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Bioorganic & Medicinal Chemistry Letters 13 (2003) 4223–4228

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

α-Substituted Hydroxamic Acids as Novel Bacterial Deformylase Inhibitor-Based Antibacterial Agents

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Received 29 April 2003; accepted 29 July 2003

Abstract—We report the synthesis and biological activity of analogues of **VRC3375** (*N*-hydroxy-3-*R*-butyl-3-[(2-*S*-(*tert*-butoxycarbonyl)-pyrrolidin-1-ylcarbonyl]propionamide), an orally active peptide deformylase inhibitor. This study explores the structure–activity relationship of various chelator groups, alpha substituents, P_2' and P_3' substituents in order to achieve optimal antibacterial activity with minimal toxicity liability.

The increase in bacterial resistance has resulted in a resurgent interest in the discovery and development of new classes of antibacterial agents.[1–4] Peptide deformylase (PDF), which catalyzes the removal of the N-terminal formyl group from newly synthesized polypeptides and is essential to bacterial growth but not required by mammalian cells, is an attractive target for the design of new antibiotics. Since deformylase inhibitors have yet to be used clinically as antibacterial drugs, compounds targeting this enzyme should avoid cross-resistance with antibacterial agents.[5]

PDF is a ferrous-containing metallohydrolase,[6,7] but a nickel-containing[8] surrogate is routinely used in the laboratory for testing inhibitors due to its increased stability. Enzymes from several bacterial species have been cloned[9] and their three-dimensional structures[10–14] and co-crystal structures[15–19] with bound inhibitors have been determined. As a metallo-enzyme, PDF lends itself to the well precedented mechanism-based rational drug design approach.[20] Using structural and mechanistic information, together with high throughput screening, several types of potent PDF inhibitors have been identified.[21–23]

Most PDF inhibitors identified to date share a common structural feature of a 'chelator + peptidomimetic' scaffold. Although compounds with many different chelators can inhibit the enzyme, only compounds containing hydroxamic acid or *N*-formyl hydroxylamine exhibit appreciable antibacterial activity.[22]

VRC3375 (compound **A**),[24] a potent PDF inhibitor with moderate oral antibacterial activity, was identified from combinatorial and medicinal chemistry efforts. Compound **A** contains the hydroxamate metal chelator pharmacophore, together with an alkyl succinate peptidomimetic scaffold. We report here the structure–activity relationships at different positions of this initial lead compound.

In this study, analogues of 2-*R*-butyl succinic acid-containing PDF inhibitors were prepared and the corresponding SAR was explored at the metal chelating site, α-substitution to hydroxamate, and the P_2'/P_3'-position (see Fig. 1). The various syntheses employed for the preparation of inhibitors are outlined in Schemes 1–8.

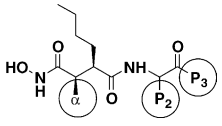

Figure 1. General structure of succinate hydroxamate analogues.

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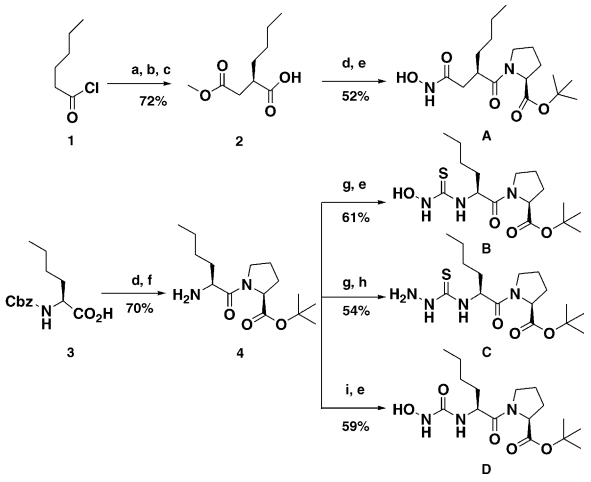
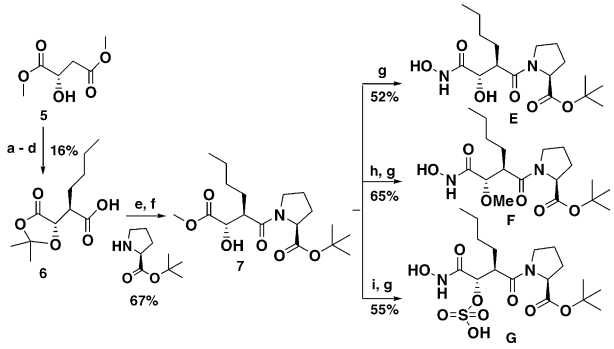
doi:10.1016/j.bmcl.2003.07.020

The synthesis of succinate hydroxamate **A** began with construction of the chiral intermediate **2**, namely mono-4-methyl-2-*R*-butylsuccinic acid.[25] Reaction of 4-*S*-benzyloxazolidinone (**1**) with hexanoyl chloride (Scheme 1) in the presence of BuLi provided the corresponding *N*-hexanoyl derivative. Alkylation with methyl bromoacetate followed by the hydrolysis under $LiOH–H_2O_2$ conditions provided the key intermediate **2**. Coupling of **2** with Pro-*O*-*t*-butyl ester in the presence of HATU followed by treatment with hydroxylamine gave the desired compound **A** after HPLC purification.

N-Cbz protected 2-amino-*S*-hexanoic acid **3** was coupled with Pro-*O*-*tert*.butyl followed by Cbz deprotection to provide amine intermediate **4**, which was further transformed to different metal chelating functionalities.



Scheme 1. VRC3375 analogues with different metal chelators. Reagents and conditions: (a) 4-(*S*)-benzyloxazolidinone, *n*-BuLi in hexane, −78 to 25 °C, 16 h; (b) NaHMDS, methyl bromoacetate, −78 to 25 °C, 16 h; (c) LiOH, 30% H_2O_2, THF, H_2O, 0 °C, 3 h; (d) Pro-*O*-*tert*-Bu, HATU, DIEA, DMF, 25 °C, 16 h; (e) dioxane, 50% aq NH_2OH, 5 °C, 16 h; (f) 10% Pd/C, H_2, ethanol, 16 h; (g) thiophosgene, $CaCO_3$, CH_2Cl_2, 0–25 °C, 2 h; (h) $NH_2–NH_2$, methanol, 0 °C, 1 h; (i) phosgene, $CaCO_3$, CH_2Cl_2, 0–25 °C, 2 h.



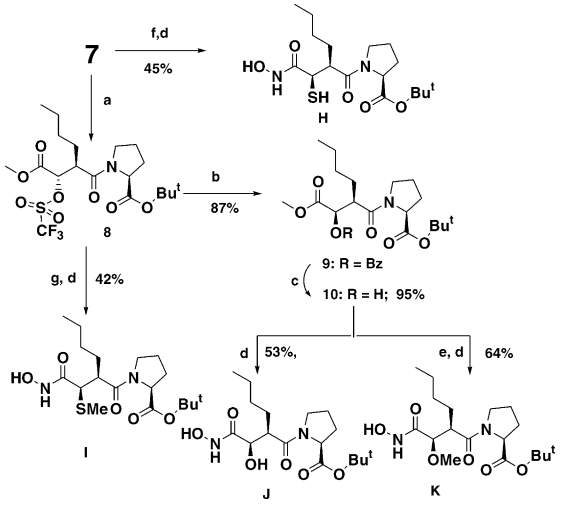
Scheme 2. Synthesis of α-(*S*)-substituted succinate hydroxamates. Reagents and conditions: (a) LDA, crotyl bromide, THF, −78 to 25 °C, 16 h; (b) 10% Pd/C, H_2, ethyl acetate, 16 h; (c) NaOH, methanol, water, 20 h; (d) 2,2-dimethoxypropane, *p*-TSA, 16 h; (e) PyBOP, HOBT, DIEA, CH_2Cl_2, 16 h; (f) methanol, 0.5 M sodium methoxide, 0 °C, 1 h; (g) dioxane, 50% aq NH_2OH, 5 °C, 16 h; (h) NaH, methyl iodide, DMF, 3 h; (i) sulphur trioxide–pyridine complex, DMF, 0–25 °C, 16 h.

Reaction of **4** with thiophosgene in the presence of $CaCO_3$ followed by treatment with hydroxylamine gave *N*-hydroxythio-urea **B**. Treatment of **4** with thiophosgene followed by reaction with hydrazine provided hydrazine thiourea **C**. Similarly, **4** was reacted with phosgene followed by reaction with hydroxylamine to yield *N*-hydroxyurea **D**.

Succinate hydroxamate analogues, with the common structure as in Figure 1, were prepared to probe the SAR at various positions.

Compounds **E**, **F**, and **G** (Scheme 2) were prepared from an α-*S*-hydroxy common intermediate **7**. Coupling of acetonide **6**, which was prepared from dimethyl malate **5** in six steps, with Pro-*O*-*t*-butyl under PyBOP condition followed by acetonide opening with sodium methoxide in methanol afforded **7**. Treatment of **7** with 50% aqueous hydroxylamine in dioxane yielded the corresponding hydroxamate **E**. Methylation of **7** with sodium hydride methyl iodide in DMF under Brimacombe[26] conditions followed by hydroxylamine treatment provided the α-*S*-methoxy derivative **F**. Compound **7** was also reacted with sulfur trioxide-pyridine complex[27] followed by reaction with hydroxylamine to give *O*-sulfo compound **G**.

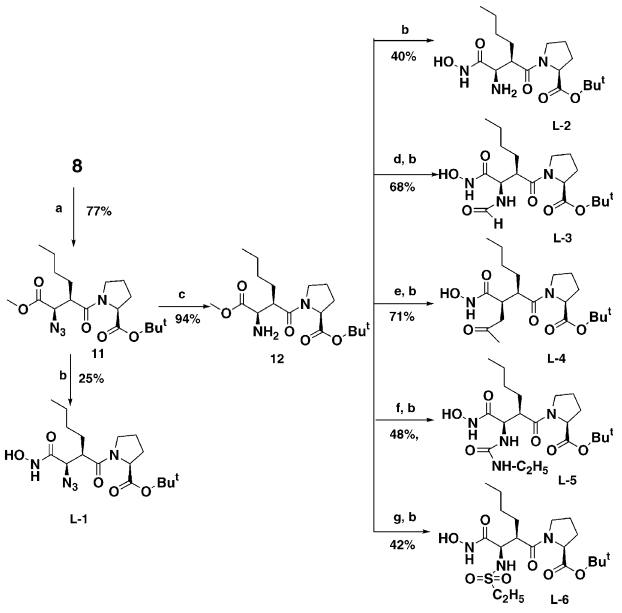
Synthesis of compounds **9**, **10**, **J**, and **K** from *S*-hydroxy intermediate **7** required inverting the stereochemistry at the α-position. This inversion was accomplished through the intermediacy of the triflate **8** which was obtained from **7** via treatment with triflic anhydride in dichloromethane (Scheme 3). Nucleophilic displacement of triflate with sodium thiomethoxide followed by reaction with hydroxylamine gave α-*R*-thio methyl compound **I**. α-*R*-Thiol analogue **H** was obtained by treatment with thioacetic acid under Mitsunobu reaction conditions followed by hydroxylamine treatment.



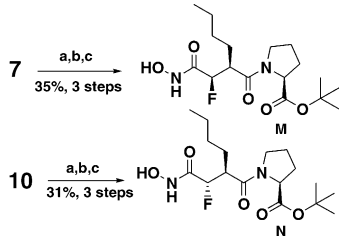
Scheme 3. Synthesis of α-(*R*)-substituted succinate hydroxamates Reagents and conditions: (a) triflic anhydride, pyridine, CH_2Cl_2, −20 to 0 °C, 2 h; (b) tetrabutyl ammonium benzoate, toluene, −30 to 0 °C, 2 h; (c) methanol, sodium methoxide, 0 °C, 4 h; (d) dioxane, 50% aq NH_2OH, 5 °C, 16 h; (e) NaH, DMF, methyl iodide, 4 h; (f) triphenylphosphine, diisopropylazo dicarboxylate, thioacetic acid, THF, 16 h; (g) sodium thiomethoxide, DMF, 16 h.

Similarly, nucleophilic displacement of triflate **8** with tetrabutylammonium benzoate[28] in toluene followed by de-*O*-benzoylation with sodium methoxide in methanol furnished α-*R*-hydroxy compound **10**. Hydroxylamine treatment of **10** resulted in the formation of compound **J**. Compound **K** was prepared via similar reaction sequences as described for the synthesis of **F** from **7**.

To access compounds **L-1**–**L-6** (Scheme 4), triflate **8** was treated with sodium azide in DMF to provide α-*R*-azido compound **11**, which on subsequent hydrogenolysis afforded amine derivative **12**. Hydroxylamine treatment of **11** and **12** provided the corresponding hydroxamates **L-1** and **L-2**. *N*-Acylation of **12** with mixed anhydride of formic acid/acetic anhydride and pyridine/acetic anhydride followed by reaction with hydroxylamine afforded *N*-formyl (**L-3**) and *N*-acetyl (**L-4**) analogues, respectively. Amino compound **12** was also treated with ethyl isocyanate and ethyl sulfonyl chloride followed by reaction with hydroxylamine to give urea (**L-5**) and sulfonamide (**L-6**) hydroxamates, respectively.



Scheme 4. Synthesis of α-(*R*)-N and *S*-substituted succinate hydroxamates. Reagents and conditions: (a) NaN_3, DMF, 16 h; (b) dioxane, 50% aq NH_2OH, 5 °C, 16 h; (c) 10% Pd/C, H_2, ethanol, 16 h; (d) HCOOH–Ac_2O, 5 °C, 16 h; (e) C_5H_5N, Ac_2O, 16 h; (f) ethyl isocyanate, pyridine, CH_2Cl_2, 0–25 °C, 3 h; (g) ethyl sulfonyl chloride, pyridine, CH_2Cl_2, 0–25 °C, 3 h.



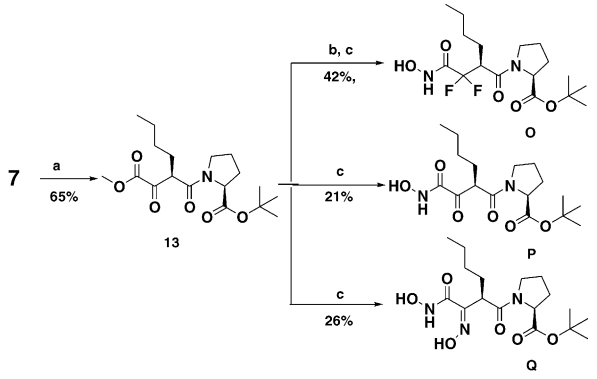
Scheme 5. Synthesis of α-fluoro substituted succinate hydroxamates Reagents and conditions: (a) triflic anhydride, pyridine, CH_2Cl_2, −20 to 0 °C, 2 h; (b) tris(dimethylamino)sulfur(trimethylsilyl) difluoride, CH_2Cl_2, −50 to 5 °C, 16 h; (c) dioxane, 50% aq NH_2OH, 5 °C, 16 h.

Nucleophilic displacement of the triflate **8** with Tris (dimethylamino)sulfur(trimethylsilyl)difluoride (TASF)[29] in methylene chloride followed by hydroxylamine treatment afforded α-*R*-fluoro analogue **M** (Scheme 5). A similar sequence of reaction was adopted for the preparation of **N** from **10** as described earlier for the synthesis of **M** from **7**.

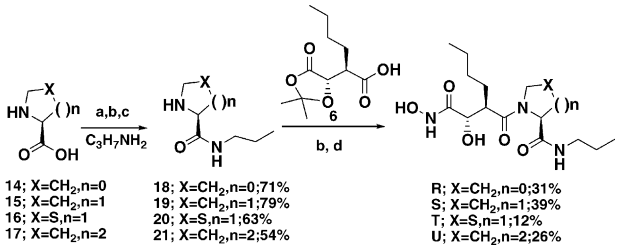
The synthesis of inhibitors containing difluoro (**O**), keto (**P**), and oxime (**Q**) functionalities at the α-position was achieved from a common α-oxo intermidate **13** (Scheme 6).

The synthesis of α-keto compound (**13**) was achieved by oxidation of α-S-hydroxy intermediate **7** with pyridinium dichromate[30] in methylene chloride. Fluorination of **13** with (diethylamino)sulfur trifluoride (DAST)[31] followed by reaction with hydroxylamine afforded bis-fluoro derivative (**O**), whereas treatment of **13** with hydroxylamine furnished a mixture of **P** and **Q** that were isolated by semi-preparative HPLC purification.

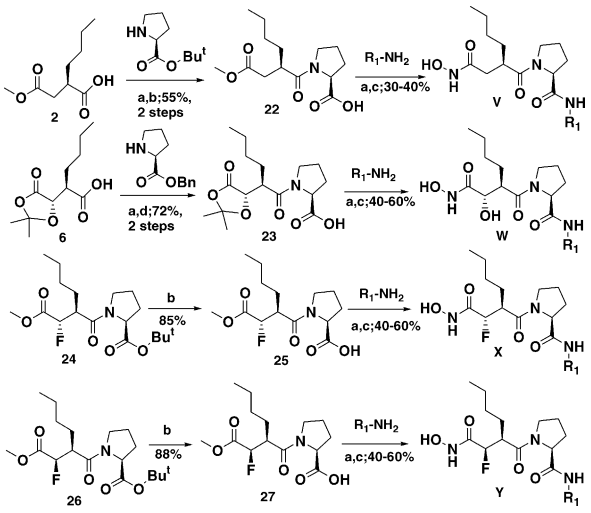
SAR was also examined at P_2'-position by substituting proline with other four- to six-membered cyclic amino acids **14**–**17** (Scheme 7). The protection of the amino functionality in these amino acids with a Boc group followed by treatment with propylamine under HATU condition and removal of Boc group with 4 M-HCl in dioxane provided the key amine intermediates **18**–**21**.



Scheme 6. Synthesis of α-keto, difluoro and oxime substituted succinate hydroxamates. Reagents and conditions: (a) pyridinium dichromate, CH_2Cl_2, 4 Å molecular sieves, 16 h; (b) *N*,*N*-dimethylamino sulfur trifluoride, CH_2Cl_2, −50 to 25 °C, 16 h; (c) dioxane, 50% aq NH_2OH, 5 °C, 16 h.



Scheme 7. Synthesis of proline mimetics. Reagents and conditions: (a) Boc anhydride, $NaHCO_3$, dioxane, water, 16 h; (b) HATU, DIEA, DMF, 25 °C, 16 h; (c) 4 M HCl in dioxane, 16 h; (d) dioxane, 50% aq NH_2OH, 5 °C, 16 h.



Scheme 8. 'One-pot' hydroxamate synthesis. Reagents and conditions: (a) HATU, DIEA, DMF, 16 h; (b) 90% aq TFA, CH_2Cl_2, 2 h; (c) dioxane, 50% aq NH_2OH, 5 °C, 8–32 h; (d) 10% Pd/C, H_2, ethyl acetate, 16 h.

Table 1. In vitro activity of **VRC3375** analogues containing different metal chelators[a]

Compd	MIC (μg/mL)			IC_{50} (μM)		
	SPN	SAU	HIN	PDF	MMP-7	K562
A	8–16	0.5–4	2–4	0.002	>200	>200
B	>64	>64	>64	2.9	>200	>200
C	>64	>64	>64	0.59	>200	>200
D	16–32	32->64	32–64	0.72	109	>200

[a]MIC values are expressed in μg/mL for SPN (*S. pneumoniae*, 3 strains), SAU (*S. aureus*, three strains), and HIN (*H. influenzae*, 3 strains). Enzyme inhibition and cytotoxicity are expressed as IC_{50} (μM) for PDF (*E. coli* Ni-containing peptide deformylase), MMP-7 (matrix metallo protease-7), and K562 (human leukemia cell K562 (ATCC #CCL-243)].

The condensation of these amines with acetonide **6** under HATU condition followed by reaction with hydroxylamine afforded the corresponding hydroxamates **R**–**U**.

A cross section of hydrophilic and hydrophobic aliphatic, alkaryl, aryl and heteroaryl amines were incorporated to explore SAR at P_3' in the α-hydroxy and α-fluoro succinate hydroxamate series. This was accomplished by developing an efficient 'one-pot' method (Scheme 8) for the synthesis of the desired inhibitors. The coupling of acid building blocks **22**, **25**, **27** (prepared from the corresponding *t*-butyl ester) and **23** (prepared from the *O*-benzyl ester) with the desired amines followed by reaction with hydroxylamine afforded the corresponding hydroxamates **V**–**Y**.

All biological evaluation was carried out as described previously.[17] In vitro data of **VRC3375** analogues with different chelators (Table 1) indicates that hydroxamate (**A**) provides the best enzyme inhibition and antibacterial activity amongst various chelators tested.

Table 2 summarizes the assay results for compounds with general structure of Figure 1 and as described in Schemes 2–8. In addition to the summary of the enzyme inhibition and antibacterial activities of these compounds, the table also includes the inhibition of a mammalian metalloprotease (MMP-7) and general cytotoxicity (K562) data. Both parameters are critical in assessing the potential of these compounds as antibacterial drugs.

Analogues of α-substituted hydroxamate were prepared to identify the most suitable groups at this position (**E**–**Q**). It is apparent that selected small substituents, such as hydroxy (**E**) and fluoro (**N**), can be tolerated; however, large groups such as methoxy (**F**), *O*-sulpho (**G**), sp^2-hybridized carbon (**P** and **Q**), thiol (**H**), and nitrogen-containing groups (**L**) result in loss of activity. While no special preference was observed for the configuration of α-hydroxy substitution (**E** and **J**), the *S*-configuration is preferred in the α-fluoro series (**M** and **N**). The *R*-isomers in α-fluoro series **Yc** and **Ym** are 10–20-fold less active in PDF inhibition and antibacterial activity than the corresponding *S*-isomers.

At the P_2'-postion, cyclic 4–6-member amino acid were incorporated. Among the analogues tested, azetidine (**R**) and proline analogues (**S**) are preferred whereas the corresponding six-membered pipecolinic inhibitor (**U**) is significantly less active. The replacement of proline with sulfur-containing thiazolidine (**T**) resulted in complete loss of antibacterial activity.

SAR of the P_3' substitution was also explored. In general, aryl or heteroaryl groups at the P_3' position considerably improved antibacterial activity. When comparing close analogues, the data suggest that increasing hydrophobicity at the P_3' position results in increased activity against *Streptococcus pneumoniae* with concomitant decreased activity against *Heamophilus influenzae* (e.g., **V-a**–**V-e**, **X-j**–**X-l**, and **W-u**–**W-v**). A proper hydrophilic and hydrophobic balance is required for maximal antibacterial activities with reduced toxicity. SAR in the **V** series suggests that hydrophobic groups improve antibacterial activity, with a concomitant increase of cytotoxicity. This observation is also true for the compounds with various aliphatic, cyclic, aryl and heteroaryl amines in the α-hydroxy (**W**) and α-fluoro (**X**) hydroxamate series. The tertiary amide substitutions dramatically reduced the cytotoxicity and MMP-7 inhibition but mainain the PDF inhibition and antibacterial activity (**X-q**–**X-t**). Pyrrolidine at P_3' (**X-r**) shows the best combination of in vitro potency, cytotoxicity and selectivity.

Selected compounds were scaled up and subjected to in vivo efficacy and pharmacokinetics studies in mice (Table 3). Although α-fluoro analogues in general exhibit a better in vitro profile than the corresponding α-hydroxy compounds, the reverse was true for the in vivo efficacy and PK profile.

In conclusion, we have identified α-substituted (hydroxy and fluoro) hydroxamates as a new class of PDF inhibitor-based antibacterial agents.

Table 2. Summary of in vitro activities of succinic hydroxamate analogues (see Fig. 1 for general structure).

Compd	α-	P_2'	P_3'	SPN(3)	SAU(3)	HIN(3)	PDF	MMP-7	K562
V-a	H	L-pro.	**a**	16	4–8	0.25–0.5	0.01	> 200	84
V-b	H	L-pro.	**b**	0.13–0.5	0.06–0.25	0.5–1	0.009	34	7
V-c	H	L-pro.	**c**	0.13–0.5	0.06–0.13	0.5–2	0.012	35	3
V-d	H	L-pro.	**d**	0.06–0.13	0.06	0.5–2	0.003	11	2
V-e	H	L-pro.	**e**	0.06–0.25	0.06–0.25	1–4	0.009	4	2
V-f	H	L-pro.	**f**	0.06–0.25	0.25–1	0.5–2	0.029	13	1
V-g	H	L-pro.	**g**	0.06–0.25	0.06–0.25	0.5–2	0.021	5	0.09
V-h	H	L-pro.	**h**	1–2	2–16	4–8	0.017	45	100
E	*S*-OH	L-pro.	**i**	8	0.25–1	4–16	0.001	28	> 28
J	*R*-OH	L-pro.	**i**	8–16	0.5–4	2–4	0.006	128	NT
F	*R*-OMe	L-pro.	**i**	64	32–> 64	32–> 64	0.05	NT	6
G	*S*-OSO_3H	L-pro.	**i**	16–32	1–4	16–32	0.03	> 200	112
N	*S*-F	L-pro.	**i**	2–4	0.25–1	1–2	0.002	111	> 28
M	*R*-F	L-pro.	**i**	16–32	2–8	16–32	0.016	139	NT
R	*S*-OH	L-aze.	**j**	1–4	0.5–4	4–8	0.0067	> 200	14
S	*S*-OH	L-pro.	**j**	4–16	1–4	2–8	0.008	105	44
T	*S*-OH	L-thiaz.	**j**	> 64	16–> 64	> 64	0.277	> 200	83
U	*S*-OH	L-pip.	**j**	16	8–> 64	16–32	0.0067	196	13
X-a	*S*-F	L-pro.	**a**	2–4	2–4	0.5–1	0.001	133	> 200
Y-a	*R*-F	L-pro.	**a**	32–64	4–16	4–8	0.027	> 32	> 200
X-j	*S*-F	L-pro.	**j**	0.25–1	0.5–2	0.5–1	0.013	35.3	> 200
X-k	*S*-F	L-pro.	**k**	0.25–0.5	0.5–1	1–2	0.016	23.9	102.9
X-l	*S*-F	L-pro.	**l**	0.25–0.5	0.12–0.5	2	0.013	13.1	21.4
X-m	*S*-F	L-pro.	**m**	0.25–2	0.5–1	0.12–0.5	0.0013	38.1	> 200
Y-m	*R*-F	L-pro.	**m**	4–8	2–8	4–8	0.016	186.7	97.5
X-n	*S*-F	L-pro.	**n**	2–16	4–16	4–8	0.007	61.3	> 200
X-o	*S*-F	L-pro.	**o**	0.13–0.5	0.5–1	2–4	0.009	16.2	64.9
X-c	*S*-F	L-pro.	**c**	0.13–0.25	0.13–0.5	1–2	0.002	0.9	24.1
Y-c	R-F	L-pro.	**c**	1–2	0.25–1	8–32	0.002	5.8	33.7
X-p	*S*-F	L-pro.	**p**	0.06–0.13	0.13–0.5	2–4	0.001	0.1	6.7
X-f	*S*-F	L-pro.	**f**	0.06–0.13	0.13–0.5	1–4	0.001	0.3	4.2
X-q	*S*-F	L-pro.	**q**	1	0.5–2	1–2	0.029	> 200	> 200
X-r	*S*-F	L-pro.	**r**	1–2	0.25–1	0.25–1	0.02	> 200	> 200
X-s	*S*-F	L-pro.	**s**	0.5–2	0.25–2	1–4	0.022	> 200	> 200
X-t	*S*-F	L-pro.	**t**	0.25–2	1–8	2–4	0.013	> 200	> 200
Xu	*S*-F	L-pro.	**u**	0.06–0.13	0.25–0.5	4–16	0.006	23.6	66.5
X-v	*S*-F	L-pro.	**v**	0.06–0.25	0.25–1	16	0.006	26.7	122.2
W-a	*S*-OH	L-pro.	**a**	16–32	2–4	2	0.01	63.5	> 200
W-j	*S*-OH	L-pro.	**j**	1–4	4–16	2–8	0.008	43.7	105
W-l	*S*-OH	L-pro.	**l**	1–4	0.5–2	4–8	0.008	20.5	21.6
W-w	*S*-OH	L-pro.	**w**	4–16	4–16	4–16	0.007	> 29	180.8
W-x	*S*-OH	L-pro.	**x**	4–16	1–4	8–16	0.008	> 27	177.9
W-o	*S*-OH	L-pro.	**o**	1–2	1–4	8–32	0.003	15.4	49.6
W-q	*S*-OH	L-pro.	**q**	4–16	1–4	2–8	0.017	> 200	> 200
W-r	*S*-OH	L-pro.	**r**	8–16	2–4	1–4	0.024	> 200	> 200
W-s	*S*-OH	L-pro.	**s**	4–32	1–4	16–32	0.013	108.4	> 200
W-t	*S*-OH	L-pro.	**t**	8	8	4	0.004	183.3	80.9
W-u	*S*-OH	L-pro.	**u**	0.25–1	0.06–0.25	32–64	0.005	9.7	109.7
W-v	*S*-OH	L-pro.	**v**	1–4	0.25–4	64	0.003	17.1	> 200

Table 3. In vivo efficacy and PK parameters of selected succinate hydroxamate PDF inhibitors

Compd	**A**	**W-a**	**X-a**	**W-r**	**X-r**	**W-c**	**X-c**
ED_{50}[a] (mg/kg)							
iv	14	1.7	1.2	1.1	5.0	3.3	2.3
po	25.6	NT	10.2	> 10	> 12.5	12	28.6
PK[b]							
$t_{(1/2)}$ (h) iv	0.3	1	0.6	0.5	0.7	0.3	0.4
AUC[b] (ng h/mL) iv	172	290	154	546	144	86.5	89.4
$t_{(1/2)}$ (h) po	0.4	1.3	1.5	1.5	2.0	NT	1.7
AUC[c] (ng h/mL) po	16.5	29.1	16.9	33.1	10.7	13.0	4.5
Oral bioavailability (%)	9.6	10	10.9	6.1	7.5	15.1	5

[a]50% Effective dose in mouse *S. aureus* septicemia infection model; The studies were carried out as previously described[17] and the data represent results of single experiments.
[b]Intravenous (iv) dosing at about 2 mg/kg and oral (po) dosing at 10 mg/kg.
[c]AUC values normalized to 1 mg/kg dose.

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