired compounds were confirmed by reversed phase HPLC or LCMS, using UV detection (215 nM): HPLC analyses were performed using a C18 TSK-GEL Super ODS 2 μm column (dimensions 50 mm × 4.6 mm). A gradient starting from 100% H_2O/0.05% TFA and reaching 20% H_2O/80% CH_3CN /0.05% TFA within 10 min at a flow rate of 1 mL/min was used. LCMS gradient starting from 100% H_2O/0.1% formic acid and reaching 20% H_2O /80% CH_3CN/0.08% formic acid within 10 min at a flow rate of 1 mL/min was used. Melting points were measured on a Büchi B-540 apparatus and are uncorrected. All commercial reagents and solvents were used without further purification. Organic layers obtained after extraction of aqueous solutions were dried over $MgSO_4$ and filtered before evaporation in vacuo. Thick layer chromatography was performed with Silica Gel 60 (Merck, 40−63 μm). Purification yields were not optimized.

2-Benzyl-*N*-(4-fluoro-benzyl)-*N*′-hydroxy-malonamide (1). See Supporting Information; white powder; yield 88%; purity 100%. ^{1}H NMR (DMSO-d_6) δ ppm: 2.96−3.10 (m, 2H), 3.35−3.40 (m, 1H), 4.16 (dd, J = 15, J = 5.7 Hz, 1H), 4.27 (dd, J = 15, J = 6 Hz, 1H), 7.04−7.27 (m, 9H), 8.40 (t, J = 5.6 Hz, NHCO), 8.93 (s, OH), 10.58 (s, CONHO). ^{13}C NMR (DMSO-d_6) δ ppm: 35.0, 42.1, 52.5, 115.5 (d, J_{CF} = 21.1 Hz), 126.8, 128.8, 129.4, 129.5 (d, J_{CF} = 8.4 Hz), 136.0 (d, J_{CF} = 2.3 Hz), 139.6, 161.7 (d, J_{CF} = 240.4 Hz), 166.3, 168.9. tr_{LCMS} 4.31 min. MS $[M + H]^+$ m/z 317. mp 193−194 °C.

***N*-(4-Fluoro-benzyl)-*N*′-hydroxy-2-[1-phenyl-meth-(*Z*)-ylidene]-malonamide ((*Z*)-2).** See Supporting Information; white powder; yield 96%; purity 99%. ^{1}H NMR (DMSO-d_6) δ 4.37 (d, J = 6.0 Hz, 2H), 7.12−7.18 (m, 2H), 7.32−7.40 (m, 5H), 7.43 (s, 1H), 7.51−7.54 (m, 2H), 8.26 (t, J = 6.0 Hz, NHCO), 9.13 (s, OH), 11.01 (s, CONHO). ^{13}C NMR (DMSO-d_6) δ ppm: 42.6, 115.6 (d, J_{CF} = 21 Hz), 129.3, 129.5, 129.9, 130.1, 130.6, 134.2, 136.2, 137.3, 161.8 (d, J_{CF} = 246 Hz), 163.5, 164.6. tr_{LCMS} 4.23 min. MS $[M + H]^+$ m/z 315.

2-[1-Phenyl-meth-(*Z*)-ylidene]-malonic Acid Monoethyl Ester ((*E*)-2). See Supporting Information; white powder; yield 70%; purity 95%. ^{1}H NMR (DMSO-d_6) δ ppm: 4.30 (d, J = 6.0 Hz, 2H), 7.08−7.37 (m, 10H), 8.86 (t, J = 6.0 Hz, NHCO), 9.08 (br s, OH), 10.70 (br s, CONHO). tr_{LCMS} 4.41 min. MS $[M + H]^+$ m/z 315.

1-Hydroxy-2-oxo-1,2-dihydro-quinoline-3-carboxylic Acid 4-Fluoro-benzylamide (3). See Supporting Information; beige powder (70%); purity 99%. ^{1}H NMR (DMSO-d_6) δ ppm: 4.58 (d, J = 6.0 Hz, 2H), 7.14−7.20 (m, 2H), 7.38−7.41 (m, 3H), 7.76−7.81 (m, 2H), 8.05 (d, J = 7.5 Hz, 1H), 8.85 (s, 1H), 10.06 (t, J = 6.0 Hz, NH), 11.82 (s, 1H, OH). ^{13}C NMR (DMSO-d_6) δ ppm: 42.5, 113.2, 115.8 (d, J_{CF} = 21 Hz), 118.4, 121.9, 123.9, 130.0 (d, J_{CF} = 8 Hz), 130.8, 134.0, 135.9, 139.7, 141.4, 158.1, 161.9 (d, J_{CF} = 240 Hz), 163.1. tr_{LCMS} 5.10 min. MS $[M + H]^+$ m/z 313.

2-Benzyl-*N*-(4-fluoro-benzyl)-*N*′-hydroxy-*N*′-methyl-malonamide (4). 2-Benzyl-malonic acid diethyl ester (7.5 g, 30 mmol) was added to a solution of KOH (1.68 g, 30 mmol) in EtOH (45 mL). The solution was stirred at room temperature for 6 h and evaporated. The residue was dissolved in $NaHCO_3$ 5% (20 mL) and extracted with ethyl acetate. The aqueous layer was acidified and extracted three times with ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated to give (**4a**) as a colorless oil (86%). Purity 99%. ^{1}H NMR (DMSO-d_6) δ 1.23 (t, J = 7.2 Hz, 3H), 3.26 (d, J = 7.8 Hz, 2H), 3.73 (t, J = 7.8 Hz, 1H), 4.19 (q, J = 7.2 Hz, 2H), 7.23−7.34 (m, 5H), 10.11 (s, 1H, COOH). MS $[M + H]^+$ m/z 223. 2-Benzyl-malonic acid monoethyl ester (**4a**) (7.556 g, 34 mmol) was dissolved in DMF (25 mL) and DIEA (7.1 mL, 41 mmol). CDI (6.06 g, 37.4 mmol) was dissolved in THF (50 mL) and added to the carboxylic acid solution. The reaction mixture was stirred at room temperature for 1.5 h and 4-fluorobenzylamine (3.872 mL, 34 mmol) dissolved in DMF (40 mL) and DIEA (11.8 mL, 68 mmol) was added. The solution was stirred at room temperature for 3 h and evaporated. The crude product was dissolved in ethyl acetate, washed 10 times with H_2O, three times with $KHSO_4$ solution (pH = 3), and with aq NaCl, dried over $MgSO_4$, filtered, and evaporated to give the ester as a beige powder (81%). Purity 95%. ^{1}H NMR (DMSO-d_6) δ 1.14 (t, J = 7.2 Hz, 3H), 3.04−3.10 (m, 2H), 3.69 (dd, J = 6.6 Hz, J = 9.0 Hz, 1H), 4.08 (q, J = 7.2 Hz, 2H), 4.19−4.23 (m, 2H), 7.05−7.09 (m, 4H), 7.19−7.28 (m, 5H), 8.60 (t, J = 5.4 Hz, NH). tr_{LCMS} 6.02 min. MS $[M + H]^+$ m/z 330. The ester (8.88 g, 27 mmol) was added to a solution of KOH (4.54 g, 81 mmol) in EtOH (50 mL). The solution was stirred at room temperature overnight and evaporated. The residue was dissolved in H_2O (20 mL) and extracted with ethyl acetate. The aqueous layer was acidified and extracted three times with ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated to give (**4b**) as a white powder (80%). Purity 99%. ^{1}H NMR (DMSO-d_6) δ 2.96−3.09 (m, 2H), 3.60 (dd, J = 6.3 Hz, J = 9.3 Hz, 1H), 4.11 (dd, J = 5.4 Hz, J = 15.3 Hz, 1H), 4.11 (dd, J = 6.3 Hz, J = 15.3 Hz, 1H), 6.97−7.06 (m, 4H), 7.16−7.29 (m, 5H), 8.53 (t, J = 6.0 Hz, NHCO), 12.61 (s, 1H, COOH). tr_{LCMS} 4.93 min. MS $[M + H]^+$ m/z 302. 2-Benzyl-*N*-(4-fluoro-benzyl)-malonamic acid (**4b**) was dissolved in DMF (4 mL), and DIEA (1.2 equiv, 0.96 mmol) and PyBrop (0,96 mmol, 124 mg) were added. The solution was stirred at room temperature for 1 min and *N*-methylhydroxylamine·HCl in DMF (4 mL), and DIEA (2.4 equiv, 332 μL) was added. The solution was stirred at room temperature overnight and evaporated. The residue was dissolved in ethyl acetate and washed three times with aq $NaHCO_3$ 5% and once with aq NaCl, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by TLC (DCM/MeOH 96/4) to give (**4**) as a white powder (40%). Purity 99%. ^{1}H NMR (DMSO-d_6) δ 2.95 (dd, J = 7.1 Hz, J = 13.6 Hz, 1H), 3.07 (s, 3H), 3.04−3.11 (m, 1H), 4.03 (t, J = 7.0 Hz, 1H), 4.16 (dd, J = 5.7 Hz, J = 15.3 Hz, 1H), 4.27 (dd, J = 6.1 Hz, J = 15.1 Hz, 1H), 7.05−7.27 (m, 9H), 8.32 (s, NH), 9.93 (s, OH). ^{13}C NMR (DMSO-d_6) δ ppm: 35.1, 36.5, 41.9, 51.1, 115.3 (d, J_{CF} = 21.1 Hz), 126.5, 128.5, 129.3, 129.4, 136.0, 140.1, 161.5 (d, J_{CF} = 241.7 Hz), 169.2, 169.4. $t_{R\ LCMS}$ 4.69 min. MS $[M + H]^+$ m/z 331.

2-(5,5-Dimethyl-[1,4,2]dioxazol-3-yl)-*N*-(4-fluoro-benzyl)-3-phenyl-propionamide (5). 2-Benzyl-*N*-(4-fluoro-benzyl)-*N*′-hydroxy-malonamide (**1**) (1.00 g, 3.16 mmol) was dissolved in DCM (100 mL) and 2,2-diethoxypropane (1.528 mL, 9.48 mmol), and camphorsulfonic acid (734 mg, 3.16 mmol) were added. The reaction mixture was stirred at room temperature for 2 h, and aq Na_2CO_3 solution (20 mL) was added. The aqueous layer was extracted four times with diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated. The residue was dissolved in dioxane (8 mL), and 0.1 N NaOH solution (8 mL) was added. The reaction mixture was stirred at room temperature for 3.5 h, water was added, and reaction mixture was extracted three times with ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated. The residue was purified by TLC (DCM/MeOH 96/4 to give (**5**) as a white powder (50%) purity 96%. ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 3H), 1.46 (s, 3H), 3.11 (dd, J = 8.1, J = 13.8 Hz, 1H), 3.30 (dd, J = 7.2, J = 14.1 Hz, 1H), 3.60 (t, J = 7.8 Hz, 1H), 4.32−4.38 (m, 2H), 6.78 (br s, NH), 6.90−6.96 (m, 2H), 7.06−7.10 (m, 2H), 7.17−7.26 (m, 5H). tr_{LCMS} 6.20 min. MS $[M + H]^+$ m/z 357.

2-Benzyl-*N*-(4-fluoro-benzyl)-*N*′-hydroxy-2-methyl-malonamide (6). Sodium (633 mg, 27.5 mmol) was added slowly to absolute EtOH (30 mL) at 0 °C. The solution was stirred at room temperature for 30 min, and diethylmethylmalonate (4.30 mL, 25 mmol) was added. The reaction mixture was stirred at 50 °C for 1 h, and benzylbromide (2.392 mL, 20 mmol) was added. The reaction mixture was stirred at 50 °C for 2 h and evaporated. The residue was dissolved in DCM and washed three times with aq $NaHCO_3$ 5%, once with NaOH solution (1N) and with H_2O, dried over $MgSO_4$, filtered, and evaporated to give 2-benzyl-2-methyl-malonic acid diethyl ester (**6a**) as a colorless oil (83%). Purity 95%. ^{1}H NMR (CD_2Cl_2) δ 1.27 (t, J = 7.2 Hz, 6H), 1.32 (s, 3H), 3.22 (s, 2H), 4.20 (q, J = 7.2 Hz, 4H), 7.13−7.16 (m, 2H), 7.23−7.33 (m, 3H). tr_{LCMS} 6.93 min. MS $[M + Na]^+$ m/z 287. Diester (**6a**) (3.854 g, 14.6 mmol) was added to a solution of KOH (819 mg, 14.6 mmol) in EtOH (50 mL). The solution was stirred at room temperature for 4 h and evaporated. The residue was dissolved in $NaHCO_3$ 5% solution (20 mL) and washed with DCM. The aqueous layer was acidified and extracted three times with DCM. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated to give 2-benzyl-2-methyl-malonic acid monoethyl ester as a white powder (80%). Purity 97%. ^{1}H NMR (CD_2Cl_2) δ: 1.30 (t, J = 7.2 Hz, 3H), 1.43 (s, 3H), 3.21 (d, J = 13.5 Hz, 1H), 3.32 (d, J = 13.5 Hz, 1H), 4.23 (q, J = 7.2 Hz, 2H), 7.17−7.20 (m, 2H), 7.28−7.35 (m, 3H). MS $[M - H]^-$ m/z 235.

2-Benzyl-2-methyl-malonic acid monoethyl ester (8.2 mmol) was dissolved in DMF (20 mL) and DIEA (4.966 mL, 28.7 mmol). EDCI (1.895 g, 9.8 mmol) and HOBt (1.505 g, 9.8 mmol) were added, the solution was stirred for 5 min, and 4-fluorobenzylamine (942 μL, 8.2 mmol) was added. The solution was stirred at room temperature overnight and evaporated. The residue was dissolved in ethyl acetate and washed four times with aq $NaHCO_3$ 5% and once with 1N HCl solution and once with aq NaCl, dried over $MgSO_4$, filtered, and evaporated to give 2-benzyl-*N*-(4-fluoro-benzyl)-2-methyl-malonamic acid ethyl ester as a white powder (66%). Purity 98%. ^{1}H NMR (DMSO-d_6) δ 1.14 (t, J = 7.2 Hz, 3H), 1.21 (s, 3H), 3.10 (d, J = 13.2 Hz, 1H), 3.17 (d, J = 13.2 Hz, 1H), 4.08 (q, J = 7.2 Hz, 2H), 4.18−4.32 (m, 2H), 7.06−7.28 (m, 9H), 8.33 (t, J = 6.0 Hz, NH). tr_{LCMS} 6.58 min. MS $[M + H]^+$ m/z 344. Ester (3.8 mmol) was added to a solution of KOH (6.405 g, 11.4 mmol) in EtOH (9 mL). The solution was stirred at room temperature overnight and evaporated. The residue was dissolved in H_2O and washed with DCM. The aqueous layer was acidified and extracted three times with DCM. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated to give 2-benzyl-*N*-(4-fluoro-benzyl)-2-methyl-malonamic acid as a beige powder (84%). Purity 95%. ^{1}H NMR (CD_2Cl_2) δ 1.86 (s, 3H), 3.06 (d, J = 13.2 Hz, 1H), 3.16 (d, J = 13.2 Hz, 1H), 4.25 (d, J = 6.0 Hz, 2H), 7.07−7.26 (m, 9H), 8.30 (t, J = 6.0 Hz, NH). $t_{R\ LCMS}$ 5.40 min. MS $[M + H]^+$ m/z 316. Acid (317 mg, 1 mmol) was dissolved in DCM (8 mL) and TEA (155 μL, 1.1 mmol). Ethyl chloroformate (105 μL, 1.1 mmol) was added dropwise at 0 °C, the solution was stirred for 40 min at 0 °C, and *O*-tritylhydroxylamine (206 mg, 0.75 mmol) in DCM (2 mL) was added. The solution was stirred at room temperature for 1 h and evaporated. The residue was dissolved in ethyl acetate and washed four times with aq $NaHCO_3$ 5% and once with 1N HCl solution and once with aq NaCl, dried over $MgSO_4$, filtered, and evaporated. The crude product was purified by TLC (DCM/MeOH 98/2) to give 2-benzyl-*N*-(4-fluoro-benzyl)-2-methyl-*N*′-trityloxy-malonamide as a white powder (60%). Purity 98%. ^{1}H NMR (DMSO-d_6) δ 0.95 (s, 3H), 2.65 (d, J = 13.5 Hz, 1H), 3.03 (d, J = 13.5 Hz, 1H), 4.14 (d, J = 5.7 Hz, 2H), 6.83−6.85 (m, 2H), 7.04−7.15 (m, 7H), 7.33 (s, 15H), 8.21 (t, J = 5.7 Hz, NH), 10.13 (s, CONHO). tr_{LCMS} 8.59 min. MS $[M - H]^-$ m/z 571. The protected hydroxamic acid (239 mg, 0.4 mmol) was dissolved in TFA 2%/DCM (0.03 M), and triisopropylsilane was added dropwise until the yellow color disappeared. The reaction mixture was stirred 5 min at room temperature, solvents were removed under reduced pressure, and the residue was washed with petroleum ether and purified by TLC (DCM/MeOH/TEA 6/1.5/2.5) to give (**6**) as a beige powder (60%). Purity 99%. ^{1}H NMR (CD_2Cl_2) δ: 1.24 (s, 3H), 2.99 (s, 2H), 4.34 (s, 2H), 7.00−7.23 (m, 9H). ^{13}C NMR ($CDCl_3$) δ ppm: 17.8, 43.3, 44.8, 53.1, 115.5 (d, J_{CF} = 21.3 Hz), 127.2, 128.4, 129.5 (d, J_{CF} = 7.5 Hz), 130.0, 133.2, 135.4, 162.2 (d, J_{CF} = 244.4 Hz), 170.1, 172.1. tr_{LCMS} 4.66 min. MS $[M + H]^+$ m/z 331.

***N*-(4-Fluoro-benzyl)-*N*′-hydroxy-malonamide (7).** *O*-Tritylhydroxylamine (468 mg, 1.7 mmol) was dissolved in DCM (10 mL), and DIEA (346 μL, 2 mmol) was added. The flask was put in an ice bath, and chlorocarbonylacetic acid ethyl ester (2 mmol, 253 μL) was added dropwise. Reaction mixture was stirred at room temperature for 3 h and washed with aq $NaHCO_3$ 5% (six times) and once with aq NaCl, dried over $MgSO_4$, filtered, and evaporated. The residue was washed with petroleum ether to give *N*-trityloxy-malonamic acid ethyl ester as a white powder (79%). Purity 99%. ^{1}H NMR (DMSO-d_6) δ ppm: 1.10 (t, J = 7.2 Hz, 3H), 2.94 (s, 2H), 3.97 (q, J = 7.2 Hz, 2H), 7.32 (s, 15H), 10.47 (s, NH). tr_{LCMS} 5.10 min. MS $(M - H)^-$ m/z 388. *N*-Trityloxy-malonamic acid ethyl ester (468 mg, 1.2 mmol) was dissolved in DCM (7 mL), and KOH (202 mg, 3.6 mmol) was added as a solution in EtOH (10 mL). The reaction mixture was stirred at room temperature overnight and evaporated. The residue was dissolved in H_2O and washed with DCM (three times). The aqueous layer was acidified by $KHSO_4$ (pH = 6) and extracted with DCM (four times). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated to give *N*-trityloxy-malonamic acid as a white powder (90%). Purity 98%. ^{1}H NMR (DMSO-d_6) δ ppm: 2.84 (s, 2H), 7.32 (s, 15H). tr_{LCMS} 5.68 min. MS $[M - H]^-$ m/z 360. Acid (360 mg, 1 mmol) was dissolved in DMF (10 mL), and DIEA (346 μL, 2 mmol), EDCI (210 mg, 1.1 mmol), and HOBt (168 mg, 1.1 mmol) were added. The reaction mixture was stirred at room temperature for 5 min, and 4-fluorobenzylamine (115 μL, 1 mmol) was added. The reaction mixture was stirred at room temperature overnight and evaporated. The crude product was dissolved in DCM, washed three times with 5% aq $NaHCO_3$ and once with aq NaCl, dried over $MgSO_4$, filtered, and evaporated. The residue was washed with petroleum ether to give *N*-(4-Fluoro-benzyl)-*N*′-trityloxy-malonamide as a white powder (85%). Purity 95%. ^{1}H NMR (DMSO-d_6) δ ppm: 2.72 (s, 2H), 4.15 (d, J = 6.0 Hz, 2H), 7.07−7.31 (m, 19H), 8.68 (br s, 1H, NHCO), 10.43 (br s, 1H, CONHO). tr_{LCMS} 6.85 min. MS $[M - H]^-$ m/z 467. The protected hydroxamic acid (190 mg, 0.4 mmol) was dissolved in TFA 2%/DCM (0.03 M), and triisopropylsilane was added dropwise until the yellow color disappeared. The reaction mixture was stirred 5 min at room temperature, solvents were removed under reduced pressure,

and the residue was washed with petroleum ether to give (**7**) as a beige powder (90%). Purity 97%. ^{1}H NMR (DMSO-d_6) δ 2.95 (s, 2H), 4.26 (d, J = 5.4 Hz, 2H), 7.10−7.16 (m, 2H), 7.29−7.33 (m, 2H), 8.51 (br s, NHCO), 8.93 (br s, OH), 10.56 (s, CONHO). ^{13}C NMR (DMSO-d_6) δ ppm: 41.3, 41.9, 115.5 (d, J_{CF} = 21.7 Hz), 129.5 (d, J_{CF} = 7.8 Hz), 135.9, 138.1, 161.6 (d, J_{CF} = 239.2 Hz), 164.2, 166.9. tr_{LCMS} 2.81 min. MS $[M + H]^+$ m/z 227.

***N*-(4-Fluoro-benzyl)-*N'*-hydroxy-2-methyl-malonamide (8).** 2-Methyl-malonic acid diethyl ester (871 mg, 5 mmol) was dissolved in EtOH (20 mL), and KOH (280 mg, 5 mmol) was added. The reaction mixture was stirred at room temperature for 4 h and evaporated. The residue was dissolved in aq 5% $NaHCO_3$ solution and washed with DCM (five times). The aqueous layer was acidified (pH = 1) and extracted with DCM (4 times). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated to give 2-methyl-malonic acid monoethyl ester as a white powder (71%). Purity 98%. ^{1}H NMR ($CDCl_3$) δ ppm: 1.29 (t, J = 7.2 Hz, 3H), 1.46 (d, J = 7.5 Hz, 3H), 3.47 (q, J = 7.5 Hz, 1H), 4.22 (q, J = 7.2 Hz, 2H), 8.88 (br s, COOH). Acid (518 mg, 3.5 mmol) was dissolved in DMF (10 mL), and DIEA (2.12 mL, 12.2 mmol), EDCI (805 mg, 4.2 mmol), and HOBt (643 mg, 4.2 mmol) were added. The reaction mixture was stirred at room temperature for 5 min, and 4-fluorobenzylamine (402 μL, 3.5 mmol) was added. The reaction mixture was stirred at room temperature overnight and evaporated. The crude product was dissolved in DCM, washed three times with aq $NaHCO_3$ 5% and once with aq NaCl, dried over $MgSO_4$, filtered, and evaporated. The residue was washed with petroleum ether to give *N*-(4-fluoro-benzyl)-2-methyl-malonamic acid ethyl ester as a white powder (75%). Purity 95%. ^{1}H NMR (CD_2Cl_2) δ ppm: 1.27 (t, J = 7.2 Hz, 3H), 1.43 (d, J = 7.2 Hz, 3H), 3.33 (q, J = 7.2 Hz, 1H), 4.19 (q, J = 7.2 Hz, 2H), 4.38 (dd, J = 6.0 Hz, J = 15.0 Hz, 1H), 4.47 (dd, J = 6.0 Hz, 15.0 Hz, 1H), 6.73 (br s, NH), 7.02−7.10 (m, 2H), 7.25−7.31 (m, 2H). tr_{LCMS} 4.52 min. MS $[M + Na]^+$ m/z 276. Ester (659 mg, 2.6 mmol) was dissolved in EtOH (10 mL), and KOH (440 mg, 7.8 mmol) was added. The reaction mixture was stirred at room temperature overnight and evaporated. The residue was dissolved in H_2O and washed with DCM (three times). The aqueous layer was acidified (pH = 1) and extracted with DCM (four times). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated to give *N*-(4-Fluoro-benzyl)-2-methyl-malonamic acid as a white powder (45%). Purity 99%. ^{1}H NMR (DMSO-d_6) δ ppm: 1.19 (d, J = 7.2 Hz, 3H), 3.32 (q, J = 7.2 Hz, 1H), 4.22 (dd, J = 6.0 Hz, 15.3 Hz, 1H), 4.30 (dd, J = 6.0 Hz, 15.3 Hz, 1H), 7.10−7.18 (m, 2H), 7.27−7.31 (m, 2H), 8.58 (t, J = 6.0 Hz, NH), 12.49 (br s, COOH). tr_{LCMS} 3.47 min. MS $[M - H]^-$ m/z 224. The previous carboxylic acid (115 mg, 0.5 mmol) was dissolved in DMF (5 mL), and DIEA (260 μL, 1.5 mmol), EDCI (108 mg, 0.55 mmol), and HOBt (86 mg, 0.55 mmol) were added. The reaction mixture was stirred at room temperature for 5 min, and *O*-tritylhydroxylamine (103 mg, 0.38 mmol) was added. The reaction mixture was stirred at room temperature overnight and evaporated. The crude product was dissolved in ethyl acetate, washed three times with aq 1 N NaOH solution and once with aq NaCl, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by TLC (DCM/MeOH 97/3) and precipitated in petroleum ether to give *N*-(4-fluoro-benzyl)-2-methyl-*N'*-trityloxy-malonamide as a white powder (19%). Purity 99%. tr_{LCMS} 7.05 min. MS $[M - H]^-$ m/z 481. The protected hydroxamic acid (34 mg; 0.07 mmol) was dissolved in TFA 2%/DCM (0.03 M), and triisopropylsilane was added drop by drop until the yellow color disappeared. The reaction mixture was stirred 5 min at room temperature, solvents were removed under reduced pressure, and the residue was washed with petroleum ether to give (**8**) as a white powder (89%). Purity 97%. ^{1}H NMR (CD_3OD) δ 1.41 (d, J = 7.2 Hz, 3H), 3.17 (q, J = 7.2 Hz, 1H), 4.37 (s, 2H), 7.02−7.07 (m, 2H), 7.29−7.34 (m, 2H). ^{13}C NMR (CD_3OD) δ ppm: 14.2, 42.0, 45.0, 114.7 (d, J_{CF} = 22.0 Hz), 128.9 (d, J_{CF} = 8.2 Hz), 134.4, 162.1 (d, J_{CF} = 244 Hz), 169.1, 171.1. tr_{LCMS} 2.98 min. MS $[M + H]^+$ m/z 241.

***N*-(4-Fluoro-benzyl)-*N'*-hydroxy-2,2-dimethyl-malonamide (9).** 2,2-Dimethylmalonic acid diethyl ester (950 μL, 5 mmol) was dissolved in EtOH (20 mL), and KOH (280 mg, 5 mmol) was added. The solution was stirred at room temperature for 4 h and evaporated. The residue was dissolved in a 5% $NaHCO_3$ solution and washed with DCM. The aqueous layer was acidified (pH = 1) and extracted three times with DCM. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated to give 2,2-dimethylmalonic acid diethyl ester as a colorless oil (79%). ^{1}H NMR ($CDCl_3$) δ 1.27 (t, J = 7.2 Hz, 3H), 1.46 (s, 6H), 4.20 (q, J = 7.2 Hz, 2H). 2,2-Dimethylmalonic acid diethyl ester (575 mg, 3.5 mmol) was dissolved in DMF (10 mL) and DIEA (2.12 mL, 12.2 mmol). EDCI (805 mg, 4.2 mmol) and HOBt (643 mg, 4.2 mmol) were added, and the reaction mixture was stirred at room temperature for 5 min. 4-Fluorobenzylamine (402 μL, 3.5 mmol) was added, and the solution was stirred overnight and evaporated. The residue was dissolved in DCM and washed three times with aq $NaHCO_3$ 5% and three times with 1N HCl solution and once with brine, dried over $MgSO_4$, filtered, and evaporated to give *N*-(4-fluoro-benzyl)-2,2-dimethyl-malonamic acid ethyl ester as a white powder (85%). Purity 95%. ^{1}H NMR (CD_2Cl_2) δ: 1.26 (t, J = 7.2 Hz, 3H), 1.47 (s, 6H), 4.18 (q, J = 7.2 Hz, 2H), 4.42 (d, J = 5.7 Hz, 2H), 6.67 (br s, NH), 7.01−7.09 (m, 2H), 7.24−7.30 (m, 2H). tr_{LCMS} 5.01 min. MS $[M + H]^+$ m/z 268. Ester (535 mg, 2 mmol) was added to a solution of KOH (337 mg, 6 mmol) in EtOH (7 mL). The solution was stirred at room temperature overnight and evaporated. The residue was dissolved in H_2O and washed with DCM. The aqueous layer was acidified and extracted three times with DCM. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated to give *N*-(4-fluoro-benzyl)-2,2-dimethyl-malonamic acid as a white powder (80%). Purity 99%. ^{1}H NMR (DMSO-d_6) δ 1.31 (s, 6H), 4.24 (d, J = 6 Hz, 2H), 7.09−7.15 (m, 2H), 7.27−7.28 (m, 2H), 8.25 (t, J = 6 Hz, NH), 12.53 (br s, COOH). tr_{LCMS} 3.78 min. MS $[M - H]^-$ m/z 238. Acid (48 mg, 0.2 mmol) was dissolved in DCM (1.5 mL) with catalytic DMF (10 μL). The mixture was cooled at 0 °C (ice bath), and oxalyl chloride (20.6 μL, 0.24 mmol) was added dropwise. The reaction mixture was stirred 45 min at 0 °C and then evaporated under reduced pressure. The residue was dissolved in DCM (1.5 mL) and cooled at 0 °C. DIEA (123 μL, 0.48 mmol) was added, and then *O*-trityl-hydroxylamine (41 mg, 0.15 mmol) was added. The reaction mixture was stirred 2 h at room temperature. The residue was dissolved in ethyl acetate and washed with $NaHCO_3$ 5% and brine. The organic phase was washed dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by TLC (DCM/MeOH 95/5) to give *N*-(4-fluoro-benzyl)-2,2-dimethyl-*N'*-trityloxy-malonamide as a white powder (63%). Purity 99%. tr_{LCMS} 7.60 min. MS $[M - H]^-$ m/z 495. The protected hydroxamic acid (31 mg, 0.062 mmol) was dissolved in TFA 2%/DCM (0.03 M), and triisopropylsilane was added drop by drop until the yellow color disappeared. The reaction mixture was stirred 5 min at room temperature, solvents were removed under reduced pressure, and the residue was washed with petroleum ether and purified by TLC (DCM/MeOH/TEA 6/1.5/2.5) to give (**9**) as a beige powder (75%). Purity 99%. ^{1}H NMR (CD_3OD) cis/trans isomer mixture (55/45) δ: 1.31 (s, 1.35H), 1.41 (s, 1.35H), 1.44 (s, 3.3H), 4.12 (s, 1.1 H), 4.37 (s, 0.9H), 7.04 (t, J = 8.7 Hz, 0.9H), 7.20 (t, J = 8.7 Hz, 1.1H), 7.28−7.31 (m, 0.9H), 7.44−7.48 (m, 1.1H). tr_{LCMS} 3.18 min. MS $[M + H]^+$ m/z 255.

Cyclopropane-1,1-dicarboxylic Acid 4-Fluoro-benzylamide Hydroxyamide (10). Cyclopropane-1,1-dicarboxylic acid diethyl ester (887 μL, 5 mmol) was dissolved in EtOH (20 mL), and KOH (280 mg, 5 mmol) was added. The solution was stirred at room temperature for 4 h and evaporated. The residue was

dissolved in a 5% $NaHCO_3$ solution and washed with DCM. The aqueous layer was acidified (pH = 1) and extracted three times with DCM. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated to give cyclopropane-1, 1-dicarboxylic acid ethyl ester (79%). ^{1}H NMR ($CDCl_3$) δ 1.28 (t, J = 7.2 Hz, 3H), 1.73−1.78 (m, 2H), 1.82−1.86 (m, 2H), 4.25 (q, J = 7.2 Hz, 2H). The previous carboxylic acid (568 mg, 3.5 mmol) was dissolved in DMF (10 mL) and DIEA (2.12 mL, 12.2 mmol). EDCI (805 mg, 4.2 mmol) and HOBt (643 mg, 4.2 mmol) were added, and the reaction mixture was stirred at room temperature for 5 min, 4-fluorobenzylamine (402 μL, 3.5 mmol) was added, and the solution was stirred overnight and evaporated. The residue was dissolved in DCM and washed three times with aq $NaHCO_3$ 5% and three times with 1N HCl solution and once with brine, dried over $MgSO_4$, filtered, and evaporated to give 1-(4-fluoro-benzylcarbamoyl)-cyclopropanecarboxylic acid ethyl ester (59%). Purity 95%. ^{1}H NMR (CD_2Cl_2) δ 1.24 (t, J = 7.2 Hz, 3H), 1.57−1.69 (m, 4H), 4.13 (q, J = 7.2 Hz, 2H), 4.47 (d, J = 5.7 Hz, 2H), 7.02−7.10 (m, 2H), 7.29−7.35 (m, 2H), 9.10 (br s, NH). tr_{LCMS} 5.52 min. MS $[M + H]^+$ m/z 266. Ester (530 mg, 2 mmol) was added to a solution of KOH (337 mg, 6 mmol) in EtOH (7 mL). The solution was stirred at room temperature overnight and evaporated. The residue was dissolved in H_2O and washed with DCM. The aqueous layer was acidified and extracted three times with DCM. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated to give 1-(4-fluoro-benzylcarbamoyl)-cyclopropanecarboxylic acid as a white powder (87%). Purity 98%, ^{1}H NMR (DMSO-d_6) δ 1.34−1.42 (m, 4H), 4.33 (d, J = 5.7 Hz, 2H), 7.10−7.18 (m, 2H), 7.28−7.34 (m, 2H), 9.06 (t, J = 5.7 Hz, NH), 13.07 (br s, COOH). tr_{LCMS} 3.96 min. MS $[M - H]^-$ m/z 236. Acid (47 mg, 0.2 mmol) was dissolved in DCM (1.5 mL) with catalytic DMF (10 μL). The mixture was cooled at 0 °C (ice bath), and oxalyl chloride (20.6 μL, 0.24 mmol) was added dropwise. The reaction mixture was stirred 45 min at 0 °C and then evaporated under reduced pressure. The residue was dissolved in DCM (1.5 mL) and cooled at 0 °C. DIEA (123 μL, 0.48 mmol) was added, and then *O*-trityl-hydroxylamine (41 mg, 0.15 mmol) was added. The reaction mixture was stirred 2 h at room temperature. The residue was dissolved in ethyl acetate and washed with $NaHCO_3$ 5% and brine. The organic phase was washed, dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by TLC (DCM/MeOH 95/5) to give cyclopropane-1,1-dicarboxylic acid 4-fluoro-benzylamide trityloxy-amide as a yellow powder (49%). Purity 99%. tr_{LCMS} 7.52 min. MS $[M - H]^-$ m/z 493. The protected hydroxamic acid (32 mg, 0.065 mmol) was dissolved in TFA 2%/DCM (0.03 M), and triisopropylsilane was added dropwise until the yellow color disappeared. The reaction mixture was stirred 5 min at room temperature, solvents were removed under reduced pressure, and the residue was washed with petroleum ether and purified by TLC (DCM/MeOH/TEA 6/1.5/2.5) to give (**10**) as a beige powder (75%). Purity 99%. ^{1}H NMR (CD_3OD) cis/trans isomer mixture (65/35) δ 1.29−133 (m, 2H), 1.37−1.41 (m, 2H), 4.12 (s, 0.7 H), 4.39 (s, 1.3 H), 7.05 (t, J = 8.7 Hz, 1.3H), 7.20 (t, J = 8.7 Hz, 0.7H), 7.29−7.35 (m, 1.3H), 7.46−7.51 (m, 0.7H). ^{13}C NMR (CD_3OD) δ ppm: 14.1, 27.1, 42.2 (A form), 42.3 (B form), 114.7 (d, J_{CF} = 22.3 Hz) (A form), 115.6 (d, J_{CF} = 22.3 Hz) (B form), 128.9 (d, J_{CF} = 8.0 Hz) (A form), 130.9 (d, J_{CF} = 8.5 Hz) (B form), 134.6 (A form), 137.6 (B form), 162.0 (d, J_{CF} = 243 Hz) (A form), 163.2 (d, J_{CF} = 247 Hz) (B form), 169.0, 170.7. tr_{LCMS} 3.18 min. MS $[M + H]^+$ m/z 253.

2-[2-(4-Fluoro-phenyl)-acetylamino]-*N*-hydroxy-3-phenyl-propionamide (11). 2-Chlorotrityl *N*-Fmoc-hydroxylamine, polymer-bound, 100−200 mesh (1.504 g, 0.68 mmol), was treated with a piperidine/DMF 20/80 cocktail for 30 min to remove the Fmoc-protecting group. The resin was washed with DMF and DCM. *N*-Fmoc-phenylalanine (1.050 g, 2.71 mmol, 4 equiv) was activated with HATU (1.030 g, 2.71 mmol, 4 equiv) in 15 mL of DMF and DIEA (895 μL, 5.42 mmol, 8 equiv). The mixture was then added to the resin. The resin was shaken overnight at room temperature and then washed with DMF and DCM. The coupling was performed twice. To remove the Fmoc protecting group, the resin was treated with a piperidine/DMF 20/80 cocktail for 30 min. Half of the resin was used for the next step. The resin was washed with DMF. 4-Fluorophenylacetic acid (210 mg, 1.35 mmol, 4 equiv) was activated with HOBt (210 mg, 1.35 mmol, 4 equiv) and TBTU (435 mg, 1.35 mmol, 4 equiv) in 7 mL of DMF and DIEA (450 μL, 2.71 mmol, 8 equiv). The mixture was then added to the resin. The resin was shaken 3 h at room temperature then washed with DMF and DCM. The coupling was performed twice, and the resin was washed with DCM. Cleavage from the resin was accomplished by treatment with a mixture of TFA (100 μL), TIS (50 μL) in DCM (5 mL) for 2 min. The resin was filtered, and the cleavage was performed five times. The filtrate was neutralized with a piperidine/methanol/water 10/45/45 mixture to avoid the conversion of hydroxamic acid into carboxylic acid. The organic solvents were evaporated under reduced pressure, and the aqueous phase was extracted four times with ethyl acetate. The combined organic layers were washed with water and brine and then dried over $MgSO_4$ and evaporated. The residue was washed with petroleum ether to obtain (**11**) as a beige powder (81%). Purity 98%. ^{1}H NMR (DMSO-d_6) δ: 2.73−2.80 (m, 1H), 2.90−2.95 (m, 1H), 3.35 (s, 2H), 4.36−4.40 (m, 1H), 7.03−7.21 (m, 9H), 8.45 (d, J = 5.7 Hz, CONH), 8.90 (s, OH), 10.74 (s, CONHO). ^{13}C NMR (DMSO-d_6) δ ppm: 38.5, 41.5, 52.2, 115.2 (d, J_{CF} = 21.1 Hz), 126.7, 128.5, 129.6, 131.2 (d, J_{CF} = 7.6 Hz), 132.9, 138.1, 161.4 (d, J_{CF} = 238.2 Hz), 168.2, 170.1. $t_{R\ LCMS}$ 4.29 min. MS $[M - H]^-$ m/z 315.

***N*-Hydroxy-benzamide (12).** Benzoic acid (**12a**) (354 mg, 2.9 mmol) was dissolved in DCM (0.4M) with catalytic DMF. To this solution cooled to 0 °C (ice bath) was added dropwise oxalyl chloride (299 μL, 3.48 mmol). The mixture was stirred at room temperature for 1 h and evaporated under reduced pressure (temp max 25 °C). The residue was dissolved in DCM (0.4M). To this solution cooled to 0 °C (ice bath) was added dropwise DIEA (1.4 mL, 1.2 g, 7.8 mmol.). Then *O*-tritylhydroxylamine (878 mg, 3.19 mmol) was added and the mixture was stirred at room temperature for 4 h. Control of reaction was performed by TLC (DCM/MeOH 95/5, UV and H_2SO_4 visualization). The mixture was washed once with aq $NaHCO_3$ 5% and three times with water, and the combined organic layers were dried over $MgSO_4$ and evaporated. *O*-Trityl hydroxamate intermediate was dissolved in TFA 2%/DCM (0.03 M), and triisopropylsilane was added dropwise until the yellow color disappeared. Solvents were removed under reduced pressure, and the residue was washed with petroleum ether to give compound (**12**) (47%). White powder; purity 100%. ^{1}H NMR 300 MHz (DMSO-d_6) δ ppm: 7.45 (m, 3H), 7.74 (d, J = 9 Hz, 2H), 9.00 (s, 1H), 11.19 (s, 1H). ^{13}C NMR (MeOD) δ ppm: 166.8, 132.2, 131.4, 128.3, 126.7. mp: 129.6−131 °C. tr_{LCMS} 2.9 min. MS $[M + H]^+$ m/z 138.

***N*-Hydroxy-2-phenyl-acetamide (13).** Phenylacetic acid (**13a**) (500 mg, 3.67 mmol) was dissolved in DCM (42 mL) with DIEA (2.43 mL, 1.9 g, 14.69 mmol). EDCI (774 mg, 4.04 mmol) and HOBt (618 mg, 4.04 mmol) were added. The mixture was stirred at room temperature for 5 min, and the *O*-tritylhydroxylamine (1.01 g, 3.33 mmol) was added. The mixture was stirred at room temperature for 5 h. The reaction mixture was evaporated under reduced pressure, and the residue was dissolved in DCM and washed three times with aq $NaHCO_3$ solution (5%) and once with water and the organic layer was dried over $MgSO_4$ and evaporated. *O*-Trityl hydroxamate intermediate was dissolved in TFA 5%/DCM (0.03 M), and triisopropylsilane was added dropwise until the yellow color disappeared. Solvents were removed under reduced pressure, and the residue was washed with petroleum ether to give compound (**13**). Yield 30%. White powder, purity 100%. ^{1}H NMR 300 MHz (DMSO-d_6)

δ ppm: 3.27 (s, 2H), 726 (m, 5H), 8.75 (br s, 1H), 10.64 (s, 1H). ^{13}C NMR (MeOD) δ ppm: 169.4, 135.1, 128.6, 128.1, 126.6, 39.2. tr_{LCMS} 2.4 min. MS $[M + H]^+$ m/z 152.

***N*-Hydroxy-3-phenyl-propionamide (14).** 3-Phenyl-propionic acid (**14a**) (500 mg, 3.33 mmol) was dissolved in DCM (40 mL). EDCI (702 mg, 3.66 mmol), HOBt (561 mg, 3.66 mmol), and DIEA (2206 μL, 13.3 mmol) were added. The mixture was stirred at room temperature for 5 min, and *O*-tritylhydroxylamine (917 mg, 3.33 mmol) was added. The mixture was stirred at room temperature for 5 h. The solvent was evaporated under reduced pressure, and the residue was dissolved in DCM and washed three times with aq $NaHCO_3$ solution (5%) and once with water and the organic layer was dried over $MgSO_4$ and evaporated. *O*-Trityl hydroxamate intermediate was dissolved in TFA 5%/DCM (0.03 M) and triisopropylsilane was added dropwise until the yellow color disappeared. Solvents were removed under reduced pressure, and the residue was washed with petroleum ether to give compound (**14**) (10%). White powder, purity 98%. ^{1}H NMR 300 MHz (DMSO-d_6) δ ppm: 2.24 (t, J = 7.2 Hz, 2H), 2.79 (t, J = 7.0 Hz, 2H) 7.29−7.16 (m, 5H), 8.68 (s, 1H), 10.35 (s, 1H). ^{13}C NMR (MeOD) δ ppm: 171.9, 142.2, 129.5, 129.4, 127.2, 35.7, 32.6. tr_{LCMS} 3.1 min. MS $[M + H]^+$ m/z 166.

***N*-Hydroxy-4-phenyl-butyramide (15).** 4-Phenyl-butyric acid (**15a**) (1 g, 6.09 mmol) was dissolved in DCM (15 mL) and DMF (30 μL) was added. The reaction mixture was cooled to 0 °C (ice bath) and oxalyl chloride (627 μL, 7.3 mmol) was added dropwise. Reaction mixture was stirred at room temperature for 1 h. The solvent was evaporated under reduced pressure, the residue was dissolved in DCM (10 mL), and *O*-tritylhydroxylamine (1425 mg, 5.17 mmol) in solution in DCM (5 mL) with DIEA (3 mL, 18.27 mmol) was added dropwise. The mixture was stirred at room temperature for 3 h and washed three times with aq $NaHCO_3$ solution (5%) and once with water, and the organic layer was dried over $MgSO_4$ and evaporated. The residue was precipitated in diethyl ether and filtrated. *O*-Trityl hydroxamate intermediate was dissolved in TFA 5%/DCM (0.03 M), and triisopropylsilane was added dropwise until the yellow color disappeared. Solvents were removed under reduced pressure, and the residue was washed with diethyl ether/pentane 50/50 and 25/75 mixture to give compound (**15**) (68%). White powder, purity 98%. ^{1}H NMR 300 MHz (DMSO-d_6) δ ppm: 1.78 (m, 2H), 1.96 (t, J = 9.0 Hz, 2H), 2.54 (t, J = 9.0 Hz, 2H), 7.33−7.10 (m, 5H), 8.66 (s, 1H), 10.35 (s, 1H). ^{13}C NMR (MeOD) δ ppm: 172.7, 142.8, 129.4, 129.3, 126.9, 36.2, 33.2, 28.6. tr_{LCMS} 4.5 min. MS $[M + H]^+$ m/z 180.

(*E*)-*N*-Hydroxy-3-phenyl-acrylamide (16). (*E*)-3-Phenyl-acrylic acid (**16a**) (300 mg, 2.02 mmol) was dissolved in DMF (20 mL). EDCI (465 mg, 2.42 mmol), HOBt (465 mg, 3.03 mmol), and NMM (890 μL, 13.3 mmol) were added. The mixture was stirred at room temperature for 5 min, and *O*-tritylhydroxylamine (669 mg, 2.42 mmol) was added. The mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure, the residue was dissolved in DCM and washed three times with aq $NaHCO_3$ (5%) and once with water and the organic layer was dried over $MgSO_4$ and evaporated. *O*-Trityl hydroxamate intermediate was dissolved in TFA 5%/DCM (19 mL) and triisopropylsilane was added dropwise until the yellow color disappeared. Solvents were removed under reduced pressure, and the residue was washed with petroleum ether to give compound (**16**) (87%). White powder, purity 98%. ^{1}H NMR 300 MHz (DMSO-d_6) δ ppm: 6.45 (d, J = 15.6 Hz, 1H), 7.38−7.56 (m, 5H + 1H), 9.03 (s, 1H), 10.09 (s, 1H). ^{13}C NMR (DMSO-d_6) δ ppm: 164.9, 140.3, 134.7, 129.5, 128.6, 127.4, 116.9. tr_{LCMS} 3.30 min. MS $[M + H]^+$ m/z 164.

***N*-Hydroxy-2-phenoxy-acetamide (17).** Phenoxyacetic acid (**17a**) (300 mg, 1.97 mmol) was dissolved in DMF (20 mL). *O*-Tritylhydroxylamine (649.8 mg, 2.36 mmol), EDCI (452.43 mg, 2.36 mmol), HOBt (451.76 mg, 2.95 mmol), and NMM (866 μL, 797.0 mg, 7.88 mmol) were added. The mixture was stirred at room temperature for 16 h.The reaction mixture was evaporated under reduced pressure, the residue was dissolved in DCM and washed three times with aq $NaHCO_3$ solution (5%) and once with water, and the organic layer was dried over $MgSO_4$ and evaporated. *O*-Trityl hydroxamate intermediate was dissolved in TFA 5%/DCM (0.03 M), and triisopropylsilane was added dropwise until the yellow color disappeared. Solvents were removed under reduced pressure, and the residue was washed with petroleum ether to give compound (**17**) (7%). White powder, purity 98%. ^{1}H NMR 300 MHz (DMSO-d_6) δ ppm: 4,62 (s, 2H), 6.94 (d, J = 8,1 Hz, 2H), 7.05 (t, J = 7.2 Hz, 1H), 7.34 (t, J = 7.8 Hz, 2H), 9.24 (br s, 1H). tr_{LCMS} 2.85 min. MS $[M + H]^+$ m/z 168.

***N*-Hydroxy-3-phenoxy-propionamide (18).** 3-Phenoxy-propionic acid (**18a**) (300 mg, 2.80 mmol) was dissolved in DMF (20 mL). EDCI (415 mg, 2.16 mmol), HOBt (415 mg, 2.70 mmol), and NMM (793 μL, 7.2 mmol) were added. The mixture was stirred at room temperature for 5 min, and O-tritylhydroxylamine (497 mg, 2.16 mmol) was added. The mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure and the residue was dissolved in DCM and washed three times with aq $NaHCO_3$ (5%) and once with water and the organic layer was dried over $MgSO_4$ and evaporated. O-Trityl hydroxamate intermediate was dissolved in TFA 5%/DCM (14 mL), and triisopropylsilane was added dropwise until the yellow color disappeared. Solvents are removed under reduced pressure, and the residue was washed with diethyl ether/pentane and petroleum ether to give compound (**18**) (37%). White powder, purity 98%. ^{1}H NMR 300 MHz (MeOD) δ ppm: 2.53 (t, J = 6.0 Hz, 1H), 4.22 (t, J = 6.0 Hz, 1H), 6.91 (m, 3H) 7.24 (m, 2H). tr_{LCMS} 3.18 min. MS $[M + H]^+$ m/z 182.

4-Cyclopropylethynyl-*N*-hydroxy-benzamide (19). Ethyl-4-iodobenzoate (1.2 mL, 7.64 mmol), triethylamine (10.2 mL, 72.4 mmol), CuI (276 mg, 1.45 mmol), $PdCl_2(PPh_3)$, and ethynylcyclopropane (622 mg, 9.41 mmol) were dissolved in DMF (28 mL). The mixture was stirred at 70 °C overnight. The solvent was evaporated under reduced pressure, and the residue was dissolved in DCM and filtrated on celite. The DCM solution was washed with brine, and the organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography (cyclohexane/ethyl acetate) to give ethyl-4-cyclopropylethynyl-benzoate (yellow oil, 90%). Purity 98%. ^{1}H NMR 300 MHz (DMSO) δ ppm: 0.85 (m, 2H), 0.92 (m, 2H), 1.31 (t, J = 6.9 Hz, 3H) 1.58 (m, 1H), 4.3 (q, J = 7.2 Hz, 2H), 7.74 (d, J = 8.7 Hz, 2H), 7.89 (d, J = 8.7 Hz, 2H). tr_{LCMS} 7.5 min. MS $[M + H]^+$ m/z 215. Ester (1.3 g, 6.07 mmol) and NaOH (486 mg, 12.15 mmol) were dissolved in EtOH (25 mL) and H_2O (500 μL). The mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure. The residue was dissolved in DCM and washed with HCl (1N) solution. The organic layer was dried over $MgSO_4$ and evaporated to give 4-cyclopropylethynylbenzoic acid (**19a**) (white solid, 98%). Purity 98%. ^{1}H NMR 300 MHz (DMSO) δ ppm: 0.76 (m, 2H), 0.91 (m, 2H), 1.57 (m, 1H), 7.44 (d, J = 8.4 Hz, 2H), 7.87 (d, J = 8.4 Hz, 2H). tr_{LCMS} 5.54 min. MS (ESI+): m/z = 187 $(M + H)^+$. mp = 220−222 °C. 4-Cyclopropylethynylbenzoic acid (1.0 g, 5.38 mmol), was dissolved in DCM (20 mL) with catalytic DMF and oxalyl chloride (577 mL, 6.72 mmol) was added dropwise at 0 °C (ice bath). The reaction mixture was stirred at 0 °C for 45 min and evaporated under reduced pressure. The residue was dissolved in DCM (20 mL) with catalytic DMF and DIEA (2.67 mL, 16.14 mmol) and *O*-tritylhydroxylamine (1.259 g, 4.573 mmol) were added. The reaction mixture was stirred at room temperature for 5 h, and the solvent was removed under reduced pressure. The residue was dissolved in DCM and washed three times with aq $NaHCO_3$ solution (5%) and once with water and the organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography (cyclohexane/ethyl acetate) to give 4-cyclopropylethynyl-*N*-trityloxy-benzamide (white solid, 46%).

Purity 98%. ^{1}H NMR 300 MHz (DMSO) δ ppm: 0.72 (m, 2H), 0.88 (m, 2H), 1.53 (m, 1H), 7.34 (m, 19H), 10.94 (s, 1H). tr_{LCMS} 8.31 min. MS $[M + H]^+$ m/z 442. mp = 155−156 °C. *O*-Trityl hydroxamate intermediate (500 mg, 1.12 mmol) was dissolved in TFA 2%/DCM (20 mL), and triisopropylsilane was added dropwise until the yellow color disappeared. Solvents were removed under reduced pressure, and the residue was washed with petroleum ether to give compound (**19**) (93%). White powder, purity 98%. ^{1}H NMR 300 MHz (DMSO-d_6) δ ppm: 0.75 (m, 2H), 0.92 (m, 2H), 1.56 (m, 1H), 7.41 (d, J = 8.5 Hz, 2H), 7.69 (d, J = 8.5 Hz, 2H), 11.24 (s, 1H). ^{13}C NMR (MeOD) δ ppm: 167.5, 132.6, 132.2, 128.9, 128.1, 97.2, 75.8, 9.1, 0.8. tr_{LCMS} 4.30 min. MS $[M + H]^+$ m/z 200. mp = 171−172 °C.

***N*-Hydroxy-2-[isobutyl-(4-methoxy-benzenesulfonyl)-amino]-acetamide (20).** To a solution of isobutylamine (3.5 mmol) in DMF (7 mL, 0.5 M) was added DIEA (608 μL, 3.5 mmol) and 4-methoxybenzenesulfonylchloride (3.5 mmol) in solution in THF (7 mL, 0.5 M). The reaction mixture was stirred at room temperature for 1 h, and the solvents were evaporated under reduced pressure. The residue was dissolved in DCM and washed with HCl 1N solution and H_2O. The organic layer was dried over $MgSO_4$ and evaporated to give intermediate (**20a**) (88%). Purity 95%. ^{1}H NMR 300 MHz ($CDCl_3$) δ ppm 0.85 (d, J = 6.7 Hz, 6H), 1.65−1.74 (m, 1H), 2.73 (t, J = 6.7 Hz, 2H), 3.86 (s, 3H), 6.94−6.99 (m, 2H), 7.76−7.78 (m, 2H). To a suspension of NaH (3 mmol) in THF (8 mL) was added (**20a**) sulfonamide (3 mmol) in THF (8 mL). The reaction mixture was stirred at room temperature for 30 min and ethylbromoacetate (3.3 mmol) was added. The reaction mixture was stirred at room temperature overnight and stopped with H_2O. THF was evaporated under reduced pressure, and the reaction mixture was extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and evaporated. The residue was purified by TLC (cyclohexane/ethyl acetate 80/20) to give intermediate (**20b**) (72%). Purity 98%. ^{1}H NMR 300 MHz ($CDCl_3$) δ ppm: 0.89 (d, J = 6.7 Hz, 6H), 1.20 (t, J = 7.1 Hz, 3H), 1.83−1.88 (m, 1H), 3.02 (d, J = 7.5 Hz, 2H), 3.86 (s, 3H), 4.01−4.13 (m, 4H), 6.94−6.99 (m, 2H), 7.75−7.81 (m, 2H). To intermediate (**20b**) (3 mmol) in MeOH (10 mL) was added hydroxylamine hydrochloride (229 mg, 3.3 mmol) and sodium methylate (12.6 mL, 6.3 mmol). The reaction mixture was stirred at room temperature overnight and solvents were evaporated. HCl solution (pH = 3) was added, and the reaction mixture was extracted with ethyl acetate (five times). The combined organic layers were dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography (DCM/MeOH) to give (**20**) as a solid (53%). Purity 98%. ^{1}H NMR 300 MHz ($CDCl_3$) δ ppm: 0.91 (d, J = 6.7 Hz, 6H), 1.78−1.84 (m, 1H), 2.94 (d, J = 7.3 Hz, 2H), 3.69 (s, 2H), 3.89 (s, 3H), 7.01 (d, J = 8.7 Hz, 2H), 7.75 (d, J = 8.8 Hz, 2H), 9.4 (s, 1H). ^{13}C NMR (DMSO-d_6) δ ppm: 164.9, 162.8, 131.5, 129.9, 114.6, 56.3, 56.1, 48.3, 26.7, 20.5. mp = 125−126 °C.

2-(Benzenesulfonyl-isobutyl-amino)-*N*-hydroxy-acetamide (21). To a solution of isobutylamine (3.5 mmol) in DMF (7 mL, 0.5 M) was added DIEA (608 μL, 3.5 mmol) and benzenesulfonylchloride (3.5 mmol) in solution in THF (7 mL, 0.5 M). The reaction mixture was stirred at room temperature for 1 h, and the solvents were evaporated under reduced pressure. The residue was dissolved in DCM and washed with HCl 1N solution and H_2O. The organic layer was dried over $MgSO_4$ and evaporated to give (**21a**) (80%). Purity 95%. ^{1}H NMR 300 MHz ($CDCl_3$) δ ppm 0.86 (d, J = 6.7 Hz, 6H), 1.67−1.76 (m, 1H), 2.75 (d, J = 6.7 Hz, 2H), 7.48−7.60 (m, 3H), 7.87−7.90 (m, 2H). To a suspension of NaH (3 mmol) in THF (8 mL) was added (**21a**) sulfonamide (3 mmol) in THF (8 mL). The reaction mixture was stirred at room temperature for 30 min and ethylbromoacetate (3.3 mmol) was added. The reaction mixture was stirred at room temperature overnight and stopped with H_2O. THF was evaporated under reduced pressure and the reaction mixture was extracted with ethyl acetate. The combined organic layers was dried over $MgSO_4$ and evaporated. The residue was purified by TLC (cyclohexane/ethyl acetate 80/20) to give intermediate (**21b**) (25%). Purity 95%. ^{1}H NMR 300 MHz ($CDCl_3$) δ ppm: 0.90 (d, J = 6.7 Hz, 6H), 1.16 (t, J = 7.1 Hz, 3H), 1.81−1.86 (m, 1H), 3.06 (d, J = 6.8 Hz, 2H), 4.00−4.13 (m, 4H), 7.46−7.60 (m, 3H), 7.81−7.85 (m, 2H). To intermediate (**21b**) (3 mmol) in MeOH (10 mL) were added hydroxylamine hydrochloride (229 mg, 3.3 mmol) and sodium methylate (12.6 mL, 6.3 mmol). The reaction mixture was stirred at room temperature overnight and solvents evaporated. HCl solution (pH = 3) was added, and the reaction mixture was extracted with ethyl acetate (5 times). The combined organic layers were dried over $MgSO_4$ and evaporated. The residue was purified by TLC (DCM/MeOH 95/5) to give (**21**) as a solid (29%). Purity 95%. ^{1}H NMR 300 MHz ($CDCl_3$) δ ppm: 0.92 (d, J = 6.7 Hz, 6H), 1.76−1.88 (m, 1H), 2.98 (d, J = 7.2 Hz, 2H), 3.72 (s, 2H), 7.54−7.67 (m, 3H), 7.81 (d, J = 8.7 Hz, 2H). ^{13}C NMR (DMSO-d_6) δ ppm: 164.7, 139.7, 133.2, 129.6, 127.7, 56.3, 48.1, 26.4, 20.3. mp = 122−123 °C.

((*R*)-1-Hydroxycarbamoyl-2-phenyl-ethyl)-carbamic Acid *tert*-Butyl Ester (22). Boc-(D)-phenylalanine (500 mg, 1.88 mmol) was dissolved in DMF (20 mL). EDCI (433 mg, 2.26 mmol), HOBt (541 mg, 2.82 mmol), and NMM (828 μL, 7.5 mmol) were added. The mixture was stirred at room temperature for 5 min, and *O*-tritylhydroxylamine (519 mg, 1.88 mmol) was added. The mixture was stirred at room temperature for 72 h. The solvent was evaporated under reduced pressure and the residue was dissolved in DCM and washed three times with aq $NaHCO_3$ solution (5%) and once with water and the organic layer was dried over $MgSO_4$ and evaporated. *O*-Trityl hydroxamate intermediate was dissolved in TFA 5%/DCM (2 mL) and triisopropylsilane (19 μL) was added. Solvents were removed under reduced pressure, and the residue was washed with diethyl ether/pentane and petroleum ether to give compound (**22**) (20%). White powder, purity 98%. ^{1}H NMR 300 MHz (MeOD) δ ppm: 1.36 (s, 9H), 2.84 (dd, J = 9.0 and 15.0 Hz, 1H), 3.04 (dd, J = 6.0 and 12.0 Hz, 1H), 4.18 (t, J = 6.0 Hz, 1H), 7.21−7.27 (m, 5H). ^{13}C NMR (MeOD) δ ppm: 169.5, 156.0, 136.9, 128.9, 128.0, 126.3, 79.2, 53.8, 38.0, 27.2. tr_{LCMS} 4.36 min. MS $[M - H]^-$ m/z 279.

Plasma Stabilities. Lithium-heparin plasma from Sprague−Dawley rats (mixed gender pool) were from Sera Laboratories International Ltd. Human plasma was a mixed gender pool from donors. PMSF (phenylmethylsulfonyl fluoride) and enalapril maleate were purchased from Sigma-Aldrich Inc. Then 40 μL of a 5 mM solution in DMSO of the sample were added to 1.960 mL of plasma, previously incubated or not with PMSF at the desired concentration, to obtain a 100 μM final solution. The mixture was gently stirred 96 h at 37 °C. Aliquots of 200 μL were taken at various times (from 0 to 96 h) and diluted with 200 μL of acetonitrile. Then 10 μL of the 2 mM solution in methanol of the internal standard were added. The mixture was centrifuged and supernatant was extracted three times with 2 mL of AcOEt. The combined organic layers were evaporated and diluted with 200 μL of methanol.

For experiments with PMSF, incubations were performed in duplicate in microtiterplates from Matrix with 80 μL of rat plasma (Sprague−Dawley pooled mixed gender from Sera Laboratories International Ltd.) for each time point. Plasma was preincubated at 37 °C 5 min and then incubated 30 min with PMSF at a final concentration of 2 mM when needed, before compound addition to a final concentration of 10 μM 1% DMSO. The reaction was terminated at 0, 1, 2, 4, 8, 24, and 48 h by the addition of acetonitrile containing the internal standard (IS). After centrifugation, supernatant was analyzed.

Analysis and quantification used a LC-MS/MS triple-quadrupole system (Varian 1200ws) under MRM or SIM detection using adequate parameters (see Supporting Information for mode of ionization, declustering potential, collision-activated dissociation, and collision energy for each compound). A calibration curve

for each compound allowed the linear relationship between concentration and signal intensity (given as peak area ratio analyte/IS). Acquisition and analysis of data were performed with MS Workstation software (version 6.3.0 or higher). The degradation half-life ($t_{1/2}$) values were calculated using the following equation: $t_{1/2} = 0.693/k$ where k is the first-order degradation rate constant. The degradation rate constant (k) was estimated by one-phase exponential decay nonlinear regression analysis of the degradation time course data using Xlfit software (version 2.1.2 or higher).

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Supporting Information Available: Mass spectrometry parameters for each compound, example of plasma stability curve of **1** and enalapril, with or without PMSF, compound **9**, prodrug **5**, structures and half-lives of hydroxamates found in the literature (iv or po conditions), and experimental conditions for compounds **1**−**3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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